Development of Catalytic Stereoselective Reductive Aldol Reactions

A Thesis Submitted for the degree of

Doctor of Philosophy

by

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Abstract

The chemistry of enolates can be considered one of the cornerstone areas in organic chemistry. Regioselective generation of an enolate in the presence of several enolisable sites can often prove to be a difficult task. Discoveries in recent years have led to new areas of enolate formation in the presence of other carbonyl groups. These include reductive aldol chemistry where direct reductive aldol coupling of an *α,β*-unsaturated carbonyl group in presence of a carbonyl electrophile enables often perfectly regioselective reactions to occur. This tandem conjugate reduction-electrophilic trapping process enables the reaction to be performed in a "one-pot" manner.

The first examples of asymmetric copper-catalysed reductive aldol reactions have been developed for the formation of a range of *β*-hydroxylactone products. A combination of $Cu(OAc)_2 \cdot H_2O$ with different bisphosphine ligands catalyses these intramolecular reductive aldol reactions. TMDS (1,1,3,3-tetramethylhydrosiloxane) is used as a stoichiometric hydride source. The reaction proceeds with high relative stereocontrol (>19:1 dr), while absolute stereocontrol remains modest (up to 83% ee). The yields range from moderate to good.

A continuous search for improved reaction conditions led to the discovery that cobalt-catalysed reductive aldol reactions have an advantage over the copper-catalysed reaction in the cases where 4-hydroxypiperidin-2-one products are formed. When $Co(acac)_2 \cdot H_2O$ is used together with Et_2Zn as the stoichiometric reductant, an increased substrate scope is observed while the diastereoselectivity of the reaction remains high. Yields are also remarkably higher compared to the results obtained with the copper catalyst. These reaction conditions are also used to perform intermolecular reductive aldol reactions between a range of *α,β*-unsaturated amides and ketones. The reactions proceed readily with high diastereoselectivities (up to >19:1 *syn:anti*) and good yields. Asymmetric variants have been studied by the use

of a chiral oxazolidine auxiliary. Although good selectivities have been obtained, this method currently suffers from the fact that the chiral auxiliary is difficult to cleave.

$Ni(acac)_2$ was also found to perform the intramolecular reductive aldol reaction. Et_2Zn was again used as the stoichiometric reductant. The nickel-catalysed reaction increased the reaction scope still further. This time both β-hydroxylactone and 4-hydroxypiperidin-2-one products were readily formed. The former proceeded with increased yields compared to those obtained with the copper catalyst, and, the latter with comparable results to those obtained with the cobalt catalyst.

To Rosa Maria

Acknowledgements

I would like to thank Dr Hon Wai Lam for the opportunity to work in his group and for introducing me into the fascinating world of reductive aldol chemistry. I am grateful for his guidange and encouragement during this project.

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I reserve this last space for the people that mean the most to me. I own my gratitude to my friends in Finland. There are too many of you to be mentioned by name but I am sure you all know who I mean. I had to come this far to realise the true meaning of your friendship. I would like to thank my family: Mother, Father, Jussi, Olli, Helmi, Kirsi and Mia. Thanks for all that unlimited support you have

given me. Finally, I would like to dedicate this manuscript to my love, Rosa Maria. You are my soulmate, my best friend, my everything. You always have that shoulder I can lean on and you constantly offer me your support. You must be some sort of gift from the Gods. The last year was hard for us because of the distance, but you still kept on smiling and bringing the smile to my face. Thank You!

Declaration

I hereby declare that, except where specific reference is made to other sources, the work contained in this thesis is the original work of my own research since the registration of the PhD degree in September 2004, and any collaboration has been 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.

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Pekka Matias Joensuu

February 2008

Abbreviation

acac	acetyl acetonate
°C	degrees Celsius
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BIPHEMP	(6,6'-dimethylbiphenyl-2,2'-diyl) bis(diphenylphosphine)
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
box	2,2'-isopropylidenebis-2-oxazoline
^{t}Bu	*tert*-butyl
*i*Bu	*iso*-butyl
DCM	dichloromethane
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMI	l,3-dimethylimidazolidinone
Cod	cyclooctadiene
dpm	dipivaloylmethane
DPPF	1,1'-diphenylphosphinoferrocene
DTMB-SEGPHOS	(4,4'-bi-1,3-benzodioxiol)-5,5'-diylbis(di(3,5-di-*t*-butyl-4-methoxyphenyl)-phosphine)
EtOAc	ethyl acetate
FAB	fast atom bombardment
HRMS	high resolution mass spectrometry
IR	infra-red

KOAc	potassium acetate
Me-Duphos	1,2-Bis(2,5-dimethylphospholano)benzene
MeO-BIPHEP	(6,6'-Dimethoxybiphenyl-2,2'-diyl) bis(diphenylphosphine)
MEMCl	2-methoxyethoxymethyl chloride
MeOH	methanol
mg	milligram
mmol	millimole
mol	mole
MOP	2-(diphenylphosphino-2-methoxy-1,1'-binaphthyl
NMR	nuclear magnetic resonance
OMP	*o*-methoxyphenyl
Ph	phenyl
Phebox	bisoxazolinylphenyl
Ph-semicorrin	4-phenyl-R-[4-phenyloxazolidin-2-ylidene]-2-oxazoline-2-acetonitrile
PMHS	poly(methylhydrosiloxane)
PMP	*p*-methoxyphenyl
(R,S)-PPF-P^{t}Bu$_2$	(R)-(-)-1-[(S)-2-Diphenylphosphino) ferrocenyl]ethylidi-*tert*-butylphosphine
(R,S)-PPF-Pxyl$_2$	(R)-(-)-1-[(S)-2-Diphenylphosphino) ferrocenyl]ethyl-bis-(3,5-dimethylphenyl) phosphine
ppm	parts per million
^{i}Pr	*iso*-propyl

p-tol-BINAP	2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl
Pybox	2,6-bis(oxazolin-2'-yl)pyridine
Quinap	1-(2-diphenylphosphino-1-naphthyl)isoquinoline
rt	room temperature
SEGPHOS	(4,4'-bi-1,3-benzodioxiol)-5,5'-diylbis(diphenylphosphine)
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TOF	turnover frequency
TON	turnover number
HPLC	high performance liquid chromatography
tlc	thin layer chromatography
TMDS	1,1,3,3-tetramethyldisiloxane
Walphos	(R)-(-)-1-[(R)-2-(2'-Diphenylphosphinophenyl) ferrocenyl]ethyldi(bis-3,5-trifluoromethylphenyl)phosphine

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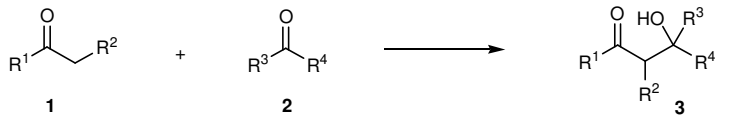
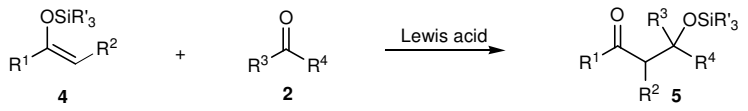
1. Chapter 1: Introduction to Reductive Aldol Reactions

Enolates are undeniably one of the most important classes of carbon nucleophiles in organic chemistry. Enolate chemistry is used in several classical transformations, including the aldol reaction.[1] The aldol reaction is the addition of the α-carbon of an enolisable carbonyl species to an aldehyde or ketone to generate a *β*-hydroxycarbonyl moiety (Eqn 1).



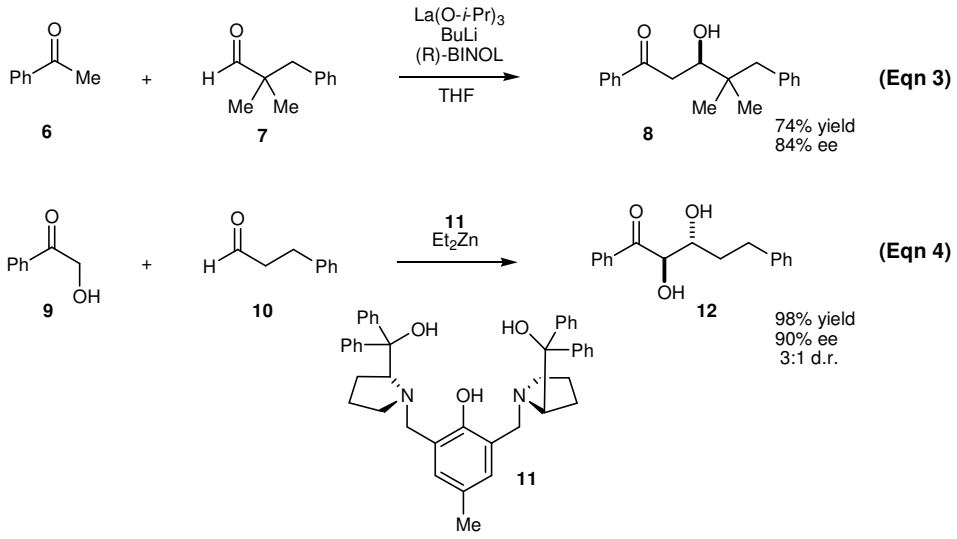
1 **2** **3** **(Eqn 1)**

Although studied for over a century,[2] one of the main problems in enolate formation, namely regioselectivity, remains only partially resolved. In the optimal case, molecules possessing multiple enolisable sites should be subject to chemo- and regioselective formation of the enolate. This is rarely the case, and often catalytic processes involving enolate formation employ modified reactants. The most common of these modified reagents are the silyl enol ethers that are used in the Mukaiyama aldol reaction (Eqn 2).[3]



4 **2** **5** **(Eqn 2)**

Some recently described examples of enantioselective catalytic direct aldol condensations use unmodified ketones as pronucleophiles.[4] Even though this progress is undeniably significant, it does not resolve the problem of regioselectivity. In these reactions, ketones possessing only one enolisable site (Eqn 3)[5] or ketones where enolate formation is directed by an α-hydroxy group (Eqn 4)[6] were utilised.



The utilisation of α,β-unsaturated carbonyl groups as 'latent' enolates enables the enolates to be formed in a regioselective manner. The enolate is formed by conjugate reduction of an α,β-unsaturated carbonyl group and if this 1,4-Reduction is followed by an aldol reaction, highly regioselective aldol product is obtained.

1.1. Rhodium-Catalysed Reductive Aldol Reactions

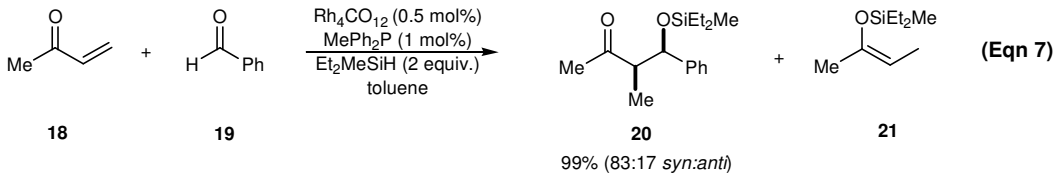
Reductive aldol reactions have been catalysed by numerous metals. In the following section, we will discuss the major developments that have been achieved so far in this area. For convenience, we will consider each metal in turn, rather than introducing the developments in chronological order.

1.1.1. Hydrosilane-Mediated and Related Reactions

The first example of a reductive aldol reaction was reported by Revis and Hilty in 1987.[7] When the reaction of methyl methacrylate (1 equiv), acetone (excess) and trimethylsilane (1.3 equiv) was carried out in the presence of a substoichiometric amount of $RhCl_3 \cdot 3H_2O$ (9 mol%) aldol product **15** was isolated in 95% yield (Eqn 5). In addition, 5% of silyl ketene acetal **16** was isolated. Silyl ketene acetal **16** was also synthesised independently and then reacted with acetone and a substoichiometric amount of $RhCl_3 \cdot 3H_2O$ to see whether the reaction proceeded through **16** as an intermediate, which could then further react with acetone. In this reaction, only 2 % of the aldol product **15** was formed. Further evidence of the assumed absence of **16**

was gained when the reaction was performed by using Spier's catalyst, H_2PtCl_6, instead of the rhodium salt (Eqn 6). Two main products, **15** and **17**, were obtained. If the reaction was performed in the absence of acetone, only **17** was formed, thus strongly suggesting that the reaction does not proceed through silyl ketene acetal. The scope of this new 'hydrosilylative condensation' was limited to esters as pro-nucleophiles, while both ketones and aldehydes could serve as electrophiles.

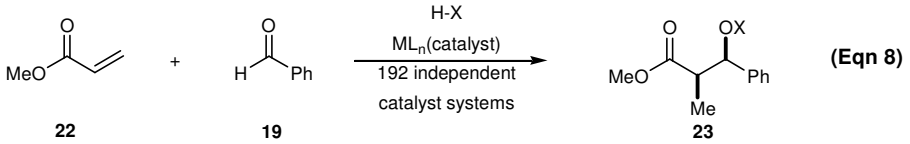
Matsuda and co-workers were the first to report successful direct coupling of *α,β*-unsaturated ketones with aldehydes and trialkylsilanes.[8] A remarkably low loading (0.5 mol %) of $Rh_4(CO)_{12}$ was utilised in the reaction between methyl vinyl ketone (**18**), PhCHO (**19**) and Et_2MeSiH to give a nearly quantitative yield of silylated aldol product **20** (Eqn 7). Modest diastereoselectivity (87:13 *syn:anti*) was observed. Before reaction conditions were optimised, the formation of silyl enol ether **21** as a side-product was the initial concern for the reaction. This was overcome by using an excess of enone and silane. Another important factor in minimising the formation of the side-product was to conduct the reaction at temperatures below 0 °C.



Although the reactions were successful using benzaldehyde as an electrophile, enolisable aldehydes failed to provide acceptable results. This problem

was surmounted by modification of the catalyst. When $Rh_4(CO)_{12}$ was mixed with $MePh_2P$ (2 equiv.) at room temperature and then used as catalyst in the reaction, enolisable aldehydes also gave reasonable results.

Although at this stage, good yields had been obtained in reductive aldol reactions with Rh-catalysts, the diastereoselectivities were poor. One reason for the lack of breakthrough in this chemistry was the fact that little was known of the mechanism of the reaction. It was very difficult to know which of the variables to change in the reaction conditions to increase the reactivity and/or the selectivity. Morken and co-workers decided to approach this problem with a high-throughput evaluation of 192 independent catalyst systems.[9] The screening was performed in glass 96-well plates. It was hypothesised that the transition metal salt, ligand and hydride source would have the biggest influence in the reaction so these were selected as variables. As a model reaction, they performed the reductive aldol reaction between methyl acrylate and benzaldehyde (Eqn 8). In the initial array, four transition metal salts, seven ligands (plus a blank) and six hydride sources were employed.



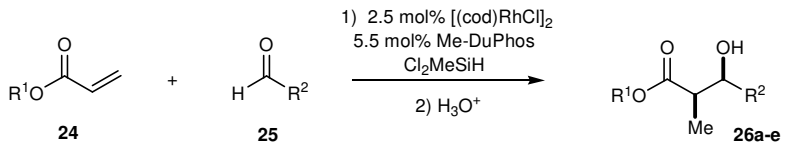
22 **19** **23** **(Eqn 8)**

Transition metal salts: $Co(acac)_2$, $[(allyl)PdCl]_2$, $[(cod)IrCl]_2$, $[(cod)RhCl]_2$
Ligands: *i*Pr-Pybox, *t*bu-Box, Ph-semicorrin, MOP, BINAP, Me-DuPhos,Quinap, no ligand
Hydride sources: Cl_2MeSiH, Et_2MeSiH, $PhSiH_3$, Ph_2SiH_2, catechol borane, Cl_3SiH

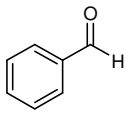
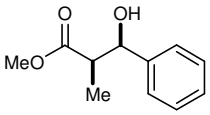
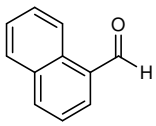
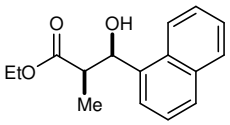
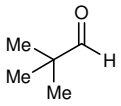
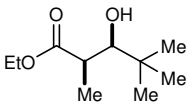
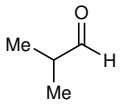
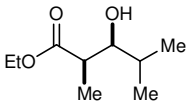
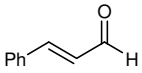
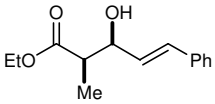
The most promising result was obtained with a catalyst system derived from combination of $[(cod)RhCl]_2$, Me-DuPhos and Cl_2MeSiH. The product **26a** was formed with 23:1 (*syn:anti*) selectivity and in 69% yield in a preparative scale reaction (Table 1.1, Entry 1). While aromatic aldehydes gave moderate yields and useful diastereoselectivities, reactions involving aliphatic aldehydes failed to give satisfactory yields, although diastereoselectivities remained high (Entries 3-4). It is noteworthy that unsaturated aldehydes can also participate in the reaction without

interference from competitive conjugate reduction (Entry 5). Remarkably, all the reactions gave racemic products, even if the ligand in use was chiral.

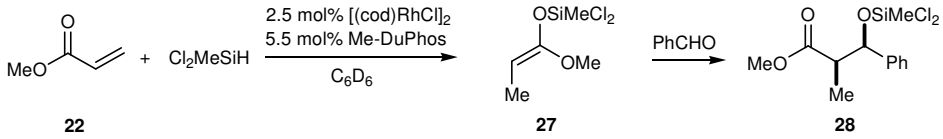
Table 1.1. Catalytic Stereoselective Reductive Aldol Reaction



24 + **25** → **26a-e**

Entry	RCHO	Product	Yield (%)	*syn:anti*
1		 **26a**	69	23:1
2		 **26b**	82	10:1
3		 **26c**	38	21:1
4		 **26d**	15	15:1
5		 **26e**	41	>20:1

Further studies of these conditions provided an explanation as to why the reaction had proceeded without giving enantiomerically enriched products.[10] When the reaction was monitored by ^{1}H NMR spectroscopy it was realised that the reaction proceeded through a silyl ketene acetal intermediate **27**. In the absence of the aldehyde, methyl acrylate (**22**) was completely converted into a new compound that was spectroscopically consistent with the silyl ketene acetal in its *E*-configuration (**27**). Subsequent addition of benzaldehyde led to a quick disappearance of the silyl ketene acetal and the silylated aldol product **28** was isolated.



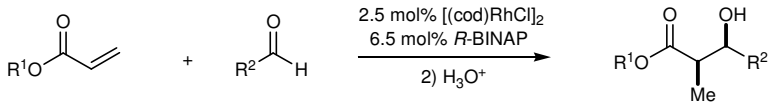
22 27 28

Scheme 1.1. Reaction pathway suggested by ^{1}H NMR studies

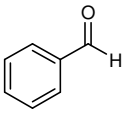
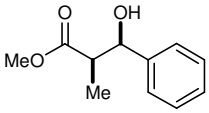
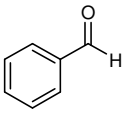
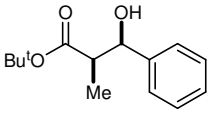
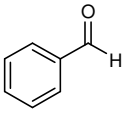
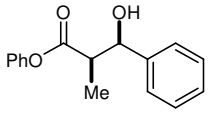
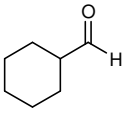
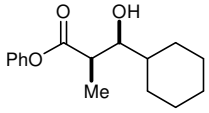
It was also found out that Rh-salt does not play a part in the final aldol addition step. This was proven by initially forming the silyl ketene acetal which was then vacuum-distilled from the metal complex, followed by the addition of benzaldehyde to this metal-free silyl ketene acetal. This led to the product **28** with high stereoselectivity. It was also observed that if the reactions were performed in two stages the yields increased dramatically, in comparison to those performed in one step.

The first enantioselective reductive aldol reaction was also developed by the group of Morken.[11] In the original high-throughput studies they found that catalyst system containing $[(cod)RhCl]_2$, *R*-BINAP and Et_2MeSiH led to the aldol product of methyl acrylate and benzaldehyde in 20% enantiomeric excess. It was also observed that in the microscale assay, the reactivity of $[(cod)RhCl]_2$ without the ligand was higher than with the ligand. It was assumed that in the microscale reaction, the complexation of the ligand was insufficient thus leaving the more active uncomplexed metal salt to react in a nonselective way. When the reactions were performed under the optimised conditions, good enantiomeric excesses were observed (Table 1.2). Although reasonable enantioselectivities were achieved, the diastereoselectivities remained poor. Stereoselectivities were highly dependent on the

Table 1.2. Rh-Catalysed Enantioselective Aldol Reactions



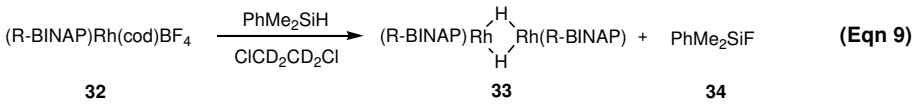
29 30 31a-d

Entry	RCHO	Product		Yield (%)	d.r. *syn:anti*	ee syn (anti)(%)
1			**31a**	37	1.7:1	91 (88)
2			**31b**	21	1.4:1	58 (38)
3			**31c**	72	3.4:1	87 (34)
4			**31d**	54	3.9:1	84 (48)

structure of the acrylates. Methyl acrylate and benzaldehyde provided the product in good enantiopurity (Entry 1). When the more bulky *tert*-butyl acrylate was used, the enantioselectivity was significantly lowered (Entry 2). Electronic effects in the acrylate component seemed to play an important role in this reaction as phenyl acrylate reacted with benzaldehyde (Entry 3) to give the aldol product with high enantioselectivity, modest diastereoselectivity and significantly higher yield than with methyl acrylate. The use of nonaromatic aldehyde gave the product **31d** with comparable enantioselectivity but diminished yield (Entry 4).

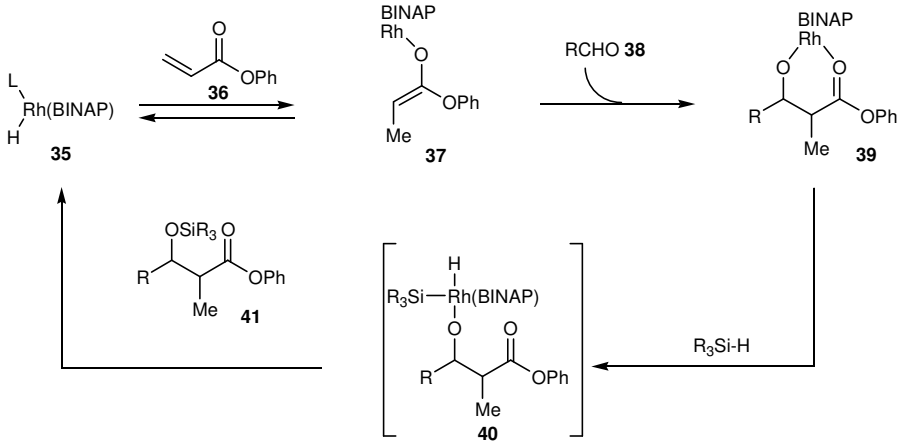
It was immediately assumed that the reaction does not proceed *via* initial formation of a silyl ketene acetal, as it had proceeded in the case where catalyst system had been formed with $[(cod)RhCl]_2$, Me-DuPhos and Et_2MeSiH (Scheme 1.1). Further investigation of the mechanism was reported in a later publication.[12] For a better understanding of the mechanism, (*R*-BINAP)Rh(cod)BF_4 was subjected to each of the reaction components (acrylate, aldehyde and silane) under similar reaction conditions as described above. Neither acrylate nor aldehyde reacted with the precatalyst, but reaction of the precatalyst with $PhMe_2SiH$ provided a free

cyclooctadiene and a C_2-symmetric species **33** (Eqn 9). ^{19}F NMR spectroscopy also indicated that $PhMe_2SiF$ (**34**) was formed.



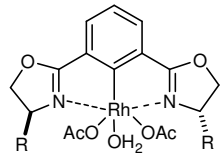
(Eqn 9)

Based on these observations, Morken and co-workers described a proposed mechanism for the reaction (Scheme 1.2). The dissociation of the bridged Rh-dimer **33** provides Rh(I)-hydride **35** that can then react with the acrylate to form an enolate **37**. This enolate then reacts with the aldehyde in an aldol addition step to form an aldolate **39**. This is followed by an oxidative addition/reductive elimination sequence with the silane to produce silylated alcohol **41** and Rh(I)-hydride (**35**) to close the catalytic cycle.

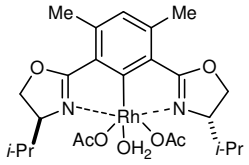


Scheme 1.2. Proposed mechanism for the Rh-catalysed reductive aldol reaction

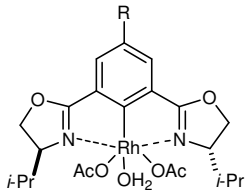
In recent years Nishiyama and co-workers have reported a series of screenings of different chiral Rh(Phebox)-complexes (Scheme 1.3) and silanes in reductive aldol reactions between *tert*-butyl acrylate and aldehydes.[13]



R = *i*-Pr, Rh(Phebox-*ip*)$(OAc)_2$ (**42a**)
R = Bn, Rh(Phebox-*bn*)$(OAc)_2$ (**42b**)



Rh(3,5-dm-Phebox)$(OAc)_2$ (**43**)

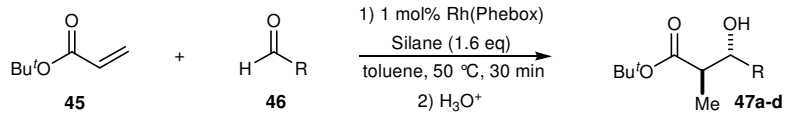


R = NO_2, Rh(4-NO_2-Phebox)$(OAc)_2$ (**44a**)
R = OMe, Rh(4-MeO-Phebox)$(OAc)_2$ (**44b**)

Scheme 1.3. Chiral Rh(Phebox)-complexes

Very high levels of *anti*-selectivities were observed (above 95:5 *anti:syn*) in most cases. Representative examples of these screenings are shown in Table 1.3.

Table 1.3. Rh(Phebox)-Catalysed Intermolecular Reductive Aldol Reaction



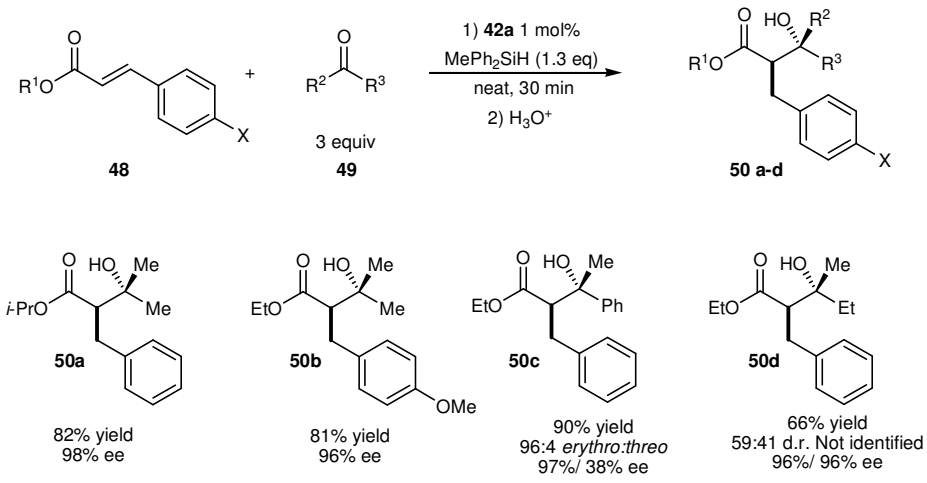
45 + **46** → **47a-d**

Entry	Catalyst	Silane	R	Yield (%)(Product)	anti:syn	ee (%) anti (syn)
1	**42a**	(EtO)Me_2SiH	Ph	93 (**47a**)	94:6	94 (2)
2	**42a**	Me_2PhSiH	Ph	93 (**47a**)	94:6	95 (5)
3	**42b**	$(EtO)_2$MeSiH	Ph	98 (**47a**)	98:2	96 (54)
4	**42a**	(EtO)Me_2SiH	4-MeO-Ph	94 (**47b**)	93:7	94 (1)
5	**42a**	$(EtO)_2$MeSiH		58 (**47c**)	95:5	95 (5)
6	**42a**	Me_2PhSiH		0 (**47c**)	-	-
7	**42a**	Me_2PhSiH	4-CF_3-Ph	95 (**47d**)	87:13	93 (27)
8	**43**	$(EtO)_2$MeSiH	Ph	98 (**47a**)	95:5	92 (7)
9	**44a**	$(EtO)_2$MeSiH	Ph	82 (**47a**)	96:4	93 (10)
10	**44b**	$(EtO)_2$MeSiH	Ph	90 (**47a**)	94:6	92 (17)

From the results, it can be seen that all the Rh(Phebox)-catalysts employed were able to mediate the reaction with comparable enantio- and diastereoselectivities. When a non-aromatic aldehyde was used the yield was considerably lower, while

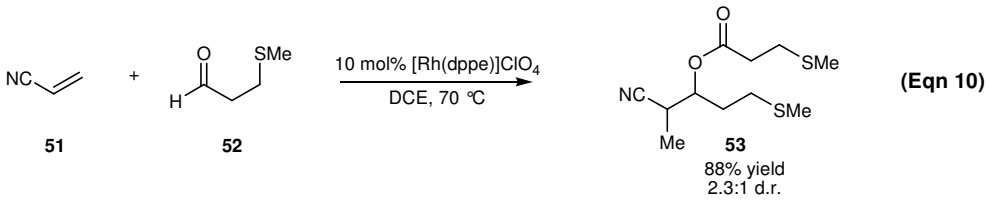
there was minimal change in the stereocontrol of the reaction (Entry 5). When the same reaction was performed using Me_2PhSiH as silane, the reaction failed to work (Entry 6). Nishiyama and co-workes also performed some test reactions to clarify the mechanism. In the absence of benzaldehyde, the conjugate reduction of methyl acrylate with Me_2PhSiH and the catalyst Rh(Phebox-ip)$(OAc)_2$ (**42a**) proceeded readily to form a mixture of corresponding *Z:E* (5:95) silyl ketene acetal.[13a] When benzaldehyde was added to this mixture, no aldol product was observed. This suggested that the reaction proceeded through a Rh-enolate complex as previously proposed by Morken and co-workers (Scheme 1.2).

Very recently, Nishiyama and co-workers reported intermolecular reductive aldol reactions between ketones and cinnamates.[14] Rh(Phebox-ip)$(OAc)_2$ (**42a**) was again used as a catalyst and $MePh_2SiH$ as a hydride source. The enantioselectivities obtained were high in most cases (Scheme 1.4). Only two examples were given where the ketone used was not symmetrical, thus resulting in the formation of two new stereocenters (**50c** and **50d**). The use of ethyl methyl ketone led to very low diastereocontrol but the enantiomeric excess was high with both of the diastereomers (**50d**). When acetophenone was used it led to a product **50c** in both very high diastereo- and enantioselectivity.



Scheme 1.4. Rh(phebox-ip)$(OAc)_2$-catalysed intermolecular reductive aldol reaction between ketones and cinnamates

In 2005 Willis and Woodward disclosed an interesting new example of catalytic reductive aldol reaction employing aldehydes as stoichiometric reductants.[15] The reaction between acrylonitrile (**51**) and 3-(methylthio)propionaldehyde **52** led to an unexpected product **53** in the presence of substoichiometric amount of $[Rh(dppe)]ClO_4$.



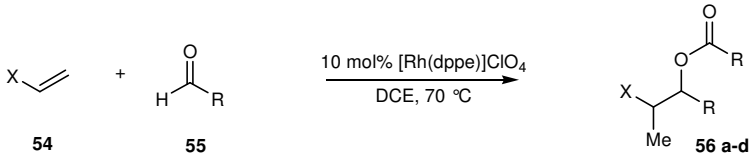
51 **52** **53**

88% yield
2.3:1 d.r.

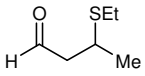
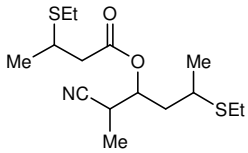
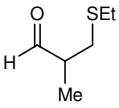
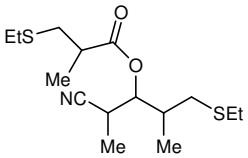
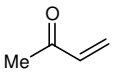
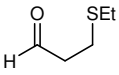
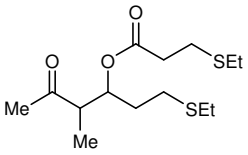
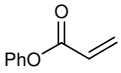
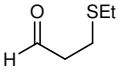
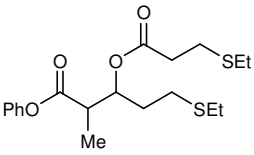
(Eqn 10)

The scope of the reaction was expanded to α,β-unsaturated ketones and esters (Table 1.4, Entries 3-4). Although these are novel reactions, they suffered from two major disadvantages; i) reactions gave products with low diastereoselectivities ii) the mixtures of diastereomers were inseparable by column chromatography.

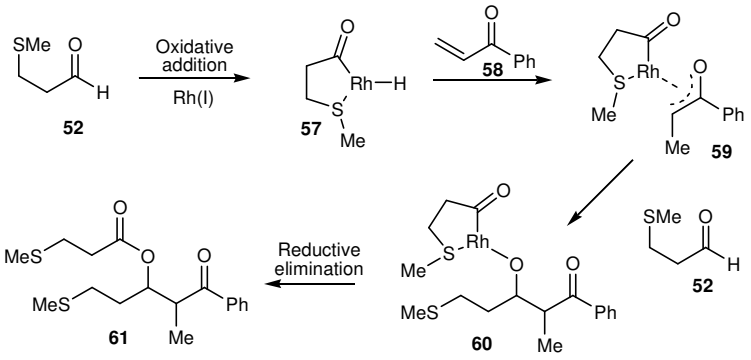
Table 1.4. Reductive Aldol Reaction Using Aldehydes as the Stoichiometric Reductants



54 55 56 a-d

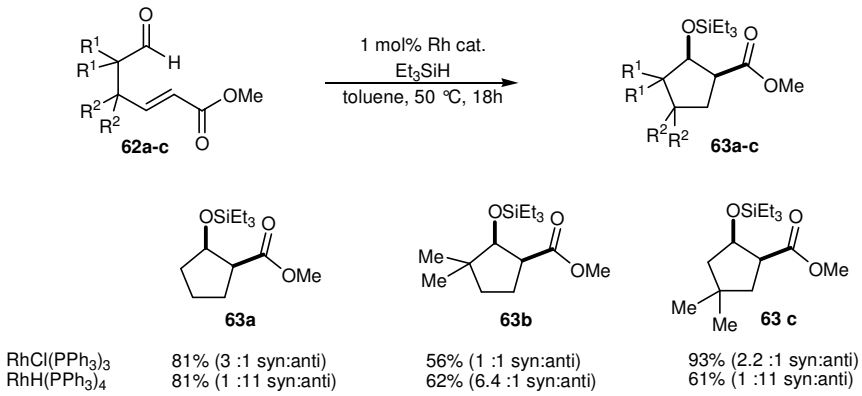
Entry	Alkene	Aldehyde	Product		d.r.	Yield (%)
1				**56a**	6.6:3.6:1	88
2				**56b**	7.5:5:1	73
3				**56c**	1.4:1	73
4				**56d**	3.3:1	67

Even having these disadvantages, the results obtained provided important knowledge of the reaction mechanisms. Willis proposed a mechanism shown in Scheme 1.5. Initially there is an oxidative addition of Rh(I) into the aldehyde C–H bond to generate chelated acyl rhodium hydride **57**. This step is followed by conjugate addition of the hydride to **58** to form rhodium enolate **59**. This enolate then participates in the aldol reaction with another molecule of the aldehyde to produce aldolate **60**. Reductive elimination of **60** gives the aldol product **61** and regenerates the Rh(I)-species.



Scheme 1.5. Proposed mechanism for the catalytic reductive aldol reaction employing aldehydes as stoichiometric reductants

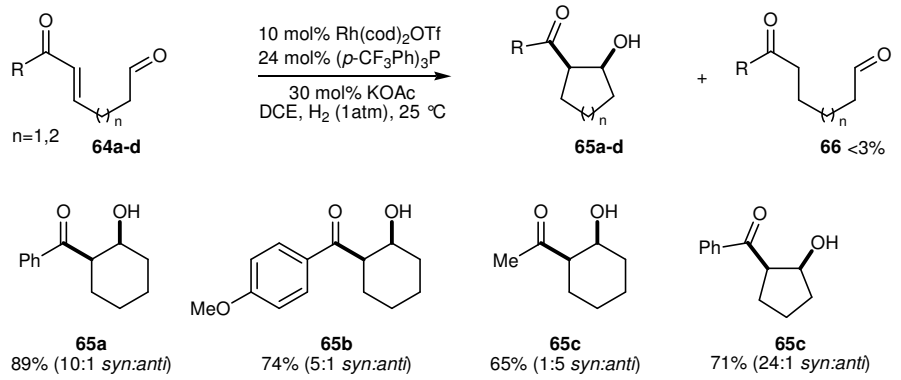
Motherwell and co-workers reported the use of a Rh-catalyst in an intramolecular reductive aldol reaction.[16,17] These cyclisations were performed at 50 °C in toluene. Two different rhodium salts were screened, namely $RhCl(PPh_3)_3$ and $RhH(PPh_3)_4$. Et_3SiH was used as the hydride source. Representative examples are shown in Scheme 1.6. It is interesting that the two rhodium salts provided opposing stereoselectivities. While $RhCl(PPh_3)_3$ provided moderate *syn*-selectivity, the more active catalyst, $RhH(PPh_3)_4$, gave mostly *anti*-product (with an exception in compound **63b**).



Scheme 1.6. Rh-catalysed intramolecular reductive aldol reactions

1.1.2. Hydrogen-Mediated Reactions

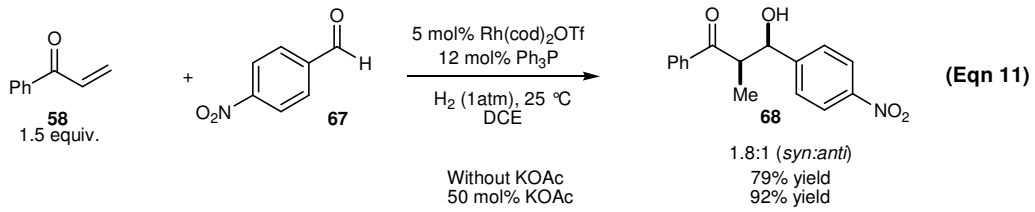
In 2002, Krische and co-workers reported a new concept in Rh-catalysed reductive aldol reactions.[18] They decided to use hydrogenation conditions to perform this reaction. It is generally accepted that rhodium-catalysed alkene hydrogenations follow three steps: i) oxidative addition of LnRh(I) to elemental hydrogen ii) alkene hydrometallation to produce LnRh(III)(alkyl)(hydride)-complex iii) reductive elimination from this complex to afford saturated product and LnRh(I) to close the catalytic cycle.[19] Krische made an assumption that under optimised conditions, the Rh-alkyl complex could react with an electrophile, i.e., it could be used as a nucleophile. The possible conjugate reduction was envisioned as the major problem. As a model system they decided to take an enone-aldehyde **64** that would react in an intramolecular manner. In the original screening of reaction conditions it was soon realised that the conjugate reduction was indeed a major problem. When the base KOAc was used together with the electron-poor phosphine ligand (p-$CF_3Ph)_3P$ and $Rh(cod)_2OTf$, conjugate reduction was diminished to very low levels (in most cases less than 3%). Under these conditions, the reductive aldol reaction proceeded in high yields with *syn:anti* selectivities ranging from moderate to good (Scheme 1.7).



Scheme 1.7. Hydrogen-mediated intramolecular reductive aldol reactions of the enone-aldehydes.

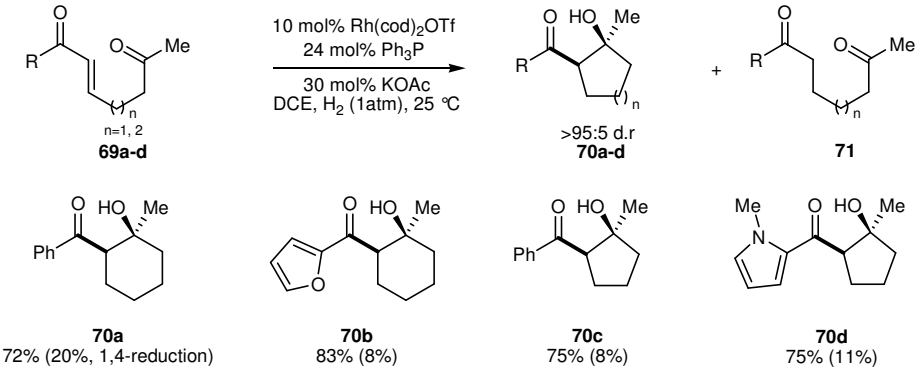
Interestingly, when aliphatic enone **64c** was used, the reaction gave the *anti*-product **65c** as a major diastereoisomer while aromatic enones gave mostly the *syn*-product. The reaction also worked in intermolecular manner (Eqn 11). The use of an excess of phenyl vinyl ketone (**58**, 1.5 equiv.) was essential since the conjugate

reduction was a competing reaction. As in the intramolecular reaction, use of base (KOAc) increased the yield significantly. This time Ph_3P was used as the ligand.



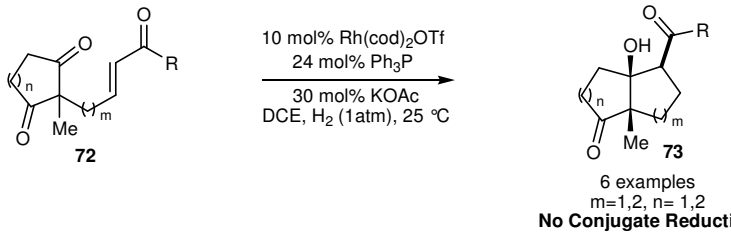
(Eqn 11)

When moving from an enone-aldehyde system to an enone-ketone system, the 1,4-reduction is potentially a greater problem. This is due to a reduced reactivity of the electrophile. Soon after his enone-aldehyde system, Krische and co-workers reported the use of an intramolecular system where they utilised ketone electrophiles.[20] In this report, the ligand was changed from $(p\text{-}CF_3Ph)_3P$ to Ph_3P keeping the reaction conditions the same as for his previous enone-aldehyde system. This readily enabled the formation of both five- and six-membered rings in good yields and excellent diastereoselectivities (Scheme 1.8).



Scheme 1.8. Hydrogen-mediated intramolecular reductive aldol reactions of enone-ketones

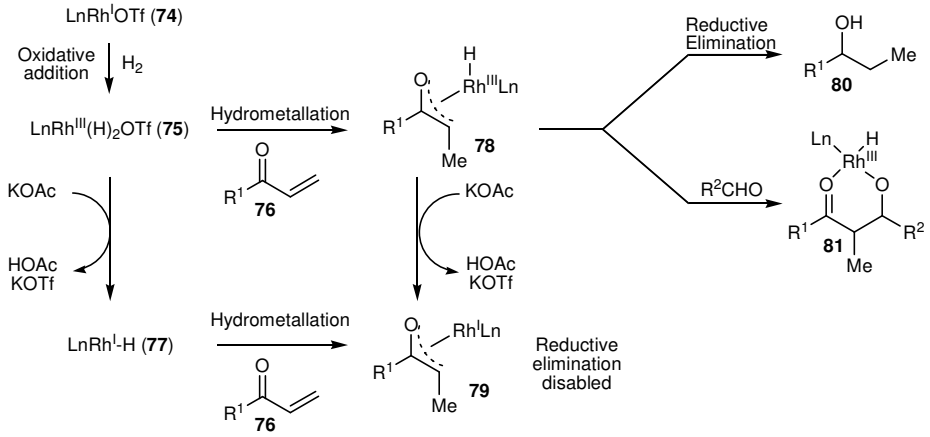
As predicted, conjugate reduction occurred as a side reaction and in addition to the main products, 8-20 % of the 1,4-reduction products were isolated. Krische also showed that by using more activated ketones, the problem of competing 1,4-reduction disappeared. When dione-containing substrates were used, no conjugate reduction was observed, as shown in Scheme 1.9 (with an exception in the case where n=2, m=2; 15% of reduction product was isolated).



Scheme 1.9. Hydrogen mediated intramolecular reductive aldol reactions of the more reactive enone-ketones

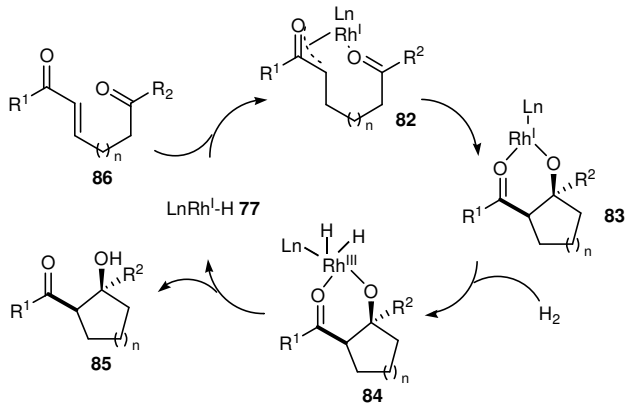
It is noteworthy that none of the reactions mentioned above worked without the use of the rhodium salt. This observation excludes the possibility of the phosphine ligand working as a Morita-Baylis-Hillman catalyst.

The role of the base as an agent decreasing the conjugate reduction product formation was next under debate. The proposed mechanism of the reaction starts with an oxidative addition of hydrogen to rhodium forming the Rh-dihydrido-complex **75** (Scheme 1.10). Since the formation of the conjugate reduction product needs to be minimised, formation of rhodium enolate **79**, rather than enolate **78** is desired. From enolate **79**, the conjugate reduction pathway is disabled. The complex **79** can be formed in two possible ways: i) through a reductive elimination of HX from complex **75** (assisted by base) to form Rh(I)-hydride **77** followed by hydrometallation of the substrate **76**, or ii) hydrometallation of the substrate **76** by Rh-complex **75** followed by reductive elimination of HX from it. The former is considered to be the dominant route. This explanation satisfies the observed fact that the presence of base increases the yield.



Scheme 1.10. Proposed mechanism for the hydrogen mediated reductive aldol reactions.

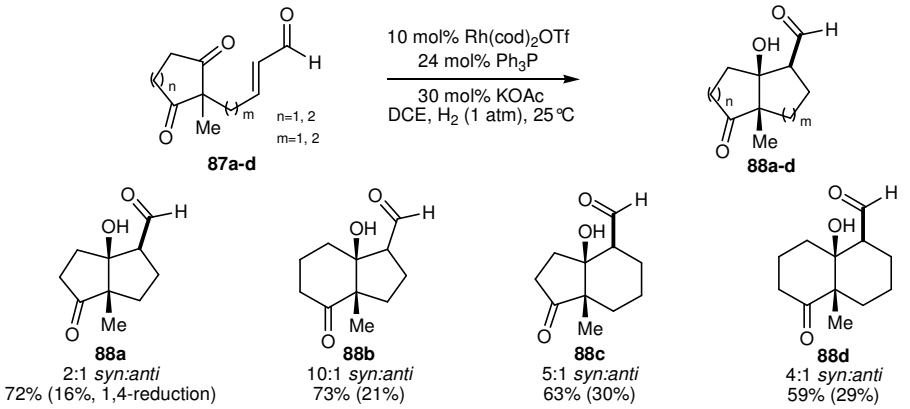
Based on these observations, the following catalytic cycle was proposed (Scheme 1.11).



Scheme 1.11. Proposed catalytic cycle for the hydrogen-mediated intramolecular reductive aldol reactions.

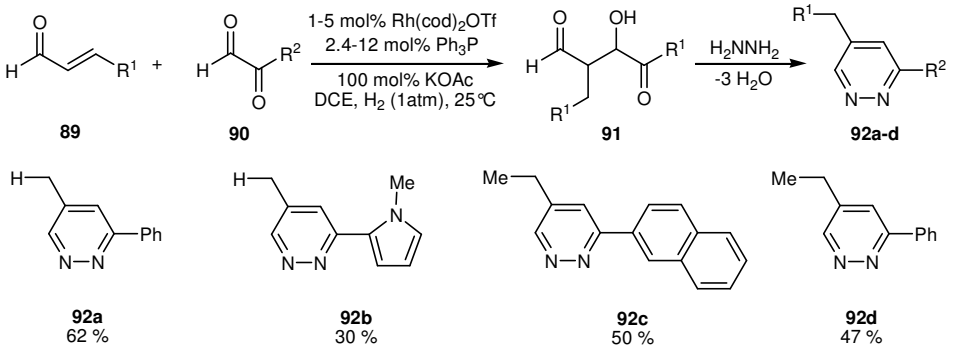
Next, Krische and co-workers decided to approach another well known problem in aldol chemistry. Reactions proceeding through metallo-aldehyde enolates are known to be difficult to work with.[21] For these kinds of cross-aldolisation reactions, indirect methods are needed; usually through imines (amine catalysis),[22] or the use of enol silanes.[23] The biggest challenge in the reactions between aldehyde enolates and ketones is the fact that aldehydes are better electrophiles, thus aldehyde enolates prefer to react with another molecule of the aldehyde rather than with a ketone. Krische assumed that this problem could be overcome by performing the

reaction in intramolecular fashion.[24] In the case of the enone-ketone substrates the use of more activated dione electrophiles was shown to diminish the 1,4-reduction (Scheme 1.9) and they decided to use this strategy in aldehyde enolates also (Scheme 1.12). The reactions proceeded with moderate diastereoselectivities and although considerable amounts of conjugate reduction occurred, isolated yields were reasonably high.



Scheme 1.12. Intramolecular reductive aldol reactions of enolates derived from aldehydes.

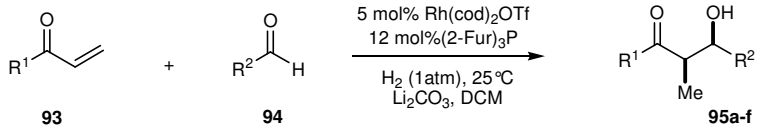
An intermolecular example of aldehyde enolate use was also reported by Krische.[25] While simple aldehydes failed to work as electrophiles, the use of glyoxals afforded aldol products in low yields and without diastereoselectivity. It was assumed that the low yields of the aldol products were partly influenced by the low stability of *β*-hydroxy aldehyde products **91**. To avoid this they decided to trap the product *in situ*. An excess of methanolic hydrazine (10 equiv.) was added to the reaction to give 3,5-substituted pyridazines as products (Scheme 1.13). Even after this procedure the yields remained very modest.



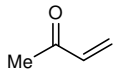
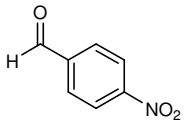
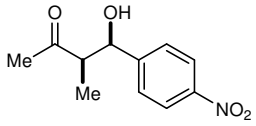
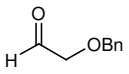
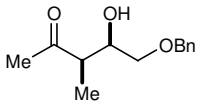
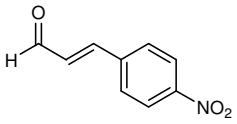
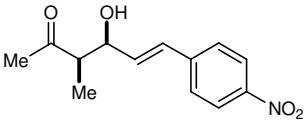
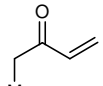
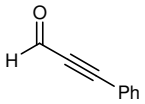
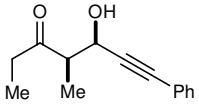
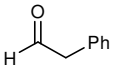
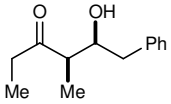
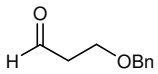
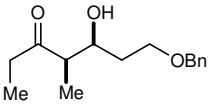
Scheme 1.13. Intramolecular reductive aldol reactions between glyoxals and aldehyde enolates.

Later, Krische and co-workers reported improved reaction conditions for the intermolecular reaction between enones and aldehydes.[26] When they first reported this intermolecular reaction it had severe limitations; only phenyl vinyl ketone could be used as a nucleophile and the diastereoselectivitities of the reaction were modest (Eqn 11).[18] Small changes in reaction conditions allowed the reaction to proceed with both methyl vinyl ketone and ethyl vinyl ketone (Table 1.5). Ph_3P was changed to $(2\text{-Fur})_3P$ as a ligand and KOAc was changed to Li_2CO_3 as base. Reactions proceeded in excellent yields and with very good *syn:anti* ratios. It was observed that the reactions using ethyl vinyl ketone usually occurred with enhanced diastereoselectivities compared with those using methyl vinyl ketone. This observation was rationalised by an assumption that ethyl vinyl ketone has an enhanced kinetic and thermodynamic preference for the formation of the *Z*-enolate due to increased $A_{1,2}$-strain in the *E*-enolate configuration.

Table 1.5. Reductive Aldol Couplings Between Vinyl Ketones and Aldehydes



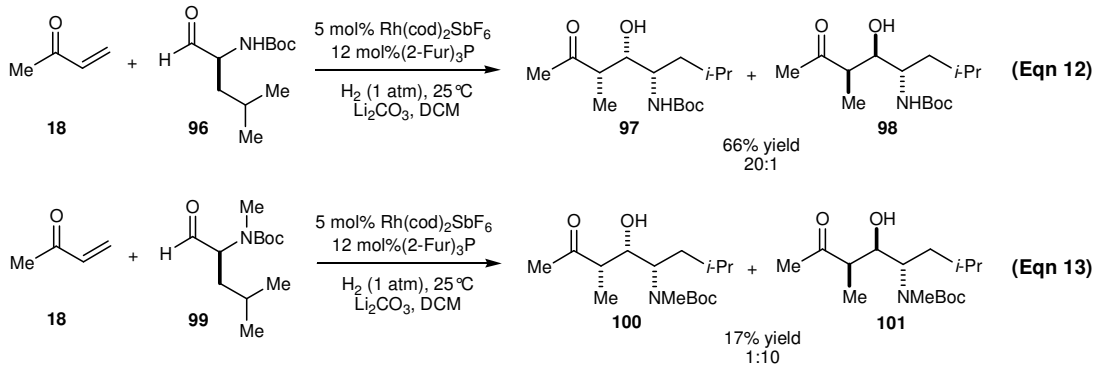
93 + 94 → 95a-f

Entry	Enone	Aldehyde	Product	Yield (%)	d.r. (*syn:anti*)
1			 **95a**	91	16:1
2			 **95b**	90	17:1
3			 **95c**	92	8:1
4			 **95d**	70	10:1
5			 **95e**	89	30:1
6			 **95f**	73	20:1

It is noteworthy that α,β-unsaturated aldehydes could also be used as electrophiles without a decrease in the yields (Entries 3 and 4). Additionally, hydrogenation condition-labile functional groups such as nitroarenes (Entry 1) and benzylic ethers (Entries 2 and 6) were well tolerated.

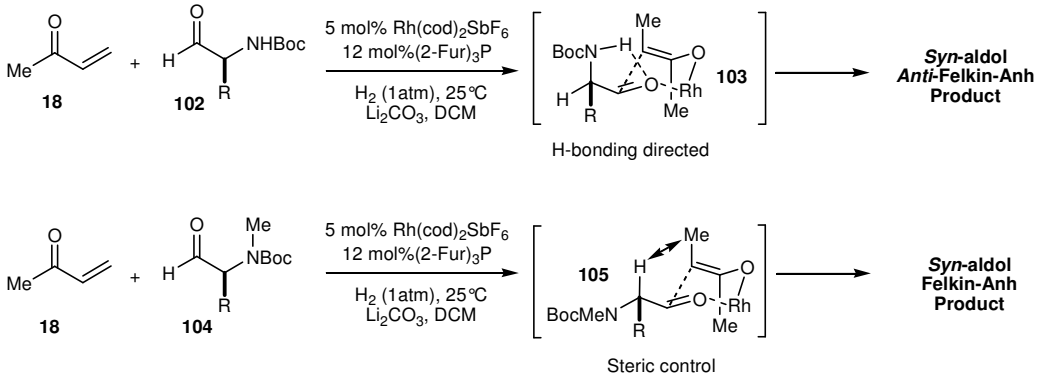
Since high level of diastereoselectivity was obtained under the reaction conditions mentioned above, Krische and co-workers decided to study substrate-directed asymmetric induction in this reaction.[27] The reactions between methyl vinyl ketone and chiral α-aminoaldehydes gave synthetically useful stereoselectivities (Eqn 12). The overall yield of the products was 66% in this case, and the major product was found to be so called anti-Felkin-Anh product **97** in a 20:1 ratio (the minor

product being the Felkin-Anh product **98**). A very interesting detail was observed when the amino group was changed from NHBoc to NMeBoc (Eqn 13). In this case the major product was found to be the Felkin-Anh product **101**, with lower selectivity (1:10 vs. 20:1). Furthermore, the overall yield of the products was diminished significantly.



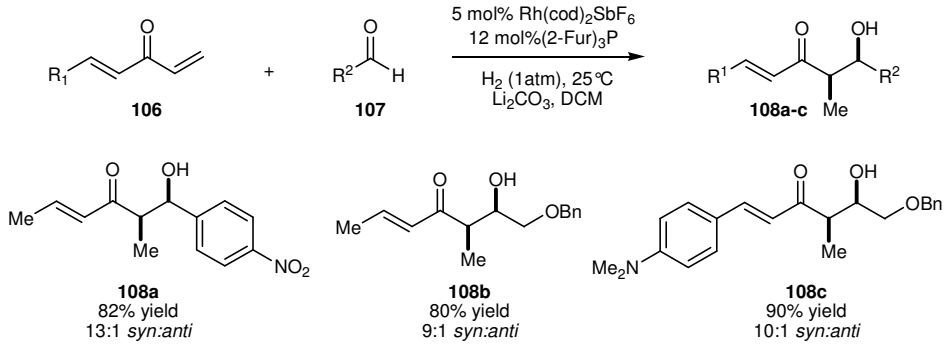
18 **96** **97** **98** **99** **100** **101**

The behaviour described above can be explained by looking at the transition state for this reaction. The reaction is expected proceed through a Zimmerman–Traxler transition state.[28] The enolate is expected to be in the *Z*-conformation. It is also expected that in the case where the amino group is NHBoc, intramolecular hydrogen bonding is more important for stereocontrol than the steric interactions (Scheme 1.14). On the other hand, when a hydrogen on the amino group is replaced by a methyl, this potential for intramolecular hydrogen bonding is removed. Now the stereochemical outcome of the reaction is based on steric control thus giving the product with Felkin-Anh-selectivity. Furthermore, it was assumed that this intramolecular hydrogen bonding not only directs the anti-Felkin-Anh selectivity but also enhances the reactivity of the aldehyde towards the nucleophile. This explains the differences between the yields obtained in the reactions in Eqn 12 and 13.



Scheme 1.14. Transition states leading to different stereochemistries.

Krische made further studies of intermolecular reductive aldol reactions by reactivity comparison of divinyl ketones (Scheme1.15).[29] Both crotyl vinyl ketone and *para*-(dimethylamino)styryl vinyl ketone reacted at the less substituted vinyl moiety to give preference for *syn*-aldol products with good yields and high *syn:anti* ratios.



Scheme 1.15. Intermolecular reductive aldol reactions between divinyl ketones and aldehydes.

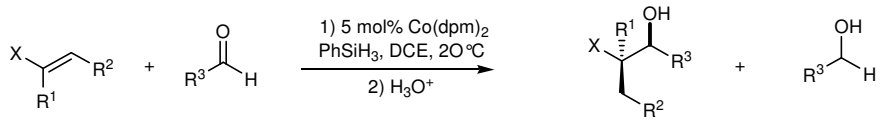
Significantly, no overreduction of the unsaturated products (**108a-c**) occured unless the reactions were left for a long time under the reaction conditions after the consumption of the original starting materials was observed.

1.2. Cobalt-Catalysed Reductive Aldol Reactions

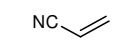
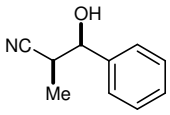
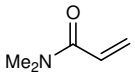
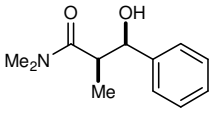
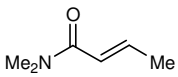
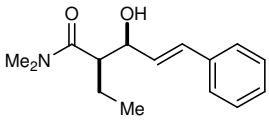
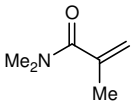
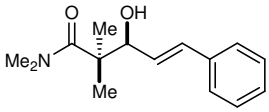
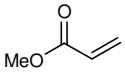
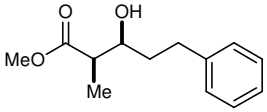
Soon after the seminal work with rhodium by Revis and Hilty,[7] Mukaiyama and co-workers reported a cobalt-catalysed intermolecular reductive aldol reaction.[30]

They found out that in the presence of a substoichiometric amount of $Co(dpm)_2$ and stoichiometric amount of $PhSiH_3$, acrylonitrile coupled with benzaldehyde in high yield producing only minor amounts of the reduced aldehyde (Table 1.6, Entry 1). The scope of the pronucleophiles that could be utilised under these conditions was found to be wide. Both *α,β*-unsaturated amides and esters gave products in good yields (Entries 2-5). Acryloyl systems were not the only ones that worked, and *α,β*-unsaturated amides or nitriles could be further substituted at both *α*- or *β*-positions.

Table 1.6. Cobalt Catalysed Intermolecular Reductive Aldol Reactions.



109 **110** **111a-e** **112**

Entry	Nucleophile	Product		Yield (%) (syn:anti)	112 (%)
1			**111a**	93 (1:1)	5
2			**111b**	95 (4:1)	3
3			**111c**	68 (72:28)	12
4			**111d**	70 (n.a.)	31
5			**111e**	62 (n.a.)	14

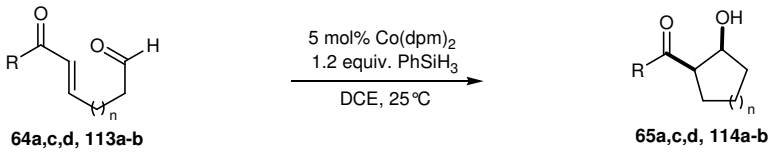
Molar ratio: Aldehyde:nitrile:silane 1:4:2, Aldehyde:amide:silane 1:1.2:1.2, Aldehyde:ester:silane 1:4:2

More interestingly, for the first time, meaningful diastereoselectivities were observed. Although diastereselectivities were modest it showed that the reductive aldol reaction had the potential to become an important tool in organic synthesis.

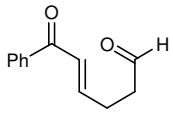
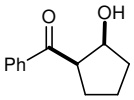
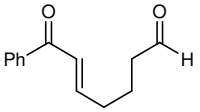
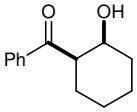
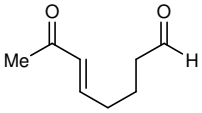
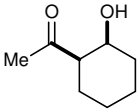
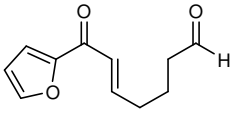
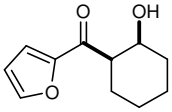
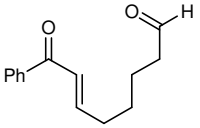
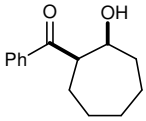
In 2001, Krische and co-workers[31] reported an intramolecular version of this reaction using the same reaction conditions as described by Mukaiyama.[30] Extremely high levels of *syn*-selectivities were observed in the reactions of enone-aldehyde

substrates (**64a,c,d** and **113a,b**). Products were isolated as practically one diastereoisomer, HPLC analysis showing >99:1 (*syn:anti*) ratio. Both five- and six-membered rings were formed in good yields and substitution at the ketone moiety could be changed from aromatic (Table 1.7, Entries 1 and 2) to heteroaromatic (Entry 4). A methyl ketone gave product in notably diminished yield (Entry 3). It was also possible to form a seven-membered ring, but the yield of this product was poor (Entry 5).

Table 1.7. Cobalt Catalysed Intermolecular Reductive Aldol Reactions.

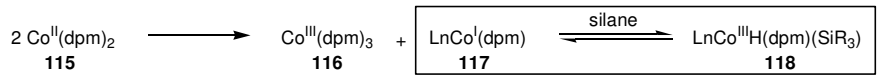


64a,c,d, 113a-b → **65a,c,d, 114a-b**

Entry	Substrate		Product		Yield (%)
1		**64d**		**65d**	70
2		**64a**		**65a**	87
3		**64c**		**65c**	38
4		**113a**		**114a**	75
5		**113b**		**114b**	35

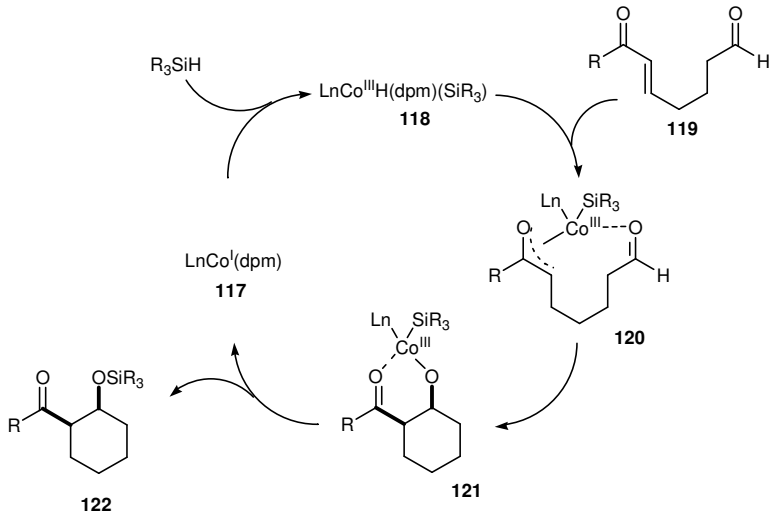
Krische decided to make mechanistic studies of this type of cyclisation reaction.[32] The biggest challenge was to explain the oxidation states of the cobalt species during the process. $Co(dpm)_2$ has a formal oxidation state of 2. Direct oxidative addition of silane to this would lead to a Co(IV)-complex that has an unstable oxidation state.[33] Since the disproportionation of Co(II) (**115**) to Co(III) (**116**) and Co(I) (**117**) had been already documented,[34] Krische took this approach to explain the mechanism (Scheme 1.16). HRMS analysis of $Co(dpm)_2$ indicated the

presence of $Co(dpm)_3$ in solution. After the disproportionation, oxidative addition of silane to Co(I) would lead to active Co(III)-complex (**118**).



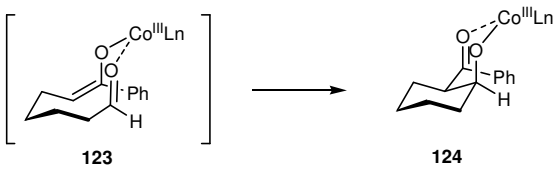
Scheme 1.16. Disproportionation to Co(II)

Now it was also possible to predict the full catalytic cycle. Hydrometallation of the enone **119** by hydrido-cobalt species **118** would lead to a cobalt enolate **120**. This is followed by carbonyl addition providing the cobalt-aldolate **121**. Reductive elimination liberates the silylated aldol product **122** and regenerates LnCo(I) **117**.



Scheme 1.17. Proposed mechanism of the Co-catalysed reductive aldol reaction

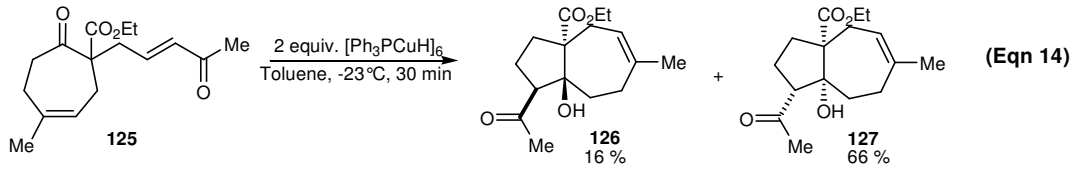
The observed high *syn*-selectivity was believed to be an outcome of the reaction proceeding through a Zimmerman-Traxler transition state.[28] It was assumed that preferential *Z*-enolate (**123**) formation is based on allylic 1,2-strain.



Scheme 1.18. Zimmerman-Traxler transition state

1.3. Copper-Mediated Reductive Aldol Reactions

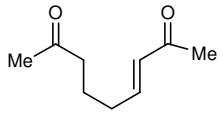
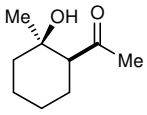
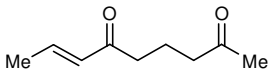
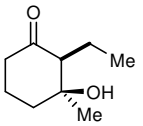
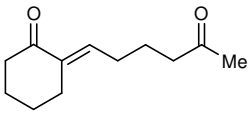
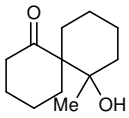
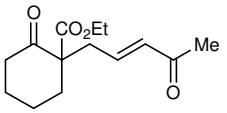
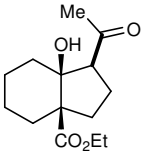
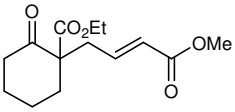
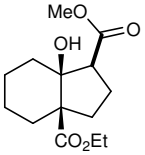
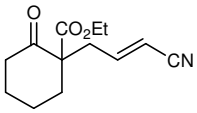
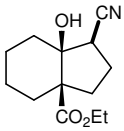
An original development in this area was based on the stoichiometric use of a copper hydride species. It was known that hexameric triphenylphosphinecopper hydride $[(Ph_3P)CuH]_6$ was able to perform a 1,4-reduction of conjugated systems, while remaining inert to simple olefins.[35] This reagent is also known as Stryker's reagent. The first example where Stryker's reagent was used in a reductive aldol reaction was reported by Chiu and co-workers in 1998.[36] They found out during their studies towards the synthesis of pseudolaric acid A that a stoichiometric use of Stryker's reagent was able to promote reductive cyclisation of the substrate **125**. When the reaction was performed at room temperature, a mixture of products was observed. The best result was achieved at –23 °C where products **126** and **127** were isolated in 16% and 66% yields respectively.



(Eqn 14)

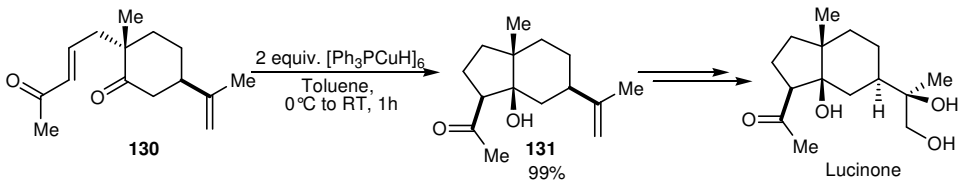
Chiu made more studies on this discovery to optimise the conditions for a broader substrate scope.[37] The use of 2.25 hydride equivalents of Stryker's reagent in toluene, at temperatures below zero, gave readily highly *syn*-stereoselective cyclisations of keto-enone substrates (Table 1.8). Significantly, both (enol*exo*)-*exo-trig* (Entries 1, 3-6) and (enol*endo*)-*exo-trig* (Entry 2) systems could be used as substrates. When the double bond was conjugated to an ester or a nitrile, elevated temperatures were required (Entries 5 and 6). It was also observed that the *cis*-configuration of substrate seemed to be less reactive than the *trans*-configuration. When a mixture of *cis:trans*-substrate was used (Entry 6), the product was obtained together with unreacted *cis*-substrate.

Table 1.8. Stryker's Reagent in Intermolecular Reductive Aldol Reactions.

Entry	Substrate		T(°C)	Product[a]		Yield (%)[b]
1		**128a**	- 40		**129a**	80
2		**128b**	- 40		**129b**	86
3		**128c**	- 25		**129c**	89[c]
4		**128d**	- 40		**129d**	86
5		**128e**	25		**129e**	84
6		**128f**	25		**129f**	66[d]

a) conditions: 2.25 equiv. $[(Ph_3P)CuH]_6$, toluene b) Only one diastereomer observed c) One diastereomer structure not determined d) 11% of starting material recovered (only *cis*-isomer).

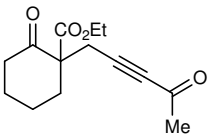
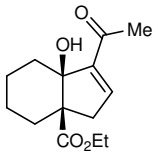
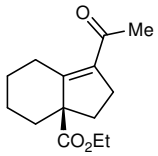
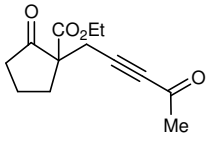
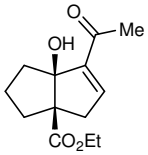
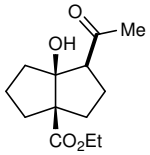
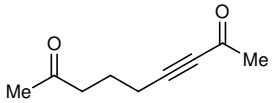
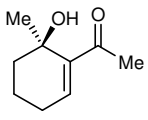
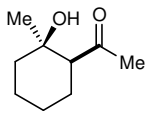
Soon after the studies described above, Chiu reported another application of this methodology in total synthesis.[38] Very effective cyclisation of the compound **130** was observed when treated with Stryker's reagent (2.7 equiv.) at 0 °C, followed by a temperature raise to 25 °C. Asymmetric induction by pre-existing stereocentres in an enantiopure substrate **130** led to one single enantiomer of the product **131** in 99% yield. From this intermediate, the total synthesis of lucinone was easily accomplished (Scheme 1.19).



Scheme 1.19. Reductive aldol cyclisation used in the totel synthesis of Lucinone

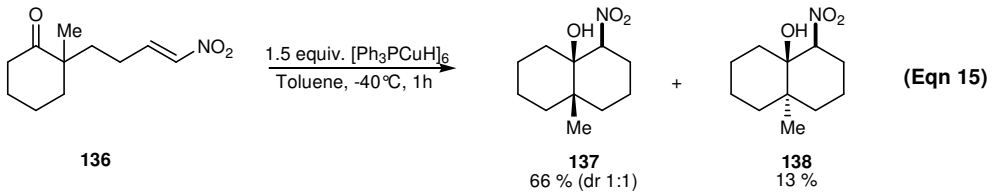
Further development of the reductive aldol reaction mediated by Stryker's reagent was achieved when Chiu and co-workers reported the use of $[(Ph_3P)CuH]_6$ in catalytic fashion.[39] When Stryker's reagent (10 mol%) was utilised together with a stoichiometric amount of the polymeric hydrosiloxane, PMHS, as a hydride source, the reactions proceeded with comparable yields to those using stoichiometric amounts of $[(Ph_3P)CuH]_6$. This method of regenerating copper hydride from Stryker's reagent with silanes was originally used for conjugate reductions.[40] In Chiu's examples, conjugated alkynones where used as substrates producing *α,β*-unsaturated ketones as products. When the reaction was performed to form bicyclic products, good selectivity of *cis*-fused bicycloalkenone were observed (Table 1.9, Entries1-4). As could be expected, the major side products were found to be over-reduced products. Two different kinds of these side products were found. One is where another conjugate reduction step reduced the remaining conjugated double bond (Entries 3-6) and the other is where dehydration migrated the double bond to its alternative conjugated isomer (Entries 1 and 2). Over-reduction is a considerable problem leading up to 39% formation of the side-product.

Table 1.9. Reductive Aldol Cyclisations of Alkynediones Catalysed By Stryker's Reagent.

Entry	Substrate / $[(Ph_3P)CuH]_6$	T(°C) (t/min)	Products/Yields (%)	
	 **132a**			
			133a	**133b**
1	Catalytic[a]	25 (15)	60	23
2	Stoichiometric[b]	- 40 (15)	56	-
	 **132b**			
			134a	**134b**
3	Catalytic	- 40 (15)	58	39
4	Stoichiometric	- 40 (30)	54	13
	 **132c**			
			135a	**135b**
5	Catalytic	- 40 (90)	62	14
6	Stoichiometric	- 40 (180)	46	-

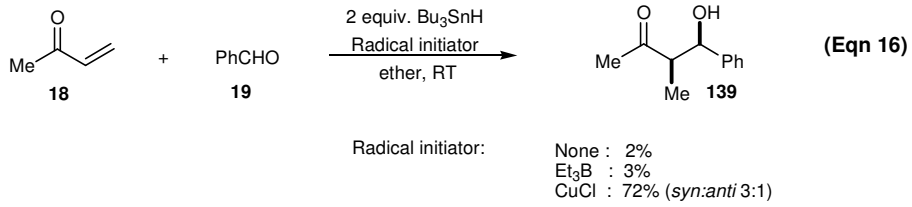
a) 10 mol % of $[(Ph_3P)CuH]_6$ 2 equiv PMHS b) 1.5 quiv. of $[(Ph_3P)CuH]_6$

Chiu also reported the stoichiometric use of Stryker's reagent in an intramolecular reductive Henry reaction.[41] Reactions were performed at low temperatures (-40 °C) to give *β*-hydroxy-nitro compounds in moderate yields (Eqn 15).



136 | **137** 66 % (dr 1:1) | **138** 13 %

Maruoka reported reaction conditions where copper played a very different role to that described above.[42] A reaction between methyl vinyl ketone and benzaldehyde proceeded to give product **139** in 2% yield in the presence of Bu_3SnH (Eqn 16). When CuCl (10 mol%) was added to the reaction, the yield was increased to 72%. The role of CuCl was as a radical initiator. The use of other known radical initiators like Et_3B did not lead to the product in increased yields in comparison to the reaction without radical initiator. It was assumed that copper played a dual role in this reaction; not only had it functioned as a radical initiator but also as a Lewis acid.



