Novel Applications of Catalytic Aza-Wittig Chemistry

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Acknowledgements

Potiusque sero quam nunquam
– Better late than never,
Unofficial Crossley family motto.

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Abstract

This thesis details recent advances in the field of redox neutral organocatalytic aza-Wittig chemistry, contributing to ongoing research into the development of novel catalytic processes for the synthesis of heterocycles. Work described herein forms the next chapter in continuing research into the organocatalytic aza-Wittig reaction first published by the Marsden group in 2008. Three distinct applications of novel catalytic aza-Wittig chemistry are reported.

The first chapter reviews recent advances in the field of organocatalytic phosphorous reactions, covering both redox-mediated and redox-neutral methodologies. While there has been a recent spate of publications detailing a range of phosphine catalysed reactions the majority detail a redox mediated system whereby the phosphine oxide waste is reduced *in situ* to the active phosphine species which undergoes traditional reaction conditions, for example the Wittig, Staudinger and Appel reactions. Work by the Denton and Marsden group offers an alternative strategy employing a system which maintains a phosphorus(V) oxidation state.

The subsequent results and discussion sections comprises four areas. Firstly, the use of hydroxamic acids and hindered ureas as masked isocyanate starting materials was investigated. The Lossen rearrangement was found to be a valid alternative to the Curtius rearrangement for the *in situ* formation of isocyanates for the application of the catalytic aza-Wittig reaction. 1,1-Diisopropyl ureas were found to behave as masked isocyanates which produced the isocyanate on heating again proving to be suitable as starting materials for the catalytic intermolecular aza-Wittig. A range of phenanthridines were synthesised using the azide-free intramolecular aza-Wittig reaction, employing hydroxamic acids as starting materials.

For the first time, the redox-neutral aza-Wittig reaction was used for the synthesis of a benzodiazepine, a biologically active seven-membered ring system. Catalyst loadings of 5 mol% were successfully employed with no loss in yield.

Finally, the metathetical nature of the catalytic aza-Wittig reaction was explored in the context of aza-enyne metathesis, an analogous reaction to the well-known metal catalysed enyne metathesis reaction. This novel reaction pathway led to the synthesis of a trisubstituted quinoline from simple and commercially available starting materials and led to interesting mechanistic observations.

Relevant experimental procedures are reported in full alongside data for synthesised compounds. Bibliographic data is also presented at the back of the report.

Contents

Abbreviations

Å	Angstrom/ 0.1 nm
Ac	Acetyl
aq.	Aqueous
Ar	Aryl group
Boc	*tert*-Butoxycarbonyl
Bn	Benzyl
br.	Broad
Bu	Butyl
Cbz	Carboxybenzyl
CDI	Carbonyl diimidazole
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
dbpf	1,10-bis(di-*tert*-butylphosphino) ferrocene
DCE	Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
DIPEA	Diisopropylethylamine
DMAD	Dimethyl acetylenedicarboxylate
DMAP	4-*N*,*N*-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DPPA	Diphenylphosphoryl azide
ee	Enantiomeric excess
eq.	Equivalents
ESI	Electrospray Ionisation
Et	Ethyl
Fmoc	Fluorenylmethyloxycarbonyl
GABA	*gamma*-Aminobutyric acid
h	Hour(s)
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
Hex	Hexyl
HMDS	Bis(trimethylsilyl)amine

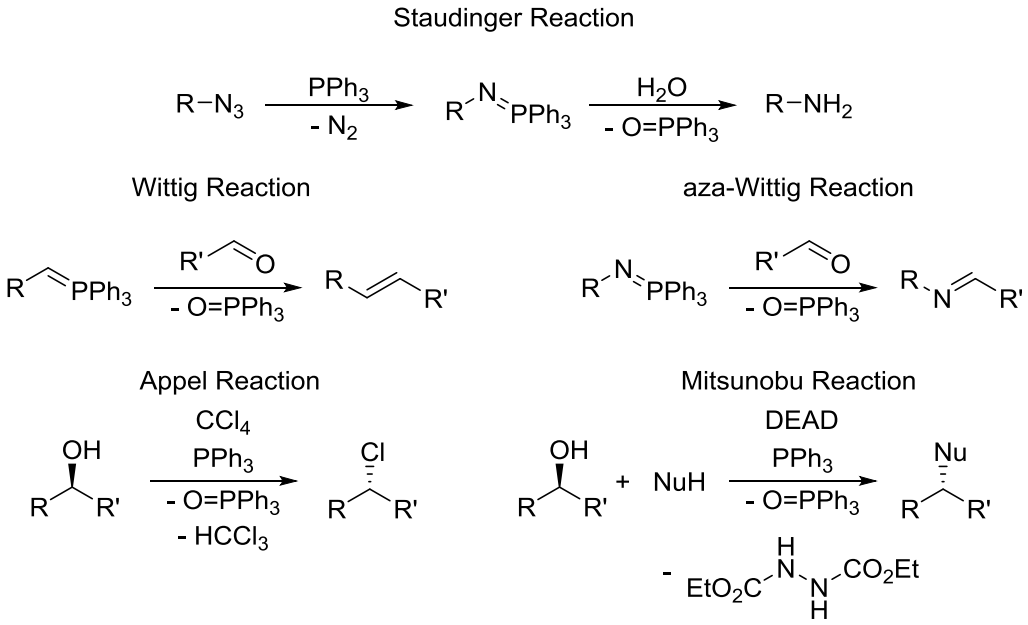
HMQC	Heteronuclear Multiple-Quantum Coherence
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
m	Meta
M	Mol dm^{-3}
Me	Methyl
Mes	Mesityl
Min	Minute(s)
MS	Mass Spectrometry
M.p.	Melting Point
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser effect
Nu	Nucleophile
o	Ortho
p	Para
Ph	Phenyl
PMB	*para*-Methoxybenzyl
Pr	Propyl
PS	Polystyrene
q	Quartet
quin	Quintet
R	Carbon substituent
RT	Room Temperature
s	Singlet
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TBME	Methyl *tert*-butyl ether
TFA	Trifluroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
Tip	2,4,6-triisopropylphenyl
TMDS	tetramethyldisiloxane
TMS	Trimethylsilyl

Chapter 1:

Catalytic Variants of Phosphorus-Mediated Reactions

1. Introduction to Catalytic Variants of Phosphorus-Mediated Reactions

Phosphine-mediated chemistry is an important weapon in the arsenal of any synthesis chemist and is employed on a multi-ton scale for the synthesis of important pharmaceuticals.[1] So influential has been the chemistry of phosphines that some of the most well-known chemists made their names working in this area. The names Staudinger, Wittig, Appel and Mitsunobu are synonymous with phosphine mediated reactions, indeed both Staudinger (1953) and Wittig (1979) received Nobel prizes in chemistry. Staudinger published work on iminophosphoranes reporting the both the Staudinger reaction and the aza-Wittig reaction, which actually predates its carbon name sake reaction by 35 years.[2, 3] Popular for formation of carbon-carbon double bonds, the Wittig reaction has been widely utilised by chemists since its discovery in 1954.[4] The Appel reaction involves the conversion of an alcohol to the corresponding alkyl halide with inversion of stereochemistry.[5] Similarly, the Mitsunobu reaction also results in inversion of stereochemistry but with the replacement of alcohol with a nucleophile (Scheme 1).[6]



Scheme 1: Important examples of phosphine-mediated reactions.

The unifying feature of these reactions is the formation of a phosphine oxide species which provides the driving force for these reactions. A phosphorus-oxygen double bond is very strong (128 kCal mol^{-1})[7] whose formation is energetically favoured allowing reactions to be carried out under generally mild reaction conditions, typically at room temperature. One major drawback associated with this strategy is disposal of large amounts of inert phosphine

oxide waste after the reaction. Traditionally phosphine oxide waste streams are incinerated due to difficulties in separation and reduction. Reducing phosphine oxides to the phosphine(III) state requires toxic activating reagents such as phosgene or combination of forcing conditions and metal hydrides to pay the energetic costs associated with cleaving this strong bond.[8] Disposal is not the only issue associated with the production of phosphine oxide waste. Removing phosphine oxides from desired products can be difficult, due to their water insolubility, amorphous solid state and polar nature, generally requiring chromatography on lab-scale which restricts their use on larger scales. Reactions producing stoichiometric phosphine oxide waste suffer from low atom efficiency because of the high molecular weight of these compounds (triphenylphosphine oxide mw = 278.29 g/mol, tributylphosphine oxide mw = 218.32 g/mol). In recent years more and more is being done to recover phosphorus compounds from waste streams because it is increasingly viewed as a finite resource due to costs associated with extracting it from minerals.[9] While it is estimated that 0.1% of rocks contain phosphorus, it is thought that at current rates of consumption reserves of economically recoverable phosphorus are expected to be depleted in 50-100 years.[9]

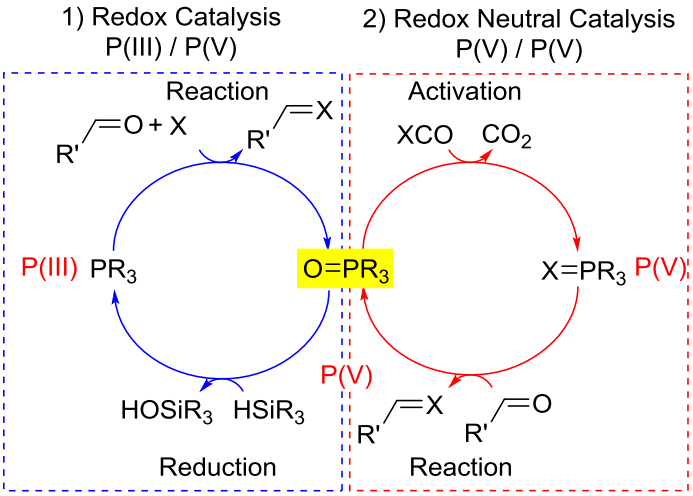
In recent years the pursuit of catalytic protocols for phosphorus-mediated reactions has become in vogue. The earliest attempts at producing a catalytic variant of phosphorus-mediated reaction veered away from phosphorus compounds and resorted to other pnictogens (group 15 elements). Arsenic,[10, 11] antimony[12] and tellurium[13] compounds have been reported to behave in an analogous manner to phosphorus but were appreciably easier to reduce, due to their weaker oxide bond, although it should be noted that the toxicity and carcinogenic hazards associated with these compounds limit their practicality, especially on an industrial scale.

On the contrary, phosphine oxides are generally non-toxic and therefore have none of the poisoning issues associated with the use of transition metal catalysts, another advantage phosphine mediated processes have over traditional metal catalysis. Two distinct pathways have been developed for organocatalytic phosphine reactions (Scheme 2). Either;

1) Redox catalysis: whereby the active phosphine(III) species is regenerated by selective *in situ* reduction of the phosphine oxide product.

2) Redox neutral catalysis: the catalyst maintains a P(V) oxidation state, with an active species in the P(V) state generated from the phosphine oxide.

Both of these methods have pros and cons and have been applied to a number of systems, with each being favoured by different academic groups for a variety of reasons.



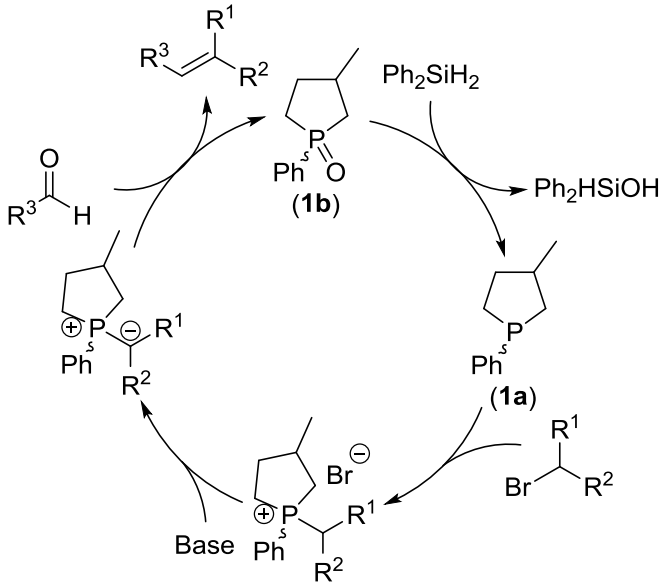
Scheme 2: Pathways developed for organocatalytic phosphine reactions.

1.1. Redox-Mediated Organocatalytic Phosphine Methodologies

Conceptually simple but practically difficult, redox methodologies require a selective reduction of phosphine oxide, leaving sensitive groups untouched.[14] Traditional reducing agents such as lithium aluminium hydride and trichlorosilane which are known to reduce phosphine oxides are incompatible with other groups such as ketones, carboxylic acids and amides which are required in a number of phosphine-mediated methodologies.[7] Recently milder silanes have been found to selectively reduce phosphine oxides, with and without the aid of a catalyst. Both O'Brien *et al.*[14-16] and van Delft *et al.*[17-19] have reported reactions utilising diphenylsilane as an *in situ* reducing agent for catalytic phosphine reactions. The first example of a phosphine-catalysed Wittig reaction was reported by O'Brien *et al.* in 2009 and has since been adopted by other groups.[20, 21] van Delft *et al.* have developed catalytic methodology for the Appel reaction,[17] Staudinger reduction[18] and the aza-Wittig reaction.[19] Both O'Brien and van Delft have reported extensively on the subject with other groups reporting briefly on the results of their redox-mediated phosphorus catalysed reactions.

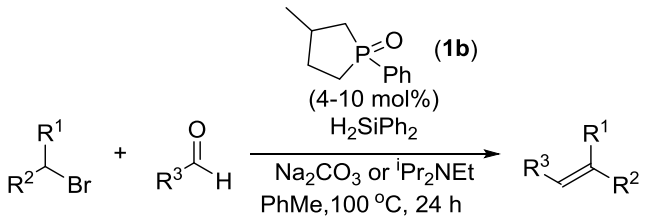
1.1.1. Redox-Mediated Catalytic Wittig Reaction

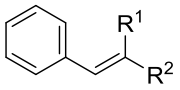
The original work by O'Brien's group produced a total 50 examples of alkenes in moderate to excellent yields with some degree of selectivity (Scheme 4). This protocol tolerated aliphatic, aromatic and heterocyclic aldehydes to produce di- and trisubstituted alkenes. Organobromides sporting esters, nitriles, ketones and electron-deficient benzyl derivatives react with the active phospholane (**1a**) species producing the corresponding phosphonium salt, which is deprotonated by a base to form the stabilised ylid species. This then undergoes the traditional Wittig step, forming the desired alkene product and the phosphole oxide which is then subsequently reduced by the silane (Scheme 3). These silanes reduce phosphine oxides with no loss of chirality at the phosphorus. The phosphine of choice for these reactions was the cyclic phospholane oxide (**1b**) which has been found to undergo reduction more rapidly than acyclic phosphines. A range of process-friendly solvents could be employed using either a biphasic system with solid sodium carbonate base suspended in solution or a single-phase system using a soluble base diisopropylethylamine (DIPEA).[15]



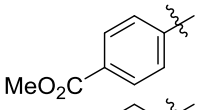
Scheme 3: Proposed mechanism for the catalytic Wittig reaction.[15]

While the average *E*/*Z* selectivity was moderate at 66:34, *E* selectivity was markedly higher for α,β-unsaturated products (Scheme 4). It was found that products derived from bromides sporting ketones and esters had higher *E* selectivities than those derived from bromoacetonitriles which was accounted to a phosphane-mediated isomerisation. This process was found to lead to the complete conversion of (*Z*)-cinnamic acid methyl ester to the (*E*)-alkene in 10.5 hours. While the propenenitrile only underwent a 6% conversion after 50 hours. Of note was the *N*-tosyl pyrrole derivative which was (*Z*)-selective (34:66, *E*:*Z*) this unusual selectivity is attributed to the *N*-tosyl group stabilising the *cis*-oxaphosphetane preventing interchange between isomers leading to the kinetic product as reported by Gilheany and Byrne.[22]

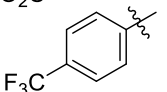




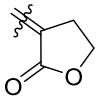
R^1	R^2	Yield	*E/Z*
CO_2Me	H	74%	>95:5
CN	H	80%	75:25
$CO_2{}^tBu$	H	96%	>95:5
CO_2Me	Me	77%	83:17
COPh	H	74%	>95:5
CO^tBu	H	90%	>95:5
COMe	Me	77%	80:20



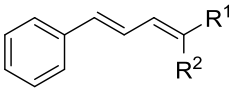
H 70% 60:40



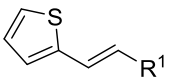
H 70% 60:40



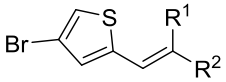
74% >95:5



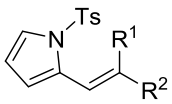
R^1	R^2	Yield	*E/Z*
CO_2Me	H	70%	83:17
COMe	Me	86%	>95:5



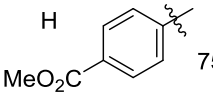
R^1	R^2	Yield	*E/Z*
CO_2Me	H	73%	>95:5
CN	H	74%	66:34



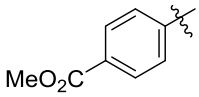
R^1	R^2	Yield	*E/Z*
CO_2Me	Me	91%	70:30
CN	Me	77%	66:34



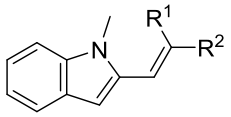
R^1	R^2	Yield	*E/Z*
CO_2Me	H	76%	50:50



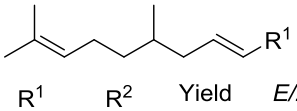
H 75% 34:66



H 68% 50:50



R^1	R^2	Yield	*E/Z*
CO_2Me	Me	89%	60:40
Me	CN	94%	40:60

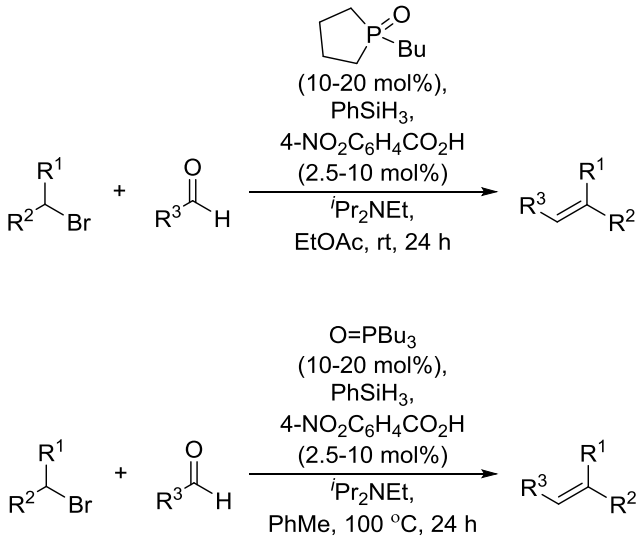


R^1	R^2	Yield	*E/Z*
CO_2Me	H	70%	88:12

91% 70:30

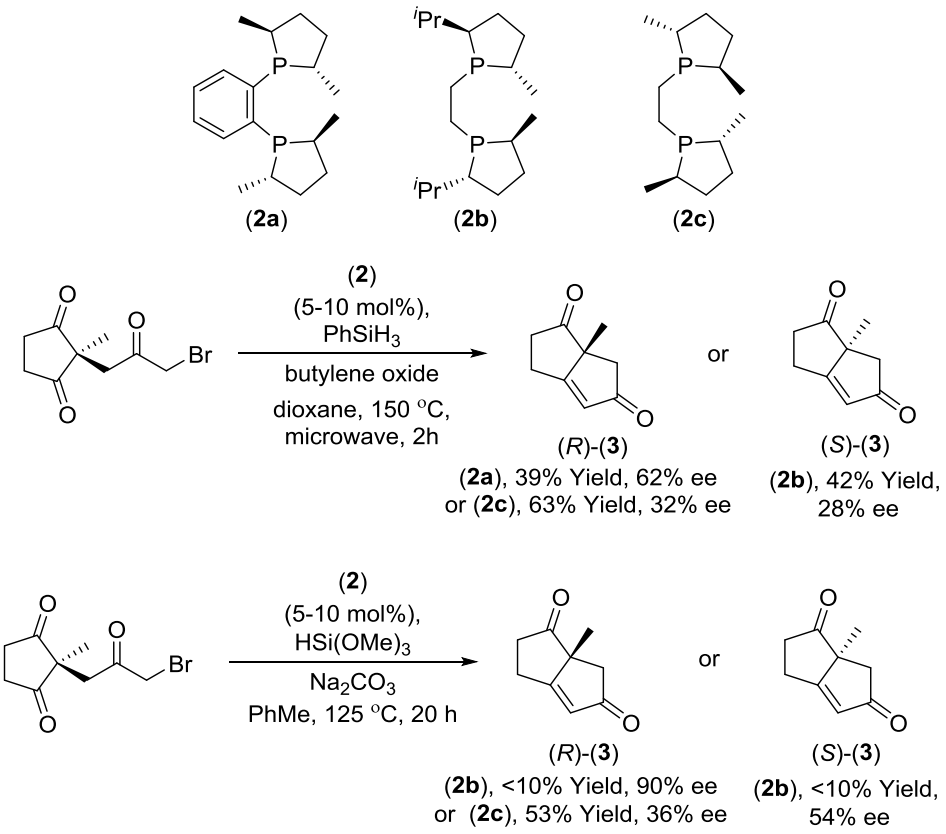
Scheme 4: Examples of products from O'Brien *et al.* catalytic Wittig chemistry.[15]

Originally prolonged high temperatures were required for the reaction to proceed, generally 100 °C for 24 hours, but more recently O'Brien reported that addition of catalytic 4-nitrobenzoic acid and a switch from diphenylsilane to phenylsilane enhanced the rate of reaction to the point that reactions could be carried out at room temperature in as little as 6 minutes. Alternatively, less active acyclic phosphines, such as triphenylphosphine, could be used alongside the 4-nitrobenzoic but to offset the reduced activity, high temperatures were required. Either system can be used with little to no loss of yield (Scheme 5).[16] The authors proposed that the 4-nitrobenzoic acid proton acts as a Lewis acid, increasing the activity of the silane, accelerating the rate of reaction. Although it should be noted that this mechanism is unlikely as the acid will be deprotonated by the DIPEA.



Scheme 5: Enhancements to redox mediated catalytic Wittig reactions.[16]

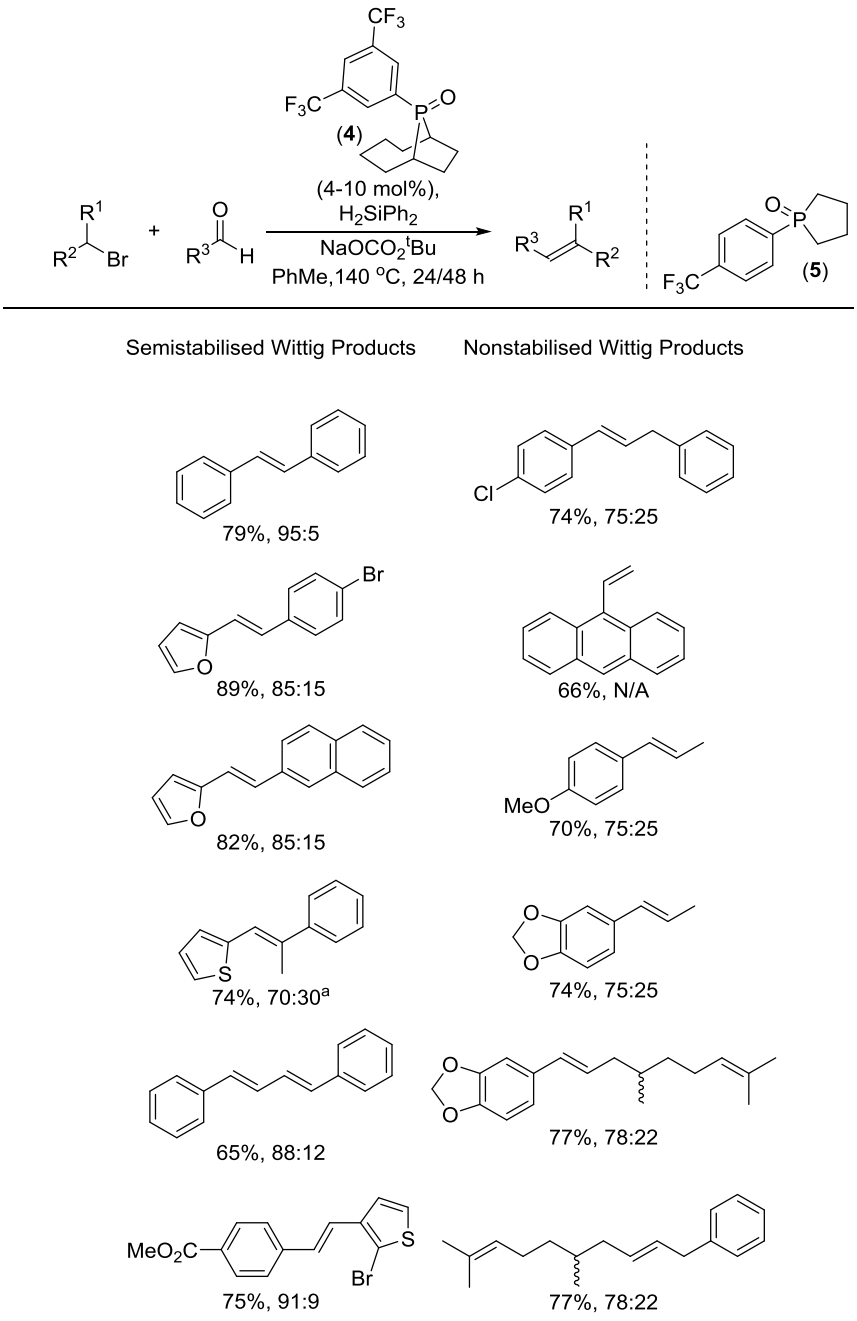
Werner *et al.* reported a set of conditions for a microwave-assisted catalytic Wittig reaction, which boasts reduced reaction times (3 hours), increased yields and the use of acyclic tributylphosphine oxide as catalyst. They also demonstrates the use of (*S*,*S*)-Me-DuPhos (**2**) as an asymmetric catalyst under these conditions to give (**3**) in a 39% yield and good *E*/*Z* selectivity of 81 : 19.[21] Before the publication of this microwave assisted protocol, Werner *et al*. reported the synthesis of (**3**) by conventional heating with *E*/*Z* selectivity up to 95 : 5, taking the honour of producing the first enantioselective catalytic Wittig reaction (Scheme 6).[20]



Scheme 6: First examples of enantioselective catalytic Wittig reaction.[20,21]

More recently, O'Brien *et al.* have published their work on the catalytic Wittig reaction of semi- and nonstabilized ylids, bearing benzyl, cinnamyl, heterocylic and aliphatic groups.[23] To enable the use of semi- and nonstabilized ylids, a stronger base had to be found, one that could deprotonate protons with higher pK_a values (pK_a 17-18 for semistabilized ylids and 22-25 for nonstabilized ylid), yet mild enough to be compatible with the reaction conditions. Typically NaHMDS, ^{n}BuLi, NaO^{t}Bu or NaOH are used for the deprotonation of non-stabilized ylids but these would not be compatible with the catalytic Wittig reaction protocol. The use of the masked base $NaCO_3{}^t$Bu met both of these demands by gradually releasing NaO^{t}Bu *in situ* avoiding undesired side reactions. With a pK_a of 18, NaO^{t}Bu would still be incapable of adequate deprotonation of nonstabilized ylids (pK_a 22-25) so the phosphine portion of the ylid had to be tuned to increase acidity. They found the optimal catalyst to be bicyclic phospholene oxide (**4**) which incorporating an electron-withdrawing aryl group to increase the acidity of the proton and an additional ring to shield one face, allowing for *E*/*Z*-selective reactions. As expected, using catalyst (**4**) led to increased *E* selectivity, increasing average selectivity from 66 : 34 observed using the cyclic phosphole (**5**) to > 95 : 5 for semistabilised system and 75 : 25 for non-stabilised ylids. Unfortunately decreased electron-density on the phosphorus reduced its activity requiring an increase in reaction temperature from 100 °C to 140 °C

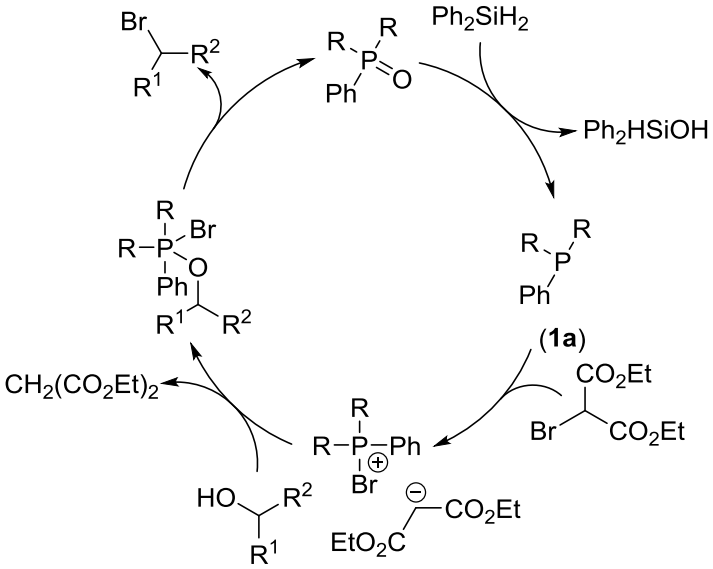
(Scheme 7). This is claimed to be the first catalytic Wittig system suitable for semi- and nonstabilised ylids, and at time of writing is the only example reported.



Scheme 7: Catalysed Wittig reaction of semi- and non-stabilized ylids. a) Catalyst (**5**) used.[23]

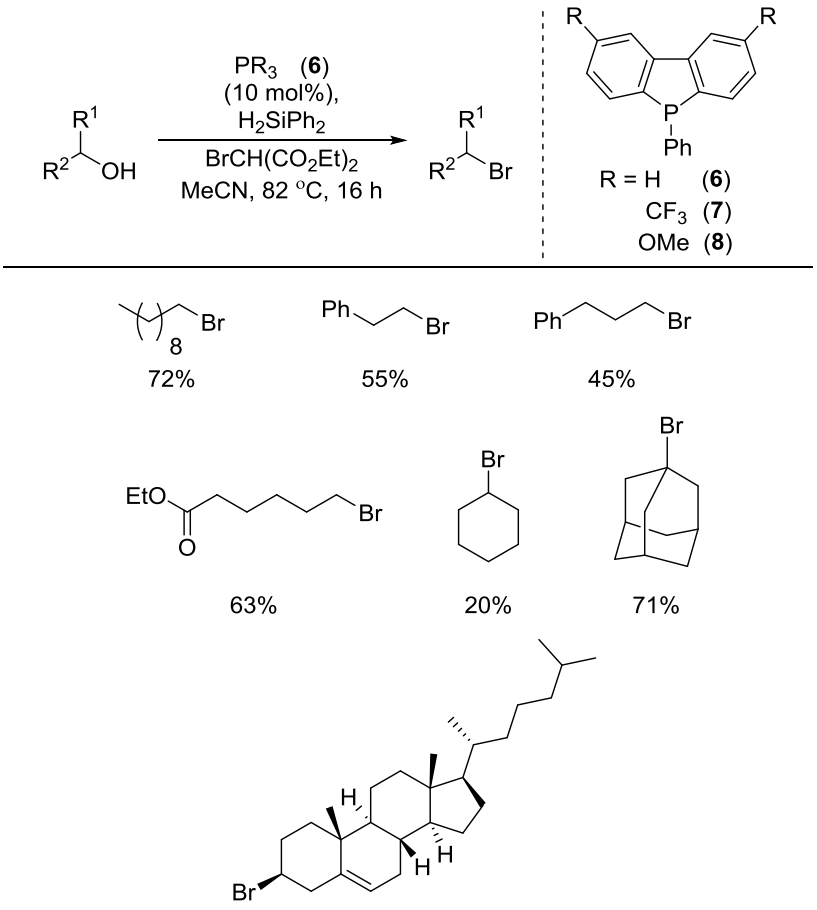
1.1.2. Redox-Mediated Catalytic Appel Reaction

The first example of redox-mediated phosphine-catalysed Appel reaction was reported by van Delft *et al.* in 2011 and involved the *in situ* reduction of substoichiometric phosphine oxide. One of the main differences between this work and O'Brien's is the use of dibenzophosphole (**6a**) as the catalyst (Scheme 8). It was hoped that the oxide of an aromatic phosphole would be a better catalyst, more readily reduced because of increased ring strain and the return to aromaticity on reduction. Interestingly, the reduction of dibenzophosphole oxide (**6b**) was found to be approximately 1.5 times slower than the reduction of O'Brien's phospholane oxide catalyst (**1b**). Even after this surprising discovery dibenzophospholes were still selected as the catalyst because of their novelty and the ability to tune their electronics. Oxides of electron-poor dibenzophosphole (**7**) sporting CF_3 groups had a decreased rate of reduction, while the oxide of the electron-rich 2,8-dimethoxy-dibenzophosphole (**8**) had an increased rate of reduction and increased nucleophilicity, which also led to low conversions due to alkylation of the phosphole by the bromide products. Unsubstituted aromatic dibenzophosphole (**6a**) was found to be superior to substituted dibenzophospholes and the aliphatic phospholane (**1a**) for the application of the catalytic Appel reaction with a yield of 82% using dibenzophosphole (**6a**), 68% for 2,8-di methoxy-dibenzophosphole (**8**) and 17% using phospholane (**1a**). A variety of bromonium donors were screened. Bromine, tetrabromomethane, *N*-bromosuccinimide, *N*-bromoacetamide and 2,4,4,6-tetrabromocyclohexa-2,5-dienone were found to react rapidly with the diphenylsilane, leading to its consumption before it could reduce the phosphine oxide. Further investigation found diethyl bromomalonate reacted sufficiently slowly with the silane allowing it to be utilised as a bromonium source.



Scheme 8: Proposed mechanism for the redox-mediated Appel reaction.

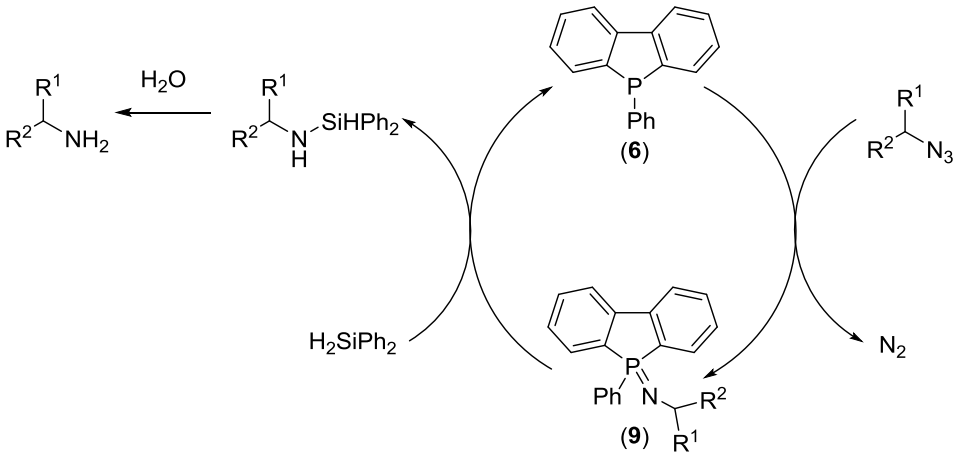
By using 10 mol% dibenzophosphole (**6**), diphenyl silane and diethyl bromomalonate, primary, secondary and tertiary alcohols were converted into the corresponding bromides (Scheme 9). Attempts were made to develop the corresponding Appel reaction for the formation of the chlorides, but no suitable chloronium donors could be found.[17]



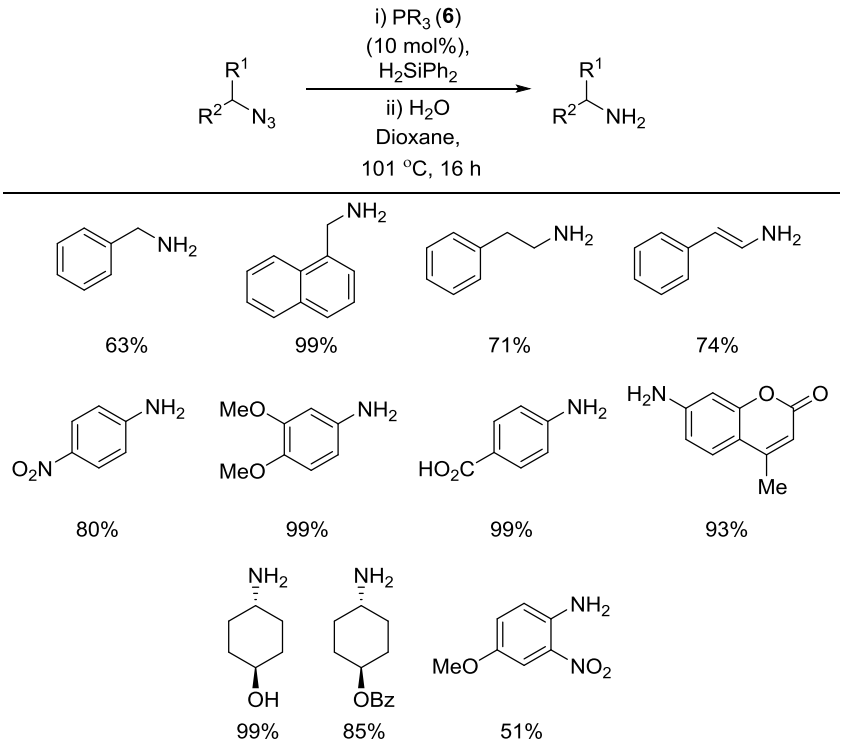
Scheme 9: Results of the van Delft's phosphine catalysed Appel reaction.[17]

1.1.3. Development of Redox-Mediated Staudinger/Aza-Wittig Reaction

The catalytic Staudinger reduction was the next reaction developed, an important step towards a redox-mediated catalytic aza-Wittig reaction.[18] Unlike traditional Staudinger methodology the catalytic reaction is carried out under anhydrous conditions due to the incompatibility of the silanes with water. Instead, upon completion of the reduction step an aqueous quench is performed to hydrolyse the silane-amine adduct. Once again van Delft *et al.* use their favoured catalyst, dibenzophosphole (**6**), and offer a comparison with triphenylphosphine. Monitoring the reduction of dibenzophosphole-derived iminophosphorane (**9**) by ^{31}P NMR shows complete conversion to phosphole (**6**) within 160 minutes, while the analogous triphenylphosphine iminophosphorane takes 20 hours to go to completion. The control reaction omitting phosphole verified that the reducing reagent alone cannot give the expected amine product. The proposed reaction mechanism involves the formation of the iminophosphorane by the classic Staudinger reaction, which is then reduced by the phenylsilane to recover the phosphine and form the silane-amine adduct which readily undergoes hydrolysis on aqueous work-up (Scheme 10). Using this methodology eleven azides were reduced to the corresponding amines including aromatic azides, benzylic azides and aliphatic azides in good to excellent yields. Reaction conditions were found to be tolerant of nitro, carboxylic acids, esters, alcohols and olefin groups (Scheme 11). Success with this reaction led the van Delft group to adapt this reaction into a catalytic aza-Wittig variant.



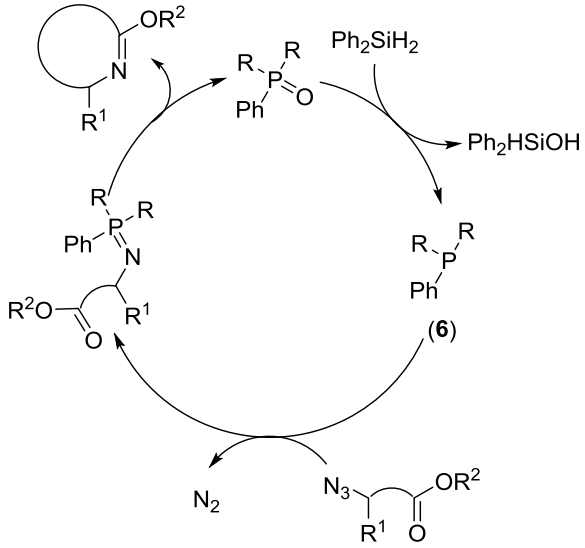
Scheme 10: Proposed catalytic cycle for van Delft's Staudinger reaction.[18]



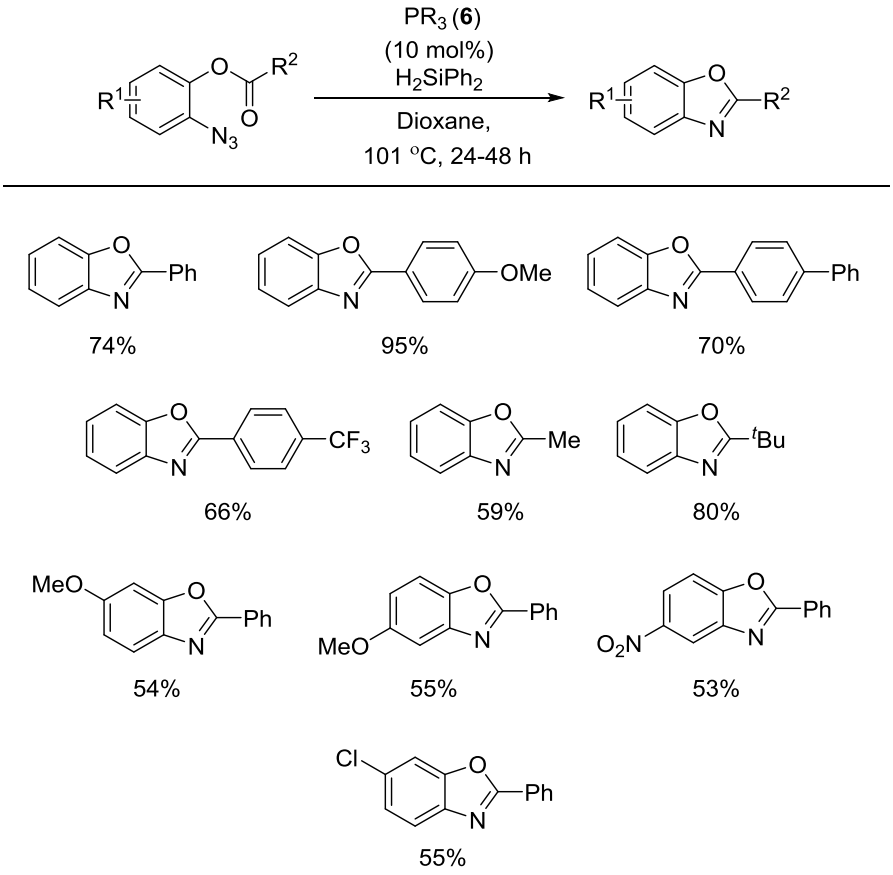
Scheme 11: Results from van Delft's catalytic Staudinger reduction.[18]

van Delft *et al.* envisaged the iminophosphole intermediate (**9**) formed during the catalytic Staudinger reaction could react with a pendant ester group to produce *N*-heterocycles via the aza-Wittig reaction (Scheme 12).[19] Competing with the desired cyclization was the undesired reaction of iminophosphorane with silane, the pathway employed in the previously mentioned Staudinger reduction. It was found that both the reduction of *N*-benzo-iminophosphorane derived from (**6**) and dibenzophosphole oxide took 20 hours to go to completion. Indeed, the reduction of the iminophosphorane was a serious complication, with the amine by-product accounting for the majority of lost yield. For the synthesis of 2-phenyl-benzoxazoles, the use of phenylsilane, a stronger reducing reagent than the previously used diphenylsilane, resulted in a lower yield (50% yield) than the less active diphenylsilane (74% yield) due to increased reduction of the iminophosphorane intermediate. In the absence of silane only 10% conversion to the aza-Wittig product was observed, accounting for a single turnover of the amount of phosphole catalyst (10 mol%). Slow addition of silane over 24 hours was found to lead to higher isolated yields for the 5-chlorobenzoxazole (65% yield vs. 55%) as did higher catalyst loadings (35 mol%, 84% yield). The optimised conditions (10 mol% of dibenzophosphole, 1.1 equivalents of diphenylsilane at 0.2 M in dioxane heated to reflux for 24 hours), produced ten benzoxazoles with a range of substituents isolated from the corresponding 2-azidophenyl esters. It was found that starting materials sporting electron-rich esters led to higher isolated yields and those with electron-poor esters suffered from lower

yields. This result are at odds with those reported for the classical aza-Wittig by Johnson *et al.* who found electron-poor esters had an accelerated rate of reaction.[24] Variations on the aromatic ring seemed to have a smaller impact on the yield, with both electron-withdrawing and electron-donating groups leading to lower yields (Scheme 13). Both of these observations suggest that the increased complexity of the catalytic system complicates electronic effects.

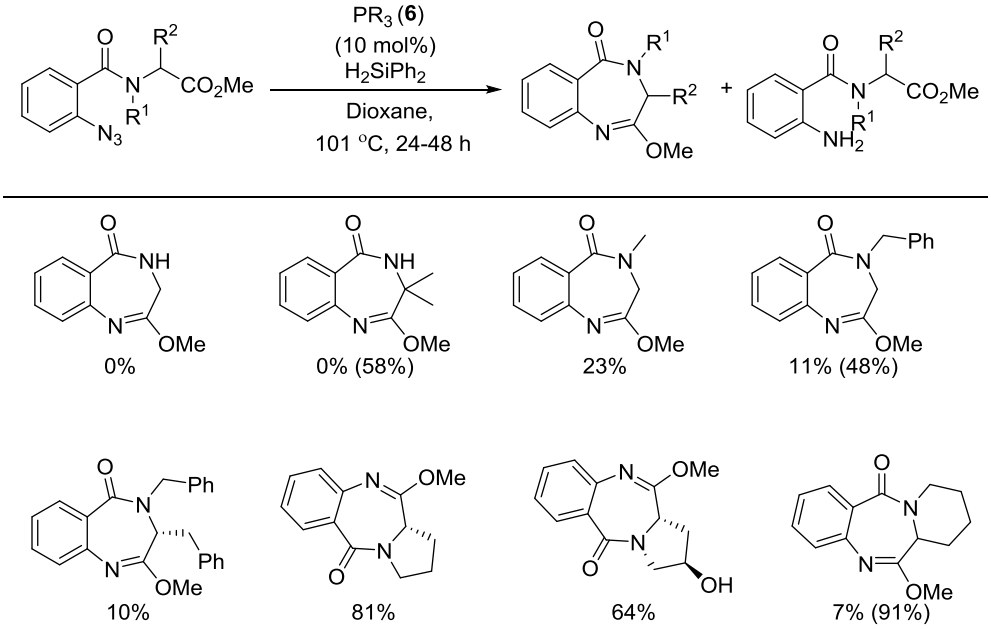


Scheme 12: Proposed mechanism for redox mediated aza-Wittig reaction.[19]



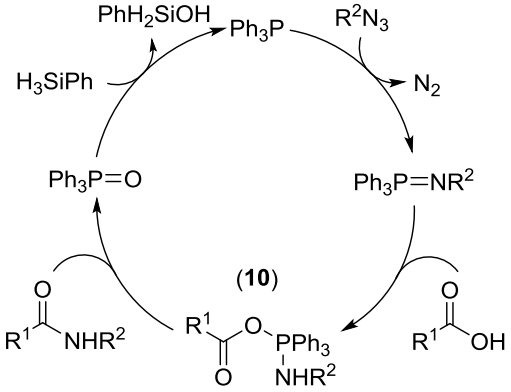
Scheme 13: Results from the redox mediated aza-Wittig reaction.[19]

Next the group turned to the synthesis of pharmaceutically interesting benzodiazepines. Using conditions optimised for the synthesis of benzoxazoles a range of benzodiazepines were produced in poor to good yields (Scheme 14). While the more constrained proline derivatives gave good yields, the flexible amino acid derivatives suffered from low yields and in some cases led to only isolation of the aniline product, formed from the direct Staudinger reduction.



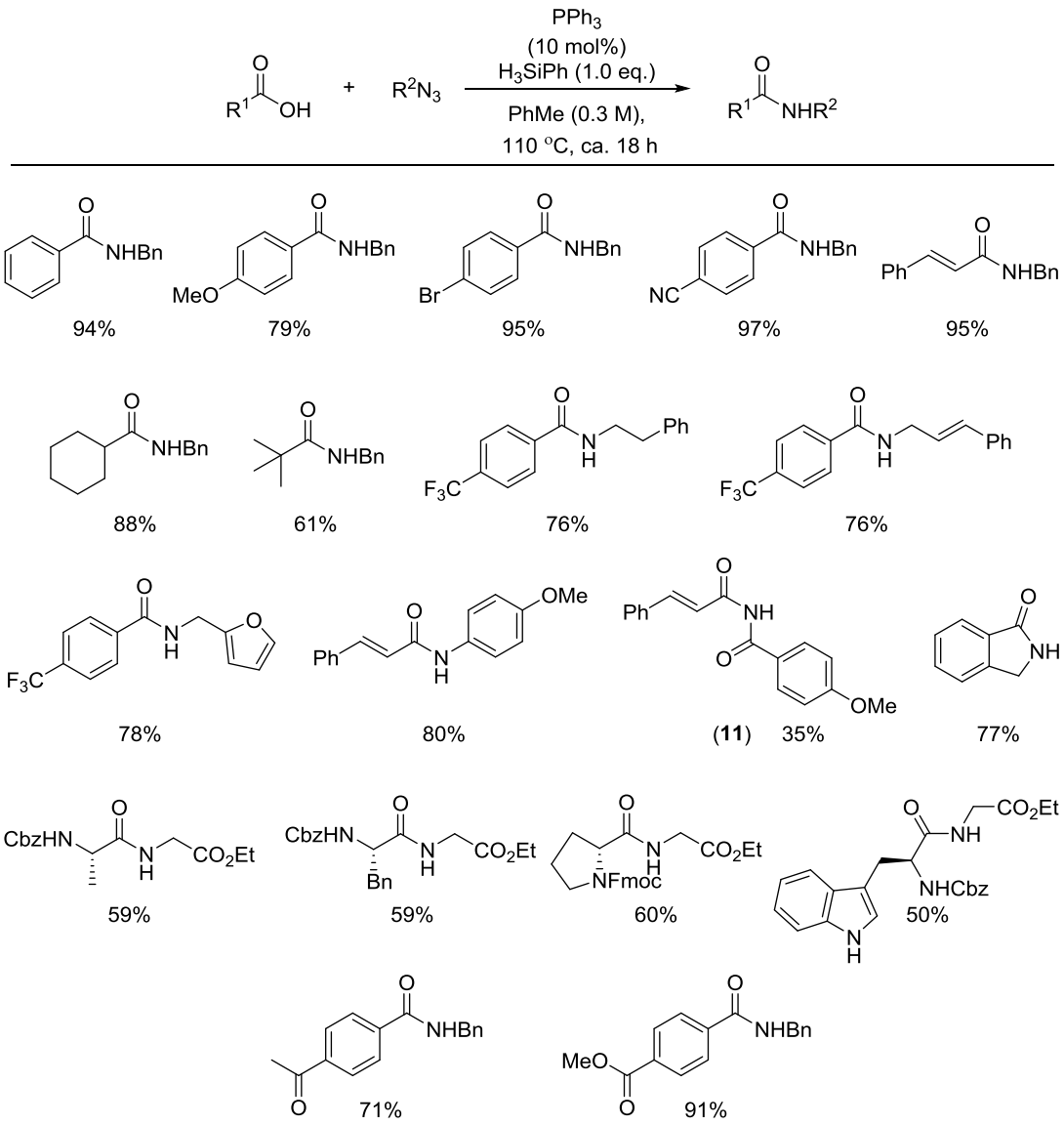
Scheme 14: Results for synthesis of benzodiazepines using redox mediated catalytic aza-Wittig reaction. (Percentages in parenthesis are yield of corresponding anilines).[19]

Another of Staudinger's reactions, the ligation of carboxylic acids with azides, has also been developed into a redox-mediated catalytic cycle by Ashfield *et al.*.[25] Similar to the aza-Wittig reaction, the Staudinger ligation reaction proceeds *via* an iminophosphorane intermediate, which adds to the carboxylic acid to form intermediate (**10**) which rearranges to the amide and phosphine oxide (Scheme 15). Aiming to reduce the amount of iminophosphorane consumed by the silane, triphenylphosphine was used as the catalyst due to the sluggish reduction of triphenylphosphine derived iminophosphoranes as reported by van Delft.[19] Using catalytic triphenylphosphine (10 mol%) and phenylsilane as the reducing agent a range of aryl and alkyl azides coupled with both aryl and alkyl carboxylic acids in high yields (Scheme 16). The reaction also worked with acyl azide to give a modest yield of imide (**11**).



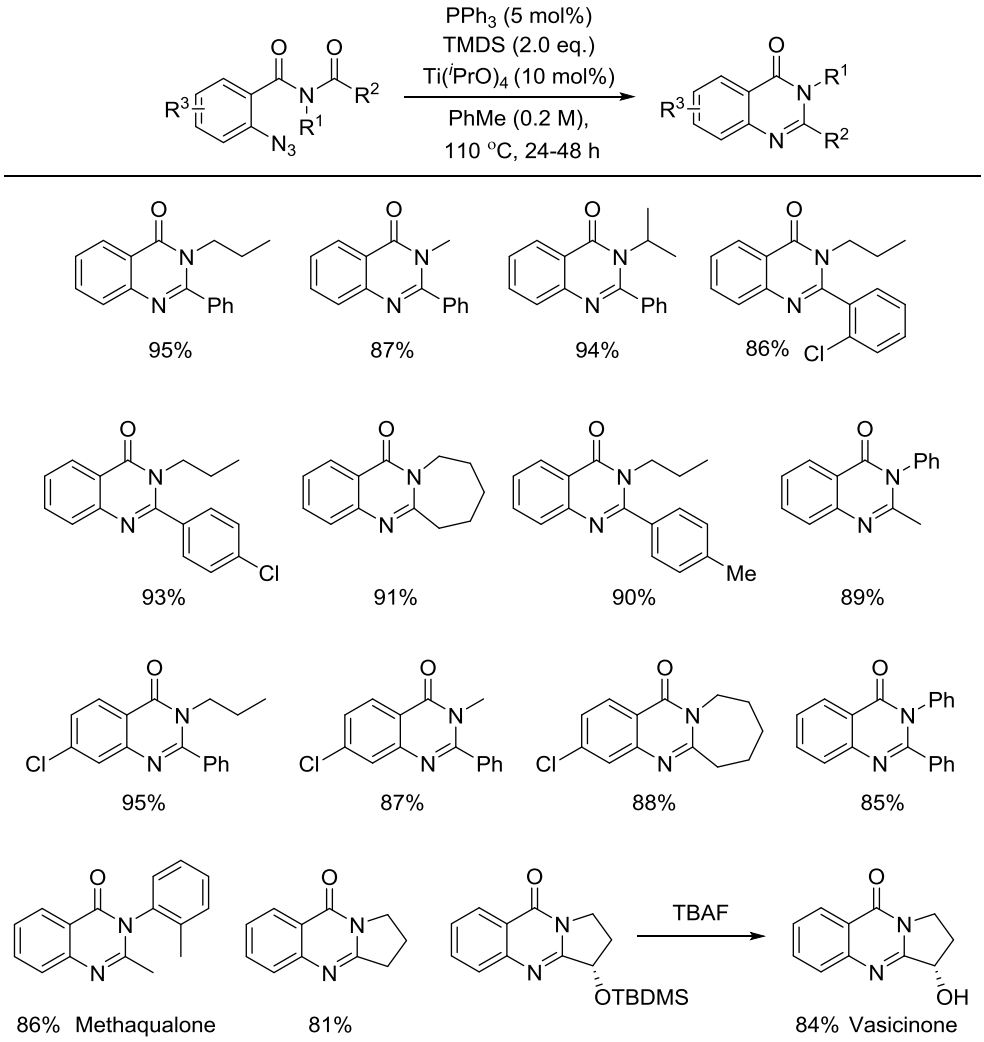
Scheme 15: Proposed mechanism for the catalytic Staudinger ligation reaction.[25]

As previously demonstrated by the redox-mediated Staudinger reaction (Scheme 10), it is feasible the iminophosphorane intermediate is reduced by the silane under the reaction conditions casting doubt on the proposed mechanism. The reaction may alternatively proceed via a silane mediated mechanism whereby the carboxylic acid is activated by the silane. However they report that pre-formed silyl ester failed to produce more than trace amounts of amide on addition of triphenylphosphine and azide, though it should be noted that phenylsilane was replaced with less reactive diphenylsilane in this test. No control reactions lacking phosphine were reported.



Scheme 16: Results of the catalytic Staudinger ligation reaction.[25]

More recently, Ding *et al.* reported a redox-mediated catalytic aza-Wittig reaction for the synthesis of quinazolinones and the natural product vasicinone using a mixture of tetramethyldisiloxane (TMDS) and 10 mol% $Ti(O^iPr)_4$ as the reductant system.[26] The advantage of this system is that the stoichiometric reductant, TMDS, is an inexpensive by-product of the silicon industry (£398/Kg[27]). While the addition of an additional catalyst is less than ideal the use of TMDS is a dramatic improvement over the use of diphenylsilane and phenylsilane both economically and environmentally. In the absence of $Ti(O^iPr)_4$ or phosphine oxide there was no reaction, no product was observed. Even replacing the TMDS and $Ti(O^iPr)_4$ with diphenyl-, phenyl- or triethylsilane failed to produce any product. Surprisingly, there proved to be little to no difference in activity between the cyclic phosphines (**1a**) and (**6**) and triphenylphosphine oxide. Optimisation studies found that catalyst loadings could be reduced to 5 mol% with no loss in yield, but the rate of reaction dropped, going from being complete in 8 hours (for 20 mol% catalyst loading) to 24 hours (for 5 mol%). Optimised conditions (5 mol% phosphine oxide, 10 mol% $Ti(O^iPr)_4$, refluxing toluene, 24 hours) gave high yields of

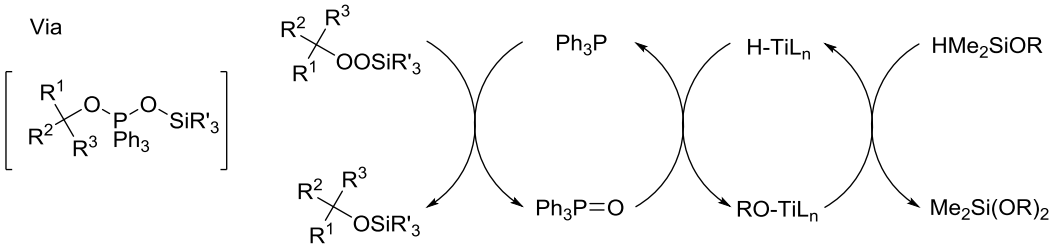


Scheme 17: Results from Ding *et al.* catalytic aza-Wittig reaction.[22]

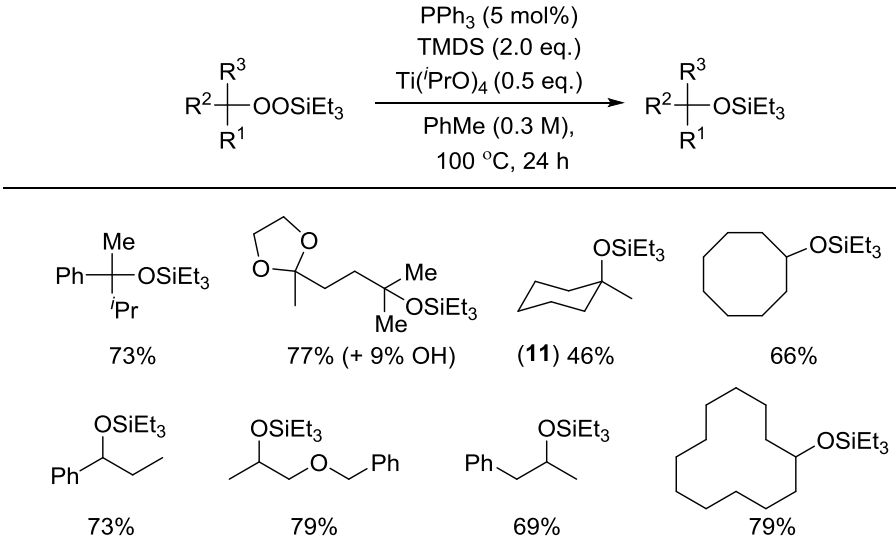
the quinazolinones from the corresponding azides, including the natural product vasicinone (Scheme 17).

In terms of future developments it is notable that alternative catalysts have been found for the chemoselective reduction of phosphine oxides using these cheap silanes as the terminal reducing agent. Beller *et al.* have reported two such reactions, the first of which utilised 10 mol% copper triflate and TMDS (3.0 eq.),[28] the second a phosphoric acid catalyst (7.5 mol%) which acts as a Lewis acid activating diethoxymethylsilane (4.0 eq.).[29] Both methods produced a range of phosphines in good to very good yields and were chemoselective tolerating aldehydes, ketones and olefins. Indium tribromide ($InBr_3$) was found by Lemaire *et al.* to be an active catalyst for the reduction of phosphine oxides using TMDS. Very low loadings of $InBr_3$ (1 mol%) proved to be comparable to the reductions using 10 mol% $Ti(O^iPr)_4$.[30]

One example of catalytic reduction was employed in the reduction of silyl protected peroxides.[31] Woerpel *et al.* developed a catalytic protocol for the reduction of triethylsilyl peroxides to the protected alcohols utilising a triphenylphosphine catalyst in a redox mediated reaction (Scheme 18). Optimisation of this reaction involved a balancing act with respect to the reducing agents; too strong (e.g. $LiAlH_4$ and Cl_3SiH) and the peroxide would be reduced to the alcohol without intervention of the phosphine, too weak and the phosphine oxide would not be reduced and the catalytic cycle would not turn over. The ideal conditions involved a mixture of $Ti(O^iPr)_4$ (5 mol%) and TMDS (2.0 eq.) as the reductants and catalytic triphenylphosphine (5 mol%) in a solution of toluene at 100 °C stirred over 24 hours. The best protecting group was found to be triethylsilyl, which was robust enough to survive the reaction conditions and aqueous work up. Trimethylsilyl protecting groups did not survive extraction, providing low isolated yields of the silyl ester. Interestingly, although un-protected peroxides were readily reduced by the mixture of $Ti(O^iPr)_4$ (5 mol%) and TMDS (2.0 eq.) in the absence of the phosphine, the silyl protected peroxides did not undergo reduction without the phosphine catalyst, leading to complete recovery of starting material. Using these optimised conditions a range of triethylsilyl esters were prepared from the corresponding protected peroxides in good yields with complete retention of configuration where applicable (Scheme 19). The low yield of (**11**) can be attributed to the volatility of the product.



