Lewis Acid-Promoted Synthesis of Novel Pyrazole Building Blocks

A thesis submitted to the University of Sheffield in partial fulfilment of the requirements for the award of Doctor of Philosophy

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“Until science is mixed with emotion, and appeals to the heart and imagination, it is like dead inorganic matter; and when it becomes so mixed and so transformed it is literature.”

John Burroughs (1889)
ABSTRACT

The present work investigated copper(II)-promoted regioselective synthesis of disubstituted pyrazole scaffolds via cycloaddition reactions between sydnones and alkynes. Cu(OTf)$_2$ has been found to mediate the formation of 1,3-pyrazoles, while Cu(OAc)$_2$·H$_2$O promotes the exclusive formation of the 1,4-regioisomer. Both transformations have been optimised and the scope has been explored for both reactions. A mechanistic proposal is also reported herein that has been derived from both experimental and theoretical investigations, the latter performed in collaboration with colleagues at Universidad del País Vasco (Spain). Furthermore, a catalytic variant of the synthesis of 1,4-disubstituted pyrazoles has been developed using Cu(OAc)$_2$ supported on modified silica gel and, in collaboration with Future Chemistry Holding BV and Radboud University (the Netherlands), this methodology has been implemented under continuous flow.

A directed cycloaddition of sydnones and alkynylboranes has also been developed. A range of substrates have been synthesised and subjected to cycloaddition conditions, showing that only pyridine- and quinoline-derived substrates afforded the desired pyrazole products. Mechanistic studies using NMR spectroscopy have also been carried out.

Finally, the diastereoselective addition of Grignard reagents to a sydnone sulfinimine derivative has been studied, using this strategy to generate bicyclic pyrazole scaffolds containing stereogenic centres after a functionalisation-cycloaddition tandem process.
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ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AAC</td>
<td>Azide-alkyne cycloaddition</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>Acetylacetonate</td>
</tr>
<tr>
<td>ACR</td>
<td>Agitating Cell Reactors</td>
</tr>
<tr>
<td>Alk</td>
<td>Alkyl</td>
</tr>
<tr>
<td>app</td>
<td>Apparent</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>bp</td>
<td>Boiling point</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>°C</td>
<td>Degrees Celsius</td>
</tr>
<tr>
<td>cat.</td>
<td>Catalyst</td>
</tr>
<tr>
<td>CDI</td>
<td>1,1'-Carbonyldiimidazole</td>
</tr>
<tr>
<td>Cl</td>
<td>Chemical ionisation</td>
</tr>
<tr>
<td>COD</td>
<td>Cyclooctadiene</td>
</tr>
<tr>
<td>Conc.</td>
<td>Concentration</td>
</tr>
<tr>
<td>Cp*</td>
<td>Pentamethylcyclopentadienyl</td>
</tr>
<tr>
<td>CuAAC</td>
<td>Copper-catalysed Azide-Alkyne Cycloaddition</td>
</tr>
<tr>
<td>CuSAC</td>
<td>Copper-catalysed Sydnone-Alkyne Cycloaddition</td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>o-DCB</td>
<td>ortho-Dichlorobenzene</td>
</tr>
<tr>
<td>DCC</td>
<td>Dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>1,2-DCE</td>
<td>1,2-Dichloroethane</td>
</tr>
<tr>
<td>DFT</td>
<td>Density Functional Theory</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-Diisopropylethylamine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-Dimethoxyethane</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-Dimethylformamide</td>
</tr>
<tr>
<td>DMI</td>
<td>1,2-Dimethylimidazole</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>dppp</td>
<td>1,3-Bis(diphenylphosphino)propane</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>E'</td>
<td>Electrophile</td>
</tr>
<tr>
<td>EI</td>
<td>Electron ionisation</td>
</tr>
<tr>
<td>eq.</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>FAB</td>
<td>Fast atom bombardment</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier transform infrared</td>
</tr>
<tr>
<td>GCMS</td>
<td>Gas chromatography – mass spectrometry</td>
</tr>
<tr>
<td>h</td>
<td>Hour(s)</td>
</tr>
<tr>
<td>n-Hex</td>
<td>$n$-Hexyl</td>
</tr>
<tr>
<td>hfacac</td>
<td>Hexafluoroacetylacetonate</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectrometry</td>
</tr>
<tr>
<td>IAN</td>
<td>Isoamyl nitrite, isopentyl nitrite</td>
</tr>
<tr>
<td>‘Pr</td>
<td>Isopropyl</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>M</td>
<td>Metal</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MHz</td>
<td>Megahertz</td>
</tr>
<tr>
<td>min</td>
<td>Minute</td>
</tr>
<tr>
<td>NBD</td>
<td>Norbornadiene</td>
</tr>
<tr>
<td>NCS</td>
<td>$N$-Chlorosuccinimide</td>
</tr>
<tr>
<td>NHC</td>
<td>$N$-Heterocyclic Carbene</td>
</tr>
<tr>
<td>NMI</td>
<td>1-Methylimidazole</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>OAc</td>
<td>Acetate</td>
</tr>
<tr>
<td>OMs</td>
<td>Mesylate (Methanesulfonate)</td>
</tr>
</tbody>
</table>
OTf  Triflate (Trifluoromethanesulfonate)
Ph   Phenyl
pH   -log\textsubscript{10}[H\textsuperscript{+}]
pKa  -log\textsubscript{10}([A\textsuperscript{-}][H\textsuperscript{+}]/[HA])
PMDTA N,N,N',N',N''-Pentamethyldiethylenetriamine
ppm  Parts per million
Pr   Propyl
Py   Pyridinyl
Pym  Pyrimidinyl
Pyr  Pyrazinyl
Quin Quinolyl
rt   Room temperature
R    Residue
RuAAC Ruthenium-catalysed Azide-Alkyne Cycloaddition
SM   Starting material
TBAI Tetrabutylammonium iodide
Tf   Triflyl (Trifluoromethanesulfonyl)
TFA  Trifluoroacetate
TFAA Trifluoroacetic anhydride
THF  Tetrahydrofuran
TLC  Thin layer chromatography
TMEDA N,N,N',N'-Tetramethylethlenediamine
TMS  Trimethylsilyl
Tol  Tolyl
Ts   Tosyl (p-Toluenesulfonyl)
X    Halogen
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Chapter 1. Metal acetylides in cycloaddition reactions

1. Introduction

Due to its importance in the agrochemical and pharmaceutical industries, materials science and bioengineering, the synthesis of small heterocyclic molecules has attracted much attention throughout the years. An easy way to access these compounds is by cycloaddition reactions; and as this review will demonstrate, by using metal acetylides these molecules can be assembled rapidly and with good control.

Cycloaddition reactions are a powerful tool to generate complex cyclic molecules using readily available starting materials and achieving high levels of atom economy, since the majority of the atoms from the starting materials are maintained in the newly generated products. Among them, 1,3-dipolar cycloaddition reactions between dipolar compounds and alkenes or, mainly, alkynes are especially important in order to generate five-membered rings, many of which are known to be characteristic cores of biologically active compounds.\textsuperscript{1,2,3,4}

The simplest alkyne unit available for synthetic purposes, acetylene, is a gas and is therefore inconvenient to use. For this reason, alkynes with higher molecular weights are more suitable for synthetic applications. In addition, alkynes tend to be quite unreactive, so activation is often needed for these reactions to proceed. A useful way to activate a triple bond is by coordination of a metal cation, thereby allowing control over the reactivity and regiochemistry. In addition, the presence of a carbon-metal bond is highly desirable because it allows further functionalization on the position bearing the metal residue.

The following report describes the most relevant transformations that lead to heterocycles through cycloaddition reactions using metal acetylides as intermediates.
2. Synthesis and applications of metal acetylides

There are a wide range of metal-alkyne complexes in which the metal is usually attached through a covalent carbon-metal bond. The most common metal-alkyne complexes are metal acetylides (with only one metal fragment / ligand, Scheme 1.a) or acetylide bridges between two or more metal fragments (Scheme 1.b). These acetylide bridges can have different configurations depending on the metal fragments involved, which will favour the formation of one type of complex over the others. The b.2 complexes are of special interest because they are considered to be organometallic analogues of 1,3-butadiynes, since isolobal properties have been observed between [M]_2C and RC_R structures, a fact that makes them very suitable for alkyne chemistry.

Scheme 1. Different metal complexes, where M is the metal fragment.

The main advantage that metal acetylides offer over the parent hydrocarbon is an enhancement of the nucleophilicity of the alkyne due to the incorporation of a carbon-metal bond. Hence, these reagents are used in electrophilic substitution reactions of the alkyne. In general, metal acetylides can be obtained from terminal alkynes and metal salts in a wide range of solvents and conditions. Base is needed to deprotonate the alkyne thus generating an acetylide anion, which can attack the metal cation and form the M-C covalent bond. Mild bases (e.g. NEt₃) are usually suitable for this deprotonation, i.e. it has been observed that the coordination of a metal to a terminal alkyne can lower the pKa of the terminal proton up to 10 units.

As for their applications, metal acetylides are employed mainly in nucleophilic additions to electrophiles, or as intermediates in alkyne-coupling reactions, such as the Sonogashira coupling. In the case of copper, for instance, the acetylides are generally polymeric materials which are very unreactive due to their high stability. However, they can be activated through processes such as oxidation with oxygen in the presence of nitrogen-containing ligands such as TMEDA or imidazole derivatives, resulting in an umpolung of reactivity, which makes these acetylides suitable for alkynylation reactions, as Evano recently reported. In this case, copper(I) acetylides are used to synthesise ynamides, ynimines and alkynylphosphonates via oxidation and further reaction with nitrogen- and phosphorus-containing nucleophiles, as shown in Scheme 2.

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Chapter 1: Metal Acetylides in Cycloaddition Reactions
Gold is another interesting metal that can provide activation of terminal alkynes to generate aromatic compounds. Scheme 3 shows an example reported by Krause where activation of a terminal alkyne by gold(III) chloride triggers the isomerisation of a range of furans to deliver the corresponding phenols via a Diels-Alder reaction and subsequent C-O bond cleavage.\textsuperscript{12}

\begin{Scheme}
\centering
\includegraphics[width=\textwidth]{Scheme3.png}
\caption{AuCl\textsubscript{3}-catalysed furan-phenol isomerisation.}
\end{Scheme}
Chapter 1: Metal Acetylides in Cycloaddition Reactions

3. Use of metal acetylides in cycloaddition reactions

As stated before, one of the most relevant uses of metal acetylides is in cycloaddition reactions because they act as activated alkynes. Among the available possibilities, the most popular example is the synthesis of triazoles from 1,3-dipolar cycloaddition reactions of azides with alkynes. However, many more examples have been reported in the past few decades making possible the generation of different heterocyclic structures using different metal catalysts.

3.1. [1,3]-Dipolar cycloaddition of azides and alkynes:

The azide-alkyne cycloaddition reaction to obtain 1,2,3-triazoles is the most studied example of 1,3-dipolar cycloaddition reactions, described for the first time by Huisgen in the 1960s. When performed in the absence of a catalyst, the regioselectivity of the reaction is quite low, and an equal mixture of isomers is usually obtained. However, in cases where R is a tertiary alkyl residue, only one isomer may be generated from the reaction because of steric effects.

\[
\begin{align*}
N^\delta^+ & \quad N^\delta^- \\
\text{R}^1 & \text{= } \text{R}^2
\end{align*}
\]

Scheme 4. Classic thermal 1,3-dipolar cycloaddition between alkynes and azides.

In addition, it has to be taken into account that a triazole can be mono-, di- or trisubstituted, thus increasing the number of possible isomers. Since there is a clear requirement for precise regiocontrol of these reactions, the regioselective alkyne-azide cycloaddition has been widely studied and many examples are reported in the literature. More recently, the Sharpless and Meldal groups independently developed the first catalytic variant using copper(I) catalysis that allowed access to 1,4-disubstituted-1,2,3-triazoles with excellent regioselectivities (11 examples, > 80% yield).

\[
\begin{align*}
\text{Ph} & \quad \text{O} & \quad \text{CuSO}_4 \cdot 5 \text{H}_2\text{O} (1 \text{ mol\%}) \\
\text{N}^\delta^+ & \quad \text{N}^\delta^- & \quad \text{Bn} \\
\text{Ph} & \quad \text{O} & \quad \text{Sodium ascorbate (5 mol\%)} \\
\text{H}_2\text{O}/\text{BuOH, 2:1, rt, 8h} & \quad \text{PhO} & \quad \text{Ph} \\
\text{91\%} & \quad \text{Ph} & \quad \text{Ph}
\end{align*}
\]

Scheme 5. CuAAC reaction described by Fokin and Sharpless in 2002.

This chemistry is known as copper-catalysed azide-alkyne cycloaddition (CuAAC), and was one of the first reactions that gave birth to what it is known today as click chemistry.
According to the *click chemistry* principles, a reaction should be wide in scope, give very high yields, generate by-products removable by non-chromatographic techniques (if generated) and be regioselective.\(^{21}\)

The main features of CuAAC chemistry include the use of readily available starting materials, the choice of using either organic or aqueous media and the avoidance of inert atmosphere. The reaction proceeds within a broad range of temperatures and is insensitive to pH (examples can be found working at pH from 4 to 12). In addition, these reactions offer a wide scope and are robust in terms of functional group compatibility.\(^{7}\) Generally, the final products can be isolated and purified using non-chromatographic techniques, such as filtration and recrystallization and they are stable to air/moisture.

The success of this chemistry promoted by copper(I) catalysis served as a precedent and, since then, many examples using different metal sources to generate metal acetylides as intermediates for azide-alkyne cycloaddition reactions have emerged. It has been observed that, depending on the nature of the metal, the regioselectivity of the products can be modulated, hence offering different mechanistic pathways to obtain complementary regioisomers.

### 3.1.1. Synthesis of di- and trisubstituted triazoles:

The generation of trisubstituted-1,2,3-triazoles can be approached by two different methodologies following 1,3-dipolar cycloaddition chemistry. One strategy is to obtain the corresponding metallotriazole after the cycloaddition reaction bearing two organic substituents besides the metal. This metallated intermediate can be quenched with an electrophile to deliver the desired trisubstituted triazole (Scheme 6).

\[
\text{Scheme 6. Pathways to generate trisubstituted 1,2,3-triazoles.}
\]

The main drawback of this chemistry is that, in order to generate the metal acetylide, only terminal alkynes can be used. Nevertheless, cases have been reported where these reactions can be used with internal alkynes as well. An alternative strategy is to use π-allyl
palladium complexes to obtain the corresponding N-allyl-trisubstituted triazoles, allowing the use of internal alkynes in this case.

Following the metallotriazole formation strategy, Micouin\textsuperscript{22} established a model to try to explain why the regioselectivity of formation of trisubstituted-1,2,3-triazoles changes depending on the nature and the equivalents of the metal acetylide needed (Scheme 7).

**Stoichiometric cycloaddition reactions**

\[
\begin{array}{c}
\text{[M]} \\
\text{[M]} \\
\text{[M]}
\end{array} + \begin{array}{c}
\text{N} \\
\text{N} \\
\text{N}
\end{array} \equiv \begin{array}{c}
\text{N} \\
\text{N} \\
\text{N}
\end{array} \equiv \begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3
\end{array} \rightarrow \begin{array}{c}
\text{R}_1^\prime \\
\text{R}_2^\prime \\
\text{[M]}
\end{array} \equiv \begin{array}{c}
\text{N} \\
\text{N} \\
\text{N}
\end{array} \equiv \begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3
\end{array}
\]

**Catalytic cycloaddition reactions**

\[
\begin{array}{c}
\equiv \\
\equiv \\
\equiv
\end{array} + \begin{array}{c}
\text{N} \\
\text{N} \\
\text{N}
\end{array} \equiv \begin{array}{c}
\text{N} \\
\text{N} \\
\text{N}
\end{array} \equiv \begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3
\end{array} \rightarrow \begin{array}{c}
\text{R}_1^\prime \\
\text{R}_2^\prime \\
\text{[M]}
\end{array} \equiv \begin{array}{c}
\text{N} \\
\text{N} \\
\text{N}
\end{array} \equiv \begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3
\end{array}
\]

Scheme 7. Different pathways for triazole formation.

They proposed that in some cases, the metal acetylide can act simply as a nucleophile attacking the organoazide to render, in this case, 1,5-disubstituted-4-metallotriazoles (Scheme 8a). However, there is another possibility where the organoazide and the metal acetylide undergo a [3 + 2] cycloaddition reaction to generate the 1,4-disubstituted-5-metallotriazole regioisomer (Scheme 8b).

(a) **Nucleophilic addition**

\[
\begin{array}{c}
\text{M} \\
\equiv \\
\equiv
\end{array} \rightarrow \begin{array}{c}
\equiv \\
\equiv
\end{array} \rightarrow \begin{array}{c}
\equiv \\
\equiv
\end{array} \rightarrow \begin{array}{c}
\equiv \\
\equiv
\end{array}
\]

(b) **1,3-Dipolar cycloaddition reaction**

\[
\begin{array}{c}
\equiv \\
\equiv \\
\equiv
\end{array} \rightarrow \begin{array}{c}
\equiv \\
\equiv \\
\equiv
\end{array}
\]

Scheme 8. Different mechanisms for the generation of disubstituted metallotriazoles.
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One of the factors affecting the different reactivity of metal acetylides may be the electronegativity of the metals employed, since mainly alkali (one valence electron) and alkaline earth (two valence electrons) metals follow the nucleophilic addition pathway whereas transition metals such as gold, silver or copper follow the cycloaddition route. In both cases, using different metals, the metalated triazole is the key reaction intermediate and it can react with electrophiles to generate more heavily substituted triazoles.

The metallo-triazole intermediates are not always stable enough to isolate, and so in some cases these reactions need to be performed as one-pot procedures to obtain the final products. If water is the chosen proton source, then disubstituted triazoles are obtained through this methodology with total control of the regiochemistry in the final products. In any case, the regiochemistry of the R¹ group (from the alkyne) and the metal in the final product will depend mainly on how the metal acetylide species approaches the organoazide.

To generate the 4-metallo-triazoles, lithium or bromomagnesium acetylides can be used as the active species. Examples of this chemistry using the Grignard acetylides were first described by Akimova et al. in the 1960s, but the yields reported for the resulting disubstituted triazoles were quite low (40-60%).

For this reason, Sharpless et al. revisited this chemistry in 2004 finding that the one-pot conditions proposed by Akimova worked much better than had been described, allowing them to exploit the scope of this chemistry to obtain 1,5-disubstituted triazoles in a regioselective manner after quenching with an electrophile. The proposed methodology is summarized in Scheme 9, where R¹ = aryl, benzyl, NH(C₆H₄)₂ and R² = phenyl, n-alkyl, cyclohexenyl.

![Scheme 9](image)

Using this procedure, both aromatic and aliphatic acetylides can be used, the latter being less reactive. With regard to the azides, electron-deficient substrates react much faster than the electron-rich analogues. This is consistent with the proposed mechanism
described in Scheme 8a, where the first step is the nucleophilic attack of the magnesium acetylide on the azide, followed by the cyclization.

This chemistry is quite versatile, since many electrophiles can be used to further functionalize the triazole in the 4-position, giving either the 1,5-disubstituted derivatives or 1,4,5-trisubstituted derivatives. Some common electrophiles are CO₂ to generate the corresponding acid, D₂O to deuterate the 4-position, I₂, aldehydes, isocyanates and chloroformates. In general, to obtain the disubstituted derivative, ammonium chloride is the most popular electrophile used to quench the reaction in order to protonate the 4-position.²⁵,²⁶

The main requirement for these reactions is strict oxygen exclusion, as oxygen can promote oxidative coupling processes between the generated triazoles and/or alkynes, giving undesired by-products if reaction times are long enough.

When studying this chemistry with Grignard reagents, Sharpless and co-workers also observed that the corresponding 1,5-disubstituted-4-bromotriazoles were detected in trace amounts. However, the formation of these species can be avoided by using EtMgCl to obtain the acetylide instead of EtMgBr.²⁵ Although the authors did not put forward a rationale, this observation is consistent with the relative bond strengths of Mg-Cl (ΔH_{bond} = 406 kJ·mol⁻¹)²⁷ and Mg-Br (ΔH_{bond} = 339 kJ·mol⁻¹).²⁷

In 2011, Croatt reported the synthesis of 1,5-disubstituted sulfonyl triazoles without using a metal catalyst.²⁸ This process required terminal alkynes and basic conditions, and best results were obtained when n-butyl lithium was used as base.

\[
\begin{array}{c}
\text{Scheme 10. Metal-free 1,3-dipolar cycloaddition of azides and alkynes.}
\end{array}
\]

In principle, the reaction is selective for the 1,5-isomer (2) but isomerisation to the 1,4-isomer (4) has been observed when recrystallizing or purifying the products using silica gel chromatography. This isomerization presumably occurs via a sulfonyl migration pathway (Scheme 11).
From a mechanistic point of view, a triazole anion is generated after the nucleophilic attack of the azide to the internal carbon of the alkyne. If an electrophile is added to the system at this point, a trisubstituted sulfonyl triazole can be generated. However, if the electrophile is just a proton source, the 1,5-disubstituted triazole is generated.

Although organolithium and organomagnesium reagents provide an interesting way to generate triazole derivatives in a regioselective fashion, stoichiometric amounts of these reagents are usually needed, moreover these strongly basic reagents can be incompatible with some substrates. An interesting alternative using metal catalysis is the one reported by Greaney and co-workers, based on the use of organozinc reagents. In a similar manner to the previous examples, once the 1,5-disubstituted-4-zincatriazole (6) is generated, it can be further derivatised by quenching with an electrophile. An alternative is to generate the disubstituted triazole directly by using ammonium chloride as the electrophile (Scheme 12).

The fact that the organozinc reagents are less nucleophilic than the corresponding lithium or magnesium derivatives has the distinct advantage that more convenient conditions can be used for subsequent reactions, and higher functional group compatibility is achieved. However, this lower reactivity and basicity has to be overcome by adding catalytic amounts of base, such as N-methyl imidazole. The addition of base is crucial to deprotonate the terminal alkyne and form the zinc acetylide intermediate (5).
The proposed mechanism for this triazole synthesis also starts with the formation of the zinc acetylide in a similar way to that described for the magnesium derivatives. However, since in this case the nucleophilicity is lower, the metal atom pre-coordinates to the terminal N of the azide in a reversible manner before undergoing the [3 + 2] cycloaddition step (Scheme 12). As in the previous example, stoichiometric amounts of the metal acetylide 5 are needed for the reaction to progress. This chemistry is especially attractive to use with azides bearing functional groups which are incompatible with the Grignard reagents, such as esters, nitriles, nitro groups, ketones or amides. It also works very well with highly hindered substrates; Greaney and co-workers managed to obtain steroid-functionalized triazoles using a hindered propargylic alcohol 7:

Choosing the proper metal catalyst, the synthesis of 5-metallotriazoles is also possible. In these cases, the key step is the [3 + 2] cycloaddition reaction, because the nucleophilicity of these metal acetylides is much lower than the lithium or magnesium analogues. Copper is the most popular metal for these transformations, mainly because it is relatively cheap, especially compared to precious metals. On the other hand, it is also possible to generate 1,4-disubstituted-5-metallotriazoles by using metal catalysis in a regioselective manner. For this purpose, silver, gold and aluminium are the most interesting examples.

Although silver(I) and gold(I) show similarities with copper(I), their role in the cycloaddition reactions between alkynes and azides is not quite the same. It has been reported that Ag(I) and Au(I) show catalytic activity only in the presence of a Cu(I) species and, for example, silver acetylides are unreactive towards these cycloadditions. However, in 2011, McNulty reported the first example of a copper-free silver-mediated azide-alkyne cycloaddition using the silver complex 8 at a 20 mol% loading.
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The combination of a silver(I) source (i.e. AgOAc) and phosphine-type ligands (i.e. 2-diphenylphosphinobenzoic acid) in the same complex allowed the formation of the desired 1,4-disubstituted triazoles regioselectively through, as suspected, a silver acetylide intermediate generated and activated from the complex 8. However, if the silver(I) salt was used in the absence of ligands, no product was observed, therefore showing that the ligands play an important role. Although using this methodology 1,4-disubstituted triazoles can be obtained, the conditions do not provide clear advantages over other procedures already reported.

In contrast, the formation of 1,4-disubstituted-5-aurated triazolates can be easily achieved through cycloaddition of gold(I) acetylides and organoazides under copper(I) catalysis. By using this methodology, the formation of C-Au bonds is made possible, which is desirable due to the stability of these bonds to both air and water.

In this case, two different pathways are possible, which make this chemistry even more versatile. The incorporation of gold can be carried out from gold(I) acetylides and organoaazides or vice versa, that is, using terminal alkynes and gold organoaazides. The first option is the most widely used.

\[
\text{AuL}_n \overset{9}{\xrightarrow{\text{rt, 12-72 h}}} \text{Bn-N}_3 \xrightarrow{[\text{Cu(MeCN)}_4]\text{PF}_6} \text{R} \quad \text{AuL}_n
\]

**Scheme 13.** Copper(I) mediated alkynylgold and azide cycloaddition reactions.

The mechanism of this cycloaddition reaction has not been fully elucidated, but the most credible hypothesis is that the reaction proceeds through a gold(I) alkynyl species (9), although direct evidence for these intermediates has not been found yet.

Another related example is the cycloaddition of aluminium acetylides with organic azides to generate 1,4-disubstituted-alumino triazoles. The advantage of these metalallocycles is the fact that the C-Al bond is stable enough to resist the cycloaddition conditions but is, at the same time, reactive enough to allow further functionalization when quenching with electrophiles (N-halosuccinimides, mainly). As seen before, copper(I) catalysis is also required in this case to promote the formation of the appropriate triazole products. Specific
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conditions include Cul (10 mol%) and the ligand pentamethyldiethylenetriamine (PMDTA, 10 mol%) which in combination successfully produce the aluminotriazoles, according to Micouin et al.22

\[
\begin{align*}
\text{AlMe}_2 & + \text{THF} & \text{Cul (10 mol%)} \\
\text{Ph} & \quad & \text{PMDTA (10 mol%)} \\
\text{Bn}_3 & \text{N}_3 & \text{Toluene, rt, 48 h} \\
\rightarrow & & \text{N-N-Bn} \\
& & \text{Ph} \\
& & \text{AlMe}_2
\end{align*}
\]

Scheme 14. Optimal conditions for the preparation of disubstituted aluminotriazoles.

A proposed mechanism provided by the authors introduces a transient \(sp^2\) geminal organobimetallic intermediate as the key species (Scheme 15). A possible explanation for the excellent regioselectivity (>99:1) achieved could be the formation of a 6-membered ring intermediate (11) comprising the alkynyl aluminium species, the copper catalyst and the organoazide.

\[
\begin{align*}
\text{Cu-L}_n \\
\text{R}^1 & = \text{Bn} \\
\text{R}^2 & = \text{Ph, } n\text{-alkyl} \\
& \text{Cu-L}_n \\
\rightarrow & \text{AlMe}_2 \\
\end{align*}
\]

Scheme 15. Proposed mechanism for the aluminotriazole formation.

As shown in the previous examples, the use of metal catalysts in organic synthesis is a very relevant and interesting research topic. However, especially considering environmental factors, alternative catalyst free chemistry has emerged as a potential avenue for further development. Recently, metal-free procedures to obtain triazoles have been reported. An example of this trend is the work by Fokin et al.35
Fokin and co-workers reported in 2010 the formation of disubstituted triazoles by using tetraalkylammonium hydroxides as bases, thus avoiding the stoichiometric amounts of metal waste generated in the previous examples.\(^{35}\)

![Scheme 16. Tetramethylammonium hydroxide-catalyzed cycloaddition.](image)

The main disadvantage of this procedure is that it is limited to arylalkynes and arylazides. A reason for this could be that arylacetylenes are very acidic in dimethylsulfoxide (the reaction medium),\(^{35}\) and thus, they can be easily deprotonated by weaker bases. However, alkylacetylenes are less acidic, so this reaction does not allow the generation of alkyl-substituted triazoles.

### 3.1.2. CuAAC vs. RuAAC – When the metal makes a difference:

Generally speaking, performing the cycloaddition reaction of an organoazide with a terminal alkyne under thermal conditions, in the absence of a metal catalyst, results in a mixture of the two possible regioisomers. DFT calculations suggest that this occurs because the activation barriers in both cases are very close, so both cycloaddition modes are accessible.\(^{7}\)

However, the reaction can be made regioselective by the introduction of a catalyst. When an organoazide reacts with a terminal alkyne in the presence of copper(I), only the 1,4-disubstituted regioisomer is obtained. In contrast, if the cycloaddition reaction takes place in the presence of ruthenium (II), only the 1,5-disubstituted regioisomer is formed (Scheme 17).

![Scheme 17. Regioselective synthesis of disubstituted triazoles.](image)
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It is well established that the addition of copper(I) in catalytic loadings allows access to 1,4-disubstituted triazoles. However, it is not so clear how this transformation takes place, although there are two main hypotheses. One mechanism operates via the formation of a copper(I) acetylide species as the reactive intermediate. An alternative mechanism suggests the participation of a copper(II) complex to accelerate the triazole formation.

The first option was proposed by Sharpless and Fokin in 2002. After the formation of a copper(I) acetylide from a terminal alkyne, the formation of a complex occurs between this species and the organoazide generating a six-membered copper(III) metallocycle (18), which resembles structure 11 in Scheme 15. This is the key step in establishing reaction regiochemistry and is also the responsible for the dramatic acceleration of the reaction rate compared to the thermal pathway.

In principle, instead of the formation of this six-membered ring transition state (18), a [3 + 2]-cycloaddition between the metalloalkyne and the azide could take place generating the metallotriazole 19. However, in accordance with DFT calculations, the pathway shown in Scheme 18 is more energetically favoured (by 12-15 kcal for the step involving the formation of the metallocycle 18, according to Sharpless and Fokin).  

Although this mechanism seems to be the most widely accepted, recently Zhu and co-workers proposed an alternative pathway for this reaction based on the formation of dinuclear copper species with mixed valence. These results imply that Cu(I) may not be the only active metal species participating in this reaction. Zhu et al. focussed on the copper-catalysed triazole formation when they observed that by using copper(II) acetate without adding any reducing agent, formation of the 1,4-disubstituted product was observed in good to excellent yields.
These observations had also previously been reported by Kantam et al., who stated that Cu(OAc)$_2$ proved to be a suitable catalyst for this transformation in water after observing no changes on the oxidation state of the metal ion during the reaction.\textsuperscript{39} In addition, among all other copper(II) salts tested Cu(OAc)$_2$ was the only one to show conversion to product in reasonable yields. This could indicate that the acetate ligand itself plays a role in the catalytic cycle.

From a mechanistic point of view, several kinetic studies have been performed to determine the most active oxidation state for copper during the cycloaddition reaction. These studies show different behaviour depending on the type of azide and the solvent used.

When using chelating azides (21-23), i.e. those organoazides capable of chelation-assisted coordination to metal species, a significant increase in reactivity is observed. This chelation facilitates the interaction between the azide and the copper centre. Hence, the usually fast formation of the copper(I) acetylide species becomes, in this case, a slower, rate determining step. Consequently, an acceleration of the reaction rate is observed as compared to when non-chelating azides are used. As for the solvents, the mechanistic pathway seems to differ between protic and aprotic solvents for the redox regeneration of the copper catalyst.\textsuperscript{38,40}

A dinuclear copper complex is likely to be the catalytic active species, according to Zhu, having one metal centre coordinated to the alkyne and the other to the azide. In addition, a mixed valence dinuclear complex would be even more suitable for the accelerated reaction, since the copper(I) centre could activate the alkyne and participate in redox steps, whereas the copper(II) centre may activate the azide being a strong Lewis acid.

From an experimental point of view, the copper catalyst may be generated in a variety of ways. Traditionally, two different sources of copper are used in these reactions. One option is the addition of copper(I) salts (e.g. CuI, CuCl, CuBr) in the presence of a base (typically Et$_3$N).\textsuperscript{19,41} However, Cu(I) salts are not very stable and are sensitive to agents like oxygen, so Cu(I) can oxidise or disproportionate. Due to this, the generation of Cu(I) in situ by reaction
of Cu(II) salts such as CuSO₄ with a reducing agent (sodium ascorbate in most cases) is generally preferred.²⁰,⁴²

However, Cu(0) metal itself has also been described to promote these reactions, generally as an activated nanoparticulate powder. Since the activated powder has high surface area, lower loadings can be used (<1 mol%). The main issue in this case is the solubility of the copper, which can be overcome by adding amine hydrochloride salts. These salts will provide slightly acidic conditions to oxidatively dissolve the copper with further stabilisation through coordination with the amine, acting as a nitrogen-based ligand.⁴³

Other copper sources reported to give successful results are copper-substituted silicotungstates, where copper cations are introduced in the vacant sites of these polymeric materials,⁴⁰ and N-heterocyclic carbene-containing copper(I) complexes, which turn out to be very stable towards oxygen, moisture and heat. The NHC ligands also provide protection to the copper(I) centre avoiding its oxidation, thereby circumventing the most common drawback when using copper(I) directly.⁴⁴ Another interesting example is a tandem process where copper(I) acetylides may react directly with azides to generate the triazole product and then, without isolation, addition of electrophiles such as N-halosuccinimides provide the desired 1,4-disubstituted-5-halotriazoles.⁴⁵

The formation of bimetallated triazoles has also been reported, where a metal azide reacts with a metal acetylide generating the desired triazoles (Scheme 19).⁴⁶ And, especially relevant for bioconjugation and labelling applications, solid phase syntheses using different polymeric resins such as propargyl- or PEG-derivatives have also been developed for click chemistry purposes. An advantage of this methodology is that it is compatible with other processes such as peptide synthesis or the Staudinger reaction.¹⁹,⁴²,⁴⁷

As shown, CuAAC chemistry is very robust and allows access to 1,4-disubstituted triazoles in a regioselective manner. Its only limitation is the fact that only terminal alkynes are suitable
substrates because of the formation of the alkynylcopper species, which can only be generated from terminal alkynes.

In an effort to generate the corresponding 1,5-disubstituted triazoles, Fokin and co-workers reported that ruthenium catalysts generate these type of compounds regioselectively. The interest in ruthenium, among all the transition metals, comes from recent reports where its use has been described in reactions such as metathesis of enynes, cycloadditions between alkynes and alkenes, cyclotrimerization of alkynes or Alder-ene reactions. However, none of the 1,3-dipolar cycloaddition reactions had been explored before the Fokin group decided to apply the ruthenium catalysis to the cycloadditions between azides and alkynes.

After catalyst screening, only [Cp*RuCl] complexes were found to show catalytic activity in the azide-alkyne cycloaddition (AAC) system, probably due to the fact that the Cp* ligand is electron rich and helps to stabilize higher formal oxidation states of the Ru atom. Some of the most popular catalytic systems for this purpose are Cp*RuCl(PPh$_3)_2$, Cp*RuCl(COD) or [Cp*RuCl]$_4$.

\[
\begin{align*}
\text{Bn}_2\text{N}_2\text{N}_2\text{N} \quad \overset{2 \text{ mol\% } \text{[Ru]}}{\text{THF, reflux}} \quad \text{Ph} \equiv \text{H} \\
\text{Yield: 93\%-100\%}
\end{align*}
\]

\textbf{Scheme 20. Ru-catalyzed AAC.}

Similar to the copper(I) catalysed case, when using ruthenium as a catalyst, the reaction is not oxygen or water sensitive. In any case, if labile oxygen coordinates to ruthenium, it can be easily replaced by other ligands such as cyclooctadiene (COD). These catalysts are also interesting because they allow the use of internal alkynes, which deliver the corresponding 1,4,5-trisubstituted triazoles in good to excellent yields (11 examples, 63-97%) and excellent regioselectivity (>99:1). This observation suggests that ruthenium acetylides may not be involved in the reaction, as Fokin et al. suggested in their proposed mechanism for this transformation.

As Scheme 21 shows, the catalytically active species is the [Cp*RuCl] complex, that is generated when the other ligands, L, are displaced, explaining why labile ligands are preferred for these catalysts. When this species (25) is formed, an oxidative coupling of the azide and the alkyne occurs to form the ruthenacycle (26). This step is irreversible and will determine the regioselectivity of the products. Next, reductive elimination takes place,
which according to DFT calculations, seems to be the rate-determining step. Finally, the triazole product 28 is released and the catalyst (24), regenerated.

In this way, access to 1,5-disubstituted triazoles is achieved, allowing the generation of the trisubstituted analogues by using internal alkynes, that could not be used with the copper(I) catalysed reaction.

3.1.3. The use of π-allyl palladium complexes:

Trisubstituted triazoles can also be obtained using a completely different approach to those employing metal acetylides. For example, π-allyl palladium complexes can be used to generate densely functionalized heterocycles.

This approach was first described in 2002 by Yamamoto and co-workers\textsuperscript{53,54} as an attempt to overcome the regioselectivity problems of the thermal azide-alkyne dipolar cycloadditions functionalizing the triazole either before or after the cycloaddition step. The proposed alternative is based on the use of multicomponent coupling reactions and a palladium catalyst (Scheme 22).
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Features of this chemistry are that it is compatible with internal alkynes, uses a low loading of the metal catalyst and shows selectivity towards alkynes in the presence of alkenes.

This transformation has been tested with alkynes conjugated to both electron-withdrawing \((R^2 = \text{COMe, CO}_2\text{Me, CHO, CN, SO}_2\text{Ph})\) and electron-donating groups \((R^2 = \text{NET}_2)\). Electron deficient alkynes react faster, although the yields for all the examples reported are poor to moderate (from 15 to 60%).

As for the mechanism, initially the formation of the π-allylpalladium azide complex 30 is proposed, and it is believed that this intermediate undergoes a 1,3-dipolar cycloaddition with the alkyne affording species 31, as shown in Scheme 23.

This complex 31 is in equilibrium with two other forms, 32 and 33, the latter one evolves through reductive elimination to give the final triazole product and regenerating Pd(0) to continue with the catalytic cycle.
This mechanism suggests that the equilibration between 31, 32 and 33 must be faster than the reductive elimination. This way, the allyl functionality ends up in the 2-position, leaving the 1-position unsubstituted in the final product.

Shortly after, in 2004, the same group reported a similar methodology taking advantage of these $\pi$-allylpalladium azide complexes to generate 1,4,5-trisubstituted triazoles employing a bimetallic catalyst with Pd(0) and Cu(I). The role of the copper in this transformation is to activate the alkyne through the formation of the copper(I) acetylide.

Scheme 24. Pd (0) and Cu (I)-mediated triazole synthesis.

The proposed mechanism for this transformation features the formation of a copper(I) acetylide from CuCl and the alkyne (generally the TMS derivative of both aryl and alkyl alkynes) extruding TMSCl. It is not clear what the next step could be because two different pathways seem feasible (Scheme 25).

Scheme 25. Proposed mechanism for the bimetallic catalyst.
One possibility (Path B) is the [3 + 2] cycloaddition between the copper acetylide and the π-allylpalladium azide complex 30 (generated from allyl carbonate, Pd (0) and trimethylsilyl azide). The generated intermediate (36) will undergo a cross-coupling step with another π-allylpalladium complex (37) ultimately regenerating 2 equivalents of Pd (0) – one for each π-allylpalladium complex – and the desired product 34.

Another possibility (Path A) is a [3 + 2] cycloaddition reaction between the copper acetylide (38) and allyl azide, which is generated by reductive elimination of the π-allylpalladium azide complex 30. In this case, the generated intermediate is a 1,4-disubstituted-5-coppertriazole (35), that will undergo another cross-coupling reaction to give the final product 34 and regenerate both Cu(I) and Pd(0).

Further studies are needed for a better understanding of this mechanism. Nonetheless, it has been shown that a catalytic approach is also feasible to obtain highly substituted triazoles preserving control over the regiochemistry of the products.

3.1.4. Synthesis of monosubstituted triazoles:

Much interest has been focused on the generation of substituted triazoles taking into account different substitution patterns and the regioselectivity. However, much less attention has been paid to the synthesis of N-monosubstituted equivalents, which are also hard to obtain with reasonable regioselectivity using direct alkylation, as mixtures are generally obtained.55,56,57

Taking this into consideration, in 2008, Fletcher described a copper-catalysed procedure using trimethylsilylacetylene and both aromatic and aliphatic azides as starting materials. Tralkylsilyl alkynes are interesting reagents because they can act as acetylene equivalents, but as they are liquids they are much easier and safer to handle than acetylene gas.

Initially, Fletcher’s aim was to take advantage of the click chemistry conditions described by Sharpless in 200220 using the CuSO₄·5H₂O / sodium ascorbate catalytic system and a base in water / ¹BuOH. However, the monosubstituted adduct was obtained together with the TMS-substituted triazole in different proportions depending on the starting materials used.
To overcome the mixture formation, two factors were studied: the solvent system and the base, resulting in a number of interesting discoveries (Table 1). A solvent screening was performed using different alcohols: MeOH, EtOH, iPrOH and tBuOH, whereby methanol gave less TMS-substituted triazole. Using water / MeOH as the solvent system, different bases were tested: K$_2$CO$_3$, KOH, Et$_3$N and pyridine. Inorganic bases gave less TMS incorporation in the products.

Table 1. Base and solvent screening.\(^{58}\)

<table>
<thead>
<tr>
<th>Base</th>
<th>Alcohol</th>
<th>% Yield (a/b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K$_2$CO$_3$</td>
<td>tBuOH</td>
<td>50/25</td>
</tr>
<tr>
<td>K$_2$CO$_3$</td>
<td>tPrOH</td>
<td>51/37</td>
</tr>
<tr>
<td>K$_2$CO$_3$</td>
<td>EtOH</td>
<td>62/3</td>
</tr>
<tr>
<td>K$_2$CO$_3$</td>
<td>MeOH</td>
<td>69/0</td>
</tr>
<tr>
<td>KOH</td>
<td>MeOH</td>
<td>50/0</td>
</tr>
<tr>
<td>Et$_3$N</td>
<td>MeOH</td>
<td>78/5</td>
</tr>
<tr>
<td>Pyridine</td>
<td>MeOH</td>
<td>40/36</td>
</tr>
<tr>
<td>-</td>
<td>MeOH</td>
<td>24/68</td>
</tr>
</tbody>
</table>

With this information in hand, a mechanism was proposed to show how the desilylated-adduct is generated.

The authors proposed that the ratio of TMS-incorporated triazoles depended on the rate of two key steps: the TMS deprotection and the cycloaddition reaction. If the deprotection is faster than the cycloaddition step, a higher concentration of TMS-free alkyne will accumulate waiting to take part in the cycloaddition reaction. Another parallel process will be the formation of the copper acetylide species. Thus, if the deprotection is fast and takes
place before the copper can coordinate forming the acetylide, loss of alkyne could be observed due to its high volatility causing a decrease in the overall yield. In contrast, if the cycloaddition reaction is faster, it is more likely to observe TMS-incorporated triazole (43) in a higher proportion.

In summary, a balance between the reaction rates of both processes is needed. Hence, in order to reduce the amounts of TMS-incorporated triazole (43), the deprotection step has to be faster than the cycloaddition but not too fast compared to the copper-complexation that promotes the cycloaddition, so as to avoid loss of alkyne.58

A control experiment was carried out by subjecting the TMS triazole adduct to the reaction conditions and monitoring for the desilylation (K2CO3, MeOH / H2O). In this case, no desilylation was observed suggesting that the C-Si bond is cleaved before cycloaddition. This methodology can be established as a one-pot procedure because the generated products are stable enough to avoid further reaction.

Considering the proposed mechanism, the fact that the inorganic bases are the ones giving the best results makes sense, since they are stronger bases than pyridine or Et3N therefore favouring the deprotonation of the alkyne and the deprotection of the TMS. Since copper probably coordinates to the alkyne before the insertion, the acetylene proton will be more acidic than in the absence of the metal.7 As for the solvent, methanol is the one giving best results and is also more acidic and the one with lowest degree of substitution, compared to iPrOH or ’BuOH, for instance. This fact makes the anion more nucleophilic, so it will attack the TMS moiety more efficiently increasing the deprotection rate. So, in conclusion, this newly developed procedure allows the regioselective synthesis of monosubstituted triazoles just by choosing the right conditions based on the CuAAC chemistry.
3.2. Other examples of cycloaddition reactions involving metal acetylides:

3.2.1. Synthesis of isoxazoles and pyrazoles:

From a pharmaceutical point of view, isoxazoles and pyrazoles are interesting heterocycles because molecules containing these structures have shown biological activity as cyclooxygenase inhibitors. Due to this fact, they are commonly found in non-steroidal anti-inflammatory drugs. Some relevant examples are shown below: the cyclooxygenase-2 (COX-2) inhibitors (Valdecoxib, Parecoxib and Celecoxib) and an arylalkanoic acid derivative (Lonazolac).\textsuperscript{2,4,59,60}

When isoxazoles are obtained by classical 1,3-dipolar cycloaddition reactions of alkynes and nitrile oxides, that is without using a catalyst, long reaction times are required and the products are generally obtained as mixtures of regioisomers. For this reason, there has been an impetus to attempt the chemistry developed for the regioselective formation of triazoles in order to obtain, by analogy, isoxazoles in a regioselective fashion \textit{via} judicious choice of metal catalysts.

This is especially important in this case because nitrile oxides are more reactive than azides (temperatures <80 °C are usually enough for the transformation to take place). This means that the formation of by-products such as furoxan dimers during the reaction is a common inconvenience, and as a consequence low yields are obtained.\textsuperscript{61} In this context, Fokin and co-workers have reported the regioselective synthesis of 3,5-disubstituted isoxazoles from nitrile oxides and terminal alkynes using Cu(I) catalysis,\textsuperscript{7,62} and the 3,4-disubstituted isomers using Ru(II) as the metal catalyst (Scheme 28).\textsuperscript{61}

In the case of copper, the CuSO\textsubscript{4}·5H\textsubscript{2}O (2 mol%) / sodium ascorbate (10 mol%) system was the chosen to generate Cu(I) \textit{in situ}; while in the case of ruthenium, [Cp*RuCl(COD)] in a 5 mol% loading turned to be the best performing catalyst, due to the same principle described for the triazole example. In both cases, either aromatic or aliphatic substrates (R\textsuperscript{1}}
or $R^3$) generated the desired product, and, in addition, the Ru chemistry is compatible with internal alkynes as well.

![Scheme 28](image)

**Scheme 28.** Dipolar cycloadditions between alkynes and nitrile oxides.

As for the mechanism of both transformations, they are analogous to the ones shown for the regioselective generation of disubstituted triazoles but using nitrile oxides instead of azides (see Scheme 18 for the copper(I) version and Scheme 21 for the ruthenium(II) variant). Accordingly, the copper(I) acetylide is the putative active species in the first case, and a ruthenacycle species is proposed to operate in the latter.

The only issue with these cycloadditions is the fact that nitrile oxides are rather unstable, so an interesting approach is the synthesis of these intermediates *in situ*, just before the cycloaddition reaction takes place. With this objective in mind, a one-pot procedure has been reported by Fokin, within a sequence for the generation of the 3,5-disubstituted products.

![Scheme 29](image)

**Scheme 29.** *In-situ* formation of the nitrile oxide.

A different synthetic strategy to azoles was developed by Micouin in 2011, whereby they reported the direct synthesis of polysubstituted isoxazoles through a metalative cyclization using aluminium, thus achieving access to 3,4,5-trisubstituted isoxazoles. The advantage of using aluminium is that the C-Al bond is reactive enough to allow further reactivity thereby avoiding a transmetallation step after the formation of the aluminoazole ring. Instead, quenching the metallocycle with an electrophile gives a direct, regioselective functionalisation at the C4 position. In the same report, the authors stated that this
chemistry is also applicable to pyrazole synthesis using hydrazonoyl chlorides instead of oximes (49).

\[
\text{Scheme 30. Formation of aluminoisoxazoles and aluminopyrazoles.}
\]

The mechanism for this transformation is quite interesting since an intramolecular trans-hydroxyalumination takes places to generate 54 instead of the usual cis addition. After that, for the 5-endodig cyclization to occur, additional Lewis acid (AlMe₃) is needed to activate the alkyne 54 and make possible the cyclization, because the aluminium acetylide species (53) is not π−acidic enough. In this case there is no formal dipolar cycloaddition reaction (Scheme 31).

\[
\text{Scheme 31. Proposed mechanism for isoxazole formation.}
\]

In summary, the use of different metals, either in catalytic loadings or in stoichiometric amounts, allows the synthesis of a variety of isoxazole derivatives with different substitution patterns in a regioselective manner.

### 3.2.2. Reaction of acetylides with nitrones:

Nitrones (58) are interesting intermediates in synthetic organic chemistry which take part in the Kinugasa coupling. This reaction was first described in 1972 as “the acetylide reaction”
and is an interesting tool to generate cis-substituted β-lactams \((59)\) stereoselectively from nitrones and copper(I) acetylides.\(^{65}\)

\[
\begin{align*}
\text{Ph} & \quad \text{Cu} \\
57 & \\
\text{1) Pyridine} & \quad 0.5-1 \text{ h, rt} \\
\text{2) Hydrolysis} & \\
\end{align*}
\]

\[\begin{array}{c}
\text{Ph} \\
58 \\
\text{R}^1 \quad \text{N} \quad \text{O} \quad \text{R}^2 \\
\text{R}^1 \quad \text{R}^2
\end{array}\]

**Scheme 32.** The Kinugasa reaction.

β-Lactams are interesting compounds from a pharmaceutical point of view because of their use as antibiotics, the mechanism of action of which is the inhibition of the bacterial cell wall synthesis. This family of compounds contains penicillins, cephalosporins, monobactams and carbapenems.\(^{66}\) In addition, they are also interesting as building blocks for synthesis of more complex molecular structures.\(^{67}\)

Despite their importance, the current methods to obtain these heterocycles have important limitations either in scope or selectivity and sometimes require the use of expensive rhodium catalysts or unstable ketenes. For this purpose, the Kinugasa coupling seems a suitable alternative for the stereoselective synthesis of the cis isomers using cheap copper catalysts.

