Enantioselective Copper-Catalysed Reductive Michael Cyclisations

Thesis Submitted in Accordance with the Requirement of The University of Edinburgh for the Degree of Doctor of Philosophy

By

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MChem (Hons)

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Declaration

I hereby declare that, except where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of the PhD degree in September 2006, and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification.

Signed

Claire Louise Oswald

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Thanks to my family – Mam, Dad and Stuart for all your support (financial and otherwise!) over the past few years. I hope you enjoy my “book”, even if this is the only page you read.

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Abstract

Hydrometalation of α,β-unsaturated carbonyl compounds provides access to reactive metal enolates, which can then be trapped by a suitable electrophile. The copper-catalysed reductive aldol reaction involves hydrometalation of an α,β-unsaturated carbonyl compound, followed by an inter- or intramolecular aldol reaction. While there have been numerous examples of copper-catalysed reductive aldol reactions reported in the literature, the corresponding reductive Michael reaction has been relatively understudied.

Herein, the copper-catalysed reductive Michael cyclisation of substrates containing two α,β-unsaturated carbonyl moieties is described. A range of structurally and electronically diverse substrates were prepared by various different methods. Both α,β-unsaturated ketones and esters underwent cyclisation, in the presence of a copper catalyst, a bisphosphine ligand, and a stoichiometric reductant, to afford 5- and 6-membered carbocyclic and heterocyclic products, with good-to-excellent levels of diastereo- and enantiocontrol. Furthermore, the diastereochemical outcome of these reactions is dependent on the specific reaction conditions used.

Abbreviations

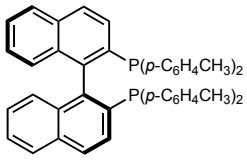
Ac	acetyl
aq	aqueous
Ar	aryl
Bn	benzyl
br	broad
COSY	Correlation Spectroscopy
d	doublet
DCE	dichloroethane
DIBAL	diisobutylaluminium hydride
DMA	dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMI	1,3-dimethylimidazolidinone
dpm	bis(2,2,6,6-tetramethyl-3,5-heptadionate)
dppf	(1,1')-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact

equiv.	equivalent
ES	electrospray
FT	Fourier transform
HMBC	Heteronuclear Multiple Bond Correlation
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	Heteronuclear Single Quantum Coherence
IR	infrared spectroscopy
LDA	lithium diisopropylamide
MOM	methoxymethyl ether
m.p.	melting point
NHC	*N*-heterocyclic carbene
NMO	*N*-methylmorpholine
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
piv	pivaloyl
PMHS	poly(methylhydrosiloxane)
PMP	4-methoxyphenyl
PMB	4-methoxybenzyl

ppm	parts per million
PTS	paratoluenesulfonic acid
Py	pyridyl
q	quartet
rt	room temperature
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldifluorosilicate
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMDS	1,1,3,3-tetramethyldisiloxane
TMS	trimethylsilyl
Tol	tolyl
Tr	triphenylmethyl

Ts	tosyl
UV	ultraviolet spectroscopy

Ligands



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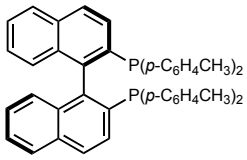

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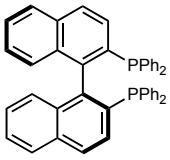

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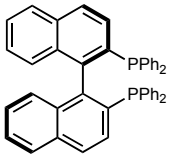

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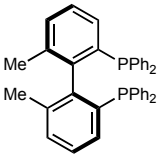

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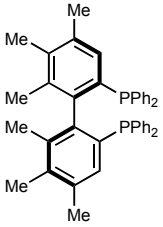

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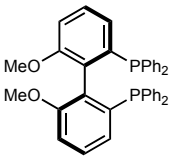

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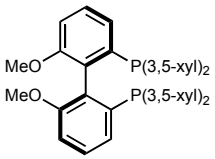

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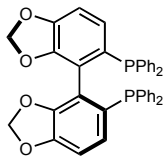

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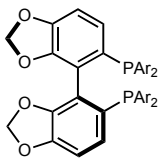

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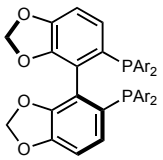

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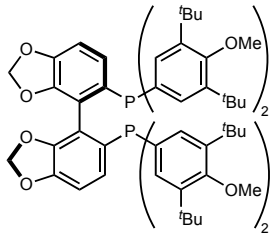

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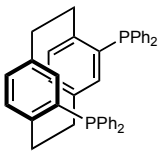

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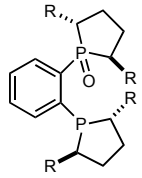

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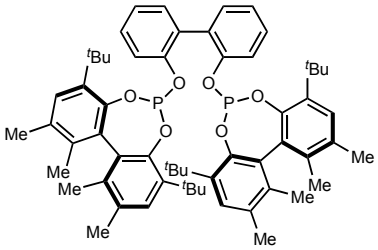

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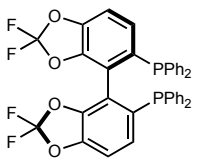

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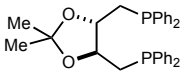

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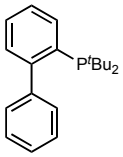

L19

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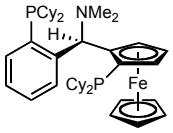

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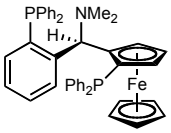

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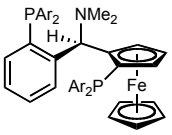

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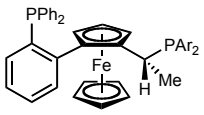

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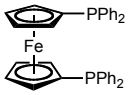

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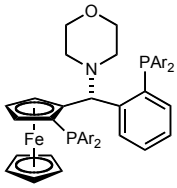

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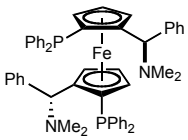

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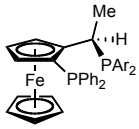

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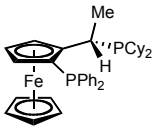

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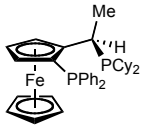

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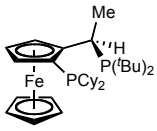

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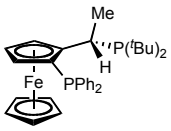

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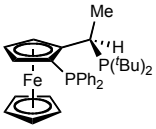

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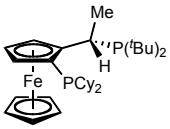


(*S*,*R*)-**L33**

1 Copper-Mediated Conjugate Reduction

1.1 Introduction

The addition of a metal hydride across an unsaturated bond is commonly referred to as hydrometalation. Although many metals have been used to accomplish this transformation, the use of copper complexes to effect the reduction of activated alkenes is a comparatively recent development.[1] In the past decade, copper hydride chemistry has emerged as a powerful tool for effecting reductions of various α,β-unsaturated compounds, ranging from α,β-unsaturated ketones, esters, and aldehydes, to other Michael acceptors, such as α,β-unsaturated nitroalkenes, sulfones, and nitriles.[2] Moreover, the development of new biaryl and ferrocenyl chiral ligands has led to asymmetric variants of such reactions, providing easy access to synthetically useful chiral building blocks.

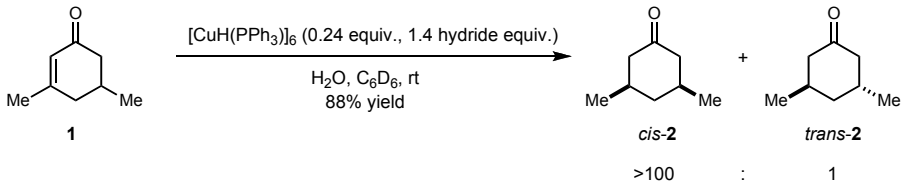
Hydrometalation of α,β-unsaturated carbonyl compounds is known to proceed *via* metal enolates, and the inter- or intramolecular trapping of these intermediates by electrophiles can result in highly stereoselective carbon–carbon bond-forming reactions.[3] Thus, domino modifications have also been achieved, including reductive aldol, Michael and Henry reactions, among others, providing rapid increases in molecular complexity with often extremely high stereocontrol.

Herein, the conjugate reduction of a range of electron–deficient alkenes will be discussed, including the development of highly enantioselective modifications. Domino processes will also be introduced, providing insight into the broad range of complex transformations achievable through copper hydride chemistry.

1.2 Stryker's Reagent

The phosphine–stabilised hexameric copper hydride species, $[CuH(PPh_3)]_6$ was discovered by Osborn and co-workers in 1972.[4] However, it was not until 1988,

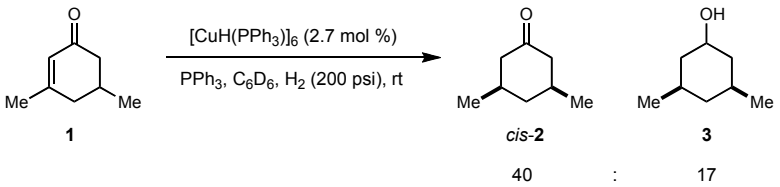
when Stryker discovered that $[CuH(PPh_3)]_6$, now commonly referred to as Stryker's reagent, could be used to effect the conjugate reduction of various α,β-unsaturated carbonyl compounds, that modern usage of copper hydride in synthesis began to develop.[5] In this seminal publication, Stryker described the stereoselective conjugate reduction of a range of α,β-unsaturated carbonyl compounds, including ketones, esters and aldehydes (Scheme 1.1).



Scheme 1.1

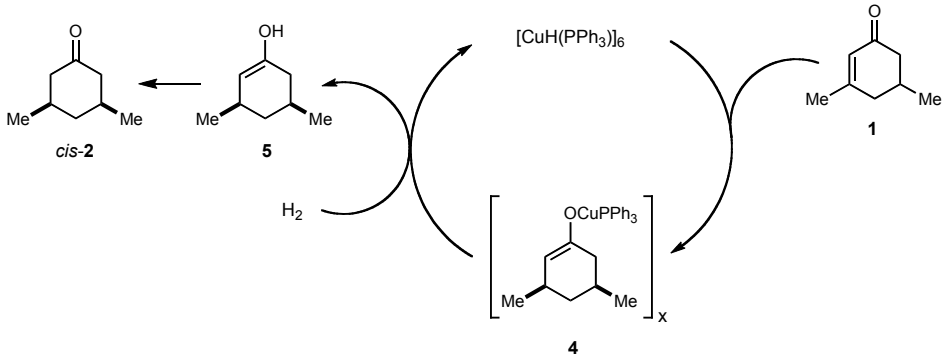
Reduction of β,β'-disubstituted enone **1** was found to be highly stereoselective, affording saturated cyclohexanone *cis*-**2** as the major product, resulting from hydride delivery to the least hindered face of the substrate. Importantly, 1,2-reduction was not observed, nor was the reduction of isolated double bonds. Furthermore, the reaction was found to be stable to water under an inert atmosphere and tolerant of a range of functionalities, including unprotected hydroxyl groups. Shortly after his initial publication, Stryker described a simple, one-pot procedure for the synthesis of $[CuH(PPh_3)]_6$, and the reagent quickly became commercially available.[6]

Stryker recognised the potential for the reaction to be made catalytic and subsequently described a method for the reduction of α,β-unsaturated ketones in the presence of a substoichiometric amount of $[CuH(PPh_3)]_6$ under a hydrogen atmosphere (Scheme 1.2).[7]



Scheme 1.2

The reaction is thought to proceed *via* copper enolate **4** (Scheme 1.3). This enolate must be capable of activating hydrogen gas heterolytically, to effect both protonation of the enolate, and regeneration of the catalyst. Although this intermediate has not been isolated, there is considerable evidence supporting its formation, including NMR signals indicative of a copper-oxygen-bonded enolate, which can be detected when the reaction is carried out in deuterated benzene.

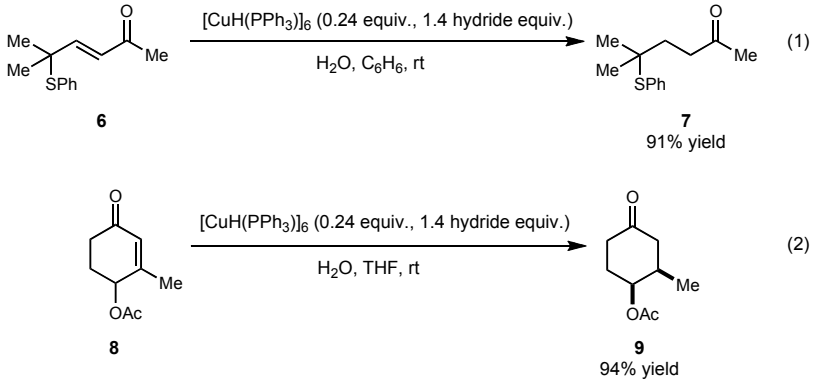


Scheme 1.3

Unfortunately, Stryker's catalytic variant required the undesirable use of high pressures of hydrogen gas and suffered from slow catalytic turnover, leaving room for improvement.

In 1990, Stryker and co-workers reported the conjugate reduction of a range of α,β-unsaturated carbonyl compounds, noting the tolerance of Stryker's reagent towards a

variety of different functional groups, including γ-sulfur, and oxygen-containing substrates (Scheme 1.4).[8]

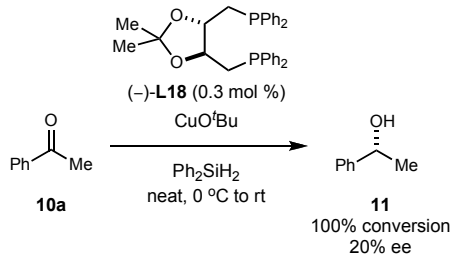


Scheme 1.4

Thiophenoxy-substituted enone **6** was found to undergo reduction in the presence of a stoichiometric amount of Stryker's reagent to afford saturated ketone **7** in excellent yield. Substrate **8**, which is substituted at the γ-position with an acetate group, was also found to undergo reduction, without loss of acetate. The authors also note that a decrease in reaction rate is observed upon addition of excess PPh_3 or when the reaction is performed in a coordinating solvent, such as THF, suggesting coordination of the copper(I) to the substrate prior to conjugate reduction.

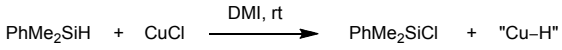
1.3 Copper-Catalysed Hydrosilylation

Despite the initial success of Stryker's reagent, a reliable catalytic variant was still sought. Furthermore, a more convenient reagent would also be beneficial, since Stryker's reagent is moderately air sensitive. In 1984, Burnner and Miehling reported the copper-catalysed reduction of acetophenone using diphenylsilane as the stoichiometric reductant (Scheme 1.5).[9]



Scheme 1.5

However, it was not until 1997 that Hosomi and co-workers established that hydride transfer from a silane to a copper(I) salt was possible in a polar, aprotic solvent, such as (1,3-dimethylimidazolidinone) (DMI) (Scheme 1.6).[10]

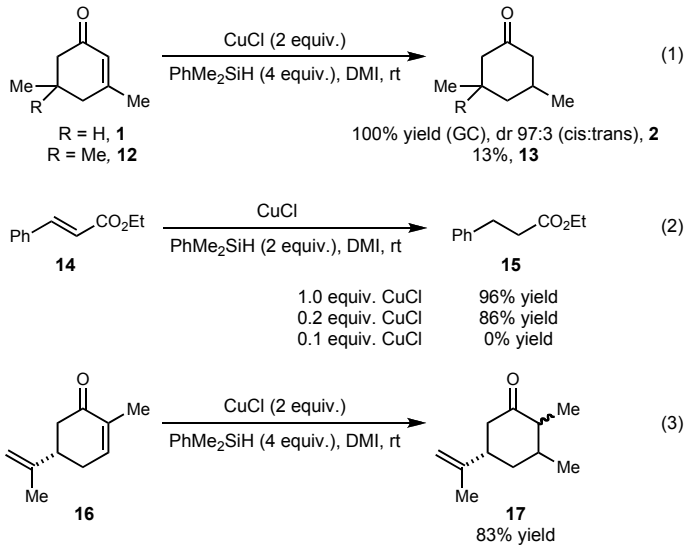


Scheme 1.6

Addition of dimethylphenylsilane to a suspension of copper(I) chloride resulted in complete consumption of the silane, along with formation of dimethylphenyl chlorosilane, a result indicative of transmetalation of the hydrosilane to copper(I) to generate a copper hydride species. Preliminary investigations revealed that solvent plays an important role in this reaction, and the use of less polar solvents such as THF or CH_2Cl_2, resulted in no reaction.

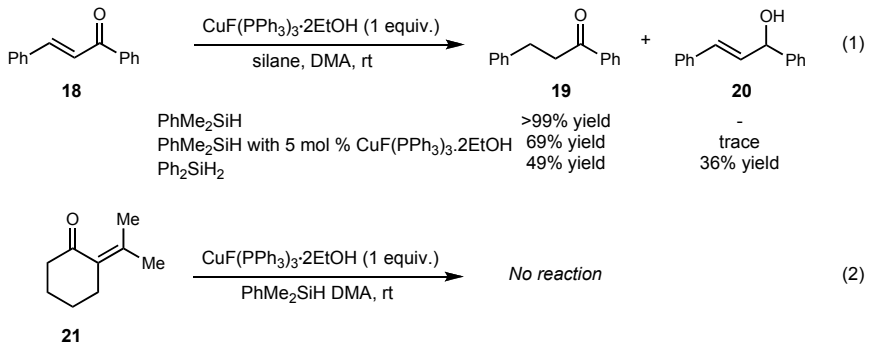
Conjugate reduction of a range of α,β-unsaturated carbonyl compounds was then carried out (Scheme 1.7). In agreement with Stryker's work,[5] the reduction of enone **1** was highly stereoselective, and proceeded to give mainly *cis*-**2**. However, replacement of the δ-proton by a methyl group, as in enone **12**, resulted in a significant decrease in the yield. The reaction was found to be tolerant of isolated olefinic double bonds, exemplified by the conjugate reduction of substrate **16**, which proceeded to give cyclohexanone **17** in 83% yield. The authors also investigated the use of substoichiometric amounts of copper(I) chloride. When 0.2 equivalents of

CuCl were used, 86% of ester **15** was obtained, however, decreasing the amount to 0.1 equivalents resulted in no reaction. Nevertheless, this result proves that it is possible to effect hydride reductions catalytically.



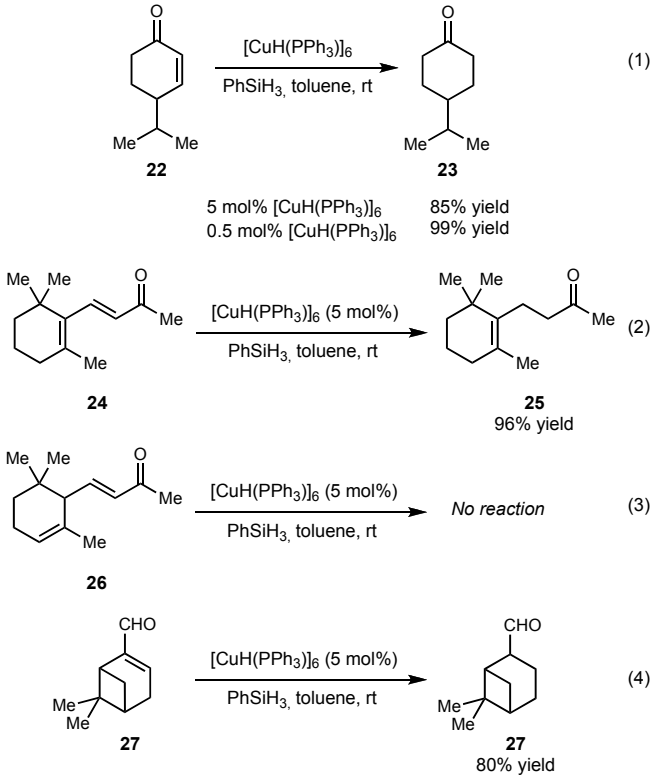
Scheme 1.7

Around the same time, Mori and co-workers published an analogous procedure for the 1,4-reduction of α,β-unsaturated ketones (Scheme 1.8).[11] Using stoichiometric $CuF(PPh_3)_3 \cdot 2EtOH$ in combination with dimethylphenylsilane, the reaction was found to be highly selective for 1,4-addition. However, if diphenylsilane was used as the reductant, a significant amount of allylic alcohol **20**, arising from 1,2-addition, was also observed. It was also noted that increased steric bulk at either the α-, or β-position inhibited reduction; for example, β,β-disubstituted enone **21** did not undergo reduction.



Scheme 1.8

Shortly after the pioneering work of Hosomi[10] and Mori,[11] Lipshutz successfully developed the first method for conjugate reduction of α,β-unsaturated carbonyl compounds using a substoichiometric amount of Stryker's reagent (Scheme 1.9).[12]



Scheme 1.9

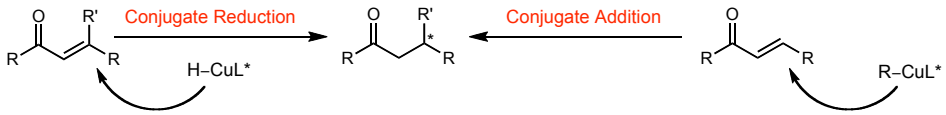
Lipshutz and co-workers reported that catalyst loadings as low as 0.5 mol % were tolerated, resulting in yields of up to 99%. Of particular interest, is the reduction of β-ionone **24**, which proceeds regioselectively to afford only the product arising from 1,4-reduction, with no concomitant 1,6-reduction. Inexplicably, α-ionone **26** did not undergo reduction. It is also noteworthy that no competing 1,2-reduction was observed, even in the case of enal **27**, which underwent reduction to give aldehyde **28** in 80% yield.

Lipshutz's work was quickly superceded by the first asymmetric copper-catalysed conjugate reduction, published by Buchwald in 1999.[13] Following this seminal publication, a plethora of reports emerged, describing 1,4-reduction of various types of α,β-unsaturated carbonyl compounds and other Michael acceptors. Due to the abundance of literature on copper-catalysed conjugate reductions, the remainder of this section will concentrate specifically on *asymmetric* conjugate reductions of various Michael acceptors.

1.4 Copper-Catalysed Asymmetric 1,4-Reduction Reactions

1.4.1 Introduction

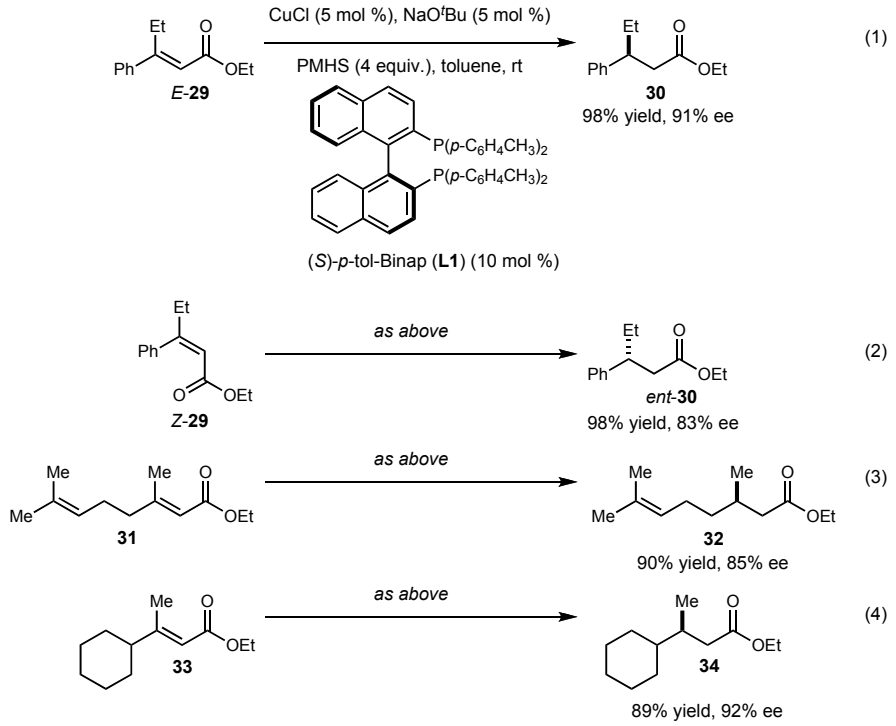
Asymmetric conjugate reduction of α,*β*-unsaturated carbonyl compounds and similar Michael acceptors allows control of absolute stereochemistry at a site *β* to an electrophilic centre. Although there are numerous methods for asymmetric conjugate addition of *nucleophiles* to various Michael acceptors,[14] the area of asymmetric *conjugate reduction* remains relatively understudied, and would provide a complementary approach towards accessing the same products (Scheme 1.10).



Scheme 1.10

1.4.2 Copper-Catalysed Asymmetric 1,4-Reductions of α,*β*-Unsaturated Esters, Ketones and Aldehydes

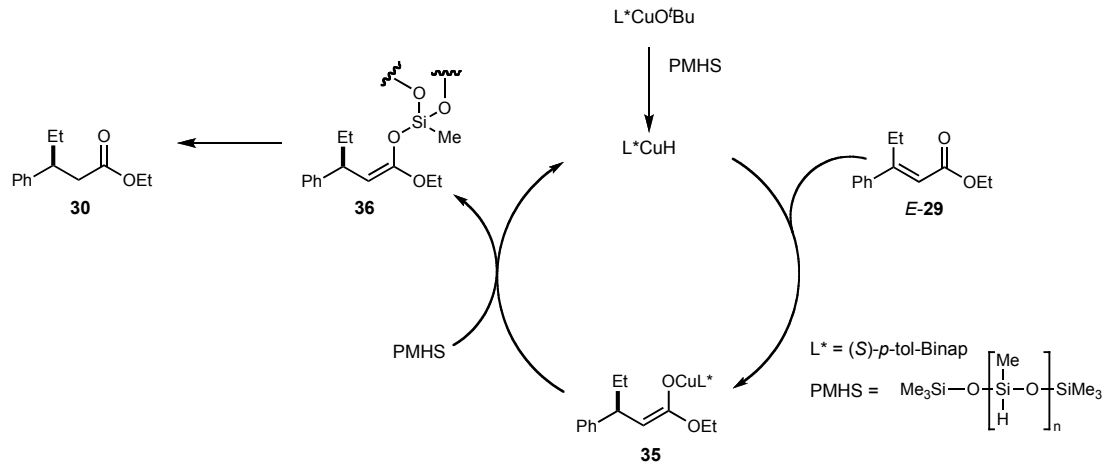
In 1999, Buchwald and co-workers began to investigate the use of copper hydride, along with chiral bisphosphine ligands to effect the asymmetric conjugate reduction of α,*β*-unsaturated esters.[13] An efficient catalyst was generated *in situ* from a combination of CuCl, NaO^{t}Bu and (*S*)-*p*-tol-Binap, followed by addition of four equivalents of polymethylhydrosiloxane (PMHS), and was subsequently used in the conjugate reduction of a series of *β*,*β*′-disubstituted α,*β*-unsaturated ethyl esters (Scheme 1.11).



Scheme 1.11

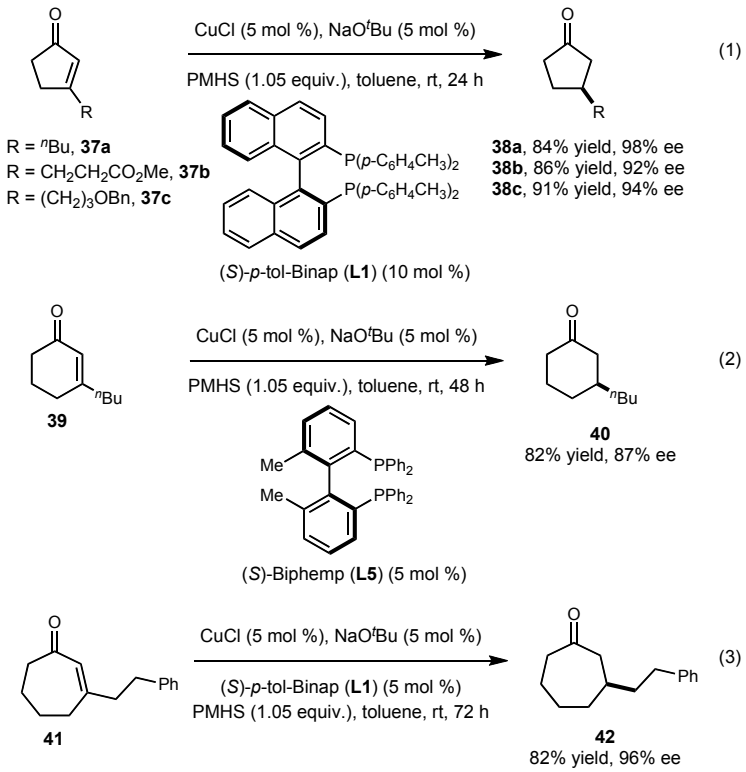
The reduced products were obtained in high yields and good enantioselectivities. Buchwald also noted that when the conjugate reductions of (*E*)- and (*Z*)-isomers of the same substrate were examined, they reacted to give products of comparable enantiomeric excess, but opposite enantiomers were obtained.

The proposed catalytic cycle involves the formation of (*p*-tol-Binap)CuO^{t}Bu from CuCl, NaO^{t}Bu, and *p*-tol-Binap (Scheme 1.12). Upon addition of PMHS, (*p*-tol-Binap)CuO^{t}Bu then undergoes σ-bond metathesis to give (*p*-tol-Binap)CuH. Conjugate reduction then occurs, to give a copper enolate intermediate **35**, which then undergoes σ-bond metathesis, giving rise to silyl ketene acetal **36** along with regeneration of the copper catalyst. Cleavage of the silyl group provides saturated product **30**.



Scheme 1.12

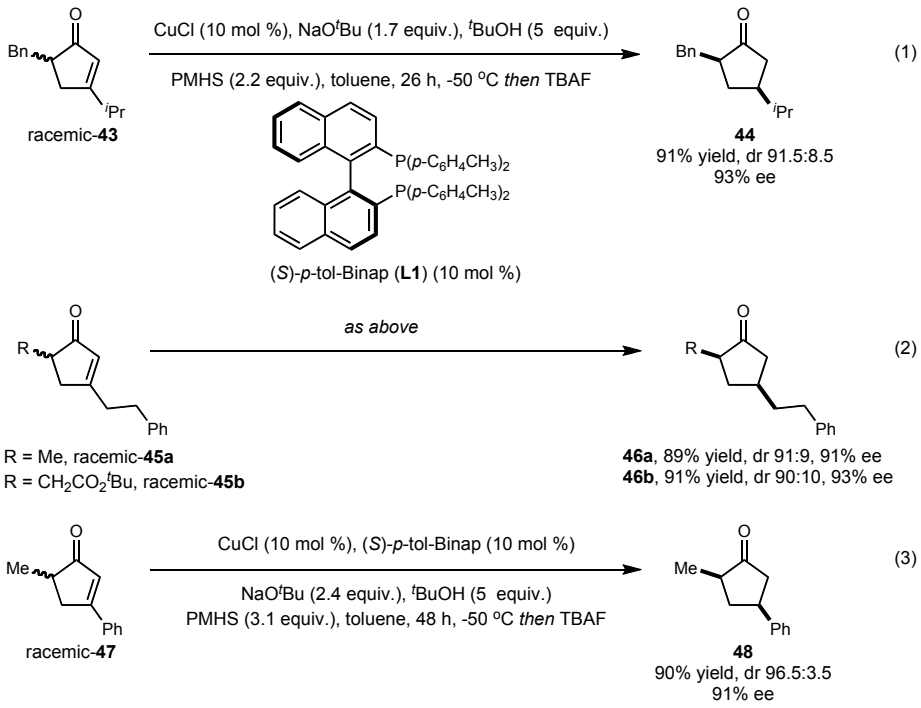
Shortly afterwards, Buchwald and co-workers reported the use of the same catalyst system to effect the reduction of β-substituted cyclic enones (Scheme 1.13).[15] In this case, however, the authors noted that it was important to limit the amount of PMHS to one equivalent, to avoid over reduction to the saturated alcohol. Furthermore, reduction of the catalyst loading to 1 mol % was found to have no effect on the enantiomeric excess, although this typically resulted in longer reaction times.



Scheme 1.13

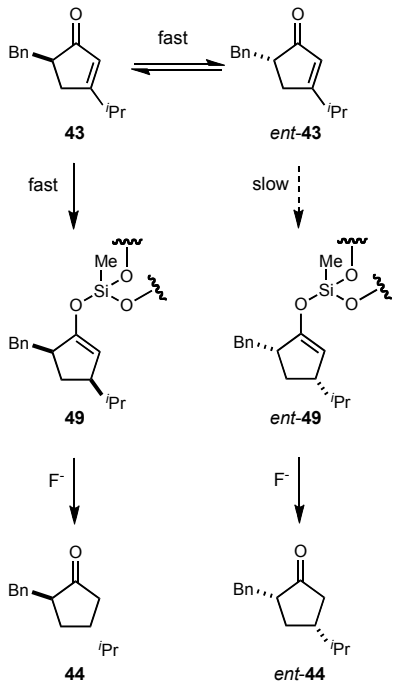
Examination of the substrate scope revealed that the catalyst is tolerant of cyclopentenones substituted at the β-position with a simple alkyl chain, or substrates containing ether or ester functionalities. However, cyclopentenones with vinyl or alkynyl substitution at the β-position, gave mixtures of products resulting from both 1,4- and 1,6-reduction.

In a remarkable extension of this work, Buchwald and co-workers carried out dynamic kinetic resolution of 3,5-dialkyl cyclopentenones, allowing simultaneous formation of two nonadjacent stereocentres (Scheme 1.14).[16]



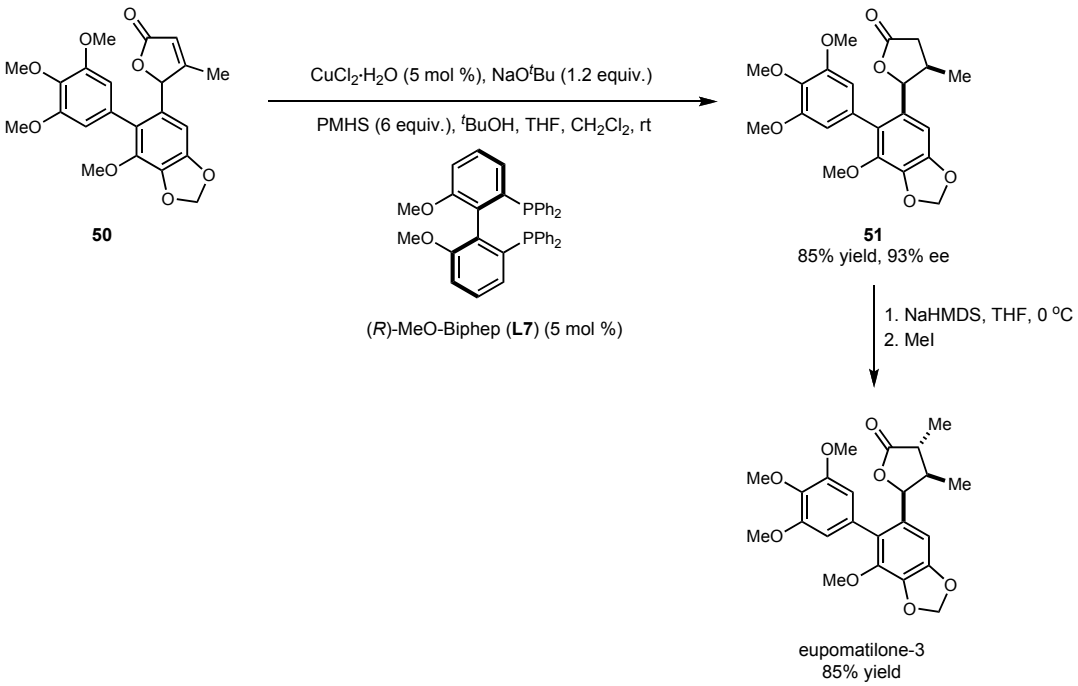
Scheme 1.14

By carrying out the conjugate reduction in the presence of a base, racemisation of the starting material was rapid (Scheme 1.15). As the more reactive enantiomer **43** underwent reduction to give the silyl enol ether **49** – which is protected from epimerization – it was replenished by the less reactive enantiomer *ent*-**43**. Low temperatures were necessary in order to increase the selectivity; however, under such conditions, racemisation of the starting material was too slow, relative to conjugate reduction. To resolve this issue, ^{t}BuOH was added in order to increase the rate of racemisation by acting as a proton source. As a result, the cyclopentanone products were obtained in high yields, diastereoselectivities, and enantioselectivities.



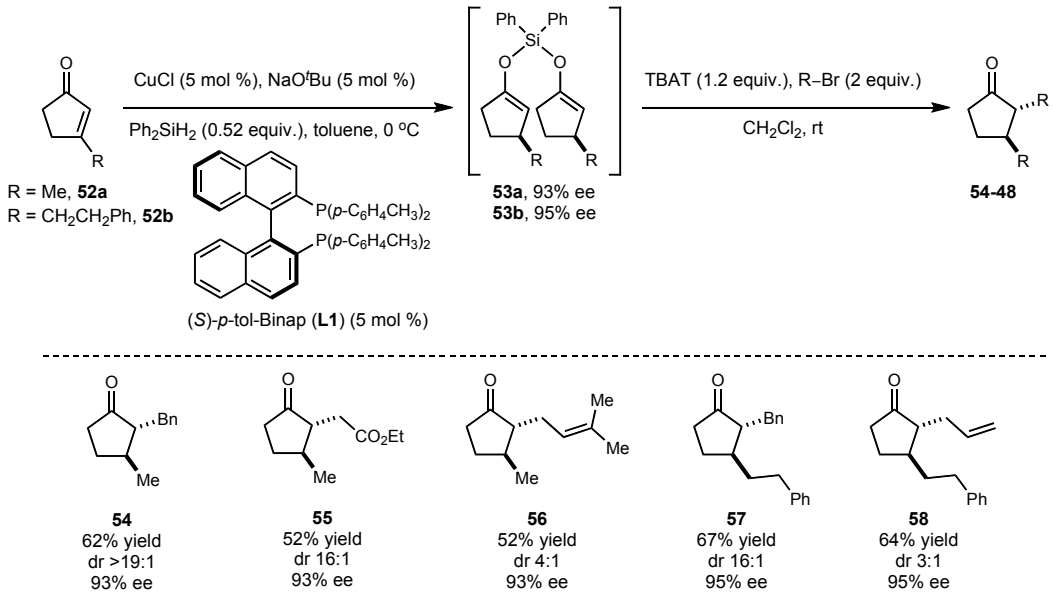
Scheme 1.15

In 2005, Buchwald applied this methodology to the total synthesis of eupomatilone-3, a target that became of great interest due to the *cis*-orientation of the substituents at C3 and C4 positions of the lactone ring.[17] Hence, the key step in this synthesis was the dynamic kinetic resolution of unsaturated lactone **50**, to give saturated lactone **51**, which was subsequently converted into the natural product by stereoselective alkylation at C5 (Scheme 1.16). In this case, MeO-Biphep was used, as opposed to *p*-tol-Binap, which was found to give slightly inferior results, and lactone **51** was isolated as a single diastereomer in 85% yield, and 93% ee. Enolisation of lactone **51** with NaHMDS, followed by alkylation with methyl iodide provided eupomatilone-3 in 85% yield.



Scheme 1.16

Following the success of their copper-catalysed asymmetric reduction of both α,*β*-unsaturated esters[13] and ketones,[15] Buchwald and co-workers devised a convenient one-pot asymmetric reduction/alkylation protocol for the synthesis of 2,3-disubstituted cyclopentanones (Scheme 1.17).[18] Conjugate reduction, using Buchwald's previously described conditions, afforded silyl enol ether **53a** or **53b**. Addition of an alkyl halide and TBAT (tetrabutylammonium triphenyldifluorosilicate), gave the α-alkylated species as the *trans*-diastereomer in all cases. In general, the alkylated products were obtained in moderate yields and good diastereoselectivites, although equilibration of the product in the presence of NaOMe in MeOH led to an increased diastereomer ratio.



54
62% yield
dr >19:1
93% ee

55
52% yield
dr 16:1
93% ee

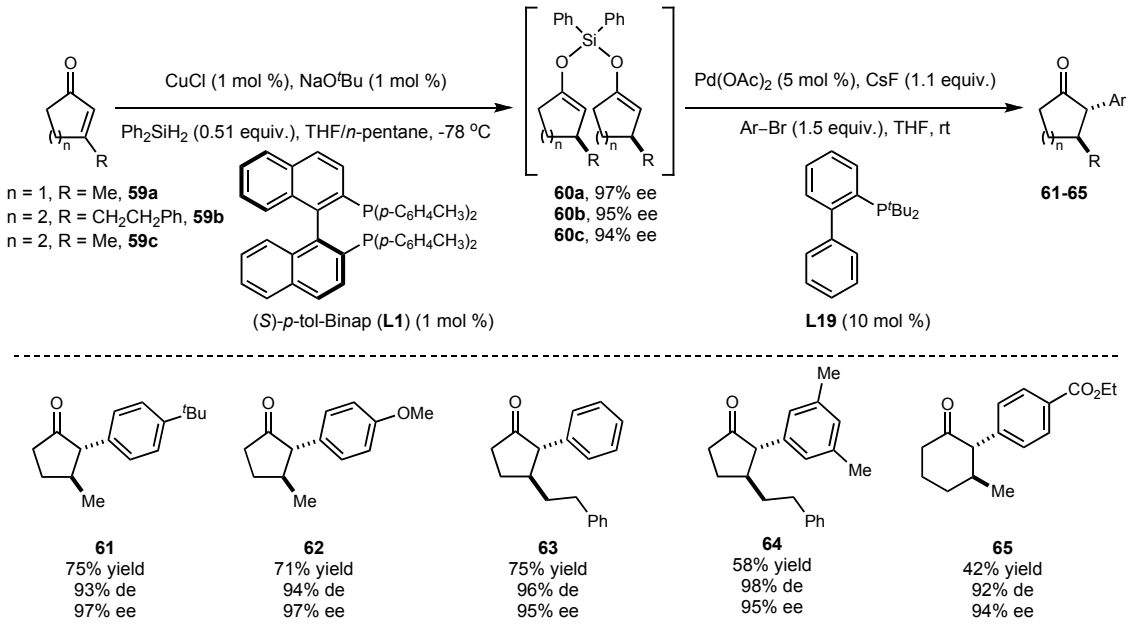
56
52% yield
dr 4:1
93% ee

57
67% yield
dr 16:1
95% ee

58
64% yield
dr 3:1
95% ee

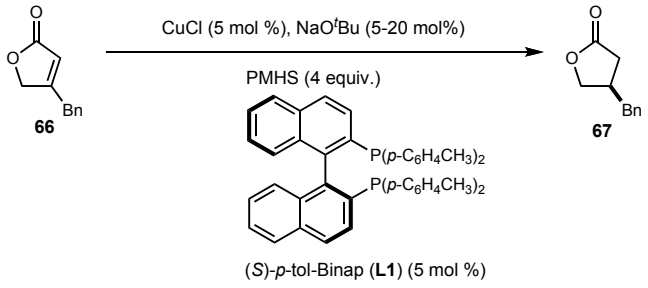
Scheme 1.17

Buchwald extended this methodology to include palladium-catalysed α-*arylations* of cyclopentenones.[19] Similarly, the first step involves asymmetric conjugate reduction of the enone, to form a silyl enol ether. Subsequent activation of the silyl enol ether by fluoride increases the nucleophilicity of the enolate, and palladium-catalysed arylation proceeds diastereoselectively to afford arylated products **61-65** in good yields. Interestingly, when screening ligands for the arylation reaction, the authors noted that (*S*)-*p*-tol-Binap inhibited the reaction, which they attributed to its higher binding affinity for palladium, relative to **L19**. Thus, in the one-pot reaction, it was necessary to reduce the quantity of (*S*)-*p*-tol-Binap to 1 mol %.



