REVISITING TRÖGER’S BASE: FUNCTIONALIZATION AND APPLICATION

A thesis submitted to attain the degree of

DOCTOR OF SCIENCES of ETH ZURICH
(Dr. sc. ETH Zurich)

presented by

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2016
To the present and the faithful departed.
“If I have seen further, it is by standing upon the shoulders of giants”

Sir Isaac Newton
Acknowledgements

Reminiscing on how I got to this point it is almost overwhelming how many people have helped me. All that I have achieved are due to the guidance, support, and generosity of others.

I would like to start by thanking my advisor, Ján Cvengroš. I was extremely fortunate to get the opportunity to come to the ETH Zürich and work with Ján. I can’t envision having a more positive PhD experience anywhere else and consider myself fortunate. I have learned a lot from Ján, who has been extremely supportive. He has been an excellent mentor and the success I have achieved during my time at the ETH is largely due to him. Alongside Ján, I would like to thank Antonio Togni for supervising my doctoral thesis and hosting me in his laboratory, and for all the support and being a great influence during my PhD. I would like to thank Prof. Jeffrey Bode for agreeing to read and co-referee my thesis. I thank Véronique Gouverneur for affording me the opportunity to work with her at the University of Oxford; the year spent in her laboratory was a dream come true. I would like to take this opportunity to thank Tim Claridge for the help with the NMR experiments carried out at Oxford. Finally, I thank Graham Sandford for hosting me in his laboratory and showing me the intricacies of fluorine gas.

I have had the great pleasure with working with a number of talented scientists, both at the ETH as well as at Oxford. Raphael Bigler and Chandan, for their valuable chemical insight. I’d like to thank Joël for being the default social secretary, an honorary member of H230, and for being around to lend a hand. Václav Matoušek for the outrageous discussions, and then some thought provoking chemical discussions. I thank Elisabeth for helping out with the X-ray crystallography. I’d like to thank Rene for the help with NMR. I’d like to thank my students - Alzbeta and Fumito- for eagerly working on the projects. I’d like to thank Julie for being an excellent proof-reader; she has an unrivalled ability to sniff out mistakes. Takuya, for proofreading my thesis, and being the ‘decent bloke.’ H230 would have been a very different place without Alex, Sandra and Peter. At Oxford, I would have been completely at sea if were not for the very talented Dr. Preshlock and Enrico, the in-house maestro, who took time to answer all of my questions, no matter how trivial. I must thank Lukas for taking care of all the X-ray crystallography. I would like to thank my laboratory mates in F12 for the amazing time in Oxford, in particular the trifecta of Thomas Charles Wilson, who was an amazing bench-partner and for tolerating all of my idiosyncrasies, the right honourable Nicholas John Taylor, for introducing me to the joys of port, formals, brass band, and starting
up flash columns at 1 AM, and finally Michael Schedler for being an eternal source of knowledge and absinthe.

I must thank the people who have been indirectly a part of this journey. My family who’ve supported, without reservation, this path I’ve taken. Ferrario Bau AG and ZBF, for the patronage over the past 6 years. Alejandro, probably the first friend I made in Zürich, for always being game to do anything. Zia Tutta d’Acqua, for the most amazing dinners and the lovely cups of coffee high up the Swiss Alps. The year spent in Oxford was made extremely fun with all the lovely people I met especially my housemates Armando, Gayatri and Fernando.
Publications

Peer reviewed publications

Poster presentations

Oral presentations
1. Synthesis and Application of N-Stereogenic Compounds, L.M. Venanzi Christmas Symposium, ETH Zürich, Zürich, Switzerland, December 2012.
2. Synthesis and Characterization of a Novel N–F Reagent derived from the Ethano-Tröger’s Base: $^1J_{(N-F)}$ Coupling Constant as Signature for the N–F Bond, LAC Christmas Symposium, ETH Zürich, Zürich, Switzerland, December 2015.
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Abstract

This thesis is focussed on exploring the Tröger’s base (TB) as a scaffold for the synthesis of phosphane based ligands, and an electrophilic fluorinating reagent. In addition, efforts towards the amine-alpha functionalisation have yielded a route for the oxygenation as well as nitrogenation of TB analogues.

Exploring the Tröger’s base (TB) as a scaffold, a library of $C_2$-symmetric phosphane ligands for Suzuki-Miyaura and Buchwald-Hartwig cross coupling reactions have been designed and synthesised via a concise two-step protocol (Chapter 2). Studies showed that the position of the phosphorus moiety played a pivotal role in catalysis.

Looking at ways to functionalise Tröger’s base and the ethylene-bridged analogues, we have discovered a method to oxidatively functionalise not only the Tröger’s base but aslo the ethylene-bridged Tröger’s base (ETB) utilizing a combination of N-bromosuccinimide (NBS) and palladium(II) acetate.

Furthermore, we have successfully extended a protocol, utilizing potassium permanganate, to oxidise the benzylic carbons of ETB (Chapter 3).
Utilising the nitrogen atoms of ETB we have successfully synthesised an electrophilic fluorinating reagent, which shows a remarkably up field $^{19}$F NMR resonance [(δ) at +103 ppm] for the N–F group (Chapter 4).

This reagent proved itself to be a potent electrophilic fluorinating reagent, and experimental data suggest that it is stronger than Selectfluor. To help characterize the N–F bond in particular, we performed 1D $^{19}$F NMR and 2D $^{19}$F-$^{15}$N heteronuclear correlation experiments with 403 and for completeness with other N–F reagents. We also measured $^1J_{FN}$ couplings constants to further characterise the N–F bond.
Zusammenfassung

In dieser Arbeit wird die Erforschung von Phosphanliganden basierend auf der Struktur der Trögerschen Base (TB) und die Anwendung eines fluorierten Derivats als elektrophiles Fluorierungsreagenz beschrieben. Zudem wurde mittels alpha-Funktionalisierung von Aminen ein Protokoll für die Synthese von neuen oxygenierten oder aminierten TB Analoga entwickelt.


Eine neue Methode für die Funktionalisierung der Trögerschen Base (TB) und ihres ethylenverbrückten Analogs (ETB) wurde entwickelt. Eine Kombination aus N-Bromosuccinimid (NBS) und Palladium(II)-acetat ermöglicht die oxidative Mono- und Difunktionalisierung in der alpha-Position der Stickstoffatome (Kapitel 3).
Ferner konnte die Methode zur selektiven Oxidation der benzyllischen Positionen in TB mittels Kaliumpermanganat auf das ethylenverbrückte Analog ETB übertragen werden (Kapitel 3).

Unter Einbezug der Stickstoffatome in ETB wurde erfolgreich ein elektrophiles Fluorierungsreagenz hergestellt, welches eine aussergewöhnlich hohe $^{19}\text{F}$ NMR Resonanzfrequenz für die N–F Gruppe aufweist ($\delta = +103$ ppm, Kapitel 4).

General Remarks
The thesis is presented as four separate chapters. Structures are numbered depending on the chapter, for easier orientations. For example **201** refers to the first structure in chapter **2**. Schemes, figures and tables are numbered in sequence within chapters. Names for compounds were generated using ChemBioDraw Ultra 15.0.
Chapter 1: Tröger’s Base

1.1 Introduction

Tröger’s base\(^1\) (TB), one of the best known organic compounds bearing stable stereogenic nitrogen atoms, has a rather inconspicuous beginning: In 1887 Carl Julius Ludwig Tröger isolated an unusual product from the condensation between \(p\)-toludine and methylal [\(\text{CH}_2(\text{OCH}_3)_2\)] in aqueous hydrochloric acid that he called “base \(\text{C}_{17}\text{H}_{18}\text{N}\)”, which we now know as Tröger’s base 101.\(^1\,^2\) Nearly half a century later, in 1935, after careful chemical analysis, Spielman assigned the structure of TB to be racemic 2,8-dimethyl-6\(H\),12\(H\)-5,11-methanodibenzo[\(b,f\)]\(1,5\)diazocine\(^3\) (Figure 1.1) which was confirmed when Wilcox published the first crystal structure of 101 in 1986.\(^4\)

![Figure 1.1 Tröger’s base 101 and its crystal structure.\(^4\)](image)

TB is a \(C_2\)-symmetric molecule consisting of a bicyclic aliphatic methanodiazocine unit bearing two fused aromatic rings that are nearly perpendicular to each other, making TB a rather rigid V-shaped molecule possessing a hydrophobic cavity (Figure 1.1). The methylene bridge between the nitrogen atoms hinders pyramidal inversion, rendering them configurationally stable stereocentres. As the stereogenic nitrogen’s are of a bridgehead variety, only the enantiomers of either the \((R,R)\) or \((S,S)\) configuration are possible, with the \((R,S)\)-TB being geometrically all but impossible.\(^2\,^a\) Prelog and Wieland were the first to resolve TB via chiral phase chromatography,\(^5\) and Wilen and co-workers determined the absolute configuration of (+)-101 via X-ray diffraction analysis of a salt of (+)-101 with \((R)\)-\((-)\)-1,1’-binaphthyl-2,2’-diyl hydrogenphosphate to be (+)-(S,S).\(^6\) TB slowly racemizes under dilute acidic conditions and a putative reversible methylene-iminium ion 102 (Scheme 1.1) is postulated as a key intermediate.\(^5\) Although there is no definitive spectroscopic evidence for the methylene-iminium 102,\(^7\) this mechanism is indirectly supported by the fact that ethylene-bridged TB analogues (See chapter 3 for more details), which are incapable of forming such stabilized iminium intermediates, do not racemize under acidic conditions.\(^8\) In concentrated acids wherein both nitrogen atoms are protonated it is not possible to form the iminium intermediate, as there is no free electron pair available to open the bridge, and
consequently racemization is not observed.

Trapp and Schurig came up with an alternative proposal which suggested a racemization pathway involving a retro-hetero-Diels–Alder ring opening followed by a hetero-Diels–Alder ring closure, via intermediate 103 (Scheme 1.2).9

However, recent work on the epimerization of fused bis-TB analogues by ion-mobility mass spectrometry (IM-MS) demonstrated that epimerization occurred via protonated species rather than the Diels-Alder route (Scheme 1.3).10

The unique structure of TB with its concave Λ-shape renders the nitrogen lone-pairs out of conjugation with the aromatic rings, and one would expect the pKa of a monoprotonated TB to lie between 5 (anilinium ion) and 10 (alkylammonium). Interestingly, Wepster, who reasoned that the benzylamine and the methylenediamine groups present in TB would lower the basicity by two pKa units, determined the pKa of the monoprotonated salt of 101 in 50 % aqueous alcohol to be 3.2.11 More recently, Wärnmark and co-workers proposed that, the low pKa is, in addition to the concave geometry, a consequence of an anomic
effect wherein the electron lone pair of one nitrogen atom overlaps with the antibonding orbital of the bond between the methylene-carbon and the second nitrogen thereby reducing the nitrogen lone pair availability for proton binding (Figure 1.2). Geometrically, the bond length of the bond between the protonated N and the bridging CH$_2$ increases relative to that in TB, whereas the bond between the other N and the bridging CH$_2$ decreases as expected for an anomeric effect, and is seen via DFT calculations.$^{2a}$

**Figure 1.2** Overlap of the lone pair of one nitrogen atom with the antibonding orbital [$\sigma^*$ (C–N)] of the bond between the methylene-carbon and the second nitrogen atom (left). Selected bond lengths in TB [N5–C13 = 1.465 Å, N11–C13 = 1.465 Å (centre) and in protonated TB [N5–C13 = 1.431 Å, N11–C13 = 1.535Å] (right).$^{2a}$
1.2 Synthesis of Tröger’s Base and its Analogues

1.2.1 Classic Tröger’s Base Synthesis

Tröger’s original synthesis involved the condensation between \( p \)-toluidine and methylal in aqueous hydrochloric acid.\(^1 \) Currently there are several different methods used to synthesize TB and its derivatives, however most of the trögeration\(^{12} \) conditions are alterations of the original conditions wherein a methylene synthetic equivalent \([\text{paraformaldehyde},^{2a,13} \text{hexamethylenetetramine},^{2a,14} \text{or dimethylsulfoxide}^{15}]\) is treated with a suitably substituted aniline-derivative\(^{13} \) under acidic conditions \([\text{HCl}_{(ROH)}^{1,16} \text{trifluoroacetic acid (TFA)},^{13} \text{methanesulfonic acid},^{17} \text{or Lewis acids such as } \text{AlCl}_3 \text{ and TiCl}_4^{18}]\) to yield the corresponding TB derivative (Scheme 1.4).

