

**New Asymmetric Metal-Catalysed
Addition Processes for Amine Synthesis**



*A thesis submitted in partial fulfilment of the requirement for the degree of
Doctor of Philosophy (DPhil)*

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A mia madre e a mio padre

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I was admitted as a probationary research student in November 2013 and as a candidate for the degree of Doctor of Philosophy in November 2014; the higher study for which this is a record was carried out in the University of Oxford between 2013 and 2017.

Allegra Franchino

Date July 2017

Signature of candidate



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Abstract

New Asymmetric Metal-Catalysed Addition Processes for Amine Synthesis

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This thesis concerns the development of novel catalytic approaches for the construction of stereocentres bearing a nitrogen atom. In 2011, the Dixon group reported a Ag(I)/cinchona-derived amino phosphine catalytic system for the activation of isocyanoacetates in asymmetric aldol and Mannich reactions. During this thesis work it was sought to extend the scope of this catalytic system to Mannich additions of other isocyanide pronucleophiles, then the focus was broadened to include Reformatsky and α -alkylation reactions of ketimine substrates.

Chapter 1 gives an overview of the state of the art with particular emphasis on catalytic enantioselective additions to ketimines and the use of activated isocyanides as pronucleophiles.

Chapter 2 describes the application of the Ag-catalysed enantio- and diastereoselective aldol reaction of isocyanoacetates to the concise asymmetric synthesis of the antibiotic chloramphenicol, which possesses a chiral stereodefined α -amino β -hydroxy motif.

Chapter 3 details our efforts to expand the scope of the Ag(I)/amino phosphine catalytic system to the activation of more challenging isocyanides lacking an electron-withdrawing group in the α -position by investigating aldol and Mannich reactions of benzyl isocyanide.

Chapter 4 describes how the scope of the Ag(I)/amino phosphine catalytic system was successfully extended to another pronucleophile, the versatile *p*-toluenesulfonylmethyl isocyanide (TosMIC). The first catalytic enantio- and diastereoselective addition of TosMIC to *N*-diphenylphosphinoyl (*N*-DPP) ketimines was developed, affording 2-imidazolines possessing two contiguous stereocentres with high yields and excellent levels of stereocontrol.

Chapter 5 describes the development of a Ni(II)-catalysed Reformatsky reaction of *N*-DPP ketimines with ethyl bromoacetate and diethylzinc, providing racemic amines bearing a quaternary stereocentre in the α -position in good yields.

Chapter 6 reports the serendipitous discovery of the α -alkylation of *N*-DPP ketimines with ethyl bromoacetate using visible light photoredox catalysis. The transformation, catalysed by ruthenium(II) and nickel(II) complexes under mild conditions, was optimised, its scope assessed and the mechanism investigated.

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Abbreviations

Ac	Acetyl
aq	Aqueous
Ar	Aryl
BEMP	2- <i>tert</i> -Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
BINOL	1,1'-Bi(2-naphthol)
Bn	Benzyl
Boc	<i>tert</i> -Butyloxycarbonyl
BOX	Bisoxazoline
Bu	Butyl
CFL	Compact fluorescent lamp
conc.	Concentrated
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIAD	Diisopropyl azodicarboxylate
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
DPP	Diphenylphosphinoyl
EDC•HCl	<i>N</i> -(3-Dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride
ee	Enantiomeric excess
EPR	Electron paramagnetic resonance
equiv	Equivalents
Et	Ethyl
EWG	Electron-withdrawing group
FCC	Flash column chromatography
GABA	γ -Aminobutyric acid
GC	Gas chromatography
HPLC	High performance liquid chromatography

HRMS	High resolution mass spectrometry
IR	Infrared
LED	Light emitting diode
LHMDS	Lithium bis(trimethylsilyl)amide
LRMS	Low resolution mass spectrometry
LUMO	Lowest unoccupied molecular orbital
Me	Methyl
MS	Molecular sieves
MVK	Methyl vinyl ketone
n. d.	Not determined
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PG	Protecting group
Ph	Phenyl
Phth	Phthaloyl
PMP	<i>para</i> -Methoxyphenyl
PMT	Photomultiplier tube
Pr	Propyl
RF	Retention factor
rt	Room temperature
S _N	Nucleophilic substitution
TosMIC	<i>p</i> -Toluenesulfonylmethyl isocyanide
TBME	<i>tert</i> -Butyl methyl ether
TEA	Triethylamine
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
TEOA	Triethanolamine
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMG	<i>N,N,N',N'</i> -Tetramethylguanidine

TMS	Trimethylsilyl
TS	Transition state
Ts	Tosyl
UV	Ultraviolet

1 General Introduction

1.1 Addition Processes for the Synthesis of Chiral Amines

1.1.1 Retrosynthetic Approaches to α -Branched Amines

Amines bearing a stereocentre in the α -position are a ubiquitous class of compounds, with many applications in the pharmaceutical and agrochemical sectors,¹ as well as in catalysis (Figure 1, top).² Commensurate with their importance and abundance, numerous methods have been developed for their preparation (Figure 1, bottom),³ such as enantioselective reduction of imines and enamides,⁴ sp^3 C–H amination^{5,6} and alkene hydroamination.⁷ A prominent role is occupied by the addition of carbanion equivalents to imines,⁸ which include the venerable Mannich,⁹ nitro-Mannich,¹⁰ Strecker,¹¹ Reformatsky,¹² dialkylzinc¹³ and Grignard addition¹⁴ reactions.

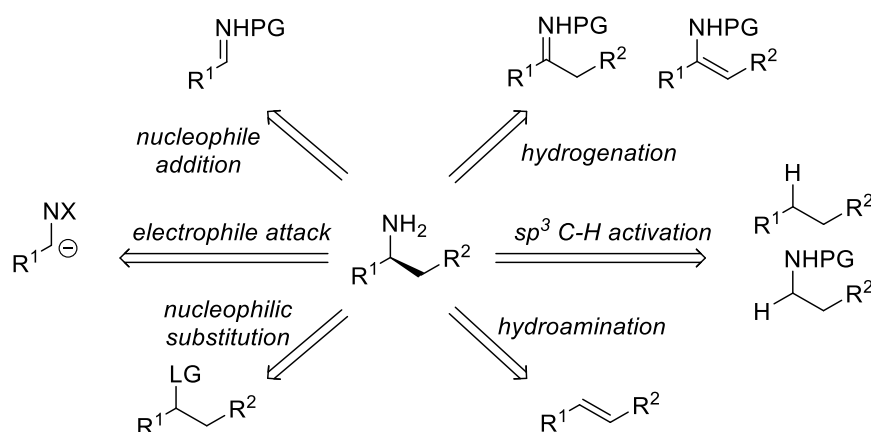
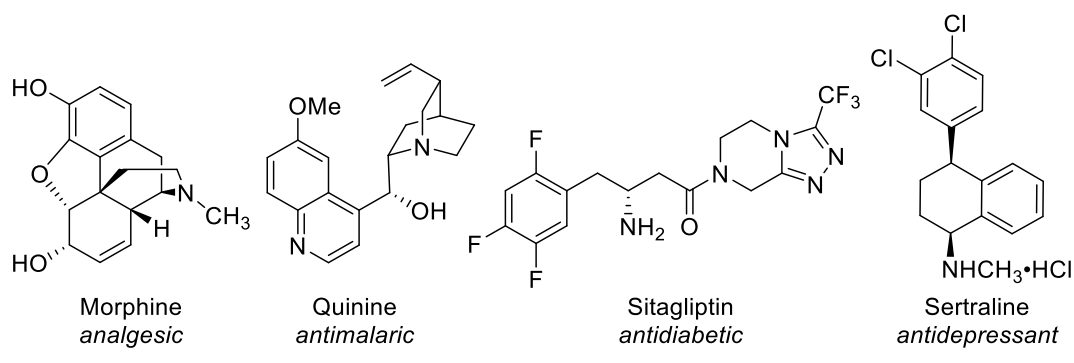


Figure 1 Top: Importance of α -branched chiral amines. Bottom: Retrosynthetic approaches to α -branched chiral amines. PG = protecting group, LG = leaving group, NX = masked amino group.

Another option is the use of ‘masked’ amine synthons where the position α to the N atom has a nucleophilic character. Such amine surrogates displaying umpolung of reactivity can be, for instance, nitroalkanes,¹⁵ isocyanides functionalised with an electron-withdrawing group,¹⁶ isothiocyanates^{17,18} or other glycine equivalents.¹⁹ Since the focus of the present thesis will be on one side on the use of activated isocyanides as pronucleophiles, and on the other on Mannich and Reformatsky reactions of ketimine electrophiles, these topics will be introduced separately in the following paragraphs.

1.1.2 Catalytic Enantioselective Additions to Ketimines

Asymmetric addition of nucleophiles (except hydrides) to imines derived from prochiral ketones allows access to chiral amines with a fully-substituted stereocentre in the α -position. Ketimine substrates are much more challenging electrophiles than their aldimine counterparts, as testified by the fact that until 2002 no catalytic enantioselective additions to ketimines had been disclosed yet, while related asymmetric reactions of aldimines were relatively well established.⁹ Indeed, compared to aldimines, ketimines display reduced electrophilicity due to the steric hindrance and the possible electron-donating effect of the additional substituent. Enantiodiscrimination between the two prochiral faces of the ketimine is also harder, as replacing the H atom with an alkyl or aryl group generally reduces the steric and electronic differences between the two substituents.^{20,21}

One strategy to overcome the lower reactivity is the use of an activating group on the imine nitrogen, which also acts as a protecting group. Ideally, it should (i) activate the substrate by lowering the LUMO, (ii) allow good differentiation of the prochiral faces of the imine and (iii) be removable under mild and selective conditions.

Ab initio calculations of the LUMO energy of various electrophiles performed by Charette and co-workers provide a quantitative estimate of the increase in electrophilicity as a function of

the electron-withdrawing ability of the protecting group (Figure 2).²² Benzaldehyde-derived imines bearing diphenylphosphinoyl, tosyl and benzoyl groups on the nitrogen are increasingly more electrophilic than benzaldehyde; on the other hand, *N*-aryl and *N*-alkyl imines are less electrophilic than the parent aldehyde.

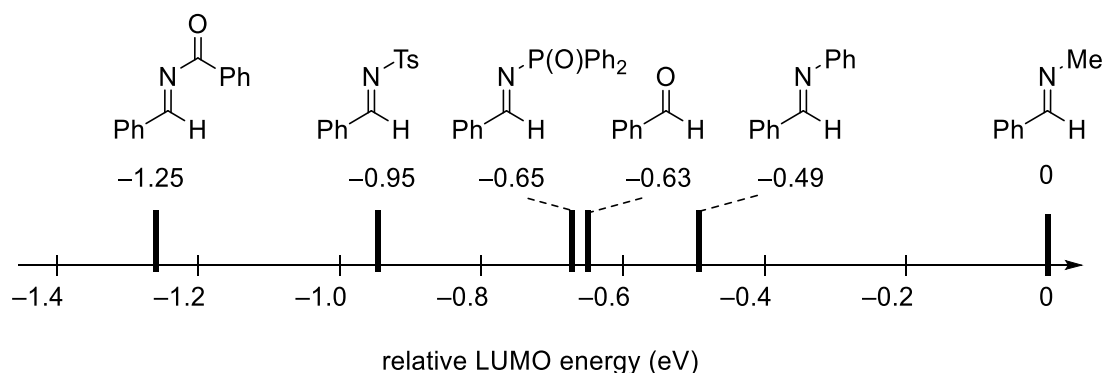


Figure 2 Calculations of the LUMO energy in eV of some electrophiles relative to *N*-methyl imine derived from benzaldehyde (geometry optimized at B3LYP/6-31G(d)).

Another challenge in the development of catalytic enantioselective additions to C=N bonds is the fact that *N*-containing substrates and products can act as ligands, posing a risk of poisoning or deactivating the metal catalyst.²³ Finally, the geometry of the double bond of the imine needs to be considered, as *E* and *Z* isomers often afford opposite enantiomers of the products, thereby diminishing the enantioselectivity of the reaction.³

Despite all the challenges discussed above, in recent years impressive progresses in the development of catalytic enantioselective additions of various pronucleophiles to ketimines have been made by the groups of Jacobsen,²⁴ Jørgensen,²⁵ Shibasaki,²⁶ Feng,²⁷ Maruoka,²⁸ Hayashi,²⁹ Nakamura³⁰ and Hoveyda³¹ among others, and the reader is referred to reviews^{20,21,32,33,34} for a more detailed account of advances in the field. Given the breadth of the topic, herein the discussion will be limited to examples of catalytic enantioselective additions to C=N and C=O bonds directly relevant to this thesis work, which will be described in the introduction of the relative chapters.

1.1.3 Properties and Synthesis of *N*-DPP Ketimines

N-Phosphinoylimines, in particular those with a *N*-diphenylphosphinoyl (*N*-DPP) group, are an increasingly popular substrate class in stereoselective organic synthesis.³⁵ *N*-DPP imines are less electrophilic than *N*-tosyl³⁶ and *N*-Boc imines.³⁷ This trend has been recently quantified by the electrophilicity scale devised by Mayr and co-workers (Figure 3),³⁸ and it is also consistent with Charette's calculation of the LUMO energy presented above (see Figure 2).

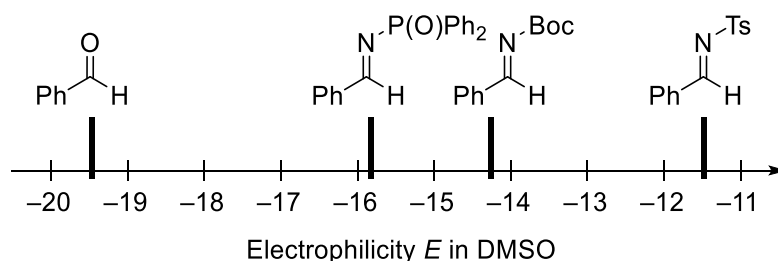
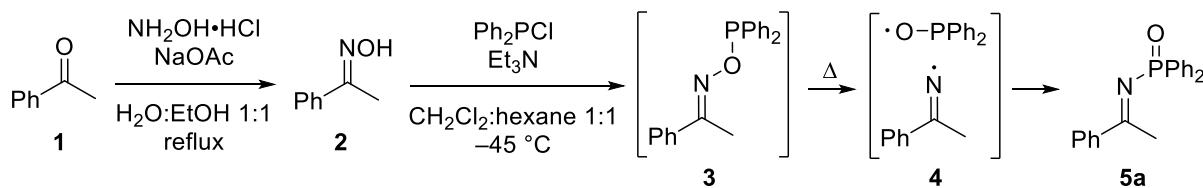


Figure 3 Mayr's quantification of electrophilicity of benzaldehyde and imines thereof.

The lower electrophilicity of *N*-DPP imines is reflected in an increased hydrolytic stability, so that they can be isolated, purified by FCC in most cases and stored at low temperature for months. Moreover, their lower reactivity can diminish uncatalysed background reactions, making them useful substrates in catalytic asymmetric addition of nucleophiles in the presence of chiral catalysts. Furthermore, the DPP group on the product amines is cleaved under mild acidic conditions,³⁹ thus making it synthetically useful.

A few methods have been developed for the synthesis of *N*-DPP imines,^{40,41} with one of the most straightforward being the direct condensation of aromatic aldehydes with diphenylphosphinamide in the presence TiCl_4 and triethylamine.⁴² The scope of the reaction, however, is limited to aromatic aldehydes, and ketones such as acetophenone are incompatible substrates because of reduced electrophilicity and competing enolisation. The most general preparation method for both *N*-DPP aldimines and ketimines is the reaction between the corresponding oxime and chlorodiphenylphosphine, first reported in 1968 by the Russian chemist Kruglyak⁴³ and later popularised by Stec.^{44,45} After the dropwise addition of

chlorodiphenylphosphine to a solution of oxime and triethylamine kept at low temperature (typically below $-40\text{ }^{\circ}\text{C}$), the reaction mixture is slowly warmed to room temperature and stirred overnight (Scheme 1).



Scheme 1 Synthesis of N-DPP ketimine 5a via the corresponding oxime and Hudson's proposed mechanism for the reaction.

Initial nucleophilic attack of the oxime **2** to the chlorodiphenylphosphine gives the unstable O-phosphinyloxime **3**, which has been detected spectroscopically. Upon warming of the reaction mixture, homolytic fission of the N-O bond takes place (observed by EPR spectroscopy) and radical recombination yields the *N*-DPP imine **5a**.^{46,47}

Low temperature ^{31}P NMR studies conducted by Shibasaki and co-workers established that *N*-DPP ketimines derived from aliphatic ketones exist in a very fast equilibrium between *E* and *Z* isomers.⁴⁸ Coalescence of the peaks in the ^{31}P NMR occurs at temperatures higher than $-40\text{ }^{\circ}\text{C}$ in CD_2Cl_2 and CD_3CN , and no nuclear Overhauser effect can be observed at room temperature to determine the geometry of the C=N bond, presumably due to fast interconversion between the two isomers on the NMR time scale. In analogy with the behaviour of *N*-sulfonyl ketimines,^{49,50} interconversion is thought to occur through in-plane inversion, a mechanism where the N-P bond swings in the C=N bond plane passing through a linear C=N-P transition state (Figure 4).⁵¹ This transition state, containing a *sp*-hybridised N atom would be stabilised by π conjugation between a filled nitrogen *p* orbital and an empty phosphorous *d* orbital.⁴⁸

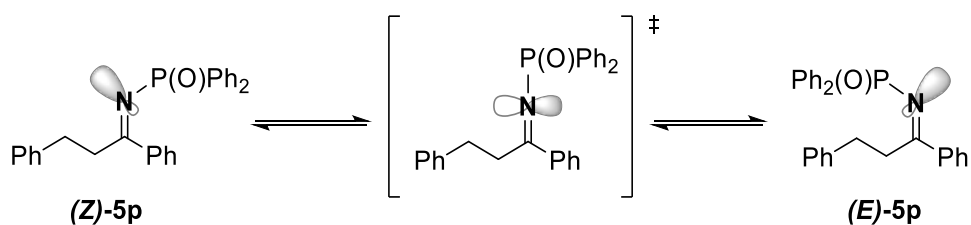


Figure 4 Proposed mechanism for the in-plane inversion of N-DPP ketimine **5p**.

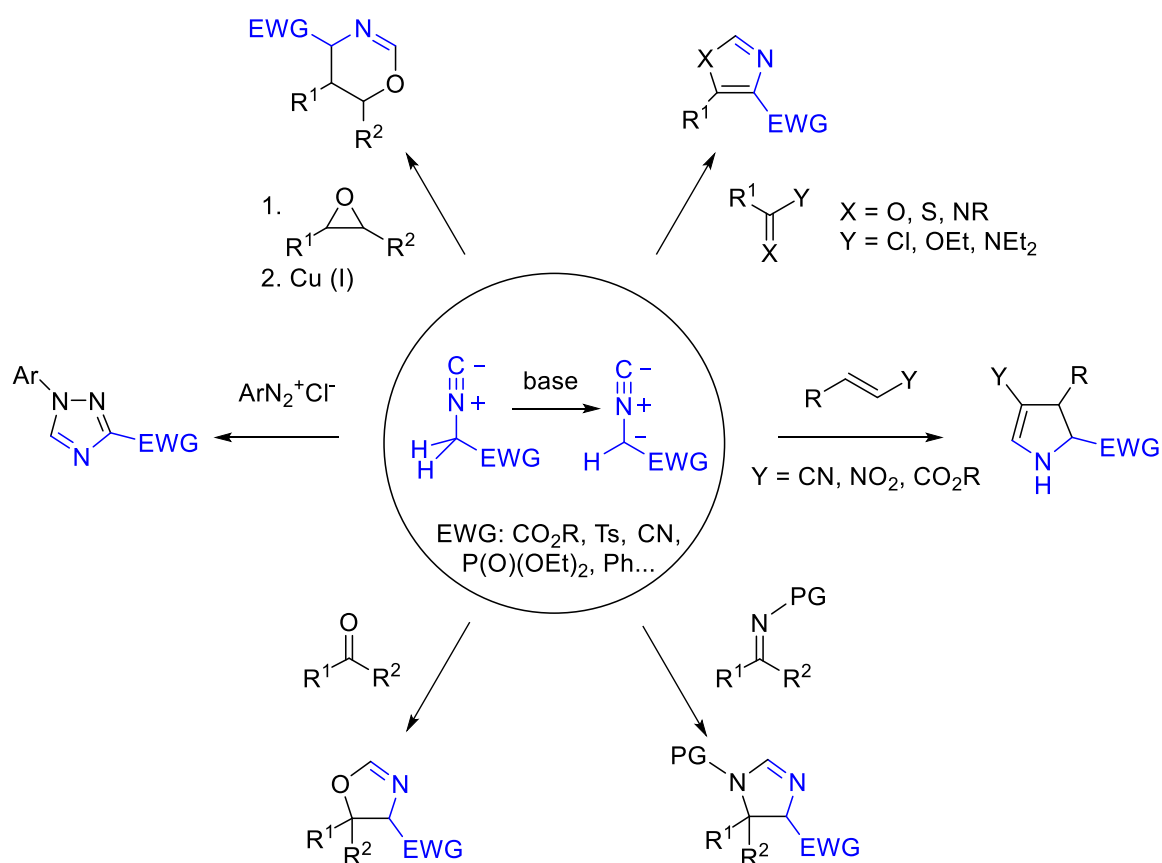
Shibasaki and co-workers also noted that the *E/Z* ratio of *N*-DPP ketimines, as determined by the ratio of peaks in the ^{31}P NMR spectra below $-40\text{ }^{\circ}\text{C}$, did not correlate with the enantioselectivity obtained in the asymmetric Strecker reaction, and therefore postulated that the reaction proceeded from one configurational isomer controlled by the Curtin–Hammet principle.⁵²

After this brief overview on ketimine electrophiles, the following paragraphs will deal with the use of activated isocyanides as pronucleophiles in addition reactions to polar $\text{C}=\text{X}$ electrophiles.

1.2 Aldol and Mannich Reactions of Isocyanoacetate Pronucleophiles

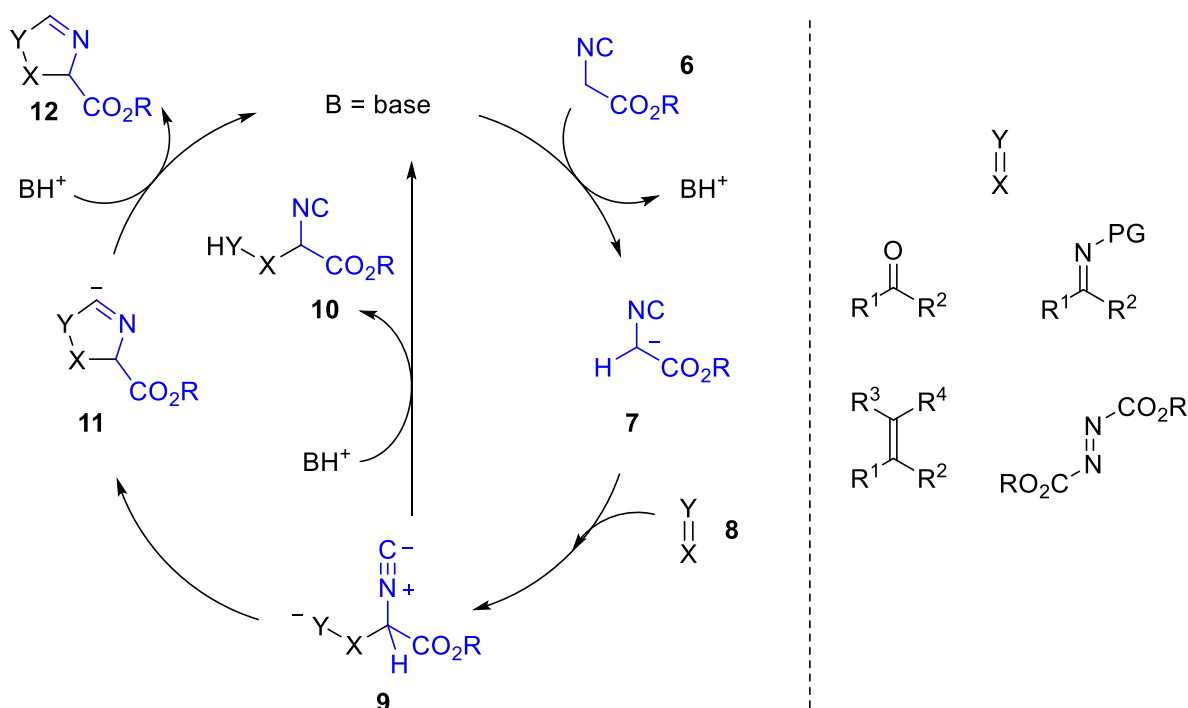
1.2.1 Activated Isocyanides as Pronucleophiles

Isocyanides are common building blocks for the synthesis of nitrogen-containing heterocycles. In all the reactions depicted in Scheme 2, the isocyanide acts as a pronucleophile with a broad variety of electrophiles.⁵³



Scheme 2 Activated isocyanides in the synthesis of N-containing heterocycles.

Deprotonation of the isocyanide with a base can be facilitated both by coordination of a Lewis acidic metal to the terminal C atom⁵⁴ and/or by the presence of an electron-withdrawing group in the α position.¹⁶ When the electron-withdrawing group is an ester functionality, the isocyanide — termed isocyanoacetate — can act as a masked glycine equivalent.⁵⁵ Base-catalysed reactions of isocyanoacetates with C=N, C=O, C=C and N=N double bonds proceed stepwise (Scheme 3).¹⁶ After deprotonation of the pronucleophile **6**, carbanion **7** attacks the double bond of the electrophile affording intermediate **9**. The latter can be protonated, thus affording the acyclic product **10** and regenerating the base, or alternatively the newly formed anion in **9** can attack the terminal isocyanide carbon intramolecularly, leading, after protonation, to the formal [3+2] cycloaddition product **12**. The selectivity between the two reaction pathways depends on the nature of substrates and reaction conditions;⁵⁶ for instance, typically metal-catalysed aldol and Mannich reactions of isocyanoacetates afford the cyclised product **12**, whereas organocatalytic variants more often stop at the acyclic adduct **10**.⁵⁷



Scheme 3 General mechanism for base-catalysed reactions of isocyanoacetates with electrophiles.

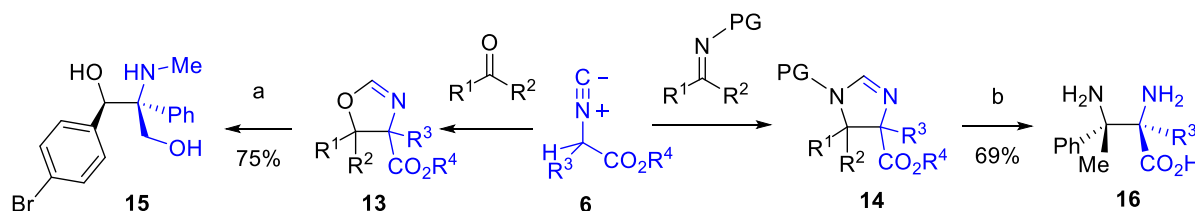
1.2.2 Aldol and Mannich Reactions of Isocyanoacetate Esters

Aldol and Mannich reactions of isocyanoacetates **6** are of special interest for a number of reasons (Scheme 4).⁵⁶ First of all, the product 2-oxazolines **13** and 2-imidazolines **14** are pharmaceutically and chemically relevant by themselves. Compounds incorporating a 2-oxazoline fragment⁵⁸ have shown for instance anti-inflammatory,⁵⁹ antimalarial,⁶⁰ antipyretic⁶¹ and antibacterial⁶² activity. Poly(2-oxazolines) prepared by cationic ring opening polymerisation have found applications in biological and biomedical contexts as coatings, membranes and drug delivery systems.⁶³

Similarly, the 2-imidazoline core is present in molecules with antihypertensive,⁶⁴ antihyperglycemic,⁶⁵ antidepressive,⁶⁶ anti-inflammatory⁶⁷ and antitumor⁶⁸ properties. It is also popular as a fragment in organocatalysts and ligands, and as precursors for *N*-heterocyclic carbenes.⁶⁹

In addition, elaboration of the products affords other valuable compounds (Scheme 4). Reductive ring opening of the heterocycle furnishes vicinal amino alcohols,⁷⁰ such as **15**, and

diamines,⁷¹ which are useful building blocks for drug discovery and ligand design. Products obtained from asymmetric aldol and Mannich reactions of isocyanoacetates possess two contiguous stereocentres, and can be readily elaborated to furnish enantioenriched β -functionalised α -amino acids such as **16**.^{72,73}

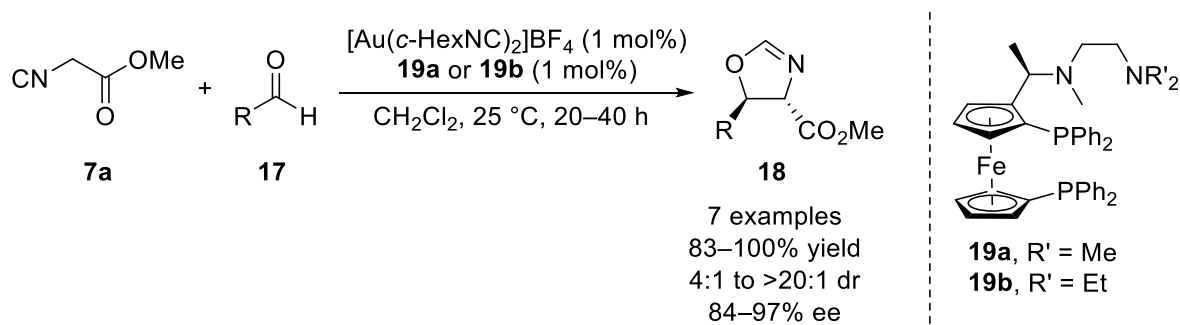


Scheme 4 Selected examples highlighting the importance of 2-oxazoline and 2-imidazoline products. (a): LiAlH₄ (5 equiv), -78 °C to rt, 16 h. (b): 1 M HCl, 3 h, reflux; then 50% aq KOH, 6 h, reflux.

1.2.3 Catalytic Enantioselective Aldol Reactions of Isocyanoacetates

Seminal studies on base-promoted reactivity of isocyanoacetates towards aldehydes and ketones were carried out by Schöllkopf and Gerhart in the late 1960s.^{74,75} Given the rapid growth of the field, the chemistry of isocyanide pronucleophiles had been already reviewed twice by the end of 1970s (by Hoppe⁷⁶ and Schöllkopf).⁷⁷ Nowadays the topic continues to attract a great deal of interest, as demonstrated by the more recent reviews.^{16,55,56,78}

The first enantio- and diastereoselective aldol reaction of isocyanoacetates was reported in 1986 by Ito and Hayashi (Scheme 5).⁷⁹ They used gold(I) as a Lewis acid to coordinate the isocyanide function, and the ferrocenyl bisphosphine **19**, possessing a tertiary amine appendix, as a ligand. Oxazolines derived from aromatic and aliphatic aldehydes were obtained in excellent yields and with very good levels of diastereo- and enantiocontrol.



Scheme 5 Ito and Hayashi's Au-catalysed enantio- and diastereoselective isocyanoacetate aldol reaction.

In the proposed stereochemical model, supported by experiments with modified ligands⁸⁰ and NMR studies of the Au(I) and Ag(I) complexes with ligand **19a**,⁸¹ the distal amine acts as a Brønsted base for deprotonating the α -position of the Au(I)-bound methyl isocyanoacetate and then the resulting ammonium ion orients the enolate towards addition of the aldehyde. Coordination of the electrophile to the metal centre of the complex could not be observed by NMR spectroscopy; however, since this technique offers a picture of a molecule's ground state, coordination of the aldehyde to Au^+ in the transition state cannot be ruled out (Figure 5).

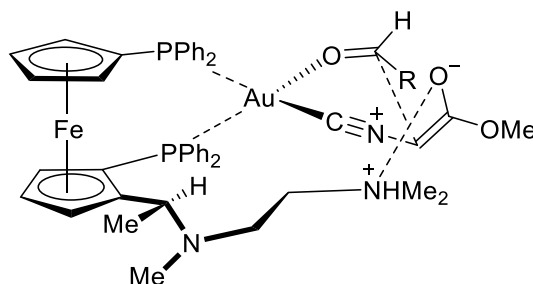
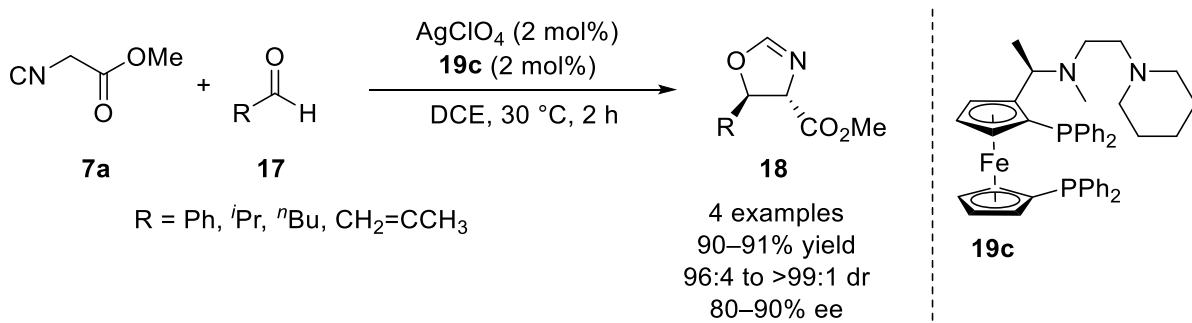


Figure 5 Proposed stereochemical model for the Au-catalysed asymmetric isocyanoacetate aldol reaction.

In addition to isocyanoacetates, isocyanoacetamides^{82,83,84} and (isocyanomethyl) phosphonates⁸⁵ were also competent pronucleophiles in the reaction. In terms of electrophiles, this catalytic system was also applied to the isocyanoacetate aldol reaction of activated ketones (α -ketoesters and α -diketones),⁸⁶ however the levels of stereoselectivity in the formation of oxazolines was generally lower than in the reaction with aldehydes.

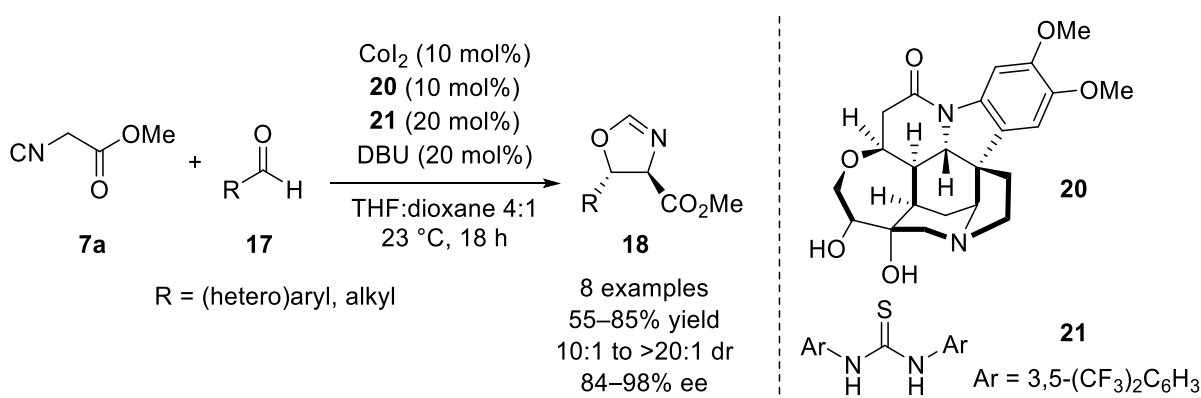
In 1991, Ito and Hayashi reported that Ag(I) in conjunction with ligand **19c** was also able to catalyse the asymmetric aldol reaction of methyl isocyanoacetate with good yield and stereoselectivity (Scheme 6).⁸⁷



Scheme 6 Ito and Hayashi's Ag-catalysed enantio- and diastereoselective isocyanoacetate aldol reaction.

Apart from Ag(I) and Au(I), several Pt(II) and Pd(II) complexes with chiral pincer ligands (specifically *N,N,N*-, *N,C,N*-, *P,C,P*-, and *S,C,S*-ligands) have been investigated in the aldol reaction of isocyanoacetates. Work done by the groups of Pregosin,⁸⁸ Venanzi,⁸⁹ Richards,⁹⁰ Zhang,⁹¹ Swager,⁹² van Koten,⁹³ Motoyama,⁹⁴ Gebbink⁹⁵ and Ahn⁹⁶ showed that these complexes, despite being generally able to promote the formation of *trans* oxazolines with good yields and dr, impart low levels of enantioinduction in the reaction (below 65% ee).

In 2011, Oh and co-workers reported a cooperative catalytic system involving a chiral Co(II)-complex with brucine-derived ligand **20** and Schreiner's thiourea **21** for the aldol reaction of isocyanoacetates with a variety of aldehydes (Scheme 7).⁹⁷



Scheme 7 Oh's Co(II)/thiourea co-catalysed asymmetric isocyanoacetate aldol reaction.

The authors proposed that the isocyanide, rather than binding to the metal, is activated by the thiourea through H-bonding and deprotonated by DBU (Figure 6). The resultant (*Z*)-configured

cobalt enolate then attacks the aldehyde, bound to the tetrahedral Co(II) complex, in a chair-like transition state.

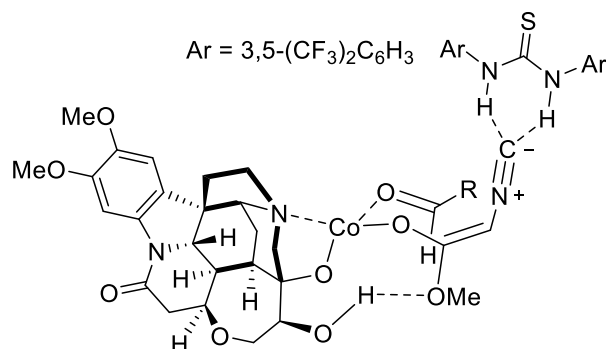
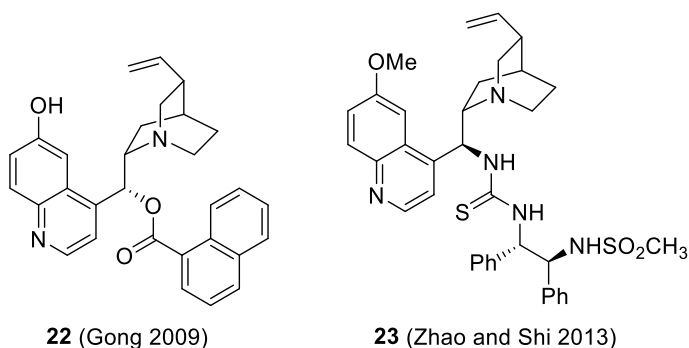


Figure 6 Proposed stereochemical model for Oh's Co(II)/thiourea co-catalysed aldol reaction.

Organocatalytic versions of the asymmetric isocyanoacetate aldol reaction have been reported by the groups of Gong⁹⁸ and Shi,⁹⁹ using cinchona-derived ester **22** and bifunctional thiourea **23** respectively (Figure 7).



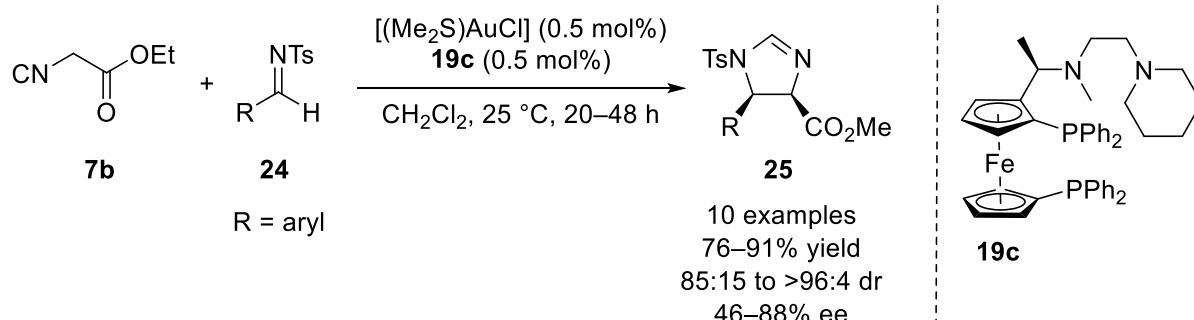
22 (Gong 2009)

23 (Zhao and Shi 2013)

Figure 7 Organocatalysts **22** and **23** for asymmetric aldol reactions of isocyanoacetates with aldehydes and isatins respectively.

1.2.4 Catalytic Enantioselective Mannich Reactions of Isocyanoacetates

The first catalytic enantioselective Mannich reaction of isocyanoacetate was reported by Lin and co-workers in 1999 using Au(I) in conjunction with Hayashi-type ligand **19c**. As opposed to aldehyde substrates (see Scheme 5), *N*-tosyl aldimines reacted to afford preferentially the *cis* diastereomer of product **25**, with moderate levels of enantioselectivity (Scheme 8).¹⁰⁰ The authors did not propose an explanation for the switch in diastereoselectivity observed with this electrophile.

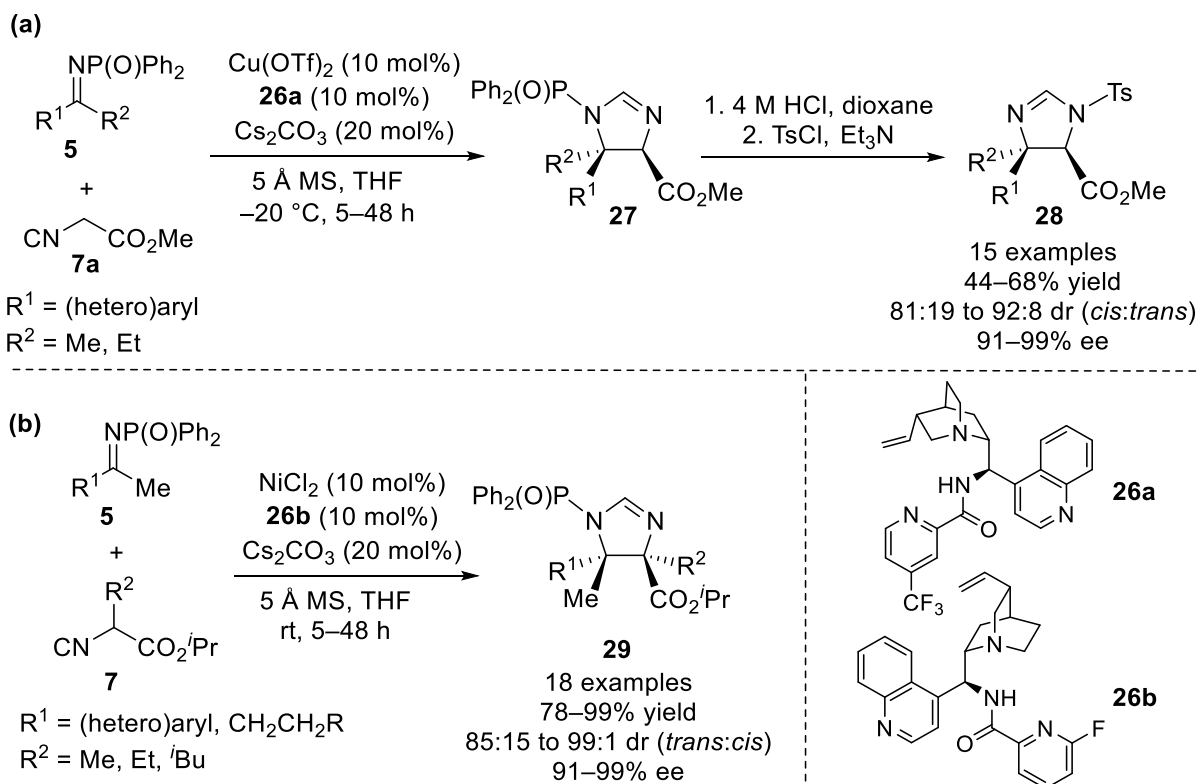


Scheme 8 Lin's Au-catalysed asymmetric aldol reaction of N-tosyl aldimines.

A breakthrough in the field came in 2014, when studies on the isocyanoacetate Mannich reactions of ketimines were published independently by our group (see Section 1.3), and by the groups of Nakamura¹⁰¹ and Zhao¹⁰² (see below).

Nakamura and co-workers reported an enantioselective Mannich reaction of isocyanoacetates with *N*-diphenylphosphinoyl (*N*-DPP) ketimines (Scheme 9a).¹⁰¹ In the presence of cinchona-derived picolinamide **26a**, Cu(OTf)₂ and Cs₂CO₃, *N*-tosyl *cis* imidazolines **28** were obtained in good yields and with excellent diastereo- and enantiocontrol. Conversion to the tosyl derivatives **28** was necessary due to the thermal instability of the initially formed *N*-DPP *cis*-configured imidazolines **27**.

Two years later, the authors found that reactions between α -substituted isocyanoacetates and *N*-DPP ketimines, which did not take place in the presence of Cu(OTf)₂, could be catalysed by NiCl₂ instead, in conjunction with picolinamide **26b** and Cs₂CO₃ (Scheme 9b).¹⁰³ In this way, *trans*-configured imidazolines **29** with two contiguous fully substituted stereocentres could be obtained with good yields and high levels of stereocontrol.



Scheme 9 Nakamura's asymmetric Mannich reactions of isocyanacetates with *N*-DPP ketimines catalysed by Cu(II) **(a)** and Ni(II) **(b)** with cinchona-derived picolinamide ligands.

The authors rationalised the formation of *cis*-configured imidazolines **27** in the Cu(II)-catalysed Mannich reaction of linear isocyanacetate pronucleophiles (Scheme 9a) by means of the stereochemical model reproduced in Figure 8, where both the *N*-DPP ketimine and the isocyanide coordinate to the Cu(II) centre.

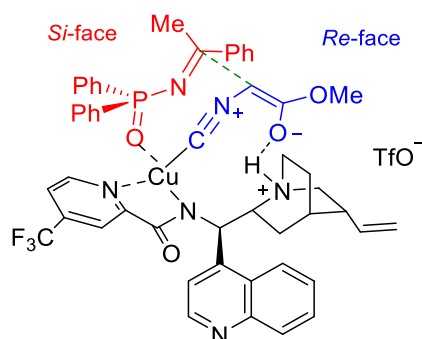
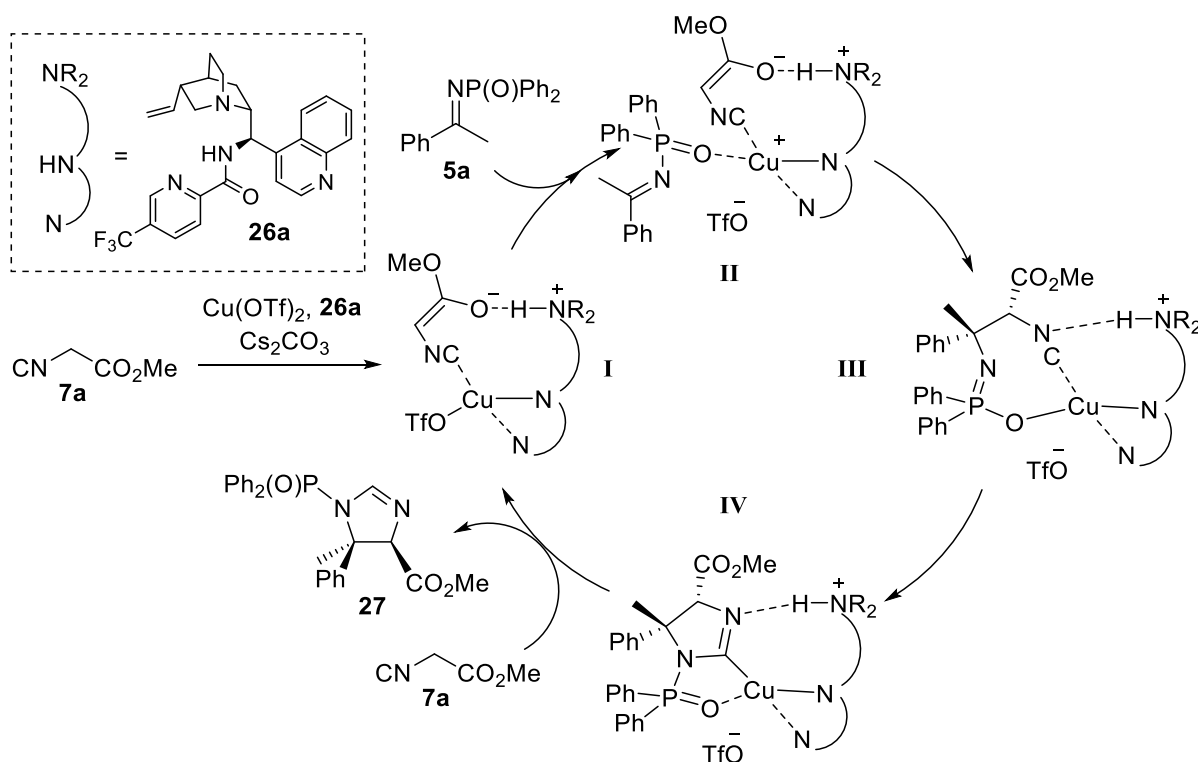


Figure 8 Proposed stereochemical model for Nakamura's Mannich addition of linear isocyanacetate pronucleophiles to *N*-DPP ketimines.

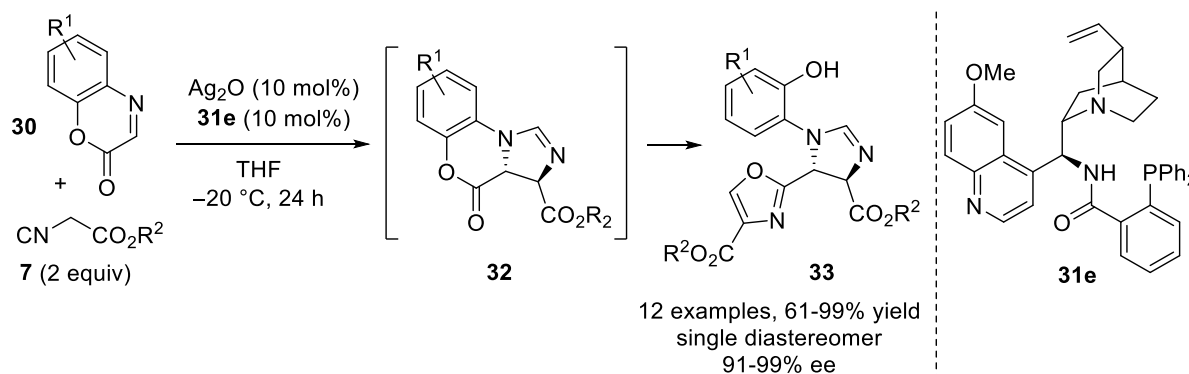
Furthermore, they proposed a unified catalytic cycle for the two transformations (Scheme 10).^{101,103} In the copper-catalysed reaction, according to the authors the active catalytic species (**I**) forms upon mixing $\text{Cu}(\text{OTf})_2$, Cs_2CO_3 , methyl isocyanoacetate **7a** and ligand **26a**. Copper(II) complex **I** was indeed observed as a cationic species by HRMS after loss of triflate. The ketimine coordinates to the metal *via* the O atom of the diphenylphosphinoyl group (**II**), and the C–C bond formation takes place within the coordination sphere of the metal (**III**, square planar Cu(II) complex) to afford, after ring closure, a copper-bound imidazoline. Ligand exchange between complex **IV** and methyl isocyanoacetate gives the product **27** and the active species **I**. In the Ni(II)-catalysed version of the reaction, the authors postulated that the species involved in the catalytic cycle are distorted tetrahedral Ni(II) complexes, where the triflate is replaced by chloride and ligand **26a** by **26b** (see Scheme 9). The Ni(II) equivalent of complex **I** was detected by LRMS after loss of chloride.



Scheme 10 Nakamura's postulated mechanism for the Cu(II)-catalysed asymmetric Mannich reaction of isocyanoacetate pronucleophiles.

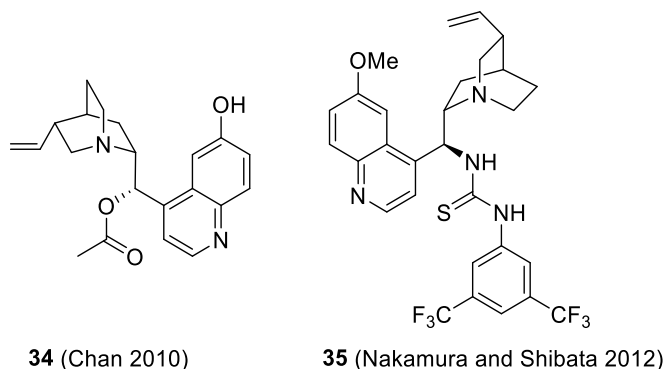
Zhao and co-workers disclosed an enantioselective Ag-catalysed double cyclisation of α -imino esters with isocyanoacetates, to generate linked oxazole-imidazolines **33** in high yield (Scheme

11).¹⁰² Aminophosphine ligand **31e**, developed in the Dixon group some years before,¹⁰⁴ imparted high diastereo- and enantiocontrol in the formation of the intermediate imidazolines **32**, which could be isolated using only 1.5 equivalents of isocyanoacetate. Under the standard reaction conditions (using 2 equivalents of isocyanoacetate), the aromatic ester group of adducts **32** cyclised, affording the oxazole ring of **33** after expulsion of the aryloxide group.



Scheme 11 Zhao's asymmetric Ag-catalysed double cyclisation of α -iminoesters with isocyanoacetates.

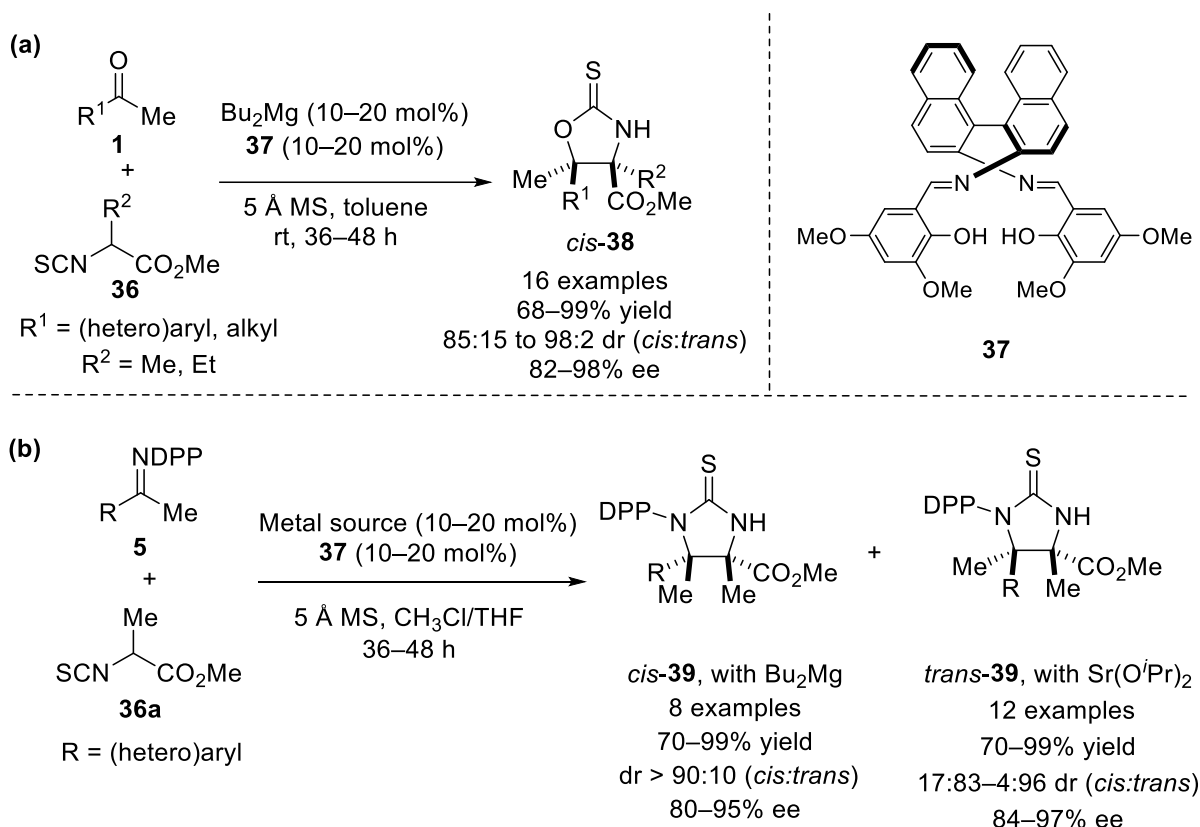
Organocatalytic versions of the Mannich reaction of isocyanoacetates have also been developed by the groups of Lu and Chan,¹⁰⁵ and Nakamura and Shibata¹⁰⁶ (Scheme 12).



Scheme 12 Organocatalysts **34** and **35** for asymmetric Mannich reactions of isocyanoacetates with N-tosyl aldimines and 2-pyridinesulfonyl-protected aldimines respectively.

Finally, it is worth remembering that a closely related approach to chiral heterocycles containing vicinal amino alcohol and 1,2-diamine moieties is offered by the catalytic enantioselective aldol and Mannich reactions of α -isothiocyanato imides (developed by Willis and co-workers)^{17,107} and α -isothiocyanato esters. The latter, which can be directly compared with isocyanoacetate pronucleophiles, were used as substrates in the addition reactions to

ketones¹⁸ and *N*-DPP ketimines¹⁰⁸ developed by Shibasaki, Matsunaga and co-workers (Scheme 13).



Scheme 13 Shibasaki and Matsunaga's catalytic enantioselective reactions of isothiocyanato esters with ketones and *N*-DPP ketimines.

The reactions of α -isothiocyanato esters **36** with ketones and ketimines can be catalysed by Schiff base **37** in the presence of Bu_2Mg , affording *cis*-configured oxazolidinethiones **38** and imidazolidinethiones **39** with high yields and stereoselectivity. Interestingly, when the Mannich reaction between **36a** and **5** was catalysed by $\text{Sr}(\text{O}^i\text{Pr})_2$, the diastereomeric products *trans*-**39** were obtained (Scheme 13b). Based on circular dichroism spectra, the authors hypothesised that the observed switch in diastereoselectivity is linked to the difference in the dihedral angles of the binaphthyl unit in $\text{Sr}(\text{II})$ and $\text{Mg}(\text{II})$ complexes of **37**.¹⁰⁸

1.3 Ag(I)/Amino Phosphine System for the Catalytic Asymmetric Activation of Isocyanoacetates

1.3.1 Design and Ligand Synthesis

The Dixon group has made important contributions in the field of enantio- and diastereoselective aldol and Mannich reactions of isocyanoacetate pronucleophiles. Inspired by the work of Ito and Hayashi (see Scheme 5),⁷⁹ in 2011 Dixon and co-workers designed a novel catalytic system for the asymmetric activation of isocyanoacetates, comprising a silver(I) salt and an amino phosphine ligand **31** (Figure 9).¹⁰⁴

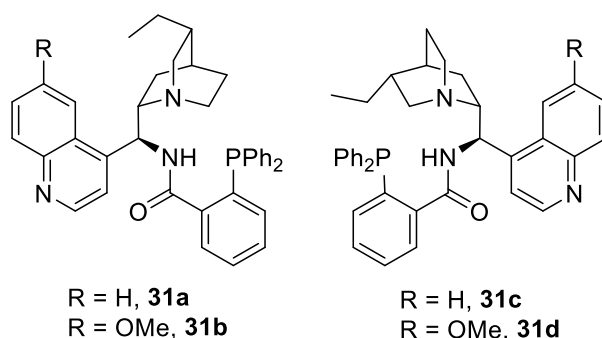
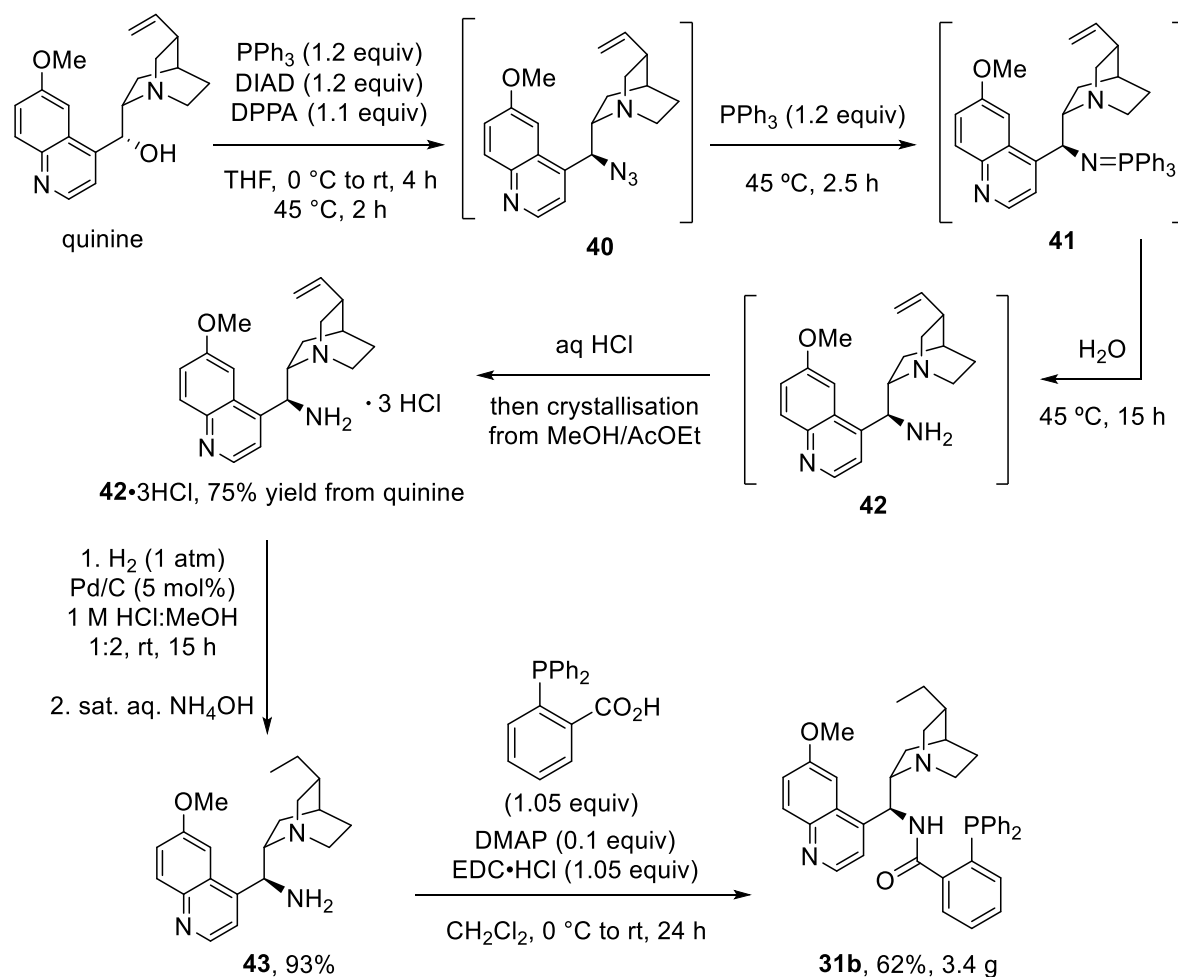


Figure 9 Dixon's amino phosphine ligands, derived from cinchona alkaloids.

According to the original design, Ag(I) would serve as the Lewis acid for isocyanide activation, while the bifunctional ligand would possess both a Lewis basic site (the phosphorous atom) and a Brønsted/Lewis basic tertiary amine functionality (the quinuclidine nitrogen) embedded within the chiral scaffold derived from commercially available cinchona alkaloids.

A small library of ligands can be easily synthesised from commercially available cinchona alkaloids in three steps, as exemplified by the synthesis of the quinine-derived ligand **31b** (Scheme 14). According to a protocol developed by Melchiorre and co-workers,¹⁰⁹ 9-amino(9-deoxy) *epi*-quinine (**42**) was prepared from quinine *via* an azide Mitsunobu reaction followed by Staudinger reduction, and recrystallised as the triple hydrochloride salt. Hydrogenation of the double bond and basification furnished **43**, which was then coupled with 2-(diphenylphosphino)benzoic acid, obtaining **31b**. Originally, the coupling step suffered from

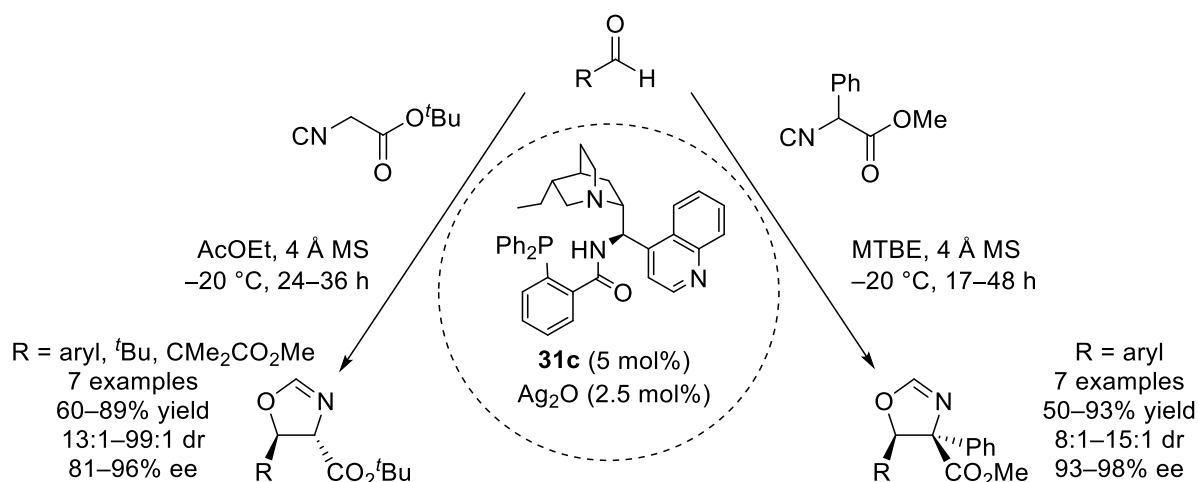
low yields ($\leq 50\%$) due to difficulties in the separation of impurities (unreacted starting materials and phosphine oxides), requiring multiple chromatographic purifications. In the course of this PhD, it was found that the yield could be improved to $>60\%$ by performing a recrystallisation from ethyl acetate after the first FCC, thus allowing us to obtain gram quantities of ligand **31b**.



Scheme 14 Synthesis of amino phosphine ligand **31b** starting from quinine. Reactions performed by A.F. in duplicate, average yields given.

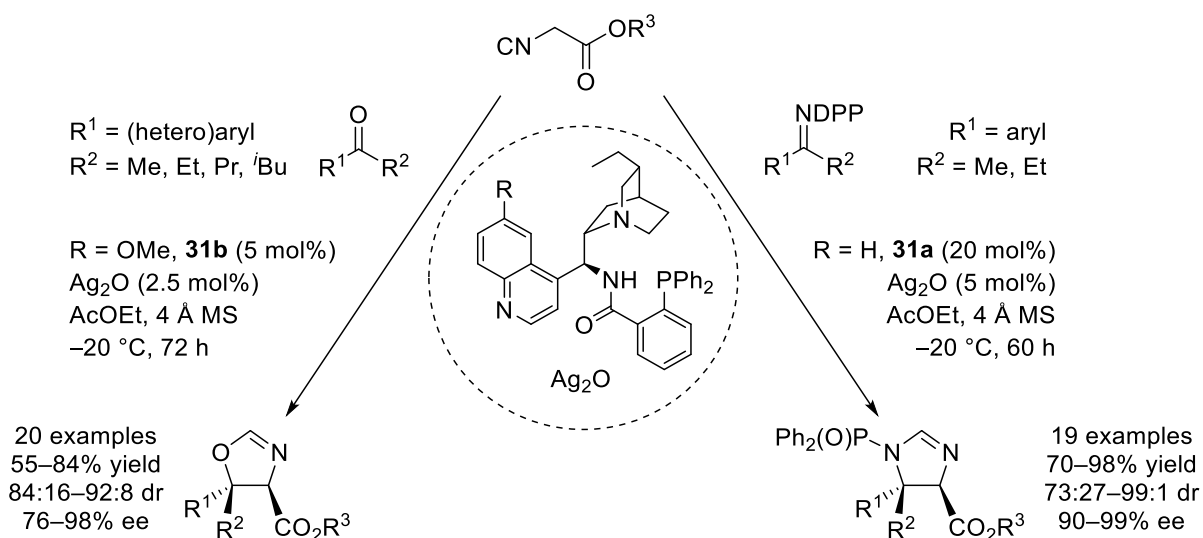
1.3.2 Amino Phosphine/Ag(I)-catalysed asymmetric Aldol and Mannich Reactions of Isocyanoacetates

It was demonstrated that the aminophosphine/silver oxide system could successfully catalyse the enantio- and diastereoselective aldol reaction between *tert*-butyl isocyanoacetate and a range of aromatic and bulky aliphatic aldehydes (Scheme 15).¹⁰⁴



Scheme 15 Enantio- and diastereoselective addition of isocyanoacetates to aldehydes catalysed by the Ag/amino phosphine system.

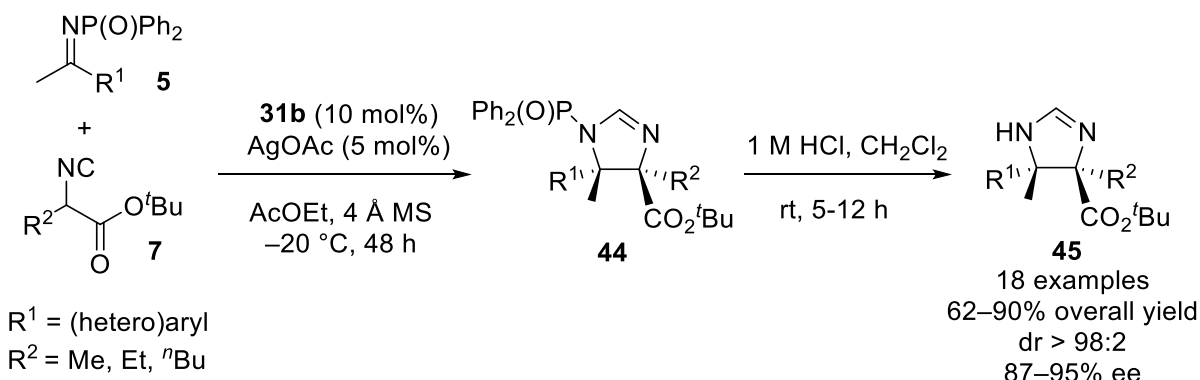
Further work done in the Dixon group showed that it was also possible to apply this catalytic system to different electrophiles. Reactions of linear isocyanoacetates with ketones¹¹⁰ and diphenylphosphinoyl-protected ketimines¹¹¹ were developed, delivering oxazolines and 2-imidazolines, respectively, with good yields and excellent stereocontrol (Scheme 16).



Scheme 16 Enantio- and diastereoselective additions of isocyanoacetates to *N*-DPP ketimines and ketones catalysed by the Ag/amino phosphine system.

Regarding the scope of the pronucleophile, only isocyanoacetate esters were explored. Within this class, α -phenyl isocyanoacetates were found to be compatible substrates in the aldol reaction of aromatic aldehydes (see Scheme 15),¹⁰⁴ and isocyanoacetates bearing linear alkyl chains in the α position were successfully used in the addition to *N*-DPP ketimines (Scheme 17).¹¹² After removal of the DPP protecting group from the unstable *N*-DPP imidazolines **44**,

products **45** with two vicinal fully substituted stereocentres were obtained with good yields and high levels of diastereo- and enantiocontrol (Scheme 17).



Scheme 17 Enantio- and diastereoselective Mannich addition of α -substituted isocyanoacetates to N-DPP ketimines catalysed by AgOAc and amino phosphine **31b**.

1.3.3 X-Ray and NMR Studies

Structural insight into the catalytic system was gained through X-Ray and NMR studies.¹¹² Single crystal X-ray diffraction of a complex of aminophosphine **31b** with silver acetate showed that in the solid state **31b** acts as a bidentate *P,N*-ligand, coordinating to Ag through the P atom of the phosphine and the quinuclidine N atom (Figure 10). The tetracoordinated silver adopts a distorted tetrahedral geometry, the other two groups around it being the acetate ion and a quinuclidine N atom belonging to another unit, so that polymeric chains are formed in the solid state. An intramolecular H-bond between the acetate ion and the amide linker of the ligand is also present, with H–O and N–O distances of 1.90 Å and 2.75 Å, respectively. In addition, the π -system of the amide linker is oriented towards Ag, with a N–Ag distance of 2.96 Å. A possible interaction between the amide and silver would transfer electron density to the metal, thereby acidifying the amide NH and thus enhancing its H-bond donor ability.

Low temperature ^1H and ^{31}P NMR studiesⁱ confirmed that a similar coordination mode of the ligand to silver was also occurring in solution. Upon addition of one equivalent of AgOAc to a

ⁱ Performed by Dr Adam Gammack Yamagata with assistance from Dr Barbara Odell.

solution of ligand **31b** in CD_2Cl_2 , quantitative formation of a silver-phosphine complex, identified as Ag(I) aminophosphine complex **46**, was observed (Figure 11 and Figure 12).

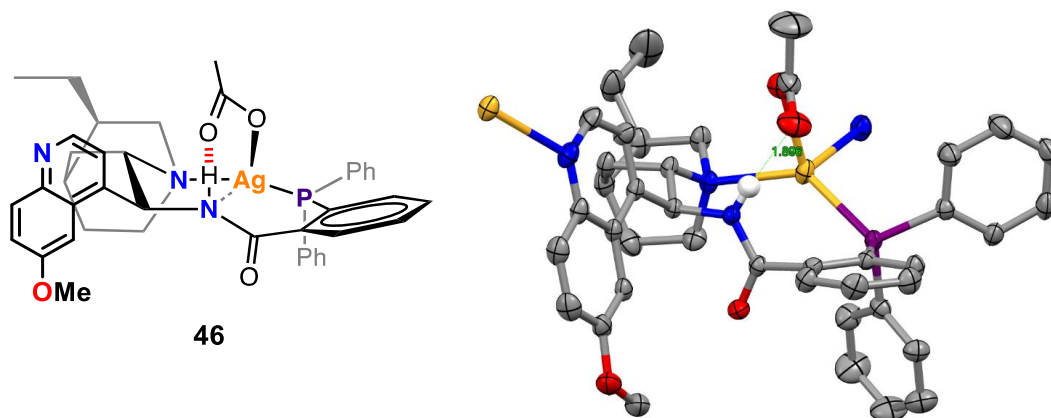


Figure 10 Single crystal X-Ray structure for $[\text{Ag}(\text{OAc})(\mathbf{31b})]$, complex **46**. ORTEP diagram with ellipsoids at 50% probability. Selected H atoms omitted for clarity.

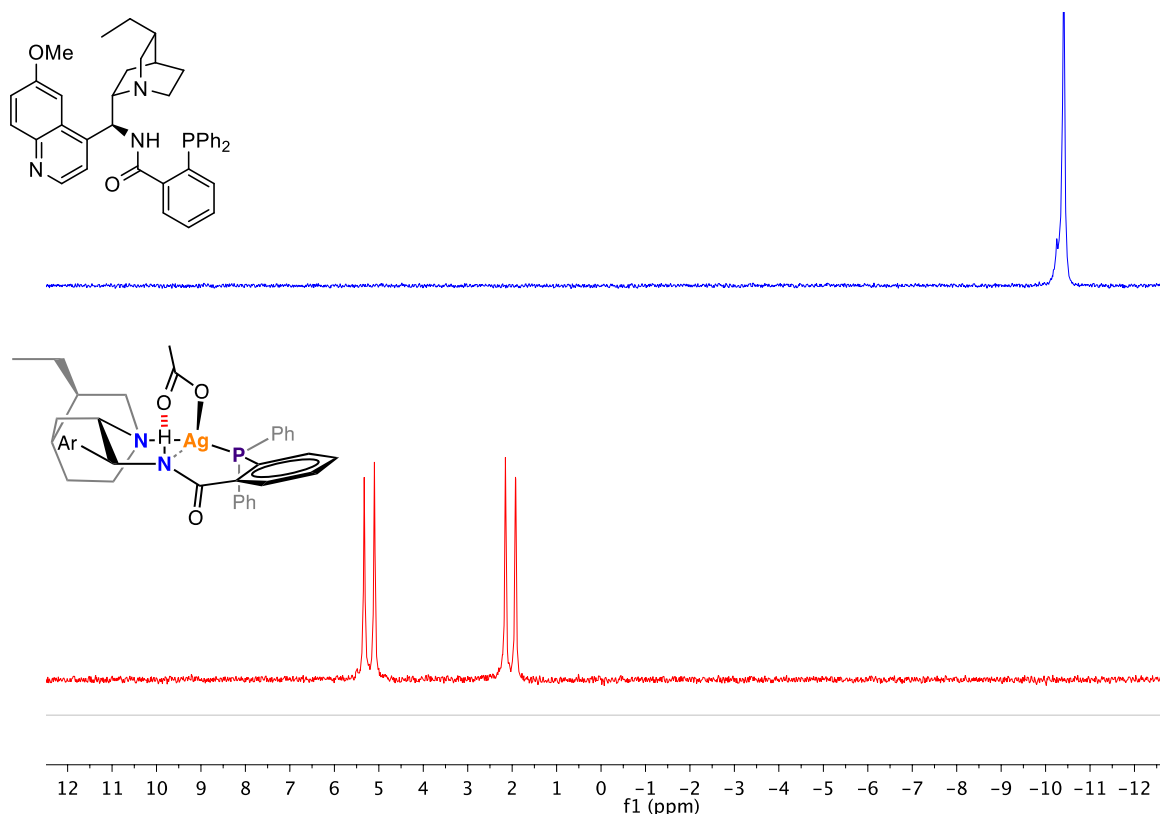


Figure 11 ^{31}P NMR studies performed at 0.02 M concentration in CD_2Cl_2 at 253 K, showing the formation of complex **46**. Reproduced with courtesy of Dr Adam Gammack Yamagata.

The two large doublets present in the ^{31}P NMR spectrum¹¹³ of complex **46** arise from $^1J_{\text{P-Ag}}$ couplings with the two silver isotopes, which have spin number $I = \frac{1}{2}$, close gyromagnetic ratios and roughly equal natural abundance ($^1J_{31\text{P-}^{107}\text{Ag}} = 597 \text{ Hz}$, $^1J_{31\text{P-}^{109}\text{Ag}} = 690 \text{ Hz}$, Figure 11).^{114,115}

Comparing the ^1H NMR spectra of ligand **31b** and complex **46** (Figure 12), it can be observed that upon complex formation the signals of the protons on the carbon atoms α to the quinuclidine N atom shifted downfield, consistent with coordination of the ligand to Ag(I) through the quinuclidine N atom. Moreover, the signal for the amide NH moved from the aromatic region to approximately 11 ppm, in line with its involvement in a H bond with the acetate ion.

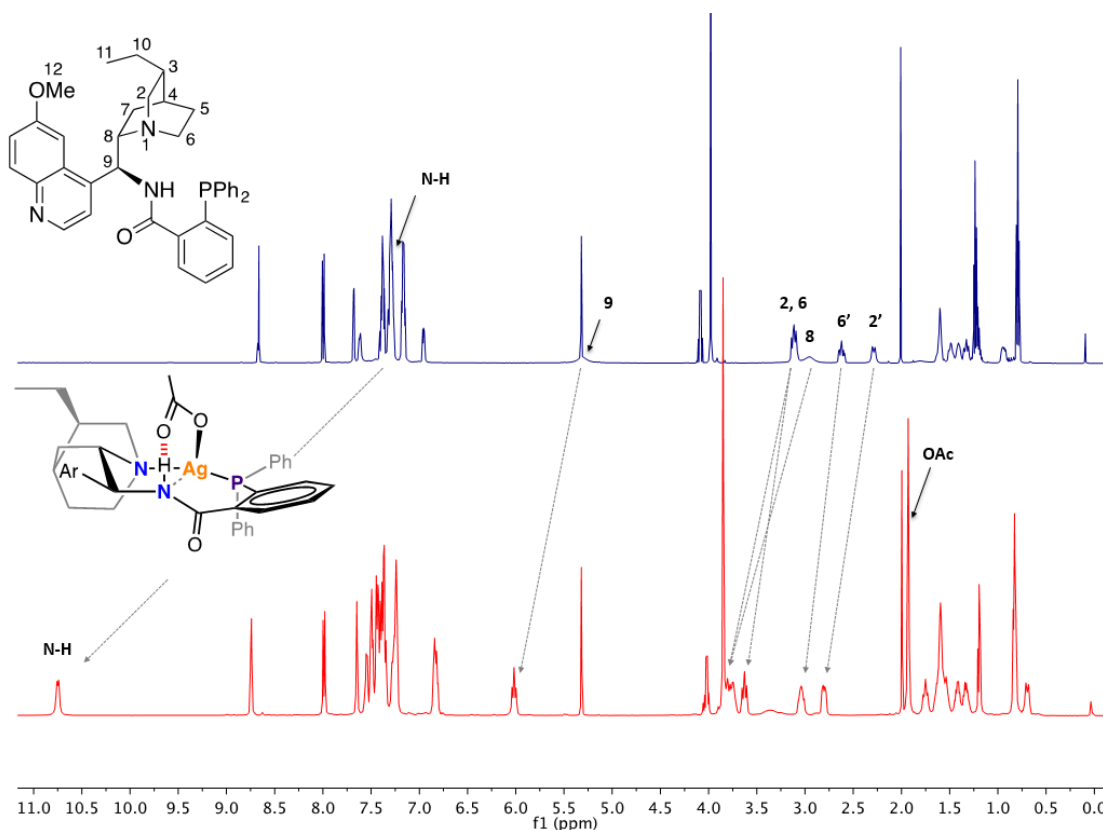


Figure 12 ^1H NMR studies performed at 0.02 M concentration in CD_2Cl_2 at 253 K, showing the formation of complex **46**. Reproduced with courtesy of Dr Adam Gammack Yamagata.

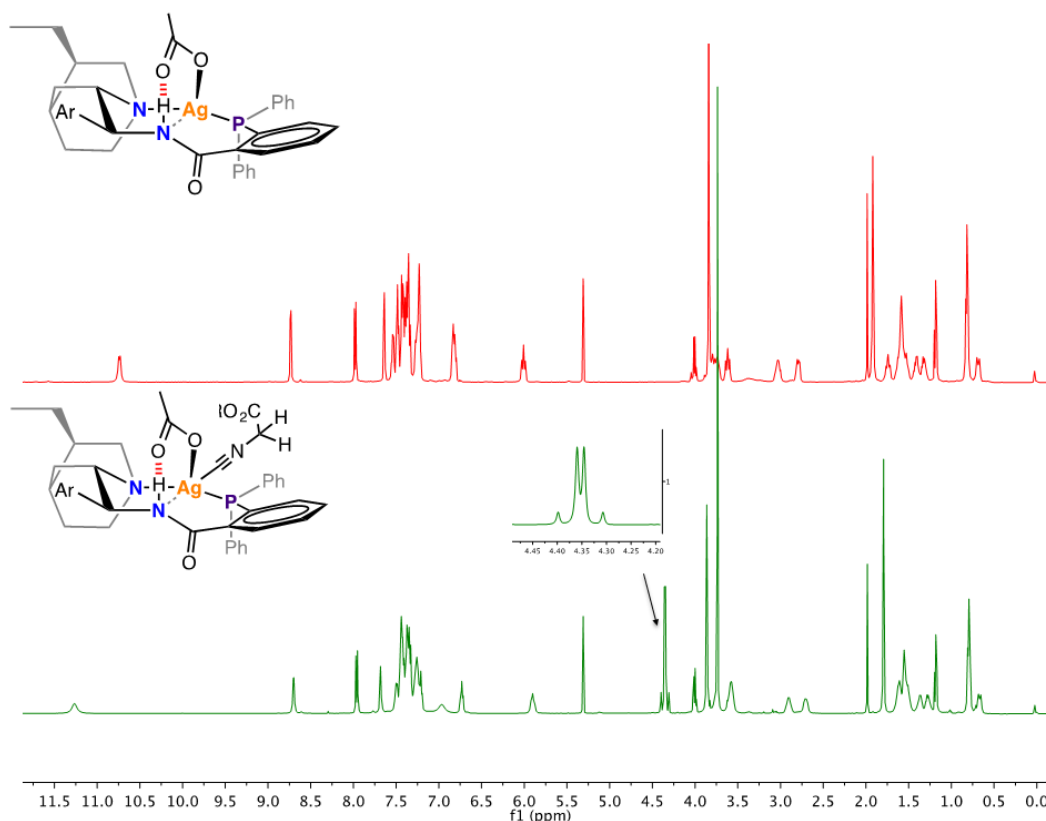


Figure 13 ^1H NMR studies performed at 0.02 M concentration in CD_2Cl_2 at 253 K, showing the coordination of methyl isocyanoacetate to complex **46**. Reproduced with courtesy of Dr Adam Gammack Yamagata.

Furthermore, it was observed that upon addition of methyl isocyanoacetate to a solution of complex **46** in CD_2Cl_2 , the two methylenic protons of the isocyanide shifted downfield and appeared as two close doublets with a strong roofing effect (AB_q spin system, Figure 13). This indicated that they had become diastereotopic, and provided convincing evidence for the coordination of the pronucleophile to the metal centre of the chiral complex, most likely through the terminal isocyanide C atom.⁵⁴

1.4 Overall Aims

Starting from this solid foundation, one of the aims of the present thesis was to extend the scope of the Ag(I)/amino phosphine catalytic system to challenging electrophile and pronucleophile classes, thereby providing new enantioselective methods to access molecules containing a valuable chiral amine fragment.

More generally, we planned to investigate the development of metal-catalysed enantioselective processes for additions to C=N bonds, without being restricted to a single catalytic system. We were primarily interested in pursuing the discovery of novel reactivity (and where possible stereocontrol) enabled by metal catalysts.

In the course of our explorations, we desired to leave some space for target oriented-synthesis, thus showcasing the utility of our catalytic methodologies, and to be ready to explore new metal-catalysed reactions, either designed based on the current state of the art or serendipitously discovered.

2 Silver-Catalysed Asymmetric Synthesis of Chloramphenicol

2.1 Chapter Overview

In this chapter the utility of the asymmetric aldol reaction of isocyanoacetates for target-based synthesis of vicinal amino alcohols was investigated. Specifically, the highly enantio- and diastereoselective aldol reaction of isocyanoacetates catalysed by the Ag/amino phosphine system was applied to the concise synthesis of the broad-spectrum antibiotic (–)-chloramphenicol. Optimisation was undertaken to adapt the asymmetric methodology to the extremely electrophilic *p*-nitrobenzaldehyde that was required as a substrate.

2.2 Introduction

2.2.1 Importance of Vicinal Amino Alcohols

Chiral molecules with a vicinal amino alcohol fragment are an important class of compounds, present among both naturally occurring products and synthetic molecules (Figure 14).⁷⁰ They have found widespread use in catalysis and in synthesis as building blocks for chiral auxiliaries, catalysts and ligands (**47–51**), and in medicinal chemistry by virtue of their pharmacological properties (**52–58**). Bioactive vicinal amino alcohols of increasing complexity include, for instance, ephedrine (**47**), the antibiotics chloramphenicol¹¹⁶ (**52**) and thiamphenicol¹¹⁷ (**53**), the antihypertensive drug Aliskiren¹¹⁸ (**54**), the protease inhibitor Saquinavir¹¹⁹ (**55**) used in the treatment of HIV and the chemotherapeutic agent Doxorubicin¹²⁰ (**56**).

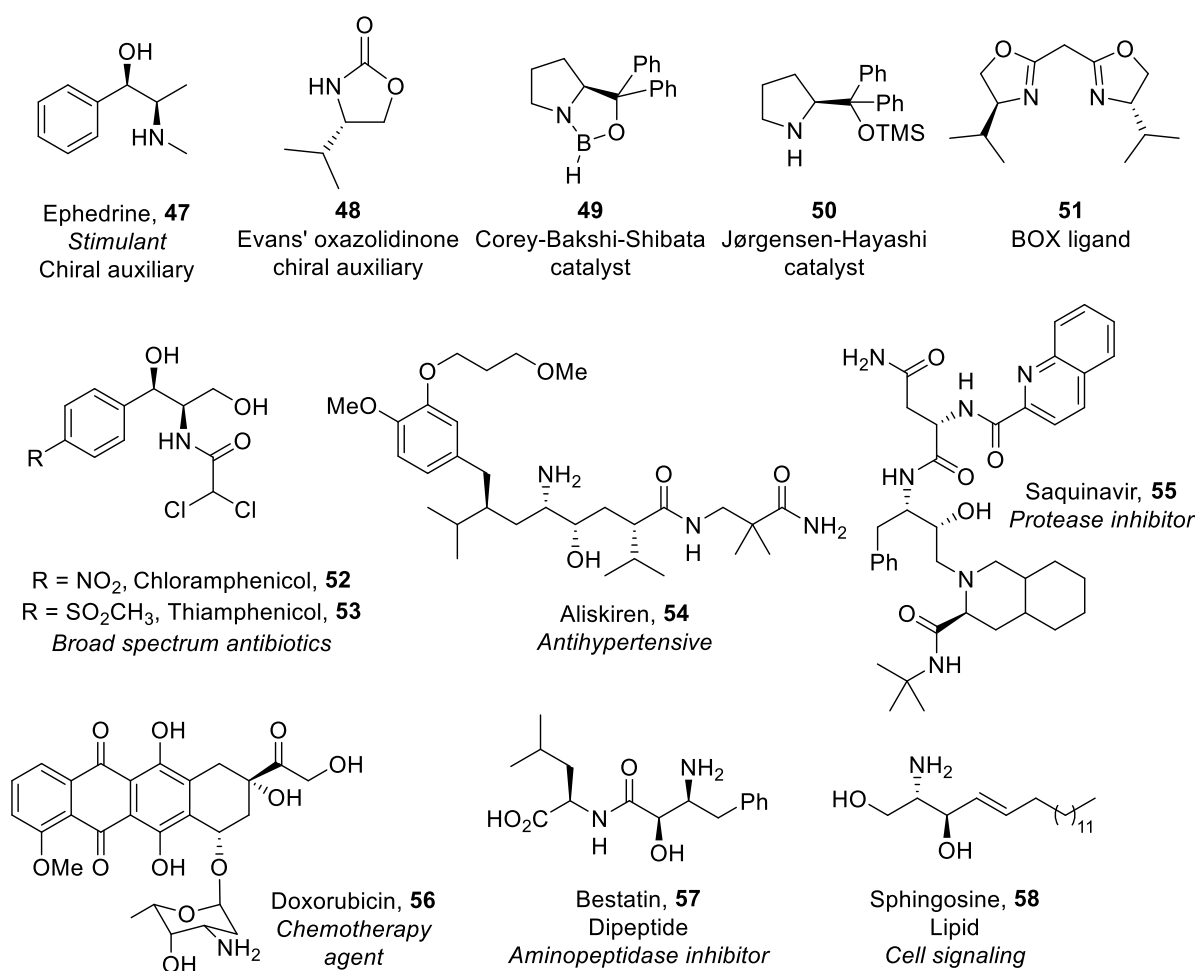


Figure 14 Examples of chiral vicinal amino alcohols and derivatives.

The synthesis of enantioenriched vicinal amino alcohols raises issues of diastereo- and enantioselectivity,¹²¹ and a variety of methods have been developed for their preparation (Figure 15).⁷⁰ Particularly valuable are simplifying disconnections that allow the formation of the C–C bond between the two heteroatom-bearing stereogenic centres, as they can provide rapid, modular and stereocontrolled construction of the key fragment.¹²² These constructive methods mainly include Mannich reactions of α -hydroxy anions and aldol reactions of α -amino pronucleophiles, for instance glycine equivalents¹²³ where the amino function has been masked as isocyanide (isocyanoacetates)^{55,124} or isothiocyanate.^{17,18} Most of the disconnections shown in Figure 15 will be exemplified in the following paragraphs in the context of asymmetric syntheses of (–)-chloramphenicol (**52**).

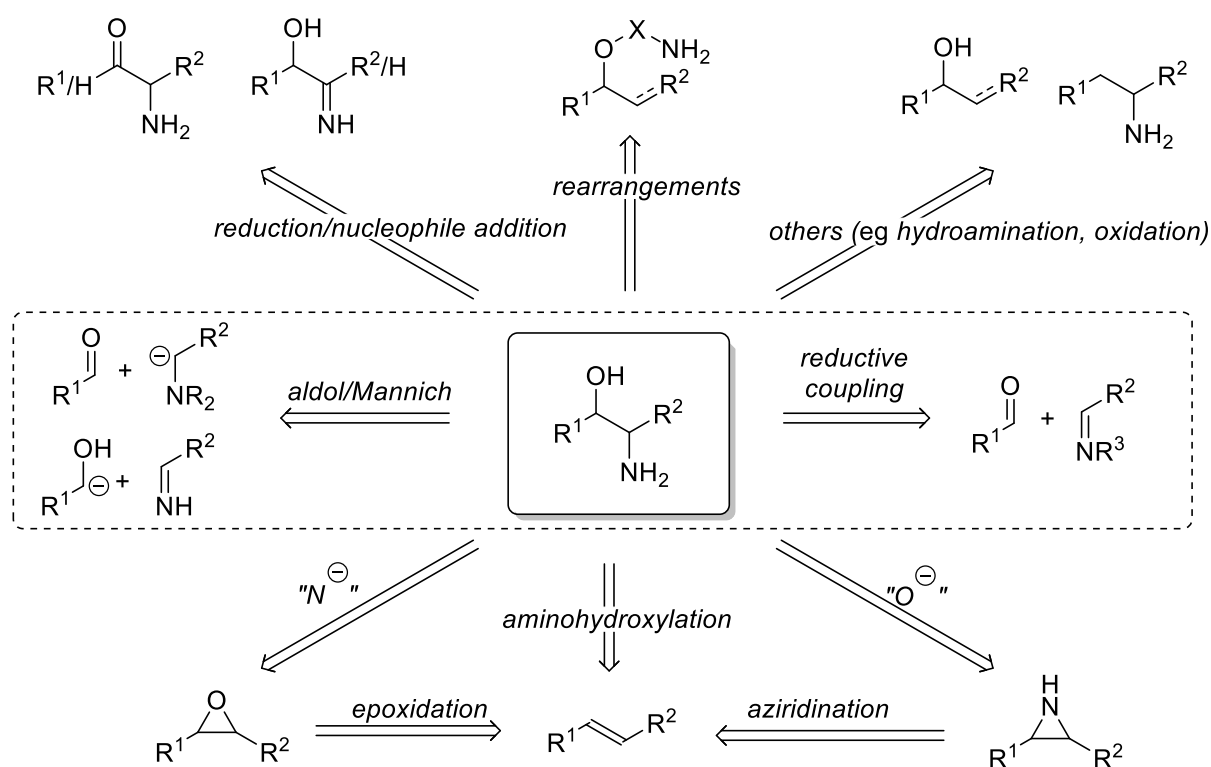
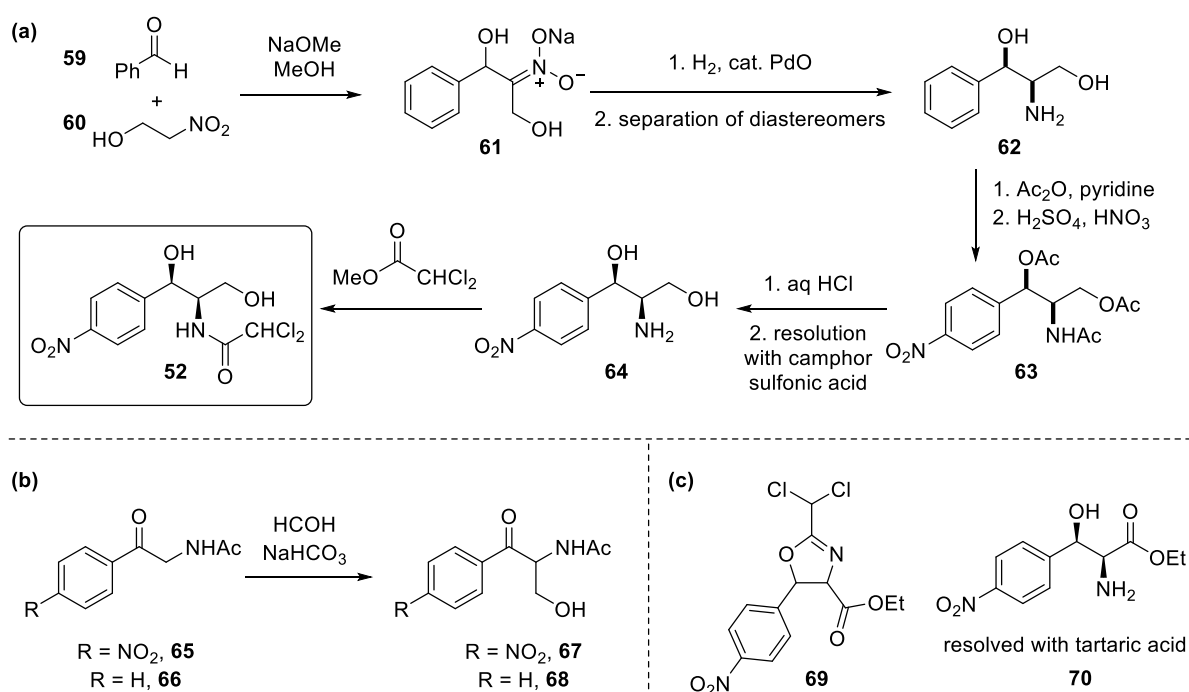


Figure 15 Some of the most common disconnections to vicinal amino alcohols. Disconnections enabling the formation of the C–C bond between the heteroatom-bearing centres are shown in the dotted box.

2.2.2 Discovery and Early Syntheses of Chloramphenicol

Chloramphenicol (**52**) is a broad-spectrum antibiotic isolated in 1947 from a culture of *Streptomyces venezuelae*, a bacterial species found in a soil sample from a mulched field near Caracas.¹¹⁶ The Parke, Davis and Co company (Detroit) that discovered its antibiotic properties adopted the trademark Chloromycetin for the compound, and carried out follow-up studies to identify its structure.¹²⁵ Active only in its 1*R*,2*R* configuration, corresponding to the levorotatory *syn* enantiomer, chloramphenicol inhibits bacterial growth by irreversibly binding to a receptor site on the 50S subunit of the ribosome, thus blocking the synthesis of proteins essentials for the proliferation of the bacteria.¹²⁶ Currently listed in the World Health Organisation list of essential medicines,¹²⁷ it is used in humans to treat conjunctivitis, meningitis, plague, cholera and typhoid fever when drugs with less side effects are not effective,¹²⁸ and finds some uses in the veterinary practice too.¹²⁹

The structure of chloramphenicol was determined in 1949 through degradation studies leading to the so-called chloramphenicol base (**64**)¹²⁵ and confirmed by independent synthesis (Scheme 18a).¹³⁰ The very first synthesis relied on a Henry reaction between benzaldehyde and 2-nitroethanol to build the core of the molecule; the nitro group on the aromatic ring was introduced by nitration at a later stage. The process involved separation of the racemic *syn/anti* (*threo/erythro*) diastereoisomers of **62** by crystallisation, and after some steps the resolution of racemic *syn*-**64** with camphorsulfonic acid. Using this route, chloramphenicol was the first naturally occurring antibiotic to be prepared on industrial scale by chemical synthesis, rather than fermentation.¹³¹ Related non-asymmetric syntheses were based on Henry reactions of nitromethane with benzaldehyde or *p*-nitrobenzaldehyde, aldol reaction of the intermediates **65** or **66** with formaldehyde and finally ketone reduction (Scheme 18b).^{132,133}



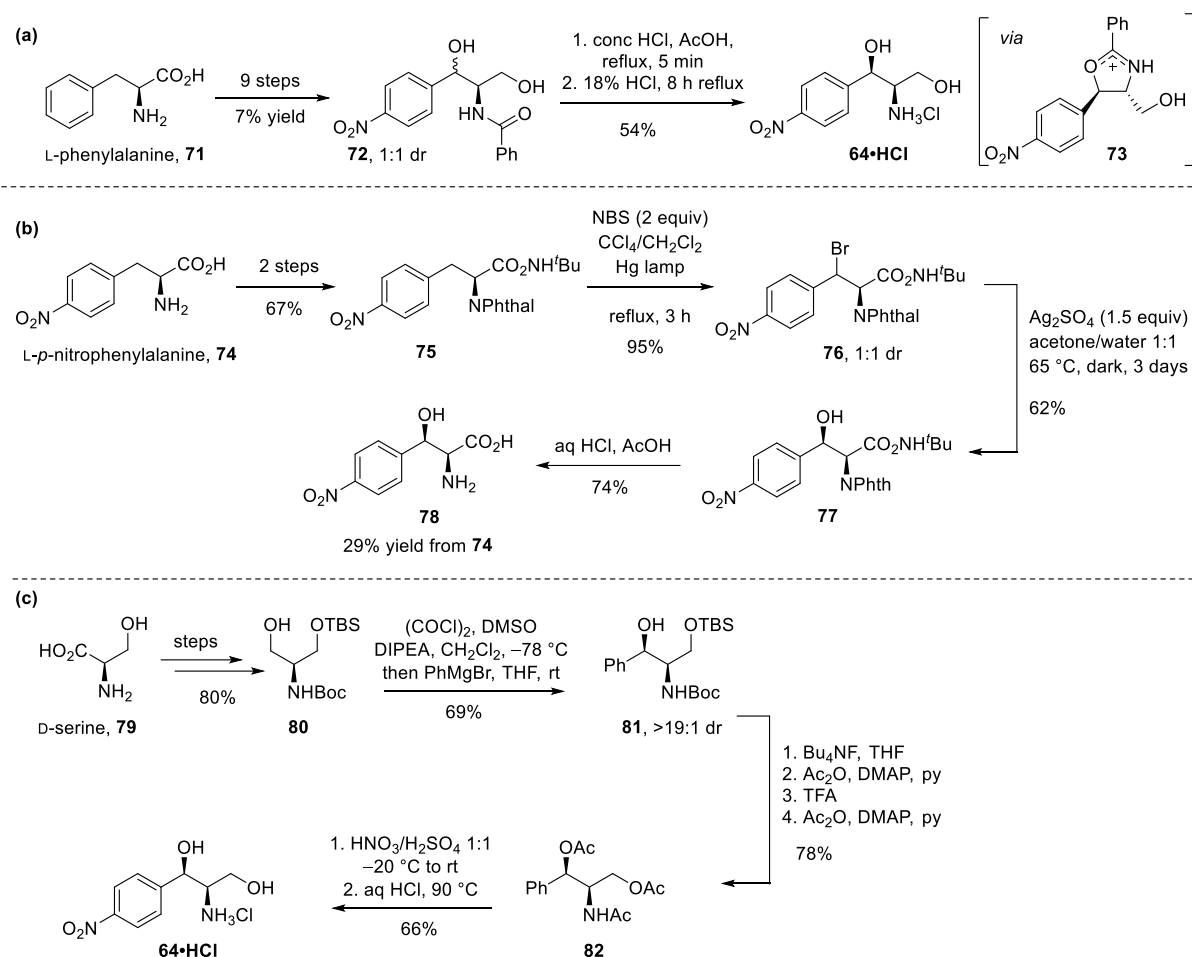
Scheme 18 (a) First synthesis of chloramphenicol (1949). (b) Key-step in early syntheses of Chloramphenicol. (c) Intermediates on industrial syntheses, whose reduction was patented by Roche.

A few years after Parke, Davis and Co disclosed the structure and the first syntheses, Roche filed several patents covering alternative routes proceeding *via* the reductions of *p*-nitrophenylserine ester derivatives **69** and **70** (Scheme 18c).¹³⁴ Resolution of **70** was carried out with tartaric acid; more recently, enzymatic resolution of the *N*-dichloroacetyl methyl ester derivative was developed.¹³⁵

2.2.3 Asymmetric Syntheses of Chloramphenicol

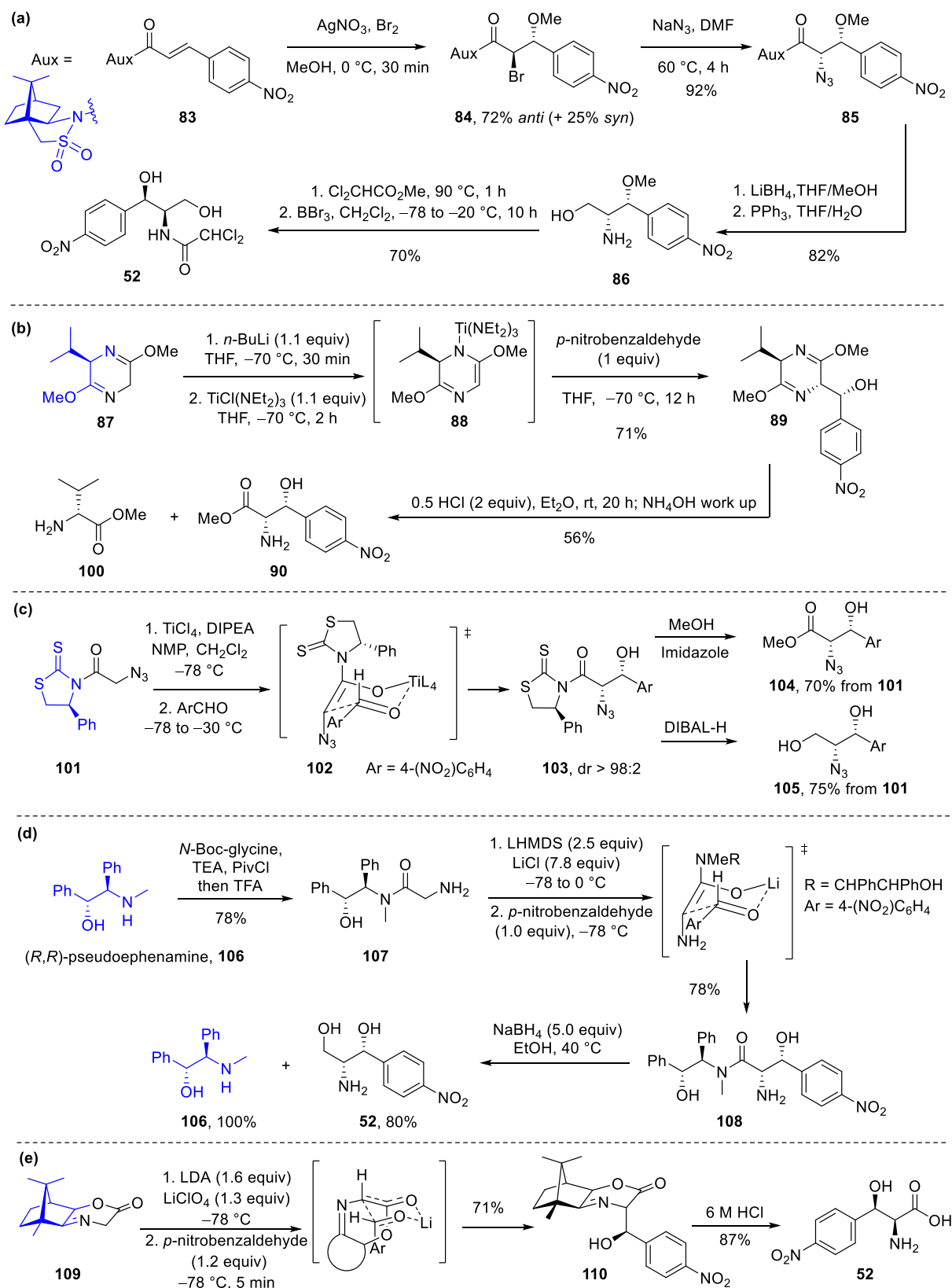
Given the small size of chloramphenicol, it is surprising to see how many different approaches to the target have been reported in the literature.

