Development of novel synthetic methodologies using boron Lewis acids

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I. List of abbreviations

ACN	Acetonitrile
AN	Acceptor number
BCB	Bicyclobutane
Bn	Benzyl
CAN	Cerium ammonium nitrate
CIE	Commission internationale de l'e´ clairage
CPA	Chiral phosphoric acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
DIPEA	*N*,*N*-Diisopropylethylamine
DMPO	5,5-Dimethyl-1-pyrroline-*N*-oxide
DMSO	Dimethyl sulfoxide
d.r.	Diastereomeric ratio
E1cB	Elimination unimolecular conjugate base
EDA	Ethyl diazoacetate
EDG	Electron donating group
ee	Enantiomeric excess
eLA	Effective Lewis acidity
EWG	Electron withdrawing group
FG	Functional group
FIA	Fluoride ion affinity

FLP	Frustrated Lewis pair
FMO	Frontier molecular orbital
FRP	Frustrated radical pair
GEI	Global electrophilicity index
gLA	Global Lewis acidity
HIA	Hydrogen ion affinity
HOMO	Highest occupied molecular orbital
HSAB	Hard soft acids and bases
iLA	Intrinsic Lewis acidity
LUMO	Lowest unoccupied molecular orbital
MO	Molecular orbital
MS	Molecular sieves
MTO	Methyl trioxorhenium
NMR	Nuclear magnetic resonance
o.n.	Overnight
p-ABSA	*p*-Acetamidobenzensulfonyl azide
PG	Protecting group
PMP	*p*-Methoxyphenyl
PTFE	Polytetrafluoroethylene
PTSA	*p*-Toluensulfonic acid
REG	Relative energy gradient
RNR	Ribonucleotide reductase
r.t.	Room temperature
SOMO	Singly occupied molecular orbital
TBAF	Tetra butylammonium fluoride

TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TBS	*tert*-Butyldimethylsilyl
TEA	Triethylamine
TEPO	Triethyl phosphine oxide
TFT	Trifluorotoluene
THP	Tetrahydropyran-
TIPS	Triisopropylsilyl
TES	Triethylsilane
TLC	Thin layer chromatography
TMAF	Tetramethylammonium fluoride
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
TS	Transition state
UHP	Urea hydrogen peroxide
VEGFR	Vascular endothelial growing factor receptor

II. Acknowledgements

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III. Abstract

The work described in this thesis concerns the use of Lewis acidic boron-based catalysts as a tool for the development of novel reaction methodologies, with a major focus on the use of $B(C_6F_5)_3$. Chapter 1 serves as a general introduction to the field of catalysis, and the impact that Lewis acids have on it. Paramount for the utilisation of Lewis acids is knowing their relative strength, hence a discussion of the available methods for assessing the Lewis acidity is also included. Chapter 2 discusses the studies undertaken for the development of a *N*-functionalisation protocol of indoles using isocyanates. After a topic-related introduction, the research work will be presented. Crucially, it has been shown that the commercially available BCl_3 outperforms $B(C_6F_5)_3$. Chapter 3 highlights the ability of $B(C_6F_5)_3$ to catalyse either a [3+2] dipolar cycloaddition of vinyl diazo esters or Mukaiyama-Mannich addition of silyl enol diazo esters by activating nitrones. Hence, after another topic-related introduction, a discussion regarding the optimisation studies, substrate scope and further functionalisation of the products will be presented. Chapter 4 builds up from the knowledge developed in Chapter 3 to establish a nitro-Mannich reaction between silyl nitronates and nitrones, again catalysed by $B(C_6F_5)_3$. After a final topic-related introduction, a discussion of the reaction optimisation, scope and further functionalisations will be presented. Finally, preliminary results of a cooperative Frustrated Lewis Pair approach will be also discussed.

IV. List of publications

1. **M. G. Guerzoni**, Y. van Ingen, E. Richards, R. L. Melen, An un-forgotten classic: the nitro-Mannich reaction between nitrones and silyl nitronates catalysed by $B(C_6F_5)_3$, *Chem. Sci.*, **2024**, 15, 2648–2654;
2. M. Pramanik, **M. G. Guerzoni**, E. Richards, R. L. Melen, Recent advance in Asymmetric Catalysis using p-block Elements, *Angew. Chem. Int. Ed.,* **2023**, e202316461;
3. K. Stefkova,† **M. G. Guerzoni**,† Y. van Ingen, E. Richards, R. L. Melen, $B(C_6F_5)_3$ Catalyzed Diastereoselective and Divergent Reactions of Vinyldiazo Esters with Nitrones: Synthesis of Highly Functionalized Diazo Reagents, *Org. Lett.,* **2023**, 25, 500–505;
4. **M. G. Guerzoni**, A. Dasgupta, E. Richards, R. L. Melen, Enantioselective applications of frustrated Lewis pairs in organic synthesis, *Chem. Catal.*, **2022**, 2, 2865–2875;
5. A. Dasgupta, Y. van Ingen, **M. G. Guerzoni**, K. Farshadfar, J. M. Rawson, E. Richards, A. Ariafard, R. L. Melen, Lewis Acid Assisted Brønsted Acid Catalysed Decarbonylation of Isocyanates: A Combined DFT and Experimental Study, *Chem. Eur. J.,* **2022**, 28, e20220142;
6. A. Dasgupta,† **M. G. Guerzoni**,† N. Alotaibi, Y. van Ingen, K. Farshadfar, E. Richards, A. Ariafard, R. L . Melen, Chemo- and regio-selective amidation of indoles with isocyanates using borane Lewis acids, *Catal. Sci. Technol.*, **2022**, 12, 5982–5990;
7. **M. G. Guerzoni**, Y. van Ingen, R. L. Melen, Recent applications of fluorinated arylborane derivatives, *Advances in Organometallic Chemistry,* 78, **2022**, 133–187.

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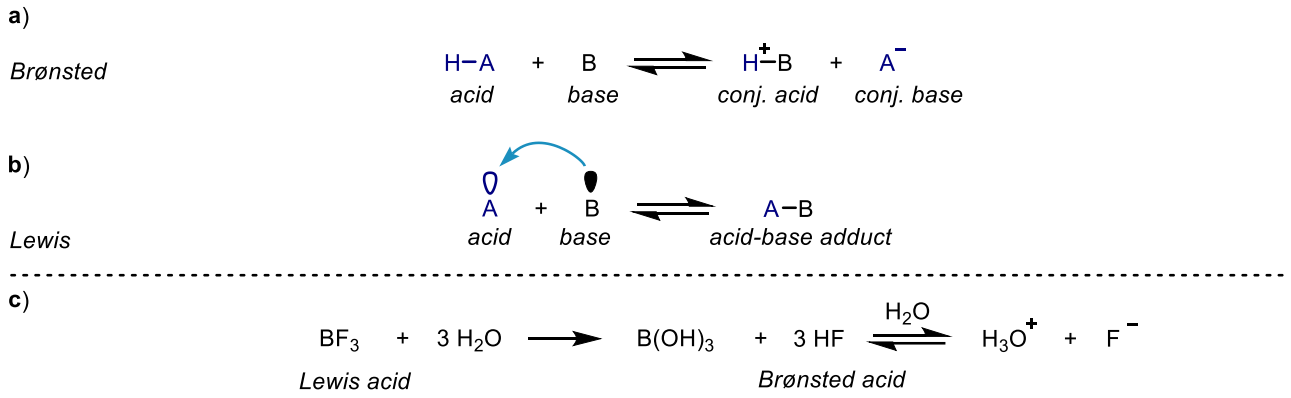
1. General introduction

Catalysis is the branch of chemistry that concerns the use of a molecule to lower the activation energy of a given reaction. This term was first coined by Berzelius in 1835 but it was not until 60 years later that its definition was expressed by Ostwald, who stated "*Catalysis is the acceleration of a slow chemical process by the presence of a foreign material*".[1,2] Nowadays catalysis possesses a pivotal position both in academia and in industry, and this can be exemplified by several Nobel prizes given to a chemical process which entails a catalytic event.[3–6] Indeed, modern society would not be sustained without the help of catalysis, since at least 80% of all manufactured products are made through a catalytic process.[7] By the earlier definition, a catalyst is a "*foreign material*" that does not directly participate in the reaction and is not consumed nor changed. Instead, it facilitates the intra- or intermolecular reaction by providing a lower energy pathway. Traditionally, the most important catalysts were derived from a transition metal (TM), owing to the extended *d*-orbitals that allow access to several oxidation states.[8] Additionally, the prompt ability to interact with specifically designed ligands still renders nowadays transition-metal catalysis the most important tool to promote chemical transformations.[9] However, despite the enormous development that these have witnessed, striving for a greener and more sustainable society has led to focusing on alternatives to transition metals. In this regard, main group elements have been subjected to intense studies in the last 20 years, and have been recently regarded as alternatives to transition metals.[10] Within the main group elements, molecules bearing atoms belonging to the *p*-block specifically have gained increased interest among the scientific community as novel catalysts.[11–13] The elements are all united by the fact that their valence electrons are located in the *p*-orbitals, and this feature makes them very good Lewis bases (LBs) (when the orbital is filled) or Lewis acids (LAs) (when the orbital is empty). For example, nitrogen is a Lewis base and it is the blueprint element in organocatalysis, a methodology employing small chiral amines to induce asymmetry, which was recently recognised with a Nobel Prize.[6] Conversely, the empty *p*-orbital arising in boron-containing molecules makes them eager to

accept electron density from another molecule, thus rendering them Lewis acids,[14,15] similarly to other elements such as Bi, Sc, Al, Zn, Ti and many others.[16]

1.1. Lewis acid catalysis

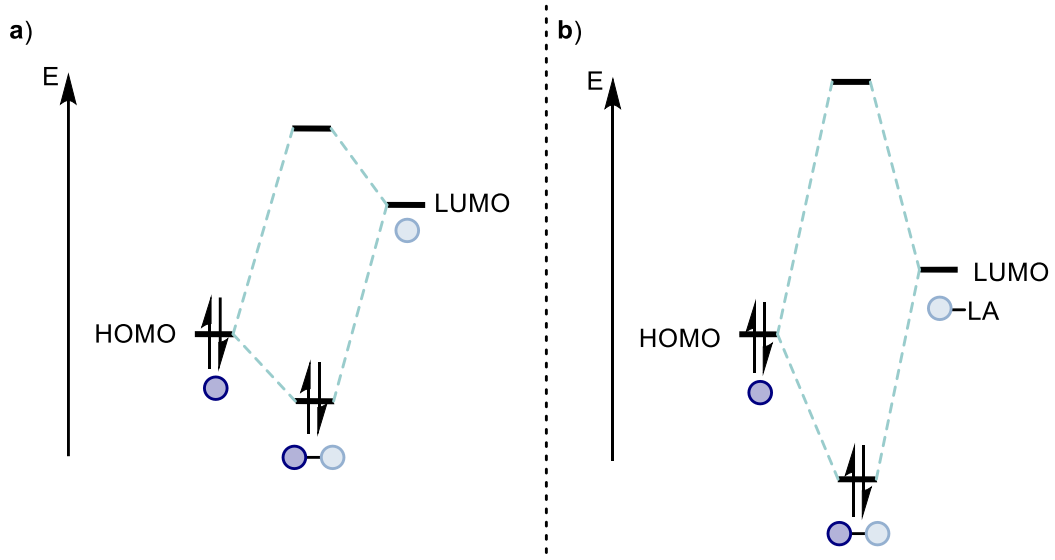
The Lewis acid-base theory was formulated by Gilbert Newton Lewis in 1923,[17] and was an extension of Brønsted and Lowry's acid-base theory, which was somewhat limited to the concept that acids liberate H^+ in solution (Scheme 1.1, a). This theory could explain why HCl behaved as an acid in solution but did not explain why BF_3 behaved as an acid as well. On the other hand, Lewis' theory states that an acid is a molecule capable of accepting electron density from a base, and thus is only dependent on the electronic structure of the molecule, rather than its chemical composition (Scheme 1.1, b). In this way, BF_3 can also be regarded as a (Lewis) acid. It should be however noted that one theory does not exclude the other. For example, BF_3 is not strictly a Brønsted acid (BA). However, its decomposition in water forms HF, which can protonate water and therefore acts as a Brønsted acid (Scheme 1.1, c).



Scheme 1.1. **a)** Brønsted and Lowry's acid-base theory. **b)** Lewis acid-base theory. **c)** BF_3 can be considered a Lewis acid, which acts as a Brønsted acid in water.

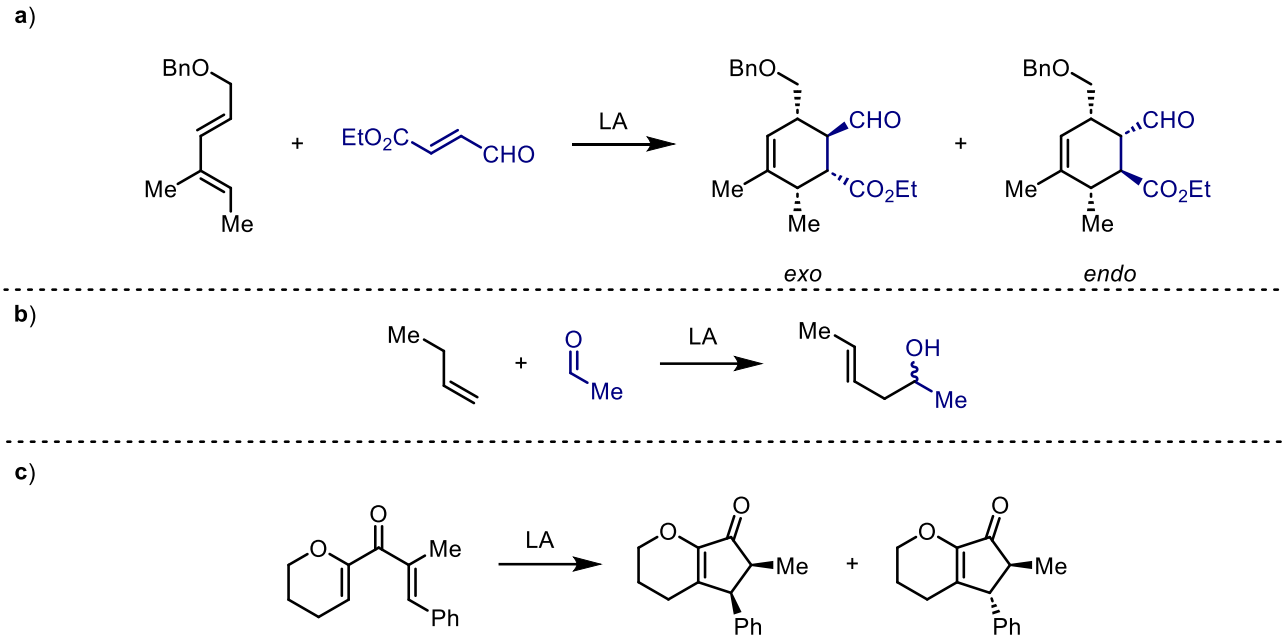
In the realm of catalysis, Lewis acids still suffer a wider and more general application compared to other types of catalysts, mainly because of their propensity to establish strong acid-base adducts with the product.[18] This feature translates into the requirement of carrying out an additional step of work-

up which leads to the decomposition of the catalyst that rarely can be recovered. Additionally, catalyst poisoning by the possible strong adduct formation sometimes requires the use of more than catalytic amounts of acid, if not stoichiometric amounts.[18] Thus, the term Lewis acid *catalysis* can sometimes be misleading if the full definition of catalysis is taken into account.[18] Still, the notion that a catalyst decreases the activation energy by lowering the energy gap between the Frontier Molecular Orbitals (FMOs) of the reactants is especially true when considering Lewis acids,[1] hence why the term *LUMO-lowering catalysis* is sometimes used (Scheme 1.2).[19,20]



Scheme 1.2. Schematic representation of the effect of Lewis acids on the LUMO of a general reactant. **a**) without Lewis acid. **b**) with Lewis acid.

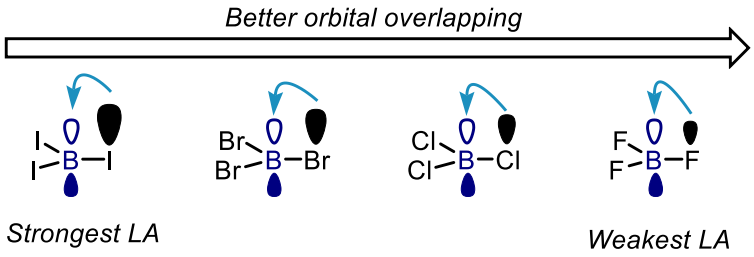
Interestingly, this paradigm has been recently challenged by proposing that the Lewis acid polarises the π orbital of the reactant, resulting in a decreased Pauli repulsion in the transition state rather than just lowering the energy of the lowest unoccupied molecular orbital (LUMO).[21] Thus, it has been suggested to use a more accurate description such as *Pauli repulsion-lowering catalysis*.[21] Independently of the terminology used, the utility of Lewis acids as catalysts is nevertheless undeniable since these are regularly used in reactions that are fundamental pillars of organic chemistry, such as Diels-Alder,[22,23] ene reactions[24,25] and many others (Scheme 1.3).[26–28]



Scheme 1.3. Examples of reactions catalysed by Lewis acids. **a**) Diels-Alder reaction **b**) Ene-alder reaction. **c**) Nazarov cyclisation.

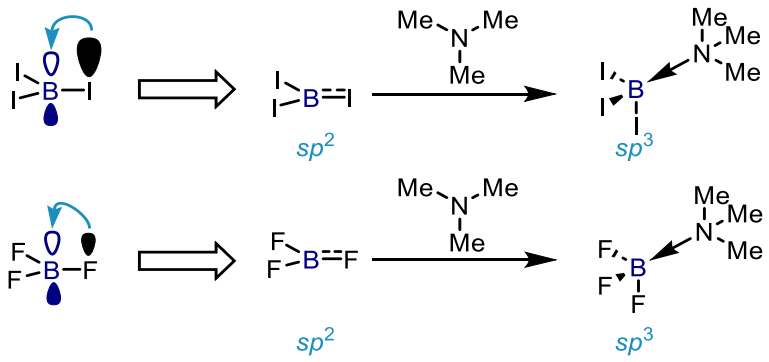
The most employed Lewis acid catalysts embed in their structure the first element of the *p*-block, boron. Boron is the 5th element of the periodic table and it is defined as a metalloid: an atom that possesses features between metals and non-metals.[29,30] For instance, it bears more valence orbitals than valence electrons, a feature commonly observed in transition metals. However, it does not form a metallic crystal lattice, due to its small atomic radius, low electron affinity and high ionisation energy.[30] Its relative abundance is 10 ppm in the Earth's crust, which renders it the second most abundant group 13 element after aluminium.[31] It also holds the 38th position as the most abundant element in the Earth's crust,[31] and this is attributable to its "unfavourable" formation, which occurs during cosmic ray spallation rather than because of supernovae nucleosynthesis.[32] Nevertheless, its wide applicability and utility stem from it being recently envisioned as a metallomimetic element, which could be used to achieve transition metal-like reactivity.[29] Additionally, in the form of the cheap and widely available boron trihalides such as BF_3, BCl_3, BBr_3 and BI_3, it can exploited as a strong Lewis acid due to the empty *p*-orbital.

Intuitively, the presence of an electronegative atom bound to the boron should enhance its inherent Lewis acidity, thus the Lewis acidity order for the boron trihalides should be BF_3>BCl_3>BBr_3>BI_3, if only this simplistic view is considered. However, the Lewis acidity trend for these species has been observed to be of the order BF_3<BCl_3<BBr_3<BI_3, and it has been later attributed, in the case of fluorine, to a more efficient π interaction between the lone pair of the fluorine with the *p*-orbital of boron, which in turn hampers its acidity to a greater extent compared to the other halogens (Scheme 1.4).[33]



Scheme 1.4. The Lewis acid trend of boron halides in terms of orbital overlapping.

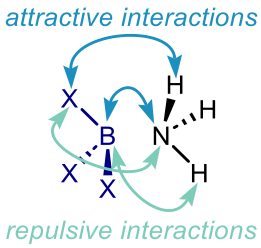
In detail, it has been widely accepted that the optimal π overlap in the case of BF_3 gives a partial double bond character to the B–F bond, which would also explain the planar nature of the molecule. When BF_3 reacts with a Lewis base such as Me_3N, it must undergo pyramidalisation which makes it adopt a sp^3 geometry. The enthalpy of this hybridisation is directly proportional to the strength of the π B–F bond, hence making more energetically demanding the hybridisation of BF_3 compared to, for example, BI_3 (Scheme 1.5).[33,34]



Scheme 1.5. Lewis acidity strength of BF_3 and BI_3 in terms of π-back donation of the halide.

Nevertheless, this consideration has been recently challenged and instead, an explanation that accounts for electrostatic aspects has been proposed (*vide infra*).[35] The variability of Lewis acid magnitude depending on the considered parameters highlights a fundamental aspect of Lewis acids: unlike Brønsted acids, whose acidity is measurable based on H^+ ion concentration in solution defying a pK_a scale, Lewis acids lack a straightforward method for gauging their acidity.[36] A discussion on the methods to determine Lewis acidity will be described in more detail in Chapter 1.2.

The reason why the Lewis acidity strength of the boron trihalides follows the order $BF_3<BCl_3<BBr_3<BI_3$ has been recently unveiled by a density functional theory (DFT)-guided relative energy gradient (REG) analysis from the group of Popelier.[35] In short, it has been demonstrated that exchange-correlation terms are not sufficient to explain the energy profile pathway when the formation of a complex of the type $X_3B–NH_3$ (where X = halogen) is calculated. Since it is known that π-back donation and hyperconjugation effects affect the exchange-correlation terms,[37] these cannot be used to rank the boron trihalides' acidities.[35] On the contrary, it is the interplay between the attractive and repulsive energies between the substituents on the boron and the interacting Lewis base that account for the observed order of acidity (Scheme 1.6).



Scheme 1.6. Schematic representation of the electrostatic interactions underpinning the Lewis acidity strength of boron trihalides.

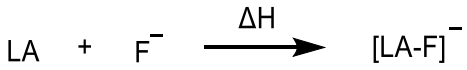
Intuitively, the higher the electronegativity of the halide is, the greater the negative charge on it will be. This can in principle increase the magnitude of the attractive interactions between the boron and nitrogen centre, however, it will also increase the repulsive interaction between the halogen and the nitrogen, as well as the repulsion between the boron and the hydrogens (Scheme 1.6).[35] On a side

note is the explanation for the highest acidity observed in the case of BH_3, which has been ascribed mainly to the energy required for its pyramidalisation, which is almost half compared to all the other boron trihalides.[35]

Given that H_2O is an exceptionally good Lewis base, it is not surprising that most of the reactions using Lewis acids must be carried out under strictly anhydrous conditions, although some reports using water-tolerant Lewis acids are known.[38] This feature is particularly true in the case of the above-mentioned boron trihalides, which are readily hydrolysed upon exposure to moisture. Therefore, in the search for new boron-based Lewis acids, researchers around the world envisioned replacing the labile B–X bond with a stronger B–C bond, where the carbon atom is part of an aromatic moiety. However, to maintain their Lewis acidity, the presence of electron-withdrawing groups (EWGs) was required, thus leading to the development of the perfluoro(halo)aryl boranes. Their most important exponent, trispentafluorophenyl borane $B(C_6F_5)_3$, will be introduced in Chapter 1.3.

1.2. Methods to determine the Lewis acidity

Before introducing the chemistry of $B(C_6F_5)_3$, it is important to describe the methods used to assess the Lewis acidity, given that a pK_a scale cannot be used for Lewis acids. However, the establishment of a unified scale of all the Lewis acids is far from being trivial, since three distinctions can arise depending on the underlying principles of the scale used.[39,40] As proposed by Greb,[40] Lewis acids can be categorised according to their *global* Lewis Acidity (gLA), which takes into account the thermodynamic energy associated with the LA-LB adduct formation. To assess this, computational methods such as Hydride Ion Affinity (HIA)[41,42] or Fluoride Ion Affinity (FIA)[43,44] have been mainly exploited. For example, FIA is defined as the negative reaction enthalpy of the binding between a fluoride anion and a given Lewis acid in the gas phase and has been demonstrated to be a valuable tool to assess the gLA (Scheme 1.7), especially if used in a multidimensional (that is, considering different metrics) approach (Eqn 1.1).[45,46]



$$FIA = -\Delta H \qquad \text{(Eqn. 1.1)}$$

Scheme 1.7. The FIA method.

The reliance of this method on the small F^- minimises steric repulsion and hampers second-order effects such as π-back bonding, charge transfer, or dispersion interactions. This renders the FIA the method of choice for the *in silico* prediction of Lewis acidity.[44] However, the non-trivial assessment of FIA *via* experimental techniques impedes a benchmarking of the computed values.[44] Additionally, the calculation is usually carried out in the gas phase with charged species, which would be strongly affected by solvation energies in an experimental setting.[44] Nevertheless, reports considering the solvation effect have also been published.[44] To overcome some of the limitations expressed above, the group of Christe introduced in their DFT calculation the experimental ionisation of carbonyl fluoride, which could be used as a reference in a (pseudo-)isodesmic reaction.[42,47] However, since F^- is a hard base according to the hard and soft acids and bases (HSAB) theory,[48] its use to calculate the Lewis acid strength can be deceptive in the case of soft acids.[36]

Another interesting *in silico* method for the determination of the *intrinsic* Lewis acidity (iLA), which considers the free uncoordinated Lewis acid,[40] was developed by Stephan, where the Global Electrophilicity Index (GEI) was introduced.[40,49] This concept, which was first disclosed by Parr in 1999,[50] lays its foundations on a chemically intuitive concept: a more electronegative and softer molecule will have a greater propensity to take up electrons, which means, that it is more Lewis acidic.[49] The GEI value (ω), expressed in eV, can be calculated using the Eqn. 1.2.

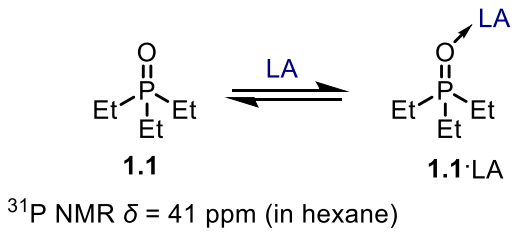
$$\omega = {\mu^2}/{2\eta} \qquad \text{(Eqn. 1.2)}$$

$$\mu = \frac{1}{2}(E_{HOMO} + E_{LUMO}) \qquad \text{(Eqn. 1.3)}$$

$$\eta = E_{HOMO} - E_{LUMO} \qquad \text{(Eqn. 1.4)}$$

Where μ is the chemical potential (Eqn. 1.3) and η is the chemical hardness (Eqn. 1.4), defined as resistance to deformation or change.[51] Thus, by knowing the energies of the FMO of the Lewis acid, it is possible to assess its Lewis acidity, without relying on the use of a base and with minimal computational demand.[49,52]

Lewis acids can also be categorised according to their *effective* Lewis acidity (eLA), which is a direct measurement of the changes in the physicochemical properties of a set Lewis base probe upon coordination with the Lewis acid. In this context, given their operational ease of use, the Gutmann-Beckett (GB)[53,54] or Childs[55] methods are the most widely employed. The former relies on the measurement of the ^{31}P NMR spectroscopic shift of the Lewis base probe triethylphosphine oxide **1.1** (TEPO) upon complexation and uses Eqn 1.5 to assess the Lewis acidity (Scheme 1.8). The new phosphorus peak corresponding to the adduct **1.1**·LA can be used to derive the Acceptor Number (AN) value through Eqn 1.5, which can exploited to create a relative scale of different Lewis acids (Table 1.1).[36]



1.1 **1.1**·LA

^{31}P NMR δ = 41 ppm (in hexane)

$$AN = 2.21 \times (\delta_{\mathbf{1.1}\cdot LA} - 41) \qquad \text{(Eqn. 1.5)}$$

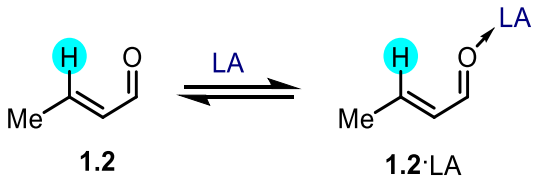
Scheme 1.8. The Gutmann-Beckett method.

Table 1.1. Literature known values of the AN for different Lewis acids.

Lewis acid	**Acceptor Number (AN)**[36]
$B(C_6F_5)_3$	76–82
BPh_3	55–69.6

$B(2,6\text{-}F_2C_6H_3)_3$	69.8
$B(3,5\text{-}(CF_3)_2C_6H_3)_3$	83.8
BH_3	76.9–93
BF_3	79.6–84
BCl_3	95.9–105.4
BBr_3	109.3
BI_3	114.9

On the other hand, the Childs method considers the ^{1}H NMR spectroscopic shift of the β-hydrogen of crotonaldehyde **1.2** upon coordination with the Lewis acid and uses Eqn 1.6 (Scheme 1.9). In this case, the scale is relative to the adduct with BBr_3, which has been given a value of 1.[55]



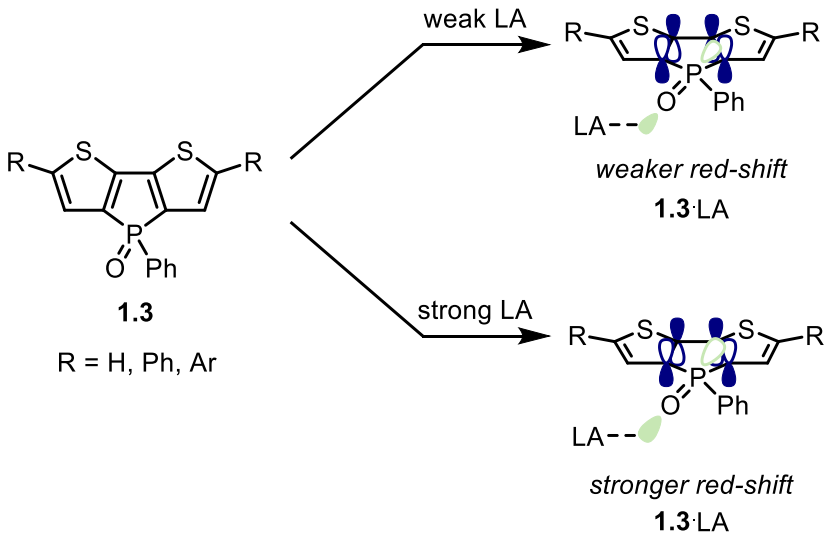
1.2 **1.2**·LA

$$Rel.\,Acidity = \frac{(\delta_{\mathbf{1.2}\cdot LA} - \delta_{\mathbf{1.2}})}{(\delta_{\mathbf{1.2}\cdot BBr_3} - \delta_{\mathbf{1.2}})} \qquad \text{(Eqn. 1.6)}$$

Scheme 1.9. The Childs method.

As shown in Table 1.1, the AN for a given Lewis acid can vary greatly, and this has been attributed to the interplay of different features.[40] In particular, the K_{eq} established upon complexation between the Lewis acid and TEPO determines the percentage of bound TEPO, which affects the measured Δδ ^{31}P. This association equilibrium depends on several experimental conditions such as solubility, temperature, concentration and solvation effects.[40] Moreover, the relative Lewis acidity can be different for different Lewis bases, such as in the case of BF_3 which establishes stronger adducts with ethers and weaker with thioethers, contrary to BH_3.[56] This behaviour can be rationalised with Pearson's HSAB principle.[36,48] Clearly, having a standardised set-up across different laboratories is

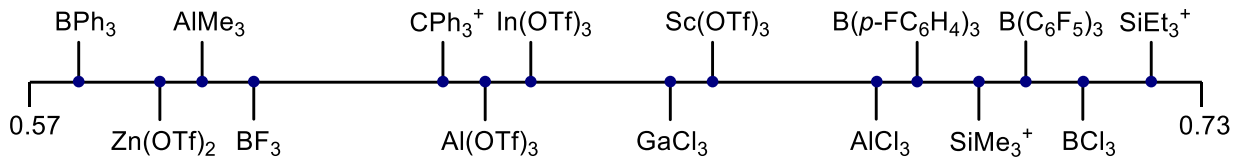
impossible, thus translating into a high degree of variability in the AN number. In addition to this aspect, London dispersions, NMR shielding contributions and deformation energies can add up to the features affecting the AN, rendering the correlation especially between gLA and eLA non-trivial.[40] Very recently it has been proposed to assess the Lewis acidity of a given molecule using a fluorescent probe **1.3** which, upon formation of the adduct, changes its emission spectra (Scheme 1.10).[57]



Scheme 1.10. The use of the phosphorus-based probe **1.3** to assess the Lewis acidity.

In detail, Baumgartner and Caputo demonstrated that the interaction of a Lewis acid with the σ*-orbital of a dithienophosphole probe **1.3** has a direct impact on the π*-system, which leads to a bathochromic shift directly proportional to the strength of the Lewis acid. However, the measurement of the emission spectra of the new adduct is not enough to assess the Lewis acidity, since it has been demonstrated that the chromaticity depends on several aspects such as hue, saturation, and brightness.[57] Therefore, by plotting the data obtained from the emission spectra into a Commission internationale de l'e´ clairage (CIE) diagram it is possible to rank all the Lewis acidity as a function of their chromaticity rather than just their absorption wavelength. Crucially, by plotting the chromaticity of the complex **1.3**·LA against three distinct probes (R = H, Ph, Ar), it is possible to obtain values independent of the single probe, in sharp contrast to the GB test which relies on only

TEPO.[57] In this way, a scale of the strength of different Lewis acids can be extrapolated and expressed in terms of Lewis Acid Units (LAU) (Scheme 1.11).



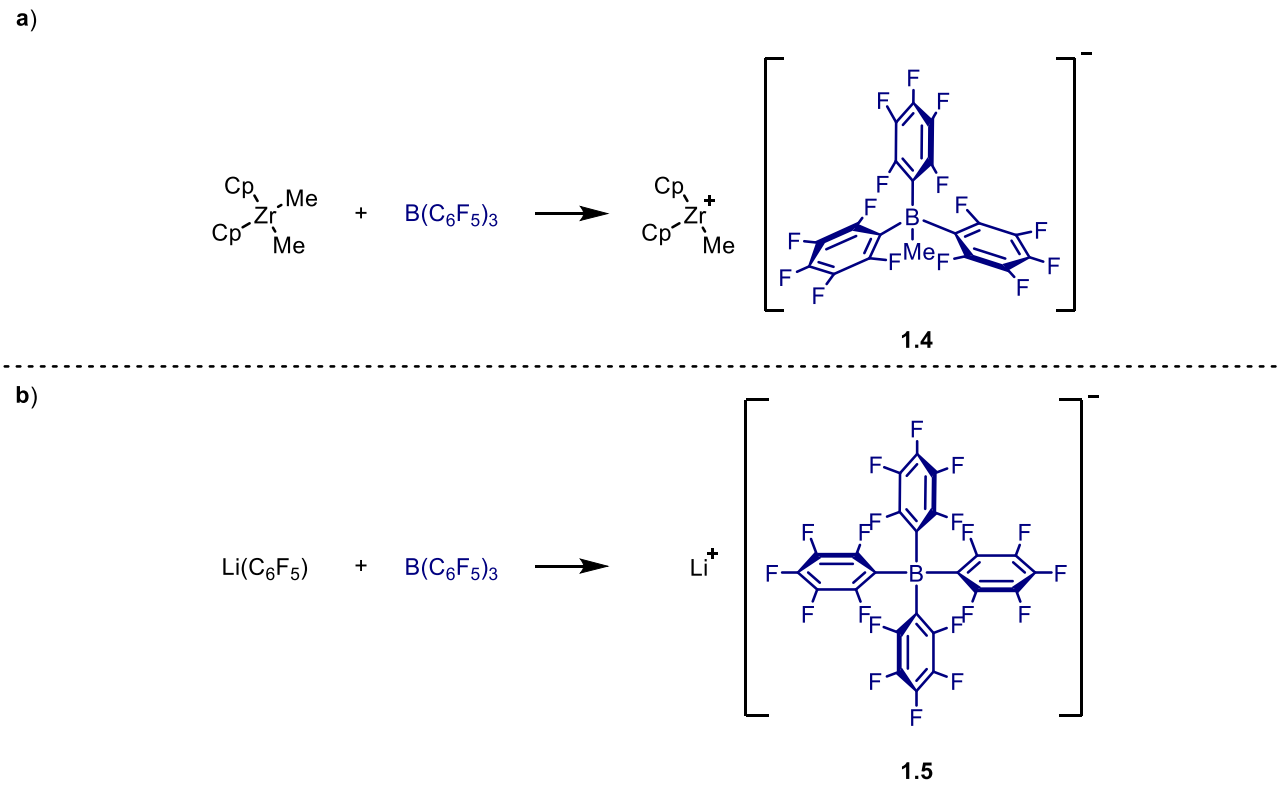
Scheme 1.11. Lewis acidity order (not to scale) of different Lewis acids according to their photophysical properties expressed in LAU.

In subsequent work, the same group greatly expanded the scope to more than 50 Lewis acids.[58] Our group also developed a similar approach to establish luminescent adducts between Lewis acids and imines as vapochromic sensors.[59]

Despite the several advancements in the field, since multiple phenomena contribute to the overall acidity, multidimensionality remains an important limitation when assessing the strength of a wide array of Lewis acids.[40] Thus, a unified Lewis acidity scale remains elusive to date.[60,61]

1.3. Trispentafluorophenyl borane and other perfluoroaryl boranes

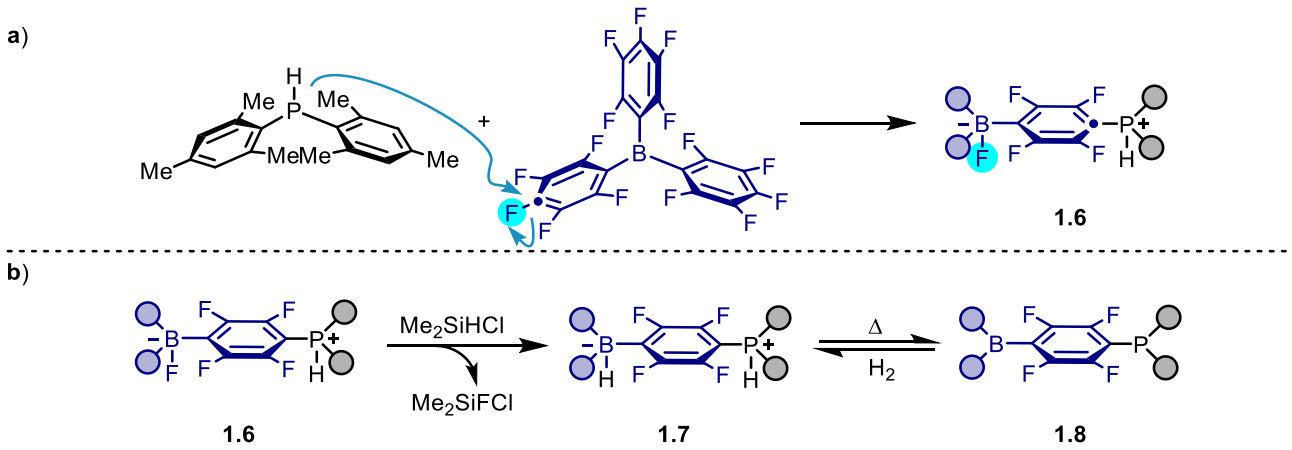
As mentioned earlier, the requirement of finding novel boron-based Lewis acids with improved hydrolytic stability led to the discovery of the class of perfluoroaryl boranes, where the most eminent example is trispentafluorophenyl borane $B(C_6F_5)_3$. This compound, first synthesised in 1963 by Massey, Park and Stone, has been heavily used as a co-catalyst or activator in polymer chemistry.[62–65] Indeed, the strong acidity of the tricoordinate boron atom makes it useful to abstract anionic ligands from metal-based pre-catalysts while forming a sterically encumbered counter anion **1.4**. The resulting metal-based catalyst can then catalyse olefin polymerisations (Scheme 1.12, a).[63,66] These species can also be synthesised *ad hoc* by reacting the Lewis acid with the desired organolithium compound,[67] giving rise to weakly-coordinating ligands such as **1.5**, commonly referred to as BAr_F ligands (Scheme 1.12, b).



Scheme 1.12. **a**) Use of $B(C_6F_5)_3$ as an activator for olefin polymerisation. **b**) Synthesis of BAr_F ligand **1.5** derived from $B(C_6F_5)_3$.

During the writing of this thesis, the first report of a tetrahedral neptunium (V) complex stabilised by **1.5** has been published, highlighting the central role that the BAr_F ligands can have in stabilising exotic chemical entities.[68]

Despite the importance of BAr_F ligands, which are extensively used nowadays to tame the reactivity of highly electrophilic and oxidising cations,[69] the importance of $B(C_6F_5)_3$ is mainly connected to the field of Frustrated Lewis Pair (FLP) chemistry, in which the seminal report from Stephan opened up the avenue for transition metal-free hydrogen activation (Scheme 1.13).[70]

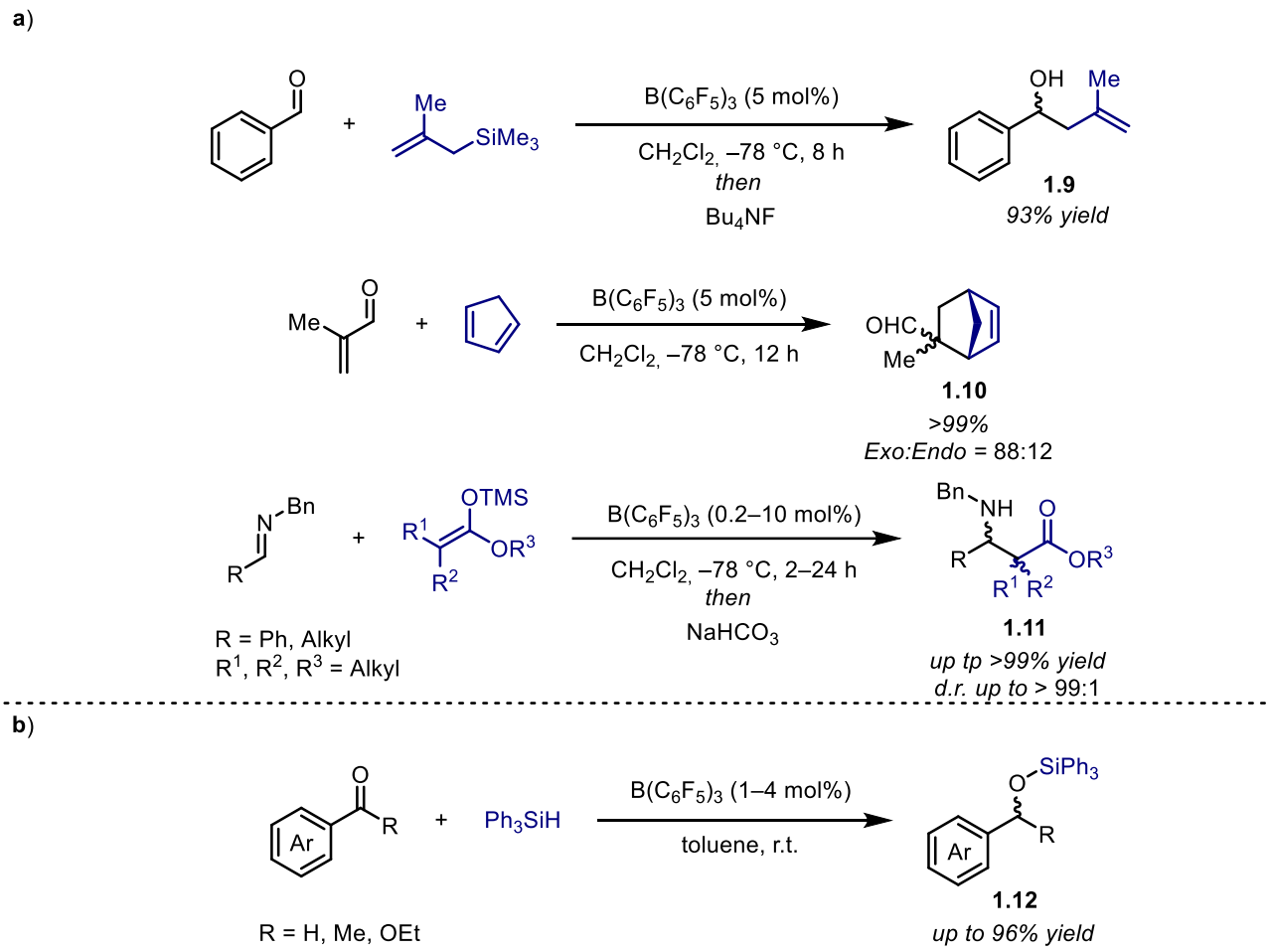


Scheme 1.13. The first example of a frustrated Lewis pair system. **a**) The synthesis of the phosphonium borate **1.6**. **b**) Transformation of **1.6** into the active FLP system **1.7**.

This landmark report highlighted for the first time the unquenched reactivity of a Lewis base, such as $PH(Mes)_2$ and the Lewis acid $B(C_6F_5)_3$ for hydrogen splitting. Instead of the classic LA-LB adduct, *p*-S_NAr can occur, leading to the formation of the hydrophosphonium fluoroborate **1.6**, which can be isolated as an air-stable solid (Scheme 1.13, a). The replacement of the fluoride bound to the boron with hydrogen can be accomplished using Me_2SiHCl, leveraging the formation of the Si–F bond as a strong driving force, which leads to the hydrophosphonium hydridoborate **1.7** (Scheme 1.13, b). This species can be formally seen as the phosphino borane **1.8** reacting with an equivalent of hydrogen. Indeed, it has been demonstrated that by simply heating compound **1.7** at 110 °C in toluene this can be converted into **1.8** with liberation of molecular hydrogen.[70] Similarly, reacting compound **1.8** with H_2 at 25 °C led to the quantitative formation of **1.7**. From this discovery the field of main group chemistry witnessed a significant advancement, revealing the ability of these elements to perform reactions previously achievable only with transition metals.[71] Additionally, while this first report showcased a diamagnetic pathway involving cations and anions, very recently several reports entailing a paramagnetic pathway involving radicals have been published.[72–78] This has culminated in the first report from the group of Lin of a Frustrated Radical Pair (FRP) mechanism to perform a regioselective C–H functionalisation of hydrocarbons.[79] Hence, not only the relatively new field of

FLP can accomplish diamagnetic or paramagnetic reactivity, but it also showcases the potential to leverage the steric bulkiness to employ reagents that would otherwise quench each other.

On the other hand, the sole use of sterically hindered Lewis acid catalyst in organic synthesis remained latent until the late 90s, when two separate reports from Yamamoto and Piers first disclosed its utility (Scheme 1.14).[80,81]

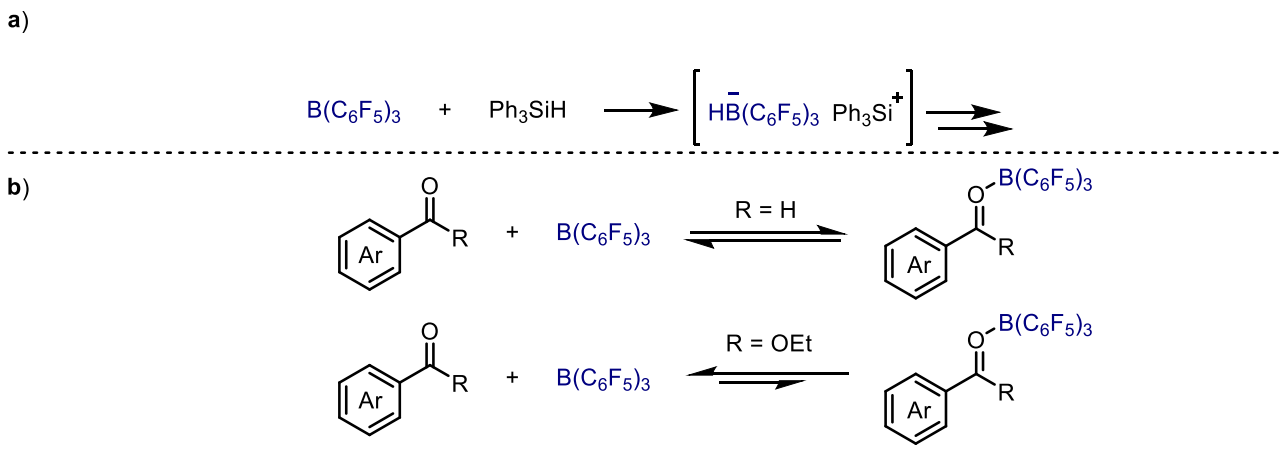


Scheme 1.14. **a**) First examples of $B(C_6F_5)_3$-catalysed reactions disclosed by Yamamoto. **b**) First examples of $B(C_6F_5)_3$-catalysed reactions disclosed by Piers.

In Yamamoto's report, $B(C_6F_5)_3$ was shown to be an efficient catalyst for the Hosomi-Sakurai allylation of aldehydes to yield **1.9**. Similarly, the catalyst was also successfully employed in the exo-selective Diels-Alder reaction to afford **1.10** and in the Mukaiyama-Mannich addition of imines to yield **1.11** (Scheme 1.14, a). However, as disclosed by the authors, all these reactions were carried

out under air, and this aspect is worth to be highlighted.[80] Indeed, in 2000 Norton, Friesner and Parkin showed that $B(C_6F_5)_3$ readily reacts with water or moisture in the air to form the corresponding water adduct which exhibits features of a Brønsted acid rather than a Lewis acid, with an acidity similar to that of HCl.[82] Therefore, it is possible to deduce that in Yamamoto's early reports, the reactions were most likely Brønsted acid catalysed.

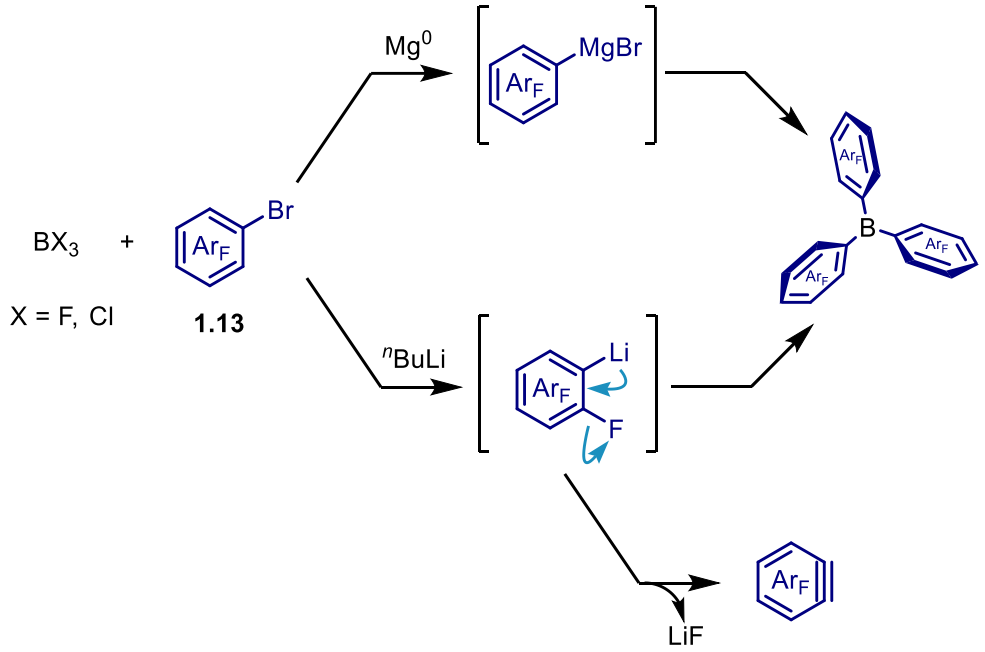
In 1996, Piers disclosed the first hydrosilylation of aldehydes, ketones and esters catalysed by $B(C_6F_5)_3$ to afford products **1.12** (Scheme 1.14, b).[74] In this work, the authors assumed that the Lewis acid was vital for the activation of the carbonyl starting material, which would then be reduced by the silane reagent. However, kinetic and competition experiments did not support such a mechanism, since it was observed that the reactivity followed the order ester>ketone>aldehyde. This apparent dichotomy was explained by considering a different role of the Lewis acid, which activates the silane by forming a silylium borohydride species (Scheme 1.15, a). In this way, the stronger the carbonyl coordinates to the Lewis acid, the less amount of free catalyst is available to activate the silane, which in turn slows the reduction to **1.12** (Scheme 1.15, b).



Scheme 1.15. **a**) Silane activation by $B(C_6F_5)_3$. **b**) Equilibrium governing the amount of free $B(C_6F_5)_3$.

From these early reports, the field of Lewis acid catalysis with perfluoroaryl boranes started to blossom, as evidenced by the plethora of reviews concerning this branch of chemistry.[52,83–87] One of the features that render the perfluoroaryl boranes appealing to the synthetic community, apart from

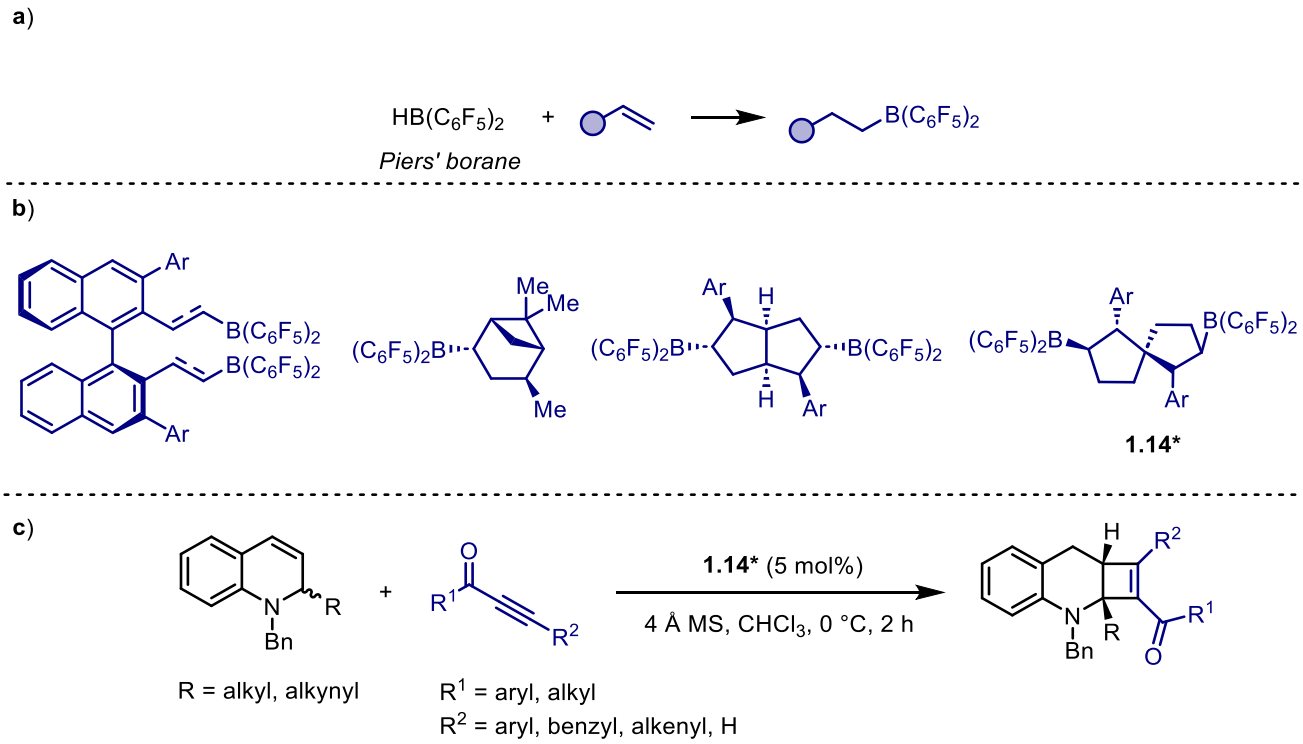
their strong acidity and improved stability, is the ease of tuning their Lewis acidity. Indeed, the synthesis of these compounds, which was described by Massey back in 1963[67] and further disclosed in a patent 30 years later,[88] relies on the reaction between commercially available perfluoro bromobenzene **1.13** with a boron halide such as BF_3 or BCl_3. These can be coupled together by either making the corresponding Grignard or organolithium reagent from **1.13**, which then reacts in a ratio of 3:1 with the boron halide (Scheme 1.16).



Scheme 1.16. Two possible ways to synthesise perfluoroaryl boranes using 3 equivalents of aryl bromide.

Although the Grignard route is usually lower yielding and requires more purification steps compared to the use of ^{n}BuLi, it is also safer. This is due to the organolithium intermediate formed via the other route, which can decompose violently if *o*-fluorine atoms are present, forming benzyne and LiF.[89] From Scheme 1.16 is evident that the possibility of accessing different perfluoroaryl boranes is limited only to the amount of commercially available perfluoroaryl bromobenzenes. Additionally, other electronegative moieties such as Cl, CF_3 and many others can be embedded in the aromatic ring, expanding even further the amount of synthesisable Lewis acids.[52]

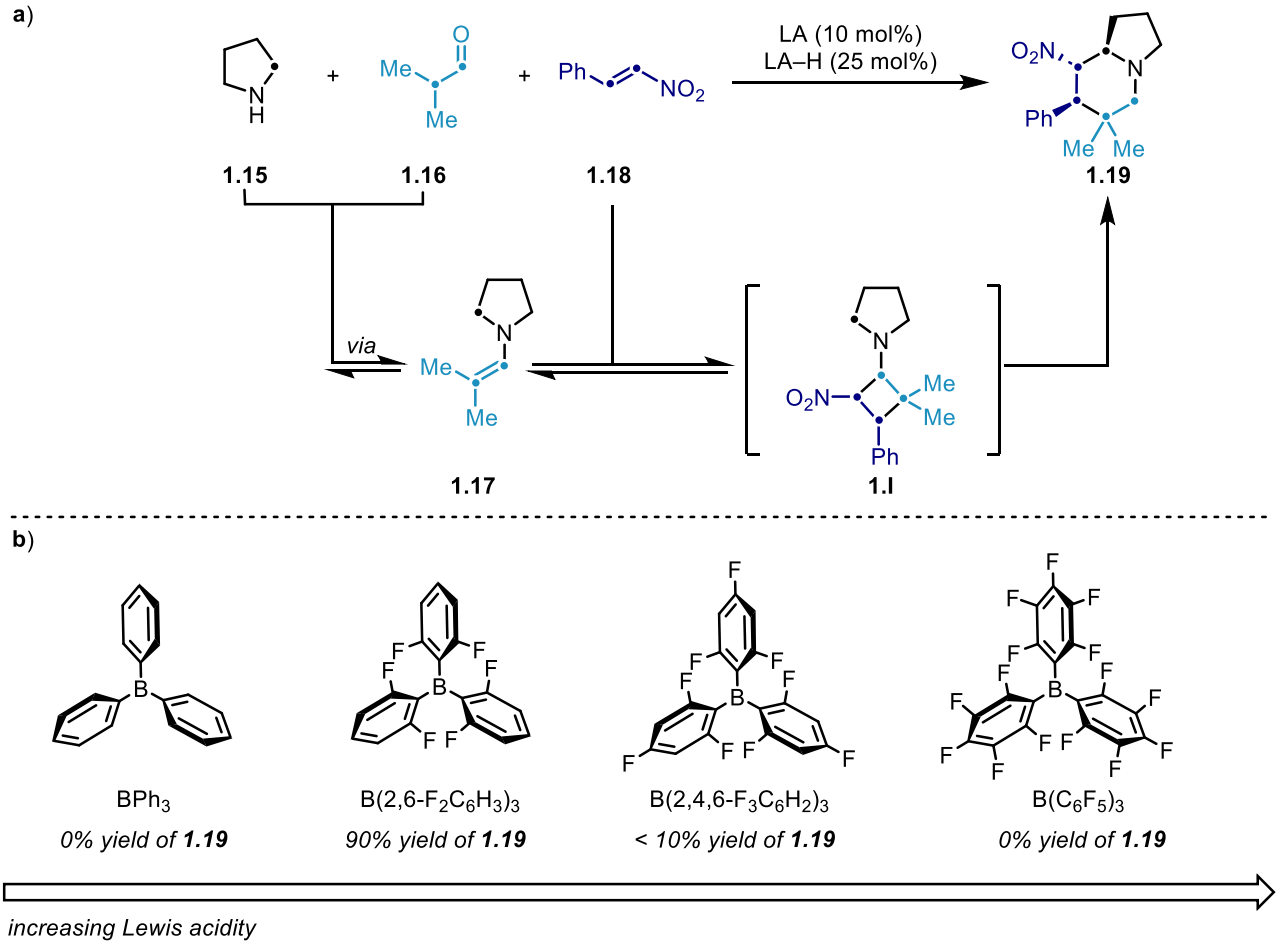
It should be also briefly mentioned another method to access novel Lewis acidic boranes which employs the so-called Piers' borane $HB(C_6F_5)_2$.[90] This species promptly undergoes hydroboration reactions with an unsaturated moiety (Scheme 1.17, a). For example, the hydroboration of unsaturated chiral moieties can allow the synthesis of novel chiral boron-based Lewis acids, employable in the field of asymmetric catalysis (Scheme 1.17, b). This field has been pioneered mainly by Du and Wang (Scheme 1.17, c).[91–94,94–98]



Scheme 1.17. **a**) The hydroboration of chiral starting materials using Piers' borane allows the synthesis of chiral Lewis acids. **b**) Selected examples of different types of chiral Lewis acids. **c**) Selected example of a [2+2] cycloaddition catalysed by the chiral Lewis acid **1.14***.

As described earlier, the feature of carefully tuning the Lewis acidity of the perfluoroaryl borane simply by changing the fluorination pattern is very appealing from a synthetic point of view, and this concept can be reinforced by highlighting two works recently published by the group of Maulide.[99,100] Indeed, it has been shown that the careful choice of the Lewis acid can have a profound impact on the reactivity.

In their first report, [99] the authors disclosed the first example of an inverse hydrogen-shuttle catalysis employing a perfluoroaryl borane (Scheme 1.18). The reaction entails the stereoselective formation of complex alkaloids by leveraging the formation of fleeting intermediates. In detail, commercially available pyrrolidines **1.15** and aldehydes **1.16** can establish an equilibrium with their corresponding enamine **1.17**. This can spontaneously react with electron-poor olefins such as **1.18** to afford the cyclobutane intermediate **1.I**, which is subjected to a Lewis acid to promote the formation of **1.19** via an *inverse* hydrogen-shuttle mechanism (Scheme 1.18, a). The reaction proved to be high-yielding when stoichiometric amounts of Lewis acid were employed, however, to render the reaction catalytic, the authors had to use as an additive catalytic quantity of pre-formed Lewis acid-hydride species.



Scheme 1.18. **a**) General reaction scheme for the Lewis acid catalysed synthesis of complex alkaloids. **b**) Reaction yield of **1.19** with different Lewis acids.

Interestingly, the reaction did not afford product **1.19** in either the presence of the strongest Lewis acid of the series $B(C_6F_5)_3$ or the weakest BPh_3 (Scheme 1.18, b). However, when using $B(2,6\text{-}F_2C_6H_3)_3$ the reaction proceeded smoothly. Even more surprisingly, the similar Lewis acid $B(2,4,6\text{-}F_3C_6H_2)_3$ only formed the product in trace amounts (10%). Although the authors did not describe the reason behind such peculiar reactivity, it is possible to infer that it arises from the balance between the acidity of the catalyst and the hydricity of the corresponding hydride species. This example highlights that the best Lewis acid for a specific transformation is not necessarily the most acidic, but rather the one with the optimal combination of features, that can also vary slightly. For this reason, the possibility to tune the substitution pattern in the aromatic rings attached to the boron atom in perfluoroaryl boranes renders them highly valuable for this purpose.

1.4. Summary

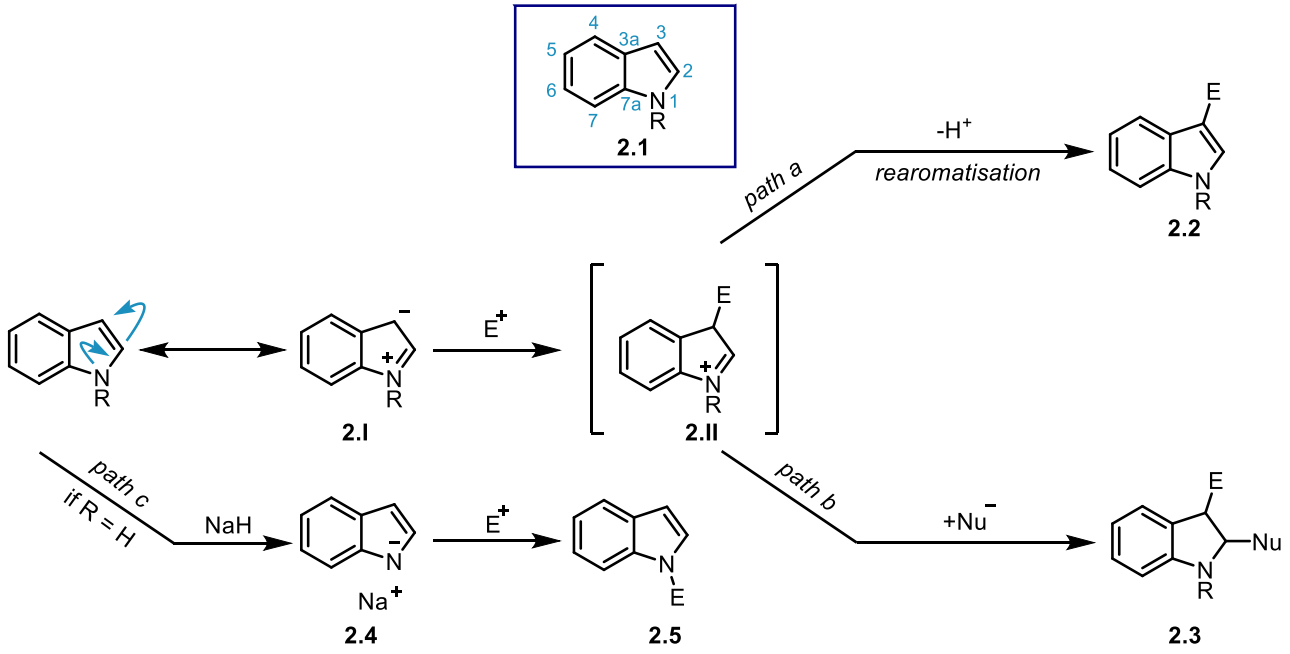
This chapter serves as an introduction to the field of Lewis acid chemistry, with a major focus on their catalytic applications. Chapter 1.1 describes what is a Lewis acid, and how it compares to a Brønsted acid. Additionally, it introduces the reader to the concept of *Pauli repulsion lowering catalysis*, underpinning the functioning of Lewis acids in catalysis. It further discusses the unexpected effect that increasingly electronegative atoms have on the acidity of boron trihalides and suggests their replacement with perfluoroaryl boranes. Chapter 1.2 describes the currently available methods to assess the Lewis acidity of boron compounds, highlighting the non-trivial nature of finding a unified scale. Finally, Chapter 1.3 introduces the chemistry of perfluoroaryl boranes and more specifically of $B(C_6F_5)_3$, showcasing its initial developments, synthesis, and applications. To this end, this catalyst is of paramount importance in the field of FLP as well as a strong Lewis acid in organic synthesis, where it has been shown that the careful choice of the catalyst can greatly affect reaction outcomes.

2. N–H functionalisation of indoles with isocyanates

This chapter describes the Lewis acid catalysed functionalisation of indoles using isocyanates. After an introduction to the chemistry of indole, its synthesis and selected examples of its functionalisation, the experimental section will specifically focus on the *N*-functionalisation of unprotected indoles.

2.1. The chemistry of indole

In 1866, during his studies on the indigo dye, Adolf von Baeyer first synthesised indole through a Zn-mediated reduction of oxindole.[101] Since this discovery, the nitrogen-containing heterocycle has gained an increasing interest in medicinal chemistry. In the human body, indole is present in the form of the amino acid tryptophan, which cannot be synthesised but only introduced with the diet. The importance of indole in medicinal chemistry might be attributed to different factors like its presence in many alkaloids, as well as its peculiar chemistry, which renders the core highly functionalisable.[102–110] In fact, indole is weakly basic due to the delocalisation of the nitrogen lone pair, which however renders its core highly electron-rich (Scheme 2.1).



Scheme 2.1. The chemistry of indole.

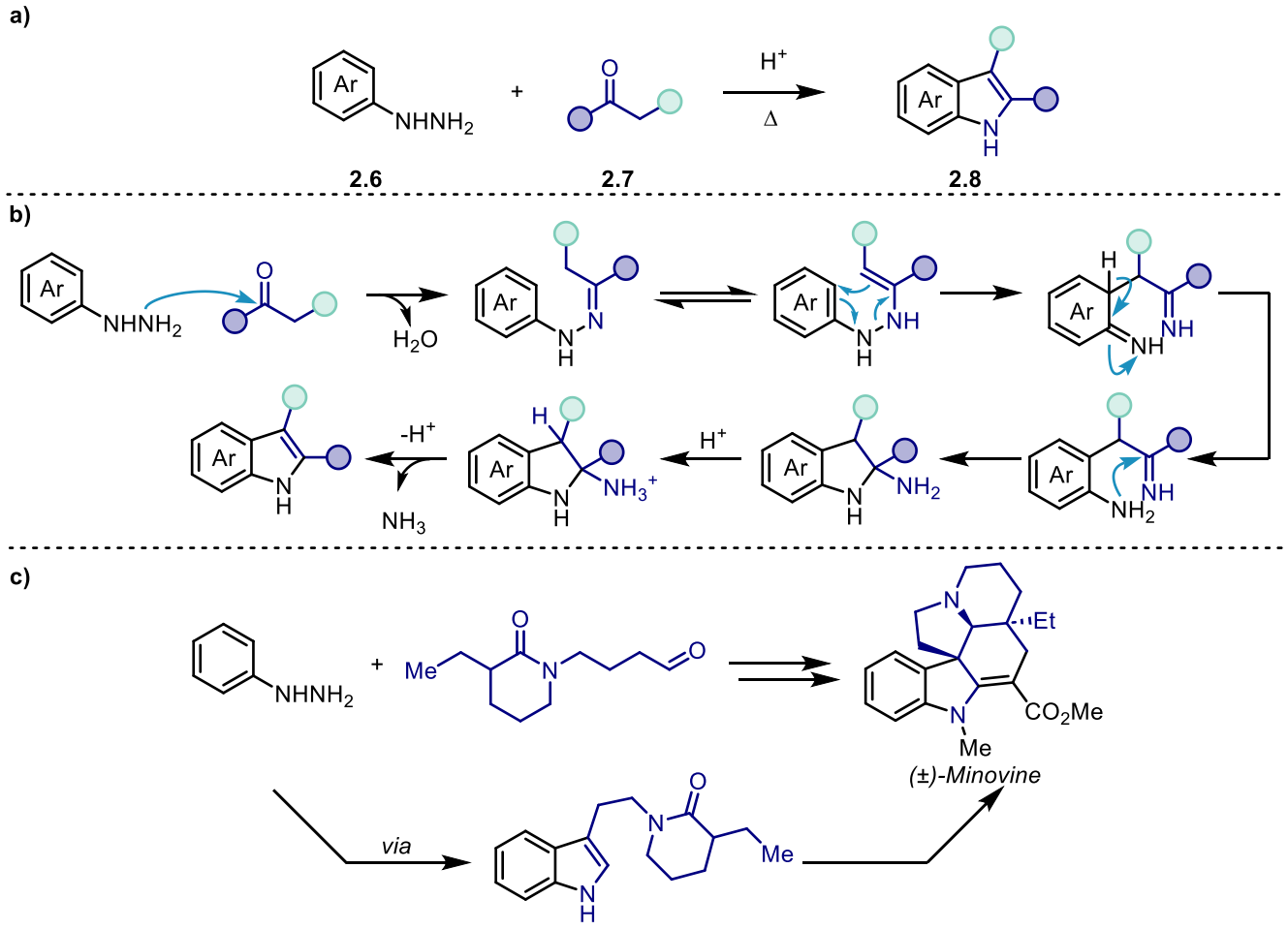
When referring to indole, chemists have adopted a numbering system which assigns 1 to the nitrogen centre and then increases the count in an anticlockwise manner according to **2.1**, numbering the quaternary carbons as 3a and 7a (Scheme 2.1, **2.1**).

In general, this 10 π-electrons heterocycle reacts with electrophiles at its 3-position, where most of the negative charge from the resonance form resides (Scheme 2.1, **2.I**). This leads to an iminium intermediate **2.II**, which can then spontaneously rearomatise to lead to compound **2.2** (Scheme 2.1, path a) or be trapped with a nucleophile, affording a difunctionalised indole **2.3** (Scheme 2.1, path b).[107] If the N1 position bears a hydrogen atom, then the unprotected indole can be treated with a strong base, such as NaH, to afford the sodium indolyl anion **2.4**, which becomes nucleophilic at the nitrogen centre and can react with electrophiles to afford **2.5** (Scheme 2.1, path c). The functionalisation of the indole at its other positions has been far less developed mainly because the heterocyclic core is the most electron-rich moiety. A thorough description of the methodologies developed for such positions falls outside the scope of this thesis.[110] For this reason, only functionalisations on N1 and C3 positions will be discussed in more detail, as well as the methods to synthesise the indole core.

2.1.1. Methods for indole synthesis

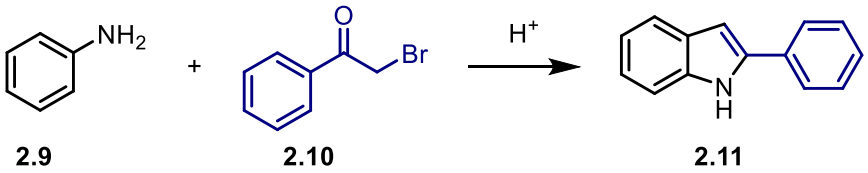
After its discovery in 1866, an urge to synthesise the indole without relying on its precursor – the 2 oxindole – started to spread. One of the first methods being developed is attributed to Emil Fischer who, in 1883, disclosed the condensation between an aromatic hydrazine **2.6** and a carbonyl compound **2.7**, usually an aldehyde or a ketone (Scheme 2.2, a).[111] The reaction mechanism starts from the nucleophilic addition of the aromatic hydrazine to the carbonyl moiety, forming a hydrazone (Scheme 2.2, b). The latter can isomerise to the corresponding enamine under the reaction conditions, which then undergoes an intramolecular Friedel-Craft alkylation. Finally, after a series of proton transfers an aminal is formed, which under acidic conditions liberates ammonia and forms the thermodynamically favoured indole **2.8** (Scheme 2.2, b). This method, albeit relying on relatively

easy to handle starting materials, requires the use of forcing conditions and the presence of strong Brønsted/Lewis acids, which sometimes hampers a broader applicability. Nevertheless, the Fischer indole synthesis has been recently applied as a key step in the synthesis of the natural product (±)-Minovine (Scheme 2.2, c).[112]



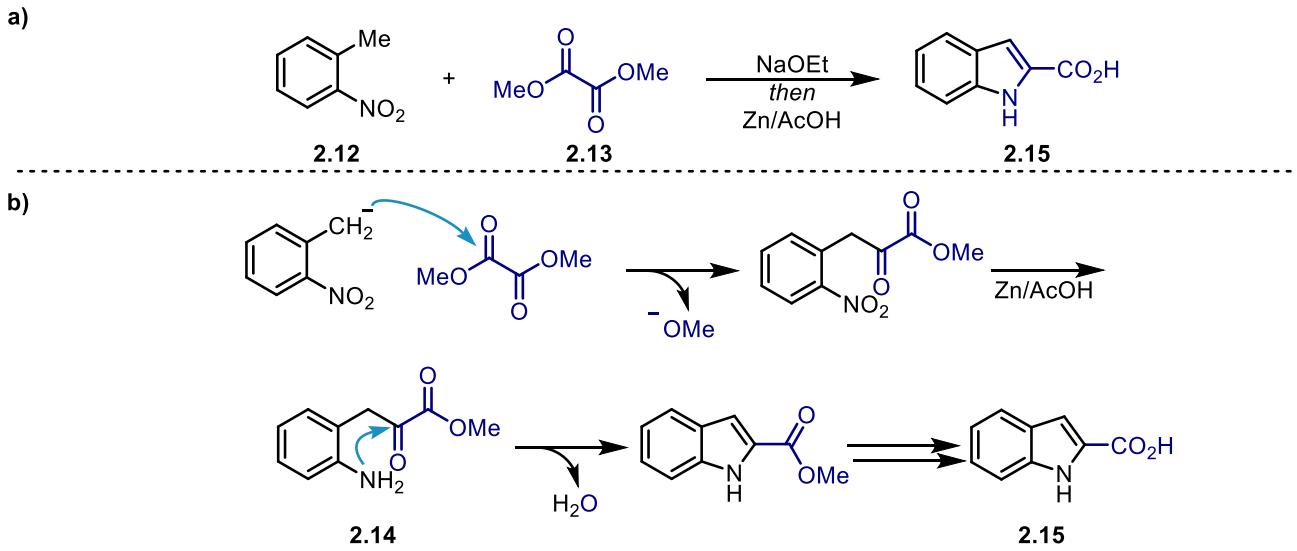
Scheme 2.2. The Fischer indole synthesis. **a)** General reaction scheme. **b)** Mechanism of the reaction. **c)** Application in natural product synthesis.

However, the need to rely on aromatic hydrazines, which are prepared from the corresponding anilines through a two-step synthesis, has prompted further studies for the synthesis of indole. Möhlau and Bischler developed a methodology which entailed the use of aniline **2.9** and α-bromo acetophenone **2.10** to afford the indole core **2.11** (Scheme 2.3).[113,114] Nevertheless, due to the harsh conditions needed, the Bischler-Möhlau indole synthesis found limited synthetic applications.



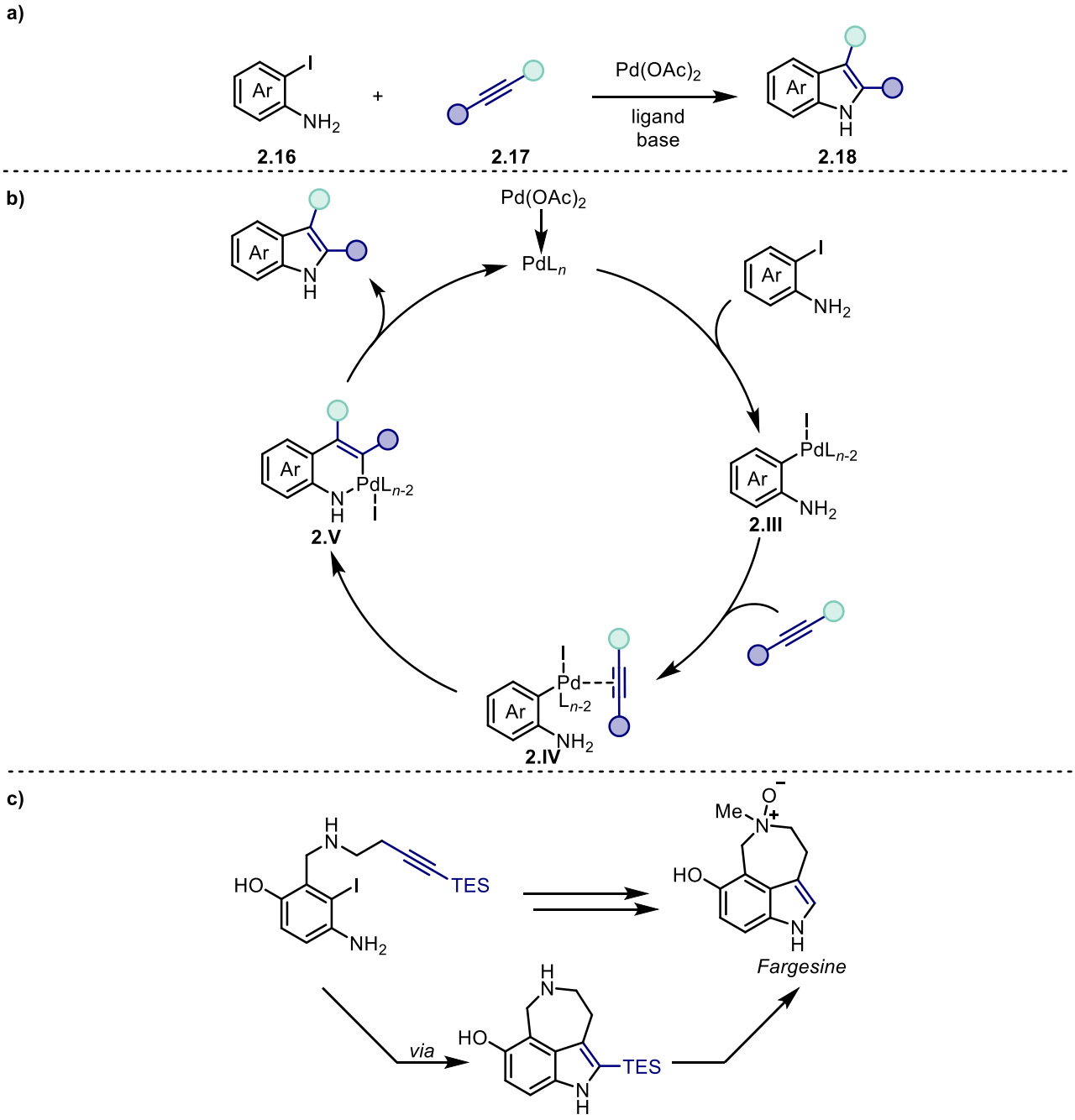
Scheme 2.3. The original Bischler-Möhlau indole synthesis.

On the other hand, the Reissert indole synthesis (Scheme 2.4, a) relies on an *o*-methyl nitroarene **2.12** which can be deprotonated by a suitable base.[115] This step renders the methylenic position nucleophilic, which can react with a suitable electrophile, e.g. an oxalate **2.13**, forming an α-keto ester (Scheme 2.4, b). *In situ* reduction of the nitro group via a Béchamp-type reaction[116] affords the corresponding aniline **2.14**, which then intramolecularly condenses with the ketone to afford the indole scaffold **2.15** (Scheme 2.4, b).



Scheme 2.4. The Reissert indole synthesis. **a)** General reaction scheme. **b)** Mechanism of the reaction.

Over several years, other indole syntheses have been disclosed, such as the Nenintzescu,[117] the Leimgruber–Batcho,[118] and the Bartoli.[119] Interestingly, the latter is one of the fewer reactions that allow the synthesis of functionalised indoles at the 7-position. More recently, in 1991, the Larock indole synthesis (Scheme 2.5, a) has also been developed,[120] becoming one of the most viable routes to the synthesis of the indole alongside the seminal Fischer indole synthesis.



Scheme 2.5. The Larock indole synthesis. **a)** General reaction scheme. **b)** Mechanism of the reaction. **c)** Application in total synthesis.

In this Pd-catalysed approach, an *o*-iodoaniline **2.16** is reacted with an alkyne **2.17**, which firstly undergoes an oxidative addition with the Pd catalyst to form the aryl-Pd species **2.III** (Scheme 2.5, b). Then, π-interaction between the alkyne and the Pd centre occurs to afford **2.IV**, which leads to a 6-membered palladacycle **2.V**. This step anticipates the subsequent reductive elimination, forming the desired indole scaffold **2.18**. Interestingly, it has been shown that the reaction is highly

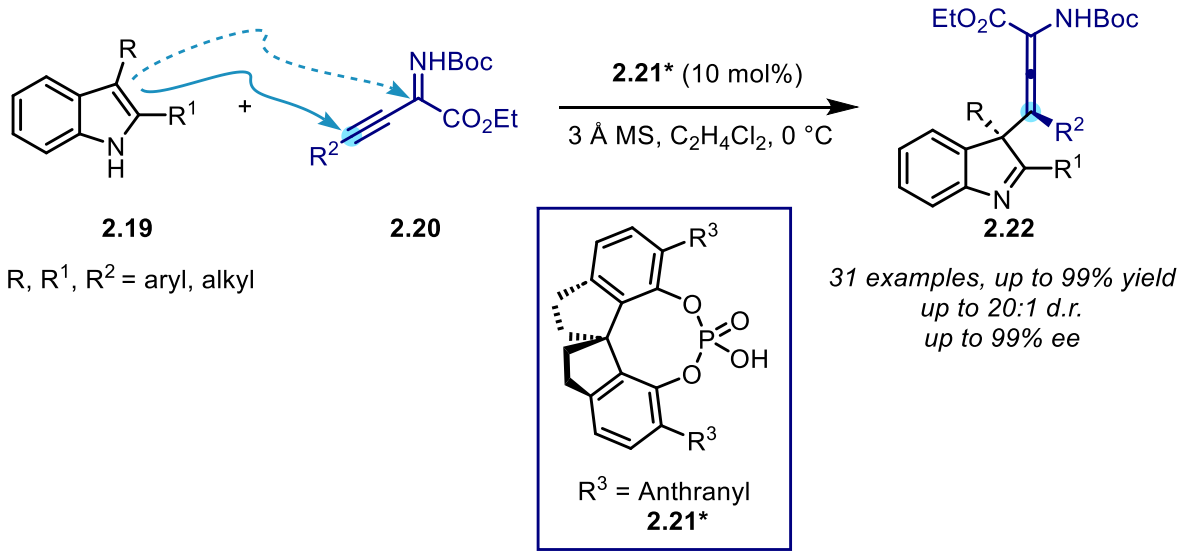
regioselective with unsymmetrical alkynes, where in the 6-membered transition state, the *sp* carbon attached to the smaller group is the one which forms the bond with the aromatic ring, to minimise the steric repulsions.[121] This method has been successfully employed in several total syntheses, such as for the synthesis of the natural product Fargesine (Scheme 2.5, c).[122]

Despite the huge diversification and the many advances that the synthesis of the indole core has witnessed, several methods are still sought for further functionalise indole. The next chapters will describe the recent advances in this field.

2.1.2. Methods for indole functionalisation at position C3

Given the high nucleophilicity of the C3 position of the indole, it is not surprising that numerous synthetic methods have been developed throughout the years to tackle the functionalisation at this position. In this chapter, only selected examples of acid-catalysed, transition metal-free approaches will be discussed.

Given the strong nucleophilicity of the C3 carbon, virtually every electrophilic reagent can react with this position. Depending on the case, the electrophile might need to be activated with an acidic catalyst. For example, noteworthy is the C3-functionalisation of indoles described by Sun, Wang and co-workers in 2020.[123] The authors have reported a method which relies on a chiral phosphoric acid (CPA) **2.21** which exerts asymmetric induction in the reaction between 2,3-disubstituted indoles **2.19** and β-alkynyl-α-imino esters **2.20** to afford tetrasubstituted indolyl allenes **2.22** (Scheme 2.6).

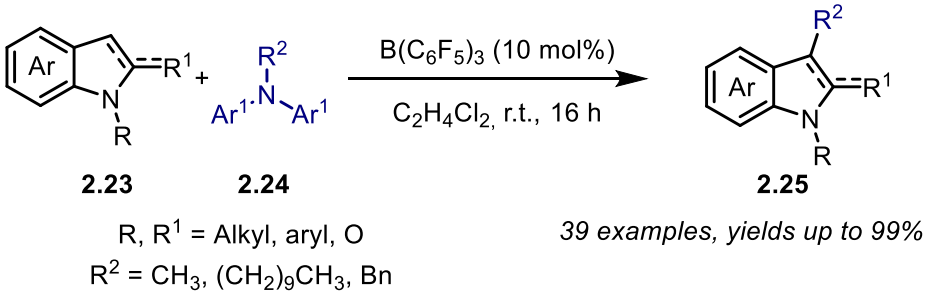


Scheme 2.6. The CPA-catalysed synthesis of axially chiral indolyl allenes.

Crucially, the reaction has been proved to be highly regioselective, since no α-addition was observed. Moreover, a transition state (TS) was proposed where the CPA forms a chiral pocket which hosts the electrophilic species and activates it for the attack from the nucleophilic indole. Mechanistic studies have also revealed the role of the 2,3-disubstitution pattern on the indole scaffold. It was observed that the selectivity decreased when 3-methyl indole was employed whereas the reaction afforded the α-addition product when the 2-methyl indole was used instead, highlighting the requirement to use 2,3-disubstituted indoles for the process to be regioselective.[123] In this context, two simple reactants can be coupled together with the aid of a CPA affording axially chiral products in high yields of up to 99%, and high diastereo- and enantioselectivities of up to >20:1 *d.r.* and 99% *ee*.[123]

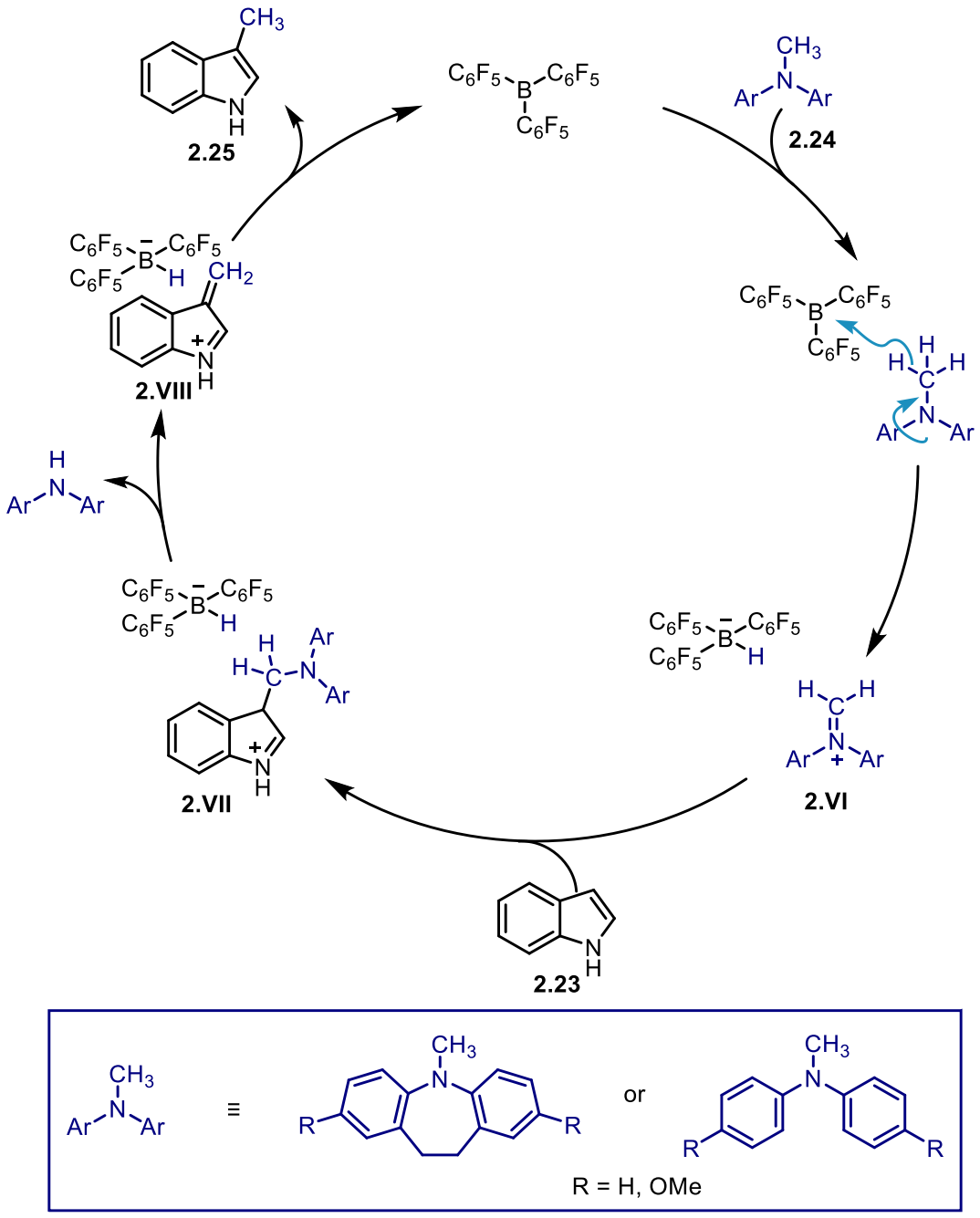
Despite the interesting approach, one intrinsic limitation stems from the use of inherently electrophilic species, such as imines. The hydrolytic instability of some imines is a well-known issue,[124,125] which sometimes requires methods for synthesising the imine directly *in situ*. In this regard, $B(C_6F_5)_3$ proved to be an efficient catalyst for the H-abstraction of aliphatic amines, which can be thus converted into the corresponding iminium derivatives and used directly.[83,126] In the realm of the C3 functionalisation of indole, a collaborative project within our group has shown that $B(C_6F_5)_3$ can form the ammonium borohydride species from an aniline derivative of the type $R_2N\text{-}CH_3$ **2.24** which then acts as a

methylating reagent for indoles or oxindoles **2.23**, affording the corresponding C3-methylated product **2.25** (Scheme 2.7).[127]



Scheme 2.7. $B(C_6F_5)_3$ catalysed alkylation of indoles and oxyindoles.

Moreover, no *N*-methylation occurs under the reaction conditions when unprotected indoles are employed, which provides a complementary tool to the classic methylation reactions using CH_3I and a base.[128] In addition, by changing the amino methylating agent, not only CH_3 moieties can be inserted into the final product, but also Bn groups. From a mechanistic point of view, based on experimental results and literature evidence from the group of Wasa,[129,130] the reaction has been proposed to proceed through the initial formation of the ammonium borohydride species **2.VI**, where the Lewis acidic catalyst does not establish a Lewis acid-base adduct with the amine because of steric hindrance. From this first intermediate, nucleophilic addition of the indole from the C3 position to the iminium species can occur, forming intermediate **2.VII** (Scheme 2.8). Subsequently, an E1cB occurs, liberating the free amine which is detected as a byproduct in the reaction mixture, and forming the indolinium borohydride species **2.VIII**. Finally, a hydride transfer from the boron to the methylene position occurs, affording the C3 methylated product **2.25** and regenerating the catalyst (Scheme 2.8).

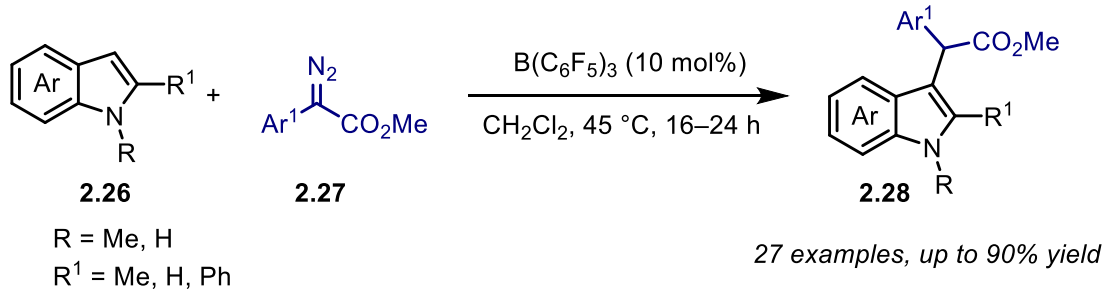


Scheme 2.8. Proposed mechanism for the methylation of indoles catalysed by $B(C_6F_5)_3$.

Deuterium labelling experiments have also proven that, although the hydride abstraction occurs preferentially from the amino reagent, partial abstraction can also occur from the N-CH_3 moiety present in protected indoles.

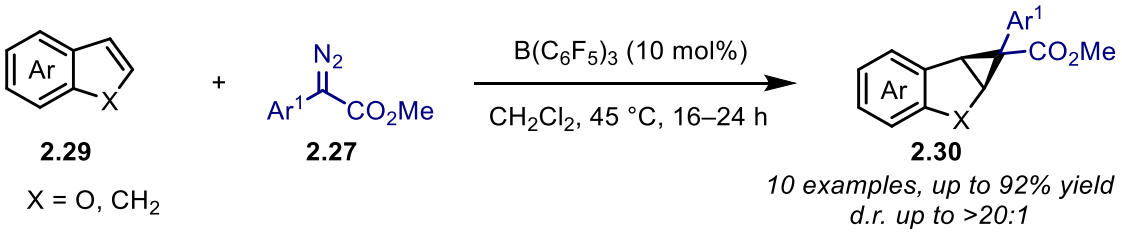
Our group has a longstanding interest in the functionalisation of indole using $B(C_6F_5)_3$. For example, in 2020, we have shown that α-diazoesters **2.27** can be activated by the boron Lewis acid to afford a

carbene equivalent which can subsequently engage in reactions with suitable nucleophiles.[131] When protected indoles or pyrroles are used as the reactive partners, C–C bond formation between the carbene and the C3 (or C5 in the case of pyrrole) position occurs, affording the corresponding C–H inserted product **2.28** (Scheme 2.9).