![Scheme 1.4 The trögeration reaction.](image)

Most of the synthetic procedures are sensitive towards both the electronic properties of the substituents and towards the substitution patterns of the aniline, and have the following common important limitations: the aromatic substituents should be electron-donating, and as well as have a substituent in the \emph{para}-position to avoid polymerization.\(^{2a,b} \) However, the trögeration protocol using paraformaldehyde and TFA\(^{13a} \) overcame these limitations and has become the most widely used method to synthesize Tröger’s base analogues bearing a wide range of both electron-donating and -withdrawing substituents on the aromatic rings. Utilizing this method it’s possible to condense aniline and paraformaldehyde to yield the di-demethylated TB analogue in 78% yield.\(^{19} \) Furthermore, this reaction shows that the absence of a substituent in the \emph{para}-position of the starting aniline does not necessarily lead to polymerization. From a mechanistic point of view, the trögeration is very interesting wherein six bonds are formed in a single reaction (Scheme 1.5).\(^{20} \)
The first step of the mechanism is an acid-catalysed condensation between $p$-toluidine and formaldehyde to form iminium ion 104, which in-turn reacts with a second equivalent of the aniline to give intermediate 105. A sequence of reactions involving the condensation between the primary amine and paraformaldehyde followed by cyclization yields intermediate 107 via 106. The secondary amine in 107 undergoes an acid catalysed condensation with formaldehyde yielding intermediate 108 that undergoes an electrophilic cyclization to give Tröger’s base 101. The rate-limiting step of the reaction sequence is the conversion of tetrahydroquinazoline derivative 107 into the more reactive intermediate 108 and the subsequent electrophilic aromatic substitution. The presence of electron-withdrawing groups on the aniline reduces the nucleophilicity of the secondary amine in 107, resulting in a further decrease in the rate of the intramolecular electrophilic substitution, and gives rise to the formation of the dihydroquinazoline A as a side reaction product (Scheme 1.5). However it is believed that CF$_3$COOH is an acid strong enough to protonate A to yield intermediate B that can accept a hydride from paraformaldehyde to regenerate 107. Further evidence for this mechanism was available from an electrospray ionization mass and tandem mass spectrometry (ESI-MS/MS) study on the TFA-mediated condensation between $p$-toluidine and hexamethylenetetramine, wherein iminium ion 104 was detected and characterized, along with the oxidized forms of intermediates 107-H and 109-H suggested by Wagner.
Further evidence was furnished when compounds 110 and 111 (Figure 1.3) were isolated during the synthesis of TB in an ionic liquid, and then subjected to the trögeration conditions at 150 °C to yield 101. 22

1.2.2 Alternative Syntheses of Tröger’s Base Analogues

Whilst the one-pot condensations of simple aniline derivatives to synthesize TB analogues are elegant, they utilize relatively harsh conditions limiting the range of functional groups that can be incorporated on the aniline ring. Furthermore TB is acid labile and the acid mediated synthesis route cannot be used effectively to synthesise enantiopure TB derivative. Furthermore, the direct condensations between aniline derivatives and formaldehyde only give access to symmetrically substituted analogues of TB. Wilcox and Sergeyev have used a step-wise method to tether two differently substituted aniline derivatives via a methylene linkage and then cyclize the intermediate with formaldehyde to yield the unsymmetrically substituted TB analogue (Scheme 1.6). 19,23
Metlesics and co-workers reported a diastereoselective synthesis of phenyl substituted Tröger bases starting with *cis* or *trans* tetrahydro-diphenyl[1,5]diazocine and formaldehyde (Scheme 1.7). They also showed that the trans and *cis*-endo isomers completely isomerize to form the *cis*-exo isomer in the presence of a strong base.24

Following Wilcox’s TB analogue synthesis based on the diastereoselective cyclization of a chiral precursor,14 Maitra and co-workers have utilized a 7-deoxycholic acid template to access a TB derivative with $dr = 7:3$ (Scheme 1.8).25
Recently Cvengroš and co-workers reported a diastereoselective synthesis of TB analogues wherein the 5,11-methylene bridge was inserted into the tetrahydrodi-benzo[b,f][1,5]diazocine framework via a double aza-Michael reaction using propiolic acid (or derivative) as the Michael acceptor (Scheme 1.9).\textsuperscript{26}

The diastereoselective version of this reaction was carried out with a derivative of propiolic acid bearing a chiral auxiliary. Accordingly, the diazocine was reacted with a Michael acceptor bearing a chiral auxiliary in hexafluoroisopropanol (HFIP) to yield the TB analogue with $dr = 73:27$ (Scheme 1.9). Interestingly, TB analogues have been synthesized by a similar method wherein the 5,11-methylene bridge is introduced on to the diazocine using formaldehyde,\textsuperscript{27} other aldehydes or ketones\textsuperscript{28} as the methylene carbon source.

It was known that (±)-101 could be resolved efficiently with chiral acids,\textsuperscript{6,18} but methods to resolve TB derivatives bearing functionalizable groups were not known until recently when Jameson and co-workers reported a tartaric acid mediated asymmetric crystallisation method to synthesize enantiopure 2,8-disubstituted TB derivatives in good to excellent yields (Scheme 1.10).\textsuperscript{29}
Tröger’s Base

This method unfortunately did not work with TB analogues bearing groups *ortho* to the nitrogen atom, whose value lies in its limited tendency to racemize compared to 1.30 Cvengroš and co-workers have recently found a solution to this problem via a chiral disulphoxide route (Scheme 1.11).31

Scheme 1.10 Resolution of 2,8-substitued TB analogues via a crystallisation-induced asymmetric transformation.

Scheme 1.11 Synthesis of enantiopure 4,10-disubstituted TB analogues.

The racemic 4,10-dibromo Tröger’s base was lithiated and quenched with the Andersen reagent, (1R,2S,5R)-(-)-menthyl (S)-p-toluenesulfinic32 affording disulfoxide as a mixture of two diastereomers[[S,S,S,11S]] and [S,S,5R,11R]] which were separated via column chromatography and then the sulfinyl moiety was replaced with bromine to yield the enantiopure dibromo TB analogue (Scheme 1.11). More recently Periasamy and co-workers have reported the resolution of 4,10-dibromo Tröger’s base with (1R)-(−)-10-camphor sulfonic acid.33
1.3 Application of Tröger’s Base and its Analogues

Until the 1980s, Tröger’s base was only used as a standard to evaluated chiral chromatographic methods.\textsuperscript{2a,b} The most well known application of TB analogues is the molecular torsional balances developed by Wilcox and Bhayana to measure weak intra-molecular interactions like aromatic face-to-edge interactions and CH–π interactions.\textsuperscript{34} The small free energy differences between the folded and unfolded conformers are calculated via NMR spectroscopy. Diederich and co-workers have used torosional balances based on a TB scaffold to study dipolar interactions between a C\textsubscript{6}(aromatic)–F bond and an amide carbonyl group.\textsuperscript{35} Furthermore they have also shown that Tröger’s base analogs can also be used to selectively functionalize C\textsubscript{60} and thus afforded enantiomerically pure fullerene derivatives.\textsuperscript{36}

Exploiting the inherent chirality of Tröger’s base, Wilen and co-workers have used (+)-101 as a chiral solvating agent to discriminate enantiomers of racemic alcohols in their \textsuperscript{1}H NMR spectra.\textsuperscript{6} More recently, McKeown and co-workers have incorporated TB derivatives into microporous polymers that work as membrane sieves for gas separations (Figure 1.4).\textsuperscript{37}

\textbf{Scheme 1.12} Tröger’ base derived molecular torsional balances.

\textbf{Figure 1.4} Tröger’s Base derived polymers for gas separation.
Demeunynck and co-workers have reported an enantioselective interaction of an acridine analogue of Tröger base with calf-thymus DNA, presumably, via minor-groove binding of the V-shaped motif rather than by the intercalation of the planar acridine moiety.\(^{38}\) Furthermore, Gunnlaugsson and co-workers have shown bis-1,8-naphthalimide based Tröger’s Bases (Figure 1.5) to be effective calf-thymus DNA binders \((K_d = 10^{-7} \text{ M})\).\(^{39}\)

![Figure 1.5 Tröger’s base analogues as DNA binding agents.](image)

Additionally, Tröger’s base analogues have been incorporated as structural elements into polymers, which have been used as gas separation membranes.\(^{37,40}\) Interestingly, despite its unique geometry and straightforward synthesis there have been not too many reports on Tröger’s bases being used in asymmetric transformations, or as organocatalysts or as ligands. In most of the reports TB 101 has been used as is, and no concrete effort has been made to rationally functionalize TB derivatives. Perhaps the first use of TB as a ligand was in the hydrosilylation of terminal alkynes. The complex TB·2RhCl\(_3\) showed catalytic activity, giving rise to the thermodynamically less stable \(cis\) products with selectivity up to 95\% (Scheme 1.13).\(^{41}\)

![Scheme 1.13 Hydrosilylation of terminal alkynes.](image)

Interestingly the iridium complex showed no catalytic activity at all in the hydrosilylation reaction. Baiker and co-workers used enantiopure \((+)-101\) as a surface modifier in the Pt/Al\(_2\)O\(_3\) mediated hydrogenation of ethyl pyruvate, forming ethyl lactate with 65\% \(ee\) (Scheme 1.14).\(^{42}\)
Shen and co-workers have used (+)-101 in the amine-promoted aziridation of chalcones yielding ees of up to 67% (Scheme 1.15).\(^43\)

(-)-101 gave rise to a 57% ee when used as an additive in the 1,4-addition of aryllithium species to \(\alpha,\beta\)-unsaturated tert-butyl esters (Scheme 1.16).\(^44\)

Harmata studied the effect of different TB chiral ligands in the additions of \(\text{Et}_2\text{Zn}\) to aromatic aldehydes. Although parent (+)-101 gave poor enantioselectivity in the resulting alcohol, 6-exo-substituted TB analogue afforded up to 86% ee (Scheme 1.17).\(^45\)

TB analogues bearing thiourea on the aromatic rings have been used as catalysts in Michael additions of malonate derivatives to nitro olefins without any enantioselectivity.\(^46\) Furthermore, substituted pyrazole analogues of TB were used as organocatalysts in one-pot Mannich reactions between aromatic aldehydes, aniline derivatives, and cyclohexanone in
aqueous media, resulting in good yields and anti/syn stereoselectivities (up to 90/10) of the products (Scheme 1.18).47

\[
\text{Ar-CHO} + \text{Ar'-NH}_2 \quad \xrightarrow{\text{TB pyrazole analogue}} \quad \text{anti} \quad \text{Ar}^1 \quad \text{HN} \quad \text{H} \quad \text{anti} \quad \text{Ar}^1 \quad \text{HN} \quad \text{H} \quad \text{Ar}^2 \quad \text{HN} \quad \text{H} \quad \text{Ar}^2
\]

**Scheme 1.18** Mannich reaction organocatalysed by a TB pyrazole analogue.

The dimeric dipalladium complex (Figure 1.6) based on a pyrazole TB architecture, was used as a catalyst in the Mizoroki-Heck C–C coupling reaction, displaying high catalytic activity with 89–93% conversion.48

![Figure 1.6 Pd4Cl8(PzTB)2 complex.](image)

Recently TB analogues bearing tethered [C-H]^+ sites have been successfully applied as catalysts in the benzoin condensation and Baylis-Hillman reaction (Scheme 1.19).49

**Scheme 1.19** TB analogues as catalysts in the benzoin condensation.
1.4 References

(21) Hudlicky, M. Reductions in Organic Chemistry; American Chemical Society, 1996.


Chapter 2: Tröger’s Base Derived P, N & P Ligands

2.1 Introduction

In the last quarter of the 20th century, a new model for carbon–carbon and carbon–heteroatom bond\(^1\) formation emerged that enhanced the ability of synthetic organic chemists to assemble complex molecular frameworks, and has altered the way we approach synthesis.\(^{1a,2}\) Amongst the myriad of metal catalysed cross-coupling reactions, the Pd-catalysed C–C and C–N cross-coupling reactions have become increasingly important, and the ease by which one is able to construct carbon–carbon or carbon–nitrogen bonds between or within functionalized and sensitive substrates provides new opportunities, particularly in total synthesis\(^{2b}\) but also in medicinal and process chemistry\(^3\) and in chemical biology\(^4\) (Fig. 2.1).