Since this coupling was first described by Kinugasa, many authors reported new conditions to increase the efficiency of the process and, especially, reduce the metal loading. In 1995, Miura reported a catalytic variant using sub-stoichiometric amounts of CuI and a ligand, obtaining the trans β-lactam in this case. Later on this group also developed an asymmetric variant using chiral ligands.\(^{68}\)

A few years later, in 2002, Fu et al. reported another catalytic variant using CuCl and bis(azaferrocene)ligands. Using these ligands, the diastereoselective synthesis of the cis β-lactam ring can be achieved with ee >70% (cis, 11 examples, \(R^1, R^2 = \) both aromatic and aliphatic, 42-65% yield).\(^{67}\)
The Kinugasa coupling

\[
\text{Ph—Cu} + \underset{\text{N Ar}}{\text{Ar}} \underset{\text{N Ar}}{\text{O}} \overset{\text{Pyridine, rt}}{\text{Ph}_2} N Ar
\]

Fu’s modification

\[
R^1 \equiv + \underset{\text{N Ar}}{\text{O}} \overset{\text{CuCl (1-2.5\%)} \text{Ligand} \text{Cy}_2 \text{NMe}}{\text{MeCN, 0 °C}} R^1, R^2 \rightarrow R^1, R^2 \text{N Ar}
\]

Scheme 33. Kinugasa coupling and Fu’s modifications.

In this context, another interesting improvement has been reported for the Kinugasa coupling using chiral ligands with a Cu(II) source in catalytic amounts. The main feature of this new catalytic system reported by Tang in 2003\(^69\) is that, for the first time, the catalyst is air stable and water tolerant, circumventing the need for inert atmosphere reactions. In addition, for the first time a Cu(II) salt was shown to be an active catalyst for this transformation, generating the cis β-lactam ring in ee >70% (cis, 12 examples, R\(^1\), R\(^2\) = aromatic, 33-98% yield). Studies on the mechanism of this transformation are ongoing.

3.2.3. Cycloaddition chemistry of pyrones:

Substituted aromatic compounds are basic building blocks for natural product synthesis and many industrial applications (for some examples, see section 3.2.1). To access these structures, many different synthetic approaches exist but these do not always allow the desired control over the regiochemistry in incorporation of the substituents on the aromatic ring.

A useful alternative is the use of cycloaddition reactions choosing already functionalized starting materials. Among all of them, 2-pyrones are interesting substrates that can undergo \([4 + 2]\) cycloaddition reactions with both alkenes and alkynes generating important scaffolds for organic synthesis.

2-Pyrones can be obtained through several methods. Two attractive and contemporary approaches consist of metal-catalysed coupling cyclisations involving alkynes,\(^70,71,72\) and the cross-coupling of electrophilic pyrones with boronic acids.\(^73\) Interestingly, gold(I) catalysis is frequently used to activate the alkynes involved in these transformations through
intermediates that resemble the metal acetylide chemistry but, in this case, they promote cascade cyclization reactions. An example reported by Schreiber is shown in Scheme 34.

\[ \text{Scheme 34. An example of gold (I)-catalysed pyrone synthesis.} \]

In order to improve the regioselectivity of these cycloaddition reactions, attention has focussed on the use of directing groups on the substrate that can pre-associate with certain reagents before undergoing a chemical transformation. A typical example is to use Lewis acids and bases to generate a complementary pair that will associate during the reaction, thus ensuring the control of the regiochemistry of the products.

The use of alkynylmetal species as a source of π electrons has a dual function, since the metal will be acting as the Lewis acid coordinating to the Lewis basic positions and, as a result, the triple bond will easily undergo the cycloaddition reaction with the pyrone core.

\[ \text{Scheme 35. General [4 + 2]-Cycloaddition reaction between pyrones and alkynes.} \]

Harrity et al. reported in 2013 the use of alkynylaluminium species in cycloaddition reactions to assess their reactivity towards 2-pyrones. To enhance the regioselectivity of the products, 2-pyrones bearing Lewis basic groups have been designed to improve coordination between the two substrates and improve the cycloaddition. As a result, diverse functionalized phenyl rings bearing groups such as amides or heteroaromatic residues were obtained under mild conditions in moderate to good yields (41-78%). However, esters and sulphur-containing functional groups did not react and the starting material was recovered in these cases.

In addition, this chemistry can be extended to Al-acetylides, thereby offering the advantage of further chemistry at the C-Al bond, allowing them to be used in subsequent reactions to obtain more functionalized products (Scheme 36). Besides classical quenching of the aluminium moiety with electrophiles such as \( \text{I}_2 \) (top), an interesting Al-B transmetallation
process was also reported (middle) and an unusual methyl lithium addition into the amide moiety (bottom).

\[ \text{Scheme 36. Examples of reactivity of aryl(dimethyl)aluminium intermediates.} \]

3.2.4. Cycloaddition chemistry of sydnones:

Sydnones are the most studied family of mesoionic compounds. Mesoionic compounds are a class of heterocycles for which non-charged representations cannot be drawn. They were first discovered by Earl and Mackney in 1935\textsuperscript{77} and in the past few years they have attracted much attention due to the discovery of their biological activity\textsuperscript{78,79,80} and the possibility of undergoing 1,3-dipolar cycloadditions with alkynes to give pyrazoles.

The cycloaddition of sydnones was first described by Huisgen during the mid-20\textsuperscript{th} century\textsuperscript{18} and since then, many examples can be found in the literature. However, when performing these reactions thermally, the 1,3-disubstituted pyrazoles are generally the products obtained. It is very difficult to access the 1,4-disubstituted regioisomers when performing the reactions without any additives.

In general, these reactions require high reaction temperatures and proceed with long reaction times giving variable regioselectivity. However, some authors reported evidence of cycloaddition reactions between sydnones and both alkenes and alkynes through alkenylmetal- or alkynylmetal-type intermediates to obtain pyrazolines or pyrazoles in high regioselectivity, or to access regioisomers that cannot be synthesised using the classical methods.

Among these, the cycloadditions using alkynes are more interesting because the cycloaddition chemistry of alkenes is quite complex and is not general for the synthesis of heterocyclic products.\textsuperscript{18,81}
Scheme 37. Mechanism of metal-mediated cycloaddition reactions with sydnones.

González-Nogal et al. reported in 2007 the synthesis of pyrazoline derivatives using vinylstannanes and vinylsilanes as dipolarophiles and N-phenylsydnone (70). The tin derivatives were found to be more reactive.

Surprisingly, when using vinylsilanes, pyrazoles 73 were also obtained due to aromatization of the obtained pyrazolines 72 under the reaction conditions. Steric effects appear to be quite important, since the most hindered vinylsilanes (71c) turned out to be unreactive (Scheme 38).82

Scheme 38. Cycloaddition reactions between N-phenylsydnone and vinylsilanes.

The reactivity of vinylstannanes is different from the previous case because no loss of CO₂ was observed, as would be expected. In this case, a tin-migration and an O-N bond cleavage takes place generating pyrazoline carboxy derivatives (74).

Scheme 39. Cycloaddition reaction between N-phenylsydnone and vinylstannane.
This group also reported the synthesis of pyrazoles using silylacetylenes and \( N \)-phenylsydnone in excellent yields. However, when alkynes bearing two different trialkysilyl groups were used, a mixture of the two possible regioisomers was obtained (Scheme 40).

\[
\begin{align*}
75a & \quad R^1 = H \\
75b & \quad R^1 = \text{SnBu}_3 \\
75c & \quad R^1 = \text{SiMe}_2\text{Ph} \\
\text{R} & \equiv \text{SiMe}_3 \\
76a & \quad 95\% \\
76b & \quad 80\% \\
76c & \quad 63\% \\
77a & \quad \text{-} \\
77b & \quad \text{-} \\
77c & \quad 34\%
\end{align*}
\]

Scheme 40. Examples of cycloaddition reactions between sydnones and silylacetylenes.  

This methodology demonstrates an efficient way to obtain trisubstituted pyrazoles with a reasonable control of the regioselectivity using disubstituted alkynes. In addition, the incorporation of a trimethylsilyl group can allow further functionalisation of these molecules, increasing the value of this route.\(^83\)^\(^84\)

Another example of cycloaddition reactions using sydnones and metal acetylides has been described very recently. In 2013, Taran reported what could be considered the \emph{click} version of the sydnone-alkyne cycloaddition reaction using copper catalysis and obtaining the 1,4-disubstituted pyrazole isomer regioselectively (CuSAC = Copper-catalyzed sydnone-alkyne cycloaddition reaction).\(^85\) The conditions for the transformation require the copper(II) sulphate – sodium ascorbate system to generate copper(I) \emph{in situ}. The main difference \emph{versus} the classical \emph{click} reaction is that, in this case, the presence of a ligand is fundamental for the reaction to take place. Phenanthroline and derivatives seem very suitable in this case. The main advantages of this methodology are the fact that mild conditions are successful (60 °C – rt), the cycloaddition can be performed in aqueous media and uses catalytic amounts of the metal (Scheme 41). However, the reaction times are long, typically ~ 16 hours.

\[
\begin{align*}
\text{O} & \equiv \text{O} \\
\text{O} & \equiv \text{O} \\
\text{N} & \equiv \text{N} \\
\text{Ar} & \equiv \text{Ar} \\
\text{CuSO}_4/L & \quad (1 \text{ eq.}) \\
\text{Triethanolamine} & \quad (1 \text{ eq.}) \\
\text{Sodium ascorbate} & \quad (2 \text{ eq.}) \\
^{13}\text{BuOH/H}_2\text{O}, 60 \^\circ\text{C}, 16 \text{ h} & \equiv \text{R}\^1
\end{align*}
\]

Scheme 41. CuSAC cycloaddition reaction.
As for the mechanism of the reaction, this group proposed a scheme where a copper(I) acetylide was generated *in situ* by analogy to the azide-alkyne examples shown previously. Hence, coordination between the metal and the N2 position of the sydnone seems likely in order to increase the nucleophilicity of the alkyne and the electrophilicity of the C4 position.\(^8\)

![Scheme 42](image.png)

Scheme 42. Proposed mechanism for the CuSAC reaction.

In conclusion, as shown above, sydnones are interesting partners for metal acetylide-mediated cycloaddition reactions, generating functionalised pyrazoles with interesting properties and different substitution patterns.
4. Conclusions

A variety of examples of cycloaddition reactions to generate interesting carbocycle or heterocycle-containing molecules has been discussed featuring the use of metal acetylides as a source of activated alkynes.

The use of metal acetylides presents several advantages, the most significant being the reduction of the number of steps in the synthetic routes presented and their dual function as a source of alkynes but also activation due to the Lewis acidity of the metal moiety. Another aspect of interest is the improvement of some of the procedures to reduce the amount of metal salt required from stoichiometric or over stoichiometric amounts to low catalytic loadings, thus contributing to a more sustainable heterocycle synthesis.

The application of these species in cycloaddition reactions offers, compared to the traditional methods to synthesize heterocycles, a straightforward alternative since in one single step, all the fragments are assembled together achieving higher atom economy.

In conclusion, this work has shown some of the most recent advances in one of the most popular and evolving aspects of organic synthesis such as the synthesis of aromatic and heteroaromatic molecules. However, not everything is discovered and many advances are still to be made.
5. Aims

The present project aims to provide rapid methodologies for the synthesis of complex pyrazole building blocks. Such compounds are of interest to the pharmaceutical and the agrochemical industries due to their reported biological activities. particularly in the latter case, pyrazole-containing molecules constitute key components of effective herbicides and pesticides. For these reasons, another aim of this project is the design and development of potential crop protection leads.

Generating pyrazoles through cycloaddition reactions between sydnones and alkynes offers an easy way to access uncommon substitution patterns and to generate highly substituted pyrazole scaffolds while maintaining high levels of regioselectivity.

![Scheme 43. General cycloaddition reaction between a sydnone and an alkyne.](image)

The main drawback to cycloaddition reactions between sydnones and alkynes is the general requirement for long reaction times (24-72 h) and high temperatures (180-200 °C). Under these extreme conditions, the sydnone substrates can decompose. Additionally, alkynes are prone to polymerisation at elevated temperatures. These two facts point out how challenging these cycloaddition reactions can be.

For this reason, the initial aim of this project is the optimisation of cycloaddition reactions between sydnones and alkynes to find conditions compatible with densely functionalised substrates and also, to prevent alkyne polymerisation. In order to do so, we propose to explore two approaches that we believe will cause an enhancement of the reaction rate: i) Lewis acid activation of the sydnone; ii) employment of a directed cycloaddition of alkynylboranes.

Finally, another important aspect of this project is to extend this chemistry to complex sydnones, which are often less stable and present difficulties when performing cycloaddition reactions. If polycyclic sydnones could be synthesised and were compatible with the reaction conditions, pyrazoles showing high levels of structural complexity could be synthesised via cycloadditions with alkynes, giving access to very interesting substrates by means of a simple procedure.
Chapter 2. The chemistry of sydnones

1. Introduction

Sydnones are the most studied members of the family of mesoionic compounds. According to the International Union of Pure and Applied Chemistry (IUPAC), the term mesoionic refers to dipolar five- or six-membered heterocyclic compounds in which both the negative and the positive charge are delocalized, and as such, non-charged forms cannot be drawn. In these cases, the formal positive charge is related to the ring whereas the formal negative charge is associated with either ring atoms or an exocyclic atom. These compounds are also considered a type of conjugated mesomeric betaines, a subclass of the betaine family which comprises structures that cannot be drawn without formal charges.

![Scheme 44. Canonical representation of the sydnone scaffold.]

There has been debate in the past as to which is the structure that best represents these compounds. However, sydnones are generally represented with a charged aromatic ring and an enolate-type exocyclic oxygen (Figure 1).

![Figure 1. Generally accepted representation of the sydnone ring.]

Sydnones possess an intriguing reactivity profile, resulting in interesting synthetic properties. Calculations on the electronic profile of the sydnone scaffold demonstrate the enolate character of the exocyclic oxygen (O6), nucleophilicity at C4 and predict acidic character for the C4-H. Experimental results have shown that the acidity of this proton is
even higher than expected for a proton α to a carbonyl group, having an estimated pKa value of 18-20. Also, infrared spectroscopy measurements on many sydnones show bands around 1730 cm⁻¹, which is indicative of the presence of a carbonyl group.

Despite this characteristic reactivity profile, sydnones are, in general, air and moisture stable solids or oils, easy to handle and useful and versatile building blocks for synthesis. Additionally, sydnones have been shown to possess interesting biological properties. To highlight some examples, Hill reported a series of 3-(2-phenylthio)-ethylsydnone derivatives with anti-inflammatory activity. After testing, some analogues proved to be more active than hydrocortisone in the adjuvant arthritis assay (Figure 2; 78, 79 and 80).

Sydnones are also known to be effective antitumor agents, and their activity is often attributed to the fact that the mesoionic heterocycle is able to promote interactions with biomolecules trigging interesting effects. In 2003, Thoman reported a series of N-phenylsydnone analogues from which 81 proved to be more active against three different cancer cell lines than the leads developed at the time against sarcoma 180, Ehrlich carcinoma and fibrous histiocytoma in mice.

![Figure 2. Examples of biologically active sydnones.](image)
2. Sydnone synthesis

For the synthesis of sydnones, there is a well established two step methodology starting from commercially available \( N \)-substituted amino acids. First, nitrosation of the amine functionality takes place using a nitrosating agent such as sodium nitrite, followed by cyclodehydration of the nitrosamine intermediate promoted typically by acetic anhydride (Scheme 45).

\[
\begin{align*}
\text{H} & \quad \text{N} - \text{CO}_2\text{H} \\
\text{R}^1 & \quad \text{N} - \text{CO}_2\text{H} \\
\quad \quad & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \ quad
Recently Taran reported the use of the more sterically hindered tert-butyl nitrite for the nitrosation step, achieving better yields than in the case of IAN (Scheme 47).\(^9\) For the cyclodehydration step, Baker showed in the 1950s that when trifluoroacetic anhydride is used instead of acetic anhydride, the reaction rate is significantly increased.\(^9\) For this reason, acetic anhydride is rarely used for this purpose nowadays.

\[
\begin{align*}
\text{Scheme 47. Evaluation of nitrosating agents for a one-pot procedure.}
\end{align*}
\]

In addition, Taran also explored alternative cyclisation reagents, showing that when acetyl chloride or thionyl chloride were used, no reaction was observed; whereas with dicyclohexyl carbodiimide (DCC) or 1,1'-carbonyldiimidazole (CDI), the corresponding sydnone was obtained in yields over 90% after 16 h under reflux conditions (Scheme 48).\(^9\)

\[
\begin{align*}
\text{Scheme 48. Optimisation of the cyclisation step.}
\end{align*}
\]

Having evaluated the improvements discussed for the sydnone synthesis, the best conditions found in the literature to-date for the cyclisation step consist of using CDI in refluxing THF for 16 h. The optimal set of conditions used in the Harrity group employs TFAA in dichloromethane at 0 °C to rt for 1.5 h, generating quite an acidic environment that is believed to slowly decompose the sydnone during the reaction.

Since it was believed that further improvement could be made in this process, an alternative strategy was evaluated in our laboratories based on the Hendrickson dehydration, described by James Hendrickson in the 1980s, while seeking the ideal dehydrating reagent.\(^9\) This reagent is generated in situ by mixing triphenylphosphine oxide and triflic anhydride in a 2:1 ratio (Scheme 49).
However, when testing this reagent under the usual conditions with IAN as the nitrosating agent, as shown in Scheme 48, $N$-phenylsydnone was obtained together with starting material ($N$-phenylglycine), both of which were contaminated by considerable amounts of triphenylphosphine oxide, which turned to be inseparable on silica gel chromatography. The challenging purification of sydnones prepared by this route coupled with the generation of triflic acid ultimately prompted us to reject this method of sydnone synthesis.

Scheme 49. Formation of Hendrickson’s reagent.

Sydnone synthesis is quite a challenging process with many factors that need to be taken into account. For this reason, one-pot procedures seem a convenient way to overcome some of the drawbacks that current procedures suffer from such as the isolation of nitrosamine intermediates or the compatibility of different sets of conditions in subsequent steps. Currently, two main one-pot procedures for sydnone synthesis can be found in the literature.

The first one was reported by Azarifar in 2006, who has developed several sydnone synthesis procedures, and features the use of dibromo-dimethylhydantoin (DBH) as a catalyst in neutral conditions. With this methodology the isolation of the nitrosamine intermediate is avoided and neutral, mild conditions can be used. Its main limitation is the fact that it is applicable only to aromatic substrates.
On the other hand, Taran reported a one-pot procedure to obtain sydnones from amino acids and, interestingly, this procedure is extended to the cycloaddition of the generated sydnones with alkynes catalysed by copper. So in this case, a one-pot procedure from the amino acids to the corresponding pyrazoles has been developed, generating the 1,4-disubstituted isomers with excellent regioselectivities.

Again, the limitation in Taran’s one-pot procedure shown in Scheme 52, is the fact that only aromatic substrates are suitable. Nonetheless, neither the nitrosamine or even the sydnone need to be isolated, and the pyrazole products can be obtained directly.

In conclusion, efforts in order to improve the synthesis of sydnones are continuously being reported because although many advances have already been made, the synthesis of $N$-aryl sydnones, $N$-alkyl sydnones or even $N$-unsubstituted sydnones still remain a challenge.
3. Substrate synthesis

For the purpose of this project, several sydnone substrates were synthesised including \(N\)-aliphatic and \(N\)-aromatic examples. The conditions employed in this case consisted of nitrosation of the corresponding amino acid with IAN followed by cyclodehydration in the presence of trifluoroacetic anhydride. When possible, commercially available amino acids were used directly, affording the corresponding sydnones in two steps after purification by recrystallisation from ethanol (Scheme 53).

\[
\begin{align*}
\text{R}^1 & \quad \text{N} \quad \text{CO}_2\text{H} & \quad \text{ONO} \quad & \quad \text{N} \quad \text{CO}_2\text{H} \\
\text{DME, rt, 5 h} & \quad & \quad \text{CH}_2\text{Cl}_2, 0^\circ\text{C} - \text{rt, 1.5 h} \\
\end{align*}
\]

\(R^1 = \text{Ph} \quad 70, 72\%
\]
\(R^1 = \text{Bn} \quad 82, 26\%

Scheme 53. Sydnone synthesis from commercially available amino acids.

This procedure gave very good yields of \(N\)-phenylsydnone on a multigram scale (15.4 g, 95.0 mmol). However, for alkyl substituents the yields were generally lower, as seen for the \(N\)-benzyl analogue. The synthesis of the \(N\)-methylsydnone was attempted using this procedure but only traces of product could be recovered after two steps. For this reason, nitrosation of sarcosine with sodium nitrite and hydrochloric acid was performed instead, affording the product in moderate yield (Scheme 54).

\[
\begin{align*}
\text{Me} & \quad \text{N} \quad \text{CO}_2\text{H} & \quad \text{NaNO}_2 \quad & \quad \text{Me} \quad \text{N} \quad \text{CO}_2\text{H} \\
\text{HCl 20\%-H}_2\text{O (2:1)} \quad & \quad \text{0 \circ C - rt, 2 h} \quad & \quad \text{CH}_2\text{Cl}_2, 0 \circ\text{C} - \text{rt, 1.5 h} \\
\end{align*}
\]

\(83, 36\%

Scheme 54. Synthesis of \(N\)-methylsydnone.

In those cases where the amino acids were not readily available, they were synthesised from the corresponding amines by alkylation with ethyl bromoacetate, affording the corresponding amino esters. The amino esters were further hydrolysed under basic conditions to give the corresponding amino acids. Again, both aromatic and aliphatic examples were synthesised to explore their reactivity in subsequent cycloaddition reactions.
In the event, \(N\)-(\(p\)-methoxyphenyl)sydnone 84 was obtained in moderate yield from \(p\)-methoxyaniline using IAN as the nitrosating reagent. (Scheme 55).

\[
\begin{align*}
\text{NH}_2 & \quad \text{OMe} \\
\text{1) NaOAc (2 eq.)} & \quad \text{EtOH, Reflux, 4 h} \\
\text{Ethyl bromoacetate (1.1 eq.)} & \quad \text{1) IAN (1.1 eq.), DME, rt, 3 h} \\
\text{H}_2\text{O-EtOH (4.5:1)} & \quad \text{2) TFAA (1.5 eq.), CH}_2\text{Cl}_2, \\
\text{Reflux, 1 h} & \quad \text{0 }\degree\text{C- rt, 1.5 h} \\
\text{84, 89\% (Over 2 steps)} & \quad \text{84, 39\%}
\end{align*}
\]

*Scheme 55.* Synthesis of \(N\)-(4-methoxyphenyl)sydnone.

\(N\)-Isopropylsydnone 85 could also be synthesised using a similar procedure starting from isopropylamine. However, similarly to the methyl case, nitrosation with IAN proved to be inefficient and so the sodium nitrate/HCl alternative had to be employed. In addition, the yield of 11\% in this case was much lower than in previous examples (Scheme 56).

\[
\begin{align*}
\text{NH}_2 & \quad \text{OMe} \\
\text{1) NaOAc (2 eq.)} & \quad \text{EtOH, Reflux, 2 h} \\
\text{Ethyl bromoacetate (0.85 eq.)} & \quad \text{1) NaNO}_2 (1 \text{ eq.),} \\
\text{H}_2\text{O-EtOH (4.5:1)} & \quad \text{HCl 10\%-H}_2\text{O (1:1), 0 }\degree\text{C, 2 h} \\
\text{Reflux, 1.5 h} & \quad \text{2) TFAA (1.5 eq.), CH}_2\text{Cl}_2, \\
\text{85, 93\% (Over 2 steps)} & \quad \text{0 }\degree\text{C- rt, 1.5 h}
\end{align*}
\]

*Scheme 56.* Synthesis of \(N\)-isopropylsydnone.

We also took the opportunity to prepare substrates containing fluorine atoms. Specifically, two aromatic substrates were synthesised containing –\(F\) and –\(\text{CF}_3\) in the 4-position of the
phenyl ring, neither of which could be synthesised from a commercially available amino acid.

In the case of the fluoride (86), alkylation of the corresponding aniline was performed as in previous examples using ethyl bromoacetate, and subsequent hydrolysis afforded the corresponding amino acid in 33% yield (Scheme 57).

However, to synthesise the –CF₃ analogue 87, a reductive amination procedure previously reported by Taran⁹⁵ was applied, since alkylation attempts failed to give the desired product.

With both amino acids in hand, the established nitrosation-cyclodehydration procedure was applied to the substrates to generate the corresponding sydnones. In both cases, IAN was the nitrosating reagent of choice, and the cyclisation was assisted by TFAA (Scheme 59). The crude sydnones were purified by recrystallisation. Sydnone 88 was recrystallised from ethanol, and obtained in a 65% yield. However, in the case of 89, dichloromethane was the solvent of choice for the recrystallisation due to the high solubility of this sydnone in ethanol. The low yield of 35% obtained in this case is partly attributed to the fact that the sydnone was quite soluble in dichloromethane as well, making the recrystallisation challenging for this substrate. Despite this, the procedure afforded enough material for use in subsequent reactions.
Having explored a variety of procedures for the synthesis of sydnones and the necessary precursors, the functionalisation and further applications of these compounds was investigated and this topic will be discussed in the following chapters.

Scheme 59. Synthesis of fluorine containing sydnones 88 and 89.
Chapter 2: The Chemistry of Sydnones

4. Conclusions

The most recent advances in the sydnone synthesis process have been reviewed showing that probably Taran’s contribution to the nitrosation step using $t$-butyl nitrite and the development of one-pot procedures are the most relevant improvements to date. Alternative processes such as the Hendrickson dehydration have been tested with unsatisfactory results, proving that the current dehydration reagents employed are more suitable in terms of isolation and purification of the resulting sydnones.
Chapter 3. Copper-promoted sydnone-alkyne cycloaddition reactions

1. Introduction

Cycloaddition reactions between sydnones and alkynes are an atom-economic and versatile route towards polysubstituted pyrazoles, as Huisgen showed in the 1960s. These reactions can be classified as [4+2] cycloaddition-retrocycloadditions with CO₂ extrusion, and proceed via the HOMO of the alkyne and the LUMO of the sydnone. However, in general these reactions require temperatures above 140 °C and long reaction times (often, over 24 h), which makes it difficult sometimes to find suitable solvents that are compatible with these conditions. In addition, decomposition of the sydnone or alkyne substrates under these conditions can reduce the scope of this method.

To begin the project, we decided to assess the real limitations of this chemistry. Accordingly, cycloaddition reactions between a range of sydnones and alkynes were initially performed under the traditional thermal conditions; that is, in the absence of any additives.

Table 2. Examples of thermal cycloadditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Conditions</th>
<th>Isolated yield (a:b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph, 70</td>
<td>Ph</td>
<td>o-DCB, 140 °C, 24 h</td>
<td>90, 76% (10:1)</td>
</tr>
<tr>
<td>2</td>
<td>Ph, 70</td>
<td>CO₂Et</td>
<td>o-DCB, 150 °C, 20 h</td>
<td>91, 66% (2:1)</td>
</tr>
<tr>
<td>3</td>
<td>iPr, 85</td>
<td>Ph</td>
<td>o-DCB, 140 °C, 16 h</td>
<td>92, 36% (&gt;95:5)</td>
</tr>
</tbody>
</table>

Table 2 shows some of the most relevant examples with both N-aromatic (Entries 1 and 2) and N-aliphatic sydnones (Entry 3). As for the regioselectivity of these reactions, the ratio between the two isomers was elucidated using ¹H-NMR spectroscopy, since the pyrazole protons are easily distinguishable for both isomers. The main feature that was considered for assignment purposes was the large doublet coupling observed between protons in the 4- and 5-positions in the pyrazole ring in the 1,3-isomers. In contrast, protons in the 3- and 5-positions of the 1,4-disubstituted analogues displayed much smaller coupling. In general,
the isomers obtained in higher ratios were the ones bearing the substituent in the 3-position. However, an interesting exception was found when ethyl propiolate was used (Entry 2) because in this case, the best ratio between isomers was only 2:1, favouring the 1,3- vs. the 1,4-disubstituted pyrazole. The reason for the low selectivity is intriguing and may reflect the electronic nature of the alkyne or the low steric volume of the ester in this case. Nonetheless, the low levels of regioselectivity are hard to overcome and also, the separation of both isomers was very hard to achieve via flash chromatography on silica gel.

In addition, we also performed thermal cycloaddition reactions on a 4-substituted sydnone (Scheme 60, Eq. 1) and using disubstituted alkynes (Scheme 60, Eq. 2), although only moderate yields of pyrazoles could be obtained in each case.

With regard to the previous reactions (Table 2 and Scheme 60), the common features include: the high temperatures required, long reaction times and variable regioselectivity, which becomes a problem especially when there is an interest in obtaining the minor regioisomers.

In a continuous effort to improve 1,3-dipolar cycloaddition reactions with sydnones, several modifications of the classical thermal reaction have been published throughout the years. To highlight a few, Yli-Kauhaluoma reported in 2009 that N-linked solid supported amino acids can be used for the synthesis of sydnones, and further cycloaddition reaction with disubstituted alkynes generates the corresponding solid-supported pyrazoles. This procedure provides N-unsubstituted pyrazoles, which can be easily isolated by cleavage from the solid support (Scheme 61).
Recently, Larock reported the synthesis of 2H-indazoles using cycloaddition reactions with both aromatic and aliphatic sydnones at room temperature, in contrast to the usual high temperature conditions for these transformations.98,99 One of the key aspects of this procedure is the use of arynes as cycloaddition partners to promote the cycloadditions, which are more reactive than common alkynes (Scheme 62).

Taran has reported another example involving sydnones that occurs at room temperature via strain promoted cycloaddition.95 In this case, the driving force of the reaction is the use of a strained alkyne such as the bicyclo-[6.1.0]-nonyne system, generating tricyclic pyrazole scaffolds (Scheme 63).
The use of sterically hindered alkynes may also have an effect on the regioselectivity outcome of these cycloadditions. This approach aims to favour one orientation of the alkyne as it approaches the sydnone during cycloaddition in order to minimize steric clashes. Examples have been reported using alkynylboronates,\textsuperscript{100,96} which offer the additional feature of incorporating boron groups that can be further functionalised via Pd cross-coupling reactions, for instance.\textsuperscript{101,102} Excellent regioselectivities can be achieved by using pinacol-derived alkynes under thermal conditions, as shown in Scheme 64.

\begin{center}
\includegraphics[width=\textwidth]{Scheme_64.png}
\end{center}

\textbf{Scheme 64.} Cycloaddition using an alkynylboronate and further cross-coupling to an aryl halide.
2. Lewis acid activation in cycloaddition reactions

We were interested in exploring an approach that exploited Lewis acids as additives in these systems in order to promote the reaction. Due to the Lewis basic character of the sydnone scaffold (Figure 3), the formation of a Lewis acid-base pair was hypothesised, which would cause a decrease in the gap between the HOMO of the alkyne and the LUMO of the sydnone, enhancing the reaction rate.

![Figure 3. Lewis basicity in the sydnone ring.](image)

In addition to that, precedent can be found in the literature for Lewis acid coordination to sydnones. Turnbull reported that AlCl₃-promoted Friedel-Crafts reactions with sydnones and acyl chlorides fail to proceed and proposed that this may be due to preferential coordination of the AlCl₃ to the sydnone, thus deactivating the ring towards electrophilic aromatic substitution.¹⁰³

Very recently, Taran reported the first example of copper(II)-catalysed cycloadditions between sydnones and alkynes, suggesting that a pre-coordination of [Cu] to the sydnone may be triggering the reaction (Scheme 65).⁸⁵,⁹¹

![Scheme 65. Taran’s copper-promoted sydnone-alkyne cycloaddition reactions.](image)

During the course of Taran’s investigations, Dr. Foster from the Harrity group undertook a screening of Lewis acids in the cycloaddition reaction between phenylacetylene and N-phenylsydnone 70. In this study, he found that, depending on the Lewis acid employed, dramatic changes were observed in terms of conversion towards the pyrazole products. Specifically, he found that Cu(OTf)₂ showed promising results in terms of acceleration of the reaction rate (full conversion was actually achieved in only 20 minutes).¹⁰⁴
addition of Cu(OTf)$_2$ seemed advantageous for the cycloaddition, I decided to further optimise these reaction conditions to enhance the cycloaddition process.
3. Cu(OTf)$_2$-promoted cycloaddition reactions

Having observed that the addition of copper(II) triflate promoted the sydnone-alkyne cycloaddition reaction, optimisation of the reaction conditions was undertaken. For this transformation, best results were obtained when using stoichiometric amounts of the Lewis acid in o-dichlorobenzene at high temperatures (140 °C) but in relatively short reaction times (1-2 h vs. 24-72 h in the thermal case). Studies were performed attempting to use sub-stoichiometric amounts of the copper(II) salt; however, they failed to achieve the same rate acceleration observed when 1 equivalent of copper(II) triflate was used, thus showing that the participation of the copper in a catalytic cycle was unlikely.

As for the applicability of the process, both N-alkyl and N-aryl pyrazoles could be generated in moderate yields, with the 1,3-disubstituted isomer constituting the major product in all cases (Table 3). However, when $R^1 = \text{Bn}$ (Entry 3) the yield was especially low (11%), due to the poor stability of the sydnone, which was believed to degrade under the reaction conditions.

Table 3. Scope for the thermal and Cu(OTf)$_2$-promoted cycloaddition reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R^1$[a]</th>
<th>$R^2$</th>
<th>$R^3$</th>
<th>(a:b)[b][c][d]</th>
<th>Cu(OTf)$_2$(a:b)[c][d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>24 h, 90, 76% (10:1)</td>
<td>1 h, 90, 69%, (&gt;95:5)</td>
</tr>
<tr>
<td>2</td>
<td>PMP</td>
<td>H</td>
<td>Ph</td>
<td>24 h; 97, 76% (10:1)</td>
<td>1 h, 97, 57% (&gt;95:5)</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>H</td>
<td>Ph</td>
<td></td>
<td>3 h, 98, 11% (&gt;95:5)</td>
</tr>
<tr>
<td>4</td>
<td>iPr</td>
<td>H</td>
<td>Ph</td>
<td></td>
<td>3.5 h; 92, 51% (&gt;95:5)</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>H</td>
<td>Ph</td>
<td></td>
<td>2 h; 99, 56% (&gt;95:5)</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>H</td>
<td>Ph</td>
<td></td>
<td>2 h; 100, 56% (&gt;95:5)</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>H</td>
<td>EtO$_2$C</td>
<td>16 h; 91, 59% (2:1)</td>
<td>20 min; 91, 56% (2:1)</td>
</tr>
<tr>
<td>8</td>
<td>PMP</td>
<td>H</td>
<td>EtO$_2$C</td>
<td>24 h; 101, 57% (2:1)</td>
<td>20 min; 101, 51% (2:1)</td>
</tr>
<tr>
<td>9</td>
<td>Ph</td>
<td>4-Tolyl</td>
<td>Ph</td>
<td>20 h, 94, 52%, (&gt;95:5)</td>
<td>2 h, 94, 31%, (&gt;95:5)</td>
</tr>
</tbody>
</table>

[a] PMP = 4-Methoxyphenyl. [b] Reactions conducted in the absence of a promoter. [c] Isolated yields after column chromatography. [d] Isomeric ratios determined using $^1$H NMR spectroscopy. See page 47. [e] Reactions not conducted in the absence of promoter.

Comparing the results in the presence and absence of Cu(OTf)$_2$, the reaction times are dramatically reduced. However, the outcome is equivalent in terms of yields and
regioselectivities. For example, in Entries 7 and 8, regioisomeric mixtures (2:1) are still obtained in the presence of the Lewis acid.

Regarding the fully substituted sydnone 93, the reaction time when employing copper(II) triflate was reduced tenfold. However, the yield was also decreased while maintaining excellent regioselectivity. This process was probably helped by the steric hindrance imparted by the 4-toly group in the C-4 position of the sydnone (Entry 9). In this case, the yield was very poor, suggesting that the substrate might degrade under the reaction conditions.

To elucidate the mechanism for the copper(II) triflate-promoted cycloaddition, test reactions were performed. N-Phenylsydnone was subjected to different reaction conditions in order to obtain information regarding possible intermediates formed during the reaction (Scheme 66).

It was observed that when heating neat sydnone or sydnone with stoichiometric amounts of another Cu(II) salt, Cu(OAc)₂·H₂O, the starting material was recovered in over 80% yield suggesting that nothing happened upon heating in solvent. However, when heating sydnone with one equivalent of Cu(OTf)₂, decomposition of the sydnone was observed through a loss of mass, gas formation (possibly CO₂) and the formation of a black solid inside the reaction vessel. This observed degradation of the sydnone under the reaction conditions could in part explain why the yields shown for the Cu(OTf)₂ transformation were quite low compared to the thermal reaction using the same substrates (Table 3, Entries 1, 2, 7-9).

Considering the possibility of a metalated sydnone as the intermediate, the synthesis of 4-Cu-3-phenylsydnone was attempted in order to test its reactivity towards cycloaddition in the presence of an alkyne. Disappointingly, when subjecting the Cu-sydnone intermediate to cycloaddition reaction conditions (Scheme 67), transmetalation with phenylacetylene...
was observed instead of pyrazole formation, since precipitation of a bright yellow solid (suspected to be phenylethynylcopper – see later) occurred. To confirm the formation of the cuprated sydnone, this intermediate was also reacted with iodobenzene in the presence of Pd(0) to generate the corresponding arylated sydnone 102. Satisfactorily, the desired product was detected in the crude proton NMR spectrum, suggesting that the 4-copper-3-phenylsydnone intermediate did form, according to previous reports by Kalinin. These results suggested that the possibility of a cuprated sydnone as an intermediate species was unlikely.

Returning to the idea of Cu(OTf)\textsubscript{2} acting simply as a Lewis acid, we proposed that infrared spectroscopy could be used to analyse the C-O bond stretching frequency of \textit{N}-phenylsydnone in three different scenarios: i) neat, ii) with Cu(OAc)\textsubscript{2}·H\textsubscript{2}O and iii) with Cu(OTf)\textsubscript{2}. The results are shown in Table 4. Since the C-O stretching frequency does not change in the presence of Cu(OAc)\textsubscript{2}·H\textsubscript{2}O but it does decrease in the presence of Cu(OTf)\textsubscript{2}, this suggests that coordination must occur in the latter case between the sydnone and the copper(II), explaining the observed acceleration in the reaction rate in this situation.

| Sydnone 70                     | 1756 |
| Sydnone 70 + Cu(OAc)\textsubscript{2}·H\textsubscript{2}O | 1757 |
| Sydnone 70 + Cu(OTf)\textsubscript{2}         | 1698 |

In order to get further insight in the mechanism of this transformation, DFT calculations were performed on the sydnone – Cu(OTf)\textsubscript{2} system in collaboration with Professor Enrique Gómez Bengoa at the Universidad del País Vasco (San Sebastián, Spain). Throughout the
theoretical studies, all energy values correspond to Gibbs Free energy ($\Delta G$) values in kcal·mol$^{-1}$. These studies showed four possible structures for sydnone-Lewis acid complexes (Figure 4), three of them being energetically favoured (that is $\Delta G < 0$ kcal·mol$^{-1}$), by coordinating the Cu(OTf)$_2$ to the different Lewis basic sites of the sydnone.

![Figure 4. Calculated sydnone-Cu(OTf)$_2$ complexes.](image)

The fact that COM-1 shows a much lower energy value compared to the rest indicates that more than 99% of the Cu(OTf)$_2$ will be complexed to the sydnone through COM-1. Thus, this provides further evidence of the Lewis acid coordination of copper(II) triflate to the sydnone, which explains why the reaction times are dramatically accelerated in the cycloaddition reaction under these conditions. However, because this coordination takes place away from the reacting atoms, it can only affect the rate of the reaction. It is therefore conceivable that it will not have an impact on the yield or the regioselective outcome of the reaction, as shown by the experimental results.$^{104}$ To summarise, although the reaction is accelerated in the presence of the Lewis acid, the regiochemistry of the products remains the same as for the thermal cycloaddition.
4. Cu(OAc)$_2$·H$_2$O-promoted cycloaddition reactions

Having observed the enhancement produced when using Cu(OTf)$_2$ to promote the reactions, a further range of copper(II)-based Lewis acids were also screened in order to further accelerate the reaction rate but also, to try to influence the isomeric ratio of the products formed. The most interesting result from this screening was the high levels of regioselectivity towards the (normally minor) 1,4-disubstituted isomer observed when using, for example, Cu(2-ethylhexanoate)$_2$ as an additive. For this reason, this additive seemed the ideal candidate in terms of conversion, regioselectivity and availability.

Reaction optimisation was carried out by testing different solvents and different quantities of Cu(2-ethylhexanoate)$_2$ for the cycloaddition reaction between sydnone 70 and phenylacetylene. With respect to solvent, o-dichlorobenzene gave better results in terms of yield (Table 5, Entry 1), which is not surprising since halogenated solvents typically provide the best results for cycloaddition reactions. However, testing different loadings of Cu(2-ethylhexanoate)$_2$ showed that stoichiometric amounts of the Lewis acid were required to achieve the best results (Table 5, Entry 2), suggesting that recycling of the copper during the reaction is unlikely.

Table 5. Conditions screening for the Cu(2-ethylhexanoate)$_2$ promoted reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Eq. (CuX$_2$)</th>
<th>Isolated yield (a:b)</th>
<th>Isolated yield (a:b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>42 % (&lt;5 : 95) (4 h)</td>
<td>55 % (&lt;5 : 95) (2 h)</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>36 % (&lt;5 : 95) (22 h)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>Traces (22 h)</td>
<td>-</td>
</tr>
</tbody>
</table>

Employment of stoichiometric amounts of Cu(2-ethylhexanoate)$_2$ as the Lewis acid in these reactions resulted in the formation of stoichiometric amounts of 2-ethylhexanoic acid. Consequently, purification of the pyrazole products was quite difficult due to the greasy character of this by-product, even after base washes or flash chromatography on silica gel. For this reason, alternative Lewis acids were considered to facilitate the purification of the products. Cu(OAc)$_2$ also appeared to reverse the normal regiochemistry of the reaction, again favouring the 1,4-disubstituted isomers. For this reason, and because it was
Chapter 3: Copper-Promoted Sydnone-Alkyne Cycloaddition Reactions

envisaged that the acetic acid by-product would be easier to separate, further optimisation was performed using a stoichiometric amount of Cu(OAc)$_2$·H$_2$O as Lewis acid in the sydnone-alkyne system. The fact that copper(II) acetate is accessible, inexpensive and very easy to handle was also advantageous.

The optimal set of conditions consisted of using one equivalent of sydnone, two equivalents of alkyne and one equivalent of Cu(OAc)$_2$·H$_2$O at 140 °C. Under these conditions, it was found that total conversion of the starting materials could be achieved in a few hours for a wide range of substrates. As Table 6 shows, several sydnones and alkynes were subjected to this set of conditions to generate the corresponding 1,4-disubstituted pyrazoles. In this case, despite the longer reaction times relative to copper(II) triflate, good to excellent yields were obtained and the regioselectivity was found to be excellent (>95:5) in favour of the 1,4-isomer in all cases. This result was in direct contrast to the Cu(OTf)$_2$ system, where 1,3-disubstituted isomers were generated.

**Table 6.** Scope for the Cu(OAc)$_2$·H$_2$O-promoted sydnone-alkyne cycloaddition reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R$^1$[a]</th>
<th>R$^2$</th>
<th>Time</th>
<th>Isolated yield (a:b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph, 70</td>
<td>Ph</td>
<td>3.5 h</td>
<td>90, 73% (&lt;5:95)</td>
</tr>
<tr>
<td>2</td>
<td>PMP, 84</td>
<td>Ph</td>
<td>5 h</td>
<td>97, 53% (&lt;5:95)</td>
</tr>
<tr>
<td>3</td>
<td>Ph, 70</td>
<td>CO$_2$Et</td>
<td>1 h</td>
<td>91, 96% (&lt;5:95)</td>
</tr>
<tr>
<td>4</td>
<td>PMP, 84</td>
<td>CO$_2$Et</td>
<td>2 h</td>
<td>101, 81% (&lt;5:95)</td>
</tr>
<tr>
<td>5</td>
<td>Ph, 70</td>
<td>o-Hex</td>
<td>3.5 h</td>
<td>103, 73% (&lt;5:95)</td>
</tr>
<tr>
<td>6</td>
<td>PMP, 84</td>
<td>o-Hex</td>
<td>3.5 h</td>
<td>104, 54% (&lt;5:95)</td>
</tr>
<tr>
<td>7</td>
<td>Ph, 70</td>
<td>Cyclohexyl</td>
<td>4 h</td>
<td>105, 100% (&lt;5:95)</td>
</tr>
<tr>
<td>8</td>
<td>PMP, 84</td>
<td>Cyclohexyl</td>
<td>2.5 h</td>
<td>106, 71% (&lt;5:95)</td>
</tr>
<tr>
<td>9</td>
<td>Ph, 70</td>
<td>Cyclohex-1-enyl</td>
<td>2.5 h</td>
<td>107, 71% (&lt;5:95)</td>
</tr>
<tr>
<td>10</td>
<td>PMP, 84</td>
<td>Cyclohex-1-enyl</td>
<td>2.5 h</td>
<td>108, 60% (&lt;5:95)</td>
</tr>
<tr>
<td>11</td>
<td>Ph, 70</td>
<td>Cyclopropyl</td>
<td>4 h</td>
<td>109, 96% (&lt;5:95)</td>
</tr>
<tr>
<td>12</td>
<td>Ph, 70</td>
<td>3-Thiophenyl</td>
<td>2.5 h</td>
<td>110, 95% (&lt;5:95)</td>
</tr>
<tr>
<td>13</td>
<td>4-FC$_6$H$_4$ , 88</td>
<td>CO$_2$Et</td>
<td>4 h</td>
<td>111, 95% (&lt;5:95)</td>
</tr>
<tr>
<td>14</td>
<td>Bn, 82</td>
<td>CO$_2$Et</td>
<td>4 h</td>
<td>112, 60% (&lt;5:95)</td>
</tr>
</tbody>
</table>

[a] PMP = 4-Methoxyphenyl.
The scope of this cycloaddition with N-aryl sydnones is quite general, since excellent regioselectivities could be obtained with both aryl and alkyl alkynes. Furthermore, the reaction possesses good functional group tolerance as the reaction proceeded in the presence of esters and heteroaromatics. Surprisingly, apart from notably decreasing the reaction times, in this case the Cu-promoter showed an improvement in terms of regioselectivity in the case of ethyl propiolate (R^2 = CO_2Et, Entries 3, 4, 13, 14), where a 2:1 selectivity was generally overturned to furnish the 1,4-disubstituted isomer with excellent regioselectivities (>95:5). Also, in the case of 3-thiophenyl (Entry 12), the yield was notably improved, maintaining again the excellent regioselectivity.

Also, sydnones bearing alkyl substituents such as N-benzylsydnone proved to be compatible with this chemistry providing the 1,4-disubstituted pyrazole in good yield and excellent regioselectivity (Entry 14). This substrate is particularly interesting because the benzyl group can be cleaved by hydrogenolysis affording the N-unsubstituted pyrazoles.

With regard to this unexpected transformation, mechanistic studies were undertaken in order to elucidate the causes of reversal of regioselectivity relative to the thermal case or the Cu(OTf)_2 promoted reaction. In the first place, classical click chemistry conditions were applied to the model substrates, N-phenylsydnone 70 and phenylacetylene, to see if this reaction showed any similarities with the above-mentioned processes. Two different approaches were tested: the use of copper(II) in the presence of sodium ascorbate,^7^ and the use of copper(I) directly in the presence of a base (Scheme 68).^41^

![Scheme 68. CuAAC typical click-chemistry conditions on the sydnone-alkyne system.](image)

Disappointingly, only starting material was recovered in both attempts, suggesting that this system might behave differently to the classical CuAAC click chemistry. As discussed earlier, Taran has recently reported click-type conditions for the sydnone-alkyne cycloaddition, showing that in the case of sydnones, a ligand is required to chelate the copper in order to
Chapter 3: Copper-Promoted Sydnone-Alkyne Cycloaddition Reactions

promote this transformation. For these cases, phenanthroline-derived ligands were found to be optimal.85

Another interesting observation while performing copper-mediated cycloadditions between sydnones and alkynes was the formation of bright coloured precipitates. For example, in the case of phenylacetylene and \( N \)-phenylsydnone in the presence of copper(II) acetate, the formation of a bright yellow insoluble precipitate was usually observed when the reaction reached 120 °C. However, the precipitate disappeared upon completion of the reaction. It was hypothesised that this intermediate could be a metal acetylide species, and control experiments showed that it only formed in the presence of both the alkyne and the Cu(II) salt. A literature search revealed that copper(I) acetylide species are actually very insoluble, bright coloured solids that can be easily synthesized due to their stability.11 It is also characteristic of these acetylides to form aggregates, revealing their polymeric nature, which contributes to their high stability and insolubility.106

To test if the observed intermediate was indeed phenylethynyl copper(I), this acetylide was synthesised according to a literature procedure reported by Lei (Scheme 69).107

\[
\text{Ph} \equiv \text{CuI, NH}_4\text{OH} \rightarrow \text{Ph} \equiv \text{Cu}_57a, 72\%
\]

Scheme 69. Synthesis of phenylethynyl copper(I).