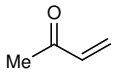
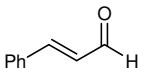
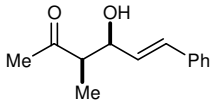
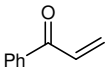
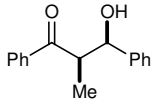
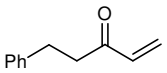
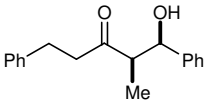
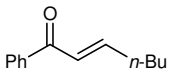
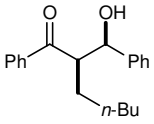
18 **19** **139**

Radical initiator:

None : 2%
Et_3B : 3%
CuCl : 72% (*syn:anti* 3:1)

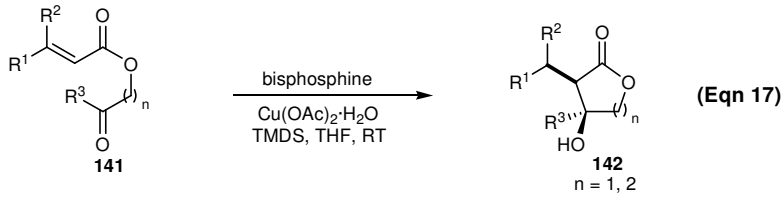
Aldol products were obtained in good yields and low diastereoselectivities with alkyl (Table 1.10, Entries 1 and 3) and aryl (Entry 2) vinyl ketones. Substitution at the *β*-position significantly lowered the reaction rate and only a small amount of product **140d** was isolated (Entry 4).

Table 1.10. Intermolecular Reductive Aldol Reactions Catalysed by Bu_3SnH and CuCl

Entry	Enone	Aldehyde	Product		Yield[a](%) (*syn:anti*)
1				**140a**	65 (1.3:1)
2		PhCHO		**140b**	85 (2.8:1)
3		PhCHO		**140c**	91 (2.6:1)
4		PhCHO		**140d**	15 (1.5:1)

a) The reaction was carried out in following conditions: enone 1 equiv., aldehyde 3 equiv., Bu_3SnH 2 equiv., CuCl 10 mol% in ether at RT.

The next major improvement in the copper-catalysed reductive aldol reaction was reported by our research group.[43] Moisture- and air-stable $Cu(OAc)_2{\cdot}H_2O$ was used as a catalyst together with bisphosphine ligands and 1,1,3,3-tetramethylsiloxane (TMDS) as a stoichiometric hydride source. Both five- and six-membered *β*-hydroxylactones were formed in moderate to good yields and very high *syn*-selectivities (>95:5). The first examples of enantioselective reductive aldol reaction where electrophile is a ketone were also described. This research will be discussed in more detail in Chapter 2.

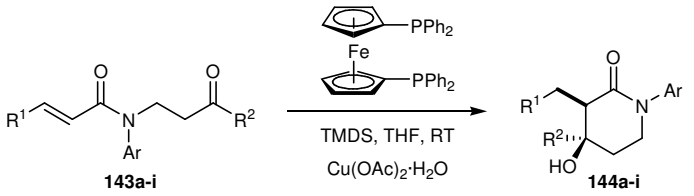


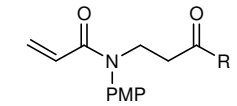
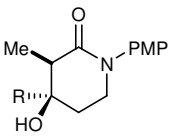
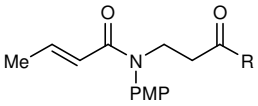
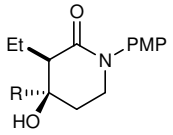
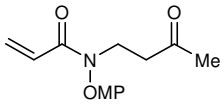
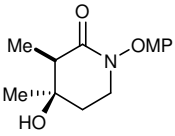
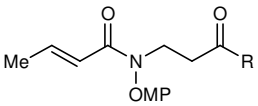
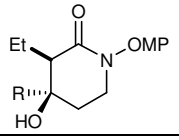
(Eqn 17)

Our group also reported an extension of this cyclisation to form 4-hydroxypiperidin-2-ones.[44] When using the same reaction conditions as described above, a range of substrates underwent cyclisation to form six-membered lactams (Table 1.11). The reaction proved to be tolerant to wide variation in the ketone component, with alkyl (Entries 1–2 and 5-8), aromatic (Entries 3 and 9) and heteroaromatic (Entry 4) ketones reacting readily. However, the reaction was less

tolerant of substitution in the α,β-unsaturated carbonyl component. Acryloyl amides were found to be the best substrates, giving the desired piperidin-2-one products for all cases examined (Entries 1–4 and 7). Although crotonoyl amides also underwent cyclisation (Entries 5–6 and 8–9), reaction rates and conversions were generally lower. When the size of the substituent at the β-position was increased further, both conjugate and ketone reduction became a problem.

Table 1.11. Catalytic Reductive Aldol Cyclisations to Form 4-Hydroxypiperidin-2-ones[a]

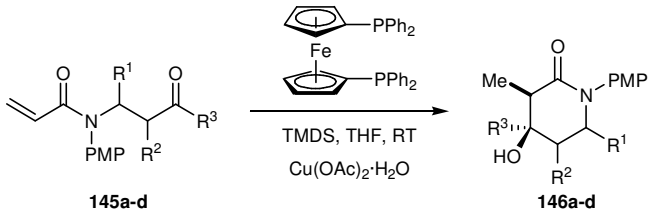


Entry	Subtrate	R	Product		Time (h)	Yield(%)[b]
1		Me **143a**		**144a**	2.5	66
2		Et **143b**		**144b**	5.5	61
3		Ph **143c**		**144c**	21	69
4		2-furyl **143d**		**144d**	24	53
5		Me **143e**		**144e**	22	55
6		Et **143f**		**144f**	24	52
7		**143g**		**144g**	4	70
8		Me **143h**		**144h**	24	70
9		Ph **143i**		**144i**	23	65

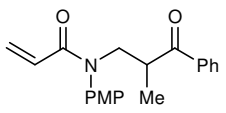
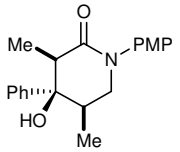
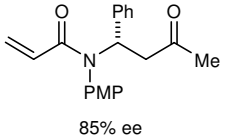
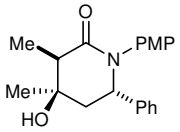
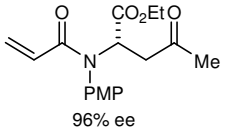
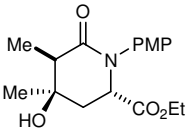
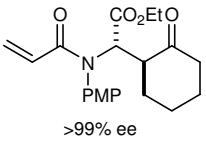
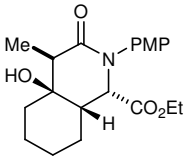
a) Conditions: 5 mol% Cu, 5 mol% DPPF, 1 equiv. TMDS b) Isolated yield

The effect of pre-existing stereocenters in the tether linking the amide and the ketone on the diastereoselectivity of the process was also examined (Table 1.12). Acrylamide **145a**, containing a methyl substituent α- to the ketone, cyclised to give a mixture of two diastereomers in a ratio of 8:1, from which the product piperidinone was isolated in 78% yield (Entry1). Enantiomerically enriched substrates were also studied (Entries 2-4). Substrates cyclised with moderate to excellent levels of internal asymmetric induction, giving the major product in moderate to good yields.

Table 1.12. Formation of C5- and 6- Substituted 4-hydroxypiperidi-2-ones[a]

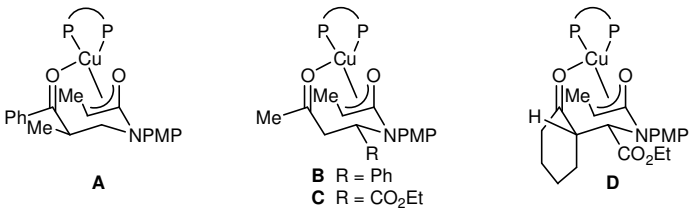


145a-d 146a-d

Entry	Substrate		Product		d.r	Yield(%)[b]
1		**145a**		**146a**	8:1	78
2	 85% ee	**145b**		**146b**	>19:1	65
3	 96% ee	**145c**		**146c**	>16:1	68
4	 >99% ee	**145d**		**146d**	5:1	66

a) Conditions: 5 mol% Cu, 5 mol% DPPF, 1 equiv. TMDS b) Isolated yield of major diastereomer

The moderate to excellent levels of asymmetric induction in these reactions may be rationalised by invoking the chelated chair-like conformations **A-D** shown in Scheme 1.20, with substituents in the tether linking the amide enolate and the ketone preferring to adopt pseudoequatorial positions.



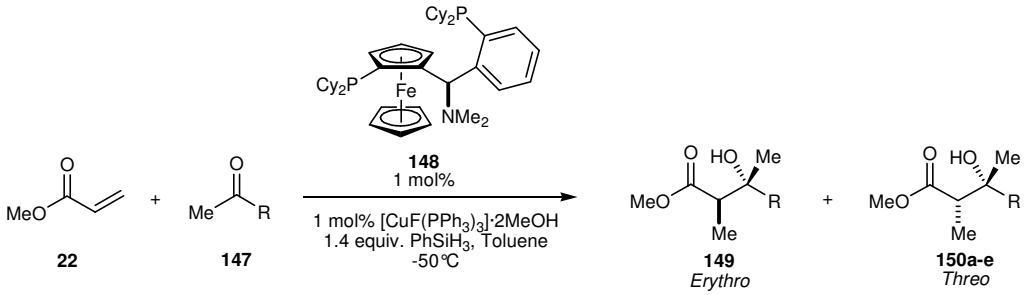
A **B** R = Ph **C** R = CO_2Et **D**

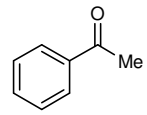
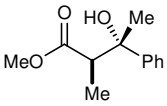
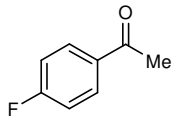
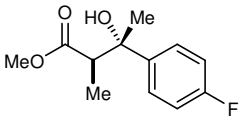
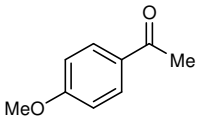
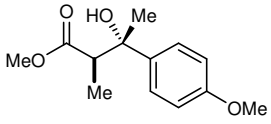
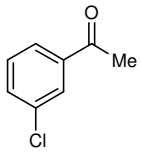
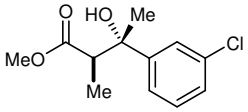
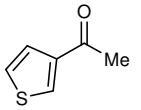
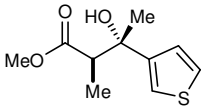
Scheme 1.20. 1,2- and 1,3-asymmetric induction rationalised by chair-like conformations.

The first asymmetric intermolecular reductive aldol reactions catalysed by copper were reported by Riant and co-workers in 2006.[45] Reactions between methyl acrylate and aromatic ketones, in the presence of catalytic amount of

[CuF(PPh$_3$)$_3$·2MeOH] and Cy-Taniaphos-ligand **148**, gave mainly the *erythro*-products with high enantioselectivities (Table 1.13). A remarkably low catalyst loading was required (1 mol% of copper and ligand) to achieve these excellent yields and stereoselectivities. PhSiH$_3$ was used as a stoichiometric hydride source. Although great stereoselectivities were achieved, the reaction was limited to the use of methyl acrylate (**22**) as pronucleophile and aromatic (Entries 1-4) or heteroaromatic methyl ketones (Entry 5) as electrophiles.

Table 1.13. Asymmetric Intermolecular Copper Catalysed Reductive Aldol Reactions



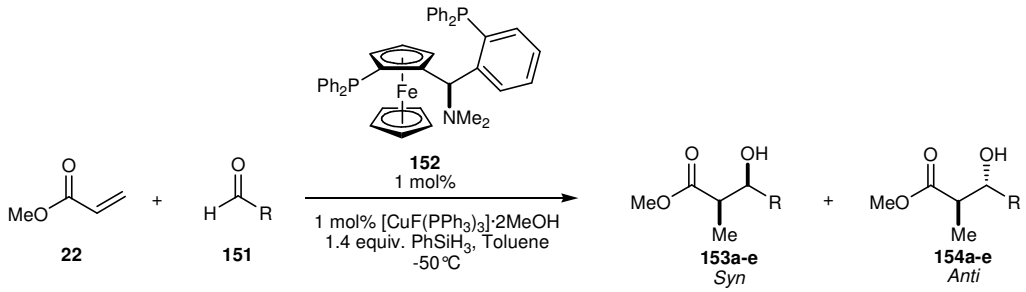
Entry	Ketone	Product(*threo*)		d.r.[a]	Yield (%)	ee (%)[b]
1			**150a**	92:8	98	95
2			**150b**	91:9	88	92
3			**150c**	92:8	31	90
4			**150d**	88:12	70	82
5			**150e**	95:5	95	95

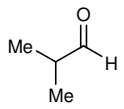
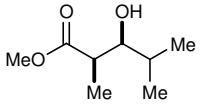
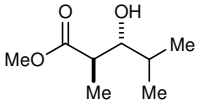
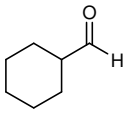
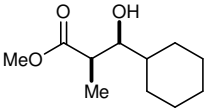
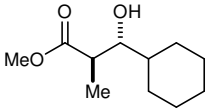
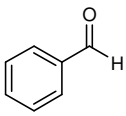
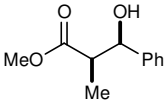
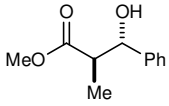
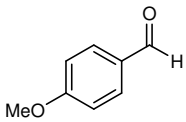
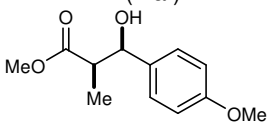
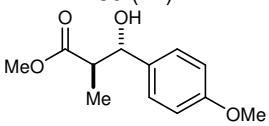
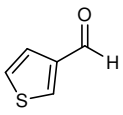
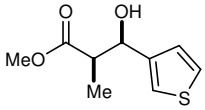
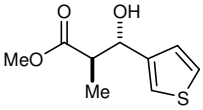
a) Threo as major isomer b) ee of threo isomer

Riant and co-workers also studied reactions using aldehydes as the electrophiles.[46] The same reaction conditions were used as mentioned above but with a ligand Ph-Taniaphos **152** instead of **148.** This catalyst system showed an

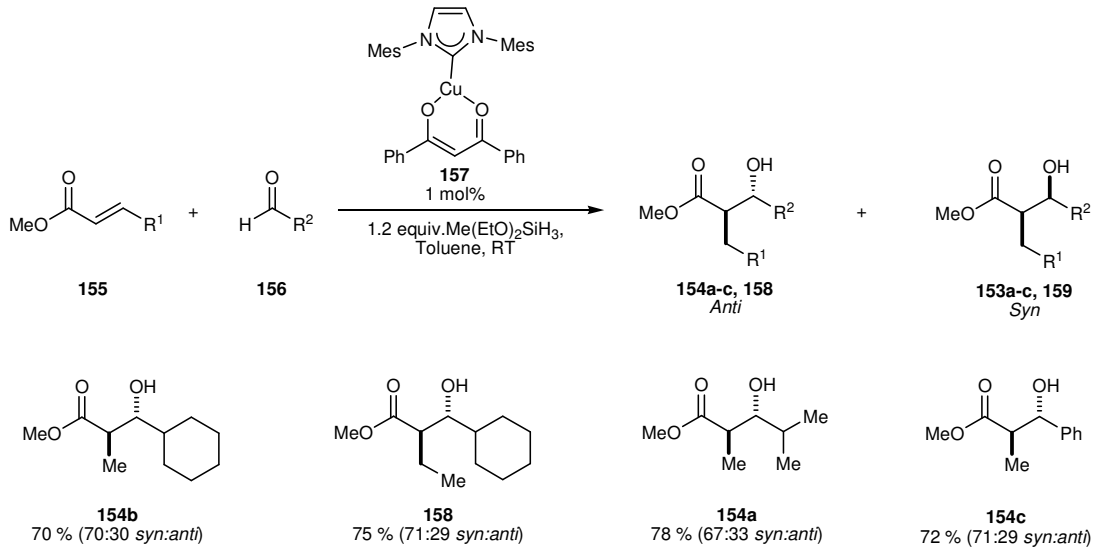
impressive activity with an estimated TON of 10.000 and TOF of 40.000 h^{-1}. When the Cy-Taniaphos **148** was used as ligand, the main product was found to be the reduced aldehyde. Aliphatic (Table 1.14, entries 1-2), aromatic (Entries 3-4) and heteroaromatic (Entry 5) aldehydes could be utilised and the products were usually obtained in good to excellent enantioselectivities and excellent conversions, but mostly with very poor diastereoselectivities. The effect that the silane had on the diastereo- and enantioselectivities was found to be very important. Silanes such as PMHS, $(Me_3SiO)_2MeSiH$ and $Me_2EtOSiH$ failed to give comparable selectivities.

Table 1.14. Asymmetric Reductive Aldol Reaction Between Acrylate and Aldehydes



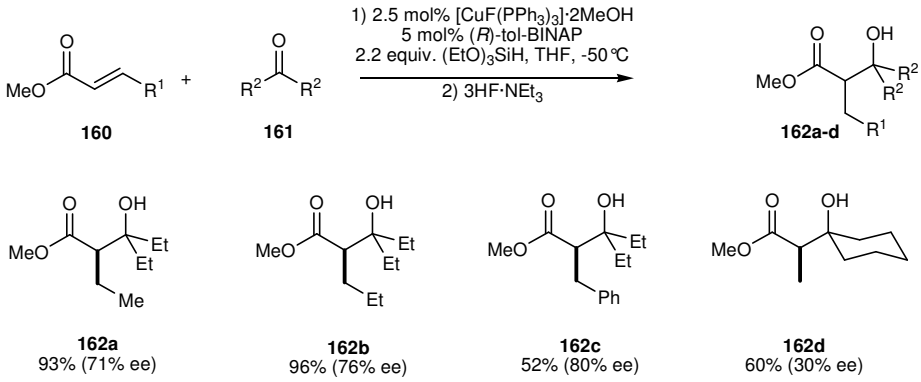
Entry	Aldehyde	Product (*syn*) Conversion (%)(ee %)		Product (*anti*) Conversion (%)(ee %)	
1		 64 (73)	**153a**	 36 (26)	**154a**
2		 77 (96)[a]	**153b**	 23 (74)[a]	**154b**
3		 41 (n.a.)	**153c**	 59 (72)	**154c**
4		 60 (68)	**153d**	 40 (72)	**154d**
5		 51 (86)	**153e**	 49 (76)	**154e**

Further extension to the chemistry described above was reported by Riant and Nolan.[47] This time the N-heterocyclic carbene-copper complex IMesCuDBM **157** was used together with $Me(SiO)_2SiH$, as a catalyst. Slightly inferior diastereoselectivities and conversions were observed (Scheme 1.21) than in the previous examples (Table 1.14).



Scheme 1.21. Intermolecular reductive aldol reactions catalysed by N-heterocyclic copper complex IMesCuDBM.

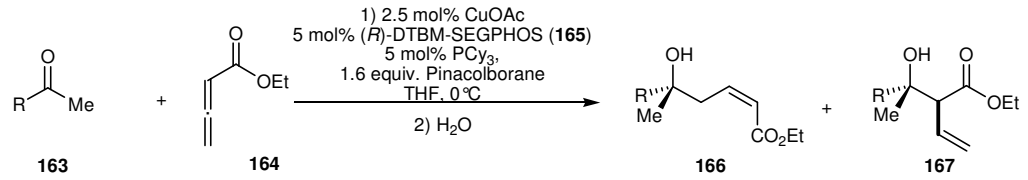
At the same time that Riant reported his successful enantioselective intermolecular reductive aldol reaction,[45] Shibasaki and Kanai reported the use of very similar conditions in this same reaction.[48] The differences between their catalyst systems were that (*R*)-tol-BINAP was used instead of Taniaphos as a ligand and $(EtO)_3SiH$ was used in the place of Ph_3SiH. While this system failed to give over 30% ee in the reaction between methyl acrylate and acetophenone, the use of symmetric ketones led to products **162a-d** with ee's ranging from moderate to good.



Scheme 1.22. Asymmetric intermolecular reductive aldol reactions.

Shibasaki and co-workers also reported a very interesting reductive aldol reaction between allenic esters and ketones.[49] Allenic ester pro-nucleophiles can attack from both γ-and α-positions, thus giving a huge regioselective challenge. In their study, ligands played an important part in resolving this problem. When different catalyst systems were studied both, the (*R*)-DTBM-SEGPHOS **165** and Taniaphos type ligand **169** proved to be excellent ligands, but with exclusively switched regioselectivities. When reactions between allenic esters and aromatic methyl ketones were performed in the presence of CuOAc, (*R*)-DTBM-SEGPHOS and pinacolborane as reductant, the γ/α-addition ratio of product was in favour of γ-addition by up to 30:1 ratio. Addition of Cy_3P as an additive was essential for this high ratio. Excellent yields and enantioselectivities were observed, as shown in Table 1.15 (Entries 1-4). The situation was changed completely when [$CuF(PPh_3)_3$·2MeOH] was used together with ligand **169**. In this case α-addition products were produced without any observation of the γ-products (Entries 5-8). Diastereoselectivities of the latter reaction ranging from 7:1 to 11:1, in favour of *syn*-product, and yields were generally good. Enantioselectivities were also satisfactory although not as high as in the γ-addition reactions.

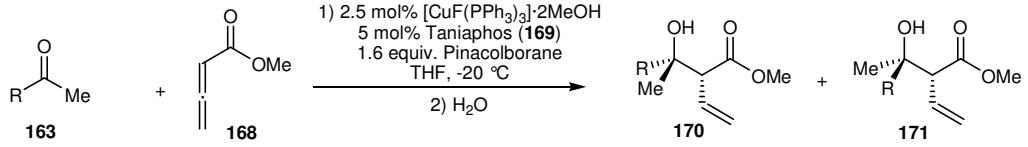
Table 1.15. Asymmetric Reductive Aldol Reaction Between Allenic Esters and Ketones.



163 164 166 167

γ-addition α-addition

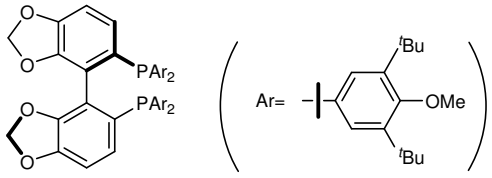
Entry	R	Product	γ:α-ratio	Yield[a] (%)	ee (%)
1	Ph	**166a**	25:1	96	99
2	*p*-Cl-Ph	**166b**	13:1	93	98
3	PhCH=CH	**166c**	30:1	97	84
4	*n*-butyl	**166d**	>8:1	86	88



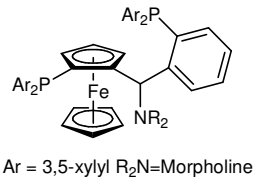
163 168 170 171

Entry	R	Product	*Syn:anti*	Yield[a] (%)	ee (%)
5	Ph	**170a**	10:1	90	67
6	*p*-Cl-Ph	**170b**	8:1	89	83
7	2-Naphtyl	**170c**	10:1	91	84
8	PhCH=CH	**170d**	9:1	87	67

a) determined by NMR spectroscopy



165
(R)-DTBM-SEGPHOS



Ar = 3,5-xylyl R_2N=Morpholine

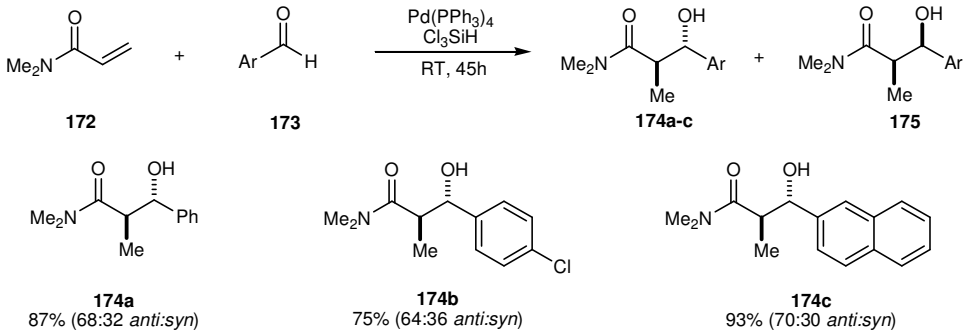
169
Taniaphos

1.4. Pd-, Ir-, In- and Ni- Catalysed Reductive Aldol Reactions

1.4.1. Palladium-Catalysed Reductive Aldol Reactions

In 1998, Kiyooka reported the palladium-catalysed reductive aldol coupling between *N,N*-dimethylacrylamide and aromatic aldehydes.[50] When $Pd(PPh_3)_4$ (5

mol%) was used together with a stoichiometric amount of Cl_3SiH, the coupling proceeded slowly (45 hours) at room temperature to afford aldol products in good to excellent yields and modest *anti*-selectivity (Scheme 1.23).

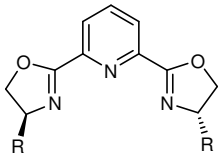


Scheme 1.23. Pd-catalysed intermolecular reductive aldol reactions.

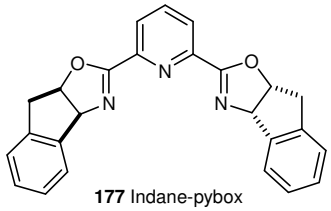
When *N,N*-dimethylacrylamide was replaced with *tert*-butyl acrylate, the product was obtained with a diminished yield but with similar values for diastereoselectivity of the *syn*-product

1.4.2. Iridium-Catalysed Reductive Aldol Reactions

In their original high-throughput study,[9] Morken and co-workers found two very efficient Rh-catalyst systems, described earlier in this chapter. This screening also revealed another potential catalyst system. The reaction between methyl acrylate and acetophenone was also catalysed by combination of $[(cod)IrCl]_2$ and *i*-Pr-Pybox-ligand. The reductive aldol product was formed in 1:1 mixture of diastereomers with 24% ee for *anti*-product and 12% ee for *syn*-product. As different Pybox-ligands may be accessed by reasonably effective and economic syntheses,[51] Morken decided to screen a library of Pybox-ligands (some of those shown in Scheme 1.24) with different Ir-salts to improve the modest preliminary results. The best catalyst system was found the be the combination of $[(cod)IrCl]_2$ and the indane-Pybox ligand **177**.



176a R=Me
176b R=*i*-Pr
176c R=*i*-Bu
176d R=*Ph*

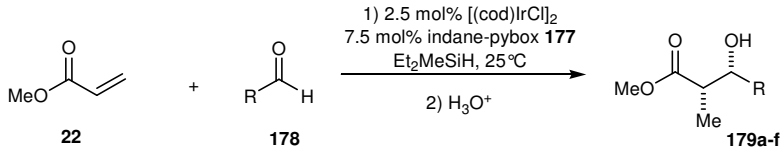


177 Indane-pybox

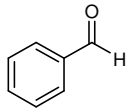
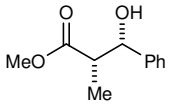
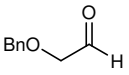
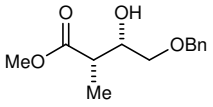
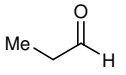
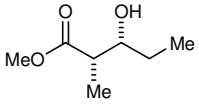
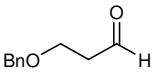
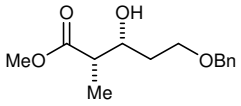
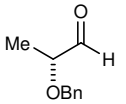
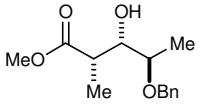
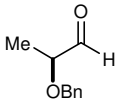
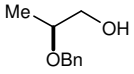
Scheme 1.24. Different Pybox-ligands

Using optimised reaction conditions, aromatic and α- and β-alkoxyaldehydes reacted readily with methyl acrylate (Table 1.16, Entries 1, 2 and 4) to give aldol products in moderate yields and with enantioselectivities ranging from good to excellent. Good *syn*-selectivities were also observed. Aliphatic aldehydes failed to provide aldol products in isolable yield (Entry 3). High level of double stereodifferentiation was observed when substrates containing pre-existing chirality were used (Entries 5-6). In the 'matched' case, both ligand control and Felkin stereoselection favoured the same product and the product was obtained in a highly stereoselective manner (Entry 5). On the other hand the 'mismatched' case failed to provide any aldol product (Entry 6). The major side product was found to be the reduced aldehyde **179f**. Although double stereodifferentiation worked well, attempts to use this catalyst system in a kinetic resolution process failed.

Table 1.16. Iridium Catalysed Asymmetric Reductive Aldol Reaction Between the Methyl Acrylate and Aldehydes.



22 178 179a-f

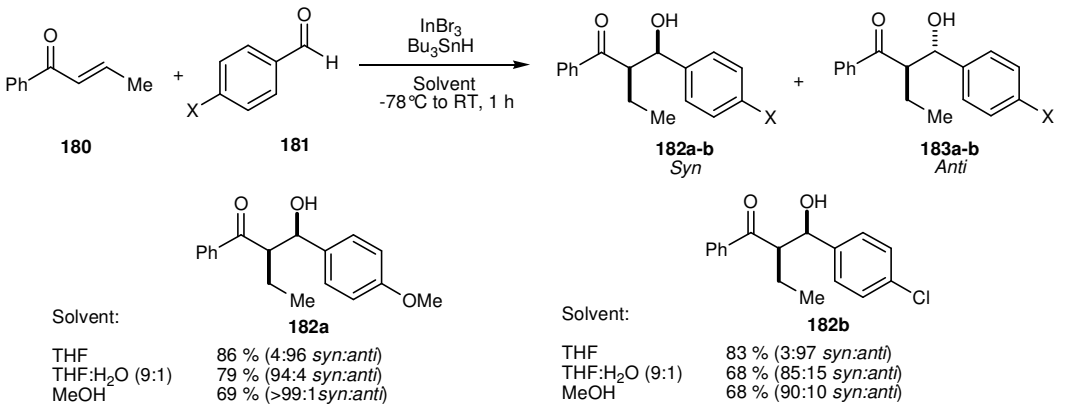
Entry	Aldehyde	Product		Yield (%)[a]	d.r. (*Syn:anti*)	ee (%)
1			**179a**	68	6.6:1	94
2			**179b**	59	9.5:1	96
3			**179c**	<5	n.a.	n.a.
4			**179d**	65	2.7:1	82
5			**179e**	50	>95:5 (>95:5)[b]	-
6			**179f**	<5[c]	n.a.	-

a) Yield of the reductive aldol product b) in parenthesis the ratio of Felkin:anti-Felkin products c) Yield of the aldol product

1.4.3. Indium-Catalysed Reductive Aldol Reactions

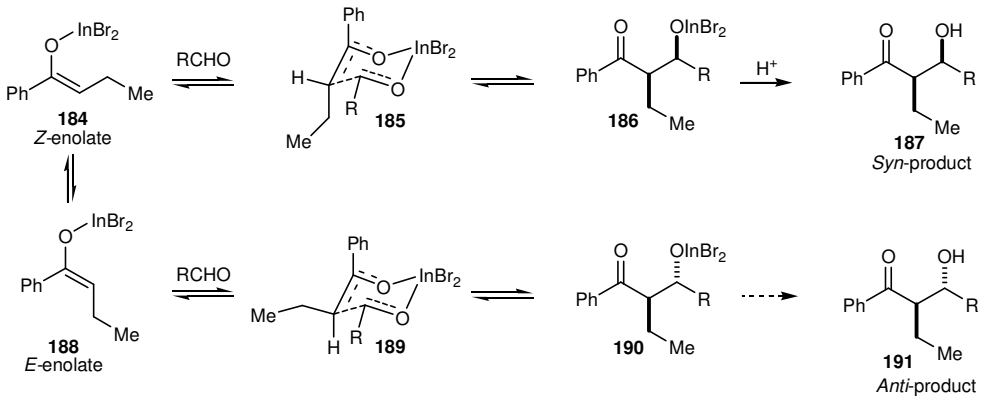
Baba disclosed in 1998 that dichloroindium hydride could be generated by the transmetallation between Bu_3SnH and $InCl_3$.[52] This indium hydride was then used in equimolar quantities to reduce acid chlorides to aldehydes.[53] When reactions between enone **180** and aromatic aldehydes were performed in the presence of preformed indium hydride, Br_2InH, an interesting solvent effect was discovered.[54] Aldol products **182** and **183** were usually formed in good yields and with excellent diastereoselectivities, but the stereoselection was highly dependent on the solvent in use (Scheme 1.25). When THF was used as solvent, product **182b** was formed in 86% yield and with a 4:96 *syn:anti* ratio. Changing the solvent to a mixture of water and THF (1:9), the *syn* product **182a** became dominant by ratio of 94:6. Methanol

further enhanced the *syn*-selectivity. Electron-deficient aldehydes also led to the product **182b** and **183b** with the same solvent effect.



Scheme 1.25. In-catalysed Intermolecular Reductive Aldol Reactions.

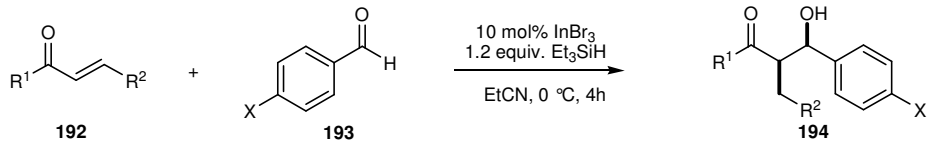
These solvent effects were explained by the reversibility of the reaction. It is assumed that the formation of *Z*-enolate **184** is preferred kinetically. This can then react with aldehyde to form an indium aldolate **186**. In the presence of a readily available proton (in MeOH and aqueous THF), this aldolate is protonated to give *syn*-product. When there is an absence of readily available protons, aldolate **186** can not be protonated and since all the steps are assumed to be reversible, a thermodynamically favoured *anti*-aldolate **190** is formed in excess. The reason for the stability can be seen if we look at the Zimmerman-Traxler transition state.[28] The transition state **189** leading to anti-aldolate **190** has one more substituent in a pseudoequatorial position.



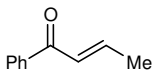
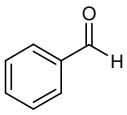
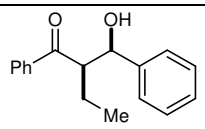
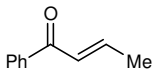
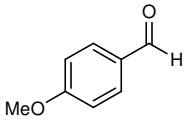
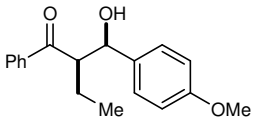
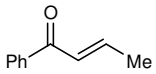
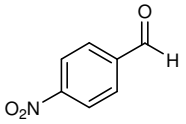
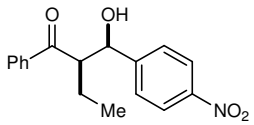
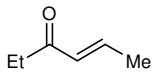
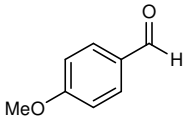
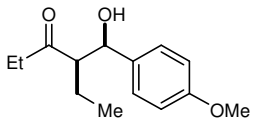
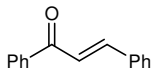
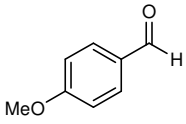
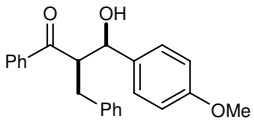
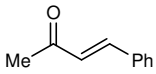
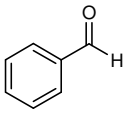
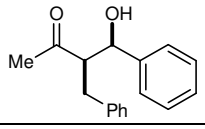
Scheme 1.26. Solvent affecting the stereochemical outcome of the reaction

Baba went further to develop this indium hydride-mediated reductive aldol reaction.[55] The use of Bu_3SnH as a stoichiometric reductant did not make it possible to use indium in catalytic fashion; instead equimolar amounts of preformed Br_2InH had to be used. Since many previously reported reductive aldol reactions used silanes as reductants, Baba decided to investigate whether In salts could form indium hydrides in the presence of trialkylsilanes. Under optimised conditions (10 mol% of $InBr_3$ together with Et_3SiH) Baba was able to perform reductive aldol reactions between enones and aromatic aldehydes in good yields and extremely high *syn*-selectivities (Table 1.17). Electron-rich aldehydes gave higher yields than electron-deficient aldehydes (Entry 2 vs. 3). Aromatic enones led usually to higher yields than aliphatic enones (Entries 1-3 and 5 vs. Entries 4 and 6).

Table 1.17. Indium Catalysed Asymmetric Reductive Aldol Reaction using Et_3SiH as stoichiometric reductant.



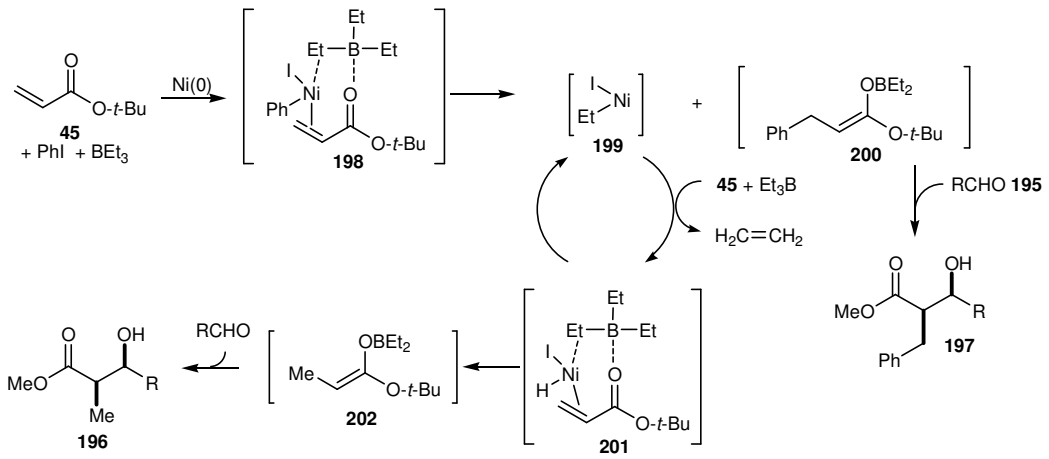
192 193 194

Entry	Enone	Aldehyde	Product		Yield (%)	Syn: anti
1				**194a**	78	92:8
2				**194b**	75	90:10
3				**194c**	59	>99:1
4				**194d**	61	>99:1
5				**194e**	82	>99:1
6				**194f**	40	>99:1

1.4.4. Nickel-Catalysed Reductive Aldol Reactions

Very recently, Montgomery and co-workers described the use of nickel in reductive aldol reactions.[56] Although this method did not provide any improvements in substrate scope or reactivity compared with existing methods, interesting mechanistic details were observed. $Ni(cod)_2$ was used as metal salt and Et_3B as reductant in this reaction between *tert*-butyl acrylate and aldehydes. These reactions required PhI as an additive in order to proceed. The side product **197** formed by Ph addition followed by aldol coupling was always observed in small quantities (Eqn 18).

This observation led to a hypotheses of the reaction mechanism. The proposed mechanism is shown in Scheme 1.27. It is assumed that addition of Ni(0) to the aryl iodide is followed by coordination of the nickel complex and Et_3B to the acrylate to form **198**. Et_3B is assumed to play a dual role in this complexation; it acts as a Lewis acid to activate the enoate and as Lewis base to activate the nickel complex.[57] Reorganisation of **198** leads to the boron enolate **200** and Ni-complex **199**. The boron enolate **200** then reacts with aldehyde to form the side product **197** that is always observed in small quantities in this reaction. The resulting ethyl(iodo)nickel species now coordinates to another molecule of acrylate, together with Et_3B, to form complex **201**. The hydride in nickel is generated by a sequence of β-hydride elimination followed by dissociation of ethylene gas. Reorganisation of the complex **201** first leads to a boron enolate **202** which further reacts with the aldehyde to give the product **196**. The ethyl(iodo)nickel species **199** is also regenerated in this step to complete the catalytic cycle.

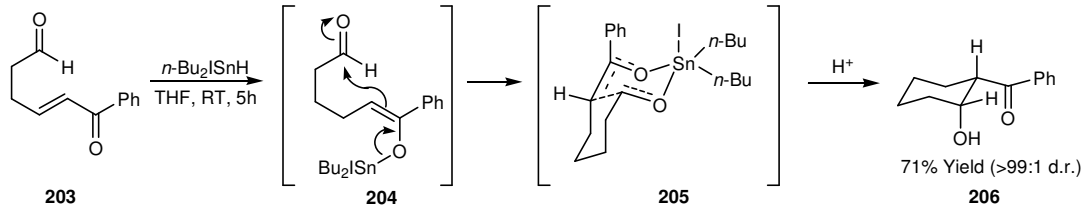


Scheme 1.27. Proposed Mechanism for the Ni-Catalysed Reductive Aldol Reaction.

1.5. Other Reductive Aldol Reactions

1.5.1. Organoiodotin-Mediated Reductive Aldol Reaction

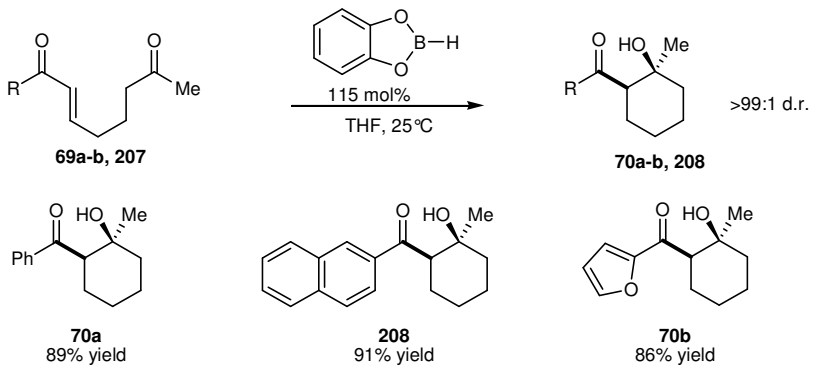
Baba disclosed a *n*-Bu_2SnIH-promoted reaction where tin hydride mediates the cyclisation of an enone-aldehyde substrate **203** (Scheme 1.28).[58] It was assumed that the reaction does not proceed *via* a radical pathway. They proposed that 1,4-addition leads to a *Z*-tin enolate **204** that immediately attacks the carbonyl group through a six-membered cyclic transition state to give the *syn*-product in 79% yield. No *anti*-product was observed.



Scheme 1.28. Organoiodotin mediated reductive aldol reaction.

1.5.2. Borane-Mediated Reductive Aldol Reaction

In 2003 Krische reported a borane-mediated reductive aldol reaction, overcoming the problem of chemoselectivity.[59] Boranes are usually found to reduce ketones readily. To minimise this problem, Krische decided to study intramolecular substrates containing enone-ketone systems (Scheme 1.29). Cyclisation of six-membered rings proceeded readily with very high diastereoselectivies.



Scheme 1.29 Borane-Mediated Reductive Aldol reaction.

1.6. Conclusions

The reductive aldol reaction has been shown to be a versatile synthetic method. This tandem reaction, which includes two steps; i) conjugate reduction, and ii) aldol addition, enables direct access to different β-hydroxycarbonyl derivatives in one step. At the time of Revis' original report in 1987, the reaction suffered from number of limitations. The scope of the reaction was very narrow and minimal diastereoselectivities were observed. Further work and developments of this reaction by a number of research groups have led to a range of high-yielding and highly diastereo-and enantioselective variants. Continued research in this field will no doubt lead to the discovery of new, more effective and more selective catalyst systems, which will enable extended synthetic utility of this important cascade transformation.

Our research in this area started with the discovery of the first enantioselective copper-catalysed reductive aldol reaction (Chapter 2). Further developments of the reaction led to a discovery of two novel catalyst systems in the area of this reaction (Chapters 3-7).

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2. Chapter 2: Copper-Catalysed Reductive Aldol Cyclisations

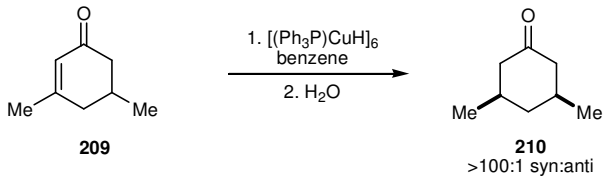
During the course of a natural product synthesis programme, we became interested in the possibility of applying reductive aldol cyclisations to the preparation of heterocyclic products. Although much progress had been achieved in reductive aldol reaction with different catalyst systems (described in Chapter 1), there was a demand for highly stereoselective reactions where the electrophile is a ketone. In the previous literature, there were no examples of intramolecular reductive aldol cyclisations forming lactones or lactams. Two main points were emphasised for this project; i) the plan was to be able to perform these reactions without the aid of a drybox, ii) to develop a catalyst system that had not been applied to reductive aldol reaction previously. Phosphine-stabilised copper hydride complexes appeared to be a good choice for evaluation in our reaction for a number of reasons. First, Chiu and co-workers had demonstrated the ability of $[(Ph_3P)CuH]_6$ used either in stoichiometric fashion, or catalytically in the presence of stoichiometric siloxane, to promote reductive aldol cyclisations in carbocycle synthesis (Chapter 1).[1] Second, recent developments in asymmetric reduction reactions catalysed by chiral copper(I)-bis-phosphine complexes suggested that in principle, a highly enantioselective process might also be realised in the present case through identification of an appropriate ligand.

2.1. Copper Hydrides Developed for Conjugate Reduction

Before going into the details of this reductive aldol reaction, it is useful to give an introduction of the development of copper hydride reagents, for conjugate reduction. The conjugate reduction of α,β-unsaturated carbonyl compounds is a well known and developed reaction where the alkene moiety is reduced and the carbonyl group stays intact. There are numerous methods available to carry out this transformation.[2] Stork was the first to demonstrate regioselective enolate formation *via* dissolving metal reduction of enones.[3] Since then, several different catalytic hydrometallative methods for reductive enolate formation have been introduced, making it an important method for selective 1,4-reduction of α,β-unsaturated

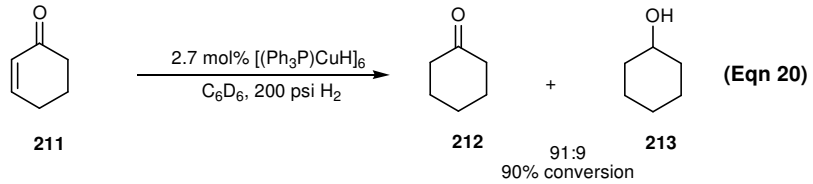
carbonyl compounds. Nowadays, these conjugate reductions can be achieved by various reducing systems, most of which are metal hydrides formed *in situ*.

Before *in situ* systems were developed, preformed hydrides such as triphenylphosphinecopper hydride hexamer $[(Ph_3P)CuH]_6$ (also known as Stryker's reagent), were commonly employed as stoichiometric reagents for the conjugate reduction of α,β-unsaturated carbonyl compounds (Eqn 19). [4]



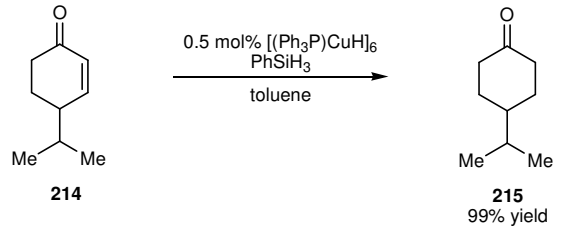
209 **210** >100:1 syn:anti **(Eqn 19)**

The reaction in Eqn 20 proceeded in high diastereoselectivity. Soon it was shown that Stryker's reagent could also be used in catalytic fashion. The hydride complex was regenerated with molecular hydrogen under high pressure.[5] Conjugate reduction of cyclohexenone proceeded readily, but the major disadvantage was the use of a high hydrogen pressure which also led to a further reduction of the ketone **212** to a saturated alcohol **213** in small amounts.



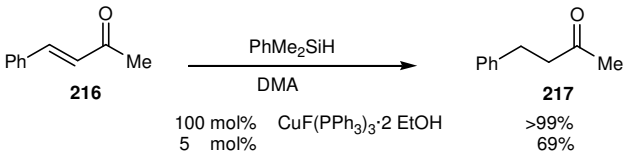
211 **212** **213** 91:9 90% conversion **(Eqn 20)**

Using organosilanes as a hydride source provided a solution to the disadvantages of the use of high hydrogen pressure. In the first example by Lipshutz and co-workers, phenylsilane was used as a hydride source to regenerate Stryker's reagent.[6] A reasonably low catalyst loading of $[(Ph_3P)CuH]_6$ (0.5 mol%) was used to achieve excellent yields in the reduction of cyclic enones (Eqn 21).



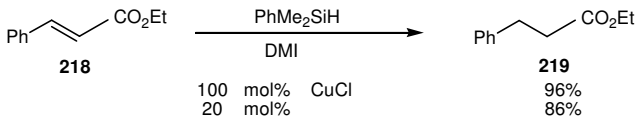
(Eqn 21)

The first examples of generation of copper hydride species for conjugate reduction from organosilanes and simple copper salts were independently reported at the same time by the groups of Mori and Hosomi.[7,8] Mori and co-workers reported hydride generation from $CuF(PPh_3)_3{\cdot}2EtOH$ with either $PhMe_2SiH$ or Et_3SiH. With stoichiometric amounts of the copper fluoride complex, the conjugate reduction of several α,β-unsaturated cyclic and acyclic ketones was achieved in high yields. The reduction also proceeded with a substoichiometric amount of the copper complex, but with clearly diminished yield (Eqn 22). DMA was used as a solvent.



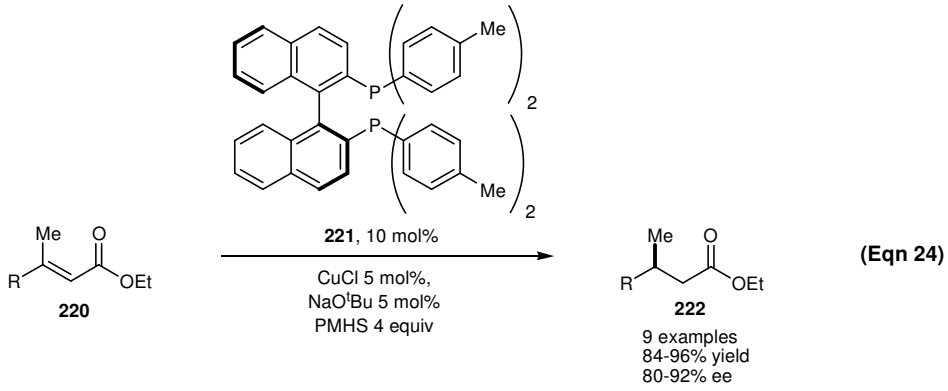
(Eqn 22)

Hosomi and co-workers reported the generation of copper hydride from CuCl and $PhMe_2SiH$. It is worth noticing that in Hosomi's example, a copper hydride species is not stabilised by phosphine ligand. Other silanes such as Ph_2SiH_2 and Et_3SiH were also tested, but the best results were obtained with $PhMe_2SiH$. Both enones and enoates underwent conjugate reduction in high yields. When the copper salt was used in substoichiometric amounts (20 mol%) the reduction still proceeded, but in lower yields (Eqn 23). When the catalyst loading was dropped to 10 mol%, no reduction was observed. Interestingly, copper hydride was formed only in the cases where DMI or DMF were used as solvents in the reaction. The use of THF, dichloromethane or acetonitrile did not lead to formation of the desired products and the starting materials were recovered.



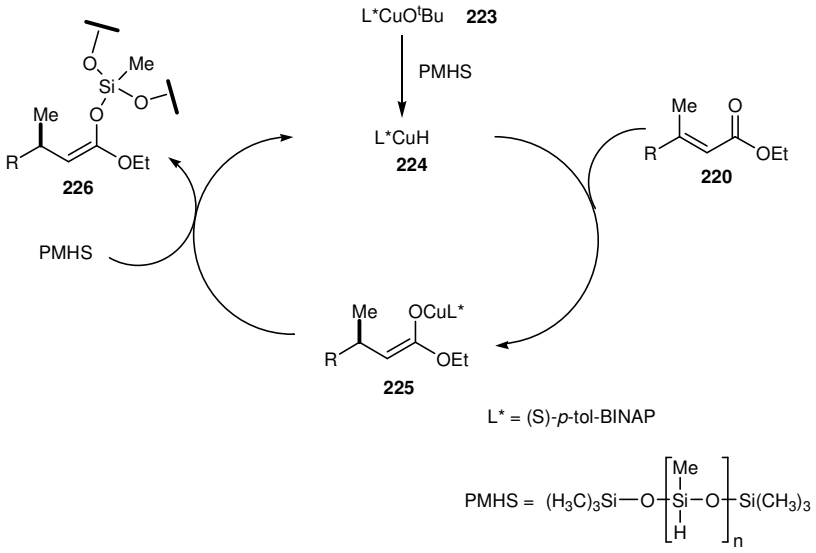
(Eqn 23)

A few years after these pioneering reports, the first example of enantioselective conjugate reduction by copper hydride species was reported.[9] Buchwald and co-workers used CuCl, NaO^{t}Bu, (*S*)-*p*-tol-BINAP (**221**) together with the economical and safe polymeric siloxane, PMHS, as the stoichiometric reductant. 1,4-Reduction of *α,β*-unsaturated esters to form *β*-stereocentres proceeded in excellent yields and good enantioselectivities. Both *E*-and *Z*-isomers were reduced in similar yields and ee's; *E*-isomers leading to *R*-product and *Z*-isomers to *S*-product.



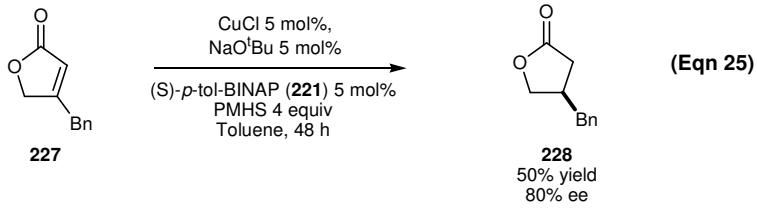
(Eqn 24)

In the proposed mechanism (Scheme 2.1), Buchwald assumed that (*p*-tol-BINAP)CuO^{t}Bu **223** complex is first formed. The addition of PMHS leads to a generation of active copper(I)-bis-phosphine hydride complex **224**. This then engages in hydrometallation with the substrate **220** to generate copper enolate **225**. This copper enolate then undergoes *σ*-bond metathesis with PMHS to form silyl ketene acetal **226.** Finally, work up with TBAF gives reduced product **222**.



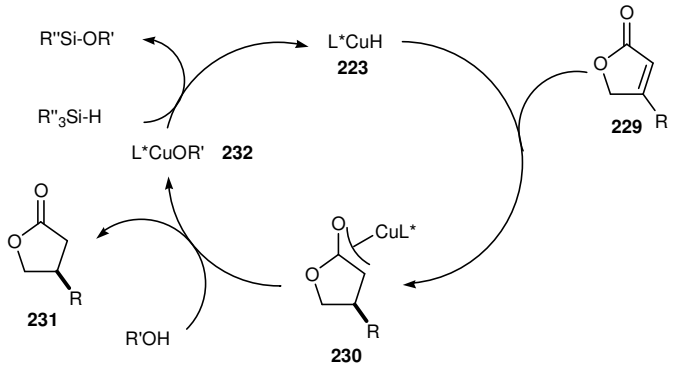
Scheme 2.1. Proposed Mechanism of the Cu-Catalysed Conjugate Reduction.

The catalyst system described above was also used for the conjugate reduction of unsaturated lactones (Eqn 25).[10] The yields and ee's were not as good as for the acyclic cases.



(Eqn 25)

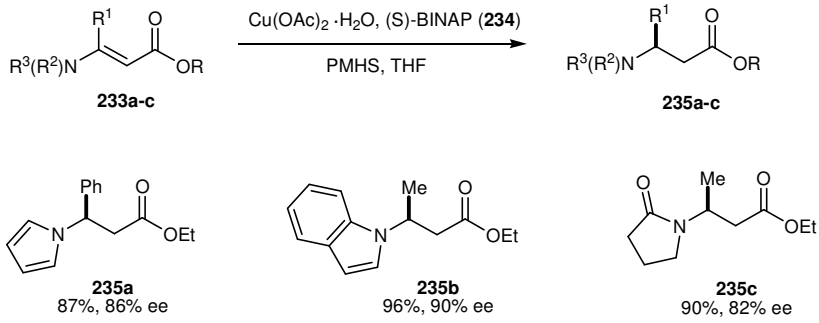
Buchwald and co-workers made the hypothesis that the lower reactivity with cyclic substrates must come from the fact that σ-bond metathesis between copper enolates and PMHS was slow. He reasoned this from the possible high *C*-bound character of the enolate. To speed up the metathesis he employed alcohol additives. An alcohol additive would rapidly protonate the copper enolate **230,** generating a copper alkoxide **232** and desired product **231**. Copper alkoxide **232** was expected to undergo σ-bond metathesis with PMHS faster than with copper enolate, regenerating the active copper hydride complex (Scheme 2.2). The reaction shown in Eqn 25 provided the product **228** in 90% yield and 93% ee when isopropanol (4 equiv.) was used as an additive.



Scheme 2.2. The Role of the Base in Cu-Catalysed Conjugate Reduction.

Another important discovery Buchwald and co-workers made in this research was that air-stable $CuCl_2 \cdot H_2O$ could be used as the copper salt. This was a big step to make this methodology more accessible as the use of a drybox was no longer needed. Use of $CuCl_2 \cdot H_2O$ was even found to give similar or slightly better yields and ee's than the use of CuCl.

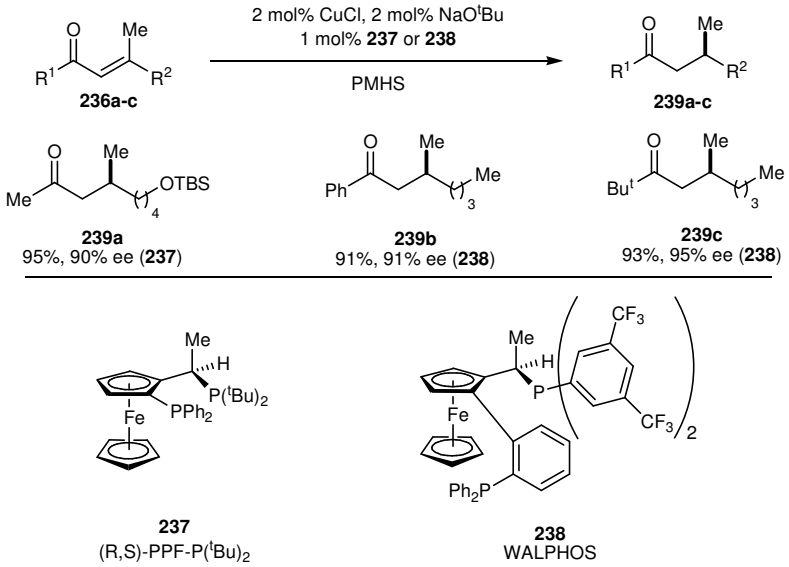
Buchwald co-workers also reported the first example of a conjugate reduction where substrates contained nitrogen at the β-position.[11] This enabled the effective formation of enantioenriched β-amino acid derivatives. This time, $Cu(OAc)_2 \cdot H_2O$ was used as a copper source and interestingly, the use of a base was not needed. Several different silanes/siloxanes and solvent systems were tested and the best result was found when THF was used as a solvent and PMHS as a hydride source (Scheme 2.3). THF was expected to be a good solvent due to the high solubility of the copper catalyst. One unexplained observation was also made; when reaction was performed under an atmosphere of air, reaction rates were higher than under inert atmosphere.



Scheme 2.3. Formation of enantioenriched *β*-amino acid derivatives.

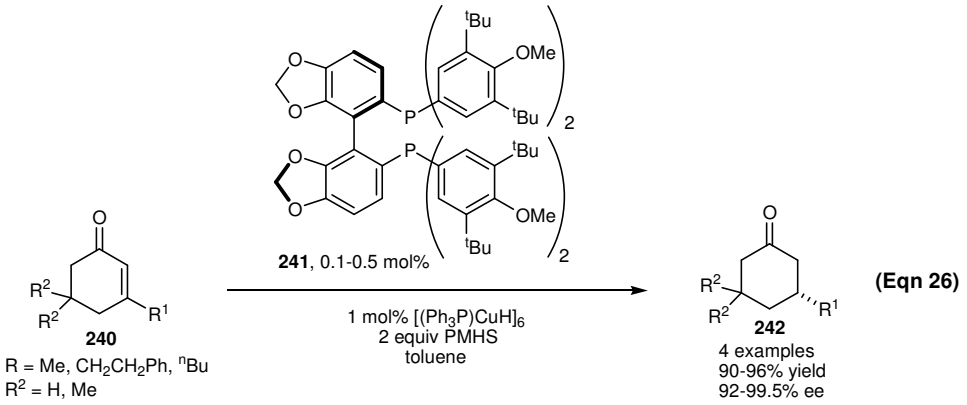
The range of successfully transformed substrates was large, including *N*-vinyl pyrroles (**235a**), *β*-unsaturated esters with an indole moiety (**235b**) and pyrrolidinone-containing (**235c**) substrates. Excellent yields and enantioslectivities were realised in all cases.

Lipshutz and co-workers were the first to report enantioselective conjugate reduction of acyclic *α,β*-unsaturated enones (Scheme 2.4).[12] The active copper hydride species was formed from CuCl and PMHS. Chiral ferrocenyl ligands (*R,S*)-PPF-P(^{t}Bu)$_2$ (**237**) or WALPHOS (**238**) were used to control the enantioselectivity. As with Buchwald's previous examples with esters (Eqn 24), *E*- and *Z*-isomers gave different enantiomers as products.



Scheme 2.4. Cu-Catalysed Conjugate Reduction of Acyclic Substrates

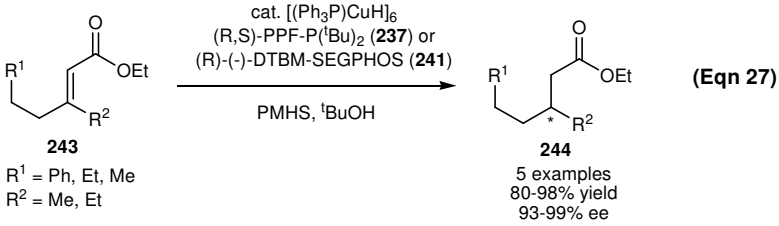
Lipshutz made also improvements to the conjugate reductions of cycloalkenones.[13] Takasago's (*R*)-(–)-DTBM-SEGPHOS (**241**) was used as a ligand. With this catalyst system, sterically hindered substrates were also reduced in good yields (Eqn 26). Another advantage of this system was that no overreduction was observed at all, even when 2 equivalents of PMHS were used. Ee's were also higher than in the previously reported examples.[14]



(Eqn 26)

Very low catalyst loadings could be employed. With the substrate where R^1=Me, R^2= Me and substrate/catalyst ratio was as high as 275 000:1, the product was formed in 88% yield and 98.5% ee. This was a very good improvement over Buchwald's system (CuCl, *p*-tol-BINAP, PMHS), were the yield was 14% and the ee was 47%.[14] Five-membered rings were also reduced with high yields and ee's. Lipshutz discovered that pinacolborane could also be used as a hydride source, producing similar yields and ee's as when using silanes as reductants. The advantage is that the boron enolates generated, are very labile and only a simple work up was needed to form the product (plug of silica).

Naturally, Lipshutz and co-workers also tried their catalyst system in the conjugate reduction of α,β-unsaturated esters.[15] As in previous examples (Scheme 2.4 and Eqn 26) chiral DTBM-SEGPHOS **241** and PPF-P(^{t}Bu)$_2$ **237** were used as ligands. In this report they used substoichiometric amounts of Stryker's reagent as the copper source with PMHS to regenerate the active catalyst (Eqn. 27).



(Eqn 27)

Several other catalytic systems have been reported in conjugate reductions of α,β-unsaturated carbonyl compounds, including those base upon cobalt and rhodium.[16,17,18] These are not reviewed here.

2.2. Copper-Catalysed Reductive Aldol Cyclisations

2.2.1. Reaction optimisation

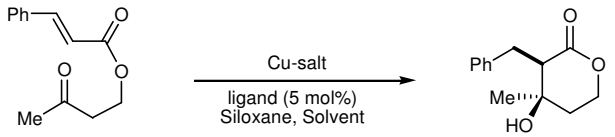
Our initial studies focused upon the cyclisation of substrate **245**, containing an α,β-unsaturated carbonyl moiety tethered to a ketone through an ester linkage (Table 2.1). We began our investigation by surveying a number of copper salts,[i] siloxanes,[ii] and bis-phosphine ligands[iii] in order to identify a suitable catalyst system. Preliminary experiments were conducted in THF using PMHS as the siloxane. Of the copper salts examined, only $Cu(OAc)_2 \cdot H_2O$ and Cu(2-ethylhexanoate)$_2$ resulted in high conversions, with $Cu(OAc)_2 \cdot H_2O$ being preferred for economic considerations. *Rac*-BINAP and DPPF performed with similar efficacy (Entries 5-8), with very low conversions being observed with DPPE, DPPB and (*S*,*S*)-Et-DuPhos. DPPF was arbitrarily chosen for subsequent experiments. For substrate **245**, PMHS and TMDS were found to be equally effective whilst $(EtO)_3SiH$, $(EtO)_2MeSiH$, Et_3SiH and Ph_2MeSiH gave product **246** in lower yields. Subsequent studies showed TMDS to give slightly cleaner reactions for a wider range of substrates. Toluene, CH_2Cl_2 and MeCN proved to be inferior solvents, although DME was similar to THF.

([i]) Copper salts examined included $CuCl_2 \cdot 2H_2O$, CuF_2, $Cu(OAc)_2 \cdot H_2O$, Cu(2-ethylhexanoate)$_2$, $Cu(OBz)_2$, and $Cu(acac)_2$.

([ii]) The inexpensive siloxanes polymethylhydrosiloxane (PMHS) and 1,1,3,3-tetramethylhydrosiloxane (TMDS) were evaluated.

([iii]) The following bis-phosphine ligands were studied: 1,2-bis(diphenylphosphino)ethane (DPPE), 1,2-bis(diphenylphosphino)butane (DPPB), 1,1′-bis(diphenylphosphino)ferrocene (DPPF), racemic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (*rac*-BINAP), and (+)-1,2-bis((2*S*,5*S*)-2,5-diethylphospholano)benzene ((*S*,*S*)-Et-DuPhos).

Table 2.1. Optimisations of Reaction Conditions[a]



245 **246**

Entry	Cu-salt	Ligand	Silane	Solvent	Yield(%)
1	$CuF\cdot(H_2O)_2$	*rac*-BINAP	TMDS	THF	(50)[b]
2	$Cu(OAc)_2\cdot H_2O$	*rac*-BINAP	$(EtO)_3SiH$	THF	(50)[b]
3	$Cu(OAc)_2\cdot H_2O$	*rac*-BINAP	$(EtO)_2MeSiH$	THF	(60)[b]
4	$Cu(OAc)_2\cdot H_2O$	*rac*-BINAP	TMDS	Toluene	(60)[b]
5	$Cu(OAc)_2\cdot H_2O$	*rac*-BINAP	PMHS	THF	72
6	$Cu(OAc)_2\cdot H_2O$	DPPF	PMHS	THF	71
7	**$Cu(OAc)_2\cdot H_2O$**	**DPPF**	**TMDS**	**THF**	**72**
8	$Cu(OAc)_2\cdot H_2O$	*rac*-BINAP	TMDS	THF	73

a) All reactions were conducted using 0.2 mmol of substrate, 5 mol% of Cu, 5 mol% of ligand, and 2 hydride equivalents of silane. b) Conversion determined by NMR analysis.

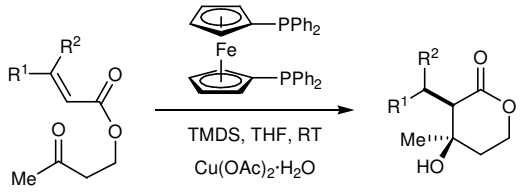
Under the conditions highlighted in Entry 7, substrate **245** cyclised to give aldol product **246** in 72 % isolated yield. The diastereoselectivity of the reaction was extremely high (>95:5 by ^{1}H NMR analysis).

2.2.2. Substrate Scope

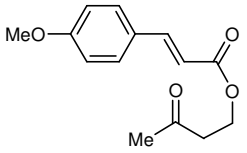
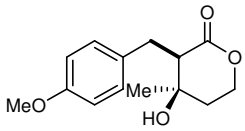
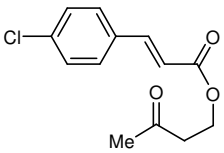
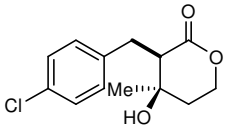
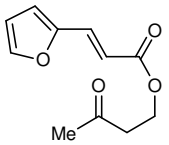
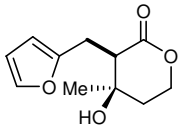
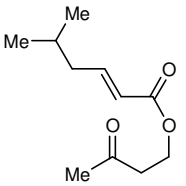
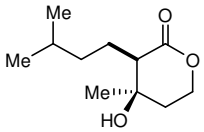
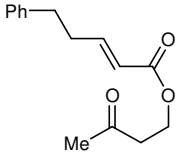
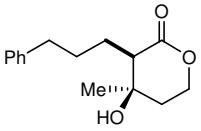
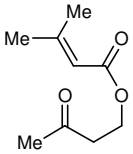
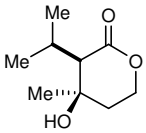
Under the obtimised conditions, a range of substrates underwent cyclisation to give β-hydroxy-δ-valerolactone products (Table 2.2). When the electrophile of the substrate was a methyl ketone, α,β-unsaturated esters containing aromatic (Entries 1 and 2), heteroaromatic (Entry 3), and alkyl (Entries 4 and 5) substituents were tolerated in the reaction, as was the trisubstituted enoate **247f** (Entry 6). Reactions proceeded at room temperature and were highly diastereoselective (>95:5 by ^{1}H NMR analysis of the unpurified reaction mixtures). However, the desired β-

hydroxylactones were often accompanied by small quantities of uncyclised side-products that had undergone reduction at the enoate, and in some cases at the ketone, resulting in moderate yields. This observation indicates that the rate of σ-bond metathesis[19] of the intermediate copper enolate with the siloxane is competitive with the rate of aldol cyclisation. This will be discussed further later in this chapter.

Table 2.2. Catalytic Reductive Aldol Cyclisations I[a]



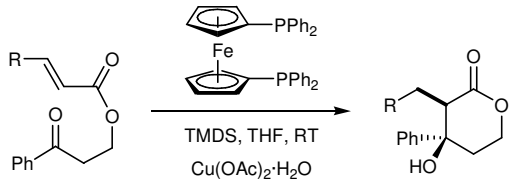
247a-f **248a-f**

Entry	Substrate		Product[b]		Yield[c]
1		**247a**		**248a**	61
2		**247b**		**248b**	65
3		**247c**		**248c**	63
4		**247d**		**248d**	73
5		**247e**		**248e**	61
6		**247f**		**248f**	62

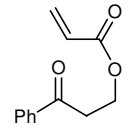
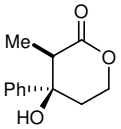
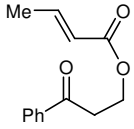
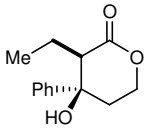
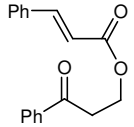
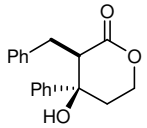
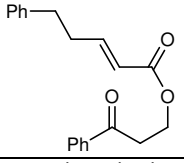
a) All reactions were conducted using 1mmol of substrate, 5 mol% of Cu, 5 mol% of ligand and 1 mmol of TMDS (2 hydride mmol) b) Only one diastereomer of product was observed by ^{1}H NMR analysis c) Isolated yield of diastereomerically pure material

The change of the methyl ketone to a phenyl ketone led to inferior reactivity. Only three substrates reacted to give β-hydroxy-δ-valerolactone products. In the case where the alkene was unsubstituted (R=H), product **250a** was formed in similar levels of yield than in the cases of the methyl ketone substrates. Substrates where the alkene was further substituted failed to go to completion, or gave no product at all (Table 2.3). The diastereoselectivities were also lower and in the case of product **250c,** the diastereomers were inseparable.

Table 2.3. Catalytic Reductive Aldol Cyclisations II[a]



249a-d 250a-c

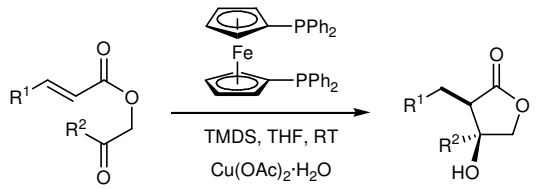
Entry	Substrate		Product		Yield(%) (*syn: anti*[b])
1		**249a**		**250a**	71 (>95:5)
2		**249b**		**250b**	50 (8:1)
3		**249c**		**250c**	47 (10:1) [c]
4		**249d**	-		n.a. [d]

a) Reactions were conducted using 1mmol of substrate, 5 mol% of Cu, 5 mol% of ligand and 1 mmol of TMDS (2 mmol of hydride) b) determined by ^{1}H NMR analysis c) Isolated as unseparable mixture of diastereomers d) No reaction was observed

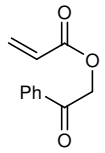
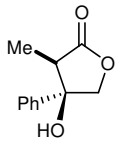
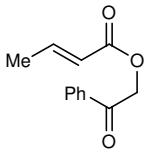
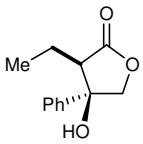
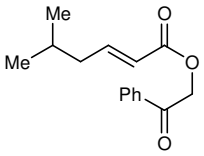
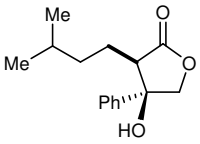
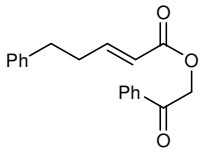
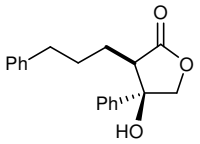
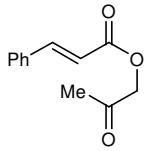
Surprisingly, the process could also be applied to the formation of five-membered lactones (Table 2.4), despite these cyclisations formally being disfavoured 5-(enol*endo*)-*exo-trig* ring closures according to Baldwin's rules.[20] Unfortunately, only substrates containing phenyl ketone proceeded to give products. Yields and diastereoselectivities were comparable to those of the six-membered lactones

presented in Table 2.2. In the case where methyl ketone substrate was used only complicated mixtures were obtained.

Table 2.4. Catalytic Reductive Aldol Cyclisations to Form Five-membered Lactones[a]



251a-e **252a-d**

Entry	Substrate		Product		Yield(%)[b]
1		**251a**		**252a**	69
2		**251b**		**252b**	72
3		**251c**		**252c**	65
4		**251d**		**252d**	60
5		**251e**	-		n.a.[c]

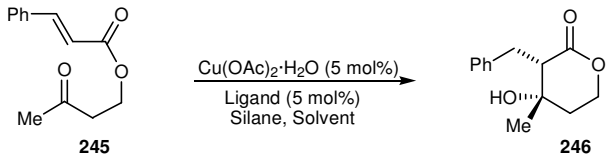
a) All reactions were conducted using 1mmol of substrate, 5 mol% of Cu, 5 mol% of ligand and 1 mmol of TMDS (2 mmol of hydride) b) Isolated yield of diastereoreomerically pure material c) A complicated mixture of unidentified products was formed.

2.2.3. Enantioselective cyclisations

Having established the viability of the basic process, we next turned our attention to the use of non-racemic chiral bis-phosphine ligands to generate enantiomerically enriched products. Since the enantioselectivies of the reaction was assumed to be dependent also on the siloxane and the solvent used in reactions, another screening of these variants was performed. First, the siloxanes were studied

(Table 2.5, Entries 1-4). Again PMHS and TMDS showed very similar reactivities, but also gave exactly the same enantioselectivities for the reaction (Entries 3 and 4). For the screening of the silanes (*S*)-BINAP was selected as the ligand. This was changed to (*S*)-MeOBIPHEP when we screened the solvents, due to its increased solubility in general. (*S*)-MeOBIPHEP also gave better enantioselectivities in the reaction in comparison to (*S*)-BINAP in THF (entries 4 and 5). When toluene and acetonitrile were used as solvents the enantioselectivities were similar to those in THF although the conversions were lower, so we decided to proceed with THF.