Some routes start from enantiopure amino acids, thereby setting the *N*-bearing stereocentre and introducing the other stereocentre by a diastereoselective reaction (Scheme 19). For instance, multi-step elaboration of L-phenylalanine delivered benzamide **72**, that underwent a diastereoselective hydrolytic rearrangement under acidic conditions via intermediate **73** (Scheme 19a).¹³⁶ Similarly, starting from L-*p*-nitrophenylalanine, hydrolysis of a 1:1 mixture of bromides **76** using silver sulfate (1.5 equivalents) afforded only the *syn* hydroxy derivative **77** (Scheme 19b).¹³⁷ Starting from D-serine, it is possible to introduce the benzylic stereocentre by a diastereoselective addition of phenyl magnesium bromide on the α -amino β -hydroxy aldehyde formed by Swern oxidation of **80** (Scheme 19c).¹³⁸ It should be noted that among the chiral starting materials only L-phenylalanine is a proteinogenic amino acid found in nature, belonging to the chiral pool.



Scheme 19 Asymmetric syntheses of chloramphenicol starting from enantiopure amino acids.

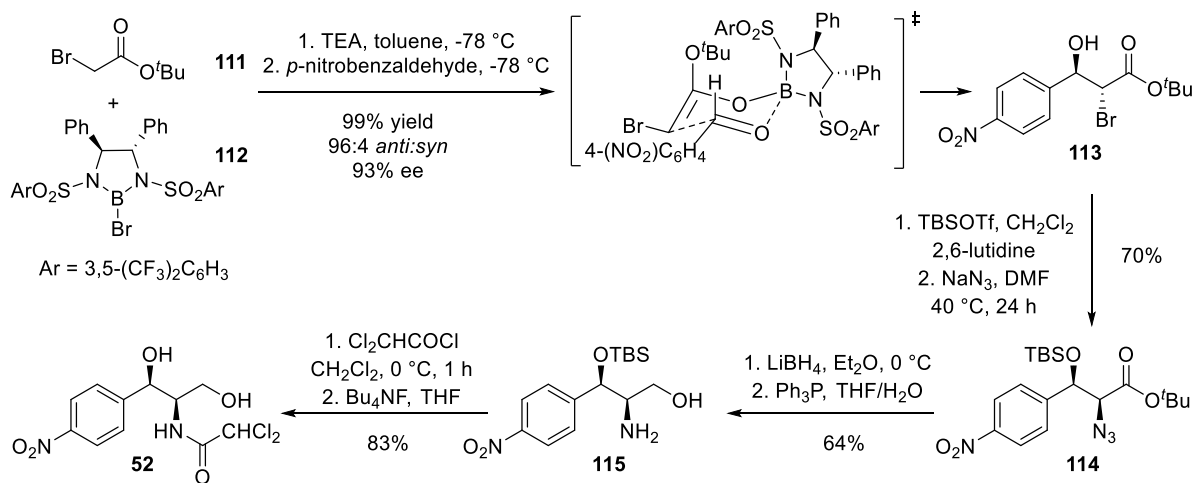
Another approach that reduces the “enantioselectivity problem” to a “diastereoselectivity problem” is the use of chiral auxiliaries (Scheme 20).



Scheme 20 Asymmetric syntheses of chloramphenicol using chiral auxiliaries.

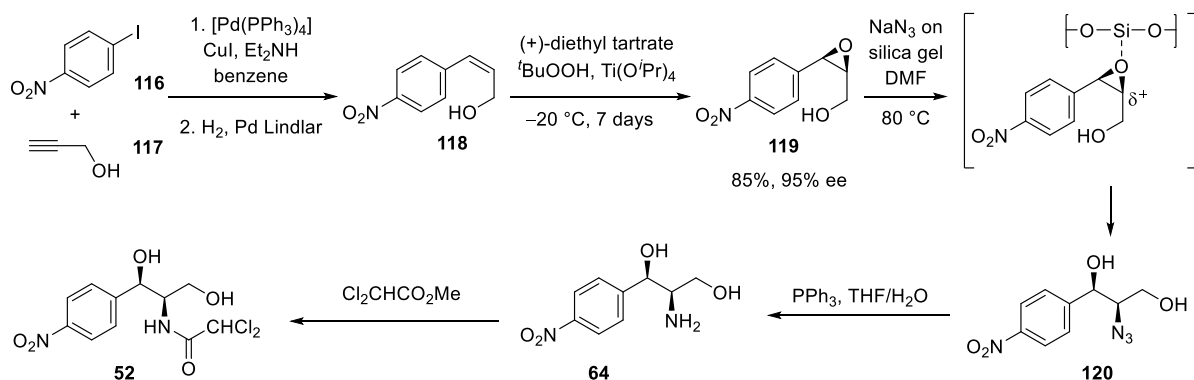
Oppolzer's camphor-derived sultam auxiliary was coupled to 4-nitrocinnamic acid, and the resulting substrate **83** underwent bromomethoxylation affording *anti* **84** in 72% yield. After S_N2 reaction with sodium azide and reductive cleavage of the auxiliary, the compound was elaborated to the target product (Scheme 20a).¹³⁹ In all the other cases, chiral auxiliaries have been employed to perform *syn* aldol reactions. In 1989, Schöllkopf used the bislactim ether **87** of the dipeptide D-Val-Gly as a chiral glycine equivalent. The titanium enolate **88** reacted with *p*-nitrobenzaldehyde to afford the desired *syn* product **89** in 71% yield. Hydrolysis of the latter gave ester **90** in 56% yield alongside recovered methyl D-Valinate (Scheme 20b).¹⁴⁰ In 2008, Franck employed a Crimmins type auxiliary, specifically a phenyl glycine derived thiazolidin-2-thione, for the aldol reaction between the titanium enolate of α -azido amide **101** and *p*-nitrobenzaldehyde (Scheme 20c).¹⁴¹ In 2014, Myers and co-workers introduced pseudoephedrine (**106**) as a practical chiral auxiliary¹⁴² for aldol reaction of pseudoephedrine glycinamide (**107**) with aldehydes and ketones.¹²² The authors suggested that reaction of the *p*-nitrobenzaldehyde with the *Z* enolate of **107** (with the α -amino group and enolate oxygen atom *cis*) proceeds *via* a Zimmerman-Traxler transition structure to deliver the *syn* aldol product **108**, whose reduction allowed a short synthesis of chloramphenicol (Scheme 20d). Notably, it was possible to recover the chiral auxiliary quantitatively, a crucial aspect addressed only by the reports of Schöllkopf and Myers. As a chiral glycine equivalent for a *syn* aldol reaction, Xu and co-workers chose the camphor-derived iminolactone **109** (Scheme 20e).¹⁴³

Corey's synthesis of chloramphenicol was based on the *anti*-selective aldol reaction between *tert*-butyl bromoacetate and *p*-nitrobenzaldehyde mediated by stoichiometric bromoborane **112**,¹⁴⁴ proceeding *via* a chiral *Z* boron enolate (with Br and OBR₂* *trans*, Scheme 21).^{145,146}

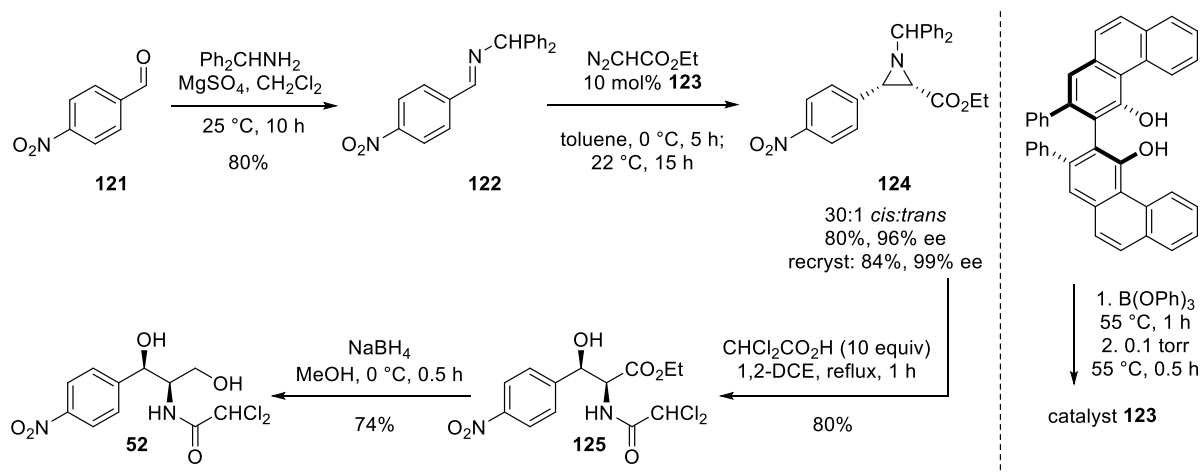


Scheme 21 Corey's synthesis of chloramphenicol via a diazaborolidine-mediated aldol reaction.

Finally, several syntheses of chloramphenicol have relied on catalytic enantioselective reactions, with Sharpless epoxidation^{147,148,149,150} and dihydroxylation^{151,152} being by far the most popular. Scheme 22 shows the first catalytic enantioselective synthesis of chloramphenicol, achieved in 1992 by Rao and co-workers *via* Sharpless epoxidation. The only exception to the general trend was the elegant, concise synthesis accomplished by Wulff in 2001 *via* a catalytic enantio- and diastereoselective aziridination (Scheme 23).^{153,154} The *cis* aziridine **124** was opened regioselectively at the benzylic position using dichloroacetic acid, then loss of the benzhydryl group followed by O to N acyl transfer delivered ester **125** in one pot. Reduction of the latter afforded chloramphenicol in 4 steps and 32% yield from *p*-nitrobenzaldehyde.



Scheme 22 Rao's first catalytic enantioselective synthesis of chloramphenicol (1992), based on Sharpless epoxidation. Yields (except for the epoxidation) not stated by the authors.

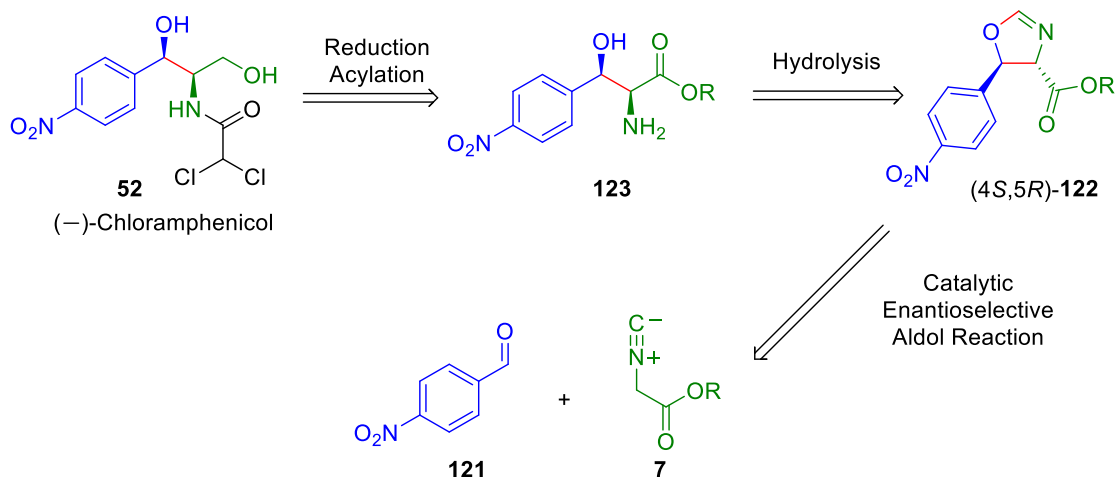


Scheme 23 Wulff's synthesis of chloramphenicol via catalytic asymmetric aziridination.

2.3 Silver-Catalysed Enantio- and Diastereoselective Synthesis of Chloramphenicol

2.3.1 Retrosynthetic Plan

Our retrosynthetic approach to chloramphenicol, outlined in Scheme 24, featured as a key-step the enantioselective isocyanoacetate aldol reaction between 4-nitrobenzaldehyde (**121**) and a suitable isocyanoacetate ester **7** to afford the *trans* oxazoline (4*S*,5*R*)-**122**.



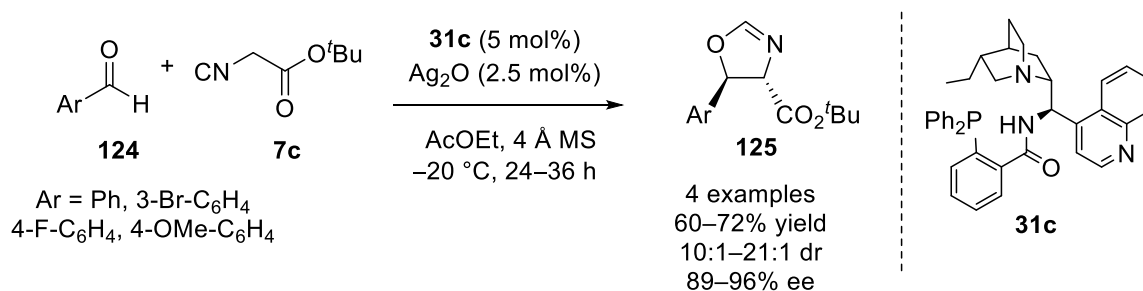
Scheme 24 Retrosynthesis of chloramphenicol based on the enantioselective catalytic aldol reaction of isocyanoacetates.

We planned to exploit our Ag/amino phosphine catalytic methodology¹⁰⁴ to set the two vicinal stereocentres of the target molecule in a diastereo-, enantioselective and atom-economical fashion. Apart from the isocyanide carbon and the ester group of isocyanoacetate **7**, all the

atoms of the starting materials would be used to build the target molecule. Standard chemical manipulation of oxazoline **122**, namely ring opening, reduction of the ester group and amide formation, would then lead to chloramphenicol.

2.3.2 Optimisation

Our investigation began by performing the reaction between *p*-nitrobenzaldehyde and *tert*-butyl isocyanoacetate under the conditions that had already been optimised for a range of aldehydes, namely in AcOEt at $-20\text{ }^{\circ}\text{C}$ and 0.3 M concentration, employing 5 mol% **31c** and 2.5 mol% silver oxide.¹⁰⁴ From previous work done in the Dixon group (Scheme 25, see also Section 1.3.2, Scheme 15), it was anticipated that the use of cinchonine-derived amino phosphine **31c** as chiral ligand in the aldol reaction would provide oxazolines **125** with the desired absolute configuration for the preparation of (–)-chloramphenicol.

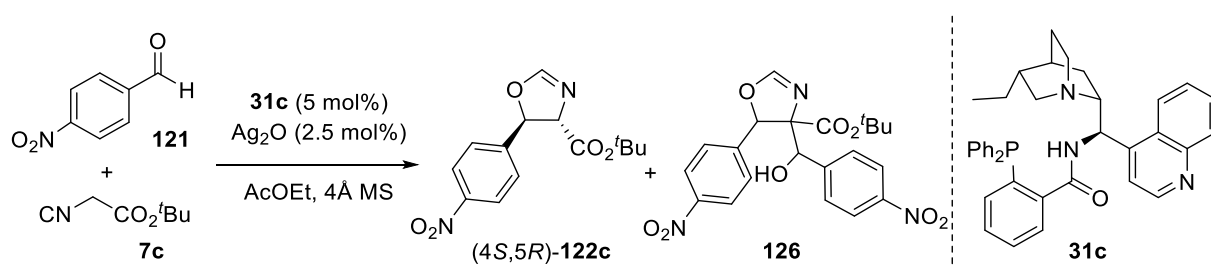


Scheme 25 Enantio- and diastereoselective addition of *tert*-butyl isocyanoacetate to aromatic aldehydes catalysed by Ag_2O and amino phosphine ligand **31c**.

To our surprise, when the reaction between *tert*-butyl isocyanoacetate **7c** and *p*-nitrobenzaldehyde **121** was performed under those optimised reaction conditions, the desired *trans* oxazoline **122c** was obtained with modest yield and low enantioselectivity (45% yield, 44% ee, Table 1, Entry 1), pointing out the need for optimisation of the reaction. From the complex reaction mixture, the double aldol side product **126** was isolated as a single diastereomer in 7% yield.ⁱⁱ Screening of several reaction parameters was therefore undertaken,

ⁱⁱ Relative configuration was not determined.

and the main findings are reported below. Decrease of the temperature to $-40\text{ }^{\circ}\text{C}$ caused the formation of racemic product (Entry 2), while adjustment of the temperature to $20\text{ }^{\circ}\text{C}$ was beneficial both for yield and enantiocontrol (59%, 53% ee, Entry 3). At this temperature, we noted that dilution of the reaction mixture lead to further improvement of yield and enantiocontrol (Entries 3–7). At 0.01 M isocyanoacetate concentration, product **122c** was obtained in 30 minutes in 70% yield, 91:9 dr and 78% ee (Entry 6). Further dilution to 0.0025 M resulted in slightly improved enantiocontrol (80% ee, Entry 7) over longer reaction time, but was discarded for practical scale-up reasons. A temperature screen at 0.01 M (Entries 8–10) confirmed that $20\text{ }^{\circ}\text{C}$ was the optimal temperature.



Entry	T (°C)	Concentration 7c (M)	Time (h)	Yield ^a (%)	Dr ^b (<i>trans</i> : <i>cis</i>)	Ee ^a (%)
1	-20	0.3	21 ^c	45	91:9	44
2	-40	0.3	8	43	93:7	1
3	20	0.3	0.25	59	91:9	53
4	20	0.15	0.25	61	91:9	57
5	20	0.05	0.5	73	91:9	68
6	20	0.01	0.5	70	91:9	78
7	20	0.0025	17	70	90:10	80
8	-20	0.01	39 ^d	66	88:12	47
9	0	0.01	16 ^c	72	90:10	72
10	50	0.01	2	61	88:12	65

Table 1 Temperature and concentration screen. Reactions performed on 0.5 (Entries 1–4) or 0.25 mmol of **7c** and 1.1 equiv of **121**. ^a For the *trans* diastereomer after FCC. ^b Dr of the crude reaction mixture determined by ¹H NMR analysis. ^c Stirred overnight, as TLC control after 3 hours indicated that the reaction was ongoing. ^d TLC control after 24 hours indicated that the reaction was ongoing.

These optimised conditions improved the solubility of the reaction components, thereby diminishing a competitive background reaction catalysed by Ag₂O only, which we hypothesized to be responsible for the poor enantioselectivity observed at lower temperature and higher concentration.ⁱⁱⁱ At the same time, dilution of the reaction mixture increased the yield of the product by reducing the amount of undesired double aldol side product **126**. Both of the issues that we encountered (*i.e.* low enantiocontrol and poor yield in the formation of desired oxazoline **122c**) can be ascribed to the high electrophilicity of *p*-nitrobenzaldehyde.

A brief solvent survey confirmed AcOEt to be the preferred choice (Table 2).

121
(1.2 equiv)

7c
(0.25 mmol, 0.05 M)

31c (5 mol%)
Ag₂O (2.5 mol%)
AcOEt, 4 Å MS
20 °C, 30–60 min

(4S,5R)-122c

31c

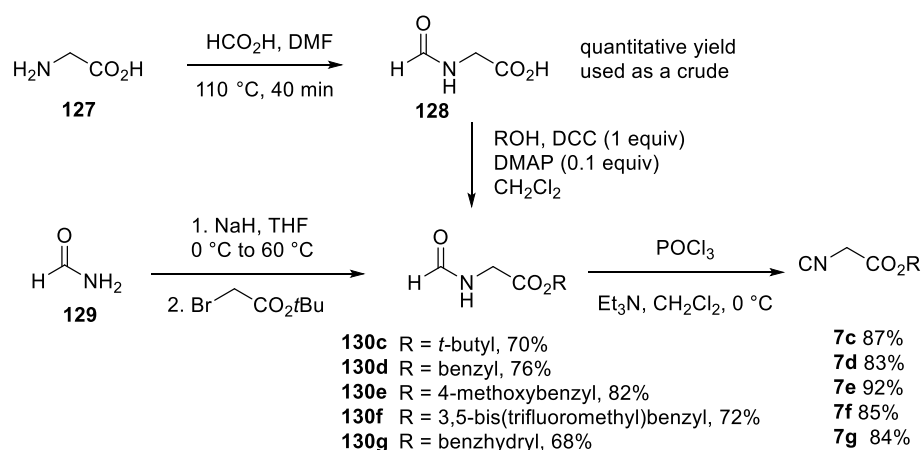
Entry	Solvent	Yield ^a (%)	Dr ^b (<i>trans</i> : <i>cis</i>)	Ee ^a (%)
1	AcOEt	73	91:9	68
2	toluene	69	91:9	60
3	CH ₃ CN	65	82:18	61
4	MTBE	78	90:10	52
5 ^c	AcOEt	44	92:8	45
6 ^c	CH ₂ Cl ₂	47	82:18	37

Table 2 Solvent screen. ^a For the *trans* diastereomer after FCC. ^b Dr of the crude reaction mixture determined by ¹H NMR analysis. ^c Reaction performed with 0.3 M **7c** concentration, starting at –78 °C and then allowing the reaction mixture to warm up to 20 °C.

With the optimised reaction conditions established, we decided to test the performance of isocyanoacetate pronucleophiles possessing different ester groups, in the hope of increasing the

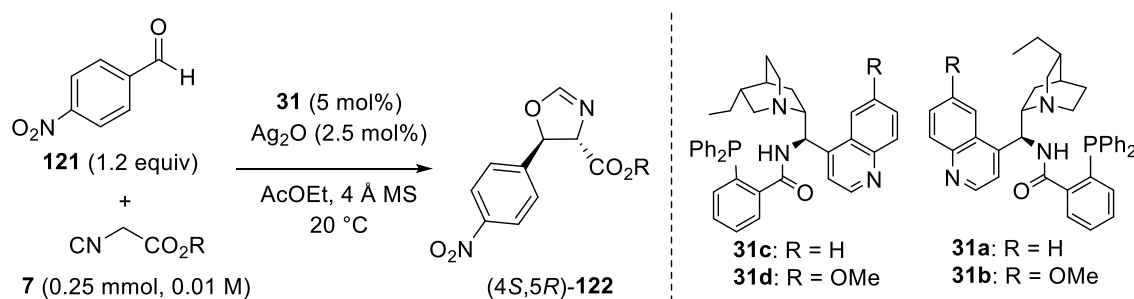
ⁱⁱⁱ A reaction run with 2.5 mol% Ag₂O without **31c** under the conditions of Table 1, Entry 1 went to completion in 19 hours affording racemic **122** in 41% yield. A reaction with 5 mol% **31c** without Ag₂O did not give any product.

levels of enantioselectivity through substrate variation. The pronucleophiles were synthesized in good yields *via* dehydration of the corresponding formamides **130** (Scheme 26).



Scheme 26 Synthesis of isocyanoacetate esters.

The isocyanoacetate esters were then tested under the optimised conditions (Table 3).



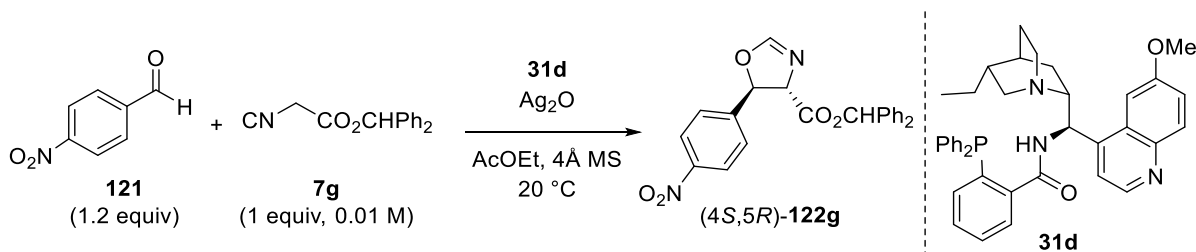
Entry	R	7	122	Ligand	Time (min)	Yield ^a (%)	Dr ^b (<i>trans</i> : <i>cis</i>)	Ee ^a (%)
1	(CH ₃) ₃ C	7c	122c	31c	30	70	91:9	78
2	CH ₃	7a	122a	31c	100	80	88:12	82
3	PhCH ₂	7d	122d	31c	180	61	90:10	87
4	PhCH ₂	7d	122d	31d	80	64	90:10	87
5	4-(OCH ₃)C ₆ H ₄ CH ₂	7e	122e	31d	60	63	89:11	86
6	3,5-(CF ₃) ₂ C ₆ H ₃ CH ₂	7f	122f	31d	60	56	90:10	84
7	Ph ₂ CH	7g	122g	31c	100	81	93:7	87
8	Ph ₂ CH	7g	122g	31d	45	78	91:9	89
9	Ph ₂ CH	7g	122g	31a	200	82	93:7	88 ^c
10	Ph ₂ CH	7g	122g	31b	60	68	92:8	93 ^c

Table 3 Pronucleophile and ligand screen. ^a For the *trans* diastereomer after FCC. ^b Dr of the crude reaction mixture determined by ¹H NMR analysis. ^c Opposite enantiomer obtained.

In terms of enantioselectivity, methyl isocyanoacetate ester **7a** performed better than its *tert*-butyl analogue **7c**, suggesting that excessive steric bulk hampered the transmission of stereochemical information. However, the presence of a benzyl or benzhydryl group was well tolerated: from isocyanoacetates **7d** and **7g** the desired oxazolines could be obtained with the highest enantioselectivity (87% ee, Entries 3 and 7). Isocyanoacetates **7e** and **7f**, possessing 4-methoxybenzyl and 3,5-bis(trifluoromethyl)benzyl groups respectively, provided enantioenriched oxazolines with similar levels of enantioselectivity (86% and 84% ee respectively, Entries 5 and 6), indicating that electronic factors were not playing a major role in enantiocontrol.

Next, the fine tuning effect of the ligand was taken into account by testing four amino phosphines prepared from 9-amino(9-deoxy) epicinchona alkaloids (Table 3). The use of quinidine-derived **31d** in the reaction of the benzhydryl isocyanoacetate **7g** resulted in further improvement to enantiocontrol (89% ee, Entry 8 vs 87% ee, Entry 7), whereas no boost in enantioselectivity was observed with benzyl isocyanoacetate **7d** (87% ee, Entry 4 vs 87% ee, Entry 3). The pseudoenantiomeric catalytic system comprising quinine-derived **31b** afforded the enantiomeric oxazoline (4*R*,5*S*)-**122g** in slightly lower yield (68%) and with better stereocontrol (92:8 dr, 93% ee, Entry 10).

Finally, catalyst loading studies confirmed the ideal Ag/ligand ratio to be 1:1, specifically 2.5 mol% Ag₂O and 5 mol% **31d** (Table 4, Entry 1). A reaction catalysed by silver oxide only, in the absence of ligand, required a much longer time to go to completion (40 hours, Entry 2), demonstrating that the background reaction was majorly suppressed under the optimised conditions. Yields and enantioselectivity remained basically unchanged when the ligand and silver loadings were doubled (Entry 3) or the Ag₂O loading was halved (Entry 4).

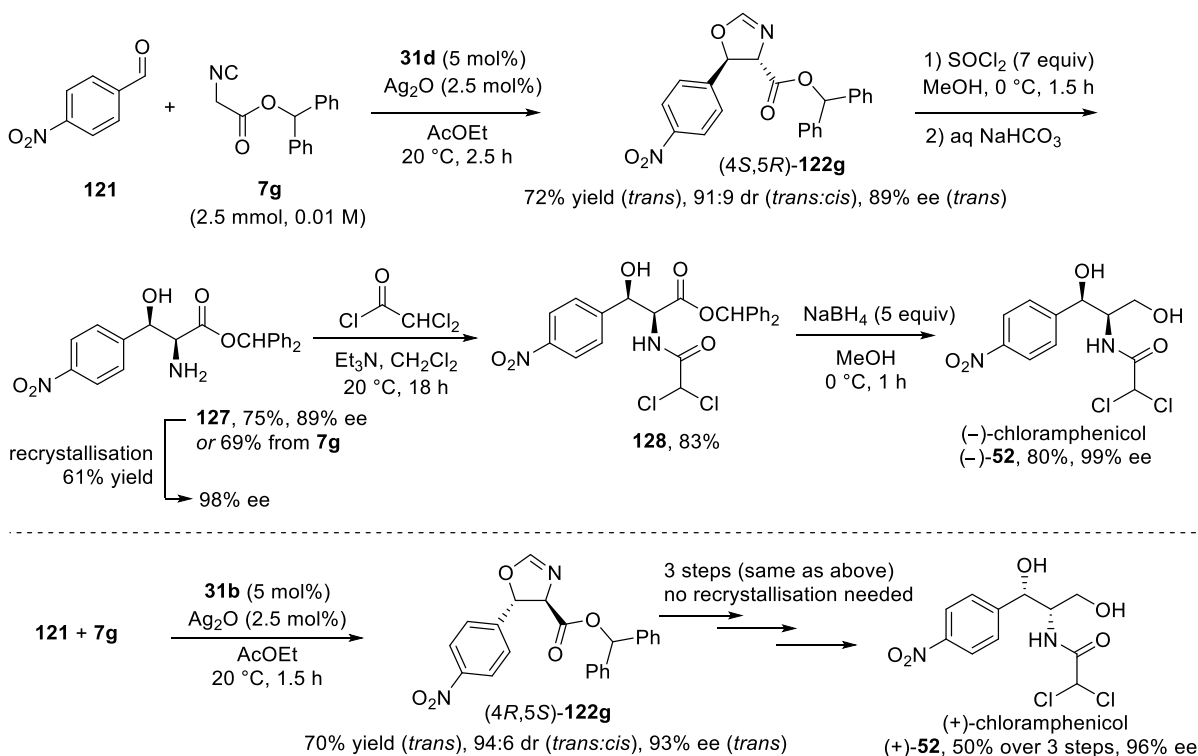


Entry	7g (mmol)	Ligand (mol%)	Ag ₂ O (mol%)	Time (h)	Yield ^a (%)	Dr ^b (trans:cis)	Ee ^a (%)
1	2.5	5	2.5	2.5	72	92:8	89
2	2.5	0	2.5	40	51	91:9	0
3	0.5	10	5	0.75	67	91:9	89
4	5.0	5	1.25	2.5	70	91:9	88

Table 4 Catalyst loading studies. ^a For the trans diastereomer after FCC. ^b Dr of the crude reaction mixture determined by ¹H NMR analysis.

2.3.3 Synthesis of Chloramphenicol

After having successfully improved the yield and stereocontrol for the key isocyanoacetate aldol reaction, that sets the two vicinal stereocentres of the target molecule, oxazoline (4S,5R)-122g was readily elaborated to (–)-chloramphenicol (Scheme 27).



Ring opening of **122g** using thionyl chloride in methanol proceeded with 75% yield to give amino alcohol **127**, whose enantiomeric purity was improved to 98% ee by a single crystallisation from toluene (61% yield, first crop). In order to circumvent the problem of the instability of **122g** to silica gel chromatography, it was found possible to use the oxazoline crude in the next step, with a beneficial outcome to the overall yield (69% of **127** from *p*-nitrobenzaldehyde and isocyanoacetate **7g**). The vicinal amino alcohol was then acylated to provide dichloroacetamide **128** in 83% yield. Finally, chemoselective reduction of the ester group with excess sodium borohydride delivered (–)-chloramphenicol in 80% yield and 99% ee.^{iv} (+)-Chloramphenicol was prepared in an analogous manner from oxazoline (4*R*,5*S*)-**122g**, obtained using the pseudoenantiomeric ligand **31b**. In summary, (–)-chloramphenicol was synthesized in 4 steps and 28% overall yield from *p*-nitrobenzaldehyde and benzhydryl isocyanoacetate ester, which in turn was prepared in 3 steps and 57% yield from commercially available starting materials. The concise synthetic route is the first one relying on a catalytic asymmetric aldol reaction.

2.4 Conclusions

As a direct demonstration of the utility of the Ag/amino phosphine asymmetric methodology for the preparation of bioactive molecules bearing an α -amino- β -hydroxy motif, a short asymmetric synthesis of the antibiotic (–)-chloramphenicol was accomplished. The synthetic route relied on the catalytic enantio- and diastereoselective aldol reaction of isocyanoacetate pronucleophiles with *p*-nitrobenzaldehyde. Extensive screening of the reaction parameters was undertaken to adapt the methodology to the particularly electrophilic substrate, eventually achieving the formation of the two contiguous stereocentres of the target molecule with good yield and enantiocontrol.

^{iv} The slight upgrade in enantiopurity was presumably linked to the chromatographic purification.^{155,156}

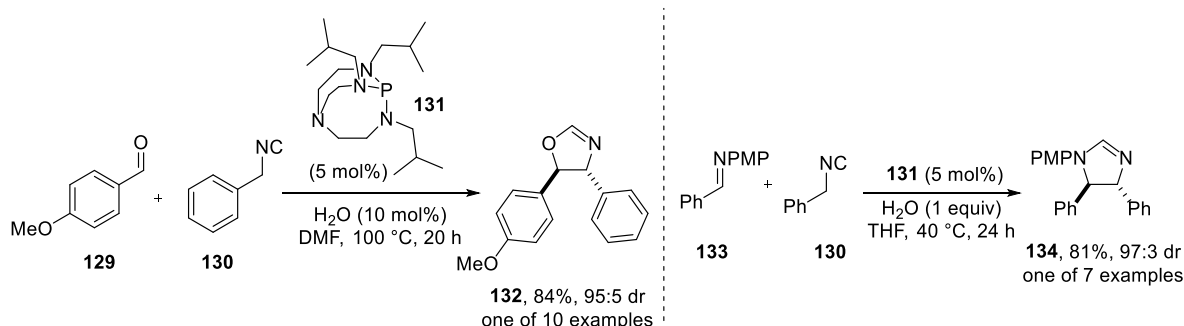
3 Studies on the Aldol and Mannich Reactions of Benzyl Isocyanide

3.1 Chapter Overview

This chapter describes our efforts in expanding the scope of the Ag(I)/amino phosphine catalytic system to the activation of isocyanides lacking the electron-withdrawing group in the α -position, such as benzyl isocyanide. The considerable lower acidity of such pronucleophiles poses a formidable challenge from a catalyst activation point of view; indeed, literature reports on catalytic aldol and Mannich reactions of non-activated isocyanides are extremely scarce. Benzyl isocyanide was investigated as a model pronucleophile in catalytic asymmetric aldol and Mannich reactions with modest success.

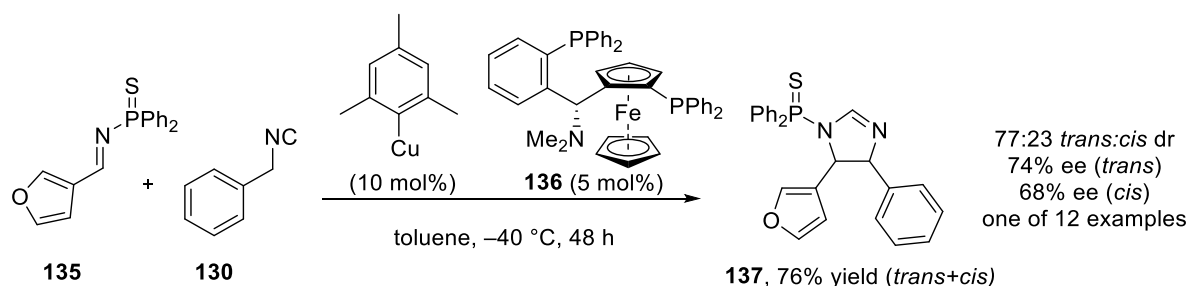
3.2 Introduction: Benzyl Isocyanide as a Pronucleophile

Traditionally, deprotonation of benzyl isocyanide ($pK_a = 27.4$ in DMSO)¹⁵⁷ has been accomplished using stoichiometric amounts of strong bases,^{158,159,160} such as *t*-BuOK ($pK_{BH^+} = 32.2$ in DMSO),¹⁶¹ *n*-BuLi and LDA. It was not until 2014 that the first catalytic aldol and Mannich reactions of benzyl isocyanide were developed.¹⁶² Kobayashi and co-workers reported the addition of benzyl isocyanide to aromatic and aliphatic aldehydes and *N*-aryl aldimines with concomitant cyclisation, to give *trans* oxazolines and imidazolines in 43–95% yield and excellent diastereoselectivity (Scheme 28). The reactions were catalysed by the proazaphosphatane **131** (Verkade base, $pK_{BH^+} \sim 33$ in CH₃CN)¹⁶³ in the presence of a controlled amount of water, which was essential for reactivity and reproducibility. On the basis of NMR studies, the authors concluded that water not only is fully compatible with the Verkade base within their solvent system, but plays a crucial role in activating the pronucleophile towards deprotonation *via* H-bonding, most probably with the terminal isocyanide carbon.



Scheme 28 Kobayashi's catalytic aldol and Mannich reactions of benzyl isocyanide.

In 2015, the group of Shibasaki reported the first, and to date only, catalytic asymmetric version of the above reactions (Scheme 29).¹⁶⁴ They described the Mannich reaction of benzyl isocyanide and aromatic *N*-(diphenylthiophosphinoyl) aldimines catalysed by mesitylcopper and Taniaphos ligand **136**, affording imidazolines with moderate levels of stereoselectivity (up to 77:23 dr and 80% ee).



Scheme 29 Shibasaki's catalytic asymmetric Mannich reaction of benzyl isocyanide.

Interestingly, aldimines bearing other protecting groups on nitrogen (DPP, BOC, 4-nitrobenzenesulfonyl and 2-pyridinesulfonyl) did not afford the desired imidazolines under the optimised conditions, suggesting that a soft-soft interaction between Cu(I) and the sulfur atom of the thioDPP protecting group was important for the activation of the electrophile.^{165,166,167} It is also important to note that mesitylcopper¹⁶⁸ is a highly Brønsted basic organometallic reagent, being able to metalate amines and *tert*-butyl alcohol in THF;¹⁶⁹ when non-basic Cu(I) species such as $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ were employed, the addition of potassium *tert*-butoxide was required for catalytic activity.

3.3 Aldol Reactions of Benzyl Isocyanide

With the aim of evaluating the performance of our Ag(I)/amino phosphine catalytic system in the aldol reaction of benzyl isocyanide, a model reaction between benzaldehyde and benzyl isocyanide was investigated using Ag₂O and quinidine-derived aminophosphine **31d** (Table 5). Pleasingly, the desired oxazolines **trans**-**138** and **cis**-**138** were produced with encouraging yields (80–75%, Entries 1–2), however their low stability to silica gel¹⁶⁴ caused isolated yields to be approximately 15% lower than NMR yields. The reaction proceeded with poor diastereo- and enantioselectivity (66:34 *trans*:*cis* dr, ~10% ee for **trans**-**138**, ~0% ee for **cis**-**138**, Entries 1–2).^v This can be only partially attributed to a Ag₂O-catalysed background reaction, as the reaction between **59** and **130** run in the absence of ligand, with 10 mol% Ag₂O for 72 h, afforded a 58:42 mixture of *trans* and *cis* oxazolines in only 19% yield (Entry 3).

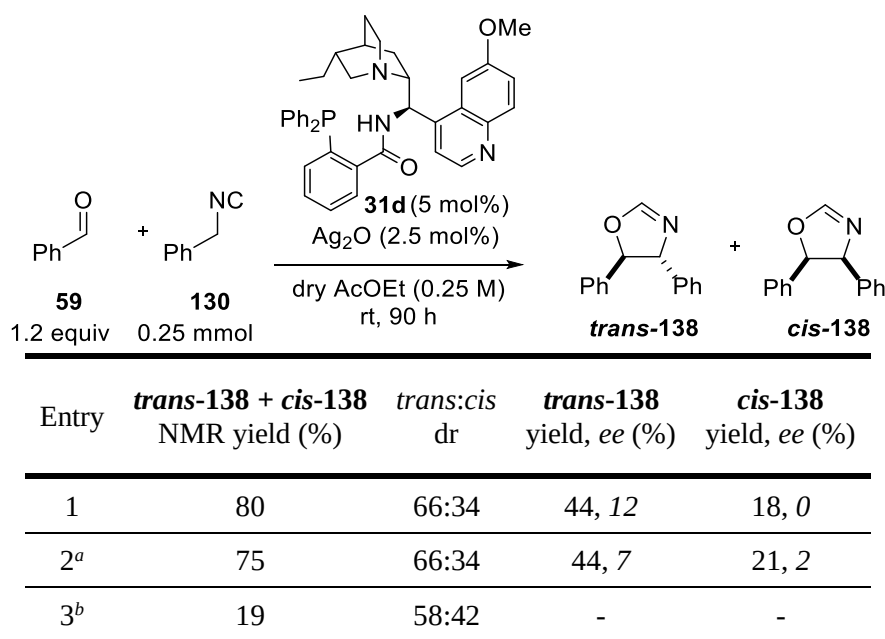
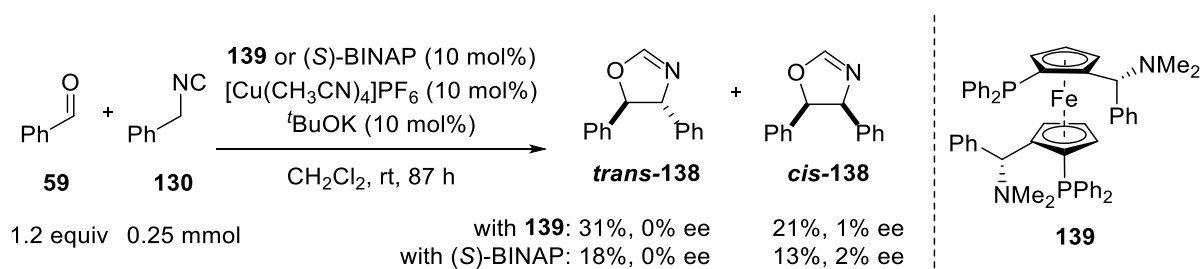


Table 5 Ag-catalysed aldol reaction between benzaldehyde and benzyl isocyanide. NMR yields and dr were determined by ¹H NMR analysis of the crude reaction mixture using mesitylene as an internal standard. Isolated yields and ee are given after purification. ^a With powdered 4 Å molecular sieves. ^b 10 mol% Ag₂O without ligand for 72 h.

^v The absolute configuration of the major enantiomer was not determined.

Unfortunately, no improvement in enantioselectivity was observed when the temperature was modified, the loading of silver and ligand changed, or AgOAc used instead of Ag₂O. Inspired by Shibasaki's work,¹⁶⁴ Ag(I) and Cu(I) salts in combination with bidentate phosphines and *t*-BuOK were also screened. Although moderate conversions were obtained with some [Cu(CH₃CN)₄]PF₆/ligand/*t*-BuOK combinations, oxazolines **trans-138** and **cis-138** were invariably produced in a racemic fashion (Scheme 30). It was thus decided to screen different electrophiles in the reactions of benzyl isocyanide, in the hope of achieving better stereocontrol.



Scheme 30 Aldol reaction between benzaldehyde and benzyl isocyanide.

3.4 Mannich Reactions of Benzyl Isocyanide

Benzaldehyde derived imines with different protecting groups on nitrogen were screened in the Mannich reaction of benzyl isocyanide employing the Ag₂O/amino phosphine system (Table 6). No conversion was registered with *N*-phenyl imine **140a** (Entry 1), while aldimines **140b** and **140c** with BOC and DPP protective groups gave the corresponding *cis* and *trans* imidazolines **141** in a practically racemic fashion (0–7% ee, Entries 2 and 5). Indeed, a control experiment revealed that the reaction between **140c** and benzyl isocyanide could be catalysed by 10 mol% Ag₂O alone, without amino phosphine **31d** (Entry 4). In line with Kobayashi's findings (see Scheme 28),¹⁶³ we noticed that reactivity was strongly influenced by traces of water. Whilst the reaction between *N*-DPP aldimine **140c** and benzyl isocyanide run in HPLC-grade ethyl acetate proceeded to complete conversion in 5 days (Entry 5), the use of ethyl acetate dried over molecular sieves and the addition of powdered molecular sieves decreased the conversion to 9% (Entry 6). Presumably, traces of water present in the solvent promote the

addition of benzyl isocyanide to aldimine **140c**. In the course of the reaction water also partially hydrolyses the starting aldimine to benzaldehyde, which then reacts with benzyl isocyanide in an aldol reaction. For this reason, whenever imidazolines were formed, also oxazolines **trans-138** and **cis-138** were produced in smaller amounts, with dr and ee values nearly identical to those obtained in the aldol reaction discussed above (compare Table 6, Entry 5 and Table 5, Entries 1–2).

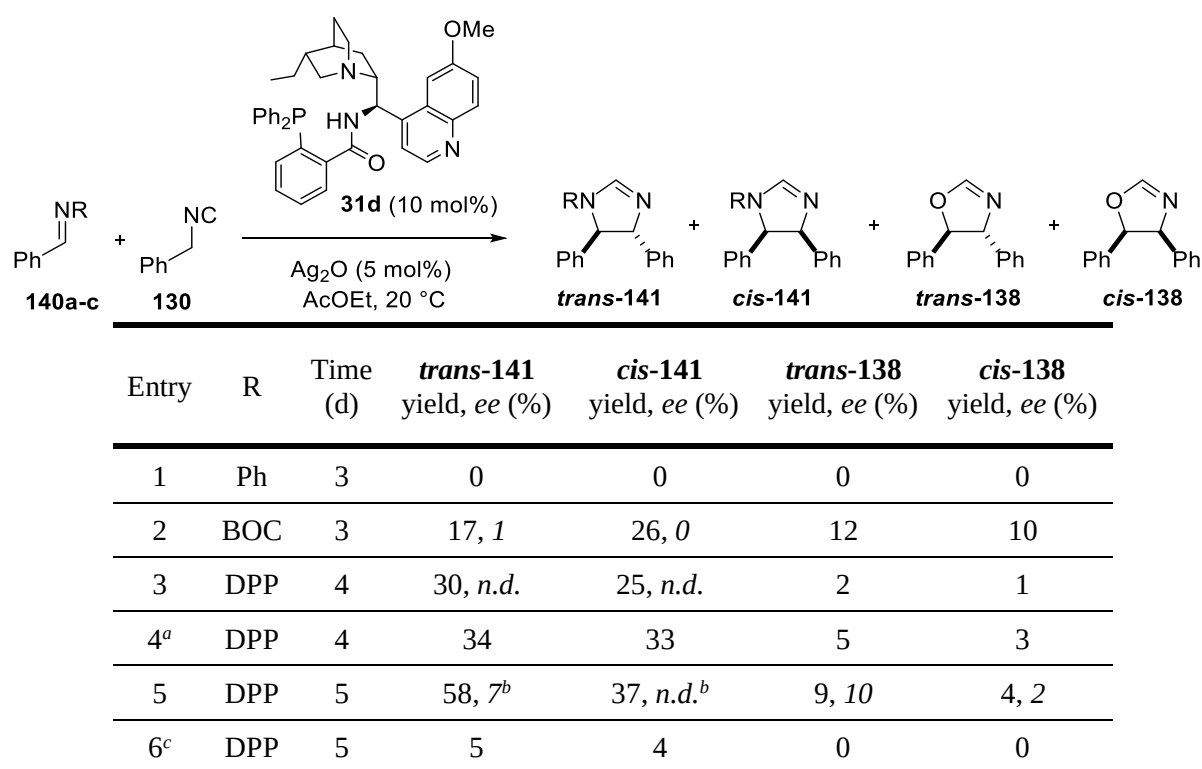


Table 6 Mannich reactions of benzyl isocyanide. Yields were determined by ¹H NMR analysis of the crude reaction mixture using mesitylene as an internal standard. Ee was determined by HPLC analysis on a chiral stationary phase after purification. HPLC-grade AcOEt was used. ^a With 10 mol% Ag₂O without ligand. ^b Ee was determined after removal of the DPP group; deprotection of N-DPP **cis-141c** yielded a meso compound. ^c Using dry AcOEt and powdered 4 Å molecular sieves.

3.5 Conclusions

The use of benzyl isocyanide as a non-activated pronucleophile in aldol and Mannich reactions was briefly investigated. Oxazolines and imidazolines were formed with moderate yields and poor diastereo- and enantioselectivity. Traces of water were found to promote the addition of benzyl isocyanide to benzaldehyde-derived N-DPP aldimine, whereas a similar effect was not

observed with benzaldehyde itself. These results, taken together with the ones detailed in Chapters 1 and 4, indicate that the presence of an electron-withdrawing group on the isocyanide is crucial to ensure reactivity and stereoselectivity in reactions catalysed by the Ag(I)/amino phosphine catalytic system.

4 Catalytic Enantio- and Diastereoselective Addition of TosMIC to Ketimines

4.1 Chapter Overview

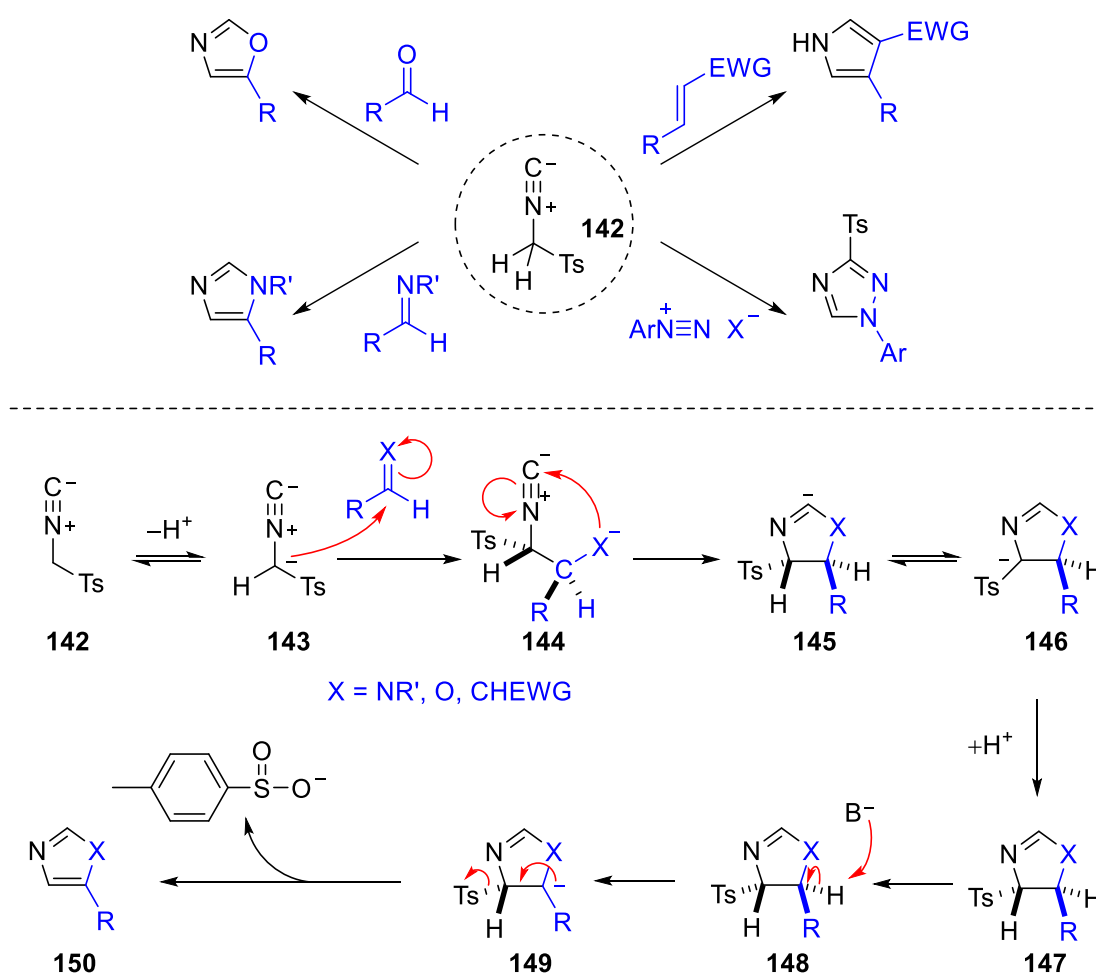
This chapter details our efforts in expanding the scope of the Ag(I)/amino phosphine catalytic system to the activation of α -functionalised isonitriles different from isocyanoacetate esters. The established catalytic system enabled the development of the first enantioselective Mannich addition of the versatile *p*-toluenesulfonylmethyl isocyanide (TosMIC) to ketimines. The reaction afforded imidazolines bearing two vicinal stereocentres with high yields and excellent diastereo- and enantiocontrol, and a wide range of (hetero)aromatic and aliphatic *N*-DPP ketimines were tolerated. Derivatisation of the reaction products provided sp^3 -rich heterocyclic scaffolds, vicinal diamines and precursors to NHC ligands, all in enantioenriched form. A mechanism and a stereochemical model were proposed to rationalise the experimental findings.

4.2 Introduction

4.2.1 Versatility of TosMIC in the Synthesis of Unsaturated Heterocycles

p-Toluenesulfonylmethyl isocyanide (TosMIC, **142**) is an activated isocyanide whose preparation and application to the synthesis of organic molecules were studied by the Dutch professor Albert Van Leusen in the 1970s.¹⁷⁰ It is a pale yellow, practically odourless crystalline solid, which is commercially available and can be stored at 0 °C for months without noticeable decomposition. Three functional groups determine the reactivity of this useful building block: the isocyanide undergoes α -additions (insertions at the terminal C atom),⁵⁴ the acidic methylene group can be easily deprotonated,¹⁶ and the tosyl substituent not only lowers the pK_a of the α -position, but can also act as a leaving group.

TosMIC can be exploited as a C–N=C synthon for the synthesis of various unsaturated 5-membered heterocycles: oxazoles,¹⁷¹ imidazoles,^{159,172} pyrroles,¹⁷³ and 1,2,4-triazoles¹⁷⁴ can be generated by reaction of TosMIC with aldehydes, aldimines, Michael acceptors and diazonium salts, respectively (Scheme 31, top). The general mechanism for these reactions involves the nucleophilic attack of the TosMIC anion **143** to the double bond of the electrophile, followed by ring closure onto the terminal isocyanide C atom. Subsequently, expulsion of the sulfinate leaving group from intermediate **149** affords the 5-membered unsaturated heterocycle **150** (Scheme 31, bottom).



Scheme 31 Van Leusen oxazole, imidazole and pyrrole synthesis using TosMIC

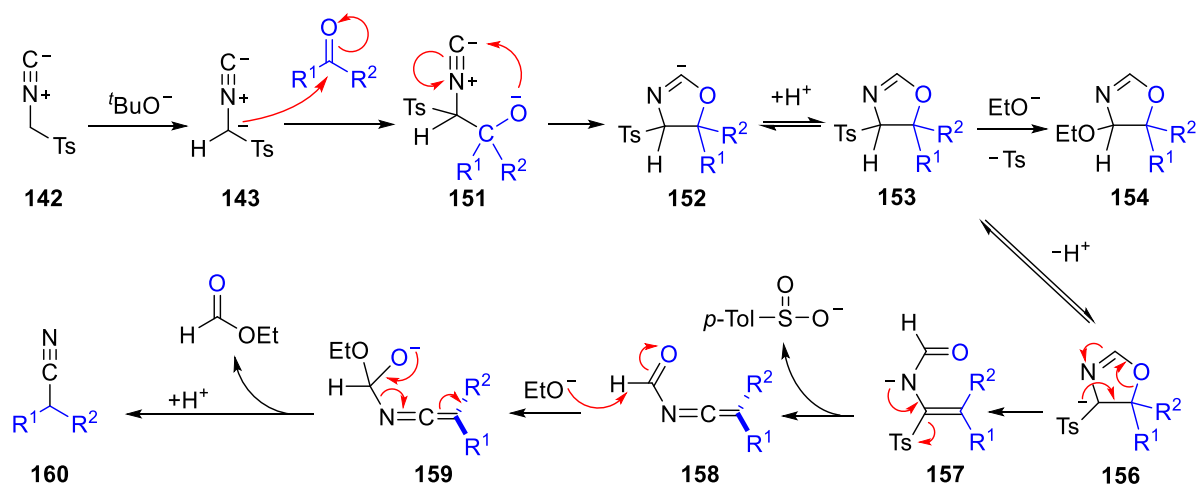
Such reactions, which are triggered by deprotonation of TosMIC, are generally performed using strong bases such as *n*-BuLi, *t*-BuOK and NaH; however, milder bases such as piperazine, morpholine, *n*-butylamine and K_2CO_3 suffice to promote the stepwise cycloaddition and in

some instances the following elimination. For example, TosMIC reacts with aldehydes in the presence of potassium carbonate in MeOH to afford oxazolines at room temperature, whereas oxazoles readily form at reflux.¹⁷¹

4.2.2 Reactions of TosMIC for the Synthesis of Non-Aromatic Compounds

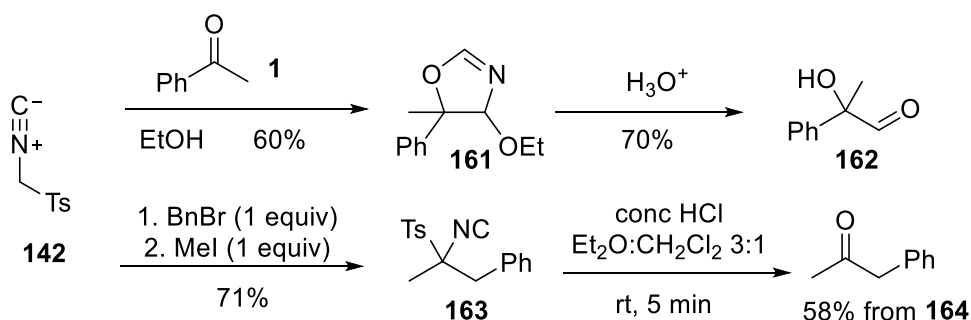
From the reaction between TosMIC and *N*-aryl aldimines in the presence of NaH (2.5 equiv) in DME at $-20\text{ }^{\circ}\text{C}$, imidazolines **147** (see Scheme 31) have been isolated exclusively as *trans* isomers. The ensuing elimination of the sulfinyl group promoted by potassium carbonate in refluxing methanol likely occurs *via* a $\text{E}_{1\text{cb}}$ pathway, since deuterium incorporation experiments proved that the C-4 position of imidazolines **147** is exchangeable under basic conditions.¹⁷⁵ Alternatively, an E_1 mechanism involving formation of a resonance-stabilised carbocation by loss of the tosyl group may be envisaged.

When ketones are employed as electrophiles instead of aldehydes, their conversion to the homologous nitriles takes place (Scheme 32).¹⁷⁵ The reaction is promoted by excess *t*-BuOK in DMSO or DME in the presence of 1–2 equivalents of EtOH or MeOH. The nucleophilic alkoxide speeds up the deformylation of ketenimine **159**. More equivalents of primary alcohols displace the tosyl substituent on oxazoline **153**, causing the undesired formation of 4-alkoxy-2-oxazoline **154**.



Scheme 32 Van Leusen nitrile synthesis from ketones using TosMIC.

Finally, the geminal isocyano and tosyl groups in TosMIC can behave as a *N,S*-acetal: upon treatment with aqueous acids α -hydroxy aldehydes such as **162** can be prepared from oxazolines,¹⁷⁶ and ketones (e.g. **164**) from α -alkylated TosMIC derivatives such as **163** (Scheme 33).¹⁷⁷



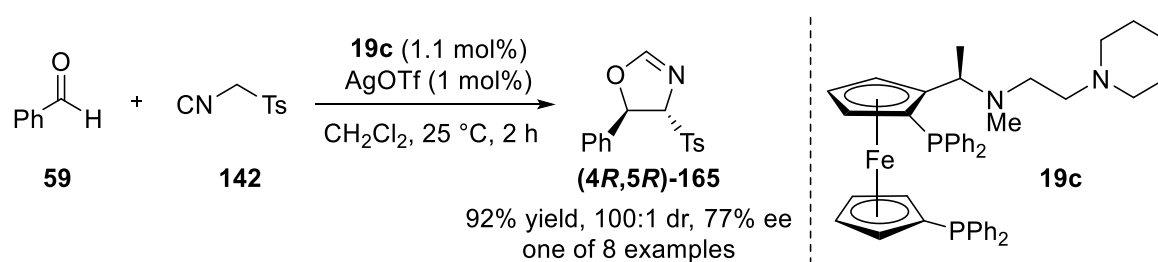
Scheme 33 Reactivity of TosMIC as a *S,N*-acetal for the synthesis of aldehydes and ketones.

4.2.3 Catalytic Enantioselective Aldol Reactions of TosMIC

Despite the multifaceted chemistry offered by TosMIC and the possibility of stopping the reactions at the chiral oxazoline or imidazoline stage, only three catalytic enantioselective aldol reactions of this isocyanide have been reported in the literature to date.

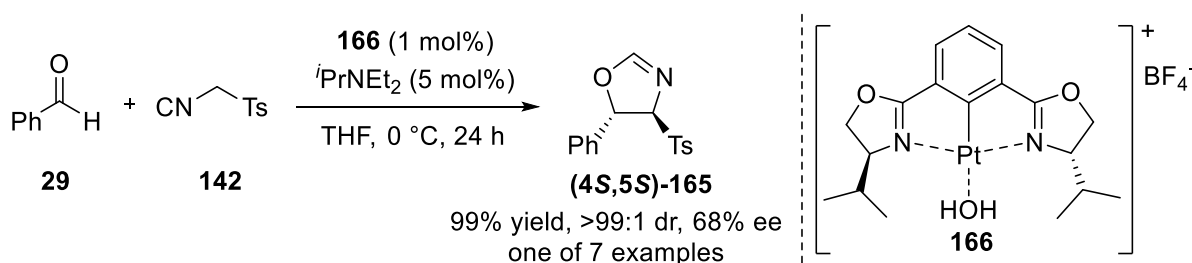
Following his seminal work with Hayashi on the gold-catalysed aldol reaction of isocyanoacetates,⁷⁹ in 1990 Ito reported the enantioselective aldol reaction between TosMIC and aldehydes catalysed by silver triflate and bis(diphenylphosphino)ferrocene ligand **19c** (Scheme 34).¹⁷⁸ The catalytic system was effective with aromatic, aliphatic and α,β -unsaturated

aldehydes, delivering *trans* oxazolines with 91–96% yields, >20:1 dr and 73–86% ee. The terminal tertiary amine functionality on the ligand was essential for catalytic activity, while the length of the linker between the ferrocenyl scaffold and the terminal N atom strongly influenced enantioselectivity in the formation of the oxazoline. These observations were consistent with the stereochemical model that Ito and Hayashi originally proposed, where the distal amine is responsible for the deprotonation of the Au-bound isocyanide, and then the resulting ammonium ion orients the enolate towards addition to the Au-coordinated aldehyde (see Section 1.2.3, Scheme 5).⁷⁹



Scheme 34 Ito's Ag-catalysed diastereo- and enantioselective aldol reaction of TosMIC with aldehydes.

A decade later, Motoyama and co-workers evaluated the catalytic performance of chiral Pd(II), Pt(II) and Pt(IV) complexes with NCN pincer ligands in the reaction between TosMIC and aldehydes.⁹⁴ Complex [(*i*-Pr-Phebox)Pt(H₂O)](BF₄) (**166**) in conjunction with Hünig's base was found to catalyse the formation of **165** with moderate enantiocontrol (25–75% ee, Scheme 35).



Scheme 35 Motoyama's Pt(II)-catalysed enantioselective aldol reaction of TosMIC with aldehydes.

The authors attributed the moderate levels of enantioselectivity to the fact that the chiral surroundings of complex **166** are not deep enough to effectively stereodifferentiate the two faces of the enolate. To rationalise the observed absolute and relative stereochemical

configurations, they proposed that addition to the carbonyl occurs from the less shielded *Si* face of the TosMIC anion in an antiperiplanar fashion (Figure 16).

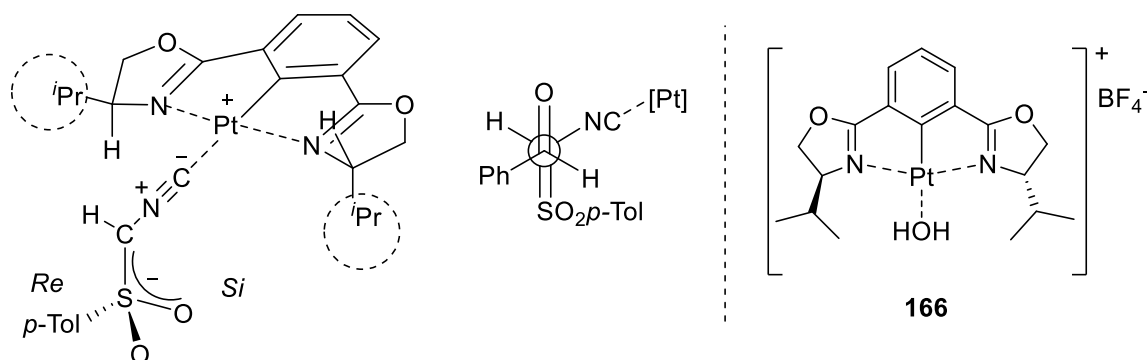
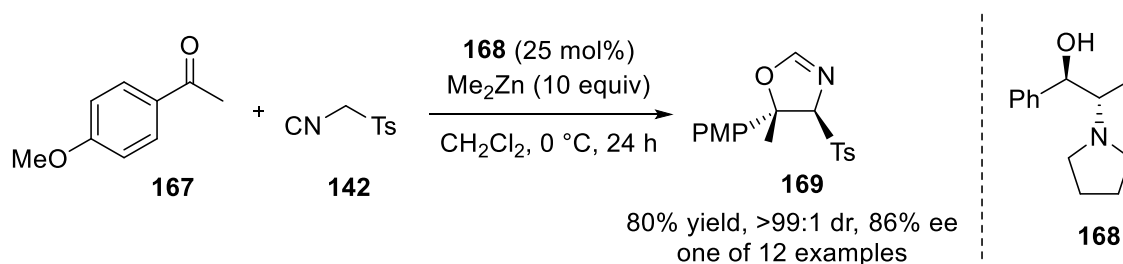


Figure 16 Proposed stereochemical model for the aldol reaction of TosMIC catalysed by complex **166**.

In 2015, the group of Cozzi developed the first, and to date only, catalytic enantioselective addition of TosMIC to ketones (Scheme 36).¹⁷⁹ Building on their previous work with dimethyl zinc and amino alcohols for additions to ketones,¹⁸⁰ the authors used excess Me_2Zn and substoichiometric amount of norephedrine-derived **168** to promote the aldol reaction of TosMIC in moderate to excellent yields (57–92%) and good levels of enantioselectivity (62–96% ee) in the formation of oxazolines such as **169**. After acid hydrolysis, the oxazolines were converted to α -hydroxy aldehydes and other building blocks bearing tertiary alcohol motifs.



Scheme 36 Cozzi's enantioselective aldol reaction between TosMIC and ketones.

From this review of the literature it is possible to ascertain that, despite the versatility of the resulting oxazoline products, only few protocols for catalytic enantioselective additions of TosMIC to $\text{C}=\text{O}$ bonds are available and none of these displays high enantioselectivity across a significant number of substrates. Even more surprisingly, no asymmetric Mannich reaction of TosMIC has yet been developed, and therefore the potential utility of enantioenriched 4-tosyl-2-imidazolines as chiral amine building blocks remains untapped.

4.3 Reaction Discovery and Optimisation

With the aim of extending the scope of our Ag(I)/amino phosphine catalytic system to the asymmetric activation of isonitriles different from isocynoacetates, we reasoned that TosMIC should have similar acidity to isocynoacetates.^{vi} We therefore recognised the opportunity of developing the first catalytic enantioselective Mannich reaction of TosMIC with imines.^{vii} *N*-Diphenylphosphinoyl ketimines were chosen as electrophiles, since they had already shown excellent reactivity and enantiofacial selectivity in the silver-catalysed Mannich reaction of isocynoacetates.^{111,112} Using 5 mol% silver oxide and 10 mol% dihydroquinine-derived ligand **31b**, previously identified as the most effective in the Mannich reaction between α -substituted isocynoacetates and *N*-DPP ketimines, reaction between acetophenone-derived ketimine **5a** and TosMIC was initially investigated in ethyl acetate as a solvent (Table 7).

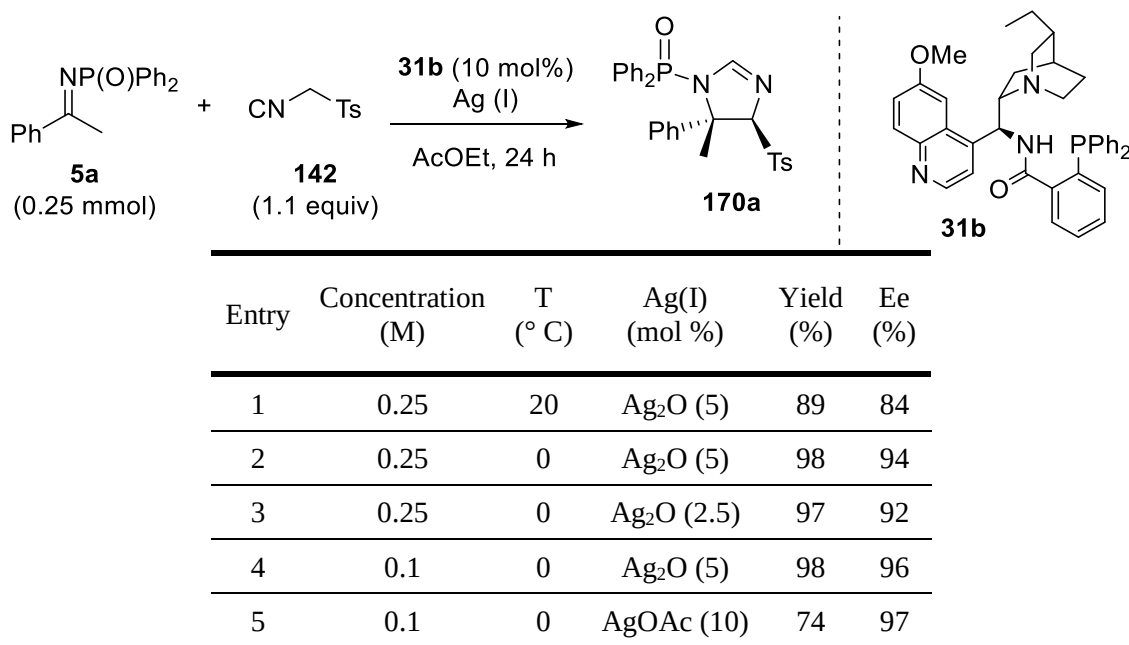


Table 7 Optimisation of the Ag-catalysed enantioselective reaction between ketimine **5a** and TosMIC.

^{vi} Data for isocyanides are not available, however it is possible to compare the pK_a values in DMSO for the following pairs: NCCH₂SO₂Ph (12.0) and NCCH₂CO₂Et (13.1);^{181,182} MeC(O)CH₂SO₂Ph (12.5) and MeC(O)CH₂CO₂Et (14.2);^{183,184} CH₃SO₂Ph (29.0) and CH₃CO₂Et (29.5).^{185,186}

^{vii} Preliminary studies of this reaction were performed by Jack Chapman, an undergraduate student working under the supervision of A.F.. His results are not included herein and can be found in Jack Chapman, Part II Thesis, University of Oxford 2016.

Very pleasingly, after 24 hours at room temperature the desired *trans* imidazoline **170a** was obtained as a single diastereomer with very good yield and enantiocontrol (89% yield, 84% ee, Entry 1). Lowering the temperature to 0 °C increased both yield and enantioselectivity (98% yield, 94% ee, Entry 2). At this temperature, decreasing the Ag₂O loading had a slight detrimental effect on enantiocontrol in the formation of **170a** (Entry 3), whereas dilution of the reaction mixture increased the ee of the product to 96% (Entry 4). The use of 10 mol% silver acetate in conjunction with **31b** promoted the reaction with marginally higher enantioselectivity but diminished yield. The decrease in yield was due to the competitive dimerisation of the pronucleophile to afford TosMIC dimer **171** (19% yield), whose structure was unambiguously confirmed by single crystal X-ray diffraction (Figure 17).

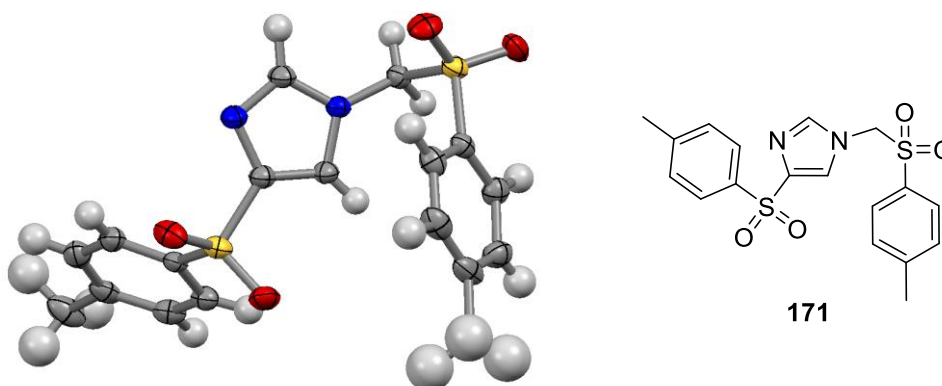
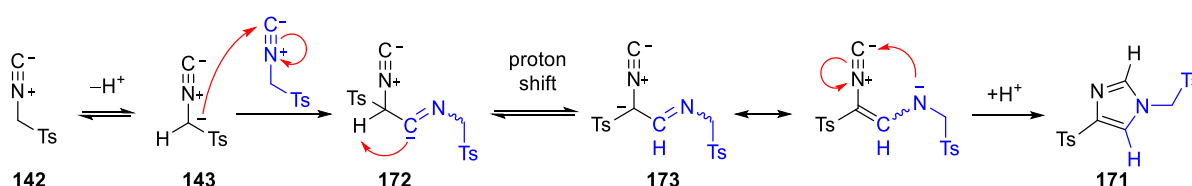


Figure 17 ORTEP diagram for TosMIC dimer **171** with ellipsoids at 50% probability.

Cyclodimerisation of TosMIC under basic conditions (K₂CO₃ in MeOH, TlOEt in DME/EtOH) was also observed by Van Leusen, who proposed a mechanism for the process (Scheme 37).¹⁷⁵ The reaction is initiated by the TosMIC anion **143** attacking the isocyanide C atom of another TosMIC molecule. After proton shift, the N atom of 1-azaallyl anion **173** closes on the remaining isocyanide moiety, and protonation gives **171**.



Scheme 37 Proposed mechanism for the dimerisation of TosMIC under basic conditions.

4.4 Substrate Scope of the Enantioselective Addition of TosMIC to Ketimines

4.4.1 Synthesis of *N*-DPP Ketimines

With the optimal conditions identified, a range of *N*-DPP ketimines were prepared from the corresponding ketones to allow an investigation into the reaction scope (Figure 18).

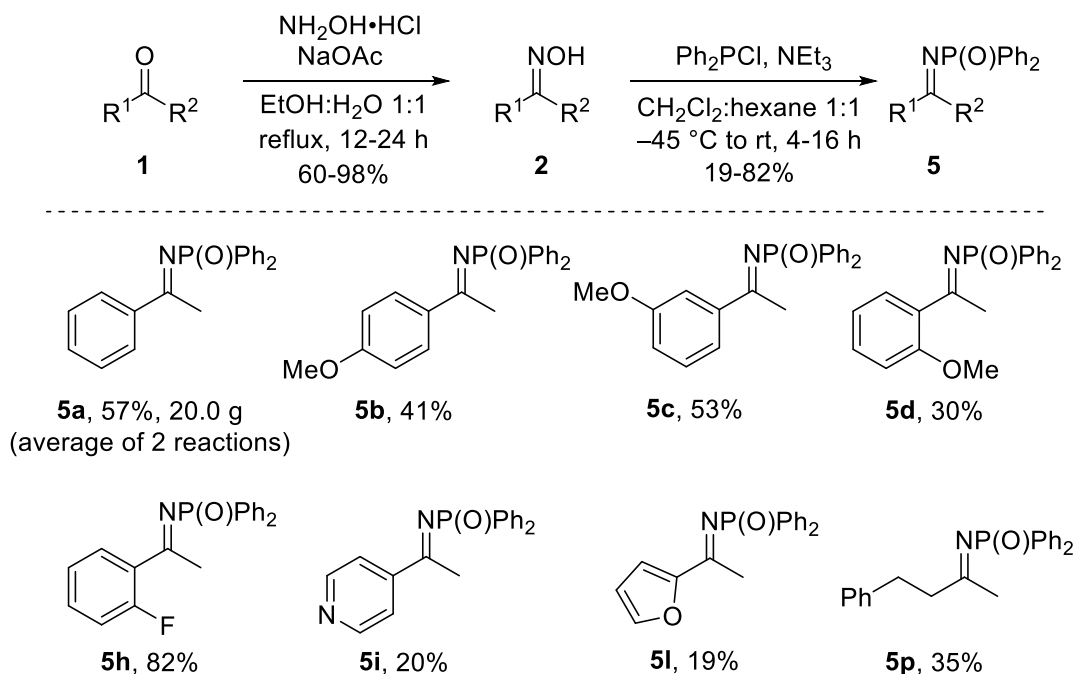


Figure 18 Two-step synthesis of *N*-DPP ketimines **5** from the corresponding ketones. Yields are given for the second step.

Following the procedure described in Section 1.1.3, oximes **2** were isolated in 60–98% yield after precipitation, and ketimines **5** were obtained in 19–82% yield after purification by FCC, followed by trituration or recrystallisation to increase the purity to >98%.^{viii} The modest yields are due to the low stability of the ketimines to silica gel and difficulties in the separation of impurities (hydrolysis products and enamines).

^{viii} The other ketimines were kindly donated by members of the Dixon group (Jack Chapman, Antonia Rinaldi, Gerard P. Robertson, Dr Alistair J. M. Farley, Dr Irene Ortín, Dr Raquel de la Campa), and repurified by A.F. when necessary.

4.4.2 Substrate Scope for the Addition of TosMIC to *N*-DPP Ketimines

Substituents on the *N*-DPP ketimines were systematically varied to thoroughly assess the substrate scope of the methodology (Figure 19). Under the optimised conditions, the reactions proceeded to full conversion within 24 hours and afforded the *trans* imidazoline as the only or largely major product (dr of the crude reaction mixture from 90:10 to >95:5). Aryl methyl ketimines with electron-donating groups (OMe), as well as electron-withdrawing substituents (F, Cl, Br) in the *para*, *meta* and *ortho* positions afforded the products **170b-h** in high yields and excellent enantiocontrol (86–97% yield, 86–97% ee). While the small fluoro substituent in *ortho* position was well-tolerated, a double loading of both ligand and Ag₂O were required to ensure full conversion for the reaction of *o*-methoxyphenyl methyl ketimine **5d**. Pleasingly, heteroaromatic ketimines reacted smoothly. Imidazolines with 2-pyridyl, 3-pyridyl and 4-pyridyl groups were prepared in 86–99% yield and 90–95% ee (**170i-k**). Products **170l** and **170m** with 2-furanyl and 2-thienyl substituents were obtained in 82% yield and 98% ee, 98% yield and 96% ee respectively. In addition, it was possible to increase the length of the alkyl chain on the ketimine delivering product **170n** with a *n*-propyl group in 88% yield and 93% ee. Interestingly, aromatic ketimine **5o** with a β -branched alkyl chain was completely unreactive. Importantly, it was possible to use aliphatic ketimines with primary, secondary and even tertiary alkyl groups. Aliphatic ketimines with phenethyl and cyclohexyl substituents afforded products **170p** and **170q** in 95% yield and 94% ee. A double loading of ligand and Ag(I), higher concentration and 5-day reaction time^{ix} were found to be necessary to accomplish TosMIC addition to *tert*-butyl methyl ketimine, obtaining **170r** in 51% yield and 82% ee. This is still a remarkable result considering the steric and electronic deactivation of this substrate.

^{ix} Single optimisation experiments indicated that all these conditions were required at the same time to push the reactivity.

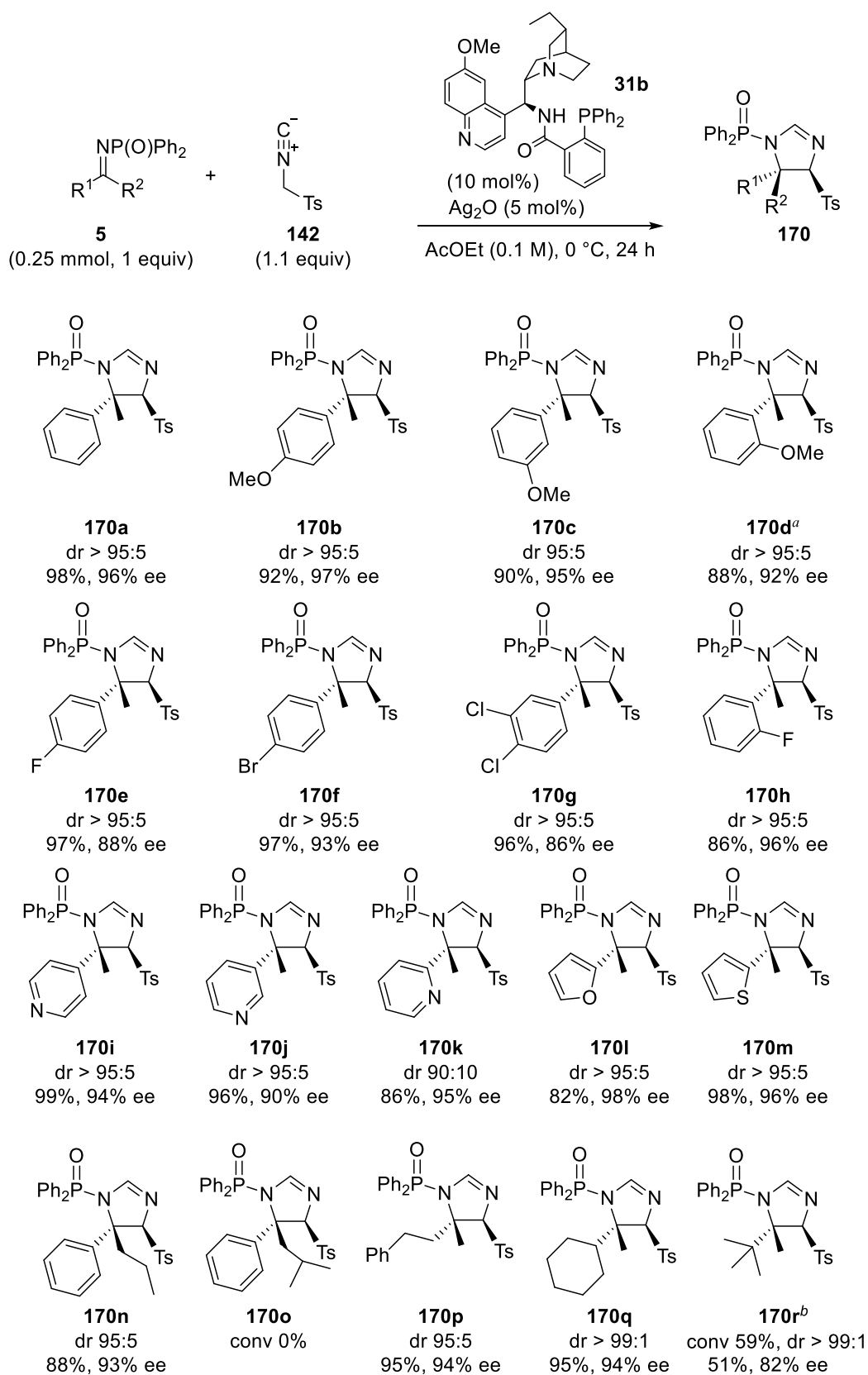


Figure 19 Substrate scope for the catalytic diastereo- and enantioselective addition of TosMIC to N-DPP ketimines. Dr (trans:cis) of the crude reaction mixture determined by ¹H NMR analysis. Isolated yields and ee given for the trans diastereomer after FCC. ^a With 20 mol% **31b** and 10 mol% Ag₂O. ^b At 0.25 M concentration for 120 h with 20 mol% **31b** and 10 mol% Ag₂O.

The major enantiomer of *p*-fluorophenyl imidazoline **170e** was recrystallised from ethyl acetate to enantiopurity (> 99.5% ee by HPLC analysis) and single crystal X-Ray diffraction allowed the determination of the absolute configuration (4*S*,5*S*, Figure 20).

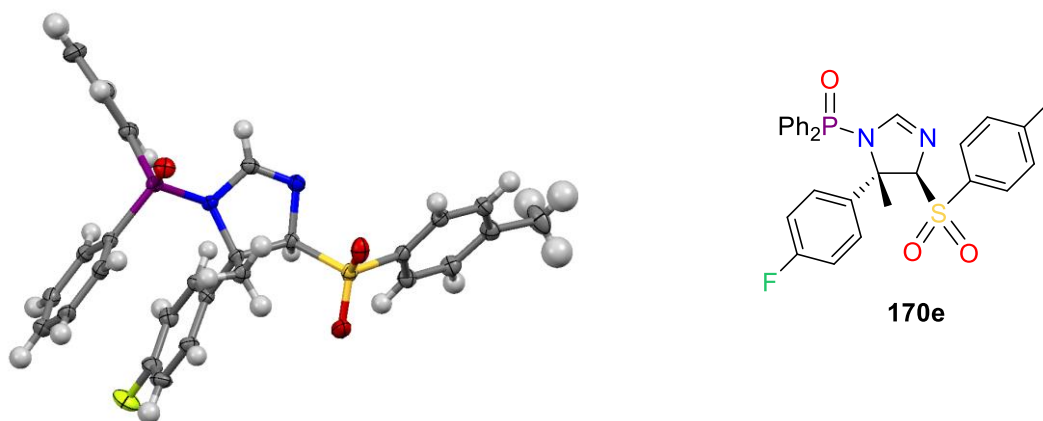


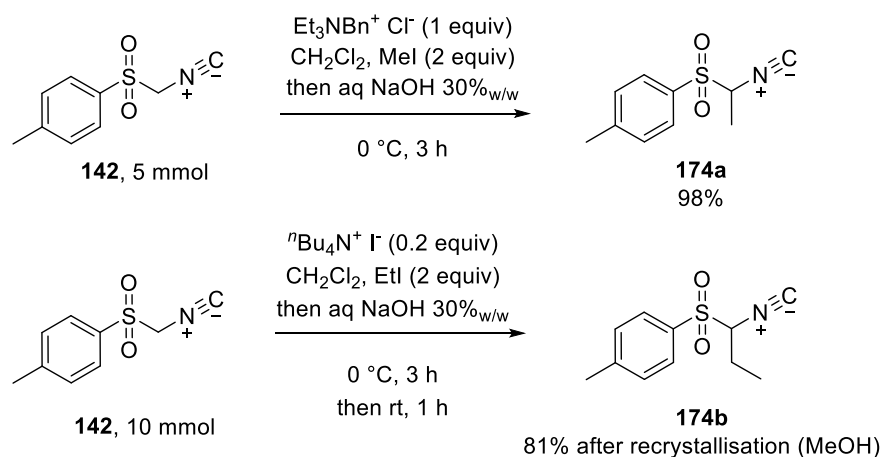
Figure 20 ORTEP diagram for **170e** with ellipsoids at 50% probability level.

The absolute and relative configuration of the other imidazoline products was assigned by analogy. NOe experiments carried out on phenethyl- and *tert*-butyl-substituted products **170p** and **170r**, and separately on both diastereomers^x of 2-pyridyl- and 2-furanyl-substituted imidazolines **170k** and **170l** confirmed the relative *trans* stereochemistry also for imidazolines with aliphatic and heteroaromatic substituents.

4.4.3 Synthesis of α -Substituted TosMIC Pronucleophiles

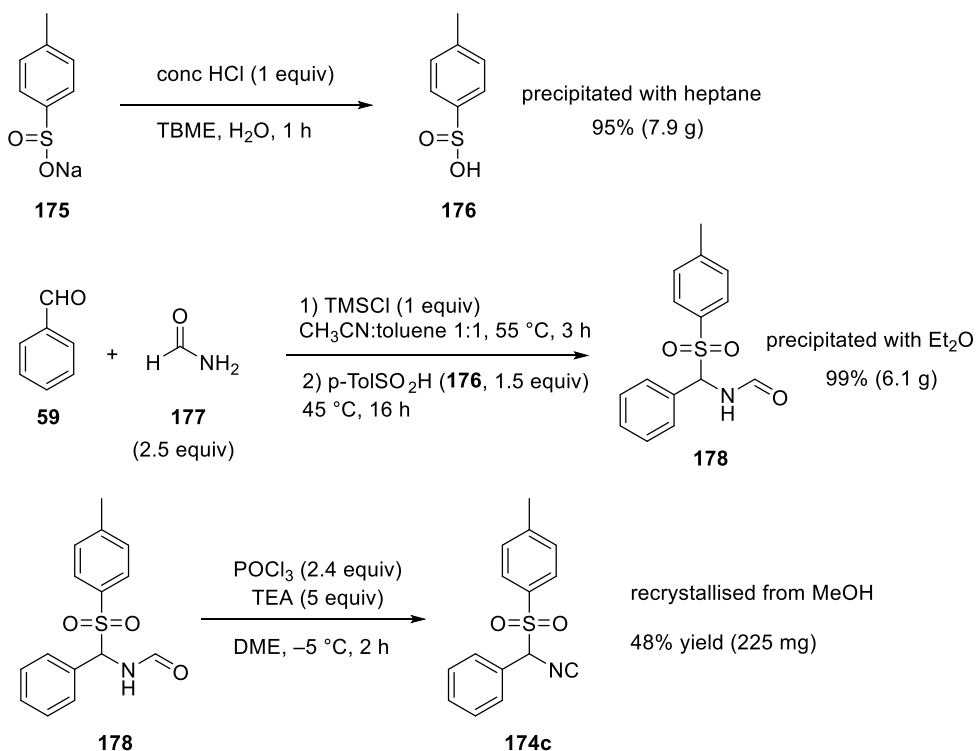
With the scope of the electrophile assessed, a range of α -substituted TosMIC derivatives were prepared in order to investigate the application of the enantioselective methodology to the formation of two vicinal, fully-substituted stereocentres. The α -methyl and α -ethyl derivatives were conveniently synthesized following an alkylation protocol under phase-transfer conditions developed by Van Leusen (Scheme 38).¹⁸⁷

^x Sufficient quantities of *cis*-**170k** and *cis*-**170l** were obtained in racemic form *via* non-enantioselective reactions (see Experimental Section).



Scheme 38 Synthesis of α -methyl and α -ethyl TosMIC derivatives **174a** and **174b**.

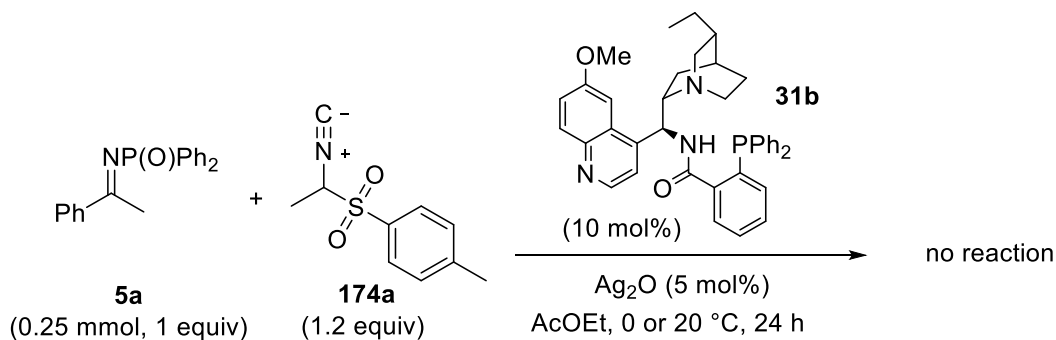
α -Phenyl substituted substrate **174c** was prepared due to its proposed greater acidity relative to **174a** and **174b**. According to the classical TosMIC synthesis, the dehydration of formamide **178**, that was prepared by reaction of formamide, benzaldehyde and *p*-toluenesulfinic acid, was performed (Scheme 39).¹⁷⁵ The latter spontaneously disproportionates over time, so had to be prepared by acidification of the stable sodium *p*-toluenesulfinate and used within 24 hours.¹⁸⁸



Scheme 39 Synthesis of α -phenyl substituted TosMIC derivative **174c**.

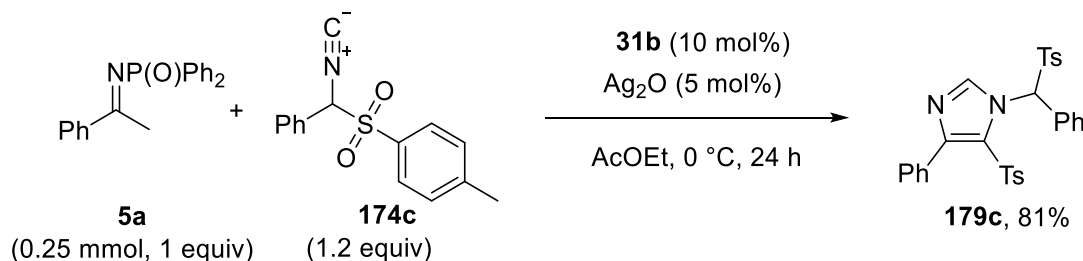
4.4.4 Screen of α -Substituted TosMIC Pronucleophiles

With the α -substituted TosMIC derivatives in hand, reaction of α -methyl substituted TosMIC **174a** with ketimine **5a** was attempted under standard conditions, but ^1H NMR analysis of the crude reaction mixture revealed quantitative recovery of the starting materials against the internal standard (Scheme 40). The reaction displayed the same profile at room temperature.



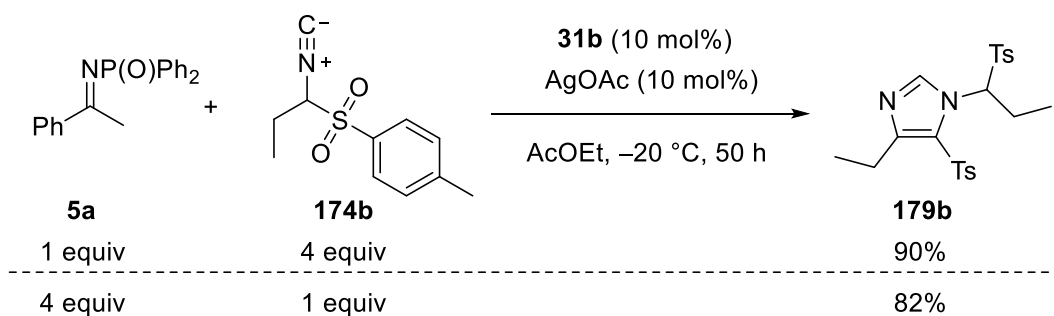
Scheme 40 Attempted reaction of α -methyl TosMIC derivative **174a** with N-DPP ketimine **5a**.

Due to the rapid degradation of α -methyl TosMIC derivative **174a** (an oil at room temperature), we decided to use the crystalline α -ethyl and α -phenyl analogues **174b** and **174c** for subsequent studies. When α -phenyl substituted TosMIC **174c** was used under the same conditions, the starting ketimine was recovered completely unreacted, while the isocyanide was found to dimerise to imidazole **179c** (Scheme 41).



Scheme 41 Reaction of α -phenyl TosMIC derivative **174c** with N-DPP ketimine **5a**. Yield of dimer based on **174c**.

In the reaction between α -ethyl TosMIC **174b** and the model ketimine **5a** an extensive range of bases, metals and ligands were screened. Unfortunately, in no case could the desired imidazoline product be observed: the only detectable reactivity was dimerisation of the pronucleophile. The relative stoichiometry of the two reaction partners was changed, but to no avail (Scheme 42).



Scheme 42 Reaction of α -ethyl TosMIC derivative **174b** with N-DPP ketimine **5a**. Yield of dimer based on **174b**.

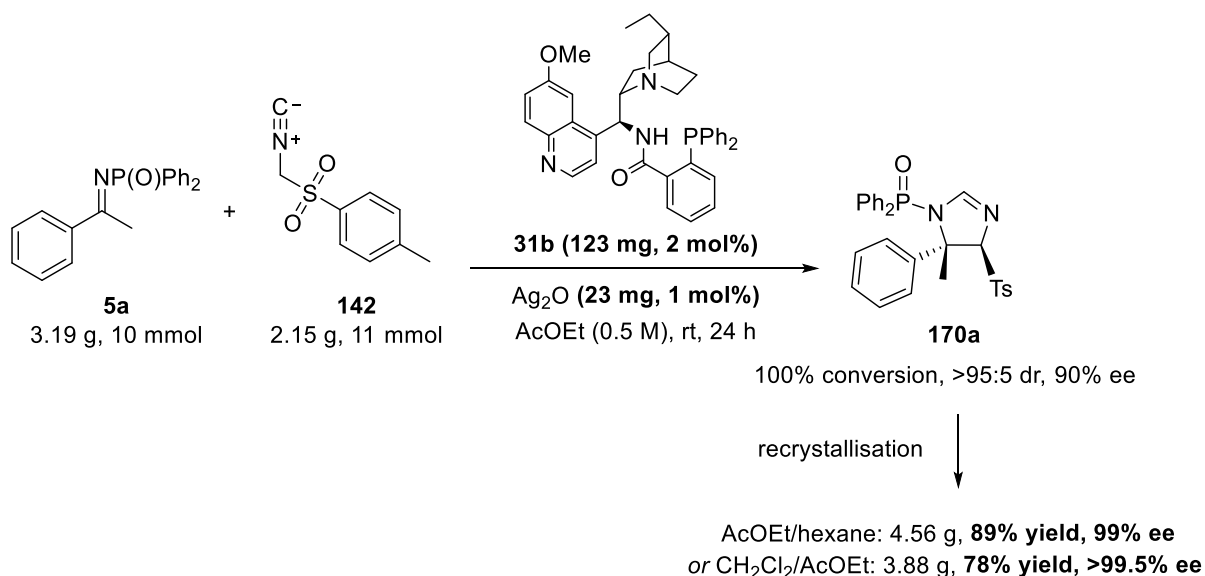
As discussed in Section 4.3, dimerisation of TosMIC is triggered by deprotonation.¹⁷⁵ Based on all of the observations described above, we suppose that after deprotonation at the α -position, the bulky TosMIC anion is more likely to attack the terminal isonitrile C atom of another TosMIC molecule rather than the more sterically hindered sp^2 C atom of the ketimine. Dimerisation is thus favoured over Mannich addition with hindered pronucleophiles (such as the α -substituted TosMIC derivatives) and/or poorly reactive electrophiles.

4.5 Synthetic Transformation of the Product

4.5.1 Preparative Scale Synthesis of 170a

The catalytic enantioselective reaction between acetophenone-derived ketimine **5a** and TosMIC was scalable and operationally simple. The substrate scope was conducted on a 0.25 mmol scale with 10% loading of ligand and Ag(I); after reoptimisation for preparative scale we were able to reduce the catalyst loading to 2 mol%, while at the same time increasing the scale to 10 mmol. It was possible to mix nearly stoichiometric amounts of the two reagents with the ligand and silver oxide in ethyl acetate, stir at room temperature under air and obtain full conversion to the *trans* imidazoline in 24 hours. The crude mixture, that appeared as a thick off-white suspension due to precipitation of the product, was diluted with CH_2Cl_2 , filtered through celite to remove the silver residues and concentrated. The filtrate could be conveniently purified by recrystallisation from ethyl acetate/dichloromethane with concomitant upgrade of the

enantiomeric excess, thus obtaining the desired product **170a** in 78% yield and greater than 99.5% ee (Scheme 43).

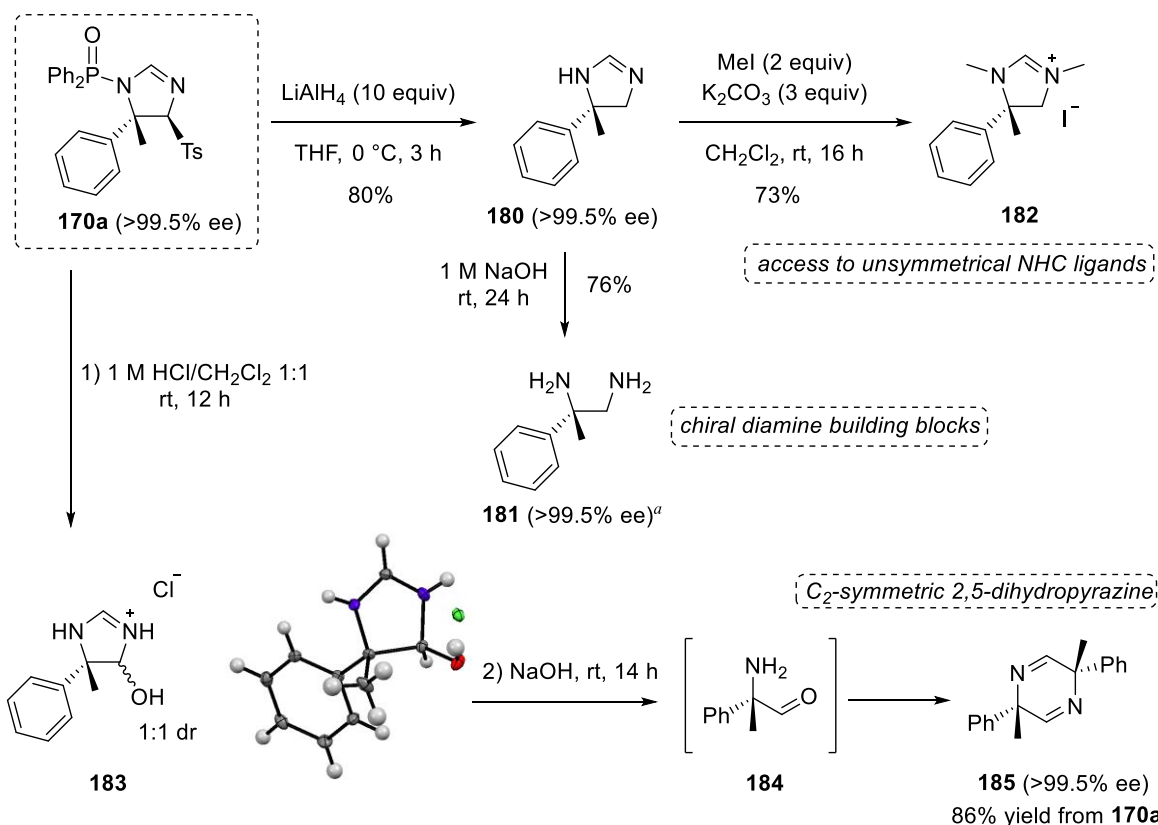


Scheme 43 Multigram synthesis of **170a**.

4.5.2 Derivatisation of **170a**

With gram quantities of enantiopure imidazoline **170a** in hand, we focused on its derivatisation to demonstrate the utility of our catalytic enantioselective methodology (Scheme 44).

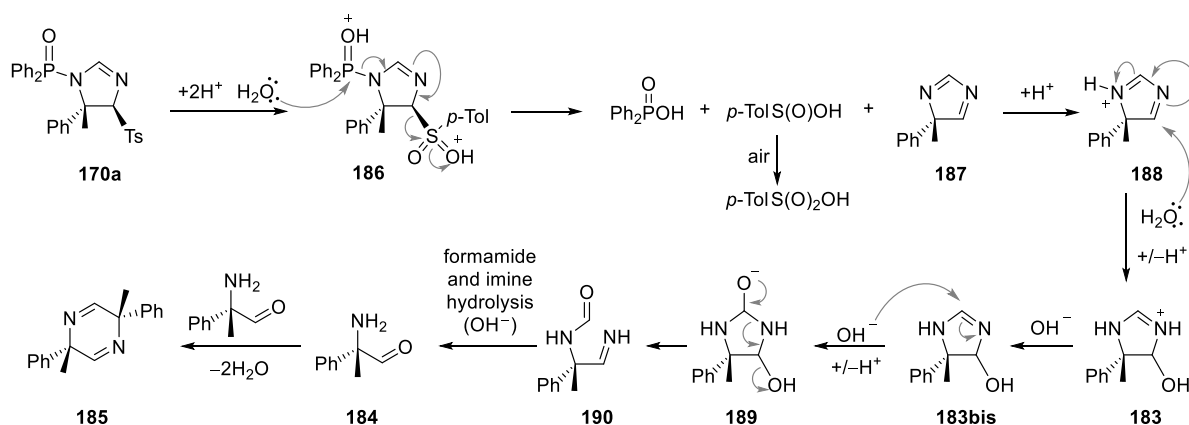
To this end, treatment of **170a** with excess lithium aluminum hydride removed both the DPP and the tosyl groups affording **180** in 80% yield without affecting the enantiopurity. The deprotected imidazoline could be hydrolysed under basic conditions, obtaining diamine **181** in high enantiopurity, or methylated on both N atoms to give imidazolium iodide **182**, a precursor to a non-symmetrical *N*-heterocyclic carbene (NHC).¹⁸⁹



Scheme 44 Synthetic utility of imidazoline **170a**. ORTEP diagram for *trans*-**183** shown with ellipsoids at 30% probability. ^a Ee of diamine **181** determined on the corresponding ditosylamide.