Phenylethynyl copper(I) (57a) proved to be an insoluble, bright yellow solid like the intermediate observed in the cycloaddition reactions. In order to confirm that both species were the same, the yellow solid observed in the cycloaddition reactions was isolated after conducting a reaction under standard conditions for only 30 minutes, filtering and washing the obtained precipitate (Scheme 70).

\[
\text{Ph} \equiv (2 \text{ eq.}) \rightarrow \text{Cu(OAc)}_2\cdot\text{H}_2\text{O (1 eq.)} \rightarrow \text{Ph} \equiv \text{Cu}_57b
\]

Scheme 70. Isolation of phenylethynyl copper(I) from the cycloaddition reaction.

Since copper(I) acetylides are in general very insoluble, routine characterisation techniques such as NMR spectroscopy that require the sample to be in solution could not be performed, which made the characterisation of these species quite challenging. Previous reports in the literature could be found where copper(I) acetylides were characterised by using elemental analysis techniques, such as combustion analysis (for C, H and N).11,106,108
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inductively coupled plasma atomic emission spectroscopy for Cu(II), melting point,\textsuperscript{107,108} infra-red spectroscopy\textsuperscript{106,108} and X-ray powder diffraction.\textsuperscript{106}

Therefore, the characterisation of these solids was based on melting point analysis (including mixed melting point), infrared spectroscopy and elemental analysis. As Table 7 shows, the characterisation data matched for both samples, strongly implying that the generated species during the cycloaddition reaction is in fact phenylethynyl copper(I).

However, elemental analysis showed that the sample obtained from the cycloaddition reactions (57b) was slightly less pure than the reference, which was prepared according to Lei’s method.

Table 7. Characterisation data for both samples of phenylethynyl copper(I).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sample</th>
<th>Melting point</th>
<th>Elemental analysis (%C,H for \textsubscript{C\textsubscript{8}H\textsubscript{5}Cu}) \textsuperscript{[a]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57b</td>
<td>226-229 °C</td>
<td>C: 57.49, H: 2.97</td>
</tr>
<tr>
<td>2</td>
<td>57a</td>
<td>226-229 °C</td>
<td>C: 58.17, H: 3.01</td>
</tr>
<tr>
<td>3</td>
<td>57a + 57b</td>
<td>226-229 °C</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Calculated %C, H for \textsubscript{C\textsubscript{8}H\textsubscript{5}Cu}: C 58.35, H 3.06.

To further confirm the role of the copper(I) acetylide in the cycloaddition reaction, both acetylides 57a and 57b were subjected to cycloaddition conditions with \textit{N}-phenylsydnone 70 (Scheme 71). Although the desired product 1,4-diphenyl-1-\textit{H}-pyrazole 90b was isolated in each case in similar yields, these values were surprisingly low when compared to the reaction performed using phenylacetylene and the copper(II) salt.

\textbf{Scheme 71.} Reaction between phenylethynyl copper(I) samples and \textit{N}-phenylsydnone.

It was hypothesised that this could be due to the polymeric nature of the acetylide once isolated, making it difficult to de-aggregate under the reaction conditions. Fokin has reported the ability of copper(I) acetylides to form thermodynamically-stable oligomers causing a decrease in reactivity.\textsuperscript{109} Nonetheless, this work has also shown that the addition of mono-dentate ligands and the use of polar-coordinating solvents such as acetonitrile can
promote higher populations of the monomeric copper(I) acetylide leading to an enhancement of the reactivity. In this case, these studies were purely mechanistic, and no further optimisation of the reaction between N-phenylsydnone and the acetylides was carried out, since the exclusive formation of the 1,4-disubstituted isomer was already established. Moreover, Taran had already demonstrated the promoting effect of added ligand.\textsuperscript{85}

The fact that copper(II) is added to the reaction but the active intermediate seems to be a copper(I) species suggested that a reductive process must take place. However, it had been shown before that the addition of reducing agents such as sodium ascorbate did not have a clear effect on the reaction between N-phenylsydnone and phenylacetylene in the presence of copper(II) acetate, suggesting that sodium ascorbate was not involved in the reduction of copper(II).

Nonetheless, there is precedent in the literature for the reduction of copper(II) by alkynes, \textit{via} processes such as the Glaser coupling,\textsuperscript{38,37,110} where a diyne species and copper(I) are generated. Moreover, examples can be found where this process has been applied to catalyse the azide-alkyne click reactions.\textsuperscript{111,112} With this in mind, and considering that an excess of the alkyne (2 eq.) was used in the present system, this option was considered. If this reduction was occurring, the corresponding 1,4-diphenyl-2,3-butadiyne \textsuperscript{113} should be generated when phenylacetylene was the alkyne of choice. Satisfactorily, after running a cycloaddition reaction under standard conditions and directly distilling the crude material using a Kugelrohr apparatus, the resulting Glaser coupled product was isolated as a white needle-shaped crystalline solid in 80\% yield, showing that copper(II) was in fact reduced by the excess of phenylacetylene during the reaction (Scheme 72). Thus, the reduction of copper(II) to copper(I) \textit{via} Glaser coupling and the subsequent generation of a copper(I) acetylide as the reactive intermediate for the transformation were demonstrated.

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {$\text{N}^+\text{Ph}$};
\node (B) at (1.5,0) {$\text{C}$};
\node (C) at (3,0) {$\text{O}$};
\node (D) at (4.5,0) {$\text{N}^+\text{Ph}$};
\node (E) at (6,0) {$\text{Ph}$};
\node (F) at (7.5,0) {$\text{Ph}$};
\node (G) at (9,0) {$\text{Ph}$};
\node (H) at (10.5,0) {$\text{Ph}$};
\node (I) at (12,0) {$\text{Ph}$};
\node (J) at (13.5,0) {$\text{Ph}$};
\draw (A) -- (B) -- (C) -- (D) -- (E) -- (F) -- (G) -- (H) -- (I) -- (J);
\node at (1,0.5) {70};
\node at (7.5,0.5) {113};
\node at (9,0.5) {90b};
\node at (13,0.5) {80\%};
\node at (11.5,0.5) {96\% (>95:5)};
\node at (6,0.5) {Cu(OAc)$_2$H$_2$O (1 eq.)};
\node at (6,-0.5) {o-DCB, 140 \textdegree C, 3.5 h};
\node at (6,-1) {Ph (2 eq.)};
\node at (6,-1.5) {Ph};
\end{tikzpicture}
\end{center}

\textit{Scheme 72. In situ reduction of copper(II).}

As a proof of concept, it was envisioned that under the right conditions, Cu(OTf)$_2$ should be able to generate the copper(I) acetylide as well. Since the main difference between the Lewis acids is their counter ions, it was hypothesised that the copper(II) acetate was able to
generate the acetylide because of the higher basicity of the acetate anion, compared to the triflate (since triflic acid is much stronger than acetic acid). The same argument can be applied to the 2-ethylhexanoate anion, which would behave in a similar way to the acetate. According to this, if the reaction conditions are basic enough, other copper(II) sources could be used to generate the corresponding acetylides.

To prove this point, \(N\)-phenylsydnone was subjected to standard cycloaddition conditions in the presence of \(\text{Cu(OTf)}_2\) and a stoichiometric amount of base. The regiochemical outcome under these reaction conditions was evaluated (Scheme 73).

![Scheme 73. Cu(OTf)_2-promoted cycloadditions in the presence of a base.](image)

Two bases were tested, an organic base (triethylamine) and an inorganic base (sodium acetate), and in both cases bright yellow precipitates were observed upon heating, indicating the formation of the copper(I) acetylide intermediate.

After 2.5 h, in both cases, the pyrazole products were obtained in comparable yields and, interestingly, an increase in the proportion of the 1,4-disubstituted pyrazole (90b) compared to the 1,3-disubstituted isomer (90a) was observed. This experiment indicates that if the reaction conditions are basic enough, the deprotonation of the Cu-coordinated alkyne is favoured, allowing the formation of the acetylide, which leads to the 1,4-disubstituted pyrazole. However, the formation of the 1,3-isomer appears to effectively compete under these conditions.

In order to confirm this mechanistic proposal, DFT studies were performed by Professor Enrique Gómez Bengoa at Universidad del País Vasco (San Sebastián, Spain). In contrast to the \(\text{Cu(OTf)}_2\) case, the formation of complexes between \(\text{Cu(OAc)}_2\) and the sydnone are highly disfavoured, which is consistent with the fact that changes in the C-O stretching frequency were not observed in the IR spectrum of this mixture (see Table 4 earlier). Interestingly, calculations have shown an energetically favoured transition state between the sydnone and the copper(I) acetylide where a tight coordination between Cu and the N2 position of the sydnone is responsible for lowering the energy barrier (Figure 5). This transition state is similar to transition states reported to be involved in the copper(I)-
catalysed azide-alkyne cycloaddition reaction.\textsuperscript{7} However, for the sydnone case, calculations show that this transition state TS-1b corresponds to a concerted but asynchronous process, where the C-C bond formation occurs first followed by the Cu-N dissociation and C-N bond formation.\textsuperscript{104}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{TS-1b}
\caption{Calculated transition state for the Cu(OAc)$_2$-mediated reaction.}
\end{figure}

Having seen the versatility of the copper(II) acetate-promoted cycloaddition reactions between sydnones and alkynes, we were interested in the use of trimethylsilylacetylene in order to incorporate trimethylsilyl groups in the pyrazole scaffold. Unexpectedly, when performing the cycloaddition reaction between \textit{N}-phenylsydnone 70 and trimethylsilylacetylene, the 1-phenyl pyrazole 114 was obtained instead of the TMS adduct, in addition to a bright yellow side product and unreacted sydnone 70. This was observed using both Cu(OAc)$_2$·H$_2$O and Cu(OTf)$_2$ promoters (Scheme 74).

\begin{scheme}
\centering
\includegraphics[width=0.5\textwidth]{Scheme74}
\caption{Cycloaddition reactions with TMS acetylene in the presence of copper(II).}
\end{scheme}

Copper(II) acetate was used as the monohydrate salt, and for this reason it was hypothesised that the protodesilylation step might originate from water present in the reaction medium. Assuming that the copper-carbon bond is not very stable, which is supported by the fact that no metalloazoles containing copper have been described in the literature, it is likely that these intermediates may be quenched by a proton source, such as water. Hence, if water is present under the reaction conditions, the formation of the non-substituted pyrazole seems feasible. To test this hypothesis, a deuterium labelling experiment was performed by adding D$_2$O before working up the reaction. In the event, no
deuterium incorporation was observed after isolation of the product, indicating that the copper is most likely quenched by a proton source during the reaction.

To try to understand how this transformation took place, the same reaction was performed using anhydrous Cu(OAc)$_2$. Interestingly, when using the corresponding anhydrous copper(II) salt, the yield of the non-substituted pyrazole dropped from 53% to 24% (Scheme 74). In this case, 63% of unreacted sydnone was recovered, compared to the Cu(OAc)$_2$·H$_2$O reaction, where only 37% of the starting material was recovered. These results suggest that water may help to promote the reaction to generate the monosubstituted N-phenylpyrazole 114, which under non-anhydrous conditions is obtained in higher yields. These issues notwithstanding, the Cu-mediated cycloaddition reaction of TMS-acetylene shows that this alkyne can be used as a non-gaseous synthetic equivalent for acetylene without the necessity of an additional step to deprotect the TMS group.
5. Conclusions

To summarise, two copper-promoted procedures have been developed for the synthesis of disubstituted pyrazoles via cycloaddition reactions between sydnones and alkynes in a regioselective manner. Also, in both cases, a significant enhancement of the reaction rate compared to the typical thermal cycloaddition reaction was observed.

For the synthesis of 1,3-disubstituted pyrazoles, Cu(OTf)₂ is the additive of choice, whereas to access the 1,4-disubstituted isomers, Cu(OAc)₂·H₂O proved to be the most effective Lewis acid.

From a mechanistic point of view, copper(II) triflate accelerates the reaction by coordination to the sydnone, as both experimental and theoretical results confirmed. However, in the case of copper(II) acetate, a copper(I) acetylide intermediate is generated, which has the ability to coordinate to the N2 position of the sydnone allowing the formation of the opposite isomer, as supported by DFT calculations.
Chapter 4: Implementation of Cu-promoted cycloadditions in continuous flow

1. An introduction to flow chemistry

In the past few decades, flow chemistry has emerged as an interesting alternative for the implementation of chemical processes. This technology is advantageous in many cases due to extremely efficient mass and heat transfer thanks to the design of the microreactors, which allow very precise control over the reaction conditions in a small, confined space. This usually results in higher reproducibility and is ideal for optimisation purposes, since volumes are very small and residence times tend to be very short. The latter is an advantage when working with short lived species or unstable intermediates, which cannot be handled otherwise under the traditional batch approach.

Another key aspect is the possibility to achieve milder reaction conditions, especially because heat transfer is also enhanced. Due to the confinement, flow reactors also facilitate the use of hazardous or explosive reagents including azides or processes such as nitration reactions, making them much safer for the operator handling the equipment. Flow chemistry is usually considered environmentally-friendly, since reduced amounts of solvents and reagents are required, thus making flow processes more time- and cost-efficient than the traditional batch variants.\textsuperscript{113,114}

A clear application of these principles has been reported very recently by Jamison, Jensen and Myerson, where the production of up to 4 different pharmaceuticals (diphenhydramine hydrochloride, lidocaine hydrochloride, diazepam and fluoxetine hydrochloride) was carried out using a compact, reconfigurable platform under continuous flow conditions.\textsuperscript{115}
2. Feasibility of the implementation strategy

Chapter 3 described the regioselective synthesis of 1,4-disubstituted pyrazoles via cycloaddition reactions of sydnones with terminal alkynes in the presence of the Cu(OAc)$_2$·H$_2$O promoter. Nonetheless, this methodology could still be further improved, since stoichiometric amounts of copper and excess of the reacting alkyne are required. Also, during the reaction, the formation of thick slurries is observed as a result of the formation of copper(I) acetylide species, which are known to be highly insoluble.$^{10,11}$

For these reasons, the use of supported catalysis and implementation of this methodology in continuous flow were considered to enhance the performance of the reaction, reduce reaction times and hopefully prevent the slurry formation. The formation of slurries is usually undesired when working under continuous flow conditions, since it causes clogging of the microreactors. However, many strategies have been reported in the literature to try to prevent this phenomenon. A well-known example reported by Ley’s group is the use of mechanical stirring in devices such as agitating cell reactors (ACR) to successfully avoid the clogging of the channels.$^{116}$

On the other hand, the use of supported catalysts to promote dipolar cycloadditions has only been reported for the established click reaction between azides and alkynes to generate triazoles. For this specific example, many different supported copper species have been shown to successfully promote the reaction, either in batch or under flow conditions. Some of the most relevant examples include Cu(0) powder, which acts both as the catalyst and the support,$^{117}$ Cul supported in Amberlyst® A-21 beads$^{118}$ and copper(I) and copper(II) salts supported in different forms of amino-modified silica gel.$^{119,120,121}$

Due to the similarities that copper-promoted sydnone-alkyne cycloadditions and the traditional click triazole synthesis show, we decided to investigate the application of these supported copper catalysts to the model reaction between N-phenylsydnone and phenylacetylene, prior to the implementation of the process in continuous flow. Some of the main advantages flow technology offers include dramatic reduction in reaction times (residence times are usually within the order of minutes or even seconds), enhanced mixing and mass transfer due to the high specific surface area of the microreactors and ease of optimisation and setup.$^{113}$
3. Use of supported catalysis in cycloaddition reactions

For an initial screening of suitable solid supports for heterogeneous catalysis, two candidates were chosen relying on previously reported examples: Amberlyst® A-21, which is an amino-functionalised polystyrene resin; and silica gel with additional amino groups incorporated which assist copper coordination to the support. As for the copper sources, the commercially available salts Cul and Cu(OAc)$_2$ were chosen, since they provided copper complexes with different oxidation states, allowing us to determine whether the oxidation state of the promoter played a role in promoting the cycloaddition.

Different types of supported catalysts were prepared by combining the aforementioned supports with the copper salts and following previously reported procedures. In the case of the silica gel, commercial silica gel (chromatography grade, 30-70 μm particle size) was first functionalised to incorporate additional amino groups by treating it with the corresponding siloxanes in refluxing toluene for 24 h (Scheme 75). After filtration and drying, the resulting modified silica was stirred with anhydrous Cu(OAc)$_2$ in ethanol for a few hours to afford the corresponding catalysts Silica-1 and Silica-2 as brightly coloured blue solids.$^{119}$

![Scheme 75. Preparation of silica-based supported catalysts.](image)

In the case of the polystyrene-based Amberlyst® A-21, this commercially available resin was pre-treated with methanol and dichloromethane before gently shaking it with the corresponding salt in acetonitrile for 16 h to generate catalysts $A$-21$\cdot$Cul and $A$-21$\cdot$Cu(OAc)$_2$ (Scheme 76).$^{122}$

![Scheme 76. Preparation of copper-supported Amberlyst(R) A-21 resin.](image)
Chapter 4: Copper-Promoted Cycloadditions in Flow

The copper content of each supported catalyst system was established using inductively coupled plasma atomic analysis (ICP-MS), and [Cu] loadings were expressed as a mass percentage (g of copper per 100 g of support). The results are summarised in Table 8.

Table 8. Copper loading of the supported catalysts.

<table>
<thead>
<tr>
<th>Matrix</th>
<th>Copper source</th>
<th>[Cu] / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silica-1</td>
<td>Cu(OAc)$_2$</td>
<td>3.22</td>
</tr>
<tr>
<td>Silica-2</td>
<td>Cu(OAc)$_2$</td>
<td>4.01 ± 0.20 $^a$</td>
</tr>
<tr>
<td>Amberlyst A-21</td>
<td>CuI</td>
<td>9.42 ± 0.18 $^a$</td>
</tr>
<tr>
<td>Amberlyst A-21</td>
<td>Cu(OAc)$_2$</td>
<td>6.62</td>
</tr>
</tbody>
</table>

$^a$ Average copper content from three different batches of supported catalyst.

With all the supported catalysts in hand, cycloaddition reactions between N-phenylsydnone and phenylacetylene were tested. Preliminary studies showed that Amberlyst A-21 beads had limited thermal stability, since they degrade at temperatures above 100 °C. For this reason, catalysts A-21·CuI and A-21·Cu(OAc)$_2$ were reacted at 80 °C. On the other hand, silica gel provides excellent thermal stability, and for this reason, catalysts Silica-1 and Silica-2 were reacted at 140 °C, which is the typical temperature for Cu-promoted cycloadditions.$^{104}$ Table 9 shows a summary of the optimisation carried out on the model substrates.

Table 9. Optimisation of copper-supported cycloaddition reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (Loading)</th>
<th>Conditions</th>
<th>Result $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A-21-Cu (60 mol%)</td>
<td>A</td>
<td>No reaction</td>
</tr>
<tr>
<td>2 $^b$</td>
<td>A-21-Cu (60 mol%)</td>
<td>A</td>
<td>Formation of homocoupled alkyne</td>
</tr>
<tr>
<td>3 $^c$</td>
<td>A-21-Cu (60 mol%)</td>
<td>A</td>
<td>100% conversion</td>
</tr>
<tr>
<td>4</td>
<td>A-21·Cu(OAc)$_2$ (40 mol%)</td>
<td>A</td>
<td>7% conversion</td>
</tr>
<tr>
<td>5 $^d$</td>
<td>Silica-1 (30 mol%)</td>
<td>B</td>
<td>100% conversion in 3 h</td>
</tr>
<tr>
<td>6</td>
<td>Silica-2 (30 mol%)</td>
<td>B</td>
<td>100% conversion in 2 h</td>
</tr>
<tr>
<td>7 $^d$</td>
<td>Silica-2 (30 mol%)</td>
<td>B</td>
<td>&gt;95% yield after 4 cycles</td>
</tr>
</tbody>
</table>

$^a$ Conversion determined by $^1$H NMR spectroscopy. $^b$ Reaction performed with + 1 eq. of TMEDA. $^c$ Reaction performed with + 1 eq. of 2,2'-bipyridine. $^d$ Reaction performed with only 1 eq. of phenylacetylene.
Taking into account the copper quantification by ICP-MS shown in Table 8, substoichiometric loadings for all 4 candidates were considered to try to perform the reaction in a catalytic fashion; ranging from 30 mol% for catalysts Silica-1 and Silica-2 to 40 mol% for A-21-Cu(OAc)$_2$ and 60 mol% for A-21-Cul, the latter being the highest loading value studied.

From the selected catalysts, results in Table 9 show that copper supported on A-21 beads was not an efficient catalyst system, since no reaction or very low conversions were achieved when performing these reactions at 80 °C (Entries 1, 4). Interestingly, the oxidation state of the copper salt made no difference, since both Cu(I) and Cu(II) were inefficient at promoting the cycloaddition. It was believed that since these processes usually require high temperatures to overcome the energy barrier for the reaction to take place, it was likely that the required reaction temperature (chosen to avoid bead degradation) was not high enough for this purpose.

However, Taran has previously shown the beneficial effect of adding nitrogen-containing ligands to perform these cycloadditions at lower temperatures. In an attempt to further test these catalytic systems, stoichiometric amounts of TMEDA and 2,2'-bipyridine were added to the reaction system. In the case of TMEDA (Entry 2), instead of the desired pyrazole product, Glaser homocoupled diyne was detected, together with unreacted sydnone.

In contrast, when adding 2,2'-bipyridine (Entry 3), full conversion to the desired 1,4-diphenylpyrazole product was observed after 6 h. Although this proved the feasibility of carrying out the reaction using a supported catalyst at a lower temperature, a purification step to separate the ligand from the pyrazole product was now required. This added complexity to the future flow implementation and for this reason, the silica-based catalysts were considered next to achieve generation of clean pyrazole product after a single step.

Satisfactorily, both Silica-1 and Silica-2 catalysts provided full conversion to the desired product after a few hours at 140 °C (Entries 5-7), even when reducing the equivalents of phenylacetylene from 2 eq. to 1 eq. Importantly, the reduction of alkyne stoichiometry in this way had not been possible when working with the non-supported Cu-promoters. In these cases, since the reaction temperature was higher already and provided very good results in terms of conversion, the addition of ligands was not believed to be necessary, thus making possible the pyrazole formation without any further purification, since the catalyst was simply removed by filtration.
Finally, Silica-2 (30 mol% loading) was the chosen catalyst for further studies, since it provided the desired product in shorter times (2 h) even when fewer equivalents of phenylacetylene were used. In addition, the same catalyst batch could be reused up to 4 times providing the diphenylpyrazole product in >95% yield (determined by $^1$H NMR spectroscopy), with a lower impurity profile and without showing any decrease in performance after each cycle; proving the robustness and reproducibility of this catalytic system.

With the optimal conditions in hand (Silica-2 30 mol%, o-dichlorobenzene, 140 °C) different sydnones and alkynes were tested to provide the scope shown in Scheme 77. These reactions were performed in Schlenk tubes under inert atmosphere, reaction times are shown in brackets and all yields quoted are for isolated products after column chromatography on silica gel.

Scheme 77. Solid-supported cycloaddition reactions performed in batch. PMP = p-methoxyphenyl, Bn = benzyl.
Pleasingly, these conditions proved to be suitable for both aromatic (Ph, PMP) and aliphatic (Bn) \(N\)-substituted sydnones, providing the desired pyrazoles in moderate to excellent yields and always maintaining excellent levels of regioselectivity towards the 1,4-disubstituted isomer. Changing the nature of the alkyne allowed the incorporation of different functionalities such as aromatic and heteroaromatic rings, alcohols, esters or aliphatic residues. However, neither (triisopropyl)silylacetylene nor propargyl bromide failed to undergo the cycloaddition recovering the starting material.

In terms of reactivity, aromatic sydnones reacted faster than the aliphatic counterparts, which are usually more prone to degradation upon heating. In the case of \(N\)-benzylsydnone, only reaction with phenylacetylene (98b) and ethyl propiolate (112b) afforded the corresponding pyrazoles after 16 h; and no reaction was observed when other alkynes were tested.

The nature of the aromatic sydnones also had an effect on the reactivity, since the electron-neutral substrates (90b, 91b, 115b, 116b, 117b) performed better than the electron-rich analogues (97b, 101b, 118b, 119b, 120b) providing pyrazole products in higher yields. The nature of the alkynes employed also affected the reactivity, with the aromatic and heteroaromatic substituted analogues providing better results (90b, 97b, 98b, 117b, 120b). We noted that cyclopentylacetylene afforded the corresponding pyrazoles in especially low yields (115b and 118b), under 35 \% in both cases, which was attributed to the high volatility of this alkyne that could be evaporating during the reaction.

The fact that only one equivalent of alkyne was required in this case to carry out the reaction caught our attention, since in the system described in Chapter 3, one extra equivalent of alkyne was required to generate the reactive copper species. This implied that the mechanism for the copper-supported reaction had to be different, and we were intrigued to find out the differences between both systems.

Experimentally, under supported catalysis conditions using \(\text{Cu(OAc)}_2\), 1,4-diphenylpyrazole was produced in quantitative yield and no Glaser homocoupled products were detected. This excluded the alkyne-mediated reduction of Cu(II) to Cu(I); implying that another species had to be involved in the copper reduction to generate the copper(I) acetylide. One possibility could be a convergent disproportion process, which can take place when employing copper(II) salts above 120 °C, as previously described by Mao and Stahl.\(^{123,124,125}\) According to Mao and co-workers, copper(II) disproportionates to the active copper(I) species and copper(III), which can in turn be further reduced to additional copper(I).\(^{123}\) This
active copper(I) species will generate the copper(I) acetylide intermediate (121) by reaction with the alkyne, and after cycloaddition, will produce a cuprous pyrazole species (122). We propose that this species can exchange with alkyne to generate the protonated pyrazole product and to regenerate the active copper(I) catalyst (Scheme 78).

Another issue to consider is the subsequent disproportionation of copper(I) to copper(0) and copper(II), which could in principle enter the disproportionation cycle again. However, copper(0) is inactive, and we found experimental evidence to support its formation. After performing the reactions in Schlenk tubes under inert atmosphere, copper mirrors were found on the glass surface, as shown in Scheme 78.

![Scheme 78. Proposed mechanism for the copper-supported cycloaddition reactions.](image)

Having successfully achieved the development of the copper-supported version of the regioselective synthesis of 1,4-disubstituted pyrazoles, and having put forward a rationale for the minor mechanistic differences, implementation of this methodology under continuous flow was next analysed.
4. Implementation of the pyrazole synthesis in flow

After the successful development of a supported catalyst for the regioselective 1,4-disubstituted pyrazole synthesis, the implementation of this methodology under continuous flow was studied.

At first glance, the requirement of a supported catalyst and temperatures above 100 °C excluded the possibility of using preassembled devices such as the FlowStartEvo (FutureChemistry Holding BV), which include syringe pumps, tubing and a microreactor cell with temperature control already connected, optimal for liquid-liquid processes.

However, the use of a solid support required a cartridge system to prepack the catalyst prior to performing the reaction and taking into account any leaching of the metal catalyst that could happen during the process. The cheapest and most efficient strategy to prepare cartridges on-demand is the use of tubing and frits or cotton wool (to block the ends after packing). Due to the temperature restrictions, stainless steel tubing (10 cm length, 1.75 mm internal diameter) was the option of choice, as shown in Figure 6.

The initial configuration of the flow system consisted of two syringe pumps (for two reagent feeds), a T-mixer unit to ensure optimal homogenisation and the prepacked cartridge, which was heated to the required temperature using a paraffin bath. Similarly to the batch reaction, the high temperature needed for the flow reaction required the use of a high boiling point solvent like o-dichlorobenzene (bp = 180.5 °C). Due to this, this solvent could not be removed in vacuo and crude materials required filtration through silica gel instead. For this reason, we hoped implementation under continuous flow would offer the possibility to tune the reaction conditions to change the solvent, hence simplifying the operations required to obtain the final pyrazole products.

Next, the optimisation of the residence time required for the reaction to proceed efficiently was pursued. N-Phenylsydnone and phenylacetylene were chosen as model substrates, both in o-dichlorobenzene solutions always ensuring a 1:1 flow ratio between them, and maintaining a reaction temperature of 140 °C. Note that in all cases, the cartridge volume corresponds to the effective volume after packing, which was calculated by mass difference.
between packed cartridge before and after soaking it with solvent (average of 3 measurements in every case). The optimisation results are summarised in Table 10.

**Table 10.** Optimisation of the residence time for the cycloaddition reactions in flow.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Residence time / min</th>
<th>Conversion[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>55%</td>
</tr>
<tr>
<td>2</td>
<td>5.0</td>
<td>95%</td>
</tr>
<tr>
<td>3</td>
<td>7.5</td>
<td>86%</td>
</tr>
<tr>
<td>4</td>
<td>10.0</td>
<td>87%</td>
</tr>
</tbody>
</table>

[a] Conversion determined by $^1$H NMR spectroscopy

A residence time of 5 minutes provided best conversion to the 1,4-disubstituted pyrazole product (Table 10, Entry 2), showing that shorter times were not effective in delivering high conversions (Entry 1). Following this trend, longer reaction times were expected to provide even higher conversions (Entries 3 and 4). However, this was found not to be the case in the present system, and a suspected reason for this is the fact that these experiments were performed over a 48 h period (Entries 1, 2 on day 1, Entries 3, 4 on day 2). These results suggested loss of catalyst efficiency over time, implying that for consistency, fresh cartridges should be prepared before every run to ensure comparable results.

Next, we turned our attention to the solvent, since we were interested in trying to tune the reaction conditions under flow to be able to use lower boiling point solvents. Satisfactorily, when performing the model reaction in toluene, 100% conversion to the pyrazole product could be achieved with a retention time of 5 minutes; the only practical implication being the introduction of a back pressure regulator (BPR). This allowed a pressure increase inside the flow system that ensured toluene remained liquid throughout the setup; otherwise, no product was obtained and only toluene was collected in the output.

While performing the flow runs, we noticed that due to the shape of the stainless steel cartridge, the paraffin bath did not allow for efficient heating at the ends of the tube, hence causing temperature gradients that were affecting the conversion. To solve this problem,
the shape of the cartridge was changed, using U-shaped tubing that could be completely immersed in the paraffin oil easily ensuring heating of the full cartridge (Figure 7).

**Figure 7.** U-shaped stainless steel cartridge packed with supported copper catalyst.

Figure 8 shows the full optimised flow setup employed for the cycloaddition reactions, with the two syringe pumps (left), the prepacked, U-shaped cartridge in the paraffin oil bath (centre) and the back pressure regulator (right).

**Figure 8.** Full flow setup to perform cycloaddition reactions.

With the new set of optimised conditions in hand, we analysed the efficiency of the cartridges over time, to estimate for how long a run could be performed without losing conversion to product. To do so, the model reaction was run over a 5-hour period collecting
aliquots at different time points and measuring conversion via \(^1\)H NMR spectroscopy (Table 11).

**Table 11.** Study of the cartridge efficiency over time.

![Diagram of copper-promoted cycloaddition](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Collection time / h</th>
<th>Collected mass / mg</th>
<th>Conversion ([a])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0:00 – 0:30</td>
<td>1.8</td>
<td>67:33</td>
</tr>
<tr>
<td>2</td>
<td>0:30 – 1:00</td>
<td>5.6</td>
<td>92:8</td>
</tr>
<tr>
<td>3</td>
<td>1:00 – 1:30</td>
<td>3.7</td>
<td>91:9</td>
</tr>
<tr>
<td>4</td>
<td>1:30 – 2:00</td>
<td>5.7</td>
<td>92:8</td>
</tr>
<tr>
<td>5</td>
<td>2:00 – 3:00</td>
<td>7.4</td>
<td>92:8</td>
</tr>
<tr>
<td>6</td>
<td>3:00 – 4:00</td>
<td>6.0</td>
<td>93:7</td>
</tr>
<tr>
<td>7</td>
<td>4:00 – 5:00</td>
<td>6.7</td>
<td>95:5</td>
</tr>
</tbody>
</table>

[a] Conversion (pyrazole : sydnone) determined by \(^1\)H NMR spectroscopy. Note that \(\phi_{sydnone} = 2 \times \phi_{alkyne}\), where \(\phi\) is flow rate.

As shown in Table 11, the system required an equilibration period (Entry 1) to ensure homogeneous mixing and saturation of the flow system with both reagent feeds, causing lower conversion within the first 30 minutes. However, after this initial stabilisation, excellent conversions were maintained throughout the 5-hour collection period (Entries 2-7), generating clean pyrazole product together with minor traces of unreacted N-phenylsydnone. The last collection aliquot (Entry 7) still afforded the desired product in good conversion, albeit with higher levels of impurities. These could be originating from heating the paraffin oil at high temperature for several hours, thus generating paraffin vapour which could dissolve into the toluene solutions containing the pyrazole products. This resulted in the presence of small aliphatic signals in the NMR spectra of the pyrazole products. To avoid this contamination, the use of collection vessels sealed with septa to prevent contact of the vapour with the toluene solutions was enough to ensure clean spectra and clean products.

According to the results shown in Table 11, cycloadditions reactions were performed over 4-5 hours, ensuring the generation of pyrazole products with high yield and high purity.
Next, the scope of the sydnone-alkyne cycloadditions under optimised conditions was explored, using the supported copper prepacked cartridges, toluene as a solvent and performing the reactions at 140 °C (Scheme 79).

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{R} & \quad \text{R'}
\end{align*}
\]

0.025 M

\[
\begin{align*}
\text{0.050 M}
\end{align*}
\]

\[
\begin{align*}
\text{Cu(OAc)}_2/\text{silica gel} & \quad \text{BPR}
\end{align*}
\]

\[
140 ^\circ \text{C, PhMe, } f_R
\]

\[
(>95:5)
\]

To quantify the yield of generated pyrazole products under continuous flow, it was necessary to determine the moles of product collected \(n(\text{Collected Product})\) over a specific period of time \(t(\text{Collection})\) and the reagent consumption over that period \([\text{SM}], \phi_{\text{SM}}\), employing the following formula:

\[
\eta_{\text{FLOW}}(\%) = \frac{n(\text{Collected Product})}{[\text{SM}] \cdot \phi_{\text{SM}} \cdot t(\text{Collection})} \cdot 100
\]

Another aspect to consider is the potential leaching of small amounts of copper from the cartridge into the pyrazole products. To check, inductively-coupled plasma mass spectrometry (ICP-MS) analysis were performed on some of the collected product samples.
in order to quantify the copper leached from the catalyst. Results showed presence of small amounts of copper in randomly selected samples of pyrazoles 91b (Ph, CO$_2$Et) and 97b (PMP; Ph): < 400 ppm of Cu after a 2-hour collection period.$^{126}$

In order to establish the scope of this technique, we employed the same substrates that were used in the supported catalysis under batch conditions. However, in flow, the residence times turned out to be substrate-dependent, so times ranging from 5 to 15 minutes were required depending on the sydnone and alkyne of choice (Scheme 79). Ethyl propiolate and phenylacetylene provided the pyrazole products in high yields with shorter residence times, similar to the batch case. In contrast, when 2-ethynylpyridine, cyclopentylacetylene or propargyl alcohol were used, the reaction proceeded more slowly and so higher residence times (10-15 min) were usually required to achieve higher conversions. Furthermore, these alkynes did not afford any product when reacted with N-benzylsydnone.

In general, the corresponding pyrazoles were obtained in good to excellent yields. However, when 2-ethynylpyridine was used, low yields were obtained (117b, 120b). This fact could be attributed to the affinity of pyridine to coordinate to copper, which could cause trapping of some of the product within the cartridge, thus impeding full recovery of the product in the output. The propargyl alcohol analogues (116b, 119b) also gave low yields, which we envisaged could be degrading inside the microreactor, since higher yields were obtained for the same substrates under batch conditions. Related to this, due to the high temperatures over extended periods of time, trans-esterification processes with the silica support could also be taking place in these cases, since clean target material was recovered without detecting any starting material in the collected fractions.

Finally, to expand the practicality of this novel platform for the synthesis of 1,4-disubstituted pyrazoles under continuous flow, the design of a scaled-up variant was considered. The current system proved to be a useful proof of concept; nonetheless, only small amounts of pyrazole products could be generated over several hours due to the reduced dimensions of the cartridges employed. For this reason, we explored larger, suitable alternatives for the stainless steel tubing to prepare bigger cartridges. The best candidate turned out to be empty stainless steel HPLC columns, which can be easily packed with our support, are thermally resistant to the required reaction conditions and can be reused for a large number of cycles. In this specific case, a 2 mL stainless steel Knauer HPLC column (ref. A2103-1) was chosen, equipped with 7 µm frits to prevent the leakage of the silica supported catalyst into the tubing lines. To complete the setup, an HPLC piston pump
and a back pressure regulator were also included. In this case, only one pump was required because we decided to simplify the system by including only one feed stream containing both reagents in solution in toluene, since they do not react at room temperature. Figure 9 shows the complete setup for the scaled up flow system, with the piston pump (left), the HPLC column and the paraffin bath to submerge the cartridge (centre) and the back pressure regulator (right).

Figure 9. Scaled-up flow system for the cycloaddition reactions.

The initial experiments at higher scale were performed using ethyl propiolate with both aromatic sydnones using the previously developed optimal conditions (140 °C, toluene, $t_a = 5 \text{ min}$), providing promising results (Scheme 80).

Scheme 80. Initial results for the scaled-up pyrazole synthesis.
When performing the reaction using the optimal conditions, full conversion was not achieved after a residence time of 5 minutes, affording the corresponding pyrazoles in low yields after purification to separate the unreacted sydnone (Scheme 80). However, the practicality of this methodology was demonstrated, since 50-100 mg of pyrazole products were produced after a few hours, showing the potential of this system if it could be further optimised.
5. Conclusions

In summary, a novel methodology to generate 1,4-disubstituted pyrazoles via cycloaddition reactions between sydnones and alkynes by means of supported catalysis has been successfully developed. After catalyst screening, Cu(OAc)$_2$ at 30 mol% loading supported in amino-modified silica gel turned to be the best candidate. Also, the alkyne stoichiometry required for the reaction has been reduced down to only one equivalent. Mechanistically, in this case the reduction of copper(II) to copper(I) is performed through disproportionation process, in contrast to the non-supported variant.

Moreover, this supported process has been implemented under continuous flow satisfactorily, having reduced the reaction times from several hours to residence times between 5 and 15 minutes. Also, the reaction solvent has been changed to toluene, with the purification and environmental considerations involved.

Finally, successful scaling-up of the reaction has been achieved producing ester-functionalised pyrazole derivatives in practically useful amounts within 2-5 hours.
Chapter 5. Lewis Acid – Base Directed Cycloaddition Reactions Between Sydnones and Alkynes

1. Introduction

As discussed in Chapter 3, the use of copper(II) salts to promote cycloaddition reactions between sydnones and alkynes shows clear advantages when compared to the traditional thermal processes. However, although the long reaction times in thermal reactions can be dramatically reduced in the presence of copper, the high reaction temperatures required are still an issue. Thus, it was deemed desirable to find methodologies that allow the regioselective synthesis of poly-substituted pyrazoles in short reaction times, at low temperatures and fully controlling the regioselectivity of the products.

A well-established strategy generally applied in organic synthesis when both stereo- and/or regiocontrol are required is the use of directing groups. Directing groups can be described as polar functional groups, which have the ability to pre-associate with another reagent in the vicinity of the reaction centre, thus influencing the outcome of the reaction. In general these interactions can be covalent or non-covalent, such as via hydrogen bonding or the formation of a Lewis acid-base pair; and the directing groups are typically unaltered during the reaction.  

According to the previous description, it was envisioned that the use of a Lewis acid-base pair would help not only to achieve milder conditions for the cycloaddition reactions between sydnones and alkynes, but also to generate fully substituted pyrazoles in a totally controlled regioselective manner, due to the coordination between the two partners.
2. Lewis Acid – Base directed cycloadditions

Previous work within the Harrity group showed the utility of these Lewis acid – Lewis base pairs in cycloaddition reactions involving alkynes and other substrates such as 2-pyrones or 1,2,4-triazines. In these reports, it was shown how the presence of directing groups affects both the reaction rate and regioselectivity of the products. For example, the simple thermal cycloaddition reaction of 2-pyrones and alkynes requires harsh reaction conditions but also the benzene derivatives were obtained as mixtures, with the best isomeric ratio being 5:3 (Scheme 81).

![Scheme 81](image)

Scheme 81. Non-directed alkyne-pyrene cycloadditions, where R is always and electron-withdrawing group.

However, when directing groups were introduced, a dramatic change was observed. The same authors showed that if in situ generated alkynyldifluoroboranes were reacted with pyridine-substituted 2-pyrones or pyrones incorporating aza heterocycles, the reaction conditions were much milder (40 °C, 10 minutes). More interestingly, total control of the regioselectivity of the products was achieved (Scheme 82).

![Scheme 82](image)

Scheme 82. Examples of directed cycloadditions with 2-pyrones.

In 2014, Harrity and co-workers published the first mechanistic study based on both experimental and theoretical results to propose a mechanism for the directed cycloadditions between 2-pyrones bearing Lewis basic moieties and the alkynyldifluoroboranes. They demonstrated that the key steps for the transformation are
rapid and reversible formation of the tris(alkynyl)borane 123 (when the phenylethynyltrifluoroborate salt is used) followed by the cycloaddition with the 2-pyrone and after disproportionation to give the corresponding benzene derived cycloadduct.\(^{127}\)

Figure 10. Tris(alkynyl)borane generated in situ from alkynyltrifluoroborate and BF\(_3\)·Et\(_2\)O.

In a similar way, the same in situ generated alkynyldifluoroboranes can react with Lewis basic triazines to generate pyridine scaffolds via an inverse electron demand aza-Diels-Alder reaction after N\(_2\) extrusion. The coordination has a dramatic effect on the reaction in this case because cycloaddition reactions between triazines and alkynes without Lewis acid groups require high temperatures, long reaction times and generate the products in low yields. However, just by incorporating a Lewis acidic group in the alkynes, these cycloadditions can be performed at just above room temperature (Scheme 83).\(^{128}\)

Scheme 83. Cycloaddition reactions between 1,2,4-triazines and alkynes.
The use of directed cycloaddition-based methodologies is very convenient to generate benzene or pyridine scaffolds, as shown, due to the difficulties of functionalising these rings once formed. By generating them via these processes, functionalisation takes place before the ring formation, expanding the versatility of the generated products.
3. Application of directed cycloadditions to the sydnone-alkyne system

Having set the precedent of this chemistry in a variety of substrates and having shown that this approach offers an easy way to gain access to aromatic and heteroaromatic systems, it was deemed appropriate to test this strategy with the sydnone-alkyne system and thus afford densely functionalised pyrazoles.

For the sydnone-alkyne cycloadditions, the proposed system is shown in Scheme 84. Similar to the previous examples, in this case it seemed feasible to attach the Lewis acid moiety to the alkyne by reacting potassium alkynyltrifluoroborate salts with BF$_3$·Et$_2$O to generate the corresponding difluoroboranes in situ. This is advantageous, since the synthesis of these alkyynes is well established.

According to Scheme 84, the sydnone partner will be the one acting as the Lewis base, so a range of sydnone substrates bearing Lewis basic groups had to be designed and synthesised. Initially, directing groups that had successfully promoted cycloadditions in previous systems seemed the most appropriate candidates. Indeed, preliminary studies carried out by a colleague within the group showed that 4-pyridyl substituted sydnones successfully underwent cycloaddition reactions with alkynyltrifluoroborate salts delivering fully substituted pyrazole rings. Therefore, the starting point in my studies focused on the synthesis of sydnones bearing amide groups, as these had also been found to be effective in 2-pyrone and 1,2,4-triazine examples.

In order to test this new approach to the cycloadditions, the first step was to synthesize the alkynyltrifluoroborate salts. These can be easily obtained following Molander’s method, which uses the reaction of organometallic alkynes, typically alkynylolithium or alkynylmagnesium halide species, with trialkyl borates and further treatment with potassium hydrogen difluoride (KHF$_2$) (Scheme 85). In most cases the corresponding trifluoroborate salts were obtained in good to excellent yields with the trimethylsilyl-substituted substrate being the most difficult since protodesilylation was sometimes
observed due to the presence of an excess of fluoride causing the generation of ethynyl trifluoroborate 130.

\[
\begin{align*}
\text{Scheme 85. Synthesis of alkynyltrifluoroborates.}
\end{align*}
\]

While the synthesis of the alkyne salts was well established, a literature search showed that not many sydnones bearing potential directing groups have been synthesized to date. Thus, routes to several novel 4-substituted sydnones had to be designed for this purpose. Amide-based directing groups were the first compound class to be investigated, as successful results had been obtained with the dimethylamide moiety in the directed cycloadditions of triazines and pyrones (Scheme 86).\textsuperscript{130,128}

To test whether the amide functionality would direct the sydnone cycloaddition process, different amide-containing sydnones were synthesized following two main pathways. The first pathway consisted of the reaction of 4-lithiated sydnones with electrophiles such as isocyanates or dimethylcarbamoyl chloride. The second pathway was employed by analogy to that previously developed for the 2-pyrone substrates.\textsuperscript{76} In this case, starting from 4-carboxy-3-phenylsydnone 131, the corresponding acyl chloride was generated \textit{in situ},
thereby activating the substrate towards amine substitution in the presence of Hünig’s base. Both procedures are summarised in Scheme 87.

\[
\begin{align*}
    &1) n\text{-BuLi} \\
    &2) E^+ \\
    &70 \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad

\text{Table 12. Amide substrates synthesised from the lithiated sydnone equivalent.}

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Electrophile (E)</th>
<th>Time</th>
<th>R¹, R²</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70, Ph</td>
<td>PhNCO</td>
<td>2.5 h</td>
<td>132, Ph, H</td>
<td>80%</td>
</tr>
<tr>
<td>2</td>
<td>70, Ph</td>
<td>Me₂NCOCl</td>
<td>5 h</td>
<td>133, Me, Me</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>83, Me</td>
<td>Me₂NCOCl</td>
<td>16 h</td>
<td>134, Me, Me</td>
<td>32%</td>
</tr>
</tbody>
</table>
As Table 12 shows, the aromatic substrates yielded the corresponding amides in excellent yields (Entries 1,2). However, the use of the aliphatic sydnone in the reaction was less successful, with an isolated yield of product in this case of only 32% (Entry 3).

The other procedure to obtain 4-amidosydnones began from the corresponding carboxylic acid 131, which was synthesized in a similar way to the previous substrates. Deprotonation with n-BuLi in THF for 30 minutes at -78 °C and then addition of the lithiated sydnone via cannula to an excess of CO$_2$(g) (Scheme 88) provided the corresponding acid on a multigram scale (2.52 g, 12.24 mmol), according to a procedure reported by Kato.$^{133}$

\[ \text{Scheme 88. Synthesis of 4-carboxy-3-phenylsydnone 131.} \]

Carboxylic acid 131 was then converted to the acyl chloride via reaction with oxalyl chloride and catalytic dimethylformamide, and further addition of the corresponding amine and diisopropylethylamine afforded the corresponding amides 135 and 136 in very good yields of 73% and 87%, respectively. In these cases, flash chromatography on silica gel was not necessary for the purification of the products, since the crude products were isolated as clean solids (Scheme 89).

\[ \text{Scheme 89. Synthesis of cyclic amides.} \]

We next wanted to subject the amide substrates to cycloaddition conditions by addition of alkynyltrifluoroborate and Lewis acid. For optimisation purposes, potassium n-hexylethynyltrifluoroborate 125 and BF$_3$·Et$_2$O was the system of choice employed to generate the Lewis acidic species in situ. In addition, as reported previously, halogenated solvents are usually best for cycloaddition reactions of this nature. In this case, dry 1,2-dichloroethane (DCE) was the solvent of choice, distilled over calcium hydride.
Table 13 shows the preliminary results for the first cycloaddition reactions performed using N-phenylamide 132. After testing different temperatures and different equivalents of both alkyne and Lewis acid, no pyrazole product could be detected in any case. Additionally, it was observed that above 60 °C, the alkyne started to polymerise (as judged by $^1$H NMR spectroscopy of the crude reaction mixture, Entry 4); proving that high temperatures were not suitable for the reaction, as alkyne was presumably destroyed before any reaction could occur.

Table 13. Cycloaddition reactions with N-phenylamide 132.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alkyne (5 eq.), BF$_3$·Et$_2$O (2 eq.), DCE, 25 °C, 3 h</td>
<td>Sydnone recovered</td>
</tr>
<tr>
<td>2</td>
<td>Alkyne (3 eq.), BF$_3$·Et$_2$O (3 eq.), DCE, 25 °C, 3 h</td>
<td>Sydnone recovered</td>
</tr>
<tr>
<td>3</td>
<td>Alkyne (3 eq.), BF$_3$·Et$_2$O (3 eq.), DCE, 60 °C, 6.5 h</td>
<td>Sydnone recovered</td>
</tr>
<tr>
<td>4</td>
<td>Alkyne (3 eq.), BF$_3$·Et$_2$O (3 eq.), DCE, 80 °C, 6 h</td>
<td>Alkyne polymerisation</td>
</tr>
</tbody>
</table>

Once again, when subjecting cyclic amides 135 and 136 to 3 equivalents of the n-hexyltrifluoroborate salt and 3 equivalents of BF$_3$·Et$_2$O in dry 1,2-DCE at 40 °C, starting material was recovered in both cases after 20 h, without detection of any product formation. The fact that these amides did not direct the cycloaddition reactions was surprising as amides had previously been shown to be excellent directing groups for this process.