![Figure 2.1](image)

**Figure 2.1** Linifanib,\(^3\) a VEGF inhibitor (left). A well-defined \(N^2\)–carcinogenic amine adduct of 2'-deoxyguanosine (right).\(^4\)

2.1.1 Palladium Catalysed Suzuki-Miyaura reaction

In the mid 1970s Negishi and co-workers in their study outlining the coupling of vinylaluminium species and aryl bromides showed that attempts to cross-couple organoboron reagents with organic halides led to no product formation.\(^5\) Suzuki and Miyaura postulated that the activation of the boron-species by utilising a negatively charged base such as an alkoxide, acetate or hydroxide ion might render the organoboron reagent nucleophilic enough for transmetallation to occur (Scheme 2.1).
1979 Miyaura, Yamada and Suzuki reported the first palladium catalysed coupling of an alkenyl-boronate with an alkenyl bromide,\textsuperscript{1b} which has now become arguably the most important carbon-carbon bond forming reaction. Over the past 35 years, contributions from several research groups have lead to improvements on what we know as the Suzuki-Miyaura cross-coupling reaction.\textsuperscript{2a,6} Amongst the palladium-catalysed cross-coupling processes, the Suzuki reaction of aryl and vinyl halides/triflates with boronic acids is a clear favourite,\textsuperscript{6a,c} and due to its robustness, it is routinely used in industry, a prime example being Merck’s antihypertensive drug – losartan.\textsuperscript{7} Whilst seminal reports typically employed catalysts featuring relatively simple ligands, such as \( \text{PPh}_3 \), several advances have been made to address more challenging substrate transformations, including the use of aryl chlorides as electrophiles,\textsuperscript{8} involving coupling between stericly hindered substrates,\textsuperscript{9} to carry out the reactions using low catalyst loadings\textsuperscript{8b,10} and under increasingly mild conditions.\textsuperscript{11} Accordingly, over the years this reaction has undergone extensive optimisation, allowing for almost any combination of aryl, alkenyl or aliphatic halide or triflate to be coupled with a wide range of alkyl, alkenyl or aryl boronic acids (Scheme 2.2).\textsuperscript{6a,10,12}

\textbf{Scheme 2.2} Generic palladium catalysed Suzuki cross-coupling.

Until the late 1990s, nearly all reports of palladium-catalysed couplings described the use of organic bromides, iodides and triflates as substrates, whilst organic chlorides were uncommon coupling partners despite the fact that organic chlorides are much more widely available and are much cheaper than the corresponding bromides and iodides. None of the palladium-catalyst combinations could effectively couple aryl chlorides with boronic acids with the exception of aryl chlorides bearing electron-withdrawing groups. The indolent
nature of chlorides is usually ascribed to the strength of the C–Cl bond (BDE for Ph–X are as follows: Cl: 96 kcal/mol; Br: 81 kcal/mol and I: 65 kcal/mol). This higher bond strength prevents the aryl chloride from oxidatively adding across the Pd(0) centre, the first step of the catalytic cycles (Scheme 2.3). To understand the role of the phosphine ligands in palladium catalysed reactions, it is helpful to evaluate the steps present along a catalytic pathway. Many palladium-catalysed reactions follow a similar mechanistic pathway and therefore a general mechanistic view can provide insight into the factors that influence catalytic activity of a palladium-ligand complex. The mechanism of the Suzuki cross-coupling reaction follows the generic oxidative addition, transmetallation, reductive elimination sequence, and is comprised of four processes as shown below: 1) Oxidative addition of the organic halide to the Pd(0) species to form the Pd(II) intermediate; 2) anion exchange from this species with one on the base (metathesis); 3) transmetallation of the alkyl/aryl-borate species, generated by the reaction of base with the organoborane, and Pd(II) species; 4) reductive elimination to yield the product and thereby regenerating the catalyst.

Scheme 2.3 General mechanism of the Suzuki-Miyaura reaction.

Hartwig and co-workers extensively studied the 14 electron Pd[P(o-C6H4Me)3]2 complex which undergoes oxidative addition leading to dimeric monophosphine palladium phenyl complex, suggesting that the monophosphane complex undergoes oxidative addition. However, the sole existence of a monophosphane-palladium complex is not always the necessary and sufficient condition for successful oxidative addition as described by Beller and co-workers who studied the relative reactivity of discreet [PdL3(diene)] complexes. Their results showed that complexes derived from PPh3 did not catalyse the couplings or aryl
chlorides, whilst those arising from $P(Cy)_3$ delivered the cross-coupled products smoothly and in high yields.\textsuperscript{8a,17} Fu and co-workers reported that their $[P(tBu)_3]_2\text{Pd}$ system delivered the best catalytic results when the ratio of ligand to Pd was unity.\textsuperscript{12a} The oxidative addition is promoted by an electron rich metal centre, and accordingly strongly $\sigma$-donating ligands such as alkyl phosphines enhance electron density at the metal centre.\textsuperscript{12h} Once oxidative addition occurs into the C–X bond, metathesis, transmetallation and reductive elimination follow. After the base abstracts the halide from the palladium, by exchanging it with $\text{HO}^-$ or $\text{RO}^-$ (Scheme 2.3), the metal centre behaves like an electrophile toward the incoming nucleophile, \textit{i.e.} the borate. It is therefore desirable for the newly generated $\text{Pd}^{\text{III}}$ centre to be electropositive to facilitate nucleophilic attack. Furthermore, the metal centre should be spatially or sterically accessible to the incoming nucleophile. Ligands around the metal centre can sterically hinder incoming nucleophiles if they are too large. However, in the reductive elimination step, larger ligand sizes tend to promote these events. It is therefore necessary to have an optimum ligand size so that neither the transmetallation nor the reductive elimination steps are inhibited. Additionally, steric bulk promotes ligand dissociation leads to the proposed active monophosphane palladium catalyst.\textsuperscript{8a,12a,h} As the oxidative addition step is a critical step and is believed to be the rate-determining step of the reaction,\textsuperscript{7,14-15} the high bond dissociation energy of aryl chlorides has rendered them not ideal coupling partners.\textsuperscript{18} This all changed in 1998 when the group of Buchwald reported the synthesis and use of dialkyl(2-biphenyl)phosphanes for the room temperature coupling of aryl chlorides and aromatic boronic acids,\textsuperscript{12f} which have now been developed in a well defined class of ligands that in addition to Suzuki cross-couplings,\textsuperscript{12h} can catalyse C–O\textsuperscript{19} and C–N\textsuperscript{20} bond forming reactions.
The group of Fu, in the same year as Buchwald, has reported the use of simpler PR$_3$ (R = tBu or Cy) electron rich phosphanes to couple electron rich aryl chlorides with phenyl boronic acid in a palladium catalysed Suzuki cross-coupling reactions.$^{8c}$ Their system comprised of [PtBu$_3$:Pd] ranging from 1.0 to 1.5, and exhibited an interesting reactivity profile wherein aryl chlorides were coupled in preference to aryl triflates (Scheme 2.4).

After these two landmark discoveries, reports in literature dealing with the coupling of aryl chlorides and boronic acids started to increase.$^{1a,9}$ For example, Beller and co-workers demonstrated that their new ligand di(1-adamantyl)-n-butylphosphan could afford excellent turnover numbers in palladium-catalysed Suzuki couplings that utilised electron rich aryl chlorides as electrophiles.$^{8b}$

### 2.1.2 Palladium Catalysed Buchwald-Hartwig Reaction

In 1983 Migita and co-workers reported the first Pd-catalysed C–N coupling of a tin-amide and an aryl bromide.$^{21}$ Approximately a decade later in 1994 Buchwald and co-workers revisited the reaction initially using a tin-amide,$^{22}$ and after another few years later they reported a palladium-catalysed coupling of aryl bromides with secondary amines utilising sodium tert-butoxide as a base.$^{23}$ Independently, Hartwig and co-workers carried out a study on the Pd-catalysed coupling of aryl bromides and secondary amines using a lithium amide
This reaction has undergone extensive developments that allow for C–N and C–O bond formation between aryl halides or triflates and a wide range of amines, or between aryl halides or triflates and alcohols.

As with the Suzuki reaction, most significant improvements have been made possible by the design of phosphane ligands (Fig. 2.3).

In most cases the ligands were designed to maximise catalyst activity by facilitating one or more of the steps in the catalytic cycle (i.e. oxidative addition, amine binding, deprotonation or reductive elimination), as well as to increase the robustness of the catalyst. The catalytic cycle is as considered in Scheme 2.6, and as with most palladium catalysed reactions the oxidative addition of Pd(0) to the aryl halide is the first step. Following this, the Pd(II)-aryl amide can be generated either by the direct displacement of the halide or by the amide via a Pd(III)-alkoxide intermediated. Finally, reductive elimination yields the desired C–N coupled product, thereby regenerating the catalyst.
Scheme 2.6 Mechanism of the Buchwald-Hartwig C–N coupling.
2.2 Motivation

Palladium-catalysed cross-coupling reactions between organometallic reagents and organic electrophiles have developed over the years into a sophisticated synthetic tool.\textsuperscript{1a,c} This methodology helped chemists to access complex architectures ranging from natural products and medicinal compounds to those in materials chemistry.\textsuperscript{2b,28} Phosphane ligands typically play a prominent role in these transformations.\textsuperscript{29} The ever-increasing demand to access new and more challenging targets has advanced the field of ligand design. Thus, the phosphane family of ligands consisting of simple representatives, such as 1,1'-bis(diphenylphosphany)ferrocene (dppf) and PPh\textsubscript{3}, which were frequently used at the infancy of palladium-catalysed cross-coupling reactions, recently expanded with the addition of tailor-made members. The development of meticulously designed electron-rich bulky phosphanes\textsuperscript{12h,18,25d,30} allowed for the sluggish reactivity of aryl chlorides and sterically hindered coupling partners\textsuperscript{9} to be addressed and also expanded the substrate scope to form bonds other than carbon–carbon, most notably carbon–nitrogen bonds.\textsuperscript{31} Despite significant achievements, the quest for alternative motifs in ligand design should not abate.

Tröger’s base is a dissymmetric molecule belonging to the C\textsubscript{2} point group.\textsuperscript{32} Despite the fact that the Tröger’s base skeleton represents an easily accessible, rigid, chiral moiety, the design of ligands profiting from the presence of this unit is rather underdeveloped.\textsuperscript{33} Prior work in the group has reported a straightforward synthesis of new S,N and Se,N doubly bidentate ligands based on Tröger’s base backbone.\textsuperscript{34} Their coordination properties in Ag(I)-complexes were studied by NMR spectroscopy as well as X-ray diffraction crystallography and showed that a single molecule of the ligand could bind two silver atoms. In this chapter we would like to report our efforts to a new class of P,N and P ligands.
2.3 Synthetic Chemistry

We approached this project with the aim of utilizing the Tröger’s base as a scaffold for new P,N-ligands, and then as P-ligands as considered further on.