Several acidic conditions were tried to effect the removal of the DPP group,³⁹ but in all cases the tosyl group was not stable to the reaction conditions. When the *N*-protected imidazoline **170a** was treated with aqueous HCl, 4-hydroxyl imidazolium chloride **183** was obtained as a ~ 1:1 mixture of epimers at C-4 in moderate yield (~40%). The poor yield reflects difficulties in purification, as several washings of the aqueous phase (1 M HCl) with 3:1 chloroform/isopropanol were needed to remove the impurities (diphenylphosphinic, *p*-toluenesulfinic and *p*-toluenesulfonic acids). Structural identification of the compound was complicated by the fact that NMR analysis could be run only in solvents where the acidic protons underwent deuterium exchange, and was solved by the X-ray structure of the *trans* diastereomer. Treatment of 4-hydroxyl imidazolium **183** with sodium hydroxide provided *C*₂-symmetric dihydropyrazine **185** via dimerisation of α -amino aldehyde **184**. A two-step, one-pot procedure was developed to avoid isolation of the imidazolium chloride, obtaining dihydropyrazine **185** in 86% yield from **170a** without erosion of enantiopurity (Scheme 44). A

plausible mechanism for the transformation is depicted in Scheme 45. Removal of the DPP group triggered elimination of the tosyl substituent, affording the Michael acceptor **187**, that underwent nucleophilic attack by water. Imidazolium chloride **183** then hydrolysed under basic conditions to α -amino aldehyde **184**. The formation of this intermediate was supported by the presence of an aldehyde peak (δ 9.45 ppm in CDCl_3) in the ^1H NMR spectrum of those hydrolysis reactions that have not gone to full completion; the peak disappeared over time converting to product **185**. In an analogous fashion, 4-tosyl and 4-alkoxy oxazolines have been shown to afford α -hydroxy aldehydes upon acidic treatment.^{176,179,190}



Scheme 45 Plausible mechanism for the formation of 2,5-dihydropyrazine **185**.

4.5.3 Endeavours towards C4-Alkylation

Since α -substituted TosMIC derivatives were not suitable reaction partners in this methodology (see Section 4.4.4), we sought to alkylate the 4-position of the product imidazolines directly by exploiting the acidity of the proton α to the tosyl group. This strategy could in principle provide more flexibility, as the introduction of alkyl groups at C-4 would simply require the use of different electrophiles, rather than the *ad hoc* preparation of TosMIC derivatives.

First of all, we ran some small-scale deuteration experiments to check whether deprotonation at C-4 was feasible. Freshly prepared lithium diisopropylamide (LDA, 2 equivalents) was added to a solution of imidazoline **170a** at -78°C , which after 30 minutes was quenched at room temperature with 1 M ND_4Cl in D_2O (Table 8). After chloroform/water extraction, the organic

phase was analysed by ^1H NMR using mesitylene as an internal standard. To our surprise, we noticed that significant amounts of ketimine **5a** and TosMIC formed. Furthermore, the recovered starting imidazoline **170a** was isolated with a lower enantiomeric excess.^{xi}

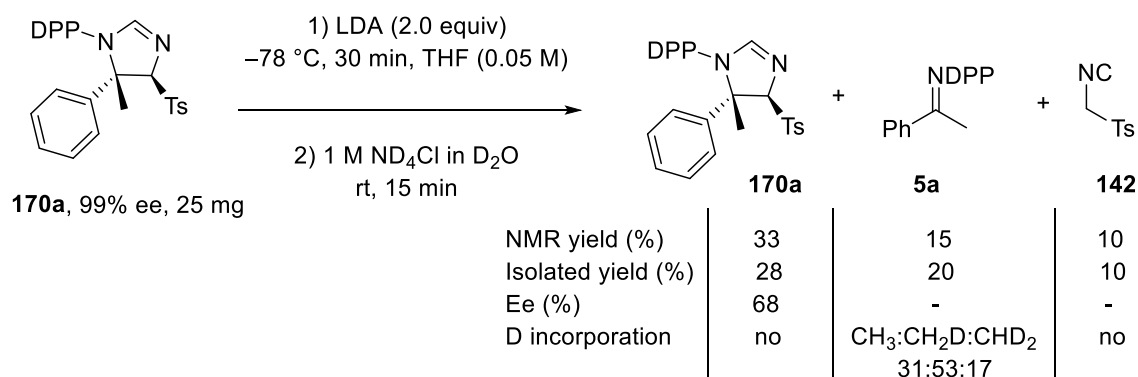
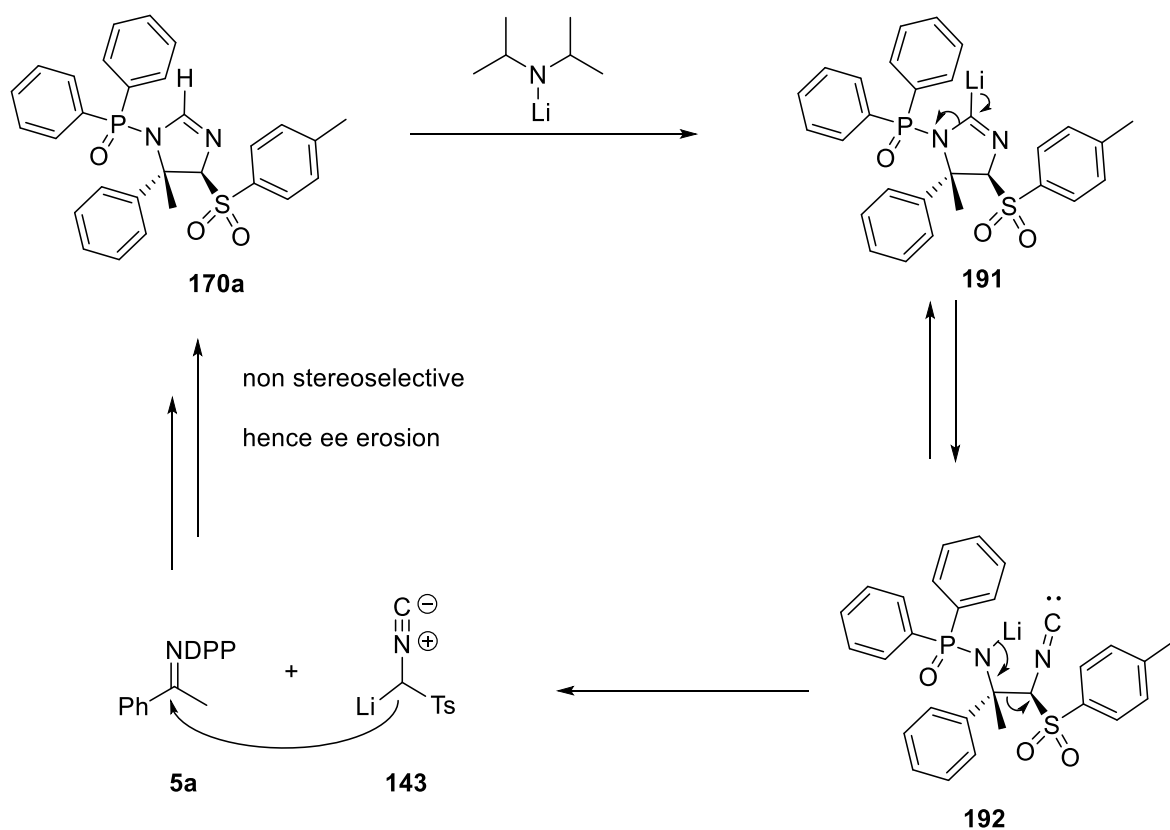


Table 8 Deuteration experiments on **170a** using LDA.

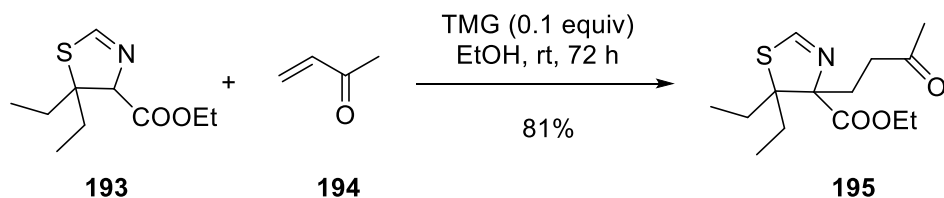
This result suggests that in the presence of a strong base the isocyanoacetate Mannich reaction between **5a** and **142** is reversible. We hypothesised that direct lithiation at C-2 takes place preferentially over deprotonation at the more sterically hindered C-4 (Scheme 46). The 2-lithiated 2-imidazoline **191** can exist in equilibrium with the open form **192** with a free isocyanide moiety; this equilibrium is well documented for 2-lithiated 2-oxazolines.⁷⁵ This intermediate fragments into ketimine **5a** and deprotonated TosMIC in a retro-Mannich reaction, and the two compounds recombine in a non-enantioselective fashion to afford imidazoline **170a**, thereby causing erosion of the enantiomeric excess. Deuterium incorporation at the α position of acetophenone-derived ketimine **5a** presumably arises from ND₄Cl quenching of the anion formed by deprotonation of **5a** by the excess LDA.

^{xi} Reactions of **170a** with other strong bases (*n*-BuLi, LHMDs) resulted either in decomposition or recovery of non-deuterated starting material.



Scheme 46 Proposed mechanism for the deprotonation of **170a** by LDA explaining the erosion of enantiomeric excess.

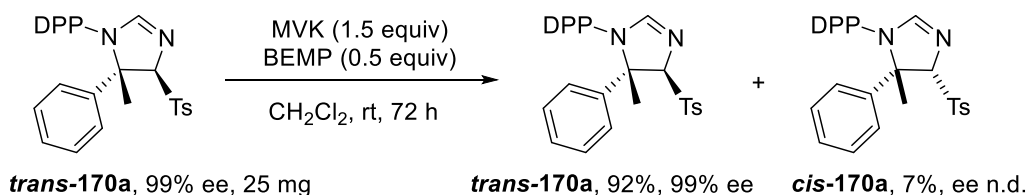
Since a deprotonation-alkylation sequence at C-4 could not be achieved using strong inorganic bases, we next attempted to functionalise the C-4 position by organocatalysed Michael additions. Although such reactions on imidazolines were not preceded in the literature, we were encouraged by a report on the tetramethylguanidine-catalysed Michael addition of thiazoline **193** to methyl vinyl ketone (Scheme 47).¹⁹¹



Scheme 47 Organocatalysed Michael addition of thiazoline **193**.

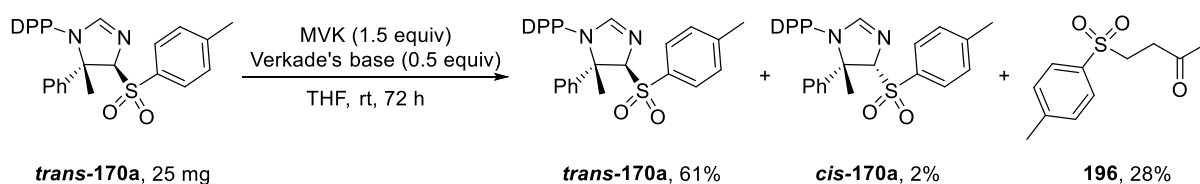
We therefore tested a series of organic bases with the aim of deprotonating the C-4 position and then performing a Michael addition with methyl vinyl ketone (MVK). When the reaction between **170a** and MVK was carried out with 20 mol% TMG (pK_{BH^+} 23.7 in CH_3CN)¹⁹² or DBU (pK_{BH^+} 23.9 in CH_3CN),¹⁹² no reaction was observed. In the presence of a stronger base

such as BEMP (pK_{BH^+} 27.6 in CH_3CN)¹⁹² the product was found to epimerise at the C-4 position: 92% of the starting material (**trans-170a**) was recovered with unchanged ee (99%) and 7% of **cis-170a** was isolated (Scheme 48). This result suggests that deprotonation at C-4 by strong organic bases is feasible, however either the following Michael addition does not take place or the addition product, being unstable, undergoes a fast retro-Michael reaction.



Scheme 48 Attempted BEMP-catalysed Michael addition between **170a** and methyl vinyl ketone.

It was thus decided to test the performance of the even more basic Verkade's base ($pK_{BH^+} \sim 33$ in CH_3CN).¹⁶³ In this case the unexpected side product β -tosyl ketone **196** formed in 28% yield, alongside *trans* and *cis* isomers of the starting material (Scheme 49). A reasonable explanation for the formation of **196** involves expulsion of the sulfinate anion as a leaving group from imidazoline **170a** (or a derivative thereof). The latter then performs a Michael addition to MVK. After expulsion of the sulfinate, the imidazoline likely decomposed to smaller fragments which was not possible to recover.



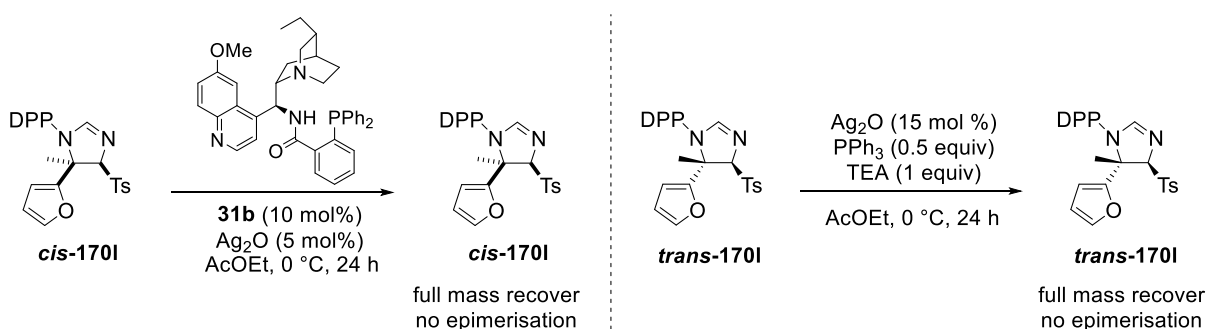
Scheme 49 Unexpected reaction of **170a** with MVK in the presence of Verkade's base.

4.6 Mechanistic Investigations

4.6.1 Additional Experiments

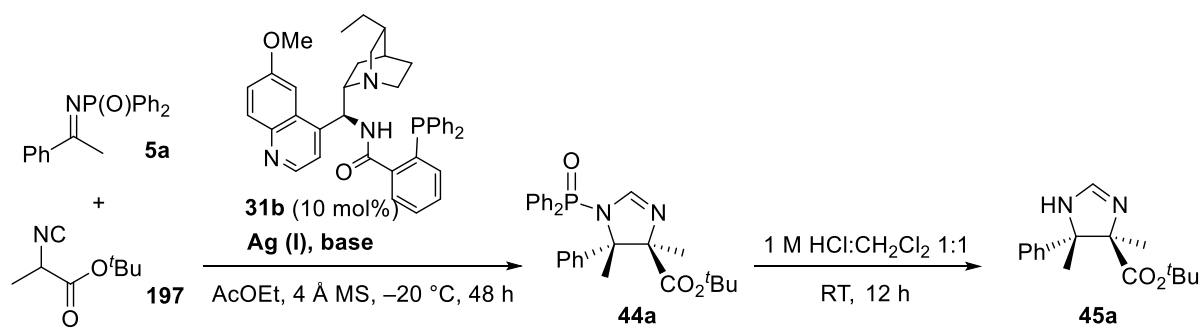
Given that a retro-Mannich reaction of imidazoline **170a** was found to take place when using LDA, and since in the enantioselective reactions a very high *trans*:*cis* dr for the crude product was observed (from 90:10 to >99:1, always higher than the dr obtained in the synthesis of the

racemic imidazolines), the reversibility of the reaction under standard conditions was studied. Experiments were run on isolated **cis-170I** and **trans-170I** under the standard enantioselective and non-enantioselective reaction conditions, respectively (Scheme 50). In both cases, no epimerisation of the imidazoline occurred, indicating that, once the product had been formed, the reaction was not reversible. This experiment, however, cannot determine whether the enhancement of diastereoselectivity in the enantioselective reaction is due to the presence of an equilibrium (reversible step) between *trans* and *cis* reaction intermediates (see Section 4.6.4) or to the inherent selectivity of the chiral ligand.



Scheme 50 Epimerisation experiments on **cis-170I** and **trans-170I**.

X-Ray and NMR studies previously performed in the group showed that ligand **31b** acts as a bidentate *N,P*-ligand for Ag(I) (see Section 1.3.3), hence the quinuclidine N atom is not available to act as a Brønsted base. With the aim of determining which component of the catalytic system was responsible for the deprotonation of the isocyanide pronucleophiles, we performed some studies with AgOAc investigating the roles of the silver(I) cation and its counterion. However, given that the undesired dimerisation of TosMIC consumes the pronucleophile and is faster when AgOAc is used instead of Ag_2O (see Section 4.3), we needed to switch to a different isocyanide to investigate the effect of the base without interference due to pronucleophile dimerisation. The Mannich reaction between α -substituted isocyanoacetate **197** and *N*-DPP ketimine **5a** was therefore chosen as a model system (Table 9, see also Scheme 17 in Section 1.3.2).¹¹²



Entry	Ag(I) (mol%)	Base (mol%)	Yield ^a (%)	Ee ^a (%)
1	AgOAc (5)	-	90	89
2	AgSbF ₆ (5)	-	<5	-
3	AgSbF ₆ (5)	ⁿ Bu ₄ NOAc (5)	84	89
4	AgSbF ₆ (5)	NaOAc (5)	19	90
5	AgSbF ₆ (5)	CsOAc (5)	17	90
6	-	ⁿ Bu ₄ NOAc (5)	<5	-

Table 9 Ag(I) and base combinations in the Mannich reaction between **5a** and **197**. ^a Yield over two steps and ee given for deprotected imidazoline **45a**.

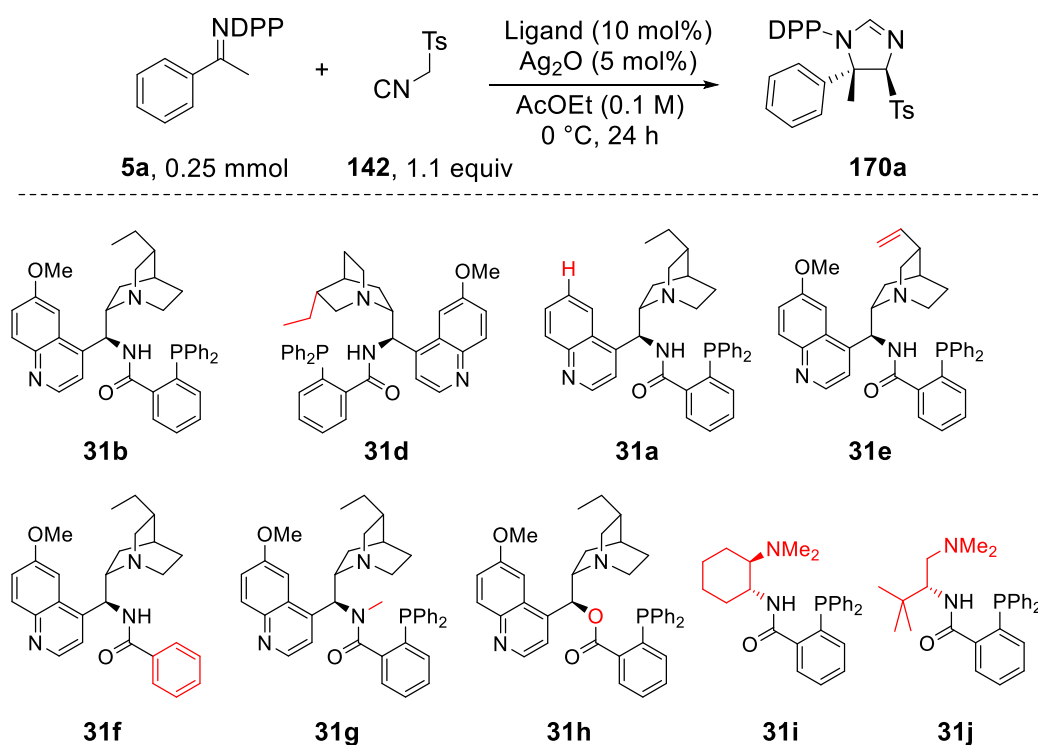
When the reaction was run using 10 mol% ligand **31b** and 5 mol% AgOAc, the deprotected imidazoline **45a** was obtained in 89% ee with a 90% yield over two steps (entry 1). If the highly effective silver acetate was replaced by AgSbF₆, that has a non basic counterion, product formation was suppressed (entry 2). However, both reactivity and enantioselectivity were restored upon addition of a soluble acetate source, namely tetrabutylammonium acetate (entry 3). A control reaction confirmed that tetrabutylammonium acetate alone could not promote the reaction in the absence of silver (entry 6), implying that the acidity of the α -position is greatly enhanced by coordination of the isocyanide to Ag(I), as confirmed by NMR studies with isocyanoacetate pronucleophiles (see Section 1.3.3). Overall, these results suggest that the basic Ag(I) counterion is the Brønsted base of our catalytic system.

4.6.2 Screen of Ligands

In order to gain some insight into the importance of the functional groups present on amino phosphine **31**, ligands with structural variations were screened in the reaction between *N*-DPP ketimine **5a** and TosMIC under the optimised conditions (Table 10).^{xii}

While quinine-derived aminophosphine **31b** gave product **170a** in 98% yield and 96% ee (entry 1), the pseudoenantiomeric ligand **31d** derived from quinidine afforded **ent-170a** in 91% yield and 91% ee (entry 2). Both cinchonidine-derived **31a**, lacking the methoxy group, and quinine-derived **31e** with a non-hydrogenated side chain showed slightly lower reactivity and enantioselectivity (entries 3 and 4). Ligand **31f** devoid of the phosphine moiety delivered the product in only 8% yield and in racemic form (entry 5), and the addition of 10 mol% exogenous triphenylphosphine did not improve its performance significantly (entry 6). This result indicates the importance of the use of a bidentate *N,P*-ligand for reactivity and stereocontrol. Aminophosphine **31g** with a methylated amido linker promoted the reaction with diminished reactivity, and lower diastereo- and enantioselectivity (61% conversion, 83:17 dr, 88% ee, entry 7), suggesting that the NH of the linker plays an important role in the reaction.

^{xii} Small samples of ligands **31a**, **31d**, **31e**, **31g**, **31i** and **31j** were kindly donated by members of the Dixon group (Dr Irene Ortín, Dr Ruben Manzano and Dr Adam D. Gammack Yamagata).



Entry	Ligand	Conversion ^a (%)	Dr ^a (<i>trans</i> : <i>cis</i>)	Yield ^b (%)	Ee ^b (%)
1	31b	100	> 99:1	98	96
2	31d	100	> 99:1	91	−91
3	31a	96	> 99:1	88	92
4	31e	81	99:1	70	93
5	31f	24	33:67	8	0
6 ^c	31f	53	68:32	34	−6
7	31g	61	83:17	51	88
8	31h	54	91:9	50	−90
9	31i	83	97:3	80	92
10	31j	6	1:2	n.d.	n.d.

Table 10 Ligand screen in the catalytic enantioselective reaction between **5a** and TosMIC. ^a Determined by ¹H NMR analysis of the crude reaction mixture. ^b For the isolated *trans* diastereomer. ^c With 10 mol% PPh₃.

Surprisingly, ligand **31h** possessing an ester linker afforded the enantiomeric product **ent-170a** in 50% yield with 90% ee (entry 8); replacement of the NH group by an O atom decreased the reactivity and imparted a switch in the enantiofacial selectivity for both reaction partners. Following crystallisation in ethyl acetate, we were able to obtain single crystal X-ray structures for dihydroquinidine-derived amino phosphines **31b** and **31f** with an amido and an ester linker,

respectively (Figure 21). In the solid phase, the two ligands adopt nearly identical structures; nevertheless, the corresponding Ag(I) complexes may have very dissimilar conformations in solution, or the activation mode of electrophile and nucleophile, hence their position in the transition state, may change significantly. It is reasonable to imagine that the NH of the amido linker is involved in the enantiodetermining step, possibly acting as a H-bond donor (see Section 4.6.4). Finally, amino phosphine ligands with a non-cinchona backbone were tested. Ligand **31i** with a *trans*-1,4-diaminocyclohexane scaffold performed well, affording the product in 80% yield and 92% ee (entry 9), while the more flexible **31j** derived from *tert*-leucine showed very poor reactivity (entry 10).

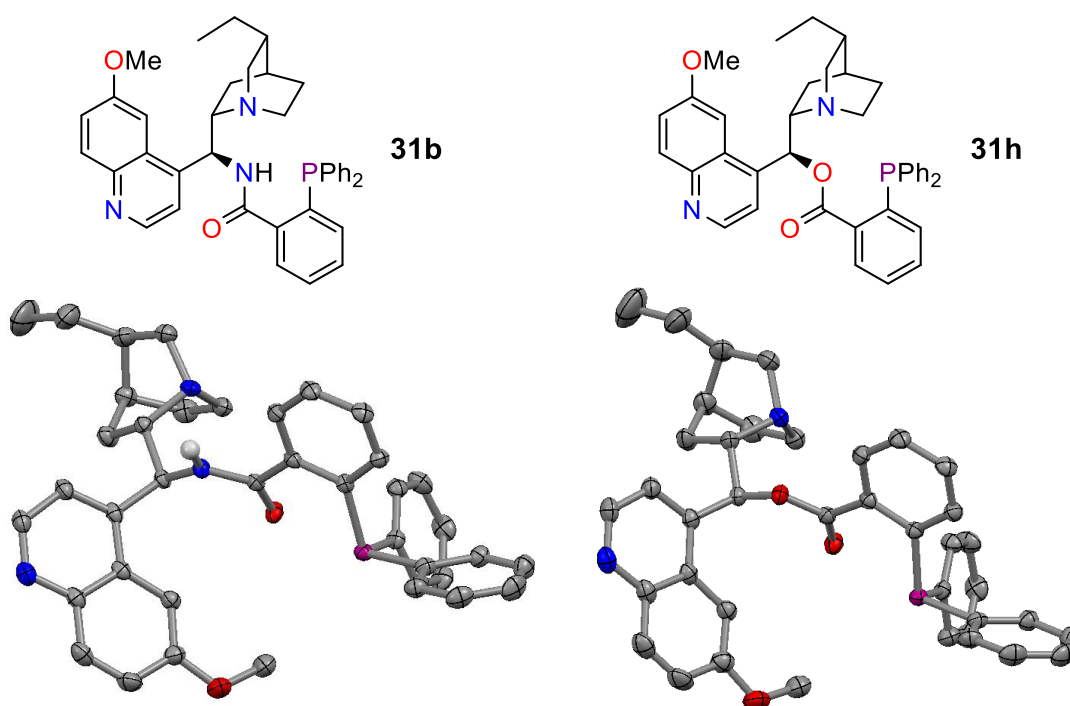


Figure 21 Single crystal X-Ray structures for amido ligand **31b** and ester ligand **31h**. ORTEP diagrams with ellipsoids at 50% probability. H atoms omitted for clarity.

4.6.3 NMR Studies

We next performed low temperature NMR experiments with TosMIC to study the behaviour of this pronucleophile in the presence of complex [Ag(OAc)(**31b**)] (Figure 22). While previous studies showed that methyl isocyanoacetate coordinates to the silver complex (see Section

1.3.3),¹¹² upon addition of TosMIC to a solution of complex $[\text{Ag}(\text{OAc})(\mathbf{31b})]$, no AB system for the two methylenic protons was detected. Instead both TosMIC (δ 4.64 ppm for the methylenic protons) and its dimer **171** (δ 5.15 ppm for the methylenic protons) were observed (blue trace), and within 2 hours all the residual TosMIC converted to the dimer (green trace).

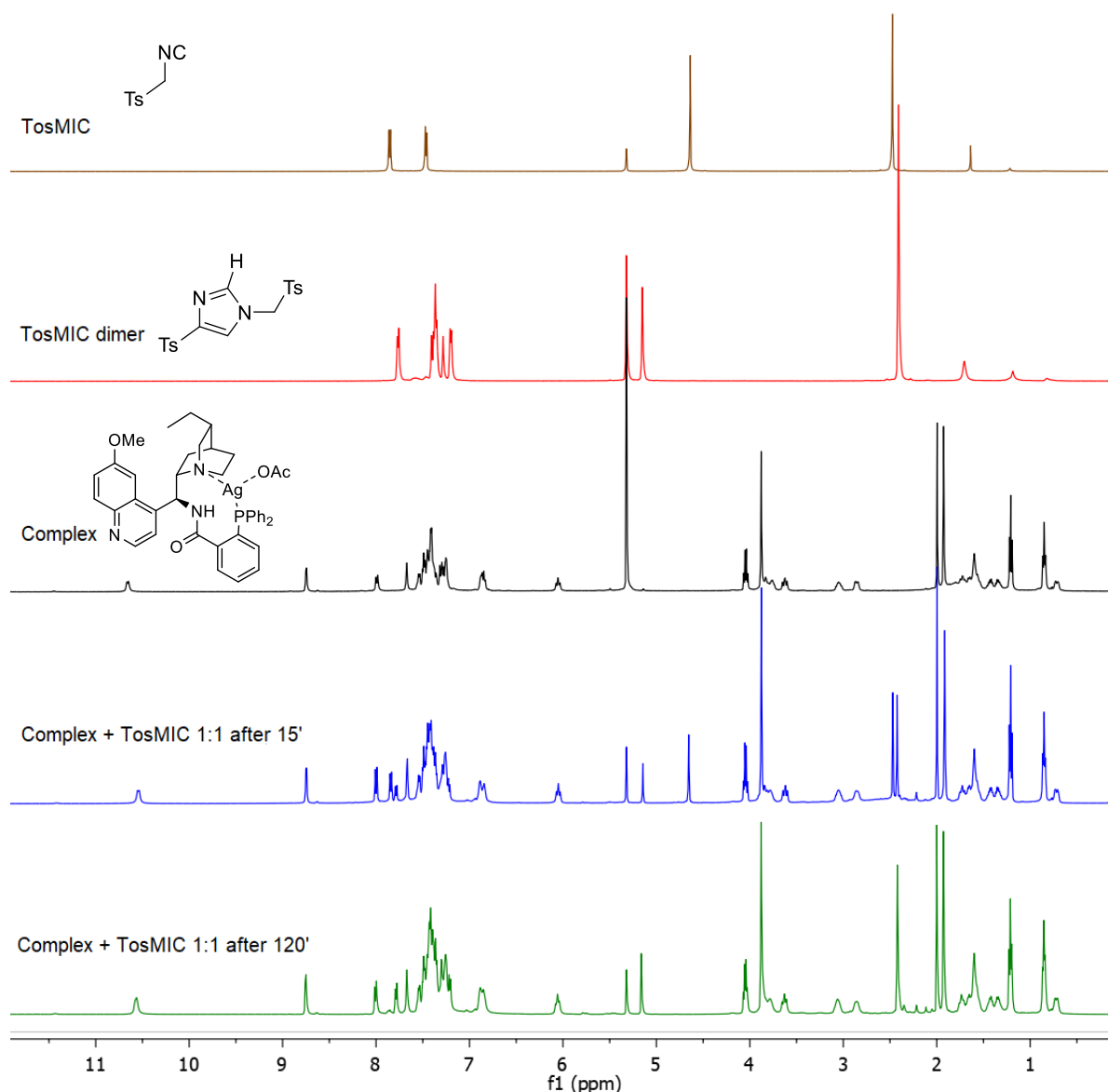


Figure 22 ^1H NMR experiments in CD_2Cl_2 at 253 K. From top to bottom ^1H NMR spectra of different samples: TosMIC (red); TosMIC dimer **171** (brown); $[\text{Ag}(\text{OAc})(\mathbf{31b})]$ complex 0.02 M (black); $[\text{Ag}(\text{OAc})(\mathbf{31b})]$ complex + TosMIC 1:1 15 minutes after the addition of TosMIC (blue); $[\text{Ag}(\text{OAc})(\mathbf{31b})]$ complex + TosMIC 1:1 2 hours after the addition of TosMIC (green).

Dimerisation of TosMIC under the conditions of the NMR experiment is accelerated by the 1:1 stoichiometry between TosMIC and silver acetate.^{xiii} We suppose that, after coordination of the isocyanide to Ag(I), deprotonation and subsequent dimerisation take place so fast that intermediates are too short-lived, and possibly too low in concentration, to be observed by NMR. Additional experiments where acetophenone-derived *N*-DPP ketimine and complex [Ag(OAc)(**31b**)] were mixed together showed no interactions between the two entities: the ¹H and ³¹P NMR spectra of the mixture was unchanged with respect to the spectra of the single components.

4.6.4 Mechanism and Stereochemical Model

In light of the experimental information gathered so far and of the studies performed in the group on aldol and Mannich reactions of isocyanoacetates (see Section 1.3), we propose the following catalytic cycle for the reaction between *N*-DPP ketimine **5a** and TosMIC **142** catalysed by Ag₂O and amino phosphine **31b** (Figure 23). We suppose that the soluble fraction of basic silver oxide (calculated $pK_{BH^+} = 24.2$ in DMSO, compare with a calculated $pK_{BH^+} = 3.3$ for AgOAc under the same conditions)¹⁹³ installs an acid/base equilibrium with TosMIC (estimated $pK_a \sim 13$ in DMSO),^{xiv} thus deprotonating the pronucleophile. The TosMIC anion coordinates to Ag (I), which is chelated by aminophosphine ligand **31b** as well, affording complex **I**. Ketimine **5a** enters the catalytic cycle and coordinates to the ligand, being activated and positioned by H-bond with the amide NH group (intermediate **II**). At this point the enantiodetermining step takes place, with the deprotonated isonitrile attacking the imine C atom

^{xiii} It was not possible to perform NMR experiments with Ag₂O due to the very low solubility.

^{xiv} Data for isocyanides are not available; pK_a values in DMSO for NCCH₂SO₂Ph (12.0), MeC(O)CH₂SO₂Ph (12.5) and CH₃SO₂Ph (29.0) can be used for the sake of comparison.

(step **II**→**III**, possibly reversible). Ring closure and protonolysis of the Ag-bound imidazoline **IV** by TosMIC releases the product and regenerates the active species **I**.

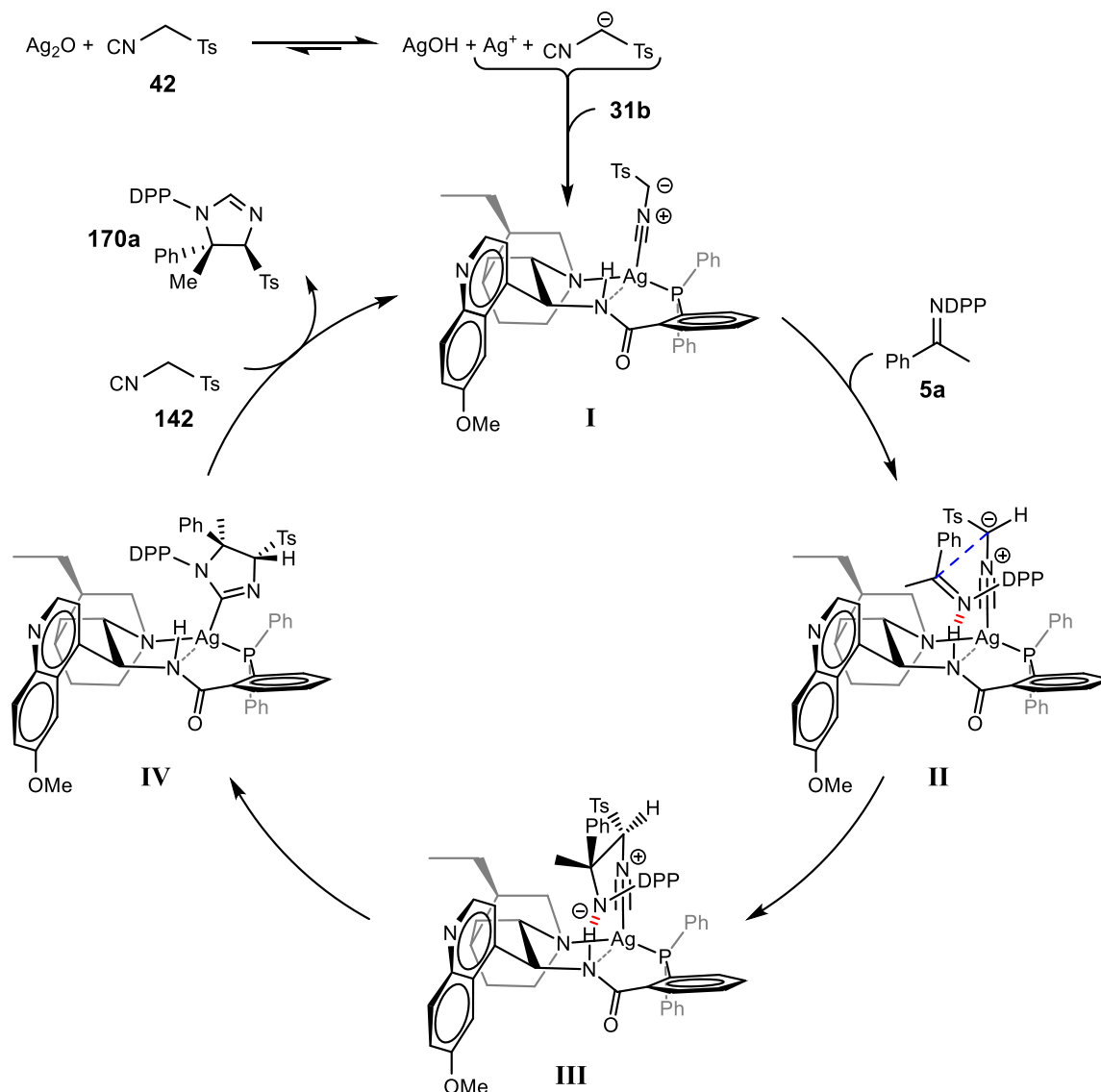


Figure 23 Proposed mechanism for the reaction between TosMIC and ketimine **5a** catalysed by Ag_2O and amino phosphine **31b**.

Our proposed stereochemical model, depicted in Figure 24, is based on the assumption that the conformation of the silver complex in solution is close to the one observed in the solid state, which is reasonable in light of the NMR studies (see Section 1.3.3).¹¹² As *N*-DPP ketimines exist as a mixture of *E* and *Z* stereoisomers rapidly interconverting at room temperature (see

Section 1.1.3),⁴⁸ the reaction is controlled by the Curtin–Hammett principle, provided that it is irreversible. On the basis of steric grounds, we hypothesised that the *Z*-configured ketimine is the reactive isomer. It is positioned and activated by H-bonding with the amido group on the ligand. The DPP group would occupy a relatively empty portion of space where the two phenyl substituents can be easily accommodated, given the free rotation about the N–P and P–C_{sp2} bonds. It is plausible that they are oriented so that π – π stacking interactions or C–H/ π (point to face) interactions with the three aromatic rings of the triarylphosphine moiety of the ligand take place; however, it is not possible to determine it with certainty without a computational analysis. Importantly, with the DPP substituent and the phenyl group both oriented away from the ligand backbone, the transition state would be able to accommodate methyl ketimines with bulky and long aliphatic groups (*e.g.* cyclohexyl and phenethyl). On the other side, the space available for the methyl group of the ketimine would be limited, and this fits well with the experimental finding that an isobutyl substituent is not tolerated, while a linear *n*-propyl chain still is (see Figure 19, substrate scope).

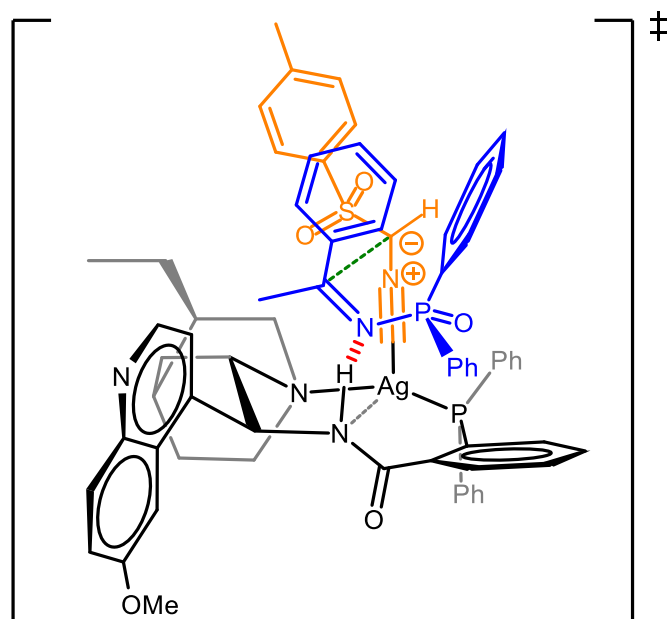


Figure 24 Proposed stereochemical model for the reaction between acetophenone-derived N-DPP ketimine and TosMIC.

The nucleophile, coordinated to Ag through the terminal isocyanide C atom, orients the tosyl substituent away from the *N*-DPP group for steric reasons and possibly because of a weak electrostatic interaction with the partial positive charge developed on the quinuclidine N atom upon coordination to Ag(I). The dipole moments associated with the C=N bond of the ketimine and C–S bond of the isocyanide would also have a favourable opposite orientation.

When the nucleophile and electrophile lie in a staggered conformation in roughly parallel planes, attack from the *Si* face of the nucleophile to the *Re* face of the ketimine along the green dotted line would deliver the imidazoline with the observed relative and absolute stereochemical configuration (Figure 24).

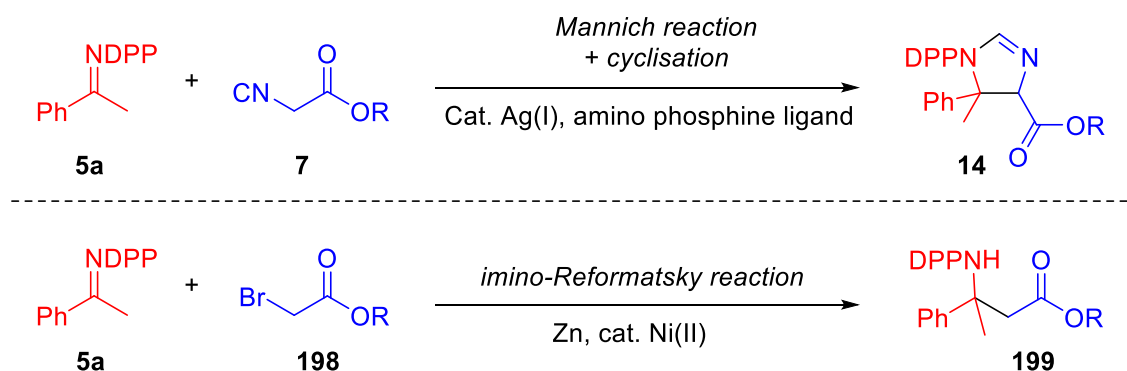
4.7 Conclusions

We successfully extended the scope of the Ag(I)/amino phosphine catalytic system to another class of activated isocyanides, realising the first enantioselective Mannich addition of *p*-toluenesulfonylmethyl isocyanide (TosMIC) to *N*-DPP ketimines. The reaction, catalysed by silver oxide and a dihydroquinine-derived *N,P*-ligand, afforded 2-imidazolines bearing two contiguous stereocentres with high yields and excellent diastereo- and enantiocontrol. The transformation was broad in scope, encompassing several (hetero)aromatic and aliphatic ketimines, operationally simple and scalable. Derivatisation of the products was carried out to provide enantioenriched vicinal diamines, precursors to NHC ligands and sp^3 -rich heterocyclic scaffolds such as 2,5-dihydropyrazine. A mechanism and a stereochemical model were proposed to rationalise the experimental findings.

5 Reformatsky Reaction of *N*-DPP Ketimines

5.1 Chapter Overview

In this chapter the development of a Ni-catalysed ketimino-Reformatsky reaction is described as an efficient method for the synthesis of amines bearing a fully substituted stereocentre at the α -position. To this end, while previous work done in the Dixon group on catalytic additions to *N*-DPP ketimines focused on Mannich reactions isocyanoacetates and TosMIC (Chapter 4), in line with the aims of the thesis we were keen to explore new reactivity, and investigated α -bromoacetate esters as pronucleophiles (Scheme 51). Attempts to devise an enantioselective variant of the ketimino-Reformatsky reaction will also be presented.



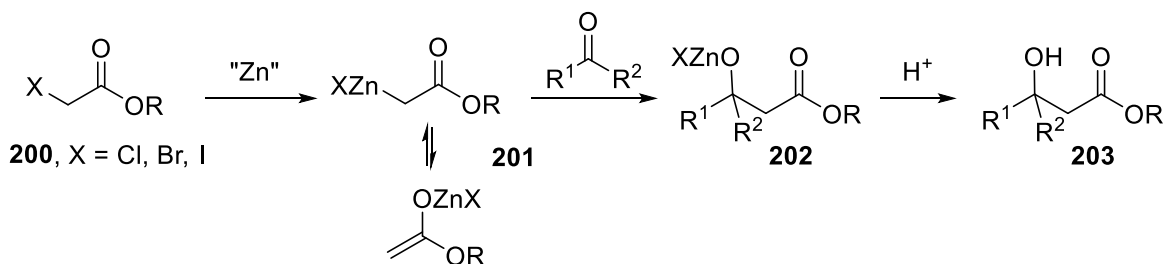
Scheme 51 Addition of enolates to ketimines for the preparation of amines bearing a fully substituted stereocentre in the α -position.

5.2 Introduction

5.2.1 Introduction to the Reformatsky Reaction

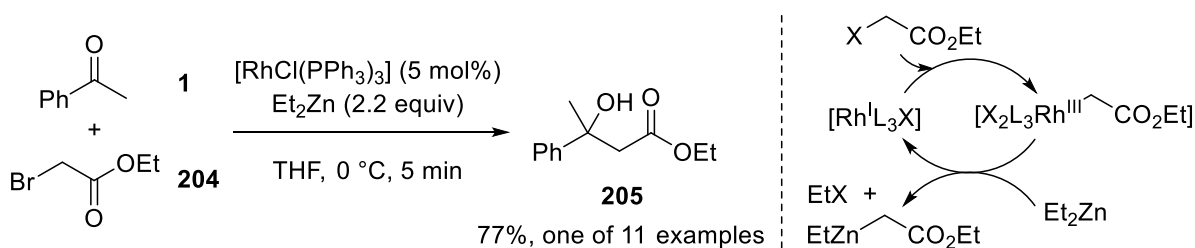
The classical Reformatsky reaction, discovered in 1887,¹⁹⁴ concerned the zinc-induced formation of β -hydroxyesters from α -haloacetate esters and aldehydes or ketones, *via* so-called Reformatsky enolates **201** (Scheme 52).¹² Nowadays, a broader definition encompasses all transformations that involve metal insertion into activated C–halogen bonds, followed by

addition to electrophiles;¹⁹⁵ instead of zinc, metals such as Cr, In, Ge, Sn, Ce and Sm have been used for the purpose,¹⁹⁶ and the reaction could also be performed electrochemically.¹⁹⁷



Scheme 52 The classical Reformatsky reaction.

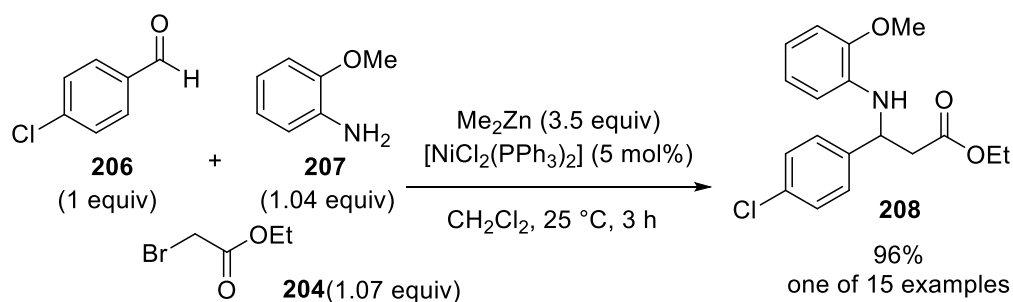
In order for the Reformatsky enolate to form, the zinc needs to be activated, by removing the surface layer of oxide and/or finely distributing the metal. Among the most commonly used additives are trichloromethylsilane, iodine and copper(I) halides;¹⁹⁵ other common forms of activated zinc are the copper-zinc couple¹⁹⁸ and Rieke zinc,¹⁹⁹ prepared by reduction of ZnCl₂ by alkali metals. The group of Knochel has introduced several valuable protocols for the preparation of soluble organozinc reagents,²⁰⁰ for instance from aromatic and aliphatic halides using Zn and LiCl,^{201,202} and by Et₂Zn-mediated halogen-zinc exchange in the presence of catalytic Cu(I), Pd(II), Mn(II) and Ni(II) salts.²⁰³ Another contribution was made in 2000 by Honda and co-workers, who employed Et₂Zn and 5 mol% Wilkinson's catalyst to develop a homogenous Reformatsky reaction between α-bromoesters and aldehydes or ketones (Scheme 53).²⁰⁴ The authors proposed the formation of the Zn enolate *via* transmetalation of a Rh(III) enolate, initially formed by oxidative addition of [RhCl(PPh₃)₃] to ethyl bromoacetate **204**.



Scheme 53 Honda's homogeneous Reformatsky reaction using Wilkinson's catalyst.

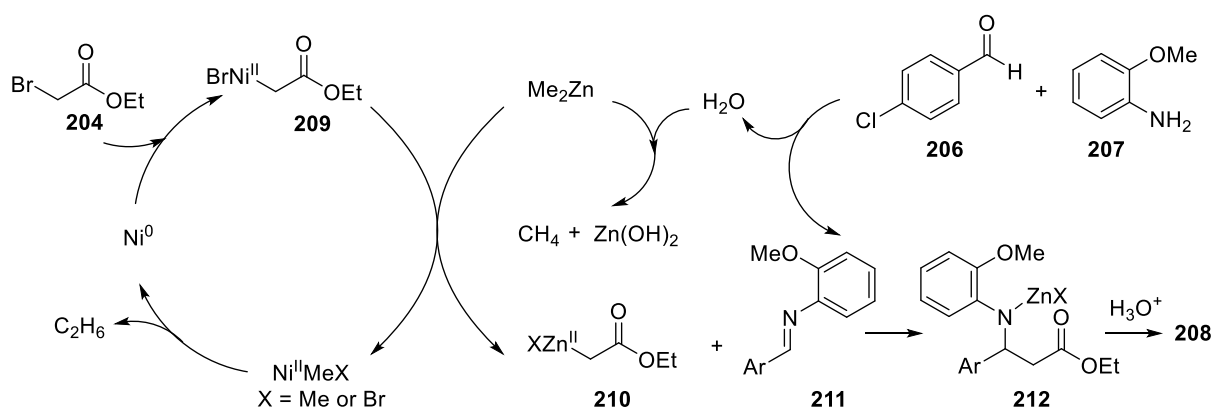
5.2.2 The Imino-Reformatsky Reaction

Imines are suitable substrates for the Reformatsky reaction, as first described by Gilman more than 70 years ago.²⁰⁵ Although the reaction holds great potential for the synthesis of β -amino esters, its utility has been limited by β -lactamisation of the products leading to a mixture of compounds and proceeding presumably *via* a Zn amide intermediate (see the analogous zinc alkoxide intermediate **202**).²⁰⁶ In 1999 this drawback was solved by Adrian and co-workers by the use of imines derived from 2-methoxyaniline. On the basis of experimental comparisons, the authors conclude that the electron-withdrawing inductive effect exerted by the methoxy group in the *ortho* position, which dominates over the mesomeric effect, decreases the nucleophilicity of the N atom in the β -amido ester intermediate, thus preventing the undesired β -lactamisation.²⁰⁶ A few years later, the same group reported a practical three-component imino-Reformatsky reaction catalysed by $[\text{NiCl}_2(\text{PPh}_3)_2]$ (Scheme 54).²⁰⁷



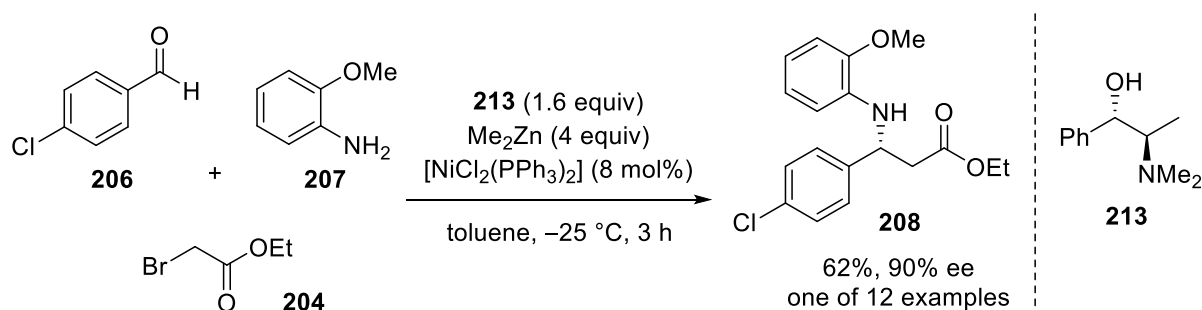
Scheme 54 Ni-catalysed three-component imino-Reformatsky reaction.

The authors proposed a Ni(0)/Ni(II) catalytic cycle involving the formation of a Ni(II) enolate by oxidative addition, followed by transmetallation to Zn(II) and subsequent attack of the reactive Reformatsky to the *in situ* formed aldimine (Scheme 55). The excess dimethylzinc was suggested to play a role also as a dehydrating agent for imine condensation.



Scheme 55 Proposed mechanism for the three-component Ni-catalysed imino-Reformatsky reaction.

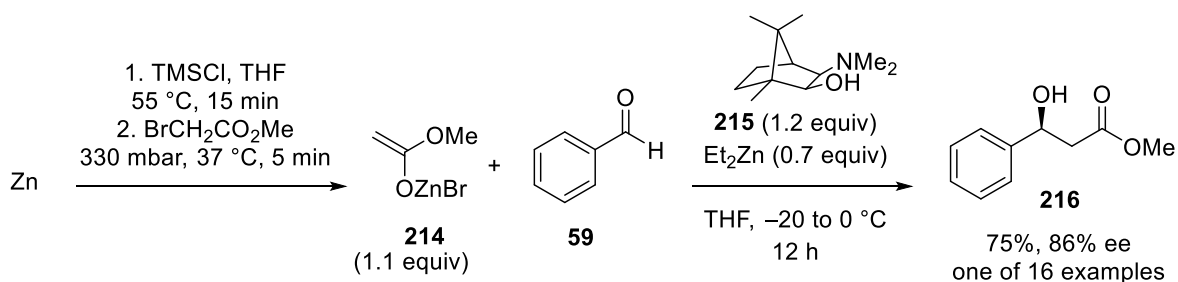
This report was the inspiration behind Cozzi's work on the ligand-mediated enantioselective Reformatsky reaction of *in situ* formed aldimines (Scheme 56).²⁰⁸ The authors used excess dimethylzinc, 1.6 equivalents of ligand *N*-methylephedrine **213** and substoichiometric amounts of $[\text{NiCl}_2(\text{PPh}_3)_2]$ as the catalyst.



Scheme 56 Cozzi's *N*-methylephedrine-mediated enantioselective imino-Reformatsky reaction.

5.2.3 Catalytic Enantioselective (Imino)-Reformatsky Reactions

Several examples of diastereoselective Reformatsky reactions have been reported,^{195,200} as well as variants with chiral auxiliaries.²⁰⁹ Nevertheless, the development of enantioselective Reformatsky reactions has been hampered for more than a century by their heterogeneous nature. Enantioselective Reformatsky reactions mediated by stoichiometric chiral ligands have been described around 2005 by the groups of Cozzi²⁰⁸ (see Scheme 56) and Knochel (Scheme 57),²¹⁰ and only after the introduction of homogenous protocols for the generation of Reformatsky enolates from dialkylzinc reagents (see Section 5.2.1), were catalytic enantioselective variants discovered (Figure 25).^{211,212}



Scheme 57 Knochel's *N,N*-dimethylaminoisoborneol-mediated enantioselective Reformatsky reaction.

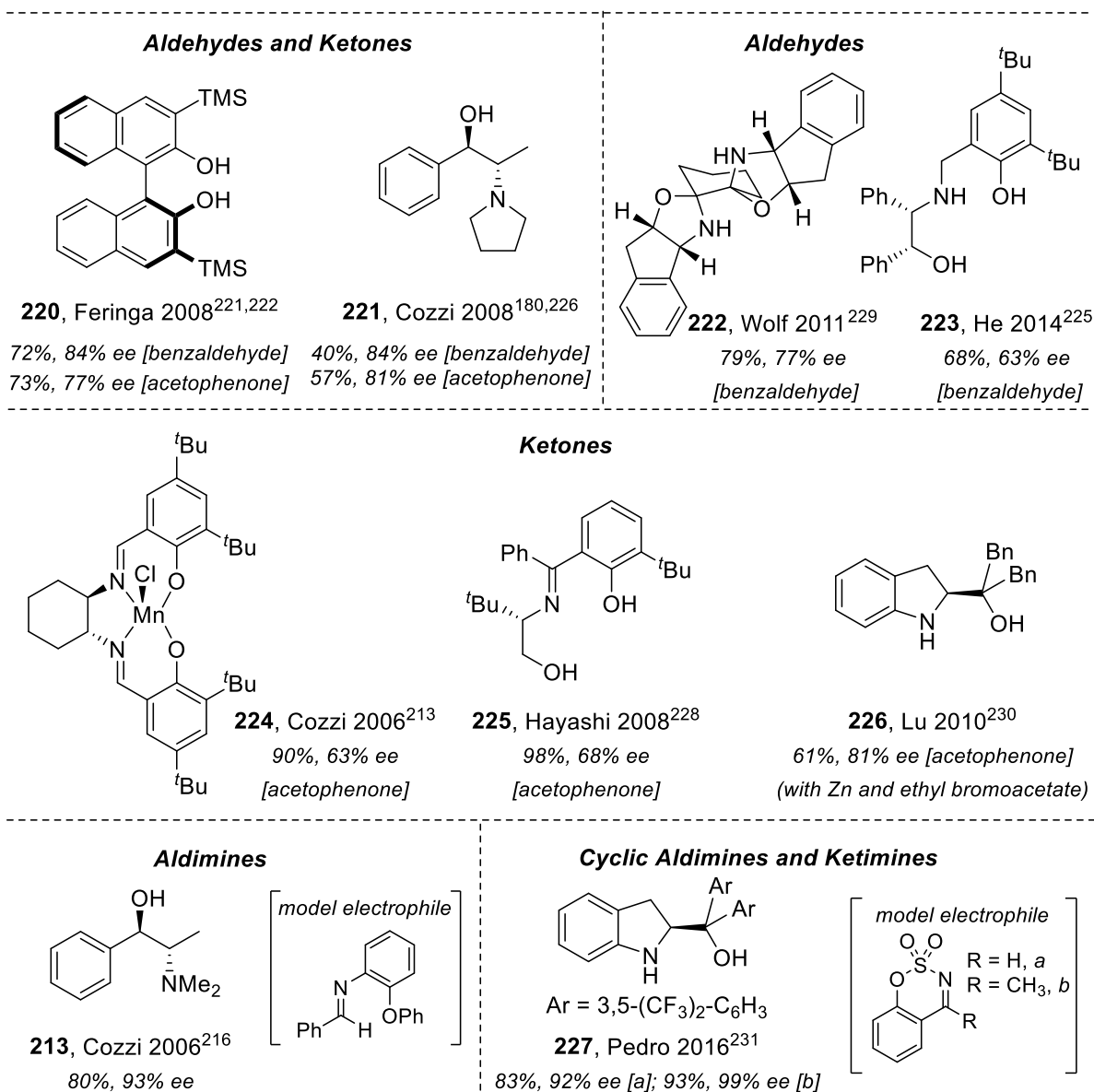
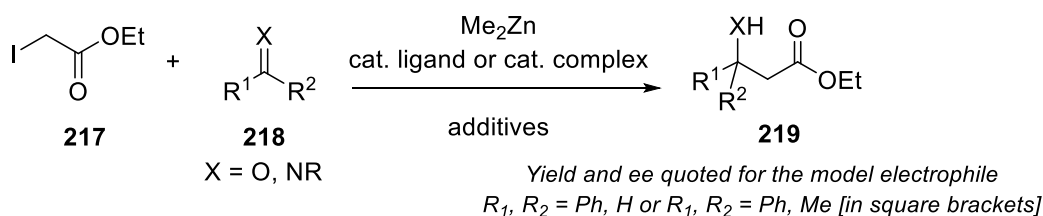
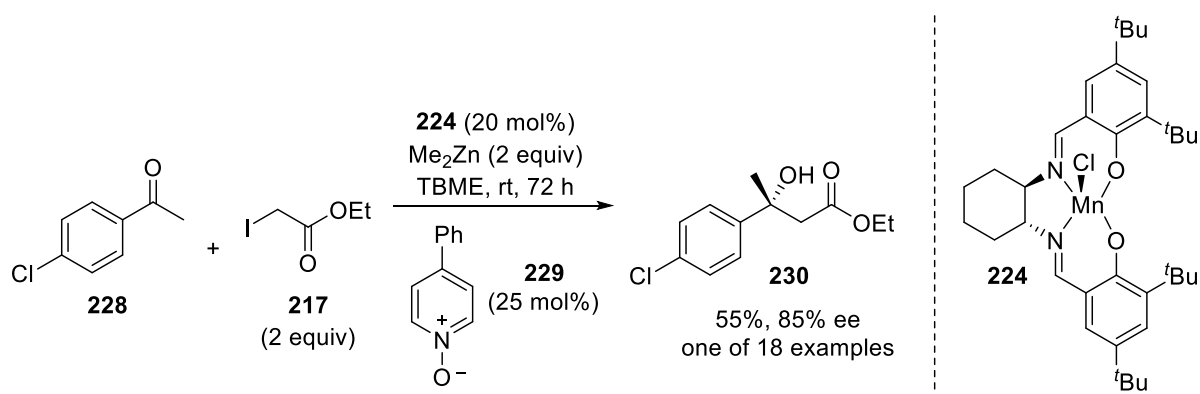


Figure 25 Synopsis of the ligands and complexes employed in catalytic enantioselective Reformatsky reactions.

Figure 25 offers an overview of all chiral ligands and complexes used so far in catalytic enantioselective Reformatsky reactions divided by substrate class. Yields and enantiomeric excesses for the reactions with the model electrophile (benzaldehyde, acetophenone or imines thereof) are also given. A quick glance reveals that most of the ligands are diols, amino alcohols or their derivatives, and that yields and levels of enantiocontrol are generally good but rarely excellent: in only one case yield and ee for the model product are both higher than 80%. All catalytic enantioselective reactions were carried out using excess dimethyl zinc and iodoacetate, except for the protocol developed by Lu,²³⁰ that involved the use of Zn powder and bromoacetate. Additives also play a crucial role in the successful development of these transformations, and below the most important examples are examined in detail.

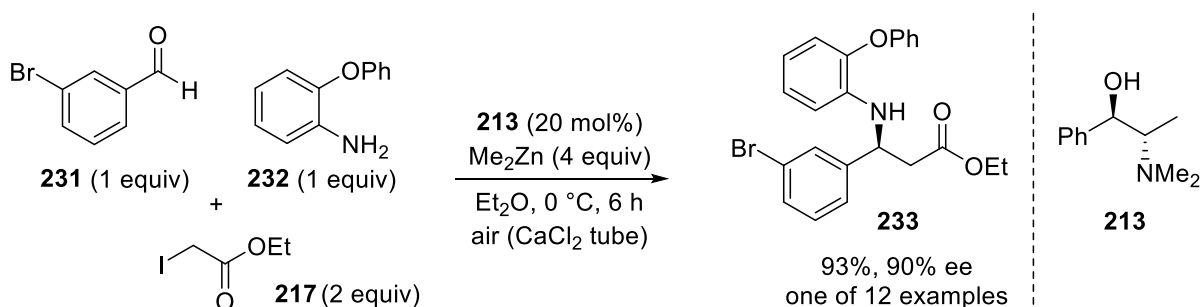
The first catalytic enantioselective Reformatsky reaction was reported by Cozzi in 2006 (Scheme 58).²¹³ Ketones were employed as electrophiles, with the aromatic ones affording the products in 45–75% yield and 63–86% ee. The Reformatsky enolate was generated from ethyl iodoacetate and dimethyl zinc, and [MnCl(salen)] complex **224** was used to impart enantioselectivity. Premixing the catalyst with pyridine *N*-oxide improved the enantiomeric excess at the expense of reactivity,²¹⁴ and the authors in hindsight postulated the involvement of radical species.²¹⁵



Scheme 58 Cozzi's catalytic enantioselective Reformatsky reaction of ketones.

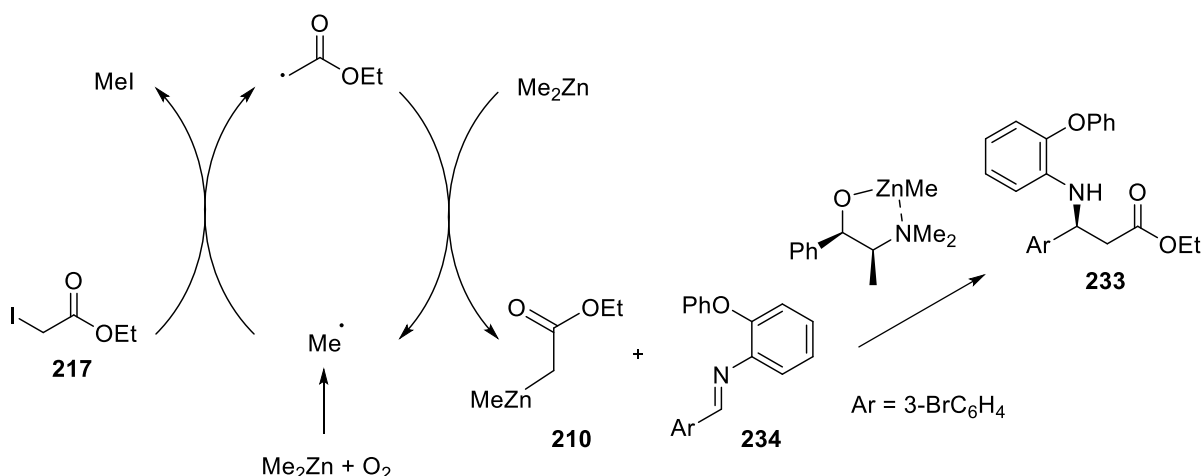
Building on his previous work with stoichiometric *N*-methyl ephedrine ligand (see Scheme 56),²⁰⁸ in 2006 Cozzi reported also the first catalytic enantioselective Reformatsky reaction of

aldimines (Scheme 59).²¹⁶ It is interesting to consider how the reaction conditions were modified to make the transformation catalytic: while the ligand was kept the same and only its loading was decreased, ethyl bromoacetate was replaced by iodoacetate, $[\text{NiCl}_2(\text{PPh}_3)_2]$ was removed and the reaction was performed under dry air using a CaCl_2 drying tube. Moreover, *o*-phenoxy aniline was used instead of *o*-methoxy aniline as it gave products with higher ee.



Scheme 59 Cozzi's catalytic enantioselective Reformatsky reaction of aldimines.

In the proposed mechanism (Scheme 60), the reaction between dimethylzinc and oxygen²¹⁷ generates a methyl radical, observed by EPR radical trapping experiments,²¹⁸ presumably via Zn peroxo species.^{219,220} The methyl radical abstracts the iodine atom from ethyl iodoacetate, and the resulting radical reacts with dimethylzinc to afford the Reformatsky enolate, regenerating the methyl radical.

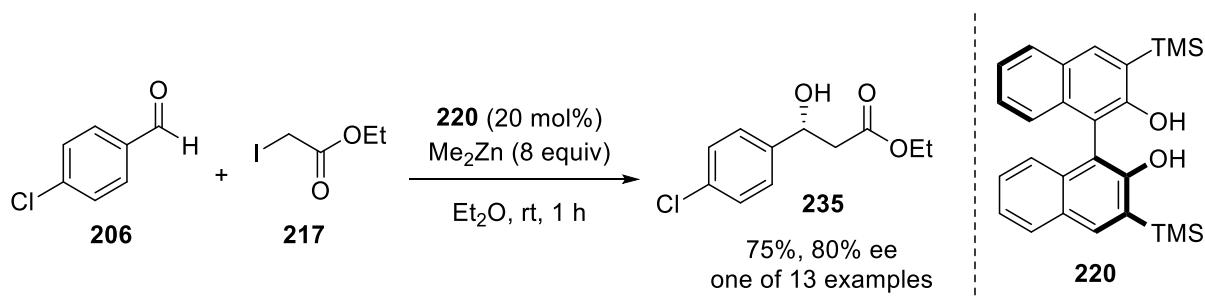


Scheme 60 Proposed catalytic cycle for Cozzi's catalytic enantioselective imino-Reformatsky reaction.

Because of their higher reactivity, aldehydes were more challenging substrates and their first enantioselective Reformatsky reaction was disclosed in 2008 by the laboratory of Feringa.²²¹

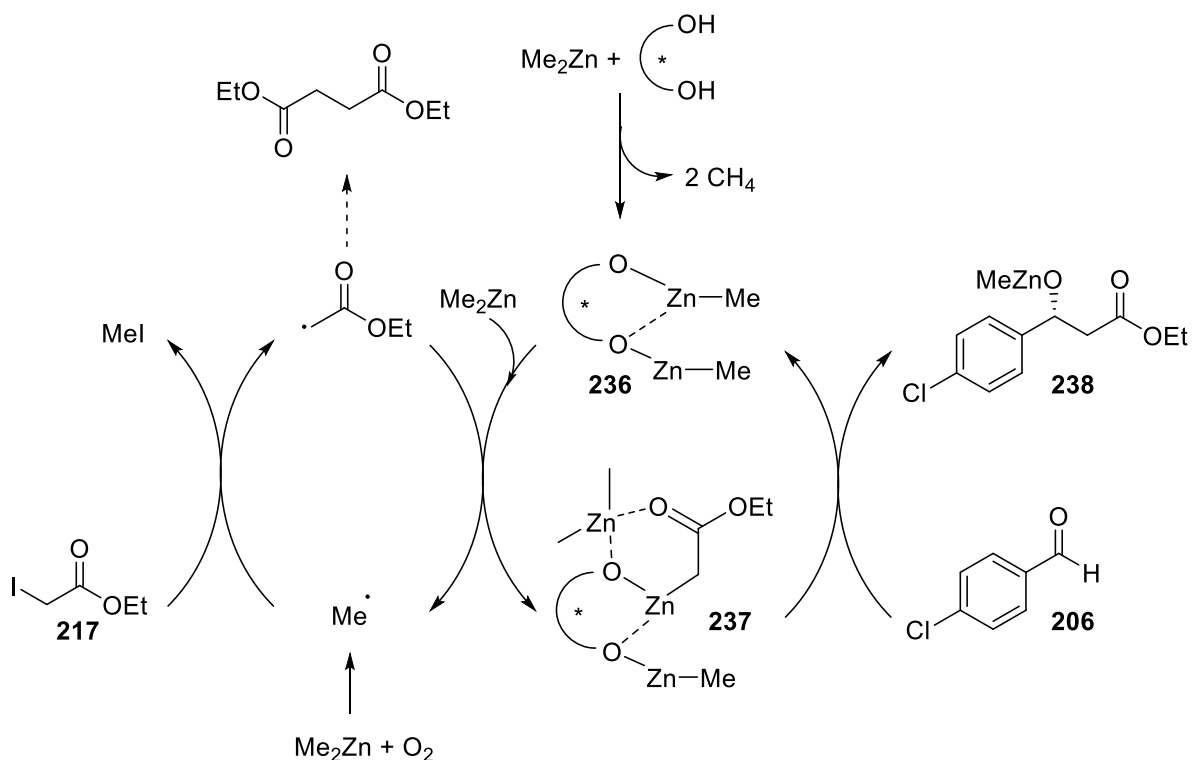
BINOL derivative 220 was employed in the Me_2Zn -promoted reaction between ethyl

iodoacetate and aromatic aldehydes with good yield (60–87%) and enantioselectivity (54–84% ee, Scheme 61).



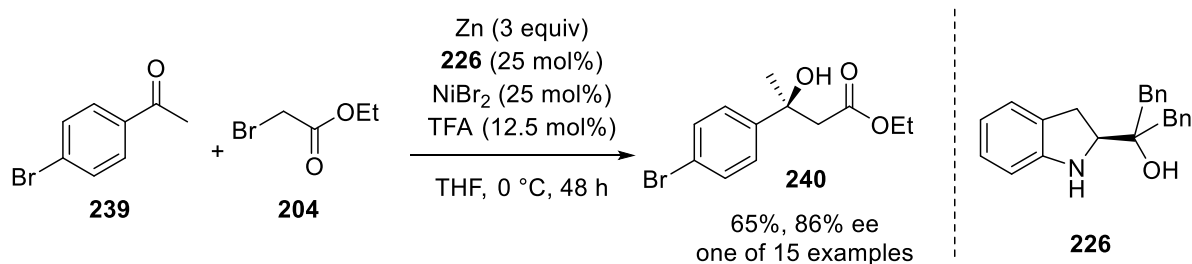
Scheme 61 Feringa's catalytic enantioselective Reformatsky reaction of aldehydes.

The same catalytic system was found to be effective also with aromatic and rigid aliphatic ketones (such as 2,2-dimethylcyclopentanone).^{222,223} Slow addition of the electrophile to the reaction mixture was required to suppress the non-catalysed reaction and the presence of air was crucial to obtain good levels of conversion. The authors proposed a mechanism in line with Cozzi's one, where the Reformatsky enolate is formed *via* a radical cycle (Scheme 62). The enolate then reacts with the binuclear chiral Zn complex **236**, which is reminiscent of the dimeric Zn-amino alkoxide species studied in detail by Noyori for the enantioselective addition of dialkylzinc reagents to aldehydes.²²⁴ The resultant chiral Zn enolate **237** reacts stereoselectively with the aldehyde to afford **238**. Under a slow rate of electrophile addition, diethyl succinate, likely formed in a termination step, was detected by GC.



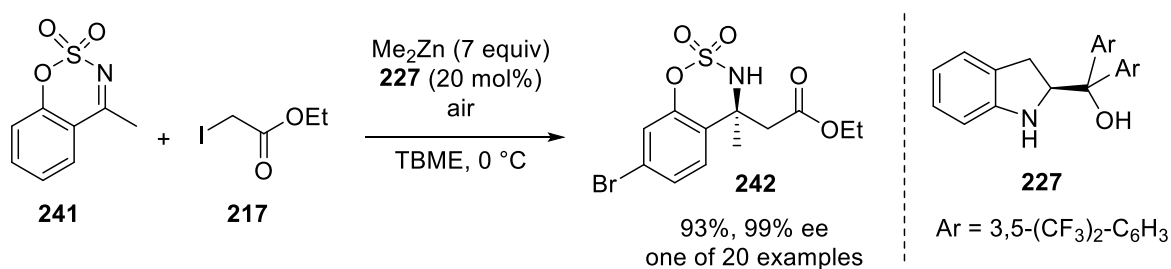
Scheme 62 Proposed mechanism for Feringa's enantioselective Reformatsky reaction.

The other protocols for enantioselective Reformatsky reactions are based on similar mechanisms, and differ from the works discussed above only in the structure of the ligand (see Figure 25) and/or the choice of the radical initiator.²²⁵ Cozzi and co-workers studied the use of a variety of oxidants for Reformatsky reactions of aldehydes and ketones,¹⁸⁰ eventually choosing 30 mol% *tert*-butyl hydroperoxide for a catalytic enantioselective Reformatsky reaction of aldehydes.²²⁶ In a related enantioselective transformation of ketones, as a radical promoter they employed catalytic CuCN in the presence of the bidentate 1,3-bis(diphenylphosphino)propane ligand.²²⁷ A mixture of Ar and O_2 gases was used by Hayashi,²²⁸ while Wolf performed the reaction under air with 1 equivalent of trimethylborate.²²⁹ Finally, the challenge of developing an enantioselective Reformatsky reaction under heterogeneous conditions was met in 2010 by Lu and co-workers.²³⁰ They used 3 equivalents of Zn powder and catalytic quantities of ligand **226**, TFA and NiBr_2 (Scheme 63). Since the product was still obtained with good yield and enantioselectivity without NiBr_2 or replacing it with MnCl_2 , the authors propose that the Ni(II) salts serve as a Lewis acid only.



Scheme 63 Lu's enantioselective heterogeneous Reformatsky reaction.

Using the related ligand **227**, in 2016 Vila, Pedro and co-workers reported a catalytic enantioselective Reformatsky reaction of aldimines and ketimines, proceeding with excellent enantiocontrol (Scheme 64).²³¹ However, the scope was limited to cyclic substrates.



Scheme 64 Vila and Pedro's catalytic enantioselective Reformatsky reaction of cyclic ketimines and aldimines.

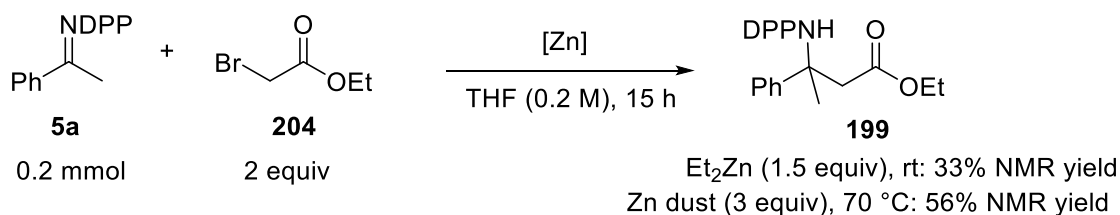
5.3 Development of a Ketimino-Reformatsky Reaction

5.3.1 Proof of Principle and Optimisation

In the context of catalytic additions to ketimines for the generation of amines bearing a fully substituted stereocentre in the α -position, we decided to investigate the ketimino-Reformatsky reaction. We were also intrigued by the possibility of devising a catalytic enantioselective variant for ketimine substrates, which at the beginning of this thesis work was completely unprecedented in the literature; to date only one example on cyclic substrates is known (see Scheme 64).²³¹

Given its excellent reactivity profile in the catalytic enantioselective addition of activated isocyanide pronucleophiles (see Chapters 1 and 4), acetophenone-derived *N*-DPP ketimine **5a** was chosen as the electrophile for our preliminary studies. The nucleophilic species was generated from ethyl bromoacetate (**204**), which is much cheaper than its iodo counterpart,

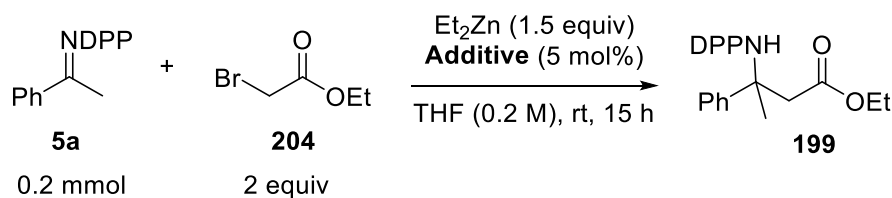
using excess diethyl zinc or zinc dust, and encouraging conversions to the desired β -amino ester **199** were observed under both homogeneous and heterogeneous reaction conditions (Scheme 65).



*Scheme 65 Proof of principle for a Reformatsky reaction between N-DPP ketimine **5a** and bromoacetate **204**. NMR yield determined by ^1H NMR analysis of the reaction mixture after work up using mesitylene as an internal standard.*

Aware of the importance of transition-metal additives for promoting Reformatsky reactions (see Section 5.2), we decided to screen different transition metal complexes at 5 mol% loading under homogeneous reaction conditions (Table 11). An arbitrary reaction time of 15 hours was chosen to compare the effects of the additives. In all cases, a boost in conversion was observed with respect to the reaction run in the absence of additives (Entry 1), however, in some cases undesired products were formed during the reaction, so the NMR yield for the Reformatsky adduct **199** remained low.^{xv} The use of Rh(I), Ni(II), Pd(II) and Pd(0) complexes delivered the product in 36–60% NMR yields (Entries 3–11). $[Co(acac)_2]$ was less effective (26% yield, Entry 2) and with Cu(I) and Cu(II) salts only traces of product were formed (Entries 12–14). In line with Adrian's report,²⁰⁷ the best complex among those screened was found to be $[NiCl_2(PPh_3)_2]$, which afforded the product in 60% yield (Entry 5). Swapping the two triphenylphosphines for bidentate ether or phosphine ligands was detrimental to the yield (Entries 6–8), and $[PdCl_2(PPh_3)_2]$ also had an inferior performance (Entry 9).

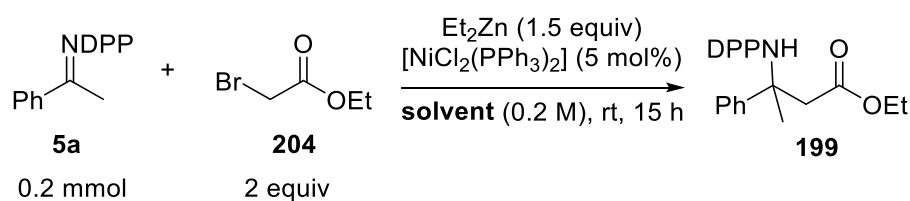
^{xv} The conversions are calculated based on the remaining amount of unreacted ketimine plus acetophenone, which originates from hydrolysis of the unreacted ketimine during the workup. Conversion values should be considered for comparison purposes only; NMR yields for the product, on the contrary, are accurate.



Entry	Additive	Conversion (%)	NMR yield (%)
1	none	36	33
2	[Co(acac) ₃]	82	26
3	[RhCl(PPh ₃) ₃]	88	42
4	[Rh(OAc) ₃]	97	43
5	[NiCl ₂ (PPh ₃) ₂]	88	60
6	[NiCl ₂ (glyme)]	77	36
7	[NiCl ₂ (dppe)]	94	38
8	[NiCl ₂ (dppp)]	79	49
9	[PdCl ₂ (PPh ₃) ₂]	72	40
10	[Pd(PPh ₃) ₄]	89	47
11	[Pd(dba) ₃]	99	54
12	CuCl	66	4
13	CuCN	71	0
14	CuCl ₂	62	6

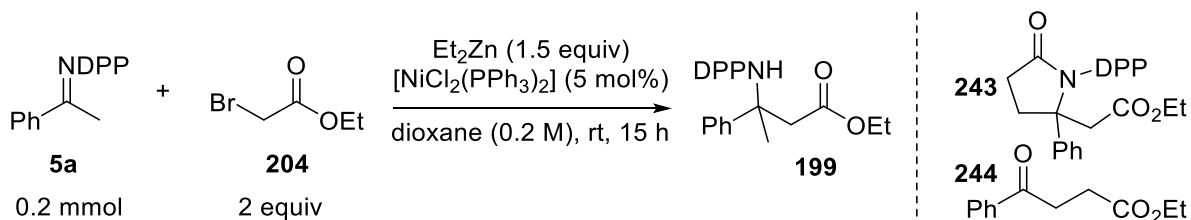
Table 11 Transition-metal additives screen in the ketimino-Reformatsky reaction between **5a** and **214**.^a Conversion (consumption of **5a**) and NMR yield for **199** were determined by ¹H NMR analysis of the reaction mixture after work up using mesitylene as an internal standard.

Next, a solvent screen was carried out using 5 mol% [NiCl₂(PPh₃)₂] (Table 12). Dioxane was identified as the optimal solvent, due to the high conversion and the clean reaction profile (88% NMR yield of the product, Entry 2), and additional experiments were performed in this solvent (Table 13). Doubling the equivalents of diethylzinc resulted in nearly full conversion, however the yield for the desired product did not increase (Entry 2, a small amount of an unidentified side product was formed).



Entry	Solvent	Conversion (%)	NMR yield (%)
1	THF	88	60
2	dioxane	89	88
3	MTBE	78	33
4	Et ₂ O	80	79
5	toluene	79	74
6	CH ₃ CN	80	59
7	CH ₂ Cl ₂	61	53

Table 12 Solvent screen in the ketimino-Reformatsky reaction between **5a** and **204**. ^a Conversion (consumption of **5a**) and NMR yield for **199** were determined by ¹H NMR analysis of the reaction mixture after work up using mesitylene as an internal standard.

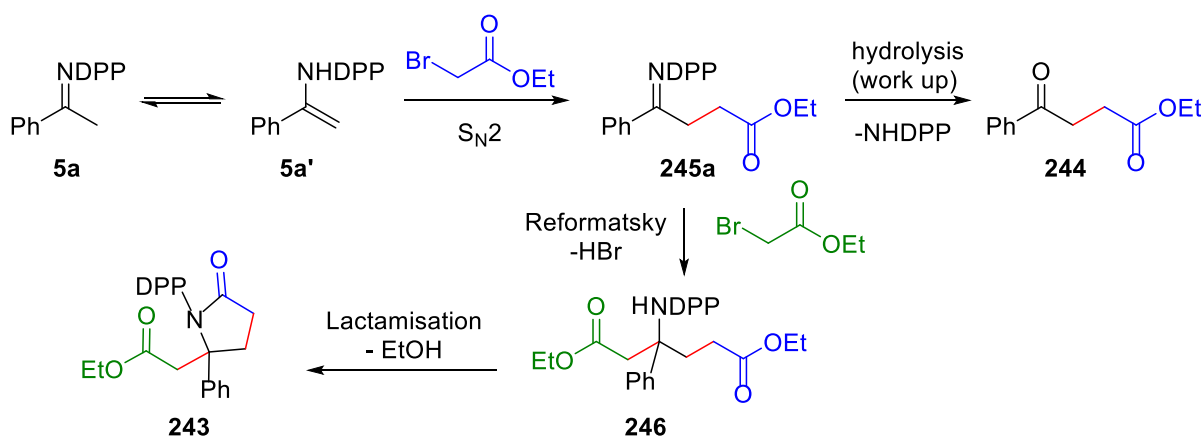


Entry	Change to conditions	Conversion (%)	NMR yield 199 (%)
1	-	89	88
2	Et ₂ Zn (3 equiv)	97	88
3	Me ₂ Zn (1.5 equiv)	79	40
4	without [NiCl ₂ (PPh ₃) ₂]	76	0
5	[NiCl ₂ (dppp)]	96	41

Table 13 Additional experiments. ^a Conversion (consumption of **5a**) and NMR yields were determined by ¹H NMR analysis of the reaction mixture after work up using mesitylene as an internal standard.

The reaction profile with dimethylzinc was less clean (Table 13, Entry 3), and significant quantities of γ -lactam **243** and β -ketoester **244** were produced (18% and 8% yield, respectively). Removal of [NiCl₂(PPh₃)₂] completely suppressed product formation, leading to a complex mixture of compounds (Entry 4). When [NiCl₂(PPh₃)₂] was replaced by [NiCl₂(dppp)], which

was the second-best Ni(II) complex in our initial additive screen (see Table 11), the product was obtained in lower yield (41%), due to formation of side product **243** (25% yield, Entry 5). Scheme 66 shows a plausible mechanism for the formation of lactam **243**. After tautomerisation of the ketimine **5a** to the enamine **5a'** (tautomerisation was found to be promoted by mild bases, such as DIPEA, see Section 6.6.2), S_N2 reaction between enamine **5a'** with ethyl bromoacetate takes place, possibly aided by deprotonation of the enamine. The resultant α -alkylated ketimine **245a** undergoes Reformatsky addition of bromoacetate to give DPP-amine **246**, which then can be deprotonated and form the 5-membered lactam **243**. Ketoester **244** is likely formed from ketimine **245a** during the aqueous work up.



Scheme 66 Plausible mechanism for the formation of γ -lactam **243**.

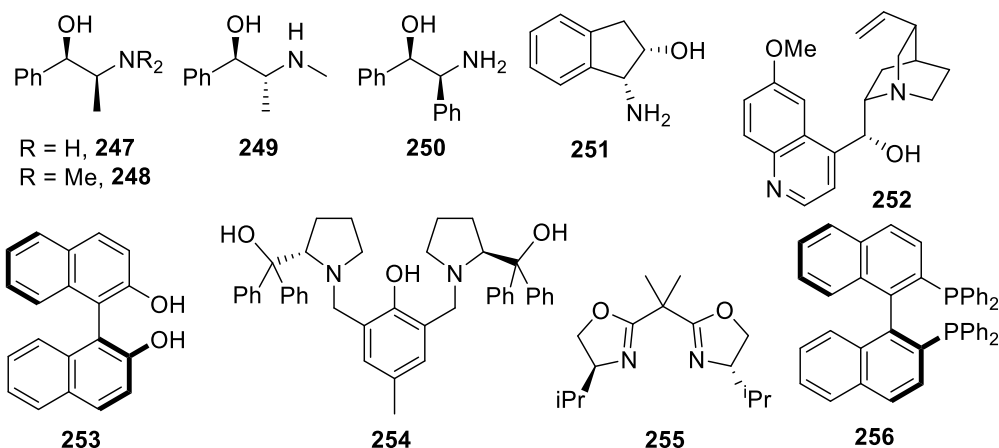
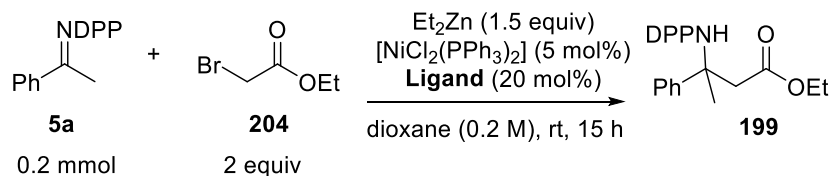
However, the nature of the Ni complex appears to be important in the formation of lactam **243** (Table 13, Entry 5 vs Entry 1), therefore the mechanism may be much more complex and involve radical or organonickel species (see Chapter 6).²⁰³

5.3.2 Attempts to Develop an Enantioselective Ketimino-Reformatsky Reaction

With optimal reactivity for the model substrate established, we next studied the possibility of imparting enantioselectivity to the reaction. A screen of chiral ligands covering many of the preferred ligand classes was thus performed (Table 14). Amino alcohols and diols **247–254** were chosen as these classes of compounds are known to be effective ligands for zinc in enantioselective Reformatsky reactions (see Figure 25); bisoxazoline **255** and BINAP were tested as ligands for nickel(II). Unfortunately, in all cases the product was obtained in practically racemic form within experimental error (Entries 1–3, 9–14).

In several reactions the formation of side products, some of which were identified and isolated, accounts for the discrepancy between the conversion and the isolated yield after FCC. For instance, β -ketoester **244** was isolated in 16% yield using cinchonine (Entry 11), and the parent α -alkylated ketimine **245a** was produced in large amounts using Pro-Phenol ligand **254** (Entry 13, the ligand is indeed normally employed with dialkylzinc for the enolisation of ketone pronucleophiles).²³² In addition, purification of the product from the remaining starting material by FCC was troublesome given the similar RF values, and only fractions containing pure products were collected for the determination of the yield and the measurement of the enantiomeric excess.

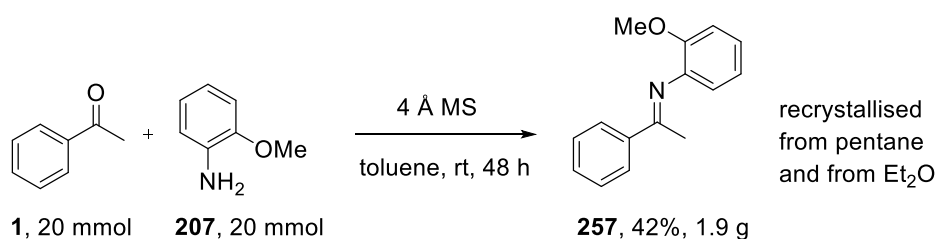
Chasing a non-zero ee, some reaction parameters were modified using ligand **249** (Entries 3–8). Although the use of 3 equivalents of diethyl zinc, and a longer reaction time at $-20\text{ }^{\circ}\text{C}$ both increased the yield of the product above 90%, they were not helpful for increasing the enantioselectivity (Entries 5 and 7).



Entry	Ligand	Change to conditions above	Conversion (%)	Yield, ee (%)
1	247	-	83	44, 0
2	248	-	76	60, 0
3	249	-	94	68, 0
4	249	In toluene	82	61, 0
5	249	At 0.1 M concentration with 3 equivalents of Et ₂ Zn	97	94, -3
6	249	Open to air through a CaCl ₂ drying tube	83	40, -2
7	249	At -20 °C in dioxane:Et ₂ O 2:3, 0.04 M, for 63 h	96	90, 1
8	249	Ketimine added after 1 h	77	44, 0
9	250	-	84	78, 0
10	251	-	85	82, 1
11	252	-	92	42, 1
12	253	-	87	60, 0
13	254	-	75	16, 3
14	255	-	80	69, 0
15	255	With Zn dust (4 equiv) and TMSCl (0.4 equiv)	78	75, 0
16	256	With 1 equiv of ligand, on 0.1 mmol scale	72	12, 0

Table 14 Ligand screen in the Reformatsky reaction between **5a** and **204**. Conversion determined by ¹H NMR analysis of the reaction mixture after work up based on the remaining amount of **5a** and acetophenone. Yield and ee given for the isolated product.

As a last attempt, we decided to replace the DPP group on the ketimine with an *o*-methoxyphenyl group, as it was the substituent of choice used in the enantioselective Reformatsky reaction of imine substrates (see Scheme 56). In principle, the lone pairs on oxygen and nitrogen could chelate the Zn centre, thus potentially activating the electrophile as well as influencing transmission of the stereochemical information. Ketimine **257** was prepared in 42% yield following literature procedures (Scheme 67).²³³



Scheme 67 Synthesis of *N*-(*o*-methoxyphenyl)ketimine **257**.

The substrate was then tested in the Reformatsky reaction with ethyl bromoacetate employing the same conditions used for the model *N*-DPP ketimine (Table 15). Overall, conversion to the desired product **258** was lower, in line with the diminished electrophilicity of the ketimine. However, enantioselectivity levels remained the same: the highest enantiomeric excess obtained for the Reformatsky adduct **258** was only 3% employing **248** as a ligand and [NiCl₂(PPh₃)₂] as an additive. Ligand **248** was the best one in terms of reactivity among those screened (45% yield, entries 1–4). Using this ligand, a few reactions with variations of parameters were performed, as optimisation had not been previously carried out for this ketimine. Omission of [NiCl₂(PPh₃)₂] completely suppressed product formation (Entry 5, as observed with *N*-DPP ketimine) and its replacement with other transition-metal complexes decreased the yield of the product, which however in some cases was still obtained with a 2–3% ee (Entries 6–9). Decrease of the temperature to 0 °C did not significantly influence reactivity nor enantiocontrol (Entry 10), while the use of iodoacetate led to a diminished yield (Entry 11). A reaction run with a superstoichiometric quantity of ligand (1.5 equiv) and excess

diethylzinc (4 equivalents) afforded the product in higher yield (69%, Entry 12), but invariably racemic form.

	257 0.2 mmol	204 1.5 equiv		258
Entry	Ligand	Change to conditions	NMR Yield (%)	Yield, ee (%)
1	248	-	52	45, 3
2	248	-	49	43, 0
3	253	-	n.d.	20, 0
4	254	-	0	-
5	248	Without [NiCl ₂ (PPh ₃) ₂]	5	5, <i>n.d.</i>
6	248	[RhCl(PPh ₃) ₃]	19	15, 0
7	248	[PdCl ₂ (PPh ₃) ₂]	34	24, 2
8	248	[Pd(PPh ₃) ₄]	25	17, 0
9	248	[Pd(dba) ₂]	16	15, 3
10	248	At 0 °C	46	41, 3
11	248	With ethyl iodoacetate	29	19, 2
12	248	Et ₂ Zn (4 equiv), ligand (1.5 equiv)	86	69, 0

Table 15 Ligand screen in the Reformatsky reaction between **5a** and **204**. NMR yield determined by ¹H NMR analysis of the reaction mixture after work up using mesitylene as an internal standard. Yield and ee given for the isolated product.

Overall, these results cast doubt on the involvement of a Reformatsky enolate (and in general Zn species such as those proposed by Cozzi and Feringa, see Section 5.2.3) in the enantiodetermining step of the reaction (attack to the C=N bond), as it is truly surprising that the ligands screened, even when used in superstoichiometric amount, cannot induce any enantioselectivity. It has previously been reported by Knochel that [Ni(acac)₂] triggers 5-*exo-trig* radical cyclisation of iodoalkenes in the presence of diethylzinc,²⁰³ therefore a mechanism proceeding *via* addition to the C=N bond of α-carbonyl radical species generated by bromoacetate with the intermediacy of Ni(II) may be imagined.²³⁴ Of course, further

experiments (for instance, the addition of radical traps and the use of pre-formed Reformatsky enolates) would be required to offer support to our speculations.

5.4 Conclusions

Research on the formation of amines bearing a tetra-substituted carbon atom in the α -position via metal-catalysed additions into ketimines was extended to Reformatsky pronucleophiles. Optimal reactivity for the Reformatsky reaction between *N*-DPP acetophenone-derived ketimine and ethyl bromoacetate has been established in a racemic fashion using Et_2Zn and catalytic $[\text{NiCl}_2(\text{PPh}_3)_2]$. Despite our efforts, it was not possible to impart any significant level of enantiocontrol to the transformation; the development of an enantioselective ketimino-Reformatsky reaction on acyclic substrates still remains an open challenge for the chemical community.

6 α -Alkylation of Ketimines using Visible Light Photoredox Catalysis

6.1 Chapter Overview

This chapter describes the α -alkylation of *N*-diphenylphosphinoyl ketimines with α -bromocarbonyl compounds using visible light photoredox catalysis.^{xvi} The transformation, that was serendipitously discovered while investigating the ketimino-Reformatsky reaction (Chapter 5), represents a new entry to photoredox-catalysed α -alkylations of carbonyl compounds and derivatives. In addition, the reaction highlights an underexplored reactivity pattern for *N*-diphenylphosphinoyl ketimines, substrates that so far have undergone nearly exclusively reductions or additions to the C=N bond. The α -alkylation proceeded with moderate yields across a range of aromatic ketimines under remarkably mild conditions: at 35 °C, in 20 hours, under blue light irradiation (1 W), in the presence of a tertiary amine and catalytic Ru- and Ni-based complexes. Chemoselective transformations of the product γ -imino esters were undertaken, providing 1,4-dicarbonyl compounds, protected GABA analogues and γ -lactams, and preliminary investigations of the mechanism through a combination of control, NMR and luminescence quenching experiments were carried out.

6.2 Introduction

6.2.1 Introduction to Photoredox Catalysis

Photoredox catalysis allows the generation of reactive intermediates with radical character by means of the photoexcitation of a catalytic quantity of a light absorbing compound

^{xvi} The work disclosed in this chapter was performed in conjunction with Antonia Rinaldi, a Master student under the supervision of A.F. and all the results have been included in this chapter for completeness.

(photocatalyst). Photocatalysts exhibit a great degree of structural diversity (Figure 26) and can belong to the classes of organic molecules,²³⁵ transition-metal complexes,^{236,237,238} inorganic clusters²³⁹ and even semiconductor quantum dots.²⁴⁰

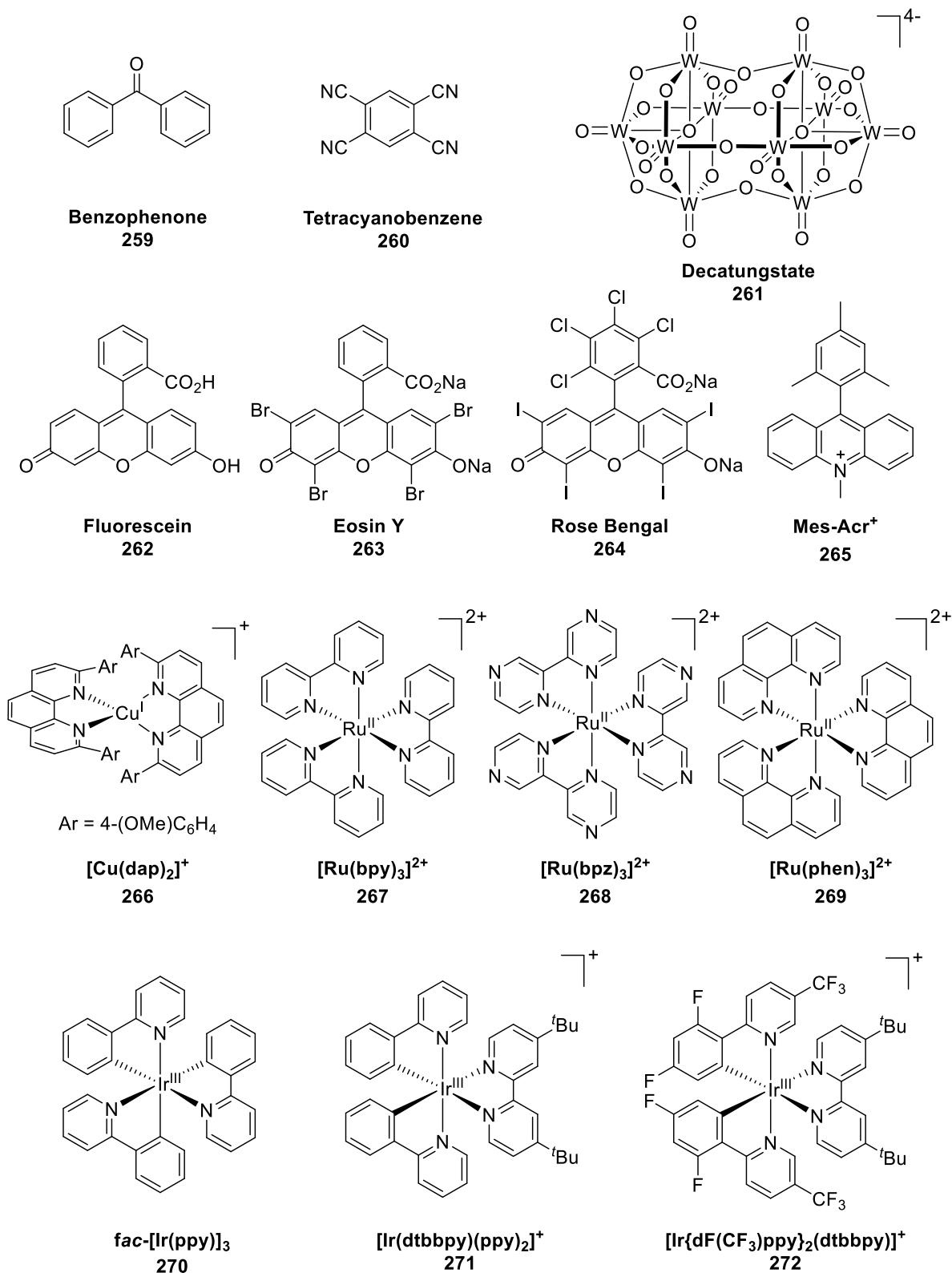


Figure 26 Selected photocatalysts.

They all share the ability of absorbing light with greater efficiency and at longer wavelengths (generally in the visible spectrum) than common organic compounds, by virtue of the extended aromatic systems in many of their structures. Photoexcitation of the catalyst initiates a series of electron, atom and/or energy transfer events leading to the formation of open-shell intermediates, that can participate in an astonishing variety of synthetically useful transformations. In recent years photoredox catalysis has gained widespread use in organic chemistry as a powerful tool for the construction of new bonds,²⁴¹ as it allows the generation of excited species usually possessing a greater reducing or oxidising power than the corresponding ground states. This permits not only to investigate new forms of reactivity, but also to catalyse known reactions by generating radical species under milder and safer conditions compared to traditional methods (such as high energy UV light, stoichiometric tin reagents and peroxides).^{235–242}

One of the most commonly used photocatalysts is $[\text{Ru}(\text{bpy})_3]^{2+}$ (**267**), a tris(2,2'-bipyridine)ruthenium complex, and its photochemical properties have been known for decades.^{243,244} The UV-visible absorption spectrum of the compound is dominated by a band centred around 452 nm (λ_{max}), corresponding to blue light. Upon absorption of a photon in the visible region, one electron in a metal-centered t_{2g} orbital is excited to the π^* orbital of the ligand, in a metal to ligand charge transfer process (MLCT, Figure 27). The excited singlet species initially generated rapidly undergoes intersystem crossing (ISC) to the lower-energy excited triplet state ($^*[\text{Ru}(\text{bpy})_3]^{2+}$). Although intersystem crossings are spin-forbidden, this one is fast because the two excited states are close in energy (in other words, their vibrational levels partially overlap, see Figure 28). On the contrary, $^*[\text{Ru}(\text{bpy})_3]^{2+}$ in its triplet state is relatively long-lived ($\tau = 1.1 \mu\text{s}$) as its decay to the singlet ground state is spin-forbidden, and can engage in single-electron transfers from/to external organic molecules. $^*[\text{Ru}(\text{bpy})_3]^{2+}$ is both a better oxidant and a better reductant than the ground state complex. When $^*[\text{Ru}(\text{bpy})_3]^{2+}$

acts as an oxidant, the hole in the t_{2g} orbital accepts an electron from a donor substrate **D**, also termed reductive quencher. The resulting $[\text{Ru}(\text{bpy})_3]^+$ species can subsequently act as a powerful single-electron reductant, regenerating the ground state $[\text{Ru}(\text{bpy})_3]^{2+}$. When $^*[\text{Ru}(\text{bpy})_3]^{2+}$ is oxidised by an acceptor molecule **A** instead, the higher-energy electron is expelled from the π^* orbital and the resulting $[\text{Ru}(\text{bpy})_3]^{3+}$ behaves as a strong oxidant.