Scheme 18: Catalytic cycles involved in the reduction of silyl peroxides.[31]



Scheme 19: Results of the catalytic reduction of silyl peroxides.[31]

1.1.4. Life-cycle Assessment of Redox-Mediated Protocols

To investigate whether the use of silane reducing agent and small amounts of phosphorus is indeed environmentally advantageous Huijbregt *et al.* published a life cycle assessment of both classical and redox-mediated Wittig and Appel reactions.[8] Their calculations show that catalytic Appel reaction does not offer any advantage with respect to greenhouse gases release or energy consumption. The production of diethyl chloromalonate, the chlorination reagent required to replace the tetrachloromethane in the catalytic reaction, requires more energy than the amount offset by replacing the phosphine reagent with silane. Interestingly, Figure 1 clearly shows the significant contribution that the solvent, acetonitrile, makes to greenhouse gas production and cumulative energy demand. Indeed it is known that in most cases solvent production adds about 75% of total energy usage.[32]

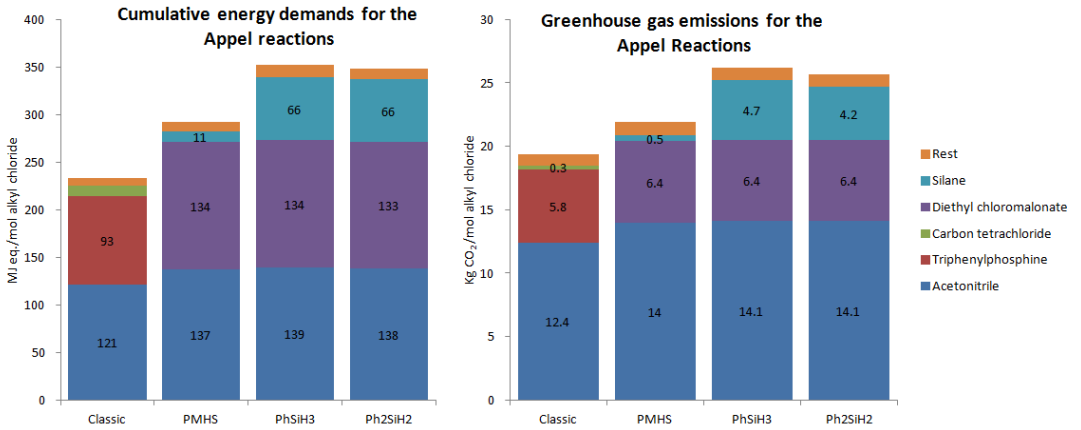


Figure 1: Life cycle assessment of redox mediated catalytic Appel reaction as calculated by Huijbregt *et al.*.[32]

However switching to a catalytic Wittig reaction offers a marked reduction in energy demands and greenhouse gas production (Figure 2). The results are even more marked when using polymethylhydrosiloxane, an industrial by-product similar to TMDS, which again shows the importance of further research into the use of by-product silanes. Diphenylsilane and phenylsilane both provide an 18% reduction in energy demands and 35% reduction in greenhouse gas emission. These results are very interesting and highlight issues that need to be addressed to improve the redox-mediated reactions, in particular the use of more environmentally friendly silanes and the use of less energy demanding solvents or reduction in the amount of solvents used.

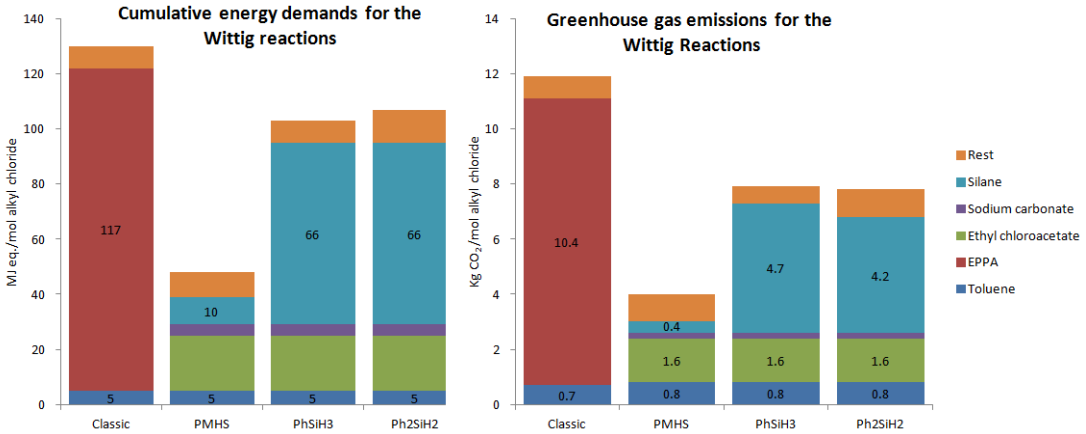
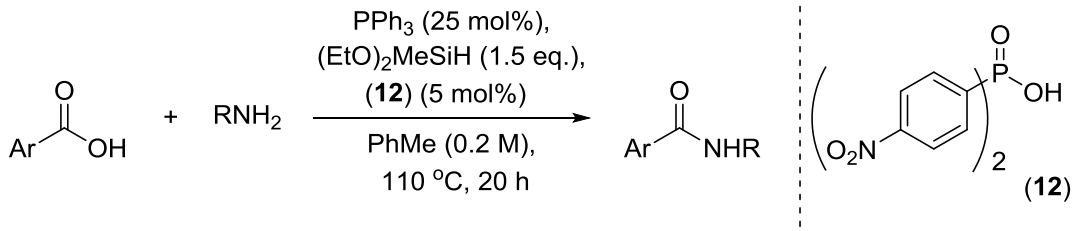
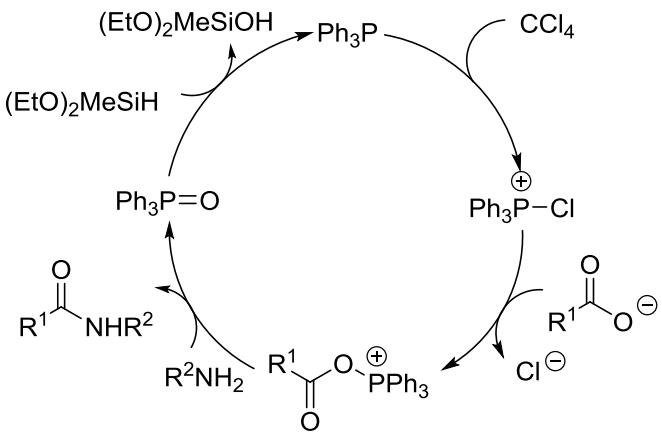


Figure 2: Life cycle assessment of redox mediated catalytic Wittig reaction as calculated by Huijbregt *et al.*.[32]

1.1.5. Miscellaneous Redox-Mediated Phosphine Catalysed Reactions

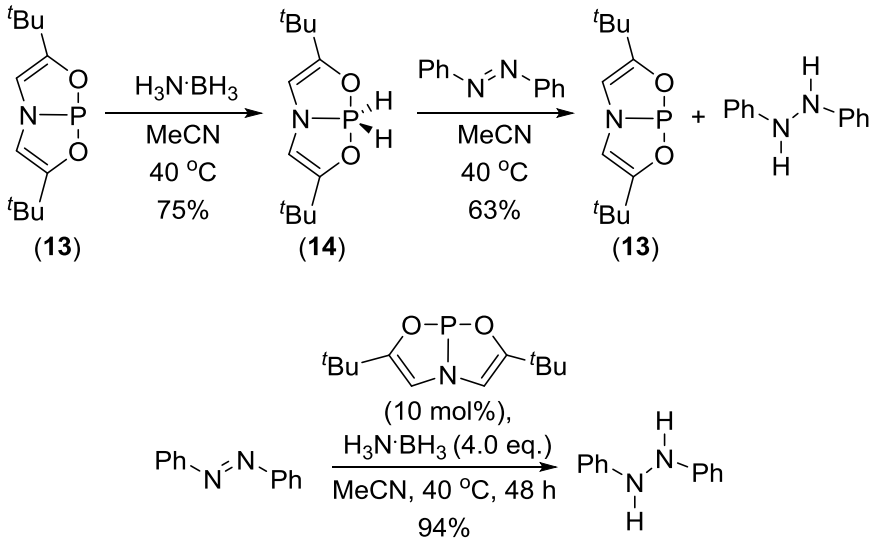
A methodology for the formation of amide bonds utilising a redox-mediated phosphine catalytic cycle has recently been reported by Mecinović *et al*.[33] It was first shown that Appel conditions (stoichiometric triphenylphosphine and CCl_4) could be used to activate carboxylic acids for the formation of amides. By introducing the phosphonic acid (**12**) catalysed reduction similar to those reported by Beller[29] to the reaction, the phosphine could be used catalytically (Scheme 20). Alternative methods for the *in situ* reduction of phosphine oxide were attempted but failed to turn the reaction over leading to little/no product. *Para*-substituted benzoic acids were coupled with benzylamine in excellent conversions (70% - 90%) with isolated yields between 54 and 76%, the *para*-methoxy benzoic give a low conversion of 52%. Picolinic and quinaldic acids gave excellent conversions of 99% and 72% yields respectively. A range of primary and secondary amines sporting both aliphatic and aromatic groups were coupled with 4-nitrobenzoic acid in good to excellent conversions (65% - 98%), with the exception of aniline which, expectedly, suffered from a low conversion (35%) attributed to low nucleophilicity. Enantiomerically pure (*S*)-1-phenylethylamine gave 90% conversions with complete retention of stereochemistry. As expected in the absence of silane and phosphonic acid the conversions were below 25%, which corresponds to the amount of triphenylphosphine in the reaction (25 mol%).





Scheme 20: Phosphine catalysed methodology for amide bond formation.[33]

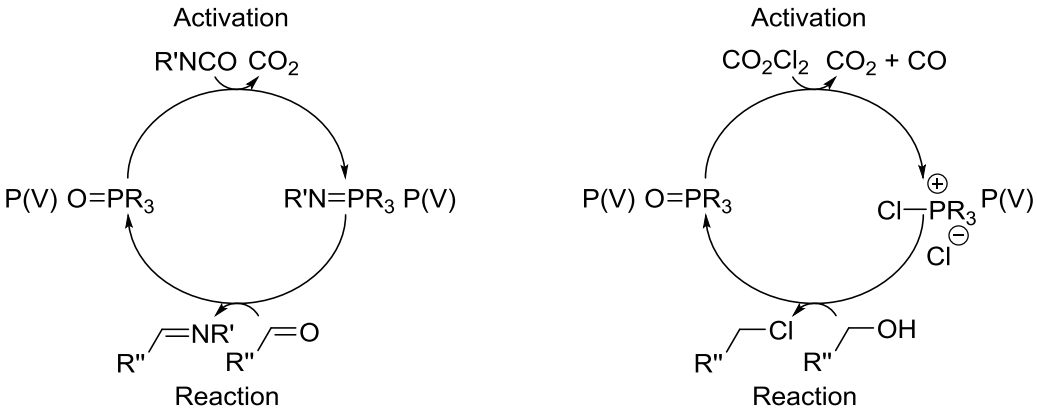
A completely novel methodology has been developed by Radosevich *et al.* which utilises a constrained phosphorus compound that emulates metal complexes ability to carry out transfer hydrogenation.[34] The phosphorus is constrained into an unusual tricoordinate T-shaped geometry by its substituents, analogous to a transition metal complex constrained by a tridentate ligands. This tricoordinate phosphine 'complex' can abstract two hydrogens from ammonia-borane to produce a trigonal bipyridal pentavalent species which was observed by ^{31}P-NMR as a triplet of triplets at δ -43.7 ppm with J = 670 and 34 Hz and ^{1}H-NMR as a pair of doublets at δ 7.95 ppm ($^{1}J_{PH}$ = 670 Hz) and δ 5.83 ppm ($^{3}J_{PH}$ = 34 Hz) displaying characteristic phosphorus-coupled doublet. It could be isolated in 75% yield by trituration and was examined using X-ray diffraction which found that the structure had distorted from the usual trigonal bipyridal towards a square pyramid shape around the phosphorus. This dihydridophosphorane was used to transfer hydrogens onto unsaturated azobenzene transforming it to 1,2-diphenylhydrazine in a 63% yield in 19 h at 40 °C. While there is no reaction between 4 equivalents of ammonia-borane and azobenzene in acetonitrile the addition of 10 mol% phosphine (**13**) leads to an 80% yield of diphenylhydrazine after 24 hours at 40 °C. Analysing the catalytic reaction using ^{31}P-NMR showed the rapid conversion of (**13**) to the dihydridophosphorane species (**14**) which remained throughout the reaction. This is the first example of a catalytic transfer hydrogenation reaction using a phosphorus complex, a territory usually reserved for transition metals (Scheme 21).



Scheme 21: Radosevich *et al.* phosphine catalysed transfer hydrogenation.[34]

1.2. Redox-Neutral Organocatalytic Phosphine Methodologies

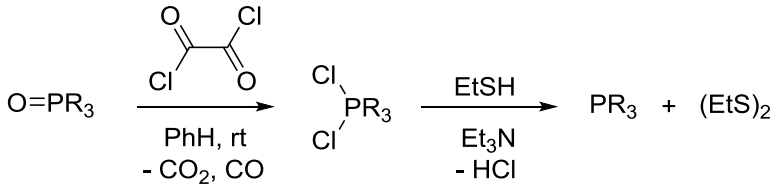
As mentioned earlier there is an alternative set of methodologies which forgo the redox cycle, instead maintaining the P(V) oxidation state throughout the reaction. Instead of undergoing reduction with silane the phosphine oxide is activated by addition of active starting material or reagent which forms the active phosphine species. These methodologies have the distinct advantage of not requiring stoichiometric amounts of reducing agents or phosphine reagents, increasing the atom efficiency drastically. Currently the two methods developed produce carbon dioxide as the major by-product and it is the loss of this gas which drives the equilibrium and the reaction (Scheme 22).



Scheme 22: Redox neutral organocatalytic phosphine catalytic cycles.

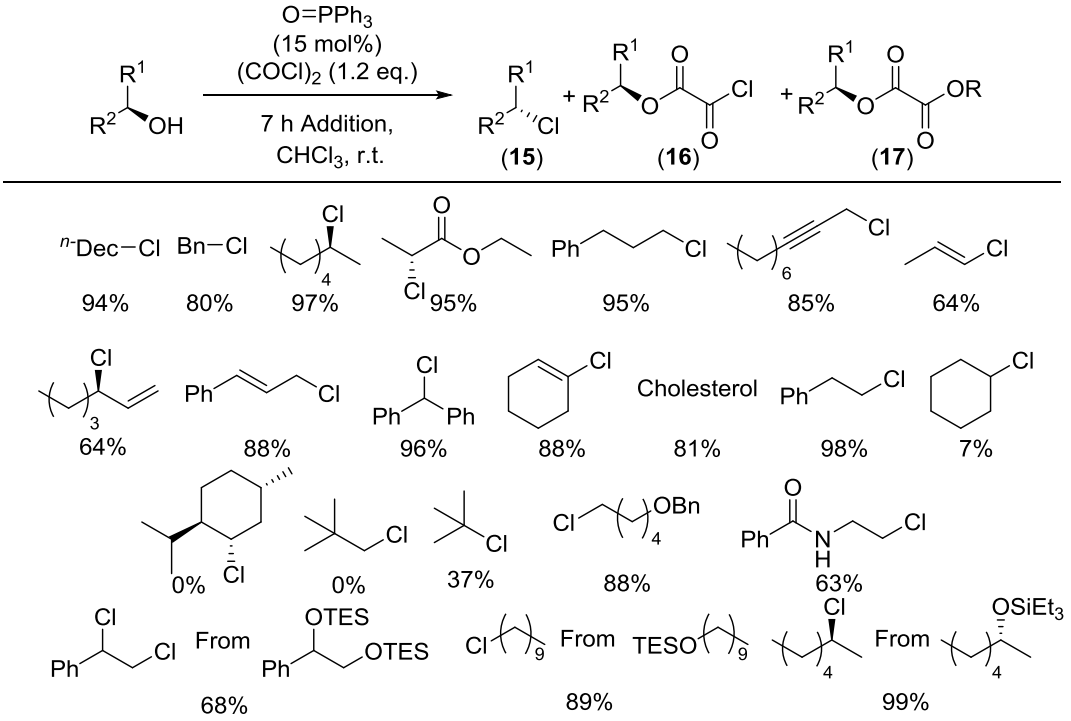
1.2.1. Reactions with Catalytically Generated Halophosphonium Salts

Denton *et al.* have developed a range of reactions based on the catalytic generation of chlorotriphenylphosphonium chloride using oxalyl chloride to recycle the phosphine oxide by-product. This underappreciated transformation was first reported by Masaki and Fukui in 1977 as the key intermediate for their novel reduction of phosphine oxides using oxalyl chloride and thiols (Scheme 23).[35] On addition of oxalyl chloride, phosphine oxides are transformed into the corresponding dichlorophosphines with the liberation of carbon dioxide and carbon monoxide. The dichlorophosphines are highly oxaphilic and can undergo addition of various oxygen containing groups such as alcohols (Appel reaction),[36, 37] epoxides (dichlorination reaction),[38] oximes[39] and aldehydes.[40]



Scheme 23: Masaki and Fukui reaction for reduction of phosphine oxide via dichlorophosphine.[35]

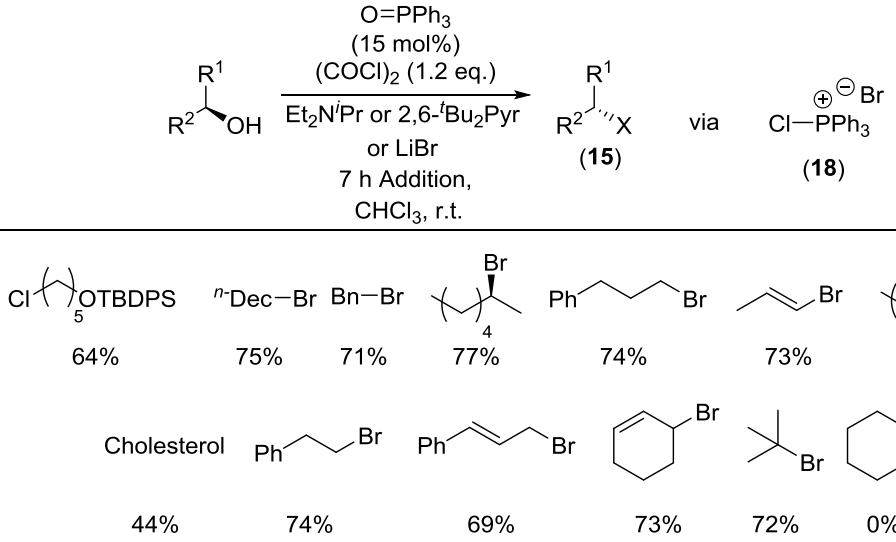
The catalytic protocol using oxalyl chloride and phosphine oxide replaces the mixture of triphenylphosphine and tetrachloromethane typically used in the Appel reaction drastically reducing the amount of waste generated and greatly increasing the atom efficiency. The catalytic Appel reaction involves the slow addition of an alcohol to a phosphine oxide oxalyl chloride mixture yielding an alkyl chloride with inversion of stereochemistry.[36, 37] To reduce the unwanted esterification of oxalyl chloride with alcohol, the solution of oxalyl chloride is added slowly throughout the reaction (Scheme 24). Slow addition over 7 hours increased the yield of the desired chloride (**15**) from 46% to 86% and dramatically reduced the formation of chlorooxalate (**16**) and diester (**17**) side products. Loadings of 15 mol% triphenylphosphine oxide led to high conversions and excellent isolated yields of primary and secondary aliphatic, allylic, benzylic and propargylic chlorides. Chiral GC and specific rotation of the products confirmed inversion of stereochemistry in all but one example, cholesterol, where possible participation of a nearby alkene led to retention of configuration. Sterically hindered alcohols,



Scheme 24: Results from the redox neutral catalytic Appel reaction.[36]

cyclohexanol, menthol and neopentyl alcohol, suffered from low yields of desired product, instead leading to the isolation of the chlorooxalates and diesters.

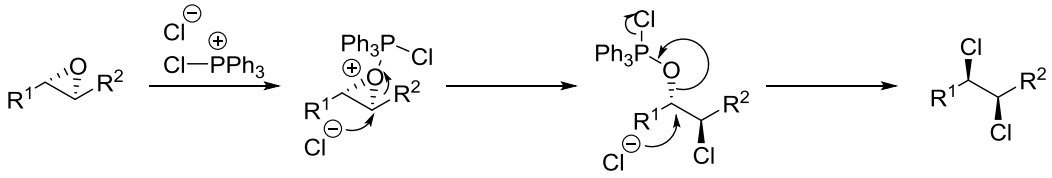
Addition of Hünig's base or 2,6-di-*tert*-butylpyridine to neutralise released HCl allows for the reaction to tolerate benzyl and TBPS protecting groups, while triethylsilyl ethers were deprotected under the reaction conditions leading to dichlorinated products. Another modification found that while the expected use of oxalyl bromide failed to provide the bromide in adequate yields, addition of 2.3 equivalents of LiBr led to the bromination reaction. It is thought that the chloride ion precipitates out of the reaction as LiCl allowing for the formation of the active phosphonium bromide salt (**18**) (Scheme 25). These results led to the development of similar catalytic nucleophilic substitution reactions.



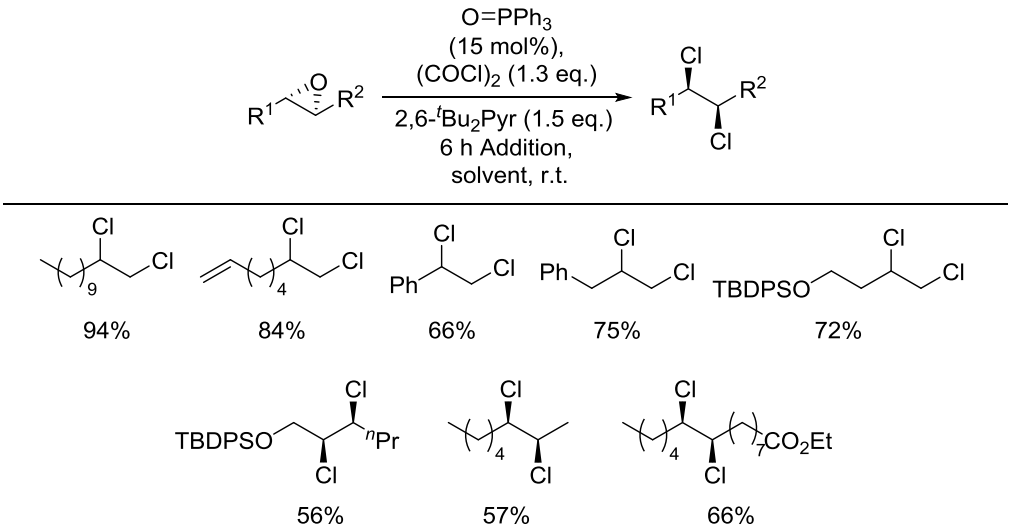
Scheme 25: Results of catalytic Appel reaction with additives.[36]

Next, this methodology was applied to the dichlorination of epoxides.[38] It was envisaged that the first step involved the formation of the dichlorophosphine, as per the previous Appel reaction; the phosphonium salt actives the epoxide allowing the first chloride ion to attack the least hindered side of the epoxide, resulting in inversion of stereochemistry. The activated alcohol formed from the opening of the epoxide then undergoes the Appel reaction as detailed above to give with dichloride with the expected inversion of the stereochemistry (Scheme 26). Initially yields were low as HCl present in oxalyl chloride reacted with the epoxides to product chlorohydrins which then led to the formation of inactive oxalate esters. Addition of the non-nucleophilic base 2,6-di-*tert*-butylpyridine prevented this side reaction, increasing yields to 69% from 58%. By increasing the amount of oxalyl chloride added throughout the reaction to 1.3 equivalents allowed for the catalyst loadings to be reduced to 15 mol% while also increasing the yield to a satisfactory 91%. Using these optimised conditions (Scheme 27) a

range of terminal epoxides underwent dichlorination at room temperature in moderate to excellent yields, alkenyl, aryl and TBDPS groups were well tolerated. At room temperature 1,2-disubstuted epoxides did not undergo dichlorination but by replacing the chloroform solvent with benzene and increasing the reaction temperature to 80 °C the internal dichlorides could be isolated in moderate yields.

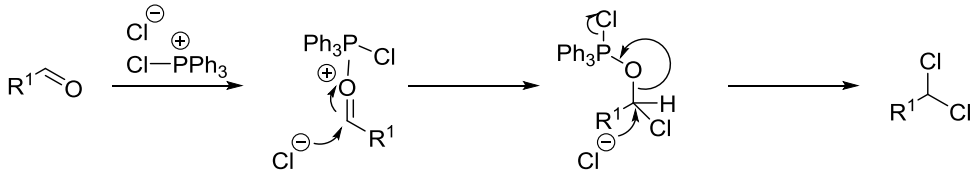


Scheme 26: Proposed mechanism for the dichlorination of epoxides.

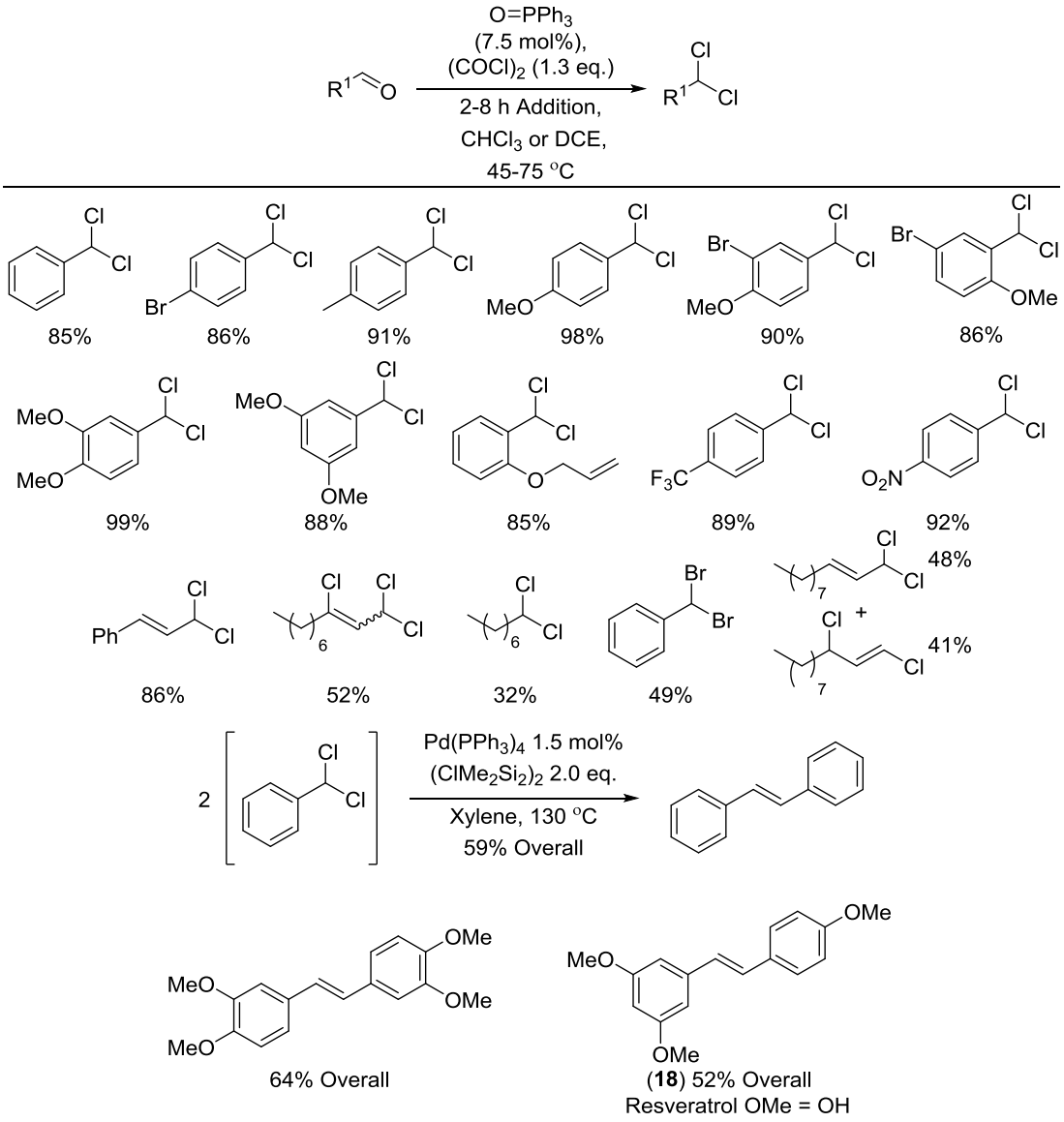


Scheme 27: Results of the dichlorination of epoxides.[38]

The catalytic protocol was adapted for the deoxydichlorination of aldehydes, an important transformation for the synthesis of geminal dichlorides (Scheme 29). Dichlorides are an important starting point for many carbon-carbon bond forming reactions as well as being a moiety known to be present in bioactive natural products.[41] This reaction was successfully employed for the conversion of substituted benzaldehydes, both electron-rich and electron-poor, cinnamaldehyde and *trans*-2-undecanal in good yields. Disappointingly, reactions with unactivated aliphatic aldehydes proceed at low conversions (Scheme 28). The 1,2-dibromides could also be formed with the use of oxalyl bromide. The synthetic precursor (**18**) to the bioactive stilbene, resveratrol, was synthesised using intermediates produced by the *in situ* application of deoxydichlorination reaction.[40]



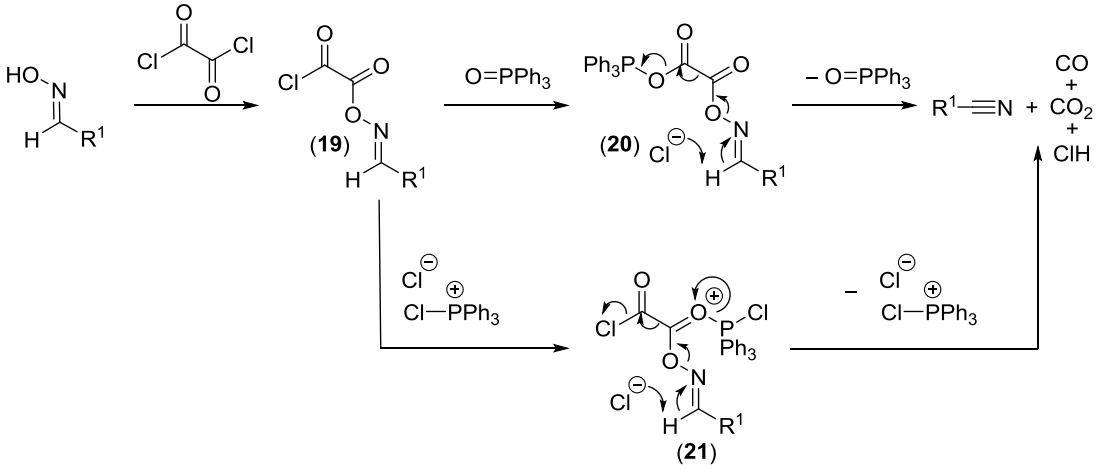
Scheme 28: Proposed mechanism for the deoxydichlorination reaction of aldehydes.[40]



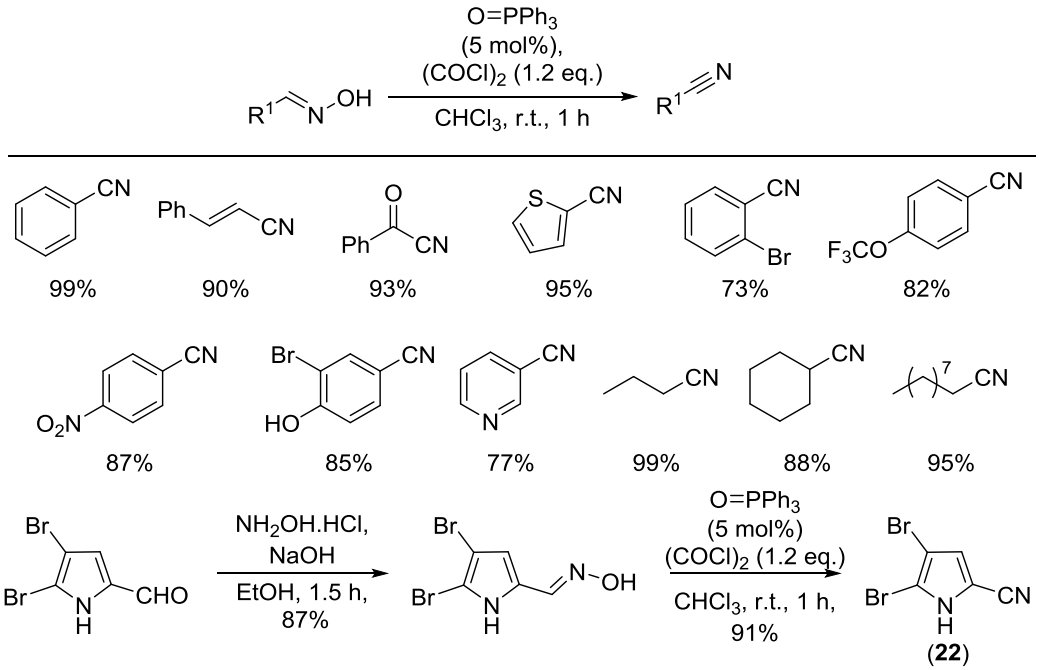
Scheme 29: Results of the deoxydichlorination reaction of aldehydes.[40]

Another interesting application for this methodology was the synthesis of nitriles via the catalysed decomposition of oximes.[39] In this case there was no need for the slow addition of oxalyl chloride to the reaction mixture as, unlike previous examples, the oxalyl chloride

ester (**19**) is active and reacts with the phosphine oxide undergoing the decomposition step via the adducts (**20**) and (**21**). This methodology was used for the decomposition of various aliphatic, aromatic and heteroaromatic oximes to the corresponding nitriles in good to excellent yields with low catalyst loadings of 5 mol% and a small excess of oxalyl chloride (1.2 eq.) at room temperature over an hour. The reaction conditions tolerated basic groups and heteroaromatics such as pyridine, pyrrole and systems incorporating nitro, ketone, hydroxy and trifluoromethoxy functional groups. These mild conditions were employed in the synthesis of natural product pyrrole nitrile (**22**), a compound found in the sea sponge *Agelas oroides* (Scheme 31).

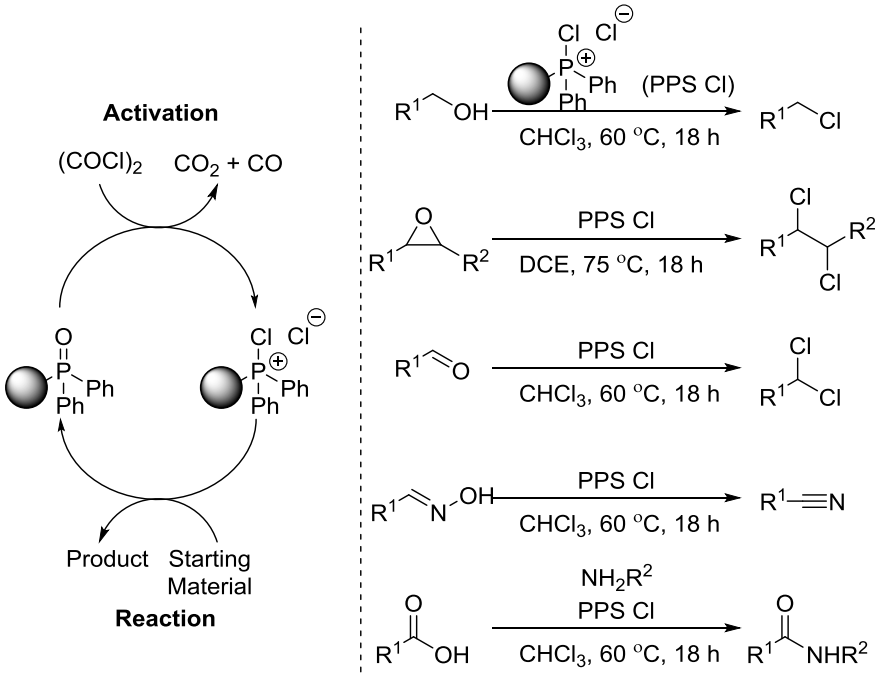


Scheme 30: Proposed mechanism for the synthesis of nitriles from oximes utilising the catalytic phosphonium salts.[38]



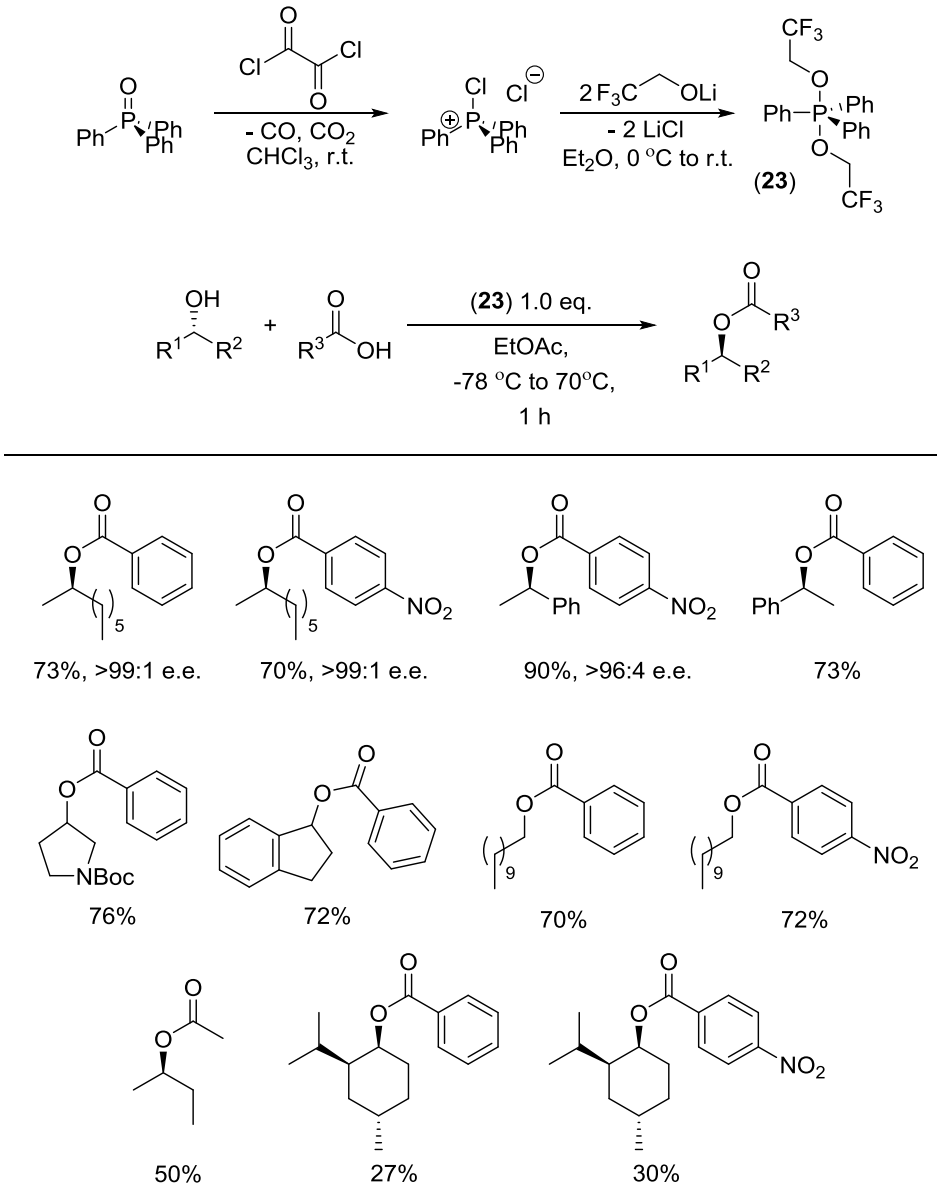
Scheme 31: Results of the synthesis of nitriles from oximes utilising the catalytic phosphonium salts.[38]

Most recently Denton *et al.* have demonstrated the use of polymer supported triphenylphosphine oxide in the Appel reaction (Scheme 24, 27 and 28) and the previously mentioned dehydration reactions (Scheme 31) to simplify the purification of the product further.[42] Commercially available supported triphenylphosphine oxide was suspended in a solution chloroform at room temperature then oxalyl chloride, oxalyl bromide or thionyl chloride was added leading to the observation of the corresponding halophosphonium salt. The polymer supported halophosphonium salt was then used in one of the above mentioned procedures (Scheme 32). The desired products could then be isolated by simple filtration and concentration under reduced pressure. In the first example, the chlorination of decanol the product was isolated in excellent yield and was considered pure by ^{1}H-NMR analysis. The recovered polymer supported reagent could then be recycled and has been proven to be reusable three times with no loss in yield. This simple modification has huge ramifications, polymer supported reagents are popular in library synthesis and continuous flow protocols.



Scheme 32: Appel reactions and dehydrations employing polymer supported triphenylphosphine oxide.[42]

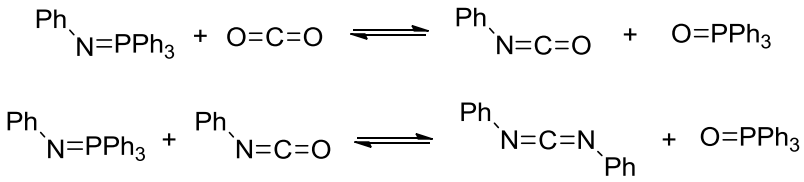
Another reaction developed by Denton *et al.* employs a dioxyphosphorane (**23**) as an alternative to the triphenylphosphine and DEAD used in the Mitsunobu reaction.[43] This redox-free Mitsunobu reaction uses stoichiometric amounts of dioxyphosphorane, which can be reformed from the phosphine oxide by-product (85% of phosphine oxide could be recovered from reaction mixture) using oxalyl chloride and lithium trifluoroethoxide (Scheme 33). Using this methodology the esterification of benzoic acids proceeded in a good yield, while acetic acid derivatives could be used giving a moderate yield of ester. Menthol also underwent esterification at a low yield, interestingly, with inversion of stereochemistry, as expected from the Mitsunobu reaction. This novel protocol may use stoichiometric amounts of phosphine reagent but there is little consumption of phosphine as it can be recovered and recycled. The biggest advantage of this system is the absence of hazardous azodiester reagent typically required for the Mitsunobu reaction.



Scheme 33: Results of redox free Mitsunobu reaction.[43]

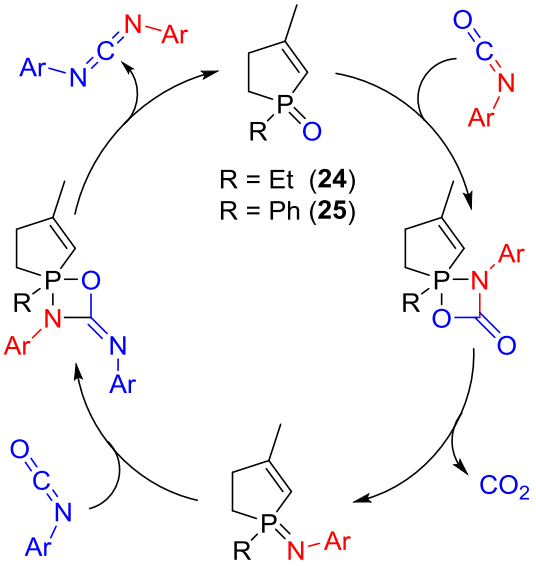
1.2.2. Development of Redox-Neutral Catalytic Aza-Wittig Reaction

The initial inspiration for the redox-neutral catalytic aza-Wittig reaction came from Staudinger's findings on the equilibrium between iminophosphoranes and phosphine oxides in the presence of carbon dioxide. Iminophosphoranes and carbon dioxide were found to be in equilibrium with the isocyanate and phosphine oxide. It was also found that the aza-Wittig formation of carbodiimides from isocyanates was reversible (Scheme 34).[2]



Scheme 34: Staudinger's observations which led to the development of catalytic carbodiimide formation.[2]

In 1962 Monagle and Campbell reported the phosphine oxide-catalysed condensation of isocyanates in the synthesis of carbodiimides.[44] It was proposed that isocyanates undergo a metathetical reaction with phosphine oxide evolving carbon dioxide and the iminophosphorane. The newly formed iminophosphorane reacts with a second equivalent of isocyanate, producing the carbodiimide and regenerating the phosphine oxide (Scheme 35). Monagle *et al.* carried out kinetic studies to gain further understanding of the mechanism. The reaction displays pseudo-first order kinetics with respect to the isocyanate. This suggests that addition of phospholene oxide to isocyanate to generate the iminophosphorane is the rate limiting step in the catalytic cycle. The second step, the nucleophilic attack of the iminophosphorane on the isocyanate is much more rapid (about 10^5-10^7 times faster).[45, 46] Therefore, there is only ever a small concentration of iminophosphorane present in the reaction at any point.



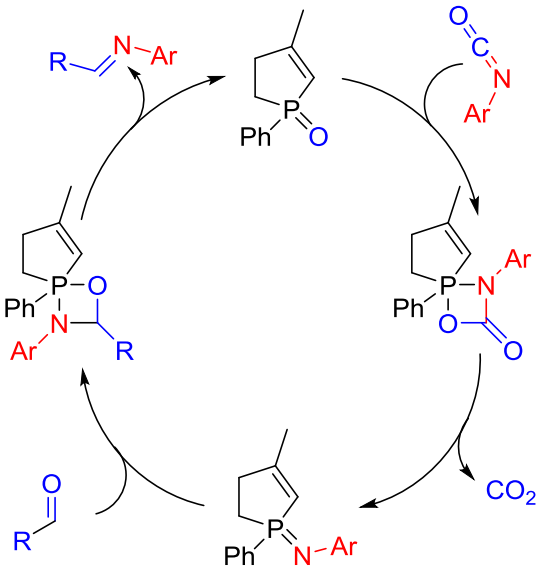
Scheme 35: Proposed catalytic cycle for Monagle's carbodiimide formation.[44]

Catalyst screens found that although the ethyl substituted phospholene oxide (**24**) is more active, due to increased nucleophilicity, a fivefold increase in rate over the phenyl analogue (**25**),[11] Compound (**25**) is generally favoured because the synthesis is considerably higher yielding and more importantly (**25**) has since been made commercially available. Campbell *et al.* found that cyclic phosphine oxides were much more active than the acylic variants (about 10^3 faster) which was attributed to the C-P-C bond angle; cyclic systems have an angle of approximately 95°, compared with 105° for acyclic systems.[47] Cyclic systems therefore benefit from a lower barrier of transition from tetrahedral (109°) (phosphine oxide) to trigonal bipyridimal (95°) (oxazaphosphetane) relieving more of the ring strain.[47, 48]As mentioned previously, Radosevich *et al.* have developed a constrained phosphorus species which favours trigonal bipyridimal confirmation which allows for some unusual transformations (Scheme 21).[34] Analogous to early attempts at redox mediated organocatalytic phosphine chemistry, alternative group V and VI oxide catalysts were screened by Monagle to investigate if the only requirement for the catalyst was a polar heteroatom oxygen bond (X-O). Triphenylarsine oxide was more active than triphenylphosphine oxide, presumably due to increased polarization of the X-O bond (5.50 D for As-O compared with 4.31 for P-O), while the analogous trimethylamine oxide compound failed to provide any observable product due to the inability to adopt a trigonal bipyridimal confirmation. This lack of catalytic activity offered further evidence for the proposed pentavalent intermediate.[11]

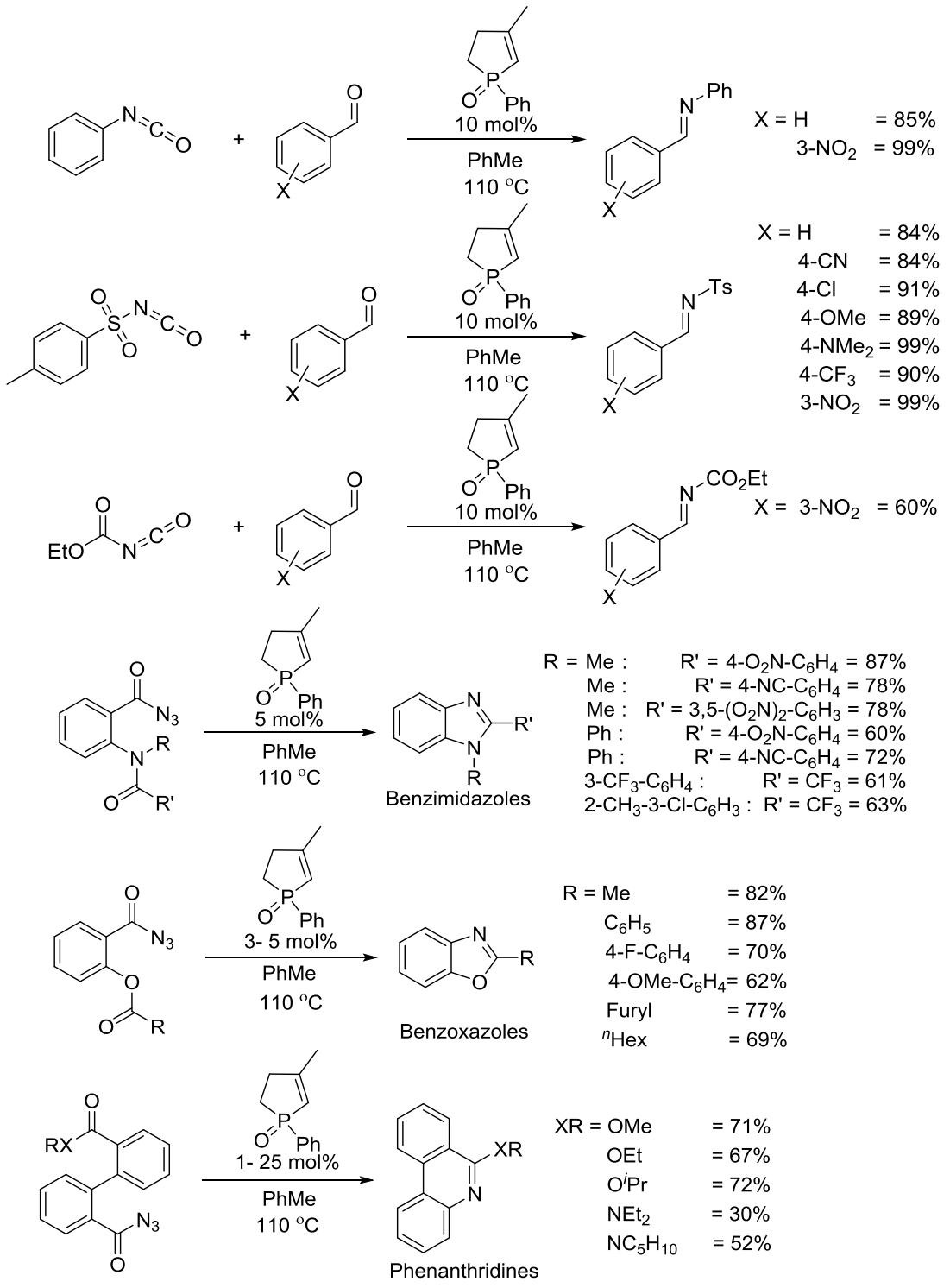
The nature of the isocyanate substrate also has an effect on the rate of reaction. As expected, electrophilic isocyanates react faster because the rate is dependent on the nucleophilic attack on the isocyanate from both the phospholene oxide and the

iminophosphorane. Steric effects also play a role in the rate of reaction; a sterically hindered isocyanate reacts slower.[49]

Marsden *et al.* have developed Monagle's catalytic carbodiimide synthesis into a more general catalytic aza-Wittig reaction which can be used to produce imines and *N*-heterocycles (Scheme 36). To favour the reaction between the iminophosphorane and desired carbonyl the competing carbodiimide formation has to be suppressed. To achieve this in the intermolecular system highly reactive aldehydes were employed or in the case of tosyl imine synthesis the competing dimerization reaction made unfavourable.[50, 51] For the cyclization reactions, diluting the reaction mixture reduced the likelihood of interaction between iminophosphorane and isocyanate, thus favouring the intramolecular reaction. Using the intramolecular methodology a range of phenanthridines, benzoxazoles and benzimidazoles were synthesised as well as electron-deficient imines using the intermolecular aza-Wittig (Scheme 37).[50-52] These reactions will be explored in greater details in later chapters.



Scheme 36: Proposed mechanism for the catalytic aza-Wittig reaction.[48]



Scheme 37: Results of the redox-neutral catalytic aza-Wittig reaction.[50-52]

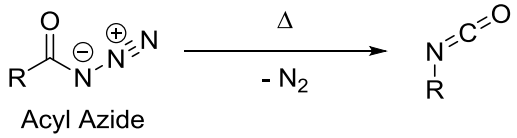
Chapter 2:

Novel Applications of Organocatalytic Aza-Wittig Chemistry

2. Development of an Azide Free Catalytic aza-Wittig Reaction

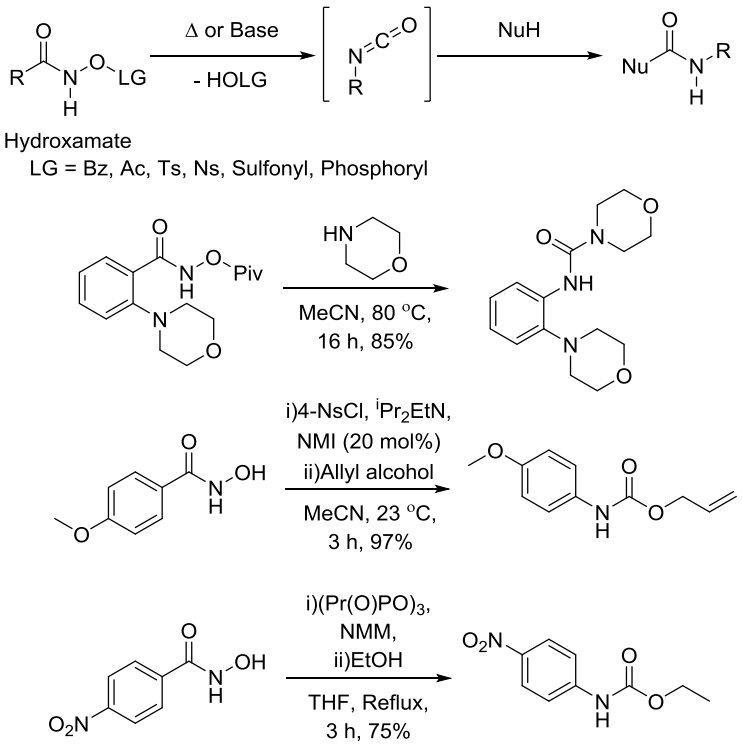
2.1. Introduction to Novel Methods for In Situ Isocyanate Synthesis

Isocyanates are fundamental to the catalytic aza-Wittig reaction developed by the Marsden group.[52] The condensation of isocyanates with phosphine oxides produces iminophosphoranes, with the liberation of carbon dioxide providing the driving force for the reaction. This chapter looks at alternative methods for the *in situ* generation of isocyanates in the catalytic aza-Wittig reaction. Currently, the most commonly employed method for the synthesis of isocyanates on a laboratory scale is the Curtius rearrangement (Scheme 38). Although this methodology is clean, mild, well studied and efficient, it involves the use of high energy acyl azides. Azides can decompose on the slightest input of energy and, in the case of small molecules, the results can be violent, which limits their use on large scale.



Scheme 38: The Curtius rearrangement.

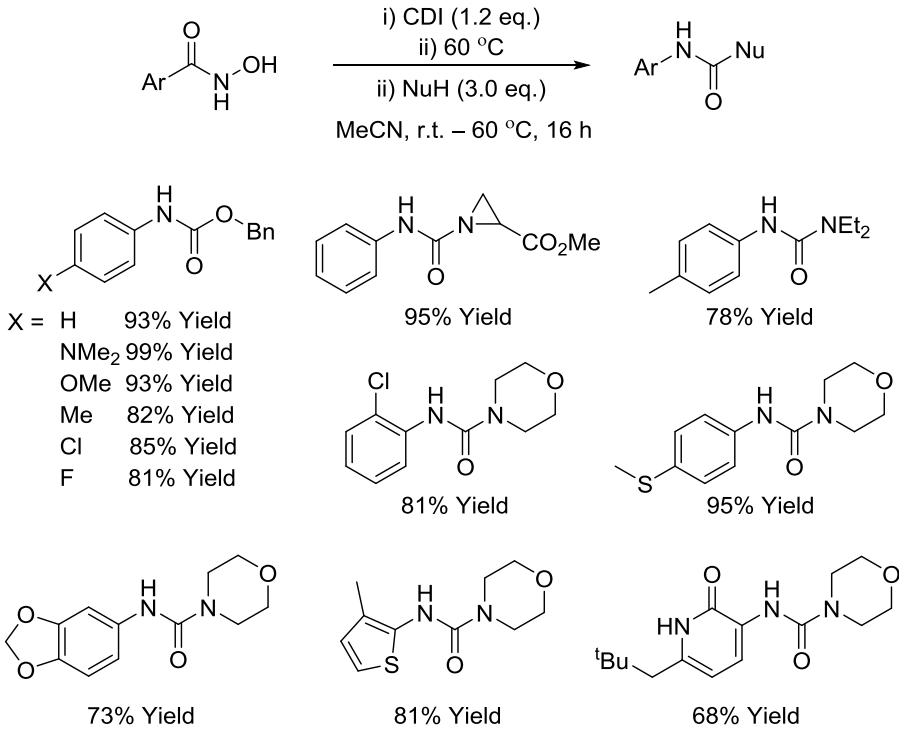
An alternative to the Curtius rearrangement is the Lossen rearrangement which involves *O*-functionalised hydroxamic acids. Electron-withdrawing groups attached to the oxygen result in it becoming a labile leaving group whose loss initiates the rearrangement. Traditionally, *O*-acyl,[53] sulfonyl[54] or phosphoryl[55] hydroxamic acid intermediates are generated *in situ* and, in some cases, forcing conditions are required to initiate the rearrangement (Scheme 39). For example, *O*-(acetoacetyl) benzohydroxamic acid undergoes thermal rearrangement between 300 and 400 °C.[56, 57] More commonly a strong base is used to initiate the rearrangement at lower temperatures, ideally with the leaving group precipitating out of solution as a salt to aid purification and prevent interaction with the isocyanate intermediate.[56] The ease of rearrangement is dependent on the nature of the leaving group, with more electron-withdrawing groups, such as sulfonyl and phosphoryl groups, reacting faster. Indeed the *O*-sulfonyl and phosphoryl hydroxamate esters rearrange so rapidly that the active *O*-substituted intermediates are not usually isolated. The R group of the hydroxamic acid also affects its propensity to rearrange, with substrates bearing electron-rich R groups tending to rearrange easier than electron-poor groups.[56]



Scheme 39: Previous results of the Lossen rearrangement.[53-57]

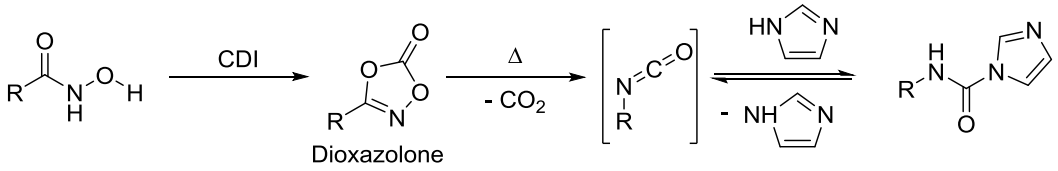
Recently a number of novel methods for the activation of hydroxamic acids for the synthesis of carbamates and ureas have been developed. These range from new phosphates,[55, 58] simple and mild sulfur reagents,[59] catalyst enhanced activation,[54, 60] to metal assisted rearrangements.[61] However, phosphate and sulphur-based methods suffer from low atom efficiencies and purification issues. For example 4-nosyl chloride (4-NsCl) has a molecular weight of 221.62 g/mol and the 4-nitrobenzenesulphonic acid by-product has to be removed. Many of the catalytic and metal assisted procedures are unsuitable for our desired application. A promising method was published by Dubé *et al.* detailing a carbonyl diimidazole (CDI) initiated Lossen rearrangement (Scheme 40).[62] In this publication they report the use of CDI to activate hydroxamic acids which rearrange in the presence of a nucleophile. This nucleophile reacts with the isocyanate intermediate to form the corresponding carbamate or urea as shown below (Scheme 40).

One of the appeals of this method is the compatibility of the reagents and by-products with the aza-Wittig reaction. It was expected that carbonyl diimidazole (CDI) would selectively react with hydroxamic acids without interacting with other groups present in the aza-Wittig reaction. Carbon dioxide and imidazole are the only by-products produced during the reaction of CDI with hydroxamic acids. Cleavage of the high energy N-O bond provides the driving force for the rearrangement. Imidazole is weakly nucleophilic and reversibly forms an imidazolyl urea with the isocyanate and wasn't expected to interact detrimentally with the desired aza-Wittig reaction.



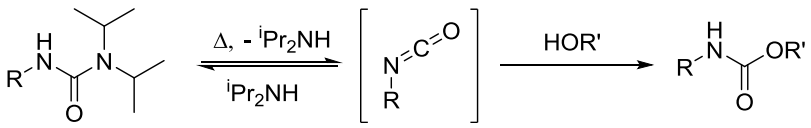
Scheme 40: Dubé *et al.* carbonyl diimidazole-mediated Lossen rearrangement results.[62]

Dubé suggested a mechanistic pathway involving the formation of a dioxazolone which undergoes decarboxylation in the presence of a nucleophile, producing an isocyanate *in situ.* This isocyanate intermediate is subsequently trapped by the nucleophile, in the absence of another nucleophile, as an imidazolyl urea (Scheme 41) which was reported by Dubé.[62] This methodology potentially offers mild *in situ* generation of isocyanates for the catalytic aza-Wittig without the need for hazardous azides.[62]

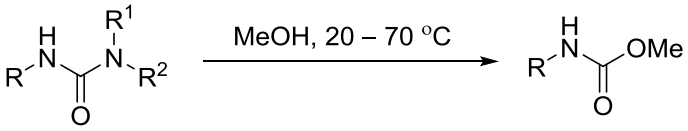


Scheme 41: Intermediates in the carbonyl diimidazole-mediated Lossen rearrangement.[62]

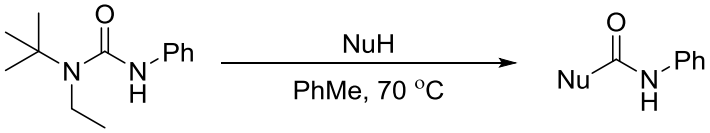
Another recent observation has led to an alternative method for the formation of isocyanates. Booker-Milburn *et al.* reported that hindered trisubstituted ureas, such as 1,1-diisopropyl-3-phenyl urea, form carbamates on heating in methanol.[63] While ureas are usually perceived as being inert, these hindered ureas were found to undergo solvolysis in a range of alcohols, yielding the carbamates expected from the reaction with isocyanates. Therefore hindered ureas could behave as masked isocyanates, dissociating into the isocyanate and amine on heating. Conditions were optimised to allow for only a small excess of nucleophile. A range of nucleophiles to be tested, providing the products expected from the capture of an isocyanate (Scheme 42) (Table 1). Bulkier ureas had a lower temperature of dissociation. For example, the solvolysis of 1,1-diisopropyl-3-phenyl urea went to completion after 18 hours at 70 °C, while the reaction of 1-*tert*-butyl-1-isopropyl-3-phenyl urea was complete within an hour at 20 °C. Since high temperatures are required for the catalytic aza-Wittig reaction, ureas could provide a method for the *in situ* generation of isocyanates under the usual reaction conditions.



Scheme 42: Hindered ureas as masked isocyanates.