Scheme 2.9. $B(C_6F_5)_3$-catalysed C–H functionalisation of indoles.

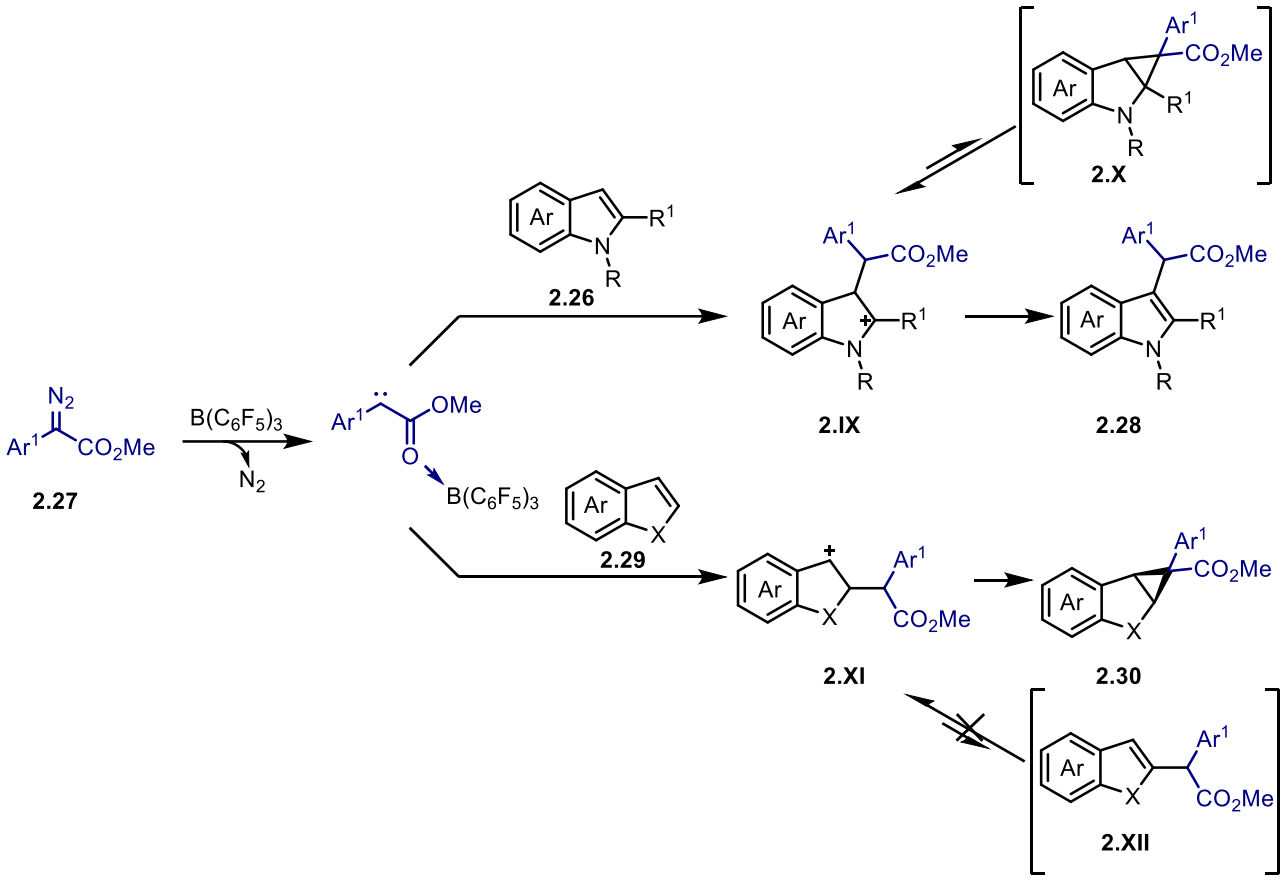
An in-depth discussion of diazoester activation with boron Lewis acids will be made in Chapter 3. Nevertheless, from a mechanistic point of view, the reaction is proposed to proceed through an initial coordination of the Lewis acid to the carbonyl moiety, which sets up the subsequent N_2 liberation with the concomitant formation of the carbene equivalent. Interestingly, in the case of indenes and benzofurans **2.29**, the reaction does not proceed through the C–H insertion pathway but instead affords the corresponding cyclopropanated product **2.30** (Scheme 2.10).



Scheme 2.10. $B(C_6F_5)_3$-catalysed cyclopropanation of benzofuranes and indenes.

A similar observation arose in the case when styrene reactants were employed instead. As an explanation, supported also by DFT analysis, it has been proposed[131] that in all the cases the cyclopropanation affords the kinetic product whereas the C–H insertion affords the thermodynamic product. However, in the case of indoles and pyrroles, the disruption of aromaticity due to the possible

formation of the cyclopropanated product **2.X** renders the overall process energetically unfeasible. Therefore, after the possible formation of a cyclopropanated indole intermediate **2.X**, a reverse transformation to **2.IX** occurs which delivers the experimentally observed product **2.28** (Scheme 2.11).[131]

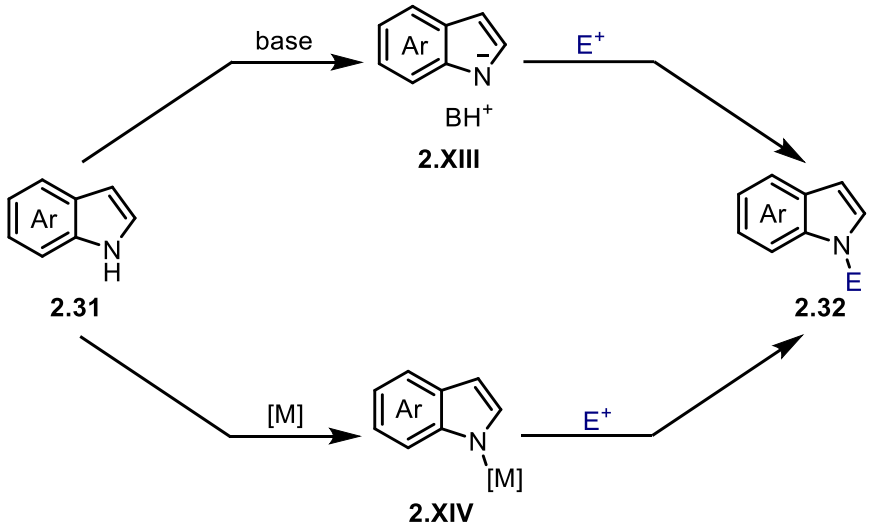


Scheme 2.11. Proposed divergent pathways for the C3-functionalisation and cyclopropanation reactions.

Moreover, it is inferred that the strong π donation of the nitrogen lone pair of the indole greatly stabilises the positive charge in **2.IX**, which hampers the formation of the cyclopropane ring. In the case of the benzofurans and indenes, the kinetic cyclopropanation product **2.30** proved to be highly stable, rendering the reverse transformation to the thermodynamic C2 functionalised product **2.XII** energetically unfeasible (Scheme 2.11). Interestingly, the authors have observed the cyclopropanation to be highly diastereoselective and have attributed this to the steric hindrance of the borane catalyst.

2.1.3. Methods for indole functionalisation at position N1

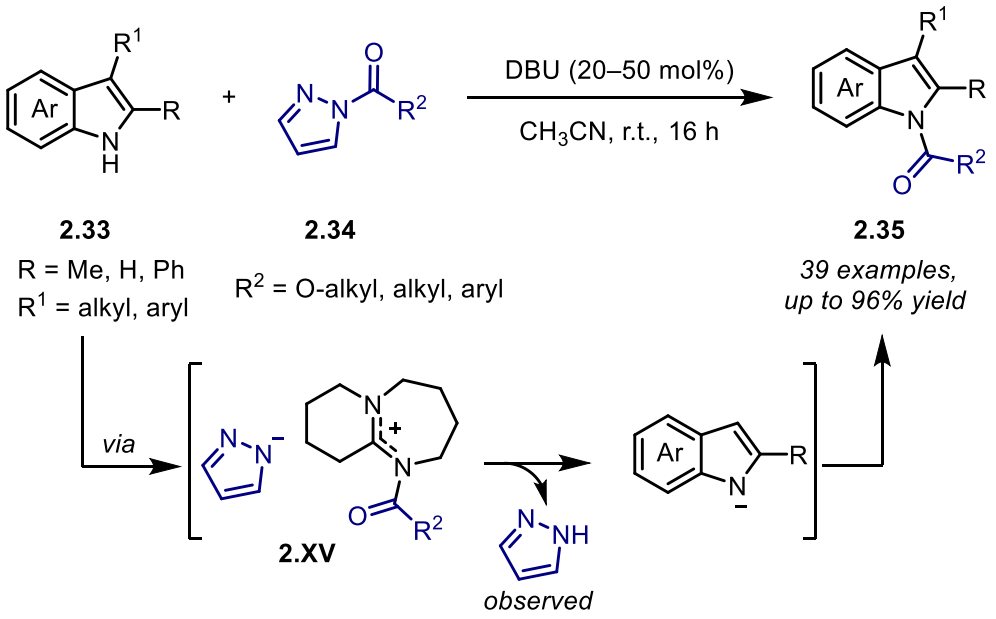
The second most readily functionalisable position of the free indole **2.31** is N1. Indeed, the pK_a of the N–H proton is 21 in dimethyl sulfoxide (DMSO), hence a strong base can potentially form the relatively stable indolyl anion **2.XIII** (Scheme 2.12). As such, the most common method to functionalise the indole at its N1 position is to pretreat the indole with a strong base (like NaH, ^{n}BuLi or a Grignard reagent) and then trap the indolyl anion with a suitable electrophile to afford **2.32**. Another method to tackle the N–H functionalisation lies in the use of transition metals,[106] which can afford the *N*-functionalised product in a Buchwald-Hartwig-type approach from intermediate **2.XIV** (Scheme 2.12).



Scheme 2.12. The two possible pathways for the N–H functionalisation of indoles.

In an attempt to overcome the use of transition metals and the use of strong bases, which can pose a limitation in terms of functional group tolerance, Sarpong developed a method relying on catalytic amounts of 1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU) to perform the *N*-acylation of indoles using an acyl imidazole **2.34**.[132] The concept underpinning their method was the matching of the basicity of the imidazole anion **2.XV** liberated in the reaction mixture and the acidity of the N–H proton of the indole, which can be abstracted by **2.XV** (Scheme 2.13). Crucially, in this way only the N–H

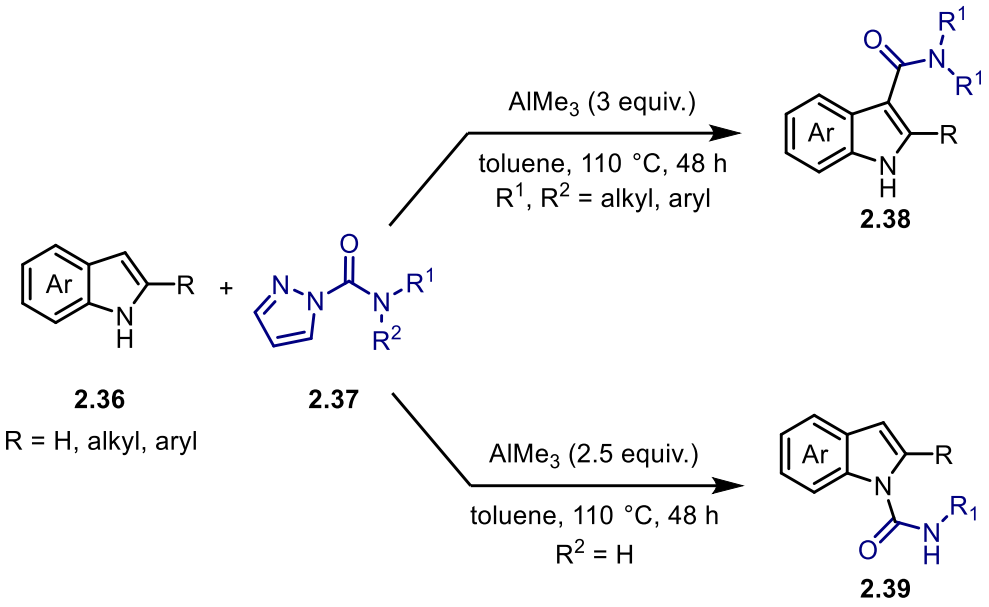
proton of the indole can be selectively functionalised, leaving unaltered other sensitive functionalities such as phenols or anilines.



Scheme 2.13. The DBU-catalysed acylation of indoles.

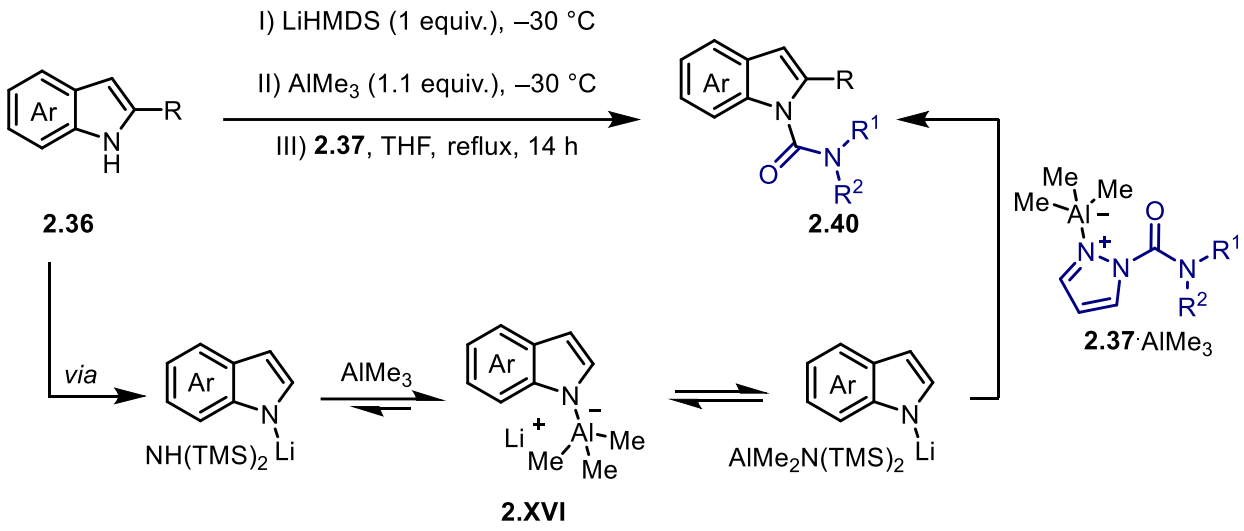
In this way a method to selectively acylate indoles has been developed, which was based on the careful consideration of the pK_a of the reactants.

A similar approach using the Lewis acid $AlMe_3$ was described by Balasubramanian and co-workers in 2013,[133] which entails one of the first examples of the application of an indole-aluminium amide complex for the synthesis of C3 or N1 functionalised indoles (Scheme 2.14).



Scheme 2.14. Diverging pathways for the functionalisation of indoles.

In detail, it has been observed that when indole **2.36** is treated with a large excess of $AlMe_3$ and a tertiary carbamoyl imidazole **2.37**, the reaction affords exclusively the C3 indolyl amide **2.38** instead of the expected *N*-functionalised product (Scheme 2.14). Interestingly, when secondary carbamoyl imidazoles are subjected to the same reaction conditions, N1 carbamoylation occurs instead of the C3 amidation, delivering the corresponding indolyl urea **2.39** (Scheme 2.14). While the latter result has been attributed to the *in situ* formation of isocyanates from secondary carbamoyl imidazoles,[133] the former required more investigations. When the authors employed conditions for the formation of an indole *ate* complex, they observed exclusive N1 functionalisation when tertiary carbamoyl imidazoles were used (Scheme 2.15).



Scheme 2.15. Formation of an indolyl ate complex with LiHMDS and $AlMe_3$.

In detail, by treating indole **2.36** with LiHMDS and $AlMe_3$, complex **2.XVI** forms. This highly nucleophilic species is too sterically hindered to react at the nitrogen centre with tertiary carbamoyl imidazoles activated by $AlMe_3$, but can do so after establishing an equilibrium with the corresponding lithium indole complex (Scheme 2.15). In the absence of LiHMDS, the reaction is diverted towards the formation of an indole aluminium amide complex, which hampers the reactivity at the sterically hindered nitrogen centre and affords the C3 functionalised product.

2.2. Aims of the project

As discussed in the previous sections, the development of new methods to functionalise the indole scaffold is important. The work from Balasubramanian *et al.*[133] prompted us to investigate the regioselective functionalisation of the indole using isocyanates, since their postulated mechanism proceeded through the *in situ* formation of an isocyanate from the secondary carbamoyl imidazole. Their methodology suffered from the need for harsh reaction conditions and the requirement of superstoichiometric amounts of a strong Lewis acid and base. On the contrary, we were curious whether a similar approach could be developed using catalytic amounts of $B(C_6F_5)_3$. This would allow us to synthesise indolyl urea products under less harsh conditions. Moreover, the importance of the

urea moiety in medicinal chemistry is undeniable, since it can establish several dipolar or H–bonding interactions with a possible target molecule.[134]

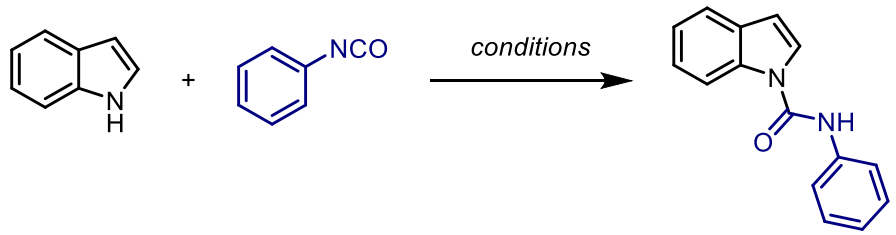
2.3. Authors contribution

My contribution to the work was carrying out all the synthetic work using unprotected indoles, as well as attempting the *in situ* formation of indoles using alkynyl anilines. Ms. Nusayabah Alotaibi carried out all the experimental work regarding the C3 functionalisation of protected indoles as well as pyrroles. Ms. Yara van Ingen measured and solved all the crystal structures. Dr. Kaveh Farshadfar carried out all the computational calculations. This work has been published in the journal Catalysis Science & Technology *Catal. Sci. Technol.*, **2022**, 12, 5982–5990.

2.4. Results and discussion

The investigation started by mixing commercially available 1*H*–indole **2.41** (1 equiv.) and phenyl isocyanate **2.42** (1.5 equiv.) in trifluorotoluene (TFT) (1.5 mL, 0.67 M) for 24 hours in the presence of $B(C_6F_5)_3$ as a catalyst (Table 1, entry 1). Since the Lewis acid catalyst can easily coordinate with water, all the manipulations were carried out in a nitrogen-filled glovebox. After weighing out the reactants and the catalyst in three separate microwave vials, these were closed with a crimper and removed from the glovebox. The solvent was then added to each vial and the three solutions were mixed. After 24 hours at room temperature, the reaction flask was opened, and a thin-layer chromatography (TLC) analysis showed the formation of an intense spot indicating the formation of the product **2.43** alongside another spot corresponding to unreacted indole starting material.

Table 2.1. Reaction optimisation table for the N–H insertion of indoles using isocyanates. Reactions were carried out on a 0.1 mmol scale and the yields refer to the isolated yield.



2.41 **2.42** **2.43**

Entry	Cat. (mol%)	Solvent (0.67 M)	T (°C)	Time (h)	Yield 2.43
1	$B(C_6F_5)_3$ (30)	TFT	25	24	12%
2	$B(C_6F_5)_3$ (30)	TFT	80	72	23%
3	$B(C_6F_5)_3$ (30)	TFT	110	24	24%
4	$B(C_6F_5)_3$ (10)	TFT	80	24	10%
5	$B(C_6F_5)_3$ (20)	TFT	80	24	14%
6	$B(C_6F_5)_3$ (30)	$C_2H_4Cl_2$	80	96	38%
7	-	TFT	80	24	-
8	$BF_3{\cdot}OEt_2$ (20)	$C_2H_4Cl_2$	87	24	46%
9	BCl_3 (20)	$C_2H_4Cl_2$	87	24	93%
10	BCl_3 (10)	$C_2H_4Cl_2$	87	24	87%
11	BCl_3 (5)	$C_2H_4Cl_2$	87	18	93%
12	BCl_3 (5)	$C_2H_4Cl_2$	60	18	93%
13	BCl_3 (1)	$C_2H_4Cl_2$	60	24	-
14	BCl_3 (5)	$C_2H_4Cl_2$	45	18	52%
15	BCl_3 (5)	$C_2H_4Cl_2$	25	18	20%

The structural assignment of product **2.43** was initially done by ^{1}H NMR spectroscopic analysis. After removal of the solvent and purification by preparative TLC, the ^{1}H NMR spectrum of the isolated product showed the disappearance of the N–H broad signal belonging to the starting material and the appearance of more signals in the aromatic region, hinting at the presence of the aromatic ring of **2.42** (Figure 2.1). Indeed, the isolated product was identified as a N–H inserted product **2.43** in 12% yield.

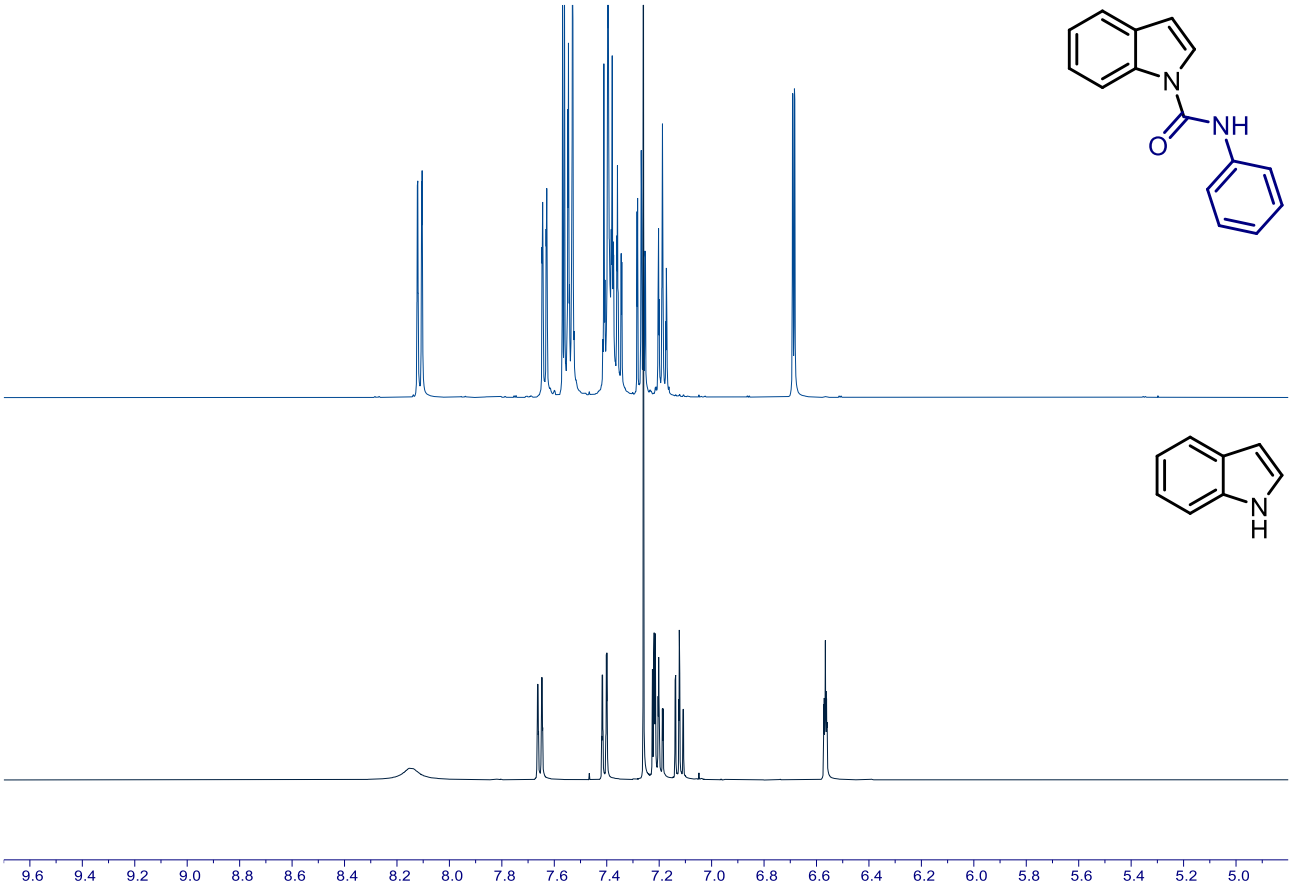


Figure 2.1. Stacked ^{1}H NMR spectra of the product **2.43** (top) and the indole starting material **2.41** (bottom).

Moreover, unequivocal structural determination was possible by slow evaporation of the pure product from a CH_2Cl_2 solution, which afforded crystals suitable for single crystal X-ray diffraction, which unambiguously showed the formation of the *N*-functionalised product (Figure 2.2).

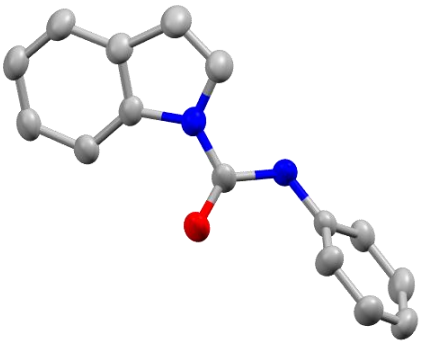


Figure 2.2. Crystal structure of the *N*-functionalised product **2.43**. Grey: carbon; Blue: Nitrogen; Red: Oxygen. Hydrogens omitted for clarity. Ellipsoids shown at 50% probability.

Some interesting aspects were noticed in the ^{1}H NMR spectrum of the product which are worth highlighting (Figure 2.3).

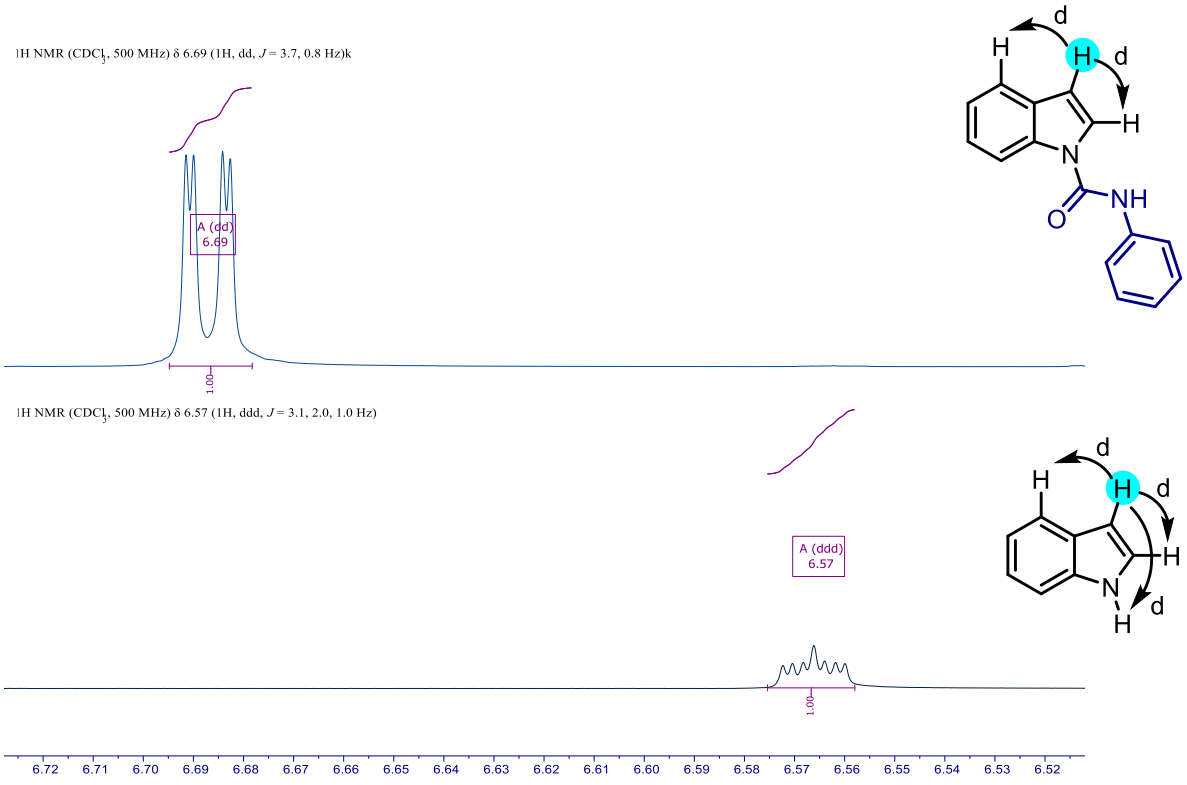


Figure 2.3. Stacked ^{1}H NMR spectra of the product **2.43** (top) and the indole starting material **2.41** (bottom).

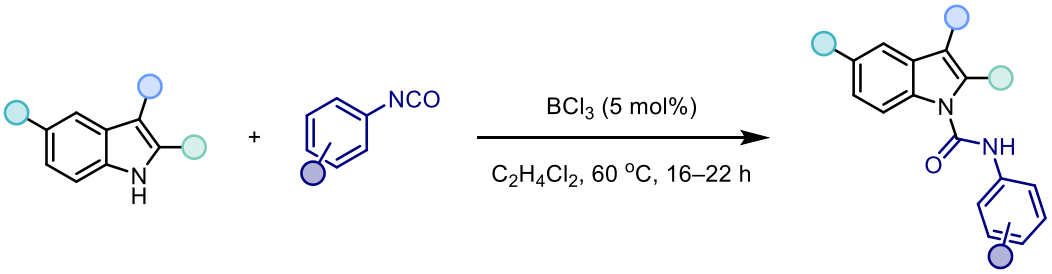
Unsurprisingly, a downfield shift of the signal corresponding to the proton in the C3 position occurred due to the presence of an amidic bond which decreases the shielding effect exerted by the lone pair of the nitrogen onto the C3 proton in the starting material (Figure 2.3). Interestingly instead, it was

possible to observe the change of the long-range ^4J coupling between the proton in C3 and the N–H proton in the starting material, which is usually a doublet of doublet of doublets (*ddd*). After the product formation, the coupling changed to a doublet of doublets (*dd*) due to the disappearance of the coupling with the N–H proton (Figure 2.3).

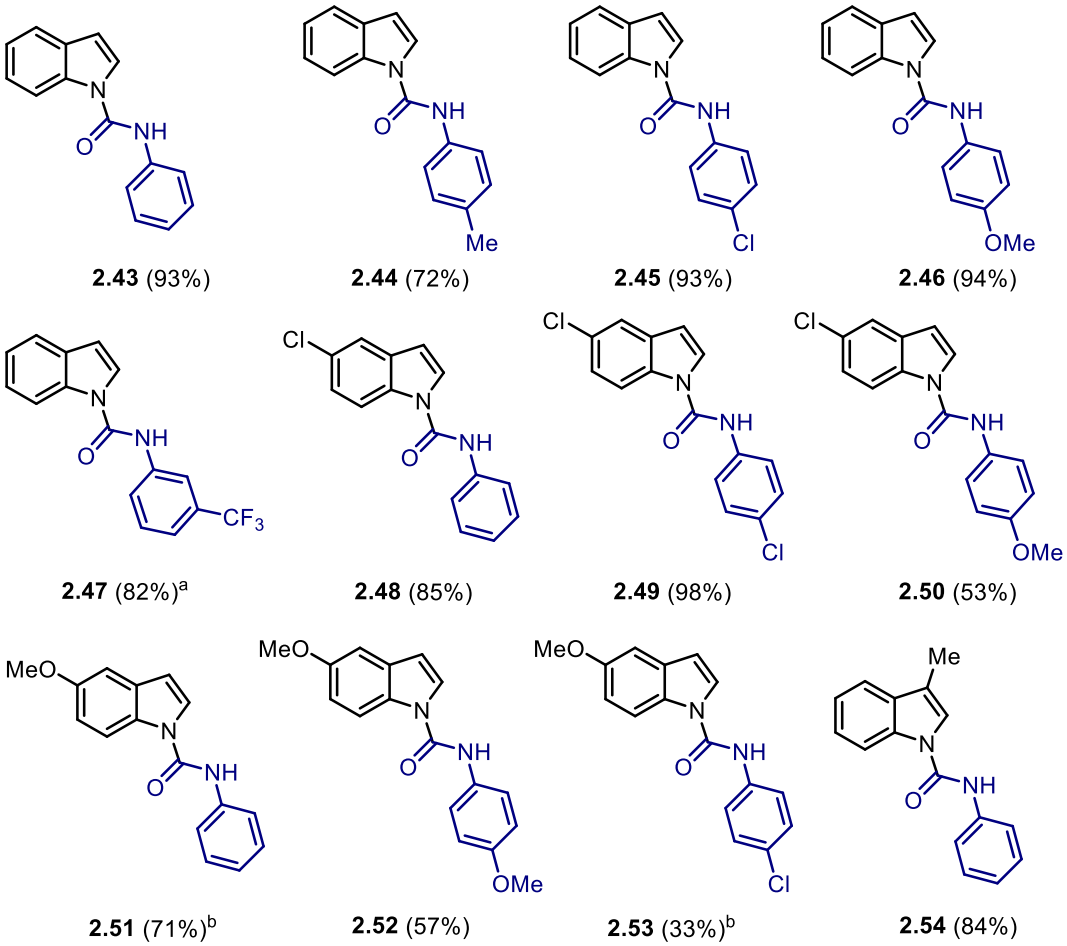
Crucially, the formation of the C3 functionalised product was not detected, despite the most nucleophilic position being the C3. With this preliminary result, a more thorough investigation for the most optimal reaction conditions was undertaken (Table 2.1). Increasing both the temperature (80 °C) and reaction time (72 hours) afforded the desired product in an unsatisfactory isolated yield of 23% (Table 2.1, entry 2). Increasing the temperature even more to 110 °C (Table 2.1, entry 3) and lowering the reaction time to 24 hours did not affect the yield. Instead, the increased temperature resulted in the formation of many decomposition products. Surprisingly, when the catalyst was switched from $B(C_6F_5)_3$ to $BF_3{\cdot}Et_2O$ – a catalyst with comparable strength – almost full conversion of the starting material was observed, with the yield of the desired product increasing to 46% (Table 2.1, entry 8). This result hinted that the Lewis acidity was not the only parameter to take into consideration, but presumably also the steric of the catalyst.

Further analysis into the reaction optimisation led to the discovery that the stronger Lewis acid BCl_3 affords the desired product in a 93% isolated yield (Table 2.1, entry 9). In sharp contrast to $BF_3{\cdot}Et_2O$ BCl_3 has been proven to be more Lewis acidic than $B(C_6F_5)_3$ by the most used experimental and computational methods such as Gutmann-Beckett, Childs, FIA and GEI.[15] The reason behind such a different Lewis acidity strength stems from the higher accessibility of the boron atom in BCl_3 which, upon coordination with a suitable Lewis base, possesses a lower strain upon pyramidalisation.[135] In search for better reaction conditions, it has been discovered that decreasing the catalyst loading from 20 mol% to 5 mol% did not have a significant impact on the isolated yield (Table 2.1, entries 10 and 11). Additionally, high reaction temperatures were not required since the same yield was obtained when the temperature was lowered to 60 °C (Table 2.1, entry 12). Decreasing the catalytic loading to

1 mol% did not afford the desired product (Table 2.1, entry 13). Finally, lowering the temperature to 45 °C or 25 °C affected the yield drastically, as observed in entries 14 and 15, which afforded product **2.43** in 52% and 20% yield, respectively. These experiments led to setting the best reaction conditions for the given transformation, which are in $C_2H_4Cl_2$ at 60 °C with 5 mol% of BCl_3 as the Lewis acid catalyst. With the optimised conditions in hand, a reaction scope was undertaken to assess the amenability of this protocol with different indoles and isocyanates (Scheme 2.16). Isocyanates possessing an electron donating group (EDG), such as -CH_3 (**2.44**) or -OCH_3 (**2.45**) afforded the N–H inserted product in good yields (72% and 94% respectively) and full regioselectivity, since again no C3 functionalised product was observed (Scheme 2.16). Similarly, isocyanates possessing halides such as -Cl (**2.45**) allowed the isolation of the corresponding product in 93% yield. In the case of entry **2.53**, the isolated yield was drastically lower (33%) due to the purification step which proved to be difficult since the compound decomposed on silica. The reaction was also scalable without negatively affecting the yield, as exemplified by compound **2.47** which was obtained in 82% yield after column chromatography on a 1 g scale using 10 mol% of catalytic loading. Interestingly, compound **2.47** is an intermediate for the synthesis of a VEGFR-2 inhibitor and its synthesis was reported using 2 equivalents of a NaH to couple the isocyanate and indole motif or using CuI as catalyst.[136] This method provides an alternative platform for its synthesis under Lewis acid catalysis regime.



a)

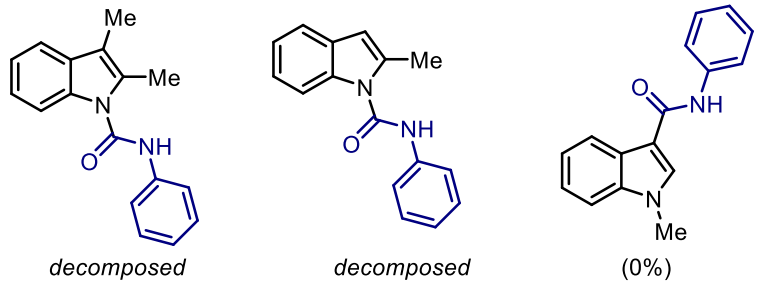


2.43 (93%) **2.44** (72%) **2.45** (93%) **2.46** (94%)

2.47 (82%)[a] **2.48** (85%) **2.49** (98%) **2.50** (53%)

2.51 (71%)[b] **2.52** (57%) **2.53** (33%)[b] **2.54** (84%)

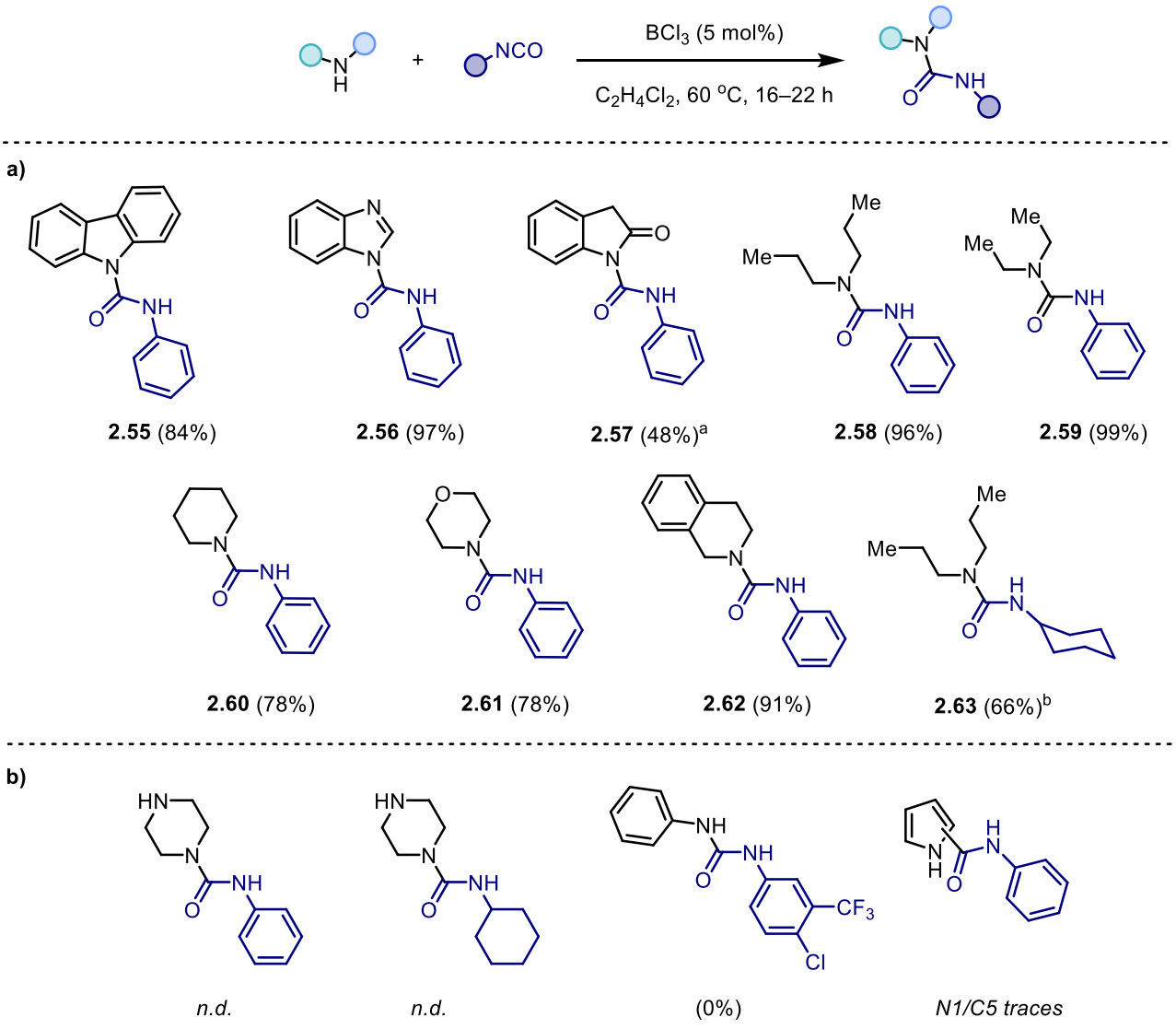
b)



decomposed *decomposed* (0%)

Scheme 2.16. **a)** Substrate scope with different unprotected indoles and isocyanates carried out on a 0.1 mmol scale. [a]Carried on a 1 g scale using 10 mol% of BCl_3 for 24 hours. [b]10 mol% of BCl_3 used. **b)** Failed substrates.

The reaction worked also when additional steric hindrance was introduced around the reactive centre as in the case of 2-methyl indole and 2,3-dimethyl indole, as evidenced by TLC analysis and crude ^{1}H NMR spectroscopic analysis. However, every attempt to purify the product led to its very quick decomposition, preventing the isolation of an analytically pure sample to include in the scope (Scheme 2.16, b). On the other hand, if the steric hindrance is removed from the reactive site, such as in the case of 3-methyl indole, the obtained product **2.54** is stable and can be obtained after preparative TLC in 84% yield. After these encouraging results, it was decided to expand the substrate scope further by including different heterocycles and non-aromatic nucleophilic amines (Scheme 2.17).

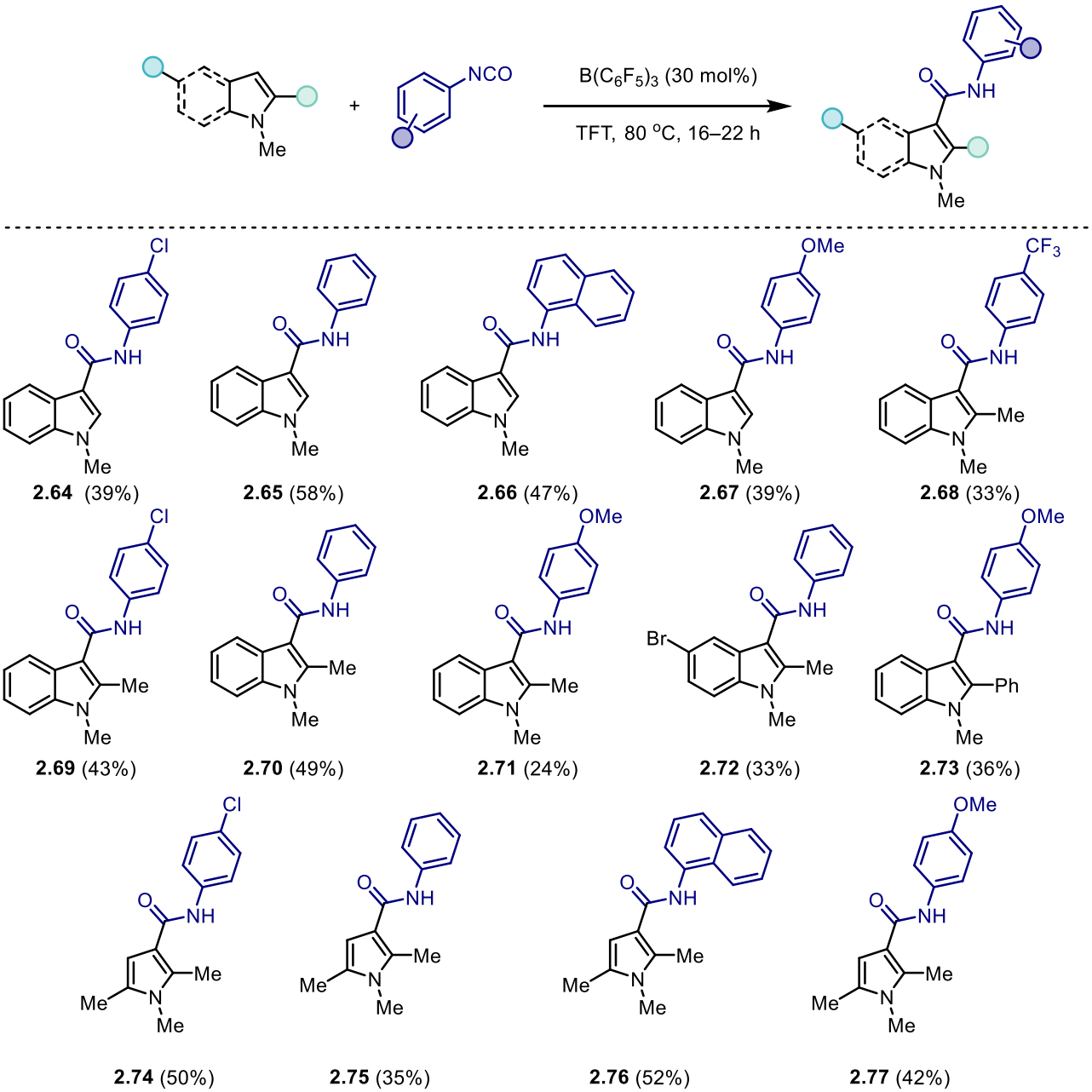


Scheme 2.17. **a)** Additional substrate scope with different *N*-heterocycles and *N*-nucleophiles carried out on a 0.1 mmol scale. [a]Reaction carried out for 24 hours. [b]10 mol% of BCl_3 used. **b)** Failed substrates.

The reaction proved to be compatible with different nitrogen heterocycles, as exemplified by the use of carbazole, benzimidazole, and 2-oxindole, which all led to the formation of the corresponding products **2.55**, **2.56** and **2.57** in 84%, 97% and 48% isolated yields, respectively (Scheme 2.17, a). The lower yield observed in the case of **2.57** can be attributed to chelate-type coordination of the boron catalyst with the amidic nitrogen and the oxygen in position 2, which hampers the overall yield of the process. Catalyst deactivation by Lewis basic moieties must be always considered when working with Lewis acid catalysts.[137,138] However, when highly basic amines such as piperidine, morpholine, diethyl/-propyl amine and tetrahydroisoquinoline were employed, the desired urea products **2.58**–**2.62** were obtained in good yields (78–99% yield) (Scheme 2.17, a). It is worth highlighting that this process doesn't strictly require a Lewis acid catalyst, since Bousfield and Camp showed that the same products can be obtained in the absence of any catalyst, albeit in slightly lower yields.[139] When piperazine was used as the nucleophilic partner of the reaction, no mono- (with 1 equiv.) or di- (with 2 equiv.) substituted ureas were obtained. Although the possibility of the formation of a small amount of the product is not entirely discarded, analysis of the crude reaction mixture proved to be complicated. In fact, copious amounts of white precipitate formed during the course of the reaction, and this was insoluble in either *d*-DMSO or D_2O. This could hint at a polymerisation side product. Disappointingly, in an attempt to synthesise the core of the drug Sorafenib, no urea product was obtained when 4-chloro-3-(trifluoromethyl)aniline was used. Finally, also pyrrole was investigated as a partner for the formation of *N*-functionalised heterocycles. Contrary to what has been observed in the presence of indole, where the reaction proved to be fully regioselective, when pyrrole was used a mixture of N1 and C5 functionalised products were detected in traces from the crude reaction mixture.

In parallel to the investigation of unprotected indoles with isocyanates, my colleague Nusaybah Alotaibi investigated the reaction with protected indoles. These results obtained by her are summarised below and have been put in my thesis only for a more complete overview and comparison of the chemistry performed in our group (Scheme 2.18). Interestingly, the reaction failed under the

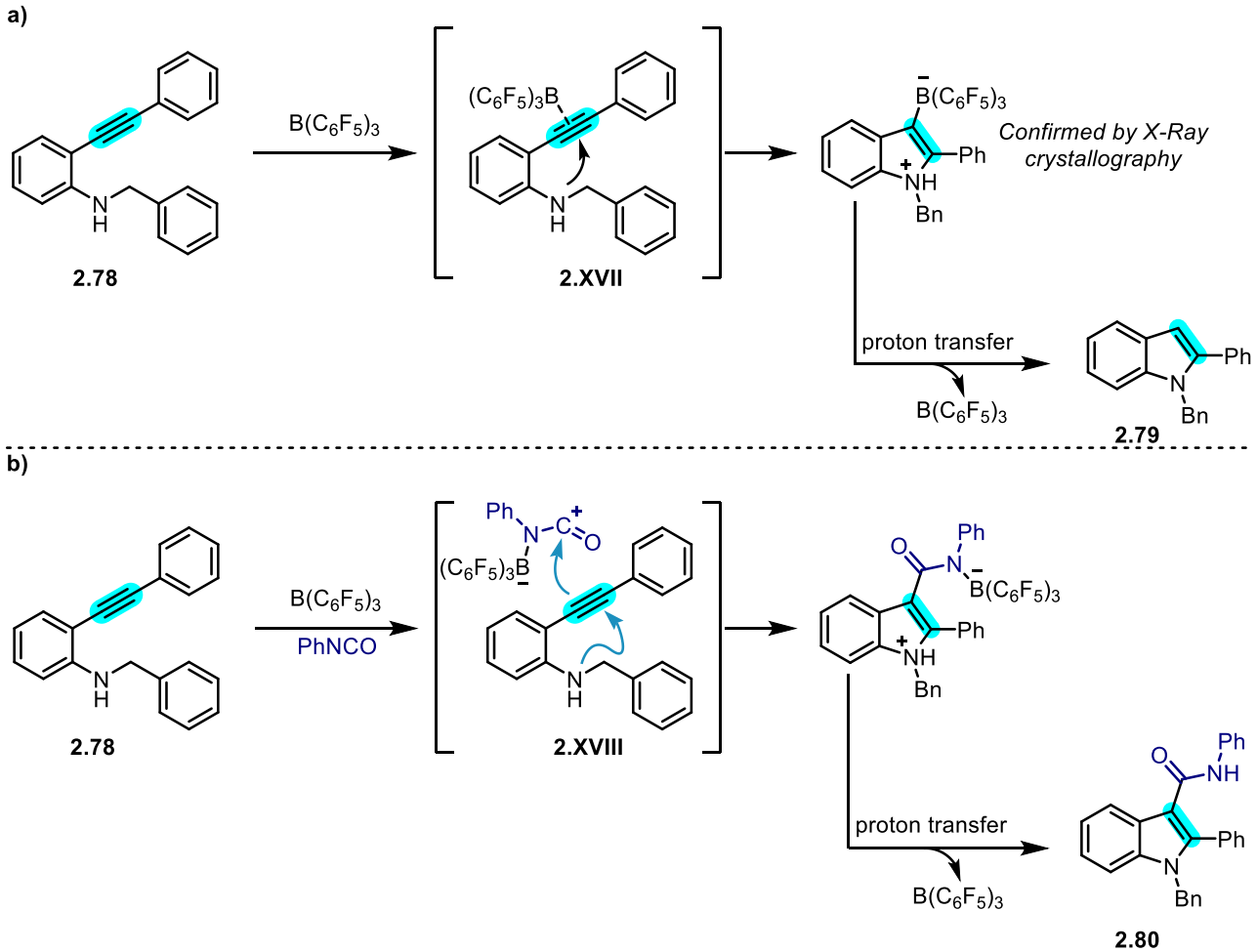
BCl_3-catalysed conditions and harsher conditions using $B(C_6F_5)_3$ were required to obtain appreciable amounts of product. This result presumably stems from the fact that the Lewis acid catalyst not only activates the isocyanate but also the indole scaffold (*vide infra*).



Scheme 2.18. Substrate scope with different *N*-methylated indoles/pyrroles and isocyanates performed by Nusaybah Alotaibi.

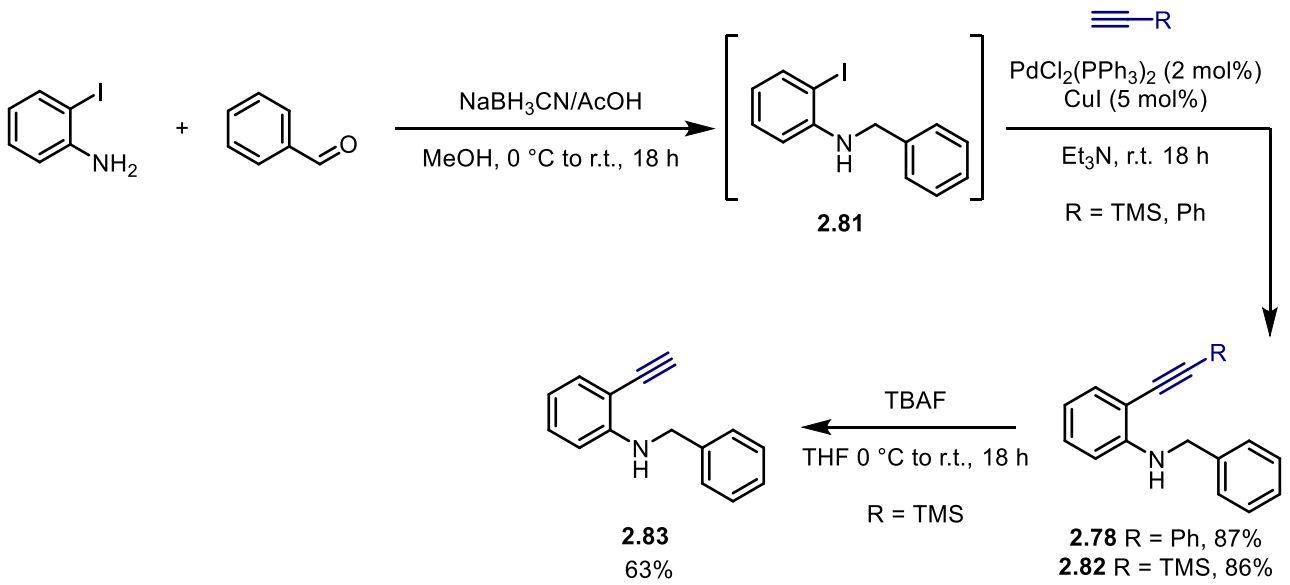
2.4.1. Attempts at the *in situ* synthesis of indole scaffolds

Under the borane catalysed conditions, the C3-functionalisation of protected indoles proved to be difficult, requiring harsh reaction conditions and high catalytic loadings. To address this limitation, we took inspiration from the work of Paradies *et al.*,[140] where they showed that 2-alkynyl anilines **2.78** can be cyclised using $B(C_6F_5)_3$ to afford Bn-protected indoles **2.79**. The reaction has been proposed to be an intramolecular hydroamination-deborylation process promoted by $B(C_6F_5)_3$, which presumably activates the alkyne moiety and triggers a 5-*endo*-dig cyclisation **2.XII** (Scheme 2.19, a). Thus, we envisioned we could trap the incipient indole **2.XIII** with a pre-activated isocyanate, affording the C3-functionalised product **2.80** in one pot (Scheme 2.19, b).



Scheme 2.19. **a)** Results from Paradies *et al.* **b)** Proposed mechanism for our approach.

Firstly, since 2-alkynyl anilines are not commercially available, they had to be prepared in three steps. The first step of the synthesis was carried out on a multigram scale, and it entailed a reductive amination between 2-iodoaniline with benzaldehyde under Gribble conditions ($NaBH_3CN$ in glacial acetic acid). After stirring the reaction at room temperature for 18 hours, and following a basic aqueous workup, the crude reaction mixture was used immediately in the next step. This was subjected to a Sonogashira cross-coupling using Wilkinson's catalyst $PdCl_2(PPh_3)_2$ (2 mol%), CuI (5 mol%) and phenyl/trimethyl silyl (TMS) acetylene as the coupling partner in Et_3N at room temperature for 24 hours. After the set amount of time, the reaction was diluted with CH_2Cl_2 and filtered through a short pad of celite before removing the solvent using rotary evaporation. Finally, the crude reaction mixture was purified by column chromatography affording the desired cross-coupled products **2.78** and **2.82** (Scheme 2.20). To investigate the substrate scope with different alkyne moieties, an additional step was required in the case of *N*-benzyl-2-((trimethylsilyl)ethynyl)aniline **2.82**, which was deprotected using tetrabutylammonium fluoride (TBAF) to afford the desilylated product **2.83** (Scheme 2.20).

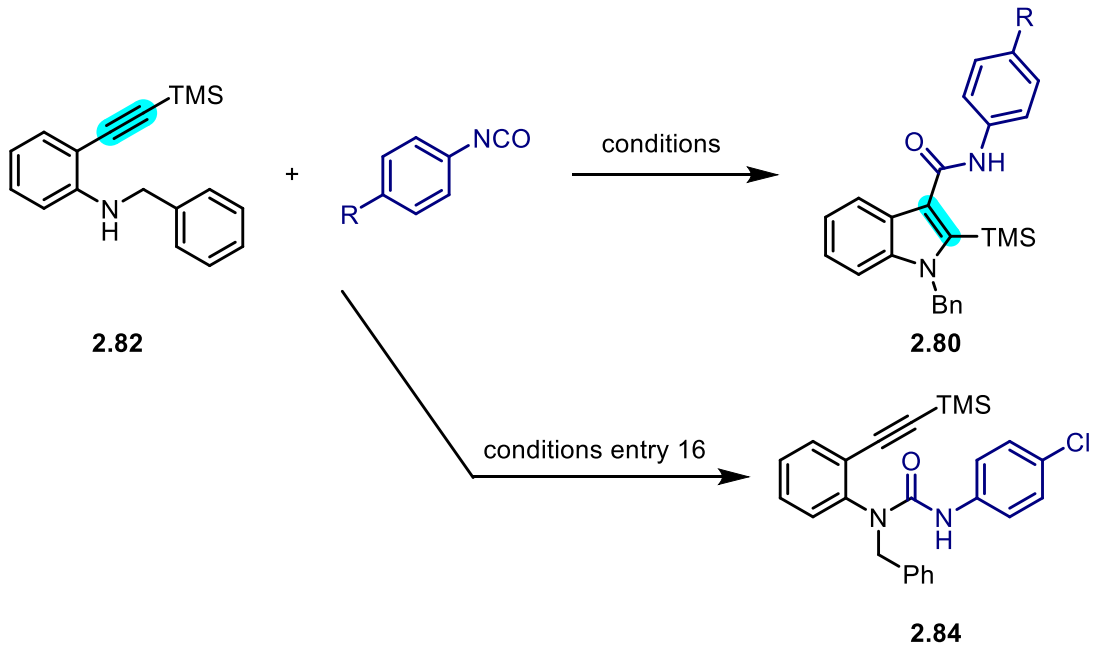


Scheme 2.20. Starting material synthesis for the intramolecular hydroamination-borylation reaction.

After preparing the desired starting materials, a reaction investigation took place to assess the feasibility of the desired transformation. Some experiments were initially undertaken with substrate

2.78 in parallel with substrate **2.82**. However, since the reactivity between the two proved to be similar, it has been decided to proceed with the reactivity investigation studies with substrate **2.82**, due to the ease of comparing the presence/absence of the TMS group, which could infer decomposition of the product via ^{1}H NMR spectroscopic analysis as well as the reduced number of peaks in the aromatic region.

Table 2.2. Conditions screening for the intramolecular cyclisation of 2-alkynyl anilines with isocyanates on a 0.1 mmol scale. [a]0.4 M instead of 0.67 M and with 4 Å MS. [b]used 10 mol% of Me_3SiOTf as an additive. [c]Yield of **2.84**.



Entry	(R)	Cat. (mol %)	Solvent (0.67 M)	T (°C)	Time (h)	Yield 2.80
1[a]	Cl	$B(C_6F_5)_3$ (5)	TFT	r.t. to 40	18	-
2[a]	Cl	$B(C_6F_5)_3$ (10)	TFT	r.t. to 40	18	-
3	Cl	$B(C_6F_5)_3$ (20)	TFT	45	24	-
4	Cl	$B(C_6F_5)_3$ (20)	TFT	80	24	-
5[b]	Cl	$B(C_6F_5)_3$ (10)	Toluene	110	24	-
6	H	$B(C_6F_5)_3$ (10)	TFT	25	24	-

7	H	$B(C_6F_5)_3$ (20)	TFT	65	24	-
8	H	$B(C_6F_5)_3$ (10)	Toluene	65	24	-
9	H	$B(C_6F_5)_3$ (10)	CH_3CN	65	24	-
10	H	$B(C_6F_5)_3$ (20)	THF	65	24	-
11	OMe	$B(C_6F_5)_3$ (20)	THF	65	24	-
12	Cl	$B(C_6F_5)_3$ (20)	TFT	–10 to 45	24	-
13	Cl	$B(2,4,6\text{-}F_3C_6H_2)_3$ (20)	TFT	–10 to 45	24	-
14	Cl	$B(3,4,5\text{-}F_3C_6H_2)_3$ (20)	TFT	–10 to 45	24	-
15	Cl	BCl_3 (5) $B(C_6F_5)_3$ (10)	TFT	r.t. to 40	18	-
16	Cl	BCl_3 (5)	$C_2H_4Cl_2$	60	18	61%[c]

As can be seen in Table 2.2, every attempt to form the desired product failed, affording only unreacted starting material, decomposition products and trace amounts of the indole derivative, deriving from the cyclisation described in Paradies' work. It has also been attempted to tackle the transformation using a dual catalytic approach (Table 2.2, entry 15). In detail, it has been envisaged to use BCl_3 to activate the isocyanate similarly to the N–H insertion reaction, and to use $B(C_6F_5)_3$ to activate the triple bond and setting up the system for the subsequent cyclisation. However, instead of the desired transformation, BCl_3 catalysed N–H insertion of the benzylic nitrogen with the isocyanate occurred, affording compound **2.84**. Indeed, after preparative TLC, a solid product was obtained which was subsequently recrystallised by slow evaporation from a CH_2Cl_2 solution affording crystals suitable for single crystal X-ray diffraction, which unambiguously showed the N–H inserted product **2.84** (Figure 2.4).

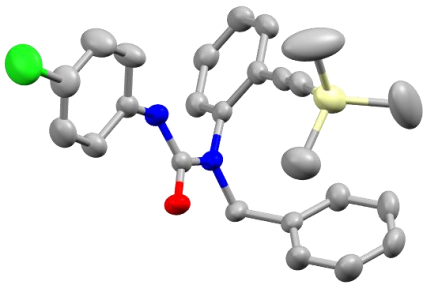
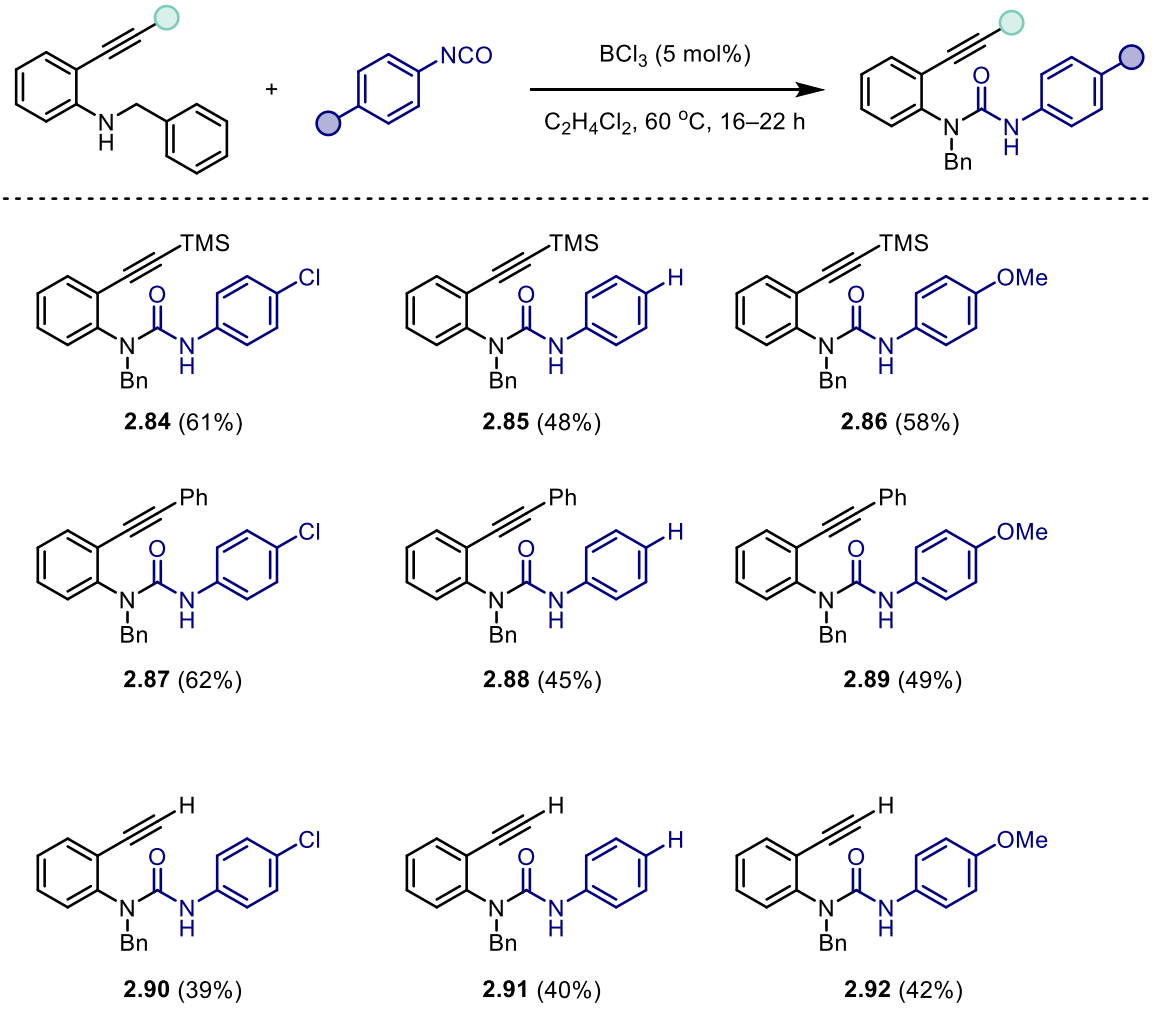


Figure 2.4. Crystal structure of compound **2.84**. Carbon: grey; nitrogen: blue; oxygen: red; chlorine: green; silicon: beige. Hydrogen atoms omitted for clarity. Ellipsoids are shown at 50% probability.

Interestingly, the same conditions applied to the N–H insertion of indoles (Table 2.2, entry 16) were also applied to these substrates, which pleasingly afforded the corresponding products in good yield (61%). Similar products to **2.84** have been recently employed as precursors to highly functionalised azaindoles,[141] indoles and benzoxazines.[142] Given the unsuccessful results for the attempted cyclisation reaction and the synthetic utility of products of the type **2.84**, it has been decided to investigate a substrate scope concerning different isocyanates and alkynyl anilines, to assess the amenability of the protocol and to evaluate the effect of EDGs or EWGs on the reactivity profile (Scheme 2.21).



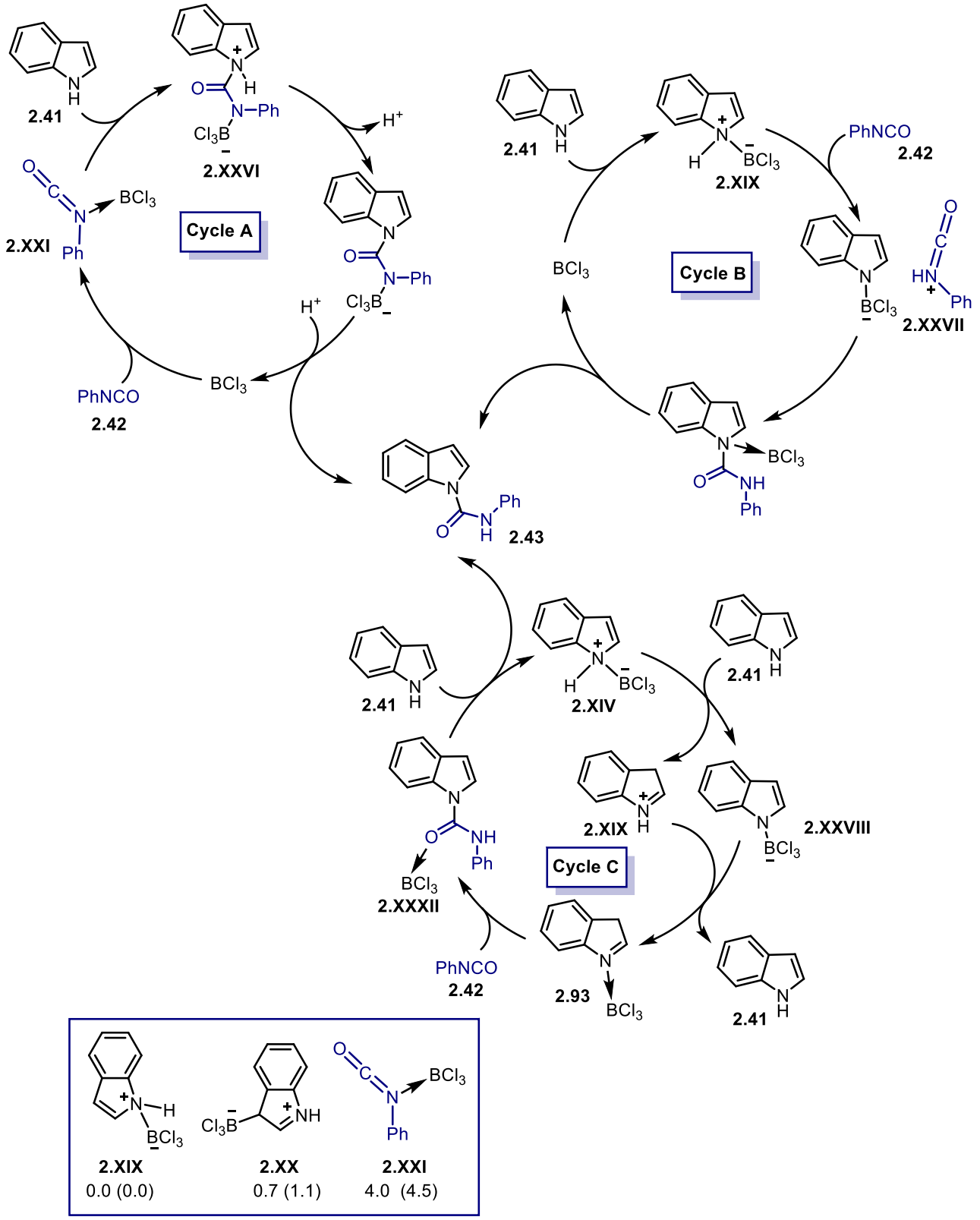
Scheme 2.21. Substrate scope between isocyanates and alkynyl benzyl amines on a 0.1 mmol scale.

The isolated yields of the products proved to be modest (39%–62%), where the highest yield was obtained with substrate **2.87** in 62% yield. The rest of the mass balance was accounted as unreacted starting material and decomposition products, without detecting a possible cyclised product. Moreover, no reactivity pattern in terms of EDG or EWG on the isocyanate was noticed, since all the products have been obtained with comparable yield. Nevertheless, as highlighted above, these products can be further transformed into valuable heterocyclic compounds, rendering the developed protocol useful for downstream transformations.

2.4.2. Computational insights and mechanistic experiments

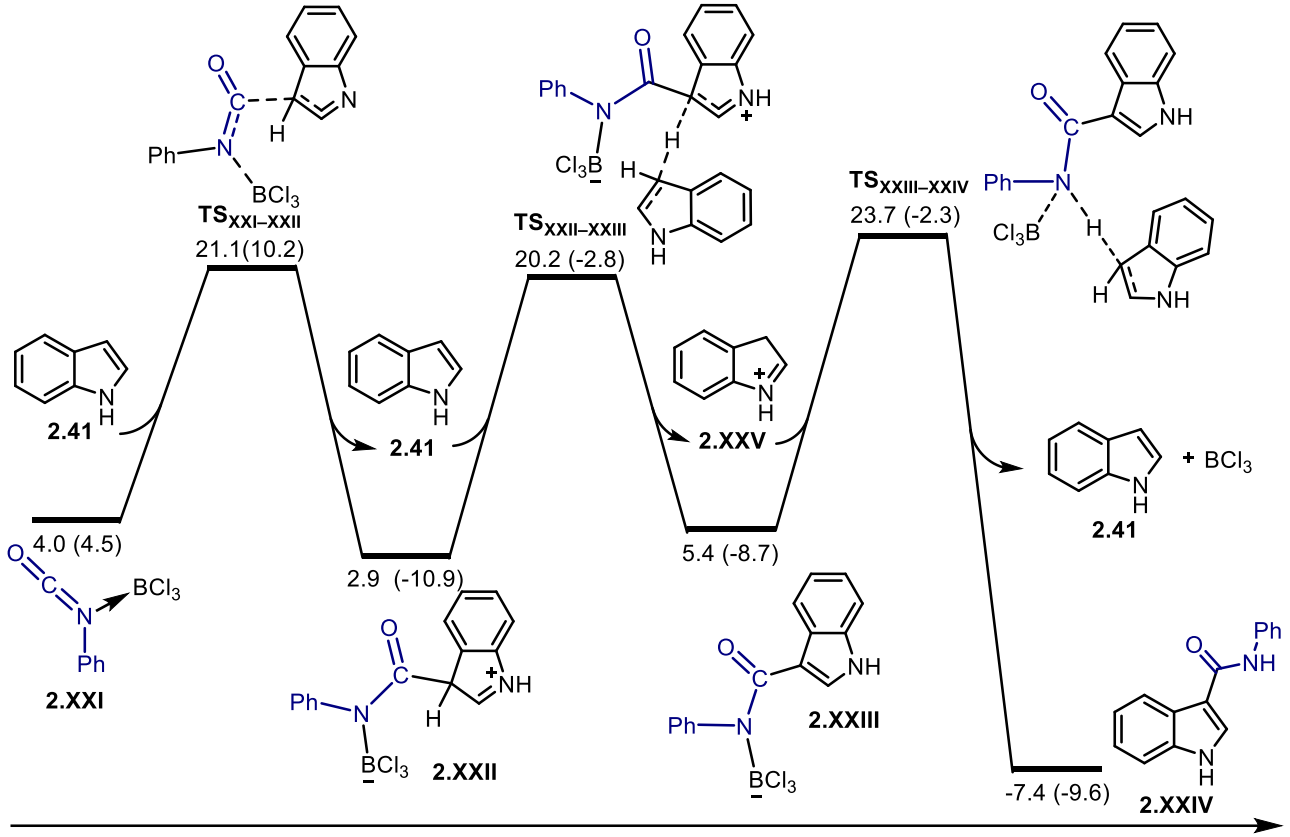
Intrigued by the peculiar regioselectivity observed for the formation of the N–H inserted products for indoles, DFT studies have been done in collaboration with the group of Prof Alireza Ariafard from the University of Tasmania by Dr. Kaveh Farshadfar to elucidate the reaction mechanism.

DFT calculations were performed at the SMD/M06-2X-D3/def2-TZVP//SMD/M06-2X/6-31G(d) level of theory in $C_2H_4Cl_2$ to compare three different catalytic cycles A, B, and C (Scheme 2.22). For these calculations, three different coordination sites can be envisaged between BCl_3 and the reactants (Scheme 2.22, insert). In particular, the boron Lewis acid can establish an acid-base Lewis adduct with the nitrogen lone pair of the indole **2.XIX**, as well as forming a C3 borylated indole adduct **2.XX**. It can also form an adduct with the nitrogen lone pair of the isocyanate leading to **2.XXI**, as we have also proved in a separate study.[143] Among them, the Lewis acid-base adduct **2.XIX** proved to be the most stable one, and was therefore set as the reference structure throughout the calculation.



Scheme 2.22. Three possible catalytic cycles for the N–H insertion of isocyanates in indoles. Insert: three possible coordination sites for BCl_3. Free energies (potential energies) are given in kcal/mol.

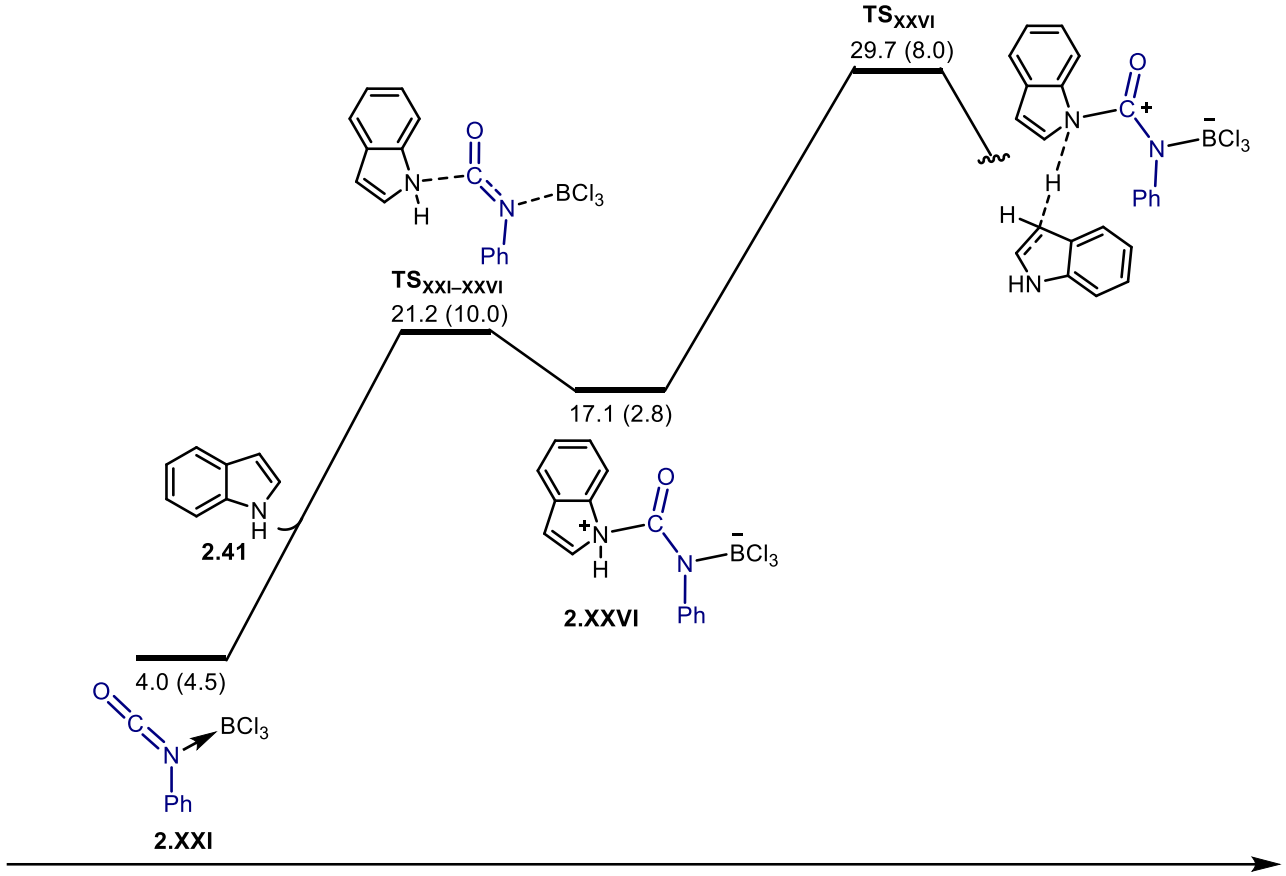
To begin with, a calculation entailing the C3-functionalisation of unprotected indoles, which in turn would allow a comparison with the N–H insertion, was undertaken. In the conventional mechanism, as depicted in Scheme 2.23, the Lewis acid BCl_3 activates the isocyanate, rendering it more electrophilic. This activation sets up the subsequent nucleophilic addition from the C3 position of the indole, known to be the most nucleophilic site in the molecule. Although boron is a highly oxyphilic element, we have shown in another work that the coordination with isocyanates preferentially occurs with the nitrogen lone pair over the oxygen with a $\Delta\Delta G = 3.5$ kcal/mol.[143] Through a series of proton transfers from **2.XXII** to **2.XXIV** aided by a second molecule of indole, the C3-functionalised product could be in principle obtained with an overall activation energy of 23.7 kcal/mol (Scheme 2.23).



Scheme 2.23. DFT computed reaction pathway for the conventional mechanism calculated using SMD/M06-2X-D3/def2-TZVP//SMD/ M06-2X/ 6-31G(d) level of theory in dichloroethane for the C3-functionalisation of 1*H*-indole using phenyl isocyanate and BCl_3 as a catalyst. Free energies (potential energies) are given in kcal/mol.

Since this pathway is in contrast with the experimental evidence, a different lower energy pathway must be responsible for the exclusive formation of the N–H inserted product. Hence, three different pathways have been calculated.

The first pathway for the exclusive N–H insertion taken into consideration includes a direct nucleophilic addition from the nitrogen centre to the activated isocyanate, with a **TS$_{XXI–XXVI}$** which lies at the same energy level as **TS$_{XXI–XXII}$** (cycle A, Scheme 2.24).

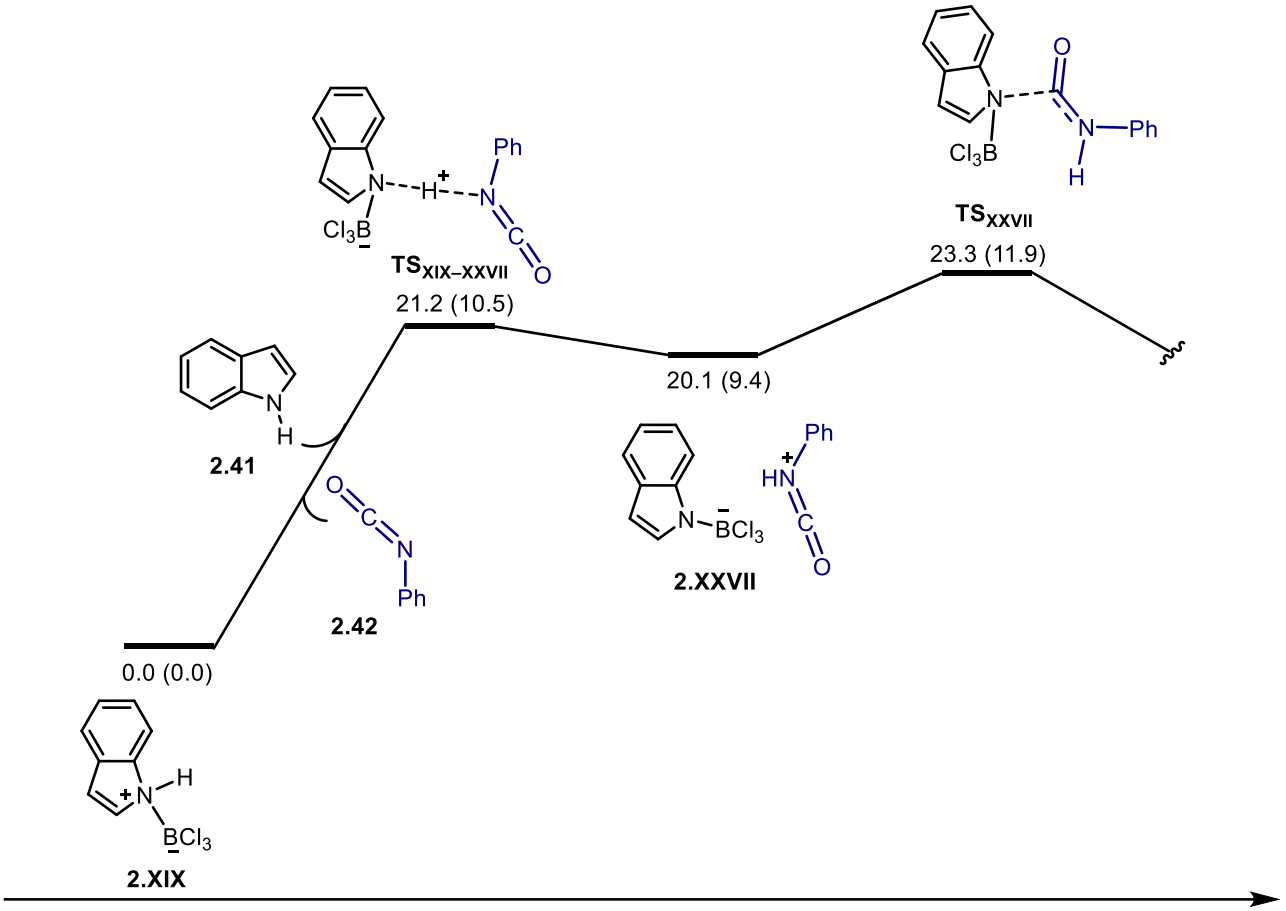


Scheme 2.24. DFT computed reaction pathway for cycle A calculated using SMD/M06-2X-D3/def2-TZVP//SMD/ M06-2X/ 6-31G(d) level of theory in dichloroethane for the *N*-functionalisation of 1*H*-indole using phenyl isocyanate and BCl_3 as a catalyst. Free energies (potential energies) are given in kcal/mol.

However, the subsequent proton transfer through **TS$_{XXVI}$** requires overcoming an energy barrier of 29.7 kcal/mol, which is too high compared to the conventional mechanism. Additionally, the unfavourable character of this pathway is due to the much lower stability of intermediate **2.XXVI**

compared to its counterpart intermediate **2.XXII**. Therefore, these results discounted cycle A as the possible operational mechanism.

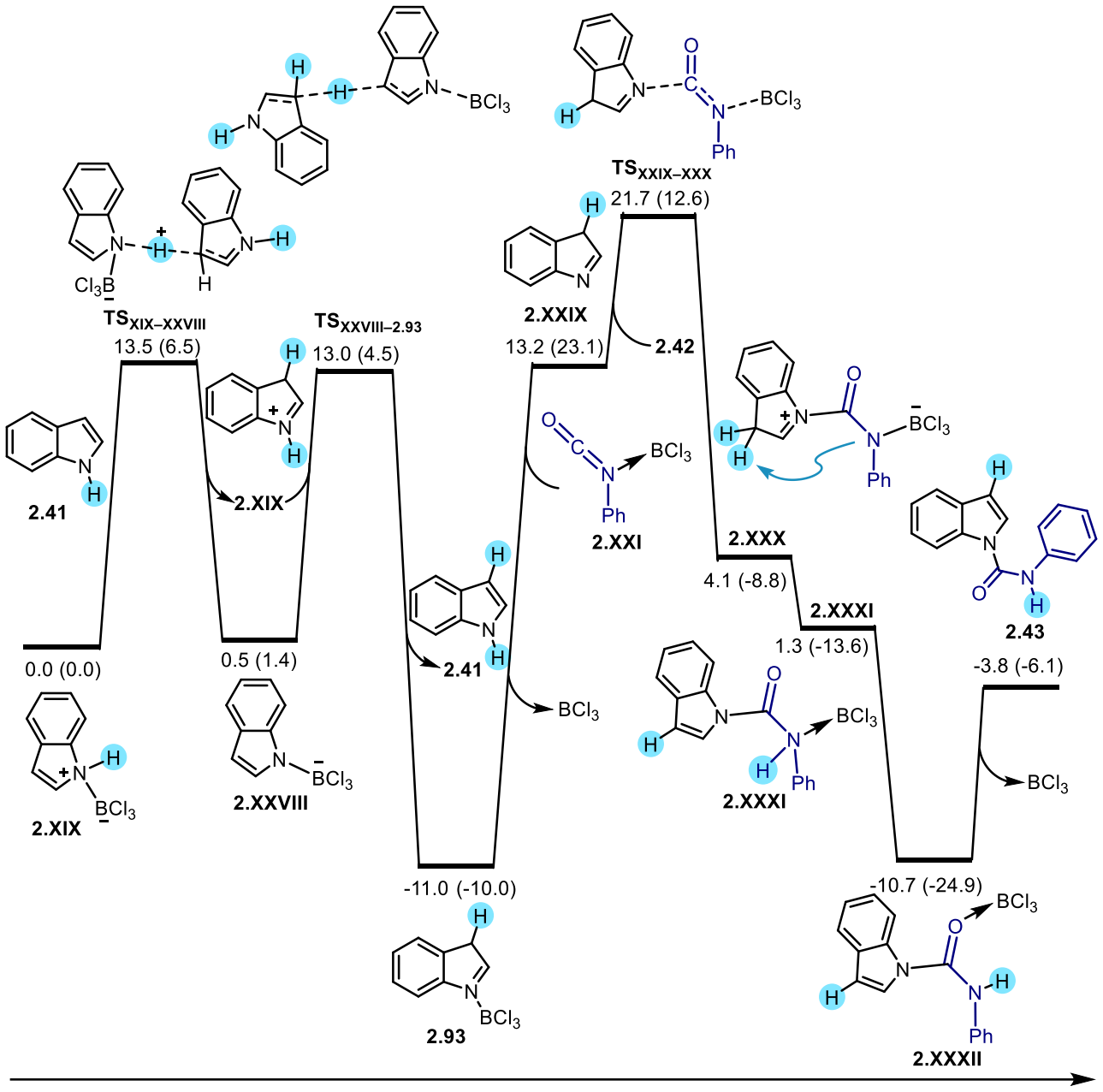
Cycle B instead considers a mechanism that takes place via the Lewis acid-assisted Brønsted acid activation mode (Scheme 2.25).[143]



Scheme 2.25. DFT computed reaction pathway for cycle B calculated using SMD/M06-2X-D3/def2-TZVP//SMD/ M06-2X/ 6-31G(d) level of theory in dichloroethane for the *N*-functionalisation of 1*H*-indole using phenyl isocyanate and BCl_3 as a catalyst. Free energies (potential energies) are given in kcal/mol.

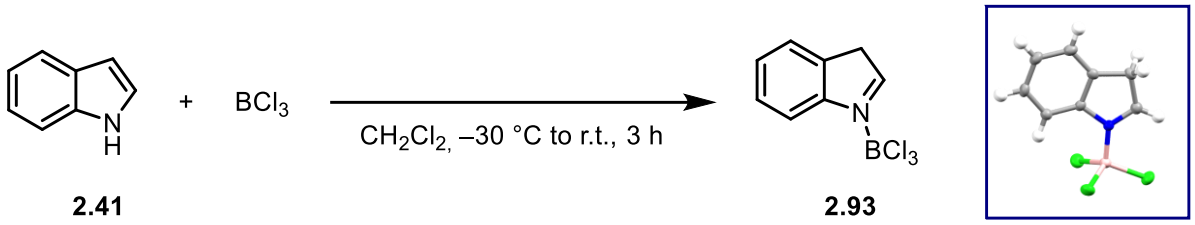
In detail, BCl_3 acts as a Lewis acid with respect to the indole, forming the adduct **2.XIX** which has become formally a Brønsted acid. This can protonate a free isocyanate molecule to afford the ion pair **2.XXVII** after surmounting an energy barrier of 21.2 kcal/mol (Scheme 2.25). However, the subsequent **TS**$_{\textbf{XXVII}}$ possesses an energy barrier which is comparable to the one calculated for the conventional mechanism in Scheme 2.23, thus discarding this pathway as the operational one as well.

Lastly, a third catalytic cycle (cycle C, Scheme 2.26) has been proposed which accounts for the selective formation of the observed product. In this mechanism, a key imine-BCl_3 boron-"*ate*" **2.93** adduct is formed in an exergonic process ($\Delta G = -11.0$ kcal/mol) after a series of proton transfers with an overall activation barrier of 13.5 Kcal/mol (**TS$_{XIX-XXVIII}$**, Scheme 2.26).[144] This low-energy pathway implies that in the presence of BCl_3, the indole first forms the imine adduct, instead of proceeding through the other possibilities described above. From this energy minimum, BCl_3 can be liberated to activate a free isocyanate molecule **2.42**. The free indolyl anion can now attack the activated isocyanate through **TS$_{XXIX-XXX}$**, with an overall activation barrier of 32.7 kcal/mol. Finally, in an exergonic process, the N–H product **2.43** forms the indole core after a 1,5-H shift and aromatisation (Scheme 2.26).



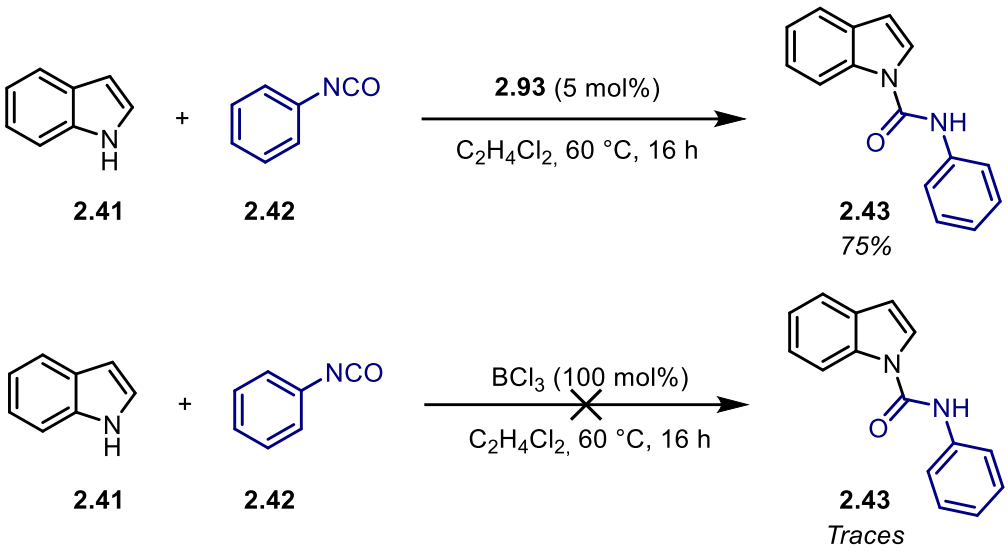
Scheme 2.26. DFT computed reaction pathway for cycle C calculated using the SMD/M06-2X-D3/def2-TZVP//SMD/ M06-2X/ 6-31G(d) level of theory in dichloroethane for the *N*-functionalisation of 1*H*-indole using phenyl isocyanate and BCl_3 as a catalyst. Free energies (potential energies) are given in kcal/mol.

To further support these findings, additional control experiments were carried out. Firstly, the imine-BCl_3 adduct was synthesised following a reported procedure.[145] In the glovebox, mixing an equimolar amount of indole and BCl_3 in CH_2Cl_2 led to the immediate formation of a white precipitate. Removal of the solvent and recrystallisation from a CH_2Cl_2 solution afforded crystals suitable for single-crystal X-ray diffraction, which unambiguously revealed the formation of adduct **2.93** (Scheme 2.27).



Scheme 2.27. Reaction Scheme for the imine-BCl_3 adduct. Insert crystal structure of compound **2.93**. Carbon: grey; nitrogen: blue; oxygen: red; boron: pink; chlorine: green. Hydrogen atoms omitted for clarity. Ellipsoids shown at 50% probability.