Scheme 1.18

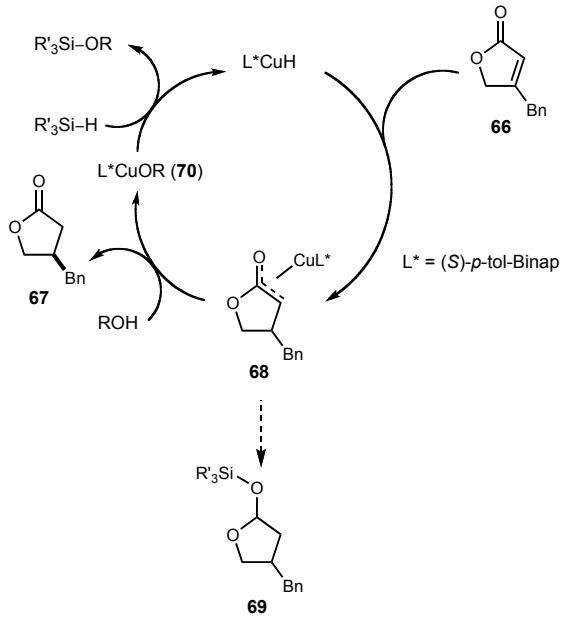
In 2003, Buchwald and co-workers discovered that the rate of conjugate reduction reactions could be dramatically accelerated upon addition of alcohols (Table 1.1).[20] Furthermore, it was found that the addition of excess alcohol could also lead to an increase in the yield of the reaction. This was realised when poor yields were obtained in the conjugate reduction of α,β-unsaturated lactone **66**, despite high conversions.



entry	solvent	additive	temperature	time	yield	ee
1	toluene	–	23 °C	48 h	50%	80%
2	cyclohexane	EtOH (4 equiv.)	23 °C	5 min	89%	–
3	THF/pentane	EtOH (4 equiv.)	-40 °C	4 h	90%	93%

Table 1.1

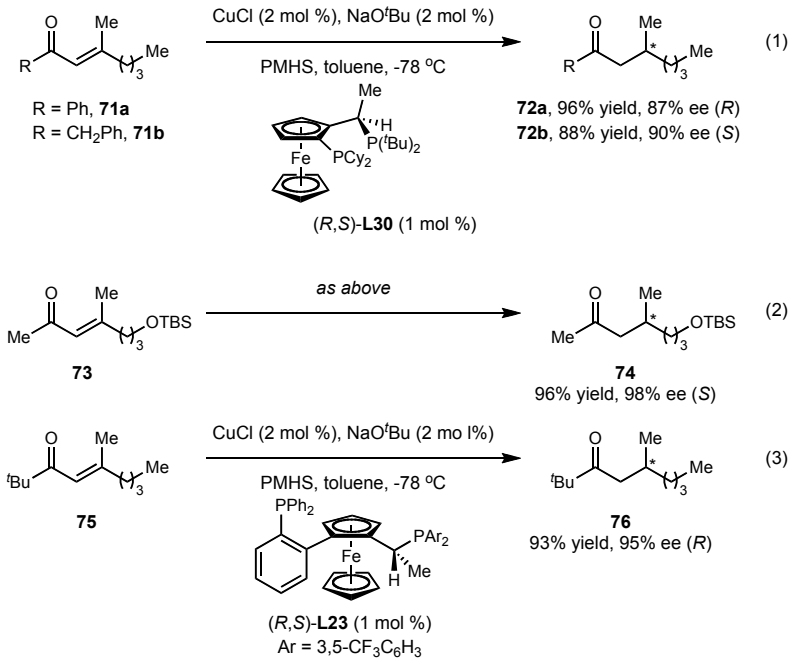
Upon closer examination of the reaction mechanism (Scheme 1.19), it was postulated that the poor mass balance was conceivably due to unwanted side reactions of either the silyl ketene acetal **69**, or the copper enolate **68**; addition of an alcohol would inhibit these side reactions by protonation of the copper enolate, providing saturated lactone **67**. The resultant copper alkoxide **70** is then protonated, regenerating the catalyst.



Scheme 1.19

Following extensive investigation, Buchwald and co-workers concluded that in the absence of any alcohol, the rate-limiting step is silylation of copper enolate **68**. In contrast, silylation of copper alkoxide **70** is much faster, owing to the rapid rate acceleration observed upon addition of alcohol. The authors attribute the slow σ-bond metathesis to a preference for a carbon-bound, as opposed to an oxygen-bound copper enolate.

Shortly afterwards, Lipshutz published the first example of 1,4-reduction of acyclic α,β-unsaturated ketones, using CuCl and NaO^{t}Bu as the precatalyst, and PMHS as the stoichiometric reductant.[21] After screening various ligands, it was found that Josiphos ligand **L30**, and Walphos ligand **L23** (Scheme 1.20) gave superior results. A range of enones underwent conjugate reduction, including sterically hindered *tert*-butyl enones and aryl enones, in excellent yields and enantioselectivites.

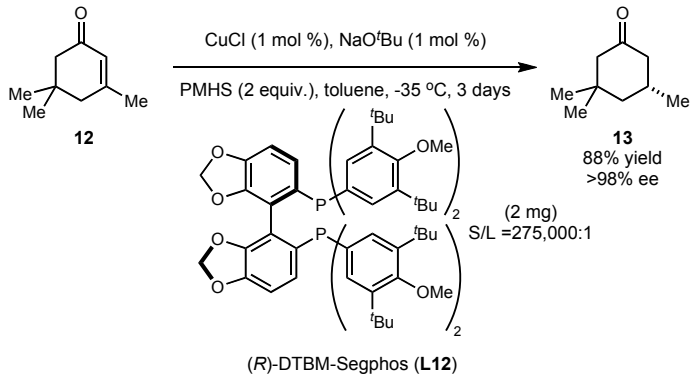


Scheme 1.20

The authors noted that steric factors do not appear to play a major role in determining enantioselectivity, exemplified by the reaction of *tert*-butyl substrate **75**, which underwent reduction to afford ketone **76** in excellent yield and enantiomeric excess. In contrast, however, a slight decrease in enantioselection was observed upon changing the R substituent from alkyl (**74**), to benzyl (**72b**), to aryl (**72a**), suggesting that stereoelectronics might be of some importance. An alternative explanation is that arene-arene interactions or arene-copper interactions are taking place, resulting in reduced enantiocontrol. Also of note is the observation that aryl ketones such as **71a**

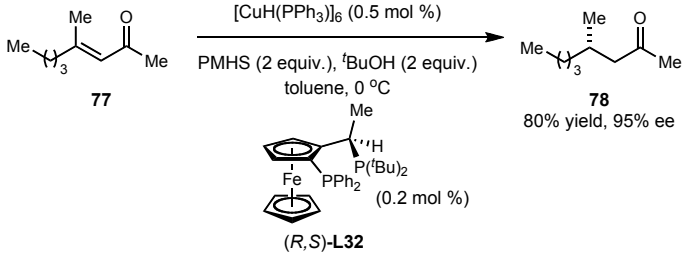
undergo reduction under the same reaction conditions to give the opposite enantiomer to that of the corresponding alkyl ketones.

In 2004, the Lipshutz group furthered this research by carrying out the conjugate reduction of cyclic α,β-unsaturated enones in the presence of DTBM-Segphos, using extremely low catalyst loadings.[22] Of particular note is the example given below (Scheme 1.21), which was conducted using 65 g of **12**, and only 2 mg of ligand, equivalent to a substrate-to-ligand rato of 275,000:1. The product was isolated in good yield and extremely high enantioselectivity, illustrating the effectiveness of this particular catalyst system. Interestingly, the authors also noted that increasing the amount of NaO^{t}Bu relative to CuCl resulted in substantial rate acceleration.



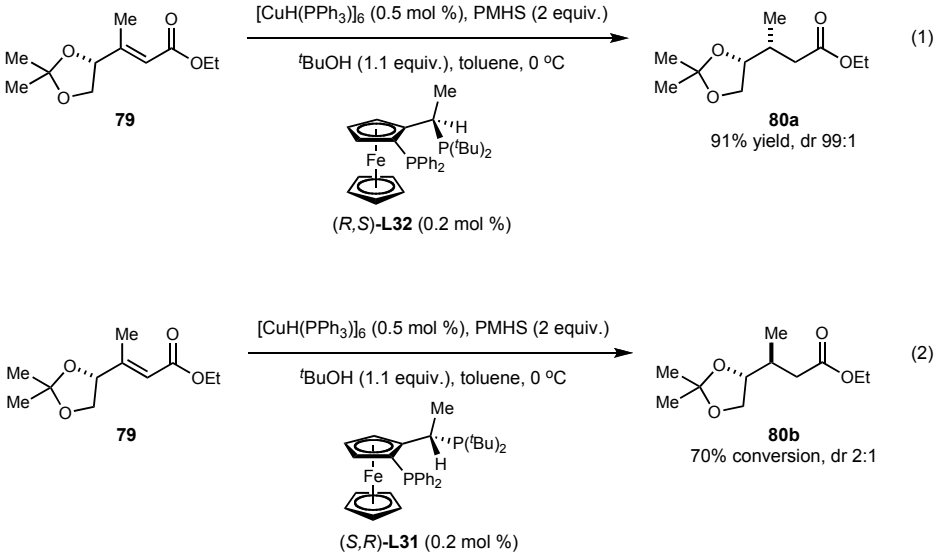
Scheme 1.21

Later that year, Lipshutz and co-workers reported the highly enantioselective reduction of α,β-unsaturated esters, using a substoichiometric amount of Stryker's reagent, and either Segphos, or Josiphos ligands.[23] Building on the initial work by Buchwald,[13,20] Lipshutz was able to carry out the highly enantioselective reduction of challenging substrate **77**, in which the substituents on the β-carbon are Me, and ^{n}Bu, illustrating the remarkably high degrees of facial selectivity obtained using this particular catalyst system (Scheme 1.22).



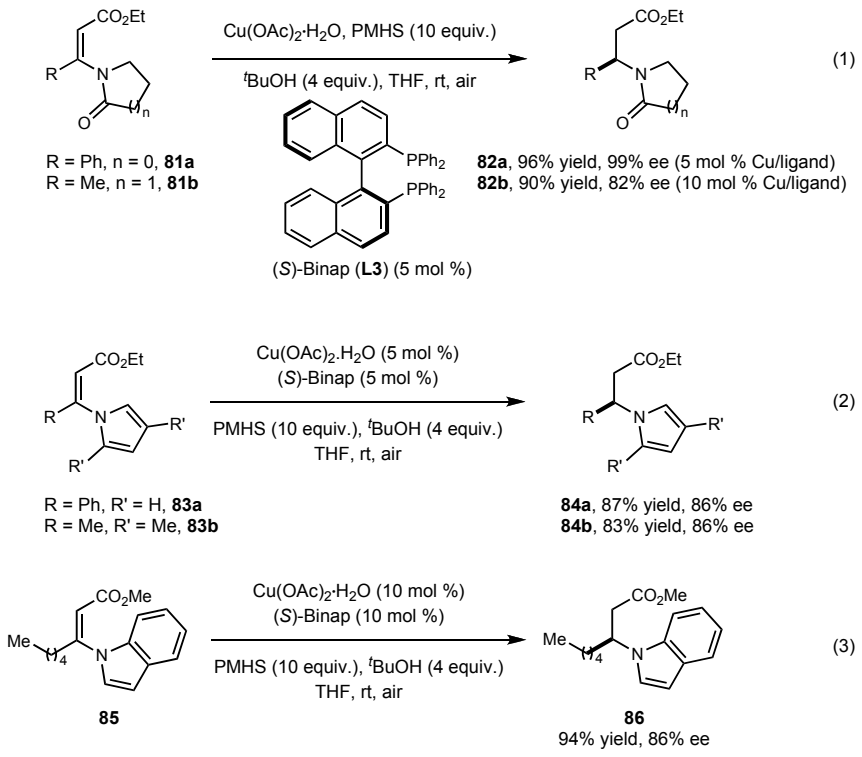
Scheme 1.22

Encouraged by these results, the authors also examined the impact of an existing stereocentre at the γ-carbon, postulating that energetically dissimilar conformations of the substrate might lead to a "matched/mismatched" situation, in which amplified diastereoselectivity is obtained using one enantiomer of the ligand (matched), and reduced diastereoselectivity is obtained using the opposite enantiomer (mismatched) (Scheme 1.23). In the event, this was found to be the case, and enoate **79** was reduced to saturated product **80** with 99:1 dr in the presence of (*R,S*)-**L32**, by attack on **79** from the *si*-face. In contrast, a significantly lower 2:1 dr was obtained when (*S,R*)-**L31** was used, by attack from the *re*-face; a mismatched situation.



Scheme 1.23

Up to this point, all examples of conjugate reduction have been limited to α,*β*-unsaturated carbonyl compounds substituted at the *β*-position with either carbon or hydrogen. However, there have been no examples of the conjugate reduction of substrates containing *β*-heteroatoms. One possible explanation for this is the interaction between the lone pair of electrons on the heteroatom and the π-system of the α,*β*-unsaturated carbonyl component. In 2004, Buchwald addressed this issue by carrying out the asymmetric conjugate reduction of a range of *β*-azoheterocyclic acid derivatives, which were chosen specifically to minimise such interactions.[24] Both *N*-vinyl pyrroles and indoles were effectively reduced, as well as both *β*- and δ-lactam substituted α,*β*-unsaturated esters (Scheme 1.24).

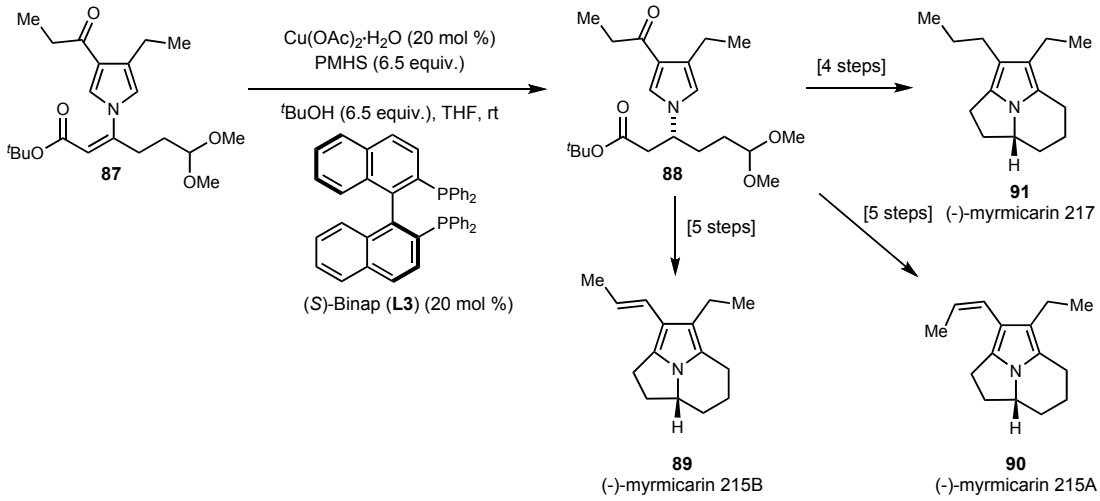


Scheme 1.24

The authors noted that exposure of the reaction mixture to air increased the rate, relative to reactions carried out in an inert atmosphere. As a consequence, however, additional PMHS was required due to competing reaction with trace amounts of

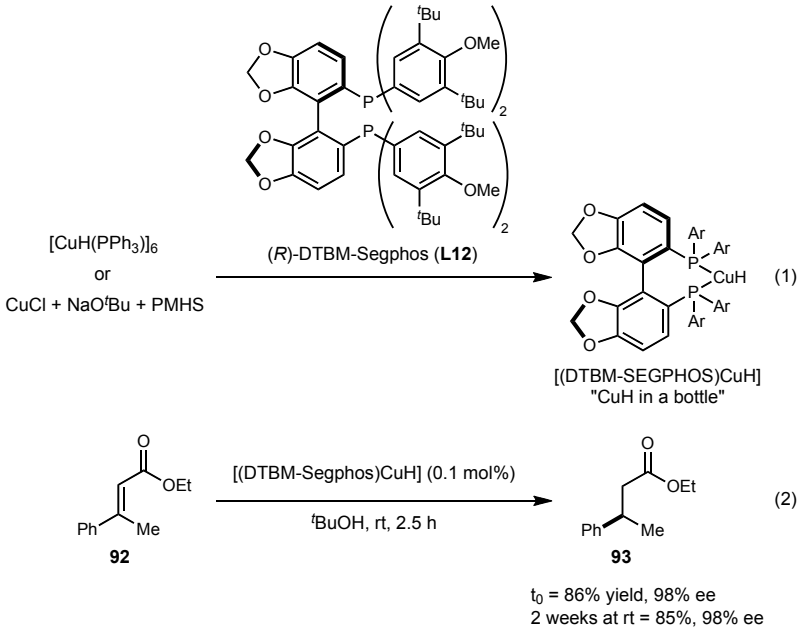
moisture in the atmosphere. It was also noted that substrates containing a lactam at the β-position typically required longer reaction times than those containing a β-indole or pyrrole substituent. The proposed explanation is that the carbonyl group of the lactam moiety coordinates to the catalyst in a non-productive way, inhibiting the reaction somewhat.

Nevertheless, Buchwald and co-workers have developed a robust method for the highly enantioselective conjugate reduction of a range α,β-unsaturated esters containing β-heteroatoms, providing access to biologically interesting β-amino acids, and their derivatives. In 2005, Movassaghi and Ondrus utilised this methodology in the total synthesis of various tricyclic myrmicarin alkaloids.[25] One of the key transformations in this synthesis is the copper-catalysed enantioselective conjugate reduction of β-pyrroyl ester **87** (Scheme 1.25). In the presence of (*S*)-Binap and copper acetate, using PMHS as the stoichiometric reductant, the reaction proceeded efficiently to give β-amino ester **88** in 89% yield and 85% ee. Intermediate **88** was subsequently converted into myrmicarin alkaloids **89**, **90** and **91**.



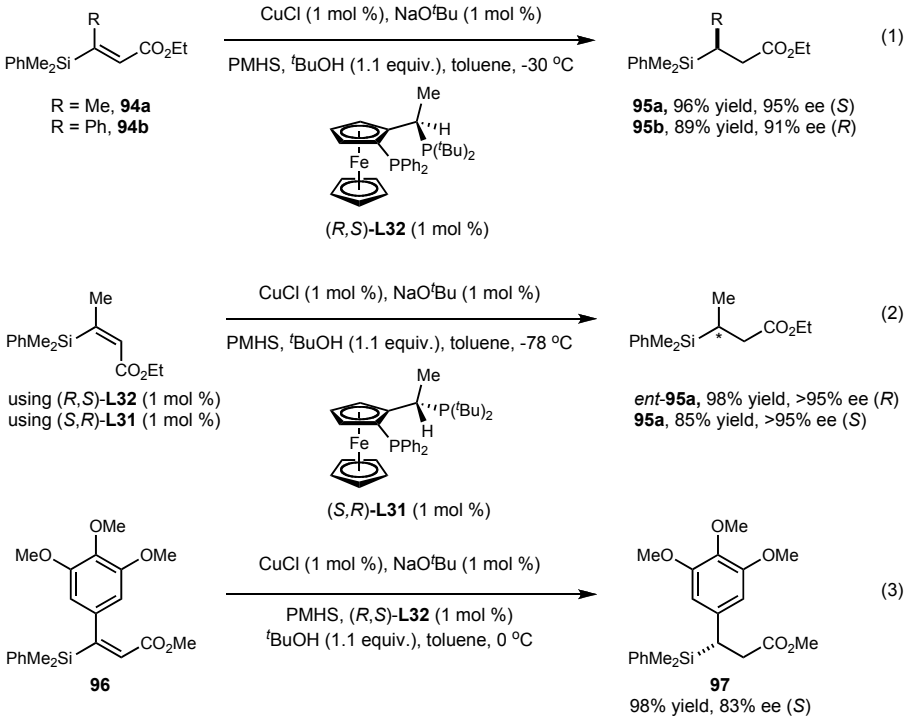
Scheme 1.25

A minor drawback of the methods for asymmetric conjugate reduction discussed so far is that the catalyst systems must be generated *in situ*. Lipshutz addressed this issue by preparing a stable "copper hydride in a bottle" for use in asymmetric conjugate reductions.[26] The catalyst is synthesised from $Cu(OAc)_2 \cdot H_2O$, NaO^{t}Bu, and (*R*)-DTBM-Segphos, in the presence of PMHS, and while one might expect copper hydrides to be unstable, it can be stored under an inert atmosphere and kept for a number of weeks without any loss in activity or selectivity (Scheme 1.26).



Scheme 1.26

Shortly after this discovery, Lipshutz reported the conjugate reduction of a range of *β*-silyl-α,*β*-unsaturated esters, furnishing enantioenriched organosilanes, which are useful intermediates in organic synthesis.[27] Despite recent success with their CuH(DTBM-Segphos) system, Lipshutz and co-workers found that this catalytic system was not particularly discriminating in this case, and far superior results were obtained with Josiphos ligand **L32** (Scheme 1.27).

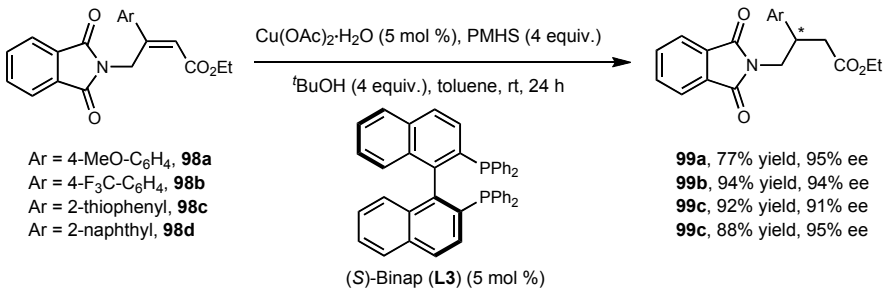


Scheme 1.27

The authors found that carrying the reactions out at low temperatures provided products with higher enantioselectivites. Unfortunately, the use of such low temperatures resulted in a considerable decrease in reaction rate, and ^{t}BuOH was required to drive the reactions to completion within a reasonable time period. However, in the case of electron-rich substrate **96**, higher temperatures were required, resulting in slightly inferior enantioselectivity. Both *E* and *Z*-enoates were found to undergo reduction to furnish products with similar enantioselectivites, but with opposite configurations. Furthermore, the availability of enantiomeric (*S*,*R*)-**L31** provides access to either stereochemistry of the resulting chiral silanes.

More recently, Zheng reported the enantioselective synthesis of a range of *β*-aryl-substituted γ-amino acid derivatives by copper-catalysed conjugate reduction of γ-phthalimido-substituted α,*β*-unsaturated esters (Scheme 1.28).[28] Following brief optimisation, $Cu(OAc)_2 \cdot H_2O$, (*S*)-Binap and PMHS emerged as the best reactions conditions and the authors noted that the use of other silanes, such as TMDS

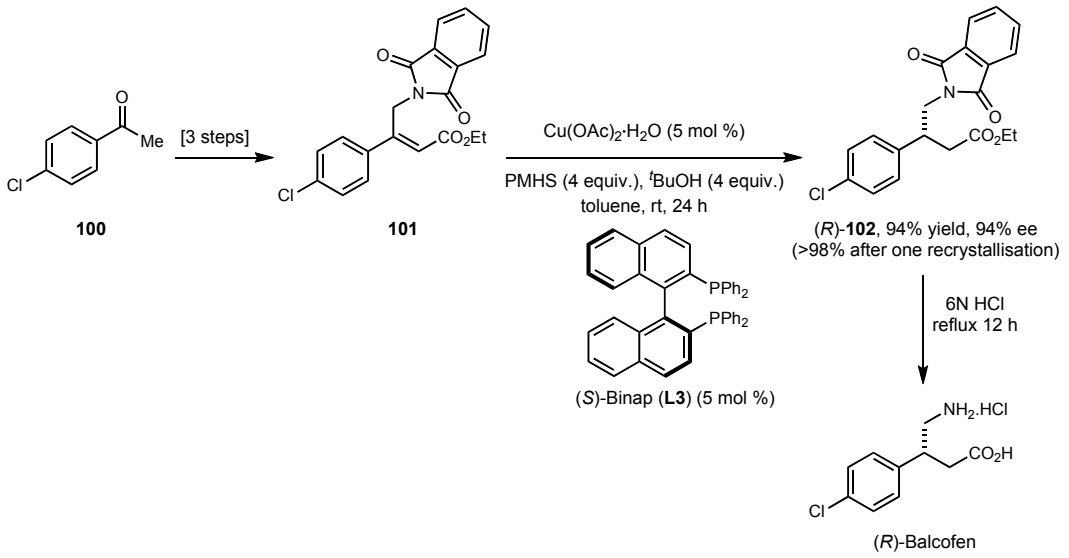
(1,1,3,3-tetramethyldisiloxane), diphenylsilane or phenylsilane had a profoundly negative effect on the rate of reaction.



Scheme 1.28

It is also evident that the electronic properties of the substituent on the phenyl ring had a negligible effect on the enantioselectivity, and enantiomeric excess ranged from 91-96% in all cases. Furthermore, due to the high crystallinity of the phthalimido group, the enantiomeric excess could be increased further by recrystallisation.

The authors applied this method to the synthesis of (*R*)-Baclofen, a chiral pharmaceutical reagent primarily used to treat disorders of the central nervous system (Scheme 1.29). (*R*)-Balcofen was obtained from *para*-chlorophenyl derivative **101**, in 98% enantiomeric excess after one recrystallisation.

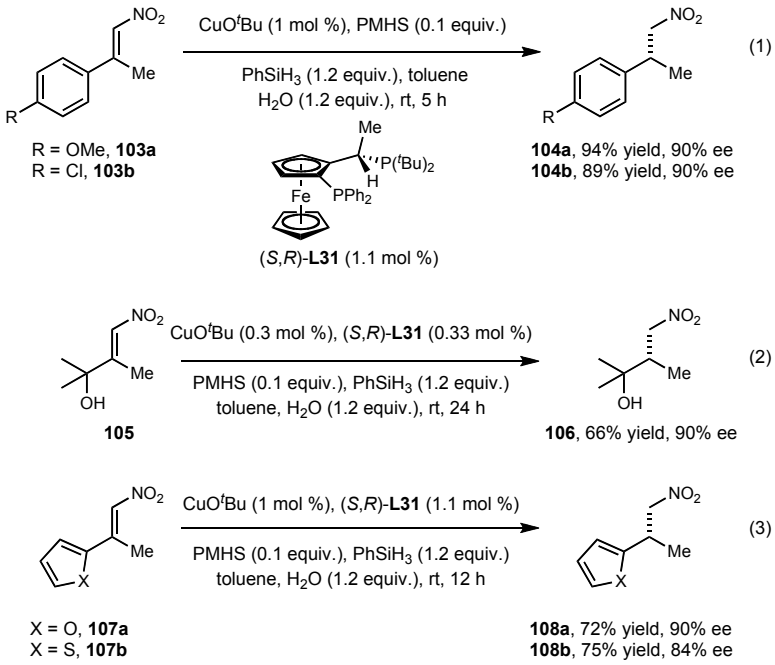


Scheme 1.29

1.4.3 Copper-Catalysed Asymmetric 1,4-Reductions of α,β-Unsaturated Nitroalkenes

Although nitro compounds have historically found great use in the dye industry, in recent years they have been employed as reactive intermediates in organic synthesis, becoming increasingly important in the synthesis of complex natural products.[29] Despite their synthetic utility and facile transformation into a variety of diverse functionalities, there are very few methods for the preparation of optically active nitroalkanes.

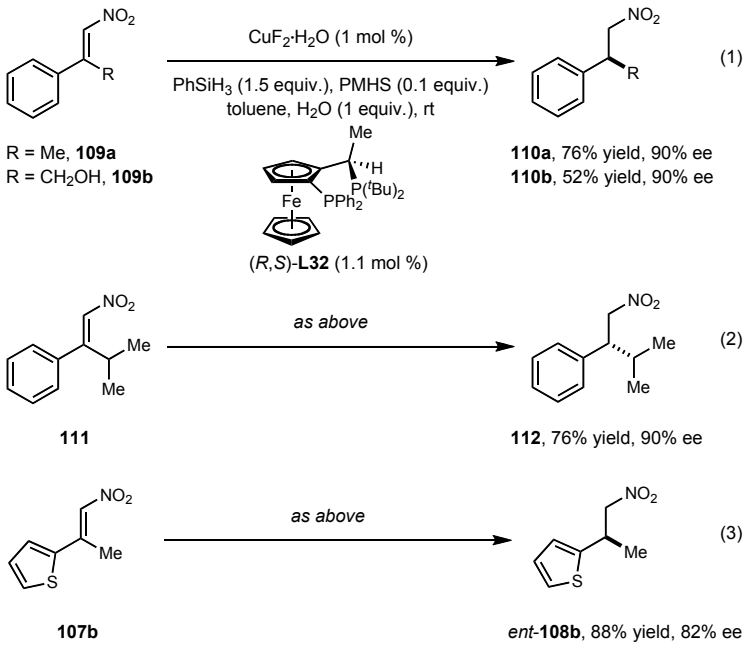
While numerous methods exist for the asymmetric conjugate addition of various nucleophiles to α,β-unsaturated nitroalkenes,[30] the corresponding conjugate *reduction* reaction remained unreported until 2003, when Carreira and co-workers successfully reported the asymmetric reduction of β,β′-disubstituted nitroalkenes.[31] A range of substrates underwent reduction, including **105**, which has an unprotected hydroxyl group (Scheme 1.30).



Scheme 1.30

Interestingly, the authors noted that if the catalyst was prepared from CuCl and NaO^{t}Bu, the rate of reaction was significantly lower than if CuO^{t}Bu was employed directly. Subsequent investigations led to the conclusion that the presence of NaCl or any other inorganic salts resulted in diminished reaction rates. Inexplicably, further rate acceleration was observed using a substoichiometric amount of PMHS, along with a stoichiometric amount of phenylsilane as the reductant. However, under these conditions the nitro group was susceptible to over-reduction, and water was required to prevent formation of the oxime.

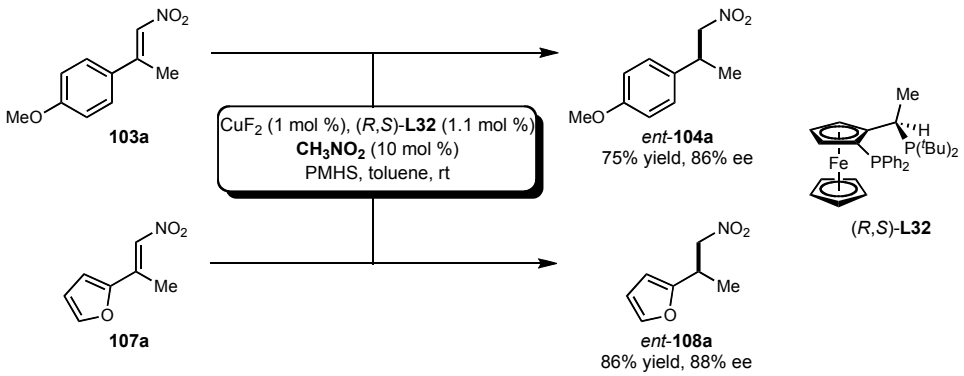
Although this proved a reliable method for the reduction of a range of substituted nitroalkenes, CuO^{t}Bu is highly air- and moisture-sensitive and Carreira and co-workers sought to find a more practical catalyst system. In 2004, they reported a more convenient method using CuF_2 as the precatalyst in the reduction of β,β'-disubstituted nitroalkenes (Scheme 1.31).[32]



Scheme 1.31

Contrary to their previous theory regarding the suppression of the catalyst by halides, Carreira and co-workers found that the reaction was tolerant of CuF_2, and proposed that the CuF_2 is sequestered from the reaction mixture by formation of strong Si–F bonds. In spite of this theory, additional phenylsilane was required, and added batchwise in order to ensure complete conversion.

It is also noteworthy that under these conditions, electron-rich substrates such as *p*-methoxyphenyl, or furanyl substrates **103a** and **107a**, failed to undergo reduction. It was previously hypothesised that the silane is responsible for the generation of the catalytic Cu(I) species from the Cu(II) precatalyst; however, in this case the authors considered the possibility that the nitroalkene could effect this transformation. This would involve tautomerisation of the nitro group to a nitronate, followed by oxidative dimerisation. Hence, in the case of more electron rich substrates this transformation would be less facile, owing to the decreased acidity of the nitroalkenes, and the active catalyst would not be generated. In the event, 10 mol % of nitromethane was required to catalyse the reaction (Scheme 1.32).



Scheme 1.32

1.4.4 Copper-Catalysed Asymmetric 1,4-Reductions of α,β-Unsaturated Nitriles

α,β-Unsaturated nitriles are valuable and easily accessible building blocks in organic chemistry, and are common motifs in many natural products.[33] However, due to their poor coordination to transition metals, the metal-catalysed asymmetric conjugate reduction of α,β-unsaturated nitriles poses some difficulties. Owing to their electronic structure, nitriles prefer end-on coordination to metal ions; thus, the linearity of the nitrile group does not provide the optimum environment for catalyst coordination, and many examples have required substrates bearing additional coordinating carboxylate or phthalimido substituents (Figure 1.1).[34]

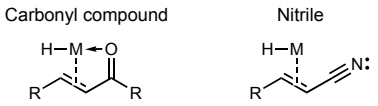
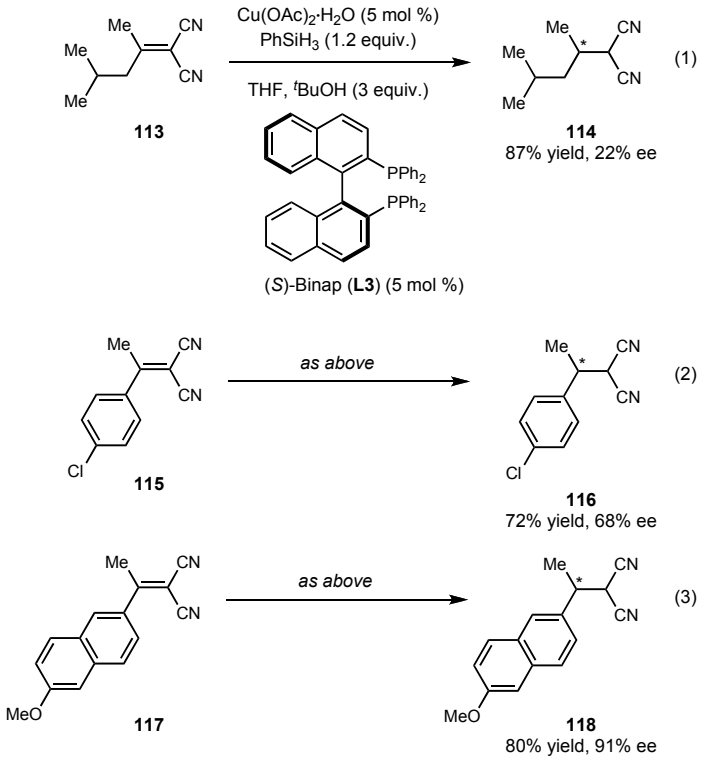


Figure 1.1

In 2005, Xu and co-workers reported the enantioselective conjugate reduction of α,β-unsaturated dinitriles, catalysed by $Cu(OAc)_2 \cdot H_2O$ and (*S*)-Binap, using phenylsilane as the stoichiometric reductant (Scheme 1.33).[35] In correlation with Carreira's findings,[31] the authors noted a significant decrease in yield when the

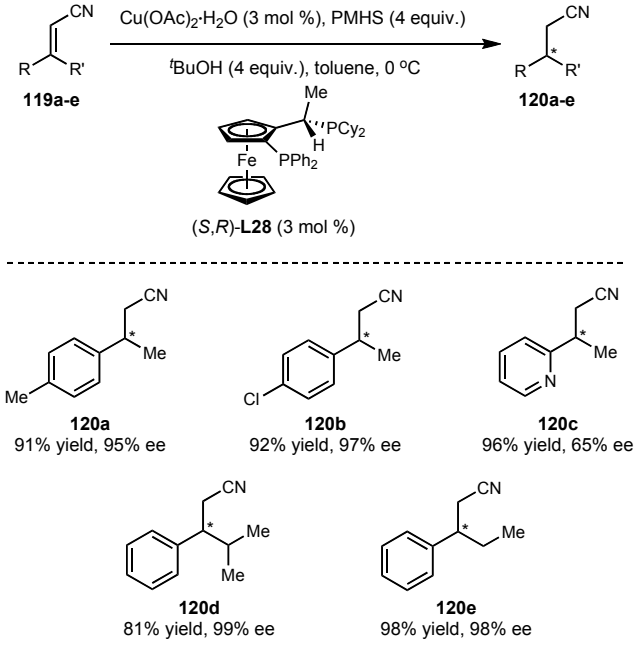
catalyst was prepared from CuCl and NaO^{t}Bu, and attributed this to the concomitant formation of NaCl, which they believed inhibited the reaction.



Scheme 1.33

In general, yields and enantioselectivites were high, with the notable exception of β,β-dialkyl substituted malononitrile **113**, which underwent reduction to give the product **114** in only 22% enantiomeric excess. It is probable that higher selectivities are only obtained when there is a greater steric difference between the two β-substituents. The electronic properties of the aryl substituent were found to have a considerable affect on the enantiomeric excess, for example, product **118**, which contains an electron-rich methoxynaphthyl group was obtained in 91% ee, whereas product **116**, containing an electron-poor *p*-chlorophenyl group was obtained in only 68% ee.

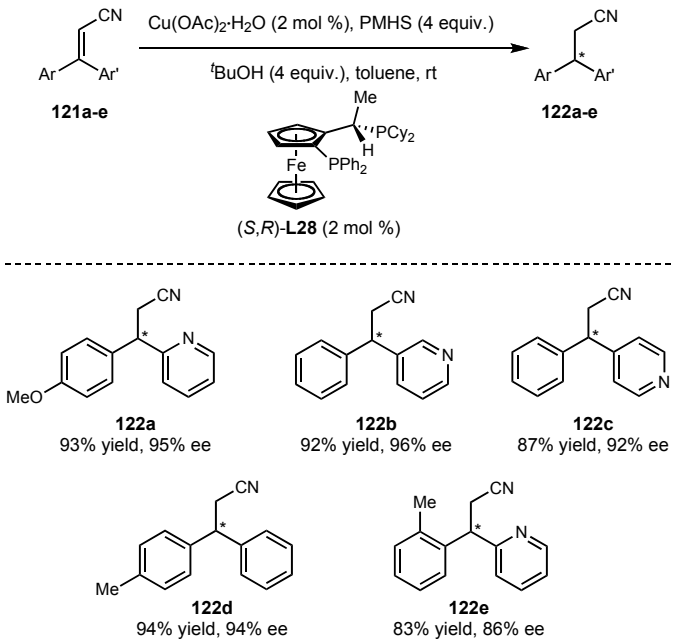
Following this initial publication, Yun and co-workers reported the highly enantioselective conjugate reduction of β,β'-disubstituted nitriles of type **119**, where R is aromatic and R' is aliphatic, catalysed by $Cu(OAc)_2 \cdot H_2O$ and Josiphos ligand **L28** (Scheme 1.34).[36]



Scheme 1.34

A range of α,β-unsaturated nitriles were found to undergo reduction, including those with electron-withdrawing, or electron-donating substituents on the aromatic ring, such as **120b** an **120a**, respectively. Bulky alkyl substituents, such as Et or ^{i}Pr were also well tolerated, providing reduced products with up to 99% enantiomeric excess.

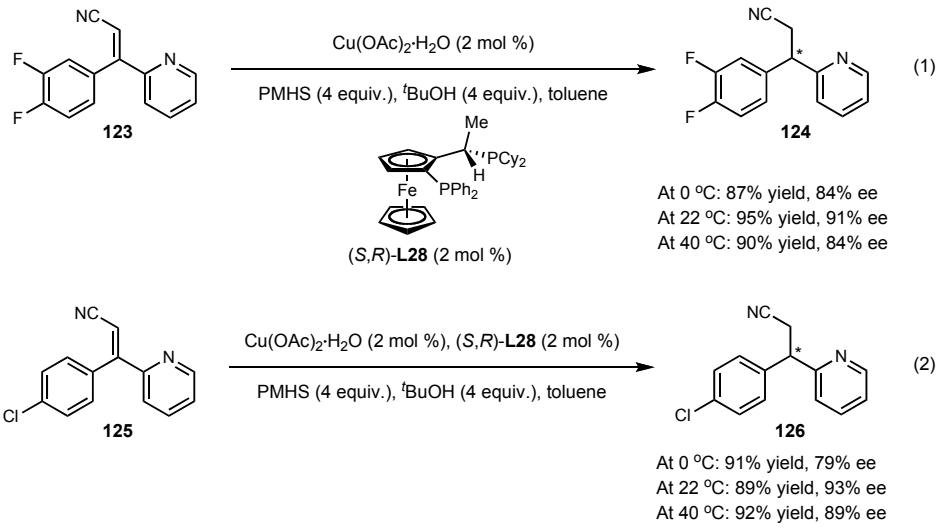
Yun and co-workers also employed the same reaction conditions to effect the asymmetric reduction of β,β'-diaryl-substituted α,β-unsaturated nitriles (Scheme 1.35).[37]



Scheme 1.35

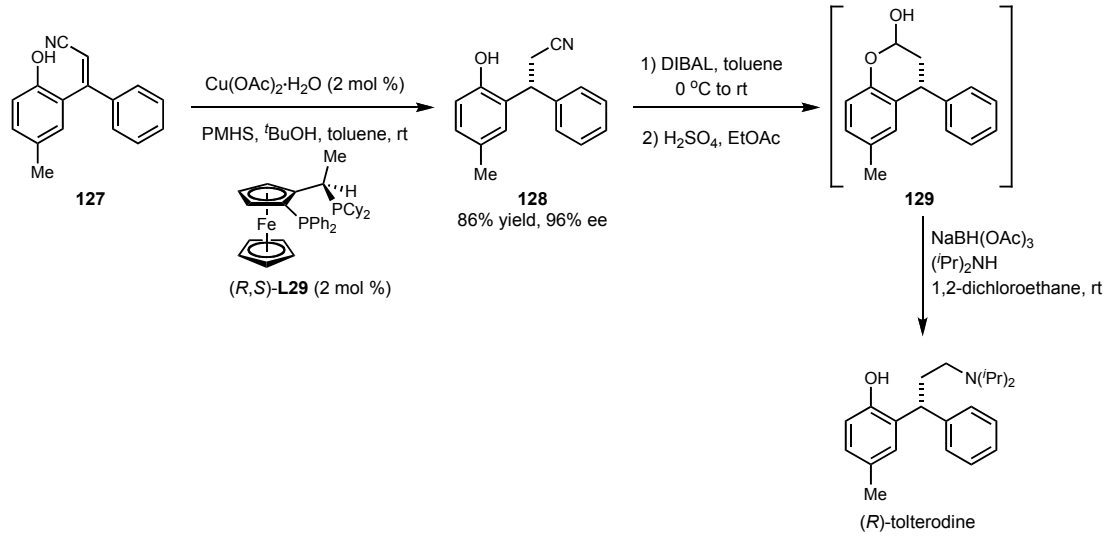
It is noteworthy that the position of the nitrogen atom on the pyridyl ring has no affect on the enantioselectivity, exemplified by substrates **122a-c**. This indicates that additional coordination between the pyridyl ring and the catalyst is not necessary to obtain high enantiomeric excess.

Interestingly, in the case of substrates **123** and **125** (Scheme 1.36), which contain halogen substituents on the aromatic ring, the enantioselectivity was found to increase upon increasing the temperature from 0 ^{o}C to room temperature, displaying an unprecedented inverse temperature dependence. Upon increasing the temperature further to 40 ^{o}C, the enantioselectivity decreased to below 90%, in both cases, suggesting the existence of an inversion temperature at approximately room temperature.



Scheme 1.36

In 2009, Yun applied this methodology to the total synthesis of (*R*)-tolterodine, a urological drug used for the treatment of an overactive bladder (Scheme 1.37).[38]



Scheme 1.37

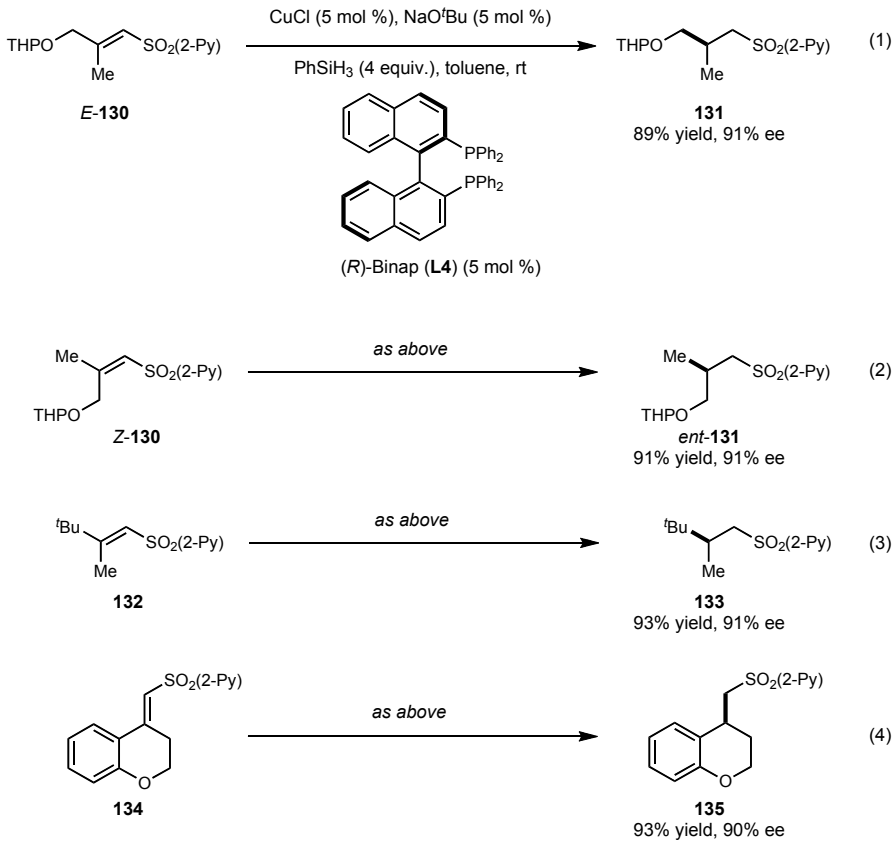
The authors found that protection of the hydroxyl group of **127** was not necessary, and conjugate reduction to (*R*)-**128** proceeded efficiently, in 86% yield and 96% ee.