![Figure 2.4 Tröger’s base derived P,N and P-ligands.](image)

2.3.1 P,N Ligands

Part of this subchapter has been reproduced in Pereira, R.; Cvengroš, J. J. Organomet. Chem. 2013, 729, 81

2.3.1.1 Ligand Synthesis

The synthetic route to these ligands commenced with the synthesis of 4,10-dibromo Tröger’s base derivative 201, by the condensation of 2-bromo-4-methylaniline with paraformaldehyde in trifluoroacetic acid. Two strategies were applied for the installment of the phosphane moieties. Typically, the lithium-bromine exchange followed by the quenching with a chlorophosphane gave the corresponding P,N ligands 202a–c (Scheme 2.7). We have observed that the stability of the di-lithiated species (upon lithium-bromine exchange of 201) is rather limited and only reactive electrophiles yielded the corresponding products in high yields. The reaction proceeded with satisfactory yields when the substituents on chlorophosphanes were phenyl or 4-methylphenyl. The increased steric hindrance in the case of bulkier chlorodialkylphosphanes resulted in prolonged reaction time during which the di-lithiated species deteriorated and the anticipated phosphanes were obtained only in low (202c), or no (202d), yields. Furthermore, the dicyclohexylphosphane ligand proved extremely sensitive towards oxidation rendering its isolation and purification exceedingly cumbersome. We have thus treated the crude reaction mixture with an excess of borane tetrahydrofuran complex (5 equiv) and isolated the ligand as its borane adduct. The deprotection was achieved by an action of diethylamine and the crude phosphane ligand 202c was directly used in catalysis. Dissatisfied with the poor outcome of the synthesis of tBu-phosphane 202d, we have attempted an alternative synthesis via palladium-catalysed phosphonation. To our delight, 202d was obtained in 26% yield. In general, the presented approach represents a concise two-step strategy for the preparation of a library of new P,N ligands. The introduction of the phosphane moiety in the last step allows for a high modularity of this protocol.
2.3.1.2 Coordination Properties

We have studied the coordination properties of the new ligands upon complexation with palladium. The solution of ligand 202a in METHYLENE CHLORIDE was added to the solution of 2 equivalents of $[\text{PdCl}_2(\text{COD})]$ in methylene chloride and the resulting solution was stirred for an hour at room temperature. The analysis of the reaction mixture by $^{31}$P NMR revealed that the signal for the free ligand at $-15.1$ ppm disappeared and single phosphine species was detected at $36.4$ ppm as a doublet ($J_{\text{H-P}} = 10.9$ Hz), which was assigned to the dipalladium complex 203a (Figure 2.5).
Similarly, the NMR experiment with the cyclohexyl analogue 202c revealed the complete disappearance of the $^{31}$P NMR signal of the free ligand upon addition of 2 equivalents of [PdCl$_2$(COD)]. The coordination resulted again in a single phosphane species at 62.4 ppm (proton decoupled $^{31}$P NMR). We were able to grow single crystals of 203a by vapor diffusion of pentane into a methylene chloride solution. The ORTEP view of 203a is shown in Figure 2.6. The X-ray analysis confirmed that a single molecule of ligand 202a is able to accommodate two palladium atoms resulting in dipalladium complex 203a. Both palladium atoms coordinate in the same fashion with square-planar geometry around palladium. The complex 203a thus retains the C$_2$-symmetry of the parent ligand.
2.3.1.3 Catalysis

With a small library of ligands in our hands we have performed some initial tests to evaluate their catalytic properties in palladium-catalysed cross-coupling reactions. A fast screen revealed that Pd(OAc)$_2$ is superior to Pd$_2$(dba)$_3$ as the palladium source for the reaction between bromobenzene and phenylboronic acid (Table 2.1, Entries 1 and 2). The use of potassium triphosphate resulted in shorter reaction time compared to caesium carbonate (Table 2.1, Entries 2 and 3). THF proved to be the most suitable solvent resulting in the lowest temperature and the highest reaction rate (Table 2.1, Entries 2, 4-7). Finally, we evaluated the potential of other synthesized ligands. The p-tolyl analogue 202b gave basically same result as 202a yielding the product in 99% yield (Table 2.1, Entry 8). Interestingly, the electron-rich bulky ligands 202c and 202d turned out to be completely inactive even after a prolonged reaction time (Table 2.1, Entries 9 and 10).

**Table 2.1** Screening of the reaction conditions (Pd-source, ligand, base, solvent, temperature) for the Suzuki cross-coupling.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Base</th>
<th>Solvent</th>
<th>Temperature [$^\circ$C]</th>
<th>Time [h]</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd$_2$(dba)$_3$</td>
<td>202a</td>
<td>K$_3$PO$_4$</td>
<td>THF</td>
<td>70</td>
<td>19</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>202a</td>
<td>K$_3$PO$_4$</td>
<td>THF</td>
<td>70</td>
<td>4</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>202a</td>
<td>Cs$_2$CO$_3$</td>
<td>THF</td>
<td>70</td>
<td>22</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>202a</td>
<td>K$_3$PO$_4$</td>
<td>Toluene</td>
<td>90</td>
<td>24</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$</td>
<td>202a</td>
<td>K$_3$PO$_4$</td>
<td>EtOH</td>
<td>75</td>
<td>17</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)$_2$</td>
<td>202a</td>
<td>K$_3$PO$_4$</td>
<td>DMF</td>
<td>100</td>
<td>5</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)$_2$</td>
<td>202a</td>
<td>K$_3$PO$_4$</td>
<td>Dioxane</td>
<td>90</td>
<td>17</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)$_2$</td>
<td>202b</td>
<td>K$_3$PO$_4$</td>
<td>THF</td>
<td>70</td>
<td>4</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)$_2$</td>
<td>202c</td>
<td>K$_3$PO$_4$</td>
<td>THF</td>
<td>70</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)$_2$</td>
<td>202d</td>
<td>K$_3$PO$_4$</td>
<td>THF</td>
<td>70</td>
<td>18</td>
<td>0</td>
</tr>
</tbody>
</table>

Reaction conditions: bromobenzene (1.5 mmol), phenylboronic acid (2.25 mmol), base (3 mmol), Pd salt (2.0 mol%), ligand (1.0 mol%), solvent (3 mL). $^a$ Isolated yields after column chromatography.

Applying the most suitable conditions, we checked a few substrates to briefly evaluate the scope and limitation of the catalyst (Table 2.2). The presence of the electron-withdrawing substituent facilitates the oxidative addition of palladium into the carbon-bromine bond resulting in shorter reaction times (Table 2.2, Entry 1). Interestingly, one or two substituents in the vicinity of the bromine atom are tolerated (Table 2.2, Entries 2 and 3). Ortho-substituted boronic acid can be also efficiently applied under these conditions (Table 2.2, Entry 4).
Table 2.2 Suzuki cross-coupling of aryl halides with arylboronic acids.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Aryl halide</th>
<th>Boronic acid</th>
<th>Time [h]</th>
<th>Yield [%]\textsuperscript{b}</th>
</tr>
</thead>
</table>
| 1     | \(202a\) | \[\begin{array}{c}
\text{O}_2\text{N} \\
\text{Br}
\end{array}\] & \[\begin{array}{c}
\text{B(OH)}_2
\end{array}\] | 1.5     | 92              |
| 2     | \(202a\) | \[\begin{array}{c}
\text{Br}
\end{array}\] & \[\begin{array}{c}
\text{B(OH)}_2
\end{array}\] | 7       | 79              |
| 3     | \(202a\) | \[\begin{array}{c}
\text{Br}
\end{array}\] & \[\begin{array}{c}
\text{B(OH)}_2
\end{array}\] | 7       | 91              |
| 4     | \(202a\) | \[\begin{array}{c}
\text{NC} \\
\text{Br}
\end{array}\] & \[\begin{array}{c}
\text{Cl}
\end{array}\] | 1.5     | 90              |
| 5     | \(202a\) | \[\begin{array}{c}
\text{O}_2\text{N} \\
\text{Br}
\end{array}\] & \[\begin{array}{c}
\text{B(OH)}_2
\end{array}\] | 22      | 0               |

\textsuperscript{a} Reaction conditions: aryl halide (1.5 mmol), arylboronic acid (2.25 mmol), \(K_3\text{PO}_4\) (3 mmol), \(\text{Pd(OAc)}_2\) (2.0 mol%), ligand (1.0 mol%), THF (3 mL), 70 °C. \textsuperscript{b} Isolated yields after column chromatography.

Unfortunately, the presented catalytic system completely failed to involve aryl chlorides in the Suzuki cross-coupling. The above-mentioned results suggest that a few sophisticated changes have to be done regarding the catalyst design.

2.3.2 Enantiopure P,N ligands

Exploiting the \(C_2\) symmetry of Tröger’s base, we embarked on the synthesis of enantiopure derivatives of \(202a\) to assess their potential in inducing asymmetry.

[Note: This section has been carried out by Fumito Saito, a semester student under my supervision.]

2.3.2.1 Ligand Synthesis

Following a protocol developed in the group,\textsuperscript{36} \((R,R)-201\) was synthesized as shown in chapter 1, scheme 1.11. The subsequent lithiation of \((R,R)-201\) followed by quenching with chlorodiphenylphosphine afforded the enantiopure phosphane ligand \(202a\) in 36% yield (Scheme 2.8).

![Scheme 2.8 Synthesis of \((R,R)-(+)\)-202a](image)
2.3.2.2 Catalysis
With the enantiopure phosphane ligand in hand, their catalytic properties were investigated. The 1,4-addition of boronic acids to electron-deficient olefins was first examined. Several conditions for the 1,4-addition of phenylboronic acid to cyclohexenone were examined (Table 2.3). The desired reaction did not proceed without the ligand (Table 2.3 entry 1). Although excellent yield was obtained at 60 °C with the phosphine ligand (R,R)-(+) -202a, all of the examined reaction conditions gave the racemic product (Table 2.3 entries 2-5).

Table 2.3 Rhodium catalysed 1,4-addition of phenylboronic acid.  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>temp. [°C]</th>
<th>yield [%]</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>toluene</td>
<td>60</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂ / toluene</td>
<td>RT</td>
<td>36</td>
<td>rac</td>
</tr>
<tr>
<td>3</td>
<td>toluene</td>
<td>RT</td>
<td>52</td>
<td>rac</td>
</tr>
<tr>
<td>4</td>
<td>toluene</td>
<td>60</td>
<td>82</td>
<td>rac</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>RT</td>
<td>41</td>
<td>rac</td>
</tr>
</tbody>
</table>

[Rh(cod)₂]BF₄ (4.1 mg, 10 μmol, 2 mol%), (R,R)-202a (6.5 μmol, 1.0 mol%), phenylboronic acid (67 μL, 0.55 mmol, 1.1 equiv), cyclohexanone (48 μL, 0.5 mmol). All yields are isolated yields after column chromatography and enantiomeric excess was determined via chiral phase HPLC.  

Next, the hydrogenation of dimethyl itaconate was studied. Unfortunately, this substrate could not be hydrogenated with the combination of [Rh(cod)₂]BF₄ and (R,R)-202a under 1 bar of H₂ atmosphere (Table 2.4, entry 1). When Pd(OAc)₂ was used, full conversion of the substrate was obtained, although the obtained product was racemic (Table 2.4, entry 2).

Table 2.4 Hydrogenation of dimethyl itaconate.  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal</th>
<th>Solvent</th>
<th>Conversion [%]</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(cod)₂]BF₄</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)₂</td>
<td>MeOH</td>
<td>&gt;99</td>
<td>rac</td>
</tr>
</tbody>
</table>

[Rh(cod)₂]BF₄ (4.1 mg, 10 μmol, 2 mol%), (R,R)-202a (6.5 μmol, 1.0 mol%), dimethyl itaconate (0.5 mmol, 1 equiv), H₂ (1 atm). All yields are isolated yields after column chromatography and enantiomeric excess was determined via chiral phase HPLC.
We next carried out the palladium-catalyzed allylic substitution reaction of rac-1,3-diphenyl-2-propenyl acetate with dimethyl malonate as a nucleophile using \((R,R)-202a\) as the chiral ligand. This reaction yielded 48% product with a modest 20% ee (Scheme 2.9). The bulkier dibenzyl malonate yielded the product with diminished enantiomeric excess (7% ee).

Scheme 2.9 Tsuji-Trost reaction with \((R,R)-202a\) as the ligand. BSA = bis(trimethylsilyl)acetamide. Yield and enantiomeric excess was determined via chiral phase HPLC.
2.3.3 P Ligands

Part of this subchapter has been reproduced in Pereira, R.; Cvengroš, J. Eur. J. Org. Chem. 2013, 4233.

The Tröger’s base-derived P,N ligands considered above (Scheme 2.7) were catalytically active in Suzuki-Miyaura cross-coupling reactions of aryl bromides. However, any attempt to employ aryl chlorides proved fruitless.\(^{35}\) In an attempt to optimise the ligand to involve aryl chlorides and sterically challenging substrates, we were curious to see the effect mediated by altering the position of the phosphorous atom on the aromatic ring. We altered the position of the phosphorus moiety and our results show that the phosphorus moiety, when para to the nitrogen atom was the yielded better results in comparison to the derivative bearing the phosphorous moiety ortho to the nitrogen of the Tröger’s base (Figure 2.4). Gratifyingly with the ligands described in scheme 2.10 we were able to couple aryl chlorides, sterically hindered aryl bromides and thereby provided a solution to the limitations of the ligands described in sections 2.3.1. Furthermore, with these 2,8-bis(phosphane) Tröger’s base-derived ligands that can effectively involve aryl chlorides in palladium-catalysed C–C we were able to perform C–N bond-forming reactions.