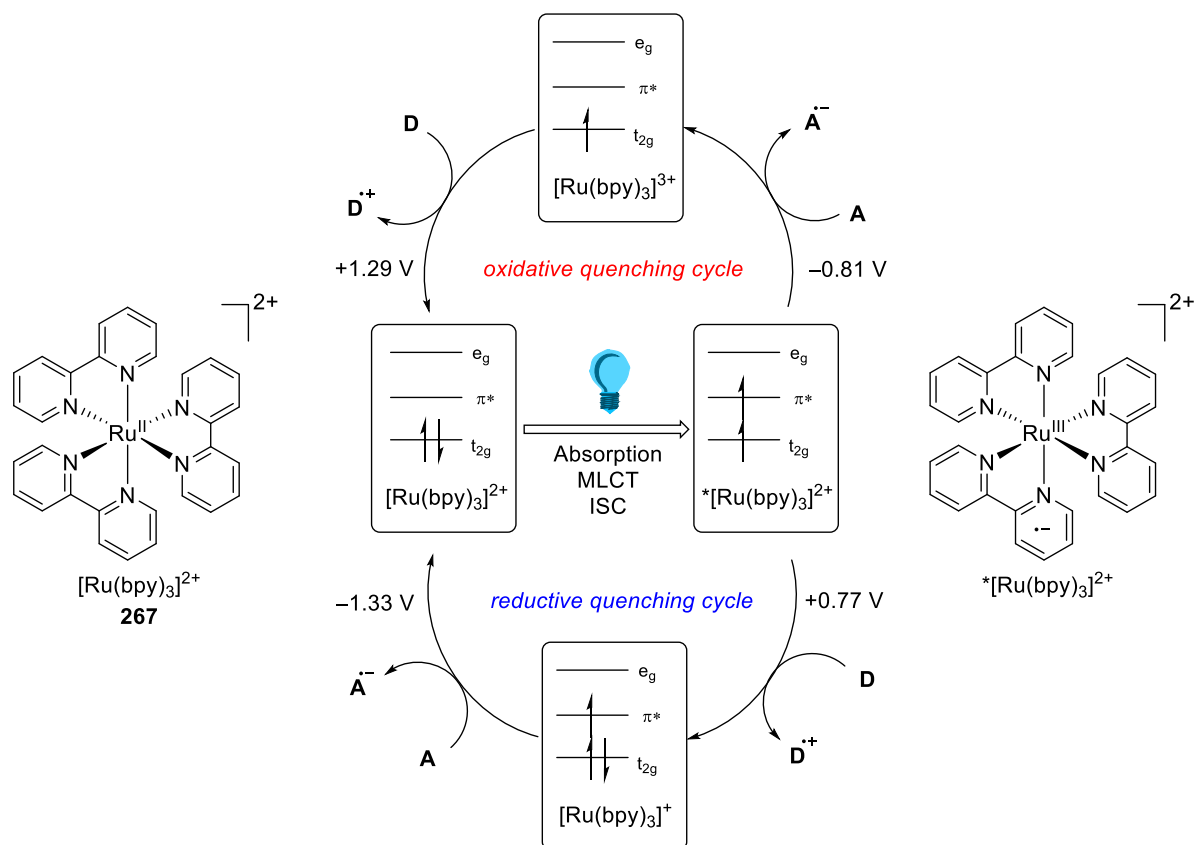


Figure 27 Photoredox cycles for $[\text{Ru}(\text{bpy})_3]^{2+}$.

The ability of a compound to act as an oxidant or a reductant is quantified by its reduction potential ($E_{1/2}$), that represents the potential associated with an electrochemical half reaction written in the sense of the reduction and quoted against a given reference electrode.^{xvii} In a given half reaction where M^n is reduced to M^{n-1} , the more negative the reduction potential of

^{xvii} When the reduction potential is measured under standard conditions (in water, at 25°C , with 1 M activity for ions participating in the reaction, 1 bar pressure for gases participating in the reaction, and metals in their pure state), it is termed standard reduction potential (E_0). E_0 is referenced against the standard hydrogen electrode (SHE), whose potential has been arbitrarily set at 0.00 V.

the redox couple ($E_{1/2}^{M^n/M^{n-1}}$), the more reducing (easier to oxidise) is the reduced form M^{n-1} . Conversely, the more positive the reduction potential, the more oxidising is the oxidised compound M^n . Therefore, comparison of the reduction potentials of different redox couples indicates which species is more likely to undergo oxidation (or reduction). The determination of reduction potentials is generally performed by cyclic voltammetry (CV), a technique where information about the redox properties of the analyte is obtained by measuring the current at the working electrode while its potential varies regularly over time. However, for some substrates, the determination of the reduction potentials by cyclic voltammetry is problematic, because they are irreversibly oxidised or reduced. In these cases, the potential of the irreversible peak observed in the cyclic voltammogram (E_p) or the half-wave potential ($E_{p/2}$) will offer good estimations of $E_{1/2}$.²⁴⁵

Besides cyclic voltammetry, another analytical method frequently employed in photoredox catalysis is photoluminescence spectroscopy.²⁴⁶ Photoluminescence is the phenomenon displayed by those molecules that absorb light and then re-emit it at a longer wavelength (Figure 28). In particular, the emission of a photon that accompanies relaxation from a singlet excited state S_1 to a ground state S_0 of the same multiplicity is termed fluorescence. Being spin-allowed, fluorescence is a fast process taking place in 0.5–20 ns. When the radiation is emitted upon decay from a triplet excited state T_1 , the process occurs over a longer time (from tens of nanoseconds to several seconds) and it is called phosphorescence.

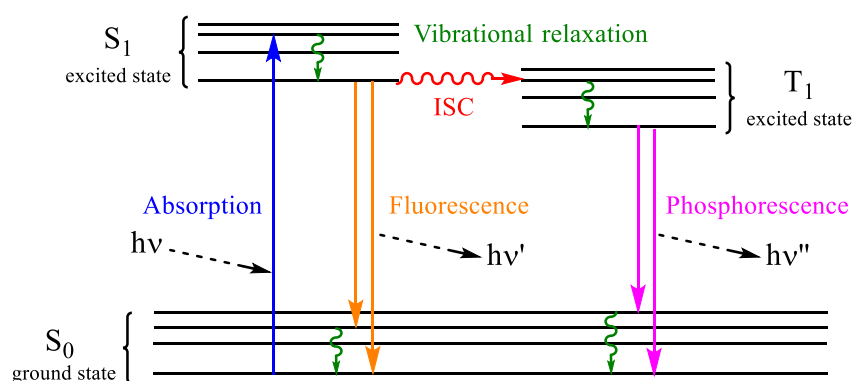


Figure 28 Jablonsky diagram illustrating radiative (straight arrows) and nonradiative (squiggly arrows) transitions between the electronic states of a molecule.

Under irradiation at 452 nm, $[\text{Ru}(\text{bpy})_3]^{2+}$ emits phosphorescence at approximately 620 nm with a given intensity I_0 , which is proportional to the concentration of $^*[\text{Ru}(\text{bpy})_3]^{2+}$. In the presence of increasing concentration of a quencher, the observed luminescence intensity (I) will decrease (quenching). This can be a result of complex formation between the ground state of the photocatalyst and the quencher (static quenching), or interactions between the luminescent excited state and the quencher (dynamic quenching, including single electron transfer and energy transfer processes). Static and dynamic quenching are described by the Stern-Volmer equation (Eqn 1 and Eqn 2), that predicts a linear relationship between the ratio I_0/I and the concentration of the quencher $[Q]$.

(Eqn 1) Static quenching: $I_0/I = 1 + K_s[Q]$ where K_s = static quenching constant

(Eqn 2) Dynamic quenching: $I_0/I = 1 + K_d[Q]$ where K_d = dynamic quenching constant

In case both dynamic and static quenching are operative at the same time, the correlation becomes quadratic (Eqn 3), and positive deviations from linearity are observed in the Stern-Volmer plot (Figure 29).

(Eqn 3) Mixed static and dynamic quenching: $I_0/I = 1 + (K_s + K_d)[Q] + K_sK_d[Q]^2$

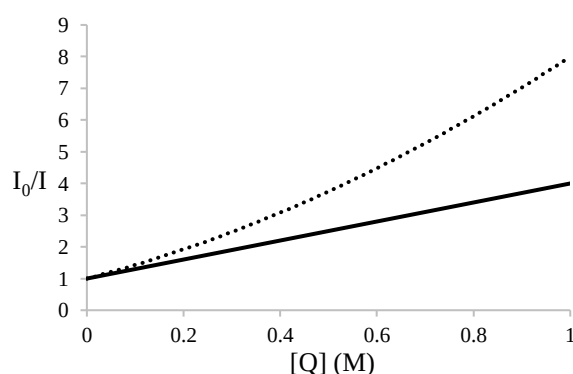


Figure 29 Representative Stern-Volmer plots for static (full line), dynamic (full line) and mixed (dotted line) quenching.

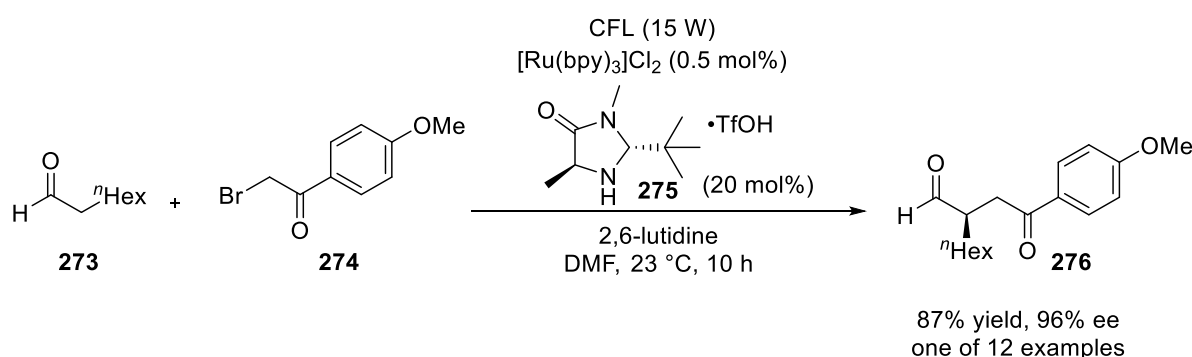
Measurements of fluorescence/phosphorescence intensities and lifetimes in the presence of a quencher are useful to determine the fate of the excited photocatalyst, as they indicate which components of the reaction mixture can act as quenchers and which quenching mechanism is

operative.²⁴⁶ Such experiments investigate the very first steps of the catalytic cycle that was presented in Figure 27; the radical cations or anions concurrently generated by SET ($\mathbf{D}^{+\bullet}$ and $\mathbf{A}^{\bullet-}$) then go on to react in a variety of ways, thus enabling new reactivity to be discovered and known transformations to be performed under different conditions.²⁴⁷

6.2.2 Photoredox-Catalysed α -Alkylation of Carbonyl Compounds and Derivatives

Classically, the general approach for the α -alkylation of carbonyl compounds involves their conversion into carbon nucleophiles (such as enamines,²⁴⁸ enolates and enol silyl ethers, either pre-formed or formed *in situ*) followed by S_N2 reaction with alkyl halides. Photoredox catalysis has recently added a new twist to this long-established reactivity, uncovering novel mechanistic pathways and often allowing the reactions to be carried out without the use of organometallic reagents nor strong bases.

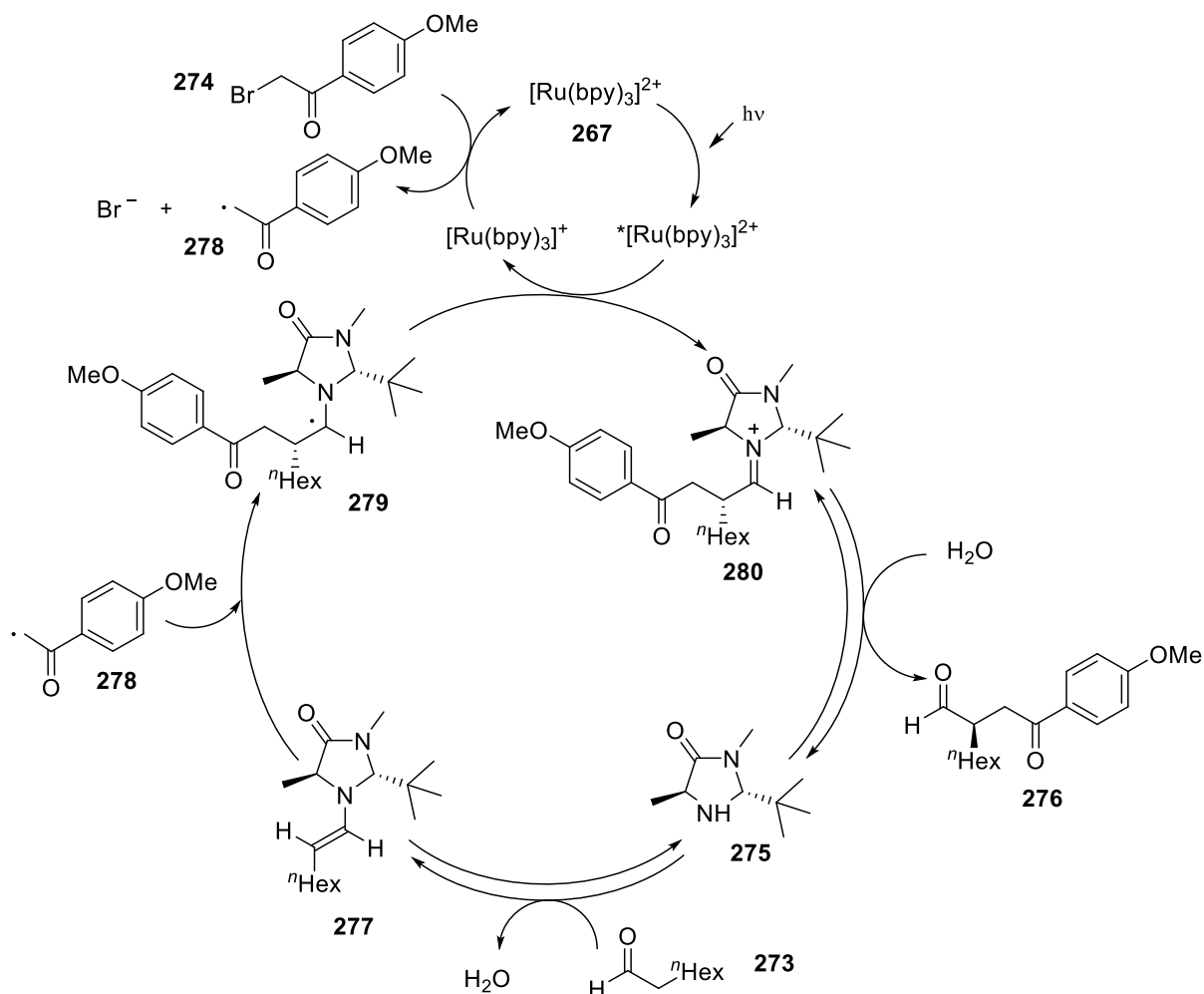
The first α -alkylation of carbonyl compounds using photoredox catalysis was reported by Nicewicz and MacMillan in 2008 (Scheme 68).²⁴⁹ They developed a catalytic enantioselective α -alkylation of aldehydes employing imidazolidinone organocatalyst **275** in conjunction with $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$ under irradiation by a compact fluorescent lamp (CFL).



Scheme 68 Nicewicz and MacMillan's asymmetric α -alkylation of aldehydes through merging organocatalysis with photoredox catalysis.

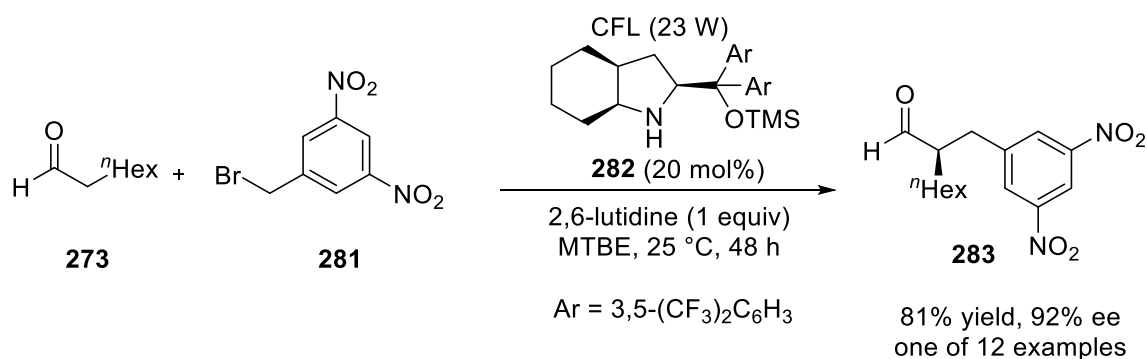
It was proposed that the *Si* face of an electron-rich enamine intermediate **277** formed by condensation of the aldehyde substrate **273** with the chiral aminocatalyst **275** is attacked by the electron-deficient α -carbonyl radical generated *via* SET reduction of the alkyl bromide by

$[\text{Ru}(\text{bpy})_3]^+$. The resulting α -amino radical **279** is then oxidised by $^*[\text{Ru}(\text{bpy})_3]^{2+}$ to the iminium ion **280**, that hydrolyses affording product **276** and the regenerated aminocatalyst **275** (Scheme 69). Analogous mechanistic manifolds based on the attack of a photoreductively generated radical to chiral enamine intermediates have been exploited by the same group for α -trifluoromethylation,²⁵⁰ α -benzylation²⁵¹ and α -cyanoalkylation²⁵² of aldehydes.



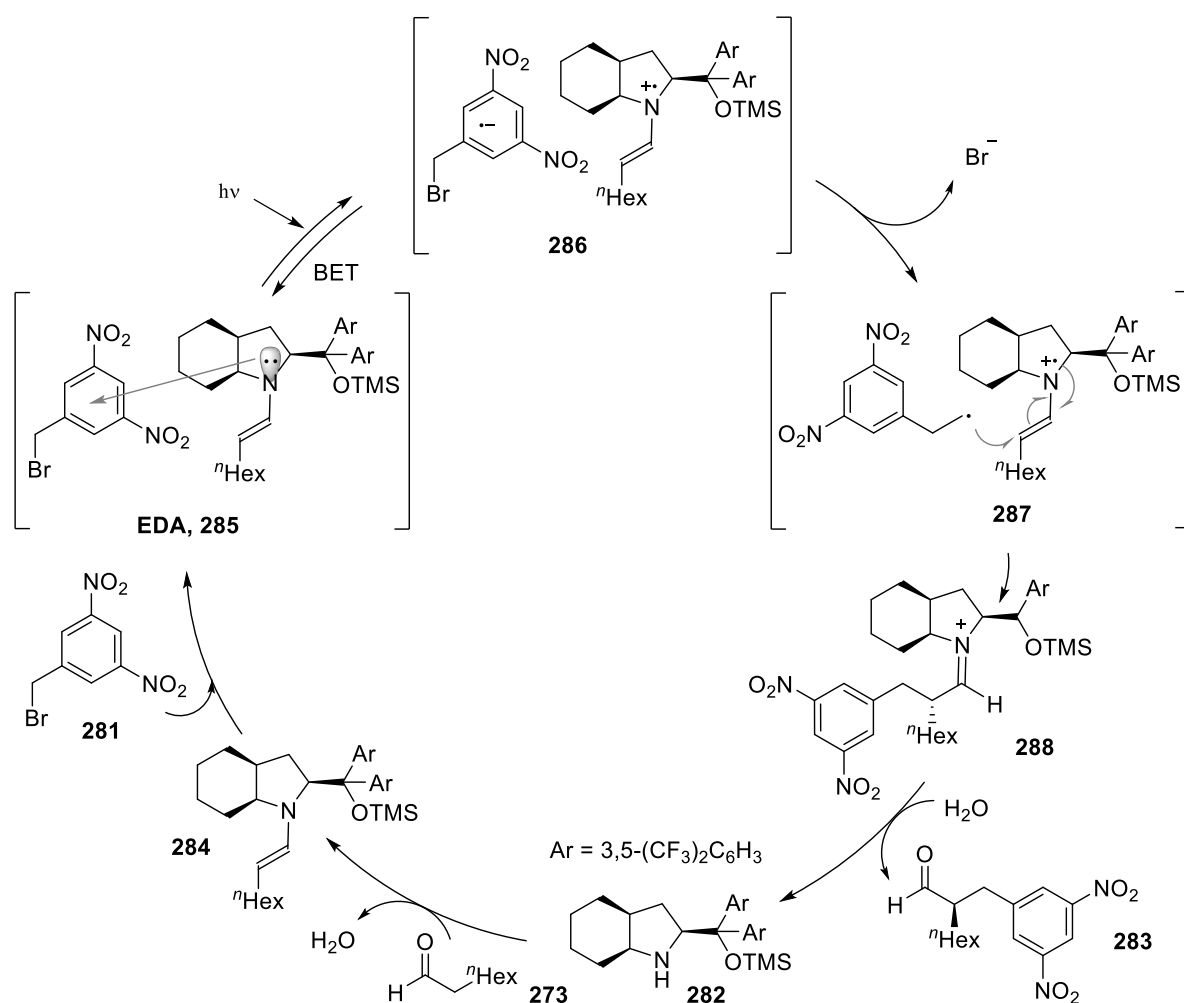
Scheme 69 Proposed catalytic cycle for the asymmetric α -alkylation of aldehydes by merging of organo- and photoredox catalysis.

A different approach to the same reaction was described in 2013 by Melchiorre and co-workers, that accomplished the asymmetric α -alkylation of aldehydes under light irradiation but in the absence of a photocatalyst (Scheme 70).²⁵³



Scheme 70 Melchiorre's asymmetric α -alkylation of aldehydes via photoexcitation of an EDA complex.

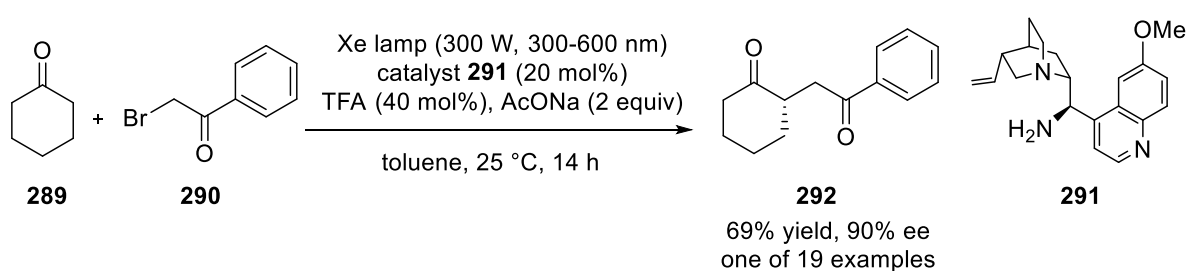
The mechanism relies on the direct photoexcitation of a coloured electron donor-acceptor complex (EDA, **285**) formed *in situ* between the electron-rich chiral enamine **284** and the electron-poor benzyl bromide **281** by $n \rightarrow \pi^*$ interaction (Scheme 71).²⁵⁴



Scheme 71 Proposed mechanism for the asymmetric α -alkylation of aldehydes via photoexcitation of an EDA complex.

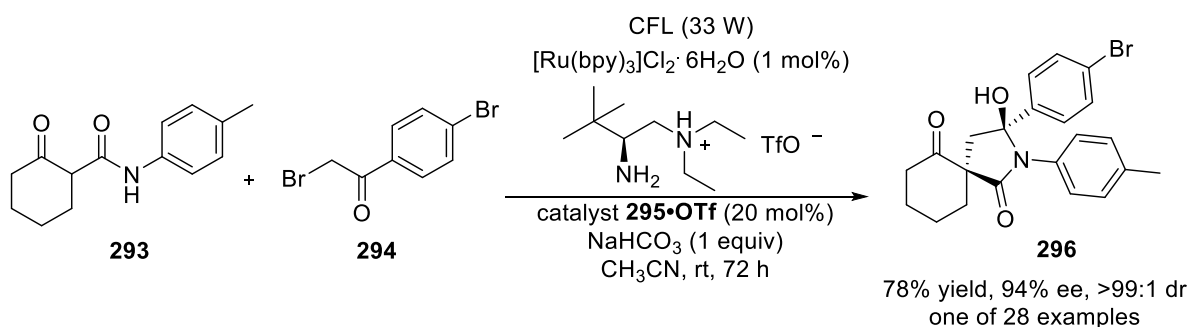
Light irradiation of the EDA promotes the transfer of one electron from the electron-rich enamine to the electron-deficient bromoalkane, and fast fragmentation of the latter (**286**) with expulsion

of bromide prevents unproductive back electron transfer (BET). The same approach has been successfully applied to the α -alkylation of cyclic ketones using a quinidine-derived amine **291** as organocatalyst (Scheme 72).²⁵⁵ Given the greater steric bulk of ketones compared to aldehydes, condensation to the enamine proceeded only with primary amines and needed to be promoted by TFA. The EDA complex formed between the enamine and phenacyl bromide **290** required irradiation in the near UV region (<385 nm), as its absorption in the visible region was too low.



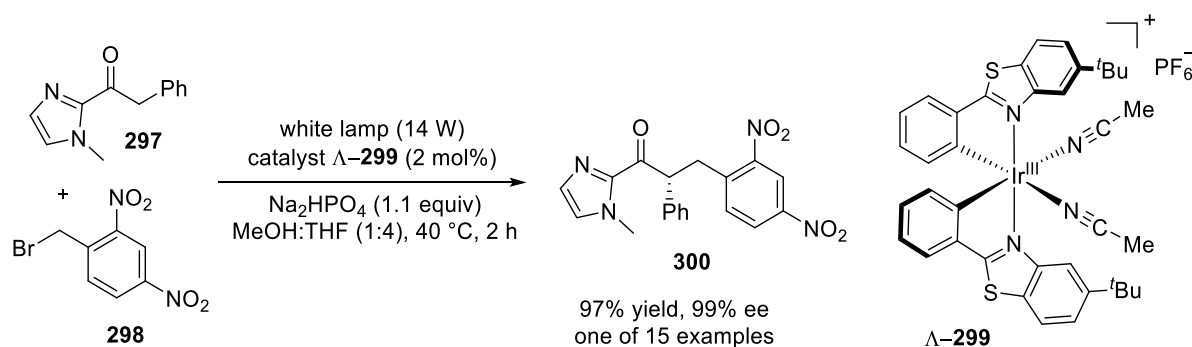
Scheme 72 Melchiorre's asymmetric α -alkylation of cyclic ketones.

Leveraging the same mechanistic pathway exploited by MacMillan (see Scheme 71), in 2014 Luo and co-workers reported the enantioselective α -alkylation of 1,3-diketones, β -ketoesters and β -ketoamides.²⁵⁶ When using *N*-aryl amides such as **293**, after α -alkylation an intramolecular ketalisation to afford spiro- γ -lactams took place spontaneously (Scheme 73). The authors attribute the high diastereoselectivity observed in this step to H-bonding between the carbonyl group of **294** and the amide N-H, as well as to π - π interactions between the aromatic rings of the two reaction partners.



Scheme 73 Luo's asymmetric α -alkylation of 1,3-dicarbonyl compounds.

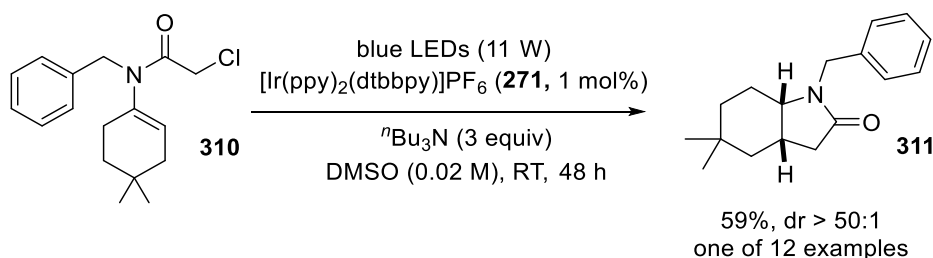
An innovative approach to photoredox-catalysed asymmetric α -alkylations was proposed in 2014 by the group of Meggers taking advantage of the inherent chirality of octahedral complexes such as $[\text{Ru}(\text{bpy})_3]^{2+}$ and $[\text{Ir}(\text{ppy})_3]$ (see Figure 26). The authors employed the enantiopure, chiral-at-metal iridium complex **299** for the α -alkylation of 2-acyl imidazoles (Scheme 74).²⁵⁷



Scheme 74 Meggers' asymmetric α -alkylation of 2-acyl imidazoles with a chiral-at-metal Ir complex.

The iridium centre of the catalyst simultaneously serves as the stereogenic centre, the catalytically active Lewis acid and the photoredox centre. In the proposed mechanism (Scheme 75), substrate **297** coordinates to iridium in a bidentate fashion. Deprotonation of **301** delivers the neutral Ir(III) enolate complex **302**, that is attacked by the α -bromocarbonyl radical **305** giving ketyl intermediate **303**. Oxidation of the latter by SET affords Ir-bound product **304** and restores the ground state of the photocatalyst, that the authors believe to be Ir(III) enolate complex **302**. This complex is an intermediate of both the asymmetric catalysis cycle and the photoredox cycle.

In the same year, Rueping and co-workers described a related intramolecular reaction, namely the visible light mediated cyclisation of α -chloroenamides affording γ -lactams (Scheme 77).²⁵⁹ The methodology, that was limited to 6-membered enamides, proceeded with moderate yields (43–67%) because of competing reductive dehalogenation delivering *N*-acetyl enamides. The authors postulate that the mechanism involves a 5-*endo-trig* cyclisation of the α -carbonyl radical on the double bond of the enamide.

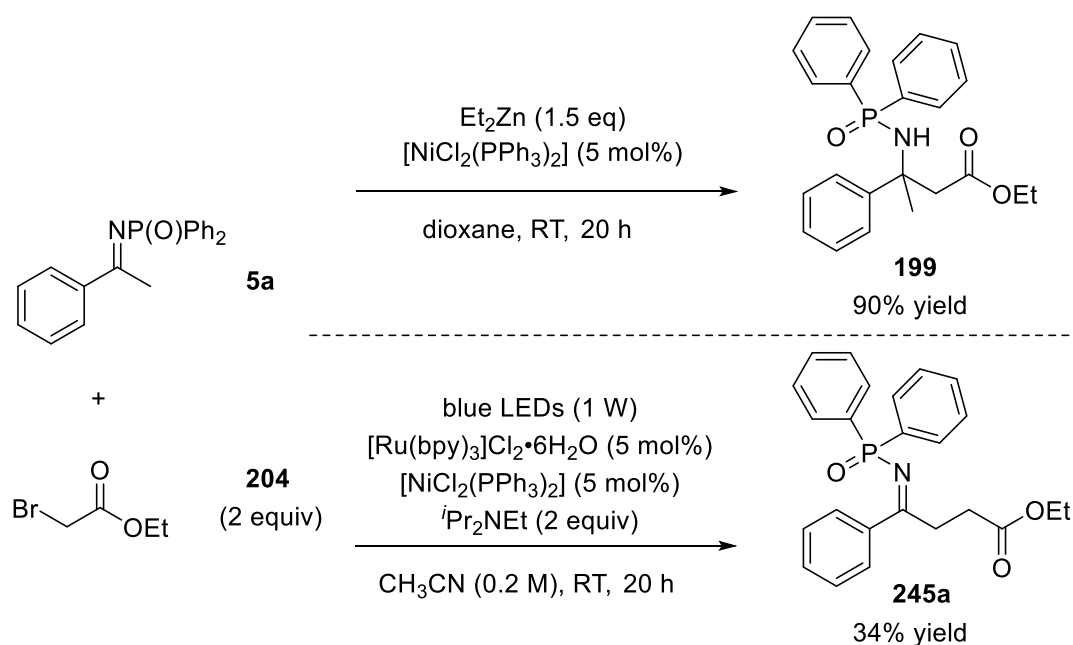


Scheme 77 Rueping's cyclisation of α -chloroenamides.

6.3 Reaction Discovery and Optimisation

6.3.1 Serendipitous Reaction Discovery

As discussed in Section 6.2.1, photoredox catalysis often allows the generation of radicals under mild conditions: generally, a small amount of photocatalyst under light irradiation. On this basis, suspecting a radical mechanism to be operative in the Reformatsky reaction between acetophenone-derived *N*-diphenylphosphinoyl (DPP) protected ketimine **5a** and ethyl bromoacetate (**204**) (Scheme 78 top, see also Chapter 5), we decided to run the reaction under conditions typical of photoredox catalysis, with the intention of generating an α -carbonyl radical from the bromoalkyl precursor. When diethylzinc was replaced by 5 mol% [Ru(bpy)₃]Cl₂·6H₂O and 2 equivalents of *N*-diisopropylethylamine (DIPEA) as a reductive quencher in acetonitrile,²⁶⁰ the outcome of the reaction changed completely. α -Alkylated ketimine **245a** was formed as the only product in 34% NMR yield, alongside unreacted starting material (Scheme 78 bottom).

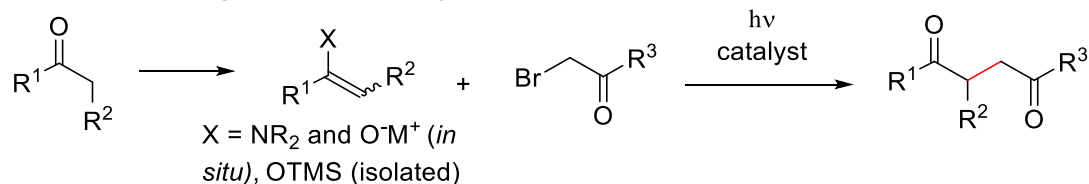


Scheme 78 Top: Reformatsky reaction between acetophenone-derived *N*-DPP ketimine **5a** and ethyl bromoacetate **204**. Bottom: α -alkylation of ketimine **5a** using photoredox catalysis. Yields calculated by ^1H NMR analysis of the reaction mixture after work-up using mesitylene as an internal standard.

The transformation highlights an underexplored reactivity pattern for *N*-DPP ketimines, which so far have been used nearly exclusively as substrates for reduction of the C=N bond and nucleophilic attack at the imine carbon.³⁵ To the best of our knowledge, the only exceptions are oxidation to oxaziridines,²⁶¹ LHMDs-promoted cascade reactions with tropones to give 1-azaazulenes,²⁶² and potassium *tert*-butoxide-promoted aldol reactions of *N*-DPP ketimines with enals²⁶³ or aromatic aldehydes²⁶⁴ to prepare pyridines.

Moreover, our preliminary result was the first example of a photoredox-catalysed intermolecular α -alkylations of ketimine or enamine substrates, whereas similar reactions of aldehydes,^{249,253} ketones,^{255,256} 2-acylimidazoles²⁵⁷ and silyl enol ethers²⁵⁸ have been reported in the last years (Section 6.2.2). We realised that, by extending that type of reactivity to a new class of substrates, *i.e.* ketimines, a mild method for the generation of valuable γ -imino esters would be realised (Figure 30). Synthetic manipulation of the products would provide access not only to 1,4-dicarbonyl compounds, but also to γ -amino esters (protected analogues of the neurotransmitter γ -aminobutyric acid, GABA),²⁶⁵ and to γ -lactams, which are found in both natural and synthetic molecules possessing a range of biological properties.²⁶⁶

Previous work using photoredox catalysis



This work: ketimine substrates

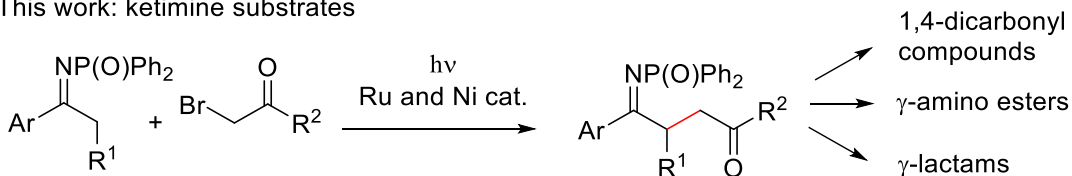


Figure 30 α -Alkylation of ketimines in the context of photoredox catalysis.

Having recognised the potential and the novelty of this serendipitously discovered transformation, we set out to study the α -alkylation of *N*-DPP ketimines using photoredox catalysis in greater detail, with the aims of:

- (i) optimising the reaction conditions;
- (ii) assessing the substrate scope;
- (iii) investigating the mechanism.

6.3.2 Reaction Optimisation

We soon realised that the task of optimising the reaction was not a trivial one, and anticipated a series of challenges in the development of the reaction arising from possible side reactions (Figure 31):

- (i) the C=N and C=O bonds of the substrates must survive the reaction conditions, *i.e.* Reformatsky-type additions to the C=N or C=O bonds, as well as hydrolysis of the ketimine should be avoided;
- (ii) starting materials and products may be involved in a ketimine/enamine equilibrium, thus complicating the reaction pathways;²⁶⁴
- (iii) overalkylation to yield **314** should be controlled;
- (iv) reductive dehalogenation of ethyl bromoacetate **204** should be avoided.

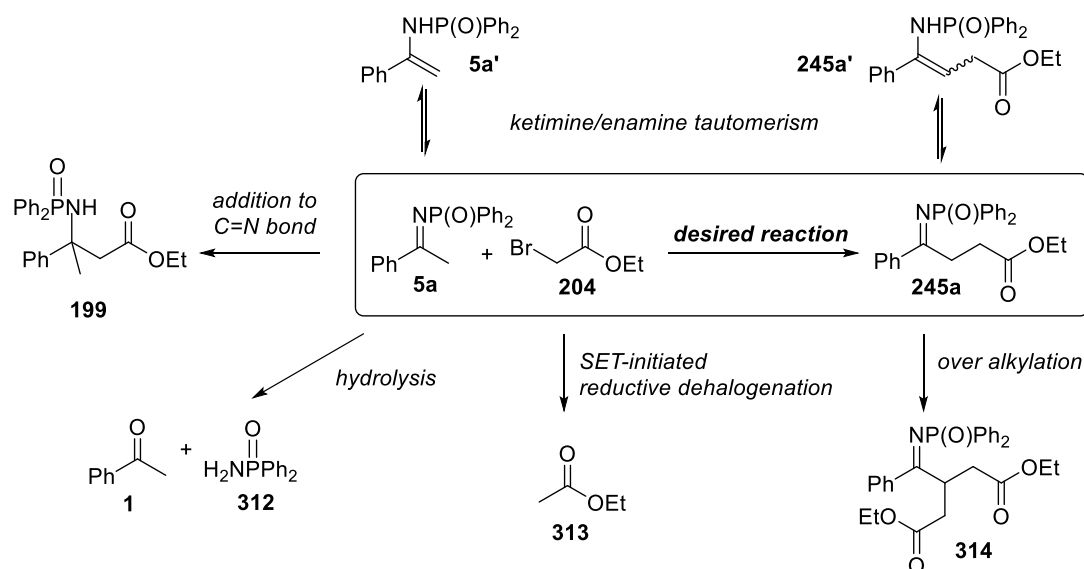


Figure 31 Side reactions potentially affecting the α -alkylation of ketimines.

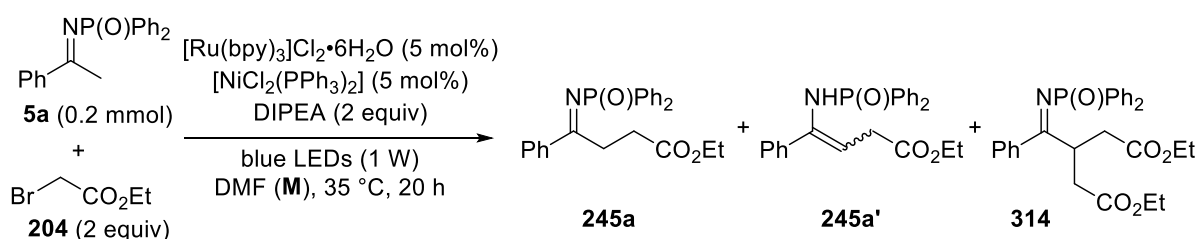
Keeping these considerations in mind, we began by screening the solvents in the model reaction between *N*-DPP acetophenone-derived ketimine **5a** and ethyl bromoacetate **204**, using 2 equivalents of DIPEA, 5 mol% $[\text{Ru}(\text{bpy})_3]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ and 5 mol% $[\text{NiCl}_2(\text{PPh}_3)_2]$ (Table 16).^{xviii}

$\text{Ph}-\text{C}(\text{N}(\text{P}(\text{O})\text{Ph}_2)=\text{CH}_2)-\text{CO}_2\text{Et}$ 5a (0.2 mmol)		$[\text{Ru}(\text{bpy})_3]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ (5 mol%) $[\text{NiCl}_2(\text{PPh}_3)_2]$ (5 mol%) DIPEA (2 equiv)		$\text{Ph}-\text{C}(\text{N}(\text{P}(\text{O})\text{Ph}_2)=\text{CH}_2)-\text{CH}_2-\text{CH}_2-\text{CO}_2\text{Et}$ 245a		$\text{Ph}-\text{C}(\text{N}(\text{P}(\text{O})\text{Ph}_2)=\text{CH}-\text{CH}_2-\text{CO}_2\text{Et})$ 245a'	
$\text{Br}-\text{CH}_2-\text{CO}_2\text{Et}$ 204 (2 equiv)		blue LEDs (1 W) solvent (0.2 M), 35 °C, 20 h					
Entry	Solvent	Conversion (%)	245a (%)	245a' (%)	Entry	Solvent	Conversion (%)
1	CH ₃ CN	34	34	0	6	AcOEt	<5
2	Acetone	29	21	3	7	benzene	<5
3	MeOH	51	32	14	8 ^a	dioxane	<5
4	DMSO	59	34	23	9 ^a	THF	<5
5	DMF	56	50	5	10	CH ₂ Cl ₂	11

Table 16 Solvent screen for the α -alkylation of ketimines. Conversion (consumption of ketimine **5a**) and NMR yields for **245a** and **245a'** were determined respectively by ³¹P and ¹H NMR analysis of the reaction mixture after work-up using mesitylene (28 μL , 0.2 mmol, 1 equiv) as an internal standard.

^{xviii} The reaction was performed at rt wrapping 5 blue LED lights (1 W total output) around a 2.5 mL glass vial; due to the light irradiation, the temperature measured in the vial at the end of the reaction was approximately 35 °C. Other light setups (photoreactor with tunable LEDs, white lamp, UV lamp) were evaluated but gave inferior results.

The reaction proceeded with encouraging conversion in polar solvents that were able to solubilise all components. DMF was selected as the solvent of choice due to the good yield and clean reaction profile (56% conversion, 50% yield for the desired ketimine **245a**, Table 1, entry 5). Then, a quick screen in DMF showed that a 0.2 M concentration of ketimine was the optimal one (Table 17, entry 3). At lower concentrations the reaction stalled, whereas at higher concentration tautomerisation to the enamine form and dialkylation to afford **314** eroded the yield of the desired product. Reversing the molar ratio of the reagents dramatically decreased the yield to 4% (entry 5), mainly because of competitive reductive dehalogenation of **204** to give ethyl acetate; on the other hand, doubling the equivalents of ethyl bromoacetate was not beneficial either (entry 6).



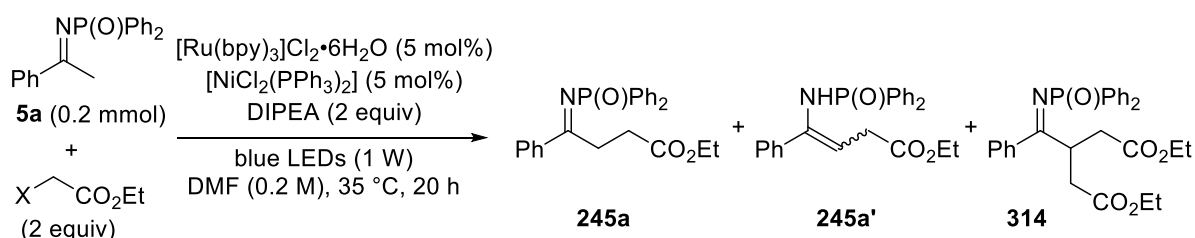
Entry	Concentration (M)	Conversion (%)	245a (%)	245a' (%)	314 (%)
1	0.067	38	37	1	0
2	0.1	46	45	1	0
3	0.2	56	50	5	1
4	0.4	60	44	11	3
5 ^a	0.2	15	11	4	0
6 ^b	0.2	33	31	2	0

Table 17 Concentration screen for the α -alkylation of ketimines. Conversion (consumption of ketimine **5a**) and NMR yields for **245a** and **245a'** were determined respectively by ^{31}P and ^1H NMR analysis of the reaction mixture after work-up using mesitylene (28 μL , 0.2 mmol, 1 equiv) as an internal standard.

^a With 2 equivalents **5a** and 1 equivalent of **204**. ^b With 4 equivalents of **204**.

Since the nature of the radical precursor can influence the product distribution,²⁶⁷ different α -haloacetates were tested (Table 18). When ethyl iodoacetate and ethyl chloroacetate were used instead of ethyl bromoacetate **204**, product **245a** was obtained with diminished yield (entries 1 and 3). In the case of ethyl chloroacetate, the low yield reflects a poor conversion, whereas the

modest yield obtained using ethyl iodoacetate arises from the presence of enamine tautomers **245a'** and dialkylated product **314**. The poor reactivity of ethyl chloroacetate is likely related to the more negative reduction potential of this substrate as a consequence of the higher $\text{sp}^3\text{C}-\text{Cl}$ bond dissociation energy (BDE).²⁶⁸ Overall, this observation supports a mechanism involving the formation of an α -carbonyl radical from the halocarbonyl precursor, presumably *via* mesolysis preceded by SET.

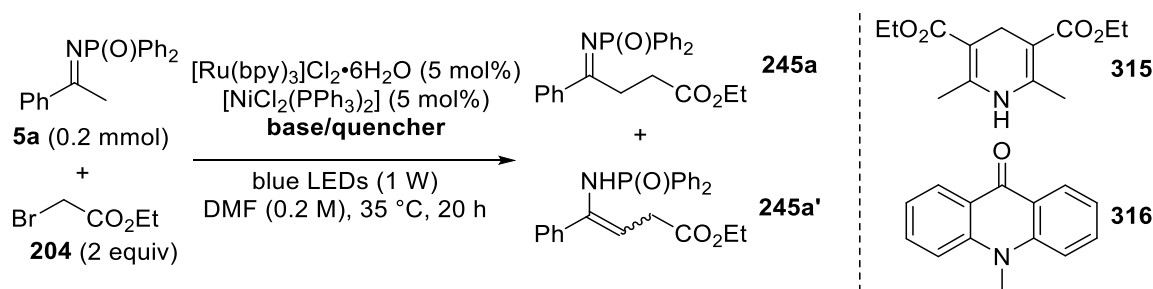


Entry	X	BDE $\text{CH}_3\text{-X}$ (kcal/mol)	unreacted 5a (%)	245a (%)	245a' (%)	314 (%)
1	Cl	83	83	12	5	0
2	Br	71	44	50	5	1
3	I	57	43	36	17	2

Table 18 Comparison between ethyl iodo-, bromo- and chloroacetate. Relative ratios were determined by ^{31}P NMR analysis of the reaction mixture after work-up.

Next, several organic and inorganic bases were trialled and their stoichiometry varied with the aim of boosting the conversion (Table 19). The use of 2 equivalents of DIPEA was confirmed to be better than 1 or 3 (entries 1–4), however the reaction appeared to stall at 56% conversion and did not proceed any further after 20 hours. The combination of DIPEA with inorganic bases, in the hope that the organic base could act as reductive quencher while the inorganic one could quench HBr, unfortunately did not lead to an increase in yield. The addition after 7 hours of 2 further equivalents of both DIPEA and ethyl bromoacetate **2** gave a conversion boost up to 72% (entry 8), but the yield for the desired product **245a** remained 45%, as enamines **245a'** and dialkylated product **314** were also formed during the reaction. Similarly, when using triethanolamine (TEOA) instead of DIPEA, the reaction proceeded to nearly full conversion (95%, entry 9), however the NMR yield for the alkylated ketimine **245a** was a modest 28%.

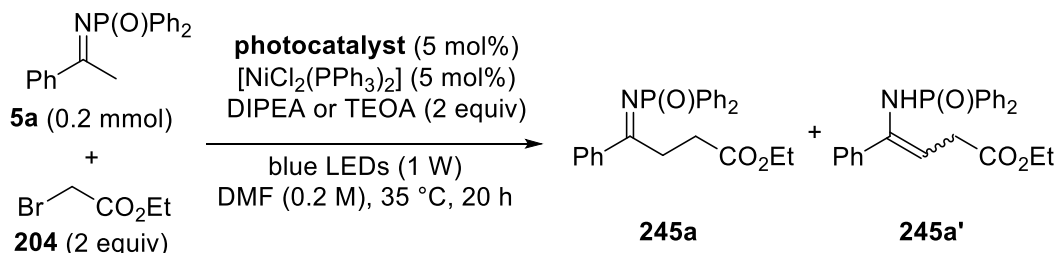
Also in this case, the poor yield was a result of the formation of *E* and *Z* enamines **245a'** (21%) and dialkylated product **314** (41%).



Entry	Base	Amount (equiv)	Conversion (%)	245a (%)	245a' (%)
1	DIPEA	2	56	50	5
2 ^a	DIPEA	2	46	45	1
3 ^a	DIPEA	1	31	31	0
4 ^a	DIPEA	3	30	24	6
5	DIPEA + NaHCO ₃	2 + 2	46	43	3
6	DIPEA + Na ₂ CO ₃	2 + 2	34	33	1
7	DIPEA + Na ₂ HPO ₄	2 + 2	49	31	15
8 ^b	DIPEA	2 + 2	72	45	14
9	N(CH ₂ CH ₂ OH) ₃	2	95	28	21
10	N(CH ₂ CH ₂ OCH ₂ CH ₂ OCH ₃) ₃	2	71	42	22
11 ^a	TEA	2	27	20	7
12 ^a	Ph ₂ N(<i>p</i> -OMeC ₆ H ₄)	2	<5	-	-
13 ^a	2,6-lutidine	2	<5	-	-
14 ^a	Na ₂ HPO ₄	2	<5	-	-
15 ^a	acridinone 315	2	<5	-	-
16 ^a	Hantzsch ester 316	2	100 ^c	0	0

Table 19 Base and reductive quencher screen for the α -alkylation of ketimines. Conversion (consumption of ketimine **5a**) and NMR yields for **245a** and **245a'** were determined respectively by ³¹P and ¹H NMR analysis of the reaction mixture after work-up using mesitylene (28 μ L, 0.2 mmol, 1 equiv) as an internal standard. ^a 0.1 M concentration of **5a**. ^b 2 further equivalents of DIPEA and **204** were added after 7 hours. ^c Decomposition observed.

At this point a range of photocatalysts was screened with DIPEA or TEOA (Table 20, see Figure 26 for their structures). [Ru(bpy)₃]Cl₂·6H₂O used in conjunction with DIPEA was confirmed to be the most effective (Entry 1).



Entry	Photocatalyst	245a ^a (%)	245a' ^b (%)
1	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O 267	50, 45 ^c	28
2 ^c	Eosin Y 263	41	23
3 ^c	[Ru(bpz) ₃](PF ₆) ₂ 268	35	19
4 ^c	[Ir{dF(CF ₃)ppy} ₂ (dtbbpy)]PF ₆ 272	16	15
5 ^c	[Ir(ppy) ₂ (dtbbpy)]PF ₆ 271	29	40
6	[Ru(phen) ₃]Cl ₂ 269	n.d.	36
7	Rose bengal disodium salt 264	n.d.	0
8	Rose bengal triethylammonium salt	n.d.	0
9	Fluorescein 262	n.d.	0

Table 20 Photocatalyst screen for the α -alkylation of ketimines. NMR yield for **245a** was determined by ¹H NMR analysis of the reaction mixture after work-up using mesitylene (28 μ L, 0.2 mmol, 1 equiv) as an internal standard. ^a DIPEA as a base. ^b TEOA as a base. ^c 0.1 M concentration of **5a**.

Our attention then turned to the nickel complex (Table 21). Omission of $[\text{NiCl}_2(\text{PPh}_3)_2]$ resulted in a lower yield of the product, showing that Ni(II), although not essential for reactivity, improves the conversion (entries 1 and 2). Among the Ni(II) additives that were tested, $[\text{NiCl}_2(\text{glyme})]$, nickel(II) acetate tetrahydrate and anhydrous NiBr_2 promoted the reaction with yields similar to those obtained with $[\text{NiCl}_2(\text{PPh}_3)_2]$ (42–47%, entries 2, 7, 9 and 12).

Entry	Nickel complex	Loading (mol %)	245a (%)
1	-	-	28 ^a
2	$[\text{NiCl}_2(\text{PPh}_3)_2]$	5	50
3	$[\text{NiCl}_2(\text{PPh}_3)_2]$	10	36
4	$[\text{NiCl}_2(\text{PPh}_3)_2]$	50	25
5	$[\text{NiCl}_2(\text{Ph}_2\text{PCH}_2\text{CH}_2\text{PPh}_2)]$	5	26
6	$[\text{NiCl}_2(\text{Ph}_2\text{PCH}_2\text{CH}_2\text{CH}_2\text{PPh}_2)]$	5	37
7	$[\text{NiCl}_2(\text{glyme})]$	5	42
8	$[\text{NiCl}_2(\text{glyme})] + \text{dtbbpy}$	5 + 5	36
9	$\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$	5	45
10	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$	5	22
11	$\text{Ni}(\text{CF}_3\text{SO}_3)_2$	5	39
12	NiBr_2	5	47
13	$[\text{Ni}(\text{cod})_2] + \text{PPh}_3$	5 + 5	36

Table 21 Nickel additives screen for the α -alkylation of ketimines. NMR yield for **245a** determined by ^1H NMR analysis of the reaction mixture after work-up using mesitylene (28 μL , 0.2 mmol, 1 equiv) as an internal standard. ^a 10% of **245a'** was also formed.

The last parameter that was taken into account was the temperature, and selected results are presented below (Table 22).

$ \begin{array}{c} \text{NP(O)Ph}_2 \\ \\ \text{Ph}-\text{C}=\text{CH}_2 \\ \text{5a (0.2 mmol)} \\ + \\ \text{Br}-\text{CH}_2-\text{CO}_2\text{Et} \\ \text{204 (2 equiv)} \end{array} \xrightarrow[\text{solvent (0.2 M), 62-65 h, T}]{\begin{array}{c} [\text{Ru}(\text{bpy})_3]\text{Cl}_2 \cdot 6\text{H}_2\text{O (5 mol\%)} \\ [\text{NiCl}_2(\text{PPh}_3)_2] \text{ (5 mol\%)} \\ \text{DIPEA or TEOA (2 equiv)} \\ \text{blue LEDs (1 W)} \end{array}} \begin{array}{c} \text{NP(O)Ph}_2 \\ \\ \text{Ph}-\text{C}=\text{CH}-\text{CH}_2-\text{CO}_2\text{Et} \\ \text{245a} \end{array} + \begin{array}{c} \text{NHP(O)Ph}_2 \\ \\ \text{Ph}-\text{C}=\text{CH}-\text{CH}=\text{CH}-\text{CO}_2\text{Et} \\ \text{245a'} \end{array} + \begin{array}{c} \text{NP(O)Ph}_2 \\ \\ \text{Ph}-\text{C}=\text{CH}-\text{CH}_2-\text{CH}_2-\text{CO}_2\text{Et} \\ \text{314} \end{array} $								
Entry	T (°C) ^a	Solvent	Base	Conversion (%)	245a (%)	245a' (%)	314 (%)	
1	35	DMF	DIPEA	56	50	5	1	
2	21	DMF	DIPEA	63	53	3	0	
3	21	DMSO	DIPEA ^b	82	65	7	2	
4	11	DMF	DIPEA	42	38	4	0	
5	11	DMF	DIPEA ^b	56	46	7	0	
6	35	DMF	TEOA	95	28	21	41	
8	21	DMF	TEOA ^b	97	26	18	31	
8	11	DMF	TEOA	86	37	29	20	
9	11	DMF	TEOA ^b	95	32	30	33	

Table 22 Temperature screen for the α -alkylation of ketimines. Conversion and NMR yields were determined respectively by ³¹P and ¹H NMR analysis of the reaction mixture after work-up using mesitylene (28 μ L, 0.2 mmol, 1 equiv) as an internal standard. ^a Temperature was measured inside the vial at the end of the reaction. ^b With 4 equivalents of base and 4 equivalents of **204**.

When the reaction was performed at room temperature in the standard setup, the temperature measured inside the vial at the end of the reaction was approximately 35 °C. Conversion was 56% using DIPEA and 95% using TEOA, however issues of product distribution (*i.e.* selectivity towards the desired alkylated ketimine **245a**) limited the yield to 50 and 28%, respectively (entries 1 and 6). In order to perform the reactions at lower temperature, the vials wrapped in the LED strip were stirred in a fridge either at 0 °C (resulting in a 21 °C temperature inside the vial at the end of the reaction) or at –15 °C (corresponding to a 11 °C temperature inside the vial). As expected, lower temperatures resulted in decreased reactivity, hence prolonged reaction times and higher amounts of base and **204** (4 equivalents) were required. On the other

hand, lower temperatures corresponded to cleaner reaction profiles with DIPEA (but not with TEOA, entries 6–9). In particular, when the model reaction was run in DMSO at 21 °C for 65 hours with 4 equivalents of DIPEA and ethyl bromoacetate, the NMR yield for the desired product increased to 65% (entry 3). This result indicates that lower temperature can improve the selectivity towards **245a**, and suggests that fine tailoring of the reaction conditions for each substrate may give better yields. However, because of safety and practicality issues (longer reaction time, larger excess of reagents) associated with this setup, the standard conditions (20 hours at 35 °C) were preferred for investigating the scope of the reaction.

6.4 Substrate Scope of the α -Alkylation of *N*-DPP Ketimines

The substrate scope of both components of the reaction was assessed using [Ru(bpy)₃]Cl₂·6H₂O (5 mol%), [NiCl₂(PPh₃)₂] (5 mol%) and 2 equivalents of either DIPEA or TEOA under 1 W blue light irradiation (Figure 32).

With respect to acetophenone-derived ketimine **5a**, ketimines possessing electron-withdrawing groups on the aromatic ring were generally found to be more reactive. The most appropriate base to carry out their alkylation was DIPEA, that compared to TEOA minimises the amounts of dialkylated product and enamine tautomers (see Table 22). Aryl methyl ketimines bearing F and Cl substituents in the para, meta and ortho positions of the aromatic ring, were alkylated affording 51–58% NMR yields of products (ketimine plus enamine tautomers, compounds **245c-f**). Isolated yields for the ketimine tautomers were somewhat lower (26–36%), as these compounds were prone to tautomerise to the enamine form in the reaction mixture.

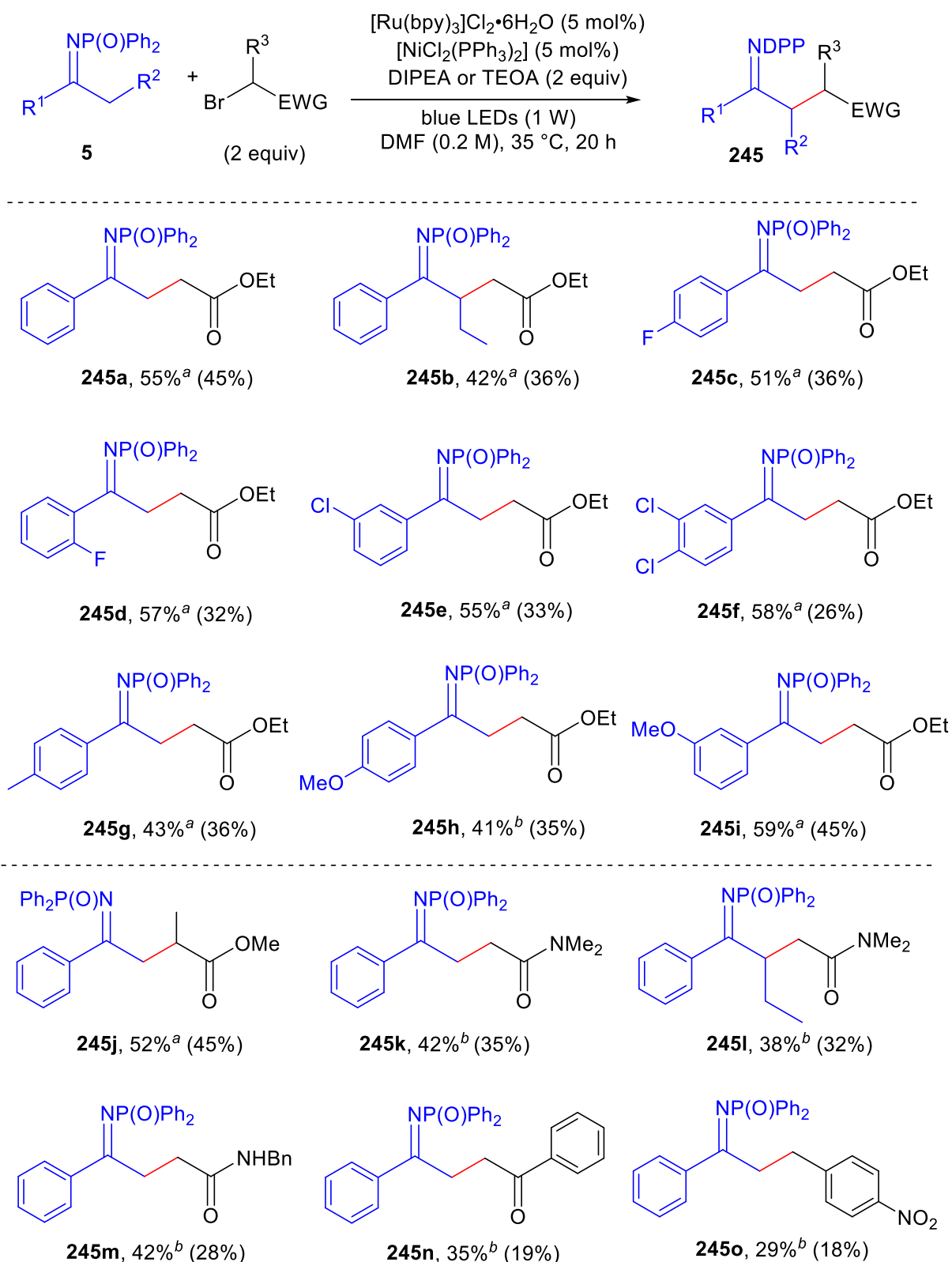


Figure 32 Substrate scope for the α -alkylation of N-diphenylphosphinoyl ketimines **5**. Reactions were performed on 0.2 mmol scale. Reaction yields (ketimine product plus enamine tautomers) were determined by ^1H NMR analysis of the reaction mixture after work-up using mesitylene as an internal standard. Isolated yields, given in parentheses, refer to spectroscopically pure product in >90% imine tautomeric form. ^a DIPEA as a base. ^b TEOA as a base.

In line with this trend, electron-rich ketimines were generally found to be less reactive than the model substrate. Alkylated ketimines with *p*-methyl (**245g**), *p*-methoxy (**245h**) and *m*-methoxy (**245i**) substituents on the aromatic ring were obtained in 35%–45% yield. Even more electron-rich ketimines, such as those derived from *tert*-butyl methyl ketone, cyclohexyl methyl ketone and 2-acetylthiophene, displayed low reactivity and gave the α -alkylated products using TEOA in 15%, 22% and 22% NMR yields respectively.

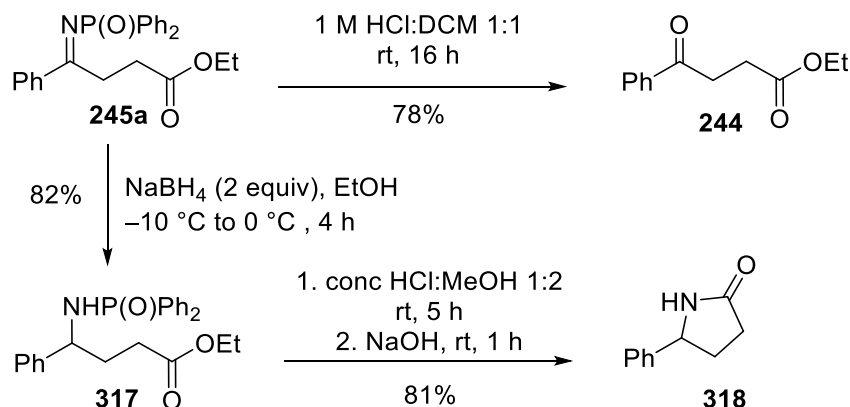
Next, the substrate scope on the bromoalkyl component was investigated. The use of ethyl 2-bromopropionate delivered product **245j** in 45% yield. Electron-withdrawing groups different from an ester could be used, although they showed lower reactivity, thus requiring the use of TEOA as a base. 2-Bromoacetamides were found to be compatible alkylating agents, delivering compounds **245k** and **245m** in 35% and 28% yield, respectively. 2-Bromoacetophenone effected the alkylation of the model ketimine in 19% yield (**245n**), while ethyl bromodifluoroacetate and diethyl bromomalonate were not suitable reaction partners. Alkylating agents lacking the α -carbonyl group (*e.g.* benzyl bromide) were not reactive, with the partial exception of *p*-nitrobenzyl bromide, that afforded product **245o** in 18% yield.

Elongating the alkyl chain on the ketimine did not affect the reactivity significantly. Indeed *N*-DPP phenyl *n*-propyl ketimine could be alkylated with ethyl bromoacetate and 2-bromo-*N,N*-dimethylacetamide obtaining compounds **245b** and **245l** with isolated yields (36% and 32% respectively) nearly comparable to those of acetophenone-derived ketimine **245a**.

6.5 Synthetic Transformations of the Product

To demonstrate synthetic applicability, chemoselective transformations of compound **245a** were performed (Scheme 79). The imine functionality was hydrolysed to afford γ -keto ester **244** in 78% yield. Reduction of the C=N bond using sodium borohydride provided γ -amino ester **317**, a protected GABA analogue, in 82% yield. Maintaining the temperature below 0 °C

was critical to avoid undesired reduction of the ester functionality and cleavage of the DPP group by attack of sodium ethoxide. Amino ester **317** could be deprotected under acidic conditions and then cyclised using sodium hydroxide in a one-pot procedure, affording γ -lactam **318** in 81% yield.

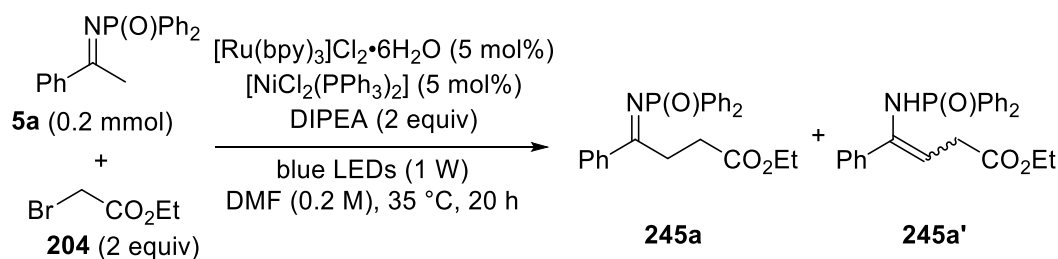


Scheme 79 Synthetic manipulations of γ -imino ester **245a**.

6.6 Mechanistic Investigations

6.6.1 Control Experiments

Control experiments were run to gather more information (Table 23). Omitting $[\text{NiCl}_2(\text{PPh}_3)_2]$ decreased conversion and yield (entries 2 and 3). No product formation was observed in the absence of base or light (entries 4 and 5), thus ruling out simple radical or $\text{S}_{\text{N}}2$ -type reactivity, while small amounts of **245a** and **245a'** were formed under light irradiation without photocatalyst (entry 6). This may be due to the direct, uncatalysed photoexcitation of the enamine tautomer of the starting ketimine^{269,270} or of a donor-acceptor complex between enamine **5a'** and ethyl bromoacetate, in line with reports from Melchiorre and coworkers (see Scheme 71).²⁵⁴ TEMPO, a stable radical acting as a trap for carbon-centred radicals generated in the course of a reaction, has been used as a mechanistic probe.²⁷¹ Addition of 1 equivalent of TEMPO inhibited product formation, indicating that radical intermediates are involved in the reaction (entry 7).



Entry	Change to conditions above	Conversion (%)	245a (%)	245a' (%)
1	none	56	50	5
2	without $[\text{NiCl}_2(\text{PPh}_3)_2]$	38	28	10
3	without $[\text{NiCl}_2(\text{PPh}_3)_2]$ for 45 h	43	33	11
4	without DIPEA	12	0	0
5	in the dark	0	0	0
6	without $[\text{Ru}(\text{bpy})_3]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$	7	4	2
7	with TEMPO (1 equiv)	10 ^a	0	0

Table 23 Control experiments. Conversion and NMR yields were determined respectively by ^{31}P and ^1H NMR analysis of the reaction mixture after work-up using mesitylene (28 μL , 0.2 mmol, 1 equiv) as an internal standard. ^a Hydrolysis of starting material to diphenylphosphinamide was observed.

Next, light dark/cycles for the reaction between **5a** and **204** using either DIPEA or TEOA were performed (Figure 33). The reaction vials were alternatively irradiated with blue light in the standard setup, then placed in a 35 °C bath covered with aluminium foil. Aliquots of the reaction mixture (50 μL) were taken every 30 or 60 minutes, diluted with CDCl_3 (400 μL) and analysed by ^{31}P NMR. The conversion plotted in the graphs represents the consumption of **5a** as determined by ^{31}P NMR analysis. Each reaction was run in duplicate and the average value of conversion is plotted in the graphs (see Section 7.7.7 in the experimental section for full data). Light/dark experiments using either base confirmed that the reaction proceeded significantly only under light irradiation.^{xix} However, according to a recent study by Yoon and co-workers,

^{xix} Minor positive and negative variations in conversion observed over dark periods are attributable to the error associated with the sampling and monitoring technique. Over time, the rate of reaction promoted by DIPEA slows down, hence the steepness of the curve in periods of light irradiation decreases.

this evidence cannot rule out the contribution of radical chain reactions to the overall mechanism.²⁶⁹

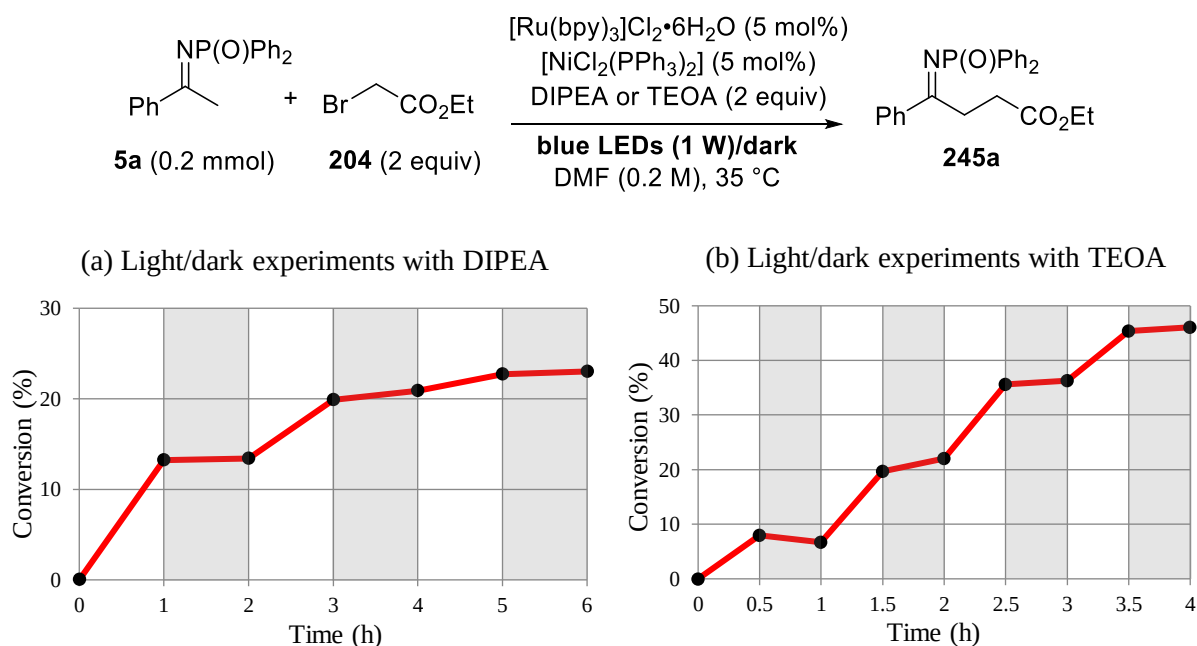
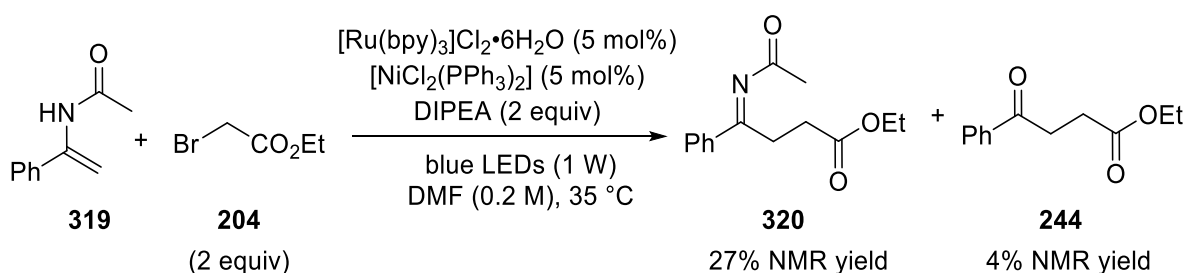


Figure 33 Light/dark experiments for the photoredox-catalysed α -alkylation of ketimines.

Finally, we decided to run the reaction on a preformed enamine. When *N*-DPP ketimine **5a** was replaced by enamide **319**, formation of the expected alkylated product **320** (alongside hydrolysed ketoester **244** and unreacted starting material, Scheme 80) was observed,^{xx} suggesting that the addition of an α -carbonyl radical to an enamide double bond is viable. Such hypothesis would be in accordance with the mechanisms postulated by Rueping for the photoredox-catalysed cyclisation of α -chloroenamides²⁵⁹ (see Scheme 77).



Scheme 80 Reaction of enamide **319** under the standard conditions.

^{xx} When the reaction was repeated in the dark, no conversion was observed (95% of unreacted enamide **319** detected by ¹H NMR analysis of the crude mixture).

6.6.2 NMR Studies on Ketimine/Enamine Tautomerism

Our mechanistic hypothesis based on the attack of an electron-deficient radical to an enamine double bond may seem to contradict the observation that electron-rich ketimines are less reactive than electron-poor ones. However, this apparent discrepancy can be explained by the unfavourable ketimine/enamine equilibrium of electron-rich substrates. The ketimine/enamine equilibrium for substrates **5a**, **5b** and **5g** (0.2 M solutions in DMSO-d₆,^{xxi} in the presence or absence of 2 equivalents of DIPEA and TEOA) was studied by ¹H and ³¹P NMR analysis (Figure 34).

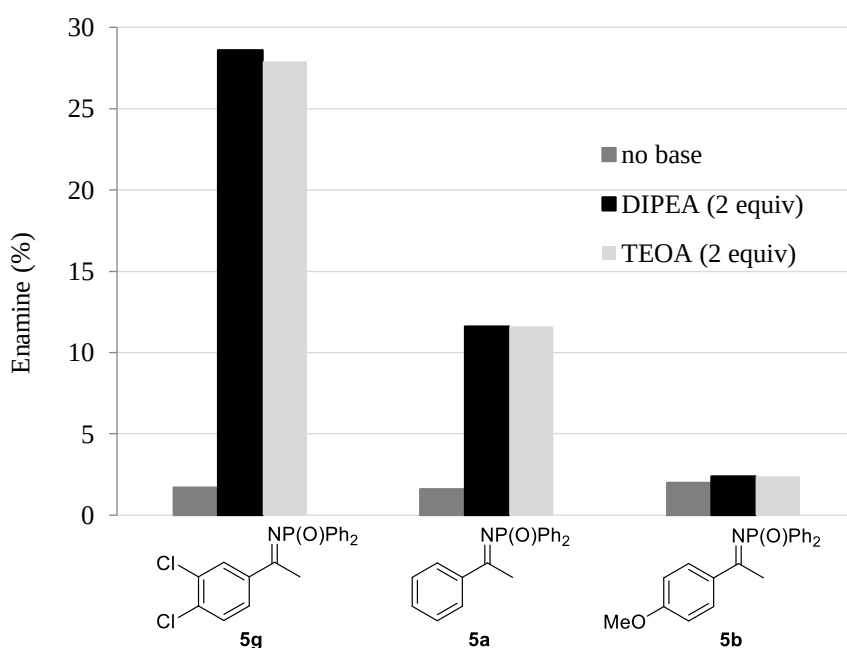


Figure 34 Percentage of enamine tautomer in 0.2 M solutions of **5g**, **5a** and **5b** in DMSO-d₆ after 5 hours, as determined by ¹H and ³¹P NMR analysis.

For all ketimines, the use of a base promoted enamine formation and no differences between DIPEA and TEOA emerged. The extent of tautomerisation appeared to be strongly dependent on the nature of the ketimine itself, with electron-poor ketimine **5g** significantly more prone to tautomerisation than the electron-rich compound **5b** (27% vs 3% enamine formed in the

^{xxi} DMSO-d₆ was chosen as a cheaper alternative to DMF-d₇ to avoid peak overlap, given that the reaction profile is very similar (see Section 6.3.2).

presence of base), and the model substrate **5a** tautomerising up to 12% at the equilibrium. For each substrate, additional data in Section 7.6, show that the ketimine/enamine equilibrium position is reached relatively quickly (within one hour), maintained for at least 48 hours and not influenced by the addition of 5 mol% $[\text{NiCl}_2(\text{PPh}_3)_2]$. Importantly, the extent of tautomerisation of the ketimines parallels their reactivity in the present photoredox-catalysed α -alkylation, thus suggesting that the reactive species is the enamine tautomer of the starting material.

6.6.3 Luminescence Quenching Studies

Spectroscopic studies were then performed to determine which species was responsible for the quenching of the phosphorescence emitted by the excited photocatalyst (see Section 6.2.1). Solutions of DIPEA, TEOA, ethyl bromoacetate **204**, 3',4'-dichloroacetophenone-derived ketimine **5g** with and without 2 equivalents of TEOA, and acetophenone-derived ketimine **5a** were prepared in DMF (0.025–0.25 M) in the presence of 1 μM $[\text{Ru}(\text{bpy})_3]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$. At such concentrations, the absorbance of each compound was less than 0.1 across the visible spectrum (400–800 nm), hence inner filter effects did not alter the luminescence measurements.²⁴⁶ The solutions were prepared under air, degassed for 15 minutes by bubbling N_2 , and then transferred under N_2 into a 1 cm quartz cuvette.

It was found that both DIPEA and a 1:2 mixture of ketimine **5g** and TEOA (ketimine:enamine ratio 79:21 by ^{31}P NMR) can act as quenchers (Figure 35).

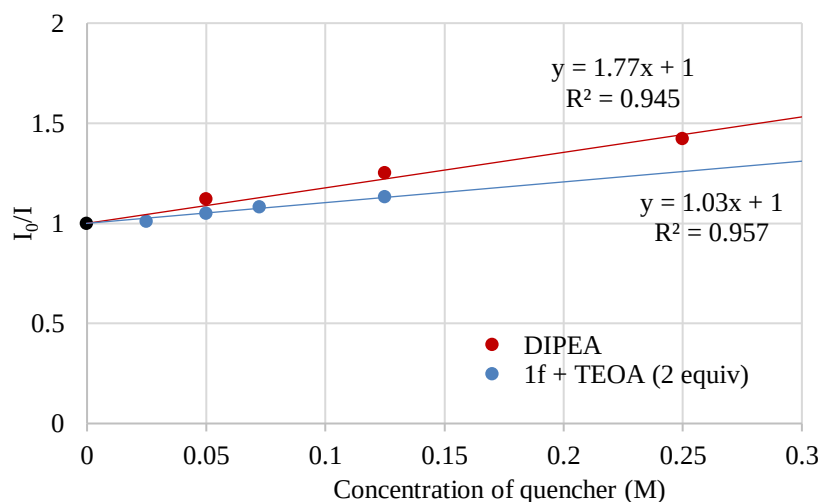


Figure 35 Luminescence quenching studies. $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ 1 μM in DMF; λ_{exc} 452 nm; λ_{em} 620 nm.

On the other hand, ketimines **5a**, **5g**, TEOA^{xxii} and ethyl bromoacetate^{xxiii} **204** did not quench the luminescence of the excited ruthenium complex (see Section 7.6.12). These results imply that, in case of ketimine **5g**, the enamine tautomer is responsible for the observed quenching. The percentage of enamine **5g'** present in the samples was measured by ³¹P NMR analysis (100 μL of DMSO- d_6 were added to 400 μL of sample to allow locking and shimming). Regardless of their concentration, all samples displayed a 79:21 ketimine:enamine ratio, in good agreement with the 72:28 ratio observed in the NMR studies for 0.2 M solutions in pure DMSO- d_6 (see Section 6.6.2). The concentration of enamine **5g'** was therefore calculated by multiplying the nominal concentration of **5g** by a factor 0.21, and was plotted against I_0/I (Figure 36). As expected, the linear correlation between concentration of the quencher and I_0/I was maintained and the value of the angular coefficient increased.

^{xxii} It is known that TEOA does not reductively quench $[Ru(bpy)_3]^{2+}$.²⁷²

^{xxiii} Similarly, it has been previously observed that α -bromocarbonyl compounds do not quench $[Ru(bpy)_3]^{2+}$ either.²⁴⁹

Entry	5g ^a (M)	5g' ^b (mM)	I (a.u.)	I ₀ /I
1	0	0	406.7	1
2	0.025	5.25	403.4	1.008
3	0.05	10.5	387.7	1.049
4	0.0725	15.2	376.5	1.080
5	0.125	26.2	359.6	1.131

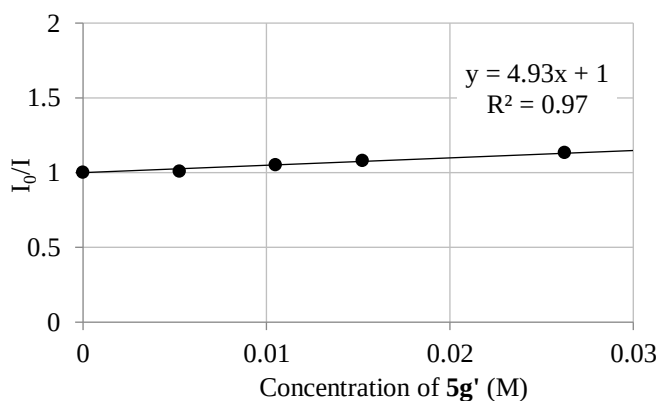


Figure 36 Luminescence measurements and Stern-Volmer plot for DMF solutions of **5g** and TEOA (2 equiv). $[\text{Ru}(\text{bpy})_3]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ 1 μM in DMF; λ_{exc} 452 nm; λ_{em} 620 nm; PMT voltage 900 V. ^a With TEOA (2 equiv). ^b Concentration of **5g'** estimated by ^1H NMR analysis.

All the luminescence quenching experiments described above were performed without $[\text{NiCl}_2(\text{PPh}_3)_2]$, that was initially excluded by the studies in consideration of the fact that the reaction still takes place in its absence. $[\text{NiCl}_2(\text{PPh}_3)_2]$ absorbs light in the visible region at both the excitation and the emission wavelengths of the photocatalyst (452 nm and 620 nm, respectively) with a maximum at 622 nm (Figure 37).^{xxiv} Indeed, the samples used for the measurements displayed a range of colors from orange to dark green (Figure 38).

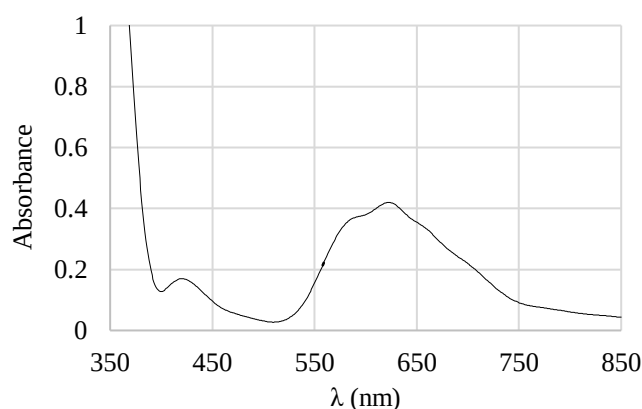


Figure 37 Electronic absorption spectrum of $[\text{NiCl}_2(\text{PPh}_3)_2]$ (12.5 mM in DMF). The visible region of the spectrum is dominated by a band at 622 nm.

^{xxiv} This property is not obviously linked to the role of $[\text{NiCl}_2(\text{PPh}_3)_2]$. It is worth remembering that the colourless $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ gave 45% yield of product (see Table 21).



Figure 38 The samples used for the Stern-Volmer studies displayed a range of colors from orange ($[\text{Ru}(\text{bpy})_3]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ 200 μM only) to dark green ($[\text{Ru}(\text{bpy})_3]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ 200 μM + $[\text{NiCl}_2(\text{PPh}_3)_2]$ 125 μM).

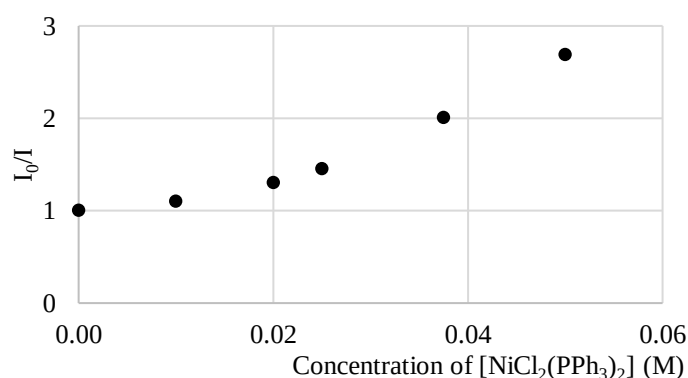


Figure 39 Luminescence quenching studies for $[\text{NiCl}_2(\text{PPh}_3)_2]$. $[\text{Ru}(\text{bpy})_3]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ 0.2 mM in DMF; λ_{exc} 452 nm; λ_{em} 620 nm.

The luminescence intensity measured in the quenching experiments decreased with increasing concentration of $[\text{NiCl}_2(\text{PPh}_3)_2]$, and the Stern-Volmer plot shows the typical upward, positive deviation from linearity that can be caused by inner filter effects or a mixed quenching process (Figure 39, see Section 6.2.1).^{xxv} Unfortunately, based on this set of experiments alone, it remains unclear whether the observed behaviour is only a result of the diminished intensity of incident light at the excitation wavelength (primary inner filter effects) and absorption of emitted photons (secondary inner filter effects) or can be, at least partially, attributed to a genuine quenching of $^*[\text{Ru}(\text{bpy})_3]^{2+}$ by $[\text{NiCl}_2(\text{PPh}_3)_2]$.

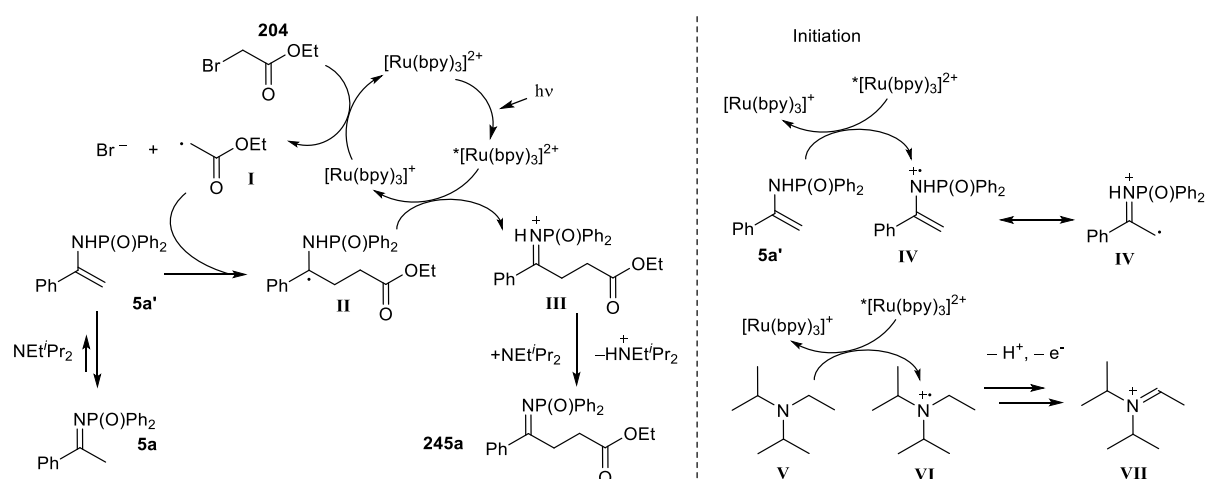
Overall, Stern-Volmer studies indicate that both DIPEA and the enamine form of the starting ketimine can quench the excited ruthenium photocatalyst. A sacrificial amount of the enamine

^{xxv} We unsuccessfully sought to apply corrections of inner filter effects to the raw data.²⁴⁶

tautomer of the starting material, whose formation is promoted by TEOA and DIPEA, can act as initiator for the catalytic cycle.

6.6.4 Proposed Mechanism

On the basis of the observations presented in the previous paragraphs and of literature precedents,²⁴⁹ we propose the mechanism depicted in Scheme 81 for the visible light-promoted, Ru-catalysed α -alkylation of *N*-diphenylphosphinoyl ketimine **5a** with ethyl bromoacetate **204**.

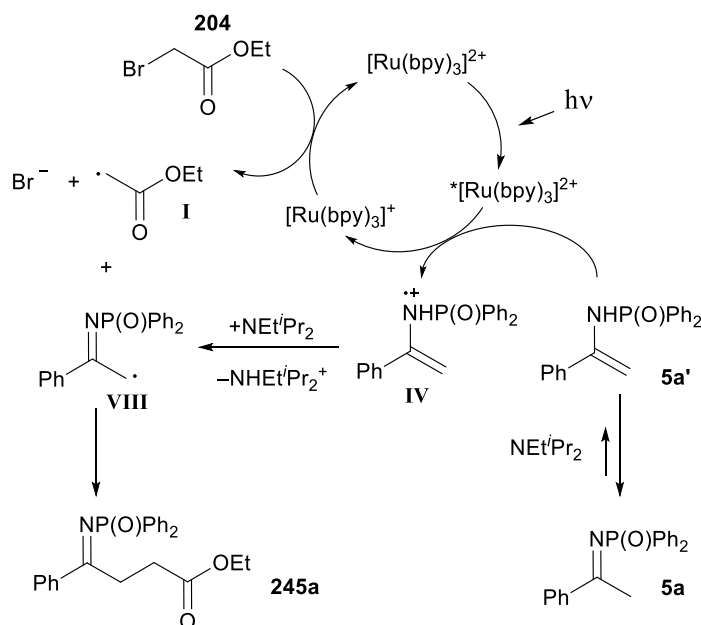


Scheme 81 Proposed mechanism for the visible light promoted, Ru-catalysed α -alkylation of *N*-DPP ketimines.

The photoexcited ruthenium catalyst is reductively quenched by DIPEA^{273,274} or by enamine **5a'** to $[\text{Ru}(\text{bpy})_3]^+$, which is then able to reduce ethyl bromoacetate generating the α -carbonyl radical **I**. This electron-deficient radical attacks the electron-rich double bond of the enamine tautomer (**5a'**) of the starting material, leading to the formation of α -amino radical **II**. The latter can be oxidised to the protonated product **III** by the $^*[\text{Ru}(\text{bpy})_3]^{2+}$ or by the less oxidising but more abundant ethyl bromoacetate, in the case a radical chain mechanism is operative.²⁶⁹ Finally, deprotonation of compound **III** affords product **245a**. Depending on the nature of the ketimine and on the reaction conditions, **5a** may tautomerise and undergo a second alkylation. The two SET steps postulated in this mechanism are predicted to be spontaneous based on reduction potentials (see Section 6.2.1): $E_{1/2}(\text{Ru}^{2+*}/\text{Ru}^+) = +0.77 \text{ V vs SCE in CH}_3\text{CN}$ ²⁷⁵ and

$E_{1/2}$ (iminium/ α -aminoradical) = ca -1.0 V vs SCE in CH_3CN ,²⁷⁶ give $\Delta E = +1.77$ V, hence $^*\text{[Ru(bpy)}_3\text{]}^{2+}$ is reduced and α -aminoradical **II** oxidised; $E_{p/2}^{\text{red}}$ (**204**) = -1.08 V vs SCE in CH_3CN ,²⁴⁵ $E_{1/2}^{\text{red}}$ (**204**) = -0.88 V vs SCE in DMF,²⁷⁷ $E_{1/2}$ ($\text{Ru}^{2+}/\text{Ru}^+$) = -1.33 V vs SCE in CH_3CN ,²⁷⁵ give $\Delta E = +0.25$ V, hence ethyl bromoacetate **204** is reduced and $[\text{Ru(bpy)}_3]^+$ oxidised.

At present, we cannot categorically exclude an alternative mechanism (Scheme 82), where α -carbonyl radical **I** couples with enamine radical cation **IV**^{278,279,280} or with α -amino radical **VIII** generated by subsequent proton abstraction). However, this mechanism appears to be less likely as α -aminoradicals ($E_{1/2}$ (iminium/ α -aminoradical) = ca -1.0 V in CH_3CN vs SCE)²⁷⁶ are much easier to oxidise than enamines (E_p (enamine radical cation/enamine) = ca $+0.4$ V in CH_3CN vs SCE),^{281,254} therefore $^*\text{[Ru(bpy)}_3\text{]}^{2+}$ should oxidise intermediate **II** preferentially over **5a'**. Moreover, the coupling between two electron-poor species such as **I** and **VIII** or **IV** would suffer from unfavourable electronic effects.



Scheme 82 Alternative mechanism involving enamine radical cations.

The beneficial effect of $[\text{NiCl}_2(\text{PPh}_3)_2]$ on yield and conversion might be linked to its ability to stabilise the radical species generated during the reaction or promote a more efficient reaction pathway.²⁸² For instance, Dexter energy transfer from the excited photocatalyst to the nickel

complex might take place and provide an alternative mechanistic manifold, as recently reported.²⁸³

6.7 Conclusions

A mild α -alkylation of *N*-diphenylphosphinoyl ketimines with α -bromocarbonyl compounds has been accomplished in moderate yields using nickel and ruthenium light-promoted catalysis. After the serendipitous discovery of the reaction, extensive optimisation was carried out trying to strike a fine balance between reactivity and selectivity, *i.e.* promoting the formation of the product while at the same time avoiding dialkylation. The substrate scope was then assessed across 12 ketimines and 6 alkyl bromides possessing an electron-withdrawing group at the α position. A reactivity trend emerged, with electron-deficient ketimines being more reactive than electron-rich substrates, presumably due to a favourable enamine/ketimine equilibrium. The product γ -imino esters were easily transformed into 1,4-dicarbonyl compounds, GABA analogues and γ -lactams. The mechanism, investigated through preliminary control, NMR and luminescence quenching experiments, likely proceeds *via* the attack of an α -carbonyl radical to the enamine tautomer of the starting material. However, more detailed spectroscopic experiments (*e.g.* fluorescence lifetime measurements, transient absorption experiments, determination of the quantum yield) as well as computational and kinetic studies would be required to fully elucidate the mechanism and clarify the role of the nickel co-catalyst.

7 Experimental Section

7.1 General Remarks

Reactions were performed with magnetic stirring under nitrogen or argon using standard Schlenk techniques, unless otherwise stated. Chemicals were obtained from commercial suppliers and used as received.

Bulk solutions were evaporated using a Büchi rotary evaporator under reduced pressure. Solvents were commercially supplied or dried by filtration through activated alumina columns (powder ~150 mesh, pore size 58 Å, basic, Sigma-Aldrich) columns. DMF, dioxane and EtOAc were stored over 4 Å molecular sieves, previously activated by heating at 200 °C under vacuum for at least 12 h. Petrol ether (PE) refers to distilled light petroleum of fraction (30 – 40 °C).

Flash column chromatography (FCC) was carried out using Geduran® silica gel 60 (40–63 µm) as stationary phase.²⁸⁴ All reactions were followed by thin-layer chromatography (TLC) when practical, using Merck Kieselgel 60 F₂₅₄ fluorescent treated silica. Visualisation was accomplished under UV light (λ_{max} 254 nm) and by staining with aqueous potassium permanganate alkaline solution or vanillin staining dip (prepared by adding 2.5 mL of concentrated H₂SO₄ to a solution of 15 g of vanillin in 250 mL EtOH 95%_{v/v}).

Enantiomeric excesses were determined by HPLC analysis on an Agilent 1200 Series instrument using the chiral stationary phase column specified in the individual experiment and by comparing the sample with the appropriate racemic mixture. HPLC samples were prepared by dissolving 1 mg of compound in EtOH:*i*-PrOH 1:1 (1 mL).

NMR spectra were recorded on Bruker spectrometers operating at 300, 400 or 500 MHz (¹H resonance). Proton and carbon chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane with the solvent resonance as internal standard.²⁸⁵ ¹H NMR spectra are reported as follows: ppm (multiplicity, coupling constants, number of protons, assignment).

The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, br = broad signal, app = apparent. Coupling constants (J) are given in Hertz (Hz) and are rounded to the nearest integer or half integer. ^{13}C , ^{19}F and ^{31}P NMR spectra were recorded with proton decoupling. Two-dimensional NMR spectroscopy experiments (COSY, HSQC and HMBC) were used where appropriate to assist in the assignment of signals in ^1H and ^{13}C spectra and data are not reported.

High resolution mass spectra were recorded by the University of Oxford mass spectrometry staff on a Bruker MicroTOF mass spectrometer equipped with an ESI source or on a Micromass GCT equipped with an EI source.

Infrared absorption spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer from a thin film (the sample was dissolved in CHCl_3 and the solvent evaporated) on a diamond ATR module. Bands (ν_{max}) are reported in wavenumbers (cm^{-1}) and their intensity is indicated as strong (s), medium (m) or weak (w).

UV-visible spectra were recorded on Perkin-Elmer Lambda 20 spectrometer using 1 cm quartz cuvettes. Luminescence spectra were recorded on a Fluorescence Spectrophotometer Varian Cary Eclipse using 1 cm quartz cuvettes.

Optical rotations were recorded using a Perkin Elmer 341 polarimeter. $[\alpha]_{\text{D}}^{\text{T}}$ values, reported in $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$, are calculated on the average value of ten consecutive readings. Concentrations (c) are quoted in g/100 mL with the appropriate number of significant figures; D refers to the D-line of sodium (589 nm); temperatures (T) are given in degrees Celsius ($^{\circ}\text{C}$).

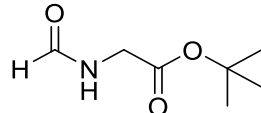
Melting points were recorded using a Reichert hot-stage microscope apparatus equipped with an analogic thermometer or a Leica Galen III hot-stage microscope apparatus with digital thermometer and are reported uncorrected.

Compound names are those generated by ACD LABS 12.0 software following the IUPAC nomenclature.

7.2 Synthesis of Chloramphenicol

7.2.1 Synthesis of *N*-Formylglycinate Esters 130

tert-Butyl *N*-formylglycinate 130c

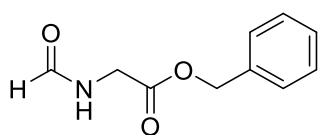
 Prepared following a literature procedure.²⁸⁶ Formamide (45.0 mL, 1.10 mol, 7.4 equiv) was added dropwise over 45 minutes to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 6.11 g, 153 mmol, 1.0 equiv) in THF (300 mL) at 0 °C. After the addition, the reaction mixture was stirred for 15 minutes at rt, then solvents were removed under reduced pressure. The resulting yellow oil was warmed to 60 °C and *tert*-butyl bromoacetate (23.0 mL, 153 mmol, 1.0 equiv) was added. The reaction mixture was stirred for 16 hours at rt, then saturated Na₂CO₃ aqueous solution (100 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 × 150 mL). The combined organic phases were washed with water, then brine, dried over Na₂SO₄, filtered and evaporated. The crude mixture was purified by FCC (from PE/AcOEt 4:1 to AcOEt), obtaining compound **130c** (17.1 g, 70%) as a pale yellow oil.

Analytical data are in accordance with those given in the literature.²⁸⁶

¹H NMR (CD₂Cl₂, 400 MHz, rotamer ratio 6:1): δ 8.18 (s, 1H, CH=O, major rotamer), 7.98 (d, *J* = 12.0 Hz, 1H, CH=O, minor rotamer), 6.59 (br s, 1H, NH), 3.91 (d, *J* = 5.5 Hz, 2H, CH₂, major rotamer), 3.85 (d, *J* = 6.5 Hz, 2H, CH₂, minor rotamer), 1.45 (s, 9H, CH₃).

¹³C NMR (CD₂Cl₂, 100 MHz): δ 169.1 (C=O), 161.4 (CH=O), 82.5 (C(CH₃)), 44.2 (CH₂, minor rotamer), 40.9 (CH₂, major rotamer), 28.1 (CH₃).

Benzyl *N*-formylglycinate **130d**



DCC (3.64 g, 17.6 mmol, 1.0 equiv) and DMAP (215 mg, 1.76 mmol, 0.1 equiv) were added in sequence to a stirred suspension of *N*-formyl glycine (2.00 g, 19.4 mmol, 1.1 equiv) and benzyl alcohol (1.8 mL, 18 mmol, 1.0 equiv) in CH₂Cl₂ (60 mL) at 0 °C. The ice bath was removed and the reaction mixture stirred for 16 hours at rt, then the insoluble solids were filtered off and solvents evaporated. Purification of the crude mixture by FCC (PE/AcOEt 1:2) afforded compound **130d** (2.60 g, 76%) as a white solid.

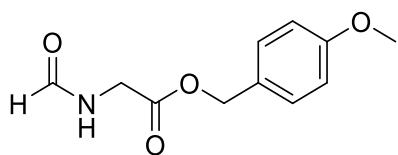
Analytical data are in accordance with those given in the literature.²⁸⁷

M.p.: 37–39 °C (lit: 40–41 °C).²⁸⁸

¹H NMR (CDCl₃, 400 MHz): δ 8.26 (s, 1H, CH=O), 7.40–7.34 (m, 5H, Ph), 6.08 (br s, 1H, NH), 5.21 (s, 2H, CH₂Ph), 4.14 (d, *J* = 5.5 Hz, 2H, NHCH₂).

¹³C NMR (CDCl₃, 100 MHz): δ 169.5 (C=O), 161.0 (CH=O), 135.1 (C_{Ar}), 128.9 (C_{Ar}H), 128.8 (C_{Ar}H), 128.6 (C_{Ar}H), 67.6 (CH₂Ph), 40.2 (NHCH₂).

(4-Methoxyphenyl)methyl *N*-formylglycinate **130e**



DCC (2.48 g, 12.0 mmol, 1.0 equiv) and DMAP (150 mg, 1.20 mmol, 0.1 equiv) were added in sequence to a stirred suspension of *N*-formyl glycine (1.36 g, 13.2 mmol, 1.1 equiv) and 4-methoxybenzyl alcohol (1.5 mL, 12 mmol, 1.0 equiv) in CH₂Cl₂ (60 mL) at 0 °C. The ice bath was removed and the reaction mixture stirred for 24 hours at rt, then filtered through Celite®. The filtrate was washed with water (15 mL) and brine (15 mL), dried over Na₂SO₄, filtered and concentrated. Purification of the crude mixture by FCC (PE/AcOEt 1:2) afforded compound **130e** (2.20 g, 82%) as a white solid.

M.p.: 56–57 °C.

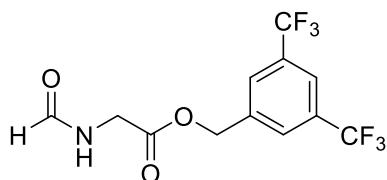
IR: 3319 (w, br), 1744 (s, OC=O), 1666 (s, HC=O), 1613 (m), 1515 (s), 1463 (w), 1386 (m), 1355 (w), 1247 (s), 1173 (s), 1031 (m), 822 (m) cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz, rotamer ratio 15:1): δ 8.21 (s, 1H, $\text{CH}=\text{O}$, major rotamer), 8.01 (d, $J = 12.0$ Hz, 1H, $\text{CH}=\text{O}$, minor rotamer), 7.28 (d, $J = 8.5$ Hz, 2H, $\text{C}_{\text{Ar}}\text{H}$), 6.88 (d, $J = 8.5$ Hz, 2H, $\text{C}_{\text{Ar}}\text{H}$), 6.38 (br s, 1H, NH , major rotamer), 6.21 (br s, 1H, NH , minor rotamer), 5.12 (s, 2H, OCH_2), 4.08 (d, $J = 5.5$ Hz, 2H, NHCH_2 , major rotamer), 3.98 (d, $J = 6.0$ Hz, 2H, NHCH_2 , minor rotamer), 3.80 (s, 3H, OCH_3).

^{13}C NMR (CDCl_3 , 100 MHz): δ 169.5 ($\text{C}=\text{O}$), 164.7 ($\text{CH}=\text{O}$, minor rotamer), 161.3 ($\text{CH}=\text{O}$, major rotamer), 160.0 (C_{Ar}), 130.5 ($\text{C}_{\text{Ar}}\text{H}$), 127.1 (C_{Ar}), 114.1 ($\text{C}_{\text{Ar}}\text{H}$), 67.4 (OCH_2), 55.4 (OCH_3), 43.3 (NHCH_2 , minor rotamer), 40.1 (NHCH_2 , major rotamer).

HRMS (ESI, MeOH): calcd. for $\text{C}_{11}\text{H}_{13}\text{NNaO}_4^+$ $[\text{M}+\text{Na}]^+$ 246.0737, found 246.0735.

[3,5-Bis(trifluoromethyl)phenyl]methyl *N*-formylglycinate **130f**



DCC (2.10 g, 10.0 mmol, 1.0 equiv) and DMAP (122 mg, 1.00 mmol, 0.1 equiv) were added in sequence to a stirred suspension of *N*-formyl glycine (1.13 g, 11.0 mmol, 1.1 equiv)

and 3,5-bis(trifluoromethyl)benzyl alcohol (2.49 g, 10.0 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) at 0 °C. The ice bath was removed and the reaction mixture stirred for 16 hours at rt, then filtered through Celite[®]. The filtrate was washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4 , filtered and evaporated to afford a white solid. Purification of the crude mixture by FCC (PE/AcOEt 2:1) afforded compound **130f** (2.37 g, 72%) as a white solid.