The synthesis of (*R*)-tolterodine was completed by reduction of nitrile **128** to lactol **129**, followed by reductive amination with diisopropylamine.

1.4.5 Copper-Catalysed Asymmetric 1,4-Reductions of α,β-Unsaturated Sulfones

In recent years, the synthetic utility of the sulfone group in organic chemistry has increased dramatically. In particular, it has proved to be of great importance in the synthesis of biologically active compounds and natural product synthesis.[39] Subsequent manipulation of the sulfone functionality can be accomplished *via* numerous methods, including alkylation, oxidation, and Julia-Kocienski olefination, among others.

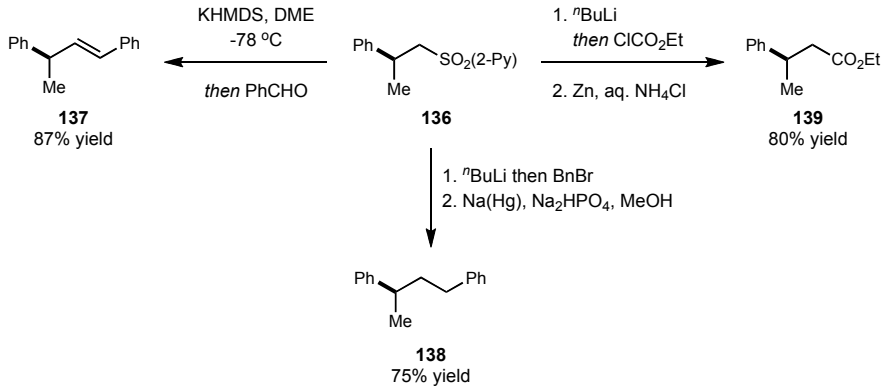
Optically active sulfones are of particular importance; recent advances in the asymmetric conjugate reduction of β,β′-disubstituted vinyl sulfones have resulted in moderate success, although enantioselectivities are modest at best, leaving room for improvement. In 2007, Carretero and co-workers published the asymmetric reduction of a range of structurally diverse α,β-unsaturated vinyl 2-pyridylsulfones to alkyl 2-pyridylsulfones in excellent yields and enantioselectivities (Scheme 1.38).[40]



Scheme 1.38

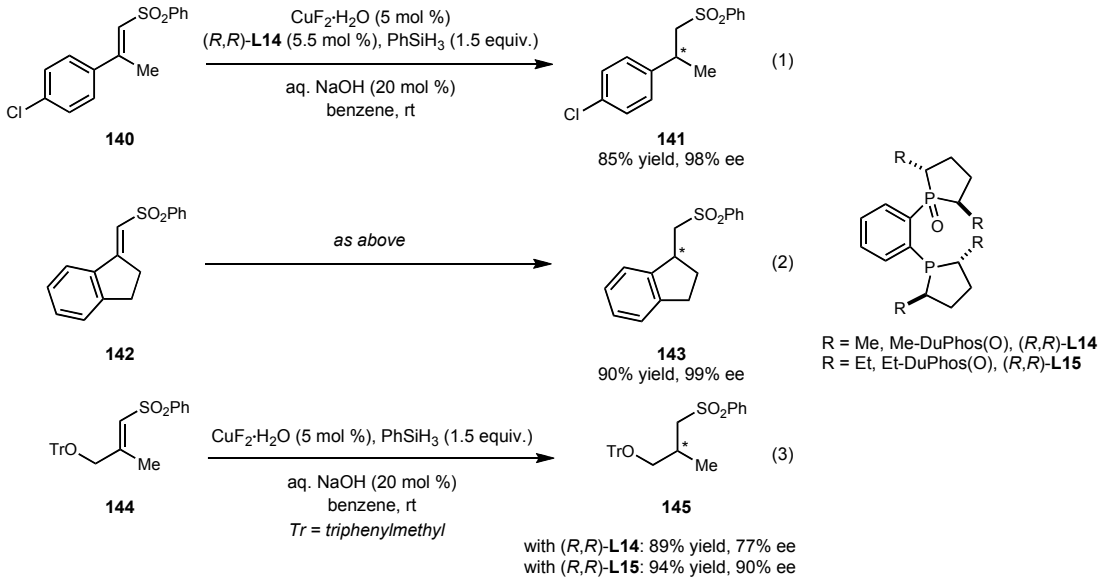
Previous investigations by the Carretero group into rhodium–catalysed conjugate addition of boronic acids to α,*β*-unsaturated 2-pyridylsulfones suggest that the mechanism involves coordination of the nitrogen atom to the metal catalyst. Thus, the 2-pyridyl group is thought to be essential to effect this transformation, and replacement by a phenyl group results in no reaction. Furthermore, in correlation with Buchwald's previous findings,[13] the *E*– and *Z*– isomers of the THP-protected substrate **130** led to opposite enantiomers of the reduced product **131**.

Carretero and co-workers illustrated the diverse range of chiral compounds accessible *via* optically active sulfones, by either functionalisation α– to the sulfonyl group, or by Julia-Kocienski olefination (Scheme 1.39).



Scheme 1.39

Almost simultaneously, Descosiers and Charette reported the enantioselective conjugate reduction of vinyl phenyl sulfones, despite Carretero's hypothesis that the 2-pyridyl group is a vital component in this reaction.[41] Using the hemilabile bidentate ligand Me-DuPhos monoxide (**L14**), and $CuF_2 \cdot H_2O$ as the copper source, a range of vinyl phenyl sulfones underwent reduction (Scheme 1.40).

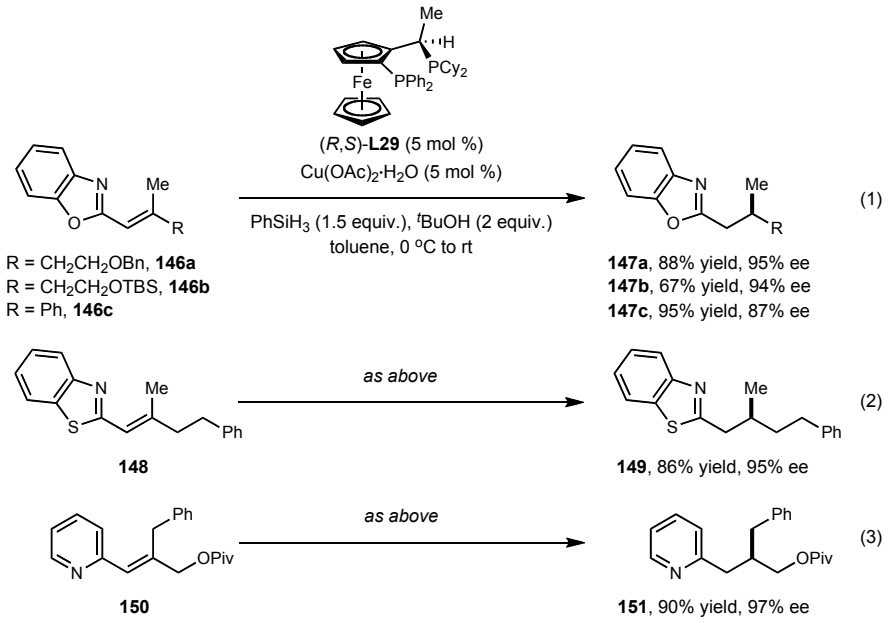


Scheme 1.40

In general, excellent yields and enantioselectivities were obtained, with the notable exception of substrate **144**, which resulted in only moderate enantioselectivity in the presence of Me-DuPhos(O). However, it was found that changing the ligand to the slightly bulkier Et-DuPhos(O) afforded alkyl sulfone **145** in 90% ee.

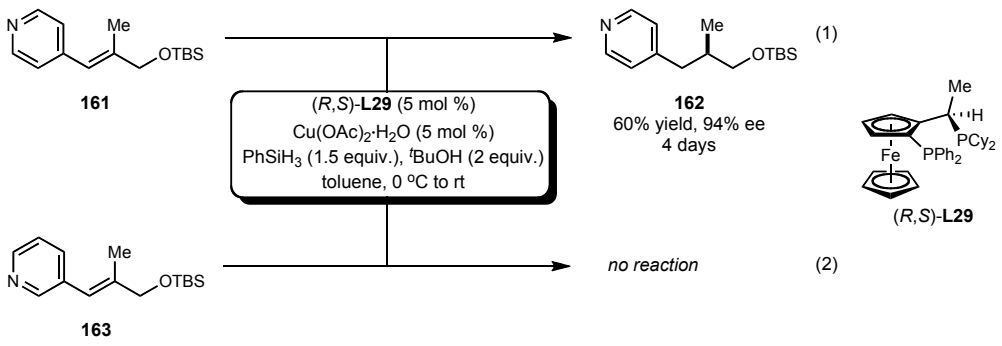
1.4.6 Copper-Catalysed Asymmetric Reduction of Other Electron–Deficient Alkenes

Thus far, the conjugate reduction of a wide range of electron–deficient alkenes, including α,β-unsaturated nitroalkenes, nitriles, sulfones, and carbonyl compounds, has been discussed. Although these examples represent the most common functional groups used to activate alkenes, our group recently discovered that nitrogen-containing aromatic heterocycles also provide sufficient activation of an adjacent alkene towards reduction.[42] A range of β,β'-disubstituted 2-alkenylheteroarenes underwent reduction in the presence of $Cu(OAc)_2 \cdot H_2O$ and Josiphos ligand **L29** to provide the corresponding saturated products with high levels of enantioselection (Scheme 1.41).



Scheme 1.41

The reaction proved tolerant of various different heterocycles, including benzoxazoles, such as **146a-c**, benzothiazole **148**, and pyridine **150**. A range of functionalities were also tolerated at the β-position, including both aliphatic and aromatic groups, and various oxygen-containing groups. The reactivity of 3- and 4-alkenylpyridines **161** and **163** was also examined (Scheme 1.42). Interestingly, 4-alkenylpyridine **161** underwent reduction to afford **162** in 60% yield, and 94% ee after 4 days, suggesting that reduction is possible without the assistance of the directing effect from the nitrogen, although the reaction is significantly slower. In contrast, 3-alkenylpyridine **163** did not undergo reduction, suggesting that the alkene must be in conjugation with a C=N moiety in order for reduction to take place.



Scheme 1.42

1.4.7 Conclusion

Copper hydride chemistry has advanced considerably during the past decade, and is currently considered to be a fundamental component of organic synthesis, providing a technique complementary to asymmetric conjugate addition reactions and hydrogenations. Typically, conjugate reduction reactions exhibit remarkable functional group diversity, and have proven tolerant to a range of different conditions, including even air and water.

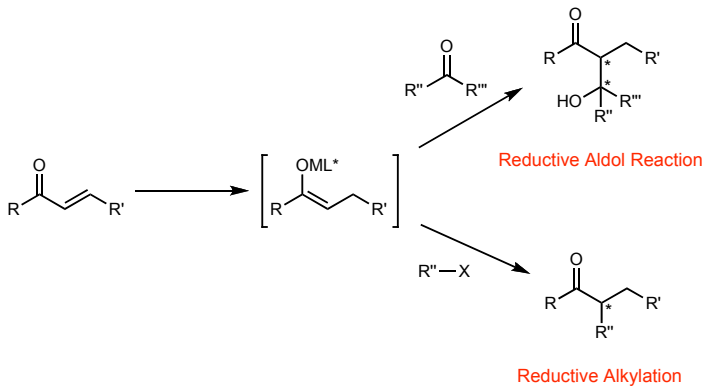
By employing commercially available, easy to handle copper sources, and readily available chiral ligands, the asymmetric conjugate reduction of a range of different α,β-unsaturated Michael acceptors has been achieved. Furthermore, recent advances in ligand development have resulted in remarkable levels of enantiocontrol, with

substrate-to-ligand ratios of up to 275,000:1 resulting in enantiomeric excesses of more than 98%. It is therefore not surprising that these reactions have found use in the synthesis of a variety of biologically active molecules, and pharmaceuticals.

1.5 Reductive Aldol Reactions and Related Modifications

1.5.1 Introduction

Thus far, most of the transformations described involve formation of a new C-H bond. As discussed previously, hydrometalation of α,β-unsaturated carbonyl compounds is known to proceed *via* metal enolates and inter- or intramolecular trapping of these intermediates by electrophiles can result in carbon-carbon bond-forming reactions.[3] Many research groups have exploited this by developing "domino" processes. Although the majority of this research has focussed on reductive aldol reactions, analogous reactions involving α,β-unsaturated nitroalkenes (reductive Henry reactions) and nitriles have also been reported, as well as reductive Mannich reactions (Scheme 1.43).



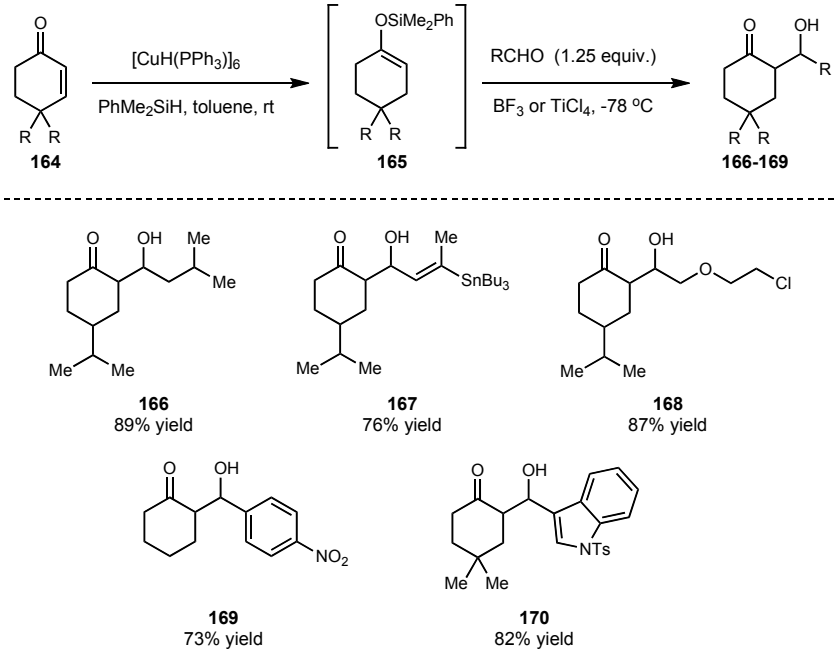
Scheme 1.43

In order to place this work into context, it is important to define the term "domino":

> "Domino reactions are described as processes of two or more bond-forming reactions under identical conditions, in which the subsequent transformation takes place at the functionalities obtained in the former transformation".
>
> - Tietze, 1993.[43]

Thus, to be considered a "domino" reaction, reduction and alkylation must occur under the same conditions, with the alkylation reagent present during reduction.

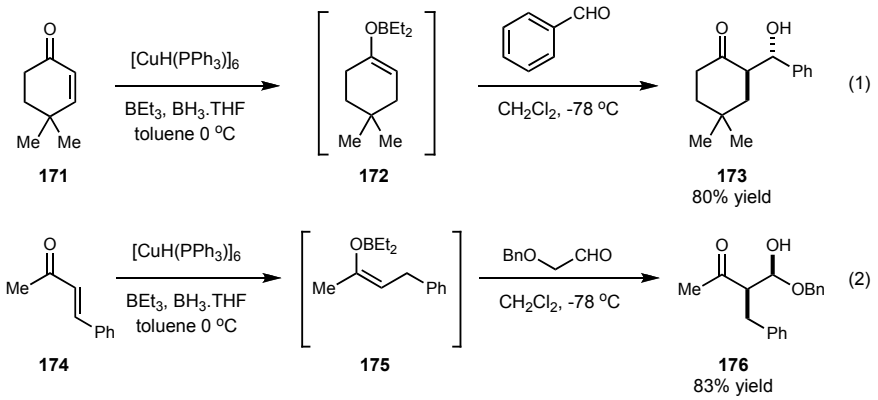
Although not regarded as a domino process, Lipshutz and co-workers devised a one-pot conjugate reduction/Mukaiyama aldol reaction in which a range of enones underwent reduction in the presence of Stryker's reagent, followed by transmetalation with a silane, to afford the corresponding silyl enol ether.[44] Subsequent addition of the desired aldehyde and Lewis acid triggered the Mukaiyama aldol process, providing the β-hydroxy ketone in good yield (Scheme 1.44).



Scheme 1.44

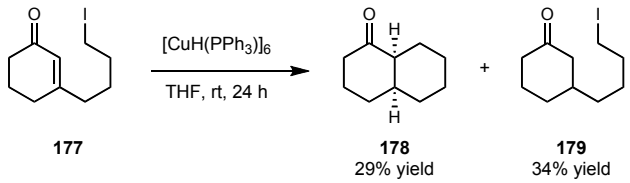
The authors noted that addition of the aldehyde at the start of the reaction resulted in competitive reduction of the aldehyde by Stryker's reagent, promoted by the Lewis acid. Furthermore, in all cases, two diastereomers were obtained, although diastereomeric ratios were not determined. In a subsequent communication, Lipshutz reported the use of diethylborane, in place of a silane, to effect a regio- and stereoselective reduction/aldol reaction *via* formation of a boron enolate (Scheme 1.45).[45] As anticipated, reduction of acyclic enones led to the regioselective formation of (*Z*)-enolates, whereas, when cyclic enones were employed,

regioselective formation of (*E*)-enolates took place. When the aldehyde was introduced into the reaction mixture, aldol reaction occurred to afford the corresponding *syn*-, and *anti*-aldol products, respectively.



Scheme 1.45

The first truly domino reductive alkylation process was reported by Stryker and co-workers in 1990. In the presence of stoichiometric $[CuH(PPh_3)]_6$, it was discovered that enone **177** underwent reductive followed by intramolecular alkylation to give *cis*-decalone **178** in 29% yield, along with ketone **179** in 34% yield (Scheme 1.46).[8] However, the authors regarded this as an undesirable side reaction, and sought to inhibit it.



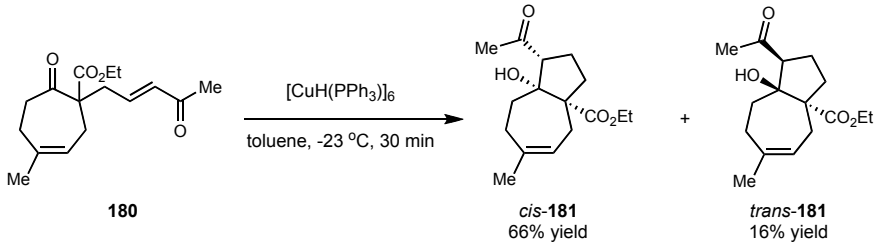
Scheme 1.46

Despite this initial discovery, subsequent reports of domino processes were not disclosed until 1998, when Chiu and co-workers discovered that the innate reactivity

of the intermediate copper enolate could be harnessed, giving rise to rapid increases in molecular complexity, in a single transformation.[46]

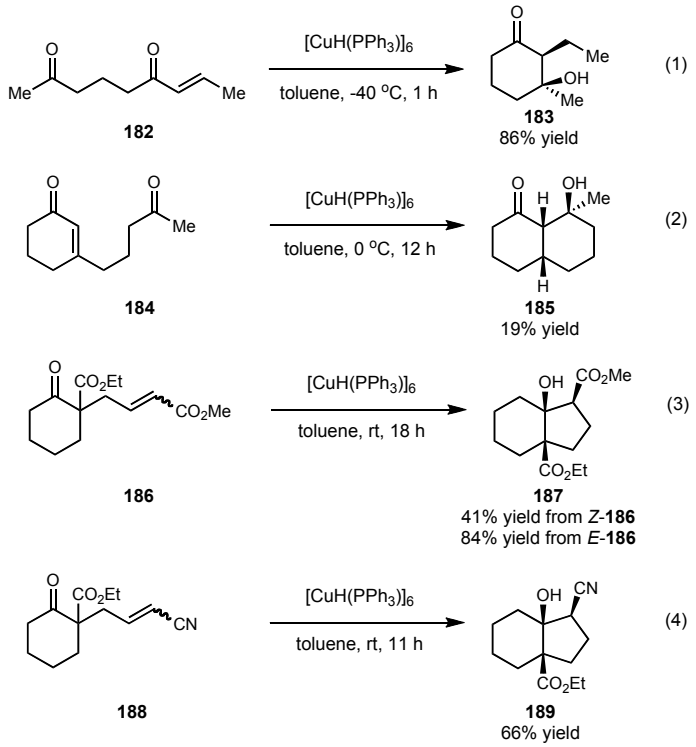
1.5.2 Stoichiometric Reductive Aldol Reactions

During the course of their studies towards the synthesis of pseudolaric acid A, Chiu and co-workers reported the intramolecular aldol reaction of enone **180**, in the presence of stoichiometric $[CuH(PPh_3)]_6$ (Scheme 1.47).[46] Although the reaction was carried out at -23 °C to increase the selectivity, two diastereomers were obtained, *cis*-**181** and *trans*-**181**, both arising from conjugate reduction, followed by aldol addition onto the tethered ketone moiety. However, only *trans*-**181** possessed the *trans*-ring junction present in the structure of pseudolaric acid A.



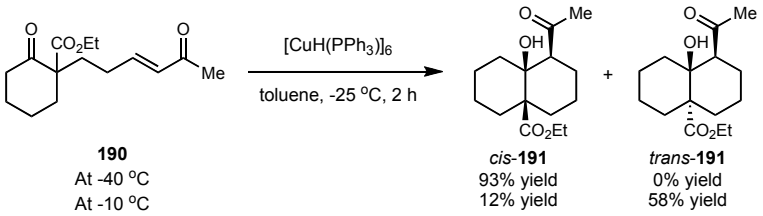
Scheme 1.47

Chiu and co-workers investigated the scope of this reaction, and found that a range of α,β-unsaturated carbonyl compounds underwent reductive cyclisation, including α,β-unsaturated nitrile **188** (Scheme 1.48).[47] Interestingly, both (enol*endo*)-*exo-trig* substrates (eq. 1) and (enol*exo*)-*exo-trig* substrates (eq. 2-4), could be used. In most cases, the cyclised products were isolated in good yields, with the notable exception of sterically hindered β,β'-disubstituted cyclic enone **184**, which only provided β-hydroxy ketone **185** in 19% yield, along with 69% recovered starting material. Futhermore, substrates bearing *trans*-double bonds, such as *trans*-enoate (*E*)-**186** underwent reaction much faster than their corresponding *cis*-isomeric counterparts; even after 18 h, a significant amount of (*Z*)-**186** was recovered from the reaction mixture and β-hydroxy ester **187**, was isolated in 41% yield.



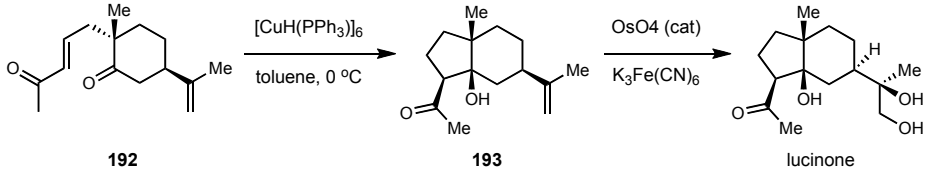
Scheme 1.48

The reactions were carried out at low temperatures to avoid dehydration of the products, with loss of the two newly formed stereocentres. Furthermore, it was found that, in the case of substrate **190** (Scheme 1.49), increasing the temperature led to a decrease in selectivity, giving rise to stereoisomer *trans*-**191**, in greater quantities relative to *cis*-**191**. Thus, the product formed at low temperatures, bearing the *cis*-ring junction, was deemed to be the kinetic product, and the product formed at higher temperatures, bearing the *trans*-ring junction, is the thermodynamic product.



Scheme 1.49

Shortly after their initial publication, Chiu and co-workers reported the synthesis of lucinone, an antispasmodic drug, in which the key transformation is a highly diastereoselective reductive aldol cyclisation.[48] The cyclisation of enantiopure enone **192** was carried out in the presence of Stryker's reagent to give **193** in 99% yield, which was easily converted to lucinone by dihydroxylation (Scheme 1.50).

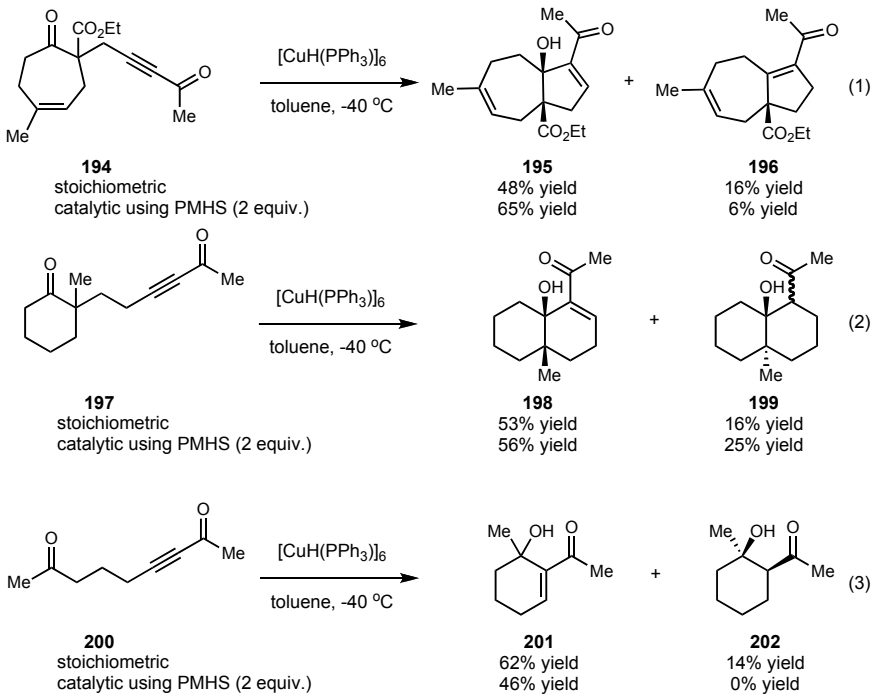


192 193 lucinone

Scheme 1.50

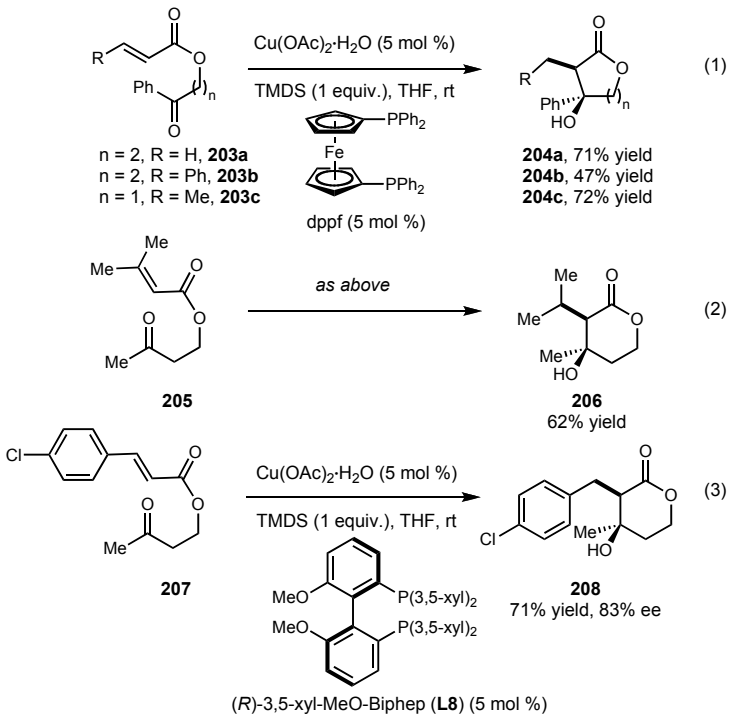
1.5.3 Catalytic Reductive Aldol Reactions

During this time, the first reports of copper-catalysed conjugate reductions had begun to emerge, providing precedent for a catalytic reductive aldol reaction. This was first realised by Chiu and co-workers in 2004.[49] Alkynones were found to undergo reductive aldol cyclisation in the presence of a substoichiometric amount of Stryker's reagent and PMHS, giving rise to *cis*-fused *β*-hydroxyenones, in yields comparable to those obtained using stoichiometric Stryker's reagent (Scheme 1.51). Although the reactions were highly diastereoselective, minor products were obtained in most cases, typically arising from over-reduction, dehydration, or reduction without cyclisation.



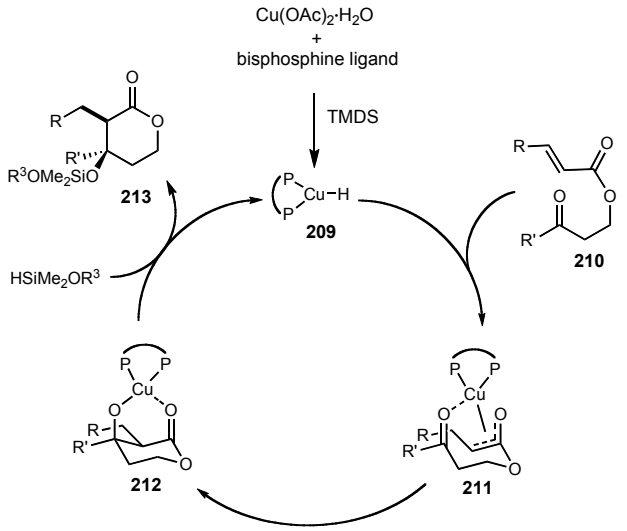
Scheme 1.51

In 2005, our research group achieved the next major development in this field, reporting the first copper-catalysed asymmetric reductive aldol reaction (Scheme 1.52).[50] In the presence of substoichiometric $Cu(OAc)_2 \cdot H_2O$, a chiral bisphosphine ligand, and TMDS, a range of α,β-unsaturated esters were found to undergo intramolecular reductive aldol reaction with tethered ketones. The β-hydroxylactone products were isolated in good yields, high *syn*-selectivites and good enantioselectivities.



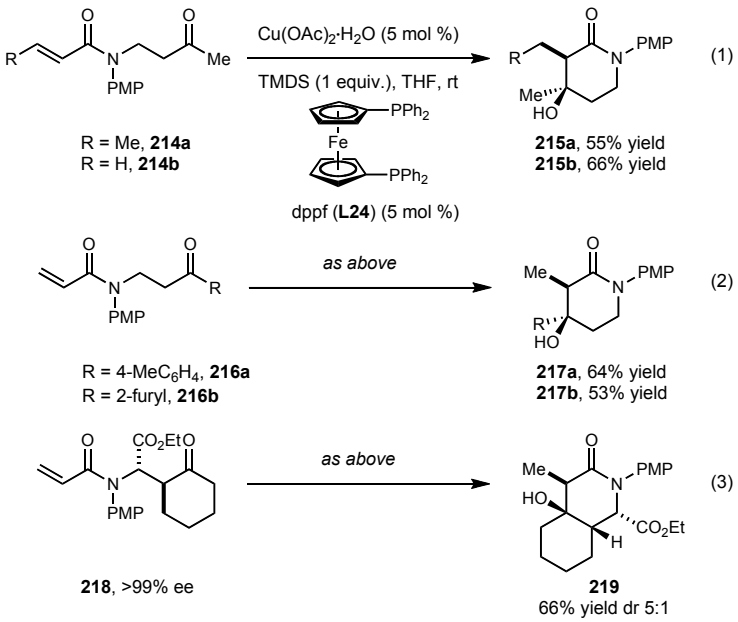
Scheme 1.52

The reaction was found to be tolerant to aromatic, heteroaromatic, and aliphatic α,*β*-unsaturated ester substituents. Although a range of chiral ligands were screened in this reaction, (*R*)-3,5-xyl-MeO-Biphep was found to give marginally superior results, providing *β*-hydroxy lactone **208** in 83% ee. The proposed catalytic cycle involves formation of a copper(I)-bisphosphine hydride complex **209**, which then undergoes hydrometalation with the substrate **210** to give copper enolate **211** (Scheme 1.53). Addition of the copper enolate to the tethered ketone affords copper aldolate **212**, which then undergoes σ-bond metathesis with the siloxane, liberating the silylated product and regenerating the catalyst.



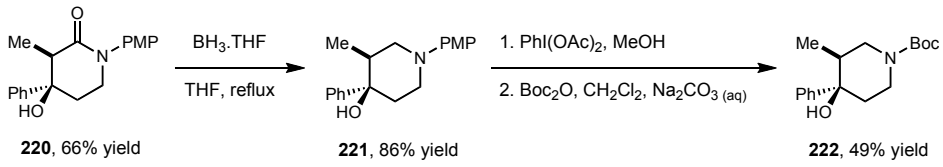
Scheme 1.53

In an extension of this work, our group used this methodology to synthesise a range of substituted piperidinones (Scheme 1.54).[51] Using the conditions developed for the corresponding ester substrates, a range of α,β-unsaturated amide substrates underwent reductive aldol cyclisation to afford the corresponding 4-hydroxypiperidin-2-one products in good yields and excellent *syn*-selectivities. Variation of the ketone substituent was well tolerated; however, the reaction was less tolerant of substitution at the α,β-unsaturated amide component, with acryloyl and crotonoyl amides giving the best results.



Scheme 1.54

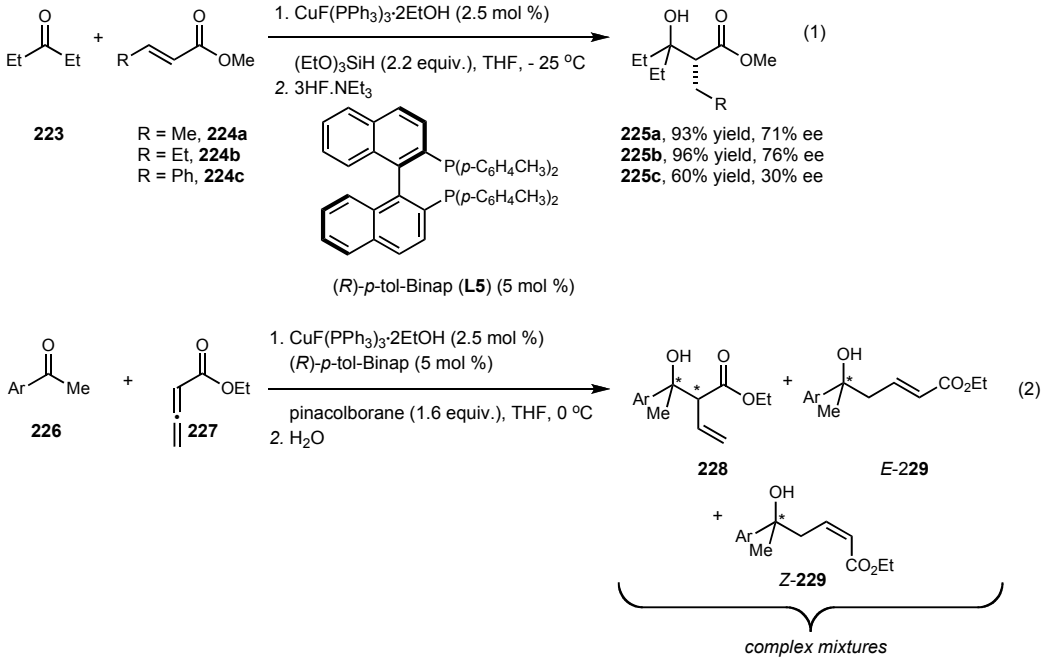
The effect of pre-existing stereocentres was also examined, exemplified by enantioenriched substrate **218**, which underwent cyclisation to give the highly substituted piperidinone **219**, containing four contiguous stereocentres with excellent levels of internal induction. The piperidinone products can easily be converted into synthetically useful piperidines by reductive removal of the carbonyl group (Scheme 1.55).



Scheme 1.55

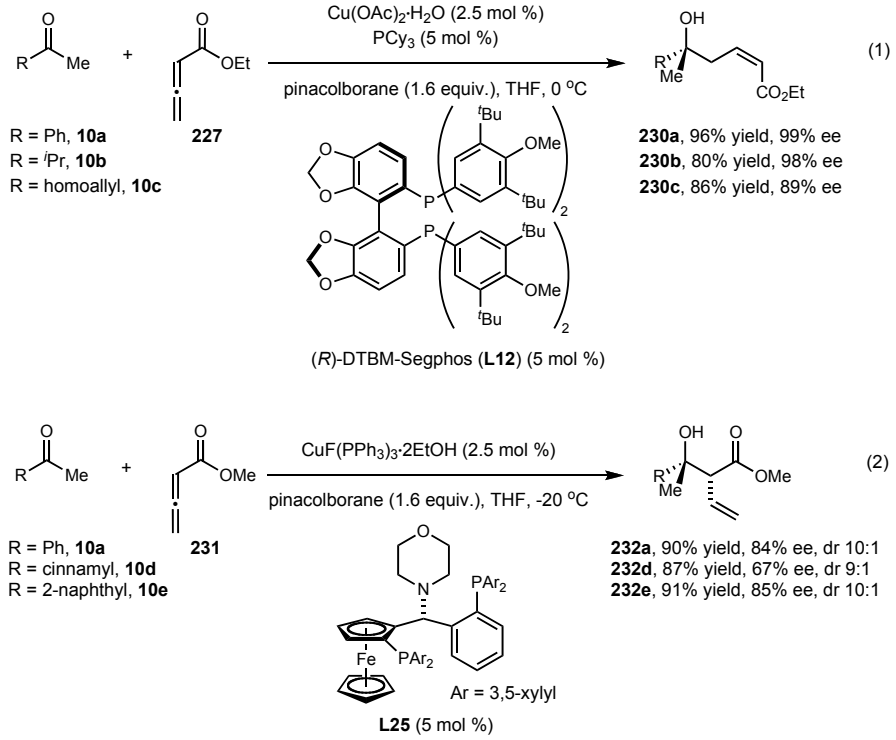
In 2005, Shibasaki and Kanai reported the enantioselective intermolecular reductive aldol reaction of various α,β-unsaturated esters to ketones.[52] Although the reaction was tolerant of a range of β-substituents on the α,β-unsaturated ester component, it was limited to symmetrical ketones; the use of prochiral ketones generally led to low

enantioselectivities. Allenic esters could also be used, although the reaction was complicated by the formation of both α- and γ-aldol products, and thereafter by formation of both *cis*- and *trans*-isomers of γ-adducts, and *syn* and *anti*-diastereomers of α-adducts.



Scheme 1.56

In a later communication, the authors resolved this issue by modifying the reaction conditions such that the α- vs. γ-selectivity could be tuned to produce the desired product – with high degrees of specificity – by the addition of extra phosphine ligand.[53] The reaction of allenic ester **227** with a range of unsymmetrical ketones was carried out in the presence of $Cu(OAc)_2 \cdot H_2O$ and (*R*)-DTBM-Segphos, using pinacolborane as the stoichiometric reductant (Scheme 1.57). The addition of PCy_3 was imperative in order to obtain high γ-*cis*-selectivities and high yields. Both aromatic and aliphatic ketones underwent reduction to afford γ-*cis*-products in excellent yields and enantioselectivities.

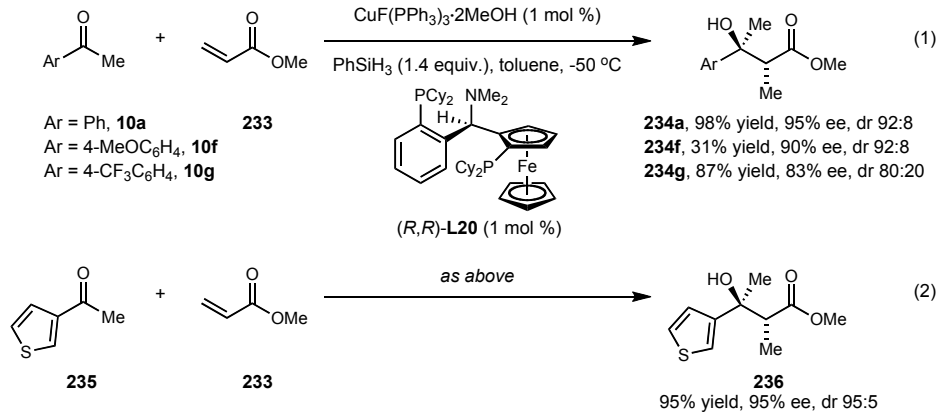


Scheme 1.57

Changing the copper source to $CuF(PPh_3)_3{\cdot}2EtOH$, and the ligand to Taniaphos ligand **L25** resulted in a switch in regioselectivity, to give exclusively α-adduct products. Once more, a range of ketones underwent reductive aldol reaction to afford *β*-hydroxy ester products in comparable yields to that of the γ-selective reaction, though enantioselectivities were somewhat lower.

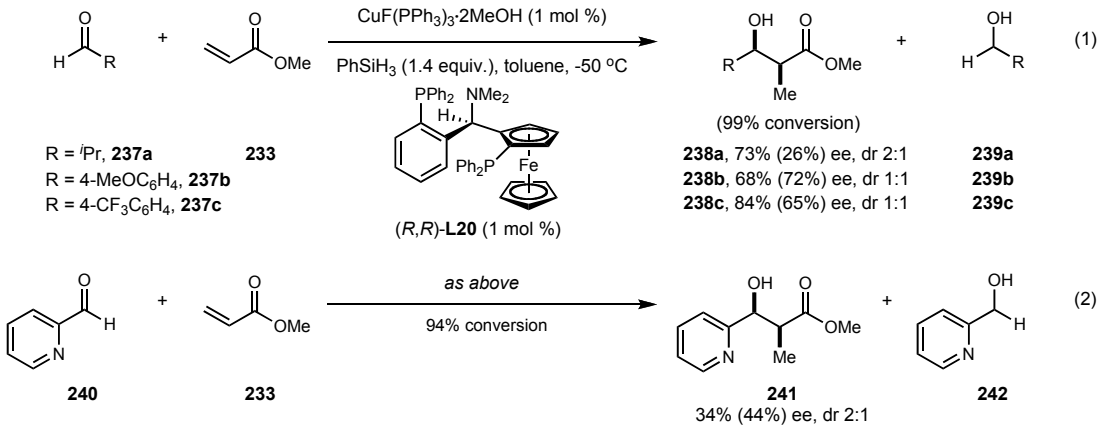
Around the same time as Shibasaki's initial publication,[52] Riant and co-workers reported the highly diastereo- and enantioselective copper-catalysed intermolecular reductive aldol reaction of methyl acrylate to a range of unsymmetrical ketones (Scheme 1.58).[54] The reaction proved tolerant of a variety of aromatic and heteroaromatic ketones, providing *β*-hydroxy ester products in generally high yields and enantioselectivities, with moderate *anti*-selectivities. The authors noted that the introduction of a halogen substituent on the aromatic ring typically reduced both the

diastereoselectivity and enantioselectivity, whereas the presence of an electron donating substituent, as in substrate **10f**, led to an increase in selectivity.



Scheme 1.58

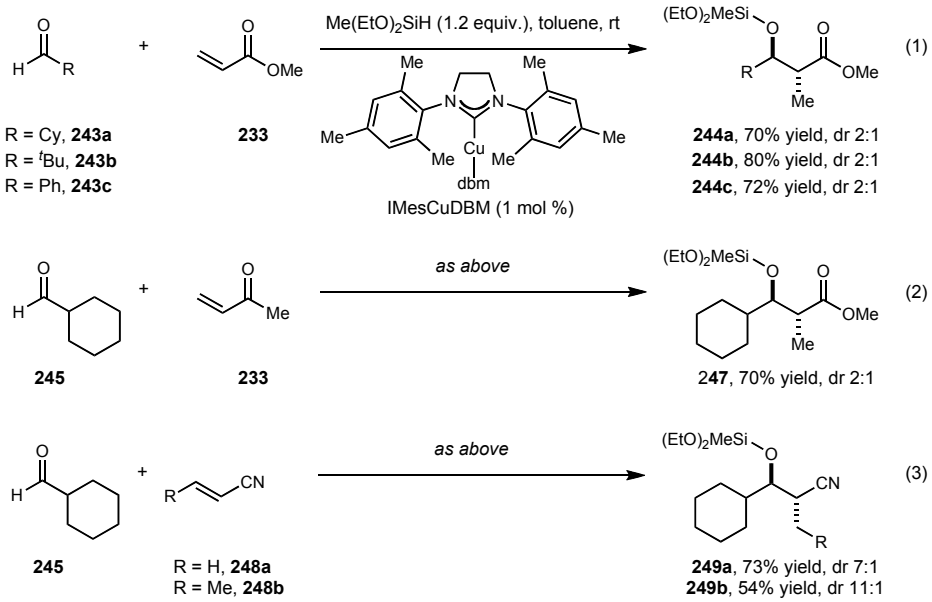
Following their initial publication, Riant and co-workers reported an analogous reaction, this time using aldehydes as the electrophilic component, allowing the formation of small propionate-type compounds (Scheme 1.59).[55] This reaction provides a significant challenge, owing to the facile reduction of the aldehyde starting material; indeed, in most cases, *ca.* 5% alcohol was produced, alongside the desired β-hydroxy ester products. However, in the case of trifluoromethyl substituted substrate **237c**, around 25% undesired alcohol **239c** was produced.