R	R'	R'	T (°C)	t (h)	Yield (%)
Ph	^{i}Pr	^{i}Pr	70	18	81
Ph	H	^{t}Bu	70	18	0
Ph	Me	^{t}Bu	70	<5 min	>99
Ph	Et	^{t}Bu	50	1	>99
Ph	Et	^{t}Bu	20	18	>99
Ph	^{i}Pr	^{t}Bu	20	1	>99
^{t}Bn	^{i}Pr	^{i}Pr	70	72	85
^{t}Bu	^{i}Pr	^{t}Bu	20	1	>99



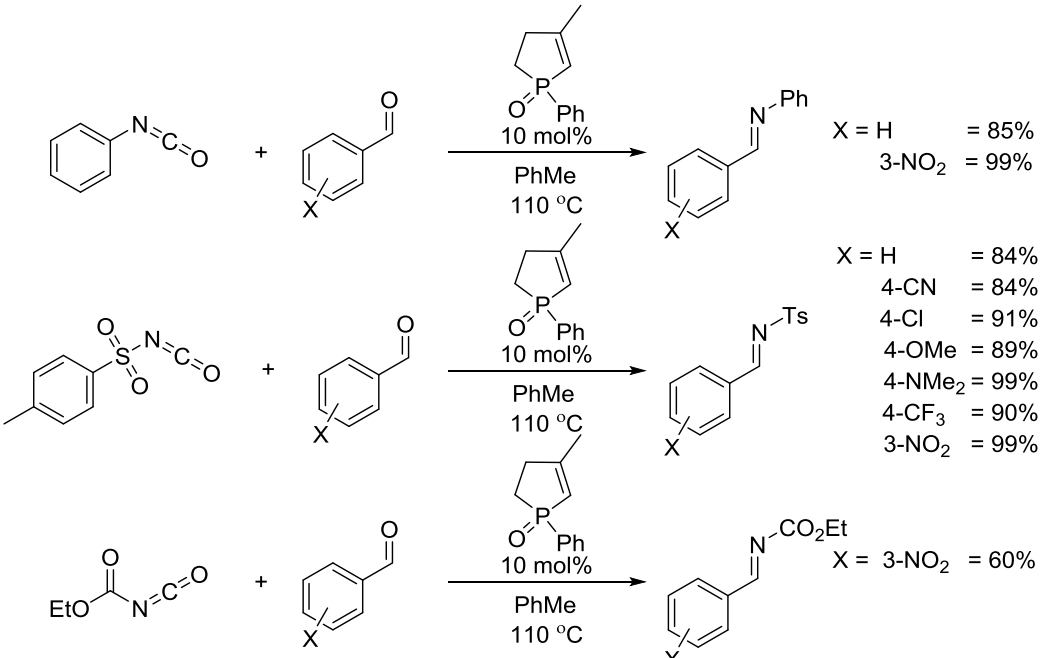
NuH (eq.)	t (h)	Yield (%)
H_2O (excess)	1	>99 (PhNC(O)NPh)
MeOH (1.1)	6	>99
^{t}BuOH (excess)	8	70
BnOH (1.1)	8	94
PhOH (2.0)	18	72
PhSH (2.0)	18	62
^{t}BuNH$_2$ (1.1)	5	>99

Table 2: Hindered ureas as masked isocyanates in the synthesis of carbamates and ureas.[63]

2.2. Results and Discussion

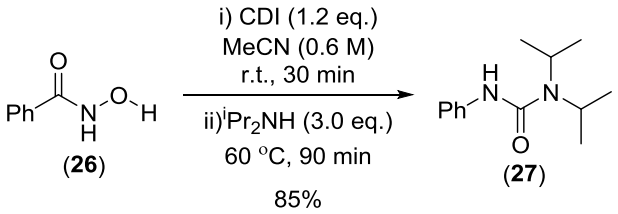
2.2.1. Developing a Protocol for Azide Free Intermolecular Aza-Wittig Reaction

Our group previously explored the application of catalytic aza-Wittig methodology for both intra and intermolecular reactions. The starting materials for these reactions were, in the case of intermolecular reactions, commercially available isocyanates or else formed *via* the Curtius rearrangement from the corresponding acyl azide. Using these methods a range of *N*-phenyl imines and electron deficient *N*-tosyl and *N*-carboxyl imines were synthesised (Scheme 43).



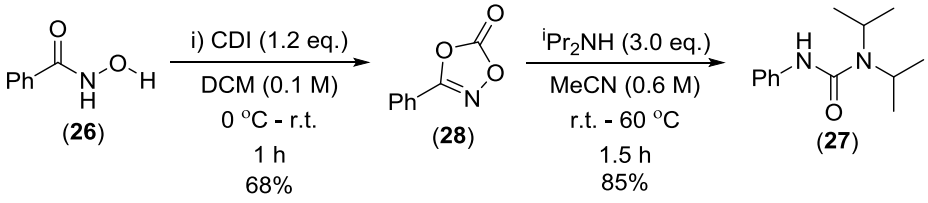
Scheme 43: Previous intermolecular catalytic aza-Wittig reaction results.

Due to the hazards associated with the use of azides, alternative methods for the synthesis of isocyanates were sought. The potential of using the methodology developed by Dubé *et al.* of was explored in the context of the catalytic aza-Wittig reaction.[62] Initially, to investigate potential starting materials for the *in situ* formation of isocyanates, the CDI-mediated Lossen rearrangement was performed in the presence of diisopropylamine to trap the isocyanate as a hindered urea. Addition of carbonyl diimidazole (CDI) to a solution of commercially available benzohydroxamic acid (**26**) in acetonitrile at room temperature and subsequent heating with diisopropylamine yielded 85% of the desired hindered urea (**27**) (Scheme 44).



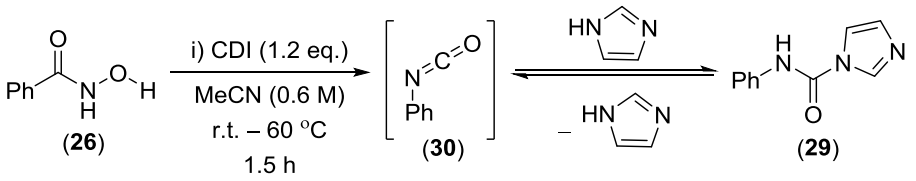
Scheme 44: CDI-mediated Lossen rearrangement as a method for the synthesis of hindered ureas.

To confirm the intermediacy of the dioxazalone in the CDI-mediated Lossen rearrangement a sample of phenyl dioxazalone (**28**) was prepared following the literature procedure.[64] Addition of CDI to the hydroxamic acid in DCM at 0 °C allowed the dioxazolone intermediate (**28**) to be isolated. The dioxazolone proved to be stable enough to survive a weakly acidic (0.5 M HCl) aqueous quench and recrystallization from DCM and hexane, furnishing us with pure dioxazalone (**28**) at an isolated yield of 68% (Scheme 45). On heating to 60 °C in the presence of diisopropylamine, the dioxazalone underwent rearrangement producing the 1,1-diisopropyl-3-phenyl urea in 85% yield (**27**) (Scheme 45), supporting the hypothesised intermediacy of dioxazalone in the CDI-mediated Lossen rearrangement.



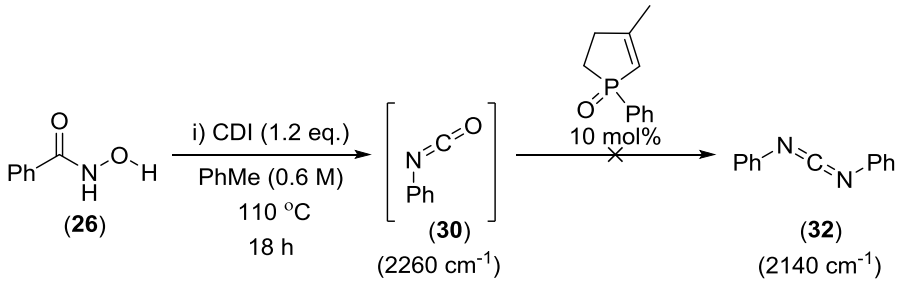
Scheme 45: Isolation and reaction of dioxazalone (**28**).

Dubé *et al.* observed that heating a mixture of dioxazalone with imidazole to 60 °C led to conversion to the imidazolyl urea. This suggested that imidazole initiated the Lossen rearrangement of dioxazolone, acting as an nucleophile, triggering decarboxylation and ultimately forming an imidazolyl urea (Scheme 46).[62] In solution it is known that imidazolyl ureas are in equilibrium with the corresponding isocyanate and imidazole (Scheme 46).[65] This dissociation makes separation of 1-imidazolyl-3-phenyl urea (**29**) from imidazole and the isocyanate (**30**) impractical. In order to confirm that the imidazole could initiate the rearrangement in the absence of an additional nucleophile a test reaction was carried out with the aim to isolate the imidazolyl urea (**29**). Both the imidazolyl urea and the side-product diphenyl urea (**31**) could be observed by NMR spectroscopy (imidazolyl urea NH 10.31 ppm singlet) and IR (imidazolyl urea (C=O) 1730 cm^{-1}). At room temperature the ^{1}H-NMR shows almost exclusively imidazolyl urea.



Scheme 46: CDI -mediated Lossen rearrangement formation of imidazolyl urea (**29**).

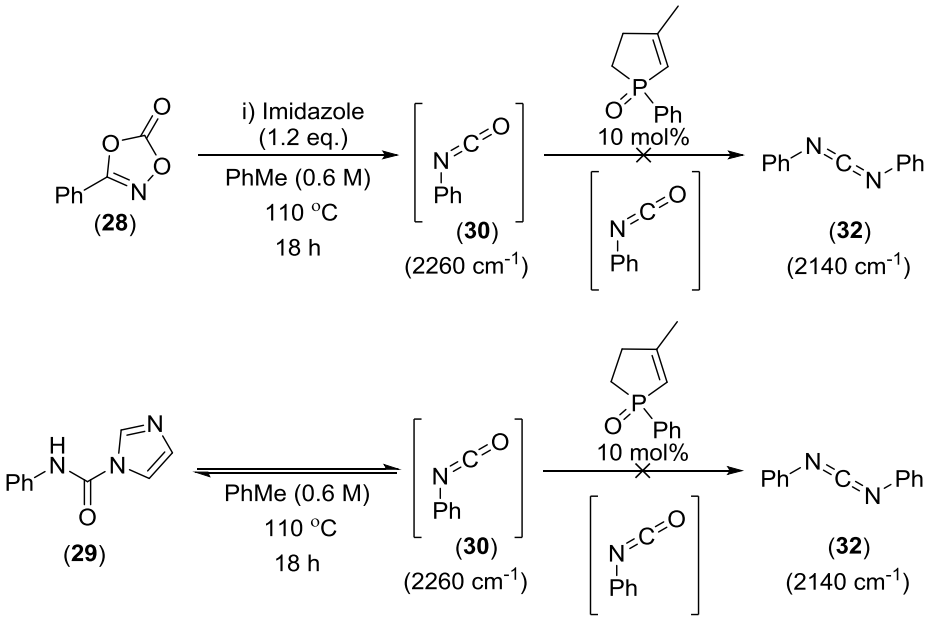
We proposed that the phospholene oxide-catalysed self-condensation reaction of the isocyanate intermediate would be the simplest system to test the compatibility of novel methods for the *in situ* synthesis of isocyanates with the aza-Wittig reaction. This self-condensation reaction is normally viewed as a side reaction, but it was hoped that by removing the need to compete with the self-condensation the reaction would be simplified. A solution of hydroxamic acid (**26**) and CDI was heated with the phospholene oxide catalyst (**25**) in an attempt to produce the expected diphenyl carbodiimide (**32**) product. The reaction was monitored by IR for the appearance and consumption of the isocyanate (2260 cm^{-1}) and the formation of the carbodiimide (2140 cm^{-1}) (Scheme 47). Unfortunately none of the expected carbodiimide product was observed by IR or ^{1}H-NMR during or after the reaction. Instead the imidazolyl urea (**29**) was observed as the major product by ^{1}H-NMR.



Scheme 47: Proposed pathway for CDI mediated Lossen and catalytic carbodiimide formation.

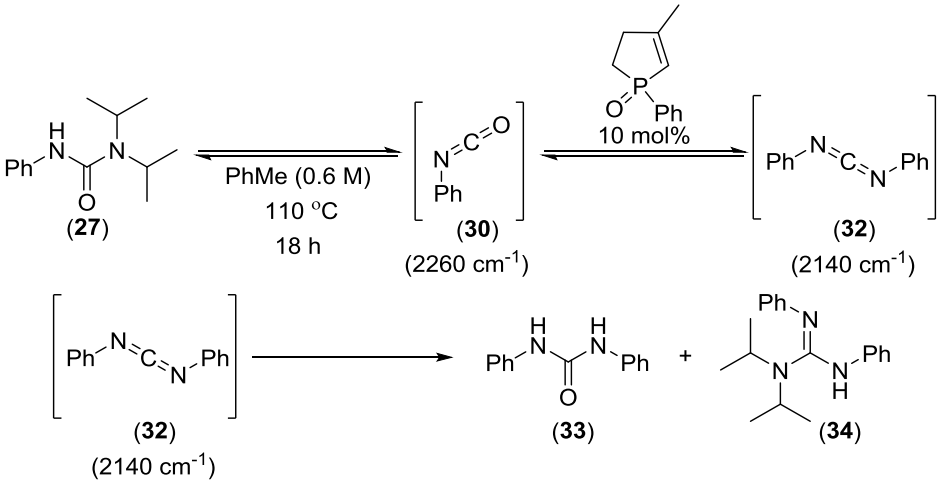
To attempt the synthesis of carbodiimide (**32**), the proposed intermediates, dioxazalone (**28**) and imidazolyl urea (**29**) were also tested (Scheme 48). Neither of the reactions showed the desired carbodiimide infra-red absorption (2140 cm^{-1}), suggesting no isocyanate self-condensation occurred with these systems. The lack of desired product may be a sign that the concentration of isocyanate remains low throughout the reaction because the excess imidazole traps it as the imidazolyl urea. For the self-condensation the rate of reaction is highly dependent on the concentration of the isocyanate as the concentration of iminophosphorane is a function of isocyanate concentration, effectively making the isocyanate second order for the

self-condensation reaction, while the formation of imidazolyl urea is only first order with respect to the isocyanate.



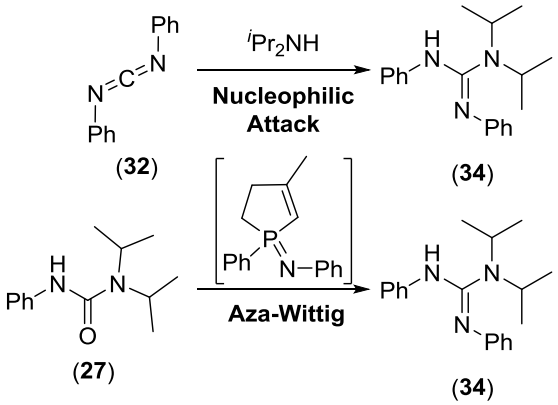
Scheme 48: Alternative starting materials for catalytic carbodiimide formation.

Satisfyingly, however, the reaction of the hindered urea did display a noticeable amount of the characteristic carbodiimide absorption (2140 cm^{-1}) during the reaction suggesting that the isocyanate was formed and had been converted by the catalyst to carbodiimide (Scheme 49). After 24 hours stirring in refluxing toluene an aliquot was removed to analyse the crude reaction mixture by ^{1}H NMR spectroscopy looking to assess the conversion to carbodiimide. Disappointingly, no signals could be found matching the literature values expected for the carbodiimide, suggesting that the carbodiimide had been consumed under the reaction conditions. Instead the majority of the reaction mixture was recovered as starting urea (**27**) and 10% of the diphenyl urea (**33**).



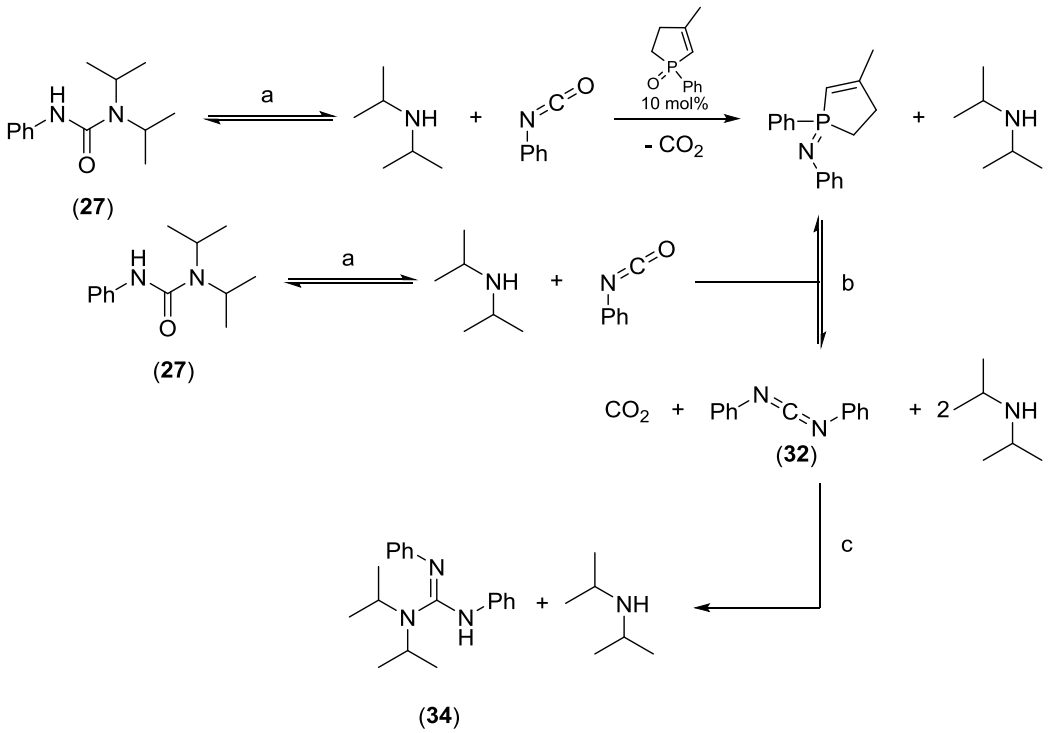
Scheme 49: Catalytic carbodiimide formation from diisopropyl urea.

Further LC-MS analysis suggested that the isocyanate self-condensation reaction using diisopropyl urea (**27**) produced the corresponding guanidine (**34**) in small but detectable quantities. While none of the characteristic guanidine signals could be detected by ^{1}H-NMR spectroscopy, the guanidine peak was prominent in the electrospray LC-MS spectrum. Guanidines are known to be very basic and readily protonated which explains the strong signal of the guanidine ions in the positive electrospray LC-MS. Two possible mechanisms could account for the formation of the guanidine (Scheme 50); either the carbodiimide had undergone nucleophilic attack by the diisopropylamine or the iminophosphorane had attacked the carbonyl of the urea. The latter is considered unlikely because ureas are notoriously weak electrophiles and there are no known examples of intermolecular aza-Wittig reactions with ureas. To examine the proposed pathway, pre-formed carbodiimide (**32**) was heated in the presence of three equivalents of diisopropylamine. Gratifyingly, this produced a concentration of guanidine (**34**) visible by ^{1}H-NMR spectroscopy, verifying that nucleophilic attack is viable under the reaction conditions.



Scheme 50: Possible routes to guanidine by-product (**34**).

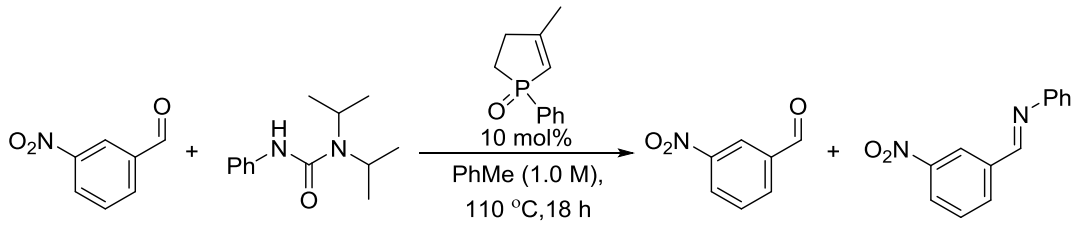
Total conversion to carbodiimide (**32**) was not observed with the hindered urea but the reaction of the unprotected isocyanate is rapid and quantitative. It could be expected that as the hindered urea (**27**) dissociates (pathway a) and isocyanate is consumed, the concentration of diisopropylamine would increase (pathway b) trapping the small amount of carbodiimide (**32**) formed, as the guanidine (**34**) (pathway c). The increased concentration of diisopropylamine would also have the effect of driving the hindered urea-isocyanate equilibrium (pathway a) back towards the urea. In turn, this would keep the concentration of isocyanate low limiting the amount of carbodiimide formed; this may account for the sluggish nature of the dissociation of hindered urea (Scheme 51).



Scheme 2: Equilibria present in condensation reaction of diisopropyl ureas.

As discussed above members of the Marsden group have utilised the catalytic aza-Wittig reaction to produce imines from isocyanates (Scheme 43).[52] This method has been employed to synthesise imines sporting *N*-aromatic groups; electron-deficient *N*-*p*-tosyl and *N*-ethoxycarbonyl imines; and azatrienes for electrocyclic ring formations.[50, 66] After disappointing results for carbodiimide formation, the next step was to attempt the synthesis of imines from the novel isocyanate equivalents. It was hoped that by reacting the iminophosphorane with an aldehyde we would observe the desired imines. Heating a solution of diisopropyl urea (**27**) and benzaldehyde in the presence of the phospholene oxide catalyst (**25**) consistently led to the observation of the signal corresponding to imine (**35a**) in the ^{1}H-NMR spectrum of the crude reaction mixture. Imines are notoriously difficult to isolate due to a tendency to hydrolyse during silica column chromatography or other methods of purification. To quantify the reaction yields the crude reaction mixtures were analysed by ^{1}H-NMR spectroscopy to gauge conversion of aldehyde to the imine. Integration of the area under the characteristic aldehyde (10.00 ppm) and imine (8.46 ppm) proton signals gives a ratio of products as a proxy for conversion. With systems using 0.9 equivalents of benzaldehyde conversions of 57% were observed. Attempting to produce higher conversions, an excess of electron-deficient 3-nitrobenzaldehyde (**36**) was used as previous work had noted an increase in yields with this aldehyde. As expected, this provided higher conversions of aldehyde to imine (**35b**). When two equivalents of 3-nitrobenzaldehyde were used a 0.96:1.00 ratio of imine (8.57 ppm) to aldehyde (10.15 ppm) was observed by ^{1}H-NMR spectroscopy, equating

to a 95% yield of aza-Wittig product. Gratifyingly, with one equivalent of the aldehyde similar yields (89%) were observed suggesting an excess was not required (Scheme 52). A known quantity of internal standard (2,5-dimethylfuran) was added to the crude NMR sample to offer additional comparison allowing for a yield calculated in relation to the internal standard.



(**36**) (**27**) (**36**) (**35b**)

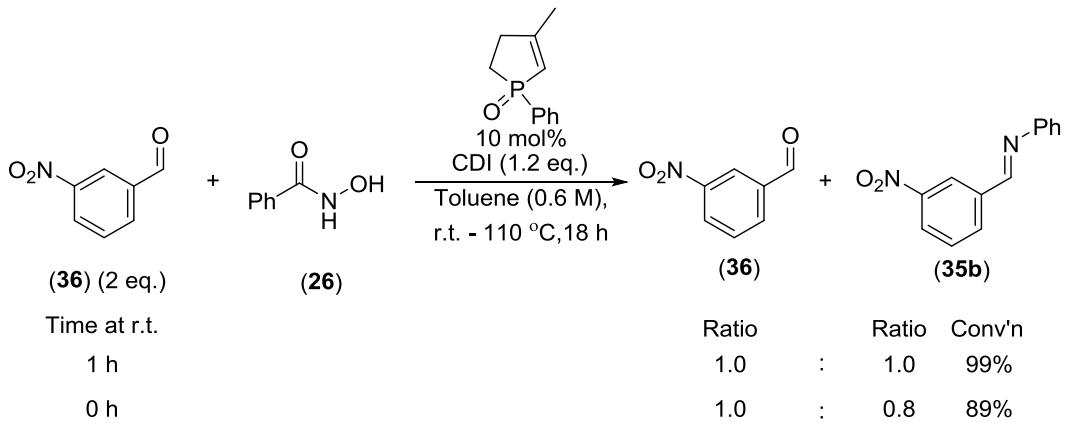
Eq.	Ratio		Ratio	Conv'n
1	1.0	:	8.1	89%
2	1.0	:	0.9	95%

Scheme 52: Results of intermolecular catalytic aza-Wittig starting from hindered urea.

Diphenyl carbodiimide (**32**) was the only side product detected by ^{1}H NMR spectroscopy accounting for loss of between four and nine percent of the isocyanate equivalent. We envisaged a possible water mediated process which would form the imine. This pathway could involve the hydrolysis of the phenyl isocyanate intermediate forming aniline which would undergo a condensation reaction with the aldehyde regenerating the water. A control reaction was run where a substoichiometric amount of water (10 mol%) was added to a stirring solution of phenyl isocyanate and imine in refluxing toluene under conditions similar to those used for the intermolecular catalytic aza-Wittig reaction. Gratifyingly, only a trace amount of imine (< 5% by crude NMR) was observed, while the major product was, as expected, the diphenyl urea formed from the nucleophilic addition of aniline to the phenyl isocyanate.

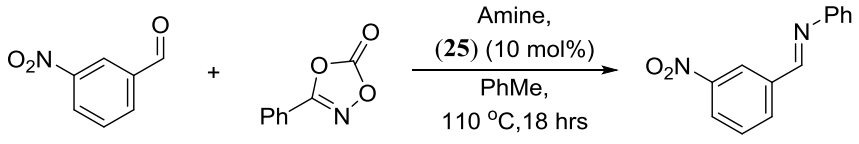
Due to the success of the hindered ureas, the feasibility of the alternative methods for *in situ* isocyanate synthesis was assessed. Initially a one-pot reaction from the hydroxamic acid was attempted. Benzohydroxamic acid (**26**) was stirred with a slight excess of CDI (1.1 eq.) in toluene at room temperature for an hour to form the active dioxazalone intermediate (**28**) before the catalyst (**25**) and 3-nitrobenzaldehyde (**36**) were added and the resulting mixture heated to reflux for 24 hours. With two equivalents of (**36**) a 1 : 1 ratio of imine to aldehyde was detected in the crude ^{1}H NMR, indicating a near quantitative conversion. With one equivalent of aldehyde there was almost quantitative conversion to imine, with diphenyl urea as the major side product (97:3 ratio (**35b**):Urea). Simplifying the reaction further, the

vessel was charged with all of the reagents in toluene before the mixture was heated to reflux giving the imine at conversions of 89% (Scheme 53).



Scheme 53: Results of the intermolecular catalytic aza-Wittig reaction starting from hindered urea.

The intermediacy of the dioxazalone (**28**) was investigated using the isolated species as the starting point for the intermolecular catalytic aza-Wittig reaction (Scheme 54). It was reported that a nucleophile was required to activate the dioxazalone so imidazole and diisopropylamine were tested. Yields were calculated using a known concentration of 2,5-dimethylfuran as an internal standard. Interestingly imidazole proved to be better than diisopropylamine (Table 2), probably due to the labile nature of the imidazolyl urea compared with the more stable diisopropyl urea. The imidazole was recovered at the end of the reaction suggesting it may be possible to use sub-stoichiometric quantities to initiate the rearrangement but this was not attempted.



(**36**) (**28**) (**35b**)

Scheme 54: Dioxazalone (**28**) as a starting material for the intermolecular catalytic aza-Wittig reaction

Equivalents (**36**)	Amine	Ratio (imine:aldehyde)	Yield (**35b**)[a] (%)
1	$^{i}Pr_2NH$(1.0 eq.)	3 : 2	58%
2	$^{i}Pr_2NH$(1.0 eq.)	2 : 3	37%
2	$^{i}Pr_2NH$(0.5 eq.)	1 : 3	23%
2	Imidazole (1.0 eq.)	1 : 1	86%

Table 3: a) Yield based on (**28**) calculated by ^{1}H-NMR using internal reference (2,5-dimethylfuran).

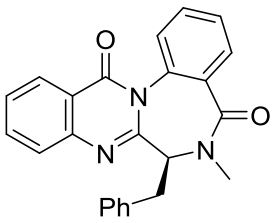
2.3. Conclusions

A range of conditions have been developed for the intermolecular catalytic aza-Wittig reaction utilising alternative starting materials, avoiding the need for azides. The Lossen rearrangement offers an alternative to the Curtius reaction for the *in situ* formation of isocyanates. Hydroxamic acids and the associated intermediate from the CDI mediated Lossen rearrangement, dioxazalone (**28**), were successfully employed to produce imine (**35b**) from the aldehyde in excellent yields. Diisopropyl urea (**27**), a masked isocyanate could also be used as a starting material for the catalytic aza-Wittig reaction, giving comparable yields to the isocyanate. The self-condensation reactions failed to provide the expected carbodiimide product, which is usually a side-product of the intermolecular catalytic aza-Wittig reaction. This reduced tendency to self-condense proves advantageous in later works.

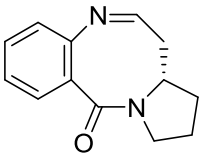
3. Application of the Azide Free Catalytic Aza-Wittig Reaction to the Synthesis of Heterocycles.

3.1. Introduction to Intramolecular Catalytic Aza-Wittig Chemistry

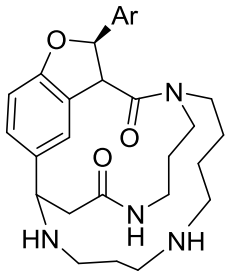
The most important application of aza-Wittig chemistry is the synthesis of *N*-heterocycles for which it has been used extensively for the synthesis of 5- and 6-membered *N*-heterocycles.[67] The strong driving forces associated with the formation of the P=O bond allow for the synthesis of otherwise difficult systems. Large rings and strained systems can be easily accessed as exemplified by the synthesis of benzomalvin A, a seven-membered benzodiazepine,[68] and benzodiazocine, an eight-membered ring system.[69] The intramolecular reaction can also be used to do condensation reactions on less active carboxyls like esters and amides, which in the case of amides is sometimes referred to as the Eguchi protocol. Mild reaction conditions also make the aza-Wittig reaction functional group tolerant making it a valuable tool for total synthesis. So robust and mild is this methodology that it has been applied to a particularly complex thirteen-membered ring system as part of the total synthesis of (-)-ephedradine A.[70]



(-)-Benzomalvin A

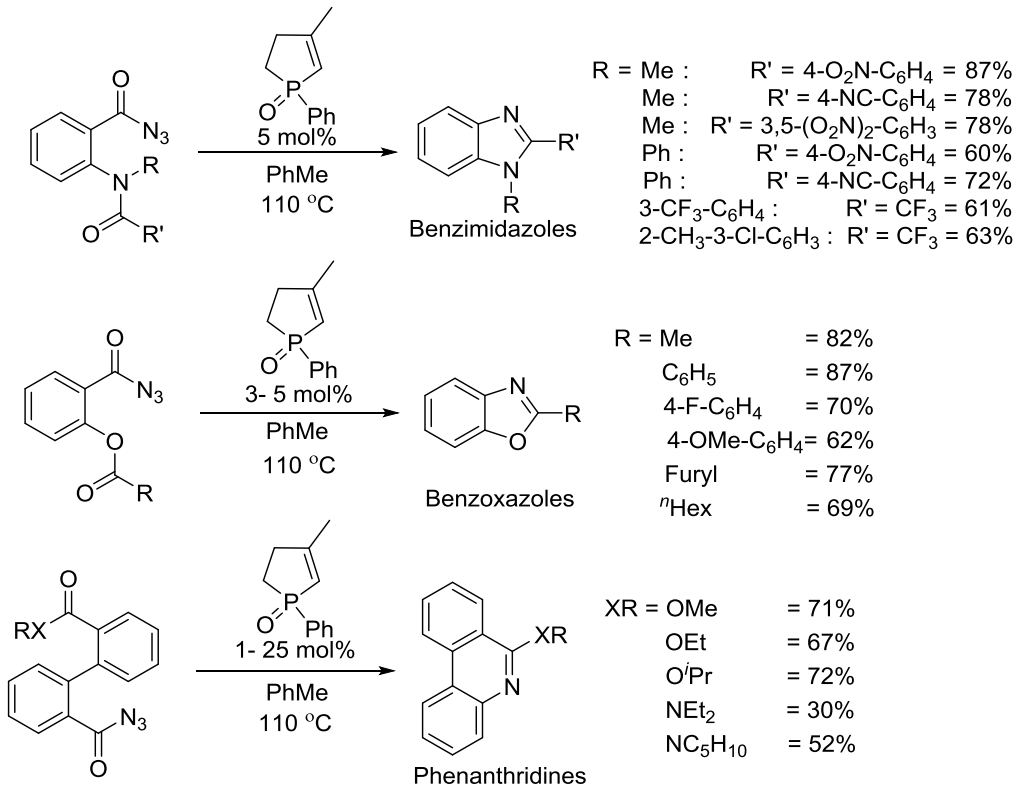


Benzodiazocine



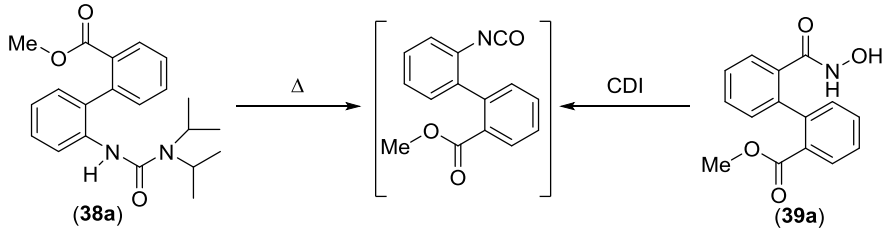
(–)-Ephedradine A

The redox-neutral catalytic variant of the aza-Wittig reaction first saw use in cyclization reactions for the synthesis of phenanthridines and benzoxazoles (Scheme 55).[52] Since then it has been utilized in the synthesis of benzimidazoles.[50] Intramolecular reactions are an ideal application for the redox-neutral catalytic aza-Wittig reaction as the competing self-condensation reaction of the isocyanates can be controlled with high dilutions which favour the cyclization. Difficulties arising from hydrolytic instability experienced during attempts to isolate carbodiimide and imine products from the intermolecular reactions, should not occur with the products of intramolecular methodologies. In contrast to imines, *N*-heterocycles are stable and can be easily isolated. This should allow for quantifiable results and isolation of analytically pure products.



Scheme 55: Previous results for the intramolecular catalytic aza-Wittig reaction.[50,52]

Previous members of the group found the synthesis of phenanthridines via catalytic aza-Wittig methodology to be robust and starting materials could be produced in two steps from commercially available materials. We therefore aimed to emulate McGonagle's methodology, utilising novel methods for *in situ* isocyanate synthesis to produce phenanthridines (Scheme 56). Utilising the catalytic aza-Wittig reaction five examples of phenanthridines were synthesised by McGonagle in good to excellent yields from the corresponding acyl azides with catalyst loadings as low as 1 mol% (Scheme 55).[52] While the ester derivatives could be successfully cyclised with catalyst loadings of between 1 and 5 mol%, reactions with the amides required higher catalyst loadings of 25 mol%. It was hoped that comparable or improved results could be achieved using either one of the novel reaction pathways first explored with the intermolecular reaction. Both of these starting materials held the potential to remove the need for hazardous azides.

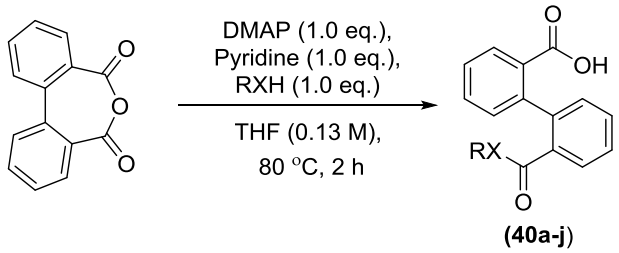


Scheme 56: Novel methods for *in situ* isocyanate synthesis.

3.2. Results and Discussion

3.2.1. Synthesis of Diphenyl Hydroxamic Acids

Emulating McGonagle's route, the first step was the synthesis of the diphenic acid esters/amides (**40a-j**). Nucleophilic addition of alcohols and amines to diphenic anhydride provided a simple route to the respective esters and amides (**40a-j**) in good yields (Table 3). These diphenic acid esters/amides were typically purified by acid-base work-up. Observed side products for this reaction were identified as the diphenic acid and diphenic diesters (or diamide) which were removed easily on acid-base work-up.



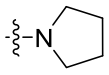
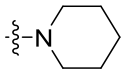
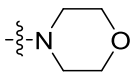
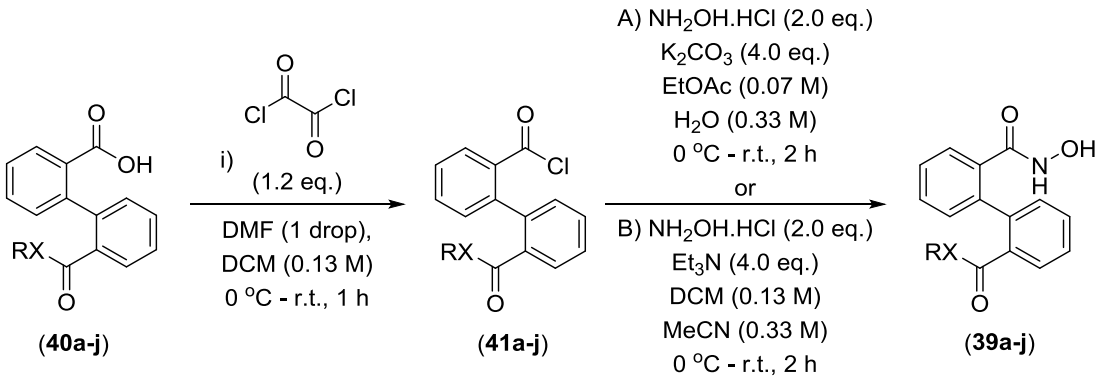
RX	Yield	RX	Yield
OMe (**40a**)	98%	OBn (**40f**)	57%
OEt (**40b**)	52%	NEt_2 (**40g**)	64%
O^{i}Pr (**40c**)	74%	 (**40h**)	82%
O^{n}Bu (**40d**)	88%	 (**40i**)	75%
O^{t}Bu (**40e**)	50%	 (**40j**)	87%

Table 4: Results from the synthesis of diphenic acid esters and amides.

Initially, attempts were made to produce the hydroxamic acids following Usachova *et al*'s method employing CDI as activating agent, which had proven successful for the synthesis of *N*-hydroxybenzamide (**26**).[71] Unfortunately, when this methodology was applied to the synthesis of hydroxamic acid (**39a**) only a small amount of the desired product was formed with the rest forming a complex mixture of unknown products. The addition of hydroxylamine hydrochloride and a base to the acid chlorides (**41a-j**) of the acids under Schotten-Baumann conditions proved the most successful method for the synthesis of the hydroxamic acids (**39a-j**). Stirring a solution of the acid in dichloromethane with oxalyl chloride and a drop of dimethylformamide provided the desired acid chlorides crude, which were then concentrated

under reduced pressure to remove unreacted oxalyl chloride. The concentrated acid chlorides (**41a-j**) were then re-dissolved in ethyl acetate before the addition of an aqueous solution of hydroxylamine hydrochloride and base. During optimisation it was found that suspending the acid chloride in a biphasic system of ethyl acetate and hydroxylamine hydrochloride salt in aqueous potassium carbonate provided the biphenyl ester hydroxamic acid (**39a-f**) in low to excellent yields (Table 4) (method a). These conditions proved unreliable for the amide substrates (**39g-j**), which suffered from poor solubility in ethyl acetate. In order to circumvent solubility issues experienced during attempts to produce the amide substituted hydroxamic acids (**39g-j**) an alternative method was developed. Adding the crude acid chloride mixture in dichloromethane to a solution of hydroxylamine hydrochloride and triethylamine in acetonitrile resulted in the formation of the desired crude hydroxamic acids. This method was applied to the synthesis of a range of amide substituted hydroxamic acids (**39g-j**) (route b).



(**40a-j**) (**41a-j**) (**39a-j**)

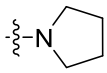
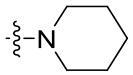
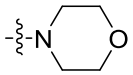
RX	Yield	Route	RX	Yield	Route
OMe (**39a**)	81%	A	NEt_2 (**39g**)	76%	A
OEt (**39b**)	69%	A	NEt_2 (**39g**)	84%	B
O^iPr (**39c**)	78%	A	 (**39h**)	60%	B
O^nBu (**39d**)	66%	A	 (**39i**)	66%	B
O^tBu (**39e**)	26%	A	 (**39j**)	52%	B
OBn (**39f**)	38%	A			

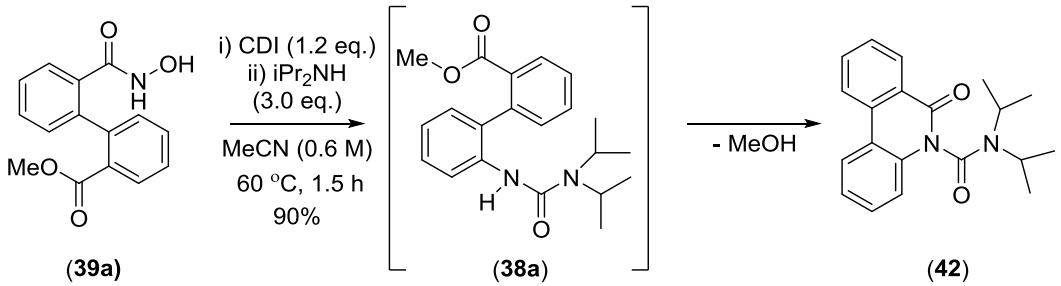
Table 5: Results of hydroxamic acid synthesis.

Similarities between the Rf of the starting acid and the hydroxamic acids made chromatograph separation troublesome. Normal silica column chromatography did not offer enough resolution to separate the desired hydroxamic acid (**39a-j**) from the starting acid (**40a-j**). Both acids and hydroxamic acids streak on TLC. Eluting the column using a mixture of solvents and 1% acetic acid allowed for separation but removal of acetic acid from the fractions proved problematic even under reduced pressure. The difference in acidity between the carboxylic acid ($pK_a \sim 4$) and hydroxamic acid ($pK_a \sim 9$) was viewed as a possible handle for separation. At pH 7 it can be assumed that the majority of hydroxamic acid will be neutral (C(O)NHOH), while the majority of the carboxylic acid will be deprotonated (COO^-). Acidification (pH = 1) of the reaction mixture removed excess hydroxylamine and neutralised left-over base. The product was then extracted from the organic phase with an aqueous solution of NaOH (1 M) and washed with organic solvent to remove neutral impurities such as the di-substituted esters/amides. Neutralising the basic aqueous phase allowed the hydroxamic acid to be extracted. Acid-base work-up aided purification but led to a low recovery of hydroxamic acid (**39**). After the work-up the product could be purified further by recrystallization from toluene. Further investigation found optimum conditions for separation to be column chromatography with a basic eluent, which allowed for the hydroxamic acid (**39a-j**) to be separated from the acid. A mixture of saturated aqueous ammonia (~ 18 M, pK_a = 9.4) and ethanol in dichloromethane (1 : 8 : 50) was polar enough to cleanly elute the desired hydroxamic acid and basic enough to cause acidic impurities to elute slower.

Of particular interest was the synthesis of the *N*-methylpiperazine amide (**39k**) which could be used for the synthesis of the biologically active *N*-methylpiperazine phenanthridine (**41k**).[72] However, the desired hydroxamic acid (**39k**) could not be isolated, possibly due to zwitterion formation between the hydroxamic acid and tertiary amine of the piperazine complicating purification. The *N*-Boc protected piperazine (**39l**) offered a route to the core of this phenanthridine (**41k**) without a basic tertiary amine group, simplifying purification. This led to a different difficulty; the acidic conditions of the oxalyl chloride step de-protected the acid-labile Boc group. To rectify this, triethylamine was added before the addition of oxalyl chloride to neutralise the acid liberated during the reaction.

Following on from the success of the hindered ureas as the starting materials for the intermolecular catalytic aza-Wittig (Scheme 52), attempts were made to produce biphenyl ureas for use in the intramolecular reaction. It was hoped that the Lossen rearrangement starting from the previously isolated hydroxamic acids (**39a-j**) could produce a range of hindered ureas providing alternative starting materials for the catalytic aza-Wittig reaction. Addition of a slight excess (1.2 eq.) of CDI to hydroxamic acid (**39a**) in acetonitrile and subsequent trapping with diisopropylamine on heating failed to produce the desired urea

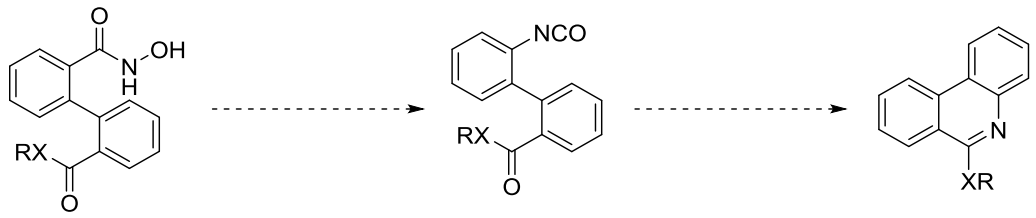
(**38a**). Instead diisopropyl carboxamide phenanthridone (**42**) was isolated at a 90% yield (Scheme 57). Presumably, this arises from the condensation reaction of the urea secondary nitrogen with the ester, liberating methanol. This observation suggests that the desired Lossen rearrangement occurs producing the urea before forming the observed side product.



Scheme 57: Attempt to produce biphenyl diisopropyl urea (**38a**).

While this may limit the application of hindered ureas as starting materials for the intramolecular aza-Wittig reaction it does demonstrate that these diphenic hydroxamic acids undergo Lossen rearrangement to produce the corresponding isocyanate intermediates which can then be trapped. It also offers insight into a possible side reaction for the CDI-mediated Lossen rearrangement which is worth consideration.

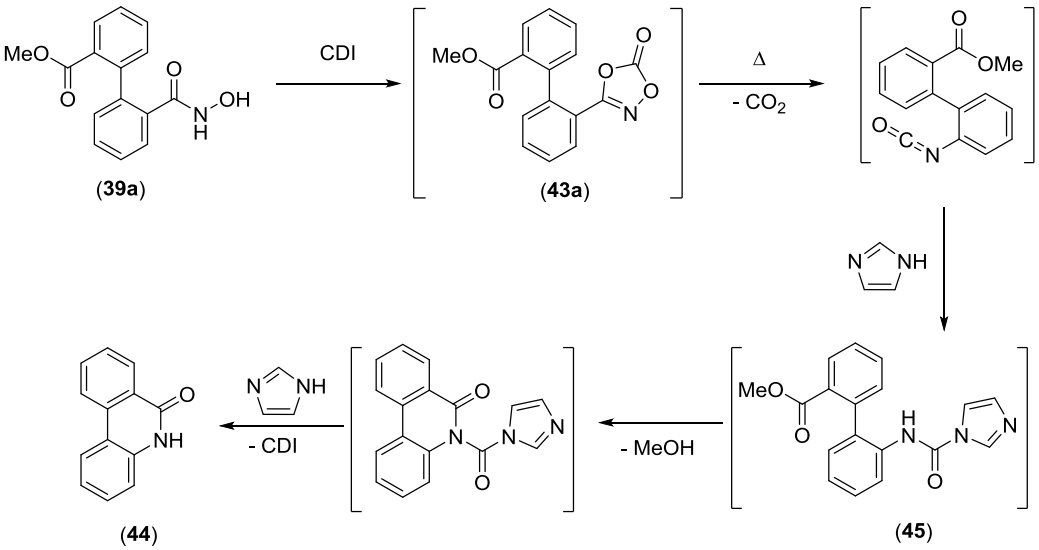
3.3. Azide-Free Synthesis of Phenanthridines



Scheme 58: Desired reaction for the azide free synthesis of phenanthridines.

Initially, the conditions optimised by McGonagle for the catalytic aza-Wittig reaction starting from acyl azides were adapted for the reaction where the isocyanate starting material was produced via the CDI-mediated Lossen rearrangement (Scheme 59). Carbonyl diimidazole was added to a solution of hydroxamic acid (**39a**) in toluene and the mixture was stirred at room temperature for half an hour before being heated to reflux for an hour. After this time a solution of phospholene oxide (20 mol%) (**25**) in toluene (0.1 M) was added to the refluxing reaction mixture and was stirred at this temperature for a further 18 hours. It was hoped that using this stepwise approach the dioxazalone (**43a**) would form at room

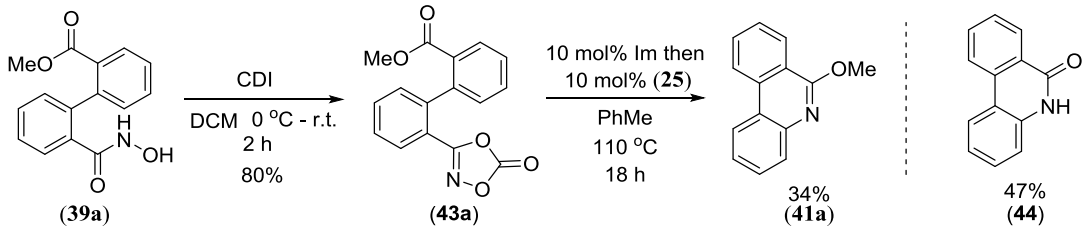
temperature, rearrange to the isocyanate on heating then undergo the catalytic aza-Wittig reaction on addition of catalyst (**25**) (Scheme 59). Unfortunately, this initial attempt failed to produce the desired product (**41a**), instead forming the phenanthridone (**44**) (90%). One suggestion for the mechanism responsible for the production of this species is a condensation reaction involving the imidazolyl urea (**45**) similar to that observed in the attempted synthesis of the hindered ureas described in Scheme 57. It is thought that the urea (**45**) would be formed by attack of imidazole on either the dioxazalone or isocyanate intermediates. The observed precipitation of the phenanthridone (**44**) would drive the equilibrium towards the by-products thus removing the imidazolyl urea (**45**) from the equation. Loss of the imidazolyl carboxamide on work-up would explain the absence of this pendant group on the observed by-product in the crude reaction mixture.



Scheme 59: Mechanistic explanation for observed phenanthridone (**44**)

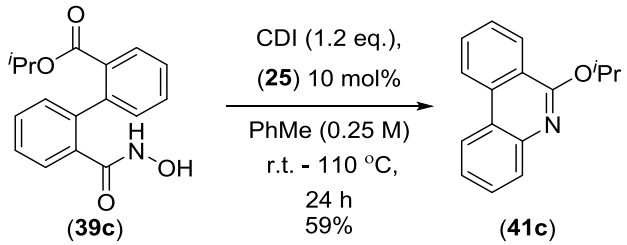
In an attempt to reduce this competing condensation reaction, the phospholene oxide catalyst was added before addition of CDI. This time the reaction was stirred at room temperature for 2 hours before being heated to reflux for 18 and afforded 24% of the desired phenanthridine (**41a**) and 67% of the phenanthridone (**44**). To gain some mechanistic insight into the reaction, the dioxazalone (**43a**) was isolated in 80% yield by the addition of CDI (1.2 eq.) to hydroxamic acid (**39a**) in dichloromethane (0.25 M) at 0 °C stirring for two hours (Scheme 60). Phenanthridone (**44**) was observed as a side product from this reaction, offering further evidence for the involvement of the imidazolyl urea intermediate (**45**) in the formation of this phenanthridone supporting the proposed mechanism, showing little/no involvement of the catalyst (**25**) or iminophosphorane intermediate in the formation of phenanthridone. When the dioxazalone (**43a)** was heated with catalytic imidazole and phospholene oxide the product

(**41a**) was isolated in 34% yield alongside the phenanthridone (**44**) as the major side product (47% yield) (Scheme 60).



Scheme 60: Synthesis of phenanthridines starting from dioxazalone.

The more hindered *iso*-propyl ester biphenyl hydroxamic acid (**39c**) was explored next, with the hope that a more hindered ester would reduce the amount of condensation product (**44**) formed. Subjecting (**39c**) to the same conditions used for the methyl ester (**39a**) (1.2 eq. CDI, 10 mol% catalyst (**25**) in toluene (0.25 M, 2 hours at room temperature, 18 hours at 110 °C) yielded 59% of the desired phenanthridine (**41c**) and 12 % yield of phenanthridone (**44**). A range of conditions were screened to optimise the reaction (Scheme 61) (Table 5).

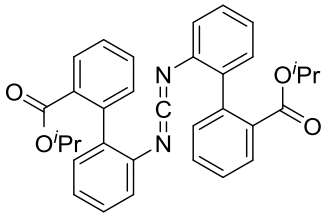


Scheme 61: Azide free synthesis of isopropyl phenanthridine.

Entry	Concentration (**39c**) (mol.dm^{-3})	Catalyst loading (**25**) (mol %)	Ratio of (**41c**) : (**44**) in crude	Isolated Yield (**41c**)
1	0.25	5%	1.0 : 1.5	40%
2	0.25	10%	1.0 : 0.2	59%
3	0.25	20%	1.0 : 0.2	69%
4	0.25	100%	1.0 : 0.1	79%
5	0.50	10%	1.0 : 0.1	74%
6	0.50	20%	1.0 : 0.1	87%
7	1.00	20%	1.0 : 0.0 : 2.2[a]	40%

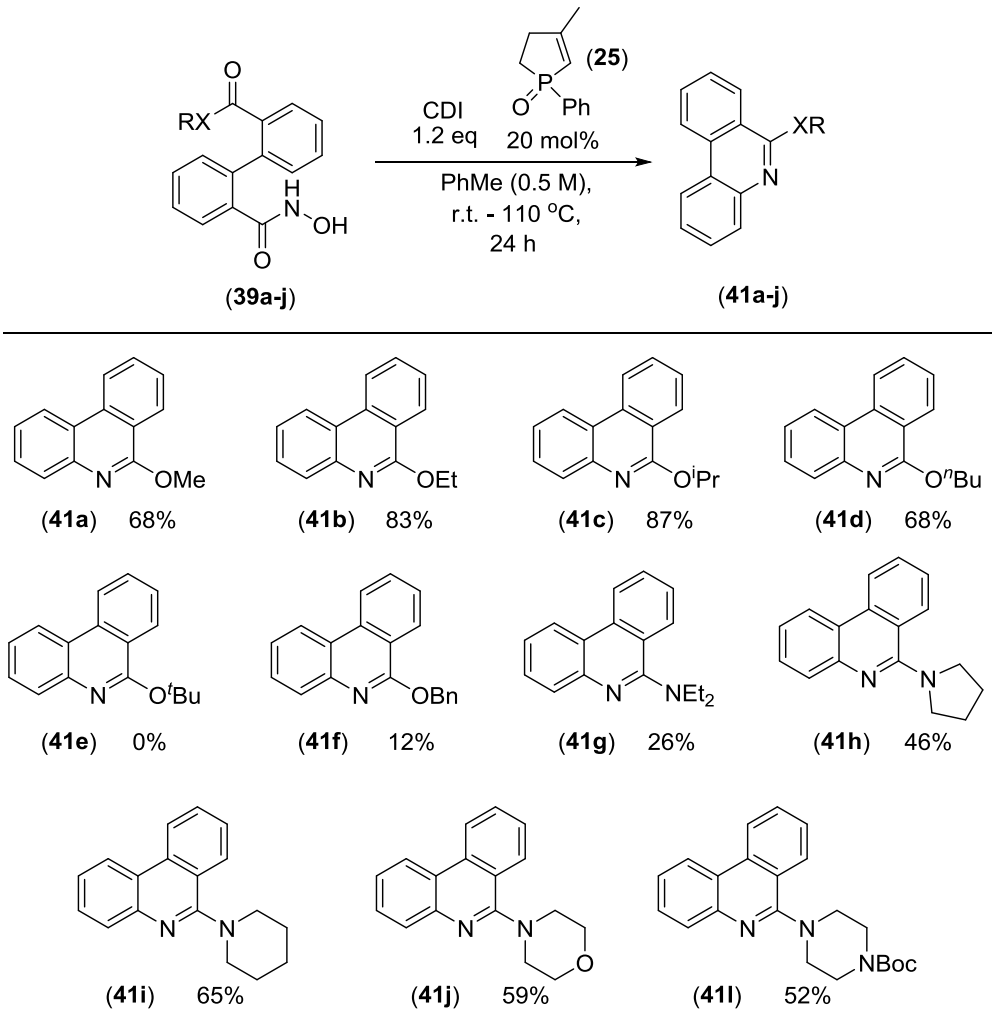
Table 6: Table of results from optimisation. a) Carbodiimide (**46c**).

Doubling the concentration and catalyst loadings significantly improved reaction yields (Entry 6), this is presumably due to the increased frequency of interactions between the catalyst and isocyanate favouring the desired aza-Wittig reaction. At high concentrations (Entry 7) a side product was observed being formed during the reaction; presumably this was the carbodiimide (**46c**). It was found to contain the characteristic IR signal at 2140 cm^{-1} and was observed as the corresponding urea by LC-MS ([M+H] $C_{33}H_{33}N_2O_5$ m/z = 537.23). It can be expected that this intermolecular self-condensation reaction would be favoured at high concentrations. It is of note that catalyst loadings could be reduced to 5% without significant lowering of yield (Entry 1). Optimum conditions were found to involve heating the reaction mixture rapidly after the addition of CDI in the presence of the catalyst, allowing for complete formation of the dioxazalone intermediate before rapid formation of the isocyanate at temperatures where the rate of reaction for the catalytic aza-Wittig reaction is sufficient to compete with the condensation reaction.



(**46c**)

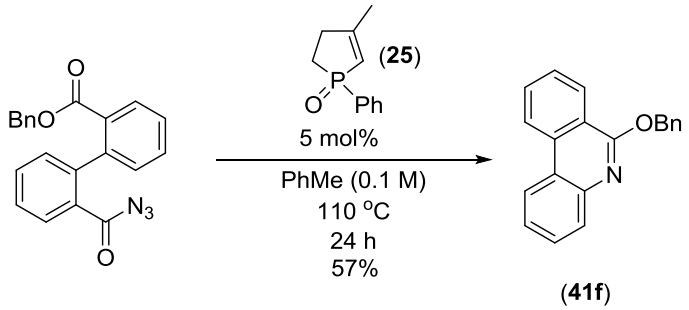
These optimum conditions were then utilised to produce a range of phenanthridines (**41a-j**) from the corresponding hydroxamic acids (**39a-j**) (Scheme 62). Substrates containing both esters and amides successfully underwent the aza-Wittig reaction.



Scheme 62: Optimised reaction conditions and Yields for the CDI-mediated Lossen rearrangement initiated catalytic aza-Wittig.

The *tert*-butyl ester containing substrate (**39e**) failed to provide the desired product (**41e**), instead undergoing condensation to form the phenanthridone (**44**) in almost quantitative yield. Presumably the bulky *tert*-butyl group prevents the iminophosphorane intermediate from accessing the carbonyl. Steric bulk can also be assumed to be the cause of the lower yield for the diethylamide system (**41g**) compared with the cyclic amides. In the cyclic amides (**41h-j**) the substituents are constrained in a ring, increasing access for the iminophosphorane to the carbonyl. Further investigation found the low yield for the benzyl ester (**41f**) system to be attributed to decomposition of the hydroxamic acid (**39f**); on heating, the starting hydroxamic acid (**39f**) decomposed producing the phenanthridone (**44**). This has been observed when on heated to reflux a solution of hydroxamic acid (**39f**) in toluene without CDI or phospholene oxide catalyst (**25**) give a quantitative yield of phenanthridone (**44**) as detected by ^{1}H-NMR spectroscopy. Phenanthridine (**41f**) proved to be stable under the reaction conditions, since

stirring a solution of independently prepared benzyl phenanthridine (**41f**), phospholene oxide (**25**) and CDI in refluxing toluene led to total recovery of starting material. A further verification came from taking the acyl azide (**47**) and subjected it to the catalytic aza-Wittig reaction conditions optimised by McGonagle (5 mol% phospholene oxide (**25**), 0.1 M in toluene, 110 °C for 24 hours)[52] which led to an isolated yield of 57% for the benzyl phenanthridine (Scheme 63). This supports the hypothesis that the hydroxamic acid is decomposing at elevated temperatures.



Scheme 63: Synthesis of benzoxy phenanthridine (**41f**) via Curtius rearrangement.

Phenanthridone side product (**44**) was insoluble in most solvent systems and proved difficult to isolate by flash column chromatography. To reliably calculate the amount of phenanthridone (**44**) produced, the ratio of phenanthridine (**41**) to phenanthridone (**44**) could be calculated from integration of the proton NMR spectra in DMSO-*d6*. Conversions were calculated from the integration of phenanthridine (**41**) (two doublets at 8.65 and 8.55 ppm) and phenanthridone (**44**) (three doublets at 8.43, 8.39 and 8.32 ppm) signals compared with an internal standard (dimethylfuran, 5.80 and 2.20 ppm) with a known concentration are presented below (Table 6).

RX	(**41**)	(**44**)	RX	(**41**)	(**44**)
OMe (**41a**)	45%	32%	O^{n}Bu (**41d**)	44%	33%
OEt (**41b**)	70%	20%	O^{t}Bu (**41e**)	0%	77%
O^{i}Pr (**41c**)	65%	26%	OBn (**41f**)	13%	87%

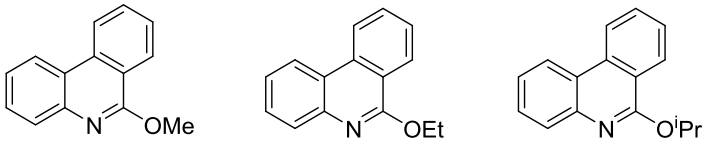
Table 7: Conversion of hydroxamic acids (**39a-f**) to phenanthridine (**41a-f**) and phenanthridone (**44**) calculated by ^{1}H-NMR.

An alternative side product was observed for the amide systems (**39g-l**), which matched the carbodiimide side product observed by McGonagle. The carbodiimide product was not observed with the ester systems under normal conditions (**39a-f**) but was noted during optimisation when reactions carried out at high concentration. Amide carbonyls are more

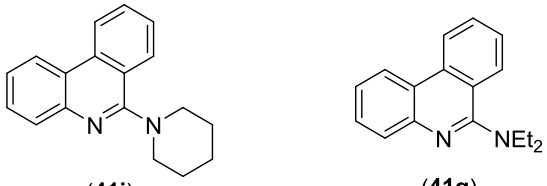
electron rich and stable preventing the condensation reaction which would lead to the phenanthridone (**44**), but this also lowers electrophilicity meaning the desired intramolecular aza-Wittig reaction is slower, favouring the intermolecular condensation reaction involved in the self-condensation pathway. The carbodiimide can be observed by IR, ^{1}H-NMR and as the urea by LC-MS. Unfortunately they are difficult to quantify by NMR due to similarities between the carbodiimides, products and starting materials. As previously mentioned, carbodiimides are unsuitable for column chromatography meaning isolation would prove difficult and is unlikely to be an accurate representation of the yield.

To reassess the role of the dioxazalone as an intermediate or alternative starting material the more hindered *iso*-propyl ester dioxazalone (**43c**) was synthesised. This was used to test the effect of different amounts of imidazole in an attempt to understand the competing intramolecular acyl substitution giving rise to phenanthridone (**44**). Using the optimised conditions for the catalytic aza-Wittig step allowed for comparison with the one-pot reaction. With no imidazole present only a trace amount of product was observed in the crude ^{1}H-NMR spectrum, with the majority of the mass balance being recovered starting material, reinforcing the idea that a nucleophile is required to initiate the CDI-mediated Lossen rearrangement. Substoichiometric amount of imidazole (20 mol%) leads to a yield comparable to the one pot reaction (79%) with trace amounts of the phenanthridone side-product (**44**) and other unknown by-products completing the mass-balance, but no observable starting material. This result supports the hypothesis that imidazole is catalytic and is required to initiate the Lossen rearrangement. With stoichiometric imidazole a high yield of the desired phenanthridine (**41c**) was isolated (66%). This yield was not as high as was isolated from the catalytic reaction which suggests that the imidazole also plays a role in the competing condensation reaction. It should be noted that in general yields are lower starting from the dioxazalone than for the one pot reaction due to the instability of starting dioxazalone (**39c**) which decomposes over time making it unsuitable as a starting material.

In conclusion, the Lossen rearrangement has been utilised as an *in situ* method for the synthesis of isocyanates for the catalytic aza-Wittig reaction with yields comparable to the Curtius variant (Scheme 64). It must be noted that higher catalyst loadings were required for the Lossen variant with esters, but lower catalyst loadings could be used for amide systems using the Lossen rearrangement rather than the Curtius. One possible explanation for this is differing side-reactions. When using the Curtius variant the carbodiimide side-product arises from the intermolecular dimerisation which occurs due to higher concentrations of the isocyanate. While with the Lossen rearrangement the isocyanate is possibly in equilibrium with the imidazolyl urea, meaning isocyanate concentration remain low throughout the reaction. The phenanthridine (**44**) side-product is possibly formed from a side reaction of the imidazolyl urea, which cannot occur in the Curtius system.