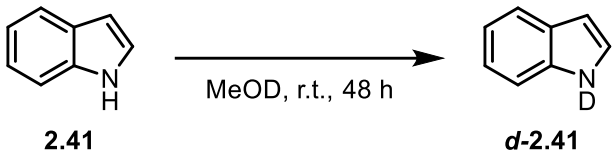
This adduct is the catalyst resting state, hence a reaction with this species instead of BCl_3 should form the desired product. Thus, instead of BCl_3, the synthesis of compound **2.43** was attempted using **2.93** which was formed in 75% yield. Moreover, free indole is important for the proton transfer process to occur. Hence, a stoichiometric amount of BCl_3 would in principle quench the reactivity by forming 1 equivalent of **2.93** from the free indole. This again proved to be the case when the same reaction was attempted with 1 equivalent of Lewis acid (Scheme 2.28).



Scheme 2.28. Mechanistic experiments to support the DFT-calculated pathway.

Lastly, a labelling experiment was also conducted. As can be seen in Scheme 2.24, the light blue highlighted N–H proton should be scrambled during the proton transfer processes. To prove this, a

deuterated indole ***d*-2.41** was first synthesised (Scheme 2.29) affording the deuterated heterocycle with a deuterium incorporation greater than 99% (Figure 2.5).



2.41 ***d*-2.41**

Scheme **2.29**. Reaction scheme for the synthesis of deuterated indole.

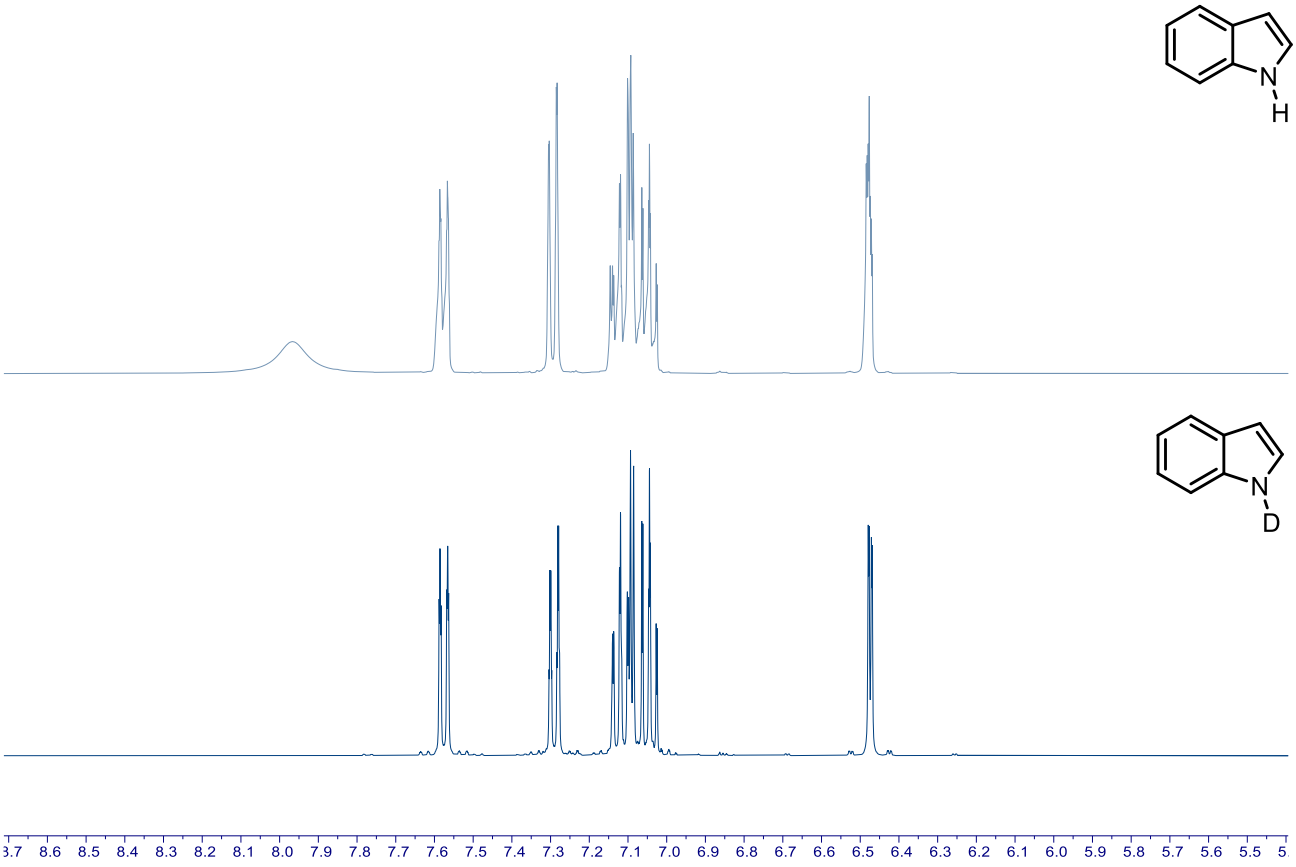
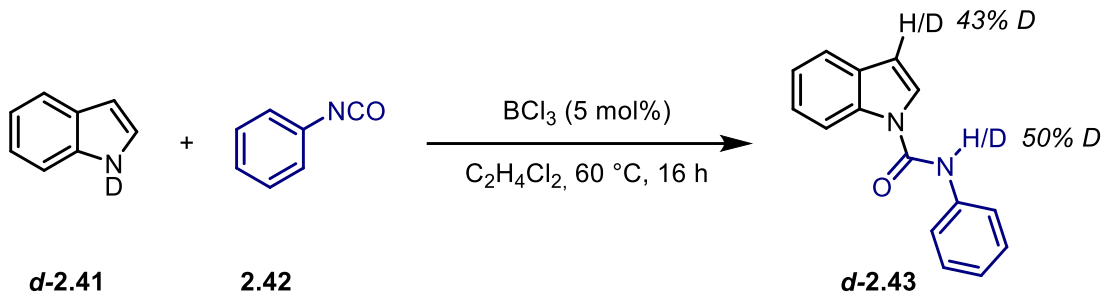


Figure **2.5**. Stacked ^{1}H NMR spectra of the indole starting material **2.41** (top) and its deuterated form ***d*-2.41** (bottom).

Subsequently, ***d*-2.41** was employed as the reactive partner in the N–H insertion reaction which, after analysis of the crude reaction mixture, proved that the scrambling took place with almost 50% deuterium incorporation into the two predicted positions (Scheme 2.30 and Figure 2.6). This last experiment further supported the DFT calculated pathway.



Scheme **2.30**. Deuterium labelling experiment.

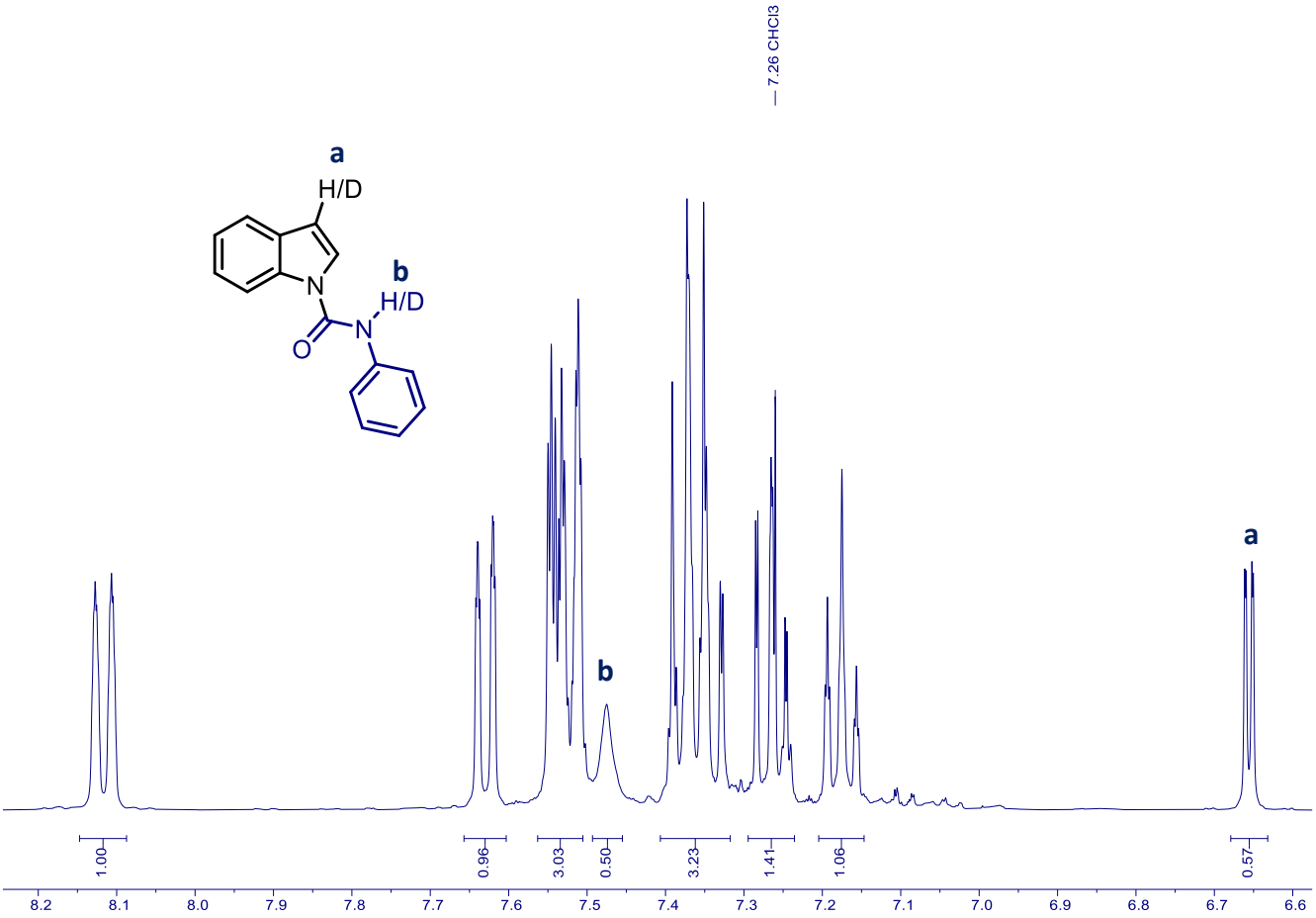
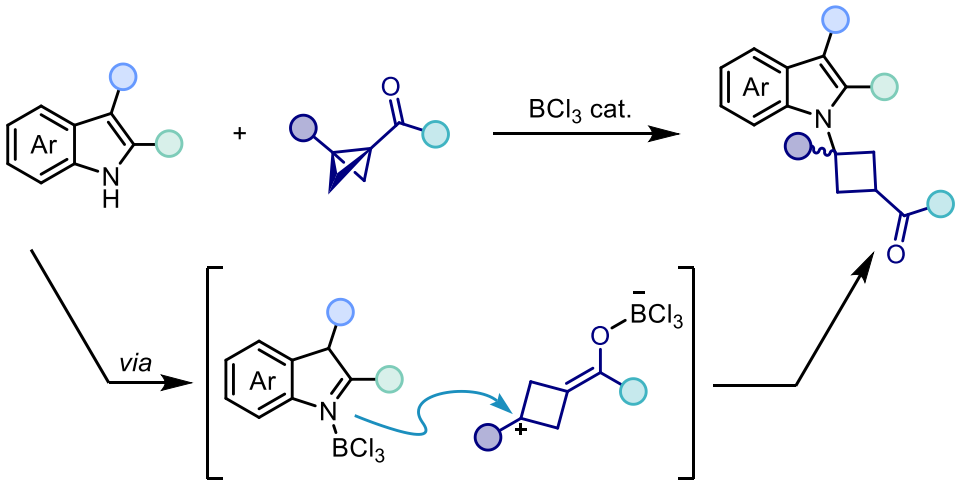


Figure **2.6**. Crude ^{1}H NMR spectrum showing the formation of ***d*-2.43**.

2.5. Conclusions

In conclusion, the work in this chapter highlights the ability of the cheap Lewis acid BCl_3 to efficiently catalyse the regioselective N–H insertion of heterocycles and, more broadly, nucleophilic amines. Anilines bearing an alkyne-tethered moiety can be also used as reactive partners, allowing the synthesis of products useful for downstream modifications.[134,141,142] Furthermore, DFT studies have

been undertaken which shed light on the formation of a boron-"*ate*"[144] complex which is responsible for the observed chemoselectivity. Additional mechanistic experiments agree with the proposed mechanism. This methodology adds up to the synthetic chemist toolbox and could be used as an alternative to the use of an excess of strong bases or the use of transition metals to functionalise indoles at the N1 position. Crucially, the activation mode of the indole scaffold which entails an imine-BCl_3 adduct can be leveraged for novel transformations with different electrophilic partners. For example, it has been recently demonstrated that bicyclobutanes (BCBs) can be used to generate an electrophilic cyclobutane upon Lewis acid addition.[146] Hence, given the rising interest of cyclobutane ring in medicinal chemistry,[147] a methodology based on the BCl_3-catalysed indole activation can be envisaged, which would install a cyclobutane on the N1 position of indole (Scheme 2.31).



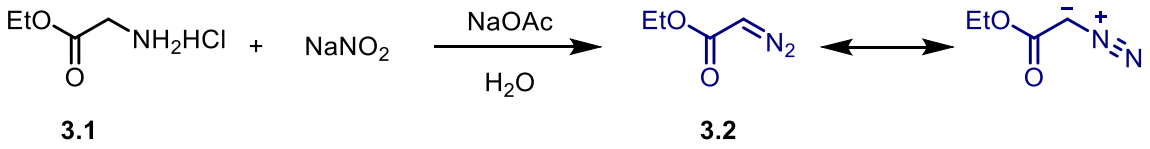
Scheme **2.31**. Possible utilisation of the BCl_3-catalysed indole activation and BCB ring opening.

3. $B(C_6F_5)_3$-catalysed [3+2] dipolar cycloaddition and Mukaiyama-Mannich addition of diazo esters with nitrones

This chapter details the [3+2] dipolar cycloaddition and the Mukaiyama-Mannich addition of nitrones with diazo esters catalysed by $B(C_6F_5)_3$. The introduction will describe the chemistry of carbenes and diazo compounds and their reactions with boron Lewis acids, whereas the chemistry of nitrones will be disclosed in more detail in Chapter 4. The results and discussion section will present the studies undertaken to develop a methodology which ultimately maintains intact the diazo functionality under Lewis acid catalysed conditions. Finally, further functionalisation of the obtained products will be presented.

3.1. The chemistry of carbenes

The discovery and initial development of diazo chemistry can be attributed to Theodor Curtius who, in 1883, first discovered that by mixing the ethyl ester of glycine **3.1** with $NaNO_2$ and NaOAc in water a highly reactive red oil can be obtained: ethyl diazoacetate (EDA) (Scheme 3.1, **3.2**).[148]

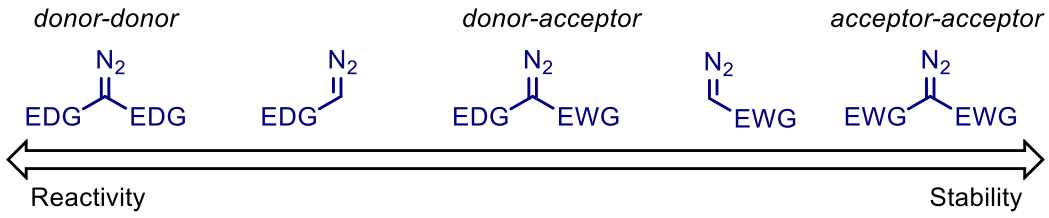


3.1 **3.2**

Scheme 3.1. The first described synthesis of ethyl diazoacetate.

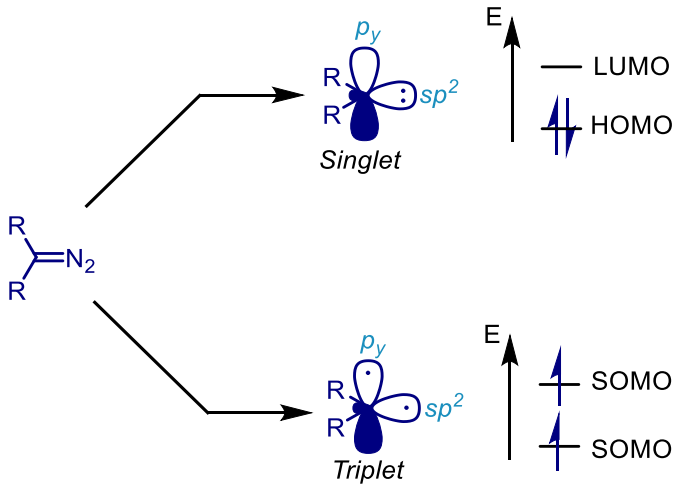
The reactive intermediate **3.2** embeds in its structure a carbon bound to two linked nitrogen atoms, with an overall neutral charge. The formation of a stable N_2 molecule upon diazo decomposition makes diazo compounds very useful sources of carbenes, hence they have been extensively used as carbene equivalents in modern synthetic organic chemistry.[149–152] The rich chemistry of diazo

compounds has been known for more than a century and it has recently flourished in coupling with photocatalysis since the carbene derived from the N_2 liberation can be easily accessed by light irradiation.[153] The reactivity of these neutral molecules can be easily understood by drawing the resonance form of **3.2**, which highlights the high basicity of the α-carbon (Scheme 3.1). This feature renders diazo compounds easily protonated at this position, forming a diazonium species which lastly can liberate N_2 in an exergonic (and sometimes explosive) fashion. Nevertheless, their high reactivity can be easily tuned by introducing EWGs which can allow a delocalisation of the α-negative charge, allowing an easier and safer manipulation (Scheme 3.2).[149,154] In general, donor-donor diazo compounds are too reactive and the derived carbene is hard to control for synthetic purposes (Scheme 3.2).[149] On the contrary, acceptor-acceptor diazo compounds require more forcing conditions to form the carbene equivalent, which in turn can decrease the functional group tolerability. With this regard, donor-acceptor diazo compounds such as α-aryl diazo esters have found broad applicability since they possess a good balance between stability and reactivity.[149]



Scheme 3.2. From left to right: increasing stability of classes of diazo compounds. From right to left: increasing reactivity of classes of diazo compounds.

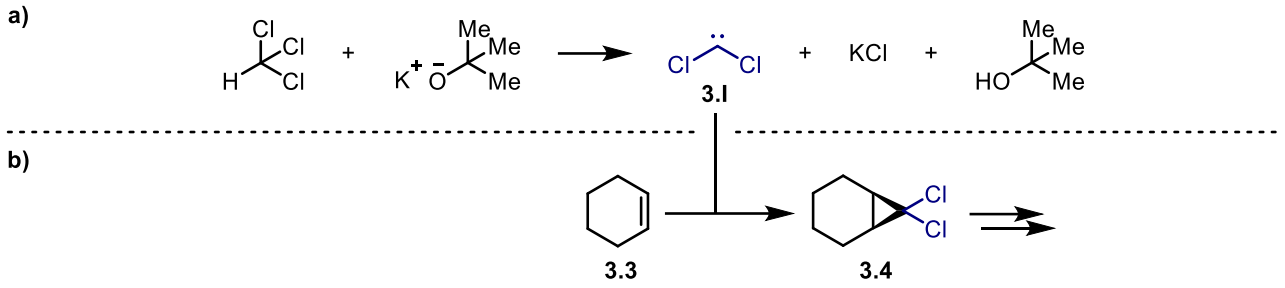
A carbene is formally defined as a molecule possessing a carbon which is not charged but possesses two valence electrons and it can be of two types: a singlet or a triplet carbene. The former is generated when the two non-bonding electrons are accommodated in an sp^2 orbital with an antiparallel spin (Scheme 3.3). The latter is formed when one of the two electrons resides in the *p*-orbital (e.g. the p_y) and the other in an sp^2-hybrid atomic orbital, giving rise to two singly occupied molecular orbitals (SOMOs) (Scheme 3.3). This different electronic structure mainly depends on the method of generation of the carbene and the nature of substituents which impart different reactivity profiles.[149]



Scheme 3.3. The two types of carbene.

Formation of singlet carbenes can be accomplished by leveraging the EWG effect of the α-substituents, which greatly stabilise the singlet state by lowering the energy of the HOMO. Historically, one of the earliest methods to generate singlet carbenes derived from the treatment of chloroform with a strong base such as KO^{t}Bu. In this way, α-elimination can occur generating the dichlorocarbene species **3.I** (Scheme 3.4, a).[155] This can further react with an olefin to perform a [2+1] cycloaddition forming **3.4** (Scheme 3.4, b). Despite the ease in generating carbenes from simple reagents, free, non-stabilised carbenes such as **3.I** have found limited synthetic utility since the high reactivity hampers a broader scope. Indeed, methylene has been classified as "the most indiscriminate reagent known in organic chemistry".[156]

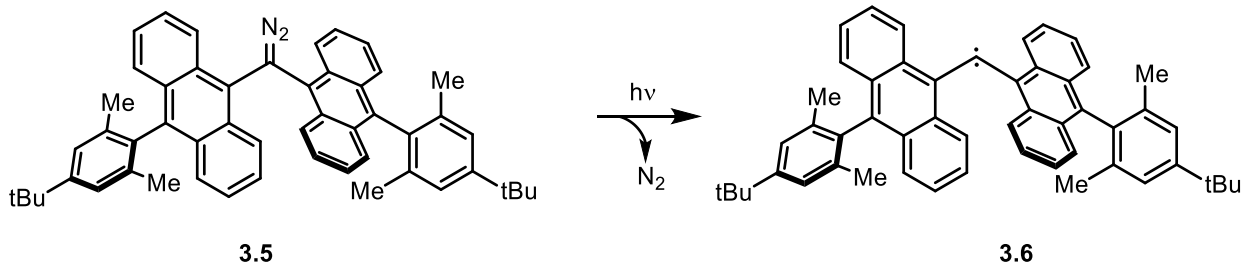
Additionally, the singlet carbene derived in this way should be not confused with the *carbenoid* derived from the famous Simmons-Smith cyclopropanation which behaves similarly but possesses different characteristics.[157,158] Interestingly, very recently the term *carbenoid* has been challenged, and it has been proposed to use it only when central tetrasubstituted carbon atoms bearing a leaving group and a bound metal are present.[159]



Scheme 3.4. **a)** Generation of dichlorocarbene from chloroform. **b)** Cyclopropanation of olefins.

Singlet carbenes derived from diazo compounds have also been used in synthetic chemistry not only as partners in cyclopropanation reactions where they react as strong Lewis acids with respect to the π-bond, but also to perform C–H insertion reactions when they react with σ-bonds.[160]

On the other hand, the formation of more elusive triplet carbene can be obtained by the photolysis of a sterically encumbered diazo, as demonstrated by the group of Tamioka in 2003.[161] The blueprint of their approach was the utilisation of a bulky and extended aromatic molecule such as **3.5**, which could stabilise the triplet state of the diradical **3.6** for up to a week under air (Scheme 3.5).



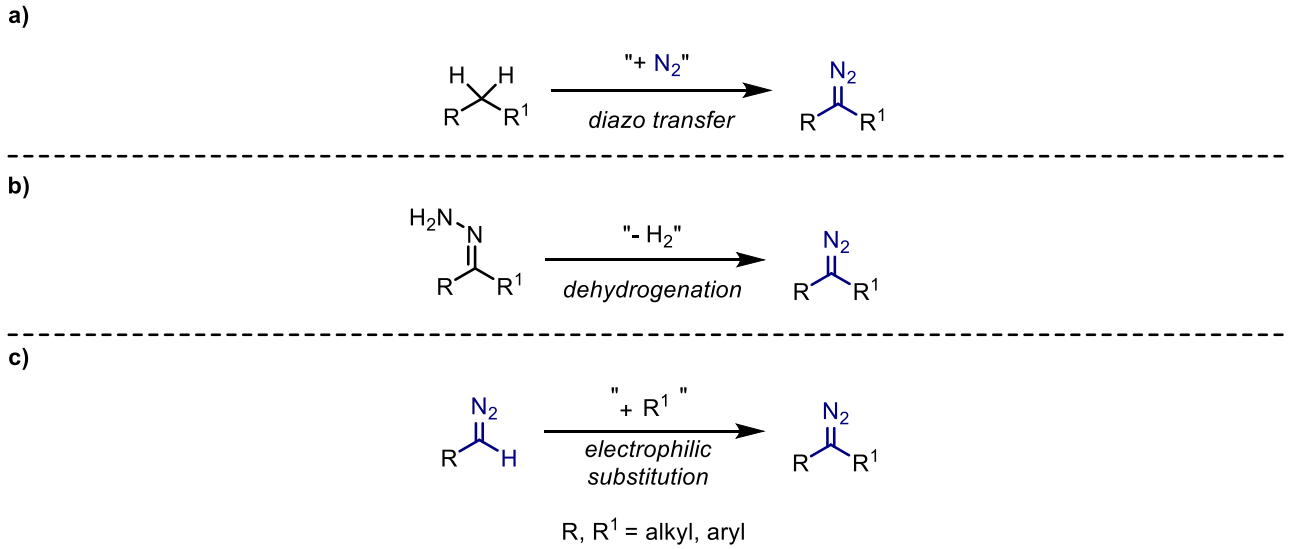
Scheme 3.5. Example of a triplet carbene derived from a diazo compound. Compound **3.6** is stable for up to a week.

In general, triplet carbenes have found limited application in synthetic chemistry, and their formation and studies are more relegated to a chemical curiosity.[162]

3.2. Synthesis of diazo compounds

Several methods are nowadays available to install the diazo functionality.[163–165] In general, a diazo group can be transferred over an activated methylene (Scheme 3.6, a) or it can be obtained by

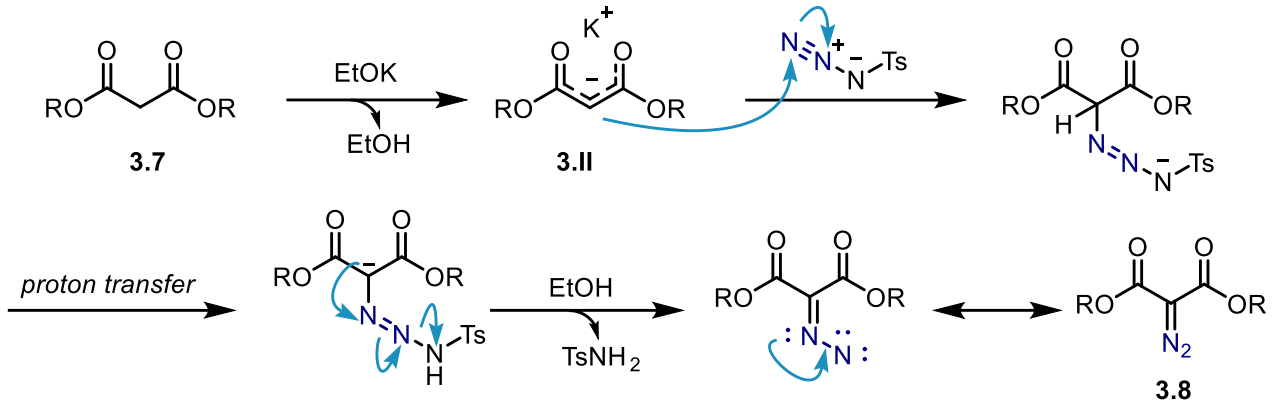
dehydrogenation of hydrazones (Scheme 3.6, b). Furthermore, functionalisation of commercially available diazo compounds by keeping the reactive functionality intact is another common method to access new diazo compounds (Scheme 3.6, c).[164]



Scheme 3.6. General approaches to synthesise diazo compounds.

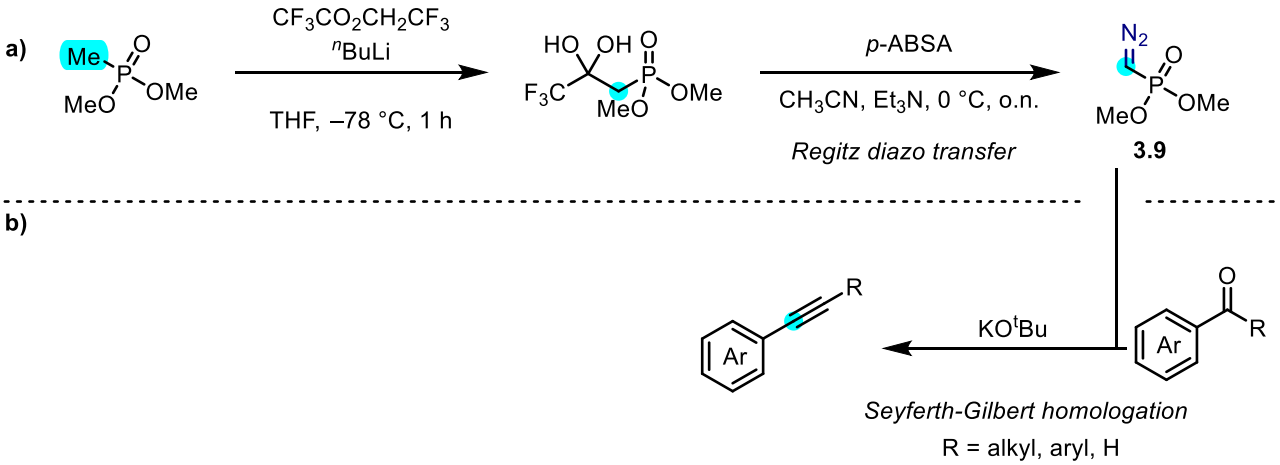
It should be noted that there are several other methods to install the diazo group,[163,164] but a thorough discussion of all the methods available falls outside the scope of this thesis. Therefore, only selected examples of the above-mentioned methods will be presented.

The most common method to obtain a diazo functionality relies on the use of an azide, historically *p*-tosyl azide (TsN_3), which is able to insert the N_2 group in activated methylenic positions in the so-called Regitz diazo transfer reaction.[165] Interestingly, the reaction was first discovered by Otto Dimroth in 1910,[166] but it became famous only after Manfred Regitz extended the scope to dicarbonyl compounds in the 1960s.[167] The reaction relies on the use of strong bases, like EtOK in the original report, to abstract α-hydrogens of the carbonyl compound **3.7**. The formed potassium enolate **3.II** can then attack the terminal nitrogen of the azide which, after proton transfer, forms the diazo compound **3.8** (Scheme 3.7).



Scheme 3.7. Reaction mechanism of the Regitz diazo transfer reaction.

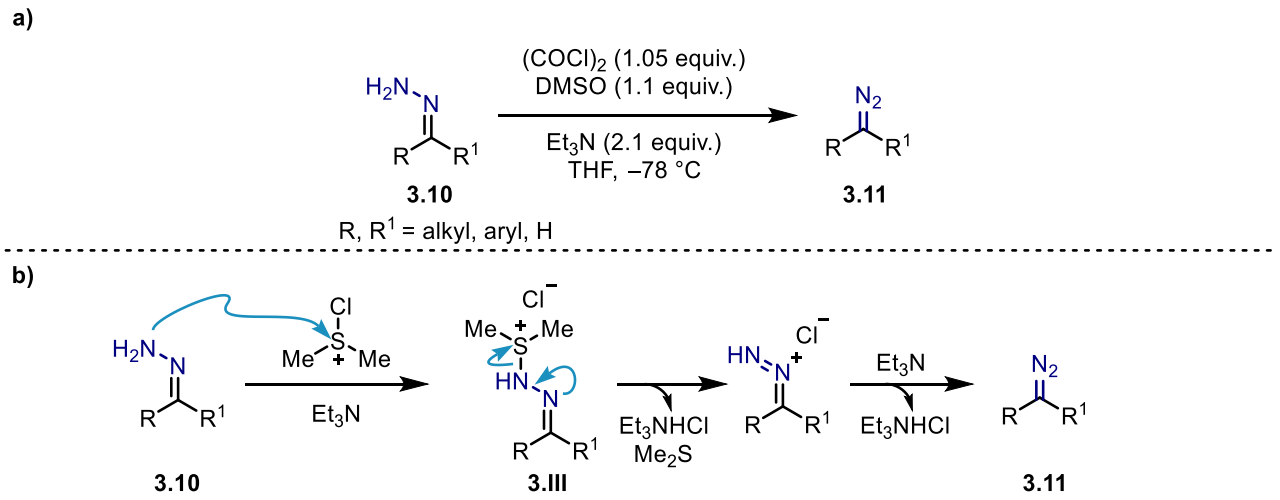
The use of TsN_3 has been largely replaced nowadays by *p*-acetamidobenzensulfonyl azide (*p*-ABSA) which reacts very similarly, but it possesses higher thermal and physical stability.[168] For example, the synthesis of dimethyl (diazomethyl)phosphonate **3.9**, key reagent for the Seyferth-Gilbert homologation reaction (Scheme 3.8, b), has been carried out *via* a Regitz diazo transfer step (Scheme 3.8, a) using *p*-ABSA.[169] The Regitz diazo transfer with *p*-ABSA and DBU or triethylamine (TEA) has been the method of choice for the synthesis of the diazo esters employed in Chapter 3.7.



Scheme 3.8. **a)** Application of the Regitz diazo transfer reaction. **b)** General reaction scheme for the Seyferth-Gilbert homologation.

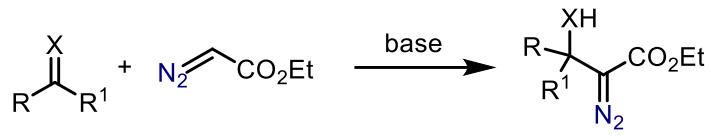
When the chosen substrate lacks acidic protons that could be abstracted by the base as in the Regitz diazo transfer, another common method to introduce the diazo functionality is the dehydrogenation of hydrazones (Scheme 3.6, b).[164,170] With this method, non-stabilised diazo compounds can also be

synthesised relying on the ease of condensation between an aldehyde (or ketone) with hydrazine hydrochloride. However, despite the existence of several methods to oxidise the hydrazone moiety to trigger the loss of formal H_2, these mainly rely on the use of toxic chemicals such as HgO, $Pb(OAc)_4$, NiO_2 etc.[170] To overcome this limitation, a method which is instead based on the use of $(COCl)_2$ and DMSO was described in 2007.[171] Similarly to the Swern oxidation,[172] oxalyl chloride and DMSO react together to form the activated DMSO (Scheme 3.9, a). This electrophilic species can then react with the nucleophilic hydrazine **3.10**, to afford intermediate **3.III** (Scheme 3.9, b). Upon liberation of Me_2S, the corresponding intermediate can form the diazo compound **3.11** under basic conditions (Scheme 3.9, b).



Scheme 3.9. **a)** Formation of diazo compounds from the dehydrogenation of hydrazones. **b)** Proposed reaction mechanism for the diazo compound formation.

Finally, another approach to synthesise diazo compounds relies on the marked acidity of the α-proton of commercially available diazo compounds such as in ethyl diazoacetate **3.2**. Indeed, this can be abstracted by a suitable base to create new diazo compounds, after reaction with an electrophile such as imines, aldehydes or ketones (Scheme 3.10).[173,174]



3.2

X = O, NH

R, R^1 = alkyl, aryl, H

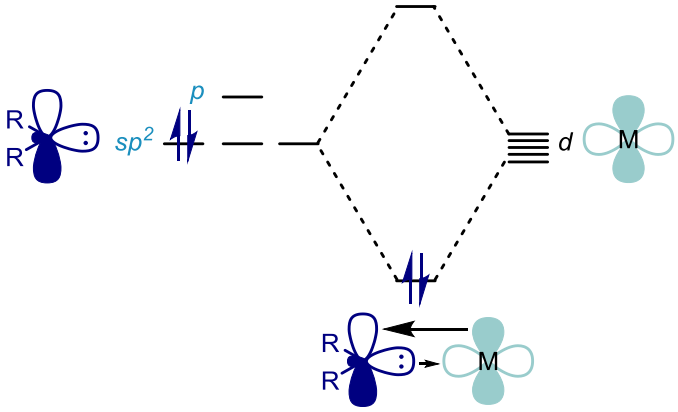
Scheme 3.10. General reaction scheme for the aldol-type condensation of EDA with electrophilic partners.

This method was utilised in Chapter 3.7 to synthesise compound **3.102**, using acetone as the electrophilic partner.

On a last note, given the inherent instability and toxicity associated with diazo compounds, their synthesis in flow has recently witnessed increased research.[151,175] In fact, flow chemistry can deliver diazo compounds while allowing the reaction to proceed into microreactors. These are better at heat exchange, possess a high surface to volume ratio and in general minimise concentration of toxic/dangerous material at a given time.[175]

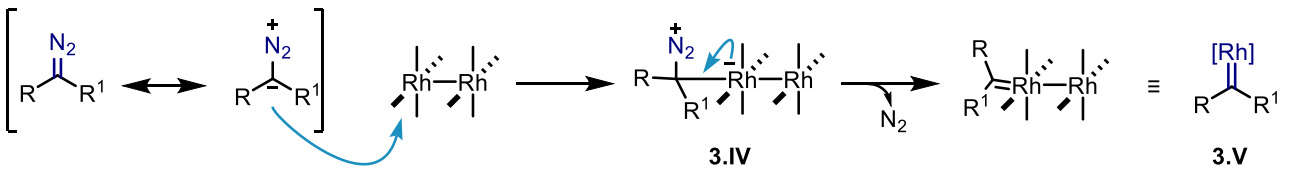
3.3. Diazo activation by transition metals

Given the inherently high reactivity of diazo compounds, their decomposition to afford the carbene can be accomplished by simple means of thermolysis or photolysis.[153,176] Nevertheless, these approaches can sometimes generate species that are too reactive, ultimately leading to reactions with poor selectivity.[177] To overcome this limitation, synthetic chemists have historically tamed the reactivity of carbenes with the use of transition metals, where the *d*-orbitals of the metal can interact with the molecular orbitals (MOs) of the carbene giving rise to a metal-carbene complex.[178] This interaction leads to the generation of new MOs which can decrease the energy of the HOMO of the carbene, rendering it less reactive and therefore more useful from a synthetic point of view (Scheme 3.11).



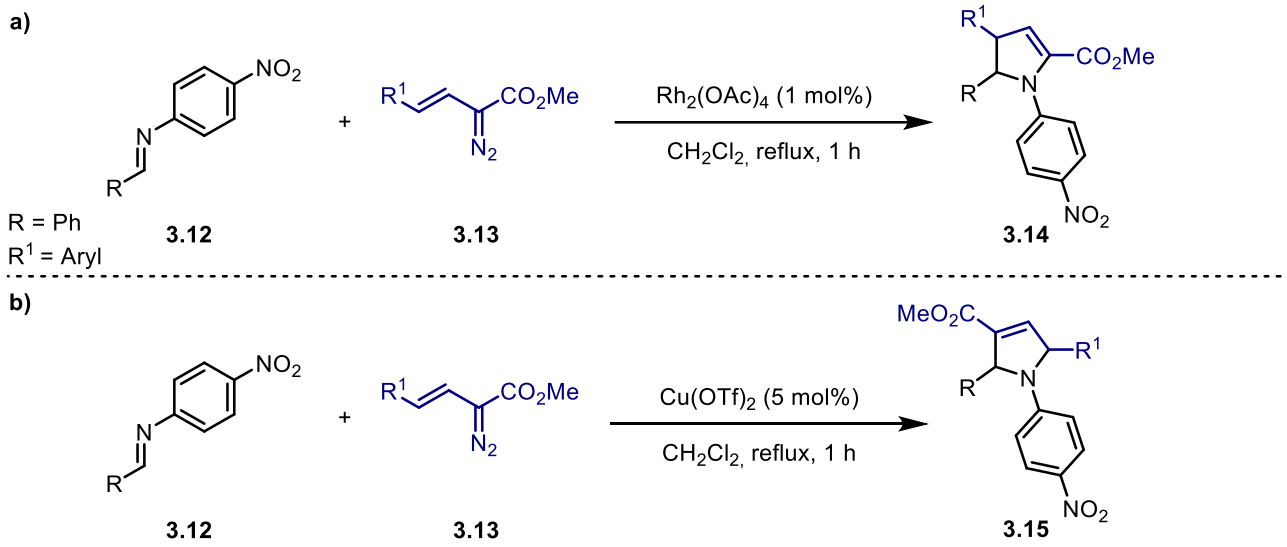
Scheme 3.11. Schematic representation of the stabilisation of the carbene by a transition metal. For simplicity, the ligand field splitting of the metal has not been represented and only the new HOMO and LUMO orbitals are shown.

The degree of stabilisation hinges on several factors that are not discussed in this thesis, but it mainly depends on the nature of the metal, as well as the chosen ligand.[179] In general, several metals can be used to perform diazo decomposition to afford the metal carbene equivalent, such as Fe, Co, Ni, Cu, Ru, Rh, Pd, Ag, Os, Ir, Pt and Au.[180] Among them, $Rh_2(OAc)_4$ is the one that has witnessed the biggest development,[181–183] and therefore selected examples using this catalyst will be described below. The formation of a Rh-carbene equivalent has been proposed to proceed through the initial complexation of the negatively polarised α-carbon to the axial site of the Rh catalyst, which affords **3.IV** (Scheme 3.12).[181] This event sets up the system for the subsequent N_2 liberation affording the metal carbene **3.V**. This step has been proposed to be the rate-limiting step of the reaction, despite this it can vary based on the specific reaction conditions.[184]



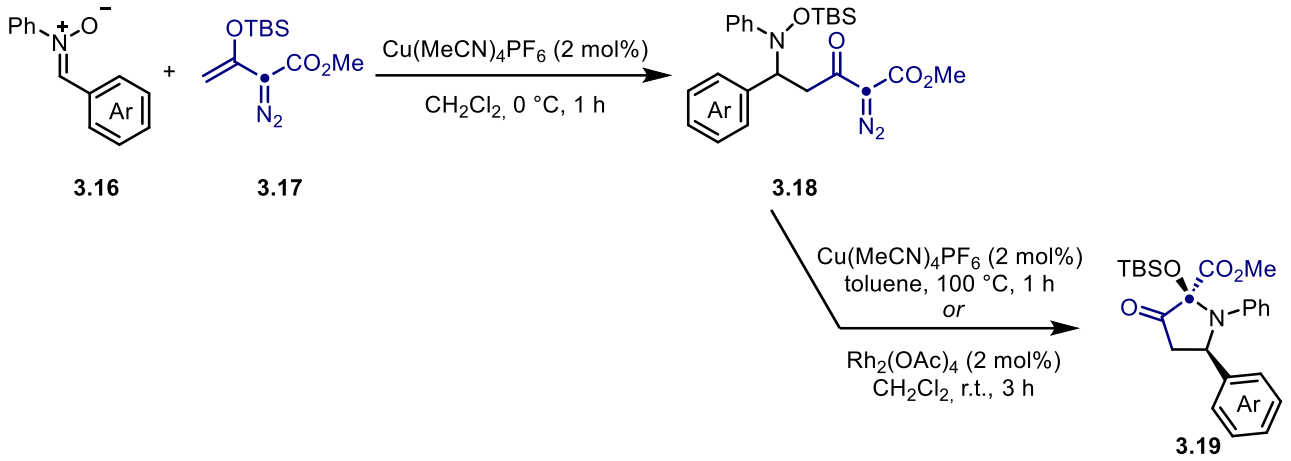
Scheme 3.12. Proposed reaction mechanism for the formation of a Rh-carbene equivalent.

Diazo activation by a Rh catalyst has been mainly pioneered by the group of Doyle,[185–195] who first described the formation of dihydropyrroles **3.14** using vinyl diazo acetate **3.13** and imines **3.12**, in yields up to 66% (Scheme 3.13, a).[189]



Scheme 3.13. Reaction scheme of the reaction between imines and vinyl diazo esters.

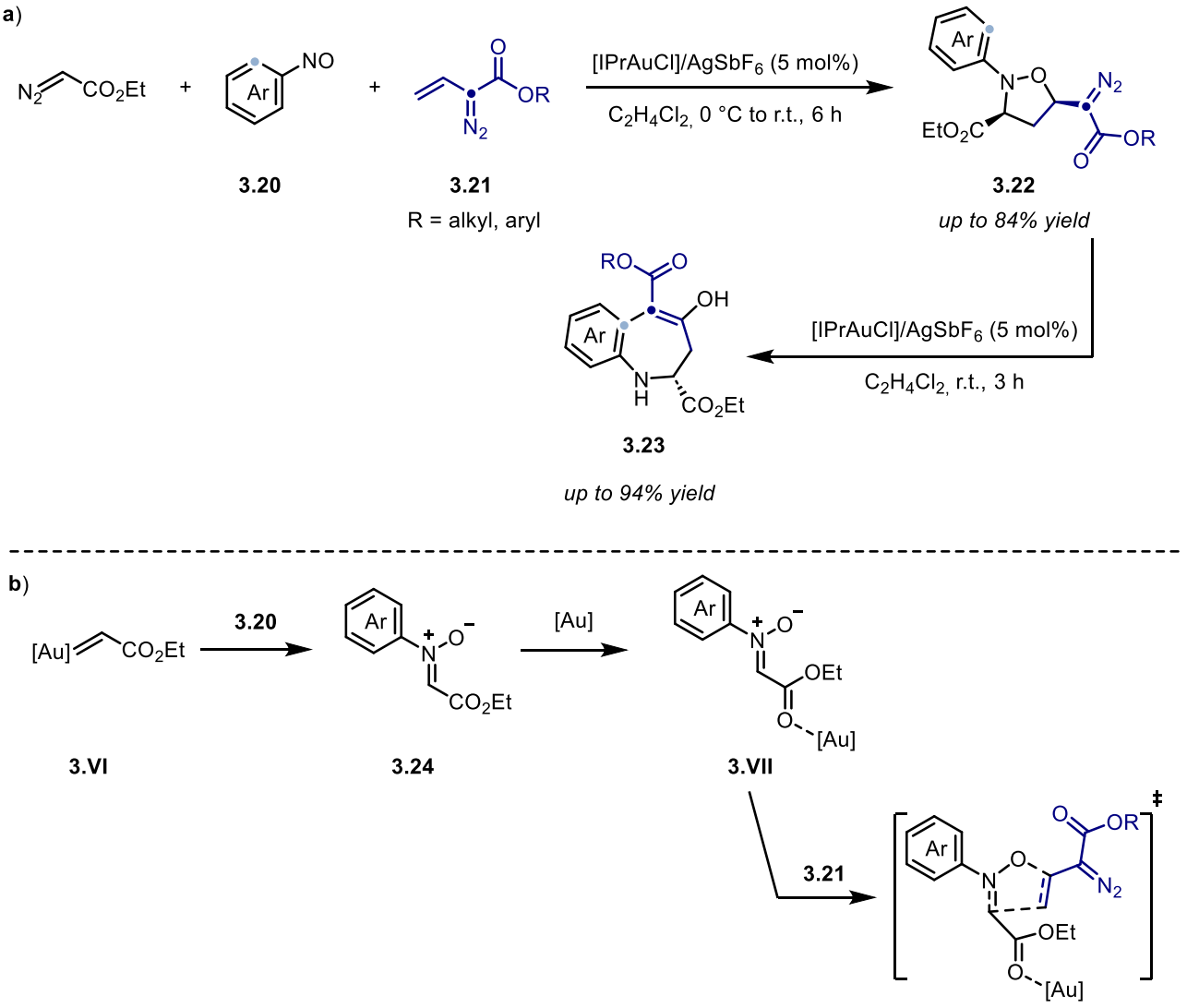
Interestingly, while $Rh_2(OAc)_4$ exclusively afforded product **3.14**, when the catalyst was switched to $Cu(OTf)_2$, the regioisomeric product **3.15** was instead obtained in 67% yield (Scheme 3.13, b). This led to the postulate of an alternative pathway, where the Cu catalyst acts as a Lewis acid and activates the imine before the diazo decomposition. Soon after, the same group developed a similar methodology where the electrophilic partner was chosen to be nitrone **3.16**, and the diazo functionality was a silyl enol ether **3.17**.[193] Under Cu-catalysed conditions, the two reactants could undergo a Mukaiyama-Mannich addition to afford **3.18**, where interestingly the diazo functionality remained intact. In a telescoped approach, by increasing the temperature to 100 °C and using the same Cu catalyst or by replacing it with $Rh_2(OAc)_4$, the diazo decomposition could be selectively targeted, affording pyrrolidinone **3.19** in 50% yield (Scheme 3.14).



Scheme 3.14. Reaction scheme for the reaction between nitrones and silyl enol diazo esters.

These early examples showcased the possibility of accessing densely functionalised heterocycles using simple starting materials coupled with the formation of a metal carbene derived from diazo esters. Moreover, the identity of the catalyst had a profound impact on the regio- and chemoselectivity of the reactions, highlighting that from the same reactants different products could be obtained, just by changing it.

A similar development was tackled by the group of Liu in 2015,[196] where it was shown that the catalytic activity of a gold catalyst can be leveraged for the synthesis of isoxazolidines **3.22** and benzo[*b*]azepines **3.23** starting from the *in situ* formation of nitrones **3.24** reacting with vinyl diazo esters **3.21** (Scheme 3.15, a).



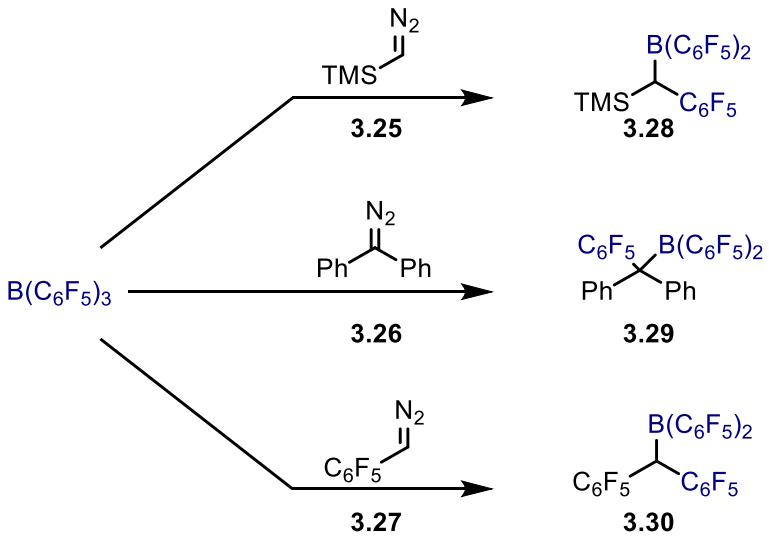
Scheme 3.15. **a**) Reaction scheme for the reaction between nitrones and vinyl diazo esters. **b**) Proposed reaction mechanism.

In contrast to most of the works developed by Doyle, the use of a gold catalyst bypasses the initial diazo decomposition of **3.21**, diverging the reactivity to a Lewis acid catalysed [3+2] dipolar cycloaddition to afford **3.22**. Mechanistically, it has been proposed that the reaction proceeds through the initial coordination of the gold catalyst with EDA, which forms a highly reactive carbene **3.VI** (Scheme 3.15, b).[196] This can subsequently react with nitrosobenzene **3.20** present in the reaction mixture, forming nitrone **3.24**. The gold Lewis acid can then shift over the newly installed carbonyl moiety affording intermediate **3.VII**, which activates the nitrone for the stereo- and regioselective [3+2] dipolar cycloaddition that forms **3.22** (Scheme 3.15, b). Crucially, under the reaction conditions,

the gold catalyst can discriminate between the diazo functionality of EDA and the one in **3.21**, selectively activating the latter over the former. Lastly, it has been observed that although the reaction could be carried out in one pot to obtain the benzo[*b*]azepine **3.23**, the process was lower yielding since it afforded the product in 56% yield. This result has been explained by inferring that side products derived from the synthesis of **3.22** can affect the catalytic activity of the gold catalyst.[196] Nevertheless, similarly to Doyle's works, also this literature example raised an important aspect which was the base of the investigation described further in this chapter: the ability of a catalyst to discriminate between similar reactive entities, and therefore changing the reaction outcome.

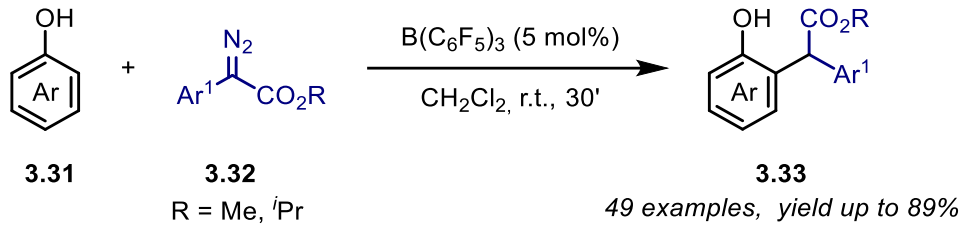
3.4. Diazo activation by borane Lewis acids

The transition metal catalysed diazo activation has been extensively studied and developed throughout the years, while diazo activation by *p*-block elements has received far less attention. However, it has been recently shown that *p*-block elements can also act in an analogous fashion to transition metal with respect to diazo activation.[10] In particular, Stephan first showed that alkyl boranes derived from $B(C_6F_5)_3$ could be synthesised by treating the electrophilic borane with stoichiometric amounts of TMS-diazomethane **3.25**, diphenyl diazomethane **3.26** or (pentafluorophenyl) diazomethane **3.27** (Scheme 3.16).[197]



Scheme 3.16. Early example of reactivity of $B(C_6F_5)_3$ with diazo compounds.

The corresponding products **3.28**–**3.30** have been rightfully envisioned as a series of new boron Lewis acids employable in FLP chemistry. However, it was not until the work of Zhang four years later that the synthetic community turned the attention to the catalytic application of $B(C_6F_5)_3$ to *activate* diazo compounds such as **3.32** and use the carbene equivalent to forge new C–C bonds as in product **3.33** (Scheme 3.17).[198]

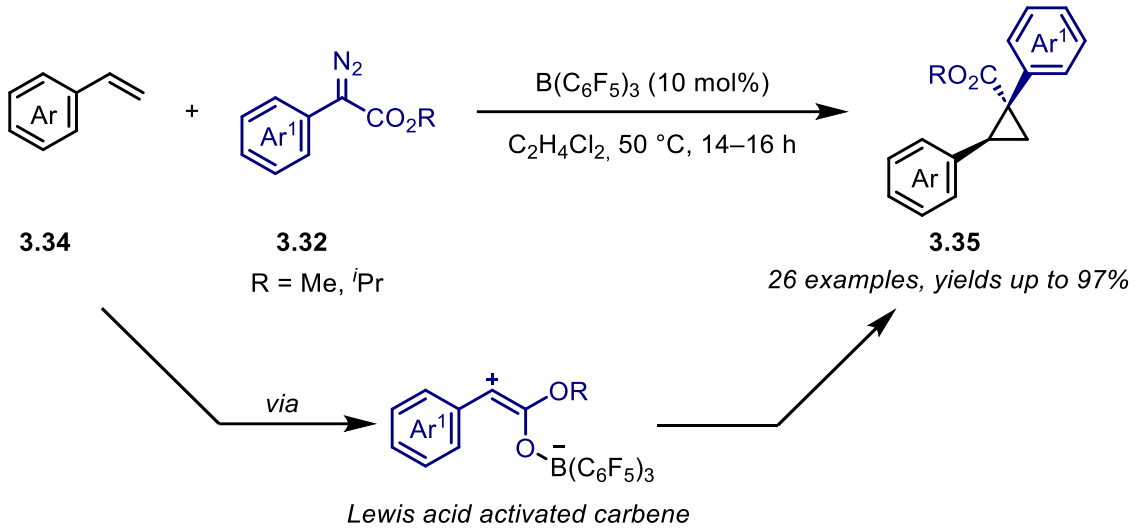


Scheme 3.17. Early example of reactivity of $B(C_6F_5)_3$ with diazo compounds.

This work showcased a selective *ortho* Friedel-Crafts functionalisation of phenols using diazo esters. The key aspects were the $B(C_6F_5)_3$-catalysed formation of an electrophilic carbene and the *ortho* selectivity, which has been attributed to H bonding between the OH group of the phenol with one fluorine atom of the catalyst.[198] In terms of the diazo activation, a separate work has shown that coordination of the Lewis acid catalyst with the diazo ester preferentially occurs with the oxygen of the carbonyl moiety over the nitrogen of the diazo.[199] This, in turn, hampered the steric hindrance during the electrophilic attack and lowered the energy of the LUMO orbital of the diazo compound by forming a conjugated system (*vide infra*).

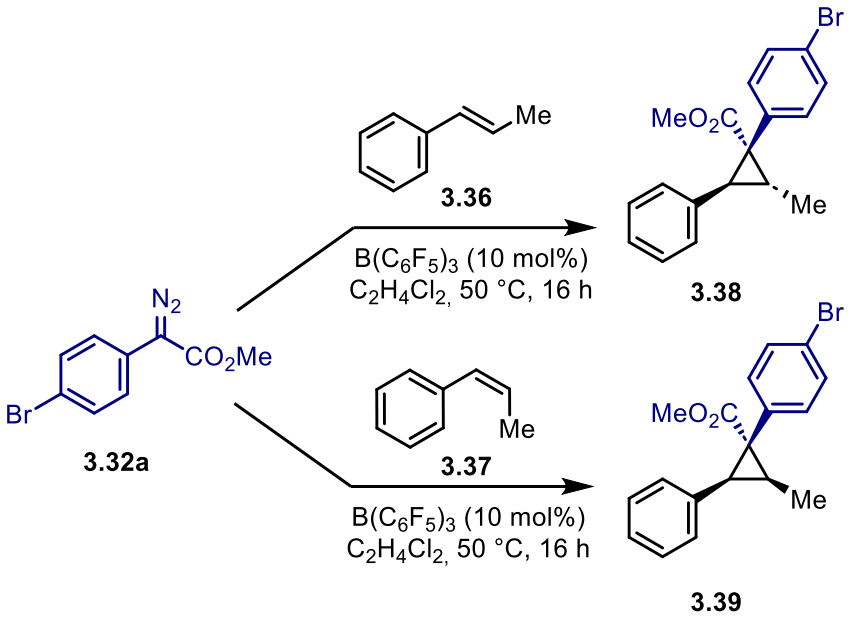
This initial work prompted extensive research on the use of $B(C_6F_5)_3$ to activate diazo compounds, where our group and others have greatly expanded the utility of $B(C_6F_5)_3$ as a catalyst or as a reactant towards diazo activation.[131,200–206] For example, in 2020 the Melen group and Wilkerson-Hill group simultaneously showed that α-aryl diazo esters **3.32** can be treated with catalytic amounts of $B(C_6F_5)_3$ to synthesise cyclopropanes from simple indenes, benzofurans or styrenes **3.34**.[131,205] It has been demonstrated that the reaction entails the formation of a Lewis acid activated carbene (*e.g.* the

conjugated system), which could react with the nucleophilic styrene in a concerted manner to afford cyclopropanes in high yields (up to 97%) and with high diastereoselectivities (Scheme 3.18).[205]



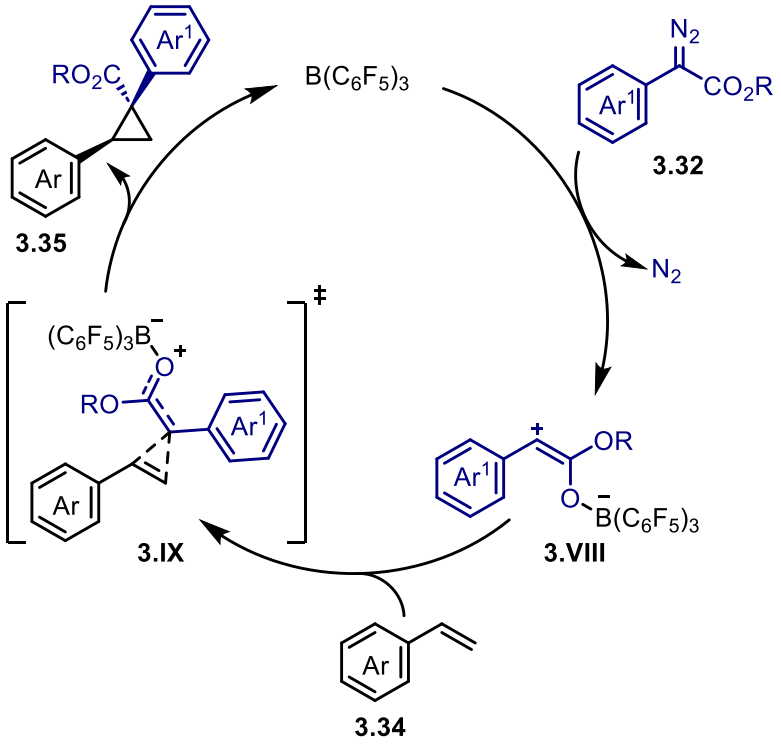
Scheme 3.18. $B(C_6F_5)_3$-catalysed cyclopropanation of styrenes with α-aryl diazo esters.

The reaction was found to be both stereospecific and stereoselective, as control experiments using *E*-*β*-methylstyrene **3.36** and *Z*-*β*-methylstyrene **3.37** gave the corresponding products **3.38** and **3.39** as single diastereoisomers (Scheme 3.19).



Scheme 3.19. Control experiments showcasing the stereoselectivity of the $B(C_6F_5)_3$-catalysed cyclopropanation of styrene derivatives.

The stability of the cyclopropane ring under the reaction conditions was also remarkable, since no change occurred to the obtained products upon heating at 50 °C with 1 equivalent of $B(C_6F_5)_3$ over 16 hours.[207] Based on these results, a tentative catalytic cycle has been proposed where the Lewis acid activated carbene **3.VIII** can undergo a concerted [2+1] cycloaddition with styrene **3.34** (Scheme 3.20).

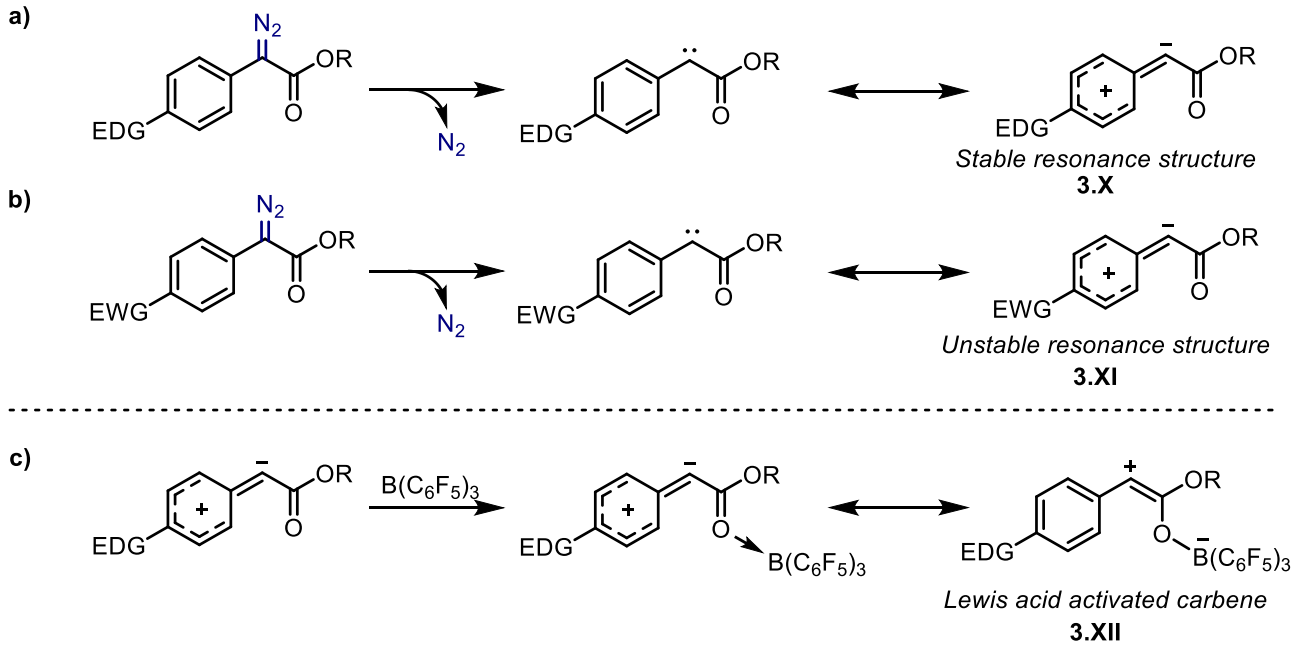


Scheme 3.20. Proposed catalytic cycle for the cyclopropanation of styrenes catalysed by $B(C_6F_5)_3$ using diazo esters.

A year later, our group disclosed a similar cyclopropanation reaction catalysed by $B(C_6F_5)_3$ but on arylacetylenes, further expanding the substrate scope.[200]

All the examples discussed so far entailed the reaction with different nucleophilic partners with α-aryl diazo esters, which are activated by the Lewis acid. Indeed, our group has shown that the presence of EDGs or EWGs in the aromatic ring of the α-aryl diazo esters play a central role in the ease of N_2 liberation and carbene formation.[208] In particular, the presence of an EDG greatly promotes the formation of a carbene equivalent, as evidenced by the formation of a stabilised resonance structure

3.X (Scheme 3.21, a). On the contrary, EWGs are less efficient in stabilising the resonance **3.XI**, thus rendering the carbene formation more energetically demanding (Scheme 3.21, b).



Scheme 3.21. Schematic representation for the formation of carbene from α-aryl diazo esters with **a)** EDGs and **b)** EWGs in *para* position. **c)** Formation of a Lewis acid activated carbene upon $B(C_6F_5)_3$ coordination.

Upon borane coordination, **3.XII** has been proven to be even more stabilised compared to **3.X**, since an overall push-pull electronic effect arises (Scheme 3.21, c).[208] Generally, the more electron density is pushed into the aromatic ring from an EDG, and the stronger the borane is bound to the carbonyl, the easier the carbene formation will be. However, it is important to highlight that, while the reaction between boranes and diazo esters affords a carbene equivalent, the activation mode using metals differs fundamentally, as described in Chapter 3.3. Indeed, unlike a "metal-carbene," no "borane-carbene" is produced and the presence of a carbonyl moiety is crucial for the Lewis acid coordination. This important aspect can be leveraged to design reactions where the carbene formation can be selectively achieved or hampered by careful tuning of the diazo and/or boron Lewis acid identity.

3.5. Aims of the project

The seminal works from the group of Doyle described in Chapter 3.3, as well as the known ability of $B(C_6F_5)_3$ to activate α-aryl diazo compounds described in Chapter 3.4, prompted us to question whether we could leverage the reactivity firstly discussed by Liu and co-workers[196] under borane-catalysed conditions. The blueprint of the methodology described in this chapter is the removal of the aromatic group from the terminal position of the diazo ester, to obtain a vinyl diazo ester such as **3.22**. This in turn hampers the initial formation of a carbene equivalent since the push effect cannot be established as described in Chapter 3.4, and the reactivity is instead diverted to a Lewis acid catalysed [3+2] dipolar cycloaddition in the presence of a coordinating nitrone. The obtained isoxazolidine products would then bear a diazo functional handle that could be leveraged for further synthetic manipulations.

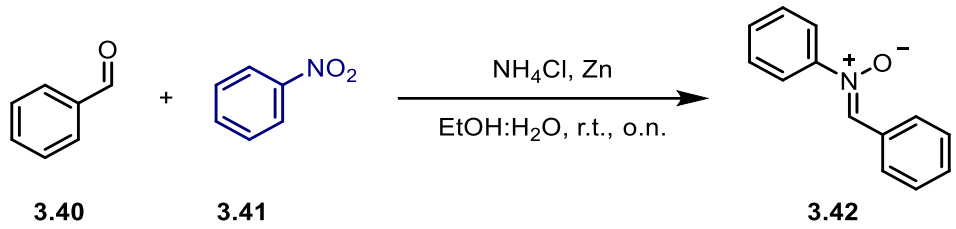
3.6. Authors contribution

This work has been carried out in collaboration with Dr Katarina Stefkova, and it has been not described elsewhere. We together synthesised the starting materials. Specifically, she prepared nitrones **3.85**–**3.90, 3.92**, **3.94**–**3.99**. She also prepared diazo compounds **3.66** and **3.100**. Moreover, she mainly dealt with the reaction optimisation and scope of the [3+2] dipolar cycloaddition. My involvement in the project was to synthesise the other starting materials as well as deal with the substrate scope of the Mukaiyama-Mannich approach. I have also investigated the subsequent functionalisation of the obtained products. Ms Yara van Ingen measured and solved the crystal structures. This work has been published in the journal Organic Letters *Org. Lett.,* **2023**, 25, 500–505.

3.7. Results and discussion

The project commenced with the synthesis of the starting materials required for the desired transformation. The non-commercial α-phenyl-*N*-phenyl nitrone **3.42** was synthesised via a

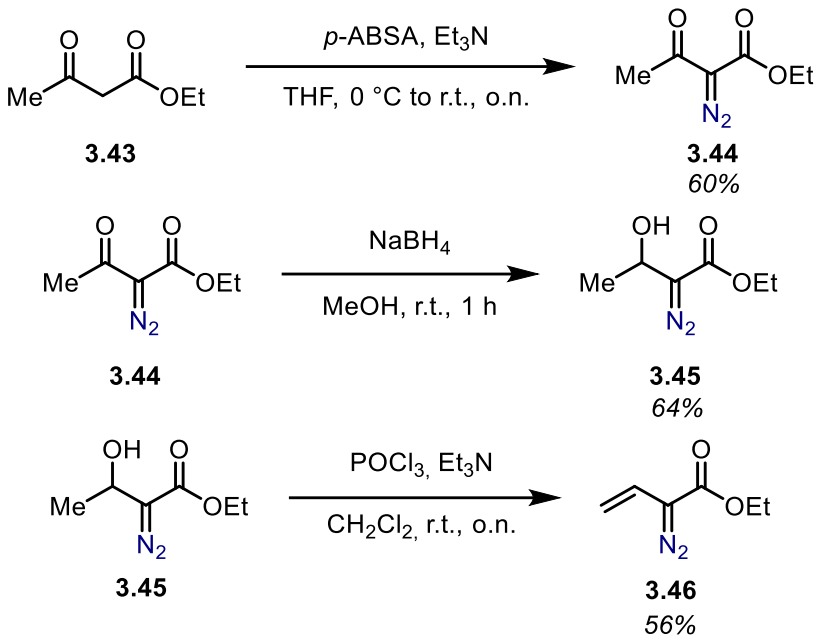
condensation reaction between nitrobenzene **3.41** and benzaldehyde **3.40** in a mixture of EtOH:H_2O in the presence of Zn and NH_4Cl (Scheme 3.22).



Scheme 3.22. Synthesis of the nitrone starting material by the *in situ* reduction of nitrobenzene to *N*-phenylhydroxylamine.

Although the reaction generally proceeds within 3 to 4 hours, it has been decided to leave it overnight to ensure full conversion of the benzaldehyde starting material.

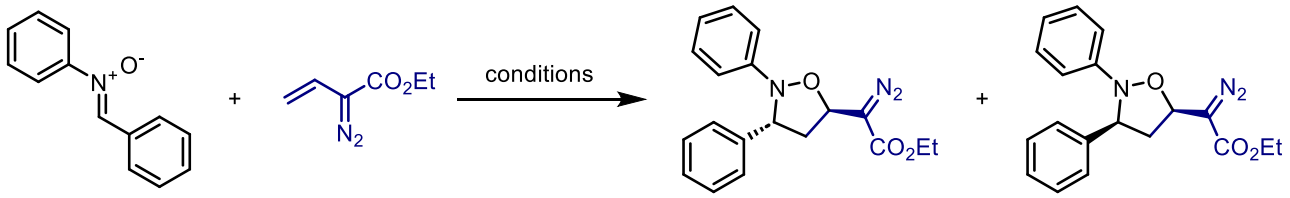
The synthesis of ethyl 2-diazobut-3-enoate **3.46**, model substrate for our investigation, started from ethyl acetoacetate **3.43**, which undergoes Regitz diazo transfer in the presence of *p*-ABSA and Et_3N in THF affording the stabilised α-diazo-β-keto diazo ester **3.44**. Although the instability of several diazo compounds is a well-known feature,[154] it was possible to purify the compound through a silica plug. The product was then subjected to a $NaBH_4$-mediated reduction to obtain the corresponding alcohol **3.45**. After an additional column chromatography purification, the obtained red oil was dehydrated using $POCl_3$ which, upon final column chromatography purification afforded the desired ethyl 2-diazobut-3-enoate **3.46** in 21% overall yield (Scheme 3.23). To ensure the lowest product decomposition, some precautions were taken such as the use of a lower temperature in the water bath of the rotavapor when removing the solvent and wrapping the product in aluminium foil to avoid photodecomposition. Moreover, all the diazo products were immediately brought inside a N_2-filled glovebox and kept in a freezer at –30 °C.



Scheme 3.23. Synthesis of diazo starting material.

With the starting materials in hand, the investigation commenced by mixing **3.42** with the vinyl diazo ester **3.46** in $C_2H_4Cl_2$ at 40 °C for 24 hours with 20 mol% of $B(C_6F_5)_3$ (Table 3.1, entry 1).

Table 3.1. Reaction optimisation table for the [3+2] dipolar cycloaddition reaction between nitrones and vinyl diazo esters. *d.r.* calculated from the crude reaction mixture by integration of the diagnostic peaks. Yield refers to the combined isolated yield of both the major and minor diastereoisomer. n.a.: not applicable.



Entry	Cat. (mol %)	Solvent	T (°C)	Time (h)	Yield 3.47	*d.r.* (anti:syn)
1	$B(C_6F_5)_3$ (20)	$C_2H_4Cl_2$	40	24	60%	83:17
2	-	$C_2H_4Cl_2$	40	36	18%	9:91
3	BPh_3 (20)	$C_2H_4Cl_2$	40	24	<5%	n.a.

4	-	$C_2H_4Cl_2$	r.t.	24	-	n.a.
5	-	$C_2H_4Cl_2$	80	24	-	n.a.
6	$BF_3{\cdot}OEt_2$ (20)	$C_2H_4Cl_2$	40	24	15%	18:82
7	B(3,4,5-$F_3C_6H_2)_3$ (20)	$C_2H_4Cl_2$	40	24	28%	38:62
8	B(2,4,6-$F_3C_6H_2)_3$ (20)	$C_2H_4Cl_2$	40	24	23%	48:52
9	TfOH (20)	$C_2H_4Cl_2$	40	24	-	n.a.
10	$B(C_6F_5)_3$ (10)	$C_2H_4Cl_2$	40	24	44%	71:29
11	$B(C_6F_5)_3$ (5)	$C_2H_4Cl_2$	40	24	26%	57:43
12	$B(C_6F_5)_3$ (20)	Toluene	40	24	74%	91:9
13	$B(C_6F_5)_3$ (20)	THF	40	24	32%	65:35
14	$B(C_6F_5)_3$ (20)	CH_2Cl_2	40	24	63%	83:17
15	$B(C_6F_5)_3$ (20)	TFT	40	24	56%	87:13
16	$B(C_6F_5)_3$ (20)	Hexane	40	24	45%	89:11
17	$B(C_6F_5)_3$ (20)	CH_3CN	40	24	-	n.a.
18	$B(C_6F_5)_3$ (20)	Toluene	r.t.	24	72%	91:9
19	$B(C_6F_5)_3$ (10)	Toluene	40	24	42%	80:20

Given the fact that diazo esters are prone to dimerisation and activation by $B(C_6F_5)_3$ on their own,[208,209] it was decided to carry out all the synthetic manipulations in a precise order. Specifically, we opted to premix the Lewis acid catalyst with the nitrone in the solvent of choice, and then add dropwise the diazo ester with the aid of a syringe pump over 30 minutes into the reaction mixture. After a set amount of time, analysis of the crude reaction mixture showed the formation of the isoxazolidine product **3.47** as a mixture of two diastereoisomers (*anti*-**3.47** and *syn*-**3.47**) in 60% yield and with 83:17 *d.r.*, alongside unreacted nitrone starting material and diazo decomposition products. Interestingly, the reaction afforded the major isoxazolidine product with opposite diastereoselectivity compared to the work of Liu and co-workers,[196] and this was confirmed by single crystal X-ray

crystallography (*vide infra*). Crucially, under this set of conditions, the diazo functionality remained untouched. A control reaction under the same reaction conditions but without the Lewis acidic catalyst showed very little product formation and, surprisingly, with opposite diastereoselectivity (9:91) as in the case of entry 1 (Table 3.1, entry 2 and Figure 3.1).

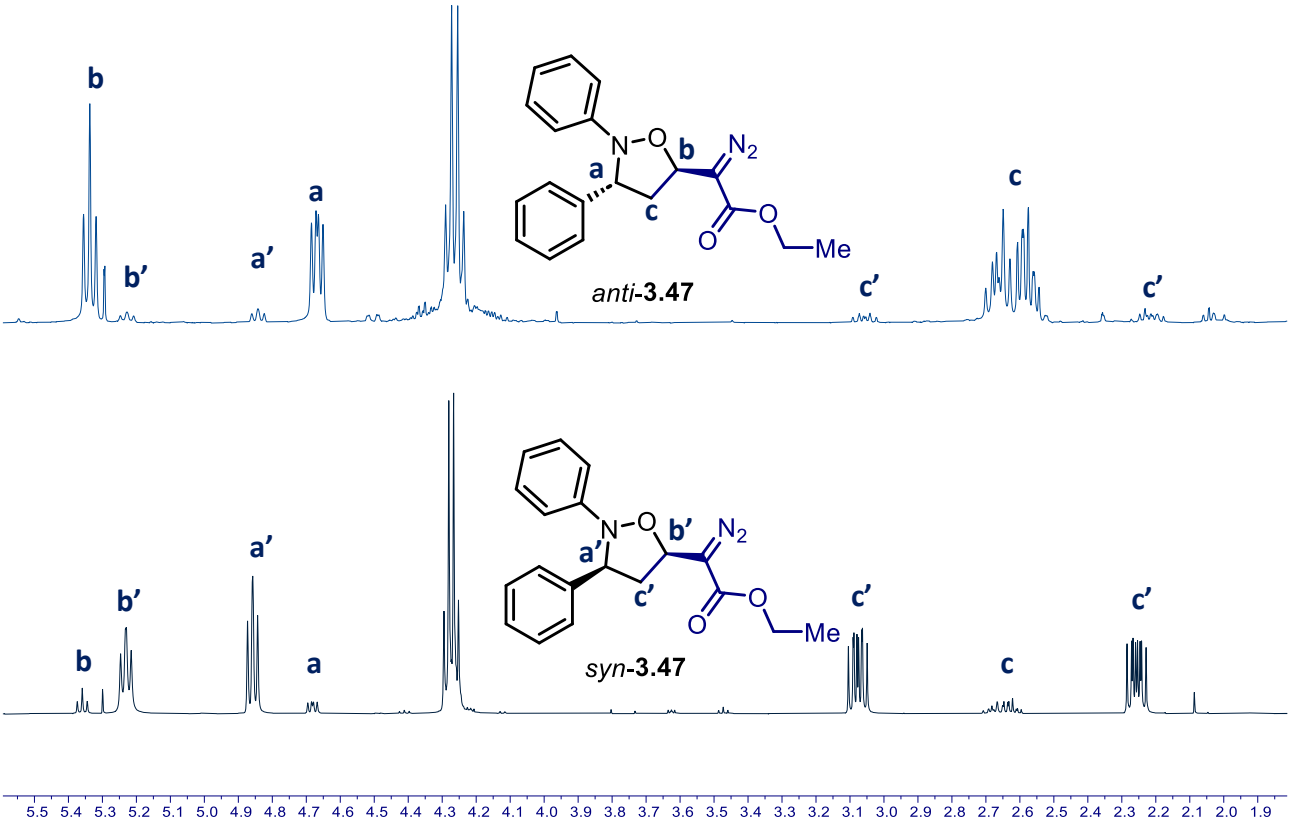
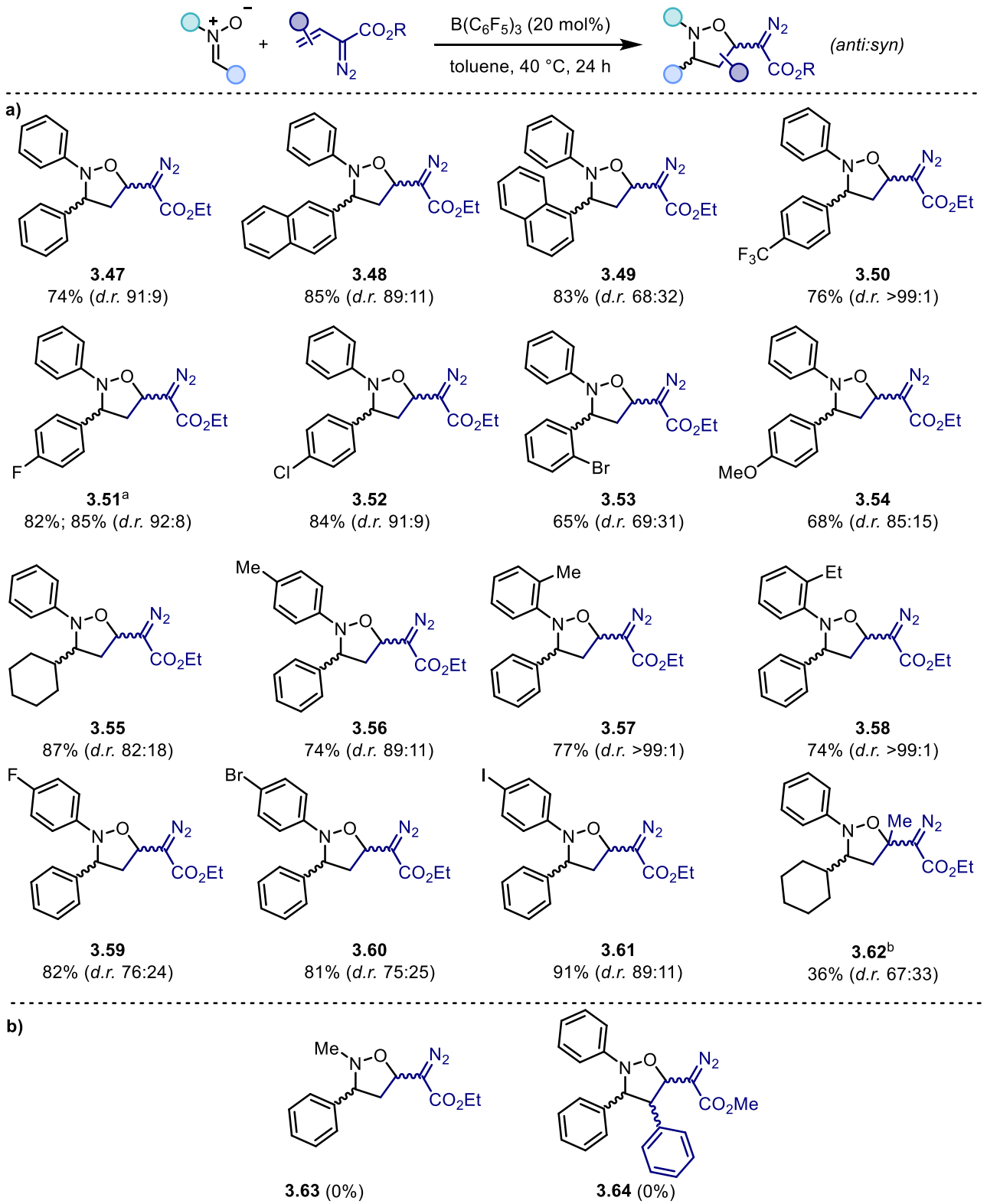


Figure 3.1. Stacked ^{1}H NMR spectra of Table **3.1** entry 12 (top) and entry 2 (bottom).

From this result it can be inferred that not only the Lewis acid catalyst is responsible for the activation of the nitrone starting material, rendering it more susceptible to attack from the vinyl diazo ester, but it also exerts effects on the diastereochemical outcome due to its large steric demand.[210,211] The former aspect is supported by the fact that when BPh_3 was used instead of $B(C_6F_5)_3$ (Table 3.1, entry 3), only traces of the products formed. Indeed, it is well known in the literature that BPh_3 is a weaker Lewis acid compared to $B(C_6F_5)_3$.[36,60] Additional control experiments at either room temperature (Table 3.1, entry 4) or at 80 °C (Table 3.1, entry 5) showed no product formation. In the former case, this can be

attributed to a thermodynamic factor, whereas in the latter this can be attributed to extensive diazo decomposition which prevents any reactivity and highlighting the need to operate at relatively low temperatures for this reaction. Interestingly, the more common Lewis acid, $BF_3{\cdot}Et2O$ did not have any effect on the reactivity, since it can be seen that the yields of entries 6 and 2 are comparable (15% and 18%, respectively). Instead, different boranes such as $B(3,4,5\text{-}F_3C_6H_2)_3$ or $B(2,4,6\text{-}F_3C_6H_2)_3$ improved the yield slightly (28% and 23% respectively) compared to the control experiment in entry 2, but they were still not as proficient as $B(C_6F_5)_3$ in entry 1. Strong Brønsted acids such as TfOH had a detrimental effect on the reactivity, leading to extensive decomposition of the diazo compound (Table 3.1, entry 9). Having identified $B(C_6F_5)_3$ as the optimal catalyst, it was attempted to lower the catalyst loading (Table 3.1, entries 10 and 11) which showed not only a diminished yield (44% and 26%), but also lower diastereoselectivity (71:29 and 57:43 respectively). Different solvents (Table 3.1, entries 12–17) showed lower yields (32%–63%) compared to $C_2H_4Cl_2$, except for toluene which formed the product not only with the best diastereoselectivity (91:9), but also the highest yield of 74%. The role of the solvent in governing the stereochemical outcome has been largely studied,[212–214] but there are still no general guidelines which can allow an exact prediction or explanation of its intimate role. However, it was shown that different solvents can switch the stereoselectivity from an enthalpic to an entropic control,[212,215] and that the solvent-solute clusters could play a pivotal role in controlling the stereoselectivity. With coordinating solvents such as THF or CH_3CN, the reactivity was highly suppressed and totally shut down in the case of the latter. Albeit there are reports in the literature using highly acidic boranes with coordinating solvents,[216] we believe that these are not compatible in our case presumably because CH_3CN coordinates strongly with $B(C_6F_5)_3$ and blocks its catalytic activity. Further control experiments in toluene showed that the reaction could be carried out also at room temperature without affecting the yield (Table 3.1, entry 18) but that relatively high catalyst loading (20 mol%) was necessary (Table 3.1, entry 19) to ensure high diastereoselectivities and yields. We therefore decided to set the optimal reaction conditions as $B(C_6F_5)_3$ (20 mol%) in

toluene, at either room temperature or 40 °C for 24 hours. With the optimised conditions in hand, we investigated the substrate scope (Scheme 3.24).



Scheme 3.24. $B(C_6F_5)_3$-catalysed [3+2] dipolar cycloaddition substrate scope. All the reactions were carried out on a 0.1 mmol scale. [a]Reaction carried out on a 1 mmol scale. [b]Reaction carried out for 3 days at r.t..

To begin with, nitrones with different substituents at the α-position were investigated. The comparison between products **3.47** and **3.48** suggests that the presence of a bulkier 2-naphthyl group does not affect the reactivity of the dipolar cycloaddition, since they were both obtained in good yields of 85% and 83% (Scheme 3.24). However, the diastereoselectivity slightly decreased in the case of product **3.49**, pointing out at the increased steric hindrance of the 1-naphthyl moiety. Interestingly, product **3.50** was obtained in high yield (76%) and with diastereoselectivity greater than 99:1, since no formation of the minor diastereoisomer was detected in the crude reaction mixture. On the other hand, when EDGs were present, such as in the case of product **3.54**, the yield remained similar (68%) but the diastereoselectivity dropped (85:15). This suggests that the overall diastereoselectivity is an interplay between electronic and steric factors. Compound **3.55**, bearing a sp^3-rich moiety such as cyclohexyl, allowed us to grow crystals by slow evaporation from a saturated CH_2Cl_2 solution of the compound. The structure was then elucidated by single crystal X-ray diffraction analysis, which revealed the relative conformation of the major isomer to be *anti* (Figure 3.2).

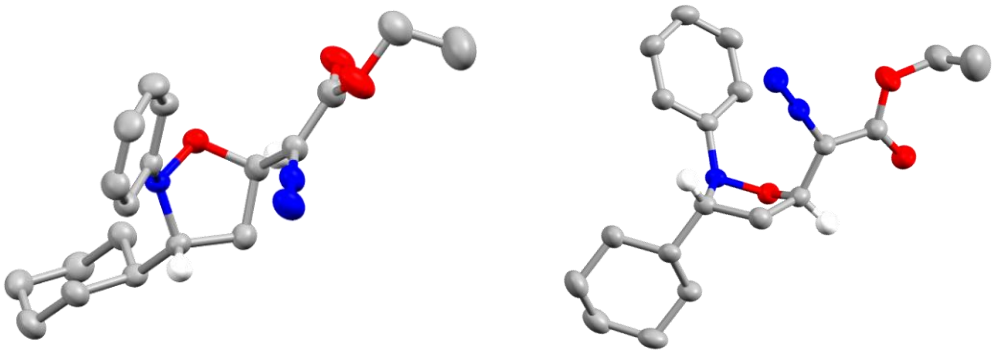
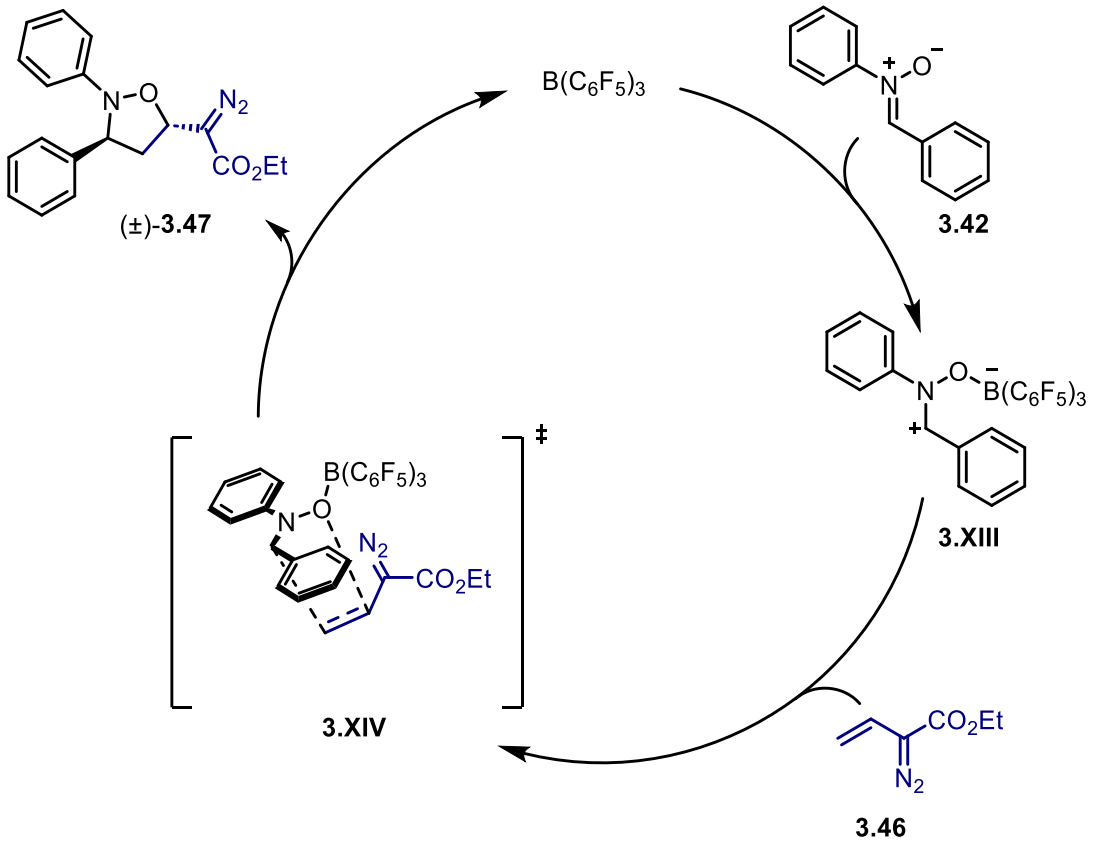


Figure 3.2. Crystal structure of the major diastereoisomer *anti*-**3.55** depicted in two different orientations to highlight the opposite relationship between the two chiral centres. Carbon: grey; oxygen: red; nitrogen: blue; hydrogen: white. Hydrogen atoms omitted for clarity, except the ones at the two chiral centres. Thermal ellipsoids drawn at 50% probability.

By analogy, we extend this observation to all the major isomers obtained in this study. The reaction proved also to be scalable since product **3.51** could be synthesised on a 1 mmol scale, without

affecting the yield nor the diastereoselectivity (82% yield for the 0.1 mmol scale and 85% for the 1 mmol scale, with 92:8 *d.r.*). Moreover, halogens did not negatively affect the reactivity nor the diastereoselectivity, since compounds **3.52**, **3.59**, **3.60**, **3.61** could be all obtained in good yields (between 81% and 91%) and diastereoselectivities (up to 91:9). Only when the bulky halogen is brought close to the reactive site, such as in the case of compound **3.53**, the yield and diastereoselectivity is lower (65% yield and 69:31 *d.r.*). This again suggests an important steric factor in determining the diastereochemical outcome. This is also exemplified in the case of substrate **3.62**, which gave the lowest yield (36%) and diastereoselectivity (67:33), because of the introduction of an additional methyl group. The reason for the low yield can be attributed to the stability of the diazo ester starting material, which is known to decompose quickly.[194] The lower diastereoselectivity can be attributed to a destabilising steric clash in the TS.[217–219] However, additional steric hindrance from the *N*-substituent on the nitrone, seems to highly favour one diastereoisomer over the other, since in the case of *o*-methyl (**3.57**) or *o*-ethyl (**3.58**) substituted *N*-phenyl rings, diastereoselectivities greater than 99:1 were observed. A dramatic effect of *N*-substituents on the nitrone had been previously disclosed by Maruoka in 2007.[220] One of the limitations of this methodology lies in the use of nitrones bearing an aliphatic moiety, since compound **3.63** was not detected in the reaction mixture. Moreover, internal diazo alkenes are not amenable to undergo [3+2] dipolar cycloaddition, since again no formation of the desired products **3.64** was observed.

From a mechanistic point of view, the reaction is proposed to proceed through an initial coordination of the Lewis acidic $B(C_6F_5)_3$ with the nitrone, which increases the electrophilicity of the α-carbon in **3.XIII** (Scheme 3.25).

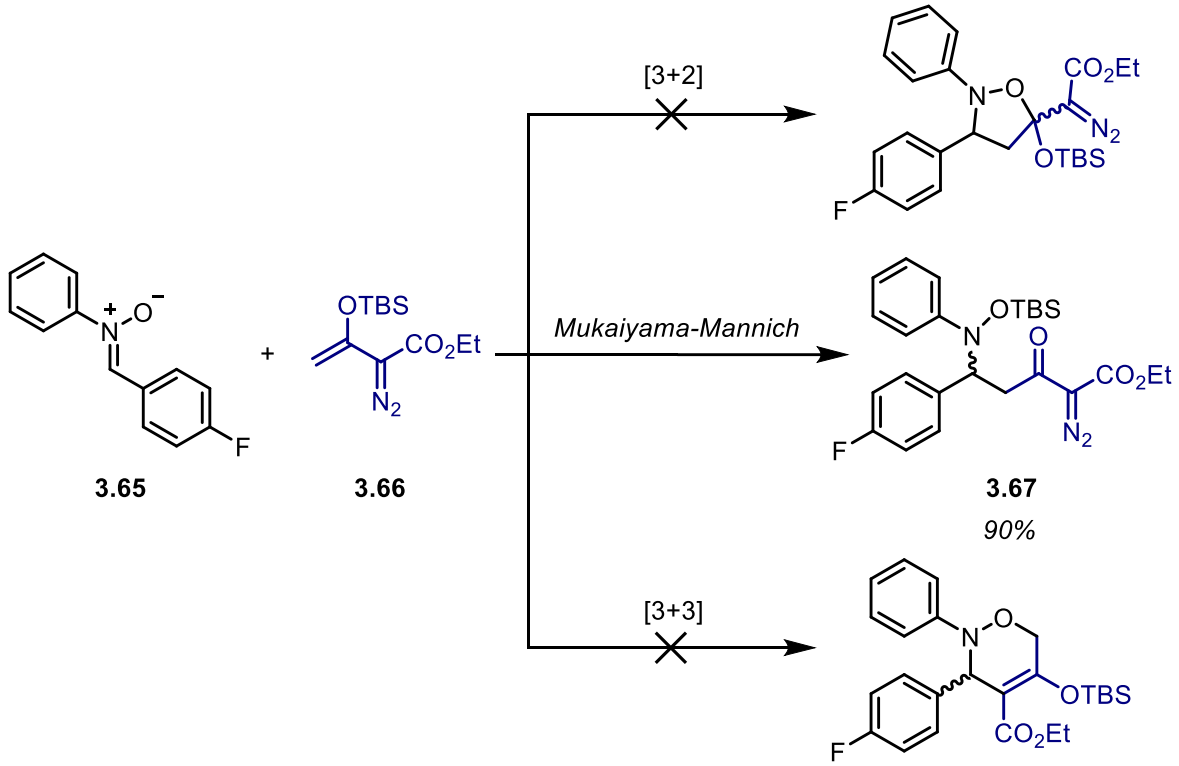


Scheme 3.25. Proposed catalytic cycle for the 1,3-dipolar cycloaddition catalysed by $B(C_6F_5)_3$.