To clarify this, cycloaddition reactions were performed with the corresponding N,N-dimethylcarbamoyl-3-phenylsydnone 133. A full screening of equivalents and temperatures was carried out in this case, in direct comparison to the N-phenylamide examples. Results for these investigations are summarised in Table 14.

Surprisingly, and by analogy to the previous examples, no reaction was observed at all, affording only recovered starting sydnone in all cases.
Table 14. Cycloaddition reaction results for the \( N,N \)-dimethyl amide 133 substrate.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alkyne (5 eq.), BF(_3)-Et(_2)O (2 eq.), DCE, 25 °C, 3 h</td>
<td>Sydnone recovered</td>
</tr>
<tr>
<td>2</td>
<td>Alkyne (3 eq.), BF(_3)-Et(_2)O (3 eq.), DCE, 25 °C, 3 h</td>
<td>Sydnone recovered</td>
</tr>
<tr>
<td>3</td>
<td>Alkyne (3 eq.), BF(_3)-Et(_2)O (3 eq.), DCE, 60 °C, 6.5 h</td>
<td>Sydnone recovered</td>
</tr>
<tr>
<td>4</td>
<td>Alkyne (3 eq.), BF(_3)-Et(_2)O (3 eq.), DCE, 80 °C, 6 h</td>
<td>Sydnone recovered</td>
</tr>
</tbody>
</table>

As reported previously, when performing the reaction at 80 °C (Table 14, Entry 4), polymerisation of the alkyne was observed. To date, it is not clear what causes this unexpected lack of reactivity in substrates 133, 135 and 136.

With regard to sydnone 133, a steric clash between the \( N \)-phenyl ring of the sydnone and the methyl groups from the amide functionality was thought to be hindering the coordination to the Lewis acid. To test this hypothesis, it was envisioned that the use of a smaller substrate, such as \( N \)-methylsydnone bearing the dimethylamide moiety, might be more accessible. In this case, cycloaddition reactions with two different alkynes were performed using the standard set of conditions (3 equivalents of the \( n \)-hexyltrifluoroborate salt and 3 equivalents of BF\(_3\)-Et\(_2\)O in dry 1,2-dichloroethane at 40 °C), to see if this change in \( N \)-substituent would be sufficient to enhance the reaction (Scheme 90).

Both \( n \)-hexyl- and phenyltrifluoroborate salts were tested in this case to make sure the nature of the alkyne did not have a detrimental effect in the process. Disappointingly, starting material was recovered in both cases after 20 h. This experiment showed that the
observed lack of reactivity could not be due to steric factors only, as even when minimising the steric clash, the reaction did not proceed at all.

Since none of the amides synthesised so far showed activity towards directed cycloadditions and bearing in mind that sydnones have, in fact, Lewis basic character, it was hypothesised that the amide functionality was not Lewis basic enough to pre-coordinate to the Lewis acid. Possibly the exocyclic O6 in the sydnone system could coordinate to the boron atom instead, thus blocking the directed cycloaddition process.

To test this hypothesis, a series of experiments were performed in order to confirm if the amide group could potentially direct a cycloaddition at all. From a Lewis acidity-basicity point of view, it could be argued that the amide group was not Lewis basic enough or that boron was not Lewis acidic enough, so these two scenarios were considered. If the system lacked sufficient Lewis acidity, maybe the use of an alternative Lewis acid on the alkyne could further promote the reaction. For this purpose, the use of alkynylaluminum reagents was considered. Similarly, as with boron, these reagents are usually generated in situ by reacting the corresponding lithiated alkyne with a freshly prepared solution of a dialkylaluminum chloride in hexanes. Thus, the corresponding aluminium(III) acetylide could be obtained and then reacted with the Lewis basic partner, in this case a sydnone. This procedure was inspired by Harrity and co-workers, where Lewis basic 2-pyrones were reacted with aluminium(III) acetylides, delivering disubstituted benzene rings in good yields and excellent regioselectivities.76

Following a parallel procedure to Crépin et al.,76 the aluminium reagent was prepared in situ by deprotonating phenylacetylene with n-BuLi at 0 °C for 30 minutes before adding a fresh solution of diethylaluminum chloride in hexanes to generate the phenylethynyl diethylaluminum species. The procedure was performed under an inert argon atmosphere due to the highly pyrophoric nature of diethylaluminum chloride. The aluminium(III) acetylide was reacted with sydnone 133, which contained the dimethylamide directing group (i.e. the best with regards to 2-pyrone reactions). In this case, 3 equivalents of the aluminium species were reacted with one equivalent of sydnone in dry DCE at room temperature. However, despite the effectiveness shown by aluminium in the pyrone system, no reaction was observed at all in this case, and the sydnone was recovered after the reaction, as seen in Scheme 91.
Chapter 5: Lewis Acid-Base Directed Cycloadditions

Having seen that modifying the Lewis acidity of the alkynylmetal did not have a positive impact on the reaction, the Lewis basicity of the amide moiety was considered next. If a directing group with higher Lewis basicity than the sydnone exocyclic oxygen could be designed, then possibly the reactivity of the resulting sydnone would increase towards the cycloaddition. It was considered that blocking of the exocyclic O6 atom would then facilitate coordination of the amide functionality to the Lewis acidic alkyne.

In order to block the O6 position, it was envisioned that the presence of additional Lewis acid would pre-coordinate to the sydnone thereby avoiding the competing coordination with the Lewis acidic alkyne. For this purpose, two approaches were evaluated: the use of BF₃ or a generated trialkynyl boron species. At first, the sydnone was pre-reacted with stoichiometric amounts of BF₃·Et₂O to observe if a BF₃-sydnone complex (137) was generated. Then the mixture was subjected to the standard conditions (3 equivalents of alkyne and 3 equivalents of Lewis acid in dry DCE at 40 °C). After 16 h, TLC analysis only showed starting material and, in fact, after the workup stage, the unreacted sydnone was recovered (Scheme 92).

The fact that no reactivity was observed in this case could be due to that, in the presence of both BF₃ and the tris(n-hexylethynyl)borane, a ligand exchange process is occurring generating something like the intermediate 138 for which a similar example has been previously reported in the literature. If this were the case, then the generated intermediate would possibly be more sterically demanding than the BF₃ complex 137. As
such, it is not surprising that poor reactivity was observed as the $n$-hexylethynyl groups would be blocking the space for the amide to coordinate with alkynyldifluoroborane.

![Figure 11. Plausible intermediate formed by ligand exchange.](image)

To further prove the effect of steric hindrance, a similar reaction was performed using an excess (6 equivalents) of the terminal ethynyltrifluoroborate salt 130, which is much smaller in size than the $n$-hexyl equivalent. The idea was that a similar complex to 138 would be generated, consequently blocking the O6 position, and after coordination the cycloaddition would take place employing the same conditions as before (Scheme 93).

![Scheme 93. Pre-coordination experiment using ethynyltrifluoroborate.](image)

Disappointingly however, the starting material was recovered after 16 h, showing that even if the tris(ethynyl)borane-sydnone complex formed, it might still be too hindered to allow the coordination between the sydnone and the difluoroborane, resulting in no reaction at all.

For this reason, since no reactivity could be observed at all in any of the cases where amide-based directing groups were used, this approach was abandoned. Nonetheless, one of the main issues of this strategy appeared to be the coordination between boron and the exocyclic O6 from the sydnone ring instead of the Lewis base. Alternative scaffolds that would prevent or avoid this coordination would therefore be highly desirable. A literature search showed two promising candidates, where the exocyclic oxygen is substituted by a sulphur atom in one case (139) and by an ethoxide group in the other (140), as shown in Figure 12.
Chapter 5: Lewis Acid-Base Directed Cycloadditions

We next proceeded with the synthesis of these sydnone analogues. Routes to both intermediates had been previously reported in the literature. Sydnone 140 was obtained by alkylation of N-phenylsydnone using a solution of Meerwein’s salt in dichloromethane, as reported by Potts in 1970.\textsuperscript{134} Initially, literature conditions provided moderate yields of the desired product but after optimisation and increasing the equivalents of the alkylating agent, the corresponding ethylated sydnone was isolated in 77% yield as a tetrafluoroborate salt (Scheme 94).

Since O-alkylation on N-phenylsydnone was successfully achieved, we next focused our attention on the alkylation of amide 133 to see if the amide moiety would direct the cycloaddition reaction once the highly Lewis basic O6 position was blocked. Unfortunately, due to the electron-withdrawing nature of the amide group, the nucleophilicity of the O6 position was dramatically reduced, and no alkylation was observed resulting in the recovery of unreacted starting material. For this reason, these alkylated substrates were no longer considered due to their limited reactivity (Scheme 95).

![Figure 12. Alternative substrates to explore for directed cycloadditions.](image)
We next turned our attention to the synthesis of sulphur-substituted sydnone analogues, since these compounds can be obtained directly from the alkylated tetrafluoroborate salts, as reported by Masuda in 1979.\textsuperscript{135}

![Scheme 96. Preparation of thiosydnone 139.]

When applying Masuda’s conditions, the desired thiosydnone was isolated as a bright yellow powder, albeit in very low yields. The reaction was attempted on several occasions to try to increase the yield by modifying the equivalents of sodium hydrosulphide without much success, since the highest yield achieved was 30%.

Next, the functionalisation of this derivative was explored. The incorporation of the dimethylcarbamoyl moiety was attempted to see if the lower expected Lewis basicity of the $S_6$ compared to the $O_6$ position would be enough to allow the directed cycloaddition.

![Scheme 97. Attempts to prepare amide derivatives from thiosydnone 139.]

However, after subjecting thiosydnone 139 to the standard conditions for amide synthesis (Scheme 97), only complex crude mixtures were obtained, and neither the starting material nor the desired product could be detected. These results suggested a decrease in stability of this substrate compared to $N$-phenylsydnone.

To get further insight in the reactivity of the sulphur analogue, some cycloaddition reactions were performed with phenylacetylene, in the presence and in the absence of copper(II) (Scheme 98). Disappointingly, degradation of the starting material was observed in all cases, likely because of the lower stability of this substrate. For this reason, this alternative approach to try to block the $O_6$ position was discontinued since it proved unsuccessful.
Instead, returning to our directed cycloaddition objective, a new approach was conceived based on directing groups containing Lewis basic nitrogen atoms that could be derived from 4-carbaldehyde-3-phenylsydnone, or the corresponding ethyl ester, as these are both readily available precursors.

To start this new approach, the synthesis of 4-(ethoxycarbonyl)-3-phenylsydnone 141 was required. Accordingly, N-phenylsydnone was deprotonated with n-BuLi at -78 °C and the lithiated sydnone was transferred to a solution of ethyl chloroformate according to a procedure reported by Harrity.136 The desired product 141 was obtained in excellent yield (94%, 2.70 g) after isolation via flash chromatography on silica gel.

This substrate 141 was in turn tested to see if coordination with Lewis acids could be observed. Table 15 shows the result of the two sets of conditions tested. No reaction
Chapter 5: Lewis Acid-Base Directed Cycloadditions

occurred in any case, and unreacted sydnone was recovered in both cases. This was not surprising as esters had not previously directed these types of cycloadditions, and this was attributed to the low Lewis basicity of the ester substrate.

Table 15. Cycloadditions with the ester 141.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alkyne (3 eq.), BF₃·Et₂O (3 eq.), DCE, 40 °C, 16 h</td>
<td>Sydnone recovered</td>
</tr>
<tr>
<td>2</td>
<td>Alkyne (5 eq.), BF₃·Et₂O (2 eq.), DCE, 40 °C, 16 h</td>
<td>Sydnone recovered</td>
</tr>
</tbody>
</table>

Sydnone 141 also functioned as a precursor to the aldehyde 142, which is usually obtained by reduction of the ester to the alcohol and further oxidation to the aldehyde.¹³⁶ For this purpose, ester 141 was reduced by lithium borohydride, the crude alcohol was clean enough to be directly oxidised. The crude alcohol was subsequently oxidised with manganese oxide (Scheme 101), delivering the corresponding aldehyde 142 in 84% yield over two steps.

![Scheme 101. Synthesis of aldehyde 140.](image)

Having achieved the synthesis of aldehyde 142, a new range of potential directing groups could be prepared with the advantage that they offered the possibility of deprotection to further functionalise the sydnone. Some of the possibilities that we envisaged could be generated from an aldehyde were imine- and oxime-type directing groups, all with Lewis basic character. This seemed a promising approach to expanding the directing groups that would promote cycloaddition reactions with alkynyldifluoroboranes.

To start, the synthesis of the abovementioned oxime- and some imine-derivatives from aldehyde 142 was attempted. For the oxime substrate, treatment of the corresponding
aldehyde with methoxylamine hydrochloride in the presence of base afforded the clean desired product directly after filtration (Scheme 102).

```
\[
\begin{array}{c}
\text{MeONH}_2\text{HCl (1.2 eq.)} \\
\text{Pyridine (4 eq.)} \\
\text{CH}_2\text{Cl}_2, \text{rt, 20 h} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{MeO} \\
\text{N} \\
\text{Ph} \\
\end{array}
\]
\[144, 80\%\]

**Scheme 102.** Preparation of the O-methyl oxime derivative.

Next, we decided to investigate the use of imine directing groups. In order to test them, a series of aliphatic imines were prepared by subjecting aldehyde 142 to a range of primary amines in the presence of alumina (Scheme 103).

```
\[
\begin{array}{c}
\text{R-NH}_2 (1 \text{ eq.}) \\
\text{Al}_2\text{O}_3 (2 \text{ eq.}) \\
\text{CH}_2\text{Cl}_2, \text{rt, time} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{R} \text{ = Cy, 145} \\
20 \text{ h} \\
100\% \\
\text{R} \text{ = Et, 146} \\
20 \text{ h} \\
92\% \\
\text{R} \text{ = }\text{t-Bu, 147} \\
3 \text{ days} \\
69\% \\
\end{array}
\]

**Scheme 103.** Preparation of N-phenylsydnone imine derivatives.

With a range of sydnone derivatives bearing Lewis basic directing groups in hand, we subjected these substrates to cycloaddition conditions to study the outcome of the reactions. The most relevant results are summarised in Table 16, showing that no pyrazole product was detected in any case. For the oxime substrate (Entry 1), only starting material was recovered whereas with imines 145, 146 and 147, hydrolysis to the aldehyde was observed (Entries 3, 4 and 5). In these last cases, hydrolysis may have occurred during the workup stage.

As aldimines and related derivatives had not been effective as directing groups, ketone derived analogues were next considered. We were especially keen to investigate the potential of forming E/Z isomers, and exploring their ability to promote the reaction.
Table 26. Cycloaddition reactions with oxime, hydrazone and imine derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (R)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Starting material recovered</td>
</tr>
<tr>
<td>2</td>
<td>MeO-N</td>
<td>Aldehyde 142 recovered</td>
</tr>
<tr>
<td>3</td>
<td>Cy-N</td>
<td>Aldehyde 142 recovered</td>
</tr>
<tr>
<td>4</td>
<td>Et-N</td>
<td>Aldehyde 142 recovered</td>
</tr>
</tbody>
</table>

For this reason, a ketone equivalent was synthesised from \( N \)-phenylsydnone 70, deprotonating with \( n \)-BuLi for 30 minutes at -78 °C and transferring the lithiated intermediate into the corresponding acyl chloride (Scheme 104).

Scheme 104. Synthesis of methylketone 148.

Next, it was necessary to generate the corresponding imines and oximes from ketone 148. However, this process proved much more complicated than expected, and we were unable to generate any of the desired imine derivatives after trying a range of conditions, including Lewis acid activation (i.e. \( \text{TiCl}_4 \)) reported by Guitián to promote imine formation in very unreactive substrates.\(^{137} \) The only substrate successfully prepared was the corresponding oxime 149, which was prepared analogous to the aldehyde example, and isolated as a single isomer which was assumed to be of the \( E \) configuration (Scheme 105).\(^{138} \)
Disappointingly, when subjecting this substrate to cycloaddition conditions in the presence of the Lewis acidic difluoroborane no reaction was observed at all, recovering the unreacted oxime after 16 h (Scheme 106).

Scheme 105. Synthesis of oxime 149.

It is still not fully understood why the substrates discussed in this chapter have proved to be completely unreactive. Our current hypothesis is that they have a relatively low Lewis basicity, especially relative to Lewis basic sites on the sydnone scaffold such as the O6 position. However, we do not have any evidence for this to-date, and we intend to undertake theoretical calculations in order to gain further insight into this idea.

At this point, we noted that the directing groups that failed to show any activity were all acyclic, and we wondered if this could have an important impact on the directed reaction, since for example pyridine had been shown to direct the cycloaddition. With this new concept in mind, a range of aromatic and aliphatic nitrogen-containing rings were evaluated towards the cycloaddition. The most relevant potential heterocyclic directing groups are summarised below (Figure 13).

Figure 23. Summary of the heterocyclic directing groups considered.

A cyclic imine was the first candidate to be explored, since we envisioned that the cyclic scaffold would ensure the E-configuration, as well as being very close in nature to the successful pyridine directing group. For this reason, the synthesis of this intermediate was
attempted based on an approach reported by Coldham\textsuperscript{139} in 2014 consisting of a nucleophilic attack followed by intramolecular cyclisation. When applying this approach to our system, different bases and solvents were explored but the desired cyclic imine was not isolated in any case (Table 17).

Table 17. Attempts for the preparation of tetrahydropyridine derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deprotonation</th>
<th>Solvent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi (1.3 eq.), -78 °C, 30 min</td>
<td>PhMe</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td>2</td>
<td>n-BuLi (1.3 eq.), -78 °C, 30 min</td>
<td>THF</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td>3</td>
<td>MeMgBr (3 eq.), -15 °C, 1 h</td>
<td>THF</td>
<td>Complex mixture (+ starting material)</td>
</tr>
</tbody>
</table>

We attribute the lack of reactivity to the low nucleophilicity of the lithiated sydnone, thus not reacting with \(\delta\)-valeronitrile. This would explain the starting material recovery after 16 h.

To try to improve our results, we decided to explore the tetrahydropyrimidine analogue instead, containing two N atoms. To do so, two different strategies were considered, the first being a palladium-catalysed multicomponent reaction using tert-butyl isocyanide as a carbon source reported by Shipman.\textsuperscript{140}

This reaction requires aryl halide starting materials, and it was envisaged that 4-halo sydnones might be good candidates. 4-iodo-\textsuperscript{150} and 4-bromo-\(N\)-phenylsydnone (\textsuperscript{151}) were easily prepared by subjecting \(N\)-phenylsydnone to iodine monochloride and
recrystallised $N$-bromosuccinimide respectively in acetic acid stirring for a few hours at room temperature in very good yields (Scheme 107). However, when subjecting the iodo derivative to Shipman’s conditions, protodeiodination was observed resulting in the recovery of only $N$-phenylsydnone. Thinking that the bromo analogue would be less prone to dehalogenation, the same reaction was performed with the bromo derivative but in this case a complex crude mixture was recovered with no signs of potential product.

Due to the lack of success this approach offered, we decided to move on to the second strategy, which consisted of the synthesis of amides containing a pendant amino group followed by cyclisation using Hendrickson’s reagent. When synthesising the requisite amides, it wasn’t clear if the protection of the amino group necessary for the subsequent cyclisation was needed. The unprotected route (using 1,3-diaminopropane for the amide synthesis) was carried through but when testing the cyclisation, no reaction was observed. For this reason, a $N$-trityl protected version of the desired aminopropane was prepared following a procedure by Balbi and co-workers. This reaction proceeded in quantitative yield and this amine was then employed in the amide synthesis as shown in Scheme 108.

![Scheme 108. Preparation of amide 152 from carboxylic acid 131.](image)

Next, Hendrickson’s reagent, prepared in situ by mixing triphenylphosphine oxide and triflic anhydride, was employed for the dehydration to generate the corresponding tetrahydropyrimidine, following conditions reported by Loughlin in 2013.

Although the reaction afforded the desired product in moderate yield, the purification of the tetrahydropyrimidine was challenging due to the presence of triphenylphosphine oxide and the sensitivity of the product, which underwent degradation on silica gel and florisil resulting in losses throughout the purification process.
In addition, when subjecting sydnone 153 to the cycloaddition conditions described before (5 equivalents of trifluoroborate and 2 equivalents of BF₃·Et₂O in dry DCE at 40 °C), degradation of the starting material was observed resulting in the recovery of a very low mass balance. Due to the high sensitivity of this substrate, no further studies were undertaken with tetrahydropyrimidine scaffolds towards cycloaddition.

Next, we focussed our attention on 5-membered ring heterocycles as no examples of this class had been used in sydnone cycloadditions, although they had been shown to be effective in pyrone cycloadditions. Primarily, we were interested in oxazoline and oxazole cores, and three different analogues were synthesised as shown below (Scheme 110).

Scheme 109. Successful cyclisation to give tetrahydropyrimidine 153.

Scheme 110. Preparation of heterocycles 155, 156 and 158.
These three substrates were all derived from 4-carboxy-3-phenylsydnone 131. Generation of the corresponding acyl chloride in situ allowed the preparation of amides 154 and 157 from propargyl amine and ethanolamine respectively in very good yields. Methylene oxazoline 155 was then generated by zinc-promoted intramolecular cyclisation, as shown by Wang in 2012,143 affording the desired product in good yield. Furthermore, treatment of this oxazoline 155 with DBU in toluene resulted in the isomerisation of the methylene alkene to generate the corresponding methyl oxazole 156 in very good yield. Finally, cyclisation of amide 157 using Hendrickson's reagent as described previously afforded unsubstituted oxazoline 158 in moderate yield.

Next, these substrates were treated with a potassium trifluoroborate salt in the presence of BF$_3$·Et$_2$O. The outcome of these reactions is summarised in Table 18.

**Table 18.** Cycloaddition reactions with heterocycles 155, 156 and 158.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (R)</th>
<th>$T$ / °C</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Substrate 1" /></td>
<td>25 °C</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Degradation (low mass)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Substrate 2" /></td>
<td>40 °C</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Degradation (low mass)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Substrate 3" /></td>
<td>25 °C</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Substrate 4" /></td>
<td>40 °C</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Substrate 5" /></td>
<td>25 °C</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Substrate 6" /></td>
<td>40 °C</td>
<td>Starting material recovered</td>
</tr>
</tbody>
</table>

Disappointingly, no conversion was observed with any of the substrates in any of the attempts. The lack of reactivity with 5-membered ring directing groups has been attributed to the fact that the generated products would be tricyclic structures with three fused 5-membered rings that we envisaged would be extremely strained, especially the B-N bond, as represented in Figure 14.
Finally, the last category of heterocycles to be explored as potential directing groups were nitrogen-containing 6-membered ring heteroaromatic systems. Among these, 2-pyrimidine, 2-pyrazine and 2-quinoline were considered.

Initially, the synthesis of these analogues was conceived by means of a palladium-catalysed direct arylation approach on 3-phenylsytndone using the corresponding heteroaryl halides, which has been recently developed within the Harrity group.\textsuperscript{144} This route proved to be successful for the pyridine, pyrazine and quinoline substrates, which were obtained in good yields, as shown in Scheme 111. However, unexpectedly, all the pyrimidine-based substrates tested were unreactive towards direct arylation.

This lack of reactivity of both the 2-bromo- and the 2-chloropyrimidine was surprising, as other analogues such as 5-bromopyrimidine undergo direct arylation without any complications. After several attempts changing the reaction conditions such as the catalyst and ligand loading, the base, use of a precatalyst system (XPhos Pd G2), the temperature or the amounts of the aryl halide, no improvements were achieved in any case, and we always...
recovered unreacted N-phenylsydnone. For this reason, studies concerning pyrimidine derivatives were postponed and will be continued in the near future.

As for the pyrazine, pyridine and quinoline substrates, these were subjected to cycloaddition reaction conditions and different results were obtained. In the first case, no formation of pyrazole product was observed under the standard reaction conditions, whereas the pyridine and the quinoline moieties did trigger the cycloaddition (Table 19). To try to understand the lack of reactivity of 2-pyrazine as a directing group, we screened different alkynyl trifluoroborates to see whether steric effects would affect the reactivity of the system. Unfortunately, changing the R^2 group on the alkyne had no effect and starting material was recovered in all cases (Entries 1-4). On the other hand, 2-pyridine (Entry 5) and 2-quinoline (Entry 6) successfully directed the cycloaddition affording the desired pyrazole products in 78% and 65% yield respectively, employing the standard conditions.

Table 19. Directed cycloadditions with pyrazinyl and quinolyl derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (R^1)</th>
<th>R^2</th>
<th>Time</th>
<th>x : y (eq.)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-Hex</td>
<td>n-Hex</td>
<td>16 h</td>
<td>5 : 2</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td>2</td>
<td>t-Bu</td>
<td>t-Bu</td>
<td>16 h</td>
<td>5 : 2</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>H</td>
<td>16 h</td>
<td>5 : 2</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>t-Bu</td>
<td>t-Bu</td>
<td>2 h</td>
<td>5 : 2</td>
<td>162, 78% (BX_2 = Dialkynyl adduct)</td>
</tr>
<tr>
<td>6</td>
<td>n-Hex</td>
<td>n-Hex</td>
<td>3 h</td>
<td>5 : 2</td>
<td>163, 65% (BX_2 = Dialkynyl adduct)</td>
</tr>
</tbody>
</table>

To confirm the regiochemistry of the pyrazole products in the cases where the directed cycloadditions were successful, X-ray crystallographic studies were performed on crystalline
pyrazole samples. Covalent bonding between the nitrogen atom from the directing group and the boron is observed, suggesting extra stabilisation of these unusual pyrazole adducts (Figure 15).

Figure 15. X-ray crystallographic structures for 2 pyrazole borane examples.
Chapter 5: Lewis Acid-Base Directed Cycloadditions

4. Conclusions

The application of Lewis acid-base directed cycloadditions has been applied to the sydnone-alkyne system for the regioselective synthesis of fully functionalised pyrazoles.

A range of potassium alkynyltrifluoroborates have been synthesised to generate alkynyldifluoroboranes in situ upon reaction with BF$_3$·Et$_2$O.

As for the Lewis bases, a range of 4-substituted sydnones have been synthesised and tested, such as amides, imines, oximes and 5- and 6-membered heteroaromatic rings among others. For most of the cases, results have been unsuccessful in terms of directed cycloaddition reactions, probably due to the lack of Lewis basicity of these substituents. Since the high Lewis basicity of the exocyclic oxygen of the sydnone ring was anticipated to cause issues, alternative scaffolds such as 6-thiosydnones or 5-ethoxy-3-phenylsydnone tetrafluoroborate salts have also been synthesised and tested without any success.

Fortunately, a pyridine analogue such as 2-quinoline has successfully directed the cycloaddition reaction with alkyne difluoroboranes towards fully substituted pyrazole products. The structure of these compounds has been confirmed via X-ray crystallographic analysis, which showed strong coordination between boron and the nitrogen atom of the directing group.
Chapter 6. Mechanistic Studies for the Directed Cycloadditions

Between Sydnones and Alkynes

1. Introduction

As discussed in Chapter 5, the reactivity of several of the directing groups chosen for this study was not as general as compared to other examples of directed cycloaddition reactions. In addition, those that did proceed effectively with sydnones afforded the corresponding dialkynylborane adducts rather than the expected difluoroborane products. For these reasons we decided to perform mechanistic studies on this reaction in order to account for the differences between sydnone cycloadditions and those carried out on tetrazines, triazines and 2-pyrones.

We employed NMR spectroscopy as a means to monitor these reactions due to the variety of nuclei that can be analysed, the relatively high sensitivity and the speed of the analysis, allowing the reactions to be studied in real time. Initially, 3 different nuclei were studied: $^1$H, $^{11}$B and $^{19}$F. For our purposes, $^{11}$B provided more information about the species involved in the reaction, mainly because this nucleus is present in all the species involved in the \textit{in situ} formation of the various alkynylboranes from a potassium alkynyltrifluoroborate and BF$_3$ (as the diethyl ether adduct) (Scheme 112).

\[
\text{R} = \text{BF}_3\text{K} \xrightarrow{\text{BF}_3\cdot\text{Et}_2\text{O}} \text{R} = \text{BF}_2 + \left(\text{R} = \text{BF}\right) + \left(\text{R} = \text{BF}_3\right) + \text{KBF}_4
\]

\textbf{Scheme 112.} Generation of alkynylborane species.
2. Initial optimisation

An exhaustive literature search showed that no spectroscopic experimental data was available regarding the process shown in Scheme 112. For this reason, we first decided to study the formation of the alkynylboranes using NMR spectroscopy in order to identify each component of this transformation. By doing this, it should be possible to identify which of the generated boranes reacts in the presence of sydnone to generate the corresponding pyrazole product.

To perform these studies, potassium ethynyltrifluoroborate 130 was initially chosen due to its simplicity, since it only possesses one proton. All the reactions were performed in deuterated CD$_2$Cl$_2$, being the closest deuterated analogue of the reaction solvent (1,2-dichloroethane) that could be accessed. However, potassium ethynyltrifluoroborate proved to be very insoluble in deuterated dichloromethane and no reaction was observed at all. However, solubility could be improved by simply switching the cation from potassium to tetraethylammonium (Scheme 113).

In this case, dissolution of the alkyne was achieved but inconsistent results were obtained in terms of conversion. This was attributed to the fact that, unlike in the case of KBF$_4$, the tetrafluoroborate salt does not precipitate and is therefore not removed from the reaction mixture. As the presence of tetrafluoroborate in solution could influence the equilibrium process, we hypothesised that we should revert to using potassium trifluoroborates for better consistency with the directed cycloaddition reactions.

In addition to this, Siebert managed to synthesise the tert-butyl trisalkynyl borane complex and reported experimental spectroscopic data. For this reason, the corresponding trifluoroborate was chosen as the model alkyne to follow the reaction. Accordingly, 3 equivalents of potassium tert-butylethynyl trifluoroborate 126 were subjected to 1 equivalent of BF$_3$·Et$_2$O in CD$_2$Cl$_2$ at 25 °C under an argon atmosphere and the reaction was monitored by NMR spectroscopy. After the addition of BF$_3$·Et$_2$O to the alkyne, precipitation of a white solid was observed, presumably KBF$_4$. Also, $^{11}$B NMR analysis of the supernatant showed the presence of three different species in solution, which were assigned to be the tri-, di- and mono-alkynylboranes, according to the equilibrium shown in Scheme 114.
Chapter 6. Mechanistic Studies for the Directed Cycloadditions

\[
\begin{align*}
&\text{t-Bu} & & \text{BF}_3\text{Et}_2\text{O} & & (1 \text{ eq.}) \\
&\text{CD}_2\text{Cl}_2 & & 25 \text{°C} & & \text{t-Bu} & & \text{BF}_2 & + & \left(\text{t-Bu} & & \right)_2\text{BF} & + & \left(\text{t-Bu} & & \right)_3\text{B} & + & \text{KBF}_4
\end{align*}
\]

**Scheme 114.** *In situ* generation of tert-butyl alkynylboranes.

It is important to note that due to the spectroscopic properties of the \(^{11}\text{B}\) nucleus, especially its fast T2 relaxation, broadening of signals often occurs impeding the observation of coupling constants. Menezes *et al.* studied this phenomenon in aryl and alkynyl trifluoroborates managing to improve the definition of \(^{11}\text{B}\) NMR spectra in d\(^6\)-dimethylsulfoxide by either increasing the temperature to increase the relaxation times of the boron nucleus or applying a modified pulse sequence.\(^{146}\) However, in our case, none of these options provided any enhancement of the \(^{11}\text{B}\) signals. Because of our Lewis acidic reaction conditions, the use of dimethylsulfoxide is incompatible; and when applying Menezes’ modified pulse sequence, the \(^{11}\text{B}\) NMR signals remained broad. For this reason, our optimal system for NMR analysis of the borane equilibration consisted of the use of standard borosilicate glass NMR tubes, CD\(_2\)Cl\(_2\) and 25 °C.

Figure 16 shows the evolution over 4 hours of the trifluoroborate salt in the presence of BF\(_3\)·Et\(_2\)O at 25 °C. The percentage values show the distribution of all the boron-containing species over time.

Despite the lack of experimental evidence concerning the establishment of the described equilibrium, Siebert and co-workers have reported spectroscopic experimental data for the trisalkynylborane complex 167 in CDCl\(_3\) (\(^{11}\text{B}\) (64 MHz) = 38 ppm (\(\Delta\text{J}/2 = 580 \text{ Hz}\)),\(^{145}\) which allowed the identification of this intermediate in our reaction mixture by analogy. Control experiments using both CDCl\(_3\) and CD\(_2\)Cl\(_2\) showed that \(^{11}\text{B}\) chemical shifts are practically the same in these solvent systems, making possible the direct comparison between spectra recorded under both conditions.

Following Siebert’s work, signal c in Figure 16 was assigned to trisalkynylborane 167. Next, since no experimental data was available for difluoroboranes 165 and 166, we turned our attention to the expected coupling patterns for these species in \(^{11}\text{B}\) NMR. For the –BF moiety, a doublet would be expected since \(I(\text{\(^{19}\text{F}\)}) = 1/2\). However, for the –BF\(_2\) analogue, a triplet should be expected due to the two F nuclei.
Chapter 6. Mechanistic Studies for the Directed Cycloadditions

![Chemical reaction diagram]

Figure 16. Reaction between the potassium trifluoroborate and BF$_3$·Et$_2$O in CD$_2$Cl$_2$ over time.

As mentioned before, due to the broadening of $^{11}$B NMR spectra, the B-F coupling was difficult to observe, which is illustrated in the spectra shown in Figure 16. For this reason, an effort was made to improve the resolution of the signals such as the use of Quartz NMR tubes (to reduce the background signal produced by the borosilicate glass from standard NMR tubes) or the screening of other solvents such as CDCl$_3$, CCl$_4$ or CD$_3$CN. Unfortunately, all of these measures proved to be unsuccessful. No enhancement was observed in terms of resolution in any case and we observed that the borane formation was hindered when switching to other solvent systems.

We next decided to run our model experiment in CD$_2$Cl$_2$ but slightly increasing the temperature to 30 °C to generate longer relaxation periods for the $^{11}$B nucleus. However, when using dichloromethane, the temperature range at which it remains liquid is a limitation due to its low boiling point (40 °C). Pleasingly, when recording $^{11}$B NMR spectra at 30 °C, a slight improvement in the definition of the signals was observed, providing further evidence for the detection of a triplet signal that was assigned to be the difluoroborane 165 (Figure 17).
According to the described equilibrium, signal $b$ was then assigned to correspond to monofluoroborane 166. This seemed reasonable since the bisalkynylfluoroborane should be more shielded than trisalkynylborane 167 due to the π donating effect of fluorine into the vacant orbital of boron, thus decreasing the chemical shift value of 166 vs. 167. To further support this assignment, other examples were found in the literature where systems composed of sequences like BF$_2$R – BF$_2$R – BF$_3$ showed the same trend in terms of $^{11}$B NMR chemical shifts. A general trend is observed whereby BFR$_2$ species are less shielded than BF$_2$R, and this one is less shielded than BF$_3$.\textsuperscript{147,148}

For example, Nöth and Wrackmeyer studied the effect of increasing the number of methyl substituents in BF$_3$ (Table 20).\textsuperscript{149}

**Table 20.** Shifts corresponding to methylboranes in CD$_2$Cl$_2$.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Me$_2$BF</th>
<th>MeBF$_2$</th>
<th>BF$_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta(^{11}$B) / ppm</td>
<td>59.0</td>
<td>28.1</td>
<td>11.6</td>
</tr>
<tr>
<td>$\delta(^{19}$F) / ppm</td>
<td>-21</td>
<td>-73</td>
<td>-128</td>
</tr>
</tbody>
</table>

Also, Odom and Ellis observed a similar decrease in chemical shifts when increasing the number of fluorine atoms in vinyl- and ethylborane substrates, as shown in Table 21.\textsuperscript{147}

**Table 21.** Shifts corresponding to vinyl- and ethylboranes in C$_6$D$_6$.

<table>
<thead>
<tr>
<th>Compound</th>
<th>(CH$_2$=CH)$_3$B</th>
<th>(CH$_2$=CH)$_2$BF</th>
<th>(CH$_2$=CH)BF$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta(^{11}$B) / ppm</td>
<td>56.4</td>
<td>42.2</td>
<td>22.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>Et$_3$B</th>
<th>Et$_2$BF</th>
<th>EtBF$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta(^{11}$B) / ppm</td>
<td>85.0</td>
<td>59.6</td>
<td>28.6</td>
</tr>
</tbody>
</table>

[a] Literature quotes negative values to denote decrease shielding. Values referenced in Table 21 are $|\delta|$, and are in line with chemical shift values of similar boranes.\textsuperscript{150}
As Figure 16 shows, difluoroborane 165 was the major species detected after treatment of the trifluoroborate salt with BF$_3$·Et$_2$O. However, after following the evolution of this equilibrium with time via $^{11}$B NMR analysis, the concentration of 165 (a) was dramatically reduced in favour of 166 (b) and especially 167 (c). This observation is consistent with the fact that the concentration of BF$_3$ also increased with time, which would be the expected result following the equilibration shown in Scheme 114 (Page 114).

The complete NMR characterisation data in CD$_2$Cl$_2$ for boranes 165, 166 and 167 is shown in Table 22.

**Table 22.** Characterisation data for the three boranes generated.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>$\delta$ ($^1$H) / ppm</th>
<th>$\delta$ ($^{11}$B) / ppm $^a$</th>
<th>$\delta$ ($^{19}$F) / ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>165 (-BF$_2$)</td>
<td>1.22 (singlet)</td>
<td>2.3 – 2.4 (triplet, $J$ = 33 Hz)</td>
<td>-134.3 to -134.8 (doublet, $J$ = 35 Hz)</td>
</tr>
<tr>
<td>166 (-BF)</td>
<td>1.23 (singlet)</td>
<td>21.5 – 22.5 (broad, $\Delta_{1/2}$ = 320 Hz)</td>
<td>-127.2 to -127.9 (multiplet)</td>
</tr>
<tr>
<td>167 (-BR$_3$)</td>
<td>1.28 (singlet)</td>
<td>34.3 – 34.7 (broad, $\Delta_{1/2}$ = 444 Hz)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

$^a$ For $^{11}$B NMR spectra BF$_3$·Et$_2$O was used as an internal reference at 0 ppm.
3. Study of the directed cycloaddition via NMR

Next, the directed cycloaddition with sydnones was considered. Previously reported DFT calculations performed on the pyrone–alkynyltrifluoroborate system have shown that the trisalkynylborane 167 is the reactive species towards cycloaddition. In this case, a disproportionation occurs prior to the cycloaddition generating 168 as the major borane and a post-cycloaddition disproportionation takes place to generate the most stable –BF₂ benzene adduct (170) from the –BAlk₂ corresponding products (169).³²⁷

In contrast, the sydnone–alkynyltrifluoroborate system afforded the pyrazole dialkynylborane exclusively and formation of the corresponding pyrazole difluoroborane was not detected in any case. Interestingly, even re-subjection of pyrazole dialkynylboranes to BF₃·Et₂O under various conditions did not result in the formation of the corresponding pyrazole difluoroboranes. Therefore, we were intrigued by the behaviour of the borane species under our reaction conditions.

For this purpose, a premixed solution of potassium tert-butylethynyl trifluoroborate (3 eq.) and BF₃·Et₂O (1 eq.) in CD₂Cl₂ was added to 4-(2-pyridinyl)-3-phenylsydnone 159 (1 eq.) and the mixture subjected to NMR analysis. Results showed that before adding the sydnone, the three borane species were present (165, 166 and 167). However, after the addition, tris(tert-butylethynyl)borane 167 was no longer detected and formation of a new boron species, attributed and confirmed to be pyrazole product 162, was observed (Scheme 116). This result provided further evidence that the trisalkynylborane 167 was the active species from the equilibrium previously described in Scheme 114 towards cycloaddition.
Figure 18. NMR monitoring of the reaction introducing sydnone.

The evolution of the different boron species present in the system was also studied based on the $^{11}$B NMR experimental data acquired (Figure 18). As expected, once sydnone was added to the mixture of alkynyl trifluoroborate and BF$_3$·Et$_2$O, the proportion of trisalkynylborane (167, c) was dramatically reduced due to pyrazole formation by reaction with the sydnone. Interestingly, the amount of BF$_3$ after sydnone addition increased with time and a slight increase was also observed for the trisalkynylborane after the addition. This could suggest some equilibration between the different borane species could be taking place after the cycloaddition. If that was the case, more trisalkynylborane and BF$_3$ would be generated by consuming difluoroborane (165, a), which dramatically decreased with time. The monofluoroborane species (166, b) seemed to be less affected since its proportion remained almost unchanged with time.
To further confirm that the trisalkynylborane intermediate was the reactive borane species towards cycloaddition, tris(3,3-dimethyl-1-butynyl)borane 167 was prepared following an independent procedure reported by Siebert and treated with 3-phenyl-4-(2-pyridinyl)sydnone 159. Pleasingly, this resulted in the formation of the desired pyrazole 162 in a 40% yield (Scheme 117).

Scheme 117. Independent preparation of trisalkynylborane and reaction with sydnone.

In addition, to try to establish a reactivity pattern, alternative sydnone substrates were subjected to the optimal reaction conditions to investigate the formation of pyrazole products. For this purpose, sydnones 70 and 133 were reacted with the premixed trifluoroborate and BF$_3$·Et$_2$O, however, the recovery of the starting material was observed in both cases.

In the case of 3-phenylsydnone 70, the lack of reactivity proved that the presence of a directing group in the 4-position was essential to achieve the cycloaddition rate enhancement. In contrast, recovery of unreacted sydnone 133 was surprising since the dimethyl amide has been previously shown to be a successful directing group in other systems such as the pyrone or the triazine systems. In this case, lower Lewis basicity compared to the sydnone scaffold could be a feasible explanation, as discussed in previous chapters.

Scheme 118 shows the overall mechanistic pathway for the directed cycloaddition between alkynyl trifluoroborates and 3-phenyl-4-(2-pyridinyl)-sydnone 159 according to the evidence provided by the NMR mechanistic studies. Following these experimental results, the reaction seems to proceed via the trisalkynylborane species exclusively.
Scheme 118. Overall mechanistic pathway according to NMR mechanistic studies.
4. Conclusions

In summary, the monitoring of the reaction between potassium alkynyltrifluoroborate salts and BF$_3$·Et$_2$O has been successfully achieved by using NMR spectroscopy, establishing the formation of three different alkynylborane species which have been successfully identified.

Upon addition of 4-(2-pyridinyl)-3-phenylsydnone, formation of the corresponding pyrazole product has been observed by means of NMR proving that the trisalkynylborane is likely to be the reactive intermediate in the cycloaddition providing further mechanistic insight into the reaction. Nonetheless, when the same methodology has been applied to other sydnone substrates such as N-phenylsydnone or the 4-dimethylcarbamoyl analogue, no cycloaddition has been observed with the trisalkynylborane species, in accord with preliminary results.
Chapter 7. Diastereoselective Grignard Additions to tert-Butanesulfinyl Imine Sydnone

1. Introduction

From a synthetic point of view, the preparation of 5-(aminomethyl)pyrazole derivatives remains a challenge, since a limited number of reports to access this scaffold can be found in the literature, and to-date, we are not aware of any diastereoselective approaches. The first report related to the preparation of these pyrazole derivatives was published by Bowman and Tivey in the 1950s.\textsuperscript{151} In this study, 1,3-diketone 174 was the chosen building block to access the corresponding pyrazole by reaction with hydrazine and subsequent free-base formation from the corresponding phthalimide derivative. Pyrazole 175 has been employed as an effective bidentate ligand for copper, as shown by Driessen in 2002 (Scheme 119).\textsuperscript{152}

\begin{center}
\begin{align*}
\text{Scheme 119. Preparation of 5-(aminomethyl)pyrazoles following Bowman and Tivey’s method.}
\end{align*}
\end{center}

More recently, the preparation of 5-(aminomethyl)pyrazole derivatives has been successfully achieved via two main strategies: reductive amination of the corresponding aldehyde precursors and substitution reactions between an amine and the corresponding halide counterpart.

**Reduction strategies:**

\begin{align*}
\text{a)} & \quad \begin{align*}
\text{O} & \quad \text{NH}_3, \text{Ni} / \text{H}_2, 57\% \\
\text{N} & \quad \text{Ph}
\end{align*} \\
\text{O} & \quad \text{H}_2\text{N} \quad \text{H}_2\text{N} \\
\text{N} & \quad \text{N} \\
\text{Ph} & \quad \text{Ph}
\end{align*}

\begin{align*}
\text{b)} & \quad \begin{align*}
\text{O} & \quad \text{Me-N} \quad \text{NH}_2 \\
\text{N} & \quad \text{Ph} \\
\text{O} & \quad \text{H}_2\text{N} \quad \text{H}_2\text{N} \\
\text{N} & \quad \text{N} \\
\text{F} & \quad \text{F}
\end{align*} \\
\text{O} & \quad \text{Me-N} \quad \text{NH}_2 \\
\text{N} & \quad \text{Ph} \\
\text{O} & \quad \text{H}_2\text{N} \quad \text{H}_2\text{N} \\
\text{N} & \quad \text{N} \\
\text{F} & \quad \text{F}
\end{align*}

\begin{center}
\begin{align*}
\text{Scheme 120. Preparation of 5-(aminomethyl)pyrazole derivatives using reductive strategies.}
\end{align*}
\end{center}
For the reductive amination approach, hydrogenation of the in situ generated imine (Scheme 120.a)\textsuperscript{153} and the reductive amination of the corresponding 5-carbaldehyde pyrazole precursor using NaBH(OAc)\textsubscript{3} as the hydride source (Scheme 120.b) have been shown to be successful.\textsuperscript{154}

On the other hand, substitution reactions have also been shown to successfully provide aminomethyl pyrazole derivatives, and two prominent examples include the nucleophilic aromatic substitution of heteroaryl chlorides (Scheme 121.a)\textsuperscript{155} or an S\textsubscript{N}2-type reaction between an alkyl iodide and a primary amine (Scheme 121.b).\textsuperscript{156,157}

**Substitution reactions:**

\textbf{a)}

\[
\begin{array}{c}
\text{H}_2\text{N}\begin{array}{c}
\text{N} \\
\text{Me}
\end{array} + \begin{array}{c}
\text{H} \\
\text{O} \\
\text{N}
\end{array} \begin{array}{c}
\text{N} \\
\text{Cl}
\end{array} \begin{array}{c}
\text{N} \\
\text{Cl}
\end{array} \rightarrow \begin{array}{c}
\text{N} \\
\text{H} \\
\text{O} \\
\text{N}
\end{array} \begin{array}{c}
\text{N} \\
\text{Cl}
\end{array} \begin{array}{c}
\text{N} \\
\text{Cl}
\end{array}
\end{array}
\]

\[
\text{MeCN, 100 °C, 4 days, 13%}
\]

\textbf{b)}

\[
\begin{array}{c}
\text{H}_2\text{N} \begin{array}{c} \\
\text{N} \end{array} \begin{array}{c} \\
\text{Me}
\end{array} + \begin{array}{c} \\
\text{O} \\
\text{F}
\end{array} \begin{array}{c} \\
\text{N}
\end{array} \text{NH}_2 \rightarrow \begin{array}{c} \\
\text{O} \\
\text{F}
\end{array} \begin{array}{c} \\
\text{N}
\end{array} \begin{array}{c} \\
\text{Me}
\end{array} \begin{array}{c} \\
\text{N}
\end{array}
\end{array}
\]

\[
\text{MeCN, 100 °C, 4 days, 13%}
\]

Interestingly, enantiopure starting materials can be employed for these transformations (see Scheme 121.b) without observing any racemisation. However, no enantio- or diastereoselective approaches have been reported to date to access these specific scaffolds.

Nowadays, a well-established methodology for the diastereoselective synthesis of chiral amines relies on the use of sulfinyl imine-based auxiliaries, developed by Jonathan Ellman in the 1990s.\textsuperscript{158} Condensation of Ellman’s sulfinimide with carbonyl compounds, often assisted by Lewis acids, provides a sulfinyl imine intermediate, which is subsequently reacted with organometallic species such as Grignard reagents. This way, the synthesis of secondary or tertiary chiral amines can be achieved with high levels of stereoselectivity.\textsuperscript{158} Moreover, after the addition, the auxiliary fragment can be cleaved under mild acidic conditions generating the corresponding amine without loss of stereocontrol.
Chapter 7. Diastereoselective Grignard Additions to Sydnones

Due to the paucity of general methods to generate chiral 5-(aminomethyl)pyrazole derivatives we decided to explore Ellman’s chemistry on the sydnone scaffold to attempt to develop a general and diastereoselective aminopyrazole synthesis.
2. Starting material synthesis and initial optimisation

First, the preparation of the sulfinimine sydnone intermediate was required. To synthesise it, we chose 4-formyl-3-phenylsydnone 142 (see Scheme 101, Page 100, for the synthesis of this compound) as the starting material. Initial tests to generate the auxiliary were carried out following conditions previously reported by Ellman\textsuperscript{159} (Scheme 122). Unfortunately, no reaction was observed in the presence of copper(II) sulphate and Ellman’s reagent, and the starting material was recovered.