2.3.3.1 Ligand Synthesis

Tröger’s base derived bis(phosphanes) \(205a–c\) were efficiently synthesized by starting from \(rac\)-2,8-dibromo-4,10- dimethyl Tröger’s base analogue \(204\) (Scheme 2.10). The lithium-bromine exchange on \(204\) followed by quenching with chlorodiphenylphosphate or chlorodicyclohexylphosphate afforded bis(phosphane) \(205a\) and \(205c\). Whilst \(205a\) was isolated in 75% yield without any issues, the purification of \(15c\) was tedious. Therefore, it was directly protected as its \(BH_3\) adduct \(205c'\) in 74% overall yield to prevent oxidation during workup and purification. Adduct \(205c'\) was then readily deprotected, typically immediately prior to its use in catalysis, with morpholine to give \(205c\) in 70% yield. In the case of tert-butyl derivative \(205b\), transmetallation to organo cuprate and an elevated reaction temperature were necessary to introduce the di-tert-butylphosphate moiety effectively. Omission of \(CuCl\) resulted in no product formation. In analogy to the previous ligand, \(205b\) was directly treated with \(BH_3\)-THF and purified as borane adduct \(205b'\) (88%). Deprotection with morpholine yielded \(205b\) in 80% yield. According to our observations, bis(phosphanes) \(205b\) and \(205c\) are bench-stable in the solid state, but their sensitivity towards oxygen increases in solution. Their ease of preparation from cheap starting materials and the high modularity of the presented strategy bodes well for further development and tuning of this family.
2.3.3.2 Coordination Properties

We attempted to clarify the nature of the catalytically active species of the ligand \textbf{205a} via $^{31}$P NMR upon complexation with palladium. A solution of ligand \textbf{205a} in deuterated methylene chloride was added to the solution of 0.0, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 1.0, 2.0 and 3.0 equivalents of [PdCl$_2$(COD)] in deuterated methylene chloride and the resulting solution was stirred for an hour at room temperature.
Figure 2.7 $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$) of 205a and increasing concentrations of palladium at 298K.

The analysis of the reaction mixture by $^{31}$P NMR revealed that the signal for the free ligand at –5.8 ppm remains relatively unaltered even in the presence of 0.4 equivalents of palladium, and only completely disappears when 0.5 equivalents of Pd are added (Figure 2.7). At 0.5 equivalents of palladium, a predominant signal set is seen at –23 ppm along with a second, much smaller, set at –32 ppm. Interestingly at higher ratios of palladium, the signal at –32 ppm dominates (Figure 2.8).
Tröger’s Base Derived P,N & P Ligands

2.3.3.3 Catalysis

With a small library of bis(phosphanes) in hand, their efficiency was first tested in Suzuki–Miyaura cross-coupling reactions. A brief screening of reaction conditions revealed that the use of Pd(OAc)$_2$ as the palladium precursor, potassium phosphate (tribasic) as the base, and toluene as the solvent were critical for an efficient outcome of the coupling reaction. As summarized in Table 2.5 the palladium complexes with ligands 205a–c efficiently catalysed the cross-coupling of aryl bromides and chlorides with arylboronic acids in short periods of time. The palladium/ligand ratio turned out to be crucial (Table 2.5, Entry 5). Although 1-chloro-2-methylbenzene (206e) could be coupled with phenylboronic acid (207a) to provide the product in 80% yield if equimolar amounts of Pd(OAc)$_2$ and 205b were used, an excess amount of palladium slowed down the reaction, and an excess amount of the ligand almost completely deactivated the catalyst. Substituents in the ortho position were tolerated both on the haloarene and on the boronic acid (Table 2.5, Entries 2-5). Moreover, the presence of electron-withdrawing groups on the aryl chlorides is not necessary (Table 2.5, Entries 5 and 9). On the basis of the results obtained, tBu ligand 205b was identified to be the most active followed by the cyclohexyl (Cy) analogue 205c, and both ligands were capable of effecting

Figure 2.8 $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$) of 205a and increasing concentrations of palladium at 298K.
the cross-coupling of aryl chlorides. Bis(diphenylphosphane) 205a turned out to be the least active in terms of its substrate scope, and its use was limited to aryl bromides.

Table 2.5 Suzuki-Miyaura cross-coupling

![Diagram](attachment:image.png)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl-X</th>
<th>R₂</th>
<th>Product</th>
<th>Ligand</th>
<th>Time [h]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br 206a</td>
<td>H</td>
<td>208aa</td>
<td>205a</td>
<td>1.5</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>206b</td>
<td>H</td>
<td>208ba</td>
<td>205a</td>
<td>2</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>Br 206c</td>
<td>H</td>
<td>208ca</td>
<td>205a</td>
<td>2</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>Br 206d</td>
<td>Cl</td>
<td>208db</td>
<td>205b</td>
<td>0.66</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>Cl 206e</td>
<td>H</td>
<td>208ea</td>
<td>205b</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>Cl 206f</td>
<td>H</td>
<td>208fa</td>
<td>205b</td>
<td>1.5</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>Cl 206g</td>
<td>H</td>
<td>208ga</td>
<td>205b</td>
<td>1.5</td>
<td>96</td>
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<tr>
<td>8</td>
<td>Cl 206h</td>
<td>H</td>
<td>208ha</td>
<td>205c</td>
<td>1.5</td>
<td>94</td>
</tr>
</tbody>
</table>
Subsequently, we turned our attention to catalytic C–N bond-forming reactions. On the basis of our results from the Suzuki–Miyaura coupling reaction, we tested the most potent ligand 205b in Buchwald–Hartwig cross-coupling reactions of aryl bromides and chlorides with morpholine. We were delighted to observe that the combination of 205b with Pd(OAc)$_2$ in refluxing toluene with sodium tert-butoxide as the base cleanly yielded the anticipated products in high yields (Table 2.6). Also in this case, ortho substituents did not hamper the outcome of the reaction. Only in the presence of strongly electron-donating groups on the aryl chloride were lower yields obtained (Table 2.6, Entries 6 and 7).

Table 2.6 Amination of aryl bromides and chlorides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl-X</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br 206k</td>
<td>MeO[DG1]209a</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>206b</td>
<td>209b</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>Br 206l</td>
<td>209c</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>Cl 206e</td>
<td>209d</td>
<td>80</td>
</tr>
</tbody>
</table>
Tröger’s Base Derived P,N & P Ligands

The phosphorus NMR data (Figure 2.8) along with data from table 2.5, entry 5 suggests the formation of a new species at -32 ppm that is catalytically active. However, in the absence of a crystal structure of this species we wanted to test for the presence of palladium nanoparticles that could possibly catalyse the reactions. We performed a mercury drop experiment, \(^{37}\) wherein a drop of mercury was added at time zero hours and in an independent experiment after 1 hour. If the reaction is purely homogeneous the mercury will not have any effect on the outcome, whilst a heterogeneous system would get poisoned and the reaction would cease.

Table 2.7 Mercury drop experiment.

<table>
<thead>
<tr>
<th>No</th>
<th>Time of addition of Hg drop [h]</th>
<th>209e [%]</th>
<th>209f [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>93</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{37}\) Isolated yield after column chromatography.

The results in table 2.7 show a complete shut down of the reaction, which indicates the presence of colloidal palladium particles. However, our experiments show that in the absence of ligand no reaction occurs suggesting that the phosphane ligands are stabilising the colloidal palladium.
2.3.4 Ethylene-bridged Tröger’s base derived P Ligands

Having discovered that the Tröger’s base derived ligands bearing the phosphorus moiety \(\text{para}\) to the nitrogen atom showed substantially higher catalytic activity that those \(\text{ortho}\) to the nitrogen atom, we decided to ascertain the effect mediated by altering the number of carbons that formed the bridge between the two nitrogen atoms of the diazocine unit.

2.3.4.1 Ligand Synthesis

Ethylene-bridged Tröger’s base derived phosphanes 212a\(\text{-}b\) were synthesized efficiently by starting from rac-2,8-dibromo-Tröger’s base analogue 210 (Scheme 2.11). The lithium-bromine exchange on 211 followed by quenching with chlorodicyclohexylphosphane afforded bis(phosphate) 212b. Which was isolated in 85% yield as its BH\(_3\) adduct 212b\(\text{'}\) in 70% overall yield to prevent oxidation during workup and purification. Adduct 212b\(\text{'}\) was then readily deprotected, typically immediately prior to its use in catalysis, with morpholine to give 212b in 70% yield. In the case of tert-butyl derivative 212a, transmetallation to organo cuprate and an elevated reaction temperature were necessary to introduce the di-tert-butylphosphane moiety effectively. As with the previous ligand, 212a was directly treated with BH\(_3\)-THF and purified as borane adduct 212a\(\text{'}\) (84%). Deprotection with morpholine yielded 212a in 80% yield.

![Scheme 2.11 Ethylene-bridged Tröger’s base derived phosphanes.](image-url)
2.3.4.2 Catalysis

The efficiency of bis(phosphanes) 212a and 212b in Suzuki–Miyaura as well as Buchwald-Hartwig cross-coupling reactions was accessed.

```
Cl      B(OH)_2
\[\text{Pd(OAc)}_2 / \text{ligand} \quad K_3\text{PO}_4\]
\[\text{solvent, temperature} \quad 90\text{°C} \quad 6\text{ h}\]
```

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Temperature [°C]</th>
<th>Time [h]</th>
<th>Yield of 208 [%]</th>
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<tr>
<td>1</td>
<td>212a</td>
<td>toluene</td>
<td>90</td>
<td>6</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>212b</td>
<td>toluene</td>
<td>90</td>
<td>6</td>
<td>86</td>
</tr>
</tbody>
</table>

*Yields determined by GC using an internal standard (DABCO)*

These ligands, unfortunately displayed identical catalytic activity as their one-carbon analogues 205b and 205c respectively. Consequently, they were not assessed any further.

2.4 Conclusions

We have developed an efficient two-step synthetic route to novel C₂-symmetric bis(phosphane) ligands based on a Tröger’s base scaffold. The synthesis is highly modular, as the phosphane moiety is introduced in the last step. Having relocated the position of the phosphorus moiety from ortho to the nitrogen to para we have improved the ligands catalytic activity. We have shown that these ligands form a versatile catalytic system with Pd(OAc)₂ for Suzuki–Miyaura cross-coupling and Buchwald–Hartwig amination reactions of aryl bromides and chlorides. Furthermore, we have synthesized an enantiopure TB derived phosphane ligand (R,R)-(+-)202a and assessed its potential as a chiral ligand, unfortunately its was only able to deliver products with modest ee values in the Tsuji-Trost reaction.
2.5 Experimental

2.5.1 General

The reactions were carried out in oven-dried glassware under argon using Schlenk techniques. All solvents were freshly distilled under argon from an appropriate drying agent before use. Flash chromatography was performed with Fluka silica gel 60. NMR spectra were measured on Bruker Avance DPX-300, DPX-400, III HD Nanobay-300 and III HD Nanobay-400 spectrometers. The chemical shifts are recorded in ppm and are referenced to 85% H₃PO₄ (for ³¹P) and to tetramethylsilane (¹H and ¹³C). The ²D lock frequency of CD₂Cl₂ or CDCl₃ was used as the internal secondary reference in all cases. High-resolution mass spectra were measured by the MS-Service of the “Laboratorium für Organische Chemie der ETH” on a Bruker Daltonics maXis ESI-QTOF.
2.5.2 Ligand Synthesis

**Synthesis of 202a**

A Schlenk flask was charged with 201 (0.82 g, 2 mmol) under argon and THF (20 mL) was added. Then it was cooled down to -78 °C and n-BuLi (1.6 M in hexane, 2.8 mL, 4.4 mmol, 2.2 equiv) was added dropwise to form a pale yellow suspension. After 10 min, chlorodiphenylphosphane (0.78 mL, 4.4 mmol, 2.2 equiv) was added dropwise and the suspension turned clear again. The stirring was continued overnight at ambient temperature. Sat. aq. NH₄Cl solution (20 mL) was added and it was extracted with methylene chloride (3 x 20 mL). Combined org. layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂ (40 g); methylene chloride /hexane 4:1) to give rac-4,10-bis(diphenylphosphino)-2,8-dimethyl-6,12-dihydro-5,11-methanodibenzob[bf]1,5 diazocine 202a as a white solid (640 mg, 53%).