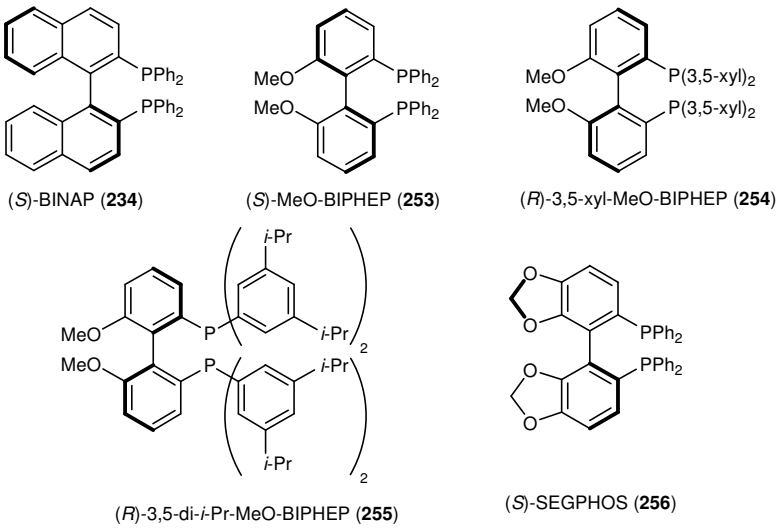
Table 2.5. Optimisation of Enantioselective Cyclisations[a]



245 **246**

Entry	Ligand	Silane	Solvent	ee(%)
1	(*S*)-BINAP (**234**)	$(EtO)_3SiH$	THF	57
2	**234**	$(EtO)_2MeSiH$	THF	61
3	**234**	PMHS	THF	62
4	**234**	TMDS	THF	62
5	(*S*)-MeO-BIPHEP (**253**)	TMDS	THF	73
6	**253**	TMDS	toluene	74
7	**253**	TMDS	MeCN	73
8	**253**	TMDS	Et_2O	n.a

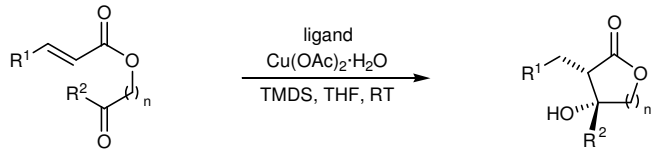
After these optimisations we started to screen different bis-phosphine ligands. The best results obtained are shown in Table 2.6 In general, the chiral ligands performed with comparable efficiency to the achiral ligand DPPF, affording the products in similar yields. However, at our current level of optimisation, the enantioselectivies obtained remain modest. While (*S*)-BINAP (**234**) gave the lactone **246** in 62% ee (Entry 1), the Roche MeO-BIPHEP ligands **253-255** and Takasago's SEGPHOS ligand **256** led to slight improvements in enantioselectivity (Entries 2–5). Similar patterns were observed for other substrates (Entries 6–18), with the best result of 83% ee being obtained using ligand **254** in the cyclisation of **247b** (Entry 13).



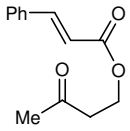
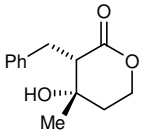
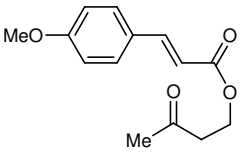
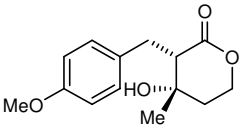
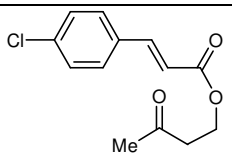
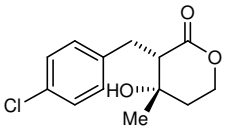
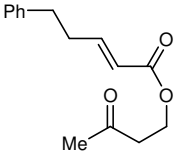
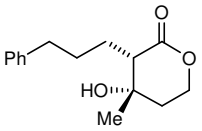
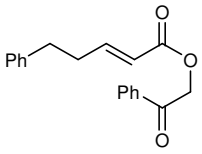
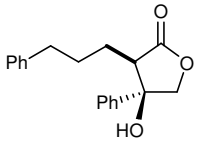
Scheme 2.5. Chiral Ligands Used for Asymmetric Cyclisations

In the case of the formation of the five-membered lactone **252d** using ligand **254**, the enantiomeric excess was only 49% (Entry 14). The absolute sense of asymmetric induction in these reactions was determined by X-ray crystallography of the chlorine-containing lactone **248b**.[21] Interestingly electron poor substrate **247b** cyclised giving higher enantioselectivities than electron rich substrate **247a**

Table 2.6. Catalytic Enantioselective Reductive Aldol Cyclisations[a]



245, 247a,b,e, 251d **246, 248a,b,e, 252d**

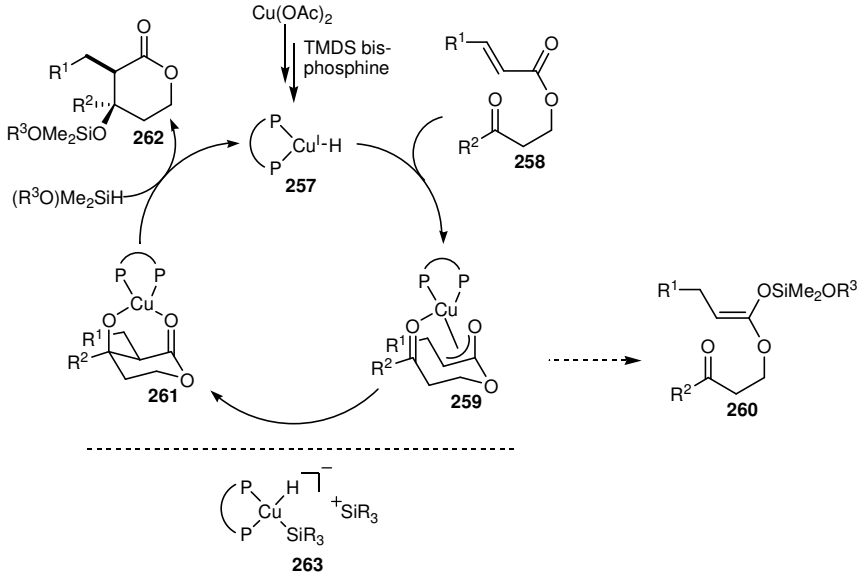
Entry	Substrate	Product	Ligand	Yield/(Conversion) (%)	ee (%)
1	 **245**	 **246**	**234**	72	62
2			**253**	73	73
3			**254**	69	70[b]
4			**255**	64	77[b]
5			**256**	62	74
6	 **247a**	 **248a**	**234**	(70)	66
7			**255**	(75)	62
8			**253**	(75)	66
9			**256**	(80)	62
10			**254**	(70)	66
11	 **247b**	 **248b**	**234**	79	73
12			**253**	71	76
13			**254**	71	83[b]
14			**256**	73	82
15	 **247e**	 **248e**	**324**	60	72
16			**253**	60	73
17			**254**	61	80[b]
18			**256**	68	80
19	 **251d**	 **252d**	**254**	51	49

a) Reaction were conducted using 0.2mmol of substrate, 5 mol% of Cu, 5 mol% of ligand and 0.2 mmol of TMDS (0.4 mmol of hydride) b) The enantiomer opposite to that depicted was obtained

2.3. Mechanism

A plausible catalytic cycle for the process is presented in Scheme 2.6. Presumably, in the presence of bis-phosphine and TMDS, reduction of copper(II) occurs to generate a copper(I)-bis-phosphine hydride complex **257**. Consistent with this hypothesis is the observation of the characteristic emerald green color of a

solution of $Cu(OAc)_2 \cdot H_2O$ (blue) and DPPF (yellow) in THF being quickly converted into a yellow solution upon addition of TMDS, which is indicative of the reduction of copper(II) and the disappearance of the associated blue color. This hydride complex then engages in hydrometallation with the substrate **258** to generate the copper enolate **259**. Now the reaction is in a phase where two possible pathways are competing. If σ-bond metathesis[19] with the siloxane happens before the aldol addition we form a silyl ketene acetal **260** which is deprotected upon acidic work-up to give reduced product. Otherwise carbonyl addition results in the copper aldolate **261**, which then undergoes σ-bond metathesis[19] with the siloxane to liberate the desired silylated product **262** (which is deprotected upon work-up), regenerating the copper(I) complex **257**. However, we do not rule out alternative mechanisms that invoke the participation of copper species such as silyl hydrido cuprates **263**.[22] Furthermore, the role played by the acetate counterions is unclear. The observed stereochemistry of the products presumably arises from preferential formation of the *Z*-copper enolate, coupled with chelation in the carbonyl addition step (as in **259**).



Scheme 2.6. Propposed Mechanism of the Cu-Catalysed Reductive Aldol Cyclisations.

A possible explanation for the ready cyclisation of substrates forming five membered lactones (Table 2.4), formally disfavoured by Baldwin's rule, is that the copper enolate intermediate (depicted as an oxa-π-allylcopper species **259**) has

significant *C*-bound character, which reduces its planarity and better enables ring closure.

2.4. Conclusions

Highly diastereoselective and modestly enantioselective copper-catalysed reductive aldol cyclisations have been developed to afford five- and six-membered β-hydroxylactones. Although the enantioselectivities obtained remained modest, these were the first examples of enantioselective reductive aldol reactions using ketones as electrophiles, and the first enantioselective intramolecular reductive aldol reactions. The products can be isolated in modest to good yields, and the reactions generally occur in highly diastereoselective fashion. Reactions were performed in a very "user-friendly" way; no glove-box or special techniques were required.

2.5. References

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2.6. Experimental

General Information

All reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. CH_2Cl_2 was distilled from CaH_2. THF was distilled from sodium benzophenone ketyl. Anhydrous DMF was purchased from Aldrich. 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40-60 °C. α,β-Unsaturated carboxylic acids used in the preparation of the cyclisation substrates were obtained as follows: 3-(2-furyl)acrylic acid, 3,3-dimethylacrylic acid and 4-chlorocinnamic acid were purchased from Aldrich; 4-methoxycinnamic acid was purchased from Fluka; (*E*)-5-methylhex-2-enoic acid was prepared from a Wadsworth-Emmons reaction of isovaleraldehyde with triethyl phosphonoacetate, followed by hydrolysis of the resulting ethyl ester, according to literature procedures;[i] (*E*)-5-phenylpent-2-enoic acid was prepared analogously using hydrocinnamaldehyde (distilled before use) in place of isovaleraldehyde.[i] 4-Chlorocinnamoyl chloride was prepared from the reaction of 4-chlorocinnamic acid with thionyl chloride according to a literature procedure.[ii] 3-Hydroxypropiophenone was prepared from ethyl benzoyl acetate according to a 3-step literature procedure.[iii] Pyridine, Et_3N and crotonoyl chloride were distilled from CaH_2. All other 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 visualised 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.[iv] Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a

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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 Bruker DPX360 (360 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 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, d_6-DMSO at 39.5 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 using the electrospray (ES) positive ion mode at the EPSRC National Mass Spectrometry Service Centre, University of Wales Swansea, or on a Kratos MS50TC spectrometer using the fast atom bombardment (FAB) technique in the mass spectrometry laboratory at the School of Chemistry, University of Edinburgh. Stated calculated mass values refer to that of the *ion* (i.e. the actual species being detected), *not* that of the neutral parent compound. Chiral HPLC analysis was performed on an Agilent 1100 instrument. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter.

Preparation of the Cyclisation Substrates

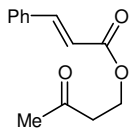
General procedure A

Oxalyl chloride (1.21 equiv) was added dropwise over 2 min to a solution of the appropriate α,β-unsaturated carboxylic acid (1.10 equiv) and DMF (0.25 equiv) in CH_2Cl_2 (0.55 M with respect to carboxylic acid) at 0 °C. The mixture was stirred at 0 °C until no more effervescence was observed (*ca.* 1 h). The resulting solution of acid chloride was then transferred to a solution of the appropriate hydroxyketone (1.0 equivalent), DMAP (0.05 equiv) and pyridine (4.0 equiv) in CH_2Cl_2 (1.0 M with

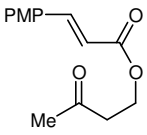
respect to hydroxyketone) over 5 min *via* cannula, and the reaction was stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution and Et_2O. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ solution (x 3), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclisation substrate.

General procedure B

This was identical to general procedure A, except that Et_3N (2.5 equiv) was used in place of pyridine.

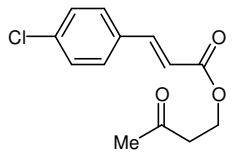


3-Oxobutyl (*E*)-3-phenylpropenoate (245). A solution of cinnamoyl chloride (1.87 g, 11.0 mmol) in CH_2Cl_2 (20 mL) was added over 5 min to a solution of 4-hydroxy-2-butanone (0.91 mL, 10.0 mmol), DMAP (61 mg, 0.50 mmol), and Et_3N (2.1 mL, 15 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The reaction was stirred at room temperature for 1 h before being quenched with saturated aqueous $NaHCO_3$ solution (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic layers were dried and concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/petrol) gave the title compound as a white solid (1.64 g, 75%). m.p. 59-61 °C; IR ($CHCl_3$) 3062, 1705 (C=O), 1632 (C=C), 1577, 1311, 1164, 997, 776, 723, 688 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.63 (1H, d, *J* = 16.0 Hz, =C**H**), 7.49-7.44 (2H, m, Ar**H**), 7.35-7.31 (3H, m, Ar**H**), 6.37 (1H, d, *J* = 16.0 Hz, =C**H**), 4.43 (2H, t, *J* = 6.3 Hz, C**H**$_2$O), 2.80 (2H, t, *J* = 6.3 Hz, C**H**$_2$CH$_2$O), 2.17 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 205.5 (C), 166.5 (C), 144.8 (CH), 134.0 (C), 130.1 (CH), 128.6 (2 x CH), 127.8 (2 x CH), 117.4 (CH), 59.1 (CH_2), 42.1 (CH_2), 30.0 (CH_3); HRMS (FAB) Exact mass calcd for $C_{13}H_{15}O_3$ $[M+H]^+$: 219.1016, found: 219.1017.

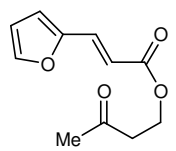


3-Oxobutyl (*E*)-3-(4-methoxyphenyl)propenoate (247a). The title compound was prepared according to general procedure B from 4-

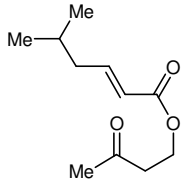
methoxycinnamic acid (1.96 g, 11.0 mmol) and 4-hydroxy-2-butanone (0.91 mL, 10.0 mmol) for a reaction time of 1 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (1.84 g, 74%). m.p. 72-74 °C; IR ($CHCl_3$) 2962, 1713 (C=O), 1634 (C=C), 1604, 1514, 1254, 1160, 1029, 984, 830 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52 (1H, d, *J* = 16.0 Hz, =C**H**), 7.35 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.78 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.17 (1H, d, *J* = 16.0 Hz, =C**H**), 4.35 (2H, t, *J* = 6.3 Hz, C$\mathbf{H}_2$O), 3.70 (3H, s, OC$\mathbf{H}_3$), 2.74 (2H, t, *J* = 6.3 Hz, C$\mathbf{H}_2$$CH_2$O), 2.11 (3H, s, C$\mathbf{H}_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 205.4 (C), 166.6 (C), 161.1 (C), 144.3 (CH), 129.4 (2 x CH), 126.6 (C), 114.7 (CH), 113.9 (2 x CH), 58.8 (CH_2), 54.9 (CH_3), 42.0 (CH_2), 29.8 (CH_3); HRMS (FAB) Exact mass calcd for $C_{14}H_{17}O_4$ $[M+H]^+$: 249.1122, found: 249.1126.



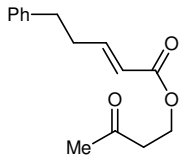
3-Oxobutyl (*E*)-3-(4-chlorophenyl)propenoate (247b). A solution of 4-chlorocinnamoyl chloride (2.21 g, 11.0 mmol) in CH_2Cl_2 (20 mL) was added over 5 min to a solution of 4-hydroxy-2-butanone (0.91 mL, 10.0 mmol), DMAP (61 mg, 0.50 mmol), and Et_3N (2.1 mL, 15 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The reaction was stirred at room temperature for 2 h before being quenched with saturated aqueous $NaHCO_3$ solution (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic layers were dried and concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/petrol) gave the title compound as a white solid (2.02 g, 79%). m.p. 54-56 °C; IR ($CHCl_3$) 2968, 1713 (C=O), 1638, 1592, 1492, 1323, 1310, 1166, 922, 820 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.62 (1H, d, *J* = 16.0 Hz, =C**H**), 7.45 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.36 (2H, d, *J* = 8.5 Hz, Ar**H**), 6.38 (1H, d, *J* = 16.0 Hz, =C**H**), 4.48 (2H, t, *J* = 6.2 Hz, C$\mathbf{H}_2$O), 2.85 (2H, t, *J* = 6.2 Hz, C$\mathbf{H}_2$$CH_2$O), 2.23 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 205.6 (C), 166.5 (C), 143.6 (CH), 136.2 (C), 132.7 (C), 129.2 (2 x CH), 129.1 (2 x CH), 118.2 (CH), 59.4 (CH_2), 42.3 (CH_2), 30.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{14}{}^{35}ClO_3$ $[M+H]^+$: 253.0626, found: 253.0624.



3-Oxobutyl (*E*)-3-furan-2-ylpropenoate (247c). The title compound was prepared according to general procedure B from 3-(2-furyl)acrylic acid (1.52 g, 11.0 mmol) and 4-hydroxy-2-butanone (0.91 mL, 10.0 mmol) for a reaction time of 3 h and purified by column chromatography (20% EtOAc/petrol) to give a yellow gum (1.23 g, 59%). IR ($CHCl_3$) 2963, 1713 (C=O), 1638 (C=C), 1361, 1305, 1263, 1209, 1160, 1018, 930 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.48 (1H, d, *J* = 1.8 Hz, C**H**), 7.42 (1H, d, *J* = 15.7 Hz, =C**H**), 6.61 (1H, d, *J* = 3.4 Hz, C**H**), 6.47 (1H, dd, *J* = 3.4, 1.8 Hz, C**H**), 6.28 (1H, d, *J* = 15.7 Hz, =C**H**), 4.45 (2H, t, *J* = 6.3 Hz, C**H**$_2$O), 2.83 (2H, t, *J* = 6.3 Hz, C**H**$_2$CH$_2$O), 2.21 (3H, s, C**H**)$_3$; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 205.4 (C), 166.4 (C), 150.4 (C), 144.6 (CH), 131.1 (CH), 114.9 (CH), 114.8 (CH), 112.1 (CH), 59.0 (CH_2), 42.0 (CH_2), 29.9 (CH_3); HRMS (FAB) Exact mass calcd for $C_{11}H_{13}O_4$ $[M+H]^+$: 209.0809, found: 209.0812.

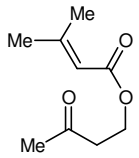


3-Oxobutyl (*E*)-5-methylhex-2-enoate (247d). The title compound was prepared according to general procedure A from (*E*)-5-methylhex-2-enoic acid (2.11 g, 16.5 mmol) and 4-hydroxy-2-butanone (1.36 mL, 15.0 mmol) for a reaction time of 12 h and purified by column chromatography (20% EtOAc/petrol) to give a pale yellow oil (1.63 g, 55%). IR (film) 2959, 1722 (C=O), 1653 (C=C), 1367, 1316, 1267, 1230, 1167, 1127, 1050 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.90 (1H, ddd, *J* = 15.4, 7.5, 7.5 Hz, =C**H**), 5.75 (1H, d, *J* = 15.4 Hz, =C**H**), 4.36 (2H, t, *J* = 6.3 Hz, C**H**$_2$O), 2.77 (2H, t, *J* = 6.3 Hz, C**H**$_2$CH$_2$O), 2.17 (3H, s, C**H**$_3$C=O), 2.07-2.02 (2H, m, C**H**$_2$CH=), 1.78-1.67 (1H, m, $(CH_3)_2$C**H**), 0.88 (6H, d, *J* = 6.6 Hz, (C**H**$_3)_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 205.7 (C), 166.3 (C), 148.9 (CH), 121.7 (CH), 60.0 (CH_2), 42.3 (CH_2), 41.4 (CH_2), 30.2 (CH_3), 27.7 (CH), 22.2 (2 x CH_3); HRMS (FAB) Exact mass calcd for $C_{11}H_{19}O_3$ $[M+H]^+$: 199.1329, found: 199.1332.

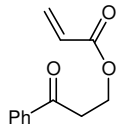


3-Oxobutyl (*E*)-5-phenylpent-2-enoate (247e). The title compound was prepared according to general procedure A from (*E*)-5-

phenylpent-2-enoic acid (775 mg, 4.4 mmol) and 4-hydroxy-2-butanone (363 μL, 4.0 mmol) for a reaction time of 12 h and purified by column chromatography (20% EtOAc/petrol) to give a yellow-orange oil (512 mg, 52%). IR (film) 3027, 2926, 1722 (C=O), 1653 (C=C), 1454, 1360, 1318, 1269, 1164, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.32-7.29 (2H, m, Ar**H**), 7.23-7.17 (3H, m, Ar**H**), 7.00 (1H, ddd, *J* = 15.7, 6.8, 6.8 Hz, =C**H**), 5.83 (1H, dt, *J* = 15.7, 1.6 Hz, =C**H**), 4.40 (2H, t, *J* = 6.3 Hz, C**H**$_2$O), 2.81-2.75 (4H, m, C**H**$_2$CH$_2$O and C**H**$_2$Ph), 2.56-2.49 (2H, m, C**H**$_2$CH=), 2.20 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 205.7 (C), 166.3 (C), 148.7 (CH), 140.7 (C), 128.5 (2 x CH), 128.3 (2 x CH), 126.2 (CH), 121.3 (CH), 59.1 (CH_2), 42.3 (CH_2), 34.2 (CH_2), 33.9 (CH_2), 30.3 (CH_3); HRMS (FAB) Exact mass calcd for $C_{15}H_{19}O_3$ $[M+H]^+$: 247.1329, found: 247.1335.

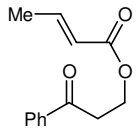


3-Oxobutyl 3-methylbut-2-enoate (247f). The title compound was prepared according to general procedure A from 3,3-dimethylacrylic acid (1.70 g, 16.5 mmol) and 4-hydroxy-2-butanone (1.37 mL, 15.0 mmol) for a reaction time of 12 h and purified by column chromatography (15% EtOAc/petrol) to give a pale yellow oil (2.10 g, 82%). IR (film) 2974, 2916, 1718 (C=O), 1652 (C=C), 1446, 1378, 1230, 1147, 1079, 851 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.54 (1H, br s, =C**H**), 4.54-4.49 (2H, m, C**H**$_2$O), 3.12-3.09 (2H, m, C**H**$_2$CH$_2$O), 2.57 (3H, s, C**H**$_3$C=C), 2.53 (3H, s, C**H**$_3$C=C), 2.29 (3H, s, C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 205.7 (C), 166.1 (C), 157.0 (C), 115.4 (CH), 58.2 (CH_2), 42.2 (CH_2), 30.0 (CH_3), 27.1 (CH_3), 19.9 (CH_3); HRMS (FAB) Exact mass calcd for $C_9H_{15}O_3$ $[M+H]^+$: 171.1016, found: 171.1019.

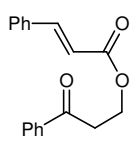


3-Oxo-3-phenylpropyl propenoate (249a). Acryloyl chloride (0.37 mL, 4.4 mmol) was added dropwise over 1 min to a solution of 3-hydroxypropiophenone (601 mg, 4.0 mmol), DMAP (31 mg, 0.25 mmol), and Et_3N (0.84 mL, 6.0 mmol) in CH_2Cl_2 (30 mL) at 0 °C and the reaction was stirred at room temperature for 1.5 h. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution (30 mL) and Et_2O (70 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (3 x 30 mL), dried ($MgSO_4$) and

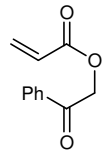
concentrated *in vacuo*. Purification of the residue by column chromatography (15% EtOAc/petrol) gave the title compound as white solid (527 mg, 65%). m.p. 38-40 °C; IR ($CHCl_3$) 2914, 1724 (C=O), 1686 (C=O), 1449, 1408, 1297, 1271, 1192, 984, 810 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.00-7.79 (2H, m, Ar**H**), 7.62-7.57 (1H, m, Ar**H**), 7.52-7.47 (2H, m, Ar**H**), 6.40 (1H, dd, *J* = 17.3, 1.5 Hz, =C**H**), 6.11 (1H, dd, *J* = 17.3, 10.4 Hz, =C**H**), 5.83 (1H, dd, *J* = 10.4, 1.5 Hz, =C**H**), 4.63 (2H, t, *J* = 6.4 Hz, C**H**$_2$O), 3.38 (2H, t, *J* = 6.4 Hz, C**H**$_2$CH$_2$O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 196.7 (C), 165.8 (C), 136.4 (C), 133.2 (CH), 130.8 (CH_2), 128.5 (2 x CH), 128.0 (CH), 127.9 (2 x CH), 59.6 (CH_2), 37.2 (CH_2); HRMS (FAB) Exact mass calcd for $C_{12}H_{13}O_3$ $[M+H]^+$: 205.0860, found: 205.0863.



3-Oxo-3-phenylpropyl (*E*)-but-2-enoate (249b). Crotonoyl chloride (0.53 mL, 5.5 mmol) was added dropwise over 1 min to a solution of 3-hydroxypropiophenone (751 mg, 5.0 mmol), DMAP (30 mg, 0.25 mmol) and pyridine (1.62 mL, 20 mmol) in CH_2Cl_2 (40 mL) at 0 °C and the reaction was stirred at room temperature for 16 h. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution (30 mL) and Et_2O (70 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (3 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (15% EtOAc/petrol) gave the title compound (595 mg, 55%) as a white solid. m.p. 42-44 °C; IR ($CHCl_3$) 2968, 1719 (C=O), 1686 (C=O), 1658 (C=C), 1448, 1265, 1180, 1104, 1033, 970 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.00-7.96 (2H, m, Ar**H**), 7.62-7.56 (1H, m, Ar**H**), 7.51-7.46 (2H, m, Ar**H**), 6.97 (1H, dq, *J* = 15.5, 6.9 Hz, =C**H**), 5.83 (1H, dq, *J* = 15.5, 1.7 Hz, =C**H**), 4.59 (2H, t, *J* = 6.4 Hz, C**H**$_2$O), 3.36 (2H, t, *J* = 6.4 Hz, C**H**$_2$CH$_2$O), 1.87 (3H, dd, *J* = 6.9, 1.7 Hz, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 196.7 (C), 165.9 (C), 144.7 (CH), 136.3 (C), 133.0 (CH), 128.3 (2 x CH), 127.7 (2 x CH), 122.1 (CH), 59.1 (CH_2), 37.1 (CH_2), 17.6 (CH_3); HRMS (FAB) Exact mass calcd for $C_{13}H_{15}O_3$ $[M+H]^+$: 219.1016, found: 219.1022.

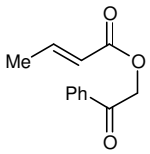


3-Oxo-3-phenylpropyl (*E*)-3-phenylpropenoate (249c). A solution of cinnamoyl chloride (733 mg, 4.4 mmol) in CH_2Cl_2 (35 mL) was added over 5 min to a solution of 3-hydroxypropiophenone (601 mg, 4.0 mmol), DMAP (27 mg, 0.20 mmol), and Et_3N (0.84 mL, 6.0 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The reaction was stirred at room temperature for 1.5 h before being quenched with saturated aqueous $NaHCO_3$ solution (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic layers were dried and concentrated *in vacuo*. Purification of the residue by column chromatography (15% EtOAc/petrol) gave the title compound as a white solid (897 mg, 80%). m.p. 68-70 °C; IR ($CHCl_3$) 2962, 1712 (C=O), 1685 (C=O), 1636 (C=C), 1449, 1331, 1312, 1170, 980, 768 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.02-7.99 (2H, m, Ar**H**), 7.68 (1H, d, *J* = 16.0 Hz, =C**H**), 7.62-7.57 (1H, m, Ar**H**), 7.53-7.47 (4H, m, Ar**H**), 7.40-7.36 (3H, m, Ar**H**), 6.42 (1H, d, *J* = 16.0 Hz, =C**H**), 4.68 (2H, t, *J* = 6.4 Hz, C**H**$_2$O), 3.41 (2H, t, *J* = 6.4 Hz, C**H**$_2$CH$_2$O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.0 (C), 166.8 (C), 145.0 (CH), 136.6 (C), 134.2 (C), 133.3 (CH), 130.3 (CH), 128.8 (2 x CH), 128.6 (2 x CH), 128.0 (4 x CH), 117.7 (CH), 59.8 (CH_2), 37.5 (CH_2); HRMS (FAB) Exact mass calcd for $C_{18}H_{17}O_3$ $[M+H]^+$: 281.1173, found: 281.1178.

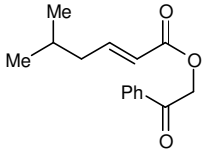


2-Oxo-2-phenylethyl propenoate (251a). Acryloyl chloride (0.47 mL, 5.5 mmol) was added dropwise over 1 min to a solution of 2-hydroxyacetophenone (695 mg, 5.0 mmol), DMAP (30 mg, 0.25 mmol), and Et_3N (1.05 mL, 7.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C and the reaction was stirred at room temperature for 1 h. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution (30 mL) and Et_2O (70 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (3 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petrol) gave the title compound as a yellow gum (670 mg, 70%). IR ($CHCl_3$) 2937, 1733 (C=O), 1703 (C=O), 1634 (C=C), 1598, 1404, 1228, 1179, 965, 755 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.96-7.93 (2H, m, Ar**H**), 7.66-7.61 (1H, m, Ar**H**), 7.53-7.49 (2H, m, Ar**H**), 6.56 (1H, dd, *J* =17.3, 1.4 Hz, =C**H**), 6.30 (1H, dd, *J*

= 17.3, 10.4 Hz, =C**H**), 5.97 (1H, dd, *J* = 10.4, 1.4 Hz, =C**H**), 5.45 (2H, s, C**H**$_2$O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 191.8 (C), 165.3 (C), 134.0 (C), 133.7 (CH), 131.9 (CH_2), 128.7 (2 x CH), 127.6 (2 x CH), 127.3 (CH), 65.9 (CH_2); HRMS (FAB) Exact mass calcd for $C_{11}H_{11}O_3$ $[M+H]^+$: 191.0703, found: 191.0708.

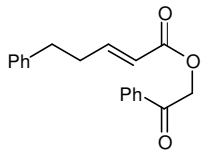


2-Oxo-2-phenylethyl (*E*)-but-2-enoate (251b). Crotonoyl chloride (0.53 mL, 5.5 mmol) was added dropwise over 1 min to a solution of 2-hydroxyacetophenone (695 mg, 5.0 mmol), DMAP (30 mg, 0.25 mmol), and pyridine (1.62 mL, 20 mmol) in CH_2Cl_2 (20 mL) at 0 °C and the reaction was stirred at room temperature for 3 h. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution (30 mL) and Et_2O (70 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (3 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/petrol) gave the title compound (512 mg, 50%) as a yellow gum. IR ($CHCl_3$) 2942, 1723 (C=O), 1707 (C=O), 1659 (C=C), 1450, 1373, 1291, 1180, 1107, 969 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.94-7.91 (2H, m, Ar**H**), 7.62-7.57 (1H, m, Ar**H**), 7.50-7.45 (2H, m, Ar**H**), 7.11 (1H, dq, *J* = 15.6, 6.9 Hz, =C**H**), 6.00 (1H, dq, *J* = 15.6, 1.7 Hz, = C**H**), 5.39 (2H, s, C**H**$_2$O), 1.92 (3H, dd, *J* = 6.9, 1.7 Hz, C**H**$_3$C=); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 192.3 (C), 165.6 (C), 146.3 (CH), 134.2 (C), 133.7 (CH), 128.7 (2 x CH), 127.7 (2 x CH), 121.6 (CH), 65.7 (CH_2), 18.1 (CH_3); HRMS (FAB) Exact mass calcd for $C_{12}H_{13}O_3$ $[M+H]^+$: 205.0860, found: 205.0865.



2-Oxo-2-phenylethyl (*E*)-5-methylhex-2-enoate (251c). The title compound was prepared according to general procedure A from (*E*)-5-methylhex-2-enoic acid (705 mg, 5.5 mmol) and 2-hydroxyacetophenone (695 mg, 5.0 mmol) for a reaction time of 3 h and purified by column chromatography (15% EtOAc/petrol) to give a colorless oil (646 mg, 52%). IR (film) 2957, 1730 (C=O), 1705 (C=O), 1654 (C=C), 1370, 1226, 1173, 1128, 981, 689 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.95-7.92 (2H, m, Ar**H**), 7.63-7.58 (1H, m, Ar**H**), 7.51-7.46 (2H, m, Ar**H**), 7.08 (1H, ddd, *J* = 15.5, 7.5, 7.5 Hz, = C**H**), 5.98

(1H, dt, J = 15.5, 1.5 Hz, =C**H**), 5.40 (2H, s, C**H**$_2$O), 2.16-2.11 (2H, m, C**H**$_2$C=), 1.84-1.73 (1H, m, (CH$_3$)$_2$C**H**), 0.94 (6H, d, J = 6.7 Hz, (C**H**$_3$)$_2$CH); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 192.3 (C), 165.7 (C), 150.1 (CH), 134.2 (C), 133.7 (CH), 128.8 (2 x CH), 127.7 (2 x CH), 121.1 (CH), 65.8 (CH$_2$), 41.5 (CH$_2$), 27.7 (CH), 22.3 (2 x CH$_3$); HRMS (FAB) Exact mass calcd for $C_{15}H_{19}O_3$ $[M+H]^+$: 247.1329, found: 247.1333.



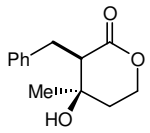
2-Oxo-2-phenylethyl (*E*)-5-phenylpent-2-enoate (251d). The title compound was prepared according to general procedure A from (*E*)-5-phenylpent-2-enoic acid (970 mg, 5.5 mmol) and 2-hydroxyacetophenone (695 mg, 5.0 mmol) for a reaction time of 3 h and purified by column chromatography (15% EtOAc/petrol) to yellow gum (711 mg, 48%). IR (CHCl$_3$) 3027, 2932, 1729 (C=O), 1703 (C=O), 1653 (C=C), 1597, 1450, 1227, 1171, 689 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.96-7.93 (2H, m, Ar**H**), 7.65-7.60 (1H, m, Ar**H**), 7.53-7.48 (2H, m, Ar**H**), 7.34-7.29 (2H, m, Ar**H**), 7.25-7.15 (4H, m, Ar**H** and =C**H**), 6.04 (1H, dt, J = 6.0, 1.6 Hz, =C**H**), 5.42 (2H, s, C**H**$_2$O), 2.82 (2H, t, J = 7.8 Hz, PhC**H**$_2$), 2.62-2.56 (2H, m, C**H**$_2$CH=); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 192.2 (C), 165.6 (C), 149.8 (CH), 134.2 (C), 133.7 (CH), 128.7 (2 x CH), 128.4 (2 x CH), 128.2 (2 x CH), 127.7 (2 x CH), 126.1 (CH), 120.6 (CH), 65.8 (CH$_2$), 34.0 (CH$_2$) 33.9 (CH$_2$); HRMS (FAB) Exact mass calcd for $C_{19}H_{19}O_3$ $[M+H]^+$: 295.1329, found: 295.1334.

Copper-Catalysed Reductive Aldol Cyclisations

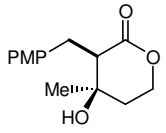
General Procedure C: Racemic Cyclisations

A solution of Cu(OAc)$_2$·H$_2$O (10.0 mg, 0.05 mmol) and DPPF (28.6 mg, 0.05 mmol) in THF (2 mL) was stirred for 15 min before TMDS (182 μL, 1.00 mmol) was added. The initially green solution was stirred until it became yellow (*ca.* 5 min), after which a solution of the substrate (1.00 mmol) in THF (2 mL + 1 mL rinse) was then added rapidly *via* cannula. The reaction was stirred at room temperature until

complete consumption of the starting material as observed by TLC analysis. The reaction was quenched by the addition of 1 M HCl (1 mL), and the mixture was stirred for 1 h before being diluted with saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclised product.

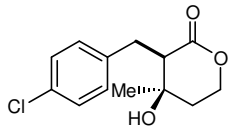


(±)-(3*R*,4*R*)-3-Benzyl-4-hydroxy-4-methyltetrahydropyran-2-one (246). The title compound was prepared according to general procedure C from **245** (218 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (40% EtOAc/petrol) to give a yellow solid (158 mg, 72%). m.p. 79-80 °C; IR ($CHCl_3$) 3433 (OH), 2972, 1728 (C=O), 1496, 1455, 1394, 1258, 1140, 748, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.38-7.30 (4H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 4.52 (1H, ddd, *J* = 12.0, 7.4, 5.0 Hz, C**H**$_2$O), 4.26 (1H, ddd, *J* = 12.0, 6.6, 5.0 Hz, C**H**$_2$O), 3.34 (1H, dd, *J* = 14.6, 7.0 Hz, PhC**H**$_2$), 3.09 (1H, dd, *J* = 14.6, 4.2 Hz, PhC**H**$_2$), 2.70 (1H, dd, *J* = 7.0, 4.2 Hz, C**H**C=O), 2.40 (1H, br s, O**H**), 2.13-1.98 (2H, m, C**H**$_2$CH$_2$O), 1.42 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.4 (C), 140.9 (C), 129.0 (2 x CH), 128.4 (2 x CH), 126.1 (CH), 71.1 (C), 64.7 (CH_2), 53.7 (CH), 38.3 (CH_2), 30.9 (CH_2), 28.8 (CH_3); HRMS (FAB) Exact mass calcd for $C_{13}H_{17}O_3$ $[M+H]^+$: 221.1173, found: 221.1177.

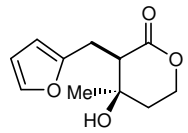


(±)-(3*R*,4*R*)-4-Hydroxy-3-(4-methoxybenzyl)-4-methyltetrahydropyran-2-one (248a). The title compound was prepared according to general procedure C from **247a** (248 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (40% EtOAc/petrol) to give a yellow solid (153 mg, 61%). m.p. 82-84 °C; IR (film) 3451 (OH), 2969, 1727 (C=O), 1611, 1513, 1248, 1179, 1109, 1033, 825 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.5 Hz, Ar**H**), 6.83 (2H, d, *J* = 8.5 Hz, Ar**H**), 4.51-4.44 (1H, m, C**H**$_2$O), 4.22 (1H, ddd, *J* = 11.3, 5.7, 5.7 Hz, C**H**$_2$O), 3.78 (3H, s, OC**H**$_3$), 3.27 (1H, dd, *J* = 14.6, 6.9 Hz, ArC**H**$_2$), 3.02 (1H, dd, *J* = 14.6, 3.6 Hz, ArC**H**$_2$), 2.62 (1H, app t, app *J* = 5.2 Hz, C**H**C=O), 2.25 (1H, br s, O**H**), 2.07-1.93

(2H, m, C**H**$_2$CH$_2$O), 1.39 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.2 (C), 158.0 (C), 132.7 (C), 130.0 (2 x CH), 113.9 (2 x CH), 71.1 (C), 64.7 (CH_2), 55.2 (CH_3), 53.8 (CH), 38.3 (CH_2), 30.1 (CH_2), 28.9 (CH_3); HRMS (FAB) Exact mass calcd for $C_{14}H_{19}O_4$ $[M+H]^+$: 251.1278, found: 251.1283.

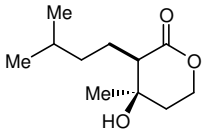


(±)-(3*R*,4*R*)-3-(4-Chlorobenzyl)-4-hydroxy-4-methyltetrahydropyran-2-one (248b). The title compound was prepared according to general procedure C from **247b** (253 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (40% EtOAc/petrol) to give a white solid (166 mg, 65%). m.p. 115-117 °C; IR ($CHCl_3$) 3433 (OH), 2972, 1728 (C=O), 1493, 1409, 1258, 1140, 1094, 1016, 818 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.26 (4H, s, Ar**H**), 4.49 (1H, ddd, *J* = 11.5, 7.6, 4.9 Hz, C**H**$_2$O), 4.25 (1H, ddd, *J* = 11.5, 6.7, 4.9 Hz, C**H**$_2$O), 3.26 (1H, dd, *J* = 14.6, 7.2 Hz, ArC**H**$_2$), 3.01 (1H, dd, *J* = 14.6, 4.1 Hz, ArC**H**$_2$), 2.38 (1H, dd, *J* = 7.2, 4.1 Hz, C**H**C=O), 2.08 (1H, ddd, *J* = 14.5, 7.6, 4.9 Hz, C**H**$_2$CH$_2$O), 1.98 (1H, ddd, *J* = 14.5, 6.7, 4.9 Hz, C**H**$_2$CH$_2$O), 1.84 (1H, br s, O**H**), 1.41 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.0 (C), 139.4 (C), 132.0 (C), 130.4 (2 x CH), 128.6 (2 x CH), 71.2 (C), 64.7 (CH_2), 53.7 (CH), 38.4 (CH_2), 30.4 (CH_2), 28.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{16}{}^{35}ClO_3$ $[M+H]^+$: 255.0782, found: 255.0782.

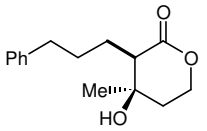


(±)-(3*R*,4*R*)-3-Furan-2-ylmethyl-4-hydroxy-4-methyltetrahydropyran-2-one (248c). The title compound was prepared according to general procedure C from **247c** (208 mg, 1.00 mmol) for a reaction time of 30 h and purified by column chromatography (30% EtOAc/petrol) to give a yellow gum (132 mg, 63%). IR ($CHCl_3$) 3440 (OH), 2973, 2930, 1730 (C=O), 1507, 1404, 1261, 1146, 1011, 736 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.29 (1H, br s, C**H**), 6.29 (1H, br s, C**H**), 6.13 (1H, br s, C**H**), 4.52-4.42 (1H, m, C**H**$_2$O), 4.24 (1H, ddd, *J* = 10.9, 5.5, 5.5 Hz, C**H**$_2$O), 3.30 (1H, dd, *J* =15.8, 5.8 Hz, C**H**$_2$CHC=O), 3.12 (1H, dd, *J* = 15.8, 5.8 Hz, C**H**$_2$CH=O), 2.77 (1H, t, *J* = 5.8 Hz, C**H**C=O), 2.58 (1H, br s, O**H**), 2.07-1.99 (1H, m, C**H**$_2$CH$_2$O), 1.97-1.90 (1H, m, C**H**$_2$CH$_2$O), 1.30 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.6 (C), 153.6

(C), 140.8 (CH), 110.7 (CH), 106.8 (CH), 70.3 (C), 64.8 (CH_2), 50.5 (CH), 38.1 (CH_2), 28.2 (CH_3), 23.7 (CH_2); HRMS (FAB) Exact mass calcd for $C_{11}H_{15}O_4$ $[M+H]^+$: 211.0965, found: 211.0971.

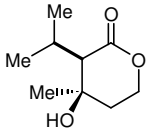


(±)-(3*R*,4*R*)-4-Hydroxy-4-methyl-3-(3-methylbutyl)tetrahydropyran-2-one (248d). The title compound was prepared according to general procedure C from **247d** (198 mg, 1.00 mmol) for a reaction time of 18 h and purified by column chromatography (30% EtOAc/petrol) to give a colorless oil (146 mg, 73%). IR (film) 3444 (OH), 2956, 2870, 1727 (C=O), 1197, 1113, 1074, 932, 749, 560 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.42 (1H, ddd, *J* = 11.7, 5.8, 5.8 Hz, C**H**$_2$O), 4.18 (1H, ddd, *J* = 11.7, 5.8, 5.8 Hz, C**H**$_2$O), 2.68 (1H, br s, O**H**), 2.18 (1H, dd, *J* = 8.4, 2.8 Hz, C**H**C=O), 1.97 (2H, app t, app *J* = 6.0 Hz, C**H**$_2$CH$_2$O), 1.82-1.71 (1H, m, C**H**$_2$CHC=O), 1.67-1.58 (1H, m, C**H**$_2$CHC=O), 1.56-1.46 (2H, m, $(CH_3)_2$CHC**H**$_2$), 1.36 (3H, s, C**H**$_3$COH), 1.21-1.13 (1H, m, $(CH_3)_2$C**H**), 0.87 (6H, d, *J* =6.3 Hz, (C**H**$_3$)$_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.9 (C), 70.7 (C), 64.6 (CH_2), 51.8 (CH), 38.5 (CH_2), 37.6 (CH_2), 28.3 (CH_3), 28.1 (CH), 22.8 (CH_2), 22.5 (CH_3), 22.2 (CH_3); HRMS (FAB) Exact mass calcd for $C_{11}H_{21}O_3$ $[M+H]^+$: 201.1486, found: 201.1491.

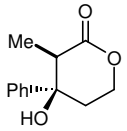


(±)-(3*R*,4*R*)-4-Hydroxy-4-methyl-3-(3-phenylpropyl)tetrahydropyran-2-one (248e). The title compound was prepared according to general procedure C from **247e** (246 mg, 1.00 mmol) for a reaction time of 18 h and purified by column chromatography (30% EtOAc/petrol) to give a yellow solid (151 mg, 61%). Slow evaporation of a $CDCl_3$ solution was found to give colorless crystals suitable for X-ray diffraction. m.p. 98-100 °C; IR ($CHCl_3$) 3443 (OH), 2929, 1728 (C=O), 1454, 1403, 1259, 1204, 1138, 749, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.30-7.26 (2H, m, Ar**H**), 7.22-7.16 (3H, m, Ar**H**), 4.43 (1H, ddd, *J* = 11.6, 5.8, 5.8 Hz, C**H**$_2$O), 4.18 (1H, ddd, *J* = 11.6. 5.8, 5.8 Hz, C**H**$_2$O), 2.67 (3H, br t, *J* = 7.5 Hz, PhC**H**$_2$ and O**H**), 2.25 (1H, dd, *J* = 8.3, 2.4 Hz, C**H**C=O), 2.11-1.85 (2H, m, C**H**$_2$CH=O), 1.96 (2H, app t, app *J* = 6.0 Hz, C**H**$_2$CH$_2$O), 1.74-1.66 (2H, m, PhCH$_2$C**H**$_2$), 1.34 (3H, s, C**H**$_3$); ^{13}C NMR (62.9

MHz, $CDCl_3$) δ 173.7 (C), 141.9 (C), 128.2 (2 x CH), 128.1 (2 x CH), 125.5 (CH), 70.6 (C), 64.6 (CH_2), 51.3 (CH_2), 51.3 (CH), 37.5 (CH_2), 35.8 (CH_2), 30.7 (CH_2), 28.2 (CH_3), 24.6 (CH_2); HRMS (FAB) Exact mass calcd for $C_{15}H_{21}O_3$ $[M+H]^+$: 249.1486, found: 249.1489.

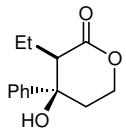


(±)-(3*R*,4*R*)-4-Hydroxy-4-methyl-3-*iso*-propyltetrahydropyran-2-one (248f). The title compound was prepared according to general procedure C from **247f** (170 mg, 1.00 mmol) for a reaction time of 30 h and purified by column chromatography (30% EtOAc/petrol) to give a white solid (106 mg, 62%). Slow evaporation of a $CDCl_3$ solution was found to give colorless crystals suitable for X-ray diffraction. m.p. 76-78 °C; IR ($CHCl_3$) 3440 (OH), 2972, 1712 (C=O), 1471, 1404, 1274, 1215, 1167, 1129, 1071 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.56 (1H, ddd, *J* = 11.3, 7.8, 6.1 Hz, C**H**$_2$O), 4.23 (1H, ddd, *J* = 11.3, 5.1, 5.1 Hz, C**H**$_2$O), 2.32 (1H, d, *J* = 1.9 Hz, C**H**CH=O), 2.32-2.23 (1H, m, $(CH_3)_2$C**H**), 1.97 (1H, br s, O**H**), 1.92-1.85 (2H, m, C**H**$_2$$CH_2$O), 1.40 (3H, s, C**H**$_3$COH), 1.24 (3H, d, *J* = 7.0 Hz, $(CH_3)_2$CH), 1.08 (3H, d, *J* = 6.8 Hz, $(CH_3)_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.6 (C), 70.7 (C), 64.7 (CH_2), 56.8 (CH), 37.0 (CH_2), 29.4 (CH_3), 26.4 (CH), 24.5 (CH_3), 19.3 (CH_3); HRMS (FAB) Exact mass calcd for $C_9H_{17}O_3$ $[M+H]^+$: 173.1172, found: 173.1178.

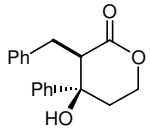


(±)-(3*R*,4*R*)-4-Hydroxy-3-methyl-3-phenyltetrahydropyran-2-one (250a). The title compound was prepared according to general procedure C from **249a** (204 mg, 1.00 mmol) for a reaction time of 20 h and purified by column chromatography (30% EtOAc/petrol) to give a white solid (146 mg, 71%). m.p. 109-110 °C; IR ($CHCl_3$) 3439 (OH), 2988, 1712 (C=O), 1409, 1307, 1263, 1207, 1049, 980, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.43-7.39 (4H, m, Ar**H**), 7.36-7.30 (1H, m, Ar**H**), 4.71 (1H, ddd, *J* = 11.3, 10.4, 4.4 Hz, C**H**$_2$O), 4.48-4.42 (1H, m, C**H**$_2$O), 3.03 (1H, q, *J* = 7.1 Hz, C**H**C=O), 2.48 (1H, ddd, *J* = 15.3, 10.4, 5.7 Hz, C**H**$_2$$CH_2$O), 2.13-2.06 (2H, m, C**H**$_2$$CH_2$O and O**H**), 1.10 (3H, d, *J* = 7.1 Hz, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.9 (C), 144.7 (C), 128.5 (2 x CH),

127.3 (CH), 124.3 (2 x CH), 74.2 (C), 65.4 (CH_2), 46.0 (CH), 38.0 (CH_2), 9.3 (CH_3); HRMS (FAB) Exact mass calcd for $C_{12}H_{15}O_3$ $[M+H]^+$: 207.1016, found: 207.1021.

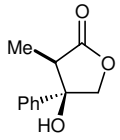


(±)-(3*R*,4*R*)-3-Ethyl-4-hydroxy-3-phenyltetrahydropyran-2-one (250b). The title compound was prepared according to general procedure C from **249b** (218 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol) to give a white solid (109 mg, 50%). m.p. 143-144 °C; IR ($CHCl_3$) 3349 (OH), 2973, 1705 (C=O), 1446, 1208, 1147, 1126, 1098, 1063, 757 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.45-7.48 (4H, m, Ar**H**), 7.36-7.29 (1H, m, Ar**H**), 4.62 (1H, ddd, *J* = 11.5, 8.4, 4.9 Hz, C**H**$_2$O), 4.41 (1H, app dt, *J* = 11.5, 5.6 Hz, C**H**$_2$O), 2.77 (1H, dd, *J* = 8.6, 2.7 Hz, C**H**C=O), 2.53 (1H, br s, O**H**), 2.41 (1H, ddd, *J* = 14.4, 8.4, 5.4 Hz, C**H**$_2$CH$_2$O), 2.12 (1H, app dt, *J* = 14.4, 5.4 Hz, C**H**$_2$CH$_2$O), 1.84-1.72 (1H, m, CH$_3$C**H**$_2$), 1.36-1.25 (1H, m, CH$_3$C**H**$_2$), 0.94 (3H, t, *J* = 7.4 Hz, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.3 (C), 145.2 (C), 128.7 (2 x CH), 127.4 (CH), 124.3 (2 x CH), 75.5 (C), 65.1 (CH_2), 52.7 (CH), 39.2 (CH_2), 18.5 (CH_2), 13.9 (CH_3); HRMS (FAB) Exact mass calcd for $C_{13}H_{17}O_3$ $[M+H]^+$: 221.1173, found: 221.1179.

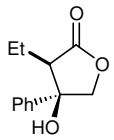


(±)-(3*R*,4*R*)-3-Benzyl-4-hydroxy-3-phenyltetrahydropyran-2-one (250c). The title compound was prepared according to general procedure C from **249c** (280 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol) to give a 10:1 inseparable diastereomeric mixture of products as a white solid (134 mg, 47%). (NMR data reported for major isomer): m.p. 180-182 °C; IR ($CHCl_3$) 3478 (OH), 2992, 1713 (C=O), 1447, 1377, 1317, 1262, 1200, 1050, 755 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.49-7.31 (5H, m, Ar**H**), 7.23-7.12 (3H, m, Ar**H**), 7.02-7.00 (2H, m, Ar**H**), 4.64 (1H, ddd, *J* = 11.5, 8.5, 4.9 Hz, C**H**$_2$O), 4.43 (1H, app dt, *J* = 11.5, 5.5 Hz, C**H**$_2$O), 3.24 (1H, dd, *J* = 7.7, 2.5 Hz, C**H**C=O), 3.09 (1H, dd, *J* = 14.0, 7.7 Hz, PhC**H**$_2$), 2.78 (1H, dd, *J* = 14.0, 2.5 Hz, PhC**H**$_2$), 2.47 (1H, ddd, *J* = 14.3, 8.5, 5.5 Hz, C**H**$_2$CH$_2$O), 2.14 (1H, app dt, *J* = 14.8, 5.2 Hz, C**H**$_2$CH$_2$O), 2.00 (1H, br s, O**H**); ^{13}C NMR (62.9 MHz, d_6-DMSO) δ 173.1 (C), 146.8 (C), 141.5 (C), 128.5 (2 x CH),

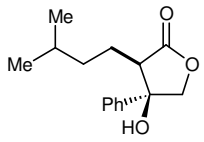
127.8 (2 x CH), 126.8 (CH), 125.4 (CH), 125.2 (2 x CH), 75.0 (C), 64.8 (CH_2), 53.0 (CH), 38.8 (CH_2), 30.7 (CH_2); HRMS (FAB) Exact mass calcd for $C_{18}H_{19}O_3$ $[M+H]^+$: 283.1329, found: 283.1335.



(±)-(3*R*,4*R*)-4-Hydroxy-3-methyl-4-phenyltetrahydrofuran-2-one (252a). The title compound was prepared according to general procedure C from **251a** (190 mg, 1.00 mmol) for a reaction time of 13 h and purified by column chromatography (30% EtOAc/petrol) to give a white solid (132 mg, 69%). m.p. 67-69 °C; IR (film) 3458 (OH), 2983, 1767 (C=O), 1449, 1385, 1188, 1112, 1021, 957, 763 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.51-7.36 (5H, m, Ar**H**), 4.42 (1H, d, *J* = 10.0 Hz, C**H**$_2$O), 4.36 (1H, d, *J* = 10.0 Hz, C**H**$_2$O), 3.06 (1H, q, *J* = 7.1 Hz, C**H**C=O), 2.51 (1H, br s, O**H**), 1.23 (3H, d, *J* = 7.1 Hz, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 177.5 (C), 139.2 (C), 129.0 (2 x CH), 128.5 (CH), 125.1 (2 x CH), 79.9 (C), 78.0 (CH_2), 45.3 (CH), 6.9 (CH_3); HRMS (FAB) Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$: 193.0860, found: 193.0864.

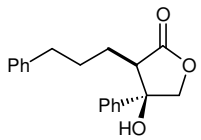


(±)-(3*R*,4*R*)-3-Ethyl-4-hydroxy-4-phenyltetrahydrofuran-2-one (252b). The title compound was prepared according to general procedure C from **251b** (204 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (20% EtOAc/petrol) to give a yellow gum (148 mg, 72%). IR ($CHCl_3$) 3465 (OH), 2970 , 1764 (C=O), 1380, 1279, 1182, 1120, 1024, 763, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.54-7.51 (2H, m, Ar**H**), 7.45-7.32 (3H, m, Ar**H**), 4.33 (2H, s, C**H**$_2$O), 2.89 (1H, t, *J* = 6.9 Hz, C**H**C=O), 2.69 (1H, br s, O**H**), 1.94-1.82 (1H, m, CH_3C**H**$_2$), 1.70-1.54 (1H, m, CH_3C**H**$_2$), 0.92 (3H, t, *J* = 7.5 Hz, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 177.3 (C), 139.8 (C), 128.8 (2 x CH), 128.3 (CH), 125.0 (2 x CH), 80.1 (C), 78.5 (CH_2), 51.9 (CH), 17.1 (CH_2), 12.3 (CH_3); HRMS (FAB) Exact mass calcd for $C_{12}H_{15}O_3$ $[M+H]^+$: 207.1016, found: 207.1023.



(±)-(3*R*,4*R*)-4-Hydroxy-3-(3-methylbutyl)-4-phenyltetrahydrofuran-2-one (252c). The title compound was

prepared according to general procedure C from **251c** (246 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (20% EtOAc/petrol) to give a yellow solid (161 mg, 65%). m.p. 67-69 °C; IR ($CHCl_3$) 3458 (OH), 2956, 1766 (C=O), 1448, 1366, 1174, 1125, 1025, 761, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.53-7.50 (2H, m, Ar**H**), 7.46-7.42 (2H, m, Ar**H**), 7.39-7.34 (1H, m, Ar**H**), 4.33 (2H, s, C**H**$_2$O), 2.92 (1H, t, *J* = 6.8 Hz, C**H**C=O), 2.53 (1H, br s, O**H**), 1.89-1.79 (1H, m, C**H**$_2$CH=O), 1.64-1.52 (1H, m, C**H**$_2$CH=O) 1.49-1.29 (2H, m, $(CH_3)_2$CHC**H**$_2$), 1.10-0.99 (1H, m, $(CH_3)_2$C**H**), 0.81 (3H, d, *J* = 6.5 Hz, C**H**$_3$), 0.76 (3H, d, *J* = 6.5 Hz, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 177.3 (C), 139.7 (C), 128.8 (2 x CH), 128.3 (CH), 125.0 (2 x CH), 80.2 (C), 78.4 (CH_2), 50.4 (CH), 36.3 (CH_2), 27.8 (CH), 22.2 (2 x CH_3), 21.5 (CH_2); HRMS (FAB) Exact mass calcd for $C_{15}H_{21}O_3$ $[M+H]^+$: 249.1486, found: 249.1490.

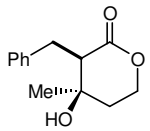


(±)-(3*R*,4*R*)-4-Hydroxy-4-phenyl-3-(3-phenylpropyl)tetrahydrofuran-2-one (252d). The title compound was prepared according to general procedure C from **251d** (294 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (20% EtOAc/petrol) to give a yellow solid (178 mg, 60%). m.p. 103-105 °C; IR ($CHCl_3$) 3447 (OH), 2930, 1770 (C=O), 1496, 1449, 1147, 1027, 966, 761, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52-7.38 (5H, m, Ar**H**), 7.25-7.13 (3H, m, Ar**H**), 7.02-7.00 (2H, m, Ar**H**), 4.35 (1H, d, *J* =10.2 Hz, C**H**$_2$O), 4.32 (1H, d, *J* = 10.2 Hz, C**H**$_2$O), 2.97 (1H, t, *J* = 6.7 Hz, C**H**C=O), 2.63 (1H, br s, O**H**), 2.52 (2H, t, *J* = 7.5 Hz, PhC**H**$_2$), 1.94-1.52 (4H, m, PhCH$_2$C**H**$_2$C**H**$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 177.1 (C), 141.6 (C), 139.6 (C), 128.9 (2 x CH), 128.3 (5 x CH), 125.8 (CH), 125.0 (2 x CH), 80.1 (C), 78.5 (CH_2), 50.1 (CH), 35.5 (CH_2), 28.7 (CH_2), 23.2 (CH_2); HRMS (FAB) Exact mass calcd for $C_{19}H_{21}O_3$ $[M+H]^+$: 297.1486, found: 297.1490.

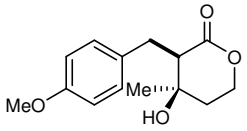
General Procedure D: Enantioselective Cyclisations

A solution of $Cu(OAc)_2 \cdot H_2O$ (2.0 mg, 0.01 mmol) and the chiral ligand (0.01 mmol) in THF (1 mL) was stirred for 15 min before TMDS (35 μL, 0.20 mmol) was added.

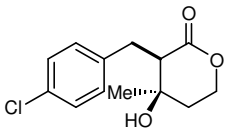
The solution was stirred for 5 min, after which a solution of the substrate (0.20 mmol) in THF (0.5 + 0.5 mL rinse) was then added rapidly *via* cannula. The reaction was stirred at room temperature until complete consumption of the starting material as observed by TLC analysis. The reaction was quenched by the addition of 1 M HCl (0.5 mL), and the mixture was stirred for 1 h before being diluted with saturated aqueous NH_4Cl solution (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclised product.



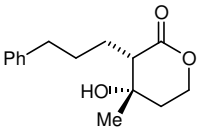
(3*R*,4*R*)-3-Benzyl-4-hydroxy-4-methyltetrahydropyran-2-one (246) (Table 2.6, Entry 4). The title compound was prepared according to general procedure D using **245** (44 mg, 0.20 mmol) and (*R*)-3,5-di-*i*Pr-MeOBIPHEP (**255**) (9.2 mg, 0.01 mmol) for a reaction time of 24 h to give the enantioenriched product **246** (28 mg, 64% yield). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (85:15 hexanes:isopropanol, 0.8 mL/min, 210 nm, 25 °C); t_r (minor) = 13.5 min, t_r (major) = 18.6 min; 77% ee; $[\alpha]_D^{22}$ –35.1 (c. 0.47, $CHCl_3$).



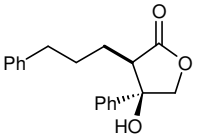
(3*R*,4*R*)-4-Hydroxy-3-(4-methoxybenzyl)-4-methyltetrahydropyran-2-one (248a) (Table 2.6, Entry 7). The title compound was prepared according to general procedure D using **247a** (50 mg, 0.20 mmol) and (*R*)-3,5-di-*i*Pr-MeOBIPHEP (**255**) (9.2 mg, 0.01 mmol) for a reaction time of 24 h to give the enantioenriched product **248a** (Enantiomeric excess was determined from the crude mixture of the product). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (85:15 hexanes:isopropanol, 0.8 mL/min, 210 nm, 25 °C); t_r (minor) = 12.8 min, t_r (major) = 16.4 min; 77% ee; $[\alpha]_D^{22}$ –35.1 (c. 0.47, $CHCl_3$).



(3*R*,4*R*)-3-(4-Chlorobenzyl)-4-hydroxy-4-methyltetrahydropyran-2-one (248b) (Table 2.6 , entry 13). The title compound was prepared according to general procedure D using **247b** (51 mg, 0.20 mmol) and (*R*)-3,5-xyl-MeO-BIPHEP (**254**) (6.9 mg, 0.01 mmol) for a reaction time of 24 h to give the enantioenriched product **248b** (36 mg, 71% yield). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (85:15 hexanes:isopropanol, 0.8 mL/min, 225 nm, 25 °C); t_r (minor) = 14.2 min, t_r (major) = 15.6 min; 83% ee; $[\alpha]_D^{21}$ –42.9 (c. 0.90, $CHCl_3$).



(3*S*,4*S*)-4-Hydroxy-4-methyl-3-(3-phenylpropyl)tetrahydropyran-2-one (248e) (Table 2.6, entry 18). The title compound was prepared according to general procedure D using **247e** (49 mg, 0.20 mmol) and (*S*)-SEGPHOS (**256**) (6.1 mg, 0.01 mmol) for a reaction time of 16 h to give the enantioenriched product **248e** (32 mg, 68% yield). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (85:15 hexanes:isopropanol, 0.8 mL/min, 210 nm, 25 °C); t_r (minor) = 11.9 min, t_r (major) = 13.7 min; 62% ee; $[\alpha]_D^{21}$ +2.2 (c. 0.90, $CHCl_3$).

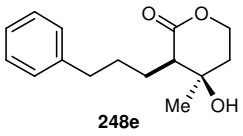


(3*R*,4*R*)-4-Hydroxy-4-phenyl-3-(3-phenylpropyl)tetrahydrofuran-2-one (252d) (Table 2.6, entry 19). The title compound was prepared according to general procedure D from **251d** (59 mg, 0.20 mmol) and (*R*)-3,5-xyl-MeO-BIPHEP (**7**) (6.9 mg, 0.01 mmol) for a reaction time of 24 h give the enantioenriched product **252d** (30 mg, 51%). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 hexanes:isopropanol, 0.8 mL/min, 210 nm, 25 °C); t_r (major) = 30.4 min, t_r (minor) = 32.7 min; 49% ee; $[\alpha]_D^{24}$ –11.1 (c. 0.90, $CHCl_3$).

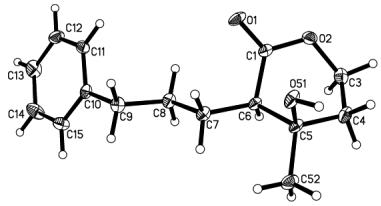
Stereochemical Determinations

Relative Stereochemistries of δ-Valerolactones

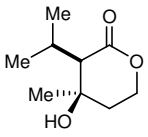
- The relative stereochemistry of the δ-valerolactone **248e** was determined by X-ray crystallography. Crystal structure data deposited at the Cambridge Crystallographic Data Center; Deposition Number: CCDC 270977.



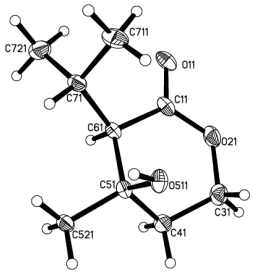
248e



- The relative stereochemistry of the δ-valerolactone **248f** was determined by X-ray crystallography. Crystal structure data deposited at the Cambridge Crystallographic Data Center; Deposition Number: CCDC 270978.

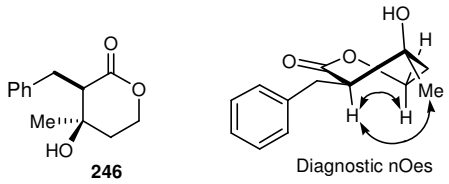


248f



- The crystal structures of **248e** and **248f** showed the δ-valerolactone rings to possess twist-boat and half-chair conformations respectively in the solid state. A NOESY experiment on the lactone **246** showed a diagnostic nOe between the methine proton and one of the protons of the methylene group adjacent to the ring oxygen, indicating the methine proton to be pseudoaxial (1,3-dipseudoaxial nOe). A further nOe between the methine proton and the protons of the methyl

group indicated the methyl group to be pseudoequatorial, thus confirming the relative stereochemistry to be as shown.



Note: Although we have depticed the lactone **246** in a twist-boat conformation, the alternative half-chair conformation does not change the stereochemical analysis.

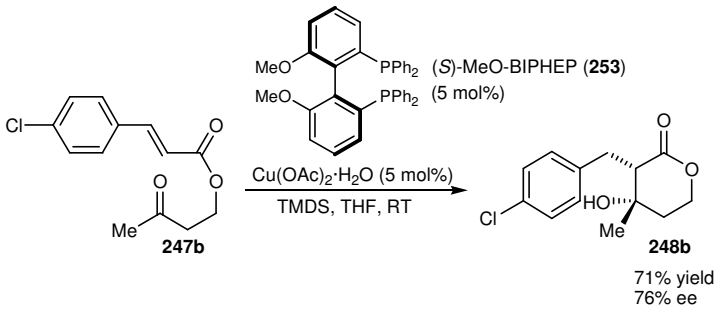
Relative Stereochemistries of γ-Butyrolactones

- The relative stereochemistries of the γ-butyrolactones **252a** and **252c** were assigned by NOESY experiments, which displayed the following enhancements:

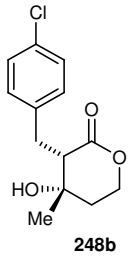
- The relative (and absolute) stereochemistry of the δ-valerolactone **248b** was determined by X-ray crystallography:

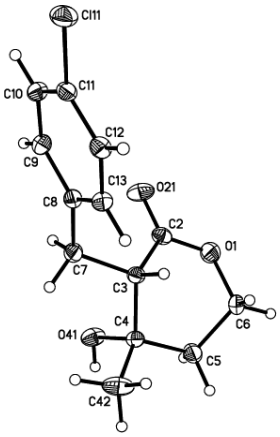
Absolute and Relative Stereochemistry of 248b

The absolute sense of stereochemical induction in the asymmetric cyclisations of substrate **247b** (Table 2.6) was determined as follows:



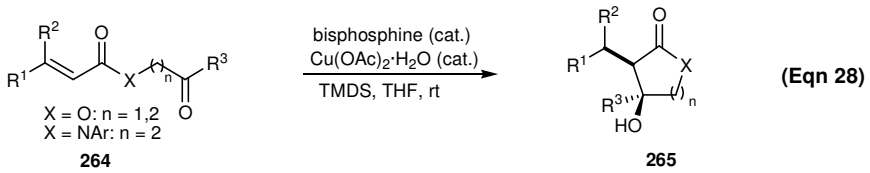
From the above reaction (Table 2, entry 7), a small quantity of the lactone **248b** (7.3 mg, 76% ee) was recrystallised from Et_2O/petrol to give colorless crystals (2.2 mg). These crystals were dissolved in CH_2Cl_2, and an aliquot of the resulting solution was analysed by HPLC using a Chiralpak AD-H column (85:15 hexanes:isopropanol, 0.8 mL/min, 225 nm, 25 °C); t_r (major) = 13.9 min, t_r (minor) = 15.5 min, which showed an increase of enantiomeric purity to 97% ee. After concentration of the solution *in vacuo*, the remaining solid was dissolved in the minimum quantity of boiling Et_2O (*ca.* 0.5 mL), and petrol (*ca.* 1.5 mL) was very gently layered on top. The next day, crystals suitable for X-ray diffraction were obtained. Crystal structure data deposited at the Cambridge Crystallographic Data Center; Deposition Number: CCDC 277908.





3. Chapter 3: Cobalt-Catalysed Reductive Aldol Cyclisations

Contributions from our group to the field of reductive aldol reactions have detailed copper(I)-bisphosphine-catalysed reductive aldol cyclisations using TMDS (1,1,3,3-tetramethylhydrosiloxane) as stoichiometric reductant that could be applied to the synthesis of β-hydroxylactones (Chapter 2)[1] and β-hydroxylactams[2] (Eqn 28).



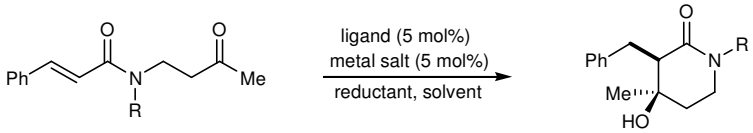
Although the products were obtained with generally high levels of diastereoselectivities (and with moderate enantioselectivities in the case of β-hydroxylactones when suitable chiral bisphosphines were employed), the process suffered from a number of limitations. First, the yields of these reactions were moderate at best (typically in the range 60-70%) due to competing side reactions. Second, the attenuated electrophilicity of α,β-unsaturated amides compared with the corresponding esters meant that productive cyclisations were limited to those amide substrates where R^1 = H or Me (with R^2 = H). Therefore, a search for improved reaction conditions was initiated to increase the scope of these cyclisations.

3.1. Optimisations

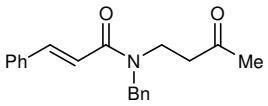
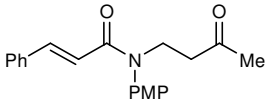
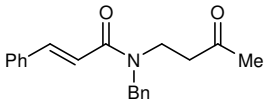
Initial investigations began with the cyclisation of cinnamic amides **266a** and **266b** (Table 3.1). Application of our previously reported copper conditions proved ineffective for substrate **266a**, providing the desired product **267a** with low conversion and mostly the starting material was recovered (Entry 1). Replacement of DPPF with *rac*-BINAP led to a similar result (Entry 2). The use of $PhSiH_3$ in place of TMDS led to again to a minimal reaction (Entry 3). Having obtained no success with copper-based catalyst systems, attention turned to the use of other metals. In conjunction with an appropriate chiral ligand, the combination of $CoCl_2$ and $NaBH_4$ has proven useful for the asymmetric conjugate reduction of α,β-unsaturated

amides.[3] Unsurprisingly, conditions employing $NaBH_4$ led to rapid reduction of the ketone of **266b**. Conditions employing cobalt salts that were developed for intermolecular reductive aldol reactions[4] and later extended to aldol cyclisations[5] also proved ineffective, providing complex mixtures (Entries 4–5). In light of recent reports of organometallic reagents with β-hydrogen-containing alkyl groups being utilised as stoichiometric reductants for a variety of transition metal-catalysed reductive couplings,[6] we examined Et_3B and Et_2Zn in our reaction. In the presence of $Co(acac)_2$ hydrate (degree of hydration ~2) (5 mol %), Et_3B resulted in no reaction (Entry 6), but we were delighted to observe that the more reactive Et_2Zn led to the formation of **267a** in >99% conversion with none of the reduced side-product being observed (Entry 7). The diasteseoselectivity of the reaction was very high; *anti*-product was not observed. No reaction occurs in the absence of $Co(acac)_2{\cdot}2H_2O$.

Table 3.1. Survey of the reaction conditions



266a-b **267a-b**

Entry	Substrate	Reagents	Solvent	Temp	Conv(%)[a]
1		$Cu(OAc)_2{\cdot}H_2O$, DPPF TMDS (1 equiv)	THF	rt	<5
2	 **266a**	$Cu(OAc)_2{\cdot}H_2O$, *rac*-BINAP, TMDS (1 equiv)	THF	rt	<5
3		$Cu(OAc)_2{\cdot}H_2O$, DPPF $PhSiH_3$ (1 equiv)	THF	rt	<5
4	 **266b**	$Co(dpm)_2$, $PhSiH_3$ (1 equiv)	THF	rt	Ca. 90[b]
5		$Co(dpm)_2$, $PhSiH_3$ (1 equiv)	DCE	Rt to 50 °C	Ca. 80[b]
6	 **266a**	$Co(acac)_2{\cdot}H_2O$ Et_3B (2 equiv)	THF/ Hexane	0 °C to rt	<5
7		$Co(acac)_2{\cdot}H_2O$ Et_2Zn (2 equiv)	THF/ Hexane	0 °C to rt	>99

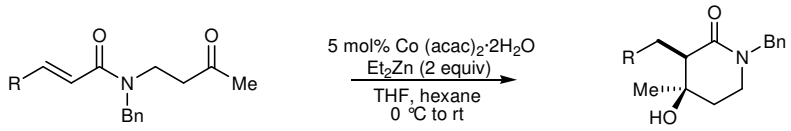
a) Determined by ^1H NMR b) A complex mixture containing unidentified side products was obtained, with only a trace (<10%) of **2a** present (reactions performed by Gordon J. Murray)

3.2. Scope of the Reaction

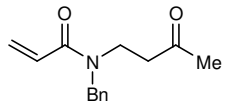
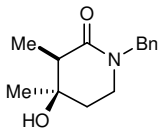
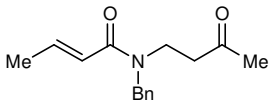
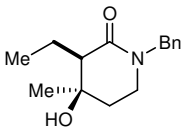
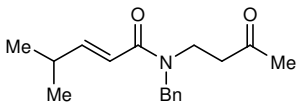
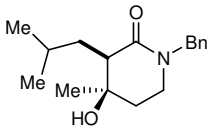
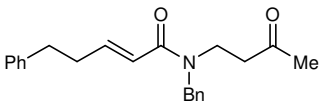
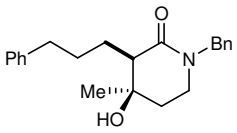
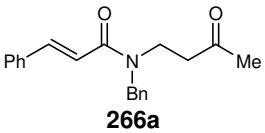
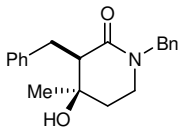
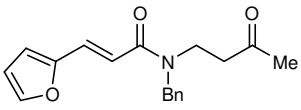
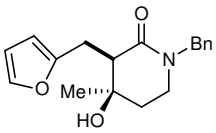
3.2.1. Amide substrates

With effective conditions identified, the scope of the process was next explored (Table 3.2). Methyl ketone substrates containing a wide range of substitution at the α,β-unsaturated amide underwent cyclisation to give 4-hydroxypiperidin-2-one products in generally excellent yields and high diastereoselectivities. In general, the reactions proceeded in very clean manner and after the work-up (simple filtering through a plug of silica using EtOAc as an eluent), ^{1}H NMR analysis of the products showed high purity. These products were further purified by column chromatography. It should be noted that the copper conditions (as in Table 1, Entry 1) proved ineffective in the majority of these examples. Aliphatic (Entires 1-4), aromatic (Entry 5) and heteroaromatic (Entry 6) substituents were all well tolerated giving the cyclised product in nearly quantitative yields

Table 3.2. Cyclisation of Six-Membered Methyl Ketone Substrates[a]



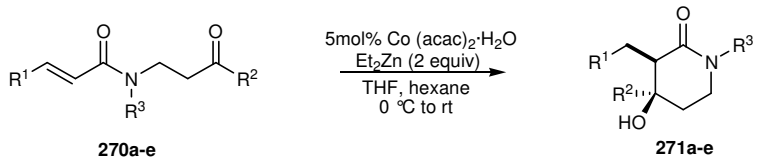
266a, 268a-e 267a, 269a-e

Entry	Substrate	Product		dr[b]	Yield(%)[c]
1	 **268a**		**269a**	9:1	88
2	 **268b**		**269b**	>19:1	99
3	 **268c**		**269c**	>19:1	>99
4	 **268d**		**269d**	>19:1	98
5	 **266a**		**267a**	>19:1	97
6	 **268e**		**269e**	>19:1	>99

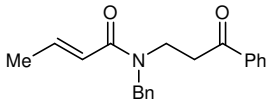
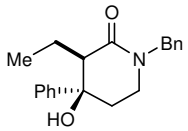
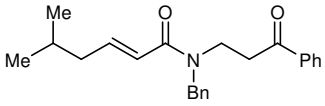
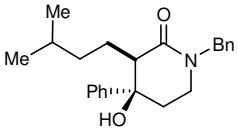
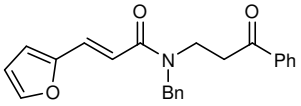
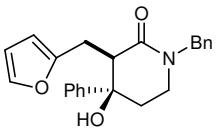
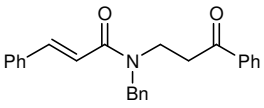
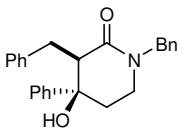
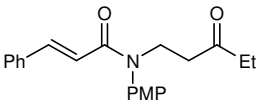
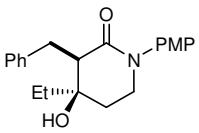
a) All reactions were performed on a 0.2 mmol scale. b) Determined by ^{1}H NMR analysis. c) Isolated yields of the major diastereomer

When the methyl ketone was changed to a phenyl ketone, cyclisations proceeded with slightly diminished yields, but diastereoselectivities remained high. When the α,β-unsaturated amide was substituted with an aliphatic group (Table 3.3, Entries1-2) the cyclisations proceeded more readily in comparison to those with an aromatic or a heteroaromatic substitution (Entries 3-4).