![Scheme 122. Initial attempt to prepare the auxiliary.](image)

We next decided to employ a stronger Lewis acid such as TiCl\textsubscript{4} to activate the carbonyl moiety, as Ellman already highlighted its promoting effect when employing more demanding substrates. Under these conditions, a screening of the equivalents of Ellman’s reagent (\(\text{((R)-2-methylpropane-2-sulfinamide)}\)) required for the condensation was carried out, starting from Ellman’s original conditions\textsuperscript{159} using 1.1 equivalents of the sulfinimine (Table 23).

Table 23. Optimisation of the condensation reaction between Ellman’s reagent and aldehyde 142.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents (“(x)”)</th>
<th>Conversion\textsuperscript{(a)}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>0 %</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>0 %</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>34%</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>54%</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>100% (up to 97% isolated yield)</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>100% (73% isolated yield)</td>
</tr>
</tbody>
</table>

\textsuperscript{(a)} Conversion determined using \(^1\text{H} \text{NMR spectroscopy on the crude mixtures.}
Optimisation showed that at least 5 equivalents of the auxiliary were required to reach full conversion (Table 23, Entries 5,6), since considerable amounts of aldehyde 142 were still detected in the crude mixtures where less auxiliary was employed (Table 23, Entries 1-4). Satisfactorily, reaction with excess (R)-2-methylpropane-2-sulfinamide in the presence of stoichiometric titanium(IV) tetrachloride provided the desired sulfinimine 176 in excellent yield after purification via silica gel flash column chromatography (Scheme 123). In addition, this reaction could be conveniently scaled up to multigram quantities and the resulting product could be stored under air at room temperature. Nonetheless, to fully prevent decomposition of sydnone 176, storage at -20 °C is recommended.

Scheme 123. Synthesis of sulfinimine sydnone derivative 176.

During the preparation of the auxiliary, different routes were studied for the synthesis of aldehyde 142 to try to increase the efficiency of the full synthetic sequence. The previously employed strategy (described in Chapter 5) consisted of the reduction of ester 141 to the corresponding alcohol with lithium borohydride followed by a benzylic oxidation mediated by manganese dioxide to deliver the target aldehyde.

Scheme 124. Different approaches for the synthesis of aldehyde 142.
Alternatively, the same intermediate was also accessed by reduction of the corresponding Weinreb amide 177, which could be generated from the corresponding carboxylic acid 131 (Scheme 124). The reduction-oxidation sequence afforded the desired product in good yields and on gram scale, with only one purification step required, albeit requiring long reaction times. On the other hand, the Weinreb amide approach offered shorter reaction times but each step required purification via flash chromatography and the overall yield was lower.

After the incorporation of the sulfinimide moiety on the sydnone ring was successfully achieved, the subsequent addition of several Grignard reagents was studied. Ethylmagnesium bromide was the organometallic chosen as model substrate to study the additions to sydnone 176, and the reactions were performed in tetrahydrofuran, which afforded good sydnone solubility and is a typical solvent employed in these transformations. Initially, we screened the temperature at which the additions were performed, and found that lower temperatures provided slightly better diastereomeric ratios (dr) (Table 24).

Table 24. Temperature screening for the Grignard addition.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature</th>
<th>dr[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0 °C</td>
<td>75:25</td>
</tr>
<tr>
<td>2</td>
<td>-78 °C</td>
<td>80:20</td>
</tr>
</tbody>
</table>

[a] Ratios determined using $^1$H NMR spectroscopy on the crude mixtures.

Next, the equivalents of the organometallic reagent were evaluated, performing the screening in THF at -78 °C. (Table 25). Varying the equivalents of Grignard reagent employed did not have a dramatic effect on the reaction, since full conversion was achieved in most cases and the diastereomeric ratios remained in the 80:20 range. However, the order of addition of the two reactive species was crucial, since the reaction performed well when the organometallic was added to the sulfinimide but complex mixtures and low conversions were obtained if the order was reversed (Table 25, Entry 3). When ethylmagnesium bromide was employed, 1.5 - 2 equivalents of the organometallic reagent afforded better results, as shown in Entries 2 and 4. However higher reproducibility
was achieved when employing 2 eq. instead of 1.5 eq. in further runs and during scaling up of the reaction.

Table 25. Equivalents of EtMgBr screening.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents</th>
<th>Time</th>
<th>Outcome[^{[a]}]</th>
<th>[\text{dr}]^[^{[b]}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>20 h</td>
<td>91% conv.</td>
<td>70:30</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>1 h</td>
<td>100% conv, 60% yield</td>
<td>80:20</td>
</tr>
<tr>
<td>3</td>
<td>1.5[^{[c]}]</td>
<td>16 h</td>
<td>Low conv., complex crude.</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>2 h</td>
<td>100% conv, 47% yield</td>
<td>80:20</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>2 h</td>
<td>100% conv, 35% yield</td>
<td>73:27</td>
</tr>
</tbody>
</table>

\[^{[a]}\] Conversion determined using \(^1\)H NMR spectroscopy on the crude mixtures; isolated yields. \[^{[b]}\] Ratios determined using \(^1\)H NMR spectroscopy on the crude mixtures. \[^{[c]}\] Inverse addition: sydnone added to Grignard reagent.

Surprisingly, when performing the model reaction in different solvents such as dichloromethane or toluene, no improvement was observed for the reaction diastereoselectivity when EtMgBr was used. In contrast, concentration proved to be important, since it had an effect in the stereochemical outcome of the reaction. Specifically, a substrate concentration of 0.085 M afforded the highest ratio under the optimal conditions (Table 26, Entry 2). Higher or lower values compared to the optimal proved to be less selective (Table 26, Entries 1, 3, 4).

Table 26. Concentration screening for the reaction with EtMgBr in THF.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Concentration</th>
<th>[\text{dr}]^[^{[b]}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.110 M</td>
<td>63:37</td>
</tr>
<tr>
<td>2</td>
<td>0.085 M</td>
<td>80:20</td>
</tr>
<tr>
<td>3</td>
<td>0.034 M</td>
<td>66:34</td>
</tr>
<tr>
<td>4</td>
<td>0.017 M</td>
<td>71:29</td>
</tr>
</tbody>
</table>

\[^{[a]}\] Ratios determined using \(^1\)H NMR spectroscopy on the crude mixtures.
Throughout the optimisation study, isolated yields of the desired products were found to vary across several runs, after purification by flash chromatography. Even when using different supports such as silica gel, florisil or basic alumina, yields remained below 50%.

We have attributed these observations to the low stability of the generated adducts to the chromatographic support. Indeed, evidence for this was obtained by dissolving a clean sample of compound 182 in dichloromethane in the presence of silica gel. After 3 h, only 59% of the mass was recovered upon filtration and removal of volatiles *in vacuo*. NMR spectroscopy confirmed that only clean sydnone 182 was recovered, albeit with a low mass balance.

Despite this fact, the optimal conditions for the Grignard addition involved the addition of 2 equivalents of EtMgBr to the substrate at -78 °C in THF at 0.085 M concentration and a reaction time of 4 h.
3. Stereochemical assignment

Next, we focused our attention on the stereochemical assignment of the obtained diastereomers. The determination of the absolute configuration of at least one pair of analogues of the series was required in order to develop a stereochemical model of the additions. For this purpose, 2 equivalents of ethylmagnesium bromide were added to sulfinimine \( \text{176} \) and the two diastereomers generated were separated by flash chromatography on basic alumina.

\[
\begin{align*}
\text{EtMgBr (2.0 eq.)} & \quad \text{(THF, -78 °C, 4 h)} \\
\text{176} & \quad \begin{array}{c}
\text{Et,} \\
\text{t-Bu}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{178} & \quad \begin{array}{c}
\text{Et,} \\
\text{t-Bu}
\end{array} \\
47\% \text{ (dr = 80 : 20)}
\end{align*}
\]

Scheme 125. Ethylmagnesium bromide addition.

Fortunately, the minor isomer obtained in the reaction (\( \text{178b} \)) turned out to be a solid, and crystals could be grown after recrystallisation from dichloromethane. X-ray crystallography analysis of the crystals allowed the determination of the configuration at both stereogenic centres, and these were assigned as \((R,S,S)\) for the minor isomer (Figure 19).

![Figure 19](relative_configuration.png)

Figure 19. Relative configuration for the minor isomer obtained from its X-ray structure. After X-ray analysis, the crystal was analysed by NMR spectroscopy and confirmed to be the minor diastereomer \( \text{178b} \).

By analogy, the absolute configuration of the major isomer \( \text{178a} \) was assigned as the \((R,S,R)\) diastereomer, as depicted.
4. Scope expansion

Having optimised the reaction and confirmed product stereochemistry in one case, we decided to explore the potential of this methodology by evaluating different Grignard reagents. When possible, commercially available reagents were employed and titrated using the phenanthroline/menthol system.\textsuperscript{160} In the cases where the corresponding organometallic species were not available, they were freshly prepared from the corresponding bromide in the presence of magnesium and iodine promoter (Scheme 126).

\[
\text{R-Br} \rightarrow_{\text{THF, } 60^\circ C, 2 \text{ h}}^{\text{Mg (2 eq.), I}_2 \text{ (cat.)}} \text{R-MgBr}
\]

\textbf{Scheme 126. Preparation of Grignard reagents.}

Alkyl (EtMgBr) and aryl (PhMgBr) derivatives were accessed using these diastereoselective additions in moderate to good yields and good dr ratios. Next, we were interested in the incorporation of alkene and alkyne-containing tethers which could potentially further participate in intramolecular cycloadditions with the sydnone core to generate polycyclic pyrazoline and pyrazole derivatives. Unfortunately, when performing the additions in THF, no selectivity was achieved and mixtures were generated in dr = 1:1 ratios in most cases (Scheme 127).

\textbf{Scheme 127. Scope of the Grignard additions in THF.}

Stereochemical assignment made by inference relative to the ethyl example (178).
Again, the generated products appeared to be unstable to purification by flash chromatography, especially in the presence of alkyne and alkene functionalities, providing a rationale for the lower isolated yields in these cases. Also, except for ethynylmagnesium bromide, which is commercially available, problems were encountered when trying to prepare other alkynylmagnesium bromide analogues, presumably due to deprotonation and dimerization or elimination of the resulting intermediates, which failed to react with the sydnone scaffold.

In an attempt to try to improve the diastereomeric ratios for the alkenyl and alkynyl substrates, some additions were also performed in dichloromethane. Satisfactorily, this change of solvent had a huge impact on the selectivity, providing $\text{dr} > 80:20$ in most cases, albeit with low to moderate isolated yields (Scheme 128).

During these experiments we identified another factor that turned out to be crucial for achieving high diastereoselectivity, which is the rate of addition of the organometallic reagent. When studying the addition of allylmagnesium bromide to the sydnone auxiliary 176, it was found that the slower the addition of the Grignard reagent to the substrate at -

\[ \text{Scheme 128. Scope of the Grignard additions in CH}_2\text{Cl}_2. \]
Stereochemical assignment was performed by inference relative to the ethyl example (178).
78 °C, the better the selectivity towards the major diastereoisomer (R,S,R) in both solvents (tetrahydrofuran and dichloromethane) (Scheme 129). For this reason, the addition of the organometallic species was always performed slowly, over 5 minute periods. However, it should be noted that the addition of the organometallic reagents was performed at room temperature, and since the reaction mixtures were at -78 °C, considerable temperature gradients were generated and not controlled, which we believe could be causing inconsistent results.

![Scheme 129. Study of the rate of addition of allylmagnesium bromide.](image)

Returning to the assignment of the product stereochemistry, we noted that in the 1H NMR spectra of the products, the chemical shifts of all the analogues seemed to follow a consistent pattern, suggesting that all the major isomers of the series had the same configuration. Specifically, the chemical shift of the -NH- proton for the minor isomer was always found to be shifted upfield relative to the major isomer. This trend was observed for all sydnone analogues shown in Schemes 127 and 128, except in the case of phenylmagnesium bromide addition whereby the diastereomers could not be easily resolved in the NMR spectrum. Table 27 summarises the shifts observed in the analysed pairs.

Table 27. NMR shifts for the sydnone adducts.

<table>
<thead>
<tr>
<th>Configuration of the generated adduct</th>
<th>δ(NH) / ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S) - Minor</td>
<td>3.70 - 4.00</td>
</tr>
</tbody>
</table>
The application of this methodology allowed access to a range of sydnone derivatives incorporating alkene moieties (181-185) that could participate in intramolecular cycloaddition processes, which were next explored.
Chapter 7. Diastereoselective Grignard Additions to Sydnones

5. Cycloadditions with the Grignard adducts

Once a range of alkene-containing sydnones had been obtained, we wondered if they could be subjected to thermal cycloaddition conditions to generate the corresponding bicyclic pyrazoline intermediates (Scheme 130). Although the small ring bicyclic compounds were likely to be too strained to be kinetically accessible, we were optimistic that larger ring systems could be synthesised.

![Chemical Structures]

Scheme 130. Envisaged intramolecular cycloaddition strategy.

To investigate whether this transformation would be successful, three different sets of conditions were screened with substrates 181-185: (a) heating at 160 °C in xylenes for 16-24 h, (b) heating at 110 °C in toluene during the same period of time and finally, (c) performing the cycloadditions at 80 °C in dichloroethane for 16-24 h.

Unfortunately, conditions a proved to be too harsh for any of the sydnones and only degradation was observed together with polymerisation, detected due to broadening of the NMR spectra. When heating at 110 °C (conditions b), mass spectrometry showed signals corresponding to the target pyrazolines for substrates 182, 183 and 184 together with the corresponding pyrazoles; which we hypothesised were generated via air oxidation of the corresponding pyrazoline products. Unfortunately, however, column chromatography failed to isolate any of these compounds, likely because of their low stability. Finally, running these reactions at 80 °C (conditions c) furnished unreacted starting material, suggesting that this temperature was not high enough to overcome the energetic barrier for the thermal cycloaddition to occur.
The problems encountered with this strategy prompted us to explore an alternative approach consisting of the incorporation of an alkyne tether to the products of the diastereoselective addition to attempt, in this manner, an intramolecular cycloaddition with the sydnone ring (Scheme 131).

![Scheme 131. Alternative intramolecular cycloaddition strategy.](image)

For this purpose, we studied the incorporation of propargylic and homopropargylic moieties which would provide, after cycloaddition, the corresponding 5- and 6-membered ring derivatives using conditions previously developed within the group for the alkylation of amines.\textsuperscript{161}

![Figure 20. Expected bicyclic pyrazole cores after cycloaddition.](image)

To access the bicyclic scaffold 186, deprotonation of the corresponding amine with sodium hydride and subsequent alkylation with propargyl bromide in the presence of the phase-transfer catalyst tetrabutylammonium iodide (TBAI) afforded the corresponding alkynylated product 188 (Scheme 132).

![Scheme 132. Propargylation of sydnone 178a.](image)

Next, sydnone 188 was heated to 110 °C in a sealed tube and satisfactorily, the desired pyrazole was isolated after silica gel flash chromatography in 53% yield after 16 h (Scheme
Attempts to increase the isolated yield employing other chromatography supports were carried out, but no improvement was observed when using alumina or florisil.

In addition, we wondered whether the application of the previously developed copper-promoted cycloadditions reactions could be beneficial for this transformation, and so the effect of adding both Cu(OTf)₂ and Cu(OAc)₂·H₂O to the intramolecular reaction was studied.

Table 28. Optimisation of the copper-promoted cycloaddition.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Conditions</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)₂ (1 eq.)</td>
<td>o-DCB, 140 °C, 2 h</td>
<td>- (Degradation)</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)₂·H₂O (1 eq.)</td>
<td>o-DCB, 140 °C, 5.5 h</td>
<td>23%</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)₂·H₂O (1 eq.)</td>
<td>PhMe, 110 °C, 5 h</td>
<td>40%</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)₂·H₂O (1 eq.)</td>
<td>DCE, 80 °C, 4 h</td>
<td>24%</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)₂·H₂O (1 eq.)</td>
<td>DCE, 80 °C, 6 h</td>
<td>26%</td>
</tr>
</tbody>
</table>

When one equivalent of Cu(OTf)₂ was added to sydnone 188 and the mixture subjected to the previously developed conditions (o-DCB, 140 °C) for 2 h, no desired pyrazole was detected. Instead a considerable mass loss and degradation of the starting material were observed (Table 28, Entry 1). On the other hand, the addition of stoichiometric amounts of copper(II) acetate proved to be more successful, since the desired pyrazole was isolated in all cases within a shorter time period (Table 28, Entries 2-5). Performing the reaction at 140 °C provided product 189 in low yield (Entry 2), and we believed that this could be attributed to unnecessarily harsh reaction conditions. For this reason, milder reaction temperatures
were tested, being 110 °C over a period of 5 h the set of conditions providing the highest yield (Entry 3).

Also, following the well-established conditions reported by Ellman, cleavage of the auxiliary using hydrochloric acid in methanol could be successfully achieved generating the deprotected analog of pyrazole 189.

Encouraged by the good results obtained for the 5-membered bicyclic scaffold, an analogous strategy was conceived for the 6-membered ring analogue employing homopropargyl bromide as the alkyne source. However, during our attempts to prepare the cycloaddition substrate, no alkylation product was detected after 16 h at room temperature. To try to improve the reaction, the use of a different leaving group on the alkyne was tested. Unfortunately, however, the homopropargyl methanesulfonate-(OMs) was also unsuccessful, even when heating the reaction in refluxing THF for 16 h. (Scheme 134).

An alternative set of conditions also developed within the group was attempted next, where sydnone 178a was treated with NaOH and K$_2$CO$_3$ for the deprotonation and using homopropargyl bromide as the alkylating agent in refluxing toluene. Disappointingly, the same lack of reactivity was observed, and the unreacted sydnone was recovered (Scheme 135).
In all cases, sydnone \(178a\) was recovered unreacted but the corresponding alkynes couldn’t be recovered in any case. This fact suggested that the alkyne could be participating in side reactions that would prevent the formation of the desired product. We hypothesised that the activated protons adjacent to the alkyne moiety could participate in an E2 elimination process triggered by amine \(178a\) after being deprotonated with sodium hydride, as depicted in Scheme 136. This would cause the degradation of the corresponding homopropargylic halide into enyne \(190\), which could easily evaporate making impossible the detection of any alkyne residue.

Scheme 136. Elimination pathway for homopropargylic reagents.

Due to the practical impossibility to generate any homopropargylic substrates, the generation of 6-membered bicyclic pyrazole scaffolds was abandoned.
6. Proposed model to explain stereochemistry

The determination of a crystal structure for one of the diastereomers obtained from the addition of ethylmagnesium bromide to sulfinimine 176 allowed the determination of the relative configuration of the pair of diastereomers 178a and 178b (Figure 21).

When comparing these results with the model developed by Ellman, we were surprised to find that the outcome of the sydnone sulfinimine addition was the opposite to the one expected following Ellman’s work. When employing the (R)-auxiliary, literature showed that the configuration of the new stereogenic centre of the major isomer generated should be (S). This can be rationalised due to coordination of the Mg centre of the organometallic reagent to the oxygen of the auxiliary, favouring a closed transition state, especially when non-coordinating solvents such as dichloromethane are employed (Figure 22). This closed transition state, in turn, favours the delivery of the nucleophile to the back face generating the corresponding (S) product.

As X-ray crystallography had showed that in the sydnone case the major isomer generated corresponded to the (R) product, we hypothesised an alternative model to explain our stereochemical outcome, based on a different coordination of the Mg centre to the Lewis basic substrate.

We believe that the exocyclic oxygen (O6) from the sydnone ring plays a coordinating role towards the Mg centre thus altering the typical coordination pattern with the sulfinimide auxiliary. In this case, an open transition state is suggested, which would favour the
addition of the R group from the opposite side, thus generating the opposite diastereomer, as observed with the sydnone substrate (Figure 23).

![Hypothesised model for the sydnone case.](image)

To gather further evidence for the effect of the O₆ oxygen in controlling reaction stereoselectivity, we wanted to use an alternative substrate that did not possess a Lewis basic atom. For this reason, the pyrazole core was chosen, since it is essentially analogous to the sydnone but without the oxygen centres.

In order to study the diastereoselectivity of the Grignard addition, the analogous pyrazole sulfinimine auxiliary had to be synthesised, and 1-phenyl-1H-pyrazole was the starting material of choice, since it is commercially available. After formylation of the lithiated intermediate with dimethylformamide, condensation of the corresponding aldehyde 191 with the Ellman auxiliary in the presence of TiCl₄ afforded the desired sulfinimine 192.

![Scheme 137. Synthesis of the pyrazole sulfinimine analogue 192.](image)

Next, the addition of ethylmagnesium bromide to substrate 192 was carried out, testing both tetrahydrofuran and dichloromethane as solvents under the standard conditions employed for the sydnone substrates. In this case, tetrahydrofuran was the solvent of choice, since full conversion could be achieved after 4 h, generating the pair of diastereomers in a dr = 88:12 (Scheme 138).

![Scheme 138. Addition of ethylmagnesium bromide to pyrazole 192.](image)
Disappointingly, both diastereomers for the ethyl pyrazole adduct 193 were isolated as oils, hence ruling out X-ray crystallography as a means to confirming their relative stereochemistry.

To try to establish a relationship between the configuration of the ethyl sydnone analogues 178 and the corresponding pyrazoles 193, an alternative approach was conceived, consisting of the transformation of the sydnone analogue into the corresponding pyrazole by means of a cycloaddition reaction. This methodology relied on the fact that a cycloaddition with trimethylsilyl acetylene followed by removal of the -SiMe$_3$ group should not epimerise the stereogenic centre of interest, thus confirming whether both the sydnone and the pyrazole models provided the same stereochemical outcome.

Accordingly, cycloaddition conditions were screened for substrate 178a, and we found that performing the reaction in the absence of solvent was required to afford the desired product. Thus, by employing an excess of trimethylsilylacetylene in a sealed tube, pyrazole 194 was generated in 42% yield after purification via flash chromatography. Next, the removal of the TMS group with a 1.0 M solution of tetrabutylammonium fluoride in refluxing THF was successfully achieved generating the desired disubstituted pyrazole 195 in 16% isolated yield (Scheme 139).

![Scheme 139. Synthesis of pyrazole 195 from the corresponding sydnone 178a.](image)

Finally, having successfully prepared pyrazole 195, the spectroscopic data for this substrate was compared with the corresponding pyrazole adduct 193 generated when adding ethylmagnesium bromide to the pyrazole sulfinimine. Surprisingly, both $^1$H NMR spectra were found to be identical. This result suggests that when using ethylmagnesium bromide, the stereochemical outcome for the addition to the sydnone and the pyrazole was the same, and so the same major isomer shown below was generated in both cases.

![193 (major) = 195](image)
To try to clarify this unexpected result, the generation of another pair of sydnone and pyrazole analogues was considered in order to gather further data. Therefore, we turned our attention to phenylmagnesium bromide as the organometallic of choice, and the addition reaction was performed on the pyrazole substrate 192. However, in this case we used dichloromethane, since full conversion a higher dr ratio obtained was achieved in this solvent (Scheme 140). It should be noted that, in all examples where both THF and CH₂Cl₂ were used, the major diastereomer was the same in both solvents.

Pleasingly, the major isomer of adduct 196 was isolated as a crystalline solid, and after recrystallisation from dichloromethane, its crystal structure could be determined, as shown in Figure 24. According to the crystal structure, the configuration of the generated stereogenic centre during the addition was assigned to be (S), in line with the classical Ellman model described in Figure 22.

To summarise the results up to this point, the Grignard addition reactions of sydnone substituted sulfonylimines appear to provide the opposite diastereomer to the one expected from Ellman’s model. On the other hand, pyrazoles appear to give different stereoisomers depending on the nature of the Grignard used. Currently, further investigations are being carried out to clarify this matter.
7. Conclusions

The diastereoselective addition of Grignard reagents to a sydnone sulfinimine derivative has been successfully developed, generating a range of sydnone derivatives containing interesting features such as a protected amine group, a newly controlled stereogenic centre and different functionalities such as alkyl, aryl, alkynyl and alkenyl residues.

Intramolecular cycloaddition reactions of the generated adducts were studied, failing to provide the desired pyrazole and pyrazoline products. However, an alternative propargylation-cycloaddition strategy has been achieved, allowing access to a bicyclic pyrazole core never previously reported before in the literature.

In addition, a model is currently being developed to understand the stereochemical outcome of the addition reactions to the sydnone core, which seems to provide the opposite major diastereomer expected following Ellman’s work.
Chapter 8. Concluding Remarks and Future Outlook

1. Concluding Remarks

The main objective of the present work has been to study the effect of Lewis acids in the cycloaddition reaction of sydnones and alkynes. Satisfactorily, we have developed regioselective processes to access both 1,3- and 1,4-disubstituted pyrazole scaffolds by means of cycloaddition reactions in the presence of copper(II) promoters. Interestingly, the nature of the Cu(II) salt has a dramatic effect on the regioselectivity of the reaction, as mechanistic studies have shown. This work clearly highlights the importance of performing mechanistic studies to fully understand chemical processes. Moreover, by attaching the Cu-salts to a solid support, the implementation of this method under continuous flow has been successfully carried out.

In a complementary study, the Lewis acid promoted “directed cycloaddition” of alkynylboranes with sydnones has been achieved using boron-based Lewis acids. Extensive directing group screening and NMR studies have highlighted the complexity of this reaction, with only pyridine-derived directing groups successfully directing the cycloaddition to give fully functionalised pyrazoles.

Finally, having confirmed Lewis acid interactions with the Lewis basic sydnone scaffold, we have successfully developed a diastereoselective addition of Grignard reagents (in this case exploiting Mg-based Lewis acids) onto sydnone substrates assisted by Ellman’s auxiliary; establishing an alternative route to incorporate amine functionalities onto highly-complex pyrazole structures.

2. Future Outlook

Three different areas have been explored within this thesis, and improvements can still be pursued in all of them. Specifically:

- **Copper-promoted cycloadditions**: although complete control over the regioselectivity of the reaction has been established by means of the Lewis acid choice and short reaction times are possible, reaction temperatures are still an issue, since \( T \geq 140 ^\circ C \) are still required. Strategies such as addition of ligands to coordinate copper could be investigated to lower the temperature of these reactions, allowing lower energy consumption, the use of greener solvents and broader applicability in terms of substrate scope and stability.
- **Directed cycloadditions:** the preliminary mechanistic studies described in this work showed how complex these processes are when the sydnone is the diene substrate. Very narrow directing group scope and lack of full understanding of the mechanism for this transformation are the main issues that could be addressed in the near future to make this methodology an even more powerful tool to access fully functionalised pyrazoles, incorporating handles such as boron for further functionalisation.

- **Diastereoselective Grignard additions:** the current low stability of the product amines and low yielding transformations undermine this route to accessing polycyclic aminopyrazole scaffolds with high potential. Preliminary studies already showed how the sulfinimine protecting group affects the stability of the sydnone substrates towards cycloaddition; an issue that should be addressed in the near future to enhance the yields of the whole synthetic sequence.
Chapter 9. Experimental Procedures

1. General Information

All reactions were conducted in flame-dried glassware under ambient conditions unless otherwise stated. THF and PhMe were dried before use over an alumina column. CH$_2$Cl$_2$ was distilled from calcium hydride. All commercially available solvents and reagents were used as supplied or purified using standard laboratory techniques according to methods described by Perrin and Armarego.$^{164}$

Thin layer chromatography was performed on aluminium-backed plates pre-coated with silica (Merck silica Kieselgel 60 F$_{254}$), which were developed using standard visualising agents: ultraviolet light, potassium permanganate or para-anisaldehyde. Flash chromatography was performed on silica gel (60 Å, mesh 40-63 µm). The solvent system used was graduated from 100% petroleum ether, increasing polarity towards the solvent mixture stated in the procedure. Melting points were obtained using a Gallenkamp apparatus, performed on recrystallised solids and are uncorrected. Optical rotation values were recorded on a Perkin Elmer 241 automatic polarimeter at 589 nm (Na-D line) with a path length of 1 dm, and are given in 10$^{-1}$ deg cm$^2$ g$^{-1}$ with concentrations (c) quoted in g 100 mL$^{-1}$.

$^1$H spectra were recorded on a Bruker AVII-500 (500 MHz), Bruker AVIII HD-400 (400 MHz), Bruker AVI-400 (400 MHz), Bruker AMX-400 (400 MHz) or DPX-400 (400 MHz). Proton magnetic resonance chemical shifts are reported from tetramethylsilane with the residual protic solvent resonance as the internal standard (CHCl$_3$: δ = 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, br = broad, m = multiplet). $^{13}$C NMR spectra were recorded on a Bruker AVII-500 (126 MHz), Bruker AVIII HD-400 (101 MHz), Bruker AVI-400 (101 MHz), Bruker AMX-400 (101 MHz) or DPX-400 (101 MHz). Carbon magnetic resonance chemical shifts are reported from tetramethylsilane with the solvent as the internal reference (CHCl$_3$: δ = 77.16 ppm). $^{19}$F NMR spectra were recorded on a Bruker AMX-400 (376 MHz) or Bruker AVIII HD-400 (376 MHz), and the chemical shifts are reported from trichlorofluoromethane. $^{11}$B NMR spectra were recorded on a Bruker AVIII HD-400 (128 MHz), and the chemical shifts are reported from BF$_3$·Et$_2$O as the internal standard (δ = 0.0 ppm). All chemical shifts are reported in ppm and the coupling constants (J) are quoted in Hz.
Infrared spectra were recorded on a Perkin-Elmer Paragon 100 FTIR spectrometer. Spectra were analysed as thin films on a KBr disc, and the most structurally relevant bands are quoted in cm\(^{-1}\). Bands are characterised as broad (br), strong (s), medium (m) or weak (w).

High-resolution mass spectra (HRMS) were performed on a MicroMass LCT operating in Electrospray mode (TOF ES+) or a MicroMass Prospec operating in FAB (FAB+), EI (EI+) or CI (CI+) modes. Ratios of pyrazole products were determined on crude reaction mixtures by gas chromatography-mass spectrometry (GCMS) analysis.
2. Experimental Procedures

**Synthesis of aminoacids**

### 2-(4-(Fluorophenyl)amino)acetic acid 86

To a stirred solution of 4-fluoroaniline (10.00 g, 89.93 mmol) in anhydrous dimethylformamide at rt, DIPEA (18.8 mL, 107.92 mmol) and after, ethyl bromoacetate (10.9 mL, 98.92 mmol) were added dropwise. The reaction was left stirring at 60 °C for 16 hours. The crude mixture was extracted with EtOAc, washed with LiCl (5%), dried over MgSO₄ and the solvent was removed in vacuo. The obtained solid was dissolved in H₂O / EtOH (4.5:1) and NaOH (4.95 g, 123.80 mmol) was added. The reaction was left stirring for 1.5 hours under reflux. Upon cooling, the mixture was acidified to pH = 5 using 10% HCl (aq) until precipitation of a solid was observed. 2-(4-(Fluorophenyl)amino)acetic acid was isolated after filtration as a pale brown solid (4.56 g, 33% yield).

**Melting point:** 134-136 °C (lit. 165-140 °C). ¹H NMR (d₆-DMSO, 400 MHz): δ 7.11 – 6.77 (m, 2H, PhH), 6.70 – 6.41 (m, 2H, PhH), 3.76 (s, 2H, -CH₂-). ¹⁹F NMR (d₆-DMSO, 376 MHz): δ -129.5 (tt, J = 9.0, 4.5 Hz). ¹³C NMR (d₆-DMSO, 100.6 MHz): δ 172.6, 154.5 (d, J = 231.0 Hz), 144.9, 115.2 (d, J = 22.0 Hz), 112.8 (d, J = 7.5 Hz), 45.1, 40.2.

### 2-((4-(Trifluoromethyl)phenyl)amino)acetic acid 87

To a stirred solution of sodium acetate (1.31 g, 16.01 mmol), glacial acetic acid (1.80 mL, 32.02 mmol), glyoxylic acid monohydrate (1.11 g, 12.01 mmol) and sodium cyanoborohydride (0.50 g, 8.01 mmol) in methanol at 0 °C, was added 4-(trifluoromethyl)aniline (1 mL, 8.01 mmol). The reaction was left stirring under a N₂ atmosphere for 2 hours. After, the crude was filtrated through celite, washed with 1% AcOH in EtOAc and brine was added. The aqueous layer was extracted with EtOAc, the organic fractions dried over MgSO₄ and the solvent was removed in vacuo. 2-((4-(Trifluoromethyl)phenyl)amino)acetic acid was isolated as a pale yellow solid (1.54 g, 88% yield).

**Melting point:** 130-132 °C (lit. 141-143 °C). ¹H NMR (d₆-DMSO, 400 MHz): δ 7.37 (d, J = 8.5 Hz, 2H, PhH), 6.66 (d, J = 8.5 Hz, 2H, PhH), 3.83 (s, 2H, -CH₂-). ¹⁹F NMR (d₆-DMSO, 376 MHz): δ -59.0. ¹³C NMR (d₆-DMSO, 100.6 MHz): δ 172.1, 126.1 (q, J = 3.5 Hz), 125.4 (q, J = 270.0 Hz), 115.7 (q, J = 32.0 Hz), 111.6, 111.6, 44.4.
**Synthesis of sydnones**

**General Procedure A**

To a stirred solution of the corresponding amino acid (1 eq.) in dimethoxyethane, was added isoamyl nitrite (1.1 eq.). The mixture was left stirring at room temperature for 5 hours. The reaction was concentrated *in vacuo* and EtOAc / diethyl ether (1:20) was added until a solid precipitated. The resulting solid was dissolved in CH$_2$Cl$_2$ at 0 °C under N$_2$ atmosphere and trifluoroacetic anhydride (1.5 eq.) was added dropwise. After 1.5 hours, the reaction was neutralized with saturated NaHCO$_3$ (aq). The organic layer was extracted with CH$_2$Cl$_2$, washed with brine, dried over MgSO$_4$ and the volatiles were removed *in vacuo*. The corresponding sydnone was isolated after recrystallisation from ethanol or CH$_2$Cl$_2$.

**N-Phenylsydnone 70**

Following the general procedure using N-phenylglycine (20.00 g, 132.30 mmol), N-phenylsydnone was isolated as a golden brown solid after recrystallisation from ethanol (16.18 g, 75% yield).

**Melting point:** 132-134 °C (lit. $^{94}$ 134 °C). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.64-7.76 (m, 5H, Ph$H$), 6.74 (s, 1H, Syd$H$). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 169.1, 135.0, 132.6, 130.4, 121.5, 93.8.

**N-Benzylsydnone 82**

Following the general procedure using N-benzylglycine (5.00 g, 24.30 mmol), N-benzylsydnone was isolated as a white brown solid after recrystallisation from ethanol (1.10 g, 26% yield).

**Melting point:** 65-67 °C (lit. $^{166}$ 65-70 °C). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.47-7.43 (m, 3H, Ph$H$), 7.40 – 7.36 (m, 2H, Ph$H$), 6.18 (s, 1H, Syd$H$), 5.35 (s, 2H, Ph-CH$_2$). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 169.3, 130.6, 130.3, 129.7, 128.8, 94.8, 57.4.
Chapter 9: Experimental Procedures

**N-(4-Fluorophenyl)sydnone 88**

Following the general procedure using 2-(4-(fluorophenyl)amino)acetic acid 86 (4.00 g, 23.64 mmol), N-(4-fluorophenyl)sydnone was isolated as a golden brown solid after recrystallisation from CH₂Cl₂ (2.75 g, 65% yield).

Melting point: 150-152 °C (lit. 154-156 °C). ¹H NMR (CDCl₃, 400 MHz): 7.81 – 7.70 (m, 2H, Ph H), 7.38 – 7.27 (m, 2H, Ph H), 6.72 (s, 1H, Syd H). ¹³C NMR (CDCl₃, 100.6 MHz): δ 168.9, 164.7 (d, J = 255.0 Hz), 131.1, 123.7 (d, J = 5.5 Hz), 117.7 (d, J = 5.5 Hz), 94.0.

**N-(4-(Trifluoromethyl)phenyl)sydnone 89**

Following the general procedure using 2-((4-(trifluoromethyl)phenyl)amino)acetic acid 87 (1.50 g, 6.85 mmol), N-(4-(trifluoromethyl)phenyl)sydnone was isolated as a pale orange solid after recrystallisation from ethanol (548 mg, 35% yield).

Melting point: 132-134 °C (lit. 131-133 °C). ¹H NMR (CDCl₃, 400 MHz): 7.98 – 7.85 (m, 4H, Ph H), 6.82 (s, 1H, Syd H). ¹⁹F NMR (CDCl₃, 377 MHz): δ -63.1. ¹³C NMR (CDCl₃, 100.6 MHz): δ 168.8, 137.3, 134.7 (q, J = 34.0 Hz), 127.8 (q, J = 3.5 Hz), 123.0 (q = 275.0 Hz), 122.1, 94.0.

**Synthesis of N-methylsydnone 83**

A solution of NaNO₂ (3.87 g, 56.12 mmol) in H₂O (12.5 mL) was added to a solution of sarcosine (5.00 g, 56.12 mmol) in HCl 20% (30 mL). The mixture was left stirring from 0 °C to rt for 2 hours. The organic layer was extracted with EtOAc, washed with brine, dried over MgSO₄ and the volatiles were removed in vacuo. The resulting oil was dissolved in 30 mL of CH₂Cl₂ at 0 °C with stirring under a N₂ atmosphere. Trifluoroacetic anhydride (11.8 mL, 84.18 mmol) was added dropwise to the mixture, which was left stirring at 0 °C to rt for 1.5 h. After that time, the reaction was neutralized with saturated NaHCO₃ and the organic layer was extracted with CH₂Cl₂, dried over MgSO₄ and the solvent was removed in vacuo. Further purification of the sydnone by filtration through a plug on silica gel (eluting solvents: petroleum ether / EtOAc) provided N-methylsydnone as a yellow oil (2.62 g, 47% yield).
**Synthesis of N-(4-methoxyphenyl)sydnone 84**

To a stirring solution of 4-methoxyaniline (10.00 g, 81.20 mmol) and sodium acetate (13.32 g, 162.40 mmol) in EtOH, ethyl bromoacetate (9.9 mL, 89.32 mmol) was added dropwise. The reaction was left stirring at reflux for 4 hours. The crude was concentrated *in vacuo*, dichloromethane was added and the resulting solid was filtered. The volatiles of the filtrate were removed *in vacuo* and the obtained solid was used without further purification. The crude solid was dissolved in H$_2$O / EtOH (4.5:1) and NaOH (4.87 g, 121.80 mmol) was added. The reaction was left stirring for 1 hour under reflux. Upon cooling, the mixture was acidified to pH = 4 using 10% HCl$_{(aq)}$ and the crude compound was directly used in the next step.

To a stirring solution of the obtained solid (8.00 g, 67.69 mmol) in dimethoxyethane, was added isoamyl nitrite (10.00 mL, 74.46 mmol). The mixture was left stirring at room temperature for 3 hours. The reaction was concentrated *in vacuo* and EtOAc / petroleum ether (1:20) was added until a pale brown solid precipitated. The resulting solid was dissolved in 40 mL of CH$_2$Cl$_2$ at 0 °C with stirring under a N$_2$ atmosphere. Trifluoroacetic anhydride (14.20 mL, 101.54 mmol) was added dropwise at 0 °C under N$_2$ atmosphere. After 1.5 hours, the reaction was neutralized with saturated NaHCO$_3$$_{(aq)}$. The organic layer was extracted with CH$_2$Cl$_2$, dried over MgSO$_4$ and the volatiles were removed *in vacuo*. N-(4-Methoxyphenyl)sydnone was isolated as a brown solid after recrystallisation from ethanol (5.12 g, 39% yield).

**Melting point:** 120-122 °C (lit.1 126 °C). $^1$H NMR (CDCl$_3$, 400 MHz): 7.64 (d, $J$ = 9.0 Hz, 2H, PMPH), 7.07 (d, $J$ = 9.0 Hz, 2H, PMPH), 6.67 (s, 1H, SydH), 3.89 (s, 3H, -OCH$_3$). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 169.2, 162.6, 127.9, 122.8, 115.4, 93.5, 96.0.
Synthesis of N-isopropylsydnone 85

\[
\text{NH}_2 + \text{BrCO}_2\text{Et} \xrightarrow{1) \text{Br} \text{NaOH}} \text{NCO}_2\text{H} \xrightarrow{2) \text{NaOH}} \text{NO} \xrightarrow{1) \text{NaNO}_2 + \text{HCl} \ 2) \text{TFAA}} \text{N}^+ \text{O} \text{N}
\]

To a stirring solution of sodium acetate (27.76 g, 338.35 mmol) and isopropylamine (1.5 mL, 169.18 mmol) in ethanol under a N\textsubscript{2} atmosphere, was added ethyl bromoacetate (15.9 mL, 143.80 mmol) dropwise. The reaction was left stirring under reflux for 1 hour. The reaction was cooled down, filtered to remove salts and the filtrate was concentrated in vacuo. The resulting solid was washed with CH\textsubscript{2}Cl\textsubscript{2} and filtered again, dried in vacuo and used without further purification. The crude solid was dissolved in H\textsubscript{2}O / EtOH (4.5:1) and NaOH (10.15 g, 253.72 mmol) was added. The reaction was left stirring for 1.5 hours under reflux. Upon cooling, the mixture was acidified to pH = 2 using 35% HCl\textsubscript{(aq)} and the resulting aminoacid was isolated by filtration giving a pale brown solid (17.18 g, 93% over 2 steps).

A solution of NaNO\textsubscript{2} (11.67 g, 169.15 mmol) in H\textsubscript{2}O (25 mL) was added to the crude. The mixture was left stirring at 0 °C for two hours. The organic layer was extracted with EtOAc, dried over MgSO\textsubscript{4} and the volatiles were removed in vacuo. The resulting solid was dissolved in 40 mL of CH\textsubscript{2}Cl\textsubscript{2} at 0 °C with stirring under a N\textsubscript{2} atmosphere. Trifluoroacetic anhydride (35.30 mL, 253.73 mmol) was added dropwise to the mixture, which was left stirring at rt for 1 h. After that time, the reaction was neutralized with saturated NaHCO\textsubscript{3} and the organic layer was extracted with CH\textsubscript{2}Cl\textsubscript{2}, dried over MgSO\textsubscript{4} and the solvent was removed in vacuo. N-Isopropylsydnone was isolated as a yellow solid after recrystallisation from CH\textsubscript{2}Cl\textsubscript{2} / petroleum ether (1.18 g, 11% yield).

**Melting point:** 46-48 °C (lit.\textsuperscript{168} 54-56 °C). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): 6.31 (s, 1H, SydH), 4.65-4.70 (m, 1H, iPrH), 1.67 (d, \textit{J} = 7.0 Hz, 6H, -CH(CH\textsubscript{3})\textsubscript{2}). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100.6 MHz): δ 169.5, 92.5, 57.7, 21.7.
**Thermal 1,3-dipolar cycloadditions between sydnones and alkynes**

**General procedure B**

A solution of the corresponding sydnone (1 eq.) and the corresponding alkyne (2 eq.) in o-dichlorobenzene in a sealed tube was left stirring at room temperature for 10-15 minutes and afterwards, heated to the corresponding appropriate temperature for a designated length of time. After cooling, the crude mixture was purified by flash chromatography on silica gel (eluting solvent: 5 % ethyl acetate in 60-40 petroleum ether, unless otherwise stated). The obtained product was recrystallized from CH$_2$Cl$_2$ – Petroleum ether (60:40).

Full characterisation of the pyrazole products can be found within the general procedure for the preparation of the title compounds using Cu(OTf)$_2$ and Cu(OAc)$_2$·H$_2$O-mediated cycloadditions.

**1,3-Diphenyl-1H-pyrazole (90a) and 1,4-diphenyl-1H-pyrazole (90b)**

Following the general procedure using N-phenylsydnone (100 mg, 0.62 mmol) and phenylacetylene (135 µL, 1.23 mmol), stirring for 24 h, the title pyrazoles were isolated as a yellow solid (104 mg, 76% yield, regioselectivity: 10:1).

**1-(PMP)-3-phenyl-1H-pyrazole (97a) and 1-(PMP)-4-phenyl-1H-pyrazole (97b)**

Following the general procedure using N-(4-methoxyphenyl)sydnone (100 mg, 0.52 mmol) and phenylacetylene (174 µL, 1.04 mmol), stirring for 22 h at 140 °C, the title pyrazoles were isolated as a pale brown solid (98 mg, 76% yield, regioselectivity: 10:1).

**3-Cyclohexenyl-1-phenyl-1H-pyrazole (105a) and 4-cyclohexenyl-1-phenyl-1H-pyrazole (105b)**

Following the general procedure using N-phenylsydnone (200 mg, 1.23 mmol) and 1-ethynylcyclohexene (290 µL, 2.47 mmol), stirring for 20 h at 150 °C, the title products were isolated as an orange oil (115 mg, 42% yield, regioselectivity: >95:5).
**Ethyl 1-phenyl-1H-pyrazole-3-carboxylate (91a) and 4-carboxylate (91b)**

Following the general procedure using N-phenylsydnone (200 mg, 1.23 mmol) and ethyl propiolate (250 µL, 2.47 mmol), stirring for 20 h at 150 °C, the title products were isolated as a yellow oil (177 mg, 66% yield, regioselectivity: 2:1).

**1-Isopropyl-3-phenyl-1H-pyrazole (92a) and 1-Isopropyl-4-phenyl-1H-pyrazole (92b)**

Following the general procedure using N-isopropylsydnone (75 mg, 0.59 mmol) and phenylacetylene (128 µL, 1.18 mmol), stirring for 16 h at 140 °C, the title products were isolated as a brown oil (40 mg, 36% yield, regioselectivity: >95:5).

**1,3-Diphenyl-5-(4-tolyl)-1H-pyrazole (94a) and 1,4-diphenyl-5-(4-tolyl)-1H-pyrazole (94b)**

Following the general procedure using N-phenyl-4-(4-tolyl)sydnone (100 mg, 0.40 mmol) and phenylacetylene (87 µL, 0.80 mmol), stirring for 20 h at 140 °C, the title products were isolated as a yellow oil (60 mg, 52% yield, regioselectivity: >95:5).
Cu(OTf)$_2$-mediated synthesis of 1,3-disubstituted-1H-pyrazoles

General procedure C

A solution of sydnone (1 eq.), the corresponding alkyne (2 eq.) and Cu(OTf)$_2$ (1 eq.) in o-dichlorobenzene (0.5 M) in a sealed tube was left stirring at room temperature for 15-20 minutes and afterwards, heated to 140 °C for a designated length of time. After cooling, the reaction mixture was quenched with 10 % HCl and water. The organic layer was extracted with CH$_2$Cl$_2$, neutralized with saturated NaHCO$_3$ (aq), washed with brine, dried over MgSO$_4$ and filtered. Finally, the volatiles were removed in vacuo. The crude product was purified by flash chromatography on silica gel (eluting solvent: 5 % ethyl acetate in 60-40 petroleum ether, unless other stated). The obtained product was recrystallized from CH$_2$Cl$_2$ – petroleum ether (60:40).

1,3-Diphenyl-1H-pyrazole 90a

Following the general procedure using N-phenylsydnone 70 (80 mg, 0.49 mmol) and phenylacetylene (108 µL, 0.99 mmol), stirring for 1 h, 1,3-diphenyl-1H-pyrazole was isolated as a pale yellow solid (75 mg, 69% yield, regioselectivity: >95:5).

Melting point: 76-80 °C (lit. 81-83 °C). $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.01 - 7.92 (m, 3H, ArH), 7.84 – 7.76 (m, 2H, PhH), 7.54 – 7.42 (m, 4H, PhH), 7.41 - 7.33 (m, 1H, PhH), 7.31 (t, J = 7.5 Hz, 1H, PhH), 6.79 (d, J = 2.0 Hz, 1H, PyzlH). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 153.0, 140.3, 133.2, 129.5, 128.8, 128.1 (x2), 126.4, 125.9, 119.1, 105.1.

1-Phenyl-3-(3-thiophenyl)-1H-pyrazole 110a

Following the general procedure using N-phenylsydnone 70 (80 mg, 0.49 mmol) and 3-ethylthiophene (97 µL, 0.99 mmol), stirring for 1 h, 1-phenyl-3-(3-thiophenyl)-1H-pyrazole was isolated as a yellow solid (18 mg, 16% yield, regioselectivity: >95:5).

Melting point: 80-83 °C (lit. 83-87 °C). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.93 (d, J = 2.5 Hz, 1H, PyzlH), 7.79 – 7.71 (m, 2H, ArH), 7.68 (dd, J = 3.0, 1.0 Hz, 1H, ArH), 7.59 (dd, J = 5.0, 1.0 Hz, 1H, ArH), 7.51 – 7.43 (m, 2H, ArH), 7.38 (dd, J = 5.0, 3.0 Hz, 1H, ArH), 7.33 – 7.23 (m, 1H,
ArH), 6.67 (d, J = 2.5 Hz, 1H, PyzlH). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 149.4, 140.3, 135.1, 129.6, 127.9, 126.4, 126.3, 126.1, 121.2, 119.2, 105.5.

1-(4-Methoxyphenyl)-3-phenyl-1H-pyrazole 9

Following the general procedure using N-(4-methoxyphenyl)sydnone 84 (95 mg, 0.49 mmol) and phenylacetylene (108 µL, 0.99 mmol), stirring for 1 h, 1-(4-methoxyphenyl)-3-phenyl-1H-pyrazole was isolated as an orange solid (71 mg, 57% yield, regioselectivity: >95:5).