**¹H NMR** (300 MHz, CDCl₃): δ [ppm] = 2.08 (s, 6H, CH₃), 4.18 (s, 2H, NCH₂N), 4.32 (d, ²J = 17.3 Hz, 2H, endo CH₂N), 4.55 (d, ²J = 17.3 Hz, 2H, exo CH₂N), 6.50 (s, 2H, Ar–H), 6.60 (s, 2H, Ar–H), 7.25-1.39 (m, 20H, Ar–H); **¹³C NMR** (75 MHz, CDCl₃): δ [ppm] = 21.4 (CH₃), 57.7 (d, Jₐ-C = 9.7 Hz, CH₂N), 67.9 (NCH₂N), 128.6, 128.7, 128.8, 128.9, 129.0, 129.1, 133.1 (d, Jₓ-C = 11.7 Hz), 133.5 (d, Jₓ-C = 19.3 Hz), 133.9, 134.4, 134.9 (d, Jₓ-C = 20.4 Hz), 137.8 (d, Jₓ-C = 11.2 Hz), 138.3 (d, Jₓ-C = 11.0 Hz), 149.3 (d, Jₓ-C = 21.1 Hz); **³¹P NMR** (162 MHz, CDCl₃): δ [ppm] = -15.1; **HRMS** (ESI): m/z [M + H]⁺ calcd for C₄₁H₅₇N₂P₂: 619.2420; found: 619.2426.

**Synthesis of 202b**

A Schlenk flask was charged with 201 (0.65 g, 1.6 mmol) under argon and THF (20 mL) was added. Then it was cooled down to -78 °C and n-BuLi (1.6 M in hexane, 2.8 mL, 4.4 mmol, 2.2 equiv) was added dropwise to form a pale yellow suspension. After 10 min, a solution of chlorodiphenylphosphine (880 mg, 3.52 mmol) in THF (5 mL) was added dropwise and the suspension turned clear again. The stirring was continued overnight at ambient temperature. Sat. aq. NH₄Cl solution (20 mL) was added and it was extracted with methylene chloride (3 x 20 mL). Combined org. layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂ (40 g); hexane/ethylacetate 10:1 to 2:1 containing 0.1% Et₃N)
to give rac-4,10-bis(di-pptolylphosphino)-2,8-dimethyl-6,12-dihydro-5,11-methanodibenzo[b,f]1,5 diazocine 202b as a white solid (354 mg, 32%).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ [ppm] = 2.08 (s, 6H, CH$_3$), 2.35 (s, 6H, CH$_3$), 2.40 (s, 6H, CH$_3$), 4.16 (s, 2H, NCH$_2$N) 4.32 (d, $^2J = 17.4$ Hz, 2H, endo CH$_2$N), 4.52(d, $^2J = 17.4$ Hz, 2H, exo CH$_2$N), 6.51 (s, 2H, Ar–H), 6.59 (s, 2H, Ar–H), 7.12 (m, 8H, Ar–H), 7.18 (m, 4H, Ar–H), 7.25 (m, 4H, Ar–H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ [ppm] = 21.0 (CH$_3$), 21.3 (CH$_3$), 21.4 (CH$_3$), 57.2 (d, $J_{C-P} = 10.5$ Hz, CH$_2$N), 67.5 (NCH$_2$N), 128.3, 128.5 (d, $J_{C-P} = 4.9$ Hz), 129.0 (d, $J_{C-P} = 7.0$ Hz), 129.3 (d, $J_{C-P} = 7.3$ Hz), 133.1 (d, $J_{C-P} = 19.5$ Hz), 133.0, 133.3, 133.7, 134.0 (d, $J_{C-P} = 10.1$ Hz), 134.4 (d, $J_{C-P} = 20.7$ Hz), 134.6 (d, $J_{C-P} = 9.8$ Hz), 137.9, 138.5, 149.3 (d, $J_{C-P} = 21.1$ Hz);

$^{31}$P NMR (162 MHz, CDCl$_3$): $\delta$ [ppm] = -17.8; HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{45}$H$_{45}$N$_2$P$_2$: 675.3052; found: 675.3042.

**Synthesis of 202c’**

The title compound was synthesized in analogy to the above-mentioned procedure for 202a starting from 201 (200 mg, 0.5 mmol). A solution of chlorodicyclohexylphosphate (256 mg, 1.1 mmol) in THF (5 mL) was used to quench the lithiated species. The reaction was allowed to reach room temperature overnight. It was then cooled to 0 °C and BH$_3$·THF (10 mL, 10 mmol of a 1 M solution in THF) was added. The reaction mixture was allowed to reach room temperature and then it was stirred for additional 6 hours. The reaction was then transferred into a sat. aq. NH$_4$Cl solution (20 mL) under argon and it was stirred for 5 min. It was extracted with methylene chloride (3 x 30 mL). Combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO$_2$ (30g); hexane/ethyl acetate 4:1 containing 0.1% Et$_3$N) to give a pale yellow solid as the borane protected rac-4,10-bis(dicyclohexylphosphino)-2,8-dimethyl-6,12-dihydro-5,11-methanodibenzo [b,f] [1,5] diazocine 202c’ as a white solid (307 mg, 62%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ [ppm] = 0.23-1.02 (br, 6H, BH$_3$), 1.16-1.97 (m, 38H, Cy), 2.07 (d, $^2J = 13.3$ Hz, 2H, Cy), 2.30 (s, 6H, CH$_3$), 2.36-2.47 (m, 2H, Cy), 2.68-2.78 (m, 2H, Cy), 3.94 (d, $^2J = 17.1$ Hz, 2H, endo CH$_2$N), 4.20 (s, 2H, NCH$_2$N), 4.69 (d, $^2J = 17.1$ Hz, 2H, exo CH$_2$N), 6.81(s, 2H, Ar–H), 7.36 (d, $J_{H-P} = 12.9$ Hz 2H, Ar–H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ [ppm] = 21.0 (Ar-CH$_3$), 25.9 (d, $J_{C-P} = 13.6$ Hz), 26.8 (d, $J_{C-P} = 11.2$ Hz), 27.0 (d, $J_{C-P} = 2.5$ Hz), 27.1 (d, $J_{C-P} = 1.9$ Hz), 27.2 (d, $J_{C-P} = 11.2$ Hz), 28.0 (d, $J_{C-P} = 36.5$ Hz), 28.5 (d, $J_{C-P} = 35.5$ Hz), 33.2 (d, $J_{C-P} = 33.9$ Hz).
Hz), 34.1 (d, J_C-P = 32.4 Hz), 57.4 (CH_N), 66.0 (NCH_N), 122.9 (d, J_C-P = 44.1 Hz), 129.0 (d, J_C-P = 5.7 Hz), 130.6 (d, J_C-P = 2.1 Hz), 134.8 (d, J_C-P = 11.5 Hz), 137.1 (d, J_C-P = 12.7 Hz), 149.3;

$^31P$ NMR (162 MHz, CDCl$_3$): $\delta$ [ppm] = 32.1; HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{61}$H$_{67}$N$_2$P$_2$B$_2$: 671.4974; found: 671.4977.

Prior to the catalytic test, the borane protected phosphane 202c’ (50 mg, 0.075 mmol) was placed into a J Young flask under argon. Dry methylene chloride (3 mL) and diethylamine (5 mL) were added and the flask was sealed. The reaction mixture was stirred at 50 °C for 24 h. It was cooled down, silica (2 g) was added and the volatiles were removed. The residue was placed at the top of a short silica column (6 g) and eluted with hexane/EtOAc 4:1 + 0.1% Et$_3$N to give a white solid (30 mg, 64%) which was briefly checked by $^1$H and $^31P$ NMR and immediately used in catalysis.

$^1H$ NMR (300 MHz, CD$_2$Cl$_2$): $\delta$ [ppm] = 0.75-2.04 (m, 44H, Cy), 2.14 (s, 6H, CH$_3$), 4.09 (s, 2H, NCH$_2$N) 4.25 (d, $^3J = 16.7$ Hz, 2H, endo CH$_3$N), 4.39 (d, $^3J = 16.7$ Hz, 2H, exo CH$_3$N), 6.61 (s, 2H, Ar-H), 6.93 (s, 2H, Ar-H); $^31P$ NMR (121 MHz, CDCl$_3$): $\delta$ [ppm] = −14.9.

Synthesis of 202d

In the glove-box, a Schlenk flask was charged with 201 (204 mg mg, 0.5 mmol), Pd(OAc)$_2$ (9.5 mg, 4.2 mmol, 4.2 mol%), NaOtBu (115 mg, 1.2 mmol, 2.4 equiv), (tBu)$_2$P (10.2 mg, 5 mmol, 5 mol%) and (tBu)$_2$PH (146.2 mg, 1.0 mmol, 2 equiv). Schlenk flask was taken out of the glove-box, dry toluene (2 mL) was added and the reaction mixture was stirred at 100 °C for 24 h under argon. It was then cooled down to room temperature and Et$_2$O (10 mL) was added and the mixture was transferred into a separation funnel. The reaction vessel was rinsed with diethyl ether (2 x 20 mL). The combined ether layers were washed with water (2 x 10 mL) and brine (2 x 10 mL). The aqueous layers were back extracted with Et$_2$O (20 mL). The combined ether layers were dried over MgSO$_4$ and the organic solvent was removed under reduced pressure. The crude material was purified via recrystallization (hexane/ethyl acetate, 1:1) to give rac-4,10-bis(di-tert-butylphosphino)-2,8-dimethyl-6,12-di-hydro-5,11-methanodibenzo[b,f][1,5]diazocine 202d a white solid (75 mg, 26%).

$^1H$ NMR (300 MHz, CDCl$_3$): $\delta$ [ppm] = 1.17 (d, $^3J_{H-P}$ = 11.4 Hz, 18H, (CH$_3$)$_3$), 1.36 (d, $^3J_{H-P}$ = 11.7 Hz, 18H, (CH$_3$)$_3$), 2.25 (s, 6H, CH$_3$), 4.16 (s, 2H, NCH$_2$N) 4.36 (d, $^3J = 17.1$ Hz, 2H, endo CH$_3$N),
Synthesis of 205a

A Schlenk flask was charged with 204 (0.82 g, 2 mmol) under argon and THF (16 mL) was added. Then it was cooled down to -78 °C and n-BuLi (1.6 M in hexane, 2.8 mL, 4.4 mmol, 2.2 equiv) was added dropwise to form a pale-yellow clear solution. After 10 min, chlorodiphenylphosphane (0.78 mL, 4.4 mmol, 2.2 equiv) was added as a single batch. The stirring was continued overnight at ambient temperature. Sat. aq. NH₄Cl solution (20 mL) was added and it was extracted with methylene chloride (3 x 20 mL). Combined org. layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂ (40 g); ethyl acetate/hexane 1:10 to 20:80; 0.1% Et₃N) to give rac-2,8-bis(diphenylphosphino)-4,10-dimethyl-6,12-dihydro-5,11-methanodibenzo [b,f][1,5]diazocine 205a as a white solid (747 mg, 75%).

¹H NMR (300 MHz, CD₂Cl₂): δ [ppm] = 2.30 (s, 6H, CH₃), 3.92 (d, ²J = 17.0 Hz, 2H, CH₂N), 4.26 (s, 2H, NCH₂N), 4.50 (d, ²J = 16.9 Hz, 2H, CH₂N), 6.75 (d, ³J_H,P = 7.9 Hz, 2H, Ar-H), 7.02 (d, ³J_H,P = 7.9 Hz, 2H, Ar-H), 7.29 (m, 20H, Ar-H); ¹³C NMR (75 MHz, CD₂Cl₂): δ [ppm] = 17.5 (Ar-CH₃), 55.4 (CH₂N), 67.9 (NCH₂N), 128.8, 128.9, 129.0, 129.1, 130.6 (d, J_C,P = 21.4 Hz), 132.1 (d, J_C,P = 10.3 Hz), 133.9, 134.1 (d, J_C,P = 19.6 Hz), 134.8 (d, J_C,P = 20.2 Hz), 138.28 (d, J_C,P = 11.4 Hz), 138.31 (d, J_C,P = 11.3 Hz), 147.71; ³¹P NMR (121.5 MHz, CD₂Cl₂): δ [ppm] = -5.8; HRMS (ESI): m/z [M+H]+ calcd for C₃₃H₃₃N₇P₂: 539.3678; found: 539.3692.