Scheme 1.59

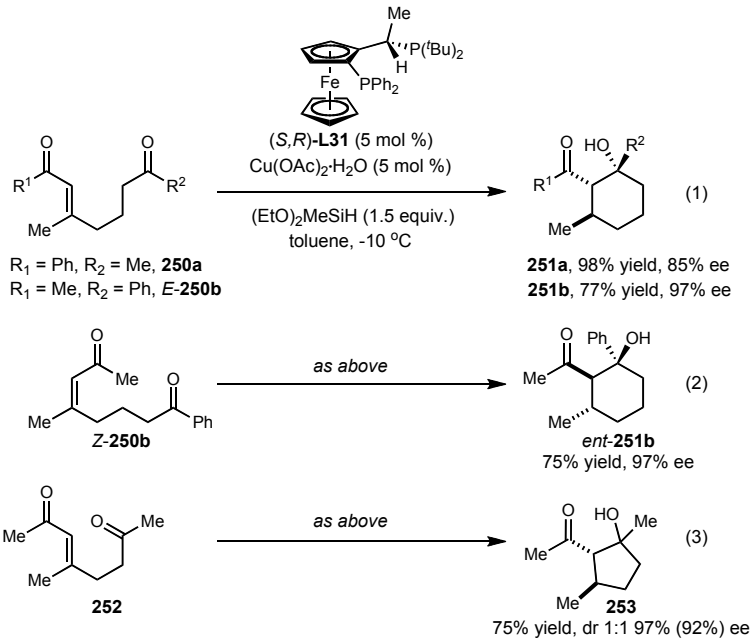
Interestingly, while isopropylaldehyde **237a** provided the product in 73% ee, no enantioselectivity was observed in the case of *tert*-butylaldehyde. Furthermore, the reaction was more efficient when aromatic or heteroaromatic, rather than aliphatic, aldehydes were employed.

Both Buchwald[56] and Yun[57] have investigated the use of *N*-heterocyclic carbene copper complexes as catalysts in conjugate reduction reactions and in 2006, Riant and Nolan extended this methodology to include intermolecular reductive aldol reactions.[58] Using 1 mol % of *N*-heterocyclic carbene copper(I) complex, IMesCuDBM, various α,β-unsaturated carbonyl compounds underwent reaction, to afford the corresponding silylated products (Scheme 1.60). The reaction was predominantly *anti*-selective and proved tolerant of a range of aldehydes, including aliphatic, aromatic and heteroaromatic aldehydes. α,β-Unsaturated nitriles also underwent reduction, providing the silylated products in high yields, with good diastereoselectities.



Scheme 1.60

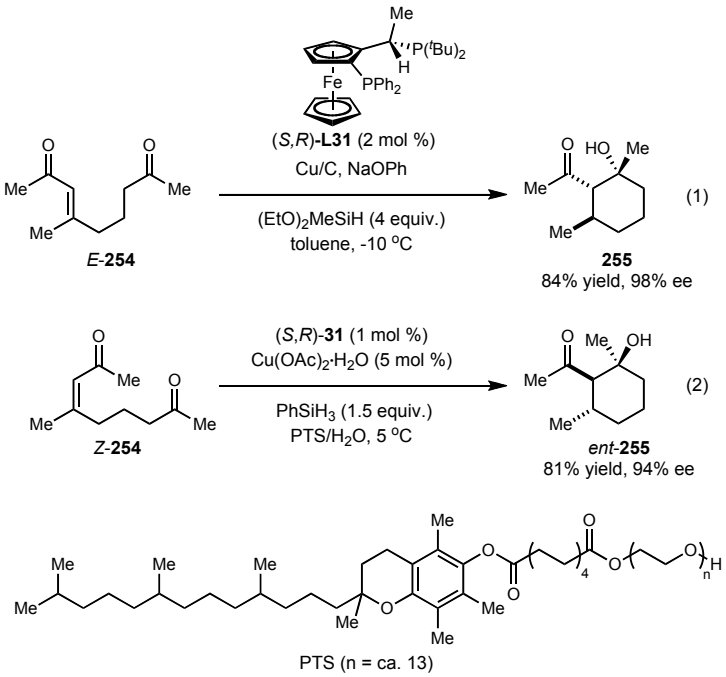
Thus far, all examples of asymmetric reductive aldol reactions have involved non-asymmetric conjugate reduction to afford a chiral copper enolate, which then controls the stereochemistry in the subsequent aldol reaction. However, in 2008 Lipshutz and co-workers reported the asymmetric intramolecular reductive aldol reaction of β,β'-disubstituted α,β-unsaturated ketones with pendant ketones (Scheme 1.61).[59] In this case, the reaction proceeds *via* asymmetric conjugate reduction, followed by asymmetric reductive aldol cyclisation, allowing the formation of three contiguous stereocentres. Both aromatic, and aliphatic enones underwent reduction to provide highly functionalised 5, and 6-membered rings with good-to-high enantioselectivity. The authors noted that both *E*- and *Z*-enones underwent reaction to give enantiomeric products, for example *E*-**250b** provided cyclised product **251b** in 77% yield and 97% ee, while Z-**250b** provided *ent*-**251b** in 75% yield and 97% ee.



Scheme 1.61

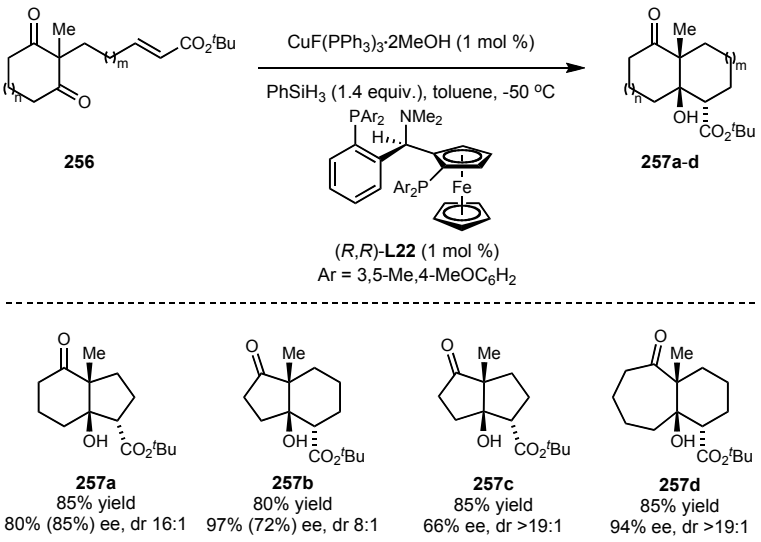
The cycloreduction of enone *E*-**254** was carried out in the presence of heterogeneous Cu/C (Scheme 1.62), conditions previously used by Lipshutz to effect the asymmetric reduction of a range of unsaturated compounds.[60] The cyclised product

was obtained in 84% yield, with 98% ee. In addition, the cycloreduction of Z-**254** was found to proceed smoothly using $Cu(OAc)_2 \cdot H_2O$ in water and non-ionic surfactant PTS, despite the inherent insolubility of *Z*-**254** in water (Scheme 1.62). In both cases, yields and enantioselectivities obtained were comparable to those obtained using $Cu(OAc)_2 \cdot H_2O$ and Josiphos ligand **L31** in toluene.



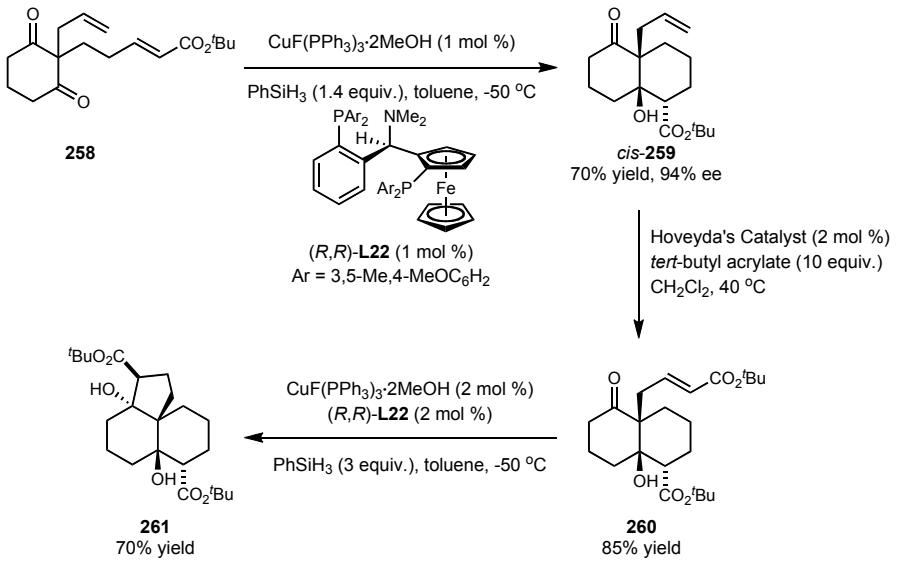
Scheme 1.62

Recently, Riant and co-workers reported the highly diastereo- and enantioselective construction of polycyclic compounds by reductive aldol cyclisations.[61] Using $CuF(PPh_3)_3 \cdot 2MeOH$ and Taniaphos ligand **L22**, a range of α,β-unsaturated esters tethered to cyclic ketones underwent reductive aldol cyclisation to afford bicyclic derivatives **257a-d** (Scheme 1.63). Predominantly *cis*-fused ring junctions were formed, and the authors noted that, in general, 6-membered rings were produced with higher enantioselectivities than 5-membered rings.



Scheme 1.63

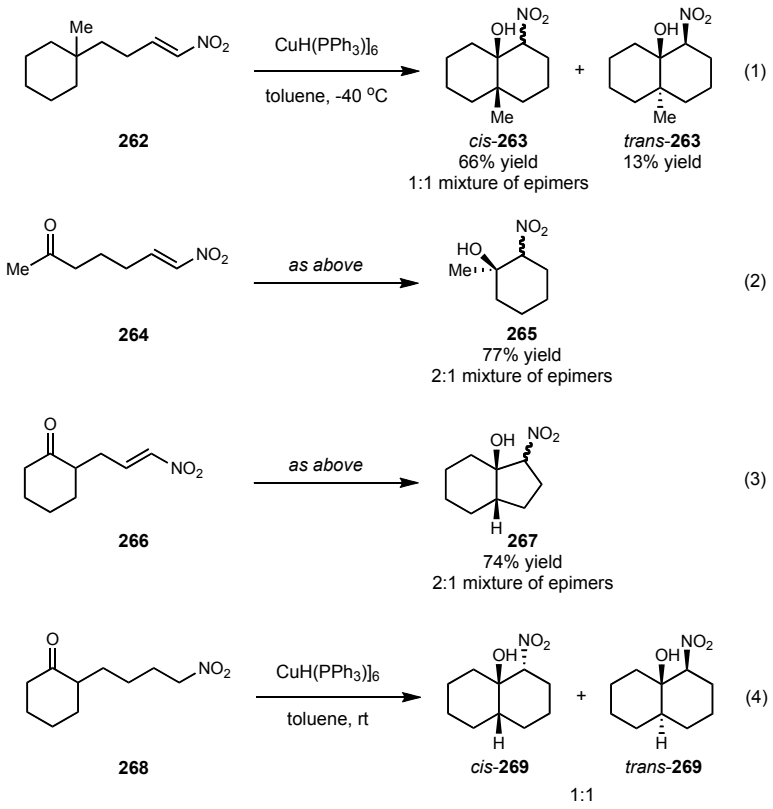
The authors extended this strategy to the synthesis of tricyclic compound **261** by cross metathesis of allyl-substituted derivative **259** with *tert*-butyl acrylate in the presence of Hoveyda's catalyst to give *tert*-butyl ester **260** (Scheme 1.64). A second reductive aldol cyclisation afforded tricyclic product **261**, containing five contiguous stereocentres, in 70% yield.



Scheme 1.64

1.5.4 Reductive Henry Reactions

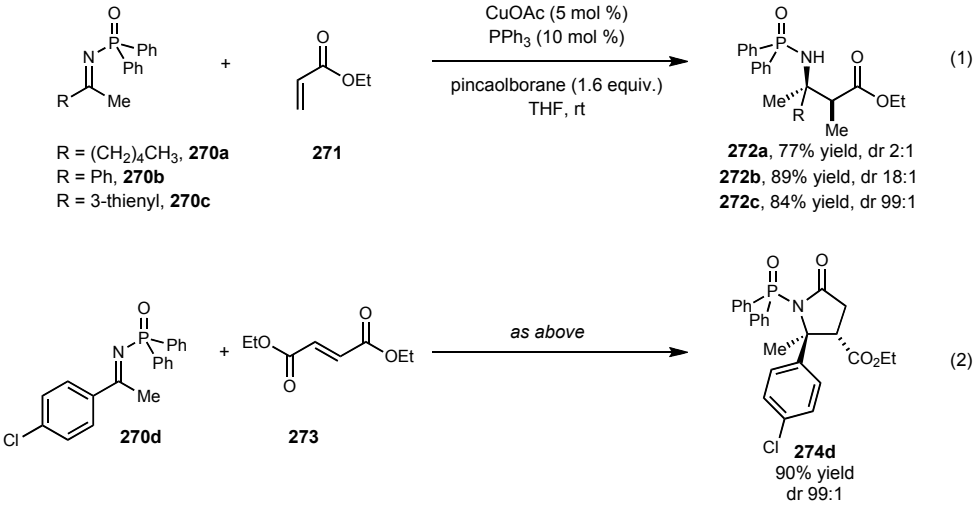
Despite numerous examples of reductive aldol reactions in the literature, the corresponding reductive Henry reaction, involving conjugate reduction of an α,β-unsaturated nitroalkene, followed by reaction with a ketone or aldehyde, has been relatively understudied. In 2005, Chiu reported the first example of a copper-catalysed reductive Henry reaction.[62] In parallel with traditional base-induced Henry reactions, which are typically less selective than aldol reactions, the intramolecular reductive Henry reactions of nitroalkenes, such as **262** (Scheme 1.65) were found to be less diastereoselective than previously reported reductive aldol reactions.[47] The authors attribute this low selectivity to the reversibility of the reaction, which gives rise to reduced diastereomer ratios after prolonged reaction time, and the acidity of the α-proton, which gives rise to mixtures of epimers. They also noted that, Stryker's reagent, while thought to be relatively non-basic, was able to induce the Henry reaction of saturated precursor **268** at room temperature to afford *cis*-**269** and *trans*-**269** in a 1:1 ratio.



Scheme 1.65

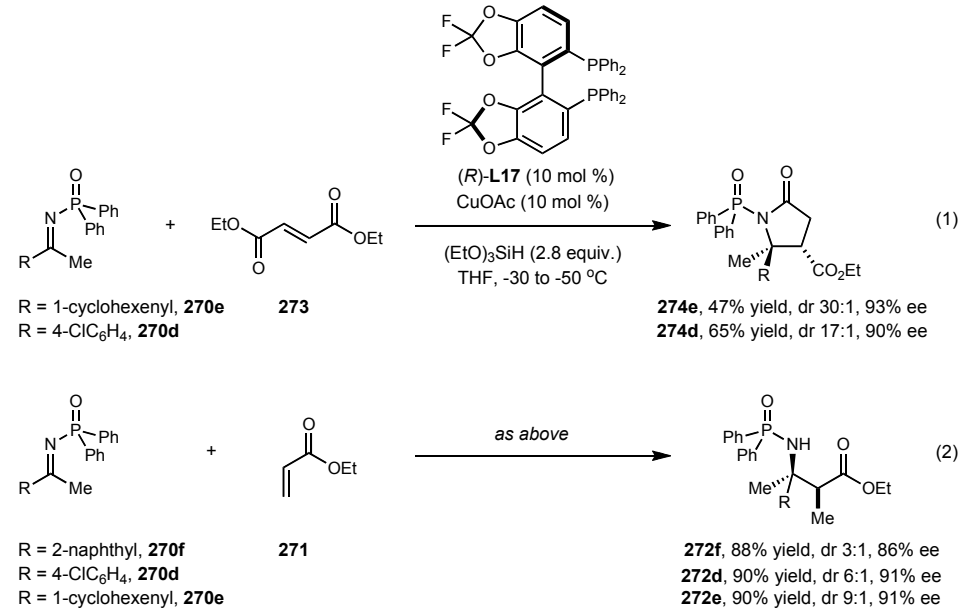
1.5.5 Reductive Mannich Reactions

In 2008, Shibasaki and co-workers reported a highly diastereo- and enantioselective copper-catalysed reductive Mannich reaction between unactivated ketimines and α,β-unsaturated esters.[63] This reaction overcomes the inherent low reactivity of ketimines, relative to aldehydes or ketones, and provides access to synthetically useful chiral β,β'-disubstituted amino acids. Initially, the authors investigated the use of pinacolborane as the stoichiometric reductant, in combination with CuOAc and PPh_3. A range of ketimines underwent reaction with ethyl acrylate to provide products **270a-c** in good yield, and diastereoselectivity (Scheme 1.66). Interestingly, when fumarate **273** was used as the pro-nucleophile, the highly substituted γ-lactam **274d** was obtained in excellent yield and selectivity.



Scheme 1.66

Unfortunately, all attempts to render the reaction enantioselective using pinacolborane proved unsuccessful. However, when $(EtO)_3SiH$ was used as the reductant, along with CuOAc and (*R*)-difluorophos (**L17**), the corresponding chiral amino acids were formed with good-to-excellent levels of enantioselection (Scheme 1.67).



Scheme 1.67

1.5.6 Conclusion

Conjugate reduction of α,β-unsaturated carbonyl compounds allows regioselective enolate formation in compounds bearing multiple carbonyl groups, which is generally difficult to achieve using traditional base-induced aldol reaction conditions. Subsequent electrophilic trapping of these enolates results in the highly diastereoselective, and in some cases, enantioselective, synthesis of complex molecules. Furthermore, the use of prochiral electrophiles leads to the formation of multiple contiguous stereocentres, with extremely high levels of stereocontrol.

Moreover, in contrast to asymmetric conjugate reduction reactions, most of the reported tandem modifications do not install a stereogenic centre at the reduction stage, but in the subsequent bond-forming step, providing further evidence for the formation of a chiral copper enolate, rather than a silyl enol ether.

1.6 Conclusion

Modern usage of copper hydride chemistry in organic synthesis is often attributed to the popularisation of $[CuH(PPh_3)]_6$ by Stryker 1988.[5] Despite these early advances, the full potential of this chemistry was not realised until the discovery that mildly hydridic silanes could be used as stoichiometric reductants to effect the copper-catalysed conjugate reduction of α,β-unsaturated carbonyl compounds.[10,11] Since then, this process has proved to be an effective method for the conjugate reduction of a range of Michael acceptors, including α,β-unsaturated sulfones, nitriles and nitroalkenes.

Furthermore, considerable effort has been devoted to the development of efficient stereoselective methods; the introduction of new chiral ligands, including ferrocenyl ligands, and axially chiral Segphos and Biphep ligands, has led to asymmetric conjugate reduction reactions exhibiting remarkably high levels of enantiocontrol.

Over the past 10 years, copper hydride chemistry has emerged as a powerful carbon-carbon bond forming process; conjugate reduction, followed by trapping with an electrophile has proved to be an extremely reliable method for the construction of multiple stereogenic centres. Both inter- and intramolecular reductive aldol reactions have been reported, in addition to the analogous reductive Henry reaction, and the reductive Mannich reaction.

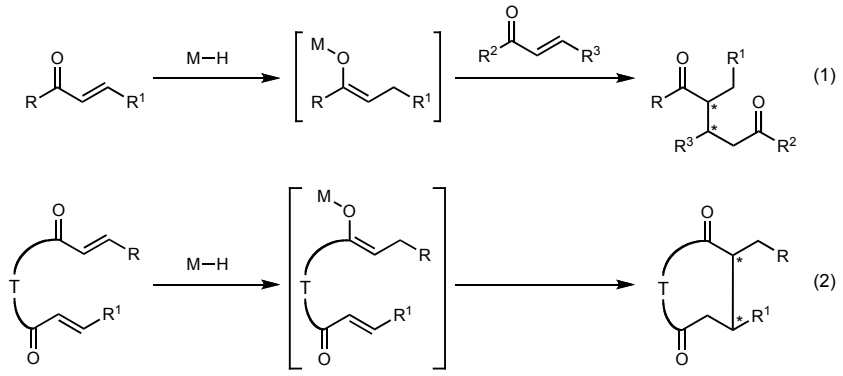
In the constantly evolving field of organic synthesis, copper hydride chemistry has proved to be a valuable and broadly applicable C-H bond forming process, providing access to structurally diverse chiral building blocks for potential use in the synthesis of biologically active natural products.

2 Enantioselective Copper-Catalysed Reductive Michael Cyclisations

2.1 Introduction

Despite numerous examples of catalytic reductive aldol reactions in the literature, the analogous reductive Michael reaction has been comparatively understudied. Indeed, only five examples of reductive Michael reactions have been reported in the literature. Furthermore, prior to the publication of the work described within this chapter, the only example of an *asymmetric* reductive Michael reaction employed a chiral secondary amine as the catalyst.

As with reductive aldol reactions, metal-catalysed reductive Michael reactions involve conjugate reduction of an α,β-unsaturated carbonyl moiety to give a metal enolate (Scheme 2.1). This enolate then undergoes reaction with a second α,β-unsaturated carbonyl moiety to provide the saturated product.

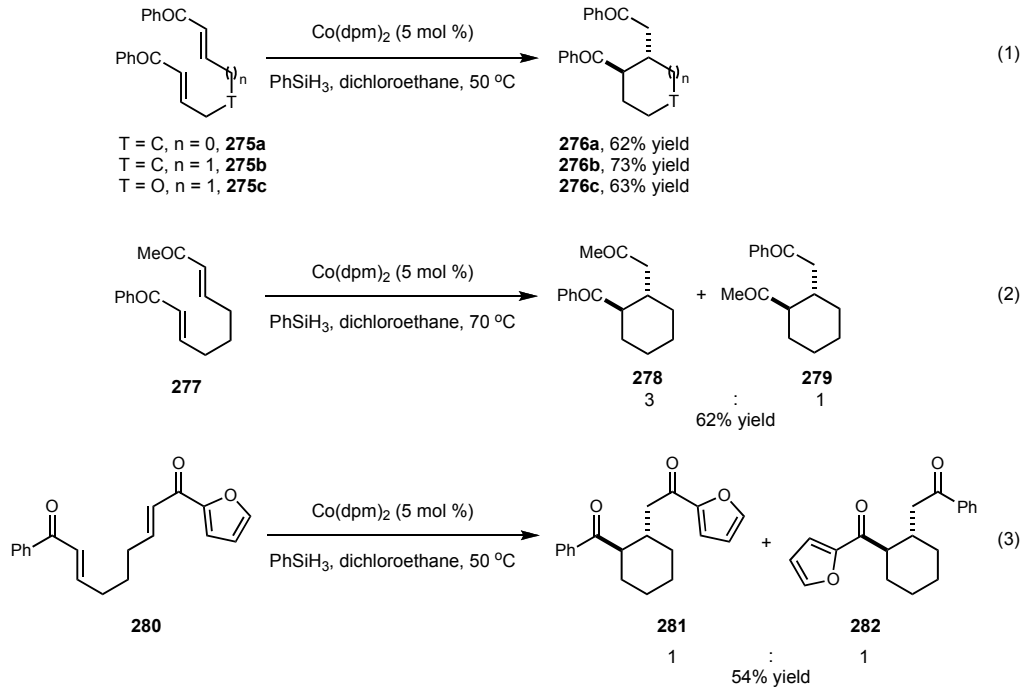


Scheme 2.1

In order to be considered efficient, reductive Michael reactions must be both chemo- and diastereoselective. In the case of *intermolecular* reductive Michael reactions, if each α,β-unsaturated carbonyl compound is different ($R \neq R^2$ and/or $R^1 \neq R^3$), reactions can be complicated by problems with chemoselectivity, giving rise to mixtures of different products. Similar issues arise with *intramolecular* reductive Michael reactions.

2.1.1 Metal-Mediated Reductive Michael Reactions

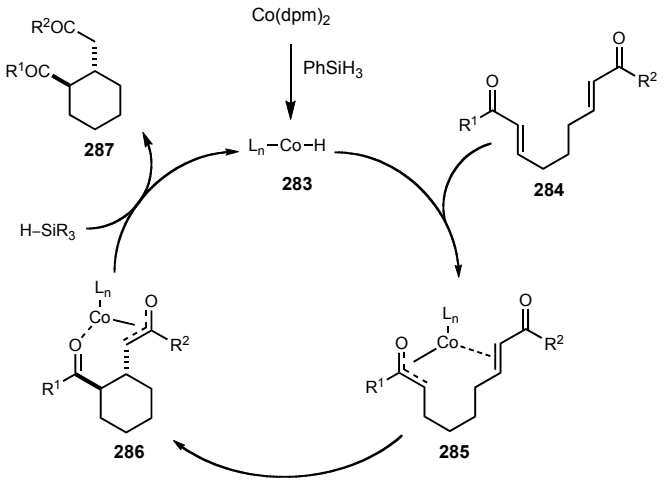
Krische reported the first reductive Michael reaction in 2001 (Scheme 2.2).[64] In the presence of a substoichiometric amount of a cobalt(II) catalyst, using phenylsilane as the stoichiometric reductant, a range of *bis*-enones underwent reductive Michael cyclisation to afford both 5- and 6-membered ring products. In all cases, the *anti*-diastereomer was obtained. Unsymmetrical enone **277** was also found to undergo reduction to afford both **278** and **279**, resulting from hydrometalation of the phenyl-substituted enone, and the methyl-substituted enone, respectively. However, a much lower level of chemoselectivity was obtained with substrate **280**, which underwent cyclisation to afford a 1:1 mixture of **281** and **282**. This poor selectivity is attributed to the small electronic difference between the phenyl group and the 2-furyl group.



Scheme 2.2

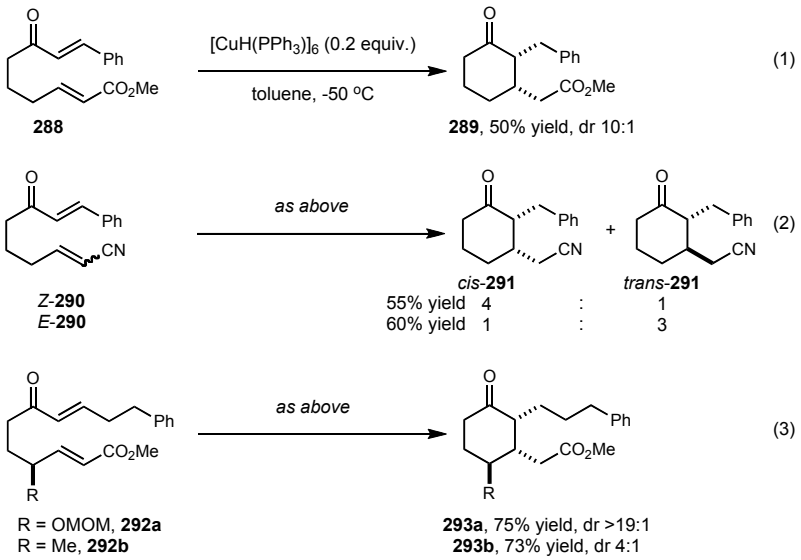
The authors propose that exposure of $Co(dpm)_2$ to phenylsilane results in cobalt hydrido species **283**, which undergoes hydrometalation with the enone to generate cobalt enolate **285** (Scheme 2.3). Conjugate addition of the enolate to the tethered

enone affords a second cobalt enolate **286**, which undergoes σ-bond metathesis to liberate the product and regenerate the active catalyst.



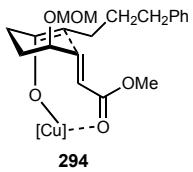
Scheme 2.3

Following this initial publication by Krische, Overman and co-workers reported an intramolecular reductive Michael reaction mediated by Stryker's Reagent (Scheme 2.4).[65] A range of 7-oxo-2,8-alkadienoic ester and nitrile substrates underwent cyclisation in good yield, with varying degrees of *cis*-selectivity. In general, substitution at the 4-position, for example in substrates **292a** and **292b**, was well tolerated, however, substitution at either the α- or *β*- position of the unsaturated ester or nitrile component resulted in reduction without cyclisation.



Scheme 2.4

The authors noted that the diastereoselectivity was dependent on various factors, including (1) solvent polarity – the stereoselectivity decreased with increasing solvent polarity, (2) the purity of the reductant – the stereoselectivity decreased with increasing amounts of PPh_3 contaminant and (3) the geometry of the α,β-unsaturated nitrile/ester component – (*E*)-alkenes resulted in higher selectivites than (*Z*)-alkenes. It was suggested that the *cis*-selectivity arises from formation of a (*Z*)-copper enolate intermediate, which then chelates with the appended α,β-unsaturated ester, represented by chair-like transition state **294** (Figure 2.1).

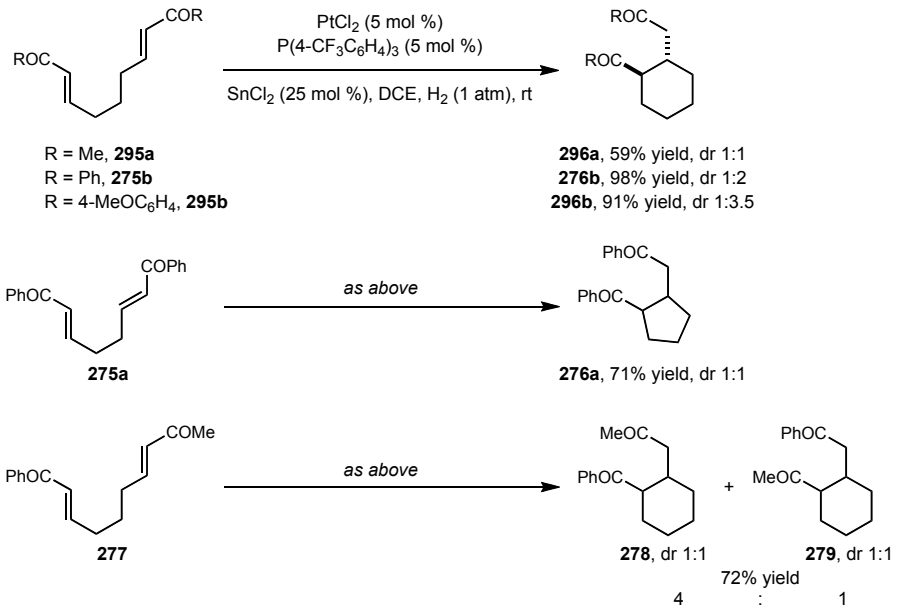


294

Figure 2.1

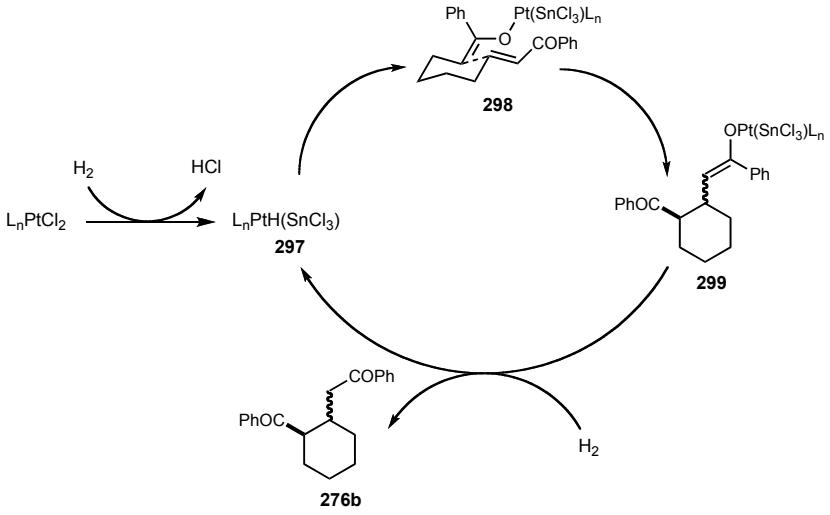
More recently, Jang and co-workers reported the platinum-catalysed reductive Michael cyclisation of a range of *bis*-enones, mediated by molecular hydrogen (Scheme 2.5).[66,67] Initial ligand screening revealed that electron-poor phosphine ligands such as $P(p\text{-}CF_3C_6H_4)_3$ provided the product in higher yield than electron-

rich ligands. Furthermore, increasing the amount of ligand relative to $PtCl_2$ resulted in increased diastereoselectivity, but significantly reduced the yield.



Scheme 2.5

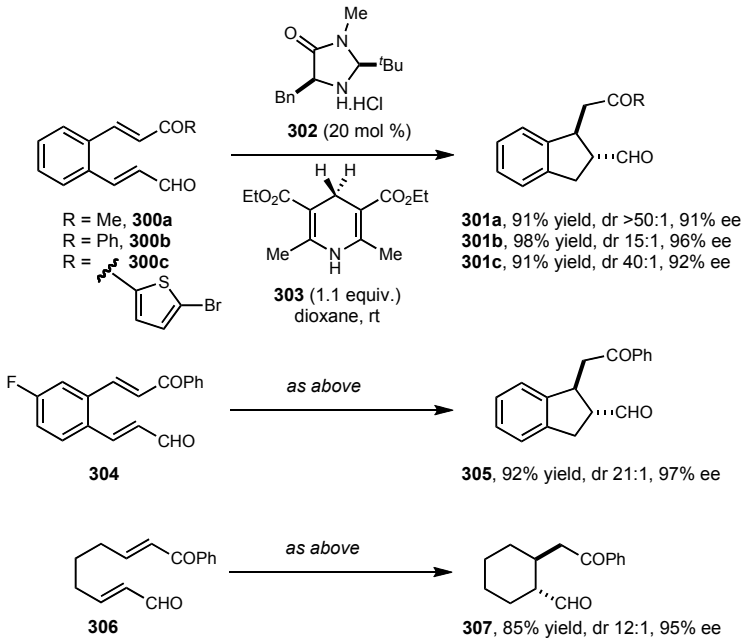
The authors proposed that $SnCl_2$ acts as a co-catalyst, activating $PtCl_2$ to afford the active catalytic species $L_nPtH(SnCl_3)$ (**279**) upon reaction with hydrogen gas (Scheme 2.6). The active catalytic species then undergoes hydrometalation with the substrate to afford intermediate **298**. Intramolecular Michael addition provides platinum enolate **299**; the low diastereoselectivity is attributed to poor coordination between the platinum ion and the oxygen in intermediate **298**. This enolate then undergoes oxidative addition with molecular hydrogen, followed by reductive elimination, to afford the product (**276b**) and regenerate the active catalytic species.



Scheme 2.6

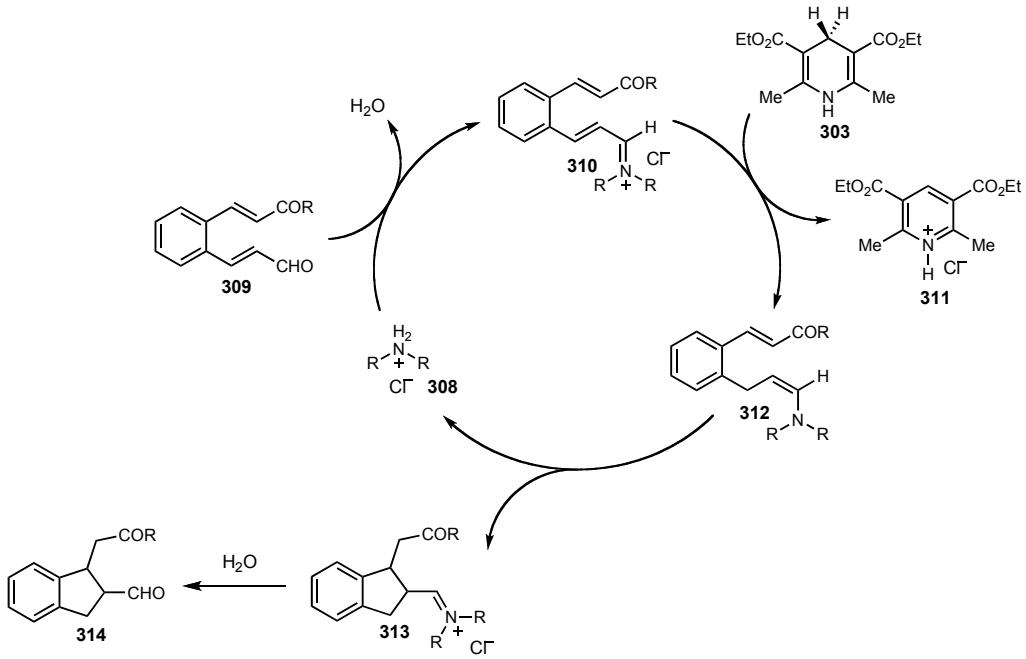
2.1.2 Organocatalysed Reductive Michael Reactions

List and co-workers reported the first asymmetric reductive Michael cyclisation in 2005, using a chiral secondary amine as the catalyst, and the Hanzsch ester as the reductant (Scheme 2.7).[68] A range of substrates underwent reductive Michael cyclisation to afford the product as the *anti*-diastereomer in high yield and enantioselectivity. The reaction was found to be tolerant of many functional groups including – at the β-position of the enone – aromatic, heteroaromatic, and aliphatic substituents. Substitution of the aromatic backbone was also well tolerated.



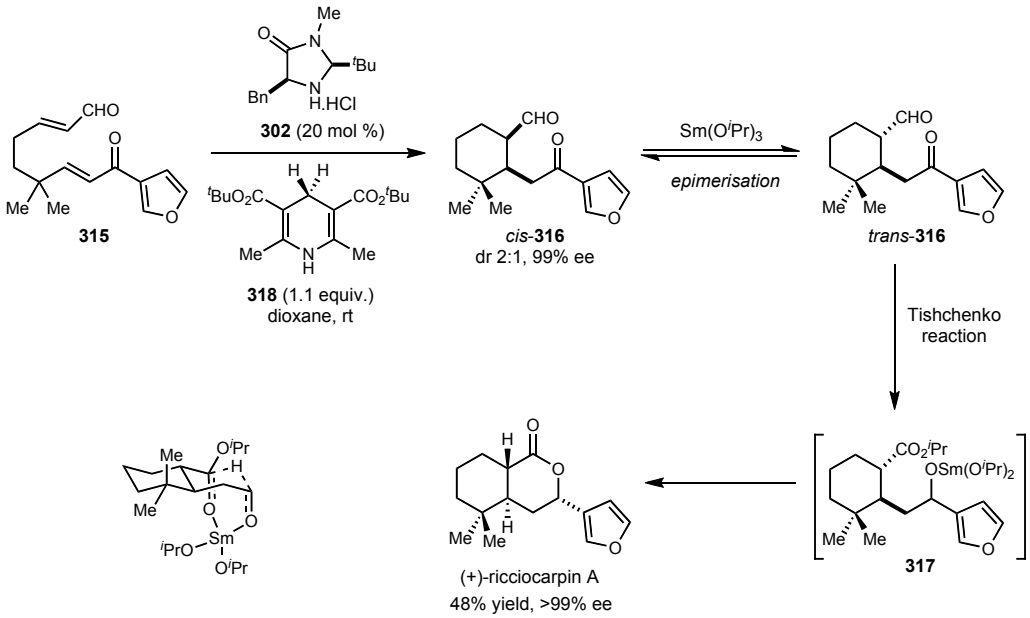
Scheme 2.7

The authors proposed that the mechanism proceeds *via* non-asymmetric imine-catalysed conjugate reduction, followed by asymmetric enamine-catalysed conjugate addition (Scheme 2.8). The enal is activated with MacMillan imidazolidinium salt **308** to form imine **310**. Hydride transfer from Hantzsch ester **303** provides enamine intermediate **312**, which subsequently undergoes conjugate addition to afford imine **313**. Hydrolysis of intermediate **313** provides the desired product.



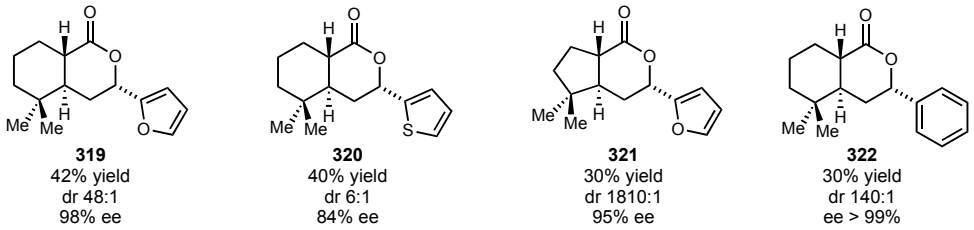
Scheme 2.8

In a notable extension of this work, List and co-workers applied this methodology to the synthesis of the natural product (+)-ricciocarpin A (Scheme 2.9).[69] The cyclisation precursor **315** was subjected to the standard reaction conditions, and underwent cyclisation to provide the undesired *cis*-isomer *cis*-**316**, with excellent enantioselectivity. Fortunately, the rate of epimerisation of *cis*-**316** is rapidly increased in the presence of $Sm(O^iPr)_3$, resulting in the formation of the more thermodynamically stable *trans*-**316**. This event is followed by a highly diastereoselective Tishchenko reaction to afford the desired natural product, (+)-ricciocarpin A, as a single diastereomer with >99% ee.



Scheme 2.9

The authors explored the generality of this novel cascade reaction by preparing a range of different cyclisation precursors, which underwent reaction to provide potentially useful analogues of (+)-ricciocarpin A, **319**-**322** (Scheme 2.10).



Scheme 2.10

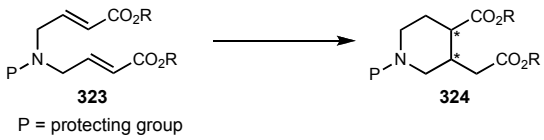
2.2 Results and Discussion

As discussed previously, hydrometalation of α,β-unsaturated carbonyl compounds provides access to reactive chiral metal enolates, which can be trapped by a suitable electrophile to afford enantiomerically enriched products. In view of the considerable success realised with asymmetric copper-catalysed reductive aldol reactions, we envisioned an asymmetric copper-catalysed reductive Michael cyclisation reaction, which represents an appropriate extension to the asymmetric reductive aldol cyclisations previously described within our group.[50,51]

2.2.1 Nitrogen-Tethered Substrates

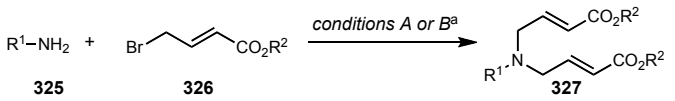
2.2.1.1 Preparation of Cyclisation Precursors

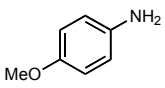
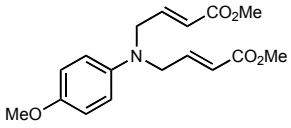
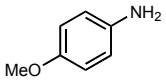
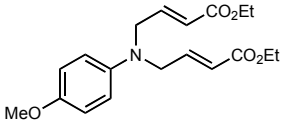
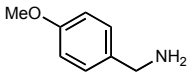
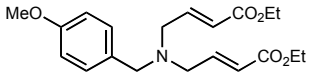
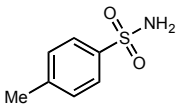
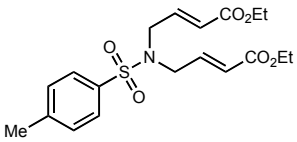
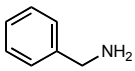
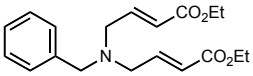
Initially, we thought it would be of interest to investigate the reductive Michael cyclisation of nitrogen-tethered *bis*-enoates, such as **323**. Cyclisation of such substrates would provide access to potentially useful chiral piperidine derivatives **324** (Scheme 2.11).



Scheme 2.11

A range of cyclisation precursors were prepared by variation of both the nitrogen protecting group and the ester substituent, providing a range of structurally and electronically diverse *bis*-enoates. In the presence of excess base, various primary amines underwent alkylation with the appropriate alkyl-4-bromocrotonate to afford the corresponding tertiary amine in moderate yield (Table 2.1).

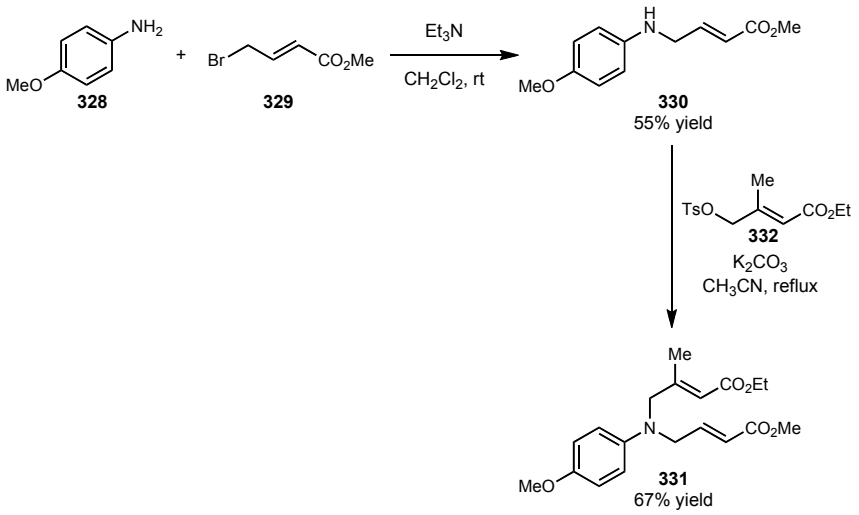


Entry	Starting Material	Conditions	Product		Yield (%)
1		A		**327a**	47
2		A		**327b**	79
3		B		**327c**	44
4		A		**327d**	53
5		B		**327e**	41

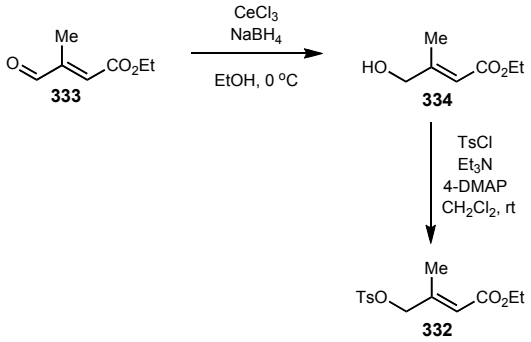
[a] Conditions A: K_2CO_3 (5 equiv.), CH_3CN, reflux; Conditions B: pyridine (2 equiv.), CH_2Cl_2, rt

Table 2.1

Unsymmetrical cyclisation precursor **331**, containing a β,β'-disubstituted enoate was also prepared (Scheme 2.12). In general, mono-alkylation of amines represents a problem, given the tendency of amines to undergo poly-alkylation. However, it was found that in the presence of triethylamine at room temperature, alkylation of 4-anisidine proceeded to afford the mono-alkylation product, **330** selectively. Subsequent alkylation of **330** with tosylate **332**, provided unsymmetrical cyclisation precursor **331**. Tosylate **332** was prepared by Luche reduction[70] of commercially available aldehyde **333** using $CeCl_3$ and $NaBH_4$, followed by tosylation under standard conditions (Scheme 2.13).