This claim is also supported by a similar transformation catalysed by BPh_3 disclosed by Krempner, who showed that this borane can activate nitrones.[221] Subsequently, the vinyl diazo ester can engage in a formal 1,3-dipolar cycloaddition, which is proposed to occur via a preferential TS **3.XIV** in which the minimisation of steric repulsions would lead to the experimentally observed major *anti* product (Scheme 3.25). The role of the catalyst would therefore be dual: it activates the nitrone and exerts diastereoselectivity by allowing the reactants to approach from the less sterically encumbered face of the nitrone.

Seeking new methods to synthesise heterocycles using $B(C_6F_5)_3$ as the catalyst, we also became interested in the exploitation of silyl enol diazo esters, which have been extensively studied by the group of Doyle.[185] Although the [3+3] process has been disclosed by his group under Rh-catalysed conditions,[222] the [3+2] event would have been unprecedented using nitrones, despite reports with different dipoles have been published.[223,224] Using the optimised conditions in Table 3.1, when nitrone

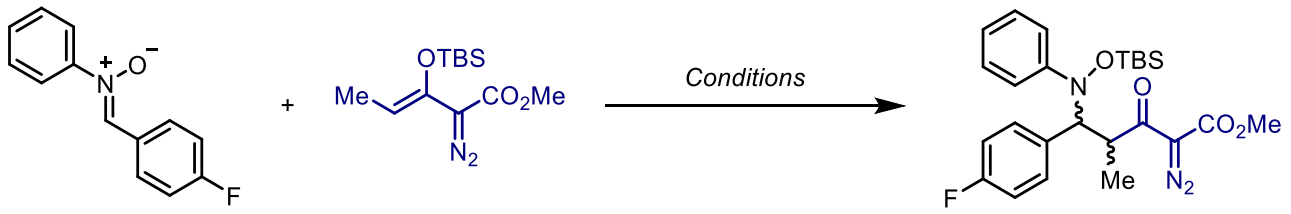
3.65 was mixed with the silyl enol diazo ester **3.66**, no [3+2] nor [3+3] cycloaddition occurred, instead formation of the Mukaiyama-Mannich **3.67** addition product was observed in 90% isolated yield (Scheme 3.26).



Scheme 3.26. Divergent reactivities of nitrone **3.65** with silyl-enol diazo esters.

The Mukaiyama-Mannich addition of silyl enol diazo esters with nitrones has been already disclosed by the groups of Doyle and Zhang, as well as others.[193,194,225] However, in all the cases the obtained product **3.67** bears only one stereocentre, and to the best of our knowledge, there were no examples which involved the formation of two chiral centres for this transformation. Because of the ability of $B(C_6F_5)_3$ to exert some diastereoselectivity due to its large steric demand, we decided to investigate the Mukaiyama-Mannich addition of nitrone **3.65** and methyl substituted silyl enol diazo esters such as **3.68**, which would form a mixture of diastereoisomeric products (Table 3.2). Initially, the same conditions applied for the [3+2] dipolar cycloaddition were applied to the Mukaiyama-Mannich addition (Table 3.2, entry 1).

Table 3.2. Optimisation table in toluene for the $B(C_6F_5)_3$-catalysed Mukaiyama-Mannich reaction. n.a.: not applicable. All the reactions were carried out for 24 hours.

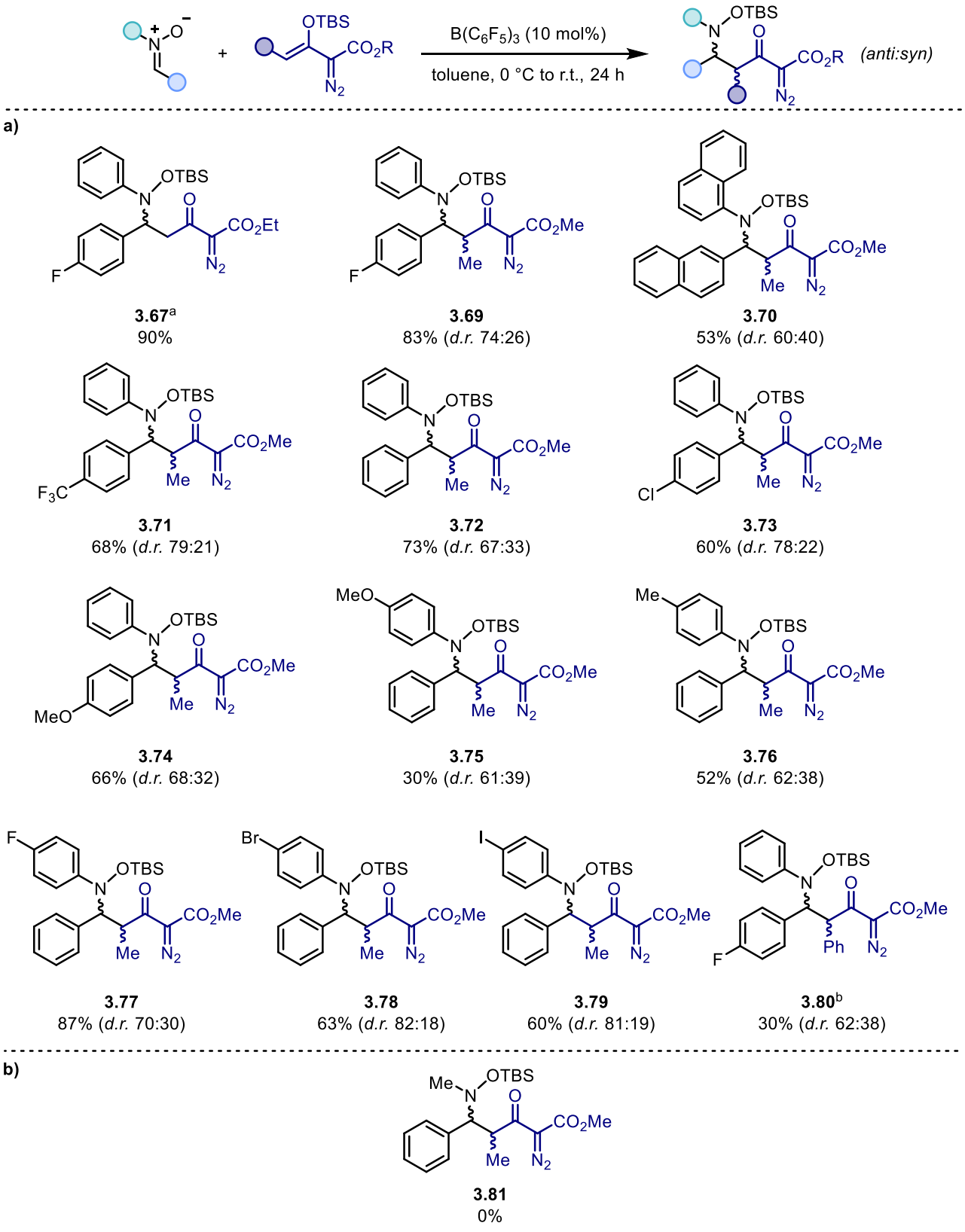


3.65 **3.68** **3.69** (*anti* + *syn*)

Entry	Lewis acid (mol %)	Equiv. of 3.68	T (°C)	Yield of 3.69	*d.r.* (anti:syn)
1	$B(C_6F_5)_3$ (20)	1.3	40	25%	77:23
2	$B(C_6F_5)_3$ (20)	1.3	r.t.	27%	77:23
3	$B(C_6F_5)_3$ (20)	2	0 to r.t.	81%	74:26
4	$B(C_6F_5)_3$ (20)	2	–10	72%	75:25
5	-	2	0 to r.t.	-	n.a.
6	$B(C_6F_5)_3$ (10)	2	0 to r.t.	83%	74:26

After prep TLC purification, the two diastereoisomeric products **3.69** were isolated in 25% yield alongside unreacted starting material. For this reason, a decrease in temperature was attempted (Table 3.2, entry 2) to prevent possible diazo decomposition. However, also in this case the yield proved to be low (27%) albeit the diastereoselectivity was unchanged (77:23). Entry 3 shows that by increasing up to two equivalents the amount of diazo ester and by carrying out the addition at 0 °C and then at room temperature the yield is positively impacted and reaches a good 81%, with the diastereoselectivity untouched (74:26). This result highlighted that an excess of diazo was necessary because of its instability. Moreover, it has also been attempted to improve the diastereoselectivity by decreasing the temperature, which unfortunately did not exert the desired effect (75:25) but only slightly decreased the yield to 72% (Table 3.2, entry 4). Finally, it is known that the silylium ions can efficiently catalyse the Mukaiyama-Mannich reaction and that the cations derived from Me_3SiNTf_2

or TMSOTf are stronger Lewis acids than $B(C_6F_5)_3$.[226,227] For this reason, a control experiment without the Lewis acid $B(C_6F_5)_3$ was undertaken which showed no product formation (Table 3.1, entry 5). This result suggests that the spontaneous formation of a TBS^+ cation in the reaction mixture is unlikely, but it doesn't fully discard the possibility of a $B(C_6F_5)_3$-*promoted* silylium-*catalysed* reaction. Lowering the catalyst loading did not negatively impact the yield, thus it has been decided to set as the optimal conditions $B(C_6F_5)_3$ 10 mol% in toluene, with 2 equivalents of silyl enol diazo ester (Table 3.1, entry 6). To ensure as much as possible the stability of the silyl enol diazo ester, its addition was carried out with a syringe pump at 0 °C over 30 minutes, and then the reaction was left to stir for 24 hours at room temperature. With the optimised conditions in hand, a substrate scope was then investigated (Scheme 3.27).



Scheme 3.27. Substrate scope of the $B(C_6F_5)_3$-catalysed Mukaiyama-Mannich addition. All the reactions were carried out on a 0.1 mmol scale. [a]20 mol% of $B(C_6F_5)_3$ were used. [b]Reaction carried out in $C_2H_4Cl_2$.

Throughout the substrate scope, the yields were moderated to high (30%–90%). Similarly to the observation made in the case of the [3+2] dipolar cycloaddition, the presence of bulky naphthyl groups on both the position of the nitrone starting material seems to negatively affect the yield (60%) as well as the *d.r.* (60:40) as evidenced for compound **3.70** (Scheme 3.27). This is also exemplified in compound **3.80** which possesses an additional phenyl ring close to the reactive site which drastically diminishes the yield (30%) and the diastereoselectivity (62:38). Moreover, under the reaction conditions, compound **3.80** has not been obtained after several attempts, but it formed only when the solvent was switched from toluene to $C_2H_4Cl_2$. The solvent effect on the outcome of a chemical reaction has been known for more than 40 years,[228] and it has been attributed to several factors such as solubility, stabilisation of the TS, effects of the catalyst-substrate interaction etc.[229] EWGs or EDGs on the nitrone were well tolerated, forming the corresponding products **3.71** and **3.74** in good yield (68% and 66%, respectively) where the diastereoselectivity seems to be positively affected by the presence of EWGs (**3.71**, 79:21 *d.r.*). This was also the case for Cl– and F–substituted nitrones, which formed compounds **3.73** and **3.69** in 60% yield and 83% yield, with 78:22 and 74:26 *d.r.*. Moreover, from compound **3.69** it was possible to grow crystals of the major isomer by slow evaporation of a CH_2Cl_2 solution. These crystals were suitable for single crystal X-ray diffraction analysis, which unambiguously revealed an *anti*-configuration of the two chiral centres (Figure 3.3).

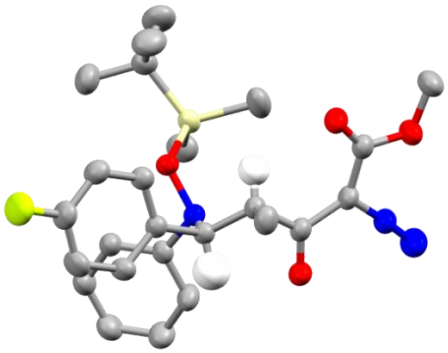
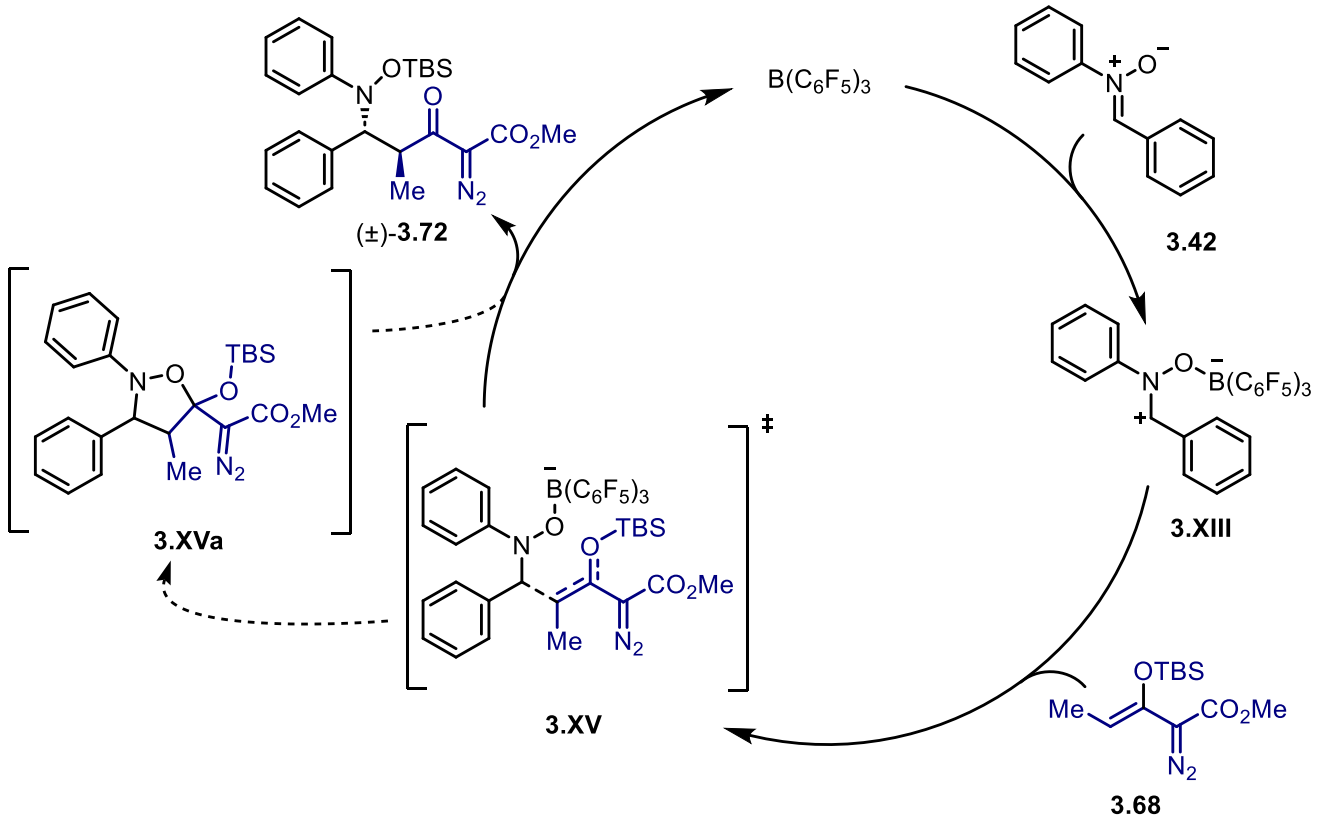


Figure 3.3. Crystal structure of compound **3.69**. Carbon: grey; oxygen: red; nitrogen: blue; fluorine: green; silicon; beige; hydrogen: white. Hydrogen atoms omitted for clarity except at the two chiral centres. Thermal ellipsoids drawn at 50% probability.

The presence of halide substituents on the *N*-aromatic ring of the nitrone exerted the same effects observed when these were on the *C*-aromatic ring. In fact, compounds **3.77**, **3.78**, and **3.79** were all obtained in good yield and very good diastereoselectivity (60%–87% yield and 70:30 to 82:18 *d.r.*). A limitation of this Mukaiyama-Mannich protocol is when *N*-aliphatic nitrones were used since product **3.81** could not be observed after several attempts.

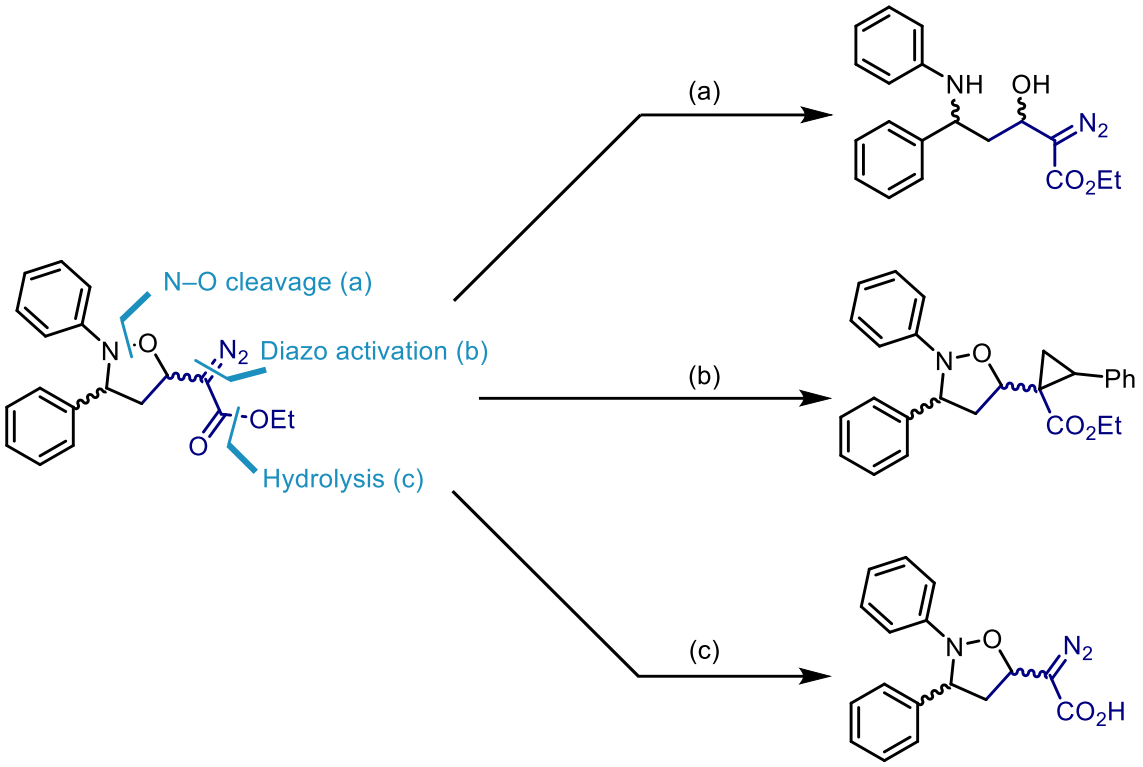
Similarly to the mechanism depicted in Scheme 3.25, the mechanism for the Mukaiyama-Mannich addition is proposed to begin with the nitrone activation by $B(C_6F_5)_3$, forming **3.XIII** (Scheme 3.28). However, instead of the [3+2] dipolar cycloaddition, the higher degree of nucleophilicity of the α-carbon of the silyl enol diazo ester sets up the nucleophilic addition to the nitrone, leading to TS **3.XV**. Finally, silyl transfer can occur forming the experimentally observed product. Additionally, another plausible mechanism entailing the formation of a ketal intermediate **3.XVa** could be operative under this protocol, as also suggested by others.[230] Future computational studies might rationalise the mechanism and explain the observed reactivity and diastereoselectivity. Currently, it is proposed that the diastereochemical outcome is governed by several factors such as steric hindrance of the catalyst, electronics of the nitrone but also the preferential coordination of the Lewis acid to one of the faces of the nitrone.



Scheme 3.28. Proposed catalytic cycle for the Mukaiyama-Mannich addition.

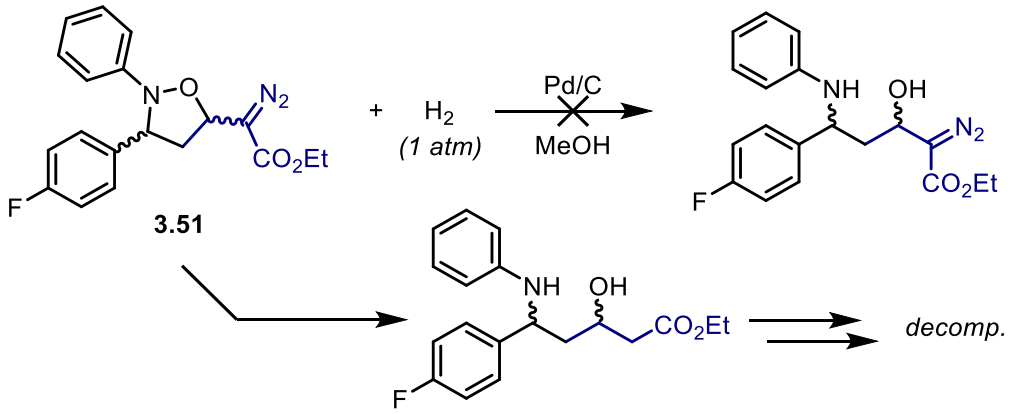
3.7.1. Further functionalisation

Having developed a protocol for the synthesis of highly functionalised diazo compounds, the next aim was to further functionalise the obtained products to assess their synthetic utility. Firstly, the attention was turned to the isoxazolidine products, which potentially possess three functionalisable positions: the N–O bond of the heterocyclic core, the ester moiety, and the diazo functionality (Scheme 3.29).



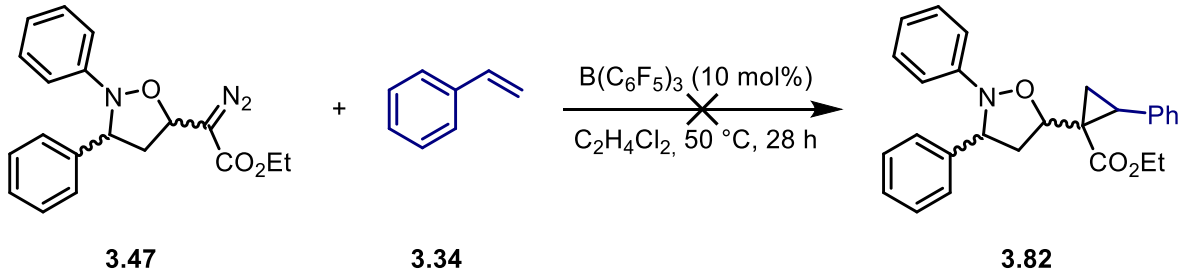
Scheme 3.29. Possible synthetic disconnections for the isoxazolidine products

Due to the labile nature of the N–O bond, isoxazolidine rings have found widespread application as synthetic intermediates for the synthesis of 1,3-aminoalcohols (Scheme 3.29, a).[231] Indeed, one of the earliest reports concerning the reductive cleavage of the N–O bond can be attributed to the father of the dipolar cycloadditions, Rolf Huisgen, in 1960.[232] In this seminal report, it has been shown that upon subjecting the isoxazolidine product to an atmosphere of H_2 using Pd/C, the N–O cleavage can be carried out in high yields. For this reason, this was also the first reaction attempted for the further functionalisation of the products. However, subjecting compound **3.51** under 1 atmosphere of H_2 using 5 mol% of Pd/C in MeOH afforded only decomposition of the isoxazolidine ring, presumably due to the side reactivity of the diazo functionality which can be hydrogenated as well (Scheme 3.30).[233,234]



Scheme 3.30. Attempted reductive cleavage of the N–O bond of compound **3.51**.

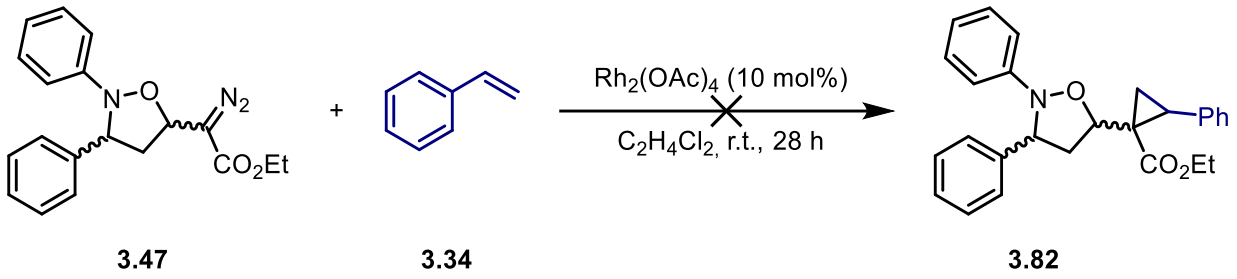
Similarly, by taking inspiration from conditions reported by Molander,[235] treatment of compound **3.51** in an aqueous solution of CH_3CO_2H in the presence of Zn dust afforded only decomposition products. For these reasons, it has been decided to tackle the selective manipulation of the diazo functionality, presumably being the most reactive moiety in the scaffold. As described earlier, in 2020 our group and the Wilkerson-Hill group showed that $B(C_6F_5)_3$ can activate α-aryl diazo esters, and that the corresponding carbene can undergo cyclopropanation with indenes or styrenes.[131,205] Thus, it has been envisaged to apply the same conditions to substrate **3.47**, which would therefore afford a new isoxazolidine ring, bearing a cyclopropyl moiety (Scheme 3.31).



Scheme 3.31. Attempted cyclopropanation of the diazo functionality using $B(C_6F_5)_3$.

Disappointingly, the reaction proved to be very messy, and no traces of the desired product **3.82** were observed. However, a major compound obtained in 13% isolated yield prompted further investigation into the process and, driven by the knowledge that $Rh_2(OAc)_4$ is a very efficient catalyst for the diazo

decomposition, the reaction has been repeated using $Rh_2(OAc)_4$ in catalytic amounts (10 mol%) (Scheme 3.32).

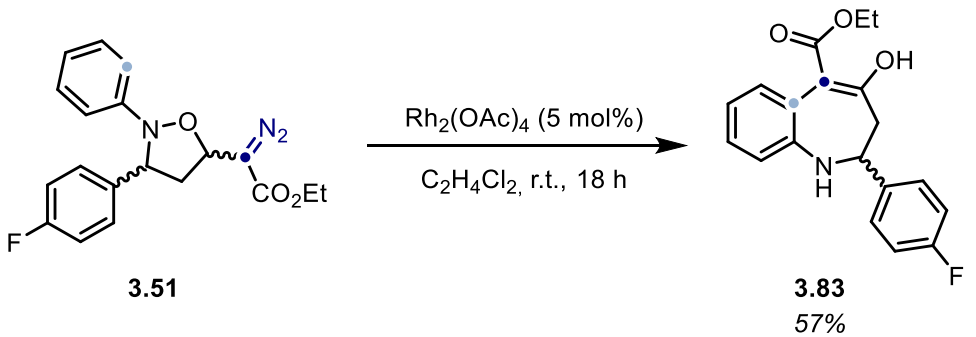


3.47 **3.34** **3.82**

Scheme 3.32. Attempted cyclopropanation of the diazo functionality using catalytic $Rh_2(OAc)_4$.

Upon addition of the Rh catalyst, the formation of bubbles could be seen, which is an indication of the formation of the carbene and N_2 gas liberation. However, also in this case the cyclopropanated product **3.82** was not detected but the unknown compound was isolated in 32% yield. This experiment led us to infer that the carbene is indeed formed under the reaction conditions either with $B(C_6F_5)_3$ or $Rh_2(OAc)_4$, but the subsequent intermolecular reaction is somehow suppressed by a faster event, presumably an intramolecular reaction. For this purpose, the reaction has been repeated without the styrene partner and indeed the unknown compound was obtained in 42% yield. Further investigation into the optimal conditions led to identify 5 mol% as the best catalytic loading with a reaction time of 18 hours which improved the yield of the product up to 57%.

With enough material in hand, it was possible to fully characterise the obtained product which was revealed to be a benzo[*b*]azepine **3.83** derived from an intramolecular C–H insertion (Scheme 3.33).



3.51 **3.83** *57%*

Scheme 3.33. Synthesis of a benzo[*b*]azepine through a Rh-catalysed diazo decomposition.

Indeed, the ^{1}H NMR showed the disappearance of the characteristic peak at 5.34 ppm, which has been previously assigned to be the proton α to the diazo functionality, and instead, a broad singlet at 3.60 ppm appeared. This has been attributed to a new N–H within the molecule. Interestingly, the benzo[*b*]azepine exists mainly as the enol tautomer, and this has been highlighted by the highly deshielded O–H proton at 13.13 ppm (Figure 3.4).

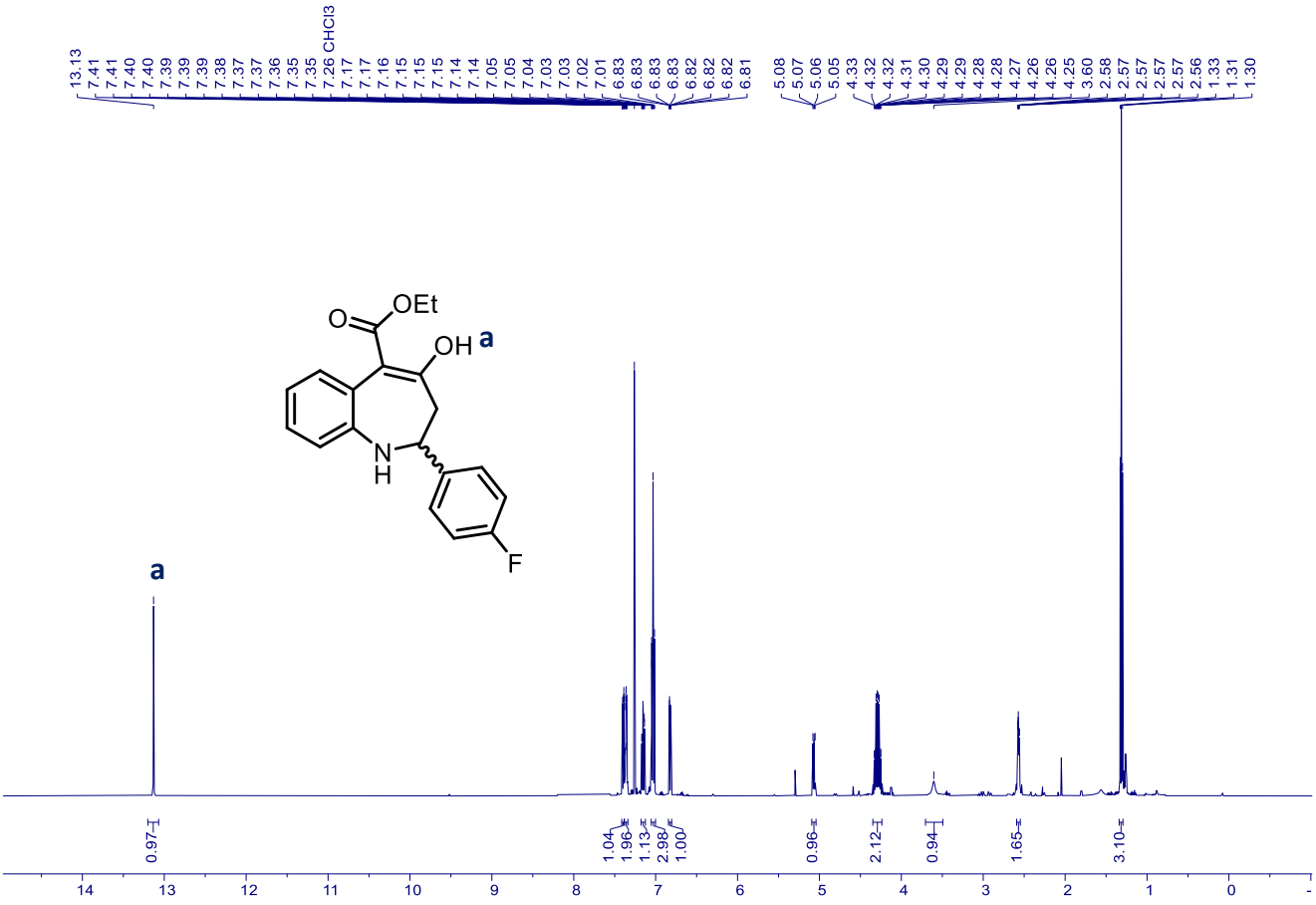
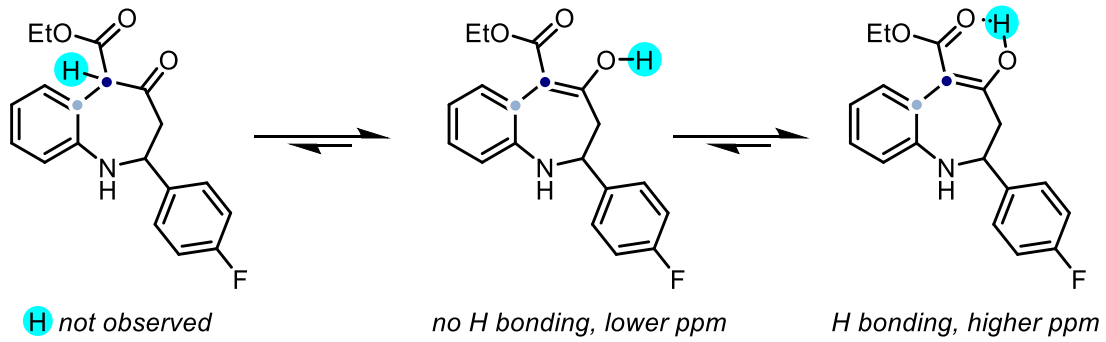


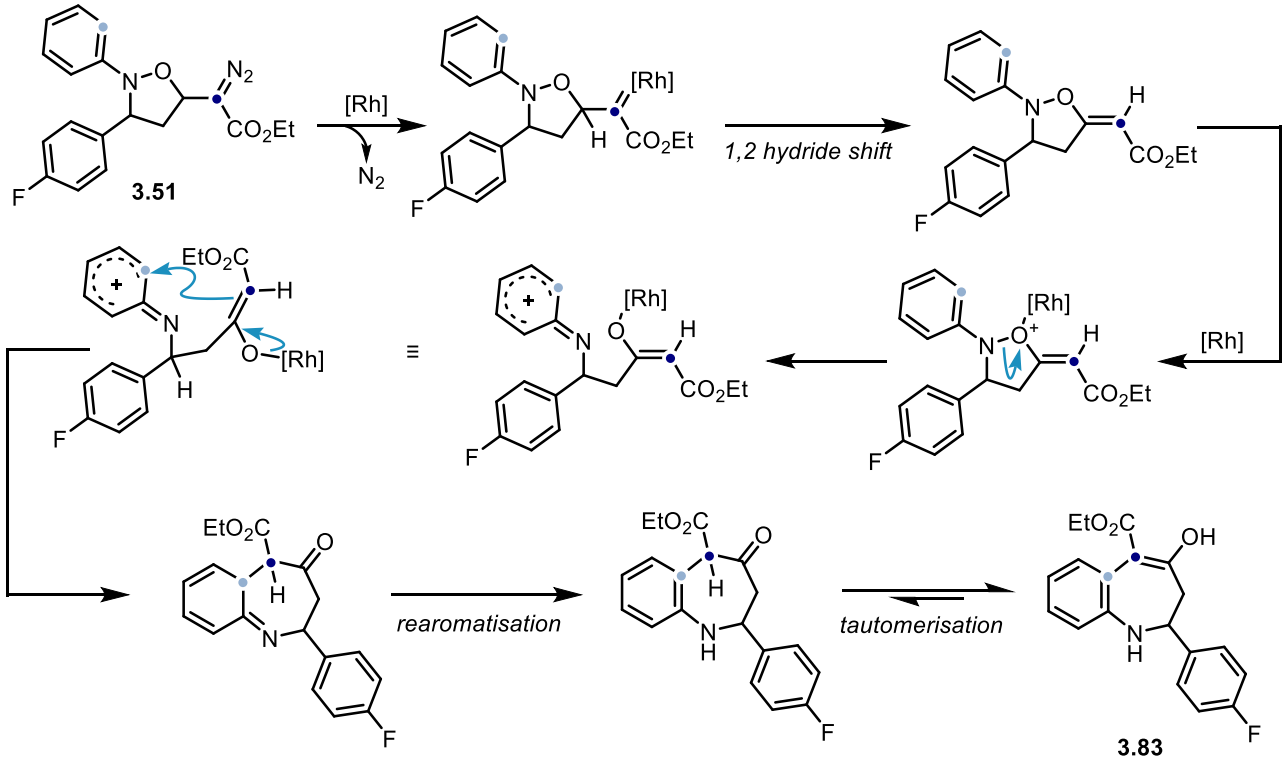
Figure 3.4. ^{1}H NMR spectrum of the benzo[*b*]azepine product **3.83**.

The downfield shift of the O–H proton can be attributed to the presence of the ester moiety, which can establish an intramolecular H bond (Scheme 3.34).[196,236]



Scheme 3.34. Schematic representation of the intramolecular H bonding in the benzo[*b*]azepine product.

This transformation has also been reported with similar substrates by Liu in the presence of a gold catalyst, where the proposed mechanism entails a 1,2-hydrogen shift followed by an intramolecular cyclisation (Scheme 3.35).[196]

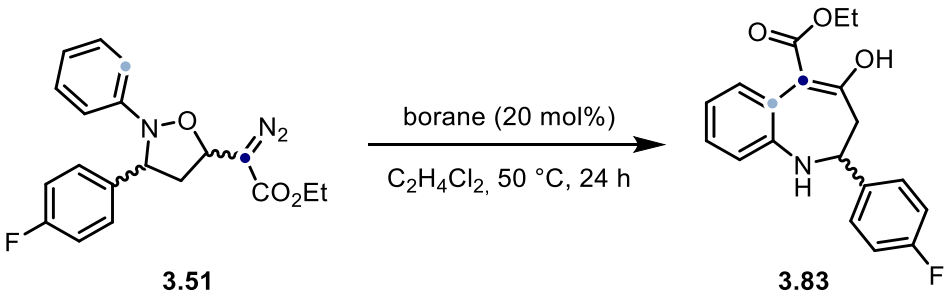


Scheme 3.35. Proposed mechanism for the formation of the benzo[*b*]azepine product **3.83**.

Since $B(C_6F_5)_3$ also afforded the benzo[*b*]azepine albeit in low yield, it has been envisaged that by careful choice of the Lewis acid the yield of the heterocycle could be improved, by minimising the possible side reactions.

This aspect has been recently highlighted by the group of Maulide where they showed that a very specific borane $B(2,6\text{-}F_2C_6H_3)_3$ was the only one proficient for their given transformation.[99] Inspired by this study, it was decided to test the hypothesis of a less strong Lewis acid, and thus preliminary experiments were undertaken (Table 3.3).

Table 3.3. Preliminary results for the borane catalysed benzo[*b*]azepine synthesis.

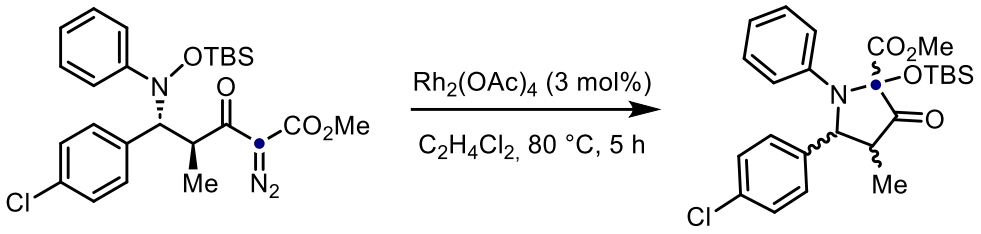


3.51 **3.83**

Entry	Borane	Yield 3.83	Acceptor Number (AN)
1	$B(2,4,6\text{-}F_3C_6H_2)_3$	33%	69[237]
2	$B(3,5\text{-}CF_3C_6H_3)_3$	10%	83.5[238]

These very preliminary results indeed suggest that a weaker Lewis acid such as $B(2,4,6\text{-}F_3C_6H_2)_3$ can be more efficient than $B(C_6F_5)_3$ for the benzo[*b*]azepine formation, since it formed product **3.83** in a moderate but improved yield of 33%. Hence, further investigations into the reaction could lead to the identification of an optimal borane for this transformation.

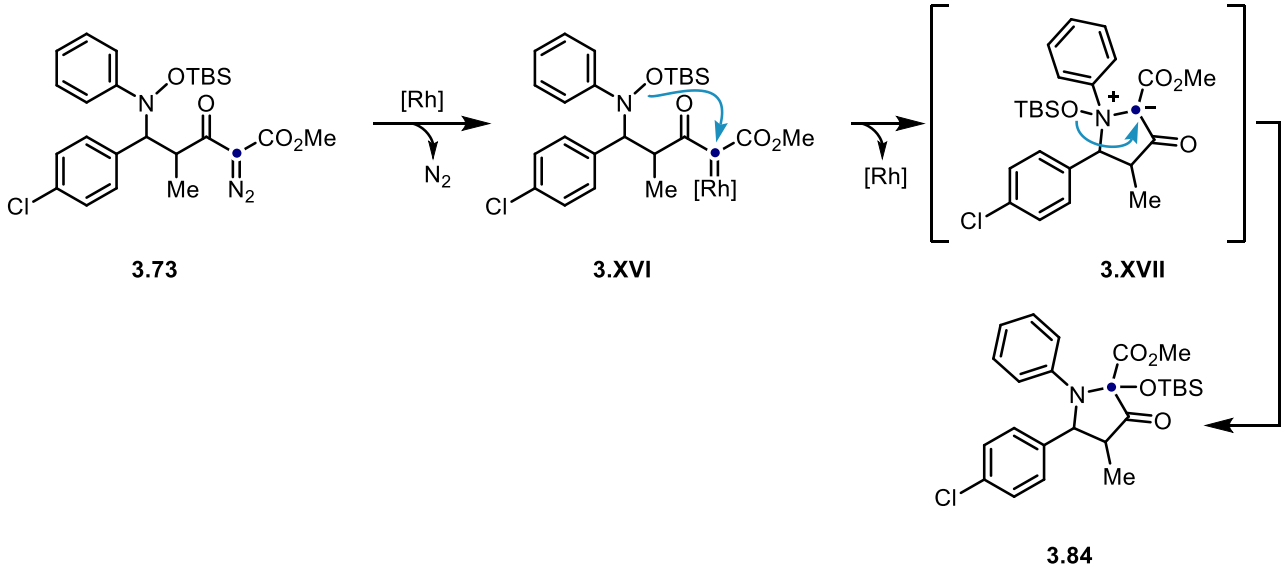
Having assessed that $Rh_2(OAc)_4$ outperforms $B(C_6F_5)_3$ for the diazo activation of complex substrates, it was decided to investigate the further functionalisation of the Mukaiyama-Mannich products using this metal-based catalyst as well. Indeed, by only using 3 mol% of $Rh_2(OAc)_4$ in $C_2H_4Cl_2$ at 80 °C for 5 hours it was possible to convert **3.73** into **3.84** which, after 1D- and 2D-NMR analysis, was assigned to be a pyrrolidinone scaffold (Scheme 3.36).



3.73 **3.84**

Scheme 3.36. Synthesis of a pyrrolidinone ring through a Rh-catalysed diazo decomposition.

Mechanistically, the reaction is proposed to proceed with the initial expected metal-carbene equivalent, which then undergoes a N–O insertion. This would lead to the formation of an ammonium ylide heterocycle **3.XVII**, which, upon OTBS 1,2-shift can form the observed product **3.84** (Scheme 3.37). The same type of product has also been observed by the group of Doyle,[193] where the authors have also shown that, in the presence of a free hydroxylamine moiety there can be a competition between N–OH and NO–H insertion, leading to different product distribution. Additionally, it has also been determined that the presence of a bulky silyl group is vital to establish a high level of stereocontrol.[193]

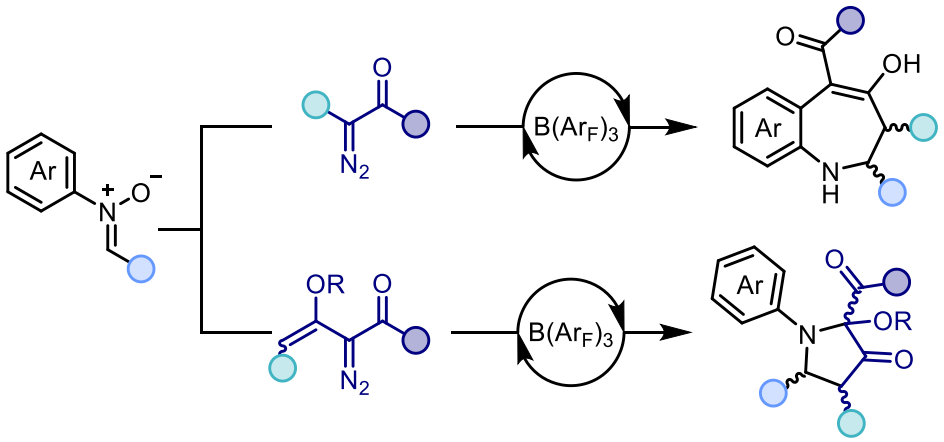


3.73 **3.XVI** **3.XVII** **3.84**

Scheme 3.37. Proposed mechanism for the formation of the pyrrolidinone product **3.84** catalysed by $Rh_2(OAc)_4$.

3.8. Conclusions

In conclusion, this work highlights the ability of $B(C_6F_5)_3$ to activate nitrones and, depending on the reactive partner, promote a diastereoselective [3+2] dipolar cycloaddition or Mukaiyama-Mannich addition in high yields (up to 90%) and with good level of diastereocontrol (up to >99:1). The bulky Lewis acid catalyst is deemed to be crucial for the stereoselectivity although the precise role remains elusive. Future experimental studies using chiral Lewis acids can shine a light on this process. Additionally, these can be supported by DFT studies. Crucially, the obtained products maintain intact the sensitive diazo functionality and they proved to be stable for several months under air without decomposition. These results are in accordance with earlier studies that support how the push-pull effect is very important for the initial activation of diazo compounds catalysed by $B(C_6F_5)_3$. Furthermore, the obtained products readily undergo diazo decomposition with either $Rh_2(OAc)_4$ or $B(C_6F_5)_3$, to afford a reactive carbene intermediate which intramolecularly cyclises to afford benzo[*b*]azepines or pyrrolidinones. Lastly, preliminary results showed that the benzo[*b*]azepines can be obtained by solely Lewis acid catalysis. Further studies might reveal an optimum catalyst for this transformation that could be also potentially carried out in an enantioselective fashion using a chiral Lewis acid. This would open the possibility to synthesise medicinally relevant scaffolds using only *p*-block elements without relying on the use of expensive transition metals (Scheme 3.38).



Scheme 3.38. Proposed one-pot synthesis of benzo[*b*]azepines or pyrrolidinones using borane catalysis.

4. The $B(C_6F_5)_3$-catalysed nitro-Mannich reaction

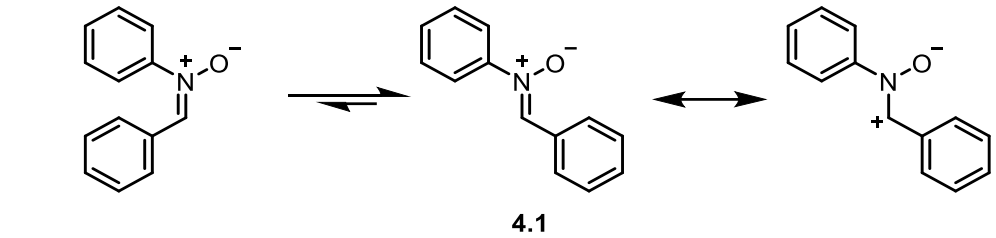
This chapter describes the development of a nitro-Mannich reaction between nitrones and silyl nitronates catalysed by $B(C_6F_5)_3$. The introduction section will give an overview of the chemistry and reactivity of nitrones and relevant examples of the nitro-Mannich reaction will be described. The results and discussion section will present the studies undertaken to develop a Lewis acid catalysed nitro-Mannich reaction. Studies to further functionalise the product will be also presented. Finally, preliminary results of an FLP-type approach of the nitro-Mannich reaction will be discussed.

4.1. The chemistry of nitrones

Nitrones, which can be seen as the *N*-oxides of iminium species, are important synthetic intermediates that have found widespread utility as 1,3-dipoles in cycloaddition reactions or as *N*-based electrophiles.[239–244] These zwitterionic species are proficient dipoles with respect to suitable dipolarophiles due to the oxygen atom. However, this atom makes them also Lewis basic, hence suitable to coordinate Lewis acids and open new reactivity patterns.[241] Given the vast literature entailing the transformations of nitrones, a complete discussion of all the possible reactions achievable with nitrones falls outside the scope of this thesis, hence only selected examples will be presented.

To begin with, it is important to set a general way for referring to nitrones. The chemical abstract nomenclature of these molecules utilises the prefix *N* for the substituents attached to the nitrogen atom and α for the substituents attached to the electrophilic carbon. This is how they will be referred to throughout the chapter. The unsaturated character of their structure allows an (*E*)-(*Z*) isomerisation (Scheme 4.1), which has been shown by DFT calculations to be solvent and substrate-dependent and likely proceeds through a radical mechanism.[245] In general, nitrones derived from aldehydes are predominantly (*Z*) but isomerisation can occur if an EWG is attached to the α position.

Their reactivity can be easily understood by drawing the resonance structure of compound **4.1**, which shows a positive charge at the α position (Scheme 4.1).[246]



4.1

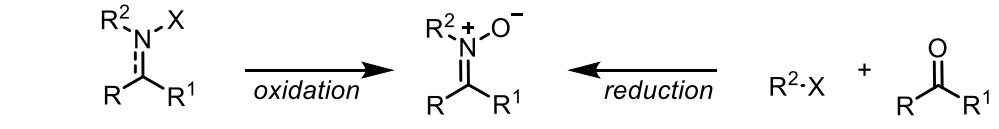
(*E*)-α-phenyl-*N*-phenyl nitrone (*Z*)-α-phenyl-*N*-phenyl nitrone

Scheme 4.1. Resonance structure of nitrones.

This renders nitrones good electrophiles that could undergo nucleophilic addition (e.g. Mannich addition) upon complexation through the oxygen atom with a metal or a Lewis acid.[241,244] In contrast to the Mannich addition on imines, the Mannich addition on nitrones can lead to an α-hydroxylamine product where the nitrogen functionality is in an intermediate oxidation state.[242] The hydroxylamine moiety has been proven to be an important scaffold to develop new antibacterial agents,[247] and it is also present in several natural products.[248,249] Moreover, it has been recently proposed that nitrones can be used as imine surrogates, since these are easier to handle, tend to be more stable despite being sufficiently reactive, and are readily available.[240]

4.1.1. Synthesis of nitrones

Several methods are nowadays available to synthesise nitrones, but they usually fall into two categories: oxidations or reductions (Scheme 4.2).[240]



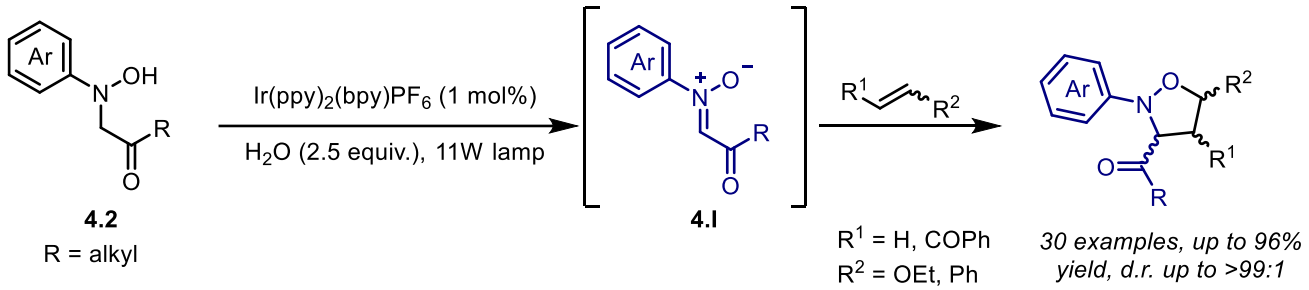
R, R^1, R^2 = alkyl, aryl, H
X = H, OH, OR

amines, aminoacids imines, hydroxylamines, isoxazolidines...

X = NO_2, NO

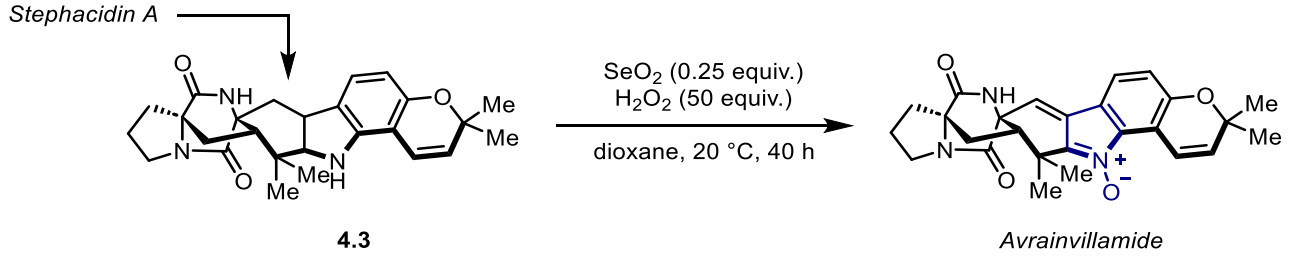
Scheme 4.2. General reaction scheme for the synthesis of nitrones.

The oxidation of *N,N*-hydroxylamines is one of the earliest methods developed for the synthesis of nitrones,[250] and it has been accomplished using different oxidants such as molecular oxygen, $KMnO_4$, yellow HgO and others. However, the toxicity and/or the regioselectivity of these reagents hampered their broader utilisation. A different approach for the synthesis of nitrones was thus disclosed by Rueping,[251] who presented a photocatalytic method which was based on an Ir photocatalyst to obtain nitrones **4.I** upon single electron oxidation of hydroxylamines **4.2** (Scheme 4.3). Crucially, the role of water as an additive was demonstrated to be pivotal and it has been proposed to help the reaction by promoting deprotonation of the ammonium radical cation formed under the reaction conditions.



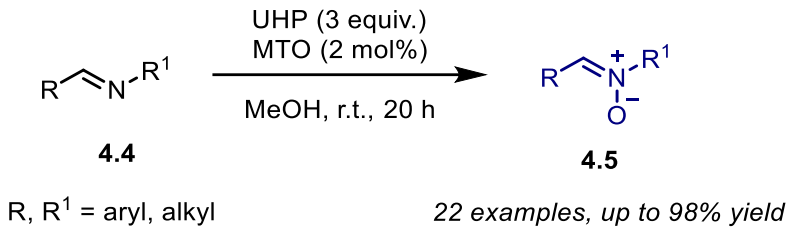
Scheme 4.3. Synthesis of nitrones by single-electron oxidation of hydroxylamines.

Despite the mild photocatalytic conditions employed, the most convenient method to form nitrones still relies on the oxidation of secondary amines, as initially discovered by Murahashi in 1984 using Na_2WO_4 and H_2O_2.[252] Nowadays, several other reports have been published using *m*-CPBA,[253] titanium,[254] or oxone.[255] Very recently, Baran demonstrated that also SeO_2 can be used in the presence of H_2O_2 to perform the selective oxidation of the secondary amine **4.3** derived from the natural product Stephacidin A, to the nitrone Avrainvillamide (Scheme 4.4).[240,256]



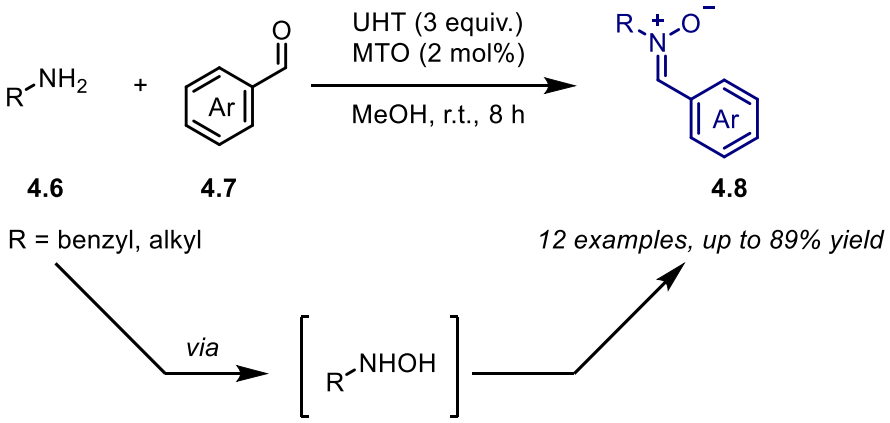
Scheme 4.4. Oxidation of secondary amines to nitrones in natural product synthesis.

However, in the case of unsymmetric secondary amines, the oxidative approach poses selectivity issues hence why an alternative approach based on the oxidation of imines can be more beneficial. To this end, the group of Goti developed a method using urea hydrogen peroxide (UHP) and catalytic amounts of methyltrioxorhenium (MTO) in MeOH to oxidise preformed imines **4.4** to the corresponding nitrones **4.5** (Scheme 4.5).[257]



Scheme 4.5. Oxidation of imines to nitrones with UHP and MTO.

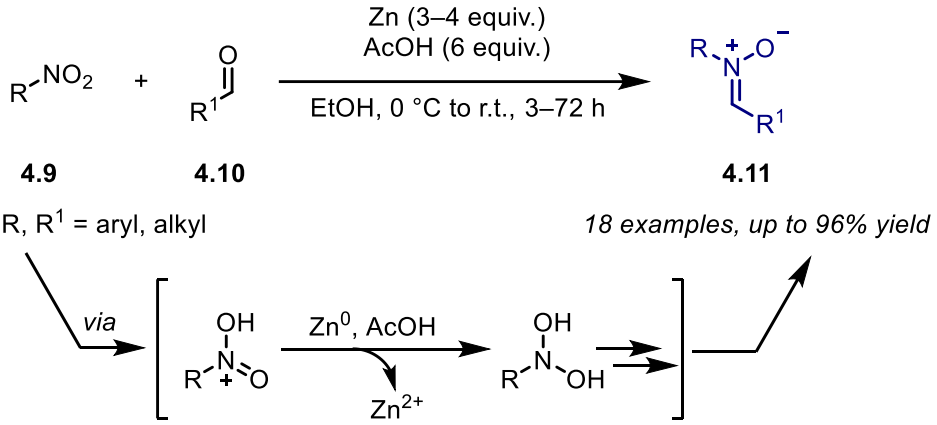
A year later, the same group developed a similar methodology relying on the use of primary amines **4.6**, which are believed to be oxidised under the reaction conditions to the corresponding hydroxylamines.[258] Condensation of these intermediates with an aldehyde **4.7** can lastly afford the corresponding nitrone **4.8** (Scheme 4.6).



Scheme 4.6. Oxidation of primary amines to nitrones with UHT and MTO.

In general, the proclivity for aerobic oxidation of several aromatic amines is a well-known drawback, which sometimes requires their distillation prior to use. Therefore, using the corresponding oxidised derivative (that is, a nitroarene) is advantageous and, in this regard, reductive conditions employing

nitroaromatics to synthesise nitrones were first disclosed by Vallée in 2001.[240,259] The simple and mild reaction conditions relied on the use of readily available starting materials such as nitro derivatives **4.9** and aromatic or aliphatic aldehydes **4.10** in the presence of zinc dust and an acidic promoter (Scheme 4.7).



Scheme 4.7. Reduction of nitro compounds for the synthesis of nitrones.

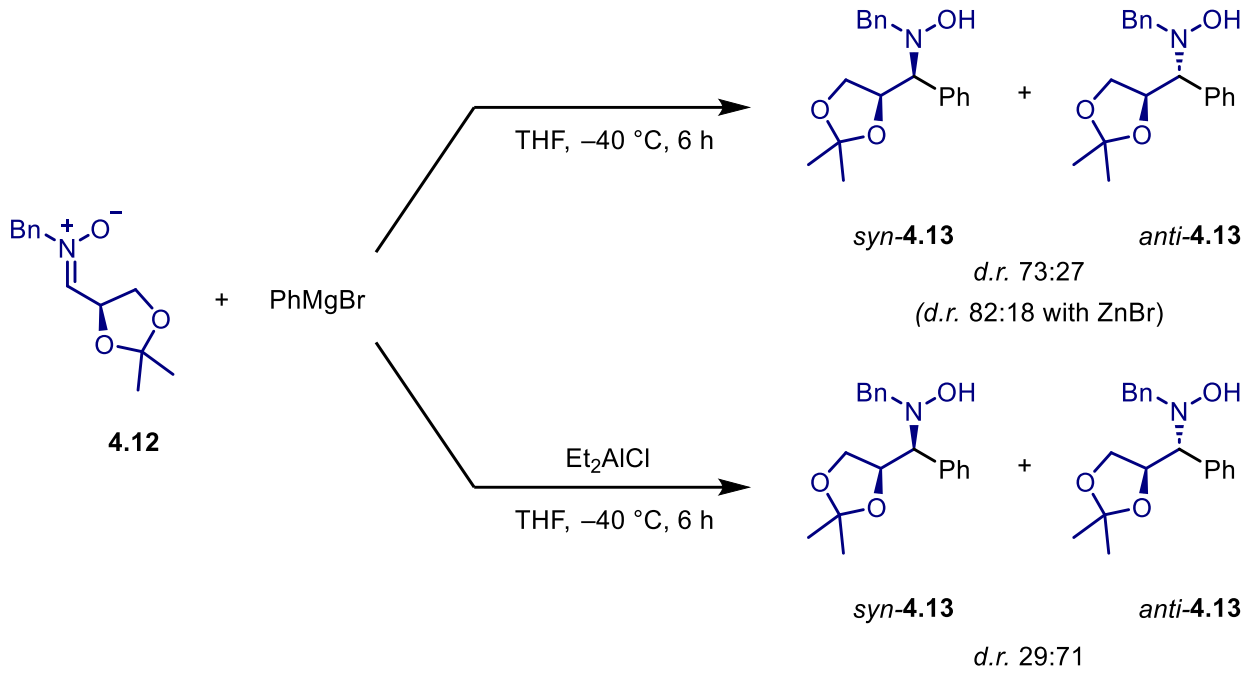
Although the authors did not disclosed a plausible reaction mechanism, it is possible to infer that it is a variation of the Béchamp reduction,[116] which is an iron-promoted reduction of nitrobenzene to aniline. In the classical mechanism, a hydroxylamine intermediate is formed first *via* a metal-promoted reduction of the nitro group, which further condenses with the aldehyde to form the nitrone. Under slightly modified conditions, this was the method of choice to synthesise the nitrones described in this thesis.

4.1.2. Reactivity of nitrones

As briefly mentioned in the previous chapters, the rich chemistry of nitrones can be categorised into two main areas: cycloaddition reactions and nucleophilic additions at the α carbon. For the aims of this chapter, only the latter aspect will be described.

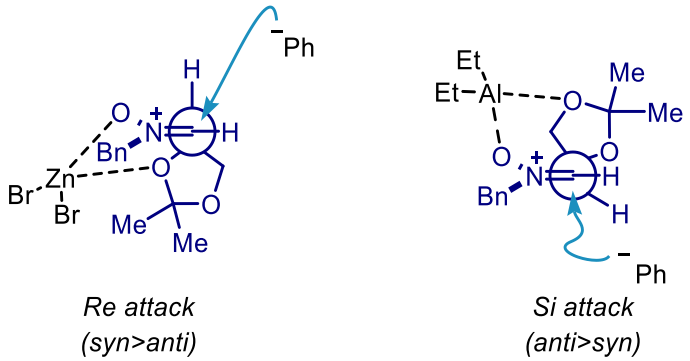
The nucleophilic addition to nitrones was first documented using Grignard reagents in 1911 by Alessandri.[244] Further studies using different nucleophiles and chiral nitrones have been undertaken by Merino starting from the 1990s, where the stereocontrolled addition was also investigated.[260–264]

For example, in 1997 it was shown that the stereocontrolled addition of Grignard reagents to nitrone **4.12** derived from glyceraldehyde (Mannich addition) could be tuned by changing the Lewis acid additive (Scheme 4.8).[264]



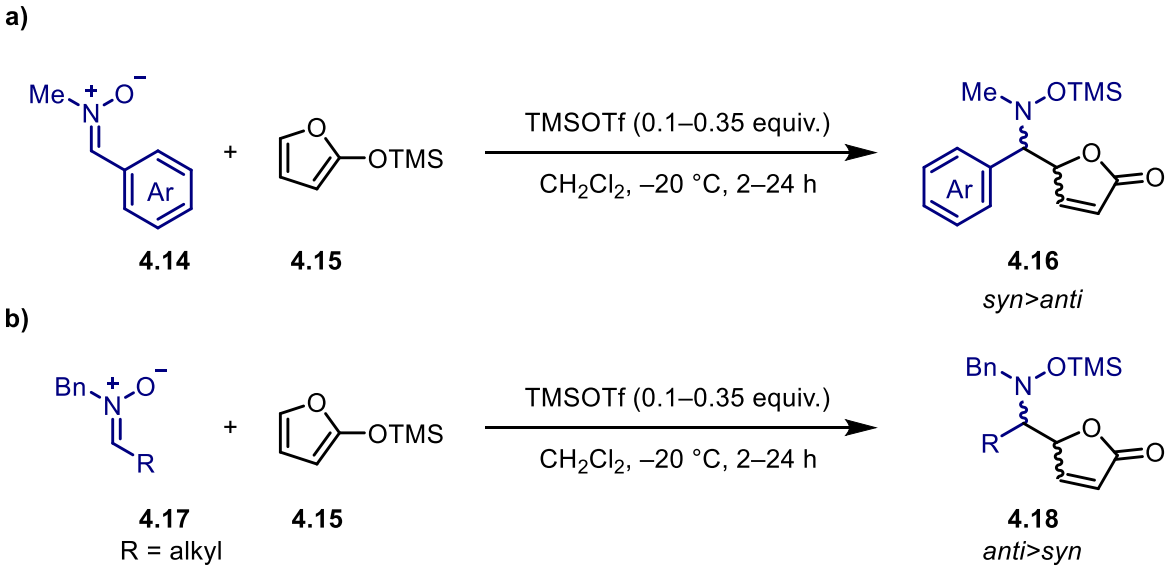
Scheme 4.8. Stereo-divergent reaction of nitrone **4.12** with Grignard reagents.

The authors observed that when the reaction is carried out without the presence of the Lewis acid Et_2AlCl, the product distribution favours product *syn*-**4.13** over *anti*-**4.13** (*d.r.* 73:27) in an overall yield of 84%. However, the presence of the Lewis acid reverses the diastereofacial selectivity favouring *anti*-**4.13** over *syn*-**4.13** (*d.r.* 21:79) in 83% yield. Oddly, adding a different Lewis acid such as $ZnBr_2$ did not reverse the diastereoselectivity, since the *d.r.* was measured to be 82:18 in favour of the *syn* isomer (Scheme 4.8). To explain this, the authors invoked a chelate model considering an external organometallic reagent delivery as the operative mechanism for the reaction, where the reversal of diastereoselectivity was attributed to the different chelation of the nitrone with the Lewis acid (Scheme 4.9).



Scheme 4.9. Chelate models for the stereoselective addition of Grignard reagents to nitrones.

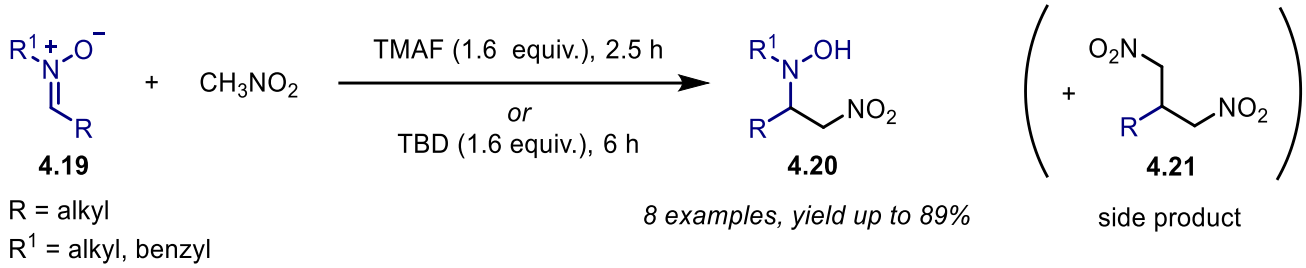
Nevertheless, there have been reports where the diastereoselectivity can be reversed not only due to this effect but also because of stabilising and destabilising effects between the reactants in the TS. For example, the Mukaiyama-Mannich addition on *N*-methyl α-aryl nitrones **4.14** using **4.15** leads to the preferential formation of the *syn* isomer of **4.16** (Scheme 4.10, a).[265] However, in the case of *N*-benzyl α-alkyl nitrones, preferential formation of the *anti* isomer occurs (Scheme 4.10, b).[265]



Scheme 4.10. Mukaiyama-Mannich addition on nitrones **4.14** and **4.17** using **4.15**.

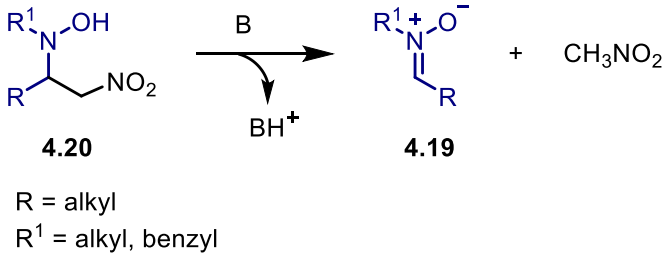
In this scenario, the authors leveraged a stereochemical model using Newman projections where the diastereoselectivity was deemed to be governed by an interplay of different effects which lowered the steric clash and favoured both π-π stacking and attractive electrostatic interactions between the nitrone and **4.15**.[265]

As noticeable, different nucleophiles give rise to different reaction names in these types of nucleophilic additions. A Grignard reagent adding over an electrophilic imine (or nitrone) does a so-called Mannich addition, whereas a silyl enol ether does a Mukaiyama-Mannich addition. By analogy, the nucleophilic nitronate anion (the enol form of a nitro group) can undergo a nitro-Mannich (or aza-Henry) addition. This helpful reaction, which allows the introduction of a nitro group α to an amine, has been recently applied also to nitrones **4.19** by the group of Behr (Scheme 4.11).[266]



Scheme 4.11. Base-promoted nitro-Mannich reaction on nitrones.

In this first example of a nitro-Mannich reaction using nitrones, the authors have observed that superstoichiometric amounts of base such as tetramethylammonium fluoride (TMAF) or 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) can effectively form a nitronate anion from the solvent nitromethane, which is thus used as both the reaction medium and as reactant. This can attack nitrones of the type **4.19** to form the corresponding α-nitro hydroxylamine **4.20** in up to 89% yield. However, one major limitation encountered by the authors was the observation of a retro-nitro-Mannich event caused by the excess of base (Scheme 4.12).[267]

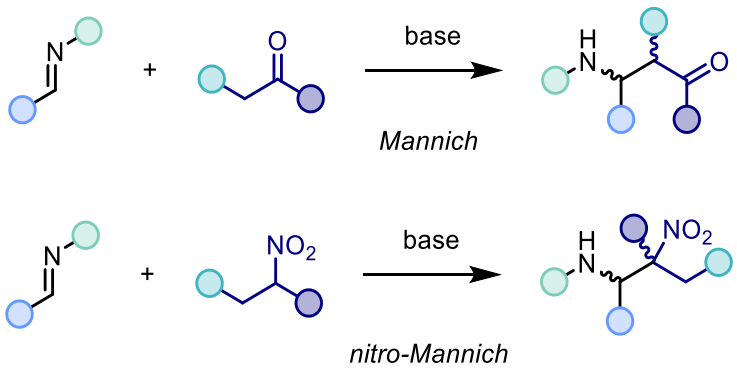


Scheme 4.12. Proposed retro nitro-Mannich step.

This rendered the reaction a formal equilibrium between **4.19** and **4.20**, requiring a large excess of nitromethane to ensure high yields. Additionally, the large excess of nucleophile compared to the nitrone triggered an important competing reaction which afforded the bis(nitromethyl) alkane **4.21** as a side product. Nevertheless, this first example of the nitro-Mannich reaction showed that it would be possible to leverage the reactivity of these species to obtain products containing two vicinal nitrogen atoms in two different oxidation states. This, in turn, would in principle allow their selective manipulation access to the 1,2-nitroamine or 1,2-diamino functionality, where the former is present in several drugs and the latter is used as a chelating moiety for transition metals (*vide infra*). For these reasons, the work from Behr was taken as inspiration for developing the methodology described further in Chapter 4.5.

4.2. The nitro-Mannich reaction

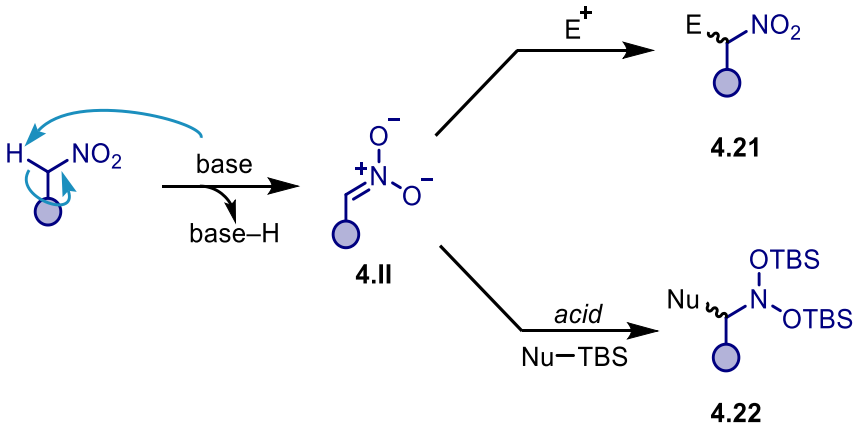
As mentioned in the previous chapter, an important reaction within the realm of C–C bond formation is the nitro-Mannich reaction, a variation of the classic Mannich reaction (Scheme 4.13).



Scheme 4.13. Comparison between the classic Mannich reaction and nitro-Mannich reaction.

The high reactivity of a nitronate anion stems from the high acidity of the α-proton of the corresponding aliphatic nitro group, which is around 10^{10} times more acidic than the proton α to a ketone functionality (pK_a [CH_3NO_2] = 10). Hence, deprotonation of aliphatic nitro compounds can occur easily by using strong bases, forming the corresponding nitronate anion **4.II** (Scheme 4.14).

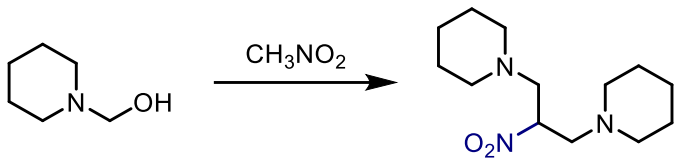
This, in turn, becomes strongly nucleophilic at the α position and reacts readily with a variety of electrophiles to afford products of the type **4.21** (Scheme 4.14).



Scheme 4.14. Diverging reactivity of nitronate anions.

Interestingly, it has been shown by List that the α carbon, inherently nucleophilic, can be rendered electrophilic by the use of a strong acid catalyst which can coordinate one of the two oxygen atoms of **4.II**.[268] This different activation mode proves that nitronate anions are ambiphilic, and products of the type **4.22** can be obtained depending on the reaction conditions (Scheme 4.14).

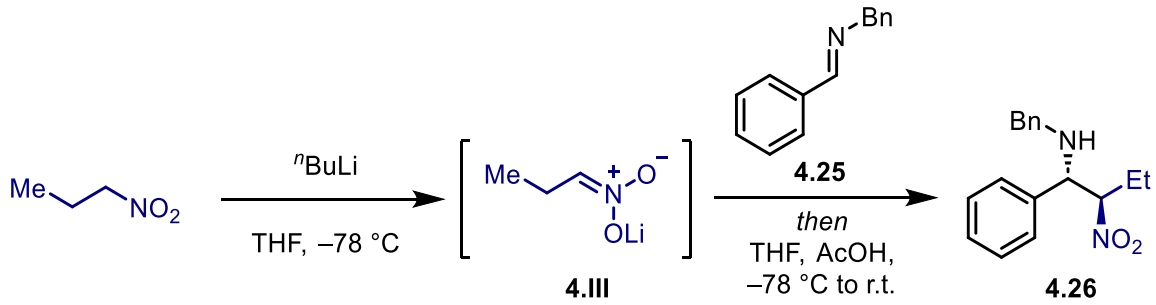
In general, the importance of the nitro-Mannich can be mainly attributed to the type of products obtainable. Indeed, upon the addition of a nitronate anion to an imine, a 1,2-nitroamine forms, where two vicinal nitrogen atoms are in opposite oxidation states, allowing their selective manipulation.[269] Additionally, the newly installed nitro group can be promptly reduced to the corresponding amine, allowing access to the 1,2-diamino functionality, important moiety in natural products and for the design of new ligands for transition metals.[270,271] The first report of the nitro-Mannich was made by Louis Henry in 1896, where it was demonstrated that nitromethane can react with an excess of amino alcohol **4.23** to form product **4.24** (Scheme 4.15).[269]



4.23 **4.24**

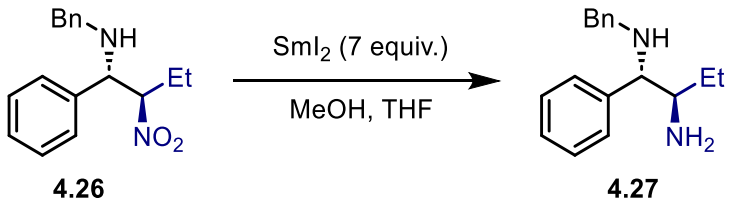
Scheme 4.15. The first report of the nitro-Mannich reaction.

Despite the synthetic utility, the reaction remained long forgotten until the group of Anderson disclosed the first stereoselective synthesis of 1,2-diamines using the nitro-Mannich reaction.[272] In this early report, treatment of nitropropane with ^{n}BuLi at –78 °C formed the corresponding lithium nitronate **4.III**. Addition of **4.25** afforded the nitro-Mannich addition product **4.26** in quantitative yield upon quenching the reaction with AcOH (Scheme 4.16).



Scheme 4.16. The first stereoselective nitro-Mannich reaction.

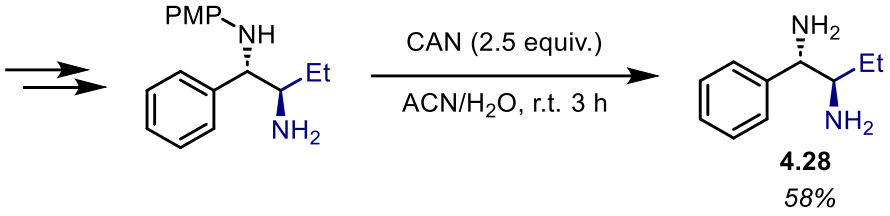
Despite the quantitative yield of product **4.26**, the authors noticed that this was very unstable during purification over silica or after storing it for a prolonged time in solution due to its propensity to undergo β-elimination. Therefore, additional reduction using SmI_2 proved to be necessary, which ultimately afforded the 1,2-diamino product **4.27** in 62% yield (Scheme 4.17).



4.26 **4.27**

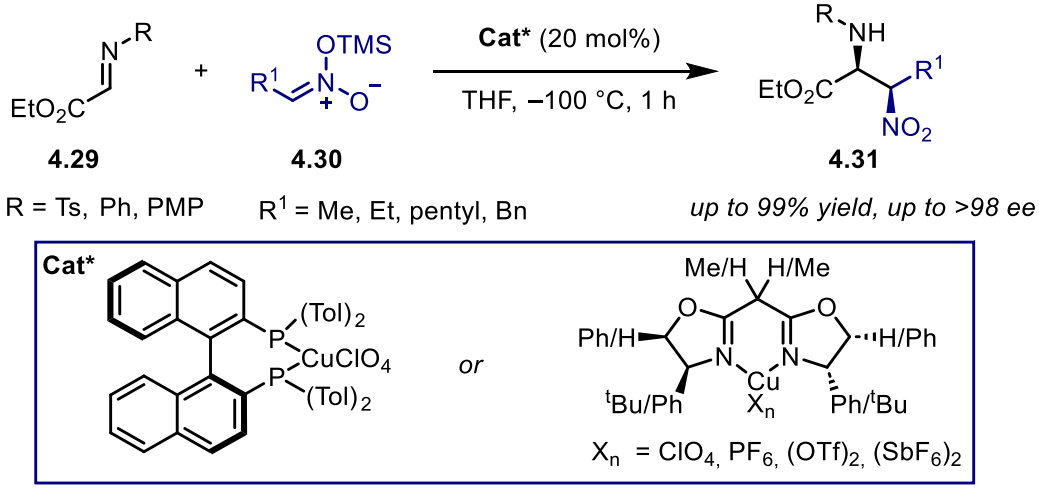
Scheme 4.17. Reduction of **4.26** using SmI_2.

Additionally, the authors also encountered stability issues when they subjected compound **4.27** to the standard debenzylation procedure using H_2 with Pd/C. Therefore, the Bn protecting group was replaced with *p*-methoxyphenyl (PMP), which could be easily cleaved with cerium ammonium nitrate (CAN) affording the diamine **4.28** (Scheme 4.18).



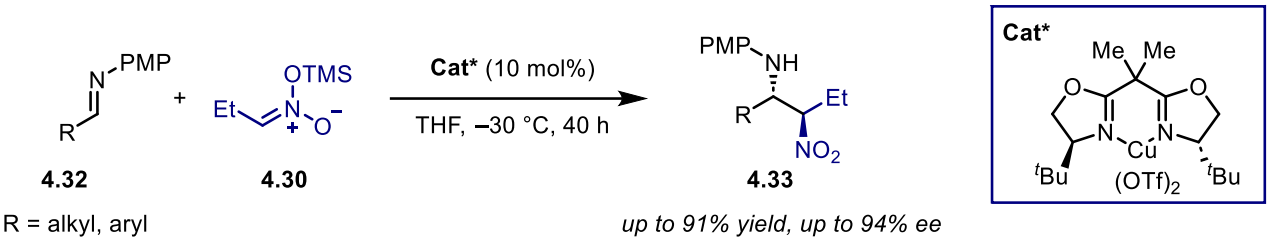
Scheme 4.18. Synthesis of the diamine **4.28** by oxidative cleavage of PMP group.

It should be also highlighted that the nitro-Mannich addition occurred only in the presence of stoichiometric amounts of AcOH (Scheme 4.16). This was later revealed to be responsible for the imine activation and raised questions about whether a chiral Lewis acid could be employed instead to exert high levels of enantioselectivities.[273] However, due to the propensity of nitronate **4.III** to act as a strong Lewis base, capping with a silyl protection of one of the coordinating oxygens would be required to avoid catalyst deactivation. This approach, called *indirect* nitro-Mannich[269] was first described by Anderson using $Sc(OTf)_3$,[273] and soon after was carried out in an enantioselective way by Jørgensen, using a chiral copper catalyst (Scheme 4.19).[274]



Scheme 4.19. The first asymmetric nitro-Mannich reaction on imines developed by Jørgensen.

In this report, imines **4.29** can react in an *indirect* nitro-Mannich approach (that is, formation and isolation of the nitronate intermediate) with silyl nitronates **4.30**, affording enantiomerically pure 1,2-nitroamine products **4.31** in up to 99% yield, using a chiral copper catalyst. The protocol was further improved in 2005 by Anderson using a similar copper catalyst but with different electrophilic imine partners (Scheme 4.20).



4.32 **4.30** **4.33**

R = alkyl, aryl

up to 91% yield, up to 94% ee

Scheme 4.20. Further development of the stereoselective nitro-Mannich reaction.

These initial reports gave new impetus to the nitro-Mannich reaction and several other reports using transition metal catalysis,[275] isothiourea organocatalysis,[276] Brønsted acid catalysis,[277] and others,[269,278] have been described using imines as electrophilic partners. Moreover, applications in total synthesis have also been disclosed.[279]

4.3. Aims of the project

Chapter 3 described the application of $B(C_6F_5)_3$ as an efficient catalyst for the Mukaiyama-Mannich addition of silyl enol diazo esters with nitrones. On the other hand, Chapter 4.2 described the introduction of a nitro group α to another nitrogen-based functionality *via* the nitro-Mannich reaction. This has been shown to be a valuable synthetic procedure because it can allow the synthesis of the 1,2-nitroamine functionality, where the orthogonal manipulation of one of the two nitrogen centres can be done. Despite the huge progress made in the field of the nitro-Mannich reaction, most of the reactions described in the literature relied on specifically designed imines, with their instability towards hydrolysis being a well-known issue. To this end, nitrones have been shown to be good imine surrogates and only one report describes their use in a *direct* nitro-Mannich reaction.[266] Therefore, based on the early reports of Anderson and Behr, it has been envisaged to develop a $B(C_6F_5)_3$-

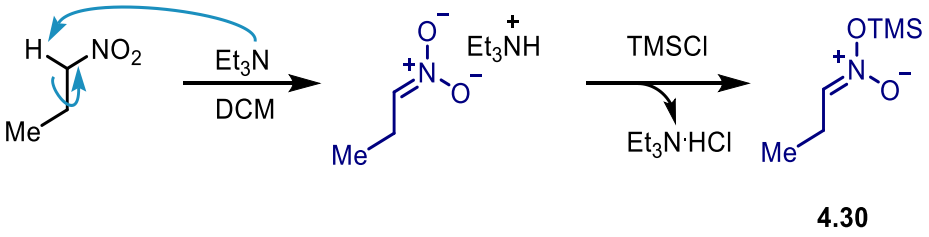
catalysed approach to the nitro-Mannich reaction, using nitrones as electrophilic partners. This would allow the synthesis of α-nitro hydroxylamine products, which could be potentially transformed into the corresponding α-nitro amines. This would also highlight once again the possibility of using nitrones as imine surrogates. Additionally, the substrate scope with respect to the nucleophile for this transformation has largely been limited to simple alkyl nitronates. To this end, a substrate scope using novel and different silyl nitronates would expand the landscape in terms of nucleophilic partners.

4.4. Authors contribution

My involvement in the project was to synthesise all the starting materials, as well as carry out the optimisation studies, the substrate scope, and the further functionalisation studies. Ms. Yara van Ingen measured and solved the crystal structures. This work has been published in the journal Chemical Science *Chem. Sci.*, **2024**, 15, 2648–2654.

4.5. Results and discussion

To begin with, the nitrone starting materials were prepared according to the Béchamp-type method described in Chapter 4.1.1, whereas the silyl nitronates were prepared by adapting a procedure described by List.[268] In general, silyl nitronates are highly unstable towards moisture, light and temperature[268] however, they are more thermally stable than lithium nitronates rendering them useful synthetic intermediates.[280] The synthesis of these species relies on the high acidity of the α-proton, which can be abstracted by the use of a base such as Et_3N. This forms an *in situ* ammonium nitronate, which can be isolated as the silyl nitronate **4.30** upon treatment with TMSCl (Scheme 4.21).

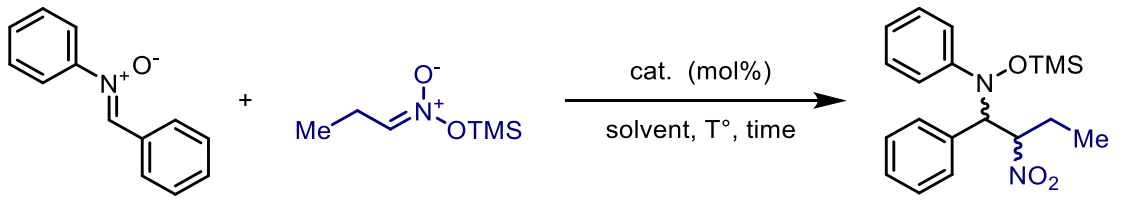


4.30

Scheme 4.21. General reaction scheme for the synthesis of silyl nitronate starting material.

The reaction was carried out in dry CH_2Cl_2 under strictly anhydrous conditions to avoid nitronate decomposition. Upon the addition of TMSCl, the formation of white smoke and a white precipitate was observed, which are inferred to derive from the formation of the $Et_3N{\cdot}HCl$ by-product. After completion of the reaction, the CH_2Cl_2 solvent was removed by putting the reaction flask under the vacuum on the Schlenk line. This afforded a yellow oil and a white solid, which was extracted three times with small amounts of pentane. The pentane extractions were then transferred into a new Schlenk flask using a filter cannula. Finally, the pentane was removed under vacuum affording a yellow oil which was immediately transferred inside a glovebox and stored in a –30 °C freezer in the dark. With the desired starting material in hand, the reaction investigation commenced by mixing nitrone **3.42** with 1.5 equivalents of silyl nitronate **4.30** in toluene at room temperature for 5.5 hours (Table 4.1 entry 1).

Table 4.1. Optimisation of the reaction conditions for the $B(C_6F_5)_3$-catalysed nitro-Mannich reaction. All reactions were carried out on a 0.1 mmol scale using 1.5 equiv. of silyl nitronate, except where otherwise stated. NMR spectroscopic yields are calculated using 1 equiv. of 1,3,5- trimethoxybenzene (TMB). [a]2 equiv. of silyl nitronate used. n.a.: not applicable. "Conversion" refers to how much nitrone starting material has been consumed over the course of the reaction, and it has been calculated based on the remaining nitrone in the crude reaction mixture.



3.42 **4.30** **4.31** *(syn+anti)*

Entry	Cat (mol%)	Solvent (0.1 M)	T (°C)	Time (h)	Yield 4.31 (Isolated)	*d.r.* (syn:anti)	Conversion 3.42
1	$B(C_6F_5)_3$ (20)	Toluene	r.t.	5.5	80% (59%)	85:15	94%
2	-	Toluene	r.t.	5.5	-	n.a.	-

3	-	Toluene	r.t.	24	traces	n.a.	<5%
4	$B(C_6F_5)_3$ (20)	CH_2Cl_2	r.t.	6	44%	86:14	48%
5	$B(C_6F_5)_3$ (20)	TFT	r.t.	6	80% (62%)	85:15	88%
6	$B(C_6F_5)_3$ (20)	THF	r.t.	6	71%	78:22	88%
7	$B(C_6F_5)_3$ (20)	Pentane	r.t.	6	82% (68%)	87:13	82%
8	$B(C_6F_5)_3$ (20)	Et_2O	r.t.	6	45%	83:17	55%
9	$B(C_6F_5)_3$ (20)	CH_3CN	r.t.	6	decomp.	n.a.	100%
10	$B(C_6F_5)_3$ (20)	Neat	r.t.	6	67%	86:14	90%
11	$B(C_6F_5)_3$ (20)	CH_2Cl_2	r.t.	6	73%	85:15	92%
12	$TsOH \cdot H_2O$ (20)	Pentane	r.t.	6	decomp.	n.a.	<5%
13	$B(C_6F_5)_3$ (20)	Pentane	r.t.	0.5	34%	78:22	58%
14	$B(C_6F_5)_3$ (20)	CH_2Cl_2	r.t.	3	77%	86:14	94%
15	$B(C_6F_5)_3$ (20)	TFT	r.t.	3	69%	84:16	94%
16	$B(C_6F_5)_3$ (20)	Pentane	r.t.	3	59%	86:14	84%
17[a]	$B(C_6F_5)_3$ (20)	CH_2Cl_2	r.t.	3	84%	86:14	>95%
18[a]	$B(C_6F_5)_3$ (20)	CH_2Cl_2	r.t.	1	79%	86:14	94%
19[a]	$B(C_6F_5)_3$ (20)	CH_2Cl_2	0	3	79%	88:12	89%
20[a]	$B(C_6F_5)_3$ (20)	CH_2Cl_2	–41	3	54%	74:26	82%
21[a]	$B(C_6F_5)_3$ (20)	CH_2Cl_2	–78	3	44%	76:24	67%
22[a]	$B(C_6F_5)_3$ (10)	CH_2Cl_2	r.t.	3	90% (81%)	86:14	100%
23[a]	$B(C_6F_5)_3$ (5)	CH_2Cl_2	r.t.	3	71%	86:14	83%
24[a]	BPh_3 (10)	CH_2Cl_2	r.t.	3	-	n.a.	-
25[a]	$BF_3 \cdot Et_2O$ (10)	CH_2Cl_2	r.t.	3	-	n.a.	-
26[a]	TFA (100)	CH_2Cl_2	r.t.	3	decomp.	n.a.	<5%

Pleasingly, the reaction afforded the desired nitro-Mannich addition product in 80% NMR spectroscopic yield as a mixture of two diastereoisomers. Subsequently, the crude reaction mixture was purified *via* preparative TLC using a mixture of cyclohexane:ethyl acetate 9:1 allowing the separation of the two diastereoisomers. Interestingly, the major diastereoisomer had always a higher R_f than the minor and appeared as an oil whereas the minor as a white solid. Thus, it was possible to grow crystals from the latter by slow evaporation of a concentrated solution of the compound in CH_2Cl_2. The obtained crystals were suitable for single crystal X-ray diffraction which showed a (±)-*(S),(R)* (or *anti*) configuration (Figure 4.1). Since throughout this study it was not possible to grow a crystal structure of the major diastereoisomer, its configuration was assumed by analogy to be (±)-*(R),(R)* (or *syn*).

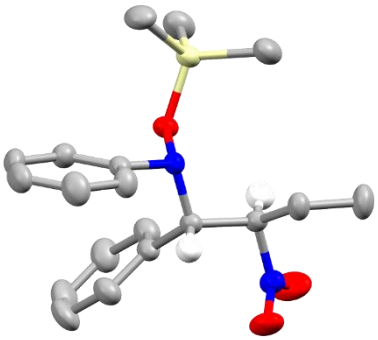


Figure 4.1. Solid state structure of compound *anti*-**4.31**. Carbon: grey; hydrogen: white; nitrogen: blue; oxygen: red; silicon: yellow. Hydrogen atoms omitted for clarity (except for the α-hydrogen atoms). Ellipsoids shown at 50% probability.

Moreover, similarly to the diazo ester products obtained in Chapter 3.3, the two diastereoisomers had diagnostic signals in the ^{1}H NMR spectrum which allowed their differentiation (Figure 4.2) In general, the major diastereoisomer showed the benzylic proton more deshielded than the one of the minor diastereoisomer (cf. doublets at 4.70 ppm and ~4.40 ppm). Additionally, the diastereotopic CH_2 protons of the minor diastereoisomer always appeared as two separate peaks in the range between 2.00 and 3.00 ppm, whereas for the major diastereoisomer these always appeared around 1.55 ppm (Figure 4.2).