Synthesis of 205b

A Schlenk flask was charged with 204 (0.41 g, 1 mmol) under argon and THF (8 mL) was added. Then it was cooled down to -78 °C and n-BuLi (1.6 M in hexane, 1.5 mL, 2.4 mmol, 2.4 equiv) was added dropwise to form a pale-yellow clear
solution. After 5 min, the flask was opened, CuCl (0.198 g, 2.0 mmol) was quickly added and the resulting suspension was stirred for 5 minutes after which di-tert-butylphosphate (0.44 g, 2.4 mmol, 2.2 equiv) was added as one batch. The resulting mixture was warmed to ambient temperature within 60 minutes. The stirring was continued at 70 °C for 36 hours. It was then cooled to 0 °C and BH₃·THF (10 mL, 10 mmol of a 1 M solution in THF) was added. The reaction mixture was allowed to reach room temperature and then it was stirred for additional 6 hours. The reaction was then transferred into a sat. aq. NH₄Cl solution (25 mL) under argon and it was stirred for 5 minutes. It was extracted with methylene chloride (3 x 75 mL). Combined organic layers were filtered over a Whatman filter paper, dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂ (30 g); hexane/ethyl acetate 4:1 containing 0.1% Et₃N) to give the borane protected rac-4,10-bis(di-tert-butylphosphino)-2,8-dimethyl-6,12-dihydro-5,11-methanodibenzo [b,f][1,5]diazocine 205b’ as a white solid as (500 mg, 88%).

1H NMR (400 MHz, CD₂Cl₂): δ [ppm] = 0.22-0.99 (br, 6H, (BH₃)₂ ), 1.25 (d, 3J = 12.8 Hz, 18H, (CH₃)₃), 1.26 (d, 3J = 12.8 Hz, 18H, (CH₃)₃), 2.44 (s, 6H, CH₃), 4.08 (d, 3J = 17.0 Hz, 2H, CH₂N), 4.27 (s, 2H, NCH₂N), 4.62 (d, 3J = 17.0 Hz, 2H, CH₂N), 7.45 (d, 3J = 8.0 Hz, 2H, Ar-H), 7.59 (d, 3J = 9.7 Hz, 2H, Ar-H); 13C NMR (101 MHz, CD₂Cl₂): δ [ppm] = 17.7 (Ar-CH₃), 29.1 (d, J₈-₇ = 1.8 Hz, C(CH₃)₃), 29.2 (d, J₈-₇ = 1.8 Hz, C(CH₃)₃), 33.4 (d, J₈-₇ = 27.1 Hz, C(CH₂N)), 55.3 (CH₂N), 67.5 (NCH₂N), 122.2 (d, J₈-₇ = 46.2 Hz), 128.3 (d, J₈-₇ = 10.3 Hz), 132.5 (br s), 133.3 (d, J₈-₇ = 8.4 Hz), 135.3 (br s), 149.4 (d, J₈-₇ = 2.5 Hz); 31P NMR (162.1 MHz, CD₂Cl₂): δ [ppm] = 43.2 (d, J₈-P = 66.3 Hz); HRMS (ESI): m/z [M+H]+ calcd for C₃₈H₅₅B₂N₂P₂: 567.4345; found: 567.4343.

Prior to the catalytic test, the borane-protected phosphane 205b’ (260 mg, 0.46 mmol) was placed into Schlenk flask under argon. Degassed morpholine (5 mL) was added and the flask was sealed. The reaction mixture was stirred at 100 °C for 3 hours. It was cooled to room temperature and the excess morpholine was removed under reduced pressure. The residue was treated with degassed ethanol and cooled to -78 °C. The clear yellow supernatant was carefully removed via cannula filtration under argon to give 205b as a white solid (197 mg, 80%) which was briefly checked by 1H and 31P NMR and immediately used in catalysis.
**Synthesis of 205c’**

A 50 ml Schlenk flask was charged with 204 (0.4 g, 1.0 mmol) under argon and THF (8 mL) was added. Then it was cooled down to -78 °C and n-BuLi (1.6 M in hexane, 1.5 mL, 2.4 mmol, 2.4 equiv) was added dropwise to form a pale-yellow clear solution. After 10 min, a solution of chlorodicyclohexylphosphane (560 mg, 2.4 mmol) in THF (5 mL) was used to quench the lithiated species. The reaction was allowed to reach room temperature overnight. It was then cooled to 0 °C and BH₃·THF (10 mL, 10 mmol of a 1M solution in THF) was added. The reaction mixture was allowed to reach room temperature and then it was stirred for additional 6 hours. The reaction was then transferred into a sat. aq. NH₄Cl solution (20 mL) under argon and it was stirred for 5 minutes. It was extracted with methylene chloride (3 x 50 mL). Combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂ (30 g); hexane/ethyl acetate 4:1 to 3:1 containing 0.1% Et₃N) to give the borane protected rac-2,8-bis(dicyclohexylphosphino)-4,10-dimethyl-6,12-dihydro-5,11 methano- dibenzo [b,f] [1,5] diazocine 205c’ as a white solid as (495 mg, 74%).

**¹H NMR** (300 MHz, CD₂Cl₂): δ [ppm] = -0.26-0.94 (br, 6H, (BH₃)₂), 0.99-1.39 (m, 20H, (C₆H₁₁)₂), 1.41-2.08 (m, 24H, (C₆H₁₁)₂), 2.43 (s, 6H, CH₃), 4.09 (d, J = 17.0 Hz, 2H, CH₂N), 4.28 (s, 2H, NCH₂N), 4.63 (d, J = 17.0 Hz, 2H, CH₂N), 7.16 (d, J = 9.2 Hz, 2H, Ar-H), 7.28 (d, J = 8.2 Hz, 2H, Ar-H); **¹³C NMR** (75 MHz, CD₂Cl₂): δ [ppm] = 17.7 (Ar-CH₃), 26.5, 26.7, 26.8, 26.9, 27.0, 27.1, 27.19, 27.22, 27.24, 27.33 27.36, 27.4, 31.6 (d, J = 34.2 Hz), 31.9 (d, J = 33.9 Hz), 55.1 (CH₃N), 67.5 (NCH₂N), 120.6 (d, J = 49.4 Hz), 128.7 (d, J = 10.4 Hz), 131.0 (d, J = 10.3 Hz), 133.4 (d, J = 5.7 Hz), 133.9 (d, J = 8.6 Hz), 149.6; **³¹P NMR** (121.5 MHz, CD₂Cl₂): δ [ppm] = 24.8 (brs); **HRMS** (ESI): m/z [M+H]+ calcd for C₄₁H₆₇B₂N₃P₂: 671.4974; found: 671.4966.

Prior to the catalytic test, the borane protected phosphane 205c’ (200 mg, 0.3 mmol) was placed into a Schlenk flask.
under argon. Degassed morpholine (3 mL) were added and the flask was sealed. The reaction mixture was stirred at 100 °C for 3 h. It was cooled to room temperature and the excess morpholine was removed under reduced pressure. The residue was treated with degassed ethanol and cooled to -78 °C. The clear yellow supernatant was carefully removed via cannula filtration under argon. Degassed methylene chloride and silica (1 g) was added to the white precipitate and the volatiles were removed. The residue was placed at the top of a short silica column (5 g) and eluted with hexane/ethyl acetate 1:2 + 0.1 % Et₃N to give 205c as a white solid (138 mg, 70%) which was briefly checked by ¹H and ³¹P NMR and immediately used in catalysis.

¹H NMR (300 MHz, CD₂Cl₂): δ [ppm] = 0.86-1.32 (m, 22H, (C₆H₁₁)₂), 1.52-1.84 (m, 22H, (C₆H₁₁)₃), 2.39 (s, 6H, CH₃), 4.02 (d, ³J = 16.9 Hz, 2H, CH₂N), 4.26 (s, 2H, NCH₂N), 4.57 (d, ³J = 16.8 Hz, 2H, CH₂N), 6.87 (d, ³J₁₂ = 7.4 Hz, 2H, Ar-H), 7.12 (d, ³J₈₋₁₀ = 6.3 Hz, 2H, Ar-H).

³¹P NMR (121.5 MHz, CD₂Cl₂): δ [ppm] = 2.5.

Synthesis of 212a’

A Schlenk flask was charged with 211 (0.394 g, 1 mmol) under argon and THF (10 mL) was added. Then it was cooled down to -78 °C and n-BuLi (1.6 M in hexane, 1.5 mL, 2.4 mmol, 2.4 equiv) was added dropwise to form a pale-yellow clear solution. After 5 min, the flask was opened, CuCl (0.198 g, 2.0mmol) was quickly added and the resulting suspension was stirred for 5 minutes after which di-tert-butyl chlorophosphane (0.469 g , 2.4 mmol, 2.4 equiv) was added as one batch. The resulting mixture was warmed to ambient temperature within 60 minutes. The stirring was continued at 70 °C for 36 hours. It was then cooled to 0 °C and BH₃·THF (10 mL, 10 mmol of a 1M solution in THF) was added. The reaction mixture was allowed to reach room temperature and then it was stirred for additional 6 hours. The reaction was then transferred into a sat. aq. NH₄Cl solution (25 mL) under argon and it was stirred for 5 minutes. It was extracted with methylene chloride (3 x 75 mL). Combined organic layers were filtered over a Whatman filter paper, dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂ (30 g); hexane/ethyl acetate 3:1 containing 0.1% Et₃N) to give the borane protected rac-4,10-bis(di-tert-butylphosphino)-6,12-dihydro-5,11-ethanodibenzo[b,f][1,5]diazocine 212a’ as a white solid as (442 mg, 84%).

¹H NMR (400 MHz, CDCl₃): δ [ppm] = 0.1-0.99 (br, 6H, (BH₃)₂), 1.11 (d, ³J = 12.8 Hz, 18H, (CH₃)₁), 1.20 (d, ³J = 12.8 Hz, 18H, (CH₃)₃), 3.65 (s, 2H, NCH₂N), 4.45 (d, ²J = 17.0 Hz, 2H,
Prior to the catalytic test, the borane-protected phosphane \textbf{212a}' (260 mg, 0.46 mmol) was placed into Schlenk flask under argon. Degassed morpholine (5 mL) was added and the flask was sealed. The reaction mixture was stirred at 100 °C for 4 hours. It was cooled to room temperature and the excess morpholine was removed under reduced pressure. The residue was treated with degassed ethanol and cooled to -78 °C. The clear yellow supernatant was carefully removed via cannula filtration under argon. The white solid was rinsed with degassed pentane (10 mL x 2) and the volatiles were removed to give 212a as a white solid (199 mg, 80%) which was briefly checked by \textsuperscript{1}H and \textsuperscript{31}P NMR and immediately used in catalysis.

\textbf{Synthesis of 212b}'

A 50 ml Schlenk flask was charged with \textbf{211} (0.394 g, 1.0 mmol) under argon and THF (8 mL) was added. Then it was cooled down to -78 °C and n-BuLi (1.6 M in hexane, 1.5 mL, 2.4 mmol, 2.4 equiv) was added dropwise to form a pale-yellow clear solution. After 10 min, a solution of chlorodicyclohexylphosphane (560 mg, 2.4 mmol) in THF (5 mL) was used to quench the lithiated species. The reaction was allowed to reach room temperature overnight. It was then cooled to 0 °C and BH\textsubscript{3},THF (10 mL, 10 mmol of a 1M solution in THF) was added. The reaction mixture was allowed to reach room temperature and then it was stirred for additional 6 hours. The reaction was then transferred into a sat. aq. NH\textsubscript{4}Cl solution (20 mL) under argon and it was stirred for 5 minutes. It was extracted with methylene chloride (3 x 50 mL). Combined organic layers.
were dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂ (30 g); hexane/ethyl acetate 4:1 to 3:1 containing 0.1% Et₃N) to give the borane protected rac-2,8-bis(dicyclohexylphosphino)-6,12-dihydro-5,11 ethano-dibenzo [b,f] [1,5] diazocone 212b’ as a white solid as (440 mg, 70%).

Prior to the catalytic test, the borane protected phosphane 212b’ (200 mg, 0.3 mmol) was placed into a Schlenk flask under argon. Degassed morpholine (3 mL) were added and the flask was sealed. The reaction mixture was stirred at 100 °C for 3 h. It was cooled to room temperature and the excess morpholine was removed under reduced pressure. The residue was treated with degassed ethanol and cooled to -78 °C. The clear yellow supernatant was carefully removed via cannula filtration under argon. The white solid was rinsed with degased pentane (10 mL × 2) and the volatiles were removed to give 212b as a white solid (138 mg, 70%) which was briefly checked by ¹H and 3¹P NMR and immediately used in catalysis.

²¹H NMR (300 MHz, CD₂Cl₂): δ [ppm] = 0.81-1.27 (m, 22H, (C₆H₁₁)₂), 1.42-1.84 (m, 22H, (C₆H₁₁)₂), 3.65 (m, 4H, NCH₂CH₂N) 4.46 (d, 3J = 16.9 Hz, 2H, CH₂N), 4.65 (d, 3J = 16.9 Hz, 2H, CH₂N), 6.96 (d, J = 8.8 Hz, 2H, Ar-H), 7.04-7.12 (m, 4H, Ar-H).