	(**41a**)	(**41b**)	(**41c**)
Curtius (10 mol% **25**): 80%	78%	72%
Lossen (20 mol% **25**): 68%	83%	87%

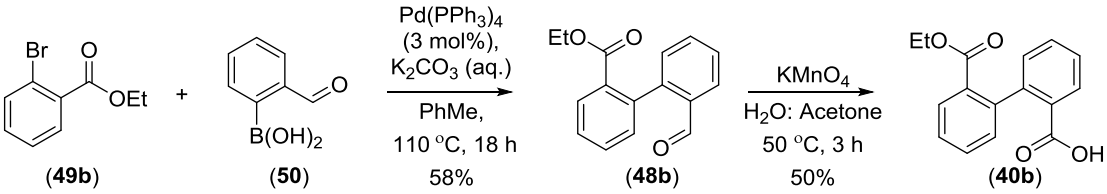


	(**41i**)	(**41g**)
Curtius (25 mol% **25**): 52%	30%
Lossen (20 mol% **25**): 65%	26%

Scheme 64: Comparison of Curtius and Lossen methodologies.

3.3.1. Starting Material Development for Substituted Phenanthridine Synthesis

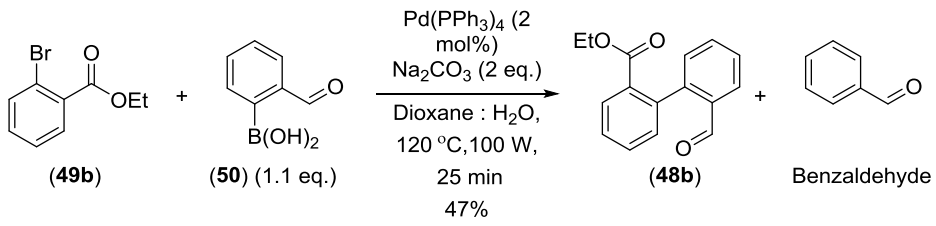
With a range of diphenic amides and esters (**41a-l**) explored, there remained the potential to place substituents on either of the two aryl rings. Cross-coupling reactions grant access to various substituted biaryls which could be used to explore the impact of electronic effects on the reaction. In the literature, Suzuki reactions are regularly employed to produce substituted biaryls with an aldehyde moiety in the 2-position which can then be oxidised to the corresponding carboxylic acids.[73-76] There are no reports of cross-coupling reactions direct from the acid with an ester or amide substituted aryl bromides or boronic acids, so it was decided to use the two step process. To probe this route the simple ethyl ester biaryl aldehyde (**48b**) was synthesised in an adequate yield (58%) following literature conditions.[74] Tetrakis(triphenylphosphine) palladium(0) (5 mol%) was added to a mixture of commercially available bromide (**49b**) (1.0 eq.) and boronic acid (**50**) (1.0 eq.) in toluene (0.06 M) and aqueous K_2CO_3 (2.0 M, 6.7 eq.) then heated to reflux for 18 hours (Scheme 65). Oxidation with potassium permanganate yielded the carboxylic acid (**40b**) in an acceptable yield (50%). A large range of aryl bromides and boronic acids are commercially available meaning there is scope to produce many substituted biaryl carboxylic acids derivatives via this method.



(**49b**) (**50**) (**48b**) (**40b**)

Scheme 65: Suzuki reaction and oxidation pathway to biaryl acid (**40b**).

Microwave irradiation provides a much more rapid heating method for Suzuki reactions.[73] Superheating the reaction mixtures in dioxane in a sealed reaction vessel to 120 °C led to reactions reaching completion in 25 minutes. Due to the short reaction times and ease of use, the microwave-assisted method was applied to the synthesis of biaryl aldehyde (**48b**). Initial attempts using a slight excess of boronic acid (**50**) (1.1 eq.) yielded less of the desired product (**48b**) (47% yield) than the standard reaction (Scheme 66). Proton NMR spectroscopy of the crude reaction mixture found that while all boronic acid had been consumed, half of the bromide (**49b**) remained unreacted. It was found that the boronic acid had undergone proto-deboronation forming benzaldehyde, which could be observed in the ^{1}H-NMR of the crude reaction mixture.

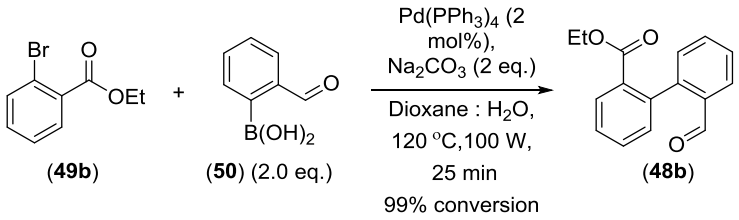


Scheme 66: Microwave assisted synthesis of biaryl (**48b**).

The speed of the reaction allowed for rapid screening of a range of conditions. Integration of aryl bromide (**49b**) and product (**48b**) signals by ^{1}H-NMR spectroscopy of the crude reaction mixture after work-up provided a rapid method for crudely quantifying conversions of bromides to biaryls (Table 7). Thorough degassing by bubbling nitrogen through the reaction solvents for half an hour improved the reaction yields (entry 1). Screening a series of commonly used bases led to no improvement in yields. While higher conversions were noted for sodium hydroxide (entry 3) and potassium phosphate (entry 5), less material was recovered after the reaction, suggesting that some mass balance might have been lost on work-up or under reduced pressure. Next, the effect of solvation was investigated. While polar protic (methanol, entry 7) and aprotic solvents (dioxane, entry 1, DMF, entry 8 and acetonitrile, entry 9) all gave comparable yields (60 − 68%), non-polar toluene led to poor conversion (entry 10) (8%), which is surprising given that the traditional method is performed in toluene. Using an alternative set of literature conditions (increased catalyst loading (5 mol%) and an anhydrous solvent system of toluene and ethanol (10 : 1 ratio)) resulted in a low conversion to the desired product (**48b**) (entry 11).[77] Fortunately, it was found that increasing the equivalents of boronic acid increased the conversion of bromide, with two equivalents of boronic acid providing complete conversion to the desired biaryl (entry 13).

Entry	Base (eq.)	Organic solvent	(**50**) (eq.)	Pd cat. loading	Conversion of (**49b**) to (**48b**)
1	Na_2CO_3 (2.0 eq.)	Dioxane	1.1 eq.	2 mol%	64%
2	K_2CO_3 (2.0 eq.)	Dioxane	1.1 eq.	2 mol%	64%
3	NaOH (2.0 eq.)	Dioxane	1.1 eq.	2 mol%	84% (lost mass)
4	$NaHCO_3$ (2.0 eq.)	Dioxane	1.1 eq.	2 mol%	64%
5	K_3PO_4 (2.0 eq.)	Dioxane	1.1 eq.	2 mol%	85% (lost mass)
6	Na_2CO_3 (4.0 eq.)	Dioxane	1.1 eq.	2 mol%	54%
7	Na_2CO_3 (2.0 eq.)	MeOH	1.1 eq.	2 mol%	66%
8	Na_2CO_3 (2.0 eq.)	DMF	1.1 eq.	2 mol%	68%
9	Na_2CO_3 (2.0 eq.)	MeCN	1.1 eq.	2 mol%	60%
10	Na_2CO_3 (2.0 eq.)	PhMe	1.1 eq.	2 mol%	8%
11	K_2CO_3 (6.7 eq.)	PhMe: EtOH	1.1 eq.	5 mol%	30%
12	Na_2CO_3 (2.0 eq.)	Dioxane	1.5 eq.	2 mol%	85%
13	Na_2CO_3 (2.0 eq.)	Dioxane	2.0 eq.	2 mol%	99%

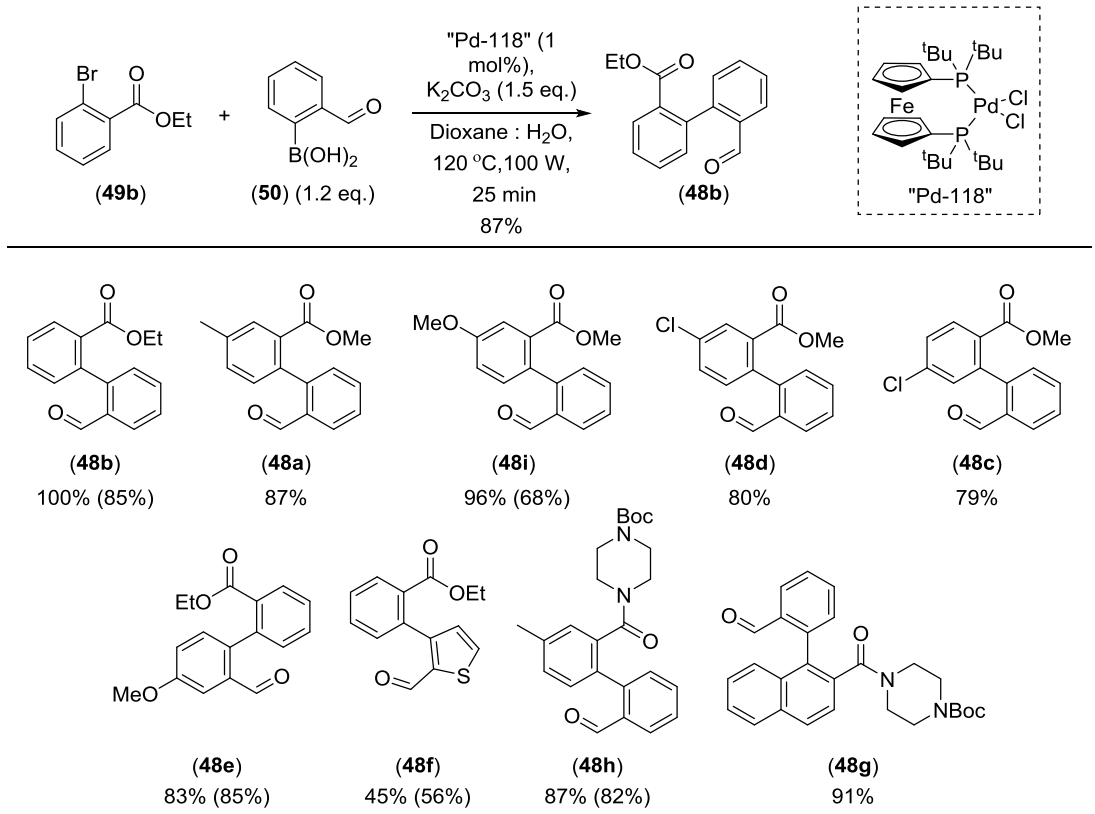
Table 8: Suzuki optimisation.



Scheme 67: Optimised conditions for Suzuki cross-coupling reaction.

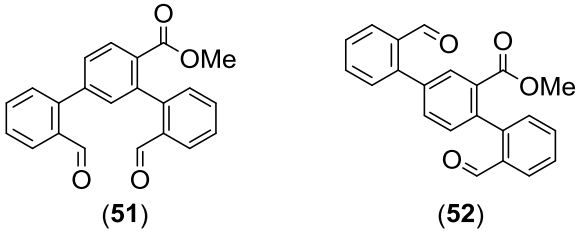
The optimised conditions were found to be addition of the bromide (1.0 eq.) to a suspension of boronic acid (2.0 eq.), $Pd(PPh_3)_4$ (2 mol%) and sodium carbonate (2.0 eq.) in a mixture of dioxane (1.7 M) and water (2.5 M) which was degassed and flushed with nitrogen for an additional 20 minutes before being heated with stirring to 120 °C for 25 minutes in a microwave (100 W) (Scheme 67). After cooling to room temperature the reaction mixture was washed with brine and extracted with ethyl acetate before being dried with sodium sulphate and concentrated under reduced pressure.

Optimised conditions provided a route to the desired aldehydes in excellent yields, but for more expensive substituted boronic acids using two equivalents of boronic acid was undesirable and limited the scale reactions could be run on. For these systems we turned to conditions reported by Moseley *et al.* using a more active palladium catalyst, $Pd(dbpf)Cl_2$, colloquially known as "Pd-118".[78] With the palladium species at the (II) oxidation state it is resistant to oxidation, a process which poses a problem for palladium(0) species such as tetrakis(triphenylphosphine) palladium(0) ($Pd(PPh_3)_4$). To produce the active palladium(0) species the starting palladium(II) species is initially reduced *in situ* by a slight excess of boronic acid. While Moseley*'s* conditions originally used traditional heating, they were easily adapted for microwave heating with a simple solvent swap from acetonitrile to dioxane. The adapted conditions were similar to those previously used. Addition of the bromide (1.0 eq.) to a suspension of boronic acid (1.2 eq.), "Pd-118" (1 mol%) and potassium carbonate (1.5 eq.) in a mixture of dioxane (0.5 M) and water (0.5 M), degassed by flushing with nitrogen for an additional 20 minutes before being heated with stirring to 120 °C for 25 minutes in a microwave (100 W) (Scheme 68). After cooling to room temperature the reaction mixture was washed with brine and extracted with ethyl acetate before being dried with Na_2SO_4 and concentrated under reduced pressure.

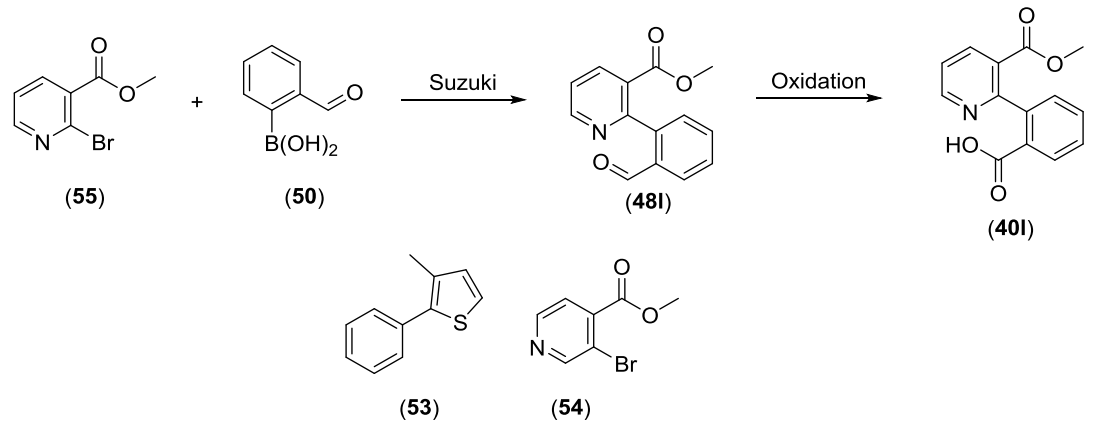


Scheme 68: Results of Suzuki reaction for the formation of biaryls. Percentages in parenthesis are yields using conditions of Moseley *et al.*.[17]

The methods furnished us with the aldehyde starting materials (**48a-h**) in good to excellent yields (56 – 99%) from the corresponding bromides and (2-formyl)phenylboronic acids on gram scale. Both sets of conditions gave similar yields, with the optimised conditions with two equivalents of boronic acids providing slightly higher yields in cases with (2-formyl)phenylboronic acid, and Moseley's conditions giving higher yields for the more difficult functionalised boronic acids (**48e** + **48f**). Under the forcing reaction conditions the chlorides on (**48c**) and (**48d**) have undergone a small degree of cross-coupling, yielding a noticeable amount of compounds believed to be triaryl ((**51**) 8% and (**52**) 7%) based on the integration of signals for the aldehyde and methyl ester at a 2:3 ratio in the crude ^{1}H-NMR spectrum. This would explain the lower isolated yield for the desired products.



Heterocycles are well known to react sluggishly in the Suzuki reaction.[78] Indeed Moseley *et al.* report that the formation of thiophenyl biaryl (**53**) took 24 hours to reach completion, rather than the usual 2 hours.[78] Even with superheating and the more active "Pd-118" catalyst a third of the starting (formyl)thiophenyl boronic acid (**50f**) and a third of the ethyl 2-bromobenzoate (**49b**) were recovered after 25 minutes, explaining the poor yield for these reactions. Moseley *et al.* report that the use of hydrochloride salts of the pyridyl bromides allowed them to undergo cross-coupling reactions. Cross-couplings were attempted with two pyridyl bromides (methyl 3-bromopyridine 4-carboxylate (**54**) and methyl 2-bromopyridine 3-carboxylate (**55**)). While the reaction of methyl 2-bromopyridine 3-carboxylate (**55**) with formylphenyl boronic acid yielded an adequate amount of the desired product (**48l**) (59% yield), 3-bromopyridine-4-carboxylate (**54**) only produced a complex mixture of products, none of which could be identified. Although (**48l**) was isolated it could not be recovered after the oxidation step, presumably due to the zwitterionic nature of the acid (**40l**).

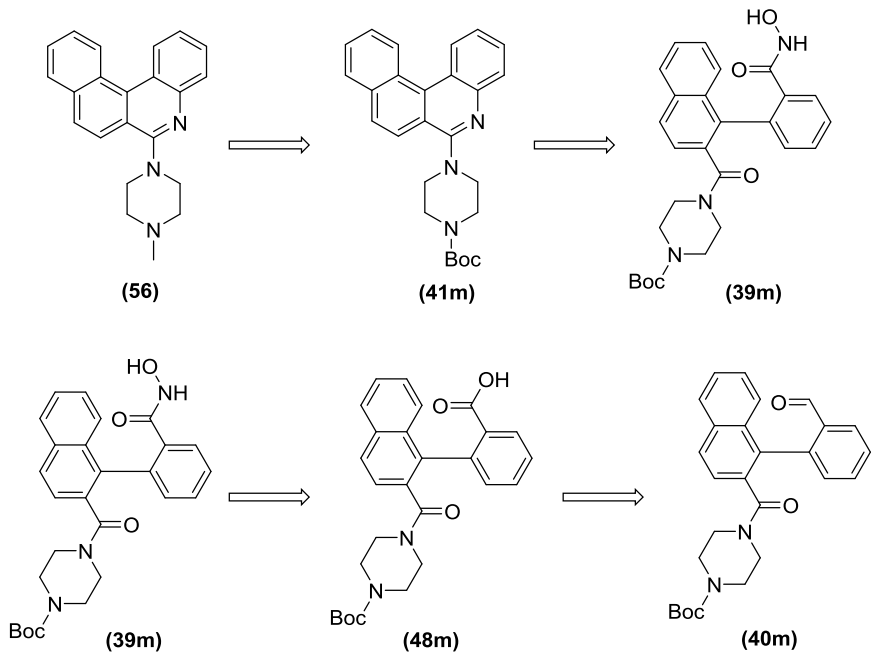


(**55**) (**50**) (**48l**) (**40l**)

(**53**) (**54**)

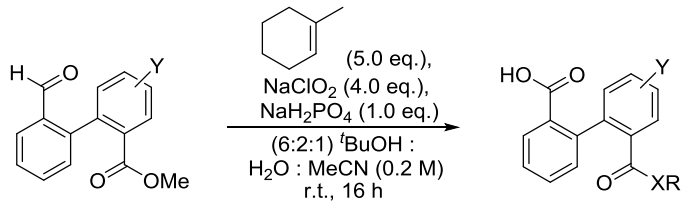
Scheme 69: Attempt at synthesis of pyridine derived biaryl acid (**40l**).

Aldehyde (**48g**) was prepared as the first step in a proposed synthesis of biologically active benzophenanthridine (**56**) which has been found to be a potent 5-HT_3 receptor antagonist (Scheme 70).[79]



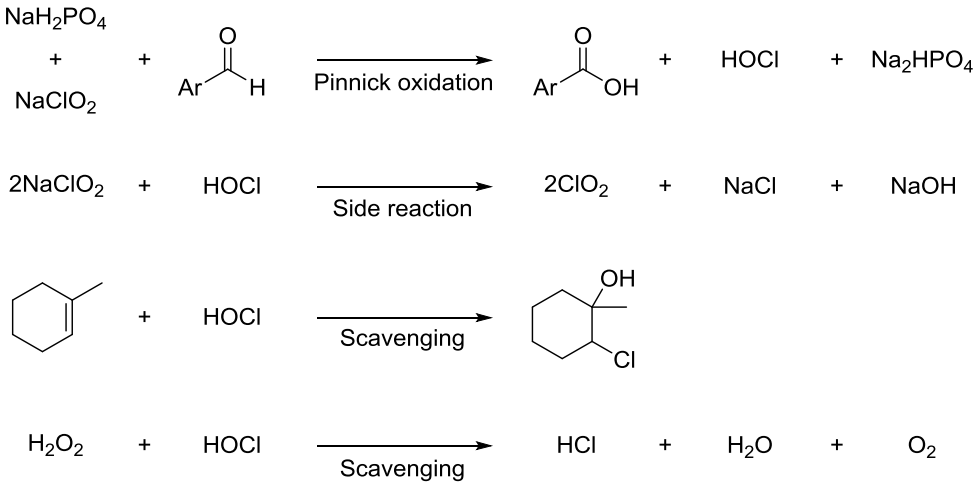
Scheme 70: Retro-synthetic analysis of biologically active benzophenanthridine (**56**).

To convert the isolated aldehydes into the required acids an oxidation step had to be performed. Originally a potassium permanganate method was used but often resulted in complex mixtures which may be attributed to the indiscriminate nature of potassium permanganate. Alternative oxidation techniques were explored in an attempt to allow for the incorporation of less robust functional groups in the biaryl products. A literature precedent has been set for the Pinnick oxidation to work selectively with similar systems.[76] The conditions reported by Miura *et al.* were adapted to use 1-methylcyclohexene rather than the low boiling 2-methyl-2-butene which would be difficult to handle. A range of acids were prepared by the addition of sodium chlorite ($NaClO_2$) (4.0 eq.) to a stirred solution of aldehyde, 1-methylcyclohexene (5.0 eq.) and monosodium phosphate (1.0 eq.) in a mixture of (6 : 2 : 1) ^{t}BuOH, water and acetonitrile for 16 hours at room temperature in good to excellent yields (58 − 99%) (Scheme 71).



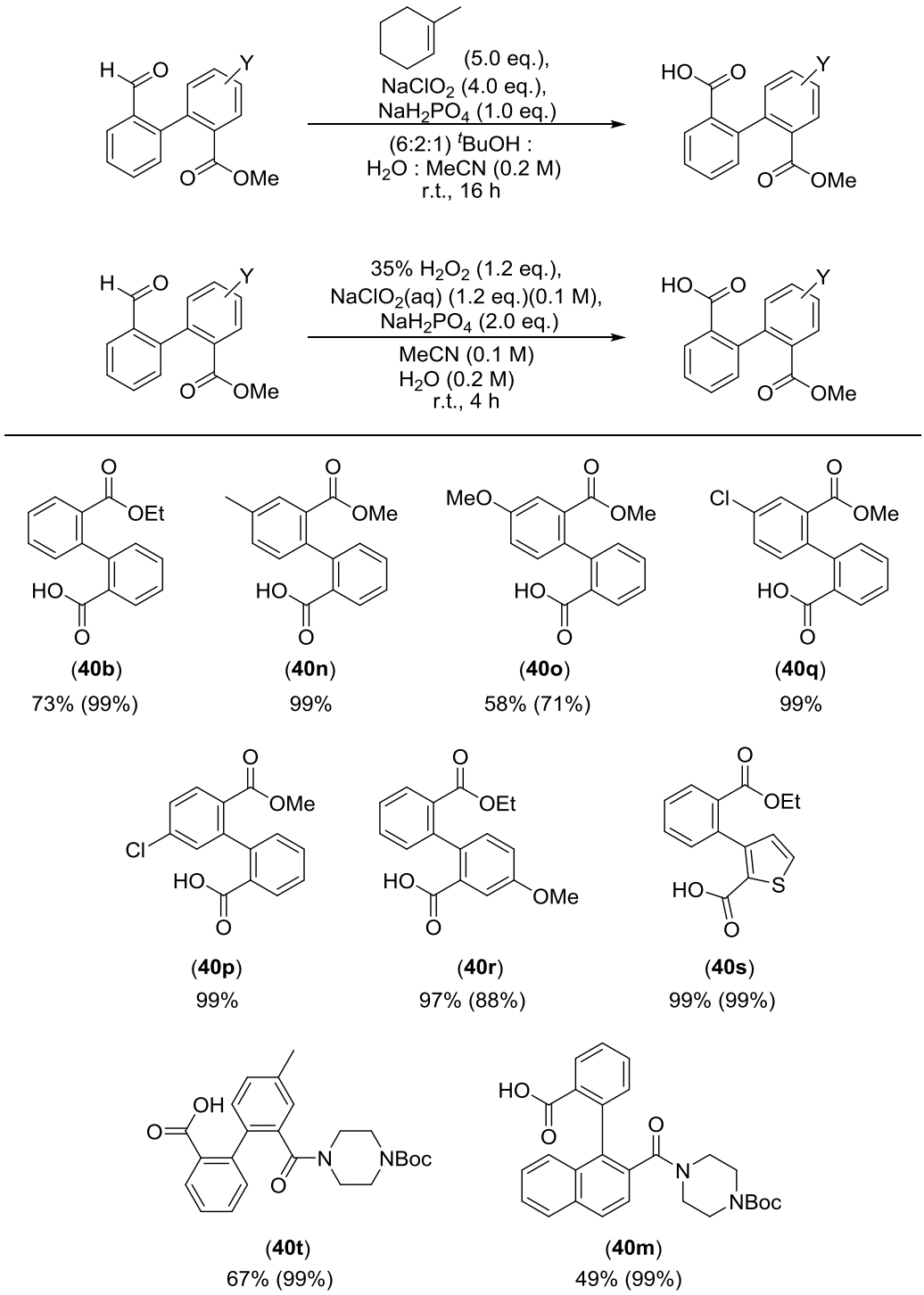
Scheme 71: Pinnick oxidation of biaryl aldehydes with 1-methyl cyclohexene scavenger.

The role of 1-methylcyclohexene is as a scavenger of hypochlorous acid (HOCl) which is formed as a by-product throughout the reaction and can consume the active sodium chlorite to produce the hazardous chlorine dioxide (ClO_2). The tertiary alkene is sacrificially oxidised by HOCl, a more powerful oxidant than the sodium chlorite ($NaClO_2$). The problem associated with using methyl cyclohexene as a scavenger is the production of aliphatic alcohol chloride products (Scheme 72). These oxidation products proved difficult to separate from the desired acids, so the use of hydrogen peroxide as a scavenger was investigated. Hydrogen peroxide reacts with the hypochlorous acid (HOCl) to produce HCl and water which are removed on work-up and O_2 which is lost as a gas.[80]



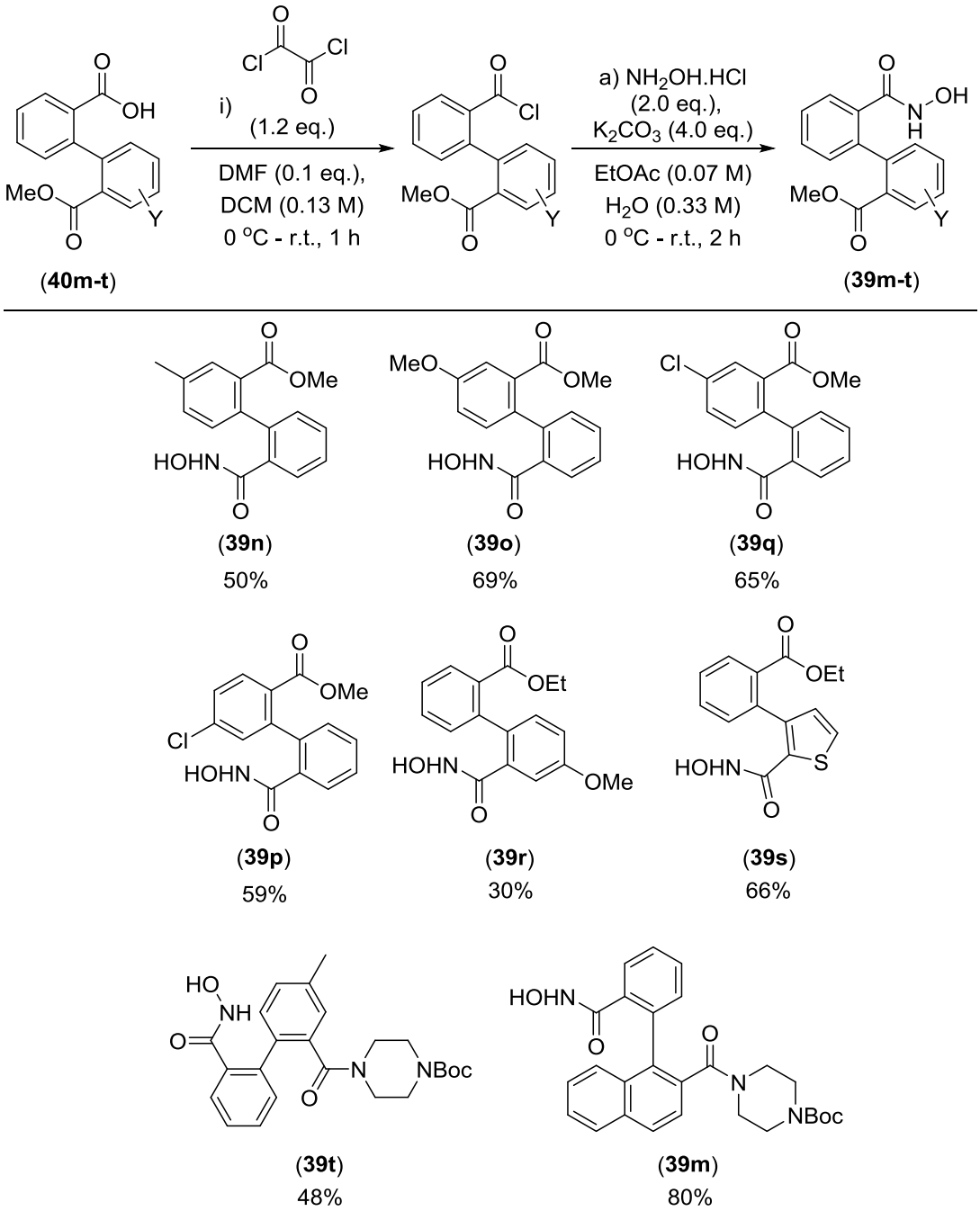
Scheme 72: Role of scavengers in the Pinnick oxidation.[80]

Using hydrogen peroxide as a chlorite scavenger gave vastly cleaner reactions and provided pure acids from the corresponding aldehydes after an acidic work-up (4 M HCl). This method was used to produce a range of acids in excellent yields (71 – 99%) (Scheme 73).



Scheme 73: Yields for Pinnick oxidation step. Percentages in parentheses are yields using hydrogen peroxide conditions.

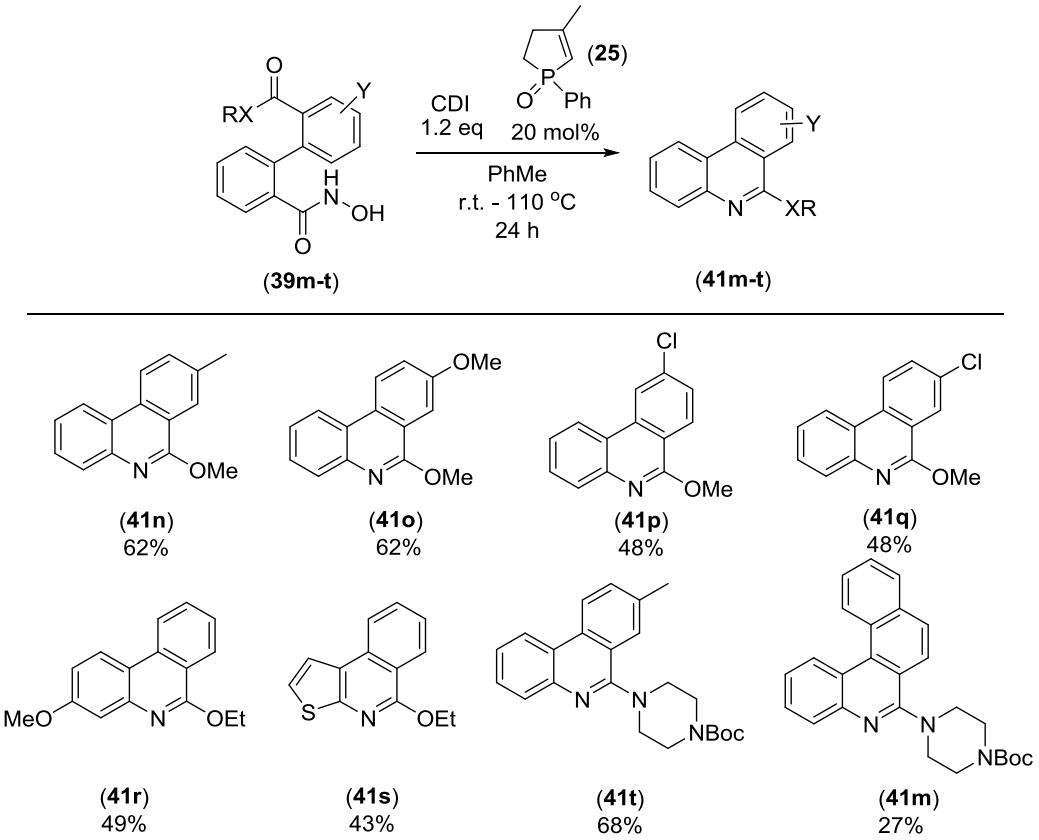
Following the reaction conditions optimised for the synthesis of unsubstituted hydroxamic acids (Table 4), the acids were transformed into the hydroxamic acids using the previously developed Schotten-Baumann conditions (Scheme 43). As detailed previously, triethylamine was added to the synthesis of *N*-Boc piperazine acid chlorides (**39m + 39t**) with the purpose of neutralising acid liberated throughout the reaction. Yields were found to be comparable to the unsubstituted systems (Scheme 74).



Scheme 74: Results from the synthesis of substituted biaryl hydroxamic acids.

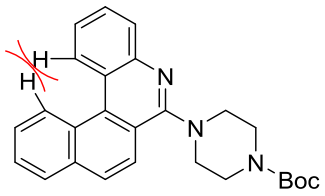
3.4. Azide-Free Synthesis of Substituted Phenanthridines

Subjecting the substituted hydroxamic acids (**39m-t**) to the conditions optimised for the synthesis of the simple phenanthridines (Scheme 62) provided the expected substituted products (**41m-t**). Substituted phenanthridines suffered from lower yields (48 – 62%) than the simple methoxy-phenanthridine (**41a**) which was isolated in a 68% yield. The difference in yields was more marked in the ethoxy systems (**41r** 49% yield and **41s** 43%) wherein the simple systems was isolated in an 83% yield. Since it can be envisaged that the aza-Wittig reaction is the nucleophilic addition of an iminophosphorane onto a carbonyl, it could be expected that electron-donating substituents on the ring sporting the carbonyl would lead to lower yields. Electron-withdrawing substituents would be expected to increase the yield of the aza-Wittig reaction. Experimental results seem to disagree with the expected hypothesis, since electron-rich systems (**41n** + **41o**) were isolated in higher yields than the electron-poor chlorides (**41p** + **41q**) (Scheme 75).



Scheme 75: Results of the azide free catalytic aza-Wittig reaction of substituted phenanthridines.

Steric effects may explain the lowest yield of the set. The naphthyl system (**41m**) had the lowest yield of all the phenanthridines, presumably because of the steric hindrance involved in aligning the iminophosphorane and the amide with two protons clashing in the planar product (Scheme 76).



Scheme 76: Steric clash involved in naphthyl derivative

3.5. Conclusions

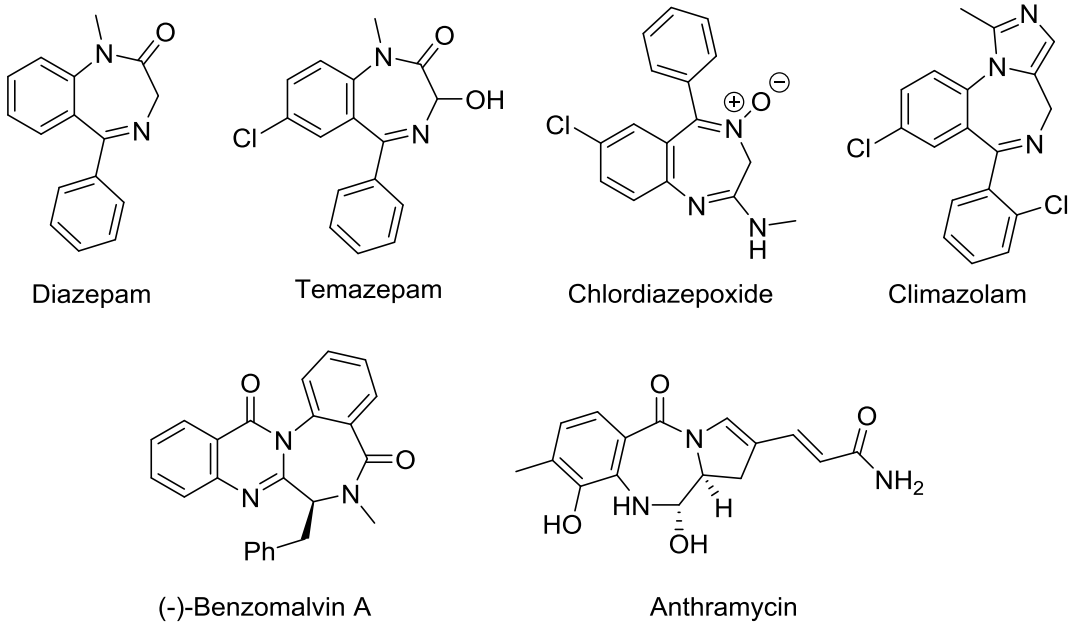
A range of phenanthridines have been synthesised using the CDI-mediated Lossen rearrangement to produce isocyanates from hydroxamic acids *in situ*. Yields are comparable to the catalytic aza-Wittig reaction utilising the Curtius rearrangement. Unfortunately catalyst loadings were higher for the Lossen mediated reaction where high loadings are required to prevent the alternative side-reaction observed for the CDI mediated Lossen rearrangement. Hydroxamic acids can be isolated in good to excellent yields starting from the corresponding acid on a gram scale.

Novel phenanthridines with various pendant amines and ethers have been produced using this new method, many in good yields. The reaction has also been used to synthesise phenanthridines sporting various functional groups on the aromatic rings. The first example of a thienoisoquinoline being synthesised via the catalytic aza-Wittig reaction is also reported.

4. Organocatalytic Aza-Wittig Reaction of Seven-Membered Heterocycles

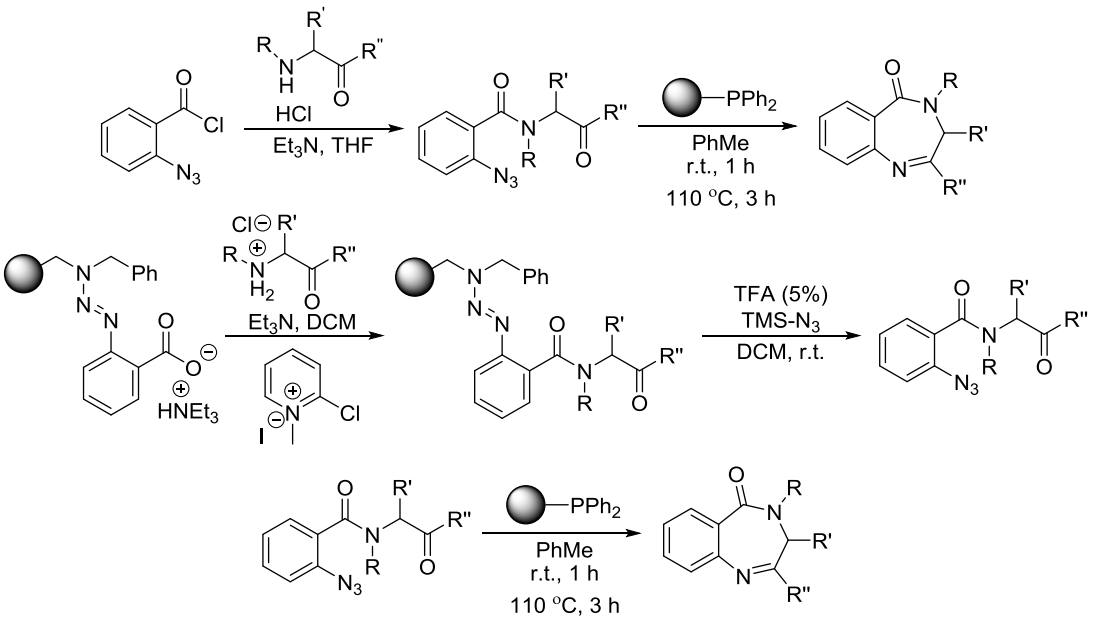
4.1. Introduction to Benzodiazepine Synthesis

Having explored the synthesis of the six-membered heterocyclic phenanthridines it seemed prudent to explore a larger ring system. Benzodiazepines seemed to be the perfect system to apply the developed methods for the azide-free catalytic aza-Wittig reaction. This seven-membered ring is an important moiety in a large number of pharmaceutically active compounds; indeed benzodiazepines are synonymous with sedatives due to the importance of diazepam (Vallium) (Scheme 77). The benzodiazepine binds to the $GABA_A$ receptor, acting as a GABA agonist enhancing the effect of the neurotransmitter, suppressing excitation in the central nervous system.[81] Due to this behaviour benzodiazepines are used in the treatment of epilepsy, delirium, psychosis, anxiety, alcohol withdrawal, seizures and insomnia. Due to the importance of these compounds the classical aza-Wittig reaction has been applied to their synthesis.

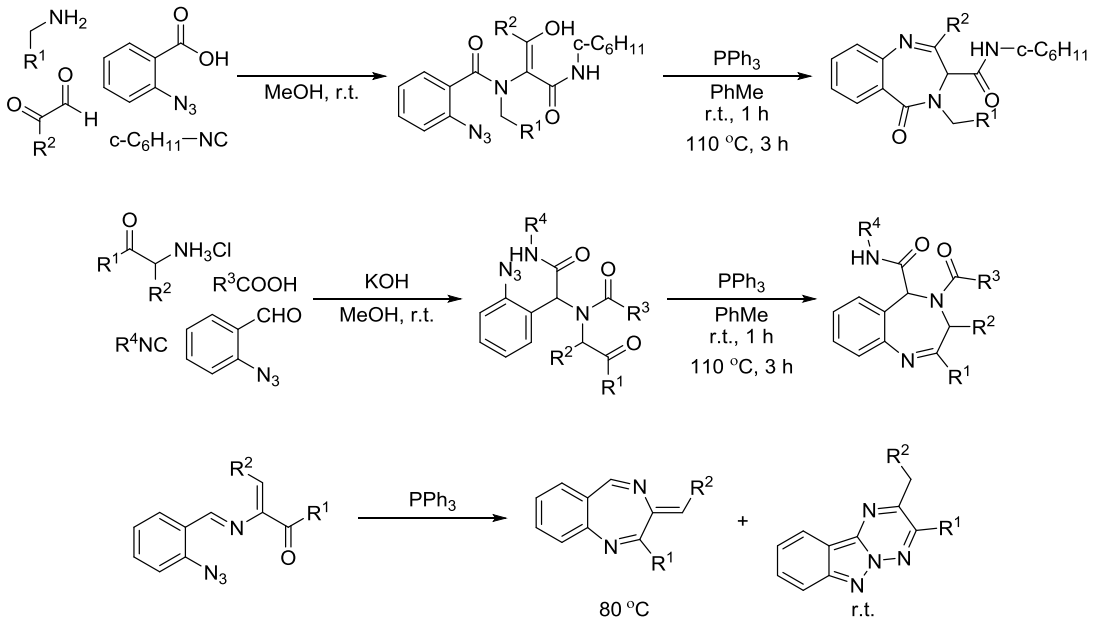


Scheme 77: Important benzodiazepines

Various groups have devised methods incorporating the aza-Wittig reaction for the synthesis of benzodiazepines (Scheme 78). The original example was a publication by Eguchi *et al.* which took an azidobenzoic acid, formed the acid chloride and added this to amino acid esters to form the azide-containing starting materials which underwent the Staudinger/aza-Wittig reaction to give the benzodiazepines in good yield.[82] Grieder *et al.* adapted this work to produce a library of benzodiazepine-quinazolinone alkaloids (circumdatins) using a polymer-supported-phosphine-mediated intramolecular aza-Wittig reaction. By using polymer-supported phosphine reagents it is possible to circumvent the issues associated with the removal of phosphine oxide by-products after the aza-Wittig reaction, allowing for the rapid synthesis of benzodiazepines. Over 120 examples were prepared in acceptable to good yields (40 - 60%) and high purity.[83] Similarly, Gil and Bräse used polymer-supported phosphine reagents to carry out the synthesis of benzodiazepines via the aza-Wittig reaction. Polymer-supported reagents were also employed in the amide bond formation reaction.[84] By utilising the Ugi reaction Torroba *et al.* managed to produce the starting materials for the Staudinger/aza-Wittig reaction in one step allowing them to synthesis a range of benzodiazepines.[85] Another example of the synthesis of benzodiazepines using an alternative set of reagents for the Ugi reaction to produce starting materials have been developed by Ding *et al.*.[86] This group has also produced a temperature dependant aza-Wittig cyclization, at 80 °C the benzodiazepines are formed, at room temperature, 1,2,4-triazino[2,3]indazoles are produced (Scheme 79).[87] Scifinder finds 21 publications involving the synthesis of benzodiazepines using aza-Wittig protocols producing 171 different benzodiazepines.[88]

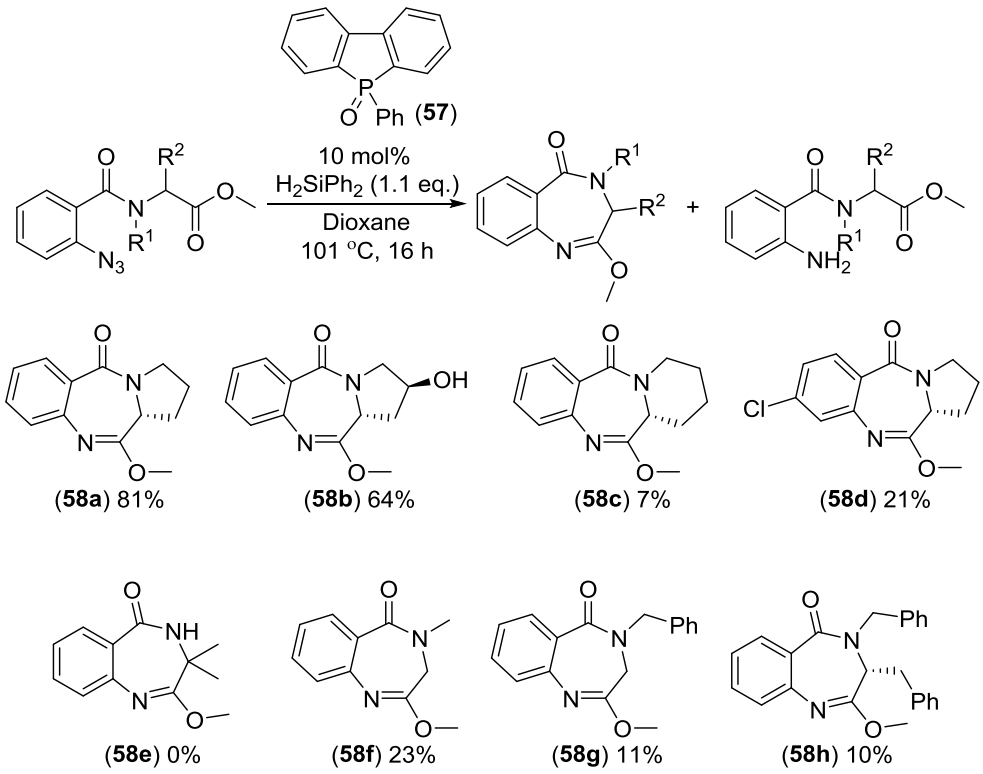


Scheme 78: Solid Supported Synthesise of Benzodiazepines.[82,83]



Scheme 79: Ugi reaction for the synthesis of starting materials for the synthesis of Benzodiazepines.[83-86]

The most recent method reported involves the catalytic Staudinger/aza-Wittig reaction mediated by *in situ* reduction detailed above (Scheme 80). van Delft *et al.* developed a protocol where the phosphine oxide (**57**) is reduced back to the phosphine using diphenylsilane.[19] While the proline derivatives (**58a**) and (**58b**) worked well, other systems suffered from low yields arising from the competing reduction of the iminophosphorane intermediate which led to recovery of the anilines. This method also required the use of hazardous azide starting materials, an issue we wished to address with the redox neutral catalytic aza-Wittig reaction.



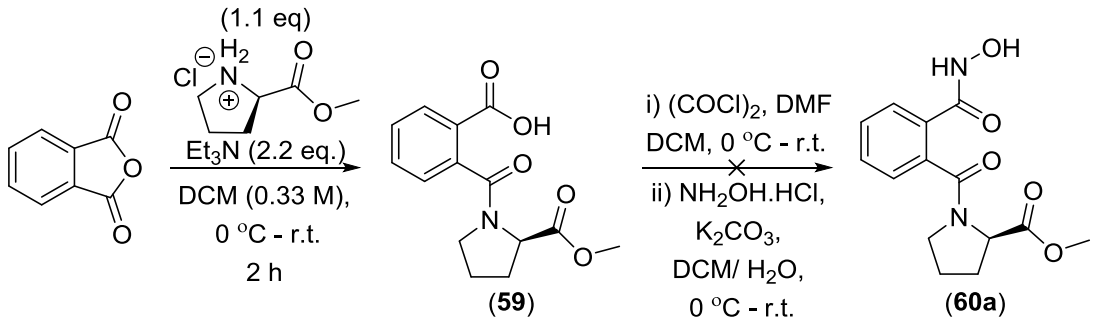
Scheme 80: Results from redox mediated catalytic aza-Wittig.[19]

It was our aim to produce a comparison between the redox neutral catalytic aza-Wittig reaction and the redox mediated catalytic aza-Wittig methodology. Due to the success of the proline derived benzodiazepines reported by van Delft it was decided to use this for preliminary investigations into the application of azide free methods for the synthesis of benzodiazepines. Initial attempts were focused on producing the hydroxamic acid starting materials.

4.2. Results and Discussion

4.2.1. Hydroxamic Acids as Potential Starting Materials for Synthesis of Benzodiazepines

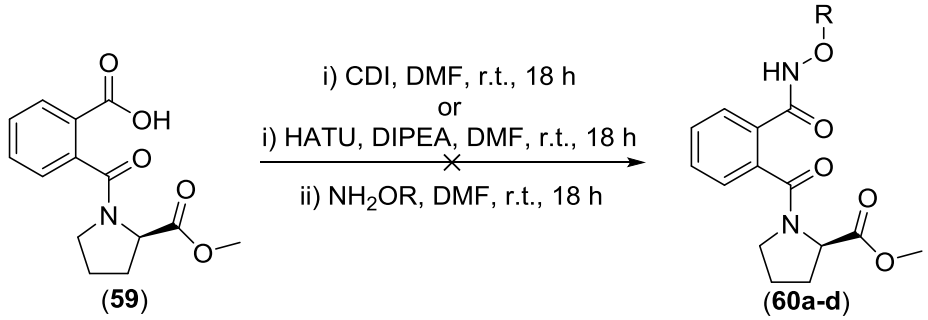
Inspired by the success of hydroxamic acids as starting materials for the synthesis of phenanthridines, the first target was to produce the corresponding hydroxamic acid for the synthesis of the benzodiazepine. To produce the required carboxylic acid (**59**) initial attempts looked to emulate previous work on the phenanthridines by opening the corresponding anhydride, in this case phthalic anhydride, with the desired nucleophile **L**-proline methyl ester. By following the literature preparation reported by Jarho *et al.*[89] multiple grams of the starting acid (**59**) were produced in good yields. Addition of phthalic anhydride to a solution of **L**-proline methyl ester hydrochloride and triethylamine in DCM at 0 °C with subsequent warming to room temperature over 2 hours furnished us with 5 grams (70% yield) of the pure starting acid (**59**). With this acid in hand the aim was to form the acid chloride and react it with the hydroxamic acid in similar conditions to those used for the synthesis of diphenyl hydroxamic acids (**39**) used previously. Unfortunately this methodology failed to produce the desired hydroxamic acid (**60a**); instead starting acid was recovered after every attempt (Scheme 81).



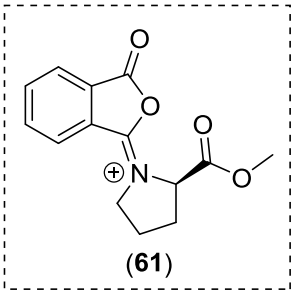
Scheme 81: Initial attempts to produce hydroxamic acid (**60a**).

Thinking this may be an issue associated with the acid chloride, other carboxylic acid activating agents were tested. Carbonyl diimidazole (CDI) and the triazole peptide coupling reagent HATU were tried and again led only to the recovery of starting acid (**59**). Next, a range of *O*-protected hydroxylamines were tested with CDI as the coupling partner. It was hoped that the mildly basic conditions expected from the liberation of imidazole would prevent deprotection of the acid labile groups. Silyl protecting groups (trimethylsilyl (TMS) and the more stable *tert*-butyldimethylsilyl (TBDMS)) were initially tried but again failed to produce the desired protected or deprotected hydroxamic acids. Next the more stable tetrahydropyryl

(THP) protecting group was used. It was hoped that because it was more acid stable than the silyl protecting groups it would survive the coupling process. Unfortunately, again none of the desired products were observed (Scheme 85). It is possible that the activated acid undergoes coupling with the adjacent carbonyl to form an anhydride like species (**61**) which is not susceptible to attack by hydroxylamine but on work up or acidification inside the LC-MS returned to the starting acid (Scheme 82).

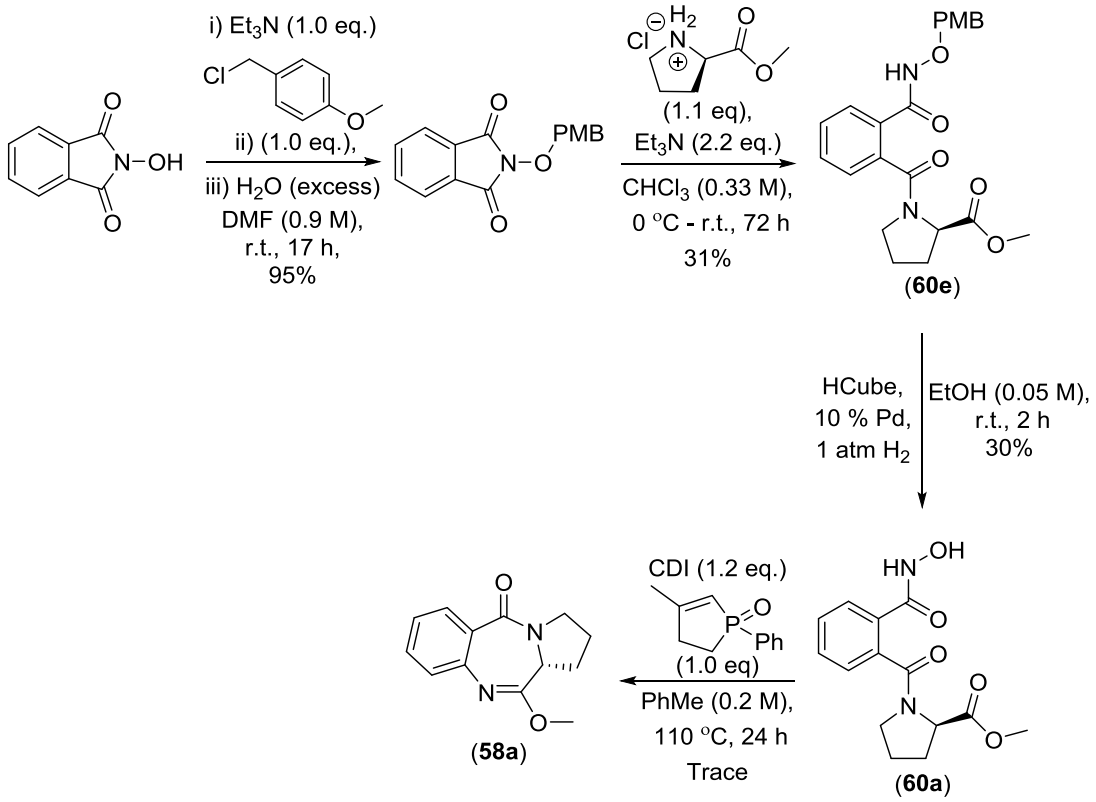


R = H (**60a**), TMS (**60b**), TBDMS (**60c**), THP (**60d**)



Scheme 82: Variations in method for hydroxamic acid (**60a-d**) synthesis.

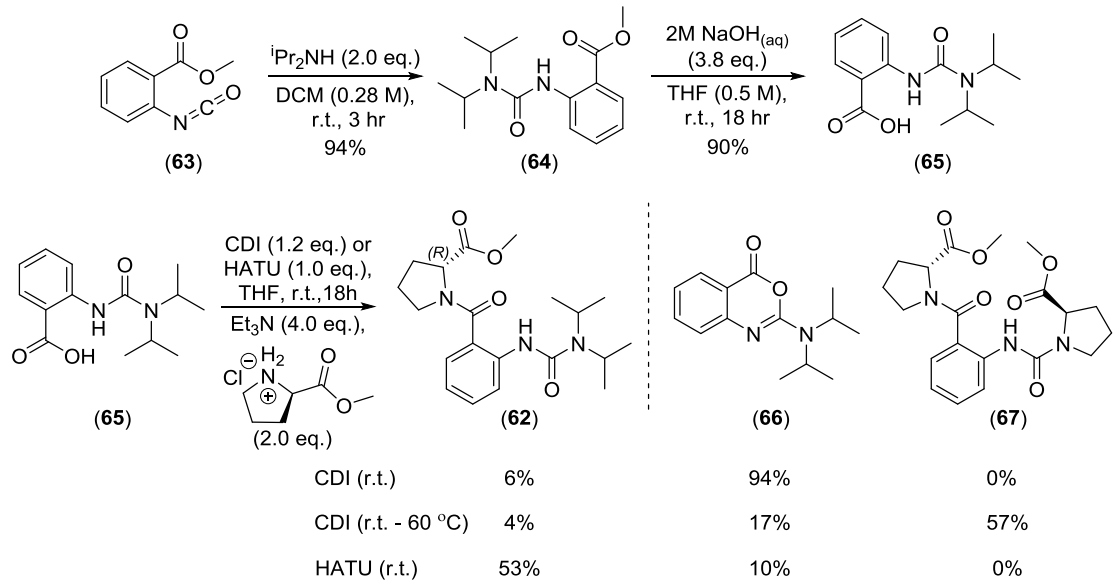
An alternative method was devised which incorporated the hydroxamic acid prior to the addition of the proline. It was hoped that by protecting *N*-hydroxyphthalamide with *para*-methoxy benzyl ether (PMB) it would behave similarly to the anhydride and allow for addition of the proline methyl ester. Gratifyingly, the desired product (**60e**) was isolated and deprotected by hydrogenolysis. This hydroxamic acid (**60a**) was then subjected to the same conditions as those used previously in the synthesis of the phenanthridines, but this time stoichiometric phospholene oxide was added to increase the likelihood of forming the desired reaction (Scheme 83). While small amounts of the desired benzodiazepine product (**58a**) were observed by LC-MS, no product could be isolated. This discouraging result directed research into alternative starting materials for the synthesis of benzodiazepine via the catalytic aza-Wittig.



Scheme 83: Initial attempts at an azide-free synthesis of benzodiazepine (**58a**).

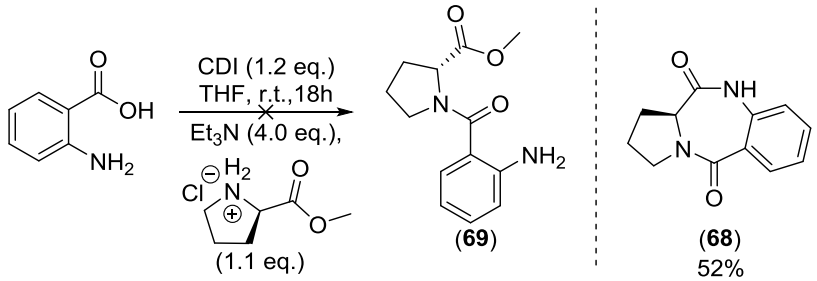
4.2.2. Hindered Ureas as Potential Starting Materials for Synthesis of Benzodiazepines

Keeping to the premise of azide-free aza-Wittig reactions, it was decided to investigate hindered urea (**62**) as the starting material. Commercially available isocyanate (**63**) provided the perfect starting point for the synthesis of the hindered urea. The first step was protection of the isocyanate as the diisopropyl urea (**64**) which was performed by the addition of diisopropylamine to a stirring solution of the isocyanate. Next was the saponification of the methyl ester to produce the carboxylic acid (**65**) using sodium hydroxide. Finally the amide bond was formed between the acid and the proline methyl ester. Initial attempts using CDI produced low quantities of the desired product (**62**) with the rest forming the benzoxazinone (**66**). There was no reaction between the benzoxazinone and proline methyl ester at room temperature. On heating the proline methyl ester reacted with (**66**) forming the amide bond but the product also underwent deprotection of the isocyanate, forming the diproline urea (**67**) (57% yield). The more active coupling reagent, HATU, successfully produced the desired urea (**62**) in good yields at room temperature (53% yield) (Scheme 84).



Scheme 84: Synthesis of hindered urea (**62**).

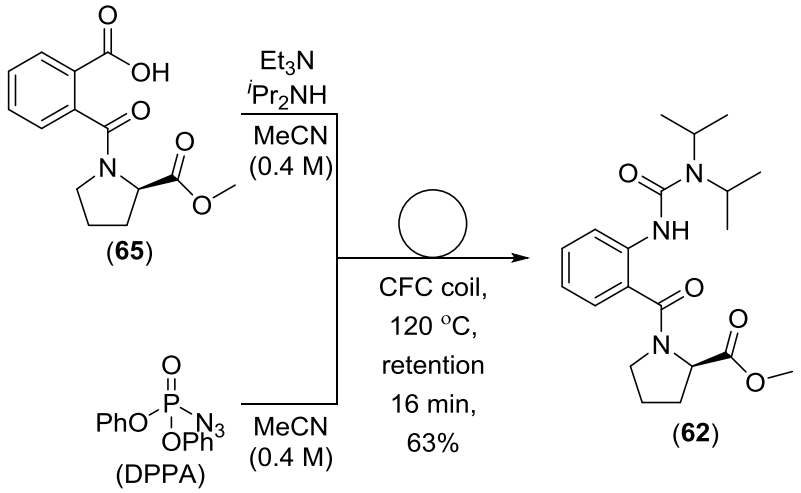
To produce the starting materials on a multigram scale the use of HATU would be costly and hazardous, so alternative methods were sought. Since installing the diisopropyl urea moiety before the proline had previously resulted in the formation of the anhydride benzoxazinone (**66**) attempts were made to change the order of addition. Starting with anthranilic acid, the aim was to form the amide bond between the acid and the proline then use diisopropylcarbamoyl chloride to install the urea. Interestingly, the activated anthranilic acid coupled with the proline, but this product then underwent a condensation reaction between the aniline nitrogen and the methyl ester to produce the benzodiazepinone (**68**) and none of the desired product (**69**) was isolated (Scheme 85). This illustrates how readily the system cyclises, boding well for the success of the aza-Wittig reaction.



Scheme 85: Failed alternative starting material synthesis method.

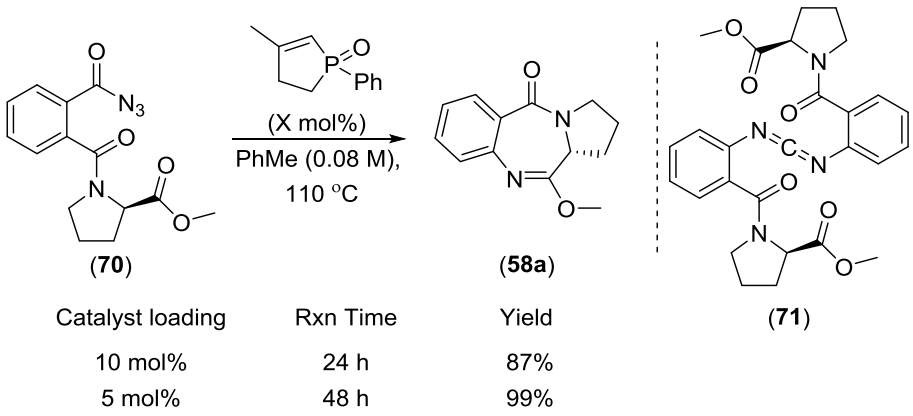
It was decided to resort to the Curtius rearrangement for the synthesis of the starting material (**62**) on scale as synthesis of grams of the acid (**65**) had already been demonstrated. To offset the hazards associated with the use of acyl azides, continuous flow protocols were

used to ensure that quantities of azide remained low. Using the method reported by Ley *et al.* for the Curtius rearrangement in flow, 10 grams of pure urea (**62**) was synthesised (Scheme 86).[90]



Scheme 86: Large scale synthesis of hindered urea (**62**) by continuous flow protocol.