Table 3.3. Cyclisation of other Six-Membered Substrates[a]

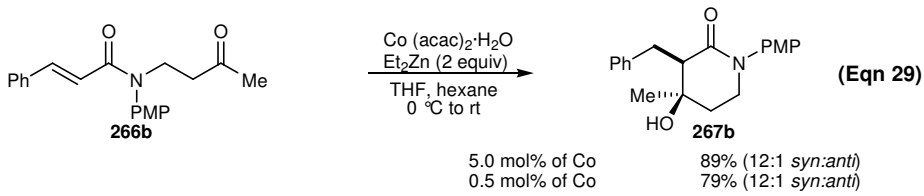


270a-e 271a-e

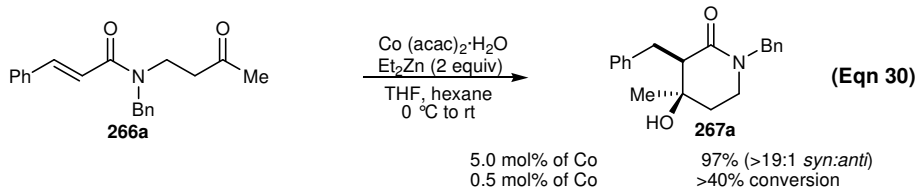
Entry	Substrate	Product		dr[b]	Yield(%)[c]
1	 **270a**		**271a**	>19:1	94
2	 **270b**		**271b**	>19:1	94
3	 **270c**		**271c**	>19:1	87
4	 **270d**		**271d**	>19:1	80
5	 **270e**		**271e**	9:1	88

a) all reactions were performed on a 0.2 mmol scale. b) Determined by ^{1}H NMR analysis. c) Isolated yields of the major diastereomer

When an ethyl ketone was utilised the cyclisation was still very effective (Entry 5). The lower diastereoselectivity (9:1 d.r.) of this reaction is known to be caused by *para*-methoxyphenyl substitution at the nitrogen. Other studies in our group have shown that *para*-methoxyphenyl substitution give lower diastereoselectivities (Eqns 29 and 30). On the other hand, substrates containing *para*-methoxyphenyl groups have been shown to be more reactive than benzyl-substituted substrates and the catalyst loading can be dropped to 0.5 mol% without major changes in the yield. Substrate **266a** gives higher diastereoselectivity in the product than **266b** with 5 mol% catalyst loading, but fails to react efficiently when a 0.5 mol% catalyst loading is used.

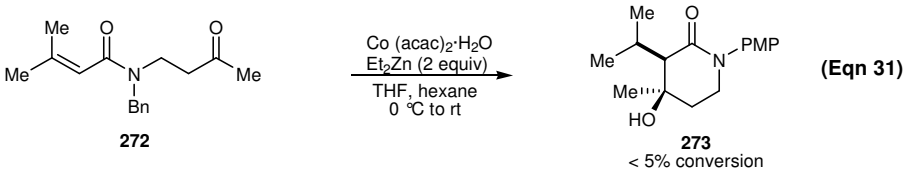


(Eqn 29)

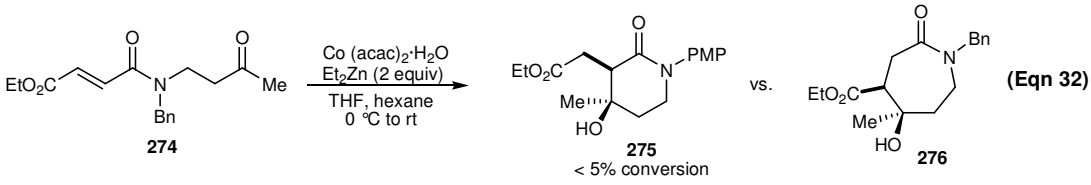


(Eqn 30)

Trisubstituted α,β-unsaturated amide **272** failed to cyclise under these conditions and mainly starting material was recovered. Substrate **274** was utilised to show whether the reaction would proceed α- to the ester or α- to the amide, forming either a six- or seven membered ring respectively. Unfortunately this substrate failed to cyclise in either way.



(Eqn 31)



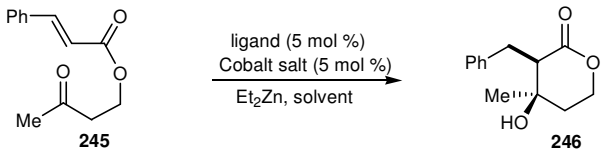
(Eqn 32)

Work done by Gordon J. Murray and Oscar Prieto in our group showed that the reaction could be applied to the formation of pyrrolidin-2-ones (five-membered lactams). Reactions proceeded with significantly lower yields and diastereoselectivities than for the formation of six-membered rings. Another drawback was the narrow scope of the substrates that cyclised effectively.

3.2.2. Ester Substrates

We then started to study whether this new catalyst system could be applied to formation of β-hydroxylactones. The substrates where an α,β-unsaturated carbonyl moiety was tethered to a ketone through an ester linkage proved to be more reactive than those with an amide linkage under the copper conditions (Chapter 2). Surprisingly, substrate **245** failed to cyclise under the cobalt-conditions optimised for the amide substrates (Table 3.4, Entry 1). It was hypothesised that by changing the electronic properties of the cobalt catalyst with different ligands, a solution to this problem might be found. $Co(acac)_2{\cdot}H_2O$ was changed to $CoCl_2$ and different mono- and bidentate phosphine ligands were screened. Interestingly, only the combination of $CoCl_2$ with electron-rich ligand Cy_2PPh provided good conversion. The use of the very similar Cy_3P failed to give product in satisfactory yields (Entry 7).

Table 3.4. Optimisations of the Reaction Conditions for the Ester Substrates[a]



245 246

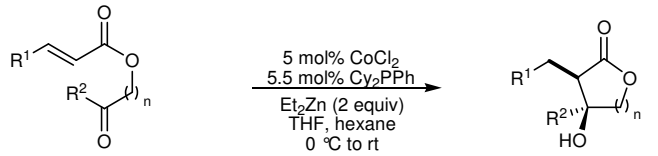
Entry	Condition	Ligand	Solvent	Conversion(%)[a]
1	$Co(acac)_2{\cdot}H_2O$, Et_2Zn (2 equiv)	-	THF	< 5
2	$Co(acac)_2{\cdot}H_2O$, Et_3B (2 equiv)	-	THF	< 5
3	$CoCl_2$, Et_2Zn (2 equiv)	-	THF	< 5
4	$Co(acac)_2{\cdot}H_2O$, Et_2Zn (2 equiv)	Ph_3P	THF	<5
5	$CoCl_2$, Et_2Zn (2 equiv)	Ph_3P	THF	<30
6	$CoCl_2$, Et_2Zn (2 equiv)	$(EtO)_3P$	THF	<5
7	$CoCl_2$, Et_2Zn (2 equiv)	Cy_3P	THF	<30
8	$CoCl_2$, Et_2Zn (2 equiv)	Cy_2PPh	THF	>99
9	$CoCl_2$, Et_2Zn (2 equiv)	Cy_2PPh	Toluene	ca. 70

a) Determined by ^1H NMR analysis

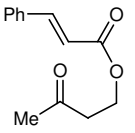
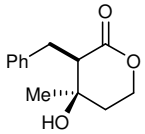
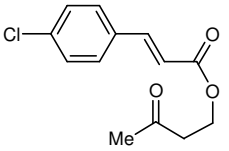
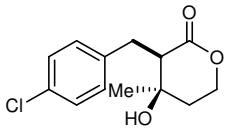
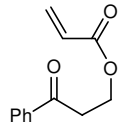
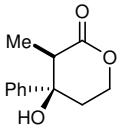
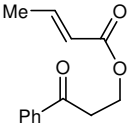
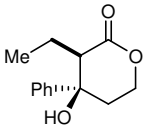
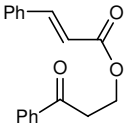
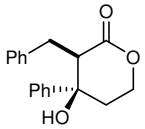
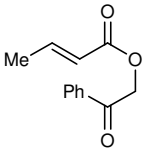
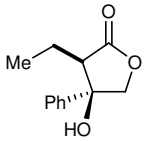
With this new catalyst system, we screened the scope of the reaction. We were surprised to realise that only a narrow selection of substrates cyclised readily. However, the successful reactions proceeded in good yields and stereoselectivities. For methyl ketone-containing substrates forming six-membered rings, only aromatic-subtituted α,β-unsaturated esters **245** and **247b** cyclised successfully. High yields

were observed in both cases. In the case of phenyl ketones, the substitutions tolerated on the alkene (R^1) were hydrogen, methyl, and phenyl (Table 3.5, Entries 3-5). Significantly lower yields were obtained compared with methyl ketone substrates. Substrate **249c** cyclised in 64% yield to give an inseparable mixture of diastereomers. Only one five-membered lactone (**252b**) was successfully obtained using this chemistry.

Table 3.5. Cyclisations of Ester Substrates[a]



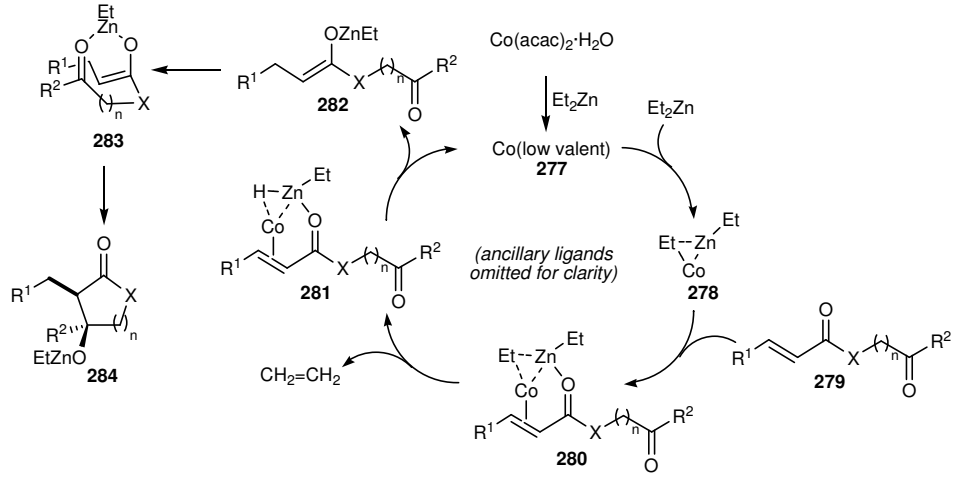
245, 247b, 249a-c, 251b → **246, 248b, 250a-c, 252b**

Entry	Substrate		Product		dr[a]	Yield (%)
1		**245**		**246**	>19:1	93
2		**247b**		**248b**	>19:1	94
3		**249a**		**250a**	>19:1	75
4		**249b**		**250b**	>19:1	64
5		**249c**		**250c**	10:1	64[b]
6		**251b**		**252b**	>19:1	53

a) Determined by ^1H NMR analysis. b) Isolated as a 10:1 inseparable mixture of diastereomers

3.3. Mechanism

The proposed mechanism will be outlined here, and further detailed discussion of the mechanism will be presented in Chapter 5. Although some studies of the mechanism have been conducted, the catalytic cycle presented in Scheme 3.1 is highly speculative at this stage. We assume that treatment of Co(II)-salt with Et_2Zn leads to an low-valent cobalt-species **277**. The oxidation state of the cobalt is unclear to us. Interaction of this low-valent Co-species with Et_2Zn may lead to intermediate **278**, involving a three-center-two-electron bridging interaction.[7] This step may be viewed as an oxidative addition of low-valent cobalt species into the zinc–ethyl bond. Coordination of **278** to the substrate would then provide **280**, which can undergo *β*-hydride elimination to provide cobalt hydride **281**. Reorganisation of **281** can then occur to provide zinc enolate **282**, which would undergo aldol-cyclisation, and low-valent Co-species, which can re-enter the catalytic cycle. The observed stereochemical outcome of the reaction may be explained by preferential formation of the *Z*-zinc enolate **283**, along with a chelated Zimmerman-Traxler-type transition state.[8]



Scheme 3.1. Proposed Mechanism of the Co-Catalysed Reductive Cyclisations

3.4. Conclusions

We have developed an efficient and highly diastereoselective cobalt-catalysed reductive aldol cyclisation that utilises Et_2Zn as stoichiometric reductant.

This study has highlighted two important features: (i) conjugate reduction of α,β-unsaturated amides using Et_2Zn, which to our knowledge has not been developed as a general synthetic method, and (ii) a new mild approach to access zinc enolates that does not require the prior formation of an alkali metal enolate (for transmetalation with a zinc halide), or the use of α-halocarbonyl compounds (which can be difficult to prepare for complex substrates). The reaction was particularly effective for the formation of β-hydroxylactams. In the case where β-hydroxylactones were formed, the catalyst proved to work for only a narrow scope of substrates.

3.5. References

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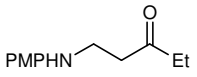
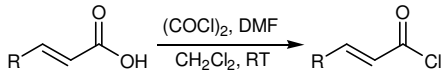
3.6. Experimental



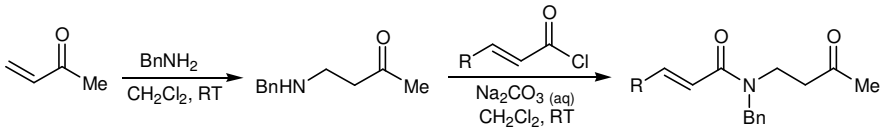
5-(4-Methoxyphenylamino)pentan-3-one (285). Prepared according to a previously reported procedure.[i,ii]

Preparation of α,β-Unsaturated Acid Chlorides: General Procedure A



Oxalyl chloride (1.21 equiv) was added dropwise over 2 min to a solution of the appropriate α,β-unsaturated carboxylic acid (1.10 equiv) and DMF (0.25 equiv) in CH_2Cl_2 (0.55 M with respect to carboxylic acid) at 0 °C. The mixture was stirred at 0 °C until no more effervescence was observed (*ca.* 1 h) to give a solution of α,β-unsaturated acid chloride which was used directly in the next step.

Preparation of Cyclisation Precursors: General Procedure B



A solution of benzylamine (1.0 equiv) and methyl vinyl ketone (1.1 equiv) in CH_2Cl_2 (2.5 mL/mmol of benzylamine) was stirred at 0 °C for 18 h. Saturated aqueous Na_2CO_3 solution (2.5 mL/mmol of benzylamine) followed by the appropriate acid chloride (neat in the case of commercially available acid chlorides, or as a solution in CH_2Cl_2 prepared according to General Procedure A, 1.21 equiv) were then added dropwise or portionwise and the mixture was stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution and CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (x 3), and the combined organic layers were washed with

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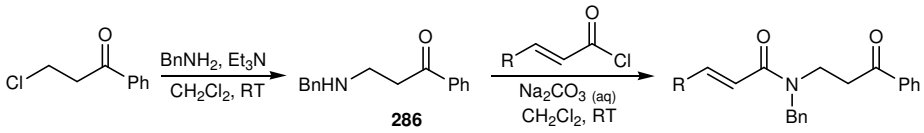
[i] Lam, H. W.; Murray, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743.
[ii] Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253.

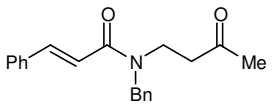
10% HCl solution (x 1), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclisation substrate.

Preparation of Cyclisation Precursors: General Procedure C



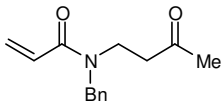
Benzylamine (1.0 equiv) was added over 1 min to a solution of 3-chloropropiophenone (1.1 equiv) and Et_3N (3.3 equiv) in THF (2.5 mL/mmol of benzylamine) at room temperature and the mixture was stirred for 18 h. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution and EtOAc. The aqueous layer was separated and extracted with EtOAc (x 2), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting amine **286** was used directly in the next step without further purification.

The appropriate α,β-unsaturated acid chloride (neat in the case of commercially available acid chlorides, or as a solution in CH_2Cl_2 prepared according to General Procedure A, 1.5 equiv) was added dropwise or portionwise to a vigorously stirred mixture of the unpurified amine **286** (1.0 equiv) in CH_2Cl_2 (1 mL/mmol of **286**) and saturated aqueous Na_2CO_3 solution (1 mL/mmol of **286**). The mixture was stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution and CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (x 3), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclisation substrate.



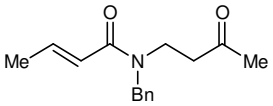
***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-3-phenylpropenamide (266a)**. The title compound was prepared according to General Procedure B from methyl vinyl ketone (1.88 mL, 22.0 mmol), benzylamine (2.18 mL, 20.0 mmol) and cinnamoyl chloride (4.03 g, 24.2 mmol) for a reaction time of 3 h. The product was purified by column chromatography (30%

EtOAc/petrol) to give a yellow solid (2.10 g, 34%) as a 2:1 mixture of rotamers. m.p. 71-73 °C; IR ($CHCl_3$) 3027, 1713 (C=O), 1648 (C=C), 1426, 1203, 1161, 1028, 978, 764, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.79 (1H, d, *J* = 15.4 Hz, PhC**H**=), 7.61-7.26 (10H, m, Ar**H**), 6.86 (1H, d, *J* = 15.4 Hz, PhCH=C**H**), 4.80 (2H, s, C$\mathbf{H}_2$Ph), 3.73 (2H, t, *J* = 6.7 Hz, $CH_2C\mathbf{H}_2N$), 2.90 (2H, t, *J* = 6.7 Hz, C$\mathbf{H}_2CH_2N$), 2.17 (3H, s, C$\mathbf{H}_3$C=O); (Minor rotamer) δ 7.85 (1H, d, *J* = 15.3 Hz, PhC**H=**), 7.61-7.26 (10H, m, Ar**H**), 7.01 (1H, d, *J* = 15.3 Hz, PhCH=C**H**), 4.76 (2H, s, C$\mathbf{H}_2$Ph), 3.76 (2H, t, *J* = 7.1 Hz, $CH_2C\mathbf{H}_2N$), 2.74 (2H, t, *J* = 7.1 Hz, C$\mathbf{H}_2CH_2N$), 2.13 (3H, s, C$\mathbf{H}_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.4 (C), 206.0 (C), 167.0 (C), 166.4 (C), 143.5 (CH), 143.1 (CH), 137.5 (C), 137.0 (C), 135.0 (C), 129.6 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 126.4 (CH), 117.1 (CH), 116.9 (CH), 52.3 (CH_2), 49.5 (CH_2), 42.9 (CH_2), 42.6 (CH_2), 41.8 (2 x CH_2), 30.2 (CH_3), 30.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{21}NO_2$ $[M+Na]^+$: 330.1465, found: 330.1465.

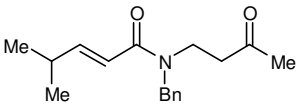


***N*-Benzyl-*N*-(3-oxobutyl)propenamide (268a)**. The title compound was prepared according to General Procedure B from methyl vinyl ketone (0.94 mL, 11.0 mmol), benzylamine (2.18 mL, 20.0 mmol) and acryloyl chloride (1.02 mL, 12.1 mmol) for a reaction time of 3 h. The product was purified by column chromatography (50% EtOAc/petrol) to give a colorless oil (1.08 g, 47%) as a 2:1 mixture of rotamers. IR (film) 3063, 1714 (C=O), 1648 (C=C), 1613, 1471, 1447, 1371, 978, 732, 699 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.39-7.28 (4H, m, Ar**H**), 7.20-7.18 (1H, m, Ar**H**), 6.56 (1H, dd, *J* = 16.7, 10.2 Hz, CH_2=C**H**), 6.41 (1H, dd, *J* = 16.7, 2.1 Hz, C$\mathbf{H}_2$=CH), 5.70 (1H, dd, *J* = 10.2, 2.1 Hz, C$\mathbf{H}_2$=CH), 4.70 (2H, s, C$\mathbf{H}_2$Ph), 3.65 (2H, t, *J* = 6.7 Hz, $CH_2C\mathbf{H}_2N$), 2.85 (2H, t, *J* = 6.7 Hz, C$\mathbf{H}_2CH_2N$), 2.14 (3H, s, C$\mathbf{H}_3$C=O); (Minor rotamer) δ 7.39-7.28 (4H, m, Ar**H**), 7.20-7.18 (1H, m, Ar**H**), 6.68 (1H, dd, *J* = 16.7, 10.3 Hz CH_2=C**H**), 6.48 (1H, dd, *J* = 16.7, 1.9 Hz, C$\mathbf{H}_2$=CH), 5.79 (1H, dd, *J* = 10.3, 1.9 Hz, C$\mathbf{H}_2$=CH), 4.68 (2H, s, C$\mathbf{H}_2$Ph), 3.63 (2H, t, *J* = 7.0 Hz, $CH_2C\mathbf{H}_2N$), 2.66 (2H, t, *J* = 7.0 Hz, C$\mathbf{H}_2CH_2N$), 2.09 (3H, s, C$\mathbf{H}_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture

of rotamers – not fully assigned) δ 206.9 (C), 205.6 (C), 166.5 (C), 165.9 (C), 137.2 (C), 136.6 (C), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH_2), 127.6 (CH), 127.3 (CH), 127.1 (CH), 126.0 (CH), 51.8 (CH_2), 48.9 (CH_2), 42.3 (CH_2), 42.0 (CH_2), 41.5 (CH_2), 41.4 (CH_2), 29.8 (CH_3), 29.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{18}NO_2$ $[M+H]^+$: 232.1332, found: 232.1332.

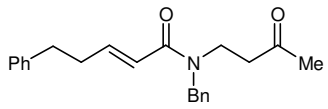


***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-but-2-enamide (268b)**. The title compound was prepared according to General Procedure B from methyl vinyl ketone (0.94 mL, 11.0 mmol), benzylamine (1.09 mL, 10.0 mmol), and crotonoyl chloride (1.29 mL, 12.1 mmol) for a reaction time of 4 h. The product was purified by column chromatography (40% EtOAc/petrol) to give a colorless oil as a 2:1 mixture of rotamers. IR (film) 2914, 1713 (C=O), 1660 (C=C), 1449, 1369, 1160, 963, 815, 732, 698 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.36-7.25 (4H, m, Ar**H**), 7.17-7.15 (1H, m, Ar**H**), 7.07-6.91 (1H, m, CH_3C**H**=), 6.20 (1H, dd, *J* = 14.9, 1.5 Hz, C**H**C=O), 4.64 (2H, s, C**H**$_2$Ph), 3.59 (2H, t, *J* = 6.7 Hz, CH_2C**H**$_2$N), 2.79 (2H, t, *J* = 6.7 Hz, C**H**$_2$$CH_2$N), 2.10 (3H, s, C**H**$_3$C=O), 1.82 (3H, dd, *J* = 6.9, 1.5 Hz, C**H**$_3$CH=); (Minor rotamer) δ 7.36-7.25 (4H, m, Ar**H**), 7.17-7.15 (1H, m, Ar**H**), 7.07-6.91 (1H, m, CH_3C**H**=), 6.29 (1H, d, *J* = 14.9 Hz, C**H**C=O), 4.64 (2H, s, C**H**$_2$Ph), 3.59 (2H, t, *J* = 7.2 Hz, CH_2C**H**$_2$N), 2.63 (2H, t, *J* = 7.2 Hz, C**H**$_2$$CH_2$N), 2.07 (3H, s, C**H**$_3$C=O), 1.90 (3H, d, *J* = 6.5 Hz, C**H**$_3$CH=); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.0 (C), 205.7 (C), 166.7 (C), 166.1 (C), 142.2 (CH), 141.9 (CH), 137.4 (C), 136.8 (C), 128.4 (CH), 128.1 (CH), 127.6 (CH), 127.1 (CH), 126.9 (CH), 126.0 (CH), 121.3 (CH), 121.0 (CH), 51.6 (CH_2), 48.8 (CH_2), 42.4 (CH_2), 41.8 (CH_2), 41.4 (CH_2), 29.8 (CH_3), 29.6 (CH_3), 17.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{19}NO_2$ $[M+H]^+$: 246.1489, found: 246.1489.



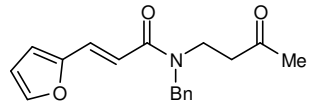
***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-4-methylpent-2-enamide (268c)**. The title compound was prepared according to General Procedure B from methyl vinyl ketone (1.88 mL, 22.0 mmol), benzylamine (2.18 mL, 20.0 mmol) and the acid chloride (prepared according General Procedure

A) derived from 4-methyl-2-pentenoic acid (2.76 g, 24.2 mmol) for a reaction time of 16 h. The product was purified by column chromatography (40% EtOAc/petrol) to give a white solid (2.36 g, 43%) as a 2:1 mixture of rotamers. m.p. 59-61 °C; IR ($CHCl_3$) 2923, 1713 (C=O), 1650 (C=C), 1423, 1214, 1161, 1016, 815, 732, 698 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.35-7.23 (4H, m, Ar**H**), 7.17-7.15 (1H, m, Ar**H**), 6.90 (1H, dd, *J* = 15.1, 7.0 Hz, CHC**H**=), 6.12 (1H, dd, *J* = 15.1, 1.0 Hz, CHCH=C**H**), 4.64 (2H, s, C$\mathbf{H}_2$Ph), 3.59 (2H, t, *J* = 6.8 Hz, $CH_2C\mathbf{H}_2N$), 2.80 (2H, t, *J* = 6.8 Hz, C$\mathbf{H}_2CH_2N$), 2.43-2.34 (1H, m, $(CH_3)_2C\mathbf{H}$), 2.10 (3H, s, C$\mathbf{H}_3$C=O), 0.99 (6H, *J* = 6.8 Hz, $(C\mathbf{H}_3)_2CH$); (Minor rotamer) δ 7.35-7.23 (4H, m, Ar**H**), 7.17-7.15 (1H, m, Ar**H**), 6.97 (1H, dd, *J* = 15.1, 7.0 Hz, CHC**H**=), 6.21 (1H, d, *J* = 15.1 Hz, CHCH=C**H**), 4.64 (2H, s, C$\mathbf{H}_2$Ar), 3.59 (2H, t, *J* = 7.1 Hz, $CH_2C\mathbf{H}_2N$), 2.62 (2H, t, *J* = 7.1 Hz, C$\mathbf{H}_2CH_2N$), 2.51-2.43 (1H, m, $(CH_3)_2C\mathbf{H}$), 2.06 (3H, s, C$\mathbf{H}_3$C=O), 1.07 (6H, d, *J* = 6.7 Hz, $(C\mathbf{H}_3)_2CH$); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.5 (C), 206.1 (C), 167.4 (C), 166.8 (C), 153.9 (CH), 153.4 (CH), 137.7 (C), 137.2 (C), 128.7 (CH), 128.5 (CH), 128.0 (CH), 127.4 (CH), 127.2 (CH), 126.4 (CH), 117.3 (CH), 116.9 (CH), 52.2 (CH_2), 49.3 (CH_2), 42.8 (CH_2), 42.3 (CH_2), 41.9 (CH_2), 41.7 (CH_2), 31.1 (CH), 30.2 (CH_3), 30.0 (CH_3), 21.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{24}NO_2$ $[M+H]^+$: 274.1802, found: 274.1803.



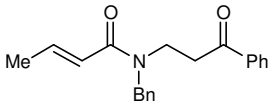
***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-5-phenylpent-2-enamide (268d)**. The title compound was prepared according to General Procedure B from methyl vinyl ketone (0.56 mL, 6.60 mmol), benzylamine (0.65 mL, 6.00 mmol), and the acid chloride (prepared according to General Procedure A) derived from (*E*)-5-phenylpent-2-enoic acid (1.34 g, 7.26 mmol) for a reaction time of 16 h. The product was purified by column chromatography (40% EtOAc/petrol) to give a pale yellow oil (1.27 g, 63%) as a 2:1 mixture of rotamers. IR ($CHCl_3$) 2924, 1712 (C=O), 1657 (C=C), 1495, 1425, 1390, 1206, 970, 735, 699 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.37-7.13 (10H, m, Ar**H**), 7.10-6.94 (1H, m, =C**H**), 6.18 (1H, d, *J* = 15.1 Hz, =C**H**), 4.59 (2H, s, NC$\mathbf{H}_2$Ph), 3.60 (2H, t, *J* = 6.7 Hz, $CH_2C\mathbf{H}_2N$), 2.84-2.46 (6H, m, C$\mathbf{H}_2CH_2N$ and PhC$\mathbf{H}_2C\mathbf{H}_2$), 2.12

(3H, s, C**H**$_3$C=O); (Minor rotamer) 7.37-7.13 (10H, m, Ar**H**), 7.10-6.94 (1H, m, =C**H**), 6.23 (1H, d, *J* = 17.1 Hz, =C**H**), 4.63 (2H, s, NC**H**$_2$Ph), 3.53 (2H, t, *J* = 7.2 Hz, C**H**$_2$N), 2.84-2.46 (6H, m, C**H**$_2$CH$_2$N and PhC**H**$_2$C**H**$_2$), 2.06 (3H, s, C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.4 (C), 206.1 (C), 167.1 (C), 166.4 (C), 146.2 (CH), 145.7 (CH), 140.8 (C), 137.6 (C), 137.1 (C), 128.8 (CH), 128.5 (CH), 128.3 (CH), 128.0 (CH), 127.5 (CH), 127.3 (CH), 126.4 (CH), 126.0 (CH), 120.9 (CH), 120.5 (CH), 52.1 (CH_2), 49.3 (CH_2), 42.7 (CH_2), 42.2 (CH_2), 41.8 (CH_2), 41.7 (CH_2), 34.4 (CH_2), 34.0 (CH_2), 30.2 (CH_3), 30.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{26}NO_2$ $[M+H]^+$: 336.1958, found: 336.1959.

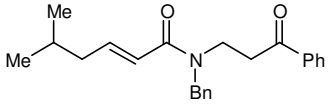


***N*-benzyl-*N*-(3-oxobutyl)-(*E*)-3-furan-2-ylpropenamide (268e)**. The title compound was prepared according to General Procedure B from methyl vinyl ketone (0.94 mL, 11.0 mmol), benzylamine (1.09 mL, 10.0 mmol) and the acid chloride (prepared according General Procedure A) derived from (2-furyl)acrylic acid (1.67 g, 12.1 mmol) for a reaction time of 14 h. The product was purified by column chromatography (40% EtOAc/petrol) to give an orange/red oil (1.56 g, 53%) as a 2:1 mixture of rotamers. IR (film) 2923, 1713 (C=O), 1650 (C=C), 1423, 1214, 1161, 1016, 815, 732, 698 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.55 (1H, d, *J* = 15.1 Hz, C**H**=CHC=O), 7.50-7.24 (6H, m, Ar**H** and C**H**), 6.78 (1H, d, *J* = 15.1 Hz, CH=C**H**C=O), 6.58 (1H, bs, C**H**), 6.46-6.45 (1H, m, C**H**), 4.77 (2H, s, C**H**$_2$Ph), 3.69 (2H, t, *J* = 6.4 Hz, CH$_2$C**H**$_2$N), 2.87 (2H, t, *J* = 6.4 Hz, C**H**$_2$CH$_2$N), 2.15 (3H, s, C**H**$_3$C=O); (Minor rotamer) δ 7.61 (1H, d, *J* = 15.2 Hz, C**H**=CHC=O), 7.50-7.24 (6H, m, Ar**H** and C**H**), 6.84 (1H, d, *J* = 15.2 Hz, CH=C**H**C=O), 6.62-6.58 (1H, m, C**H**), 6.50-6.49 (1H, m, C**H**), 4.74 (2H, s, C**H**$_2$Ar), 3.71 (2H, t, *J* = 6.9 Hz, CH$_2$C**H**$_2$N), 2.74 (2H, t, *J* = 6.9 Hz, C**H**$_2$CH$_2$N), 2.13 (3H, s, C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.5 (C), 206.1 (C), 166.9 (C), 166.3 (C), 151.5 (C), 143.9 (CH), 137.6 (C), 137.1 (C), 130.3 (CH), 129.9 (CH), 128.8 (CH), 128.6 (CH), 128.0 (CH), 127.6 (CH), 127.4 (CH), 126.6 (CH), 114.6 (CH), 114.3 (CH), 114.2 (CH), 114.0 (CH), 112.1 (CH) 52.2 (CH_2), 49.6 (CH_2), 43.1 (CH_2), 42.5 (CH_2), 41.9 (CH_2), 30.2

(CH_3), 30.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{18}H_{20}NO_3$ $[M+H]^+$: 298.1438, found: 298.1441.

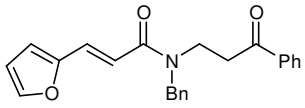


***N*-Benzyl-*N*-(3-oxo-3-phenylpropyl)-(*E*)-but-2-enamide (270a)**. The title compound was prepared according to General Procedure C from 3-chloropropiophenone (927 mg, 5.50 mmol), benzylamine (0.55 mL, 5.0 mmol) and crotonoyl chloride (0.72 mL, 7.5 mmol) for a reaction time of 5 h. The product was purified by column chromatography (20% EtOAc/$CHCl_3$) to give a colorless gum (1.27 g, 86%) as a 2:1 mixture of rotamers. IR ($CHCl_3$) 2914, 1713 (C=O), 1660 (C=C), 1449, 1369, 1160, 963, 815, 732, 698 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.96 (2H, d, *J* = 6.7 Hz, Ar**H**), 7.60-7.53 (1H, m, Ar**H**), 7.47-7.43 (2H, m, Ar**H**), 7.38-7.20 (5H, m, Ar**H**), 7.11-6.95 (1H, m, $CH_3C\mathbf{H}$=), 6.24 (1H, dd, *J* = 14.9, 1.4 Hz, CH_3CH=C**H**), 4.72 (2H, s, C$\mathbf{H}_2$Ph), 3.79 (2H, t, *J* = 6.8 Hz, $CH_2C\mathbf{H}_2N$), 3.37 (2H, t, *J* = 6.8 Hz, C$\mathbf{H}_2CH_2N$), 1.82 (3H, dd, *J* = 6.8, 1.4 Hz, C$\mathbf{H}_3$CH=); (Minor rotamer) δ 7.85 (2H, d, *J* = 6.7 Hz, Ar**H**), 7.60-7.53 (1H, m, Ar**H**), 7.47-7.43 (2H, m, Ar**H**), 7.38-7.20 (5H, m, Ar**H**), 7.11-6.95 (1H, m, $CH_3C\mathbf{H}$=), 6.36 (1H, d, *J* = 14.6 Hz, CH_3CH=C**H**), 4.71 (2H, s, C$\mathbf{H}_2$Ph), 3.79 (2H, t, *J* = 7.4 Hz, $CH_2C\mathbf{H}_2N$), 3.17 (2H, t, *J* = 6.8 Hz, C$\mathbf{H}_2CH_2N$), 1.91 (3H, d, *J* = 6.5 Hz, C$\mathbf{H}_3$CH=); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 198.9 (C), 197.7 (C), 167.3 (C), 166.5 (C), 143.0 (CH), 142.4 (CH), 137.7 (C), 137.2 (C), 136.5 (C), 136.2 (C), 133.5 (CH), 133.1 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.5 (CH), 127.3 (CH), 126.4 (CH), 121.6 (CH), 121.2 (CH), 52.3 (CH_2), 49.3 (CH_2), 43.2 (CH_2), 42.5 (CH_2), 38.0 (CH_2), 37.2 (CH_3), 18.1 (CH_3); IR ($CHCl_3$) 2914, 1713 (C=O), 1660 (C=C), 1449, 1369, 1160, 963, 815, 732, 698 cm^{-1}; HRMS (ES) Exact mass calcd for $C_{20}H_{22}NO_2$ $[M+H]^+$: 308.1645, found: 308.1643.



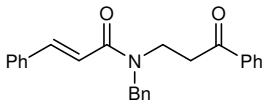
***N*-benzyl-*N*-(3-oxo-3-phenylpropyl)-(*E*)-5-methylhex-2-enamide (270b)**. The title compound was prepared according to General Procedure C from 3-chloropropiophenone (1.85 mg, 11.0 mmol), benzylamine (1.10 mL, 10.0 mmol) and the acid chloride (prepared

according to General Procedure A) derived from (*E*)-5-methylhex-2-enoic acid (1.92 g, 15.0 mmol) for a reaction time of 15 h. The product was purified by column chromatography (15% EtOAc/$CHCl_3$) to give a yellow oil (1.62 g, 46%) as a 2:1 mixture of rotamers. IR ($CHCl_3$) 2955, 1680 (C=O), 1656 (C=C), 1447, 1368, 1211, 1028, 980, 844, 742 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 8.02-8.00 (2H, m, Ar**H**), 7.62-7.58 (1H, m, Ar**H**), 7.51-7.46 (2H, m, Ar**H**), 7.41-7.24 (5H, m, Ar**H**), 7.01 (1H, dt, *J* = 15.0, 7.5 Hz, $CH_2C\mathbf{H}$=), 6.24 (1H, d, *J* = 15.0 Hz, CH_2CH=C**H**), 4.76 (2H, s, C$\mathbf{H}_2$Ph), 3.83 (2H, t, *J* = 6.8 Hz, $CH_2C\mathbf{H}_2N$), 3.41 (2H, t, *J* = 6.8 Hz, C$\mathbf{H}_2CH_2N$), 2.10-2.06 (2H, m, C$\mathbf{H}_2$CH=), 1.86-1.68 (1H, m, $(CH_3)_2C\mathbf{H}$), 0.92 (6H, d, *J* = 6.8 Hz, $(C\mathbf{H}_3)_2CH$); (Minor rotamer) δ 7.88 (2H, d, *J* = 15.0 Hz, Ar**H**), 7.64-7.58 (1H, m, Ar**H**), 7.51-7.46 (2H, m, Ar**H**), 7.41-7.24 (5H, m, Ar**H**), 7.08 (1H, dt, *J* = 14.9, 7.4 Hz, $CH_2C\mathbf{H}$=), 6.35 (1H, d, *J* = 14.9 Hz, CH_2CH=C**H**), 4.75 (2H, s, C$\mathbf{H}_2$Ph), 3.83 (2H, t, *J* = 7.4 Hz, $CH_2C\mathbf{H}_2N$), 3.21 (2H, t, *J* = 7.4 Hz, C$\mathbf{H}_2CH_2N$), 2.18-2.14 (2H, m, C$\mathbf{H}_2$CH=), 1.86-1.68 (1H, m, $(CH_3)_2C\mathbf{H}$), 0.97 (6H, d, *J* = 6.6 Hz, $(C\mathbf{H}_3)_2CH$); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 198.9 (C), 197.6 (C), 167.3 (C), 166.5 (C), 146.8 (CH), 146.1 (CH), 137.7 (C), 137.2 (C), 136.5 (C), 136.2 (C), 133.4 (CH), 133.1 (CH), 128.7 (CH), 128.5 (CH), 128.0 (CH), 127.8 (CH), 127.4 (CH), 127.3 (CH), 126.4 (CH), 121.1 (CH), 120.7 (CH), 52.3 (CH_2), 49.3 (CH_2), 43.3 (CH_2), 42.5 (CH_2), 41.7 (CH_2), 41.6 (CH_2), 38.0 (CH_2), 37.2 (CH_2), 27.8 (CH), 22.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{23}H_{28}NO_2$ $[M+H]^+$: 350.2115, found: 350.2114.



***N*-Benzyl-*N*-(3-oxo-3-phenylpropyl)-(*E*)-3-furan-2-ylpropenamide (270c)**. The title compound was prepared according to General Procedure C from 3-chloropropiophenone (1.85 g, 11.0 mmol), benzylamine (1.10 mL, 10.0 mmol) and 3-(2-furyl)acrylic acid (2.07 g, 15.0 mmol) for a reaction time of 5 h. The product was purified by column chromatography (15% EtOAc/$CHCl_3$) to give an orange gum (2.26 g, 63%) as a 2:1 mixture of rotamers. IR ($CHCl_3$) 2942, 1682 (C=O), 1651 (C=C), 1487, 1324, 1213, 971, 733, 692, 594 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 8.01 (2H, d, *J* = 7.7 Hz, Ar**H**), 7.61-7.28 (9H, m, Ar**H**), 7.58 (1H, d, *J* = 15.1 Hz, =C**H**), 6.82 (1H, d, *J* = 15.1 Hz, =C**H**),

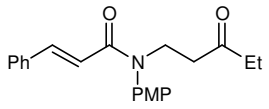
6.58 (1H, d, *J* = 3.3 Hz, C**H**) 6.46-6.45 (1H, m, C**H**), 4.84 (2H, s, NC**H**$_2$Ph), 3.88 (2H, t, *J* = 6.8 Hz, C**H**$_2$N), 3.43 (2H, t, *J* = 6.8 Hz, C**H**$_2$CH$_2$N); (Minor rotamer) δ 7.90 (2H, d, *J* = 7.6 Hz, Ar**H**), 7.64 (1H, d, *J* = 15.0 Hz, =C**H**), 7.61-7.28 (9H, m, Ar**H**), 6.91 (1H, d, *J* = 15.0 Hz, =C**H**), 6.61 (1H, d, *J* = 3.2 Hz, C**H**) 6.49-6.48 (1H, m, C**H**), 4.81 (2H, s, NC**H**$_2$Ph), 3.92 (2H, t, *J* = 7.4 Hz, C**H**$_2$N), 3.27 (2H, t, *J* = 7.4 Hz, C**H**$_2$CH$_2$N); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 198.7 (C), 197.5 (C), 166.9 (C), 166.2 (C), 151.3 (C), 143.8 (CH), 137.5 (C), 137.0 (C), 136.4 (C), 136.1 (C), 133.3 (CH), 133.0 (CH), 130.2 (CH), 129.7 (CH), 128.7 (CH), 128.4 (CH), 127.9 (CH), 127.8 (CH), 127.4 (CH), 127.2 (CH), 126.4 (CH), 114.6 (CH), 114.2 (CH), 114.0 (CH), 113.9 (CH), 112.0 (CH), 52.2 (CH_2), 49.4 (CH_2), 43.2 (CH_2), 42.5 (CH_2), 38.1 (CH_2), 37.0 (CH_2); HRMS (ES) Exact mass calcd for $C_{23}H_{22}NO_3$ $[M+H]^+$: 360.1594, found: 360.1590.



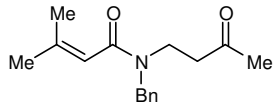
_N_-benzyl-_N_-(3-oxo-3-phenylpropyl)-(_E_)-3-phenylpropenamide (270d)

The title compound was prepared according to General Procedure C from 3-chloropropiophenone (1.85 mg, 11.0 mmol), benzylamine (1.10 mL, 10.0 mmol) and the acid chloride (prepared according to General Procedure A) derived from (*E*)-5-methylhex-2-enoic acid (2.50 g, 15.0 mmol) for a reaction time of 3 h. The product was purified by column chromatography (20% EtOAc/$CHCl_3$) to give a yellow oil (2.40 g, 67 %) as a 2:1 mixture of rotamers. m.p.99-101 °C; IR ($CHCl_3$) 2940, 1681 (C=O), 1648 (C=C), 1449, 1326, 1208, 977, 764, 735, 689 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 8.04-8.02 (2H, m, Ar**H**), 7.82 (1H, d, *J* = 15.4 Hz, =C**H**), 7.63-7.30 (13H, m, Ar**H**), 6.89 (1H, d, *J* = 15.4 Hz, =C**H**), 4.88 (2H, s, C**H**$_2$Ar), 3.91 (2H, t, *J* = 6.8 Hz, C**H**$_2$N), 3.47 (2H, t, *J* = 6.8 Hz, C**H**$_2$CH$_2$N); (Minor rotamer) δ δ 7.91-7.89 (2H, m, Ar**H**), 7.88 (1H, d, *J* = 15.3 Hz, =C**H**), 7.63-7.30 (13H, m, Ar**H**), 7.05 (1H, d, *J* = 15.3 Hz, =C**H**), 4.83 (2H, s, C**H**$_2$Ar), 3.96 (2H, t, *J* = 6.8 Hz, C**H**$_2$N), 3.27 (2H, t, *J* = 6.8 Hz, C**H**$_2$CH$_2$N);^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 199.0 (C), 197.7 (C), 167.2 (C), 166.5 (C), 143.8 (CH), 143.2 (CH), 137.6 (C), 137.1 (C), 136.6 (C), 136.2 (C), 135.1 (C), 133.5 (CH), 133.2 (CH), 129.7 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.1 (CH), 127.9

(CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 126.5 (CH), 117.3 (CH), 116.8 (CH), 52.6 (CH_2), 49.6 (CH_2), 43.6 (CH_2), 42.7 (CH_2), 38.1 (CH_2), 37.2 (CH_2); HRMS (ES) Exact mass calcd for $C_{23}H_{28}NO_2$ $[M+H]^+$: 350.2115, found: 350.2114.

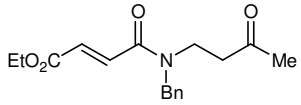


***N*-(4-Methoxyphenyl)-*N*-(3-oxopentyl)-(*E*)-3-phenylpropenoate (270e)**. Cinnamoyl chloride (500 mg, 3.00 mmol) was added portionwise to a vigorously stirred mixture of the amine **285** (415 mg, 2.00 mmol) in CH_2Cl_2 (2 mL) and saturated aqueous Na_2CO_3 solution (2 mL). The mixture was stirred at room temperature for 18 h. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution and CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 5mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The mixture was purified by column chromatography (15% EtOAc/$CHCl_3$) to give a light beige solid (656 mg, 97%). m.p. 105-107 °C; IR ($CHCl_3$) 2936, 1710 (C=O), 1660 (C=C), 1509, 1395, 1247, 1180, 836, 765, 684 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.66 (1H, d, *J* = 15.6 Hz, PhC**H**=), 7.31-7.29 (5H, m, Ar**H**), 7.14 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.96 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.30 (1H, d, *J* = 15.6 Hz, PhCH=C**H**), 4.07 (2H, d, *J* = 7.3 Hz, C**H**$_2$N), 3.86 (3H, s, OC**H**$_3$), 2.79 (2H, t, *J* = 7.3 Hz, C**H**$_2$CH$_2$N), 2.45 (2H, q, *J* = 7.3 Hz, CH$_3$C**H**$_2$), 1.04 (3H, t, *J* = 7.3 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 209.5 (C), 166.1 (C), 158.9 (C), 141.7 (CH), 135.0 (C), 134.4 (C), 129.4 (CH), 129.2 (2 x CH), 128.5 (2 x CH), 127.7 (2 x CH), 118.6 (CH), 114.7 (2 x CH), 55.4 (CH_3), 45.3 (CH_2), 40.1 (CH_2), 35.9 (CH_2), 7.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{21}H_{24}NO_3$ $[M+H]^+$: 338.1751, found: 338.1752.



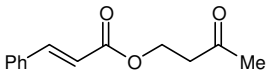
***N*-Benzyl-*N*-(3-oxobutyl)-3-methylbut-2-enamide (272)**. The title compound was prepared according to General Procedure B from methyl vinyl ketone (1.88 mL, 22.0 mmol), benzylamine (2.18 mL, 20.0 mmol) and the acid chloride (prepared according General Procedure A) derived from 3,3-dimethylacrylic acid (2.87 g, 24.2 mmol) for a reaction time of 16 h. The product was purified by column chromatography (40% EtOAc/petrol) to give yellow oil (2.72 g, 52%) as a 2:1 mixture of rotamers. IR (film) 2912, 1714 (C=O),

1620 (C=C), 1452, 1371, 1163, 942, 846, 735, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.34-7.14 (5H, m, Ar**H**), 5.83 (1H, s, =C**H**), 4.58 (2H, s, C$\mathbf{H}_2$Ph), 3.54 (2H, t, *J* = 6.8 Hz, C$\mathbf{H}_2$N), 2.75 (2H, t, *J* = 6.8 Hz, C$\mathbf{H}_2$CH_2N), 2.09 (3H, s, C$\mathbf{H}_3$C=O), 1.96 (3H, s, (C$\mathbf{H}_3$)$_2$C), 1.78 (3H, s, (C$\mathbf{H}_3$)$_2$C); (Minor rotamer) δ 7.34-7.14 (5H, m, Ar**H**), 5.91 (1H, s, =C**H**), 4.60 (2H, s, C$\mathbf{H}_2$Ph), 3.54 (2H, t, *J* = 7.2 Hz, C$\mathbf{H}_2$N), 2.59 (2H, t, *J* = 7.2 Hz, C$\mathbf{H}_2$CH_2N), 2.03 (3H, s, C$\mathbf{H}_3$C=O), 1.99 (3H, s, (C$\mathbf{H}_3$)$_2$C), 1.85 (3H, s, (C$\mathbf{H}_3$)$_2$C); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.2 (C), 206.0 (C), 168.6 (C), 168.0 (C), 147.8 (C), 137.6 (C), 137.0 (C), 128.6 (CH), 128.3 (CH), 127.7 (CH), 127.3 (CH), 127.1 (CH), 126.5 (CH), 117.5 (CH), 117.2 (CH), 52.3 (CH_2), 48.0 (CH_2), 42.2 (CH_2), 42.0 (CH_2), 41.6 (CH_2), 40.9 (CH_2), 30.0 (CH_3), 29.8 (CH_3), 26.3 (CH_3), 26.1 (CH_3), 20.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{22}NO_2$ $[M+H]^+$: 260.1645, found: 260.1644.

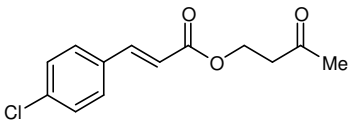


Ethyl (*E*)-3-[*N*-benzyl-*N*-(3-oxobutyl)carbamoyl]acrylate (274). The title compound was prepared according to General Procedure B from methyl vinyl ketone (1.88 mL, 22.0 mmol), benzylamine (2.18 mL, 20.0 mmol) and the acid chloride (prepared according to General Procedure A) derived from mono-ethyl fumarate (3.93 g, 24.2 mmol) for a reaction time of 16 h. The product was purified by column chromatography (40% EtOAc/petrol) to give light yellow solid (2.51g, 55 %) as a 2:1 mixture of rotamers. IR ($CHCl_3$) 2983, 1716 (C=O), 1651 (C=O), 1625 (C=C), 1447, 1297, 1163, 1031, 973, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.37-7.15 (6H, m, Ar**H** and =C**H**), 6.84 (1H, d, *J* = 15.3 Hz, =C**H**), 4.68 (2H, s, C$\mathbf{H}_2$Ph), 4.28-4.17 (2H, m, OC$\mathbf{H}_2$), 3.61 (2H, t, *J* = 6.4 Hz, CH_2C$\mathbf{H}_2$N), 2.79 (2H, t, *J* = 6.4 Hz, C$\mathbf{H}_2$$CH_2$N), 2.10 (3H, s, C$\mathbf{H}_3$C=O), 1.33-1.25 (3H, m, OCH_2C$\mathbf{H}_3$); (Minor rotamer) δ 7.46 (1H, d, *J* = 15.4 Hz, =C**H**)**,** 7.37-7.15 (5H, m, Ar**H** and =C**H**), 6.88 (1H, d, *J* = 15.4 Hz, =C**H**), 4.65 (2H, s, C$\mathbf{H}_2$Ph), 4.28-4.17 (2H, m, OC$\mathbf{H}_2$), 3.63 (2H, t, *J* = 6.8 Hz, CH_2C$\mathbf{H}_2$N), 2.63 (2H, t, *J* = 6.8 Hz, C$\mathbf{H}_2$$CH_2$N), 2.04 (3H, s, C$\mathbf{H}_3$C=O), 1.33-1.25 (3H, m, OCH_2C$\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 206.8 (C), 205.3 (C), 165.4 (C), 165.3 (C), 165.1 (C), 164.7 (C),

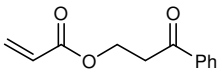
136.9 (C), 136.2 (C), 133.4 (CH), 131.9 (CH), 131.7 (CH), 128.8 (CH), 128.6 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 126.5 (CH), 60.9 (CH_2), 52.4 (CH_2), 49.2 (CH_2), 42.5 (CH_2), 42.2 (CH_2), 41.9 (CH_2), 41.4 (CH_2), 29.9 (CH_3), 29.8 (CH_3), 13.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{22}NO_4$ $[M+H]^+$: 304.1543, found: 304.1541.



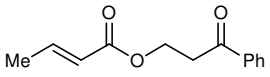
3-Oxobutyl (*E*)-3-phenylpropenoate (245).[iii] Prepared according to a previously reported procedure. [iii]



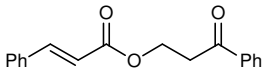
3-Oxobutyl (*E*)-3-(4-chlorophenyl)propenoate (247b). Prepared according to a previously reported procedure.[iii]



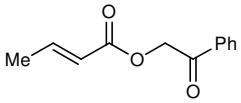
3-Oxo-3-phenylpropyl propenoate (249a). Prepared according to a previously reported procedure.[iii]



3-Oxo-3-phenylpropyl (*E*)-but-2-enoate (249b). Prepared according to a previously reported procedure.[iii]



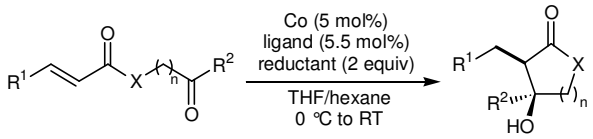
3-Oxo-3-phenylpropyl (*E*)-3-phenylpropenoate (249c). Prepared according to a previously reported procedure.[iii]



2-Oxo-2-phenylethyl (*E*)-but-2-enoate (251b). Prepared according to a previously reported procedure.[iii]

[iii] Lam, H. W.; Joensuu, P. M.; *Org. Lett.* **2005**, *7*, 4225 or Chapter One (Experimental)

Cobalt-Catalysed Reductive Aldol Cyclisations



Using $Co(acac)_2/Et_2Zn$: General Procedure D

A solution of the substrate (0.20 mmol) and $Co(acac)_2 \cdot 2H_2O$ (2.6 mg, 0.01 mmol) in THF (1.5 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 0.40 mL, 0.40 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 1 h and then at room temperature until complete consumption of starting material as observed by TLC analysis. Workup was carried out according to one of the procedures described below.

Using $CoCl_2/Cy_2PPh/Et_2Zn$: General Procedure E

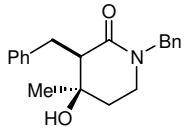
A solution of the substrate (0.20 mmol), $CoCl_2$ (1.3 mg, 0.01 mmol) and Cy_2PPh (3.0 mg, 0.011 mmol) in THF (1.5 mL) was stirred at room temperature for 30 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 0.40 mL, 0.40 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 1 h and then at room temperature until complete consumption of starting material as observed by TLC analysis. Workup was carried out according to one of the procedures described below.

Workup A

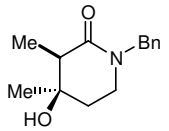
The reaction mixture was filtered through a short plug of SiO_2 (*ca*. 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclised product.

Workup B

The reaction was quenched carefully with saturated aqueous NH_4Cl solution (10 mL) and the mixture was then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclised product.

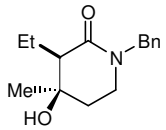


(±)-(3*R*,4*R*)-1,3-Dibenzyl-4-hydroxy-4-methylpiperidin-2-one (267a). The title compound was prepared according to General Procedure D from **266a** (61 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (60% EtOAc/petrol) to give a white solid (60 mg, 97%). m.p. 137-139 °C; IR ($CHCl_3$) 3399 (OH), 2928, 1617 (C=O), 1495, 1452, 1353, 1267, 1030, 740, 700 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.44-7.41 (2H, m, Ar**H**), 7.39-7.28 (7H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 4.76 (1H, d, *J* = 14.7 Hz, NC**H**$_2$Ph), 4.58 (1H, d, *J* = 14.7 Hz, NC**H**$_2$Ph), 3.47 (1H, ddd, *J* = 12.2, 9.1, 5.6 Hz, CH_2C**H**$_2$N), 3.37 (1H, dd, *J* = 14.4, 5.4 Hz, C**H**$_2$CH), 3.23 (1H, dd, *J* = 14.4, 5.4 Hz, C**H**$_2$CH), 3.16-3.09 (1H, m, CH_2C**H**$_2$N), 2.73 (1H, t, *J* = 5.4 Hz, CH_2C**H**), 1.92-1.78 (3H, m, C**H**$_2$$CH_2$N and O**H**), 1.31 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.1 (C), 141.9 (C), 137.1 (CH), 129.2 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 127.9 (2 x CH), 127.2 (C), 126.0 (C), 71.0 (C), 54.2 (CH), 50.4 (CH_2), 43.0 (CH_2), 35.2 (CH_2), 32.8 (CH_2), 28.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{24}NO_2$ $[M+H]^+$: 310.1802, found: 310.1802.

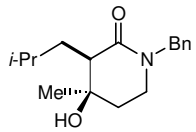


(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-3,4-dimethylpiperidin-2-one (269a). The title compound was prepared according to General Procedure D from **268a** (46 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (80% EtOAc/petrol) to give a white solid (41 mg, 88%). m.p.155-157 °C; IR ($CHCl_3$) 3335 (OH), 2980, 1605 (C=O), 1496, 1509, 1360, 1236, 1196, 927, 735 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.33-7.22 (5H, m, Ar**H**), 4.76 (1H, d, *J* = 14.8 Hz, C**H**$_2$Ph),

4.40 (1H, d, J = 14.8 Hz, C**H**$_2$Ph), 3.44 (1H, ddd, J = 12.1, 10.2, 5.3 Hz, CH$_2$C**H**$_2$N), 3.09 (1H, ddd, J = 12.1, 6.1, 3.9 Hz, CH$_2$C**H**$_2$N), 2.38 (1H, q, J = 7.3 Hz, CH$_3$C**H**), 1.99 (1H, br s, O**H**), 1.90 (1H, ddd, J = 13.6, 5.3, 3.9 Hz, C**H**$_2$CH$_2$N), 1.79 (1H, ddd, J = 13.6, 10.2, 6.1 Hz, C**H**$_2$CH$_2$N), 1.33 (3H, d, J = 7.3 Hz, C**H**$_3$CH), 1.31 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.7 (C), 137.2 (C), 128.5 (2 x CH), 127.8 (2 x CH), 127.2 (CH), 69.9 (C), 50.2 (CH$_2$), 46.7 (CH), 42.9 (CH$_2$), 34.8 (CH$_2$), 28.3 (CH$_3$), 10.4 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{14}H_{19}NO_2$ $[M+H]^+$: 234.1489, found: 234.1491.

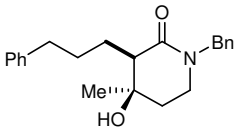


(±)-(3*R*,4*R*)-1-Benzyl-3-ethyl-4-hydroxy-4-methylpiperidin-2-one (269b). The title compound was prepared according to General Procedure D from **268b** (49 mg, 0.20 mmol) for a reaction time of 14 h followed by Workup A and purification by column chromatography (70% EtOAc/petrol) to give a white solid (48 mg, 97%). m.p. 94-96 °C; IR ($CHCl_3$) 3408 (OH), 2964, 1621 (C=O), 1496, 1453, 1269, 1149, 929, 732, 702 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.33-7.23 (5H, m, Ar**H**), 4.64 (1H, d, J = 14.7 Hz, NC**H**$_2$Ph), 4.51 (1H, d, J = 14.7 Hz, NC**H**$_2$Ph), 3.39-3.32 (1H, m, C**H**$_2$N), 3.10-3.03 (1H, m, C**H**$_2$N), 2.19 (1H, dd, J = 7.3, 3.8 Hz, CH$_2$C**H**), 1.96-1.81 (3H, m) and 1.79-1.69 (2H, m, C**H**$_2$CH$_2$N, CH$_3$C**H**$_2$, and O**H**), 1.30 (3H, s, C**H**$_3$COH), 1.21 (3H, t, J = 7.3 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.9 (C), 137.3 (C), 128.5 (2 x CH), 127.9 (2 x CH), 127.2 (CH), 70.6 (C), 54.2 (CH), 50.0 (CH$_2$), 43.1 (CH$_2$), 34.1 (CH$_2$), 28.3 (CH$_3$), 20.6 (CH$_2$), 14.6 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{15}H_{21}NO_2$ $[M+H]^+$: 248.1645, found: 248.1645.

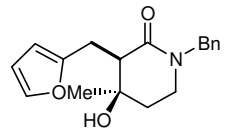


(±)-(3*R*,4*R*)-1-Benzyl-3-*iso*-butyl-4-hydroxy-4-methylpiperidin-2-one (269c). The title compound was prepared according to General Procedure D from **268c** (55 mg, 0.20 mmol) for a reaction time of 8 h using Workup A and purified by column chromatography (50% EtOAc/petrol) to give a white solid (55 mg, >99%). m.p. 113-115 °C; IR ($CHCl_3$) 3407 (OH), 2954, 1620 (C=O), 1495, 1452, 1267, 1150, 1116, 732, 700 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.37-7.27 (5H, m, Ar**H**), 4.72 (1H, d, J = 14.7 Hz,

C**H**$_2$Ph), 4.49 (1H, d, *J* = 14.8 Hz, C**H**$_2$Ph), 3.41 (1H, ddd, *J* = 12.3, 7.9, 5.8 Hz, CH$_2$C**H**$_2$N), 3.15-3.08 (1H, m, CH$_2$C**H**$_2$N), 2.32 (1H, dd, *J* = 8.2, 2.8 Hz, CH$_2$C**H**), 2.11-1.93 (2H, m), 1.84-1.71 (3H, m) and 1.46 (1H, ddd, *J* = 13.6, 9.2, 3.0 Hz, C**H**$_2$CH$_2$N, (CH$_3$)$_2$C**H**C**H**$_2$ and O**H**), 1.32 (3H, s, C**H**$_3$COH), 1.03 (3H, d, *J* = 6.7 Hz, (C**H**$_3$)$_2$CH), 0.99 (3H, d, *J* = 6.7 Hz, (C**H**$_3$)$_2$CH); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 172.3 (C), 137.3 (C), 128.5 (2 x CH), 127.9 (2 x CH), 127.2 (CH), 127.9 (2 x CH), 127.2 (CH), 70.6 (C), 50.2 (CH), 50.0 (CH$_2$), 43.0 (CH$_2$), 36.4 (CH$_2$), 34.2 (CH$_2$), 28.2 (CH$_3$), 27.7 (CH), 23.5 (CH$_3$), 21.7 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{17}H_{26}NO_2$ [M+H]$^+$: 276.1958, found: 276.1960.

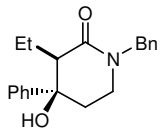


(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-4-methyl-3-(3-phenylpropyl)piperidin-2-one (269d). The title compound was prepared according to General Procedure D from **268d** (67 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (64 mg, 95%). m.p. 120-122 °C; IR ($CHCl_3$) 3410 (OH), 2928, 1620 (C=O), 1496, 1452, 1269, 1142, 931, 734, 700 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.34-7.16 (10H, m, Ar**H**), 4.66 (1H, d, *J* = 14.7 Hz, NC**H**$_2$Ph), 4.50 (1H, d, *J* = 14.7 Hz, NC**H**$_2$Ar), 3.39-3.31 (1H, m, C**H**$_2$N), 3.10-3.03 (1H, m, C**H**$_2$N), 2.72-2.68 (2H, m, PhC**H**$_2$CH$_2$), 2.29-2.26 (1H, m, CH$_2$C**H**), 2.18-2.04 (1H, m) and 1.94-1.67 (6H, m, PhCH$_2$C**H**$_2$C**H**$_2$, C**H**$_2$CH$_2$N and O**H**), 1.27 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.8 (C), 142.4 (C), 137.2 (C), 128.5 (2 x CH), 128.4 (2 x CH), 128.2 (2 x CH), 127.9 (2 x CH), 127.2 (CH), 125.6 (CH), 70.5 (C), 52.5 (CH), 50.0 (CH$_2$), 43.0 (CH$_2$), 36.2 (CH$_2$), 34.1 (CH$_2$), 31.5 (CH$_2$), 28.3 (CH$_3$), 27.1 (CH$_2$). HRMS (FAB) Exact mass calcd for $C_{22}H_{28}NO_2$ [M+H]$^+$: 338.2120, found: 338.2119.

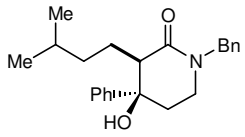


(±)-(3*R*,4*R*)-1-Benzyl-3-furan-2-ylmethyl-4-hydroxy-4-methylpiperidin-2-one (269e). The title compound was prepared according to General Procedure D from **268e** (59 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (59 mg, >99%). Slow

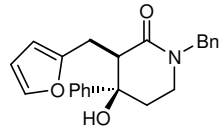
diffusion of petrol into a CH_2Cl_2 solution of **269e** was found to give colorless crystals suitable for X-ray diffraction. m.p. 120-122 °C; IR ($CHCl_3$) 3409 (OH), 2925, 1620 (C=O), 1496, 1452, 1270, 1146, 1008, 731, 705 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.37-7.26 (6H, m, Ar**H** and C**H**), 6.36-6.34 (1H, m, C**H**), 6.20-6.19 (1H, m, C**H**), 4.72 (1H, d, *J* = 14.7 Hz, NC**H**$_2$Ar), 4.57 (1H, d, *J* = 14.7 Hz, NC**H**$_2$Ar), 3.46 (1H, ddd, *J* = 12.1, 9.1, 5.9 Hz, CH_2C**H**$_2$N), 3.40 (1H, dd, *J* = 15.5, 4.9 Hz, C**H**$_2$CH), 3.32 (1H, dd, *J* = 15.5, 6.2 Hz, C**H**$_2$CH), 3.14-3.08 (1H, m, CH_2C**H**$_2$N), 2.76 (1H, app t, *J* = 5.6 Hz, CH_2C**H**), 2.11 (1H, br s, O**H**), 1.87-1.76 (2H, m, C**H**$_2$$CH_2$N), 1.29 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.1 (C), 154.5 (C), 140.7 (CH), 137.1 (C), 128.5 (2 x CH), 127.8 (2 x CH), 127.2 (CH), 110.8 (CH), 106.9 (CH), 70.2 (C), 51.5 (CH), 50.4 (CH_2), 42.9 (CH_2), 35.5 (CH_2), 28.4 (CH_2), 25.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{18}H_{22}NO_3$ $[M+H]^+$: 300.1594, found: 300.1593.



(±)-(3*R*,4*R*)-1-Benzyl-3-ethyl-4-hydroxy-4-phenylpiperidin-2-one (271a). The title compound was prepared according to General Procedure D from **270a** (61 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (58 mg, 94%). m.p. 199-201 °C; IR ($CHCl_3$) 3384 (OH), 2948, 1604 (C=O), 1491, 1445, 1238, 1146, 755, 705, 682 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.50-7.28 (10H, m, Ar**H**), 4.77 (1H, d, *J* = 14.7 Hz, C**H**$_2$Ph), 4.61 (1H, d, *J* = 14.7 Hz, C**H**$_2$Ph), 3.57 (1H, ddd, *J* = 12.1, 10.5, 5.2 Hz, CH_2C**H**$_2$N), 3.16 (1H, ddd, *J* = 12.1, 6.2, 3.5 Hz, CH_2C**H**$_2$N), 2.74 (1H, dd, *J* = 7.3, 3.4 Hz, CH_2C**H**), 2.26 (1H, ddd, *J* = 14.0, 10.5, 6.2 Hz, C**H**$_2$$CH_2$N), 2.01 (1H, ddd, *J* = 14.0, 5.2, 3.5 Hz, C**H**$_2$$CH_2$N), 1.98 (1H, br s, O**H**), 1.92-1.80 (1H, m, CH_3C**H**$_2$), 1.59-1.48 (1H, m, CH_3C**H**$_2$), 1.07 (3H, t, *J* = 7.4 Hz, C**H**$_3$$CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.8 (C), 145.9 (C), 137.3 (C), 128.6 (4 x CH), 127.9 (2 x CH), 127.3 (2 x CH), 124.5 (2 x CH), 75.6 (C), 52.7 (CH), 50.2 (CH_2), 43.3 (CH_2), 36.6 (CH_2), 20.2 (CH_2), 14.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{24}NO_2$ $[M+H]^+$: 310.1802, found: 310.1803.

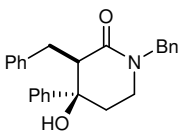


(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-3-(3-methylbutyl)-4-phenylpiperidin-2-one (271b). The title compound was prepared according to General Procedure D from **270b** (70 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (66 mg, 94%). m.p. 134-136 °C; IR ($CHCl_3$) 3399 (OH), 2952, 1617 (C=O), 1494, 1451, 1353, 1242, 758, 733, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.49-7.28 (10H, m, Ar**H**), 4.80 (1H, d, *J* = 14.7 Hz, C**H**$_2$Ph), 4.56 (1H, d, *J* = 14.7 Hz, C**H**$_2$Ph), 3.57 (1H, ddd, *J* = 12.1, 10.6, 5.2 Hz, CH_2C**H**$_2$N), 3.16 (1H, ddd, *J* = 12.1, 6.2, 3.5 Hz, CH_2C**H**$_2$N), 2.78 (1H, dd, *J* = 7.4, 3.1 Hz, C**H**C=O), 2.27 (1H, ddd, *J* = 14.0, 10.6, 6.2 Hz, C**H**$_2$$CH_2$N), 2.10 (1H, br s, O**H**), 2.02 (1H, ddd, *J* = 14.0, 5.2, 3.5 Hz, C**H**$_2$$CH_2$N), 1.87-1.77 (1H, m), 1.68-1.58 (1H, m), 1.48-1.38 (2H, m) and 1.15-1.05 (1H, m, $(CH_3)_2$C**H**C**H**$_2$C**H**$_2$), 0.78 (3H, d, *J* = 6.0 Hz, (C**H**$_3$)$_2$CH), 0.76 (3H, d, *J* = 6.0 Hz, (C**H**$_3$)$_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.9 (C), 145.8 (C), 137.2 (C), 128.5 (4 x CH), 127.9 (2 x CH), 127.2 (2 x CH), 124.6 (2 x CH), 75.4 (C), 51.5 (CH), 50.2 (CH_2), 43.3 (CH_2), 39.4 (CH_2), 36.3 (CH_2), 28.1 (CH), 24.6 (CH_2), 22.4 (CH_3), 22.2 (CH_3); HRMS (FAB) Exact mass calcd for $C_{23}H_{30}NO_2$ $[M+H]^+$: 352.2272, found: 352.2272.



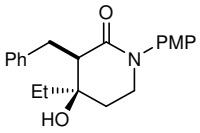
(±)-(3*R*,4*R*)-1-Benzyl-3-furan-2-ylmethyl-4-hydroxy-4-phenylpiperidin-2-one (271c). The title compound was prepared according to General Procedure D from **270c** (72 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (59 mg, 79%). m.p. 120-122 °C; IR ($CHCl_3$) 3398 (OH), 2925, 1624 (C=O), 1495, 1447, 1354, 1073, 911, 758, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.44-7.25 (10H, m, Ar**H**), 7.23 (1H, dd, *J* = 1.9, 0.8 Hz, C**H**), 6.21 (1H, dd, *J* = 3.1, 1.9 Hz, C**H**), 5.97 (1H, d, *J* = 3.1 Hz, C**H**), 4.68 (2H, s, NC**H**$_2$Ph), 3.58 (1H, ddd, *J* = 11.6, 11.6, 4.8 Hz, C**H**$_2$N), 3.32 (1H, t, *J* = 5.2 Hz, CH_2C**H**), 3.21 (1H, dd, *J* = 15.3, 5.2 Hz, C**H**$_2$CH), 3.16-3.10 (1H, m, C**H**$_2$N), 3.01 (1H, dd, *J* = 15.3, 5.2 Hz, C**H**$_2$CH), 2.59 (1H, br s, O**H**), 2.20 (1H, ddd, *J* = 13.9, 11.3, 6.1 Hz, C**H**$_2$$CH_2$N), 1.91 (1H, ddd, *J* = 13.9, 4.8, 2.7 Hz, C**H**$_2$$CH_2$N);

^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.0 (C), 153.7 (C), 145.4 (C), 140.8 (CH), 137.1 (C), 128.5 (4 x CH), 127.9 (2 x CH), 127.2 (CH), 127.1 (CH), 124.4 (2 x CH), 110.7 (CH), 107.4 (CH), 74.9 (C), 50.6 (CH), 50.5 (CH_2), 43.4 (CH_2), 37.1 (CH_2), 24.7 (CH_2); HRMS (ES) Mass calcd for $C_{23}H_{24}NO_3$ $[M+H]^+$: 362.1751, found: 362.1753.



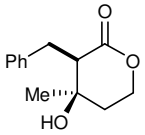
(±)-(3*R*,4*R*)-1,3-Dibenzyl-4-Hydroxy-4-phenylpiperidin-2-one(271d)

The title compound was prepared according to General Procedure D from **270d** (74 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (65 mg, 87%). m.p. 190-192 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.47-7.08 (15H, m, Ar**H**), 4.77 (1H, d, *J* = 14.8 Hz NC**H**$_2$Ar), 4.71 (1H, d, *J* = 14.8 Hz NC**H**$_2$Ar), 3.60 (1H, ddd, *J* = 12.2, 11.0, 5.2 Hz C**H**$_2$N), 3.26 (1H, dd, *J* = 6.2, 3.6 Hz CH_2C**H**), 3.19 (1H, ddd, *J* = 12.2, 6.2, 2.9 Hz C**H**$_2$N), 3.14 (1H, dd, *J* = 14.0, 3.6 Hz C**H**$_2$CH), 3.06 (1H, dd, *J* = 14.0, 6.2 Hz C**H**$_2$CH), 2.28 (1H, ddd, *J* = 14.0, 11.0, 6.2 Hz C**H**$_2$$CH_2$N), 2.05 (1H, br s, O**H**), 1.98 (1H, ddd, *J* = 14.0, 5.2, 2.9 Hz C**H**$_2$$CH_2$N); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.0 (C), 145.5 (C), 141.1 (C), 137.1 (C), 129.5 (2 x CH), 128.6 (4 x CH), 128.3 (2 x CH), 127.8 (2 x CH), 127.3 (2 x CH), 126.0 (CH), 124.7 (2 x CH), 75.9 (C), 53.4 (CH), 50.5 (CH_2), 43.5 (CH_2), 37.0 (CH_2), 31.2 (CH_2); IR ($CHCl_3$) 3399 (OH), 2925, 1617 (C=O), 1495, 1451, 1244, 1076, 755, 732, 699 cm^{-1}; HRMS (FAB) Exact mass calcd for $C_{25}H_{26}NO_2$ $[M+H]^+$: 372.1959, found: 372.1957.

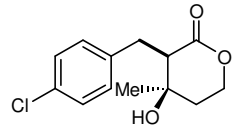


(±)-(3*R*,4*R*)-3-Benzyl-4-ethyl-4-hydroxy-1-(4-methoxyphenyl)piperidin-2-one (271e). The title compound was prepared according to General Procedure D from **270e** (67 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (50% EtOAc/hexane) to give a white solid (60 mg, 88%). m.p. 131-132 °C; IR ($CHCl_3$) 3419 (OH), 2963, 1633 (C=O), 1510, 1442, 1296, 1244, 829, 732, 701 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.42 (2H, dm, *J* = 7.1 Hz, Ar**H**), 7.34-7.30 (2H, m, Ar**H**), 7.24-7.18 (3H, m, Ar**H**), 6.96 (2H, dm, *J* = 9.0 Hz, Ar**H**), 3.87-

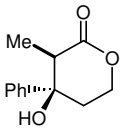
3.80 (1H, m, C**H**$_2$N), 3.84 (3H, s, OC**H**$_3$), 3.52-3.46 (1H, m, C**H**$_2$N), 3.35 (1H, dd, *J* = 14.3, 5.6 Hz, C**H**$_2$CH), 3.19 (1H, dd, *J* = 14.3, 4.8 Hz, C**H**$_2$CH), 2.84 (1H, app t, *J* = 5.2 Hz, CH$_2$C**H**), 2.05-1.93 (2H, m, C**H**$_2$CH$_2$N), 1.79-1.71 (2H, m, CH$_3$C**H**$_2$), 1.66 (1H, br s, O**H**), 0.95 (3H, t, *J* = 7.5 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.7 (C), 158.0 (C), 141.8 (C), 136.2 (C), 129.4 (2 x CH), 128.4 (2 x CH), 127.3 (2 x CH), 126.0 (CH), 114.4 (2 x CH), 73.5 (C), 55.4 (CH), 52.8 (CH_3), 47.2 (CH_2), 33.4 (CH_2), 32.2 (CH_2), 32.0 (CH_2), 7.8 (CH_3); HRMS (FAB) Exact mass calcd for $C_{21}H_{26}NO_3$ $[M+H]^+$: 340.1908, found: 340.1913.