Melting point: 96-98 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.94 – 7.88 (m, 2H, ArH), 7.86 (d, J = 2.5 Hz, 1H, PyzlH), 7.71 – 7.64 (m, 2H, PMPH), 7.47 – 7.39 (m, 2H, PhH), 7.37 – 7.29 (m, 1H, PhH), 7.03 – 6.95 (m, 2H, PMPH), 6.75 (d, J = 2.5 Hz, 1H, PyzlH), 3.86 (s, 3H, -OCH$_3$). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 158.3, 152.7, 134.2, 133.4, 128.8, 128.2, 128.0, 125.9, 120.9, 104.7, 55.7.

1-Benzyl-3-phenyl-1H-pyrazole 9a

Following the general procedure using N-benzylsydnone 82 (77 mg, 0.44 mmol) and phenylacetylene (96 µL, 0.88 mmol), stirring for 1 h, 1-benzyl-3-phenyl-1H-pyrazole was isolated as an orange solid (13 mg, 11% yield, regioselectivity: >95:5).

Melting point: 55-60 °C (lit. 169 58-61 °C). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.85 – 7.80 (m, 2H, ArH), 7.42 – 7.25 (m, 9H, ArH), 6.59 (d, J = 2.5 Hz, 1H, PyzlH), 5.37 (s, 2H, BnH). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 151.7, 136.7, 133.7, 130.8, 128.9, 128.7, 128.1, 127.8, 127.7, 125.8, 103.5, 56.2.

1-Isopropyl-3-phenyl-1H-pyrazole 92a

Following the general procedure using N-isopropylsydnone 85 (75 mg, 0.59 mmol) and phenylacetylene (128 µL, 1.17 mmol), stirring for 3.5 h, 1-isopropyl-3-phenyl-1H-pyrazole was isolated as a brown oil (56 mg, 51% yield, regioselectivity: >95:5).

$^1$H NMR (CDCl$_3$, 400 MHz): δ 7.86 – 7.80 (m, 2H, ArH), 7.46 – 7.37 (m, 3H, PyzlH, PhH), 7.33 – 7.27 (m, 1H, PhH), 6.55 (d, J = 2.5 Hz, 1H, PyzlH), 4.57 (hept, J = 6.5 Hz, 1H, -NCH(CH$_3$)$_2$), 1.56 (d, J = 6.5 Hz, 6H, -NCH(CH$_3$)$_2$). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 150.8, 134.0, 128.6, 127.4 (x2), 125.7, 102.4, 53.9, 23.1. FTIR: $\nu_{\text{max}}$ 3064 (w), 2978 (m), 2930 (m), 1606 (w), 1498 (m), 1457 (m), 1415 (w), 1385 (w), 1359 (w), 1343 (w), 1259 (m), 1220 (m), 1086 (w), 1073 (w), 1045 (w), 991 (w), 948 (w), 749 (s), 694 (s), 643 (w) cm$^{-1}$. HRMS: m/z [MH$^+$] calc. for C$_{12}$H$_{15}$N$_2$: 187.1205, found: 187.1230.
Chapter 9: Experimental Procedures

1-Ethyl-3-phenyl-1H-pyrazole 99a

Following the general procedure using N-ethylsydnone (70 mg, 0.61 mmol) and phenylacetylene (134 µL, 1.23 mmol), stirring for 2 h, 1-ethyl-3-phenyl-1H-pyrazole was isolated as a brown oil (59 mg, 56% yield, regioselectivity: >95:5).

$^1$H NMR (CDCl$_3$, 400 MHz): δ 7.84 – 7.80 (m, 2H, ArH), 7.43 – 7.37 (m, 3H, PyzlH, PhH), 7.33 – 7.27 (m, 1H, PhH), 6.55 (d, $J = 2.5$ Hz, 1H, PyzlH), 4.22 (q, $J = 7.5$ Hz, 2H, -NCH$_2$CH$_3$), 1.53 (t, $J = 7.5$ Hz, 3H, -NCH$_2$C$_3$H$_3$). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 151.3, 133.8, 129.6, 128.7, 127.5, 125.6, 102.7, 47.2, 15.8.

1-Methyl-3-phenyl-1H-pyrazole 100a

Following the general procedure using N-methylsydnone 83 (80 mg, 0.80 mmol) and phenylacetylene (175 µL, 1.60 mmol), stirring for 2 h, 1-methyl-3-phenyl-1H-pyrazole was isolated as a brown solid (71 mg, 56% yield, regioselectivity: >95:5).

Melting point: 49-53 °C (lit: 54-55 °C$^{171}$). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.85 – 7.77 (m, 2H, ArH), 7.45 – 7.26 (m, 4H, PyzlH, PhH), 6.54 (d, $J = 2.5$ Hz, 1H, PyzlH), 3.94 (s, 3H, -NCH$_3$). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 151.3, 133.6, 131.4, 128.7, 127.5, 125.6, 102.9, 39.1.

1,3-Diphenyl-5-(4-tolyl)-1H-pyrazole 94a

Following the general procedure using N-phenyl-4-(4-tolyl)sydnone 93 (100 mg, 0.40 mmol) and phenylacetylene (87 µL, 0.8 mmol), stirring for 2 h, 1,3-diphenyl-5-(4-tolyl)-1H-pyrazole was isolated as a brown solid (39 mg, 31% yield, regioselectivity: >95:5).

Melting point: 49-53 °C (lit: 54-55 °C$^{171}$). $^1$H NMR (CD$_2$D$_4$, 400 MHz): δ 8.46 – 8.37 (m, 2H, ArH), 7.67 – 7.61 (m, 2H, PhH), 7.59 – 7.53 (m, 2H, ArH), 7.46 – 7.40 (m, 3H, ArH), 7.39 – 7.34 (m, 2H, ArH), 7.24 – 7.17 (m, 3H, ArH), 7.11 – 7.06 (m, 2H, ArH), 7.00 (s, 1H, PyzlH), 2.27 (s, 3H, -CH$_3$). $^{13}$C NMR (CD$_2$D$_4$, 100.6 MHz): δ 152.3, 144.6, 141.1, 138.2, 134.2, 129.4, 129.1, 129.0, 128.9, 128.6, 128.2, 127.1, 126.3, 125.5, 105.6, 21.1.
**Cu(OAc)$_2$·H$_2$O-mediated synthesis of 1,4-disubstituted-1H-pyrazoles**

**General procedure D**

![Cu(OAc)$_2$·H$_2$O-mediated synthesis of 1,4-disubstituted-1H-pyrazoles](image)

To a stirring solution of sydnone (1 eq.) and Cu(OAc)$_2$ monohydrate (1 eq.) in o-dichlorobenzene (0.21 - 0.25 M) under N$_2$ at room temperature, was added the alkyne (2 eq.). The mixture was left stirring at room temperature for 15-20 minutes and afterwards, heated at 150 °C for the designated length of time. After cooling, the reaction mixture was quenched with 10 % HCl(aq) and water. The organic layer was extracted with CH$_2$Cl$_2$, neutralized with saturated NaHCO$_3$ (aq), washed with NaOH (1 M) and brine, dried over MgSO$_4$ and filtered. Finally, the volatiles were removed in vacuo. The crude product was purified by flash chromatography on silica gel (eluting solvent: 5 % ethyl acetate in 60-40 petroleum ether, unless otherwise stated). The obtained product was recrystallized from CH$_2$Cl$_2$ – petroleum ether (60:40).

**1,4-Diphenyl-1H-pyrazole 9b**

Following the general procedure using N-phenylsydnone 70 (200 mg, 1.23 mmol) and phenylacetylene (270 µL, 2.47 mmol), stirring for 3.5 h, 1,4-diphenyl-1H-pyrazole was isolated as a yellow solid (199 mg, 73% yield, regioselectivity: >95:5).

**Melting point:** 92-94 °C (Lit: 95-96 °C$^{172}$). $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.17 (s, 1H, PyzlH), 8.01 (s, 1H, PyzlH), 7.80 – 7.71 (m, 2H, PhH), 7.61 – 7.54 (m, 2H, PhH), 7.53 – 7.45 (m, 2H, PhH), 7.44 – 7.36 (m, 2H, PhH), 7.30 – 7.27 (m, 2H, PhH).

$^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 140.2, 138.9, 132.2, 129.6, 129.1, 127.0, 126.7, 125.8, 125.0, 123.4, 119.2.

**4-Cyclohexenyl-1-phenyl-1H-pyrazole 10b**

Following the general procedure using N-phenylsydnone 70 (200 mg, 1.23 mmol) and 1-ethynylcyclohexene (290 µL, 2.47 mmol), stirring for 2.5 h, 4-cyclohexenyl-1-phenyl-1H-pyrazole was isolated as an orange solid (195 mg, 71% yield, regioselectivity: >95:5).

**Melting point:** 42-48 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.83 (s, 1H, PyzlH), 7.78 (s, 1H, PyzlH), 7.70 – 7.63 (m, 2H, PhH), 7.49 – 7.39 (m, 2H, PhH), 7.30 – 7.22 (m, 1H, PhH), 6.11 (m, 1H, =CH-), 2.39 – 2.28 (m, 2H, -CH$_2$-), 2.22 – 2.14 (m, 2H, -CH$_2$-), 1.82 – 1.62
(m, 4H, -CH$_2$-). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 140.3, 137.9, 129.5, 128.1, 126.9, 126.3, 122.4, 122.0, 118.9, 27.6, 25.5, 22.8, 22.4. FTIR: $\nu_{\text{max}}$ 3050 (w), 2928 (s), 2833 (w), 1717 (w), 1674 (w), 1601 (s), 1558 (m), 1504 (s), 1462 (w), 1448 (m), 1406 (m), 1337 (w), 1229 (m), 1194 (w), 1034 (m), 953 (s), 840 (w), 756 (s) cm$^{-1}$. HRMS: m/z [MH$^+$/] calc. for C$_{15}$H$_{16}$N$_2$: 225.1392, found: 225.1387.

4-Cyclohexyl-1-phenyl-1H-pyrazole 105b

Following the general procedure using N-phenylsydnone 70 (100 mg, 0.62 mmol) and 1-ethynylcyclohexane (161 µL, 1.24 mmol). In this case, a further 2 equivalents of alkyne were added after 2.5 h, and heated for a further 1.5 h. 4-Cyclohexyl-1-phenyl-1H-pyrazole was isolated as a yellow oil (140 mg, 100 % yield, regioselectivity: >95:5).

$^1$H NMR (CDCl$_3$, 400 MHz): δ 7.69 (s, 1H, PyzlH), 7.67 – 7.61 (m, 2H, PhH), 7.58 (s, 1H, PyzlH), 7.47 – 7.36 (m, 2H, PhH), 7.29 – 7.19 (m, 1H, PhH), 2.63 – 2.50 (m, 1H, -CH$_2$-), 2.05 – 1.95 (m, 2H, -CH$_2$-). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 140.4, 139.7, 130.4, 129.4, 126.0, 123.5, 118.9, 34.5, 34.2, 26.5, 26.2. FTIR: $\nu_{\text{max}}$ 3050 (w), 2925 (s), 2851 (m), 1758 (w), 1601 (s), 1504 (s), 1462 (w), 1448 (m), 1404 (m), 1348 (w), 1214 (w), 1046 (w), 1029 (w), 985 (w), 954 (m), 850 (w), 755 (s) cm$^{-1}$. HRMS: m/z [MH$^+$/] calc. for C$_{15}$H$_{18}$N$_2$: 227.1548, found: 227.1558.

4-Cyclopentyl-1-phenyl-1H-pyrazole 109b

Following the general procedure using N-phenylsydnone 70 (100 mg, 0.62 mmol) and cyclopropylacetylene (105 µL, 1.24 mmol). In this case, a further 2 equivalents of alkyne were added after 2 h, and heated for a further 2 h. 4-Cyclopentyl-1-phenyl-1H-pyrazole was isolated as a yellow oil (109 mg, 96% yield, regioselectivity: >95:5).

$^1$H NMR (CDCl$_3$, 400 MHz): δ 7.68 (s, 1H, PyzlH), 7.67 – 7.61 (m, 2H, PhH), 7.52 (s, 1H, PyzlH), 7.45 – 7.38 (m, 2H, PhH), 7.27 – 7.21 (m, 1H, PhH), 1.82 – 1.71 (m, 1H, -CH$_2$-), 0.93 – 0.86 (m, 2H, -CH$_2$-), 0.61 – 0.55 (m, 2H, -CH$_2$-). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 140.3, 139.7, 129.4, 126.7, 124.0, 118.8, 7.9, 5.6. FTIR: $\nu_{\text{max}}$ 3083 (w), 3005 (w), 1601 (s), 1505 (s), 1463 (w), 1414 (m), 1397 (m), 1329 (w), 1190 (w), 1039 (w), 1022 (w), 997 (m), 954 (s), 756 (s), 690 (m), 665 (m) cm$^{-1}$. HRMS: m/z [MH$^+$/] calc. for C$_{12}$H$_{12}$N$_2$: 185.1079, found: 185.1084.
1-Phenyl-4-(3-thiophenyl)-1H-pyrazole 11b

Following the general procedure using N-phenylsydnone 70 (100 mg, 0.62 mmol) and 3-ethynylthiophene (122 µL, 1.23 mmol), stirring for 2.5 h, 1-phenyl-4-(3-thiophenyl)-1H-pyrazole was isolated as a pale brown solid (133 mg, 95% yield, regioselectivity: >95:5).

Melting point: 108-110 °C. 1H NMR (CDCl₃, 400 MHz): δ 8.09 (d, J = 1.0 Hz, 1H, PyzlH), 7.93 (d, J = 1.0 Hz, 1H, PyzlH), 7.75 – 7.70 (m, 2H, ArH), 7.51 – 7.44 (m 2H, ArH), 7.41 – 7.37 (m, 1H, ArH), 7.36 – 7.27 (m, 3H, ArH). 13C NMR (CDCl₃, 100.6 MHz): δ 140.1, 139.2, 132.9, 129.6, 126.7, 126.4, 126.2, 123.4, 120.4, 119.2, 119.1.

Ethyl 1-phenyl-1H-pyrazole-4-carboxylate 91b

Following the general procedure using N-phenylsydnone 70 (200 mg, 1.23 mmol) and ethyl propiolate (250 µL, 2.47 mmol), stirring for 1 h, ethyl 1-phenyl-1H-pyrazole-4-carboxylate was isolated as a pale yellow solid (253 mg, 95% yield, regioselectivity: >95:5).

Melting point: 92-95 °C (lit: 90-93 °C). 1H NMR (CDCl₃, 400 MHz): δ 8.41 (s, 1H, PyzlH), 8.10 (s, 1H, PyzlH), 7.78 – 7.65 (m, 2H, PhH), 7.54 – 7.43 (m, 2H, PhH), 7.39 – 7.30 (m, 1H, PhH), 4.34 (q, J = 7.0 Hz, 2H, -OCH₂CH₃), 1.37 (t, J = 7.0 Hz, 3H, -OCH₂CH₃). 13C NMR (CDCl₃, 100.6 MHz): δ 163.0, 142.3, 139.6, 130.1, 129.7, 127.7, 119.7, 117.1, 77.3, 60.6, 14.5.

4-n-Hexyl-1-phenyl-1H-pyrazole 103b

Following the general procedure using N-phenylsydnone 70 (100 mg, 0.62 mmol) and 1-octyne (182 µL, 1.23 mmol), 4-n-hexyl-1-phenyl-1H-pyrazole was isolated as an orange solid (102 mg, 73% yield, regioselectivity: >95:5).

Melting point: 28-30 °C. 1H NMR (CDCl₃, 400 MHz): δ 7.70 (s, 1H, PyzlH), 7.69 – 7.63 (m, 2H, PhH), 7.55 (s, 1H, PyzlH), 7.46 – 7.39 (m, 2H, PhH), 7.28 – 7.21 (m, 1H, PhH), 2.52 (t, J = 7.5 Hz, 2H, -CH₂-), 1.66 – 1.55 (m, 2H, -CH₂-), 1.41 – 1.25 (m, 6H, -CH₂-), 0.90 (t, J = 7.0 Hz, 3H, -CH₃). 13C NMR (CDCl₃, 100.6 MHz): δ 141.1, 140.4, 129.4, 126.0, 124.7, 124.2, 118.8, 31.8, 30.9, 29.1, 24.3, 22.7, 14.2. FTIR: νₘₐₓ 3052 (w), 2056 (s), 2028 (s), 2857 (s), 1758 (w), 1061 (s), 1505 (s), 1464 (m), 1396 (s), 1329 (w), 1213 (m), 1073 (w), 1042 (m), 1016 (m), 953 (s), 853 (w), 755 (s) cm⁻¹. HRMS: m/z [MH⁺] calc. for C₁₅H₂₀N₂: 229.1705, found: 229.1701.
1-(4-Methoxyphenyl)-4-phenyl-1H-pyrazole 97b

Following the general procedure using N-(4-methoxyphenyl)sydnone 84 (200 mg, 1.04 mmol) and phenylacetylene (290 µL, 2.08 mmol), stirring for 5 h, 1-(4-methoxyphenyl)-4-phenyl-1H-pyrazole was isolated as a pale yellow solid (139 mg, 53% yield, regioselectivity: >95:5).

Melting point: 125-128 °C (lit: 124-125 °C). 1H NMR (CDCl3, 400 MHz): δ 8.07 (s, 1H, PyzlH), 7.97 (s, 1H, PyzlH), 7.63 (d, J = 9.0 Hz, 2H, PMPH), 7.58 – 7.53 (m, 2H, PhH), 7.44 – 7.37 (m, 2H, PhH), 7.30 – 7.24 (m, 1H, PhH), 6.99 (d, J = 9.0 Hz, 2H, PMPH), 3.86 (s, 3H, -OCH3).

13C NMR (CDCl3, 100.6 MHz): δ 158.5, 138.4, 134.0, 132.2, 129.1, 126.8, 125.8, 124.7, 123.6, 120.9, 114.7, 55.7.

FTIR: νmax 3130 (w), 3050 (w), 2932 (m), 2835 (w), 1716 (w), 1667 (m), 1556 (m), 1544 (m), 1517 (s), 1462 (m), 1445 (m), 1408 (m), 1303 (m), 1248 (s), 1172 (m), 1109 (w), 1037 (m), 956 (m), 831 (m), 798 (w) cm⁻¹. HRMS: m/z [MH]+ calc. for C16H18N2O: 255.1497, found: 255.1501.

4-Cyclohexenyl-1-(4-methoxyphenyl)-1H-pyrazole 108b

Following the general procedure using N-(4-methoxyphenyl)sydnone 84 (200 mg, 1.04 mmol) and 1-ethynylcyclohexene (245 µL, 2.08 mmol), stirring for 5.5 h, 4-cyclohexenyl-1-(4-methoxyphenyl)-1H-pyrazole was isolated as a yellow solid (151 mg, 57% yield, regioselectivity: >95:5).

Melting point: 58-64 °C. 1H NMR (CDCl3, 400 MHz): δ 7.74 (s, 1H, PyzlH), 7.73 (s, 1H, PyzlH), 7.60 – 7.51 (m, 2H, PMPH), 7.00 – 6.92 (m, 2H, PMPH), 6.08 (tt, J = 4.0, 1.5 Hz, 1H, -CH2-), 3.83 (s, 3H, -OCH3), 2.32 (tt, J = 6.0, 2.5 Hz, 2H, -CH2-), 2.21 – 2.15 (m, 2H, -CH2-), 1.76 (qd, J = 6.0, 2.5 Hz, 2H, -CH2-), 1.67 (td, J = 6.0, 2.5 Hz, 2H, -CH2-). 13C NMR (CDCl3, 100.6 MHz): δ 158.2, 137.3, 134.2, 128.2, 126.5, 122.2, 122.1, 120.6, 114.6, 55.7, 27.6, 25.5, 22.8, 22.4.

FTIR: νmax 3130 (w), 3050 (w), 2932 (m), 2835 (w), 1716 (w), 1667 (m), 1556 (m), 1544 (m), 1517 (s), 1462 (m), 1445 (m), 1408 (m), 1303 (m), 1248 (s), 1172 (m), 1109 (w), 1037 (m), 956 (m), 831 (m), 798 (w) cm⁻¹. HRMS: m/z [MH]+ calc. for C16H18N2O: 255.1497, found: 255.1501.

4-Cyclohexyl-1-(4-methoxyphenyl)-1H-pyrazole 106b

Following the general procedure using N-(4-methoxyphenyl)sydnone 84 (100 mg, 0.52 mmol) and 1-ethynylcyclohexene (136 µL, 1.04 mmol). In this case, a further 2 equivalents of alkyne were added after 2.5 h, and heated for a further 2.5 h. 4-Cyclohexyl-1-(4-methoxyphenyl)-1H-pyrazole was isolated as a yellow oil (91 mg, 68% yield, regioselectivity: >95:5).

1H NMR (CDCl3, 400 MHz): δ 7.59 (s, 1H, PyzlH), 7.56 (s, 1H, PyzlH), 7.57 – 7.51 (m, 2H, PMPH), 6.99 – 6.88 (m, 2H, PMPH), 3.83 (s, 3H, -OCH3), 2.61 – 2.47 (m, 1H, -CH-), 2.05 – 1.94 (m, 2H, -CH2-), 1.88 – 1.67 (m, 4H, -CH2-), 1.44 – 1.28 (m, 4H, -CH2-). 13C NMR (CDCl3, 100.6 MHz): δ 158.0, 139.1, 134.4, 130.0, 123.6, 120.5, 114.5, 55.7, 34.6, 34.2, 26.5, 26.3.
FTIR: \( \nu_{\text{max}} \) 3050 (w), 2925 (s), 2851 (s), 1750 (w), 1518 (s), 1447 (m), 1400 (m), 1247 (s), 1168 (m), 1108 (w), 1049 (m), 1034 (m), 985 (w), 956 (m), 830 (m), 798 (w) cm\(^{-1}\).

HRMS: m/z [M+H\(^+\)] calc. for C\(_{16}\)H\(_{20}\)N\(_2\)O: 257.1654, found: 257.1664.

**Ethyl 1-(4-methoxyphenyl)-1H-pyrazole-4-carboxylate 10b**

Following the general procedure using N-(4-methoxyphenyl)sydnone 84 (200 mg, 1.04 mmol) and ethyl propiolate (211 \( \mu \)L, 2.08 mmol), stirring for 2 h, ethyl 1-(4-methoxyphenyl)-1H-pyrazole-4-carboxylate was isolated as a pale yellow solid (207 mg, 81% yield, regioselectivity: >95:5).

**Melting point:** 76-78 °C (lit: 77-79 °C\(^1\)).

**\( ^1 \)H NMR (CDCl\(_3\), 400 MHz):** \( \delta \) 8.30 (s, 1H, PyzH), 8.06 (s, 1H, PyzH), 7.59 (d, \( J = 9.0 \) Hz, 2H, PMPH), 6.98 (d, \( J = 9.0 \) Hz, 2H, PMPH), 4.33 (q, \( J = 7.0 \) Hz, 2H, -OCH\(_2\)CH\(_3\)), 3.84 (s, 3H, -OCH\(_3\)), 1.37 (t, \( J = 7.0 \) Hz, 3H, -OCH\(_2\)C\(_3\)H\(_7\)).

**\( ^{13} \)C NMR (CDCl\(_3\), 100.6 MHz):** \( \delta \) 163.1, 159.1, 142.0, 133.2, 130.1, 121.4, 116.7, 114.8, 60.5, 55.7, 14.5.

**4-n-Hexyl-1-(4-methoxyphenyl)-1H-pyrazole 104b**

Following the general procedure using N-(4-methoxyphenyl)sydnone 84 (100 mg, 0.52 mmol) and 1-octyne (154 \( \mu \)L, 1.04 mmol), stirring for 3.5 h, 4-n-hexyl-1-(4-methoxyphenyl)-1H-pyrazole was isolated as a yellow solid (72 mg, 54% yield, regioselectivity: >95:5).

**Melting point:** 32-34 °C.

**\( ^1 \)H NMR (CDCl\(_3\), 400 MHz):** \( \delta \) 7.60 (s, 1H, PyzH), 7.58 – 7.53 (m, 2H, PMPH), 7.51 (s, 1H, PyzH), 6.98 – 6.91 (m, 2H, PMPH), 3.82 (s, 3H, -OCH\(_3\)), 2.56 – 2.46 (m, 2H, -CH\(_2\)-), 1.65 – 1.53 (m, 2H, -CH\(_2\)-), 1.39 – 1.26 (m, 6H, -CH\(_2\)-CH\(_3\)), 0.92 – 0.85 (m, 3H, -CH\(_3\)).

**\( ^{13} \)C NMR (CDCl\(_3\), 100.6 MHz):** \( \delta \) 158.0, 140.5, 134.3, 124.9, 123.8, 120.5, 114.5, 55.6, 31.8, 30.9, 29.1, 24.3, 22.7, 14.2.

FTIR: \( \nu_{\text{max}} \) 3087 (w), 3000 (w), 2956 (s), 2929 (s), 2856 (m), 1568 (w), 1518 (s), 1465 (m), 1443 (m), 1399 (m), 1302 (m), 1247 (s), 1181 (m), 1169 (m), 1108 (w), 1045 (m), 1030 (w), 956 (m), 831 (m), 799 (w) cm\(^{-1}\).

**HRMS: m/z [M+H\(^+\)] calc. for C\(_{16}\)H\(_{22}\)N\(_2\)O: 259.1810, found: 259.1822.**

**Ethyl 1-(4-fluorophenyl)-1H-pyrazole-4-carboxylate 111b**

Following the general procedure using N-(4-fluorophenyl)sydnone 88 (200 mg, 1.11 mmol) and ethyl propiolate (225 \( \mu \)L, 2.22 mmol), stirring for 4 h, ethyl 1-(4-fluorophenyl)-1H-pyrazole-4-carboxylate was isolated as a white solid (249 mg, 95% yield, regioselectivity: >95:5).

**Melting point:** 118-120 °C (lit: 120-122 °C\(^2\)).

**\( ^1 \)H NMR (CDCl\(_3\), 400 MHz):** \( \delta \) 8.34 (s, 1H, PyzH), 8.08 (s, 1H, PyzH), 7.74 – 7.61 (m, 2H, PhH), 7.21 – 7.14 (m, 2H, PhH), 6.84 (d, \( J = 9.0 \) Hz, 2H, PMPH), 6.84 – 6.92 (m, 2H, PMPH), 4.33 (q, \( J = 7.0 \) Hz, 2H, -OCH\(_2\)CH\(_3\)), 3.84 (s, 3H, -OCH\(_3\)), 1.37 (t, \( J = 7.0 \) Hz, 3H, -OCH\(_2\)C\(_3\)H\(_7\)).

**\( ^{13} \)C NMR (CDCl\(_3\), 100.6 MHz):** \( \delta \) 163.1, 159.1, 142.0, 133.2, 130.1, 121.4, 116.7, 114.8, 60.5, 55.7, 14.5.
4.33 (q, J = 7.0 Hz, 2H, -OCH$_2$CH$_3$), 1.37 (t, J = 7.0 Hz, 3H, -OCH$_2$CH$_3$). \(^{19}F\) NMR (CDCl$_3$, 235 MHz): δ -114.1 (tt, J = 8.5, 4.5 Hz).
\(^{13}C\) NMR (CDCl$_3$, 100.6 MHz): δ 163.0 (d, J = 20.0 Hz), 160.6, 142.4, 135.9, 130.2, 121.7 (d, J = 8.5 Hz), 117.2, 116.6 (d, J = 23.0 Hz), 60.6, 14.5.

**Ethyl 1-benzyl-1H-pyrazole-4-carboxylate 112b**

Following the general procedure using N-benzyldyne 82 (100 mg, 0.57 mmol) and ethyl propiolate (115 µL, 1.14 mmol). In this case, a further 2 equivalents of alkyne were added after 2 h, and heated for a further 2 h. Ethyl 1-benzyl-1H-pyrazole-4-carboxylate was isolated as a yellow solid (79 mg, 60% yield, regioselectivity: >95:5).

Melting point: 56-58 °C (lit: 62-63 °C\(^{175}\)). \(^1H\) NMR (CDCl$_3$, 400 MHz): δ 7.93 (d, J = 0.5 Hz, 1H, PzylH), 7.85 (d, J = 0.5 Hz, 1H, PzylH), 7.34 (m, 3H, PhH), 7.27 – 7.19 (m, 2H, PhH), 5.28 (s, 2H, Ph-CH$_2$), 4.25 (q, J = 7.0 Hz, 2H, -OCH$_2$CH$_3$), 1.30 (t, J = 7.0 Hz, 3H, -OCH$_2$CH$_3$). \(^{13}C\) NMR (CDCl$_3$, 100.6 MHz): δ 163.0, 141.3, 135.4, 132.7, 129.0, 128.5, 128.0, 115.6, 60.2, 56.5, 14.4. FTIR: \(\nu_{\text{max}}\) 3133 (w), 2982 (w), 1715 (s), 1555 (m), 1456 (w), 1408 (w), 1225 (s), 1183 (m), 1113 (w), 1027 (m), 995 (w), 769 (w) cm$^{-1}$. HRMS: m/z [MH$^+$] calc. for C$_{13}$H$_{14}$N$_2$O$_2$: 231.1134, found: 231.1140.

**Synthesis of phenylethynyl copper 57a\(^{107}\)**

To a stirred solution of phenylacetylene (1.04 mL, 10.50 mmol) in ethanol (50 mL), a solution of Cul (2.02 g, 10.50 mmol) in ammonium hydroxide (20 mL) was added dropwise. After 15 minutes, the yellow precipitate formed was collected by filtration, washed with ethanol, water and diethyl ether and dried in vacuo providing the phenylethynyl copper as a bright yellow solid (1.26 g, 72% yield).

Melting point: 226-229 °C (lit.\(^{176}\) 229 °C). FTIR (CDCl$_3$, 400 MHz): \(\nu_{\text{max}}\) 3047 (w), 1929 (w), 1594 (m), 1571 (m), 1481 (s), 1440 (s), 1156 (w), 1069 (m), 1026 (m), 959 (w), 917 (m), 905 (m), 744 (s), 682 (s), 521 (s), 510 (s) cm$^{-1}$. **Elemental Analysis**: Calc. for C$_8$H$_5$Cu: C, 58.35, H, 3.06. Found: C, 58.17, H, 3.01.
**Preparation of the supported catalysts**

**a) Amberlyst® A-21 supported copper:**

Wet Amberlyst® A-21 beads directly purchased from Sigma-Aldrich were subjected to a pre-drying treatment before supporting the copper catalysts (CuI and Cu(OAc)$_2$ in this case). To do so, the resin was left to soak in methanol for 30 minutes, filtered and washed with methanol (x 3 times). The same procedure was sub-sequentially repeated using dichloromethane and after, the resin was dried under vacuum for 16 h.

Next, the corresponding copper salt (2.0 mmol / g of A-21) was dissolved in acetonitrile and the dry A-21 added to the solution. The mixture was left under orbital stirring for 16 h and after, filtered, washed with acetonitrile (x 2 times), dichloromethane (x 2 times) and dried under vacuum for 16 h.

Quantification of the copper loading was determined by ICP-MS analysis: 9.42 ± 0.18% (wt) (A-21·CuI) and 6.62% (wt) (A-21·Cu(OAc)$_2$).

**b) Silica-supported copper:**

![Diagram of precursors S-1 and S-2]

**Synthesis of precursor S-1:**

To a stirring solution of silica gel (30-70 μm, 60A, 1.1 eq.) in dry toluene was added (3-aminopropyl)trimethoxysilane (APTES) (1 eq.) and the mixture was heated at reflux under inert atmosphere over 24 h. Upon cooling, the silica was filtered, washed with acetone (x 2 times), dichloromethane (x 2 times) and dried under vacuum for 16 h.

**Synthesis of precursor S-2:**

To a stirring solution of silica gel (30-70 μm, 60A, 1.1 eq.) in dry toluene was added [3-(2-aminoethylamino)propyl]trimethoxysilane (AAPTS) (1 eq.) and the mixture was heated at reflux under inert atmosphere over 24 h. Upon cooling, the silica was filtered, washed with acetone (x 2 times), dichloromethane (x 2 times) and dried under vacuum for 16 h.
Preparation of **Silica**1 and **Silica**-2:

For the copper incorporation, to a stirred solution of the corresponding modified silica (**S-1** or **S-2**) in ethanol, Cu(OAc)$_2$ was added (0.5 mmol / g of silica) and the mixture was left stirring under inert atmosphere for 4 h. After, silica was filtered, washed with acetone (x 2 times), methanol (x 2 times) and dried under vacuum for 8 hours.

Quantification of the copper loading was determined by ICP-MS analysis: 3.22% (wt) (**Silica-1**) and 4.01 ± 0.20% (wt) (**Silica-2**).
Batch synthesis of 1,4-disubstituted-1H-pyrazoles using supported Cu catalysts

General procedure E

\[ \text{[Cu]=Silica-2 (0.3 eq.)} \]

\[ \alpha\text{-DCB, 140 °C, 1-16 h} \]

\[ (>95:5) \]

To a stirring solution of sydnone (1 eq.) and supported catalyst Silica-2 (0.3 eq., 4.02% Cu) in \( \alpha \)-dichlorobenzene (0.20 - 0.25 M) under \( \text{N}_2 \) at room temperature, was added the alkyne (1 eq.). The mixture was left stirring at room temperature for 5 minutes and afterwards, heated at 140 °C for the designated length of time. After cooling, the reaction mixture was filtered and the crude product was purified by flash chromatography on silica gel (eluting solvent: 5 % ethyl acetate in heptane, unless otherwise stated). Further purification of the pyrazole products could be obtained by recrystallisation from CH\(_2\)Cl\(_2\) – heptane if required.

Full characterisation of the some of the pyrazole products can be found within the general procedure for the preparation of the title compounds using Cu(OAc)\(_2\)·H\(_2\)O-mediated cycloadditions.

1,4-Diphenyl-1H-pyrazole 90b

Following the general procedure using \( N \)-phenylsydnone (100 mg, 0.62 mmol) and phenylacetylene (70 μL, 0.62 mmol) for 2 h, 1,4-diphenyl-1H-pyrazole was isolated as a yellow solid (135 mg, 100% yield, regioselectivity: >95:5).

1-(p-Methoxyphenyl)-4-phenyl-1H-pyrazole 97b

Following the general procedure using \( N \)-(p-methoxyphenyl)sydnone (100 mg, 0.52 mmol) and phenylacetylene (57 μL, 0.52 mmol) for 5 h, 1-(p-methoxyphenyl)-4-phenyl-1H-pyrazole was isolated as a pale orange solid (110 mg, 85% yield, regioselectivity: >95:5).

1-Benzyl-4-phenyl-1H-pyrazole 98b

Following the general procedure using \( N \)-benzylsydnone (100 mg, 0.57 mmol) and phenylacetylene (62 μL, 0.57 mmol) for 16 h, 1-benzyl-4-phenyl-1H-pyrazole was isolated as a pale yellow solid (63 mg, 47% yield, regioselectivity: >95:5).

Melting point: 92-94 °C (lit. 92-94 °C\(^{172}\)). 1H NMR (CDCl\(_3\), 500 MHz): δ 7.84 (s, 1H, PyzlH), 7.62 (s, 1H, PyzlH), 7.49 – 7.44 (m, 2H, Ph-H), 7.39 – 7.31 (m, 5H, Ph-H), 7.29 – 7.25 (m, 2H, Ph-H).
**Chapter 9: Experimental Procedures**

\[ \text{PhH}, 7.25 - 7.19 \text{ (m, 1H, PhH), 5.35 \text{ (s, 2H, Ph-CH}_2-).} \]  \( ^{13} \text{C NMR (CDCl}_3, 126 \text{ MHz):} \delta 137.1, 136.5, 132.6, 129.0 (x2), 128.3, 127.9, 126.5, 126.3, 125.6, 123.6, 56.4. \]

**Ethyl 1-phenyl-1H-pyrazole-4-carboxylate 91b**

Following the general procedure using N-phenylsydnone (100 mg, 0.62 mmol) and ethyl propiolate (63 \( \mu \)L, 0.62 mmol) for 6 h, ethyl 1-phenyl-1H-pyrazole-4-carboxylate was isolated as a yellow solid (94 mg, 71% yield, regioselectivity: >95:5).

**Ethyl 1-(p-methoxyphenyl)-1H-pyrazole-4-carboxylate 101b**

Following the general procedure using N-(p-methoxyphenyl)sydnone (100 mg, 0.52 mmol) and ethyl propiolate (53 \( \mu \)L, 0.52 mmol) for 6 h, ethyl 1-benzyl-1H-pyrazole-4-carboxylate was isolated as a yellow solid (60 mg, 47% yield, regioselectivity: >95:5).

**Ethyl 1-benzyl-1H-pyrazole-4-carboxylate 112b**

Following the general procedure using N-benzylsydnone (100 mg, 0.57 mmol) and ethyl propiolate (58 \( \mu \)L, 0.57 mmol) for 16 h, ethyl 1-benzyl-1H-pyrazole-4-carboxylate was isolated as an amorphous pale yellow solid (28 mg, 21% yield, regioselectivity: >95:5).

**1-Phenyl-4-(2-pyridinyl)-1H-pyrazole 117b**

Following the general procedure using N-phenylsydnone (100 mg, 0.62 mmol) and 2-ethynylpyridine (62 \( \mu \)L, 0.62 mmol) for 7 h, 1-phenyl-4-(2-pyridinyl)-1H-pyrazole was isolated as a pale brown solid (95 mg, 70% yield, regioselectivity: >95:5).

\[ \text{Melting point: 94-96 °C (lit. 86-88 °C)^{91}.} \]  \( ^1 \text{H NMR (CDCl}_3, 500 \text{ MHz):} \delta 8.60 \text{ (ddd, } J = 5.0, 2.0, 1.0 \text{ Hz, PyH}), 8.50 \text{ (d, } J = 0.5 \text{ Hz, 1H, PyzH}), 8.18 \text{ (s, 1H, PyzH)}, 7.79 - 7.73 \text{ (m, 2H, PhH)_1}, 7.69 \text{ (td, } J = 7.5, 2.0 \text{ Hz, 1H, PyH}), 7.54 \text{ (dt, } J = 7.5, 1.0 \text{ Hz, 1H, PyH}), 7.51 - 7.44 \text{ (m, 2H, PhH)}, 7.35 - 7.28 \text{ (m, 1H, PhH)}, 7.14 \text{ (ddd, } J = 7.5, 5.0, 1.0 \text{ Hz, 1H, PyH}). \]  \( ^{13} \text{C NMR (CDCl}_3, 126 \text{ MHz):} \delta 151.6, 149.9, 140.0, 139.3, 136.8, 129.6, 126.9, 125.4, 125.3, 121.6, 119.9, 119.2. \]

**1-(p-Methoxyphenyl)-4-(2-pyridinyl)-1H-pyrazole 120b**

Following the general procedure using N-(p-methoxyphenyl)sydnone (100 mg, 0.52 mmol) and 2-ethynylpyridine (53 \( \mu \)L, 0.52 mmol) for 7.5 h, 1-(p-methoxyphenyl)-4-(2-pyridinyl)-1H-pyrazole was isolated as a pale brown solid (89 mg, 68% yield, regioselectivity: >95:5).
Melting point: 98-100 °C. 1H NMR (CDCl₃, 400 MHz): δ 8.58 (ddd, J = 5.0, 1.5, 1.0 Hz, 1H, PyH), 8.39 (s, 1H, PyzH), 8.14 (s, 1H, PyzH), 7.71 – 7.60 (m, 3H, PhH), 7.52 (dt, J = 7.5, 1.0 Hz, 1H, PyH), 7.12 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H, PyH), 7.06 – 6.93 (m, 2H, PhH), 3.83 (s, 3H, -OC₃H₃).

13C NMR (CDCl₃, 126 MHz): δ 158.6, 151.7, 149.8, 138.8, 136.8, 133.8, 125.4, 125.0, 121.5, 120.9, 119.8, 114.7, 55.7.

FTIR: νmax 3434 (br, s), 1643 (m), 1598 (m), 1519 (s), 1304 (w), 1250 (m), 1173 (w), 1036 (w), 962 (w), 834 (w), 781 (m) cm⁻¹.


(1-Phenyl-1H-pyrazol-4-yl)methanol 116b

Following the general procedure using N-phenylsydnone (100 mg, 0.62 mmol) and propargyl alcohol (36 μL, 0.62 mmol) for 20 h, (1-phenyl-1H-pyrazol-4-yl)methanol was isolated as a white solid (51 mg, 47% yield, regioselectivity: >95:5).

Melting point: 62–64 °C. 1H NMR (CDCl₃, 500 MHz): δ 7.91 (s, 1H, PyzH), 7.70 (s, 1H, PyzH), 7.67 – 7.62 (m, 2H, PhH), 7.47 – 7.40 (m, 2H, PhH), 7.31 – 7.26 (m, 1H, PhH), 4.66 (s, 2H, -CH₂OH), 1.95 (s, 1H, -CH₂OH).

13C NMR (CDCl₃, 126 MHz): δ 140.5, 140.1, 129.6, 126.7, 125.8, 123.6, 119.2, 56.2.

FTIR: νmax 3354 (br), 2922 (w), 1599 (m), 1571 (m), 1503 (s), 1404 (s), 1209 (w), 1046 (m), 996 (m), 954 (m), 757 (m) cm⁻¹.

HRMS: m/z [MH⁺] calc. for C₁₀H₁₀N₂O: 175.0866, found: 175.0864.

(1-(p-Methoxyphenyl)-1H-pyrazol-4-yl)methanol 119b

Following the general procedure using N-(p-methoxyphenyl)sydnone (100 mg, 0.52 mmol) and propargyl alcohol (31 μL, 0.52 mmol) for 20 h, (1-(p-methoxyphenyl)-1H-pyrazol-4-yl)methanol was isolated as a white solid (58 mg, 55% yield, regioselectivity: >95:5).

Melting point: 82–84 °C. 1H NMR (CDCl₃, 500 MHz): δ 7.80 (s, 1H, PyzH), 7.65 (s, 1H, PyzH), 7.55 – 7.51 (m, 2H, PhH), 6.96 – 6.92 (m, 2H, PhH), 4.63 (s, 2H, -CH₂OH), 3.82 (s, 3H, -OCH₃), 2.12 (s, 1H, -CH₂OH).

13C NMR (CDCl₃, 126 MHz): δ 158.4, 140.1, 129.6, 126.7, 125.8, 119.2, 56.2. FTIR: νmax 3354 (br), 2922 (w), 1599 (m), 1571 (m), 1503 (s), 1404 (s), 1209 (w), 1046 (m), 996 (m), 954 (m), 757 (m) cm⁻¹.

HRMS: m/z [MH⁺] calc. for C₁₀H₁₀N₂O: 175.0866, found: 175.0864.

4-Cyclopentyl-1-phenyl-1H-pyrazole 115b

Following the general procedure using N-phenylsydnone (100 mg, 0.62 mmol) and cyclopentylacetylene (72 μL, 0.62 mmol) for 6 h, 4-cyclopentyl-1-phenyl-1H-pyrazole was isolated as a yellow oil (44 mg, 33% yield, regioselectivity: >95:5).
1H NMR (CDCl₃, 500 MHz):  δ 7.73 (t, J = 0.5 Hz, 1H, PyzH), 7.71 – 7.67 (m, 2H, PhH), 7.60 (s, 1H, PyzH), 7.48 – 7.41 (m, 2H, PhH), 7.31 – 7.24 (m, 1H, PhH), 3.05 – 2.94 (m, 1H, -CH₂), 2.17 – 2.02 (m, 2H, -CH₂), 1.86 – 1.76 (m, 2H, -CH₂), 1.76 – 1.65 (m, 2H, -CH₂), 1.64 – 1.51 (m, 2H, -CH₂).

13C NMR (CDCl₃, 126 MHz):  δ 140.4, 140.1, 129.4, 128.8, 126.0, 123.9, 118.9, 35.9, 34.4, 25.1.

FTIR: νmax 3435 (br), 2954 (s), 2868 (m), 1643 (m), 1602 (s), 1505 (s), 1463 (w), 1403 (m), 1331 (w), 1016 (w), 954 (m), 755 (m) cm⁻¹.


Following the general procedure using N-(p-methoxyphenyl)sydnone (100 mg, 0.52 mmol) and cyclopentylacetylene (60 μL, 0.52 mmol) for 6 h, 4-cyclopentyl-1-(p-methoxyphenyl)-1H-pyrazole was isolated as an orange oil (36 mg, 28% yield, regioselectivity: >95:5).

1H NMR (CDCl₃, 500 MHz):  δ 7.57 – 7.54 (m, 2H, PhH), 7.53 (s, 1H, PyzH), 6.98 – 6.91 (m, 2H, PhH), 3.83 (s, 3H, -OCH₃), 3.03 – 2.88 (m, 1H, -CH₂), 2.11 – 2.00 (m, 2H, -CH₂), 1.82 – 1.72 (m, 2H, -CH₂), 1.71 – 1.61 (m, 2H, -CH₂), 1.61 – 1.45 (m, 2H, -CH₂), 1.45 (m, 2H, -CH₂), 1.31 (m, 2H, -CH₂), 1.26 (m, 2H, -CH₂).

13C NMR (CDCl₃, 126 MHz):  δ 158.0, 139.6, 134.3, 128.4, 124.1, 120.6, 114.6, 55.7, 35.9, 34.5, 25.1. FTIR: νmax 2954 (m), 2868 (w), 1518 (s), 1464 (w), 1400 (w), 1246 (m), 1181 (w), 1170 (w), 1048 (m), 1035 (m), 956 (m), 830 (m) cm⁻¹. HRMS: m/z [MH⁺] calc. for C₁₅H₁₈N₂O: 243.1000, found: 243.1000.

**Flow set-up for the synthesis of 1,4-disubstituted-1H-pyrazoles**

Cartridge assembly:

Both ends of a U-shaped 10-cm Stainless steel tubing (1/8” OD, 1.75 mm ID, a) were blocked with cotton wool, fitted with assembled flat bottom super flangeless fittings + metal ferrules (1/8” OD, P-359, IDEX, b) and male nut parts (LT-215, IDEX, c). These connections were mounted onto flat unions (P-703-01, IDEX, d). For the filling of the cartridges, only one end was blocked at first, the cartridge was filled with the catalyst employing vacuum suction and after, the other end was blocked to seal the cartridge.
Microreactor setup:

All gas-tight syringes (5 mL, B-247, FutureChemistry Holding BV) were mounted on syringe pumps (B-230, FutureChemistry Holding BV, max flow rate: 35 mL/h, min flow rate: 0.73 μL/h) and connected to Tefzel® tubing (1/16” OD, 1529, IDEX) via female Luer adapters (P-628, IDEX). Throughout the flow system, all the tubing (Tefzel® 1/16” OD, 1529, IDEX) was assembled with super flangeless nut connections (P-287, IDEX) and assembled ferrules (P-259, IDEX) in order to achieve leak-free fluid connections. Also, a 5 bar back pressure regulator (B-444, FutureChemistry Holding BV, 25-75 psi pressure range) guaranteed pressurisation inside the system before eluting into a collection flask (see Figure 1).

![Figure 3. Flow set-up including back pressure regulator (detail, right).](image)
Flow synthesis of 1,4-disubstituted-1H-pyrazoles

General procedure F

Two feed solutions were employed: stream A containing the sydnone of choice in toluene (0.025 M), and stream B containing the alkyne in toluene (0.050 M), both driven by syringe pumps ($\phi_A = 2\phi_B$). These were mixed in a PEEK T-mixer connection (P-713, IDEX) before entering the microreactor (consisting of a 10 cm stainless steel cartridge packed with the supported copper catalyst) at 140 °C for 5 to 15 minutes. By removing the solvent in vacuo, the desired pyrazole products were obtained. In some cases, further purification was achieved by flash chromatography on silica gel (5-10% ethyl acetate in heptane) and/or by recrystallisation from dichloromethane/heptane.

Full characterisation of the pyrazole products can be found within the general procedure for the preparation of the title compounds in batch.

Yield calculation for reactions performed under flow conditions:

For the reactions performed in flow, yields were calculated taking into account the total moles of product obtained ($n$) the flow rate ($\phi_{SM}$) and the concentration ([SM]) of the starting material and the overall collection time (t) as shown in the equation below.

$$\eta_{FLOW}(\%) = \frac{n \text{(Collected Product)}}{[SM] \times \phi_{SM} \times t \text{(Collection)}} \times 100$$

1,4-Diphenyl-1H-pyrazole 90b

Following the general procedure using N-phenylsydnone (0.025 M) and phenylacetylene (0.050 M) with retention time = 5 min, total flow = 31.00 $\mu$L·min

1-(p-Methoxyphenyl)-4-phenyl-1H-pyrazole 97b

Following the general procedure using N-(p-methoxyphenyl)sydnone (0.025 M) and phenylacetylene (0.050 M) with retention time = 5 min, total flow = 31.90
μL·min⁻¹ and collecting for 2 h, 1-(p-methoxyphenyl)-4-phenyl-1H-pyrazole was isolated as a pale yellow solid (12 mg, 75% yield, regioselectivity: >95:5).

1-Benzyl-4-phenyl-1H-pyrazole 98b

Following the general procedure using N-benzylsydnone (0.025 M) and phenylacetylene (0.050 M) with retention time = 5 min, total flow = 20.60 μL·min⁻¹ and collecting for 2 h, 1-benzyl-4-phenyl-1H-pyrazole was isolated as a pale yellow solid (11 mg, 77% yield, regioselectivity: >95:5).