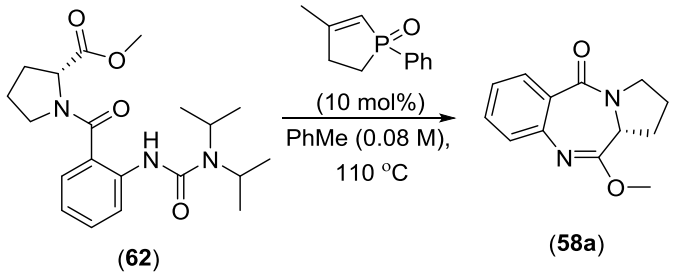
With the hindered urea in hand it was possible to investigate the application of diisopropyl ureas as masked isocyanates for the intramolecular catalytic aza-Wittig reaction. To compare the urea (**62**) with the simple isocyanate, the acyl azide (**70**) was subjected to the conditions optimised by McGonagle for the intramolecular catalytic aza-Wittig reaction. The isolated acyl azide was heated to reflux in toluene with the phospholene oxide catalyst. With catalyst loadings of 10 mol% phospholene oxide the reaction was complete within 24 hours yielding 87% of the pure desired benzodiazepine and the remainder appearing to be the dimerisation product, carbodiimide (**71**). Lowering catalyst loadings to 5 mol% led to longer reaction times, with the reaction taking 48 hour to reach completion, but a higher yield of the benzodiazepine was observed (99% yield) (Scheme 87). These yields were satisfying especially with such low catalyst loadings, and compare very favourably to the redox-mediated catalytic aza-Wittig reaction. The aim was now to replicate those impressive yields using the diisopropyl masked isocyanates.



Scheme 87: Application of the Curtius rearrangement for the synthesis of benzodiazepines via the catalytic aza-Wittig reaction.

Initial results for the reaction of hindered urea (**62**) were far less impressive, yields of the benzodiazepine between 36% and 47% were observed with the remaining mass balance (53 − 64%) being made up of recovered starting materials (Scheme 88). Results were highly variable, with a general trend that yields increased when less solvent remained, due either to increased flow of nitrogen, vented reaction vessel, increased reaction temperatures or deliberate removal of solvent on condensation. Reactions which were actively boiled dry by bubbling nitrogen throughout the reaction led to near quantitative conversions (90 – 100%). The use of solid supported reagents was also investigated as a method of increasing yields. When solid supported acids were placed in the reaction mixture the observed yield decreased and a complex mixture of by-products were observed. Solid-supported reagents were suspended such that they were held above the reaction mixture exposing the refluxing solvent and diisopropylamine to the reagents. It was hoped that the solid-supported acids would trap the diisopropylamine driving the equilibrium towards the desired isocyanate. Indeed, it was found that yields increased when reagents were held like this, with complete conversion observed by ^{1}H-NMR for a number of reagents, PS-tosyl chloride, Amberlyst, Dowex and most surprisingly 4Å MS (Scheme 88). The use of solid-supported reagents also led to reactions going to dryness, a fact which would explain the indiscriminate behaviour of the reagents, suggesting that the increased conversions might be due to the physical properties of the solid supported reagents rather than their chemistry. The observation that reactions going to dryness had increased conversion can be attributed to removal of diisopropylamine by the azeotrope effect throughout the reaction. By removing the diisopropylamine from the reaction mixture the equilibrium between the urea and the isocyanate shifts towards the isocyanate, leading to more of the aza-Wittig reaction and the formation of benzodiazepine (**58a**). Without this shift in equilibrium the amount of diisopropylamine builds up as the reaction progresses

meaning that rate of benzodiazepine (**58a**) formation drops and conversions remain low. Unfortunately, the removal of solvent during the reaction would be unfavourable on industrial application. Due to this, the reaction was not examined further as it was impractical. This was a highly disappointing outcome for a promising area of research.



Scheme 88: The use of hindered ureas as starting materials for the benzodiazepine (**58a**).

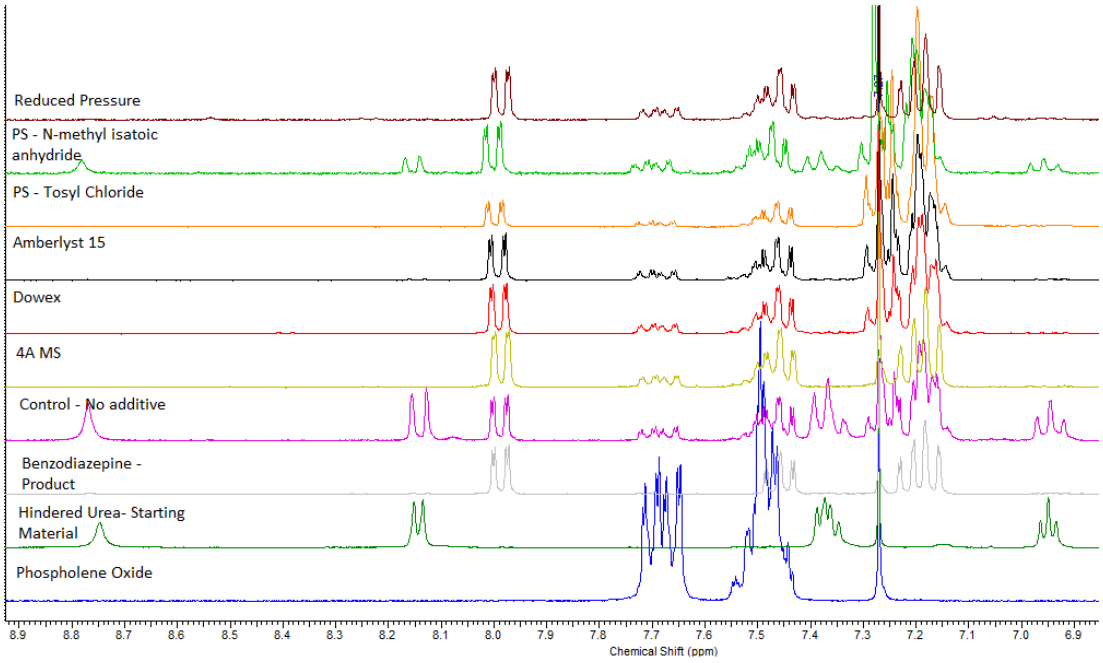


Figure 3: ^{1}H-NMR of crude reaction mixtures for the synthesis of benzodiazepine (**58a**) comparing the use of solid-supported reagents.

4.3. Conclusions

The redox neutral catalytic aza-Wittig reaction has been applied to the synthesis of a 7-membered ring system namely the benzodiazepines. While only a single example was synthesised, there is the potential to produce a wide variety of benzodiazepines using this methodology. Trace amounts of the desired product were produced from the reaction starting from hydroxamic acids, offering proof of concept. Hindered ureas behaved as masked isocyanates but yields were found to be highly variable and dependant on the removal of diisopropylamine. The Curtius rearrangement was found to be the most reliable method for the *in situ* formation of isocyanate starting materials for intramolecular catalytic aza-Wittig chemistry of seven member rings. Starting from acyl azide (**70**) the benzodiazepine (**58a**) was synthesised with 10 mol% of phospholene oxide yielding 86% of product. Catalyst loadings could be reduced to 5 mol% with an increased yield (99%) but longer reaction times. These results were an improvement on those reported by van Delft which relied on the redox mediated catalytic aza-Wittig reaction.[19]

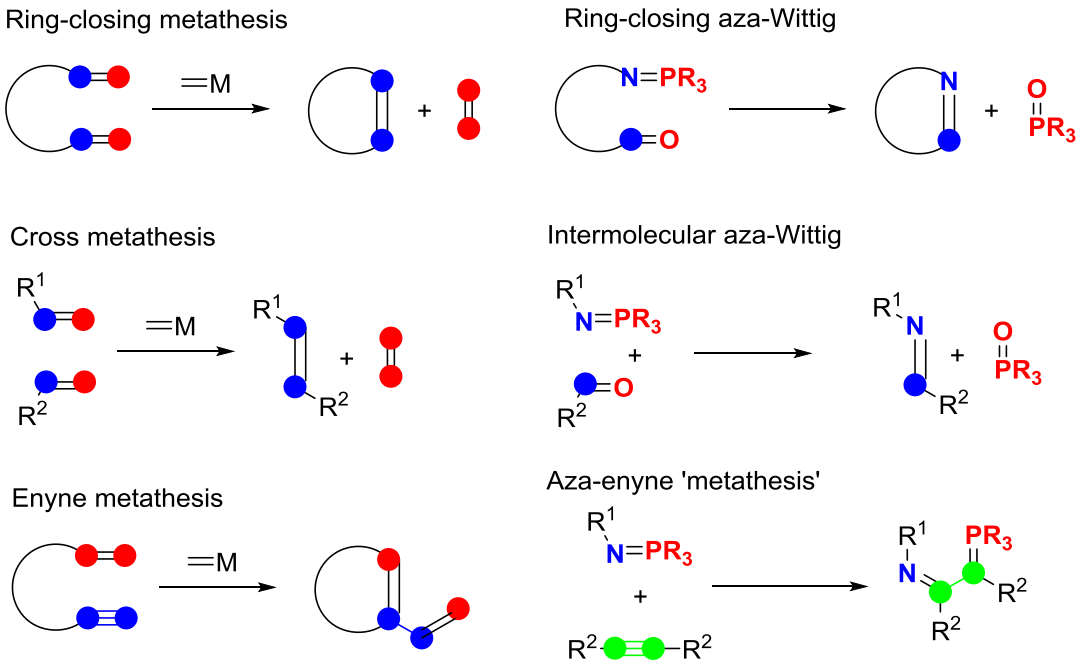
4.4. Future Work

This area of research holds a lot of potential since benzodiazepines are an important moiety in a large range of pharmaceutically active compounds. The scope of the application of catalytic aza-Wittig chemistry in this area should be expanded to incorporate more amino-acid derivatives and possibly some other seven membered ring systems. Use of hindered urea and hydroxamic acid starting materials should be optimised so the reaction is more reliable and yields higher. By focusing on this area it would be possible to become less reliant on hazardous azides.

5. Organocatalytic Aza-Enyne Metathesis Cascade Reaction

5.1. Introduction to the Aza-Enyne Metathesis Cascade Reaction

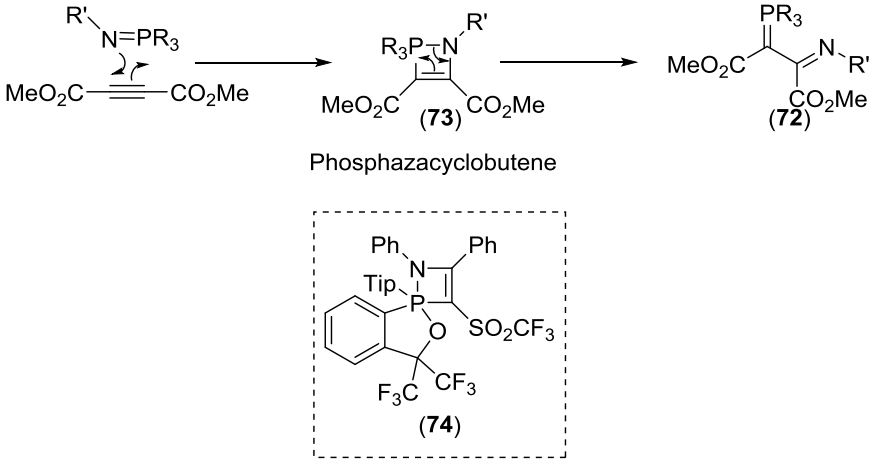
Iminophosphoranes can be viewed as analogous to metallocarbenes in metathetical reactions. The aza-Wittig reaction can be viewed as metathetical in nature as it involves a transfer of groups, in this case the transfer of the NR moiety from the iminophosphorane to the carbonyl carbon. The intermolecular aza-Wittig reaction can be viewed as being similar to cross-metathesis and the intramolecular reaction as being a ring closing metathesis. Computational studies of the aza-Wittig reaction also predict that the reaction goes via two 4-membered oxazaphosphetane cycles, similar to the metallocyclobutene intermediates observed in the metathesis reaction.[91] Another form of metathesis, enyne metathesis, also has an aza-Wittig analogue, the cyclization of iminophosphoranes with alkynes (Scheme 89).



Scheme 894: Analogies between metathesis and aza-Wittig reactions.

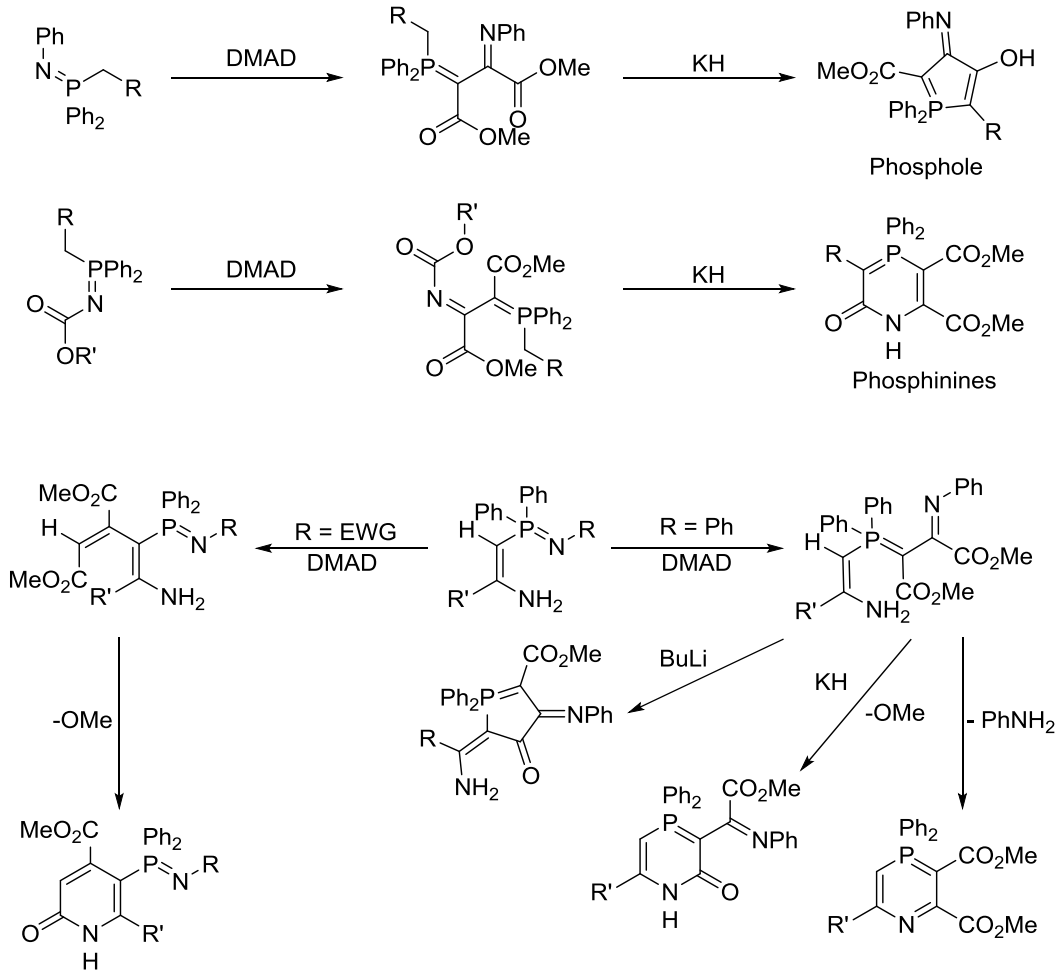
In 1964 Brown *et al.* proposed a mechanism for the reaction of iminophosphoranes with dimethyl acetylenedicarboxylate (DMAD) to give the 1 : 1 adduct (**72**) where the reaction proceeds *via* a phosphazacyclobutene intermediate (**73**) (Scheme 90).[92] In most cases intermediates like (**73**) cannot be isolated as it is highly strained and rapidly rearrange on the slightest input of energy. However, Kawashima set out to produce a thermally stable

azaphosphetine and succeeded, isolated (**74**) and analysed the structure through X-ray crystallography. It is thought that the electron-deficient nature of this azaphosphetine and the bulky 2,4,6-triisopropylphenyl (Tip) group prevent rearrangement. Surprisingly, this azaphosphetine (**74**) proved to be stable up to 180 °C and was chemically inactive towards both benzaldehyde and phenyl isocyanate.[93]



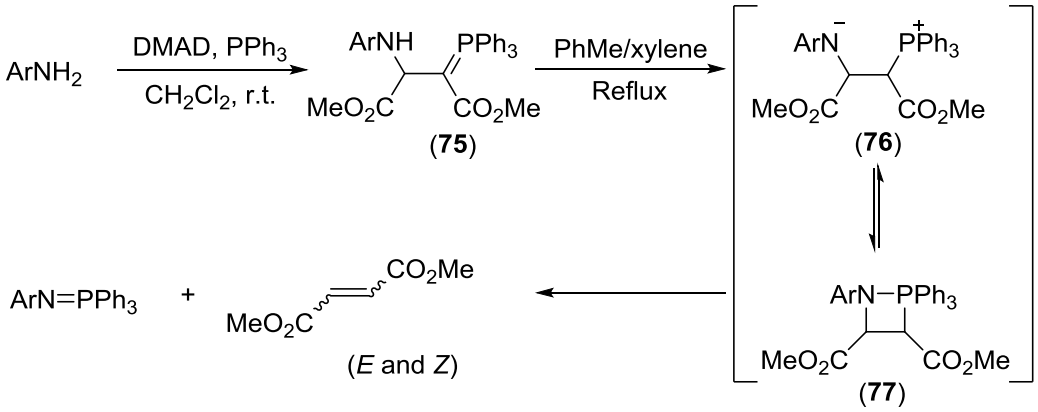
Scheme 90: Brown *et a*l. findings and Kawashima *et al.* thermally stable azaphosphetine (**74**).[92,93]

Since 1985, Barluenga *et al.* have been exploiting aza-enyne metathesis chemistry by reacting iminophosphoranes with DMAD to create substituted phospholes and aza-phosphinines (Scheme 94).[94-96] It was found that electron-deficient iminophosphoranes, such as *N*-2,4-dinitrophenyl, *N*-benzoyl, *N*-ethoxycarbonyl and *N*-tosyl-triphenylphosphimine would not undergo addition with DMAD, suggesting the nitrogen of the iminophosphorane usually acts as a nucleophile.[92] Barluenga *et al.* exploit this by cyclising an enamine attached to the phosphine end of an iminophosphorane with DMAD; in this way a range of 2-pyridones sporting a pendant iminophosphorane could be formed (Scheme 91).[95] To offset the deactivating effect of electron withdrawing groups, the *P*-phenyl groups could be substituted by an aliphatic group, increasing activity to the point that *N*-benzoyl and *N*-ethoxycarbonyl undergo addition to alkynes.[94] Palacios continued Barluenga's work, increasing the scope to include iminophosphoranes bearing *N*-phosphonate, *N*-iminophosphorane and *N*-vinyl groups.[97]



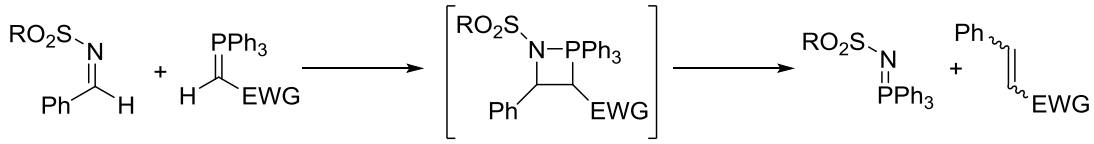
Scheme 91: Application of aza-enyne chemistry for the synthesis of *P*-heterocycles.[94-97]

Other metathesis-like phosphorus-based reactions have been reported, suggesting that this behaviour could be general to iminophosphoranes.[98] Serendipity led to the discovery that the reverse reaction could be used to synthesise aryl iminophosphoranes in a fashion reminiscent of the aza-enyne metathesis. When an aniline and triphenylphosphine were mixed with a solution of dimethyl acetylenedicarboxylate (DMAD) in dichloromethane, an ylide (**75**) formed. On heating to reflux in toluene or xylene the ylide undergoes a proton shift to form a betaine (**76**), then aza-phosphetane (**77**) which fragments to form the iminophosphorane and a mixture of dimethyl fumarate and dimethyl maleate (Scheme 92).[98] While it is assumed that the formation of the betaine is a stepwise process, the fragmentation of the azaphosphetane is likely to involve a reverse [2+2] cycloaddition similar to aza-enyne metathesis.



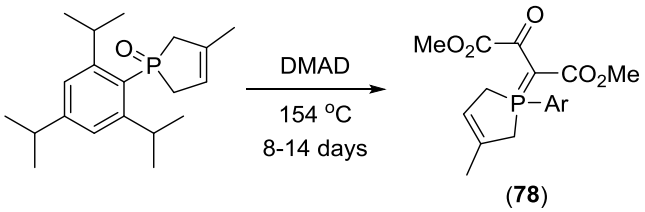
Scheme 92: Reverse aza-enyne metathesis-like synthesis of iminophosphoranes.[98]

Another example of the reverse metathesis-like nature of imines and phosphines being used to form iminophosphoranes is the Wittig reaction of electronically stabilized phosphonium ylides with *N*-sulfonyl imines. As predicted, this produces an alkene stereoselectively and an iminophosphorane, via an aza-phosphetane intermediate (Scheme 93).[99]



Scheme 93: Wittig reaction with *N*-sulfonyl imine.[99]

Analogous to the aza-enyne metathesis of iminophosphoranes, phosphine oxides can undergo a metathetical reaction with DMAD to form a stabilised phosphonium ylide (**78**). Luckily, this reaction is sluggish even in refluxing xylenes, requiring more energy input than the reaction with iminophosphoranes (154 °C for 8-14 days)[100, 101-102] (Scheme 94). This reaction may prove an issue for the development of a catalytic aza-enyne cascade reaction. If the addition of phosphine oxide (**25**) occurred under the same conditions as the desired iminophosphorane metathesis, the phospholene oxide catalyst would be consumed, shutting down the reaction.



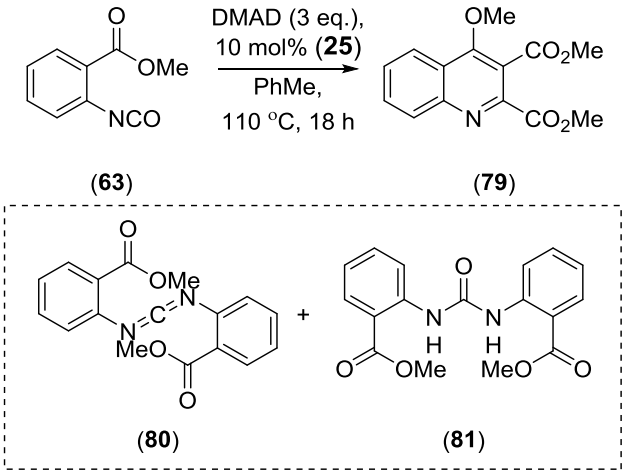
Scheme 94: Phosphine oxide analogue of aza-enyne metathesis reaction with DMAD.[100-102]

The aim of this chapter is to explore the possibility of developing a phosphorane catalysed aza-enyne metathesis cascade reaction. It is hoped that an iminophosphorane formed catalytically from a commercially available isocyanate and phospholene oxide catalyst (**25**) can react with an alkyne in a metathetical manner to produce *N*-heterocycles. The stoichiometric cascade reaction would be also be investigated with the aim of aiding mechanistic understanding.

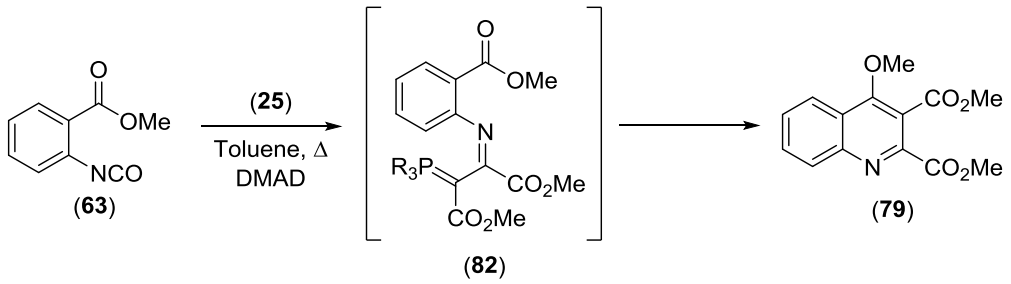
5.2. Results and Discussion

5.2.1. Developing Organocatalytic Aza-Enyne Metathesis Cascade Reaction

Previous attempts by the Marsden group indicated that aza-enyne metathesis could be successfully catalysed by phospholene oxide (**25**).[50, 103] Initial results found that quinolines could be synthesised from commercially available isocyanato ester (**63**) through a metathetical reaction with electron deficient alkyne, dimethyl acetylenedicarboxylate (DMAD). It was found that slow addition of a dilute solution of the isocyanate (**63**) into a concentrated solution of the alkyne (DMAD) and phospholene oxide catalyst (**25**) (Scheme 95) gave the highest conversions. Slow addition was used to limit the concentration of isocyanate in the reaction in an attempt to control dimerization to the carbodiimide (**80**). Using three equivalents of DMAD favoured the aza-enyne metathesis over carbodiimide formation. The previous best recorded conversion to desired product (**79**) was 60% by ^{1}H NMR.[50, 103] Removal of DMAD and related impurities from the reaction mixture proved to be problematic, preventing isolation. Application of ion exchange column SCX-2 allowed the isolation of the pure quinoline product in 25% yield.

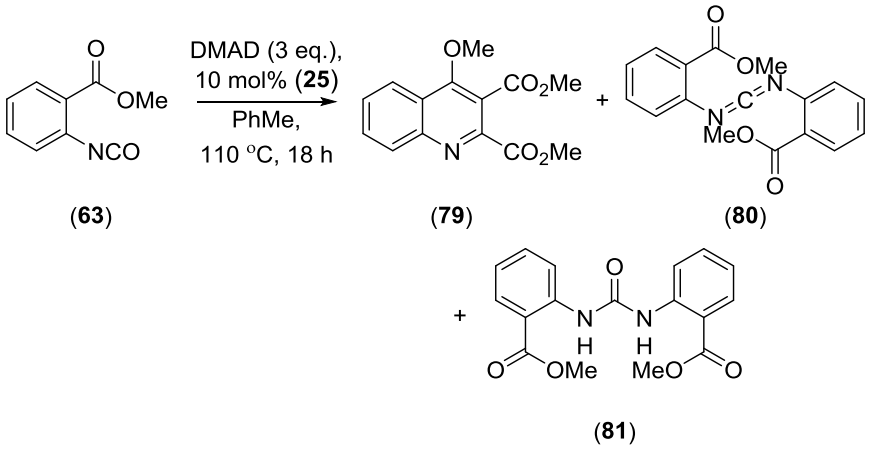


Scheme 95: Organocatalytic aza-enyne metathesis cascade reaction.



Scheme 96: Proposed ylide intermediate.

Expanding upon previous work, attempts were made to further optimise the organocatalyzed aza-enyne metathesis cascade reaction. Previous work had identified the ^{1}H-NMR signals for each of the commonly observed products. Quinoline (**79**) has a characteristic set of aromatic protons forming two doublets between 8.26 – 8.19 ppm. The methoxy signal at 4.17 ppm is also characteristic of this product. Carbodiimide (**80**) can be observed as a doublet of doublets at 7.90 ppm and urea (**81**) as a doublet at 8.55 ppm. The rate of isocyanate addition has been shown to have a substantial effect on the distribution of products, so this was the first variable investigated. Previous results found addition of a 0.5 M solution of isocyanate to a 6.0 M solution of 3 equivalents of DMAD and 10 mol% phospholene oxide gave the best ratio of products (60% quinoline : 26% carbodiimide : 14% urea) (Table 8) (Entry 2). Addition of a dilute solution of isocyanate (0.25 M) over 16 hours resulted in a 1:1 ratio of quinoline (**79**) to carbodiimide (**80**) in the crude reaction mixture; while no better than previous results, this is the best ratio of products from this set of experiments (Entry 5). Purification with SCX ion exchange column allowed the quinoline to be isolated in a 25% yield, the highest isolated yield to date for this system. According to the ratio of products in the crude reaction mixture, the self-condensation reaction would account for the consumption of 66% of the starting isocyanate, while the rest of the mass balance was found to be a complex mixture of DMAD-related by-products, the urea and methyl anthranilate. These results suggest that iminophosphorane has a substantial preference for the aza-Wittig self-condensation reaction over the desired aza-enyne metathesis which is favoured by limiting isocyanate concentration.



(**63**) (**79**) (**80**)

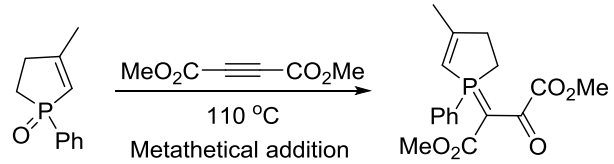
(**81**)

Entry	Conditions	^{1}H NMR ratios ((**79**) : (**80**) : (**81**))	Isolated yield (**79**)
1[a]	1.5 eq. DMAD, 10 mol% Cat., (0.3 M) PhMe	22 : 74 : 4	–
2[a]	3 eq. DMAD, 10 mol% Cat., (2 M) PhMe, 7 hr add. (0.5 M)	60 : 26 : 14	–
3	3 eq. DMAD, 5 mol% Cat., (2 M) PhMe, 6 hr add. (0.5 M)	30 : 32 : 38	-
4	3 eq. DMAD, 10 mol% Cat., (2 M) PhMe, 6 hr add. (0.5 M)	20 : 57 : 23	13%
5	3 eq. DMAD, 10% Cat., (2 M) PhMe, 16 hr add. (0.25 M)	49 : 50 : 1	25%
6	3 eq. DMAD, 100% Cat., (2 M) PhMe, 7 hr add. (0.5 M)	68 : 0 : 10 : 22[b]	-

Table 9: Results from aza-enyne metathesis cascade reaction. [a] previous unpublished work, [b] adduct (**83**)

Intriguingly, little to none of the characteristic phospholene oxide alkene doublet at 6.96 ppm was observed by ^{1}H-NMR in the crude reaction mixtures, which might justify the low yields. Consumption of phospholene oxide would explain the low yield observed. Heating a mixture of phospholene oxide (**25**) (1 eq.) and DMAD (3 eq.) in toluene at reflux for 24 hours led to an interesting observation, a small amount of phospholene oxide reacted with DMAD to form an observable amount of an adduct. Similarities between the ^{1}H-NMR and LC-MS spectra of this unknown adduct and the ylide (**78**) previously reported by Kegelvich (Scheme 94)[100] supports the theory that this is the phospholene oxide adduct (**83**) (Scheme 97).

Unfortunately (**83**) could not be isolated from the crude reaction mixture of phospholene oxide and DMAD by-products.



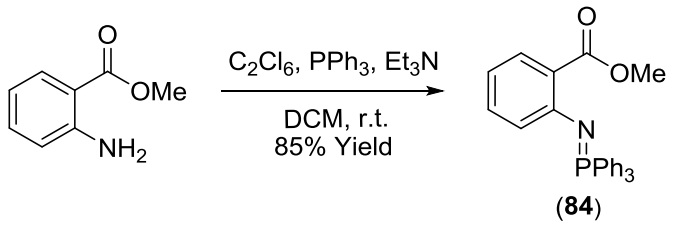
(**25**) (**83**)

Scheme 97: Addition of phospholene oxide to DMAD.

In an attempt to understand the reaction in greater detail the reaction was run with stoichiometric phospholene oxide. Using slow addition of isocyanate into a concentrated solution of stoichiometric phospholene oxide and DMAD the effective concentration of catalyst was very high, meaning that there would be many more equivalents of phospholene oxide compared with the isocyanate. The hope was that the effective concentration of phospholene oxide would remain high throughout the reaction driving the formation of the iminophosphorane which would undergo metathesis with the acetylene rather than with the relatively low concentration of isocyanate. The idea was that the isocyanate would be trapped as the iminophosphorane before the dimerization reaction could occurred. While this successfully reduced the amount of carbodiimide produced, some of the adduct (**83**) was observed by LC-MS contaminating the desired quinolone product (Table 8, entry 6).

5.2.2. Stoichiometric Aza-Enyne Metathesis Cascade Reaction

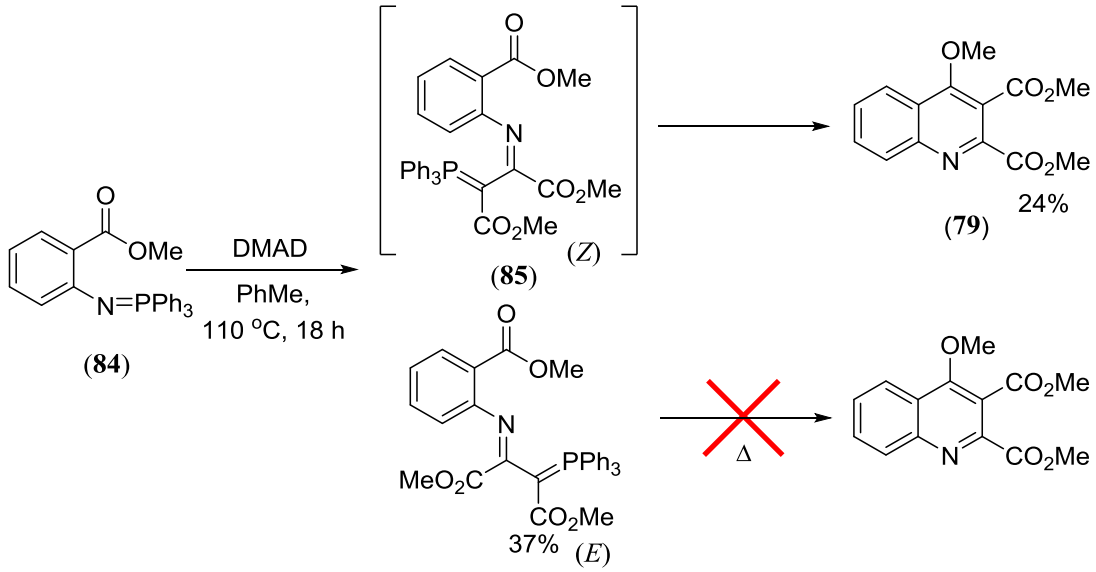
To further probe the mechanism of the reaction, the known methyl anthranilate-derived iminophosphorane (**84**)[104] was prepared following the literature procedure[105] and reacted with the alkyne DMAD. Studying the reaction of pre-formed iminophosphorane with DMAD avoided the added complication of the self-condensation reaction, potentially allowing weaknesses in the addition step to be highlighted. These weaknesses could then be addressed for application in the catalytic aza-enyne metathesis reaction. We prepared the iminophosphorane (**84**) by an Appel-modified Kirsanov reaction utilising triphenylphosphine, hexachloroethane and triethylamine to form the reactive dichlorotriphenylphosphine intermediate which reacts with a methyl anthranilate to produce the iminophosphorane (**84**) (Scheme 98).[105] Using this method the iminophosphorane (**84**) could be produced at yields of 85% from simple, inexpensive starting material in one step. The fact that there was a literature precedent for the formation of (**84**) made this a useful starting material for investigations into the stoichiometric reaction. Although it should be noted that triphenylphosphine oxide is a poor catalyst for the redox-neutral catalytic aza-Wittig reaction with isocyanates and would behave differently to the phospholene oxide in the aza-enyne metathesis reaction



Scheme 98: Appel modified Kirsanov for the synthesis of iminophosphorane (**84**).

To emulate the optimised catalytic reaction conditions used, the iminophosphorane was stirred with three equivalents of DMAD in refluxing toluene over 18 hours. The desired quinoline (**79**) product was isolated in 24% yield, which was lower than expected. Alongside this, there was 37% yield of what ^{1}H, ^{13}C, ^{31}P NMR spectroscopy and HRMS analysis suggested to be the ylid intermediate (**85**). X-ray crystallography confirmed the ylid intermediate as the (*E*) isomer of the imine (**85**) (Figure 4)**.** Surprisingly, the (*E*)-ylid (**85**) remained stable under further heating at reflux in toluene and at higher temperatures in a microwave, not forming the expected quinoline (**79**) (Scheme 99). This result suggests that the barrier of rotation for the imine is too high for this isomer to adopt the active (*Z*)-

configuration in which the phosphorus ylid could interact with the carbonyl of the ester to carry out the Wittig step.



Scheme 99: Stoichiometric aza-enyne metathesis with iminophosphorane and DMAD.

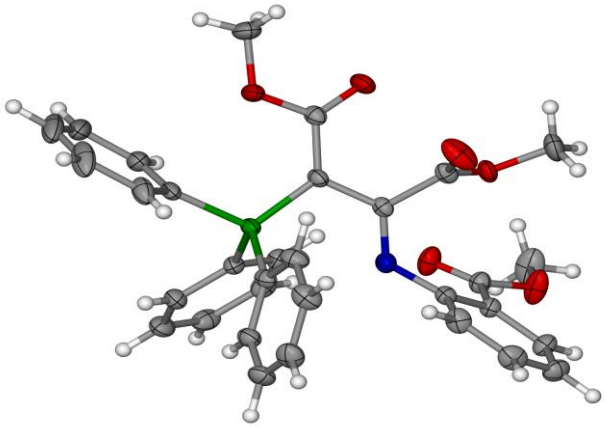
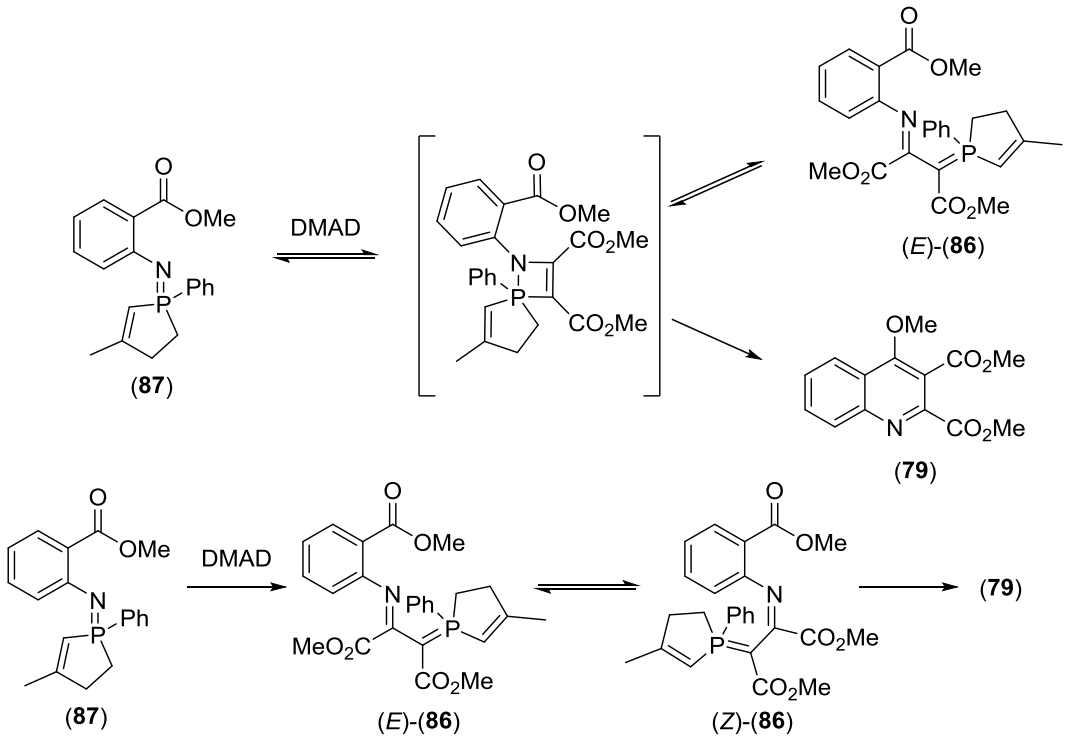


Figure 4: Molecular structure of (**85**)-(*E*). Displacement ellipisoid are at the 50% probablity level.

It was thought that an inactive species, such as ylid (**60**)-(*E*), formed in the catalytic reaction explaining the low yields experienced. Such a species would trap the catalyst, preventing the regeneration of the phospholene oxide and would prevent the turnover of the catalytic cycle. Further examination of the catalytic aza-enyne metathesis crude reaction mixture failed to find any evidence that a similar species had been formed during the catalytic aza-enyne reaction. Differences between the cyclic phospholene (**25b**) and triphenylphosphine in the isolated iminophosphorane (**85**) may explain why none of the intermediate was observed. Cyclic phosphines such as phospholene catalyst (**25**) are known to adopt four

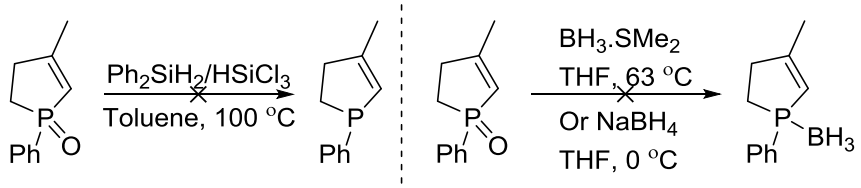
membered rings, such as oxazaphosphetane, more readily than acyclic phosphines such as triphenylphosphine due to bond angle reducing ring strain, which is used as an explanation for the enhanced reactivity of cyclic phosphines in the catalytic aza-Wittig reaction as explained by Campbell.[44, 46] Increased stability of the four membered ring intermediate potentially allows for an equilibrium between (*E*)-(**85**) and the intermediate established. Irreversible formation of the quinoline would drive the reaction towards the desired product and the consumption of the (*E*)-isomer. Alternatively, it can be envisaged that the phospholene derived adduct (**86**) may have a weaker imine bond resulting in more rotation between the configurations (Scheme 100). A third possibility is that the inactive (*E*)-adduct is formed during the reaction, but then consumed in some other unobserved pathway. The aim was to synthesise and test the iminophospholene (**87**) to provide experimental evidence to prove or disprove these hypotheses.



Scheme 100: Possible method for the conversion of (*Z*) to (*E*) ylid.

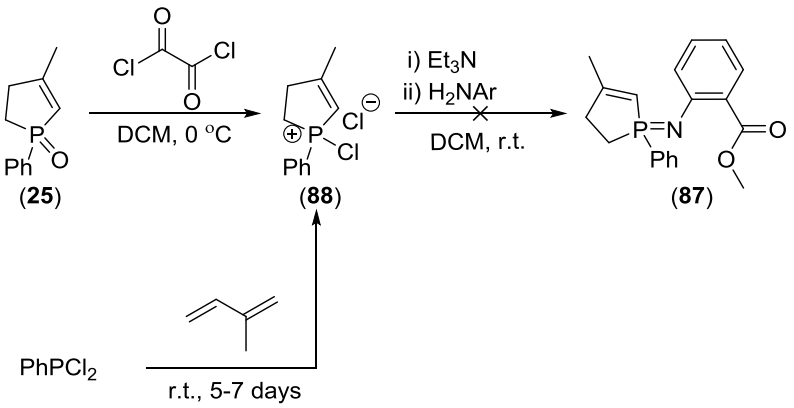
Many methods were used in an attempt to produce the iminophospholene (**87**). Initially, the Appel-modified Kirsanov reaction, which proved so successful for the triphenyl phosphine based iminophosphorane, was attempted. It was envisaged that reduction of the phospholene oxide would provide the corresponding phosphine, which would react with hexachloroethane and methyl anthranilate to give the iminophospholene. A range of reductants were explored (Scheme 101); diphenylsilane, reducing agent of choice for the reductive catalytic aza-Wittig reaction employed by van Delft *et al.*;[19] trichlorosilane, known to reduce phosphine oxides

effectively;[106] a number of borane reagents were explored as there is a literature precedent for their use in the synthesis of phosphine-borane complexes from phosphine oxides.[106] Unfortunately, none of the reduced phospholene or phosphine-borane complex could be isolated or observed by ^{31}P-NMR spectroscopy, with complete recovery of starting phospholene oxide observed.



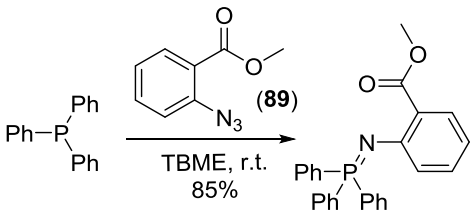
Scheme 101: Attempts to reduce phospholene oxide (**25**).

The next method attempted was a modification to Kirsanov reaction inspired by Denton *et al.* and Fukui.[35, 36] Oxalyl chloride was added to phospholene oxide to produce dichlorophosphine, which were added to methyl anthranilate in an attempt to produce the iminophosphoranes. This method was inspired by the work of Denton *et al.* who utilised oxalyl chloride to produce dichlorophosphines catalytically for use in the Appel reaction.[36-38] Similar methodology has been employed by Yano *et al.* for the one-pot reduction of phosphine oxides.[107] It was hoped that this method would allow for a range of phosphine oxides to undergo the dichlorination reaction and be trapped with methyl anthranilate. The phospholene dichloride (**88**) was observed by ^{31}P and ^{1}H NMR spectroscopy matching the literature values (^{31}P 98.8 ppm).[108] Additionally the dichloride was produced by the addition of dichlorophenyl phosphine to isoprene, a method commonly used for the synthesis of the phospholene oxide catalyst (**25**) (Scheme 102). While these methods did provide a successful route to the phospholene dichloride, they failed to produce the desired iminophosphorane, instead leading to the recovery of the phospholene oxide and methyl anthranilate.

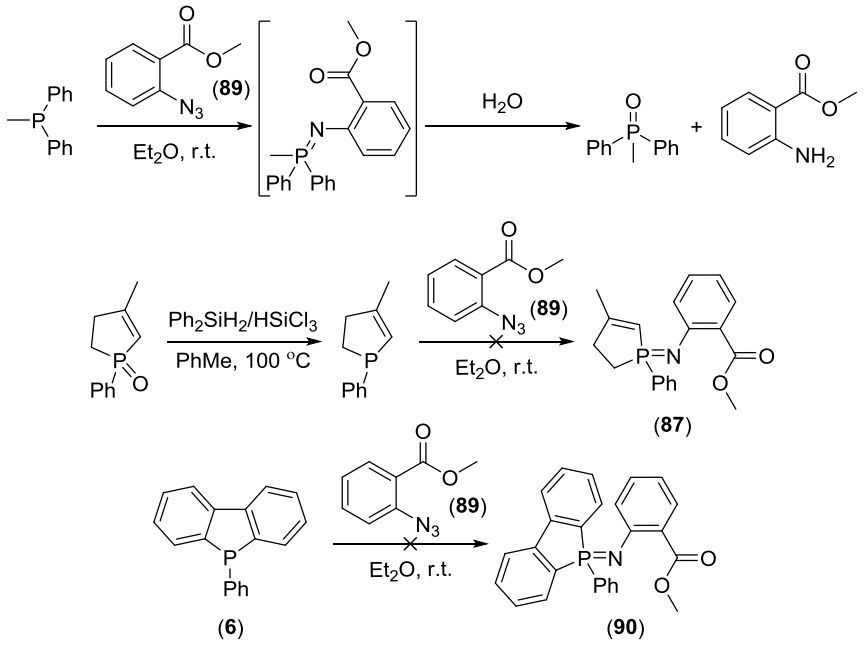


Scheme 102: Attempt to form iminophosphorane (**87**) using modified Kirsanov reaction.

The final method attempted involved the commercially available azide (**89**). The Staudinger reaction between azides and phosphines are well studied[2, 3] and though no examples have utilised this particular phospholene, reactions with the azido methyl benzoate (**89**) are known.[109] Stirring the azide with triphenylphosphine in methyl *tert*-butyl ether (TBME) provided the iminophosphorane (**84**) in excellent yield (85%) (Scheme 103). In order to investigate the effect of phosphine on the chemistry of the iminophosphorane the Staudinger reaction was attempted with a range of phosphines. Replacing a phenyl group with a methyl group was expected to increase reactivity. Disappointingly, the corresponding reaction with diphenylmethylphosphine failed to produce the iminophosphorane, instead yielding the phosphine oxide and methyl anthranilate, as expected of the reduction in the presence of water. Following the method employed by Barluenga *et al.* using more stringent anhydrous procedures also failed to result in the isolation of desired iminophosphorane.[109] The same was true for attempts to trap the azide with the dibenzophosphole (**6**) favoured by van Delft (Scheme 104). No attempts were made to produce the azide or to investigate other azides as (**89**) was commercially available and matched the desired product.[18]



Scheme 103: Staudinger reactions with triphenylphosphine.



Scheme 104: Staudinger reaction for the synthesis of iminophosphoranes.

It is possible that the desired iminophosphorane is too hydrolytically unstable to be isolated when incorporating more active phosphines such as diphenylmethylphosphine and the phospholene. With this in mind attempts were made to avoid the isolation of the iminophosphorane and to form it (**87**) in the presence of DMAD so that the iminophosphorane would be trapped rapidly by DMAD forming the corresponding ylid. Disappointingly, this also failed to provide the desired product, leading to the isolation of methyl anthranilate, phospholene oxide and polymerised DMAD.

While the results for the stoichiometric aza-enyne reaction of iminophosphorane with DMAD were disappointing, initial results gave important mechanistic insight into the catalytic reaction. It also suggests that the nature of the phosphine plays an important role in the stability of iminophosphoranes, especially with an electron-deficient *N*-aryl group which would enhance the rate of hydrolysis of the iminophosphorane as expected of the Staudinger reduction.

5.3. Aza-enyne Metathesis Conclusions

Conditions for the first phosphine oxide catalysed aza-enyne metathesis were optimised and the mechanism involved probed. It was shown that phospholene oxide can be utilised in a cascade reaction involving the addition of catalytically produced iminophosphine across an alkyne for the synthesis of tri-substituted quinoline (**79**). Unfortunately isolated yields were low (25%) and the majority of starting material was consumed by the self-condensation reaction to give the carbodiimide.

The stoichiometric reaction offered some mechanistic insight and offered a potential explanation for the low yields experienced. It was found that the stoichiometric reaction with an iminophosphorane derived from triphenylphosphine led to 60% isolated yield of addition products with 24% yield of the desired quinoline (**79**) and 37% yield of the novel (*E*)-ylid (**85**). This inactive ylid species (**85**) did not undergo the expected Wittig reaction even under forceful heating, which suggests it could possibly be a unobserved pathway producing by-product in the catalytic aza-enyne metathesis cascade reaction. Attempts to vary the phosphine moiety failed to provide the desired iminophosphorane starting materials.

5.4. Future Work

Given more time it may have been possible to screen a range of phosphine oxides and find alternative which would favour the aza-enyne cascade reaction over the self-condensation reaction. Alternatively, an iminophosphorane could have been found to limit the formation of the undesired stable (*E*)-isomer which was observed in the stoichiometric reaction. Another area of modification is the *N*-aryl portion of the iminophosphorane substituents on the ring may have affected reactivity and the use of amides could have been investigated, possibly producing a range of quinolines bearing the amine moiety. Corresponding *ortho*-isocyanatobenzamides might also undergo the catalytic aza-enyne metathesis cascade reaction infavor of the self-condensation reaction.

Another area of interest is the possibility of an intramolecular cascade reaction whereby a pendant alkyne group undergoes intramolecular addition of an iminophosphorane to form a heterocycle. The advantage of this method is that the undesired dimerisation reaction could be controlled using high dilution conditions.

Experimental

Novel Applications of Organocatalytic Aza-Wittig Chemistry

6. Experimental

6.1. General Experimental Techniques

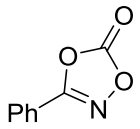
All reactions were carried out under an atmosphere of dry nitrogen using oven-dried glassware and dried solvent unless stated. Dried solvents dispensed from Innovate Technology Pure Solv MD solvent purification system. Triethylamine, pyridine and morpholine were distilled from KOH onto 4Å molecular sieves before use. Isopropanol was distilled from 3Å molecular sieves onto 4Å molecular sieves before use. The phospholene oxide catalyst was distilled by Kugelrohr before use to remove trace water, DCM and other impurities. All solvents used for analysis were analytical grade solvents. All other solvents and reagents were purchased from commercial sources and were used without purification. Petrol refers to light petroleum (b.p. 40-60 ºC).

Flash column chromatography was performed using Fischer Matrix silica gel (35-70 μm) or pre-packed Biotage or Redisep silica cartridges running on Biotage Isolera machine. Thin layer chromatography was conducted using pre-coated silica plates (Merck silica Kieselgel $60F_{254}$). Spots were visualized using UV fluorescence (λ_{max} = 254 nm), then stained and heated with potassium permanganate and in the case of hydroxamic acids $FeCl_3$ in methanol. All chromatography eluents were BDH GPR grade and used without purification.

^{1}H NMR spectra were recorded at 300 MHz on a Bruker DPX 300 or 500 MHz on a Bruker Avance 500 spectrometer, using an internal deuterium lock. ^{1}H NMR chemical shifts (δ) are quoted in parts per million with respect to the standard tetramethylsilane at 0 ppm and coupling constant (*J*) values are quoted in Hz. Estimated purity calculated using integration of ^{1}H NMR taking difference between total spectra and accounted signals, assume >95% unless otherwise stated. ^{13}C NMR spectra were recorded with broadband proton decoupling at 75 or 125 MHz. Assignments were made on the basis of chemical shift and coupling data, using ^{1}H-^{13}C HMQC, DEPT, HMBC and nOe experiments where necessary. ^{31}P NMR spectra were recorded with broadband proton decoupling at 121 MHz. Infra-red spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer, with absorption reported in wavenumbers (cm^{-1}) Mass Spectra were recorded on a Bruker HCT Ultra LC-MS instrument or a Bruker MicroTOF spectrometer (using electrospray techniques). Accurate molecular weights were obtained by peak matching using perfluorokerosene as a standard. Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Specific rotation was determined using Optical Activity AA-10 polarimeter on sodium D line (589 nm), with concentrations giving in g/100ml.

6.2. Experimental Procedures from Chapter 2

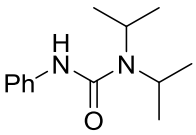
3-Phenyl-1,4,2-dioxazol-5-one (28)[64]



To a stirred suspension of *N*-hydroxybenzamide (**26**) (137 mg, 1.00 mmol, 1.00 eq.) in CH_2Cl_2 (10 mL, 0.10 M) at 0 °C was added CDI (162 mg, 1.00 mmol, 1.00 eq.). The reaction mixture was allowed to warm to room temperature over an hour, after which time the mixture was treated with 0.5 M HCl (10 mL). Aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were then dried ($MgSO_4$) and concentrated under reduced pressure. Crystallisation from CH_2Cl_2 and petroleum ether provided 3-phenyl-1,4,2-dioxazol-5-one (**28**) (110 mg, 0.68 mmol, 68% yield) as a colourless amorphous solid. Data agrees with literature values.[64]

M.p. (Petrol/CH_2Cl_2; colourless amorphous solid): 63 – 64 °C (lit.[64] 63 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87 (2H, dd, *J* = 7.2, 1.2 Hz, Ar**H**), 7.66 (1H, td, *J* = 7.2, 1.2 Hz, Ar**H**), 7.56 (2H, td, *J* = 7.2, 1.2 Hz, Ar**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.0 (C), 154.3 (C), 134.6 (2 × CH), 130.1 (CH), 127.0 (2 × CH), 120.5 (C); IR (ν_{max}, solid, cm^{-1}) 3074, 2922, 2245, 2101, 2058, 1955, 1941, 1900, 1858, 1817, 1613, 1753, 1498, 1448, 1396, 1367, 1177, 1072, 973, 752; Data in accordance with literature values.[64]

1,1-Diisopropyl-3-phenyl urea (27)[62]



Method A) To a stirred solution of *N*-hydroxybenzamide (**26**) (41 mg, 0.30 mmol, 1.00 eq.) in acetonitrile (0.50 mL, 0.60 M) was added CDI (65 mg, 0.40 mmol, 1.20 eq.). After stirring for 30 minutes the reaction mixture was heated to 60 °C then diisopropylamine (0.13 mL, 0.92 mmol, 3.00 eq.) was added. After 90 minutes of stirring the reaction was cooled to room temperature. The reaction mixture was diluted with ethyl acetate and the reaction was quenched with saturated ammonium chloride solution (2 × 10 mL), water (10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure.

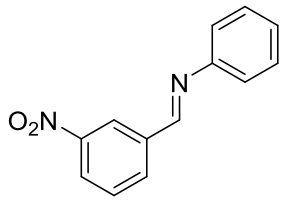
Crystallisation from boiling toluene provided 1,1-diisopropyl-3-phenyl urea (**27**) (56 mg, 0.26 mmol, 85% yield) as a colourless solid.

Method B) To a stirred solution of 3-phenyl-1,4,2-dioxazol-5-one (**28**) (49 mg, 0.30 mmol, 1.00 eq.) in acetonitrile (0.50 mL, 0.60 M) was added diisopropylamine (0.13 mL, 0.92 mmol, 3.00 eq.), then heated to 60 °C. After 90 minutes of stirring the reaction was cooled to room temperature. The reaction mixture was diluted with ethyl acetate and the reaction was quenched with saturated ammonium chloride solution (2 × 10 mL), water (10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Crystallisation from boiling toluene provided 1,1-diisopropyl-3-phenyl urea (**27**) (56 mg, 0.26 mmol, 85% yield) as colourless needles.

Method C) To a stirred solution of diisopropylamine (5.80 mL, 41.0 mmol, 1.20 eq.) in CH_2Cl_2 (150 mL, 0.27 M) at 0 °C was added phenyl isocyanate (**30**) (6.50 mL, 34.0 mmol, 1.00 eq.). The reaction mixture was allowed to warm up to room temperature before the reaction was quenched with 2 M aqueous HCl (2 × 100 mL). The organic mixture was dried (Na_2SO_4), concentrated under reduced pressure and crystallised from toluene to provide 1,1-diisopropyl-3-phenyl urea (**27**) (7.50 g, 34.0 mmol, 99% yield) as colourless needles.

M.p. (PhMe; colourless needles): 123 °C (lit.[110]: 123 – 124 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.22 (4H, m, Ar**H**), 7.03 – 6.95 (1H, m, Ar**H**), 6.17 (1H, br. s, N**H**), 4.00 (2H, septet, J = 7.0 Hz, N(C**H**)$_2$), 1.32 – 1.34 (12H, d, J = 7.0 Hz, 4 × C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.5 (C), 139.3 (C), 128.6 (CH), 122.4 (CH), 119.6 (2 × CH), 45.4 (2 × CH), 21.3 (4 × CH_3); IR (ν_{max}, solid, cm^{-1}) 3271, 2970, 1631, 1594, 1526, 1447, 1333. Data agrees with literature values.[110]

N-[(3-Nitrophenyl)methylene]benzenamine (35b) [111]



Method A) To a stirred mixture of 1,1-diisopropyl-3-phenyl urea (**27**) (132 mg, 0.600 mmol, 1.00 eq.) and 3-methyl-1-phenyl-2-phospholene oxide (**25**) (12 mg, 0.060 mmol, 1.00 eq.) in toluene (0.6 mL, 0.10 M) was added 3-nitrobenzaldehyde (**36**) (91 mg, 0.60 mmol, 1.00 eq.). After refluxing at 110 °C for 18 hours the mixture was concentrated under reduced pressure and a ^{1}H-NMR spectrum of a sample taken from the crude reaction mixture. The product, *N*-[(3-nitrophenyl)methylene]benzenamine (**35b**) was crystallised from dry diethyl ether and hexanes for spectroscopic analysis. Conversions were calculated using ^{1}H-NMR of the crude reaction mixture looking at the ratio between the CHO signal (10.00 ppm) of the aldehyde and CHNPh signal of the imine (8.55 ppm).

Method B) To a stirred mixture of 3-phenyl-1,4,2-dioxazol-5-one (**28**) (0.15 mmol, 1.00 eq.), imidazole or diisopropylamine (0.15 mmol, 1.00 eq.) and 3-methyl-1-phenyl-2-phospholene oxide (**25**) (3.0 mg, 0.02 mmol, 10 mol%) in toluene (0.25 mL, 0.60 M) was added 3-nitrobenzaldehyde (**36** (45 mg, 0.30 mmol, 2.00 eq.). After refluxing at 110 °C for 18 hours the mixture was concentrated under reduced pressure and a ^{1}H-NMR spectrum of a sample taken from the crude. The product, *N*-[(3-nitrophenyl)methylene]benzenamine (**35b**) was crystallised from dry diethyl ether and hexanes for spectroscopic analysis. Conversions were calculated using ^{1}H-NMR of the crude reaction mixture looking at the ratio between the CHO signal (10.00 ppm) of the aldehyde and CHNPh signal of the imine (8.55 ppm).

Method C) To a stirred mixture of *N*-hydroxybenzamide (**26**) (0.60 mmol, 1.00 eq.) in toluene (1.00 mL, 0.60 M) was added CDI (117 mg, 0.720 mmol, 1.20 eq.). After an hour at room temperature 3-methyl-1-phenyl-2-phospholene oxide (**25**) (3.0 mg, 0.02 mmol, 10 mol%) and 3-nitrobenzaldehyde (**36**) (45 mg, 0.30 mmol, 2.00 eq.) were added and the reaction mixture heated to reflux for 18 hours. The mixture was concentrated under reduced pressure and a ^{1}H-NMR spectrum of a sample taken from the crude. The product, *N*-[(3-nitrophenyl)methylene]benzenamine (**35b**) was crystallised from dry diethyl ether and hexanes for spectroscopic analysis. Conversions were calculated using ^{1}H-NMR of the crude reaction mixture looking at the ratio between the CHO signal (10.00 ppm) of the aldehyde and CHNPh signal of the imine (8.55 ppm).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (1H, t, *J* = 2.0 Hz, Ar**H**), 8.55 (1H, s, N=C**H**), 8.33 (1H, ddd, *J* = 8.0, 2.5, 1.0 Hz, Ar**H**), 8.25 (1H, dt, *J* = 7.5, 1.0 Hz, Ar**H**), 7.67 (1H, t, *J* = 8.0 Hz, Ar**H**), 7.46 (2H, t, *J* = 7.5 Hz, Ar**H**), 7.32 – 7.24 (3H, m, Ar**H)**; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.2 (CH), 150.9 (C), 148.7 (C), 137.9 (C), 134.1 (CH), 129.8 (CH), 129.3 (CH), 126.9 (CH), 125.6 (CH), 123.5 (CH), 120.9 (CH); IR (ν_{max}, solid, cm^{-1}) 3084, 3058, 2885, 1614, 1532, 1353, 1321, 1192, 1092, 1077, 811. Data agrees with literature.[111]

6.3. Experimental Procedures from Chapter 3

6.3.1. General procedure A

A microwave vial was charged with $Pd(PPh_3)_4$ (120 mg, 0.10 mmol, 0.02 eq.), the boronic acid (10.00 mmol, 2.00 eq.), sodium carbonate (1.06 g, 10.0 mmol, 2.0 eq.) and, if solid, the bromide (5.00 mmol, 1.00 eq.) before being sealed and flushed with nitrogen. The solids were then dissolved in a mixture of dioxane (3.0 mL, 3.3 M) and water (2.0 mL, 5.0 M) with stirring; if liquid, the bromide was added after addition of solvent. The reaction mixture was then degassed by bubbling dry nitrogen for 20 minutes before being placed in the microwave. The reaction mixture was stirred and heated to 120 °C at 100 W for 25 minutes, after which time the reaction mixture was allowed to cool to room temperature and was extracted from brine (10 mL) with ethyl acetate (2 × 10 mL). The combined organics were washed with brine (20 mL) and dried over Na_2SO_4 before being concentrated under reduced pressure. The crude was purified by silica column chromatography (20% ethyl acetate in hexane).