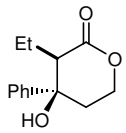
((±)-(3*R*,4*R*)-3-Benzyl-4-hydroxy-4-methyltetrahydropyran-2-one (246). The title compound was prepared according to General Procedure E from **245** (44 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup B and purification by column chromatography (50% EtOAc/petrol) to give a white solid (41 mg, 93%) that displayed identical spectroscopic data to those reported previously.[iii]



(±)-(3*R*,4*R*)-3-(4-Chlorobenzyl)-4-hydroxy-4-methyltetrahydro -pyran-2-one (248b). The title compound was prepared according to General Procedure E from **247b** (51 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup B and purification by column chromatography (50% EtOAc/petrol) to give a white solid (48 mg, 94%) that displayed identical spectroscopic data to those reported previously.[iii]

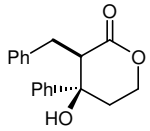


(±)-(3*R*,4*R*)-4-Hydroxy-3-methyl-3-phenyltetrahydropyran-2-one (250a). The title compound was prepared according to General Procedure E from **249a** (41 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup B and purification by column chromatography (50% EtOAc/petrol) to give a white solid (31 mg, 75%) that displayed identical spectroscopic data to those reported previously.[iii]

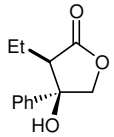


(±)-(3*R*,4*R*)-3-Ethyl-4-hydroxy-3-phenyltetrahydropyran-2-one (250b).

The title compound was prepared according to General Procedure E from **249b** (44 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup B and purification by column chromatography (50% EtOAc/petrol) to give a white solid (28 mg, 64%) that displayed identical spectroscopic data to those reported previously.[iii]



(±)-(3*R*,4*R*)-3-Benzyl-4-hydroxy-3-phenyltetrahydropyran-2-one (250c). The title compound was prepared according to General Procedure E from **249c** (56 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup B and purification by column chromatography (50% EtOAc/petrol) to give a to give a 10:1 inseparable diastereomeric mixture of products as a white solid (36 mg, 64%) that displayed identical spectroscopic data to those reported previously.[iii]

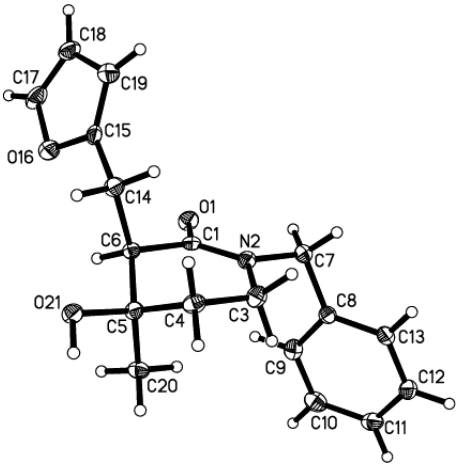


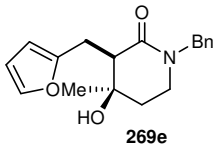
(±)-(3*R*,4*R*)-3-Ethyl-4-hydroxy-4-phenyltetrahydrofuran-2-one (252b).

The title compound was prepared according to General Procedure E from **251b** (41 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup B and purification by column chromatography (50% EtOAc/petrol) to give a white solid (22 mg, 53%) that displayed identical spectroscopic data to those reported previously.[iii]

Stereochemical Determinations

- The relative stereochemistry of **269e** was determined by X-ray crystallography. Crystal structure data deposited at the Cambridge Crystallographic Data Center; Deposition Number: CCDC 607850.



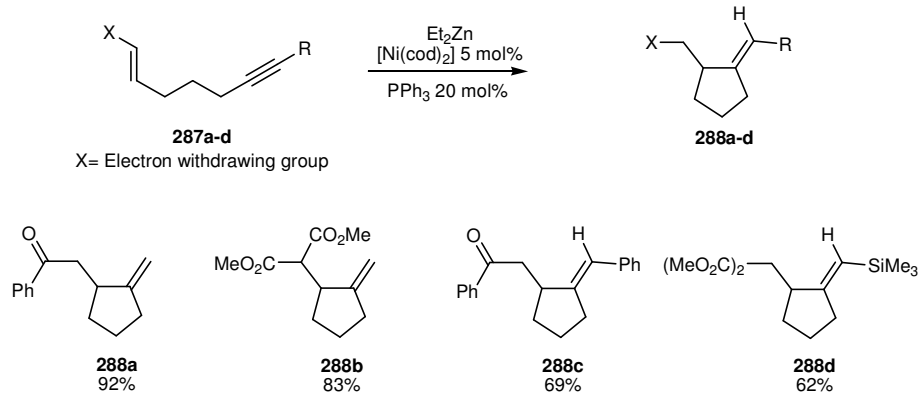


269e

4. Chapter 4: Nickel-Catalysed Reductive Aldol Cyclisations

4.1. Introduction

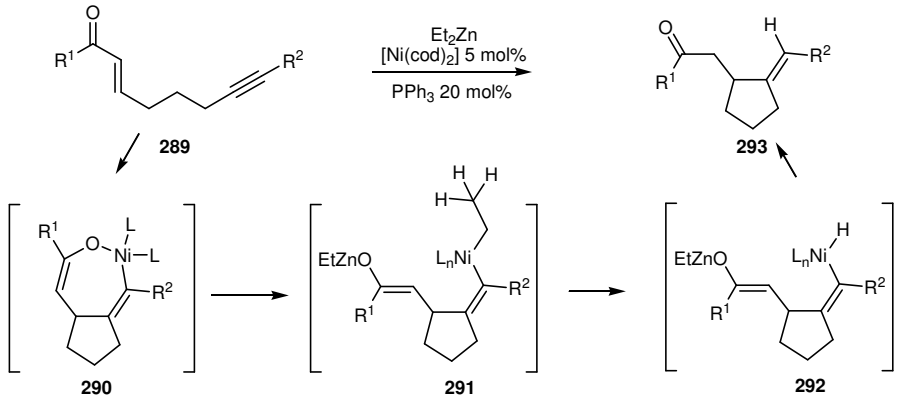
Nickel-catalysed reductive couplings and cyclisation reactions have recently emerged as powerful methods for accessing numerous polyfunctionalised products.[1] Typically operating under mild conditions, these three-component reactions enable rapid increases in molecular complexity from relatively simple starting materials, with often high levels of diastereo- and enantiocontrol. Using reductants such as triethylborane, diethylzinc and silanes, a variety of reactions have been developed that couple unsaturated species such as alkynes, 1,3-dienes, 1,3-enynes and allenes with an array of electrophiles that include aldehydes ketones imines and epoxides. With α,β-unsaturated carbonyl compounds as reaction partners, many processes reported to date result in carbon-carbon bond formation at the β-position. For example, Montgomery and co-workers have described reductive cyclisation of electron deficient alkenes with a range of tethered unsaturation where coupling at the β-position was the predominant pathway (Scheme 4.1).[2]



Scheme 4.1 Reductive cyclisation of electron deficient alkenes.

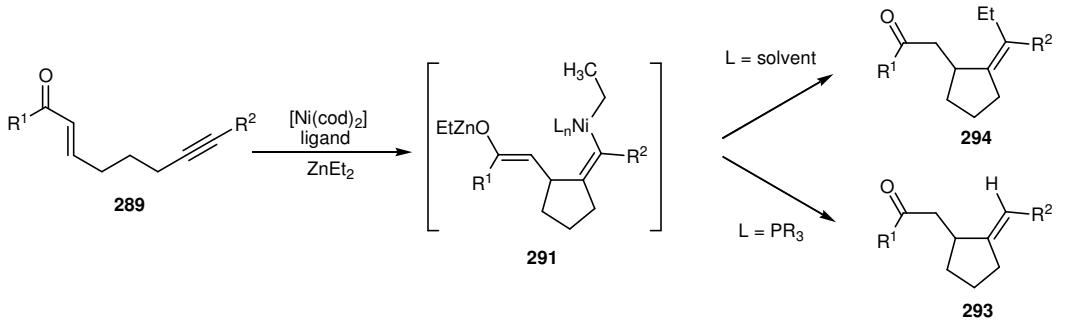
The proposed mechanism of these reactions is presented in Scheme 4.2. It is believed that oxidative cyclisation of an enone and an alkyne with Ni(0) produces a metallocycle **290**. This is followed by transmetallation of organometallic reductant to

generate intermediate **291**. Next, β-hydride elimination gives complex **292**. The product is formed by reductive elimination of **292**.



Scheme 4.2. Proposed mechanism of the Ni-catalysed reductive cyclisation.

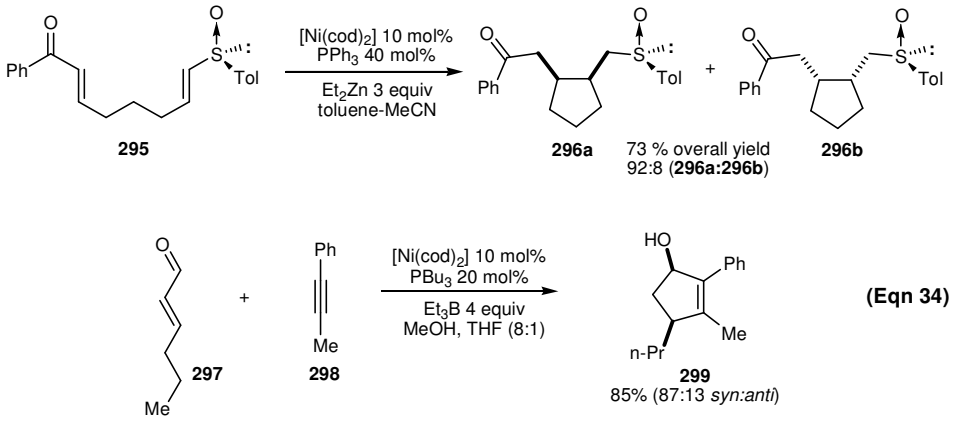
A very interesting ligand effect was also observed. When Ni(0) catalyst was used together with trialkylphosphane ligand, a hydride transfer product is observed. In the absence of any added ligand, the reductive elimination occurs from complex **291** to form a product where alkyl group transfer is observed **294**. It was simply assumed that coordination of an electron deficient phosphine ligand to the nickel facilitates the β-hydride elimination.



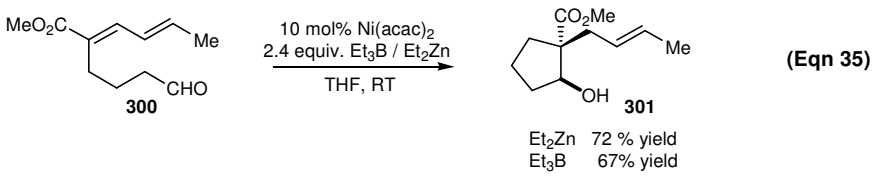
Scheme 4.3. Ligand effect in Ni-Catalysed Reductive Cyclisation.

More work on the reactions where carbon-carbon bond formation occurs at the β-position of the α,β-unsaturated carbonyl compounds was carried out by Tanaka and co-workers. They reported a very similar carbocyclisation of enones to vinyl sulfoxides (Eqn 33).[3] In addition, Montgomery's group have recently described a

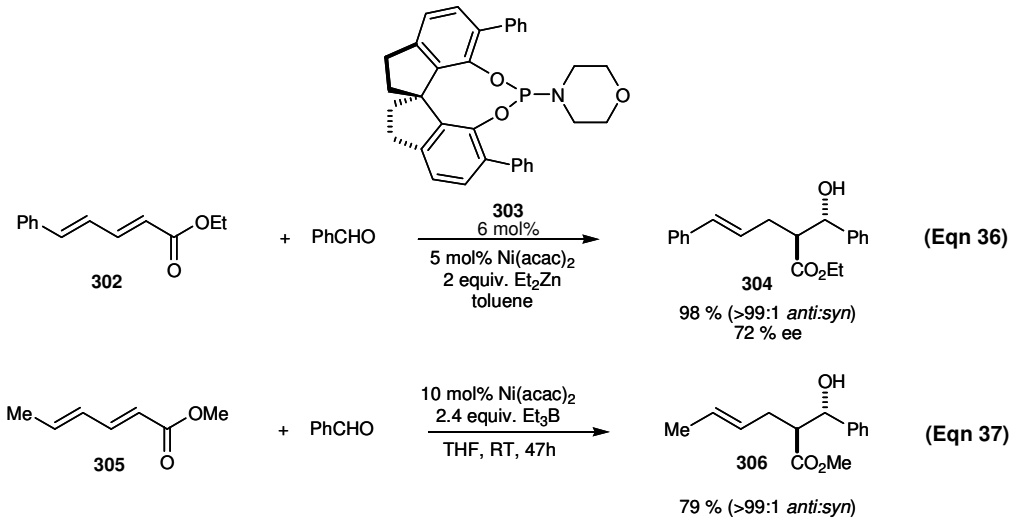
[3+2] reductive cycloaddtion of enals with alkynes where coupling occurred at the β-position (Eqn 34).[4]



In contrast, corresponding reactions where coupling occurs at the α-position of an α,β-unsaturated carbonyl have been rare. Tamaru and co-workers have reported an intramolecular homoallylation of aldehydes using $Ni(acac)_2$ and triethylborane or diethylzinc as a reductant.[5] These cyclisations are reminiscent of reductive aldol reactions: however, it is the diene functionality of the substrates that is essential for the reaction to proceed, rather than the α,β-unsaturated ester. In fact, most of the examples reported were in the absence of the ester group. The formation of the five-membered ring occurred readily at room temperature (Eqn 35). It is worth mentioning that while giving similar yields, the reductants triethylborane and diethylzinc displayed dramatic differences in their reactivity. When triethylborane was used, a reaction time of 34 h was required for the reaction to reach completion. When the reagent was changed to diethylzinc, the reaction time was reduced to 15 min.



Both Zhou[6] and Tamaru[7] have reported independently an intermolecular coupling of dienyl esters with aldehydes (Eqns 36 and 37). Again, $Ni(acac)_2$ was used as the nickel source, and either triethylborane or diethylzinc were used as reductant. Good yields and high diastereoselectivities were reported. Zhou utilised a phosphoramidate ligand **303** to perform this reaction enantioselectively. Modest enantiocontrol was observed for *anti*-product. Again the presence of the diene functionality played a vital role for a successful reaction.



Very recently, Montgomery reported the first example of a Ni-catalysed reductive aldol reaction between acrylate esters and aldehydes, where aryl halides were found to be essential reaction ingredients.[8] This work was discussed in detail in Chapter 1 (1.4.4).

4.2. Nickel-Catalysed Reductive Aldol Cyclisations

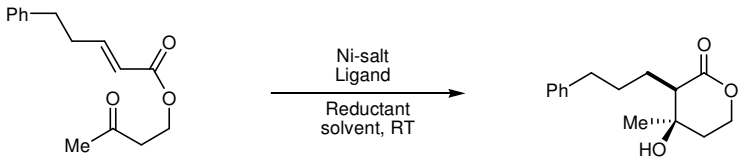
Given the wealth of literature that exists in the area of catalytic reductive couplings catalysed by nickel, the dearth of corresponding reductive aldol reactions was surprising. The development of new processes would considerably expand the repertoire of synthetic methods available to organonickel chemistry, and would provide complementary approaches for executing reductive aldol couplings.

As part of our research program directed at the development of new stereoselective transition metal-catalysed reductive cyclisations, we had already disclosed two different catalyst systems that were able to perform reactions of this type (discussed in Chapters 2 and 3).[9] Cobalt-catalysed cyclisations provided a big step forward in the reaction scope and yields of the cyclisation of substrates where α,β-unsaturated carbonyl moieties are tethered to a ketone through an amide linkage, in comparison to what had been achieved with our copper conditions.[9] We were still interested in improving the reaction with certain amide substrates that failed to cyclise under our cobalt conditions and to identify a catalyst system that would improve the results gained for the cyclisation of ester substrates. Nickel was expected to provide these improvement since it had been used in similar kind of reductive reactions (see introduction 4.1).

4.2.1. Reaction optimisation

Our studies into nickel-catalysed reactions began with a focus on the use of silanes/siloxanes as stoichiometric reductant. Various combinations of different nickel salts and silanes/siloxanes were screened without any success in the cyclisation of substrate **247e** (Table 4.1**,** Entries 1-11). Changing the reductant to Et_3B (Entry 12) did not alter the situation: however, when Et_2Zn was utilised, almost full conversion to product **248e** was observed (Entry 13). Other nickel salts failed to give the product in similar yields than $Ni(acac)_2$.

Table 4.1. Screening of the Reaction Conditions for the Ni-Catalysed Cyclisations[a]



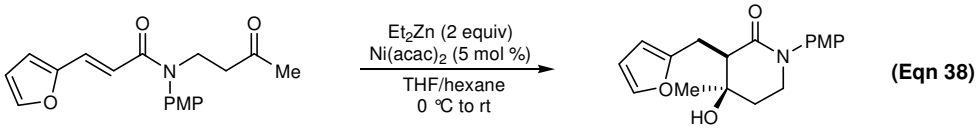
247e **248e**

Entry	Reagents	Ligand	Solvent	Conversion(%)[b]
1	$Ni(acac)_2$, Et_3SiH (2 equiv)	-	THF	-
2	$Ni(acac)_2$, Et_3SiH (2 equiv)	-	Tolune	-
3	$Ni(acac)_2$, Et_3SiH (2 equiv)	-	MeCN	-
4	$Ni(acac)_2$, Et_3SiH (2 equiv)	-	DCM	
5	$Ni(acac)_2$, TMDS (1 equiv)	-	THF	-
6	$Ni(acac)_2$, PMHS (2 equiv)	-	THF	-
7	$Ni(acac)_2$, Et_3SiH (2 equiv)	*rac*-BINAP	THF	-
8	$Ni(acac)_2$, Et_3SiH (2 equiv)	DPPF	THF	-
9	$NiBr_2(MeOCH_2CH_2OMe)$, Et_3SiH (2 equiv)	-	THF	-
10	$NiBr_2(PPh_3)_2$, Et_3SiH (2 equiv)	-	THF	-
11	$NiCl_2(Ph_2PCH_2CH_2PPh_2)$, Et_3SiH (2 equiv)	-	THF	-
12	$Ni(acac)_2$, Et_3B (2 equiv)	-	THF	-
13	$Ni(acac)_2$, Et_2Zn (2 equiv)	-	THF	>90
14	$NiBr_2(MeOCH_2CH_2OMe)$, Et_2Zn (2 equiv)	-	THF	~70
15	$NiBr_2(MeOCH_2CH_2OMe)$, Et_2Zn (2 equiv)	-	THF	~70

a) all reactions were perfomed on a 0.2 mmol scale. 10 mol% of Ni was used. b) Determined by ^1H NMR analysis

Further optimisation enabled the use of 5 mol% of $Ni(acac)_2$ and it was soon discovered that the addition of diethylzinc was best performed at 0 °C and after addition, the reaction was left to warm up to room temperature. Under these conditions the product **248e** was isolated in 85% yield (>19:1 d.r.) (Table 4.4, Entry 2) which is a great improvement in comparison to 61% yield when our copper conditions were used and < 5% conversion when cobalt-conditions were used.[10]

We immediately studied whether these reaction conditions would enable us to cyclise α,β-unsaturated amide substrates where there is a substitution at the double bond (most of these failed to cyclise under copper conditions).[10] When the reaction of substrate **307** was performed under these conditions, a 75% isolated yield of the major (*syn*) isomer was obtained, with the diastereoselectivity being 9:1. This result was comparable to those obtained under the cobalt conditions.[11]



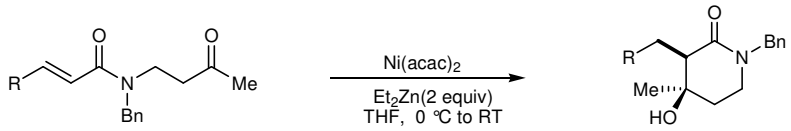
307 308 75 % (9:1 *syn:anti*) (Eqn 38)

Before exploring the scope of the reaction, there was a severe problem to overcome: the reproducibility of the results was very poor. When the cyclisation of substrate **307** was performed a second time, a lower yield and diasterereoselectivity were observed. It was quite soon realised that the reaction was sensitive to small changes in the procedure. If the time of the addition of diethylzinc was altered, the diastereoselectivity seemed to change. It was observed that the best results were obtained by the addition of diethylzinc in one portion.

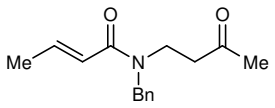
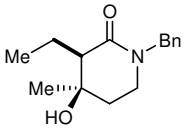
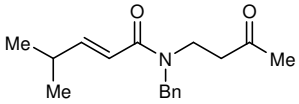
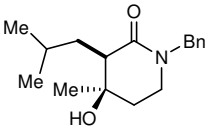
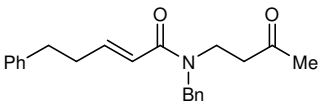
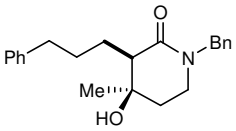
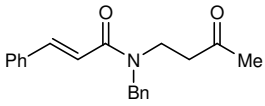
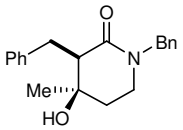
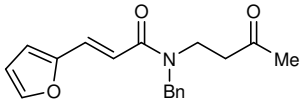
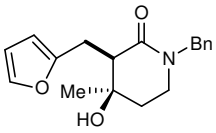
4.2.2. Reaction Scope for Amide Substrates

Our investigation into nickel-catalysed reductive aldol cyclisations commenced with reactions that provide six-membered β-hydroxylactams as the products (Table 4.2). A benzyl substituent at the nitrogen was utilised since these substrates systematically led to products in higher diastereoselectivities than those with *para*-methoxyphenyl substitution (see the differences between Eqn 38 and Table 4.2, Entry 5). A range of methyl ketone substrates (**266a, 268c-e)** that did not react under our copper conditions[10] smoothly underwent cyclisation to furnish 4-hydroxypiperidin-2-ones (**267a, 269c-e).** A variety of substituents on the alkene were well tolerated, varying from aliphatic (Entries 1-3) to aromatic (Entry 4) and heteroaromatic (Entry 5). The diastereoselectivities of the reactions were again very high (>19:1 *syn:anti*) and the yields nearly quantitative. Overall, the results presented in Table 4.2 are comparable to those that we had reported previously using $Co(acac)_2 \cdot H_2O$ as the pre-catalyst.[11]

Table 4.2. Cyclisation of the Methyl Ketone Amide Substrates[a]



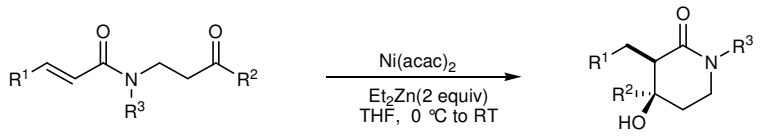
266a, 268b-e 267a, 269b-e

Entry	Substrate	Product		dr[b]	Yield(%)[c]
1	 **268b**		**269b**	>19:1	97
2	 **268c**		**269c**	>19:1	98
3	 **268d**		**269d**	>19:1	95
4	 **266a**		**267a**	>19:1	97
5	 **268e**		**269e**	>19:1	>99

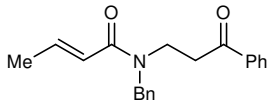
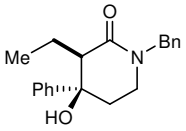
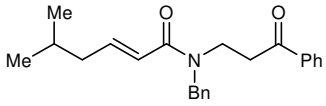
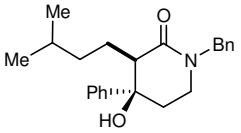
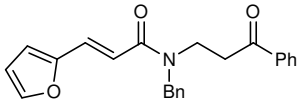
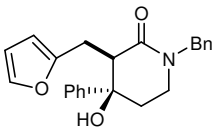
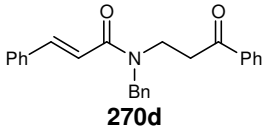
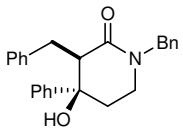
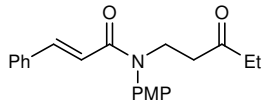
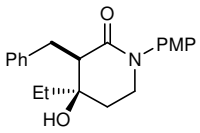
a) all reaction were performed on a 0.2 mmol scale b) Determined by ^{1}H NMR c) Isolated yields of the major diastereomer

Changing the methyl ketone to a phenyl ketone led to substrates that underwent cyclisations with slightly diminished yields. More significantly, the diastereoselectivities of these reactions were reduced from >19:1 to 12:1 and 9:1 for substrates with alkyl substituents on the acrylamide (Entries 1 and 2). This behaviour was not observed under the cobalt conditions.[11] Surprisingly, an aromatic substituent on the acrylamide led to much inferior reactivity and conversion to product **271d** was minimal (Entry 4). An ethyl ketone substrate led to product in comparable yield to those with methyl ketones (Entry 5).

Table 4.3. Cyclisations of the Phenyl Ketone Amide Substrates[a]



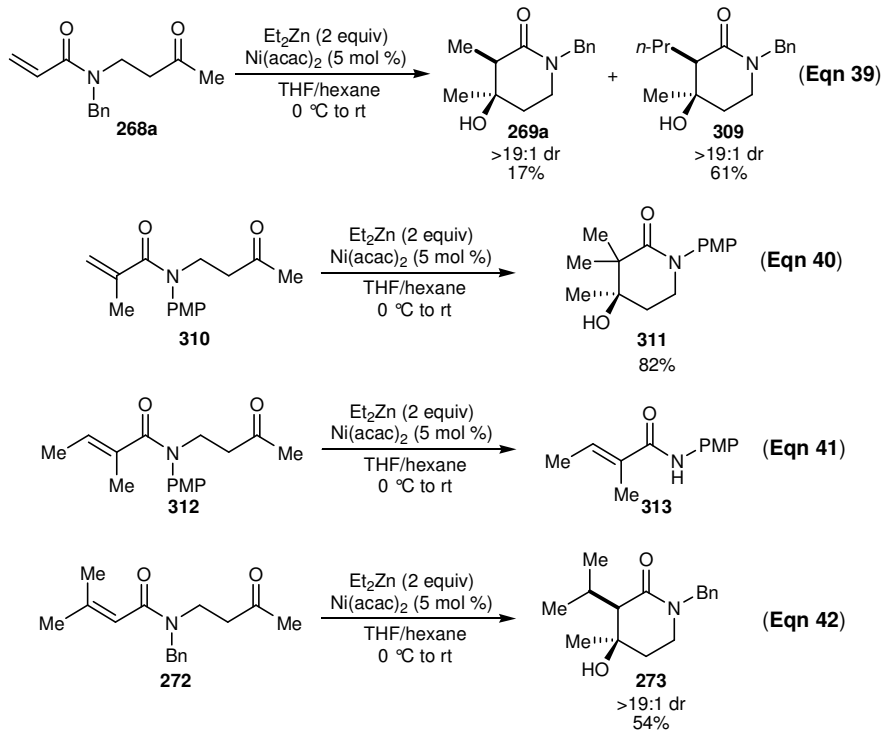
270a-e **271a-e**

Entry	Substrate	Product		dr[b]	Yield(%)[c]
1	 **270a**		**271a**	9:1	84
2	 **270b**		**271b**	12:1	84
3	 **270c**		**271c**	>19:1	79
4	 **270d**		**271d**	n.a.	<10[b]
5	 **270e**		**271e**	9:1	82

a) All reaction were performed on a 0.2 mmol scale b) Determined by ^{1}H NMR analysis c) Isolated yields of the major diastereomer

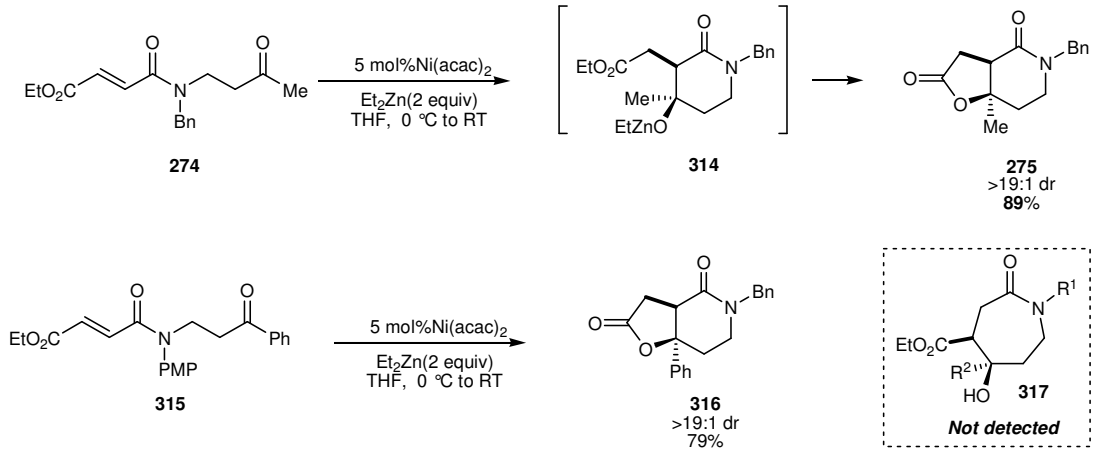
The simple β-unsubstituted acrylamide **268a** provided the anticipated reductive cyclisation product **269a** as only a minor component, with the major product obtained being *alkylative* cyclisation product **309** (Eqn 39). This result contrasts strongly with that we have obtained previously using $Co(acac)_2 \cdot H_2O$ as the pre-catalyst in place of $Ni(acac)_2$, where reductive cyclisation product was obtained in 88% yield with none of the alkylative product detected.[11] However, substitution at the α-position of the acrylamide re-established reductive cyclization as the dominant pathway, as illustrated by the cyclization of methacrylamide **310** to provide lactam

311 containing two contiguous quaternary centers in 82% yield (Eqn 40).[i] Efforts to extend the scope of these reactions to trisubstituted α,β-unsaturated amides were partially successful; although tiglic amide **312** did not undergo cyclization (furnishing elimination product **313** instead)[i] (Eqn 41), α,β-unsaturated amide **272** provided lactam **273** in 54% yield (Eqn 5). It should be noted that attempted cyclizations of substrates **272**, **310** and **312** using $Co(acac)_2 \cdot 2H_2O$[11] were completely unsuccessful.



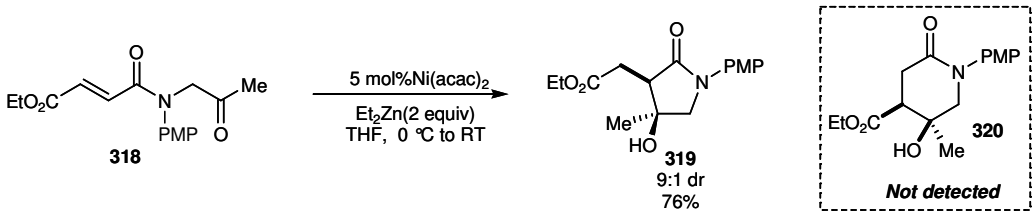
Substrate **274** afforded the bicyclic product **275,** as result of presumed tertiary zinc alkoxide **314** produced on initial reductive cyclisation undergoing lactonisation with pendant ester (Scheme 4.4). The phenyl ketone substrate **315** also underwent the same transformation. Notably, none of the alternative regioisomeric products **317**, resulting from cyclisation *α*- to the ester rather than the amide, were detected in the product mixtures.

[i] Reaction performed by Gordon J. Murray



Scheme 4.4. Formation of Bicyclic products

The regioselectivity of the reaction was further tested by reacting substrate **318** under these reaction conditions. On this occasion the anticipated product **320** should be strongly favoured by Baldwin's rule.[12] This product would be so called (enol-*exo*)- *exo-trig* system forming a six membered ring. An alternative product **319** could be the result of an (enol-*endo*)-*exo-trig* system forming a five membered ring, which is disfavoured by Baldwin's rule. To our surprise product **319** was isolated in 76% yield and product **320** was not detected. Lactonisation to provide a bicyclic product did not occur.



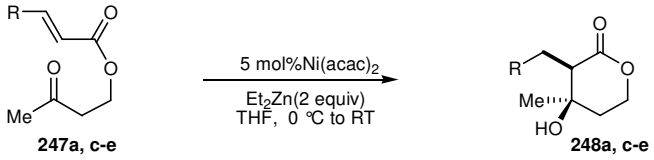
Scheme 4.5. Selective formation of the five-membered ring

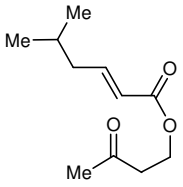
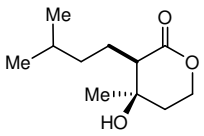
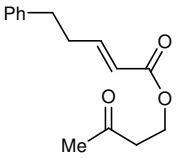
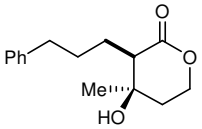
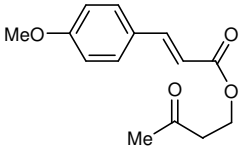
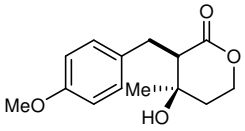
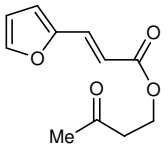
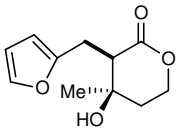
4.2.3. Reaction Scope for the Ester Substrates

The cyclisations of oxygen-linked precursors were studied next. The $Ni(acac)_2/Et_2Zn$ combination was found to lead to efficient cyclisations to afford a range of β-hydroxylactones with the substrates bearing methyl ketone. Furthermore,

compared to their amide-tethered counterparts (Table 4.4), these reactions display similar tolerance of substitution at both the α,β-unsaturated carbonyl component and at the ketone. However, attempts to prepare five-membered β-hydroxylactones using this chemistry have not yet been successful.

Table 4.4. Cyclisations of Methyl Ketone Ester Substrates[a]

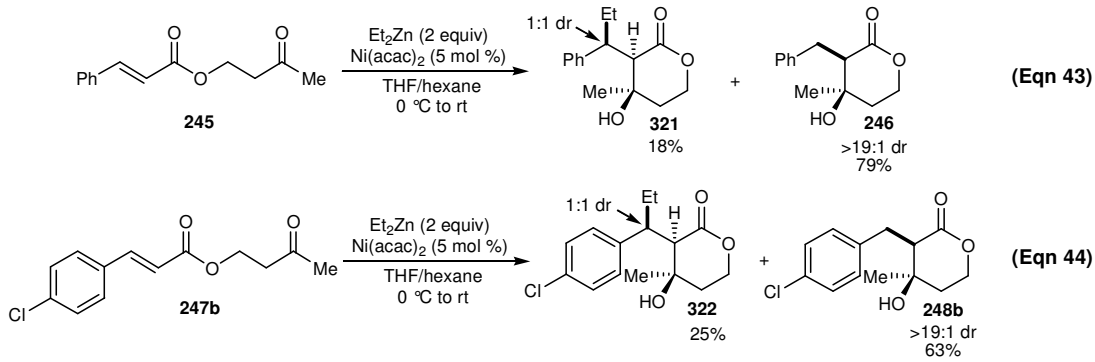


Entry	Substrate		Product		dr[b]	yield(%)[c]
1		**247d**		**248d**	>19:1	77
2		**247e**		**248e**	>19:1	85
3		**247a**		**248a**	>19:1	76
4		**247c**		**248c**	>19:1	81

a) all reactions were performed on a 0.2 mmol scale b) Determined by ^{1}H NMR c) Isolated yields of the major diastereomer

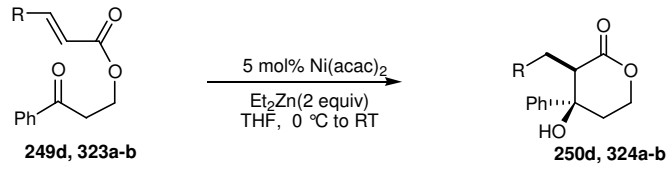
With cinnamate ester substrates however, an interesting electronic effect was observed. While a *p*-methoxy-substituted precursor gave the reductive aldol product **248a** in 76% yield (Table 4.4, Entry 3), less electron-rich substrates **245** and **247b** provided significant quantities of *alkylative* aldol products **321** and **322** respectively as *ca*. 1:1 mixtures of inseparable diastereoisomers (Eqn 43 and 44). It appears that as the aromatic group becomes more electron-deficient, the degree of alkylative aldol cyclisation becomes more significant. For lactones **321** and **322** we assume that the relative configuration at C3 and C4 are identical to those of the reductive aldol

products **246** and **248b** respectively, and that the diastereomeric compositions are due to epimers at the benzylic centres.

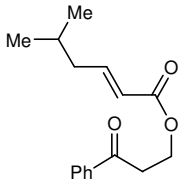
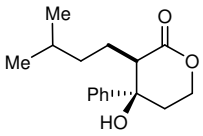
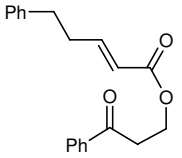
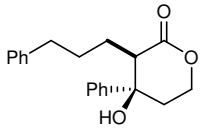
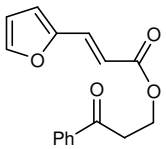
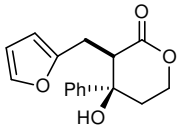


When the electrophile was changed from a methyl ketone to a phenyl ketone, *alkylative* cyclisation became a problem. In the cyclisation of substrates **259d** and **323b,** small quantities of *alkylative* aldol products were always present and the reductive aldol products could not be isolated from the mixture of addition products. When substrate **323a** was cyclised, no *alkylative* cyclisation product was observed, but on the other hand product was isolated as 5.5:1 mixture of diastereomers.

Table 4.5. Cyclisations of Methyl Ketone Ester Substrates[a]



249d, 323a-b — 250d, 324a-b

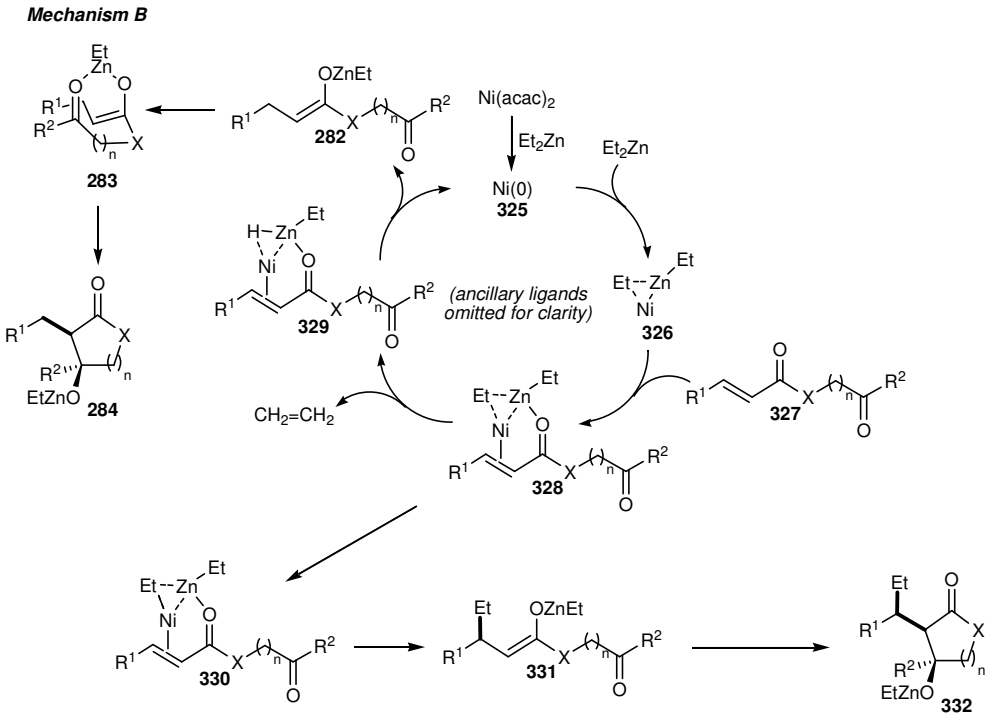
Entry	Substrate		Product		dr[b]	yield (%)[c]
1		**323a**		**324a**	5.5:1	84[d]
2		**249d**		**250d**	≥10:1	76[e]
3		**323b**		**324b**	n.d	75[f]

a) all reactions were performed on a 0.2 mmol scale b) Determined by ^{1}H NMR c) Isolated yields of the major diastereomer d) Isolated as 5.5:1 mixture of diastereomers [e]Accompanied by <5% of alkylative cyclisation product as an inseparable impurity. Cited yield of **250d** has been adjusted to reflect this impurity. [f] Accompanied by *ca.* 10% of alkylative cyclisation product as an inseparable impurity, making determination of the diastereomeric ratio of**324b** difficult. Cited yield of **324b** has been adjusted to reflect this impurity.

4.3. Mechanism

The discussion of the mechanism will be left to Chapter 5 and only the most probable catalytic cycle for the reaction will be discussed here. The mechanism follows closely the one shown in Chapter 3 in the case where the transition metal is cobalt (Scheme 3.1). Interaction of Ni(0) with Et_2Zn is assumed to lead to intermediate **326**, again containing a three-center-two-electron bridging interaction.[13] Coordination of **326** to the substrate would then provide **328**, which can either undergo *β*-hydride elimination to provide nickel hydride **329** or directly transmetallate the ethyl to nickel to form complex **330**. Reorganisation of **329** can then occur to provide zinc enolate **282**, which would undergo aldol-cyclisation, and Ni(0), which can reenter the catalytic cycle. In another possible route, reductive elimination of complex **330** would lead to an ethyl addition and formation of Zn-enolate. This is followed by aldol-cyclisation to give the *alkylative* product **332** that is observed in some cases. The observed stereochemical outcome of the reaction may

be explained by preferential formation of the *Z*-zinc enolate **283**, along with a chelated Zimmerman-Traxler-type transition state.[14]



Scheme 4.6. Proposed Mechanism of the Ni-Catalysed Reductive Cyclisations.

4.4. Conclusions

We have shown that in the presence of Et_2Zn, $Ni(acac)_2$ serves as a highly effective precatalyst for the reductive aldol cyclisation of substrates containing an α,β-unsaturated carbonyl moiety tethered to a ketone through either an amide or an ester. In these reactions, diethylzinc acts a stoichiometric reducing agent, formally delivering a hydride to the β-position of the α,β-unsaturated carbonyl component of the cyclisation precursor, leading to the formation of β-hydroxylactams and β-hydroxylactones with good to high levels of diastereoselection. A notable feature of these reactions is the broad tolerance of variation of the ketone, the β-substituent of the α,β-unsaturated carbonyl component, and the nitrogen protecting group in the case of amide-linked precursors to give a range of five- and six-membered products.

4.5. References

[1] For a excellent review, see: Montgomery, J. *Angew. Chem. Int. Ed.,* **2004**, *43*, 3890.
[2] a) Montgomery, J.; Savchenko, A., V. *J. Am. Chem. Soc.* **1996**, *118*, 2099. b) Montgomery, J.; Oblinger, E.; Savchenko, A., V. *J. Am. Chem. Soc.* **1997**, *119*, 4911.
[3] Maezakin, N.; Sawamoto, H.; Ishihara, H.; Tanaka, T. *Chem. Commun.* **2005**, 3992
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[11] See Chapter 3
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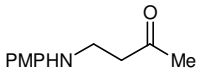
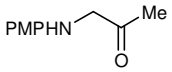
4.6. Experimental

The preparation of substrates **245** and **247a-247e** have been described in the Experimental part of Chapter 2

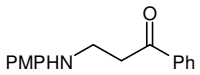
The preparation of substrates **266a, 268a-268e, 270a-270e, 272,** and **274** have been described in the Experimental part of Chapter 3



4-(4-Methoxyphenylamino)butan-2-one (333). Prepared according to a previously reported procedure.[i]

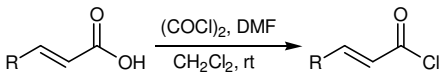


1-(4-Methoxyphenyl)aminopropanone (334). Prepared according to a previously reported procedure.[ii]



3-(4-Methoxyphenylamino)-1-phenylpropan-1-one (335). Prepared according to a previously reported procedure.[i]

Preparation of α,β-Unsaturated Acid Chlorides: General Procedure A



Oxalyl chloride (1.10 equiv) was added dropwise over 2 min to a solution of the appropriate α,β-unsaturated carboxylic acid (1.00 equiv) and DMF (0.25 equiv) in CH_2Cl_2 (0.55 M with respect to carboxylic acid) at 0 °C. The mixture was stirred at 0 °C until no more effervescence was observed (*ca.* 1 h) to give a solution of α,β-unsaturated acid chloride which was used directly in the next step.

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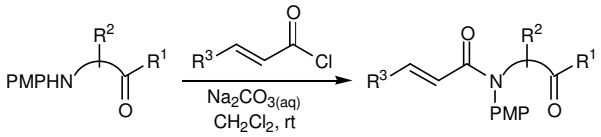
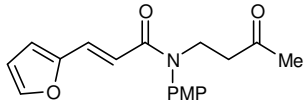
[i] Lam, H. W.; Murray, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743.

[ii]. Lam, H. W.; Joensuu, P. M.; Murray, G. J.; Fordyce, E. A. F.; Prieto, O.; Luebbers, T. *Org. Lett.* **2006**, *8*, 3729.

Preparation of Amide-Tethered Cyclisation Precursors: General Procedure B

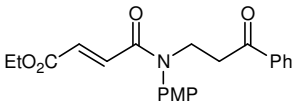


The appropriate α,β-unsaturated acid chloride (neat in the case of commercially available acid chlorides, or as a solution in CH_2Cl_2 prepared according to General Procedure A, 1.5 equiv) was added dropwise or portionwise to a vigorously stirred mixture of the appropriate aminoketone (1.0 equiv) in CH_2Cl_2 (1 mL/mmol of aminoketone) and saturated aqueous Na_2CO_3 solution (1 mL/mmol of aminoketone). The mixture was stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution and CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (x 3), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclisation substrate.

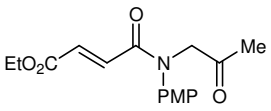


***N*-(4-Methoxyphenyl)-*N*-(3-oxobutyl)-(*E*)-3-furan-2-ylpropenamide (307)**. The title compound was prepared according to General Procedure B from the amine **333** (1.00 g, 5.20 mmol) and the acid chloride (prepared according to General Procedure A) derived from 3-(2-furyl)acrylic acid (1.10 g, 7.80 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol→50% EtOAc/petrol) to give a yellow/orange solid (1.01 g, 61%). m.p. 94-95 ºC; IR ($CHCl_3$) 2934, 1713 (C=O), 1664 (C=O), 1614, 1511, 1392, 1250, 1017, 840, 748 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.39 (1H, d, *J* = 15.3 Hz, C**H**=CHC=O), 7.31 (1H, d, *J* = 1.6 Hz, C**H**), 7.09 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.93 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.47 (1H, d, *J* = 3.3 Hz, C**H**), 6.36 (1H, dd, *J* = 3.3, 1.6 Hz, C**H**), 6.14 (1H, d, *J* = 15.3 Hz, C**H**C=O), 4.02 (2H, t, *J* = 7.4 Hz, C$\mathbf{H}_2$N), 3.84 (3H, s, OC$\mathbf{H}_3$), 2.77 (2H, t, *J* = 7.4 Hz, C$\mathbf{H}_2$$CH_2$N), 2.13 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 207.0 (C), 168.2 (C), 158.9 (C), 151.5 (C), 143.8 (CH), 134.4 (C), 129.3 (2 x CH), 128.5 (CH), 116.3 (CH), 114.8 (2

x CH), 113.7 (CH), 112.0 (CH), 55.4 (CH_3), 45.2 (CH_2), 41.5 (CH_2), 30.0 (CH_3); HRMS (ES) Mass calcd for $C_{18}H_{20}NO_4$ $[M+H]^+$: 314.1387, found: 314.1386.



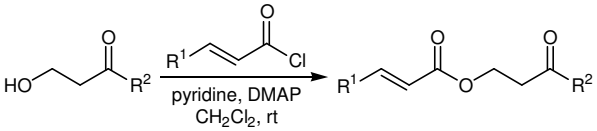
Ethyl (*E*)-3-[*N*-(4-methoxyphenyl)-*N*-(3-oxo-3-phenylpropyl)carbamoyl]acrylate (315). The title compound was prepared according to General Procedure B from the amine **335** (663 mg, 2.60 mmol) and the acid chloride (prepared according to General Procedure A) derived from mono-ethyl fumarate (562 mg, 3.90 mmol) for a reaction time of 6 h and purified by column chromatography (30% EtOAc/petrol→50% EtOAc/petrol) to give a yellow/brown oil that solidified upon standing to a yellow solid (841 mg, 85%). m.p. 58-59 °C; IR ($CHCl_3$) 2981, 1717 (C=O), 1682 (C=O), 1630 (C=C), 1510, 1161, 1030, 840, 742, 691 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* = 7.9 Hz, Ar**H**), 7.52-7.48 (1H, m, Ar**H**), 7.41-7.37 (2H, m, Ar**H**), 7.06 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.88 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.80-6.79 (2H, m, C**H**=C**H**), 4.19-4.09 (4H, m, OC$\mathbf{H}_2$ and C$\mathbf{H}_2$N), 3.77 (3H, s, OC$\mathbf{H}_3$), 3.30 (2H, t, *J* = 7.4 Hz, C$\mathbf{H}_2$$CH_2$N), 1.20 (3H, t, *J* = 7.1 Hz, $OCH_2C\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.9 (C), 165.4 (C), 164.2 (C), 159.2 (C), 136.4 (C), 134.1 (CH), 133.5 (C), 133.1 (CH), 130.9 (CH), 128.8 (2 x CH), 128.4 (2 x CH), 127.9 (2 x CH), 114.9 (2 x CH), 60.8 (CH_2), 55.3 (CH_3), 46.2 (CH_2), 36.2 (CH_2), 13.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{24}NO_5$ $[M+H]^+$: 382.1649, found: 382.1648.



Ethyl (*E*)-3-[*N*-(4-methoxyphenyl)-*N*-(3-oxopropyl)carbamoyl] acrylate (318). The title compound was prepared according to General Procedure B from the amine **334** (1.07 g, 6.00 mmol) and the acid chloride (prepared according to General Procedure A) derived from mono-ethyl fumarate (1.37 g, 9.00 mmol) for a reaction time of 16 h and purified by column chromatography (50% EtOAc/hexanes) to give a beige solid (1.60 g, 86%). m.p. 49-50 °C; IR ($CHCl_3$) 2981, 1726 (C=O), 1656 (C=O), 1636 (C=C), 1512, 1426, 1030, 842, 735, 603 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.18 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.90-6.78 (2H, m, C**H**=C**H**), 6.88 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.49 (2H, s, C$\mathbf{H}_2$N), 4.14 (2H, q, *J* = 7.1 Hz, OC$\mathbf{H}_2$), 3.80 (3H, s, OC$\mathbf{H}_3$), 2.15 (3H,

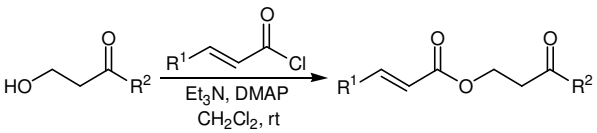
s, C**H**$_3$C=O), 1.22 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 201.4 (C), 165.3 (C), 164.2 (C), 159.3 (C), 134.1 (C), 133.2 (CH), 131.4 (CH), 128.8 (2 x CH), 114.8 (2 x CH), 60.8 (CH_2), 59.8 (CH_2), 55.3 (CH_3), 27.0 (CH_3), 13.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{20}NO_5$ $[M+H]^+$: 306.1336, found: 306.1336.

Preparation of Ester-Tethered Cyclisation Precursors: General Procedure C

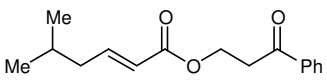


The appropriate α,β-unsaturated acid chloride (neat in the case of commercially available acid chlorides, or as a solution in CH_2Cl_2 prepared according to General Procedure A, 1.1 equiv) was added dropwise or portionwise to a vigorously stirred mixture of the appropriate hydroxyketone (1.0 equiv), DMAP (0.05 equiv) and pyridine (4.0 equiv) in CH_2Cl_2 (1.0 M with respect to hydroxyketone) over 5 min *via* cannula, and the reaction was stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution and Et_2O. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ solution (x 3), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclisation substrate.

Preparation of Ester-Tethered Cyclisation Precursors: General Procedure D

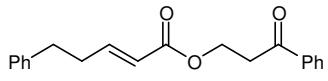


This method was identical to General Procedure C, except that Et_3N (1.5 equiv) was used in place of pyridine.

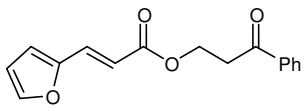


3-Oxo-3-phenylpropyl (*E*)-5-methylhex-2-enoate (323a). The title compound was prepared according to

General Procedure C from 3-hydroxypropiophenone (751 mg, 5.00 mmol) and the acid chloride (prepared according to General Procedure A) derived from (*E*)-5-methylhex-2-enoic acid (705 mg, 5.50 mmol) for a reaction time of 16 h and purified by column chromatography (20% EtOAc/petrol) to give a colorless oil (600 g, 46%). IR (film) 2958, 1720 (C=O), 1687 (C=O), 1654 (C=C), 1449, 1265, 1218, 984, 749, 690 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.93 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.56-7.52 (1H, m, Ar**H**), 7.45-7.41 (2H, m, Ar**H**), 6.94-6.83 (1H, m, C**H**=CHC=O), 5.75 (1H, dd, *J* = 15.7, 1.3 Hz, C**H**C=O), 4.55 (2H, t, *J* = 6.4 Hz, C$\mathbf{H}_2$O), 3.32 (2H, t, *J* = 6.4 Hz, C$\mathbf{H}_2$$CH_2$O), 2.03 (2H, app t, *J* = 7.1 Hz, CHC$\mathbf{H}_2$CH), 1.77-1.63 (1H, m, $(CH_3)_2$C**H**), 0.87 (6H, d, *J* = 6.7 Hz, (C$\mathbf{H}_3$)$_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.0 (C), 166.3 (C), 148.6 (CH), 136.5 (C), 133.2 (CH), 128.5 (2 x CH), 127.9 (2 x CH), 121.7 (CH), 59.4 (CH_2), 41.3 (CH_2), 37.3 (CH_2), 27.6 (CH), 22.2 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{21}O_3$ $[M+H]^+$: 261.1485, found: 261.1489.

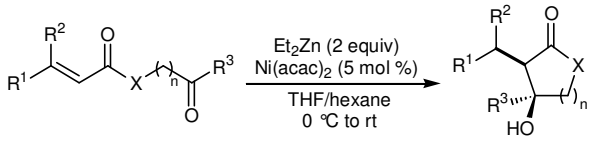


3-Oxo-3-phenylpropyl (*E*)-5-phenylpent-2-enoate (249d). The title compound was prepared according to General Procedure C from 3-hydroxypropiophenone (751 mg, 5.00 mmol) and the acid chloride (prepared according to General Procedure A) derived from (*E*)-5-phenylpent-2-enoic acid (969 mg, 5.50 mmol) for a reaction time of 16 h and purified by column chromatography (20% EtOAc/petrol) to give a colorless oil (926 g, 60%). IR (film) 2925, 1722 (C=O), 1691 (C=O), 1652 (C=C), 1450, 1178, 1088, 976, 750, 699 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.03-8.01 (2H, m, Ar**H**), 7.65-7.61 (1H, m, Ar**H**), 7.54-7.50 (2H, m, Ar**H**), 7.35-7.31 (2H, m, Ar**H**), 7.26-7.20 (3H, m, Ar**H**), 7.05 (1H, dt, *J* = 15.7, 6.8 Hz, C**H**=CHC=O), 5.88 (1H, dt, *J* = 15.7, 1.6 Hz, C**H**C=O), 4.64 (2H, t, *J* = 6.4 Hz, C$\mathbf{H}_2$O), 3.38 (2H, t, *J* = 6.4 Hz, C$\mathbf{H}_2$$CH_2$O), 2.80 (2H, t, *J* = 7.8 Hz, PhC$\mathbf{H}_2$), 2.58-2.52 (2H, m, C$\mathbf{H}_2$CH=); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 196.9 (C), 166.2 (C), 148.5 (CH), 140.6 (C), 136.5 (C), 133.2 (CH), 128.5 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 127.9 (2 x CH), 126.0 (CH), 121.3 (CH), 59.4 (CH_2), 37.3 (CH_2), 34.1 (CH_2), 33.7 (CH_2); HRMS (ES) Exact mass calcd for $C_{20}H_{24}NO_3$ $[M+NH_4]^+$: 326.1751, found: 326.1749.



3-Oxo-3-phenylpropyl (*E*)-3-furan-2-ylpropenoate (323b). The title compound was prepared according to General Procedure D from 3-hydroxypropiophenone (1.52 g, 10.0 mmol) and 3-(2-furyl)acrylic acid (1.52 g, 11.0 mmol) for a reaction time of 16 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (1.70 g, 63%). m.p. 85-87 °C; IR (film) 2959, 1707 (C=O), 1637 (C=C), 1448, 1210, 1162, 974, 929, 748, 689 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.02-8.00 (2H, m, Ar**H**), 7.64-7.63 (1H, m, Ar**H**), 7.53-7.49 (3H, m, Ar**H** and C**H**), 7.43 (1H, d, *J* = 15.7 Hz, C**H**=CHC=O), 6.62 (1H, d, *J* = 3.4 Hz, C**H**), 6.48 (1H, dd, *J* = 3.4, 1.8 Hz, C**H**), 6.32 (2H, d, *J* = 15.7 Hz, C**H**C=O), 4.67 (2H, t, *J* = 6.4 Hz, C$\mathbf{H}_2$O), 3.41 (2H, t, *J* = 6.4 Hz, C$\mathbf{H}_2$$CH_2$O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.0 (C), 166.8 (C), 150.7 (C), 144.7 (CH), 136.6 (C), 133.3 (CH), 131.3 (CH), 128.6 (2 x CH), 128.0 (2 x CH), 115.3 (CH), 114.8 (CH), 112.2 (CH), 59.7 (CH_2), 37.4 (CH_2); HRMS (ES) Exact mass calcd for $C_{16}H_{15}O_4$ $[M+H]^+$: 271.0965, found: 271.0966.

Nickel-Catalysed Reductive Aldol Cyclisations: General Procedure E



A solution of the substrate (0.20 mmol) and $Ni(acac)_2$ (2.7 mg, 0.01 mmol) in THF (1.5 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 0.40 mL, 0.40 mmol) was then added over 1 min. The reaction was stirred at 0 °C for 1 h and then at room temperature until complete consumption of starting material as observed by TLC analysis. Workup was carried out according to one of the procedures described below.

Nickel-Catalysed Reductive Aldol Cyclisations: General Procedure F

A solution of the substrate (1.00 mmol) and $Ni(acac)_2$ (13.5 mg, 0.01 mmol) in THF (7.5 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 2.0 mL, 2.0 mmol) was then added over 1 min.

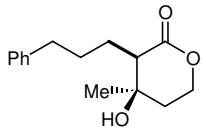
The reaction was stirred at 0 °C for 1 h and then at room temperature until complete consumption of starting material as observed by TLC analysis. Workup was carried out according to one of the procedures described below.

Workup A

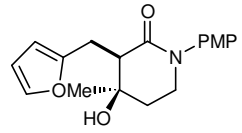
The reaction mixture was filtered through a short plug of SiO_2 (*ca*. 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclised product.

Workup B

The reaction was quenched carefully by the addition of 1 M HCl (1 mL), and the mixture was stirred for 1 h before being diluted with saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclised product.



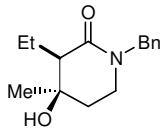
(±)-(3*R*,4*R*)-4-Hydroxy-4-methyl-3-(3-phenylpropyl)tetrahydropyran-2-one (248e). The title compound was prepared according to General Procedure E from **247e** (49 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup B and purification by column chromatography (30% EtOAc/petrol) to give a white solid (42 mg, 85%) that displayed identical spectroscopic data to those reported previously.[iii]



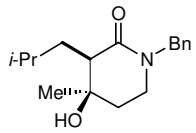
(±)-(3*R*,4*R*)-3-Furan-2-ylmethyl-4-hydroxy-1-(4-methoxyphenyl)-4-methylpiperidin-2-one (308). The title compound was prepared according to General Procedure E from

[iii] Lam, H. W.; Joensuu, P. M.; *Org. Lett.* **2005**, *7*, 4225 or Chapter 2 (experimental)

307 (63 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (30% EtOAc/$CHCl_3$) to give a white solid (47 mg, 75%). m.p. 150-152 °C; IR (film) 3410, 2934, 1631 (C=O), 1604, 1511, 1442, 1297, 1244, 1145, 1033 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.33 (1H, dd, *J* = 1.9, 0.8 Hz, C**H**), 7.14 (2H, dm, *J* = 9.0 Hz, Ar**H**), 6.90 (2H, dm, *J* = 9.0 Hz, Ar**H**), 6.31 (1H, dd, *J* = 3.2, 1.9 Hz, C**H**), 6.16 (1H, dd, *J* = 3.2, 0.8 Hz, C**H**), 3.84 (1H, ddd, *J* = 12.2, 10.0, 5.2 Hz, CH_2CH_2N), 3.80 (3H, s, OCH_3), 3.45-3.39 (1H, m, CH_2CH_2N), 3.37 (1H, dd, *J* = 15.6, 5.0 Hz, CH_2CH), 3.25 (1H, dd, *J* = 15.6, 6.2 Hz, CH_2CH), 2.79 (1H, dd, *J* = 6.2, 5.0 Hz, CH_2CH), 2.18 (1H, s, O**H**), 2.02-1.94 (1H, m, CH_2CH_2N), 1.88 (1H, dt, *J* = 13.7, 4.9 Hz, CH_2CH_2N), 1.32 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.5 (C), 158.0 (C), 154.5 (C), 140.6 (CH), 136.2 (C), 127.3 (2 x CH), 114.4 (2 x CH), 110.9 (CH), 107.0 (CH), 70.3 (C), 55.4 (CH_3), 51.8 (CH), 47.2 (CH_2), 36.2 (CH_2), 28.6 (CH_3), 24.8 (CH_2); HRMS (FAB) Exact mass calcd for $C_{18}H_{22}NO_4$ $[M+H]^+$: 316.1543, found: 316.1542.

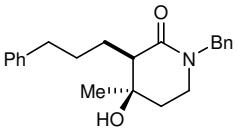


(±)-(3*R*,4*R*)-1-Benzyl-3-ethyl-4-hydroxy-4-methylpiperidin-2-one (269b). The title compound was prepared according to General Procedure E from **268b** (49 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (70% EtOAc/petrol) to give a white solid (48 mg, 97%) that displayed identical spectroscopic data to those reported previously.[iv]

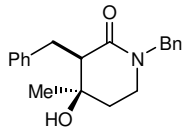


(±)-(3*R*,4*R*)-1-Benzyl-3-*iso*-butyl-4-hydroxy-4-methylpiperidin-2-one (269c). The title compound was prepared according to General Procedure E from **268c** (55 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (54 mg, 98%) that displayed identical spectroscopic data to those reported previously.[iv]

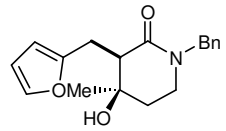
[iv] Lam, H. W.; Joensuu, P., M.; Murray, G. J.; Fordyce, E. A. F.; Prieto, O.; Luebbers, T. *Org. Lett.* **2006**, *8*, 3729 or Chapter 3 (experimental)



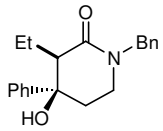
(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-4-methyl-3-(3-phenylpropyl)piperidin-2-one (269d). The title compound was prepared according to General Procedure E from **268d** (67 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (64 mg, 95%) that displayed identical spectroscopic data to those reported previously.[iv]



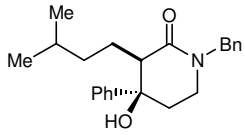
(±)-(3*R*,4*R*)-1,3-Dibenzyl-4-hydroxy-4-methylpiperidin-2-one (267a). The title compound was prepared according to General Procedure E from **266a** (61 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (60% EtOAc/petrol) to give a white solid (60 mg, 97%) that displayed identical spectroscopic data to those reported previously.[iv]



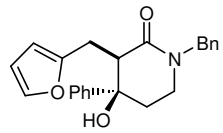
(±)-(3*R*,4*R*)-1-Benzyl-3-furan-2-ylmethyl-4-hydroxy-4-methylpiperidin-2-one (269e). The title compound was prepared according to General Procedure E from **268e** (59 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (59 mg, >99%) that displayed identical spectroscopic data to those reported previously.[iv]



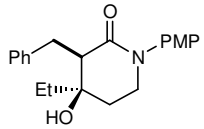
(±)-(3*R*,4*R*)-1-Benzyl-3-ethyl-4-hydroxy-4-phenylpiperidin-2-one (271a). The title compound was prepared according to General Procedure E from **270a** (61 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (52 mg, 84%) that displayed identical spectroscopic data to those reported previously.[iv]



(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-3-(3-methylbutyl)-4-phenylpiperidin-2-one (271b). The title compound was prepared according to General Procedure E from **270b** (70 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (59 mg, 84%) that displayed identical spectroscopic data to those reported previously.[iv]

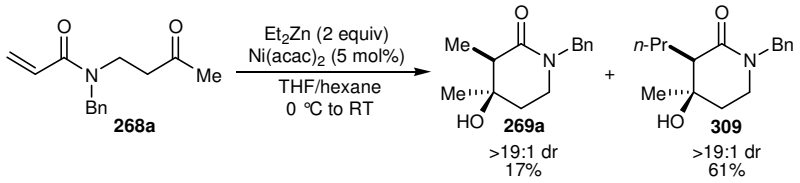


(±)-(3*R*,4*R*)-1-Benzyl-3-furan-2-ylmethyl-4-hydroxy-4-phenylpiperidin-2-one (271c). [iv] The title compound was prepared according to General Procedure E from **270c** (72 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (59 mg, 79%) that displayed identical spectroscopic data to those reported previously.[iv]



(±)-(3*R*,4*R*)-3-Benzyl-4-ethyl-4-hydroxy-1-(4-methoxyphenyl)piperidin-2-one (271e). The title compound was prepared according to General Procedure E from **270e** (67 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (40% EtOAc/petrol) to give a white solid (56 mg, 82%) that displayed identical spectroscopic data to those reported previously. [iv]

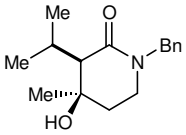
(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-3,4-dimethylpiperidin-2-one (269a) and (±)-(3*R*,4*R*)-1-benzyl-4-hydroxy-4-methyl-3-propylpiperidin-2-one (309).



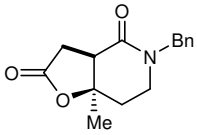
General Procedure G was followed using substrate **268a** (46 mg, 0.20 mmol) for a reaction time of 14 h and the reaction mixture was subjected to Workup A followed

by purification by column chromatography (50% EtOAc/petrol) to give the *lactam* **309** (32 mg, 61%) as a white solid, followed by the lactam **269a** (8 mg, 17%) as a white solid that displayed identical spectroscopic data to those reported previously.[iv]

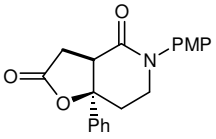
Data for **309**: m.p. 72-74 °C; IR ($CHCl_3$) 3399 (OH), 2959, 1619 (C=O), 1496, 1453, 1266, 1149, 935, 731, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.38-7.27 (5H, m, Ar**H**), 4.71 (1H, d, *J* = 14.6 Hz, NC**H**$_2$Ph), 4.52 (1H, d, *J* = 14.6 Hz, NC**H**$_2$Ph), 3.41 (1H, ddd, *J* = 12.3, 7.5, 5.9 Hz, CH_2C**H**$_2$N), 3.12 (1H, ddd, *J* = 12.3, 6.2, 6.2 Hz, CH_2C**H**$_2$N), 2.29 (1H, dd, *J* = 6.1, 4.3 Hz, CH_2C**H**), 2.00-1.94 (1H, m, C**H**$_2$$CH_2$N), 1.86-1.69 (4H, m, C**H**$_2$$CH_2$N, CH_3C**H**$_2$ and O**H**), 1.63-1.52 (2H, m, C**H**$_2$CH), 1.34 (3H, s, C**H**$_3$COH), 1.01 (3H, t, *J* = 7.1 Hz, C**H**$_3$$CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.0 (C), 137.3 (C), 128.5 (2 x CH), 128.0 (2 x CH), 127.3 (CH), 70.7 (C), 52.4 (CH), 50.1 (CH_2), 43.1 (CH_2), 34.2 (CH_2), 29.6 (CH_2), 28.3 (CH_3), 23.2 (CH_2), 14.3 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{24}NO_2$ $[M+H]^+$: 262.1802, found: 262.1800.



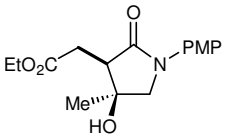
(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-4-methyl-3-*iso*-propylpiperidin-2-one (373). The title compound was prepared according to General Procedure E from **372** (52 mg, 0.20 mmol) for a reaction time of 14 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (28 mg, 54%). m.p. 108-110 °C; IR ($CHCl_3$) 3408 (OH), 2964, 1621 (C=O), 1496, 1453, 1265, 1147, 926, 737, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.36-7.27 (5H, m, Ar**H**), 4.62 (2H, s, C**H**$_2$Ph), 3.41 (1H, ddd, *J* = 12.5, 6.6, 5.9 Hz, CH_2C**H**$_2$N), 3.05 (1H, ddd, *J* = 12.5, 7.1, 5.9 Hz, CH_2C**H**$_2$N), 2.37-2.29 (2H, m, $(CH_3)_2$C**H** and C**H**C=O), 1.96 (1H, ddd, *J* = 13.4, 7.1, 5.9 Hz, C**H**$_2$$CH_2$N), 1.86 (1H, br s, O**H**), 1.72 (1H, ddd, *J* = 13.4, 6.6, 5.9 Hz, C**H**$_2$$CH_2$N), 1.32 (3H, s, C**H**$_3$COH), 1.32 (3H, d, *J* = 6.9 Hz, $(CH_3)_2$CH), 1.07 (3H, d, *J* = 6.8 Hz, $(CH_3)_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.5 (C), 137.2 (C), 128.4 (2 x CH), 128.2 (2 x CH), 127.2 (CH), 70.9 (C), 57.9 (CH), 49.9 (CH_2), 43.0 (CH_2), 34.1 (CH_2), 29.0 (CH_3), 26.8 (CH), 25.7 (CH_3), 19.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{24}NO_2$ $[M+H]^+$: 262.1802, found: 262.1802.



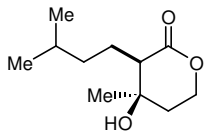
(±)-(3a*R*,7a*R*)-5-Benzyl-7a-methylhexahydrofuro[3,2-*c*]pyridine-2,4-dione (275). The title compound was prepared according to General Procedure E from **274** (61 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (46 mg, 89%). m.p. 114-115 °C; IR ($CHCl_3$) 3510 (OH), 2976, 1778 (C=O), 1643 (C=O), 1496, 1292, 1147, 948, 735, 708 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.36-7.27 (3H, m, Ar**H**), 7.24-7.22 (2H, m, Ar**H**), 4.76 (1H, d, *J* = 14.6 Hz, C**H**$_2$Ph), 4.46 (1H, d, *J* = 14.6 Hz, C**H**$_2$Ph), 3.42-3.35 (1H, m, $CH_2C\mathbf{H}_2N$), 3.21-3.14 (2H, m, $CH_2C\mathbf{H}_2N$ and C**H**$_2$CH), 3.04 (1H, dd, *J* = 10.4, 3.1 Hz, $CH_2C\mathbf{H}$), 2.92 (1H, dd, *J* = 18.1, 3.1 Hz, C**H**$_2$CH), 2.16-2.10 (1H, m, C**H**$_2CH_2N$), 1.90 (1H, ddd, *J* = 14.4, 9.9, 4.6 Hz, C**H**$_2CH_2N$), 1.50 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.2 (C), 168.3 (C), 136.0 (C), 128.5 (2 x CH), 127.6 (2 x CH), 127.4 (CH), 83.3 (C), 50.1 (CH), 46.2 (CH), 41.9 (CH_2), 33.8 (CH_2), 32.6 (CH_2), 26.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{18}NO_3$ $[M+H]^+$: 260.1281, found: 260.1281.



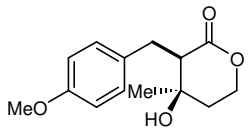
(±)-(3a*R*,7a*R*)-5-(4-Methoxyphenyl)-7a-phenylhexahydrofuro [3,2-*c*]pyridine-2,4-dione (316). The title compound was prepared according to General Procedure E from **315** (76 mg, 0.20 mmol) for a reaction time of 18 h followed by Workup A and purification by column chromatography (25% EtOAc/$CHCl_3$→35% EtOAc/$CHCl_3$) to give a white solid (53 mg, 79%). IR ($CHCl_3$) 2930, 1783 (C=O), 1650 (C=O), 1511, 1248, 1031 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.47-7.38 (5H, m, Ar**H**), 7.21 (2H, dm, *J* = 8.7 Hz, Ar**H**), 6.95 (2H, dm, *J* = 8.7 Hz, Ar**H**), 4.02 (1H, ddd, *J* = 13.0, 9.3, 5.4 Hz, C**H**$_2$N), 3.83 (3H, s, OC**H**$_3$), 3.63-3.57 (2H, m, C**H**$_2$N and C**H**$_2$CH), 2.99-2.87 (2H, m, C**H**$_2$C**H**), 2.52-2.41 (2H, m, C**H**$_2CH_2N$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.6 (C), 168.8 (C), 158.5 (C), 141.3 (C), 135.0 (C), 129.1 (2 x CH), 128.6 (CH), 126.9 (2 x CH), 124.3 (2 x CH), 114.6 (2 x CH), 86.4 (C), 55.5 (CH_3), 47.8 (CH), 47.0 (CH_2), 34.9 (CH_2), 33.6 (CH_2); HRMS (FAB) Mass calcd for $C_{20}H_{20}NO_4$ $[M+H]^+$: 338.1392, found: 338.1395.



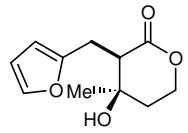
Ethyl [(3*R*,4*S*)-4-Hydroxy-1-(4-methoxyphenyl)-4-methyl-2-oxopyrrolidin-3-yl]acetate (319). The title compound was prepared according to General Procedure G from **318** (61 mg, 0.20 mmol) for a reaction time of 14 h followed by Workup A and purification by column chromatography (40% EtOAc/petrol) to give a white solid (47 mg, 76%). m.p. 79-81 °C. IR ($CHCl_3$) 3399 (OH), 2928, 1617 (C=O), 1495, 1451, 1269, 1146, 918, 732, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.45 (2H, d, *J* = 9.1 Hz, Ar**H**), 6.89 (2H, d, *J* = 9.1 Hz, Ar**H**), 4.48 (1H, br s, O**H**), 4.25-4.17 (2H, m, OC**H**$_2$), 3.88 (1H, d, *J* = 9.4 Hz, C**H**$_2$N), 3.79 (3H, s, OC**H**$_3$), 3.57 (1H, d, *J* = 9.4 Hz, C**H**$_2$N), 3.14 (1H, dd, *J* = 12.1, 3.7 Hz, CH$_2$C**H**), 3.13 (1H, dd, *J* = 18.7, 3.7 Hz, C**H**$_2$CH), 2.60 (1H, dd, *J* = 18.7, 12.1 Hz, C**H**$_2$CH), 1.35 (3H, s, C**H**$_3$COH), 1.31 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.1 (C), 170.9 (C), 156.7 (C), 132.0 (C), 121.7 (2 x CH), 114.0 (2 x CH), 72.9 (C), 61.4 (CH_2), 60.2 (CH_2), 55.4 (CH_3), 50.6 (CH), 30.8 (CH_2), 23.3 (CH_3), 14.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{22}NO_5$ $[M+H]^+$: 308.1492, found: 308.1494.