M.p.: 79–81 °C.

IR: 3300 (w, br), 1757 (s, OC=O), 1665 (s, HC=O), 1540 (w), 1391 (w), 1358 (w), 1289 (s), 1232 (m), 1169 (m), 1118 (s), 887 (w), 705 (w), 684 (w) cm^{-1} .

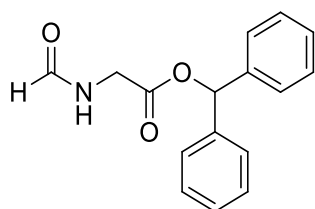
^1H NMR (CDCl_3 , 400 MHz, rotamer ratio 15:1): δ 8.27 (s, 1H, CH=O , major rotamer), 8.06 (d, J = 11.5 Hz, 1H, CH=O , minor rotamer), 7.86 (s, 1H, C_{ArH}), 7.82 (s, 2H, C_{ArH}), 6.22 (br s, 1H, NH), 5.30 (s, 2H, OCH_2), 4.17 (d, J = 5.5 Hz, 2H, NHCH_2 , major rotamer), 4.10 (d, J = 5.5 Hz, 2H, NHCH_2 , minor rotamer).

^{13}C NMR (CDCl_3 , 100 MHz): δ 169.3 (C=O), 164.4 (CH=O , minor rotamer), 161.2 (CH=O , major rotamer), 137.7 (C_{Ar}), 132.3 (q, $^2J_{\text{CF}}$ = 34.0 Hz, C_{Ar}), 128.4 (q, $^3J_{\text{CF}}$ = 3.0 Hz, C_{ArH}), 123.3 (q, $^1J_{\text{CF}}$ = 273.0 Hz, CF_3), 122.7 (C_{ArH} , sept, $^3J_{\text{CF}}$ = 3.5 Hz), 65.7 (OCH_2), 43.2 (NHCH_2 , minor rotamer), 40.0 (NHCH_2 , major rotamer).

^{19}F NMR (CDCl_3 , 376.5 MHz): δ -63.0.

HRMS (ESI, MeOH): calcd. for $\text{C}_{12}\text{H}_9\text{F}_6\text{NNaO}_3^+$ $[\text{M}+\text{Na}]^+$ 352.0379, found 352.0370.

Diphenylmethyl *N*-formylglycinate **130g**



DCC (6.81 g, 33.0 mmol, 1.1 equiv) and DMAP (4.03 g, 33.0 mmol, 1.1 equiv) were added in sequence to a stirred suspension of *N*-formylglycine (3.74 g, 36.0 mmol, 1.2 equiv) and diphenylmethanol (5.53 g, 30.0 mmol, 1.0 equiv) in CH_2Cl_2 (150 mL) at rt. The

reaction mixture was stirred for 65 hours, then filtered through Celite[®]. The filtrate was washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4 , filtered and concentrated. Purification of the crude mixture by FCC (PE/AcOEt 1:1) afforded compound **130g** (5.51 g, 68%) as a white solid.

Analytical data are in accordance with those given in the literature.¹¹¹

M.p.: 96–98 °C (lit: 96–98 °C).¹¹¹

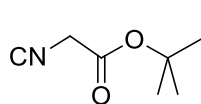
^1H NMR (CDCl_3 , 400 MHz, rotamer ratio 9:1): δ 8.17 (s, 1H, CH=O , major rotamer), 7.99 (s, 1H, CH=O , minor rotamer), 7.38–7.28 (m, 10H, C_{ArH}), 6.93 (s, 1H, CHPh_2), 6.40 (br s, 1H,

NH, major rotamer), 6.24 (br s, 1H, NH, minor rotamer) 4.17 (d, $J = 5.5$ Hz, 2H, CH₂, major rotamer), 4.02 (d, $J = 6.5$ Hz, 2H, CH₂, minor rotamer).

¹³C NMR (CDCl₃, 100 MHz): δ 168.8 (C=O), 161.5 (CH=O), 139.4 (C_{Ar}), 128.6 (C_{Ar}H), 128.2 (C_{Ar}H), 127.0 (C_{Ar}H), 78.2 (CHPh₂), 40.0 (CH₂).

7.2.2 Synthesis of Isocyanoacetate Esters 7

tert-Butyl isocyanoacetate 7c



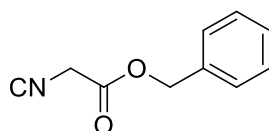
Prepared according to a literature procedure.²⁸⁶ POCl₃ (7.48 mL, 80.2 mmol, 1.1 equiv) was added dropwise over 20 minutes to a stirred solution of *tert*-butyl 2-formamidoacetate (**130c**, 11.6 g, 72.9 mmol, 1.0 equiv) and Et₃N (24.4 mL, 175 mmol, 2.4 equiv) in CH₂Cl₂ (150 mL) at 0 °C. Upon addition, the colorless reaction mixture became cloudy and turned orange, then brown. After stirring at 0 °C for 15 minutes, saturated NaHCO₃ aqueous solution (100 mL) was added and the phases were separated. The aqueous layer was extracted twice with CH₂Cl₂ (150 mL), then the collected organic phases were washed with brine, dried over K₂CO₃ and filtered. Evaporation of solvents afforded a brown oil, which was purified by FCC (PE/AcOEt 4:1). Compound **7c** (8.92 g, 87%) was obtained as a pale yellow liquid.

Analytical data are in accordance with those given in the literature.²⁸⁶

¹H NMR (CDCl₃, 400 MHz): δ 4.08 (s, 2H, CH₂), 1.43 (s, 9H, CH₃).

¹³C NMR (CDCl₃, 100 MHz): δ 162.9 (C=O), 160.3 (NC), 83.9 (C(CH₃)₃), 44.2 (CH₂), 27.7 (CH₃).

Benzyl isocyanoacetate 7d



Prepared according to a literature procedure.²⁸⁹ POCl₃ (1.33 mL, 14.2 mmol, 1.1 equiv) was added dropwise over 5 minutes to a stirred

solution of benzyl 2-formamidoacetate (**130d**, 2.50 g, 12.9 mmol, 1.0 equiv) and Et₃N (6.1 mL, 44 mmol, 3.4 equiv) in CH₂Cl₂ (40 mL) at 0 °C. Upon addition, the pale yellow solution turned pink, then orange. After stirring at 0 °C for 1.5 hours, a Na₂CO₃ aqueous solution (4 g in 20 mL of water) was added, the biphasic reaction mixture was stirred at rt for 5 minutes, water (20 mL) was then added and the phases were separated. The aqueous layer was extracted twice with CH₂Cl₂ (60 mL), then the combined organic phases were washed with brine, dried over K₂CO₃ and filtered. Evaporation of solvents afforded a brown oil, which was purified by FCC (PE/AcOEt 3:1). Compound **130d** (1.88 g, 83%) was obtained as a yellow solid.

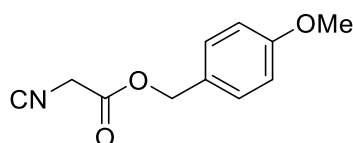
Analytical data are in accordance with those given in the literature.²⁸⁹

M.p.: 31–33 °C (lit: 27.8–28.5 °C).²⁸⁹

¹H NMR (CDCl₃, 400 MHz): δ 7.39 (s, 5H, Ph), 5.23 (s, 2H, CH₂Ph), 4.22 (s, 2H, NCH₂).

¹³C NMR (CDCl₃, 100 MHz): δ 163.9 (C=O), 161.1 (NC), 134.4 (C_{Ar}), 128.7 (C_{Ar}H), 128.6 (C_{Ar}H), 128.5 (C_{Ar}H), 68.1 (CH₂Ph), 43.4 (NCH₂).

(4-Methoxyphenyl)methyl isocyanoacetate **7e**



POCl₃ (920 μL, 9.86 mmol, 1.1 equiv) was added dropwise over 5 minutes to a stirred solution of 2-formamidoacetate **130e** (2.00 g, 8.96 mmol, 1.0 equiv) and Et₃N (3.0 mL, 22 mmol, 2.4 equiv)

in CH₂Cl₂ (45 mL) at 0 °C. After stirring at 0 °C for 2.5 hours, the reaction mixture was quenched by addition of saturated NaHCO₃ aqueous solution (15 mL). The phases were separated and the aqueous layer was extracted with CH₂Cl₂ (25 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated. The crude mixture was purified by FCC (CH₂Cl₂), affording compound **7e** (1.70 g, 92%) as a yellow solid.

M.p.: 39–41 °C.

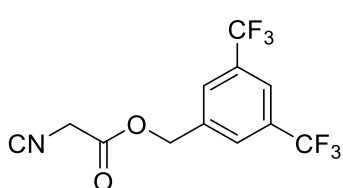
IR: 2162 (m, N≡C), 1754 (s, C=O), 1613 (m), 1515 (s), 1462 (w), 1383 (w), 1350 (w), 1245 (s), 1196 (s), 1174 (s), 1010 (m), 821 (m), 705 (w) cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ 7.31 (d, *J* = 8.5 Hz, 2H, C_{Ar}H), 6.90 (d, *J* = 8.5 Hz, 2H, C_{Ar}H), 5.18 (s, 2H, OCH₂), 4.22 (s, 2H, NCH₂), 3.81 (s, 3H, OCH₃).

¹³C NMR (CDCl₃, 100 MHz): δ 164.0 (C=O), 161.4 (NC), 160.2 (C_{Ar}), 130.7 (C_{Ar}H), 126.6 (C_{Ar}), 114.2 (C_{Ar}H), 68.4 (OCH₂), 55.4 (OCH₃), 43.7 (NCH₂).

HRMS (ESI, MeOH): calcd. for C₁₁H₁₂NO₃⁺ [M+H]⁺ 206.0812, found 206.0810.

[3,5-Bis(trifluoromethyl)phenyl]methyl isocyanoacetate **7f**



POCl₃ (0.62 mL, 6.7 mmol, 1.1 equiv) was added dropwise over 5 minutes to a stirred solution of 2-formamidoacetate **130f** (2.00 g, 6.07 mmol, 1.0 equiv) and Et₃N (2.0 mL, 15 mmol, 2.4 equiv)

in CH₂Cl₂ (30 mL) at 0 °C. After stirring at 0 °C for 1.5 hours, the reaction mixture was quenched by addition of saturated NaHCO₃ aqueous solution (15 mL). The phases were separated and the aqueous layer was extracted with CH₂Cl₂ (30 mL). The combined organic phases were dried over Na₂SO₄, filtered and evaporated to afford an orange oil. The crude mixture was purified by FCC (CH₂Cl₂), obtaining compound **7f** (1.60 g, 85%) as a pale yellow solid.

M.p.: 61–62 °C.

IR: 2165 (w, N≡C), 1766 (m, C=O), 1613 (m), 1394 (w), 1350 (w), 1278 (s), 1173 (s), 1129 (s), 1022 (w), 890 (w), 844 (w), 795 (w), 683 (m) cm⁻¹.

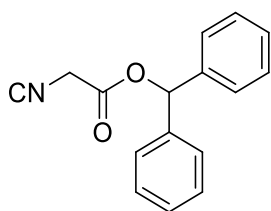
¹H NMR (CDCl₃, 400 MHz): δ 7.89 (s, 1H, C_{Ar}H), 7.84 (s, 2H, C_{Ar}H), 5.35 (s, 2H, OCH₂), 4.33 (s, 2H, NCH₂).

^{13}C NMR (CDCl_3 , 100 MHz): δ 163.8 ($\text{C}=\text{O}$), 162.3 (NC), 136.9 (C_{Ar}), 132.4 (q, $^2J_{\text{CF}} = 34.0$ Hz, C_{Ar}), 128.6 (q, $^3J_{\text{CF}} = 2.0$ Hz, C_{ArH}), 123.1 (q, $^1J_{\text{CF}} = 273.0$ Hz, CF_3), 123.0 (sept, $^3J_{\text{CF}} = 3.5$ Hz, C_{ArH}), 66.6 (OCH_2), 43.5 (NCH_2).

^{19}F NMR (CDCl_3 , 376.5 MHz): δ -63.0.

HRMS (EI): calcd. for $\text{C}_{12}\text{H}_7\text{F}_6\text{NO}_2^+$ $[\text{M}]^+$ 311.0381, found 311.0390.

Diphenylmethyl isocyanoacetate **7g**



Prepared following a literature procedure.¹¹¹ A solution of 2-formamidoacetate **130g** (4.00 g, 14.8 mmol, 1.0 equiv) and Et_3N (5.0 mL, 36 mmol, 2.4 equiv) in CH_2Cl_2 (75 mL) was cooled to 0 °C, then POCl_3 (1.5 mL, 16 mmol, 1.1 equiv) was added dropwise over 10

minutes. During the addition the reaction mixture turned yellow. The reaction mixture was stirred at 0 °C for 1.5 hours, then saturated Na_2CO_3 aqueous solution was added (30 mL) and the phases were separated. The organic layer was washed with water (30 mL), brine (30 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude mixture was purified by FCC (PE/AcOEt 4:1) affording compound **7g** (3.13 g, 84%) as a pale orange solid.

Analytical data are in accordance with those given in the literature.^{111,290}

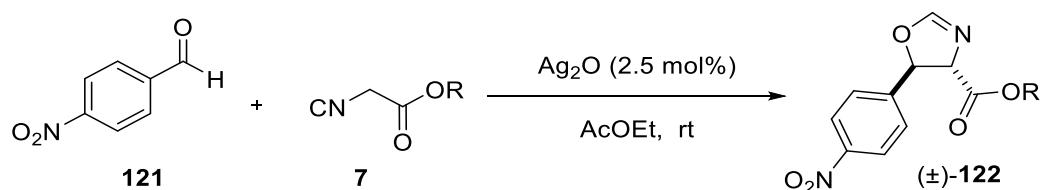
M.p.: 54 °C (lit: 57 °C).²⁹⁰

^1H NMR (CDCl_3 , 400 MHz): δ 7.39–7.33 (m, 10H, C_{ArH}), 6.99 (s, 1H, CHPh_2), 4.30 (s, 2H, CH_2).

^{13}C NMR (CDCl_3 , 100 MHz): δ 163.1 ($\text{C}=\text{O}$), 161.7 (NC), 138.9 (C_{Ar}), 128.8 (C_{ArH}), 128.5 (C_{ArH}), 127.1 (C_{ArH}), 79.3 (CHPh_2), 43.7 (CH_2).

7.2.3 Synthesis and Characterisation of Oxazolines 122

General Procedure I for the synthesis of racemic oxazolines 122



Ag_2O (1.4 mg, 0.0063 mmol, 0.025 equiv) was added to a stirred solution of isocyanoacetate **7** (0.250 mmol, 1.0 equiv) and 4-nitrobenzaldehyde **121** (42.0 mg, 0.275 mmol, 1.1 equiv) in AcOEt (25 mL). The resulting mixture was stirred at rt until the isocyanoacetate was consumed (as judged by TLC, PE/ AcOEt 4:1, stained with vanillin staining dip). The reaction mixture was quickly filtered through Celite[®] eluting with AcOEt . The filtrate was concentrated under reduced pressure and purified by FCC (PE/ AcOEt) obtaining **(±)-122**.

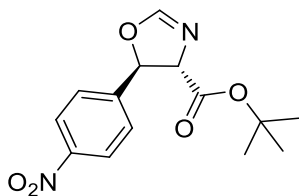
General Procedure II for the asymmetric synthesis of oxazolines 122



The desired ligand **31** (0.0125 mmol, 0.05 equiv), Ag_2O (1.4 mg, 0.0063 mmol, 0.025 equiv) and powdered 4 Å molecular sieves (72 mg per 0.25 mmol of **7**) were stirred in AcOEt (15 mL) at rt for 15 minutes. A solution of isocyanoacetate **7** (0.250 mmol, 1.0 equiv) in AcOEt (5 mL) was then added. After approximately 5 minutes, a solution of 4-nitrobenzaldehyde (42.0 mg, 0.275 mmol, 1.1 equiv) in AcOEt (5 mL) was added, then the reaction mixture was stirred at rt until the isocyanoacetate was consumed (as judged by TLC, PE/ AcOEt 4:1, stained with vanillin staining dip). The reaction mixture was quickly filtered through Celite[®] eluting with

AcOEt. The filtrate was concentrated under reduced pressure and purified by FCC with the eluent indicated below for each compound.

tert*-Butyl (4*S*,5*R*)-5-(4-nitrophenyl)-4,5-dihydro-1,3-oxazole-4-carboxylate **122c*



Obtained according to General Procedure **II**, using **31c** (7.3 mg, 0.0125 mmol, 0.05 equiv) and *tert*-butyl isocynoacetate **7c** (35.3 mg, 0.250 mmol, 1.0 equiv). The crude mixture was purified by FCC

(from PE/AcOEt 4:1 to 1:1) obtaining compound **122c** (51.1 mg, 70%) as an off-white solid.

Enantiomeric excess (78% ee) determined by HPLC under the following conditions: Chiralpak OD column, hexane/*i*-PrOH 90:10, flow 1.0 mL/min, λ 254 nm, *t* (major) = 13.6 min, *t* (minor) = 16.8 min.

M.p.: 65–70 °C.

IR: 2980 (w), 2927 (w), 1747 (s, C=O), 1637 (m, C=N), 1603 (w), 1511 (s, NO₂ asymmetric), 1346 (s, NO₂ symmetric), 1315 (w), 1229 (m), 1151 (s), 1109 (m), 1081 (s), 1051 (s), 1014 (w), 968 (m), 841 (s), 787 (m), 751 (w), 721 (m), 697 (m), 667 (m) cm⁻¹.

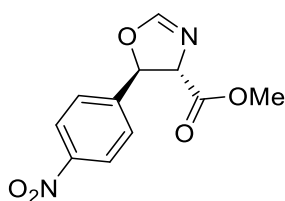
¹H NMR (DMSO-*d*₆, 500 MHz): δ 8.29 (d, *J* = 8.5 Hz, 2H, C_{Ar}H), 7.61 (d, *J* = 8.5 Hz, 2H, C_{Ar}H), 7.54 (d, *J* = 2.0 Hz, 1H, N=CH), 5.75 (d, *J* = 7.5 Hz, 1H, OCHAr), 4.49 (dd, *J* = 7.5, 2.0 Hz, 1H, NCHCH), 1.46 (s, 9H, CH₃).

¹³C NMR (DMSO-*d*₆, 125 MHz): δ 168.8 (C=O), 156.4 (C=N), 147.5 (C_{Ar}), 146.7 (C_{Ar}), 127.0 (C_{Ar}H), 124.0 (C_{Ar}H), 81.9 (C(CH₃)₃), 80.1 (OCHAr), 75.6 (NCHCH), 27.6 (CH₃).

HRMS (ESI, MeOH): calcd. for C₁₄H₁₆N₂NaO₅⁺ [M+Na]⁺ 315.0951, found 315.0957.

[α]_D²⁰: +119 (c 1.43, AcOEt, sample with 65% ee).

Methyl (4*S*,5*R*)-5-(4-nitrophenyl)-4,5-dihydro-1,3-oxazole-4-carboxylate **122a**



Obtained according to General Procedure **II**, using **31c** (7.3 mg, 0.0125 mmol, 0.05 equiv) and methyl isocyanoacetate (26.1 mg, 0.250 mmol, 1.0 equiv). The crude mixture was purified by FCC (PE/AcOEt 3:2 to 1:2) obtaining compound **122a** (50.0 mg, 80%) as a pale yellow oil.

Enantiomeric excess (82% ee) determined by HPLC: Chiralpak AD column, hexane/*i*-PrOH 85:15, flow 1.0 mL/min, λ 240 nm, *t* (minor) = 17.3 min, *t* (major) = 26.6 min.

IR: 1739 (m, C=O), 1628 (m, C=N), 1606 (w), 1520 (s, NO₂ asymmetric), 1437 (w), 1346 (s, NO₂ symmetric), 1205 (m), 1097 (s), 973 (w), 852 (m), 736 (m), 696 (m) cm⁻¹.

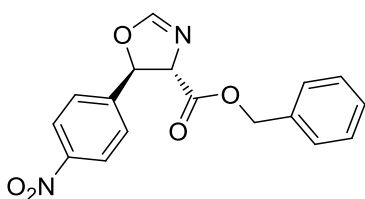
¹H NMR (CDCl₃, 400 MHz): δ 8.26 (d, *J* = 8.5 Hz, 2H, C_{Ar}H), 7.52 (d, *J* = 8.5 Hz, 2H, C_{Ar}H), 7.13 (d, *J* = 2.0 Hz, 1H, N=CH), 5.80 (d, *J* = 8.0 Hz, 1H, OCHAr), 4.58 (dd, *J* = 8.0, 2.0 Hz, 1H, NCHCH), 3.87 (s, 3H, CH₃). ¹H NMR is in accordance with that given in the literature.²⁹¹

¹³C NMR (CDCl₃, 100 MHz): δ 170.5 (C=O), 156.1 (C=N), 148.2 (C_{Ar}), 146.1 (C_{Ar}), 126.4 (C_{Ar}H), 124.4 (C_{Ar}H), 80.9 (OCHAr), 75.7 (NCHCH), 53.3 (CH₃).

HRMS (ESI, MeOH): calcd. for C₁₁H₁₀N₂NaO₅⁺ [M+Na]⁺ 273.0482, found 273.0481.

[α]_D²⁰: +198 (c 0.15, AcOEt, sample with 82% ee).

Benzyl (4*S*,5*R*)-5-(4-nitrophenyl)-4,5-dihydro-1,3-oxazole-4-carboxylate **122d**



Obtained according to General Procedure **II**, using **31c** (7.3 mg, 0.0125 mmol, 0.05 equiv) and benzyl isocyanoacetate (**7d**, 43.8 mg, 0.250 mmol, 1.0 equiv). The crude mixture was purified by

FCC (PE/AcOEt 4:1 to 3:1) obtaining compound **122d** (49.8 mg, 61%) as a pale yellow solid.

Enantiomeric excess (87% ee) determined by HPLC: Chiralpak AD column, hexane/*i*-PrOH 85:15, flow 1.0 mL/min, λ 254 nm, *t* (minor) = 25.3 min, *t* (major) = 28.4 min.

M.p.: 85–87 °C.

IR: 3090 (w), 2962 (w), 2837 (w), 1728 (s, C=O), 1628 (m, C=N), 1606 (w), 1519 (s, NO₂ asymmetric), 1459 (w), 1380 (w), 1348 (s, NO₂ symmetric), 1315 (w), 1242 (s), 1213 (s), 1079 (s), 1039 (w), 1014 (w), 964 (m), 912 (w), 890 (w), 856 (m), 845 (m), 770 (m), 759 (s), 717 (m), 699 (s) cm⁻¹.

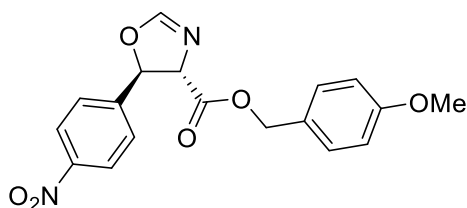
¹H NMR (DMSO-d₆, 400 MHz): δ 8.26 (d, *J* = 8.5 Hz, 2H, C_{Ar}NO₂H), 7.61 (d, *J* = 8.5 Hz, 2H, C_{Ar}NO₂H), 7.57 (d, *J* = 2.0 Hz, 1H, N=CH), 7.42–7.35 (m, 5H, Ph), 5.88 (d, *J* = 7.5 Hz, 1H, OCHAr), 5.23 (s, 2H, OCH₂Ph), 4.71 (dd, *J* = 7.5, 2.0 Hz, 1H, NCHCH).

¹³C NMR (DMSO-d₆, 100 MHz): δ 169.6 (C=O), 156.7 (C=N), 147.5 (C_{Ar}NO₂), 146.4 (C_{Ar}NO₂), 135.5 (C_{Ph}), 128.5 (C_{Ar}H), 128.2 (C_{Ar}H), 128.1 (C_{Ar}H), 127.1 (C_{Ar}H), 124.0 (C_{Ar}H), 80.0 (OCHAr), 74.7 (NCHCH), 66.7 (OCH₂Ph).

HRMS (ESI, MeOH): calcd. for C₁₇H₁₄N₂NaO₅⁺ [M+Na]⁺ 349.0795, found 349.0796.

[α]_D²⁰: +103 (c 0.75, AcOEt, sample with 87% ee).

(4-Methoxyphenyl)methyl (4*S*,5*R*)-5-(4-nitrophenyl)-4,5-dihydro-1,3-oxazole-4-carboxylate **122e**



Obtained according to General Procedure **II**, using **31d** (7.7 mg, 0.0125 mmol, 0.05 equiv) and isocyanoacetate **7e** (51.3 mg, 0.250 mmol, 1.0 equiv). The crude mixture was purified by FCC (PE/AcOEt 3:1 to 1:1) obtaining compound **122e** (56.1 mg, 63%) as a pale yellow oil.

Enantiomeric excess (86% ee) determined by HPLC: Chiralpak AD column, hexane/*i*-PrOH 80:20, flow 1.0 mL/min, λ 254 nm, *t* (minor) = 26.2 min, *t* (major) = 30.5 min.

IR: 3359 (w, br), 2935 (w), 2840 (w), 1739 (m, C=O), 1684 (m), 1629 (w, C=N), 1611 (w), 1516 (s, NO₂ asymmetric), 1462 (w), 1347 (s, NO₂ symmetric), 1248 (s), 1175 (m), 1108 (m), 1032 (m), 968 (w), 835 (w), 824 (w), 720 (w) cm⁻¹.

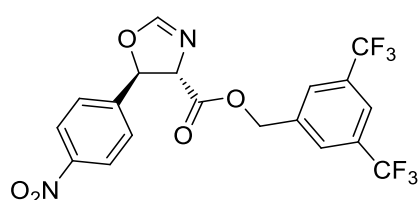
^1H NMR (DMSO- d_6 , 400 MHz): δ 8.26 (d, J = 8.5 Hz, 2H, $\text{C}_{\text{ArNO}_2}\text{H}$), 7.60 (d, J = 8.5 Hz, 2H, $\text{C}_{\text{ArNO}_2}\text{H}$), 7.57 (d, J = 2.0 Hz, 1H, $\text{N}=\text{CH}$), 7.35 (d, J = 9.0 Hz, 2H, $\text{C}_{\text{ArOMe}}\text{H}$), 6.95 (d, J = 9.0 Hz, 2H, $\text{C}_{\text{ArOMe}}\text{H}$), 5.85 (d, J = 7.5 Hz, 1H, OCHAr), 5.15 (s, 2H, OCH_2Ar), 4.66 (dd, J = 7.5, 2.0 Hz, 1H, NCHCH), 3.75 (s, 3H, OCH_3).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 169.6 ($\text{C}=\text{O}$), 159.3 (C_{ArOMe}), 156.7 ($\text{C}=\text{N}$), 147.5 (C_{ArNO_2}), 146.4 (C_{ArNO_2}), 130.1 ($\text{C}_{\text{ArOMe}}\text{H}$), 127.4 (C_{ArOMe}), 127.0 ($\text{C}_{\text{ArNO}_2}\text{H}$), 124.0 ($\text{C}_{\text{ArNO}_2}\text{H}$), 113.9 ($\text{C}_{\text{ArOMe}}\text{H}$), 80.0 (OCHAr), 74.7 (NCHCH), 66.6 (OCH_2Ar), 55.1 (OCH_3).

HRMS (ESI, MeOH): calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{NaO}_6^+ [\text{M}+\text{Na}]^+$ 379.0890, found 379.0901.

$[\alpha]_D^{20}$: +142 (c 0.33, AcOEt, sample with 86% ee).

[3,5-Bis(trifluoromethyl)phenyl]methyl (4*S*,5*R*)-5-(4-nitrophenyl)-4,5-dihydro-1,3-oxazole-4-carboxylate **122f**



Obtained according to General Procedure **II**, using **31d** (7.7 mg, 0.0125 mmol, 0.05 equiv) and isocyanoacetate **7f** (77.8 mg, 0.250 mmol, 1.0 equiv). The crude mixture was purified by FCC (PE/AcOEt 3:1) obtaining compound **122f** (64.7 mg, 56%) as a clear oil.

Enantiomeric excess (84% ee) determined by HPLC: Chiralpak AD column, hexane/*i*-PrOH 80:20, flow 1 mL/min, λ 254 nm, t (minor) = 8.5 min, t (major) = 11.2 min.

IR: 1749 (w), 1712 (m, $\text{C}=\text{O}$), 1628 (w, $\text{C}=\text{N}$), 1526 (m, NO_2 asymmetric), 1349 (m, NO_2 symmetric), 1278 (s), 1222 (m), 1172 (s), 1131 (s), 1108 (s), 890 (w), 843 (m), 705 (m), 602 (m) cm^{-1} .

^1H NMR (DMSO- d_6 , 500 MHz): δ 8.24 (d, J = 9.0 Hz, 2H, $\text{C}_{\text{ArNO}_2}\text{H}$), 8.15 (s, 2H, $\text{C}_{\text{ArCF}_3}\text{H}$), 8.08 (s, 1H, $\text{C}_{\text{ArCF}_3}\text{H}$), 7.63 (d, J = 9.0 Hz, 2H, $\text{C}_{\text{ArNO}_2}\text{H}$), 7.60 (d, J = 2.0 Hz, 1H, $\text{N}=\text{CH}$), 5.94 (d, J = 7.5 Hz, 1H, OCHAr), 5.41 (s, 2H, OCH_2Ar), 4.81 (dd, J = 7.5, 2.0 Hz, 1H, NCHCH).

^{13}C NMR (DMSO- d_6 , 125 MHz): δ 169.5 ($\text{C}=\text{O}$), 156.9 ($\text{C}=\text{N}$), 147.5 (C_{ArNO_2}), 146.4 (C_{ArNO_2}), 139.2 (C_{ArCF_3}), 130.4 (q, $^2J_{\text{CF}}$ = 33.0 Hz, C_{ArCF_3}), 128.7 (q, $^3J_{\text{CF}}$ = 3.0 Hz, $\text{C}_{\text{ArCF}_3}\text{H}$), 127.2

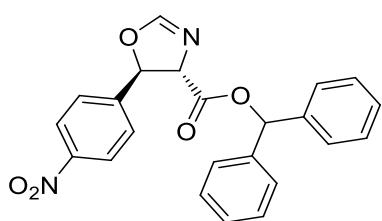
($\underline{\text{C}}_{\text{ArNO}_2\text{H}}$), 123.9 ($\underline{\text{C}}_{\text{ArNO}_2\text{H}}$), 123.3 (q, $^1J_{\text{CF}} = 273.0$ Hz, $\underline{\text{C}}_{\text{F}_3}$), 121.9 (m, $\underline{\text{C}}_{\text{ArCF}_3\text{H}}$), 79.9 ($\underline{\text{OCHAr}}$), 74.6 ($\underline{\text{NCHCH}}$), 65.2 ($\underline{\text{OCH}_2\text{Ar}}$).

^{19}F NMR (DMSO- d_6 , 470.6 MHz): δ -61.3.

HRMS (ESI, MeOH): calcd. for $\text{C}_{19}\text{H}_{13}\text{F}_6\text{N}_2\text{O}_5^+$ $[\text{M}+\text{H}]^+$ 463.0723, found 463.0713.

$[\alpha]_{\text{D}}^{20}$: +135 (c 0.29, AcOEt, sample with 84% ee).

Diphenylmethyl (4*S*,5*R*)-5-(4-nitrophenyl)-4,5-dihydro-1,3-oxazole-4-carboxylate **122g**



Obtained according to General Procedure **II**, using **31d** (7.7 mg, 0.0125 mmol, 0.05 equiv) and isocyanoacetate **7g** (62.8 mg, 0.250 mmol, 1.0 equiv). The crude mixture was purified by FCC (from PE/AcOEt 4:1 to PE/AcOEt 3:1) obtaining

compound (**4*S*,5*R***)-**122f** (78.4 mg, 78%) as an off-white solid.

Enantiomeric excess (89% ee) determined by HPLC: Chiralpak OD column, hexane/*i*-PrOH 85:15, flow 1.0 mL/min, λ 254 nm, t (major) = 26.1 min, t (minor) = 31.6 min.

M.p.: 39–41 °C.

IR: 1737 (m, C=O), 1627 (m, C=N), 1606 (w), 1522 (s, NO_2 asymmetric), 1496 (w), 1454 (w), 1347 (s, NO_2 symmetric), 1222 (m), 1176 (s), 971 (m), 850 (m), 836 (m), 748 (m), 697 (s), 647 (w) cm^{-1} .

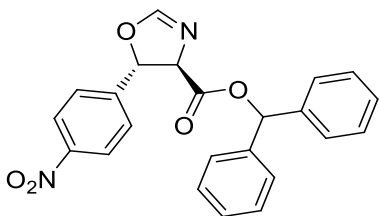
^1H NMR (DMSO- d_6 , 400 MHz): δ 8.27 (d, $J = 8.5$ Hz, 2H, $\underline{\text{C}}_{\text{ArNO}_2\text{H}}$), 7.62–7.60 (m, 3H, $\underline{\text{C}}_{\text{ArNO}_2\text{H}}$ and $\underline{\text{N=CH}}$), 7.45–7.30 (m, 10H, Ph), 6.90 (s, 1H, $\underline{\text{OCHPh}_2}$), 5.87 (d, $J = 7.5$ Hz, 1H, $\underline{\text{OCHAr}}$), 4.86 (dd, $J = 7.5, 2.0$ Hz, 1H, $\underline{\text{NCHCH}}$).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 168.8 ($\underline{\text{C}}=\text{O}$), 156.9 ($\underline{\text{C}}=\text{N}$), 147.5 ($\underline{\text{C}}_{\text{ArNO}_2}$), 146.3 ($\underline{\text{C}}_{\text{ArNO}_2}$), 140.0 ($\underline{\text{C}}_{\text{Ar}}$), 139.9 ($\underline{\text{C}}_{\text{Ar}}$), 128.6 ($\underline{\text{C}}_{\text{ArH}}$), 128.5 ($\underline{\text{C}}_{\text{ArH}}$), 128.0 ($\underline{\text{C}}_{\text{ArH}}$), 127.9 ($\underline{\text{C}}_{\text{ArH}}$), 127.2 ($\underline{\text{C}}_{\text{ArH}}$), 126.7 ($\underline{\text{C}}_{\text{ArH}}$), 126.4 ($\underline{\text{C}}_{\text{ArNO}_2\text{H}}$), 124.0 ($\underline{\text{C}}_{\text{ArNO}_2\text{H}}$), 80.0 ($\underline{\text{OCHAr}}$), 77.7 ($\underline{\text{OCHPh}_2}$), 74.8 ($\underline{\text{NCHCH}}$).

HRMS (ESI, MeOH): calcd. for C₂₃H₁₈N₂NaO₅⁺ [M+Na]⁺ 425.1108, found 425.1114.

[α]_D²⁰: +152 (c 0.37, AcOEt, sample with 89% ee).

Diphenylmethyl (4*R*,5*S*)-5-(4-nitrophenyl)-4,5-dihydro-1,3-oxazole-4-carboxylate **122g**



Obtained according to General Procedure **II** using **31b** (7.7 mg, 0.0125 mmol, 0.05 equiv) and isocyanoacetate **7g** (62.8 mg, 0.250 mmol, 1.0 equiv), then purified by FCC (from PE/AcOEt 4:1 to PE/AcOEt 3:1) obtaining **(4*R*,5*S*)-122g** (68.4 mg, 68%)

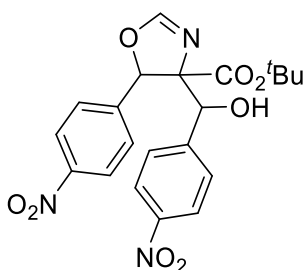
as an off-white solid.

Enantiomeric excess (93% ee) determined by HPLC: Chiralpak OD column, hexane/*i*-PrOH 85:15, flow 1 mL/min, λ 254 nm, t (minor) = 27.6 min, t (major) = 31.5 min.

[α]_D²⁰: −156 (c 0.37, AcOEt, sample with 93% ee).

7.2.4 Synthesis and Characterisation of **126**

tert-Butyl 4-[hydroxy(4-nitrophenyl)methyl]-5-(4-nitrophenyl)-4,5-dihydro-1,3-oxazole-4-carboxylate **126**



To a stirred solution of *tert*-butyl isocyanoacetate **7c** (70.5 mg, 0.50 mmol, 1.0 equiv) and *p*-nitrobenzaldehyde (90.7 mg, 0.60 mmol, 1.2 equiv) in CH₂Cl₂ (3 mL) kept at 0 °C, was added DBU (6.4 μL, 0.05 mmol, 0.1 equiv). Upon addition, the reaction mixture turned brown.

After stirring at 0 °C for 40 minutes, the reaction mixture was diluted with CH₂Cl₂ and washed with water. The organic phase was dried over Na₂SO₄, filtered and evaporated to obtain a yellow residue. Purification of the crude by FCC (PE:AcOEt 8:2 to 6:4) afforded compound **126** (109 mg, 82% yield based on *p*-nitrobenzaldehyde) as a yellow solid. Relative configuration and ee were not determined.

Compound **126** was also obtained as a side product in unoptimised reactions between *tert*-butyl isocyanoacetate **7c** (35.3 mg, 0.250 mmol, 1.0 equiv) and *p*-nitrobenzaldehyde (42.4 mg, 0.275 mmol, 1.1 equiv).

M.p.: 196–198 °C.

IR: 3325 (w, br), 2923 (m, br), 2854 (w), 1713 (m, C=O), 1633(m), 1515 (s, NO₂ asymmetric), 1348 (s, NO₂ symmetric), 1157 (m), 1121 (m), 1094 (m), 1071(m), 858 (m), 831 (w), 808 (w), 734(w), 746 (m), 708 (m), 693 (m), 650 (w) cm⁻¹.

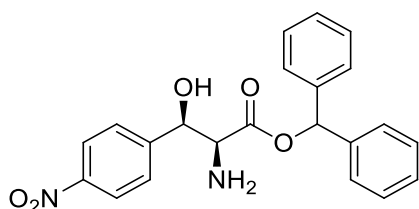
¹H NMR (DMSO-d₆, 400 MHz): δ 8.28 (d, *J* = 9.0 Hz, 2H, C_{Ar}H), 8.20 (d, *J* = 9.0 Hz, 2H, C_{Ar}H), 7.69 (s, 1H, N=CH), 7.77 (d, *J* = 9.0 Hz, 2H, C_{Ar}H), 7.61 (d, *J* = 9.0 Hz, 2H, C_{Ar}H), 6.31 (d, *J* = 6.0 Hz, 1H, OH), 5.91 (s, 1H, OCH_{Ar}), 5.19 (d, *J* = 6.0 Hz, 1H, CHOH), 0.75 (s, 9H, CH₃).

¹³C NMR (DMSO-d₆, 125 MHz): δ 166.6 (C=O), 156.5 (C=N), 148.1 (C_{Ar}), 147.5 (C_{Ar}), 146.9 (C_{Ar}), 144.4 (C_{Ar}), 130.4 (C_{Ar}H), 128.6 (C_{Ar}H), 123.3 (C_{Ar}H), 122.6 (C_{Ar}H), 86.6 (NCCO₂), 82.6 (OCH_{Ar}), 81.6 (C(CH₃)₃), 74.6 (CHOH), 26.5 (CH₃).

HRMS (ESI, MeOH): calcd. for C₂₁H₂₂N₃O₈⁺ [M+H]⁺ 444.1401, found 444.1391.

7.2.5 Synthesis and Characterisation of 127

Diphenylmethyl (2*S*,3*R*)-2-amino-3-hydroxy-3-(4-nitrophenyl)propanoate (2*S*,3*R*)-127



A solution of oxazoline (**4*S*,5*R*)-122g** (683 mg, 1.70 mmol, 1.0 equiv) in MeOH (12 mL) was cooled to 0 °C. A solution of thionyl chloride (862 μL, 11.9 mmol, 7.0 equiv) in MeOH (12 mL) was cooled to 0 °C and then added dropwise over

15 minutes to the reaction flask. The resulting mixture was stirred at 0 °C for 1.5 hours, then quenched by addition of solid NaHCO₃. Volatiles were removed under reduced pressure and the residue was taken up in CH₂Cl₂ and water. The phases were separated and the aqueous layer

was extracted three times with CH₂Cl₂. The combined organic phases were washed with brine, dried over Na₂SO₄, filtered and evaporated to obtain a brown oil. Purification of the crude mixture by FCC (PE/AcOEt 3:2 to 1:2) gave the title compound **(2S,3R)-127** (499 mg, 75%) as a pale yellow solid.

Crystallisation was performed as follow. Compound **127** (150.0 mg, 90% ee) was dissolved in toluene (1 mL) at 100 °C, then slowly allowed to cool down to rt. The resulting solution was left for 16 h at 0 °C, then for 4 days at –20 °C, during which a pale yellow solid formed. Toluene was removed with a pipette, then the solid was washed with toluene at rt (3 × 1 mL), each time decanting the solvent off, and dried under high vacuum (92.0 mg, 61% crystallisation yield, 98% ee, pale yellow needles).

Enantiomeric excess was determined by HPLC: Chiralpak AD column, hexane/*i*-PrOH 70:30, flow 0.8 mL/min, λ 220 nm, t (major) = 12.4 min, t (minor) = 15.3 min.

M.p. (toluene): 116–118 °C.

IR: 2923 (w, br), 1716 (m, C=O), 1600 (w), 1513 (m, NO₂ asymmetric), 1345 (m, NO₂ symmetric), 1224 (m), 1197 (m), 998 (w), 920 (w), 771 (m), 742 (m), 701 (s) cm⁻¹.

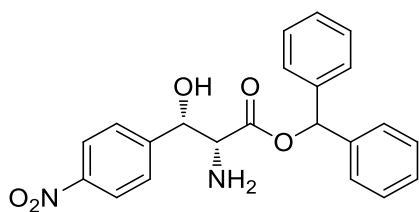
¹H NMR (DMSO-d₆, 400 MHz): δ 8.10 (d, *J* = 8.5 Hz, 2H, C_{Ar}NO₂H), 7.60 (d, *J* = 8.5 Hz, 2H, C_{Ar}NO₂H), 7.45–7.22 (m, 10H, Ph), 6.77 (s, 1H, CHPh₂), 5.93 (d, *J* = 5.0 Hz, 1H, OH), 5.06 (app t, *J* = 4.5 Hz, 1H, ArCHOH), 3.70 (d, *J* = 4.0 Hz, 1H, CHNH₂), 1.79 (br s, 2H, NH₂).

¹³C NMR (DMSO-d₆, 100 MHz): δ 172.4 (C=O), 150.7 (C_{Ar}NO₂), 146.5 (C_{Ar}NO₂), 140.6 (C_{Ar}), 140.4 (C_{Ar}), 128.5 (C_{Ar}H), 128.3 (C_{Ar}H), 127.8 (C_{Ar}H), 127.6 (C_{Ar}H), 126.7 (C_{Ar}H), 126.4 (C_{Ar}NO₂H), 122.8 (C_{Ar}NO₂H), 76.7 (CHPh₂), 73.7 (ArCHOH), 60.8 (CHNH₂).

HRMS (ESI, MeOH): calcd. for C₂₂H₂₁N₂O₅⁺ [M+H]⁺ 393.1445, found 393.1434.

[α]_D²⁰: +22 (c 0.20, AcOEt, sample with 89% ee).

Diphenylmethyl (2*R*,3*S*)-2-amino-3-hydroxy-3-(4-nitrophenyl)propanoate (2*R*,3*S*)-127

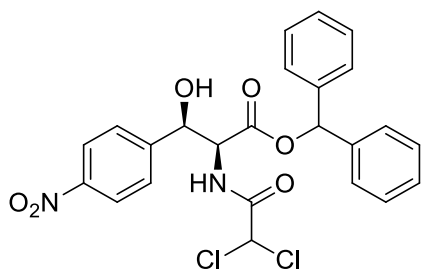


Synthesized and purified in an identical fashion starting from **(4*R*,5*S*)-122g**. Compound **(2*R*,3*S*)-127** was obtained as an off-white solid in 76% yield and was not crystallised. $[\alpha]_D^{25}$: -31 (c 0.20, AcOEt, sample with 94% ee).

(±)-127 was prepared in an identical fashion from **(±)-122g**.

7.2.6 Synthesis and Characterisation of 128

Diphenylmethyl (2*S*,3*R*)-2-(2,2-dichloroacetamido)-3-hydroxy-3-(4-nitrophenyl)propanoate (2*S*,3*R*)-128



Dichloroacetyl chloride (25 μ L, 0.25 mmol, 1.1 equiv) was added dropwise over 3 minutes to a stirred solution of **(2*S*,3*R*)-127** (90.0 mg, 0.223 mmol, 1.0 equiv) and Et₃N (35 μ L, 0.25 mmol, 1.1 equiv) in CH₂Cl₂ (2.5 mL) at 0 °C. The

reaction mixture was stirred at rt for 16 hours, then saturated NaHCO₃ aqueous solution (5 mL) was added. The phases were separated and the aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 5 mL). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered and evaporated. Purification of the crude mixture by FCC (PE/AcOEt 7:3) afforded compound **(2*S*,3*R*)-128** (93.2 mg, 83%) as a pale yellow solid.

Enantiomeric excess (98% ee) determined by HPLC: Chiralpak AD column, hexane/*i*-PrOH 70:30, flow 0.8 mL/min, λ 220 nm, t (minor) = 20.1 min, t (major) = 26.5 min.

M.p.: 130–136 °C.

IR: 3552 (w, br), 3332 (m, br), 2854 (w), 1741 (s, OC=O), 1683 (s, NC=O), 1543 (m), 1506 (s, NO₂ asymmetric), 1454 (w), 1344 (s, NO₂ symmetric), 1299 (m), 1274 (m), 1203 (s), 1107 (m), 1068 (m), 1013 (w), 974 (w), 954 (w), 852 (w), 812 (m), 758 (s), 696 (s) cm⁻¹.

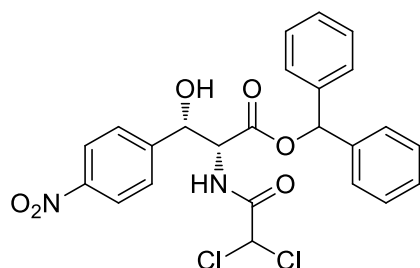
^1H NMR (DMSO- d_6 , 400 MHz): δ 9.10 (d, J = 9.0 Hz, 1H, NH), 8.15 (d, J = 9.0 Hz, 2H, $\text{C}_{\text{ArNO}_2}\text{H}$), 7.72 (d, J = 9.0 Hz, 2H, $\text{C}_{\text{ArNO}_2}\text{H}$), 7.50–7.22 (m, 10H, Ph), 6.86 (s, 1H, CHPh_2), 6.59 (s, 1H, CHCl_2), 6.50 (d, J = 4.5 Hz, 1H, OH), 5.49 (t, J = 4.0 Hz, 1H, ArCHOH), 4.89 (dd, J = 9.0, 3.0 Hz, 1H, CHNH).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ 168.0 (CO_2), 163.9 (CONH), 149.0 (C_{ArNO_2}), 146.8 (C_{ArNO_2}), 140.3 (C_{Ar}), 140.2 (C_{Ar}), 128.5 (C_{ArH}), 128.4 (C_{ArH}), 127.9 (C_{ArH}), 127.7 (C_{ArH}), 127.6 (C_{ArH}), 126.6 (C_{ArH}), 126.3 ($\text{C}_{\text{ArNO}_2}\text{H}$), 123.0 ($\text{C}_{\text{ArNO}_2}\text{H}$), 77.6 (CHPh_2), 71.2 (ArCHOH), 65.8 (CHCl_2), 58.4 (CHNH).

HRMS (ESI, MeOH): calcd. for $\text{C}_{24}\text{H}_{20}^{35}\text{Cl}_2\text{N}_2\text{NaO}_6^+$ $[\text{M}+\text{Na}]^+$ 525.0591, found 525.0588.

$[\alpha]_{\text{D}}^{25}$: -0.85 (c 1.00, AcOEt, sample with 87% ee).

Diphenylmethyl (2*R*,3*S*)-2-(2,2-dichloroacetamido)-3-hydroxy-3-(4-nitrophenyl)propanoate (2*R*,3*S*)-128



Synthesized and purified in identical fashion starting from **(2*R*,3*S*)-127**. Compound **(2*R*,3*S*)-128** was obtained as a pale yellow solid in 82% yield.

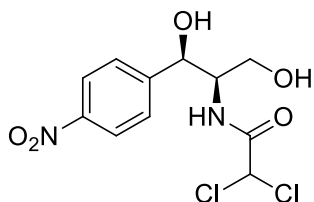
$[\alpha]_{\text{D}}^{25}$: $+0.84$ (c 1.00, AcOEt, sample with 93% ee).

(±)-128 was prepared in an identical fashion from **(±)-127**.

7.2.7 Synthesis and Characterisation of (–)-chloramphenicol and (+)-chloramphenicol 52

2,2-Dichloro-*N*-[(1*R*,2*R*)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-yl]acetamide

(–)-Chloramphenicol, (–)-52



Sodium borohydride (28.2 mg, 0.745 mmol, 5.0 equiv) was added in one portion to a stirred suspension of **(2*S*,3*R*)-128** (75.0 mg, 0.149 mmol, 1.0 equiv) in methanol (0.8 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, then quenched by adding H₂O (15 mL). AcOEt (15 mL) was added and the phases separated. The aqueous layer was extracted with AcOEt (3 × 10 mL). The combined organic phases were dried over Na₂SO₄, filtered and evaporated. Purification of the crude mixture by FCC (PE/AcOEt 3:7 to 2:8) afforded (–)-Chloramphenicol (–)-52 (38.5 mg, 80%) as a pale yellow solid.

Enantiomeric excess (99% ee) determined by HPLC: Chiralpak AD-H column, hexane/*i*-PrOH 90:10, flow 1.0 mL/min, λ 220 nm, *t* (major) = 11.5 min, *t* (minor) = 19.7 min.

Spectroscopic data are in accordance with those given in the literature.¹³⁵

M.p.: 150–151 °C. (Lit.: 150–151 °C).¹²⁵

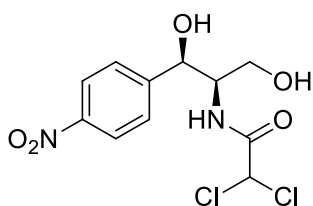
¹H NMR (acetone-*d*₆, 500 MHz): δ 8.19 (d, *J* = 8.5 Hz, 2H, C_{Ar}NO₂H), 7.71 (d, *J* = 8.5 Hz, 2H, C_{Ar}NO₂H), 7.52 (d, *J* = 8.0 Hz, 1H, NH), 6.36 (s, 1H, CHCl₂), 5.34 (m, 1H, ArCH₂OH), 5.23 (1H, d, *J* = 4.5 Hz, ArCH₂OH), 4.25 (1H, dd, *J* = 6.0, 5.0 Hz, CH₂OH), 4.17 (1H, m, CHNH), 3.81 (1H, app dt, *J* = 10.5, 6.5 Hz, CH_AH_BOH), 3.71 (1H, app dt, *J* = 10.5, 5.0 Hz, CH_AH_BOH).

¹³C-NMR (acetone-*d*₆, 125 MHz): δ 164.4 (C=O), 151.4 (C_{Ar}NO₂), 148.1 (C_{Ar}NO₂), 128.2 (C_{Ar}NO₂H), 123.9 (C_{Ar}NO₂H), 71.2 (ArCH₂OH), 67.5 (CHCl₂), 62.2 (CH₂OH), 57.9 (CHNH).

$[\alpha]_D^{25}$: –25.1 (c 1.00, AcOEt, sample with 99% ee). Lit.: $[\alpha]_D^{23}$ = –25.5 (c = 1, AcOEt).¹²⁵

2,2-Dichloro-*N*-[(1*S*,2*S*)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-yl]acetamide

(+)-Chloramphenicol, (+)-52



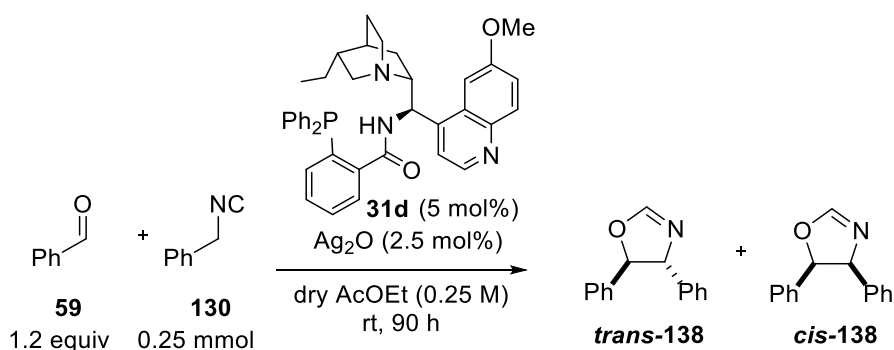
The enantiomer (+)-52 was prepared from (**2*R*,3*S*)-128 in identical fashion, obtaining a pale yellow solid in 80% yield.**

$[\alpha]_{\text{D}}^{25}$: +24.4 (c 1.00, AcOEt, sample with 96% ee).

(±)-52 was prepared mixing equimolar quantities (1.0 mg) of the two enantiomers.

7.3 Aldol and Mannich Reactions of Benzyl Isocyanide

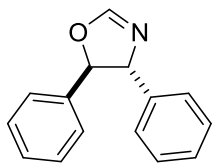
7.3.1 Synthesis of Characterisation of *trans*-138 and *cis*-138



A mixture of ligand **31d** (7.7 mg, 0.013 mmol, 0.05 equiv) and Ag₂O (1.4 mg, 0.0063 mmol, 0.025 equiv) in AcOEt (1 mL) was stirred for 15 minutes under Ar. Benzyl isocyanide (31.7 μL, 0.25 mmol, 1 equiv) and, after 5 minutes, freshly distilled benzaldehyde (30.5 μL, 0.30 mmol, 1.2 equiv) were added to the reaction mixture. After stirring at rt for 90 h, the reaction mixture was filtered through Celite[®] washing with AcOEt. The filtrate was evaporated and dissolved in CDCl₃ (approximately 0.5 mL), then mesitylene was added as an internal standard (35.5 μL, 0.25 mmol, 1 equiv). The mixture was analysed by ¹H NMR to determine NMR yields and dr (*trans*:*cis* 66:34). Purification of the crude mixture by FCC (PE/AcOEt 15:1 + 1% TEA to PE/AcOEt 2:1 + 1% TEA) afforded compounds ***trans*-138** (24.5 mg, 44%) and ***cis*-138** (10.0 mg, 18%).

The racemic compounds ($\pm$)-**trans-138** and ($\pm$)-**cis-138** were prepared following a literature procedure.¹⁶²

trans-4,5-Diphenyl-4,5-dihydro-1,3-oxazole trans-138



Obtained as a colourless oil (24.5 mg, 44%). Enantiomeric excess (12% ee) determined by HPLC: Chiralpak AS-H column, hexane/*i*-PrOH 95:5, flow 1.0 mL/min, λ 220 nm, t (minor) = 8.6 min, t (major) = 12.2 min. The

absolute configuration of the major enantiomer was not determined.

Characterisation data are in accordance with those given in the literature.¹⁶²

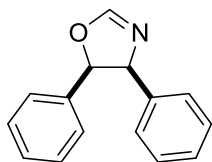
IR: 3063, 3031, 2924, 1687, 1629, 1495, 1454, 1093, 946, 757, 698, 617 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ 7.36–7.14 (m, 11H, $\text{C}_{\text{Ar}}\text{H}$ and $\text{N}=\text{CH}$), 5.12 (d, J = 8.0 Hz, 1H, OCHPh), 4.97 (dd, J = 8.0, 2.0 Hz, 1H, NCHPh).

^{13}C NMR (CDCl_3 , 100 MHz): δ 155.1 ($\text{N}=\text{CH}$), 141.5 (C_{Ar}), 140.0 (C_{Ar}), 129.1 ($\text{C}_{\text{Ar}}\text{H}$), 129.0 ($\text{C}_{\text{Ar}}\text{H}$), 128.8 ($\text{C}_{\text{Ar}}\text{H}$), 128.0 ($\text{C}_{\text{Ar}}\text{H}$), 126.7 ($\text{C}_{\text{Ar}}\text{H}$), 125.9 ($\text{C}_{\text{Ar}}\text{H}$), 88.0 (OCHPh), 77.7 (NCHPh).

LRMS (ESI, MeOH): calcd. for $\text{C}_{15}\text{H}_{14}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 224.1, found 224.1.

cis-4,5-Diphenyl-4,5-dihydro-1,3-oxazole cis-138



Obtained as a white solid (10.0 mg, 18%). Enantiomeric excess (0% ee) determined by HPLC: Chiralpak AD-H column, hexane/*i*-PrOH 90:10, flow 1.0 mL/min, λ 220 nm, t_1 = 10.7 min, t_2 = 12.4 min.

Mp: 160–166 $^{\circ}\text{C}$.

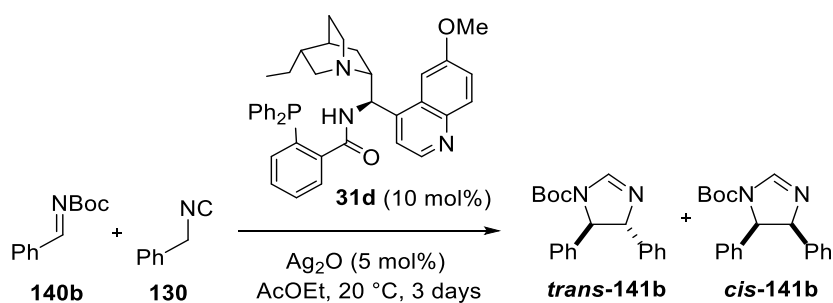
IR: 3062, 3032, 2924, 1633, 1493, 1454, 1097, 1030, 949, 729, 697, 619 cm^{-1} .

^1H NMR (CD_2Cl_2 , 400 MHz): δ 7.32 (d, J = 2.0 Hz, 1H, $\text{N}=\text{CH}$), 7.06–7.01 (m, 6H, $\text{C}_{\text{Ar}}\text{H}$), 6.94–6.90 (m, 4H, $\text{C}_{\text{Ar}}\text{H}$), 5.82 (d, J = 10.5 Hz, 1H, OCHPh), 5.54 (dd, J = 10.5, 2.0 Hz, 1H, NCHPh).

^{13}C NMR (CD_2Cl_2 , 100 MHz): 155.9 ($\text{N}=\underline{\text{C}}\text{H}$), 137.9 ($\underline{\text{C}}_{\text{Ar}}$), 136.8 ($\underline{\text{C}}_{\text{Ar}}$), 128.3 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 128.0 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 127.9 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 127.7 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 127.3 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 126.9 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 84.3 ($\text{O}\underline{\text{C}}\text{HPh}$), 73.4 ($\text{N}\underline{\text{C}}\text{HPh}$).

HRMS (ESI, MeOH): calcd. for $\text{C}_{15}\text{H}_{14}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 224.10699, found 224.10721.

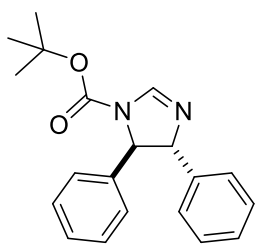
7.3.2 Synthesis of Characterisation of *trans*-141b and *cis*-141b



To a stirred mixture of ligand **31d** (15.3 mg, 0.025 mmol, 0.1 equiv), Ag_2O (2.9 mg, 0.013 mmol, 0.05 equiv) and *N*-Boc imine **140b** (77 mg, 0.28 mmol, 1.5 equiv) in AcOEt (1 mL), benzyl isocyanide (31.7 μL , 0.25 mmol, 1 equiv) was added to the reaction mixture. After stirring at rt for 3 days, the reaction mixture was filtered through Celite[®] washing with AcOEt . The filtrate was evaporated and the residue dissolved in CDCl_3 (approximately 0.5 mL), then mesitylene was added as an internal standard (35.5 μL , 0.25 mmol, 1 equiv). The mixture was analysed by ^1H NMR to determine NMR yields and dr (*trans*:*cis* 39:61). Purification of the crude mixture by FCC (PE/ AcOEt 15:1 + 1% TEA to PE/ AcOEt 3:1 + 1% TEA) afforded compounds *trans*-**141b** (4.4 mg, 5%) and *cis*-**141b** (14.1 mg, 17%).

The racemic compounds ($\pm$)-*trans*-**141b** and ($\pm$)-*cis*-**141b** were prepared in analogous fashion, using 10 mol% Ag_2O without ligand.

***tert*-Butyl *trans*-4,5-diphenyl-4,5-dihydro-1*H*-imidazole-1-carboxylate *trans*-141b**



Off-white amorphous solid (4.4 mg, 5%). Enantiomeric excess (1% ee) determined by HPLC: Chiralpak AD-H column, hexane/*i*-PrOH 95:5, flow 0.5 mL/min, λ 220 nm, t (minor) = 25.8 min, t (major) = 27.7 min. IR: 3285, 2977, 2851, 1719, 1624, 1367, 1168, 1144, 759, 698,

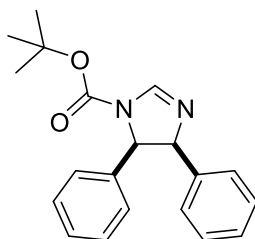
626 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ 7.94 (br s, 1H, $\text{N}=\text{CH}$), 7.39–7.20 (m, 10H, C_{ArH}), 5.14 (br s, 1H, $\text{PhCHN}=\text{C}$), 4.72 (br s, 1H, PhCHNCO), 1.27 (s, 9H, $\text{C}(\text{CH}_3)_3$).

^{13}C NMR (CDCl_3 , 100 MHz): δ 154.9 ($\text{C}=\text{O}$), 149.4 ($\text{C}=\text{NH}$), 142.0 (C_{Ar}), 142.0 (C_{Ar}), 129.0 (C_{ArH}), 128.9 (C_{ArH}), 128.0 (C_{ArH}), 127.9 (C_{ArH}), 126.4 (C_{ArH}), 126.0 (C_{ArH}), 82.6 ($\text{C}(\text{CH}_3)_3$), 81.3 ($\text{PhCHN}=\text{C}$), 68.1 (PhCHNCO), 28.0 (CH_3).

HRMS (ESI, MeOH): calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_2^+$ $[\text{M}+\text{H}]^+$ 323.17540, found 323.17554.

***tert*-Butyl *cis*-4,5-diphenyl-4,5-dihydro-1*H*-imidazole-1-carboxylate *cis*-141b**



Off-white amorphous solid (14.1 mg, 17%). Enantiomeric excess (0% ee) determined by HPLC: Chiralpak AD-H column, hexane/*i*-PrOH 95:5, flow 1.0 mL/min, λ 220 nm, t_1 = 16.1 min, t_2 = 25.0 min.

IR: 3382, 3349, 3064, 3032, 2930, 1716, 1685, 1656, 1624, 1520, 1455,

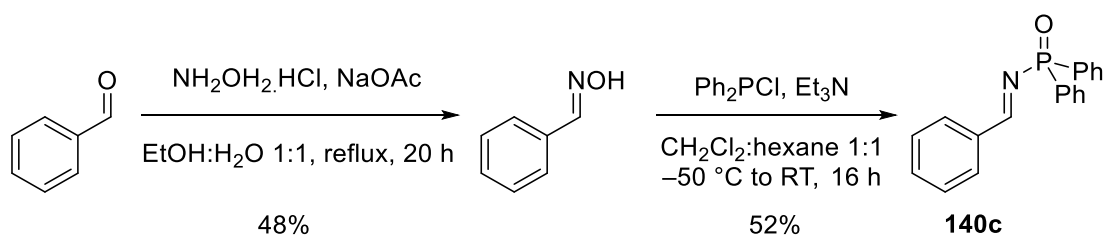
1369, 1294, 1251, 1169, 1146, 754, 698 cm^{-1} .

^1H NMR (CD_2Cl_2 , 400 MHz): δ 7.96 (br s, 1H, $\text{N}=\text{CH}$), 7.06–6.96 (m, 8H, C_{ArH}), 6.82 (dd, J = 8.0, 1.5 Hz, 2H, C_{ArH}), 5.68 (br d, J = 10.5 Hz, 1H, $\text{PhCHN}=\text{C}$), 5.33 (br d, J = 10.5 Hz, 1H, PhCHNCO), 1.27 (s, 9H, $\text{C}(\text{CH}_3)_3$).

^{13}C NMR (CD_2Cl_2 , 100 MHz): δ 155.1 ($\text{C}=\text{O}$), 150.3 ($\text{C}=\text{NH}$), 138.3 (C_{Ar}), 138.1 (C_{Ar}), 128.4 (C_{ArH}), 128.0 (C_{ArH}), 127.8 (C_{ArH}), 127.3 (C_{ArH}), 127.2 (C_{ArH}), 127.0 (C_{ArH}), 82.4 ($\text{C}(\text{CH}_3)_3$), 76.3 ($\text{PhCHN}=\text{C}$), 64.7 (PhCHNCO), 28.0 (CH_3).

HRMS (ESI, MeOH): calcd. for $C_{20}H_{23}N_2O_2^+$ $[M+H]^+$ 323.17540, found 323.17532.

7.3.3 Synthesis of Characterisation of **140c**



To a stirred solution of sodium acetate (6.15 g, 75 mmol, 1.5 equiv) and hydroxylamine hydrochloride (5.21 g, 75 mmol, 1.5 equiv) in $EtOH:H_2O$ 1:1 (50 mL), benzaldehyde (5.1 mL, 50 mmol, 1 equiv) was added at rt. The reaction mixture was refluxed for 20 hours, then $EtOH$ was removed under reduced pressure and CH_2Cl_2 was added. Phases were separated and the aqueous layer was extracted twice with CH_2Cl_2 . Organic phases were washed with brine, dried over Na_2SO_4 and evaporated. Distillation at $125\text{ }^{\circ}C$ under 30 mbar pressure afforded the desired oxime (2.88 g, 48%) as a pale yellow oil, which was used directly in the next step.

To a stirred solution of the oxime (2.88 g, 23.7 mmol, 1.0 equiv) in $CH_2Cl_2:hexane$ 1:1 (80 mL) kept at $-50\text{ }^{\circ}C$, Et_3N (3.64 mL, 26.1 mmol, 1.1 equiv) was added. After 10 minutes, Ph_2PCl (4.69 mL, 26.5 mmol, 1.1 equiv) was added with a syringe pump over 20 minutes, during which the solution became a cloudy yellow suspension. The reaction mixture was then allowed to warm up to rt, stirred for 16 h and filtered through Celite[®] washing the filter cake with $CH_2Cl_2:Et_2O$ 1:1 (2×30 mL). The yellow filtrate was evaporated keeping the temperature of the water bath below $30\text{ }^{\circ}C$, and purified by FCC (PE:AcOEt 4:1 + 1% TEA to 1:2 + 1% TEA). Impure fractions were triturated in Et_2O for 2 hours, then the white solid was collected on sinter funnel and dried. Compound **140c** (3.74 g, 52%) was obtained as a white solid.

Spectroscopic data are in agreement with those given in the literature.^{292,293}

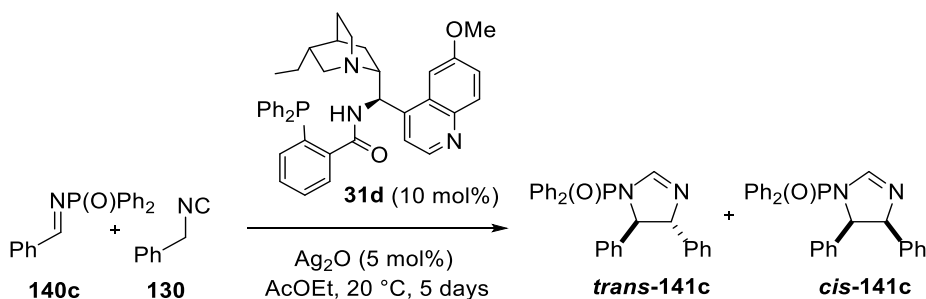
M.p.: $135\text{--}136\text{ }^{\circ}C$ (lit: $136\text{--}137\text{ }^{\circ}C$).²⁹³

^1H NMR (CDCl_3 , 400 MHz): δ 9.33 (d, $^3J_{\text{HP}} = 32.0$ Hz, 1H, $\text{N}=\text{CH}$), 8.02 (d, $J = 7.0$ Hz, 2H, $\text{C}_{\text{Ph}}\text{H}_{\text{ortho}}$), 7.95 (app ddt, $J = 12.0, 7.0, 1.5$ Hz, 4H, $\text{C}_{\text{ArP}}\text{H}_{\text{meta}}$), 7.58 (td, $J = 7.5, 2.0$ Hz, 1H, $\text{C}_{\text{Ph}}\text{H}_{\text{para}}$), 7.53–7.43 (m, 8H, $\text{C}_{\text{Ph}}\text{H}_{\text{meta}}$, $\text{C}_{\text{ArP}}\text{H}_{\text{para}}$ and $\text{C}_{\text{ArP}}\text{H}_{\text{ortho}}$).

^{13}C NMR (CDCl_3 , 100 MHz): δ 173.9 (d, $^2J_{\text{CP}} = 7.9$ Hz, $\text{N}=\text{CH}$), 136.0 (d, $^3J_{\text{PC}} = 24.5$ Hz, $\text{N}=\text{CC}_{\text{Ph}}$), 133.8 ($\text{C}_{\text{Ph}}\text{H}_{\text{para}}$), 133.1 (d, $^1J_{\text{PC}} = 127.5$ Hz, PC_{Ar}), 132.0 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\text{C}_{\text{ArP}}\text{H}_{\text{para}}$), 131.7 (d, $^3J_{\text{PC}} = 9.0$ Hz, $\text{C}_{\text{ArP}}\text{H}_{\text{meta}}$), 130.4 ($\text{C}_{\text{Ph}}\text{H}$), 129.1 ($\text{C}_{\text{Ph}}\text{H}$), 128.6 (d, $^2J_{\text{PC}} = 12.5$ Hz, $\text{C}_{\text{ArP}}\text{H}_{\text{ortho}}$).

^{31}P NMR (CDCl_3 , 162 MHz): δ 24.9.

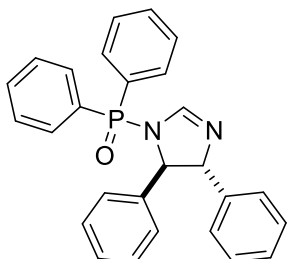
7.3.4 Synthesis of Characterisation of *trans*-141c and *cis*-141c



To a stirred mixture of ligand **31d** (30.7 mg, 0.05 mmol, 0.1 equiv), Ag_2O (5.8 mg, 0.025 mmol, 0.05 equiv) and *N*-DPP imine **140c** (152.7 mg, 0.50 mmol, 1 equiv) in HPLC-grade AcOEt (2 mL), benzyl isocyanide (95.1 μL , 0.75 mmol, 1.5 equiv) was added. After stirring at rt for 5 days, the reaction mixture was filtered through Celite[®] washing with AcOEt . The filtrate was evaporated and the residue dissolved in CDCl_3 (approximately 0.5 mL), then mesitylene was added as an internal standard (71 μL , 0.5 mmol, 2 equiv). The mixture was analysed by ^1H NMR to determine NMR yields and dr (*trans*:*cis* 62:38). Purification of the crude mixture by FCC (PE/ AcOEt 15:1 + 1% TEA to PE/ AcOEt 1:4 + 1% TEA) afforded in order of elution compounds *trans*-**138** (7.1 mg, 6% yield, 10% ee), *cis*-**138** (3.5 mg, 3% yield, 2% ee), *trans*-**141c** (83.1 mg, 39% yield, 7% ee) and *cis*-**141c** (44.1 mg, 21% yield, ee not determined).

The racemic compounds ($\pm$)-**trans-141c** and ($\pm$)-**cis-141c** were prepared in analogous fashion, using 10 mol% Ag₂O without ligand.

***trans*-1-(diphenylphosphoryl)-4,5-diphenyl-4,5-dihydro-1*H*-imidazole *trans*-141c**



Glassy solid (83.1 mg, 39%). Enantiomeric excess (7% ee) determined after removal of DPP group (see next reaction). The absolute configuration of the major enantiomer was not determined.

M.p.: 83–86 °C.

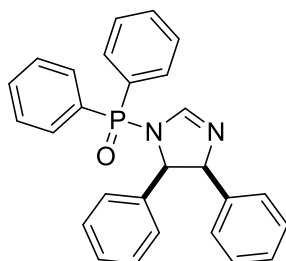
IR: 3060, 3030, 2919, 2230, 1613, 1494, 1455, 1439, 1214, 1111, 1076, 988, 925, 755, 727, 695, 626 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 7.66 (dd, J = 12.5, 7.5 Hz, 2H, C_{Ar}PH_{ortho}), 7.58 (dd, J = 12.5, 7.5 Hz, 2H, C_{Ar}PH_{ortho}), 7.49 (t, J = 7.0 Hz, 1H, C_{Ar}PH_{para}), 7.42 (t, J_{HH} = 7.5 Hz, 1H, C_{Ar}PH_{para}), 7.39–7.34 (m, 5H, C_{Ar}H, CHCHCP and N=CH), 7.30–7.26 (m, 3H, C_{Ar}H and C_{Ar}PH_{meta}), 7.21 (d, J = 7.5 Hz, 2H, C_{Ar}H), 7.17–7.13 (m, 3H, C_{Ar}H), 6.95 (d, J = 6.0 Hz, 2H, C_{Ar}H), 5.17 (br d, J = 5.5 Hz, 1H, C=NCHPh), 4.63 (dd, J = 5.5 Hz, 4.5 Hz, 1H, PNCHPh).

¹³C NMR (CDCl₃, 125 MHz): δ 151.1 (d, $^2J_{PC}$ = 5.5 Hz, N=CH), 142.2 (C_{Ar}), 142.0 (C_{Ar}), 132.8 (d, $^4J_{PC}$ = 3.0 Hz, C_{Ar}PH_{para}), 132.5 (d, $^4J_{PC}$ = 3.5 Hz, C_{Ar}PH_{para}), 132.2 (d, $^3J_{PC}$ = 10.0 Hz, C_{Ar}PH_{meta}), 132.1 (d, $^3J_{PC}$ = 10.0 Hz, C_{Ar}PH_{meta}), 129.6 (d, $^1J_{PC}$ = 130.0 Hz, PC_{Ar}), 129.5 (d, $^1J_{PC}$ = 130.0 Hz, PC_{Ar}), 128.9 (C_{Ar}H), 128.8 (d, $^2J_{PC}$ = 13.5 Hz, C_{Ar}H_{ortho}), 128.7 (C_{Ar}H), 128.6 (d, $^2J_{PC}$ = 13.5 Hz, C_{Ar}H_{ortho}), 127.9 (C_{Ar}H), 127.8 (C_{Ar}H), 126.7 (C_{Ar}H), 126.4 (C_{Ar}H), 81.8 (d, $^3J_{PC}$ = 6.5 Hz, C=NCHPh), 69.8 (s, PNCHPh).

³¹P NMR (CDCl₃, 202 MHz): δ 20.5.

HRMS (ESI, MeOH): calcd. for C₂₇H₂₄N₂OP⁺ [M+H]⁺ 423.16208, found 423.16208.



***cis*-1-(diphenylphosphoryl)-4,5-diphenyl-4,5-dihydro-1*H*-imidazole *cis*-141c**

Obtained as a colourless solid as a 62:38 mixture of ***cis*-141c** and ***trans*-141c** (overall 71.2 mg, of which ***cis*-141c** 44.1 mg, 21% yield).

Characterised as a 62:38 mixture of ***cis*-141c** and ***trans*-141c**.

M.p.: 142–146 °C.

IR (data for *cis* isomer only): 3060, 2923, 2229, 1612, 1494, 1455, 1439, 1211, 1118, 991, 919, 727, 694 cm⁻¹.

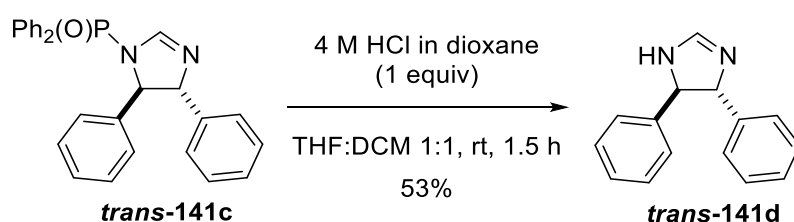
¹H NMR (CDCl₃, 500 MHz, data for *cis* isomer only): δ 7.73 (dd, *J* = 12.5, 7.5 Hz, 2H, C_{Ar}H), 7.64 (dd, *J* = 12.5, 7.5 Hz, 2H, C_{Ar}H), 7.51–7.45 (m, C_{Ar}H, 3H, N=CH), 7.40–7.32 (m, 3H, C_{Ar}H), 7.00–6.80 (m, 9H, C_{Ar}H), 6.59 (d, *J* = 7.0 Hz, 2H, C_{Ar}H), 5.80 (dd, *J* = 10.5, 2.5 Hz, 1H, C=NCHPh), 5.10 (d, *J* = 10.5, 3.0 Hz, 1H, PNCHPh).

¹³C NMR (CDCl₃, 125 MHz, data for *cis* isomer only): δ 152.0 (d, ²*J*_{PC} = 4.5 Hz, N=CH), 137.5 (C_{Ar}), 137.0 (C_{Ar}), 132.7 (d, ⁴*J*_{PC} = 3.0 Hz, C_{Ar}PH_{para}), 132.2 (d, ⁴*J*_{PC} = 3.0 Hz, C_{Ar}PH_{para}), 130.3 (d, ¹*J*_{PC} = 129.0 Hz, PC_{Ar}), 132.2–132.1 (m, C_{Ar}H), 129.5 (d, ¹*J*_{PC} = 129.0 Hz, PC_{Ar}), 128.8 (C_{Ar}H), 128.7 (C_{Ar}H), 128.6 (C_{Ar}H), 127.9 (C_{Ar}H), 127.8 (C_{Ar}H), 127.5 (C_{Ar}H), 127.4 (C_{Ar}H), 127.2 (C_{Ar}H), 76.7 (d, ³*J*_{PC} = 7.0 Hz, C=NCHPh), 66.7 (d, ²*J*_{PC} = 2.0 Hz, PNCHPh).

³¹P NMR (CDCl₃, 202 MHz, data for *cis* isomer only): δ 20.4.

HRMS (ESI, MeOH): calcd. for C₂₇H₂₄N₂OP⁺ [M+H]⁺ *m/z* 423.16208, found *m/z* 423.16213.

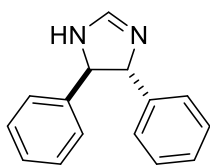
7.3.5 Synthesis of Characterisation of ***trans*-141d** and ***cis*-141d**



To a stirred solution of **trans-141c** (40 mg, 0.095 mmol, 1 equiv) in THF:CH₂Cl₂ 1:1 (2 mL), 4 M HCl in dioxane (47 μ L, 0.19 mmol, 2 equiv) was added. after stirring at rt for 1.5 h, CH₂Cl₂ (10 mL) and aqueous saturated NaHCO₃ solution (5 mL) were added. Phases were separated, and the aqueous layer was extracted again with CH₂Cl₂ (2 $\times$ 10 mL). The combined organic phases were dried over Na₂SO₄, filtered and evaporated. The crude residue was purified by FCC (CHCl₃:MeOH:sat aq NH₄OH 100:3:1), obtaining compound **trans-141d** (11.5 mg, 53%) as an amorphous solid.

Following the same procedure starting from a 62:38 mixture of **cis-141c** and **trans-141c**, after purification the meso compound **cis-141d** was obtained as an amorphous solid in 30% yield.

trans-4,5-diphenyl-4,5-dihydro-1H-imidazole trans-141d



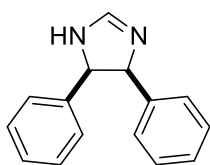
Amorphous solid (11.5 mg, 53%). Enantiomeric excess (7% ee) determined by HPLC: Chiralcel OD-3 column, hexane/*i*-PrOH 85:15, flow 1.0 mL/min, λ 254 nm, *t* (minor) = 6.7 min, *t* (major) = 9.6 min. The absolute configuration of the major enantiomer was not determined.

Characterisation data are in agreement with the literature.¹⁶⁴

¹H NMR (CDCl₃, 400 MHz): δ 7.40–7.25 (m, 11H, C_{Ar}H and N=CH), 4.72 (br s, 2H, CHPh).

¹³C NMR (CDCl₃, 100 MHz): δ 153.6 (N=CH), 143.2 (C_{Ar}), 128.9 (C_{Ar}H), 127.7 (C_{Ar}H), 126.7 (C_{Ar}H), 74.0 (CHPh).

cis-4,5-diphenyl-4,5-dihydro-1H-imidazole cis-141d



Amorphous solid (4.3 mg, 30%).

IR: 3660, 3187, 2981, 2889, 1667, 1602, 1494, 1454, 1384, 1251, 1155, 1075, 954, 766, 698 cm⁻¹.

^1H NMR (CDCl_3 , 400 MHz): δ 7.50–7.47 (m, 2H, $\text{C}_{\text{Ar}}\text{H}$ and $\text{N}=\text{CH}$), 7.37–7.22 (m, 2H, $\text{C}_{\text{Ar}}\text{H}$), 7.07–6.98 (m, 4H, $\text{C}_{\text{Ar}}\text{H}$), 6.92–6.90 (m, 3H, $\text{C}_{\text{Ar}}\text{H}$), 5.28 (s, 2H, CHPh).

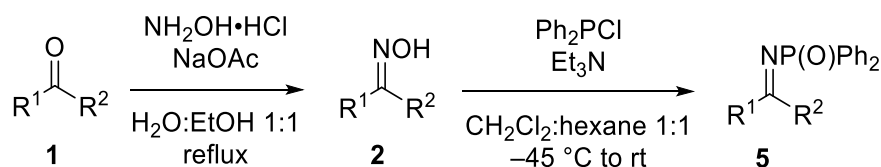
^{13}C NMR (CDCl_3 , 100 MHz): δ 155.2 ($\text{N}=\text{CH}$), 138.5 (C_{Ar}), 127.8 ($\text{C}_{\text{Ar}}\text{H}$), 127.6 ($\text{C}_{\text{Ar}}\text{H}$), 127.0 ($\text{C}_{\text{Ar}}\text{H}$), 69.5 (CHPh).

HRMS (ESI, MeOH): calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2^+$ $[\text{M}+\text{H}]^+$ 223.12298, found 223.12280.

7.4 TosMIC Addition to *N*-DPP Ketimines

7.4.1 Synthesis and Characterisation of *N*-DPP Ketimines 5

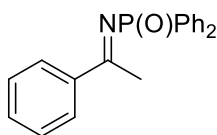
General Procedure III for the synthesis of *N*-DPP Ketimines



According to a literature procedure,²⁹⁴ to a stirred solution of sodium acetate (1.5 equiv) and hydroxylamine hydrochloride (1.5 equiv) in $\text{EtOH}:\text{H}_2\text{O}$ 1:1 (1.8 M), ketone **1** (1 equiv) was added at rt. The reaction mixture was refluxed for 10–20 hours, EtOH was removed under vacuum and the mixture was then put at 0°C until precipitation occurred. The precipitated oxime **2** was filtered, washed with ethanol at 0°C , dried under vacuum and used in the next step without further purification.

To a stirred solution of oxime **2** (1.0 equiv) in CH_2Cl_2 :hexane 1:1 (0.3 M) kept at -45°C , Et_3N (1.1 equiv) was added. After 10 minutes, Ph_2PCl (1.1 equiv) was added with a syringe pump over 20 minutes, during which the solution became a cloudy yellow suspension. The reaction mixture was then allowed to slowly warm up to rt, stirred for 16 h and filtered through Celite[®] washing the filter cake with CH_2Cl_2 : Et_2O 1:1 (2×30 mL). The yellow filtrate was evaporated keeping the temperature of the water bath below 30°C . Purification by FCC, trituration or recrystallisation as indicated in the specific procedures yielded the desired *N*-DPP ketimine **5**.

N*-(1-Phenylethylidene)diphenylphosphinic amide **5a*



Prepared according to General Procedure **III** from 100 mmol of the corresponding oxime. Purification of the crude by FCC (PE:EtOAc 1:1 to pure EtOAc) followed by trituration of the impure fractions in Et₂O afforded

5a (20 g, 57% yield, average of two reactions run on this scale) as a white solid.

Data are consistent with those given in the literature.²⁹⁴

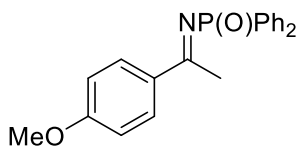
M.p.: 130–132 °C (lit. 128–130 °C).²⁶⁴

¹H NMR (400 MHz, CDCl₃): δ 8.10–7.95 (m, 6H), 7.53–7.35 (m, 9H), 2.97 (d, ⁴*J*_{HP} = 2.0 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 181.2 (d, ²*J*_{PC} = 8.0 Hz, C=N), 139.1 (d, ³*J*_{PC} = 23.0 Hz, N=CC_{Ar}), 134.5 (d, ¹*J*_{PC} = 131.0 Hz, PC_{Ar}), 132.2, 131.3 (d, ³*J*_{PC} = 9.5 Hz, C_{Ar}P_H_{meta}), 131.1 (d, ⁴*J*_{PC} = 3.0 Hz, C_{Ar}P_H_{para}), 128.3, 128.1 (d, ²*J*_{PC} = 12.0 Hz, C_{Ar}P_H_{ortho}), 127.6, 22.7 (d, ³*J*_{PC} = 13.0 Hz, CH₃).

³¹P NMR (162 MHz, CDCl₃): δ 18.9.

N*-[1-(4-Methoxyphenyl)ethylidene]diphenylphosphinic amide **5b*



Prepared according to General Procedure **III** from 18 mmol of the corresponding oxime. Purification of the crude by FCC (DCM:EtOAc 2:1 to 1:2) followed by precipitation in EtOAc afforded **5b** (2.57 g,

41% yield) as a white solid.

Spectroscopic data are consistent with those given in the literature.²⁹⁴

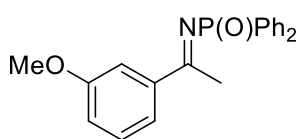
M.p.: 120–122 °C.

¹H NMR (400 MHz, CDCl₃): δ 8.09 (d, *J* = 8.0 Hz, 2H), 7.98–7.93 (m, 4H), 7.43–7.40 (m, 6H), 6.96 (d, *J* = 8.0 Hz, 2H), 3.88 (s, 3H, OCH₃), 2.92 (d, ⁴*J*_{HP} = 2.0 Hz, 3H, CH₃).

^{13}C NMR (100 MHz, CDCl_3): δ 180.6 (d, $^2J_{\text{PC}} = 8.0$ Hz, $\text{C}=\text{N}$), 163.2 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 135.0 (d, $^1J_{\text{PC}} = 131.0$ Hz, PC_{Ar}), 132.0 (d, $^3J_{\text{PC}} = 25.0$ Hz, $\text{N}=\text{CC}_{\text{Ar}}$), 131.5 (d, $^3J_{\text{PC}} = 9.5$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 131.1 (d, $^4J_{\text{PC}} = 2.5$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 130.1 ($\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{OCH}_3$), 128.3 (d, $^2J_{\text{PC}} = 12.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$), 113.7 ($\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{OCH}_3$), 55.5 (OCH_3), 22.7 (d, $^3J_{\text{PC}} = 13.0$ Hz, CH_3).

^{31}P NMR (162 MHz, CDCl_3): δ 18.5.

***N*-[1-(3-Methoxyphenyl)ethylidene]diphenylphosphinic amide 5c**



Prepared according to General Procedure **III** from 10 mmol of the corresponding oxime. Purification of the crude by FCC (PE:EtOAc 1:1 to 1:2) afforded **5c** (1.86 g, 53% yield) as a white solid.

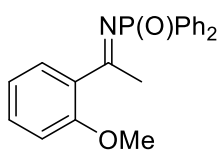
Spectroscopic data are consistent with those given in the literature.²⁹⁴

^1H NMR (400 MHz, CDCl_3): δ 8.05–7.93 (m, 4H), 7.70–7.60 (m, 2H), 7.49–7.34 (m, 7H), 7.12–7.05 (m, 1H), 3.87 (s, 3H, OCH_3), 2.95 (d, $^4J_{\text{HP}} = 2.0$ Hz, 3H, CH_3).

^{13}C NMR (100 MHz, CDCl_3): δ 181.0 (d, $^2J_{\text{PC}} = 8.0$ Hz, $\text{C}=\text{N}$), 159.5 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 140.8 (d, $^3J_{\text{PC}} = 24.0$ Hz, $\text{N}=\text{CC}_{\text{Ar}}$), 135.0 (d, $^1J_{\text{PC}} = 131.0$ Hz, PC_{Ar}), 131.4 (d, $^3J_{\text{PC}} = 9.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 131.3 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 129.4, 128.3 (d, $^2J_{\text{PC}} = 13.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$), 120.4, 117.7, 113.3, 55.3 (OCH_3), 22.9 (d, $^3J_{\text{PC}} = 13.0$ Hz, CH_3).

^{31}P NMR (162 MHz, CDCl_3): δ 18.9.

***N*-[1-(2-Methoxyphenyl)ethylidene]diphenylphosphinic amide 5d**



Prepared according to General Procedure **III** from 18 mmol of the corresponding oxime. Purification of the crude by FCC (DCM:EtOAc 2:1 to 1:2) followed by trituration in Et_2O afforded **5d** (1.89 g, 30% yield) as a white solid.

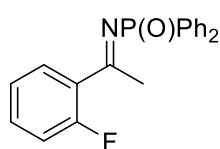
Spectroscopic data are consistent with those given in the literature.²⁹⁴

^1H NMR (400 MHz, CDCl_3): δ 8.00–7.93 (m, 4H), 7.64 (d, $J = 7.5$ Hz, 1H), 7.47–7.35 (m, 7H), 7.00 (t, $J = 7.5$ Hz, 1H), 6.94 (d, $J = 8.0$ Hz, 1H), 3.81 (s, 3H, OCH_3), 2.90 (d, $^4J_{\text{HP}} = 2.0$ Hz, 3H, CH_3).

^{13}C NMR (100 MHz, CDCl_3): δ 185.0 (d, $^2J_{\text{PC}} = 8.0$ Hz, $\text{C}=\text{N}$), 157.8 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 134.9 (d, $^3J_{\text{PC}} = 24.0$ Hz, $\text{N}=\text{CC}_{\text{Ar}}$), 133.0 (d, $^1J_{\text{PC}} = 131.0$ Hz, PC_{Ar}), 131.3 (d, $^3J_{\text{PC}} = 9.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 131.3 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 131.4, 130.0, 128.3 (d, $^2J_{\text{PC}} = 13.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$), 120.4, 111.3, 55.4 (OCH_3), 28.0 (d, $^3J_{\text{PC}} = 13.0$ Hz, CH_3).

^{31}P NMR (162 MHz, CDCl_3): δ 18.4.

N*-[1-(2-Fluorophenyl)ethylidene]diphenylphosphinic amide **5h*



Prepared according to General Procedure **III** from 10 mmol of the corresponding oxime. Purification of the crude by FCC (PE:EtOAc 6:4 to 1:2) afforded **5h** (2.77 g, 82% yield) as a white solid.

Spectroscopic data are consistent with those given in the literature.¹¹¹

M.p.: 99–100 °C (lit. 98–100 °C).¹¹¹

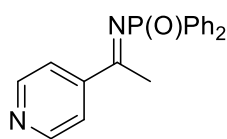
^1H NMR (400 MHz, CDCl_3): δ 8.05–7.93 (m, 4H), 7.89 (td, $J = 7.5, 2.0$ Hz, 1H), 7.57–7.37 (m, 7H), 7.22 (t, $J = 7.5$ Hz, 1H), 7.11 (dd, $J = 11.0, 8.8$ Hz, 1H), 2.97 (dd, $J = 4.0, 2.0$ Hz, 3H, CH_3).

^{13}C NMR (100 MHz, CDCl_3): δ 181.1 (dd, $^2J_{\text{PC}} = 7.0$ Hz, $^4J_{\text{FC}} = 2.5$ Hz, $\text{C}=\text{N}$), 161.5 (d, $^1J_{\text{FC}} = 255.0$ Hz, $\text{C}_{\text{Ar}}\text{F}$), 134.2 (d, $^1J_{\text{PC}} = 130.0$ Hz, PC_{Ar}), 133.5 (d, $J = 9.0$ Hz, $\text{N}=\text{CC}_{\text{Ar}}$), 131.5 (d, $^3J_{\text{PC}} = 9.5$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 131.3 (d, $^4J_{\text{PC}} = 2.5$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 130.3 (d, $J_{\text{FC}} = 2.5$ Hz), 128.6 (m), 128.3 (d, $^2J_{\text{PC}} = 12.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$), 124.2 (d, $J_{\text{FC}} = 4.0$ Hz), 116.7 (d, $J_{\text{FC}} = 23.0$ Hz), 27.3 (dd, $^3J_{\text{PC}} = 13.0$ Hz, $^4J_{\text{FC}} = 7.0$ Hz, CH_3).

^{31}P NMR (162 MHz, CDCl_3): δ 20.0.

^{19}F NMR (376 MHz): δ –110.0.

N*-[1-(Pyridin-4-yl)ethylidene]diphenylphosphinic amide **5i*



Prepared according to General Procedure **III** from 17 mmol of the corresponding oxime. Purification of the crude by FCC (CH₂Cl₂ to CH₂Cl₂:TEA 95:5) followed by trituration in Et₂O afforded **5i** (1.05 g, 20% yield) as an off-white solid.

M.p.: 134–136 °C.

IR: 3445 (w), 3057 (w), 1644 (s), 1437 (m), 1273 (m), 1198 (s), 1121 (s), 1107 (m), 810 (s), 724 (s), 695 (s) cm⁻¹.

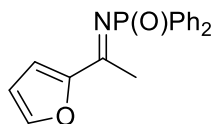
¹H NMR (400 MHz, CDCl₃): δ 8.78 (dd, *J* = 6.0, 1.5 Hz, 2H, NC_{Ar}HC_{Ar}H), 8.10–7.95 (m, 4H), 7.83 (dd, *J* = 6.0, 1.5 Hz, 2H, NC_{Ar}HC_{Ar}H), 7.54–7.41 (m, 6H), 2.96 (d, ⁴*J*_{HP} = 2.0 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 179.9 (d, ²*J*_{PC} = 7.5 Hz, C=N), 150.8 (NC_{Ar}HC_{Ar}H), 146.0 (d, ³*J*_{PC} = 24.5 Hz, N=CC_{Ar}), 133.9 (d, ¹*J*_{PC} = 131.0 Hz, PC_{Ar}), 131.9 (d, ⁴*J*_{PC} = 3.0 Hz, C_{Ar}PH_{para}), 131.7 (d, ³*J*_{PC} = 9.0 Hz, C_{Ar}PH_{meta}), 128.7 (d, ²*J*_{PC} = 12.5 Hz, C_{Ar}PH_{ortho}), 121.2 (NC_{Ar}HC_{Ar}H), 22.9 (d, ³*J*_{PC} = 12.0 Hz, CH₃).

³¹P NMR (162 MHz, CDCl₃): δ 19.8.

HRMS (ESI): calcd. for C₁₉H₁₈N₂O₄P⁺ [M+H]⁺ 321.11513, found 321.11528.

N*-[1-(2-Furyl)ethylidene]diphenylphosphinic amide **5l*



Prepared according to General Procedure **III** from 5.5 mmol of the corresponding oxime. Purification of the crude by FCC (PE:EtOAc 2:8 to EtOAc) followed by trituration in Et₂O afforded **5l** (320 mg, 19% yield) as a yellow solid.

Spectroscopic data are consistent with those given in the literature.²⁹⁴

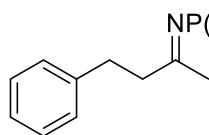
M.p.: 164–169 °C.

^1H NMR (400 MHz, CDCl_3): δ 8.07–7.90 (m, 4H), 7.62 (br s, 1H, $\text{OC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 7.52–7.35 (m, 6H), 7.24 (d, $J = 3.5$ Hz, 1H, $\text{OC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 6.55 (dd, $J = 3.5, 2.0$ Hz, 1H, $\text{OC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 2.80 (d, $^4J_{\text{HP}} = 2.0$ Hz, 3H, CH_3).

^{13}C NMR (100 MHz, CDCl_3): δ 170.2 (d, $^2J_{\text{PC}} = 5.0$ Hz, $\text{C}=\text{N}$), 154.4 (d, $^3J_{\text{PC}} = 30.0$ Hz, $\text{N}=\text{C}_{\text{Ar}}$), 146.5 ($\text{OC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 134.8 (d, $^1J_{\text{PC}} = 131.0$ Hz, PC_{Ar}), 131.6 (d, $^3J_{\text{PC}} = 9.5$ Hz, $\text{C}_{\text{Ar}}\text{P}_{\text{Hmeta}}$), 131.3 (d, $^4J_{\text{PC}} = 2.5$ Hz, $\text{C}_{\text{Ar}}\text{P}_{\text{Hpara}}$), 128.4 (d, $^2J_{\text{PC}} = 13.0$ Hz, $\text{C}_{\text{Ar}}\text{P}_{\text{Hortho}}$), 116.5 ($\text{OC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 112.6 ($\text{OC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 22.2 (d, $^3J_{\text{PC}} = 13.0$ Hz, CH_3).

^{31}P NMR (162 MHz, CDCl_3): δ 19.6.

***N*-(1-Methyl-3-phenylpropylidene)diphenylphosphinic amide 5p**



Prepared according to General Procedure **III** from 10 mmol of the corresponding oxime. Purification of the crude by FCC (PE:EtOAc 1:1) afforded **5p** (1.21 g, 35% yield) as a pale yellow powder.

Spectroscopic data are consistent with those given in the literature.⁴⁸

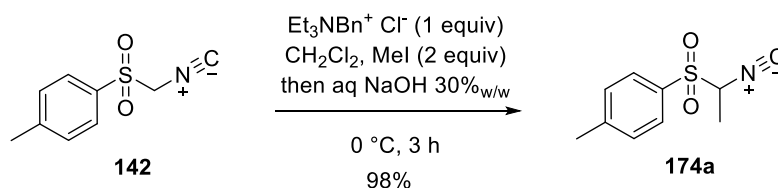
^1H NMR (500 MHz, CDCl_3): δ 7.93 (ddt, $J = 12.0, 8.5, 1.5$ Hz, 4H), δ 7.50 (tq, $J = 7.0, 1.5$ Hz, 2H), 7.47–7.40 (m, 4H), 7.28 (t, $J = 7.5$ Hz, 2H), 7.21–7.17 (m, 3H), 3.04 (t, $J = 7.5$ Hz, 2H, CH_2), 2.90 (t, $J = 7.5$ Hz, 2H, CH_2), 2.50 (d, $^4J_{\text{HP}} = 2.0$ Hz, 3H, CH_3).

^{13}C NMR (100 MHz, CDCl_3): δ 190.2 (d, $^2J_{\text{PC}} = 10.0$ Hz, $\text{C}=\text{N}$), 141.0 ($\text{CH}_2\text{C}_{\text{Ar}}$), 134.7 (d, $^1J_{\text{PC}} = 130.0$ Hz, PC_{Ar}), 131.7 (d, $^3J_{\text{PC}} = 9.5$ Hz, $\text{C}_{\text{Ar}}\text{P}_{\text{Hmeta}}$), 131.4 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\text{C}_{\text{Ar}}\text{P}_{\text{Hpara}}$), 128.6 ($\text{C}_{\text{Ar}}\text{H}$), 128.4 (d, $^2J_{\text{PC}} = 13.0$ Hz, $\text{C}_{\text{Ar}}\text{P}_{\text{Hortho}}$), 128.4 ($\text{C}_{\text{Ar}}\text{H}$), 126.0 ($\text{C}_{\text{Ar}}\text{H}$), 45.2 (CH_2), 31.8 (CH_2), 27.2 (d, $^3J_{\text{PC}} = 16.0$ Hz, CH_3).

^{31}P NMR (162 MHz, CDCl_3): δ 18.1.

7.4.2 Synthesis of α -Substituted TosMIC Pronucleophiles 174

1-(1-Isocyanoethanesulfonyl)-4-methylbenzene 174a

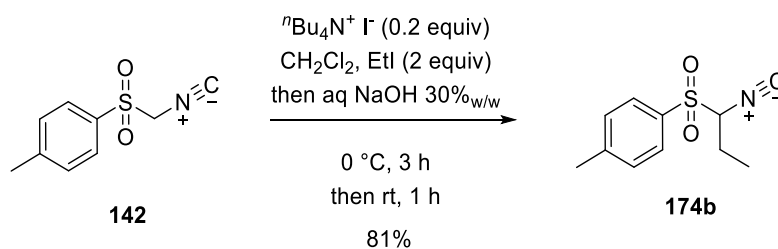


Following a literature procedure,¹⁸⁷ TosMIC (0.976 g, 5 mmol, 1 equiv) and benzyltriethylammonium chloride (1.14 g, 5 mmol, 1 equiv) were dissolved in CH_2Cl_2 (10 mL). The solution was cooled to 0 °C, then iodomethane (0.62 mL, 10 mmol, 2 equiv) and 30%_{w/w} aq NaOH (10 mL) were added. The reaction mixture was stirred at 0 °C for 3 hours, then poured into a separatory funnel and diluted with water (50 mL) and CH_2Cl_2 (10 mL). Phases were separated and the aqueous layer was extracted twice with CH_2Cl_2 (20 mL). Combined organic phases were dried over Na_2SO_4 , filtered and evaporated to give a yellow oil, which was purified by FCC (PE/AcOEt 8:2). The title compound **174a** (1.02 g, 98%) was obtained as a yellow oil. Spectroscopic data match those given in the literature.¹⁸⁷

^1H NMR (CDCl_3 , 400 MHz): δ 7.87 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 4.59 (q, J = 7.0 Hz, 1H, CH), 2.49 (s, 3H, $\text{C}_{\text{Ar}}\text{CH}_3$), 1.74 (d, J = 7.0 Hz, 3H, CHCH_3).

LRMS (ESI, MeOH): calcd. for $\text{C}_{10}\text{H}_{12}\text{NO}_2\text{S}^+ [\text{M}+\text{H}]^+$ 210.1, found 210.1.

1-(1-Isocyanopropane-1-sulfonyl)-4-methylbenzene 174b



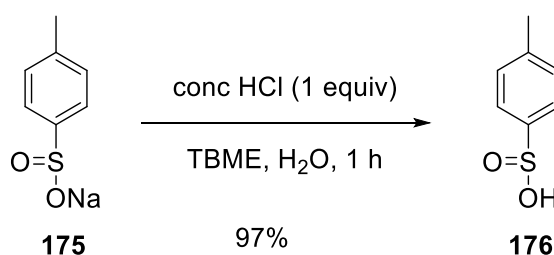
Following a literature procedure,¹⁸⁷ TosMIC (1.95 g, 10 mmol, 1 equiv) and tetrabutylammonium iodide (738 mg, 2 mmol, 0.2 equiv) were dissolved in CH_2Cl_2 (20 mL).

The solution was cooled to 0 °C, then iodoethane (1.61 mL, 20 mmol, 2 equiv) and 30%_{w/w} aq NaOH (20 mL) were added. The reaction mixture was stirred at 0 °C for 3 hours, then at rt for one hour. Water (50 mL) and CH₂Cl₂ (20 mL) were added, phases separated and the aqueous layer was extracted twice with CH₂Cl₂ (30 mL). Combined organic phases were dried over Na₂SO₄, filtered and evaporated. The crude was purified by FCC (PE/AcOEt 8:2 to 1:1). The product was recrystallised from MeOH obtaining compound **174b** (1.8 g, 81%) as a beige solid. M.p.: 55–56 °C (lit: 56–57 °C).¹⁸⁷

¹H NMR (CDCl₃, 400 MHz): δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 4.41 (dd, *J* = 10.5, 4.0 Hz, 1H, CHCH₂CH₃), 2.48 (s, 3H, C_{Ar}CH₃), 2.25 (ddq, *J* = 14.5, 7.5, 4.0 Hz, 1H, CHCH_AH_BCH₃), 1.87 (ddq, *J* = 14.5, 10.5, 7.5 Hz, 1H, CHCH_AH_BCH₃), 1.17 (t, *J* = 7.5 Hz, 3H, CHCH₂CH₃).

¹³C NMR (CDCl₃, 100 MHz): δ 165.0 (NC), 146.7, 131.3, 130.3, 130.2, 74.4 (CH), 22.6 (CH₂CH₃), 21.9 (C_{Ar}CH₃), 10.1 (CH₂CH₃).

4-Methylbenzene-1-sulfinic acid **176**



Following a literature procedure,¹⁸⁸ sodium *p*-toluenesulfinate (13.4 g, 75.2 mmol, 1 equiv) was dissolved in water (77 mL). To the clear solution TBME (67 mL) and then 37%_{w/w} HCl (4.4 mL, dropwise over 5 minutes) were added. The colorless biphasic solution turned cloudy yellow. After stirring for 20 minutes, heptane was added (80 mL) and the precipitate was collected on buchner. Compound **176** (7.94 g, 97%) was obtained as a yellow powder, stored in the darkness and used within 24 hours.

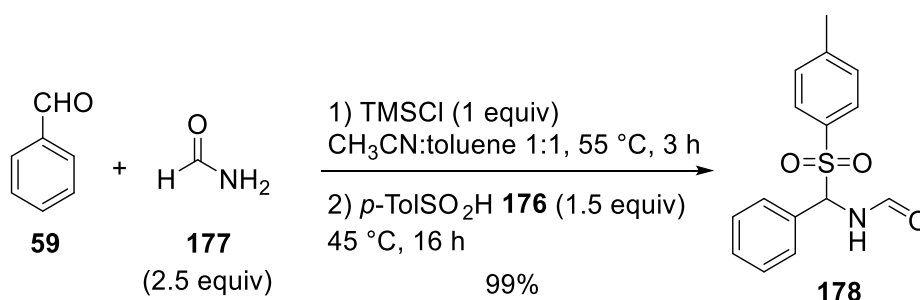
Spectroscopic data match those given in the literature.¹⁸⁸

M.p.: 84–86 °C (lit: 85–86 °C).¹⁸⁸

¹H NMR (DMSO-d₆, 400 MHz): δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 2.37 (s, 3H).