Alternatively, the $Pd(PPh_3)_4$ could be replaced with 1,10-bis(di-*tert*-butylphosphino) ferrocene palladium dichloride ($Pd(dbpf)Cl_2$, "Pd-118") employing the conditions optimised by Moseley *et al.* requiring fewer equivalents of boronic acid.[78] A microwave vial was charged with Pd-118 (22 mg, 0.04 mmol, 0.01 eq.), the boronic acid (4.20 mmol, 1.20 eq.), potassium carbonate (724 mg, 5.25 mmol, 1.50 eq.) and the bromide (3.50 mmol, 1.00 eq.). The solids were then dissolved in dioxane (7 mL, 0.5 M) and water (7 mL. 0.5 M). The reaction mixture was then degassed by bubbling dry nitrogen through the mixture for 20 minutes before being placed in the microwave. The mixture was stirred and heated to 120 °C at 100 W for 25 minutes, after which time the reaction mixture was allowed to cool to room temperature and was extracted from water (15 mL) with ethyl acetate (2 × 15 mL). The combined organics were washed with brine (20 mL) and dried over Na_2SO_4 before being concentrated under reduced pressure. The crude was purified by silica column chromatography (20% ethyl acetate in hexane).

6.3.2. General procedure B

A mixture of 4-dimethylaminopyridine (2.69 g, 12.0 mmol, 1.00 eq.), diphenic anhydride (2.69 g, 12.0 mmol, 1.00 eq.), nucleophile (12.0 mmol, 1.00 eq.) and pyridine (0.96 mL, 12 mmol, 1.0 eq.) in THF (30 mL, 0.40 M) was heated to reflux with stirring for 2 hours. After this time the reaction mixture was cooled to room temperature before being quenched

with 2M HCl (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organics were washed with brine (20 mL) and dried over Na_2SO_4 before being concentrated under reduced pressure. If required, the crude was purified by flash column chromatography (silica, 30% ethyl acetate in hexane).

6.3.3. General procedure C

To a stirred solution of aldehyde (**48a-h**) (1.00 mmol, 1.00 eq.) in a mixture of *tert*-butyl alcohol (3 mL), water (1 mL) and acetonitrile (0.5 mL), (6 : 2 : 1 ratio, 0.28 M) was added monosodium phosphate (156 mg, 1.00 mmol, 1.00 eq.) and 1-methyl-cyclohexene (590 μL, 5.00 mmol, 5.00 eq.). Sodium chlorite (360 mg, 4.00 mmol, 4.00 eq.) was added portionwise to the reaction mixture. After 16 hours stirring at room temperature the reaction mixture was partitioned between ethyl acetate (10 mL) and water (10 mL). The organics were washed with brine and dried (Mg_2SO_4) before being concentrated under reduced pressure. The desired products were purified by flash column chromatography (0 − 100% gradient of ethyl acetate in hexane) and crystallised if required.

Alternatively, hydrogen peroxide could be used instead of 1-methylcyclohexene for a reaction with fewer by-products. To a stirred solution of aldehyde (**48a-h**) (0.85 mmol, 1.0 eq.) in a mixture of acetonitrile (8.5 mL) and water (3.5 mL) (2.4 : 1, 0.07 M) was added monosodium phosphate (265 mg, 1.70 mmol, 2.00 eq.) and aqueous hydrogen peroxide (35% wt., 0.70 mL, 1.0 mmol, 1.2 eq.). A solution of sodium chlorite (90 mg, 1.0 mmol, 1.2 eq.) in water (10 mL, 0.10 M) was added dropwise to the reaction mixture over an hour resulting in the evolution of gas. After an additional 3 hours stirring at room temperature the reaction mixture was quenched with 4M HCl (aq) (10 mL) and extracted with ethyl acetate (10 mL). The combined organics were washed with brine and dried (Mg_2SO_4) before being concentrated under reduced pressure. The crude reaction mixture was pure enough after extraction to take through to the next step without further purification.

6.3.4. General procedure D

To a stirred solution of biphenyl-2,2'-dicarboxylic acid 2-ester (**40a-t**) (8.00 mmol, 1.00 eq.) in CH_2Cl_2 (60 mL, 0.13 M) was added DMF (10 mol%) then oxalyl chloride (850 μL, 10.0 mmol, 1.20 eq.). The reaction mixture was stirred for an hour before the volatiles

were removed under reduced pressure before being re-dissolved in ethyl acetate (120 mL, 0.06 M) and cooled to 0 °C. To this solution hydroxylamine hydrochloride (1.11 g, 16.0 mmol, 2.00 eq.) and potassium carbonate (4.42 g, 32.0 mmol, 4.00 eq.) were added portionwise over 5 minutes to the reaction mixture followed by the addition of water (24 mL). Once the addition was complete the reaction was allowed to warm up to room temperature. After 2 h of stirring, 2M HCl (20 mL) was added and extracted with ethyl acetate (2 × 30 mL). The organic phase was washed with brine (60 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica, CH_2Cl_2 : EtOH : $NH_4.OH_{(aq)}$ (50 : 8 : 1)). The product was crystallised with either ethyl acetate and hexane or toluene.

6.3.5. General procedure E

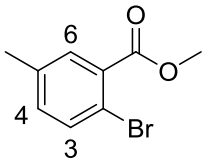
To a stirred solution of biphenyl-2,2'-dicarboxylic acid 2-amide (**40a-t**) (8.00 mmol, 1.00 eq.) and oxalyl chloride (850 µL, 10.0 mmol, 1.20 eq.) in CH_2Cl_2 (60 mL, 0.13 M) was added DMF (10 mol%). The reaction mixture was stirred for an hour before being added to a solution of hydroxylamine hydrochloride (1.11 g, 16.0 mmol, 2.00 eq.) and triethylamine (4.50 mL, 32.0 mmol, 4.00 eq.) in acetonitrile (30 mL, 0.26 M) at 0 °C. Once the addition was complete the reaction was allowed to warm up to room temperature. After 16 hours of stirring, the mixture was quenched with 1M NaOH (30 mL) and washed with ethyl acetate (2 × 30 mL), neutralised with 2M HCl (15 mL) to pH 7 and extracted with ethyl acetate (2 × 30 mL). The organic phase was washed with brine (60 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica, CH_2Cl_2 : EtOH : $NH_4.OH_{(aq)}$ (50 : 8 : 1)). The product could be crystallised from either ethyl acetate and hexane or toluene.

6.3.6. General procedure F

To a stirred mixture of 2'-hydroxycarbamoyl-biphenyl-2-carboxylic acid ester (**39a-t**) (1.00 mmol, 1.00 eq.) and 3-methyl-1-phenyl-2-phospholene oxide (41 mg, 0.20 mmol, 20 mol %) in toluene (2 mL, 0.5 M) was added CDI (196 mg, 1.20 mmol, 1.20 eq.) reaction was heated from room temperature to reflux over 20 minutes and maintained at reflux for a further 24 hours, after which time the reaction was cooled to room temperature and the crude reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (silica, 20% ethyl acetate in petrol).

6.4. Experimental Results from Chapter 3

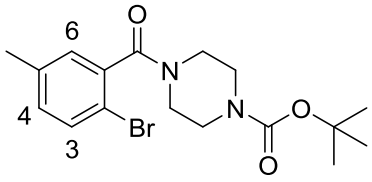
Methyl 2-bromo-5-methylbenzoate (49a) [112]



To a stirred solution of 2-bromo-5-methyl benzoic acid (2.15 g, 10.0 mmol, 1.00 eq.) in CH_2Cl_2 (125 mL, 0.800 M) was added oxalyl chloride (1.28 mL, 15.0 mmol, 1.50 eq.) and DMF (0.50 mL). This mixture was stirred at room temperature for an hour before being concentrated under reduced pressure and dissolved in methanol (12 mL, 0.30 mol, 30.0 eq.). After stirring at room temperature for 16 hours the reaction mixture was diluted with ethyl acetate (50 mL) and quenched with water (2 × 50 mL) and 2 M NaOH (50 mL). The organics were washed with brine (20 mL) and dried over Na_2SO_4 before being concentrated under reduced pressure. The crude was purified by flash column chromatography (silica, 30% ethyl acetate in hexane). Isolated the desired product, methyl 2-bromo-5-methylbenzoate (**49a**) (2.06 g, 9.00 mmol, 90% yield), as a colourless oil.

^{1}H NMR (501 MHz, $CDCl_3$) δ 7.60 (1 H, d, *J* = 1.9 Hz, **H6**), 7.52 (1 H, d, *J* = 8.2 Hz, **H3**), 7.13 (1 H, dd, *J* = 8.2, 1.9 Hz, **H4**), 3.93 (3 H, s, OC**H**$_3$), 2.33 (3 H, s, ArC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3 (**C**OOMe), 137.7(**C**CH$_3$), 134.6 (**C**H), 133.9 (**C**H), 132.4 (**C**H), 132.3 (**C1**), 118.7 (**C2**), 52.9 (COO**C**H$_3$), 21.2 (**C**H$_3$); IR (ν_{max}, thin film (neat), cm^{-1}) 3448, 2996, 2951, 2924, 1734, 1598, 1574, 1471, 1434, 1393, 1300, 1252, 1205, 1113, 1030; HRMS (ESI) Calcd. for $C_9H_{10}{}^{79}BrO_2$ $[M+H]^+$ 228.9858; Found 228.9852. Data agrees with literature values.[112]

tert-Butyl 4-(2-bromo-5-methylbenzoyl)piperazine-1-carboxylate (49h)

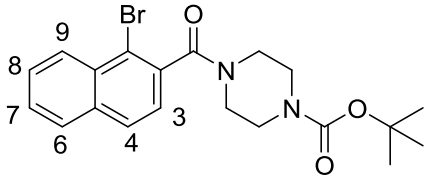


To a stirred solution of 2-bromo-5-methyl benzoic acid (430 mg, 2.00 mmol, 1.00 eq.) in CH_2Cl_2 (25 mL, 0.08 M) was added oxalyl chloride (257 µL, 3.00 mmol, 1.50 eq.) and DMF (0.10 mL). This mixture was stirred at room temperature for an hour before being concentrated under reduced pressure and dissolved in diethyl ether (25 mL, 0.08 M). To this

solution was added dropwise a mixture of 1-Boc piperazine (558 mg, 3.00 mmol, 1.50 eq.) and diisopropylethylamine (523 µL, 3.00 mmol, 1.50 eq.) in diethyl ether (10 mL, 0.30 M). After stirring at room temperature for 16 hours the reaction mixture was diluted with diethyl ether (10 mL) and quenched with water (2 × 10 mL). The combined organics were washed with brine (20 mL) and dried over Na_2SO_4 before being concentrated under reduced pressure. The crude was purified by flash column chromatography (silica, 30% ethyl acetate in hexane). Isolated the desired product, *tert*-butyl 4-(2-bromo-5-methylbenzoyl)piperazine-1-carboxylate (**49h**) (720 mg, 1.90 mmol, 94% yield), as a colourless solid.

M.p. (hexane/$CHCl_3$; colourless needles): 147 – 148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (1 H, d, *J* = 8.8 Hz, **H3**), 7.06 (1 H, d, *J* = 8.8 Hz, **H4**), 7.06 (1 H, br. s, **H6**), 3.88 – 3.79 (1 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 3.76 – 3.67 (1 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 3.57 – 3.46 (3 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 3.39 – 3.31 (1 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 3.30 – 3.23 (1 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 3.19 – 3.13 (1 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 2.31 (3 H, s, C**H**$_3$), 1.46 (9 H, s, NBoc); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1 (**C**(O)N), 154.5 (N**C**(O)O^{t}Bu), 137.4 (**C5**), 135.1 (**C1**), 132.6 (**C**H), 131.3 (**C**H), 128.3 (**C**H), 115.6 (**C2**), 80.4 (O**C**(CH$_3$)$_3$), 46.6 (N(**C**H$_2$**C**H$_2$)$_2$N), 41.5 (N(**C**H$_2$**C**H$_2$)$_2$N), 28.4 (OC(**C**H$_3$)$_3$), 20.9 (**C**H3); IR (ν_{max}, solid, cm^{-1}) 3003, 2965, 2979, 2922, 2864, 1682, 1644, 1446, 1421, 1364, 1286, 1265, 1244, 1211, 1166, 1122, 1082, 1035, 1007; HRMS (ESI) Calcd. for $C_{17}H_{23}{}^{79}BrN_2NaO_3$ $[M+Na]^+$ 405.0784; Found 405.0785.

tert-Butyl 4-[(1-bromonaphthalen-2-yl)carbonyl]piperazine-1-carboxylate (49g)

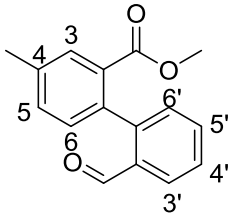


To a stirred solution of 2-bromo-2-naphthoic acid (1.00 g, 4.00 mmol, 1.00 eq.) in CH_2Cl_2 (50 mL, 0.08 M) was added oxalyl chloride (544 µL, 6.00 mmol, 1.50 eq.) and DMF (0.20 mL). This mixture was stirred at room temperature for an hour before being concentrated under reduced pressure and dissolved in diethyl ether (50 mL, 0.08 M). To this solution was added dropwise a mixture of 1-Boc piperazine (1.12 g, 6.00 mmol, 1.50 eq.) and diisopropylethylamine (1.05 mL, 6.00 mmol, 1.50 eq.) in diethyl ether (20 mL, 0.30 M). After stirred at room temperature for 16 hours the reaction mixture was diluted with diethyl ether (20 mL) and quenched with water (2 × 20 mL). The combined organics were washed with brine (20 mL) and dried over Na_2SO_4 before being concentrated under reduced pressure. The crude was purified by flash column chromatography (silica, 30% ethyl acetate in hexane).

Isolated the desired product, *tert*-butyl 4-[(1-bromonaphthalen-2-yl)carbonyl]piperazine-1-carboxylate (**49g**) (1.34 g, 3.20 mmol, 80% yield), as a colourless solid.

M.p. (hexane/ CH_2Cl_2; colourless needles): 133 – 134 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (1 H, d, *J* = 8.2 Hz, **H9**), 7.88 (1 H, d, *J* = 8.3 Hz, **H4**), 7.86 (1H, dd, *J* = 7.8, 0.5 Hz, **H6**), 7.66 (1 H, ddd, *J* = 8.2, 7.0, 1.0 Hz, **H8**), 7.59 (1 H, ddd, *J* = 7.8, 7.0, 0.9 Hz, **H7**), 7.31 (1 H, d, *J* = 8.3 Hz, **H3**), 3.92 (1 H, dt, *J* = 13.3, 5.3 Hz, N(C**H**$_2$C**H**$_2$)$_2$N), 3.83 – 3.73 (1 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 3.59 (2 H, t, *J* = 5.1 Hz, N(C**H**$_2$C**H**$_2$)$_2$N), 3.52 – 3.47 (1 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 3.40 – 3.32 (1 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 3.32 – 3.24 (1 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 3.23 – 3.14 (1 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 1.45 (9 H, s, NBoc); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4 (**C**(O)N), 154.5 (N**C**(O)O^{t}Bu), 135.5 (**C2**), 134.1 (**C5**), 131.9 (**C10**), 128.8 (**C6**), 128.4 (**C7**), 128.3 (**C4**), 127.6 (**C8**), 127.3 (**C9**), 123.8 (**C3**), 119.5 (**C1**), 80.4 (O**C**(CH$_3$)$_3$), 46.6 (N(**C**H$_2$**C**H$_2$)$_2$N), 41.5 (N(**C**H$_2$**C**H$_2$)$_2$N), 28.4 (OC(**C**H$_3$)$_3$); IR (ν_{max}, solid, cm^{-1}) 3244, 3068, 2981, 2932, 2891, 2852, 1686, 1626, 1556, 1466, 1420, 1364, 1324, 1274, 1260, 1165, 1122, 1069, 1030, 1020; HRMS (ESI) Calcd. for $C_{20}H_{24}{}^{79}BrN_2O_3$ $[M+H]^+$ 419.0965; Found 419.0967.

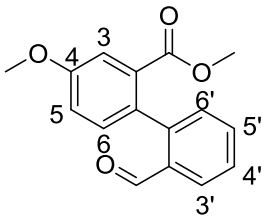
Methyl 2'-formyl-4-methyl-[1,1'-biphenyl]-2-carboxylate (48a)



Prepared following the general method A with $Pd(PPh_3)_4$ (120 mg, 0.100 mmol, 0.02 eq.) using 2-formylphenyl boronic acid (1.50 g, 10.0 mmol, 2.00 eq.) and methyl-2-bromo-5-methylbenzoate (**49a**) (1.14 g, 5.00 mmol, 1.00 eq.). The reaction gave the desired product as a 1 : 1 mixture with benzaldehyde. This mixture was purified by column chromatography (20% ethyl acetate in hexane). Isolated the desired product, methyl 2'-formyl-4-methyl-[1,1'-biphenyl]-2-carboxylate (**48a**) (1.11 g, 4.40 mmol, 87% yield), as a colourless solid.

M.p. (hexane/ CH_2Cl_2; colourless cuboids): 60 – 61 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (1 H, s, C**H**O), 8.00 (1 H, dd, *J* = 7.7, 1.3 Hz, **H3'**), 7.86 (1 H, s, **H3**), 7.59 (1 H, ddd, *J* = 7.7, 7.7, 1.3 Hz, **H5'**), 7.49 (1 H, ddd, *J* = 7.7, 7.7 0.9 Hz, **H4'**), 7.39 (1 H, dd, *J* = 7.7, 1.3 Hz, **H5**), 7.23 (1 H, dd, *J* = 7.7, 0.9 Hz, **H6'**), 7.18 (1 H, d, *J* = 7.7 Hz, **H6**), 3.60 (3 H, s, COOC**H**$_3$), 2.47 (3 H, s, C**H**$_3$); ^{13}C NMR (127 MHz, $CDCl_3$) δ 191.8 (**C**HO), 167.4 (**C**OOMe), 145.3 (**C1'**), 138.2 (**C1**), 136.4 (**C4**), 134.0 (**C2'**), 133.1 (**C5'**), 132.4 (**C5**), 131.6 (**C3**), 130.9 (**C3'**), 130.3 (**C2**), 130.3 (**C4'**), 127.7 (**C6**), 127.3 (**C6'**), 52.0 (O**C**H$_3$), 21.0 (**C**H$_3$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3030, 2946, 2848, 2759, 1721, 1694, 1595, 1501, 1430, 896, 836, 791, 777; HRMS (ESI) Calcd. for $C_{16}H_{14}NaO_3$ $[M+Na]^+$ 277.0835; Found 277.0840.

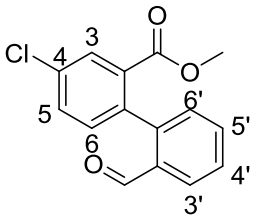
Methyl 2'-formyl-4-methoxy-[1,1'-biphenyl]-2-carboxylate (48b)



Prepared following the general method A with $Pd(PPh_3)_4$ (120 mg, 0.100 mmol, 0.02 eq.) using 2-formylphenyl boronic acid (1.50 g, 10.0 mmol, 2.00 eq.) and methyl-2-bromo-5-methoxybenzoate (806 μL, 5.00 mmol, 1.00 eq.). The reaction gave the desired product as a 1:1 mixture with benzaldehyde. This mixture was purified by column chromatography (20% ethyl acetate in hexane). Isolated the desired product, methyl 2'-formyl-4-methoxy-[1,1'-biphenyl]-2-carboxylate (**48b**) (1.29 g, 4.70 mmol, 96% yield), as a colourless solid.

M.p. (hexane/CH_2Cl_2; colourless cuboids): 76 – 77 °C; ^{1}H NMR (500MHz, $CDCl_3$) δ 9.84 (1 H, s, C**H**O), 8.02 (1 H, dd, *J* = 7.8, 0.9 Hz, **H3'**), 7.61 (1 H, ddd, *J* = 7.8, 7.4, 1.4 Hz, **H4'**), 7.58 (1 H, d, *J* = 2.7 Hz, **H3**), 7.52 (1 H, ddd, *J* = 7.8, 7.4, 0.9 Hz, **H5'**), 7.26 (1 H, dd, *J* = 7.8, 1.4 Hz, **H6'**), 7.23 (1 H, d, *J* = 8.2 Hz, **H6**), 7.15 (1 H, dd, *J* = 8.2, 2.7 Hz, **H5**), 3.94 (3 H, s, C**H**$_3$O), 3.63 (3 H, s, C**H**$_3$O); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.9 (**C**HO), 167.1 (**C**OOMe), 159.3 (**C4**), 145.1 (**C1'**), 134.2 (**C2'**), 133.1 (**C3'**), 132.9 (**C5'**), 131.6 (**C2**), 131.5 (**C1**), 130.5 (**C6**), 127.7 (**C6'**), 127.3 (**C5'**), 117.8 (**C5**), 115.0 (**C6**), 55.6 (**C**H$_3$), 52.1 (**C**H$_3$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3075, 2952, 2835, 2766, 1719, 1686, 1596, 1575, 1562, 1502, 1476, 1440, 1287, 1215, 1077, 1051, 887, 832, 822, 787, 777; HRMS (ESI) Calcd. for $C_{16}H_{14}NaO_4$ $[M+Na]^+$ 293.0784; Found 273.0787.

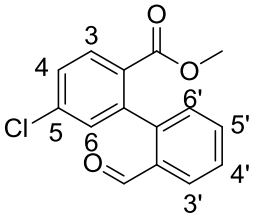
Methyl 4-chloro-2'-formyl-[1,1'-biphenyl]-2-carboxylate (48d)



Prepared following the general method A with $Pd(PPh_3)_4$ (120 mg, 0.100 mmol, 0.02 eq.) using 2-formylphenyl boronic acid (1.50 g, 10.0 mmol, 2.00 eq.) and methyl-2-bromo-5-chlorobenzoate (1.30 g, 5.00 mmol, 1.00 eq.). The reaction gave the desired product as a 1:1 mixture with benzaldehyde. This mixture was purified by column chromatography (20% ethyl acetate in hexane). Isolated the desired product, methyl 4-chloro-2'-formyl-[1,1'-biphenyl]-2-carboxylate (**48d**) (1.10 g, 4.00 mmol, 80% yield), as a colourless solid.

M.p. (hexane/CH_2Cl_2; colourless needles): 166 – 167 °C; ^{1}H NMR (500MHz, $CDCl_3$) δ 9.81 (1 H, s, C**H**O), 8.04 (1 H, d, *J* = 2.3 Hz, **H3**), 8.00 (1 H, dd, *J* = 7.7, 1.5 Hz, **H3'**), 7.61 (1 H, ddd, *J* = 7.7, 7.7, 1.5 Hz, **H5'**), 7.56 (1 H, dd, *J* = 8.2, 2.3 Hz, **H5**), 7.54 (1 H, br. t, *J* = 7.5 Hz, **H4'**), 7.24 (1 H, d, *J* = 8.2 Hz, **H6**), 7.22 (1 H, dd, *J* = 7.7, 1.3 Hz, **H6'**), 3.64 (3 H, s, OC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.3 (**C**HO), 165.9 (**C**OOMe), 143.5 (**C1**), 138.1 (**C1'**), 134.3 (**C2**), 133.9 (**C2'**), 133.3 (**C5'**), 132.8 (**C5**), 131.8 (**C4**), 130.7 (**C3**), 130.4 (**C6**), 130.1 (**C3'**), 128.2 (**C4'**), 128.2 (**C6'**), 52.3 (O**C**H$_3$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3054, 2988, 2879, 2833, 2685, 2538, 1728, 1689, 1599, 1572, 1497, 1474, 1435, 1416, 1274, 1262, 1192, 1084, 1004, 835, 750, 701; HRMS (ESI) Calcd. for $C_{15}H_{11}{}^{35}ClNaO_3$ $[M+Na]^+$ 297.0289; Found 297.0288.

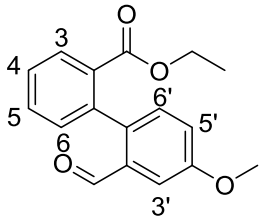
Methyl 5-chloro-2'-formyl-[1,1'-biphenyl]-2-carboxylate (48c)



Prepared following the general method A with $Pd(PPh_3)_4$ (120 mg, 0.100 mmol, 0.02 eq.) using 2-formylphenyl boronic acid (960 mg, 6.40 mmol, 2.00 eq.) and methyl-2-bromo-4-chlorobenzoate (785 mg, 3.20 mmol, 1.00 eq.). The reaction gave the desired product as a 1:1 mixture with benzaldehyde. This mixture was purified by column chromatography (20% ethyl acetate in hexane). Isolated the desired product, methyl 5-chloro-2'-formyl-[1,1'-biphenyl]-2-carboxylate (**48c**) (686 mg, 2.50 mmol, 79% yield), as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (1 H, s, C**H**O), 8.02 (1 H, d, *J* = 8.4 Hz, **H3**), 8.00 (1 H, dd, *J* = 7.2, 1.4 Hz, **H3'**), 7.63 (1 H, ddd, *J* = 7.5, 7.3, 1.4 Hz, **H5'**), 7.55 (1 H, ddd, *J* = 7.3, 7.3, 1.1 Hz, **H4'**), 7.50 (1 H, dd, *J* = 8.4, 2.1 Hz, **H4**), 7.31 (1 H, d, *J* = 2.1 Hz, **H6**), 7.24 (1 H, dd, *J* = 7.5, 1.1 Hz, **H6'**), 3.64 (3 H, s, C**H**$_3$O); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.2 (**C**HO), 166.2 (**C**OOMe), 143.4 (**C1**), 141.6 (**C5**), 138.1 (**C1'**), 133.8 (**C2'**), 133.3 (**C5'**), 131.8 (**C3**), 131.5 (**C6**), 129.9 (**C6'**), 128.7 (**C4**), 128.4 (**C2**), 128.3 (**C4'**), 128.2 (**C3'**), 52.2 (O**C**H$_3$); IR (ν_{max}, solid, cm^{-1}) 3053, 2986, 1725, 1697, 1590, 1560, 1435, 1266, 1106, 1019, 736; HRMS (ESI) Calcd. for $C_{15}H_{11}{}^{35}ClNaO_3$ $[M+Na]^+$ 297.0289; Found 297.0286.

Ethyl 2'-formyl-4'-methoxy-[1,1'-biphenyl]-2-carboxylate (48e)

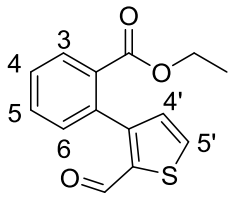


Prepared following the general method A with "Pd-118" (27 mg, 0.05 mmol, 0.01 eq.) using 2-formyl-4-methoxy-phenyl boronic acid (1.20 g, 6.50 mmol, 1.20 eq.) and ethyl 2-bromobenzoate (874 μL, 5.50 mmol, 1.00 eq.). The crude reaction mixture was purified by column chromatography (20% ethyl acetate in hexane). Isolated the desired product, ethyl 2'-formyl-4'-methoxy-[1,1'-biphenyl]-2-carboxylate (**48e**) (1.34 g, 4.70 mmol, 85% yield, 98% purity, 2% anisaldehyde), as a colourless oil.

^{1}H NMR (501 MHz, $CDCl_3$) δ 9.65 (1 H, s, C**H**O), 8.04 (1 H, dd, *J* = 7.9, 1.3 Hz, **H3**), 7.98 (1 H, d, *J* = 8.5 Hz, **H6'**), 7.58 (1 H, ddd, *J* = 7.5, 7.5, 1.3 Hz, **H5**), 7.52 (1 H, ddd, *J* = 7.9,

7.5, 1.1 Hz, **H4**), 7.31 (1 H, dd, *J* = 7.5, 1.1 Hz, **H6**), 7.01 (1 H, dd, *J* = 8.5, 2.6 Hz, **H5'**), 6.73 (1 H, d, *J* = 2.6 Hz, **H3'**), 4.14 − 4.00 (2 H, m, OC**H**$_2$CH$_3$), 3.88 (3 H, s, C**H**$_3$O), 1.01 (3 H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.2 (**C**HO), 166.9 (**C**OOEt), 163.3 (**C4'**), 147.9 (**C1**), 139.0 (**C2'**), 131.4 **(C5**), 131.3 (**C3**), 131.0 (**C1'**), 130.3 (**C6'**), 129.7 (**C4**), 128.2 (**C6**), 127.8 (**C2**), 114.9 (**C5'**), 113.7 (**C3'**), 61.0 (O**C**H$_2$CH$_3$) 55.6 (O**C**H$_3$), 13.7 (OCH$_2$**C**H$_3$); IR (ν_{max}, thin film ($CDCl_3$), cm^{-1}) 3155, 3053, 2984, 2940, 2842, 1714, 1681, 1596, 1566, 1562, 1464, 1382, 1298, 1264, 1094, 1017; HRMS (ESI) Calcd. for $C_{17}H_{16}NaO_4$ $[M+Na]^+$ 307.0941; Found 307.0942.

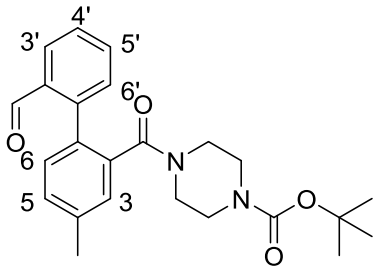
Ethyl 2-(2'-formylthiophen-3'-yl)benzoate (48f)



Prepared following the general method A with "Pd-118" (32 mg, 0.06 mmol, 0.01 eq.) using 2-formyl-thiophene-3-boronic acid (1.20 g, 7.80 mmol, 1.20 eq.) and ethyl 2-bromobenzoate (1.03 mL, 6.50 mmol, 1.00 eq.). The crude reaction mixture was purified by column chromatography (20% ethyl acetate in hexane). Isolated the desired product, ethyl 2-(2'-formylthiophen-3'-yl)benzoate (**48f**) (378 mg, 1.45 mmol, 45% yield), as a yellow oil.

^{1}H NMR (501 MHz, $CDCl_3$) δ 9.61 (1 H, s, C**H**O), 8.04 (1 H, dd, *J* = 7.3, 1.4 Hz, **H3**), 7.71 (1 H, d, *J* = 5.0 Hz, **H5'**), 7.59 (1 H, ddd, *J* = 7.3, 7.3 1.4 Hz, **H5**), 7.54 (1 H, dd, *J* = 7.3, 7.3 Hz, **H4**), 7.37 (1 H, d, *J* = 7.3 Hz, **H6**), 7.08 (1 H, d, *J* = 5.0 Hz, **H4'**), 4.13 (2 H, q, *J* = 6.9 Hz, OC**H**$_2$CH$_3$), 1.10 (3 H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.4 (**C**HO), 166.9 (**C**OOEt), 150.7 (**C1'**), 138.9 (**C2'**), 134.5 (**C1**), 132.9 (**C5**), 131.6 (**C4'**), 131.5 (**C3**), 131.5 (**C2**), 130.0 (**C6**), 130.6 (**C5'**), 128.8 (**C4**), 61.2 (O**C**H$_2$CH$_3$), 13.8 (OCH$_2$**C**H$_3$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3057, 2984, 2820, 1715, 1660, 1599, 1420, 1382, 1365, 1294, 1266, 1206, 1135, 1090, 1064, 906, 737; HRMS (ESI) Calcd. for $C_{14}H_{12}NaO_3S$ $[M+Na]^+$ 283.0399; Found 283.0407.

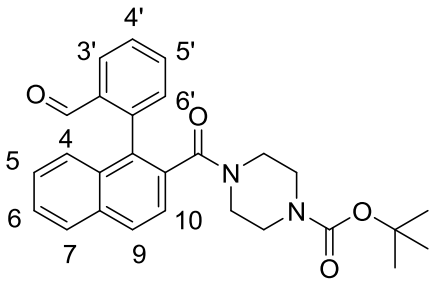
tert-Butyl 4-(2'-formyl-4-methyl-[1,1'-biphenyl]-2-carbonyl)piperazine-1-carboxylate (48h)



Prepared following the general method A with $Pd(PPh_3)_4$ (120 mg, 0.100 mmol, 0.02 eq.) using 2-formylphenyl boronic acid (1.50 g, 10.0 mmol, 2.00 eq.) and *tert*-butyl 4-(2-bromo-5-methylbenzoyl)piperazine-1-carboxylate (**49h**) (1.90 g, 5.00 mmol, 1.00 eq.). The reaction gave the desired product as a mixture with benzaldehyde. This mixture was purified by column chromatography (50% ethyl acetate in hexane). Isolated the desired product, *tert*-butyl 4-(2'-formyl-4-methyl-[1,1'-biphenyl]-2-carbonyl)piperazine-1-carboxylate (**48h**) (1.78 g, 4.40 mmol, 87% yield), as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 89 – 90 °C; ^{1}H NMR (340 K, 501 MHz, DMSO-d_6) δ 9.76 (1 H, br. s, C**H**O), 7.88 (1 H, dd, *J* = 7.8, 1.1 Hz, **H5**), 7.68 (1 H, ddd, *J* = 7.5, 7.5, 1.4 Hz, **H4'** or **H5'**), 7.56 (1 H, dd, *J* = 7.6, 7.6 Hz, **H4'** or **5'**), 7.36 (1 H, ddd, *J* = 7.9, 7.9, 0.9 Hz, **H3'** or **H6'**), 7.36 (1 H, ddd, *J* = 7.9, 7.9, 0.9 Hz, **H3'** or **H6'**), 7.21 − 7.28 (2 H, m, **H6** and **H3**), 3.49 − 3.12 (4 H, m, N(C**H**$_2$CH$_2$)$_2$N), 3.08 – 2.90 (4 H, m, N(CH$_2$C**H**$_2$)$_2$N), 2.42 (3 H, s, C**H**$_3$), 1.37 (9 H, s, NBoc); ^{13}C NMR (340 K, 126 MHz, DMSO-d_6) δ 191.1 (**C**HO), 168.1 (Ar**C**(O)N), 153.7 (N**C**(O)O^{t}Bu), 142.6 (**C1'**), 138.0 (**C5'**), 136.1 (**C3'**), 133.9 (**C3**), 133.3 (**C5**), 131.9 (**C1**), 131.8 (**C2**), 131.0 (**C4**), 130.8 (**C2'**), 129.4 (**C6**), 128.2 (**C6'**), 79.2 (**C**(CH$_3$)$_3$), 45.9 (br, **C**H$_2$), 43.0 (br, **C**H$_2$), 28.0 (C(**C**H$_3$)$_3$), 20.6 (**C**H$_3$) (**C4'** missing); IR (ν_{max}, solid, cm^{-1}) 2975, 2923, 2860, 1690, 1632, 1596, 1457, 1415, 1364, 1284, 1241, 1208, 1195, 1163, 1130, 1113, 1072, 1053, 1018; HRMS (ESI) Calcd. for $C_{24}H_{29}N_2O_4$ $[M+H]^+$ 409.2121; Found 409.2133.

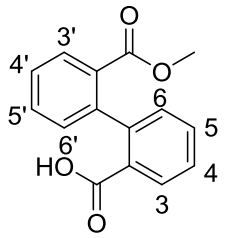
tert-Butyl 4-(1-(2'-formylphenyl)-2-naphthoyl)piperazine-1-carboxylate (48g)



Prepared following the general method A with $Pd(PPh_3)_4$ (120 mg, 0.100 mmol, 0.02 eq.) using 2-formylphenyl boronic acid (525 mg, 3.60 mmol, 2.00 eq.) and *tert*-butyl 4-[(1-bromonaphthalen-2-yl)carbonyl]piperazine-1-carboxylate (**49g**) (752 mg, 1.80 mmol, 1.00 eq.). The reaction gave the desired product as a mixture with benzaldehyde. This mixture was purified by column chromatography (50% ethyl acetate in hexane). Isolated the desired product, *tert*-butyl 4-(1-(2'-formylphenyl)-2-naphthoyl)piperazine-1-carboxylate (**48g**) (726 mg, 1.60 mmol, 91% yield), as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 101 – 103 °C; ^{1}H NMR (340 K, 501 MHz, DMSO-d_6) δ 9.48 (1 H, s, CHO), 8.11 (1 H, d, *J* = 8.4 Hz, **H9**), 8.06 (1 H, d, *J* = 8.2 Hz, **H3'**), 7.98 (1 H, d, *J* = 7.6 Hz, **H7**), 7.78 (1 H, ddd, *J* = 7.5, 7.5, 1.4 Hz, **H5**), 7.66 (1 H, dd, *J* = 7.6, 7.6 Hz, **H6**), 7.59 (1 H, ddd, *J* = 8.0, 6.9, 0.9 Hz, **H4'**), 7.52 (1 H, d, *J* = 8.4 Hz, **H10**), 7.49 (1 H, ddd, *J* = 8.1, 7.0, 1.1 Hz, **H5'**), 7.44 (1 H, dd, *J* = 7.5, 0.6 Hz, **H4**), 7.25 (1 H, d, *J* = 8.5 Hz, **H6'**), 3.30 (3 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$N), 3.14 (5 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$N), 1.38 (9 H, s, NBoc); ^{13}C NMR (340 K, 126 MHz, DMSO-d_6) δ 190.9 (**C**HO), 168.0 (Ar**C**(O)N), 153.7 (N**C**(O)O^{t}Bu), 134.9 (**C2**), 134.0 (**C1'**), 133.5 (Ar**C**H), 132.7 (**C2'**), 132.3 (**C1**), 131.9 (Ar**C**H), 128.8 (Ar**C**H), 128.3 (Ar**C**H), 127.4 (Ar**C**H), 126.7 (Ar**C**H), 125.6 (Ar**C**H), 123.0 (Ar**C**H), 79.2 (**C**(CH$_3$)$_3$), 46.0 (**C**H$_2$), 43.4 (**C**H$_2$), 43.0 (**C**H$_2$), 40.8 (**C**H$_2$), 28.0 (C(**C**H$_3$)$_3$), (21 of 25 expected carbon signals observed, missing 2 Ar**C**H, **C3** + **C**8); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3058, 3004, 2981, 2935, 2864, 2844, 2752, 1694, 1637, 1597, 1421, 1366, 1275, 1261, 1169, 1031, 818, 764, 750. HRMS (ESI) Calcd. for $C_{27}H_{29}N_2O_4$ $[M+H]^+$ 445.2122; Found 445.2131.

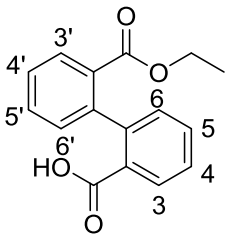
2'-(Methoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (40a) [52]



Prepared following the general method B using methanol (0.48 mL, 12 mmol, 1.0 eq.) as the nucleophile. Crystallization from ethyl acetate and hexane gave 2'-(methoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40a**) (2.02 g, 7.90 mmol, 98% yield) as a cream solid.

M.p. (hexane/ethyl acetate; colourless plates): 111.2 – 112.0 °C (Lit.[52] 111 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (1 H, dd, *J* = 7.8, 1.2 Hz, **H3**), 8.00 (1 H, dd, *J* = 7.7, 1.8 Hz, **H3'**), 7.55 − 7.51 (2 H, m, **H4/H4'** or **H5/H5'**), 7.43 − 7.41 (2 H, m, **H4/H4'** or **H5/H5'**), 7.19 (1 H, dd, *J* = 7.7, 0.9 Hz, **H6**), 7.18 (1 H, dd, *J* = 7.7, 0.9 Hz, **H6'**), 3.61 (3 H, s, COOC**H**$_3$); ^{13}C NMR (76 MHz, $CDCl_3$) δ 172.5 (C), 168.0 (C), 144.1 (C), 143.4 (C), 132.6 (Ar**C**H), 132.0 (Ar**C**H), 130.9 (Ar**C**H), 130.8 (Ar**C**H), 130.6 (Ar**C**H), 130.3 (Ar**C**H), 129.5 (C), 128.9 (C), 127.7 (Ar**C**H), 52.3 (CH_3) (14 of 15 expected carbon signals observed); IR (ν_{max}, solid, cm^{-1}) 2950, 1717, 1676, 1593, 1569, 1429, 1253, 1135, 1080, 942, 754; HRMS (ESI) Calcd. for $C_{15}H_{12}NaO_4$ $[M+Na]^+$ 279.0628; Found 279.0630. Data agrees with literature values.[52]

2'-(Ethoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (40b)

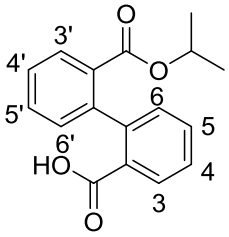


Prepared following the general method B using ethanol (0.70 mL, 12 mmol, 1.0 eq.) as the nucleophile. Crystallization from ethanol gave 2'-(ethoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40b**) (1.69 g, 6.24 mmol, 52% yield) as a colourless solid.

M.p. (EtOH; colourless needles): 91 – 93 °C (Lit. [52] 92 – 93 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (1 H, dd, *J* = 7.9, 1.1 Hz, **H3**), 7.99 (1 H, dd, *J* = 7.9, 1.4 Hz, **H3'**), 7.57 − 7.40 (4 H, m, **H4**, **H4'**, **H5** and **H5'**), 7.21 − 7.16 (2 H, 2dd, *J* = 7.3, 1.1 Hz, **H6** and **H6'**), 4.06 (2 H, qd, *J* = 7.2, 1.4 Hz, OC**H**$_2$Me), 1.01 (3 H, t, *J* = 1.7 Hz, OCH_2C**H**$_3$); ^{13}C NMR (76 MHz, $CDCl_3$) δ 171.9 (C), 167.4 (C), 144.0 (C), 142.7 (C), 132.1 (Ar**C**H), 131.4 (Ar**C**H), 130.5 (Ar**C**H), 130.4 (Ar**C**H), 130.1 (Ar**C**H), 130.0 (Ar**C**H), 129.6 (C), 128.6 (C), 127.2 (Ar**C**H), 127.2 (Ar**C**H),

68.8 (O**C**H_2Me), 13.7 (CH_3); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3066, 2985, 1701, 1599, 1575, 1476, 1444, 1406, 1368, 1294, 1137, 1098; HRMS (ESI) Calcd. for $C_{16}H_{14}NaO_4$ $[M+Na]^+$ 293.0784; Found 293.0791. Data agrees with literature values.[52]

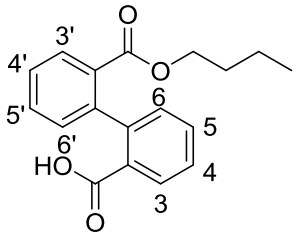
2'-(Isopropoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (40c)



Prepared following the general method B using 2-propanol (0.96 mL, 12 mmol) as the nucleophile. Purification by column chromatography (30% ethyl acetate in petrol) gave 2'-(isopropoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40c**) (2.51 g, 8.82 mmol, 74% yield) as a colourless solid.

M.p. (hexane/ ethyl acetate; colourless cubes): 105 – 107 °C (Lit.[52](EtOH): 105°C)^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (1 H, dd, *J* = 7.7, 1.4 Hz, **H3**), 7.96 (1 H, dd, *J* = 7.7, 1.1 Hz, **H3'**), 7.54 − 7.36 (4 H, m, **H4**, **H4'**, **H5** and **H5'**), 7.17 − 7.13 (2 H, m, **H6** and **H6'**), 4.94 (1 H, sept, *J* = 6.2 Hz, OC**H**$(Me)_2$), 1.03 (3 H, d, *J* = 6.2 Hz, C**H**$_3$), 0.88 (3 H, *J* = 6.2 Hz, C**H**$_3$); ^{13}C NMR (76 MHz, $CDCl_3$) δ 171.3 (C), 167.1 (C), 143.9 (C), 142.4 (C), 132.0 (Ar**C**H), 131.2 (Ar**C**H), 130.4 (C), 130.4 (Ar**C**H), 130.2 (Ar**C**H), 130.1 (Ar**C**H), 129.9 (Ar**C**H), 128.8 (C), 127.3 (Ar**C**H), 127.2 (Ar**C**H), 68.3 (O**C**H$(Me)_2$), 21.4 (**C**H_3), 21.3 (**C**H_3); IR (ν_{max}, solid, cm^{-1}) 3065, 2982, 1699, 1657, 1599, 1575, 1443, 1353, 1292, 1139, 1106; HRMS (ESI) Calcd. for $C_{17}H_{16}NaO_4$ $[M+Na]^+$ 285.1121; Found 285.1118. Data agrees with literature values.[52]

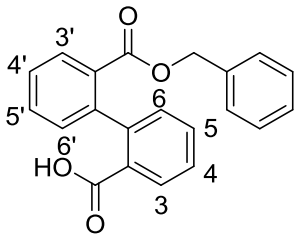
2'-(Butoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (40d)



Prepared following the general method B using *n*-butanol (1.11 mL, 12.0 mmol) as the nucleophile. The reaction yielded 2'-(butoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40d**) (3.16 g, 10.6 mmol, 88% yield) as a slightly yellow oil and was used without further purification.

M.p. (hexane/ ethyl acetate; colourless needles): 51 – 53 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (1 H, dd, *J* = 7.7, 1.4 Hz, **H3**), 8.03 (1 H, dd, *J* = 7.8, 1.1 Hz, **H3'**), 7.53 (1 H, ddd, *J* = 7.6, 7.5, 1.4 Hz, **H5**), 7.49 (1 H, ddd, *J* = 7.5, 7.5, 1.4 Hz, **H5'**), 7.46 – 7.38 (2 H, m, **H4'** and **H6'**), 7.21 (1 H, dd, *J* = 7.6, 0.9 Hz, **H6**), 7.18 (1 H, ddd, *J* = 7.7, 7.5, 0.9 Hz, **H4**), 4.02 (2 H, m, OC**H**$_2$CH$_2$CH$_2$CH$_3$), 1.36 (2 H, ap. quin, *J* = 6.9 Hz, C**H**$_2$), 1.17 (2 H, ap. sextet, *J* = 7.3 Hz, C**H**$_2$), 0.84 (3 H, t, *J* = 7.33 Hz, C**H**$_3$); ^{13}C NMR (76 MHz, $CDCl_3$) δ 172.0 (C), 167.5 (C), 144.1 (C), 142.8 (C), 132.1 (Ar**C**H), 131.4 (Ar**C**H), 130.6 (Ar**C**H), 130.5 (Ar**C**H), 130.2 (Ar**C**H), 130.1 (Ar**C**H), 129.7 (C), 128.6 (C), 127.2 (Ar**C**H), 127.1 (Ar**C**H), 64.8 (CH_2), 30.3 (CH_2), 19.1 (CH_2), 13.7 (CH_3); IR (ν_{max}, thin film, cm^{-1}) 3062, 2961, 1719, 1599, 1574, 1442, 1407, 1385, 1290, 1136, 1082; HRMS (ESI) Calcd. for $C_{18}H_{18}NaO_4$ $[M+Na]^+$ 321.1097; Found 321.1108.

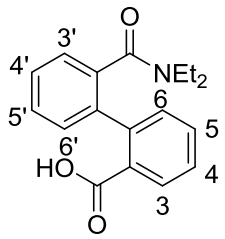
2'-((Benzyloxy)carbonyl)-[1,1'-biphenyl]-2-carboxylic acid (40f)



Prepared following the general method B using benzyl alcohol (1.26 mL, 12.0 mmol) as the nucleophile. Crystallization from toluene gave 2'-((benzyloxy)carbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40f**) (2.28 g, 6.87 mmol, 57% yield) as a colourless solid. Alternatively the crude reaction mixture could be used without further purification.

M.p. (hexane/ ethyl acetate; colourless plates): 111-112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (1 H, dd, *J* = 7.9, 0.9 Hz, **H3**), 7.94 (1 H, dd, *J* = 7.8, 1.0 Hz, **H3'**), 7.51 (1 H, ddd, *J* = 7.5, 7.5, 1.2 Hz, **H4** or **H4'**), 7.47 (1 H, ddd, *J* = 7.5, 7.5, 1.2 Hz, **H4** or **H4'**), 7.41 (1 H, ddd, *J* = 7.6, 7.6, 1.1 Hz, **H5** or **H5'**), 7.35 (1 H, ddd, *J* = 7.7, 7.7, 1.0 Hz, **H5** or **H5'**), 7.25 (3 H, ap. t, *J* = 3.4 Hz, OCH_2C_6**H**$_5$), 7.22 – 7.14 (2 H, m, **H6** and **H6'**), 7.12 – 7.10 (2 H, m, OCH_2C_6**H**$_5$), 5.05 (2H, s, OC**H**$_2C_6H_5$); ^{13}C NMR (76 MHz, $CDCl_3$) δ 171.2 (C), 167.1 (C), 143.6 (C), 142.9 (C), 135.5 (C) 132.3 (CH), 132.1 (CH), 131.6 (CH), 130.6 (CH), 130.5 (C), 130.3 (CH), 130.3 (CH), 130.1 (CH), 129.2 (C), 129.1 (C), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.3 (CH), 127.2 (CH), 66.8 (O**C**H$_2$Ph); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 2986, 2651, 2530, 1698, 1598, 1576, 1442, 1410, 1286, 1137, 1079; HRMS (ESI) Calcd. for $C_{21}H_{16}NaO_4$ $[M+Na]^+$ 355.0941; Found 355.0954.

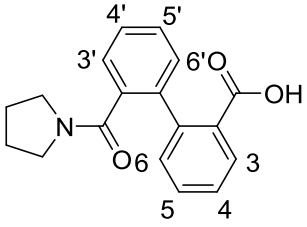
2'-(Diethylcarbamoyl)-[1,1'-biphenyl]-2-carboxylic acid (40g) [52]



Prepared following the general method B using diethylamine (1.23 mL, 12.0 mmol) as the nucleophile. On addition of acid a white precipitate formed which was filtered to give 2'-(diethylcarbamoyl)-[1,1'-biphenyl]-2-carboxylic acid (**40g**) (2.30 g, 7.74 mmol, 64% yield) as an insoluble colourless solid.

M.p. (EtOH; colourless cubes): 177 – 179 °C (Lit.[52] 178 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (1 H, d, *J* = 7.3 Hz, **H3** or **H3'**), 7.50 − 7.44 (3 H, m, Ar**H**), 7.41 (1 H, dd, *J* = 6.9, 6.9 Hz, Ar**H**), 7.37 − 7.30 (2 H, m, Ar**H**), 7.04 (1 H, d, *J* = 6.9 Hz, **H6** or **H6'**), 3.57 (1 H, quin, *J* = 6.9 Hz, $N(C\mathbf{H}_2CH_3)_2$), 3.50 (1 H, quin, *J* = 6.9 Hz, $N(C\mathbf{H}_2CH_3)_2$), 3.37 (1 H, dq, *J* = 14.2, 7.1 Hz, $N(C\mathbf{H}_2CH_3)_2$), 3.20 (1 H, sxt, *J* = 6.4 Hz, $N(C\mathbf{H}_2CH_3)_2$), 1.25 (3 H, t, *J* = 6.6 Hz, $N(CH_2C\mathbf{H}_3)_2$), 0.90 (3 H, t, *J* = 7.1 Hz, $N(CH_2C\mathbf{H}_3)_2$); ^{13}C NMR (76 MHz, $CDCl_3$) δ 172.2 (**C**OOH), 170.5 (**C**ONR_2), 138.5 (C), 136.8 (C), 135.7 (C), 133.7 (C), 130.3 (Ar**C**H), 129.8 (Ar**C**H), 129.6 (Ar**C**H), 128.6 (Ar**C**H), 128.4 (Ar**C**H), 128.2 (Ar**C**H), 128.1 (Ar**C**H), 124.7 (Ar**C**H), 43.4 (CH_2), 39.3 (CH_2), 14.1 (CH_3), 11.8 (CH_3); IR (ν_{max}, solid, cm^{-1}) 2969, 2933, 2874, 2757, 2609, 2483, 1715, 1592, 1574, 1487, 1461, 1441, 1389, 1347, 1292, 1244, 1216, 1046; HRMS (ESI) Calcd. for $C_{18}H_{20}NO_3$ $[M+H]^+$ 298.1438; Found 298.1433. Data agrees with literature values.[52]

2'-(Pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-2-carboxylic acid (40h)

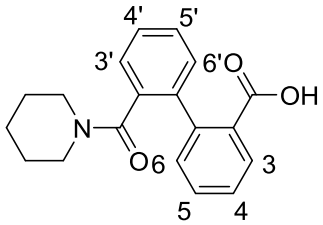


Prepared following the general method B using pyrrolidine (0.99 mL, 12 mmol) as the nucleophile. On addition of acid a white precipitate formed which was filtered to give 2'-(pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40h**) (2.92 g, 9.90 mmol, 82% yield) as an insoluble colourless solid.

M.p. (EtOH; colourless needles): 198 – 203 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.81 (1 H, br. S, COO**H**), 7.77 (1 H, d, *J* = 7.6 Hz, **H3** or **H3'**), 7.52 (1 H, dd, *J* = 7.3, 7.3 Hz, Ar**H**),

7.47 − 7.32 (4 H, m, Ar**H**), 7.27 (1 H, d, *J* = 7.6 Hz, **H6** or **H6'**), 7.22 (1 H, dd, *J* = 6.3, 1.1 Hz, **H6** or **H6'**), 3.16 (4 H, br. s, N(C**H**$_2$)$_2$), 1.66 (2 H, quin, *J* = 6.4 Hz, N(CH$_2$C**H**$_2$)$_2$), 1.55 (2 H, br. s, N(CH$_2$C**H**$_2$)$_2$); ^{13}C NMR (76 MHz, $CDCl_3$) δ 170.7 (**C**OOH), 170.6 (**C**ONR$_2$), 138.6 (C), 137.2 (C), 135.5 (C), 134.2 (C), 130.5 (Ar**C**H), 130.0 (Ar**C**H), 129.8 (Ar**C**H), 128.6 (Ar**C**H), 128.3 (Ar**C**H), 128.2 (Ar**C**H), 128.1 (Ar**C**H), 125.6 (Ar**C**H), 49.5 (NCH$_2$), 45.9 (NCH$_2$), 26.0 (CH$_2$), 24.3 (CH$_2$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3155, 2983, 2901, 1817, 1793, 1721, 1642, 1603, 1583, 1566, 1469, 1382, 1297, 1216, 1165, 1096; HRMS (ESI) Calcd. for $C_{18}H_{18}NO_3$ $[M+H]^+$ 296.1281; Found 296.1289.

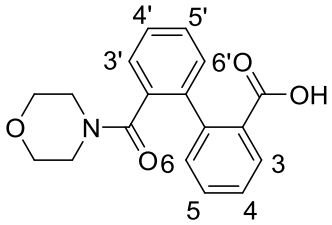
2'-(Piperidine-1-carbonyl)-[1,1'-biphenyl]-2-carboxylic acid (40i) [52]



Prepared following the general method B using piperidine (1.20 mL, 12.0 mmol) as the nucleophile. On addition of acid a white precipitate formed which was filtered to give 2'-(piperidine-1-carbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40i**) (2.80 g, 9.05 mmol, 75% yield) as an insoluble colourless solid.

M.p. (EtOH; colourless needles): 156 – 158 °C (Lit.[52] 157 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (1 H, d, *J* = 6.9 Hz, **H3** or **H3'**), 7.49 − 7.37 (4 H, m, Ar**H**), 7.29 (2 H, br. s, Ar**H**), 7.03 (1 H, d, *J* = 6.9 Hz, **H6** or **H6'**), 3.82 − 3.08 (10 H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.8 (**C**OOH), 170.6 (**C**ONR$_2$), 139.1 (C), 137.1 (C), 135.5 (C), 133.1 (C), 131.7 (Ar**C**H), 129.9 (Ar**C**H), 129.7 (Ar**C**H), 128.6 (Ar**C**H), 128.4 (Ar**C**H), 128.4 (Ar**C**H), 128.1 (Ar**C**H), 125.5 (Ar**C**H), 48.7 (N**C**H$_2$), 43.3 (N**C**H$_2$), 26.7 (CH$_2$), 25.5 (CH$_2$), 24.2 (CH$_2$); IR (ν_{max}, solid, cm^{-1}) 3051, 2962, 2935, 2851, 1696, 1579, 1567, 1447, 1433, 1252, 1229; HRMS (ESI) Calcd. for $C_{19}H_{20}NO_3$ $[M+H]^+$ 310.1438; Found 310.1450. Data agrees with literature values.[52]

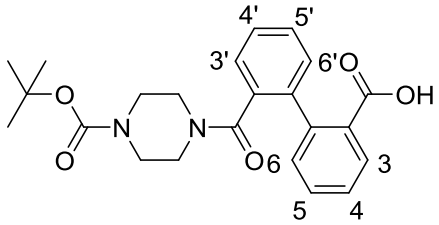
2'-(Morpholine-4-carbonyl)-[1,1'-biphenyl]-2-carboxylic acid (40j)



Prepared following the general method B using morpholine (1.40 mL, 12.0 mmol) as the nucleophile. On addition of acid a white precipitate formed which was filtered to give 2'-(morpholine-4-carbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40j**) (3.25 g, 10.5 mmol, 87% yield) as an insoluble colourless solid.

M.p. (EtOH; colourless needles): 212 – 214 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.82 (1 H, br. s, COO**H**), 7.83 (1 H, d, *J* = 7.4 Hz, **H3** or **H3'**), 7.55 (1 H, ddd, *J* = 7.5, 7.5, 1.0 Hz, Ar**H**), 7.48 (1 H, ddd, *J* = 7.5, 7.5, 1.0 Hz, Ar**H**), 7.44 − 7.29 (4 H, m, Ar**H**), 7.27 − 7.17 (1 H, m, Ar**H**), 3.42 (2 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$O), 3.18 (2 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$O), 2.99 (3 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$O), 2.78 (1 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$O); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.7 (**C**OOH), 168.1 (**C**ONR$_2$), 139.2 (C), 137.6 (C), 134.9 (C), 132.0 (C), 130.9 (Ar**C**H), 130.6 (Ar**C**H), 129.8 (Ar**C**H), 129.6 (Ar**C**H), 128.4 (Ar**C**H), 127.7 (Ar**C**H), 127.3 (Ar**C**H), 127.0 (Ar**C**H), 65.9 (O**C**H$_2$), 65.6 (O**C**H$_2$), 46.3 (**C**H$_2$N), 41.4 (**C**H$_2$N); IR (ν_{max}, solid, cm^{-1}) 2983, 2912, 2853, 2587, 2458, 1701, 1582, 1567, 1436, 1264, 1247, 1236; HRMS (ESI) Calcd. for $C_{18}H_{17}NNaO_4$ $[M+Na]^+$ 334.1050; Found 334.1054.

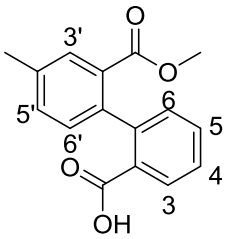
2'-(4-(tert-Butoxycarbonyl)piperazine-1-carbonyl)-[1,1'-biphenyl]-2-carboxylic acid (40l)



Prepared following the general method B on a 24 mmol scale using *N*-Boc piperazine (4.46g, 24.0 mmol, 1.00 eq.) as the nucleophile. On addition of acid a white precipitate formed which was filtered to give 2'-(4-(*tert*-butoxycarbonyl)piperazine-1-carbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40l**) (6.46 g, 15.6 mmol, 66% yield) as an insoluble colourless amorphous solid.

M.p. (hexane/ ethyl acetate; colourless needles): 151 – 152 °C; ^{1}H NMR (340 K, 501 MHz, DMSO-d_6) δ 12.64 − 12.37 (1 H, br., COO**H**), 7.81 (1 H, dd, *J* = 7.7, 1.1 Hz, **H3** or **H3'**), 7.52 (1 H, ddd, *J* = 7.6, 7.6, 1.4 Hz, Ar**H**), 7.45 (1 H, ddd, *J* = 7.7, 7.7, 1.3 Hz, Ar**H**), 7.43 − 7.38 (2 H, m, Ar**H**), 7.36 − 7.32 (1 H, m, Ar**H**), 7.31 (1 H, d, *J* = 7.5 Hz, **H6** or **H6'**), 7.26 − 7.20 (1 H, m, Ar**H**), 3.35 (2 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$N), 3.14 (6 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$N), 1.36 (9 H, s, Boc**H**); ^{13}C NMR (340 K, 126 MHz, DMSO-d_6) δ 168.5 (**C**OOH), 168.4 (C), 153.7 (C), 139.3 (C), 138.0 (C), 135.1 (C), 132.1 (C), 131.0 (Ar**C**H), 130.5 (Ar**C**H), 130.0 (Ar**C**H), 129.5 (Ar**C**H), 128.3 (Ar**C**H), 127.7 (Ar**C**H), 127.3 (Ar**C**H), 126.7 (Ar**C**H), 79.2 (**C**(CH$_3$)$_3$), 47.5 (br, CH$_2$), 42.2 (br, CH$_2$), 28.0 (C(**C**H$_3$)$_3$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 2986, 2924, 2868, 2767, 2604, 1714, 1691, 1583, 1568, 1448, 1418, 1365, 1289, 1250, 1230, 1166, 1126, 1110, 1015; HRMS (ESI) Calcd. for $C_{23}H_{27}N_2O_5$ $[M+H]^+$ 411.1914; Found 411.1919.

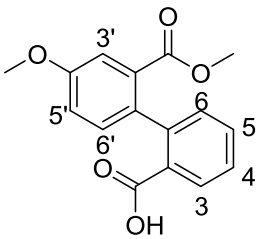
2'-(Methoxycarbonyl)-4'-methyl-[1,1'-biphenyl]-2-carboxylic acid (40n)



Prepared following the general procedure C using 1-methylcyclohexene and methyl 2'-formyl-4-methyl-[1,1'-biphenyl]-2-carboxylate (**48a**) (1.02 g, 4.00 mmol, 1.00 eq.). This mixture was purified by column chromatography (gradient of 0 − 100% ethyl acetate in hexane). Isolated the desired product, 2'-(methoxycarbonyl)-4'-methyl-[1,1'-biphenyl]-2-carboxylic acid (**40n**) (1.11 g, 4.00 mmol, 99% yield, purity >95%), as a yellow solid.

M.p. (hexane/ethyl acetate; colourless amorphous solid): 157 – 159 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 − 8.36 (1 H, br, COO**H**), 8.00 (1 H, ddd, *J* = 7.7, 1.4 Hz, **H3**), 7.78 (1 H, d, *J* = 1.3 Hz, **H3'**), 7.53 (1 H, ddd, *J* = 7.5, 7.5 1.4 Hz, **H5**), 7.44 (1 H, ddd, *J* = 7.7, 7.5 1.3 Hz, **H4**), 7.35 (1 H, dd, *J* = 7.7, 1.3 Hz, **H5'**), 7.16 (1 H, dd, *J* = 7.5, 1.3 Hz, **H6**), 7.11 (1 H, d, *J* = 7.7 Hz, **H6'**), 3.66 (3 H, s, COOC**H**$_3$), 2.45 (3 H, s, ArC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0 (**C**OOH), 168.0 (**C**OOMe), 143.4 (C), 140.0 (C), 137.0 (C), 132.3 (Ar**C**H), 131.8 (Ar**C**H), 130.5 (Ar**C**H), 130.4 (Ar**C**H), 130.3 (Ar**C**H), 130.3 (Ar**C**H), 129.1 (C), 127.1 (CH), 51.9 (O**C**H$_3$), 21.0 (**C**H$_3$) (15 of 16 expected carbon signals observed); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 2924, 2650, 2577, 1721, 1694, 1672, 1597, 1572, 1449, 1435, 1406, 1294, 1248, 1201, 1099, 1083, 948; HRMS (ESI) Calcd. for $C_{16}H_{14}NaO_4$ $[M+Na]^+$ 293.0784; Found 293.0787**.**

4'-Methoxy-2'-(methoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (40o)

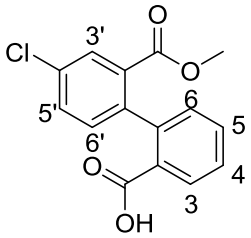


Prepared following the general procedure C with hydrogen peroxide using methyl 2'-formyl-4-methoxy-[1,1'-biphenyl]-2-carboxylate (**48b**) (804 mg, 3.00 mmol, 1.00 eq.). The reaction produced the desired product as a colourless solid. This mixture was purified by column chromatography (gradient of 0 − 100% ethyl acetate in hexane). Isolated the desired

product, 4'-methoxy-2'-(methoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40o**) (610 mg, 2.10 mmol, 71% yield), as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 167 – 168 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (1 H, dd, *J* = 7.8, 1.2 Hz, **H3**), 7.53 (1 H, ddd, *J* = 7.6, 7.6, 1.2 Hz, **H5**), 7.50 (1 H, d, *J* = 2.7 Hz, **H3'**), 7.42 (1 H, ddd, *J* = 7.6, 7.6, 1.3 Hz, **H4**), 7.17 (1 H, dd, *J* = 7.6, 1.3 Hz, **H6**), 7.12 (1 H, d, *J* = 8.4 Hz, **H6'**), 7.07 (1 H, dd, *J* = 8.4, 2.7 Hz, **H5'**), 3.90 (3 H, s, OC**H**$_3$), 3.63 (3 H, s, COOC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5 (**C**OOH), 167.8 (C), 158.6 (C), 143.0 (C), 135.0 (C), 131.9 (Ar**C**H), 131.5 (Ar**C**H), 130.7 (Ar**C**H), 130.3 (C), 130.3 (Ar**C**H), 129.2 (C), 127.2 (Ar**C**H), 117.7 (Ar**C**H), 114.6 (Ar**C**H), 55.5 (**C**H$_3$), 52.1 (**C**H$_3$); IR (ν_{max}, thin film ($CDCl_3$), cm^{-1}) 3434 (br), 3055, 2987, 2953, 2839, 1726, 1698, 1608, 1574, 1509, 1436, 1320, 1289, 1265, 1227, 1080, 1050; HRMS (ESI) Calcd. for $C_{16}H_{14}NaO_5$ $[M+Na]^+$ 309.0737; Found 309.0733.