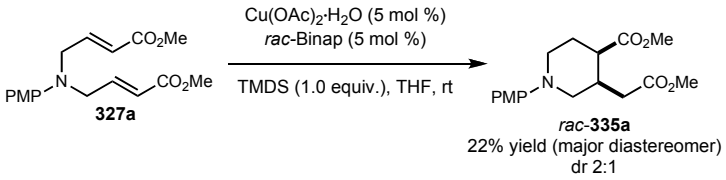
Scheme 2.12



Scheme 2.13

2.2.1.2 Ligand Optimisation

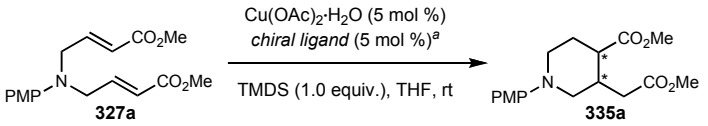
Initially, it was decided to use the conditions previously developed within the group to effect reductive aldol cyclisations. Thus, in the presence of a substoichiometric amount of copper acetate, and *rac*-Binap, using TMDS as the stoichiometric reductant, the reductive Michael cyclisation of substrate **327a** was carried out (Scheme 2.14).

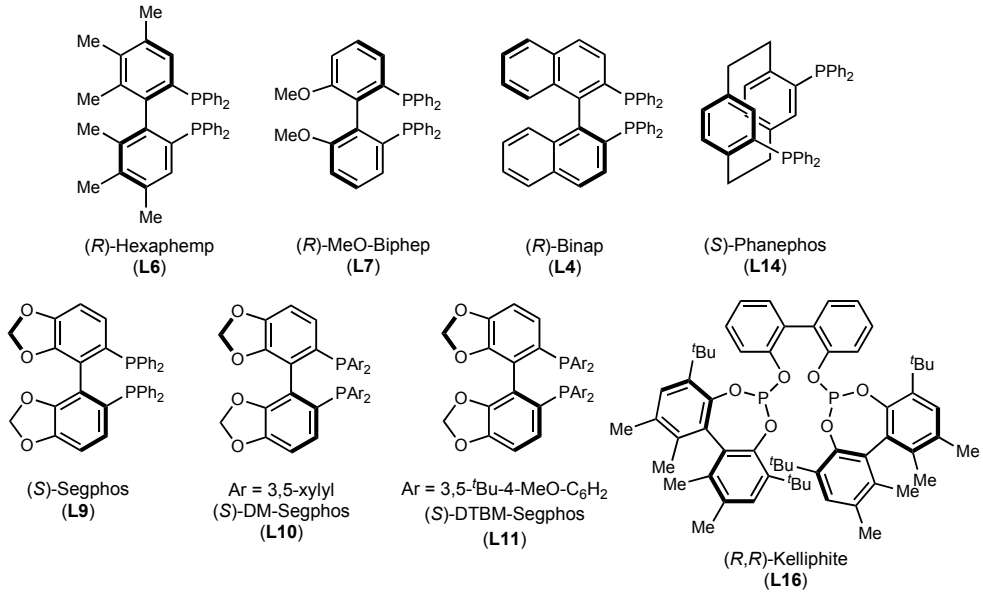


Scheme 2.14

Subesquent derivitisation of a related compound, **335b** revealed the major diastereomer to be the *syn*-product (*see Section 2.2.1.3*). The stereochemistry of **335a** was assigned by direct comparison of ^{1}H NMR data obtained from both compounds.

Following this, a range of chiral ligands were screened (Table 2.2) and the resulting enantiomeric excess was determined by chiral HPLC analysis of the crude reaction mixture using either an AD-H or an OD-H column. In general, Binap, Biphep and Segphos ligands performed with similar efficacy, providing cyclised product **335a**, with high enantioselectivity, albeit with low diastereoselectivity (dr ~ 2:1 in most cases). Conversely, (*S*)-Phanephos and sterically bulky (*R*,*R*)-Kelliphite resulted in no reaction.





Entry	Ligand	dr[a]	ee (major diastereomer) (%)[b]	ee (minor diastereomer) (%)[b]
1	**L6**	1:1	80 (+)	80 (+)
2	**L7**	2:1	91 (+)	93 (+)
3	**L4**	2:1	91 (+)	84 (+)
4	**L14**	*no reaction*	*no reaction*	*no reaction*
5	**L9**	2:1	90 (–)	91 (–)
6	**L10**	2:1	91 (–)	89 (–)
7	**L11**	2:1	86 (–)	87 (–)
8	**L16**	*no reaction*	*no reaction*	*no reaction*

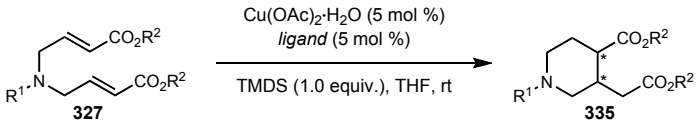
[a] Determined by ^{1}H NMR analysis of the unpurified reaction mixture. [b] Enantiomeric excess was determined by chiral HPLC analysis of the unpurified reaction mixture. The sign of optical rotation is provided in parentheses.

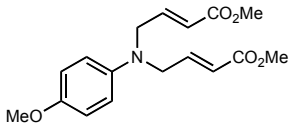
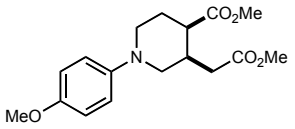
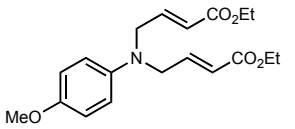
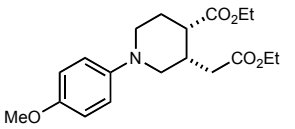
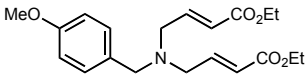
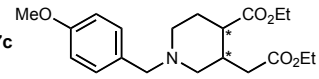
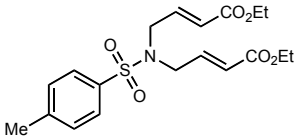
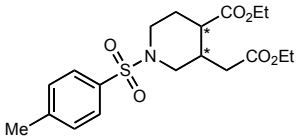
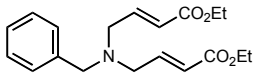
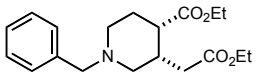
Table 2.2

2.2.1.3 Substrate Scope

The reductive Michael cyclisations of substrates **327a-e** were then carried out, both racemically, using *rac*-Binap or dppf, and in the presence of a chiral ligand (Table 2.3). The cyclisation of *para*-methoxyphenyl-protected enoate **327a** proceeded smoothly to provide substituted piperidine **335a** as 2:1 mixture of diastereomers, with 93% ee and 92% ee, for the major and minor diastereomers respectively (Entry 1). The analogous ethyl-ester substrate **327b** also underwent cyclisation to afford **335b** as a 4:1 mixture of diastereomers, in 91% ee (major diastereomer) (Entry 2). Although *para*-methoxybenzyl-protected enoate **327c** did undergo cyclisation when conducted with *rac*-Binap, the product was isolated as a 2:1 mixture of inseparable diastereomers in 48% yield; thus, the enantioselective reaction was not carried out

(Entry 3). Disappointingly, tosyl-protected substrate **327d** did not undergo cyclisation, even following prolonged heating (Entry 4). Interestingly, although benzyl-protected enoate **327e** did undergo cyclisation, no enantiomeric excess was obtained when the reaction was conducted with (*R*)-MeO-Biphep (Entry 5). Further screening with a range of chiral ligands also resulted in no enantioselection.



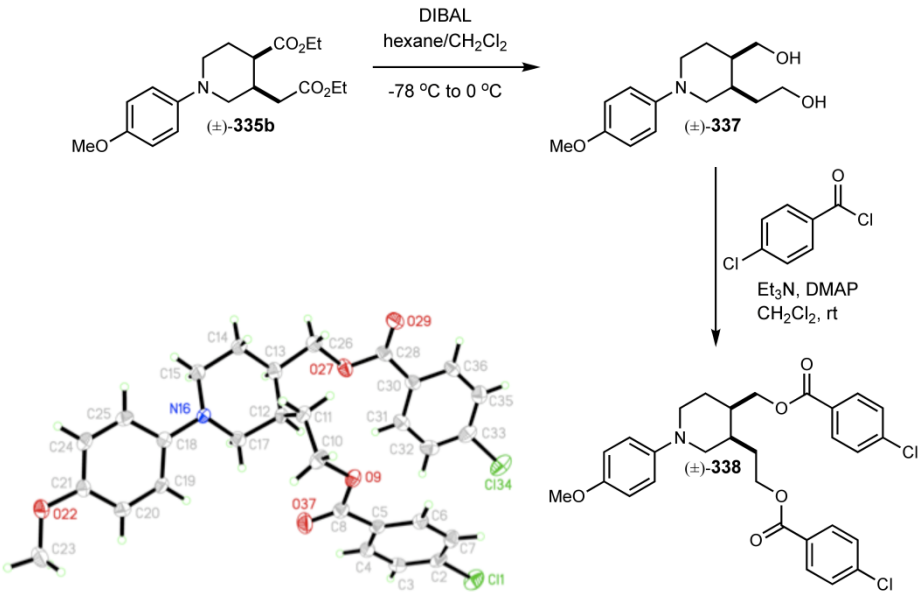
Entry	Starting Material		Product		dr[a]	Yield (%)	ee (%)[b]
1[c]		**327a**		**335a**	2:1	49	93 (92)
2[d]					2:1	22	-
3[e]		**327b**		**335b**	4:1	41[f]	91[g]
4[h]					3:1	36[f]	-
5[h]		**327c**		**335c**	2:1	48[i]	-
6		**327d**		**335d**		*no reaction*	
7[d]		**327e**		**335e**	2:1	37	-

[a] Determined by ^{1}H NMR analysis of the unpurified reaction mixture. [b] Determined by chiral HPLC analysis of the unpurified reaction mixture. Enantiomeric excess of major (minor). Absolute configuration not assigned. [c] Reaction conducted with (*R*)-MeO-Biphep. [d] Reaction conducted with *rac*-Binap. [e] Reaction conducted with (*S*)-DM-Segphos. [f] Yield of major diastereomer only. [g] Enantiomeric excess of major diastereomer only. [h] Reaction conducted with dppf. [i] Yield of an inseparable mixture of diastereomers.

Table 2.3

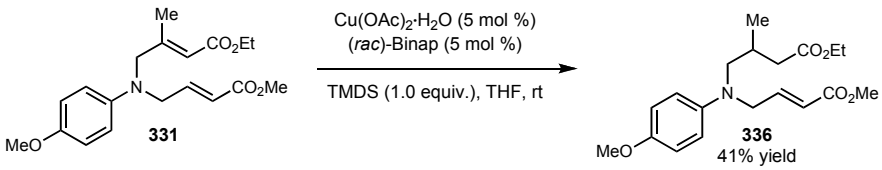
In order to determine the relative stereochemistry of *para*-methoxyphenyl-protected piperidine derivative **335b**, racemic product (±)-**335b** was reduced with DIBAL to provide diol **337**, which was then acylated with *para*-chlorobenzoyl chloride to afford (±)-**338** (Scheme 2.15). Fortunately, recrystallisation of (±)-**338** gave crystals that were suitable for X-ray crystallography, which confirmed the relative

stereochemistry of (±)-**338**, and thus (±)-**335b** to be *syn*. The relative stereochemistry of compounds **335a** and **335e** was determined by analogy with **335b** based on distinctive ^{1}H NMR signals present in all three compounds.



Scheme 2.15

Unsymmetrical cyclisation precursor **331** was subjected to the same reaction conditions (Scheme 2.16). However, only reduced product **336** was isolated, resulting from conjugate reduction at the least sterically hindered site followed by protonation, rather than conjugate addition to the tethered β,β'-disubstituted enoate moiety. The propensity of the enolate to undergo protonation as opposed to conjugate additions is most likely due to the steric hindrance around the β-carbon.



Scheme 2.16

The proposed transition state for the reaction is shown in Figure 2.2. The chiral copper catalyst is coordinated to both carbonyl groups, resulting in the observed *cis*-selectivity.

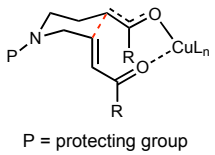


Figure 2.2

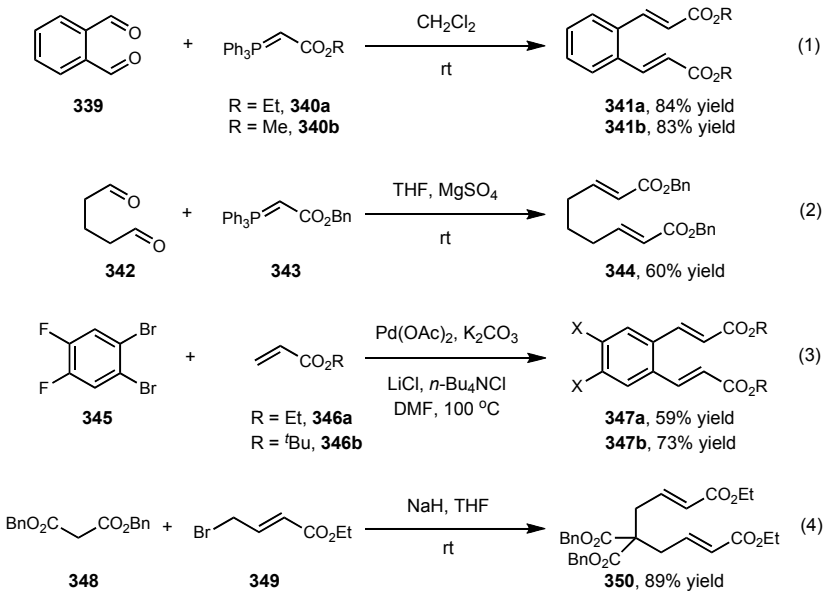
2.2.1.4 Conclusions

The reductive Michael cyclisations of a range of nitrogen-tethered α,*β*-unsaturated esters were carried out, providing the corresponding piperidine derivatives in moderate yields. In general, *para*-methoxyphenyl-protected substrates **327a** and **327b** gave superior results, affording the *cis*-isomeric products with up to 93% ee. Conversely, the cyclisation of benzyl-protected derivative **327e** resulted in no enantioselection. It is possible that the lone pair of electrons on the nitrogen atom is coordinating to the catalyst in an unproductive manner, reducing the enantiocontrol. This effect would be particularly prevalent in benzyl-derivative **327e**, in which the nitrogen lone pair is significantly more basic than in the corresponding *para*-methoxyphenyl-derivatives. Thus, we turned our attention towards substrates that do not contain a coordinating atom such as nitrogen.

2.2.2 Carbon- and Oxygen-Tethered α,β-Unsaturated Ester Substrates

2.2.2.1 Preparation of Cyclisation Precursors

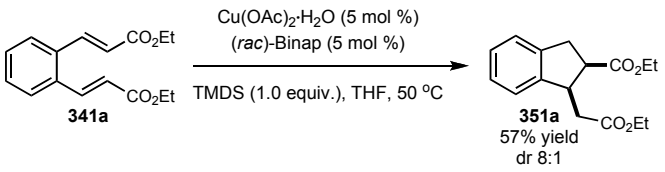
Carbon-tethered cyclisation precursors were prepared according to several different methods (Scheme 2.17). Taking advantage of commercially available building blocks **339** and **345**, aromatic-tethered cyclisation precursors were synthesised by either Wittig reaction (Eqn. 1), or Heck reaction (Eqn. 3). Carbon-tethered *bis*-benzyl enoate **344** was also prepared by a Wittig reaction using commercially available glutaric dialdehyde (**342**) (Eqn. 2). Finally, cyclisation precursor **350** was prepared in good yield from dibenzylmalonate (**348**) (Eqn. 4).



Scheme 2.17

2.2.2.2 Ligand Optimisation

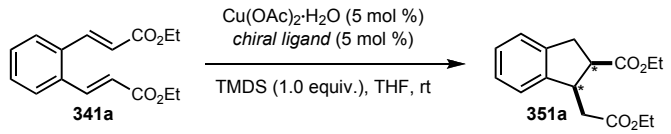
Initially, the reaction of *bis*-enoate **341a** was carried out in the presence of copper acetate, *rac*-Binap and TMDS (Scheme 2.18). Gratifyingly, complete consumption of the starting material was observed at 50 °C, and the product was isolated in 57% yield as an 8:1 mixture of inseparable diastereomers.

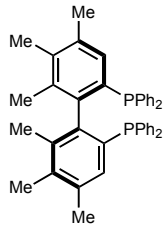


Scheme 2.18

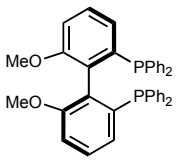
The relative stereochemistry of compound **351a** was proposed to be *syn* by direct comparison of the ^{1}H NMR data of compound **351a** and an analogous compound, *cis*-**375**, whose stereochemistry was determined to be syn based on nOe experiments (*see Section 2.2.3.2*).

We then turned our attention towards the use of chiral bisphosphine ligands (Table 2.4). The enantiomeric excess of compound **351a** was determined by HPLC analysis of the crude reaction mixture using either an AD-H or an OD-H column. The cyclisation of *bis*-enoate **341a** proceeded smoothly in the presence of all of the biaryl ligands to afford indane derivative **351a** in good conversion (>85% in all cases). In parallel with results obtained with using the nitrogen-tethered substrates, Biphep (Entry 2), Binap (Entry 3), and Segphos (Entry 4) ligands generally provided comparable levels of diastereo- and enantioselection. However, results obtained using (*S*)-Segphos were marginally superior.

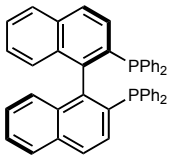




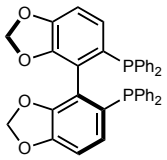
(*R*)-Hexaphemp (**L6**)



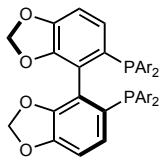
(*R*)-MeO-Biphep (**L7**)



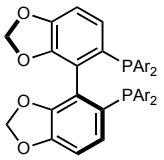
(*R*)-Binap (**L4**)



(*S*)-Segphos (**L9**)



Ar = 3,5-xylyl
(*S*)-DM-Segphos (**L10**)



Ar = 3,5-^{t}Bu-4-MeO-C_6H_2
(*S*)-DTBM-Segphos (**L11**)

Entry	Ligand	dr[a]	ee (%)[b]
1	**L6**	5:1	84 (+)
2	**L7**	6:1	92 (+)
3	**L4**	6:1	87 (+)
4	**L9**	10:1	94 (–)
5	**L10**	9:1	84 (–)
6	**L11**	6:1	81 (–)

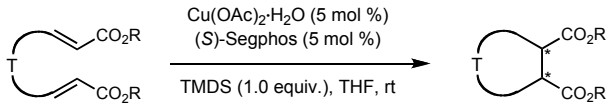
[a] Determined by ^{1}H NMR analysis of the unpurified reaction mixture. [b] Determined by chiral HPLC analysis of the unpurified reaction mixture. Enantiomeric excess of major diastereomer. The absolute stereochemistry of **351a** was not determined. The sign of optical rotation is provided in parentheses.

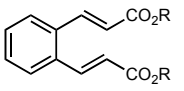
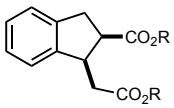
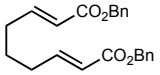
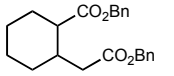
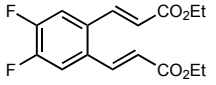
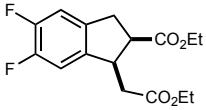
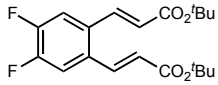
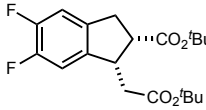
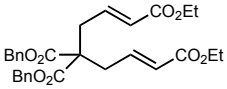
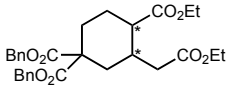
Table 2.4

2.2.2.3 Substrate Scope

With optimised conditions in hand, the reductive Michael cyclisations of a range of precursors were carried out (Table 2.5). The yield and diastereomer ratio of the corresponding racemic reactions, conducted with *rac*-Binap are displayed in parentheses in Table 2.5. Using (*S*)-Segphos, cyclisation of *bis*-ethyl ester **341a** provided indane derivative **351a** as a 12:1 mixture of diastereomers, with 91% ee for the major diastereomer (Entry 1). The corresponding methyl ester also underwent cyclisation to provide **351b** with slightly lower diastereoselectivity, but with similarly high enantioselectivity (Entry 2). Unfortunately, *bis*-benzyl ester substrate **344** did not undergo cyclisation, instead a complex mixture of unidentified products was obtained (Entry 3). The effect of substitution on the aromatic ring was

investigated; gratifyingly, cyclisation of *bis*-ethyl ester derivative **347a** proceed smoothly to afford **353a** as a 7:1 mixture of diastereomers, with 92% ee (Entry 4).



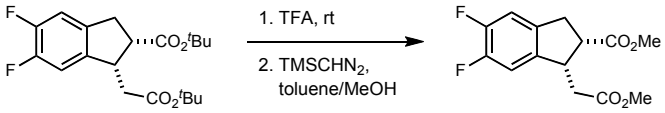
Entry	Starting Material		Product		Yield (%)[a]	dr[b]	ee (%)[c]
1		R = Et, **341a**		**351a**	57 (57)[d]	12:1 (8:1)	91
2		R = Me, **341b**		**351b**	41 (48)[d]	6:1 (5:1)	93
3		**344**		**352**	*mixture of unidentified products*		
4		**347a**		**353a**	53 (48)	7:1 (7:1)	92
5[e]		**347b**		**353b**	54 (49)	8:1 (8:1)	90[f]
6		**350**		**354**	-	*no reaction*	-

[a] Yield of pure major diastereomer unless otherwise specified. The yield of the racemic reaction, conducted with (*rac*)-Binap is provided in parentheses. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixture. The diastereomer ratio of the racemic reaction is provided in parentheses. [c] Enantiomeric excess of major diastereomer as determined by chiral HPLC analysis. Absolute stereochemistry not determined. [d] Yield of an inseparable mixture of diastereomers. [e] Reaction conducted with (*R*)-Binap. [f] Enantiomeric excess determined by conversion to compound **355** (*vide infra*).

Table 2.5

Increasing the steric bulk of the ester substituent was also tolerated, exemplified by *bis*-*tert*-butyl ester substrate **347b**, which underwent cyclisation using (*R*)-Binap to afford the corresponding indane derivative in 54% yield, with 90% ee (Entry 5). Unfortunately, malonate-derived cyclisation precursor **350** did not undergo cyclisation, even after prolonged heating (Entry 6). The reduced reactivity of precursor **350** could be a result of unproductive 2-point binding of the catalyst to the dibenzylmalonate moiety.

It should be noted that the enantiomeric excess of *tert*-butyl ester **353b** could not be determined by HPLC analysis due to unresolved enantiomer peaks. Thus, it was necessary to convert this product into methyl ester analogue **355** by hydrolysis, followed by methylation of the *bis*-acid with trimethylsilyldiazomethane to afford **355**, from which the enantiomeric excess was determined to be 90%.



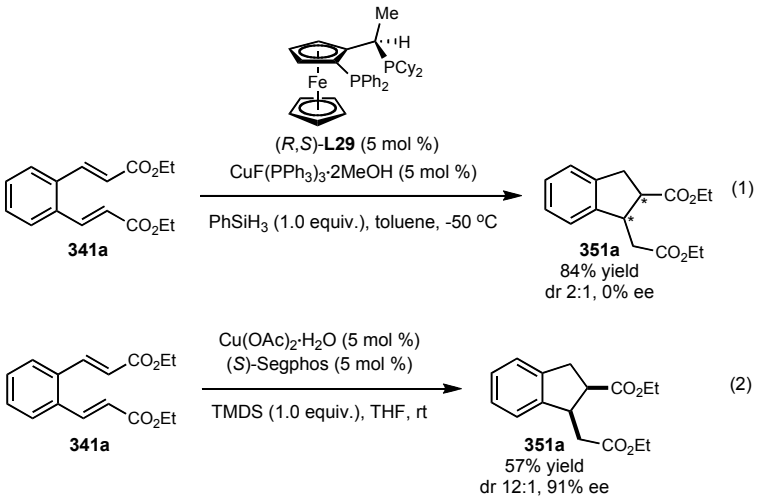
353b **355**, 52% yield, 90% ee

Scheme 2.19

The relative stereochemistry of compounds **351a**, **351b**, **353a** and **353b** was proposed to be *syn* based on nOe experiments carried out on a related compound (compound *cis*-**375**, *see Section 2.2.3.2*). Unfortunately, the absolute configurations of these products could not be determined by X-ray crystallography.

Thus far, reductive Michael cyclisations carried out in the presence of copper acetate, a bisphosphine ligand, and TMDS, have generally resulted in diastereoselective and highly enantioselective formation of 5- and 6-membered rings. Unfortunately, however, the yields of the cyclised products have been moderate, despite high conversions and high mass recovery following reaction work-up with a mild acid. Various attempts to increase the yield, including the addition of ^{t}BuOH to the reaction mixture, or quenching the reaction with strong acid or a fluoride source such as TBAF, had a negligible effect. Furthermore, quenching the reaction with TBAF, as opposed to mild acid, resulted in a significantly lower mass recovery; however, following column chromatography, the yield of the reaction was comparable with those obtained from reactions which had been quenched with mild acid. This conundrum prompted us to reassess our reaction conditions, and revisit the literature in order to find a solution.

Thus, a range of different copper sources, ligands and reductants were screened for activity. In general, it was found that the selectivity (both diastereo- and enantio-) could not compete with that obtained using our previous reaction conditions. Significantly, in the presence of $CuF(PPh_3)_3{\cdot}2MeOH$, and josiphos ligand **L29**, *bis*-enoate **341a** underwent reduction to provide cyclised product **351a** as a *racemic* 2:1 mixture of diastereomers (Scheme 2.20, Eqn 1). However, it is particularly noteworthy that the product was isolated in 84% yield, which is much higher than the yield obtained using our previous conditions (Scheme 2.20, Eqn 1). Subsequent investigations revealed that the high yield is most likely a result of using phenylsilane as the reductant, instead of TMDS. Unfortunately, the use of phenylsilane with copper acetate and (*S*)-Segphos resulted in a complex mixture of unidentified products. Thus, taking into consideration the diastereo- and enantioselectivity of these reactions, our previously reported reaction conditions gave superior results.

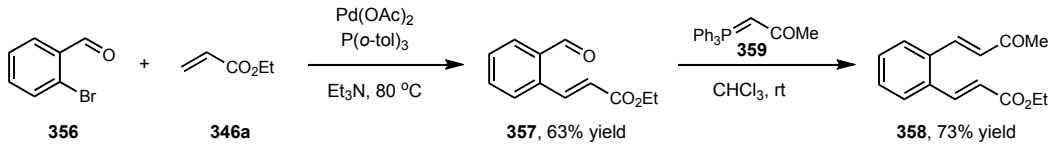


Scheme 2.20

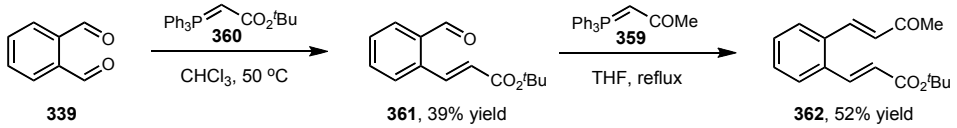
2.2.2.4 Mixed α,β-Unsaturated Ketone and Ester substrates

Unsymmetrical substrates, bearing an α,β-unsaturated methyl ketone tethered to an α,β-unsaturated ester were synthesised in two steps from commercially available starting materials (Scheme 2.21 – Scheme 2.23). Cyclisation precursor **358** was synthesised from 2-bromobenzaldehyde (**356**) by a Heck reaction, followed by a

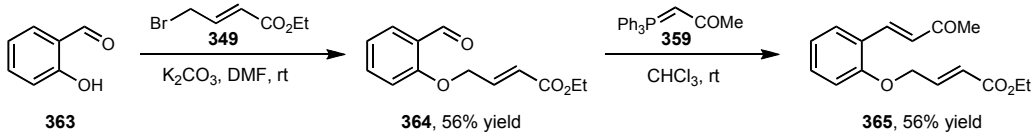
Wittig reaction of intermediate **357** with methyl ketone ylide **359** (Scheme 2.21). In an effort to synthesise a symmetrical *bis*-*tert*-butyl ester substrate, it was discovered that the reaction of phthaldialdehyde (**339**) with *tert*-butyl ester ylide **360** provided mono-adduct **361**, selectively, despite using 2 equivalents of ylide (Scheme 2.22). Subsequent Wittig reaction provided cyclisation precursor **362** in 52% yield. Oxygen-tethered substrate **365** was synthesised from salicaldehyde (**363**) by simple alkylation, followed by a Wittig reaction (Scheme 2.23). Successful cyclisation of this substrate would provide an interesting 6,7-fused ring system.



Scheme 2.21



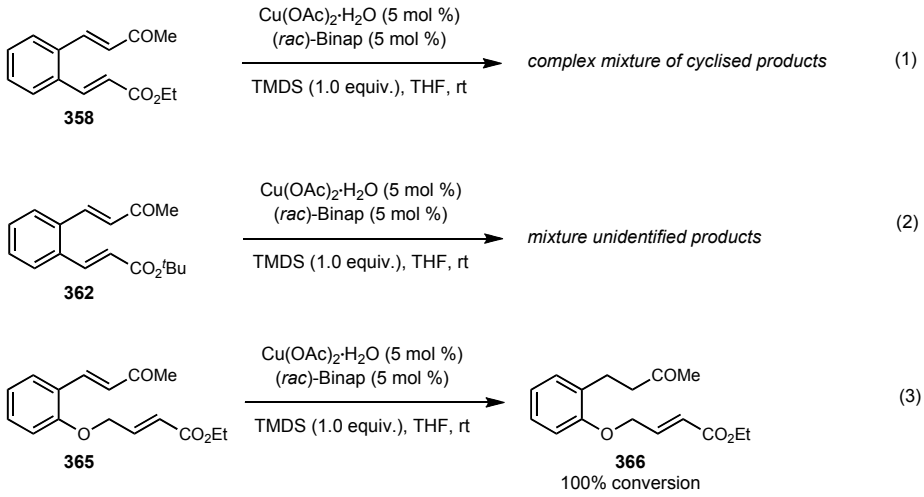
Scheme 2.22



Scheme 2.23

It was anticipated that the electronic difference between an enone and an enoate would be sufficient enough to result in chemoselective cyclisation by conjugate reduction of the more electrophilic α,β-unsaturated ketone component, followed by cyclisation onto the α,β-unsaturated ester. However, in the event, reaction of **358** resulted in an inseparable mixture of products, most likely consisting of mixtures of diastereo- and regioisomers of cyclised products, and reduced substrate that did not undergo cyclisation (Scheme 2.24, Eqn 1). Furthermore, attempted cyclisation of

tert-butyl ester analogue **362** resulted in a complex mixture of unidentified products (Eqn 2). Finally, oxygen-tethered substrate **365** underwent reduction at the α,β-unsaturated ketone but did not cyclise, providing **366** in 100% conversion (Eqn 3).

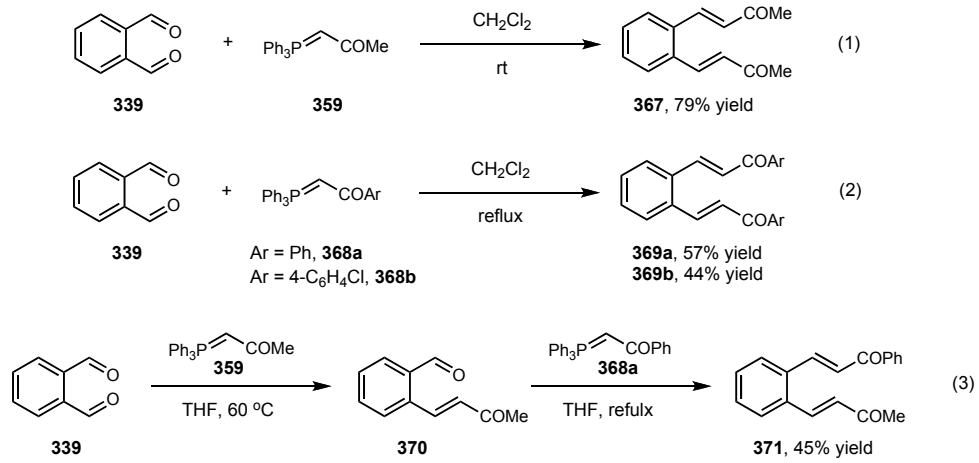


Scheme 2.24

2.2.3 Carbon- and Oxygen-Tethered α,β-Unsaturated Ketone Substrates

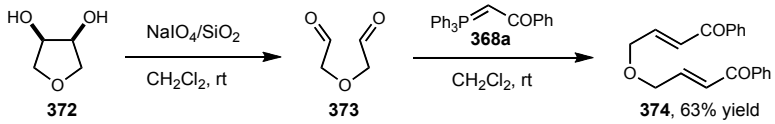
2.2.3.1 Preparation of Cyclisation Precursors

In addition to the α,β-unsaturated ester substrates, a range of α,β-unsaturated ketone cyclisation precursors was also prepared (Scheme 2.25). *Bis*-methyl ketone substrate **367**, and aromatic ketone cyclisation precursors **369a** and **369b** were prepared by Wittig reaction of phthaldialdehyde (**339**) and the appropriate ylide under the same conditions used to prepare the corresponding *bis*-ester precursors. Mixed ketone substrate **371** was prepared in a one-pot procedure, by sequential addition of methyl ketone ylide **359**, followed by phenyl ketone ylide **368a**.



Scheme 2.25

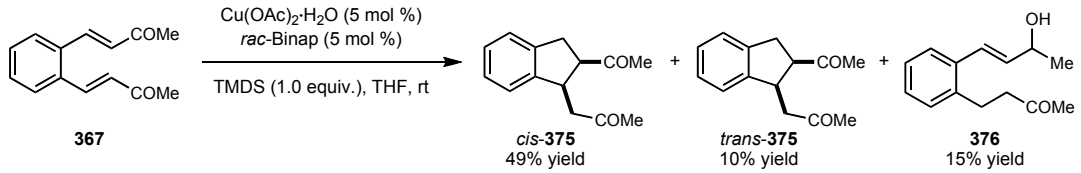
Oxygen-tethered cyclisation precursor **374** was also prepared in a one-pot procedure starting with oxidative cleavage of commercially available *cis*-diol **372** using silica gel-supported $NaIO_4$,[71] followed by addition of phenyl ketone ylide **368a**, to provide diallyl ether **374** in 63% yield (Scheme 2.26).



Scheme 2.26

2.2.3.2 Optimisation and Scope

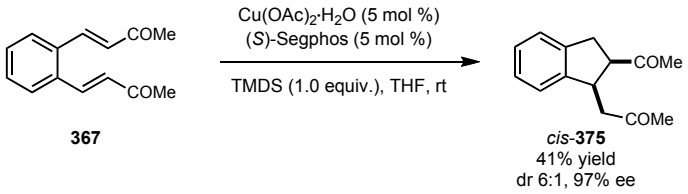
Initially, the *bis*-enone substrates were subjected to the conditions that had proved most successful in effecting the cyclisation of the *bis*-enoate substrates (*see Section 2.2.2.3*). As anticipated, methyl ketone substrate **367** underwent cyclisation to provide *syn*-indane derivative *cis*-**375** as the major diastereomer, in 49% yield and *trans*-**375** as the minor diastereomer in 10% yield (Scheme 2.27). Interestingly, a small amount of compound **376**, resulting from direct reduction of the ketone carbonyl group was also observed in this reaction.



367 | *cis*-**375** 49% yield | *trans*-**375** 10% yield | **376** 15% yield

Scheme 2.27

When the reaction was conducted in the presence of (*S*)-Segphos, as opposed to *rac*-Binap, no 1,2-reduction product was observed and *cis*-**375** was isolated in 41% yield, and 97% ee (Scheme 2.28).



367 | *cis*-**375** 41% yield dr 6:1, 97% ee

Scheme 2.28

The relative stereochemistry of indane *cis*-**375** was determined by nOe experiments conducted on both diastereomers of **375**, which displayed the diagnostic enhancements shown in Figure 2.3. The relative stereochemistries of indanes **351a**, **351b**, **353a** and **353b**, which displayed similar ^{1}H NMR data, were assigned by analogy.

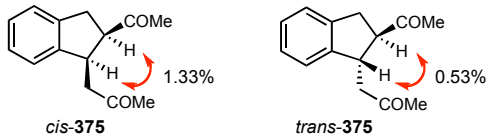
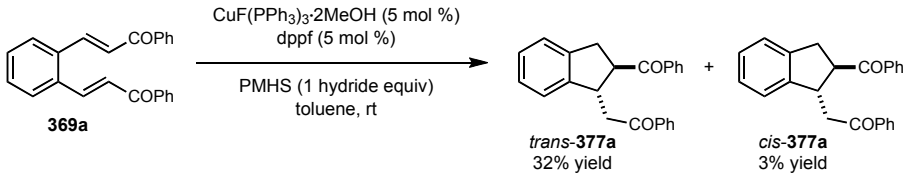


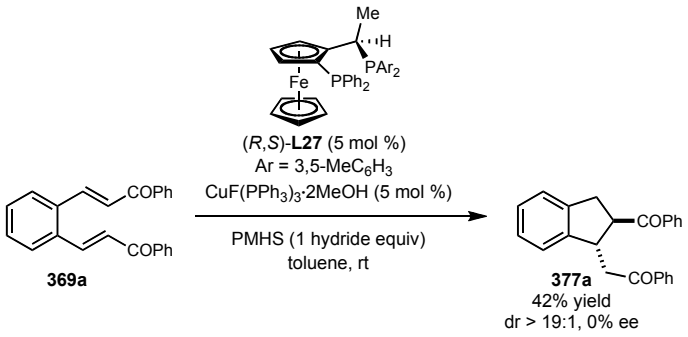
Figure 2.3

Unfortunately, efforts to apply our standard reaction conditions to substrates **369a**, **369b** and **371**, which contain aromatic ketones, were unsuccessful, resulting in complex mixtures of unidentified products. Thus, investigations were undertaken to find workable conditions for these substrates. Following extensive experimentation, it was found that *bis*-enone **369a** underwent cyclisation in the presence of $CuF(PPh_3)_3 \cdot 2MeOH$ and dppf using PMHS (polymethylhydrosiloxane) as the stoichiometric reductant, to afford *trans*-**377a** in 32% yield and *cis*-**377a** in 3% yield (dr > 10:1).



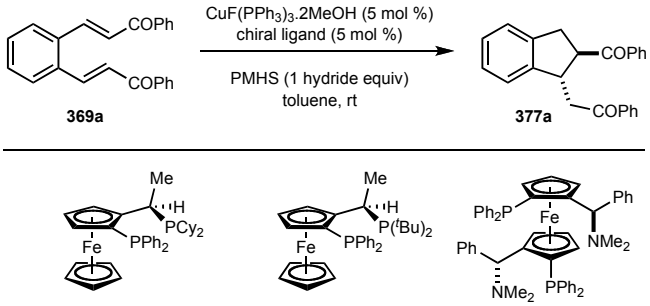
Scheme 2.29

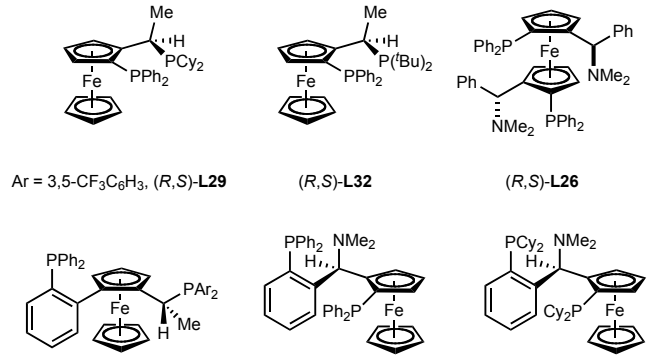
Encouraged by this result, we attempted to render the reaction enantioselective using Josiphos ligand (*R*,*S*)-**L27** (Scheme 2.30). Although this lead to an increase in diastereoselectivity and yield, *trans*-**377a** was isolated as a racemic mixture.



Scheme 2.30

Following this result, we began screening various Josiphos, Mandyphos and Taniaphos ligands, and found that Taniaphos ligand (*R*,*R*)-**L21** gave superior levels of enantioselection (Table 2.6).



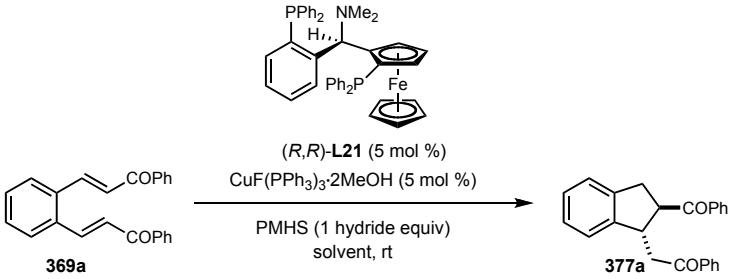


Entry	Ligand	ee (%)[a]
1	**L29**	10 (+)
2	**L32**	6 (–)
3	**L26**	32 (+)
4	**L23**	6 (–)
5	**L21**	44 (–)
6	**L20**	0

[a] Determined by chiral HPLC analysis of the unpurified reaction mixture. Enantiomeric excess of major diastereomer. Diastereomeric ratio > 10:1 in all cases. The absolute stereochemistry of **377a** was not determined. The sign of optical rotation is provided in parentheses.

Table 2.6

With the ligand in hand, the effect of different solvents and solvent mixtures on the enantioselectivity was investigated (Table 2.7). Conducting the reaction in toluene at -25 ^{o}C afforded the highest enantiomeric excess (Entry 1). However, in this case, conversion was only 40%, possibly owing to the low solubility of **369a** in toluene. Although carrying out the reaction in mixtures of THF and toluene increased conversion, a significant decrease in enantioselectivity was observed (Entries 2 and 3). The use of acetonitrile appeared to inhibit the reaction (Entry 4), whereas the use of dichloromethane led to a complete loss in enantiocontrol (Entry 5). Ultimately, it was discovered that conducting the reaction in toluene at 0 ^{o}C provided a reasonable compromise between enantioselectivity and conversion (Entry 6).

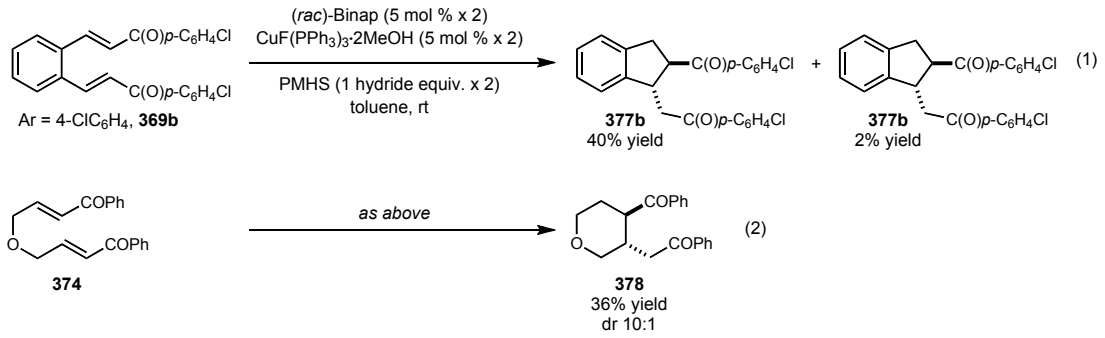


Entry	Solvent	Temperature (^{o}C)	Conversion (%)[a]	ee (%)[b]
1	toluene	-25	40	90
2	toluene/THF (1:1)	-25	80	60
3	toluene/THF (1:2)	-25	100	60
4	tolueneCH_3CN (1:1)	-10	0	-
5	toluene/CH_2Cl_2 (1:2)	-10	67	0
6	toluene	0	70	77

[a] Determined by ^{1}H NMR anaylsis of the unpurified reaction mixture. [b] Determined by chiral HPLC analysis of the unpurified reaction mixture.