Ethyl 1-phenyl-1H-pyrazole-4-carboxylate 91b

Following the general procedure using N-phenylsydnone (0.025 M) and ethyl propiolate (0.050 M) with retention time = 5 min, total flow = 31.41 μL·min⁻¹ and collecting for 2 h, ethyl 1-phenyl-1H-pyrazole-4-carboxylate was isolated as a yellow solid (13 mg, 95% yield, regioselectivity: >95:5).

Ethyl 1-(p-methoxyphenyl)-1H-pyrazole-4-carboxylate 101b

Following the general procedure using N-(p-methoxyphenyl)sydnone (0.025 M) and ethyl propiolate (0.050 M) with retention time = 5 min, total flow = 30.00 μL·min⁻¹ and collecting for 2.5 h, ethyl 1-(p-methoxyphenyl)-1H-pyrazole-4-carboxylate was isolated as a pale yellow solid (10 mg, 56% yield, regioselectivity: >95:5).

1-Phenyl-4-(2-pyridinyl)-1H-pyrazole 117b

Following the general procedure using N-phenylsydnone (0.025 M) and 2-ethynylpyridine (0.050 M) with retention time = 5 min, total flow = 30.00 μL·min⁻¹ and collecting for 3 h, 1-phenyl-4-(2-pyridinyl)-1H-pyrazole was isolated as a pale yellow solid (5 mg, 24% yield, regioselectivity: >95:5).

1-(p-Methoxyphenyl)-4-(2-pyridinyl)-1H-pyrazole 120b

Following the general procedure using N-(p-methoxyphenyl)sydnone (0.025 M) and 2-ethynylpyridine (0.050 M) with retention time = 10 min, total flow = 15.00 μL·min⁻¹ and collecting for 5 h, 1-(p-methoxyphenyl)-4-(2-pyridinyl)-1H-pyrazole was isolated as a pale yellow solid (5 mg, 26% yield, regioselectivity: >95:5).

(1-Phenyl-1H-pyrazol-4-yl)methanol 116b

Following the general procedure using N-phenylsydnone (0.025 M) and propargyl alcohol (0.050 M) with retention time = 15 min, total flow = 10.00
μL·min⁻¹ and collecting for 6 h 15 min, (1-phenyl-1H-pyrazol-4-yl)methanol was isolated as a pale yellow solid (2 mg, 18% yield, regioselectivity: >95:5).

(1-\(\text{p-Methoxyphenyl}\)-1H-pyrazol-4-yl)methanol 119b

Following the general procedure using \(N\)-\(\text{p-Methoxyphenyl}\)sydnone (0.025 M) and propargyl alcohol (0.050 M) with retention time = 15 min, total flow = 10.00 μL·min⁻¹ and collecting for 6 h, (1-\(\text{p-Methoxyphenyl}\)-1H-pyrazol-4-yl)methanol was isolated as a white solid (4 mg, 33% yield, regioselectivity: >95:5).

4-Cyclopentyl-1-phenyl-1H-pyrazole 115b

Following the general procedure using \(N\)-phenylsydnone (0.025 M) and cyclopentylacetylene (0.050 M) with retention time = 15 min, total flow = 10.00 μL·min⁻¹ and collecting for 5 h, 4-cyclopentyl-1-phenyl-1H-pyrazole was isolated as a yellow oil (8 mg, 73% yield, regioselectivity: >95:5).

4-Cyclopentyl-1-\(\text{p-Methoxyphenyl}\)-1H-pyrazole 118b

Following the general procedure using \(N\)-\(\text{p-Methoxyphenyl}\)sydnone (0.025 M) and cyclopentylacetylene (0.050 M) with retention time = 15 min, total flow = 10.00 μL·min⁻¹ and collecting for 5.5 h, 4-cyclopentyl-1-\(\text{p-Methoxyphenyl}\)-1H-pyrazole was isolated as an orange oil (3 mg, 24% yield – 38% conversion, regioselectivity: >95:5).
Flow set-up for the scaled-up synthesis of 1,4-disubstituted-1H-pyrazoles

Cartridge assembly:

An empty stainless steel HPLC Column (12.5 x 0.46 cm, A2103-1, KNAUER) was filled with the catalyst and sealed using 7 μm pore-size frits.

Microreactor setup:

The feed stock from a glass container was injected into the flow system with a piston pump (Smartline Pump 100, KNAUER) and connected to Tefzel® tubing (1/16” OD, 1529, IDEX) with super flangeless nut connections (P-287, IDEX) and assembled ferrules (P-259, IDEX) in order to achieve leak-free fluid connections. Also, a 5 bar back pressure regulator (B-444, FutureChemistry Holding BV) guaranteed pressurisation inside the system before eluting into a collection flask (see Figure 2).

*Note that best results were obtained when a glass container for the oil bath was employed instead of a stainless steel container as shown in the figure below.

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Figure 4. Scaled-up flow system.
Chapter 9: Experimental Procedures

**Scaled-up flow synthesis of 1,4-disubstituted-1H-pyrazoles**

**General procedure G**

\[
\begin{align*}
\text{N} & \quad \text{Cu(OAc)}_2\text{silica gel} \\
\text{R} & \quad \text{BPR} \\
\text{140 °C, PhMe, 5 min} \\
\text{ (>95:5)}
\end{align*}
\]

One feed solution was employed containing the sydnone of choice (0.0125 M) and the alkyne (0.0125 M) in toluene, driven by a piston pump, which entered the microreactor (an empty 12.5 x 0.46 cm stainless steel HPLC column packed with the supported copper catalyst) at 140 °C for 5 minutes. By removing the solvent in vacuo, the desired pyrazole products were obtained. Further purification was achieved by flash chromatography on silica gel (5-10% ethyl acetate in heptane).

Full characterisation of the pyrazole products can be found within the general procedure for the preparation of the title compounds in batch.

**Ethyl 1-phenyl-1H-pyrazole-4-carboxylate 91b**

Following the general procedure using \(N\)-phenylsydnone and ethyl propiolate with retention time = 5 min, total flow = 0.44 mL min\(^{-1}\) and collecting for 2 h, ethyl 1-phenyl-1H-pyrazole-4-carboxylate was isolated as a yellow solid (36 mg, 44% yield, regioselectivity: >95:5).

**Ethyl 1-(p-methoxyphenyl)-1H-pyrazole-4-carboxylate 101b**

Following the general procedure using \(N\)-(p-methoxyphenyl)sydnone and ethyl propiolate with retention time = 5 min, total flow = 0.26 mL min\(^{-1}\) and collecting for 5 h, ethyl 1-(p-methoxyphenyl)-1H-pyrazole-4-carboxylate was isolated as a pale yellow solid (72 mg, 30% yield, regioselectivity: >95:5).
**Synthesis of alkynyltrifluoroborate salts:**

**General procedure $^{131,177,178}$**

To a stirred solution of the alkyne (1 eq.) in anhydrous THF, $n$-BuLi was added dropwise at -78 °C under a N$_2$ atmosphere. After 1 h, B(OMe)$_3$ (1.5 eq.) was added dropwise at -78 °C and the mixture was kept under these conditions for 1 h. The reaction was warmed up slowly to -20 °C and then an aqueous solution of KHF$_2$ (6 eq., 3 M) was added. The mixture was left stirring at -20 °C for 1 h and then warmed up to room temperature for 1 h. The solvent was removed *in vacuo*, the crude mixture redissolved in acetone and filtered. Further purification of the alkynyltrifluoroborate was achieved by recrystallisation from hot acetone and diethyl ether.

**Potassium phenylethynyl trifluoroborate 124**

Following the general procedure using phenylacetylene (5.0 g, 48.96 mmol), the desired product was recrystallised as a white solid (8.9 g, 80% yield).

Melting point: 280 °C (decomp.) (lit.$^{131}$ 238 °C). $^1$H NMR ($d_6$-DMSO, 400 MHz): δ 7.38 – 7.18 (m, 5H, PhH). $^{13}$C NMR ($d_6$-DMSO, 100.6 MHz): δ 130.9, 128.2, 126.7, 125.5, 89.3. $^{19}$F NMR ($d_6$-DMSO, 376 MHz): δ -131.7. $^{11}$B NMR ($d_6$-DMSO, 128 MHz): δ -1.5.

**Potassium $n$-hexylethynyl trifluoroborate 125**

Following the general procedure using 1-octyne (5.4 g, 48.96 mmol), the desired product was recrystallised as a white solid (6.7 g, 63% yield).

Melting point: 276-278 °C (decomp.) (lit.$^{177}$ 275 °C). $^1$H NMR ($d_6$-DMSO, 400 MHz): δ 2.00 – 1.92 (m, 2H, -CH$_2$-), 1.42 – 1.14 (m, 8H, -CH$_2$-), 0.86 (t, J = 7.0 Hz, 3H, -CH$_3$). $^{13}$C NMR ($d_6$-DMSO, 100.6 MHz): δ 88.7, 30.1, 29.0, 28.1, 22.1, 18.9, 14.0. $^{19}$F NMR ($d_6$-DMSO, 376 MHz): δ -131.0. $^{11}$B NMR ($d_6$-DMSO, 128 MHz): δ -1.8.

**Potassium 3,3-dimethylbutynyl trifluoroborate 126**

Following the general procedure using 1-octyne (5.4 g, 48.96 mmol), the desired product was recrystallised as a white solid (6.7 g, 63% yield).
Following the general procedure using 3,3-dimethylbut-1-yne (1.0 g, 12.17 mmol), the desired product was recrystallised as a white solid (1.7 g, 73% yield).

**Melting point**: 290 °C (decomp.) (lit.177 290 °C). $^1$H NMR (d$_6$-DMSO, 400 MHz): δ 1.09 (s, 9H, -CH$_3$). $^{13}$C NMR (d$_6$-DMSO, 100.6 MHz): δ 97.4, 31.6, 26.9. $^{19}$F NMR (d$_6$-DMSO, 376 MHz): δ -130.8. $^{11}$B NMR (d$_6$-DMSO, 128 MHz): δ –1.6.

**Potassium trimethylsilylethynyl trifluoroborate 127**

Following the general procedure using trimethylsilylacetylene (3.0 g, 30.54 mmol), the desired product was recrystallised as a white solid (3.3 g, 54% yield).

**Melting point**: 206 °C (decomp.) (lit.131 210 °C). $^1$H NMR (d$_6$-DMSO, 400 MHz): δ 0.04 (s, 9H, -SiCH$_3$). $^{13}$C NMR (d$_6$-DMSO, 100.6 MHz): δ 93.4, 0.5. $^{19}$F NMR (d$_6$-DMSO, 376 MHz): δ -132.5. $^{11}$B NMR (d$_6$-DMSO, 128 MHz): δ -2.3.

**Potassium ethynylcyclohex-1-enyl trifluoroborate 128**

Following the general procedure using ethynylcyclohex-1-ene (5.0 g, 47.09 mmol), the desired product was recrystallised as a white solid (8.2 g, 82% yield).

**Melting point**: 160 °C (decomp.) $^1$H NMR (d$_6$-DMSO, 400 MHz): δ 5.80 – 5.70 (m, 1H, -C=CH), 2.03 – 1.90 (m, 4H, -CH$_2$), 1.59 – 1.32 (m, 4H, -CH$_2$). $^{13}$C NMR (d$_6$-DMSO, 100.6 MHz): δ 130.1, 122.3, 91.3, 29.5, 25.0, 22.1, 21.4. $^{19}$F NMR (d$_6$-DMSO, 376 MHz): δ -131.3. $^{11}$B NMR (d$_6$-DMSO, 128 MHz): δ -1.5.

**Potassium 2-methyl-but-1-en-3-ynyl trifluoroborate 129**

Following the general procedure using 2-methyl-1-buten-3-yne (3.0 g, 45.39 mmol), the desired product was recrystallised as a white solid (5.6 g, 72% yield).

**Melting point**: 158 °C (decomp.) (lit.131 156 °C). $^1$H NMR (d$_6$-DMSO, 400 MHz): δ 5.02 (dq, J = 3.0, 1.5 Hz, 1H, =CH$_2$), 5.00 – 4.98 (m, 1H, =CH$_2$), 1.76 – 1.74 (m, 3H, -CH$_3$). $^{13}$C NMR (d$_6$-DMSO, 100.6 MHz): δ 128.5, 118.4, 90.8 (br), 24.0. $^{19}$F NMR (d$_6$-DMSO, 376 MHz): δ -131.8. $^{11}$B NMR (d$_6$-DMSO, 128 MHz): δ -1.6.
Chapter 9: Experimental Procedures

**Synthesis of potassium ethynyl trifluoroborate**

To a stirred solution of ethynylmagnesium bromide [0.33 M in THF] (150 mL, 50.0 mmol) in anhydrous THF, B(OMe)\(_3\) (8.40 mL, 75 mmol) was added dropwise at -78 °C under a N\(_2\) atmosphere. After 1 h, the reaction was warmed up slowly to -20 °C and then, an aqueous solution of KHF\(_2\) (23.4 g, 300 mmol) was added. The mixture was left stirring at rt for 2 h and then, the solvent was removed \textit{in vacuo}. The crude mixture was redissolved in acetone and filtered. Potassium ethynyltrifluoroborate was isolated as a white solid after recrystallisation from hot acetone and diethyl ether (4.50 mg, 68%).

**Melting point:** 208-210 °C (decomp.) (lit.\(^{179}\) 211-212 °C). \(^1\)H NMR (\(d_6\)-DMSO, 400 MHz): \(\delta\) 1.91 (s, 1H, -\(\text{CH}\)). \(^{13}\)C NMR (\(d_6\)-DMSO, 100.6 MHz): \(\delta\) 78.9. \(^{19}\)F NMR (\(d_6\)-DMSO, 376 MHz): \(\delta\) -132.4. \(^{11}\)B NMR (\(d_6\)-DMSO, 128 MHz): \(\delta\) -2.2.

**Synthesis of tetraethylammonium ethynyltrifluoroborate**

To a stirred solution of potassium ethynyltrifluoroborate (500 mg, 3.79 mmol) in a mixture of CH\(_2\)Cl\(_2\)-H\(_2\)O (4:1) at rt, an aqueous solution of Et\(_4\)N(OH) (35% w/w, 15.4 mL, 37.90 mmol) was added dropwise and the mixture was left to stir at rt. After 1.5 h, the crude mixture was extracted with CH\(_2\)Cl\(_2\), dried over MgSO\(_4\) and the volatiles were removed \textit{in vacuo} affording the desired product as a white solid (774 mg, 92% yield).

**Melting point:** 202-204 °C (lit.\(^{180}\) 211-213 °C). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 3.32 (q, \(J = 7.5\) Hz, 8H, -\(\text{CH}_2\text{CH}_3\)), 1.81 (br s, 1H, -\(\text{CH}\)). \(^{13}\)C NMR (CDCl\(_3\), 100.6 MHz): \(\delta\) 77.4, 52.7, 7.7. \(^{19}\)F NMR (CDCl\(_3\), 376 MHz): \(\delta\) -134.9. \(^{11}\)B NMR (CDCl\(_3\), 128 MHz): \(\delta\) -1.8.
Sydnone functionalisation

**Synthesis of 4-carboxy-N-phenylsydnone 131**

![Chemical Structure](image)

To a stirred solution of *N*-phenylsydnone (2.00 g, 12.33 mmol) in anhydrous THF at -78 °C under a N₂ atmosphere, *n*-BuLi (6.30 mL, 13.56 mmol) was added dropwise and the mixture was left to stir at -78 °C. After 30 min, the resulting intermediate was transferred via cannula to a flask containing a large excess of CO₂(g) at -78 °C under a N₂ atmosphere. The mixture was left to stir at -78 °C for 20 min. After that, the reaction was extracted with EtOAc, and the aqueous layer was acidified with 10% HCl to pH = 2 until precipitation of a solid was observed. 4-Carboxy-*N*-phenylsydnone was isolated after filtration and recrystallisation from hot ethanol as a pale yellow solid (2.52 g, 99% yield).

**Melting point:** 180-182 °C. ¹H NMR (d₆-DMSO, 400 MHz): δ 13.35 (s, 1H, -COOH), 7.79 – 7.74 (m, 2H, PhH), 7.73 – 7.68 (m, 1H, PhH), 7.66 – 7.60 (m, 2H, PhH). ¹³C NMR (d₆-DMSO, 100.6 MHz): δ 164.5, 157.6, 135.3, 132.0, 129.2, 125.6, 100.6.

**Synthesis of 4-ethoxycarbonyl-N-phenylsydnone 141**

![Chemical Structure](image)

To a stirred solution of *N*-phenylsydnone (3.00 g, 18.50 mmol) in anhydrous THF at -78 °C under a N₂ atmosphere, *n*-BuLi (9.30 mL, 20.35 mmol) was added dropwise and the mixture was left to stir at -78 °C. After 30 min, the resulting intermediate was transferred via cannula to a stirred solution of ethyl chloroformate chloride (8.80 mL, 92.50 mmol) in anhydrous THF at -78 °C under a N₂ atmosphere. The mixture was left to warm to rt for 20 h. After that, the reaction was quenched with brine, extracted with CH₂Cl₂, dried over MgSO₄ and the solvent was removed *in vacuo*. 4-(Ethoxycarbonyl)-*N*-phenylsydnone was isolated as a pale yellow solid after recrystallisation from 60-40 petroleum ether / CH₂Cl₂.
(4.21 g, 97% yield). Further purification could be achieved by flash chromatography on silica gel (eluting solvent: 50% ethyl acetate in 60-40 petroleum ether).

**Melting point:** 100-104 °C (lit.\textsuperscript{136} 105-106 °C). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \( \delta \) 7.74 – 7.67 (m, 1H PhH), 7.66 – 7.59 (m, 2H, PhH), 7.55 – 7.50 (m, 2H, PhH), 4.26 (q, \( J = 7.0 \) Hz, 2H, -OCH\textsubscript{2}CH\textsubscript{3}), 1.25 (t, \( J = 7.0 \) Hz, 3H, -OCH\textsubscript{2}CH\textsubscript{3}). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100.6 MHz): \( \delta \) 164.6, 157.2, 134.9, 132.6, 129.6, 125.1, 99.8, 61.8, 14.2.

**Synthesis of 4-(hydroxymethyl)-N-phenylsydnone 143\textsuperscript{136}**

![Chemical structure](attachment:image.png)

To a stirred solution of lithium borohydride (1.23 g, 56.36 mmol) in anhydrous THF at 0 °C under a N\textsubscript{2} atmosphere, 4-(ethoxycarbonyl)-N-phenylsydnone 141 (3.30 g, 14.09 mmol) in anhydrous THF was added dropwise and the mixture was left to warm to rt. After 16 h, the crude mixture was poured into a saturated solution of NaHCO\textsubscript{3}, extracted with EtOAc, dried over MgSO\textsubscript{4} and the solvent was removed \textit{in vacuo} affording the desired product as a yellow solid (2.19 g, 81% yield).

**Melting point:** 97-99 °C (lit.\textsuperscript{136} 98-100 °C). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \( \delta \) 7.86 – 7.78 (m, 2H, PhH), 7.72 – 7.60 (m, 3H, PhH), 4.48 (s, 2H, -CH\textsubscript{2}OH), 4.10 (br, 1H, -CH\textsubscript{2}OH). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100.6 MHz): \( \delta \) 169.1, 134.0, 132.6, 130.3, 124.5, 108.3, 51.3.

**Synthesis of 4-formyl-N-phenylsydnone 142\textsuperscript{136}**

**Procedure 1:**

![Chemical structure](attachment:image.png)

4-(Hydroxymethyl)-N-phenylsydnone 141 (2.75 g, 14.31 mmol) was added to a stirring solution of manganese dioxide (12.50 g, 143.10 mmol) in dichloromethane at rt. After 16 h, the crude mixture was filtered through a short pad of celite and the volatiles were removed \textit{in vacuo} affording 4-formyl-N-phenylsydnone as a yellow solid (2.05 g, 74% yield). Further
purification could be achieved by flash chromatography on silica gel (eluting solvent: 40% ethyl acetate in 60-40 petroleum ether).

**Procedure 2:**

A 1.0 M solution of DIBAL-H in toluene (22.4 mL, 22.39 mmol) was slowly added to a stirring solution of Weinreb’s amide 177 (1.86 g, 7.46 mmol) in toluene at -78 °C. After 4 h, the crude mixture was quenched with methanol and left to warm to rt. The organic fraction was extracted with dichloromethane, washed with 10% aqueous HCl, dried over MgSO₄ and the volatiles, removed in vacuo. The crude product was purified by flash chromatography on silica gel (eluting solvent: 30% ethyl acetate in 60-40 petroleum ether), affording 4-formyl-N-phenylsydnone as a yellow solid (738 mg, 52% yield).

**Melting point:** 138-140 °C (lit. 136-115-117 °C, without purification). ¹H NMR (CDCl₃, 400 MHz): δ 9.58 (s, 1H, -CHO), 7.74 (ddt, J = 8.0, 6.5, 1.5 Hz, 1H, PhH), 7.68 – 7.60 (m, 4H, PhH).

¹³C NMR (CDCl₃, 100.6 MHz): δ 174.8, 166.6, 133.7, 133.3, 130.0, 124.7, 105.2.

**Synthesis of 4-(methoxy(methyl)carbamoyl)-N-phenylsydnone 177**

To a stirred solution of acid 131 (1.83 g, 8.88 mmol) and catalytic dimethylformamide in anhydrous CH₂Cl₂ at rt under a N₂ atmosphere, (COCl)₂ (1.5 mL, 17.75 mmol) was added dropwise and the mixture was left to stir at rt. After 2 h, a mixture of N,O-dimethylhydroxylamine hydrochloride (1.04 g, 10.66 mmol) and Et₃N (3.7 mL, 26.64 mmol) was added dropwise and the mixture was left to stir. After 16 h, the reaction was quenched with brine, extracted with CH₂Cl₂, dried over MgSO₄ and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (eluting solvent: 40% ethyl acetate in 60-40 petroleum ether), affording Weinreb’s amide 177 as a yellow oil (1.86 g, 84% yield).
\(^{1}H\) NMR (CDCl\(_3\), 400 MHz): \(\delta 7.67 - 7.61\) (m, 1H, Ph\(H\)), 7.61 - 7.49 (m, 4H, Ph\(H\)), 3.85 (s, 3H, -OCH\(_3\)), 3.27 (s, 3H, -NCH\(_3\)). \(^{13}C\) NMR (CDCl\(_3\), 100.6 MHz): \(\delta 164.5, 157.4, 134.9, 132.4, 129.8, 124.1, 102.9, 62.3, 33.4\). FTIR: \(\nu_{\text{max}}\) 1765 (s), 1651 (m), 1480 (m), 1443 (w), 1269 (w), 1173 (w), 1051 (w), 990 (w), 770 (w), 692 (w) cm\(^{-1}\). HRMS: m/z [MH\(^{+}\)] calc. for C\(_{11}\)H\(_{11}\)N\(_3\)O\(_4\): 250.0822, found: 250.0821.

**Synthesis of 3-Phenyl-4-(phenylcarbamoyl)-sydnone 132**

![Diagram](image)

To a stirred solution of N-phenylsydnone (500 mg, 3.08 mmol) in anhydrous THF at -78 °C under a N\(_2\) atmosphere, n-BuLi (1.85 mL, 4.63 mmol) was added and the mixture was left to stir at -78 °C. After 30 min, the resulting intermediate was transferred via cannula to a stirred solution of N-phenylisocyanate (1.00 mL, 9.24 mmol) in anhydrous THF at -78 °C under a N\(_2\) atmosphere. The mixture was left to warm to rt for 2.5 h. After that, the reaction was quenched with a mixture of HCl 1M and water (1:5, 120 mL), extracted with CH\(_2\)Cl\(_2\), dried over MgSO\(_4\) and the solvent was removed in vacuo. The crude product was purified by recrystallisation from a mixture of 60-40 petroleum ether / CH\(_2\)Cl\(_2\), and the desired product was isolated as a fluffy pale yellow solid (660 mg, 77% yield).

**Melting point:** 188-190 °C. \(^{1}H\) NMR (CDCl\(_3\), 400 MHz): \(\delta 9.39\) (s, 1H, -NH\(C=O\)), 7.77 - 7.68 (m, 1H, Ph\(H\)), 7.65 - 7.58 (m, 4H, Ph\(H\)), 7.56 (d, \(J = 7.5\) Hz, 2H, Ph\(H\)), 7.31 (t, \(J = 8.0\) Hz, 2H, Ph\(H\)), 7.12 (t, \(J = 7.5\) Hz, 1H, Ph\(H\)). \(^{13}C\) NMR (CDCl\(_3\), 100.6 MHz): \(\delta 167.2, 153.2, 137.0, 134.5, 132.6, 129.4, 129.1, 125.3, 125.0, 120.4, 102.3\). FTIR: \(\nu_{\text{max}}\) 3312 (w), 3062 (w), 1806 (w), 1766 (s), 1669 (s), 1601 (s), 1547 (s), 1495 (m), 1467 (s), 1293 (m), 1246 (m), 1203 (m), 1149 (m), 1064 (m), 908 (m), 769 (s), 757 (s), 691 (s) cm\(^{-1}\). HRMS: m/z [MH\(^{+}\)] calc. for C\(_{15}\)H\(_{11}\)N\(_3\)O\(_3\): 282.0879, found: 282.0890.
Synthesis of 4-((dialkylcarbamoyl)-substituted sydnone

General procedure I

To a stirred solution of sydnone (1 eq.) in anhydrous THF at -78 °C under a N₂ atmosphere, n-BuLi (1.5 eq.) was added dropwise and the mixture was left to stir at -78 °C. After 30 min, the resulting intermediate was transferred via cannula to a stirred solution of N-dimethylcarbamoyl chloride (5 eq.) in anhydrous THF at -78 °C under a N₂ atmosphere. The mixture was left to warm to rt for the specified time. After that, the reaction was quenched with brine, extracted with CH₂Cl₂, dried over MgSO₄ and the solvent was removed in vacuo. The crude product was purified by recrystallisation from a mixture of 60-40 petroleum ether / CH₂Cl₂.

4-(Dimethylcarbamoyl)-3-phenylsydnone 133

Following the general procedure using N-phenylsydnone (500 mg, 3.01 mmol) after 5 h, the desired product was isolated as a pale orange solid (572 mg, 80% yield).

Melting point: 158-160 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.68 – 7.62 (m, 1H, PhH), 7.61 – 7.51 (m, 4H, PhH), 3.26 (s, 3H, -NCH₃), 2.99 (s, 3H, -NCH₃). ¹³C NMR (CDCl₃, 100.6 MHz): δ 164.8, 157.6, 135.0, 132.4, 129.8, 124.0, 103.6, 38.3, 35.6. FTIR: νmax 3067 (w), 1765 (m), 1743 (m), 1398 (w), 1052 (m), 928 (w), 779 (m), 770 (m), 742 (w), 691 (w) cm⁻¹. HRMS: m/z [MH⁺] calc. for C₁₁H₁₃N₃O₃: 234.0879, found: 234.0887.

4-(Dimethylcarbamoyl)-3-methylsydnone 134

Following the general procedure using N-methylsydnone (500 mg, 5.00 mmol), the desired product was isolated as a yellow solid (276 mg, 32% yield).

Melting point: 138-140 °C. ¹H NMR (CDCl₃, 400 MHz): δ 4.27 (s, 3H, Ar-N-CH₃), 3.17 (s, 3H, -N-CH₃), 3.04 (s, 3H, -N-CH₃). ¹³C NMR (CDCl₃, 100.6 MHz): δ 164.6, 158.2, 102.9, 40.6, 38.3, 35.7. FTIR: νmax 3031 (w), 2956 (w), 1773 (s), 1628 (s), 1513 (m), 1457 (m), 1418 (m), 1372 (m), 1318 (m), 1251 (m), 1133 (m), 1088 (m), 1048 (m), 978 (w). HRMS: m/z [MH⁺] calc. for C₁₁H₁₃N₃O₃: 234.0879, found: 234.0887.
1454 (m), 1436 (m), 1420 (m), 1305 (m), 1150 (m), 1098 (m), 1075 (m), 1027 (m), 759 (m) cm⁻¹. **HRMS:** m/z [MH⁺] calc. for C₆H₉N₃O₃: 172.0722, found: 172.0724.

**General procedure J**

To a stirred solution of sydnone (1 eq.) and catalytic dimethylformamide in anhydrous CH₂Cl₂ at rt under a N₂ atmosphere, (COCl₂) (1.3 eq.) was added dropwise and the mixture was left to stir at rt. After 1 h, a mixture of DIPEA (1 eq.) and the corresponding amine (2 eq.) was added dropwise and the mixture was left to stir for the designated period of time. After that, the reaction was quenched with saturated NaHCO₃, extracted with CH₂Cl₂, dried over MgSO₄ and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (eluting solvent: 20% ethyl acetate in 60-40 petroleum ether).

3-Phenyl-4-(pyrrolidine-1-carbonyl)sydnone 1

Following the general procedure using 4-carboxy-3-phenylsydnone (200 mg, 0.97 mmol) and pyrrolidine (162 µL, 1.94 mmol), after 1.5 h, the desired product was isolated as a pale yellow solid (184 mg, 73%).

**Melting point:** 164-166 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.67 – 7.61 (m, 1H, PhH), 7.60 – 7.52 (m, 4H, PhH), 3.82 (t, J = 6.5 Hz, 2H, -N-CH₂-), 3.50 (t, J = 7.0 Hz, 2H, -N-CH₂-). ¹³C NMR (CDCl₃, 100.6 MHz): δ 164.9, 155.5, 135.1, 132.4, 129.8, 124.2, 104.3, 47.2, 46.6, 26.1, 24.2. **FTIR:** νmax 3507 (w), 2975 (w), 2925 (w), 2863 (w), 1758 (s), 1634 (s), 1476 (s), 1454 (m), 1262 (w), 1067 (w), 913 (w), 764 (m), 732 (m), 688 (w) cm⁻¹. **HRMS:** m/z [MH⁺] calc. for C₁₃H₁₃N₃O₃: 260.1035, found: 260.1046.

3-Phenyl-4-(morpholine-1-carbonyl)sydnone 1

Following the general procedure using 4-carboxy-3-phenylsydnone (200 mg, 0.97 mmol) and morpholine (170 µL, 1.94 mmol), after 3 h, the desired product was isolated as a pale yellow solid (231 mg, 87%).

**Melting point:** 125-127 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.76 – 7.45 (m, 5H, PhH), 3.97 – 3.49 (m, 8H, -N-CH₂-C₂H₂-O-). ¹³C NMR (CDCl₃, 100.6 MHz): δ 164.8, 156.5, 135.0, 132.6, 129.9, 124.0, 103.0, 67.5, 66.7, 47.9, 43.2. **FTIR:** νmax 3507 (w), 2969 (w), 2860 (w), 1757 (s), 1638 (s), 1478 (s), 1445 (m), 1270 (m), 1210 (m), 1113...
(m), 1019 (m), 917 (w), 833 (w), 763 (w), 735 (w), 690 (w) cm\(^{-1}\). **HRMS:** m/z [MH\(^+\)] calc. for C\(_{13}\)H\(_{13}\)N\(_3\)O\(_4\): 276.0984, found: 276.0981.

**Synthesis of 4-((methoxyimino)methyl)-N-phenylsydnone 144**

![Chemical Structure](image)

4-Formyl-N-phenylsydnone 142 (150 mg, 0.80 mmol), was added to a stirring solution of O-methylhydroxylamine hydrochloride (79 mg, 0.95 mmol) and pyridine (255 µL, 3.16 mmol) in anhydrous CH\(_2\)Cl\(_2\) under a N\(_2\) atmosphere. The reaction was left stirring at rt and after 16 h, the volatiles were removed *in vacuo*. The residue was re-dissolved in CH\(_2\)Cl\(_2\), filtered through a short pad of celite and the volatiles removed *in vacuo*. The crude product was purified by recrystallisation from petroleum ether – CH\(_2\)Cl\(_2\) providing oxime 144 as a pale yellow solid (163 mg, 94% yield).

**Melting point:** 128-130 °C. \(^1\)H NMR (CDCl\(_3\), 400 MHz): δ 7.74 (s, 1H, -CH=N-), 7.73 – 7.68 (m, 1H, PhH), 7.67 – 7.61 (m, 2H, PhH), 7.58 – 7.53 (m, 2H, PhH), 3.87 (s, 3H, -NOCH\(_3\)). \(^{13}\)C NMR (CDCl\(_3\), 100.6 MHz): δ 165.1, 134.8, 133.7, 132.7, 130.2, 125.1, 103.2, 62.9. **FTIR:** \(\nu_{\text{max}}\) 2917 (w), 2849 (w), 2253 (w), 1774 (m), 1752 (s), 1484 (m), 1263 (m), 1046 (s), 911 (s), 733 (s) cm\(^{-1}\). **HRMS:** m/z [MH\(^+\)] calc. for C\(_{10}\)H\(_9\)N\(_3\)O\(_3\): 220.0722, found: 220.0726.

**Synthesis of 4-iminomethyl-N-phenylsydnone derivatives**

![Chemical Structure](image)

To a stirred solution of the corresponding amine (1 eq.) and basic alumina (2 eq.) in dry dichloromethane at 0 °C, a solution of 4-formyl-N-phenylsydnone (1 eq.) in dry dichloromethane was added dropwise over 10 minutes. After stirring at 0 °C for the specified period of time, the crude mixture was filtered through a short pad of celite, washed with dichloromethane and the volatiles removed *in vacuo*, affording the desired product that was used directly without further purification.
### 4-((Cyclohexylimino)methyl)-N-phenylsydnone 145

Following the general procedure using cyclohexylamine (61 µL, 0.53 mmol) and stirring for 5.5 h at 0 °C, 4-((cyclohexylimino)methyl)-N-phenylsydnone was obtained as an orange solid (142 mg, 100% yield).

**Melting point:** 96-98 °C. 

**1H NMR (CDCl$_3$, 400 MHz):** δ 8.01 (s, 1H, -CH=N-), 7.70 – 7.63 (m, 1H, PhH), 7.62 – 7.54 (m, 4H, PhH), 3.07 - 2.97 (m, 1H, -CH$_2$-), 1.68 – 1.50 (m, 5H, -CH$_2$-). 

**13C NMR (CDCl$_3$, 100.6 MHz):** δ 166.8, 142.7, 134.4, 132.2, 129.6, 125.4, 105.7, 104.1, 34.1, 25.6, 24.2.

**FTIR:** $\nu_{\text{max}}$ 2929 (m), 2854 (m), 1765 (s), 1634 (w), 1477 (m), 1451 (m), 1264 (w), 1074 (w), 764 (m), 735 (w) cm$^{-1}$.

**HRMS:** m/z [MH$^+$] calc. for C$_{15}$H$_{17}$N$_3$O$_2$: 272.1399, found: 272.1393.

### Synthesis of 4-((ethylimino)methyl)-N-phenylsydnone 146

Following the general procedure using ethylamine (0.26 mL, 2.0 M solution in THF, 0.53 mmol) and stirring for 16 h at 0 °C to rt, 4-((ethylimino)methyl)-N-phenylsydnone was obtained as a yellow solid (105 mg, 92% yield).

**Melting point:** 112-113 °C. 

**1H NMR (CDCl$_3$, 400 MHz):** δ 7.97 (t, $J = 1.5$ Hz, 1H, -CH=N-), 7.75 – 7.67 (m, 1H, PhH), 7.66 – 7.56 (m, 4H, PhH), 3.50 (qd, $J = 7.5$, 1.5 Hz, 2H, -CH$_2$-), 1.15 (t, $J = 7.5$ Hz, 3H, -CH$_3$). 

**13C NMR (CDCl$_3$, 100.6 MHz):** δ 166.3, 144.8, 134.0, 132.6, 129.9, 125.2, 105.7, 57.1, 16.2. 

**FTIR:** $\nu_{\text{max}}$ 3058 (w), 2966 (w), 2932 (w), 1801 (m), 1776 (s), 1749 (m), 1624 (m), 1577 (w), 1458 (w), 1377 (w), 1358 (m), 1286 (m), 1074 (m), 943 (w), 881 (w), 764 (m), 731 (w) cm$^{-1}$.

**HRMS:** m/z [MH$^+$] calc. for C$_{11}$H$_{11}$N$_3$O$_2$: 218.0930, found: 218.0919.

### Synthesis of 4-((tert-butylimino)methyl)-N-phenylsydnone 147

Following the general procedure using tert-butylamine (56 µL, 0.53 mmol) and stirring for 96 h at 0 °C to rt, 4-((tert-butylimino)methyl)-N-phenylsydnone was obtained as a yellow oil (92 mg, 70% yield).

**1H NMR (CDCl$_3$, 400 MHz):** δ 7.97 (s, 1H, -CH=N-), 7.69 – 7.64 (m, 1H, PhH), 7.62 – 7.53 (m, 4H, PhH), 1.06 (s, 9H, -CH$_3$). 

**13C NMR (CDCl$_3$, 100.6 MHz):** δ 166.5, 142.5, 134.1, 132.3, 129.6, 125.2, 105.6, 62.7, 23.9.

**NOTE:** this compound was very sensitive to hydrolysis and when recording IR or MS, it hydrolysed back to the starting aldehyde straight away, thus being impossible to obtain the
corresponding characterisation data. **FTIR:** $v_{\text{max}}$ 3064 (w), 2969 (m), 1771 (s), 1756 (m), 1623 (m), 1477 (m), 1265 (m), 1070 (w), 770 (m) cm$^{-1}$. **LCMS:** $m/z [\text{MH}^+]= 191.0$.

**Synthesis of 4-acetyl-N-phenylsydnone 148**

![Diagram of synthesis](image)

To a stirred solution of N-phenylsydnone (2.00 g, 12.33 mmol) in anhydrous THF at -78 °C under a N$_2$ atmosphere, n-BuLi (6.50 mL, 13.57 mmol) was added dropwise and the mixture was left to stir at -78 °C. After 30 min, the resulting intermediate was transferred via cannula to a flask containing acetyl chloride (4.40 mL, 61.67 mmol) at -78 °C under a N$_2$ atmosphere. The mixture was left to warm to rt and stirred for 24 hours. After that, the reaction was quenched with brine, extracted with CH$_2$Cl$_2$, dried over MgSO$_4$ and the volatiles were removed in vacuo. The crude product was purified by flash chromatography on silica gel (eluting solvent: 30% EtOAc in petroleum ether). 4-Acetyl-N-phenylsydnone was isolated as a pale yellow solid after recrystallisation from CH$_2$Cl$_2$ / petroleum ether (912 mg, 36% yield).

**Melting point:** 138-139 °C (lit.$^{181}$ 143-145 °C). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.72 – 7.65 (m, 1H, PhH), 7.64 – 7.57 (m, 2H, PhH), 7.51 – 7.44 (m, 2H, PhH), 2.53 (s, 3H, -CH$_3$). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 184.4, 166.4, 135.1, 132.5, 129.6, 125.0, 106.2, 28.3.

**Synthesis of 4-(1-(methoxyimino)ethyl)-N-phenylsydnone 149**

![Diagram of synthesis](image)

4-Acetyl-N-phenylsydnone (300 mg, 1.47 mmol), was added to a stirring solution of O-methylhydroxylamine hydrochloride (147 mg, 1.76 mmol) and pyridine (600 µL, 7.35 mmol) in refluxing methanol under a N$_2$ atmosphere. The reaction was stirred for 16 h and cooled to rt, extracted with EtOAc, dried over MgSO$_4$ and the volatiles were removed in vacuo. The
crude product was purified by flash chromatography on silica gel (eluting solvent: 10% EtOAc in petroleum ether) providing the product as a dark orange solid (181 mg, 53% yield).

**Melting point:** 58-60 °C. **1H NMR** (CDCl₃, 400 MHz): δ 7.63 (t, J = 7.5 Hz, 1H, PhH), 7.56 (t, J = 7.5 Hz, 2H, PhH), 7.48 (t, J = 7.5 Hz, 2H, PhH), 3.56 (s, 3H, -OC₃H₃), 2.15 (s, 3H, -CH₃). **13C NMR** (CDCl₃, 100.6 MHz): δ 166.8, 143.5, 135.8, 131.8, 129.4, 125.4, 104.7, 62.3, 12.3. **FTIR:** νmax 2935 (w), 1758 (s), 1485 (m), 1372 (w), 1285 (w), 1185 (w), 1149 (w), 1048 (s), 895 (m) cm⁻¹. **HRMS:** m/z [MH⁺] calc. for C₁₁H₁₁N₃O₃: 234.0879, found: 234.0887.

**Synthesis of N-(triphenylmethyl)propane-1,3-diamine**

To a stirred solution of trityl chloride (627 mg, 2.25 mmol) in chloroform at rt, 1,3-diaminopropane (2.80 mL, 33.72 mmol) was added dropwise. After 2 h, water was added, the organic layer was extracted with CH₂Cl₂, dried over MgSO₄ and the volatiles removed in vacuo. The crude product was purified by flash chromatography on silica gel (eluting solvent: EtOH / CH₂Cl₂ / Et₃N 20:78:2). N-(Triphenylmethyl)propane-1,3-diamine was isolated as a white solid (730 mg, 100% yield).

**Melting point:** 69-71 °C. **1H NMR** (CDCl₃, 400 MHz): δ 7.55 – 7.44 (m, 6H, PhH), 7.29 (dd, J = 10.5, 5.0, 6H, PhH), 7.20 (t, J = 7.5 Hz, 3H, PhH), 2.79 (t, J = 7.0 Hz, 2H, -CH₂), 2.22 (t, J = 7.0 Hz, 2H, -CH₂), 1.64 (p, J = 7.0 Hz, 2H, -CH₂). **13C NMR** (CDCl₃, 100.6 MHz): δ 146.2, 128.7, 127.9, 126.3, 71.0, 41.5, 40.6, 34.7.

**Synthesis of N-phenyl-4-((3-(tritylamino)propyl)carbamoyl)sydnone**

To a stirred solution of 4-carboxy-N-phenylsydnone (326 mg, 1.58 mmol) and catalytic DMF in dry dichloromethane at 0 °C, oxalyl chloride (174 µL, 2.05 mmol) was added dropwise. After 1 h stirring at rt, the volatiles were removed in vacuo, the crude mixture was resuspended in dry dichloromethane and added dropwise to a mixture of DIPEA (0.60 mL, 3.48 mmol) and N-(triphenylmethyl)propane-1,3-diamine (1.00 g, 3.16 mmol) at 0 °C. The
reaction was left to stir at rt for 16 h and after, quenched with saturated NaHCO₃, extracted with dichloromethane and dried over MgSO₄. The crude product was purified by flash chromatography on silica gel (eluting solvent: 30% EtOAc in petroleum ether) affording the desired product as a white solid (667 mg, 84% yield).

**Melting point:** 63-64 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.70 – 7.64 (m, 1H, PhH), 7.63 – 7.50 (m, 5H, PhH), 7.47 – 7.41 (m, 5H, PhH), 7.27 – 7.22 (m, 6H, PhH), 7.20 – 7.13 (m, 3H, PhH), 3.46 (dd, J = 13.5, 6.5 Hz, 2H, -CH₂), 2.17 (t, J = 6.5 Hz, 2H, -CH₂), 1.73 (p, J = 6.5 Hz, 2H, -CH₂). ¹³C NMR (CDCl₃, 100.6 MHz): δ 167.3, 155.5, 146.2, 134.7, 132.5, 129.3, 128.8, 127.9, 126.4, 125.4, 102.2, 71.1, 41.2, 37.6, 30.9. FTIR: νₘₐₓ 3351 (w), 3059 (w), 2927 (w), 2854 (w), 1746 (s), 1670 (m), 1543 (m), 1490 (m), 1470 (m), 1447 (m), 1209 (m), 909 (m), 766 (w) cm⁻¹.

**HRMS:** m/z [MH⁺] calc. for C₃₁H₂₈N₄O₃: 505.2240, found: 505.2223.

**Synthesis of 3-phenyl-4-(prop-2-yn-1-ylcarbamoyl)sydnone 154**

To a stirred solution of 4-carboxy-N-phenysydnone (1.00 g, 4.85 mmol) and a drop of DMF in dry dichloromethane at 0 °C, oxalyl chloride (0.82 mL, 9.70 mmol) was added dropwise. After 2 h stirring at rt, the volatiles were removed in vacuo, the crude mixture was dissolved in dry dichloromethane and added dropwise to a mixture of DIPEA (0.85 mL, 4.85 mmol) and propargylamine (0.62 mL, 9.70 mmol) at 0 °C. The reaction was left to stir at rt for 16 h and after, quenched with saturated NaHCO₃, extracted with dichloromethane and dried over MgSO₄. The crude product was purified by recrystallisation from dichloromethane / petroleum ether affording the desired product as a pale brown solid (936 mg, 79% yield).

**Melting point:** 142-144 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.75 – 7.66 (m, br, 2H, -NH- and PhH), 7.64 – 7.53 (m, 4H, PhH), 4.11 (dd, J = 5.5, 2.5 Hz, 2H, -CH₂), 2.23 (t, J = 2.5 Hz, 1H, -CH). ¹³C NMR (CDCl₃, 100.6 MHz): δ 167.2, 155.1, 134.5, 132.6, 129.4, 125.3, 101.7, 78.8, 72.0, 28.6. FTIR: νₘₐₓ 3429 (br), 3337 (m), 3291 (w), 1748 (s), 1666 (s), 1539 (m), 1492 (w), 1470 (w), 1451 (w), 1420 (w), 1291 (w), 1264 (w), 1208 (w), 1072 (w), 883 (w), 792 (w) cm⁻¹. HRMS: m/z [MH⁺] calc. for C₁₂H₉N₃O₃: 244.0722, found: 244.0732.
**Synthesis of 4-((2-hydroxyethyl)carbamoyl)-3-phenylsydnone 157**

To a stirred solution of 4-carboxy-N-phenylsydnone (1.00 g, 4.85 mmol) and a drop of DMF in dry dichloromethane at 0 °C, oxalyl chloride (530 µL, 6.31 mmol) was added dropwise. After 1.5 h stirring at rt, the volatiles were removed in vacuo, the crude mixture was dissolved in dry dichloromethane and added dropwise to a mixture of DIPEA (1.70 mL, 9.70 mmol) and 2-aminoethanol (0.64 mL, 10.67 mmol) at 0 °C. The reaction was left to stir at rt for 16 h and after, quenched with water, extracted with dichloromethane and dried over MgSO₄. The crude product was purified by flash chromatography on silica gel (eluting solvent: 80% EtOAc in petroleum ether) affording the desired product as a pale yellow solid (977 mg, 81% yield).

**Melting point:** 98-99 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.80 (s, 1H, -NH), 7.74 – 7.63 (m, 1H, PhH), 7.62 – 7.50 (m, 4H, PhH), 3.66 (s, 2H, -CH₂OH), 3.44 (dd, J = 10.5, 6.0 Hz, 2H, -CH₂NH), 2.98 (br, 1H, -OH). ¹³C NMR (CDCl₃, 100.6 MHz): δ 167.2, 156.1, 134.5, 132.4, 129.3, 125.3, 102.1, 61.6, 41.8. FTIR: νmax 3352 (br), 2931 (w), 1750 (s), 1666 (s), 1544 (s), 1471 (m), 1356 (w), 1301 (w), 1212 (m), 1057 (m), 919 (w), 764 (m) cm⁻¹. HRMS: m/z [MH⁺] calc. for C₁₁H₁₁N₃O₄: 250.0828, found: 250.0839.

**Synthesis of 4-(5-methylene-4,5-dihydrooxazol-2-yl)-N-phenylsydnone 155**

A solution of 3-phenyl-4-(prop-2-yn-1-ylcarbamoyl)sydnone 154 (250 mg, 1.03 mmol) and zinc iodide (1.30 g, 4.11 mmol) in anhydrous CH₂Cl₂ under a N₂ atmosphere was stirred for 72 hours. After that, water was added and the reaction mixture was extracted with CH₂Cl₂, dried over MgSO₄ and the volatiles were removed in vacuo. The crude product was purified by flash chromatography on silica gel (eluting solvent: 30% EtOAc in petroleum ether) providing the product as a white solid (147 mg, 58% yield).
Melting point: 128-130 °C. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.75 – 7.65 (m, 1H, PhH), 7.65 – 7.48 (m, 4H, PhH), 4.55 (dd, $J = 6.0$, 3.0 Hz, 1H, -C=CH$_2$), 4.47 (t, $J = 3.0$ Hz, 2H, -CH$_2$-), 4.27 (dd, $J = 6.0$, 3.0 Hz, 1H, -C=CH$_2$). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 164.9, 157.0, 152.7, 134.7, 132.7, 129.5, 125.1, 97.9, 85.2, 57.2. FTIR: $\nu_{\text{max}}$ 3416 (br), 2923 (m), 2853 (w), 1787 (s), 1655 (m), 1481 (m), 1308 (w), 1266 (w), 1130 (w), 1050 (m), 862 (w) cm$^{-1}$. HRMS: m/z [MH$^+$] calc. for C$_{12}$H$_9$N$_3$O$_3$: 244.0722, found: 244.0729.

Synthesis of 4-(5-methyloxazol-2-yl)-N-phenylsydnone 156

1,8-Diazabicycloundec-7-ene (0.10 mL, 0.66 mmol), was added to a stirring solution of 4-(5-methylene-4,5-dihydrooxazol-2-yl)-N-phenylsydnone 155 (146 mg, 0.60 mmol) in dry toluene under a N$_2$ atmosphere. The reaction was left stirring at rt and after 16 h, the volatiles were removed in vacuo. The crude product was purified by flash chromatography on silica gel (eluting solvent: 30% EtOAc in petroleum ether) affording the product as a yellow solid (107 mg, 73% yield).