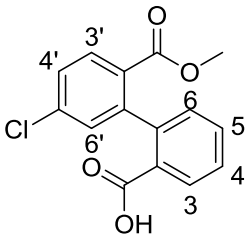
4'-Chloro-2'-(methoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (40q)



Prepared following the general procedure C with 1-methylcyclohexene using methyl 4-chloro-2'-formyl-[1,1'-biphenyl]-2-carboxylate (**48d**) (1.00 g, 3.60 mmol, 1.00 eq.). This mixture was purified by column chromatography (gradient of 0 − 100% ethyl acetate in hexane). Isolated the desired product, 4'-chloro-2'-(methoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40q**) (1.06 g, 3.60 mmol, 99% yield, purity >95%), as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 174 – 175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (1 H, dd, *J* = 7.6, 1.4 Hz, **H3**), 7.99 (1 H, d, *J* = 2.3 Hz, **H3'**), 7.57 (1 H, ddd, *J* = 7.6, 7.6, 1.4 Hz, **H5**), 7.51 (1 H, dd, *J* = 8.2, 2.3 Hz, **H5'**), 7.47 (1 H, ddd, *J* = 7.6, 7.6, 1.1 Hz, **H4**), 7.16 (1 H, dd, *J* = 7.6, 1.1 Hz, **H6**), 7.17 (1 H, d, *J* = 8.2 Hz, **H6'**), 3.65 (3 H, s, COOC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2 (**C**OOH), 166.2 (C), 142.6 (C), 141.5 (C), 133.2 (C), 132.3 (Ar**C**H), 131.6 (Ar**C**H), 131.5 (Ar**C**H), 130.7 (Ar**C**H), 130.7 (C), 130.3 (Ar**C**H), 129.9 (Ar**C**H), 128.3 (C), 127.6 (Ar**C**H), 52.0 (**C**H$_3$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3075 (br), 2957, 2872, 2673, 2545, 1728, 1689, 1599, 1573, 1474, 1436, 1415, 1274, 1191, 1147, 1083, 1047, 1004; HRMS (ESI) Calcd. for $C_{15}H_{11}{}^{35}ClNaO_4$ $[M+Na]^+$ 313.0238; Found 313.0240.

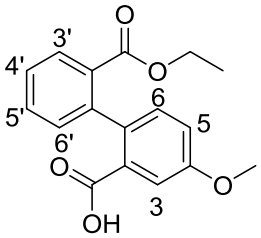
5'-Chloro-2'-(methoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (40p)



Prepared following the general procedure C with 1-methylcyclohexene using methyl 5-chloro-2'-formyl-[1,1'-biphenyl]-2-carboxylate (**48c**) (659 mg, 2.40 mmol, 1.00 eq.). This mixture was purified by column chromatography (gradient of 0 − 100% ethyl acetate in hexane). Isolated the desired product, 5'-chloro-2'-(methoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40p**) (697 mg, 2.40 mmol, 99% yield, purity >95%), as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 143 – 144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (1 H, dd, *J* = 7.9, 1.3 Hz, **H3**), 7.95 (1 H, d, *J* = 8.5 Hz, **H3'**), 7.58 (1 H, ddd, *J* = 7.6, 7.6, 1.3 Hz, **H5**), 7.47 (1 H, ddd, *J* = 7.9, 7.6, 1.2 Hz, **H4**), 7.41 (1 H, dd, *J* = 8.5, 2.2 Hz, **H4'**), 7.21 (1 H, d, *J* = 2.2 Hz, **H6'**), 7.18 (1 H, dd, *J* = 7.6, 1.2 Hz, **H6**), 3.62 (3 H, s, COOC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2 (**C**OOH), 166.6 (C), 144.8 (C), 142.4 (C), 137.7 (C), 132.3 (Ar**C**H), 131.3 (Ar**C**H), 130.6 (Ar**C**H), 130.2 (Ar**C**H), 130.1 (Ar**C**H), 128.2 (C), 127.7 (Ar**C**H), 127.7 (C), 127.5 (Ar**C**H), 52.0 (**C**H$_3$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3063 (br), 2966, 2872, 2662, 2542, 1730, 1693, 1592, 1568, 1473, 1439, 1415, 1250, 1192, 1143, 1086, 1020; HRMS (ESI) Calcd. for $C_{15}H_{11}{}^{35}ClNaO_4$ $[M+Na]^+$ 313.0238; Found 313.0237.

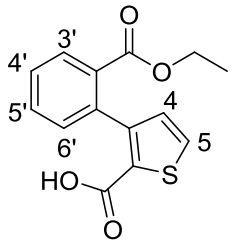
2'-(Ethoxycarbonyl)-4-methoxy-[1,1'-biphenyl]-2-carboxylic acid (40r)



Prepared following the general procedure C with hydrogen peroxide using ethyl 2'-formyl-4'-methoxy-[1,1'-biphenyl]-2-carboxylate (**48e**) (1.00 g, 3.50 mmol, 1.00 eq.). The reaction mixture was purified by column chromatography (gradient of 0 − 100% ethyl acetate in hexane). Isolated the desired product, 2'-(ethoxycarbonyl)-4-methoxy-[1,1'-biphenyl]-2-carboxylic acid (**40r**) (923 mg, 3.10 mmol, 88% yield), as a cream solid.

M.p. (hexane/ethyl acetate; colourless needles): 104 – 105 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (1 H, d, *J* = 8.8 Hz, **H6**), 8.00 (1 H, dd, *J* = 7.6, 1.2 Hz, **H3'**), 7.52 (1 H, ddd, *J* = 7.6, 7.5, 1.2 Hz, **H5'**), 7.44 (1 H, ddd, *J* = 7.6, 7.6, 1.3 Hz, **H4'**), 7.20 (1 H, dd, *J* = 7.6, 1.1 Hz, **H6'**), 6.93 (1 H, dd, *J* = 8.8, 2.6 Hz, **H5**), 6.67 (1 H, d, *J* = 2.6 Hz, **H3**), 4.09 (2 H, qq, *J* = 7.2, 3.2 Hz, COOC**H**$_2$CH$_3$), 3.85 (3 H, s, CH_3), 1.05 (3 H, t, *J* = 7.1 Hz, COOCH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1 (**C**OOH), 167.1 (C), 162.4 (C), 146.7 (C), 142.9 (C), 133.0 (Ar**C**H), 131.3 (Ar**C**H), 129.9 (Ar**C**H), 129.9 (Ar**C**H), 129.6 (C), 127.2 (Ar**C**H), 120.7 (C), 115.9 (Ar**C**H), 112.4 (Ar**C**H), 60.6 (**C**H$_2$CH$_3$) 55.5 (**C**H$_3$), 13.7 (**C**H$_3$); IR (ν_{max}, thin film ($CDCl_3$), cm^{-1}) 2981, 2650, 2557, 1727, 1682, 1599, 1568, 1474, 1440, 413, 1397 1367, 1334, 1259, 1186, 1140, 1110, 1080, 1016; HRMS (ESI) Calcd. for $C_{17}H_{16}NaO_5$ $[M+Na]^+$ 323.0890; Found 323.0893.

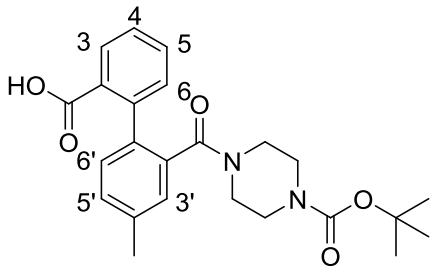
3-(2-(Ethoxycarbonyl)-4-methylphenyl)thiophene-2-carboxylic acid (40s)



Prepared following the general procedure C with hydrogen peroxide using ethyl 2-(2'-formylthiophen-3'-yl)benzoate (**48f**) (800 mg, 3.00 mmol, 1.00 eq.). The reaction mixture was purified by column chromatography (gradient of 0 − 100% ethyl acetate in hexane). Isolated the desired product, 3-(2-(ethoxycarbonyl)-4-methylphenyl)thiophene-2-carboxylic acid (**40s**) (833 mg, 3.00 mmol, 99% yield), as a yellow solid.

M.p. (hexane/CH_2Cl_2; colourless needles): 158 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (1 H, dd, *J* = 7.8, 1.3 Hz, **H3'**), 7.56 (1 H, d, *J* = 5.0 Hz, **H5**), 7.52 (1 H, ddd, *J* = 7.5, 7.5, 1.3 Hz, **H5'**), 7.45 (1 H, ddd, *J* = 7.6, 7.6, 1.2 Hz, **H4'**), 7.26 (1 H, dd, *J* = 7.8, 1.2 Hz, **H6'**), 6.98 (1 H, d, *J* = 5.0 Hz, **H4**), 4.11 (2 H, q, *J* = 7.0 Hz, COOC**H**$_2$CH$_3$), 1.09 (3 H, t, *J* = 7.3 Hz, COOCH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1 (**C**OOH), 166.9 (C), 149.1 (C), 136.9 (C), 131.5 (Ar**C**H), 131.3 (Ar**C**H), 131.1 (Ar**C**H), 130.4 (Ar**C**H), 130.4 (Ar**C**H), 130.2 (Ar**C**H), 127.9 (Ar**C**H), 127.1 (C), 60.8 (O**C**H$_2$CH$_3$), 13.8 (OCH$_2$**C**H$_3$); IR (ν_{max}, solid, cm^{-1}) 3062, 2985, 2855, 2639, 2569, 1707, 1650, 1599, 1571, 1539, 1440, 1421, 1364, 1281, 1252, 1133, 1102, 1065, 1041; HRMS (ESI) Calcd. for $C_{14}H_{12}NaO_4S$ $[M+Na]^+$ 299.0348; Found 299.0354.

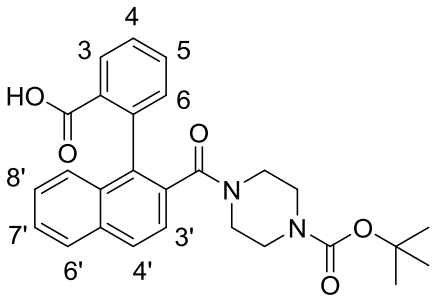
2'-(4-(tert-Butoxycarbonyl)piperazine-1-carbonyl)-4'-methyl-[1,1'-biphenyl]-2-carboxylic acid (40t)



Prepared following the general procedure C with hydrogen peroxide using *tert*-butyl 4-(2'-formyl-4-methyl-[1,1'-biphenyl]-2-carbonyl)piperazine-1-carboxylate (**48h**) (816 mg, 2.00 mmol, 1.00 eq.). The reaction mixture was purified by column chromatography (gradient of 0 − 100% ethyl acetate in hexane). Isolated the desired product, 2'-(4-(*tert*-butoxycarbonyl)piperazine-1-carbonyl)-4'-methyl-[1,1'-biphenyl]-2-carboxylic acid (**40t**) (848 mg, 2.00 mmol, 99% yield), as a yellow solid.

M.p. (hexane/ethyl acetate; yellow needles): 118 – 120 °C; ^{1}H NMR (340 K, 501 MHz, DMSO-d_6) δ 7.79 (1 H, dd, *J* = 7.7, 1.4 Hz, **H3**), 7.51 (1 H, ddd, *J* = 7.6, 7.6, 1.4 Hz, **H5**), 7.44 (1 H, ddd, *J* = 7.5, 7.5, 1.2 Hz, **H4**), 7.29 (1 H, dd, *J* = 7.7, 1.2 Hz, **H6**), 7.23 (1 H, dd, *J* = 7.8, 1.3 Hz, **H5'**), 7.16 (1 H, d, 1.3 Hz, **H3'**), 7.11 (1 H, d, *J* = 7.8 Hz, **H6'**), 3.86 (1 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$N), 3.80 − 3.60 (3 H, br. m, N(C**H**$_2$C**H**$_2$)$_2$N), 3.51 (1 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$N), 3.46 − 3.05 (3 H, br. m, N(C**H**$_2$C**H**$_2$)$_2$N), 2.37 (3 H, s, C**H**$_3$), 1.37 (9 H, s, COOC(C**H**$_3$)$_3$); ^{13}C NMR (340 K, 126 MHz, DMSO-d_6) δ 168.6 (C), 168.5 (C), 153.7 (C), 139.2 (C), 136.7 (C), 135.0 (C), 134.9 (C), 132.2 (C), 130.9 (**C6**), 130.4 (**C5**), 129.8 (**C6'**), 129.4 (**C3**), 129.0 (**C5'**), 127.5 (**C4**), 127.3 (**C3'**), 79.2 (**C**(CH$_3$)$_3$), 45.7 (br, **C**H$_2$), 43.3 (br, **C**H$_2$), 42.9 (br, **C**H$_2$), 40.9 (br, **C**H$_2$), 28.0 (C(**C**H$_3$)$_3$), 20.5 (**C**H$_3$); IR (ν_{max}, solid, cm^{-1}) 3004, 2978, 2921, 2874, 2594, 1709, 1678, 1592, 1508, 1473, 1417, 1364, 1284, 1248, 1162, 1128, 1077, 1042, 1020; HRMS (ESI) Calcd. for $C_{24}H_{29}N_2O_5$ $[M+H]^+$ 425.2071; Found 425.2086.

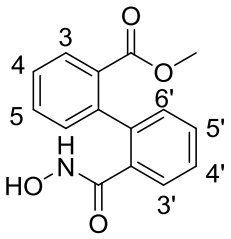
2-(2'-(4-(tert-Butoxycarbonyl)piperazine-1-carbonyl)naphthalen-1'-yl)benzoic acid (40m)



Prepared following the general procedure C with hydrogen peroxide using *tert*-butyl 4-(1-(2'-formylphenyl)-2-naphthoyl)piperazine-1-carboxylate (**48g**) (400 mg, 0.900 mmol, 1.00 eq.). The reaction mixture was purified by column chromatography (gradient of 0 − 100% ethyl acetate in hexane). Isolated the desired product, 2-(2'-(4-(*tert*-butoxycarbonyl)piperazine-1'-carbonyl)naphthalen-1-yl)benzoic acid (**40m**) (413 mg, 0.900 mmol, 99% yield), as a yellow solid.

M.p. (hexane/ethyl acetate; colourless needles): 123 – 124 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (1 H, d, *J* = 8.4 Hz, Ar**H**), 7.90 (1 H, d, *J* = 8.2 Hz, Ar**H**), 7.82 (1 H, d, *J* = 7.3 Hz, Ar**H**), 7.61 − 7.50 (3 H, m, Ar**H**), 7.43 (1 H, t, *J* = 7.5 Hz, Ar**H**), 7.35 (1 H, d, *J* = 8.4 Hz, Ar**H**), 7.22 (1 H, d, *J* = 8.5 Hz, Ar**H**), 7.07 (1 H, d, *J* = 7.2 Hz, Ar**H**), 3.84 − 3.76 (1 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 3.71 − 3.57 (2 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 3.55 (2 H, s, N(C**H**$_2$C**H**$_2$)$_2$N), 3.48 − 3.42 (1 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 3.29 − 3.21 (1 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 3.17 − 3.09 (1 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 1.47 (9 H, s, NBoc); ^{1}H NMR (340 K, 501 MHz, DMSO-d_6) δ 8.00 (1 H, br. s, Ar**H**), 7.96 (2 H, d, *J* = 8.5 Hz, Ar**H**), 7.63 (1 H, td, *J* = 7.5, 1.3 Hz, Ar**H**), 7.56 (1 H, td, *J* = 7.7, 1.3 Hz, Ar**H**), 7.52 (1 H, td, *J* = 7.5, 1.1 Hz, Ar**H**), 7.45 − 7.39 (2 H, m, Ar**H**), 7.33 (1 H, d, *J* = 7.1 Hz, Ar**H**), 7.27 (1 H, d, *J* = 8.5 Hz, Ar**H**), 3.30 (3 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$N), 3.14 (5 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$N), 1.40 (9 H, s, COOC(C**H**$_3$)$_3$); ^{13}C NMR (340 K, 126 MHz, DMSO-d_6) δ 168.6 (C), 168.0 (C), 167.4 (C), 153.7 (C), 137.2 (C), 132.7 (C), 132.0 (C), 131.2 (Ar**C**H), 129.8 (Ar**C**H), 128.1 (Ar**C**H), 127.9 (Ar**C**H), 127.5 (Ar**C**H), 126.6 (Ar**C**H), 126.2 (Ar**C**H), 125.6 (C), 123.4 (C), 79.2 (**C**(CH$_3$)$_3$), 45.8 (br), 43.3 (br), 40.9 (br), 28.0 (C(**C**H$_3$)$_3$) (21 of 23 expected carbon signals observed); IR (ν_{max}, solid, cm^{-1}) 3058, 2975, 2927, 2862, 2606, 1718, 1692, 1633, 1584, 1476, 1418, 1393, 1364, 1286, 1246, 1233, 1162, 1126, 1074, 1053, 1032, 1017; HRMS (ESI) Calcd. for $C_{27}H_{29}N_2O_5$ $[M+H]^+$ 461.2071; Found 461.2083.

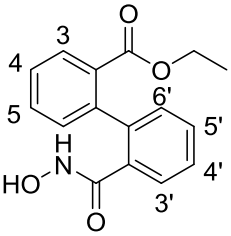
Methyl 2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (39a)



Prepared following the general procedure D using 2'-(methoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40a**) (1.56 g, 6.00 mmol, 1.00 eq.). Isolated the desired product, methyl 2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (**39a**) (1.32 g, 4.80 mmol, 81% yield), as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 129 – 131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (1H, br, NHO**H** or N**H**OH), 7.87 (1 H, dd, *J* = 7.7, 1.4 Hz, **H3**), 7.70 − 7.67 (1 H, m, **H3'**), 7.51 (1 H, ddd, 7.5, 7.5, 1.4 Hz, **H5**) 7.48 − 7.41 (3H, m, **H4**, **H4'** and **H5'**), 7.21 (1 H, dd, *J* = 7.2, 1.5 Hz, **H6**), 7.08 − 7.05 (1 H, m, **H6'**) 3.76 (3H, s, OC**H**$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.4 (C), 166.5 (C), 140.9 (C), 139.4 (C), 131.9 (**C5**), 131.5 (C), 130.7 (**C6**), 130.3 (CH), 130.2 (C), 129.6 (**C3**), 129.3 (**C6'**), 128.5 (**C3'**), 128.1 (CH), 127.9 (CH), 52.7 (CH_3); IR (ν_{max}, solid, cm^{-1}) 3302, 3061, 2953, 2870, 1702, 1673, 1643, 1594, 1575, 1436, 1313, 1277, 1138, 771, 754; HRMS (ESI) Calcd. for $C_{15}H_{13}NNaO_4$ $[M+Na]^+$ 294.0737; Found 294.0741.

Ethyl 2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (39b)

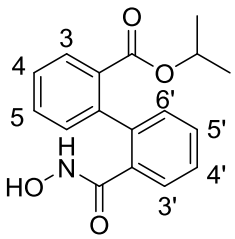


Prepared following the general procedure D using 2'-(ethoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40b**) (2.16 g, 8.00 mmol, 1.00 eq.). Isolated the desired product, ethyl 2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (**39b**) (1.57 g, 6.24 mmol, 78% yield), as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 112 – 114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (1 H, br, NHO**H** or N**H**OH), 7.89 (1 H, dd, *J* = 7.7, 1.5 Hz, **H3**), 7.75 (1 H, dd, *J* = 6.8, 2.0 Hz, **H3'**), 7.51 (1 H, ddd, *J* = 7.5, 7.5, 1.5 Hz, **H5**), 7.48 − 7.41 (3 H, m, **H4**, **H4'** and **H5'**), 7.21 (1 H, dd, *J* = 7.4, 0.8 Hz, **H6**), 7.08 (1 H, dd, *J* = 6.8, 2.0 Hz, **H6'**), 4.26 − 4.17 (2 H, m, OC**H**$_2$Me), 1.14 (3 H, t, *J* = 7.1 Hz, C**H**$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.8 (C),

166.7 (C), 140.6 (C), 139.6 (C), 131.7 (**C5**), 130.7 (C), 130.5 (**C6**), 130.3 (CH), 130.2 (C), 129.5 (**C3**), 129.4 (**C6'**), 128.5 (**C3'**), 128.0 (Ar**C**H), 127.8 (Ar**C**H), 61.6 (CH_2), 13.8 (CH_3); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3194 (br), 3062, 2983, 2902, 1702, 1654, 1596, 1574, 1471, 1368, 1292, 1137, 1091, 1017, 756; HRMS (ESI) Calcd. for $C_{16}H_{15}NNaO_4$ $[M+Na]^+$ 308.0893; Found 308.0886.

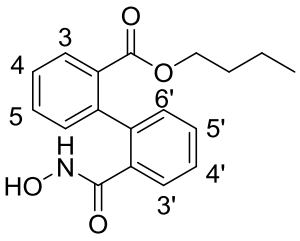
Isopropyl 2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (39c)



Prepared following the general procedure D using 2'-(isopropoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40c**) (2.27 g, 8.00 mmol, 1.00 eq.). Isolated the desired product, isopropyl 2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (**39c**) (1.86 g, 6.22 mmol, 78% yield), as a colourless solid.

M.p. (Et_2O; colourless needles): 127 – 129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (1 H, br, NHO**H** or N**H**OH), 7.75 (1 H, d, *J* = 7.5 Hz, **H3**), 7.67 (1 H, d, *J* = 7.0 Hz **H3'**), 7.45 − 7.35 (4 H, m, Ar**H**), 7.14 (1 H, d, *J* = 7.5 Hz, **H6**), 7.00 (1 H, d, *J* = 7.5 Hz, **H6'**), 6.94 (1 H, br, N**H**), 4.96 (1 H, sept, *J* = 6.5 Hz, OC**H**$(Me)_2$), 1.10 (3 H, d, *J* = 6.5 Hz, C**H**$_3$), 1.00 (3 H, d, *J* = 6.5 Hz, C**H**$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.1 (C), 166.2 (C), 140.3 (C), 139.5 (C), 131.5 (**C5**), 131.4 (C), 131.3 (**C6**) 130.4 (C), 130.3 (Ar**C**H), 129.4 (**C3**), 129.4 (**C6'**), 128.6 (**C3'**), 128.1 (Ar**C**H), 127.9 (Ar**C**H), 69.6 (Ar**C**H), 21.7 (CH_3), 21.3 (CH_3); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3302, 3067, 2983, 2930, 1703, 1657, 1597, 1575, 1468, 1376, 1293, 1105, 1091; HRMS (ESI) Calcd. for $C_{17}H_{17}NNaO_4$ $[M+Na]^+$ 322.1050; Found 322.1050.

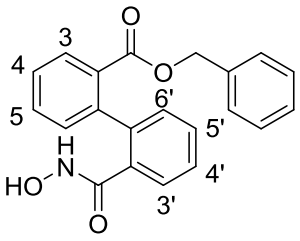
Butyl 2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (39d)



Prepared following the general procedure D using 2'-(butoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40d**) (1.45 g, 4.86 mmol, 1.00 eq.). Isolated the desired product, butyl 2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (**39d**) (1.00 g, 3.19 mmol, 66% yield) as colourless oil. The product was slowly crystallised from toluene to form an off-white solid.

M.p. (toluene; colourless needles): 123 – 125 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (1H, br, NHO**H** or N**H**OH), 7.86 (1H, d, *J* = 7.3 Hz, **H3**), 7.72 (1H, dd, *J* = 6.9, 1.4 Hz, **H3'**), 7.54 − 7.42 (4H, m, Ar**H**), 7.21 (1H, d, *J* = 7.1 Hz, **H6**), 7.08 (1H, dd, *J* = 6.9, 1.4 Hz, **H6'**), 4.22 − 4.10 (2H, m, OC**H**$_2$CH$_2$-), 1.53 (2H, ap. quin, *J* = 6.9 Hz -CH$_2$C**H**$_2$CH$_2$-) 1.30 (2H, ap. sextet, *J* = 7.3 Hz, C**H**$_2$), 0.90 (3H, t, *J* = 7.3 Hz, C**H**$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.1 (C), 166.4 (C), 140.6 (C), 139.5 (C), 131.7 (**C5**), 130.7 (C), 130.6 (**C6**), 130.3 (C), 129.5 (**C3**), 129.1 (**C6'**), 128.6 (**C3'**), 128.2 (Ar**C**H), 128.1 (Ar**C**H), 127.9 (Ar**C**H), 65.7 (CH$_2$), 30.4 (CH$_2$), 19.1 (CH$_2$) 13.7 (CH$_3$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3379, 2960, 1704, 1658, 1597, 1574, 1470, 1388, 1291, 1137, 1090, 755; HRMS (ESI) Calcd. for $C_{18}H_{19}NNaO_4$ $[M+Na]^+$ 336.1206; Found 336.1209.

Benzyl 2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (39f)

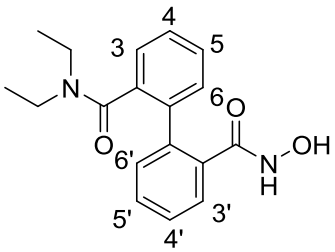


Prepared following the general procedure D using 2'-((benzyloxy)carbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40f**) (2.66 g, 8.00 mmol, 1.00 eq.). Isolated the desired product, benzyl 2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (**39f**) (1.06 g, 3.05 mmol, 38% yield), as colourless oil. The product was slowly crystallised from room temperature toluene to form an off-white solid.

M.p. (toluene; colourless plates): 144 – 145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (1H, br, NHO**H** or N**H**OH), 7.87 (1H, dd, *J* = 7.5, 1.5 Hz, **H3**), 7.65 − 7.62 (1H, m, **H3'**), 7.52 − 7.41

(4H, m, Ar**H**), 7.35 − 7.33 (3H, m Ar**H**), 7.24 − 7.17 (3H, m, Ar**H**), 7.08 − 7.06 (1H, m, **H6'**), 5.14, (2H, s, OC**H**$_2$Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.7 (C), 166.4 (C), 140.7 (C), 139.5 (C), 134.9 (C) 131.8 (**C5**), 131.4 (C), 130.7 (**C6**), 130.3 (Ar**C**H), 130.3 (C), 129.7 (**C3**), 129.4 (**C6'**), 128.7 (Ar**C**H), 128.6 (**C3'**), 128.5 (Ar**C**H), 128.5 (Ar**C**H), 128.1 (Ar**C**H), 127.9 (Ar**C**H), 67.6 (O**C**H$_2$Ph); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3599, 3426 (br), 1710, 1666, 1609, 1496, 1454, 1421, 1387, 1014; HRMS (ESI) Calcd. for $C_{21}H_{18}NO_4$ $[M+H]^+$ 348.1230; Found 321.1233.

N2,N2-Diethyl-N2'-hydroxy-[1,1'-biphenyl]-2,2'-dicarboxamide (39g)

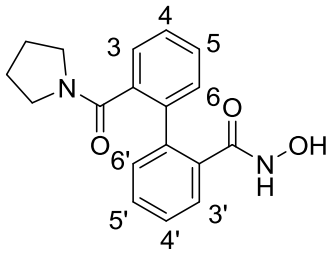


Prepared following the general procedure E using 2'-(diethylcarbamoyl)-[1,1'-biphenyl]-2-carboxylic acid (**40g**) (891 mg, 3.00 mmol, 1.00 eq.). On addition of acid a white precipitate formed which was filtered to give *N*2,*N*2-diethyl-*N*2'-hydroxy-[1,1'-biphenyl]-2,2'-dicarboxamide (**39g**) (869 mg, 2.78 mmol, 93% yield, purity 90%) as a colourless solid.

Also prepared following the general procedure D using 2'-(diethylcarbamoyl)-[1,1'-biphenyl]-2-carboxylic acid (**40g**) (891 mg, 3.00 mmol, 1.00 eq.). On addition of acid a white precipitate formed which was filtered to give *N*2,*N*2-diethyl-*N*2'-hydroxy-[1,1'-biphenyl]-2,2'-dicarboxamide (**39g**) (711 mg, 2.30 mmol, 76% yield) as a colourless solid.

M.p. (EtOH; colourless cubes): 156 – 157 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.02 (1 H, br, NHO**H** or N**H**OH), 7.72 (1 H, d, *J* = 7.3 Hz, **H3'**), 7.46 − 7.36 (4 H, m, Ar**H**), 7.31 − 7.29 (1 H, m, **H3**), 7.23 − 7.22 (1 H, m, **H6**), 7.02 (1 H, d, *J* = 7.3 Hz, **H6'**), 6.92 (1 H, br, N**H**OH or NHO**H**), 3.67 − 3.56 (1 H, m, NC**H**$_2$Me), 3.56 − 3.46 (1 H, m, NC**H**$_2$Me), 3.34 − 3.24 (1 H, m, NC**H**$_2$Me), 3.17 − 3.06 (1 H, m, NC**H**$_2$Me), 1.23 (3 H, t, *J* = 7.1 Hz, C**H**$_3$), 0.87 (3 H, t, *J* = 7.1 Hz, C**H**$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.7 (C), 165.4 (C), 138.3 (C), 137.6 (C), 133.4 (C), 130.4 (C), 129.7 (Ar**C**H), 129.4 (Ar**C**H), 129.2 (Ar**C**H), 129.1 (Ar**C**H), 128.3 (Ar**C**H), 128.2 (Ar**C**H), 127.9 (Ar**C**H), 124.7 (Ar**C**H), 43.1 (N(**C**H$_2$CH$_3$)$_2$), 38.7 (N(**C**H$_2$CH$_3$)$_2$), 14.0 (N(CH$_2$**C**H$_3$)$_2$), 11.8 (N(CH$_2$**C**H$_3$)$_2$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3433, 3054, 2987, 1723, 1634, 1606, 1592, 1506, 1438, 1422, 1157, 1007; HRMS (ESI) Calcd. for $C_{18}H_{20}N_2NaO_3$ $[M+Na]^+$ 335.1366; Found 335.1360.

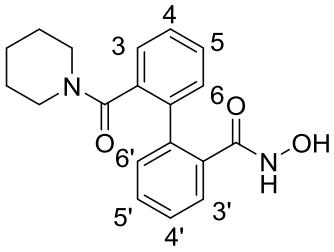
N-Hydroxy-2'-(pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-2-carboxamide (39h)



Prepared following the general procedure E using 2'-(pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40h**) (2.36 g, 8.00 mmol, 1.00 eq.). Isolated the desired product, *N*-hydroxy-2'-(pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-2-carboxamide (**39h**) (1.49 g, 4.80 mmol, 60% yield), as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 204 – 205 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.00 (1 H, br, NHO**H** or N**H**OH), 7.71 (1 H, dd, *J* = 7.8, 0.9 Hz, **H3**), 7.46 − 7.35 (5 H, m, Ar**H**), 7.20 (1 H, dd, *J* = 6.9, 1.8 Hz, **H6'**), 7.03 (1 H, br, N**H**OH or NHO**H**), 6.97 (1 H, dd, *J* = 7.3, 0.9 Hz, **H6**), 3.61 − 3.28 (4 H, m, NC**H**$_2$), 2.04 − 1.81 (4 H, m, NCH$_2$C**H**$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.7 (C), 170.5 (C), 138.6 (C), 137.3 (C), 135.5 (C), 134.3 (C), 130.5 (Ar**C**H CH), 130.0 (Ar**C**H), 129.8 (Ar**C**H), 128.6 (Ar**C**H), 128.3 (Ar**C**H), 128.2 (Ar**C**H), 128.1 (Ar**C**H), 125.6 (Ar**C**H), 49.4 (CH_2), 45.9 (CH_2), 26.0 (CH_2), 24.3 (CH_2); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3432, 3055, 2986, 1725, 1643, 1604, 1582, 1567, 1455, 1438, 1382, 1265; HRMS (ESI) Calcd. for $C_{18}H_{19}N_2O_3$ $[M+H]^+$ 310.1351; Found 310.1298.

N-Hydroxy-2'-(piperidine-1-carbonyl)-[1,1'-biphenyl]-2-carboxamide (39i)

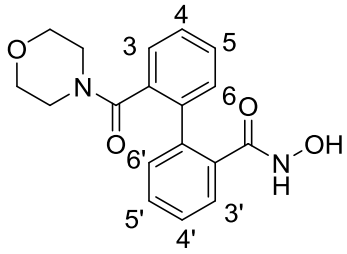


Prepared following the general procedure E using 2'-(piperidine-1-carbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40i**) (2.47 g, 8.00 mmol, 1.00 eq.). Isolated the desired product, *N*-hydroxy-2'-(piperidine-1-carbonyl)-[1,1'-biphenyl]-2-carboxamide (**39i**) (2.05 g, 6.33 mmol, 79% yield, purity 85%, 15% **40i**), as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 170 – 171 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.10 (1 H, br. s, NHO**H** or N**H**OH), 7.74 (1 H, dd, *J* = 7.7, 1.1 Hz, **H3**), 7.46 (1 H, ddd, *J* =

7.6, 7.6, 1.3 Hz, Ar**H**), 7.42 − 7.39 (3 H, m, Ar**H**), 7.29 − 7.27 (1 H, dd, *J* = 6.2, 2.1 Hz, **H3'**), 7.21 (1 H, dd, *J* = 6.9, 2.0 Hz, **H6'**), 7.02 (1 H, d, *J* = 7.4 Hz, **H6**), 6.93 (1 H, br, N**H**OH or NHO**H**), 3.56 − 3.47 (4 H, m, N(C**H**$_2$CH$_2$)$_2$CH$_2$), 1.68 − 1.46 (6 H, m, N(CH$_2$C**H**$_2$)$_2$C**H**$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.5 (C), 165.1 (C), 139.1 (C), 138.6 (C), 134.3 (C), 133.2 (C) 130.0 (Ar**C**H), 129.5 (Ar**C**H), 129.2 (Ar**C**H), 129.1 (Ar**C**H), 128.6 (Ar**C**H), 128.3 (Ar**C**H), 127.8 (Ar**C**H), 125.5 (Ar**C**H), 48.5 (CH_2), 42.7 (CH_2), 26.5 (CH_2), 25.5 (CH_2), 24.3 (CH_2); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3428, 3055, 2946, 1653, 1606, 1446, 1286, 1005; HRMS (ESI) Calcd. for $C_{19}H_{20}N_2NaO_3$ $[M+Na]^+$ 347.1366; Found 347.1363.

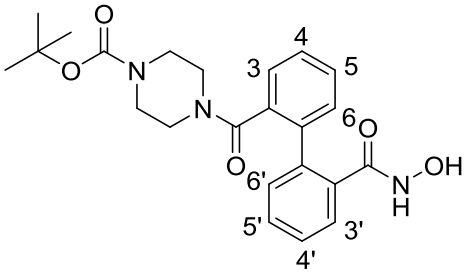
N-Hydroxy-2'-(morpholine-4-carbonyl)-[1,1'-biphenyl]-2-carboxamide (39j)



Prepared following the general procedure E using 2'-(morpholine-4-carbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40j**) (2.47 g, 8.00 mmol, 1.00 eq.). Isolated the desired product, *N*-hydroxy-2'-(morpholine-4-carbonyl)-[1,1'-biphenyl]-2-carboxamide (**39j**) (1.49 g, 4.17 mmol, 52% yield), as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 186 – 188 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.72 (1 H, br, NHO**H** or N**H**OH), 7.74 (1 H, d, *J* = 7.8 Hz, **H3**), 7.45 (1 H, dd, *J* = 7.3, 7.3 Hz, Ar**H**), 7.44 − 7.42 (3 H, m, Ar**H**), 7.30 − 7.27 (1 H, m, **H3'**), 7.24 − 7.21 (1 H, m, **H6'**), 6.99 (1 H, d, *J* = 6.9 Hz, **H6**), 3.77 − 3.46 (8 H, m, N(C**H**$_2$C**H**$_2$)$_2$O); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.5 (C), 164.7 (C), 138.9 (C), 136.6 (C), 133.3 (C), 133.2 (C) 130.2 (Ar**C**H), 129.7 (Ar**C**H), 129.2 (Ar**C**H), 129.1 (Ar**C**H), 128.5 (Ar**C**H), 128.4 (Ar**C**H), 128.0 (Ar**C**H), 125.6 (Ar**C**H), 66.9 (CH_2), 66.7 (CH_2), 47.8 (CH_2), 42.2 (CH_2); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3431, 3055, 2986, 1653, 1611, 1438, 1421, 1301, 1005; HRMS (ESI) Calcd. for $C_{18}H_{18}N_2NaO_4$ $[M+Na]^+$ 349.1159; Found 349.1163.

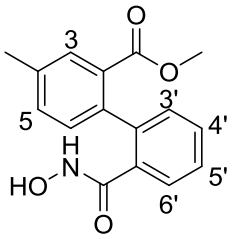
tert-Butyl-4-(2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carbonyl)piperazine-1-carboxylate (39l)



Prepared following the general procedure D using 2'-(4-(*tert*-butoxycarbonyl)piperazine-1-carbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40l**) (656 mg, 1.60 mmol, 1.00 eq.). Column chromatography eluting with ethyl acetate (0 – 100% gradient of ethyl acetate in hexane), yielded *tert*-butyl 4-(2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carbonyl)piperazine-1-carboxylate (**39l**) (225 mg, 0.529 mmol, 33% yield, purity 85%, 15% **40l**) as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 112 – 114 °C; ^{1}H NMR (340 K, 501 MHz, DMSO-d_6) δ 7.83 (1 H, d, *J* = 7.8 Hz, **H3**), 7.58 (1 H, ddd, *J* = 7.6, 7.6, 1.4 Hz, Ar**H**), 7.49 (1 H, ddd, *J* = 7.6, 7.6, 1.1 Hz, Ar**H**), 7.47 − 7.40 (2 H, m, Ar**H**), 7.40 − 7.33 (2 H, m, Ar**H**), 7.20 (1 H, dd, *J* = 5.6, 3.2 Hz, Ar**H**), 3.33 (2 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$N), 3.22 – 2.58 (6 H, br. m, N(C**H**$_2$C**H**$_2$)$_2$N), 1.36 (9 H, s, Boc**H**) (missing N**H**O**H**); ^{13}C NMR (340 K, 126 MHz, DMSO-d_6) δ 168.7 (**C**(O)NHOH), 167.8 (C), 153.2 (C), 131.4 (C), 130.5 (Ar**C**H), 130.1 (C), 129.3 (Ar**C**H), 129.2 (Ar**C**H), 129.1 (C), 128.0 (Ar**C**H), 127.4 (Ar**C**H), 127.0 (Ar**C**H), 126.5 (Ar**C**H), 79.2 (**C**(CH$_3$)$_3$), 36.8 (br, **C**H$_2$), 36.3 (br, **C**H$_2$), 35.8 (br, **C**H$_2$), 35.1 (br, **C**H$_2$), 27.6 (OC(**C**H$_3$)$_3$) (missing 2 **C**=O); IR (ν_{max}, thin film (CH$_2$Cl$_2$), cm^{-1}) 3060, 3006, 2979, 2929, 2857, 1717, 1680, 1620, 1460, 1404, 1362, 1290, 1260, 1248, 1230, 1158, 1122, 1109, 1010, 1002; HRMS (ESI) Calcd. for $C_{23}H_{28}N_3O_5$ $[M+H]^+$ 426.2023; Found 426.2036.

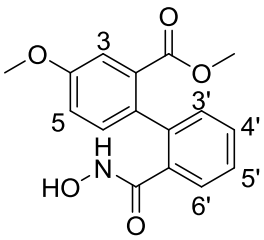
Methyl-2'-(hydroxycarbamoyl)-4-methyl-[1,1'-biphenyl]-2-carboxylate (39n)



Prepared following the general procedure D using 2'-(methoxycarbonyl)-4'-methyl-[1,1'-biphenyl]-2-carboxylic acid (**40n**) (969 mg, 3.50 mmol, 1.00 eq.). Isolated the desired product, methyl 2'-(hydroxycarbamoyl)-4-methyl-[1,1'-biphenyl]-2-carboxylate (**39n**) (496 mg, 1.74 mmol, 50% yield), as a colourless oil.

^{1}H NMR (501 MHz, $CDCl_3$) δ 9.21 (1 H, br. s, NHO**H** or N**H**OH), 7.71 (1 H, dd, *J* = 6.3, 2.7 Hz, **H3'**), 7.68 (1 H, d, *J* = 1.2 Hz, **H3**), 7.48 − 7.41 (2 H, m, **H4'** and **H5'**), 7.33 (1 H, dd, *J* = 7.7, 1.2 Hz, **H5**), 7.12 (1 H, d, *J* = 7.7 Hz, **H6**), 7.06 (1 H, dd, *J* = 6.0, 2.7 Hz, **H6'**), 3.75 (3 H, s, COOC**H**$_3$), 2.44 (3 H, s, ArC**H**$_3$); ^{13}C NMR (127 MHz, $CDCl_3$) δ 169.5 (**C**(O)NHOH), 166.6 (**C**OOMe), 139.5 (C), 138.1 (C), 136.0 (C), 132.6 (Ar**C**H), 131.6 (C), 130.6 (Ar**C**H), 130.3 (Ar**C**H), 130.1 (Ar**C**H), 130.0 (C), 129.5 (Ar**C**H), 128.5 (Ar**C**H), 127.8 (Ar**C**H), 52.6 (COO**C**H$_3$), 21.0 (Ar**C**H$_3$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3434, 3269, 3055, 2987, 2954, 2759, 1708, 1660, 1473, 1437, 1422, 1306, 1265, 1210, 1109, 1092, 896; HRMS (ESI) Calcd. for $C_{16}H_{15}NNaO_4$ [M+Na]$^+$ 308.0893; Found 308.0896.

Methyl-2'-(hydroxycarbamoyl)-4-methoxy-[1,1'-biphenyl]-2-carboxylate (39o)

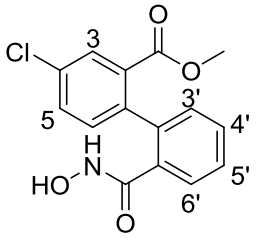


Prepared following the general procedure D using 4'-methoxy-2'-(methoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40o**) (715 mg, 2.50 mmol, 1.00 eq.). Isolated the desired product, methyl 2'-(hydroxycarbamoyl)-4-methoxy-[1,1'-biphenyl]-2-carboxylate (**39o**) (518 mg, 1.72 mmol, 69% yield), as a colourless oil.

^{1}H NMR (501 MHz, $CDCl_3$) δ 9.43 − 8.52 (1 H, br. s, NHO**H** or N**H**OH), 7.65 (1 H, dd, *J* = 5.7, 3.2 Hz, **H3'**), 7.44 − 7.40 (2 H, m, **H4'** and **H5'**), 7.37 (1 H, d, *J* = 2.7 Hz, **H3**), 7.13 (1 H, d, *J* = 8.4 Hz, **H6**), 7.05 (1 H, dd, *J* = 5.4, 3.5 Hz, **H6'**), 7.03 (1 H, dd, *J* = 8.4, 2.7 Hz,

H5), 3.86 (3 H, s, ArOC**H**$_3$), 3.73 (3 H, s, COOC**H**$_3$) (missing N**H**OH or NHO**H**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0 (**C**(O)NHOH), 167.0 (**C**OOMe), 159.0 (C), 139.3 (C), 133.0 (C), 132.0 (C), 131.9 (**C6**), 131.2 (**C**), 131.1 (**C4'** or **C5'**), 129.8 (**C6'**), 128.5 (**C3'**), 127.7 (**C4'** or **C5'**), 117.7 (**C5**), 114.7 (**C3**), 55.5 (ArO**C**H$_3$), 52.6 (COO**C**H$_3$); IR (ν_{max}, thin film ($CDCl_3$), cm^{-1}) 3400, 3153, 2945, 1793, 1711, 1655, 1607, 1466, 1436, 1383, 1321, 1293, 1262, 1228, 1086, 1041; HRMS (ESI) Calcd. for $C_{16}H_{16}NNaO_5$ $[M+Na]^+$ 324.0842; Found 324.0843.

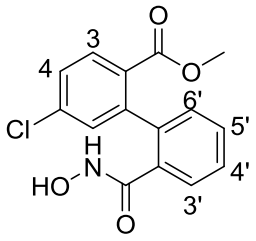
Methyl 4-chloro-2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (39q)



Prepared following the general procedure D using 4'-chloro-2'-(methoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40q**) (1.02 g, 3.50 mmol, 1.00 eq.). Isolated the desired product, methyl 4-chloro-2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (**39q**) (692 mg, 2.26 mmol, 65% yield) as a colourless oil.

^{1}H NMR (501 MHz, $CDCl_3$) δ 7.85 (1 H, d, *J* = 2.2 Hz, **H3**), 7.67 (1 H, dd, *J* = 6.2, 2.8 Hz, **H3'**), 7.50 – 7.45 (3 H, m, **H5** and **H4'** and **H5'**), 7.18 (1 H, d, *J* = 8.2 Hz, **H6**), 7.08 – 7.04 (1 H, m, **H6'**), 3.76 (3 H, s, COOC**H**$_3$) (missing N**H**OH and NHO**H**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4 (**C**(O)NHOH), 166.4 (**C**OOMe), 139.4 (C), 138.5 (C), 138.1 (C), 134.1 (C), 132.1 (Ar**C**H), 131.8 (Ar**C**H), 131.6 (C), 131.5 (C), 130.5 (Ar**C**H), 129.6 (Ar**C**H), 129.4 (Ar**C**H), 128.4 (Ar**C**H), 128.2 (Ar**C**H), 52.87 (COO**C**H$_3$); IR (ν_{max}, thin film ($CDCl_3$), cm^{-1}) 3233, 3057, 2953, 1715, 1659, 1592, 1470, 1436, 1396, 1290, 1264, 1147, 1108, 1086, 1005; HRMS (ESI) Calcd. for $C_{15}H_{12}{}^{35}ClNNaO_3$ $[M+Na]^+$ 328.0347; Found 328.0353.

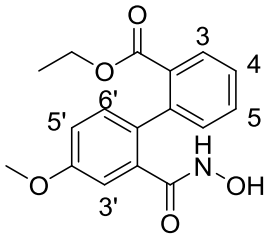
Methyl 5-chloro-2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (39p)



Prepared following the general procedure D using 5'-chloro-2'-(methoxycarbonyl)-[1,1'-biphenyl]-2-carboxylic acid (**40p**) (720 mg, 2.20 mmol, 1.00 eq.). Isolated the desired product, methyl 5-chloro-2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (**39p**) (401 mg, 1.31 mmol, 59% yield), as a colourless oil.

^{1}H NMR (501 MHz, $CDCl_3$) δ 9.20 (1 H, s, NHO**H** or N**H**OH), 7.82 (1 H, d, *J* = 8.4 Hz, **H3**), 7.65 (1 H, dd, *J* = 5.8, 3.2 Hz, **H3'**), 7.50 – 7.44 (2 H, m, **H4'** and **H5'**), 7.42 (1 H, dd, *J* = 8.4, 2.1 Hz, **H4**) 7.24 (1 H, d, *J* = 1.9 Hz, **H6**), 7.09 – 7.03 (1 H, m, **H6'**), 3.74 (3 H, s, COOC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3 (**C**(O)NHOH), 166.5 (**C**OOMe), 142.9 (C), 138.4 (C), 138.1 (C), 131.5 (C), 131.1 (Ar**C**H), 130.9 (Ar**C**H), 130.5 (Ar**C**H), 129.2 (Ar**C**H), 128.5 (C), 128.4 (Ar**C**H), 128.3 (2 × Ar**C**H), 52.7 (COO**C**H$_3$); IR (ν_{max}, thin film ($CDCl_3$), cm^{-1}) 3400, 2917, 1709, 1655, 1590, 1560, 1468, 1436, 1388, 1298, 1105, 1020; HRMS (ESI) Calcd. for $C_{15}H_{12}{}^{35}ClNNaO_3$ $[M+Na]^+$ 328.0347; Found 328.0351.

Ethyl-2'-(hydroxycarbamoyl)-4'-methoxy-[1,1'-biphenyl]-2-carboxylate (39r)

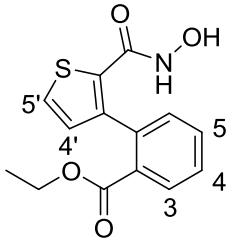


Prepared following the general procedure D using 2'-(ethoxycarbonyl)-4-methoxy-[1,1'-biphenyl]-2-carboxylic acid (**40r**) (511 mg, 1.80 mmol, 1.00 eq.). Isolated the desired product, ethyl 2'-(hydroxycarbamoyl)-4'-methoxy-[1,1'-biphenyl]-2-carboxylate (**39r**) (164 mg, 0.55 mmol, 30% yield), as a colourless solid.

M.p. (hexane/CH_2Cl_2; colourless needles): 63 – 65 °C; ^{1}H NMR (501 MHz, $CDCl_3$) δ 8.46 (2 H, br. s, N**H**O**H**), 7.82 (1 H, dd, *J* = 7.4, 1.5 Hz, **H3**), 7.55 (1 H, d, *J* = 8.6 Hz, **H6'**), 7.42 (1 H, ddd, *J* = 7.5, 7.5, 1.3 Hz, **H4** or **H5**), 7.37 (1 H, ddd, *J* = 7.5, 7.5, 1.3 Hz, **H4** or **H5**), 7.16 (1 H, dd, *J* = 7.4, 1.0 Hz, **H6**), 6.89 (1 H, dd, *J* = 8.6, 2.6 Hz, **H5'**), 6.56 (1 H, d, *J* = 2.6 Hz,

H3'), 4.13 (2 H, m, OC**H**$_2$CH$_3$), 3.75 (3 H, s, C**H**$_3$O), 1.09 (3 H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5 (**C**(O)NHOH), 166.9 (**C**OOEt), 160.6 (C), 141.7 (C), 140.8 (C), 131.6 (C), 130.6 (**C4** or **C5**), 130.4 (**C6**), 130.3 (**C6'**), 129.6 (**C3**), 127.9 (**C4** or **C5**), 124.5 (C), 115.0 (**C3'**), 113.0 (**C5'**), 61.5 (COO**C**H$_2$CH$_3$), 55.4 (O**C**H$_3$), 13.8 (COO**C**H$_2$CH$_3$); IR (ν_{max}, thin film ($CDCl_3$), cm^{-1}) 3176, 2980, 2938, 2905, 2839, 1702, 1651, 1600, 1568, 1474, 1441, 1389, 1367, 1324, 1292, 1260, 1212, 1094, 1017; HRMS (ESI) Calcd. for $C_{17}H_{18}NO_5$ $[M+H]^+$ 316.1179; Found 316.1186.

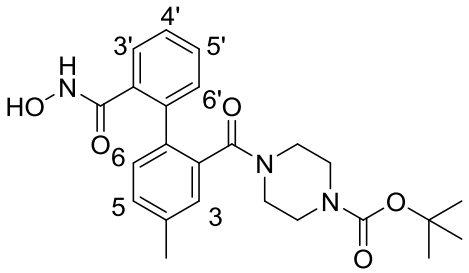
Ethyl 2-(2'-(hydroxycarbamoyl)thiophen-3'-yl)-5-benzoate (39s)



Prepared following the general procedure D using 3-(2-(ethoxycarbonyl)-4-methylphenyl)thiophene-2-carboxylic acid (**40s**) (227 mg, 0.82 mmol, 1.00 eq.). Isolated the desired product, ethyl 2-(2-(hydroxycarbamoyl)thiophen-3-yl)-5-benzoate (**39s**) (155 mg, 0.533 mmol, 66% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (1 H, dd, *J* = 7.7, 1.4 Hz, **H3**), 7.57 (1 H, ddd, *J* = 7.5, 7.5, 1.4 Hz, **H5**), 7.51 (1 H, ddd, *J* = 7.6, 7.6, 1.3 Hz, **H4**), 7.47 (1 H, d, *J* = 5.0 Hz, **H5'**), 7.29 (1 H, dd, *J* = 7.5, 1.3 Hz, **H6**), 6.85 (1 H, d, *J* = 5.0 Hz, **H4'**), 4.14 (2 H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 1.10 (3 H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$) (missing N**H**O**H**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3 (C), 161.7 (C), 141.9 (C), 135.7 (C), 132.2 (**C5**), 131.1 (C), 130.8 (**C6**), 130.6 (**C4'**), 130.5 (**C3**), 130.5 (C), 128.9 (**C5'**), 128.7 (**C4**), 61.5 (O**C**H$_2$CH$_3$), 13.8 (OCH$_2$**C**H$_3$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3170, 3106, 2980, 2902, 1704, 1638, 1599, 1573, 1540, 1475, 1444, 1410, 1367, 1287, 1256, 1206, 1135, 1090; HRMS (ESI) Calcd. for $C_{14}H_{14}NO_4S$ $[M+H]^+$ 292.0637; Found 292.0637.

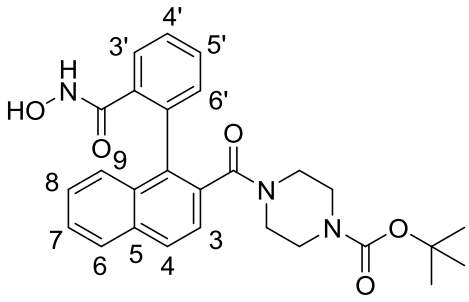
tert-Butyl 4-(2'-(hydroxycarbamoyl)-4-methyl-[1,1'-biphenyl]-2-carbonyl)piperazine-1-carboxylate (39t)



Prepared following the general procedure D using 2'-(4-(*tert*-butoxycarbonyl)piperazine-1-carbonyl)-4'-methyl-[1,1'-biphenyl]-2-carboxylic acid (**40t**) (848 mg, 2.00 mmol, 1.00 eq.) and with the addition of DIPEA (520 μL, 3.00 mmol, 1.50 eq.) to prevent deprotection of the Boc group. Isolated the desired product, *tert*-butyl 4-(2'-(hydroxycarbamoyl)-4-methyl-[1,1'-biphenyl]-2-carbonyl)piperazine-1-carboxylate (**39t**) (419 mg, 0.954 mmol, 48% yield) as a colourless foam.

^{1}H NMR (340 K, 501 MHz, DMSO-d_6) δ 10.80 (1 H, br. s, O**H**), 8.74 (1 H, br. s, N**H**OH), 7.48 – 7.37 (3 H, m, Ar**H**), 7.27 – 7.11 (4 H, m, Ar**H**), 3.11 (8 H, s, N(C**H**$_2$C**H**$_2$)$_2$N), 2.37 (3 H, s, ArC**H**$_3$), 1.38 (9 H, s, NBoc); ^{1}H NMR (501 MHz, $CDCl_3$) δ 11.65 (1 H, s, O**H**), 7.70 (1 H, d, *J* = 6.8 Hz, **H3'**), 7.43 (1 H, dd, *J* = 7.4, 7.4 Hz, **H4'**), 7.39 (1 H, dd, *J* = 7.5, 7.5 Hz, **H5'**), 7.21 (1 H, d, *J* = 7.5 Hz, **H6**), 7.10 (1 H, d, *J* = 7.8 Hz, **H5**), 7.06 (1 H, s, **H3**), 6.96 (1 H, br. s, **H6'**), 3.65 (1 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$N), 3.61 – 3.42 (5 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 3.35 (1 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$N), 3.23 (1 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$N), 2.41 (3 H, s, ArC**H**$_3$), 1.46 (9 H, s, NBoc); ^{13}C NMR (340 K, 126 MHz, DMSO-d_6) δ 169.0 (C), 165.7 (C), 153.7 (C), 150.4 (C), 137.8 (C), 137.0 (C), 135.2 (C), 134.5 (C), 130.2 (**C6**), 129.4 (**C5**), 129.3 (**C3'**), 129.1 (**C4'** and **C5'**), 128.2 (**C6'**), 127.2 (**C3**), 79.1 (**C**(CH$_3$)$_3$), 45.9 (**C**H$_2$), 43.6 (**C**H$_2$), 42.8 (**C**H$_2$), 41.0 (**C**H$_2$), 28.0 (C(**C**H$_3$)$_3$), 20.5 (**C**H$_3$); IR (ν_{max}, solid, cm^{-1}) 3183, 2975, 2926, 2858, 1688, 1654, 1606, 1476, 1415, 1364, 1364, 1330, 1286, 1245, 1160, 1127, 1093, 1077, 1049, 1016; HRMS (ESI) Calcd. for $C_{24}H_{29}N_3NaO_5$ $[M+Na]^+$ 462.1999; Found 462.2010.

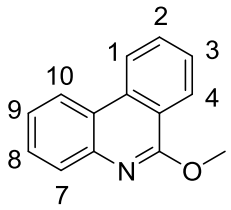
tert-Butyl 4-(1-(2'-(hydroxycarbamoyl)phenyl)-2-naphthoyl)piperazine-1-carboxylate (39m)



Prepared following the general procedure D using 2-(2'-(4-(*tert*-butoxycarbonyl)piperazine-1'-carbonyl)naphthalen-1-yl)benzoic acid (**40m**) (276 mg, 0.599 mmol, 1.00 eq.) with the addition of DIPEA (156 μL, 0.900 mmol, 1.50 eq.) to prevent deprotection of the Boc group. Isolated the desired product, *tert*-butyl 4-(1-(2-(hydroxycarbamoyl)phenyl)-2-naphthoyl)piperazine-1-carboxylate (**39m**) (229 mg, 0.482 mmol, 80% yield), as a colourless foam.

^{1}H NMR (501 MHz, $CDCl_3$) δ 11.84 (1 H, s, O**H**), 7.91 (1 H, d, *J* = 8.0 Hz, **H3**), 7.86 (1 H, d, *J* = 8.1 Hz, **H9**), 7.78 (1 H, d, *J* = 7.6 Hz, **H3'**), 7.55 (1 H, t, *J* = 7.6 Hz, **H4'**) 7.53 – 7.44 (2 H, m, **H5'** and **H8**), 7.38 (1 H, t, *J* = 8.0 Hz, **H7**), 7.32 (1 H, dd, *J* = 8.4, 1.4 Hz, **H4**), 7.22 (1 H, d, *J* = 8.2 Hz, **H6**), 7.02 (1 H, d, *J* = 7.4 Hz, **H6'**), 3.80 – 3.60 (1 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 3.60 – 3.42 (5 H, m, N(C**H**$_2$C**H**$_2$)$_2$N), 3.37 (1 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$N), 3.26 (1 H, br. s, N(C**H**$_2$C**H**$_2$)$_2$N), 1.58 (9 H, s, NBoc); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2 (C), 164.7 (C), 154.4 (C), 136.6 (C), 135.0 (C), 134.7 (C), 133.4 (C), 132.3 (C), 131.0 (C), 130.2 (**C4**' and **C5'**), 129.4 (**C3'**), 129.2 (**C6'**), 128.9 (**C3**), 128.0 (**C9**), 127.7 (**C7**), 127.4 (**C8**), 126.5 (**C6**), 122.0 (**C4**), 80.7 (**C**(CH$_3$)$_3$), 47.1 (**C**H$_2$), 43.7 (C), 41.7 (**C**H$_2$), 28.4 (C(**C**H$_3$)$_3$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3184, 3004, 2973, 2935, 2861, 1690, 1652, 1595, 1458, 1416, 1364, 1283, 1244, 1211, 1162, 1132, 1115, 1051, 1016. HRMS (ESI) Calcd. for $C_{27}H_{30}N_3O_5$ $[M+H]^+$ 476.2180; Found 476.2197.

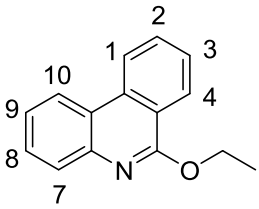
6-Methoxyphenanthridine (41a)



Prepared following general procedure F using methyl 2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (**39a**) (271 mg, 1.00 mmol, 1.00 eq.). Column chromatography (20% ethyl acetate in hexane) provided 6-methoxyphenanthridine (**41a**) (144 mg, 0.689 mmol, 69% yield) as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 55 – 56 °C (Lit.[52] 54.5 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (1 H, d, *J* = 8.4 Hz, **H10**), 8.42 (1 H, dd, *J* = 8.1, 0.8 Hz, **H1**), 8.37 (1 H, dd, *J* = 8.1, 0.6 Hz, **H7**), 7.92 (1 H, dd, *J* = 8.2, 0.6 Hz, **H4**), 7.81 (1 H, ddd, *J* = 8.1, 7.2, 1.3 Hz, **H9**), 7.67 − 7.61 (2 H, m, **H3** and **H8**), 7.50 (1 H, ddd, *J* = 8.2, 7.1, 1.3 Hz, **H2**). 4.25 (3 H, s, OC**H**$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.2 (C), 142.3 (C), 133.7 (C), 130.8 (Ar**C**H), 128.8 (Ar**C**H), 127.8 (Ar**C**H), 127.2 (Ar**C**H), 125.0 (Ar**C**H), 124.4 (Ar**C**H), 122.1 (Ar**C**H), 121.9 (Ar**C**H), 121.5 (C), 119.1 (C), 53.6 (CH_3); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3080, 2947, 2927, 2854, 1622, 1591, 1532, 1488, 1473, 1436, 1359, 1323, 1227, 1097; HRMS (ESI) Calcd. for $C_{14}H_{12}NO$ $[M+H]^+$ 210.0913; Found 210.0912. Data agrees with literature values.[52]

6-Ethoxyphenanthridine (41b)

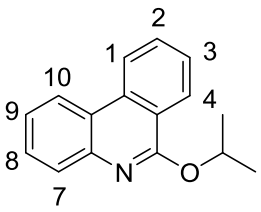


Prepared following general procedure F using ethyl 2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (**39b**) (285 mg, 1.00 mmol, 1.00 eq.). Column chromatography (20% ethyl acetate in hexane) provided 6-ethoxyphenanthridine (**41b**) as a colourless solid (185 mg, 0.831 mmol, 83% yield).