(±)-(3*R*,4*R*)-4-Hydroxy-4-methyl-3-(3-methylbutyl)tetrahydropyran-2-one (248d). The title compound was prepared according to General Procedure E from **247d** (40 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup B and purification by column chromatography (30% EtOAc/petrol) to give a colorless oil (31 mg, 77%) that displayed identical spectroscopic data to those reported previously.[iii]

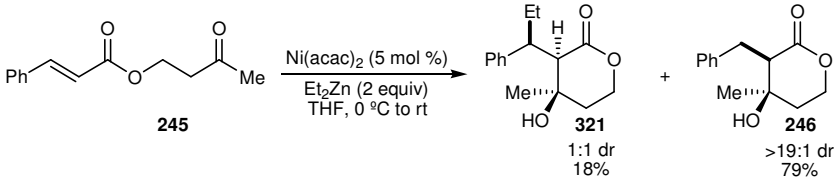


(±)-(3*R*,4*R*)-4-Hydroxy-3-(4-methoxybenzyl)-4-methyltetrahydropyran-2-one (248a). The title compound was prepared according to General Procedure E from **247a** (50 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup B and purification by column chromatography (40% EtOAc/petrol) to give a white solid (38 mg, 76%) that displayed identical spectroscopic data to those reported previously.[iii]



(±)-(3*R*,4*R*)-3-Furan-2-ylmethyl-4-hydroxy-4-methyltetrahydropyran-2-one (248c). The title compound was prepared according to General Procedure E from **247c** (42 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup B and purification by column chromatography (30% EtOAc/petrol) to give a white solid (34 mg, 81%) that displayed identical spectroscopic data to those reported previously.[iii]

(±)-(3*R*,4*R*)-4-Hydroxy-4-methyl-3-[(*RS*)-1-phenylpropyl]tetrahydropyran-2-one (321) and (±)-(3*R*,4*R*)-3-benzyl-4-hydroxy-4-methyltetrahydropyran-2-one (246)

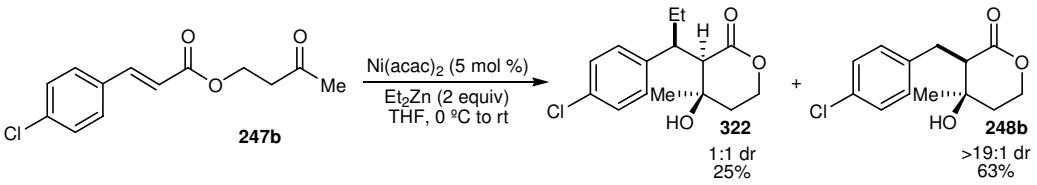


General Procedure F was followed using substrate **245** (218 mg, 1.00 mmol) for a reaction time of 16 h and the reaction mixture was subjected to Workup B followed by purification by column chromatography (20% EtOAc/petrol) to give the *lactone* **321** (45 mg, 18%) as a 1:1 mixture of diastereomers as a colorless gum, followed by the lactone **246** (174 mg, 79%) as a white solid that displayed identical spectroscopic data to those reported previously.[iii]

Data for **321** (1:1 mixture of diastereomers): IR ($CHCl_3$) 3436 (OH), 2967, 1709 (C=O), 1454, 1262, 1149, 1120, 1073, 766, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.47-7.24 (5H, m, Ar**H**), 4.60 (0.5H, ddd, *J* = 11.4, 8.0, 4.8 Hz, C**H**$_2$O), 4.32-4.13 (1.5H, m, C**H**$_2$O), 3.29-3.23 (0.5H, m, CH_2C**H**), 3.18-3.12 (0.5H, m, CH_2C**H**), 2.90 (1H, d, *J* = 4.0 Hz, C**H**C=O), 2.32-2.17 (0.5H, m, C**H**$_2$$CH_2$O), 2.08-1.71 (4.5H, m, C**H**$_2$$CH_2$O, CH_3C**H**$_2$ and O**H**), 1.43 (1.5H, s, C**H**$_3$COH), 1.39 (1.5H, s, C**H**$_3$COH), 0.86 (1.5H, t, *J* = 7.3 Hz, C**H**$_3$$CH_2$), 0.77 (1.5H, t, *J* = 7.3 Hz, C**H**$_3$$CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.6 (C), 171.4 (C), 144.4 (C), 142.2 (C), 129.5 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.1 (CH), 126.6 (CH), 71.1 (C), 70.9 (C), 65.1

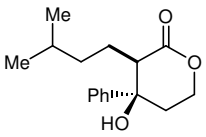
(CH_2), 65.0 (CH_2), 58.6 (CH), 57.0 (CH), 46.2 (CH), 45.3 (CH), 36.4 (CH_2), 35.7 (CH_2), 29.7 (CH_3), 29.5 (CH_3), 29.3 (CH_2), 26.9 (CH_2), 12.8 (CH_3), 12.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{24}NO_3$ $[M+NH]^+$: 266.1751, found: 266.1750.

(±)-(3*R*,4*R*)-4-Hydroxy-4-methyl-3-[(*RS*)-1-(4-chlorophenyl)propyl]tetrahydropyran-2-one (322) and (±)-(3*R*,4*R*)-3-(4-chlorobenzyl)-4-hydroxy-4-methyltetrahydropyran-2-one (248b)

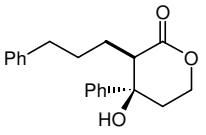


General Procedure F was followed using substrate **247b** (253 mg, 1.00 mmol) for a reaction time of 8 h and the reaction mixture was subjected to Workup B followed by purification by column chromatography (20% EtOAc/petrol) to give the *lactone* **322** (71 mg, 25%) as a 1:1 mixture of diastereomers as a white solid, followed by the lactone **248b** (160 mg, 63%) as a white solid that displayed identical spectroscopic data to those reported previously.[iii]

Data for **322** (1:1 mixture of diastereomers): m.p. 77-79 °C; IR ($CHCl_3$) 3430 (OH), 2931, 1708 (C=O), 1492, 1408, 1262, 1210, 1093, 1014, 830 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.43-7.40 (1H, m, Ar**H**), 7.37-7.29 (3H, m, Ar**H**), 4.60 (0.5H, ddd, *J* = 11.4, 8.5, 4.7 Hz, C**H**$_2$O), 4.31-4.12 (1.5H, m, C**H**$_2$O), 3.29-3.24 (0.5H, m, CH_2C**H**), 3.14-3.09 (0.5H, m, CH_2C**H**), 2.87 (0.5H, d, *J* = 3.3 Hz, C**H**C=O), 2.77 (0.5H, d, *J* = 3.4 Hz, C**H**C=O), 2.24-2.11 (0.5H, m, C**H**$_2$$CH_2$O), 2.06-1.69 (4.5H, m, C**H**$_2$$CH_2$O, CH_3C**H**$_2$ and O**H**), 1.43 (1.5H, s, C**H**$_3$COH), 1.42 (1.5H, s, C**H**$_3$COH), 0.83 (1.5H, t, *J* = 7.3 Hz, C**H**$_3$$CH_2$), 0.77 (1.5H, t, *J* = 7.3 Hz, C**H**$_3$$CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.4 (C), 171.3 (C), 143.4 (C), 140.7 (C), 132.7 (C), 132.0 (C), 130.9 (2 x CH), 130.1 (C), 128.7 (2 x CH), 128.6 (2 x CH), 70.9 (C), 70.0 (C), 65.2 (CH_2), 64.9 (CH_2), 58.3 (CH), 57.1 (CH), 45.4 (CH), 44.6 (CH), 36.4 (CH_2), 35.6 (CH_2), 29.6 (CH_3), 29.5 (CH_3), 29.3 (CH_2), 26.4 (CH_2), 12.7 (CH_3), 12.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{23}{}^{35}ClNO_3$ $[M+NH_4]^+$: 300.1361, found: 300.1362.

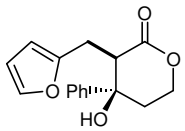


(±)-(3*R*,4*R*)-4-Hydroxy-3-(3-methylbutyl)-4-phenyltetrahydropyran-2-one (324a). General Procedure E was followed using **323a** (52 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup B and purification by column chromatography (30% EtOAc/petrol) to give the title compound and its diastereomer as a 5.5:1 inseparable mixture as a white solid (44 mg, 84%). m.p. 116-118 °C; IR ($CHCl_3$) 3366 (OH), 2953, 1703 (C=O), 1447, 1210, 1110, 1065, 934, 755, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.43-7.39 (4H, m, Ar**H**), 7.35-7.29 (1H, m, Ar**H**), 4.63 (1H, ddd, *J* = 11.4, 8.4, 4.9 Hz, C**H**$_2$O), 4.41 (1H, ddd, *J* = 11.4, 5.7, 5.3 Hz, C**H**$_2$O), 2.80 (1H, dd, *J* = 8.5, 2.6 Hz, C**H**C=O), 2.43 (1H, ddd, *J* = 14.7, 8.4, 5.3 Hz, C**H**$_2$CH$_2$O), 2.28 (1H, br s, O**H**), 2.13 (1H, ddd, *J* = 14.7, 5.7, 4.9 Hz, C**H**$_2$CH$_2$O), 1.83-1.73 (1H, m, C**H**$_2$CH$_2$CHC=O), 1.52-1.41 (1H, m, C**H**$_2$CH$_2$CHC=O), 1.39-1.30 (1H, m, C**H**$_2$CHC=O), 1.27-1.18 (1H, m, C**H**$_2$CHC=O), 1.06-0.94 (1H, m, (CH$_3$)$_2$C**H**), 0.72 (3H, d, *J* = 6.5 Hz, (C**H**$_3$)$_2$CH), 0.70 (3H, d, *J* = 6.5 Hz, (C**H**$_3$)$_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.3 (C), 145.2 (C), 128.7 (2 x CH), 127.5 (CH), 124.3 (2 x CH), 75.6 (C), 65.1 (CH_2), 51.2 (CH), 39.2 (CH_2), 38.3 (CH_2), 27.8 (CH), 22.9 (CH_2), 22.4 (CH_3), 22.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{26}NO_3$ $[M+NH_4]^+$: 280.1907, found: 280.1903.



(±)-(3*R*,4*R*)-4-Hydroxy-4-phenyl-3-(3-phenylpropyl)tetrahydropyran-2-one (250d). General Procedure E was followed using **249d** (62 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup B and purification by column chromatography (30% EtOAc/petrol) to give the title compound and the corresponding alkylative aldol cyclisation product as a >95:5 inseparable mixture as a white solid (50 mg, 76% (adjusted yield of **21f**)). m.p. 100-102 °C; IR ($CHCl_3$) 3366 (OH), 2953, 1703 (C=O), 1447, 1210, 1110, 1065, 934, 755, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.41-7.38 (4H, m, Ar**H**), 7.35-7.31 (1H, m, Ar**H**), 7.23-7.18 (2H, m, Ar**H**), 7.15-7.11 (1H, m, Ar**H**), 7.03-7.01 (2H, m, Ar**H**), 4.62 (1H, ddd, *J* = 11.5, 8.7, 4.8 Hz, C**H**$_2$O), 4.40 (1H, ddd, *J* = 11.5, 5.5, 5.5 Hz, C**H**$_2$O), 2.84 (1H, dd, *J* = 8.3, 2.7 Hz, C**H**C=O),

2.46 (2H, t, *J* = 7.7 Hz, PhC**H**$_2$), 2.43 (1H, ddd, *J* = 14.2, 8.7, 5.5 Hz, C**H**$_2$CH$_2$O), 2.31 (1H, br s, O**H**), 2.10 (1H, ddd, *J* = 14.2, 5.5, 4.8 Hz, C**H**$_2$CH$_2$O), 2.00-1.79 (2H, m, C**H**$_2$CH$_2$CHC=O), 1.50-1.42 (1H, m, C**H**$_2$CHC=O), 1.34-1.25 (1H, m, C**H**$_2$CHC=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.3 (C), 145.0 (C), 141.9 (C), 128.7 (2 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 127.5 (CH), 125.6 (CH), 124.3 (2 x CH), 75.4 (C), 65.1 (CH_2), 51.0 (CH), 39.1 (CH_2), 35.5 (CH_2), 30.5 (CH_2), 24.9 (CH_2); HRMS (ES) Exact mass calcd for $C_{20}H_{26}NO_3$ $[M+NH_4]^+$: 328.1907, found: 328.1906.



(±)-(3*R*,4*R*)-3-Furan-2-ylmethyl-4-hydroxy-4-phenyltetrahydropyran-2-one (324b). General Procedure E was followed using **323b** (54 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup B and purification by column chromatography (70% EtOAc/petrol) to give the title compound and the corresponding alkylative aldol cyclisation product as a 9:1 inseparable mixture as white solid (46 mg, 75% (adjusted yield of **21g**)). m.p. 108-110 °C; IR ($CHCl_3$) 3436 (OH), 2972, 1727 (C=O), 1447, 1408, 1266, 1198, 1011, 754, 701 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.45-7.38 (4H, m, Ar**H**), 7.33-7.27 (1H, m, Ar**H**), 7.20 (1H, dd, *J* = 1.9, 0.8 Hz, C**H**), 6.19 (1H, dd, *J* = 3.2, 1.9 Hz, C**H**), 5.96 (1H, dd, *J* = 3.2, 0.8 Hz, C**H**), 4.67 (1H, ddd, *J* = 11.4, 9.6, 4.6 Hz, C**H**$_2$O), 4.42 (1H, ddd, *J* = 11.4, 5.5, 4.6 Hz, C**H**$_2$O), 3.39 (1H, dd, *J* = 6.5, 4.5 Hz, C**H**C=O), 3.07 (1H, dd, *J* = 15.5, 6.5 Hz, C**H**$_2$CH), 2.93 (1H, dd, *J* = 15.5, 4.5 Hz, C**H**$_2$CH), 2.72 (1H, br s, O**H**), 2.43 (1H, ddd, *J* = 14.7, 9.6, 5.5 Hz, C**H**$_2$CH$_2$O), 2.08 (1H, ddd, *J* = 14.7, 9.6, 5.5 Hz, C**H**$_2$CH$_2$O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.9 (C), 152.7 (C), 144.4 (C), 141.0 (CH), 128.7 (2 x CH), 127.5 (CH), 124.3 (2 x CH), 110.7 (CH), 107.4 (CH), 75.0 (C), 65.3 (CH_2), 50.2 (CH), 39.5 (CH_2), 23.9 (CH_2); HRMS (ES) Exact mass calcd for $C_{16}H_{17}O_4$ $[M+H]^+$: 273.1121, found: 273.1120.

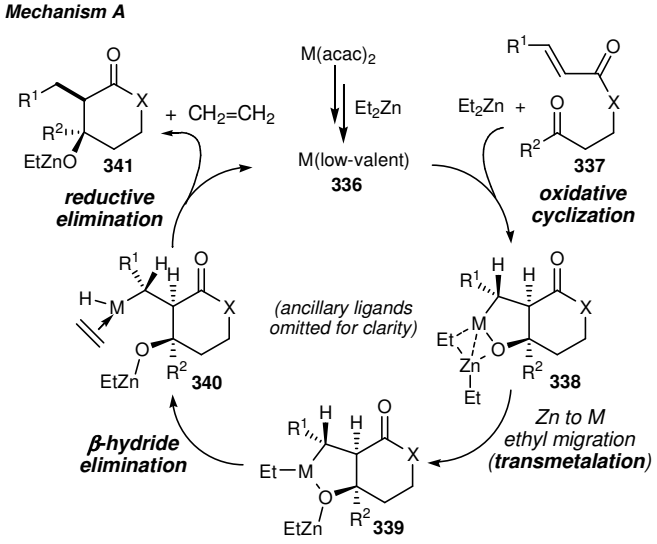
5. Chapter 5: Mechanisms of the Nickel- and Cobalt-Catalysed Reductive Aldol Cyclisations

5.1. Studies towards the mechanism

Numerous mechanistic possibilities (often speculative) have been advanced to explain the outcome of nickel-catalysed reductive couplings and cyclisations.[1] It is well known that treatment of $Ni(acac)_2$ with Et_2Zn leads to reduction of Ni(II) to Ni(0) (which is the generally accepted active catalytic species), and we assume that this initial step is also operative in the reductive aldol reactions described in chapter 4. We believe that $Co(acac)_2 \cdot H_2O$ behaves in very similar way although we do not know the oxidation state of the cobalt after it has reacted with Et_2Zn. This is the reason we will call the cobalt-species in reaction as "low-valent cobalt". In the mechanisms that we propose, we will generally talk of "metal" which in this context means nickel or cobalt. Based on prior literature precedent for nickel, two possible mechanistic pathways for the present reactions seemed reasonable.

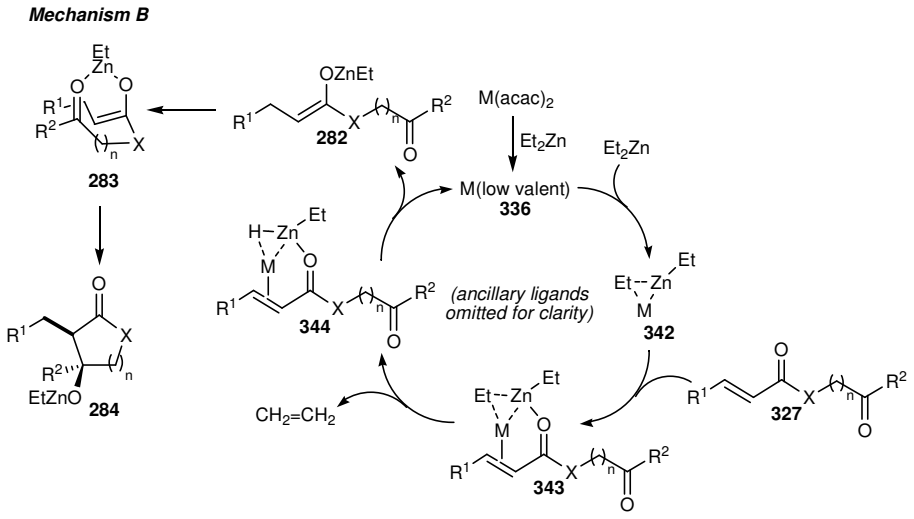
A significant number of nickel-catalysed reductive coupling and cyclisations are consistent with the intervention of metallacyclic intermediates, formed by the oxidative cyclisation of Ni(0) with two π-components.[1] Further support for the involvement of metallacycles in these reactions comes in the form of oxidative cyclisation products that have been isolated and characterised by X-ray crystallography.[2,3] A possible catalytic cycle invoking metallacycle participation for the reactions described herein is depicted in Scheme 5.1. Oxidative cyclisation of low-valent metal **336** (nickel or cobalt) with the alkene and the ketone of the substrate **337** would result in metallacycle **338**. By analogy with a detailed study conducted by Schlegel, Montgomery and co-workers,[3a] we suggest that diethylzinc would facilitate oxidative cyclisation by: (i) Lewis acid activation of the ketone through binding with zinc, and (ii) Lewis basic activation of the metal through a three-centre-two-electron bridging of a zinc–ethyl bond. Cleavage of the oxametallacyle by transmetalation would provide metal–ethyl species **339**, which can then undergo β-hydride elimination to generate metal hydride **340**. Finally, reductive

elimination of **340** would provide zinc alkoxide **341** (which would be protonated upon workup to give the product), ethylene, and low-valent metal, which would reenter the catalytic cycle. Within this mechanistic scenario, the relative stereochemistries of the major diastereomers obtained in these reactions may be explained by the preference for formation of the bicyclic metallacycle **338** with a *cis*-ring junction, as opposed to a likely higher energy *trans*-ring junction.



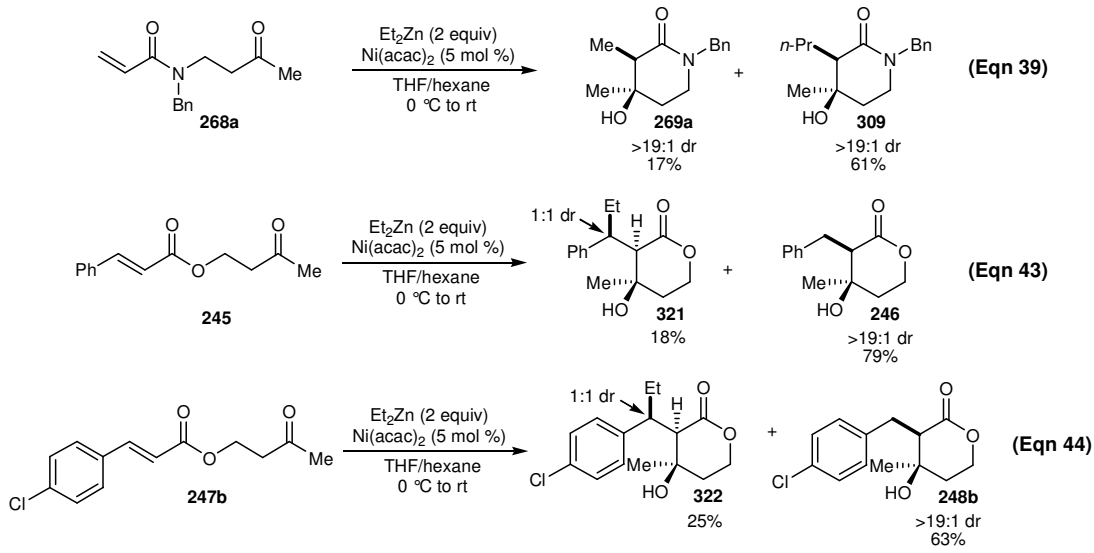
Scheme 5.1. A possible Reaction Mechanism Invoking Metallacycle Participation

A second, alternative catalytic cycle is illustrated in Scheme 2. Interaction of low-valent metal with Et_2Zn may lead to intermediate **342**, containing a three-centre-two-electron bridging interaction.[3a] Coordination of **342** to the substrate would then provide **343**, which can undergo β-hydride elimination to provide metal hydride **344**. Reorganisation of **344** can then occur to provide zinc enolate **282**, which would undergo aldol cyclisation, and low-valent metal, which can reenter the catalytic cycle. Here, the observed stereochemical outcome of the reactions may be explained by preferential formation of the *Z*-zinc enolate **282**, along with a chelated Zimmerman–Traxler-type transition state **283**.[4]

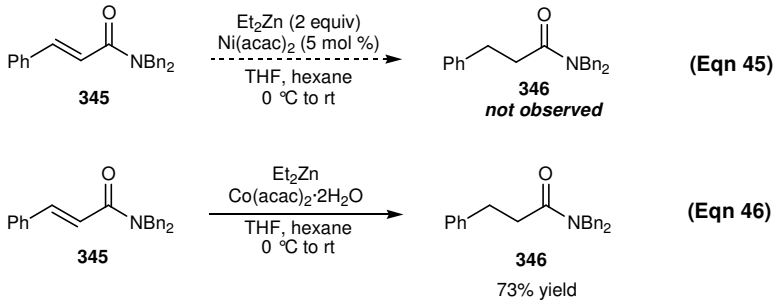


Scheme 5.2. A possible Reaction Mechanism Invoking Zinc Enolate Formation.

If mechanism B is operative, the formation of *alkylative* aldol cyclisation products in varying quantities from precursors **268a** and **245** and **247b** (Eqn 39, 43 and 44) might be accounted for by the particular steric and/or electronic properties of these particular substrates enabling conjugate addition from **343** to compete with β-hydride elimination to **344**. Alternatively, the formation of **309** from substrate **268a** (Eqn 39) can be explained using mechanism A if reductive elimination from **339** competes effectively with β-hydride elimination to **340**. However, the isolation of alkylative cyclisation products **321** and **322** (Eqn 43 and 44) as 1:1 mixtures of diastereomers might be more difficult to rationalise by a metallacycle pathway, assuming all steps in mechanism A are stereospecific.

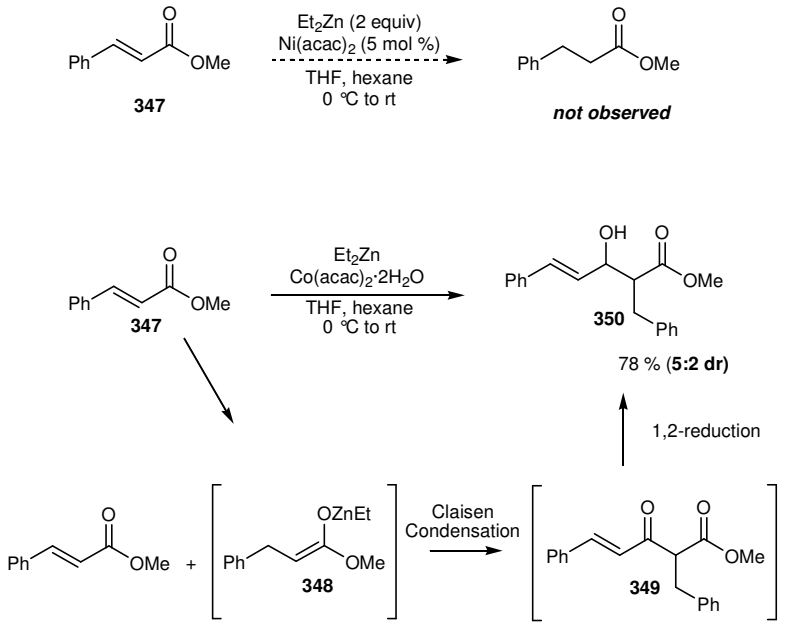


To shed light on these two possibilities, we examined the reaction of α,β-unsaturated amide **345** lacking the pendant ketone electrophile to our standard reaction conditions (Eqn 45). In principle, mechanism B (Scheme 5.2) does not require the participation of the ketone until the zinc enolate **282** is formed, whereas in mechanism A (Scheme 5.1), the ketone is an essential component for oxidative cyclisation to occur to provide oxametallacycle **338**. Therefore, if mechanism B is operative, we might expect to observe the simple conjugate reduction product **346**.[5,6]



In the event, exposure of **345** to our standard reaction conditions with $Ni(acac)_2$[7] provided only a complex mixture, with none of the amide **346** being observed. It was assumed that product formed was oligomeric in nature. To our surprise, when nickel was changed to cobalt,[8] conjugate reduction product **346** was isolated in 73% yield. This result demonstrated that the reaction mechanism for these two metals is presumably different or simply the reactivities of the catalysts are very

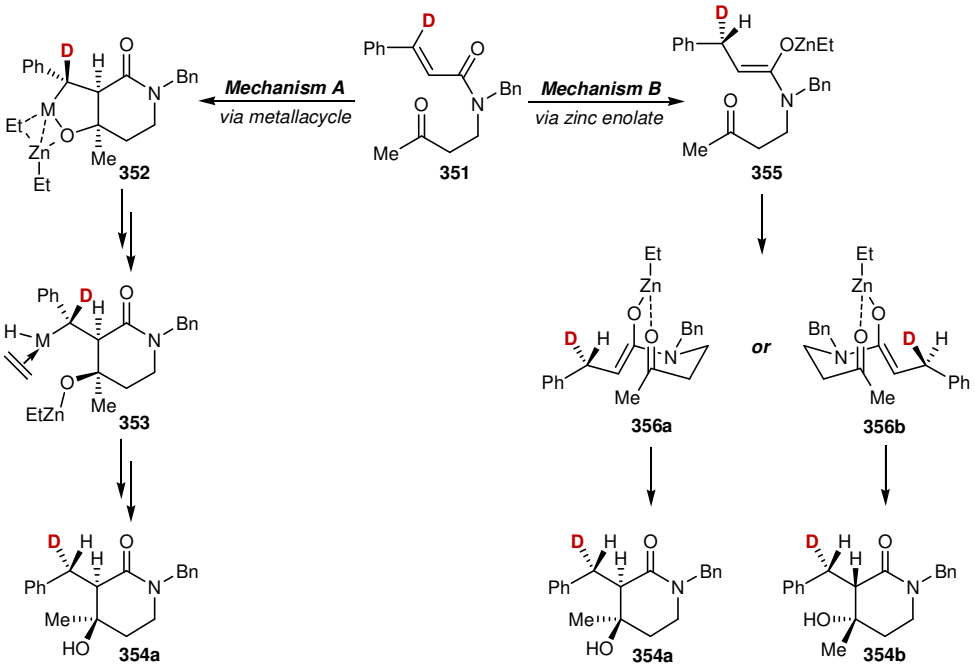
different. It also demonstrated that a second electrophilic component is not required for the reaction to proceed. This was further studied with methyl cinnamate (**347**) as a substrate. When standard nickel conditions were used,[7] a complicated mixture of products was formed (Scheme 5.3). When nickel was replaced by cobalt,[8] an interesting transformation was observed. Dimerisation of methyl cinnamate occurred to give product **350,** presumably by sequential Claisen condensation–ketone-reduction. If this is the case, it would mean that we form zinc enolate **348** as an intermediate. This result raises an interesting question: why does the reduction occur in a 1,2-manner and not in a 1,4-manner as expected? Although we do not know how this reaction proceeds, the result obtained shows that the mechanism is likely to be more complicated than just simple metal hydride formation.



Scheme 5.3. Transition Metal-Catalysed Intermolecular Reactions.

Although these reactions provided lot of interesting information, they were rather inconclusive. We also decided to conduct the reductive cyclisation of deuterium-labeled substrate **351**, which was prepared in straightforward fashion.[9] If a metallacycle-based mechanism (Scheme 5.1) were operative, the concerted nature of the oxidative cyclisation to form **351** would be expected to provide metallacycle **352** with the relative stereochemistry shown (Scheme 5.4). An eventual reductive

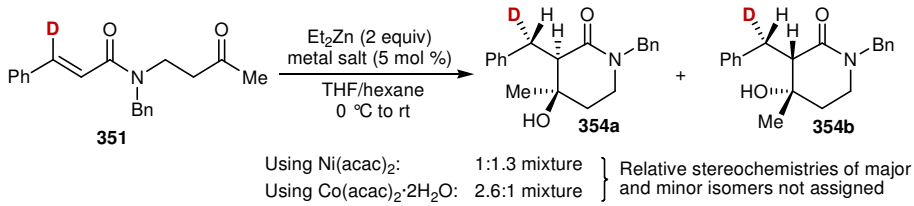
elimination of a metal hydride **353** that proceeds with retention of configuration would be expected to provide only one diastereoisomer **354a** of the cyclised product. However, if the alternative mechanism invoking the intervention of a zinc enolate **355** were operative, we would expect a 1:1 mixture of two product diastereoisomers **354a** and **354b** would be formed, since diastereomeric Zimmerman–Traxler-type transition states **356a** and **356b** should be virtually identical in energy.



Scheme 5.4. Expected Stereochemical Outcomes of Reductive Cyclisation of Deuterium-Labeled Substrate **351** Under Mechanisms A and B

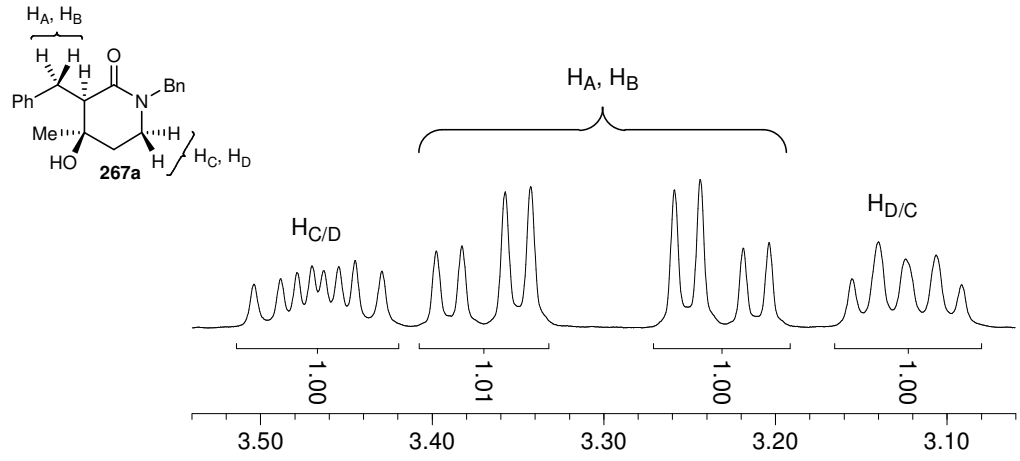
In the event, the nickel-catalysed reductive cyclisation of **351** provided a 1:1.3 inseparable mixture of diastereomeric products **354a** and **354b** (relative stereochemistries of major and minor diastereomers not assigned) as determined by ^{1}H NMR analysis of the unpurified reaction mixture (Scheme 5.5 and Scheme 5.6, spectrum (b)). That a non-equimolar ratio of diastereomers was obtained was confirmed after removal of trace impurities by column chromatography,[10] and this result proved to be repeatable. Several possible explanations may be invoked to rationalise this result. First, *both* mechanisms A and B are operative as competing pathways. Second, mechanism A is operative, but one (or more) of the reaction steps is (are) not stereospecific, e.g. due to configurational lability of a carbon–metal bond

leading to epimerisation. Third, mechanism B is operative, but the diastereomeric transition

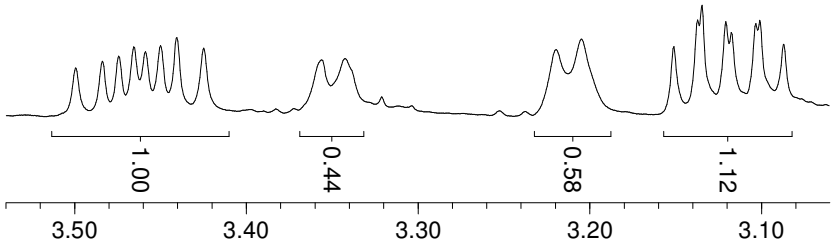


Scheme 5.5. Reductive Cyclisation of Deuterium-Labeled Substrate **351**

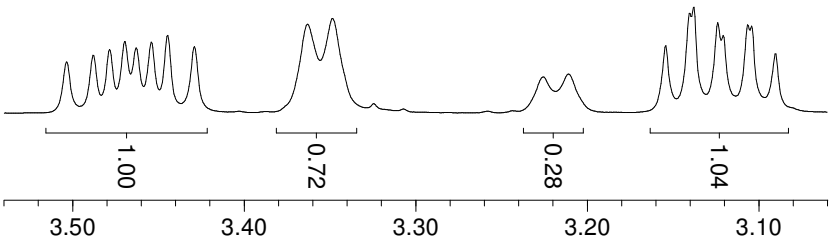
(a) Unlabeled reference



(b) Unpurified product **354a**/**354b** obtained using $Ni(acac)_2/Et_2Zn$



(c) Unpurified product **354a**/**354b** obtained using $Co(acac)_2{\cdot}2H_2O/Et_2Zn$



Scheme 5.6. ^{1}H NMR Spectra of Unlabeled Reference and Diastereomeric Products Obtained

states **356a** and **356b** have sufficiently different energies to result in the observed diastereomeric ratio. Fourth, mechanisms A and B represent oversimplified descriptions, and the true mechanism is appreciably more complex than these limiting cases. At present, we disfavour the first three explanations and in the absence of further data, we prefer the fourth option. While mechanism A (or a

variation thereof) cannot be completely discounted on the available evidence, we prefer a variant of mechanism B on the basis of this deuterium-labeling study. Issues that were not discussed within the context of mechanism B that could be responsible for a non-equimolar distribution of diastereomers **354a/354b** include the nature/hapticity of zinc enolate intermediates (oxa-π-allyl species, *C*-bound versus *O*-bound enolates), changes in this hapticity, during the course of the reaction, and prior association of the pendant ketone with the reactive metal species in initial enolate formation. A clearer picture of the mechanistic pathways associated with these reactions must therefore await additional studies.

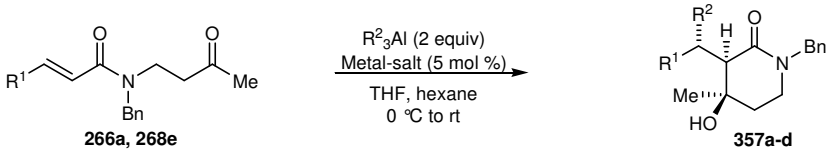
When cyclisation of the deuterium-labeled substrate **351** was conducted using $Co(acac)_2 \cdot 2H_2O$ as the precatalyst (Scheme 5.5), a non-equimolar ratio of diastereomeric products **354a** and **354b** was obtained again, but compared to the result obtained using $Ni(acac)_2$, the magnitude of diastereoselection was increased, and most importantly, *the sense of diastereoselection was reversed* (2.6:1 diastereomeric mixture, see Scheme 5.6, spectrum (c)). While the differences between the $Ni(acac)_2/Et_2Zn$ and $Co(acac)_2 \cdot 2H_2O/Et_2Zn$ reagent combinations are highlighted by the generally broader substrate scope of the nickel system, and their divergent behavior with simple β-unsubstituted acrylamides such as **268a** and with substrates such as **345** and **347** lacking a pendant ketone, the results of this isotopic labeling study also point to differences in their detailed mechanisms, that are still unclear to us.

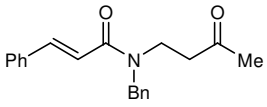
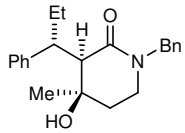
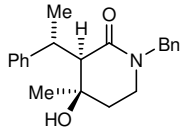
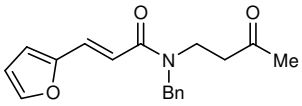
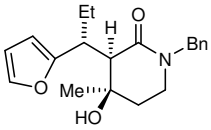
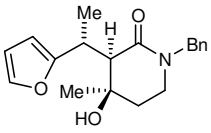
5.2. Other Observations

We decided to employ other stoichiometric reductants to see how they would alter the reaction. When trialkylaluminiums were used as reagent, interestingly, only alkylative cyclisations were observed in both of the metal salts utilised on substrates **266a** and **268e** (Table 5.1). The diastereoselectivities were very high (>19:1) and the reactions were very clean. When Et_3Al was used (entries 1-2 and 5-6) the products where isolated in good yields. When Me_3Al was used (entries 3-4 and 7-8) the reaction proceeded cleanly giving *ca.* 100% conversion: however when the crude

mixtures were purified by column chromatography, isolated yields were low. We could not find a solution to this problem. It is worth mentioning that the use of Me_2Zn did not lead to a cyclisation and the starting materials were recovered.

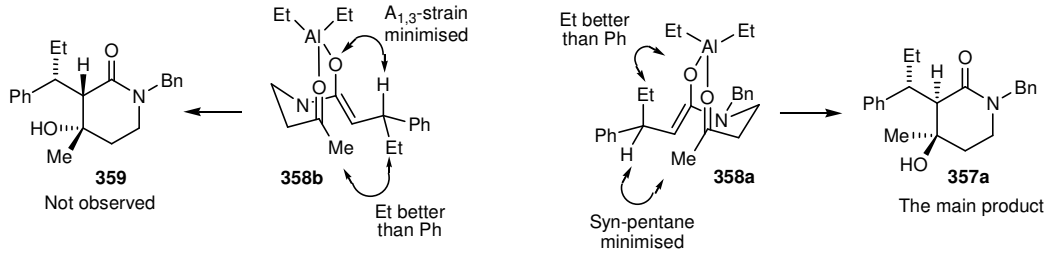
Table 5.1. Alkylative Cyclisations



Entry	Metal	Substrate	R^2		Yield(%)[b]
1	$Co(acac)_2{\cdot}H_2O$	 **266a**	Et	 **357a**	99
2	$Ni(acac)_2$		Et		97
3	$Co(acac)_2{\cdot}H_2O$		Me	 **357b**	62
4	$Ni(acac)_2$		Me		57
5	$Co(acac)_2{\cdot}H_20$	 **268e**	Et	 **357c**	96
6	$Ni(acac)_2$		Et		90
7	$Co(acac)_2{\cdot}H_2O$		Me	 **357d**	51
8	$Ni(acac)_2$		Me		45

a) all reaction performed in 0.2 mmol scale b) isolated yield

The relative stereochemistry of compound **357a** was determined by X-ray crystallography.[11] The stereochemical outcome can be explained by observing the Zimmerman–Traxler-type transition states **358a** and **358b**. A minimised *syn*-pentane interaction seems to be the dominating factor in determing the stereochemistry. A transition state leading to product **359** would have minimised $A_{1,3}$-strain, but this product was not observed.



Scheme 5.7. Relative stereochemistry of the alkylative cyclisations.

5.3. Conclusions

Possible mechanisms for transition metal-catalysed-reductive cyclisations have been discussed, and a deuterium labeling study designed to probe the stereochemical outcome of cyclisation within the context of these mechanisms has revealed the complex nature of these reactions. Even that the experiments performed provided plenty of information of the possible mechanism of the reaction, further work is needed to further clarify it. An interesting class of fully *alkylative* cyclisations were also discovered by a change of the reductant Et_2Zn to R_3Al.

5.4. References

[1] For review, see: Montgomery, J. *Angew. Chem. Int. Ed. Engl.*, **2004**, *43*, 3890.

[2] (a) Ogoshi, S.; Ikeda, H.; Kurosawa, H. *Angew. Chem.*, *Int. Ed.* **2007**, *46*, 4930. (b) Ogoshi, S.; Tonomori, K.; Oka, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 7077. (c) Ogoshi, S.; Ueta, M.; Arai, T.; Kurosawa, H. *J. Am. Chem. Soc.* **2005**, *127*, 12810. (d) Ogoshi, S.; Oka, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2004**, *126*, 11802.

[3] (a) Hratchian, H. P.; Chowdhury, S. K.; Gutiérrez-García, V. M.; Amarasinghe, K. K. D.; Heeg, M. J.; Schlegel, H. B.; Montgomery, J. *Organometallics* **2004**, *23*, 4636. (b) Amarsinghe, K. K. D.; Chowdhury, S. K.; Heeg, M. J.; Montgomery, J. *Organometallics* **2001**, *20*, 370.

[4] Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

[5] Conjugate reductions of sterically hindered di- and trisubstituted enones in low yields have been observed previously in attempted conjugate addition reactions using $Ni(acac)_2/Et_2Zn$. See: (a) Chaloner, P. A.; Hitchcock, P. B.; Langadianou, E.; Readney, M. J. *Tetrahedron Lett.* **1991**, *32*, 6037. (b) Bolm, C.; Ewald, M.; Felder, M. *Chem. Ber.* **1992**, *125*, 1205.

[6] For $Co(acac)_2/Et_2Zn$-mediated conjugate reduction of chalcone, see: de Vries, A. H. M.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 1377.

[7] Chapter 4

[8] Chapter 3

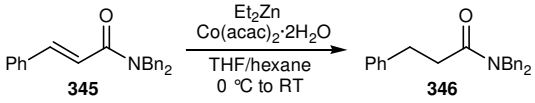
[9] See Experimental part for details.

[10] Purification of the product of the reaction (by $Ni(acac)_2$) depicted in Scheme 5.5 by column chromatography gave **354a/354b** in a 1:1.5 ratio (relative stereochemistries of major and minor isomers not assigned).

[11] Crystal grown by Mairi Rudkin

5.5. Experimental

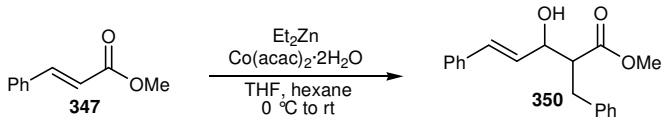
Conjugate Reduction of α,β-Unsaturated Amide 346[i]



A solution of the known cinnamic amide **345**[ii] (66 mg, 0.20 mmol) and $Co(acac)_2{\cdot}2H_2O$ (2.6 mg, 0.01 mmol) in THF (1.5 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 0.40 mL, 0.40 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 1 h and then at room temperature for 2h. The reaction mixture was filtered through a short plug of SiO_2 (*ca*. 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/hexane) afforded the amide **346** (48 mg, 73%) that displayed identical spectroscopic data to those reported previously.[i]

The reaction was performed also using $Ni(acac)_2$ (2.7 mg, 0.01 mmol). The crude mixture was analysed by ^1H NMR spectroscopy showing a complicated mixture of products. Purification of the residue by column chromatography (20% EtOAc/hexane) did not lead to a separation of the mixture.

Dimerisation of methyl cinnamate: (E)-methyl 2-benzyl-3-hydroxy-5-phenylpent-4-enoate



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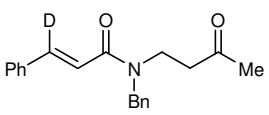
[i] Aoyagi, Y.; Asakura, R.; Kondoh, N.; Yamamoto, R.; Kuromatsu, T.; Shimura, A.; Ohta, A. *Synthesis* **1996,** 970.

[ii] .Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D. *J. Chem. Soc.*, *Perkin Trans. 1* **2000**, 3765.

A solution of the commercially available methyl cinnamate **347** (162 mg, 1.00 mmol) and $Co(acac)_2 \cdot 2H_2O$ (12.9 mg, 0.05 mmol) in THF (5.0 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 0.40 mL, 0.40 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 1 h and then at room temperature for 6 h. The reaction mixture was filtered through a short plug of SiO_2 (*ca*. 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/hexane) afforded the amide **350** (116 mg, 78%) as 2:5 mixture of diastereomers. m.p. 90-92 °C; IR ($CHCl_3$) 3449, 2950. 1732 (C=O), 1495, 1448, 1437, 1166, 968, 748, 698 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) signed as 2:5 mixture of diastereomers. Major diastereomer; δ 7.46-7.25 (10H, m, Ar**H**), 6.72 (1H, d, *J* = 15.9 Hz, ArC**H**), 6.33 (1H, dd, *J* = 15.9, 6.7 Hz, ArCHC**H**), 4.60 (1H, app.t, *J* = 5.4 Hz, C**H**OH), 3.64 (3H, s, C**H**$_3$O), 3.14 (3H, m, ArC**H**$_2$CH, ArCH$_2$C**H**) Minor diastereomer; δ 7.46-7.25 (10H, m, Ar**H**), 6.71 (1H, d, *J* = 15.9 Hz, ArC**H**), 6.28 (1H, dd, *J* = 15.9, 6.4 Hz, ArCHC**H**), 4.49 (1H, app.t, *J* = 5.7 Hz, C**H**OH), 3.66 (3H, s, C**H**$_3$O), 3.14 (3H, m, ArC**H**$_2$CH, ArCH$_2$C**H**); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of diastereomers – not fully assigned) δ 174.7 (C), 174.2 (C), 139.0 (C), 138.4 (C), 136.3 (C), 132.1 (CH), 131.8 (CH), 129.5 (2 x CH), 128.8 (2 x CH), 128.5 (2 x CH), 128.4 (CH), 127.8 (CH), 126.5 (CH), 126.3 (CH), 72.9 (CH), 72.7 (CH), 55.4 (CH_3), 53.3 (CH_3), 51.6 (CH), 35.2 (CH_2), 33.7 (CH_2); HRMS (FAB) Exact mass calcd for $C_{19}H_{21}O_3$ $[M+H]^+$: 297.1480, found: 297.1482.

The reaction was performed also using $Ni(acac)_2$ (13.5 mg, 0.05 mmol). The crude mixture was analysed by ^1H NMR spectroscopy showing a complicated mixture of products. Purification of the residue by column chromatography (20% EtOAc/hexane) did not lead to a separation of the mixture.

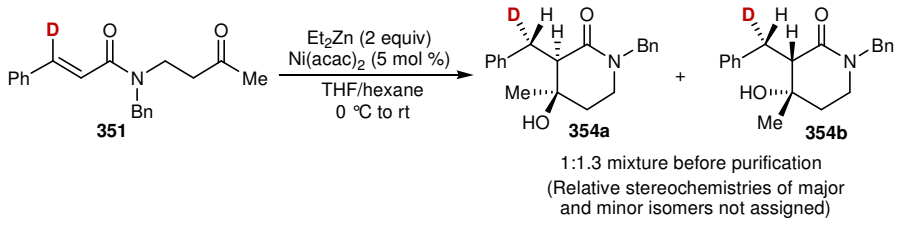
Preparation and Cyclisation of Deuterium-Labeled Substrate 351



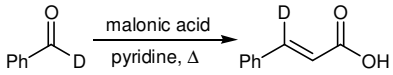
***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-3-deuterio-3-phenylpropenamide (351)**. The title compound was prepared

according to General Procedure B (chapter 4, experimental) from methyl vinyl ketone (361 μL, 4.00 mmol), benzylamine (393 μL, 3.60 mmol) and the acid chloride (prepared according General Procedure A in Chapter 4, (experimental) derived from *(E)*-3-deuteriocinnamic acid[iii] (603 mg, 3.60 mmol) for a reaction time of 16 h and purified by column chromatography (40% EtOAc/petrol) to give light yellow solid (518 mg, 47%) as a 2:1 mixture of rotamers. m.p. 54-56 ºC; IR ($CHCl_3$) 2923, 1713 (C=O), 1638 (C=O), 1600 (C=C), 1496, 1370, 1206, 1162, 871, 734, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.47 (2H, d, *J* = 5.6 Hz, Ar**H**), 7.42-7.26 (8H, m, Ar**H**), 6.86 (1H, s, =C**H**), 4.79 (2H, s, C**H**$_2$Ph), 3.72 (2H, t, *J* = 6.7 Hz, $CH_2C\mathbf{H}_2N$), 2.89 (2H, t, *J* = 6.7 Hz, C**H**$_2CH_2N$), 2.16 (3H, s, C**H**$_3$C=O); (Minor rotamer) δ 7.59 (2H, d, *J* = 6.3 Hz, Ar**H**), 7.42-7.26 (8H, m, Ar**H**), 7.01 (1H, s, =C**H**), 4.75 (2H, s, C**H**$_2$Ph), 3.76 (2H, t, *J* = 6.7 Hz, $CH_2C\mathbf{H}_2N$), 2.73 (2H, t, *J* = 6.7 Hz, C**H**$_2CH_2N$), 2.11 (3H, s, C**H**$_3$C=O); ^{13}C NMR (90.6 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.2 (C), 205.9 (C), 166.9 (C), 166.3 (C), 137.5 (CH, t, J_D = 20.4 Hz), 137.0 (CH, t, J_D = 23.7 Hz), 134.9 (C), 134.8 (C), 129.5 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 126.3 (CH), 117.0 (CH), 116.7 (CH), 52.1 (CH_2), 49.3 (CH_2), 42.7 (CH_2), 42.4 (CH_2), 41.7 (2 x CH_2), 30.1 (CH_3), 29.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{21}DNO_2$ $[M+H]^+$: 309.1708, found: 309.1707.

(±)-(3*R*,4*R*)-1-Benzyl-3-[(*RS*)-deuteriophenylmethyl]-4-hydroxy-4-methylpiperidin-2-one (354).



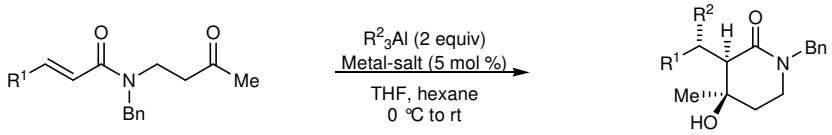
[iii]. *(E)*-3-Deuteriocinnamic acid is a known compound (see: Krüger, J.; Manmontri, B.; Fels, G. *Eur. J. Org. Chem.* **2005**, 1402). We prepared this compound from the Knoevenagel condensation of commercially available deuteriobenzaldehyde with malonic acid.



General Procedure G was followed using substrate **351** (62 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A to give **354** as a 1:1.3 inseparable mixture of diastereomers. Purification of the residue by column chromatography (70% EtOAc/petrol) gave **354** as a white solid (52 mg, 84%) as a 1:1.5 inseparable mixture of diastereomers. m.p. 114-116 ºC; IR ($CHCl_3$) 3399 (OH), 2928, 1617 (C=O), 1495, 1451, 1269, 1146, 918, 732, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.43-7.41 (2H, m, Ar**H**), 7.39-7.29 (7H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 4.75 (1H, d, *J* = 14.7 Hz, C**H**$_2$Ph), 4.58 (1H, d, *J* = 14.7 Hz, C**H**$_2$Ph), 3.47 (1H, ddd, *J* = 12.2, 9.0, 5.6 Hz, CH_2C**H**$_2$N), 3.35 (0.5H, d, *J* = 5.3 Hz, C**H**D), 3.22 (0.5H, d, *J* = 5.4 Hz, C**H**D), 3.13 (1H, ddd, *J* = 12.2, 5.9, 5.1 Hz, CH_2C**H**$_2$N), 2.72 (1H, d, *J* = 5.4 Hz, C**H**CH=O), 1.92-1.80 (2H, m, C**H**$_2CH_2$N), 1.76 (1H, br s, O**H**), 1.31 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.1 (C), 141.9 (C), 137.1 (C), 129.2 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 127.9 (2 x CH), 127.2 (CH), 126.0 (CH), 71.0 (C), 54.2 (CH), 50.4 (CH_2), 43.0 (CH_2), 35.2 (CH_2), 32.5 (**C**HD, t, J_D = 19.5 Hz), 28.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{23}DNO_2$ $[M+H]^+$: 311.1864, found: 311.1862.

The same procedure was followed using $Co(acac)_2{\cdot}2H_2O$ (2.6 mg, 0.01 mmol) in place of $Ni(acac)_2$ to give **354** as a 2.6:1 inseparable mixture of diastereomers.

Nickel-Catalysed Alkylative Cyclisations: General Procedure A



A solution of the substrate (0.20 mmol) and $Ni(acac)_2$ (2.7 mg, 0.01 mmol) (in THF (1.5 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and Et_3Al (1 M solution in hexane, 0.40 mL, 0.40 mmol) was then added over 1 min. The reaction was stirred at 0 °C for 1 h and then at room temperature until complete consumption of starting material as observed by TLC analysis. The reaction was quenched carefully by the addition of 1 M HCl (1 mL), and the mixture was stirred

for 1 h before being diluted with saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclised product.

Nickel-Catalysed Alkylative Aldol Cyclisations: General Procedure B

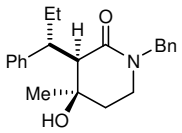
Like procedure A, but instead of Et_3Al, Me_3Al (2 M solution in hexane, 0.20 mL, 0.20 mmol) was used.

Cobalt-Catalysed Alkylative Aldol Cyclisations: General Procedure C

Like procedure B, but instead of $Ni(acac)_2$, $Co(acac)_2{\cdot}2H_2O$ (2.6 mg, 0.01 mmol) was used.

Cobalt-Catalysed Alkylative Aldol Cyclisations: General Procedure D

Like procedure B, but instead of $Ni(acac)_2$, $Co(acac)_2{\cdot}2H_2O$ (2.6 mg, 0.01 mmol) was used.

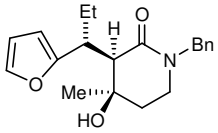


(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-4-methyl-3-((*R*)-1-phenylpropyl)piperidin-2-one(357a)

The title compound was prepared according to general procedure A from **266a** (61 mg, 0.20 mmol) for a reaction time of 8 h and purified by column chromatography (60% EtOAc/petrol) to give a white solid (65 mg, 96%). m.p. 155-156 °C; IR ($CHCl_3$) 3390 (OH), 2967, 2252, 1631 (C=O), 1495, 1453, 1381, 908, 733, 650 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.50-7.47 (2H, m, Ar**H**), 7.40-7.31 (7H, m, Ar**H**), 7.27-7.22 (1H, m, Ar**H**), 4.71 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 4.62 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 3.37 (1H, ddd, *J* = 12.4, 6.8, 4.2 Hz, $CH_2C\mathbf{H}_2N$), 3.13-3.05 (2H, m, $CH_2C\mathbf{H}_2N$ and C**H**CH_2CH_3), 2.89 (1H, dd, *J* = 4.7, 1.6 Hz, C**H**C=O), 2.10-1.89 (2H, m, C**H**$_2CH_2N$), 1.75-1.66 (2H, m, CHC**H**$_2CH_3$), 1.39 (1H, br s, O**H**), 1.26 (3H, s, C**H**$_3$COH), 0.74 (3H, t, *J* = 7.3 Hz, C**H**$_3CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.3 (C), 145.8 (C), 137.1 (C), 128.8 (2 x CH), 128.5(4 x CH), 128.4 (2 x CH), 127.4 (CH), 126.3 (CH), 71.3 (C), 59.7 (CH), 50.1 (CH_2), 46.2

(CH), 43.4 (CH_2), 32.4 (CH_2), 28.4 (CH_3), 27.3 (CH_2), 12.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{28}NO_2$ $[M+H]^+$: 338.2115 found: 338.2116.

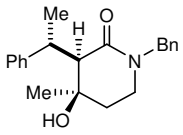
With Procedure C: reaction time of 8 h and purified by column chromatography (60% EtOAc/petrol) to give a white solid (67 mg, 99%).



(3*R*,4*R*)-1-Benzyl-3-((*R*)-1-(furan-2-yl)propyl)-4-hydroxy-4-methylpiperidin-2-one (357c)

The title compound was prepared according to general procedure A from **268e** (61 mg, 0.20 mmol) for a reaction time of 8 h and purified by column chromatography (60% EtOAc/petrol) to give a white solid (59 mg, 90%). m.p. 168-170 °C; IR ($CHCl_3$) 3434 (OH), 2914, 1629 (C=O), 1454, 1381, 1262, 1096, 906, 736, 651 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.38-7.29 (6H, m, Ar**H** and C**H**), 6.36 (1H, dd, *J* = 3.2, 1.9 Hz, C**H**), 6.21-6.20 (1H, m, C**H**), 4.71 (1H, d, *J* = 14.6 Hz, NC**H**$_2$Ar), 4.57 (1H, d, *J* = 14.6 Hz, NC**H**$_2$Ar), 3.67-3.62 (1H, m, C**H**$_2$CH$_2$N), 3.29 (1H, ddd, *J* = 12.3, 6.0, 6.0 Hz, C**H**$_2$N), 3.07 (1H, ddd, *J* = 12.3, 7.7, 6.0 Hz, C**H**$_2$N), 2.80 (1H, dd, *J* = 3.4, 0.6 Hz, C**H**C=O), 2.26-2.15 (1H, m, C**H**$_2$CH$_3$), 2.10 (1H, br s, O**H**), 1.91-1.80 (1H, m, C**H**$_2$CH$_3$), 1.72-1.65 (1H, m, C**H**CH$_2$), 1.49 (1H, ddd, *J* = 13.4, 7.7, 6.0 Hz, C**H**$_2$CH$_2$N), 1.36 (3H, s, C**H**$_3$COH), 0.94 (3H, t, *J* = 7.3 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.3 (C), 156.6 (C), 140.9 (CH), 137.1 (C), 128.5 (2 x CH), 128.1 (2 x CH), 127.3 (CH), 110.7 (CH), 107.3 (CH), 70.9 (C), 57.1 (CH), 50.4 (CH_2), 43.2 (CH_2), 40.7 (CH), 34.2 (CH_2), 28.9 (CH_3), 26.5 (CH_2), 13.0 (CH_3)**;** HRMS (ES) Exact mass calcd for $C_{20}H_{26}NO_3$ $[M+H]^+$: 328.1907, found: 328.1909.

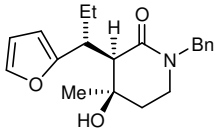
With Procedure C: reaction time of 8 h and purified by column chromatography (60% EtOAc/petrol) to give a white solid (63 mg, 96%).



(±)-(3*R*,4*R*)-1-benzyl-4-Hydroxy-4-methyl-3-((*R*)-1-phenylethyl)piperidin-2-one(357b)

The title compound was prepared according to general procedure B from **266a** (61 mg, 0.20 mmol) for a reaction time of 8 h and purified by column chromatography (60% EtOAc/petrol) to give a white solid (37 mg, 57%). m.p. 166-167 °C; IR ($CHCl_3$) 3155 (OH), 2942, 1793, 1632 (C=O), 1494, 1382, 1095, 902, 722, 651 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.48-7.45 (2H, m, Ar**H**), 7.37-7.28 (7H, m, Ar**H**), 7.23-7.18 (1H, m, Ar**H**), 4.67 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 4.60 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 3.45-3.33 (2H, m, C**H**$_2$CH$_2$N and C**H**$_2$N), 3.06 (1H, ddd, *J* = 12.5, 9.0, 6.3 Hz, CH$_2$C**H**$_2$N), 2.85 (1H, dd, *J* = 4.6, 1.6 Hz, C**H**C=O), 2.04 (1H, ddd, *J* = 13.4, 9.0, 6.6 Hz, C**H**$_2$CH$_2$N), 1.74-1.67 (1H, m, C**H**CH$_3$), 1.38 (3H, d, *J* = 7.3 Hz, C**H**$_3$CH), 1.29 (1H, s, O**H**), 1.27 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.1 (C), 148.1 (C), 137.1 (C), 128.7 (2 x CH), 128.6 (2 x CH), 128.4 (2 x CH), 127.8 (2 x CH), 127.5 (CH), 126.2 (CH), 71.4 (C), 59.3 (CH), 50.1 (CH_2), 43.3 (CH_2), 38.2 (CH), 32.7 (CH_2), 28.6 (CH_3), 21.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{21}H_{26}NO_2$ $[M+H]^+$: 324.1958, found: 324.1956.

With Procedure D: reaction time of 8 h and purified by column chromatography (60% EtOAc/petrol) to give a white solid (40 mg, 62%).



(3*R*,4*R*)-1-benzyl-3-((*R*)-1-(furan-2-yl)ethyl)-4-hydroxy-4-methylpiperidin-2-one (357d)

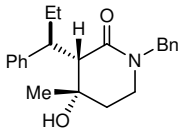
The title compound was prepared according to general procedure B from **268e** (61 mg, 0.20 mmol) for a reaction time of 8 h and purified by column chromatography (60% EtOAc/petrol) to give a white solid (28 mg, 45%). m.p. 168-170 °C; IR ($CHCl_3$) 3062 (OH), 2892, 1693 (C=O), 1601, 1494, 1368, 1266, 1226, 909, 736 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.38-7.28 (6H, m, Ar**H** and C**H**), 6.36 (1H, dd, *J* = 3.2, 1.8 Hz, C**H**), 6.18 (1H, dt, *J* = 3.2, 0.9 Hz, C**H**), 4.73 (1H, d, *J* = 14.6 Hz, NC**H**$_2$Ar), 4.57 (1H, d, *J* = 14.6 Hz, NC**H**$_2$Ar), 3.82-3.75 (1H, m, C**H**$_2$CH$_2$N), 3.38 (1H, ddd, *J* = 12.5, 6.7, 5.8 Hz, C**H**$_2$N), 3.09 (1H, ddd, *J* = 12.5, 6.7, 6.0 Hz, C**H**$_2$N), 2.87 (1H, d, *J* = 2.5 Hz, C**H**C=O), 1.84 (1H, br s, O**H**), 1.83-

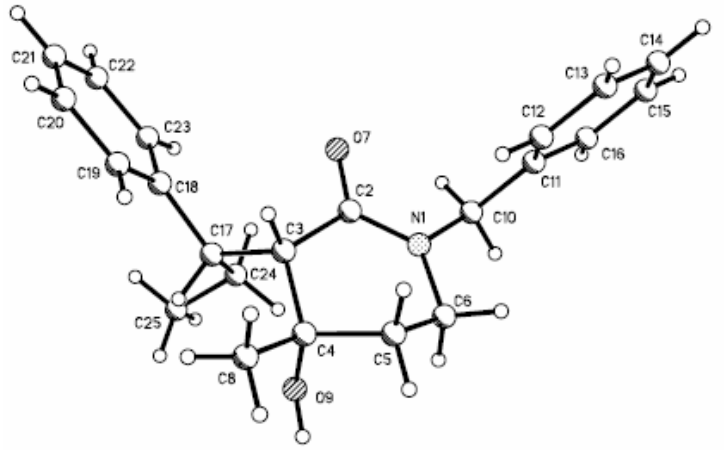
1.65 (2H, m, $CH_3C\mathbf{H}$ and $C\mathbf{H}_2CH_2N$) 1.54 (3H, d, J = 7.3 Hz, $C\mathbf{H}_3CH$), 1.40 (3H, s, $C\mathbf{H}_3COH$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 169.6 (C), 159.1 (C), 140.6 (CH), 137.1 (CH), 128.5 (2 x CH), 128.2 (2 x CH), 127.3 (CH), 110.6 (CH), 105.1 (CH), 71.1 (C), 56.4 (CH), 50.2 (CH_2), 43.0 (CH_2), 34.5 (CH_2), 32.0 (CH), 29.1 (CH_3), 17.7 (CH_3)**;** HRMS (ES) Exact mass calcd for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1751, found: 314.1747.

With Procedure D: reaction time of 8 h and purified by column chromatography (60% EtOAc/petrol) to give a white solid (32 mg, 51%).

Stereochemical Determinations

The relative stereochemistry of **357a** was determined by X-ray crystallography.





6. Cobalt-Catalysed Intermolecular Reductive Aldol Reaction[i]

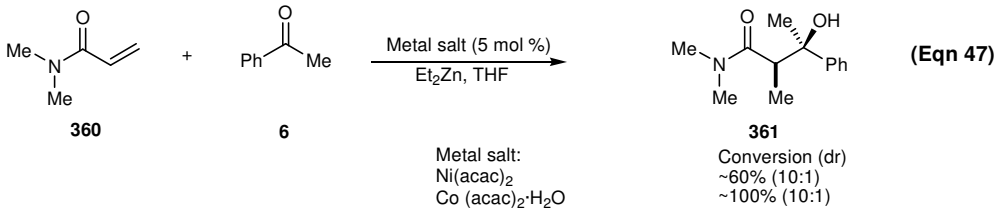
Since the nickel- and cobalt-catalysed reductive aldol cyclisations proceeded readily, we next turned our attention to a possible intermolecular reaction. Zinc enolates are an important class of reagents for organic synthesis, readily reacting with a range of electrophiles[1,2,3] and exhibiting lower basicity and greater functional group compatibility compared to their alkali metal counterparts. Even though there are several methods to access zinc enolates by using stoichiometric zinc sources,[4,5] we were sure our method would provide interesting contribution to the field, since current methods for the formation of zinc enolates suffer from several limitations. The first method involves the transmetalation of an alkali metal enolate with a zinc halide, which necessitates the use of strong alkali metal amide bases at low temperatures in a prior enolisation step that may be accompanied by regioselectivity problems when more than one site of enolisation is available. The second method involves the reaction of a suitable zinc source (zinc powder, organozinc reagents) with an α-halocarbonyl compound, with or without catalysis.[1] Advantages of this method are the use of milder, less basic conditions, often complete regioselectivity and the ability to have the electrophile present *in situ*. The utility of this methodology is evidenced by the Reformatsky reaction and its variants, which are still widely practiced in synthesis today.[1] However, the use of α-halocarbonyls compounds as zinc enolate precursors is not without limitations. Although simple α-halocarbonyls are readily available, more complex substrates require the installation of the halide in a separate step, which may pose problems when sensitive functional groups are present. The third method to prepare zinc enolates is *via* the catalytic conjugate addition of organozinc reagents to an α,β-unsaturated carbonyl compound.[6] Although this method may benefit from the advantages of chemically robust, readily available precursors and high regioselectivity of enolate formation under mild conditions, the α,β-unsaturated carbonyl compounds that may be employed are often restricted to enones. More synthetically versatile but less reactive α,β-unsaturated carboxylic acid derivatives remain challenging substrates for catalytic organozinc

[i] The work in this chapter was done in collaboration with Ralph J.R. Lumby

conjugate additions.[7] Furthermore, this method necessitates the formation of a carbon–carbon bond and often a new stereogenic centre. Although desired in some cases, other synthetic applications may not require this increase in complexity. Therefore, we thought that the development of an analogous method that results in the formation of a *carbon–hydrogen bond* using α,β-unsaturated carboxylic acid derivatives should be of utility. As already discussed in Chapters 3-5 we believe we have developed a method to form zinc enolates that meets these criteria.

6.1. Screening of the possible substrates

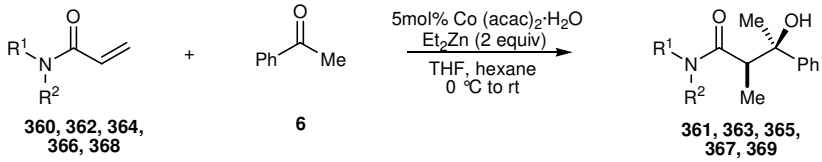
The first reaction to be tested was between commercially available *N,N*-dimethyl acrylamide (**360**) and acetophenone (**6**). Reactions were performed with both the nickel and the cobalt conditions. Both gave aldol product **361**: however the cobalt conditions proved to be more effective, resulting in full conversion.



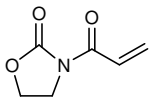
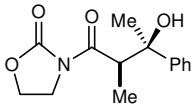
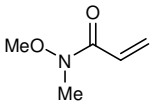
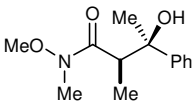
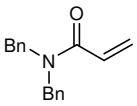
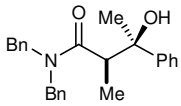
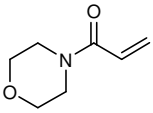
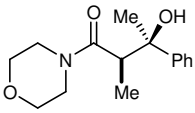
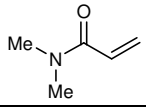
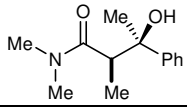
(Eqn 47)

The use of different amides was studied to see whether changing the substitution at nitrogen would affect reactivity (Table 6.1). An oxazolidinone susbtrate **362** failed to react and only starting materials were recovered (Entry 1). The same result occured with the Weinreb amide **364**. *N,N*-Dibenzyl acrylamide **366**, 4-acryloyl morpholine **368** and *N,N*-dimethyl acrylamide **360** all reacted to give the corresponding aldol product with comparable conversions and similar diastereoselectivities (Entries 3-5).

Table 6.1. Screening of Different Amide Substrates



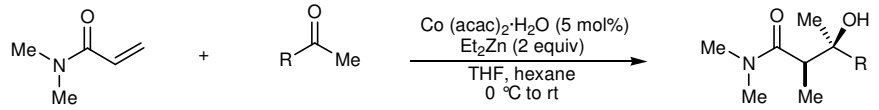
360, 362, 364, 366, 368 | **6** | **361, 363, 365, 367, 369**

Entry	Substrate		Product		dr	Conversion
1		**362**		**363**	-	-
2		**364**		**365**	-	-
3		**366**		**367**	9:1	~100 %
4		**368**		**369**	7:1	~100 %
5		**360**		**361**	10:1	~100 %

6.2. Reaction Scope

Reactions with *N,N*-dimethyl acrylamide **360** and 4-acryloyl morpholine **368** were chosen for further screening with different ketones (Table 6.2 and 6.3).

Table 6.2.[ii] Reactions of N,N-dimethyl acrylamide with Representative Ketones[a]

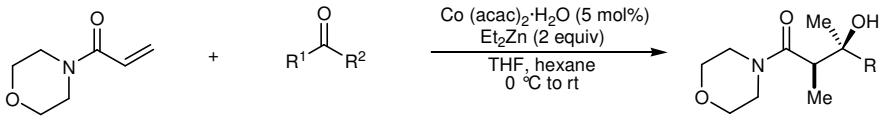


360 **370** **361a-h** + diasteereomer **371**

Entry	R	Product(s)	dr[b]	Yield(s)(%)[c]
1	Ph	**361a**	5:1	75
2	2-MePh	**361b**	9:1	68
3	4-MePh	**361c**	5.5:1	75
4	4-MeOPh	**361d**	6:1	84
5	2-BrPh	**361e**	7:1	56
6	4-BrPh	**361f**	3.5:1	73 (15)
7	2-naphthyl	**361g**	5:1	78
8	2-furyl	**361h**	2.5:1	66 (25)

a) Reactions were conducted using 1.0 mmol of **360** and 1.1 mmol of ketone in THF (10 mL) and hexane (2 mL) for 1–29 h. b) Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. c) Isolated yield of major diastereomer; numbers in parentheses refer to yields of minor diastereomers if isolated.

Table 6.3.[ii] Reactions of Morpholine Acrylate with Representative Ketones[a]



368 **372a-i** **369a-i** + diastereomer **373**

Entry	R[1]	R[1]	Product(s)	dr[b]	Yield(s)(%)[c]
1	Me	Ph	**369a**	5.5:1	80
2	Me	2-MePh	**369b**	9:1	84
3	Me	4-MeOPh	**369c**	6.5:1	85
4	Me	2-naphthyl	**369d**	4.5:1	82 (17)
5	Me	2-furyl	**369e**	3:1	72 (22)
6	Me	*i*-Pr	**369f**	1:1	33 (31)
7	Me	*i*-Bu	**369g**	1:1	35 (36)
8	Et	Ph	**369h**	6:1	75
9	Ph	Ph	**369i**	na	62

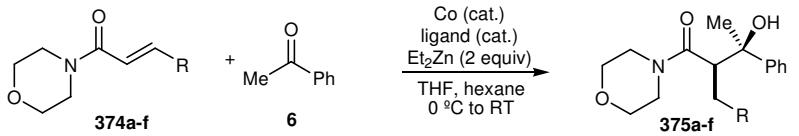
a) Reactions were conducted using 1.0 mmol of **368** and 1.1 mmol of ketone in THF (10 mL) and hexane (2 mL) for 1–29 h. b) Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. c) Isolated yield of major diastereomer; numbers in parentheses refer to yields of minor diastereomers if isolated.

[ii] Reactions performed by Ralph J.R. Lumby

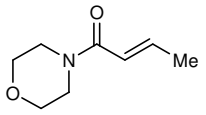
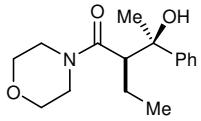
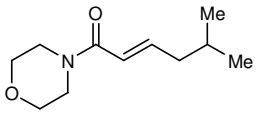
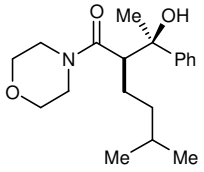
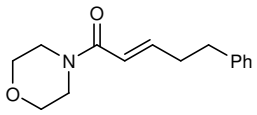
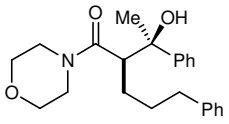
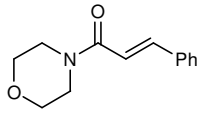
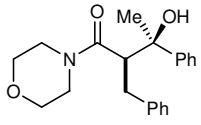
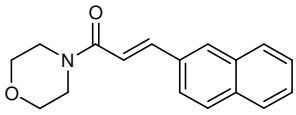
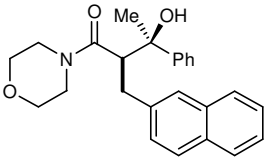
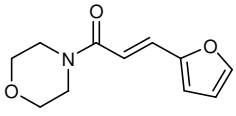
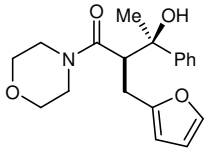
Amides **360** and **368** underwent smooth reductive aldol reactions with a range of acetophenone derivatives containing substituents of varying electronic properties to provide the corresponding aldol products with up to 9:1 diastereomeric ratio and 85% isolated yield of the major diastereomer (Table 6.1, Entries 1–6, and Table 6.2, Entries 1–3). The beneficial effect of *ortho*-substitution in the acetophenone on the diastereoselectivity of the reaction should be noted (Table 6.1, Entries 2 and 5, and Table 6.2, Entry 2). Reactions with ketones containing naphthyl and furyl substituents were successful (Table 6.1, entries 7–8 and Table 6.2, Entries 4–5), as was reaction of **368** with propiophenone (Table 6.2, Entry 8) and benzophenone (Table 6.2, Entry 9). Although aliphatic ketones were also found to be competent substrates from a reactivity standpoint, their reactions exhibit no diastereoselection (Table 6.2, Entries 6–7).

We next studied the effect of the substitution at β-position in the reaction of α,β-unsaturated morpholine amides with acetophenone (Table 6.4). Both linear and branched alkyl groups were tolerated (Entries 1–3), as were aromatic (Entries 4–5) and heteroaromatic (Entry 6) substituents. All these substrates showed similar reactivity to 4-acryloyl morpholine **368** but the reaction proceeded with significantly higher diastereoselectivity. Alkyl-substituted morpholine amides **374a-374c** failed to provide any aldol product when $Co(acac)_2{\cdot}2H_2O$ was used as the precatalyst. This deficiency could be overcome by changing $Co(acac)_2{\cdot}2H_2O$ to a combination of $CoCl_2$ and the electron-rich phosphine ligand Cy_2PPh.[8]

Table 6.4. Substituted Amide Substrates[a]



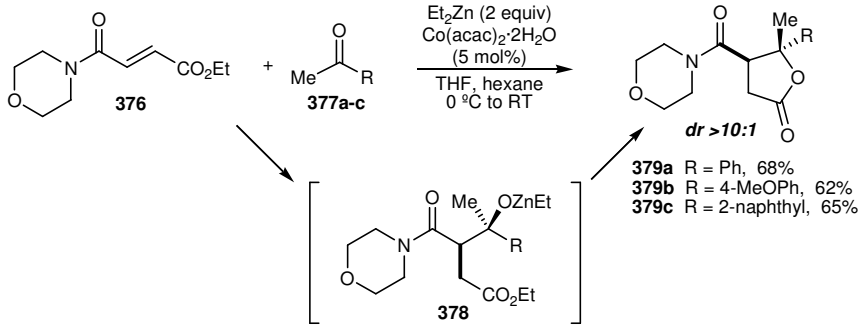
Method A: $Co(acac)_2 \cdot 2H_2O$ (5 mol%)
Method B: $CoCl_2$ (5 mol%), Cy_2PPh (5.5 mol%)

Run	Method	Substrate	Product	dr[b]	Yield (%)[c]
1	B	 **374a**	 **375a**	>19:1	76
2	B	 **374b**	 **375b**	>19:1	85
3	B	 **374c**	 **375c**	16:1	81
4	A	 **374d**	 **375d**	>19:1	71
5	A	 **374e**	 **375e**	10:1	74
6	A	 **374f**	 **375f**	9:1	84

a) Reactions were conducted using 1.0 mmol of **374a-f** and 1.1 mmol of acetophenone in THF (10 mL) and hexane (2 mL) for 2–6 h. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c] Isolated yield of major diastereomer. [d] Yield of a 16:1 inseparable mixture of diastereomers.

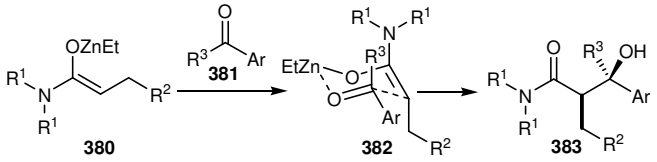
Unsaturated amide **376** provided an interesting regiochemical problem, since it contains an α,β-unsaturated amide that also forms part of an α,β-unsaturated ester. It was therefore of interest to observe whether conjugate reduction would be successful, and if so, whether an amide enolate or an ester enolate would result. In the event, reductive aldol reaction of **376** with a range of methyl ketones provided

lactones **377a-377c** in 62–68% yield as a result of the intermediate zinc alkoxides **378** cyclising onto the pendant ethyl ester (Scheme 6.1). These experiments demonstrate that conjugate reduction of **376** occurred to generate the morpholine amide enolate preferentially.



Scheme 6.1. Reductive Aldol Coupling of **376** with Various Ketones Producing Lactones.

The diastereochemical outcomes of these reactions are consistent with the participation of *Z*-zinc enolates **378** and chelated chair-like Zimmerman–Traxler transition states[9] in which the larger aromatic substituent of the ketone prefers to reside in a less sterically hindered pseudoequatorial position (as in **380**) (Scheme 3).