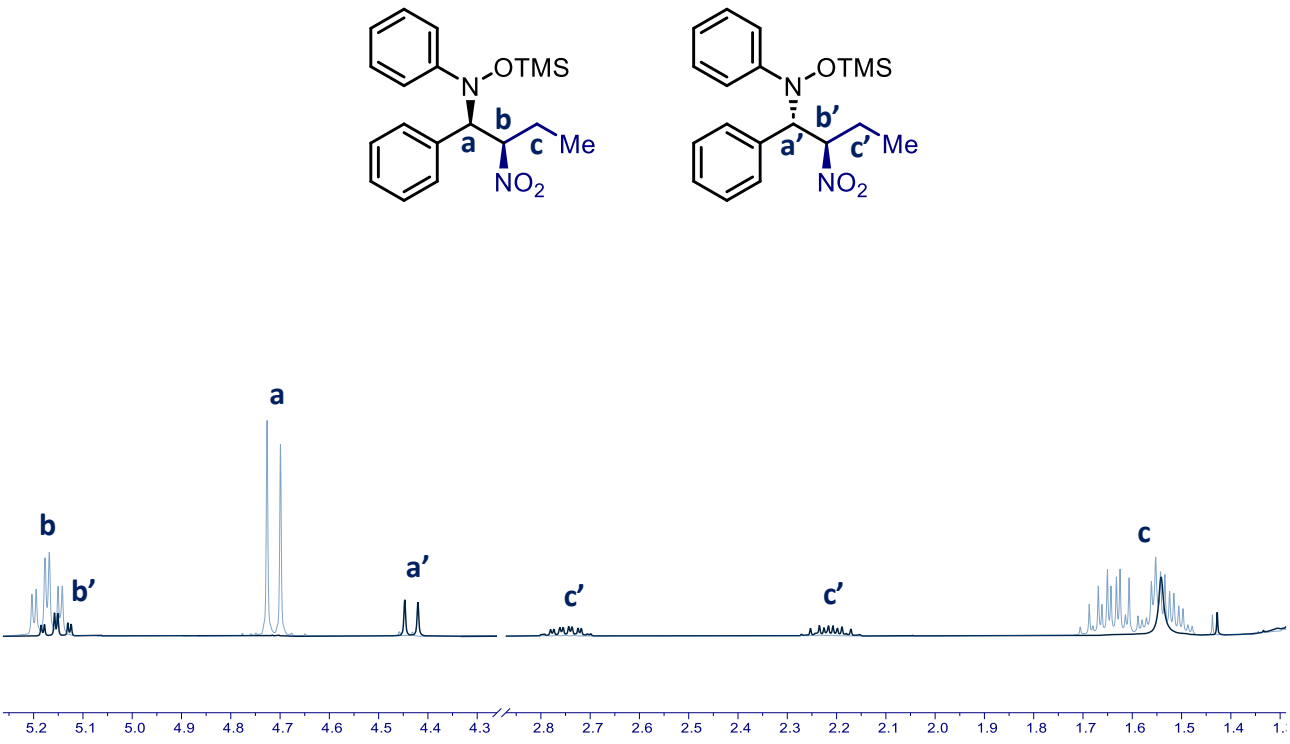


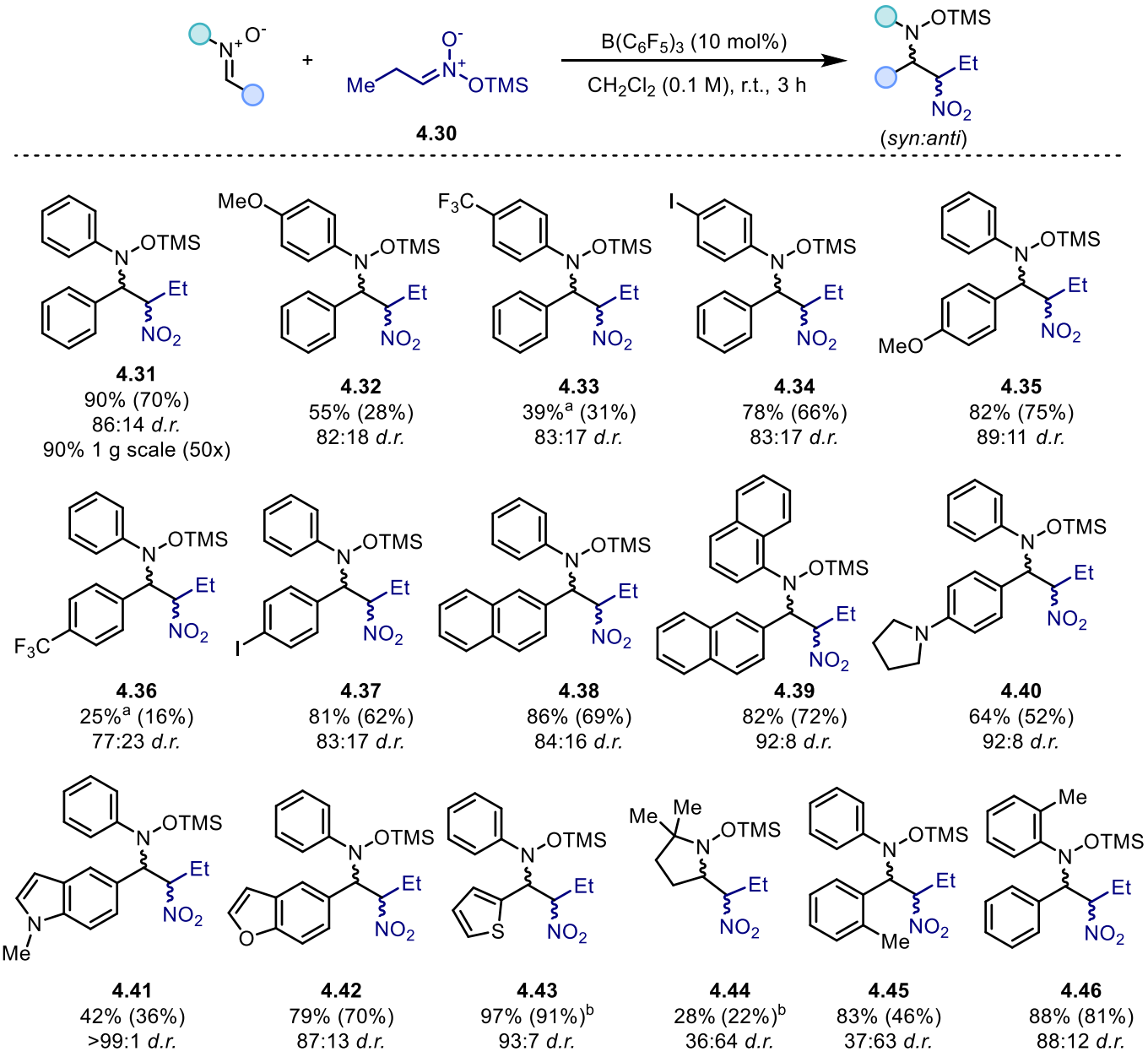
Figure 4.2. Overlayed ^{1}H NMR spectra of compound *syn*-**4.31** and *anti*-**4.31**.

Having identified the two diastereoisomers, the next objective was to find the optimal reaction conditions for the transformation (Table 4.1). To begin with, control experiments without the presence of the catalyst showed no product formation (Table 4.1, entries 2 and 3). These experiments were crucial in determining that, similarly to the work described in Chapter 3.4, the Lewis acid $B(C_6F_5)_3$ is the actual catalyst and not the TMS^+ that might be liberated in the reaction mixture upon silyl nitronate degradation. Next, different solvents were screened (Table 4.1, entries 4–11) and, among them, TFT (entry 5), pentane (entry 7) and CH_2Cl_2 (entry 11) showed the best yields and diastereoselectivities. In detail, TFT and pentane gave yields comparable to entry 1 (80% and 82% respectively), with also the same diastereoselectivity (85:15 and 87:13 respectively). CH_2Cl_2, on the other hand, performed less efficiently in terms of yield (73%) but with good diastereoselectivity (85:15). Coordinating solvents such as THF (71%, 78:22 *d.r.*), Et_2O (45%, 83:17 *d.r.*) or CH_3CN (decomposition) negatively impacted the yield and the diastereoselectivity. From these results, it is

clear that THF is able to coordinate $B(C_6F_5)_3$ and slightly affect its catalytic activity, but the effect is not as pronounced as when Et_2O is used. On the other hand, the small CH_3CN is capable of strongly interacting with $B(C_6F_5)_3$, shutting down any catalytic activity and causing side reactions which ultimately lead to decomposition. The good result with pentane was deemed peculiar due to the observed initial insolubility of the starting materials, which became fully soluble only after 6 hours. Thus, further investigations took place, assessing whether also a strong Brønsted acid such as *p*-toluensulfonic acid (PTSA) could catalyse the reaction (Table 4.1, entry 12) but this only led to decomposition products. When the reaction was run for only 30 minutes instead, the yield of the product was 34% (Table 4.1, entry 13) and a lot of unreacted starting material was detected from ^1H NMR analysis. This led to the conclusion that the silyl nitronate decomposes over time in the reaction mixture forming 1-nitropropane, which is itself a solvent. This, in turn, could help in solubilising the catalyst and the nitrone starting material which are insoluble in only pentane. Performing the reaction for only 3 hours with the best solvents detected (TFT, CH_2Cl_2 and pentane) supported the claim of silyl nitronate decomposition over time in pentane (Table 4.1, entry 16) since the product was formed in 59% yield. However, in the same reaction time, TFT or CH_2Cl_2 (Table 4.1, entries 14 and 15) afforded the product in 77% and 69% yield, respectively. For this reason, pentane was discarded as a possible solvent for the reaction scope and the choice was made on CH_2Cl_2, due to the higher availability compared to TFT. Increasing the amount of silyl nitronate up to 2 equivalents (Table 4.1, entry 17) greatly increased the yield to 84%, whilst the diastereoselectivity remained the same (86:14). However, decreasing the reaction time to 1 hour (Table 4.1, entry 18) slightly decreased the yield to 79%, thus it was decided to set as 3 hours the reaction time. Next, an improvement on the diastereoselectivity was attempted by lowering the temperature of the reaction[281] (Table 4.1, entries 19-21) but, as the temperature went down, the reaction became more sluggish with the yield constantly decreasing (79%, 54% and 44% respectively) so it was decided to carry out the reaction at room temperature. With all the parameters set, a reaction with the best conditions was attempted and pleasingly the product formed in 90% yield with a good diastereoselectivity of 86:14 (Table 4.1, entry

22). Lastly, control experiments with a less strong Lewis acid such as BPh_3 or with a common Lewis acid such as $BF_3 \cdot Et_2O$ did not form the product under the optimised conditions (Table 4.1, entries 24 and 25). Similarly, trifluoroacetic acid (TFA) did not promote the reaction (Table 4.1, entry 26), supporting the claim that the reaction is not operative under Brønsted acid catalysis.

With the optimised conditions in hand, a substrate scope investigation took place concerning different nitrones (Scheme 4.22). To begin with, an investigation to assess the effect of EDGs and EWGs on the reaction was undertaken. As can be seen in Scheme 4.22, EDGs were well tolerated, since compound **4.35** was obtained in good yield (82%) and diastereoselectivity (89:11) (Scheme 4.22). The parent compound **4.32**, that is the one bearing the methoxy group on the *N*-aromatic ring, was formed in lower amounts (55%) albeit without affecting the diastereoselectivity (82:18). This result is presumably due to the stability of the product itself, which was noted to undergo quick self-degradation. EWGs present on the nitrone such as CF_3 rendered the reaction very sluggish, requiring longer reaction times to obtain appreciable amounts of product. Indeed, compound **4.33** was obtained in only 39% yield after 24 hours without however any negative effect on the diastereoselectivity. On the other hand, compound **4.36** was obtained in an unsatisfactory yield of 25%, and the diastereoselectivity decreased to 77:23 *d.r.*. A direct comparison between **4.32**, **4.33**, **4.35** and **4.36** might suggest that the electronic effects on the α-aromatic ring have a more pronounced effect on the overall reactivity compared to the electronics on the *N*-aromatic ring.



Scheme 4.22. Substrate scope for the $B(C_6F_5)_3$-catalysed nitro-Mannich reaction with different nitrones. All reactions were carried out on a 0.1 mmol scale under the optimised conditions. Yields refer to the ^{1}H NMR spectroscopic yield of both the major and minor diastereoisomer calculated from the crude reaction using 1 equiv. of 1,3,5-trimethoxybenzene as an internal standard. Isolated yield of the major diastereoisomer in parentheses. [a]Reaction carried out for 24 h. [b]Obtained as mixture of diastereoisomers.

Halogens such as iodide were well tolerated in the reaction protocol, affording the corresponding products **4.34** and **4.37** in 78% and 81% yield respectively, with the same *d.r.* of 83:17. These products are in principle further functionalisable under transition metal-catalysed conditions. Bulkier naphthyl

groups such as in products **4.38** and **4.39** did not negatively impact the reactivity, since these were obtained in a good yield of 86% and 82% respectively, with a very good level of diastereocontrol in compound **4.39** (*d.r.* 92:8). Next, different heterocycles were screened under the reaction conditions, and they all afforded the corresponding products **4.40**, **4.41**, **4.42**, **4.43** in very good yield and diastereoselectivity (42%–97% and 87:13–99:1 *d.r.*). From compound **4.42** it was possible to grow a crystal of the minor diastereoisomer which was suitable for single crystal X-ray diffraction, showing once again the *anti*-arrangement (Figure 4.3).

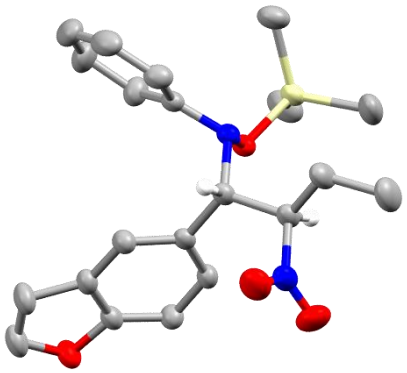
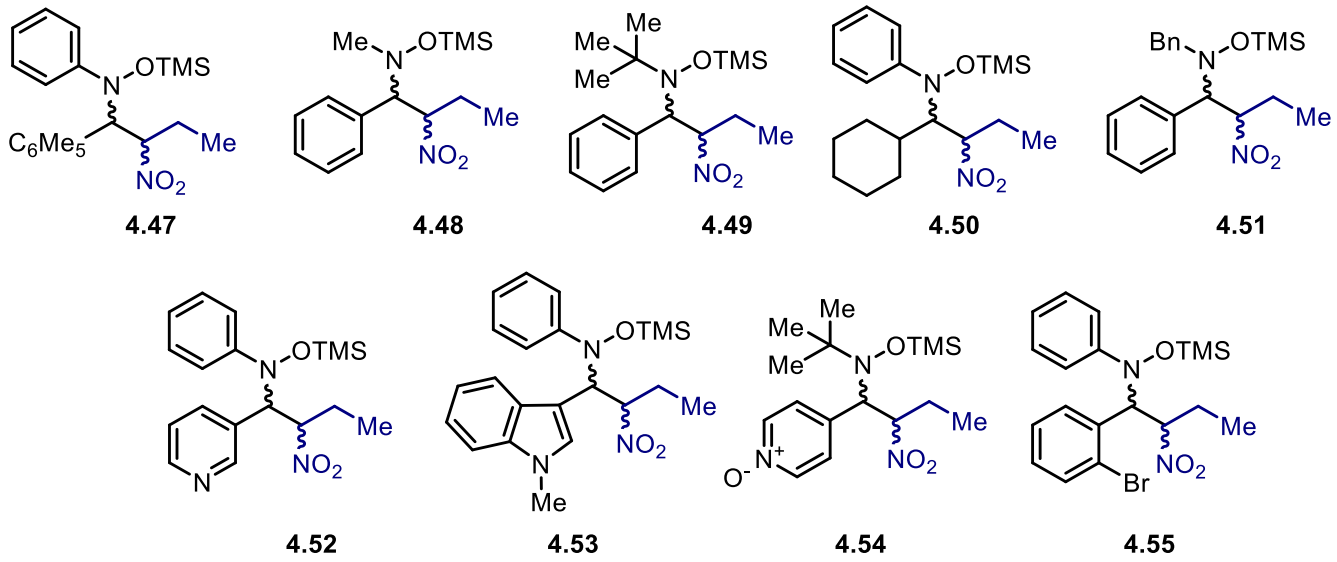


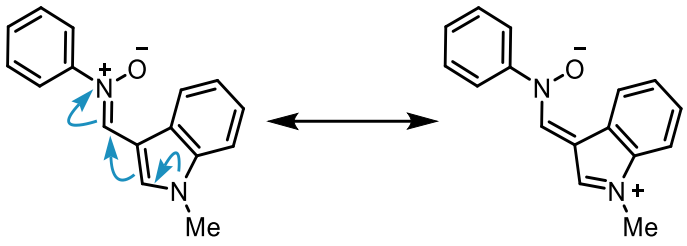
Figure 4.3. Solid state structure of *anti*-**4.42**. Ellipsoids shown at 50% probability. Carbon: grey; hydrogen: white; nitrogen: blue; oxygen: red; silicon: yellow. Hydrogen atoms omitted for clarity (except for the α-hydrogen atom).

Interestingly, compound **4.41** was obtained with full diastereocontrol, albeit the yield was slightly suppressed. On the other hand, the parent product **4.53** was not detected under the reaction conditions (Scheme 4.23).



Scheme 4.23. Failed attempted products for the $B(C_6F_5)_3$-catalysed nitro-Mannich reaction with different nitrones. All reactions were carried out on a 0.1 mmol scale under the optimised conditions.

This result can presumably be attributed to the delocalisation of the nitrogen lone pair of the indole moiety over the sp^2 carbon of the nitrone, which hampers its electrophilicity (Scheme 4.24).



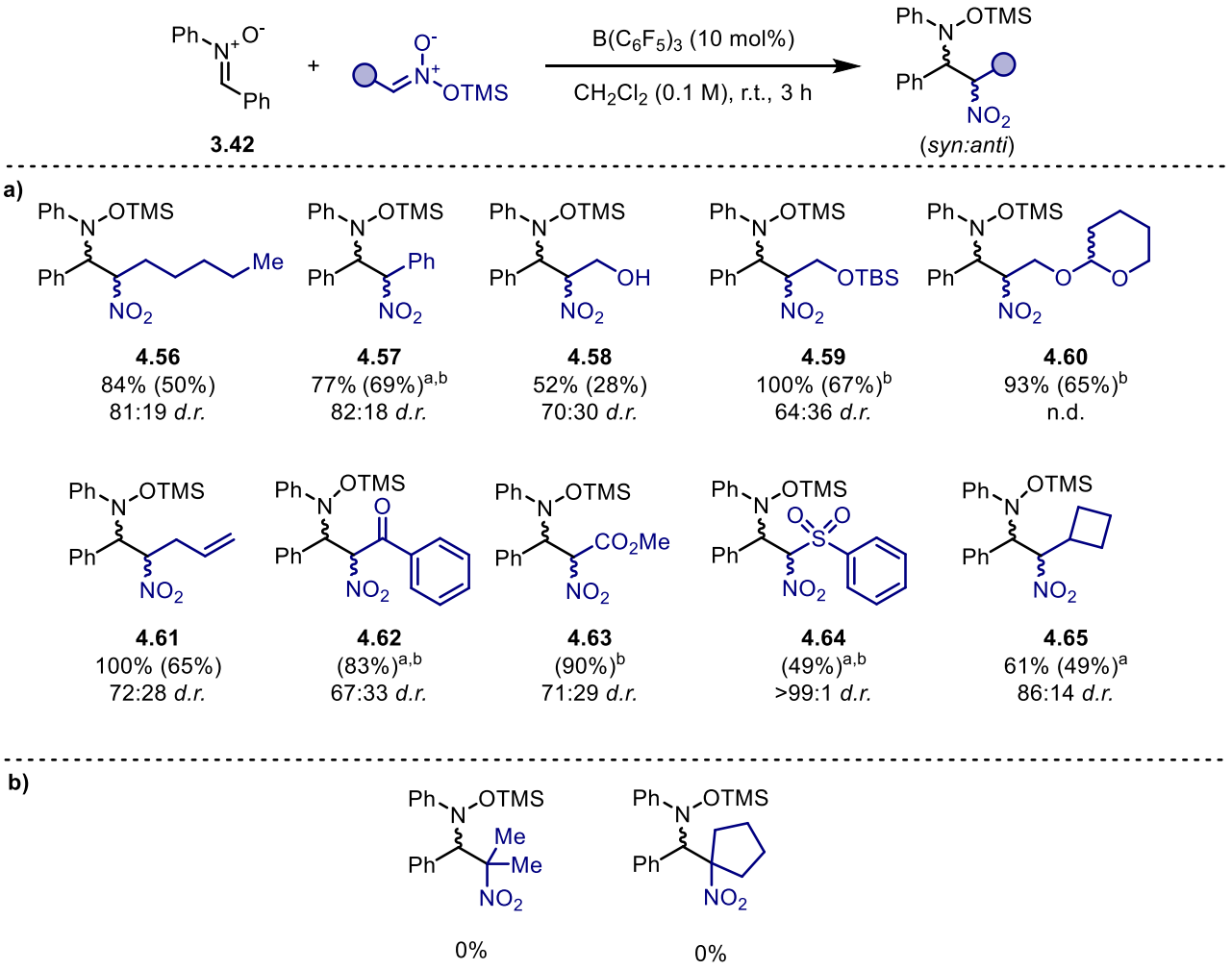
Scheme 4.24. Resonance structure of compound **4.77**, which might account for the absence of reactivity at the α-carbon.

When the commercial nitrone 5,5-Dimethyl-1-Pyrroline-N-Oxide (DMPO) was used under the reaction conditions, an inseparable mixture of two diastereoisomers **4.44** was obtained which revealed an opposite diastereoselectivity when the crude reaction mixture was analysed by ^{1}H NMR spectroscopy. Similarly, when α-*o*-tolyl nitrone was employed, the diastereoselectivity of the product **4.45** was again reversed to an unsatisfactory 37:63, without affecting the yield (83%). The steric effect of this *o*-methyl group has already been observed in other works, and it has been attributed to the non-planar conformation that the nitrone assumes.[282–284] Moreover, as described in the introductory

section, the reversal of diastereoselectivity in the nucleophilic additions on nitrones can occur in the presence of Lewis acids.[241,285] Additionally, the effect of sterically encumbered Lewis acids on the cycloaddition of nitrones has been documented as well.[286] Thus, it is possible to assume that the opposite diastereoselectivity observed might be due to an interplay of these effects. On the other hand, when the *o*-methyl substituent was brought over the *N*-aromatic ring that is, far away from the reaction centre, the reaction afforded the corresponding product **4.46** in a yield of 88% with the usual diastereoselectivity of 88:12. These contrasting results led to the hypothesis that steric congestion around the α-carbon of the nitrone might hamper the nucleophilic addition of the silyl nitronate and affect the diastereochemical outcome by increasing the steric clash in the transition state. To test this, nitrone bearing an *o*-bromo substituent on the α-phenyl ring was subjected to the reaction conditions, and no formation of product **4.55** was detected (Scheme 4.23). Similarly, the pentamethylphenyl group (Ph*)[287] completely suppressed the reactivity and did not afford product **4.47**. These results further support that steric hindrance plays a central role in this reactivity. Additionally, it was also observed that the reaction suffers from the presence of strong coordinating groups since no pyridine or pyridine *N*-oxide substituents were tolerated, given that no traces of products **4.52** or **4.54** were detected (Scheme 4.23). Aliphatic groups at either the *N* or α position did not form the corresponding products **4.48**–**4.50**. In the case of **4.50**, this can be again attributed to additional steric hindrance due to the cyclohexyl substituent. Finally, the reaction was proved to be also scalable since product **4.31** could be synthesised on a gram scale without affecting the yield or the diastereoselectivity (Scheme 4.22).

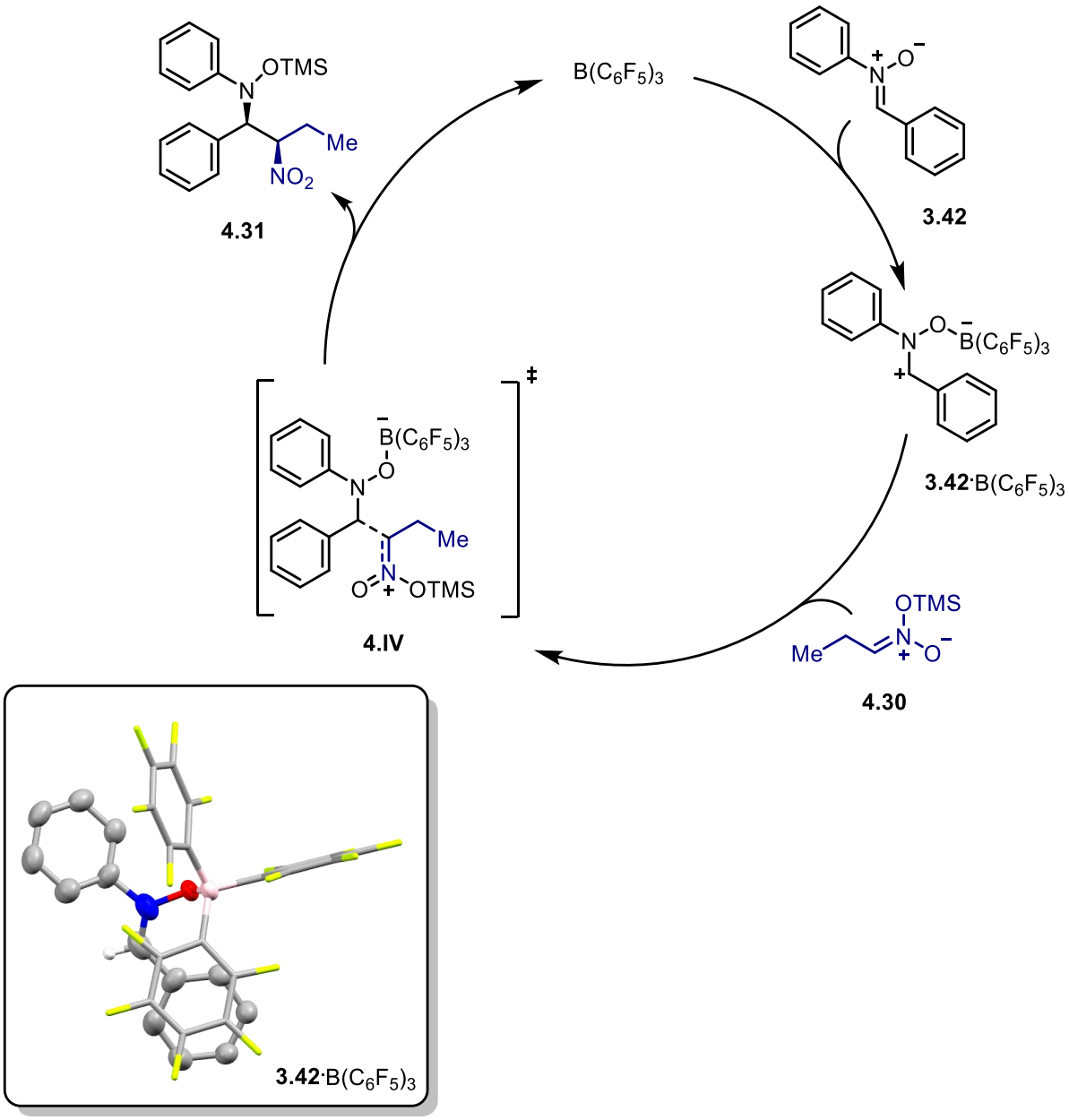
After having assessed the substrate scope for different nitrones, the next aim of the project was to assess which kind of silyl nitronate could be synthesised and used under the optimised reaction conditions. It is important to highlight that the literature describing the use of different silyl nitronates is scarce, and this can be attributed to their high instability. Indeed, although the nitro-Mannich reaction using silyl nitronates has been known for more than a century, this has mainly relied on the use of aliphatic[268,272,288] or benzylic[289] silyl nitronates. To begin with, it was assessed whether a longer

aliphatic chain would affect the reactivity and/or the diastereoselectivity. These proved to be unaffected for product **4.56** (84% yield, 81:19 *d.r.*), compared to the model substrate **4.31** (Scheme 4.25). Similarly, compound **4.57** was obtained with good yield (77%) and *d.r.* (82:18). Silyl nitronate **4.82** was also subjected to the reaction conditions but unfortunately, during purification of the product **4.58**-OTMS, which was detected in the crude ^{1}H NMR spectrum, the TMS group attached to the alcohol moiety did not survive the acidity of the silica gel, affording the unprotected alcohol **4.58** in an unsatisfactory yield of 28%. Interestingly, the diastereoselectivity also proved to be negatively affected (70:30), which might suggest parasitic coordination of the alcoholic moiety with $B(C_6F_5)_3$. In order to evaluate a more stable protecting group, compounds **4.59** (bearing a TBS protection) and **4.60** (bearing a tetrahydropyranyl (THP) protection) were subjected to the optimised conditions. Pleasingly, these were obtained in quantitative and 93% yield, respectively. Nevertheless, in the case of compound **4.59,** the diastereoselectivity was negatively affected (64:36) reinforcing the hypothesis of unwanted coordination with the catalyst. Compound **4.61**, bearing an alkene moiety was also successfully synthesised in quantitative yield and very good *d.r.* of 72:28, providing a product which bears an additional synthetic handle. Crucially, the presented protocol allowed the synthesis of densely functionalised products such as **4.62**, **4.63** and **4.64** in moderate to good yields (49%–90%). Moreover, despite the high acidity of the α-NO_2 proton, these products did not undergo retro-nitro-Mannich under the reaction conditions, which is a known issue for this reaction. Finally, sp^3-rich moieties could also be embedded into the process, since compound **4.65** bearing a cyclobutane ring was synthesised in a good yield of 61% and with 86:14 *d.r.*. The major limitation of this protocol resides in the use of secondary silyl nitronates since no product formation was observed. Once again, this is presumably due to the high steric hindrance around the reactive centre which hampers the reactivity.



Scheme 4.25. **a**) Substrate scope with respect to silyl nitronates. Yields refer to the ^{1}H NMR spectroscopic yield of both the major and minor diastereoisomers calculated from the crude reaction using 1 equiv. of 1,3,5-trimethoxybenzene as an internal standard. Isolated yield of the major diastereoisomer in parentheses. All reactions were carried out on a 0.1 mmol scale under the optimised conditions. [a]Reaction carried out for 24 h. [b]Obtained as mixture of diastereoisomers. **b**) Failed substrates.

Mechanistically, the reaction is proposed to proceed *via* a similar mechanism depicted in Scheme 3.30 in Chapter 3. Initial coordination of the Lewis acid with the nitrone starting material leads to the activated species **3.42**·$B(C_6F_5)_3$ which can engage in a nucleophilic addition with the silyl nitronate, leading to TS **4.IV** (Scheme 4.26).



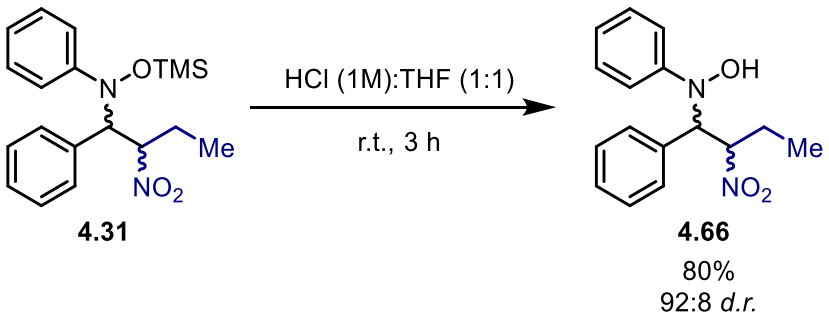
Scheme 4.26. Proposed reaction mechanism. Insert: solid state structure of **3.42**·$B(C_6F_5)_3$. Ellipsoids shown at 50% probability except for the C_6F_5 groups for clarity. Carbon: grey; hydrogen: white; nitrogen: blue; oxygen: red; boron: pink; fluorine: light green. Hydrogen atoms omitted for clarity except for the α-hydrogen atom.

From this point, the liberation of the Lewis acid catalyst can occur with concomitant silyl migration over the nitrone's oxygen atom, forming product **4.31**. As proposed by Doyle in a different work,[193] the silyl migration might have an important role in the diastereoselectivity of the process, and future studies concerning the use of different silyl groups on the nitronate (TBS, TIPS etc.) might highlight

this aspect. Furthermore, competition experiments using different silyl groups on different silyl nitronates might reveal if such migration occurs intra- or intermolecularly.

4.4.1. Further functionalisation

The methodology presented herein allows the synthesis of α-nitro TMS-protected hydroxylamine scaffolds in high yields and good diastereoselectivities. The presence of two functional handles in the molecule prompted studies of their further transformation into synthetically relevant scaffolds. Indeed, it has been shown by Leonori that hydroxylamines can be used as nitrogen radical precursors, owing to the labile nature of the N–O bond.[290] Very recently it has also been proposed that free *N*-substituted hydroxylamines can be used as antibacterial agents.[247] Specifically, these can act as radical scavengers and can inhibit the bacterial ribonucleotide reductase (RNR) enzyme, which is responsible for bacterial proliferation. Based on these premises, the first transformation tackled was the removal of the TMS group under mildly acidic conditions,[291] which was accomplished by treating compound **4.31** in a mixture of 1M HCl:THF (1:1) at room temperature for 3 hours. Pleasingly, product **4.66** was obtained as a mixture of diastereoisomers in 80% isolated yield after a simple aqueous basic workup (Scheme 4.27).

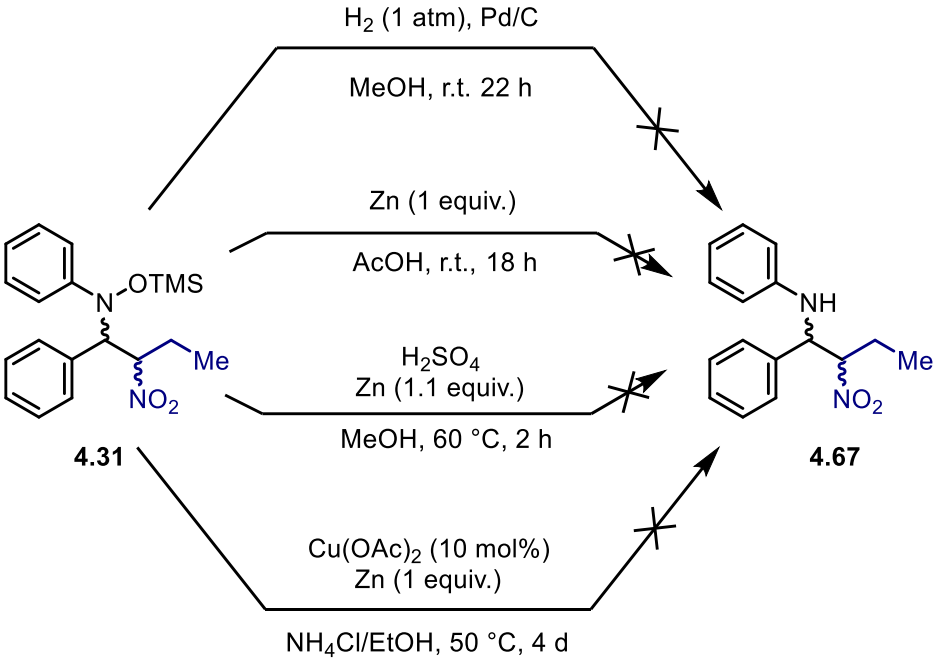


4.31 **4.66**
80%
92:8 *d.r.*

Scheme 4.27. Removal of the TMS group under acidic conditions.

However, despite the TMS-protected derivative **4.31** being stable, the free hydroxylamine **4.66** was prone to degradation, since it was not possible to obtain an analytically pure sample of the minor diastereoisomer. This, in turn, would also explain the slight improvement observed in the diastereoselectivity of the product which is presumably due to a decomposition pathway. Indeed,

hydroxylamine decomposition has been observed also by Behr.[266] The removal of the OTMS group from **4.31** to obtain a secondary amine was also attempted, but in all the attempts made the desired product **4.67** did not form, and only unreacted starting material or decomposition products were obtained (Scheme 4.28).

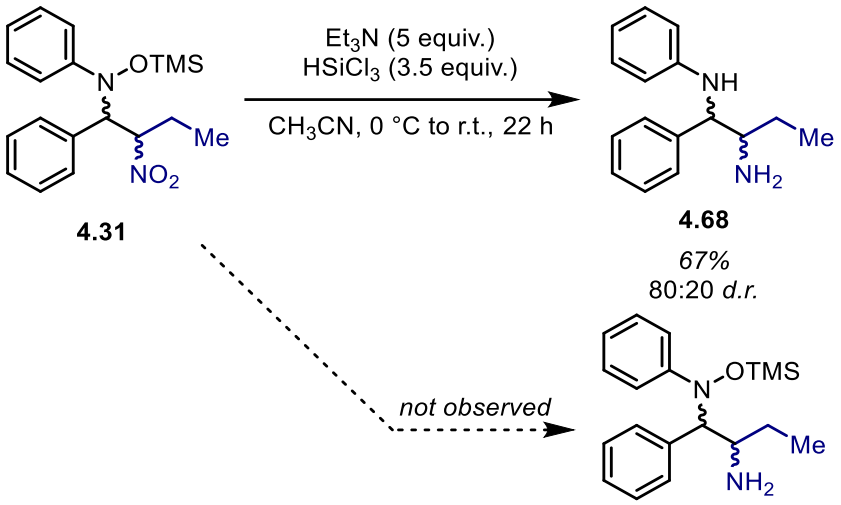


Scheme 4.28. Attempted reactions for the OTMS-cleavage of substrate **4.67**.

Next, it was attempted to further transform the nitro group, which possesses a contradictory position in medicinal chemistry.[292] Indeed, despite the reported toxicity associated with it, the many transformations it can undergo make it very important for synthetic purposes. For example, one of the most important transformations is its reduction to an amine.[293] Additionally, it can also be transformed into a nitrile or isonitrile moiety.[294,295] Lastly, it can also be interconverted into a carbonyl functionality *via* the Nef reaction, expanding even further the synthetic utility of the molecule.[296]

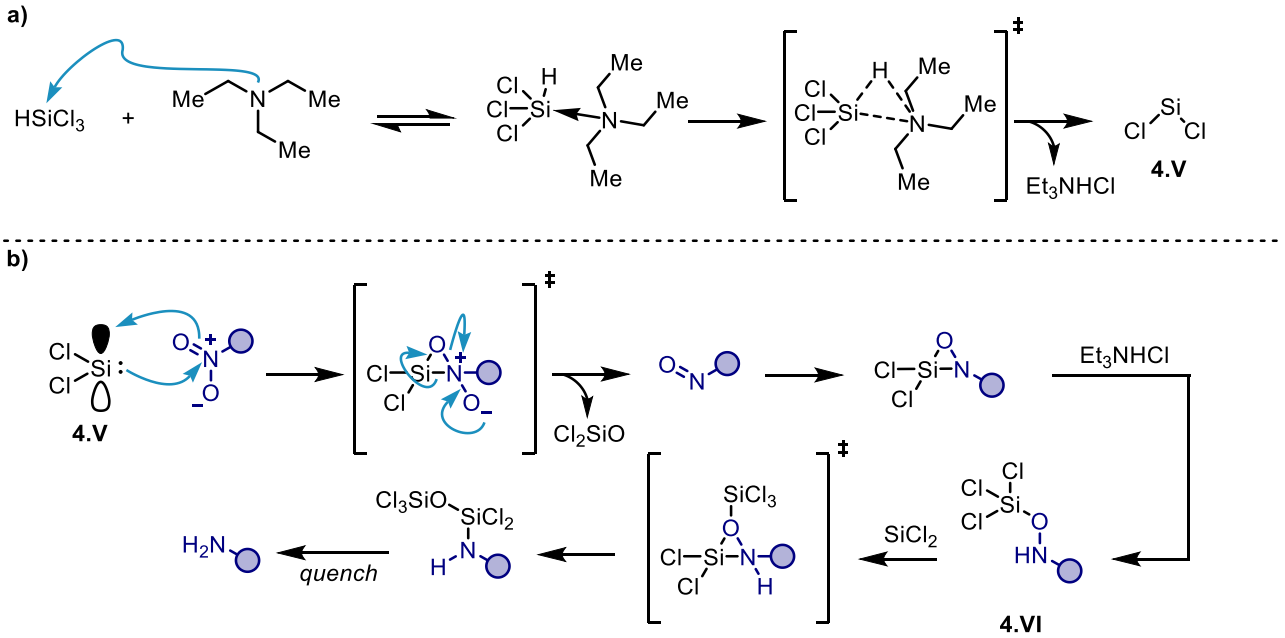
In order to selectively reduce the aliphatic nitro group, inspiration was taken from the work of Benaglia *et al*. who showed that $HSiCl_3$ can be used as an efficient reducing agent for nitro groups in the presence of a strong Lewis base.[297] However, instead of the selective reduction of the sole nitro group, the reaction afforded the diamino product **4.68** in a good yield of 67% (Scheme 4.29). In this

case, due to the presence of a strong base, some degree of epimerisation at the α-nitro carbon can occur, which might explain the slightly lower diastereoselectivity of 80:20 observed (Scheme 4.29).



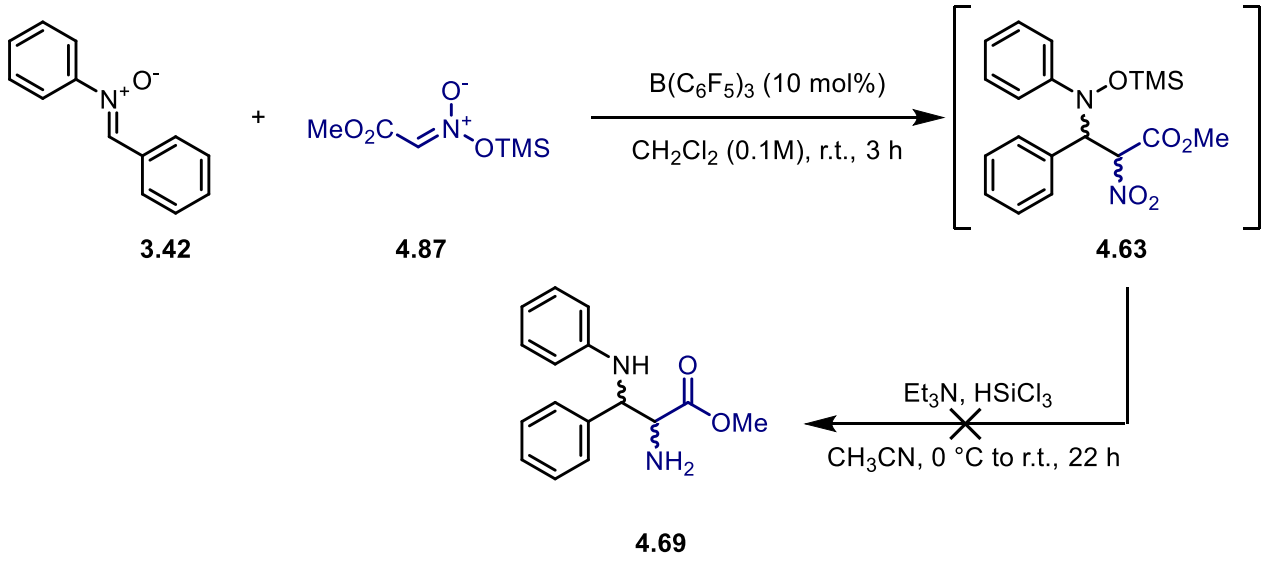
Scheme 4.29. Attempted reactions for the OTMS-cleavage of substrate **4.68**.

The reason why also the hydroxylamine is reduced to the secondary amine under the reaction conditions can be ascribed to the operative mechanism proposed by Benaglia.[297] Mechanistically, it has been proposed that in the presence of a strong base, the silane forms a dichlorosilylene **4.V**, which is the real reducing agent (Scheme 4.30, a).[297,298] This has also been supported by additional DFT studies which also highlighted that most likely it reacts as the base stabilised adduct $Et_3N–SiCl_2$.[298] This species, which is the heavier analogue of dichlorocarbene[299] reacts *via* a chelotropic mechanism with the nitro group, lastly forming the amine species (Scheme 4.30, b). Since the mechanism proceeds through the formation of a silyl protected hydroxylamine intermediate **4.VI**, it is possible to infer that this moiety is not stable under the reaction conditions, hence why only product **4.68** has been detected.



Scheme 4.30. General reaction mechanism for the reduction of the nitro group with $SiCl_2$.

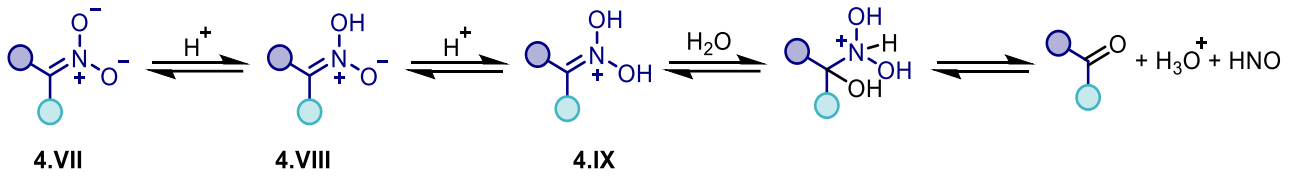
With this efficient protocol in hand, the synthesis of an unnatural amino acid **4.69** in a telescoped approach was also attempted (Scheme 4.31). Unfortunately, the reaction led only to decomposition. It is suggested that product **4.63** is not stable under the strongly basic conditions employed.



Scheme 4.31. Telescoped approach for the synthesis of an unnatural amino acid **4.69**.

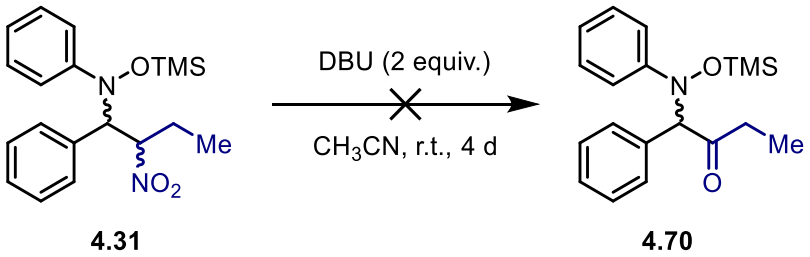
Finally, a Nef reaction was also attempted to transform the nitro group into a carbonyl functionality. Historically, the reaction has been developed by treating nitronate salt **4.VII** under strongly acidic

conditions (pH<1), since it has been proven that products distribution **4.VII-4.VIII** is pH-dependent (Scheme 4.32).[300]



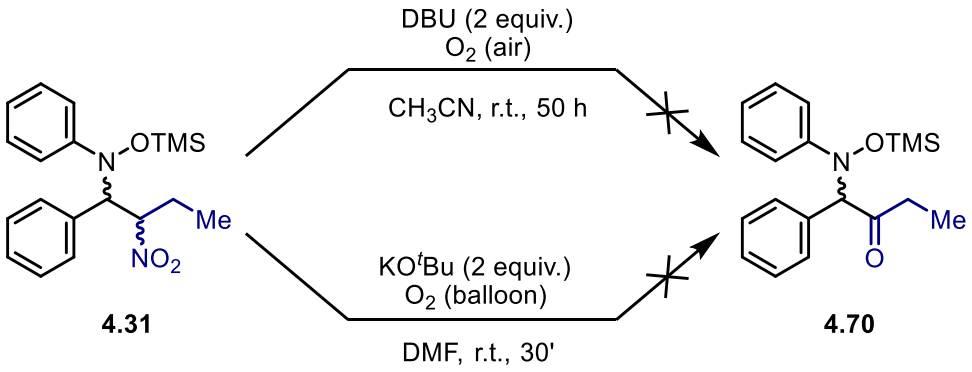
Scheme 4.32. General reaction mechanism for the Nef reaction.

However, the harsh conditions initially described for the Nef reaction pose limitations in terms of functional group tolerability hence why throughout the years efforts have been devoted to the development of milder methodologies.[301] Nowadays, several methods are available to perform the Nef reaction, which can be either under reductive or oxidative conditions, with or without a base.[302] Since product **4.31** possesses an acid-sensitive functionality, it was decided to perform the reaction using a base, taking inspiration from the work of Ballini (Scheme 4.33).[303]



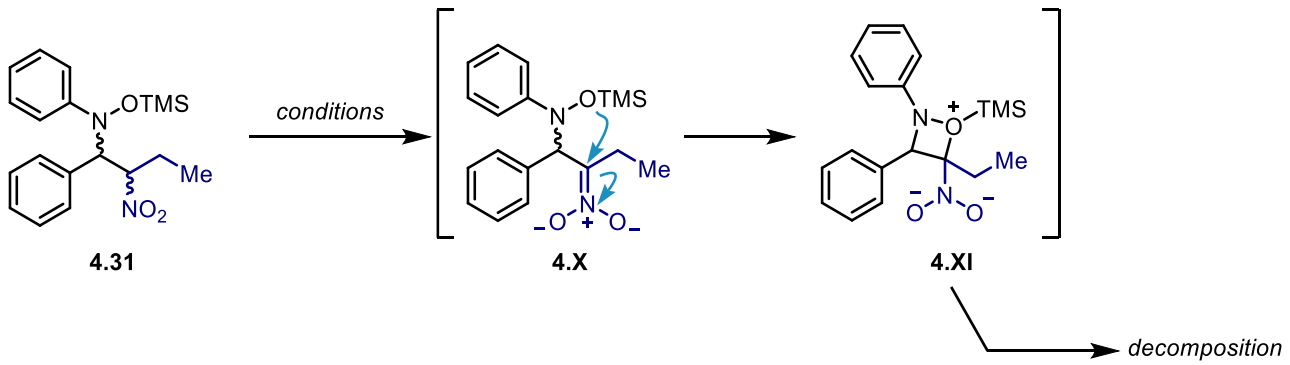
Scheme 4.33. Attempted Nef reactions using DBU.

However, the reaction only decomposed the starting material, and no traces of the product were detected. Hence, it was presumed that the long reaction time required for the transformation might have a negative effect on the stability of the starting material and/or the product. For this reason, another approach was attempted using molecular oxygen, which has been described to act as an oxidant and renders the base-promoted Nef reaction faster (Scheme 4.34).[302] Two reactions were carried out, one under air in 50 hours, and one under a saturated atmosphere of oxygen for only 30 minutes.



Scheme 4.34. Attempted Nef reactions using molecular oxygen.

Disappointingly, both experiments again caused the starting material to decompose, and no traces of the desired product **4.70** were detected. The reason behind this decomposition might be asserted to the presence of a nucleophilic moiety in **4.31** (e.g. the hydroxylamine). Since all Nef methods rely on the *in situ* formation of an electrophilic nitronate species **4.X**, this can potentially react with the hydroxylamine *via* an intramolecular nucleophilic addition to form **4.XI**, which ultimately leads to the observed decomposition (Scheme 4.35).

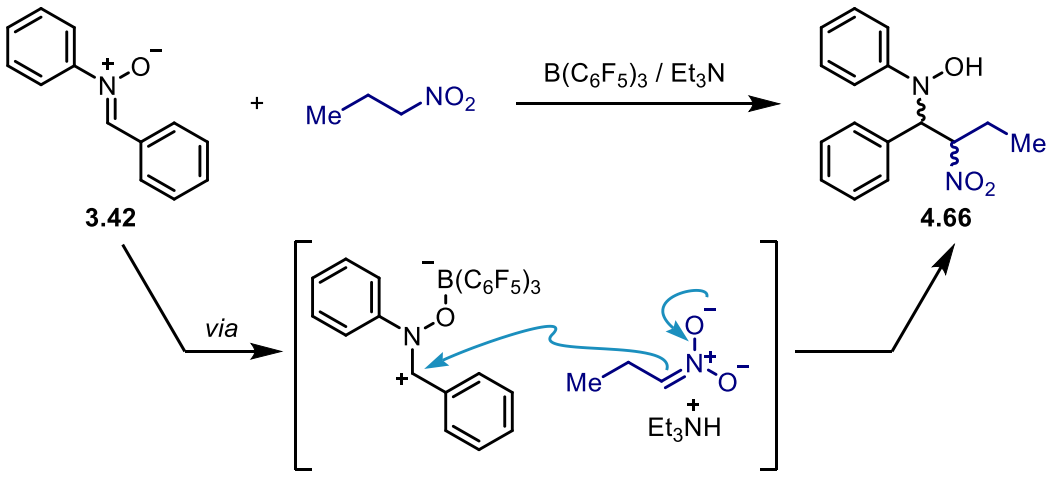


Scheme 4.35. Possible explanation for the failed Nef reaction.

This event, called *interrupted Nef reaction* has been exploited recently as a new synthetic method to diversify the reactions accomplishable with nitro groups,[304,305] and could be leveraged in the future for new transformations if the decomposition pathway could be suppressed.

4.4.2. Cooperative FLP approach

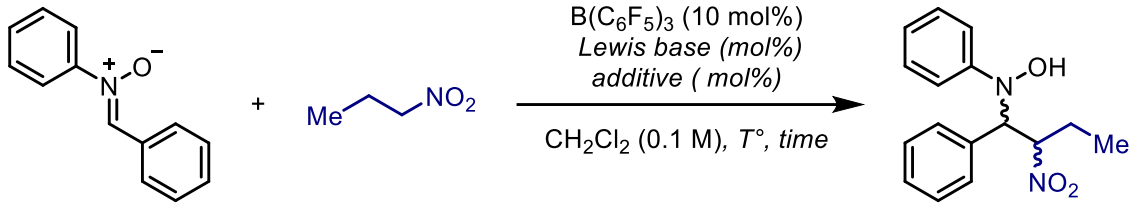
A major limitation of the protocol described herein is the use of pre-formed silyl nitronates, which require the use of strictly anhydrous conditions. Additionally, some of them are prone to fast degradation requiring their utilisation as soon as they have been made. Therefore, a different approach, that is a *direct* nitro-Mannich,[269] would overcome this limitation by allowing the synthesis of the nitronate *in situ* and consuming it as soon as it forms. This would, in turn, remove one synthetic step from the methodology and could also increase the type and number of nitronates employable. To this end, inspiration was taken from the works developed by Wasa[129,130,306–308] where the concept of FLP was used in the realm of Cooperative Catalysis.[309] In short, by taking advantage of the unquenched reactivity of a Lewis acid and a Lewis base (the FLP), these can be used to activate one or two different substrates in the reaction mixture in a cooperative approach. Since the synthesis of the silyl nitronates used in this study requires the use of a Lewis base, it was envisaged to attempt their synthesis *in situ*, through an FLP-type approach (Scheme 4.36).



Scheme 4.36. Proposed mechanism for the FLP-type nitro-Mannich reaction.

Hence, preliminary investigations took place by reacting nitrone **3.42** and nitropropane under different sets of conditions (Table 4.2).

Table 4.2. Preliminary results for the FLP-type nitro-Mannich reaction. ^{1}H NMR spectroscopic yields are calculated using 1 equiv. of 1,3,5- trimethoxybenzene. n.a.: not applicable. [a]Yield of **4.31**.



3.42 **4.66**

Entry	Lewis base (mol%)	Additive (mol%)	Time (h)	T (°C)	Yield of 4.66	*d.r. (syn:anti)*
1	TEA (20)	-	21	r.t.	-	n.a.
2	PMP (20)	-	24	40	-	n.a.
3	DIPEA (20)	-	24	40	-	n.a.
4	DBU (20)	-	24	40	-	n.a.
5	TMP (20)	-	24	40	-	n.a.
6	TEA (100)	-	24	r.t.	-	n.a.
7	TEA (105)	TMSCl (105)	24	r.t.	17%[a]	87:13
8	DIPEA (105)	TMSCl (105)	24	r.t.	24%[a]	75:25

To begin with, a reaction using only 20 mol % of TEA was attempted but it only furnished unreacted starting material (Table 4.2, entry 1). Therefore, different sterically hindered bases were screened such as PMP, DIPEA, DBU and TMP but none of them furnished the desired product at 40 °C (Table 4.2, entries 2-5). Despite in the proposed mechanism in Scheme 4.36 the Lewis base should be working under a catalytic regime, it was attempted to increase its amount up to 1 equivalent (Table 4.2, entry 6) but also in this case the reaction did not afford the desired product **4.66**. At this point, it was envisaged that the free hydroxylamine that might form during the reaction conditions might have a negative effect on the catalytic performance of $B(C_6F_5)_3$. Additionally, it has already been observed that the free hydroxylamine **4.66** obtained after the acidic cleavage of compound **4.31** is not stable.

Hence, 1.05 equivalents of TMSCl were added as an additive, in an attempt to increase the stability of the product (Table 4.2, entry 7). Pleasingly, in this case, the reaction formed the desired TMS-protected product **4.31** in 17% yield and 87:13 *d.r.* (Table 4.2, entry 7). Switching the base to the more sterically hindered DIPEA improved the yield up to 24% but had a negative impact on the *d.r.* (75:25) (Table 4.2, entry 8). Although preliminary, these results show that an FLP-type approach is indeed feasible, and this could be in the future optimised to reach high yields and diastereoselectivities. Potentially, reaction conditions which do not require the use of TMSCl can also be identified. Finally, the base seems to have an important role in the diastereoselectivity of the reaction and further studies might also reveal the nature of this.

4.6. Conclusions

The work described in this chapter highlights the ability of $B(C_6F_5)_3$ to catalyse the nitro-Mannich reaction in good yields (up to 100%) and very good diastereoselectivities (up to >99:1). The methodology is amenable to accept a variety of nitrones and silyl nitronates, with the only limitation being deactivated nitrones and secondary silyl nitronates. The obtained products can be further transformed into 1,2-diamino or 1-hydroxylamine 2-nitro motif in good yields. On the other hand, the Nef reaction proved to be cumbersome presumably due to an intramolecular event which caused the product to decompose. Nevertheless, additional studies in this direction might reveal the exact mechanism and offer new opportunities leveraging the interrupted Nef reactivity. Finally, preliminary results have shown the possibility of performing a *direct* nitro-Mannich relying on the unquenched reactivity of an FLP system. The careful choice of the Lewis acid and base might have a profound impact on the diastereoselectivity of the process, opening the possibility to carry out a highly enantio- and diastereoselective reaction by choosing a suitable chiral Lewis acid and/or base.

5. General conclusions and outlook

This thesis describes the use of boron-based Lewis acids in organic synthesis, for the development of novel synthetic methodologies. While the major focus has been on the application of $B(C_6F_5)_3$ which has been proven to be a promising catalyst for different transformations, it has also been shown that it is not always the best Lewis acid catalyst. For example, in Chapter 2, a methodology entailing the *N*-functionalisation of indoles using isocyanates has been shown to proceed in high yields with the simple BCl_3, which outperforms $B(C_6F_5)_3$ for the given transformation. However, in the case of the C3-functionalisation of protected indoles, BCl_3 is completely ineffective while $B(C_6F_5)_3$ can exert some catalytic activity, albeit under harsher conditions. Similarly, in Chapter 3, we have demonstrated that $B(C_6F_5)_3$ is a proficient catalyst for the [3+2] dipolar cycloaddition of nitrones with vinyl diazo esters or for the Mukaiyama-Mannich addition of nitrones with silyl enol diazo esters. Notably, $B(C_6F_5)_3$ can be used as an orthogonal catalyst with respect to Rh since it avoids the initial diazo decomposition and leads to entirely different products albeit starting from the same reactants. However, when diazo activation is required to promote further reactivity and access benzo[*b*]azepine products, again the strong acidity of $B(C_6F_5)_3$ plays against a positive reaction outcome and a less acidic catalyst such as $B(2,4,6\text{-}F_3C_6H_2)_3$ seems to work better. Chapter 4 finally highlights the ability of $B(C_6F_5)_3$ to efficiently catalyse the *indirect* nitro-Mannich reaction between nitrones and silyl nitronates, allowing the synthesis of several α-nitro silyl hydroxylamines. In this case, $B(C_6F_5)_3$ proved to be the best catalyst among the ones tested, however, preliminary studies indicated that it might not be optimal for carrying out a *direct* nitro-Mannich reaction, and, to this end, further research may identify a more suitable catalyst.

Overall, the studies undertaken during the course of this PhD highlight that the Lewis acidity of boron catalysts plays a crucial role in reaction outcomes, and careful design of novel catalysts might open up avenues for the synthesis of previously inaccessible products. As suggested at the end of the previous chapters, if there was more time, it would have been interesting to assess whether a BCl_3

activation of indoles could be extended to BCBs, and potentially be generalised to several electrophiles. It would have been also valuable to assess if the silyl group in the Mukaiyama-Mannich addition of nitrones with silyl enol diazo ester is important for the observed reactivity/diastereoselectivity. This could have been done by changing the silicon chloride derivative during the synthesis of the silyl enol diazo compound and subsequently evaluating the reaction outcome. Furthermore, additional screening of different boron-based Lewis acids could have been carried out to find the optimal one for the synthesis of benzo[*b*]azepine or pyrrolidinone scaffolds. Finally, a thorough reaction optimisation for the cooperative FLP approach for the *direct* nitro-Mannich reaction could have been undertaken, which would have potentially expanded the substrate scope with also a possible highlight of the diastereochemical role of the Lewis acid/base.

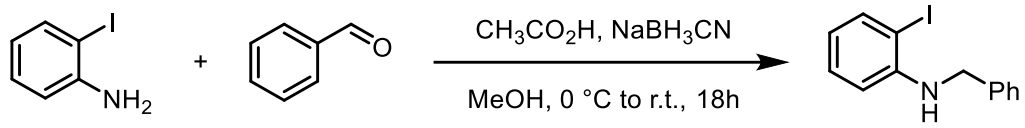
6. Experimental section

6.1. General experimental

Except where otherwise stated, all reactions and manipulations were carried out under an atmosphere of dry, O_2-free nitrogen using standard double-manifold techniques with a rotary oil pump. A nitrogen-filled glove box (MBraun) was used to manipulate solids including the storage of starting materials, ambient temperature reactions, product recovery and sample preparation for analysis. All solvents (dichloromethane, hexane, acetonitrile, toluene) were dried by employing a Grubbs-type column system (Innovative Technology) or a solvent purification system MB SPS-800 and stored under a nitrogen atmosphere. Anhydrous (with Sure/Seal) $C_2H_4Cl_2$ and TFT were purchased from Merck and dried over molecular sieves before use. Deuterated solvents were distilled and/or dried over molecular sieves before use. Chemicals were purchased from commercial suppliers and used as received. All the perfluoroaryl boranes were prepared as per the standard literature report.[204] Thin Layer Chromatography (TLC) was performed on pre-coated aluminium sheets of Merck silica gel 60 F254 (0.20 mm). ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance II 300 or 400 or Bruker Avance 500 spectrometers. All coupling constants are absolute values and are expressed in Hertz (Hz). ^{13}C NMR spectra were measured as ^{1}H decoupled. Yields are given as isolated yields except where otherwise stated. Where diastereoisomers are formed, the reported yields are the combined isolated yields of major and minor diastereoisomers. Unless stated otherwise, all characterisation reported is that of the major diastereoisomer. Chemical shifts are expressed as parts per million (ppm, δ) downfield of tetramethylsilane and are referenced to $CDCl_3$ (7.26/77.16 ppm). The description of signals includes s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet, br. = broad. All spectra were analysed assuming a first order approximation. IR-Spectra were measured on a Shimadzu IRAffinity-1 photo-spectrometer. Mass spectra were measured on a Waters LCT Premier/XE or a Waters GCT Premier spectrometer. Ions were generated by Electrospray (ES) or Electron Impact (EI). The molecular ion peaks values are quoted for molecular ion plus hydrogen ($M+H^+$) or molecular ion (M^+).

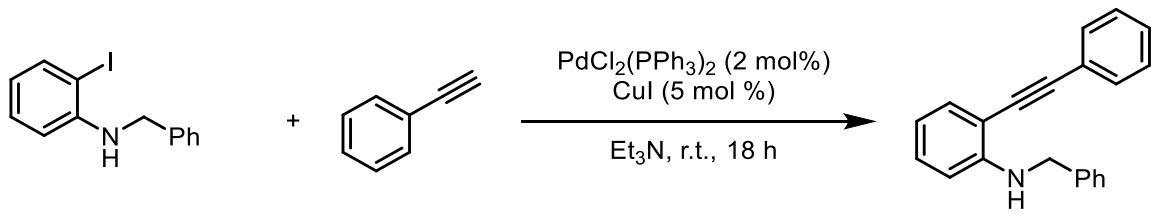
6.1.1. Chapter 2: Synthesis and characterisation of starting materials

Synthesis of N-Benzyl o-iodoaniline (**2.81**)



Synthesised by the procedure illustrated by Wang and co-workers,[310] the following procedure was performed under a moisture and oxygen-free N_2 atmosphere. A two-necked round bottom flask was charged with *o*-iodoaniline (10 g, 45.7 mmol, 1 equiv) and benzaldehyde (11.1 mL, 109.6 mmol, 2.4 equiv.) and dissolved in methanol (MeOH) (180 mL). The solution was cooled to 0 °C then acetic acid (CH_3CO_2H) (10.5 ml, 182.8 mmol, 4 equiv.) was added dropwise under vigorous stirring. Sequentially, sodium cyanoborohydride ($NaBH_3CN$) (5.74 g, 91,4 mmol, 2 equiv.) was added portion-wise letting the evolution of gas cease before adding a new portion. The reaction mixture was left to react overnight (ca. 18 h) and was then quenched with cold water, leading to the immediate formation of a white precipitate. The organic solvent was removed *in vacuo* and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The organic phases were collected, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*, leaving a yellow oil which was used in the next step without further purification.

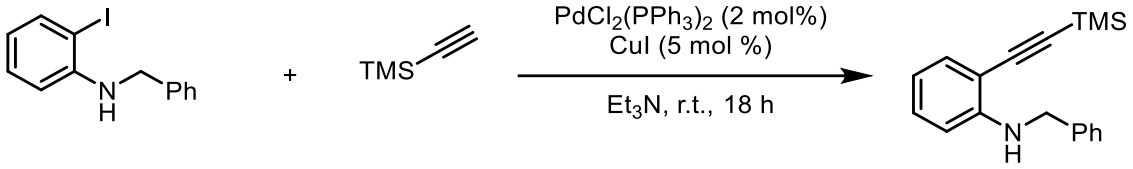
Synthesis of N-benzyl-2-(phenylethynyl)aniline (**2.78**)



Synthesised in accordance to a reported procedure,[310] a one-necked Schlenk round bottom flask was charged with *N*-Benzyl *o*-iodoaniline (2 g, 6.5 mmol, 1 equiv.), dissolved in triethylamine (Et_3N) (26 mL). To this solution, phenylacetylene (1.4 mL, 13 mmol, 2 equiv.) was added dropwise. Sequentially,

$PdCl_2(PPh_3)_2$ (2.2 mg, 3 μmol, 0.02 equiv) was added and the reaction mixture was stirred for 5 minutes before adding CuI (1.5 mg, 8 μmol, 0.05 equiv.). The reaction was left to stir at room temperature until completion (24 h). After consumption of the starting material, checked by TLC, the solvent was removed under vacuum leading to a dark oil which was passed through a silica plug. The crude reaction mixture was purified by column chromatography using hexane/ethyl acetate (100:0 to 90:10 v/v) as the eluent to afford the desired product as a yellow solid (1.60 g, 5.7 mmol, 87% yield). **^{1}H NMR** (500 MHz, $CDCl_3$, 298K) δ: 7.46–7.41 (m, 2H, Ar–C**H**), 7.37–7.19 (m, 9H, Ar–C**H**), 7.11 (ddd, *J*=8.7, 7.4, 1.6, 1H, Ar–C**H**), 6.62 (td, *J*=7.5, 1.1, 1H, Ar–C**H**), 6.53 (dd, *J*=8.3, 1.1, 1H, Ar–C**H**), 5.09 (br. s, 1H, N**H**), 4.40 (d, *J*=5.8, 2H, C$\mathbf{H}_2$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 148.8 (Ar–**C**), 139.2 (Ar–**C**), 132.3 (Ar–**C**), 131.6 (Ar–**C**), 130.1 (Ar–**C**), 128.5 (Ar–**C**), 128.3 (Ar–**C**), 128.3 (Ar–**C**), 127.4 (Ar–**C**), 127.3 (Ar–**C**), 123.4 (Ar–**C**), 116.8, (Ar–**C**) 110.1 (Ar–**C**), 107.7 (Ar–**C**), 95.4 (C≡**C**), 86.1 (C≡**C**), 47.8 (**C**H_2). Data agrees with literature values.[310]

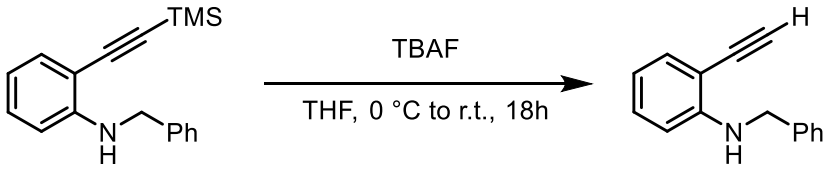
Synthesis of N-benzyl-2-((trimethylsilyl)ethynyl)aniline (**2.82**)



Synthesised in accordance to a reported procedure,[310] a one-necked round-bottomed Schlenk flask was charged with *N*-Benzyl *o*-iodoaniline (2 g, 6.5 mmol, 1 equiv.) and dissolved in Et_3N (26 mL). To this solution, trimethylsilylacetylene (1.9 mL, 13 mmol, 2 equiv.) was added dropwise. Sequentially, $PdCl_2(PPh_3)_2$ (2 mg, 3 μmol, 0.02 equiv.) was added and the reaction mixture was stirred for 5 minutes before adding CuI (2 mg, 8 μmol, 0.05 equiv.). The reaction was left to stir at room temperature until completion (18 h). After consumption of the starting material, checked by TLC, the solvent was removed *in vacuo* leading to a dark oil which was passed through a silica plug. The crude reaction mixture was purified by column chromatography using hexane/ethyl acetate (100:0 to 95:5) as the eluent to afford the desired product as a yellow oil (1.6 g, 5.6 mmol, 86% yield).

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 7.19–7.03 (m, 6H, Ar–C**H**), 6.93 (m, 1H, Ar–C**H**), 6.39 (tt, *J*=7.5, 0.8, 1H, Ar–C**H**), 6.36–6.31 (m, 1H, Ar–C**H**), 4.84 (br. s, 1H, N**H**), 4.20 (d, *J*=2.7, 2H, CH_2), 0.00 (s, 9H, TMS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 149.4 (Ar–**C**), 139.2 (Ar–**C**), 132.2 (Ar–**C**), 130.3 (Ar–**C**), 128.8 (Ar–**C**), 127.4 (Ar–**C**), 127.3 (Ar–**C**), 116.5 (Ar–**C**), 109.9 (Ar–**C**), 107.6 (Ar–**C**), 102.2 (C≡**C**), 100.6 (C≡**C**), 47.9 (**C**H_2), 0.2 (TMS). Data agrees with literature values.[310]

Synthesis of N-benzyl-2-ethynylaniline (**2.83**)



Synthesised in accordance to a reported procedure, a one necked round bottomed Schlenk flask was charged with *N*-benzyl-2-((trimethylsilyl)ethynyl)aniline (0.7 g, 2.5 mmol, 1 equiv.) dissolved in THF (20 mL) and cooled to 0 °C. To this solution, tetra-*n*-butylammonium fluoride (TBAF) (3 mL, 3 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was stirred until completion (18 h). After consumption of the starting material, checked by TLC, water was added to the reaction mixture, leading to the formation of a white precipitate. The ethereal solvent was removed *in vacuo* and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic phases were then collected, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a golden yellow oil which was purified by column chromatography using hexane:ethyl acetate (100:0 to 95:5 v/v) as the eluent affording the desired product as a yellow oil (0.33 g, 1.6 mmol, 63% yield).

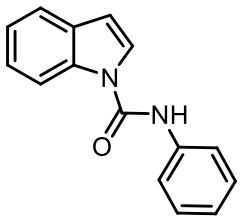
^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 7.28–7.19 (m, 5H, Ar–C**H**), 7.16 (m, 1H, Ar–C**H**), 7.05 (m, 1H, Ar–C**H**), 6.52 (td, *J*=7.5, 1.1, 1H, Ar–C**H**), 6.45 (dd, *J*=8.3, 1.0, 1H, Ar–C**H**), 4.98 (br. s 1H, N**H**), 4.29 (d, *J*=5.7, 2H, C$\mathbf{H}_2$), 3.28 (s, 1H, C**H**). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 149.5 (Ar–**C**), 139.1 (Ar–**C**), 132.8 (Ar–**C**), 130.5 (Ar–**C**), 128.8 (Ar–**C**), 127.3 (Ar–**C**), 116.5 (Ar–**C**),

110.0 (Ar–**C**), 106.4 (Ar–**C**), 83.2 (C≡**C**), 80.9 (C≡**C**), 47.7 (**C**H_2). Data agrees with literature values.[310]

6.1.2. Chapter 2: Synthesis and characterisation of *N*–functionalised products

General Procedure 1 (GP1): In the glovebox, three glass microwave vials were charged separately with 1H–indole (1 equiv.), aryl isocyanate (1.5 equiv.), and BCl_3 [1M solution in hexane] (5 mol %), and then capped with a septum. The three vials were brought outside the glovebox and 0.5 mL of $C_2H_4Cl_2$ were added to each vial using a syringe. Ar–NCO solution was added to the BCl_3 solution, and the resulting solution was added to the indole solution dropwise with vigorous stirring at room temperature. All the reactions were carried out at an optimum temperature 60 °C for 16–24 h. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using hexane/ethyl acetate as eluent. For 0.1 mmol scale reaction, 5% catalyst loading require 5 µL of the BCl_3-hexane (1M) solution (a micropipette was used to make a quick transfer the catalyst into the reaction vial and then closed with a cap with septum immediately using a crimper).

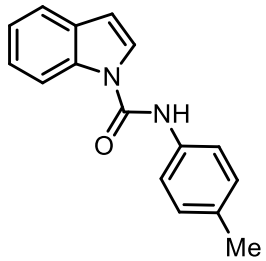
Synthesis of N-phenyl-1H-indole-1-carboxamide (**2.43**)



Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), indole (12 mg, 0.10 mmol), and phenyl isocyanate (16 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.43***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.43*** was obtained as a white solid. Yield: 22 mg, 0.09 mmol, 93%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 8.11 (dd, *J* = 8.3, 0.9 Hz, 1H, Ar–C**H**), 7.64 (dt, *J* = 7.8, 1.3, 0.8 Hz, 1H, Ar–C**H**), 7.56 (d, *J* = 3.7 Hz, 1H, indole C2**H**), 7.57–7.50 (m, 2H, Ar–C**H**), 7.43–7.32 (m, 4H, Ar–C**H**), 7.29–7.25 (m, 1H, Ar–C**H**), 7.21–7.17 (m, 1H, Ar–C**H**), 6.69 (dd, *J* = 3.7, 0.8 Hz, 1H, indole C3**H**). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 149.6, 137.2, 135.2, 130.6, 129.5, 125.0, 124.7, 124.2, 122.8, 121.6, 120.5, 114.1, 107.9. Data agrees with literature values.[311]

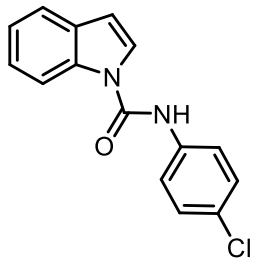
Synthesis of N-(p-tolyl)-1H-indole-1-carboxamide (**2.44**)



Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), indole (12 mg, 0.10 mmol), and *p*-tolyl isocyanate (19 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.44***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.44*** was obtained as a brown solid. Yield: 25 mg, 0.07 mmol, 72%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 8.02 (d, *J* = 9.2 Hz, 1H, Ar–C**H**), 7.53 (dd, *J* = 7.8, 1.0 Hz, 1H, Ar–C**H**), 7.44 (d, *J* = 3.6 Hz, 1H, indole C2**H**), 7.33 (br. s, 1H, N**H**), 7.30 (d, *J* = 8.4 Hz, 2H, Ar–C**H**), 7.24 (t, *J* = 8.4 Hz, 1H, Ar–C**H**), 7.19–7.14 (m, 1H, Ar–C**H**), 7.07 (d, *J* = 8.1 Hz, 2H, Ar–C**H**), 6.55 (d, *J* = 3.6 Hz, 1H, indole C3**H**), 2.25 (s, 3H, C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 149.9, 135.2, 134.7, 134.5, 130.4, 129.8, 124.5, 124.3, 122.7, 121.5, 120.8, 114.2, 107.7, 21.0. Data agrees with literature values.[312]

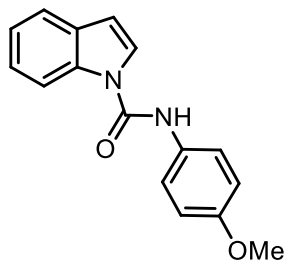
Synthesis of N-(4-chlorophenyl)-1H-indole-1-carboxamide (**2.45**)



Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), indole (12 mg, 0.10 mmol), and 4-chlorophenyl isocyanate (23 mg, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.45***. The crude reaction mixture was purified *via* preparative thin layer chromatography using hexane/ethyl acetate as eluent The desired compound ***2.45*** was obtained as an off-white solid. Yield: 25 mg, 0.09 mmol, 93%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 7.99 (d, *J* = 9.3 Hz, 1H, Ar–C**H**), 7.52 (d, *J* = 8.8 Hz, 1H, indole C3**H**), 7.40 (d, *J* = 3.7 Hz, 1H, Ar–C**H**), 7.39 (br. s, 1H, N**H**), 7.37–7.33 (m, 2H, Ar–C**H**), 7.27–7.19 (m, 3H, Ar–C**H**), 7.18–7.13 (m, 1H, Ar–C**H**), 6.55 (d, *J* = 3.7 Hz, 1H, indole C2**H**) . **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 149.7, 135.7, 135.2, 130.5, 130.1, 129.4, 124.7, 124.0, 123.0, 121.9, 121.6, 114.2, 108.2. Data agrees with literature values.[312]

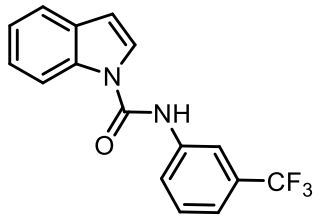
Synthesis of N-(4-methoxyphenyl)-1H-indole-1-carboxamide (**2.46**)



Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), indole (12 mg, 0.10 mmol), and 4-methoxy phenyl isocyanate (19 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.46***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.46*** was obtained as an off-white solid. Yield: 25 mg, 0.09 mmol, 94%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 8.01 (d, *J* = 8.1 Hz, 1H, Ar–C**H**), 7.51 (d, *J* = 7.8 Hz, 1H, Ar–C**H**), 7.42 (d, *J* = 3.7 Hz, 1H, indole C2**H**), 7.33 (br., s, 1H, N**H**), 7.27 (d, *J* = 9.0 Hz, 2H, Ar–C**H**), 7.22 (t, *J* = 8.4 Hz, 1H, Ar–C**H**), 7.16–7.12 (m, 1H, Ar–C**H**), 6.76 (d, *J* = 9.0 Hz, 2H, Ar–C**H**), 6.52 (d, *J* = 3.7 Hz, 1H, indole C3**H**), 3.68 (s, 3H, OMe). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 157.1, 150.2, 135.3, 130.4, 129.9, 124.5, 124.2, 122.9, 122.7, 121.5, 114.5, 114.2, 107.7, 55.7. Data agrees with literature values.[313]

Synthesis of N-(3-(trifluoromethyl)phenyl)-1H-indole-1-carboxamide (**2.47**)

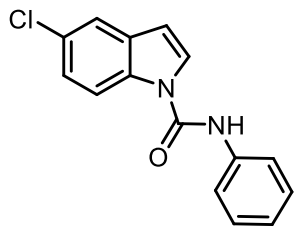


Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 0.85 ml, 0.85 mmol), indole (1 g, 8.5 mmol), and 3-trifluoromethyl-phenyl isocyanate (1.8 mL, 12.8 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.47***. The crude reaction mixture was purified *via* column chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.47*** was obtained as an off-white solid. Yield: 2.0 g, 6.97 mmol, 82%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 8.05 (dd, *J* = 8.3, 0.9 Hz, 1H, Ar–C**H**), 7.77 (br. s, 1H, N**H**), 7.70–7.64 (m, 1H, Ar–C**H**), 7.57 (dt, *J* = 7.8, 1.0 Hz, 1H, indole C2**H**), 7.46 (d, *J* = 3.6 Hz, 2H, Ar–C**H**), 7.43 (t, *J* = 8.0 Hz, 1H, Ar–C**H**), 7.36 (m, 1H, Ar–C**H**), 7.30 (m, 1H, Ar–C**H**), 7.25–7.18 (m, 1H, Ar–C**H**), 6.63 (dd, *J* = 3.7, 0.8 Hz, 1H, Indole C3**H**). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 149.6, 137.8, 135.3, 131.9 (q, $J_{C–F}$ = 32.7 Hz), 130.5, 130.0, 124.9, 123.9 (q, $J_{C–F}$ = 272.4 Hz), 123.6,

123.5, 123.1, 122.8, 121.7, 121.54-121.45 (q, J_{C-F} = 3.8 Hz), 117.2 (q, *J* = 4.0 Hz), 114.2, 108.5. Data agrees with literature values.[312]

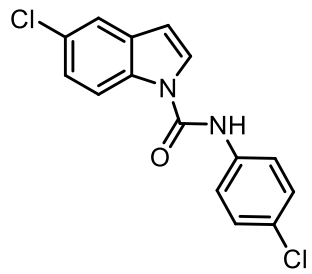
Synthesis of 5-chloro-N-phenyl-1H-indole-1-carboxamide (**2.48**)



Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), 5-chloro-indole (15 mg, 0.10 mmol), phenyl isocyanate (16 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.48***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.48*** was obtained as a green solid. Yield: 23 mg, 0.09 mmol, 85%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 8.09 (d, *J* = 8.8 Hz, 1H, Ar–C**H**), 7.58 (d, *J* = 2.7 Hz, 1H, Ar–C**H**), 7.53 (d, *J* = 3.7 Hz, 1H, Indole C2**H**), 7.52–7.49 (m, 2H, Ar–C**H**), 7.41–7.36 (m, 2H, Ar–C**H**), 7.34 (br. s, 1H, N**H**), 7.29 (dd, *J* = 8.8, 2.1 Hz, 1H, Ar–C**H**), 7.21–7.17 (m, 1H, Ar–C**H**), 6.61 (dd, *J* = 3.7, 0.8 Hz, 1H, Indole C3**H**). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 149.4, 136.9, 133.9, 131.4, 129.5, 128.5, 125.2, 125.0, 124.9, 121.0, 120.7, 115.6, 107.4. **IR ν_{max}** (cm^{-1}): 3294, 3138, 3063, 1678 (C=O), 1599, 1574, 1526, 1445, 1364, 1333, 1266, 1248, 1200, 1092, 1067, 1032. **HRMS** (EI) [M] [$C_{15}H_{11}ON_2{}^{35}Cl$]: calculated. 270.0554, found: 270.0552.

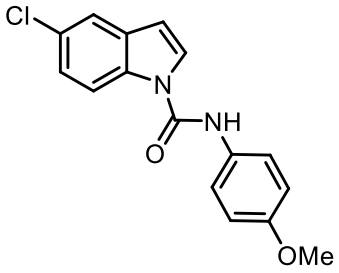
Synthesis of 5-chloro-N-(4-chlorophenyl)-1H-indole-1-carboxamide (**2.49**)



Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), 5-chloro-indole (15 mg, 0.10 mmol), and 4-chloro-phenylisocyanate (23 mg, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.49***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.49*** was obtained as an off-white solid. Yield: 30 mg, 0.10 mmol, 98%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 8.06 (d, *J* = 8.9 Hz, 1H, Ar–C**H**), 7.57 (d, *J* = 2.1 Hz, 1H, Ar–C**H**), 7.49 (d, *J* = 3.7 Hz, 1H, Indole C2**H**), 7.46–7.42 (m, 2H, Ar–C**H**), 7.36 (br. s, 1H, N**H**), 7.35–7.31 (m, 2H, Ar–C**H**), 7.29 (dd, *J* = 8.9, 2.1 Hz, 1H, Ar–C**H**), 6.60 (d, *J* = 3.8 Hz, 1H, Indole C3**H**). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 149.3, 135.5, 133.9, 131.4, 130.4, 129.4, 128.6, 125.0, 124.8, 122.0, 121.0, 115.6, 107.7. **IR ν_{max}** (cm^{-1}): 330, 1676 (C=O), 1593, 1518, 1493, 1449, 1400, 1329, 1285, 1244, 1200, 1090, 1067, 1015. **HRMS** (EI) [M] [$C_{15}H_{10}ON_2{}^{35}Cl_2$]: calculated. 304.0165, found: 304.0169.

Synthesis of 5-chloro-N-(4-methoxyphenyl)-1H-indole-1-carboxamide (**2.50**)

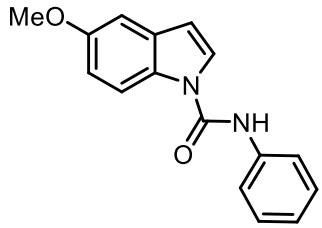


Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), 5-chloro-indole (15 mg, 0.10 mmol), and 4-methoxy-phenyl isocyanate (19 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.50***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.50*** was obtained as an off-white solid. Yield: 16 mg, 0.05 mmol, 53%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 8.10 (d, *J* = 8.9 Hz, 1H, Ar–C**H**), 7.58 (d, *J* = 2.1 Hz, 1H, Ar–C**H**), 7.52 (d, *J* = 3.7 Hz, 1H, Indole C2**H**), 7.43–7.36 (m, 2H, Ar–C**H**), 7.29 (dd, *J* = 8.9, 2.1 Hz, 1H, Ar–C**H**), 7.25 (br., s, 1H, N**H**), 6.96–6.87 (m, 2H, Ar–C**H**), 6.61 (dd, *J* = 3.7, 0.8 Hz, 1H, Indole C3**H**), 3.81 (s, 3H, OMe). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 157.2, 149.8, 133.9, 131.3, 129.6, 128.3, 124.9, 124.8, 123.0, 120.9, 115.6, 114.6, 107.3, 55.7. **IR** ν_{max} (cm^{-1}): 3320, 2924, 2853, 1937, 1881, 1709, 1678 (C=O), 1601, 1572, 1514, 1474, 1441, 1414, 1360, 1333, 1302, 1265, 1244, 1198, 1173, 1109, 1090, 1063, 1032. **HRMS** (ES+) [M+H] [$C_{16}H_{14}O_2N_2{}^{35}Cl$]$^{+}$: calculated. 301.0744, found: 301.0735.

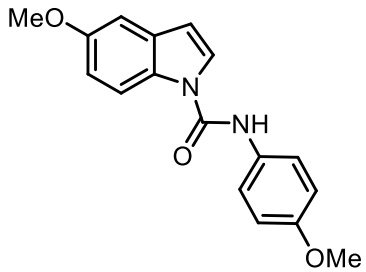
Synthesis of 5-methoxy-N-phenyl-1H-indole-1-carboxamide (**2.51**)

Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), 5-methoxy indole (15 mg, 0.10 mmol), and phenyl isocyanate (16 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.51***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.51*** was obtained as an off-white solid. Yield: 19 mg, 0.07 mmol, 71%.



^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 8.01 (d, *J* = 9.8 Hz, 1H, Ar–C**H**), 7.53–7.48 (m, 3H, Ar–C**H** and Indole C2**H**), 7.43 (br. s, 1H, N**H**), 7.37 (t, *J* = 8.1 Hz, 2H, Ar–C**H**), 7.20–7.14 (m, 1H, Ar–C**H**), 7.07 (d, *J* = 2.4 Hz, 1H, Ar–C**H**), 6.96 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar–C**H**), 6.58 (d, *J* = 3.5 Hz, 1H, Indole C3**H**), 3.86 (s, 3H, OMe). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 155.9, 149.7, 137.2, 131.3, 130.2, 129.4, 124.9, 124.6, 120.6, 115.1, 113.6, 107.7, 103.8, 55.8. **IR ν_{max}** (cm^{-1}): 3245, 3066, 1671 (C=O), 1594, 1542, 1471, 1438, 1308, 1263, 1202, 1148, 1115, 1021. **HRMS** (EI) [M] [$C_{16}H_{14}O_2N_2$]: calculated. 266.1050, found: 266.1049.

Synthesis of 5-methoxy-N-(4-methoxyphenyl)-1H-indole-1-carboxamide (**2.52**)

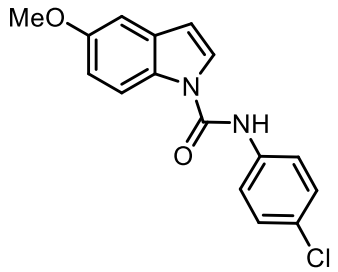


Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), 5-methoxy-indole (15 mg, 0.10 mmol), and 4-methoxy-phenylisocyanate (19 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.52***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.52*** was obtained as an off-white solid. Yield: 17 mg, 0.06 mmol, 57%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 8.02 (d, *J* = 9.0 Hz, 1H, Ar–C**H**), 7.51 (d, *J* = 3.6 Hz, 1H, Indole C2**H**), 7.43–7.37 (m, 2H, Ar–C**H**), 7.22 (br. s, 1H, N**H**), 7.08 (d, *J* = 2.6 Hz, 1H, Ar–C**H**), 6.97 (dd, *J* = 9.0, 3.0 Hz, 1H, Ar–C**H**), 6.94–6.87 (m, 2H, Ar–C**H**), 6.60 (dd, *J* = 3.6, 0.8 Hz, 1H, Indole C3**H**), 3.86 (s, 3H, OMe), 3.81 (s, 3H, OMe). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 157.1,

155.9, 150.1, 131.3, 130.2, 130.0, 124.6, 122.9, 115.1, 114.6, 113.7, 107.6, 103.7, 55.8, 55.7. **IR ν_{max}** (cm^{-1}): 3310, 3138, 2999, 2936, 2833, 1672 (C=O), 1613, 1601, 1512, 1474, 1414, 1368, 1335, 1298, 1254, 1211, 1198, 1150, 1121, 1032. **HRMS** (EI) [M] [$C_{17}H_{16}O_3N_2$]: calculated. 296.1055, found: 296.1056.

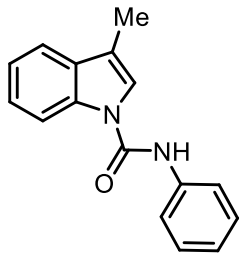
Synthesis of N-(4-chlorophenyl)-5-methoxy-1H-indole-1-carboxamide (**2.53**)



Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), 5-methoxy indole (15 mg, 0.10 mmol), and 4-chloro phenyl isocyanate (23 mg, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.53***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.53*** was obtained as an off-white solid. Yield: 10 mg, 0.03 mmol, 33%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 8.00 (d, *J* = 9.0 Hz, 1H, Ar–C**H**), 7.50 (d, *J* = 3.7 Hz, 1H, Indole C2**H**), 7.49–7.45 (m, 2H, Ar–C**H**), 7.37–7.33 (m, 2H, Ar–C**H**), 7.30 (br. s, 1H, N**H**), 7.08 (d, *J* = 2.5 Hz, 1H, Ar–C**H**), 6.98 (dd, *J* = 9.0, 2.6 Hz, 1H, Ar–C**H**), 6.62 (dd, *J* = 3.6, 0.8 Hz, 1H, Ar–C**H**), 3.87 (s, 3H, OMe). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 156.1, 149.5, 135.8, 131.3, 130.1, 130.0, 129.4, 124.4, 121.7, 115.0, 113.8, 108.1, 103.9, 55.9. **IR** ν_{max} (cm^{-1}): 2833, 2351, 1715, 1668 (C=O), 1645, 1634, 1622, 1614, 1595, 1568, 1506, 1495, 1472, 1457, 1445, 1402, 1368, 1337, 1310, 1290, 1263, 1209, 1182, 1152, 1121, 1106, 1094, 1020, 1013. **HRMS** (EI) [M] [$C_{16}H_{13}O_2N_2{}^{35}Cl$]: calculated. 300.0660, found: 300.0663.

Synthesis of 3-methyl-N-phenyl-1H-indole-1-carboxamide (**2.54**)

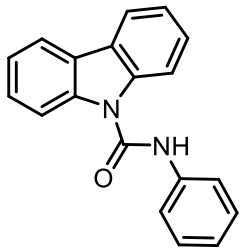


Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), 3-methylindole (13 mg, 0.10 mmol), and methoxy-phenylisocyanate (16 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.54***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate

as eluent. The desired compound ***2.54*** was obtained as an off-white solid. Yield: 21 mg, 0.08 mmol, 84%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 8.04 (dt, *J* = 8.3, 0.9 Hz, 1H, Ar–C**H**), 7.48–7.44 (m, 1H, Ar–C**H**), 7.43 (dd, *J* = 8.6, 1.1 Hz, 2H, Ar–C**H**), 7.31–7.28 (m, 1H, Ar–C**H**), 7.29–7.23 (m, 3H, Ar–C**H**), 7.20 (s, 1H, indole C2**H**), 7.18-7.17 (m, 1H, Ar–C**H**), 7.09–7.04 (m, 1H, Ar–C**H**), 2.20 (d, *J* = 1.3 Hz, 3H, C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 149.8, 137.3, 135.7, 131.2, 129.3, 124.72, 124.67, 122.4, 121.0, 120.5, 119.5, 117.3, 114.4, 9.8. **IR ν_{max}** (cm^{-1}): 3246, 3107, 3048, 2965, 2916, 2857, 1670 (C=O), 1597, 1528, 1447, 1343, 1215, 1088. **HRMS** (EI) [M] [$C_{16}H_{14}ON_2$]: calculated. 250.1101, found: 250.1102.

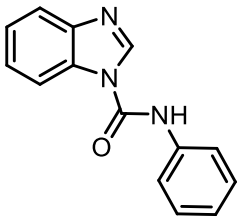
Synthesis of N-phenyl-9H-carbazole-9-carboxamide (**2.55**)



Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), carbazole (16 mg, 0.10 mmol), and phenyl isocyanate (16 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.55***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.55*** was obtained as a white solid. Yield: 24 mg, 0.08 mmol, 84%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 8.04 (d, *J* = 10.8 Hz, 4H, Ar–C**H**), 7.62–7.58 (m, 2H, Ar–C**H**), 7.53 (br., s, 1H, N**H**), 7.52–7.47 (m, 2H, Ar–C**H**), 7.47–7.41 (m, 2H, Ar–C**H**), 7.40–7.34 (m, 2H, Ar–C**H**), 7.23–7.19 (m, 1H, Ar–C**H**). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 150.2, 138.3, 137.3, 129.5, 127.3, 125.4, 124.9, 122.8, 120.5, 120.1, 113.6. **IR** ν_{max} (cm^{-1}): 3260, 1668 (C=O), 1599, 1526, 1445, 1352, 1327, 1310, 1256, 1236, 1219, 1200, 1120, 1078, 1028. **HRMS** (ES+) [M+H] $[C_{19}H_{15}ON_2]^+$: calculated. 287.1184, found: 287.1186.

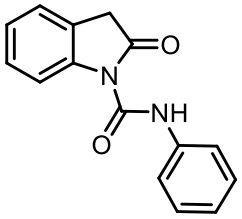
Synthesis of N-phenyl-1H-benzo[d]imidazole-1-carboxamide (**2.56**)



Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), benzoimidazole (12 mg, 0.10 mmol), and phenyl isocyanate (16 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.56***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.56*** was obtained as a white solid. Yield: 23 mg, 0.10 mmol, 97%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 9.11 (br., s, 1H, N**H**), 8.48 (dd, *J* = 8.5, 0.9 Hz, 1H, Ar–C**H**), 8.12 (s, 1H, C2**H**), 7.76 (dt, *J* = 8.0, 1.0 Hz, 1H, Ar–C**H**), 7.71–7.64 (m, 2H, Ar–C**H**), 7.62 –7.53 (m, 1H, Ar–C**H**), 7.44–7.36 (m, 2H, Ar–C**H**), 7.37–7.30 (m, 1H, Ar–C**H**), 7.17 (tt, *J* = 7.4, 1.1 Hz, 1H, Ar–C**H**). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 148.9, 139.3, 137.9, 137.3, 129.4, 129.3, 126.0, 124.5, 123.7, 121.2, 119.8, 115.0. **IR** ν_{max} (cm^{-1}): 3358, 1722 (C=O), 1591, 1522, 1497, 1466, 1441, 1427, 1416, 1368, 1352, 1325, 1310, 1297, 1269, 1229, 1217, 1175, 1156, 1142, 1113, 1080, 1034, 1020, 1009. **HRMS** (EI) [M] [$C_{14}H_{11}ON_3$]: calculated. 237.0897, found: 237.0895.