Melting point: 176-178 °C. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.73 – 7.66 (m, 1H, PhH), 7.65 – 7.54 (m, 4H, PhH), 6.84 – 6.46 (m, 1H, -C=CH-N-), 2.28 (d, $J = 1.0$ Hz, 3H, -CH$_3$). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 165.2, 150.0, 148.6, 134.5, 132.6, 129.7, 125.2, 124.7, 99.5, 11.0. FTIR: $\nu_{\text{max}}$ 3063 (w), 2961 (w), 2924 (m), 2853 (m), 1776 (s), 1601 (w), 1464 (w), 1307 (m), 1260 (w), 1005 (w), 865 (w), 824 (w) cm$^{-1}$. HRMS: m/z [MH$^+$] calc. for C$_{12}$H$_9$N$_3$O$_3$: 244.0722, found: 244.0713.

Synthesis of 4-(4,5-dihydrooxazol-2-yl)-3-phenylsydnone 158

Trifluoromethanesulfonic anhydride (0.76 mL, 4.54 mmol) was added dropwise to stirring triphenylphosphine oxide (3.03 g, 10.90 mmol) in dry dichloromethane at 0 °C under a N$_2$ atmosphere. After 30 min, sydnone 157 (755 mg, 3.03 mmol) in dry dichloromethane (10
mL) was added dropwise to the mixture and the reaction was left to warm to room temperature over 16 h. After, the reaction was quenched with water and the layers separated. The aqueous layer was neutralised with saturated NaHCO$_3$, extracted with ethyl acetate and dried over MgSO$_4$. The crude product was purified by flash chromatography on silica gel (eluting solvent: 50-60% EtOAc in petroleum ether) affording the desired product as a yellow solid (155 mg, 22% yield).

**Melting point:** 118-120 °C.  $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.70 – 7.65 (m, 1H, PhH), 7.62 – 7.53 (m, 4H, PhH), 4.21 (t, $J = 9.5$ Hz, 2H, -CH$_2$), 3.94 (t, $J = 9.5$ Hz, 2H, -CH$_2$). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 165.8, 153.7, 134.8, 132.5, 129.5, 125.1, 99.0, 67.8, 54.7. FTIR: $\nu_{\text{max}}$ 2924 (w), 1788 (s), 1765 (s), 1629 (m), 1502 (m), 1273 (s), 1158 (m), 1045 (s), 909 (w), 768 (m), 729 (m), 692 (m), 638 (w) cm$^{-1}$. **HRMS:** m/z [MH$^+$] calc. for C$_{11}$H$_8$N$_3$O$_3$: 232.0722, found: 232.0733.
Synthesis of 4-iodo-N-phenylsydnone 150

To a stirred solution of N-phenylsydnone (1.50 g, 9.25 mmol) and sodium acetate (3.04 g, 37.00 mmol) in glacial acetic acid (20 mL) at rt, was added iodine monochloride (0.70 mL, 13.87 mmol) dissolved in glacial acetic acid (10 mL). The mixture was left to react at rt for 2 h. After, water was added to the reaction until precipitation was observed. 4-iodo-N-phenylsydnone was isolated after filtration as a tan solid (2.04 g, 77% yield).

Melting point: 158-159 °C (lit. 161-163 °C). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.74 – 7.69 (m, 1H PhH), 7.68 – 7.62 (m, 2H, PhH), 7.61 – 7.56 (m, 2H, PhH). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 168.9, 135.3, 132.7, 130.2, 125.2, 50.8.

Synthesis of 4-bromo-N-phenylsydnone 151

To a stirred solution of N-phenylsydnone (2.00 g, 12.33 mmol) in glacial acetic acid (20 mL) at rt, was added N-bromosuccinimide (2.40 g, 13.57 mmol). The mixture was left to react at rt for 2 h. After, water was added to the reaction until precipitation was observed. 4-Bromo-N-phenylsydnone was isolated after filtration as a pale orange solid (2.50 g, 84% yield).

Melting point: 136-137 °C (lit. 137-139 °C). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.76 – 7.60 (m, 5H PhH). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 165.8, 134.0, 132.8, 130.2, 124.9, 84.2.
Synthesis of 5-ethoxy-N-phenylsydnone tetrafluoroborate salt 140\textsuperscript{134}

To a stirred solution of \( \text{N-phenylsydnone sydnone} \) (1.50 g, 9.25 mmol) in anhydrous dichloromethane at rt under argon, triethyloxonium tetrafluoroborate (18.5 mL, 1.0 M in \( \text{CH}_2\text{Cl}_2 \), 18.50 mmol) was added dropwise, and the mixture was left to stir. After 16 hours, the volatiles were removed \textit{in vacuo}. Recrystallisation from isopropanol afforded the desired product as a pale brown solid (1.97 g, 77\% yield).

\textbf{Melting point:} 68-70 °C (lit.\textsuperscript{134} 68-70 °C). \(^1\)H NMR (\textit{CDCl}_3, 400 MHz): \( \delta \) 8.58 (s, 1H, Syd\textit{H}), 8.15 – 7.84 (m, 2H, Ph\textit{H}), 7.74 – 7.66 (m, 1H, Ph\textit{H}), 7.63 – 7.51 (m, 2H, Ph\textit{H}), 4.80 (q, \( J = 7.0 \) Hz, 2H, \(-\text{OCH}_2\text{CH}_3\)), 1.49 (t, \( J = 7.0 \) Hz, 3H, \(-\text{OCH}_2\text{CH}_3\)). \(^{13}\)C NMR (\textit{CDCl}_3, 100.6 MHz): \( \delta \) 173.6, 134.6, 133.2, 130.8, 122.5, 103.0, 76.2, 14.2.

Synthesis of 6-thio-N-phenylsydnone 139\textsuperscript{135}

To a stirred solution of 5-ethoxy-N-phenylsydnone (1.89 g, 6.80 mmol) in ethanol at -78 °C under a \( \text{N}_2 \) atmosphere, a solution of NaHS·H\textsubscript{2}O (0.61 g, 8.16 mmol) in ethanol was added dropwise, and the mixture left to react for 1 h. After that, the reaction was left to warm to rt, water was added and the crude extracted with dichloromethane. The organic fraction was dried over Mg\textsubscript{2}SO\textsubscript{4} and the volatiles removed \textit{in vacuo}. The crude product was purified by recrystallisation from isopropanol and the desired product was isolated as a fluffy pale yellow solid (320 mg, 26\% yield).

\textbf{Melting point:} 142-144 °C (lit.\textsuperscript{135} 167-168 °C, isopropanol). \(^1\)H NMR (\textit{CDCl}_3, 400 MHz): \( \delta \) 7.76 – 7.71 (m, 3H, Ph\textit{H}), 7.70 – 7.64 (m, 2H, Ph\textit{H}), 7.50 (s, 1H, Syd\textit{H}). \(^{13}\)C NMR (\textit{CDCl}_3, 100.6 MHz): \( \delta \) 190.8, 133.3, 130.8, 121.7, 116.6.
Synthesis of 4-(heteroaryl)-N-phenylsydnone derivatives

General procedure K

\[
\begin{align*}
\text{Ph} & \quad \text{Pd(OAc)}_2 (5 \text{ mol\%}) \\
\quad & \quad \text{XPhos (10 mol\%)} \\
\quad & \quad \text{Ar-X (1.5 eq.)} \\
\quad & \quad \text{K}_2\text{CO}_3 (2 \text{ eq.}) \\
\quad & \quad \text{DMF, 120 °C, 16 h}
\end{align*}
\]

To a stirred solution of N-phenylsydnone (1 eq.), Pd(OAc)$_2$ (5 mol%), XPhos (10 mol%) and K$_2$CO$_3$ (2 eq.) in dry DMF, the corresponding aryl halide (1.5 eq.) was added and the mixture was left to stir at 120 °C under a N$_2$ atmosphere. After 16 h, the reaction was quenched with brine, extracted with EtOAc, washed with 5% LiCl, dried over MgSO$_4$ and the volatiles were removed in vacuo. The crude product was purified by flash chromatography on silica gel (eluting solvent: 20-40% EtOAc in petroleum ether). Further purification was achieved by recrystallisation from CH$_2$Cl$_2$ / petroleum ether.

**N-Phenyl-4-(p-tolyl)sydnone 93**

Following the general procedure using p-chlorotoluene (1.10 mL, 9.26 mmol), the desired product was recrystallised as a pale brown solid (821 mg, 53% yield).

**Melting point:** 136-138 °C (lit.$^{101}$ 141-143 °C). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.69 – 7.62 (m, 1H, PhH), 7.61 – 7.53 (m, 2H, PhH), 7.53 – 7.44 (m, 2H, PhH), 7.20 – 7.15 (m, 2H, TolH), 7.09 (d, $J = 8.0$ Hz, 2H, TolH), 2.31 (s, 3H, $-$CH$_3$). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 167.3, 139.1, 134.9, 132.2, 130.3, 129.6, 127.4, 125.0, 121.6, 108.2, 21.5. FTIR: $\nu_{\text{max}}$ 3217 (w), 2923 (m), 2853 (w), 1745 (s), 1596 (m), 1510 (m), 1463 (w), 1446 (w), 1281 (w), 1037 (m), 832 (w) cm$^{-1}$. HRMS: m/z [MH$^+$] calc. for C$_{17}$H$_{11}$N$_3$O$_2$: 290.0924, found: 290.0918.

**4-(2-Pyridyl)-N-phenylsydnone 159**

Following the general procedure using 2-bromopyridine (0.90 mL, 9.25 mmol), the desired product was recrystallised as a pale yellow solid (1.03 g, 70% yield).

**Melting point:** 135-136 °C (lit.$^{103}$ 142-143 °C). $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.22 (ddd, $J = 5.0$, 2.0, 1.0 Hz, 1H, PyH), 8.06 (dt, $J = 8.0$, 1.0 Hz, 1H, PyH), 7.72 (td, $J = 8.0$, 2.0, 1H, PyH), 7.66 – 7.59 (m, 1H, PhH), 7.57 – 7.51 (m, 2H, PhH), 7.51 – 7.45 (m, 2H, PhH),
7.10 (ddd, \( J = 7.5, 5.0, 1.0 \) Hz, 1H, Pyr\( H \)). \(^{13}\)C NMR (CDCl\(_3\), 100.6 MHz): \( \delta \) 167.1, 149.1, 144.9, 136.8, 136.1, 131.6, 129.3, 125.2, 122.7, 121.8, 107.1.

4-(2-Pyrazinyl)-N-phenysydnone 160

Following the general procedure using 2-chloropyrazine (0.41 mL, 4.63 mmol), the desired product was recrystallised as a pale orange solid (562 mg, 76% yield).

Melting point: 164-166 °C. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 9.33 (d, \( J = 1.5 \) Hz, 1H, Pyr\( H \)), 8.40 (d, \( J = 2.5 \) Hz, 1H, Pyr\( H \)), 8.19 (dd, \( J = 2.5, 1.5, 1H, Pyr\( H \) ), 7.71 – 7.63 (m, 1H, Ph\( H \)), 7.62 – 7.54 (m, 2H, Ph\( H \)), 7.53 – 7.45 (m, 2H, Ph\( H \)). \(^{13}\)C NMR (CDCl\(_3\), 100.6 MHz): \( \delta \) 166.4, 143.4, 143.2, 142.9, 141.5, 135.6, 132.1, 129.6, 125.2, 105.0. FTIR: \( \nu _{\max } \) 2922 (w), 1744 (s), 1573 (w), 1508 (m), 1391 (w), 1276 (m), 1165 (w), 1125 (w), 1060 (w), 1018 (s), 773 (m) cm\(^{-1}\). HRMS: m/z [MH\(^+\)] calc. for C\(_{12}\)H\(_8\)N\(_4\)O\(_2\): 241.0726, found: 241.0716.

N-Phenyl-4-(2-quinolinyl)sydnone 161

Following the general procedure using 2-bromoquinoline (387 mg, 1.86 mmol), the desired product was recrystallised as a bright yellow solid (556 mg, 62% yield).

Melting point: 126-128 °C. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 8.29 (d, \( J = 8.5 \) Hz, 1H, Quin\( H \)), 8.18 (d, \( J = 8.5 \) Hz, 1H, Quin\( H \)), 7.75 (dd, \( J = 8.0, 1.0, 1H, Quin\( H \) ), 7.72 – 7.67 (m, 1H, Quin\( H \)), 7.63 – 7.50 (m, 5H, Ph\( H \) + Quin\( H \)), 7.48 – 7.42 (m, 1H, Ph\( H \)), 7.29 (d, \( J = 8.5 \) Hz, 1H, Quin\( H \)). \(^{13}\)C NMR (CDCl\(_3\), 100.6 MHz): \( \delta \) 167.1, 147.1, 144.7, 136.7, 136.5, 131.4, 129.8, 129.1, 129.0, 127.6, 127.0, 126.8, 125.6, 118.7, 107.1. FTIR: \( \nu _{\max } \) 3217 (w), 2923 (m), 2853 (w), 1745 (s), 1596 (m), 1510 (m), 1463 (w), 1446 (w), 1281 (w), 1037 (m), 832 (w) cm\(^{-1}\). \(^3\) HRMS: m/z [MH\(^+\)] calc. for C\(_{17}\)H\(_{11}\)N\(_3\)O\(_2\): 290.0924, found: 290.0918.
Directed cycloadditions between alkynyltrifluoroborate salts and sydnones

**General procedure L**

To a suspension of sydnone (1 eq.) and potassium alkynyltrifluoroborate (5 eq.) in dichloroethane (0.2 M) under a nitrogen atmosphere at 25 °C was added a solution of BF$_3$Et$_2$O (2 eq.) in dichloroethane (0.4 M). The reaction was stirred for 2-4 hours at 25 °C and after, quenched with brine. The resulting mixture was extracted with dichloromethane, the combined organic layers dried over MgSO$_4$, filtered through a short pad of celite and concentrated *in vacuo*. Further purification was achieved, when required, by flash chromatography on silica gel (eluting solvent: 20-40% EtOAc in petroleum ether).

**1-Phenyl-3-tert-butyl-4-(di-tert-butylethynyl)borane-5-(2-pyridyl)pyrazole 162**

Following the general procedure using sydnone 159 (50 mg, 0.21 mmol) and potassium tert-butylethynyltrifluoroborate (233 mg, 1.05 mmol), pyrazole 162 was isolated as a pale yellow solid (73 mg, 78% yield).

Melting point: 222-224 °C. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.80 – 8.68 (m, 1H, PyH), 7.80 (td, $J = 8.0, 1.5$ Hz, 1H, PyH), 7.58 – 7.47 (m, 4H, PhH), 7.42 – 7.36 (m, 1H, PhH), 7.33 – 7.26 (m, 2H, PyH), 1.53 (s, 9H, -C(CH$_3$)$_3$), 1.17 (s, 18H, -C(CH$_3$)$_3$). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 147.2, 145.7, 142.4, 141.1, 140.2, 129.5, 127.9, 125.0, 121.3, 117.0, 105.1, 88.1 (br), 33.7, 31.6, 30.6, 28.0 (NOTE: 1 sp and 1 sp$^2$ carbon not observed). $^{11}$B NMR (CDCl$_3$, 128 MHz): $\delta$ -10.7. FTIR: $\nu_{\text{max}}$ 2967 (s), 2927 (m), 2900 (m), 2865 (m), 2185 (m), 1621 (s), 1595 (m), 1521 (s), 1498 (s), 1484 (s), 1458 (m), 1360 (m), 1256 (s), 1117 (w), 1062 (m), 987 (m), 910 (m), 863 (m), 781 (m), 764 (m) cm$^{-1}$. HRMS: m/z [MH$^+$] calc. for C$_{30}$H$_{36}$BN$_3$: 450.3081, found: 450.3095.
1-Phenyl-3-n-hexyl-4-(di-octynylborane)-5-(2-quinolinyl)pyrazole 163

Following the general procedure using sydnone 161 (50 mg, 0.17 mmol) and potassium(1-octyn-1-yl)trifluoroborate (187 mg, 0.86 mmol), pyrazole 163 was isolated as a yellow solid (66 g, 65% yield).

Melting point: 98-100 °C. ¹H NMR (CDCl₃, 400 MHz): δ 9.19 (dd, J = 8.5, 0.5 Hz, 1H, QuinH), 8.25 (d, J = 8.5 Hz, 1H, QuinH), 7.89 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H, QuinH), 7.86 – 7.82 (m, 1H, QuinH), 7.63 – 7.51 (m, 5H, PhH), 7.48 – 7.40 (m, 2H, QuinH), 2.96 – 2.82 (m, 2H, CH₂), 2.24 – 2.07 (m, 4H, CH₂), 2.02 (dt, J = 15.5, 7.5 Hz, 2H, -CH₂), 1.53 – 1.13 (m, 22H, CH₂), 0.90 (t, J = 7.0 Hz, 3H, CH₃), 0.82 (t, J = 7.0 Hz, 6H, CH₃). ¹³C NMR (CDCl₃, 100.6 MHz): δ 155.4, 148.0, 143.2, 142.5, 142.3, 140.0, 132.3, 129.6, 128.4, 128.3, 127.3, 127.1, 125.3, 124.8, 115.2, 97.2, 32.0, 31.6, 29.7, 29.4, 29.3, 29.1, 28.8, 22.9, 22.7, 20.3, 14.4, 14.2 (NOTE: 1 sp and 1 sp² carbon not observed). ¹¹B NMR (CDCl₃, 128 MHz): δ -11.3. FTIR: νmax 3435 (s, br), 2955 (m), 2928 (s), 2856 (w), 1597 (m), 1539 (m), 1466 (w), 1010 (w), 757 (w), 700 (w) cm⁻¹. HRMS: m/z [MH⁺] calc. for C₄₀H₅₀BN₃: 584.4176, found: 584.4198.
**Synthesis of (R)-4-(((tert-butylsulfinyl)imino)methyl)-N-phenylsydnone 176**

To a stirred solution of 4-formyl-N-phenylsydnone (2.0 g, 10.51 mmol) and (R)-2-methylpropane-2-sulfinamide (7.21 g, 52.55 mmol) in dichloromethane at 0 °C under a N₂ atmosphere, TiCl₄ (1.15 mL, 10.51 mmol) was added dropwise, and the mixture left to warm to rt over 24 h. After that, the crude mixture was filtered through a short pad of celite and the volatiles were removed in vacuo. Purification by flash chromatography on silica gel (eluting solvent: 40% ethyl acetate in 60-40 petroleum ether) afforded (R)-4-(((tert-butylsulfinyl)imino)methyl)-N-phenylsydnone as a dark yellow solid (2.75 g, 89% yield).

**Melting point:** 141-143 °C. ¹H NMR (CDCl₃, 400 MHz): δ 8.26 (s, 1H, -CHN), 7.75 – 7.68 (m, 1H, PhH), 7.68 – 7.61 (m, 2H, PhH), 7.61 – 7.53 (m, 2H, PhH), 1.05 (s, 9H, -C(CH₃)₃). ¹³C NMR (CDCl₃, 100.6 MHz): δ 165.0, 146.1, 133.7, 133.0, 130.3, 125.1, 105.5, 58.3, 22.4. FTIR: νmax 3435 (s, br), 2955 (m), 2928 (s), 2856 (w), 1597 (m), 1539 (m), 1466 (w), 1010 (w), 757 (w), 700 (w) cm⁻¹. HRMS: m/z [MH⁺] calc. for C₁₃H₁₃N₃O₃S: 294.0907, found: 294.0906. [α]D²³: -57.7 (c = 1.01, CHCl₃).
Synthesis of 4-((R)-1-((R)-tert-butylsulfinamido))-N-phenylsydnone derivatives:

**General procedure M**

To a stirred solution of (R)-4-(((tert-butylsulfinyl)imino)methyl)-N-phenylsydnone 176 (1 eq.) in dichloromethane or tetrahydrofuran at -78 °C under a N\textsubscript{2} atmosphere, the corresponding Girihard reagent (2 eq.) was carefully added dropwise (over approx. 5 min.) and the mixture left to stir at -78 °C for 2-4 h. After that, the crude mixture was quenched with brine or saturated NH\textsubscript{4}Cl\textsubscript{(aq)}, extracted with dichloromethane and concentrated in vacuo. Purification by flash chromatography on silica gel or basic alumina (eluting solvent: 50% - 75% ethyl acetate in 60-40 petroleum ether) afforded the desired sydnone adducts.

4-((R)-1-((R)-tert-butylsulfinamido)propyl)-N-phenylsydnone 178a and 4-((S)-1-((R)-tert-butylsulfinamido)propyl)-N-phenylsydnone 178b:

Following the general procedure using ethylmagnesium bromide (0.68 mL, 1.02 mmol) in tetrahydrofuran, sydnone 178a was isolated as an orange oil (160 mg, 48% yield) and sydnone 178b was isolated as a pale yellow solid (42 mg, 13% yield).

**1H NMR (CDCl\textsubscript{3}, 400 MHz):** δ 7.74 – 7.61 (m, 5H, PhH), 4.50 (d, J = 10.0 Hz, 1H, -NH), 3.90 (dt, J = 10.0, 7.5 Hz, 1H, -CHNH), 1.99 – 1.82 (m, 2H, -CH\textsubscript{2}CH\textsubscript{3}), 1.21 (s, 9H), 0.85 (t, J = 7.5 Hz, 3H, -CH\textsubscript{2}CH\textsubscript{3}). **13C NMR (CDCl\textsubscript{3}, 100.6 MHz):** δ 167.6, 133.5, 132.5, 130.4, 125.7, 110.3, 56.7, 53.3, 28.0, 22.8, 10.9. **FTIR:** ν\textsubscript{max} 2967 (m), 1734 (s), 1475 (m), 1248 (w), 1066 (m), 771 (w), 693 (w) cm\textsuperscript{-1}. **HRMS:** m/z [MH\textsuperscript{+}] calc. for C\textsubscript{15}H\textsubscript{21}N\textsubscript{3}O\textsubscript{3}S: 324.1376, found: 324.1379. [α]\textsubscript{D}\textsuperscript{23}: -75.6 (c = 1.09, CHCl\textsubscript{3}).

**Melting point:** 142-144 °C. **1H NMR (CDCl\textsubscript{3}, 400 MHz):** δ 7.74 – 7.58 (m, 5H, PhH), 4.14 (td, J = 9.5, 6.0 Hz, 1H, -CHNH), 3.78 (d, J = 6.0 Hz, 1H, -NH), 2.23 – 2.08 (m, 1H, -CH\textsubscript{2}CH\textsubscript{3}), 1.95 – 1.81 (m, 1H, -CH\textsubscript{2}CH\textsubscript{3}), 1.20 (s, 9H), 0.83 (t, J = 7.5 Hz, 3H, -CH\textsubscript{2}CH\textsubscript{3}). **13C NMR (CDCl\textsubscript{3}, 100.6 MHz):** δ 166.8, 133.5, 132.6, 130.4, 125.4, 108.1, 56.5, 51.6, 27.4, 22.7, 10.9. **FTIR:** ν\textsubscript{max} 2968 (m), 2930 (m), 2877 (w), 1737 (s), 1475 (m), 1460 (m), 1258 (m), 1058
(m), 1026 (m), 914 (w), 770 (m), 692 (m) cm\(^{-1}\). **HRMS:** m/z [MH\(^+\)] calc. for C\(_{15}\)H\(_{21}\)N\(_3\)O\(_3\)S: 324.1376, found: 324.1377. [\([\alpha]\)\(_D\)]\(_{23}\): -124.6 (c = 0.35, CHCl\(_3\)).

**4-((R)-1-((R)-tert-butylsulfinamido)(phenyl)methyl)-N-phenylsydnone 179a:**

Following the general procedure using phenylmagnesium bromide (0.32 mL, 0.96 mmol) in tetrahydrofuran, sydnone 179 was isolated as a 80:20 mixture of diastereomers as an orange oil (146 mg, 77% yield). The major isomer could be separated via flash chromatography of the mixture of diastereomers (eluting solvent: EtOAc/petroleum ether 40-60 50%) and was isolated in 13% yield.

\( ^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.72 – 7.66 (m, 1H, PhH), 7.65 – 7.59 (m, 2H, PhH), 7.58 – 7.52 (m, 2H, PhH), 7.37 – 7.30 (m, 3H, PhH), 7.29 – 7.24 (m, 2H, PhH), 5.26 (d, \(J = 9.0\) Hz, 1H, -C(H)=N), 5.20 (d, \(J = 9.0\) Hz, 1H, -N\(H\)-), 1.23 (s, 9H, -C(CH\(_3\))\(_3\)).

\( ^{13}\)C NMR (CDCl\(_3\), 100.6 MHz): \(\delta\) 167.9, 138.7, 133.4, 132.7, 130.4, 129.2, 128.7, 126.9, 125.3, 109.3, 56.9, 54.5, 22.8.

**FTIR:** \(v\)\(_{\text{max}}\) 3448 (w, br), 2961 (w), 1736 (s), 1495 (w), 1474 (m), 1456 (m), 1250 (m), 1063 (m), 920 (w), 769 (m), 736 (m), 694 (m) cm\(^{-1}\). **HRMS:** m/z [MH\(^+\)] calc. for C\(_{19}\)H\(_{21}\)N\(_3\)O\(_3\)S: 372.1376, found: 372.1380. [\([\alpha]\)\(_D\)]\(_{23}\): -108.1 (c = 0.54, CHCl\(_3\)).

**4-((R)-1-((R)-tert-butylsulfinamido)allyl)-N-phenylsydnone 181a:**

Following the general procedure using vinylmagnesium bromide (0.68 mL, 0.68 mmol) in dichloromethane, sydnone 181a was isolated as an orange oil (38 mg, 34% yield).

\( ^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.75 – 7.68 (m, 1H, PhH), 7.67 – 7.62 (m, 4H, PhH), 6.03 – 5.90 (m, 1H, -C(H)=CH\(_2\)), 5.27 (d, \(J = 10.5\) Hz, 1H, -C(H)=CH\(_2\)), 5.19 (d, \(J = 17.0\) Hz, 1H, -C(H)=CH\(_2\)), 4.74 – 4.63 (m, 2H, -N\(H\)- and -C(H)=CH\(_2\)), 1.21 (s, 9H, -C(CH\(_3\))\(_3\)).

\( ^{13}\)C NMR (CDCl\(_3\), 100.6 MHz): \(\delta\) 167.6, 134.4, 133.4, 132.7, 130.4, 125.2, 118.1, 108.2, 56.7, 53.1, 22.7. **FTIR:** \(v\)\(_{\text{max}}\) 2960 (w), 1734 (s), 1475 (m), 1249 (w), 1063 (m), 934 (w), 769 (m), 693 (w) cm\(^{-1}\). **HRMS:** m/z [MH\(^+\)] calc. for C\(_{15}\)H\(_{19}\)N\(_3\)O\(_3\)S: 322.1220, found: 322.1220. [\([\alpha]\)\(_D\)]\(_{23}\): -127.3 (c = 0.75, CHCl\(_3\)).

**4-((R)-1-((R)-tert-butylsulfinamido)-3-butenyl)-N-phenylsydnone 185a:**

Following the general procedure using allylmagnesium bromide (0.68 mL, 0.68 mmol) in dichloromethane, sydnone 185a was isolated as an orange oil (65 mg, 56% yield).
\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.72 – 7.62 (m, 5H, PhH), 5.63 – 5.43 (m, 1H, -C(H)=CH\(_{2}\)), 5.11 – 5.08 (m, 1H, -C(H)=CHH), 5.06 (m, 1H, -C(H)=CHH), 4.51 (d, \(J = 10.0\) Hz, 1H, -NH), 4.07 (ddd, \(J = 10.0, 9.0, 7.0\) Hz, 1H, -CHNH), 2.66 (m, 2H, -CH\(_2\)), 1.20 (s, 9H, -C(CH\(_3\))\(_3\)). \(^{13}\)C NMR (CDCl\(_3\), 100.6 MHz): \(\delta\) 167.6, 133.4, 132.7, 132.5, 130.3, 125.7, 119.7, 109.7, 56.7, 51.5, 38.8, 22.7. FTIR: \(\nu_{\text{max}}\) 2060 (w), 1725 (s), 1475 (m), 1365 (w), 1244 (w), 1177 (w), 1065 (m), 924 (w), 772 (m), 693 (w) cm\(^{-1}\). HRMS: m/z [MH\(^+\)] calc. for C\(_{18}\)H\(_{20}\)N\(_2\)O\(_3\)S: 336.1376, found: 336.1379. \([\alpha]_D^{23}\): -107.0 (c = 1.08, CHCl\(_3\)).

\(4-([R]-1-((R)-\text{tert}-\text{butylsulfamido})-4\text{-pentenyl}-N\text{-phenylsydnone} 182a:

Following the general procedure using 3-butenylmagnesium bromide (0.68 mL, 0.68 mmol) in dichloromethane, sydnone 182a was isolated as an orange oil (48 mg, 40% yield).

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.72 – 7.62 (m, 5H, PhH), 5.70 – 5.54 (m, 1H, -C(H)=CH\(_{2}\)), 4.93 – 4.90 (m, 1H, -C(H)=CHH), 4.90 – 4.85 (m, 1H, -C(H)=CHH), 4.50 (d, \(J = 10.0\) Hz, 1H, -NH), 4.09 – 4.00 (m, 1H, CHNH), 2.10 – 2.02 (m, 2H, -CH\(_2\)), 2.02 – 1.85 (m, 2H, -CH\(_2\)), 1.21 (s, 9H, -C(CH\(_3\))\(_3\)). \(^{13}\)C NMR (CDCl\(_3\), 100.6 MHz): \(\delta\) 167.7, 136.5, 133.4, 132.5, 130.4, 125.5, 116.2, 110.2, 56.7, 50.8, 33.8, 29.9, 22.8. FTIR: \(\nu_{\text{max}}\) 2926 (w), 1730 (s), 1475 (m), 1254 (w), 1066 (m), 919 (w), 771 (w), 693 (w) cm\(^{-1}\). HRMS: m/z [MH\(^+\)] calc. for C\(_{17}\)H\(_{21}\)N\(_2\)O\(_3\)S: 350.1533, found: 350.1537. \([\alpha]_D^{23}\): -134.2 (c = 0.95, CHCl\(_3\)).

\(4-([R]-1-((R)-\text{tert}-\text{butylsulfamido})-5\text{-hexenyl}-N\text{-phenylsydnone} 183a:

Following the general procedure using 4-pentenylmagnesium bromide (1.13 mL, 1.02 mmol) in dichloromethane, sydnone 183a was isolated as an orange oil (89 mg, 48% yield).

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.74 – 7.62 (m, 5H, PhH), 5.67 (ddt, \(J = 17.0, 10.5, 6.5\) Hz, 1H, -C(H)=CH\(_{2}\)), 4.93 – 4.91 (m, 1H, -C(H)=CHH), 4.91 – 4.86 (m, 1H, -C(H)=CHH), 4.50 (d, \(J = 10.0\) Hz, 1H, -NH), 4.00 (dt, \(J = 10.0, 8.0\) Hz, 1H, -CHNH), 2.04 – 1.93 (m, 2H, -CH\(_2\)), 1.93 – 1.78 (m, 2H, -CH\(_2\)), 1.39 – 1.28 (m, 2H, -CH\(_2\)), 1.21 (s, 9H, -C(CH\(_3\))\(_3\)). \(^{13}\)C NMR (CDCl\(_3\), 100.6 MHz): \(\delta\) 167.6, 137.8, 133.5, 132.5, 130.4, 125.6, 115.4, 110.4, 56.7, 51.4, 33.9, 32.8, 25.1, 22.8. FTIR: \(\nu_{\text{max}}\) 2928 (w), 2159 (m), 1733 (s), 1474 (m), 1251 (w), 1068 (m), 912 (w), 771 (m), 693 (m) cm\(^{-1}\). HRMS: m/z [MH\(^+\)] calc. for C\(_{18}\)H\(_{22}\)N\(_2\)O\(_3\)S: 364.1689, found: 364.1609. \([\alpha]_D^{23}\): -78.9 (c = 0.90, CHCl\(_3\)).
4-\((R)-1-((R)\text{-tert-butylsulfinamido})-6\text{-heptenyl}\)-\(N\text{-phenylsydnone}\) \(184a\):

Following the general procedure using 5-hexenylmagnesium bromide (1.84 mL, 1.02 mmol) in dichloromethane, sydnone \(184a\) was isolated as an orange oil (86 mg, 44% yield).

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.73 – 7.63 (m, 5H, Ph\(H\)), 5.70 (ddt, \(J = 17.0, 10.5, 6.5\) Hz, 1H, -C(\(H\)=CH\(_2\))), 4.97 – 4.93 (m, 1H, -C(\(H\)=CH\(_2\))), 4.93 – 4.90 (m, 1H, -C(\(H\)=CH\(_2\))), 4.50 (d, \(J = 10.5\) Hz, 1H, -NH), 3.98 (dt, \(J = 10.5, 7.5\) Hz, 1H, -CHNH), 2.00 – 1.94 (m, 2H, -CH\(_2\)), 1.93 – 1.79 (m, 2H, -CH\(_2\)), 1.38 – 1.22 (m, 4H, -CH\(_2\)), 1.21 (s, 9H, -C(CH\(_3\))\(_3\)). \(^{13}\)C NMR (CDCl\(_3\), 100.6 MHz): \(\delta\) 167.6, 138.4, 133.5, 132.5, 130.4, 125.6, 114.9, 110.5, 56.6, 51.6, 34.5, 33.5, 28.1, 25.5, 22.8. FTIR: \(\nu_{\text{max}}\) 2927 (m), 1734 (s), 1474 (w), 1246 (w), 1068 (m), 771 (w), 693 (w) cm\(^{-1}\). HRMS: m/z [MH\(^+\)] calc. for C\(_{19}\)H\(_{27}\)N\(_3\)O\(_3\)S: 378.1846, found: 378.1850. \([\alpha]_D^{23}\) -49.1 (c = 0.55, CHCl\(_3\)).
Functionalisation of the 4-((R)-1-((R)-tert-butylsulfinamido)-N-phenylsydnone derivatives:

Synthesis of 4-((R)-2-methyl-N-(2-propyn-1-yl)propan-2-yl-1-((R)-tert-butylsulfinamido)propyl)-N-phenylsydnone 188

To a stirred solution of sodium hydride (69 mg, 60% dispersion in mineral oil, 1.71 mmol) in tetrahydrofuran at 0 °C under a N₂ atmosphere, sydnone 178a (139 mg, 0.43 mmol) was added and the mixture was left to stir at 0 °C. After 30 min, tetrabutylammonium iodide (16 mg, 0.04 mmol) and propargyl bromide (0.19 mL, 1.71 mmol) were added and the reaction was left to warm to rt over 20 h. After, the reaction was quenched with saturated NH₄Cl (aq), extracted with dichloromethane, dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (eluting solvent: 40% ethyl acetate in 60-40 petroleum ether), and the desired product was isolated as an orange oil (150 mg, 97% yield).

1H NMR (CDCl₃, 400 MHz): δ 7.75 – 7.57 (m, 5H, PhH), 4.11 – 4.01 (m, 2H, N-CH₂ and -N-CH-Syd), 3.50 (dd, J = 19.0, 2.5 Hz, 1H, -C(H)CH), 2.69 (ddq, J = 14.5, 10.5, 7.5 Hz, 1H, -C(H)CH₃), 2.20 – 2.07 (m, 2H, -C(H)CH₃ and -CCH), 1.12 (s, 9H, -C(CH₃)₃), 0.95 (t, J = 7.5 Hz, 3H, -CH₂CH₃).

13C NMR (CDCl₃, 100.6 MHz): δ 167.8, 133.6, 132.6, 130.2, 125.9, 107.5, 81.2, 72.0, 60.2, 58.8, 29.9, 23.2, 22.9, 11.7. FTIR: νₘₐₓ 2965 (m), 2923 (s), 2853 (m), 2032 (w), 1746 (m), 1600 (m), 1515 (m), 1458 (m), 1364 (w), 1255 (w), 1067 (s), 759 (m), 694 (m) cm⁻¹. HRMS: m/z [MH⁺] calc. for C₁₈H₂₃N₃O₃S: 362.1533, found: 362.1537. [α]D²³: 91.8 (c = 1.16, CHCl₃).
Synthesis of (R)-5-((R)-tert-butylsulfinyl)-6-ethyl-1-phenyl-1,4,5,6-tetrahydropyrrolo[2,4-c]pyrazole 189

A stirred solution of sydnone 188 (153 mg, 0.42 mmol) in toluene was heated at 110 °C for 20 h in a sealed tube. After cooling to room temperature, the volatiles were removed in vacuo and the crude product was purified by flash chromatography on silica gel (eluting solvent: 40% ethyl acetate in 60-40 petroleum ether), affording the desired product as a brown oil (72 mg, 53% yield).

^1H NMR (CDCl$_3$, 400 MHz): δ 7.52 – 7.48 (m, 2H, Ph$H$), 7.47 – 7.41 (m, 2H, Ph$H$), 7.39 (s, 1H, Pyzl$H$), 7.33 – 7.27 (m, 1H, Ph$H$), 5.26 (app q, J = 3.5 Hz, 1H, Pyzl-CH-N), 4.82 (d, J = 12.0 Hz, 1H, Pyzl(CH-N)), 3.88 (dd, J = 12.0, 3.5 Hz, 1H, Pyzl-(CH)N), 1.72 – 1.66 (m, 2H, -C(=CH$_2$)CH$_3$ and -CH(CH$_3$)$_3$), 1.29 (s, 9H, -C(CH$_3$)$_3$), 0.63 (t, J = 7.5 Hz, 3H, -CH$_2$CH$_3$). ^13C NMR (CDCl$_3$, 100.6 MHz): δ 144.8, 139.5, 133.3, 129.6, 127.0, 126.5, 120.8, 66.3, 58.0, 39.8, 27.4, 24.0, 7.8. FTIR: ν$_{max}$ 2964 (m), 2926 (m), 2873 (m), 1600 (m), 1515 (m), 1457 (m), 1426 (m), 1364 (w), 1331 (w), 1131 (w), 1067 (s), 993 (m), 758 (s), 694 (m), 641 (m) cm$^{-1}$. HRMS: m/z [MH$^+$] calc. for C$_{17}$H$_{23}$N$_3$OS: 318.1635, found: 318.1634. [α]$_D^{23}$: -102.5 (c = 0.40, CHCl$_3$).

Synthesis of (R)-2-methyl-N-((R)-1-(1-phenyl-3-trimethylsilyl-1H-pyrazol-5-yl)propyl)propane-2-sulfinamide 194

A solution of sydnone 178a (35 mg, 0.108 mmol) in neat trimethylsilylacetylene was stirred at room temperature for 5-10 minutes in a sealed tube and afterwards, heated to 80 °C for 48 h. After cooling, the crude mixture was purified by flash chromatography on silica gel (eluting solvent: 50 % ethyl acetate in 60-40 petroleum ether) affording the desired pyrazole 194 as an orange oil (15 mg, 42% yield).
$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.54 – 7.36 (m, 5H, PhH), 6.47 (s, 1H, PyzH), 4.40 (dd, $J = 11.0$, 4.0 Hz, 1H, Pyzl-CH-N), 3.40 (d, $J = 4.0$ Hz, 1H, -NH-), 1.93 – 1.71 (m, 2H, -CH$_2$CH$_3$), 1.18 (s, 9H, -SO-C(CH$_3$)$_3$), 0.76 (t, $J = 7.5$ Hz, 3H, -CH$_2$CH$_3$), 0.31 (s, 9H, -SiC(CH$_3$)$_3$).

$^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 153.7, 144.1, 139.7, 129.4, 128.6, 116.4, 111.2, 56.0, 52.7, 30.1, 22.7, 10.2, -0.9. FTIR: $\nu_{\text{max}}$ 2958 (w), 2924 (m), 2854 (w), 1501 (m), 1457 (w), 1248 (m), 1055 (m), 980 (m), 841 (s), 760 (m), 696 (m) cm$^{-1}$. HRMS: m/z [MH$^+$] calc. for C$_{19}$H$_{31}$N$_3$OSSi: 378.2030, found: 378.2040. $[\alpha]_D^{23}$: -60.6 (c = 0.97, CHCl$_3$).

**Synthesis of 2-methyl-N-((R)-1-(1-phenyl-1H-pyrazol-5-yl)propyl)propane-2-sulfinamide 195 (via cycloaddition)**

A stirred solution of pyrazole 194 (15 mg, 0.040 mmol) and tetrabutylammonium fluoride (0.40 mL, 1.0 M, 0.40 mmol) in tetrahydrofuran was heated at 80 °C for 24 h. After cooling to room temperature, the reaction was quenched with saturated NaHCO$_3$(aq), extracted with CH$_2$Cl$_2$, dried over MgSO$_4$ and the volatiles were removed in vacuo. The crude product was purified by flash chromatography on silica gel (eluting solvent: 50% ethyl acetate in 60-40 petroleum ether), affording the desired product as an orange oil (2 mg, 16% yield).

NOTE: The compound showed identical spectroscopic data to 193.
**Preparation of the pyrazole sulfinimine model analogues:**

**Synthesis of 1-phenyl-1H-pyrazole-5-carbaldehyde 191**

To a stirred solution of 1-phenyl-1H-pyrazole (3.20 mL, 24.25 mmol) in anhydrous THF at -78 °C under a N₂ atmosphere, n-BuLi (12.10 mL, 26.70 mmol) was added dropwise and the mixture was left to stir at -78 °C. After 2 h, dimethylformamide (2.00 mL, 26.70 mmol) was added dropwise and the mixture was left stirring to warm to rt for 20 hours. After that, the reaction was quenched with 10% HCl (aq), neutralised with 1.0 M NaOH (aq), extracted with EtOAc, dried over MgSO₄ and the volatiles were removed in vacuo. The crude product was purified by flash chromatography on silica gel (eluting solvent: 10% EtOAc in petroleum ether) affording the desired pyrazole 191 as a yellow oil (2.79 g, 67% yield).

**1H NMR (CDCl₃, 400 MHz):** δ 9.88 (s, 1H, -CHO), 7.76 (d, J = 2.0 Hz, 1H, PyzH), 7.54 – 7.46 (m, 5H, PhH), 7.11 (d, J = 2.0 Hz, 1H, PyzH).

**13C NMR (CDCl₃, 100.6 MHz):** δ 180.0, 140.5, 129.5 (x2), 129.2, 125.7, 119.3, 112.4.

**Synthesis of (R)-5-(((tert-butylsulfinyl)imino)methyl)-1-phenyl-1H-pyrazole 192**

To a stirred solution of 1-phenyl-1H-pyrazole-5-carbaldehyde (1.0 g, 5.81 mmol) and (R)-2-methylpropane-2-sulfinamide (3.98 g, 29.04 mmol) in dichloromethane at 0 °C under a N₂ atmosphere, TiCl₄ (0.64 mL, 5.81 mmol) was added dropwise, and the mixture left to warm to rt over 24 h. After that, the crude mixture was filtered through a short pad of celite and the volatiles were removed in vacuo. Purification by flash chromatography on silica gel (eluting solvent: 20% ethyl acetate in 60-40 petroleum ether) afforded (R)-5-(((tert-butylsulfinyl)imino)methyl)-1-phenyl-1H-pyrazole as a dark yellow oil (1.50 g, 90% yield).

**1H NMR (CDCl₃, 400 MHz):** δ 8.52 (s, 1H, -CHO), 7.76 (d, J = 2.0 Hz, 1H, PyzH), 7.60 – 7.40 (m, 5H, PhH), 7.04 (d, J = 2.0 Hz, 1H, PyzH), 1.19 (s, 9H, -C(CH₃)₃).

**13C NMR (CDCl₃, 100.6 MHz):** δ 151.2, 140.7, 138.3, 129.6, 129.2, 125.9, 110.2, 58.3, 22.7, 21.4. **FTIR:** νmax 2962
(w), 2926 (w), 1688 (w), 1591 (m), 1500 (m), 1365 (m), 1315 (m), 1132 (m), 1084 (s), 925 (m), 804 (m), 765 (s), 695 (m) cm⁻¹. HRMS: m/z [MH⁺] calc. for C₁₄H₁₈NO₃S: 276.1165, found: 276.1169. [α]D₂₃: -158.7 (c = 0.32, CHCl₃).

**Synthesis of (R)-2-methyl-N-[(R)-1-(1-phenyl-1H-pyrazol-5-yl)propyl]propane-2-sulfinamide 193 (via Grignard addition)**

![192](attachment:image1.png) → EtMgBr (2 eq.) THF, -78 °C, 4 h → ![193](attachment:image2.png)

To a stirred solution of (R)-5-(((tert-butylsulfinyl)imino)methyl)-1-phenyl-1H-pyrazole 192 (500 mg, 1.82 mmol) in tetrahydrofuran at -78 °C under a N₂ atmosphere, ethylmagnesium bromide (1.25 mL, 3.63 mmol) was carefully added dropwise (over approx. 5 min.) and the mixture left to stir at -78 °C for 4 h. After that, the crude mixture was quenched with saturated NH₄Cl(aq), extracted with dichloromethane and concentrated in vacuo. Purification by flash chromatography on basic alumina (eluting solvent: 50% ethyl acetate in 60-40 petroleum ether) afforded the desired pyrazole product as an orange oil (301 mg, 54% yield).

**¹H NMR (CDCl₃, 400 MHz):** δ 7.65 (d, J = 2.0 Hz, 1H, PyzlH), 7.52 – 7.41 (m, 5H, PhH), 6.42 (d, J = 2.0 Hz, 1H, PyzlH), 4.47 – 4.38 (m, 1H, Pyzl-C-H-N), 3.41 (d, J = 4.5 Hz, 1H, -NH-), 1.95 – 1.75 (m, 2H, -CH₂CH₃), 1.18 (s, 9H, -C(aryl)₃), 0.79 (t, J = 7.5 Hz, 3H, -CH₂CH₃).

**¹³C NMR (CDCl₃, 100.6 MHz):** δ 144.3, 140.3, 139.5, 129.5, 128.7, 126.3, 105.2, 56.1, 52.8, 30.1, 22.7, 10.2. FTIR: νmax 3210 (w), 2963 (m), 1600 (w), 1503 (s), 1456 (m), 1397 (m), 1366 (w), 1203 (w), 1054 (s), 929 (m), 766 (m), 697 (m) cm⁻¹. HRMS: m/z [MH⁺] calc. for C₁₆H₂₃N₃OS: 306.1635, found: 306.1638. [α]D₂₃: -87.8 (c = 0.70, CHCl₃).

**Synthesis of (R)-2-methyl-N-[(S)-phenyl(1-phenyl-1H-pyrazol-5-yl)methyl]propane-2-sulfinamide 196**

![192](attachment:image3.png) → PhMgBr (2 eq.) CH₂Cl₂, -78 °C, 4 h → ![196a](attachment:image4.png)

To a stirred solution of (R)-5-(((tert-butylsulfinyl)imino)methyl)-1-phenyl-1H-pyrazole 192 (100 mg, 0.363 mmol) in dichloromethane at -78 °C under a N₂ atmosphere, phenylmagnesium bromide (0.24 mL, 0.726 mmol) was carefully added dropwise (over
approx. 5 min.) and the mixture left to stir at −78 °C for 4 h. After that, the crude mixture was quenched with saturated NH₄Cl(aq), extracted with dichloromethane and concentrated in vacuo. Purification by flash chromatography on basic alumina (eluting solvent: 50% ethyl acetate in 60-40 petroleum ether) afforded the desired pyrazole product as a yellow solid (58 mg, 45% yield).

**Melting point:** 66-68 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.67 (d, J = 2.0 Hz, 1H, PyzlH), 7.44 – 7.35 (m, 3H, PhH), 7.33 – 7.25 (m, 5H, PhH), 7.23 – 7.15 (m, 2H, PhH), 6.53 (d, J = 2.0 Hz, 1H, PyzlH), 5.69 (d, J = 2.5 Hz, 1H, Pyzl-CH-N), 3.59 (d, J = 2.5 Hz, 1H, -NH-), 1.23 (s, 9H, -C(CH₃)₃). ¹³C NMR (CDCl₃, 100.6 MHz): δ 143.5, 140.1, 139.4, 129.3, 129.1, 128.8, 128.6, 128.2, 127.7, 126.3, 125.9, 106.7, 56.2, 22.7. FTIR: νmax 2924 (m), 2854 (w), 1599 (w), 1502 (s), 1455 (m), 1397 (m), 1199 (w), 1058 (s), 766 (m), 697 (s) cm⁻¹. HRMS: m/z [MH⁺] calc. for C₂₀H₂₃N₃OS: 354.1635, found: 354.1640. [α]D²³: −76.2 (c = 0.32, CHCl₃).
Chapter 10. References

35. Kwok, S. W.; Fotsing, J. R.; Fraser, R. J.; Rodionov, V. O.; Fokin, V. V., Org. Lett. 2010, 12, 4217-4219.
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Chapter 11. Appendix

The enclosed CD contains data for the following X-ray crystal structures:

1-Phenyl-3-tert-butyl-4-di-tert-butylethynyl)borane)-5-(2-pyridyl)pyrazole (162)

1-Phenyl-3-n-hexyl-4-di-octynylborane)-5-(2-quinolyl)pyrazole (163)

4-((S)-1-((R)-tert-butylsulfinamido)propyl)-N-phenylsydnone (178b)
(R)-2-methyl-N-((S)-phenyl(1-phenyl-1H-pyrazol-5-yl)methyl)propane-2-sulfinamide (196a)