Scheme 6.2. Model for Stereochemical Outcome.

The stereochemistry was determined by comparison with the literature data of known compound **361a**. The relative stereochemistry of compounds **361d, 369f, 369g** were determined by X-ray crystallography.

6.3. Conclusions

Zinc enolates generated through cobalt-catalysed conjugate reduction of α,β-unsaturated amides using diethylzinc as the stoichiometric reductant undergo in situ

diastereoselective aldol reactions with ketones to provide tertiary β-hydroxycarbonyl compounds in good yields.

6.4. References

[1] For the reaction of zinc enolates with aldehydes and ketones, see: (a) Reformatsky, S. *Chem. Ber.* **1887**, *20*, 1210. For reviews of the Reformatsky reaction, see: (b) Fürstner, A. *Synthesis* **1989**, 571. (c) Ocampo, R.; Dolbier, W. R., Jr. *Tetrahedron* **2004**, *60*, 9325. (d) Cozzi, P. G. *Angew. Chem.*, *Int. Ed.* **2007**, *46*, 2568.

[2] For selected examples of the reaction of zinc enolates with imines, see: (a) Gilman, H.; Speeter, M. *J. Am. Chem. Soc.* **1943**, *65*, 2255. (b) Adrian, J. C., Jr.; Snapper, M. L. *J. Org. Chem.* **2003**, *68*, 2143. (c) Cozzi, P. G.; Rivalta, E. *Angew. Chem.*, *Int. Ed.* **2005**, *44*, 3600.

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[4] For other recent methods of stoichiometric zinc enolate formation not discussed above, see: (a) Ikeda, Z.; Hirayama, T.; Matsubara, S. *Angew. Chem.*, *Int. Ed.* **2006**, *45*, 8200. (b) Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2007**, *16*, 4105. (c) Hlavinka, M. L.; Hagadorn, J. R. *Tetrahedron Lett.* **2006**, *47*, 5049. (d) Hlavinka, M. L.; Greco, J. F.; Hagadorn, J. R. *Chem. Commun.* **2005**, 5304.

[5] For selected examples of catalytic zinc enolate generation using *substoichiometric* quantities of chiral bimetallic zinc complexes, see: (a) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M.. *J. Am. Chem. Soc.* **2004**, *126*, 8777. (b) Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2582. (c) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169. (d) Trost, B. M.; Hisaindee, S. *Org. Lett.* **2006**, *8*, 6003. (e) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778. (f) Trost, B. M.; Shin, S.; Sclafani, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8602. (g) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367. (h) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003.

[6] For an early report, see: (a) Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Tetrahedron Lett.* **1996**, *37*, 5141. For selected examples of sequential catalytic asymmetric conjugate addition–electrophilic trapping reactions using organozinc reagents, see: (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem.*, *Int. Ed. Engl.* **1997**, *36*, 2620. (c) Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2002**, *67*, 7244. (d) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 1104. (e) Alexakis, A.; Trevitt, G. P.; Bernardinelli, G. *J. Am. Chem. Soc.* **2001**, *123*, 4358. (f) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755. (g) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.*

2002, *124*, 779. (h) Agapiou, K.; Cauble, D. F.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4528.

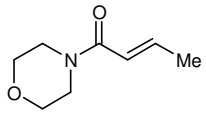
[7] For recent examples of catalytic enantioselective conjugate additions of organozinc reagents to α,β-unsaturated carboxylic acid derivatives, see: (a) Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem.*, *Int. Ed.* **2005,** *44*, 5306. (b) Hird, A. W.; Hoveyda, A. H. *Angew. Chem.*, *Int. Ed.* **2003**, *42*, 1276. (c) Schuppan, J.; Minaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, 792.

[8] Chapter 3

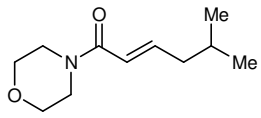
[9] Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

6.5. Experimental

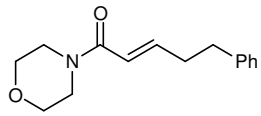
Preparation of β-Substituted α,β-Unsaturated Morpholine Amide Substrates



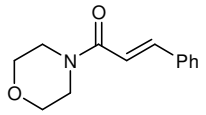
(*E*)-1-Morpholin-4-ylbut-2-en-1-one (374a).[i] Prepared according to a previously reported procedure.[ii]



(*E*)-5-Methyl-1-morpholin-4-ylhex-2-en-1-one (374b).[ii] Prepared according to a previously reported procedure. [iii]

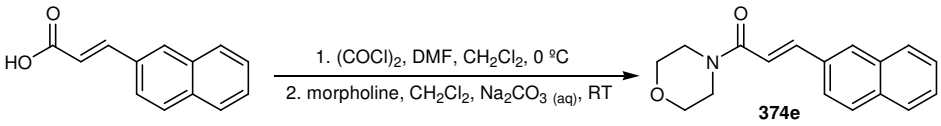


(*E*)-1-Morpholin-4-yl-5-phenyl-pent-2-en-1-one (374c).[iii] Prepared according to a previously reported procedure.[iv]



(*E*)-1-Morpholin-4-yl-3-phenylpropenone (374d). Prepared according to a previously reported procedure.[iv]

(*E*)-1-Morpholin-4-yl-3-naphthalen-2-ylpropenone (374e)



To a solution of (2-naphthyl)acrylic acid (1.49 g, 7.50 mmol) and DMF (0.16 mL, 2.06 mmol) in CH_2Cl_2 (14 mL) at 0 ºC was added oxalyl chloride (712 μL, 8.25 mmol) dropwise over 2 min and the mixture was stirred at 0 ºC for 1 h. The resulting

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[i] Ando, K.; Tsuji, E.; Ando, Y.; Kunitomo, J.-i.; Kobayashi, R.; Yokomizo, T.; Shimizu, T.; Yamashita, M.; Ohta, S.; Nabe, T.; Kohno, S.; Ohishi, Y. *Org. Biomol. Chem.* **2005**, *3*, 2129.

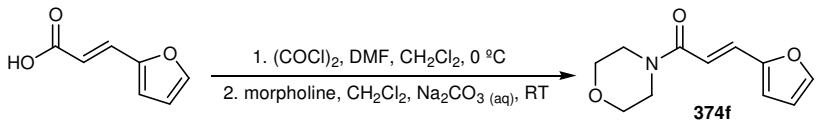
[ii] Janecki, T.; Bodalski, R.; Wieczorek, M.; Bujacz, G. *Tetrahedron* **1995**, *51*, 1721.

[iii]. Tosaki, S.-y.; Horiuchi, Y.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Chem. Eur. J.* **2004**, *10*, 1527.

[iv]. Badioli, Michele; Ballini, Roberto; Bartolacci, Massimo; Bosica, Giovanna; Torregiani, Elisabetta; Marcantoni, Enrico. *J. Org. Chem.* **2002**, *67*, 8938.

acid chloride solution was then transferred *via* cannula to a vigorously stirred mixture of morpholine (0.44 mL, 5.00 mmol) in CH_2Cl_2 (5 mL) and saturated aqueous Na_2CO_3 solution (5 mL) and the reaction was stirred for 2 h. The mixture was partitioned between saturated aqueous $NaHCO_3$ solution (30 mL) and CH_2Cl_2 (30 mL), and the aqueous layer was separated and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (70% EtOAc/petrol) gave the *α,β-unsaturated morpholine amide* **374e** (1.28 g, 96%) as a white solid. m.p. 146-148 °C; IR ($CHCl_3$) 2985, 2860, 1644 (C=O), 1591(C=C), 1442, 1269, 1115, 982, 819, 727 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.90 (1H, s, Ar**H**), 7.86 (1H, d, *J* = 15.4 Hz, ArC**H**=), 7.85-7.79 (3H, m, Ar**H**), 7.65 (1H, dd, *J* = 8.6, 1.6 Hz, Ar**H**), 7.50-7.46 (2H, m, Ar**H**), 6.95 (1H, d, *J* = 15.4 Hz, ArCH=C**H**), 3.72-3.70 (8H, m, 2 x O**C**$\mathbf{H}_2$**C**$\mathbf{H}_2$N); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 165.4 (C), 143.0 (CH), 133.8 (C), 133.2 (C), 132.4 (C), 129.1 (CH), 128.4 (CH), 128.3 (CH), 127.6 (CH), 126.8 (CH), 126.5 (CH), 123.4 (CH), 116.6 (CH), 66.7 (2 x CH_2), 46.1 (CH_2), 42.3 (CH_2); HRMS (ES) Exact mass calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$: 268.1332, found: 268.1334.

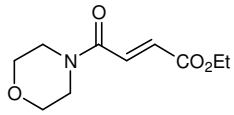
(*E*)-3-Furan-2-yl-1-morpholin-4-ylpropenone (374f)



374f

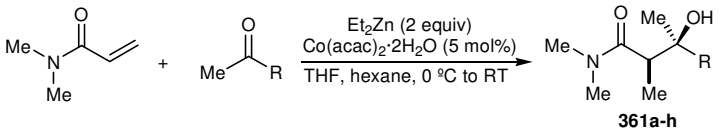
To a solution of (2-furyl)acrylic acid (2.07 g, 15.0 mmol) and DMF (0.32 mL, 4.13 mmol) in CH_2Cl_2 (27 mL) at 0 ºC was added oxalyl chloride (1.42 mL, 16.5 mmol) dropwise over 2 min and the mixture was stirred at 0 ºC for 1 h. The resulting acid chloride solution was then transferred *via* cannula to a vigorously stirred mixture of morpholine (0.87 mL, 10.0 mmol) in CH_2Cl_2 (10 mL) and saturated aqueous Na_2CO_3 solution (10 mL) and the reaction was stirred for 4 h. The mixture was partitioned between saturated aqueous $NaHCO_3$ solution (50 mL) and CH_2Cl_2 (50 mL), and the aqueous layer was separated and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (70% EtOAc/petrol) gave the *α,β-unsaturated morpholine amide* **374f** (1.96 g, 95%) as a white solid. m.p. 106-108 °C; IR ($CHCl_3$)

2963, 2864, 1653 (C=O), 1458, 1362, 1258, 1113, 962, 811, 739 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.44 (1H, d, *J* = 15.1 Hz, O=CCH=C**H**), 7.41-7.40 (1H, m, C**H**), 6.73 (1H, d, *J* = 15.1 Hz, O=CC**H**), 6.52 (1H, d, *J* = 3.4 Hz, C**H**), 6.42 (1H, dd, *J* = 3.4, 1.8 Hz, C**H**), 3.86-3.48 (8H, m, 2 x OC$\mathbf{H}_2$C$\mathbf{H}_2$N); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 165.2 (C), 151.4 (C), 143.8 (CH), 129.8 (CH), 113.9 (2 x CH), 112.1 (CH), 66.7 (2 x CH_2), 46.1 (CH_2), 42.5 (CH_2); HRMS (ES) Exact mass calcd for $C_{11}H_{14}NO_3$ $[M+H]^+$: 208.0968, found: 208.0972.



(*E*)-4-Morpholin-4-yl-4-oxobut-2-enoic acid ethyl ester (376). Prepared according to a previously reported procedure.[v]

Reductive Aldol Reactions Using *N*,*N*-Dimethylacrylamide: General Procedure A



To a solution $Co(acac)_2{\cdot}2H_2O$ (12.9 mg, 0.05 mmol), *N,N*-dimethylacrylamide (103 μL, 1.00 mmol) and the appropriate ketone (1.10 mmol) in THF (10 mL) at 0 °C was added Et_2Zn (1 M solution in hexane, 2.0 mL, 2.0 mmol) dropwise over 1 min. The reaction was stirred at 0 °C until complete consumption of the acrylamide as observed by TLC analysis. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (3 mL) and the resulting mixture was stirred for 15 minutes. Further saturated aqueous NH_4Cl solution (30 mL) was added, and the mixture was then extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the aldol product(s).

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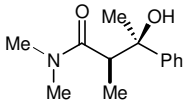
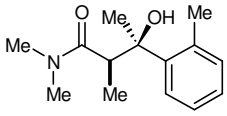
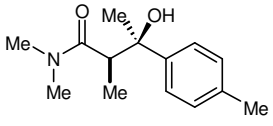
[v]. Campbell, P. G.; Sumrell, G.; Schramm, C. H. *J. Org. Chem.* **1961**, *26*, 697.



(±)-(2*R*,3*R*)-3-Hydroxy-*N*,*N*,2-trimethyl-3-phenylbutanamide (361a) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General Procedure A from acetophenone (127 μL, 1.10 mmol) for a reaction time of 2 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (166 mg, 75%) that displayed spectral data consistent with those reported previously.[vi]

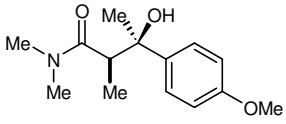


(±)-(2*R*,3*R*)-3-Hydroxy-*N*,*N*,2-trimethyl-3-(2-methylphenyl)butanamide (361b) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General Procedure A from 2′-methylacetophenone (144 μL, 1.10 mmol) for a reaction time of 4 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (157 mg, 68%). m.p. 61-63 °C; IR ($CHCl_3$) 3324 (OH), 2973, 2934, 1619 (C=O), 1463, 1415, 1399, 1059, 765, 729 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.73 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.23-7.11 (3H, m, Ar**H**), 6.01 (1H, br s, O**H**), 3.38 (1H, q, *J* = 7.0 Hz, CH_3C**H**), 3.17 (3H, s, NC**H**$_3$), 3.05 (3H, s, NC**H**$_3$), 2.53 (3H, s, ArC**H**$_3$), 1.61 (3H, s, C**H**$_3$COH), 0.94 (3H, d, *J* = 7.0 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 177.7 (C), 143.4 (C), 133.4 (C), 132.3 (CH), 127.1 (CH), 126.6 (CH), 125.8 (CH), 75.7 (C), 41.1 (CH), 37.6 (CH_3), 35.6 (CH_3), 28.9 (CH_3), 22.8 (CH_3), 12.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{21}NO_2Na$ $[M+Na]^+$: 258.1465, found: 258.1466.

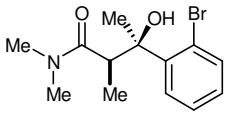


(±)-(2*R*,3*R*)-3-Hydroxy-*N*,*N*,2-trimethyl-3-(4-methylphenyl)butanamide (361c) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General Procedure A from 4'-methylacetophenone (147 μL, 1.10 mmol) for a reaction time of 4 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (186 mg, 79%). m.p. 112-114 °C; IR ($CHCl_3$) 3336 (OH), 2973, 2932, 1619 (C=O), 1513, 1461, 1415, 1072, 821 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ

7.35 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.16 (2H, d, *J* = 8.1 Hz, Ar**H**), 5.87 (1H, br s, O**H**), 3.15 (3H, s, NC**H**$_3$), 3.05 (3H, s, NC**H**$_3$), 2.99 (1H, q, *J* = 7.1 Hz, CH$_3$C**H**), 2.35 (3H, s, ArC**H**$_3$), 1.51 (3H, s, C**H**$_3$COH), 0.89 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 177.8 (C), 143.0 (C), 135.9 (C), 128.7 (2 x CH), 124.8 (2 x CH), 74.6 (C), 43.8 (CH), 37.7 (CH_3), 35.5 (CH_3), 30.1 (CH_3), 21.0 (CH_3), 12.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{22}NO_2$ $[M+H]^+$: 236.1645, found: 236.1646.



(±)-(2*R*,3*R*)-3-Hydroxy-3-(4-methoxyphenyl)-*N*,*N*,2-trimethylbutanamide (361d) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General Procedure A from 4'-methoxyacetophenone (165 mg, 1.10 mmol) for a reaction time of 3 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (212 mg, 84%). m.p. 108-110 °C; IR ($CHCl_3$) 3336 (OH), 2971, 2934, 1616 (C=O), 1513, 1461, 1416, 1397, 1247, 1176 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.39 (2H, dm, *J* = 9.0 Hz, Ar**H**), 6.89 (2H, dm, *J* = 9.0 Hz, Ar**H**), 5.87 (1H, br s, O**H**), 3.82 (3H, s, OC**H**$_3$) 3.15 (3H, s, NC**H**$_3$), 3.04 (3H, s, NC**H**$_3$), 2.96 (1H, q, *J* = 7.1 Hz, CH$_3$C**H**), 1.51 (3H, s, C**H**$_3$COH), 0.89 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 177.8 (C), 158.1 (C), 138.2 (C), 126.0 (2 x CH), 113.3 (2 x CH), 74.5 (C), 55.2 (CH_3), 43.9 (CH), 37.7 (CH_3), 35.5 (CH_3), 30.0 (CH_3), 12.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{22}NO_3$ $[M+H]^+$: 252.1594, found: 252.1594.



(±)-(2*R*,3*R*)-3-(2-Bromophenyl)-3-hydroxy-*N*,*N*,2-trimethylbutanamide (361e) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General Procedure A from 2'-bromoacetophenone (148 μL, 1.10 mmol) for a reaction time of 29 h and purified by column chromatography (10% EtOAc/petrol) to give an off-white solid (169 mg, 56%). m.p. 74-76 °C; IR ($CHCl_3$) 3313 (OH), 2972, 2934, 1619 (C=O), 1460, 1419, 1399, 1313, 1015, 758 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.08-8.05 (1H, m, Ar**H**),

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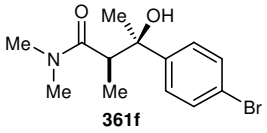
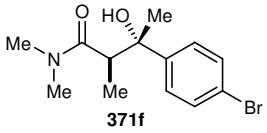
[vi]. Taniguchi, M.; Hideaki, F.; Koichiro, O.; Kiitiro, U. *Tetrahedron Lett.* **1992**, *33*, 4353.

7.58-7.55 (1H, m, Ar**H**), 7.37-7.33 (1H, m, Ar**H**), 7.13-7.08 (1H, m, Ar**H**), 6.32 (1H, br s, O**H**), 4.21 (1H, q, *J* = 7.0 Hz, $CH_3C\mathbf{H}$), 3.23 (3H, s, $NC\mathbf{H}_3$), 3.06 (3H, s, $NC\mathbf{H}_3$), 1.73 (3H, s, $C\mathbf{H}_3COH$), 0.86 (3H, d, *J* = 7.0 Hz, $C\mathbf{H}_3CH$); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 177.5 (C), 143.7 (C), 134.5 (CH), 129.7 (CH), 128.4 (CH), 127.4 (CH), 118.7 (C), 75.3 (C), 38.3 (CH), 37.6 (CH_3), 35.5 (CH_3), 26.9 (CH_3), 12.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{18}{}^{79}BrNO_2$ $[M+H]^+$: 300.0594, found: 300.0594.

(±)-(2*R*,3*R*)-3-(4-Bromophenyl)-3-hydroxy-*N*,*N*,2-trimethylbutanamide (361f) and (±)-(2*R*,3*S*)-3-(4-bromophenyl)-3-hydroxy-*N*,*N*,2-trimethylbutanamide (*anti*)(371f) (Reaction performed by R.J.R. Lumby).



361f



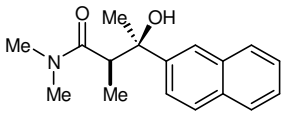
371f

General Procedure A was followed using 4'-bromoacetophenone (219 mg, 1.10 mmol) for a reaction time of 22 h and the reaction mixture was purified by column chromatography (20% EtOAc/petrol) to give the *aldol product* **361f** (207 mg, 73%) as an off-white solid followed by the *aldol product* **371f** (45 mg, 15%) as an off-white solid.

Data for **361f**: m.p. 98-100 °C; IR ($CHCl_3$) 3335 (OH), 2973, 2933, 1619 (C=O), 1489, 1461, 1415, 1399, 1074, 1009 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.48 (2H, d, *J* = 8.7 Hz, Ar**H**), 7.35 (2H, d, *J* = 8.7 Hz, Ar**H**), 5.97 (1H, br s, O**H**), 3.15 (3H, s, $NC\mathbf{H}_3$), 3.05 (3H, s, $NC\mathbf{H}_3$), 2.95 (1H, q, *J* = 7.0 Hz, $CH_3C\mathbf{H}$), 1.50 (3H, s, $C\mathbf{H}_3COH$), 0.87 (3H, d, *J* = 7.0 Hz, $C\mathbf{H}_3CH$); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 177.4 (C), 145.1 (C), 131.1 (C), 126.9 (2 x CH), 120.4 (2 x CH), 74.5 (CH), 43.6 (CH), 37.7 (CH_3), 35.6 (CH_3), 29.8 (CH_3), 12.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{19}{}^{79}BrNO_2$ $[M+H]^+$: 300.0594, found: 300.0593.

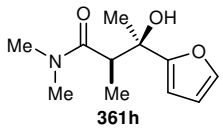
Data for **371f**: m.p. 65-67 °C; IR ($CHCl_3$) 3337 (OH), 2936, 1617 (C=O), 1483, 1394, 1306, 1089, 1008, 930, 823 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.7 Hz, Ar**H**), 7.28 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.10 (1H, s, O**H**), 3.13 (1H, q, *J* = 7.0

Hz, CH_3CH), 2.86 (3H, s, NCH_3), 2.67 (3H, s, NCH_3), 1.42 (3H, s, CH_3COH), 1.34 (3H, d, J = 7.0 Hz, CH_3CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 176.8 (C), 148.1 (C), 131.0 (2 x CH), 126.4 (2 x CH), 120.3 (C), 74.6 (C), 43.0 (CH), 37.2 (CH_3), 35.1 (CH_3), 27.2 (CH_3), 12.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{19}{}^{79}BrNO_2$ $[M+H]^+$: 300.0594, found: 300.0592.

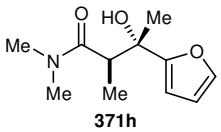


(±)-(2*R*,3*R*)-3-Hydroxy-*N*,*N*,2-trimethyl-3-naphthalen-2-ylbutanamide (361g) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General Procedure A from 2-acetonaphthone (187 mg, 1.10 mmol) for a reaction time of 3 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (212 mg, 78%). m.p. 112-114 °C; IR ($CHCl_3$) 3334 (OH), 2973, 2933, 1618 (C=O), 1457, 1416, 1398, 1182, 1129, 748 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.05 (1H, s, Ar**H**), 7.90-7.87 (1H, m, Ar**H**), 7.85-7.82 (2H, m, Ar**H**), 7.51-7.46 (3H, m, Ar**H**), 6.08 (1H, br s, O**H**), 3.20 (3H, s, NCH_3), 3.14 (1H, q, J = 7.1 Hz, CH_3CH), 3.08 (3H, s, NCH_3), 1.61 (3H, s, CH_3COH), 0.90 (3H, d, J = 7.1 Hz, CH_3CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 177.6 (C), 143.2 (C), 133.2 (C), 132.2 (C), 128.2 (CH), 127.7 (CH), 127.4 (CH), 125.9 (CH), 125.6 (CH), 124.0 (CH), 123.1 (CH), 74.9 (C) 43.5 (CH), 37.7 (CH_3), 35.6 (CH_3), 30.0 (CH_3), 12.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1645, found: 272.1646.

(±)-(2*R*,3*R*)-3-Furan-2-yl-3-hydroxy-*N*,*N*,2-trimethylbutanamide (361h) and (±)-(2*R*,3*S*)-3-furan-2-yl-3-hydroxy-*N*,*N*,2-trimethylbutanamide (371h) (Reaction performed by R.J.R. Lumby).



361h



371h

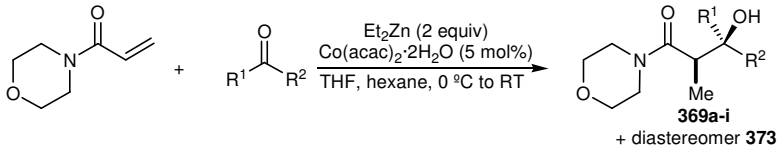
General Procedure A was followed using 2-furyl methyl ketone (121 mg, 1.10 mmol) for a reaction time of 1 h and the reaction mixture was purified by column

chromatography (20% EtOAc/petrol) to give *aldol product* **361h** (130 mg, 66%) as a white solid followed by *aldol product* **371h** (49 mg, 25%) as a colorless oil.

Data for **361h**: m.p. 78-80 °C; IR ($CHCl_3$) 3348 (OH), 2978, 2935, 1622 (C=O), 1461, 1399, 1154, 1076, 1002, 736 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.33-7.32 (1H, m, C**H**), 6.35-6.34 (2H, m, 2 x C**H**), 5.78 (1H, br s, O**H**), 3.14 (3H, s, NC**H**$_3$), 3.11 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 3.03 (3H, s, NC**H**$_3$), 1.52 (3H, s, C**H**$_3$COH), 0.98 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 177.2 (C), 157.8 (C), 140.8 (CH), 110.1 (CH), 105.2 (CH), 73.4 (C), 41.6 (CH), 37.6 (CH_3), 35.3 (CH_3), 27.8 (CH_3), 12.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{11}H_{17}NO_3Na$ $[M+Na]^+$: 234.1101, found: 234.1103.

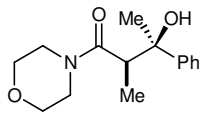
Data for **371h**: IR (film) 3409 (OH), 2989, 2938, 1619 (C=O), 1505, 1400, 1154, 1069, 938, 737 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.27 (1H, s, Ar**H**), 6.28 (1H, dd, *J* = 3.2, 1.9 Hz, Ar**H**), 6.21 (1H, dd, *J* = 3.2, 0.9 Hz, Ar**H**), 5.98 (1H, br s, O**H**), 3.23 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 2.94 (3H, s, NC**H**$_3$), 2.80 (3H, s, NC**H**$_3$), 1.47 (3H, s, C**H**$_3$COH), 1.28 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 177.0 (C), 161.0 (C), 140.7 (CH), 110.4 (CH), 104.2 (CH), 72.4 (C), 41.0 (CH), 37.2 (CH_3), 35.2 (CH_3), 24.9 (CH_3), 11.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{11}H_{18}NO_3$ $[M+H]^+$: 212.1281, found: 212.1281.

Reductive Aldol Reactions Using 4-Acryloylmorpholine: General Procedure B

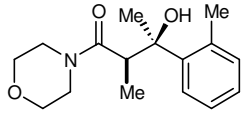


To a solution $Co(acac)_2{\cdot}2H_2O$ (12.9 mg, 0.05 mmol), 4-acryloylmorpholine (126 μL, 1.00 mmol) and the appropriate ketone (1.10 mmol) in THF (10 mL) at 0 °C was added Et_2Zn (1 M solution in hexane, 2.0 mL, 2.0 mmol) dropwise over 1 min. The reaction was stirred at 0 °C until complete consumption of 4-acryloylmorpholine as observed by TLC analysis. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (3 mL) and the resulting mixture was stirred for 15 minutes. Further saturated aqueous NH_4Cl solution (30 mL) was added, and the mixture was

then extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the aldol product(s).

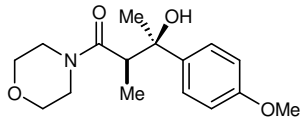


(±)-(2*R*,3*R*)-3-Hydroxy-2-methyl-1-morpholin-4-yl-3-phenylbutan-1-one (369a) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General Procedure B from acetophenone (127 μL, 1.10 mmol) for a reaction time of 4 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (210 mg, 80%). m.p. 129-131 °C; IR ($CHCl_3$) 3366 (OH), 2971, 2928, 2856, 1614 (C=O), 1462, 1445, 1231, 1117, 1022 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.48-7.45 (2H, m, Ar**H**), 7.39-7.33 (2H, m, Ar**H**), 7.27-7.22 (1H, m, Ar**H**), 5.66 (1H, br s, O**H**), 3.81-3.54 (8H, m, 2 x OC**H**$_2$C**H**$_2$N), 2.96 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 1.55 (3H, s, C**H**$_3$COH), 0.91 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 176.0 (C), 145.7 (C), 127.9 (2 x CH), 126.4 (CH), 124.8 (2 x CH), 74.6 (C), 66.8 (CH_2), 66.7 (CH_2), 46.2 (CH_2), 43.3 (CH), 41.8 (CH_2), 29.8 (CH_3), 12.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{22}NO_3$ $[M+H]^+$: 264.1594, found: 264.1590.



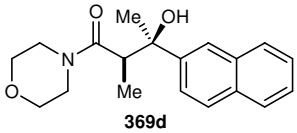
(±)-(2*R*,3*R*)-3-Hydroxy-2-methyl-3-(2-methylphenyl)-1-morpholin-4-ylbutan-1-one (369b) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General Procedure B from 2′-methylacetophenone (144 μL, 1.10 mmol) for a reaction time of 4 h and purified by column chromatography (20% EtOAc/petrol) to give a colorless oil (231 mg, 84%). IR (film) 3349 (OH), 2972, 2928, 2856, 1614 (C=O), 1464, 1439, 1230, 1117, 1020 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.68 (1H, d, *J* = Hz, Ar**H**), 7.22-7.10 (3H, m, Ar**H**), 5.74 (1H, br s, O**H**), 3.81-3.55 (8H, m, 2 x OC**H**$_2$C**H**$_2$N), 3.31 (1H, q, *J* = 7.0 Hz, CH_3C**H**), 2.52 (3H, s, ArC**H**$_3$), 1.63 (3H, s, C**H**$_3$COH), 0.96 (3H, d, *J* = 7.0 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 176.0 (C), 143.1 (C), 133.5 (C), 132.4 (CH), 126.9 (CH), 126.7 (CH), 125.7 (CH), 75.8 (C), 66.8 (CH_2), 66.7 (CH_2), 46.3 (CH_2), 42.0 (CH), 40.8 (CH_2), 28.9 (CH_3), 22.8

(CH_3), 13.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{24}NO_3$ $[M+H]^+$: 278.1751, found: 278.1750.

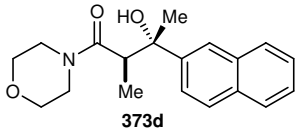


(±)-(2*R*,3*R*)-3-Hydroxy-3-(4-methoxyphenyl)-2-methyl-1-morpholin-4-ylbutan-1-one (369c) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General Procedure B from 4′-methoxyacetophenone (165 mg, 1.10 mmol) for a reaction time of 6 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (249 mg, 85%). m.p. 77-79 °C; IR ($CHCl_3$) 3366 (OH), 2970, 2931, 2856, 1612 (C=O), 1513, 1464, 1246, 1232, 1117 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.37 (2H, dm, *J* = 9.0 Hz, Ar**H**), 6.89 (2H, dm, *J* = 9.0 Hz, Ar**H**), 5.58 (1H, br s, O**H**), 3.82 (3H, s, OC**H**$_3$) 3.79-3.53 (8H, m, 2 x OC**H**$_2$C**H**$_2$N), 2.90 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 1.53 (3H, s, C**H**$_3$COH), 0.91 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); δ 176.3 (C), 158.1 (C), 138.0 (C), 126.0 (2 x CH), 113.3 (2 x CH), 74.4 (C), 66.8 (CH_2), 66.7 (CH_2), 55.1 (CH_3), 46.3 (CH_2), 43.5 (CH), 41.9 (CH_2), 29.9 (CH_3), 12.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{24}NO_4$ $[M+H]^+$: 294.1700, found: 294.1700.

(±)-(2*R*,3*R*)-3-Hydroxy-2-methyl-1-morpholin-4-yl-3-naphthalen-2-ylbutan-1-one (369d) and (±)-(2*R*,3*S*)-3-hydroxy-2-methyl-1-morpholin-4-yl-3-naphthalen-2-ylbutan-1-one (373d) (Reaction performed by R.J.R. Lumby).



369d



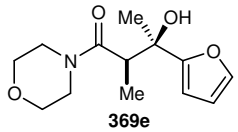
373d

General Procedure B was followed using 2-acetonaphthone (187 mg, 1.10 mmol) for a reaction time of 4 h and the reaction mixture was purified by column chromatography (20% EtOAc/petrol) to give the *aldol product* **369d** (255 mg, 82%) as a white solid followed by the *aldol product* **373d** (54 mg, 17%) as an off-white solid.

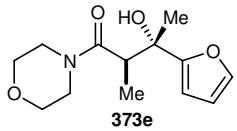
Data for **369d**: m.p. 97-99 °C; IR ($CHCl_3$) 3358 (OH), 2972, 2927, 2856, 1612 (C=O), 1468, 1437, 1231, 1117, 1026 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.04 (1H, s, Ar**H**), 7.90-7.82 (3H, m, Ar**H**), 7.52-7.44 (3H, m, Ar**H**), 5.87 (1H, br s, O**H**), 3.84-3.58 (8H, m, 2 x OC**H**$_2$C**H**$_2$N), 3.09 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 1.64 (3H, s, C**H**$_3$COH), 0.92 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 176.0 (C), 143.0 (C), 133.1 (C), 132.1 (C), 128.1 (CH), 127.7 (CH), 127.3 (CH), 125.9 (CH), 125.6 (CH), 123.9 (CH), 123.0 (CH), 74.9 (C), 66.8 (CH_2), 66.7 (CH_2), 46.3 (CH_2), 43.1 (CH), 41.9 (CH_2), 29.9 (CH_3), 13.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1751, found: 314.1749.

Data for **373d**: m.p. 105-107 °C; IR ($CHCl_3$) 3349 (OH), 2973, 2924, 2854, 1609 (C=O), 1442, 1233, 1115, 1067, 1030 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.90 (1H, s, Ar**H**), 7.83-7.79 (3H, m, Ar**H**), 7.50-7.43 (3H, m, Ar**H**), 6.00 (1H, br s, O**H**), 3.47-3.14 (7H, m, 2 x OC**H**$_2$C**H**$_2$N), 2.96-2.86 (2H, m, CH_3C**H** and OCH_2C**H**$_2$N), 1.58 (3H, s, C**H**$_3$COH), 1.41 (3H, d, *J* = 7.0 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.4 (C), 145.9 (C), 133.1 (C), 132.1 (C), 128.0 (CH), 127.7 (CH), 127.4 (CH), 126.1 (CH), 125.7 (CH), 123.3 (CH), 123.0 (CH), 74.9 (C), 66.4 (CH_2), 66.2 (CH_2), 46.0 (CH_2), 42.6 (CH), 41.5 (CH_2), 27.1 (CH_3), 12.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1751, found: 314.1753.

(±)-(2*R*,3*R*)-3-Furan-2-yl-3-hydroxy-2-methyl-1-morpholin-4-ylbutan-1-one (369e) and (±)-(2*R*,3*S*)-3-furan-2-yl-3-hydroxy-2-methyl-1-morpholin-4-ylbutan-1-one (373e) (Reaction performed by R.J.R. Lumby).



369e



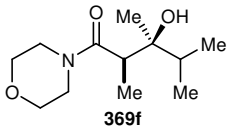
373e

General Procedure B was followed using 2-furyl methyl ketone (121 mg, 1.10 mmol) for a reaction time of 4 h and the reaction mixture was purified by column chromatography (20% EtOAc/petrol) to give the *aldol product* **369e** (187 mg, 72%) as a colorless oil followed by *aldol product* **373e** (54 mg, 22%) as a colorless oil.

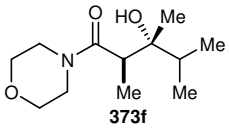
Data for **369e**: IR (film) 3388 (OH), 2976, 2932, 2858, 1617 (C=O), 1465, 1440, 1233, 1117, 1026 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.35-7.34 (1H, m, C**H**), 6.38-6.37 (2H, m, 2 x C**H**), 5.40 (1H, br s, O**H**), 3.80-3.56 (8H, m, 2 x OC**H**$_2$C**H**$_2$N), 3.10 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 1.56 (3H, s, C**H**$_3$COH), 1.02 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 175.5 (C), 157.6 (C), 140.8 (CH), 110.2 (CH), 105.3 (CH), 73.4 (C), 66.8 (CH_2), 66.7 (CH_2), 46.2 (CH_2), 41.8 (CH_2), 41.2 (CH_2), 27.7 (CH_3), 13.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{20}NO_4$ $[M+H]^+$: 254.1387, found: 254.1388.

Data for **373e**: IR (film) 3409 (OH), 2979, 2926, 2860, 1616 (C=O), 1469, 1445, 1232, 1115, 1031 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.29-7.28 (1H, m, Ar**H**), 6.31-6.30 (1H, m, Ar**H**), 6.24-6.23 (1H, m, Ar**H**), 5.68 (1H, br s, O**H**), 3.71-3.28 (8H, m, 2 x OC**H**$_2$C**H**$_2$N), 3.22 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 1.47 (3H, s, C**H**$_3$COH), 1.29 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.6 (C), 160.9 (C), 140.8 (CH), 110.5 (CH), 104.6 (CH), 72.5 (C), 66.7 (CH_2), 66.5 (CH_2), 46.2 (CH_2), 41.8 (CH_2), 40.5 (CH), 24.9 (CH_3), 11.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{12}H_{24}NO_3$ $[M+H]^+$: 230.1751, found: 230.1749.

(±)-(2*R*,3*S*)-3-Hydroxy-2,3,4-trimethyl-1-morpholin-4-ylpentan-1-one (369f) and (±)-(2*R*,3*R*)-3-hydroxy-2,3,4-trimethyl-1-morpholin-4-ylpentan-1-one (373f) (Reaction performed by R.J.R. Lumby).



369f



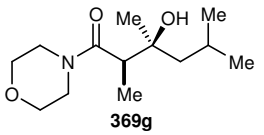
373f

General Procedure B was followed using 3-methyl-2-butanone (118 μL, 1.10 mmol) for a reaction time of 4 h and the reaction mixture was purified by column chromatography (30% EtOAc/petrol) to give the *aldol product* **369f** (75 mg, 33%) as a pale yellow solid followed by the *aldol product* **373f** (71 mg, 31%) as a pale yellow oil. Slow evaporation of a hexane solution of **369f** provided colorless crystalline crystals that were suitable for X-ray crystallography.

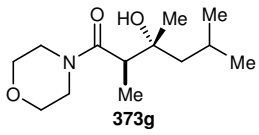
Data for **369f**: m.p. 55-57 ºC; IR ($CHCl_3$) 3398 (OH), 2964, 1614 (C=O), 1465, 1371, 1266, 1231, 1117, 1031, 1011 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.31 (1H, s, O**H**), 3.74 -3.53 (8H, m, 2 x O**C**$\mathbf{H}_2$**C**$\mathbf{H}_2$N), 2.78 (1H, q, *J* = 7.1 Hz, CH_3**C**$\mathbf{H}$**C**=O), 2.01-1.94 (1H, m, **C**$\mathbf{H}(CH_3)_2$), 1.21 (3H, d, *J* = 7.1 Hz, **C**$\mathbf{H}_3$CHC=O), 1.02 (3H, s, **C**$\mathbf{H}_3$COH), 0.99 (3H, d, *J* = 7.0 Hz, CH(**C**$\mathbf{H}_3)_2$), 0.81 (3H, d, *J* = 7.0 Hz, CH(**C**$\mathbf{H}_3)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.7 (C), 74.4 (C), 66.9 (CH_2), 66.7 (CH_2), 46.3 (CH_2), 41.8 (CH_2), 38.9 (CH), 32.9 (CH), 20.0 (CH_3), 17.2 (CH_3), 16.3 (CH_3), 11.4 (CH_3); HRMS (ES) Exact mass calcd for $C_{12}H_{24}NO_3$ $[M+H]^+$: 230.1751, found: 230.1750.

Data for **373f:** IR (film) 3399 (OH), 2963, 1613 (C=O), 1466, 1301, 1266, 1231, 1117, 1030, 919 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.83 (1H, s, O**H**), 3.75-3.49 (8H, m, 2 x O**C**$\mathbf{H}_2$**C**$\mathbf{H}_2$N), 2.82 (1H, q, *J* = 7.1 Hz, CH_3**C**$\mathbf{H}$**C**=O), 1.85-1.78 (1H, m, **C**$\mathbf{H}(CH_3)_2$), 1.21 (3H, d, *J* = 7.1 Hz, **C**$\mathbf{H}_3$CHC=O), 1.00 (3H, d, *J* = 5.4 Hz, CH(**C**$\mathbf{H}_3)_2$) 0.98 (3H, s, **C**$\mathbf{H}_3$COH), 0.80 (3H, d, *J* = 6.9 Hz, CH(**C**$\mathbf{H}_3)_2$); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 176.4 (C), 75.5 (C), 66.8 (CH_2), 66.7 (CH_2), 46.1 (CH_2), 41.6 (CH_2), 38.7 (CH), 36.1 (CH), 18.4 (CH_3), 17.3 (CH_3), 17.0 (CH_3), 12.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{12}H_{24}NO_3$ $[M+H]^+$: 230.1751, found: 230.1749.

(±)-(2*R*,3*S*)-3-Hydroxy-2,3,5-trimethyl-1-morpholin-4-ylhexan-1-one (369g) and (±)-(2*R*,3*R*)-3-hydroxy-2,3,5-trimethyl-1-morpholin-4-ylhexan-1-one (373g) (Reaction performed by R.J.R. Lumby).



369g

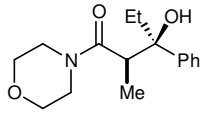


373g

General Procedure B was followed using 4-methyl-2-pentanone (138 μL, 1.10 mmol) for a reaction time of 3 h and the reaction mixture was purified by column chromatography (10% EtOAc/petrol) to give the *aldol product* **369g** (86 mg, 35%) as a colorless crystalline solid that was suitable for X-ray crystallography followed by the *aldol product* **373g** (87 mg, 36%) as a colorless oil.

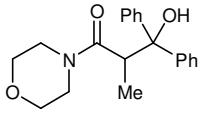
Data for **369g**: m.p. 43-45 ºC; IR (film) 3399 (OH), 2955, 2867, 1615 (C=O), 1466, 1439, 1266, 1228, 1118, 1026 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.49 (1H, br s, O**H**), 3.78-3.65 (6H, m, 2 x OC**H**$_2$C**H**$_2$N), 3.63-3.50 (2H, m, 2 x OC**H**$_2$C**H**$_2$N), 2.65 (1H, q, *J* = 7.1 Hz, CH_3C**H**C=O), 1.87-1.77 (1H, m, C**H**$(CH_3)_2$), 1.53 (1H, dd, *J* = 14.1, 7.4 Hz, C**H**$_2$CH$(CH_3)_2$), 1.33 (1H, dd, *J* = 14.1, 4.6 Hz, C**H**$_2$CH$(CH_3)_2$), 1.25 (3H, s, C**H**$_3$COH), 1.21 (3H, d, *J* = 7.1 Hz, C**H**$_3$CHC=O), 1.06 (3H, d, *J* = 6.6 Hz, CH(C**H**$_3)_2$), 0.98 (3H, d, *J* = 6.6 Hz, CH(C**H**$_3)_2$); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 176.4 (C), 72.9 (C), 66.9 (CH_2), 66.7 (CH_2), 47.4 (CH_2), 46.3 (CH_2), 41.9 (CH), 41.7 (CH_2), 26.3 (CH_3), 25.1 (CH_3), 24.2 (CH_3), 23.9 (CH), 12.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{26}NO_3$ $[M+H]^+$: 244.1907, found: 244.1909.

Data for **373g**: IR (film) 2409 (OH), 2953, 1615 (C=O), 1457, 1265, 1229, 1116, 1028, 848, 750 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.36 (1H, br s, O**H**), 3.71-3.43 (8H, m, 2 x OC**H**$_2$C**H**$_2$N), 2.57 (1H, q, *J* = 7.1 Hz, CH_3C**H**C=O), 2.60-2.54 (1H, m, C**H**$(CH_3)_2$), 1.38 (1H, dd, *J* = 14.0, 7.3 Hz, C**H**$_2$CH$(CH_3)_2$), 1.27 (1H, dd, *J* = 14.0, 4.4 Hz, C**H**$_2$CH$(CH_3)_2$), 1.16 (3H, d, *J* = 7.1 Hz, C**H**$_3$CHC=O), 1.13 (3H, s, C**H**$_3$COH), 0.96 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3)_2$), 0.87 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3)_2$); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 176.4 (C), 73.3 (C), 66.8 (CH_2), 66.6 (CH_2), 50.3 (CH_2), 46.1 (CH_2), 41.9 (CH), 41.6 (CH_2), 25.2 (CH_3), 24.2 (CH_3 and CH), 23.4 (CH_3), 12.4 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{26}NO_3$ $[M+H]^+$: 244.1907, found: 244.1909.



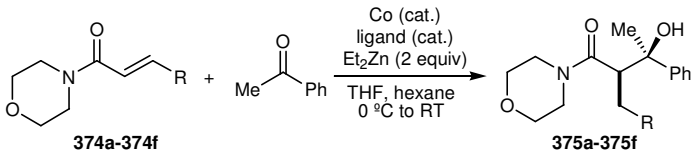
(±)-(2*R*,3*R*)-3-Hydroxy-2-methyl-1-morpholin-4-yl-3-phenylpentan-1-one (369h) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General Procedure B from propiophenone (132 μL, 1.10 mmol) for a reaction time of 7 h and purified by column chromatography (30% EtOAc/petrol) to give a white solid (207 mg, 75%). m.p. 147-149 °C; IR ($CHCl_3$) 3349 (OH), 2970, 2932, 2857, 1612 (C=O), 1447, 1230, 1117, 1028, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.42-7.33 (4H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 5.42 (1H, s, O**H**), 3.81-3.56 (8H, m, 2 x OC**H**$_2$C**H**$_2$N), 2.97 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 1.90-1.71 (2H, m, CH_3C**H**$_2$C), 0.89 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH), 0.67 (3H, t, *J* = 7.3 Hz, C**H**$_3$CH$_2$C); ^{13}C NMR (62.9

MHz, $CDCl_3$) δ 176.4 (C), 143.3 (C), 128.0 (2 x CH), 126.3 (CH), 125.6 (2 x CH), 77.7 (C), 66.9 (CH_2), 66.8 (CH_2), 46.4 (CH_2), 43.2 (CH), 41.9 (CH_2), 34.2 (CH_2), 13.0 (CH_3), 7.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{24}NO_3$ $[M+H]^+$: 278.1751, found: 278.1754.



3-Hydroxy-2-methyl-1-morpholin-4-yl-3,3-diphenylpropan-1-one (369i) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General Procedure B from benzophenone (200 mg, 1.10 mmol) for a reaction time of 3 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (202 mg, 62%). m.p. 108-110 °C; IR ($CHCl_3$) 3324 (OH), 2971, 2922, 2856, 1613 (C=O), 1448, 1230, 1116, 1032, 751 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52-7.46 (4H, m, Ar**H**), 7.33-7.26 (4H, m, Ar**H**), 7.21-7.15 (2H, m, Ar**H**), 6.43 (1H, s, O**H**), 3.78 (1H, q, *J* = 7.0 Hz, $CH_3C\mathbf{H}$), 3.73-3.42 (8H, m, 2 x $OC\mathbf{H}_2C\mathbf{H}_2N$), 1.17 (1H, d, *J* = 7.0 Hz, $C\mathbf{H}_3CH$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.7 (C), 148.0 (C), 144.6 (C), 128.2 (2 x CH), 128.1 (2 x CH), 126.7 (CH), 126.5 (CH), 125.5 (2 x CH), 125.2 (2 x CH), 78.6 (C), 66.7 (CH_2), 66.5 (CH_2), 46.1 (CH_2), 41.7 (CH_2), 41.4 (CH), 12.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{24}NO_3$ $[M+H]^+$: 326.1751, found: 326.1752.

Reductive Aldol Reactions Using *β*-Substituted *α,β*-Unsaturated Morpholine Amides



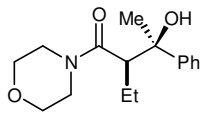
Using $Co(acac)_2{\cdot}2H_2O/Et_2Zn$: General Procedure C

To a solution $Co(acac)_2{\cdot}2H_2O$ (12.9 mg, 0.05 mmol), the appropriate *α,β*-unsaturated morpholine amide (1.00 mmol) and acetophenone (127 μL, 1.10 mmol) in THF (10 mL) at 0 °C was added Et_2Zn (1 M solution in hexane, 2.0 mL, 2.0 mmol) in one portion. The reaction was stirred at 0 °C for 2 min and then at room temperature until

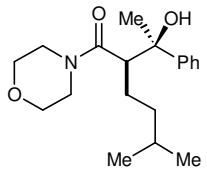
complete consumption of the *α,β*-unsaturated morpholine amide as observed by TLC analysis. The reaction was filtered through a short plug of SiO_2 (*ca*. 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the aldol product.

Using $CoCl_2$/Cy_2PPh/Et_2Zn: General Procedure D

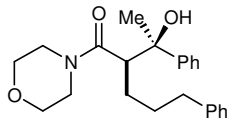
To a solution $CoCl_2$ (6.5 mg, 0.05 mmol), Cy_2PPh (15.9 mg, 0.055 mmol), the appropriate *α,β*-unsaturated morpholine amide (1.00 mmol) and acetophenone (127 μL, 1.10 mmol) in THF (10 mL) at 0 °C was added Et_2Zn (1 M solution in hexane, 2.0 mL, 2.0 mmol) in one portion. The reaction was stirred at 0 °C for 2 min and then at room temperature until complete consumption of the *α,β*-unsaturated morpholine amide as observed by TLC analysis. The reaction mixture was filtered through a short plug of SiO_2 (*ca*. 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the aldol product.



(±)-(2*R*,3*R*)-2-Ethyl-3-hydroxy-1-morpholin-4-yl-3-phenylbutan-1-one (375a). The title compound was prepared according to General Procedure D from *α,β*-unsaturated morpholine amide **374a** (155 mg, 1.00 mmol) for a reaction time of 2 h and purified by column chromatography (30% EtOAc/petrol) to give a white solid (210 mg, 76%). m.p. 97-98 °C; IR ($CHCl_3$) 3376 (OH), 2968, 2858, 1613 (C=O), 1446, 1230, 1118, 1034, 849, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.46-7.43 (2H, m, Ar**H**), 7.33-7.29 (2H, m, Ar**H**), 7.23-7.18 (1H, m, Ar**H**), 5.33 (1H, br s, O**H**), 3.79-3.60 (8H, m, 2 x O**C**$\mathbf{H}_2$**C**$\mathbf{H}_2$N), 2.91 (1H, dd, *J* = 10.9, 3.6 Hz, CH_2**C**H), 1.83-1.69 (1H, m, **C**$\mathbf{H}_2$$CH_3$), 1.46 (3H, s, **C**$\mathbf{H}_3$COH), 1.22-1.11 (1H, m, **C**$\mathbf{H}_2$$CH_3$), 0.68 (3H, t, *J* = 7.5 Hz, CH_2**C**$\mathbf{H}_3$); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 175.0 (C), 145.9 (C), 127.9 (2 x CH), 126.4 (CH), 124.7 (2 x CH), 74.6 (C), 66.8 (CH_2), 66.5 (CH_2), 50.7 (CH), 46.6 (CH_2), 41.9 (CH_2), 29.8 (CH_3), 21.2 (CH_2), 12.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{24}NO_3$ $[M+H]^+$: 278.1751, found: 278.1751.

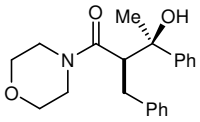


(±)-(*R*)-2-[(*R*)-1-Hydroxy-1-phenylethyl]-5-methyl-1-morpholin-4-ylhexan-1-one (375b). The title compound was prepared according to General Procedure D from *α,β*-unsaturated morpholine amide **374b** (197 mg, 1.00 mmol) for a reaction time of 5 h and purified by column chromatography (30% EtOAc/petrol) to give a white solid (270 mg, 85%). m.p. 75-76 °C; IR ($CHCl_3$) 3377 (OH), 2958, 2866, 1613 (C=O), 1463, 1232, 1118, 1035, 849, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.45-7.43 (2H, m, Ar**H**), 7.33-7.29 (2H, m, Ar**H**), 7.23-7.18 (1H, m, Ar**H**), 5.26 (1H, br s, O**H**), 3.75-3.59 (8H, m, 2 x OC$\mathbf{H}_2$C$\mathbf{H}_2$N), 2.94 (1H, dd, *J* = 10.7, 3.4 Hz, C**H**C=O), 1.80-1.69 (1H, m, C$\mathbf{H}_2$CHC=O), 1.46 (3H, s, C$\mathbf{H}_3$COH), 1.35-1.24 (1H, m, C$\mathbf{H}_2$CHC=O), 1.19-1.10 (1H, m, C**H**$(CH_3)_2$), 1.00-0.89 (1H, m, C$\mathbf{H}_2$CH$(CH_3)_2$), 0.87-0.77 (1H, m, C$\mathbf{H}_2$CH$(CH_3)_2$), 0.69 (3H, t, *J* = 5.1 Hz, CH(C$\mathbf{H}_3)_2$), 0.67 (3H, t, *J* = 5.0 Hz, CH(C$\mathbf{H}_3)_2$); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 175.2 (C), 145.9 (C), 127.9 (2 x CH), 126.4 (CH), 124.7 (2 x CH), 74.7 (C), 66.9 (CH_2), 66.6 (CH_2), 49.2 (CH), 46.6 (CH_2), 42.0 (CH_2), 36.7 (CH_3), 29.9 (CH_2), 27.8 (CH), 26.0 (CH_2), 22.5 (CH_2), 21.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{30}NO_3$ $[M+H]^+$: 320.2220, found: 320.2222.

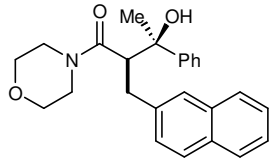


(±)-(*R*)-2-[(*R*)-1-Hydroxy-1-phenylethyl]-1-morpholin-4-yl-5-phenylpentan-1-one (375c). The title compound was prepared according to General Procedure D from *α,β*-unsaturated morpholine amide **374c** (245 mg, 1.00 mmol) for a reaction time of 5 h and purified by column chromatography (30% EtOAc/petrol) to give a 16:1 inseparable mixture of diastereoisomers as a white solid (298 mg, 81%). m.p. 76-77 °C; IR ($CHCl_3$) 3378 (OH), 2969, 2857, 1609 (C=O), 1445, 1230, 1116, 1030, 910, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.56-7.54 (2H, m, Ar**H**), 7.43-7.39 (2H, m, Ar**H**), 7.35-7.17 (4H, m, Ar**H**), 7.07-7.15 (2H, m, Ar**H**), 5.34 (1H, br s, O**H**), 3.82-3.59 (8H, m, 2 x OC$\mathbf{H}_2$C$\mathbf{H}_2$N), 3.07 (1H, dd, *J* = 10.5, 3.3 Hz, CH_2C**H**), 2.53-2.40 (2H, m, C$\mathbf{H}_2$Ar), 1.99-1.87 (1H, m, CHC$\mathbf{H}_2$), 1.57 (3H, s, C$\mathbf{H}_3$COH), 1.57-1.47 (1H, m, CHC$\mathbf{H}_2$), 1.39-1.25 (2H, m, CH_2C$\mathbf{H}_2CH_2$); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 174.8 (C), 145.8 (C), 141.7 (C) 128.0 (2 x CH), 127.9 (4

x CH), 126.4 (CH), 125.5 (CH), 124.7 (2 x CH), 74.6 (C), 66.7 (CH_2), 66.4 (CH_2), 49.0 (CH), 46.4 (CH_2), 41.8 (CH_2), 35.7 (CH_2), 29.6 (CH_3), 29.5 (CH_2), 27.9 (CH_2); HRMS (ES) Exact mass calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2220, found: 368.2223.

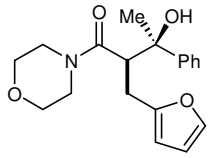


(2*R*,3*R*)-2-Benzyl-3-hydroxy-1-morpholin-4-yl-3-phenylbutan-1-one (375d). The title compound was prepared according to General Procedure C from *α,β*-unsaturated morpholine amide **374d** (217 mg, 1.00 mmol) for a reaction time of 6 h and purified by column chromatography (30% EtOAc/petrol) to give a white solid (241 mg, 71%). m.p. 126-127 °C; IR ($CHCl_3$) 3349 (OH), 2970, 2859, 1611 (C=O), 1446, 1233, 1116, 846, 750, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.58-7.56 (2H, m, Ar**H**), 7.45-7.40 (2H, m, Ar**H**), 7.33-7.28 (1H, m, Ar**H**), 7.23-7.13 (3H, m, Ar**H**), 6.98-6.96 (2H, m, Ar**H**), 5.72 (1H, br s, O**H**), 3.85-3.80 (1H, m, OC**H**$_2$CH$_2$N), 3.62-3.57 (1H, m, OC**H**$_2$CH$_2$N), 3.37-3.14 (5H, m, 2 x OC**H**$_2$C**H**$_2$N), 2.99 (1H, app t, *J* = 12.5 Hz, CH$_2$C**H**), 2.89-2.83 (1H, m, OCH$_2$C**H**$_2$N), 2.51-2.40 (2H, m, C**H**$_2$Ph), 1.49 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 174.3 (C), 145.8 (C), 139.4 (C) 129.0 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 126.7 (CH), 126.5 (CH), 124.8 (2 x CH), 74.8 (C), 66.4 (CH_2), 65.9 (CH_2), 52.1 (CH), 46.2 (CH_2), 41.8 (CH_2), 34.7 (CH_2), 30.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{21}H_{26}NO_3$ $[M+H]^+$: 340.1907, found: 340.1909.



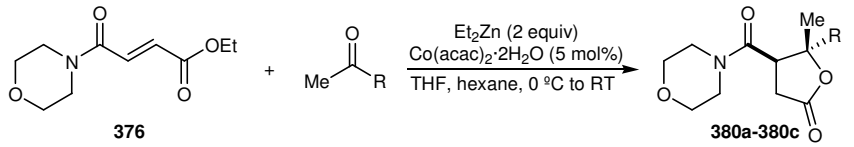
(±)-(2*R*,3*R*)-3-Hydroxy-1-morpholin-4-yl-2-naphthalen-2-ylmethyl-3-phenylbutan-1-one (375e). The title compound was prepared according to General Procedure C from *α,β*-unsaturated morpholine amide **374e** (267 mg, 1.00 mmol) for a reaction time of 6 h and purified by column chromatography (30% EtOAc/petrol) to give a white solid (289 mg, 74%). m.p. 137-139 °C; IR ($CHCl_3$) 3357 (OH), 2970, 2858, 1610 (C=O), 1446, 1233, 1116, 909, 732, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.78-7.76 (1H, m, Ar**H**), 7.71-7.69 (2H, m, Ar**H**), 7.65-7.63 (2H, m, Ar**H**), 7.50-7.40 (5H, m, Ar**H**), 7.37-7.33 (1H, m, Ar**H**), 7.07 (1H, dd, *J* = 8.4, 1.4 Hz, Ar**H**), 5.80 (1H, br s, O**H**), 3.78-3.72 (1H, m, OC**H**$_2$CH$_2$N), 3.53-3.47 (1H, m, OC**H**$_2$CH$_2$N), 3.38-3.29 (2H, m, OC**H**$_2$CH$_2$N), 3.23-3.07 (4H, m, 2 x OCH$_2$C**H**$_2$N), 2.78-2.72 (1H, m, C**H**$_2$CH), 2.61

(1H, dd, J = 12.8, 2.7 Hz, C**H**CH_2), 2.21-2.15 (1H, m, C**H**$_2$CH), 1.54 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 174.2 (C), 145.8 (C), 136.7 (C), 133.3 (C), 131.9 (C), 128.2 (2 x CH), 127.9 (CH), 127.5 (2 x CH), 127.1 (2 x CH), 126.7 (CH), 126.2 (CH), 125.5 (CH), 124.8 (CH), 74.9 (C), 66.3 (CH_2), 65.6 (CH_2), 52.0 (CH), 46.0 (CH_2), 41.7 (CH_2), 34.8 (CH_2), 29.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{25}H_{28}NO_3$ $[M+H]^+$: 390.2064, found: 390.2070.



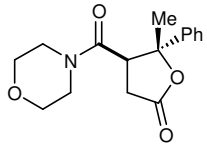
(±)-(2*R*,3*R*)-2-Furan-2-ylmethyl-3-hydroxy-1-morpholin-4-yl-3-phenylbutan-1-one (375f). The title compound was prepared according to General Procedure C from *α,β*-unsaturated morpholine amide **374f** (207 mg, 1.00 mmol) for a reaction time of 6 h and purified by column chromatography (30% EtOAc/petrol) to give a white solid (278 mg, 84%). m.p. 65-66 °C; IR ($CHCl_3$) 3366 (OH), 2970, 2859, 1613 (C=O), 1446, 1231, 1116, 919, 735, 703 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.58-7.56 (2H, m, Ar**H**), 7.43-7.39 (2H, m, Ar**H**), 7.33-7.27 (1H, m, Ar**H**), 7.26 (1H, d, J = 1.5 Hz, C**H**), 6.24 (1H, dd, J = 3.1, 1.5 Hz, C**H**), 5.93 (1H, d, J = 3.1 Hz, C**H**), 5.66 (1H, br s, O**H**), 3.83-3.77 (1H, m, OC**H**$_2$CH$_2$N), 3.71-3.65 (1H, m, OC**H**$_2$CH$_2$N), 3.53-3.40 (5H, m, 2 x OC**H**$_2$C**H**$_2$N), 3.28-3.16 (2H, m, OCH$_2$C**H**$_2$N and C**H**CH_2), 3.11 (1H, dd, J = 14.7, 11.8 Hz, C**H**$_2$CH), 2.45 (1H, dd, J = 14.7, 3.2 Hz, C**H**$_2$CH), 1.54 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 174.2 (C), 153.1 (C), 145.3 (C), 141.1 (CH), 128.2 (2 x CH), 126.7 (CH), 124.8 (2 x CH), 110.5 (CH), 106.7 (CH), 74.5 (C), 66.6 (CH_2), 66.3 (CH_2), 48.5 (CH), 46.2 (CH_2), 41.9 (CH_2), 30.0 (CH_3), 27.0 (CH_2); HRMS (ES) Exact mass calcd for $C_{19}H_{24}NO_4$ $[M+H]^+$: 330.1700, found: 330.1698.

Reductive Aldol Reactions Using *α,β*-Unsaturated Morpholine Amide 12: General Procedure E

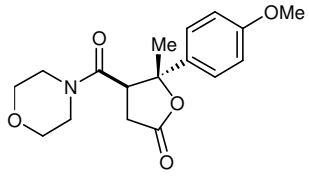


376 380a-380c

To a solution $Co(acac)_2 \cdot 2H_2O$ (12.9 mg, 0.05 mmol), *α,β*-unsaturated morpholine amide **376** (213 mg, 1.00 mmol) and the appropriate ketone (1.10 mmol) in THF (10 mL) at 0 °C was added Et_2Zn (1 M solution in hexane, 2.0 mL, 2.0 mmol) in one portion. The reaction was stirred at 0 °C for 2 min and then at room temperature until complete consumption of the *α,β*-unsaturated morpholine amide **376** as observed by TLC analysis. The reaction mixture was filtered through a short plug of SiO_2 (*ca.* 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the product.

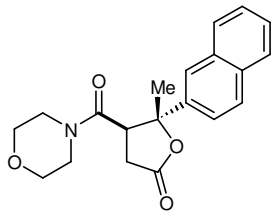


(±)-(4*R*,5*R*)-5-Methyl-4-(morpholine-4-carbonyl)-5-phenyltetrahydrofuran-2-one (379a). The title compound was prepared according to General Procedure E from acetophenone (127 μL, 1.10 mmol) for a reaction time of 6 h and purified by column chromatography (80% EtOAc/petrol) to give a white solid (196 mg, 68%). m.p. 145-147 °C; IR ($CHCl_3$) 3531 (OH), 2984, 2859, 1788 (C=O), 1643 (C=O), 1445, 1244, 1116, 910, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.39-7.31 (5H, m, Ar**H**), 3.76-3.39 (6H, m, 2 x O**C**$\mathbf{H}_2$**C**$\mathbf{H}_2$N), 3.32-3.19 (2H, m, **C**HCH_2 and **C**$\mathbf{H}_2$CH), 3.14-3.07 (1H, m, $OCH_2C\mathbf{H}_2N$), 2.92-2.86 (1H, m, $OCH_2C\mathbf{H}_2N$), 2.59 (1H, dd, *J* = 17.5, 8.0 Hz, **C**$\mathbf{H}_2$CH), 1.67 (3H, s, **C**$\mathbf{H}_3$COH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 174.7 (C), 167.5 (C), 143.1 (C), 128.9 (2 x CH), 128.4 (CH), 124.4 (2 x CH), 86.5 (C), 66.6 (CH_2), 66.2 (CH_2), 48.4 (CH), 46.1 (CH_2), 42.4 (CH_2), 33.4 (CH_2), 22.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{23}N_2O_4$ $[M+NH_4]^+$: 307.1652, found: 307.1648.



(±)-(4*R*,5*R*)-5-(4-Methoxyphenyl)-5-methyl-4-(morpholine-4-carbonyl)tetrahydrofuran-2-one (379b). The title compound was prepared according to General Procedure E from 4'-methoxyacetophenone (165 mg, 1.10 mmol) for a reaction time of 6 h and purified by column chromatography (80% EtOAc/petrol) to give a white solid (197 mg, 62%). m.p. 136-138 °C; IR ($CHCl_3$)

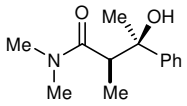
3524 (OH), 2967, 2858, 1785 (C=O), 1645 (C=O), 1460, 1251, 1117, 834, 733 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.92 (2H, d, *J* = 8.9 Hz, Ar**H**), 3.80 (3H, s, OC**H**$_3$), 3.78-3.41 (6H, m, 2 x OC**H**$_2$C**H**$_2$N), 3.33-3.25 (2H, m, C**H**CH$_2$ and C**H**$_2$CH), 3.14-3.07 (1H, m, OCH$_2$C**H**$_2$N), 2.93-2.86 (1H, m, OCH$_2$C**H**$_2$N), 2.63 (1H, dd, *J* = 17.5, 8.1 Hz, C**H**$_2$CH), 1.66 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 174.7 (C), 167.4 (C), 159.4 (C), 134 (C), 125.9 (2 x CH), 114.0 (2 x CH), 86.3 (C), 66.5 (CH_2), 66.2 (CH_2), 55.2 (CH_3), 48.7 (CH), 46.1 (CH_2), 42.4 (CH_2), 33.4 (CH_2), 22.3 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{25}N_2O_5$ $[M+NH_4]^+$: 337.1758, found: 337.1758.



(±)-(4*R*,5*R*)-5-Methyl-4-(morpholine-4-carbonyl)-5-naphthalen-2-yltetrahydrofuran-2-one (379c). The title compound was prepared according to General Procedure E from 2-acetonaphthone (165 mg, 1.10 mmol) for a reaction time of 6 h and purified by column chromatography (80% EtOAc/petrol) to give a white solid (220 mg, 65%). m.p. 144-146 °C; IR ($CHCl_3$) 3526 (OH), 2984, 2858, 1785 (C=O), 1638 (C=O), 1441, 1238, 1117, 822, 732 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.91-7.82 (4H, m, Ar**H**), 7.54-7.45 (3H, m, Ar**H**), 3.82-3.49 (5H, m, 2 x OC**H**$_2$C**H**$_2$N), 3.34-3.27 (2H, m, C**H**CH$_2$ and C**H**$_2$CH), 3.24-3.18 (1H, m, OCH$_2$C**H**$_2$N), 3.13-3.07 (1H, m, OCH$_2$C**H**$_2$N), 2.91-2.85 (1H, m, OCH$_2$C**H**$_2$N), 2.67 (1H, dd, *J* = 17.5, 8.1 Hz, C**H**$_2$CH), 1.80 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 174.8 (C), 167.6 (C), 140.2 (C), 132.7 (C), 129.1 (CH), 128.1 (2 x CH), 127.5 (CH), 126.9 (CH), 126.8 (C), 123.6 (CH), 122.0 (CH), 86.6 (C), 66.6 (CH_2), 66.2 (CH_2), 48.0 (CH), 46.2 (CH_2), 42.5 (CH_2), 33.4 (CH_2), 22.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{25}N_2O_4$ $[M+NH_4]^+$: 357.1809, found: 357.1806.

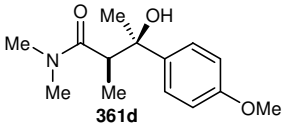
Stereochemical Determinations

- The relative stereochemistry of the known aldol product **361a** was assigned by comparison with literature spectral data.[vi]

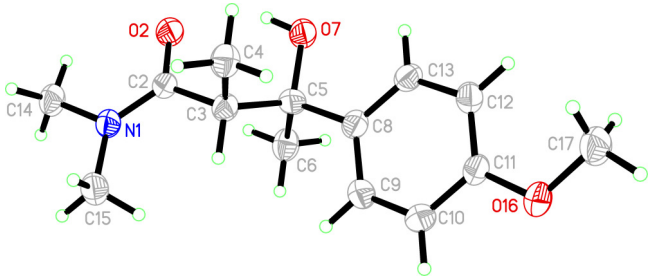


361a

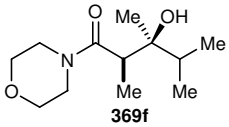
- The relative stereochemistry of **361d** was determined by X-ray crystallography.



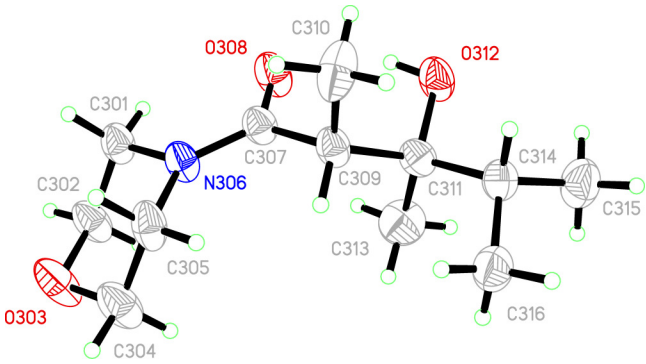
361d



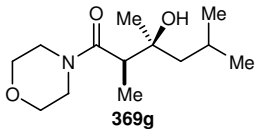
- The relative stereochemistry of **369f** was determined by X-ray crystallography.



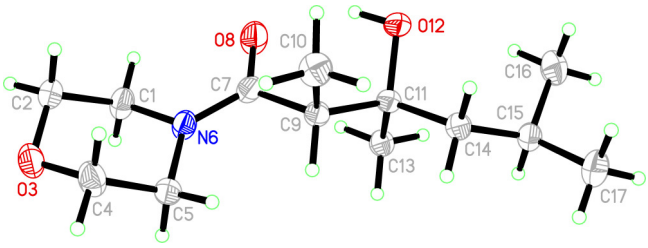
369f



- The relative stereochemistry of **389g** was determined by X-ray crystallography.



369g



- The relative stereochemistries of the remaining products were assigned by analogy.

7. Asymmetric Intermolecular Reductive Aldol Reactions[i]

Since cobalt-catalysed intermolecular reductive aldol reactions of *α,β*-unsaturated amides with ketones gave promising levels of diastereoselectivity, we next decided to study whether we could perform the same reaction in asymmetric fashion. Stereocontrolled aldol reactions with ketone electrophiles enable access to chiral tertiary alcohols, structural units that are present in numerous biologically active molecules. Compared with aldehydes[1] however, there are few effective methods for controlling the absolute stereochemical outcome of ketone aldol reactions.[2,3,4] Factors responsible for this paucity include the attenuated reactivity of ketones compared with aldehydes, problems with retroaldolisation, and smaller differences in steric properties between the two substituents attached to the ketone carbonyl. The latter feature is often manifested in low levels of diastereoselectivity and enantiofacial discrimination. Although a number of approaches to address these challenges have been documented, there remains room for improvement, since existing procedures often display suboptimal selectivities or narrow substrate scope. Therefore, the development of new, complementary methods for conducting asymmetric ketone aldol reactions continues to be a valuable endeavour. We decided to study whether chiral zinc-enolates could be trapped with ketones, thus controlling the absolute stereochemistry.

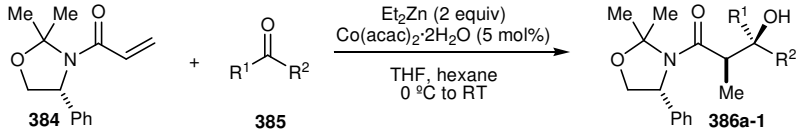
7.1. Scope of the Reaction

The success of such a strategy rested upon identification of a chiral auxiliary that would allow the reaction to proceed efficiently, and impart high levels of enolate diastereofacial selectivity. Although *N*-alkenoyloxazolidinones seemed an obvious first choice,[1a] these substrates did not provide aldol products under our conditions. Fortunately, *N*-acryloyloxazolidine **384**[5] was found to meet our desired criteria, reacting with acetophenone to afford aldol product **386a** in 73% yield and with 11:1 diastereoselectivity (Table 7.1, Entry 1). Further exploration of ketone scope

[i] The work in this chapter was done in collaboration with Ralph J.R. Lumby

revealed that acetophenone derivatives containing substituents of varying electronic properties were tolerated, giving aldol products in 58-76% yields and with up to 12:1 diastereoselectivity (Entries 2–6). Acryloyloxazolidine **384** also underwent reaction with ketones bearing naphthyl (Entries 7 and 9), heteroaromatic (Entry 8) and ethyl substituents (Entry 9).

Table 7.1.[ii] Cobalt-Catalysed Reductive Aldol Reactions of N-Acryloyloxazolidinine XX with Representative ketones[a]



Entry	R^1	R^2	Product	dr[b,c]	Yield(%)[d]
1	Me	Ph	**386a**	11:1	73
2	Me	4-MePh	**386b**	9:1	76
3	Me	3-MePh	**386c**	12:1	72
4	Me	4-MeOPh	**386d**	8.5:1	72
5	Me	4-BrPh	**386e**	12:1	63
6	Me	3-ClPh	**386f**	7:1	58
7	Me	2-Naphthyl	**386g**	13:1	75
8	Me	2-thienyl	**386h**	6:1	61
9	Et	6'-MeO-2-Naphthyl	**386i**	6:1	59

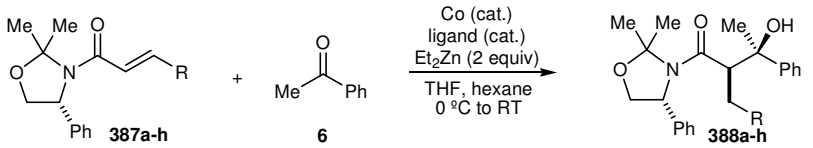
a) Reactions were conducted using 1.0 mmol of **384** and 1.1 mmol of ketone in THF (5 mL) and hexane (2 mL) for 3–17 h. b) Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. c) dr = (major isomer):Σ(other isomers). d) Isolated yield of major diastereomer.

After studying the scope of the ketones, we studied the effect of the substitution on the double bond. Table 7.2 resents the results of reaction of a range of *N*-alkenoyloxazolidines **387a-387h** with acetophenone. These data illustrate that substitution at the acrylamide has a greatly beneficial effect on reaction diastereoselectivity (≥15:1). In addition, the reactions of **387a-387h** were cleaner than those of *N*-acryloyloxazolidine **384**, which resulted in higher isolated yields of

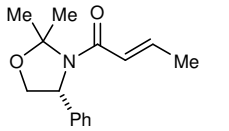
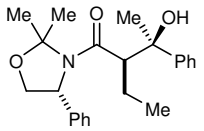
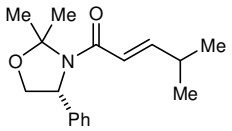
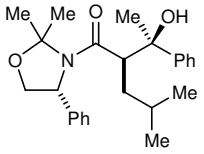
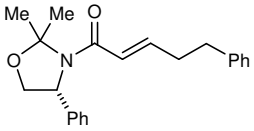
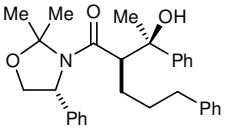
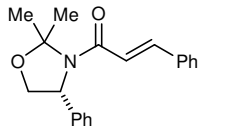
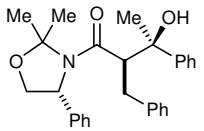
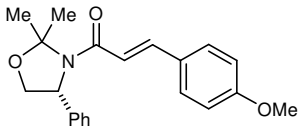
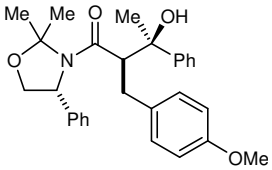
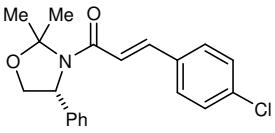
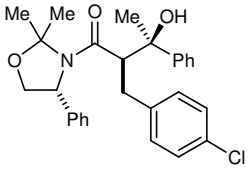
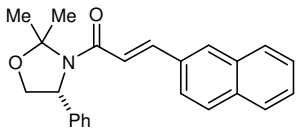
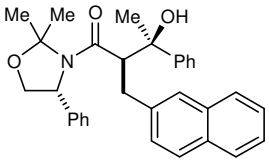
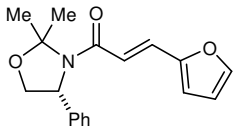
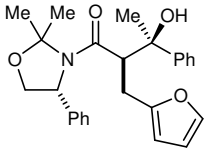
[ii] Reactions performed by Ralph J.R. Lumby

products (Table 7.1). Aromatic- and heteroaromatic-substituted *N*-alkenoyloxazolidines were the best substrates in these reactions, affording aldol products in 83–90% yield as one observable diastereomer (>19:1 by ^{1}H NMR analysis) (Entries 4–8). With alkyl-substituted acrylamides **387a-387c**, incomplete conversions were observed using $Co(acac)_2 \cdot 2H_2O$ as the pre-catalyst, but the combination of $CoCl_2$ and Cy_2PPh provided improved results (Entries 1–3).