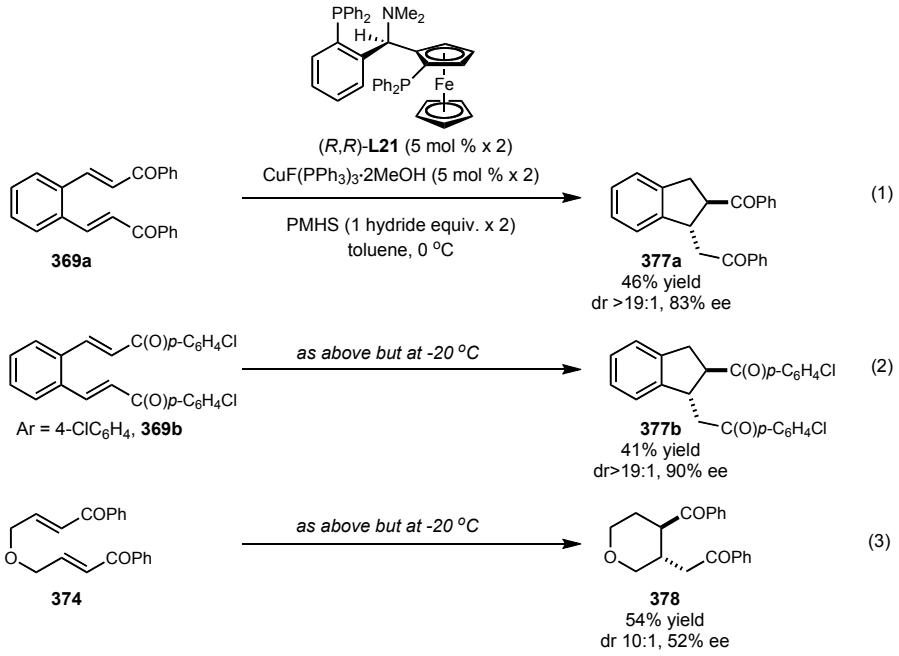
Table 2.7

With the optimised conditions in hand, the reductive Michael cyclisations of aromatic ketones **369a**, **369b** and **374** were carried out. The racemic cyclisations of substrates **369b** and **374** proceeded smoothly at room temperature to provide the corresponding products in good yield, with excellent diastereoselectivity (Scheme 2.31). To ensure high conversions, reactions were carried out using 5 mol % catalyst and ligand, with 1 equivalent of PMHS, and then stirred overnight, followed by addition of a further 5 mol % catalyst and ligand, and 1 equivalent of PMHS, and allowed to stir overnight.



Scheme 2.31

The corresponding enantioselective cyclisations were carried out using (*R*,*R*)-**L21**, at reduced temperature in order to ensure high enantioselectivity (Scheme 2.32). *Bis*-phenyl ketone **369a** underwent cyclisation to afford indane derivative *trans*-**377a** as the anti-diastereomer in 46% yield and 93% ee. Substrate **369b**, containing *para*-chlorophenyl ketones, was found to be more soluble in toluene than **369a**, allowing the reaction to be conducted at a lower temperature, and giving rise to increased enantiocontrol. Thus, the cyclised product was isolated in 41% yield and 90% ee. Finally, oxygen-tethered cyclisation precursor **374** also underwent reaction to provide tetrahydropyran **378** in 54% yield, albeit with somewhat lower enantioselectivity.



Scheme 2.32

The relative and absolute stereochemistry of indane **377b** was determined by X-ray crystallography (Figure 2.4) and the absolute stereochemistry of **377a** was assigned by analogy. The relative stereochemistry of tetrahydropyran **374** was assigned on the basis of comparison with literature ^{1}H NMR spectroscopic data.[64]

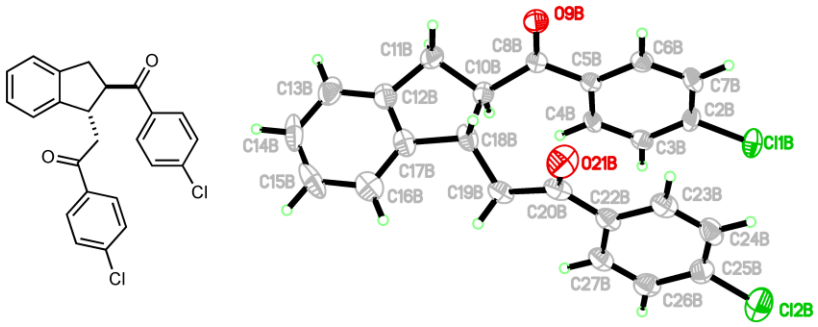
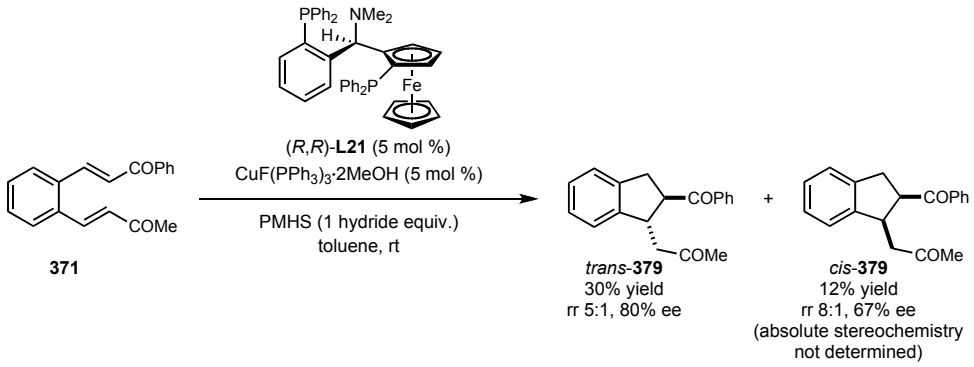


Figure 2.4

The chemoselectivity of this reaction was also evaluated, with the cyclisation of unsymmetrical ketone precursor **371**. In the event, **371** underwent cyclisation to afford two diastereomeric products, *trans*-**379** and *cis*-**379**, in 80% ee and 67% ee, respectively. Both products were isolated as an inseparable mixture of regioisomers,

and through the use of various 2D NMR techniques (HMBC, HSQC, COSY) it was revealed that the major regioisomer arises from conjugate addition to the phenyl-substituted enone, followed by cyclisation onto the methyl-substituted enone. Furthermore, this substrate did not require batchwise addition of catalyst, ligand and PMHS, as the reaction was found to be complete after stirring overnight with 5 mol % catalyst, and ligand and 1 equivalent of PMHS.



Scheme 2.33

The relative stereochemistries of indanes *cis*-**379** and *trans*-**379** were assigned on the basis of nOe experiments, which displayed the diagnostic enhancements shown in Figure 2.5. The absolute stereochemistry of *trans*-**379** was assigned by analogy to indane **377b**, whose stereochemistry was determined by X-ray crystallography (*vide supra*).

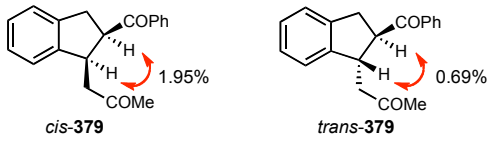
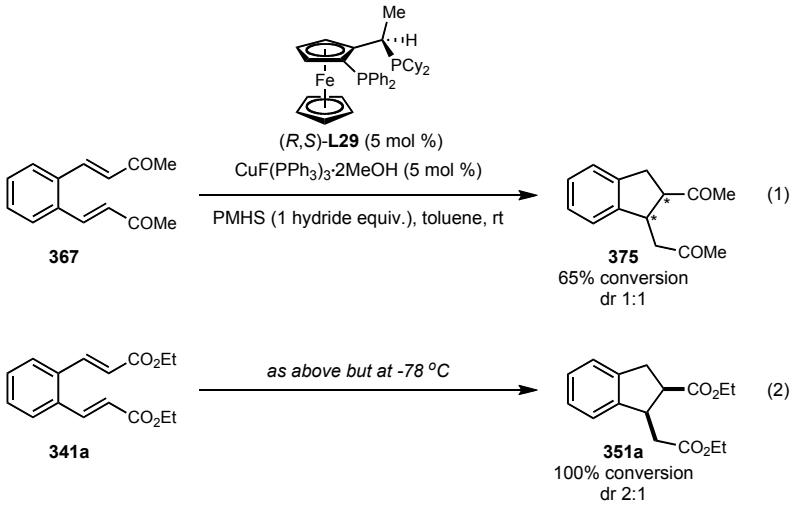


Figure 2.5

Interestingly, the diastereochemical outcome of these reactions is opposite to that obtained upon cyclisation of α,*β*-unsaturated ester substrates, and *bis*-methyl ketone substrate **367**, in the presence of $Cu(OAc)_2 \cdot H_2O$, (*S*)-Segphos, and TMDS. Thus, it was of interest to evaluate the cyclisation of these substrates in the presence of

$CuF(PPh_3)_3{\cdot}2MeOH$, a Josiphos ligand and PMHS in order to establish whether the diastereochemical outcome is dependent on the substrate, or the reaction conditions (Scheme 2.34). In the event, *bis*-methyl ketone **367** underwent cyclisation to afford indane **375** as a 1:1 mixture of diastereomers and *bis*-ethyl ester **341a** provided *syn*-indane **351a**. However, the diastereoselectivity was significantly lower than that obtained using the previously reported conditions.



Scheme 2.34

On the basis of these results, it is possible that in each case, the reaction proceeds *via* two different transition states, giving rise to either *syn*- or *anti*-diastereoselectivity, depending on which substrate and/or conditions are used. Although one might assume that the reaction proceeds *via* the *Z*-enolate, the possibility that the reaction proceeds *via* an *E*-enolate cannot be ruled out. Furthermore, the nature of the copper enolate gives rise to further ambiguity; it is not known whether the reaction proceeds *via* an oxygen- (**380**) or carbon-bound copper enolate (**381**), or an intermediate oxo-π-allyl species (**382**) (Figure 2.6).

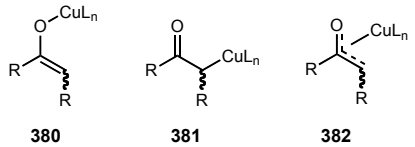


Figure 2.6

In addition, the tendency for aromatic ketones to react differently to aliphatic ketones and esters suggests that π-π stacking interactions might also be significant. Thus, further investigation is required before it will be possible to determine the exact mechanism of this reaction. Nevertheless, it is possible to identify four possible transition states, **A-D** (Figure 2.7) in which the copper is within close proximity of both carbonyl groups to allow 2-point binding to occur. These transition states could potentially give rise to either *syn* or *anti*-products, depending on (1) the conformation of the α,*β*-unsaturated carbonyl component (s-*cis* vs. s-*trans*) and (2) the stereochemistry of the copper enolate (*E* vs. *Z*).

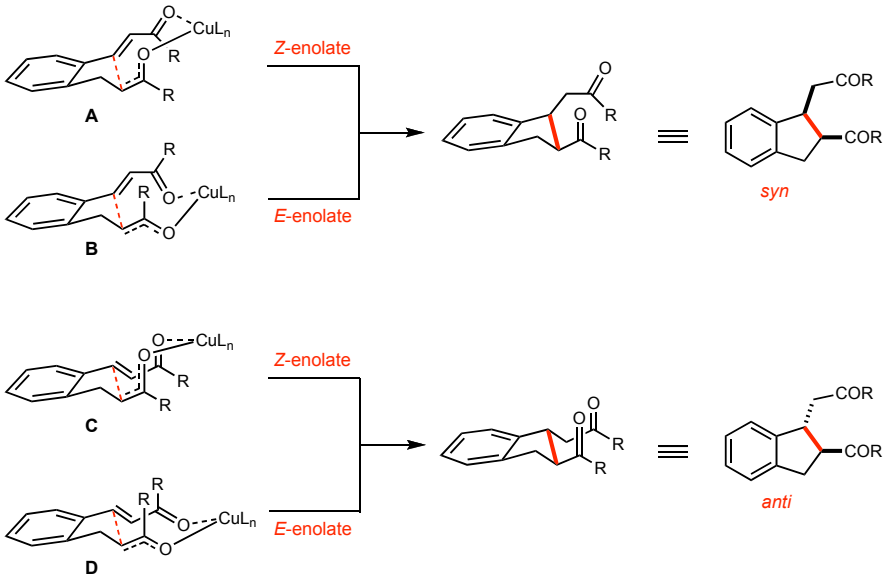
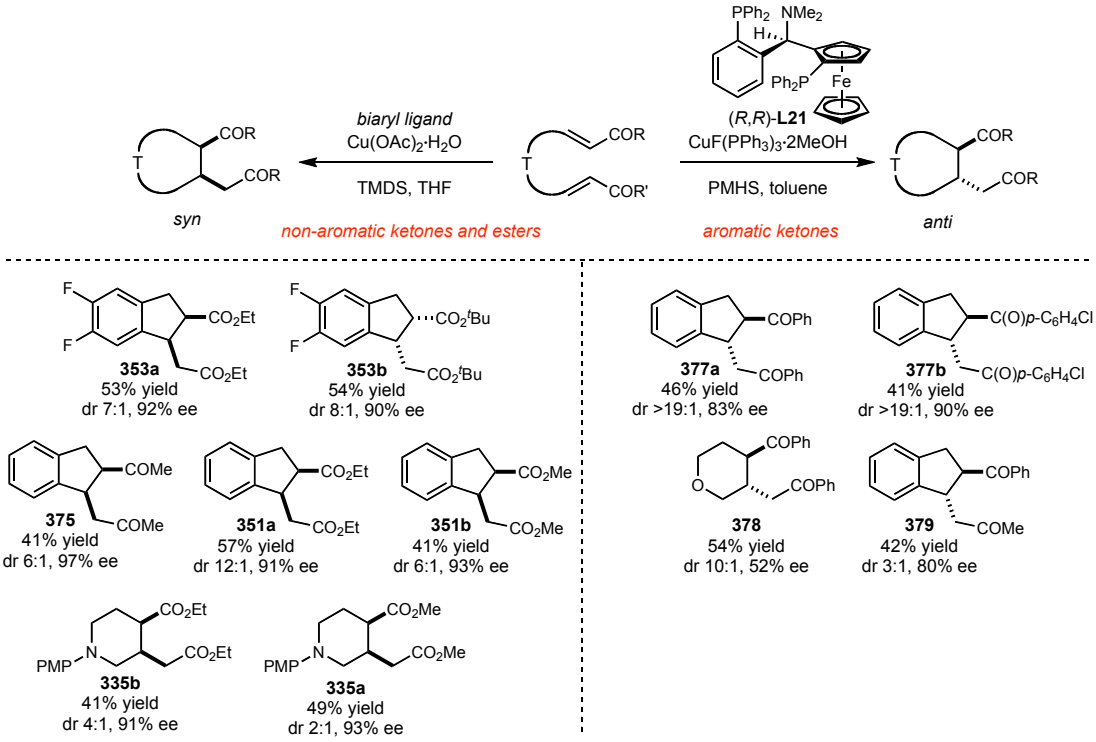


Figure 2.7

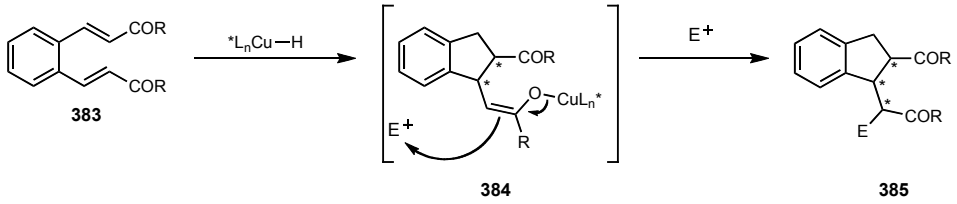
2.3 Conclusions and Future Work

Herein, enantioselective copper-catalysed reductive Michael cyclisations of a range of different cyclisation precursors has been reported. To our knowledge, this represents the first example of an asymmetric metal-catalysed reductive Michael reaction. A range of structurally and electronically diverse cyclisation precursors were prepared by various different methods. Substrates containing both α,β-unsaturated ketones and esters underwent cyclisation, to afford 5- and 6- membered ring carbocyclic and heterocyclic products, with good-to-excellent levels of diastereo- and enantiocontrol (Scheme 2.35). Substrates containing α,β-unsaturated esters and non-aromatic ketones underwent cyclisation to provide enantiomerically enriched *syn*-indane derivatives. In contrast, cyclisation precursors containing aromatic ketones provided *anti*-indane derivatives. Furthermore, heteroatom-tethered precursors **327b** and **374** underwent cyclisation to afford synthetically useful enantioenriched heterocycles, **335b** and **378**.



Scheme 2.35

A possible extension of this work could include a cascade reaction, in which a *bis*-α,β-unsaturated carbonyl compound **383** undergoes intramolecular Michael reaction, to provide copper enolate **384**. In the presence of a suitable electrophile, enolate **384** could undergo asymmetric intermolecular trapping to provide **385**, which contains 3 contiguous stereocentres.



383 **384** **385**

Scheme 2.36

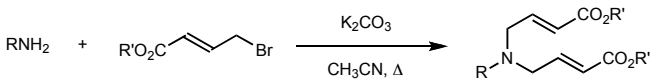
2.4 Experimental

2.4.1 General Information

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. Toluene and THF were dried and purified by passage through activated alumina columns using a solvent purification system from http://www.glasscontoursolventsystems.com. All commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.[72] Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in $CHCl_3$. ^1H NMR spectra were recorded on a Burker AVA600 (600 MHz) spectrometer, a Bruker DMX500 (500 MHz) spectrometer, a Bruker DPX360 (360 MHz) spectrometer or a Bruker ARX250 (250 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker AVA600 (600 MHz, 150.9) spectrometer, a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer or a Finnigan MAT 95XP spectrometer at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea, or on a Finnigan MAT 900 XLT spectrometer or a Kratos MS50TC spectrometer at the School of Chemistry, University of Edinburgh. Chiral HPLC analysis was performed on an Agilent 1100 instrument. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter.

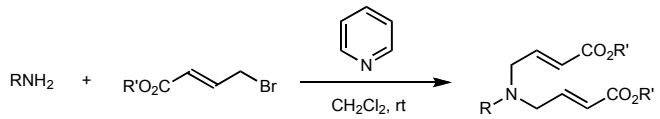
2.4.2 Preparation of Cyclisation Precursors

General Procedure A: Synthesis of Nitrogen-Tethered Cyclisation Precursors

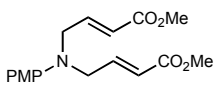


To a solution of K_2CO_3 (6.91 g, 50.0 mmol) and the appropriate amine (10.0 mmol, 1 equiv.) in CH_3CN (30 mL) at reflux was added the appropriate alkyl-4-bromocrotonate (22.0 mmol, 2.2 equiv.). The reaction mixture was stirred at reflux for 20 h before it was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with Et_2O (2 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography gave the cyclisation precursor.

General Procedure B: Synthesis of Nitrogen-Tethered Cyclisation Precursors



To a solution of the appropriate amine (5.0 mmol, 1 equiv.) in CH_2Cl_2 (20 mL) was added pyridine (0.80 mL, 10.0 mmol), followed by ethyl 4-bromocrotonate (2.02 mL, 11.0 mmol). The reaction mixture was stirred for 16 h at room temperature before it was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by column chromatography gave the cyclisation precursor.

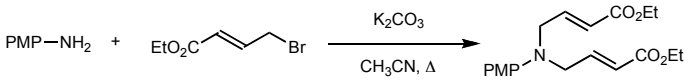


(2*E*,2'*E*)-dimethyl-4,4'-(4-methoxyphenylazanediyl)dibut-2-enoate (327a)

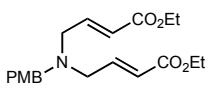
The title compound was prepared according to General Procedure A from 4-anisidine (1.23 g, 10.0 mmol) and methyl 4-bromocrotonate (2.59 mL, 22.0 mmol), and purified by column chromatography (10% EtOAc/hexane→30% EtOAc/hexane) to give the *diallylamine* **327a** (1.47 g, 46%) as a solid. R_f = 0.23 (25% EtOAc/hexanes);

m.p. 66-68 °C. IR ($CHCl_3$) 2950, 2834, 1723 (C=O), 1654, 1513, 1436, 1275, 1241, 1168, 1035 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.96 (2H, dt, *J* = 15.7, 4.6 Hz, 2 x C**H**=CHC=O), 6.80 (2H, d, *J* = 9.1 Hz, Ar**H**), 6.60 (2H, d, *J* = 9.1 Hz, Ar**H**), 5.95 (2H, dt, *J* = 15.7, 1.9 Hz, 2 x C**H**C=O), 4.01 (4H, dd, *J* = 4.6, 1.9 Hz, 2 x NC**H**$_2$), 3.75 (3H, s, OC**H**$_3$), 3.72 (6H, s, 2 x CO_2C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.4 (2 x C), 152.3 (C), 144.6 (2 x CH), 141.9 (C), 121.8 (2 x CH), 114.8 (2 x CH), 114.4 (2 x CH), 55.6 (CH_3), 52.3 (2 x CH_2), 51.5 (2 x CH_3); HRMS (EI) Exact mass calcd for $C_{17}H_{21}NO_5$ $[M]^+$: 319.1414, found: 319.1414.

(2*E*,2'*E*)-Diethyl 4,4'-(4-methoxyphenylazanediyl)dibut-2-enoate (327b)

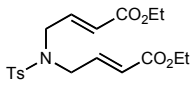


To a solution of K_2CO_3 (10.36 g, 75.0 mmol) and 4-anisidine (3.69 g, 30.0 mmol) in CH_3CN (300 mL) at reflux was added ethyl-4-bromocrotonate (11.9 mL, 66.0 mmol). The reaction mixture was stirred at reflux for 20 h, cooled to room temperature, quenched with saturated aqueous NH_4Cl (100 mL), and extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane→30% EtOAc/hexane) gave the *diallylamine* **327b** (7.90 g, 79%) as an oil. R_f = 0.40 (25% EtOAc/hexanes); IR (film) 2982, 2937, 2904, 2833, 1716 (C=O), 1657, 1515, 1464, 1368, 1273 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.95 (2H, dt, *J* = 15.7, 4.5 Hz, 2 x C**H**=CHC=O), 6.80 (2H, dm, *J* = 9.1 Hz, Ar**H**), 6.60 (2H, dm, *J* = 9.1 Hz, Ar**H**), 5.93 (2H, dt, *J* = 15.7, 1.9 Hz, 2 x C**H**C=O), 4.18 (4H, q, *J* = 7.1 Hz, 2 x OC**H**$_2$CH$_3$), 4.01 (4H, dd, *J* = 4.5, 1.9 Hz, 2 x NC**H**$_2$), 3.74 (3H, s, OC**H**$_3$), 1.27 (6H, t, *J* = 7.1 Hz, 2 x OCH_2C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.0 (2 x C), 152.2 (C), 144.3 (2 x CH), 142.0 (C), 122.2 (2 x CH), 114.8 (2 x CH), 114.2 (2 x CH), 60.4 (2 x CH_2), 55.6 (CH_3), 52.3 (2 x CH_2), 14.1 (2 x CH_3); HRMS (EI) Exact mass calcd for $C_{19}H_{25}NO_5$ $[M]^+$: 347.1727, found: 347.1729.



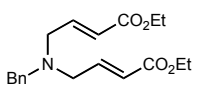
(*E*)-4-(*E*)-3-Ethoxycarbonylallyl-4-methoxybenzylaminobut-2-enoic acid ethyl ester (327c)

The title compound was prepared according to General Procedure B from 4-methoxybenzylamine (645 µl, 5.00 mmol) and purified by column chromatography (10% Et_2O/hexane→30% Et_2O/hexane) gave the *diallylamine* **327c** (790 mg, 44%) as an oil. R_f = 0.37 (25% EtOAc/hexanes); IR (film) 2981, 2936, 2905, 2834, 2816, 1729, 1716 (C=O), 1657, 1611, 1512 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.22 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.93 (2H, dt, *J* = 15.7, 5.8 Hz, 2 x C**H**=CHC=O), 6.84 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.02 (2H, dt, *J* = 15.7, 1.6 Hz, 2 x C**H**C=O), 4.18 (4H, q, *J* = 7.1 Hz, 2 x OC**H**$_2$CH$_3$), 3.78 (3H, s, OC**H**$_3$), 3.53 (2H, s, C**H**$_2$Ph), 3.18 (4H, dd, *J* = 5.8, 1.6 Hz, 2 x NC**H**$_2$), 1.28 (6H, t, *J* = 7.1 Hz, 2 x OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.1 (2 x C), 158.8 (C), 145.6 (2 x CH), 130.1 (C), 129.7 (2 x CH), 122.9 (2 x CH), 113.7 (2 x CH), 60.2 (2 x CH_2), 57.7 (CH_2), 55.1 (CH_3), 54.3 (2 x CH_2), 14.1 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{28}NO_5$ $[M+H]^+$: 362.1962, found: 362.1961.



(*E*)-4-[((*E*)-3-Ethoxycarbonylallyltoluene-4-sulfonyl)-amino]but-2-enoic acid ethyl ester (327d)

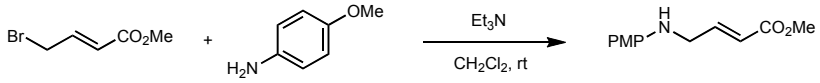
The title compound was prepared according to General Procedure A from *p*-toluene sulfonamide (1.71 g, 10.0 mmol) and ethyl 4-bromocrotonate (3.96 mL, 22.0 mmol), and purified by column chromatography (20% EtOAc/hexane→50% EtOAc/hexane), followed by recrystallisation from CH_2Cl_2/hexane to give the *diallylamine* **327d** (1.04 g, 53%) as a white solid. R_f = 0.14 (25% EtOAc/hexanes); m.p. 78-80 ^oC; IR ($CHCl_3$) 2983, 2925, 1717 (C=O), 1662, 1598, 1447, 1342, 1304, 1276, 1161, 1096, 1037 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.73 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.35 (2H, d, *J* = 8.3 Hz, Ar**H**), 6.69 (2H, dt, *J* = 15.7, 5.9 Hz, 2 x C**H**=CHC=O), 5.90 (2H, dt, *J* = 15.7, 1.4 Hz, 2 x C**H**C=O), 4.20 (4H, q, *J* = 7.1 Hz, 2 x OC**H**$_2$CH$_3$), 3.97 (4H, dd, *J* = 5.9, 1.4 Hz, 2 x NC**H**$_2$), 2.46 (3H, s, ArC**H**$_3$), 1.30 (6H, t, *J* = 7.1 Hz, 2 x OCH$_2$C**H**$_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 165.3 (2 x C), 143.9 (C), 141.3 (2 x CH), 136.3 (C), 129.8 (2 x CH), 127.1 (2 x CH), 124.4 (2 x CH), 60.5 (2 x CH_2), 48.0 (2 x CH_2), 21.4 (CH_3), 14.0 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{29}N_2O_6S$ $[M+NH_4]^+$: 413.1741, found: 413.1740.



(*E*)-4-Benzyl-(*E*)-3-ethoxycarbonylallylaminobut-2-enoic acid ethyl ester (327e)

The title compound was prepared according to General Procedure B from benzylamine (545 µl, 5.00 mmol) and purified by column chromatography (10% Et_2O/hexane→30% Et_2O/hexane) gave the *diallylamine* **327e** (655 mg, 41%) as an oil. R_f = 0.57 (25% EtOAc/hexanes); IR (film) 2981, 2937, 2905, 2805, 1717, 1657 (C=O), 1454, 1368, 1302, 1270 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.35-7.26 (5H, m, Ar**H**), 6.97 (2H, dt, *J* = 15.7, 5.8 Hz, 2 x C**H**=CHC=O), 6.06 (2H, dt, *J* = 15.7, 1.7 Hz, 2 x C**H**C=O), 4.21 (4H, q, *J* = 7.1 Hz, 2 x OC**H**$_2$CH$_3$), 3.63 (2H, s, C**H**$_2$Ph), 3.24 (4H, dd, *J* = 5.8, 1.7 Hz, 2 x NC**H**$_2$), 1.31 (6H, t, *J* = 7.1 Hz, 2 x OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.0 (2 x C), 145.4 (2 x CH), 138.2 (C), 128.5 (2 x CH), 128.3 (2 x CH), 127.2 (CH), 123.0 (2 x CH), 60.3 (2 x CH_2), 58.3 (CH_2), 54.4 (2 x CH_2), 14.1 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{26}NO_4$ $[M+H]^+$: 332.1856, found: 332.1856.

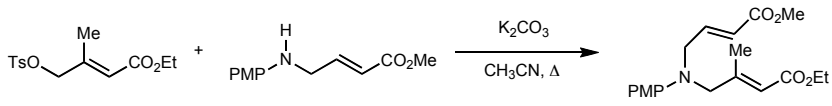
(*E*)-4-(4-Methoxyphenylamino)but-2-enoic acid ethyl ester (330)



To a solution of 4-anisidine (1.23 g, 10.0 mmol) in CH_2Cl_2 (50 ml) was added triethylamine (6.97 mL, 50.0 mmol), followed by methyl-4-bromo-crotonate (1.17 mL, 10.0 mmol). The reaction was stirred at room temperature for 20 h before it was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (10% EtOAc/hexane→30% EtOAc/hexane) to give *mono-allylamine* **330** (0.58 g, 55%) as an oil. R_f = 0.26 (25% EtOAc/hexanes); IR (film) 2951, 2835, 1718 (C=O), 1684, 1512, 1437, 1362, 1245, 1168, 1172 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.05 (1H, dt, *J* = 15.7, 4.7 Hz, C**H**=CHC=O), 6.79 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.57 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.06 (1H, dt, *J* = 15.7, 2.0 Hz, C**H**C=O), 3.90 (2H, dd, *J* = 4.7, 2.0 Hz, NC**H**$_2$), 3.76 (3H, s, OC**H**$_3$), 3.74 (3H, s, CO_2C**H**$_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.6 (C), 152.2 (C), 146.1 (CH), 141.3

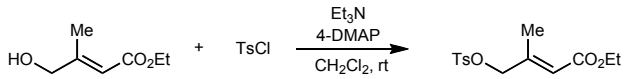
(C), 121.1 (CH), 114.7 (2 x CH), 114.0 (2 x CH), 55.5 (CH_3), 51.3 (CH_3), 45.5 (CH_2).

(*E*)-4-[(*E*)-3-Methoxycarbonylallyl-(4-methoxyphenyl)amino]-3-methylbut-2-enoic acid ethyl ester (331)



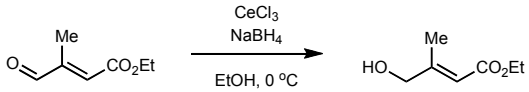
To a solution of K_2CO_3 (248.8 mg, 1.80 mmol) and (*E*)-4-(4-methoxyphenylamino)but-2-enoic acid ethyl ester (**330**) (315.5 mg, 1.50 mmol) in CH_3CN (5 mL) at reflux was added (*E*)-3-methyl-4-(toluene-4-sulfonyloxy)but-2-enoic acid ethyl ester (**334**) (248.8 mg, 1.8 mmol) in CH_3CN (2.5 mL) *via* cannula. The reaction mixture was allowed to stir at reflux for 20 h before it was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with diethyl ether (2 x 5 mL). The combined organic layers were washed with brine (2 x 5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane→30% EtOAc/hexane) gave cyclisation precursor **331** as an orange solid (350.1 mg, 67%). R_f = 0.26 (25% EtOAc/hexanes); m.p. 75-77 ^oC; IR ($CHCl_3$) 2954, 2890, 1973, 1722 (C=O), 1666, 1598, 1446, 1401, 1367, 1172 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.94 (1H, dt, *J* = 15.7, 4.4 Hz, C**H**=CHCO$_2$CH$_3$), 6.78 (2H, d, *J* = 9.2 Hz, Ar**H**), 6.53 (1H, d, *J* = 9.2 Hz, Ar**H**), 5.90 (1H, dt, *J* = 15.7, 1.9 Hz, C**H**CO$_2$CH$_3$), 5.77 (1H, q, *J* = 1.4 Hz, C**H**CO$_2$CH$_2$CH$_3$), 4.12 (2H, q, *J* = 7.1 Hz C**H**$_2$CH$_3$), 4.02 (1H, dd, *J* = 4.4, 1.9 Hz, C=CHC**H**$_2$N), 3.83 (2H, br s, C=C(CH$_3$)C**H**$_2$N), 3.72 (3H, s, OC**H**$_3$), 3.70 (1H, s, CO$_2$C**H**$_3$), 2.13 (3H, d, *J* = 1.4 Hz, C=CC**H**$_3$), 1.24 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.6 (C), 166.5 (C), 154.4 (C), 152.1 (C), 144.4 (CH), 142.1 (C), 121.9 (CH), 114.8 (3 x CH), 113.7 (2 x CH), 59.7 (CH_2), 58.9 (CH_2), 55.7 (CH_3), 51.9 (CH_2), 51.5 (CH_3), 16.5 (CH_3), 14.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{26}NO_5$ $[M+H]^+$: 348.1805, found: 348.1802.

(*E*)-3-Methyl-4-(toluene-4-sulfonyloxy)but-2-enoic acid ethyl ester (332)



To a solution of (*E*)-4-Hydroxy-3-methylbut-2-enoic acid ethyl ester (**334**) (1.44 g, 10.0 mmol) and Et_3N (2.09 mL, 15.0 mmol) in CH_2Cl_2 (200 mL) at 0 ^oC was added tosyl chloride (2.29 g, 12.0 mmol), followed by 4-dimethylaminopyridine (0.12 g, 1.00 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 20 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude mixture by column chromatography (10% EtOAc/hexane→30% EtOAc/hexane) gave **332** as a colourless oil (2.44 g, 81%). R_f = 0.67 (25% EtOAc/hexanes); IR (film) 2982, 2930, 1923, 1717, 1666, 1598, 1446, 1400, 1367, 1172 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.33 (2H, d, *J* = 8.5 Hz, Ar**H**), 5.84 (1H, m, C=C**H**), 4.45 (2H, m, OC**H**$_2$), 4.12 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 2.42 (3H, s, ArC**H**$_3$), 2.03 (3H, m, C=CC**H**$_3$), 1.24 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 165.5 (C), 148.5 (C), 145.0 (C), 132.4 (C), 129.8 (2 x CH), 127.7 (2 x CH), 117.5 (CH), 72.3 (CH_2), 59.8 (CH_2), 21.4 (CH_3), 15.1 (CH_3), 13.9 (CH_3).

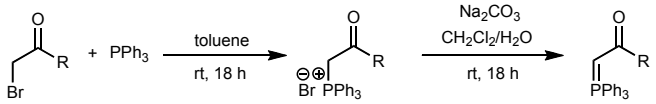
(*E*)-4-Hydroxy-3-methylbut-2-enoic acid ethyl ester[73] (334)



$CeCl_3$ (7.80 g, 21.0 mmol) was added in one portion to a stirred solution of ethyl-3-methyl-4-oxocrotonate (2.84 g, 20.0 mmol) in EtOH (315 mL) at 0 ^oC. After 10 mins, $NaBH_4$ (0.90 g, 24.0 mmol) was added in small portions over 5 mins. The mixture was allowed to warm to room temperature and stir for 17 h, before it was quenched with saturated aqueous NH_4Cl (100 mL). The EtOH was removed *in vacuo* and the remaining residue was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with brine (2 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give acohol **334** a pale yellow oil (2.87 g, 100%), which was used

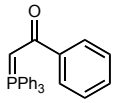
without further purification and displayed spectral data consistent with those described previously.[73]

General Procedure C: Preparation of Phosphonium Ylides

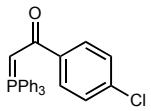


A solution of the appropriate 2-bromoketone (20.0 mmol) in toluene (15 mL) was added dropwise over 10 min to a solution of triphenylphosphine (5.25 g, 20.0 mmol) in toluene (15 mL). The reaction mixture was stirred at room temperature for 18 h, and the resulting phosphonium salt was filtered and oven-dried. The phosphonium salt was obtained in quantitative yield, and was used without further purification.

Na_2CO_3 (3.18 g, 30.0 mmol) was added to a suspension of the phosphonium salt (20.0 mmol) in H_2O (60 mL) and CH_2Cl_2 (60 mL). The mixture was stirred at room temperature for 18 h and then transferred to a separating funnel. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to leave the ylide, which was used without further purification.

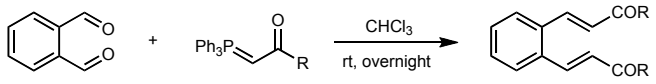


(Phenylacylidene)triphenylphosphorane (368a).[74] The title compound was prepared according to General Procedure A from 2-bromoacetophenone (3.98 g, 20.0 mmol) and the resultant ylide (6.11 g, 80%) displayed spectral data consistent with those described previously.[74]



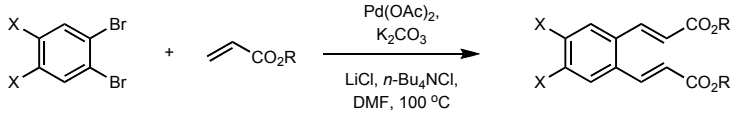
1-(4-Chlorophenyl)-2-(triphenylphosphanylidene)ethanone (368b).[75] The title compound was prepared according to General Procedure A from 2-bromo-4′-chloroacetophenone (4.67 g, 20.0 mmol) and the resultant ylide (9.20 g, 74%) displayed spectral data consistent with those described previously.[75]

General Procedure D: Wittig Reactions

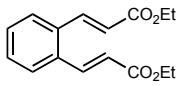


To a solution of phthaldialdehyde (670 mg, 5.00 mmol) in $CHCl_3$ (60 mL) was added the appropriate ylide (12.5 mmol). The mixture was stirred at room temperature for 16 h and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclization precursor.

General Procedure E: Heck Reactions

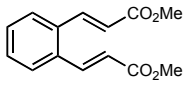


To a suspension of $Pd(OAc)_2$ (90 mg, 0.40 mmol), *n*-Bu_4NCl (1.14 g, 5.00 mmol), K_2CO_3 (3.45 g, 25.0 mmol), and LiCl (212 mg, 5.00 mmol) in DMF (25 mL) was added 1,2-dibromo-4,5-difluorobenzene (1.36 g, 5.00 mmol) and the appropriate alkyl acrylate (25.0 mmol). The mixture was stirred at 100 °C for 18 h, cooled to room temperature, diluted with Et_2O (25 mL), and washed with H_2O (50 mL). The aqueous layer was extracted with Et_2O (2 x 50 mL), and the combined organic layers were washed with brine (2 x 100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by column chromatography gave the cyclization precursor.



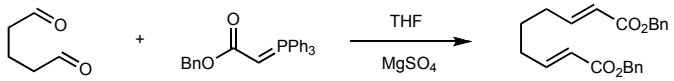
(*E*)-3-[2-{(*E*)-2-Ethoxycarbonylvinyl}phenyl]acrylic acid ethyl ester (341a).[76] The title compound was prepared according to General Procedure D from ethyl (triphenylphosphoranylidene)acetate (4.35 g, 12.5 mmol) and purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) followed by recrystallization from CH_2Cl_2/hexane to give **341a** as a white solid (1.15 g, 84%), which displayed spectral data consistent with those described previously.[76] R_f = 0.50 (25% EtOAc/hexanes); m.p. 73-75 °C; IR ($CHCl_3$) 3063, 2986, 2942, 2906, 1710 (C=O), 1702 (C=O), 1477, 1363, 1309, 1184 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.03 (2H, d, *J* = 15.8 Hz, 2 x C**H**=CHC=O), 7.58-7.56 (2H, m, Ar**H**), 7.41-7.38 (2H, m, Ar**H**), 6.35 (2H, d, *J* = 15.8 Hz, 2 x C**H**C=O), 4.28 (4H, q, *J* = 7.1 Hz, 2 x OC**H**$_2$CH$_3$), 1.35 (6H, t, *J* = 7.1 Hz, 2 x OCH$_2$C**H**$_3$); ^{13}C NMR

(62.9 MHz, $CDCl_3$) δ 166.4 (2 x C), 141.2 (2 x CH), 134.3 (2 x C), 129.9 (2 x CH), 127.6 (2 x CH), 121.9 (2 x CH), 60.7 (2 x CH_2), 14.3 (2 x CH_3); HRMS (EI) Exact mass calcd for $C_{16}H_{18}O_4$ $[M]^+$: 274.1200, found: 274.1200.



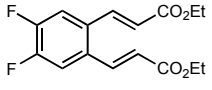
(*E*)-3-[2-{(*E*)-2-Methoxycarbonylvinyl}phenyl]acrylic acid methyl ester (341b).[77] The title compound was prepared according to General Procedure D from methyl (triphenylphosphoranylidene)acetate (4.18 g, 12.5 mmol) and purified by column chromatography (10% EtOAc/hexane→30% EtOAc/hexane) followed by recrystallization from EtOAc/hexane to give **341b** as a white solid (1.08 g, 83%), which displayed spectral data consistent with those described previously.[77] R_f = 0.37 (25% EtOAc/hexanes); m.p. 63-65 °C; IR ($CHCl_3$) 2951, 1718 (C=O), 1635, 1596, 1435, 1314, 1277, 1249, 1216, 1195 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.03 (2H, d, *J* = 15.8 Hz, 2 x C**H**=CHC=O), 7.58-7.55 (2H, m, Ar**H**), 7.41-7.38 (2H, m, Ar**H**), 6.35 (2H, d, *J* = 15.8 Hz, 2 x C**H**C=O), 3.83 (6H, 2 x OC**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.8 (2 x C), 141.4 (2 x CH), 134.2 (2 x C), 130.0 (2 x CH), 127.6 (2 x CH), 121.4 (2 x CH), 51.8 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{18}NO_4$ $[M+NH_4]^+$: 264.1230, found: 264.1228.

(2*E*,7*E*)-Nona-2,7-dienedioic acid dibenzyl ester (344)

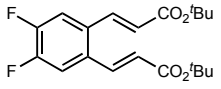


To a solution of benzyl (triphenylphosphoranylidene)acetate (1.43 g, 3.5 mmol) in THF (8 mL) was added glutaric dialdehyde solution (50% solution in water, 181 uL, 1.0 mmol), followed by $MgSO_4$ (*c.a.* 1.2 g) and the reaction mixture was stirred for 48 h. After filtration, and concentration *in vacuo*, the resulting solid was purified by column chromatography (10% EtOAc/hexane) to give the *bis*-α,*β*-unsaturated ester **344** (220 mg, 60%) as a colourless oil. R_f = 0.51 (25% EtOAc/hexanes); IR (film) 3033, 2938, 1712 (C=O), 1652, 1455, 1316, 1289, 1264, 1169, 1146 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.41-7.32 (10H, m, Ar**H**), 7.01 (2H, dt, *J* = 15.6, 6.9 Hz, 2 x C**H**=CHCO), 5.91 (2H, dm, *J* = 15.6 Hz, 2 x C**H**C=O), 5.20 (4H, s, 2 x C**H**$_2$Ph), 2.25 (4H, qd, *J* = 7.4, 1.5 Hz, 2 x CH=CHC**H**$_2$), 1.69-1.61 (2H, m, CH=CHCH$_2$C**H**$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.1 (2 x C), 148.6 (2 x CH), 136.0 (2 x C), 128.4 (2 x

CH), 128.1 (6 x CH), 121.5 (4 x CH), 66.0 (2 x CH_2), 31.3 (2 x CH_2), 26.1 (CH_2); HRMS (ES) Exact mass calcd for $C_{23}H_{25}O_4$ $[M+H]^+$: 365.1747, found: 365.1754.

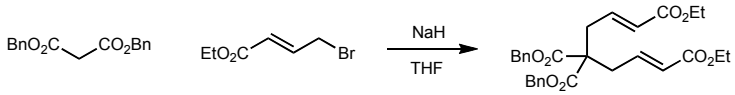


(*E*)-3-[2-{(*E*)-2-Ethoxycarbonylvinyl}-4,5-difluorophenyl]acrylic acid ethyl ester (346a). The title compound was prepared according to General Procedure E from ethyl acrylate (2.72 mL, 25.0 mmol) and purified by column chromatography (10% EtOAc/hexane→30% EtOAc/hexane) to give **346a** as a pale yellow solid (0.91 g, 59%). R_f = 0.55 (25% EtOAc/hexanes); m.p. 112-114 °C; IR ($CHCl_3$) 3050, 2990, 1705 (C=O), 1505, 1305, 1266, 1169, 1096, 973, 909 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.92 (2H, d, *J* = 15.8 Hz, 2 x C**H**=CHC=O), 7.38 (2H, app t, J_{H-F} = 9.4 Hz, Ar**H**), 6.29 (2H, d, *J* = 15.8 Hz, 2 x C**H**C=O), 4.29 (4H, q, *J* = 7.1 Hz, 2 x C**H**$_2$$CH_3$), 1.35 (6H, t, *J* = 7.1 Hz, 2 x CH_2C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 165.9 (2 x C), 151.1 (2 x C, dd, J_{C-F} = 255.4, 15.1 Hz), 138.9 (2 x CH), 131.4 (2 x C, t, J_{C-F} = 4.8 Hz), 122.8 (2 x CH), 116.2 (2 x CH, dd, J_{C-F} = 11.3, 8.0 Hz), 60.9 (2 x CH_2), 14.2 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{20}F_2NO_4$ $[M+NH_4]^+$: 328.1355, found: 328.1355.