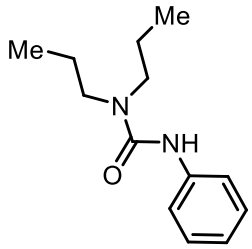
Synthesis of 2-oxo-N-phenylindoline-1-carboxamide (**2.57**)



Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), oxindole (13 mg, 0.10 mmol), and phenyl isocyanate (16 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.57***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.57*** was obtained as an off-white solid. Yield: 12 mg, 0.05 mmol, 48%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 10.69 (br. s, 1H, N**H**), 8.32 (d, *J* = 8.2 Hz, 1H, Ar–C**H**), 7.64–7.53 (m, 2H, Ar–C**H**), 7.40–7.33 (m, 3H, Ar–C**H**), 7.29 (d, *J* = 8.9 Hz, 1H, Ar–C**H**), 7.19 (t, *J* = 8.0 Hz, 1H, Ar–C**H**), 7.15 (tt, *J* = 7.4, 1.2 Hz, 1H, Ar–C**H**), 3.81 (s, 2H, C**H**$_2$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 177.8, 149.6, 141.7, 137.2, 129.2, 128.6, 124.9, 124.7, 124.1, 123.0, 120.7, 116.9, 37.2. Data agrees with literature values.[314]

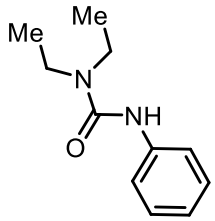
Synthesis of 3-phenyl-1,1-dipropylurea (**2.58**)



Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), dipropylamine (14 µL, 0.10 mmol), and phenyl isocyanate (16 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.58***. The crude reaction mixture was purified *via* silica plug using hexane/ethyl acetate as eluent. The desired compound ***2.58*** was obtained as a white solid. Yield: 21 mg, 0.10 mmol, 96%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 7.33–7.28 (m, 2H, Ar–C**H**), 7.23–7.17 (m, 2H, Ar–C**H**), 6.94 (tt, *J* = 7.4, 1.2 Hz, 1H, Ar–C**H**), 6.25 (br. s, 1H, N**H**), 3.19 (t, *J* = 7.8 Hz, 4H, α-C**H**$_2$), 1.57 (m, *J* = 7.4 Hz, 4H, *β*-C**H**$_2$), 0.87 (t, *J* = 7.4 Hz, 6H, C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 155.0, 139.4, 128.9, 122.8, 119.8, 49.5, 22.0, 11.5. Data agrees with literature values.[314]

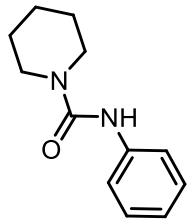
Synthesis of 1,1-diethyl-3-phenylurea (**2.59**)



Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), diethylamine (14 µL, 0.10 mmol), and phenyl isocyanate (16 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.59***. The crude reaction mixture was purified *via* silica plug using hexane/ethyl acetate as eluent. The desired compound ***2.59*** was obtained as a white solid. Yield: 19 mg, 0.10 mmol, 99%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 7.35–7.29 (m, 2H, Ar–C**H**), 7.24–7.17 (m, 2H, Ar–C**H**), 6.94 (tt, *J* = 7.3, 1.2 Hz, 1H, Ar–C**H**), 6.25 (br. s, 1H, N**H**), 3.30 (q, *J* = 7.1 Hz, 4H, *α*-C**H**$_2$), 1.15 (t, *J* = 7.2 Hz, 6H, C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 154.7, 139.4, 128.9, 122.9, 119.9, 41.7, 14.1. Data agrees with literature values.[139]

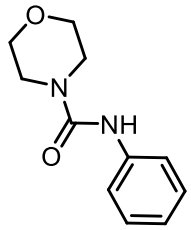
Synthesis of N-phenylpiperidine-1-carboxamide (**2.60**)



Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), piperidine (10 µL, 0.10 mmol), and phenyl isocyanate (16 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.60***. The crude reaction mixture was purified *via* a silica-plug using hexane/ethyl acetate as eluent. The desired compound ***2.60*** was obtained as a white solid. Yield: 16 mg, 0.08 mmol, 78%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 7.31–7.25 (m, 2H, Ar–C**H**), 7.23–7.16 (m, 2H, Ar–C**H**), 6.93 (tt, *J* = 7.3, 1.1 Hz, 1H, Ar–C**H**), 6.39 (br., s, 1H, N**H**), 3.37–3.35 (m, 4H, C$\mathbf{H}_2$), 1.55–1.51 (m, 6H, C$\mathbf{H}_2$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 155.1, 139.4, 128.9, 122.9, 119.9, 45.3, 25.8, 24.5. Data agrees with literature values.[139]

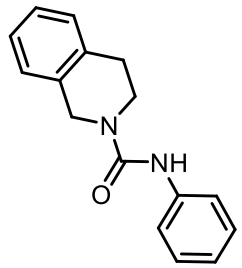
Synthesis of N-phenylmorpholine-4-carboxamide (**2.61**)



Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), morpholine (9 µL, 0.10 mmol), and phenyl isocyanate (16 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.61***. The crude reaction mixture was purified *via* silica plug using hexane/ethyl acetate as eluent. The desired compound ***2.61*** was obtained as a white solid. Yield: 16 mg, 0.078 mmol, 78%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 7.28–7.23 (m, 2H, Ar–C**H**), 7.23–7.18 (m, 2H, Ar–C**H**), 6.98 (tt, *J* = 7.3, 1.3 Hz, 1H, Ar–C**H**), 6.49 (br. s, 1H, N**H**), 3.63 (t, *J* = 4.6 Hz, 4H, N–C$\mathbf{H}_2$), 3.38 (t, *J* = 5.2 Hz, 4H, O–C$\mathbf{H}_2$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 155.3, 138.8, 129.0, 123.5, 120.3, 66.6, 44.3. Data agrees with literature values.[139]

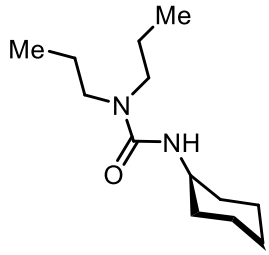
Synthesis of N-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxamide (**2.62**)



Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), tetrahydroisoquinoline (13 µL, 0.10 mmol), and phenyl isocyanate (16 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.62***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.62*** was obtained as an off-white solid. Yield: 23 mg, 0.09 mmol, 91%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 7.42–7.38 (m, 2H, Ar–C**H**), 7.31–7.27 (m, 2H, Ar–C**H**), 7.23–7.16 (m, 3H, Ar–C**H**), 7.15–7.12 (m, 1H, Ar–C**H**), 7.04 (tt, *J* = 7.3, 1.2 Hz, 1H, Ar–C**H**), 6.56 (br., s, 1H, N**H**), 4.66 (s, 2H, α-N benzylic C**H**$_2$), 3.72 (t, *J* = 5.9 Hz, 2H), 2.92 (t, *J* = 5.9 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 155.1, 139.1, 135.1, 133.2, 129.0, 128.5, 126.9, 126.6, 126.5, 123.2, 120.2, 45.8, 41.7, 29.1. Data agrees with literature values.[139]

Synthesis of 3-cyclohexyl-1,1-dipropylurea (**2.63**)



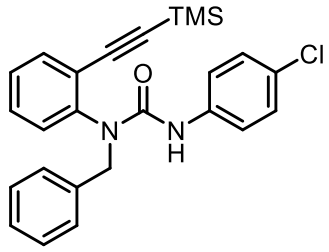
Synthesised in accordance with *GP1* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), di-propylamine (14 µL, 0.10 mmol), and cyclohexyl isocyanate (19 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.63***. The crude reaction mixture was purified *via a* silica-plug using hexane/ethyl acetate as eluent. The desired compound ***2.63*** was obtained as a white solid. Yield: 15 mg, 0.07 mmol, 66%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 4.11 (br. s, 1H, N**H**), 3.63 (m, 1H, C**H**), 3.11 (t, *J* = 8.2 Hz, 4H, α-N–C**H**$_2$), 1.97–1.89 (m, 2H, C**H**$_2$), 1.69–1.62 (m, 2H, Cy–C**H**$_2$), 1.54 (m, *J* = 7.4 Hz, 4H, β-N–C**H**$_2$), 1.41–1.28 (m, 2H, Cy–C**H**$_2$), 1.24 (s, 1H, Cy–C**H**$_2$), 1.19–1.02 (m, 3H, Cy–C**H**$_2$), 0.88 (t, *J* = 7.4 Hz, 6H, C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 157.2, 49.3, 49.1, 34.2, 25.9, 25.2, 21.9, 11.5. Data agrees with literature values.[315]

6.1.3. Chapter 2: Synthesis and characterisation of *N*–functionalised 2-alkynyl products

General Procedure 2 (GP2): In the glovebox, three glass microwave vial were charged separately with alkyne derivatives (1 equiv.), aryl isocyanate (1.5 equiv.), and BCl_3 [1M solution in hexane] (5 mol%), and then capped with a septum. The three vials were brought outside the glovebox and 0.5 mL of DCE were added to each vial using a syringe. Ar–NCO solution was added to the BCl_3 solution and the resulting solution was added to the indole solution dropwise with vigorous stirring at room temperature. All the reactions were carried out at an optimum temperature 60 °C for 22–24 h. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using hexane/ethyl acetate as eluent.

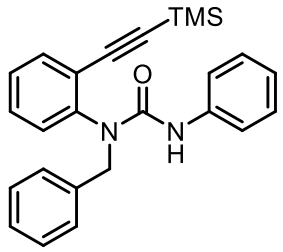
Synthesis of 1-benzyl-3-(4-chlorophenyl)-1-(2-((trimethylsilyl)ethynyl)phenyl)urea (**2.84**)



Synthesised in accordance with *GP2* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), *N*-benzyl-2-((trimethylsilyl)ethynyl)aniline (28 mg, 0.10 mmol), and 4-chlorophenyl isocyanate (23 mg, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.84***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.84*** was obtained as an off-white solid. Yield: 26 mg, 0.06 mmol, 61%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 7.56–7.52 (m, 1H, Ar–C**H**), 7.29–7.19 (m, 9H, Ar–C**H**), 7.15 (s, 2H, Ar–C**H**), 7.00–6.95 (m, 1H, Ar–C**H**), 6.01 (br. s, 1H, N**H**), 5.28 (br., s, 1H, benzyl C$\mathbf{H}_2$)*, 4.53 (br. s, 1H, benzyl C$\mathbf{H}_2$), 0.13 (s, 9H, C$\mathbf{H}_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 154.1, 142.5, 138.0, 137.8, 134.2, 130.1, 130.0, 129.11, 129.08, 128.8, 128.5, 128.0, 127.5, 123.6, 121.0, 101.8, 100.3, 52.5, -0.2. **IR ν_{max}** (cm^{-1}): 3320, 2957, 2158, 1661 (C=O), 1591, 1559, 1506, 1493, 1481, 1458, 1447, 1427, 1398, 1364, 1321, 1300, 1283, 1271, 1262, 1242, 1219, 1198, 1173, 1113, 1090, 1076, 1040, 1030, 1013. **HRMS** (ES+) [M+H] $[C_{25}H_{26}OSiCl]^+$: calculated. 433.1503, found: 433.1495.

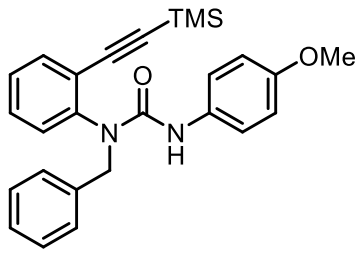
Synthesis of 1-benzyl-3-phenyl-1-(2-((trimethylsilyl)ethynyl)phenyl)urea (**2.85**)



Synthesised in accordance with *GP2* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), *N*-benzyl-2-((trimethylsilyl)ethynyl)aniline (28 mg, 0.10 mmol), and phenyl isocyanate (16 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.85***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.85*** was obtained as a white solid. Yield: 19 mg, 0.05 mmol, 48%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 7.60–7.53 (m, 1H, Ar–C**H**), 7.32–7.19 (m, 11H, Ar–C**H**), 7.03–6.94 (m, 2H, Ar–C**H**), 6.03 (br. s, 1H, N**H**), 5.34 (br., s, 1H, benzyl C**H**$_2$), 4.62 (br. s, 1H, benzyl C**H**$_2$), 0.16 (s, 9H, C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 154.3, 142.7, 139.2, 138.2, 134.2, 130.1, 130.0, 129.1, 128.8, 128.4, 128.3, 127.4, 123.6, 123.1, 119.8, 101.6, 100.5, 52.4, -0.2. **IR ν_{max}** (cm^{-1}): 3428, 3061, 3030, 2957, 2160, 1674 (C=O), 1595, 1518, 1501, 1483, 1439, 1400, 1364, 1310, 1269, 1248, 1219, 1196, 1155, 1109, 1078, 1044, 1030. **HRMS** (ES+) [M+H] $[C_{25}H_{27}N_2OSi]^+$: calculated. 399.1893, found: 399.1886.

Synthesis of 1-benzyl-3-(4-methoxyphenyl)-1-(2-((trimethylsilyl)ethynyl)phenyl)urea (**2.86**)

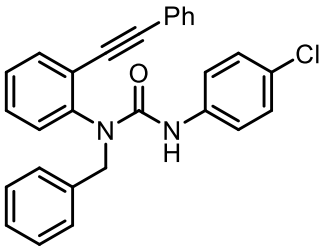


Synthesised in accordance with *GP2* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), *N*-benzyl-2-((trimethylsilyl)ethynyl)aniline (28 mg, 0.10 mmol), and 4-methoxyphenyl isocyanate (19 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.86***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.86*** was obtained as a light brown solid. Yield: 25 mg, 0.06 mmol, 58%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 7.56–7.52 (m, 1H, Ar–C**H**), 7.29–7.16 (m, 10H, Ar–C**H**), 7.02–6.96 (m, 1H, Ar–C**H**), 6.77 (d, *J* = 8.9 Hz, 2H, Ar–C**H**), 5.88 (br. s, 1H, N**H**), 5.32 (br. s, 1H, benzyl C**H**$_2$), 4.58 (br. s, 1H, benzyl C**H**$_2$) 3.74 (s, 3H, OMe), 0.17 (s, 9H, C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 155.9, 154.8, 142.9, 138.3, 134.2, 132.3, 130.2, 130.0, 129.1, 128.4, 128.2,

127.3, 123.6, 122.2, 114.1, 101.5, 100.6, 55.6, 52.4, -0.1. **IR ν_{max}** (cm^{-1}): 3429, 2955, 2160, 1670. (C=O), 1595, 1510, 1483, 1464, 1447, 1410, 1356, 1296, 1219, 1196, 1179, 1109, 1074, 1032. **HRMS** (ES+) [M+H] $[C_{26}H_{29}N_2O_2Si]^+$: calculated. 429.1998, found: 429.1984.

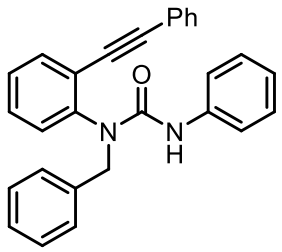
Synthesis of 1-benzyl-3-(4-chlorophenyl)-1-(2-(phenylethynyl)phenyl)urea (**2.87**)



Synthesised in accordance with *GP2* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), *N*-benzyl-2-(phenylethynyl)aniline (28 mg, 0.10 mmol), and 4-chlorophenyl isocyanate (23 mg, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.87***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.87*** was obtained as an off-white solid. Yield: 27 mg, 0.06 mmol, 62%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 7.63 (dd, *J* = 7.6, 1.7 Hz, 1H, Ar–C**H**), 7.44 (m, 2H, Ar–C**H**), 7.38–7.26 (m, 7H, Ar–C**H**), 7.26–7.18 (m, 5H, Ar–C**H**), 7.15 (d, *J* = 8.8 Hz, 2H, Ar–C**H**), 7.05 (d, *J* = 9.2 Hz, 1H, Ar–C**H**), 6.09 (br. s, 1H, N**H**), 5.37 (br. s, 1H, benzyl C$\mathbf{H}_2$), 4.60 (br. s, 1H, benzyl C$\mathbf{H}_2$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 154.4, 141.9, 137.9, 137.6, 133.8, 131.9, 130.2, 129.8, 129.1, 129.0, 128.8, 128.7, 128.6, 128.4, 128.0, 127.5, 123.8, 122.4, 121.1, 95.8, 85.0, 52.7. **IR ν_{max}** (cm^{-1}): 3422, 3318, 3061, 3030, 2922, 2853, 1667 (C=O), 1591, 1508, 1491, 1447, 1398, 1358, 1304, 1285, 1234, 1200, 1177, 1159, 1090, 1070, 1042, 1026, 1011. **HRMS** (ES+) [M+H] $[C_{28}H_{22}N_2OCl]^+$: calculated. 437.1421, found: 429.1415.

Synthesis of 1-benzyl-3-phenyl-1-(2-(phenylethynyl)phenyl)urea (**2.88**)

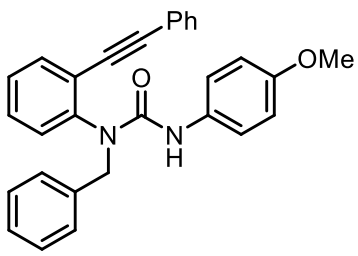


Synthesised in accordance with *GP2* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), *N*-benzyl-2-(phenylethynyl)aniline (28 mg, 0.10 mmol), and phenyl isocyanate (16 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.88***. The crude reaction mixture was purified *via* preparative thin-layer chromatography

using hexane/ethyl acetate as eluent. The desired compound ***2.88*** was obtained as a yellow solid. Yield: 18 mg, 0.04 mmol, 45%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 7.65 (d, *J* = 7.7 Hz, 1H, Ar–C**H**), 7.48 (d, *J* = 1.6 Hz, 2H, Ar–C**H**), 7.33 (m, 9H, Ar–C**H**), 7.25–7.17 (m, 5H, Ar–C**H**), 7.06 (d, *J* = 7.7 Hz, 1H, Ar–C**H**), 7.01–6.95 (m, 1H, Ar–C**H**), 6.10 (br. s, 1H, N**H**), 5.35 (br. s, 1H, Benzyl C**H**$_2$), 4.65 (br. s, 1H, Benzyl C**H**$_2$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 154.6, 142.2, 139.1, 138.2, 133.8, 132.0, 130.3, 129.8, 129.1, 128.93, 128.89, 128.6, 128.5, 128.4, 127.4, 124.0, 123.2, 122.6, 120.0, 95.8, 85.2, 52.6. **IR ν_{max}** (cm^{-1}): 3426, 3321, 3061, 3030, 2959, 2924, 1674 (C=O), 1595, 1520, 1495, 1479, 1439, 1362, 1312, 1261, 1238, 1200, 1179, 1157, 1101, 1028. **HRMS** (ES+) [M+H] $[C_{28}H_{23}N_2O]^+$: calculated. 403.1810, found: 403.1802.

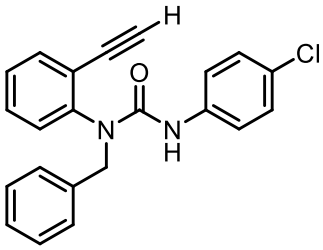
Synthesis of 1-benzyl-3-(4-methoxyphenyl)-1-(2-(phenylethynyl)phenyl)urea (**2.89**)



Synthesised in accordance with *GP2* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), *N*-benzyl-2-(phenylethynyl)aniline (28 mg, 0.10 mmol), and 4-methoxyphenyl isocyanate (19 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.89***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.89*** was obtained as a brown oil. Yield: 21 mg, 0.05 mmol, 49%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 7.64 (dd, *J* = 7.6, 1.7 Hz, 1H, Ar–C**H**), 7.51–7.47 (m, 2H, Ar–C**H**), 7.37–7.28 (m, 7H, Ar–C**H**), 7.26–7.17 (m, 5H, Ar–C**H**), 7.07 (dd, *J* = 7.8, 1.5 Hz, 1H, Ar–C**H**), 6.76 (d, *J* = 9.0 Hz, 2H, Ar–C**H**), 5.98 (br. s, 1H, N**H**), 5.38 (br., s, 1H, benzyl C**H**$_2$), 4.66 (br. s, 1H, benzyl C**H**$_2$), 3.74 (s, 3H, OMe). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 156.0, 155.1, 142.4, 138.3, 133.8, 132.1, 132.0, 130.3, 129.7, 129.1, 128.9, 128.52, 128.46, 128.4, 127.4, 123.9, 122.7, 122.5, 114.1, 95.6, 85.3, 55.6, 52.6. **IR ν_{max}** (cm^{-1}): 3426, 3323, 3061, 3030, 2928, 2833, 2218, 1665(C=O), 1595, 1508, 1495, 1479, 1464, 1410, 1356, 1296, 1231, 1207, 1179, 1107, 1071, 1028. **HRMS** (ES+) [M+H] $[C_{29}H_{25}N_2O_2]^+$: calculated. 433.1916, found: 433.1909.

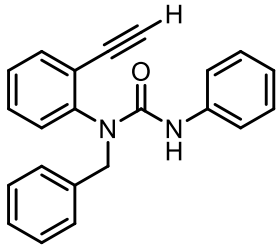
Synthesis of 1-benzyl-3-(4-chlorophenyl)-1-(2-ethynylphenyl)urea (**2.90**)



Synthesised in accordance with *GP2* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), *N*-benzyl-2-ethynylaniline (21 mg, 0.10 mmol), and 4-chlorophenyl isocyanate (23 mg, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.90***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.90*** was obtained as an off-white solid. Yield: 14 mg, 0.04 mmol, 39%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 7.58 (dd, *J* = 7.3, 2.0 Hz, 1H, Ar–C**H**), 7.28 (m, 2H, Ar–C**H**), 7.23–7.18 (m, 8H, Ar–C**H**), 7.16–7.13 (m, 2H, Ar–C**H**), 6.93 (dd, *J* = 7.3, 1.9 Hz, 1H, Ar–C**H**), 5.95 (br. s, 1H, N**H**), 5.35 (br. s, 1H, benzyl C**H**$_2$), 4.41 (br. s, 1H, benzyl C**H**$_2$), 3.25 (s, 1H, alkyne C**H**). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 154.2, 142.5, 137.8, 137.6, 134.8, 130.44, 130.36, 129.1, 128.9, 128.7, 128.5, 128.2, 127.6, 122.7, 121.1, 83.6, 79.2, 52.5. **IR ν_{max}** (cm^{-1}): 3271, 2922, 2853, 1655, 1589, 1571, 1514, 1487, 1435, 1424, 1400, 1372, 1360, 1312, 1287, 1262, 1238, 1225, 1188, 1177, 1090, 1076, 1049, 1026, 1011. **HRMS** (ES+) [M+H] $[C_{22}H_{18}N_2OCl]^+$: calculated. 361.1108, found: 361.1104.

Synthesis of 1-benzyl-1-(2-ethynylphenyl)-3-phenylurea (**2.91**)

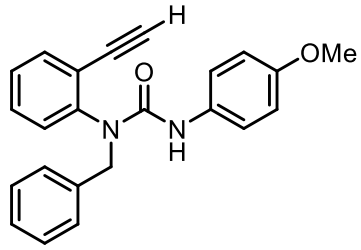


Synthesised in accordance with *GP2* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), *N*-benzyl-2-ethynylaniline (21 mg, 0.10 mmol), and phenyl isocyanate (16 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.91***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.91*** was obtained as an off-white solid. Yield: 13 mg, 0.04 mmol, 40%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 7.63 (dd, *J* = 7.3, 2.0 Hz, 1H, Ar–C**H**), 7.37–7.27 (m, 8H, Ar–C**H**), 7.24 (m, 3H, Ar–C**H**), 7.04–6.97 (m, 2H, Ar–C**H**), 6.00 (br. s, 1H, N**H**), 5.00 (br. s, 2H, benzyl

C**H**$_2$), 3.30 (s, 1H, alkyne C**H**). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 154.4, 142.7, 139.0, 138.1, 134.7, 130.5, 130.4, 129.1, 128.9, 128.6, 128.5, 127.5, 123.2, 122.8, 119.9, 83.5, 79.3, 52.4. **IR ν_{max}** (cm^{-1}): 3291, 3260, 3061, 3030, 2924, 2853, 1655 (C=O), 1616, 1595, 1568, 1559, 1522, 1503, 1486, 1439, 1368, 1312, 1242, 1211, 1188, 1157, 1078, 1044, 1028. **HRMS** (ES+) [M+H] $[C_{22}H_{19}N_2O]^+$: calculated. 327.1497, found: 327.1490.

Synthesis of 1-benzyl-1-(2-ethynylphenyl)-3-(4-methoxyphenyl)urea (**2.92**)

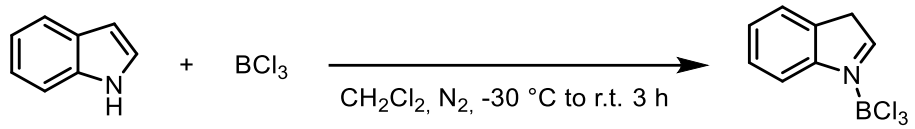


Synthesised in accordance with *GP2* using BCl_3 (1 M in hexane, 5 µL, 0.005 mmol), *N*-benzyl-2-ethynylaniline (21 mg, 0.10 mmol), and 4-methoxyphenyl isocyanate (19 µL, 0.15 mmol) in 1,2-$C_2H_4Cl_2$ to afford ***2.92***. The crude reaction mixture was purified *via* preparative thin-layer chromatography using hexane/ethyl acetate as eluent. The desired compound ***2.92*** was obtained as a pale-yellow solid. Yield: 15 mg, 0.04 mmol, 42%.

^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ: 7.62–7.55 (m, 1H, Ar–C**H**), 7.31–7.14 (m, 11H, Ar–C**H**), 6.97–6.93 (m, 1H, Ar–C**H**), 6.79–6.73 (m, 2H, Ar–C**H**), 5.83 (br. s, 1H, N**H**), 5.36 (br. s, 1H, benzyl C**H**$_2$), 4.50 (br. s, 1H, benzyl C**H**$_2$), 3.72 (s, 3H, OMe), 3.27 (s, 1H, alkyne C**H**). **^{13}C NMR** (126 MHz, $CDCl_3$, 298K) δ: 156.0, 154.9, 142.9, 138.2, 134.7, 132.0, 130.5, 130.3, 129.1, 128.5, 128.4, 127.4, 122.8, 122.3, 114.2, 83.4, 79.4, 55.7, 52.4. **IR ν_{max}** (cm^{-1}): 3426, 3283, 3063, 3030, 3001, 2930, 2833, 1663(C=O), 1595, 1510, 1483, 1464, 1447, 1412, 1356, 1314, 1296, 1233, 1211, 1179, 1107, 1074, 1030. **HRMS** (ES+) [M+H] $[C_{23}H_{21}N_2O_2]^+$: calculated. 357.1603, found: 357.1593.

6.1.4. Chapter 2: Experiments to support the proposed mechanism

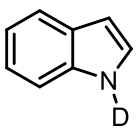
Synthesis of **2.93**



In a nitrogen filled glovebox, indole (1 equiv., 0.6 g, 4.78 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to -30 °C. To this solution, BCl_3 was added dropwise (1M in CH_2Cl_2, 4.78 mL, 4.78 mmol) and the reaction mixture was stirred at 23 °C for 3 h. Next, the solution was decanted and the pink solid obtained was washed several times with pentane. Compound **2.93** was obtained as a pink solid. Yield: 0.8 g, 3.23 mmol, 68%.

^{1}H NMR (400 MHz, CD_2Cl_2, 298K) δ: 9.38 (d, *J* = 3.0 Hz, 1H, indole C2**H**), 8.30 (d, *J* = 7.3 Hz, 1H, Ar–C**H**), 7.61 (d, *J* = 7.1 Hz, 2H, Ar–C**H**), 7.52 (m, 2H, Ar–C**H**), 4.18 (s, 2H, indole C3**H**). **^{13}C NMR** (101 MHz, CD_2Cl_2, 298 K) δ: 175.5, 129.6, 128.9, 125.1, 122.2, 41.7. **^{11}B NMR** (128 MHz, CD_2Cl_2, 298 K) δ: 5.8. Data agrees with literature values.[316]

Synthesis of ***d*-2.43**



In a dried 10 mL Schlenk tube, indole (0.5 g, 4.28 mmol) was dissolved in MeOD (2.5 mL) and the mixture was stirred at room temperature for 4 hours. Then the mixture was concentrated under vacuum to remove the solvent. MeOD (4.5 mL) was added into the Schlenk tube again and the mixture was stirred at room temperature for another 4 hours. The same experimental procedure was repeated a third time. After that, the resulting mixture was concentrated under vacuum and the solid brought inside the glovebox. The desired product ***d-2.43*** was obtained in quantitative yield along with >99% D content.

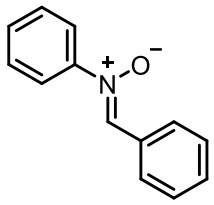
^{1}H NMR (400 MHz, $CDCl_3$, 298K) δ: 7.66 (ddd, *J* = 7.9, 1.3, 0.9, 1H, Ar–C**H**), 7.41 (dq, *J* = 8.1, 1.0, 1H, Ar–C**H**), 7.23–7.17 (m, 2H, Ar–C**H** & indole C2**H**), 7.12 (ddd, *J* = 8.1, 7.1, 1.1, 1H, Ar–

C**H**), 6.57 (dd, *J* = 3.2, 1.0, 1H, indole C3**H**). **^{13}C NMR** (101 MHz, $CDCl_3$, 298K) δ: 135.8, 128.0, 124.1, 122.1, 120.9, 119.9, 111.1, 102.7. Data agrees with literature values.[317]

6.1.5. Chapter 3: Synthesis and characterisation of nitrone starting materials

General procedure 3 (GP3): nitrobenzene (1 equiv.), benzaldehyde (1.1 equiv.), and NH_4Cl (1.2 equiv.) were added to a 1:1 mixture of ethanol:water (2 mL/mmol) and the resulting mixture was stirred for 5 minutes at room temperature. The mixture was then cooled to 0 °C, and Zn dust (2 equiv.) was added portion-wise over 30 minutes. Subsequently, the reaction was slowly warmed to room temperature and stirred overnight. The resulting mixture was then filtered through a pad of celite, and the organics were extracted using CH_2Cl_2 (3 × 40 mL), washed with brine (1 × 40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude compound was purified by recrystallisation using ethanol or ethyl acetate.

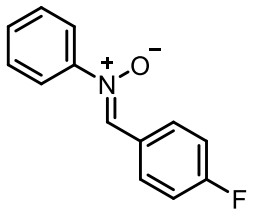
*Synthesis of N,1-diphenylmethanimine oxide (***3.42***)*



Synthesised in accordance with *GP3*, using nitrobenzene (1.7 mL, 16.6 mmol), benzaldehyde (2.0 mL, 19.6 mmol), NH_4Cl (1.14 g, 21.5 mmol), Zn dust (2.14 g, 33.1 mmol). The crude compound was recrystallised from ethanol to afford the product (**3.42**) as a white solid. Yield: 1.5 g, 7.4 mmol, 76%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 8.48–8.25 (m, 2H, Ar–C**H**), 7.93 (s, 1H, C**H**), 7.83–7.74 (m, 2H, Ar–C**H**), 7.53–7.43 (m, 6H, Ar–C**H**). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 149.1, 138.0, 133.6, 130.32, 130.25, 130.2, 129.3, 121.8, 97.1. Data agrees with literature values.[318]

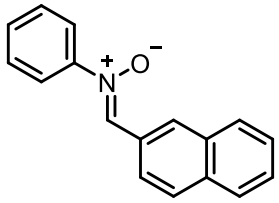
*Synthesis of 1-(4-fluorophenyl)-N-phenylmethanimine oxide (**3.65**)*



Synthesised in accordance with *GP3*, using nitrobenzene (1 mL, 9.8 mmol), 4-fluorobenzaldehyde (1.1 mL, 11.7 mmol), NH_4Cl (678 mg, 12.7 mmol), Zn dust (1.3 g, 19.5 mmol). The crude compound was recrystallised from ethanol to afford the product (**3.65**) as a white solid. Yield: 1.5 g, 7.0 mmol, 70%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 8.51–8.40 (m, 2H, Ar–C**H**), 7.91 (s, 1H, C**H**), 7.80–7.74 (m, 2H, Ar–C**H**), 7.54–7.43 (m, 3H, Ar–C**H**), 7.21–7.13 (m, 2H, Ar–C**H**). **^{19}F NMR** (471 MHz, $CDCl_3$, 298 K) δ: -106.7. **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 163.81 (d, $J_{C\text{-}F}$=253.7 Hz), 149.1, 133.5, 131.5 (d, $J_{C\text{-}F}$=8.3), 130.2, 129.4, 127.3 (d, $J_{C\text{-}F}$=3.4), 121.9, 116.0 (d, $J_{C\text{-}F}$=21.8). Data agrees with literature values.[318]

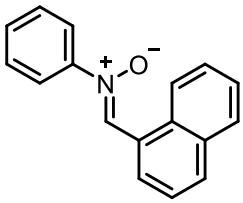
*Synthesis of 1-(naphthalen-2-yl)-N-phenylmethanimine oxide (**3.85**)*



Synthesised in accordance with *GP3*, using nitrobenzene (1 mL, 9.8 mmol), 2-naphthaldehyde (1.8 g, 8.8 mmol), NH_4Cl (678 mg, 12.7 mmol), Zn dust (1.3 g, 19.5 mmol). The crude compound was recrystallised from ethanol to afford the product (**3.85**) as an off-white solid. Yield: 1.5 g, 6.1 mmol, 62%.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 9.50–9.42 (m, 1H, Ar–C**H**), 8.08 (s, 1H, C**H**), 8.04–7.96 (m, 2H, Ar–C**H**), 7.89 (d, J = 8.6, 1H, Ar–C**H**), 7.86–7.80 (m, 3H, Ar–C**H**), 7.60–7.46 (m, 5H, Ar–C**H**). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 149.2, 134.7, 134.5, 133.3, 130.1, 129.5, 129.3, 129.2, 128.2, 128.0, 127.8, 127.7, 126.7, 126.3, 121.9. Data agrees with literature values.[318]

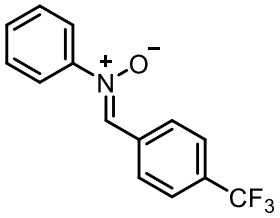
*Synthesis 1-(naphthalen-1-yl)-N-phenylmethanimine oxide (***3.86***)*



Synthesised in accordance with *GP3*, using nitrobenzene (1 mL, 9.8 mmol), 1-naphthaldehyde (1.6 mL, 11.7 mmol), NH_4Cl (678 mg, 12.7 mmol), Zn dust (1.3 g, 19.5 mmol). The crude compound was recrystallised from ethanol to afford the product (**3.86**) as an off-white solid. Yield: 1.3 g, 5.3 mmol, 54%.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 9.78 (dd, *J* = 7.6, 1.2, 1H, Ar–C**H**), 8.67 (s, 1H, C**H**), 8.04 (dd, *J* = 7.8, 1.8, 1H, Ar–C**H**), 7.92 (d, *J* = 8.2, 1H, Ar–C**H**), 7.89–7.79 (m, 3H, Ar–C**H**), 7.59 (t, *J* = 7.9, 1H, Ar–C**H**), 7.55–7.42 (m, 5H, Ar–C**H**). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 149.7, 133.4, 131.5, 130.8, 130.5, 129.9, 129.3, 129.2, 127.0, 127.0, 125.9, 125.7, 125.7, 121.9, 121.7. Data agrees with literature values.[319]

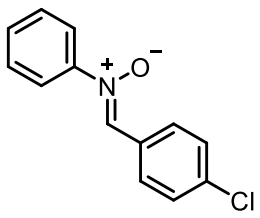
*Synthesis of N-phenyl-1-(4-(trifluoromethyl)phenyl)methanimine oxide (***3.87***)*



Synthesised in accordance with *GP3*, using nitrobenzene (1 mL, 9.8 mmol), 4-(trifluoromethyl)benzaldehyde (1.6 mL, 11.7 mmol), NH_4Cl (678 mg, 12.7 mmol), Zn dust (1.3 g, 19.5 mmol). The crude compound was recrystallised from ethanol to afford the product (**3.87**) as a white solid. Yield: 1.2 g, 4.3 mmol, 45%.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 8.51 (d, *J* = 8.2, 2H, Ar–C**H**), 8.00 (s, 1H, C**H**), 7.84–7.77 (m, 2H, Ar–C**H**), 7.73 (dd, *J* = 8.5, 1.5, 2H, Ar–C**H**), 7.54–7.47 (m, 3H, Ar–C**H**). **^{19}F NMR** (376 MHz, $CDCl_3$, 298 K) δ: -62.9. **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 149.1, 133.9, 133.2, 131.9 (q, $J_{C\text{-}F}$=32.4), 130.6, 129.5, 129.1, 125.7 (q, $J_{C\text{-}F}$=3.8), 123.9 (q, $J_{C\text{-}F}$=271.1), 121.9. Data agrees with literature values.[319]

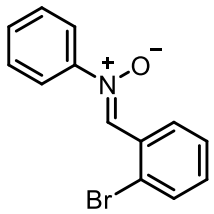
*Synthesis of 1-(4-chlorophenyl)-N-phenylmethanimine oxide (***3.88***)*



Synthesised in accordance with *GP3*, using nitrobenzene (1 mL, 9.8 mmol), benzaldehyde (0.9 mL, 8.8 mmol), NH_4Cl (678 mg, 12.7 mmol), Zn dust (1.3 g, 19.5 mmol). The crude compound was recrystallised from ethanol to afford the product (**3.88**) as a white solid. Yield: 1.3 g, 5.8 mmol, 72%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 8.43–8.29 (m, 2H, Ar–C**H**), 7.91 (s, 1H, C**H**), 7.82–7.69 (m, 2H, Ar–C**H**), 7.56–7.37 (m, 5H, Ar–C**H**). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 149.1, 136.5, 133.5, 130.3, 130.2, 129.4, 129.3, 129.1, 121.8. Data agrees with literature values.[318]

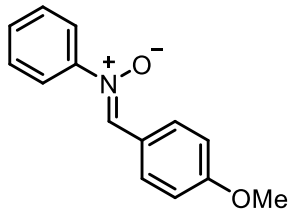
*Synthesis of 1-(2-bromophenyl)-N-phenylmethanimine oxide (***3.89***)*



Synthessed in accordance with *GP3*, using nitrobenzene (1 mL, 9.8 mmol), 2-bromobenzaldehyde (1.4 mL, 11.7 mmol), NH_4Cl (678 mg, 12.7 mmol), Zn dust (1.3 g, 19.5 mmol). The crude compound was recrystallised from ethanol to afford the product (**3.89**) as a white solid. Yield: 2.3 g, 8.2 mmol, 83%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 9.51 (dd, J = 8.0, 1.7, 1H, Ar–C**H**), 8.42 (s, 1H, C**H**), 7.85–7.74 (m, 2H, Ar–C**H**), 7.67 (dd, J = 8.0, 1.3, 1H, Ar–C**H**), 7.56–7.42 (m, 4H, Ar–C**H**), 7.30 (td, J = 7.7, 1.7, 1H, Ar–C**H**). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 149.6, 133.3, 133.1, 131.9, 130.4, 129.9, 129.7, 129.4, 128.0, 124.3, 122.0. Data agrees with literature values.[320]

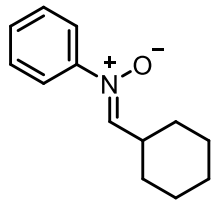
*Synthesis of 1-(4-methoxyphenyl)-N-phenylmethanimine oxide (***3.90***)*



Synthesised in accordance with *GP3*, using nitrobenzene (1 mL, 9.8 mmol), 4-methoxybenzaldehyde (1.34 mL, 11.7 mmol), NH_4Cl (678 mg, 12.7 mmol), Zn dust (1.3 g, 19.5 mmol). The crude compound was recrystallised from ethanol to afford the product (**3.90**) as a white solid. Yield: 1.1 g, 4.8 mmol, 50%.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 8.45–8.37 (m, 2H, Ar–C**H**), 7.86 (s, 1H, C**H**), 7.81–7.74 (m, 2H, Ar–C**H**), 7.52–7.40 (m, 3H, Ar–C**H**), 7.06–6.96 (m, 2H, Ar–C**H**), 3.88 (s, 3H, C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 161.6, 149.0, 134.3, 131.2, 129.7, 129.2, 123.8, 121.7, 114.1, 55.5 (**C**H_3). Data agrees with literature values.[318]

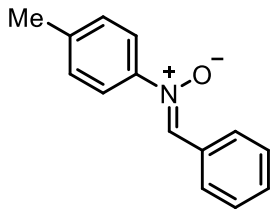
*Synthesis of 1-cyclohexyl-N-phenylmethanimine oxide (***3.91***)*



Synthesised in accordance with *GP3*, nitrobenzene (1 mL, 9.8 mmol), cyclohexanecarbaldehyde (1,4 mL, 11.7 mmol), NH_4Cl (678 mg, 12.7 mmol), Zn dust (1.3 g, 19.5 mmol). The crude compound was recrystallised from ethanol to afford the product (**3.91**) as a white solid. Yield: 1.4 g, 6.9 mmol, 70%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.67–7.61 (m, 2H, Ar–C**H**), 7.49–7.37 (m, 3H Ar–C**H**), 7.03 (d, J=7.5, 1H, C**H**), 3.21 (m, 1H, C**H**), 2.02 (m, C**H**$_2$), 1.81–1.67 (m, 3H, C**H**$_2$), 1.52–1.40 (m, 2H, C**H**$_2$), 1.29 (m, 3H, C**H**$_2$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 148.1, 143.7, 129.9, 129.2, 121.9, 35.8, 29.0, 26.1, 25.4. Data agrees with literature values.[319]

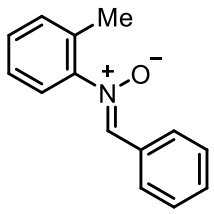
*Synthesis of 1-phenyl-N-(p-tolyl)methanimine oxide (***3.92***)*



Synthesised in accordance with *GP3*, using 4-nitrotoluene (1.0 g, 7.3 mmol), benzaldehyde (0.9 mL, 8.8 mmol), NH_4Cl (0.51 g, 9.5 mmol), Zn dust (0.95 g, 14.5 mmol). The crude compound was recrystallised from ethanol to afford the product (**3.92**) as a white solid. Yield: 1.1 g, 5.0 mmol, 67%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 8.45–8.32 (m, 2H, Ar–C**H**), 7.90 (s, 1H, C**H**), 7.66 (d, *J* = 8.1, 2H, Ar–C**H**), 7.46 (m, 3H, Ar–C**H**), 7.25 (d, *J* = 8.1, 2H, Ar–C**H**), 2.40 (s, 3H, C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 146.8, 140.2, 134.2, 130.8, 130.8, 129.7, 129.1, 128.6, 121.6, 21.2 (**C**H_3). Data agrees with literature values.[321]

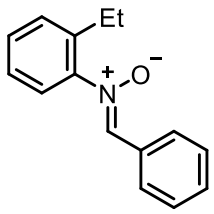
*Synthesis of N-(2-methylphenyl)-1-phenylmethanimine oxide (***3.93***)*



Synthesised in accordance with *GP3*, using 2-nitrotoluene (1.0 g, 7.3 mmol), benzaldehyde (0.9 mL, 8.8 mmol), NH_4Cl (0.51 g, 9.5 mmol), Zn dust (0.95 g, 14.5 mmol). The crude compound was recrystallised from ethanol to afford the product (**3.93**) as a white solid. Yield: 1.3 g, 5.9 mmol, 82%.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 8.41–8.32 (m, 2H, Ar–C**H**), 7.57 (s, 1H, C**H**), 7.51–7.45 (m, 3H, Ar–C**H**), 7.40 (dd, *J* = 7.6, 1.5, 1H, Ar–C**H**), 7.37–7.27 (m, 3H, Ar–C**H**), 2.44 (s, 3H, C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 148.8, 137.6, 131.9, 131.6, 131.0, 130.6, 129.5, 128.9, 128.8, 126.8, 123.5, 17.2 (**C**H_3). Data agrees with literature values.[321]

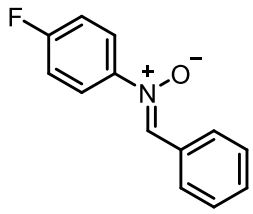
*Synthesis of N-(2-ethylphenyl)-1-phenylmethanimine oxide (***3.94***)*



Synthesised in accordance with *GP3*, using 1-ethyl-2-nitrobenzene (1.1 mL, 8 mmol), benzaldehyde (0.9 mL, 8.8 mmol), NH_4Cl (0.51 g, 9.5 mmol), Zn dust (0.95 g, 14.5 mmol). The crude compound was recrystallised from ethanol to afford the product (**3.94**) as a white solid. Yield: 1.3 g, 5.8 mmol, 72%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 8.29–8.27 (m, 2H, Ar–C**H**), 7.51 (s, 1H, C**H**), 7.41–7.40 (m, 3H, Ar–C**H**), 7.33–7.27 (m, 3H, Ar–C**H**), 7.21–7.18 (m, 1H, Ar–C**H**), 2.72 (q, J = 7.6 Hz, 2H, C**H**$_2$), 1.20 (t, J = 7.6 Hz, 3H, C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 148.4, 137.8, 137.7, 130.9, 130.5, 129.8, 129.7, 128.8, 128.7, 126.7, 123.6, 23.8 (**C**H_2), 15.1 (**C**H_3). **IR ν_{max}** (cm^{-1}): 2978, 1570, 1487, 1440, 1402, 1301, 1184. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{15}H_{16}NO]^+$: 226.1232, found 226.1228.

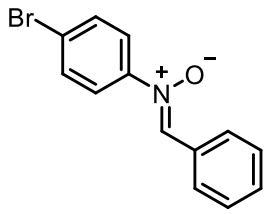
*Synthesis of N-(4-fluorophenyl)-1-phenylmethanimine oxide (***3.95***)*



Synthesised in accordance with *GP3*, using 1-ethyl-2-nitrobenzene (1.1 mL, 8 mmol), benzaldehyde (0.9 mL, 8.8 mmol), NH_4Cl (0.51 g, 9.5 mmol), Zn dust (0.95 g, 14.5 mmol). The crude compound was recrystallised from ethanol to afford the product (**3.95**) as a white solid. Yield: 1.3 g, 5.8 mmol, 66%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 8.46–8.34 (m, 2H, Ar–C**H**), 7.88 (s, 1H, C**H**), 7.78 (m, 2H, Ar–C**H**), 7.48 (m, 3H, Ar–C**H**), 7.21–7.12 (m, 2H, Ar–C**H**). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 163.1 (d, $J_{C\text{-}F}$=250.5 Hz), 145.4, 134.7, 131.2, 130.7, 129.2, 128.8, 123.8 (d, $J_{C\text{-}F}$=8.8), 116.2 (d, $J_{C\text{-}F}$=23.2). **^{19}F NMR** (471 MHz, $CDCl_3$, 298 K) δ: -110.40. Data agrees with literature values.[322]

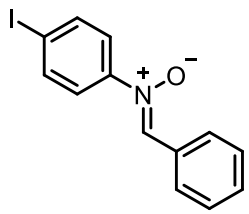
*Synthesis of N-(4-bromophenyl)-1-phenylmethanimine oxide (***3.96***)*



Synthesised in accordance with *GP3*, using 1-ethyl-2-nitrobenzene (1.1 mL, 8 mmol), benzaldehyde (0.9 mL, 8.8 mmol), NH_4Cl (0.51 g, 9.5 mmol), Zn dust (0.95 g, 14.5 mmol). The crude compound was recrystallised from ethanol to afford the product (**3.96**) as a white solid. Yield: 1.3 g, 5.8 mmol, 45%.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 8.46–8.33 (m, 2H, Ar–C**H**), 7.91 (s, 1, C**H**), 7.71–7.65 (m, 2H, Ar–C**H**), 7.63–7.58 (m, 2H, Ar–C**H**), 7.54–7.41 (m, 3H, Ar–C**H**). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 148.0 (**C**H), 134.8 (Ar–**C**H), 132.4 (Ar–**C**H), 131.4 (Ar–**C**H), 130.6 (Ar–**C**H), 129.3 (Ar–**C**H), 128.9 (Ar–**C**H), 124.0 (Ar–**C**H), 123.4 (Ar–**C**H). Data agrees with literature values.[323]

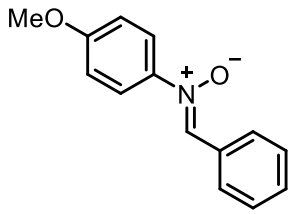
*Synthesis of N-(4-iodophenyl)-1-phenylmethanimine oxide (***3.97***)*



Synthesised in accordance with *GP3*, using 1-iodo-4-nitrobenzene (2 g, 8 mmol), benzaldehyde (0.9 mL, 8.8 mmol), NH_4Cl (0.51 g, 9.5 mmol), Zn dust (0.95 g, 14.5 mmol). The crude compound was recrystallised from ethanol to afford the product (**3.97**) as a purple solid. Yield: 2.1 g, 6.5 mmol, 81%.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 8.37 (d, *J* = 3.6 Hz, 2H, Ar–CH), 7.90 (s, 1H, CH), 7.79 (d, *J* = 8.2 Hz, 2H, Ar–CH), 7.54–7.46 (m, 5H, Ar–CH). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 148.6, 138.3, 134.7, 131.3, 130.4, 129.2, 128.8, 123.5, 95.6. **IR ν_{max}** (cm^{-1}): 3053, 2981, 1583, 1546, 1477, 1444, 1413, 1190, 1066. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{13}H_{11}NOI]^+$: 323.9885, found 323.9888.

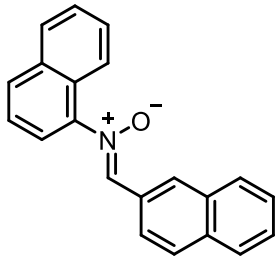
*Synthesis of N-(4-methoxyphenyl)-1-phenylmethanimine oxide (***3.98***)*



Synthesised in accordance with *GP3*, using 1-ethyl-2-nitrobenzene (1.1 mL, 8 mmol), benzaldehyde (0.9 mL, 8.8 mmol), NH_4Cl (0.51 g, 9.5 mmol), Zn dust (0.95 g, 14.5 mmol). The crude compound was recrystallised from ethanol to afford the product (**3.98**) as a white solid. Yield: 1.3 g, 5.8 mmol, 52%.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 8.43–8.26 (m, 2H, Ar–C**H**), 7.88 (s, 1H, C**H**), 7.78–7.68 (m, 2H, Ar–C**H**), 7.53–7.44 (m, 3H, Ar–C**H**), 7.02–6.90 (m, 2H, Ar–C**H**), 3.87 (s, 3H, OC**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 160.8, 142.6, 133.8, 131.0, 130.9, 129.1, 128.8, 123.1, 114.2, 55.8 (O**C**H_3). Data agrees with literature values.[323]

*Synthesis of N-(naphthalen-1-yl)-1-(naphthalen-2-yl)methanimine oxide (***3.99***)*



Synthesised in accordance with *GP3*, using 1-nitronaphtalene (1.4 g, 8 mmol), 2-Naphthaldehyde (1.4 g, 8.8 mmol), NH_4Cl (513 mg, 9.6 mmol), Zn dust (1.1 g, 16 mmol). The crude compound was recrystallised from ethyl acetate to afford the product (**3.99**) as a yellow solid. Yield: 1.3 g, 4.4 mmol, 55%.

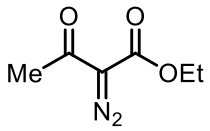
^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 9.52 (s, 1H, Ar–C**H**), 8.20–8.19 (m, 1H, Ar–C**H**), 8.03–7.87 (m, 7H, Ar–C**H** and C**H**), 7.67 (d, J = 7.2 Hz, 1H, Ar–C**H**), 7.59–7.52 (m, 5H, Ar–C**H**). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 146.2, 138.9, 134.6, 134.4, 133.3, 130.1, 129.6, 129.2, 128.3, 128.2, 127.9, 127.84, 127.82, 127.7, 127.2, 127.1, 126.8, 126.2, 125.0, 122.9, 120.5. **IR ν_{max}** (cm^{-1}): 3057, 1693, 1598, 1556, 1506, 1402, 1388, 1379, 1361, 1350, 1267, 1228, 1217, 1170, 1163, 1128, 1116, 1060, 1022. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{21}H_{16}NO]^+$: 298.1232; found 298.1227.

6.1.6. Chapter 3: Synthesis and characterisation of diazo ester starting materials

General procedure 4 (GP4): Following a slightly modified literature reported procedure,[13] α-diazo-β-keto ester (1 equiv.) and anhydrous triethylamine (1.2 equiv.) were dissolved in 5 mL/mmol of anhydrous dichloromethane. The reaction mixture was cooled to 0 °C and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.1 equiv.) was added dropwise. The reaction was allowed to warm to room temperature and was stirred for up to 24 hours. After completion (monitored by TLC), the reaction was diluted with ethyl acetate (30 mL) and quenched with saturated $NaHCO_3$. The organic layer was washed with water (2 × 40 mL), brine (1 × 40 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude compound was purified *via* a silica plug using silica gel (Merck, 60 Å, 230–400 mesh particle size) and hexane/ethyl acetate as eluent.

In most of the products the α-carbon of the diazo functionality could not be observed in the ^{13}C NMR.

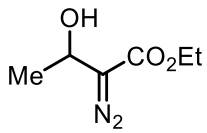
*Synthesis of ethyl 2-diazo-3-oxobutanoate (***3.44***)*



Synthesised in accordance with a reported procedure,[324] ethyl acetoacetate (46.1 mmol, 5.9 mL, 1 equiv.) was dissolved in 60 mL of an anhydrous THF. Then, *p*-ABSA was added in one portion (50.7 mmol, 12.2 g, 1.1 equiv.) The mixture was then cooled to 0 °C and triethyl amine was added dropwise (55.3 mmol., 7.7 mL, 1.2 eq.). The resulting solution was stirred at room temperature for 18 hours after which it was quenched with NH_4Cl and extracted with EtoAc (3 × 20 mL). The organic fractions were then collected, dried using a rotary evaporator, and the crude residue was purified *via* a silicon plug using 90:10 hexane/EtOAc as eluent. The compound (**3.44**) was obtained as a yellow oil. Yield: 4.25 g, 27.2 mmol, 60%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 4.30 (q, J = 7.1, 2H, C**H**$_2$), 2.48 (s, 3H, C**H**$_3$), 1.33 (t, J = 7.1, 3H, C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 190.4, 161.6, 61.6, 28.4, 14.5. Data agrees with literature values.[324]

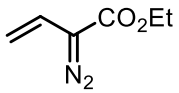
*Synthesis of ethyl 2-diazo-3-hydroxybutanoate (***3.45***)*



Synthesised in accordance with a reported procedure,[324] ethyl 2-diazo-3-oxobutanoate (2.00 g, 12.8 mmol, 1 equiv.), was dissolved in 20 mL of dry MeOH. The solution was cooled to 0 °C and then $NaBH_4$ (0.97 g, 25.6 mmol, 2 equiv.) was added portionwise. The reaction was let to stir for 30 minutes at 0 °C and then an additional hour at room temperature. The mixture was then quenched with distilled H_2O and extracted with EtOAc (3 × 30 mL). The organic fractions were then collected and dried using a rotary evaporator affording a crude orange oil which was purified *via* column chromatography using hexane/ethyl acetate (80:20 v/v) as eluent. The compound (**3.45**) was obtained as a yellow oil. Yield: 1.30 g, 8.2 mmol, 64%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 5.01–4.86 (m, 1H, C**H**), 4.25 (m, 2H, C**H**$_2$), 2.76 (br. s, 1H, O**H**), 1.40 (dd, *J* = 6.6, 0.9, 3H, C**H**$_3$), 1.28 (td, *J* = 7.1, 0.9, 3H, C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 166.7 (**C**=O), 62.7, 61.2, 19.7, 14.6. Data agrees with literature values.[324]

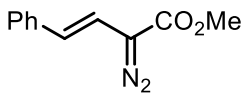
*Synthesis of ethyl 2-diazobut-3-enoate (***3.46***)*



Synthesised in accordance with a reported procedure,[324] ethyl 2-diazo-3-hydroxybutanoate (1.3 g, 8.2 mmol, 1 equiv.) was dissolved in 60 mL of dry CH_2Cl_2. Triethylamine was then added (4.6 mL, 32.9 mmol, 4 equiv.) and the resulting solution was cooled to 0 °C. Next, $POCl_3$ (1.2 ml, 12.3 mmol, 1.5 equiv.) was added dropwise. The reaction was left to stir overnight at room temperature, after which it was directly filtered through a silica plug to remove the excess of triethylamine. The crude oil was finally purified via column chromatography using hexane/ethyl acetate (90:10 v/v) as eluent. The compound (**3.46**) was obtained as a red oil. Yield: 640 mg, 4.6 mmol, 56%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 6.17 (dd, *J* = 17.4, 11.0, 1H, C**H**), 5.11 (d, *J* = 11.2, 1H, C$\mathbf{H}_2$), 4.85 (d, *J* = 17.4, 1H, C$\mathbf{H}_2$), 4.27 (q, *J* = 7.1, 1H, C$\mathbf{H}_2$), 1.30 (t, *J* = 7.1, 3H, C$\mathbf{H}_3$) **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 165.1 (**C**=O), 120.7 (**C**H_2), 107.5 (**C**H), 61.3 (**C**H_2), 14.6 (**C**H_3). Data agrees with literature values.[324]

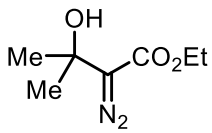
*Synthesis of methyl (E)-2-diazo-4-phenylbut-3-enoate (***3.100***)*



1,8-Diazabicyclo[5.4.0]undec-7-ene (1.1 mL, 7.2 mmol, 1.2 equiv.) was added dropwise into a solution of (3*E*)-4-phenylbut-3-enoic acid methyl ester (1.0 mL, 6 mmol., 1 equiv.) and 4-acetamidobenzenesulfonyl azide (2.0 g, 8.3 mmol, 1.4 equiv.) in 40 mL of anhydrous acetonitrile at 0 °C. Upon complete addition, the reaction mixture was stirred for an additional 2 hours at 0 °C and subsequently quenched with saturated NH_4Cl (25 mL). The organics were extracted with diethyl ether (3 × 30 mL), washed with brine (1 × 40 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified *via* column chromatography using silica gel (Merck, 60 Å, 230–400 mesh particle size) and hexane/ethyl acetate (92:8 v/v) as eluent. The compound (**3.100**) was obtained as a red solid. Yield: 920 mg, 4.5 mmol, 76%.

^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ: 7.39–7.27 (m, 4H, Ar–C**H**), 7.24–7.16 (m, 1H, Ar–C**H**), 6.48 (d, *J* = 16.2, 1H, C**H**), 6.20 (d, *J* = 16.3, 1H, C**H**), 3.86 (s, 3H, C$\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$, 298 K) δ: 136.9, 128.8, 127.2, 126.0, 123.2, 111.4, 52.5. Data agrees with literature values.[189]

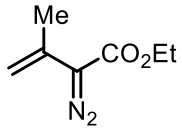
*Synthesis of ethyl 2-diazo-3-hydroxy-3-methylbutanoate (***3.101***)*



Following the reported method,[194] a solution of acetone (0.74 mL, 10 mmol, 1 equiv.) and ethyl diazo acetate (15% in toluene, 8.5 mL, 10 mmol, 1 equiv.) in THF (20 mL) was cooled to -78 °C. To this solution, lithium diisopropylamide (1M in THF, 12 ml, 12 mmol, 1.2 equiv.) was added dropwise. The resulting orange solution was quenched with water after stirring at -78 °C for 2 hours. The crude reaction mixture was extracted with EtOAc (3 × 20 mL) after which the organic layers were combined, treated with brine, and dried over $MgSO_4$. The solvent was then evaporated using a stream of compressed air giving 1.58 g of ethyl 2-diazo-3-hydroxy-3-methylbutanoate (**3.101**) as yellow oil (92%). The intermediate was stored at -50 °C until needed for the second step.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 4.24 (q, *J* = 7.1, 2H, C**H**$_2$), 3.79 (br. s, 1H, O**H**), 1.51 (s, 6H, C**H**$_3$), 1.28 (t, *J* = 7.1, 3H, C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 167.4 (**C**=O), 68.7, 61.0, 28.8, 14.6. Data agrees with literature values.[194]

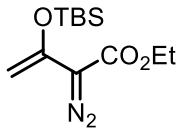
*Synthesis of ethyl 2-diazo-3-methylbut-3-enoate (***3.102***)*



A solution of ethyl 2-diazo-3-hydroxy-3-methylbutanoate (0.34 g, 2 mmol, 1 equiv.,) and triethylamine (2.8 mL, 20 mmol, 10 equiv.) in CH_2Cl_2 (20 mL) was cooled to 0 °C. Separately, $POCl_3$ (0.37 mL, 4 mmol, 2 equiv.) was dissolved in 8 mL of CH_2Cl_2 which was then added dropwise to the reaction mixture. The reaction was stirred at 0 °C for an additional 5 min before letting it warm to room temperature. The progress of the reaction was checked by TLC (~20 hours). After completion, the reaction mixture was filtered, and the solvent removed. The crude product was purified by flash chromatography using 9:1 Hexane:EtOAc to give ethyl 2-diazo-3-methylbut-3-enoate (**3.102**) as a yellow oil (170 mg, 1.1 mmol, 55%). The product was immediately used for the cycloaddition reaction due to its reported instability.

^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ: 5.35 (m, 1H, C**H**), 4.89 (qd, *J* = 1.5, 1.1, 1H, C**H**), 4.25 (q, *J* = 7.1, 2H, C$\mathbf{H}_2$), 1.94 (dd, *J* = 1.5, 0.7, 3H, C$\mathbf{H}_3$), 1.29 (t, *J* = 7.1, 3H, C$\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$, 298 K) δ: 165.4 (**C**=O), 127.3, 110.2, 60.9, 21.4, 14.6. Data agrees with literature values.[194]

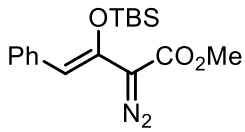
*Synthesis of ethyl 3-((tert-butyldimethylsilyl)oxy)-2-diazobut-3-enoate (***3.66***)*



Synthesised in accordance with ***GP4***, using methyl 2-diazo-3-oxobutanoate (1.4 g, 10 mmol, 1 equiv.), triethylamine (1.7 mL, 12 mmol, 1.2 equiv.), and *tert*-butyldimethylsilyl trifluoromethanesulfonate (2.5 mL, 11 mmol, 1.1 equiv.) in 50 mL of dry dichloromethane. The crude compound was purified *via* a silica plug using hexane/ethyl acetate (95:5 v/v) as eluent. The compound (**3.66**) was obtained as a red oil. Yield: 2.4 g, 8.8 mmol, 88%

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 4.98 (d, *J* = 1.8 Hz, 1H, C**H**), 4.25–4.18 (m, 3H, C**H**+C$\mathbf{H}_2$), 1.27 (t, *J* = 7.2 Hz, 3H, C$\mathbf{H}_3$), 0.91 (s, 9H, TBS), 0.21(s, 6H, TBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 164.9, 152.9, 113.7, 82.3, 60.4, 22.5, 18.0, 14.2, -5.2. Data agrees with literature values.[325]

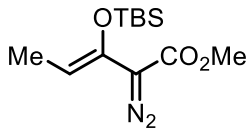
*Synthesis of methyl (Z)-3-((tert-butyldimethylsilyl)oxy)-2-diazopent-3-enoate (***3.103***)*



Synthesised in accordance with ***GP4***, using methyl 2-diazo-3-oxopentanoate (0.8 g, 4.9 mmol, 1 equiv.), triethylamine (0.8 mL, 5.9 mmol, 1.2 equiv.), and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.2 mL, 5.4 mmol, 1.1 equiv.) in 20 mL of dry dichloromethane. The crude compound was purified *via* a silica plug using hexane/ethyl acetate (98:2 v/v) as eluent. The compound (**3.103**) was obtained as a red oil. Yield: 1.0 g, 3.7 mmol, 75%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.49 (m, 2H, Ar–C**H**), 7.28–7.23 (m, 2H, Ar–C**H**), 7.16–7.12 (m, 1H, Ar–C**H**), 6.38 (s, 1H, C**H**), 3.84 (s, 3H, C$\mathbf{H}_3$), 0.95 (s, 9H, TBS), -0.07 (s, 6H, TBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 165.1, 136.4, 133.9, 129.2, 128.0, 126.3, 111.4, 52.2, 25.9, 18.3, -4.7. Data agrees with literature values.[326]

*Synthesis of methyl (Z)-3-((tert-butyldimethylsilyl)oxy)-2-diazo-4-phenylbut-3-enoate (**3.68**)*



Synthesised in accordance with ***GP4***, methyl 2-diazo-3-oxo-4-phenylbutanoate (1.6 g, 7.5 mmol, 1 equiv.), triethylamine (1.3 mL, 9.0 mmol, 1.2 equiv.), and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.9 mL, 8.3 mmol, 1.1 equiv.) in 35 mL of dry dichloromethane. The crude compound was purified via column chromatography using hexane/ethyl acetate (98:2 v/v) as eluent. The compound (**3.68**) was obtained as an orange solid. Yield: 2.4 g, 7.2 mmol, 96%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 5.25 (q, *J* = 7.0, 1H, C**H**), 3.78 (s, 3H, C**H**$_3$), 1.67 (d, *J* = 7.0, 3H, C**H**$_3$), 0.96 (s, 9H, TBS), 0.15 (s, 6H, TBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 165.6, 148.7, 110.1, 52.0, 25.8, 18.4, 12.0, -4.5. Data agrees with literature values.[194]

6.1.7. Chapter 3: Synthesis and characterisation of products

General procedure 5 (GP5): Tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] (20 mol%), nitrone (1 equiv.) and 4 Å MS were charged in a microwave vial and then dissolved in 0.5 mL of anhydrous toluene. The mixture was stirred for 5 minutes at room temperature. Subsequently, vinyldiazo ester (2 equiv.), dissolved in 0.8 mL of anhydrous toluene, was added *via* syringe pump for 30 minutes into the reaction mixture. After complete addition, the reaction was heated to 40 °C and stirred in the dark for up to 24 hours. After completion, all volatiles were evaporated, and the crude compound was purified *via* preparative thin layer chromatography using hexane/ethyl acetate as eluent.

General procedure 6 (GP6): Tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] (10 mol%), nitrone (1 equiv.) and 4 Å MS were charged in a microwave vial and then dissolved in 0.5 mL of anhydrous toluene. The mixture was stirred for 5 minutes at 0°C. Subsequently, enoldiazo ester (2 equiv.) was dissolved in 0.8 mL of anhydrous toluene and was added *via* syringe pump for 30 minutes into the reaction mixture. After complete addition, the reaction was allowed to reach room temperature over the course

of 3 hours and stirred for up to 24 hours. After completion, all volatiles were evaporated, and the crude compound was purified *via* preparative thin layer chromatography using hexane/ethyl acetate as eluent.

3.9.3.1 Synthesis and Spectral Characterisation of Isoxazolidine-Derived Diazo Products

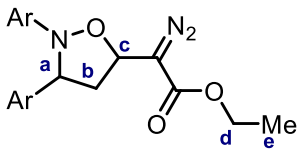
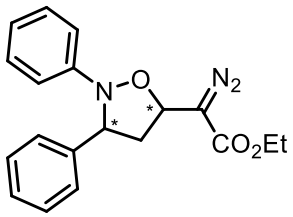


Figure 3.9.3.1.1. Labelling of isoxazolidine-derived diazo products

The characteristic protons and carbons were assigned according to the labelling in the general structure in Figure S2. Peak assignment has been done by carrying out 2D-NMR analysis on compounds **3.62**.

In most of the products the α-carbon of the diazo functionality could not be observed in the ^{13}C NMR.

*Synthesis of (±)-ethyl 2-diazo-2-(2,3-diphenylisoxazolidin-5-yl)acetate (***3.47***)*



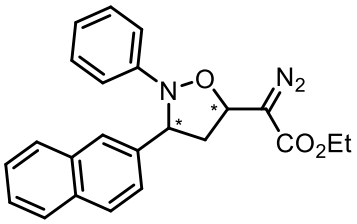
Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.42** (20 mg, 0.1 mmol), vinyldiazo ester **3.46** (28 mg, 0.2 mmol) in toluene to afford **3.47**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.47**) was obtained as an inseparable mixture of diastereoisomers (91:9) as a yellow oil. Yield: 25 mg, 0.07 mmol, 74 %.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.50–7.47 (m, Ar–C**H**), 7.41–7.37 (m, Ar–C**H**), 7.32–7.25 (m, Ar–C**H**), 7.22–7.19 (m, Ar–C**H**), 7.05–7.03 (m, Ar–C**H**), 6.98–6.92 (m, Ar–C**H**), 5.36 (t, J = 7.3 Hz, 1H, C**H**^{c}, major isomer), 5.23 (dd, J = 8.8, 6.8 Hz, C**H**^{c}, minor isomer), 4.87–4.84 (m, C**H**^{a}, minor

isomer), 4.69 (dd, J = 8.3, 5.5 Hz, 1H, C**H**^{a}, major isomer), 4.30–4.24 (m, C**H**$_2^{d}$), 3.08 (ddd, J = 12.5, 8.2, 6.8 Hz, C**H**^{b}, minor isomer), 2.71–2.60 (m, 2H, C**H**^{b}, major isomer), 2.26 (ddd, J = 12.5, 8.8, 6.6 Hz, C**H**^{b}, minor isomer), 1.30 (t, J = 7.1 Hz, C**H**$_3^{e}$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 165.3 (**C**=O), 151.6, 150.7, 141.9, 141.2, 129.1, 129.06, 129.03, 128.8, 127.8, 127.7, 126.7, 126.3, 122.3, 122.2, 115.6, 114.8, 72.9, 72.7, 70.9, 69.0, 61.3, 42.9, 41.7, 14.6. **IR ν_{max}** (cm^{-1}): 2981, 2935, 2094 (C=N_2), 1691 (C=O), 1597, 1489, 1450, 1371, 1298, 1259, 1244, 1109, 1026. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{19}H_{20}N_3O_3]^+$: 338.1505, found: 338.1504.

*Synthesis of (±)-ethyl 2-diazo-2-(3-(naphthalen-2-yl)-2-phenylisoxazolidin-5-yl)acetate (**3.48**)*

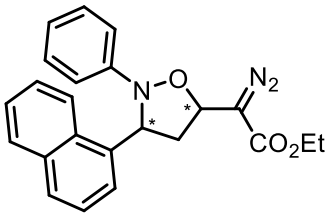
Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.85** (25 mg, 0.1 mmol), vinyldiazo ester **3.46** (28 mg, 0.2 mmol) in toluene to afford **3.48**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.48**) was obtained as a yellow oil. Yield: 33 mg, 0.08 mmol, 85 %.



^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.96 (s, 1H, Ar–C**H**), 7.89–7.83 (m, 3H, Ar–C**H**), 7.61 (dd, J = 8.5, 1.8 Hz, 1H, Ar–C**H**), 7.52–7.48 (m, 2H, Ar–C**H**), 7.22–7.18 (m, 2H, Ar–C**H**), 7.01–6.99 (m, 2H, Ar–C**H**), 6.95– 6.92 (m, 1H, Ar–C**H**), 5.42 (t, J = 7.3 Hz, 1H, C**H**^{c}), 4.84 (dd, J = 8.5, 5.7 Hz, 1H, C**H**^{a}), 4.28 (m, 2H, C**H**$_2^{d}$), 2.78–2.68 (m, 2H, C**H**^{b}), 1.30 (t, J = 7.1 Hz, 3H, C**H**$_3^{e}$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 150.7, 138.6, 133.5, 133.1, 129.0, 128.8, 128.1, 127.8, 126.5, 126.2, 125.7, 124.6, 122.3, 115.6, 72.9 (**C**H^{c}), 69.3 (**C**H^{a}), 61.4 (**C**H$_2^{d}$), 41.8 (**C**H$_2^{b}$), 14.6 (**C**H$_3^{e}$). **IR ν_{max}** (cm^{-1}): 3059, 2983, 2096 (C=N_2), 1693 (C=O), 1597, 1489, 1373, 1300, 1242, 1109, 1018. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{23}H_{22}N_3O_3]^+$: 388.1661, found 388.1660.

The C=O carbon could not be observed.

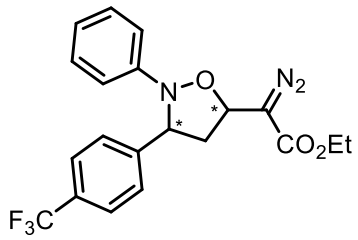
*Synthesis of (±)-ethyl 2-diazo-2-(3-(naphthalen-1-yl)-2-phenylisoxazolidin-5-yl)acetate (**3.49**)*



Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.86** (25 mg, 0.1 mmol), vinyldiazo ester **3.46** (28 mg, 0.2 mmol) in toluene to afford **3.49**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.49**) was obtained as an inseparable mixture of diastereoisomers (68:32) as a yellow oil. Yield: 32 mg, 0.08 mg, 83%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 8.07 (d, *J* = 8.6 Hz, Ar–C**H**), 8.02 (d, *J* = 8.6 Hz, Ar–C**H**), 7.98–7.94 (m, Ar–C**H**), 7.85–7.83 (m, Ar–C**H**), 7.59–7.49 (m, Ar–C**H**), 7.28 (dd, *J* = 8.8, 7.3 Hz, Ar–C**H**), 7.21 (dd, *J* = 8.8, 7.3 Hz, Ar–C**H**), 7.09 (dd, *J* = 8.8, 1.1 Hz, Ar–C**H**), 6.99– 6.92 (m, Ar–C**H**), 5.54 (dd, *J* = 8.5, 6.3 Hz, C**H**^{c}, minor isomer), 5.42 (dd, *J* = 8.9, 4.7 Hz, 1H, C**H**^{c}, major isomer), 5.37 (dd, *J* = 8.1, 6.7 Hz, C**H**^{a}), 4.28 (m, 2H, C**H**$_2$^{d}), 3.33 (ddd, *J* = 12.6, 8.5, 7.0 Hz, C**H**^{b}, minor isomer), 2.91 (dt, *J* = 12.5, 8.5 Hz, 1H, C**H**^{b}, major isomer), 2.62 (ddd, *J* = 12.5, 6.8, 4.7 Hz, 1H, C**H**^{b}, major isomer), 2.26 (ddd, *J* = 12.6, 8.7, 6.3 Hz, C**H**^{b}, minor isomer), 1.31 (t, *J* = 7.1 Hz, C**H**$_3$^{e}). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 165.3 (**C**=O), 151.8, 150.9, 137.2, 136.4, 134.19, 134.16, 130.16, 130.10, 129.38, 129.34, 129.2, 128.8, 128.29, 128.28, 126.5, 126.4, 126.09, 126.06, 125.8, 125.7, 124.3, 123.7, 122.97, 122.90, 122.1, 122.0, 115.2, 114.6, 73.0, 72.9, 68.6, 66.4, 61.3, 42.1, 40.4, 14.6. **IR ν_{max}** (cm^{-1}): 3059, 2980, 2096 (C=N_2), 1689 (C=O), 1597, 1489, 1396, 1373, 1300, 1259, 1244, 1114. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{23}H_{22}N_3O_3]^+$: 388.1661; found 388.1656.

*Synthesis of (±)-ethyl 2-diazo-2-(2-phenyl-3-(4-(trifluoromethyl)phenyl)isoxazolidin-5-yl)acetate (**3.50**)*

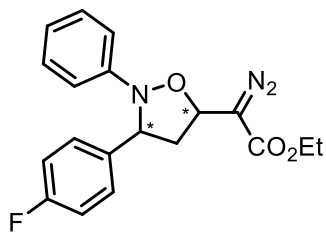


Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.87** (27 mg, 0.1 mmol), vinyldiazo ester **3.46** (28 mg, 0.2 mmol) in toluene to afford **3.50**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.50**) was obtained as a yellow oil. Yield: 31 mg, 0.07 mmol, 76%,

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.65–7.61 (m, 4H, Ar–C**H**), 7.23 (dd, *J* = 8.7, 7.4 Hz, 2H, Ar–C**H**), 6.98–6.92 (m, 3H, Ar–C**H**), 5.34 (t, *J* = 7.4 Hz, 1H, C**H**^{c}), 4.78 (dd, *J* = 8.6, 5.0 Hz, 1H, C**H**^{a}), 4.27 (m, C**H**$_2^d$), 2.73 (dt, *J* = 12.8, 8.2 Hz, 1H, C**H**^{b}), 2.59 (ddd, *J* = 12.6, 7.3, 5.1 Hz, 1H, C**H**^{b}), 1.29 (t, *J* = 7.1 Hz, 3H, C**H**$_3^e$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 165.2 (**C**=O), 150.3, 145.3, 145.3, 130.2 (q, $J_{C–F}$ = 32.5 Hz), 128.9, 127.1, 126.0 (q, $J_{C–F}$ = 3.8 Hz), 122.6, 115.5, 73.1 (**C**H^c), 68.5 (**C**H^a), 61.4 (**C**H$_2^d$), 41.3 (**C**H$_2^b$), 14.6 (**C**H$_3^e$). **^{19}F NMR** (471 MHz, $CDCl_3$, 298 K) δ: -62.51. **IR ν_{max}** (cm^{-1}): 2987, 2939, 2096 (C=N_2), 1691 (C=O), 1597, 1489, 1373, 1323, 1301, 1165, 1120, 1109, 1066, 1016. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{20}H_{19}N_3O_3F_3]^+$: 406.1379, found 406.1375.

The C=O carbon could not be observed.

*Synthesis of (±)-ethyl 2-diazo-2-(3-(4-fluorophenyl)-2-phenylisoxazolidin-5-yl)acetate (**3.51**)*



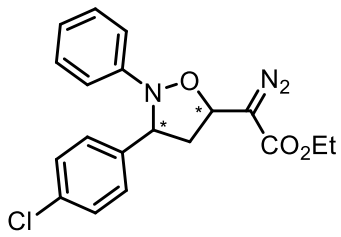
Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.65** (22 mg, 0.1 mmol), vinyldiazo ester **3.46** (28 mg, 0.2 mmol) in toluene to afford **3.51**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography

using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.51**) was obtained as a yellow oil. Yield: 29 mg, 0.08 mmol, 82%.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ:7.47–7.44 (m, 2H, Ar–C**H**), 7.23–7.19 (m, 2H, Ar–C**H**), 7.06–7.04 (m, 2H, Ar–C**H**), 6.97–6.93 (m, 3H, Ar–C**H**), 5.34 (t, *J* = 7.4 Hz, 1H, C**H**^{c}), 4.67 (dd, *J* = 8.3, 5.3 Hz, 1H, C**H**^{a}), 4.27 (m, 2H, C**H**$_2$^{d}), 2.70–2.55 (m, 2H, C**H**$_2$^{b}), 1.29 (t, *J* = 7.1 Hz, 3H, C**H**$_3$^{e}). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 162.4 (d, $J_{C–F}$ = 246.2 Hz), 150.4, 136.8 (d, $J_{C–F}$ = 3.2 Hz), 128.8, 128.4 (d, $J_{C–F}$ = 8.1 Hz), 122.5, 116.0, 115.7, 72.9 (**C**H^a), 68.4 (**C**H^c), 61.4 (**C**H$_2$^{d}), 41.6 (**C**H$_2$^{b}), 14.6 (**C**H$_3$^{e}). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: -114.67. **IR ν_{max}** (cm^{-1}): 2987, 2931, 2096 (C=N_2), 1693 (C=O), 1598, 1508, 1489, 1373, 1300, 1261, 1224, 1174, 1157, 1112, 1097, 1014. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{19}H_{19}N_3O_3F]^+$: 356.1410, found 356.1411.

The C=O carbon could not be observed.

*Synthesis of (±)-ethyl 2-diazo-2-(3-(4-fluorophenyl)-2-phenylisoxazolidin-5-yl)acetate (**3.52**)*



Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.88** (23 mg, 0.1 mmol), vinyldiazo ester **3.46** (28 mg, 0.2 mmol) in toluene to afford **3.52**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.52**) was obtained as a yellow oil. Yield: 30 mg, 0.08 mmol, 84%.

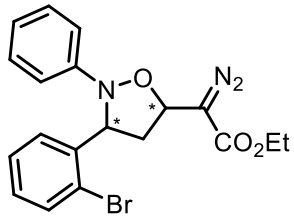
^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.43 (d, *J* = 8.2 Hz, 2H, Ar–C**H**), 7.35 (d, *J* = 8.6 Hz, 2H, Ar–C**H**), 7.23–7.19 (m, 2H, Ar–C**H**), 6.97–6.92 (m, 3H, Ar–C**H**), 5.33 (t, *J* = 7.4 Hz, 1H, C**H**^{c}), 4.67 (dd, *J* = 8.4, 5.2 Hz, 1H, C**H**^{a}), 4.26 (q, *J* = 7.1 Hz, 2H, C**H**$_2$^{d}), 2.71–2.53 (m, 2H, C**H**$_2$^{b}), 1.29 (t, *J* = 7.1 Hz, 3H, C**H**$_3$^{e}). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 150.3, 139.6, 133.6, 129.1, 128.9, 128.2, 122.5, 115.7, 72.9 (**C**H^c), 68.4 (**C**H^a), 61.4 (**C**H$_2$^{d}), 41.5 (**C**H$_2$^{b}), 14.6 (**C**H$_3$^{e}). **IR ν_{max}** (cm^{-1}): 2985,

2937, 2096 (C=N_2), 1693 (C=O), 1597, 1489, 1398, 1373, 1300, 1261, 1209, 1172, 1111, 1089, 1056, 1014. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{19}H_{19}N_3O_3Cl]^+$: 372.1115, found 372.1115.

The C=O carbon could not be observed.

*Synthesis of (±)-ethyl 2-(3-(2-bromophenyl)-2-phenylisoxazolidin-5-yl)-2-diazoacetate (**3.53**)*

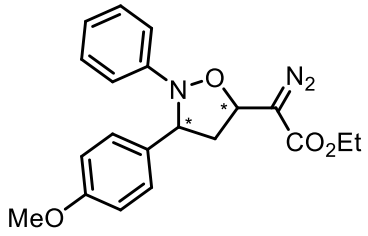
Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.89** (28 mg, 0.1 mmol), vinyldiazo ester **3.46** (28 mg, 0.2 mmol) in toluene to afford **3.53**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.53**) was obtained as a yellow oil. Yield: 27, mg, 0.06 mmol, 65%.



^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.81 (d, *J* = 7.8 Hz, 1H, Ar–C**H**), 7.60 (d, *J* = 8.0 Hz, 1H, Ar–C**H**), 7.35 (t, *J* = 7.6 Hz, 1H, Ar–C**H**), 7.24–7.16 (m, 3H, Ar–C**H**), 6.96–6.92 (m, 3H, Ar–C**H**), 5.31 (t, *J* = 7.5 Hz, 1H, C**H**^{c}), 5.10 (dd, *J* = 8.6, 4.3 Hz, 1H, C**H**^{a}), 4.27 (q, *J* = 7.1 Hz, 2H, C**H**$_2^d$), 2.79–2.72 (m, 1H, C**H**^{b}), 2.54–2.48 (m, 1H, C**H**^{b}), 1.29 (t, *J* = 7.1 Hz, 3H, C**H**$_3^e$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 150.6, 140.3, 132.9, 129.2, 128.9, 128.6, 128.2, 122.16, 122.10, 114.9, 73.1 (**C**H^c), 68.3 (**C**H^a), 61.4 (**C**H$_2^d$), 39.7 (**C**H$_2^b$), 14.6 (**C**H$_3^e$). **IR ν_{max}** (cm^{-1}): 2094 (C=N_2), 1693 (C=O), 1597, 1489, 1257, 1244, 1022. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{19}H_{19}N_3O_3Br]^+$: 416.0610, found 416.0610.

The C=O carbon could not be observed.

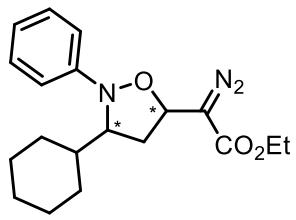
*Synthesis of (±)-ethyl 2-diazo-2-(3-(4-methoxyphenyl)-2-phenylisoxazolidin-5-yl)acetate (**3.54**)*



Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.90** (23 mg, 0.1 mmol), vinyldiazo ester **3.46** (28 mg, 0.2 mmol) in toluene to afford **3.54**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.54**) was obtained as an off-white solid. Yield: 25 mg, 0.06 mmol, 68%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.39 (d, *J* = 8.9 Hz, 2H, Ar–C**H**), 7.21–7.18 (m, 2H, Ar–C**H**), 6.96–6.90 (m, 5H, Ar–C**H**), 5.35 (t, *J* = 7.3 Hz, 1H, C**H**^{c}), 4.61 (dd, *J* = 8.1, 5.7 Hz, 1H, C**H**^{a}), 4.29–4.25 (m, 2H, C**H**$_2$^{d}), 3.81 (s, 3H, Ar–OC**H**$_3$), 2.67–2.57 (m, 2H, C**H**$_2$^{b}), 1.30 (t, *J* = 7.1 Hz, 3H, C**H**$_3$^{e}). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 165.4 (**C**=O), 159.2, 150.6, 133.0, 128.7, 128.0, 122.4, 115.8, 114.3, 72.7(**C**H^c), 68.7 (**C**H^a), 61.3 (**C**H$_2$^{d}), 55.4 (Ar–O**C**H$_3$), 41.8 (**C**H$_2$^{b}), 14.6 (**C**H$_3$^{e}). **IR ν_{max}** (cm^{-1}): 2983, 2929, 2096 (C=N$_2$), 1693 (C=O), 1612, 1598, 1512, 1373, 1300, 1246, 1174, 1111, 1033. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{20}H_{22}N_3O_4]^+$: 368.1610, found 368.1609.

*Synthesis of (±)-ethyl 2-(3-cyclohexyl-2-phenylisoxazolidin-5-yl)-2-diazoacetate (**3.55**)*

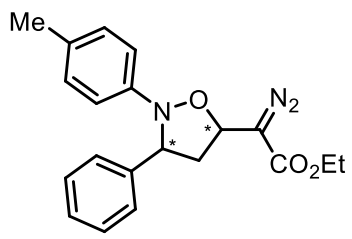


Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.91** (20 mg, 0.1 mmol), vinyldiazo ester **3.46** (28 mg, 0.2 mmol) in toluene to afford **3.55**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.55**) was obtained as a yellow solid. Yield: 30 mg, 0.08 mmol, 87%

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.25–7.22 (m, 2H, Ar–C**H**), 6.99– 6.97 (m, 2H, Ar–C**H**), 6.91–6.88 (m, 1H, Ar–C**H**), 5.31 (t, *J* = 7.3 Hz, 1H, C**H**^{c}), 4.25 (q, *J* = 7.1 Hz, 2H, C**H**$_2$^{d}), 3.56 (td, *J*

= 8.0, 3.2 Hz, 1H, C**H**[a]), 2.48 (ddd, *J* = 13.1, 7.6, 3.3 Hz, 1H, C**H**), 2.07–1.98 (m, 2H, C**H**$_2$), 1.82–1.78 (m, 3H, C**H**), 1.73– 1.70 (m, 1H, C**H**), 1.59– 1.55 (m, 2H, C**H**), 1.28 (t, *J* = 7.1 Hz, 3H, C**H**$_3$[e]), 1.26–1.05 (m, 4H, C**H**). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 165.6 (**C**=O), 152.6, 128.9, 121.3, 114.2, 74.9, 70.6, 61.3, 41.1, 33.4, 30.8, 29.8, 26.5, 26.2, 14.6 (**C**H_3[e]). **IR ν_{max}** (cm^{-1}): 2924, 2852, 2092 (C=N_2), 1693 (C=O), 1597, 1485, 1448, 1251. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{19}H_{26}N_3O_3]^+$: 344.1974, found 344.1975.

*Synthesis of (±)-ethyl 2-diazo-2-(3-phenyl-2-(p-tolyl)isoxazolidin-5-yl)acetate (**3.56**)*

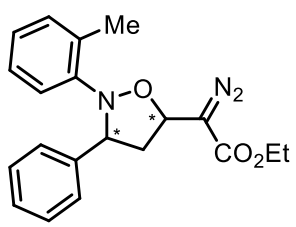


Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.92** (21 mg, 0.1 mmol), vinyldiazo ester **3.46** (28 mg, 0.2 mmol) in toluene to afford **3.56**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.56**) was obtained as a yellow oil. Yield: 26 mg, 0.07 mmol, 74%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.48 (d, *J* = 7.1 Hz, 2H, Ar–C**H**), 7.37 (t, *J* = 7.5 Hz, 2H, Ar–C**H**), 7.31–7.28 (m, 1H, Ar–C**H**), 7.01 (d, *J* = 8.2 Hz, 2H, Ar–C**H**), 6.87 (d, *J* = 8.5 Hz, 2H, Ar–C**H**), 5.34 (t, *J* = 7.4 Hz, 1H, C**H**[c]), 4.61 (dd, *J* = 8.1, 5.9 Hz, 1H, C**H**[a]), 4.27 (m, 2H, C**H**$_2$[d]), 2.69–2.59 (m, 2H, C**H**$_2$[b]), 2.25 (s, Ar–C**H**$_3$), 1.30 (t, *J* = 7.1 Hz, 3H, C**H**$_3$[e]). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 148.1, 141.0, 132.1, 129.3, 128.9, 127.8, 126.9, 116.3, 72.6 (**C**H_2[c]), 69.4 (**C**H_2[a]), 61.3 (**C**H_2[d]), 41.8 (**C**H_2[b]), 20.7 (Ar–**C**H_3), 14.6 (**C**H_3[e]). **IR ν_{max}** (cm^{-1}): 2980, 2924, 2094 (C=N_2), 1693 (C=O), 1506, 1450, 1373, 1298, 1259, 1109. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{20}H_{22}N_3O_3]^+$: 352.1661, found 352.1661.

The C=O carbon could not be observed.

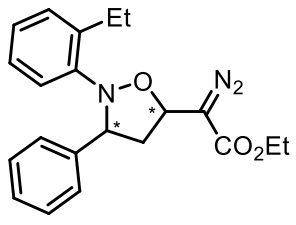
*Synthesis of (±)-ethyl 2-diazo-2-(3-phenyl-2-(o-tolyl)isoxazolidin-5-yl)acetate (**3.57**)*



Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.93** (21 mg, 0.1 mmol), vinyldiazo ester **3.46** (28 mg, 0.2 mmol) in toluene to afford **3.57**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.57**) was obtained as a yellow oil. Yield: 27 mg, 0.07 mmol, 77%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.41–7.39 (m, 2H, Ar–C**H**), 7.30 (t, *J* = 7.4 Hz, 2H, Ar–C**H**), 7.25–7.23 (m, 2H, Ar–C**H**), 7.12–7.08 (m, 2H, Ar–C**H**), 7.02– 6.98 (m, 1H, Ar–C**H**), 5.31 (t, *J* = 7.8 Hz, 1H, C**H**^{c}), 4.62 (t, *J* = 6.9 Hz, 1H, C**H**^{a}), 4.28 (m, 2H, C**H**$_2$^{d}), 2.70 (t, *J* = 7.2 Hz, 2H, C**H**$_2$^{b}), 2.17 (s, 3H, Ar–C**H**$_3$), 1.31 (t, *J* = 7.1 Hz, 3H, C**H**$_3$^{e}). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 165.4 (C=O), 146.6, 139.1, 133.0, 130.8, 128.6, 127.8, 126.9, 126.2, 125.5, 119.4, 72.2 (**C**H^c), 68.2 (**C**H^a), 61.3 (**C**H$_2$^{d}), 41.2 (**C**H$_2$^{b}), 18.53 (Ar–**C**H$_3$), 14.6 (**C**H$_3$^{e}). **IR ν_{max}** (cm^{-1}): 2983, 2929, 2092 (C=N_2), 1693 (C=O), 1600, 1479, 1450, 1375, 1300, 1265, 1111. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{20}H_{22}N_3O_3]^+$: 352.1661, found 352.1659.

*Synthesis of (±)-ethyl 2-diazo-2-(2-(2-ethylphenyl)-3-phenylisoxazolidin-5-yl)acetate (**3.58**)*

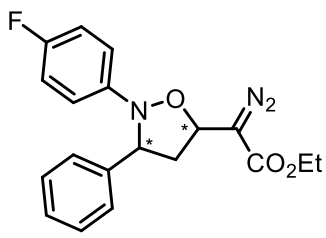


Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.94** (23 mg, 0.1 mmol), vinyldiazo ester **3.46** (28 mg, 0.2 mmol) in toluene to afford **3.58**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.58**) was obtained as a yellow oil. Yield: 27 mg, 0.07 mg, 74%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.40–7.38 (m, 2H, Ar–C**H**), 7.31–7.28 (m, 3H, Ar–C**H**), 7.25–7.22 (m, 1H, Ar–C**H**), 7.16–7.06 (m, 3H, Ar–C**H**), 5.31 (t, *J* = 7.8 Hz, 1H, C**H**^{c}), 4.61 (t, *J* = 7.2 Hz, 1H, C**H**^{a}), 4.27 (m, 2H, C**H**$_2$^{d}), 2.75–2.54 (m, 4H), 1.30 (t, *J* = 7.1 Hz, 3H, C**H**$_3$), 1.10 (t, *J* = 7.5 Hz, 3H, C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 145.5, 140.0, 139.0, 128.9, 128.6, 127.8, 127.6, 126.3, 126.2, 120.1, 72.0 (**C**H^c), 68.4 (**C**H^a), 61.2 (**C**H$_2$^{d}), 41.7 (**C**H$_2$^{b}), 24.0, 14.7, 14.6. **IR ν_{max}** (cm^{-1}): 2964, 2931, 2092 (C=N_2), 1693 (C=O), 1489, 1450, 1375, 1300, 1263, 1111, 1028. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{21}H_{24}N_3O_3]^+$: 366.1818, 366.1818.

The C=O carbon could not be observed.

*Synthesis of (±)-ethyl 2-diazo-2-(2-(4-fluorophenyl)-3-phenylisoxazolidin-5-yl)acetate (**3.59**)*

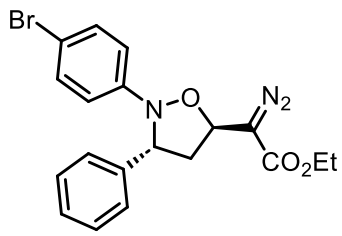


Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.95** (22 mg, 0.1 mmol), vinyldiazo ester **3.46** (28 mg, 0.2 mmol) in toluene to afford **3.59**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.59**) was obtained as a yellow oil. Yield: 29 mg, 0.08 mmol, 82%.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.46–7.44 (m, 2H, Ar–C**H**), 7.39–7.29 (m, 3H, Ar–C**H**), 6.94–6.86 (m, 4H, , Ar–C**H**), 5.35 (t, *J* = 7.4 Hz, 1H, C**H**^{c}), 4.52 (dd, *J* = 8.3, 6.3 Hz, 1H, , C**H**^{a}), 4.27 (q, *J* = 7.4, 6.7 Hz, 2H, C**H**$_2$^{d}), 2.74–2.61 (m, 2H, C**H**$_2$^{b}), 1.30 (t, *J* = 7.1 Hz, 3H, C**H**$_3$^{e}). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 158.9 (d, J_{C-F} = 241.2 Hz), 146.4 (d, J_{C-F} = 2.5 Hz), 140.5, 129.1, 128.1, 127.1, 118.1 (d, J_{C-F} = 7.9 Hz), 115.4 (d, J_{C-F} = 22.5 Hz), 72.7 (**C**H^c), 69.9 (**C**H^a), 61.4 (**C**H$_2$^{d}), 42.0 (**C**H$_2$^{b}), 14.6 (**C**H$_3$^{e}). **^{19}F NMR** (376 MHz, $CDCl_3$, 298 K) δ: -121.11. **IR ν_{max}** (cm^{-1}): 2098 (C=N_2), 1693 (C=O), 1502, 1300, 1226, 1112, 1028. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{19}H_{19}N_3O_3F]^+$: 356.1410, found 356.1411.

The C=O carbon could not be observed.