Table 7.2. Reactions of Acetophenone with Representative N-alkenoyloxazolidines[a]

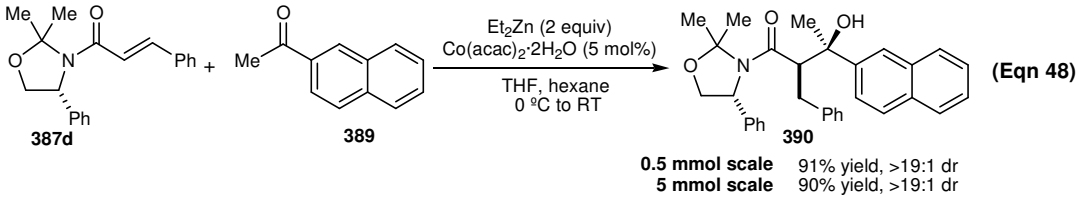


Method A: $Co(acac)_2 \cdot 2H_2O$ (5 mol%)
Method B: $CoCl_2$ (5 mol%), Cy_2PPh (5.5 mol%)

Entry	Method	Substrate		Product		Yield(%) dr
1	B		**387a**		**388a**	82 (16:1)
2	B		**387b**		**388b**	79 (15:1)
3	B		**387c**		**388c**	80 (15:1)
4	A		**387d**		**388d**	86 (>19:1)
5	A		**387e**		**388e**	86 (>19:1)
6	A		**387f**		**388f**	84 (>19:1)
7	A		**387g**		**388g**	90 (>19:1)
8	A		**387h**		**388g**	83 (>19:1)

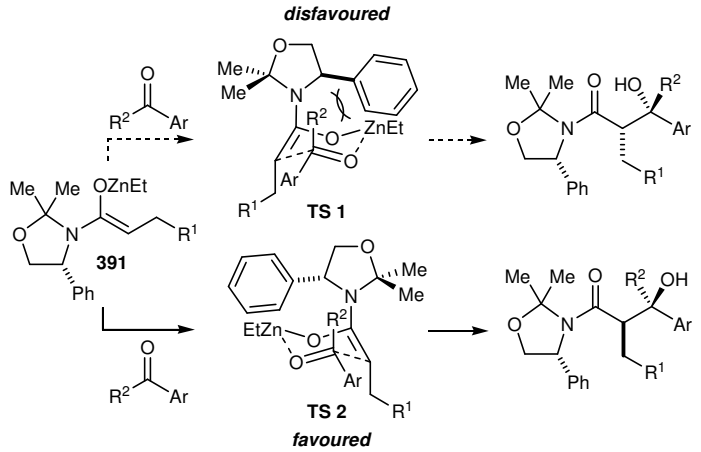
a) Reactions were conducted using 0.5 mmol of **387a-387h** and .55 mmol of Acetophenone in THF (2.5 mL) and hexane (1 mL) for 4–6 h. b) Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. c) dr = (major isomer):Σ(other isomers). d) Isolated yield of major diastereomer.

The yields and diastereoselectivities of these reactions are maintained on increasing the scale. For example, reaction of cinnamoyl-substituted oxazolidine **387d** with 2-acetonaphthone to give **390** on 0.5 mmol and 5 mmol scales gave comparable results (Eqn 48)**.**



(Eqn 48)

The sense of asymmetric induction observed in these reactions[6] is consistent with the intervention of *Z*-zinc enolates **391** and chelated chair-like Zimmerman–Traxler transition states[7] in which the larger aromatic substituents of the ketone resides in a less sterically hindered pseudoequatorial position (Scheme 1). We suggest that in the transition state, the *geminal* dimethyl groups of the oxazolidine are oriented anti to the enolate oxygen to minimise unfavorable nonbonding interactions. Inspection of alternative transition states **TS 1** and **TS 2** reveals that the oxazolidine phenyl substituent suffers fewer nonbonding interactions in **TS 2**, which leads to the observed stereochemistry of the major isomer.

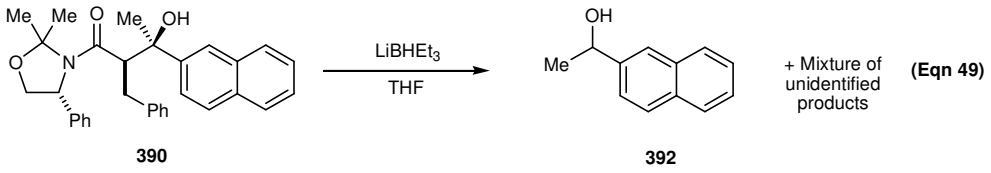


Scheme 7.1. Model for Stereochemical Outcome.

7.2. Removal of the Auxiliary

Although the levels of asymmetric induction observed in these reactions were high, allowing efficient access to chiral tertiary alcohol-containing aldol products, we needed to find an efficient method to remove the auxiliary to establish this method as a useful methodology.

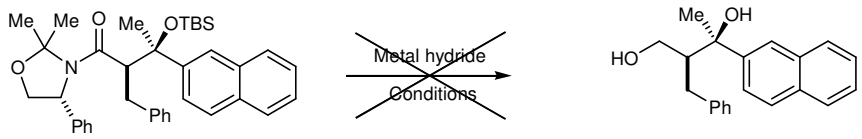
Reduction of tertiary amides into the corresponding alcohols is known to be a problematic issue.[8] The use of $LiAlH_4$[9] or diborane[10] has been shown to favour the formation of the tertiary amine. Nowadays, many new metal hydrides have been developed to favour the formation of the corresponding alcohol. These include lithium triethylborohydride ($LiBHEt_3$, superhydride)[11], Lithium pyrrolididotrihydroborate ($Li(CH_2)_4NBH_3$)[12], Lithium amidotrihydroborate (LiH_2NBH_3, "LAB")[13]. Having many potentials tools at hand we decided to try these methods for the removal of oxazolidine auxiliary. We first started by studying the removal of auxiliary from substrate **390** with superhydride. The only product we were able to identify was the alcohol **392** which is produced presumably by retro-aldol–ketone-reduction sequence.



390 **392** **(Eqn 49)**

We next decided to protect the tertiary alcohol **390** with a TBS group, and we evaluated several different reducing agents under a variety of reaction conditions to remove the auxiliary from **393**. Unfortunately, only complicated mixtures of products were obtained and these mixtures proved to be very difficult to purify. The only identified product in certain cases (Entries 3 and 9) was the again the alcohol **392**. This proved that the TBS ether was not stable under certain conditions at reflux temperatures.

Table 7.3. Trials of Removal the Chiral Auxiliary With Metal Hydrides



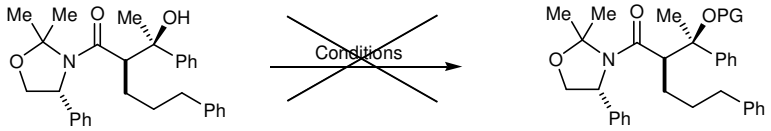
393 394

Entry	Metal Hydride	Solvent, Temperature	Observations
1	$LiBHEt_3$	THF, 0 °C	No reaction
2	$LiBHEt_3$	THF, rt	Low conversion, unidentified products
3	$LiBHEt_3$	THF, reflux	Mixture of products, **392**[a] observed
4	$Li(CH_2)_4NBH_3$	THF, 0 °C	No Reaction
5	$Li(CH_2)_4NBH_3$	THF, RT to reflux	Mixture of unidentified products
6	LiH_2NBH_3	THF, 0 °C	Low conversion, unidentified products
7	LiH_2NBH_3	THF, rt	Low conversion, unidentified products
8	LiH_2NBH_3	THF, reflux	Low conversion, unidentified products
9	LiH_2NBH_3	dioxane, reflux	Mixture of products, **392**[a] observed

a) Determined by ^{1}H NMR analysis of the unpurified reaction mixture.

Next we attempted to protect the alcohol with a more stable protecting group. We decided to try MEM-, Bn- and Ac-protecting groups. Unfortunately we did not have any success in protecting the tertiary alcohol in any case (Table 7.4).

Table 7.4. Trials of introducing different protecting groups



388c 395

Entry	PG	Conditions	Observations
1	Bn	BnBr, NaH, THF, 0 °C to rt	Mixture of unidentified products
2	Bn	BnBr, $N(Bu)_4I$, NaH, BnBr, 0 °C to rt	Mixture of unidentified products
3	Bn	Benzyl-tricholoacetimidate, CF_3SO_3H, DCM, 0 °C	Starting material recovered
4	Bn	Benzyl-tricholoacetimidate, CF_3SO_3H, DCM, 0 °C to rt	Mixture of unidentified products
5	Bn	Benzyl-tricholoacetimidate, CSA, DCM, 0 °C to rt	Starting material recovered
6	MEM	MEMCl, *i*-Pr_2NEt, DCM, rt	Starting material recovered
7	MEM	MEMCl, *i*-Pr_2NEt, DCE, reflux	Starting material recovered
8	MEM	MEMCl, *i*-Pr_2NEt, $N(Bu)_4I$, DCE, reflux	Starting material recovered
9	Ac	Ac_2O, DMAP, Et_3N, DCM, 0 °C	Starting material recovered
10	Ac	Ac_2O (as solvent), DMAP, Et_3N, 0 °C	Starting material recovered

We believe that the difficulty of introducing the protecting group to our products (**388a-388h** and **300**) is not just caused by the extreme steric hindrance in the vicinity of the tertiary alcohol. From ^{1}H-NMR of all the products a clear hydrogen bonding signal can be observed in the region between 6ppm-5ppm (see Experimental part). It seems that the nature of this hydrogen bonding, together with the fact that we are dealing with a tertiary alcohol, makes it difficult to protect. The reason why TBS-protecting group could be introduced so readily is unclear to us. The protection of these substrates is currently under investigation in our laboratories.

7.3. Conclusions and Future work

Zinc enolates generated by cobalt-catalysed conjugate reduction of readily accessible chiral *N*-alkenoyloxazolidines undergo highly diastereoselective aldol reactions with ketones to provide tertiary β-hydroxycarbonyl compounds. This method is scalable, operates under ambient temperatures, and allows for significant variation of the α-substituent in the products. Currently, a disadvantage of the reaction is that so far we have not been able to remove the chiral auxiliary. Possible future work could involve an extensive screening of reaction conditions to find a way to introduce a protecting group to our tertiary alcohol. This protecting group should be stable under the conditions needed for the cleavage of the auxiliary. Another option is to design a new chiral auxiliary that is easier to cleave.

7.4. References

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[5] a) Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8631. (b) Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8645. For the use of chiral oxazolidines in a related reaction, see: (c) Lettan, R. B., II; Reynolds. T. E.; Galliford, C. V.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 15566.

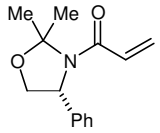
[6] The stereochemistries of **386a**, **386d** and **388f** were confirmed by X-ray crystallography. The stereochemistries of the remaining aldol products were assigned by analogy.

[7] Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

[8] Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.
[9] Uffer, H.; Schlittler, E. *Helv. Chim. Acta* **1948**, *31*, 1397.
[10] Brown, H. C.; Heim, P. *J. Am. Chem. Soc.* **1964**, *86*, 3566.
[11] Brown, H. C.; Kim, S. C.; *Synthesis* **1977**, 635.
[12] Hutchins, R. O.; Learn, K.; El-Telbany, F.; Stercho, Y. P. *J. Org. Chem.* **1976**, *41*, 1778.
[13] Myers, A. G.; Yang, B. H.; Kopecky, D.J. *Tetrahedron Lett.* **1996**, *37*, 3623.

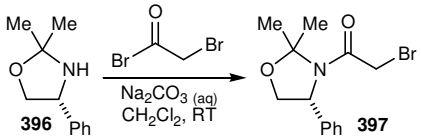
7.5. Experimental

Preparation of *N*-alkenoyloxazolidines



(4*R*)-2,2-Dimethyl-4-phenyl-3-[(*E*)-propenoyl]oxazolidine (384). Prepared according to a previously reported procedure.[i]

(4*R*)-3-Bromoacetyl-2,2-dimethyl-4-phenyloxazolidine (397)



Bromoacetyl bromide (7.2 mL, 82.5 mmol) was added in one portion to a vigorously stirred mixture of the oxazolidine **396**[i] (9.75 g, 55.0 mmol) in CH_2Cl_2 (55 mL) and saturated aqueous Na_2CO_3 solution (220 mL), and the mixture was stirred at room temperature for 4 h. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution (100 mL) and CH_2Cl_2 (100 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 100 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (15% EtOAc/hexane) gave the *bromoamide* **397** (10.14 g, 62%) as a light brown solid. m.p. 90-92 °C; $[\alpha]_D^{21}$ –190 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2985, 1660 (C=O), 1400, 1379, 1255, 1237, 1137, 1066, 844, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.40-7.36 (2H, m, Ar**H**), 7.34-7.29 (3H, m, Ar**H**), 5.07 (1H, dd, *J* = 6.6, 2.7 Hz, C**H**$_2$O), 4.39 (1H, dd, *J* = 9.0, 6.6 Hz, C**H**N), 3.91 (1H, dd, *J* = 9.0, 2.7 Hz, C**H**$_2$O), 3.55 (1H, d, *J* = 11.0 Hz, C**H**$_2$Br), 3.44 (1H, d, *J* = 11.0 Hz, C**H**$_2$Br), 1.86 (3H, s, C(C**H**$_3$)$_2$), 1.63 (3H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.7 (C), 140.3 (C), 129.0 (2 x CH), 128.1 (CH), 125.6 (2 x CH), 96.4 (C), 71.2 (CH_2), 61.0 (CH), 29.2 (CH_2), 25.0 (CH_3), 22.2 (CH_3); HRMS (FAB) Exact mass calcd for $C_{13}H_{17}{}^{79}BrNO_2$ $[M+H]^+$: 298.0438, found: 298.0444.

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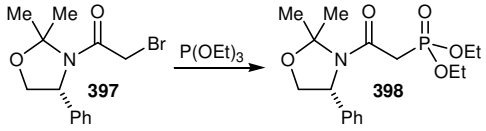
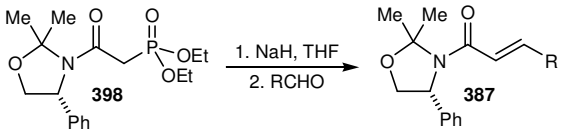
[i] Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8631.

(4*R*)-3-Diethylphosphonacetyl-2,2-dimethyl-4-phenyloxazolidine (398)



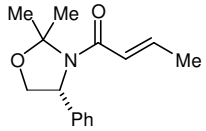
A stirred solution of the bromoamide **397** (10.40 g, 35.0 mmol) in triethyl phosphite (70 mL) was heated at 120 °C for 2 h. Excess triethyl phosphite was removed by distillation to leave the *phosphonate* **398** (11.82 g, 95%) as a yellow oil. $[\alpha]_D^{21}$ –114 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2985, 1654 (C=O), 1419, 1392, 1365, 1254, 1052, 1025, 974, 704 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.41-7.36 (2H, m, Ar**H**), 7.34-7.29 (3H, m, Ar**H**), 5.39 (1H, dd, *J* = 6.5, 1.9 Hz, OC**H**$_2$CHN), 4.40 (1H, dd, *J* = 8.9, 6.5 Hz, C**H**N), 4.22-4.05 (4H, m, P(OC**H**$_2$CH$_3$)$_2$), 3.91 (1H, dd, *J* = 8.9, 1.9 Hz, OC**H**$_2$CHN), 2.83 (1H, dd, *J* = 20.3, 14.2 Hz, C**H**$_2$P), 2.61 (1H, dd, *J* = 23.5, 14.2 Hz, C**H**$_2$P), 1.86 (3H, s, C(C**H**$_3$)$_2$), 1.65 (3H, s, C(C**H**$_3$)$_2$), 1.37-1.33 (3H, m, CH$_2$C**H**$_3$), 1.32-1.28 (3H, m, CH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 162.2 (C, d, J_P = 5.3 Hz), 140.8 (C), 128.7 (2 x CH), 127.6 (CH), 125.8 (2 x CH), 95.9 (C), 70.8 (CH_2), 62.5 (CH_2, d, J_P = 6.4 Hz), 61.8 (CH_2, d, J_P = 6.4 Hz), 60.9 (CH), 35.9 (CH_2, d, J_P = 130.8 Hz), 25.0 (CH_3), 22.3 (CH_3), 16.0 (CH_3, d, J_P = 5.8 Hz), 15.9 (CH_3, d, J_P = 5.7 Hz); ^{31}P NMR (101.2 MHz, $CDCl_3$) δ 21.7; HRMS (FAB) Exact mass calcd for $C_{13}H_{27}NO_5P$ $[M+H]^+$: 356.1622, found: 356.1627.

Wadsworth–Emmons Reactions: General Procedure A

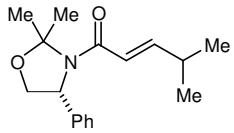


A solution of the phosphonate **398** (1.42 g, 4.00 mmol) in THF (15 mL) was added *via* cannula to a suspension of NaH (60% dispersion in mineral oil, 160 mg, 4.00 mmol) in THF (15 mL) over 3 min at 0 °C. The mixture was then stirred at room temperature for 30 min before being cooled to 0 °C. The appropriate aldehyde (1

equiv) was added dropwise or portionwise over 5 min, and the mixture was then stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (20 mL), followed by the addition of Et_2O (20 mL). The organic layer was separated and washed with NH_4Cl solution (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/hexane) afforded the *N*-alkenoyloxazolidine.

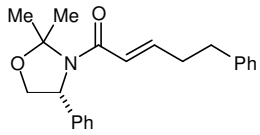


(4*R*)-3-[(*E*)-But-2-enoyl]-2,2-dimethyl-4-phenyloxazolidine (387a). Prepared according to a previously reported procedure.[ii]

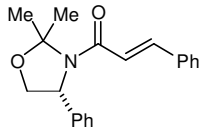


(4*R*)-2,2-Dimethyl-3-[(*E*)-4-methylpent-2-enoyl]-4-phenyloxazolidine (387b). The title compound was prepared according to General Procedure A from isobutyraldehyde (363 μL, 4.00 mmol) for a reaction time of 5 h and purified by column chromatography (20% EtOAc/hexane) to give a yellow solid (910 mg, 83%). m.p. 90-92 °C; $[\alpha]_D^{21}$ – 120 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2961, 1660 (C=O), 1455, 1396, 1361, 1256, 1068, 980, 846, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.30-7.18 (5H, m, Ar**H**), 6.72 (1H, dd, *J* = 15.1, 6.6 Hz, C**H**=CHC=O), 5.66 (1H, dd, *J* = 15.1, 1.2 Hz, CH=C**H**C=O), 4.95 (1H, dd, *J* = 6.6, 2.8 Hz, C**H**$_2$O), 4.31 (1H, dd, *J* = 8.9, 6.6 Hz, C**H**N), 3.84 (1H, dd, *J* = 8.9, 2.8 Hz, C**H**$_2$O), 2.21-2.11 (1H, m, C**H**$(CH_3)_2$), 1.82 (3H, s, C(C**H**$_3)_2$), 1.63 (3H, s, C(C**H**$_3)_2$), 0.79 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3)_2$), 0.76 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.8 (C), 151.7 (CH), 141.4 (C), 128.5 (2 x CH), 127.3 (CH), 125.7 (2 x CH), 120.1 (CH), 95.7 (C), 71.0 (CH_2), 61.0 (CH), 30.3 (CH), 25.0 (CH_3), 23.2 (CH_3), 20.9 (2 x CH_3); HRMS (FAB) Exact mass calcd for $C_{17}H_{24}NO_2$ $[M+H]^+$: 274.1802, found: 274.1807.

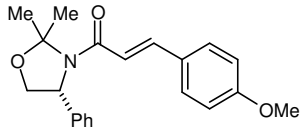
[ii]. Kanemasa, S.; Suenaga, H.; Onimura, K. *J. Org. Chem.* **1994**, *59*, 6949.



(4*R*)-2,2-Dimethyl-3-[(*E*)-5-phenylpent-2-enoyl]-4-phenyloxazolidine (387c). The title compound was prepared according to General Procedure A from hydrocinnamaldehyde (527 μL, 4.00 mmol) for a reaction time of 5 h and purified by column chromatography (20% EtOAc/hexane) to give a yellow oil (1.12 g, 83%). $[\alpha]_D^{21}$ –98.0 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2983, 1660 (C=O), 1495, 1375, 1252, 1141, 1068, 848, 735, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.40-7.16 (8H, m, Ar**H**), 7.08 (2H, d, *J* = 7.1 Hz, Ar**H**), 6.88 (1H, dt, *J* = 14.9, 6.9 Hz, C**H**=CHC=O), 5.79 (1H, d, *J* = 14.9 Hz, CH=C**H**C=O), 4.93 (1H, dd, *J* = 6.5, 2.4 Hz, C$\mathbf{H}_2$O), 4.38 (1H, dd, *J* = 8.9, 6.5 Hz, C**H**N), 3.93 (1H, dd, *J* = 8.9, 2.4 Hz, C$\mathbf{H}_2$O), 2.65-2.51 (2H, m, C$\mathbf{H}_2$Ph), 2.39-2.28 (2H, m, C$\mathbf{H}_2$$CH_2$Ph), 1.90 (3H, s, C(C$\mathbf{H}_3$)$_2$), 1.71 (3H, s, C(C$\mathbf{H}_3$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.8 (C), 144.8 (CH), 141.5 (C), 140.9 (C), 128.8 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 127.7 (CH), 125.9 (3 x CH), 123.5 (CH), 96.1 (C), 71.3 (CH_2), 61.2 (CH), 34.2 (CH_2), 33.6 (CH_2), 25.3 (CH_3), 23.4 (CH_3); HRMS (FAB) Exact mass calcd for $C_{22}H_{26}NO_2$ $[M+H]^+$: 336.1959, found: 336.1966.

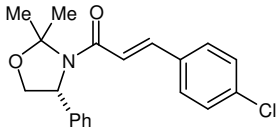


(4*R*)-2,2-Dimethyl-4-phenyl-3-[(*E*)-3-phenylpropenoyl]oxazolidine (387d). Prepared according to a previously reported procedure.[ii]

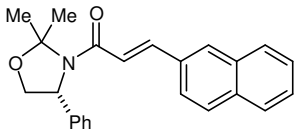


(4*R*)-3-[(*E*)-3-(4-Methoxyphenyl)propenoyl)-2,2-dimethyl-4-phenyloxazolidine (387e). The title compound was prepared according to General Procedure A from *p*-anisaldehyde (489 μL, 4.00 mmol) for a reaction time of 16 h and purified by column chromatography (30% EtOAc/hexane) to give a yellow solid (1.09 g, 76%). m.p. 125-127 °C; $[\alpha]_D^{21}$ –382 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2983, 1649 (C=O), 1511, 1422, 1395, 1304, 1242, 1173, 826, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.55 (1H, d, *J* = 15.3 Hz, ArC**H**=), 7.42-7.28 (5H, m, Ar**H**), 7.19 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.80 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.27 (1H, d, *J* = 15.3 Hz, ArCH=C**H**), 5.10 (1H, dd, *J* = 6.6, 2.6 Hz, C$\mathbf{H}_2$O), 4.43 (1H, dd, *J* = 8.9, 6.6 Hz, C**H**N), 3.97 (1H, dd, *J* = 8.9, 2.6

Hz, C**H**$_2$O), 3.79 (3H, s, OC**H**$_3$), 1.94 (3H, s, C(C**H**$_3$)$_2$), 1.75 (3H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 164.2 (C), 160.8 (C), 141.8 (C), 141.7 (CH), 129.3 (2 x CH), 129.0 (2 x CH), 127.9 (CH), 127.7 (C), 126.0 (2 x CH), 117.8 (CH), 114.1 (2 x CH), 96.3 (C), 71.4 (CH_2), 61.4 (CH), 55.3 (CH_3), 25.4 (CH_3), 23.5 (CH_3); HRMS (FAB) Exact mass calcd for $C_{21}H_{24}NO_3$ $[M+H]^+$: 338.1751, found: 338.1751.

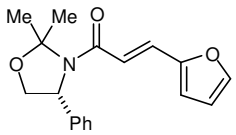


(4*R*)-3-[(*E*)-3-(4-Chlorophenyl)propenoyl)-2,2-dimethyl-4-phenyloxazolidine (387f). The title compound was prepared according to General Procedure A from 4-chlorobenzaldehyde (562 mg, 4.00 mmol) for a reaction time of 16 h and purified by column chromatography (30% EtOAc/hexane) to give a yellow solid (1.15 g, 84%). m.p. 117-119 °C; $[\alpha]_D^{21}$ –342 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2984, 1651 (C=O), 1568, 1492, 1393, 1301, 1245, 971, 819, 702 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.53 (1H, d, *J* = 15.4 Hz, ArC**H**=), 7.42-7.28 (5H, m, Ar**H**), 7.20 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.12 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.39 (1H, d, *J* = 15.4 Hz, ArCH=C**H**), 5.11 (1H, dd, *J* = 6.5, 2.6 Hz, C**H**$_2$O), 4.42 (1H, dd, *J* = 8.9, 6.5 Hz, C**H**N), 3.96 (1H, dd, *J* = 8.9, 2.6 Hz, C**H**$_2$O), 1.95 (3H, s, C(C**H**$_3$)$_2$), 1.75 (3H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.2 (C), 141.4 (C), 140.2 (CH), 135.1 (C), 133.3 (C), 128.9 (2 x CH), 128.6 (4 x CH), 127.8 (CH), 125.7 (2 x CH), 120.6 (CH), 96.1 (C), 71.2 (CH_2), 61.2 (CH), 25.1 (CH_3), 23.3 (CH_3); HRMS (FAB) Exact mass calcd for $C_{20}H_{21}{}^{35}ClNO_2$ $[M+H]^+$: 342.1256, found: 342.1261.



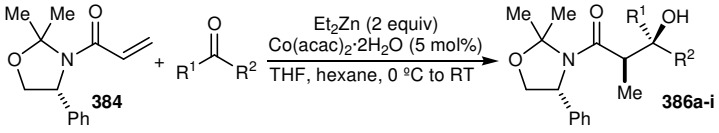
(4*R*)-2,2-Dimethyl-3-[(*E*)-3-(naphthalen-2-yl)propenoyl)-4-phenyloxazolidine (387g). The title compound was prepared according to General Procedure A from 2-naphthaldehyde (625 mg, 4.00 mmol) for a reaction time of 16 h and purified by column chromatography (30% EtOAc/hexane) to give a yellow solid (1.09 g, 76%). m.p. 131-133 °C; $[\alpha]_D^{21}$ –402 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2984, 1651 (C=O), 1401, 1362, 1255, 1239, 1068, 848, 749, 701 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.83-7.79 (3H, m, Ar**H**), 7.75-7.73 (2H, m, Ar**H**), 7.51-7.43 (6H, m, ArC**H**= and Ar**H**),

7.39-7.31 (2H, m, Ar**H**), 6.56 (1H, d, *J* = 15.3 Hz, ArCH=C**H**), 5.16 (1H, dd, *J* = 6.6, 2.8 Hz, C**H**$_2$O), 4.48 (1H, dd, *J* = 8.9, 6.6 Hz, C**H**N), 4.03 (1H, dd, *J* = 8.9, 2.8 Hz, C**H**$_2$O), 2.03 (3H, s, C(C**H**$_3$)$_2$), 1.84 (3H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.8 (C), 141.8 (CH), 141.7 (C), 133.7 (C), 133.1 (C), 132.4 (C), 129.2 (CH), 129.0 (2 x CH), 128.3 (3 x CH), 127.9 (CH), 127.5 (CH), 126.8 (CH), 126.4 (CH), 125.9 (2 x CH), 123.3 (CH), 120.4 (CH), 96.3 (C), 71.3 (CH_2), 61.4 (CH), 25.3 (CH_3), 23.5 (CH_3); HRMS (FAB) Exact mass calcd for $C_{24}H_{30}NO_2$ $[M+H]^+$: 358.1802, found: 358.1807.

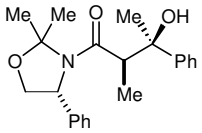


(4*R*)-3-[(*E*)-3-(Furan-2-yl)propenoyl)-2,2-dimethyl-4-phenyloxazolidine (387h). The title compound was prepared according to General Procedure A from 2-furaldehyde (331 μL, 4.00 mmol) for a reaction time of 5 h and purified by column chromatography (20% EtOAc/hexane) to give a light yellow solid (1.02 g, 84%). m.p. 94-96 °C; $[\alpha]_D^{21}$ –384 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2985, 1651 (C=O), 1557, 1484, 1392, 1246, 1067, 974, 746, 701 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.40-7.33 (5H, m) and 7.30-7.23 (2H, m, Ar**H**, C**H**=CHC=O, and C**H**), 6.41 (1H, d, *J* = 3.3 Hz, C**H**), 6.36-6.30 (2H, m, CH=C**H**C=O and C**H**), 5.09 (1H, dd, *J* = 6.4, 2.1 Hz, C**H**$_2$O), 4.38 (1H, dd, *J* = 8.9, 6.4 Hz, C**H**N), 3.94 (1H, dd, *J* = 8.9, 2.1 Hz, C**H**$_2$O), 1.93 (3H, s, C(C**H**$_3$)$_2$), 1.73 (3H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.4 (C), 151.1 (C), 143.8 (CH), 141.5 (C), 128.7 (2 x CH), 128.5 (CH), 127.5 (CH), 125.7 (2 x CH), 117.4 (CH), 113.7 (CH), 111.8 (CH), 96.0 (C), 71.1 (CH_2), 60.9 (CH), 25.2 (CH_3), 23.1 (CH_3); HRMS (FAB) Exact mass calcd for $C_{18}H_{20}NO_3$ $[M+H]^+$: 298.1438, found: 298.1443.

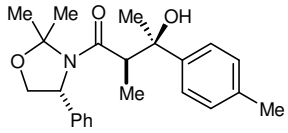
Cobalt-Catalysed Reductive Aldol Reactions of *N*-Acryloyloxazolidine 384 With Various Ketones: General Procedure



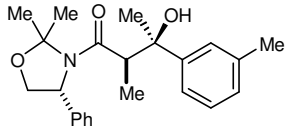
A solution of the *N*-alkenoyloxazolidine **384** (231 mg, 1.00 mmol), the appropriate ketone (1.10 mmol) and $Co(acac)_2 \cdot 2H_2O$ (12.9 mg, 0.05 mmol) in THF (5.0 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 2.00 mL, 2.00 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature until complete consumption of the *N*-alkenoyloxazolidine as observed by TLC analysis. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (30 mL) and the mixture was then extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the aldol product.



(4*R*)-3-[(2*R*,3*R*)-3-Hydroxy-2-methyl-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (386a) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General procedure B from acetophenone (130 μL, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (257 mg, 73%). Recrystallisation of a CH_2Cl_2/hexane solution of **386a** at –20 °C was found to give colorless crystals suitable for X-ray diffraction. m.p. 215-217 °C; $[\alpha]_D^{21}$ –231 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3388 (OH), 2980, 2933, 2878, 1624 (C=O), 1458, 1420, 1065, 765, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.53-7.48 (2H, m, Ar**H**), 7.47-7.42 (3H, m, Ar**H**); 7.23-7.12 (3H, m, Ar**H**), 6.94 (2H, app d, *J* = 7.2 Hz, Ar**H**), 5.48 (1H, br s, O**H**), 4.77 (1H, dd, *J* = 6.6, 2.2 Hz, C**H**$_2$O), 4.41 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 3.99 (1H, dd, *J* = 9.1, 2.2 Hz, C**H**$_2$O), 2.60 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 1.98 (3H, s, C(C**H**$_3$)$_2$), 1.67 (3H, s, C(C**H**$_3$)$_2$), 0.99 (3H, s, C**H**$_3$COH), 0.90 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.2 (C), 145.8 (C), 142.0 (C), 129.2 (2 x CH), 128.5 (CH), 127.8 (2 x CH), 126.7 (2 x CH), 126.1 (CH), 124.5 (2 x CH), 96.3 (C), 74.6 (C), 71.0 (CH_2), 61.6 (CH), 46.7 (CH), 29.6 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 12.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{28}NO_3$ $[M+H]^+$: 354.2064, found: 354.2064.

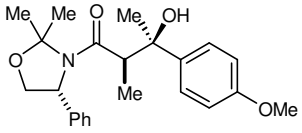


(4*R*)-3-[(2*R*,3*R*)-3-Hydroxy-2-methyl-3-(4-methylphenyl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (386b) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General procedure B from 4′-methylacetophenone (155 μL, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (280 mg, 76%). m.p. 171-173 °C; $[\alpha]_D^{21}$ –249 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3398 (OH), 2985, 2932, 1621 (C=O), 1458, 1423, 1377, 1303, 1205, 1065 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52-7.48 (2H, m, Ar**H**), 7.46-7.41 (3H, m, Ar**H**), 7.03-7.01 (2H, m, Ar**H**), 6.82 (2H, d, *J* = 7.9 Hz, Ar**H**), 5.43 (1H, s, O**H**), 4.77 (1H, dd, *J* = 6.6, 2.2 Hz, C**H**$_2$O), 4.40 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 3.98 (1H, dd, *J* = 9.1, 2.2 Hz, C**H**$_2$O), 2.58 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 2.29 (3H, s, ArC**H**$_3$), 1.98 (3H, s, C(C**H**$_3$)$_2$), 1.67 (3H, s, C(C**H**$_3$)$_2$), 0.98 (3H, s, C**H**$_3$COH), 0.90 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.3 (C), 142.9 (C), 142.0 (C), 135.6 (C), 129.1 (2 x CH), 128.5 (3 x CH), 126.7 (2 x CH), 124.4 (2 x CH), 96.2 (C), 74.6 (C), 71.0 (CH_2), 61.6 (CH), 46.7 (CH), 29.7 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 20.9 (CH_3), 12.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2220, found: 368.2218.

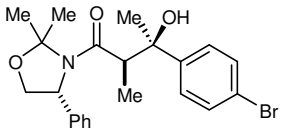


(4*R*)-3-[(2*R*,3*R*)-3-Hydroxy-2-methyl-3-(3-methylphenyl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (386c) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General procedure B from 3′-methylacetophenone (150 μL, 1.10 mmol) for a reaction time of 17 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (278 mg, 72%). m.p. 95-97 °C; $[\alpha]_D^{21}$ –199 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3398 (OH), 2980, 2933, 2878, 1624 (C=O), 1419, 1302, 1066, 845, 705 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.54-7.49 (2H, m, Ar**H**), 7.47-7.43 (3H, m, Ar**H**), 7.09 (1H, t, *J* = 7.7 Hz, Ar**H**), 6.96 (1H, d, *J* = 7.7 Hz, Ar**H**), 6.75-6.73 (2H, m, Ar**H**), 5.41 (1H, s, O**H**), 4.78 (1H, dd, *J* = 6.6, 2.2 Hz, C**H**$_2$O), 4.41 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 3.98 (1H, dd, *J* = 9.1, 2.2 Hz, C**H**$_2$O), 2.61 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 2.28 (3H, s, ArC**H**$_3$), 1.99 (3H, s, C(C**H**$_3$)$_2$), 1.67 (3H, s, C(C**H**$_3$)$_2$), 0.99 (3H, s, C**H**$_3$COH), 0.91 (3H, d, *J* = 7.1 Hz,

C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.2 (C), 145.7 (C), 142.0 (C), 137.2 (C), 129.1 (2 x CH), 128.4 (CH), 127.6 (CH), 126.8 (CH), 126.7 (2 x CH), 125.2 (CH), 121.5 (CH), 96.1 (C), 74.6 (C), 70.9 (CH_2), 61.6 (CH), 46.6 (CH), 29.6 (CH_3), 25.5 (CH_3), 22.6 (CH_3), 21.5 (CH_3), 12.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2221, found: 368.2230.

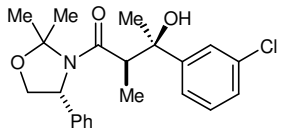


(4*R*)-3-[(2*R*,3*R*)-3-Hydroxy-3-(4-methoxyphenyl)-2-methylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (386d) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General procedure B from 4′-methoxyacetophenone (165 mg, 1.10 mmol) for a reaction time of 17 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (274 mg, 72%). Recrystallisation of an EtOAc/hexane solution of **386d** at –20 °C was found to give colorless crystals suitable for X-ray diffraction. m.p. 183-185 °C; $[\alpha]_D^{21}$ –222 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3366 (OH), 2984, 2971, 2928, 1617 (C=O), 1510, 1250, 1177, 1065, 841 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.52-7.47 (2H, m, Ar**H**), 7.46-7.42 (3H, m, Ar**H**), 6.85 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.75-6.73 (2H, m, Ar**H**), 5.44 (1H, br s, O**H**), 4.77 (1H, dd, *J* = 6.6, 2.1 Hz, C**H**$_2$O), 4.40 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 3.98 (1H, dd, *J* = 9.1, 2.1 Hz, C**H**$_2$O), 3.76 (3H, s, OC**H**$_3$), 2.54 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 1.98 (3H, s, C(C**H**$_3$)$_2$), 1.66 (3H, s, C(C**H**$_3$)$_2$), 0.97 (3H, s, C**H**$_3$COH), 0.90 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.3 (C), 157.9 (C), 142.0 (C), 138.0 (C), 129.1 (2 x CH), 128.5 (CH), 126.7 (2 x CH), 125.6 (2 x CH), 113.1 (2 x CH), 96.2 (C), 74.4 (C), 71.0 (CH_2), 61.6 (CH), 55.1 (CH_3), 46.8 (CH), 29.6 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 12.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{23}H_{29}NO_4$ $[M+H]^+$: 384.2169, found: 384.2167.

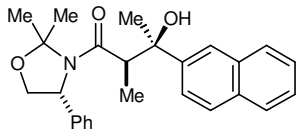


(4*R*)-3-[(2*R*,3*R*)-3-(4-Bromophenyl)-3-hydroxy-2-methylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (386e) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General procedure B from 4′-bromoacetophenone (219 mg, 1.10 mmol) for a reaction time of 16 h and purified by

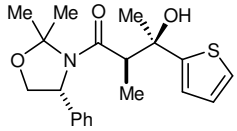
column chromatography (5% EtOAc/petrol) to give a white solid (273 mg, 63%). m.p. 132-134 °C; $[\alpha]_D^{21}$ –236 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3418 (OH), 2981, 2933, 2878, 1625 (C=O), 1457, 1411, 1066, 840, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52-7.40 (5H, m, Ar**H**), 7.33-7.31 (2H, m, Ar**H**), 6.79 (2H, d, *J* = 8.3 Hz, Ar**H**), 5.48 (1H, s, O**H**), 4.75 (1H, dd, *J* = 6.6, 2.2 Hz,), 4.40 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 3.98 (1H, dd, *J* = 9.1, 2.2 Hz, C**H**$_2$O), 2.53 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 1.97 (3H, s, C(C**H**$_3$)$_2$), 1.66 (3H, s, C(C**H**$_3$)$_2$), 0.96 (3H, s, C**H**$_3$COH), 0.88 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.9 (C), 144.9 (C), 141.9 (C), 130.8 (2 x CH), 129.2 (2 x CH), 128.6 (CH), 126.7 (2 x CH), 126.5 (2 x CH), 120.1 (C), 96.3 (C), 74.4 (C), 71.0 (CH_2), 61.6 (CH), 46.5 (CH), 29.4 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 12.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{27}{}^{79}BrNO_3$ $[M+H]^+$: 432.1169, found: 432.1168.



(4*R*)-3-[(2*R*,3*R*)-3-(4-Bromophenyl)-3-hydroxy-2-methylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (386f) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General procedure B from 3′-chloroacetophenone (143 μL, 1.10 mmol) for a reaction time of 17 h and purified by column chromatography (5% EtOAc/petrol) to give a colorless oil (225 mg, 58%). $[\alpha]_D^{21}$ –162 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3418 (OH), 2981, 2934, 2877, 1627 (C=O), 1419, 1205, 1066, 842, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.54-7.49 (2H, m, Ar**H**), 7.48-7.42 (3H, m, Ar**H**), 7.15-7.10 (2H, m, Ar**H**), 6.89-6.83 (2H, m, Ar**H**), 5.45 (1H, s, O**H**), 4.75 (1H, dd, *J* = 6.7, 2.2 Hz, C**H**$_2$O), 4.40 (1H, dd, *J* = 9.1, 6.7 Hz, C**H**N), 3.99 (1H, dd, *J* = 9.1, 2.2 Hz, C**H**$_2$O), 2.58 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 1.97 (3H, s, C(C**H**$_3$)$_2$), 1.66 (3H, s, C(C**H**$_3$)$_2$), 0.93 (3H, s, C**H**$_3$COH), 0.89 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.8 (C), 148.0 (C), 141.9 (C), 133.9 (C), 129.3 (2 x CH), 129.1 (CH), 128.6 (CH), 126.7 (2 x CH), 126.3 (CH), 1245.0 (CH), 122.7 (CH), 96.2 (C), 74.4 (C), 70.9 (CH_2), 61.7 (CH), 46.5 (CH), 29.4 (CH_3), 25.5 (CH_3), 22.7 (CH_3), 12.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{27}{}^{35}ClNO_3$ $[M+H]^+$: 388.1675, found: 388.1675.

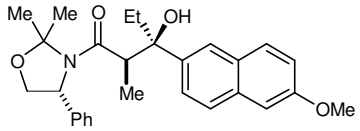


(4*R*)-3-[(2*R*,3*R*)-3-Hydroxy-2-methyl-3-(naphthalen-2-yl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (386g) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General procedure B from 2′-acetonaphthone (187 mg, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (302 mg, 75%). m.p. 215-217 °C; $[\alpha]_D^{21}$ –11.2 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3410 (OH), 2980, 2933, 2878, 1624 (C=O), 1456, 1418, 1377, 1299, 1065 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.78-7.76 (2H, m, Ar**H**), 7.67 (1H, d, *J* = 8.7 Hz, Ar**H**), 7.61-7.40 (8H, m, Ar**H**), 6.86-6.84 (1H, m, Ar**H**), 5.59 (1H, br s, O**H**), 4.80 (1H, dd, *J* = 6.6, 2.2 Hz, C**H**$_2$O), 4.42 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 4.01 (1H, dd, *J* = 9.1, 2.2 Hz, C**H**$_2$O), 2.74 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 2.02 (3H, s, C(C**H**$_3$)$_2$), 1.69 (3H, s, C(C**H**$_3$)$_2$), 1.09 (3H, s, C**H**$_3$COH), 0.91 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.2 (C), 143.2 (C), 142.1 (C), 133.1 (C), 132.0 (C), 129.3 (2 x CH), 128.6 (CH), 128.1 (CH), 127.4 (CH), 127.3 (CH), 126.8 (2 x CH), 125.8 (CH), 125.4 (CH), 123.5 (CH), 122.8 (CH), 96.3 (C), 74.9 (C), 71.0 (CH_2), 61.7 (CH), 46.6 (CH), 29.6 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 12.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{26}H_{30}NO_3$ $[M+H]^+$: 404.2220, found: 404.2221.



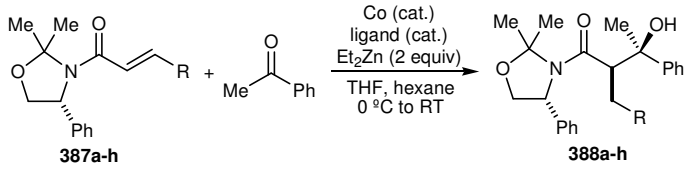
(4*R*)-3-[(2*R*,3*R*)-3-Hydroxy-2-methyl-3-(thiophen-2-yl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (386h) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General procedure B from 2-acetylthiophene (119 μL, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (20% EtOAc/petrol) followed by recrystallisation from CH_2Cl_2/hexane to give a white solid (220 mg, 61%). m.p. 143-145 °C; $[\alpha]_D^{21}$ –11.8 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3399 (OH), 2983, 2933, 2878, 1625 (C=O), 1422, 1237, 1066, 844, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.50-7.39 (5H, m, Ar**H**), 7.09 (1H, dd, *J* = 5.1, 1.2 Hz, C**H**), 6.86 (1H, dd, *J* = 5.1, 3.5 Hz, C**H**), 6.35 (1H, dd, *J* = 3.5, 1.2 Hz, C**H**), 5.57 (1H, s, O**H**), 4.76 (1H, dd, *J* = 6.6, 2.1 Hz, C**H**$_2$O), 4.40 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 3.99 (1H, dd, *J* = 9.1, 2.1 Hz, C**H**$_2$O), 2.60 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 1.96

(3H, s, C(C**H**$_3$)$_2$), 1.65 (3H, s, C(C**H**$_3$)$_2$), 1.04 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH), 1.00 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.8 (C), 151.0 (C), 141.8 (C), 129.1 (2 x CH), 128.4 (CH), 126.6 (2 x CH), 126.5 (CH), 123.1 (CH), 121.0 (CH), 96.2 (C), 74.7 (C), 70.9 (CH_2), 61.5 (CH), 47.7 (CH), 30.6 (CH_3), 25.5 (CH_3), 22.6 (CH_3), 12.4 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{26}NO_3S$ $[M+H]^+$: 360.1628, found: 360.1637.



(4*R*)-3-[(2*R*,3*R*)-3-Hydroxy-2-methyl-3-(thiophen-2-yl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (386i) (Reaction performed by R.J.R. Lumby). The title compound was prepared according to General procedure B from 6′-methoxy-2′-propiononaphthone (236 mg, 1.10 mmol) for a reaction time of 3 h and purified by column chromatography (20% EtOAc/petrol) followed by recrystallisation from CH_2Cl_2/hexane to give a white solid (265 mg, 59%). m.p. 164-166 °C; $[\alpha]_D^{21}$ –3.9 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3388 (OH), 2975, 2935, 2877, 1623 (C=O), 1417, 1266, 1173, 1067, 703 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.66 (1H, d, *J* = 8.8 Hz, Ar**H**), 7.58-7.45 (7H, m, Ar**H**), 7.12 (1H, dd, *J* = 8.9, 5.6 Hz, Ar**H**), 7.08 (1H, d, *J* = 2.5 Hz, Ar**H**), 5.21 (1H, s, O**H**), 4.79 (1H, dd, *J* = 6.6, 2.1 Hz, C**H**$_2$O), 4.41 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 3.99 (1H, dd, *J* = 9.1, 2.1 Hz, C**H**$_2$O), 3.91 (3H, s, OC**H**$_3$), 2.67 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 2.00 (3H, s, C(C**H**$_3$)$_2$), 1.67 (3H, s, C(C**H**$_3$)$_2$), 1.65-1.55 (1H, m, C**H**$_2$CH$_3$), 0.96-0.85 (1H, m, C**H**$_2$CH$_3$), 0.90 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH), 0.43 (3H, t, *J* = 7.3 Hz, CH_2C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.5 (C), 157.3 (C), 142.1 (C), 138.6 (C), 132.9 (C), 129.5 (CH), 129.2 (2 x CH), 128.5 (CH), 126.7 (2 x CH), 126.2 (CH), 124.5 (CH), 123.7 (CH), 118.5 (CH), 105.3 (CH), 96.2 (C), 77.9 (C), 71.0 (CH_2), 61.6 (CH), 55.2 (CH_3), 46.8 (CH), 33.3 (CH_2), 25.7 (CH_3), 22.6 (CH_3), 12.3 (CH_3), 7.7 (CH_3 HRMS (ES) Exact mass calcd for $C_{28}H_{34}NO_4$ $[M+H]^+$: 448.2483, found: 448.2490.

Cobalt-Catalysed Reductive Aldol Reactions of *N*-Alkenoyloxazolidines 387a-387h With Acetophenone

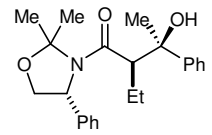


Using $Co(acac)_2{\cdot}2H_2O/Et_2Zn$: General Procedure C

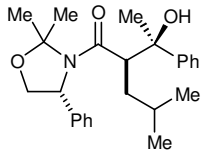
A solution of the appropriate *N*-alkenoyloxazolidine (0.50 mmol), acetophenone (65 μL, 0.55 mmol) and $Co(acac)_2{\cdot}2H_2O$ (6.4 mg, 0.025 mmol) in THF (2.5 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 1.00 mL, 1.00 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature until complete consumption of the *N*-alkenoyloxazolidine as observed by TLC analysis. The reaction mixture was filtered through a short plug of SiO_2 using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography afforded the aldol product.

Using $CoCl_2/Cy_2PPh/Et_2Zn$: General Procedure D

A solution of the appropriate *N*-alkenoyloxazolidine (0.50 mmol), the acetophenone (65 μL, 0.55 mmol), $CoCl_2$ (3.2 mg, 0.025 mmol) and Cy_2PPh (7.5 mg, 0.0275 mmol) in THF (2.5 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 1.00 mL, 1.00 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature until complete consumption of the *N*-alkenoyloxazolidine as observed by TLC analysis. The reaction mixture was filtered through a short plug of SiO_2 using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography afforded the aldol product.

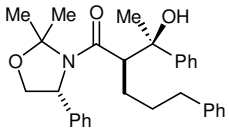


(4*R*)-3-[(2*R*,3*R*)-2-Ethyl-3-hydroxy-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (388a). The title compound was prepared according to General Procedure D from *N*-alkenoyloxazolidine **387a** (123 mg, 0.50 mmol) for a reaction time of 14 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (150 mg, 82%). m.p. 131-133 °C; $[\alpha]_D^{21}$ –226 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3387 (OH), 2973, 1620 (C=O), 1457, 1408, 1308, 1133, 1067, 766, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.54-7.42 (5H, m, Ar**H**), 7.24-7.13 (3H, m, Ar**H**), 6.98 (2H, d, *J* = 7.3 Hz, Ar**H**), 5.33 (1H, s, O**H**), 4.94 (1H, dd, *J* = 6.6, 1.6 Hz, C**H**$_2$O), 4.41 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 4.00 (1H, dd, *J* = 9.1, 1.6 Hz, C**H**$_2$O), 2.67 (1H, dd, *J* = 10.8, 4.0 Hz, C**H**C=O), 2.01 (3H, s, C(C**H**$_3$)$_2$), 1.87-1.74 (1H, m, C**H**$_2$CH$_3$), 1.72 (3H, s, C(C**H**$_3$)$_2$), 1.21-1.10 (1H, m, C**H**$_2$CH$_3$), 0.87 (3H, t, *J* = 6.6 Hz, CH$_2$C**H**$_3$), 0.78 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.7 (C), 146.1 (C), 142.0 (C), 129.1 (2 x CH), 128.6 (CH), 127.7 (2 x CH), 127.4 (2 x CH), 126.1 (CH), 124.6 (2 x CH), 96.6 (C), 74.9 (C), 70.8 (CH_2), 61.9 (CH), 53.6 (CH), 29.8 (CH_3), 25.7 (CH_3), 22.6 (CH_3), 21.7 (CH_2), 12.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2220, found: 368.2221.

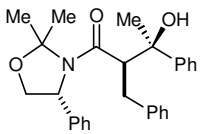


(4*R*)-3-[(2*R*,3*R*)-2-*iso*-Butyl-3-hydroxy-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (388b). The title compound was prepared according to General Procedure D from *N*-alkenoyloxazolidine **387b** (137 mg, 0.50 mmol) for a reaction time of 14 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (156 mg, 79%). m.p. 195-197 °C; $[\alpha]_D^{21}$ –182 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3346 (OH), 2954, 1612 (C=O), 1456, 1409, 1303, 1130, 1067, 768, 705 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.54-7.41 (5H, m, Ar**H**), 7.23-7.11 (3H, m, Ar**H**), 6.97 (2H, d, *J* = 7.3 Hz, Ar**H**), 5.25 (1H, s, O**H**), 4.90 (1H, dd, *J* = 6.6, 1.6 Hz, C**H**$_2$O), 4.41 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 4.00 (1H, dd, *J* = 9.1, 1.6 Hz, C**H**$_2$O), 2.74 (1H, dd, *J* = 10.1, 3.2 Hz, C**H**C=O), 2.01 (3H, s, C(C**H**$_3$)$_2$), 1.76-1.67 (1H, m, C**H**$_2$CH(CH$_3$)$_2$), 1.61 (3H, s, C(C**H**$_3$)$_2$), 1.32-1.20 (1H, m, C**H**(CH$_3$)$_2$), 1.04 (1H, ddd, *J* = 14.1, 9.5, 3.2 Hz, C**H**$_2$CH(CH$_3$)$_2$), 0.82 (3H, d, *J* = 6.5 Hz, CH(C**H**$_3$)$_2$), 0.77 (3H, s, C**H**$_3$COH), 0.75

(3H, d, J = 6.5 Hz, CH(C**H**$_3$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.3 (C), 146.1 (C), 141.9 (C), 129.2 (2 x CH), 128.6 (CH), 127.7 (2 x CH), 127.2 (2 x CH), 126.1 (CH), 124.5 (2 x CH), 96.6 (C), 75.3 (C), 70.9 (CH_2), 61.6 (CH), 50.6 (CH), 38.5 (CH_2), 30.2 (CH_3), 26.0 (CH), 25.6 (CH_3), 23.9 (CH_3), 22.7 (CH_3), 22.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{25}H_{34}NO_3$ $[M+H]^+$: 396.2533, found: 396.2534.

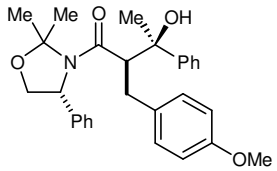


(4*R*)-3-[(2*R*,3*R*)-3-Hydroxy-3-phenylbutanoyl-2-(3-phenylpropyl)]-2,2-dimethyl-4-phenyloxazolidine (388c). The title compound was prepared according to General Procedure D from *N*-alkenoyloxazolidine **387c** (168 mg, 0.50 mmol) for a reaction time of 14 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (182 mg, 80%). m.p. 130-132 °C; $[\alpha]_D^{21}$ –190 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3398 (OH), 3028, 1619 (C=O), 1427, 1397, 1066, 1053, 837, 740, 706 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.59-7.48 (5H, m, Ar**H**), 7.34-7.22 (6H, m, Ar**H**), 7.11 (2H, d, J = 7.2 Hz, Ar**H**), 7.06 (2H, d, J = 7.2 Hz, Ar**H**), 5.41 (1H, s, O**H**), 4.86 (1H, dd, J = 6.5, 1.5 Hz, C**H**$_2$O), 4.37 (1H, dd, J = 9.1, 6.5 Hz, C**H**N), 4.01 (1H, dd, J = 9.1, 1.5 Hz, C**H**$_2$O), 2.77 (1H, dd, J = 9.9, 4.0 Hz, C**H**C=O), 2.52 (2H, t, J = 7.2 Hz, C**H**$_2$Ar), 2.07 (3H, s, C(C**H**$_3$)$_2$), 1.94-1.82 (1H, m, CHC**H**$_2$CH$_2$), 1.76 (3H, s, C(C**H**$_3$)$_2$), 1.69-1.56 (1H, m, CHC**H**$_2$CH$_2$), 1.50-1.31 (2H, m, CH$_2$C**H**$_2$CH$_2$), 0.89 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.6 (C), 146.0 (C), 141.9 (C), 141.8 (C), 129.1 (2 x CH), 128.5 (CH), 128.3 (2 x CH), 128.1 (2 x CH), 127.7 (2 x CH), 127.2 (2 x CH), 126.1 (CH), 125.7 (CH), 124.6 (2 x CH), 96.5 (C), 74.8 (C), 70.8 (CH_2), 61.7 (CH), 52.3 (CH), 36.2 (CH_2), 29.8 (CH_3 and CH_2), 28.4 (CH_2), 25.6 (CH_3), 22.5 (CH_3); HRMS (FAB) Exact mass calcd for $C_{30}H_{36}NO_3$ $[M+H]^+$: 458.2690, found: 458.2687.



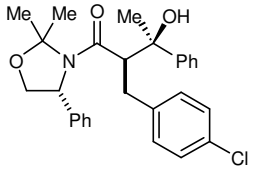
(4*R*)-3-[(2*R*,3*R*)-2-Benzyl-3-hydroxy-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (388d). The title compound was prepared according to General Procedure C from *N*-alkenoyloxazolidine **387d** (154 mg, 0.50 mmol) for a reaction time of 4 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid

(184 mg, 86%). m.p. 139-141 °C; $[\alpha]_D^{21}$ –286 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3387 (OH), 3026, 1620 (C=O), 1455, 1421, 1301, 1249, 1065, 843, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52-7.41 (3H, m, Ar**H**), 7.39-7.24 (8H, m, Ar**H**), 7.14-7.09 (4H, m, Ar**H**), 5.56 (1H, s, O**H**), 3.68 (1H, dd, *J* = 9.0, 6.4 Hz, C**H**N), 3.62 (1H, dd, *J* = 9.0, 1.3 Hz, C**H**$_2$O), 3.35 (1H, app d, *J* = 5.4 Hz, C**H**$_2$O), 3.05 (1H, app t, *J* = 12.5 Hz, C**H**C=O), 2.90 (1H, dd, *J* = 11.9, 2.6 Hz, C**H**$_2$Ph), 2.43 (1H, dd, *J* = 13.0, 2.6 Hz, C**H**$_2$Ph), 1.98 (3H, s, C(C**H**$_3$)$_2$), 1.65 (3H, s, C(C**H**$_3$)$_2$), 0.92 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.9 (C), 146.0 (C), 142.1 (C), 140.0 (C), 129.1 (2 x CH), 128.9 (2 x CH), 128.5 (2 x CH), 128.3 (CH), 127.9 (2 x CH), 127.0 (2 x CH), 126.7 (CH), 126.3 (CH), 124.5 (2 x CH), 96.3 (C), 75.3 (C), 70.4 (CH_2), 60.5 (CH), 55.7 (CH), 34.9 (CH_2), 29.7 (CH_3), 25.5 (CH_3), 22.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{28}H_{32}NO_3$ $[M+H]^+$: 430.2377, found: 430.2382.

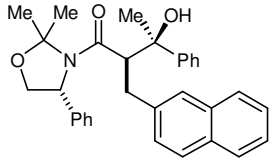


(4*R*)-3-[(2*R*,3*R*)-3-Hydroxy-2-(4-methoxybenzyl)-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (388e). The title compound was prepared according to General Procedure C from *N*-alkenoyloxazolidine **387e** (169 mg, 0.50 mmol) for a reaction time of 6 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (198 mg, 86%). m.p. 115-117 °C; $[\alpha]_D^{21}$ –304 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3386 (OH), 3027, 1618 (C=O), 1511, 1456, 1418, 1109, 1066, 768, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52-7.41 (3H, m, Ar**H**), 7.36-7.22 (5H, m, Ar**H**), 7.07-7.05 (2H, m, Ar**H**), 7.02 (2H, d, *J* = 8.6 Hz, Ar**H**), 6.90 (2H, d, *J* = 8.6 Hz, Ar**H**), 5.56 (1H, s, O**H**), 3.83 (3H, s, OC**H**$_3$), 3.75 (1H, dd, *J* = 9.0, 6.5 Hz, C**H**N), 3.65 (1H, dd, *J* = 9.0, 1.1 Hz, C**H**$_2$O), 3.47 (1H, app d, *J* = 5.8 Hz, C**H**$_2$O), 3.00 (1H, dd, *J* = 13.1, 11.9 Hz, C**H**C=O), 2.88 (1H, dd, *J* = 11.9, 2.4 Hz, C**H**$_2$Ar), 2.36 (1H, dd, *J* = 13.1, 2.4 Hz, C**H**$_2$Ar), 1.98 (3H, s, C(C**H**$_3$)$_2$), 1.66 (3H, s, C(C**H**$_3$)$_2$), 0.91 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.0 (C), 158.4 (C), 146.0 (C), 142.1 (C), 131.9 (C), 130.0 (2 x CH), 128.9 (2 x CH), 128.3 (CH), 127.9 (2 x CH), 127.0 (2 x CH), 126.2 (CH), 124.4 (2 x CH), 113.8 (2 x CH), 96.2 (C), 75.2 (C), 70.4 (CH_2), 60.6 (CH), 55.7 (CH), 55.2 (CH_3), 34.0 (CH_2), 29.7

(CH_3), 25.4 (CH_3), 22.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{29}H_{34}NO_4$ $[M+H]^+$: 460.2482, found: 460.2482.

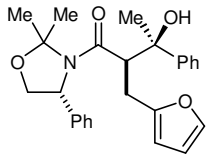


(4*R*)-3-[(2*R*,3*R*)-2-(4-Chlorobenzyl)-3-hydroxy-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (388f). The title compound was prepared according to General Procedure C from *N*-alkenoyloxazolidine **387f** (171 mg, 0.50 mmol) for a reaction time of 6 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (194 mg, 84%). Slow evaporation of a $CDCl_3$ solution of **4f** was found to give colorless crystals suitable for X-ray diffraction. m.p. 139-140 °C; $[\alpha]_D^{21}$ –304 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3398 (OH), 3027, 1627 (C=O), 1493, 1423, 1313, 1296, 910, 767, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.53-7.43 (3H, m, Ar**H**), 7.36-7.23 (7H, m, Ar**H**), 7.04 (4H, dm, *J* = 8.4 Hz, Ar**H**), 5.46 (1H, s, O**H**), 3.76 (1H, dd, *J* = 9.1, 6.5 Hz, C**H**N), 3.68 (1H, dd, *J* = 9.1, 1.3 Hz, C**H**$_2$O), 3.48 (1H, dd, *J* = 6.5, 1.3 Hz, C**H**$_2$O), 3.00 (1H, dd, *J* = 13.1, 11.9 Hz, C**H**C=O), 2.88 (1H, dd, *J* = 11.9, 2.7 Hz, C**H**$_2$Ar), 2.37 (1H, dd, *J* = 13.1, 2.7 Hz, C**H**$_2$Ar), 1.98 (3H, s, C(C**H**$_3$)$_2$), 1.62 (3H, s, C(C**H**$_3$)$_2$), 0.89 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.6 (C), 145.8 (C), 141.9 (C), 138.5 (C), 132.5 (C), 130.5 (2 x CH), 129.0 (2 x CH), 128.5 (4 x CH), 128.0 (2 x CH), 127.1 (2 x CH), 126.4 (CH), 124.5 (CH), 96.4 (C), 75.2 (C), 70.4 (CH_2), 60.8 (CH), 55.4 (CH), 34.2 (CH_2), 29.6 (CH_3), 25.5 (CH_3), 22.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{28}H_{31}{}^{35}ClNO_3$ $[M+H]^+$: 464.1987, found: 464.1990.



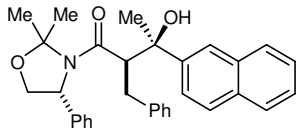
(4*R*)-3-[(2*R*,3*R*)-3-Hydroxy-2-(naphthalen-2-ylmethyl)-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (388g). The title compound was prepared according to General Procedure C from *N*-alkenoyloxazolidine **387g** (179 mg, 0.50 mmol) for a reaction time of 16 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (216 mg, 90%). m.p. 136-138 °C; $[\alpha]_D^{21}$ –358 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3389 (OH), 3026, 1620 (C=O), 1420, 1302, 1249, 1067,

908, 733, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.94-7.88 (2H, m, Ar**H**), 7.85 (2H, d, *J* = 8.6 Hz, Ar**H**), 7.61-7.51 (5H, m, Ar**H**), 7.38-7.29 (5H, m, Ar**H**), 7.14-7.11 (2H, m, Ar**H**), 6.99 (1H, br s, Ar**H**), 5.72 (1H, s, O**H**), 3.73 (1H, dd, *J* = 9.0, 6.4 Hz, C**H**N), 3.66 (1H, dd, *J* = 9.0, 1.1 Hz, C**H**$_2$O), 3.38 (1H, app d, *J* = 5.9 Hz, C**H**$_2$O), 3.15 (1H, dd, *J* = 12.6, 12.0 Hz, C**H**C=O), 3.06 (1H, dd, *J* = 12.0, 1.8 Hz, C**H**$_2$Ar), 2.48 (1H, dd, *J* = 12.6, 1.8 Hz, C**H**$_2$Ar), 2.05 (3H, s, C(C**H**$_3$)$_2$), 1.71 (3H, s, C(C**H**$_3$)$_2$), 1.07 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.9 (C), 143.2 (C), 142.2 (C), 139.9 (C), 133.1 (C), 132.1 (C), 129.1 (2 x CH), 129.0 (2 x CH), 128.4 (3 x CH), 128.1 (CH), 127.6 (CH), 127.3 (CH), 127.1 (2 x CH), 126.7 (CH), 125.9 (CH), 125.5 (CH), 123.6 (CH), 122.7 (CH), 96.3 (C), 75.5 (C), 70.4 (CH_2), 60.5 (CH), 55.5 (CH), 35.0 (CH_2), 29.7 (CH_3), 25.5 (CH_3), 22.1 (CH_3);); HRMS (ES) Exact mass calcd for $C_{32}H_{34}NO_3$ $[M+H]^+$: 480.2533, found: 480.2539.



(4*R*)-3-[(2*R*,3*R*)-2-(Furan-2-ylmethyl)-3-hydroxy-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (388h). The title compound was prepared according to General Procedure C from *N*-alkenoyloxazolidine **387h** (149 mg, 0.50 mmol) for a reaction time of 4 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (174 mg, 83%). m.p. 96-98 °C; $[\alpha]_D^{21}$ –298 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3378 (OH), 3028, 1622 (C=O), 1456, 1378, 1066, 1013, 914, 767, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.55-7.51 (2H, m, Ar**H**), 7.47-7.43 (4H, m, Ar**H**), 7.33-7.29 (2H, m, Ar**H**), 7.25-7.21 (1H, m, Ar**H**) 7.09-7.07 (2H, m, Ar**H**, C**H**), 6.38 (1H, dd, *J* = 3.2, 1.9 Hz, C**H**), 6.03 (1H, d, *J* = 3.2 Hz, C**H**), 5.56 (1H, s, O**H**), 4.00 (1H, dd, *J* = 8.8, 6.5 Hz, C**H**$_2$N), 3.87 (1H, dd, *J* = 6.5, 1.2 Hz, C**H**$_2$O), 3.82 (1H, dd, *J* = 8.8, 1.2 Hz, C**H**$_2$O), 3.13 (1H, dd, *J* = 13.1, 11.8 Hz, C**H**C=O), 3.07 (1H, dd, *J* = 11.8, 1.7 Hz, C**H**$_2$CHC=O), 2.39 (1H, dd, *J* = 13.1, 1.7 Hz, C**H**$_2$CH), 1.99 (3H, s, C(C**H**$_3$)$_2$), 1.61 (3H, s, C(C**H**$_3$)$_2$), 0.89 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.6 (C), 153.7 (C), 145.4 (C), 142.3 (C), 141.0 (CH), 129.0 (2 x CH), 128.4 (CH), 127.9 (2 x CH), 127.2 (2 x CH), 126.4 (CH), 124.5 (2 x CH), 110.9 (CH), 107.1 (CH), 96.3 (C), 74.8 (C), 70.6 (CH_2), 60.7 (CH), 52.4 (CH), 29.7 (CH_3), 26.8 (CH_2), 25.5 (CH_3), 22.1

(CH_3); HRMS (ES) Exact mass calcd for $C_{26}H_{30}NO_4$ $[M+H]^+$: 420.2169, found: 420.2171.

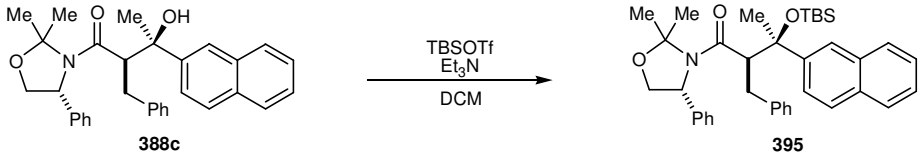


(4*R*)-3-[(2*R*,3*R*)-2-Benzyl-3-hydroxy-3-(naphthalen-2-yl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (390). *On a 0.50 mmol scale:* A solution of the *N*-alkenoyloxazolidine **387d** (154 mg, 0.50 mmol), 2′-acetonaphthone (94 mg, 0.55 mmol) and $Co(acac)_2{\cdot}2H_2O$ (6.4 mg, 0.025 mmol) in THF (2.5 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 1.00 mL, 1.00 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature for 6 h. The reaction mixture was filtered through a short plug of SiO_2 using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *aldol product* **390** (218 mg, 91%) as a white solid.

On a 5.00 mmol scale: A solution of the *N*-alkenoyloxazolidine **387d** (1.54 g, 5.00 mmol), 2′-acetonaphthone (936 mg, 5.50 mmol) and $Co(acac)_2{\cdot}2H_2O$ (64 mg, 0.25 mmol) in THF (25 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 10.0 mL, 10.0 mmol) was then added over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature for 16 h. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (20 mL), and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *aldol product* **390** (2.16 g, 90%) as a white solid. m.p. 139-141 °C; $[\alpha]_D^{21}$ –374 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3389 (OH), 3026, 1622 (C=O), 1455, 1417, 1377, 1066, 909, 768, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.82-7.76 (2H, m, Ar**H**), 7.82-7.79 (1H, m, Ar**H**) 7.55-7.13 (12H, m, Ar**H**), 7.07 (2H, br s, Ar**H**), 5.53 (1H, s, O**H**), 3.35 (1H, app d, *J* = 8.7 Hz, C**H**$_2$O), 3.22-3.09 (2H, m, C**H**$_2$O and C**H**C=O), 3.17 (1H, dd, *J* = 8.7, 6.6 Hz, C**H**$_2$N), 2.93 (1H, dd, *J* = 11.9, 2.8 Hz, C**H**$_2$Ph), 2.52 (1H, dd, *J* = 13.2, 2.8 Hz, C**H**$_2$Ph), 1.91 (3H, s, C(C**H**$_3$)$_2$), 1.53 (3H, s, C(C**H**$_3$)$_2$), 0.87 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.9 (C), 145.0 (C), 142.0 (C),

137.3 (C), 133.2 (C), 132.0 (C), 128.9 (2 x CH), 128.3 (CH), 128.2 (CH), 128.0 (2 x CH), 127.7 (CH), 127.5 (CH), 127.3 (CH), 127.1 (2 x CH), 127.0 (CH), 126.5 (CH), 126.4 (CH), 125.6 (CH), 124.5 (2 x CH), 96.1 (C), 75.3 (C), 70.1 (CH_2), 60.5 (CH), 55.6 (CH), 35.1 (CH_2), 29.7 (CH_3), 25.5 (CH_3), 22.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{32}H_{34}NO_3$ $[M+H]^+$: 480.2533, found: 480.2532.

Preparation of TBS-protected substrate 395



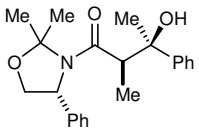
388c **395**

TBSOTf (1.7 mmol, 390 μL) was added to solution of substrate **xx** (1 mmol, 460 mg) and Et_3N (2.0 mmol, 280 μL) in DCM (10 mL) at 0°C. Solution was stirred at 0°C for 10 min and then at the room temperature for 1h. 10 mL of $NaHCO_3$ was added and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (5 % EtOAc/petrol) afforded the product **395** (90%, 534 mg) as a white solid. m.p. 122-124 °C; IR ($CHCl_3$) 3026, 1618 (C=O), 1455, 1417, 1377, 1216, 1066, 909, 768, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.81-7.78 (1H, m, Ar**H**), 7.67-7.65 (2H, m, Ar**H**), 7.50-7.38 (6H, m, Ar**H**), 7.34-7.23 (4H, m, Ar**H**), 7.07-7.03 (2H, m, Ar**H**), 6.90 (1H, dd, *J* = 8.7, 1,7 Hz, Ar**H**), 6.74-6.72 (H, m, Ar**H**), 3.46 (1H, dd, *J* = 8.8, 6.4 Hz, C**H**N), 3.29-3.20 (3H, m, C**H**$_2$O, PhC**H**$_2$), 3.08 (1H, app d, *J* = 8.7 Hz, C**H**$_2$O), 3.00-2.93 (1H, m, C**H**O), 1.87 (3H, s, C**H**$_3$CO), 1.62 (3H, s, (C**H**$_3$)$_2$C), 1.54 (3H, s, (C**H**$_3$)$_2$C), 1.15 (9H, s, $(CH_3)_3C$), 0.27 (3H, s, C**H**$_3$Si), -0.18 (3H, s, C**H**$_3$Si); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.7 (C), 144.2 (C), 142.4 (C), 140.7 (C), 132.7 (C), 131.9 (C), 129.4 (2 x CH), 128.6 (2 x CH), 128.5 (CH), 127.5 (CH), 127.1 (CH), 126.7 (CH), 126.6 (2 x CH), 126.3 (2 x CH), 125.3 (2 x CH), 125.1 (2 x CH), 124.7 (CH), 95.7 (C), 78.7 (C), 70.7 (CH_2), 60.0 (CH), 59.4 (CH), 35.8 (CH_2), 26.4 (4 x CH_3), 25.3 (CH_3), 22.1 (C), 18.8 (CH_3),

-1.4 (CH_3), -2.5 (CH_3); HRMS (FAB) Exact mass calcd for $C_{38}H_{48}NO_3Si$ $[M+H]^+$: 594.3399, found: 594.3397.

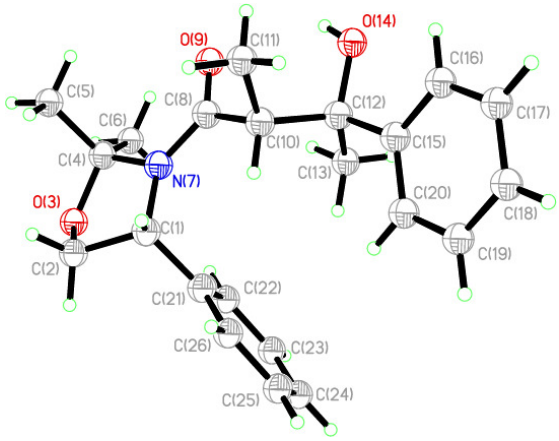
Stereochemical Determinations

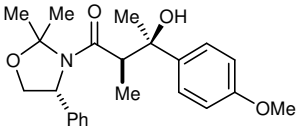
- The relative stereochemistries of **386a**, **386d** and **388f** were determined by X-ray crystallography. Crystal structure data deposited at the Cambridge Crystallographic Data Center; Deposition Numbers: CCDC 634191–634193, respectively.



386a

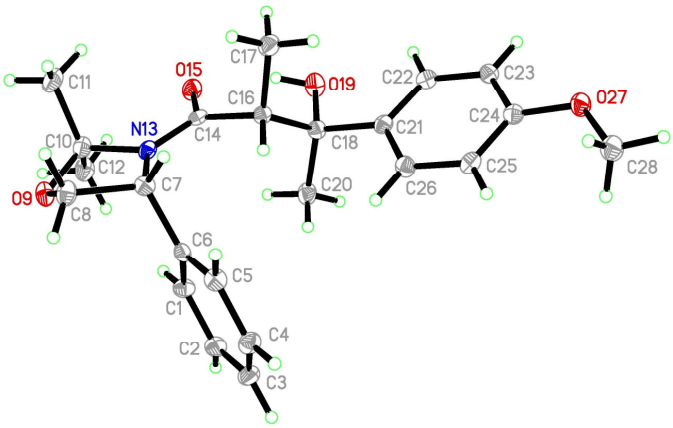
CCDC 634191

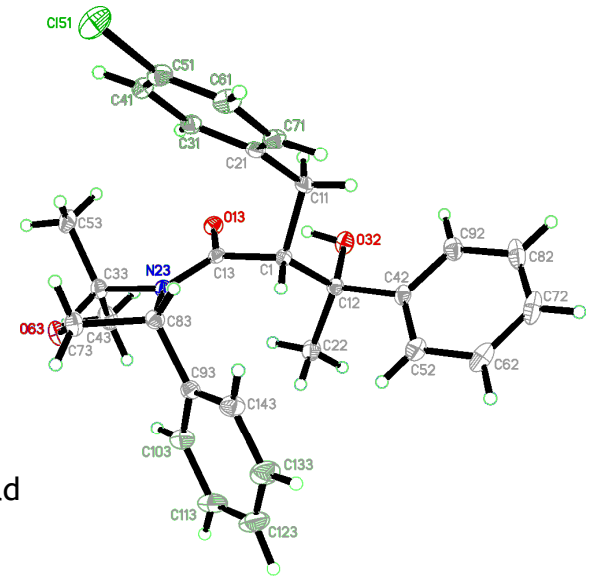


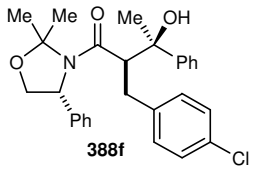


386d

CCDC 634192







388f

CCDC 634193

- The relative stereochemistries of the remaining products were assigned by analogy.

Appendix

List of publications

1. **Cu(I)-Catalyzed Reductive Aldol Cyclizations: Diastereo- and Enantioselective Synthesis of β-Hydroxylactones,** Lam, H. W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225.

2. **Diastereoselective Cobalt-Catalyzed Reductive Aldol Cyclizations Using Diethylzinc as the Stoichiometric Reductant,** Lam, H. W.; Joensuu, P. M.; Murray, G. J.; Fordyce, E. A. F.; Prieto, O.; Luebbers, T. *Org. Lett.* **2006**, *8*, 3729.

3. **Diastereoselective Intermolecular Cobalt-Catalyzed Reductive Aldol Reactions of α,β-Unsaturated Amides with Ketones,** Lumby, R. J. R.; Joensuu, P. M.; Lam, H. W. *Org. Lett.* **2007**, *9*, 4367.