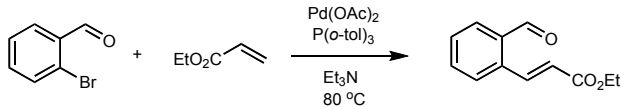
(*E*)-3-[2-{(*E*)-2-*tert*-Butoxycarbonylvinyl}-4,5-difluorophenyl]acrylic acid *tert*-butyl ester (346b). The title compound was prepared according to General Procedure E from *tert*-butyl acrylate (3.66 mL, 25.0 mmol) and purified by column chromatography (5% EtOAc/hexane→10% EtOAc/hexane) to give **346b** as a white solid (1.34 g, 73%). R_f = 0.67 (25% EtOAc/hexanes); m.p. 104-106 °C; IR ($CHCl_3$) 2980, 1710 (C=O), 1635, 1502, 1368, 1297, 1259, 1152, 849 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.02 (2H, d, *J* = 15.8 Hz, 2 x C**H**=CHC=O), 6.41 (2H, d, *J* = 15.8 Hz, C**H**C=O), 7.55 (2H, app t, J_{H-F} = 9.5 Hz, Ar**H**), 1.74 (18H, s, 2 x C(C**H**$_3$)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 165.1 (2 x C), 150.9 (2 x C, dd, J_{C-F} = 254.8, 15.1 Hz), 138.0 (2 x CH), 131.5 (2 x C, t, J_{C-F} = 4.8 Hz), 124.5 (2 x CH), 116.0 (2 x CH, dd, J_{C-F} = 11.2, 8.0 Hz), 81.1 (2 x C), 28.1 (6 x CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{24}F_2O_4Na$ $[M+Na]^+$: 389.1531, found: 389.1535.

(2*E*,7*E*)-5,5-*Bis*-benzyloxycarbonyl-nona-2,7-dienedioic acid diethyl ester (350)



To a solution of NaH (0.88 g, 22.0 mmol, 2.2 eq) in THF (40 mL) was added dibenzyl malonate (4.45 mL, 10.0 mmol), dropwise over 5 min at 0 °C. The reaction mixture was stirred at 0 °C for 15 minutes before it was allowed to warm to room temperature. Ethyl 4-bromocrotonate (3.97 mL, 22.0 mmol, 2.2 eq) was then added and the reaction was allowed to stir at room temperature for 17 h. The reaction mixture was then quenced with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (2 x 30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane→15% EtOAc/hexane) gave *bis*-α,*β*-unsaturated ester **350** (4.53 g, 89%). R_f = 0.47 (25% EtOAc/hexanes); IR (film) 3034, 2981, 1722 (C=O), 1656, 1497, 1456, 1368, 1315, 1271, 1174 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.34-7.32 (6H, m, Ar**H**), 7.28-7.24 (4H, m, Ar**H**), 6.73 (2H, dt, *J* = 15.5, 7.8 Hz, 2 x C**H**=CHC=O), 5.81 (2H, dt, *J* = 15.5, 1.3 Hz, 2 x C**H**C=O), 5.13 (4H, s, 2 x C$\mathbf{H}_2$Ph), 4.17 (4H, q, *J* = 7.1 Hz, 2 x OC$\mathbf{H}_2$$CH_3$), 3.81 (2H, dd, *J* = 7.8, 1.3 Hz, 2 x CH=CHC$\mathbf{H}_2$), 1.29 (6H, t, *J* = 7.1 Hz, 2 x OCH_2C$\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 169.3 (2 x C), 165.5 (2 x C), 141.2 (2 x CH), 134.8 (2 x C), 128.5 (4 x CH), 128.5 (2 x CH), 128.3 (4 x CH), 125.7 (2 x CH), 67.6 (2 x CH_2), 60.4 (2 x CH_2), 56.9 (C), 35.5 (2 x CH_2), 14.1 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{29}H_{33}O_8$ $[M+H]^+$: 509.2170, found: 509.2173.

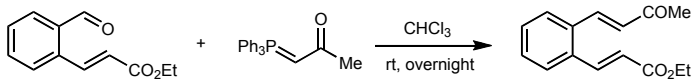
(*E*)-3-(2-Formylphenyl)acrylic acid ethyl ester (357)



To a solution of $Pd(OAc)_2$ (112 mg, 1.00 mmol) and P(*o*-tol)$_3$ (304 mg, 1.0 mmol) in Et_3N (40 mL) at 80 °C was added 2-bromobenzaldehyde (0.85 mL, 5.00 mmol), followed by ethyl acrylate (0.54 mL, 5.00 mmol). The reaction mixture was stirred at 80 °C for 18 h, before the addition of 1 M HCl (50 mL), and extraction with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL),

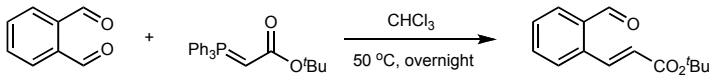
dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane→20% EtOAc/hexane) gave **357** as a yellow oil (644 mg, 63%). R_f = 0.39 (25% EtOAc/hexanes); IR (film) 2981, 2939, 1713 (C=O), 1635, 1595, 1569, 1367, 1318, 1286, 1182 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 10.31 (1H, s, C**H**O), 8.52 (1H, d, *J* = 15.9 Hz, C**H**=CHC=O), 7.90-7.87 (1H, m, Ar**H**), 7.65-7.54 (3H, m, Ar**H**), 6.38 (1H, d, *J* = 15.9 Hz, C**H**C=O), 4.30 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 1.36 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 191.7 (CH), 166.1 (C), 140.8 (CH), 136.6 (C), 133.9 (CH), 132.1 (CH), 129.8 (CH), 127.9 (CH), 123.2 (CH), 60.7 (CH_2), 14.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{12}H_{13}O_3$ $[M+H]^+$: 205.0859, found: 205.0860.

(*E*)-3-[2-((*E*)-3-Oxobut-1-enyl)phenyl]acrylic acid ethyl ester (358)



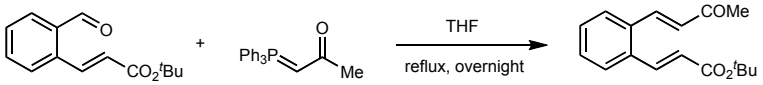
To a solution of (*E*)-3-(2-Formylphenyl)acrylic acid ethyl ester (**357**) (459.0 mg, 2.25 mmol) in $CHCl_3$ (25 mL) was added (acetylmethylene)triphenylphosphorane (860 mg, 2.70 mmol). The reaction mixture was stirred at room temperature for 20 h, before the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography (10% EtOAc/hexane) to give **358** as a yellow oil (401 mg, 73%). R_f = 0.19 (25% EtOAc/hexanes); IR (film) 2981, 2929, 1713 (C=O), 1673, 1634, 1609, 1315, 1284, 1258, 1179 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.03 (1H, d, *J* = 15.8 Hz, **H**C=CHCO$_2$CH$_2$CH$_3$), 7.87 (1H, d, *J* = 16.1 Hz, **H**C=CHCOCH$_3$), 7.60-7.57 (2H, m, Ar**H**), 7.43-7.40 (2H, m, Ar**H**), 6.62 (1H, d, *J* = 16.1 Hz, C**H**COCH$_3$), 6.36 (1H, d, *J* = 15.8 Hz, C**H**CO$_2$CH$_2$CH$_3$), 4.29 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 2.41 (3H, s, C**H**$_3$C=O), 1.38 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.8 (C), 166.3 (C), 141.1 (CH), 139.8 (CH), 134.4 (C), 134.2 (C), 130.3 (CH), 130.1 (CH), 130.0 (CH), 127.7 (CH), 127.6 (CH), 122.0 (CH), 60.7 (CH_3), 27.7 (CH_2), 14.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{17}O_3$ $[M+H]^+$: 245.1172, found: 245.1174.

(*E*)-3-(2-Formylphenyl)acrylic acid *tert*-butyl ester (361)



To a solution of phthaldialdehyde (1.00 g, 7.45 mmol) in $CHCl_3$ (90 mL), was added (triphenylphosphanylidene)acetic acid *tert*-butyl ester (5.60 g, 14.9 mmol). The reaction mixture was heated to 50 ^oC and stirred for 16 h, after which it was allowed to cool to room temperature and the solvent was removed *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane→30% EtOAc/hexane), afforded the mono-adduct product **361** as a yellow oil (672 mg, 39%). R_f = 0.50 (25% EtOAc/hexanes); IR (film) 2978, 1708 (C=O), 1633, 1595, 1568, 1482, 1392, 1368, 1324, 1289 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 10.33 (1H, s, C**H**O), 8.42 (1H, d, *J* = 15.9 Hz, C**H**=CHC=O), 7.88 (1H, dd, *J* = 7.4, 1.4 Hz, Ar**H**), 7.65-7.58 (3H, m, Ar**H**), 6.32 (1H, d, *J* = 15.9 Hz, C**H**C=O), 1.55 (3H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 192.1 (CH), 164.9 (C), 141.9 (CH), 136.7 (C), 136.2 (C), 133.5 (CH), 132.1 (CH), 129.3 (CH), 128.9 (CH), 128.2 (CH), 43.6 (C), 26.4 (3 x CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{17}O_3$ $[M+H]^+$: 232.1149, found: 232.1152.

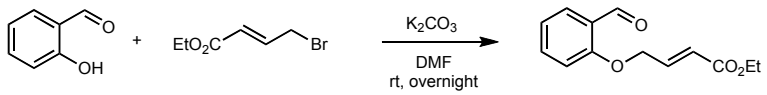
(*E*)-3-[2-((*E*)-3-Oxobut-1-enyl)phenyl]acrylic acid *tert*-butyl ester (362)



To a solution of (*E*)-3-(2-formylphenyl)acrylic acid *tert*-butyl ester (**361**) (671 mg, 2.89 mmol) in THF (30 mL) was added (acetylmethylene)triphenylphosphorane (1.38 g, 4.34 mmol). The reaction mixture was heated to reflux and stirred for 16 h, after which it was allowed to cool to room temperature, and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography to afford cyclisation precursor **362** (406 mg, 52%) as a yellow oil, which solidified on standing. R_f = 0.50 (25% EtOAc/hexanes); m.p. 70-72 ^oC; IR (film) 2978, 2931, 1707 (C=O), 1673, 1634, 1609, 1477, 1367, 1322, 1255 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.95 (1H, d, *J* = 15.8 Hz, C**H**=CHCO$_2$C(CH$_3$)$_3$, 7.88 (1H, d, *J* = 16.1 Hz, C**H**=CHCOCH$_3$), 7.59-7.57 (2H, m, Ar**H**), 7.41-7.39 (2H, m, Ar**H**), 6.62 (1H, d, *J* = 16.1 Hz C**H**COCH$_3$), 6.30 (1H, d, *J* = 15.8 Hz, C**H**CO$_2$C(CH$_3$)$_3$), 2.42 (3H, s, C**H**$_3$C=O), 1.55 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 198.0 (C), 165.7

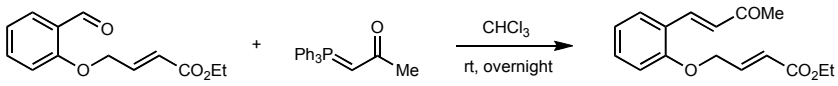
(C), 140.1 (CH), 140.0 (CH), 134.6 (C), 134.1 (C), 130.4 (CH), 130.2 (CH), 129.8 (CH), 127.6 (CH), 127.5 (CH), 123.9 (CH), 80.9 (C), 28.2 (4 x CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{24}NO_3$ $[M+NH_4]^+$: 290.1751, found: 290.1746.

2-((*E*)-4-Ethoxypenta-2,4-dienyloxy)benzaldehyde[78] (364)

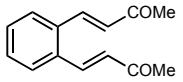


To a solution of K_2CO_3 (1.38 g, 10.0 mmol) in DMF (10 mL) was added salicaldehyde (0.73 mL, 10.0 mmol), followed by ethyl 4-bromocrotonate (1.80 mL, 10.0 mmol). The reaction mixture was stirred at room temperature for 20 h, before it was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude mixture by column chromatography (5% EtOAc/hexane→20% EtOAc/hexane) gave **364** as a yellow oil (1.31 g, 56%), which displayed spectral data consistent with those described previously.[78] IR (film) 2982, 1720 (C=O), 1688 (C=O), 1075, 1483, 1459, 1304, 1289, 1240, 1182 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 10.53 (1H, d, *J* = 0.7 Hz, C**H**O), 7.84 (1H, dd, *J* = 7.7, 1.8 Hz, Ar**H**), 7.53 (1H, ddd, *J* = 8.4, 7.3, 1.9 Hz, Ar**H**), 7.13-7.031 (2H, m, ArH and C**H**=CHCO$_2$Et) 6.94 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.21 (1H, td, *J* = 15.8, 2.0, 2.0 Hz, C**H**CO$_2$Et), 4.82 (2H, dd, *J* = 4.1, 2.1 Hz, OC**H**$_2$), 4.21 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 1.29 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (201 MHz, $CDCl_3$) δ 189.2 (CH), 189.2 (C), 165.7 (C), 160.1 (C), 141.1 (CH), 135.8 (CH), 128.7 (CH), 122.4 (CH), 121.3 (CH), 112.5 (CH), 67.0 (CH_2), 60.6 (CH_2), 14.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{18}NO_4$ $[M+NH_4]^+$: 252.1230, found: 252.1233.

(*E*)-4-[2-((*E*)-3-Oxobut-1-enyl)phenoxy]but-2-enoic acid ethyl ester (365)

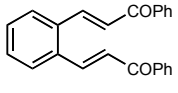


To a solution of 2-((*E*)-4-ethoxypenta-2,4-dienyloxy)benzaldehyde (**364**) (750 mg, 3.20 mmol) in $CHCl_3$ (50 mL) was added acetylmethylene)triphenylphosphorane (1.12 g, 3.52 mmol). The reaction mixture was stirred at room temperature for 20 h, after which the solvent was removed *in vacuo*. Purification of the residue by column chromatography (40% Et_2O/hexane→80% Et_2O/hexane) gave **365** as a yellow solid (1.31 g, 56%). R_f = 0.43 (50% EtOAc/hexanes); m.p. 54-56 ^oC; IR (film) 2982, 1719 (C=O), 1667, 1618, 1599, 1487, 1458, 1361, 1304, 1261 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.93 (1H, d, *J* = 16.5 Hz, C**H**=CHCOCH$_3$), 7.58 (1H, dd, *J* = 7.6, 1.5 Hz, Ar**H**), 7.35 (1H, ddd, *J* = 8.4, 7.6, 1.5 Hz, Ar**H**), 7.11 (1H, dt, *J* = 15.8, 4.2 Hz, C**H**=CHCO$_2$CH$_2$CH$_3$), 7.01 (1H, t, *J* = 7.6 Hz, Ar**H**), 6.87 (1H, app d, *J* = 8.4 Hz, Ar**H**), 6.75 (1H, d, *J* = 16.5 Hz, C**H**COCH$_3$), 6.18 (1H, dt, *J* = 15.8, 2.0 Hz, C**H**CO$_2$CH$_2$CH$_3$), 4.81 (2H, dd, *J* = 4.2, 2.0 Hz, OC**H**$_2$CH=CH), 4.23 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 2.41 (3H, s, C**H**$_3$C=O), 1.31 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 198.8 (C), 165.8 (C), 156.5 (C), 141.8 (CH), 138.1 (CH), 131.7 (CH), 128.3 (CH), 128.0 (CH), 123.8 (C), 122.4 (CH), 121.5 (CH), 112.3 (CH), 66.9 (CH_2), 60.6 (CH_2), 27.2 (CH_3), 14.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{19}O_4$ $[M+H]^+$: 275.1278, found: 275.1278.

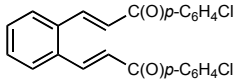


(*E*)-4-[2-{(*E*)-3-Oxobut-1-enyl}phenyl]but-3-en-2-one (367).[77] The title compound was prepared according to General Procedure D from (acetylmethylene)triphenylphosphorane (3.98 g, 12.5 mmol) and purified by column chromatography (10% EtOAc/hexane→30% EtOAc/hexane) to give **367** as an off-white solid (846 mg, 79%), which displayed spectral data consistent with those described previously.[77] R_f = 0.18 (25% EtOAc/hexanes); m.p. 89-91 °C; IR ($CHCl_3$) 3038, 1675 (C=O), 1653, 1621, 1595, 1474, 1363, 1255, 1217, 1201 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 16.0 Hz, 2 x C**H**=CHC=O), 7.57 (2H, d, *J* = 5.8, 3.4 Hz, Ar**H**), 7.40 (2H, dd, *J* = 5.8, 3.4 Hz, Ar**H**), 6.61 (2H, d, *J* = 16.0 Hz, 2 x C**H**C=O), 2.38 (6H, s, 2 x C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.6 (2 x C), 139.5 (2 x CH), 134.4 (2 x C), 130.2 (2 x CH), 130.1 (2 x CH), 127.6 (2 x

CH), 27.9 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{18}NO_2$ $[M+NH_4]^+$: 232.1332, found: 232.1330.



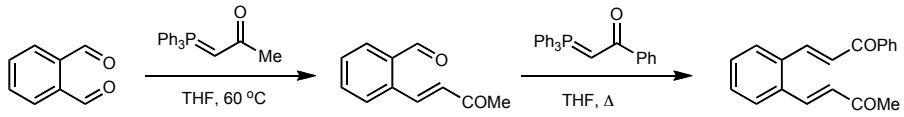
(*E*)-3-[2-{(*E*)-3-Oxo-3-phenylpropenyl}phenyl]-1-phenylpropenone (369a).[77] The title compound was prepared according to General Procedure D, but heated to reflux from (phenylacylidene)triphenylphosphorane (4.75 g, 12.5 mmol) and purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) followed by recrystallization from CH_2Cl_2/hexane to give **369a** as a pale yellow solid (832 mg, 57%), which displayed spectral data consistent with those described previously.[77] R_f = 0.35 (25% EtOAc/hexanes); m.p. 125-127 °C; IR ($CHCl_3$) 3061, 3026, 1661 (C=O), 1604 (C=O), 1475, 1447, 1331, 1301, 1215, 1016 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 15.6 Hz, 2 x C**H**=CHC=O), 8.06-8.03 (4H, m, Ar**H**), 7.72 (2H, dd, *J* = 5.7, 3.4 Hz, Ar**H**), 7.62-7.57 (2H, m, Ar**H**), 7.53-7.46 (6H, m, Ar**H**), 7.44 (2H, d, *J* = 15.6 Hz, 2 x C**H**C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 190.0 (2 x C), 141.6 (2 x CH), 137.8 (2 x C), 135.3 (2 x C), 132.9 (2 x CH), 130.1 (2 x CH), 128.7 (4 x CH), 128.6 (4 x CH), 128.1 (2 x CH), 126.0 (2 x CH); HRMS (ES) Exact mass calcd for $C_{24}H_{19}O_2$ $[M+H]^+$: 339.1380, found: 339.1385.



(*E*)-1-(4-Chlorophenyl)-3-{2-[(*E*)-3-(4-chlorophenyl)-3-oxopropenyl]phenyl}propenone (369b). The title compound was prepared according to General Procedure D, but heated to reflux from 1-(4-chlorophenyl)-2-(triphenylphosphanylidene)ethanone (5.18 g, 12.5 mmol) and purified by column chromatography (1% MeOH/$CHCl_3$→5% MeOH/$CHCl_3$) followed by recrystallization from CH_2Cl_2/hexane to give **369b** as a pale yellow solid (895 mg, 44%). R_f = 0.45 (25% EtOAc/hexanes); m.p. 155-157 °C; IR ($CHCl_3$) 3061, 1662 (C=O), 1604, 1590, 1487, 1400, 1327, 1301, 1215, 1176 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 15.5 Hz, 2 x C**H**=CHC=O), 8.02-7.98 (4H, m, Ar**H**), 7.72 (2H, dd, *J* = 5.7, 3.5 Hz, Ar**H**), 7.51-7.48 (6H, m, Ar**H**), 7.40 (2H, d, *J* = 15.5 Hz, 2 x C**H**C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 188.6 (2 x C), 142.1 (2 x CH), 139.5 (2 x C), 136.1 (2 x C), 135.3 (2 x C), 130.3 (2 x CH), 130.0 (4 x CH),

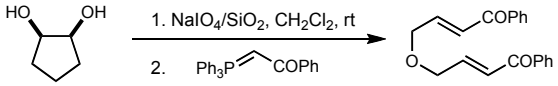
129.0 (4 x CH), 128.3 (2 x CH), 125.5 (2 x CH); HRMS (EI) Exact mass calcd for $C_{24}H_{16}O_2{}^{35}Cl_2$ $[M]^+$: 406.0522, found: 406.0520.

(*E*)-4-[2-{(*E*)-3-Oxo-3-phenylpropenyl}phenyl]but-3-en-2-one[77] (371)



To a solution of phthaldialdehyde (268 mg, 2.00 mmol) in THF (5 mL) at 60 °C was added a solution of (acetylmethylene)triphenylphosphorane (637 mg, 2.00 mmol) in THF (10 mL) dropwise *via* cannula over 30 min, and the mixture was stirred at 60 °C for 18 h. (Phenacylidene)triphenylphosphorane (761 mg, 4.00 mmol) was added and the resulting mixture was stirred at reflux for a further 18 h before being concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane→30% EtOAc/hexane) gave cyclization precursor **371** as an orange oil (248 mg, 45%), which displayed spectral data consistent with those described previously.[77] R_f = 0.27 (25% EtOAc/hexanes); IR (film) 3062, 2924, 2853, 1667 (C=O), 1605 (C=O), 1333, 1300, 1287, 1256, 1217 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.16 (1H, d, *J* = 15.5 Hz, C**H**=CHCOPh), 8.06-8.03 (2H, m, Ar**H**), 7.93 (1H, d, *J* = 16.1 Hz, C**H**=CHCOCH$_3$), 7.73-7.70 (1H, m, Ar**H**), 7.64-7.59 (2H, m, Ar**H**), 7.55-7.50 (2H, m, Ar**H**), 7.48-7.44 (2H, m, Ar**H**), 7.45 (1H, d, *J* = 15.5 Hz, C**H**COPh), 6.64 (1H, d, *J* = 16.1 Hz, C**H**COCH$_3$), 2.41 (3H, s, C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.9 (C), 189.8 (C), 141.2 (CH), 139.9 (CH), 137.8 (C), 134.9 (C), 134.7 (C), 133.0 (CH), 130.5 (CH), 130.2 (CH), 130.1 (CH), 128.6 (2 x CH), 128.5 (2 x CH), 127.8 (CH), 127.7 (CH), 125.7 (CH), 27.5 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{19}H_{17}O_2$ $[M+H]^+$: 277.1223, found: 277.1226.

(*E*)-4-[(*E*)-4-Oxo-4-phenylbut-2-enyloxy]-1-phenylbut-2-en-1-one (374)

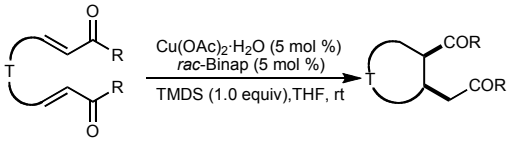


To a suspension of silica gel-supported $NaIO_4$[71] (2.00 g) in CH_2Cl_2 (5 mL) was added 1,4-anhydroerythritol (82 μL, 1.00 mmol) and the mixture was stirred at room temperature for 1 h. (Phenylacylidene)triphenylphosphorane (950 mg, 2.50 mmoL)

was then added in one portion and the mixture was stirred for a further 16 h, before it was filtered through a sintered glass funnel, using CH_2Cl_2 (3 x 10 mL) as eluent. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (5% EtOAc/hexane→40% EtOAc/hexane) to give the diallyl ether **374** (192 mg, 63%) as a yellow oil. R_f = 0.26 (25% EtOAc/hexanes); IR (film) 2922, 1673 (C=O), 1625, 1596, 1484, 1328, 1285, 1212, 1130, 691 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.00-7.97 (4H, m, Ar**H**), 7.61-7.56 (2H, m, Ar**H**), 7.51-7.46 (4H, m, Ar**H**), 7.25 (2H, dt, *J* = 15.5, 1.9 Hz, 2 x C**H**=CHC=O), 7.09 (2H, dt, *J* = 15.5, 4.0 Hz, 2 x C**H**C=O), 4.38 (4H, dd, *J* = 4.0, 1.9 Hz, 2 x OC**H**$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 190.1 (2 x C), 143.7 (2 x CH), 137.5 (2 x C), 133.0 (2 x CH), 128.6 (8 x CH), 125.0 (2 x CH), 69.9 (2 x CH_2); LRMS (ES) 635 ($[2M+Na]^+$, 25), 329 ($[M+Na]^+$, 100).

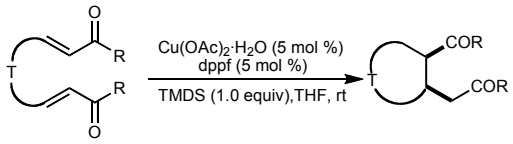
2.4.3 Racemic Reductive Michael Cyclisations

General Procedure F: Racemic Reductive Michael Cyclisations with $Cu(OAc)_2 \cdot H_2O$, *rac*-Binap and TMDS

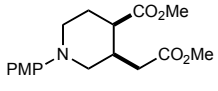


A solution of $Cu(OAc)_2 \cdot H_2O$ (4.0 mg, 0.02 mmol) and *rac*-Binap (12.5 mg, 0.02 mmol) in THF (0.4 mL) was stirred for 15 min before TMDS (71 μL, 0.40 mmol) was added. The initially blue solution was stirred until it became yellow (*ca.* 5 min), after which a solution of the substrate (0.40 mmol) in THF (0.4 + 0.2 mL rinse) was then added rapidly *via* cannula. The reaction mixture was stirred at room temperature for 18 h. The reaction was quenched by the addition of 1 M HCl (1 mL), and the mixture was extracted with CH_2Cl_2 (3 x 1 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/hexane) afforded the cyclised product.

General Procedure G: Racemic Reductive Michael Cyclisations with $Cu(OAc)_2 \cdot H_2O$, dppf and TMDS



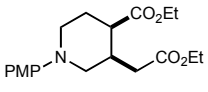
A solution of $Cu(OAc)_2 \cdot H_2O$ (4.0 mg, 0.02 mmol) and dppf (11.1 mg, 0.02 mmol) in THF (0.4 mL) was stirred for 15 min before TMDS (71 μL, 0.40 mmol) was added. The solution was stirred until for 5 min, after which a solution of the substrate (0.40 mmol) in THF (0.4 + 0.2 mL rinse) was then added rapidly *via* cannula. The reaction mixture was stirred at room temperature for 18 h. The reaction was quenched by the addition of 1 M HCl (1 mL), and the mixture was extracted with CH_2Cl_2 (3 x 1 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/hexane) afforded the cyclised product.



***Cis*-3-Methoxycarbonylmethyl-1-(4-methoxyphenyl)piperidine-4-carboxylic acid methyl ester (335a)**

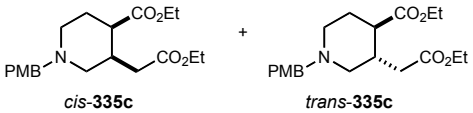
The title compound was prepared using a slight modification of the quantities described in General Procedure F from **327a** (159 mg, 0.50 mmol), $Cu(OAc)_2 \cdot H_2O$ (5.0 mg, 0.025 mmol), *rac*-Binap (15.6 mg, 0.025 mmol) and TMDS (88 μL, 0.50 mmol) and purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) to give the *substituted piperidine* as an oil (35 mg, 22 %). R_f = 0.57 (50% EtOAc/hexanes); IR (film) 2980, 2955, 2937, 2906, 1731 (C=O), 1512, 1294, 1248, 1178, 1037 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.88 (2H, d, *J* = 9.1 Hz, Ar**H**), 6.82 (2H, d, *J* = 9.2 Hz, Ar**H**), 3.77 (1H, s, OC**H**$_3$), 3.71 (3H, s, $CO_2C\mathbf{H}_3$), 3.69 (3H, s, $CO_2C\mathbf{H}_3$), 3.48-3.35 (2H, m, NC**H**$_2$CH and NC**H**$_2$CH$_2$), 2.88-3.63 (5H, m, NC**H**$_2$CH, NCH$_2$C**H** NC**H**$_2$CH$_2$, C**H**CO$_2$CH$_3$ and C**H**$_2$C=O), 2.33 (1H, ddd, *J* = 16.1, 2.6 Hz, C**H**$_2$C=O), 2.05-1.90 (2H, m, NCH$_2$C**H**$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.0 (C), 173.2 (C), 153.8 (C), 146.2 (C), 119.1 (2 x CH), 114.3 (2 x CH), 55.5 (CH_3), 55.3 (CH_2), 51.6 (CH_3), 51.5 (CH_3), 49.8 (CH_2), 43.5 (CH), 33.2 (CH), 32.6

(CH_2), 24.3 (CH_2); HRMS (ES) Exact mass calcd for $C_{17}H_{24}NO_5$ $[M+H]^+$: 322.1649, found: 322.1651.



Cis-3-Ethoxycarbonylmethyl-1-(4-methoxyphenyl)piperidine-4-carboxylic acid ethyl ester (335b)

The title compound was prepared using a slight modification of the quantities described in General Procedure G, from **327b** (173 mg, 0.50 mmol), $Cu(OAc)_2 \cdot H_2O$ (5.0 mg, 0.025 mmol), dppf (13.8 mg, 0.025 mmol) and TMDS (88 μL, 0.50 mmol) and purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) to give the *substituted piperidine* as an oil (63 mg, 36%). R_f = 0.32 (25% EtOAc/hexanes); IR (film) 2980, 2955, 2937, 2906, 1731 (C=O), 1512, 1294, 1248, 1178, 1037 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.88 (2H, d, *J* = 9.2 Hz, Ar**H**), 6.82 (2H, d, *J* = 9.2 Hz, Ar**H**), 4.17 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 4.15 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 3.77 (3H, s, C**H**$_3$), 3.46 (1H, ddd, *J* = 12.2, 4.4, 1.4 Hz, NC**H**$_2$CH), 3.39 (1H, dtd, *J* = 11.3, 4.4, 1.2 Hz, NC**H**$_2$CH$_2$), 2.86 (1H, dd, *J* = 12.2, 2.6 Hz, NC**H**$_2$CH), 2.85-2.62 (4H, m, NC**H**$_2$CH$_2$, C**H**C=O, C**H**$_2$C=O, and NCH$_2$C**H**), 2.31 (1H, ddd, *J* = 15.9, 3.4, 1.1 Hz, C**H**$_2$C=O), 2.01-1.88 (2H, m, NCH$_2$C**H**$_2$), 1.28 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$), 1.27 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.6 (C), 172.9 (C), 153.8 (C), 146.4 (C), 119.1 (2 x CH), 114.3 (2 x CH), 60.4 (2 x CH_2), 55.5 (CH_3), 55.3 (CH_2), 49.7 (CH_2), 43.6 (CH), 33.3 (CH_2), 32.9 (CH), 24.4 (CH_2), 14.2 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{27}NO_5$ $[M+H]^+$: 350.1962, found: 350.1958.

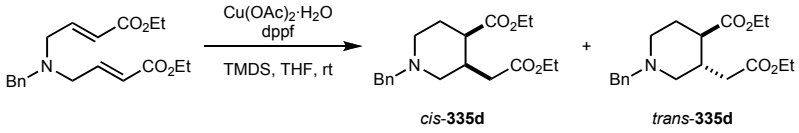


Cis-Ethoxycarbonylmethyl-1-(4-methoxybenzyl)piperidine-4-carboxylic acid ethyl ester (_cis_-335c) and _Trans_-Ethoxycarbonylmethyl-1-(4-methoxybenzyl)piperidine-4-carboxylic acid ethyl ester (_trans_-335c)

General Procedure G was followed using **327c** (145 mg, 0.40 mmol). Purification by column chromatography (10% EtOAc/hexane→50% EtOAc/hexane) gave a 2:1 mixture of inseparable diastereomers as an oil (69 mg, 48%). R_f = 0.28 (25% EtOAc/hexanes); IR (film) 2980, 2933, 2906, 1732 (C=O), 1612, 1512, 1299, 1247,

1179, 1035 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (mixture of diastereomers – not fully assigned) δ 7.13 (2H, dd, *J* = 8.6, 2.4, Ar**H)**, 6.78-6.74 (m, Ar**H**), 4.083-3.964 (m), 3.71 (3H, s, OC**H**$_3$ major), 3.71 (3H, s, OC**H**$_3$ minor), 3.408-3.258 (m), 2.84 (1H, dd, *J* = 11.1, 2.0 Hz, NC**H**$_2$CH major), 2.78-2.75 (m), 2.69-2.63 (m), 2.52-2.46 (m), 2.36-2.20 (m) 2.11-2.00 (m), 1.87 (1H, td, *J* = 10.9, 3.2 Hz), 1.79-1.67 (m), 1.19-1.09 (m, CH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) (mixture of diastereomers – not fully assigned) δ 174.5 (C), 173.8 (C), 172.8 (C), 171.9 (C), 158.6 (C), 158.5 (C), 130.1 (2 x CH), 130.0 (2 x C), 129.9 (2 CH), 113.4 (2 x CH), 113.4 (2 CH), 62.1 (CH_2), 62.0 (CH_2), 60.3 (CH_2), 60.3 (CH_2), 60.2 (CH_2), 60.1 (CH_2), 57.6 (2 x CH_2), 55.1 (2 x CH_3), 52.4 (CH_2), 52.2 (CH_2), 46.8 (CH), 37.1 (CH_2), 34.6 (CH), 33.0 (CH), 31.9 (CH_2), 28.6 (CH_2), 22.2 (CH_2), 14.1 (CH_3), 14.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{30}NO_5$ $[M+H]^+$: 364.2118, found: 364.2117.

1-Benzyl-3-ethoxycarbonylmethylpiperidine-4-carboxylic acid ethyl ester (*trans*-335d) and 1-Benzyl-3-ethoxycarbonylmethylpiperidine-4-carboxylic acid ethyl ester (*cis*-335d)



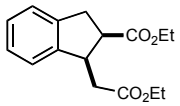
cis-**335d** *trans*-**335d**

General procedure G was followed using **327d** (126 mg, 0.40 mmol). Purification by column chromatography (10% EtOAc/hexane→40% EtOAc/hexane) gave the *piperidine trans*-**335d** as an oil (18 mg, 14%), followed by the *piperidine cis*-**335d** as an oil (29 mg, 22%).

Data for *trans*-**335d**: R_f = 0.4 (25% EtOAc/hexanes); IR (film) 2979, 1965, 2803, 1732 (C=O), 1495, 1454, 1376, 1258, 1175, 1032 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.25 (4H, app d, *J* = 4.5 Hz, Ar**H**), 7.25-7.20 (1H, m, Ar**H**), 4.13 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 4.09 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 3.52 (1H, d, *J* = 13.3 Hz, NC**H**$_2$Ph), 3.41 (1H, d, *J* = 13.3 Hz, NC**H**$_2$Ph), 2.81-2.74 (2H, m), 2.62-2.53 (2H, m), 2.29-2.24 (1H, m), 2.19-2.07 (2H, m), 1.92-1.73 (3H, m) 1.25 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$), 1.20 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.9 (C), 172.9 (C), 138.7 (C), 128.7 (2 x CH), 128.1 (2 x CH), 126.9 (CH), 62.8 (CH_2),

60.3 (CH_2), 60.2 (CH_2), 56.5 (CH_2), 52.7 (CH_2), 43.8 (CH), 33.2 (CH), 32.0 (CH_2), 22.4 (CH_2), 14.2 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{28}NO_4$ $[M+H]^+$: 334.2013, found: 334.2014.

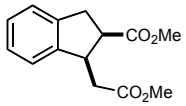
Data for *cis*-**335d**: R_f = 0.35 (25% EtOAc/hexanes); IR (film) 2936, 2806, 2359, 2341, 1733 (C=O), 1495, 1455, 1374, 1275, 1182 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.31 (4H, app d, *J* = 4.4 Hz, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 4.14 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 4.07 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 3.53 (1H, d, *J* = 13.2 Hz, NC**H**$_2$Ph), 3.46 (1H, d, *J* = 13.2 Hz, NC**H**$_2$Ph), 2.93 (1H, dd, *J* = 10.9, 2.9 Hz, NC**H**$_2$CH), 2.85 (1H, dt, *J* = 11.2, 2.9 Hz, NC**H**$_2$CH$_2$), 2.48-2.36 (2H, m), 2.20-2.01 (2H, m), 2.03-1.97 (1H, m), 1.87-1.80 (3H m), 1.26 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$), 1.19 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.5 (C), 171.9 (C), 138.2 (C), 128.9 (2 x CH), 128.2 (2 x CH), 127.0 (CH), 62.8 (CH_2), 60.4 (CH_2), 60.3 (CH_2), 57.8 (CH_2), 52.5 (CH_2), 46.8 (CH), 37.2 (CH_2), 34.7 (CH), 28.7 (CH_2), 14.2 (CH_3), 14.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{28}NO_4$ $[M+H]^+$: 334.2013, found: 334.2010.



Cis-1-Ethoxycarbonylmethylindan-2-carboxylic acid ethyl ester (351a)

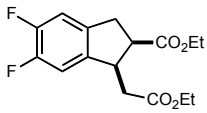
The title compound was prepared according to General Procedure F, but heated to 50 ^oC from **341a** (104 mg, 0.40 mmol) and purified by column chromatography (5% EtOAc/hexane) to give an 8:1 inseparable mixture of diastereomers as a colourless oil (63 mg, 57%). R_f = 0.57 (25% EtOAc/hexanes); IR (film) 2981, 2938, 1734 (C=O), 1478, 1374, 1308, 1295, 1254, 1214, 1178 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (major diastereomer) δ 7.24-7.16 (4H, m, Ar**H**), 4.16 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 4.15 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 3.97 (1H, app q, *J* = 7.7 Hz, C**H**CH$_2$C=O), 3.50 (1H, app q, *J* = 8.1 Hz, CH$_2$C**H**C=O), 3.32 (1H, dd, *J* = 15.9, 8.4 Hz, C**H**$_2$CHC=O), 3.06 (1H, dd, *J* = 15.9, 8.0 Hz, C**H**$_2$CHC=O), 2.64 (1H, dd, *J* = 16.1, 7.1 Hz, CHC**H**$_2$C=O), 2.53 (1H, dd, *J* = 16.1, 8.0 Hz, CHC**H**$_2$C=O), 1.29 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$), 1.26 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) (major diastereomer) δ 173.4 (C), 172.1 (C), 143.9 (C), 141.3 (C), 127.3 (CH), 126.7 (CH), 124.5 (CH), 123.9 (CH), 60.5 (CH_2), 60.4 (CH_2), 47.8 (CH), 43.1 (CH), 36.1 (CH_2),

34.0 (CH_2), 14.2 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{21}O_4$ $[M+H]^+$: 277.1434, found: 277.1435.



Cis-1-Methoxycarbonylmethylindan-2-carboxylic acid methyl ester (351b)

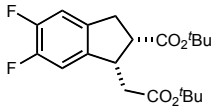
The title compound was prepared according to General Procedure F, but heated to 50 ^oC from **341b** (98 mg, 0.40 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a 5:1 inseparable mixture of diastereomers as a colourless oil (47 mg, 48%). R_f = 0.33 (25% EtOAc/hexanes); IR (film) 2951, 1736 (C=O), 1479, 1436, 1366, 1294, 1254, 1219, 1195, 1169 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$, major) δ 7.26-7.16 (4H, m, Ar**H**), 3.97 (1H, app q, *J* = 7.7 Hz, C**H**CH_2C=O), 3.70 (3H, s, C**H**$_3$), 3.69 (3H, s, C**H**$_3$), 3.53 (1H, app q, *J* = 8.1 Hz, CH_2C**H**C=O), 3.33 (1H, dd, *J* = 15.9, 8.1 Hz, C**H**$_2$CHC=O), 3.01 (1H, dd, *J* = 15.9, 8.1 Hz, C**H**$_2$CHC=O), 2.63 (1H, dd, *J* = 16.2, 7.7 Hz, CHC**H**$_2$C=O), 2.53 (1H, dd, *J* = 16.2, 7.7 Hz, CHC**H**$_2$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.8 (C), 172.6 (C), 143.8 (C), 141.2 (C), 127.4 (CH) 126.8 (CH), 124.6 (CH), 123.8 (CH), 51.6 (CH_3), 51.5 (CH_3), 47.5 (CH), 43.1 (CH), 36.0 (CH_2), 34.0 (CH_2); HRMS (ES) Exact mass calcd for $C_{14}H_{17}O_4$ $[M+H]^+$: 249.1121, found: 249.1122.



Cis-1-Ethoxycarbonylmethyl-5,6-difluoroindan-2-carboxylic acid ethyl ester (353a)

The title compound was prepared according to General Procedure F, but using half of all quantities from **347a** (62 mg, 0.20 mmol) and purified by column chromatography (2.5% EtOAc/hexane→5% EtOAc/hexane) to give the *indane* **353a** as a colourless oil (30 mg, 48%). R_f = 0.57 (25% EtOAc/hexanes); IR (film) 2984, 1733 (C=O), 1498, 1375, 1338, 1291, 1257, 1181, 1095, 1034 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.00 (1H, app t, $J_{H\text{-}F}$ = 7.2 Hz, Ar**H**), 6.98 (1H, app t, $J_{H\text{-}F}$ = 7.2 Hz, Ar**H**) 4.20-4.11 (4H, m, 2 x C**H**$_2$$CH_3$), 3.92-3.85 (1H, m, C**H**CH_2C=O), 3.51 (1H, app q, *J* = 8.1 Hz CH_2C**H**C=O), 3.25 (1H, dd, *J* = 16.1, 7.9 Hz, C**H**$_2$CHC=O), 2.99 (1H, dd, *J* = 16.1, 8.0 Hz, C**H**$_2$CHC=O), 2.60 (1H, dd, *J* = 16.3, 6.7 Hz, CHC**H**$_2$C=O), 2.47 (1H, dd, *J* = 16.3, 8.5 Hz, CHC**H**$_2$C=O), 1.27 (3H, t, *J* = 7.1, CH_2C**H**$_3$), 1.26 (3H, t, *J* = 7.1, CH_2C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.7 (C),

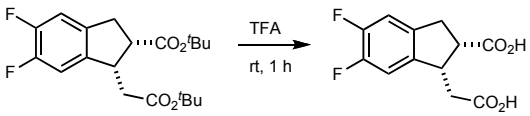
171.7 (C), 149.9 (C, dd, $J_{C\text{-}F}$ = 241.4, 8.4 Hz), 149.5 (C, dd, $J_{C\text{-}F}$ = 243.8, 11.2 Hz), 139.8 (C, dd, $J_{C\text{-}F}$ = 5.8, 3.1 Hz), 137.3 (C, dd, $J_{C\text{-}F}$ = 6.4, 3.2 Hz), 113.0, (2 x CH, t, $J_{C\text{-}F}$ = 17.7 Hz), 60.8 (CH_2), 60.7 (CH_2), 48.2 (CH), 42.6 (CH), 35.8 (CH_2), 33.5 (CH_2), 14.2 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{22}F_2NO_4$ $[M+NH_4]^+$: 330.1511, found: 330.1515.



Cis-1-_tert_-Butoxycarbonylmethyl-5,6-difluoroindan-2-carboxylic acid _tert_-butyl ester (353b)

The title compound was prepared according to General Procedure F from **347b** (146 mg, 0.40 mmol) and purified by column chromatography (2.5% EtOAc/hexane→10% EtOAc/hexane) to give the *indane* **353b** as a colourless oil (72 mg, 49%). R_f = 0.67 (25% EtOAc/hexanes); IR (film) 2979, 2933, 1727 (C=O), 1498, 1368, 1341, 1291, 1257, 1152, 844 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.03-6.95 (2H, m, Ar**H**), 3.79 (1H, app q, J = 7.7 Hz, C**H**CH_2C=O), 3.39 (1H, app q, J = 7.8 Hz, CH_2C**H**C=O), 3.15 (1H, dd, J = 16.0, 7.8 Hz, C**H**$_2$CHC=O), 2.94 (1H, dd, J = 16.0, 7.8 Hz, C**H**$_2$CHC=O), 2.56 (1H, dd, J = 15.8, 5.8 Hz, CHC**H**$_2$C=O), 2.38 (1H, dd, J = 15.8, 9.4 Hz, CHC**H**$_2$C=O), 1.45 (18H, s, 2 x C(C**H**$_3$)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.1 (C), 171.2 (C), 149.7 (C, dd, $J_{C\text{-}F}$ = 243.1, 10.3 Hz), 149.3 (C, dd, $J_{C\text{-}F}$ = 243.6, 11.8 Hz), 140.2 (C, dd, $J_{C\text{-}F}$ = 5.7, 3.0 Hz), 137.5 (C, dd, $J_{C\text{-}F}$ = 6.2, 3.2 Hz), 113.0, (2 x CH, dd, $J_{C\text{-}F}$ = 18.2, 4.8 Hz), 81.0 (C), 80.9 (C), 49.3 (CH), 42.8 (CH), 36.6 (CH_2), 33.6 (CH_2), 28.0 (6 x CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{26}F_2O_4Na$ $[M+Na]^+$: 391.1691, found: 391.1694.