¹³C NMR (DMSO-d₆, 100 MHz): δ 145.9, 141.3, 129.5, 124.5, 21.0.

N-[(4-Methylbenzene-1-sulfonyl)(phenyl)methyl]formamide **178**



Following a literature procedure,¹⁷⁵ CH₃CN (11 mL), toluene (11 mL), benzaldehyde (2.14 mL, 21.2 mmol, 1 equiv) and formamide (2.10 mL, 52.8 mmol, 2.5 equiv) were put in a 2-neck flask equipped with a reflux condenser. TMSCl (2.94 mL, 23.2 mmol, 1.1 equiv) was added and the mixture stirred at 55 °C for 3 hours. *p*-Toluenesulfinic acid **176** (4.94 g, 31.7 mmol, 1.5 equiv) was added and the mixture stirred at 45 °C for 16 hours. After cooling down to rt, Et₂O (11 mL), then water (55 mL) were added and the resulting mixture was stirred until a creamy white suspension was obtained. The suspension was left at 0 °C for 45 minutes, then the precipitate was collected on sinter funnel and dried, obtaining compound **178** (6.17 g, 99%) as a white solid.

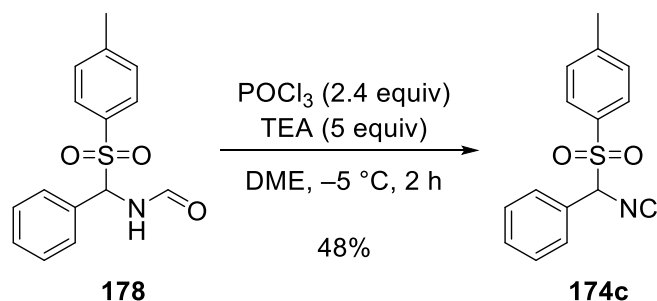
Spectroscopic data match those given in the literature.¹⁷⁵

M.p.: 159–162 °C (lit: 160–162 °C).¹⁷⁵

¹H NMR (CDCl₃, 400 MHz, rotamer ratio 6:1, data for the major rotamer): δ 8.14 (br s, 1H, HCO), 7.72 (d, *J* = 8.0 Hz, 2H), 7.48–7.36 (m, 5H, Ph), 7.32 (d, *J* = 8.0 Hz, 2H), 6.94 (br d, *J* = 10.5 Hz, 1H, NH), 6.31 (d, *J* = 10.5 Hz, 1H, CH), 2.44 (s, 3H, CH₃).

^{13}C NMR (CDCl_3 , 100 MHz): δ 159.6 ($\text{H}\underline{\text{C}}\text{O}$), 145.8, 133.2, 130.2, 130.0, 129.5, 129.0, 128.9, 128.4, 70.6 ($\underline{\text{C}}\text{H}$), 21.9 ($\underline{\text{C}}\text{H}_3$).

1-[Isocyano(phenyl)methanesulfonyl]-4-methylbenzene **174c**



Following a literature procedure,¹⁷⁵ POCl_3 (0.39 mL, 4.2 mmol, 2.4 equiv) was added dropwise over 5 minutes to a stirred suspension of **178** (500 mg, 1.73 mmol, 1 equiv) in DME (3.5 mL) at -10°C . A triethylamine solution in DME (1.2 mL TEA in 1 mL DME, 8.64 mmol, 5 equiv) was then added dropwise over 10 minutes keeping the temperature at -10°C . The resultant mixture was stirred at -5°C for 1.5 hours, then cold water was added until a brown solid precipitate. The solid was collected and recrystallised from MeOH, obtaining **174c** (225 mg, 48%) as a beige solid.

Data match those given in the literature.¹⁷⁵

M.p.: $130\text{--}131^\circ\text{C}$ (lit: $128\text{--}129^\circ\text{C}$).¹⁷⁵

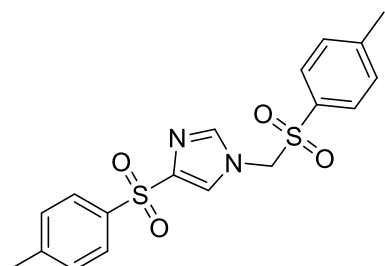
^1H NMR (CDCl_3 , 400 MHz): δ 7.60 (d, $J = 8.5$ Hz, 2H), 7.45 (t, $J = 7.0$ Hz, 1H), 7.42–7.36 (m, 2H), 7.34–7.30 (m, 4H), 5.62 (s, 1H, $\underline{\text{C}}\text{H}$), 2.46 (s, 3H, $\underline{\text{C}}\text{H}_3$).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.1 ($\text{N}\underline{\text{C}}$), 146.7, 130.8, 130.6, 130.1, 129.9, 128.9, 128.5, 126.7, 76.6 ($\underline{\text{C}}\text{H}$), 21.9 ($\underline{\text{C}}\text{H}_3$).

7.4.3 Characterisation of TosMIC Dimers

4-(4-Methylbenzene-1-sulfonyl)-1-[(4-methylbenzene-1-sulfonyl)methyl]-1H-imidazole

171



Off-white solid, recrystallised from MeOH. Structure confirmed by X-Ray structure determination (see Appendix).

Data match those reported in the literature.¹⁷⁵

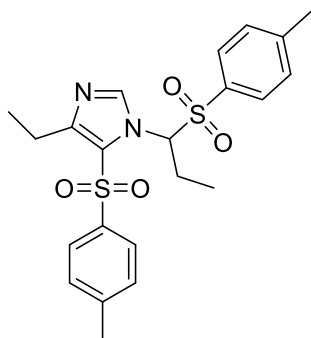
M.p.: 179–181 °C (lit: 179–180 °C).¹⁷⁵

¹H NMR (CDCl₃, 400 MHz): δ 7.86 (d, *J* = 8.5 Hz, 2H, C_{Ar}SO₂C_{Ar}C_{Ar}H_{C_{Ar}H}), 7.45 (d, *J* = 8.5 Hz, 2H, CH₂SO₂C_{Ar}C_{Ar}H_{C_{Ar}H}), 7.39 (d, *J* = 1.5 Hz, 1H, C=CHN), 7.33 (d, *J* = 8.0 Hz, 2H, C_{Ar}SO₂C_{Ar}C_{Ar}H_{C_{Ar}H}), 7.29 (d, *J* = 1.5 Hz, 1H, N=CHN), 7.24 (d, *J* = 8.0 Hz, 2H, CH₂SO₂C_{Ar}C_{Ar}H_{C_{Ar}H}), 5.11 (s, 2H, CH₂), 2.45 (s, 3H, CH₃), 2.43 (s, 3H, CH₃).

¹³C NMR (CDCl₃, 100 MHz): δ 147.2 (C_{Ar}), 144.7 (C_{Ar}), 143.6 (C_{Ar}), 139.6 (N=CHN), 137.5 (C_{Ar}), 131.4 (C_{Ar}), 130.7 (C_{Ar}SO₂H), 129.9 (C_{Ar}SO₂H), 128.8 (C_{Ar}SO₂H), 128.1 (C_{Ar}SO₂H), 123.8 (C=CHN), 66.6 (CH₂), 22.0 (C_{Ar}CH₃), 21.8 (C_{Ar}CH₃).

HRMS (ESI): calcd. for C₁₈H₁₇N₂O₄S₂⁺ [M+H]⁺ 389.06352, found 389.06348.

4-Ethyl-5-(4-methylbenzene-1-sulfonyl)-1-[1-(4-methylbenzene-1-sulfonyl)propyl]-1H-imidazole 179b



Off-white solid.

M.p.: 116–118 °C.

IR: 2976 (w), 2935 (w), 1596 (m), 1524 (m), 1457 (m), 1323 (s), 1241 (m), 1149 (s), 1126 (s), 1081 (m), 814 (m), 754 (m), 704 (m), 681 (s), 664 (s), 634 (m) cm⁻¹.

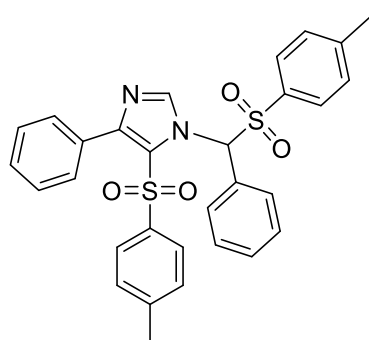
¹H NMR (CDCl₃, 400 MHz): δ 7.95 (s, 1H, N=CHN), 7.58 (d, *J* = 8.5 Hz, 2H, C_{Ar}SO₂C_{Ar}C_{Ar}H_{C_{Ar}H}), 7.58 (d, *J* = 8.5 Hz, 2H, CH₂SO₂C_{Ar}C_{Ar}H_{C_{Ar}H}), 7.28 (d, *J* = 8.0 Hz, 2H,

$\text{C}_{\text{Ar}}\text{SO}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 7.25 (d, $J = 8.0$ Hz, 2H, $\text{CH}_2\text{SO}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 6.10 (dd, $J = 11.5, 4.0$ Hz, 1H, $\text{NCHCH}_\text{A}\text{H}_\text{B}\text{CH}_3$), 2.81 (dq, $J = 14.5, 7.5$ Hz, 1H, $\text{C}_{\text{Ar}}\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_3$), 2.70 (dq, $J = 14.5, 7.5$ Hz, 1H, $\text{C}_{\text{Ar}}\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_3$), 2.47 (ddq, $J = 15.0, 4.0, 7.5$ Hz, 1H, $\text{NCHCH}_\text{A}\text{H}_\text{B}\text{CH}_3$), 2.43 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.17 (ddq, $J = 15.0, 11.5, 7.5$ Hz, 1H, $\text{NCHCH}_\text{A}\text{H}_\text{B}\text{CH}_3$), 1.13 (t, $J = 7.5$ Hz, 3H, $\text{C}_{\text{Ar}}\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_3$), 0.72 (t, $J = 7.5$ Hz, 3H, $\text{NCHCH}_\text{A}\text{H}_\text{B}\text{CH}_3$).

^{13}C NMR (CDCl_3 , 100 MHz): δ 152.8 ($\text{EtNC}=\text{CN}$), 146.2 ($\text{C}_{\text{Ar}}\text{SO}_2$), 144.8 ($\text{C}_{\text{Ar}}\text{SO}_2$), 139.4 ($\text{C}_{\text{Ar}}\text{SO}_2$), 139.1 ($\text{N}=\text{CHN}$), 132.1 ($\text{C}_{\text{Ar}}\text{SO}_2$), 130.0 ($\text{C}_{\text{Ar}}\text{SO}_2\text{H} \times 2$), 129.5 ($\text{C}_{\text{Ar}}\text{SO}_2\text{H}$), 126.8 ($\text{C}_{\text{Ar}}\text{SO}_2\text{H}$), 124.1 ($\text{NC}=\text{CNTs}$), 74.6 (CH), 22.1 (CH_2), 22.0 ($\text{C}_{\text{Ar}}\text{CH}_3$), 21.9 ($\text{C}_{\text{Ar}}\text{CH}_3$), 21.7 (CH_2), 13.9 ($\text{C}_{\text{Ar}}\text{CH}_2\text{CH}_3$), 9.7 (CHCH_2CH_3).

HRMS (ESI): calcd. for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}_4\text{S}_2^+$ $[\text{M}+\text{H}]^+$ 447.14068, found 447.14010.

5-(4-Methylbenzene-1-sulfonyl)-1-[(4-methylbenzene-1-sulfonyl)(phenyl)methyl]-4-phenyl-1H-imidazole 179c



Fluffy pale yellow solid.

M.p.: 67–70 °C.

IR: 3064 (w), 3032 (w), 2994 (w), 1596 (w), 1484 (m), 1325 (s), 1232 (m), 1153 (s), 1085 (w), 812 (w), 754 (m), 702 (s), 665 (s) cm^{-1} .

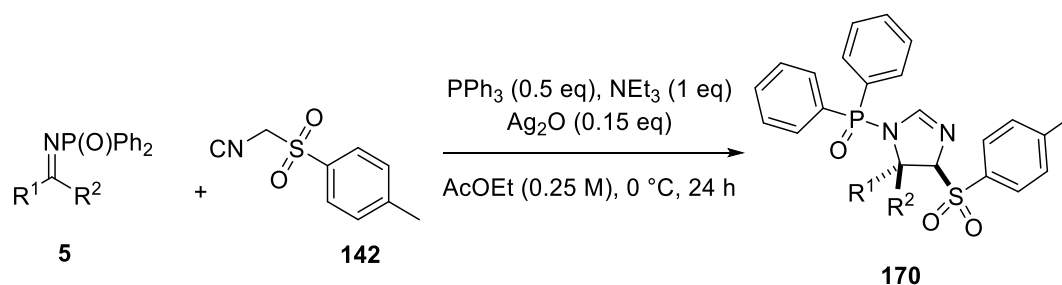
^1H NMR (CDCl_3 , 400 MHz): δ 8.61 (s, 1H, $\text{N}=\text{CHN}$), 7.75 (s, 1H, NCHPh), 7.70 (d, $J = 8.5$ Hz, 2H, $\text{SO}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 7.65–7.57 (m, 2H, $\text{C}_{\text{Ph}}\text{H}$), 7.53–7.29 (m, 10H, $\text{C}_{\text{Ph}}\text{H}$ and $\text{SO}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 7.01 (d, $J = 8.5$ Hz, 2H, $\text{SO}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 6.88 (d, $J = 8.5$ Hz, 2H, $\text{SO}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 2.48 (s, 3H, CH_3), 2.23 (s, 3H, CH_3).

^{13}C NMR (CDCl_3 , 100 MHz): δ 149.4 ($\text{NC}=\text{CN}$), 146.2 ($\text{C}_{\text{Ar}}\text{SO}_2$), 144.4 ($\text{C}_{\text{Ar}}\text{SO}_2$), 140.3 ($\text{N}=\text{CHN}$), 138.4 ($\text{C}_{\text{Ar}}\text{SO}_2$), 132.7 (C_{Ar}), 132.1 ($\text{C}_{\text{Ar}}\text{SO}_2$), 130.4 ($\text{C}_{\text{Ar}}\text{H}$), 130.2 ($\text{C}_{\text{Ar}}\text{H}$), 129.6

($\underline{\text{C}}_{\text{ArSO}_2\text{H}}$), 129.4 ($\underline{\text{C}}_{\text{ArSO}_2\text{H}}$), 129.3 ($\underline{\text{C}}_{\text{ArSO}_2\text{H}}$), 129.2 ($\underline{\text{C}}_{\text{ArH}}$), 129.1 ($\underline{\text{C}}_{\text{ArH}}$), 129.0 ($\underline{\text{C}}_{\text{Ar}}$), 127.7 ($\underline{\text{C}}_{\text{ArH}}$), 126.6 ($\underline{\text{C}}_{\text{ArSO}_2\text{H}}$), 124.8 ($\text{NC}=\underline{\text{C}}\text{N}$), 76.0 ($\text{N}\underline{\text{C}}\text{HPh}$), 21.9 ($\text{C}_{\text{Ar}}\underline{\text{C}}\text{H}_3$), 21.5 ($\text{C}_{\text{Ar}}\underline{\text{C}}\text{H}_3$).
 HRMS (ESI): calcd. for $\text{C}_{30}\text{H}_{27}\text{N}_2\text{O}_4\text{S}_2^+$ $[\text{M}+\text{H}]^+$ 543.14068, found 543.14047.

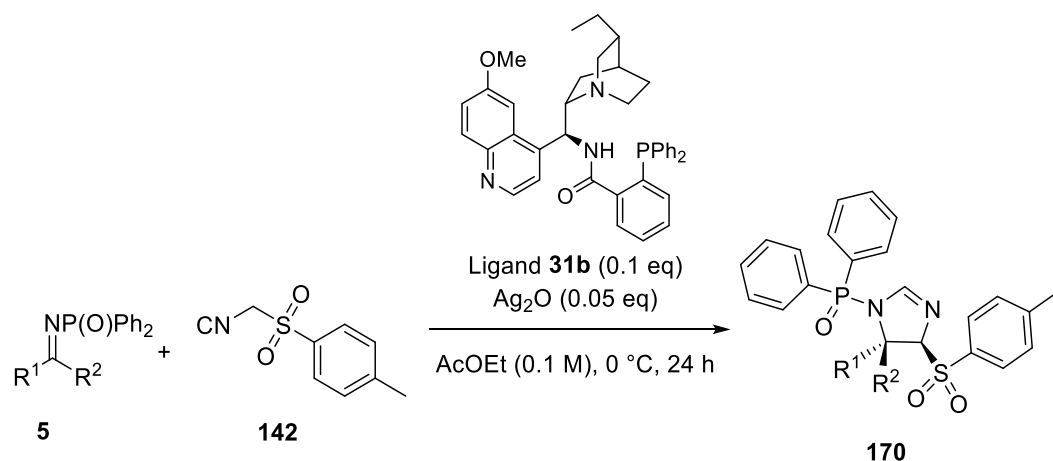
7.4.4 Synthesis and Characterisation of Imidazolines 170

General Procedure IV for the synthesis of racemic imidazolines 170



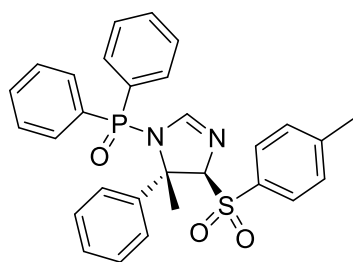
Triethylamine (35 μL , 0.25 mmol, 1 equiv) was added to a suspension of *N*-DPP ketimine **5** (0.25 mmol, 1 equiv), *p*-toluenesulfonylmethyl isocyanide (53.7 mg, 0.275 mmol, 1.1 equiv), Ag_2O (8.7 mg, 0.038 mmol, 0.15 equiv) and triphenylphosphine (32.8 mg, 0.125 mmol, 0.5 equiv) in dry AcOEt (1 mL). The heterogeneous mixture was cooled to $0\text{ }^\circ\text{C}$ and stirred in the dark for 24 hours. The reaction mixture was filtered through celite in a glass pipette eluting with CH_2Cl_2 . Evaporation of the filtrate yielded a crude mixture, that was purified by FCC obtaining the racemic imidazoline **170** as a single diastereomer.

General Procedure V for the asymmetric synthesis of imidazolines 170



To a mixture of *N*-diphenylphosphinyl ketimine **5** (0.25 mmol, 1 equiv), *p*-toluenesulfonylmethyl isocyanide (53.7 mg, 0.275 mmol, 1.1 equiv), ligand **31b** (15.3 mg, 0.025 mmol, 0.1 equiv) and Ag₂O (2.9 mg, 0.013 mmol, 0.05 equiv), dry AcOEt was added (2.5 mL). The heterogeneous mixture was then stirred in the dark at 0 °C for 24 hours. The reaction mixture was filtered through celite in a glass pipette eluting with DCM. Evaporation of the filtrate yielded a crude mixture, that was checked by ¹H NMR and ³¹P NMR (CDCl₃, mesitylene as an internal standard [35 μL, 0.25 mmol, 1 equiv]) to determine conversion and dr. The crude mixture was purified by FCC on silica gel obtaining *trans* imidazoline **170** as a single diastereomer.

((4*S*,5*R*)-5-Methyl-5-phenyl-4-tosyl-4,5-dihydro-1*H*-imidazol-1-yl)diphenylphosphine oxide **170a**



mg).

Prepared according to General Procedure V, using *N*-DPP ketimine **5a** (79.8 mg, 0.25 mmol). Purification of the crude mixture (conversion 100%, dr > 95:5) by FCC (AcOEt:PE 1:1 to 7:3) afforded product **170a** as a white solid in 98% yield (126

The ee was determined by HPLC: Chiralpak IB column, hexane/*iso*-propanol 85:15, 1 mL/min, λ 220 nm, *t* (major) = 28.6 min, *t* (minor) = 39.2 min (96% ee).

RF: 0.20 (AcOEt:PE 1:1).

M.p.: 92–94 °C.

IR: 3059 (w), 2232 (w), 1597 (s), 1438 (m), 1317 (m), 1233 (s), 1147 (s), 1084 (s), 910 (m), 723 (s), 697 (s), 670 (m), 655 (m) cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ 7.82–7.76 (m, 4H), 7.69–7.64 (m, 2H), 7.61–7.57 (m, 2H), 7.53–7.45 (m, 4H), 7.37 (m, 2H), 7.33–7.25 (m, 5H), 7.21 (br s, 1H, $\text{N}=\underline{\text{CH}}$), 5.06 (d, J = 1.5 Hz, 1H, $\underline{\text{CHT}}$ s), 2.40 (s, 3H, $\text{C}_{\text{Ar}}\underline{\text{CH}}_3$), 2.30 (s, 3H, $\text{NC}\underline{\text{CH}}_3$).

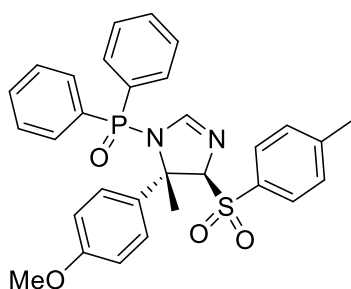
^{13}C NMR (CDCl_3 , 126 MHz): δ 156.5 (d, $^2J_{\text{PC}}$ = 7.5 Hz, $\text{N}=\underline{\text{CH}}$), 145.3 ($\underline{\text{C}}_{\text{Ar}}$), 145.2 ($\underline{\text{C}}_{\text{Ar}}$), 136.0 ($\underline{\text{C}}_{\text{Ar}}\underline{\text{CH}}_3$), 133.1 (app t, $^4J_{\text{PC}}$ = 4.0 Hz, $\underline{\text{C}}_{\text{Ar}}\text{P}_{\text{para}}$), 132.6 (d, $^3J_{\text{PC}}$ = 10.5 Hz, $\underline{\text{C}}_{\text{Ar}}\text{P}_{\text{meta}}$), 132.1 (d, $^3J_{\text{PC}}$ = 11.0 Hz, $\underline{\text{C}}_{\text{Ar}}\text{P}_{\text{meta}}$), 131.1 (d, $^1J_{\text{PC}}$ = 126.0 Hz, $\text{P}\underline{\text{C}}_{\text{Ar}}$), 130.1 (d, $^1J_{\text{PC}}$ = 122.0 Hz, $\text{P}\underline{\text{C}}_{\text{Ar}}$), 129.6 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 129.1 (d, $^2J_{\text{PC}}$ = 13.5 Hz, $\underline{\text{C}}_{\text{Ar}}\text{H}_{\text{ortho}}$), 128.9 (d, $^2J_{\text{PC}}$ = 14.0 Hz, $\underline{\text{C}}_{\text{Ar}}\text{H}_{\text{ortho}}$), 128.9 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 128.1 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 125.0 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 97.7 (d, $^3J_{\text{PC}}$ = 7.0 Hz, $\underline{\text{CHT}}$ s), 71.8 ($\text{NC}\underline{\text{CH}}_3$), 21.8 ($\text{C}_{\text{Ar}}\underline{\text{CH}}_3$), 20.3 ($\text{NC}\underline{\text{CH}}_3$).

^{31}P NMR (CDCl_3 , 162 MHz): δ 22.4.

HRMS (ESI): calcd. for $\text{C}_{29}\text{H}_{28}\text{N}_2\text{O}_3\text{P}^{32}\text{S}^+$ $[\text{M}+\text{H}]^+$ 515.15528, found 515.15442.

$[\alpha]_{\text{D}}^{25}$: –128 (c = 1.00 in CHCl_3).

((4*S*,5*S*)-5-(4-Methoxyphenyl)-5-methyl-4-tosyl-4,5-dihydro-1*H*-imidazol-1-yl)diphenylphosphine oxide **170b**



Prepared according to General Procedure **V**, using *N*-DPP ketimine **5b** (83.7 mg, 0.25 mmol). Purification of the crude mixture (conversion 100%, dr > 95:5) by FCC (AcOEt:PE 7:3) afforded product **170b** as a white solid in 92% yield (125 mg).

The ee was determined by HPLC: Chiralpak IB column, hexane/*iso*-propanol 80:20, 1 mL/min, λ 220 nm, *t* (major) = 24.1 min, *t* (minor) = 43.8 min (97% ee).

RF: 0.15 (AcOEt:PE 1:1). M.p.: 91–94 °C.

IR: 3059 (w), 2931 (w), 2233 (w), 1597 (m), 1512 (m), 1438 (m), 1228 (s), 1146 (s), 1122 (s), 912 (m), 727 (s), 700 (s), 661 (s) cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ 7.73–7.68 (m, 4H), 7.59–7.48 (m, 4H), 7.45–7.37 (m, 4H), 7.23–7.17 (m, 4H), 7.11 (br s, 1H, $\text{N}=\text{CH}$), 6.73 (d, J = 8.5 Hz, 2H, $\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{OCH}_3$), 4.99 (s, 1H, CHTs), 3.72 (s, 3H, OCH_3), 2.32 (s, 3H, $\text{C}_{\text{Ar}}\text{CH}_3$), 2.21 (s, 3H, NCCH_3).

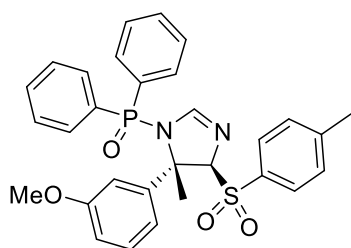
^{13}C NMR (CDCl_3 , 126 MHz): δ 159.3 ($\text{C}_{\text{Ar}}\text{OMe}$), 156.3 (d, $^2J_{\text{PC}}$ = 7.5 Hz, $\text{N}=\text{CH}$), 145.1 (C_{Ar}), 137.4 (C_{Ar}), 136.1 (C_{Ar}), 133.1 (d, $^4J_{\text{PC}}$ = 3.0 Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 133.0 (d, $^4J_{\text{PC}}$ = 3.0 Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 132.5 (d, $^3J_{\text{PC}}$ = 10.5 Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 132.0 (d, $^3J_{\text{PC}}$ = 11.0 Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 131.0 (d, $^1J_{\text{PC}}$ = 124.5 Hz, PC_{Ar}), 130.1 (d, $^1J_{\text{PC}}$ = 128.0 Hz, PC_{Ar}), 129.5 ($\text{C}_{\text{Ar}}\text{H}$), 129.4 ($\text{C}_{\text{Ar}}\text{H}$), 129.0 (d, $^2J_{\text{PC}}$ = 13.5 Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$), 128.9 (d, $^2J_{\text{PC}}$ = 13.5 Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$), 126.3 ($\text{C}_{\text{Ar}}\text{H}$), 114.1 ($\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{OCH}_3$), 97.9 (d, $^3J_{\text{PC}}$ = 7.0 Hz, CHTs), 71.4 (d, $^2J_{\text{PC}}$ = 2.5 Hz, NCCH_3), 55.4 (OCH_3), 21.8 ($\text{C}_{\text{Ar}}\text{CH}_3$), 20.3 (NCCH_3).

^{31}P NMR (CDCl_3 , 162 MHz): δ 22.2.

HRMS (ESI): calcd. for $\text{C}_{30}\text{H}_{30}\text{N}_2\text{O}_4\text{P}^{32}\text{S}^+$ $[\text{M}+\text{H}]^+$ 545.16584, found 545.16553.

$[\alpha]_{\text{D}}^{25}$: –125 (c = 1.00 in CHCl_3).

((4*S*,5*S*)-5-(3-Methoxyphenyl)-5-methyl-4-tosyl-4,5-dihydro-1*H*-imidazol-1-yl)diphenylphosphine oxide 170c



Prepared according to General Procedure V, using *N*-DPP ketimine **5c** (83.7 mg, 0.25 mmol). Purification of the crude mixture (conversion 100%, dr > 95:5) by FCC (AcOEt:PE 1:1 to 7:3) afforded product **170c** as a white solid in 90% yield (122 mg).

The ee was determined by HPLC: Chiralpak OD-H column, hexane/*iso*-propanol 70:30, 1 mL/min, λ 220 nm, *t* (minor) = 11.8 min, *t* (major) = 17.9 min (95% ee).

RF: 0.41 (AcOEt:PE 7:3).

M.p.: 54–55 °C.

IR: 3060 (w), 2935 (w), 2836 (w), 2234 (w), 1598 (s), 1437 (m), 1228 (s), 1147 (s), 1124 (s), 911 (m), 728 (s), 700 (s), 667 (s) cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ 7.82–7.77 (m, 4H), 7.70–7.65 (m, 2H), 7.61–7.55 (m, 2H), 7.52–7.44 (m, 4H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.25–7.20 (m, 2H, N=CH and C_{Ar}H), 6.97 (dd, *J* = 8.0, 1.5 Hz, 1H, C_{Ar}OMeH), 6.90 (t, *J* = 2.0 Hz, 1H, C_{Ar}OMeH), 6.81 (dd, *J* = 8.0, 2.5 Hz, 1H, C_{Ar}OMeH), 5.07 (br s, 1H, CHTs), 3.75 (s, 3H, OCH₃), 2.39 (s, 3H, C_{Ar}CH₃), 2.29 (s, 3H, NCCH₃).

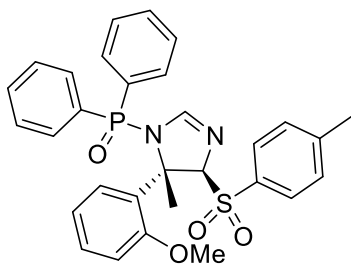
¹³C NMR (CDCl₃, 126 MHz): δ 159.9 (C_{Ar}OMe), 156.4 (d, ²*J*_{PC} = 7.5 Hz, N=CH), 146.9 (C_{Ar}), 145.1 (C_{Ar}), 136.0 (C_{Ar}CH₃), 133.1 (d, ⁴*J*_{PC} = 3.0 Hz, C_{Ar}P_Hpara), 133.0 (d, ⁴*J*_{PC} = 3.0 Hz, C_{Ar}P_Hpara), 132.6 (d, ³*J*_{PC} = 11.0 Hz, C_{Ar}P_Hmeta), 132.1 (d, ³*J*_{PC} = 11.0 Hz, C_{Ar}P_Hmeta), 131.0 (d, ¹*J*_{PC} = 124.5 Hz, PC_{Ar}), 130.1 (d, ¹*J*_{PC} = 128.0 Hz, PC_{Ar}), 130.0 (C_{Ar}H), 129.6 (C_{Ar}H), 129.5 (C_{Ar}H), 129.1 (d, ²*J*_{PC} = 13.5 Hz, C_{Ar}H_{ortho}), 128.9 (d, ²*J*_{PC} = 13.5 Hz, C_{Ar}H_{ortho}), 117.3 (C_{Ar}OMeH), 113.5 (C_{Ar}OMeH), 111.0 (C_{Ar}OMeH), 97.7 (d, ³*J*_{PC} = 7.0 Hz, CHTs), 71.8 (d, ²*J*_{PC} = 2.5 Hz, NCCH₃), 55.4 (OCH₃), 21.8 (C_{Ar}CH₃), 20.4 (NCCH₃).

³¹P NMR (CDCl₃, 162 MHz): δ 22.3.

HRMS (ESI): calcd. for C₃₀H₂₉N₂NaO₄P³²S⁺ [M+Na]⁺ 567.14779, found 567.14575.

[α]_D²⁵: –113 (*c* = 1.00 in CHCl₃).

(4*S*,5*S*)-5-(2-Methoxyphenyl)-5-methyl-4-tosyl-4,5-dihydro-1*H*-imidazol-1-yl)diphenylphosphine oxide **170d**



Prepared according to a modified General Procedure **V**, using *N*-DPP ketimine **5d** (83.7 mg, 0.25 mmol) and doubling the loading of ligand **31b** (30.8 mg, 0.05 mmol, 0.2 equiv) and Ag₂O (5.8 mg, 0.025 mmol, 0.1 equiv). Purification of the crude mixture

(conversion 98%, dr > 95:5) by FCC (AcOEt:PE 1:1 to 7:3) afforded product **170d** as a white solid in 88% yield (120 mg).

The ee was determined by HPLC: Chiralpak IB column, hexane/*iso*-propanol 70:30, 1 mL/min, λ 220 nm, t (major) = 17.7 min, t (minor) = 25.0 min (92% ee).

RF: 0.27 (AcOEt:PE 7:3).

M.p.: 63–65 °C.

IR: 3060 (w), 2924 (w), 2851 (w), 2231 (w), 1604 (m), 1438 (m), 1225 (s), 1146 (s), 1122 (s), 912 (m), 727 (s), 701 (s), 666 (s) cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ 7.83–7.77 (m, 4H), 7.62–7.65 (m, 3H), 7.51–7.45 (m, 3H), 7.40–7.25 (m, 6H), 7.08 (br s, 1H, N=CH), 7.25–7.20 (m, 2H, N=CH and C_{Ar}H), 6.87 (dd, *J* = 7.5, 1.0 Hz, 1H, C_{Ar}OMeH), 6.80 (dd, *J* = 8.0, 1.0 Hz, 1H, C_{Ar}OMeH), 5.33 (d, *J* = 2.0 Hz, 1H, CHTs), 3.72 (s, 3H, OCH₃), 2.41 (s, 3H, C_{Ar}CH₃), 2.33 (s, 3H, NCCH₃).

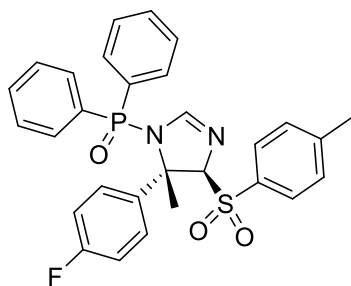
¹³C NMR (CDCl₃, 126 MHz): δ 156.8 (C_{Ar}OMe), 154.9 (d, ²*J*_{PC} = 7.5 Hz, N=CH), 144.7 (C_{Ar}), 136.8 (C_{Ar}CH₃), 132.9 (d, ⁴*J*_{PC} = 3.0 Hz, C_{Ar}P_Hpara), 132.6 (d, ⁴*J*_{PC} = 2.5 Hz, C_{Ar}P_Hpara), 132.5 (d, ³*J*_{PC} = 10.5 Hz, C_{Ar}P_Hmeta), 132.1 (d, ³*J*_{PC} = 10.5 Hz, C_{Ar}P_Hmeta), 130.7 (d, ¹*J*_{PC} = 127.5 Hz, PC_{Ar}), 130.6 (C_{Ar}OMe), 129.8 (C_{Ar}H), 129.8 (d, ¹*J*_{PC} = 126.0 Hz, PC_{Ar}), 129.6 (C_{Ar}H), 129.3 (C_{Ar}H), 128.8 (d, ²*J*_{PC} = 13.5 Hz, C_{Ar}Hortho), 128.6 (d, ²*J*_{PC} = 13.0 Hz, C_{Ar}Hortho), 127.5 (C_{Ar}OMeH), 120.8 (C_{Ar}OMeH), 111.2 (C_{Ar}OMeH), 95.6 (d, ³*J*_{PC} = 7.0 Hz, CHTs), 70.94 (NCCH₃), 55.0 (OCH₃), 21.7 (C_{Ar}CH₃), 21.6 (NCCH₃).

^{31}P NMR (CDCl_3 , 162 MHz): δ 20.3.

HRMS (ESI): calcd. for $\text{C}_{30}\text{H}_{30}\text{N}_2\text{O}_4\text{P}^{32}\text{S}^+$ $[\text{M}+\text{H}]^+$ 545.16584, found 545.16553.

$[\alpha]_{\text{D}}^{25}$: -69 ($c = 0.35$ in CHCl_3).

((4*S*,5*S*)-5-(4-Fluorophenyl)-5-methyl-4-tosyl-4,5-dihydro-1*H*-imidazol-1-yl)diphenylphosphine oxide **170e**



Prepared according to General Procedure V, using *N*-DPP ketimine **5e** (84.3 mg, 0.25 mmol). Purification of the crude mixture (conversion 100%, dr > 95:5) by FCC (AcOEt:PE 1:1 to 6:4) afforded product **170e** as a white solid in 97% yield (129 mg).

The ee was determined by HPLC: two consecutive Chiralpak IB columns, hexane/*iso*-propanol 80:20, 0.8 mL/min, λ 220 nm, t (major) = 41.6 min, t (minor) = 48.4 min (88% ee).

RF: 0.45 (AcOEt:PE 6:4).

M.p.: 87–90 °C.

IR: 3060 (w), 2235 (w), 1597 (m), 1509 (m), 1438 (m), 1226 (s), 910 (m), 846 (m), 726 (s), 699 (s), 660 (s) cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ 7.83–7.77 (m, 4H), 7.66–7.47 (m, 8H), 7.36–7.30 (m, 4H), 7.17 (br s, 1H, $\text{N}=\text{CH}$), 6.98 (t, $J = 9.0$ Hz, 2H, $\text{C}_{\text{Ar}}\text{FH}$), 5.02 (d, $J = 1.5$ Hz, 1H, CHTs), 2.40 (s, 3H, $\text{C}_{\text{Ar}}\text{CH}_3$), 2.30 (s, 3H, NCCH_3).

^{13}C NMR (CDCl_3 , 126 MHz): δ 162.3 (d, $^1J_{\text{CF}} = 248.0$ Hz, $\text{C}_{\text{Ar}}\text{F}$), 156.3 (d, $^2J_{\text{PC}} = 7.5$ Hz, $\text{N}=\text{CH}$), 145.2 (C_{Ar}), 141.1 (d, $J = 3.0$ Hz, $\text{C}_{\text{Ar}}\text{F}$), 135.8 ($\text{C}_{\text{Ar}}\text{CH}_3$), 133.2 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\text{C}_{\text{Ar}}\text{PH}_{\text{para}}$), 133.1 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\text{C}_{\text{Ar}}\text{PH}_{\text{para}}$), 132.5 (d, $^3J_{\text{PC}} = 10.5$ Hz, $\text{C}_{\text{Ar}}\text{PH}_{\text{meta}}$), 131.9 (d, $^3J_{\text{PC}} = 10.5$ Hz, $\text{C}_{\text{Ar}}\text{PH}_{\text{meta}}$), 130.9 (d, $^1J_{\text{PC}} = 124.5$ Hz, PC_{Ar}), 129.9 (d, $^1J_{\text{PC}} = 128.0$ Hz, PC_{Ar}), 129.6 ($\text{C}_{\text{Ar}}\text{H}$), 129.5 ($\text{C}_{\text{Ar}}\text{H}$), 129.1 (d, $^2J_{\text{PC}} = 13.5$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$), 128.9 (d, $^2J_{\text{PC}} = 13.5$ Hz,

$\underline{C}_{ArH_{ortho}}$), 126.9 (d, $^3J_{CF} = 8.0$ Hz, $\underline{C}_{ArF}$ H), 115.6 (d, $^2J_{CF} = 21.5$ Hz, $\underline{C}_{ArF}$ H), 97.7 (d, $^3J_{PC} = 7.0$ Hz, $\underline{CHTs}$), 71.3 (d, $^2J_{PC} = 2.5$ Hz, $\underline{NCCH_3}$), 21.8 ($\underline{C}_{ArCH_3}$), 20.4 ($\underline{NCCH_3}$).

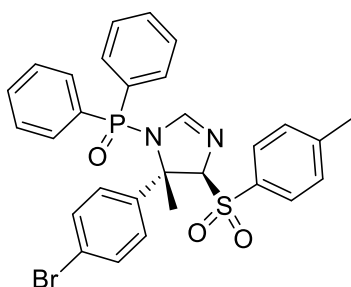
^{31}P NMR ($CDCl_3$, 162 MHz): δ 22.5.

^{19}F NMR ($CDCl_3$, 376 MHz): δ -114.3.

HRMS (ESI): calcd. for $C_{29}H_{27}N_2O_3FP^{32}S^+$ $[M+H]^+$ 533.14585, found 533.14600.

$[\alpha]_D^{25}$: -128 ($c = 1.00$ in $CHCl_3$).

((4*S*,5*S*)-5-(4-Bromophenyl)-5-methyl-4-tosyl-4,5-dihydro-1*H*-imidazol-1-yl)diphenylphosphine oxide **170f**



Prepared according to General Procedure **V**, using *N*-DPP ketimine **15f** (99.6 mg, 0.25 mmol). Purification of the crude mixture (conversion 100%, dr > 95:5) by FCC (AcOEt:PE 1:1) afforded product **170f** as a white solid in 97% yield (144 mg).

The ee was determined by HPLC: Chiralpak IB column, hexane/*iso*-propanol 80:20, 1 mL/min, λ 220 nm, t (major) = 15.1 min, t (minor) = 20.7 min (93% ee).

RF: 0.30 (AcOEt:PE 1:1).

M.p.: 93–95 °C.

IR: 3058 (w), 2924 (w), 1598 (s), 1438 (m), 1318 (m), 1229 (s), 1147 (s), 753 (m), 729 (m), 702 (s), 659 (s) cm^{-1} .

^1H NMR ($CDCl_3$, 400 MHz): δ 7.77–7.70 (m, 4H), 7.60–7.36 (m, 8H), 7.34 (d, $J = 9.0$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 7.16 (d, $J = 9.0$ Hz, 2H), 7.07 (br s, 1H, $N=CH$), 4.93 (dd, $J = 1.5, 1.0$ Hz, 1H, $\underline{CHTs}$), 2.31 (s, 3H, $\underline{C}_{ArCH_3}$), 2.22 (s, 3H, $\underline{NCCH_3}$).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 156.2 (d, $^2J_{PC} = 7.5$ Hz, $N=CH$), 145.2 ($\underline{C}_{Ar}$), 144.3 ($\underline{C}_{Ar}$), 135.7 ($\underline{C}_{ArCH_3}$), 133.2 (d, $^4J_{PC} = 3.0$ Hz, $\underline{C}_{ArPH_{para}}$), 133.1 (d, $^4J_{PC} = 3.0$ Hz, $\underline{C}_{ArPH_{para}}$), 132.4 (d, $^3J_{PC} = 11.0$ Hz, $\underline{C}_{ArPH_{meta}}$), 131.9 ($\underline{C}_{ArH}$), 131.9 (d, $^3J_{PC} = 11.0$ Hz, $\underline{C}_{ArPH_{meta}}$), 130.7 (d, $^1J_{PC} = 124.0$

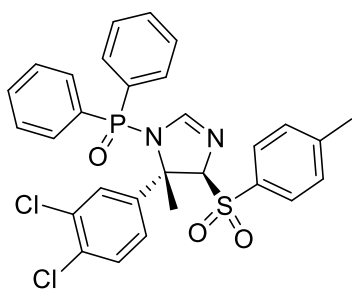
Hz, PC_{Ar}), 129.9 (d, $^1J_{\text{PC}} = 128.0$ Hz, PC_{Ar}), 129.6 (C_{ArH}), 129.4 (C_{ArH}), 129.1 (d, $^2J_{\text{PC}} = 13.0$ Hz, $\text{C}_{\text{ArH}_{\text{ortho}}}$), 128.9 (d, $^2J_{\text{PC}} = 13.5$ Hz, $\text{C}_{\text{ArH}_{\text{ortho}}}$), 126.8 (C_{ArH}), 122.2 (C_{ArBr}), 97.4 (d, $^3J_{\text{PC}} = 7.0$ Hz, CHTs), 71.3 (d, $^2J_{\text{PC}} = 2.5$ Hz, NCCH_3), 21.8 (C_{ArCH_3}), 20.2 (NCCH_3).

^{31}P NMR (CDCl_3 , 162 MHz): δ 22.6.

HRMS (ESI): calcd. for $\text{C}_{29}\text{H}_{27}\text{N}_2\text{O}_3^{79}\text{BrP}^{32}\text{S}^+ [\text{M}+\text{H}]^+$ 593.06579, found 593.06421.

$[\alpha]_{\text{D}}^{25}$: -105 ($c = 1.00$ in CHCl_3).

((4*S*,5*S*)-5-(3,4-Dichlorophenyl)-5-methyl-4-tosyl-4,5-dihydro-1*H*-imidazol-1-yl)diphenylphosphine oxide **170g**



Prepared according to General Procedure V, using *N*-DPP ketimine **5g** (97.1 mg, 0.25 mmol). Purification of the crude mixture (conversion 100%, dr > 95:5) by FCC ($\text{AcOEt}:\text{PE}$ 1:1) afforded product **170g** as a white solid in 96% yield (140 mg).

The ee was determined by HPLC: Chiralpak IB column, hexane/*iso*-propanol 80:20, 1 mL/min, λ 220 nm, t (major) = 14.5 min, t (minor) = 16.9 min (86% ee).

RF: 0.30 ($\text{AcOEt}:\text{PE}$ 1:1).

M.p.: 98–106 °C.

IR: 3057 (w), 2924 (w), 2855 (w), 2232 (w), 1597 (s), 1438 (m), 1318 (m), 1229 (s), 1146 (s), 1124 (s), 728 (s), 700 (s), 678 (s), 660 (s) cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): δ 7.86–7.78 (m, 4H), 7.68–7.48 (m, 8H), 7.40 (d, $J = 8.5$ Hz, 1H, C_{ArClH}), 7.38 (d, $J = 2.5$ Hz, 1H, C_{ArClH}), 7.32 (d, $J = 8.0$ Hz, 2H), 7.24 (dd, $J = 8.5, 2.5$ Hz, 1H, C_{ArClH}), 7.13 (br s, 1H, N=CH), 4.97 (d, $J = 1.5$ Hz, 1H, CHTs), 2.42 (s, 3H, C_{ArCH_3}), 2.32 (s, 3H, NCCH_3).

^{13}C NMR (CDCl_3 , 126 MHz): δ 156.2 (d, $^2J_{\text{PC}} = 7.0$ Hz, N=CH), 145.4 (C_{Ar}), 145.3 (C_{Ar}), 135.6 (C_{ArCH_3}), 133.4 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\text{C}_{\text{ArPH}_{\text{para}}}$), 133.0 (C_{ArCl}), 132.4 (d, $^3J_{\text{PC}} = 11.0$ Hz,

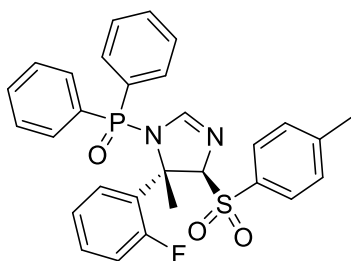
$\underline{\text{C}}_{\text{Ar}}\text{P}\underline{\text{H}}_{\text{meta}}$), 132.3 ($\underline{\text{C}}_{\text{Ar}}\text{Cl}$), 131.8 (d, $^3J_{\text{PC}} = 11.0$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{P}\underline{\text{H}}_{\text{meta}}$), 130.7 (d, $^1J_{\text{PC}} = 124.0$ Hz, $\text{P}\underline{\text{C}}_{\text{Ar}}$), 130.6 (d, $^1J_{\text{PC}} = 124.0$ Hz, $\text{P}\underline{\text{C}}_{\text{Ar}}$), 130.3 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 129.6 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 129.5 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 129.2 (d, $^2J_{\text{PC}} = 13.5$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{H}_{\text{ortho}}$), 129.1 (d, $^2J_{\text{PC}} = 13.5$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{H}_{\text{ortho}}$), 127.5 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 124.5 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 97.2 (d, $^3J_{\text{PC}} = 7.0$ Hz, $\underline{\text{C}}_{\text{HTs}}$), 70.9 (d, $^2J_{\text{PC}} = 3.0$ Hz, $\text{N}\underline{\text{C}}\text{CH}_3$), 21.8 ($\text{C}_{\text{Ar}}\underline{\text{C}}\text{H}_3$), 20.0 ($\text{N}\underline{\text{C}}\underline{\text{C}}\text{H}_3$).

^{31}P NMR (CDCl_3 , 162 MHz): δ 22.9.

HRMS (ESI): calcd. for $\text{C}_{29}\text{H}_{26}\text{N}_2\text{O}_3^{35}\text{Cl}_2\text{P}^{32}\text{S}^+ [\text{M}+\text{H}]^+ 583.07733$, found 583.07680.

$[\alpha]_{\text{D}}^{25}$: -112 ($c = 1.00$ in CHCl_3).

((4*S*,5*S*)-5-(2-Fluorophenyl)-5-methyl-4-tosyl-4,5-dihydro-1*H*-imidazol-1-yl)diphenylphosphine oxide 170h



Prepared according to General Procedure V, using *N*-DPP ketimine **5h** (84.3 mg, 0.25 mmol). Purification of the crude mixture (conversion 100%, dr > 95:5) by FCC (AcOEt:PE 1:1) afforded product **170h** as a white solid in 86% yield (114 mg).

The ee was determined by HPLC: Chiralpak AS column, hexane/*iso*-propanol 70:30, 0.5 mL/min, λ 220 nm, t (major) = 29.8 min, t (minor) = 43.2 min (96% ee).

RF: 0.37 (AcOEt:PE 7:3).

M.p.: 77–79 °C.

IR: 3061 (w), 2923 (w), 2853 (w), 2234 (w), 1560 (m), 1233 (s), 1146 (s), 1121 (s), 910 (m), 726 (s), 700 (s), 664 (s) cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ 7.82 (dd, $J = 13.0, 8.0$ Hz, 2H), 7.73 (d, $J = 8.0$ Hz, 2H), 7.50–7.33 (m, 7H), 7.30–7.11 (m, 5H), 7.03 (m, 2H, $\text{C}_{\text{Ar}}\underline{\text{H}}$ and $\text{N}=\underline{\text{C}}\underline{\text{H}}$), 6.87 (dd, $J = 12.5, 8.0$ Hz, 1H), 5.14 (br s, 1H, $\underline{\text{C}}\underline{\text{HTs}}$), 2.31 (s, 3H, $\underline{\text{C}}\underline{\text{H}}_3$), 2.30 (s, 3H, $\underline{\text{C}}\underline{\text{H}}_3$).

^{13}C NMR (CDCl_3 , 126 MHz): δ 160.2 (d, $^1J_{\text{CF}} = 248.0$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{F}$), 155.0 (d, $^2J_{\text{PC}} = 7.0$ Hz, $\text{N}=\underline{\text{C}}\underline{\text{H}}$), 145.1 ($\underline{\text{C}}_{\text{Ar}}$), 136.2 ($\underline{\text{C}}_{\text{Ar}}\text{CH}_3$), 133.2 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{P}\underline{\text{H}}_{\text{para}}$), 132.9 (d, $^4J_{\text{PC}} = 3.0$

Hz, $\underline{\text{C}}_{\text{ArP}}\text{H}_{\text{para}}$), 132.4 (d, $^3J_{\text{PC}} = 10.5$ Hz, $\underline{\text{C}}_{\text{ArP}}\text{H}_{\text{meta}}$), 131.9 (d, $^3J_{\text{PC}} = 10.5$ Hz, $\underline{\text{C}}_{\text{ArP}}\text{H}_{\text{meta}}$), 131.2 (d, $^2J_{\text{CF}} = 9.1$ Hz, $\underline{\text{C}}_{\text{ArF}}$), 130.4 (d, $^1J_{\text{PC}} = 128.0$ Hz, $\text{P}\underline{\text{C}}_{\text{Ar}}$), 130.4m(d, $J_{\text{CF}} = 9.5$ Hz, $\underline{\text{C}}_{\text{ArF}}\text{H}$), 129.6 ($\underline{\text{C}}_{\text{ArH}}$), 129.5 ($\underline{\text{C}}_{\text{ArH}}$), 129.4 (d, $^1J_{\text{PC}} = 124.5$ Hz, $\text{P}\underline{\text{C}}_{\text{Ar}}$), 129.1 (d, $^2J_{\text{PC}} = 13.5$ Hz, $\underline{\text{C}}_{\text{ArH}}\text{ortho}$), 128.8 (d, $^2J_{\text{PC}} = 13.5$ Hz, $\underline{\text{C}}_{\text{ArH}}\text{ortho}$), 127.8 (d, $J_{\text{CF}} = 3.0$ Hz, $\underline{\text{C}}_{\text{ArF}}\text{H}$), 96.4 (d, $^3J_{\text{PC}} = 6.5$ Hz, $^4J_{\text{CF}} = 3.0$ Hz, $\underline{\text{C}}\text{HTs}$), 39.9 (d, $J = 2.0$ Hz, $\text{N}\underline{\text{C}}\text{CH}_3$), 21.8 ($\underline{\text{C}}\text{H}_3$), 21.0 ($\underline{\text{C}}\text{H}_3$).

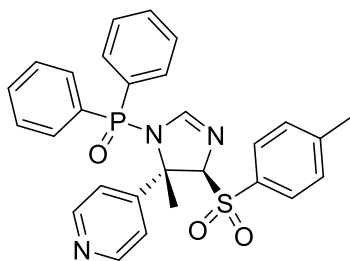
^{31}P NMR (CDCl_3 , 162 MHz): δ 21.0.

^{19}F NMR (CDCl_3 , 376 MHz): δ -110.4.

HRMS (ESI): calcd. for $\text{C}_{29}\text{H}_{27}\text{N}_2\text{O}_3\text{FP}^{32}\text{S}^+ [\text{M}+\text{H}]^+$ 533.14585, found 533.14417.

$[\alpha]_{\text{D}}^{25}$: -81 ($c = 0.55$ in CHCl_3).

((4*S*,5*S*)-5-Methyl-5-(pyridin-4-yl)-4-tosyl-4,5-dihydro-1*H*-imidazol-1-yl)diphenylphosphine oxide **170i**



Prepared according to General Procedure **V**, using *N*-DPP ketimine **5i** (80.1 mg, 0.25 mmol). Purification of the crude mixture (conversion 100%, dr > 95:5) by FCC ($\text{AcOEt}:\text{MeOH}$ 100:0 to 95:5) afforded product **170i** as an off-white solid in 99%

yield (128 mg).

The ee was determined by HPLC: Chiralpak AD-H column, hexane/*iso*-propanol 70:30, 1 mL/min, λ 220 nm, t (minor) = 33.1 min, t (major) = 37.8 min (94% ee).

RF: 0.32 ($\text{AcOEt}:\text{MeOH}$ 9:1).

M.p.: 82–83 °C.

IR: 3059 (w), 2235 (w), 1594 (m), 1438 (w), 1318 (m), 1222 (s), 1147 (m), 1124 (m), 1106 (m), 910 (m), 725 (s), 699 (s), 654 (s) cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ 8.51 (d, $J = 5.5$ Hz, 2H, $\text{N}\underline{\text{C}}_{\text{Ar}}\underline{\text{H}}$), 7.80 (dd, $J = 13.0$, 7.5 Hz, 2H), 7.71 (d, $J = 8.0$ Hz, 2H, $\text{SO}_2\text{C}_{\text{Ar}}\underline{\text{C}}_{\text{Ar}}\underline{\text{H}}$), 7.62–7.40 (m, 8H), 7.25 (d, $J = 5.5$ Hz, 2H,

NC_{Ar}HC_{Ar}H), 7.22 (d, *J* = 8.0 Hz, 2H, SO₂C_{Ar}C_{Ar}HC_{Ar}H), 7.06 (s, 1H, N=CH), 4.86 (s, 1H, CHTs), 2.31 (s, 3H, C_{Ar}CH₃), 2.21 (s, 3H, NCCH₃).

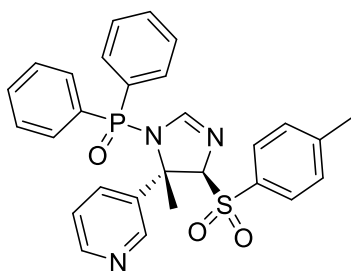
¹³C NMR (CDCl₃, 100 MHz): δ 156.2 (d, ²*J*_{PC} = 7.0 Hz, N=CH), 153.8 (NC_{Ar}), 150.4 (NC_{Ar}H) 145.3 (C_{Ar}), 135.4 (C_{Ar}CH₃), 133.4 (d, ⁴*J*_{PC} = 3.0 Hz, C_{Ar}P_Hpara), 133.3 (d, ⁴*J*_{PC} = 3.0 Hz, C_{Ar}P_Hpara), 132.3 (d, ³*J*_{PC} = 11.0 Hz, C_{Ar}P_Hmeta), 131.8 (d, ³*J*_{PC} = 11.0 Hz, C_{Ar}P_Hmeta), 130.6 (d, ¹*J*_{PC} = 123.5 Hz, PC_{Ar}), 129.6 (d, ¹*J*_{PC} = 128.0 Hz, PC_{Ar}), 129.5 (C_{Ar}H), 129.4 (C_{Ar}H), 129.2 (d, ²*J*_{PC} = 13.5 Hz, C_{Ar}Hortho), 128.9 (d, ²*J*_{PC} = 13.5 Hz, C_{Ar}Hortho), 119.7 (NC_{Ar}HC_{Ar}H), 96.6 (d, ³*J*_{PC} = 6.5 Hz, CHTs), 71.0 (d, ²*J*_{PC} = 2.5 Hz, NCCH₃), 21.7 (C_{Ar}CH₃), 19.6 (NCCH₃).

³¹P NMR (CDCl₃, 162 MHz): δ 22.7.

HRMS (ESI): calcd. for C₂₈H₂₇N₃O₃P³²S⁺ [M+H]⁺ 516.15053, found 516.14990.

[α]_D²⁵: −126 (*c* = 1.00 in CHCl₃).

((4*S*,5*S*)-5-Methyl-5-(pyridin-3-yl)-4-tosyl-4,5-dihydro-1*H*-imidazol-1-yl)diphenylphosphine oxide **170j**



Prepared according to General Procedure **V**, using *N*-DPP ketimine **5j** (80.1 mg, 0.25 mmol). Purification of the crude mixture (conversion 100%, dr > 95:5) by FCC (AcOEt:MeOH 10:0 to 9:1) afforded product **170j** as a white solid in 96% yield (124 mg).

The ee was determined by HPLC: Chiralpak OD-H column, hexane/*iso*-propanol 60:40, 1 mL/min, λ 220 nm, *t* (major) = 10.1 min, *t* (minor) = 25.2 min (90% ee).

RF: 0.37 (AcOEt:MeOH 9:1).

M.p. 48–49 °C.

IR: 3057 (w), 1597 (m), 1438 (m), 1318 (m), 1228 (s), 1147 (s), 1125 (s), 753 (m), 729 (m), 701 (s), 659 (m) cm^{−1}.

^1H NMR (CDCl_3 , 400 MHz): δ 8.66 (d, $J = 2.5$ Hz, 1H, $\text{NC}_{\text{Ar}}\underline{\text{H}}\text{C}_{\text{Ar}}$), 8.54 (d, $J = 5.0$ Hz, 1H, $\text{NC}_{\text{Ar}}\underline{\text{H}}\text{C}_{\text{Ar}}\text{H}$), 7.88 (dd, $J = 13.0, 7.5$ Hz, 2H), 7.80 (d, $J = 8.0$ Hz, 2H, $\text{SO}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\underline{\text{H}}$), 7.75 (d, $J = 8.0$ Hz, 1H, $\text{NC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{HC}_{\text{Ar}}\underline{\text{H}}$), 7.60–7.55 (m, 6H), 7.51–7.46 (m, 2H), 7.32 (d, $J = 8.0$ Hz, 2H, $\text{SO}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\underline{\text{H}}$), 7.27–7.25 (m, 1H, $\text{NC}_{\text{Ar}}\text{HC}_{\text{Ar}}\underline{\text{H}}\text{C}_{\text{Ar}}\text{H}$), 7.13 (s, 1H, $\text{N}=\underline{\text{C}}\text{H}$), 5.00 (s, 1H, $\underline{\text{C}}\text{HTs}$), 2.41 (s, 3H, $\text{C}_{\text{Ar}}\underline{\text{C}}\text{H}_3$), 2.35 (s, 3H, $\text{NC}\underline{\text{C}}\text{H}_3$).

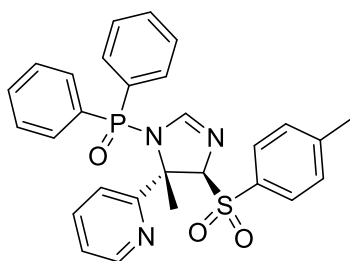
^{13}C NMR (CDCl_3 , 126 MHz): δ 156.4 (d, $^2J_{\text{PC}} = 7.0$ Hz, $\text{N}=\underline{\text{C}}\text{H}$), 149.3 ($\text{NC}_{\text{Ar}}\text{HC}_{\text{Ar}}$), 147.1 ($\text{NC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 145.4 ($\underline{\text{C}}_{\text{Ar}}$), 140.9 ($\text{NC}_{\text{Ar}}\text{HC}_{\text{Ar}}$), 135.7 ($\underline{\text{C}}_{\text{Ar}}\text{CH}_3$), 133.4 (app t, $^4J_{\text{PC}} = 3.0$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{P}_{\text{H}}\text{para}$), 132.7 ($\text{NC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 132.5 (d, $^3J_{\text{PC}} = 11.0$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{P}_{\text{H}}\text{meta}$), 132.0 (d, $^3J_{\text{PC}} = 11.0$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{P}_{\text{H}}\text{meta}$), 130.5 (d, $^1J_{\text{PC}} = 128.5$ Hz, PC_{Ar}), 130.1 (d, $^1J_{\text{PC}} = 123.5$ Hz, PC_{Ar}), 129.7 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 129.6 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 129.3 (d, $^2J_{\text{PC}} = 13.5$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{H}_{\text{ortho}}$), 129.1 (d, $^2J_{\text{PC}} = 13.5$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{H}_{\text{ortho}}$), 123.5 ($\text{NC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 97.2 (d, $^3J_{\text{PC}} = 6.5$ Hz, $\underline{\text{C}}\text{HTs}$), 70.5 (d, $^2J_{\text{PC}} = 2.5$ Hz, $\text{NC}\underline{\text{C}}\text{H}_3$), 21.8 ($\text{C}_{\text{Ar}}\underline{\text{C}}\text{H}_3$), 20.0 ($\text{NC}\underline{\text{C}}\text{H}_3$).

^{31}P NMR (CDCl_3 , 162 MHz): δ 22.7.

HRMS (ESI): calcd. for $\text{C}_{28}\text{H}_{27}\text{N}_3\text{O}_3\text{P}^{32}\text{S}^+ [\text{M}+\text{H}]^+$ 516.15053, found 516.15009.

$[\alpha]_{\text{D}}^{25}$: -89 ($c = 1.00$ in CHCl_3).

((4*S*,5*S*)-5-Methyl-5-(pyridin-2-yl)-4-tosyl-4,5-dihydro-1*H*-imidazol-1-yl)diphenylphosphine oxide **170k**



Prepared according to General Procedure **V**, using *N*-DPP ketimine **5k** (80.1 mg, 0.25 mmol). Purification of the crude mixture (conversion 100%, dr 90:10) by FCC (AcOEt:pentane 7:3) afforded product **170k** as an off-white solid in 86% yield

(111 mg).

The ee was determined by HPLC using Chiralpak OD-H column, hexane/*iso*-propanol 85:15, 1 mL/min, λ 220 nm, t (minor) = 33.5 min, t (major) = 38.9 min (95% ee).

RF: 0.34 (AcOEt).

M.p.: 89–91 °C.

IR: 3057 (w), 2992 (w), 1597 (m), 1437 (m), 1317 (m), 1226 (s), 1146 (s), 1124 (m), 751 (s), 729 (m), 701 (s), 659 (s) cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ 8.48 (d, $J = 4.5$ Hz, 1H, $\text{NC}_{\text{Ar}}\underline{\text{H}}$), 7.99–7.84 (m, 2H), 7.82 (d, $J = 8.0$ Hz, 2H, $\text{SO}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\underline{\text{H}}$), 7.70–7.50 (m, 7H), 7.49 (dd, $J = 7.5, 1.5$ Hz, 1H, $\text{NC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{HC}_{\text{Ar}}\underline{\text{H}}$), 7.38 (td, $J = 7.5, 3.5$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H, $\text{SO}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\underline{\text{H}}$), 7.13 (ddd, $J = 7.0, 5.0, 1.5$ Hz, 1H, $\text{NC}_{\text{Ar}}\text{HC}_{\text{Ar}}\underline{\text{H}}$), 7.00 (br s, 1H, $\text{N}=\underline{\text{CH}}$), 5.67 (d, $J = 2.0$ Hz, 1H, CHTs), 2.41 (s, 3H, $\text{C}_{\text{Ar}}\underline{\text{CH}_3}$), 2.38 (s, 3H, $\text{NC}\underline{\text{CH}_3}$).

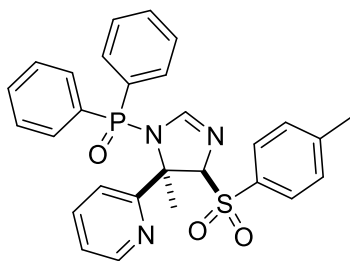
^{13}C NMR (CDCl_3 , 126 MHz): δ 161.7 (NC_{Ar}), 156.5 (d, $^2J_{\text{PC}} = 7.0$ Hz, $\text{N}=\underline{\text{CH}}$), 149.3 ($\text{NC}_{\text{Ar}}\underline{\text{H}}$), 144.9 ($\underline{\text{C}}_{\text{Ar}}$), 136.9 ($\text{NC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{HC}_{\text{Ar}}\underline{\text{H}}$), 136.3 ($\underline{\text{C}}_{\text{Ar}}\text{CH}_3$), 133.2 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{P}_{\text{H}}\text{para}$), 132.8 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{P}_{\text{H}}\text{meta}$), 132.5 (d, $^3J_{\text{PC}} = 11.0$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{P}_{\text{H}}\text{meta}$), 132.1 (d, $^3J_{\text{PC}} = 11.0$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{P}_{\text{H}}\text{meta}$), 130.7 (d, $^1J_{\text{PC}} = 125.0$ Hz, PC_{Ar}), 130.5 (d, $^1J_{\text{PC}} = 128.0$ Hz, PC_{Ar}), 129.6 ($\underline{\text{C}}_{\text{Ar}}\underline{\text{H}}$), 129.5 ($\underline{\text{C}}_{\text{Ar}}\underline{\text{H}}$), 129.1 (d, $^2J_{\text{PC}} = 13.5$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{H}_{\text{ortho}}$), 128.8 (d, $^2J_{\text{PC}} = 13.5$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{H}_{\text{ortho}}$), 123.0 ($\text{NC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{HC}_{\text{Ar}}\underline{\text{H}}$), 120.5 ($\text{NC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{HC}_{\text{Ar}}\underline{\text{H}}$), 95.6 (d, $^3J_{\text{PC}} = 7.0$ Hz, $\underline{\text{CHTs}}$), 72.8 (d, $^2J_{\text{PC}} = 3.0$ Hz, $\text{NC}\underline{\text{CH}_3}$), 21.8 ($\text{C}_{\text{Ar}}\underline{\text{CH}_3}$), 20.0 ($\text{NC}\underline{\text{CH}_3}$).

^{31}P NMR (CDCl_3 , 162 MHz): δ 22.2.

HRMS (ESI): calcd. for $\text{C}_{28}\text{H}_{27}\text{N}_3\text{O}_3\text{P}^{32}\text{S}^+ [\text{M}+\text{H}]^+$ 516.15053, found 516.15051.

$[\alpha]_{\text{D}}^{25}$: -166 ($c = 1.00$ in CHCl_3).

cis-5-Methyl-5-(pyridin-2-yl)-4-tosyl-4,5-dihydro-1H-imidazol-1-yl)diphenylphosphine oxide *cis*-170k



Prepared according to General Procedure **IV**, using *N*-DPP ketimine **5k** (80.1 mg, 0.25 mmol). Purification of the crude mixture (conversion 100%, dr *trans*:*cis* 46:54) by FCC (AcOEt:pentane 4:6 to 10:0) afforded racemic ***cis*-170k** as a

white solid in 40% yield (52 mg), as well as racemic ***trans*-170k** as a white solid in 33% yield (42 mg).

RF: 0.20 (AcOEt).

M.p.: 90–92 °C.

IR: 3057 (w), 2236 (w), 1590 (m), 1437 (m), 1320 (m), 1225 (m), 1106 (s), 913 (m), 728 (s), 701 (s), 666 (m) cm⁻¹.

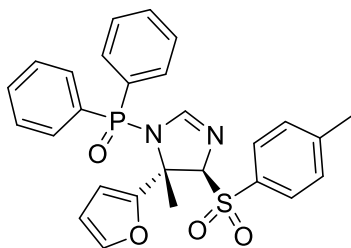
¹H NMR (CDCl₃, 400 MHz): δ 8.52 (d, *J* = 4.5 Hz, 1H, NC_{Ar}H), 7.99–7.84 (m, 2H), 7.67 (d, *J* = 8.5 Hz, 2H, SO₂C_{Ar}C_{Ar}H), 7.60–7.43 (m, 8H), 7.36 (td, *J* = 8.0, 3.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H, SO₂C_{Ar}C_{Ar}HC_{Ar}H), 7.23 (dd, *J* = 2.0, 1.0 Hz, 1H, 1H, N=CH), 7.20 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H, NC_{Ar}HC_{Ar}H), 5.15 (d, *J* = 2.0 Hz, 1H, CHTs), 2.39 (s, 3H, C_{Ar}CH₃), 2.13 (s, 3H, NCCH₃).

¹³C NMR (CDCl₃, 126 MHz): δ 155.9 (NC_{Ar}), 155.8 (d, ²*J*_{PC} = 7.0 Hz, N=CH), 148.2 (NC_{Ar}H), 144.8 (C_{Ar}), 136.4 (NC_{Ar}HC_{Ar}HC_{Ar}H), 136.3 (C_{Ar}CH₃), 133.0 (d, ⁴*J*_{PC} = 3.0 Hz, C_{Ar}PH_{para}), 132.8 (d, ⁴*J*_{PC} = 3.0 Hz, C_{Ar}PH_{para}), 132.5 (d, ³*J*_{PC} = 11.0 Hz, C_{Ar}PH_{meta}), 132.2 (d, ³*J*_{PC} = 10.5 Hz, C_{Ar}PH_{meta}), 130.8 (d, ¹*J*_{PC} = 126.0 Hz, PC_{Ar}), 130.7 (d, ¹*J*_{PC} = 131.0 Hz, PC_{Ar}), 129.6 (C_{Ar}H), 129.1 (C_{Ar}H), 129.0 (d, ²*J*_{PC} = 13.5 Hz, C_{Ar}H_{ortho}), 128.6 (d, ²*J*_{PC} = 13.5 Hz, C_{Ar}H_{ortho}), 123.4 (NC_{Ar}HC_{Ar}HC_{Ar}H), 123.2 (NC_{Ar}HC_{Ar}HC_{Ar}HC_{Ar}H), 97.9 (d, ³*J*_{PC} = 7.5 Hz, CHTs), 72.8 (d, ²*J*_{PC} = 3.0 Hz, NCCH₃), 28.0 (NCCH₃), 21.8 (C_{Ar}CH₃).

³¹P NMR (CDCl₃, 162 MHz): δ 21.4.

HRMS (ESI): calcd. for $C_{28}H_{27}N_3O_3P^{32}S^+$ $[M+H]^+$ 516.15053, found 516.15057.

((4*S*,5*S*)-5-(Furan-2-yl)-5-methyl-4-tosyl-4,5-dihydro-1*H*-imidazol-1-yl)diphenylphosphine oxide **170I**



Prepared according to General Procedure V, using *N*-DPP ketimine **5I** (77.3 mg, 0.25 mmol). Purification of the crude mixture (conversion 100%, dr > 95:5) by FCC (AcOEt:pentane 1:1 to 7:3) afforded product **170I** as an off-white solid in 82%

yield (104 mg).

The ee was determined by HPLC: Chiralpak OD-H column, hexane/*iso*-propanol 80:20, 1 mL/min, λ 220 nm, *t* (minor) = 19.3 min, *t* (major) = 22.7 min (98% ee).

RF: 0.38 (pentane:AcOEt 2:8).

M.p.: 73–75 °C.

IR: 3059 (w), 2991 (w), 1600 (s), 1439 (m), 1319 (m), 1223 (s), 1149 (s), 1124 (s), 751 (s), 729 (s), 701 (s), 660 (s) cm^{-1} .

^1H NMR ($CDCl_3$, 500 MHz): δ 7.82 (d, J = 8.5 Hz, 2H, $SO_2C_{Ar}C_{Ar}H$), 7.81–7.72 (m, 2H), 7.61 (td, J = 7.5, 1.5 Hz, 1H), 7.58–7.48 (m, 5H), 7.40 (dd, J = 8.0, 2.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H, $SO_2C_{Ar}C_{Ar}HC_{Ar}H$), 7.13 (dd, J = 2.0, 1.0 Hz, 1H, $OC_{Ar}HC_{Ar}HC_{Ar}H$), 7.00 (t, J = 1.5 Hz, 1H, $N=CH$), 6.25 (dd, J = 3.5, 1.0 Hz, 1H, $OC_{Ar}HC_{Ar}HC_{Ar}H$), 6.16 (dd, J = 3.5, 2.0 Hz, 1H, $OC_{Ar}HC_{Ar}HC_{Ar}H$), 5.32 (d, J = 1.5 Hz, 1H, $CHTs$), 2.42 (s, 3H, $C_{Ar}CH_3$), 2.35 (s, 3H, $NCCH_3$).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.6 (d, $^2J_{PC}$ = 7.5 Hz, $N=CH$), 154.5 (OC_{Ar}), 145.1 (C_{Ar}), 142.4 ($OC_{Ar}H$), 136.0 ($C_{Ar}CH_3$), 133.2 (d, $^4J_{PC}$ = 3.5 Hz, $C_{Ar}P_{H_{para}}$), 132.8 (d, $^4J_{PC}$ = 3.0 Hz, $C_{Ar}P_{H_{para}}$), 132.4 (d, $^3J_{PC}$ = 10.5 Hz, $C_{Ar}P_{H_{meta}}$), 132.0 (d, $^3J_{PC}$ = 10.5 Hz, $C_{Ar}P_{H_{meta}}$), 130.6 (d, $^1J_{PC}$ = 126.0 Hz, PC_{Ar}), 130.0 (d, $^1J_{PC}$ = 126.5 Hz, PC_{Ar}), 129.6 ($C_{Ar}H$), 129.6 ($C_{Ar}H$), 129.1 (d, $^2J_{PC}$ = 13.5 Hz, $C_{Ar}H_{ortho}$), 128.7 (d, $^2J_{PC}$ = 13.5 Hz, $C_{Ar}H_{ortho}$), 110.9 ($OC_{Ar}HC_{Ar}HC_{Ar}H$), 108.9

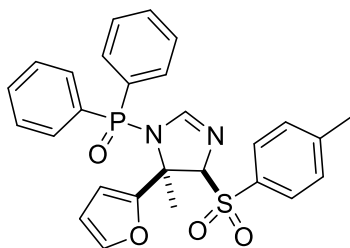
(OC_{Ar}HC_{Ar}HC_{Ar}H), 93.8 (d, $^3J_{PC}$ = 7.0 Hz, CHTs), 67.0 (d, $^2J_{PC}$ = 3.0 Hz, NCCH₃), 21.8 (C_{Ar}CH₃), 19.4 (NCCH₃).

^{31}P NMR (CDCl₃, 162 MHz): δ 21.5.

HRMS (ESI): calcd. for C₂₇H₂₆N₂O₄P³²S⁺ [M+H]⁺ 505.13454, found 505.13409.

$[\alpha]_{\text{D}}^{25}$: -179 (c = 1.00 in CHCl₃).

***cis*-5-(Furan-2-yl)-5-methyl-4-tosyl-4,5-dihydro-1H-imidazol-1-yl)diphenylphosphine oxide *cis*-170I**



Prepared according to General Procedure **IV**, using *N*-DPP ketimine **5I** (77.3 mg, 0.25 mmol). Purification of the crude mixture (conversion 80%, dr *trans*:*cis* 67:43) by FCC (AcOEt:pentane 4:6 to 10:0) afforded racemic ***cis*-170I** as an off-

white solid in 26% yield (33 mg), as well as racemic ***trans*-170I** as an off-white solid in 28% yield (35 mg).

RF: 0.14 (pentane:AcOEt 2:8).

M.p.: 118–120 °C.

IR: 3059 (w), 2924 (w), 2231 (w), 1598 (s), 1439 (m), 1326 (m), 1221 (s), 1149 (s), 1124 (s), 729 (s), 703 (s), 656 (m) cm⁻¹.

^1H NMR (CDCl₃, 500 MHz): δ 7.82 (ddd, J = 12.5, 8.5, 1.5 Hz, 2H, C_{Ar}P_H), 7.75 (d, J = 8.5 Hz, 2H, SO₂C_{Ar}C_{Ar}H), 7.62–7.47 (m, 6H), 7.36 (td, J = 7.5, 3.5 Hz, 2H), 7.30–7.27 (m, 3H), 7.17 (br s, 1H, N=CH), 6.24 (dd, J = 3.5, 2.0 Hz, 1H, OC_{Ar}HC_{Ar}HC_{Ar}H), 6.15 (d, J = 3.5 Hz, 1H, OC_{Ar}HC_{Ar}HC_{Ar}H), 5.01 (d, J = 2.0 Hz, 1H, CHTs), 2.40 (s, 3H, C_{Ar}CH₃), 2.01 (s, 3H, NCCH₃).

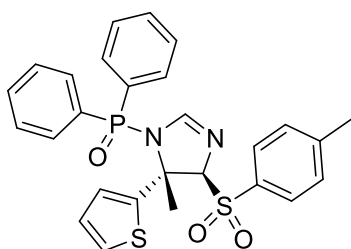
^{13}C NMR (CDCl₃, 126 MHz): δ 155.3 (d, $^2J_{PC}$ = 7.0 Hz, N=CH), 150.0 (OC_{Ar}), 144.9 (C_{Ar}), 142.1 (OC_{Ar}H), 136.0 (C_{Ar}CH₃), 133.2 (d, $^4J_{PC}$ = 3.0 Hz, C_{Ar}P_H_{para}), 132.8 (d, $^4J_{PC}$ = 3.0 Hz,

$\underline{C}_{Ar}P\underline{H}_{para}$), 132.3 (d, $^3J_{PC} = 10.5$ Hz, $\underline{C}_{Ar}P\underline{H}_{meta}$), 132.2 (d, $^3J_{PC} = 11.0$ Hz, $\underline{C}_{Ar}P\underline{H}_{meta}$), 130.7 (d, $^1J_{PC} = 127.0$ Hz, $P\underline{C}_{Ar}$), 129.6 ($\underline{C}_{Ar}H$), 129.3 ($\underline{C}_{Ar}H$), 129.1 (d, $^2J_{PC} = 13.0$ Hz, $\underline{C}_{Ar}H_{ortho}$), 128.5 (d, $^2J_{PC} = 14.0$ Hz, $\underline{C}_{Ar}H_{ortho}$), 111.2 ($OC_{Ar}H\underline{C}_{Ar}HC_{Ar}H$), 110.6 ($OC_{Ar}HC_{Ar}H\underline{C}_{Ar}H$), 93.4 (d, $^3J_{PC} = 7.0$ Hz, $\underline{C}HTs$), 66.5 (d, $^2J_{PC} = 3.0$ Hz, $N\underline{C}CH_3$), 27.3 ($N\underline{C}CH_3$), 21.8 ($C_{Ar}\underline{C}H_3$).

^{31}P NMR ($CDCl_3$, 162 MHz): δ 20.8.

HRMS (ESI): calcd. for $C_{27}H_{26}N_2O_4P^{32}S^+$ $[M+H]^+$ 505.13454, found 505.13437.

((4S,5S)-5-(Thiophen-2-yl)-5-methyl-4-tosyl-4,5-dihydro-1H-imidazol-1-yl)diphenylphosphine oxide 170m



Prepared according to General Procedure **V**, using *N*-DPP ketimine **5m** (81.3 mg, 0.25 mmol). Purification of the crude mixture (conversion 100%, dr > 95:5) by FCC (AcOEt:pentane 4:6) afforded product **170m** as an off-white solid in 98% yield

(127 mg).

The ee was determined by HPLC: Chiralpak OD-H column, hexane/*iso*-propanol 85:15, 1 mL/min, λ 230 nm, t (minor) = 26.6 min, t (major) = 32.1 min (96% ee).

RF: 0.48 (AcOEt).

M.p.: 73–75 °C.

IR: 3062 (w), 1597 (s), 1438 (m), 1317 (m), 1228 (s), 1147 (s), 1124 (s), 752 (m), 729 (m), 701 (s), 662 (s) cm^{-1} .

^1H NMR ($CDCl_3$, 500 MHz): δ 7.84 (ddd, $J = 13.0, 8.5, 1.5$ Hz, 2H, $C_{Ar}P\underline{H}$), 7.80 (d, $J = 8.5$ Hz, 2H, $SO_2C_{Ar}C_{Ar}\underline{H}$), 7.70–7.59 (m, 3H), 7.58–7.51 (m, 3H), 7.45 (td, $J = 7.5, 3.5$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H, $SO_2C_{Ar}C_{Ar}H\underline{C}_{Ar}H$), 7.19 (dd, $J = 5.0, 1.0$ Hz, 1H, $SC_{Ar}\underline{H}C_{Ar}HC_{Ar}H$), 7.10 (t, $J = 1.0$ Hz, 1H, $N=\underline{C}H$), 6.97 (dd, $J = 3.5, 1.0$ Hz, 1H, $SC_{Ar}HC_{Ar}H\underline{C}_{Ar}H$), 6.87 (dd, $J =$

5.0, 3.5 Hz, 1H, SC_{Ar}HC_{Ar}H_CArH), 5.16 (d, *J* = 1.5 Hz, 1H, CHTs), 2.42 (s, 3H, C_{Ar}CH₃), 2.38 (s, 3H, NCCH₃).

¹³C NMR (CDCl₃, 126 MHz): δ 156.2 (d, ²*J*_{PC} = 7.0 Hz, N=C_H), 149.9 (SC_{Ar}), 145.1 (C_{Ar}), 135.8 (C_{Ar}CH₃), 133.2 (d, ⁴*J*_{PC} = 3.5 Hz, C_{Ar}P_H_{para}), 133.1 (d, ⁴*J*_{PC} = 3.0 Hz, C_{Ar}P_H_{para}), 132.6 (d, ³*J*_{PC} = 11.0 Hz, C_{Ar}P_H_{meta}), 132.0 (d, ³*J*_{PC} = 11.0 Hz, C_{Ar}P_H_{meta}), 130.9 (d, ¹*J*_{PC} = 124.5 Hz, PC_{Ar}), 130.0 (d, ¹*J*_{PC} = 128.0 Hz, PC_{Ar}), 129.6 (C_{Ar}H), 129.6 (C_{Ar}H), 129.0 (d, ²*J*_{PC} = 13.5 Hz, C_{Ar}H_{ortho}), 128.9 (d, ²*J*_{PC} = 13.5 Hz, C_{Ar}H_{ortho}), 127.1 (C_{Ar}SH), 125.3 (C_{Ar}SH), 124.5 (C_{Ar}SH), 97.3 (d, ³*J*_{PC} = 7.0 Hz, CHTs), 69.5 (d, ²*J*_{PC} = 2.5 Hz, NCCH₃), 21.8 (C_{Ar}CH₃), 20.9 (NCCH₃).

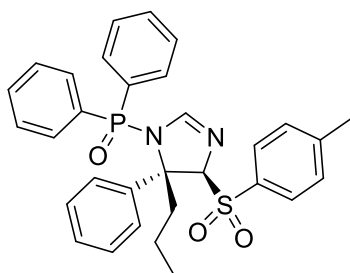
³¹P NMR (CDCl₃, 162 MHz): δ 22.4.

HRMS (ESI): calcd. for C₂₇H₂₆N₂O₃P³²S₂⁺ [M+H]⁺ 521.11170, found 521.11102.

[α]_D²⁵: −195 (*c* = 1.00 in CHCl₃).

((4*S*,5*S*)-5-Phenyl-5-propyl-4-tosyl-4,5-dihydro-1*H*-imidazol-1-yl)diphenylphosphine

oxide **170n**



Prepared according to General Procedure **V**, using *N*-DPP ketimine **5n** (86.9 mg, 0.25 mmol). Purification of the crude mixture (conversion 94%, dr *trans*:*cis* 95:5) by FCC (AcOEt:PE 4:6) afforded product **170n** as a white solid in 88% yield

(119 mg).

The ee was determined by HPLC: Chiralpak IB column, hexane/*iso*-propanol 70:30, 1 mL/min, λ 220 nm, *t* (major) = 8.1 min, *t* (minor) = 9.8 min (93% ee).

RF: 0.38 (AcOEt:PE 1:1).

M.p.: 84–85 °C.

IR: 3060 (w), 2964 (w), 2871 (w), 2235 (w), 1597 (m), 1439 (m), 1320 (m), 1221 (s), 1143 (s), 1074 (s), 910 (m), 726 (s), 697 (s), 658 (s) cm^{−1}.

^1H NMR (CDCl_3 , 400 MHz): δ 8.17–8.04 (m, 2H), 7.80 (d, $J = 8.5$ Hz, 2H, $\text{SO}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 7.75–7.54 (m, 8H), 7.51–7.45 (m, 2H), 7.35–7.30 (m, 4H), 7.23 (t, $J = 7.5$ Hz, 1H), 6.98 (br s, 1H, $\text{N}=\text{CH}$), 5.14 (s, 1H, CHTs), 3.05–2.82 (m, 2H, $\text{NCCH}_2\text{CH}_2\text{CH}_3$), 2.60–2.54 (m, 2H, $\text{NCCH}_2\text{CH}_2\text{CH}_3$), 2.40 (s, 3H, $\text{C}_{\text{Ar}}\text{CH}_3$), 0.43 (t, $J = 7.0$ Hz, 3H, $\text{NCCH}_2\text{CH}_2\text{CH}_3$).

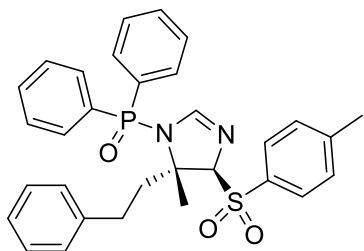
^{13}C NMR (CDCl_3 , 126 MHz): δ 157.6 (d, $^2J_{\text{PC}} = 8.0$ Hz, $\text{N}=\text{CH}$), 145.0 (C_{Ar}), 142.5 (C_{Ar}), 136.3 ($\text{C}_{\text{Ar}}\text{CH}_3$), 133.1 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 133.0 (d, $^3J_{\text{PC}} = 10.5$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 133.0 (d, $^3J_{\text{PC}} = 3.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 131.9 (d, $^3J_{\text{PC}} = 10.4$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 132.0 (d, $^1J_{\text{PC}} = 123.5$ Hz, PC_{Ar}), 130.9 (d, $^1J_{\text{PC}} = 117.5$ Hz, PC_{Ar}), 129.6 ($\text{C}_{\text{Ar}}\text{H}$), 129.5 ($\text{C}_{\text{Ar}}\text{H}$), 129.3 (d, $^2J_{\text{PC}} = 13.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$), 129.0 (d, $^2J_{\text{PC}} = 13.5$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$), 128.6 ($\text{C}_{\text{Ar}}\text{H}$), 127.8 ($\text{C}_{\text{Ar}}\text{H}$), 126.1 ($\text{C}_{\text{Ar}}\text{H}$), 97.3 (d, $^3J_{\text{PC}} = 7.0$ Hz, CHTs), 78.6 (d, $^2J_{\text{PC}} = 2.0$ Hz, NCCH_3), 34.1 ($\text{NCCH}_2\text{CH}_2\text{CH}_3$), 21.8 ($\text{C}_{\text{Ar}}\text{CH}_3$), 19.5 ($\text{NCCH}_2\text{CH}_2\text{CH}_3$), 13.9 ($\text{NCCH}_2\text{CH}_2\text{CH}_3$).

^{31}P NMR (CDCl_3 , 162 MHz): δ 22.0.

HRMS (ESI): calcd. for $\text{C}_{31}\text{H}_{32}\text{N}_2\text{O}_3\text{P}^{32}\text{S}^+ [\text{M}+\text{H}]^+ 543.18658$, found 543.18652.

$[\alpha]_{\text{D}}^{25}$: -167 ($c = 0.84$ in CHCl_3).

((4*S*,5*S*)-5-Methyl-5-phenethyl-4-tosyl-4,5-dihydro-1*H*-imidazol-1-yl)diphenylphosphine oxide **170p**



Prepared according to General Procedure **V**, using *N*-DPP ketimine **5p** (86.9 mg, 0.25 mmol). Purification of the crude mixture (conversion 94%, dr 95:5) by FCC ($\text{AcOEt}:\text{PE}$ 4:6 to 6:4) afforded product **170p** as a white solid in 95% yield (129 mg).

The ee was determined by HPLC: Chiralpak IA column, hexane/*iso*-propanol 70:30, 1 mL/min, λ 220 nm, t (minor) = 11.3 min, t (major) = 20.4 min (94% ee).

RF: 0.46 ($\text{AcOEt}:\text{PE}$ 1:1).

M.p.: 68–70 °C.

IR: 3060 (w), 2923 (w), 2234 (w), 1595 (s), 1438 (m), 1290 (m), 1231 (s), 1122 (s), 1107 (s), 911 (m), 728 (s), 700 (s), 666 (s) cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ 8.01 (ddd, $J = 13.0, 8.0, 1.5$ Hz, 2H, $\text{C}_{\text{Ar}}\text{P}\underline{\text{H}}$), 7.83 (d, $J = 8.0$ Hz, 2H, $\text{SO}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\underline{\text{H}}$), 7.72–7.53 (m, 6H), 7.50–7.43 (m, 2H), 7.35 (d, $J = 8.0$ Hz, 2H, $\text{SO}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\underline{\text{H}}$), 7.32–7.25 (m, 4H), 7.23–7.17 (m, 1H), 6.78 (d, $J = 1.5$ Hz, 1H, $\text{N}=\underline{\text{C}}\text{H}$), 4.89 (d, $J = 1.5$ Hz, 1H, $\text{C}\underline{\text{H}}\text{T}\text{s}$), 2.82–2.64 (m, 1H), 2.61–2.47 (m, 2H), 2.44 (s, 3H, $\text{C}_{\text{Ar}}\underline{\text{C}}\text{H}_3$), 2.34–2.15 (m, 1H), 1.91 (s, 3H, $\text{NC}\underline{\text{C}}\text{H}_3$).

^{13}C NMR (CDCl_3 , 126 MHz): δ 156.6 (d, $^2J_{\text{PC}} = 7.5$ Hz, $\text{N}=\underline{\text{C}}\text{H}$), 145.1 ($\underline{\text{C}}_{\text{Ar}}$), 141.0 ($\underline{\text{C}}_{\text{Ar}}$), 135.9 ($\underline{\text{C}}_{\text{Ar}}\text{CH}_3$), 133.4 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{P}\text{H}_{\text{para}}$), 133.2 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{P}\text{H}_{\text{para}}$), 132.7 (d, $^3J_{\text{PC}} = 10.5$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{P}\text{H}_{\text{meta}}$), 131.8 (d, $^3J_{\text{PC}} = 11.0$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{P}\text{H}_{\text{meta}}$), 131.4 (d, $^1J_{\text{PC}} = 120.5$ Hz, $\text{P}\underline{\text{C}}_{\text{Ar}}$), 129.6 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 129.5 (d, $^1J_{\text{PC}} = 130.0$ Hz, $\text{P}\underline{\text{C}}_{\text{Ar}}$), 129.3 (d, $^2J_{\text{PC}} = 13.0$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{H}_{\text{ortho}}$), 129.1 (d, $^2J_{\text{PC}} = 13.5$ Hz, $\underline{\text{C}}_{\text{Ar}}\text{H}_{\text{ortho}}$), 128.7 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 126.3 ($\underline{\text{C}}_{\text{Ar}}\text{H}$), 93.1 (d, $^3J_{\text{PC}} = 7.0$ Hz, $\text{C}\underline{\text{H}}\text{T}\text{s}$), 71.1 (d, $^2J_{\text{PC}} = 3.0$ Hz, $\text{NC}\underline{\text{C}}\text{H}_3$), 46.4 ($\text{NC}\underline{\text{C}}\text{H}_2\text{CH}_2\text{Ph}$), 30.2 ($\text{NCCH}_2\underline{\text{C}}\text{H}_2\text{Ph}$), 21.8 ($\text{C}_{\text{Ar}}\underline{\text{C}}\text{H}_3$), 20.7 ($\text{NC}\underline{\text{C}}\text{H}_3$).

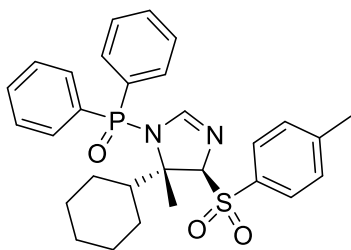
^{31}P NMR (CDCl_3 , 162 MHz): δ 22.7.

HRMS (ESI): calcd. for $\text{C}_{31}\text{H}_{32}\text{N}_2\text{O}_3\text{P}^{32}\text{S}^+ [\text{M}+\text{H}]^+$ 543.18658, found 543.18641.

$[\alpha]_{\text{D}}^{25}$: –240 ($c = 1.00$ in CHCl_3).

((4*S*,5*S*)-5-Cyclohexyl-5-methyl-4-tosyl-4,5-dihydro-1*H*-imidazol-1-yl)diphenyl

phosphine oxide **170q**



Prepared according to General Procedure **V**, using *N*-DPP ketimine **7q** (81.3 mg, 0.25 mmol). Purification of the crude mixture (conversion 100%, dr > 95:5) by FCC (PE:AcOEt 6:4) afforded product **170q** as a white solid in 94% yield (122 mg).

The ee was determined by HPLC: Chiralpak OD-H column, hexane/*iso*-propanol 95:5, 1 mL/min, λ 240 nm, *t* (minor) = 30.7 min; *t* (major) = 37.9 min (98% ee).

RF: 0.42 (AcOEt:PE 1:1).

M.p.: 87–90 °C.

IR: 2929 (m), 2854 (w), 2234 (w), 1600 (s), 1438 (m), 1316 (m), 1218 (s), 913 (w), 728 (s), 701 (s), 657 (m) cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 7.95 (ddd, *J* = 13.0, 8.5, 1.5 Hz, 2H, C_{Ar}PH), 7.83 (d, *J* = 8.0 Hz, 2H, SO₂C_{Ar}C_{Ar}H), 7.69–7.52 (m, 6H), 7.47 (td, *J* = 7.5, 3.5 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H, SO₂C_{Ar}C_{Ar}HC_{Ar}H), 6.76 (d, *J* = 1.5 Hz, 1H, N=CH), 4.86 (d, *J* = 1.5 Hz, 1H, CHTs), 2.42 (s, 3H, C_{Ar}CH₃), 2.38–1.95 (m, 1H, CCH), 1.92 (s, 3H, NCCH₃), 1.90–1.65 (m, 4H), 1.46–1.22 (m, 4H), 1.07 (m, 1H), 0.74 (m, 1H).

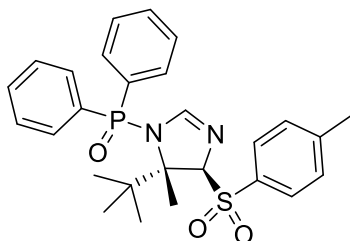
¹³C NMR (CDCl₃, 126 MHz): δ 156.3 (d, ²*J*_{PC} = 8.0 Hz, N=CH), 144.9 (C_{Ar}), 136.2 (C_{Ar}CH₃), 133.2 (d, ⁴*J*_{PC} = 3.0 Hz, C_{Ar}PH_{para}), 133.1 (d, ⁴*J*_{PC} = 3.0 Hz, C_{Ar}PH_{para}), 132.6 (d, ³*J*_{PC} = 10.5 Hz, C_{Ar}PH_{meta}), 131.7 (d, ³*J*_{PC} = 11.0 Hz, C_{Ar}PH_{meta}), 131.4 (d, ¹*J*_{PC} = 122.0 Hz, PC_{Ar}), 130.5 (d, ¹*J*_{PC} = 130.0 Hz, PC_{Ar}), 129.6 (C_{Ar}H), 129.5 (C_{Ar}H), 129.2 (d, ²*J*_{PC} = 13.0 Hz, C_{Ar}H_{ortho}), 129.1 (d, ²*J*_{PC} = 13.5 Hz, C_{Ar}H_{ortho}), 90.6 (d, ³*J*_{PC} = 7.0 Hz, CHTs), 74.7 (d, ²*J*_{PC} = 3.0 Hz, NCCH₃), 48.6 (NCCH), 25.4 (NCCH₃), 31.7 (CH₂), 26.2 (CH₂), 26.0 (CH₂), 25.9 (CH₂), 21.8 (C_{Ar}CH₃), 19.5 (CH₂).

³¹P NMR (CDCl₃, 162 MHz): δ 22.5.

HRMS (ESI): calcd. for $C_{29}H_{34}N_2O_3P^{32}S^+$ $[M+H]^+$ 521.20223, found 521.20178.

$[\alpha]_D^{25}$: -211 ($c = 1.00$ in $CHCl_3$).

((4*S*,5*S*)-5-(*tert*-Butyl)-5-methyl-4-tosyl-4,5-dihydro-1*H*-imidazol-1-yl)diphenyl phosphine oxide **170r**



Prepared according to a modified General Procedure **V**, using *N*-DPP ketimine **5r** (74.8 mg, 0.25 mmol), ligand **31b** (30.7 mg, 0.05 mmol, 0.2 equiv) and Ag_2O (5.8 mg, 0.025 mmol, 0.1 equiv) in $AcOEt$ (1 mL) for 120 hours. Purification of the crude mixture

(conversion 59%, dr > 95:5) by FCC (PE:AcOEt 7:3 to 6:4) afforded product **170r** as a white solid in 51% yield (63 mg).

The ee was determined by HPLC: Chiralpak OD-H column, hexane/*iso*-propanol 90:10, 1 mL/min, λ 220 nm, t (minor) = 15.1 min, t (major) = 18.6 min (82% ee).

RF: 0.47 (AcOEt:PE 1:1).

M.p.: 72–75 °C.

IR: 2971 (m), 1610 (s), 1438 (m), 1318 (m), 1242 (s), 1183 (m), 1147 (s), 1121 (s), 1053 (m), 727 (s), 698 (s), 662 (m) cm^{-1} .

^1H NMR ($CDCl_3$, 500 MHz): δ 8.06–7.92 (m, 2H), 7.80 (d, $J = 8.0$ Hz, 2H, $SO_2C_{Ar}C_{Ar}H$), 7.74–7.54 (m, 6H), 7.51–7.47 (m, 2H), 7.34 (d, $J = 8.0$ Hz, 2H, $SO_2C_{Ar}C_{Ar}HC_{Ar}H$), 6.94 (br s, 1H, $N=CH$), 5.00 (t, $J = 2.0$ Hz, 1H, $CHTs$), 2.43 (s, 3H, $C_{Ar}CH_3$), 1.95 (s, 3H, $NCCCH_3$), 1.10 (s, 3H, $NCCCH_3$).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 157.3 (d, $^2J_{PC} = 8.5$ Hz, $N=CH$), 145.0 (C_{Ar}), 136.4 ($C_{Ar}CH_3$), 145.2 (C_{Ar}), 133.1 ($C_{Ar}P_{Hpara}$), 133.0 (d, $^1J_{PC} = 124.0$ Hz, PC_{Ar}), 132.8 (d, $^3J_{PC} = 10.5$ Hz, $C_{Ar}P_{Hmeta}$), 131.7 (d, $^3J_{PC} = 11.0$ Hz, $C_{Ar}P_{Hmeta}$), 130.7 (d, $^1J_{PC} = 125.0$ Hz, PC_{Ar}), 129.7 ($C_{Ar}H$), 129.5 ($C_{Ar}H$), 129.2 (d, $^2J_{PC} = 13.0$ Hz, $C_{Ar}H_{ortho}$), 128.9 (d, $^2J_{PC} = 13.5$ Hz, $C_{Ar}H_{ortho}$), 91.9 (d,

$^3J_{PC} = 5.5$ Hz, $\underline{C}$ HTs), 78.7 ($\underline{N}\underline{C}\underline{C}H_3$), 40.1 ($\underline{N}\underline{C}\underline{C}\underline{C}H_3$), 25.4 ($\underline{N}\underline{C}\underline{C}H_3$), 21.8 ($\underline{C}_{Ar}\underline{C}H_3$), 15.5 ($\underline{N}\underline{C}\underline{C}\underline{C}H_3$).

^{31}P NMR ($CDCl_3$, 162 MHz): δ 23.6.

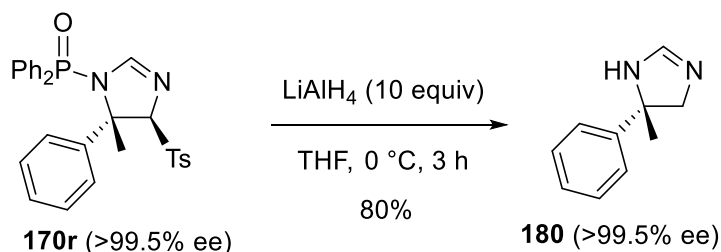
HRMS (ESI): calcd. for $C_{27}H_{32}N_2O_3P^{32}S^+$ $[M+H]^+$ 495.18658, found 495.18643.

$[\alpha]_D^{25}$: -156 ($c = 0.50$ in $CHCl_3$).

The enantiomeric compound **ent-170r** was prepared according to a modified General Procedure **V**, using *N*-DPP ketimine **5r** (74.8 mg, 0.25 mmol), ligand **31d** (30.7 mg, 0.05 mmol, 0.2 equiv) and Ag_2O (5.8 mg, 0.025 mmol, 0.1 equiv) in $AcOEt$ (1 mL) for 96 hours. Purification of the crude mixture (conversion 45%, dr > 95:5) FCC (PE: $AcOEt$ 7:3 to 6:4) afforded compound **ent-170r** as a white solid in 42% yield (52 mg) and 72% ee.

7.4.5 Synthesis and Characterisation of **180**

(5*S*)-5-Methyl-5-phenyl-4,5-dihydro-1*H*-imidazole **180**



To a stirred suspension of **170r** (100 mg, 0.194 mmol, 1 equiv, >99.5% ee) in THF (2 mL) kept at 0 °C, a 1 M $LiAlH_4$ solution in THF (1.94 mL, 1.94 mmol, 10 equiv) was added dropwise over 10 minutes. The reaction mixture was stirred at 0 °C for 3 hours (check completion by MS), then diluted with Et_2O (20 mL) and quenched by sequential dropwise addition of H_2O (75 μ L), aqueous NaOH 15%_{w/w} (75 μ L) and H_2O (225 μ L). The resulting suspension was stirred for 5 minutes, anhydrous Na_2SO_4 added, the suspension stirred again for 5 minutes and then filtered over celite washing with Et_2O (20 mL). The filtrate was evaporated and the crude residue purified by FCC ($CHCl_3$: $MeOH$ 10:0 to 8:2), obtaining compound **180** (25.0 mg, 80%)

as a pale yellow oil. The enantiomeric excess of the product was determined by PLC: Chiralpak AD-H column, hexane/*i*-PrOH 95:5, flow 1.0 mL/min, λ 220 nm, t (minor) = 17.5 min, t (major) = 22.1 min (>99.5% ee).

RF: 0.22 (CHCl₃:MeOH 8:2).

IR: 3179 (w), 2966 (w), 2923 (w), 2862 (w), 1597 (s), 1493 (w), 1444 (m), 1313 (w), 1157 (w), 963 (w), 762 (m), 700 (s) cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 7.37 (dd, J = 8.5, 1.5 Hz, 2H, C_{Ar}H_{ortho}), 7.32 (t, J = 8.0 Hz, 2H, C_{Ar}H_{meta}), 7.25–7.19 (m, 2H, C_{Ar}H_{para} and N=CH), 4.88 (br s, 1H, NH), 3.67 (dd, J = 11.5, 1.0 Hz, 1H, NCH_AH_B), 3.60 (dd, J = 11.5, 1.0 Hz, 1H, NCH_AH_B), 1.56 (s, 3H, CH₃).

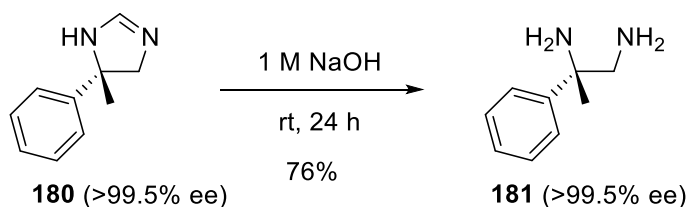
¹³C NMR (CDCl₃, 126 MHz): δ 153.0 (N=CH), 147.6 (C_{Ar}), 128.6 (C_{Ar}H), 126.8 (C_{Ar}H_{para}), 125.3 (C_{Ar}H), 68.0 (NCH₂), 62.7 (NCCH₃), 29.0 (NCCH₃).

HRMS (ESI): calcd. for C₁₀H₁₃N₂⁺ [M+H]⁺ 161.10732, found 161.10724.

$[\alpha]_D^{25}$: +92 (c = 1.00 in CHCl₃).

7.4.6 Synthesis and Characterisation of 181

(2S)-2-Phenylpropane-1,2-diamine 181



A biphasic mixture of **180** (67.6 mg, 0.42 mmol, 1 equiv, >99.5% ee) in 1 M aqueous NaOH (4.2 mL) was vigorously stirred at rt for 24 h. To the reaction mixture was then added CH₂Cl₂ (10 mL), phases were separated and the aqueous layer was extracted with CH₂Cl₂ (7 × 10 mL). The combined organic phases were dried over Na₂SO₄, filtered and evaporated, obtaining compound **181** (48.2 mg, 76%) as a yellow oil. The ee was determined after tosylation (see next reaction).

Spectroscopic data match those given in the literature for the racemic compound.²⁹⁵

¹H NMR (CDCl₃, 400 MHz): δ 7.44 (d, *J* = 8.0 Hz, 2H, C_{Ar}H_{ortho}), 7.33 (t, *J* = 8.0 Hz, 2H, C_{Ar}H_{meta}), 7.22 (t, *J* = 8.0 Hz, 1H, C_{Ar}H_{para}), 2.91 (d, *J* = 13.0 Hz, 1H, NCH_AH_B), 2.73 (d, *J* = 13.0 Hz, 1H, NCH_AH_B), 1.42 (s, 3H, CH₃), 1.36 (br s, 4H, NH₂).