*Synthesis of (±)-ethyl 2-((3R,5R)-2-(4-bromophenyl)-3-phenylisoxazolidin-5-yl)-2-diazoacetate (anti-**3.60**)*

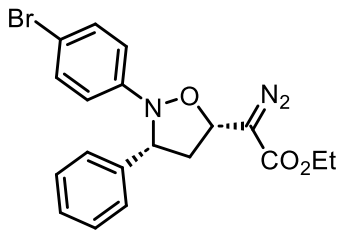


Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.96** (28 mg, 0.1 mmol), vinyldiazo ester **3.46** (28 mg, 0.2 mmol) in toluene to afford *anti*-**3.60**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (*anti*-**3.60**) was obtained as yellow oil. Yield: 28 mg, 0.06 mmol, 67%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.46–7.45 (m, 2H, Ar–C**H**), 7.39–7.36 (m, 2H, Ar–C**H**), 7.33–7.28 (m, 3H, Ar–C**H**), 6.82–6.79 (m, 2H, Ar–C**H**), 5.36 (t, *J* = 7.2 Hz, 1H, C**H**^{c}), 4.60 (dd, *J* = 8.5, 5.6 Hz, 1H, C**H**^{a}), 4.27 (q, *J* = 7.1 Hz, 2H, C**H**$_2$^{d}), 2.74–2.60 (m, 2H, C**H**$_2$^{b}), 1.30 (t, *J* = 7.1 Hz, 3H, C**H**$_3$^{e}). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 149.6, 140.7, 131.6, 129.1, 128.0, 126.7, 117.3, 114.8, 73.0 (**C**H^c), 69.1 (**C**H^a), 61.4 (**C**H$_2$^{d}), 41.8 (**C**H$_2$^{b}), 14.6 (**C**H$_3$^{e}). **IR ν_{max}** (cm^{-1}): 2098 (C=N_2), 1693 (C=O), 1485, 1267, 1244. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{19}H_{19}N_3O_3Br]^+$: 416.0610, found 416.0609.

The C=O carbon could not be observed.

*Synthesis of ethyl (±)-2-((3R,5S)-2-(4-bromophenyl)-3-phenylisoxazolidin-5-yl)-2-diazoacetate (syn-**3.60**)*

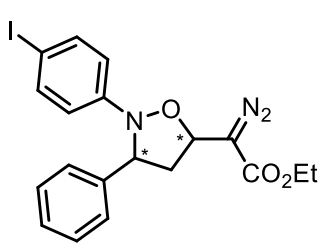


Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.96** (28 mg, 0.1 mmol), vinyldiazo ester **3.46** (28 mg, 0.2 mmol) in toluene to afford *syn*-**3.60**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (*syn*-**3.60**) was obtained as yellow oil. Yield: 6 mg, 0.01 mmol, 14%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.44 (d, *J* = 7.7 Hz, 2H, Ar–C**H**), 7.39 (t, *J* = 7.5 Hz, 2H, Ar–C**H**), 7.37–7.30 (m, 3H, Ar–C**H**), 6.90 (d, *J* = 8.7 Hz, 2H, Ar–C**H**), 5.19 (t, *J* = 7.8 Hz, 1H, C**H**^{c}), 4.77 (t, *J* = 7.6 Hz, 1H, C**H**^{a}), 4.28 (q, *J* = 7.1 Hz, 2H, C**H**$_2^d$), 3.11–3.05 (m, 1H, C**H**^{b}), 2.29–2.23 (m, 1H, C**H**^{b}), 1.31 (t, *J* = 7.1 Hz, 3H, C**H**$_3^e$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 150.7, 141.4, 132.0, 129.1, 127.9, 126.3, 116.6, 114.7, 72.9 (**C**H^c), 71.0 (**C**H^a), 61.4 (**C**H$_2^d$), 42.9 (**C**H$_2^b$), 14.6 (**C**H$_3^e$). **IR** ν_{max} (cm^{-1}): 2926, 2852, 2098 (C=N_2), 1737, 1693 (C=O), 1483, 1398, 1377, 1300, 1242, 1174, 1028. **HRMS** (ES+) $[M\text{-}N_2+H]^+$ calculated for $[C_{19}H_{19}NO_3Br]^+$: 388.0548, found 388.0541.

The C=O carbon could not be observed.

*Synthesis of (±)-ethyl 2-diazo-2-(2-(4-iodophenyl)-3-phenylisoxazolidin-5-yl)acetate (**3.61**)*

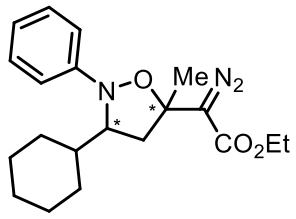


Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.97** (31 mg, 0.1 mmol), vinyldiazo ester **3.46** (28 mg, 0.2 mmol) in toluene to afford **3.61**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.61**) was obtained as a yellow oil. Yield: 42 mg, 0.09 mg, 91%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.48–7.44 (m, 4H, Ar–C**H**), 7.38 (t, *J* = 7.5 Hz, 2H, Ar–C**H**), 7.33–7.29 (m, 1H, Ar–C**H**), 6.69 (d, *J* = 9.0 Hz, 2H, Ar–C**H**), 5.36 (t, *J* = 7.2 Hz, 1H, C**H**^{c}), 4.61 (dd, *J* = 8.5, 5.5 Hz, 1H, C**H**^{a}), 4.26 (q, *J* = 7.1 Hz, 2H, C**H**$_2^d$), 2.74–2.59 (m, 2H, C**H**$_2^b$), 1.29 (t, *J* = 7.1 Hz, 3H, C**H**$_3^e$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 150.3, 140.8, 137.5, 129.1, 128.0, 126.7, 117.5, 84.8 (**C**H^b), 73.1 (**C**H^a), 68.9 (**C**H^b), 61.4 (**C**H$_2^d$), 41.8 (**C**H$_2^b$), 14.6 (**C**H$_3^e$). **IR ν_{max}** (cm^{-1}): 2981, 2096 (C=N$_2$), 1693 (C=O), 1583, 1481, 1373, 1300, 1261, 1111. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{19}H_{19}N_3O_3I]^+$: 464.0471, found 464.0468.

The C=O carbon could not be observed.

*Synthesis of (±)-ethyl 2-(3-cyclohexyl-5-methyl-2-phenylisoxazolidin-5-yl)-2-diazoacetate (**3.62**)*



Synthesised in accordance with a slightly modified *GP5* (room temperature instead of 40 °C and for 3 days instead of 24 hours), using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.91** (20 mg, 0.1 mmol), vinyldiazo ester **3.102** (31 mg, 0.2 mmol) in toluene to afford **3.62**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (95:5 v/v) as eluent. The desired product (**3.62**) was as a yellow oil. Yield: 13 mg, 0.04 mmol, 36%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.31–7.26 (m, 2H, Ar–C**H**), 7.14–7.08 (m, 2H, Ar–C**H**), 7.01 (tt, *J* = 7.3, 1.1 Hz, 1H, Ar–C**H**), 4.32–4.18 (m, 2H, C**H**$_2^d$), 3.50 (dt, *J* = 8.9, 6.0 Hz, 1H, C**H**$_2^a$), 2.81 (dd, *J* = 12.9, 5.9 Hz, 1H, C**H**$_2^b$), 2.26 (dd, *J* = 12.9, 8.9 Hz, 1H, CH$_2^b$), 1.88–1.65 (m, 5H, C**H**), 1.64–1.57 (m, 1H, C**H**), 1.56 (s, 3H, C**H**$_3$), 1.30 (t, *J* = 7.1 Hz, 3H, C**H**$_3^e$), 1.28–1.13 (m, 3H, C**H**), 1.08–0.95 (m, 2H, C**H**). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 165.9 (**C**=O), 151.2, 128.8, 123.0, 117.2, 78.1, 70.4 (**C**H^a), 60.6 (**C**H^d), 42.6 (**C**H^b), 40.7 (**C**H), 31.4 (**C**H$_2$), 27.6 (**C**H$_2$), 26.7 (**C**H$_2$), 26.6 (**C**H$_2$), 26.2 (**C**H$_2$), 25.8 (**C**H$_3$), 14.7 (**C**H$_3^e$). **IR ν_{max}** (cm^{-1}): 2980, 2926, 2853, 2099 (C=N$_2$), 1688

(C=O), 1599, 1489, 1451, 1370, 1310, 1258, 1180, 1068. **HRMS** (ES+) $[M\text{-}N_2+H]^+$ calculated for $[C_{20}H_{28}NO_3]^+$: 330.2069, found 330.2079.

3.9.3.2 Synthesis and spectral characterisation of Mukaiyama-Mannich addition diazo products

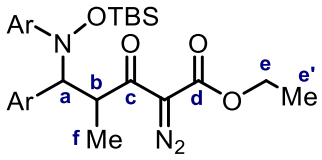
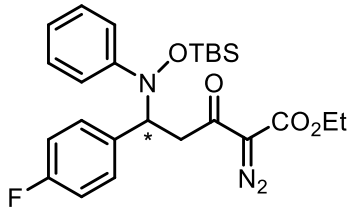


Figure 3.9.3.2.1. General labelling of Mukaiyama-Mannich addition products.

The characteristic protons and carbons were assigned according to the labelling in the general structure in Figure S3. Peak assignment has been done by carrying out 2D-NMR spectroscopic analysis on compounds *anti*-**3.69**.

In most of the products the α-carbon of the diazo functionality could not be observed in the ^{13}C NMR.

*Synthesis ethyl (±)-5-(((tert-butyldimethylsilyl)oxy)(phenyl)amino)-2-diazo-5-(4-fluorophenyl)-3-oxopentanoate (**3.68**)*

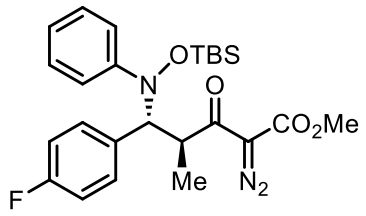


Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (10 mg, 0.02 mmol), nitrone **3.65** (21.5 mg, 0.1 mmol), enoldiazo ester **3.68** (54.1 mg, 0.2 mmol) in toluene to afford **3.68**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.68**) was obtained as a yellow oil. Yield: 42 mg, 0.09 mmol, 90%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.21–7.15 (m, 2H, Ar–C**H**), 7.16–7.11 (m, 2H, Ar–C**H**), 7.04 (d, J = 7.9 Hz, 2H, Ar–C**H**), 6.99 (t, J = 7.3 Hz, 1H, Ar–C**H**), 6.90 (t, J = 8.7 Hz, 2H, Ar–C**H**), 4.91 (dd, J = 8.5, 5.5 Hz, 1H, C**H**^{a}), 4.32 (m, 2H, C**H**^{e}), 3.72 (dd, J = 17.5, 8.6 Hz, 1H, C**H**^{b}), 3.53–3.44

(m, 1H, C**H**^{b}), 1.34 (t, J = 7.1 Hz, 3H, C**H**$^{e'}$), 0.93 (s, 9H, OTBS), -0.05 (br. s, 3H, OTBS), -0.38 (br. s, 3H, OTBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 190.4 (**C**=O^{c}), 162.4 (d, $J_{C–F}$ = 245.6 Hz), 161.3 (**C**=O^{d}), 152.5, 131.4 (d, $J_{C–F}$ = 7.9 Hz), 128.2, 124.1, 121.1, 114.5 (d, $J_{C–F}$ = 21.1 Hz), 76.7, 69.2 (**C**H^{a}), 61.6(**C**H^{e}), 40.6 (**C**H^{b}), 26.3 (OTBS), 18.1 (OTBS), 14.5 (**C**H$^{e'}$), -4.8 (OTBS), -5.3 (OTBS). **^{19}F NMR** (471 MHz, $CDCl_3$, 298 K) δ: -115.06. **IR ν_{max}** (cm^{-1}): 2980, 2957, 2930, 2889, 2857, 2133 (C=N_2), 1715 (C=O^{d}), 1655 (C=O^{c}), 1651, 1605, 1595, 1508, 1487, 1472, 1391, 1373, 13112, 1300, 1256, 1219, 1206, 1173, 1159, 1126, 1074, 1061, 1015. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{25}H_{33}N_3O_4SiF]^+$: 486.2224, found 486.2222.

*Synthesis of methyl (±)-(4S,5R)-5-(((tert-butyldimethylsilyl)oxy)(phenyl)amino)-2-diazo-5-(4-fluorophenyl)-4-methyl-3-oxopentanoate (anti-**3.69**)*

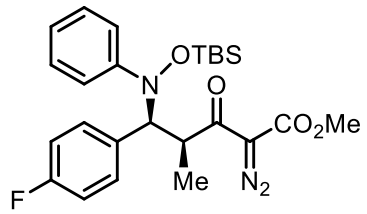


Synthesised in accordance with *GP6*, using $B(C_6F_5)_3$ (5 mg, 0.01 mmol), nitrone **3.65** (21.5 mg, 0.1 mmol), enoldiazo ester **3.68** (54.1 mg, 0.2 mmol) in toluene to afford **3.69**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (95:5 v/v) as eluent. The desired product (*anti*-**3.69**) was obtained as a white solid. Yield: 26 mg, 0.05 mmol, 53%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.11 (dd, J = 8.4, 7.3 Hz, 2H, Ar–C**H**), 7.00–6.84 (m, 7H, Ar–C**H**), 4.74 (d, J = 11.1 Hz, 1H, C**H**^{a}), 4.32 (dq, J = 11.0, 7.1 Hz, 1H, C**H**^{b}), 3.89 (s, 3H, C**H**$_3^{e}$), 0.90 (s, 9H, OTBS), 0.84 (d, J = 7.2 Hz, 3H, C**H**$_3^{f}$), -0.03 (br. s, 3H, OTBS), -0.36 (br. s, 3H, OTBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 194.6 (**C**=O^{c}), 162.4 (d, $J_{C–F}$ = 245.3 Hz), 161.7 (**C**=O^{d}), 153.3, 132.7 (d, $J_{C–F}$ = 7.8 Hz), 130.2, 127.8, 124.1, 121.4, 114.0 (d, $J_{C–F}$ = 21.0 Hz), 76.0, 75.3 (**C**H^{a}), 52.4 (**C**H^{e}), 43.5 (**C**H^{b}), 26.3 (OTBS), 18.1 (OTBS), 16.7 (**C**H^{f}), -4.5 (OTBS), -5.2 (OTBS). **^{19}F NMR** (471 MHz, $CDCl_3$, 298 K) δ: -115.21. **IR ν_{max}** (cm^{-1}): 2955, 2930, 2893, 2857, 2141 (C=N_2), 1721 (C=O^{d}), 1655 (C=O^{c}), 1603, 1595, 1508, 1485, 1437, 1377, 1317, 1298, 1250, 1223, 1202, 1159,

1140, 1123, 1094, 1005. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{25}H_{33}N_3O_4FSi]^+$: 486.2224, found 486.2224.

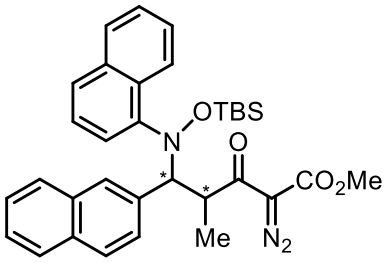
*Synthesis of methyl (±)-(4S,5S)-5-(((tert-butyldimethylsilyl)oxy)(phenyl)amino)-2-diazo-5-(4-fluorophenyl)-4-methyl-3-oxopentanoate (syn-**3.69**)*



Synthesised in accordance with *GP6*, using $B(C_6F_5)_3$ (5 mg, 0.01 mmol), nitrone **3.65** (21.5 mg, 0.1 mmol), enoldiazo ester **3.68** (54.1 mg, 0.2 mmol) in toluene to afford **3.69**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (95:5 v/v) as eluent. The desired product (*syn*-**3.69**) was obtained as a white solid. Yield: 15 mg, 0.03 mmol, 30%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.17–7.12 (m, 2H, Ar–C**H**), 7.01–6.96 (m, 1H, Ar–C**H**), 6.84–6.74 (m, 6H, Ar–C**H**), 4.62 (br. s, 1H, C**H**^{a}), 4.30 (br. s, 1H, C**H**^{b}), 3.87 (s, 3H, C**H**$_3^e$), 1.62 (d, J = 6.6 Hz, 3H, C**H**$_3^f$), 0.93 (s, 9H, OTBS), 0.28 (br. s, 3H, OTBS), -0.17 (br. s, 3H, OTBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 195.2 (**C**=O^c), 162.3 (d, J_{C-F} = 245.1 Hz) 161.4 (**C**=O^d), 131.7 (d, J_{C-F} = 7.9 Hz), 131.2, 128.0, 123.9, 121.0, 113.8 (d, J_{C-F} = 20.9 Hz), 76.4, 60.5, 52.4 (**C**H^e), 43.3 (**C**H^b) , 26.4 (OTBS), 18.2 (OTBS), 17.7 (**C**H^f), -4.1 (OTBS), -4.7 (OTBS). **^{19}F NMR** (471 MHz, $CDCl_3$, 298 K) δ: -115.49. **IR ν_{max}** (cm^{-1}): 2957, 2930, 2857, 2141 (C=N_2), 1719 (C=O^d), 1655 (C=O^c), 1595, 1508, 1485, 1437, 1370, 1362, 1304, 1258, 1221, 1209, 1202, 1161, 1125, 1096. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{25}H_{33}N_3O_4FSi]^+$: 486.2224, found 486.2227.

*Synthesis of methyl (±)-5-(((tert-butyldimethylsilyl)oxy)(naphthalen-1-yl)amino)-2-diazo-4-methyl-5-(naphthalen-2-yl)-3-oxopentanoate (**3.70**)*

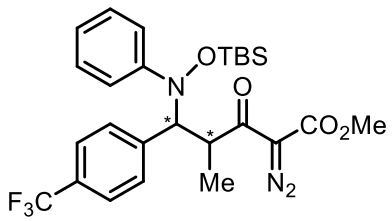


Synthesised in accordance with *GP6*, using $B(C_6F_5)_3$ (5 mg, 0.01 mmol), nitrone **3.99** (29.7 mg, 0.1 mmol), enoldiazo ester **3.68** (54.1 mg, 0.2 mmol) in toluene to afford **3.70**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.70**) was obtained as a yellow oil. Yield: 30 mg, 0.05 mmol, 53%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 8.44 (d, *J* = 7.8 Hz, 1H, Ar–C**H**), 7.85 (d, *J* = 7.9 Hz, 1H, Ar–C**H**), 7.75 (d, *J* = 8.1 Hz, 2H, Ar–C**H**), 7.58–7.53 (m, 2H, Ar–C**H**), 7.53–7.48 (m, 3H, Ar–C**H**), 7.41 (t, *J* = 7.3 Hz, 3H, Ar–C**H**), 6.93 (t, *J* = 7.8 Hz, 1H, Ar–C**H**), 6.48 (d, *J* = 7.6 Hz, 1H, Ar–C**H**), 5.09 (dq, *J* = 13.0, 6.6 Hz, 1H, C**H**^{b}), 4.47 (d, *J* = 10.9 Hz, 1H, C**H**^{a}), 3.91 (s, 3H, C**H**^{e}), 1.90 (d, *J* = 6.7 Hz, 3H, C**H**^{f}), 0.98 (s, 9H, OTBS), 0.48 (s, 3H, OTBS), -0.37 (s, 3H, OTBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 195.1 (**C**=O^c), 161.5 (**C**=O^d), 148.0, 134.1, 132.9, 128.4, 128.3, 127.5, 127.0, 125.8, 125.6, 125.5, 124.9, 124.8, 122.8, 120.2, 76.4, 74.4, 52.4 (**C**H^e), 26.4 (OTBS), 18.2 (OTBS), 17.7 (**C**H^f), -3.7 (OTBS), -4.8 (OTBS). **IR ν_{max}** (cm^{-1}): 3051, 2953, 2928, 2855, 2137 (C=N_2), 1721 (C=O^d), 1657(C=O^c), 1593, 1574, 1506, 1435, 1379, 1362, 1306, 1256, 1202, 1128, 1005. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{33}H_{38}N_3O_4Si]^+$: 568.2632, found 568.2634.

Quaternary carbons of the two naphtyl groups could not be observed.

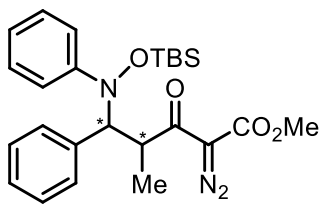
*Synthesis of methyl (±)-5-(((tert-butyldimethylsilyl)oxy)(phenyl)amino)-2-diazo-4-methyl-3-oxo-5-(4-(trifluoromethyl)phenyl)pentanoate (**3.71**)*



Synthesised in accordance with *GP6*, using $B(C_6F_5)_3$ (5 mg, 0.01 mmol), nitrone **3.87** (26.5 mg, 0.1 mmol), enoldiazo ester **3.68** (54.1 mg, 0.2 mmol) in toluene to afford **3.71**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (95:5 v/v) as eluent. The desired product (**3.71**) was obtained as a yellow oil. Yield: 36 mg, 0.07 mmol, 68%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.45 (d, *J* = 8.8 Hz, 2H, Ar–C**H**), 7.14–7.09 (m, 4H, Ar–C**H**), 7.00–6.95 (m, 1H, Ar–C**H**), 6.91 (d, *J* = 8.8 Hz, 2H, Ar–C**H**), 4.83 (d, *J* = 11.1 Hz, 1H, C**H**^{a}), 4.37 (dq, *J* = 11.1, 7.1 Hz, 1H, C**H**^{b}), 3.89 (s, 3H, C**H**$_3$^{e}), 0.90 (s, 9H, OTBS), 0.83 (d, *J* = 7.2 Hz, 3H, C**H**$_3$^{f}), -0.02 (br. s, 3H, OTBS), -0.36 (br. s, 3H, OTBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 194.3 (**C**=O^c), 161.7 (**C**=O^d), 153.0, 138.5, 131.5, 129.7 (q, J_{C-F} = 32.2 Hz), 128.0, 124.4 (q, J_{C-F} = 272.0 Hz), 124.3, 124.1 (q, J_{C-F}= 3.8 Hz), 121.4, 76.1, 75.6 (**C**H^a), 52.4 (**C**H^e), 43.2 (**C**H^b), 26.3 (OTBS), 18.1 (OTBS), 16.7 (**C**H^f), -4.5 (OTBS), -5.3 (OTBS). **^{19}F NMR** (376 MHz, $CDCl_3$, 298 K) δ: -62.36. **IR ν_{max}** (cm^{-1}): 2957, 2930, 2893, 2859, 2141 (C=N_2), 1721 (C=O^d), 1655(C=O^c), 1618, 1595, 1485, 1452, 1437, 1377, 1321, 1308, 1300, 1252, 1204, 1163, 1123, 1105, 1069, 1018, 1007. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{26}H_{33}N_3O_4F_3Si]^+$: 536.2192, found 536.2192.

*Synthesis of methyl (±)-5-(((tert-butyldimethylsilyl)oxy)(phenyl)amino)-2-diazo-4-methyl-3-oxo-5-phenylpentanoate (**3.72**)*

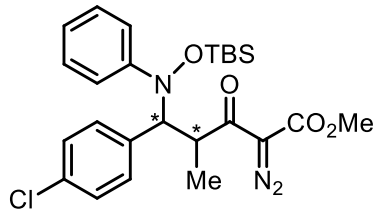


Synthesised in accordance with *GP6*, using $B(C_6F_5)_3$ (5 mg, 0.01 mmol), nitrone **3.42** (19.7 mg, 0.1 mmol), enoldiazo ester **3.68** (54.1 mg, 0.2 mmol) in toluene to afford **3.72**. All volatiles were removed *in vacuo* and

the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (95:5 v/v) as eluent. The desired product (**3.72**) was obtained as a white solid. Yield: 34 mg, 0.07 mmol, 73%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.25–7.15 (m, 3H, Ar–C**H**), 7.13–7.08 (m, 2H, Ar–C**H**), 7.01 (d, *J* = 7.2 Hz, 2H, Ar–C**H**), 6.98–6.90 (m, 3H, Ar–C**H**), 4.76 (d, *J* = 11.1 Hz, 1H, C**H**^{a}), 4.41–4.33 (m, 1H, C**H**^{b}), 3.89 (s, 3H, C**H**$_3^e$), 0.90 (s, 9H, OTBS), 0.85 (d, *J* = 7.1 Hz, 3H, C**H**$_3^f$), -0.04 (br. s, 3H, OTBS), -0.36 (br. s, 3H, OTBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 194.8 (**C**=O^c), 161.8 (**C**=O^d), 153.5, 134.6, 131.3, 127.8, 127.5, 127.1, 123.9, 121.5, 76.1 (**C**H^a), 52.3 (**C**H^e), 43.4 (**C**H^b), 26.3 (OTBS), 18.1 (OTBS), 16.8 (**C**H^f), -4.5 (OTBS), -5.2 (OTBS). **IR ν_{max}** (cm^{-1}): 2955, 2930, 2886, 2857, 2141 (C=N_2), 1724 (C=O^d), 1659 (C=O^c), 1595, 1485, 1452, 1437, 1375, 1327, 1304, 1256, 1206, 1123, 1078, 1009. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{25}H_{34}N_3O_4Si]^+$: 468.2319, found 468.2318.

*Synthesis of methyl (±)-5-(((tert-butyldimethylsilyl)oxy)(phenyl)amino)-5-(4-chlorophenyl)-2-diazo-4-methyl-3-oxopentanoate (**3.73**)*

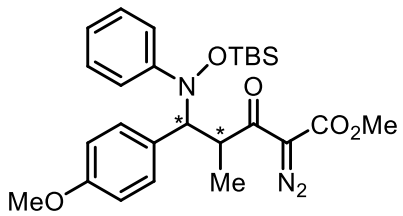


Synthesised in accordance with *GP6*, using $B(C_6F_5)_3$ (5 mg, 0.01 mmol), nitrone **3.88** (23.1 mg, 0.1 mmol), enoldiazo ester **3.68** (54.1 mg, 0.2 mmol) in toluene to afford **3.73**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.73**) was obtained as an off-white solid. Yield: 30 mg, 0.06 mmol, 60%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.17–7.14 (m, 2H, Ar–C**H**), 7.12 (dd, *J* = 8.5, 7.3 Hz, 2H, Ar–C**H**), 7.00–6.94 (m, 1H, Ar–C**H**), 6.93–6.90 (m, 4H, Ar–C**H**), 4.73 (d, *J* = 11.1 Hz, 1H, C**H**^{a}), 4.32 (dq, *J* = 11.1, 7.1 Hz, 1H, C**H**^{b}), 3.89 (s, 3H, C**H**^{e}), 0.90 (s, 9H, OTBS), 0.83 (d, *J* = 7.2 Hz, 3H, C**H**^{f}),

-0.02 (br. s, 3H, OTBS), -0.36 (br. s, 3H, OTBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 194.5 (**C**=O^c), 161.7 (**C**=O^d), 153.2, 133.4, 132.9, 132.5, 127.9, 127.3, 124.1, 121.4, 76.0, 75.4 (**C**H^a), 52.4 (**C**H^e), 43.4 (**C**H^b), 26.3 (OTBS), 18.1 (OTBS), 16.7 (**C**H^f), -4.5 (OTBS), -5.3 (OTBS). **IR ν_{max}** (cm^{-1}): 2955, 2930, 2884, 2857, 2139 (C=N_2), 1721 (C=O^d), 1655 (C=O^c), 1593, 1485, 1452, 1437, 1408, 1375, 1315, 1300, 1256, 1250, 1204, 1123, 1090, 1005. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{25}H_{33}N_3O_4SiCl]^+$: 502.1929, found 502.1931.

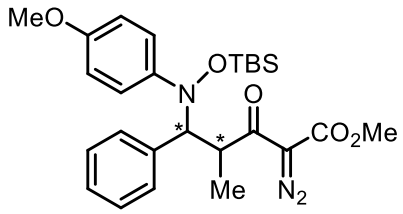
*Synthesis of methyl (±)-5-(((tert-butyldimethylsilyl)oxy)(phenyl)amino)-2-diazo-5-(4-methoxyphenyl)-4-methyl-3-oxopentanoate (**3.74**)*



Synthesised in accordance with *GP6*, using $B(C_6F_5)_3$ (5 mg, 0.01 mmol), nitrone **3.90** (22.7 mg, 0.1 mmol), enoldiazo ester **3.68** (54.1 mg, 0.2 mmol) in toluene to afford **3.74**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.74**) was obtained as a yellow oil. Yield: 33 mg, 0.06 mmol, 66%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.11 (dd, *J* = 8.4, 7.2 Hz, 2H, Ar–C**H**), 6.98–6.87 (m, 5H, Ar–C**H**), 6.72 (d, *J* = 9.0 Hz, 2H, Ar–C**H**), 4.70 (d, *J* = 11.1 Hz, 1H, C**H**^{a}), 4.32 (dq, *J* = 11.1, 7.1 Hz, 1H, C**H**^{b}), 3.89 (s, 3H, C**H**^{e}), 3.77 (s, 3H, Ar–OC**H**$_3$), 0.91 (s, 9H, OTBS), 0.84 (d, *J* = 7.1 Hz, 3H, C**H**^{f}), -0.03 (br. s, 3H, OTBS), -0.36 (br. s, 3H, OTBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 194.9 (**C**=O^c), 161.8 (**C**=O^d), 159.0, 153.6, 132.3, 127.7, 126.7, 123.8, 121.5, 112.5, 76.0, 75.5 (**C**H^a), 55.2 (Ar–O**C**H$_3$), 52.3 (**C**H^e), 43.6 (**C**H^b), 26.3(OTBS), 18.1 (OTBS), 16.8 (**C**H^f), -4.5 (OTBS), -5.2 (OTBS). **IR ν_{max}** (cm^{-1}): 2930, 2857, 2139 (C=N_2), 1721 (C=O^d), 1655 (C=O^c), 1611, 1595, 1586, 1512, 1487, 1472, 1462, 1452, 1435, 1375, 1362, 1321, 1300, 1250, 1202, 1179, 1142, 1123, 1107, 1078, 1061, 1036, 1005. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{26}H_{36}N_3O_5Si]^+$: 498.2424, found 498.2423.

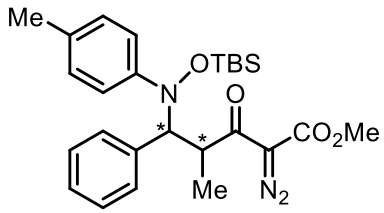
*Synthesis of methyl (±)-5-(((tert-butyldimethylsilyl)oxy)(4-methoxyphenyl)amino)-2-diazo-4-methyl-3-oxo-5-phenylpentanoate (**3.75**)*



Synthesised in accordance with *GP6*, using $B(C_6F_5)_3$ (5 mg, 0.01 mmol), nitrone **3.98** (22.7 mg, 0.1 mmol), enoldiazo ester **3.68** (54.1 mg, 0.2 mmol) in toluene to afford **3.75**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.75**) was obtained as a yellow oil. Yield: 15 mg, 0.03 mmol, 30%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.23–7.17 (m, 3H, Ar–C**H**), 7.03 (d, *J* = 7.0 Hz, 2H, Ar–C**H**), 6.82 (d, *J* = 8.8 Hz, 2H, Ar–C**H**), 6.64 (d, *J* = 9.1 Hz, 2H, Ar–C**H**), 4.66 (d, *J* = 10.9 Hz, 1H, C**H**^{a}), 4.28 (dq, *J* = 11.0, 7.1 Hz, 1H, C**H**^{b}), 3.88 (s, 3H, C**H**^{e}), 3.74 (s, 3H, Ar–OC**H**$_3$), 0.86 (s, 9H, OTBS), 0.81 (d, *J* = 7.1 Hz, 3H, C**H**^{f}), -0.09 (br. s, 3H, OTBS), -0.34 (br. s, 3H, OTBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 194.9 (**C**=O^c), 161.8 (**C**=O^d), 156.5, 146.3, 135.1, 131.4, 127.5, 127.2, 123.5, 112.8, 76.1, 75.9 (**C**H^a), 55.4 (Ar–O**C**H$_3$), 52.3 (**C**H^e), 43.5 (**C**H^b), 26.2 (OTBS), 18.1 (OTBS), 16.8 (**C**H^f), -4.6 (OTBS), -5.2 (OTBS). **IR ν_{max}** (cm^{-1}): 2955, 2928, 2855, 2139 (C=N_2), 1724 (C=O^d), 1659 (C=O^c), 1503, 1456, 1437, 1375, 1325, 1304, 1246, 1206, 1123, 1036, 1009. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{26}H_{36}N_3O_5Si]^+$: 498.2424, found 498.2426.

*Synthesis of methyl (±)-5-(((tert-butyldimethylsilyl)oxy)(p-tolyl)amino)-2-diazo-4-methyl-3-oxo-5-phenylpentanoate (**3.76**)*

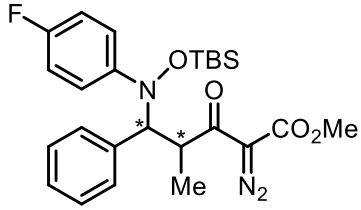


Synthesised in accordance with *GP6*, using $B(C_6F_5)_3$ (5 mg, 0.01 mmol), nitrone **3.92** (21.1 mg, 0.1 mmol), enoldiazo ester **3.68** (54.1 mg, 0.2 mmol) in toluene to afford **3.76**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin

layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.76**) was obtained as a yellow oil. Yield: 25 mg, 0.05 mmol, 52%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.23–7.16 (m, 3H, Ar–C**H**), 7.03 (d, *J* = 7.1 Hz, 2H, Ar–C**H**), 6.89 (d, *J* = 7.5 Hz, 2H, Ar–C**H**), 6.80 (d, *J* = 8.2 Hz, 2H, Ar–C**H**), 4.71 (d, *J* = 11.0 Hz, 1H, C**H**^{a}), 4.32 (dq, *J* = 11.0, 7.1 Hz, 1H, C**H**^{b}), 3.89 (s, 3H, C**H**^{e}), 2.25 (s, 3H, Ar-C**H**$_3$), 0.88 (s, 9H, OTBS), 0.82 (d, *J* = 7.1 Hz, 3H, C**H**^{f}), -0.08 (br. s, 3H, OTBS), -0.35 (br. s, 3H, OTBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 194.8 (**C**=O^c), 161.8 (**C**=O^d), 150.7, 135.1, 133.5, 131.3, 128.3, 127.4, 127.1, 121.8, 76.04 (**C**H^a), 75.96, 52.3 (**C**H^e), 43.4 (**C**H^b), 26.3 (OTBS), 21.0 (Ar–**C**H$_3$), 18.1 (OTBS), 16.8 (**C**H^f), -4.5 (OTBS), -5.2 (OTBS). **IR ν_{max}** (cm^{-1}): 3030, 2955, 2928, 2884, 2857, 2139 (C=N_2), 1721 (C=O^d), 1655 (C=O^c), 1505, 1472, 1452, 1435, 1375, 1323, 1302, 1256, 1250, 1204, 1123, 1007. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{26}H_{36}N_3O_4Si]^+$: 482.2475, found 482.2475.

*Synthesis of methyl (±)-5-(((tert-butyldimethylsilyl)oxy)(4-fluorophenyl)amino)-2-diazo-4-methyl-3-oxo-5-phenylpentanoate (**3.77**)*

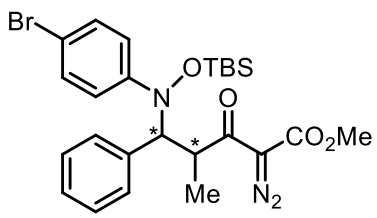


Synthesised in accordance with *GP6*, using $B(C_6F_5)_3$ (5 mg, 0.01 mmol), nitrone **3.95** (21.5 mg, 0.1 mmol), enoldiazo ester **3.68** (54.1 mg, 0.2 mmol) in toluene to afford **3.77**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.77**) was obtained as a yellow oil. Yield: 42 mg, 0.08 mmol, 87%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.24–7.16 (m, 3H, Ar–C**H**), 6.99 (d, *J* = 7.3 Hz, 2H, Ar–C**H**), 6.88–6.83 (m, 2H, Ar–C**H**), 6.82–6.76 (m, 2H, Ar–C**H**), 4.66 (d, *J* = 11.1 Hz, 1H, C**H**^{a}), 4.32 (dq, *J* = 11.0, 7.1 Hz, 1H, C**H**^{b}), 3.89 (s, 3H, C**H**^{e}), 0.88 (s, 9H, OTBS), 0.84 (d, *J* = 7.1 Hz, 3H, C**H**^{f}), -0.03 (br. s, 3H, OTBS), -0.34 (br. s, 3H, OTBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 194.8 (**C**=O^c),

161.7 (**C**=O[c]), 159.7 (d, J_{C-F} = 241.9 Hz), 149.4, 134.2, 131.4, 127.7, 127.2, 123.2, 114.4 (d, J_{C-F} = 22.3 Hz), 76.2 (**C**H[a]), 76.0, 52.4 (**C**H[e]), 43.5 (**C**H[b]), 26.2 (OTBS), 18.1 (OTBS), 16.7 (**C**H[f]), -4.5 (OTBS), -5.3 (OTBS). **^{19}F NMR** (471 MHz, $CDCl_3$, 298 K) δ: -119.45. **IR ν_{max}** (cm^{-1}): 2955, 2930, 2886, 2857, 2139 (C=N_2), 1721 (C=O[d]), 1655 (C=O[c]), 1601, 1499, 1472, 1454, 1437, 1376, 1325, 1304, 1256, 1250, 1225, 1202, 1148, 1123, 1094, 1007, 1001. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{25}H_{33}N_3O_4FSi]^+$: 486.2224, found 486.2224.

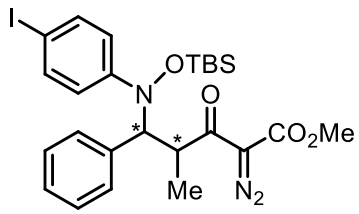
*Synthesis of methyl (±)-5-((4-bromophenyl)((tert-butyldimethylsilyl)oxy)amino)-2-diazo-4-methyl-3-oxo-5-phenylpentanoate (**3.78**)*



Synthesised in accordance with *GP6*, using $B(C_6F_5)_3$ (5 mg, 0.01 mmol), nitrone **3.96** (27.6 mg, 0.1 mmol), enoldiazo ester **3.68** (54.1 mg, 0.2 mmol) in toluene to afford **3.78**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.78**) was obtained as a yellow oil. Yield: 34 mg, 0.06 mmol, 63%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.24–7.17 (m, 5H, Ar–C**H**), 6.99 (d, *J* = 6.7 Hz, 2H, Ar–C**H**), 6.81 (d, *J* = 8.5 Hz, 2H, Ar–C**H**), 4.70 (d, *J* = 11.0 Hz, 1H, C**H**[a]), 4.34 (dq, *J* = 11.1, 7.1 Hz, 1H, C**H**[b]), 3.89 (s, 3H, C**H**[e]), 0.90 (s, 9H, OTBS), 0.85 (d, *J* = 7.1 Hz, 3H, C**H**[f]), -0.02 (br. s, 3H, OTBS), -0.35 (br. s, 3H, OTBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 194.8 (**C**=O[c]), 161.7 (**C**=O[d]), 152.8, 133.8, 131.3, 130.8, 127.7, 127.3, 123.2, 116.8, 76.1 (**C**H[a]), 52.4 (**C**H[e]), 43.4 (**C**H[b]), 26.2 (OTBS), 18.1 (OTBS), 16.7 (CH[f]), -4.4 (OTBS), -5.2 (OTBS). **IR ν_{max}** (cm^{-1}): 2955, 2928, 2857, 2141(C=N_2), 1719 (C=O[d]), 1655 (C=O[c]), 1479, 1435, 1327, 1302, 1256, 1250, 1204, 1123, 1007. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{25}H_{33}N_3O_4SiBr]^+$: 546.1424, found 546.1425.

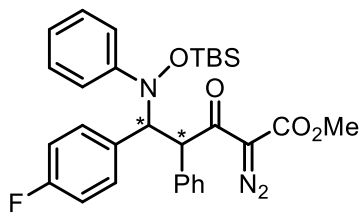
*Synthesis methyl (±)-5-(((tert-butyldimethylsilyl)oxy)(4-iodophenyl)amino)-2-diazo-4-methyl-3-oxo-5-phenylpentanoate (**3.79**)*



Synthesised in accordance with *GP6*, using $B(C_6F_5)_3$ (5 mg, 0.01 mmol), nitrone **3.97** (32.3 mg, 0.1 mmol), enoldiazo ester **3.68** (54.1 mg, 0.2 mmol) in toluene to afford **3.79**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.79**) was obtained as a yellow oil. Yield: 35 mg, 0.06 mmol, 60%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.40 (d, *J* = 8.8 Hz, 2H, Ar–C**H**), 7.24–7.17 (m, 3H, Ar–C**H**), 6.99 (d, *J* = 7.0 Hz, 2H, Ar–C**H**), 6.69 (d, *J* = 8.4 Hz, 2H, Ar–C**H**), 4.71 (d, *J* = 11.1 Hz, 1H, C**H**^{a}), 4.34 (dq, *J* = 11.1, 7.1 Hz, 1H, C**H**^{b}), 3.89 (s, 3H, C**H**^{e}), 0.89 (s, 9H, OTBS), 0.84 (d, *J* = 7.1 Hz, 3H, C**H**^{f}), -0.03 (s, 3H, OTBS), -0.35 (s, 3H, OTBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 194.7 (**C**=O^c), 161.7 (**C**=O^d), 153.6, 136.8, 133.9, 131.3, 127.7, 127.3, 123.5, 87.7, 76.1 (**C**H^a), 52.4 (**C**H^e), 43.3 (**C**H^b), 26.2 (OTBS), 18.1 (OTBS), 16.7 (**C**H^f), -4.4 (OTBS), -5.2 (OTBS). **IR ν_{max}** (cm^{-1}): 2953, 2928, 2884, 2857, 2139 (C=N_2), 1719 (C=O^d), 1655 (C=O^c), 1582, 1478, 1460, 1454, 1435, 1391, 1375, 1362, 1327, 1300, 1256, 1250, 1204, 1142, 1123, 1061. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{25}H_{33}N_3O_4Si^{127}I]^+$: 594.1285, found 594.1288.

*Synthesis of methyl (±)-5-(((tert-butyldimethylsilyl)oxy)(phenyl)amino)-2-diazo-5-(4-fluorophenyl)-3-oxo-4-phenylpentanoate (**3.80**)*



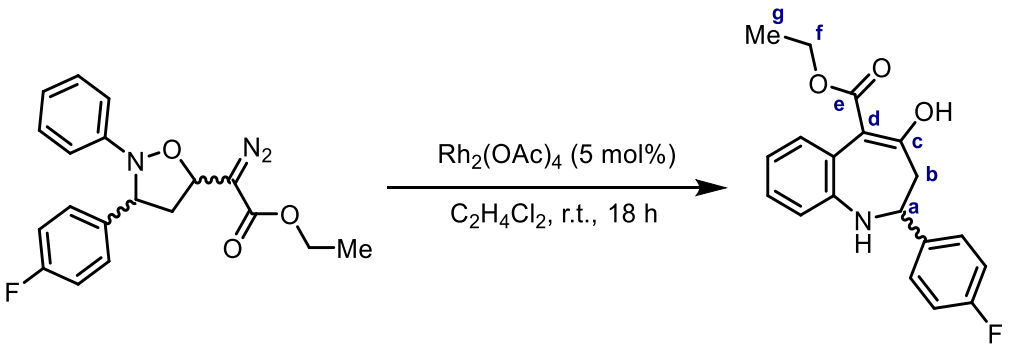
Synthesised in accordance with *GP5*, using $B(C_6F_5)_3$ (5 mg, 0.01 mmol), nitrone **3.65** (21.5 mg, 0.1 mmol), enoldiazo ester **3.103** (66.4 mg, 0.2 mmol) in toluene to afford **3.80**. All volatiles were removed *in vacuo* and the crude compound was purified *via* preparative thin layer

chromatography using silica gel and hexane/ethyl acetate (90:10 v/v) as eluent. The desired product (**3.80**) was obtained as a yellow oil. Yield: 16 mg, 0.03 mmol, 30%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.21 (d, *J* = 8.1 Hz, 2H, Ar–C**H**), 7.14 (dd, *J* = 8.5, 7.3 Hz, 2H, Ar–C**H**), 7.07–7.02 (m, 2H, Ar–C**H**), 7.01–6.95 (m, 4H, Ar–C**H**), 6.87–6.81 (m, 2H, Ar–C**H**), 6.65 (t, *J* = 8.9 Hz, 2H, Ar–C**H**), 5.64 (d, *J* = 11.7 Hz, 1H, C**H**^{b}), 5.26 (d, *J* = 11.4 Hz, 1H, C**H**^{a}), 3.84 (s, 3H, C**H**^{e}), 0.96 (s, 9H, OTBS), 0.03 (s, 3H, OTBS), -0.34 (s, 3H, OTBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 190.7 (**C**=O^c), 161.9 (d, $J_{C\text{-}F}$ = 245.0 Hz), 161.5 (**C**=O^d), 135.6, 132.9 (d, $J_{C\text{-}F}$ = 8.0 Hz), 130.1, 128.3, 127.9, 127.2, 124.3, 121.7, 113.5 (d, $J_{C–F}$ = 21.0 Hz), 75.8 (**C**H^a), 54.0 (**C**H^b), 52.3 (**C**H^e), 26.3, 18.2 (OTBS), -4.5 (OTBS), -5.2 (OTBS). **^{19}F NMR** (471 MHz, $CDCl_3$, 298 K) δ: -115.58. **IR ν_{max}** (cm^{-1}): 3063, 3034, 2955, 2928, 2857, 2137 (C=N_2), 1721 (C=O^d), 1655 (C=O^c), 1605, 1508, 1485, 1437, 1360, 1316, 1298, 1258, 1225, 1202, 1159, 1132, 1084, 1007. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{30}H_{35}N_3O_4FSi]^+$: 548.2381, found 548.2382.

6.1.8. Chapter 3: Further reactivity

*Synthesis of ethyl (±)-2-(4-fluorophenyl)-4-hydroxy-2,3-dihydro-1H-benzo[b]azepine-5-carboxylate (**3.83**)*

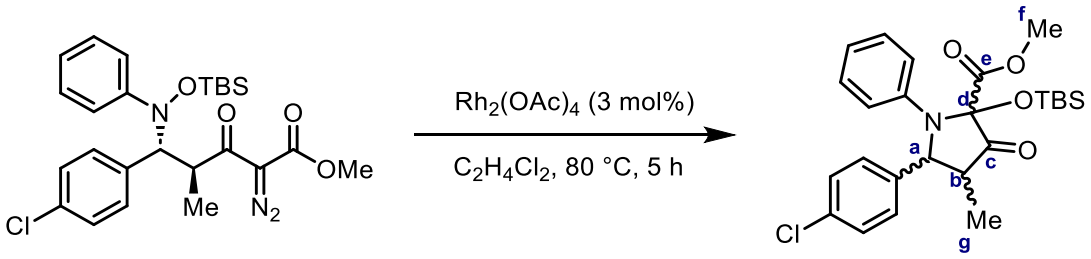


Following a reported method,[16] a microwave vial was charged with $Rh_2(OAc)_4$ (4.6 mg, 0.1 mmol, 0.05 equiv.), closed with a polytetrafluoroethylene (PTFE) crimper cap and evacuated/backfilled 3 times with nitrogen. Then, dry $C_2H_4Cl_2$ (1 mL) was added. Separately, ethyl 2-diazo-2-(3-(4-

fluorophenyl)-2-phenylisoxazolidin-5-yl)acetate (**3.51**) (74 mg, 2.1 mmol, 1 equiv.) was dissolved in dry $C_2H_4Cl_2$ (1 mL). This solution was then added dropwise to the $Rh_2(OAc)_4$ suspension. The reaction mixture was then left to stir overnight at room temperature. After 18 h, the reaction was stopped, and the reaction mixture was passed through a short pad of Celite. The solvent was removed and the crude oil was purified by flash column chromatography (9:1 hexane:EtOAc) to afford the desired product (**3.83**) as a yellow oil. Yield: 39 mg, 1.2 mmol, 57%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 13.13 (s, 1H, O**H**), 7.40 (dd, *J* = 8.0, 1.8 Hz, 1H, Ar–C**H**), 7.38–7.34 (m, 2H, Ar–C**H**), 7.18–7.12 (m, 1H, Ar–C**H**), 7.06–7.01 (m, 3H, Ar–C**H**), 6.82 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar–C**H**), 5.07 (dd, *J* = 7.6, 5.8 Hz, 1H, C**H**^{a}), 4.35–4.23 (m, 2H, C**H**$_2^f$), 2.61–2.51 (m, 2H, C**H**$_2^b$), 1.31 (t, *J* = 7.1 Hz, 3H, C**H**$_3^g$). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 174.8 (**C**^{c}), 171.7 (**C**=O), 162.5 (d, $J_{C\text{-}F}$ = 246.1 Hz), 143.8, 140.7, 132.1, 127.9 (d, $J_{C\text{-}F}$ = 8.1 Hz), 127.6, 126.2, 122.0, 121.5, 115.7 (d, $J_{C\text{-}F}$ = 21.6 Hz), 101.1 (**C**^{d}), 68.6 (**CH**^{a}), 61.1 (**CH**^{f}), 39.5 (**CH**^{b}), 14.3 (**CH**^{g}). **^{19}F NMR** (471 MHz, $CDCl_3$, 298 K) δ: -114.36. **IR ν_{max}** (cm^{-1}): 3352 (OH), 3055, 2980, 2928, 1713, 1638 (C=O), 1602 (C=C), 1506, 1474, 1398, 1379, 1341, 1329, 1294, 1281, 1260, 1219, 1157, 1096, 1059, 1015. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{19}H_{19}NO_3F]^+$: 328.1349, found 328.1349.

*Synthesis of methyl (±)-2-((tert-butyldimethylsilyl)oxy)-5-(4-chlorophenyl)-4-methyl-3-oxo-1-phenylpyrrolidine-2-carboxylate (**3.84**).*



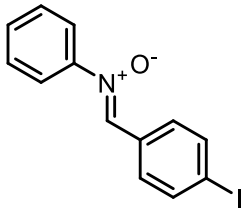
Following a reported method,[17] a microwave vial was charged with $Rh_2(OAc)_4$ (2 mg, 0.05 mmol, 0.03 equiv.), closed with a PTFE crimper cap and evacuated/backfilled 3 times with nitrogen. Then,

dry $C_2H_4Cl_2$ (1 mL) was added. Separately, methyl 5-(((tert-butyldimethylsilyl)oxy)(phenyl)amino)-5-(4-chlorophenyl)-2-diazo-4-methyl-3-oxopentanoate (**3.73**) (75 mg, 0.15 mmol, 1 equiv.) was dissolved in dry $C_2H_4Cl_2$ (1 mL). This solution was then added dropwise to the $Rh_2(OAc)_4$ suspension dropwise. The reaction mixture was then left to stir for 5 hours at 80 °C. After complete consumption of the starting material, the reaction was stopped, and the reaction mixture was passed through a short pad of Celite. The solvent was removed and the crude oil was purified by flash column chromatography (9:1 hexane:EtOAc) to afford the desired product (**3.84**) as a yellow oil. Yield: 44 mg, 0.09 mmol, 62%.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.39–7.35 (m, 2H, Ar–C**H**), 7.32–7.28 (m, 2H, Ar–C**H**), 7.13–7.06 (m, 2H, Ar–C**H**), 6.90 (dd, *J* = 8.9, 1.1, 2H, Ar–C**H**), 6.85–6.80 (m, 1H, Ar–C**H**), 4.62 (d, *J* = 7.5, 1H, C**H**^{a}), 3.50 (s, 3.54, C**H**^{f}), 2.63–2.56 (m, 1H, C**H**^{b}), 1.33 (d, *J* = 7.0, 3H, C**H**^{g}), 0.99 (s, 9H, OTBS), 0.37 (s, 3H, OTBS), 0.16 (s, 3H, OTBS). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ: 207.0 (**C**^{c}), 169.4(**C**^{e}), 143.2, 140.4, 133.5, 129.5, 128.8, 127.5, 121.3, 117.5, 92.0, 65.8 (**C**H^a), 53.0 (**C**H^f), 49.8 (**C**H^b), 25.9 (OTBS), 18.8 (OTBS), 11.8 (**C**H^g), -3.1 (OTBS), -3.4 (OTBS). **IR ν_{max}** (cm^{-1}): 2953, 2930, 2884, 2857, 1771 (C=O), 1755 (C=O), 1599, 1503, 1491, 1456, 1339, 1250, 1171, 1134, 1090, 1074, 1015. **HRMS** (ES+) $[M+H]^+$ calculated for $[C_{25}H_{33}NO_4SiCl]^+$: 474.1867, found 474.1864.

6.1.9. Chapter 4: Synthesis and characterisation of nitrones starting materials

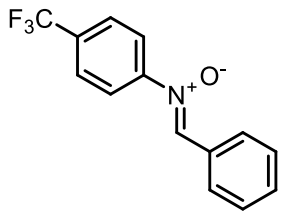
Synthesis of (Z)-1-(4-iodophenyl)-N-phenylmethanimine oxide **4.71**.



Synthesised according to *GP3* using 4-iodobenzaldehyde (1.16 g, 5.00 mmol), nitrobenzene (0.52 mL, 5.0 mmol), NH_4Cl (0.35 g, 6.5 mmol) and Zn powder (0.65 g, 10.1 mmol) in ethanol:water for 18 hours. Purification of the crude reaction by recrystallisation from EtOH gave nitrone **4.71** as a pale yellow solid (0.14 g, 0.07 mmol, 9%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 8.16–8.10 (m, 2H, Ar–C**H**), 7.88 (s, 1H, C**H**), 7.85–7.80 (m, 2H, Ar–C**H**), 7.80–7.74 (m, 2H, Ar–C**H**), 7.53–7.44 (m, 3H, Ar–C**H**). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 149.2, 134.7, 131.1, 130.8, 130.0, 129.3, 129.2, 128.8, 121.9. Data agrees with literature values.[327]

Synthesis of (Z)-1-phenyl-N-(4-(trifluoromethyl)phenyl)methanimine oxide **4.72**.

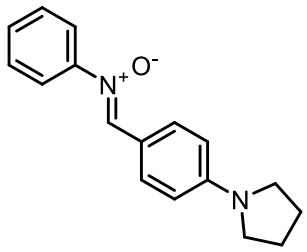


Synthesised according to *GP3* using benzaldehyde (0.35 mL, 3.4 mmol), 1-nitro-4-(trifluoromethyl)benzene (0.65 g, 3.4 mmol), NH_4Cl (0.24 g, 4.4 mmol) and Zn powder (0.44 g, 6.8 mmol) in ethanol:water for 18 hours. Purification of the crude reaction by recrystallisation from EtOH gave nitrone **4.72** as a white powder (0.26 g, 0.98 mmol, 29%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 8.43–8.38 (m, 2H, Ar–C**H**), 7.96 (s, 1H, C**H**), 7.93 (d, J = 8.1, 2H, Ar–C**H**), 7.79–7.75 (m, 2H, Ar–C**H**), 7.53–7.49 (m, 3H, Ar–C**H**). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 151.2, 135.5, 131.6, 130.2, 129.3, 128.8, 126.5 (q, J_{C-F}=3.8), 122.34. **^{19}F NMR** (376 MHz, $CDCl_3$, 298 K) δ: -62.67. Data agrees with literature values.[328]

Due to overlapping signals, it was not possible to observe two C–F couplings.

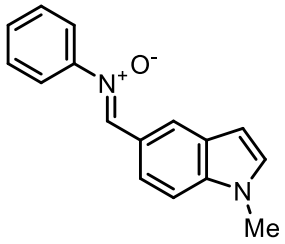
Synthesis of (Z)-N-phenyl-1-(4-(pyrrolidin-1-yl)phenyl)methanimine oxide **4.73**.



Synthesised according to *GP3* using 4-(pyrrolidin-1-yl)benzaldehyde (2.00 g, 11.4 mmol), nitrobenzene (1.17 mL, 11.4 mmol), NH_4Cl (0.79 g, 14.8 mmol) and Zn powder (1.48 g, 22.8 mmol) in ethanol:water for 18 hours. Purification of the crude reaction by recrystallisation from EtOH gave nitrone **4.73** as a yellow powder (0.72 g, 2.7 mmol, 24%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 8.33 (d, *J* = 8.9, 1H, Ar–C**H**), 7.78 (m, 2H, Ar–C**H**), 7.45 (m, 1H, Ar–C**H**), 7.40 (m, 1H, Ar–C**H**), 6.60 (d, *J* = 9.2, 1H, Ar–C**H**), 3.38 (m, 4H, N–C**H**$_2$–CH_2), 2.04 (m, 4H, N–CH_2–C**H**$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 149.6 (Ar–**C**), 149.1 (Ar–**C**), 135.2 (**C**H), 131.6 (Ar–**C**), 129.1 (Ar–**C**), 121.6 (Ar–**C**), 118.5 (Ar–**C**), 111.4 (Ar–**C**), 47.7 (N–**C**H_2–CH_2), 25.6 (N–CH_2–**C**H_2). **IR ν_{max}** (cm^{-1}): 3042, 2965, 2866, 2837, 1678, 1609, 1593, 1518, 1489, 1456, 1377, 1337, 1300, 1263, 1159, 1136, 1028. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{17}H_{19}N_2O]^+$: 267.1497, found 267.1496.

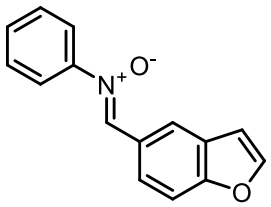
Synthesis of (Z)-1-(1-methyl-1H-indol-5-yl)-N-phenylmethanimine oxide **4.74**.



Synthesised according to *GP3* using 1-methyl-1H-indole-5-carbaldehyde (0.5 g, 3.1 mmol), nitrobenzene (0.32 mL, 3.1 mmol), NH_4Cl (0.22 g, 4.1 mmol) and Zn powder (0.41 g, 6.2 mmol) in ethanol:water for 2 hours. Purification of the crude reaction by recrystallisation from EtOH gave nitrone **4.74** as an orange powder (0.42 g, 1.7 mmol, 54%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 9.06 (m, 1H, Ar–C**H**), 8.10 (dd, *J* = 8.7, 1.6, 1H, Ar–C**H**), 8.03 (s, 1H, C**H**), 7.88–7.78 (m, 2H, Ar–C**H**), 7.54–7.44 (m, 3H, Ar–C**H**), 7.40 (dt, *J* = 8.7, 0.8, 1H, Ar–C**H**), 7.11 (d, *J* = 3.1, 1H, C2**H**), 6.61 (dd, *J* = 3.1, 0.9, 1H, C3**H**), 3.84 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 149.4 (Ar–**C**), 138.1 (Ar–**C**), 136.2 (**C**H), 130.2 (**C**1), 129.5 (Ar–**C**), 129.2 (Ar–**C**), 128.5(Ar–**C**), 123.8 (Ar–**C**), 123.3(Ar–**C**), 122.6 (Ar–**C**), 121.9 (Ar–**C**), 109.4 (Ar–**C**), 102.9 (**C**2), 33.1 (**C**H_3). **IR ν_{max}** (cm^{-1}): 3096, 3061, 2941, 1672, 1607, 1555, 1489, 1451, 1424, 1400, 1368, 1344, 1304, 1244, 1190, 1148, 1103, 1063, 1024. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{16}H_{15}N_2O]^+$: 251.1184, found 251.1189.

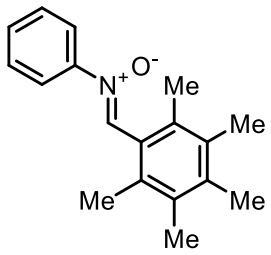
Synthesis of (Z)-1-(benzofuran-5-yl)-N-phenylmethanimine oxide **4.75**.



Synthesised according to *GP3* using 1-benzofuran-5-carbaldehyde (0.73 g, 5.0 mmol), nitrobenzene (0.51 mL, 5.0 mmol), NH_4Cl (0.35 g, 6.5 mmol) and Zn powder (0.65 g, 9.9 mmol) in ethanol:water for 18 hours. Purification of the crude reaction by recrystallisation from EtOAc gave nitrone **4.75** as a light orange solid (0.36 g, 1,5 mmol, 30%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 9.18 (d, *J* = 1.7, 1H, Ar–C**H**), 8.04–7.98 (m, 2H, Ar–C**H**+ C**H**), 7.85–7.76 (m, 2H, Ar–C**H**), 7.68 (d, *J* = 2.2, 1H, C1**H**), 7.57 (m, 1H, Ar–C**H**), 7.54–7.45 (m, 3H, Ar–C**H**), 6.86 (dd, *J* = 2.2, 1.0, 1H, C2**H**). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 156.1 (Ar–**C**), 149.2 (Ar–**C**), 146.2 (Ar–**C**), 135.0 (**C**H), 129.9 (Ar–**C**), 129.3 (Ar–**C**), 127.9 (Ar–**C**), 126.6 (**C**1), 126.0 (Ar–**C**), 122.5 (Ar–**C**), 121.9 (Ar–**C**), 111.8 (Ar–**C**), 107.4 (**C**2). **IR ν_{max}** (cm^{-1}): 3104, 3057, 1591, 1557, 1487, 1458, 1439, 1397, 1344, 1325, 1269, 1211, 1190, 1146, 1125, 1109, 1065, 1024. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{15}H_{12}NO_2]^+$: 238.0868, found 238.0866.

Synthesis of (Z)-1-(2,3,4,5,6-pentamethylphenyl)-N-phenylmethanimine oxide **4.76**.

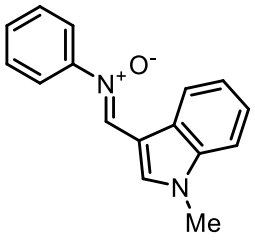


Synthesised according to *GP3* using 2,3,4,5,6-pentamethylbenzaldehyde (0.88 g, 5.0 mmol), nitrobenzene (0.51 mL, 5.0 mmol), NH_4Cl (0.35 g, 6.5 mmol) and Zn powder (0.65 g, 9.9 mmol) in ethanol:water for 24 hours. Purification of the crude reaction by recrystallisation from EtOH gave nitrone **4.76** as a white powder (0.15 g, 0.56 mmol 11%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 8.15 (s, 1H, C**H**), 7.84–7.78 (m, 2H, Ar–C**H**), 7.58–7.43 (m, 3H, Ar–C**H**), 2.27 (s, 6H, C**H**$_3$), 2.26 (s, 3H, C**H**$_3$), 2.24 (s, 6H, C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 148.7 (Ar–**C**), 137.1 (**C**H), 133.0 (Ar–**C**), 132.7 (Ar–**C**), 130.2(Ar–**C**), 129.3 (Ar–**C**), 129.3 (Ar–**C**), 126.5(Ar–**C**), 122.2 (Ar–**C**), 17.6 (**C**H$_3$), 17.1 (**C**H$_3$), 16.5 (**C**H$_3$). **IR ν_{max}** (cm^{-1}): 3057, 2938,

1587, 1541, 1487, 1458, 1385, 1371, 1296, 1192, 1105, 1057, 1022, 1001. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{18}H_{22}NO]^+$: 268.1701, found 268.1706.

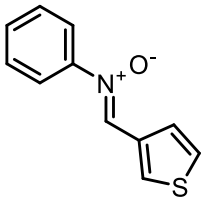
Synthesis of (Z)-1-(1-methyl-1H-indol-3-yl)-N-phenylmethanimine oxide **4.77**.



Synthesised according to *GP3* using 1-methyl-1*H*-indole-3-carbaldehyde (2.00 g, 12.6 mmol), nitrobenzene (1.3 mL, 12.6 mmol), NH_4Cl (0.87 g, 16.5 mmol) and Zn powder (1.66 g, 25.3 mmol) in ethanol:water for 24 hours. Purification of the crude reaction by recrystallisation from EtOH gave nitrone **4.77** as a white powder (0.61 g, 2.4 mmol, 20%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 9.17 (s, 1H, C**H**), 8.35 (d, *J* = 0.7, 1H, C2**H**), 7.92–7.83 (m, 2H, Ar–C**H**), 7.76 (dt, *J* = 7.9, 1.0, 1H, Ar–C**H**), 7.58–7.47 (m, 2H, Ar–C**H**), 7.47–7.40 (m, 2H, Ar–C**H**), 7.35 (ddd, *J* = 8.2, 7.0, 1.2, 1H, Ar–C**H**), 7.27 (ddd, *J* = 8.0, 7.0, 1.1, 1H, Ar–C**H**), 3.90 (s, 3H, C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 148.0 (Ar–**C**), 136.9 (**C**2), 134.4 (**C**H), 129.2 (Ar–**C**), 129.1 (Ar–**C**), 127.7 (**C**1), 127.2 (Ar–**C**), 123.3 (Ar–**C**), 121.3 (Ar–**C**), 121.2 (Ar–**C**), 118.2 (Ar–**C**), 110.3 (Ar–**C**), 107.5 (Ar–**C**), 33.6 (**C**H$_3$). **IR ν_{max}** (cm^{-1}): 3121, 3055, 3007, 1676, 1655, 1601, 1570, 1535, 1514, 1474, 1431, 1379, 1346, 1325, 1244, 1192, 1175, 1130, 1121, 1074, 1059, 1028, 1013. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{16}H_{15}N_2O]^+$: 251.1184, found 251.1190.

Synthesis of (Z)-N-phenyl-1-(thiophen-3-yl)methanimine oxide **4.78**.



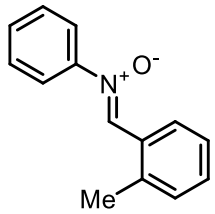
Synthesised according to *GP3* using thiophene-3-carbaldehyde (0.39 mL, 4.5 mmol), nitrobenzene (0.46 mL, 4.48 mmol), NH_4Cl (0.31 g, 5.8 mmol) and Zn powder (0.58 g, 9.0 mmol) in ethanol:water for 24 hours. Purification of the crude reaction by recrystallisation from EtOH gave nitrone **4.78** as a red solid (0.05 g, 0.25 mmol, 6%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 9.16 (dt, *J* = 3.1, 1.0, 1H, Ar–C**H**), 8.07 (d, *J* = 0.6, 1H, C**H**), 7.83–7.69 (m, 2H, Ar–C**H**), 7.51–7.43 (m, 4H, Ar–C**H**), 7.39 (dd, *J* = 5.1, 3.0, 1H, Ar–C**H**).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ: 148.2 (Ar–**C**H), 131.6 (Ar–**C**H), 130.4 (Ar–**C**H), 130.1 (**C**H), 129.4 (Ar–**C**H), 128.3 (Ar–**C**H), 125.6 (Ar–**C**H), 121.7 (Ar–**C**H). Data agrees with literature values.[284]

A quaternary carbon could not be observed.

Synthesis of (Z)-N-phenyl-1-(o-tolyl)methanimine oxide **4.79**.



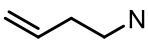
Synthesised according to *GP3* using 2-methylbenzaldehyde (0.98 mL, 8.4 mmol), nitrobenzene (0.85 mL, 8.4 mmol), NH_4Cl (0.58 g, 10.7 mmol) and Zn powder (1.09 g, 16.6 mmol) in ethanol:water for 24 hours. Purification of the crude reaction by recrystallisation from EtOH gave nitrone **4.79** as a red powder (0.48 g, 2.3 mmol, 27%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 9.49–9.13 (m, 1H, Ar–C**H**), 8.07 (s, 1H, C**H**), 7.82–7.72 (m, 2H, Ar–C**H**), 7.55–7.42 (m, 3H, Ar–C**H**), 7.41–7.31 (m, 2H, Ar–C**H**), 7.25 (m, 1H, Ar–C**H**), 2.45 (s, 3H, C**H**$_3$) **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 149.8 (Ar-**C**H), 137.1 (**C**H), 132.1 (Ar–**C**H), 130.9 (Ar–**C**H), 130.5 (Ar–**C**H), 130.0 (Ar–**C**H), 129.3 (Ar–**C**H), 129.1 (Ar–**C**H), 128.1 (Ar–**C**H), 126.6 (Ar–**C**H), 122.1 (Ar–**C**H), 20.1 (**C**H$_3$). Data agrees with literature values.[284]

6.1.10. Chapter 4: Synthesis and characterisation of nitro starting materials

General procedure 7 (GP7): Under air, the bromo starting material (1 equiv.) was dissolved in DMSO (0.1 M). To this solution, $NaNO_2$ (2 equiv.) was added portion wise over the course of 5 minutes and the reaction mixture was left to stir for 3 hours at room temperature. Subsequently, the reaction was quenched with ice and extracted several times with Et_2O. The organic layers were then collected and dried over $MgSO_4$ and the solvent was removed under a stream of compressed air. The remaining oil was then purified with a static vacuum-short path distillation to afford the nitro compound which was then used for the next step without further purification.

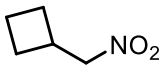
Synthesis of 4-nitrobut-1-ene **4.80**.



Synthesised according to *GP7* using 4-bromobut-1-ene (2.00 mL, 19.3 mmol) and $NaNO_2$ (2.70 g, 38.5 mmol) in DMSO for 3 hours. After distillation, 4-nitrobut-1-ene **4.80** was obtained as a colourless oil (0.48 g, 4.8 mmol, 24%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 5.76 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H, C**H**), 5.30–5.07 (m, 2H, C**H**$_2$), 4.43 (t, *J* = 7.0 Hz, 2H, C**H**$_2$), 2.82–2.65 (m, 2H, C**H**$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 131.9 (**C**H), 119.0 (**C**H$_2$), 74.8 (**C**H$_2$), 31.4 (**C**H$_2$). Data agrees with literature values.[329]

Synthesis of (nitromethyl)cyclobutane **4.81**.

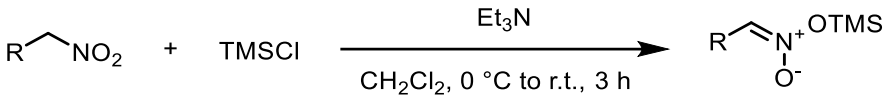


Synthesised according to *GP7* using (bromomethyl)cyclobutane (2.00 mL, 17.9 mmol) and $NaNO_2$ (2.47 g, 35.7 mmol) in DMSO for 3 hours. After distillation, 0.41 mg of

(nitromethyl)cyclobutane **4.81** were obtained as a yellow oil containing 37% of unreacted (bromomethyl)cyclobutene and DMSO.

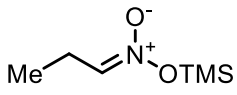
^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 4.38 (d, *J* = 7.6, 2H αC**H**$_2$), 3.01 (tt, *J* = 10.2, 6.6, 1H, C**H**), 2.05–1.64 (m, 6H, C**H**$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 80.2 (α**C**H_2), 33.5 (**C**H), 27.3 (**C**H_2), 25.8 (**C**H_2), 18.2 (**C**H_2), 17.0 (**C**H_2). **IR ν_{max}** (cm^{-1}): 2255, 1638, 1549, 1375, 1319, 1015. **HRMS** (EI): $[M]^+$ calculated for $[C_5H_9NO_2]^+$: 115.06278, found 115.0628.

6.1.11. Chapter 4: Synthesis and characterisation of silyl nitronate starting materials



General procedure 8 (GP8): The nitro compound (1 equiv.) and TMSCl (1.05 equiv.) were dissolved in anhydrous CH_2Cl_2 (0.05 M) and cooled to 0 °C. To the resulting mixture freshly distilled Et_3N (1.05 equiv.) was added in one portion and the solution was left to stir at 0 °C for 15 minutes. Then, the ice bath was removed, and the reaction was left to stir for 3 h at room temperature. Subsequently, the solvent was removed using a secondary trap and the remaining white solid was washed three times with anhydrous pentane. Each washing was transferred to a dry vessel by filter cannula. The pentane was subsequently removed using a secondary trap and the leftover yellow oil was then transferred inside a nitrogen-filled glovebox and stored in a -38 °C freezer in the dark. Due to the reported[268] instability of the silyl nitronates towards light, air and temperature, full characterisation was not possible and only ^{1}H NMR and ^{13}C NMR spectra are given. The configuration of all the silyl nitronates has been assigned based on the *J* value which is consistent with a cis (or (*E*)) configuration. In the case of **4.92** and **4.93**, we believe that the TMS group sits between the two negatively charged oxygen atoms, giving rise to a symmetric molecule which yields only one 2 peaks for compound **4.92** and 3 peaks for compound **4.93**.

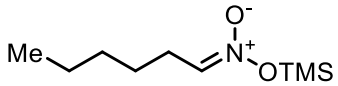
Synthesis of trimethylsilyl (E)-propylideneazinate **4.30**.



Synthesised according to *GP8* using 1-nitropropane (1.00 mL, 11.2 mmol), TMSCl (1.5 mL, 11.8 mmol) and Et_3N (1.6 mL, 11.8 mmol) in dichloromethane for 3 hours. After removal of the solvent, compound **4.30** was obtained as a pale-yellow oil (0.78 g, 4.8 mmol, 43%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 6.09 (t, *J* = 6.3, 1H, C**H**), 2.31 (qd, *J* = 7.6, 6.3, 2H, C**H**$_2$), 1.08 (t, *J* = 7.7, 3H, C**H**$_3$), 0.31 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 118.4 (**C**H), 20.1 (**C**H_2), 10.4 (**C**H_3), 0.1 (TMS–**C**H_3).

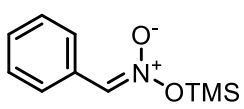
Synthesis of trimethylsilyl (E)-hexylideneazinate **4.82**.



Synthesised according to *GP8* using 1-nitrohexane (1.10 mL, 7.9 mmol), TMSCl (1.02 mL, 8.3 mmol) and Et_3N (1.15 mL, 8.3 mmol) in dichloromethane for 3 hours. After removal of the solvent, compound **4.82** was obtained as a yellow oil (1.15 g, 5.7 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 6.09 (t, *J* = 6.4, 1H, C**H**), 2.28 (td, *J* = 7.5, 6.5, 2H, C**H**$_2$), 1.48 (m, 2H, C**H**$_2$), 1.36–1.23 (m, 4H, C**H**$_2$), 0.94–0.81 (m, 3H, C**H**$_3$), 0.30 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 117.5 (**C**H), 31.6 (**C**H_2), 26.5 (**C**H_2), 25.7 (**C**H_2), 22.5 (**C**H_2), 14.1 (**C**H_2), 0.1 (TMS–**C**H_3).

Synthesis of trimethylsilyl (E)-benzylideneazinate **4.83**.

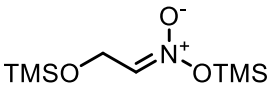


Synthesised according to *GP8* using (nitromethyl)benzene (0.42 mL, 3.6 mmol), TMSCl (0.51 mL, 4.0 mmol) and Et_3N (0.56 mL, 4.0 mmol) in dichloromethane

for 3 hours. After removal of the solvent, compound **4.83** was obtained as a yellow oil (0.55 g, 2.6 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.90–7.83 (m, 2H, Ar–C**H**), 7.43–7.30 (m, 3H, Ar–C**H**), 7.03 (s, 1H, C**H**), 0.38 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 129.6 (Ar–**C**H), 129.3 (Ar–**C**H), 128.7 (Ar–**C**H), 127.5 (Ar–**C**H), 116.4 (**C**H), 0.1 (TMS–**C**H_3).

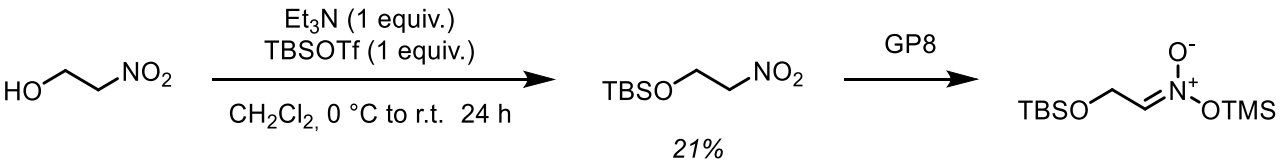
Synthesis of trimethylsilyl (E)-(2-((trimethylsilyl)oxy)ethylidene)azinate **4.84**.



Synthesised according to *GP8* using 2-nitroethan-1-ol (0.50 mL, 7.0 mmol), TMSCl (1.86 mL, 14.6 mmol) and Et_3N (2.04 mL, 14.6 mmol) in dichloromethane for 3 hours. After removal of the solvent, compound **4.84** was obtained as a yellow oil (0.96 g, 4.1 mmol, 58%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 6.23 (t, *J* = 5.3, 1H, C**H**), 4.35 (d, *J* = 5.3, 2H, C**H**$_2$), 0.29 (s, 9H, TMS–C**H**$_3$), 0.12 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 116.7 (**C**H), 57.8 (**C**H_2), 0.1 (TMS–**C**H_3), -0.5 (TMS–**C**H_3).

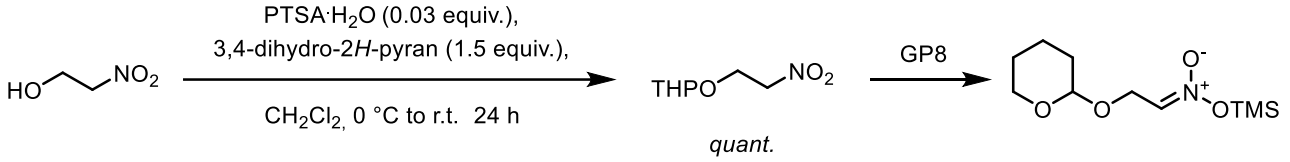
Synthesis of trimethylsilyl (E)-(2-((tert-butyldimethylsilyl)oxy)ethylidene)azinate **4.85**.



Synthesised according to *GP8* using tert-butyldimethyl(2-nitroethoxy)silane[330] (0.59 g, 2.9 mmol), TMSCl (0.38 mL, 3.0 mmol) and Et_3N (0.42 mL, 3.0 mmol) in dichloromethane for 3 hours. After removal of the solvent, compound **4.85** was obtained as a yellow oil (0.61 g, 2.2 mmol, 77%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 6.24 (t, *J* = 5.1, 1H, C**H**), 4.40 (d, *J* = 5.1, 3H, C**H**$_2$), 0.89 (s, 9H, TBS–C**H**$_3$), 0.31 (s, 9H, TMS–C**H**$_3$), 0.08 (s, 6H, TBS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 117.2 (**C**H), 58.5 (**C**H$_2$), 25.9 (TBS–**C**H$_3$), 18.4 (TBS–**C**), 0.1 (TMS–**C**H$_3$), -5.3 (TBS–**C**H$_3$).

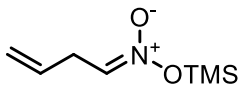
Synthesis of trimethylsilyl (E)-(2-((tert-butyldimethylsilyl)oxy)ethylidene)azinate **4.86**.



Synthesised according to *GP8* using 2-(2-nitroethoxy)tetrahydro-2*H*-pyran[330] (0.50 g, 2.9 mmol), TMSCl (0.38 mL, 3.0 mmol) and Et_3N (0.38 mL, 3.0 mmol) in dichloromethane for 3 hours. After removal of the solvent, compound **4.86** was obtained as a yellow oil (0.47 g, 1.9 mmol, 67%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 6.31 (t, *J* = 5.6, 1H, C**H**), 4.64 (m, 1H, O–C**H**–O), 4.39–4.28 (m, 2H, C**H**$_2$), 3.87–3.81 (m, 1H, O–C**H**$_2$), 3.54–3.49 (m, 1H, O–C**H**$_2$), 1.83–1.48 (m, 6H, C**H**$_2$), 0.30 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 114.6 (**C**H), 99.2 (O–**C**H–O), 62.5 (**C**H$_2$), 61.8 (O–**C**H$_2$), 30.5 (**C**H$_2$), 25.4 (**C**H$_2$), 19.4 (**C**H$_2$), 0.0 (TMS–**C**H$_3$).

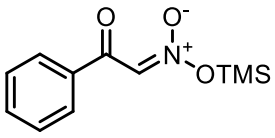
Synthesis of trimethylsilyl (E)-but-3-en-1-ylideneazinate **4.87**.



Synthesised according to *GP8* using *4-nitrobut-1-ene* (0.48 g, 4.8 mmol), TMSCl (0.63 mL, 5.0 mmol) and Et_3N (0.69 mL, 5.0 mmol) in dichloromethane for 3 hours. After removal of the solvent, compound **4.87** was obtained as a yellow oil (0.55 g, 67%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 6.12 (td, *J*=6.3, 1.1, 1H, C**H**), 5.81–5.71 (m, 1H, vinylic C**H**), 5.15–5.07 (m, 2H, vinylic C**H**$_2$), 3.01 (m, 2H, C**H**$_2$), 0.28 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 131.3 (**C**H), 117.7 (vinylic **C**H$_2$), 114.6 (vinylic **C**H), 30.7 (**C**H$_2$), 0.0, (TMS–**C**H$_3$).

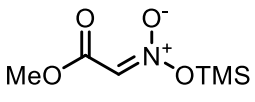
Synthesis of trimethylsilyl (E)-(2-oxo-2-phenylethylidene)azinate **4.88**.



Synthesised according to *GP8* using 2-nitro-1-phenylethan-1-one (1.00 g, 6.1 mmol), TMSCl (0.81 mL, 6.4 mmol) and Et_3N (0.89 mL, 6.4 mmol) in dichloromethane for 3 hours. After removal of the solvent, compound **4.88** was obtained as a yellow oil (0.19 g, 0.8 mmol, 13%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.57–7.38 (m, 6H, Ar–C**H**+C**H**), 0.26 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 160.1 (**C**=O), 134.4 (Ar–**C**), 132.0 (Ar–**C**), 129.0 (Ar–**C**), 127.1 (Ar–**C**), 121.9 (**C**H), 0.8 (TMS–**C**H$_3$).

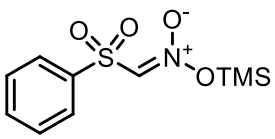
Synthesis of methyl (E)-2-(oxido((trimethylsilyl)oxy)azaneylidene)acetate **4.89**.



Synthesised according to *GP8* using methyl 2-nitroacetate (0.39 mL, 4.2 mmol), TMSCl (0.56 mL, 4.4 mmol) and Et_3N (0.62 mL, 4.4 mmol) in dichloromethane for 18 hours. After removal of the solvent, compound **4.89** was obtained as a yellow oil (0.32 g, 1.7 mmol, 40%).

^{1}HNMR (400 MHz, $CDCl_3$, 298 K) δ: 6.69 (s, 1H, C**H**), 3.77 (s, 3H, OC**H**$_3$), 0.32 (s, 9H, TMS–C**H**$_3$). **^{13}CNMR** (101 MHz, $CDCl_3$, 298 K) δ: 161.1 (**C**=O), 107.2 (**C**H), 52.1 (O**C**H$_3$), -0.3 (TMS–**C**H$_3$).

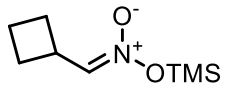
Synthesis of trimethylsilyl (E)-((phenylsulfonyl)methylene)azinate **4.90**.



Synthesised according to *GP8* using nitromethyl phenyl sulfone (0.50 g, 2.5 mmol), TMSCl (0.33 mL, 2.6 mmol) and Et_3N (0.36 mL, 2.6 mmol) in dichloromethane for 3 hours. After removal of the solvent, compound **4.90** was obtained as a yellow oil (0.12 g) and used as is without further purification.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 8.03–7.97 (m, 2H, Ar–C**H**), 7.64–7.50 (m, 3H, Ar–C**H**), 7.21 (br. s, 1H, C**H**), 0.24 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 134.9 (Ar–**C**), 129.6 (Ar–**C**), 129.4 (Ar–**C**), 129.0 (Ar–**C**), 124.4 (**C**H), -0.5 (TMS–**C**H_3).

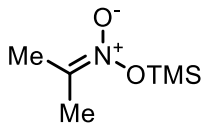
Synthesis of trimethylsilyl (E)-(cyclobutylmethylene)azinate **4.91**.



Synthesised according to *GP8* using *(nitromethyl)cyclobutane* (0.42 g, 3.7 mmol), TMSCl (0.49 mL, 3.8 mmol) and Et_3N (0.53 mL, 3.8 mmol) in dichloromethane for 3 hours. After removal of the solvent the yellow oil was also distilled, affording compound **4.91** as a yellow oil (0.15 g).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 6.16 (d, J = 7.0, 1H, C**H**), 3.41–3.31 (m, 1H, C**H**), 2.29–2.21 (m, 2H, C**H**$_2$), 2.01–1.84 (m, 4H, C**H**$_2$), 0.28 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 120.8 (**C**H), 32.2 (**C**H), 26.9(**C**H_2), 19.3 (**C**H_2), 0.1 (TMS–**C**H_3).

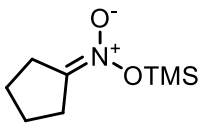
Synthesis of trimethylsilyl propan-2-ylideneazinate **4.92**.



Synthesised according to *GP8* using 2-nitropropane (0.51 mL, 5.6 mmol), TMSCl (0.75 mL, 5.9 mmol) and Et_3N (0.82 mL, 5.9 mmol) in dichloromethane for 18 hours. After removal of the solvent, compound **4.92** was obtained as a yellow oil (0.65 g, 72%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 1.97 (s, 6H, C**H**$_3$), 0.28 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 121.4 (**C**), 18.5 (**C**H_3), 0.4 (TMS–**C**H_3).

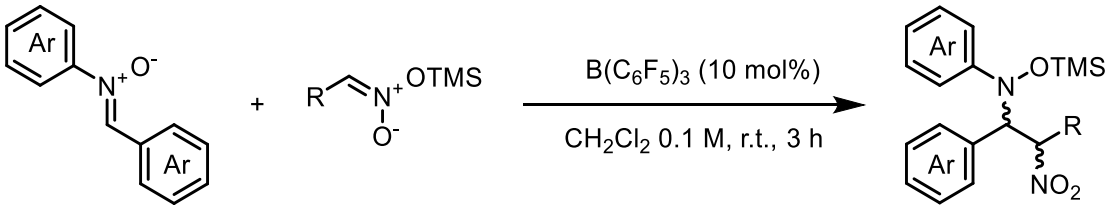
Synthesis of trimethylsilyl cyclopentylideneazinate **4.93**.



Synthesised according to *GP8* using nitrocyclopentane (0.25 mL, 2.4 mmol), TMSCl (0.31 mL, 2.5 mmol) and Et_3N (0.35 mL, 2.5 mmol) in dichloromethane for 18 hours. After removal of the solvent, compound **4.93** was obtained as a green oil (0.36 g, 1.9 mmol, 82%).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 2.49–2.46 (m, 4H, C**H**$_2$), 1.79–1.75 (m, 4H, C**H**$_2$), 0.31–0.02 (m, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 132.5 (**C**), 30.0 (**C**H_2), 25.6 (**C**H_2), 0.4(TMS–**C**H_3).

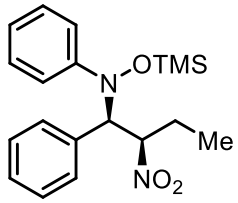
6.1.12. Chapter 4: Synthesis and characterisation of products



General procedure 9 (GP9): Inside a nitrogen-filled glovebox, nitrone (1 equiv.), $B(C_6F_5)_3$ (5 mg, 0.01 mmol) and a Teflon-coated magnetic stirring bar were added to a microwave vial, which was subsequently closed with a crimp cap. Silyl-nitronate (2 equiv.) was added to another microwave vial, which was also closed with a crimp cap. The two vials were taken out from the glovebox, and 0.5 mL of solvent was added to each vessel (1 mL in total). Subsequently, the solution of silyl-nitronate was added dropwise at room temperature to the solution of $B(C_6F_5)_3$ and nitrone under vigorous stirring (500–1000 rpm) and left to react for the set amount of time. After completion, the crimp cap was removed and the crude reaction mixture was transferred to a 10 mL round bottom flask in order to remove all the volatiles with rotary evaporation. To the crude product, 1 equiv. of 1,3,5-trimethoxybenzene and 0.5 mL of $CDCl_3$ were added to calculate the NMR spectroscopic yield. After

the NMR spectroscopic measurement, the crude reaction solution was dried under vacuum and purified either with preparative TLC or column chromatography to afford the desired product.

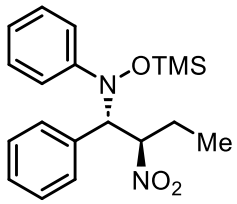
*Synthesis of (±)-N-((1R,2R)-2-nitro-1-phenylbutyl)-N-phenyl-O-(trimethylsilyl)hydroxylamine syn-***4.31**.



Synthesised according to *GP9* using nitrone **3.42** (19.7 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 9:1 mixture of cyclohexane:ethyl acetate afforded *syn*-**4.31** as a yellow oil (25 mg, 70%). R_f 0.74 (Cy:AcOEt 8:2).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.28 (m, 1H, Ar–C**H**), 7.21 (m, 2H, Ar–C**H**), 7.16–7.11 (m, 2H, Ar–C**H**), 7.00 (m, 1H, Ar–C**H**), 6.91 (d, *J* = 7.0, 2H, Ar–C**H**), 6.89–6.86 (m, 2H, Ar–C**H**), 5.17 (td, *J* = 10.6, 3.5, 1H, C**H**–NO_2), 4.71 (d, *J* = 10.9, 1H, C**H**–N), 1.71–1.61 (m, 1H, C$\mathbf{H}_2$), 1.56–1.50 (m, 1H, C$\mathbf{H}_2$), 0.89 (t, *J* = 7.4, 3H, C$\mathbf{H}_3$), 0.08 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.1 (Ar–**C**), 131.9 (Ar–**C**), 130.8 (Ar–**C**), 128.5 (Ar–**C**), 128.2 (Ar–**C**), 127.8 (Ar–**C**), 124.6 (Ar–**C**), 121.1 (Ar–**C**), 91.0 (**C**–NO_2), 76.9 (**C**–N), 25.5 (**C**H_2), 10.1 (**C**H_3), -0.2 (TMS–**C**H_3). **IR** ν_{max} (cm^{-1}): 3065, 3032, 2965, 2899, 2160, 1975, 1595, 1580, 1553 (asym. NO_2), 1485, 1452, 1373, 1341, 1323, 1312, 1252 (sym. NO_2), 1206, 1084, 1015. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{19}H_{27}N_2O_3Si]^+$: 359.1791, found 359.1785.

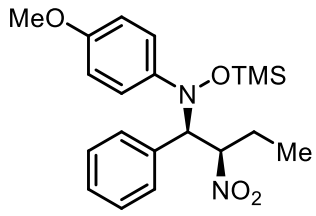
*Synthesis of (±)-N-((1S,2R)-2-nitro-1-phenylbutyl)-N-phenyl-O-(trimethylsilyl)hydroxylamine anti-***4.31**.



Synthesised according to *GP9* using nitrone **3.42** (19.7 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 9:1 mixture of cyclohexane:ethyl acetate afforded *anti*-**4.31** as a white solid (4 mg, 11%). R_f 0.56 (Cy:AcOEt 8:2).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.22 (m, 1H, Ar–C**H**), 7.19–7.12 (m, 4H, Ar–C**H**), 7.00 (m, 1H, Ar–C**H**), 6.96 (dd, *J* = 7.0, 1.6, 2H, Ar–C**H**), 6.84 (dd, *J* = 8.6, 1.2, 2H, Ar–C**H**), 5.15 (td, *J* = 10.9, 2.7, 1H, C**H**–NO_2), 4.43 (d, *J* = 10.7, 1H, C**H**–N), 2.75 (m, 1H, C**H**$_2$), 2.21 (m, 1H, C**H**$_2$), 1.11 (t, *J* = 7.4, 3H, C**H**$_3$), 0.07 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.2 (Ar–**C**), 131.6 (Ar–**C**), 130.4 (Ar–**C**) 128.5 (Ar–**C**), 128.4 (Ar–**C**), 127.4 (Ar–**C**), 124.4 (Ar–**C**), 120.4 (Ar–**C**), 90.9 (**C**–NO_2), 76.6 (**C**–N), 26.7 (**C**H_2), 10.4 (**C**H_3), 1.2 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 2963, 2930, 2207, 2156, 2041, 2031, 1952, 1593, 1543 (asym. NO_2), 1485, 1454, 1377, 1302, 1258 (sym. NO_2), 1202, 1076, 1017. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{19}H_{27}N_2O_3Si]^+$: 359.1791, found 359.1778.

Synthesis of (±)-N-(4-methoxyphenyl)-N-((1R,2R)-2-nitro-1-phenylbutyl)-O-(trimethylsilyl)hydroxyl amine syn-**4.32**.

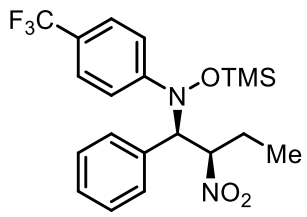


Synthesised according to *GP9* using nitrone **3.98** (22.7 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 9:1 mixture of cyclohexane:ethyl acetate afforded *syn*-**4.32** as a yellow oil (11 mg, 28%). R_f 0.72 (Cy:AcOEt 9:1). *This compound is not stable under ambient conditions, and it decomposes over a short period of time*.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.30–7.28 (m, 1H, Ar–C**H**), 7.23–7.19 (m, 2H, Ar–C**H**), 6.91 (m, 2H, Ar–C**H**), 6.80–6.76 (m, 2H, Ar–C**H**), 6.67–6.63 (m, 2H, Ar–C**H**), 5.08 (td, *J* = 10.6, 3.4, 1H,

C**H**–NO_2), 4.60 (d, *J* = 10.8, 1H, C**H**–N), 3.74 (s, 3H, OC**H**$_3$), 1.61 (m, 1H, C**H**$_2$), 1.48 (m, 1H, C**H**$_2$), 0.86 (t, *J* = 7.4, 3H, C**H**$_3$), 0.04 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 156.9 (Ar–**C**), 144.9 (Ar–**C**), 132.4 (Ar–**C**), 130.9 (Ar–**C**), 128.4 (Ar–**C**), 127.8 (Ar–**C**), 123.3 (Ar–**C**), 113.3 (Ar–**C**), 91.2 (**C**–NO_2), 76.9 (**C**–N), 55.4 (O**C**H_3), 25.5 (**C**H_2), 10.2 (**C**H_3), -0.2 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 3032, 2957, 2836, 2033, 2024, 1607, 1587, 1553 (asym. NO_2), 1503, 1456, 1441, 1414, 1373, 1341, 1323, 1298, 1246 (sym. NO_2), 1206, 1180, 1163, 1105, 1084, 1034. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{20}H_{29}N_2O_4Si]^+$: 389.1897, found 389.1893.

Synthesis of (±)-N-((1R,2R)-2-nitro-1-phenylbutyl)-N-(4-(trifluoromethyl)phenyl)-O-(trimethylsilyl) hydroxylamine syn-**4.33**.

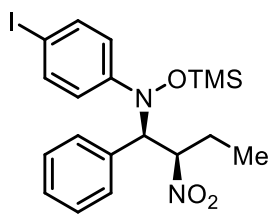


Synthesised according to *GP9* using nitrone **4.72** (26.5 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 24 hours. Purification of the crude reaction mixture through preparative TLC with a 9:1 mixture of cyclohexane:ethyl acetate afforded *syn*-**4.33** as a yellow oil (13 mg, 31%). R_f 0.65 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.41 (d, *J* = 8.2, 2H, Ar–C**H**), 7.30 (m, 1H, Ar–C**H**), 7.22 (m, 2H, Ar–C**H**), 6.99 (d, *J* = 8.1, 2H, Ar–C**H**), 6.91 (d, *J* = 7.0, 2H, Ar–C**H**), 5.19 (m, 1H, C**H**–NO_2), 4.77 (d, *J* = 11.0, 1H, C**H**–N), 1.70–1.52 (m, 2H, C**H**$_2$), 0.90 (t, *J* = 7.4, 3H, C**H**$_3$), 0.10 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 155.4 (Ar–**C**), 131.2 (Ar–**C**), 130.6 (Ar–**C**), 128.9 (Ar–**C**), 128.0 (Ar–**C**), 125.6 (m, **C**F_3), 120.4 (Ar–**C**), 90.7 (**C**–NO_2), 76.8 (**C**–N), 25.5 (**C**H_2), 10.1 (**C**H_3), -0.2 (TMS–**C**H_3). **^{19}F NMR** (376 MHz, $CDCl_3$, 298K) δ: -61.93. **IR ν_{max}** (cm^{-1}): 3032, 2974, 2940, 2328, 2205, 2182, 2031, 2014, 1614, 1555 (asym. NO_2), 1508, 1454, 1414, 1375, 1323 (sym. NO_2), 254, 1218, 1165, 1121, 1109, 1067, 1011. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{20}H_{26}N_2O_3F_3Si]^+$: 427.1665, found 427.1660.

Due to overlapping signals, it was not possible to observe one C–F coupling.

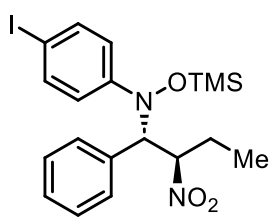
*Synthesis of (±)-N-(4-iodophenyl)-N-((1R,2R)-2-nitro-1-phenylbutyl)-O-(trimethylsilyl)hydroxylamine syn-***4.34**.