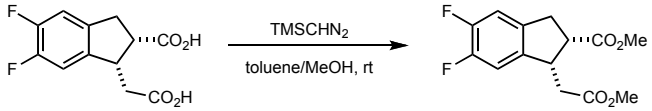
Cis-1-Carboxymethyl-5,6-difluoroindan-2-carboxylic acid (385)



Trifluoroacetic acid (approximately 1 mL) was added to **353b** (38 mg, 0.10 mmol) and the mixture was stirred at room temperature for 1 h. The excess trifluoroacetic acid was removed *in vacuo* and the *bis-acid* was isolated as a yellow solid (> quantitative yield) and used without further pruification. mp. 162-164 ^oC; ^1H NMR (600 MHz, CD_3OD) δ 7.13-7.10 (2H, m, Ar**H**), 3.84 (1H, app q, J = 7.5 Hz,

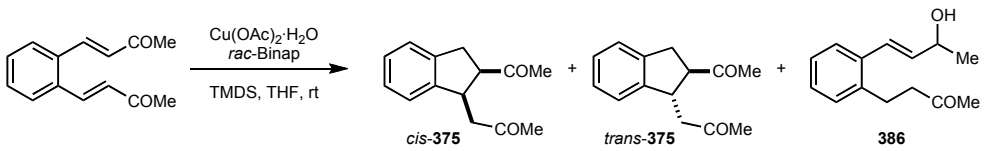
C**H**CH_2C=O), 3.55 (1H, app q, J = 8.0 Hz, CH_2C**H**C=O), 3.21 (1H, dd, J = 16.0, 7.8 Hz, C**H**$_2$CHC=O), 3.03 (1H, dd, J = 16.0, 8.0 Hz, C**H**$_2$CHC=O), 2.68 (1H, dd, J = 16.3, 6.3 Hz, CHC**H**$_2$C=O), 2.51 (1H, dd, J = 16.3, 8.8 Hz, CHC**H**$_2$C=O); ^{13}C NMR (150.9 MHz, CD_3OD) δ 176.3 (C), 175.5 (C), 151.20 (C, dd, $J_{C\text{-}F}$ = 244.6, 13.3 Hz), 150.74 (C, dd, $J_{C\text{-}F}$ = 243.8, 13.3 Hz), 142.07 (C, dd, $J_{C\text{-}F}$ = 6.3, 3.0 Hz), 139.58 (C, dd, $J_{C\text{-}F}$ = 6.3, 2.9 Hz), 114.23 (CH, d, $J_{C\text{-}F}$ = 18.1 Hz), 113.80 (CH, d, $J_{C\text{-}F}$ = 18.1 Hz), 49.6 (CH), 43.9 (CH), 36.6 (CH_2), 34.6 (CH_2); HRMS (ES) Exact mass calcd for $C_{12}H_{11}F_2O_4$ $[M+H]^+$: 257.0620, found: 257.0622.

Cis-5,6-Difluoro-1-methoxycarbonylmethylindan-2-carboxylic acid methyl ester (355)



Trimethylsilyldiazomethane (2.0 M in Et_2O, 75 µl, 0.15 mmol) was added dropwise over 1 min to a solution of **385** (19.5 mg, 0.08 mmol) in MeOH (0.1 mL) and toluene (0.15 mL), and the mixture was stirred at room temperature for 16 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (5% EtOAc/hexane→20% EtOAc/hexane) to give the *bis-methyl ester* **355** (7 mg, 32%) as a colourless oil. R_f = 0.37 (25% EtOAc/hexanes); IR (film) 2955, 1736 (C=O), 1497, 1438, 1336, 1264, 1170, 912, 825, 739 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.03-6.97 (2H, m, Ar**H**), 3.90 (1H, app q, J = 7.7 Hz, C**H**CH_2C=O), 3.71 (3H, s, OC**H**$_3$), 3.70 (3H, s, OC**H**$_3$), 3.54 (1H, app q, J = 8.1 Hz, CH_2C**H**C=O), 3.26 (1H, dd, J = 16.0, 8.2 Hz, C**H**$_2$CHC=O), 3.01 (1H, dd, J = 16.0, 8.0 Hz, C**H**$_2$CHC=O), 2.60 (1H, dd, J = 16.4, 7.0 Hz, CHC**H**$_2$C=O), 2.49 (1H, dd, J = 16.4, 8.1 Hz, CHC**H**$_2$C=O); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 173.2 (C), 172.2 (C), 150.0 (C, dd, $J_{C\text{-}F}$ = 246.9, 13.2 Hz), 149.6 (C, dd, $J_{C\text{-}F}$ = 245.9, 13.2 Hz), 139.7 (C, dd, $J_{C\text{-}F}$ = 5.8, 3.2 Hz), 137.2 (C, dd, $J_{C\text{-}F}$ = 6.2, 3.1 Hz), 113.4-113.1 (m, CH), 112.9-112.7 (m, CH), 51.8 (2 x CH_3), 48.0 (CH), 42.7 (CH), 35.7 (CH_2), 33.5 (CH_2); HRMS (ES) Exact mass calcd for $C_{14}H_{18}F_2NO_4$ $[M+NH_4]^+$: 302.1198, found: 302.1196.

***Cis*-2-Acetylindan-1-yl)propan-2-one (*cis*-375), *trans*-2-Acetylindan-1-yl)propan-2-one (*trans*-375), and 4-[2-((*E*)-3-Hydroxybut-1-enyl)phenyl]butan-2-one (386)**



General Procedure F was followed using **367** (86 mg, 0.4 mmol). Purification by column chromatography (5% EtOAc/hexane→20% EtOAc/hexane) gave the *indane cis*-**375** as a colourless oil (42 mg, 49%), followed by the *indane trans*-**375** as a colourless oil (10 mg, 12%), followed by the *allylic alcohol* **386** as a colourless oil (13 mg, 15%).

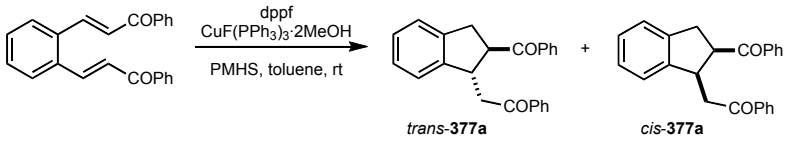
Data for *cis*-**375**: R_f = 0.29 (25% EtOAc/hexanes); IR (film) 2942, 2855, 1712 (C=O), 1478, 1459, 1420, 1365, 1259, 1206, 1164 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.22-7.12 (4H, m, Ar**H**), 4.02 (1H, td, *J* = 8.0, 5.9 Hz, C**H**CH_2C=O), 3.65 (1H, dt, *J* = 9.4, 7.8 Hz, CH_2C**H**C=O), 3.26 (1H, dd, *J* = 16.0, 9.5 Hz, C**H**$_2$CHC=O), 2.92 (1H, dd, *J* = 16.0, 7.8 Hz, C**H**$_2$CHC=O), 2.82 (1H, dd, *J* = 18.2, 8.0 Hz, CHC**H**$_2$C=O), 2.52 (1H, dd, *J* = 18.2, 5.9 Hz, CHC**H**$_2$C=O), 2.22 (3H, s, C**H**$_3$), 2.08 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 210.4 (C), 207.4 (C), 144.9 (C), 141.2 (C), 127.2 (CH) 126.9 (CH), 124.6 (CH), 123.8 (CH), 54.7 (CH), 45.0 (CH_2), 41.9 (CH), 33.5 (CH_2), 31.0 (CH_3) 30.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{17}O_2$ $[M+H]^+$: 217.1223, found: 217.1225.

Data for *trans*-**375**: R_f = 0.17 (25% EtOAc/hexanes); IR (film) 2945, 2923, 1711 (C=O), 1480, 1458, 1422, 1361, 1259, 1162, 1042 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.21-7.18 (3H, m, Ar**H**), 7.14-7.11 (1H, m, Ar**H**), 4.01-3.95 (1H, m, C**H**CH_2C=O), 3.30-3.19 (1H, m, C**H**$_2$CHC=O), 3.14-3.04 (2H, m, C**H**$_2$CHC=O and CH_2C**H**C=O), 2.95 (1H, dd, *J* = 16.8, 5.9 Hz, CHC**H**$_2$C=O), 2.67 (1H, dd, *J* = 16.8, 8.1 Hz, CHC**H**$_2$C=O), 2.28 (3H, s, C**H**$_3$), 2.21 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 209.2 (C), 207.7 (C), 144.2 (C), 140.7 (C), 127.2 (CH) 127.0 (CH), 124.5 (CH),

123.6 (CH), 58.1 (CH), 49.1 (CH_2), 42.3 (CH), 34.8 (CH_2), 30.3 (CH_3) 28.4 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{17}O_2$ $[M+H]^+$: 217.1223, found: 217.1224.

Data for **386**: R_f = 0.12 (25% EtOAc/hexanes); IR (film) 3448 (OH), 2970, 2925, 1714 (C=O), 1452, 1364, 1161, 1061, 967, 754 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.45-7.43 (1H, m, Ar**H**), 7.20-7.13 (1H, m, Ar**H**), 6.80 (1H, dd, *J* = 15.7, 1.1 Hz, C**H**=CHCH(OH)), 6.16 (1H, dd, *J* = 15.7, 6.3 Hz, CH=C**H**CH(OH)), 4.52 (1H, pd, *J* = 6.3, 1.1 Hz, C**H**(OH)), 2.96 (2H, t, *J* = 7.8 Hz, C**H**$_2$$CH_2$C=O), 2.70 (2H, t, *J* = 7.8 Hz, CH_2C**H**$_2$C=O), 2.14 (3H, s, C**H**$_3$C=O, 1.84 (1H br s, O**H**), 1.39 (3H, d, *J* = 6.3 Hz, CH(OH)C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 208.0 (C), 138.3 (C), 135.8 (CH), 135.5 (C), 129.3 (CH), 127.8 (CH), 126.6 (CH), 126.5 (CH), 126.3 (CH), 68.9 (CH), 44.5 (CH_2), 30.1 (CH_3), 27.1 (CH_2), 23.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{22}NO_2$ $[M+NH_4]^+$: 236.1645, found: 236.1649.

Trans-2-Benzoylindan-1-yl]-1-phenylethanone (_trans_-377a)[79] and _Cis_-2-Benzoylindan-1-yl]-1-phenylethanone (_cis_-377a)

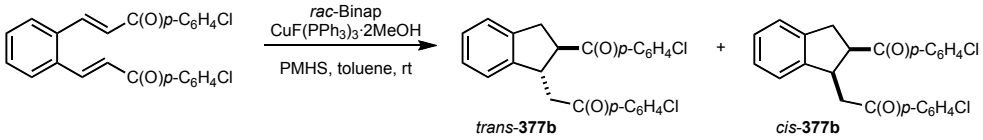


A solution of $CuF(PPh_3)_3.2MeOH$ (20 mg, 0.02 mmol), dppf (11.1 mg, 0.02 mmol) and **369a** (135 mg, 0.4 mmol) in toluene (1.5 mL) was stirred for 30 min at room temperature, after which a solution of PMHS (24 μL, 0.4 mmol) in toluene (0.4 mL) was added rapidly *via* cannula. The reaction mixture was stirred at room temperature for 24 h before the addition of a solution of more $CuF(PPh_3)_3.2MeOH$ (20 mg, 0.02 mmol), dppf (11.1 mg, 0.02 mmol), and PMHS (24 μL, 0.4 mmol) in toluene (0.5 mL) was added rapidly *via* cannula. The reaction was quenched by the addition of 1 M HCl (5 mL), and the mixture was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane→20% EtOAc/hexane) gave the *indane trans*-**377a** as a white solid (43 mg, 32%) that displayed spectral data consistent with those reported previously,[79] followed by the *indane cis*-**377a** (4 mg, 3%) as a yellow oil.

Data for *trans*-**377a**: R_f = 0.50 (25% EtOAc/hexanes); IR (film) 2981, 2938, 1734 (C=O), 1478, 1374, 1308, 1295, 1254, 1214, 1178 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99-7.93 (4H, m, Ar**H**), 7.58-7.53 (2H, m, Ar**H**), 7.48-7.42 (4H, m, Ar**H**), 7.24-7.19 (4H, m, Ar**H**), 4.44 (1H, app q, *J* = 6.8 Hz, C**H**CH_2C=O), 4.15 (1H, dt, *J* = 9.2, 7.0 Hz, CH_2C**H**C=O), 3.53 (1H, dd, *J* = 16.7, 5.9 Hz, CHC**H**$_2$C=O), 3.45 (1H, dd, *J* = 16.0, 9.2 Hz, C**H**$_2$CHC=O), 3.27 (1H, dd, *J* = 16.7, 7.7 Hz, CHC**H**$_2$C=O), 3.12 (1H, dd, *J* = 16.0, 7.4 Hz, C**H**$_2$CHCOPh); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 200.7 (C), 198.8 (C), 144.9 (C), 140.7 (C), 136.9 (C), 136.6 (C), 133.1 (CH), 133.0 (CH), 128.6 (4 x CH), 128.5 (2 x CH), 128.1 (2 x CH), 127.1 (CH), 127.0 (CH), 124.4 (CH), 123.9 (CH), 52.6 (CH), 43.9 (CH_2), 43.1 (CH), 36.9 (CH_2); HRMS (ES) Exact mass calcd for $C_{24}H_{21}O_2$ $[M+H]^+$: 341.1536, found: 341.1538.

Data for *cis*-**377a**: R_f = 0.55 (25% EtOAc/hexanes); IR (film) 2925, 1725, 1682 (C=O), 1596, 1448, 1365, 1222, 1152, 749, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (2H, d, *J* = 7.3 Hz, Ar**H**), 7.74 (2H, d, *J* = 7.3 Hz, Ar**H**), 7.59 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.49 (3H, t, *J* = 7.8 Hz, Ar**H**), 7.36 (2H, t, *J* = 7.8 Hz, Ar**H**), 7.29 (1H, d, *J* = 7.4 Hz, Ar**H**), 7.24 (1H, d, *J* = 7.4 Hz, Ar**H**), 7.20 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.15 (1H, t, *J* = 7.4 Hz, Ar**H**), 4.61 (1H, dt, *J* = 9.3, 7.9 Hz, CH_2C**H**C=O), 4.38 (1H, app q, *J* = 7.2 Hz, C**H**CH_2C=O), 3.65 (1H, dd, *J* = 16.0, 9.4 Hz, C**H**$_2$CHC=O), 3.16 (1H, dd, *J* = 17.8, 7.9 Hz, CHC**H**$_2$C=O), 3.11 (1H, dd, *J* = 17.8, 6.5 Hz, CHC**H**$_2$C=O), 3.07 (1H, dd, *J* = 16.0, 7.7 Hz, C**H**$_2$CHC=O); ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.8 (C), 198.5 (C), 145.0 (C), 141.3 (C), 137.0 (C), 137.0 (C), 133.3 (CH), 132.9 (CH), 128.8 (3 x CH), 128.4 (2 x CH), 127.9 (3 x CH), 127.2 (CH), 126.8 (CH), 124.7 (CH), 124.5 (CH), 50.4 (CH), 43.4 (CH_2), 40.1 (CH_2), 34.0 (CH); HRMS (ES) Exact mass calcd for $C_{24}H_{21}O_2$ $[M+H]^+$: 341.1536, found: 341.1539.

***Trans*-2-(4-Chlorobenzoyl)indan-1-yl]-1-(4-chlorophenyl)ethanone (*trans*-377b) and *Cis*-2-(4-Chlorobenzoyl)indan-1-yl]-1-(4-chlorophenyl)ethanone (*cis*-377b)**

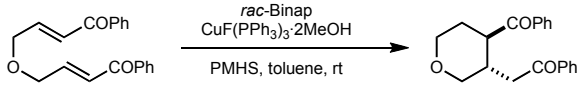


A solution of $CuF(PPh_3)_3{\cdot}2MeOH$ (20 mg, 0.02 mmol), *rac*-Binap (12.4 mg, 0.02 mmol) and **369b** (163 mg, 0.40 mmol) in toluene (1.5 mL) was stirred for 30 min at room temperature, after which a solution of PMHS (24 μL, 0.40 mmol) in toluene (0.4 mL) was added rapidly *via* cannula. The reaction mixture was stirred at room temperature for 24 h before a solution of more $CuF(PPh_3)_3{\cdot}2MeOH$ (20 mg, 0.02 mmol), *rac*-Binap (12.4 mg, 0.02 mmol), and PMHS (24 μL, 0.40 mmol) in toluene (0.5 mL) was added rapidly *via* cannula. After stirring for a further 24 h at room temperature the reaction was quenched carefully by the addition of 1 M HCl (5 mL), the mixture was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (2.5% EtOAc/hexane→10% EtOAc/hexane) gave the *indane trans*-**377b** as a white solid (63 mg, 40%), followed by the *indane cis*-**377b** (3 mg, 2%) as a yellow oil.

Data for *trans*-**377b**: m.p. 130-132 °C; R_f = 0.55 (25% EtOAc/hexanes); IR (film) 2925, 1680 (C=O), 1589, 1570, 1401, 1220, 1092, 1012, 817, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.88 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.45 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.42 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.28-7.21 (4H, m, Ar**H**), 4.43-4.39 (1H, m, C**H**CH_2C=O), 4.08 (1H, dt, *J* = 9.2, 7.1 Hz, CH_2C**H**C=O), 3.53 (1H, dd, *J* = 16.7, 5.5 Hz, CHC**H**$_2$C=O), 3.44 (1H, dd, *J* = 16.0, 9.2 Hz, C**H**$_2$CHC=O), 3.21 (1H, dd, *J* = 16.7, 8.2 Hz, CHC**H**$_2$C=O), 3.09 (1H, dd, *J* = 16.0, 7.4 Hz, C**H**$_2$CHC=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 199.4 (C), 197.6 (C), 144.4 (C), 140.4 (C), 139.7 (C), 139.4 (C), 135.0 (C), 134.8 (C), 129.9 (2 x CH), 129.5 (2 x CH), 128.9 (4 x CH), 127.3 (CH), 127.1 (CH), 124.4 (CH), 123.7 (CH), 52.5 (CH), 43.8 (CH_2), 43.0 (CH), 36.9 (CH_2); HRMS (ES) Exact mass calcd for $C_{24}H_{18}Cl_2O_2Na$ $[M+Na]^+$: 431.0576, found: 431.0577.

Data for *cis*-**377b**: R_f = 0.87 (25% EtOAc/hexanes); IR (film) 2925, 2802, 1682 (C=O), 1589, 1263, 1092, 913, 834, 743, 516 cm^{-1}; H NMR (600 MHz, $CDCl_3$) 7.93 (2H, d, *J* = 8.6 Hz, Ar**H**), 7.68 (2H, d, *J* = 8.6 Hz, Ar**H**), 7.45 (2H, d, *J* = 8.6 Hz, Ar**H**), 7.35 (2H, d, *J* = 8.6 Hz, Ar**H**), 7.30-7.27 (1H, m, Ar**H**), 7.23-7.21 (2H, m, Ar**H**), 7.19-7.16 (1H, m, Ar**H**), 4.55 (1H, app q, *J* = 8.6 Hz, $CH_2C\mathbf{H}C$=O), 4.34 (1H, app q, *J* = 7.3 Hz, $C\mathbf{H}CH_2C$=O), 3.59 (1H, dd, *J* = 16.0, 9.3 Hz, $C\mathbf{H}_2CHC$=O), 3.20 (1H, dd, *J* = 17.7, 7.3 Hz, $CHC\mathbf{H}_2C$=O), 3.10-3.06 (2H, m, $CHC\mathbf{H}_2C$=O and $C\mathbf{H}_2CHC$=O); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 199.913 (C), 197.2 (C), 144.7 (C), 141.2 (C), 139.8 (C), 139.5 (C), 135.4 (C), 135.2 (C), 129.7 (2 x CH), 129.3 (2 x CH), 129.1 (2 x CH), 128.8 (2 x CH), 127.4 (CH), 126.9 (CH), 124.7 (CH), 124.2 (CH), 49.9 (CH), 43.4 (CH), 40.2 (CH_2), 34.2 (CH_2); HRMS (ES) Exact mass calcd for $C_{24}H_{19}Cl_2O_2$ $[M+H]^+$: 409.0757, found: 409.0753.

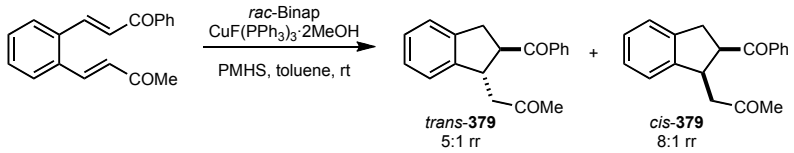
Trans-4-Benzoyltetrahydropyran-3-yl]-1-phenylethanone (378)[80]



A solution of $CuF(PPh_3)_3$·2MeOH (5 mg, 0.005 mmol), *rac*-Binap (3.1 mg, 0.005 mmol) and **374** (61.2 mg, 0.20 mmol) in toluene (0.5 mL) was stirred for 30 min at room temperature, after which a solution of PMHS (6 μL, 0.10 mmol) in toluene (0.2 mL) was added rapidly *via* cannula. The reaction mixture was stirred at room temperature for 24 h before a solution of more $CuF(PPh_3)_3$·2MeOH (5 mg, 0.005 mmol), *rac*-Binap (3.4 mg, 0.005 mmol), and PMHS (6 μL, 0.10 mmol) in toluene (0.3 mL) was added rapidly *via* cannula. After stirring at room temperature for a further 24 h, the reaction was quenched carefully by the addition of 1 M HCl (2 mL), the mixture was extracted with CH_2Cl_2 (3 x 2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane→50% EtOAc/hexane) gave the tetrahydropyran **378** (23 mg, 36%) as a pale yellow oil, which displayed spectral data consistent with those described previously.[80] R_f = 0.26 (25% EtOAc/hexanes); IR (film) 2923, 2852, 1678 (C=O), 1596, 1448, 1280, 1213, 1138, 959, 700 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.99 (4H, dd, *J* = 13.5, 7.3 Hz, Ar**H**), 7.62-7.43 (6H, m, Ar**H**), 4.10-4.01 (2H, m, $OC\mathbf{H}_2CH$ and $OC\mathbf{H}_2CH_2$), 3.61-3.54 (2H, m, $OC\mathbf{H}_2CH_2$

and C**H**C=O), 3.36 (1H, t, *J* = 10.8 Hz, OC**H**$_2$CH), 3.14 (1H, dd, *J* = 15.5, 3.6 Hz, C**H**$_2$C=O), 2.90-2.80 (1H, m, OCH$_2$C**H**), 2.63 (1H, dd, *J* = 15.5, 9.3 Hz, C**H**$_2$C=O), 1.92 (1H, ddd, *J* = 13.5, 6.0, 2.6 Hz, OCH$_2$C**H**$_2$), 1.82-1.70 (1H, m, OCH$_2$C**H**$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 201.6 (C), 198.7 (C), 136.4 (C), 136.1 (C), 133.4 (CH), 133.2 (CH), 128.8 (2 x CH), 128.6 (2 x CH), 128.3 (2 x CH), 128.3 (2 x CH), 70.8 (CH_2), 67.3 (CH_2), 47.1 (CH), 39.8 (CH_2), 33.8 (CH), 30.3 (CH_2); LRMS (ES) 639 ([2M+Na]$^+$, 100), 331 ([M+Na]$^+$, 78).

Trans-2-Benzoylindan-1-yl]propan-2-one (_trans_-379) and _Cis_-2-benzoylindan-1-yl]propan-2-one (_cis_-379)



A solution of $CuF(PPh_3)_3$·2MeOH (20 mg, 0.02 mmol), *rac*-Binap (12.4 mg, 0.02 mmol) and **371** (110 mg, 0.40 mmol) in toluene (1.0 mL) was stirred for 30 min at room temperature, after which a solution of PMHS (24 μL, 0.40 mmol) in toluene (0.6 mL) was added rapidly *via* cannula. The reaction mixture was stirred at room temperature for 24 h before the reaction was quenched by the addition of 1 M HCl (5 mL), the mixture was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane→20% EtOAc/hexane) gave the *indane cis*-**379** (10 mg, 9%) as a yellow oil, followed by the *indane trans*-**379** (24 mg, 22%) as a yellow oil.

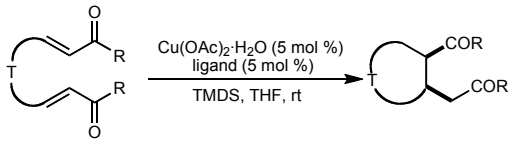
Data for *trans*-**379** (isolated as a 5:1 mixture of inseparable regioisomers): R_f = 0.31 (25% EtOAc/hexanes); IR (film) 2920, 1712 (C=O), 1681 (C=O), 1448, 1361, 1230, 1161, 750, 721, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (major regioisomer) δ 8.00 (2H, dd, *J* = 8.3, 1.2 Hz, Ar**H**), 7.59 (1H, tt, *J* = 7.4, 1.0 Hz, Ar**H**), 7.50 (2H, t, *J* = 7.7 Hz, Ar**H**), 4.28 (1H, app q, *J* = 6.8 Hz, C**H**CH$_2$COCH$_3$), 4.06 (1H, dt, *J* = 9.0, 7.5 Hz, CH$_2$C**H**COPh), 3.41 (1H, dd, *J* = 16.0, 9.3 Hz, C**H**$_2$CHCOPh), 3.08 (1H, dd, *J* = 16.0, 7.9 Hz, C**H**$_2$CHCOPh), 2.99 (1H, dd, *J* = 16.2, 6.0 Hz, CHC**H**$_2$COCH$_3$), 2.72 (1H, dd, *J* = 16.2, 7.6 Hz, CHC**H**$_2$COCH$_3$), 2.18 (3H, s, C**H**$_3$); Diagnostic peaks

of the minor regioisomer were observed at δ 4.16 (1H, dt, *J* = 8.4, 6.0 Hz, C**H**CH_2COPh *or* CH_2C**H**$COCH_3$), 3.49 (1H, dd, *J* = 17.3, 5.2 Hz, CHC**H**$_2$COPh *or* C**H**$_2$$CHCOCH_3$) 3.14 (1H, dd, *J* = 14.6, 6.5 Hz, CHC**H**$_2$COPh *or* C**H**$_2$$CHCOCH_3$), 2.32 (3H, s, C**H**$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) (major regioisomer) δ 207.7 (C), 200.7 (C), 144.5 (C), 140.6 (C), 136.6 (C), 133.1 (CH), 128.7 (2 x CH), 128.5 (2 x CH), 127.1 (CH), 127.0 (CH), 124.3 (CH), 123.6 (CH), 52.5 (CH), 48.7 (CH_2), 42.6 (CH), 36.9 (CH_2), 30.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{22}NO_2$ $[M+NH_4]^+$: 296.1645, found: 296.1646.

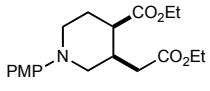
Data for *cis*-**379** (isolated as an 8:1 mixture of inseparable regioisomers): R_f = 0.45 (25% EtOAc/hexanes); IR (film) 2925, 1708 (C=O), 1679 (C=O), 1596, 1448, 1364, 1251, 1228, 1162, 751 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) (Major regioisomer) δ 8.03 (2H, dd, *J* = 8.4, 1.2 Hz, Ar**H**), 7.62-7.58 (1H, m, Ar**H**), 7.50 (2H, t, *J* = 8.4, 1.2 Hz, Ar**H**), 7.27-7.16 (4H, m, Ar**H**), 4.51 (1H, dt, *J* = 9.5, 7.8 Hz, CH_2C**H**COPh), 4.17 (1H, app q, *J* = 7.4 Hz, C**H**CH_2COCH_3), 3.56 (1H, dd, *J* = 15.9, 9.5 Hz, C**H**$_2$CHCOPh), 3.01 (1H, dd, *J* = 15.9, 7.7 Hz, C**H**$_2$CHCOPh), 2.64 (1H, dd, *J* = 17.8, 6.7 Hz, CHC**H**$_2$$COCH_3$), 2.59 (1H, dd, *J* = 17.8, 7.6 Hz, CHC**H**$_2$$COCH_3$), 1.95 (3H, s, C**H**$_3$); Diagnostic peaks of the minor regioisomer were observed at δ 4.27 (1H, app q, *J* = 6.9 Hz, C**H**CH_2COPh), 3.77 (1H, dt, *J* = 9.1, 7.8 Hz, CH_2C**H**$COCH_3$), 3.36 (1H, dd, *J* = 18.0, 7.6 Hz, CHC**H**$_2$COPh), 3.35 (1H, dd, *J* = 15.8, 9.3 Hz, C**H**$_2$$CHCOCH_3$), 3.09 (1H, dd, *J* = 18.0, 6.1 Hz, CHC**H**$_2$COPh), 2.99 (1H, dd, *J* = 15.8, 7.7 Hz, C**H**$_2$$CHCOCH_3$), 2.26 (3H, s, C**H**$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) (major regioisomer) δ 207.1 (C), 200.9 (C), 145.0 (C), 141.3 (C), 137.0 (C), 133.4 (CH), 128.8 (2x CH), 128.3 (2 x CH), 127.2 (CH), 126.8 (CH), 124.7 (CH), 124.2 (CH), 50.0 (CH), 44.9 (CH_2), 43.1 (CH), 33.9 (CH_2), 30.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{22}NO_2$ $[M+NH_4]^+$: 296.1645, found: 296.1650.

2.4.4 Enantioselective Reductive Michael Cyclisations

General Procedure H: Enantioselective Reductive Michael Cyclisations with $Cu(OAc)_2 \cdot H_2O$ and TMDS

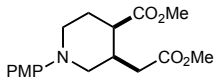


A solution of $Cu(OAc)_2 \cdot H_2O$ (4.0 mg, 0.02 mmol) and the appropriate chiral ligand (0.02 mmol) in THF (0.4 mL) was stirred for 15 min before TMDS (71 μL, 0.40 mmol) was added. The initially blue solution was stirred until it became yellow (*ca.* 5 min), after which a solution of the substrate (0.40 mmol) in THF (0.4 + 0.2 mL rinse) was then added rapidly *via* cannula. The mixture was stirred at room temperature for 18 h, quenched carefully with 1 M HCl (1 mL), diluted with H_2O (15 mL) and then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*, and purification of the residue by column chromatography (EtOAc/hexane) afforded the cyclized product.



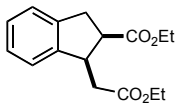
***Cis*-3-Ethoxycarbonylmethyl-1-(4-methoxyphenyl)piperidine-4-carboxylic acid ethyl ester (335a)**.

The title compound was prepared using a slight modification of the quantities described in General Procedure H from **327a** (104 mg, 0.30 mmol), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol), TMDS (55 μL, 0.30 mmol) and (*S*)-DM-Segphos (10.8 mg, 0.015 mmol) to the enantioenriched product (43 mg, 41%). R_f = 0.32 (25% EtOAc/hexanes); $[\alpha]_D^{21}$ –88.5 (c. 0.66, CH_2Cl_2); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:isopropanol, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 11.6 min, t_r (major) = 12.9 min; 91% ee.



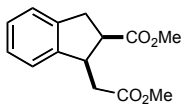
Cis-3-Meoxycarbonylmethyl-1-(4-methoxyphenyl)piperidine-4-carboxylic acid methyl ester (335b)

The title compound was prepared using a slight modification of the quantities described in General Procedure H from **327b** (159 mg, 0.50 mmol), $Cu(OAc)_2 \cdot H_2O$ (5.0 mg, 0.025 mmol), TMDS (88 μL, 0.50 mmol) and (*R*)-MeO-biphep (14.6 mg, 0.025 mmol) to give the enantioenriched product (52.2 mg, 33%). Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (99:1 hexanes:isopropanol, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 13.9 min, t_r (minor) = 15.9 min; 93% ee; $[\alpha]_D^{21}$ +37.3 (c. 0.04, CH_2Cl_2).



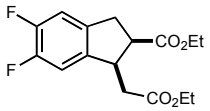
***Cis*-1-Ethoxycarbonylmethylindan-2-carboxylic acid ethyl ester (351a)**.

The title compound was prepared according to General Procedure H from **341a** (110 mg, 0.40 mmol) and (*S*)-Segphos (12.2 mg, 0.02 mmol) and purified by column chromatography (5% EtOAc/hexane) to give the enantioenriched product as a 12:1 inseparable mixture of diastereomers (63 mg, 57%). $[\alpha]_D^{21}$ +27.0 (c. 0.74, CH_2Cl_2); Enantiomeric excess of the major diastereomer was determined by HPLC with a Chiralpak OD-H column (99.5:0.5 hexane:isopropanol, 0.5 mL/min, 225 nm, 0 °C); t_r (major) = 17.0 min, t_r (minor) = 18.1 min; 94% ee.



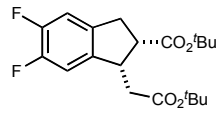
***Cis*-Methoxycarbonylmethylindan-2-carboxylic acid methyl ester (351b)**.

The title compound was prepared according to General Procedure H from **341b** (98 mg, 0.40 mmol) and (*S*)-Segphos (12.2 mg, 0.02 mmol) and purified by column chromatography (5% EtOAc/hexane) to give the enantioenriched product as a 6:1 inseparable mixture of diastereomers (41 mg, 41%). $[\alpha]_D^{21}$ +25.3 (c. 0.32, CH_2Cl_2); Enantiomeric excess of the major diastereomer was determined by HPLC with a Chiralpak AD-H column (99.5:0.5 hexane:isopropanol, 0.5 mL/min, 210 nm, 0 °C); t_r (minor) = 19.0 min, t_r (major) = 20.7 min; 93% ee.



***Cis*-1-Ethoxycarbonylmethyl-5,6-difluoroindan-2-carboxylic acid ethyl ester (353a)**.

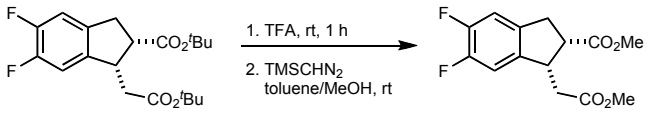
The title compound was prepared according to General Procedure H, but using half of all quantities from **347a** (62 mg, 0.20 mmol) and (*S*)-Segphos (6.1 mg, 0.01 mmol) and purified by column chromatography (2.5% EtOAc/hexane→5% EtOAc/hexane) to give the enentioenriched product (33 mg, 53%). $[\alpha]_D^{21}$ +37.3 (c. 1.13, CH_2Cl_2); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (99:1 hexane:isopropanol, 0.8 mL/min, 210 nm, 25 °C); t_r (minor) = 10.7 min, t_r (major) = 11.5 min; 92% ee.



***Cis*-1-*tert*-Butoxycarbonylmethyl-5,6-difluoroindan-2-carboxylic acid *tert*-butyl ester (353b)**.

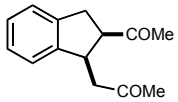
The title compound was prepared according to General Procedure H, but using half of all quantities, from **347b** (73 mg, 0.20 mmol) and (*R*)-Binap (6.2 mg, 0.01 mmol) and purified by column chromatography (2.5% EtOAc/hexane→10% EtOAc/hexane) to give the enantioenriched product (39 mg, 54%). $[\alpha]_D^{21}$ –46.7 (c. 1.97, CH_2Cl_2); Enantiomeric excess was determined from **353b**.

***Cis*-5,6-Difluoro-1-methoxycarbonylmethylindan-2-carboxylic acid methyl ester (355)**



TFA (1 mL) was added to **353b** (25 mg, 0.07 mmol) and the resulting solution was stirred at room temperature for 1 h. The reaction was concentrated *in vacuo* and the resulting *bis-acid* was dissolved in a mixture of MeOH (0.1 mL) and toluene (0.2 mL). Trimethylsilyldiazomethane (2.0 M in Et_2O, 70 μL, 0.14 mmol) was added dropwise over 1 min and the mixture was stirred at room temperature for 16 h. The reaction was concentrated *in vacuo* and the residue was purified by column chromatography (5% EtOAc/hexane→20% EtOAc/hexane) to give the enantioenriched product **355** (10 mg, 52%). $[\alpha]_D^{21}$ –56.3 (c. 0.36, CH_2Cl_2);

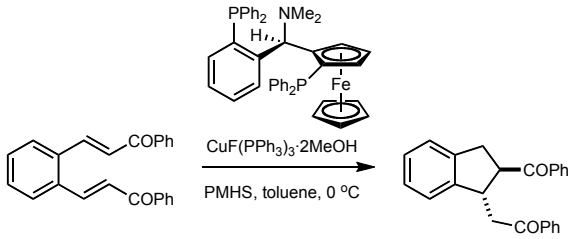
Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (99:1 hexane:isopropanol, 0.8 mL/min, 230 nm, 25 °C); t_r (major) = 16.6 min, t_r (minor) = 21.6 min; 90% ee.



Cis-2-Acetylindan-1-yl)propan-2-one (_cis_-375).

The title compound was prepared according to General Procedure H from **367** (86 mg, 0.4 mmol) and (*S*)-Segphos (12.2 mg, 0.02 mmol) and purified by column chromatography (5% EtOAc/hexane→20% EtOAc/hexane) to give the enantioenriched product (36 mg, 41%). $[\alpha]_D^{21}$ +17.8 (c. 1.35, CH_2Cl_2); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (99:1 hexane:isopropanol, 0.8 mL/min, 225 nm, 25 °C); t_r (minor) = 19.2 min, t_r (major) = 20.6 min; 97% ee.

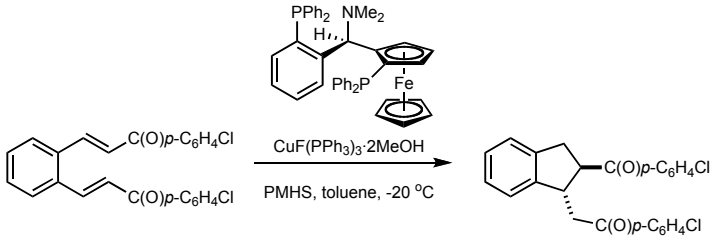
2-[(1*S*,2*R*)-2-Benzoylindan-1-yl]-1-phenylethanone[79] (377a)



A solution of $CuF(PPh_3)_3$·2MeOH (20 mg, 0.02 mmol), Taniaphos ligand (*R*,*R*)-**L21** (13.7 mg, 0.02 mmol) and **369a** (135 mg, 0.40 mmol) in toluene (1.5 mL) was stirred for 30 min at room temperature, after which the mixture was cooled to 0 °C. A solution of PMHS (24 μL, 0.40 mmol) in toluene (0.4 mL) was added rapidly *via* cannula. The reaction mixture was stirred at 0 °C for 24 h before a solution of more $CuF(PPh_3)_3$·2MeOH (20 mg, 0.02 mmol), (*R*,*R*)-**L21** (13.7 mg, 0.02 mmol), and PMHS (24 μL, 0.40 mmol) in toluene (0.5 mL) was added rapidly *via* cannula. After stirring at 0 °C for a further 24 h, the reaction was quenched carefully by the addition of 1 M HCl (5 mL), the mixture was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane→20% EtOAc/hexane) gave the enantioenriched product **377a** (62 mg, 46%). $[\alpha]_D^{21}$ –33.3 (*c*. 2.38, CH_2Cl_2); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column

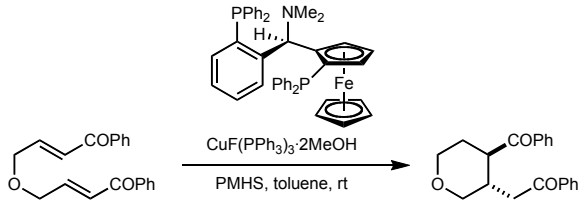
(90:10 hexane:isopropanol, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 36.7 min, t_r (major) = 39.9 min; 83% ee.

2-[(1*S*,2*R*)-2-(4-Chlorobenzoyl)indan-1-yl]-1-(4-chlorophenyl)ethanone (377b)



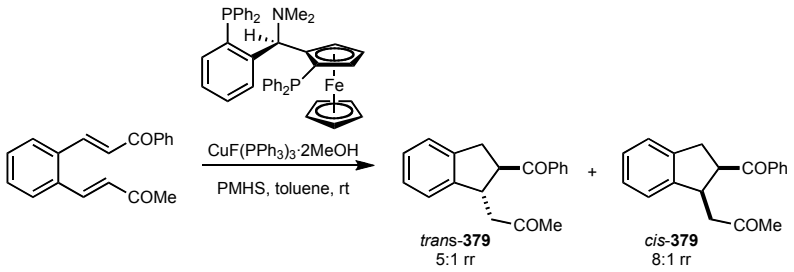
A solution of $CuF(PPh_3)_3{\cdot}2MeOH$ (5 mg, 0.005 mmol), Taniaphos ligand (*R*,*R*)-**L21** (3.4 mg, 0.005 mmol) and **369b** (41 mg, 0.10 mmol) in toluene (0.5 mL) was stirred for 30 min at room temperature, after which the mixture was cooled to –20 °C and a solution of PMHS (6 μL, 0.10 mmol) in toluene (0.2 mL) was added rapidly *via* cannula. The reaction mixture was stirred at –20 °C for 24 h before a solution of more $CuF(PPh_3)_3{\cdot}2MeOH$ (5 mg, 0.005 mmol), (*R*,*R*)-**L21** (3.4 mg, 0.005 mmol), and PMHS (6 μL, 0.10 mmol) in toluene (0.3 mL) was added rapidly *via* cannula. After stirring at –20 °C for a further 24 h, the reaction was quenched carefully by the addition of 1 M HCl (2 mL), the mixture was extracted with CH_2Cl_2 (3 x 2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (2.5% EtOAc/hexane→10% EtOAc/hexane) gave the enantioenriched product **377b** (17 mg, 41%) as a white solid. Recrystallization of **376b** from CH_2Cl_2/hexane gave colorless crystals that were suitable for X-ray crystallography. $[\alpha]_D^{21}$ –109.5 (c. 0.73, CH_2Cl_2); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (80:20 hexane:isopropanol, 0.8 mL/min, 230 nm, 25 °C); t_r (major) = 41.3 min, t_r (minor) = 56.0 min; 90% ee.

2-[(3*S*,4*R*)-4-Benzoyltetrahydropyran-3-yl]-1-phenylethanone[80] (378)



A solution of $CuF(PPh_3)_3$·2MeOH (5 mg, 0.005 mmol), Taniaphos ligand (*R*,*R*)-**L21** (3.4 mg, 0.005 mmol) and **374** (30.6 mg, 0.10 mmol) in toluene (0.5 mL) was stirred for 30 min at room temperature, after which the mixture was cooled to –20 °C and a solution of PMHS (6 μL, 0.10 mmol) in toluene (0.2 mL) was added rapidly *via* cannula. The reaction mixture was stirred at –20 °C for 24 h before a solution of more $CuF(PPh_3)_3$·2MeOH (5 mg, 0.005 mmol), (*R*,*R*)-**L21** (3.4 mg, 0.005 mmol), and PMHS (6 μL, 0.10 mmol) in toluene (0.3 mL) was added rapidly *via* cannula. After stirring at –20 °C for a further 24 h, the reaction was quenched carefully by the addition of 1 M HCl (2 mL), the mixture was extracted with CH_2Cl_2 (3 x 2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane→50% EtOAc/hexane) gave the enantioenriched product **378** (17 mg, 54%). $[\alpha]_D^{21}$ –9.8 (c. 0.41, CH_2Cl_2); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (90:10 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 20.5 min, t_r (minor) = 23.8 min; 52% ee.

1-[(1*S*,2*R*)-2-Benzoylindan-1-yl]propan-2-one (*trans*-379) and 1-[(1*R*,2*R*)-2-benzoylindan-1-yl]propan-2-one (*cis*-379)



A solution of $CuF(PPh_3)_3$·2MeOH (20 mg, 0.02 mmol), Taniaphos ligand (*R*,*R*)-**L21** (13.7 mg, 0.02 mmol) and **371** (111 mg, 0.40 mmol) in toluene (1 mL) was stirred for 30 min at room temperature, after which a solution of PMHS (24 μL, 0.40 mmol)

in toluene (0.6 mL) was added rapidly *via* cannula. The mixture was stirred at room temperature for 24 h, quenched carefully with 1 M HCl (5 mL), and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane→20% EtOAc/hexane) gave the *indane cis*-**379** (13 mg, 12%) as a yellow oil, followed by the *indane trans*-**379** (33 mg, 30%) as a yellow oil.

Data for *trans*-**379** (isolated as a 5:1 mixture of inseparable regioisomers): $[\alpha]_D^{21}$ – 95.0 (c. 1.01, CH_2Cl_2); Enantiomeric excess of the major regioisomer was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:isopropanol, 0.8 mL/min, 225 nm, 25 °C); t_r (minor) = 24.3 min, t_r (major) = 25.8 min; 80% ee.

Data for *cis*-**379** (isolated as an 8:1 mixture of inseparable regioisomers): $[\alpha]_D^{21}$ – 50.0 (c. 0.36, CH_2Cl_2); Enantiomeric excess of the major regioisomer was determined by HPLC with a Chiralpak AD-H column (95:05 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 13.6 min, t_r (minor) = 19.7 min; 67% ee.

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4 Appendix

Publications

Enantioselective Copper-Catalysed Reductive Michael Cyclizations. Oswald, C.L.; Peterson, J. P.; Lam. H. W. *Org. Lett.* **2009**, *11*, 4504-4507.