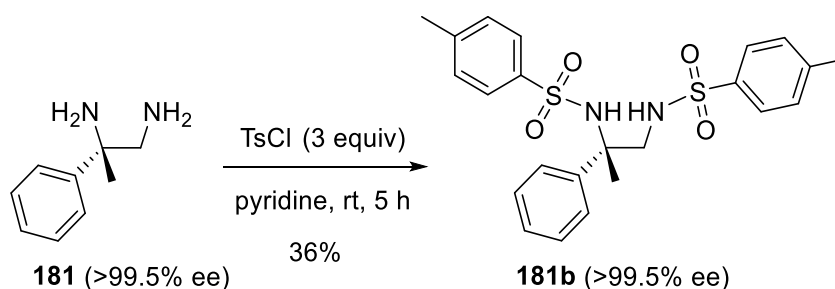
¹³C NMR (CDCl₃, 100 MHz): δ 147.2 (C_{Ar}), 128.3 (C_{Ar}H), 126.4 (C_{Ar}H_{para}), 125.5 (C_{Ar}H), 56.2 (NCCH₃), 54.9 (NCH₂), 28.8 (NCCH₃).

HRMS (ESI): calcd. for C₉H₁₅N₂⁺ [M+H]⁺ 151.12298, found 151.12246.

[α]_D²⁵: +24.4 (*c* = 1.00 in CHCl₃).

7.4.7 Synthesis and Characterisation of 181b

4-Methyl-*N*-[(2*S*)-2-[(4-methylphenyl)sulfonylamino]-2-phenylpropyl]benzene sulfonamide **181b**



To a colorless solution of **181** (83 mg, 0.55 mmol, 1 equiv, >99.5% ee) in pyridine (4 mL) kept at 0 °C, tosyl chloride (316 mg, 1.65 mmol, 3 equiv) was added. Upon addition, the solution turned yellow; it was then stirred at rt for 5 hours. Most of the pyridine was removed under vacuum, then the brown oily residue was taken up in CH₂Cl₂ (20 mL) and 1 M HCl (10 mL). Phases were separated and the aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic phases were dried over Na₂SO₄, filtered and evaporated. The crude was purified by FCC (PE:AcOEt 8:2 to 7:3), obtaining compound **181b** (90.8 mg, 36%) as a fluffy pale yellow solid.

The ee was determined by HPLC: Chiralpak AD-H column, hexane/*iso*-propanol 70:30, 1 mL/min, λ 220 nm, *t* (major) = 30.6 min, *t* (minor) = 43.3 min (> 99.5% ee).

RF: 0.26 (PE:AcOEt 7:3).

M.p.: 60–62 °C.

IR: 3279 (m), 2923 (w), 1325 (m), 1156 (s), 1090 (m), 665 (s).

^1H NMR (CDCl_3 , 400 MHz): δ 7.71 (d, J = 8.0 Hz, 2H, $\text{SO}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 7.50 (d, J = 8.0 Hz, 2H, $\text{SO}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{H}$), 7.29 (d, J = 8.0 Hz, 2H, $\text{SO}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 7.21–7.09 (m, 7H, Ph and $\text{SO}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}\text{HC}_{\text{Ar}}\text{H}$), 5.79–5.61 (m, 1H, NH), 5.30–5.01 (m, 1H, NH), 3.40 (dd, J = 13.0, 6.0 Hz, 1H, $\text{NCH}_{\text{A}}\text{H}_{\text{B}}$), 3.20 (dd, J = 13.0, 8.5 Hz, 1H, $\text{NCH}_{\text{A}}\text{H}_{\text{B}}$), 2.42 (s, 3H, $\text{C}_{\text{Ar}}\text{CH}_3$), 2.37 (s, 3H, $\text{C}_{\text{Ar}}\text{CH}_3$), 1.57 (s, 3H, NCCH_3).

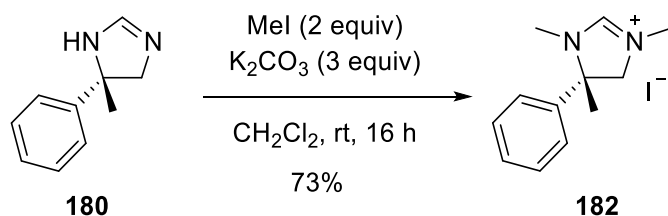
^{13}C NMR (CDCl_3 , 100 MHz): δ 143.8 (C_{Ar}), 143.1 (C_{Ar}), 141.5 (C_{Ar}), 139.3 (C_{Ar}), 133.8 (C_{Ar}), 130.0 ($\text{C}_{\text{Ar}}\text{H}$), 129.5 ($\text{C}_{\text{Ar}}\text{H}$), 128.5 ($\text{C}_{\text{Ar}}\text{H}$), 127.6 ($\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 127.1 ($\text{C}_{\text{Ar}}\text{H}$), 127.0 ($\text{C}_{\text{Ar}}\text{H}$), 125.9 ($\text{C}_{\text{Ar}}\text{H}$), 60.7 (NCCH_3), 52.6 (NCH_2), 25.1 (NCCH_3), 21.7 ($\text{C}_{\text{Ar}}\text{CH}_3$), 21.6 ($\text{C}_{\text{Ar}}\text{CH}_3$).

HRMS (ESI): calcd. for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_4\text{S}_2^+ [\text{M}+\text{H}]^+$ 459.14068, found 459.14043.

$[\alpha]_{\text{D}}^{25}$: +52.9 (c = 1.00 in CHCl_3).

7.4.8 Synthesis and Characterisation of 182

(5*S*)-1,3,5-Trimethyl-5-phenyl-4,5-dihydro-1*H*-imidazol-3-ium iodide 182



Following a literature procedure,¹⁸⁹ to a stirred suspension of **180** (100 mg, 0.624 mmol, 1 equiv) and K_2CO_3 (313 mg, 2.24 mmol, 3.6 equiv) in CH_2Cl_2 (3 mL) kept at 0 °C, methyl iodide (80 μL , 1.25 mmol, 2 equiv) was added. The reaction mixture was stirred at rt for 16 hours,

then filtered through celite washing with CH₂Cl₂ (5 mL) and concentrated. To the residue Et₂O (15 mL) was added, and a white precipitate formed. The solid was collected on buchner, washed with pentane (3 × 10 mL) and dried under vacuum, obtaining compound **182** (130 mg, 73%) as an off-white solid.

M.p.: 126–128 °C.

IR: 3453 (m), 2932 (w), 1655 (s), 1446 (w), 1315 (w), 1278 (w), 769 (m), 701 (m) cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 9.53 (s, N=CH), 7.57–7.25 (m, 5H, C_{Ar}H), 4.01 (d, *J* = 11.5 Hz, 1H, NCH_AH_B), 3.87 (d, *J* = 11.5 Hz, 1H, NCH_AH_B), 3.39 (s, 3H, NCH₃), 3.03 (s, 3H, NCH₃), 1.93 (s, 3H, CCH₃).

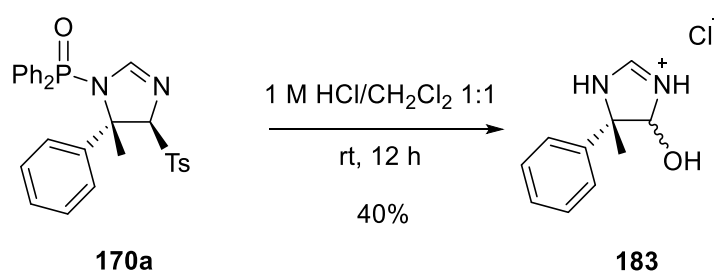
¹³C NMR (CDCl₃, 126 MHz): δ 157.8 (N=CH), 138.9 (C_{Ar}), 129.6 (C_{Ar}H), 129.3 (C_{Ar}H_{para}), 125.9 (C_{Ar}H), 69.6 (NCH₂), 66.2 (NCCCH₃), 35.9 (NCH₃), 30.3 (NCH₃), 22.5 (NCCCH₃).

HRMS (ESI): calcd. for C₁₂H₁₇N₂⁺ [M–I]⁺ 189.13863, found 189.13874.

[α]_D²⁵: –27.3 (*c* = 2.63 in CHCl₃).

7.4.9 Synthesis and Characterisation of 183

(5*S*)-4-Hydroxy-5-methyl-5-phenyl-4,5-dihydro-1*H*-imidazol-3-ium chloride **183**



A biphasic solution of **170a** (515 mg, 1.0 mmol, 1 equiv, >99.5% ee) in 1 M HCl (5 mL, 5 mmol, 5 equiv) and CH₂Cl₂ (5 mL) was vigorously stirred at rt for 12 h. The reaction mixture was then diluted with 1 M HCl (5 mL) and CH₂Cl₂ (5 mL), phases were separated and the aqueous layer was washed with CH₂Cl₂ (5 × 5 mL) and then CHCl₃:*i*-PrOH 3:1 (10 × 5 mL) to

remove DPPOH, TsH and TsOH. Evaporated of the aqueous layer afforded compound **183** (85.0 mg, 40%) as a yellow solid in approximately 3:2 dr.

M.p.: 262–263 °C.

IR: 3056 (m, NH), 2900 (m), 2923 (w), 1620 (m), 1540 (w), 1447 (w), 1108 (m), 1066 (m), 762 (m), 699 (s) cm⁻¹.

¹H NMR (D₂O, 400 MHz, dr 3:2): δ 8.33 (s, 1H, N=CH), 7.53–6.89 (m, 5H, Ph), 5.35 (s, 1H, CHOH, major diastereomer), 5.34 (s, 1H, CHOH, minor diastereomer), 1.56 (s, 3H, CH₃, major diastereomer), 1.49 (s, 3H, CH₃, minor diastereomer).

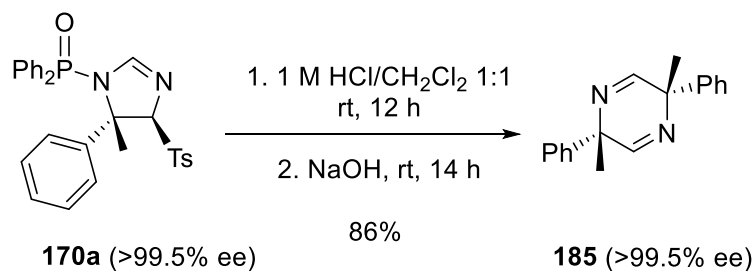
¹³C NMR (D₂O, 100 MHz): δ 155.4 (N=CH), 141.6 (C_{Ar}, minor diastereomer), 135.4 (C_{Ar}, major diastereomer), 129.8 (C_{Ar}H), 128.5 (C_{Ar}H), 128.4 (C_{Ar}H), 126.3 (C_{Ar}H), 125.6 (C_{Ar}H), 124.2 (C_{Ar}H), 88.0 (CHOH, minor diastereomer), 86.8 (CHOH, major diastereomer), 69.8 (NCCH₃, major diastereomer), 69.3 (NCCH₃, minor diastereomer), 25.2 (NCCH₃, major diastereomer), 19.7 (NCCH₃, minor diastereomer).

HRMS (ESI): calcd. for C₁₀H₁₃ON₂⁺ [M–Cl]⁺ 177.10224, found 177.10235.

[α]_D²⁵: +27 (c = 0.2 in H₂O).

7.4.10 Synthesis and Characterisation of **185**

(2*S*,5*S*)-2,5-Dimethyl-2,5-diphenyl-2,5-dihydropyrazine **185**



A biphasic solution of **170a** (103 mg, 0.2 mmol, 1 equiv, >99.5% ee) in 1 M HCl (1 mL, 1 mmol, 5 equiv) and CH₂Cl₂ (1 mL) was vigorously stirred at rt for 12 hours, then powdered NaOH was added portionwise (200 mg, 5.0 mmol, 25 equiv) and the reaction mixture stirred

for 14 hours. The reaction mixture was then diluted with water (5 mL) and CH₂Cl₂ (10 mL), phases were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered and evaporated to afford compound **185** (22.6 mg, 86%) as a white solid.

The ee was determined by HPLC: Chiralpak AD-H column, hexane/*iso*-propanol 80:20, 1 mL/min, λ 220 nm, t (minor) = 7.4 min, t (major) = 18.7 min (> 99.5% ee).

RF: 0.49 (pentane:AcOEt 4:6).

M.p.: 100–105 °C.

IR: 3032 (w), 2968 (w), 2926 (w), 1651 (m), 1491 (m), 1439 (m), 1076 (m), 1027 (m), 873 (w), 857 (w), 760 (m), 698 (s) cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ 8.11 (s, 2H, N=CH), 7.32–7.16 (m, 10H, Ph), 1.69 (s, 6H, CH₃).

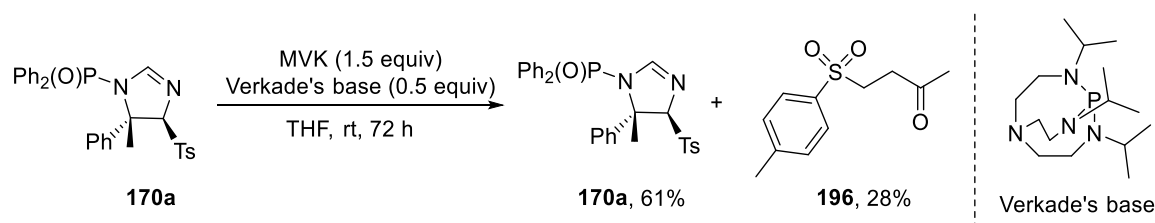
¹³C NMR (CDCl₃, 75 MHz): δ 164.7 (N=CH), 142.1 (C_{Ar}), 128.8 (C_{Ar}H), 127.5 (C_{Ar}H_{para}), 126.2 (C_{Ar}H), 58.0 (NCCH₃), 27.3 (NCCH₃).

HRMS (ESI): calcd. for C₁₈H₁₉N₂⁺ [M+H]⁺ 263.15428, found 263.15423.

[α]_D²⁵: +286 (c = 1.00 in CHCl₃).

7.4.11 Synthesis and Characterisation of 196

4-(4-Methylbenzene-1-sulfonyl)butan-2-one **196**



To an orange solution of **170a** (25.7 mg, 0.05 mmol, 1 equiv) and Verkade's base (2,8,9-triisopropyl-2,5,8,9-tetraaza-1-phosphabicyclo[3,3,3]undecane, 7.5 mg, 0.025 mmol, 0.5 equiv) in THF (1 mL), methyl vinyl ketone (7 μL, 0.075 mol, 1.5 equiv) was added. Upon

addition the color turned pink. The reaction mixture was stirred at rt for 72 hours, then was diluted with 1 M aq NH_4Cl (5 mL) and CH_2Cl_2 (10 mL), phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 , filtered and evaporated. The crude was purified by FCC (PE:EtOAc 9:1 to 2:8) obtaining in order of elution **196** (3.2 mg, 28%, white solid) and **170a** (15.7 mg, 61%, off-white solid).

Spectroscopic data match those given in the literature.²⁹⁶

M.p.: 73–74 °C (lit: 72–73 °C).²⁹⁷

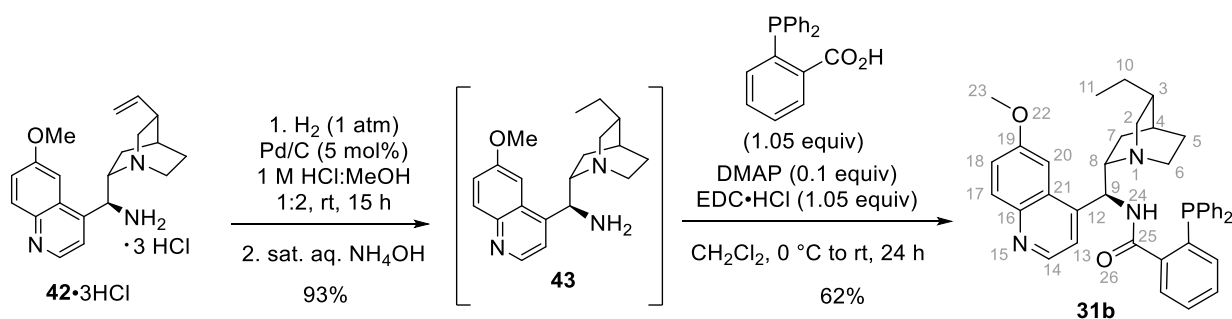
^1H NMR (CDCl_3 , 400 MHz): δ 7.79 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 3.35 (t, J = 7.5 Hz, 2H, $\text{SO}_2\text{CH}_2\text{CH}_2$), 2.91 (t, J = 7.5 Hz, 2H, $\text{SO}_2\text{CH}_2\text{CH}_2$), 2.45 (s, 3H, $\text{C}_{\text{Ar}}\text{CH}_3$), 2.17 (s, 3H, COCH_3).

^{13}C NMR (CDCl_3 , 100 MHz): δ 203.5 ($\text{C}=\text{O}$), 144.7 (C_{Ar}), 136.0 (C_{Ar}), 130.1 ($\text{C}_{\text{Ar}}\text{H}$), 128.0 ($\text{C}_{\text{Ar}}\text{H}$), 50.8 (SO_2CH_2), 63.3 (COCH_2), 29.8 (CH_3), 21.6 ($\text{C}_{\text{Ar}}\text{CH}_3$).

LRMS (ESI): calcd. for $\text{C}_{11}\text{H}_{14}\text{NaO}_3\text{S}^+ [\text{M}+\text{Na}]^+$ 249.1, found 249.0.

7.4.12 Synthesis and Characterisation of Ligands

Synthesis and Characterisation of **31b**



Following a literature procedure,¹¹¹ **42·HCl** (4.00 g, 9.24 mmol, 1 equiv) was dissolved 2:1 MeOH/1 M aq HCl (34:17 mL) and 10% Pd/C (492 mg, 0.462 mmol, 0.05 equiv) was added. The reaction mixture was stirred under hydrogen (1 atm) for 15 h at room temperature and then

filtered through Celite washing with water and MeOH. The filtrate was concentrated under reduced pressure. The residue was taken up in water (5 mL) and aq sat NH_4OH (10 mL). CH_2Cl_2 (30 mL) was added, phases were separated and the aqueous layer was extracted twice with CH_2Cl_2 . Combined organic phases were washed with brine, dried over Na_2SO_4 , filtered and evaporated to afford **43** (2.79 g, 93% yield) as a orange oil, which was used in the next step without further purification.

43 (2.78 g, 9.21 mmol, 1 equiv) was dissolved in CH_2Cl_2 (170 mL), then 2-(diphenylphosphino)benzoic acid (2.96 g, 9.68 mmol, 1.05 equiv) and DMAP (112 mg, 0.92 mmol, 0.1 equiv) were added. The solution was cooled to 0 °C, EDC·HCl (1.86 g, 9.68 mmol, 1.05 equiv) was added portionwise, and resulting mixture was stirred at rt for 24 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL), and washed with water (20 mL), aq sat NaHCO_3 (20 mL) and brine (10 mL). The organic phase was dried over Na_2SO_4 , filtered and evaporated. Purification by FCC (EtOAc to EtOAc/MeOH 8:2), followed by recrystallisation from EtOAc afforded **31b** (3.40 g, 62%) as colourless needles.

Data match those given in the literature.¹¹¹

RF: 0.40 (EtOAc/MeOH 9:1).

M.p. (AcOEt): 105–106 °C (lit: 104–105 °C).¹¹¹

IR: 3054 (w), 2930 (m), 2861 (w), 1655 (m, C=O), 1621 (m), 1509 (m), 1476 (m), 1433 (m), 1240 (m), 1021 (w), 746 (s), 697 (m) cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): δ 8.65 (d, J = 4.5 Hz, 1H, CH_{14}), 8.01 (d, J = 9.0 Hz, 1H, CH_{17}), 7.69 (d, J = 3.0 Hz, 1H, CH_{20}), 7.67–7.60 (m, 1H, C_{ArH}), 7.44–7.33 (m, 2H, CH_{18} , C_{ArH}), 7.31–7.23 (m, 9H, $\text{C}_{\text{ArH}} \times 7$, CH_{13} , NH), 7.20–7.14 (m, 4H, C_{ArH}), 6.91 (dd, J = 8.0, 4.0 Hz, 1H), 5.40 (br s, 1H, CH_9), 3.97 (s, 3H, CH_3 -23), 3.09 (m, 2H, CH_aH_b -2, CH_aH_b -6), 2.93 (br s, 1H, CH_8), 2.59 (ddd, J = 15.5, 11.0, 5.0 Hz, 1H, CH_aH_b -6), 2.36–2.18 (m, 1H, CH_aH_b -2), 1.70–1.54 (m, 2H, CH_4 , CH_aH_b -5), 1.51–1.43 (m, 1H, CH_aH_b -5), 1.43–1.37 (m,

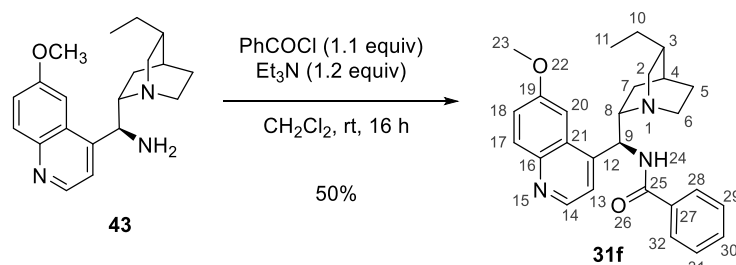
1H, CH-3), 1.36–1.30 (m, 1H, CH_aH_b-7), 1.24–1.12 (m, 2H, CH₂-10), 0.88 (dd, *J* = 13.0, 6.0 Hz, 1H, CH_aH_b-7), 0.80 (t, *J* = 7.5 Hz, 3H, CH₃-11).

¹³C NMR (CDCl₃, 126 MHz, P–C coupling not removed): δ 169.0 (C=O), 157.7 (C-19), 147.7 (CH-14), 144.8 (C-16 or C-12), 141.7 (d, *J* = 26.0 Hz), 137.4 (d, *J* = 11.5 Hz), 137.0 (d, *J* = 12.0 Hz), 135.6 (d, *J* = 22.5 Hz), 134.4, 133.9, 133.8, 133.7, 133.6, 131.7 (CH-17), 130.2 (CH-30), 128.9, 128.8, 128.7, 128.66, 128.61, 128.56, 128.50, 121.6 (CH-18), 119.7 (CH-13), 102.4 (CH-20), 60.1 (CH-8 or CH-9), 57.7 (CH₂-2), 55.8 (CH₃-23), 51.5 (CH-8 or CH-9), 41.2 (CH₂-6), 37.4 (CH-3), 28.7 (CH₂-5), 27.5 (CH₂-10), 26.1 (CH₂-7), 25.3 (CH-4), 12.1 (CH₃-11).

³¹P NMR (CDCl₃, 202 MHz): δ –10.5.

[α]_D²⁵: –15.4 (*c* = 1.00 in CHCl₃); lit: [α]_D²⁰: –15.5 (*c* = 0.4 in CHCl₃).¹¹¹

Synthesis and Characterisation of 31f



Following a literature procedure,¹¹² to a stirred solution of **43** (1.15 g, 3.53 mmol, 1 equiv) and triethylamine (0.59 mL, 4.3 mmol, 1.2 equiv) in CH₂Cl₂ (17 mL), benzoyl chloride (0.45 mL, 3.8 mmol, 1.1 equiv) was added dropwise over 5 minutes. The resulting yellow solution was stirred for 16 hours at room temperature, then CH₂Cl₂ (20 mL) and 4 M aq NaOH (10 mL) were added. Phases were separated, the aqueous layer was extracted twice with CH₂Cl₂ (60 mL), then the combined organic phases were dried over Na₂SO₄ and filtered. Evaporation of solvents afforded a pale orange foamy solid, which was purified by FCC (CH₂Cl₂ to CH₂Cl₂/MeOH 9:1). Compound **31f** (765 mg, 50%) was obtained as a pale yellow solid.

Data match those given in the literature.¹¹²

RF: 0.52 (CH₂Cl₂/MeOH 9:1).

M.p.: 90–91 °C (lit: 90–91 °C).¹¹²

IR: 2931 (m), 2862 (w), 1643 (s, C=O), 1621 (s), 1509 (s), 1475 (s), 1261 (m), 755 (m), 713 (m) cm⁻¹.

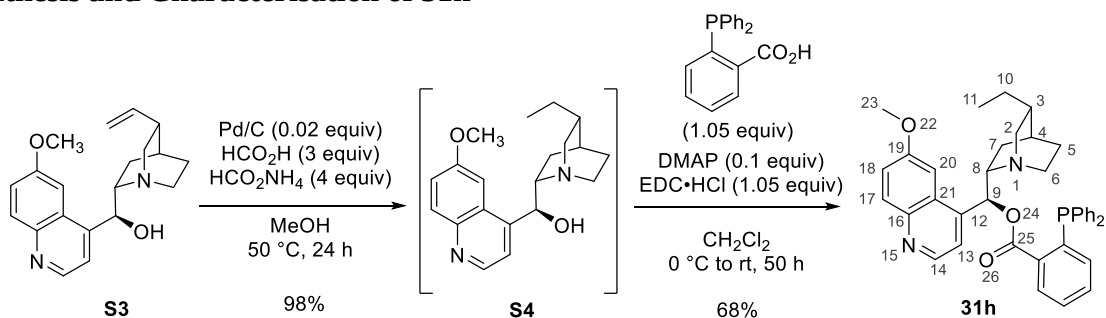
¹H NMR (CDCl₃, 500 MHz): δ 8.73 (d, *J* = 4.5 Hz, 1H, CH-14), 8.03 (d, *J* = 9.0 Hz, 1H, CH-17), 7.95 (br s, 1H, NH-24), 7.87–7.77 (m, 2H, CH-28, CH-32), 7.73 (d, *J* = 2.5 Hz, 1H, CH-20), 7.50–7.44 (m, 2H, CH-13, CH-30), 7.42–7.36 (m, 3H, CH-18, CH-29, CH-31), 5.37 (br s, 1H, CH-9), 3.98 (s, 3H, CH₃-23), 3.27 (dd, *J* = 13.5, 10.0 Hz, 1H, CH_aH_b-2), 3.25–3.20 (m, 1H, CH-8), 3.19–3.08 (m, 1H, CH_aH_b-6), 2.73 (ddd, *J* = 13.5, 11.0, 5.5 Hz, 1H, CH_aH_b-6), 2.48 (ddd, *J* = 13.5, 5.5, 2.5 Hz, 1H, CH_aH_b-2), 1.73–1.62 (m, 2H, CH-4, CH_aH_b-5), 1.59–1.50 (m, 1H, CH_aH_b-5), 1.49–1.43 (m, 1H, CH-3), 1.44–1.38 (m, 1H, CH_aH_b-7), 1.33–1.15 (m, 2H, CH₂-10), 1.04 (dd, *J* = 13.5, 6.5 Hz, 1H, CH_aH_b-7), 0.81 (t, *J* = 7.5 Hz, 3H, CH₃-11).

¹³C NMR (CDCl₃, 126 MHz): δ 167.3 (C=O), 157.9 (C-19), 147.7 (CH-14), 145.5 (C-16, C-12), 134.0 (C-27), 132.0 (CH-17), 131.7 (CH-30), 128.6 (CH-29, CH-31), 128.4 (C-21), 127.3 (CH-28, CH-32), 121.6 (CH-18), 119.7 (CH-13), 102.0 (CH-20), 60.1 (CH-8, CH-9), 57.8 (CH₂-2), 55.8 (CH₃-23), 41.1 (CH₂-6), 37.3 (CH-3), 28.6 (CH₂-5), 27.5 (CH₂-10), 26.0 (CH₂-7), 25.2 (CH-4), 12.1 (CH₃-11).

HRMS (ESI): calcd. for C₂₇H₃₂N₃O₂⁺ [M+H]⁺ 430.24890, found 430.24879.

[α]_D²⁵: –175 (*c* = 0.50 in CHCl₃). Lit [α]_D²⁵: –145 (*c* = 0.50 in CHCl₃).¹¹²

Synthesis and Characterisation of 31h



Following a literature procedure,¹¹² a vigorously stirred solution yellow solution of **S3** (1.44

g, 4.44 mmol, 1 equiv) in MeOH (7 mL) at rt, formic acid (0.50 mL, 13.3 mmol, 3 equiv) was added dropwise over 5 minutes. The solution turned bright yellow upon addition. Next, ammonium formate (1.12 g, 17.8 mmol, 4 equiv) and 10% Pd/C (100 mg, 0.094 mmol, 0.02 equiv) were added in sequence. The reaction mixture was stirred at rt for 5 hours, then at 50 °C for 24 h. After cooling down to rt, formic acid (184 μ L, 1.1 equiv) was added dropwise over 5 minutes and the reaction mixture was filtered through Celite washing the filter cake with MeOH. The bright yellow filtrate was evaporated and the residue taken up in water (5 mL) and aq sat NH_4OH (5 mL). CH_2Cl_2 (20 mL) was added, phases were separated and the aqueous layer was extracted twice with CH_2Cl_2 . Combined organic phases were washed with brine, dried over Na_2SO_4 , filtered and evaporated to afford **S4** (1.47 g, 99% yield) as a yellow oil, which was used in the next step without further purification.

S4 (1.39 g, 4.26 mmol, 1 equiv) was dissolved in CH_2Cl_2 (60 mL), then 2-(diphenylphosphino)benzoic acid (1.37 g, 4.47 mmol, 1.05 equiv) and DMAP (52 mg, 0.43 mmol, 0.1 equiv) were added. The mixture was cooled to 0 °C, EDC·HCl (857 mg, 4.47 mmol, 1.05 equiv) was added, and resulting solution was stirred at room temperature for 50 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc, washed with aq sat NaHCO_3 , and then brine. The organic phase was dried over Na_2SO_4 , filtered and evaporated. Purification by FCC (EtOAc to EtOAc/MeOH 9:1), followed by recrystallisation from EtOAc afforded product **31h** (1.77 g, 68%) as colourless needles.

Data match those given in the literature.¹¹²

RF: 0.64 (EtOAc/MeOH 9:1).

M.p. (AcOEt): 85–86 °C.

IR: 3054 (w), 2930 (m), 2862 (w), 1711 (m, C=O), 1621 (m), 1508 (m), 1475 (m), 1433 (m), 1250 (s), 907 (s), 729 (s), 696 (s) cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): δ 8.71 (d, J = 4.5 Hz, 1H, CH -14), 8.15 (ddd, J = 8.0, 4.0, 1.5 Hz, 1H, $\text{C}_{\text{Ar}}\text{H}$), 8.02 (d, J = 9.0 Hz, 1H, CH -17), 7.60 (d, J = 3.0 Hz, 1H, CH -20), 7.46–7.25 (m, 7H, CH -18, CH -13, $\text{C}_{\text{Ar}}\text{H} \times 5$), 7.22 (td, J = 7.5, 2.0 Hz, 2H), 7.17–7.02 (m, 5H), 6.86 (ddd, J = 8.0, 4.0, 1.5 Hz, 1H), 6.60 (d, J = 10.0 Hz, 1H, CH -9), 3.94 (s, 3H, CH_3 -23), 3.50 (app q, J = 9.5 Hz, 1H, CH -8), 3.35–3.06 (m, 2H, CH_2H_b -2, CH_2H_b -6), 2.61 (ddd, J = 15.0, 10.5, 5.0 Hz, 1H, CH_2H_b -6), 2.48 (ddd, J = 14.0, 4.5, 2.5 Hz, 1H, CH_2H_b -2), 1.59 (br s, 1H, CH -4), 1.56–1.47 (m, 1H, CH_2H_b -5), 1.46–1.30 (m, 5H, CH -3, CH_2H_b -5, CH_2H_b -7, CH_2 -10), 0.84 (t, J = 7.5 Hz, 3H, CH_3 -11), 0.80–0.68 (m, 1H, CH_2H_b -7).

^{13}C NMR (CDCl_3 , 126 MHz, P–C coupling not removed): ^{13}C NMR (CDCl_3 , 126 MHz): δ 165.9 (d, J = 3.0 Hz, $\text{C}=\text{O}$), 157.9 (C -19), 147.4 (CH -14), 144.8 (C -16 or C -12), 141.5 (C -16 or C -12), 140.6 (d, J = 28.0 Hz, C_{Ar}), 138.0 (d, J = 12.0 Hz, C_{Ar}), 137.8 (d, J = 12.0 Hz, C_{Ar}), 134.2, 134.1, 134.0 (d, J = 21.0 Hz), 133.7 (d, J = 20.5 Hz), 131.9 ($\text{C}_{\text{Ar}}\text{H}$), 131.6 (CH -17), 131.0 (d, J = 2.5 Hz), 128.5, 128.4, 128.3, 128.1 (C -21), 128.0, 127.9, 122.0 (CH -18), 120.6 (CH -13), 101.8 (CH -20), 71.8 (CH -9), 58.9 (CH -8), 57.7 (CH_2 -2), 55.6 (CH_3 -23), 41.5 (CH_2 -6), 37.4 (CH -3), 28.7 (CH_2 -5), 27.7 (CH_2 -10), 25.2 (CH -4 and CH_2 -7), 12.2 (CH_3 -11).

^{31}P NMR (CDCl_3 , 202 MHz): δ –4.5.

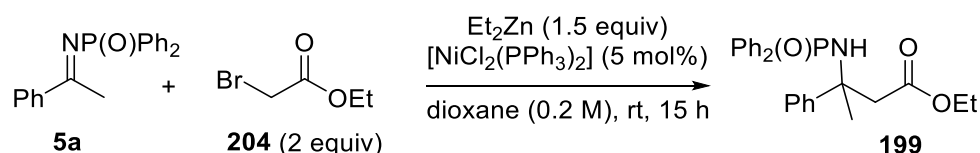
HRMS (ESI): calcd. for $\text{C}_{39}\text{H}_{40}\text{N}_2\text{O}_3\text{P}^+$ $[\text{M}+\text{H}]^+$ 615.27711, found 615.27710.

$[\alpha]_{\text{D}}^{25}$: –57 (c = 0.50 in CHCl_3). Lit: $[\alpha]_{\text{D}}^{25}$: –70 (c = 0.50 in CHCl_3).¹¹²

7.5 Ketimino-Reformatsky Reaction

7.5.1 Synthesis and Characterisation of 199

Ethyl 3-[(diphenylphosphoryl)amino]-3-phenylbutanoate 199



Ketimine **5a** (63.9 mg, 0.2 mmol, 1 equiv), [NiCl₂(PPh₃)₂] (6.5 mg, 0.01 mmol, 0.05 equiv) were put into an oven-dried flash and three vacuum/Ar cycles were performed. Dioxane (1 mL) was added and to the resultant stirred solution ethyl bromoacetate (45 μ L, 0.4 mmol, 2 equiv) and then diethylzinc (0.3 mL of a 1 M solution in hexanes, 0.3 mmol, 1.5 equiv) were added in sequence. The reaction mixture was stirred at room temperature for 15 hours, quenched by addition of 5 mL H₂O and stirred for 5 minutes. 1 M HCl (5 mL) and CH₂Cl₂ (20 mL) were then added and phases separated. The aqueous layer was extracted again with CH₂Cl₂ (2 $\times$ 20 mL), then the combined organic phases were dried over Na₂SO₄, filtered and evaporated. The crude residue was purified by FCC (Et₂O to Et₂O:acetone 9:1), obtaining compound **5a** (71.8 mg, 88%) as a thick whitish oil.

When performing the ligand screen, the ligand was put into the flask at the beginning together with the other solids. Enantiomeric excess of the product was determined by HPLC: Chiralpak IA column, hexane/*i*-PrOH 85:15, flow 1.0 mL/min, λ 220 nm, t_1 = 15.8 min, t_2 = 23.2 min.

IR: 2980 (m), 1720 (s, C=O), 1495 (m), 1438 (w), 1397 (w), 1380 (w), 1202 (s), 1121 (s), 1110 (s), 1029 (w), 754 (w), 727 (w), 699 (s) cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 7.99 (ddd, J = 12.0, 8.0, 1.5 Hz, 2H, C_{Ar}PH_{meta}), 7.88 (ddd, J = 12.0, 8.0, 1.5 Hz, 2H, C_{Ar}PH_{meta}), 7.56 (d, J = 8.5 Hz, 2H, C_{Ar}H_{ortho}) 7.48–7.40 (m, 6H, C_{Ar}PH_{ortho} and C_{Ar}PH_{para}), 7.32 (t, J = 8.0 Hz, 2H, C_{Ar}H_{meta}), 7.22 (t, J = 7.0 Hz, 1H, C_{Ar}H_{para}), 5.07 (d, $^2J_{PH}$ = 5.5 Hz, 1H, NH), 3.93 (app qq, J = 7.0 Hz, 4.0 Hz, 2H, OCHAHBCH₃), 3.37 (d, J = 16.0 Hz, 1H, CHAHBCO), 3.10 (d, J = 16.0 Hz, 1H, CHAHBCO), 1.51 (s, 3H, CH₃), 1.06 (t, J = 7.0 Hz, 3H, OCH₂CH₃).

¹³C NMR (CDCl₃, 126 MHz): δ 172.3 (C=O), 146.9 (d, $^3J_{PC}$ = 7.5 Hz, C_{Ar}), 135.2 (d, $^1J_{PC}$ = 126.5 Hz, PC_{Ar}), 134.9 (d, $^1J_{PC}$ = 131.5 Hz, PC_{Ar}), 132.2 (d, $^3J_{PC}$ = 9.5 Hz, C_{Ar}H_{meta}), 131.6 (app t, $^4J_{PC}$ = 3.5 Hz, C_{Ar}H_{para}), 131.2 (d, $^3J_{PC}$ = 9.5 Hz, C_{Ar}H_{meta}), 128.7 (d, $^2J_{PC}$ = 12.5 Hz, C_{Ar}H_{ortho}), 128.4 (d, $^2J_{PC}$ = 13.0 Hz, C_{Ar}H_{ortho}), 128.5 (C_{Ar}H), 126.9 (C_{Ar}H_{para}), 125.1 (C_{Ar}H),

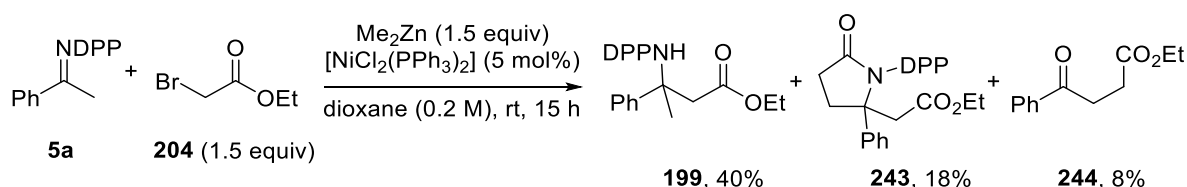
60.5 (OCH₂CH₃), 58.9 (d, ²J_{PC} = 3.0 Hz, NC), 47.7 (d, ³J_{PC} = 2.0 Hz, CH₂CO), 29.8 (d, ³J_{PC} = 4.0 Hz, CCH₃), 14.1 (OCH₂CH₃).

³¹P NMR (CDCl₃, 162 MHz): δ 20.8.

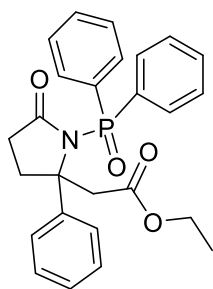
HRMS (ESI, MeOH): calcd. for C₂₄H₂₆NNaO₃P⁺ [M+Na]⁺ 430.15425, found 430.15413.

7.5.2 Synthesis and Characterisation of 243

Ethyl (1-diphenylphosphoryl-5-oxo-2-phenylpyrrolidin-2-yl)acetate **243**



Ketimine **5a** (63.9 mg, 0.2 mmol, 1 equiv), [NiCl₂(PPh₃)₂] (6.5 mg, 0.01 mmol, 0.05 equiv) were put into an oven-dried flash and three vacuum/Ar cycles were performed. Dioxane (1 mL) was added and to the resultant stirred solution ethyl bromoacetate (33 μL, 0.3 mmol, 1.5 equiv) and then dimethylzinc (0.15 mL of a 2 M solution in toluene, 0.3 mmol, 1.5 equiv) were added in sequence. The reaction mixture was stirred at room temperature for 15 hours, quenched by addition of 5 mL H₂O and stirred for 5 minutes. 1 M HCl (5 mL) and CH₂Cl₂ (20 mL) were then added and phases separated. The aqueous layer was extracted again with CH₂Cl₂ (2 × 20 mL), then the combined organic phases were dried over Na₂SO₄, filtered and evaporated. The crude residue was purified by FCC (PE:Et₂O 9:1 to Et₂O to Et₂O:acetone 9:1), obtaining in order of elution compound **244** (3.4 mg, 8%, see section 7.6.4 for data), compound **243** (16.1 mg, 18%, ee not determined, colorless oil, see below for data) and compound **199** (32.6 mg, 40%).



IR: 3057 (w), 1732 (m, C=O), 1703 (s, C=O), 1437 (w), 1215 (s), 1179 (s), 1123 (m), 1029 (w), 751 (m), 729 (m), 695 (s) cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): δ 7.84–7.79 (m, 2H, $\text{C}_{\text{ArP}}\text{H}_{\text{meta}}$), 7.54–7.49 (m, 3H, $\text{C}_{\text{ArP}}\text{H}_{\text{meta}}$ and C_{ArH}), 7.47–7.42 (m, 3H, C_{ArH}), 7.30–7.25 (m, 4H, C_{ArH}), 7.20–7.16 (m, 3H, C_{ArH}), 4.09 (dq, $J = 10.5, 7.0$ Hz, 1H,

$\text{OCH}_\text{A}\text{H}_\text{B}\text{CH}_3$), 4.07 (d, $J = 17.0$ Hz, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{CO}_2$), 3.98 (dq, $J = 10.5, 7.0$ Hz, 1H, $\text{OCH}_\text{A}\text{H}_\text{B}\text{CH}_3$), 3.60 (d, $J = 17.0$ Hz, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{CO}$), 2.85–2.75 (m, 2H, $\text{COCH}_\text{A}\text{H}_\text{B}\text{CH}_\text{D}\text{H}_\text{E}$), 2.70–2.63 (m, 1H, $\text{COCH}_\text{A}\text{H}_\text{B}\text{CH}_\text{D}\text{H}_\text{E}$), 2.47–2.743 (m, 1H, $\text{COCH}_\text{A}\text{H}_\text{B}\text{CH}_\text{D}\text{H}_\text{E}$), 1.18 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3).

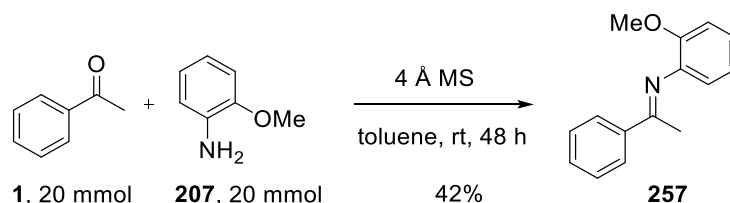
^{13}C NMR (CDCl_3 , 126 MHz): δ 179.9 (d, $^2J_{\text{PC}} = 3.0$ Hz, $\text{NC}=\text{O}$), 171.2 ($\text{OC}=\text{O}$), 145.5 (C_{Ar}), 132.7 (d, $^3J_{\text{PC}} = 11.0$ Hz, $\text{C}_{\text{ArP}}\text{H}_{\text{meta}}$), 132.2 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\text{C}_{\text{ArP}}\text{H}_{\text{para}}$), 132.0 (d, $^3J_{\text{PC}} = 11.5$ Hz, $\text{C}_{\text{ArP}}\text{H}_{\text{meta}}$), 132.0 (d, $^1J_{\text{PC}} = 143.8$ Hz, PC_{Ar}), 131.0 (d, $^1J_{\text{PC}} = 141.5$ Hz, PC_{Ar}), 128.3 (C_{ArH}), 128.1 (d, $^2J_{\text{PC}} = 14.0$ Hz, $\text{C}_{\text{ArP}}\text{H}_{\text{ortho}}$), 127.7 (d, $^2J_{\text{PC}} = 14.0$ Hz, $\text{C}_{\text{ArP}}\text{H}_{\text{ortho}}$), 127.5 ($\text{C}_{\text{ArH}}\text{para}$), 125.9 (C_{ArH}), 69.0 (d, $^2J_{\text{PC}} = 2.0$ Hz, NC), 60.6 (OCH_2CH_3), 42.8 (CH_2CO_2), 36.2 (d, $^3J_{\text{PC}} = 6.0$ Hz, COCH_2CH_2), 31.6 (d, $^3J_{\text{PC}} = 5.5$ Hz, COCH_2CH_2), 14.2 (OCH_2CH_3).

^{31}P NMR (CDCl_3 , 162 MHz): δ 29.8.

HRMS (ESI, MeOH): calcd. for $\text{C}_{26}\text{H}_{26}\text{NNaO}_4\text{P}^+$ $[\text{M}+\text{Na}]^+$ 470.14917, found 470.14950.

7.5.3 Synthesis and Characterisation of 257

N-(2-Methoxyphenyl)-1-phenylethan-1-imine 257



Prepared according to a literature procedure.²³³ 4 Å Molecular sieves (16 g) were put into an oven-dried flash and three vacuum/Ar cycles were performed. Toluene (20 mL), acetophenone

(2.33 mL, 20 mmol, 1 equiv) and *o*-anisidine (2.26 mL, 20 mmol, 1 equiv) were added in sequence. The reaction mixture was stirred at room temperature for 48 hours and then filtered to remove the MS washing with CH₂Cl₂. The filtrate was evaporated. The residue was crystallised from pentane at –15 °C, and then again from diethyl ether at –15 °C. Compound **257** (1.91 g, 42%) was obtained as a yellow solid.

Data match those given in the literature.²³³

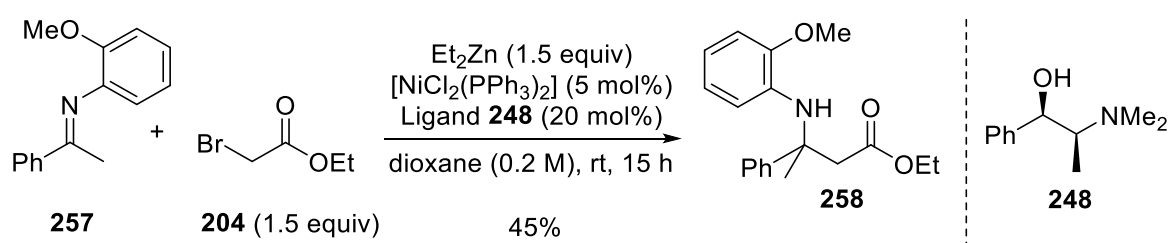
M.p.: 47–48 °C (lit: 48.0–48.5 °C).²³³

¹H NMR (400 MHz, CDCl₃): δ 8.08–8.05 (m, 2H, C_{Ph}H_{ortho}), 7.50–7.46 (m, 3H, C_{Ph}H_{meta} and C_{Ph}H_{para}), 7.12 (td, *J* = 8.0, 2.0 Hz, 1H, NC_{Ar}C_{Ar}HC_{Ar}H), 7.02 (td, *J* = 7.5, 1.5 Hz, 1H, MeOC_{Ar}C_{Ar}HC_{Ar}H), 6.97 (dd, *J* = 8.0, 1.5 Hz, 1H, NC_{Ar}C_{Ar}H), 6.84 (dd, *J* = 7.5, 2.0 Hz, 1H, MeOC_{Ar}C_{Ar}H), 3.81 (s, 3H, OCH₃), 2.22 (s, 3H, CCH₃).

¹³C NMR (100 MHz, CDCl₃): δ 167.0 (C=N), 148.9 (OC_{Ar}), 140.6 (C_{Ar}), 139.4 (C_{Ar}), 130.4 (C_{Ar}H), 128.3 (C_{Ar}H), 127.3 (C_{Ar}H), 124.2 (C_{Ar}H), 120.9 (C_{Ar}H), 120.6 (C_{Ar}H), 111.6 (C_{Ar}H), 55.6 (OCH₃), 17.8 (CCH₃).

7.5.4 Synthesis and Characterisation of **258**

Ethyl 3-(2-methoxyanilino)-3-phenylbutanoate **258**



Ketimine **257** (45 mg, 0.2 mmol, 1 equiv), [NiCl₂(PPh₃)₂] (6.5 mg, 0.01 mmol, 0.05 equiv) and (1*R*,2*S*)-(-)-*N*-methylephedrine **248** (7.2 mg, 0.04 mmol, 0.2 equiv) were put into an oven-dried flash and three vacuum/Ar cycles were performed. Dioxane (1 mL) was added and to the resultant stirred solution ethyl bromoacetate (33 μL, 0.3 mmol, 1.5 equiv) and then diethylzinc

(0.3 mL of a 1 M solution in hexanes, 0.3 mmol, 1.5 equiv) were added in sequence. The reaction mixture was stirred at room temperature for 15 hours, quenched by addition of 1 M HCl (5 mL). Et₂O (20 mL) was added, phases separated and the aqueous layer was extracted again with Et₂O (2 × 20 mL). The combined organic phases were dried over Na₂SO₄, filtered and evaporated. The crude residue was purified by FCC (PE:Et₂O 98:2 to 90:10), obtaining compound **258** (28.2 mg, 45%) as a yellow oil.

Enantiomeric excess of the product (3%) was determined by HPLC: Chiralpak OJ column, hexane/*i*-PrOH 90:10, flow 1.0 mL/min, λ 220 nm, t (minor) = 10.5 min, t (major) = 16.8 min. IR: 3403 (w), 2980 (m), 2927 (m), 1729 (s, C=O), 1602 (m), 1514 (s), 1492 (m), 1254 (s), 1226 (s), 1029 (s), 739 (m), 701 (m) cm⁻¹.

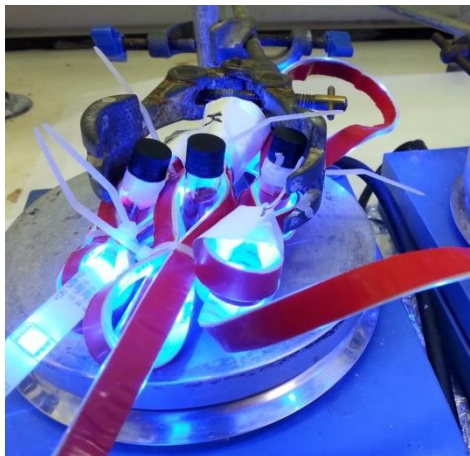
¹H NMR (CDCl₃, 500 MHz): δ 7.50 (d, *J* = 7.5 Hz, 2H, C_{Ph}H_{ortho}), 7.33 (t, *J* = 7.5 Hz, 3H, C_{Ph}H_{meta}), 7.24 (t, *J* = 7.5 Hz, 1H, C_{Ph}H_{para}), 6.77 (dd, *J* = 8.0, 1.5 Hz, 1H, NC_{Ar}C_{Ar}H), 6.58 (td, *J* = 8.0, 2.0 Hz, 1H, NC_{Ar}C_{Ar}HC_{Ar}H), 6.52 (td, *J* = 8.0, 1.5 Hz, 1H, MeOC_{Ar}C_{Ar}HC_{Ar}H), 5.96 (dd, *J* = 8.0, 2.0 Hz, 1H, MeOC_{Ar}C_{Ar}H), 5.70 (br s, 1H, NH), 4.10 (q, *J* = 7.0 Hz, 2H, OCH₂CH₃), 3.91 (s, 3H, OCH₃), 2.95 (d, *J* = 14.0 Hz, 1H, CH_AH_BCO), 2.76 (d, *J* = 14.0 Hz, 1H, CH_AH_BCO), 1.79 (s, 3H, CCH₃), 1.19 (t, *J* = 7.0 Hz, 3H, OCH₂CH₃).

¹³C NMR (CDCl₃, 126 MHz): δ 171.0 (C=O), 147.8 (OC_{Ar}), 146.1 (CC_{Ar}), 135.5 (NC_{Ar}), 128.8 (C_{Ph}H_{meta}), 126.9 (C_{Ph}H_{para}), 125.8 (C_{Ph}H_{ortho}), 120.5 (OC_{Ar}C_{Ar}HC_{Ar}H), 116.6 (NC_{Ar}C_{Ar}HC_{Ar}H), 114.0 (OC_{Ar}C_{Ar}H), 109.7 (NC_{Ar}C_{Ar}H), 60.7 (OCH₂CH₃), 57.2 (CCH₃), 55.8 (OCH₃), 48.3 (CH₂CO), 25.4 (CCH₃), 14.2 (OCH₂CH₃).

HRMS (ESI, MeOH): calcd. for C₁₉H₂₄NO₃⁺ [M+H]⁺ 314.17507, found 314.17508.

7.6 Photoredox-Catalysed α -Alkylation of *N*-DPP Ketimines

7.6.1 General Remarks



Photoredox reactions were run using Tingkam waterproof strip RGB 150 LEDs 30 W output set on blue light at maximum intensity. Five LED lights (1 W total output) were wrapped around each vial on a stir plate (see picture), then the setup was covered with Al foil.

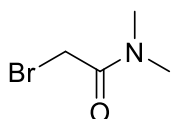
Bulk solutions were evaporated using a Büchi rotary evaporator under reduced pressure keeping the

temperature below 30 °C.

7.6.2 Synthesis of Starting Materials

N-Diphenylsphinoyl ketimines **5a–5i** were prepared from the corresponding ketones *via* the oximes according to General Procedure **III**.

2-Bromo-*N,N*-dimethylacetamide

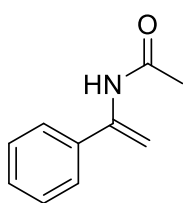


Prepared by Antonia Rinaldi under the supervision of A.F.. To a solution of 2-bromoacetyl bromide (1.7 mL, 20 mmol, 1 equiv) in CH₂Cl₂ (35 mL), dimethylammonium chloride (2.44 g, 30 mmol, 1.5 equiv) was added. The suspension was cooled to 0 °C and trimethylamine (4.88 mL, 35 mmol, 1.75 equiv) was added dropwise over 10 minutes. The reaction was stirred overnight, allowing to warm up to room temperature, then filtered. The filtrate was evaporated and the crude was purified by flash column chromatography (Et₂O) to give the title compound as a yellow oil in 32% yield (1.04 g). Spectroscopic data match those given in the literature.²⁹⁸

^1H NMR (CDCl_3 , 400 MHz): δ 3.92 (s, 2H, CH_2), 3.10 (s, 3H, CH_3), 2.99 (s, 3H, CH_3).

^{13}C NMR (CDCl_3 , 100 MHz): δ 166.8 ($\text{C}=\text{O}$), 38.4 (CH_3), 36.2 (CH_3), 26.3 (CH_2).

N-(1-Phenylethenyl)acetamide **319**



Prepared by Antonia Rinaldi under the supervision of A.F. *via* the corresponding oxime according to a literature procedure.²⁹⁹ To a solution of NaOAc (12.3 g, 150 mmol, 1.5 equiv) and $\text{NH}_2\text{OH}\cdot\text{HCl}$ (10.4 g, 150 mmol, 1.5 equiv) in EtOH/ H_2O (1:1, 100 mL), acetophenone (11.7 mL, 100 mmol, 1.0 equiv) was added at room temperature, then the reaction mixture was refluxed overnight. EtOH was removed *in vacuo* and the aqueous solution was cooled to room temperature, then to 0 °C until precipitation of an off-white solid was observed. The solid was collected on Buchner. (*E*)-1-phenylethan-1-one oxime was obtained in 90% yield as an off-white solid (12.1 g).

To a solution of the oxime (5.0 g, 37 mmol, 1 equiv) in toluene (55 mL), Ac_2O (10.5 mL, 111 mmol, 3 equiv), AcOH (6.3 mL, 111 mmol, 3 equiv), Fe (4.3 g, 78 mmol, 2.1 equiv, Aldrich-325 mesh) and a few drops of TMSCl were added. After stirring at 70 °C for 15 hours, the mixture was cooled to room temperature and filtered over Celite, washing with toluene (2×30 mL). The filtrate was washed with 2 M NaOH (2×110 mL), dried over MgSO_4 , filtered and evaporated under reduced pressure. The crude was purified by flash column chromatography (PE:AcOEt 8:2 to 6:4), affording compound **319** as an orange solid in 36% yield (2.15 g).

Characterisation data match those given in the literature.³⁰⁰

M.p.: 83–84 °C (lit: 89–90 °C).³⁰⁰

^1H NMR (400 MHz, CDCl_3): δ 8.29 (s, broad, NH), 7.37–7.27 (m, 5H, $\text{C}_{\text{Ar}}\text{H}$), 5.59 (s, 1H, $\text{N}=\text{CH}$), 5.04 (s, 1H, $\text{N}=\text{CH}$), 1.84 (s, 3H, CH_3).

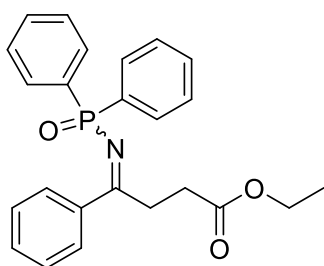
LRMS (ESI, MeOH): calcd. for $\text{C}_{10}\text{H}_{11}\text{NNaO}^+$ $[\text{M}+\text{Na}]^+$ 184.1, found 184.2.

7.6.3 Synthesis and Characterisation of α -Alkylated Ketimines

General Procedure VI for the α -alkylation of ketimines

Ketimine **5** (0.2 mmol, 1 equiv), [Ru(bpy)₃]Cl₂·H₂O (7.5 mg, 0.01 mmol, 0.05 equiv) and [NiCl₂(PPh₃)₂] (6.5 mg, 0.01 mmol, 0.05 equiv) were put into an oven dried vial equipped with a magnetic stir bar and a pierceable cap. After 3 vacuum/Ar cycles, dried DMF (1 mL), then either DIPEA (70 μ L, 0.4 mmol, 2 equiv) or triethanolamine (60 μ L, 0.4 mmol, 2 equiv) and finally ethyl bromoacetate (45 μ L, 0.4 mmol, 2 equiv) were added under argon. The pierced cap was quickly replaced with a new one under a stream of inert gas and the vial wrapped with the blue LEDs strips, so that 5 LED lights (0.2 mW each, $\lambda_{\text{max}} \sim 460$ nm) were in contact with the vial (see Paragraph 7.6.1). After stirring for 20 hours, the solution was diluted with 20 mL of Et₂O and washed with aqueous 5%_{w/w} LiCl solution (3 $\times$ 10 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was analysed by ¹H and ³¹P NMR, using mesitylene as internal standard (28 μ L, 0.2 mmol, 1 equiv), then purified by flash column chromatography. Ketimines were obtained as a mixture of *E* and *Z* isomers rapidly interconverting at room temperature at the NMR time scale, so that only one set of signals was observed (see Section 1.1.3).

Ethyl-4-[(diphenylphosphoryl)imino]-4-phenylbutanoate **245a**



Prepared according to General Procedure **VI** using ketimine **5a** and ethyl bromoacetate as substrates, and DIPEA as a base. Purified by FCC (Et₂O to Et₂O/acetone 9:1) obtaining **245a** as a yellow oil in 45% yield (38.1 mg).

IR: 3058 (w), 2981 (w), 1731 (s, C=O), 1634 (s, C=N), 1438 (m), 1201 (s), 1121 (m), 1107 (m), 725 (s), 696 (s) cm⁻¹.

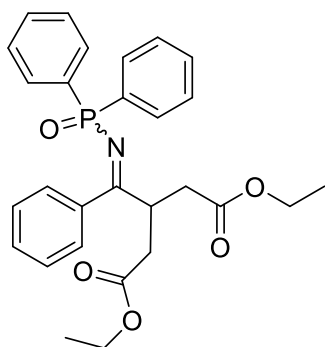
^1H NMR (CDCl_3 , 400 MHz): δ 8.02–7.94 (m, 6H), 7.53 (tt, $J = 7.5, 1.5$ Hz, 1H, $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 7.48–7.40 (m, 8H), 4.04 (q, $J = 7.0$ Hz, 2H, OCH_2CH_3), 3.65 (dt, $^4J_{\text{HP}} = 1.0$ Hz, $^3J_{\text{HH}} = 8.0$ Hz, 2H, $\text{N}=\text{CCH}_2$), 2.67 (t, $^3J_{\text{HH}} = 8.0$ Hz, 2H, $\text{N}=\text{CCH}_2\text{CH}_2$), 1.17 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3).

^{13}C NMR (CDCl_3 , 126 MHz): δ 184.0 (d, $^2J_{\text{PC}} = 8.0$ Hz, $\text{C}=\text{N}$), 172.0 (COOEt), 138.2 (d, $^3J_{\text{PC}} = 22.5$ Hz, $\text{N}=\text{CC}_{\text{Ar}}$), 134.7 (d, $^1J_{\text{PC}} = 131.0$ Hz, PC_{Ar}), 132.4 ($\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 131.7 (d, $^3J_{\text{PC}} = 9.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 131.6 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 128.8 ($\text{C}_{\text{Ar}}\text{H}$), 128.6 (d, $^2J_{\text{PC}} = 12.5$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$), 128.2 ($\text{C}_{\text{Ar}}\text{H}$), 60.8 (OCH_2CH_3), 32.6 (CH_2COOEt), 31.5 (d, $^3J_{\text{PC}} = 13.0$ Hz, NCCCH_2), 14.2 (CH_3).

^{31}P NMR (CDCl_3 , 162 MHz): δ 18.1.

HRMS (ESI, MeOH): calcd for $\text{C}_{24}\text{H}_{25}\text{O}_3\text{NP}^+ [\text{M}+\text{H}]^+$ 406.15666, found 406.15668.

Diethyl-3-[(diphenylphosphoryl)imino](phenyl)methyl] pentanedioate **314**



Obtained as a side product following General Procedure **VI** using ketimine **5a** and ethyl bromoacetate as substrates, and TEOA as a base. Purified by FCC (Et_2O to Et_2O /acetone 9:1) obtaining **314** as a yellow oil in 20% yield (19.7 mg).

IR: 2957 (w), 2924 (w), 2854 (w), 1731 (s, $\text{C}=\text{O}$), 1638 (m, $\text{C}=\text{N}$),

1438 (w), 1373 (w), 1203 (m), 1121 (w), 1107 (w), 1027 (w), 753 (w), 725 (m), 697 (m) cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): δ 7.78 (ddd, $J = 12.0, 8.5, 1.5$ Hz, 4H, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 7.61 (d, $J = 7.0$ Hz, 2H, $\text{C}_{\text{Ar}}\text{H}$), 7.48–7.30 (m, 9H, $\text{C}_{\text{Ar}}\text{H}$), 4.02 (m, 1H, NCCCH), 3.92 (dq, $J = 17.5, 7.0$ Hz, 4H, OCH_2CH_3), 2.97 (dd, $J = 16.5, 7.5$ Hz, 2H, $\text{N}=\text{CCH}(\text{CH}_\text{A}\text{H}_\text{B})_2$), 2.65 (dd, $J = 16.5, 6.5$ Hz, 2H, $\text{N}=\text{CCH}(\text{CH}_\text{A}\text{H}_\text{B})_2$), 1.11 (t, $J = 7.0$ Hz, 6H, OCH_2CH_3).

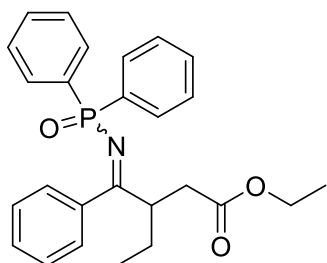
^{13}C NMR (CDCl_3 , 126 MHz): δ 189.2 (d, $^2J_{\text{PC}} = 10.0$ Hz, $\text{C}=\text{N}$), 171.7 ($\text{C}=\text{O}$), 139.0 (d, $^3J_{\text{PC}} = 13.5$ Hz, $\text{N}=\text{CC}_{\text{Ar}}$), 134.3 (d, $^1J_{\text{PC}} = 130.5$ Hz, PC_{Ar}), 132.5 ($\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 131.7 (d, $^3J_{\text{PC}} = 9.5$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 131.4 (d, $^4J_{\text{PC}} = 2.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 130.9 ($\text{C}_{\text{Ar}}\text{H}$), 128.2 (d, $^2J_{\text{PC}} = 12.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$),

128.1 ($\underline{\text{C}}_{\text{ArH}}$), 60.9 (OCH_2CH_3), 43.2 (d, $^3J_{\text{PC}} = 17.5$ Hz, NCCH), 36.8 (CHCH_2CO), 14.2 (OCH_2CH_3).

^{31}P NMR (CDCl_3 , 162 MHz): δ 16.7.

HRMS (ESI, MeOH): calcd. for $\text{C}_{28}\text{H}_{30}\text{O}_5\text{N}_3\text{NaP}^+ [\text{M}+\text{Na}]^+$ 514.17538, found 514.17537.

Ethyl-3-[[[(diphenylphosphoryl)imino](phenyl)methyl] pentanoate **245b**



Prepared according to General Procedure **VI** using the corresponding ketimine and ethyl bromoacetate as substrates, and DIPEA as a base. Purified by FCC ($\text{Et}_2\text{O}/\text{PE}$ 9:1) obtaining **245b** as a yellow oil in 36% yield (31.2 mg).

IR: 3058 (w), 2963 (w), 2929 (w), 1731 (s, $\text{C}=\text{O}$), 1640 (m, $\text{C}=\text{N}$), 1438 (m), 1182 (s), 1122 (m), 1029 (w), 724 (m), 697 (s) cm^{-1} .

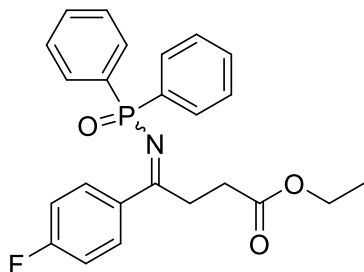
^1H NMR (CDCl_3 , 400 MHz): δ 7.92 (ddd, $J = 12.0, 8.0, 1.5$ Hz, 2H, $\text{C}_{\text{ArH}}\underline{\text{H}}_{\text{meta}}$), 7.69 (ddd, $J = 12.0, 7.5, 1.0$ Hz, 2H, $\text{C}_{\text{ArH}}\underline{\text{H}}_{\text{meta}}$), 7.58–7.55 (m, 2H, C_{ArH}), 7.45–7.28 (m, 9H, C_{ArH}), 3.94 (qd, $J = 11.0, 7.0$ Hz, 1H, $\text{OCH}_\text{A}\underline{\text{H}}_\text{B}\text{CH}_3$), 3.84 (qd, $J = 11.0, 7.0$ Hz, 1H, $\text{OCH}_\text{A}\underline{\text{H}}_\text{B}\text{CH}_3$), 3.59–3.52 (m, 1H, NCCH), 3.21 (dd, $J = 17.0, 10.0$ Hz, 1H, $\text{CH}_\text{A}\underline{\text{H}}_\text{B}\text{CO}$), 2.63 (dd, $J = 17.0, 4.5$ Hz, 1H, $\text{CH}_\text{A}\underline{\text{H}}_\text{B}\text{CO}$), 1.84–1.72 (m, 1H, $\text{CHCH}_\text{A}\underline{\text{H}}_\text{B}\text{CH}_3$), 1.61–1.53 (m, 1H, $\text{CHCH}_\text{A}\underline{\text{H}}_\text{B}\text{CH}_3$), 1.09 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3), 0.79 (t, $J = 7.5$ Hz, 3H, CHCH_2CH_3).

^{13}C NMR (CDCl_3 , 100 MHz): δ 191.1 (d, $^2J_{\text{PC}} = 10.5$ Hz, $\underline{\text{C}}=\text{N}$), 172.7 ($\underline{\text{C}}=\text{O}$), 140.1 (d, $^3J_{\text{PC}} = 14.5$ Hz, $\text{N}=\underline{\text{C}}_{\text{Ar}}$), 135.4 (d, $^1J_{\text{PC}} = 134.0$ Hz, $\text{P}\underline{\text{C}}_{\text{Ar}}$), 134.2 (d, $^1J_{\text{PC}} = 133.5$ Hz, $\text{P}\underline{\text{C}}_{\text{Ar}}$), 131.8 (d, $^3J_{\text{PC}} = 9.0$ Hz, $\underline{\text{C}}_{\text{ArH}}\text{meta}$), 131.7 (d, $^3J_{\text{PC}} = 9.1$ Hz, $\underline{\text{C}}_{\text{ArH}}\text{meta}$), 131.4 (d, $^4J_{\text{PC}} = 2.7$ Hz, $\underline{\text{C}}_{\text{ArH}}\text{para}$), 131.1 (d, $^4J_{\text{PC}} = 2.8$ Hz, $\underline{\text{C}}_{\text{ArH}}\text{para}$), 130.6 ($\underline{\text{C}}_{\text{ArH}}\text{para}$), 128.4 (d, $^2J_{\text{PC}} = 12.6$ Hz, $\underline{\text{C}}_{\text{ArH}}\text{ortho}$), 128.2 (d, $^2J_{\text{PC}} = 12.6$ Hz, $\underline{\text{C}}_{\text{ArH}}\text{ortho}$), 128.0 ($\underline{\text{C}}_{\text{Ar}}$), 127.9 ($\underline{\text{C}}_{\text{Ar}}$), 60.6 (OCH_2CH_3), 48.8 (d, $^3J_{\text{PC}} = 16.6$ Hz, NCCH), 36.6 (CHCH_2CO), 26.2 (CHCH_2CH_3), 14.2 (OCH_2CH_3), 11.6 (CHCH_2CH_3).

^{31}P NMR (CDCl_3 , 162 MHz): δ 16.0.

HRMS (ESI, MeOH): calcd for $\text{C}_{26}\text{H}_{29}\text{O}_3\text{NP}^+$ $[\text{M}+\text{H}]^+$ 434.18796, found 434.18791.

Ethyl-4-[(diphenylphosphoryl)imino]-4-(4-fluorophenyl) butanoate **245c**



Prepared by Antonia Rinaldi according to General Procedure **VI** using the corresponding ketimine and ethyl bromoacetate as substrates, and DIPEA as a base. Purified by FCC (Et_2O) obtaining **245c** as a yellow oil in 36% yield (30.5 mg).

IR: 3058 (w), 1731 (s, C=O), 1631 (s, C=N), 1588 (s), 1372 (m), 1235 (m), 1202 (s), 1156 (s), 1122 (m), 1106 (m), 725 (s), 696 (s) cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): δ 8.03 (dd, $^3J_{\text{ortho}} = 9.0$ Hz, $^4J_{\text{HF}} = 5.5$ Hz, 2H, $\text{FCCHC}_{\text{ArH}}$), 7.97–7.92 (m, 4H, $\text{C}_{\text{ArHmeta}}$), 7.49–7.41 (m, 6H, $\text{C}_{\text{ArHortho}}$ and $\text{C}_{\text{ArHpara}}$), 7.16 (app t, $^3J_{\text{HF}} = ^3J_{\text{ortho}} = 8.5$ Hz, 2H, FCC_{ArH}), 4.05 (q, $J = 7.0$ Hz, 2H, OCH_2CH_3), 3.65 (dt, $^4J_{\text{HP}} = 1.0$ Hz, $^3J_{\text{HH}} = 8.0$ Hz, 2H, $\text{N}=\text{CCH}_2$), 2.68 (t, $^3J_{\text{HH}} = 8.0$ Hz, 2H, $\text{N}=\text{CCH}_2\text{CH}_2$), 1.17 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3).

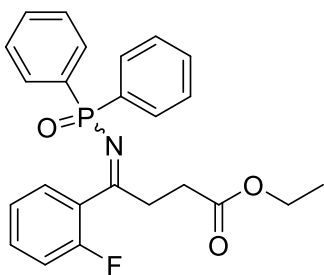
^{13}C NMR (CDCl_3 , 126 MHz): δ 182.6 (d, $^2J_{\text{PC}} = 7.5$ Hz, CN), 172.0 (COOEt), 165.5 (d, $^1J_{\text{CF}} = 254.0$ Hz, CF), 134.6 (d, $^1J_{\text{PC}} = 131.0$ Hz, PC_{Ar}), 134.5 (dd, $^3J_{\text{PC}} = 22.5$ Hz, $^4J_{\text{CF}} = 3.0$ Hz, $\text{N}=\text{CC}_{\text{Ar}}$), 131.7 (d, $^3J_{\text{PC}} = 9.0$ Hz, $\text{C}_{\text{ArHmeta}}$), 131.6 ($\text{C}_{\text{ArHpara}}$), 130.8 (d, $^3J_{\text{CF}} = 9.0$ Hz, $\text{FCCHC}_{\text{ArH}}$), 128.6 (d, $^2J_{\text{PC}} = 12.5$ Hz, $\text{C}_{\text{ArHortho}}$), 128.2 (C_{ArH}), 115.9 (d, $^2J_{\text{CF}} = 22.0$ Hz, FCC_{ArH}), 60.9 (OCH_2), 32.5 ($\text{N}=\text{CCH}_2\text{CH}_2$), 31.0 (d, $J = 12.5$ Hz, $\text{N}=\text{CCH}_2$), 14.2 (OCH_2CH_3).

^{31}P NMR (CDCl_3 , 162 MHz): δ 18.2.

^{19}F NMR (CDCl_3 , 376 MHz): δ -106.6.

HRMS (ESI, MeOH): calcd. for $\text{C}_{24}\text{H}_{24}\text{O}_3\text{NFP}^+$ $[\text{M}+\text{H}]^+$ 424.14723, found 424.14703.

Ethyl-4-[(diphenylphosphoryl)imino]-4-(2-fluorophenyl)butanoate **245d**



Prepared by Antonia Rinaldi according General Procedure **VI** using the corresponding ketimine and ethyl bromoacetate as substrates, and DIPEA as a base. Purified by FCC (Et₂O) obtaining **245d** as a yellow oil in 32% yield (27.1 mg). Characterised as a 1:0.6:0.6 mixture of ketimine:*E*-enamine:*Z*-enamine.

IR: 3059 (w), 2981 (w), 1731 (s, C=O), 1649 (m, C=N), 1449 (m), 1204 (s), 1121 (s), 1107 (m), 755 (m), 725 (s), 697 (s) cm⁻¹.

¹H NMR (CDCl₃, 500 MHz, data for the ketimine tautomer): δ 7.97–7.92 (app ddt, *J* = 12.0, 7.0, 1.5 Hz, 2H, C_{Ar}H_{meta}), 7.47–7.33 (m, 8H, C_{Ar}H_{ortho}, C_{Ar}H_{para} and C_{Ar}H), 7.18–7.14 (m, 2H, C_{Ar}H), 4.03 (q, *J* = 7.0 Hz, 2H, OCH₂CH₃), 3.40–3.37 (m, 2H, N=CCH₂), 2.76 (t, *J* = 7.0 Hz, 2H, N=CCH₂CH₂), 1.16 (t, *J* = 7.0 Hz, 3H, OCH₂CH₃).

Data for the enamine tautomer 1 (configuration not determined): δ 7.94 (ddd, *J* = 12.5, 8.5, 1.5 Hz, 4H, C_{Ar}H_{meta}), 7.53–7.29 (m, 8H, C_{Ar}H_{ortho}, C_{Ar}H_{para} and C_{Ar}FH), 7.13–7.01 (m, 1H, C_{Ar}FH), 6.90 (td, *J* = 7.5, 1.2 Hz, 1H, C_{Ar}FH), 5.58 (td, ³*J*_{HH} = 7.5 Hz, ⁴*J*_{PH} = 1.0 Hz, 1H, NHC=CH), 4.65 (d, ²*J*_{PH} = 9.0 Hz, 1H, NH), 3.93 (d, *J* = 7.0 Hz, 2H, OCH₂CH₃), 2.75 (t, ³*J*_{HH} = 7.5 Hz, 2H, C=CHCH₂), 1.10 (t, *J* = 7.0 Hz, 3H, OCH₂CH₃).

Data for the enamine tautomer 2 (configuration not determined): δ 7.78 (ddd, *J* = 12.0, 8.5, 1.5 Hz, 4H, C_{Ar}H_{meta}), 7.53–7.29 (m, 8H, C_{Ar}H_{ortho}, C_{Ar}H_{para} and C_{Ar}FH), 7.13–7.01 (m, 1H, C_{Ar}FH), 6.76 (ddd, *J* = 10.5, 8.0, 1.0 Hz, 1H, C_{Ar}FH), 5.91 (d, ²*J*_{PH} = 7.5 Hz, 1H, NH), 5.23 (t, *J* = 7.5 Hz, 1H, NHC=CH), 4.14 (d, *J* = 7.0 Hz, 2H, OCH₂CH₃), 3.40–3.37 (m, 2H, C=CHCH₂), 1.24 (t, *J* = 7.0 Hz, 3H, OCH₂CH₃).

¹³C NMR (CDCl₃, 126 MHz, data for the ketimine tautomer): δ 182.6 (d, ²*J*_{PC} = 9.5 Hz, C_N), 172.3 (COOEt), 159.3 (d, ¹*J*_{CF} = 250.0 Hz, CF), 134.1 (d, ¹*J*_{PC} = 130.5 Hz, PC_{Ar}), 132.3 (d, ³*J*_{FC}

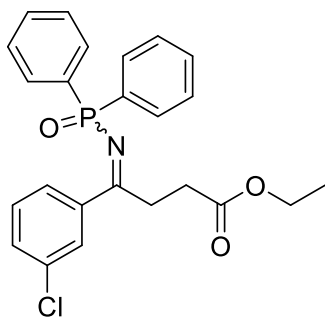
= 9.0 Hz, $\underline{\text{C}}_{\text{ArF}}\text{H}$), 131.7 (d, $^3J_{\text{PC}} = 9.0$ Hz, $\underline{\text{C}}_{\text{ArH}}\text{meta}$), 131.6 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\underline{\text{C}}_{\text{ArH}}\text{para}$), 130.1 (d, $^3J_{\text{CF}} = 8.5$ Hz, $\underline{\text{C}}_{\text{ArF}}\text{H}$), 128.5 (d, $^2J_{\text{PC}} = 13.0$ Hz, $\underline{\text{C}}_{\text{ArH}}\text{ortho}$), 126.5 (dd, $^2J_{\text{CF}} = 13.0$ Hz, $^3J_{\text{PC}} = 3.0$ Hz, FCC_{Ar}), 124.2 (d, $^4J_{\text{CF}} = 3.0$ Hz, $\underline{\text{C}}_{\text{ArF}}\text{H}$), 115.3 (d, $^2J_{\text{CF}} = 22.0$ Hz, $\text{FCC}_{\text{Ar}}\text{H}$), 60.9 (OCH_2), 37.1 (d, $^3J_{\text{PC}} = 16.5$ Hz, $^4J_{\text{CF}} = 3.5$ Hz, $\text{N}=\text{CCH}_2$), 30.9 ($\text{N}=\text{CCH}_2\text{CH}_2$), 14.2 (OCH_2CH_3).

^{31}P NMR (CDCl_3 , 162 MHz): δ 17.7 (ketimine form), 17.6 and 17.4 (enamines).

^{19}F NMR (CDCl_3 , 376 MHz): δ -113.1 (ketimine form), -131.0 and -113.9 (enamines).

HRMS (ESI, MeOH): calcd. for $\text{C}_{24}\text{H}_{24}\text{O}_3\text{NFP}^+$ $[\text{M}+\text{H}]^+$ 424.14723, found 424.14703.

Ethyl-4-[(diphenylphosphoryl)imino]-4-(3-chlorophenyl) butanoate **245e**



Prepared by Antonia Rinaldi according to General Procedure **VI** using the corresponding ketimine and ethyl bromoacetate as substrates, and DIPEA as a base. Purified by FCC ($\text{Et}_2\text{O}/\text{PE}$ 1:9 to Et_2O) obtaining **245e** as a yellow oil in 33% yield (29.0 mg).

Characterised as a 1:0.5:0.3 mixture of ketimine:enamine:enamine,

NMR data are given for the ketimine tautomer.

IR: 3058 (w), 2980 (w), 1731 (s, $\text{C}=\text{O}$), 1632 (m, $\text{C}=\text{N}$), 1565 (w), 1438 (m), 1187 (s), 1180 (s) 1122 (m), 1106 (m), 725 (s), 695 (s) cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): δ 7.92–7.96 (m, 4H, $\text{C}_{\text{ArH}}\text{meta}$), 7.50–7.30 (m, 10H, C_{ArH}), 4.05 (q, $J = 7.0$ Hz, 2H, OCH_2CH_3), 3.60 (td, $^3J_{\text{HH}} = 8.0$ Hz, $^4J_{\text{HP}} = 1.0$ Hz, 2H, $\text{N}=\text{CCH}_2$), 2.66 (t, $J = 8.0$ Hz, 2H, $\text{N}=\text{CCH}_2\text{CH}_2$), 1.17 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3).

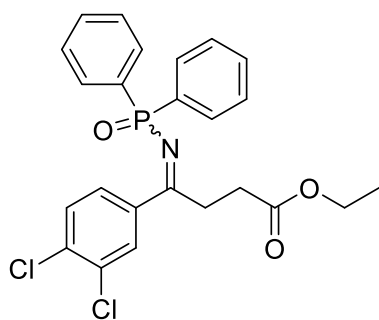
^{13}C NMR (CDCl_3 , 126 MHz): δ 182.6 (d, $^2J_{\text{PC}} = 8.0$ Hz, $\text{C}=\text{N}$), 171.8 (COOEt), 140.0 (d, $^3J_{\text{PC}} = 22.5$ Hz, $\text{N}=\text{CC}_{\text{Ar}}$), 134.9 (CCl), 134.2 (d, $^1J_{\text{PC}} = 131.0$ Hz, PC_{Ar}), 132.1 ($\text{C}_{\text{ArCl}}\text{H}$), 131.6 (d, $^3J_{\text{PC}} = 9.0$ Hz, $\text{C}_{\text{ArH}}\text{meta}$), 131.6 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\text{C}_{\text{ArH}}\text{para}$), 130.0 ($\text{C}_{\text{ArCl}}\text{H}$), 128.8 (C_{ArH}), 128.6

(d, $^2J_{PC} = 12.5$ Hz, $\underline{C}_{ArH_{ortho}}$), 128.1 ($\underline{C}_{ArClH}$), 126.1 ($\underline{C}_{ArClH}$), 60.9 ($O\underline{C}H_2CH_3$), 32.3 ($\underline{C}H_2COOEt$), 31.6 (d, $^3J_{PC} = 12.5$ Hz, $N\underline{C}CH_2$), 14.1 ($\underline{C}H_3$).

^{31}P NMR ($CDCl_3$, 162 MHz): δ 18.6.

HRMS (ESI, MeOH): calcd. for $C_{24}H_{24}O_3N^{35}ClP^+ [M+H]^+$ 440.11768, found 440.11789.

Ethyl-4-(3,4-dichlorophenyl)-4-[(diphenylphosphoryl)imino] butanoate **245f**



Prepared by Antonia Rinaldi according to General Procedure **VI** using the corresponding ketimine and ethyl bromoacetate as substrates, and DIPEA as a base. Purified by FCC (Et_2O/PE 1:9 to Et_2O) obtaining **245f** as a yellow oil in 26% yield (24.7 mg).

Characterised as a 1:0.5:0.3 mixture of ketimine:enamine:enamine, NMR data are given for the ketimine tautomer.

IR: 1733 (s, $C=O$), 1640 (m, $C=N$), 1438 (m), 1208 (m), 1106 (m), 1029 (m), 726 (m), 696 (m) cm^{-1}

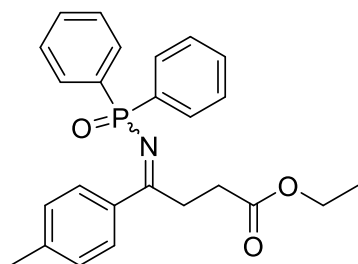
^1H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, $^3J_{meta} = 2.0$ Hz, 1H, C_{ArClH}), 7.93 (ddd, $J = 12.0, 8.0, 1.6$ Hz, 4H, $C_{ArH_{meta}}$), 7.76 (m, 1H, C_{ArClH}), 7.50–7.36 (m, 7H, $C_{ArH_{ortho}}$, $C_{ArH_{para}}$ and C_{ArClH}), 4.05 (q, $J = 7.0$ Hz, 2H, $O\underline{C}H_2CH_3$), 3.58 (td, $^3J_{HH} = 8.0$ Hz, $^4J_{HP} = 1.5$ Hz, 2H, $N=C\underline{C}H_2$), 2.67 (t, $J = 8.0$ Hz, 2H, $N=C\underline{C}H_2CH_2$), 1.18 (t, $J = 7.0$ Hz, 3H, $OCH_2\underline{C}H_3$).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 181.7 (d, $^2J_{PC} = 7.5$ Hz, $\underline{C}=N$), 171.9 ($\underline{C}OOEt$), 138.4 (d, $^3J_{PC} = 23.0$ Hz, $N=C\underline{C}_{Ar}$), 136.8 ($\underline{C}Cl$), 135.9 ($\underline{C}Cl$), 134.1 (d, $^1J_{PC} = 131.0$ Hz, $P\underline{C}_{Ar}$), 131.7 (d, $^3J_{PC} = 9.0$ Hz, $\underline{C}_{ArH_{meta}}$), 132.2 (d, $^4J_{PC} = 3.5$ Hz, $\underline{C}_{ArH_{para}}$), 130.8 ($\underline{C}_{ArClH}$), 130.1 ($\underline{C}_{ArClH}$), 128.7 (d, $^2J_{PC} = 12.5$ Hz, $\underline{C}_{ArH_{ortho}}$), 127.4 ($\underline{C}_{ArClH}$), 61.0 ($O\underline{C}H_2CH_3$), 31.7 (d, $^3J_{PC} = 12.5$ Hz, $N\underline{C}CH_2$), 30.5 ($\underline{C}H_2CO_2Et$), 14.2 ($\underline{C}H_3$).

^{31}P NMR ($CDCl_3$, 162 MHz): δ 18.7

HRMS (ESI, MeOH): calcd. for $C_{24}H_{23}O_3N^{35}Cl_2P^+ [M+H]^+$ 474.07871, found 474.07867.

Ethyl-4-[(diphenylphosphoryl)imino]-4-(4-methylphenyl) butanoate **245g**



Prepared by Antonia Rinaldi according to General Procedure **VI** using the corresponding ketimine and ethyl bromoacetate as substrates, and DIPEA as a base. Purified by FCC (Et₂O) obtaining **245g** as a yellow oil in 36% yield (30.2 mg).

IR: 2980 (w), 1731 (s, C=O), 1630 (s, C=N), 1603 (s), 1438 (m), 1202 (s), 1182 (s), 1121 (m), 1105 (m), 724 (s), 696 (s) cm⁻¹.

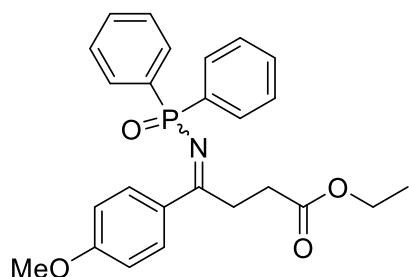
¹H NMR (CDCl₃, 500 MHz): δ 7.99 (ddd, *J* = 12.0, 8.0, 1.5 Hz, 4H, C_{Ar}H_{meta}), 7.95 (d, *J* = 8.5 Hz, 2H, C_{Ar}H), 7.49–7.42 (m, 6H, C_{Ar}H_{ortho} and C_{Ar}H_{para}), 7.29 (d, *J* = 8.0 Hz, 2H, C_{Ar}H), 4.07 (q, *J* = 7.0 Hz, 2H, OCH₂CH₃), 3.65 (t, *J* = 8.0 Hz, 2H, N=CCH₂), 2.68 (t, *J* = 8.0 Hz, 2H, N=CCH₂CH₂), 2.44 (s, 3H, CH₃), 1.20 (t, *J* = 7.0 Hz, 3H, OCH₂CH₃).

¹³C NMR (CDCl₃, 126 MHz): δ 183.8 (d, ²*J*_{PC} = 8.0 Hz, C=N), 172.2 (COOEt), 143.4 (C_{Ar}CH₃), 135.5 (d, ³*J*_{PC} = 23.0 Hz, N=CC_{Ar}), 134.9 (d, ¹*J*_{PC} = 131.5 Hz, PC_{Ar}), 131.7 (d, ³*J*_{PC} = 9.0 Hz, C_{Ar}H_{meta}), 131.5 (d, ⁴*J*_{PC} = 3.0 Hz, C_{Ar}H_{para}), 129.6 (C_{Ar}H), 128.6 (d, ²*J*_{PC} = 12.5 Hz, C_{Ar}H_{ortho}), 128.5 (C_{Ar}H), 60.9 (OCH₂CH₃), 32.7 (CH₂COOEt), 31.4 (d, ³*J*_{PC} = 13.0 Hz, NCC_{Ar}), 21.7 (CCH₃), 14.2 (OCH₂CH₃).

³¹P NMR (CDCl₃, 162 MHz): δ 17.9.

HRMS (ESI, MeOH): calcd. for C₂₅H₂₇O₃NP⁺ [M+H]⁺ 420.17231, found 420.17199.

Ethyl-4-[(diphenylphosphoryl)imino]-4-(4-methoxyphenyl)butanoate **245h**



Prepared by Antonia Rinaldi according to General Procedure **VI** using the corresponding ketimine and ethyl bromoacetate as substrates, and TEOA as a base. Purified by FCC (Et₂O) obtaining **245h** as a yellow oil in 35% yield (30.5 mg).

IR: 2981 (w), 1731 (m, C=O), 1629 (m, C=N), 1596 (s), 1569 (m), 1438 (m), 1258 (m), 1201 (s), 1177 (s), 1121 (m), 1105 (m), 724 (m), 696 (m) cm^{-1} .

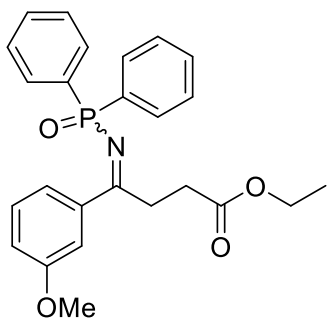
^1H NMR (CDCl_3 , 500 MHz): δ 8.05 (d, $J = 9.0$ Hz, 2H, $\text{C}_{\text{Ar}}\text{H}_{\text{COCH}_3}$), 7.96 (ddd, $J = 12.0, 8.0, 1.5$ Hz, 4H, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 7.49–7.42 (m, 6H, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$ and $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 6.96 (d, $J = 9.0$ Hz, 2H, $\text{C}_{\text{Ar}}\text{HCHCOCH}_3$), 4.05 (q, $J = 7.0$ Hz, 2H, OCH_2CH_3), 3.87 (s, 3H, OCH_3), 3.62 (td, $^3J_{\text{HH}} = 8.0$ Hz, $^4J_{\text{PH}} = 1.0$ Hz, 2H, $\text{N}=\text{CCH}_2$), 2.66 (t, $^3J_{\text{HH}} = 8.0$ Hz, 2H, $\text{N}=\text{CCH}_2\text{CH}_2$), 1.18 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3).

^{13}C NMR (CDCl_3 , 126 MHz): δ 182.7 (d, $^2J_{\text{PC}} = 7.5$ Hz, $\text{C}=\text{N}$), 172.2 (COOEt), 163.4 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 135.1 (d, $^1J_{\text{PC}} = 131.5$ Hz, PC_{Ar}), 131.7 (d, $^3J_{\text{PC}} = 9.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 131.4 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 130.8 (d, $^3J_{\text{PC}} = 25.5$ Hz, $\text{N}=\text{CC}_{\text{Ar}}$), 130.6 ($\text{C}_{\text{Ar}}\text{HCHCOCH}_3$), 128.5 (d, $^2J_{\text{PC}} = 12.5$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$), 114.1 ($\text{C}_{\text{Ar}}\text{HCOCH}_3$), 60.9 (OCH_2CH_3), 55.7 (OCH_3), 32.9 (CH_2COOEt), 31.1 (d, $^3J_{\text{PC}} = 12.5$ Hz, NCCH_2), 14.2 (OCH_2CH_3).

^{31}P NMR (CDCl_3 , 162 MHz): δ 17.7.

HRMS (ESI, MeOH): calcd. for $\text{C}_{25}\text{H}_{27}\text{O}_4\text{NP}^+$ $[\text{M}+\text{H}]^+$ 436.16722, found 436.16793.

Ethyl-4-[(diphenylphosphoryl]imino]-4-(3-methoxyphenyl) butanoate **245i**



Prepared by Antonia Rinaldi according to General Procedure **VI** using the corresponding ketimine and ethyl bromoacetate as substrates, and DIPEA as a base. Purified by FCC (Et_2O) obtaining **245i** as a yellow oil in 45% yield (39.2 mg).

IR: 2981 (w), 1731 (s, C=O), 1631 (m, C=N), 1578 (m), 1437 (m), 1203 (s), 1121 (m), 1106 (m), 1045 (m), 725 (s), 697 (m) cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): 7.96 (ddt, $J = 12.0, 6.5, 1.5$ Hz, 4H, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), δ 7.55 (d, $J = 2.0$ Hz, 1H, CCHCOCH_3), 7.53 (d, $J = 5.0$ Hz, 1H, CHCHCOCH_3), 7.49–7.40 (m, 6H, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$ and $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 7.37 (t, $J = 8.0$ Hz, 1H, CHCHCOCH_3), 7.07 (dd, $J = 8.0, 3.0$ Hz, 1 H,

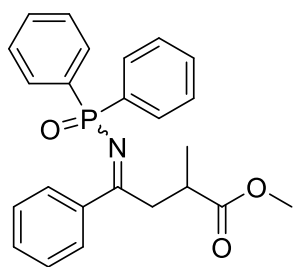
CHCHCHCOCH₃), 4.05 (q, $J = 7.0$ Hz, 2H, OCH₂CH₃), 3.86 (s, 3H, OCH₃), 3.62 (td, $^3J_{HH} = 8.0$ Hz, $^4J_{PH} = 1.0$ Hz, 2H, N=CC_H), 2.66 (t, $J = 8.0$ Hz, 2H, N=CCH₂CH₂), 1.18 (t, $J = 7.0$ Hz, 3H, OCH₂CH₃).

¹³C NMR (CDCl₃, 126 MHz): δ 183.9 (d, $^2J_{PC} = 8.0$ Hz, C=N), 172.1 (C=O), 159.9 (C_{Ar}OCH₃), 139.7 (d, $^3J_{PC} = 22.5$ Hz, N=CC_{Ar}), 134.7 (d, $^1J_{PC} = 131.0$ Hz, PC_{Ar}), 131.7 (d, $^3J_{PC} = 9.0$ Hz, C_{Ar}H_{meta}), 131.6 (d, $^4J_{PC} = 3.0$ Hz, C_{Ar}H_{para}), 129.8 (CHCHCHCOCH₃), 128.6 (d, $^2J_{PC} = 12.5$ Hz, C_{Ar}H_{ortho}), 120.8 (CHCHCOCH₃), 118.0 (CHCHCHCOCH₃), 113.8 (CC_{Ar}HCOCH₃), 60.9 (OCH₂CH₃), 55.7 (OCH₃), 32.9 (CH₂COOEt), 31.1 (d, $^3J_{PC} = 12.5$ Hz, NCCH₂), 14.2 (OCH₂CH₃).

³¹P NMR (CDCl₃, 162 MHz): δ 18.0.

HRMS (ESI, MeOH): calcd. for C₂₅H₂₇O₄NP⁺ [M+H]⁺ 436.16722, found 436.16721.

Methyl-4-[(diphenylphosphoryl)imino]-2-methyl-4-phenyl butanoate **245j**



Prepared by Antonia Rinaldi according to General Procedure **VI** using ketimine **5a** and methyl 2-bromopropionate as substrates, and DIPEA as a base. Purified by FCC (Et₂O) obtaining **245j** as a yellow oil in 45% yield (36.5 mg).

IR: 3057 (w), 2972 (w), 2951 (w), 1734 (m, C=O), 1632 (m, C=N), 1438 (m), 1280 (w), 1202 (s), 1120 (m), 1107 (m), 818 (w), 754 (w), 725 (m), 697 (m) cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ 8.04–7.93 (m, 6H), 7.55–7.41 (m, 9H), 3.65 (app dt, $J = 6.0$ Hz, $^4J_{PH} = 1.5$ Hz, 2H, NCCH₂), 3.41 (s, 3H, OCH₃), 2.98 (app sext, $J = 7.5$ Hz, 1H, CHCO), 1.14 (d, $J = 7.0$ Hz, 3H, CH₃CHCO).

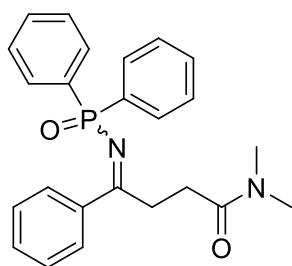
¹³C NMR (CDCl₃, 100 MHz): δ 183.5 (d, $^2J_{PC} = 8.0$ Hz, C=N), 175.5 (C=O), 138.8 (d, $^3J_{PC} = 22.5$ Hz, N=CC_{Ar}), 135.1 (d, $^1J_{PC} = 131.0$ Hz, PC_{Ar}), 134.9 (d, $^1J_{PC} = 131.5$ Hz, PC_{Ar}), 132.3 (C_{Ar}H), 131.8 (d, $^3J_{PC} = 9.0$ Hz, C_{Ar}H_{meta}), 131.5 (d, $^4J_{PC} = 2.5$ Hz, C_{Ar}H_{para}), 131.7 (d, $^3J_{PC} =$

9.0 Hz, $\underline{\text{C}}_{\text{ArH}_{\text{meta}}}$), 128.7 ($\underline{\text{C}}_{\text{ArH}}$), 128.6 (d, $^2J_{\text{PC}} = 12.5$ Hz, $\underline{\text{C}}_{\text{ArH}_{\text{ortho}}}$), 128.5 (d, $^2J_{\text{PC}} = 12.5$ Hz, $\underline{\text{C}}_{\text{ArH}_{\text{ortho}}}$), 128.3 ($\underline{\text{C}}_{\text{ArH}}$), 51.8 ($\underline{\text{OCH}}_3$), 39.3 (d, $^3J_{\text{PC}} = 12.0$ Hz, $\text{NCC}\underline{\text{H}}_2$), 39.1 ($\underline{\text{CHCH}}_3$), 16.9 ($\underline{\text{CHCH}}_3$).

^{31}P NMR (CDCl_3 , 162 MHz): δ 17.7.

HRMS (ESI, MeOH): calcd. for $\text{C}_{24}\text{H}_{25}\text{O}_3\text{NP}^+$ $[\text{M}+\text{H}]^+$ 406.15666, found 406.15629.

4-[(diphenylphosphoryl)imino]-*N,N*-dimethyl-4-phenylbutanamide **245k**



Prepared by Antonia Rinaldi according to General Procedure **VI** using ketimine **5a** and 2-bromo-*N,N*-dimethylacetamide as substrates, and TEOA as a base. Purified by FCC (AcOEt to AcOEt:MeOH 9:1) obtaining **245k** as a yellow oil in 35% yield (28.3 mg).

IR: 3436 (w), 3057 (w), 2980 (w), 1632 (s, C=N and C=O), 1438 (m), 1198 (m), 1107 (m), 725 (m), 695 (m) cm^{-1} .

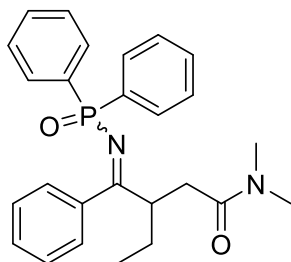
^1H NMR (CDCl_3 , 400 MHz): δ 8.13 (d, $J = 7.0$ Hz, 2H, $\underline{\text{C}}_{\text{ArH}}$), 7.96 (ddt, $J = 12.0, 8.0, 1.5$ Hz, 4H, $\underline{\text{C}}_{\text{ArH}_{\text{meta}}}$), 7.56–7.52 (m, 1H, $\underline{\text{C}}_{\text{ArH}}$), 7.49–7.41 (m, 8H, $\underline{\text{C}}_{\text{ArH}}$), 3.62 (t, $J = 8.0$ Hz, 2H, $\text{NCC}\underline{\text{H}}_2$), 2.94 (s, 3H, NCH_3), 2.88 (s, 3H, NCH_3), 2.71 (2H, t, $J = 8.0$ Hz, $\text{NCC}\underline{\text{H}}_2\text{CH}_2$).

^{13}C NMR (CDCl_3 , 100 MHz): δ 185.2 (d, $^2J_{\text{PC}} = 7.5$ Hz, $\underline{\text{C}}=\text{N}$), 171.2 ($\underline{\text{C}}=\text{O}$), 138.1 (d, $^3J_{\text{PC}} = 23.0$ Hz, $\text{N}=\underline{\text{C}}_{\text{Ar}}$), 134.9 (d, $^1J_{\text{PC}} = 131.0$ Hz, PC_{Ar}), 132.7 ($\underline{\text{C}}_{\text{ArH}}$), 131.7 (d, $^3J_{\text{PC}} = 9.0$ Hz, $\underline{\text{C}}_{\text{ArH}_{\text{meta}}}$), 128.9 ($\underline{\text{C}}_{\text{ArH}}$), 128.6 ($\underline{\text{C}}_{\text{ArH}}$), 128.5 (d, $^2J_{\text{PC}} = 12.5$ Hz, $\underline{\text{C}}_{\text{ArH}_{\text{ortho}}}$), 37.4 (NCH_3), 35.7 (NCH_3), 32.1 ($\underline{\text{CH}}_2\text{CO}$), 32.1 (d, $^3J_{\text{PC}} = 12.5$ Hz, $\text{NCC}\underline{\text{H}}_2$).

^{31}P NMR (CDCl_3 , 162 MHz): δ 18.3.

HRMS (ESI, MeOH): calcd for $\text{C}_{24}\text{H}_{26}\text{O}_2\text{N}_2\text{P}^+$ $[\text{M}+\text{H}]^+$ 405.17264, found 405.17178.

3-[[[(diphenylphosphoryl)imino](phenyl)methyl]-*N,N*-dimethylpentanamide **245l**



Prepared by Antonia Rinaldi according to General Procedure **VI** using the corresponding ketimine and 2-bromo-*N,N*-dimethylacetamide as substrates, and TEOA as a base. Purified by FCC (AcOEt:PE 1:1 to AcOEt) obtaining **245l** as a yellow oil in 32% yield (27.7 mg).

IR: 2962 (w), 2927 (w), 2873 (w), 1639 (s, C=N and C=O), 1438 (w), 1201 (m), 1121 (m), 851 (w), 724 (m), 698 (m) cm^{-1} .

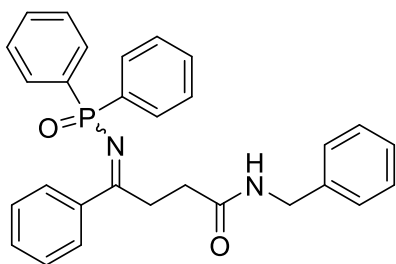
^1H NMR (CDCl_3 , 300 MHz): δ 7.82–7.71 (m, 4H, $\text{C}_{\text{Ar}}\text{H}$ and $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 7.69 (ddt, $J = 12.0, 6.5, 1.5$ Hz, 2H, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 7.43–7.27 (m, 9H), 3.79–3.73 (m, 1H, NCCH), δ 3.51 (dd, $J = 16.5$ Hz, 10.5 Hz, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{CO}$), 2.91 (s, 3H, NCH_3), 2.69 (s, 3H, NCH_3), 2.57 (dd, $J = 16.5$ Hz, 4.0 Hz, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{CO}$), 1.81 (app sept, $J = 7.0$ Hz, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_3$), 1.61 (app sept, $J = 7.0$ Hz, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_3$), 0.85 (t, $J = 7.5$ Hz, 3H, CH_2CH_3).

^{13}C NMR (CDCl_3 , 75 MHz): δ 192.2 (d, $^2J_{\text{PC}} = 9.5$ Hz, $\text{C}=\text{N}$), 171.8 (CO), 140.8 (d, $^3J_{\text{PC}} = 17.0$ Hz, $\text{N}=\text{CC}_{\text{Ar}}$), 135.9 (d, $^1J_{\text{PC}} = 134.5$ Hz, PC_{Ar}), 134.6 (d, $^1J_{\text{PC}} = 129.0$, PC_{Ar}), 131.8 (d, $^3J_{\text{PC}} = 9.5$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 131.6 (d, $^3J_{\text{PC}} = 9.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), δ 131.2 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 131.0 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 130.9 ($\text{C}_{\text{Ar}}\text{H}$), 128.6 ($\text{C}_{\text{Ar}}\text{H}$), 128.3 (d, $^2J_{\text{PC}} = 12.5$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$), 128.1 (d, $^2J_{\text{PC}} = 12.5$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$), 128.0 ($\text{C}_{\text{Ar}}\text{H}$), 47.2 (d, $^3J_{\text{PC}} = 14.0$ Hz, NCCH), 37.2 (NCH_3), 36.4 (CH_2CO), 35.4 (NCH_3), 26.3 (d, $^4J_{\text{PC}} = 1.5$ Hz, CH_2CH_3), 12.2 (CH_2CH_3).

^{31}P NMR (CDCl_3 , 162 MHz): δ 15.3.

HRMS (ESI, MeOH): calcd. for $\text{C}_{26}\text{H}_{30}\text{O}_2\text{N}_2\text{P}^+$ $[\text{M}+\text{H}]^+$ 433.20394, found 433.20360.

***N*-benzyl-4-[(diphenylphosphoryl)imino]-4-phenylbutanamide 245m**



Prepared by Antonia Rinaldi according the General Procedure **VI** using ketimine **5a** and 2-bromo-*N*-benzylacetamide as substrates, and TEOA as a base. Purified by FCC (CH₂Cl₂ to CH₂Cl₂:MeOH 95:5) obtaining **245m** as a yellow oil in 28%

yield (26.1 mg).

IR: 3061 (w), 2924 (w), 1657 (m, C=O), 1630 (m, C=N), 1574 (w), 1452 (m), 1311 (m), 1288 (w), 1186 (m), 1160 (m), 1122(w), 1106 (w), 1094 (w), 753 (w), 726 (m), 692 (s) cm⁻¹.

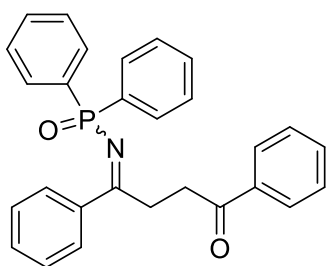
¹H NMR (CDCl₃, 400 MHz): δ 8.12 (d, *J* = 7.0 Hz, 2H, C_{Ar}H), 8.04 (t, *J* = 6.0 Hz, 1H, NH), 7.92 (ddd, *J* = 12.0, 8.0, 1.5 Hz, 4H, C_{Ar}H_{meta}), 7.63–7.38 (m, 10H, C_{Ar}H), 7.32 (d, *J* = 5.0 Hz, 4H, C_{Ar}H), 4.46 (d, *J* = 6.0 Hz, 2H, NCH₂Ph), 3.61 (t, *J* = 8.5 Hz, 2H, NCCH₂), 2.62 (t, *J* = 8.0 Hz, 2H, NCCH₂CH₂).