M.p. (hexane/ethyl acetate; colourless needles): 56 – 58 °C (Lit.[52] 55 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (1 H, d, *J* = 8.2 Hz, **H10**), 8.43 (1 H, d, *J* = 8.2 Hz, **H1**), 8.41 (1 H, d, *J* = 8.2 Hz, **H7**) 7.89 (1 H, d, *J* = 8.2 Hz, **H4**), 7.81 (1 H, ddd, *J* = 8.2, 7.4, 1.2 Hz, **H9**), 7.65 (1 H, ddd, *J* = 7.4, 7.4 0.7 Hz, **H8**), 7.63 (1 H, ddd, *J* = 7.3, 7.3, 1.2 Hz, **H2**), 7.49 (1 H, ddd, *J* = 8.1, 7.3, 1.1 Hz, **H3**), 4.73 (2 H, quin, *J* = 7.0 Hz, OC**H**$_2$CH$_3$), 1.57 (3 H, t, *J* = 7.0 Hz,

$OCH_2C\mathbf{H}_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.9 (C), 143.4 (C), 134.8 (C), 130.8 (**C9**), 128.7 (**C3**), 127.8 (**C4**), 127.2 (**C8**), 125.1 (**C7**), 124.3 (**C2**), 122.4 (C), 122.1 (**C1**), 121.8 (**C10**), 120.2 (C), 62.0 (OCH_2), 14.7 (CH_3); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3054, 2986, 2918, 1619, 1591, 1488, 1375, 1318, 1265, 1089, 896; HRMS (ESI) Calcd. for $C_{15}H_{14}NO$ $[M+H]^+$ 221.1070; Found 224.1078. Data agrees with literature values.[52]

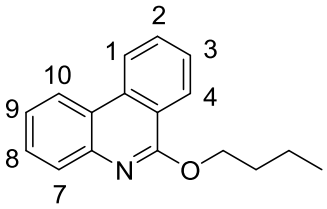
6-Isopropoxyphenanthridine (41c)



Prepared following general procedure F using isopropyl 2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (**39c**) (299 mg, 1.00 mmol, 1.00 eq.). Column chromatography (20% ethyl acetate in hexane) provided 6-isopropoxyphenanthridine (**41c**) (206 mg, 0.869 mmol, 87% yield) as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 73 – 74 °C (Lit.[52] 73 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (1 H, d, *J* = 8.1 Hz, **H10**), 8.42 (1 H, d, *J* = 8.2, **H1**), 8.40 (1 H, dd, *J* = 8.1, 0.7 Hz, **H7**), 7.87 (1 H, dd, *J* = 8.1, 1.2 Hz, **H4**), 7.82 (1 H, ddd, *J* = 8.3, 7.0, 1.4 Hz, **H9**), 7.67 − 7.60 (2 H, m, **H3** and **H8**), 7.49 (1H, ddd, *J* = 8.1, 7.0, 1.4 Hz, **H2**), 5.79 (1 H, sept, *J* = 6.2 Hz, $OC\mathbf{H}(Me)_2$), 1.52 (6 H, d, *J* = 6.2 Hz, 2 × $C\mathbf{H}_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.7 (C), 144.0 (C), 135.2 (C), 130.1 (**C9**), 128.2 (**C3**), 127.5 (**C4**), 126.5 (**C8**), 124.5 (**C7**), 123.5 (**C2**), 122.7 (C), 121.6 (**C1**), 121.4 (**C10**), 121.0 (C), 68.7 ($CHMe_2$), 22.6 (Me); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3078, 2981, 2930, 2871, 1618, 1589, 1377, 1314, 1109; HRMS (ESI) Calcd. for $C_{16}H_{16}NO$ $[M+H]^+$ 238.1226; Found 238.1218. Data agrees with literature values.[52]

6-Butoxyphenanthridine (41d)

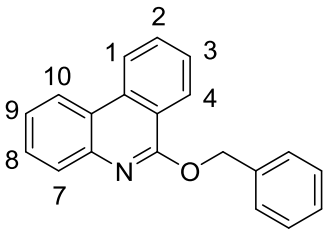


Prepared following general procedure F using butyl 2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (**39d**) (313 mg, 1.00 mmol, 1.00 eq.). Column chromatography (20%

ethyl acetate in petrol) provided 6-butoxyphenanthridine (**41d**) (171 mg, 0.681 mmol, 68% yield) as a colourless solid.

M.p. (hexane/ CH_2Cl_2; colourless needles): 49 – 50 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (1 H, d, *J* = 8.2 Hz, **H10**), 8.42 (1 H, dd, *J* = 8.2, 1.4 Hz, **H1**), 8.42 (1 H, dd, *J* = 8.2, 1.4 Hz, **H7**), 7.94 (1 H, dd, *J* = 8.2, 0.9 Hz, **H4**), 7.80 (1 H, ddd, *J* = 8.2, 7.6, 1.4 Hz, **H9**), 7.68 − 7.64 (2 H, m, **H3** and **H8**), 7.50 (1 H, ddd, *J* = 8.2, 7.6, 1.4 Hz, **H2**), 4.70 (2 H, t, *J* = 6.6 Hz, OC**H**$_2$CH$_2$-), 1.97 (2 H, ap. quin., *J* = 6.6 Hz, C**H**$_2$), 1.66 (2 H, tq, *J* = 7.6, 7.5 Hz, C**H**$_2$), 1.10 (3 H, t, *J* = 7.6 Hz, C**H**$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.0 (C), 143.5 (C), 134.8 (C), 130.8 (**C9**), 128.7 (**C3**), 128.3 (**C4**), 127.8 (**C8**), 127.2 (**C7**), 125.3 (**C2**), 125.1 (**C1**), 124.2 (**C10**), 122.4 (C), 120.3 (C), 65.9 (OCH_2), 31.2 (CH_2), 19.6 (CH_2), 14.0 (CH_3); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3052, 2960, 2932, 1620, 1590, 1488, 1465, 1398, 1342, 1320, 1265, 1088, 739; HRMS (ESI) Calcd. for $C_{17}H_{18}NO$ $[M+H]^+$ 252.1383; Found 252.1380.

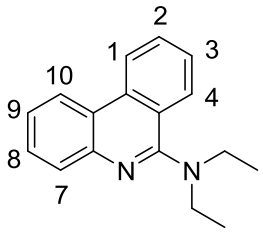
6-(Benzyloxy)phenanthridine (41f)



Prepared following general procedure F on a smaller scale using benzyl 2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (**39f**) (165 mg, 0.516 mmol, 1.00 eq.). Column chromatography (20% ethyl acetate in petrol) provided 6-(benzyloxy)phenanthridine (**41f**) (17 mg, 0.06 mmol, 12% yield) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (1 H, d, *J* = 8.2 Hz, **H10**), 8.43 − 8.49 (2 H, m, **H1** and **H7**), 7.95 (1 H, d, *J* = 8.0 Hz, **H4**), 7.83 (1 H, ddd, *J* = 7.7, 7.7, 1.4 Hz, **H9**), 7.70 − 7.61 (4 H, m, **H3** and **H8** and Ar**H**), 7.55 − 7.35 (4 H, m, **H2** and Ar**H**), 5.75 (2 H, s, OC**H**$_2$Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.5 (C), 142.2 (C), 136.4 (C), 133.8 (C), 129.9 (CH), 127.7 (CH), 127.4 (2CH), 127.1 (2CH), 126.8 (2CH), 126.2 (CH), 124.1 (CH), 123.4 (CH), 121.5 (C), 121.1 (CH), 120.8 (CH), 119.0 (C), 66.7 (OCH_2); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3067, 3034, 2925, 2851, 1620, 1590, 1579, 1488, 1470, 1462, 1391, 1342, 1315, 1224, 1123, 1086, 728; HRMS (ESI) Calcd. for $C_{20}H_{16}NO$ $[M+H]^+$ 286.1226; Found 286.1234.

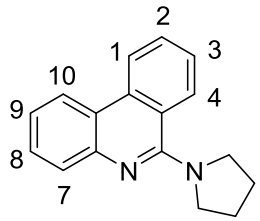
N,N-Diethylphenanthridin-6-amine (41g)



Prepared following general procedure F using *N*2,*N*2-diethyl-*N*2'-hydroxy-[1,1'-biphenyl]-2,2'-dicarboxamide (**39g**) (312 mg, 1.00 mmol, 1.00 eq.). Column chromatography (20% ethyl acetate in petrol) provided the *N*,*N*-diethylphenanthridin-6-amine (**41g**) (65 mg, 0.26 mmol, 26% yield) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (1 H, d, *J* = 8.2 Hz, **H10**), 8.45 (1 H, d, *J* = 8.2 Hz, **H1**), 8.27 (1 H, d, *J* = 8.2 Hz, **H7**), 7.98 (1 H, d, *J* = 7.8 Hz, **H4**), 7.77 (1 H, dd, *J* = 7.8, 7.8 Hz, **H9**), 7.66 (1 H, ddd, *J* = 8.2, 8.2, 1.4 Hz, **H3**), 7.63 (1 H, ddd, *J* = 8.2, 8.2, 1.4 Hz, **H8**), 7.49 (1 H, ddd, *J* = 7.8, 7.8, 0.9 Hz, **H2**), 3.60 (4 H, q, *J* = 7.3 Hz, $N(C\mathbf{H}_2CH_3)_2$), 1.32 (6 H, t, *J* = 7.3 Hz, $N(CH_2C\mathbf{H}_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.1 (C), 144.4 (C), 135.4 (C), 130.2 (CH), 129.0 (CH), 128.8 (CH), 127.1 (CH), 126.9 (CH), 124.6 (CH), 123.2 (C), 123.0 (CH), 122.7 (C), 122.2 (CH), 46.2 (2 × CH_2), 13.7 (2 × CH_3); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3071, 2969, 2931, 1611, 1581, 1566, 1461, 1349, 1288, 1230, 1071, 729; HRMS (ESI) Calcd. for $C_{17}H_{19}N_2$ $[M+H]^+$ 251.1543; Found 251.1554. Data agrees with literature values.[52]

6-(Pyrrolidin-1-yl)phenanthridine (41h)

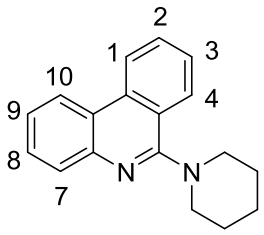


Prepared following general procedure F using *N*-hydroxy-2'-(pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-2-carboxamide (**39h**) (310 mg, 1.00 mmol, 1.00 eq.). Column chromatography (20% ethyl acetate in petrol) provided 6-(pyrrolidin-1-yl)phenanthridine (**41h**) (114 mg, 0.460 mmol, 46% yield) as a colourless solid.

M.p. (hexane/ CH_2Cl_2; colourless needles): 92 – 94 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (1 H, d, *J* = 8.2 Hz, **H10**), 8.36 (1 H, d, *J* = 7.8 Hz, **H1**), 8.29 (1 H, d, *J* = 8.2 Hz, **H7**), 7.79 (1 H, d, *J* = 7.8 Hz, **H4**), 7.74 (1 H, dd, *J* = 7.3, 7.3 Hz **H9**), 7.56 (1 H, dd, *J* = 7.6, 7.6 Hz, **H3**), 7.56 (1 H, dd, *J* = 7.6, 7.6 Hz, **H8**), 7.34 (1 H, dd, *J* = 7.3, 7.3 Hz, **H2**), 3.50 – 3.40 (4 H, m, $N(C\mathbf{H}_2CH_2)_2$), 1.96 – 1.80 (4 H, m, $N(CH_2C\mathbf{H}_2)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3 (C), 144.1 (C), 135.0 (C), 130.1 (CH), 128.7 (Ar**C**H), 128.5 (Ar**C**H), 126.9 (Ar**C**H), 126.7

(Ar**C**H), 124.5 (Ar**C**H), 122.7 (Ar**C**H), 122.6 (C), 122.0 (C), 121.9 (Ar**C**H), 52.6 (N(**C**$H_2CH_2)_2$), 26.3 (N(CH_2**C**$H_2)_2$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3078, 2981, 2930, 2871, 1618, 1589, 1377, 1314, 1109; HRMS (ESI) Calcd. for $C_{17}H_{17}N_2$ $[M+H]^+$ 249.1386; Found 249.1385.

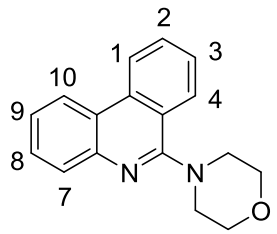
6-(Piperidin-1-yl)phenanthridine (41i)



Prepared following general procedure F using *N*-hydroxy-2'-(piperidine-1-carbonyl)-[1,1'-biphenyl]-2-carboxamide (**39i**) (324 mg, 1.00 mmol, 1.00 eq.). Column chromatography (20% ethyl acetate in petrol) provided 6-(piperidin-1-yl)phenanthridine (**41i**) (170 mg, 0.649 mmol, 65% yield) as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 86 – 87 °C (Lit.[52] 86 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (1 H, d, *J* = 8.2 Hz, **H10**), 8.42 (1 H, d, *J* = 7.8 Hz, **H1**), 8.23 (1 H, d, *J* = 8.2 Hz, **H7**), 7.97 (1 H, d, *J* = 8.2 Hz, **H4**), 7.75 (1 H, dd, *J* = 7.8, 7.8 Hz **H9**), 7.64 (1 H, dd, *J* = 6.9, 6.9 Hz, **H3**), 7.62 (1 H, dd, *J* = 7.8, 7.8 Hz, **H8**), 7.48 (1 H, dd, *J* = 7.6, 7.6 Hz, **H2**), 3.48 (4 H, t, *J* = 6.0 Hz, N(C**H**$_2CH_2)_2CH_2$), 1.90 (4 H, t, *J* = 6.0 Hz, N(CH_2C**H**$_2)_2CH_2$), 1.75 (2 H, quin, *J* = 6.0 Hz, N($CH_2CH_2)_2$C**H**$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 161.2 (C), 144.0 (C), 134.9 (C), 129.9 (Ar**C**H), 128.6 (Ar**C**H), 128.4 (Ar**C**H), 126.8 (Ar**C**H), 126.6 (Ar**C**H), 124.4 (Ar**C**H), 122.5 (Ar**C**H), 122.4 (C), 121.9 (C), 121.8 (Ar**C**H), 52.5 (2 × CH_2), 26.2 (2 × CH_2), 24.9 (CH_2); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3054, 2986 2938, 2849, 1611, 1582, 1567 1464, 1419, 1384, 1370, 1224, 1119, 1011; HRMS (ESI) Calcd. for $C_{18}H_{19}N_2$ $[M+H]^+$ 263.1543; Found 263.1549. Data agrees with literature values.[52]

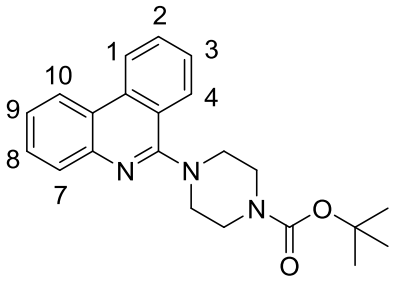
4-(Phenanthridin-6-yl)morpholine (41j)



Prepared following general procedure F using *N*-hydroxy-2'-(morpholine-1-carbonyl)-[1,1'-biphenyl]-2-carboxamide (**39j**) (326 mg, 1.00 mmol, 1.00 eq.). Column chromatography (20% ethyl acetate in petrol) provided 4-(phenanthridin-6-yl)morpholine (**41j**) (156 mg, 0.591 mmol, 59% yield) as a colourless solid.

M.p. (hexane/ CH_2Cl_2; colourless needles): 98 – 101 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (1 H, d, *J* = 8.2 Hz, **H10**), 8.44 (1 H, d, *J* = 8.2 Hz, **H1**), 8.22 (1 H, d, *J* = 8.2 Hz, **H7**), 7.97 (1 H, d, *J* = 8.2 Hz, **H4**), 7.78 (1 H, dd, *J* = 7.8, 7.8 Hz, **H9**), 7.65 (1 H, dd, *J* = 7.5, 7.5 Hz, **H3**), 7.63 (1 H, dd, *J* = 7.5, 7.5 Hz, **H8**), 7.51 (1 H, dd, *J* = 7.5, 7.5 Hz, **H2**), 4.02 (4 H, t, *J* = 4.6 Hz, N(C**H**$_2$C**H**$_2$)$_2$O), 3.53 (4 H, t, *J* = 4.6 Hz, N(C**H**$_2$C**H**$_2$)$_2$O); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.9 (C), 143.7 (C), 135.0 (C), 130.2 (Ar**C**H), 128.8 (Ar**C**H), 128.6 (Ar**C**H), 126.7 (Ar**C**H), 126.4 (Ar**C**H), 124.9 (Ar**C**H), 122.8 (Ar**C**H), 122.7 (C), 121.9 (Ar**C**H), 121.3 (C), 67.1 (2 × CH_2), 51.7 (2 × CH_2); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3069, 2962, 2915, 2850, 1611, 1581, 1455, 1382, 1363, 1222, 1116, 1020, 862; HRMS (ESI) Calcd. for $C_{17}H_{17}N_2O$ $[M+H]^+$ 265.1335; Found 265.1345.

tert-Butyl 4-(phenanthridin-6-yl)piperazine-1-carboxylate (41l)

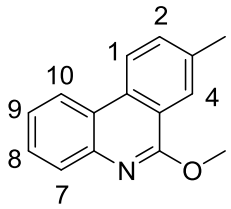


Prepared following general procedure F using *tert*-butyl 4-(2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carbonyl)piperazine-1-carboxylate (**39l**) (106 mg, 0.249 mmol, 1.00 eq.). Column chromatography (20% ethyl acetate in petrol) provided *tert*-butyl 4-(2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carbonyl)piperazine-1-carboxylate (**41l**) (46 mg, 0.13 mmol, 52% yield) as a colourless solid.

M.p. (hexane/ CH_2Cl_2; colourless needles): 155 – 158 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (1 H, d, *J* = 8.2 Hz, **H10**), 8.43 (1 H, d, *J* = 8.1 Hz, **H1**), 8.20 (1 H, d, *J* = 8.2 Hz, **H7**), 7.94

(1 H, br. s, **H4**), 7.79 (1 H, dd, *J* = 7.6, 7.6 Hz, **H9**), 7.66 – 7.60 (2 H, m, **H3** and **H8**), 7.51 (1 H, ddd, *J* = 8.1, 4.6, 0.5 Hz, **H2**), 3.77 – 3.70 (4 H, br. s, $N(CH_2C\mathbf{H}_2)_2N$), 3.47 (4 H, s, $N(C\mathbf{H}_2CH_2)_2N$), 1.51 (9H, s, NBoc); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9 (C), 155.0 (C), 143.7 (C), 135.0 (C), 130.3 (**C8**), 128.8 (**C2** or **C9**), 128.5 (**C1**), 126.8 (**C2** or **C9**), 126.3 (**C10**), 125.0 (**C3**), 122.8 (**C7**), 122.6 (C), 121.8 (C), 121.3 (**C4**), 79.9 (C), 51.1 ($N(CH_2\mathbf{C}H_2)_2N$), 43.4 ($N(\mathbf{C}H_2CH_2)_2N$), 28.5 ($C(\mathbf{C}H_3)_3$); IR (ν_{max}, thin film ($CDCl_3$), cm^{-1}) 3069, 2978, 2917, 2849, 1686, 1610, 1582, 1525, 1459, 1418, 1366, 1279, 1249, 1222, 1166, 1125, 1017; HRMS (ESI) Calcd. for $C_{22}H_{25}N_3O_2$ $[M+H]^+$ 364.2019; Found 364.2029.

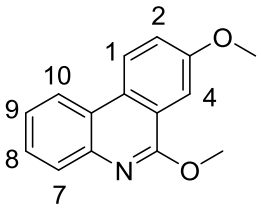
6-Methoxy-3-methylphenanthridine (41n)



Prepared following general procedure F using methyl 2'-(hydroxycarbamoyl)-4-methyl-[1,1'-biphenyl]-2-carboxylate (**39n**) (428 mg, 1.50 mmol, 1.00 eq.). Column chromatography (20% ethyl acetate in petrol) provided 6-methoxy-3-methylphenanthridine (**41n**) (207 mg, 0.928 mmol, 62% yield) as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 82 − 83 °C; ^{1}H NMR (501 MHz, $CDCl_3$) δ 8.40 (1 H, d, *J* = 8.4 Hz, **H1**), 8.39 (1 H, dd, *J* = 8.1, 1.3 Hz, **H10**), 8.16 (1 H, d, *J* = 1.9 Hz, **H4**), 7.91 (1 H, d, *J* = 8.0 Hz, **H7**), 7.64 (1 H, dd, *J* = 8.4, 1.9 Hz, **H2**), 7.60 (1 H, ddd, *J* = 8.3, 7.1, 1.4 Hz, **H8**), 7.48 (1 H, ddd, *J* = 8.3, 7.1, 1.4 Hz, **H9**) 4.25 (3 H, s, $COOC\mathbf{H}_3$), 2.57 (3 H, s, $ArC\mathbf{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1 (C), 157.8 (C), 137.3 (C), 132.6 (C), 132.6 (Ar**C**H), 130.0 (C), 128.3 (Ar**C**H), 127.6 (Ar**C**H), 126.2 (C), 124.6 (Ar**C**H), 124.4 (Ar**C**H), 121.9 (Ar**C**H), 121.8 (Ar**C**H), 53.7 ($O\mathbf{C}H_3$), 21.6 ($Ar\mathbf{C}H_3$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3061, 2956, 2919, 2857, 1587, 1539, 1471, 1445, 1360, 1322, 1230, 1094, 1035, 1003; HRMS (ESI) Calcd. for $C_{15}H_{14}NO$ $[M+H]^+$ 224.1069; Found 224.1070.

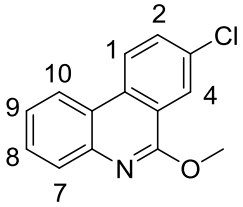
3,6-Dimethoxyphenanthridine (41o)



Prepared following general procedure F using methyl 2'-(hydroxycarbamoyl)-4-methoxy-[1,1'-biphenyl]-2-carboxylate (**39o**) (64 mg, 0.21 mmol, 1.00 eq.). Column chromatography (20% ethyl acetate in petrol) provided 3,6-dimethoxyphenanthridine (**41o**) (31 mg, 0.13 mmol, 62% yield) as a colourless solid.

M.p. (Petrol/ CH_2Cl_2; colourless needles): 83 – 85 °C; ^{1}H NMR (501 MHz, $CDCl_3$) δ 8.38 (1 H, d, *J* = 9.0 Hz, **H1**), 8.33 (1 H, dd, *J* = 8.1, 1.2 Hz, **H10**), 7.89 (1 H, dd, *J* = 8.1, 1.2 Hz, **H7**), 7.69 (1 H, d, *J* = 2.7 Hz, **H4**), 7.58 (1 H, ddd, *J* = 8.2, 7.1, 1.4 Hz, **H8**), 7.46 (1 H, ddd, *J* = 8.2, 7.1, 1.3 Hz, **H9**), 7.40 (1 H, dd, *J* = 9.0, 2.8 Hz, **H2**), 4.24 (3 H, s, OC**H**$_3$), 3.97 (3 H, s, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9 (C), 158.6 (C), 142.3 (C), 128.9 (C), 127.8 (Ar**C**H), 127.7 (Ar**C**H), 124.4 (Ar**C**H), 123.6 (Ar**C**H), 122.6 (C), 121.6 (Ar**C**H), 121.4 (Ar**C**H), 121.3 (C), 104.9 (Ar**C**H), 55.6 (O**C**H$_3$), 53.6 (O**C**H$_3$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3060, 2944, 2838, 1624, 1581, 1537, 1488, 1470, 1453, 1433, 1370, 1354, 1318, 1283, 1233, 1215, 1097; HRMS (ESI) Calcd. for $C_{15}H_{14}NO_2$ $[M+H]^+$ 240.1015; Found 240.1019.

3-Chloro-6-methoxyphenanthridine (41q)

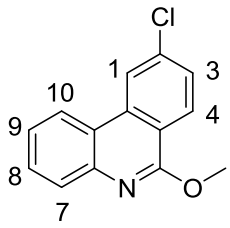


Prepared following general procedure F using methyl 4-chloro-2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (**39q**) (612 mg, 2.00 mmol, 1.00 eq.). Column chromatography (20% ethyl acetate in petrol) provided 3-chloro-6-methoxyphenanthridine (**41q**) (234 mg, 0.963 mmol, 48% yield) as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 100 – 101 °C; ^{1}H NMR (501 MHz, $CDCl_3$) δ 8.34 (1 H, d, *J* = 8.8 Hz, **H1**), 8.30 (1 H, dd, *J* = 8.1, 1.1 Hz, **H10**), 8.28 (1 H, d, *J* = 2.2 Hz, **H4**), 7.88 (1 H, dd, *J* = 8.2, 1.2 Hz, **H7**), 7.69 (1 H, dd, *J* = 8.8, 2.3 Hz, **H2**), 7.63 (1 H, ddd, *J* = 8.3, 7.1, 1.4 Hz, **H8**), 7.47 (1 H, ddd, *J* = 8.2, 7.1, 1.3 Hz, **H9**), 4.21 (3 H, s, OC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1 (C), 143.2 (C), 133.2 (C), 133.1 (C), 131.3 (**C2**), 129.0 (**C8**), 127.9 (**C7**), 124.7 (**C9**), 124.5 (**C4**), 123.6 (**C1**), 122.0 (C**10**), 121.8 (C), 121.0 (C), 53.7

(O**C**H_3); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3073, 2951, 2851, 1617, 1587, 1530, 1471, 1435, 1360, 1318, 1226, 1124, 1080; HRMS (ESI) Calcd. for $C_{14}H_{11}{}^{35}ClNO$ $[M+H]^+$ 244.0524; Found 244.0520.

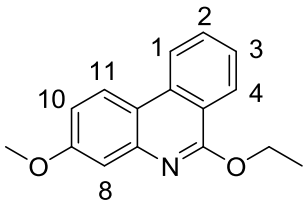
2-Chloro-6-methoxyphenanthridine (41p)



Prepared following general procedure F using methyl 5-chloro-2'-(hydroxycarbamoyl)-[1,1'-biphenyl]-2-carboxylate (**39p**) (367 mg, 1.20 mmol, 1.00 eq.). Column chromatography (20% ethyl acetate in petrol) provided 2-chloro-6-methoxyphenanthridine (**41p**) (138 mg, 0.568 mmol, 51% yield) as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 104 – 105 °C; ^{1}H NMR (501 MHz, $CDCl_3$) δ 8.39 (1 H, d, *J* = 1.9 Hz, **H1**), 8.26 (1 H, dd, *J* = 8.1, 0.8 Hz, **H10**), 8.23 (1 H, d, *J* = 8.6 Hz, **H4**), 7.87 (1 H, dd, *J* = 8.1, 0.8 Hz, **H7**), 7.63 (1 H, ddd, *J* = 8.2, 7.2, 1.3 Hz, **H8**), 7.54 (1 H, dd, *J* = 8.6, 2.0 Hz, **H3**), 7.46 (1 H, ddd, *J* = 8.2, 7.2, 1.3 Hz, **H9**), 4.21 (3 H, s, OC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7 (C), 143.8 (C), 137.3 (C), 136.1 (C), 129.4 (**C8**), 127.9 (**C7**), 127.7 (**C3**), 126.7 (**C4**), 124.6 (**C9**), 122.1 (**C10**), 121.6 (**C1**), 121.4 (C), 118.3 (C), 53.7 (O**C**H_3); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3069, 3002, 2950, 2848, 1614, 1588, 1487, 1472, 1429, 1356, 1337, 1314, 1231, 1182, 1102, 1022; HRMS (ESI) Calcd. for $C_{14}H_{11}{}^{35}ClNO$ $[M+H]^+$ 244.0524; Found 244.0520.

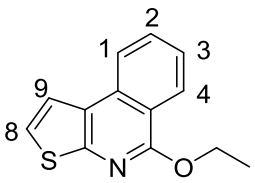
6-Ethoxy-9-methoxyphenanthridine (41r)



Prepared following general procedure F using ethyl 2'-(hydroxycarbamoyl)-4'-methoxy-[1,1'-biphenyl]-2-carboxylate (**39r**) (95 mg, 0.30 mmol, 1.00 eq.). Column chromatography (20% ethyl acetate in petrol) provided 6-ethoxy-9-methoxyphenanthridine (**41r**) (37 mg, 0.15 mmol, 49% yield) as a colourless amorphous solid.

^{1}H NMR (501 MHz, $CDCl_3$) δ 8.44 (1 H, d, *J* = 8.3 Hz, **H11**), 8.38 (1 H, dd, *J* = 8.1, 1.3 Hz, **H1** or **H4**), 7.82 (1 H, d, *J* = 2.8 Hz, **H8**), 7.80 – 7.77 (2 H, m, **H2** or **H3** and **H1** or **H4**), 7.63 (1 H, ddd, *J* = 8.1, 7.1, 1.1 Hz, **H2** or **H3**), 7.26 (1 H, dd, *J* = 8.3, 2.8 Hz, **H10**), 4.67 (2 H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 3.98 (3 H, s, O**C**H$_3$), 1.54 (3 H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5 (C), 156.6 (C), 134.4 (C), 130.5 (Ar**C**H), 129.0 (Ar**C**H), 127.2 (**C2** or **C3**), 125.1 (**C1** or **C4**), 123.7 (C), 123.1 (C), 121.8 (**C11**), 120.3 (C), 117.8 (**C9**), 104.1 (**C7**), 61.7 (O**C**H$_2$CH$_3$), 55.7 (O**C**H$_3$), 14.7 (OCH$_2$**C**H$_3$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3020, 2972, 2925, 2896, 2853, 1621, 1590, 1531, 1499, 1438, 1398, 1371, 1317, 1244, 1217, 1154, 1118, 1098, 1031; HRMS (ESI) Calcd. for $C_{16}H_{16}NO_2$ $[M+H]^+$ 254.1175; Found 254.1175.

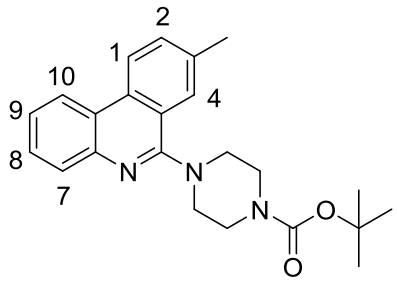
6-Ethoxythieno[2,3-c]isoquinoline (41s)



Prepared following general procedure F using ethyl 2-(2-(hydroxycarbamoyl)thiophen-3-yl)-5-benzoate (**39s**) (145 mg, 0.498 mmol, 1.00 eq.). Column chromatography (30% ethyl acetate in petrol) provided 6-ethoxythieno[2,3-c]isoquinoline (**41s**) (49 mg, 0.21 mmol, 43% yield) as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 68 – 69 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (1 H, d, *J* = 8.3 Hz, **H1 or H4**), 8.13 (1 H, d, *J* = 8.2 Hz, **H1** or **H4**), 7.76 (1 H, ddd, *J* = 8.2, 7.1, 1.2 Hz, **H2** or **H3**), 7.69 (1 H, d, *J* = 5.8 Hz, **H9**), 7.55 (1 H, ddd, *J* = 8.2, 7.1, 1.1 Hz, **H2** or **H3**), 7.31 (1 H, d, *J* = 5.9 Hz, **H8**), 4.65 (2 H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 1.54 (3 H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8 (C), 153.4 (C), 133.7 (C), 130.8 (**C2** or **C3**), 125.6 (**C2** or **C3**), 125.3 (**C1** or **C4**), 123.1 (C), 122.6 (**C1** or **C4**), 121.0 (**C8**), 119.7 (**C9**), 117.8 (C), 62.5 (O**C**H$_2$CH$_3$), 14.6 (OCH$_2$**C**H$_3$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3066, 2978, 2931, 2897, 1620, 1574, 1554, 1473, 1463, 1440, 1374, 1344, 1298, 1265, 1245, 1160, 1105, 1076, 1030; HRMS (ESI) Calcd. for $C_{13}H_{12}NOS$ $[M+H]^+$ 230.0634; Found 230.0632.

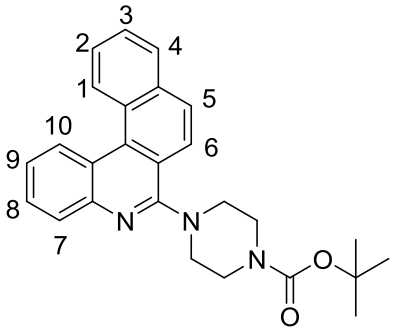
tert-Butyl 4-(3-methylphenanthridin-6-yl)piperazine-1-carboxylate (41t)



Prepared following general procedure F using 2' *tert*-butyl 4-(2'-(hydroxycarbamoyl)-4-methyl-[1,1'-biphenyl]-2-carbonyl)piperazine-1-carboxylate (**39t**) (416 mg, 0.952 mmol, 1.00 eq.). Column chromatography (20% ethyl acetate in petrol) provided tert-butyl 4-(3-methylphenanthridin-6-yl)piperazine-1-carboxylate (**41t**) (242 mg, 0.642 mmol, 68% yield) as an colourless amorphous solid.

^{1}H NMR (501 MHz, $CDCl_3$) δ 8.46 (1 H, d, *J* = 8.4 Hz, **H1**), 8.40 (1 H, dd, *J* = 8.1, 0.8 Hz, **H10**), 7.97 (1 H, s, **H4**), 7.91 (1 H, d, *J* = 8.0 Hz, **H7**), 7.63 – 7.58 (2 H, m, **H2** and **H8**), 7.48 (1 H, ddd, *J* = 8.1, 7.3, 1.1 Hz, **H9**), 3.77 – 3.71 (4 H, m, N(C**H**$_2$CH$_2$)$_2$N), 3.48 – 3.42 (4 H, m, N(CH$_2$C**H**$_2$)$_2$N), 2.58 (3 H, s, ArC**H**$_3$), 1.51 (9 H, s, N-Boc); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7 (C), 155.0 (C), 143.3 (C), 136.7 (C), 132.8 (C), 131.9 (Ar**C**H), 128.5 (Ar**C**H), 128.3 (Ar**C**H), 125.7 (Ar**C**H), 124.9 (Ar**C**H), 122.8 (C), 122.7 (Ar**C**H), 121.7 (Ar**C**H), 121.5 (C), 79.8 (C), 77.2 (Ar**C**H$_3$), 51.3 (N(**C**H$_2$CH$_2$)$_2$N), 43.7 (N(CH$_2$**C**H$_2$)$_2$N), 28.4 (C(**C**H$_3$)$_3$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3059, 2974, 2924, 2852, 1687, 1572, 1521, 1476, 1456, 1420, 1391, 1263, 1202, 1165, 1054, 1034, 998, 969, 829, 759, 735; HRMS (ESI) Calcd. for $C_{23}H_{28}N_3O_2$ $[M+H]^+$ 378.2176; Found 378.2176.

tert-Butyl 4-(benzo[k]phenanthridin-8-yl)piperazine-1-carboxylate (41m)



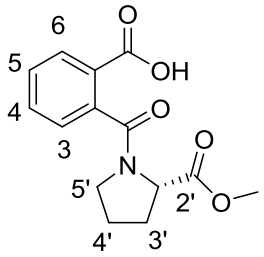
Prepared following general procedure F using *tert*-butyl 4-(1-(2-(hydroxycarbamoyl)phenyl)-2-naphthoyl)piperazine-1-carboxylate (**39m**) (90 mg, 0.20 mmol, 1.00 eq.). Column chromatography (20% ethyl acetate in petrol) provided *tert*-butyl 4-

(benzo[k]phenanthridin-8-yl)piperazine-1-carboxylate (**41m**) (22 mg, 0.05 mmol, 27% yield) as a colourless solid.

M.p. (hexane/ CH_2Cl_2 yellow needles): 181 – 184 °C; ^{1}H NMR (501 MHz, $CDCl_3$) δ 9.11 – 9.05 (1 H, m, Ar**H**), 8.89 (1 H, d, *J* = 8.3 Hz, Ar**H**), 8.13 (1 H, d, *J* = 8.8 Hz, Ar**H**), 8.08 – 8.00 (2 H, m, Ar**H**), 7.90 (1 H, d, *J* = 8.8 Hz, Ar**H**), 7.74 – 7.70 (2 H, m, Ar**H**), 7.68 (1 H, dd, *J* = 7.6, 7.6 Hz, Ar**H**), 7.53 (1 H, dd, *J* = 7.5, 7.5 Hz, Ar**H**), 3.78 – 3.69 (4 H, m, N(C**H**$_2$CH$_2$)$_2$N), 3.52 – 3.42 (4 H, m, N(C**H**$_2$CH$_2$)$_2$N), 1.52 (9 H, s, N-Boc); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7 (C), 155.0 (C), 145.6 (C), 134.7 (C), 134.3 (C), 129.6 (C), 128.8 (Ar**C**H), 128.4 (Ar**C**H), 128.4 (Ar**C**H), 128.3 (Ar**C**H), 127.6 (Ar**C**H), 127.4 (Ar**C**H), 126.9 (Ar**C**H), 126.5 (Ar**C**H), 124.7 (Ar**C**H), 123.0 (C), 122.7 (Ar**C**H), 120.1 (C), 79.9 (C), 51.3 (N(**C**H$_2$CH$_2$)$_2$N), 43.7 (N(CH$_2$**C**H$_2$)$_2$N), 28.5 (C(**C**H$_3$)$_3$); IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3055, 2972, 2924, 2854, 1696, 1569, 1478, 1459, 1422, 1365, 1247, 1170, 1123, 1080, 1025, 825, 760, 742; HRMS (ESI) Calcd. for $C_{26}H_{28}N_3O_2$ $[M+H]^+$ 414.2176; Found 414.2182.

6.5. Experimental Procedures from Chapter 4

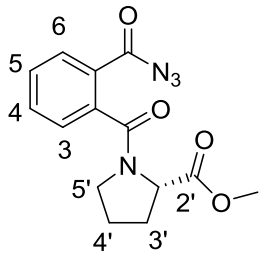
2-{[(2S)-2'-(Methoxycarbonyl)pyrrolidin-1-yl]carbonyl}benzoic acid (65)



Prepared following the literature procedure reported by Jarho *et al*.[89] To a stirred solution of L-proline methyl ester hydrochloride salt (4.00 g, 24.0 mmol, 1.10 eq.) in CH_2Cl_2 (75 mL, 0.32 M) at room temperature was added triethylamine (6.67 mL, 48.0 mmol, 2.20 eq.). After 10 minutes phthalic anhydride (3.23 g, 22.0 mmol, 1.00 eq.) was added portionwise and the reaction mixture left to stir at room temperature for 4 hours. The reaction mixture is then washed with 2 M HCl (2 × 50 mL) and the organics dried with brine and Na_2SO_4 before being concentrated under reduced pressure. Recrystallization from ethyl acetate and hexane provided 2-{[(2S)-2'-(methoxycarbonyl)pyrrolidin-1-yl]carbonyl}benzoic acid (**65**) (2.73 g, 9.85 mmol, 45% yield) as a colourless solid.

M.p. (hexane/ethyl acetate; colourless needles): 138 – 140 °C; $[\alpha]^{22}_D$ – 77.5 (*c* = 1.39, MeOH); ^{1}H NMR (501 MHz, $CDCl_3$) δ 10.65 (1 H, br. s, COO**H**) 8.05 (1 H, dd, *J* = 7.8, 1.2 Hz, **H3** or **H6**), 7.61 (1 H, ddd, *J* = 7.5, 7.5, 1.2 Hz, **H5** or **H4**), 7.47 (1 H, ddd, *J* = 7.8, 7.8 1.0 Hz, **H4** or **H5**), 7.43 (1 H, dd, *J* = 7.5, 1.0 Hz, **H6** or **H3**), 4.76 (1 H, dd, *J* = 8.7, 4.9 Hz, **H2'**), 3.80 (3 H, s, COOC**H**$_3$), 3.32 (1 H, ddd, *J* = 10.2, 7.1, 6.2 Hz, **H5'a**), 3.23 (1 H, dt, *J* = 10.2, 6.9 Hz, **H5'b**), 2.33 (1 H, ddd, *J* = 15.9, 12.8, 8.7 Hz, **H3'a**), 2.09 – 1.85 (3 H, m, **H4'** and **H3'b**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7 (**C**OOMe), 170.1 (**C**(O)N), 169.3 (**C**OOH), 138.8 (**C2**), 133.2 (**C5** or **C4**), 131.0 (**C3** or **C6**), 129.1 (**C4** or **C5**), 127.2 (**C6** or **C3**), 127.0 (**C1**), 58.6 (**C2'**), 52.4 (COO**C**H$_3$), 48.9 (**C5'**), 29.6 (**C3'**), 24.7 (**C4'**); IR (ν_{max}, solid, cm^{-1}) 2978, 2883, 2778, 2606, 2486, 1735, 1712, 1603, 1589, 1493, 1449, 1432, 1344, 1238, 1204, 1174, 1139, 1077, 1037, 993, 973, 927, 903, 852, 792, 773; HRMS (ESI) Calcd. for $C_{28}H_{30}N_2NaO_{10}$ $[2M+Na]^+$ 577.1793; Found 577.1797.

Methyl (2S)-1-[2-(azidocarbonyl)benzoyl]pyrrolidine-2'-carboxylate (70)

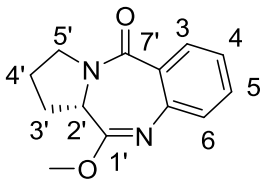


To a stirred solution of 2-{[(2S)-2'-(Methoxycarbonyl)pyrrolidin-1-yl]carbonyl}benzoic acid (**65**) (2.50 g, 9.00 mmol, 1.10 eq.) in acetone (23 mL, 0.36 M) and triethylamine (1.40 mL, 10.0 mmol, 1.20 eq.) at room temperature was added DPPA (1.77 mL, 8.20 mmol, 1.00 eq.) After 24 hours the reaction mixture was checked by IR for consumption of DPPA (2170 cm^{-1}) and formation of acyl azide (2136 cm^{-1}). When DPPA had been consumed the reaction mixture was concentrated under reduced pressure and the residue redissolved in ethyl acetate (20 mL), washed with saturated $NaHCO_3$ (aq) (2 × 30 mL) and dried with brine and Na_2SO_4. The combined organics were concentrated under reduced pressure before being purified by column chromatography (gradient 0 − 100% ethyl acetate) yielding methyl (2*S*)-1-[2-(azidocarbonyl)benzoyl]pyrrolidine-2-carboxylate (**70**) (882 mg, 2.90 mmol, 32% yield) as a colourless oil.

CAUTION: All azides should be treated as potentially explosive and were routinely prepared and handled behind a blast shield using glassware free from transition metal contamination. Residual sodium azide and DPPA present in the aqueous phase after workup were quenched by stirring with 20% aq. $NaNO_2$ (40% excess) followed by dropwise addition of 20% aq. H_2SO_4.

^{1}H NMR (501 MHz, $CDCl_3$) δ 7.97 (1 H, dd, *J* = 7.9, 1.1 Hz, **H3** or **H6**), 7.64 (1 H, ddd, *J* = 7.5, 7.5, 1.2 Hz, **H5** or **H4**), 7.47 (1 H, ddd, *J* = 7.9, 7.9, 4.0 Hz, **H4** or **H5**), 7.44 (1 H, dd, *J* = 7.5, 1.1 Hz, **H6** or **H3**), 4.76 (1 H, dd, *J* = 8.7, 4.9 Hz, **H2'**), 3.80 (3 H, s, COOC**H**$_3$), 3.32 (1 H, ddd, *J* = 10.0, 7.3, 6.0 Hz, **H5'a**), 3.19 (1 H, dt, *J* = 10.0, 6.8 Hz, **H5'b**), 2.34 (1 H, ddd, *J* = 15.7, 12.7, 7.5 Hz, **H3'a**), 2.12 – 1.85 (3 H, m, **H4'** and **H3'b**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6 (**C**OOMe), 171.8 (**C**(O)N), 168.8 (**C**ON_3), 139.0 (**C2**), 134.1 (**C5** or **C4**), 130.3 (**C3** or **C6**), 129.1 (**C4** or **C5**), 127.7 (**C6** or **C3**), 127.4 (**C1**), 58.4 (**C2'**), 52.3 (COO**C**H_3), 48.7 (**C5'**), 29.6 (**C3'**), 24.8 (**C4'**); IR (ν_{max}, neat, cm^{-1}) 2954, 2880, 2135 (CON_3), 1741, 1693, 1637, 1491, 1446, 1415, 1363, 1238, 1173, 1092, 1036, 987, 924, 863, 779; HRMS (ESI) Calcd. for $C_{28}H_{28}N_8NaO_8$ $[2M+Na]^+$ 627.1922; Found 627.1919.

(11aS)-11-Methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (58a)

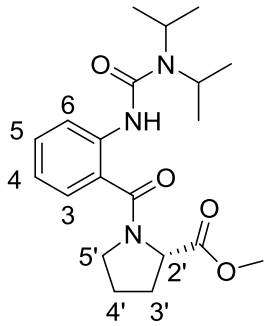


Prepared by a modification of procedure of A. McGonagle for the catalytic aza-Wittig reaction of phenanthridines.[52] A solution of methyl (2*S*)-1-[2-(azidocarbonyl)benzoyl]pyrrolidine-2-carboxylate (**70**) (604 mg, 2.00 mmol, 1.00 eq.) in anhydrous toluene (10 mL, 0.20 M) was heated to reflux. The reaction was monitored by IR following the disappearance of the azide (2133 cm^{-1}) and the formation of isocyanate (2269 cm^{-1}). Upon complete consumption of the acyl azide a solution of phospholene oxide (**25**) (19 mg, 0.10 mmol, 5 mol%) in anhydrous toluene (14 mL, 0.007 M) was added to the solution of isocyanate. The reaction mixture was stirred at reflux under nitrogen and monitored by LC-MS to follow the disappearance of the isocyanate and associated products. After 48 hours the crude reaction mixture was concentrated under reduced pressure. Purification by flash chromatography (gradient of 0 − 50% ethyl acetate in hexane) provided (11a*S*)-11-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (**58a**) (457 mg, 1.99 mmol, 99% yield) as a colourless solid.

(11a*S*)-11-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (**58a**) could also be prepared with 10 mol% of phospholene oxide (**25**) (38 mg, 0.20 mmol, 10 mol%) with 24 hours of stirring, yielding the desired product (**58a**) (397 mg, 173 mmol, 87% yield) as a colourless solid.

M.p. (hexane/dichloromethane; colourless cubes): 201 – 203 °C; $[\alpha]^{22}_{D}$ + 663.0 (*c* = 0.47 g/ml, MeOH) (Lit: $[\alpha]^{25}_{D}$ = +537.8, c = 1.41, EtOH); ^{1}H NMR (501 MHz, $CDCl_3$) δ 7.98 (1 H, dd, *J* = 7.9, 1.6 Hz, **H3** or **H6**), 7.45 (1 H, ddd, *J* = 8.1, 7.7, 1.6 Hz, **H5** or **H4**), 7.20 (1 H, ddd, *J* = 7.9, 7.7, 1.2 Hz, **H4** or **H5**), 7.16 (1 H, dd, *J* = 8.1, 1.2 Hz, **H6**), 3.99 (1 H, dd, *J* = 5.8, 2.3 Hz, **H2'**), 3.90 (3 H, s, OC**H**$_3$), 3.90 – 3.84 (1 H, m, **H5'a**), 3.57 – 3.48 (1 H, m, **H5'b**), 2.68 – 2.57 (1 H, m, **H3'a**), 2.09 – 1.97 (3 H, m, **H4'** and **H3'b**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0 (**C1'**), 162.5 (**C7'**), 144.3 (**C1**), 131.7 (**C5** or **C4**), 130.4 (**C3** or **C6**), 127.6 (**C7'**), 126.6 (**C6** or **C3**), 124.3 (**C4** or **C5**), 54.7 (O**C**H$_3$ or **C2'**), 54.6 (O**C**H$_3$ or **C2'**), 47.0 (**C5'**), 26.7 (**C3'**), 24.1 (**C4'**); IR (ν_{max}, solid, cm^{-1}) 2994, 2951, 2877, 1645, 1631, 1616, 1599, 1458, 1411, 1320, 762; HRMS (ESI) Calcd. for $C_{13}H_{14}N_2O_2$ $[M+H]^+$ 231.1128; Found 231.1129. Data agrees with literature values.[19]

Methyl (2S)-1-{2-[(diisopropylcarbamoyl)amino]benzoyl}pyrrolidine-2-carboxylate (62)



Conditions A: To a stirred solution of 2-{[(2S)-2'-(methoxycarbonyl)pyrrolidin-1-yl]carbonyl} benzoic acid (**65**) (2.77 g, 10.0 mmol, 1.10 eq.) in anhydrous acetone (23 mL, 0.39 M) and triethylamine (1.50 mL, 11.0 mmol, 1.20 eq.) at room temperature was added DPPA (1.94 mL, 9.00 mmol, 1.00 eq.) After 24 hours the reaction mixture was checked by IR for consumption of DPPA (2170 cm^{-1}) and formation of acyl azide (2136 cm^{-1}). When DPPA had been consumed the reaction mixture was concentrated under reduced pressure and redissolved in ethyl acetate (30 mL), washed with saturated $NaHCO_3$(aq) (2 × 30 mL) and dried with brine and Na_2SO_4. The combined organics were concentrated under reduced pressure at room temperature. The residue was redissolved in anhydrous toluene (150 mL, 0.06 M) and heated to reflux (110 °C) for half an hour before being cooled to 60 °C. To the stirred solution of isocyanate, diisopropylamine (2.56 mL, 18.0 mmol, 2.00 eq.) was added. After a further two hours at 60 °C the isocyanate had been consumed and the reaction mixture was partitioned between ethyl acetate (100 mL) and 2 M HCl (2 × 100 mL). The combined organics were dried with brine and Na_2SO_4 and were concentrated under reduced pressure. Purification by flash chromatography, (gradient of 0 − 50% ethyl acetate in hexane) provided methyl (2*S*)-1-{2-[(diisopropylcarbamoyl)amino]benzoyl}pyrrolidine-2-carboxylate (**62**) (2.13 g, 5.70 mmol, 63% yield) as a colourless crystalline solid.

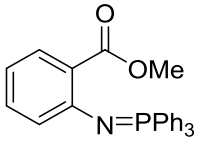
Alternatively, methyl (2*S*)-1-{2-[(diisopropylcarbamoyl)amino]benzoyl}pyrrolidine-2-carboxylate (**62**) could be produced on large scale using continuous flow methodology developed by Ley *et al.*[90] Prepared using a Vaportech R4 system as the flow and heating system. A solution of 2-{[(2S)-2-(methoxycarbonyl)piperidin-1-yl]carbonyl}benzoic acid (**65**) (12.2 g, 44.0 mmol, 1.1 eq.), triethylamine (11.2 mL, 80.0 mmol, 2.0 eq.) and diisopropylamine (17.1 mL, 120 mmol, 3.0 eq.) in anhydrous acetonitrile (200 mL, 0.2 M) was prepared and placed in a jar with screw lid, adapted for use with the flow system (channel 1). This solution was mixed with a solution of DPPA (8.6 mL, 40 mmol, 1.0 eq.) in acetonitrile (200 mL, 0.2 M) placed in a jar with screw lid, adapted for use with the flow system (channel 2) using a T-mixing piece (individual flow rate 0.25 mL min^{-1} each). The combined streams were directed to a 10 mL CFC coil heated to 120 °C (retention time of 16 min). Upon

completion the crude reaction mixture was collected and tested for consumption of DPPA (2170 cm^{-1}) and acyl azide (2136 cm^{-1}) before being concentrated under reduced pressure. The reaction mixture was redissolved in ethyl acetate (600 mL) and washed with 2M HCl (2 × 200 mL) and saturated $NaHCO_3$(aq) (200 mL), dried with brine and Na_2SO_4 and concentrated under reduced pressures. Trituration with diethyl ether gave methyl (2*S*)-1-{2-[(diisopropylcarbamoyl)amino]benzoyl}pyrrolidine-2-carboxylate (**62**) (9.41 g, 25.1 mmol, 63% yield) as colourless needles.

M.p. (hexane/ethyl acetate; colourless cubes): 101 – 103 °C; $[\alpha]^{22}_D$ – 50.5 (*c* = 1.33, MeOH); ^{1}H NMR (501 MHz, $CDCl_3$) δ 8.67 (1 H, s, ArN**H**C(O)NiPr$_2$), 8.10 (1 H, d, *J* = 8.3 Hz, **H3** or **H6**), 7.35 – 7.26 (2 H, m, **H3** or **H6** and **H4** or **H5**), 6.89 (1 H, dd, *J* = 7.4,7.4 Hz, **H4** or **H5**), 4.56 (1 H, dd, *J* = 8.5, 4.0 Hz, **H2'**), 3.84 (2 H, dt, *J* = 13.4, 6.7 Hz, N(C**H**C$_2$H$_6$)$_2$), 3.69 (3 H, s, COOC**H**$_3$), 3.68 – 3.54 (2 H, m, **H5'**), 2.32 – 2.18 (1 H, m, **H3'a**), 2.02 – 1.90 (2 H, m, **H3'b** and **H4'a**), 1.87 – 1.76 (1 H, m, **H4'b**), 1.28 (12 H, d, *J* = 6.9 Hz, N(CHC$_2$**H**$_6$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4 (**C**OOMe), 169.6 (Ar**C**(O)N), 154.3 (N**C**(O)N^{i}Pr$_2$), 139.4 (**C1**), 131.1 (**C5**), 127.4 (**C3**), 122.4 (**C2**), 121.8 (**C6**), 120.4 (**C4**), 59.1 (**C2'**), 52.1 (O**C**H$_3$), 50.5 (**C5'**), 46.0 (N**C**H(CH$_3$)$_2$), 29.3 (**C3'**), 25.2 (**C4'**), 21.1 (NCH(**C**H$_3$)$_2$); IR (ν_{max}, solid, cm^{-1}) 3308, 2967, 2935, 2878, 1743, 1659, 1580, 1508, 1413, 1301, 1149, 762; HRMS (ESI) Calcd. for $C_{20}H_{30}N_3O_4$ $[M+H]^+$ 376.2231; Found 376.2240.

6.6. Experimental Procedures from Chapter 5

Methyl 2-((triphenylphosphoranylidene)amino) benzoate (84).[105]



Methyl 2-((triphenylphosphoranylidene)amino) benzoate (**84**) was prepared following the procedure of Wamhoff *et al.*[105] A mixture of hexachloroethane (2.37 g, 10.0 mmol, 1.00 eq.) and triphenylphosphine (3.15 g, 12.0 mmol, 1.20 eq.) in CH_2Cl_2 (30 mL, 0.33 M) was stirred at room temperature for 5 minutes before triethylamine (2.78 mL, 20.0 mmol, 2.00 eq.) and methyl anthranilate (1.29 mL, 10.0 mmol, 1.00 eq.) were added. After 20 hours the reaction was poured onto distilled water (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. Trituration with EtOH gave the desired product (**84**) (3.60 g, 8.76 mmol, 88% yield) as a colourless solid.

M.p. (CH_2Cl_2/hexane, colourless needles): 163 − 166 °C (lit.[104]: 164 − 166 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (6 H, m, PPh_3**H**), 7.67 (1 H, ddd, *J* = 7.4, 2.2, 2.2 Hz, Ar**H**), 7.58 − 7.43 (9H, m, PPh_3**H**), 6.97 (1 H, ddd, *J* = 7.4, 7.4, 1.6 Hz, Ar**H**), 6.65 (1 H, dd, *J* = 7.4, 7.4 Hz, Ar**H**), 6.54 (1 H, d, *J* = 7.4 Hz, Ar**H**), 3.91 (3 H, s, CO_2C**H**$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.7 (d, *J* = 1.3 Hz, C), 151.4 (C), 132.8 (d, *J* = 9.9 Hz, Ar**C**H), 132.2 (d, *J* = 9.9 Hz, C), 131.8 (d, *J* = 2.8 Hz, Ar**C**H), 131.5 (Ar**C**H), 131.1 (d, *J* = 1.6 Hz, Ar**C**H) 128.7 (d, *J* = 12.1 Hz, Ar**C**H), 125.9 (C), 123.4 (d, *J* = 10.7 Hz, Ar**C**H), 116.6 (Ar**C**H), 51.1 (O**C**H$_3$); ^{31}P NMR (300 MHz, $CDCl_3$) δ 0.98; IR (ν_{max}, thin film (CH_2Cl_2), cm^{-1}) 3061, 1692, 1591, 1475, 1356, 1295, 1249, 1120; Data agrees with literature values.[104]

Standard protocol for the catalytic aza-enyne metathesis cascade reaction.

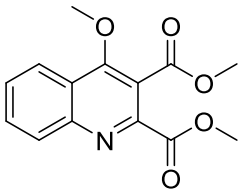
To a stirred mixture of DMAD (3.00 mmol, 3.00 eq.) and 3-methyl-1-phenyl-2-phospholene oxide (**25**) (20 mg, 0.10 mmol, 10 mol%) in refluxing toluene (0.5 mL, 2 M) was added a solution of isocyanato ester (**63**) (1.00 mmol, 1.0 eq.) in toluene (2 or 4 mL, 0.50 or 0.25 M) over a set number of hours (6, 7 or 16 hours). After the slow addition the reaction was left until 18 hours had passed. A ^{1}H NMR spectrum of the crude reaction mixture was taken to work out the ratio of products. In some cases the reaction was purified using an SCX column which was first equilibrated with methanol and then flushed through with diethyl ether to

remove the formed urea, methanol to remove DMAD based impurities then finally flushed through with 1N ammonia in methanol solution to remove the quinoline product. If further purification was required column chromatography and recrystallization from ethyl acetate and hexanes was used.

Standard protocol for the stoichiometric aza-enyne metathesis cascade reaction.

To a stirred mixture of DMAD (3.00 mmol, 3.00 eq.) in toluene (2.5 mL, 0.40 M) was added iminophosphorane (**84**) (1.00 mmol, 1.00 eq.). The reaction was then heated to reflux. A ^{1}H NMR of the crude reaction mixture was taken to work out the ratio of products. The reaction was purified using an SCX column which was first equilibrated with methanol and then flushed through with diethyl ether to remove the formed urea, methanol to remove DMAD based impurities then finally flushed through with 1N ammonia in methanol solution to remove the quinoline and the imine product. If further purification was required column chromatography (50% ethyl acetate in hexanes) was used.

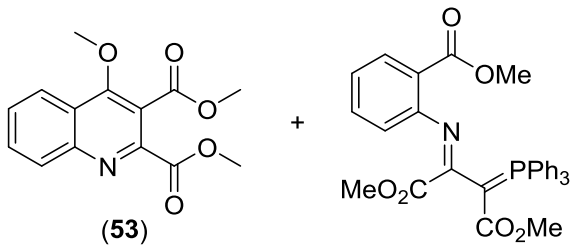
2,3-Quinolinedicarboxylic acid, 4-methoxy-, 2,3-dimethyl ester (79).[113]



Prepared following the general procedure for catalytic aza-enyne metathesis using slow addition of 2-isocyanato-benzoic acid, methyl ester (**63**) (177 mg 1.00 mmol, 1.00 eq.) in toluene (0.5 mL, 2 M) added over 16 hours to a solution of dimethyl acetylenedicarboxylate (368 μL, 3.00 mmol, 3.00 eq.) and phospholene oxide (**25**) (20 mg, 0.10 mmol, 10 mol%) in refluxing toluene (4.0 mL, 0.25 M). Purification using an SCX column (eluting with 1M NH_3 in MeOH) and subsequent column chromatography (50% ethyl acetate in hexane) gave the highest isolated yield of the quinoline product, 2,3-quinolinedicarboxylic acid, 4-methoxy-, 2,3-dimethyl ester, (**79**) (69 mg, 0.25 mmol, 25% yield).

M.p. (hexane/ethyl acetate; colourless needles): 60 − 61 °C (lit.[113]: 64 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 − 8.19 (2 H, m, Ar**H**), 7.86 − 7.80 (1 H, m, Ar**H**), 7.71 − 7.66 (1 H, m, Ar**H**), 4.17 (3 H, s, OC**H**$_3$), 4.05 (3 H, s, CO_2C**H**$_3$), 4.02 (3 H, s, CO_2C**H**$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.8 (C), 165.4 (C), 162.1 (C), 148.5 (C), 147.0 (C), 131.5 (CH), 130.4 (CH), 128.7 (CH), 124.0 (C), 122.5 (CH), 117.5 (C), 62.5 (CH_3), 53.5 (OCH_3), 53.2 (OCH_3); IR(ν_{max}, solid ,cm^{-1}) 3022, 2988, 2947, 2861, 1723, 1716, 1616, 1580, 1564, 1498, 1360, 1257, 1236, 1214, 1045, 967, 770; HRMS (ESI) Calcd. for $C_{14}H_{13}NNaO_5$ $[M+Na]^+$ 298.0686; Found 298.0682. Data agrees with literature values.[113]

2,3-Quinolinedicarboxylic acid, 4-methoxy-, 2,3-dimethyl ester (79) and 2-(2-methoxycarbonylphenylimino)-3-(triphenyl-λ5-phosphanylidene)-succinic acid dimethyl ester (85)



Prepared following the general procedure for stoichiometric aza-enyne metathesis using dimethyl acetylenedicarboxylate (368 μL, 3.00 mmol, 3.00 eq.) and methyl 2-((triphenylphosphoranylidene)amino)benzoate (**84**) (411 mg, 1.00 mmol, 1.00 eq.). Purification using an SCX column (eluting with 1 M NH3 in MeOH) and subsequent column chromatography (50% ethyl acetate in hexane) gave the isolated desired quinoline product (**79**) (65 mg, 0.24 mmol, 24% yield) as a brown solid and the imine 2-(2-methoxycarbonylphenylimino)-3-(triphenyl-λ5-phosphanylidene)-succinic acid dimethyl ester (**85**) (203 mg, 0.367 mmol, 37% yield) as a brown solid.

2,3-Quinolinedicarboxylic acid, 4-methoxy-, 2,3-dimethyl ester (**79**): M.p. (hexane/ethyl acetate; colourless needles): 60 − 61 °C (lit.[113]: 64 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 − 8.19 (2 H, m, Ar**H**), 7.86 − 7.80 (1 H, m, Ar**H**), 7.71 − 7.66 (1 H, m, Ar**H**), 4.17 (3 H, s, OC**H**$_3$), 4.05 (3 H, s, CO_2C**H**$_3$), 4.02 (3 H, s, CO_2C**H**$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.8 (C), 165.4 (C), 162.1 (C), 148.5 (C), 147.0 (C), 131.5 (CH), 130.4 (CH), 128.7 (CH), 124.0 (C), 122.5 (CH), 117.5 (C), 62.5 (CH_3), 53.5 (OCH_3), 53.2 (OCH_3); IR(ν_{max}, solid ,cm^{-1}) 3022, 2988, 2947, 2861, 1723, 1716, 1616, 1580, 1564, 1498, 1360, 1257, 1236, 1214, 1045, 967,

770; HRMS (ESI) Calcd. for $C_{14}H_{13}NNaO_5$ $[M+Na]^+$ 298.0686; Found 298.0682. Data agrees with literature values.[113]

2-(2-methoxycarbonylphenylimino)-3-(triphenyl-λ5-phosphanylidene)-succinic acid dimethyl ester (**85**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 − 7.87 (6 H, m, PPh_3**H**), 7.67 (1 H, dd, *J* = 7.7, 0.8 Hz, Ar**H**), 7.59 − 7.47 (9 H, m, PPh_3**H**), 7.00 (1 H, dd, *J* = 7.3, 7.3 Hz, Ar**H**), 6.82 (1 H, dd, *J* = 7.3, 7.3 Hz, Ar**H**), 5.60 (1 H, d, *J* = 7.7 Hz, Ar**H**), 3.83 (3 H, s, $CO_2C\mathbf{H}_3$), 3.49 (3 H, s, $CO_2C\mathbf{H}_3$), 3.28 (3 H, s, $CO_2C\mathbf{H}_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.5 (d, *J* = 14.8 Hz, C), 167.0 (C), 166.0 (d, *J* = 13.2 Hz, C), 159.2 (d, *J* = 7.1 Hz, C), 151.2 (C), 134.2 (d, *J* = 10.0 Hz, Ar**C**H), 132.0 (d, *J* = 2.9 Hz, Ar**C**H), 131.7 (Ar**C**H), 130.3 (Ar**C**H), 128.5 (d, *J* = 12.6 Hz, Ar**C**H), 126.3 (C), 125.1 (C), 122.3 (C), 121.8 (Ar**C**H), 120.7 (Ar**C**H) 51.7 (OCH_3), 51.2 (OCH_3), 49.8 (OCH_3); ^{31}P NMR (300 MHz, $CDCl_3$) δ 17.7 (s); IR(ν_{max}, thin film (CH_2Cl_2),cm^{-1}) 3063, 2993, 2949, 1728 , 1651 , 1645 , 1581, 1563, 1484, 1435, 1359, 1298, 1271,1219,1197, 1172, 1106, 1082; HRMS (ESI) Calcd. for $C_{32}H_{29}NO_6P$ $[M+H]^+$ 554.1727; Found 554.1717.

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