Synthesised according to *GP9* using nitrone **3.97** (32.3 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 95:5 mixture of cyclohexane:ethyl acetate afforded *syn*-**4.34** as a yellow oil (32 mg, 66%). R_f 0.76 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.44 (m, 2H, Ar–C**H**), 7.29 (m, 1H, Ar–C**H**), 7.23 (m, 2H, Ar–C**H**), 6.91 (d, *J* = 6.9, 2H, Ar–C**H**), 6.64 (m, 2H, Ar–C**H**), 5.13 (td, *J* = 10.5, 3.5, 1H, C**H**–NO_2), 4.66 (d, *J* = 10.9, 1H, C**H**–N), 1.63 (m, 1H, C$\mathbf{H}_2$), 1.52 (m, 1H, C$\mathbf{H}_2$), 0.88 (t, *J* = 7.4, 3H, C$\mathbf{H}_3$), 0.07 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.1 (Ar–**C**), 137.3 (Ar–**C**), 131.4 (Ar–**C**), 130.7 (Ar–**C**), 128.7 (Ar–**C**), 127.9 (Ar–**C**), 123.1 (Ar–**C**), 90.8 (**C**–NO_2), 88.4 (Ar–**C**), 76.8, (**C**–N), 25.5 (**C**H_2), 10.1 (**C**H_3), -0.2 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 3026, 2986, 2326, 2205, 2166, 2033, 2018, 1983, 1721, 1680, 1553 (asym. NO_2), 1478, 1454, 1391, 1373, 1312, 1252 (sym. NO_2), 1209, 1101, 1003. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{19}H_{26}N_2O_3Si^{127}I]^+$: 485.0757, found 485.0757.

*Synthesis of (±)-N-(4-iodophenyl)-N-((1S,2R)-2-nitro-1-phenylbutyl)-O-(trimethylsilyl)hydroxylamine anti-***4.34**.

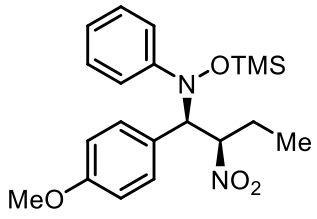


Synthesised according to *GP9* using nitrone **3.97** (32.3 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 95:5

mixture of cyclohexane:ethyl acetate afforded *anti*-**4.34** as a white solid (6 mg, 12%). R_f 0.70 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.46 (m, 2H, Ar–C**H**), 7.23 (m, 1H, Ar–C**H**), 7.16 (m, 2H, Ar–C**H**), 6.98–6.96 (m, 2H, Ar–C**H**), 6.61 (m, 2H, Ar–C**H**), 5.12 (td, *J* = 10.9, 2.7, 1H, C**H**–NO_2), 4.38 (d, *J* = 10.8, 1H, C**H**–N), 2.69 (m, 1H, C$\mathbf{H}_2$), 2.19 (m, 1H, C$\mathbf{H}_2$), 1.10 (t, *J* = 7.4, 3H, C$\mathbf{H}_3$), 0.07 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.3 (Ar–**C**), 137.5 (Ar–**C**), 131.2 (Ar–**C**), 130.3 (Ar–**C**), 128.8 (Ar–**C**), 127.6 (Ar–**C**), 122.5 (Ar–**C**), 90.7 (**C**–NO_2), 88.0 (Ar–**C**), 76.6 (**C**–N), 26.7 (**C**H_2), 10.4 (**C**H_3), -0.1 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 3063, 3030, 2986, 2957, 2851, 2326, 2151, 2016, 1580, 1551 (asym. NO_2), 1495, 1478, 1454, 1391, 1373, 1299, 1252 (sym. NO_2), 1206, 1169, 1101, 1078, 1057, 1003. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{19}H_{26}N_2O_3Si^{127}I]^+$: 485.0757, found 485.0757.

Synthesis of (±)-N-((1R,2R)-1-(4-methoxyphenyl)-2-nitrobutyl)-N-phenyl-O-(trimethylsilyl)hydroxyl amine syn-**4.35**.

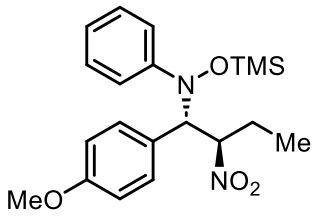


Synthesised according to *GP9* using nitrone **3.90** (22.7 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 9:1 mixture of cyclohexane:ethyl acetate afforded to afford *syn*-**4.35** as a yellow oil (29 mg, 75%). R_f 0.72 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.16–7.12 (m, 2H, Ar–C**H**), 6.99 (m, 1H, Ar–C**H**), 6.89–6.87 (m, 2H, Ar–C**H**), 6.83 (d, *J* = 8.1, 2H, Ar–C**H**), 6.730 (m, 2H, Ar–C**H**), 5.12 (td, *J* = 10.5, 3.6, 1H, C**H**–NO_2), 4.65 (d, *J* = 10.9, 1H, C**H**–N), 3.77 (s, 3H, OC$\mathbf{H}_3$), 1.63 (m, 1H, C$\mathbf{H}_2$), 1.53 (m, 1H, C$\mathbf{H}_2$), 0.88 (t, *J* = 7.4, 3H, C$\mathbf{H}_3$), 0.07 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 159.6 (Ar–**C**), 152.2 (Ar–**C**), 131.8 (Ar–**C**), 128.2 (Ar–**C**), 124.5 (Ar–**C**), 124.0 (Ar–**C**), 121.1 (Ar–**C**),

113.1 (Ar–**C**), 91.2 (**C**–NO_2), 76.3 (**C**–N), 55.2 (O**C**H_3), 25.5 (**C**H_2), 10.1 (**C**H_3), -0.2 (TMS–**C**H_3). **IR** ν_{max} (cm^{-1}): 3057, 2957, 2837, 1611, 1595, 1586, 1553 (asym. NO_2), 1512, 1487, 1460, 1443, 1422, 1373, 1341, 1323, 1306, 1285, 1250 (sym. NO_2), 1229, 120, 1180, 1130, 1105, 1078, 1034. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{20}H_{29}N_2O_4Si]^+$: 389.1897, found 389.1885.

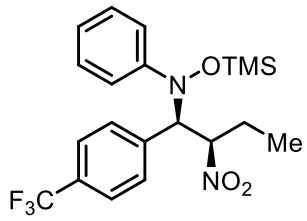
*Synthesis of (±)-N-((1S,2R)-1-(4-methoxyphenyl)-2-nitrobutyl)-N-phenyl-O-(trimethylsilyl)hydroxyl amine anti-***4.35**.



Synthesised according to *GP9* using nitrone **3.90** (22.7 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 9:1 mixture of cyclohexane:ethyl acetate afforded to afford *anti*-**4.35** as a white solid (2 mg, 5%). R_f 0.66 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.16 (m, 2H, Ar–C**H**), 7.0 (m, 1H, Ar–C**H**), 6.89 (m, 2H, Ar–C**H**), 6.85–6.82 (m, 2H, Ar–C**H**), 6.67 (d, *J*=8.9, 2H, Ar–C**H**), 5.10 (td, *J* = 10.9, 2.7, 1H, C**H**–NO_2), 4.36 (d, *J* = 10.7, 1H, C**H**–N), 3.74 (s, 3H, OC**H**$_3$), 2.74 (m, 1H, C**H**$_2$), 2.20 (m, 1H, C**H**$_2$), 1.10 (t, *J* = 7.4, 3H, C**H**$_3$), 0.07 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.3 (Ar–**C**), 131.6 (Ar–**C**), 128.4 (Ar–**C**), 124.3 (Ar–**C**), 120.5 (Ar–**C**), 112.8 (Ar–**C**), 91.3 (**C**–NO_2), 76.2 (**C**–N), 55.2 (O**C**H_3), 26.7 (**C**H_2), 10.5 (**C**H_3), -0.1 (TMS–**C**H_3). **IR** ν_{max} (cm^{-1}): 2955, 2924, 2853, 1611, 1593, 1553 (asym. NO_2), 1514, 1487, 1456, 1373, 1252 (asym. NO_2), 1204, 1180, 1034. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{20}H_{29}N_2O_4Si]^+$: 389.1897, found 389.1878.

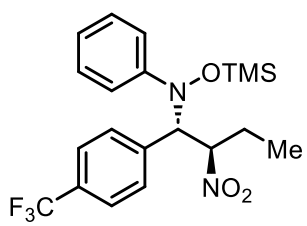
Synthesis of (±)-N-((1R,2R)-2-nitro-1-(4-(trifluoromethyl)phenyl)butyl)-N-phenyl-O-(trimethylsilyl) hydroxylamine syn-**4.36**.



Synthesised according to *GP9* using nitrone **3.87** (26.5 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 24 hours. Purification of the crude reaction mixture through preparative TLC with a 9:1 mixture of cyclohexane:ethyl acetate afforded to afford *syn*-**4.36** as a yellow oil (7 mg, 16%). R_f 0.76 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.47 (d, *J* = 8.1, 2H, Ar–C**H**), 7.15 (m, 2H, Ar–C**H**), 7.04–7.00 (m, 3H, Ar–C**H**), 6.85 (dd, *J* = 8.6, 1.3, 2H, Ar–C**H**), 5.17 (td, *J* = 10.6, 3.4, 1H, C**H**–NO_2), 4.77 (d, *J* = 11.0, 1H, C**H**–N), 1.70–1.60 (m, 1H, C$\mathbf{H}_2$), 1.52–1.45 (m, 1H, C$\mathbf{H}_2$), 0.90 (t, *J* = 7.4, 3H, C$\mathbf{H}_3$), 0.08 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 151.6, (Ar–**C**), 135.6 (Ar–**C**), 131.1 (Ar–**C**), 130.5 (Ar–**C**), 128.5 (Ar–**C**), 124.9 (Ar–**C**), 124.8 (Ar–**C**), 124.7 (q, $J_{C–F}$=3.6, **C**F_3), 120.8 (Ar–**C**), 90.5 (**C**–NO_2), 76.4 (**C**–N), 25.4 (**C**H_2), 10.1 (**C**H_3), -0.2 (TMS–**C**H_3). **^{19}F NMR** (376 MHz, $CDCl_3$, 298K) δ: -62.64. **IR ν_{max}** (cm^{-1}): 2986, 2959, 2855, 2332, 2166, 2160, 2151, 2033, 2012, 2000, 1618, 1595, 1557 (asym. NO_2), 1487, 1420, 1375, 1323 (sym. NO_2), 1254, 1206, 1167, 1126, 1103, 1067, 1018. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{20}H_{26}N_2O_3F_3Si]^+$: 427.1665, found 427.1662.

Synthesis of (±)-N-((1S,2R)-2-nitro-1-(4-(trifluoromethyl)phenyl)butyl)-N-phenyl-O-(trimethylsilyl) hydroxylamine anti-**4.36**.

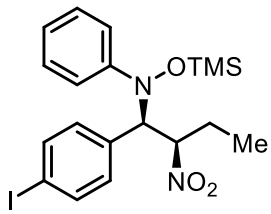


Synthesised according to *GP9* using nitrone **3.87** (26.5 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 24 hours. Purification of the crude reaction mixture through preparative TLC with a

9:1 mixture of cyclohexane:ethyl acetate afforded to afford *anti*-**4.36** as a white solid (3 mg, 7%). R_f 0.68 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.40 (d, *J* = 9.4, 2H, Ar–C**H**), 7.20–7.15 (m, 2H, Ar–C**H**), 7.07–7.01 (m, 3H, Ar–C**H**), 6.83–6.80 (m, 2H, Ar–C**H**), 5.14 (td, *J* = 10.9, 2.7, 1H, C**H**–NO_2), 4.47 (d, *J*=10.8, 1H, C**H**–N), 2.78 (m, 1H,, C$\mathbf{H}_2$), 2.24 (m, C$\mathbf{H}_2$), 1.13 (t, *J* = 7.4, 3H, C$\mathbf{H}_3$), 0.08 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 130.7 (Ar–**C**), 128.6 (Ar–**C**), 124.82 (Ar–**C**), 124.8 (m, **C**F_3), 120.33 (Ar–**C**), 90.64 (**C**–NO_2), 76.23 (**C**–N), 26.67 (**C**H_2), 10.34 (**C**H_3), -0.13 (TMS–**C**H_3). *Due to the small amount of product formed, quaternary carbons could not be detected*. **^{19}F NMR** (376 MHz, $CDCl_3$, 298K) δ: -62.65. **IR ν_{max}** (cm^{-1}): 3034, 2959, 2926, 2855, 1595, 1553 (asym. NO_2), 1487,1452, 1422, 1373, 1323 (sym. NO_2), 1256, 1202, 167, 1125, 1099, 1067, 1018. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{20}H_{26}N_2O_3F_3Si]^+$: 427.1665, found 427.1655.

Synthesis of (±)-N-((1R,2R)-1-(4-iodophenyl)-2-nitrobutyl)-N-phenyl-O-(trimethylsilyl)hydroxylamine syn-**4.37**.

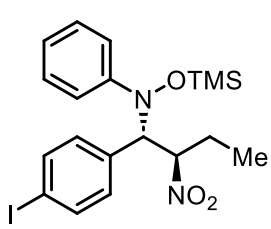


Synthesised according to *GP9* using nitrone **4.71** (32.3 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 9:1 mixture of cyclohexane:ethyl acetate afforded to afford *syn*-**4.37** as a yellow oil (30 mg, 62%). R_f 0.94 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.54 (d, *J*=8.5, 2H, Ar–C**H**), 7.15 (td, *J*=7.3, 1.8, 2H, Ar–C**H**), 7.01 (m, 1H, Ar–C**H**), 6.86 (dd, *J*=8.5, 1.2, 2H, Ar–C**H**), 6.64 (d, *J*=7.9, 2H, Ar–C**H**), 5.11 (td, *J*=10.5, 3.4, 1H, C**H**–NO_2), 4.65 (d, *J*=10.9, 1H, C**H**–N), 1.63 (m, 1H, C$\mathbf{H}_2$), 1.52 (m, 1H, C$\mathbf{H}_2$), 0.89 (t, *J*=7.4, 3H, C$\mathbf{H}_3$), 0.07 (s, 9H, TMS–C$\mathbf{H}_3$). R*f*: 0.94 (Cy:AcOEt 9:1). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 151.7 (Ar–**C**), 136.9 (Ar–**C**), 132.5 (Ar–**C**), 131.3 (Ar–**C**), 128.4 (Ar–**C**), 124.7 (Ar–**C**),

120.9 (Ar–**C**), 94.7 (Ar–**C**), 90.6 (**C**–NO_2), 76.4 (**C**–N), 25.4 (**C**H_2), 10.1 (**C**H_3), -0.2 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 3063, 2959, 2035, 1593, 1587, 1553 (asym. NO_2), 1485,1452, 1402, 1373, 1308, 1252 (sym. NO_2), 1206, 1099, 1080, 1063, 1007. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{19}H_{26}N_2O_3Si^{127}I]^+$: 485.0757, found 485.0756.

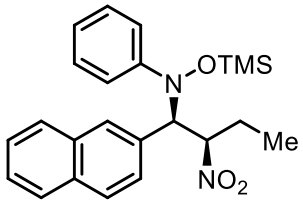
*Synthesis of (±)-N-((1R,2R)-1-(4-iodophenyl)-2-nitrobutyl)-N-phenyl-O-(trimethylsilyl)hydroxylamine anti-***4.37**.



Synthesised according to *GP9* using nitrone **4.71** (32.3 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 9:1 mixture of cyclohexane:ethyl acetate afforded to afford *anti*-**4.37** as a white solid (4 mg, 8%). R_f 0.86 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.48 (d, *J*=8.3, 2H, Ar–C**H**), 7.18 (dd, *J*=8.4, 7.3, 2H, Ar–C**H**), 7.02 (m, 1H, Ar–C**H**), 6.83 (dd, *J*=8.6, 1.2, 2H, Ar–C**H**), 6.68 (d, *J*=8.3, 2H, Ar–C**H**), 5.07 (td, *J*=10.9, 2.7, 1H, C**H**–NO_2), 4.35 (d, *J*=10.7, 1H, C**H**–N), 2.75 (m, 1H, C$\mathbf{H}_2$), 2.27–2.15 (m, 1H, C$\mathbf{H}_2$), 1.11 (t, *J*=7.4, 3H, C$\mathbf{H}_3$), 0.07 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 151.9 (Ar–**C**), 136.6 (Ar–**C**), 132.1 (Ar–**C**), 131.1 (Ar–**C**), 128.6 (Ar–**C**), 124.7 (Ar–**C**), 120.4 (Ar–**C**), 94.9 (Ar–**C**), 90.7 (**C**–NO_2), 76.3 (**C**–N), 26.6 (**C**H_2), 10.3 (**C**H_3), -0.1 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 2957, 2153, 2023, 1998, 1587, 1551 (asym. NO_2), 1508, 1485, 1458, 1406, 1375, 1333, 1298, 1252 (sym. NO_2), 1202, 1072, 1024, 1007. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{19}H_{26}N_2O_3Si^{127}I]^+$: 485.0757, found 485.0752.

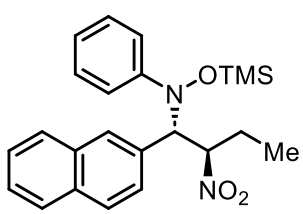
Synthesis of (±)-N-((1R,2R)-1-(naphthalen-2-yl)-2-nitrobutyl)-N-phenyl-O-(trimethylsilyl)hydroxyl amine syn-**4.38**.



Synthesised according to *GP9* using nitrone **3.85** (24.7 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 95:5 mixture of cyclohexane:ethyl acetate afforded *syn*-**4.38** as a yellow oil (28 mg, 69%). R_f 0.68 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.81 (d, *J* = 6.7, 1H, Ar–C**H**), 7.71 (t, *J* = 7.4, 2H, Ar–C**H**), 7.51–7.43 (m, 2H, Ar–C**H**), 7.32 (s, 1H, Ar–C**H**), 7.15–7.10 (m, 3H, Ar–C**H**), 7.02–6.98 (m, 1H, Ar–C**H**), 6.90 (d, *J* = 8.5, 2H, Ar–C**H**), 5.29 (td, *J* = 10.6, 3.4, 1H, C**H**–NO_2), 4.89 (d, *J* = 10.9, 1H, C**H**–N), 1.67 (m, 1H, C$\mathbf{H}_2$), 1.53 (m, 1H, C$\mathbf{H}_2$), 0.89 (t, *J* = 7.4, 3H, C$\mathbf{H}_3$), 0.11 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.0 (Ar–**C**), 133.2 (Ar–**C**), 132.8 (Ar–**C**), 130.5 (Ar–**C**), 129.6 (Ar–**C**), 128.3 (Ar–**C**), 128.2 (Ar–**C**), 128.0 (Ar–**C**), 127.7 (Ar–**C**), 127.2 (Ar–**C**), 126.5 (Ar–**C**), 126.2 (Ar–**C**), 124.7 (Ar–**C**), 121.2 (Ar–**C**), 91.1 (**C**–NO_2), 77.0 (**C**–N), 25.6 (**C**H_2), 10.1 (**C**H_3), -0.2 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 3059, 2961, 2035, 2023, 2008, 1998, 1595, 1553 (asym. NO_2), 1508, 1485, 1373, 1341, 1252 (sym. NO_2), 1206, 1080. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{23}H_{29}N_2O_3Si]^+$: 409.1947, found 409.1947.

Synthesis of (±)-N-((1S,2R)-1-(naphthalen-2-yl)-2-nitrobutyl)-N-phenyl-O-(trimethylsilyl)hydroxylamine anti-**4.38**.

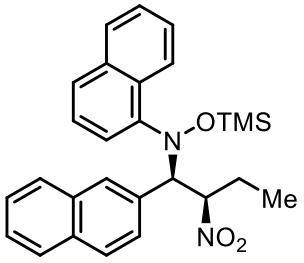


Synthesised according to *GP9* using nitrone **3.85** (24.7 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a

95:5 mixture of cyclohexane:ethyl acetate afforded *anti*-**4.38** as a white solid (3 mg, 7%). R_f 0.62 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.77–7.74 (m, 1H, Ar–C**H**), 7.68–7.66 (m, 1H, Ar–C**H**), 7.64–7.62 (m, 1H, Ar–C**H**), 7.44–7.39 (m, 3H, Ar–C**H**), 7.16–7.12 (m, 3H, Ar–C**H**), 7.00 (m, 1H, Ar–C**H**), 6.86–6.84 (m, 2H, Ar–C**H**), 5.28 (td, *J* = 10.8, 2.7, 1H, C**H**–NO_2), 4.61 (d, *J* = 10.6, 1H, C**H**–N), 2.81 (m, 1H, C$\mathbf{H}_2$), 2.26 (m, 1H, C$\mathbf{H}_2$), 1.14 (t, *J* = 7.4, 3H, C$\mathbf{H}_3$), 0.08 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.2 (Ar–**C**), 133.4 (Ar–**C**), 132.6 (Ar–**C**), 130.0 (Ar–**C**), 129.4 (Ar–**C**), 128.5 (Ar–**C**), 128.4 (Ar–**C**), 128.3 (Ar–**C**), 128.0 (Ar–**C**), 127.6 (Ar–**C**), 126.8 (Ar–**C**), 126.3 (Ar–**C**), 125.9 (Ar–**C**), 124.5 (Ar–**C**), 120.5 (Ar–**C**), 91.0 (**C**–NO_2), 76.7 (**C**–N), 26.8 (**C**H_2), 10.4 (**C**H_3), 1.2 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 3061, 2924, 2351, 2195, 2135, 2008, 1998, 1975, 1593, 1553 (asym. NO_2), 1506, 1485, 1373, 1254 (sym. NO_2), 1092, 1022. **HRMS** (EC): $[M]^+$ calculated for $[C_{23}H_{28}N_2O_3{}^{28}Si]^+$: 408.18637, found 408.1863.

Synthesis of (±)-N-(naphthalen-1-yl)-N-((1R,2R)-1-(naphthalen-2-yl)-2-nitrobutyl)-O-(trimethylsilyl) hydroxylamine syn-**4.39**.

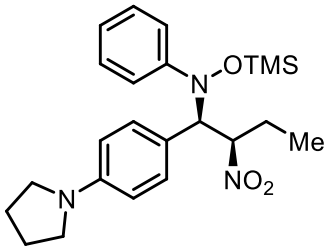


Synthesised according to *GP9* using nitrone **3.99** (29.7 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 95:5 mixture of cyclohexane:ethyl acetate afforded to afford *syn*-**4.39** as a yellow oil (33 mg, 72%). R_f 0.93 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 8.27 (d, *J* = 9.7, 1H, Ar–C**H**), 7.83–7.28 (m, 11H, Ar–C**H**), 6.89 (t, *J* = 7.9, 1H, Ar–C**H**), 6.60 (dd, *J* = 7.6, 1.2, 1H, Ar–C**H**), 5.59 (td, *J* = 10.7, 3.3, 1H, C**H**–NO_2), 4.81 (d, *J* = 10.6, 1H, C**H**–N), 1.72 (m, 1H, C$\mathbf{H}_2$), 1.54–1.49 (m, 1H, C$\mathbf{H}_2$), 0.91 (t, *J* = 7.4, 3H, C$\mathbf{H}_3$), 0.08 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 146.7 (Ar–**C**), 134.0 (Ar–

C), 133.2 (Ar–**C**), 132.7 (Ar–**C**), 130.1 (Ar–**C**), 128.2 (Ar–**C**), 128.2 (Ar–**C**), 127.6 (Ar–**C**), 127.3 (Ar–**C**), 126.5 (Ar–**C**), 126.3 (Ar–**C**), 126.1 (Ar–**C**), 126.0(Ar–**C**), 125.7 (Ar–**C**), 124.7 (Ar–**C**), 123.0 (Ar–**C**), 120.4 (Ar–**C**), 90.6 (**C**–NO_2), 74.2 (**C**–N), 26.0 (**C**H_2), 10.2 (**C**H_3), 0.1 (TMS–**C**H_3). **IR** ν_{max} (cm^{-1}): 3053, 2957, 2195, 1973, 1593, 1553 (asym. NO_2), 1508, 1458, 1439, 1389, 1373, 1341, 1252 (sym. NO_2), 1221, 1132, 1082. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{27}H_{31}N_2O_3Si]^+$: 459.2104, found 459.2101.

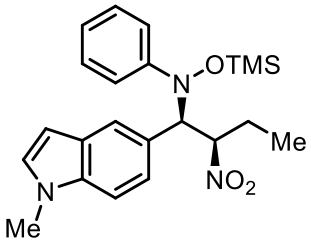
*Synthesis of (±)-N-((1R,2R)-2-nitro-1-(4-(pyrrolidin-1-yl)phenyl)butyl)-N-phenyl-O-(trimethylsilyl)hydroxylamine syn-***4.40**.



Synthesised according to *GP9* using nitrone **4.73** (26.6 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 24 hours. Purification of the crude reaction mixture through preparative TLC with a 9:1 mixture of cyclohexane:ethyl acetate afforded to afford *syn*-**4.40** as a yellow oil (22 mg, 52%). R_f 0.79 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.17–7.12 (m, 2H, Ar–C**H**), 6.99 (m, 1H, Ar–C**H**), 6.93–6.90 (m, 2H, Ar–C**H**), 6.74 (d, *J* = 8.0, 2H, Ar–C**H**), 6.38 (d, *J* = 8.2, 2H, Ar–C**H**), 5.11 (td, *J* = 10.3, 3.7, 1H, C**H**–NO_2), 4.60 (d, *J* = 10.9, 1H, C**H**–N), 3.25 (tt, *J* = 6.6, 3.0, 4H, Het-C**H**$_2$), 1.99 (m, 4H, Het-C**H**$_2$), 1.69–1.50 (m, 2H, C**H**$_2$), 0.87 (t, *J* = 7.4, 3H, C**H**$_3$), 0.07 (s, 9H, TMS–C**H**$_3$). R*f*: 0.80 (Cy:AcOEt 9:1). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.5 (Ar–**C**), 147.6 (Ar–**C**), 131.7 (Ar–**C**), 128.1 (Ar–**C**), 124.2 (Ar–**C**), 121.2 (Ar–**C**), 110.7 (Ar–**C**), 91.6 (**C**–NO_2), 76.7 (**C**–N), 47.6 (Het-**C**H_2), 25.6 (Het-**C**H_2), 25.6 (**C**H_2), 10.2 (**C**H_3), -0.1 (TMS–**C**H_3). **IR** ν_{max} (cm^{-1}): 3038, 2967, 2835, 2160, 2153, 2008, 1975, 1877, 1613, 1595, 1553 (asym. NO_2), 1522, 1487, 1460, 1373, 1341, 1294, 1250 (sym. NO_2), 1207, 1188, 1159, 1078. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{23}H_{34}N_3O_3Si]^+$: 428.2369, found 428.2369.

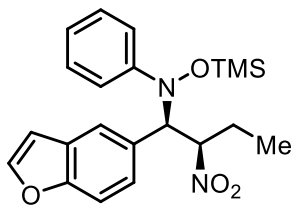
Synthesis of (±)-N-((1R,2R)-1-(1-methyl-1H-indol-5-yl)-2-nitrobutyl)-N-phenyl-O-(trimethylsilyl) hydroxylamine syn-**4.41**.



Synthesised according to *GP9* using nitrone **4.74** (25.0 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 9:1 mixture of cyclohexane:ethyl acetate afforded to afford *syn*-**4.41** as a yellow oil (15 mg, 36%). R_f 0.87 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.18–7.14 (m, 2H, Ar–C**H**), 7.13–7.08 (m, 2H, Ar–C**H**), 7.02 (d, *J* = 3.1, 1H, CH=C**H**–NMe), 6.97 (m, 1H, Ar–C**H**), 6.91–6.88 (m, 2H, Ar–C**H**), 6.79 (d, *J* = 8.4, 1H, Ar–C**H**), 6.40 (dd, *J* = 3.1, 0.8, 1H, C**H**=CH–NMe), 5.22 (td, *J* = 10.6, 3.4, 1H, C**H**–NO_2), 4.82 (d, *J* = 10.8, 1H, C**H**–N), 3.77 (s, 3H, N–C$\mathbf{H}_3$), 1.69–1.59 (m, 1H, C$\mathbf{H}_2$), 1.53–1.47 (m, 1H, C$\mathbf{H}_2$), 0.86 (t, *J* = 7.4, 3H, C$\mathbf{H}_3$), 0.09 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.5(Ar–**C**), 136.6 (Ar–**C**), 129.2 (Ar–**C**), 128.1 (Ar–**C**), 127.9 (Ar–**C**), 124.3 (Ar–**C**), 124.3 (Ar–**C**), 123.5 (Ar–**C**), 123.0 (Ar–**C**), 121.4 (Ar–**C**), 108.4 (CH=**C**H–NMe), 101.4 (**C**H=CH–NMe), 91.8 (**C**–NO_2), 77.4 (**C**–N), 33.0 (N–**C**H_3), 25.7 (**C**H_2), 10.2 (**C**H_3), -0.1 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 2957, 1595, 1551 (asym. NO_2), 1514, 1487, 1451, 1424, 1373, 1341, 1302, 1250 (sym. NO_2), 1206, 1153, 1080. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{22}H_{30}N_3O_3Si]^+$: 412.2056, found 412.2059.

Synthesis of (±)-N-((1R,2R)-1-(benzofuran-5-yl)-2-nitrobutyl)-N-phenyl-O-(trimethylsilyl) hydroxylamine syn-**4.42**.

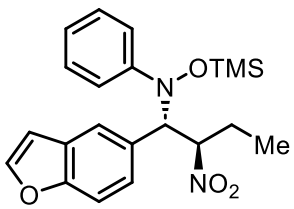


Synthesised according to *GP9* using nitrone **4.75** (23.7 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a

9:1 mixture of cyclohexane:ethyl acetate afforded *syn*-**4.42** as a yellow oil (28 mg, 70%). R_f 0.73 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.59 (d, *J* = 2.2, 1H, CH=C**H**–O), 7.34 (d, *J* = 8.5, 1H, Ar–C**H**), 7.16 (s, 1H, Ar–C**H**), 7.14–7.09 (m, 2H, Ar–C**H**), 6.98 (m, 1H, Ar–C**H**), 6.87 (dd, *J* = 8.5, 1.3, 3H, Ar–C**H**), 6.69 (dd, *J* = 2.2, 1.0, 1H, C**H**=CH–O), 5.20 (td, *J* = 10.6, 3.4, 1H, C**H**–NO_2), 4.82 (d, *J* = 10.9, 1H, C**H**–N), 1.72–1.58 (m, 1H, C$\mathbf{H}_2$), 1.49 (m, 1H, C$\mathbf{H}_2$), 0.88 (t, *J* = 7.4, 3H, C$\mathbf{H}_3$), 0.09 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 154.86 (Ar–**C**), 152.1 (Ar–**C**), 145.4 (CH=**C**H–O), 128.2 (Ar–**C**), 127.0 (Ar–**C**), 126.9 (Ar–**C**), 126.6 (Ar–**C**), 124.5 (Ar–**C**), 123.5 (Ar–**C**), 121.2 (Ar–**C**), 110.7 (Ar–**C**), 106.8 (**C**H=CH–O), 91.4 (**C**–NO_2), 76.9 (**C**–N), 25.6 (**C**H_2), 10.1(**C**H_3), -0.2 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 2959, 2033, 1975, 1595, 1555 (asym. NO_2), 1487, 1468, 1375, 1331, 1316, 1263, 1252 (sym. NO_2), 1207, 1132, 1082, 1032. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{21}H_{27}N_2O_4Si]^+$: 399.1740, found 399.1742.

Synthesis of (±)-N-((1S,2R)-1-(benzofuran-5-yl)-2-nitrobutyl)-N-phenyl-O-(trimethylsilyl)hydroxylamine anti-**4.42**.

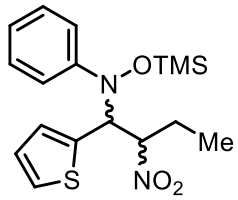


Synthesised according to *GP9* using nitrone **4.75** (23.7 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 9:1 mixture of cyclohexane:ethyl acetate afforded to afford *anti*-**4.42** as a white solid (4 mg, 10%). R_f 0.63 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.54 (d, *J* = 2.2, 1H, CH=C**H**–O), 7.26 (d, *J* = 8.5, 2H, Ar–C**H**), 7.23 (d, *J* = 1.8, 1H, Ar–C**H**), 7.17–7.12 (m, 2H, Ar–C**H**), 7.00 (m, 1H, Ar–C**H**), 6.84–6.82 (m, 2H, Ar–C**H**), 6.65 (dd, *J* = 2.2, 1.0, 1H, C**H**=CH–O), 5.19 (td, *J* = 10.8, 2.6, 1H, C**H**–NO_2), 4.54 (d, *J* = 10.7, 1H, C**H**–N), 2.78 (m, 1H, C$\mathbf{H}_2$), 2.25 (m, 1H, C$\mathbf{H}_2$), 1.12 (t, *J* = 7.4, 3H, C$\mathbf{H}_3$), 0.08 (s, 9H,

TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 155.0 (Ar–**C**), 152.2 (Ar–**C**), 145.1(CH=**C**H–O), 128.4 (Ar–**C**), 126.8 (Ar–**C**), 126.7 (Ar–**C**), 126.2 (Ar–**C**), 124.4 (Ar–**C**), 123.2 (Ar–**C**), 120.5 (Ar–**C**), 110.3(Ar–**C**), 106.9 (**C**H=CH–O), 91.4, (**C**–NO_2), 76.7 (**C**–N), 26.8 (**C**H_2), 10.5 (**C**H_3), -0.1 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 2957, 2926, 1595, 1551 (asym. NO_2), 1487, 1468, 1373, 1331, 1296, 1252 (sym. NO_2), 1202, 1130, 1078, 1030. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{21}H_{27}N_2O_4Si]^+$: 399.1740, found 399.1742.

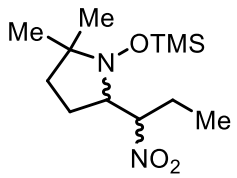
Synthesis of (±)-methyl -2-nitro-1-(thiophen-2-yl)butyl)-N-phenyl-O-(trimethylsilyl)hydroxylamine **4.43**.



Synthesised according to *GP9* using nitrone **4.78** (20.3 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 24 hours. Purification of the crude reaction mixture through preparative TLC with a 9:1 mixture of cyclohexane:ethyl acetate afforded **4.43** as a pale yellow oil (33 mg, 91%). Obtained as a mixture of diastereoisomers. R_f 0.86 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.20 (dd, *J* = 4.9, 3.0, 1H, Ar–C**H**), 7.17–7.13 (m, 2H, Ar–C**H**), 7.00 (m, 1H, Ar–C**H**), 6.91–6.88 (m, 2H, Ar–C**H**), 6.84–6.82 (m, 2H, Ar–C**H**), 5.08 (td, *J* = 10.5, 3.5, 1H, C**H**–$NO_{2\ major+minor}$), 4.82 (d, *J* = 10.8, 1H, C**H**–N_{major}), 4.55 (d, *J* = 10.6, 1H, C**H**–N_{minor}), 2.72 (m, 1H, C$\mathbf{H}_{2minor}$), 2.19 (m, 1H, C$\mathbf{H}_{2minor}$), 1.71–1.59 (m, 1H, C$\mathbf{H}_{2major}$), 1.57–1.47 (m, 1H, C$\mathbf{H}_{2major}$) 1.09 (t, *J* = 7.4, 3H, C$\mathbf{H}_{3minor}$), 0.89 (t, *J* = 7.4, 3H, C$\mathbf{H}_{3major}$), 0.07 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.2 (Ar–**C**), 132.5 (Ar–**C**), 129.1 (Ar–**C**), 128.8 (Ar–**C**), 128.4(Ar–**C**), 128.3 (Ar–**C**), 126.0 (Ar–**C**), 125.9(Ar–**C**), 124.8 (Ar–**C**), 124.6 (Ar–**C**), 124.0 (Ar–**C**), 120.9 (Ar–$\mathbf{C}_{major}$), 120.3 (Ar–**C**), 91.9(**C**–NO_{2minor}), 91.1 (**C**–NO_{2major}), 72.5 (**C**–N_{major}), 72.1 (**C**–N_{minor}), 26.4 (**C**H_{2minor}), 25.4 (**C**H_{2major}), 10.4 (**C**H_{3minor}), 10.1 (**C**H_{3major}), -0.2 (TMS–C$\mathbf{H}_{3major+minor}$). **IR ν_{max}** (cm^{-1}): 2970, 1595, 1553 (asym. NO_2), 1487, 1452, 1373, 1250 (sym. NO_2), 1207, 1080. **HRMS** (ES+): $[M+1]^+$ calculated for $[C_{17}H_{25}N_2O_3SiS]^+$: 365.1355, found 365.1359.

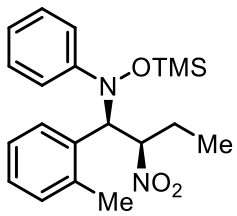
Synthesis of (±)-2,2-dimethyl-5-(1-nitropropyl)-1-((trimethylsilyl)oxy)pyrrolidine **4.44**.



Synthesised according to *GP9* using DMPO (11.3 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through flash column chromatography with a 9:1 mixture of cyclohexane:ethyl acetate afforded to afford **4.44** as a colourless oil (6 mg, 22%). Obtained as a mixture of diastereoisomers. R_f 0.72 (Cy:AcOEt 9:1). [$KMnO_4$ stain]

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 4.66 (dt, *J* = 10.3, 4.2, 1H, C**H**–NO_{2minor}), 4.49 (m, 1H, C**H**–NO_{2major}), 3.54 (m, 1H, C**H**–$NOTMS_{major}$), 3.20 (m, 1H, C**H**–$NOTMS_{minor}$), 2.13–1.48 (m, 19H, C**H**$_{2major+minor}$), 1.12 (s, 3H, C**H**$_{3major}$), 1.07 (s, 3H, C**H**$_{3minor}$), 1.04 (s, 3H, C**H**$_{3major}$), 1.00 (s, 3H, C**H**$_{3minor}$), 1.00–0.96 (m, 3H, C**H**$_{3major+minor}$), 0.22 (s, 9H, TMS–C**H**$_{3minor}$), 0.17 (s, 9H, TMS–C**H**$_{3major}$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: δ 91.5 (**C**–NO_{2major}), 90.3(**C**–NO_{2minor}), 68.6 (**C**–$NOTMS_{minor}$), 68.4 (**C**–$NOTMS_{major}$), 65.1 (**C**$(Me_2)NOTMS_{major}$), 64.9 (**C**$(Me_2)NOTMS_{minor}$), 35.1 (**C**H_2), 34.3 (**C**H_2), 27.9 (**C**H_{3major}), 27.7(**C**H_{3minor}), 24.9 (**C**H_2), 20.9 (**C**H_2), 20.4 (**C**H_2), 19.4 (**C**H_2) (**C**H_{3major}), 19.3 (**C**H_2), 18.6 (**C**H_{3minor}), 10.9 (**C**H_{3major}), 10.6 (**C**H_{3minor}), 1.0 (TMS–**C**H_{3minor}), 0.9 (TMS–**C**H_{3major}). **IR ν_{max}** (cm^{-1}): 2969, 2938, 2882, 2164, 2153, 2000, 1547 (asym. NO_2), 1458, 1364, 1308, 1250 (sym. NO_2), 1173, 1146, 1080. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{12}H_{27}N_2O_3Si]^+$: 275.1791, found 275.1797.

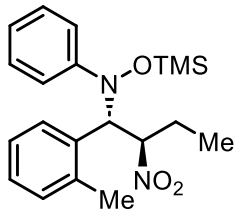
Synthesis of (±)-N-((1R,2R)-2-nitro-1-(o-tolyl)butyl)-N-phenyl-O-(trimethylsilyl)hydroxylamine syn- **4.45**.



Synthesised according to *GP9* using nitrone **4.79** (21.1 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 18 hours. Purification of the crude reaction mixture through preparative TLC with a 95:5 mixture of cyclohexane:ethyl acetate afforded to afford *syn*-**4.45** as a colourless oil (9 mg, 24%). R_f 0.78 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.21–7.10 (m, 5H, Ar–C**H**), 7.04–6.99 (m, 2H, Ar–C**H**), 6.93–6.89 (m, 2H, Ar–C**H**), 5.15–5.08 (m, 2H, C**H**–NO_2,C**H**–N), 1.72 (s, 3H, Ar-C$\mathbf{H}_3$), 1.62–1.52 (m, 1H, C$\mathbf{H}_2$), 1.49–1.41 (m, 1H, C$\mathbf{H}_2$), 0.85 (t, *J* = 7.4, 3H, C$\mathbf{H}_3$), 0.06 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.3 (Ar–**C**), 138.5 (Ar–**C**), 130.6 (Ar–**C**), 130.3 (Ar–**C**), 128.5 (Ar–**C**), 128.3 (Ar–**C**), 128.1 (Ar–**C**), 125.2 (Ar–**C**), 125.1 (Ar–**C**), 121.9 (Ar–**C**), 121.0 (Ar–**C**), 92.0 (**C**–NO_2), 70.8 (**C**–N), 25.1 (Ar–**C**H_3), 19.7 (**C**H_2), 10.2 (**C**H_3), -0.2 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 2959, 1595, 1557 (asym. NO_2), 1487, 1462, 1373, 1339, 1302, 1252 (sym. NO_2), 1207, 1094, 1015. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{20}H_{29}N_2O_3Si]^+$: 373.1947, found 373.1948.

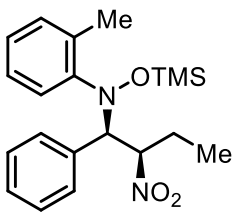
*Synthesis of (±)-N-((1S,2R)-2-nitro-1-(o-tolyl)butyl)-N-phenyl-O-(trimethylsilyl)hydroxylamine anti-***4.45**.



Synthesised according to *GP9* using nitrone **4.79** (21.1 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 18 hours. Purification of the crude reaction mixture through preparative TLC with a 9:1 mixture of cyclohexane:ethyl acetate afforded to afford *anti*-**4.45** as a colourless oil (17 mg, 46%). R_f 0.72 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.48–7.45 (m, 1H, Ar–C**H**), 7.19–7.10 (m, 4H, Ar–C**H**), 7.03 (m, 1H, Ar–C**H**), 6.93–6.89 (m, 3H, Ar–C**H**), 5.13 (td, *J* = 10.8, 2.7, 1H, C**H**–NO_2), 4.79 (d, *J* = 10.6, 1H, C**H**–N), 2.76 (m, 1H, C$\mathbf{H}_2$), 2.19 (m, 1H, C$\mathbf{H}_2$), 1.65 (s, 3H, Ar–C$\mathbf{H}_3$), 1.10 (t, *J* = 7.4, 3H, C$\mathbf{H}_3$), 0.04 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.6 (Ar–**C**), 138.5 (Ar–**C**), 130.3 (Ar–**C**), 130.1 (Ar–**C**), 129.9 (Ar–**C**), 128.5 (Ar–**C**), 128.3 (Ar–**C**), 124.9 (Ar–**C**), 124.8 (Ar–**C**), 121.0 (Ar–**C**), 91.4 (**C**–NO_2), 70.4 (**C**–N), 27.0 (Ar–**C**H_3), 19.5 (**C**H_2), 10.5 (**C**H_3), -0.2 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 3026, 2961, 1595, 1551 (asym. NO_2), 1487, 1458, 1452, 1373, 1341, 1252 (sym. NO_2), 1204, 1163, 1076, 1024. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{20}H_{29}N_2O_3Si]^+$: 373.1947, found 373.1944.

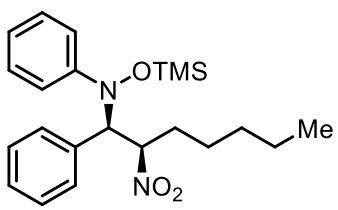
*Synthesis of (±)-N-((1R,2R)-2-nitro-1-phenylbutyl)-N-(o-tolyl)-O-(trimethylsilyl)hydroxylamine syn-***4.46**.



Synthesised according to *GP9* using nitrone **3.93** (21.1 mg, 0.1 mmol) and nitronate **4.30** (32.3 mg, 0.2 mmol) in dichloromethane for 18 hours. Purification of the crude reaction mixture through preparative TLC with a 95:5 mixture of cyclohexane:ethyl acetate afforded to afford *syn*-**4.46** as a colourless oil (30 mg, 81%). R_f 0.79 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.30–7.27 (m, 1H, Ar–C**H**), 7.22–7.21 (m, 2H, Ar–C**H**), 7.07 (d, *J* = 7.6, 2H, Ar–C**H**), 6.91 (t, *J* = 7.3, 1H, Ar–C**H**), 6.72 (t, *J* = 7.7, 1H, Ar–C**H**), 6.42 (d, *J* = 8.1, 1H, Ar–C**H**) 5.32 (td, *J* = 10.8, 3.2, 1H, C**H**–NO_2), 4.30 (d, *J* = 10.6, 1H, C**H**–N), 2.28 (s, 3H, Ar–C**H**$_3$), 1.72–1.60 (m, 1H, C**H**$_2$), 1.53–1.42 (m, 1H, C**H**$_2$), 0.88 (t, *J* = 7.4, 3H, C**H**$_3$), 0.02 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 149.3 (Ar–**C**), 132.4 (Ar–**C**), 131.1 (Ar–**C**), 130.6 (Ar–**C**), 130.3 (Ar–**C**), 128.5 (Ar–**C**), 127.8 (Ar–**C**), 125.4 (Ar–**C**), 125.2 (Ar–**C**), 123.8 (Ar–**C**), 90.6 (**C**–NO_2), 73.7 (**C**–N), 25.7 (Ar–**C**H_3), 17.7 (**C**H_2), 10.2 (**C**H_3), -0.01 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 2957, 1555 (asym. NO_2), 1483, 1454, 1373, 1339, 1310, 1250 (sym. NO_2), 1211, 1186, 1109, 1082, 1049, 1034. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{20}H_{29}N_2O_3Si]^+$: 373.1947, found 373.1947.

*Synthesis of (±)-N-((1R,2R)-2-nitro-1-phenylheptyl)-N-phenyl-O-(trimethylsilyl)hydroxylamine syn-***4.56**.

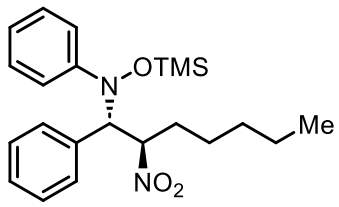


Synthesised according to *GP9* using nitrone **3.42** (19.7 mg, 0.1 mmol) and nitronate **4.82** (40.7 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with

a 95:5 mixture of cyclohexane:ethyl acetate afforded *syn*-**4.56** as a colourless oil (20 mg, 50%). R_f 0.90 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.28 (m, 1H, Ar–C**H**), 7.23–7.18 (m, 2H, Ar–C**H**), 7.15–7.11 (m, 2H, Ar–C**H**), 6.99 (m, 1H, Ar–C**H**), 6.90–6.85 (m, 4H, Ar–C**H**), 5.24 (td, *J* = 10.9, 3.0, 1H, C**H**–NO_2), 4.70 (d, *J* = 10.9, 1H, C**H**–N), 1.69–1.60 (m, 1H, C$\mathbf{H}_2$), 1.43–1.14 (m, 7H, C$\mathbf{H}_2$), 0.81 (t, *J* = 7.0, 3H, C$\mathbf{H}_3$), 0.08 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.1 (Ar–**C**), 131.9 (Ar–**C**), 130.7 (Ar–**C**), 128.5 (Ar–**C**), 128.2 (Ar–**C**), 127.8 (Ar–**C**), 124.5 (Ar–**C**), 121.0 (Ar–**C**), 89.7 (**C**–NO_2), 77.2 (**C**–N), 31.9 (**C**H_2), 30.9 (**C**H_2), 25.3 (**C**H_2), 22.4 (**C**H_2), 14.0 (**C**H_3), -0.2 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 2957, 2930, 2860, 1595, 1557 (asym. NO_2), 1485, 1452, 1377, 1252 (sym. NO_2), 1204, 1026. **HRMS** (ES+): $[M+1]^+$ calculated for $[C_{22}H_{33}N_2O_3Si]^+$: 401.2260, found 401.2263.

*Synthesis of (±)-N-((1S,2R)-2-nitro-1-phenylheptyl)-N-phenyl-O-(trimethylsilyl)hydroxylamine anti-***4.56**.

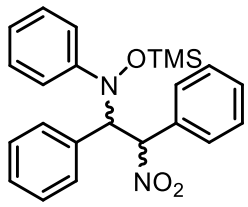


Synthesised according to *GP9* using nitrone **3.42** (19.7 mg, 0.1 mmol) and nitronate **4.82** (40.7 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 95:5 mixture of cyclohexane:ethyl acetate afforded *anti*-**4.56** as a colourless oil (5 mg, 13%). R_f 0.85 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.24–7.20 (m, 1H, Ar–C**H**), 7.19–7.12 (m, 4H, Ar–C**H**), 7.00 (m, 1H, Ar–C**H**), 6.97–6.95 (m, 2H, Ar–C**H**), 6.86–6.83 (m, 2H, Ar–C**H**), 5.21 (td, *J* = 10.9, 2.6, 1H, C**H**–NO_2), 4.42 (d, *J* = 10.6, 1H, C**H**–N), 2.69–2.62 (m, 1H, C$\mathbf{H}_2$), 2.24–2.11 (m, 1H, C$\mathbf{H}_2$), 1.40–1.25 (m, 6H, C$\mathbf{H}_2$), 0.93 (m, 3H, C$\mathbf{H}_3$), 0.06 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.2 (Ar–**C**), 130.4 (Ar–**C**), 128.5 (Ar–**C**), 128.4(Ar–**C**), 127.4 (Ar–**C**), 124.4 (Ar–**C**), 120.5 (Ar–**C**), 89.8 (**C**–NO_2), 77.2 (**C**–N), 33.3 (**C**H_2), 31.6 (**C**H_2), 25.8 (**C**H_2), 22.6 (**C**H_2), 14.1 (**C**H_3), -

0.1 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 2957, 2928, 2862, 1553 (asym. NO_2), 1485, 1452, 1377, 1252 (sym. NO_2), 1202. **HRMS** (ES+): $[M+1]^+$ calculated for $[C_{22}H_{33}N_2O_3Si]^+$: 401.2260, found 401.2265.

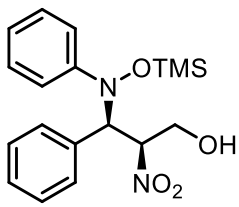
Synthesis of (±)-N-(2-nitro-1,2-diphenylethyl)-N-phenyl-O-(trimethylsilyl)hydroxylamine **4.57**.



Synthesised according to *GP9* using nitrone **3.42** (19.7 mg, 0.1 mmol) and nitronate **4.83** (41.9 mg, 0.2 mmol) in dichloromethane for 24 hours. Purification of the crude reaction mixture through preparative TLC with a 95:5 mixture of cyclohexane:ethyl acetate afforded to afford **4.57** as a colourless oil (28 mg, 69%). Obtained as a mixture of diastereoisomers. R_f 0.73 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.72 (dd, *J* = 6.6, 3.0, 1H, Ar–C**H**), 7.41–7.37 (m, 3H, Ar–C**H**), 7.29–7.26 (m, 1H, Ar–C**H**), 7.21–7.16 (m, 5H, Ar–C**H**), 7.09–7.04 (m, 2H, Ar–C**H**), 7.02–6.96 (m, 4H, Ar–C**H**), 6.94–6.89 (m, 1H, Ar–C**H**), 6.84–6.74 (m, 2H, Ar–C**H**), 6.39 (d, *J* = 11.2, 1H, C**H**–NO_{2minor}), 6.23 (d, *J* = 11.4, 1H, C**H**–NO_{2major}), 5.37 (d, *J* = 11.3, 1H, C**H**–N_{major}), 5.34 (d, *J* = 11.1, 1H, C**H**–N_{minor}), 0.14 (s, 9H, TMS–C$\mathbf{H}_{3major}$), -0.23 (s, 9H TMS–C$\mathbf{H}_{3minor}$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.1 (Ar–**C**), 151.9 (Ar–**C**), 133.7 (Ar–**C**), 132.4 (Ar–**C**), 131.0 (Ar–**C**), 131.0 (Ar–**C**), 130.1 (Ar–**C**), 130.0 (Ar–**C**), 129.8 (Ar–**C**), 129.44 (Ar–**C**), 128.8 (Ar–**C**), 128.7 (Ar–**C**), 128.3 (Ar–**C**), 128.2 (Ar–**C**), 128.0 (Ar–**C**), 127.9 (Ar–**C**), 127.3 (Ar–**C**), 125.7 (Ar–**C**), 124.7 (Ar–**C**), 124.0(Ar–**C**), 121.1 (Ar–**C**), 120.3 (Ar–**C**), 92.4 (**C**–NO_{2major}), 91.6 (**C**–NO_{2minor}), 76.5 (**C**–N_{major}), 74.1 (**C**–N_{minor}), -0.2 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 3063, 3034, 2957, 2903, 2166, 2045, 1973, 1802, 1595, 1555 (asym. NO_2), 1485, 1454, 1360, 1296, 1252 (sym. NO_2), 1204, 1076, 1024. **HRMS** (ES+): $[M+H]^+$ calculated for $[C_{23}H_{27}N_2O_3Si]^+$: 407.1791, found 407.1794.

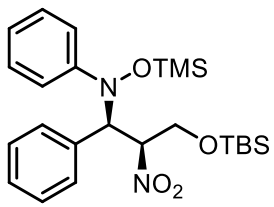
*Synthesis of (±)- (2S,3R)-2-nitro-3-phenyl-3-(phenyl((trimethylsilyl)oxy)amino)propan-1-ol syn-***4.58**.



Synthesised according to *GP9* using nitrone **3.42** (19.7 mg, 0.1 mmol) and nitronate **4.84** (47.9 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 8:2 mixture of cyclohexane:ethyl acetate afforded to afford *syn*-**4.58** as a yellow oil (10 mg, 28%). R_f 0.23 (Cy:AcOEt 9:1) .

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.29 (m, 1H, Ar–C**H**), 7.24–7.20 (m, 2H, Ar–C**H**), 7.16–7.11 (m, 2H, Ar–C**H**), 7.02–7.00 (m, 1H, Ar–C**H**), 6.98–6.96 (m, 2H, Ar–C**H**), 6.91–6.88 (m, 2H, Ar–C**H**), 5.38 (m, 1H, C**H**–NO_2), 4.85 (d, *J*=10.9, 1H, C**H**–N), 3.79–3.70 (m, 2H, C$\mathbf{H}_2$), 1.70 (br. s, 1H, O**H**), 0.07 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 151.8 (Ar–**C**), 131.4 (Ar–**C**), 130.6 (Ar–**C**), 128.9 (Ar–**C**), 128.3 (Ar–**C**), 128.0 (Ar–**C**), 124.8 (Ar–**C**), 121.3 (Ar–**C**), 90.3 (**C**–NO_2), 74.0 (**C**–N), 62.7 (**C**H_2), -0.2 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 3431 (OH), 3063, 3032, 2959, 2033, 2000, 1665, 1595, 1557 (asym. NO_2), 1487, 1452, 1366, 1312, 1252 (sym. NO_2), 1202, 1071. **HRMS** (CI): $[M]^+$ calculated for $[C_{18}H_{24}N_2O_4Si]^+$: 360.14999, found 360.1497.

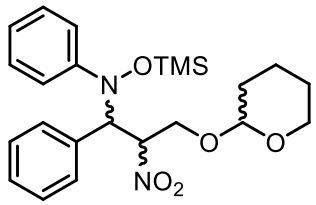
*Synthesis of (±)-N-(3-((tert-butyldimethylsilyl)oxy)-2-nitro-1-phenylpropyl)-N-phenyl-O-(trimethylsilyl) hydroxylamine syn-***4.59**.



Synthesised according to *GP9* using nitrone **3.42** (19.7 mg, 0.1 mmol) and nitronate **4.85** (55.5 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 95:5 mixture of cyclohexane:ethyl acetate afforded to afford *syn*-**4.59** as a yellow oil (33 mg, 70%). Obtained as a mixture of diastereoisomers. R_f 0.84 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.30–7.11 (m, 8H, Ar–C**H**), 7.03–6.97 (m, 3H, Ar–C**H**), 6.95–6.84 (m, 4H, Ar–C**H**), 5.44 (m, 1H, C**H**–NO_{2major}), 5.34 (m, 1H, C**H**–NO_{2minor}), 4.81 (d, *J* = 11.0, 1H, C**H**–N_{minor}), 4.62–4.55 (m, 2H, C$\mathbf{H}_{2major}$), 4.38 (dd, *J* = 10.9, 8.5, 1H, C**H**–N_{major}), 3.72 (dd, *J* = 11.3, 7.8, 1H, C$\mathbf{H}_{2minor}$), 3.64 (dd, *J* = 11.3, 3.3, 1H, C$\mathbf{H}_{2minor}$), 0.91 (s, 9H, TMS–C$\mathbf{H}_{3major}$), 0.81 (s, 9H TMS–C$\mathbf{H}_{3minor}$), 0.11 (s, 9H, TBS–C$\mathbf{H}_{3minor}$), 0.08 (s, 3H, TBS–C$\mathbf{H}_{3major}$), 0.08 (s, 3H, TBS–C$\mathbf{H}_{3major}$), 0.07 (s, 9H, TBS–C$\mathbf{H}_{3major}$), -0.08 (s, 3H, TBS–C$\mathbf{H}_{3minor}$), -0.14 (s, 3H, TBS–C$\mathbf{H}_{3minor}$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 151.9 (Ar–**C**), 151.9 (Ar–**C**), 131.5 (Ar–**C**), 131.5 (Ar–**C**), 130.7 (Ar–**C**), 130.3 (Ar–**C**), 128.7 (Ar–**C**), 128.6 (Ar–**C**), 128.4 (Ar–**C**), 128.2 (Ar–**C**), 127.8 (Ar–**C**), 127.6 (Ar–**C**), 124.6 (Ar–**C**), 124.4 (Ar–**C**), 121.1 (Ar–**C**), 120.2 (Ar–**C**), 90.4 (**C**–NO_{2minor}), 90.2 (**C**–NO_{2major}), 73.9 (**C**–N_{minor}), 73.0 (**C**–N_{major}), 64.3 (**C**H_{2major}), 63.2 (**C**H_{2minor}), 25.8 (TMS–**C**H_{3major}), 25.7 (TMS–**C**H_{3minor}), 18.3 (TBS–**C**$_{major}$), 18.2 (TBS–**C**$_{minor}$), -0.1 (TBS–**C**H_{3major}), -0.2 (TBS–**C**H_{3major}), -5.45 (TBS–**C**H_{3major}), -5.48 (TBS–**C**H_{3minor}), -5.6 (TBS–**C**H_{3minor}), -5.8 (TBS–**C**H_{3minor}). **IR ν_{max}** (cm^{-1}): 2955, 2930, 2859, 1595, 1557 (asym. NO_2), 1487, 1389, 1362, 1252 (sym. NO_2), 1204, 1119, 1007. **HRMS** (ES+): $[M+1]^+$ calculated for $[C_{24}H_{39}N_2O_4Si_2]^+$: 475.2448, found 475.2448.

Synthesis of (±)-N-(2-nitro-1-phenyl-3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)-N-phenyl-O-(trimethylsilyl)hydroxylamine **4.60**.

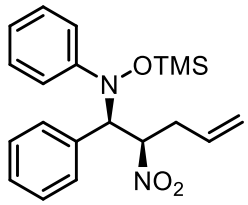


Synthesised according to *GP9* using nitrone **3.42** (19.7 mg, 0.1 mmol) and nitronate **4.86** (49.5 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 95:5 mixture of cyclohexane:ethyl acetate afforded to afford **4.60** as yellow oil (30 mg, 68%). Obtained as a mixture of distereoisomers. R_f 0.55 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.28 (m, 1H), 7.26–7.10 (m, 10H), 7.03–6.99 (m, 4H), 6.95–6.84 (m, 7H), 5.57–5.46 (m, 3H, C**H**–NO_2), 4.84–4.72 (m, 2H), 4.64–4.50 (m, 3H), 4.43 (dd, *J* =

10.9, 3.0, 1H), 4.26 (t, *J* = 3.4, 1H), 4.19 (dd, *J* = 11.1, 9.1, 1H), 3.91–3.83 (m, 1H), 3.75–3.68 (m, 2H), 3.61–3.53 (m, 2H), 3.44–3.21 (m, 3H), 1.87–1.34 (m, 15H), 0.08 (s, 19H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 151.8, 151.7, 131.4, 131.4, 130.7, 130.6, 130.4, 130.4, 128.7 128.7, 128.4, 128.2, 127.8, 127.6, 127.5, 124.7, 124.7, 124.6, 124.5, 121.3, 121.2, 120.5, 120.5, 99.8, 99.6, 98.0, 97.3, 89.0, 88.4, 88.2, 88.1, 74.4, 73.8, 73.5, 68.4, 67.5, 67.3, 65.8, 62.2, 62.2, 61.6, 60.9, 30.4, 30.3, 30.0, 25.5, 25.4, 25.3, 25.2, 19.1, 19.0, 18.6, 18.2, -0.1, -0.12, -0.2. **IR ν_{max}** (cm^{-1}): 2949, 1595, 1557 (asym. NO_2), 1485, 1454, 1371, 1252 (sym. NO_2), 1202, 1125, 1069, 1036. **HRMS** (ES+): $[M+1]^+$ calculated for $[C_{23}H_{33}N_2O_5Si]^+$: 445.2159, found 445.2158.

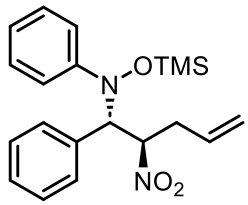
Synthesis of (±)-N-((1R,2R)-2-nitro-1-phenylpent-4-en-1-yl)-N-phenyl-O-(trimethylsilyl)hydroxylamine syn-**4.61**.



Synthesised according to *GP9* using nitrone **3.42** (19.7 mg, 0.1 mmol) and nitronate **4.87** (34.7 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 95:5 mixture of cyclohexane:ethyl acetate afforded to afford *syn*-**4.61** as a colourless oil (24 mg, 65%). R_f 0.80 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.29 (m, 1H, Ar–C**H**), 7.24–7.19 (m, 2H, Ar–C**H**), 7.16–7.11 (m, 2H, Ar–C**H**), 7.00 (m, 1H, Ar–C**H**), 6.92 (d, *J*=6.9, 2H, Ar–C**H**), 6.90–6.86 (m, 2H, Ar–C**H**), 5.65 (m, 1H, C**H**=CH_2), 5.33–5.22 (m, 1H, C**H**–NO_2), 5.07 (dq, *J* = 10.2, 1.2, 1H, CH=C**H**$_2$), 4.97 (dq, *J* = 17.0, 1.4, 1H, CH=C**H**$_2$), 4.72 (d, *J* = 10.9, 1H, C**H**–N), 2.36–2.21 (m, 2H, C**H**$_2$), 0.07 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.0 (Ar–**C**), 131.6 (Ar–**C**), 131.1 (Ar–**C**), 130.8 (**C**H=CH_2), 128.6 (Ar–**C**), 128.2 (Ar–**C**), 127.9 (Ar–**C**), 124.6 (Ar–**C**), 121.1 (Ar–**C**), 119.8 (CH=**C**H_2), 89.3 (**C**–NO_2), 76.6 (**C**–N), 36.5 (**C**H_2), -0.2 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 2957, 1757, 1645, 1595, 1557 (asym. NO_2), 1485, 1452, 1435, 1371, 1310, 1252 (sym. NO_2), 1204, 1026. **HRMS** (ES+): $[M+1]^+$ calculated for $[C_{20}H_{27}N_2O_3Si]^+$: 371.1791, found 371.1793.

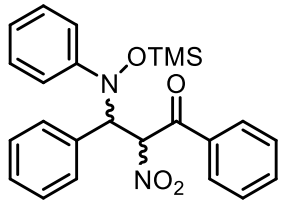
*Synthesis of (±)-N-((1S,2R)-2-nitro-1-phenylpent-4-en-1-yl)-N-phenyl-O-(trimethylsilyl)hydroxylamine anti-***4.61**.



Synthesised according to *GP9* using nitrone **3.42** (19.7 mg, 0.1 mmol) and nitronate **4.87** (34.7 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through preparative TLC with a 95:5 mixture of cyclohexane:ethyl acetate afforded to afford *anti*-**4.61** as a colourless oil (8 mg, 22%). R_f 0.70 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.25–7.18 (m, 2H, Ar–C**H**), 7.18–7.13 (m, 3H, Ar–C**H**), 7.03–6.96 (m, 3H, Ar–C**H**), 6.87–6.84 (m, 2H, Ar–C**H**), 5.87 (m, 1H, C**H**=CH_2), 5.32–5.21 (m, 3H, CH=C**H**$_2$+C**H**–NO_2), 4.45 (d, *J* = 10.7, 1H, C**H**–N), 3.49–3.43 (m, 1H, C**H**$_2$), 2.96–2.87 (m, 1H, C**H**$_2$), 0.08 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.1 (Ar–**C**), 131.5 (Ar–**C**), 131.3 (Ar–**C**), 130.4 (**C**H=CH_2), 128.6 (Ar–**C**), 128.5 (Ar–**C**), 127.5 (Ar–**C**), 124.5 (Ar–**C**), 120.5 (Ar–**C**), 120.0 (CH=**C**H_2), 88.8 (**C**–NO_2), 76.3 (**C**–N), 37.5 (**C**H_2), 0.0 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 2957, 2924, 2853, 1595, 1553 (asym. NO_2), 1485, 1454, 1373, 1252 (sym. NO_2). **HRMS** (ES+): $[M+1]^+$ calculated for $[C_{20}H_{27}N_2O_3Si]^+$: 371.1791, found 371.1793.

Synthesis of (±)-2-nitro-1,3-diphenyl-3-(phenyl((trimethylsilyl)oxy)amino)propan-1-one **4.62**.

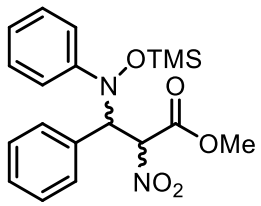


Synthesised according to *GP9* using nitrone **3.42** (19.7 mg, 0.1 mmol) and nitronate **4.88** (47.5 mg, 0.2 mmol) in dichloromethane for 3 hours. Purification of the crude reaction mixture through flash column chromatography with a 9:1 mixture of cyclohexane:ethyl acetate with 1% Et_3N afforded **4.62** as a yellow oil (36 mg, 83%). Obtained as a mixture of distereoisomers. R_f 0.76 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 8.24–8.22 (m, 1H, Ar–C**H**), 7.89–7.85 (m, 2H, Ar–C**H**), 7.71–7.41 (m, 7H, Ar–C**H**), 7.25–7.05 (m, 7H, Ar–C**H**), 7.04 (d, *J*=4.6, 1H, C**H**–NO_{2major}), 7.00 (dd, *J* =

8.6, 1.1, 4H, Ar–C**H**), 6.96–6.93 (m, 2H, Ar–C**H**+ C**H**–NO_{2minor}), 6.87 (dd, *J* = 8.2, 1.3, 2H, Ar–C**H**), 5.56 (d, *J* = 10.3, 1H, C**H**–N_{minor}), 5.43 (d, *J* = 10.7, 1H, C**H**–N_{major}), 0.14 (s, 9H, TMS–C$\mathbf{H}_{3major}$), -0.20 (s, 9H, TMS–C$\mathbf{H}_{3minor}$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 187.2 (**C**=O_{major}), 185.3 (**C**=O_{major}), 151.7 (Ar–**C**), 151.6 (Ar–**C**), 135.3 (Ar–**C**), 134.7 (Ar–**C**), 131.2 (Ar–**C**), 130.7 (Ar–**C**), 130.5 (Ar–**C**), 129.6 (Ar–**C**), 129.3 (Ar–**C**), 129.2 (Ar–**C**), 129.1 (Ar–**C**), 129.0 (Ar–**C**), 128.8 (Ar–**C**), 128.6 (Ar–**C**), 128.4 (Ar–**C**), 128.3 (Ar–**C**), 128.0 (Ar–**C**), 127.7 (Ar–**C**), 125.1 (Ar–**C**), 124.8 (Ar–**C**), 121.5 (Ar–**C**), 121.0 (Ar–**C**), 120.9 (Ar–**C**), 119.6 (Ar–**C**), 88.3 (**C**–NO_{2major}), 88.1 (**C**–NO_{2minor}), 74.5 (**C**–N_{major}), 73.9 (**C**–N_{minor}), -0.2 (TMS–**C**H_{3major}), -0.4 (TMS–**C**H_{3minor}). **IR ν_{max}** (cm^{-1}): 3063, 2928, 1697 (C=O), 1636, 1597, 1560 (asym. NO_2), 1518, 1449, 1439, 1377, 1341, 1316, 1260 (sym. NO_2), 1227, 1069, 1024, 1001. **HRMS** (ES+): $[M+1]^+$ calculated for $[C_{24}H_{27}N_2O_4Si]^+$: 435.1740, found 435.1747.

Synthesis of (±)-methyl 2-nitro-3-phenyl-3-(phenyl((trimethylsilyl)oxy)amino)propanoate **4.63**.

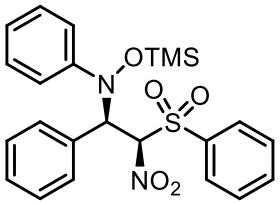


Synthesised according to *GP9* using nitrone **3.42** (19.7 mg, 0.1 mmol) and nitronate **4.89** (38.3 mg, 0.2 mmol) in dichloromethane for 24 hours. Purification of the crude reaction mixture through flash column chromatography with a 9:1 mixture of cyclohexane:ethyl acetate with 1% Et_3N afforded **4.63** as a yellow oil (35 mg, 90%). Obtained as a mixture of distereoisomers. R_f 0.65 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.29–7.24 (m, 2H, Ar–C**H**), 7.22–7.13 (m, 6H, Ar–C**H**), 7.07–6.95 (m, 8H, Ar–C**H**), 5.89 (d, *J* = 10.8, 2H, C**H**–$NO_{2major+minor}$), 5.22–5.17 (m, 2H, C**H**–$N_{major+minor}$), 3.90 (s, 3H, OC$\mathbf{H}_{3minor}$), 3.45 (s, 3H, OC$\mathbf{H}_{3major}$), 0.05 (s, 9H, TMS–C$\mathbf{H}_{3major}$), 0.02 (s, 9H, TMS–C$\mathbf{H}_{3minor}$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 163.6 (**C**=O_{minor}), 163.0 (**C**=O_{major}), 151.5 (Ar–**C**), 151.4 (Ar–**C**), 130.8 (Ar–**C**), 130.3 (Ar–**C**), 130.3 (Ar–**C**), 129.1 (Ar–**C**), 129.0 (Ar–**C**), 128.4 (Ar–**C**), 127.9 (Ar–**C**), 127.7 (Ar–**C**), 125.0 (Ar–**C**), 121.2 (Ar–**C**), 89.4 (**C**–NO_{2major}), 88.6 (**C**–NO_{2minor}), 74.2 (**C**–N_{major}), 73.8 (**C**–N_{minor}), 53.9 (O**C**H_{3minor}), 53.5 (O**C**H_{3major}), -0.38 (TMS–**C**H_{3major}), -0.41

(TMS–**C**H_{3minor}). **IR** ν_{max} (cm^{-1}): 2957, 1755 (C=O), 1562 (asym. NO_2), 1485, 1454, 1437, 1364, 1308, 1252 (sym. NO_2), 1204, 1167, 1071, 1024. **HRMS** (ES+): $[M+1]^+$ calculated for $[C_{19}H_{25}N_2O_5Si]^+$: 389.1533, found 389.1542.

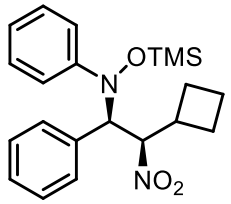
Synthesis of (±)-N-((1R,2R)-2-nitro-1-phenyl-2-(phenylsulfonyl)ethyl)-N-phenyl-O-(trimethylsilyl)hydroxylamine syn-**4.64**.



Synthesised according to *GP9* using nitrone **3.42** (19.7 mg, 0.1 mmol) and nitronate **4.90** (54.7 mg, 0.2 mmol) in dichloromethane for 24 hours. Purification of the crude reaction mixture through flash column chromatography with a 8:2 mixture of cyclohexane:ethyl acetate afforded *syn*-**4.64** as an off white oil (23 mg, 49%). R_f 0.55 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.60 (tt, *J* = 6.9, 1.8, 1H, Ar–C**H**), 7.40–7.34 (m, 4H, Ar–C**H**), 7.29–7.24 (m, 1H, Ar–C**H**), 7.13–7.05 (m, 4H, Ar–C**H**), 7.00 (m, 1H, Ar–C**H**), 6.76–6.74 (m, 4H, Ar–C**H**), 6.33 (d, *J* = 11.4, 1H, C**H**–NO_2), 4.88 (d, *J* = 11.4, 1H, C**H**–N), 0.02 (s, 9H, TMS–C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 150.8 (Ar–**C**), 135.7 (Ar–**C**), 135.0 (Ar–**C**), 132.0(Ar–**C**), 129.9 (Ar–**C**), 129.7 (Ar–**C**), 129.5(Ar–**C**), 129.3 (Ar–**C**), 129.2 (Ar–**C**), 128.4 (Ar–**C**), 127.7 (Ar–**C**), 127.3 (Ar–**C**), 125.3 (Ar–**C**), 121.2 (Ar–**C**), 103.6 (**C**–NO_2), 74.2 (**C**–N), -0.1 (TMS–**C**H_3). **IR** ν_{max} (cm^{-1}): 2957, 2924, 2855, 1568 (asym. NO_2), 1485, 1449, 1346 (asym. SO_2), 1252 (sym. NO_2), 1190, 1157 (sym. SO_2), 1082, 1024. **HRMS** (ES+): $[M+1]^+$ calculated for $[C_{23}H_{27}N_2O_5SiS]^+$: 471.1410, found 471.1410.

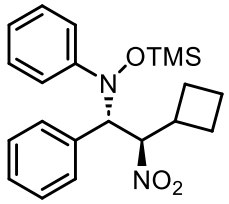
Synthesis of (±)-N-((1R,2R)-2-cyclobutyl-2-nitro-1-phenylethyl)-N-phenyl-O-(trimethylsilyl) hydroxylamine syn-**4.65**.



Synthesised according to *GP9* using nitrone **3.42** (19.7 mg, 0.1 mmol) and nitronate **4.91** (37.5 mg, 0.1 mmol) in dichloromethane for 24 hours. Purification of the crude reaction mixture through flash column chromatography with a 8:2 mixture of cyclohexane:ethyl acetate afforded *syn*-**4.65** as an off white oil (23 mg, 49%). R_f 0.91 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.26 (dt, *J* = 14.7, 1.3, 1H, Ar–C**H**), 7.20–7.16 (m, 2H, Ar–C**H**), 7.14–7.09 (m, 2H, Ar–C**H**), 7.00–6.96 (m, 3H, Ar–C**H**), 6.90–6.88 (m, 2H, Ar–C**H**), 5.17 (dd, *J* = 10.8, 7.7, 1H, C**H**–NO_2), 4.65 (d, *J* = 10.9, 1H, C**H**–N), 2.49–2.38 (m, 1H, C**H**), 2.05–1.95 (m, 1H, C$\mathbf{H}_2$), 1.70–1.50 (m, 4H, C$\mathbf{H}_2$), 1.26–1.22 (m, 1H, C$\mathbf{H}_2$), 0.07 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.1 (Ar–**C**), 131.8 (Ar–**C**), 131.0 (Ar–**C**), 128.5 (Ar–**C**), 128.2 (Ar–**C**), 127.6 (Ar–**C**), 124.6 (Ar–**C**), 121.2 (Ar–**C**), 92.8 (**C**–NO_2), 76.3 (**C**–N), 37.3 (**C**H), 27.1 (**C**H_2), 24.3 (**C**H_2), 17.3 (**C**H_2), -0.2 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 3032, 2953, 2870, 1595, 1551 (asym. NO_2), 1485, 1452, 1377, 1250 (sym. NO_2), 1202, 1072, 1026. **HRMS** (ES+): $[M+1]^+$ calculated for $[C_{21}H_{29}N_2O_3Si]^+$: 385.1947, found 385.1949.

Synthesis of (±)-N-((1S,2R)-2-cyclobutyl-2-nitro-1-phenylethyl)-N-phenyl-O-(trimethylsilyl)hydroxyl amine anti-**4.65**.

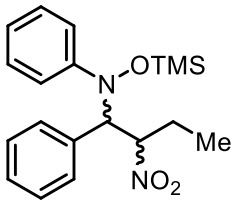


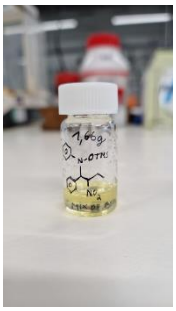
Synthesised according to *GP9* using nitrone **3.42** (19.7 mg, 0.1 mmol) and nitronate **4.91** (37.5 mg, 0.1 mmol) in dichloromethane for 24 hours. Purification of the crude reaction mixture through flash column chromatography with a 8:2 mixture of cyclohexane:ethyl acetate afforded *anti*-**4.65** as a white solid (3 mg, 8%). R_f 0.89 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.22–7.13 (m, 5H, Ar–C**H**), 7.03–6.96 (m, 3H, Ar–C**H**), 6.87–6.85 (m, 2H, Ar–C**H**), 5.29 (dd, *J* = 10.4, 4.5, 1H, C**H**–NO_2), 4.43 (d, *J* = 10.4, 1H, C**H**–N), 3.57–3.47 (m, 1H, C**H**), 2.21–2.09 (m, 3H, C$\mathbf{H}_2$), 1.89–1.86 (m, 2H, C$\mathbf{H}_2$), 1.78–1.72 (m, 1H, C$\mathbf{H}_2$), 0.05 (s, 9H, TMS–C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 152.3 (Ar–**C**), 132.6 (Ar–**C**), 130.0 (Ar–**C**), 128.4 (Ar–**C**), 128.4 (Ar–**C**), 127.6(Ar–**C**), 124.3 (Ar–**C**), 120.3 (Ar–**C**), 90.5 (**C**–NO_2), 73.4 (**C**–N), 36.3 (**C**H), 25.2 (**C**H_2), 23.5 (**C**H_2), 16.9(**C**H_2), 0.0 (TMS–**C**H_3). **IR ν_{max}** (cm^{-1}): 2955, 1595, 1549 (asym. NO_2), 1485, 1454, 1375, 1252 (sym. NO_2), 1204, 1024. **HRMS** (CI): $[M]^+$ calculated for $[C_{21}H_{28}N_2O_3Si]^+$: 385.18637, found 385.1862.

6.1.13. Chapter 4: Further reactivity

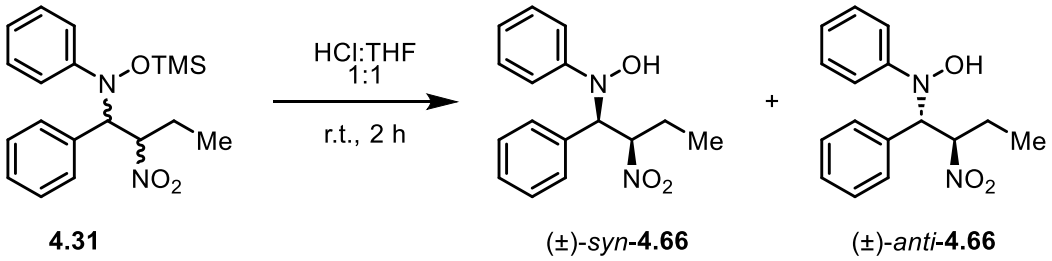
1g scale reaction for the synthesis of (±)-N-2-nitro-1-phenylbutyl)-N-phenyl-O-(trimethylsilyl)hydroxylamine **4.31**.





Synthesised according to *GP9* using nitrone **3.42** (1.00 g, 5.1 mmol) and nitronate **4.30** (1.64 g, 10.1 mmol) in dichloromethane for 24 hours. Purification of the crude reaction mixture with column chromatography with a 9:1 mixture of cyclohexane:ethyl acetate afforded a mixture of diastereoisomers of **4.31** as a yellow oil (1.66 g, 91%).

Synthesis of (±)-N-(2-nitro-1-phenylbutyl)-N-phenylhydroxylamine **4.66**.

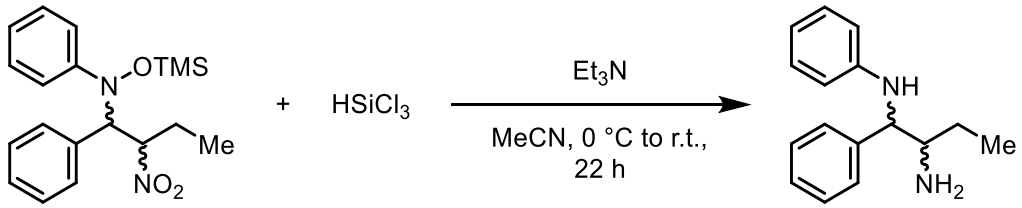


4.31 (±)-*syn*-**4.66** (±)-*anti*-**4.66**

Following a reported method,[291] *N*-(2-nitro-1-phenylbutyl)-*N*-phenyl-*O*-(trimethylsilyl) hydroxylamine **4.31** (71.7 mg, 0.2 mmol) was dissolved in 2 mL of a 1:1 mixture of HCl (1 M) and THF. The resulting mixture was left to stir at room temperature for 2 hours. Then, the reaction was quenched with a saturated solution of $NaHCO_3$ until a pH of ~8 was reached. The aqueous layer was extracted 3 times with EtOAc, the organic layers where then collected, washed with brine, and dried over $MgSO_4$. The solvent was subsequently removed affording 55 mg of yellow oil which contained a mixture of the major and minor hydroxylamine derivatives in a diasteromeric ratio of 92:8. Only for the purpose of this work, the diasteroisomers were separated through a flash column chromatography using a 9:1 mixture of cyclohexane/EtOAc. During the purification, we observed decomposition of the minor diastereoisomer (±)-*anti*-**4.66**. After column chromatography, 43 mg of a colourless oil of compound (±)-*syn*-**4.66** was obtained (75%). R*f*: 0.46 (Cy:AcOEt 9:1).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.29–7.22 (m, 3H, Ar–C**H**), 7.18–7.12 (m, 4H, Ar–C**H**), 6.93–6.91 (m, 3H, Ar–C**H**), 5.46 (td, *J* = 11.1, 2.9, 1H, C**H**–NO_2), 5.19 (br. s, 1H, O**H**), 4.75 (d, *J* = 10.9, 1H, C**H**–N), 1.90 (m, 1H, C$\mathbf{H}_2$), 1.52 (m, 1H, C$\mathbf{H}_2$), 0.96 (t, *J* = 7.3, 3H, C$\mathbf{H}_3$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 150.4 (Ar–**C**), 131.9 (Ar–**C**), 129.8 (Ar–**C**), 128.8 (Ar–**C**), 128.5 (Ar–**C**), 128.3 (Ar–**C**), 123.1 (Ar–**C**), 118.0 (Ar–**C**), 91.5 (**C**–NO_2), 74.5 (**C**–N), 24.7 (**C**H_2), 10.5 (**C**H_3). **IR ν_{max}** (cm^{-1}): 3499 (OH), 3063, 3030, 2972, 2938, 1597, 1549 (NO), 1489, 1452, 1373, 1344, 1314, 1262, 1217, 1194, 1129, 1086, 1030. **HRMS** (CI): $[M]^+$ calculated for $[C_{16}H_{18}N_2O_3]^+$: 286.13119, found 286.1311.

Synthesis of (±)-N1,1-diphenylbutane-1,2-diamine **4.68**.



4.31 **4.68**

Adapting a reported method,[297] *N*-(2-nitro-1-phenylbutyl)-*N*-phenyl-*O*-(trimethylsilyl) hydroxylamine **4.31** (71,7 mg, 0.2 mmol) was dissolved in 2 mL of anhydrous and degassed MeCN. The solution was cooled to 0 °C and $HSiCl_3$ (0.08 mL, 0.7 mmol) was added. Subsequently, Et_3N (0.14 mL, 1.0 mmol) was added dropwise under vigorous stirring. The resulting mixture was left to stir for further 10 minutes at 0 °C and then at room temperature overnight. The reaction was then quenched with a saturated solution of $NaHCO_3$ until a pH of ~8 was reached. The aqueous layer was extracted 3 times with EtOAc, the organic layers where then collected, washed with brine, and dried over $MgSO_4$. The solvent was subsequently removed affording 43 mg of a yellow oil which contained a mixture of the major and minor diamine derivatives in a diastereomeric ratio of 80:20. The crude reaction mixture could be further purified by an H_3O^+/OH^- aqueous workup affording 33 mg of a pale yellow oil (69%). For the purpose of this study, no column chromatography was undertaken as the diamine product could be obtained in relatively high purity. R*f*: 0.29 (CH_2Cl_2 + 5% MeOH).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ: 7.32–7.10 (m, 7H, Ar–C**H**), 7.01–6.91 (m, 2H, Ar–C**H**), 6.53 (tt, *J* = 7.3, 1.1, 1H, Ar–C**H**), 6.48–6.41 (m, 2H, Ar–C**H**$_{major}$), 5.05 (br. s, 1H, N**H**) 4.28 (d, *J* = 4.4, 1H, C**H**–NH$_{minor}$), 4.22 (d, *J* = 3.9, 1H, C**H**–NH$_{major}$), 2.98 (m, 1H, C**H**–NH$_{2major}$), 2.94–2.88 (m, 1H, C**H**–NH$_{2minor}$), 2.41–2.15 (br. s, 2H, N**H**$_2$) 1.63–1.51 (m, 1H, C**H**$_{2major+minor}$), 1.44–1.35 (m, 1H, C**H**$_{2major+minor}$), 0.91 (t, *J* = 7.5, 3H, C**H**$_{3major+minor}$). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ: 147.8 (Ar–**C**), 142.5 (Ar–**C**), 129.2 (Ar–**C**), 129.1 (Ar–**C**), 129.0 (Ar–**C**), 128.9 (Ar–**C**), 128.8 (Ar–**C**), 128.7 (Ar–**C**), 128.4 (Ar–**C**), 127.9 (Ar–**C**), 127.3 (Ar–**C**), 127.1 (Ar–**C**), 126.93 (Ar–**C**), 126.87 (Ar–**C**), 116.8 (Ar–**C**), 114.3 (Ar–**C**), 113.5 (Ar–**C**), 113.2 (Ar–**C**), 61.4 (**C**H–NH$_{minor}$), 60.5 (**C**H–

NH_{major}), 58.6 (**C**H–NH_{2major}), 57.6 (**C**H–NH_{2minor}), 27.6 (**C**$H_{2major+minor}$), 11.1 (**C**$H_{3major+minor}$). **IR** ν_{max} (cm^{-1}): 3358 (NH_2), 3051, 3024, 2961, 2930, 2874, 1599 (NH), 1501, 1451, 1427, 1379, 1317, 1260, 1179, 1153, 1076, 1028. **HRMS** (ES+): $[M+1]^+$ calculated for $[C_{16}H_{21}N_2]^+$: 241.1705, found 241.1709.

6.1.14. X-ray refinement data

Table S1. Crystal data and structure refinement for compound **2.43**.

Compound	**2.43**
Empirical formula	$C_{15}H_{12}N_2O$
M_r	236.27
Crystal system	Monoclinic
Space group	$P2_1/c$
Temperature (K)	180
a, *b*, *c* (Å)	5.5956 (4), 23.7388 (13), 9.2195 (6)
α, β, γ (°)	90, 99.725 (7), 90
Volume, V (Å^3)	1207.05 (14)
Z	4
Density, calc (g cm^{-3})	1.300
Absorption coefficient, μ (mm^{-1})	0.08
Crystal size (mm)	0.30 × 0.20 × 0.08
Radiation type	Mo K\a
Wavelength (Å)	0.71073
θ range (°)	4.1–28.3
Index ranges	$-7 \leq h \leq 6$
	$-32 \leq k \leq 29$
	$-12 \leq l \leq 9$
Reflections collected	6033
Independent reflections	2867
R(int)	0.025
Absorption correction	Gaussian
Data / restraints / parameters	2867 / 1 / 173
Goodness of fit, S	1.08
Final R indices [I>2σ(I)]	$R_1 = 0.0519$
	$wR_2 = 0.1231$
R indices (all data)	$R_1 = 0.0725$
	$wR_2 = 0.1371$
Max/Min residual electron density (e-Å^{-3})	0.53, -0.19

Table S2. Crystal data and structure refinement for compound **3.55**.

Compound	**3.55**
Empirical formula	$C_{19}H_{25}N_3O_3$
M_r	343.42
Crystal system	Monoclinic
Space group	C2/*c*
Temperature (K)	293
a, *b*, *c* (Å)	22.7917(12), 5.3754(4). 29.5181(18)
α, β, γ (°)	90, 94.943(5), 90
Volume, V (Å^3)	3602.9(4)
Z	8
Density, calc (g cm^{-3})	1.266
Absorption coefficient, μ (mm^{-1})	0.70
Crystal size (mm)	0.49 × 0.15 × 0.09
Radiation type	Cu K\a
Wavelength (Å)	1.54178
θ range (°)	4.7–71.9
Index ranges	-27 ≤ h ≤ 27
	-6 ≤ k ≤6
	-35 ≤ l ≤ 35
Reflections collected	15686
Independent reflections	3555
R(int)	0.051
Absorption correction	Gaussian
Data / restraints / parameters	3555 / 0 / 228
Goodness of fit, S	1.05
Final R indices [I>2σ(I)]	R_1 = 0.0557
	wR_2 = 0.1403
R indices (all data)	R_1 = 0.0740
	wR_2 = 0.1571
Max residual electron density (e^-Å^{-3})	0.60
Min residual electron density (e^-Å^{-3})	-0.41

Table S3. Crystal data and structure refinement for compound **2.84**.

Compound	**2.84**
Empirical formula	$C_{25}H_{25}ClN_2OSi$
M_r	433.01
Crystal system	Triclinic
Space group	P-*1*
Temperature (K)	200
a, *b*, *c* (Å)	10.0506 (6), 12.4111 (9), 19.1784 (12)
α, β, γ (°)	99.504 (5), 93.559 (5), 90.568 (5)
Volume, V (Å^3)	2354.4 (3)
Z	4
Density, calc (g cm^{-3})	1.222
Absorption coefficient, μ (mm^{-1})	2.06
Crystal size (mm)	0.18 × 0.13 × 0.03
Radiation type	Cu K\a
Wavelength (Å)	1.54178
θ range (°)	3.9–72.0
Index ranges	-10 ≤ h ≤ 12
	-15 ≤ k ≤ 15
	-23 ≤ l ≤ 19
Reflections collected	17234
Independent reflections	9111
R(int)	0.069
Absorption correction	Gaussian
Data / restraints / parameters	9111 / 30 / 578
Goodness of fit, S	0.97
Final R indices [I>2σ(I)]	R_1 = 0.0588
	wR_2 = 0.1384
R indices (all data)	R_1 = 0.1023
	wR_2 = 0.1677
Max/Min residual electron density (*e*$^-$Å^{-3})	0.28, -0.41

Table S4. Crystal data and structure refinement for compound **2.93**.

Compound	**2.93**
Empirical formula	$C_8H_7BCl_3N$
M_r	243.31
Crystal system	Monoclinic
Space group	*C*2/*m*
Temperature (K)	180
a, *b*, *c* (Å)	15.121 (2), 6.9264 (7), 9.8879 (13)
α, β, γ (°)	90, 109.906 (14), 90
Volume, V (Å^3)	973.7 (2)
Z	4
Density, calc (g cm^{-3})	1.598
Absorption coefficient, μ (mm^{-1})	0.89
Crystal size (mm)	0.64 × 0.27 × 0.15
Radiation type	Mo K\a
Wavelength (Å)	0.71073
θ range (°)	4.1 – 28.4
Index ranges	-20 ≤ h ≤ 20
	-9 ≤ k ≤ 7
	-13 ≤ l ≤ 12
Reflections collected	2544
Independent reflections	1257
R(int)	0.024
Absorption correction	Gaussian
Data / restraints / parameters	1257 / 0 / 76
Goodness of fit, S	1.12
Final R indices [I>2σ(I)]	R_1 = 0.0378
	wR_2 = 0.0754
R indices (all data)	R_1 = 0.0518
	wR_2 = 0.0830
Max/Min residual electron density (*e*$^-$Å^{-3})	0.34, -0.24

Table S5. Crystal data and structure refinement for compound **3.69**.

Compound	**3.69**
Empirical formula	$C_{25}H_{32}FN_3O_4Si$
M_r	485.62
Crystal system	Monoclinic
Space group	$P2_1/n$
Temperature (K)	293
a, b, c (Å)	9.8475(3), 10.9203(2), 24.8357(6)
α, β, γ (°)	90, 100.494(2), 90
Volume, V (Å^3)	2626.10(11)
Z	4
Density, calc (g cm^{-3})	1.228
Absorption coefficient, μ (mm^{-1})	1.138
Crystal size (mm)	0.426 x 0.185 x 0.097
Radiation type	Cu K\a
Wavelength (Å)	1.54178
θ range (°)	4.3790-73.0050
Index ranges	$-11 \leq h \leq 12$
	$-13 \leq k \leq 13$
	$-26 \leq l \leq 30$
Reflections collected	5177
Independent reflections	4451
R(int)	0.0308
Absorption correction	Gaussian
Data / restraints / parameters	5177 / 0 / 321
Goodness of fit, S	1.021
Final R indices [I>2σ(I)]	$R_1 = 0.0443$
	$wR_2 = 0.1048$
R indices (all data)	$R_1 = 0.0373$
	$wR_2 = 0.0976$
Max residual electron density (e^-Å^{-3})	0.330
Min residual electron density (e^-Å^{-3})	-0.243

Table S6. Crystal data and structure refinement for compound *anti*-**4.31**.

Compound	*anti*-**4.31**
Empirical formula	$C_{19}H_{26}N_2O_3Si$
M_r	358.51
Crystal system	Monoclinic
Space group	Cc
Temperature (K)	200
a, *b*, *c* (Å)	15.3631(5), 11.8472(3), 22.4626(7)
α, β, γ (°)	90, 90.492(3), 90
Volume, V (Å^3)	4088.3(2)
Z	8
Density, calc (g cm^{-3})	1.165
Absorption coefficient, μ (mm^{-1})	0.133
Crystal size (mm)	0.496 × 0.192 × 0.149
Radiation type	Mo K\α
Wavelength (Å)	0.71073
θ range (°)	3.439–29.719
Index ranges	-16 ≤ h ≤ 20
	-15 ≤ k ≤ 15
	-30 ≤ l ≤ 28
Reflections collected	19513
Independent reflections	7966
R(int)	0.0218
Absorption correction	Gaussian
Data / restraints / parameters	7966 / 2 / 472
Goodness of fit, S	1.149
Final R indices [I>2σ(I)]	R_1 = 0.0364
	wR_2 = 0.0952
R indices (all data)	R_1 = 0.0409
	wR_2 = 0.0988
Max residual electron density (e^-Å^{-3})	0.229
Min residual electron density (e^-Å^{-3})	-0.159

Table S7. Crystal data and structure refinement for compound *anti*-**4.42**.

Compound	*anti*-**4.42**
Empirical formula	$C_{19}H_{26}N_2O_4Si$
M_r	398.53
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Temperature (K)	200
a, *b*, *c* (Å)	9.9467(4), 10.7574(6), 19.8365(9)
α, β, γ (°)	90, 90, 90
Volume, V (Å^3)	2122.52(17)
Z	4
Density, calc (g cm^{-3})	1.247
Absorption coefficient, μ (mm^{-1})	0.14
Crystal size (mm)	1.00 × 0.44 × 0.17
Radiation type	Mo K\α
Wavelength (Å)	0.71073
θ range (°)	3.439–29.719
Index ranges	$-12 \leq h \leq 13$
	$-13 \leq k \leq 12$
	$-27 \leq l \leq 25$
Reflections collected	9161
Independent reflections	4976
R(int)	0.015
Absorption correction	Gaussian
Data / restraints / parameters	4976 / 0 / 257
Goodness of fit, S	1.03
Final R indices [I>2σ(I)]	R_1 = 0.0418
	wR_2 = 0.0354
R indices (all data)	R_1 = 0.0858
	wR_2 = 0.0816
Max residual electron density (e^-Å^{-3})	0.22
Min residual electron density (e^-Å^{-3})	-0.19

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