¹³C NMR (CDCl₃, 100 MHz): δ 184.5 (d, ²*J*_{PC} = 8.0 Hz, C=N), 171.8 (C=O), 139.0 (CH₂C_{Ar}), 137.8 (d, ³*J*_{PC} = 23.0 Hz, N=C_{Ar}), 134.8 (d, ¹*J*_{PC} = 131.5 Hz, PC_{Ar}), 133.2 (C_{Ar}H), 131.9 (d, ⁴*J*_{PC} = 3.0 Hz, C_{Ar}H_{para}), 131.6 (d, ³*J*_{PC} = 9.0 Hz, C_{Ar}H_{meta}), 129.1 (C_{Ar}H), 128.7 (d, ²*J*_{PC} = 12.5 Hz, C_{Ar}H_{ortho}), 128.6 (C_{Ar}H), 128.5 (C_{Ar}H), 127.8 (C_{Ar}H), 127.2 (C_{Ar}H), 43.5 (NCH₂Ph), 36.7 (CH₂CO), 33.6 (d, ³*J*_{PC} = 13.0 Hz, NCCH₂).

³¹P NMR (CDCl₃, 162 MHz): δ 19.9.

HRMS (ESI, MeOH): calcd for C₂₉H₂₈O₂N₂P⁺ [M+H]⁺ 467.18829, found 467.18865.

***N*-(4-oxo-1,4-diphenylbutylidene)-*P,P*-diphenylphosphinic amide 245n**



Prepared by Antonia Rinaldi according to General Procedure **VI** using ketimine **5a** and 2-bromoacetophenone as substrates, and TEOA as a base. Purified by FCC (Et₂O:PE 8:2) obtaining **245n** as a yellow oil in 19% yield (16.6 mg).

IR: 3057 (w), 2980 (w), 1686 (m, C=O), 1630 (m, C=N), 1594 (w), 1575 (w), 1450 (w), 1437 (m), 1282 (w), 1203 (s), 1121 (m), 1106 (m), 829 (w), 746 (m), 725 (s), 692 (s) cm⁻¹.

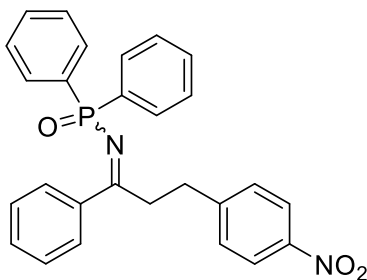
¹H NMR (CDCl₃, 400 MHz): δ 8.08 (d, *J* = 7.5 Hz, 2H, C_{Ar}H), 7.97 (ddd, *J* = 12.0, 8.0, 2.0 Hz, 4H, C_{Ar}H_{meta}), 7.90 (d, *J* = 7.0 Hz, 2H, C_{Ar}H), 7.61–7.35 (m, 12H, C_{Ar}H), 3.74 (t, *J* = 8.0 Hz, 2H, NCCH₂CH₂), 3.37 (t, *J* = 8.0 Hz, 2H, NCCH₂CH₂).

¹³C NMR (CDCl₃, 100 MHz): δ 198.0 (C=O), 185.3 (d, ²*J*_{PC} = 7.5 Hz, C=N), 138.3 (d, ³*J*_{PC} = 22.5 Hz, N=CC_{Ar}), 136.5 (COC_{Ar}), 134.8 (d, ¹*J*_{PC} = 130.5 Hz, PC_{Ar}), 133.3 (C_{Ar}H), 132.6 (C_{Ar}H), 131.7 (d, ³*J*_{PC} = 9.0 Hz, C_{Ar}H_{meta}), 131.6 (d, ⁴*J*_{PC} = 3.0 Hz, C_{Ar}H_{para}), 128.9 (C_{Ar}H), 128.7 (C_{Ar}H), 128.6 (d, ²*J*_{PC} = 12.5 Hz, C_{Ar}H_{ortho}), 128.5 (C_{Ar}H), 128.4 (C_{Ar}H), 37.1 (CH₂CO), 31.1 (d, ³*J*_{PC} = 12.5 Hz, NCCH₂).

³¹P NMR (CDCl₃, 162 MHz): δ 18.3.

HRMS (ESI, MeOH): calcd. for C₂₈H₂₅O₂NP⁺ [M+H]⁺ 438.16174, found 438.16174.

N*-[3-(4-nitrophenyl)-1-phenylpropylidene]-*P,P*-diphenylphosphinic amide **245o*



Prepared by Antonia Rinaldi according to General Procedure **VI** using ketimine **5a** and 4-nitrobenzyl bromide as substrates, and TEOA as a base. Purified by FCC (pentane:AcOEt 1:1) obtaining **245o** as a yellow oil in 18% yield (16.3 mg).

IR: 1630 (m, C=N), 1516 (m, NO₂ asymmetric), 1344 (s, NO₂ symmetric), 1201 (m), 1121 (w), 1106 (w), 724 (m), 694 (m) cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 8.05 (d, *J* = 7.5 Hz, 2H, C_{Ph}H_{ortho}), 7.94 (d, *J* = 9.0 Hz, 2H, C_{Ar}H_{CNO2}), 7.93–7.89 (m, 4H, C_{Ar}H_{meta}), 7.60 (tt, *J* = 7.5, 2.5 Hz, 1H, C_{Ph}H_{para}), 7.54 (t, *J* = 7.5 Hz, 2H, C_{Ph}H_{meta}), 7.49–7.36 (m, 6H, C_{Ar}H_{ortho} and C_{Ar}H_{para}), 7.32 (d, *J* = 9.0 Hz, 2H, C_{Ar}H_{HCNO2}), 3.81 (td, ³*J*_{HH} = 8.0 Hz, ⁴*J*_{PH} = 1.5 Hz, 2H, NCCH₂CH₂), 3.04 (t, *J* = 8.0 Hz, 2H, NCCH₂CH₂).

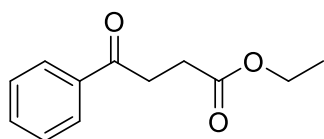
^{13}C NMR (CDCl_3 , 126 MHz): δ 183.0 (d, $^2J_{\text{PC}} = 7.5$ Hz, $\text{C}=\text{N}$), 147.7 (CNO_2), 138.2 (d, $^3J_{\text{PC}} = 23.5$ Hz, $\text{N}=\text{CC}_{\text{Ar}}$), 134.7 (d, $^1J_{\text{PC}} = 132.0$ Hz, PC_{Ar}), 132.8 ($\text{C}_{\text{PhH}_{\text{para}}}$), 131.6 (d, $^3J_{\text{PC}} = 9.0$ Hz, $\text{C}_{\text{ArH}_{\text{meta}}}$), 129.7 ($\text{C}_{\text{ArHCHCNO}_2}$), 129.1 ($\text{C}_{\text{PhH}_{\text{meta}}}$), 128.6 (d, $^2J_{\text{PC}} = 12.5$ Hz, $\text{C}_{\text{ArH}_{\text{ortho}}}$), 128.3 ($\text{C}_{\text{PhH}_{\text{ortho}}}$), 123.7 ($\text{C}_{\text{ArHCNO}_2}$), 36.6 (d, $^3J_{\text{PC}} = 12.0$ Hz, NCCH_2), 34.7 (CH_2CO).

^{31}P NMR (CDCl_3 , 162 MHz): δ 18.0.

HRMS (ESI, MeOH): calcd. for $\text{C}_{27}\text{H}_{24}\text{O}_3\text{N}_2\text{P}^+ [\text{M}+\text{H}]^+$ 455.15191, found 455.15200.

7.6.4 Synthesis and Characterisation of 244

Ethyl 4-oxo-4-phenylbutanoate 244



A biphasic mixture of ketimine **245a** (40.5 mg, 0.10 mmol, 1 equiv) in 1 M $\text{HCl}:\text{CH}_2\text{Cl}_2$ 1:1 (1.5 mL) was vigorously stirred at room temperature for 18 hours. The reaction mixture was diluted with water and CH_2Cl_2 , phases were separated and the aqueous layer was extracted twice with CH_2Cl_2 . Combined organic phases were dried over Na_2SO_4 , filtered and evaporated. The crude product was purified by FCC ($\text{PE}:\text{Et}_2\text{O}$ 8:2), obtaining compound **244** (16.1 mg, 78%) as a clear oil. Data match those given in the literature.³⁰¹

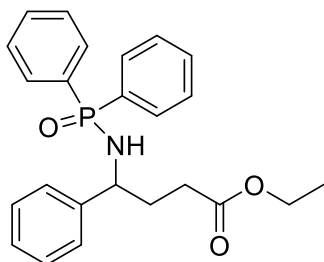
IR: 2981 (w), 2919 (w), 1731 (s, $\text{EtOC}=\text{O}$), 1686 (s, $\text{PhC}=\text{O}$), 1597 (w), 1449 (m), 1217 (s), 1161 (s), 1030 (m), 749 (s), 691 (s) cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): δ 7.99 (dd, $J_{\text{ortho}} = 8.0$ Hz, $J_{\text{meta}} = 1.0$ Hz, 2H, CH_{ortho}), 7.56 (tt, $J_{\text{ortho}} = 7.5$ Hz, $J_{\text{meta}} = 1.0$ Hz, 1H, CH_{para}), 7.47 (t, $J_{\text{ortho}} = 8.0$ Hz, 2H, CH_{meta}), 4.16 (q, $J = 7.5$ Hz, 2H, OCH_2CH_3), 3.32 (t, $J = 7.0$ Hz, 2H, $\text{COCH}_2\text{CH}_2\text{CO}_2\text{Et}$), 2.76 (t, $J = 7.0$ Hz, 2H, $\text{COCH}_2\text{CH}_2\text{CO}_2\text{Et}$), 1.27 (t, $J = 7.5$ Hz, 3H, OCH_2CH_3).

^{13}C NMR (CDCl_3 , 126 MHz): δ ppm 198.1 ($\text{C}=\text{O}$), 172.9 (COOEt), 136.6 (C_{Ar}), 133.2 (C_{ArH}), 128.6 (C_{ArH}), 128.0 (C_{ArH}), 60.7 (OCH_2CH_3), 33.4 ($\text{COCH}_2\text{CH}_2\text{CO}_2\text{Et}$), 28.3 ($\text{COCH}_2\text{CH}_2\text{CO}_2\text{Et}$), 14.2 (OCH_2CH_3).

7.6.5 Synthesis and Characterisation of 317

Ethyl 4-((diphenylphosphoryl)amino)-4-phenylbutanoate 317



To a stirred solution of ketimine **245a** (92.5 mg, 0.228 mmol, 1 equiv) in EtOH (6.5 mL) at -5°C , sodium borohydride (9.4 mg, 0.247 mmol, 1.1 equiv) was added. The reaction mixture was stirred at -5°C for 1 hour, then a further equivalent of sodium

borohydride (9.4 mg, 0.247 mmol, 1.1 equiv) was added. After stirring at -5°C for another hour, the reaction was quenched by sequential addition of water (10 mL) and saturated aqueous solution of NaHCO_3 (15 mL). The aqueous phase was extracted 3 times with CH_2Cl_2 , then the collected organic phases were dried over Na_2SO_4 , filtered and evaporated. The crude product was purified by FCC (Et_2O :acetone 95:5 to 70:30) affording compound **317** (76.2 mg, 82%) as an off-white solid.

M.p.: $138\text{--}140^{\circ}\text{C}$.

IR: 3191 (w), 3175 (w), 2923 (w), 1730 (s, C=O), 1457 (m), 1438 (m), 1186 (s), 1122 (m), 1110 (m), 747 (m), 724 (m), 698 (s) cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ 7.75 (ddd, $J = 12.0, 8.5, 1.5$ Hz, 2H, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 7.63 (ddd, $J = 12.0, 7.5, 1.0$ Hz, 2H, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 7.42–7.28 (m, 4H, $\text{C}_{\text{Ar}}\text{H}$), 7.24–7.12 (m, 5H, $\text{C}_{\text{Ar}}\text{H}$), 7.10–7.05 (m, 2H, $\text{C}_{\text{Ar}}\text{H}$), 4.10 (m, 1H, NCH), 3.93 (q, $J = 7.0$ Hz, 2H, OCH_2CH_3), 3.54 (dd, $J = 10.0, 7.0$ Hz, 1H, NH), 2.40–2.30 (m, 1H, $\text{CH}_2\text{CH}_\text{A}\text{H}_\text{B}\text{CO}$), 2.23–2.10 (m, 2H, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_2\text{CO}$, $\text{CH}_2\text{CH}_\text{A}\text{H}_\text{B}\text{CO}$), 2.07–1.98 (m, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}_2\text{CO}$), 1.09 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3).

^{13}C NMR (CDCl_3 , 126 MHz): δ 173.5 (COOEt), 143.3 (d, $^3J_{\text{PC}} = 5.0$ Hz, C_{Ar}), 133.2 (d, $^1J_{\text{PC}} = 128.0$ Hz, PC_{Ar}), 132.7 (d, $^3J_{\text{PC}} = 10.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 132.0 (d, $^1J_{\text{PC}} = 130.5$ Hz, PC_{Ar}), 132.0 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 131.9 (d, $^4J_{\text{PC}} = 3.0$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{para}}$), 131.9 (d, $^3J_{\text{PC}} = 9.5$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{meta}}$), 128.8 ($\text{C}_{\text{Ar}}\text{H}$), 128.6 (d, $^2J_{\text{PC}} = 12.5$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$), 128.4 (d, $^2J_{\text{PC}} = 12.5$ Hz, $\text{C}_{\text{Ar}}\text{H}_{\text{ortho}}$), 127.5

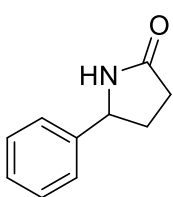
(C_{Ar}H_{para}), 126.5 (C_{Ar}H), 60.6 (OCH₂CH₃), 55.5 (NHCH), 34.5 (d, ³J_{PC} = 4.0 Hz, NCHCH₂), 31.4 (CH₂CH₂CO), 14.3 (OCH₂CH₃).

³¹P NMR (CDCl₃, 162 MHz): δ 22.7.

HRMS (ESI, MeOH): calcd. for C₂₄H₂₇O₃NP⁺ [M+H]⁺ 408.17231, found 408.17212.

7.6.6 Synthesis and Characterisation of 318

5-Phenylpyrrolidin-2-one 318



To a solution of amino ester **317** (70.6 mg, 0.173 mmol, 1 equiv) in MeOH (1.7 mL), 37%_{w/w} HCl (0.9 mL, ca 57 equiv) was added dropwise over 5 minutes.

The reaction mixture was stirred at room temperature for 5 hours, then water (5 mL) and powdered NaOH (485 mg, ca 70 equiv) were added. After stirring for 1 hour, the reaction mixture was extracted 4 times with CH₂Cl₂. The combined organic phases were dried over Na₂SO₄, filtered and evaporated. The crude product was purified by FCC (PE:AcOEt 1:9 to pure AcOEt) affording γ-lactam **318** (22.7 mg, 81%) as an off-white solid. Data match those given in the literature.³⁰²

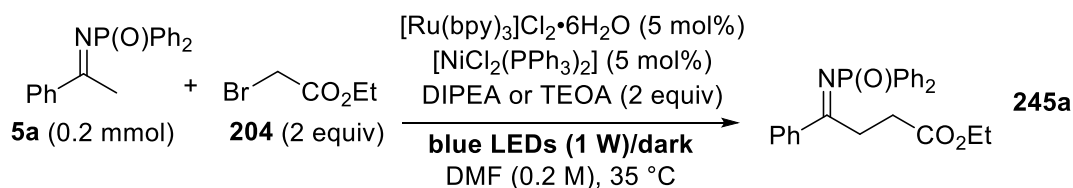
RF (AcOEt): 0.26.

M.p.: 106–108 °C (lit: 103.0–103.5 °C).³⁰²

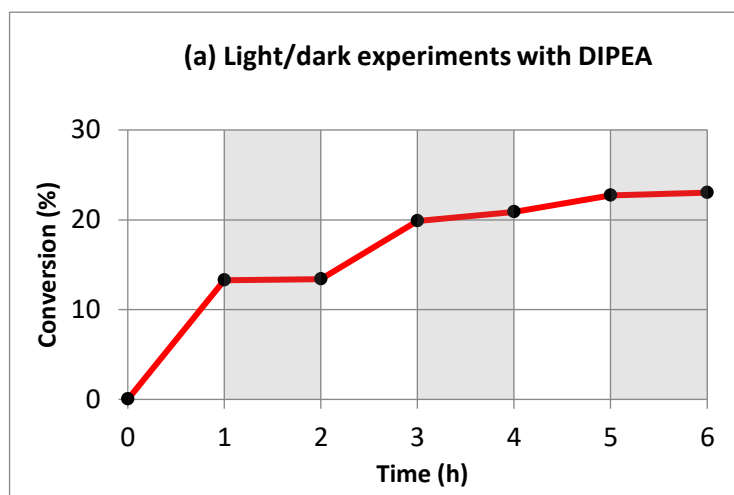
¹H NMR (CDCl₃, 400 MHz): δ 7.40–7.34 (m, 2H, C_{Ar}H), 7.32–7.28 (m, 3H, C_{Ar}H), 6.19 (broad s, NH), 4.75 (t, *J* = 7.1 Hz, 1H, NCH), 2.63–2.52 (m, 1H, NCHCH_AH_BCH₂CO), 2.50–2.36 (m, 2H, NCHCH₂CH₂CO), 1.97 (dddd, *J* = 12.6, 9.2, 8.1, 6.6 Hz, 1H, NCHCH_AH_BCH₂CO).

¹³C NMR (CDCl₃, 126 MHz): δ 178.8 (CO), 142.6 (C_{Ar}), 129.0 (C_{Ar}H), 127.9 (C_{Ar}H), 125.7 (C_{Ar}H), 58.2 (NCH), 31.4 (NCHCH₂), 30.4 (CH₂CO).

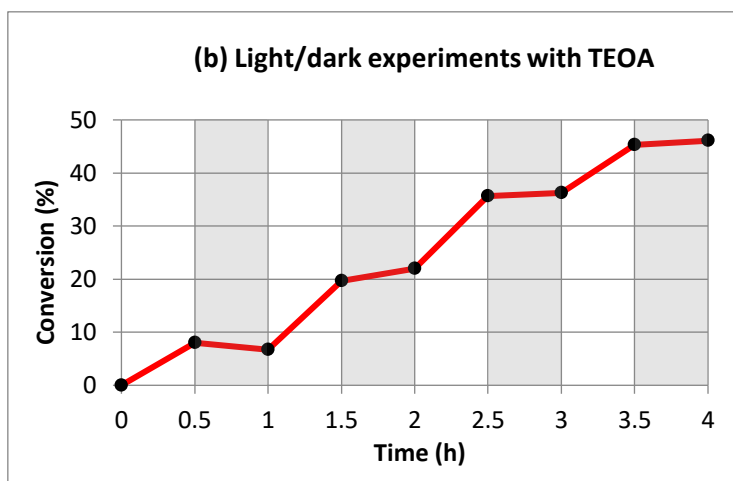
7.6.7 Light/Dark Cycles



Light dark/cycles for the reaction between **5a** and **204** using either DIPEA or TEOA were performed. The reaction vials were alternatively irradiated with blue light in the standard setup, then placed in a 35 °C bath covered with aluminium foil. Aliquots of the reaction mixture (50 μL) were taken every 30 or 60 minutes, diluted with CDCl_3 (400 μL) and analysed by ^{31}P NMR. The conversion plotted in the graphs represents the consumption of **5a** as determined by ^{31}P NMR analysis. Each reaction was run in duplicate and the average value of conversion is plotted in the graphs.



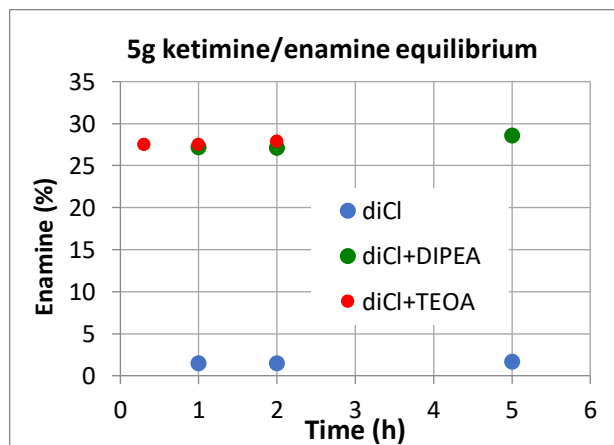
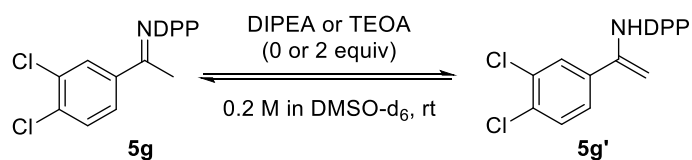
Time (h)	Rxn 1 conv (%)	Rxn 2 conv (%)	Average conv (%)
1	12.9	13.6	13.3
2	12.8	14.0	13.4
3	21.0	18.8	19.9
4	21.9	19.8	20.9
5	23.2	22.3	22.7
6	23.0	23.1	23.0



Time (h)	Rxn 1 conv (%)	Rxn 2 conv (%)	Average conv (%)
0.5	9.7	8.0	8.9
1	8.7	6.7	7.7
1.5	21.2	19.7	20.4
2	21.3	22.0	21.6
2.5	27.6	35.6	31.6
3	27.0	36.3	31.6
3.5	30.3	45.3	37.9
4	30.8	46.1	38.4

Using either base, the reaction proceeded significantly only under light irradiation. Minor positive and negative variations in conversion observed over dark periods are attributable to the error associated with the sampling and monitoring technique. Variations between the duplicates are due to reproducibility issues; however please note that in every single reaction the start/stop trend with on/off irradiation is evident. Over time, the rate of reaction promoted by DIPEA slows down, hence the steepness of the curve under light irradiation decreases.

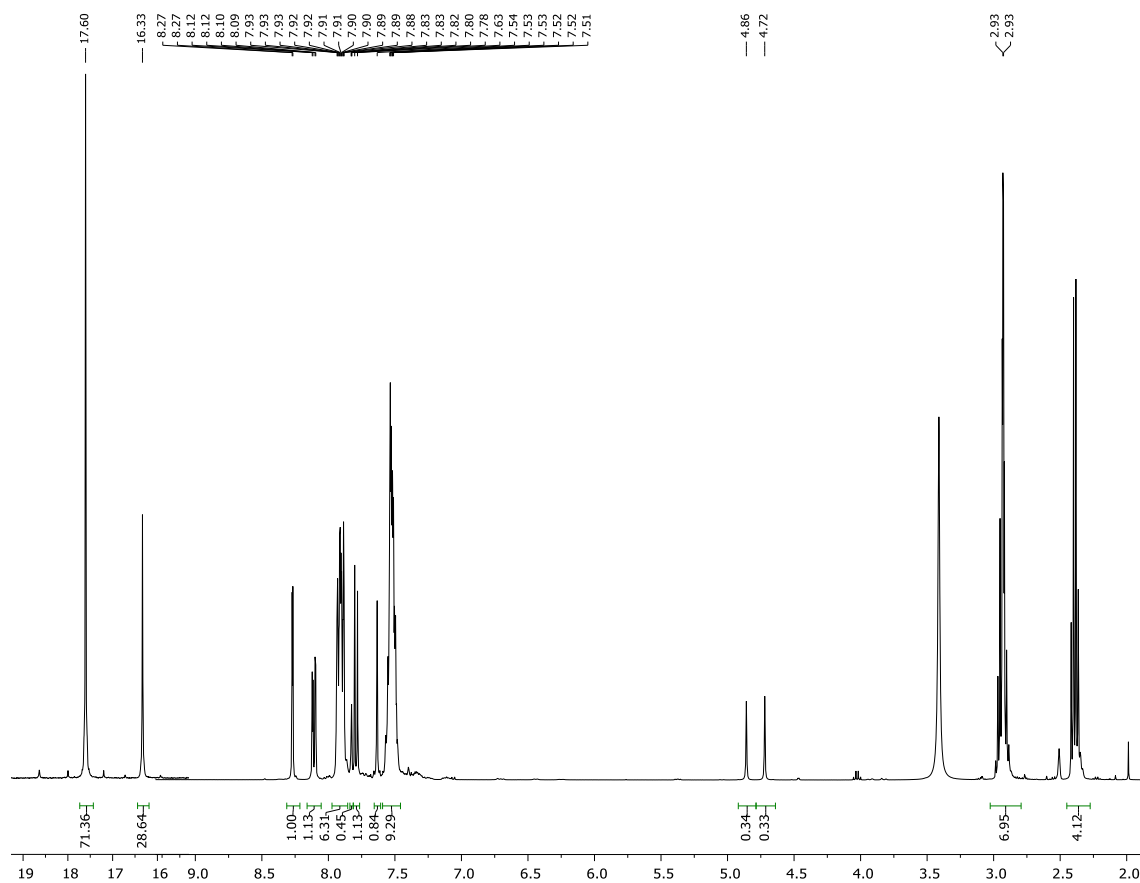
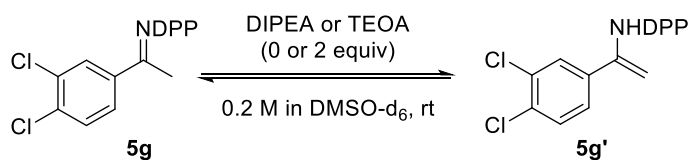
7.6.8 NMR Studies on the Ketimine/Enamine Equilibrium for Substrate 5g



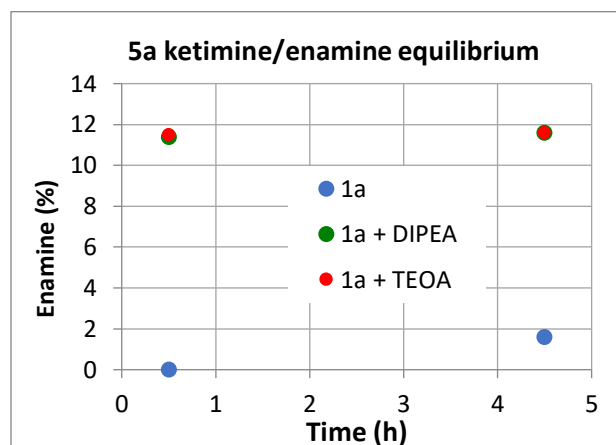
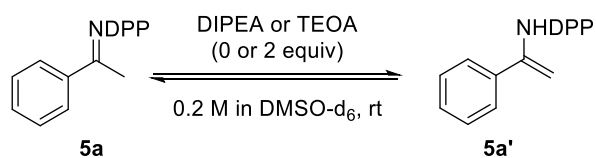
	5g	5g + DIPEA	5g + TEOA
time (h)	enamine (%)	enamine (%)	enamine (%)
0.3	na	na	27.5
1	1.5	27.2	27.5
2	1.5	27.1	27.9
5	1.7	28.6	na
48	5.6	27.0	27.0 ^a

^a With 5 mol% [NiCl₂(PPh₃)₂].

Diagnostic NMR peaks



7.6.9 NMR Studies on Ketimine/Enamine Equilibrium for Substrate 5a



	5a	5a + DIPEA	5a + TEOA
time (h)	enamine (%)	enamine (%)	enamine (%)
0.5	0	11.4	11.5
4.5	1.6	11.6	11.6

Chemical reaction scheme showing the equilibrium between **5a** (N,N-diphenylmaleimide) and **5a'** (N,N-diphenylmaleimide derivative) in the presence of DIPEA or TEOA (0 or 2 equiv) in 0.2 M DMSO-d₆ at room temperature (rt).

¹H NMR spectrum (400 MHz, DMSO-d₆) of the mixture. The spectrum shows peaks corresponding to the structures, with chemical shifts (ppm) and integrations provided.

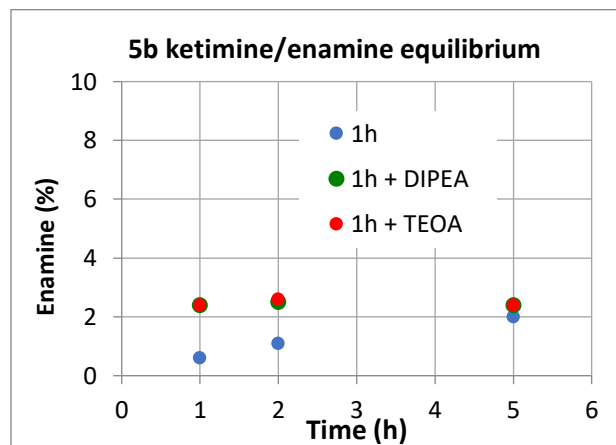
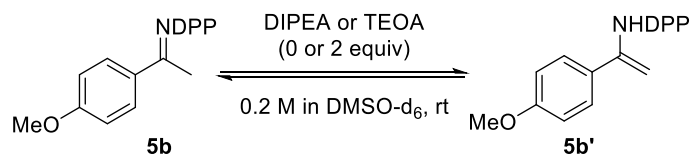
Chemical shifts (ppm): 16.91, 15.88, 8.16, 8.15, 8.15, 8.14, 8.14, 7.94, 7.94, 7.93, 7.92, 7.92, 7.91, 7.90, 7.89, 7.89, 7.62, 7.60, 7.56, 7.56, 7.55, 7.55, 7.54, 7.53, 7.53, 7.52, 7.52, 7.51, 7.51, 7.50, 7.50, 7.49, 7.49, 4.81, 4.61, 4.39, 4.38, 4.37, 3.47, 3.45, 3.44, 3.42, 3.41, 2.92, 2.92, 2.58, 2.56, 2.55, 2.51.

Integrations: 88.57, 11.43, 2.02, 4.54, 0.08, 0.45, 8.89, 0.50, 0.12, 0.12, 3.00.

¹H NMR (DMSO-d₆, 400 MHz): δ 4.91 (s, 1H, C=CH_AH_B, **5a'**), 4.91 (s, 1H, C=CH_AH_B, **5a'**),

2.92 (d, $^4J_{HP} = 2.0$ Hz, 3H, CH_3 , **5a**)

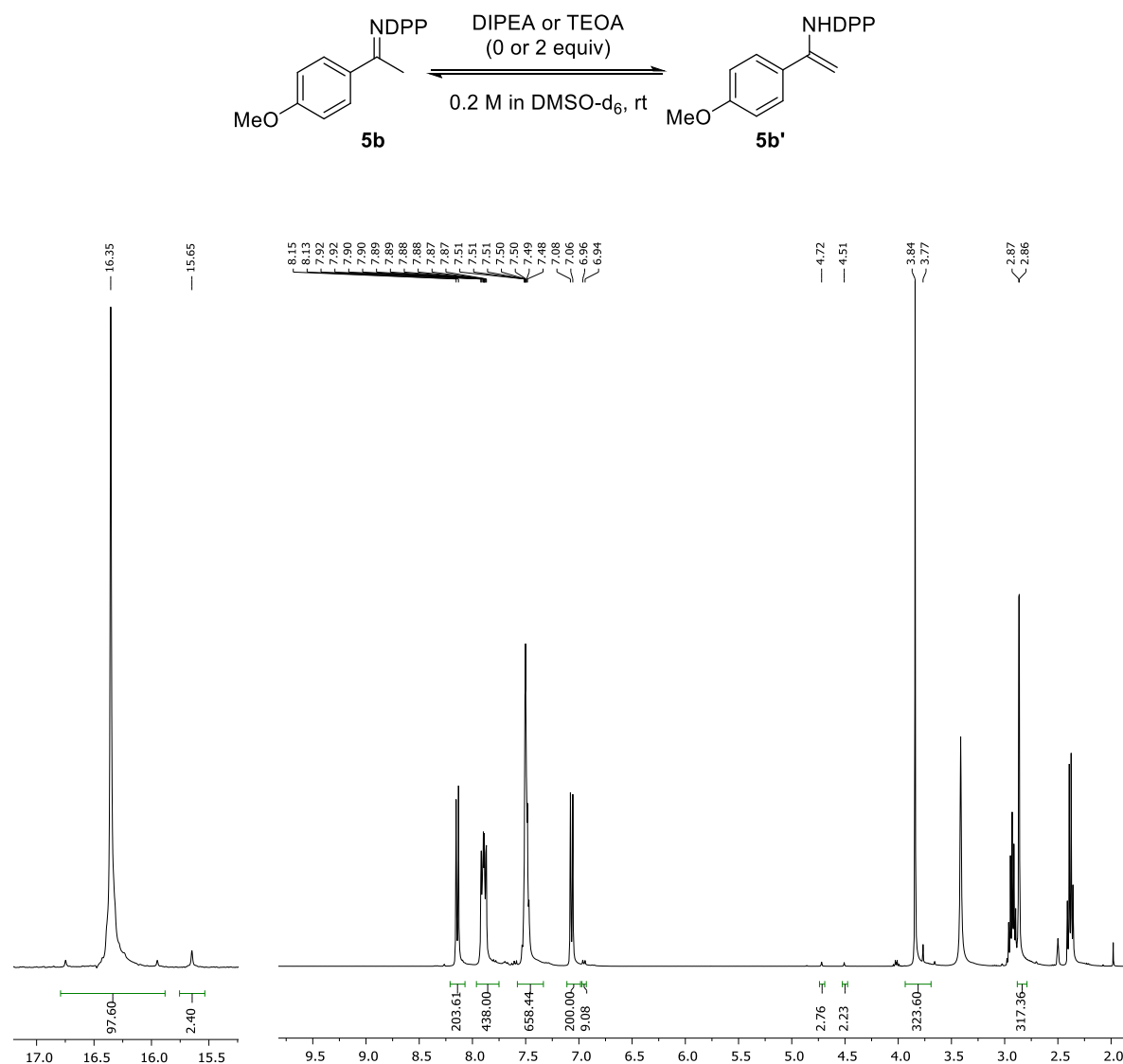
7.6.10 NMR Studies on Ketimine/Enamine Equilibrium for Substrate 5b



	5b	5b + DIPEA	5b + TEOA
time (h)	enamine (%)	enamine (%)	enamine (%)
1	0.6	2.4	2.4
2	1.1	2.5	2.6
5	2.0	2.4	2.4
48	2.5	2.5	3.0, 3.5 ^a

^a With 5 mol% [NiCl₂(PPh₃)₂].

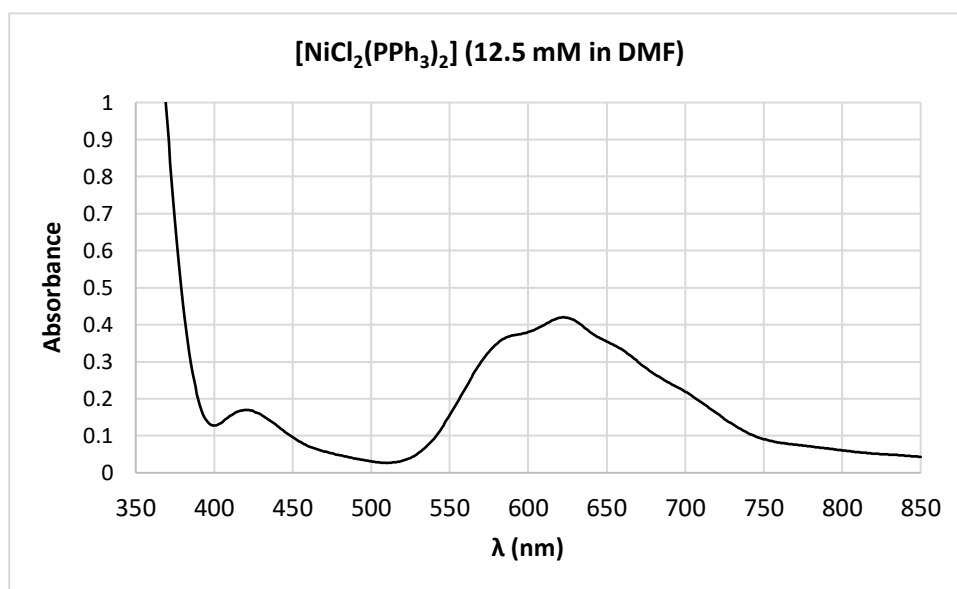
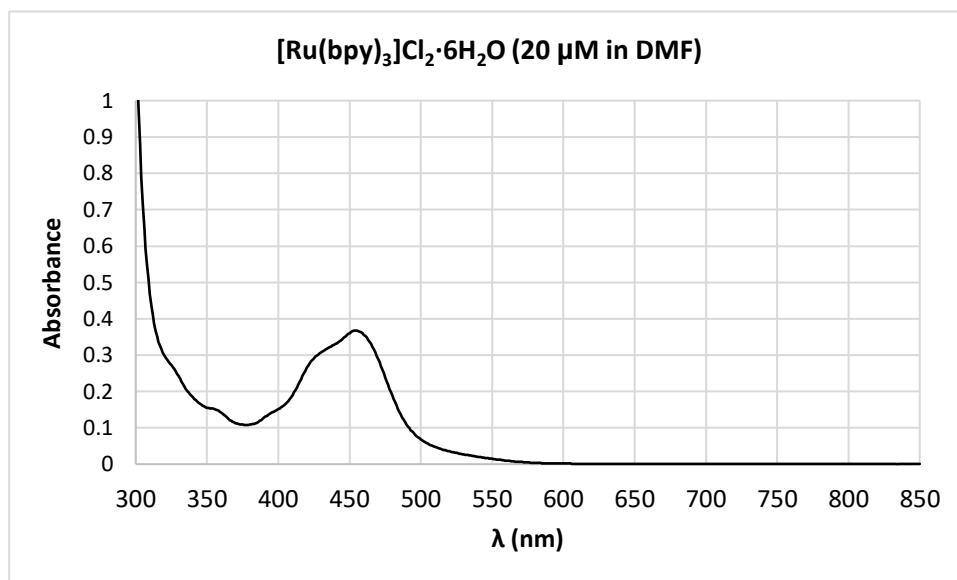
Diagnostic NMR peaks



³¹P NMR (DMSO-d₆, 162 MHz): δ 16.4 (**5b**), 15.7 (**5b'**).

¹H NMR (DMSO-d₆, 400 MHz): δ 7.07 (d, *J* = 9.0 Hz, 2H, C_{Ar}HCHCOCH₃, **5b**), 6.95 (d, *J* = 9.0 Hz, 2H, C_{Ar}HCHCOCH₃, **5b'**), 4.72 (s, 1H, C=CH_AH_B, **5b'**), 4.51 (s, 1H, C=CH_AH_B, **5b'**), 2.86 (d, ⁴*J*_{HP} = 2.0 Hz, 3H, CH₃, **5b**).

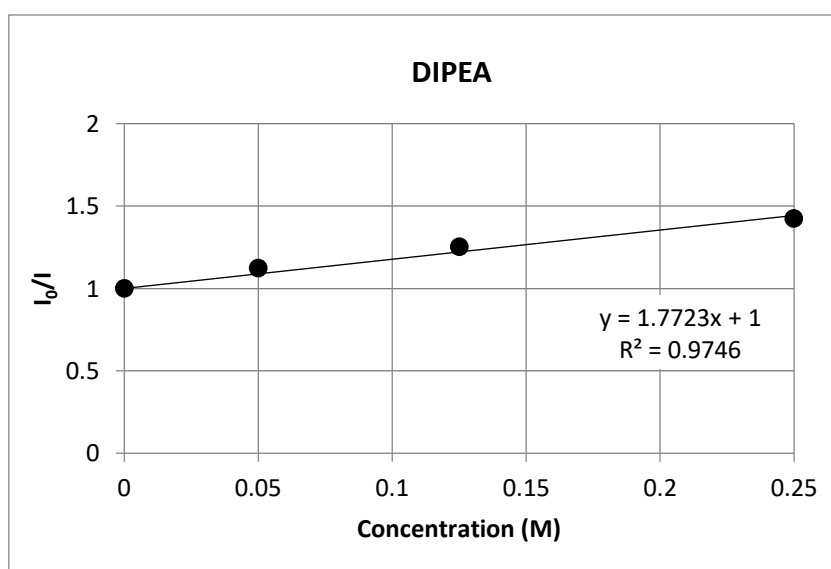
7.6.11 UV-Visible Absorption Spectra



7.6.12 Luminescence Quenching Studies

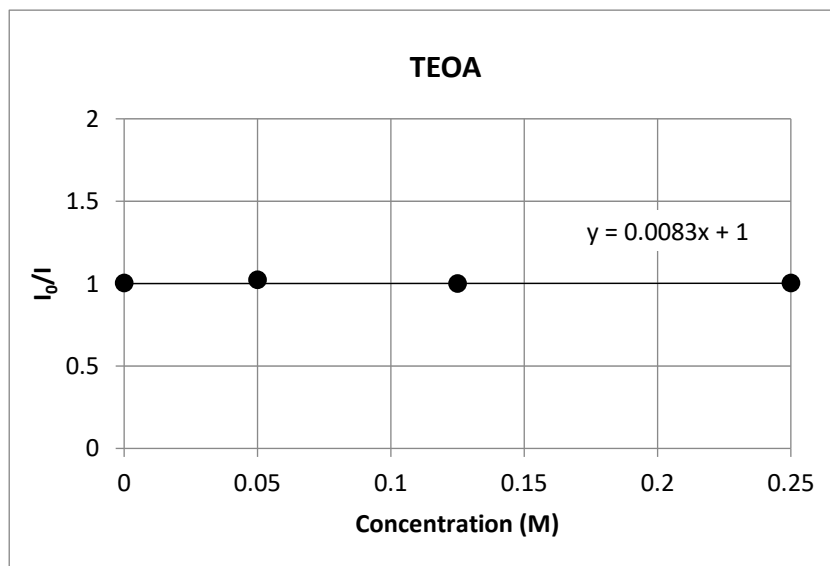
Luminescence experiments were performed to determine which species could be responsible for the quenching of the excited photocatalyst. Solutions (0.025–0.25 M in DMF) of DIPEA, TEOA, ethyl bromoacetate **204**, ketimine **5g** with and without 2 equivalents of TEOA, and ketimine **5a** were prepared in the presence of 1 μ M [Ru(bpy)₃]Cl₂·6H₂O. The absorbance of all compounds at 0.25 M concentration in DMF is less than 0.1 across the visible spectrum (350–850 nm), hence inner filter effects do not alter the luminescence measurements.

The solutions were prepared under air, degassed for 15 minutes by bubbling N₂ and then transferred under N₂ into a 1 cm quartz cuvette. The excitation wavelength was set at 452 nm and the emission was recorded at 620 nm in arbitrary units.



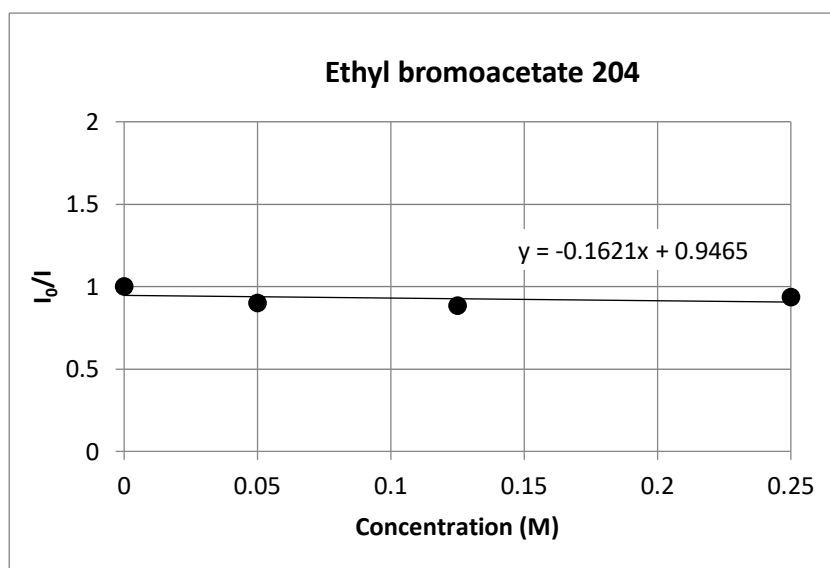
DIPEA (M)	I (a.u.)	I_0/I
0	403.3	1
0.05	359.5	1.122
0.125	322.3	1.252
0.25	283.7	1.421

[Ru(bpy)₃]Cl₂·6H₂O 1 μ M in DMF; PMT voltage 900 V; λ_{exc} 452 nm; λ_{em} 620 nm



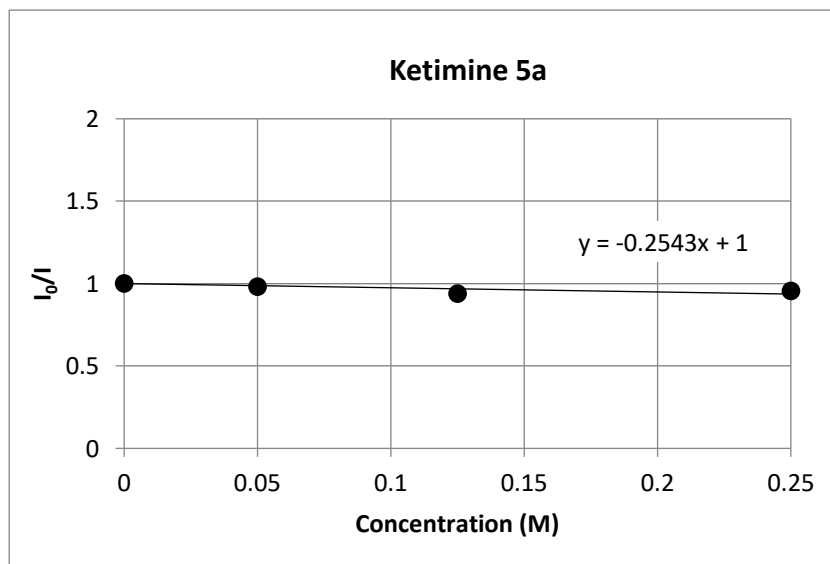
TEOA (M)	I (a.u.)	I_0/I
0	403.3	1
0.05	395.1	1.021
0.125	404.6	0.997
0.25	403.3	1.000

[Ru(bpy)₃]Cl₂·6H₂O 1 μ M
in DMF; PMT voltage 900 V;
 λ_{exc} 452 nm; λ_{em} 620 nm



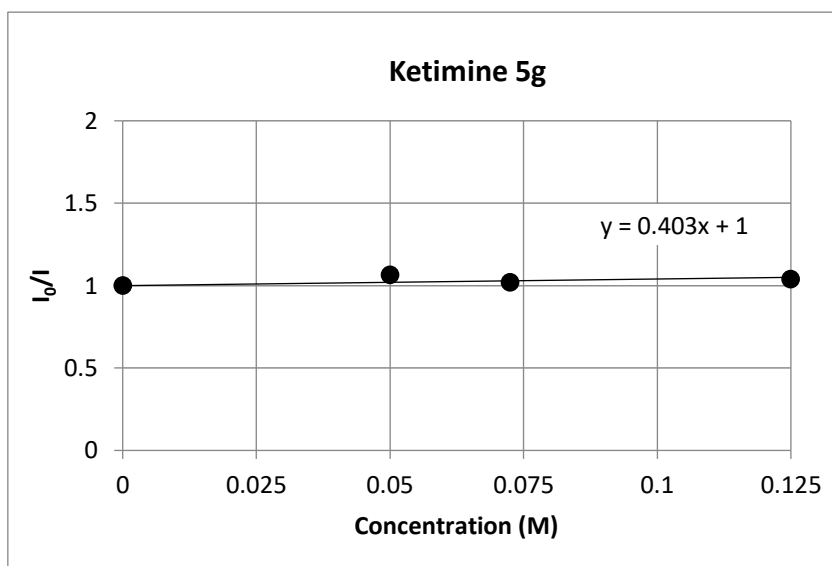
204 (M)	I (a.u.)	I_0/I
0	403.3	1
0.05	448.9	0.899
0.125	456.9	0.883
0.25	431.1	0.936

[Ru(bpy)₃]Cl₂·6H₂O 1 μ M
in DMF; PMT voltage 900 V;
 λ_{exc} 452 nm; λ_{em} 620 nm



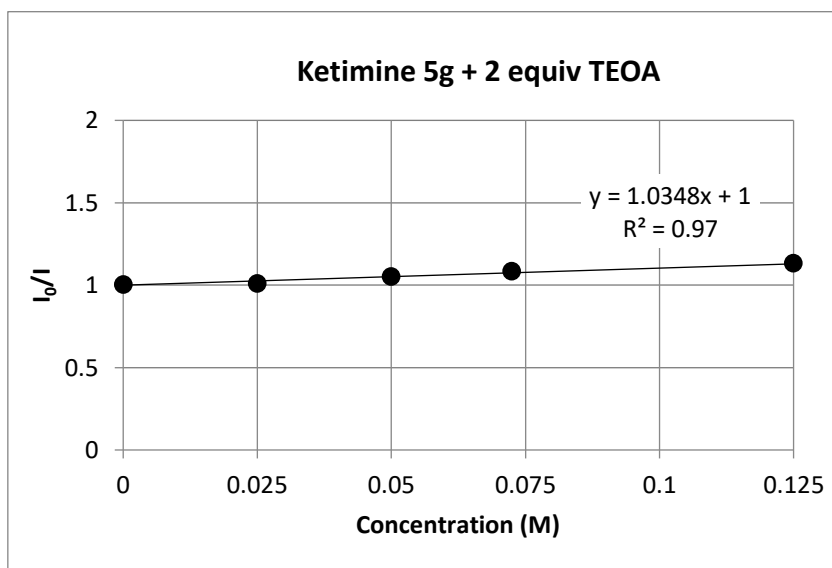
5a (M)	I (a.u.)	I_0/I
0	403.3	1
0.05	411.0	0.981
0.125	430.4	0.937
0.25	423.2	0.953

[Ru(bpy)₃]Cl₂·6H₂O 1 μ M
in DMF; PMT voltage 900 V;
 λ_{exc} 452 nm; λ_{em} 620 nm



5g (M)	I (a.u.)	I₀/I
0	406.7	1
0.05	382.8	1.062
0.0725	399.1	1.019
0.125	391.3	1.039

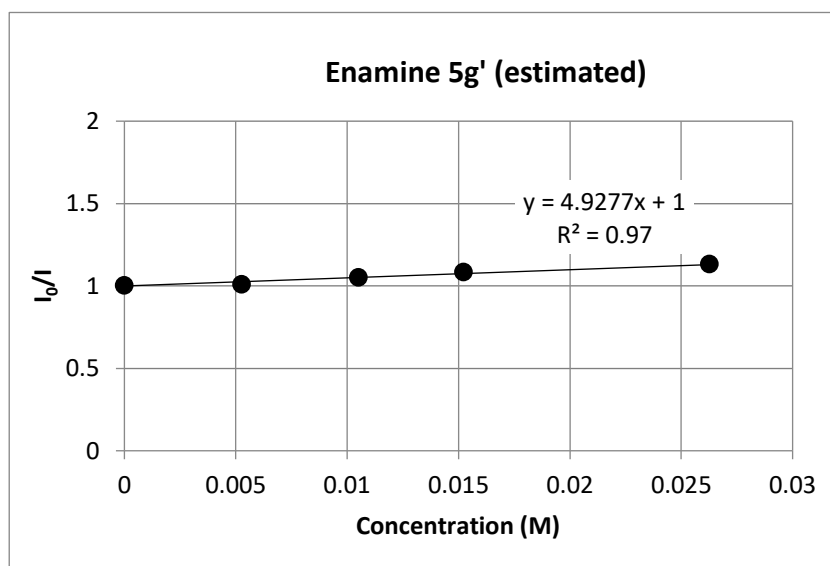
[Ru(bpy)₃]Cl₂·6H₂O 1 μM
in DMF; PMT voltage 900 V;
λ_{exc} 452 nm; λ_{em} 620 nm



5g + TEOA (M)	I (a.u.)	I₀/I
0	406.7	1
0.025	403.4	1.008
0.05	387.7	1.049
0.0725	376.5	1.080
0.125	359.6	1.131

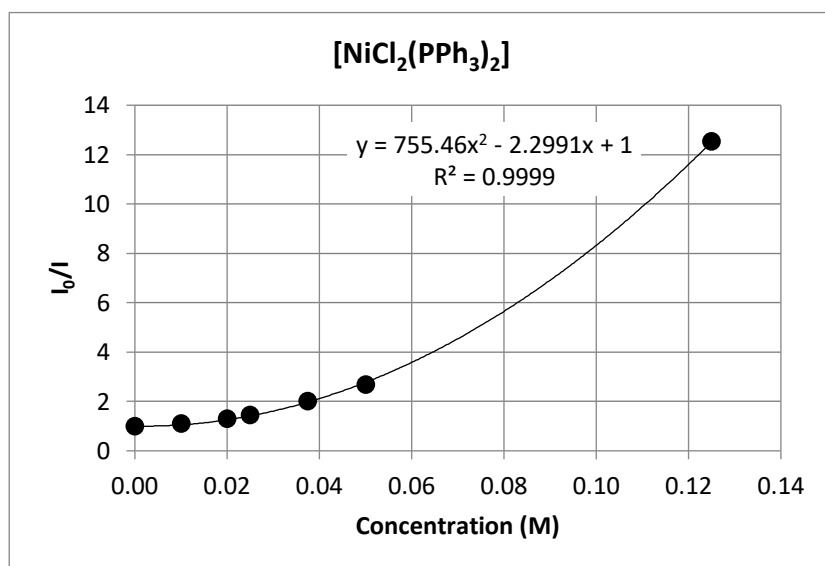
[Ru(bpy)₃]Cl₂·6H₂O 1 μM
in DMF; PMT voltage 900 V;
λ_{exc} 452 nm; λ_{em} 620 nm

The percentage of enamine **5g'** present in the samples of **5g** with 2 equivalents of TEOA was measured by ³¹P NMR analysis (100 μL of DMSO-d₆ were added to 400 μL of sample to allow locking and shimming). Regardless of their concentration (0.025–0.125 M), all samples displayed a 79:21 ketimine:enamine ratio. The concentration of enamine **5g'** was therefore calculated by multiplying the nominal concentration of **5g** by a factor 0.21, and was plotted against I₀/I. As expected, the linear correlation between concentration of the quencher and I₀/I was maintained and the value of the angular coefficient (slope) increased.



5g' (mM)	I (a.u.)	I₀/I
0	406.7	1
5.25	403.4	1.008
10.5	387.7	1.049
15.2	376.5	1.080
26.2	359.6	1.131

[Ru(bpy)₃]Cl₂·6H₂O 1 μM
in DMF; PMT voltage 900 V;
λ_{exc} 452 nm; λ_{em} 620 nm



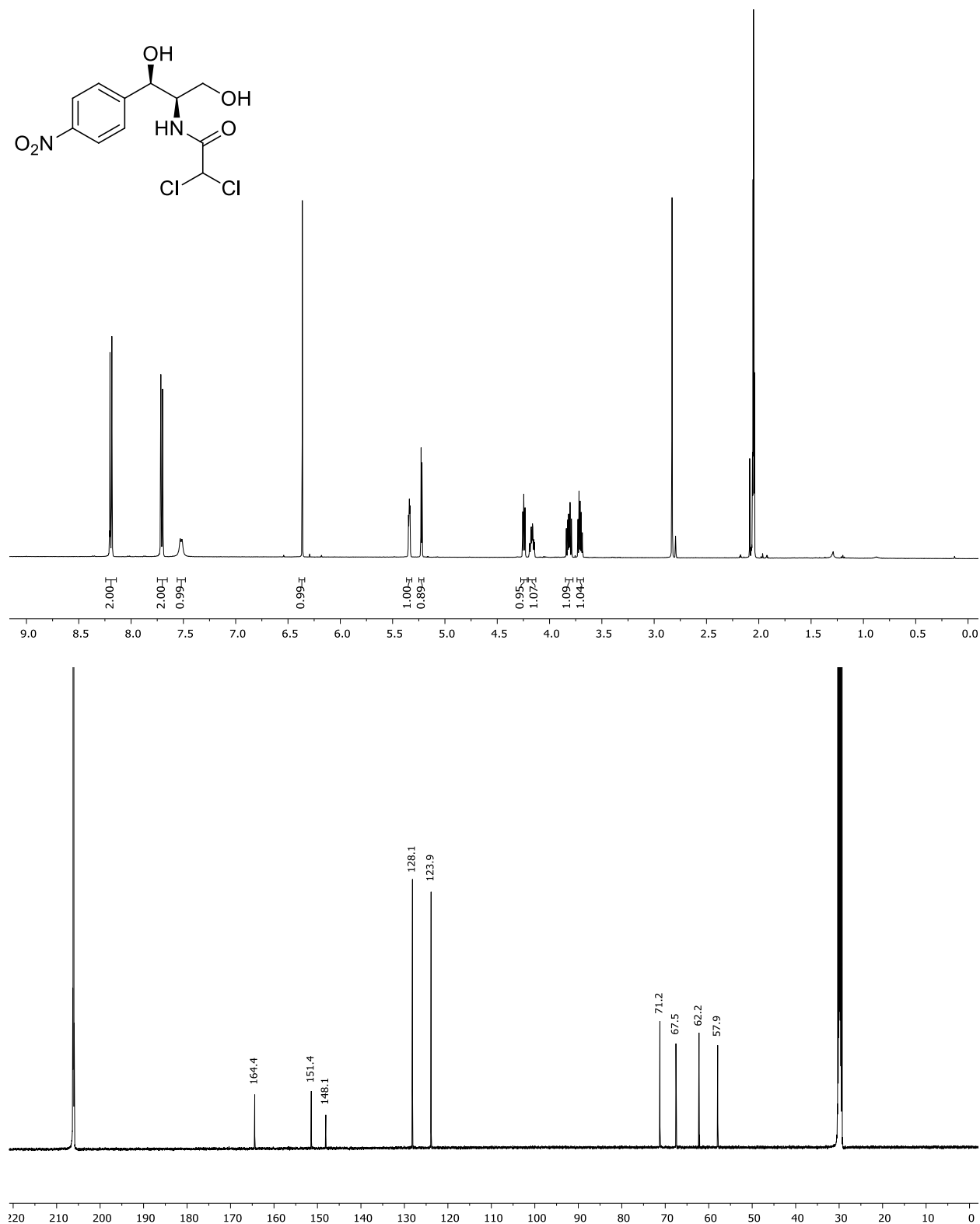
[Ni] (mM)	I (a.u.)	I₀/I
0	222.1	1
10	208.0	1.101
20	175.0	1.302
25	153.2	1.450
37.5	114.3	2.004
50	82.70	2.686
125	17.73	12.53

[Ru(bpy)₃]Cl₂·6H₂O 200 μM
in DMF; PMT voltage 600 V;
λ_{exc} 452 nm; λ_{em} 620 nm

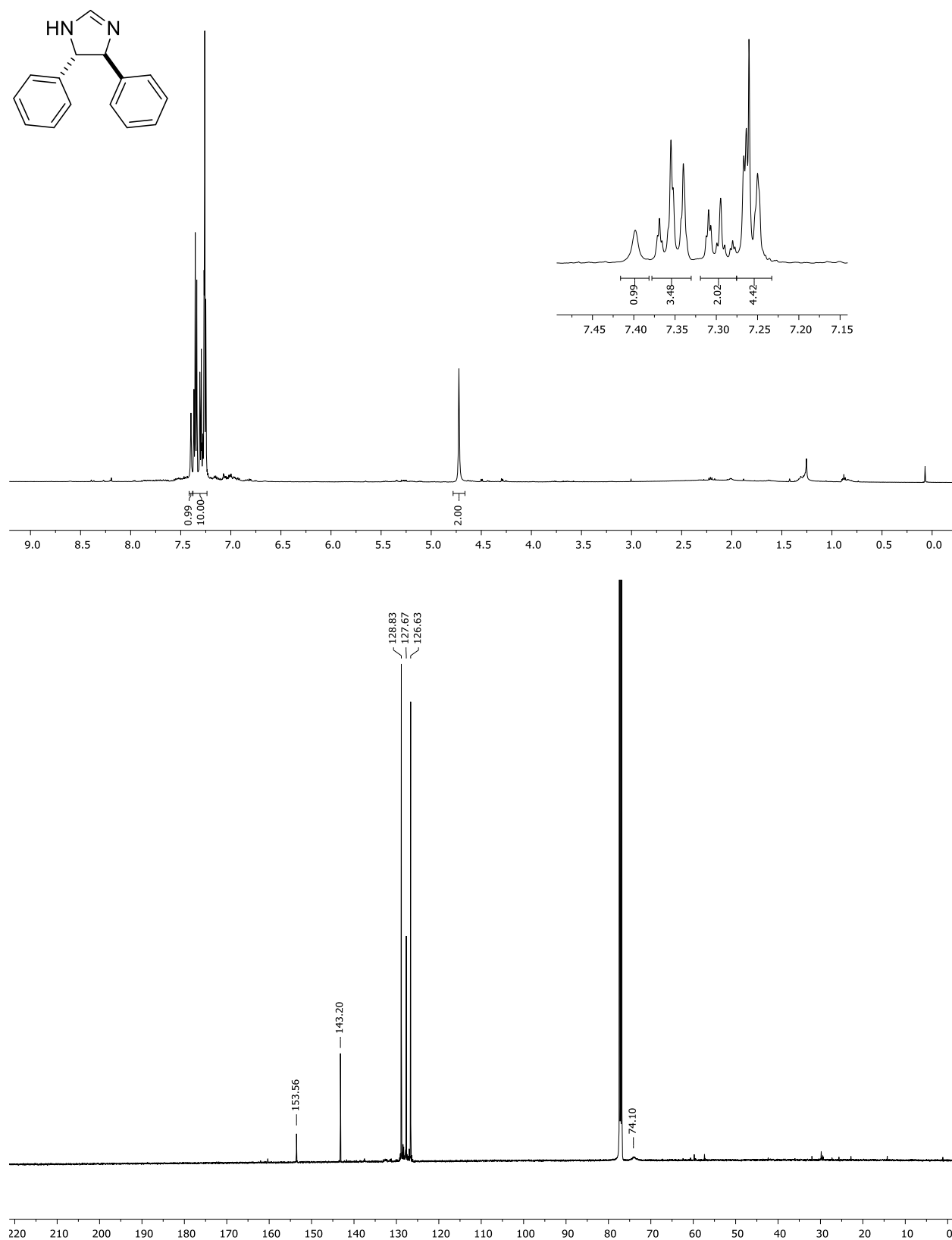
8 Appendices

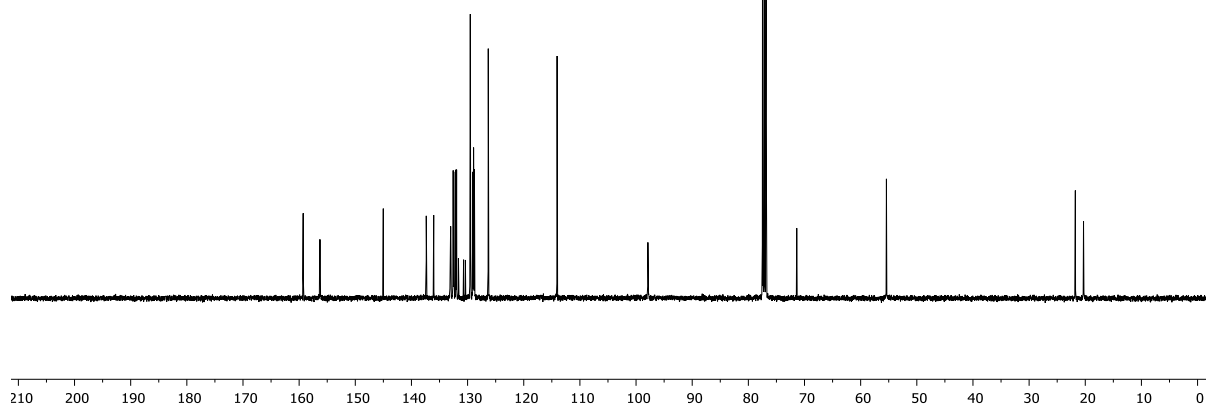
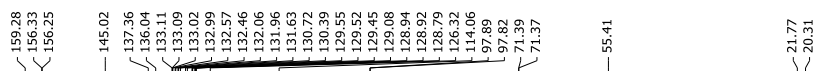
8.1 Representative NMR Spectra

8.1.1 ^1H and ^{13}C NMR of Chloramphenicol, (–)-52 (CD_3COCD_3)

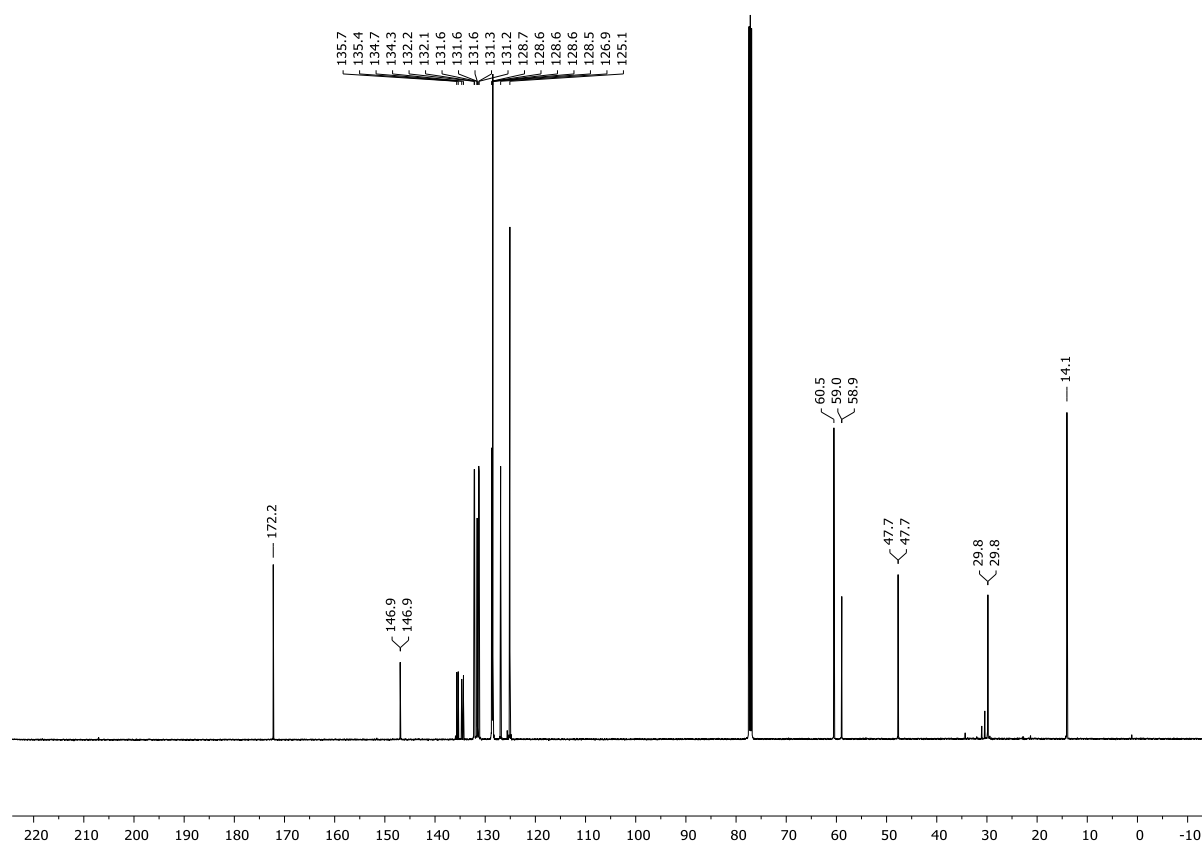
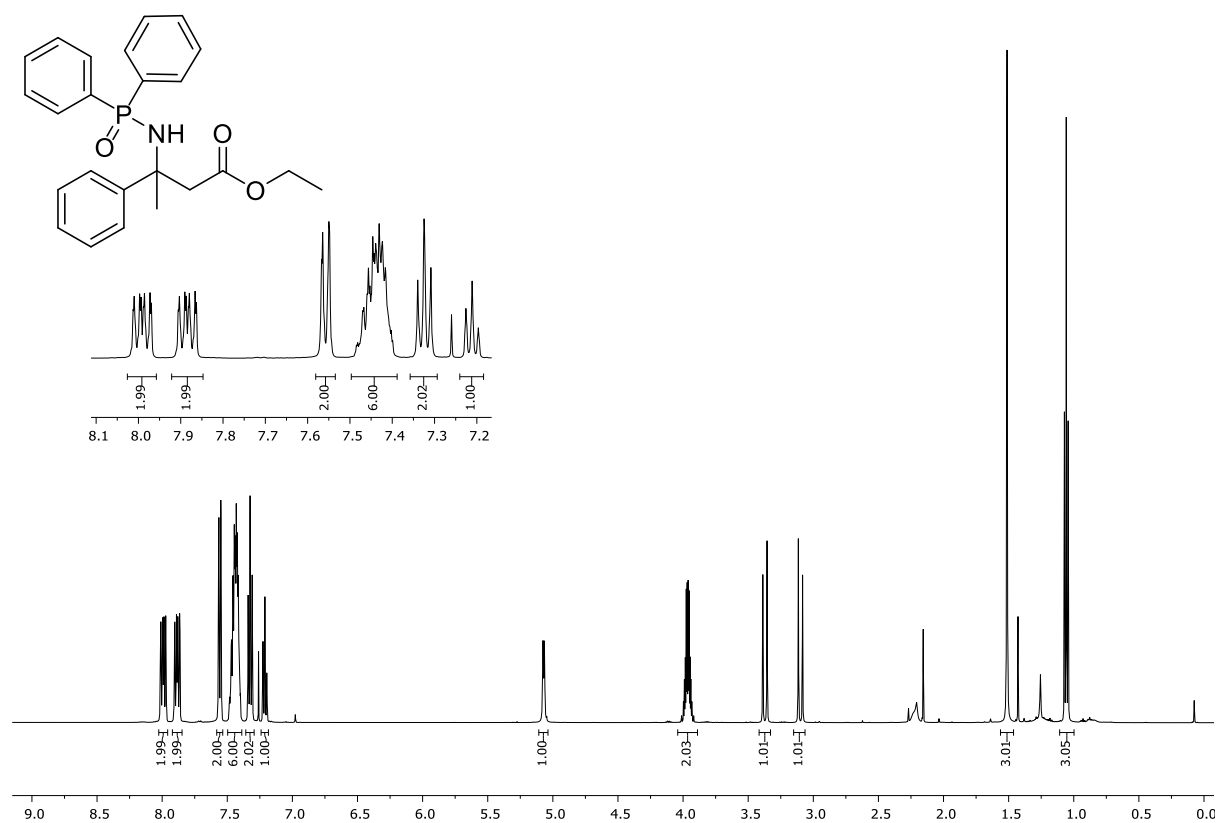


8.1.2 ^1H and ^{13}C NMR of *trans*-141d (CDCl_3)

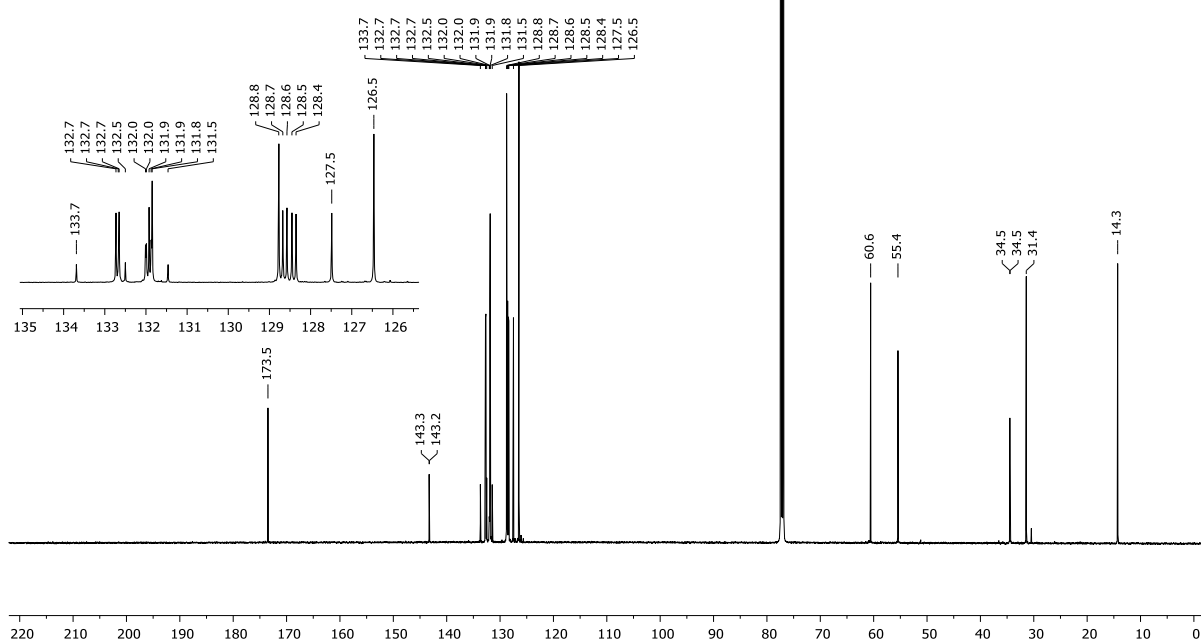
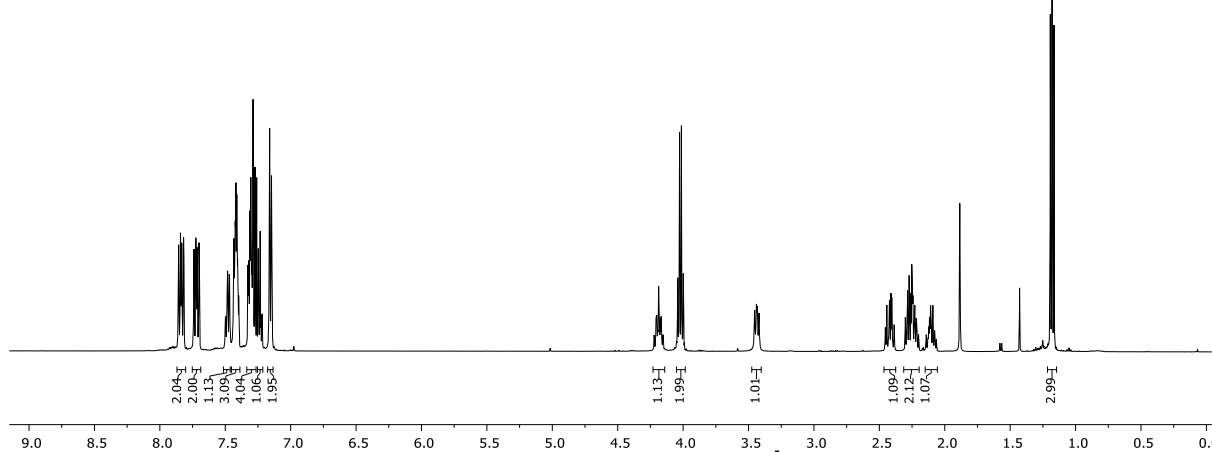
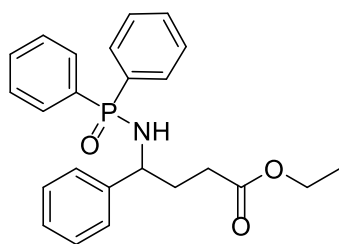




8.1.4 ^1H and ^{13}C NMR of 199 (CDCl_3)



8.1.5 ^1H and ^{13}C NMR of 317 (CDCl_3)

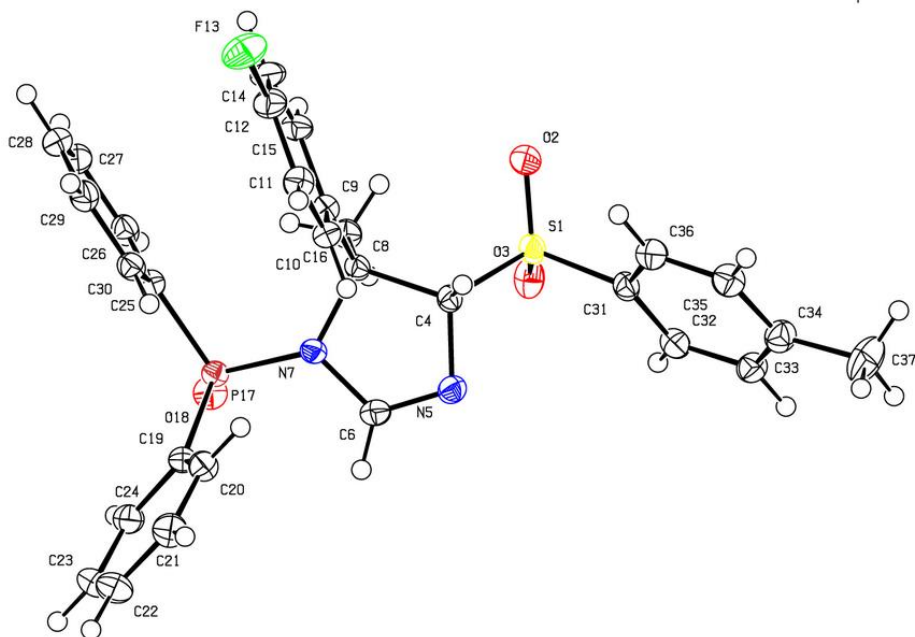


No. of reflections	2327
No. of parameters	289
No. of restraints	1
H-atom treatment	Only H-atom coordinates refined
$\Delta\rho_{\max}$, $\Delta\rho_{\min}$ (e Å ⁻³)	0.31, -0.26

S1—O2	1.437 (3)	C13—C14	1.357 (5)
S1—O3	1.442 (3)	C14—S15	1.746 (3)
S1—C4	1.757 (3)	C14—N25	1.382 (4)
S1—C11	1.798 (3)	S15—O16	1.433 (3)
C4—C5	1.385 (5)	S15—O17	1.434 (2)
C4—C9	1.390 (5)	S15—C18	1.760 (3)
C5—C6	1.379 (5)	C18—C19	1.387 (5)
C6—C7	1.392 (6)	C18—C23	1.396 (5)
C7—C8	1.379 (6)	C19—C20	1.396 (5)
C7—C10	1.513 (4)	C20—C21	1.382 (5)
C8—C9	1.394 (4)	C21—C22	1.397 (5)
C11—N12	1.440 (4)	C21—C24	1.506 (4)
N12—C13	1.383 (4)	C22—C23	1.396 (4)
N12—C26	1.361 (4)	N25—C26	1.321 (4)
O2—S1—O3	118.98 (14)	C13—C14—S15	126.9 (2)
O2—S1—C4	109.26 (16)	C13—C14—N25	111.8 (3)
O3—S1—C4	109.75 (16)	S15—C14—N25	121.3 (2)
O2—S1—C11	108.39 (15)	C14—S15—O16	107.64 (15)
O3—S1—C11	105.32 (15)	C14—S15—O17	106.81 (15)
C4—S1—C11	104.04 (13)	O16—S15—O17	119.95 (16)
S1—C4—C5	119.7 (3)	C14—S15—C18	105.72 (13)
S1—C4—C9	118.3 (2)	O16—S15—C18	107.51 (16)
C5—C4—C9	121.9 (3)	O17—S15—C18	108.37 (14)
C4—C5—C6	119.0 (4)	S15—C18—C19	119.6 (2)
C5—C6—C7	120.6 (4)	S15—C18—C23	119.2 (2)
C6—C7—C8	119.4 (3)	C19—C18—C23	121.2 (3)
C6—C7—C10	120.3 (4)	C18—C19—C20	118.9 (3)
C8—C7—C10	120.3 (4)	C19—C20—C21	121.5 (3)
C7—C8—C9	121.3 (4)	C20—C21—C22	118.5 (3)
C8—C9—C4	117.8 (3)	C20—C21—C24	121.4 (4)
S1—C11—N12	112.9 (2)	C22—C21—C24	120.1 (4)
C11—N12—C13	126.8 (3)	C21—C22—C23	121.4 (3)
C11—N12—C26	126.2 (2)	C18—C23—C22	118.5 (3)
C13—N12—C26	106.9 (3)	C14—N25—C26	103.9 (3)

N12—C13—C14 104.9 (3) N12—C26—N25 112.4 (3)

8.2.2 X-Ray Diffraction Data for 170e



Crystal data

Chemical formula	$\text{C}_{29}\text{H}_{26}\text{FN}_2\text{O}_3\text{PS}$
M_r	532.57
Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	150
a, b, c (Å)	9.5487 (2), 13.4875 (2), 10.1073 (2)
β (°)	101.630 (2)
V (Å ³)	1274.98 (3)
Z	2
Radiation type	Cu $K\alpha$
μ (mm ⁻¹)	2.08
Crystal size (mm)	0.05 × 0.10 × 0.15

Data collection

Diffractometer	Oxford Diffraction SuperNova
Absorption correction	Multi-scan <i>CrysAlis PRO</i> , (Agilent, 2011)
$T_{\min}, T_{\max}$	0.70, 0.73
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	15543, 5265, 5135
R_{int}	0.023
$(\sin \theta/\lambda)_{\max}$ (Å ⁻¹)	0.630

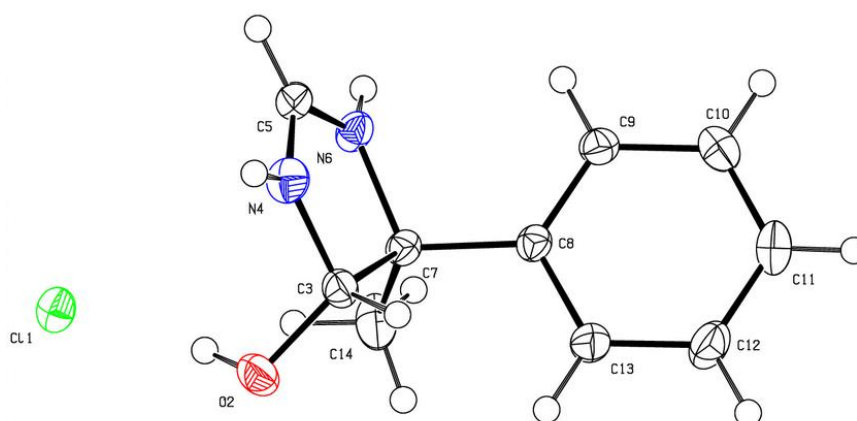
Refinement

$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.025, 0.063, 1.00
No. of reflections	5265
No. of parameters	335
No. of restraints	1
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{\max}$, $\Delta\rho_{\min}$ (e Å ⁻³)	0.22, -0.23
Absolute structure	Flack (1983), 2503 Friedel-pairs
Absolute structure parameter	-0.007 (9)

S1—O2	1.4412 (12)	P17—C25	1.8052 (15)
S1—O3	1.4402 (12)	C19—C20	1.401 (2)
S1—C4	1.8115 (14)	C19—C24	1.395 (2)
S1—C31	1.7633 (16)	C20—C21	1.384 (2)
C4—N5	1.4560 (19)	C21—C22	1.391 (3)
C4—C8	1.5820 (19)	C22—C23	1.385 (3)
N5—C6	1.274 (2)	C23—C24	1.391 (2)
C6—N7	1.3875 (19)	C25—C26	1.394 (2)
N7—C8	1.5101 (16)	C25—C30	1.397 (2)
N7—P17	1.7048 (12)	C26—C27	1.397 (2)
C8—C9	1.521 (2)	C27—C28	1.387 (3)
C8—C16	1.5296 (19)	C28—C29	1.393 (2)
C9—C10	1.396 (2)	C29—C30	1.384 (2)
C9—C15	1.390 (2)	C31—C32	1.386 (2)
C10—C11	1.387 (2)	C31—C36	1.395 (2)
C11—C12	1.381 (2)	C32—C33	1.388 (2)
C12—F13	1.3587 (19)	C33—C34	1.394 (2)
C12—C14	1.369 (2)	C34—C35	1.399 (2)
C14—C15	1.393 (2)	C34—C37	1.503 (2)
P17—O18	1.4800 (11)	C35—C36	1.388 (2)
P17—C19	1.7949 (14)		
O2—S1—O3	119.26 (8)	N7—P17—C19	102.99 (6)
O2—S1—C4	105.90 (7)	O18—P17—C19	113.08 (7)
O3—S1—C4	109.88 (7)	N7—P17—C25	104.38 (6)
O2—S1—C31	108.55 (8)	O18—P17—C25	112.80 (7)
O3—S1—C31	108.05 (7)	C19—P17—C25	107.50 (6)
C4—S1—C31	104.21 (7)	P17—C19—C20	123.09 (11)
S1—C4—N5	110.59 (10)	P17—C19—C24	117.03 (11)
S1—C4—C8	115.11 (10)	C20—C19—C24	119.68 (13)
N5—C4—C8	108.21 (11)	C19—C20—C21	119.94 (15)

C4—N5—C6	105.51 (12)	C20—C21—C22	119.98 (16)
N5—C6—N7	118.39 (13)	C21—C22—C23	120.50 (15)
C6—N7—C8	106.84 (11)	C22—C23—C24	119.78 (16)
C6—N7—P17	119.70 (10)	C19—C24—C23	120.09 (15)
C8—N7—P17	125.58 (9)	P17—C25—C26	117.80 (12)
N7—C8—C4	97.81 (10)	P17—C25—C30	122.03 (11)
N7—C8—C9	110.32 (11)	C26—C25—C30	120.17 (14)
C4—C8—C9	110.27 (11)	C25—C26—C27	119.47 (15)
N7—C8—C16	109.15 (11)	C26—C27—C28	120.09 (15)
C4—C8—C16	113.67 (12)	C27—C28—C29	120.30 (15)
C9—C8—C16	114.38 (12)	C28—C29—C30	119.92 (15)
C8—C9—C10	119.16 (13)	C25—C30—C29	120.04 (14)
C8—C9—C15	121.92 (13)	S1—C31—C32	119.08 (12)
C10—C9—C15	118.92 (14)	S1—C31—C36	119.28 (12)
C9—C10—C11	121.14 (14)	C32—C31—C36	121.55 (15)
C10—C11—C12	117.86 (15)	C31—C32—C33	118.48 (15)
C11—C12—F13	118.27 (15)	C32—C33—C34	121.84 (15)
C11—C12—C14	122.96 (15)	C33—C34—C35	118.07 (15)
F13—C12—C14	118.77 (15)	C33—C34—C37	121.01 (16)
C12—C14—C15	118.46 (14)	C35—C34—C37	120.88 (16)
C14—C15—C9	120.66 (14)	C34—C35—C36	121.37 (15)
N7—P17—O18	115.18 (6)	C31—C36—C35	118.67 (14)

8.2.3 X-Ray Diffraction Data for 183



Crystal data

Chemical formula

$\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}$

M_r

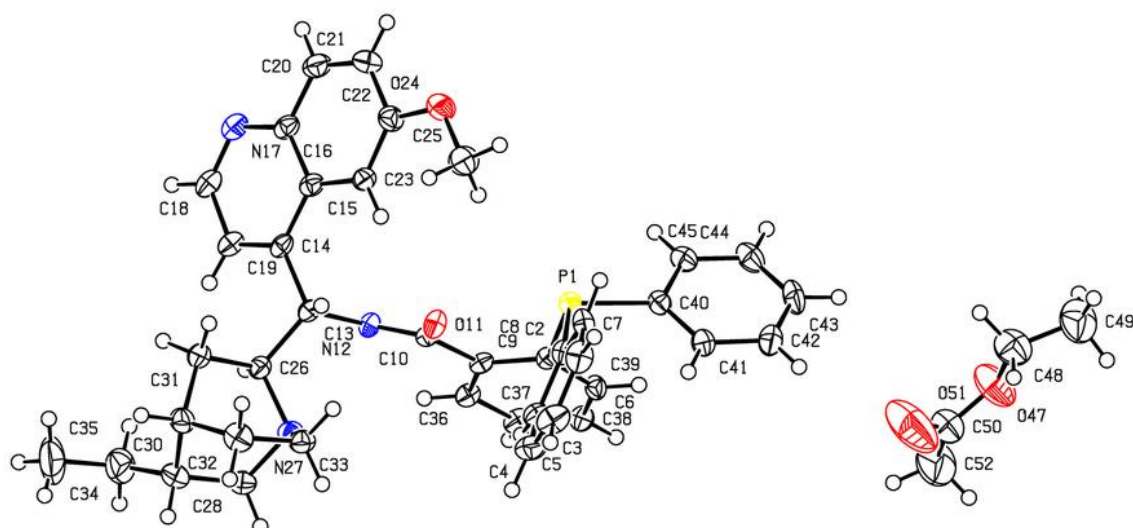
212.68

Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	0
a, b, c (Å)	6.1089 (1), 7.8879 (1), 22.2127 (3)
V (Å ³)	1070.35 (1)
Z	7
Radiation type	Cu $K\alpha$
μ (mm ⁻¹)	2.91
Crystal size (mm)	0.30 × 0.10 × 0.05
<u>Data collection</u>	
Diffractometer	Oxford Diffraction SuperNova
Absorption correction	Multi-scan <i>DENZO/SCALEPACK</i> (Otwinowski & Minor, 1997)
$T_{\min}, T_{\max}$	0.63, 1.00
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	21664, 2237, 2155
R_{int}	0.052
$(\sin \theta/\lambda)_{\max}$ (Å ⁻¹)	0.629
<u>Refinement</u>	
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.023, 0.055, 0.72
No. of reflections	2230
No. of parameters	137
No. of restraints	7
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\max}, \Delta\rho_{\min}$ (e Å ⁻³)	0.22, -0.12
Absolute structure	Flack (1983), 908 Friedel-pairs
Absolute structure parameter	-0.004 (11)

O2—C3	1.3914 (17)	C7—C14	1.5237 (19)
C3—N4	1.4659 (19)	C8—C9	1.3861 (19)
C3—C7	1.5742 (18)	C8—C13	1.3947 (19)
N4—C5	1.3049 (19)	C9—C10	1.397 (2)
C5—N6	1.2985 (18)	C10—C11	1.378 (2)
N6—C7	1.4751 (17)	C11—C12	1.385 (2)
C7—C8	1.5301 (18)	C12—C13	1.389 (2)
O2—C3—N4	111.52 (11)	N6—C7—C14	109.59 (12)
O2—C3—C7	116.31 (12)	C8—C7—C14	109.83 (11)
N4—C3—C7	101.66 (11)	C7—C8—C9	122.46 (12)

C3—N4—C5	110.92 (11)	C7—C8—C13	118.46 (12)
N4—C5—N6	113.46 (11)	C9—C8—C13	118.92 (13)
C5—N6—C7	111.16 (11)	C8—C9—C10	120.31 (13)
C3—C7—N6	101.18 (11)	C9—C10—C11	120.38 (14)
C3—C7—C8	110.83 (11)	C10—C11—C12	119.68 (14)
N6—C7—C8	111.51 (11)	C11—C12—C13	120.18 (14)
C3—C7—C14	113.66 (13)	C8—C13—C12	120.54 (14)

8.2.4 X-Ray Diffraction Data for 31b·AcOEt



Crystal data

Chemical formula	C ₄₃ H ₄₈ N ₃ O ₄ P
<i>M</i> _r	701.85
Crystal system, space group	Monoclinic, <i>P</i> 2 ₁
Temperature (K)	150
<i>a</i> , <i>b</i> , <i>c</i> (Å)	14.5344 (5), 8.0148 (2), 16.6128 (6)
β (°)	102.342 (3)
<i>V</i> (Å ³)	1890.51 (7)
<i>Z</i>	8
Radiation type	Cu Kα
μ (mm ⁻¹)	1.01
Crystal size (mm)	0.20 × 0.20 × 0.15

Data collection

Diffractometer	Oxford Diffraction SuperNova
Absorption correction	Multi-scan <i>CrysAlis PRO</i> , (Agilent, 2011)

$T_{\min}, T_{\max}$	0.96, 1.00
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	20624, 7759, 7360
R_{int}	0.033
$(\sin \theta/\lambda)_{\max}$ ($\text{\AA}^{-1}$)	0.629

Refinement

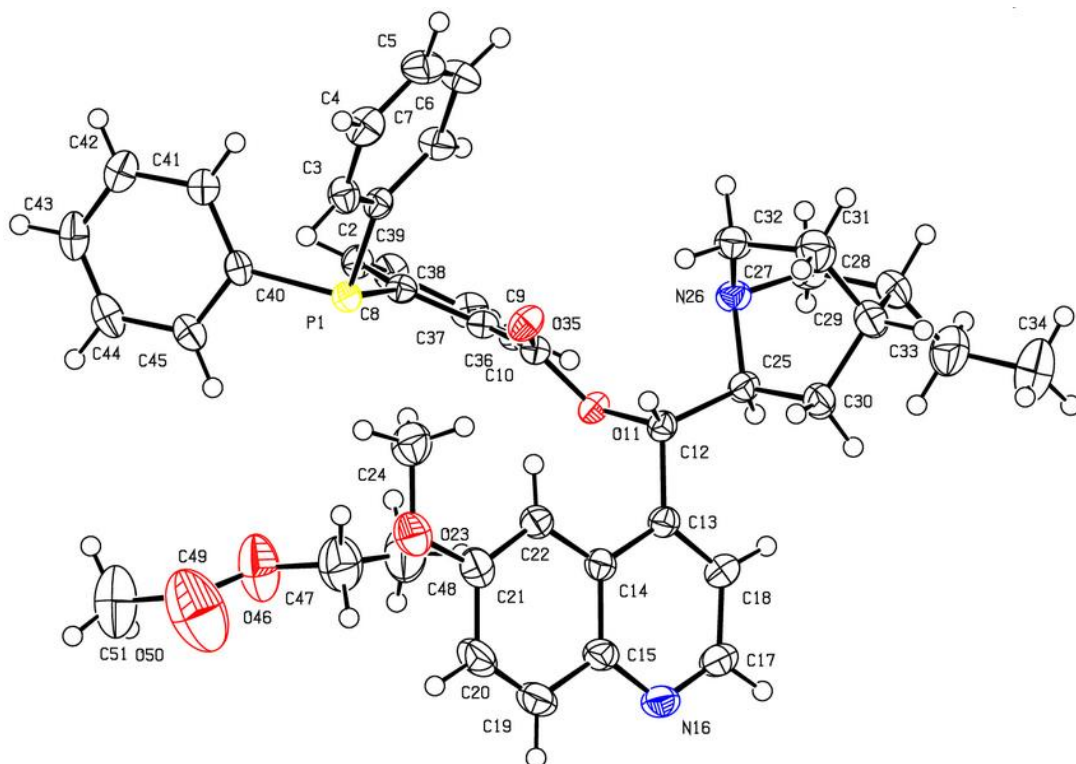
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.041, 0.114, 0.82
No. of reflections	7759
No. of parameters	464
No. of restraints	4
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\max}, \Delta\rho_{\min}$ ($\text{e \AA}^{-3}$)	0.50, -0.45
Absolute structure	Flack (1983), 3554 Friedel-pairs
Absolute structure parameter	0.00 (2)

P1—C2	1.829 (2)	C22—C23	1.378 (3)
P1—C8	1.852 (2)	C22—O24	1.360 (3)
P1—C40	1.848 (2)	O24—C25	1.429 (3)
C2—C3	1.395 (3)	C26—N27	1.477 (3)
C2—C7	1.399 (3)	C26—C31	1.549 (3)
C3—C4	1.387 (3)	N27—C28	1.488 (3)
C4—C5	1.387 (4)	N27—C33	1.469 (3)
C5—C6	1.386 (4)	C28—C29	1.552 (4)
C6—C7	1.384 (4)	C29—C30	1.542 (3)
C8—C9	1.412 (3)	C29—C34	1.523 (4)
C8—C39	1.400 (3)	C30—C31	1.531 (3)
C9—C10	1.502 (3)	C30—C32	1.529 (4)
C9—C36	1.392 (3)	C32—C33	1.541 (4)
C10—O11	1.229 (3)	C34—C35	1.527 (5)
C10—N12	1.351 (3)	C36—C37	1.389 (3)
N12—C13	1.456 (3)	C37—C38	1.385 (3)
C13—C14	1.533 (3)	C38—C39	1.388 (3)
C13—C26	1.539 (3)	C40—C41	1.384 (3)
C14—C15	1.427 (3)	C40—C45	1.404 (3)
C14—C19	1.370 (3)	C41—C42	1.404 (3)
C15—C16	1.424 (3)	C42—C43	1.388 (4)
C15—C23	1.426 (3)	C43—C44	1.383 (4)

C16—N17	1.360 (3)	C44—C45	1.385 (4)
C16—C20	1.425 (3)	O47—C48	1.448 (4)
N17—C18	1.307 (3)	O47—C50	1.284 (4)
C18—C19	1.410 (3)	C48—C49	1.457 (5)
C20—C21	1.359 (4)	C50—O51	1.220 (5)
C21—C22	1.414 (4)	C50—C52	1.490 (6)
C2—P1—C8	106.01 (10)	C21—C22—O24	114.0 (2)
C2—P1—C40	100.48 (10)	C23—C22—O24	125.2 (2)
C8—P1—C40	99.23 (10)	C15—C23—C22	120.0 (2)
P1—C2—C3	124.27 (17)	C22—O24—C25	117.73 (19)
P1—C2—C7	117.17 (17)	C13—C26—N27	112.41 (17)
C3—C2—C7	118.5 (2)	C13—C26—C31	111.41 (18)
C2—C3—C4	120.5 (2)	N27—C26—C31	111.37 (18)
C3—C4—C5	120.5 (2)	C26—N27—C28	106.79 (17)
C4—C5—C6	119.5 (2)	C26—N27—C33	111.97 (17)
C5—C6—C7	120.2 (2)	C28—N27—C33	107.35 (18)
C2—C7—C6	120.8 (2)	N27—C28—C29	112.61 (19)
P1—C8—C9	121.60 (16)	C28—C29—C30	107.0 (2)
P1—C8—C39	120.02 (16)	C28—C29—C34	111.5 (3)
C9—C8—C39	117.53 (19)	C30—C29—C34	114.7 (2)
C8—C9—C10	119.98 (19)	C29—C30—C31	110.0 (2)
C8—C9—C36	120.0 (2)	C29—C30—C32	108.8 (2)
C10—C9—C36	120.0 (2)	C31—C30—C32	107.8 (2)
C9—C10—O11	120.86 (18)	C30—C31—C26	108.16 (19)
C9—C10—N12	116.39 (18)	C30—C32—C33	108.5 (2)
O11—C10—N12	122.74 (19)	C32—C33—N27	112.06 (19)
C10—N12—C13	122.58 (17)	C29—C34—C35	114.3 (3)
N12—C13—C14	108.38 (17)	C9—C36—C37	120.9 (2)
N12—C13—C26	111.46 (17)	C36—C37—C38	120.0 (2)
C14—C13—C26	112.89 (17)	C37—C38—C39	119.1 (2)
C13—C14—C15	120.65 (19)	C8—C39—C38	122.4 (2)
C13—C14—C19	121.6 (2)	P1—C40—C41	125.03 (18)
C15—C14—C19	117.7 (2)	P1—C40—C45	116.19 (18)
C14—C15—C16	117.3 (2)	C41—C40—C45	118.8 (2)
C14—C15—C23	123.8 (2)	C40—C41—C42	120.8 (2)
C16—C15—C23	118.9 (2)	C41—C42—C43	119.8 (2)
C15—C16—N17	123.6 (2)	C42—C43—C44	119.5 (2)
C15—C16—C20	119.1 (2)	C43—C44—C45	120.9 (2)
N17—C16—C20	117.3 (2)	C40—C45—C44	120.2 (2)
C16—N17—C18	116.9 (2)	C48—O47—C50	118.7 (3)
N17—C18—C19	124.3 (2)	O47—C48—C49	107.5 (3)

C18—C19—C14	120.1 (2)	O47—C50—O51	120.7 (4)
C16—C20—C21	120.8 (2)	O47—C50—C52	112.6 (3)
C20—C21—C22	120.3 (2)	O51—C50—C52	125.9 (4)
C21—C22—C23	120.8 (2)		

8.2.5 X-Ray Diffraction Data for 31h·AcOEt



Crystal data

Chemical formula	C ₄₃ H ₄₇ N ₂ O ₅ P
<i>M</i> _r	702.32
Crystal system, space group	Monoclinic, <i>P</i> 2 ₁
Temperature (K)	150
<i>a</i> , <i>b</i> , <i>c</i> (Å)	14.3835 (2), 8.0835 (1), 16.6952 (2)
β (°)	103.0392 (14)
<i>V</i> (Å ³)	1891.08 (2)
<i>Z</i>	2
Radiation type	Cu <i>K</i> α
μ (mm ⁻¹)	1.02
Crystal size (mm)	0.30 × 0.20 × 0.10

Data collection

Diffractometer	Oxford Diffraction SuperNova
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Absorption correction	Multi-scan <i>DENZO/SCALEPACK</i> (Otwinowski & Minor, 1997)
$T_{\min}, T_{\max}$	0.60, 1.00
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	19166, 5741, 5644
R_{int}	0.018
$(\sin \theta/\lambda)_{\max}$ ($\text{\AA}^{-1}$)	0.630
<u>Refinement</u>	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.039, 0.103, 0.89
No. of reflections	5718
No. of parameters	602
No. of restraints	228
H-atom treatment	Only H-atom coordinates refined
$\Delta\rho_{\max}, \Delta\rho_{\min}$ ($\text{e \AA}^{-3}$)	0.23, -0.23
Absolute structure	Flack (1983), 1551 Friedel-pairs
Absolute structure parameter	-0.01 (2)

P1—C2	1.825 (2)	C21—C22	1.369 (3)
P1—C8	1.847 (2)	C21—O23	1.362 (3)
P1—C40	1.839 (2)	O23—C24	1.427 (3)
C2—C3	1.392 (3)	C25—N26	1.476 (3)
C2—C7	1.391 (3)	C25—C30	1.550 (3)
C3—C4	1.387 (3)	N26—C27	1.480 (3)
C4—C5	1.379 (3)	N26—C32	1.467 (3)
C5—C6	1.383 (4)	C27—C28	1.561 (4)
C6—C7	1.387 (3)	C28—C29	1.524 (4)
C8—C9	1.413 (3)	C28—C33	1.529 (4)
C8—C39	1.402 (3)	C29—C30	1.529 (3)
C9—C10	1.480 (3)	C29—C31	1.534 (4)
C9—C36	1.391 (3)	C31—C32	1.544 (4)
C10—O11	1.343 (2)	C33—C34	1.520 (6)
C10—O35	1.208 (3)	C36—C37	1.386 (3)
O11—C12	1.455 (2)	C37—C38	1.383 (3)
C12—C13	1.516 (3)	C38—C39	1.391 (3)
C12—C25	1.534 (3)	C40—C41	1.395 (3)
C13—C14	1.433 (3)	C40—C45	1.396 (3)
C13—C18	1.371 (3)	C41—C42	1.395 (3)
C14—C15	1.418 (3)	C42—C43	1.379 (4)
C14—C22	1.424 (3)	C43—C44	1.373 (4)
C15—N16	1.365 (3)	C44—C45	1.392 (3)

C15—C19	1.424 (3)	O46—C47	1.445 (4)
N16—C17	1.310 (3)	O46—C49	1.277 (4)
C17—C18	1.408 (3)	C47—C48	1.451 (5)
C19—C20	1.343 (4)	C49—O50	1.219 (5)
C20—C21	1.420 (4)	C49—C51	1.498 (6)
C2—P1—C8	106.36 (9)	C20—C21—O23	114.0 (2)
C2—P1—C40	101.58 (9)	C22—C21—O23	125.5 (2)
C8—P1—C40	99.54 (9)	C14—C22—C21	120.1 (2)
P1—C2—C3	116.83 (15)	C21—O23—C24	117.33 (18)
P1—C2—C7	124.50 (16)	C12—C25—N26	112.16 (15)
C3—C2—C7	118.59 (19)	C12—C25—C30	110.71 (18)
C2—C3—C4	120.7 (2)	N26—C25—C30	111.08 (18)
C3—C4—C5	120.4 (2)	C25—N26—C27	106.36 (16)
C4—C5—C6	119.2 (2)	C25—N26—C32	112.20 (18)
C5—C6—C7	120.9 (2)	C27—N26—C32	107.50 (18)
C2—C7—C6	120.2 (2)	N26—C27—C28	112.1 (2)
P1—C8—C9	120.84 (16)	C27—C28—C29	107.41 (19)
P1—C8—C39	120.64 (14)	C27—C28—C33	110.9 (3)
C9—C8—C39	117.46 (18)	C29—C28—C33	114.7 (2)
C8—C9—C10	120.64 (18)	C28—C29—C30	110.2 (2)
C8—C9—C36	120.6 (2)	C28—C29—C31	108.9 (2)
C10—C9—C36	118.73 (17)	C30—C29—C31	107.59 (19)
C9—C10—O11	111.27 (17)	C25—C30—C29	108.21 (19)
C9—C10—O35	124.56 (16)	C29—C31—C32	107.8 (2)
O11—C10—O35	124.17 (18)	C31—C32—N26	112.52 (19)
C10—O11—C12	118.26 (15)	C28—C33—C34	114.3 (4)
O11—C12—C13	105.39 (16)	C9—C36—C37	120.48 (18)
O11—C12—C25	107.73 (16)	C36—C37—C38	119.9 (2)
C13—C12—C25	114.60 (15)	C37—C38—C39	119.9 (2)
C12—C13—C14	120.07 (17)	C8—C39—C38	121.54 (18)
C12—C13—C18	122.24 (19)	P1—C40—C41	124.86 (16)
C14—C13—C18	117.58 (19)	P1—C40—C45	116.34 (16)
C13—C14—C15	117.22 (19)	C41—C40—C45	118.8 (2)
C13—C14—C22	123.71 (19)	C40—C41—C42	120.2 (2)
C15—C14—C22	119.05 (19)	C41—C42—C43	120.1 (2)
C14—C15—N16	123.6 (2)	C42—C43—C44	120.2 (2)
C14—C15—C19	118.8 (2)	C43—C44—C45	120.3 (2)
N16—C15—C19	117.6 (2)	C40—C45—C44	120.3 (2)
C15—N16—C17	117.20 (19)	C47—O46—C49	119.7 (3)
N16—C17—C18	123.8 (2)	O46—C47—C48	107.8 (3)
C17—C18—C13	120.5 (2)	O46—C49—O50	121.5 (4)

C15—C19—C20	121.1 (2)	O46—C49—C51	113.9 (3)
C19—C20—C21	120.5 (2)	O50—C49—C51	124.5 (4)
C20—C21—C22	120.5 (2)		

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