³¹P NMR (121.5 MHz, CD₂Cl₂): δ [ppm] = -0.01.

2.5.3 Catalysis

General procedure for Suzuki cross-coupling

A Schlenk flask was charged with aryl halide (1.0 mmol), arylboronic acid (1.5 mmol, 1.5 equiv), K₂PO₄ (2.0 mmol, 2 equiv), Pd(OAc)₂ (0.015 mmol, 1.5 mol%), ligand (0.015 mmol, 1.5 mol%) and dry toluene (3.0 mL). The flask was degassed by freeze-pump thaw cycles (3x), then stirred at 90 °C under argon for a specified time and then cooled down to room
temperature. It was diluted with methylene chloride (10 mL), silica gel (2 g) was added and the volatiles were removed under reduced pressure. The crude product loaded on silica gel was then purified via column chromatography.

1,1'-Biphenyl 208aa

The product was isolated as a white solid (98%) upon column chromatography with hexane as an eluent.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ [ppm] = 7.37 (m, 2H, Ar-H), 7.47 (m, 4H, Ar-H), 7.62 (m, 4H, Ar-H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ [ppm] = 127.3, 127.4, 128.9, 141.4; MS (EI); m/z [M]$^+$ calcd for C$_{12}$H$_{10}$: 154.07; found: 154.0.

9-Phenylanthracene 208ba

The product was isolated as a white solid (99%) upon column chromatography with hexane as an eluent.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ [ppm] = 7.33-7.38 (m, 2H, Ar-H), 7.42-7.50 (m, 4H, Ar-H), 7.55-7.68 (m, 5H, Ar-H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ [ppm] = 125.7, 125.9, 126.0, 127.1, 127.3, 128.1, 128.8, 128.9, 130.7, 131.8, 131.9, 137.6, 139.3; MS (EI): m/z [M]$^+$ calcd for C$_{20}$H$_{14}$: 254.1; found: 254.0.

2,6-Dimethyl-1,1'-biphenyl 208ca

The product was isolated as a colourless oil (98%) upon column chromatography with hexane as an eluent.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ [ppm] = 2.06 (s, 6H, CH$_3$), 7.11-7.20 (m, 5H, Ar-H), 7.33-7.38 (m, 1H, Ar-H), 7.42-7.47 (m, 2H, Ar-H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ [ppm] = 20.6, 126.6, 127.0, 127.3, 128.4, 129.0, 136.1, 141.1, 141.9; MS (EI): m/z [M]$^+$ calcd for C$_{14}$H$_{14}$: 182.1; found: 182.1.

2'-Chloro-2,6-dimethyl-[1,1'-biphenyl]-4-amine 208db

The product was isolated as a yellow solid (95%) upon column chromatography with hexane/ethyl acetate 3:1 as an eluent.

$^1$H NMR (300 MHz, CD$_2$Cl$_2$): $\delta$ [ppm] = 1.89 (s, 6H, CH$_3$), 3.66 (br s, 2H, NH$_2$), 6.46 (s, 2H, Ar-H), 7.15 (m, 1H, Ar-H), 7.32 (m, 2H, Ar-H), 7.49 (m, 1H, Ar-H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$): $\delta$ [ppm] = 20.6, 114.2, 127.5, 128.8, 129.9, 130.0, 132.4, 134.7, 137.6,
140.4, 146.6; \textbf{IR} (ATR): $\tilde{\nu}$ [cm$^{-1}$] = 3421.5, 3330.5, 2916.9, 1618.0, 1576.0, 1462.6, 1439.7, 1425.5, 1376.6, 1328.5, 1282.6 1170.3, 1123.1, 1066.9, 1032.3, 1002.4, 944.5 855.9, 843.7, 739.5, 667.1; \textbf{HRMS} (ESI): m/z [M+H]$^+$ calcd for C$_{14}$H$_{15}$ClN: 232.0888; found: 232.088.

\textbf{M.p.} = 100.4 °C;

2-Methyl-1,1'-biphenyl 208ea

The product was isolated as a clear oil (80%) upon column chromatography with hexane as an eluent.

$^1$\textbf{H NMR} (300 MHz, CDCl$_3$): $\delta$ [ppm] = 2.34 (s, 3H, CH$_3$), 7.30-7.33 (m, 4H, Ar-$H$), 7.37-7.42 (m, 3H, Ar-$H$), 7.45-7.51 (m, 2H, Ar-$H$); $^{13}$\textbf{C NMR} (75 MHz, CDCl$_3$): $\delta$ [ppm] = 20.6, 125.8, 126.8, 127.3, 128.1, 129.2, 129.8, 130.3, 135.4, 141.9, 142.1; \textbf{MS} (EI): m/z [M]$^+$ calcd for C$_{13}$H$_{12}$: 168.1; found: 168.1.

(1,1'-Biphenyl)-4-carbonitrile 208fa

The product was isolated as a white powder (94%) upon column chromatography with hexane/ethyl acetate 10:1 as an eluent.

$^1$\textbf{H NMR} (300 MHz, acetone-d$_6$): $\delta$ [ppm] = 7.43-7.53 (m, 3H, Ar-$H$), 7.61-7.64 (m, 2H, Ar-$H$), 7.69-7.76 (m, 4H, Ar-$H$); $^{13}$\textbf{C NMR} (75 MHz, acetone-d$_6$): $\delta$ [ppm] = 111.5, 119.4, 127.7, 128.2, 129.2, 129.6, 133.1, 139.7, 146.1; \textbf{MS} (EI): m/z [M]$^+$ calcd for C$_{13}$H$_9$N: 179.03; found: 179.1.

1-[(1,1'-biphenyl)-4-yl]ethanone 208ga

The product was isolated as a white powder (96%) upon column chromatography with hexane as an eluent.

$^1$\textbf{H NMR} (300 MHz, CD$_2$Cl$_2$): $\delta$ [ppm] = 2.60 (s, 3H, CH$_3$), 7.37-7.42 (m, 1H, Ar-$H$), 7.44-7.50 (m, 2H, Ar-$H$), 7.63-7.67 (m, 2H, Ar-$H$), 7.69-7.73 (m, 2H, Ar-$H$), 8.00-8.04 (m, 2H, Ar-$H$); $^{13}$\textbf{C NMR} (75 MHz, CD$_2$Cl$_2$): $\delta$ [ppm] = 27.1 (CH$_3$), 127.6, 127.7, 128.7, 129.3, 129.5, 136.5, 140.4, 146.1, 197.9 (CO); \textbf{MS} (EI): m/z [M]$^+$ calcd for C$_{14}$H$_{12}$O: 196.09; found: 196.1.

4-Nitro-1,1'-biphenyl 208ha

The product was isolated as a yellow powder (94%) upon column chromatography with hexane/ethyl acetate 10:1 as an eluent.

$^1$\textbf{H NMR} (300 MHz, CD$_2$Cl$_2$): $\delta$ [ppm] = 7.42-7.53 (m, 3H, Ar-$H$), 7.63-7.67
(m, 2H, Ar-H), 7.74-7.77 (m, 2H, Ar-H), 8.25-8.3 (m, 2H, Ar-H); $^{13}$C-NMR (75 MHz, CD$_2$Cl$_2$): δ [ppm] = 124.5, 127.9, 128.4, 129.4, 129.7, 139.3, 147.7, 148.1; MS (EI): m/z [M]$^+$ calcd for C$_{12}$H$_9$NO$_2$: 199.0; found: 199.0.

3,5-Dimethoxy-1,1'-biphenyl 208ia

The product was isolated as a yellow powder (50% (94% in xylene)) upon column chromatography with hexane as an eluent.

$^1$H NMR (300 MHz, CDCl$_3$): δ [ppm] = 3.88 (s, 6H, CH$_3$), 6.52 (d, J = 3 Hz, 1H, Ar-H), 6.78 (d, J = 3 Hz, 2H, Ar-H), 7.39 (m, 1H, Ar-H), 7.47 (m, 2H, Ar-H), 7.62 (m, 2H, Ar-H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ [ppm] = 55.5 (OCH$_3$), 99.4, 105.5, 127.3, 127.6, 128.8, 141.3, 143.6, 161.1; MS (EI): m/z [M]$^+$ calcd for C$_{14}$H$_{14}$O$_2$: 214.1; found: 214.0.

General procedure for Buchwald-Hartwig cross-coupling

A Schlenk flask was charged with aryl halide (1.0 mmol), morpholine (1.5 mmol, 1.5 equiv), NaOtBu (1.2 mmol, 1.2 equiv), Pd(OAc)$_2$ (0.015 mmol, 1.5 mol%), ligand 205b (0.015 mmol, 1.5 mol%) and dry toluene (3.0 mL). The flask was degassed by freeze-pump thaw cycles (3x), then stirred at 110 °C under argon for 15 hours and then cooled down to room temperature. It was diluted with methylene chloride (10 mL), silica gel (2 g) was added and the volatiles were removed under reduced pressure. The crude product loaded on silica gel was then purified via column chromatography.

4-(4-Methoxyphenyl)morpholine 209a

The product was isolated as a yellow solid (96% from 206k, 45% from 206m) upon column chromatography with hexane/ethyl acetate 10:1 to 3:1 as an eluent.

$^1$H NMR (300 MHz, CDCl$_3$): δ [ppm] = 3.05 (m, 4H, CH$_2$), 3.77 (s, 3H, OCH$_3$), 3.86 (m, 4H, CH$_2$), 6.87 (m, 4H, Ar-H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ [ppm] = 50.9, 55.6, 67.1, 114.6, 117.9, 145.7, 154.1; HRMS (ESI): m/z [M+H]$^+$ calcd for C$_{12}$H$_{14}$NO$_2$, 194.1176; found 194.1177.

4-(Anthracen-9-yl)morpholine 209b

The product was isolated as a yellow solid (93%) upon column chromatography with hexane/ethyl acetate 19:1 to 10:1 as an eluent.

$^1$H NMR (300 MHz, CDCl$_3$): δ [ppm] = 3.55 (m, 4H, CH$_2$), 4.05 (m, 4H, CH$_3$), 7.44-7.54 (m, 4H, Ar-H), 8.02 (m, 2H, Ar-H), 8.34 (s, 1H, Ar-H), 8.55 (d, J = 8.3 Hz, 2H, Ar-H); $^{13}$C
Tröger’s Base Derived P,N & P Ligands

NMR (75 MHz, CDCl₃): δ [ppm] = 51.8, 68.6, 124.6, 125.2, 125.4, 125.5, 129.1, 130.6, 132.7, 143.5; MS (EI): m/z [M⁺] calcd for C₁₉H₁₉NO: 263.13; found: 263.2.

4-(4-Nitrophenyl)morpholine 209c

The product was isolated as a yellow solid (95%) upon column chromatography with hexane/ethyl acetate 4:1 as an eluent.

¹H NMR (300 MHz, CD₂Cl₂): δ [ppm] = 3.36 (m, 4H, C₅H₂), 3.83 (m, 4H, C₅H₂), 6.85 (d, J = 9.5 Hz, 2H, Ar-H); ¹³C NMR (75 MHz, CD₂Cl₂): δ [ppm] = 47.6, 66.8, 113.1, 126.2, 139.3, 155.7; MS (EI): m/z [M⁺] calcd for C₁⁰H₁₂N₂O₃: 208.8; found: 208.1.

4-(o-toly)lmorpholine 209d

The product was isolated as a clear oil (80%) upon column chromatography with hexane/ethyl acetate 19:1 as an eluent.

¹H NMR (300 MHz, CDCl₃): δ [ppm] = 2.33 (s, 3H, C₅H₃), 2.92 (m, 4H, C₅H₂), 3.86 (m, 4H, C₅H₂), 7.01 (m, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ [ppm] = 18.1, 52.4, 67.5, 119.1, 123.5, 126.7, 131.3, 132.7, 151.3; MS (EI): m/z [M⁺] calcd for C₁₁H₁₅NO: 177.13; found: 177.1.

4-(p-toly)morpholine 209e

The product was isolated as a white solid (93%) upon column chromatography with hexane/ethyl acetate 4:1 containing 0.1% Et₃N as an eluent.

¹H NMR (300 MHz, CDCl₃): δ [ppm] = 2.3 (s, 3H, C₅H₃), 3.13 (m, 4H, C₅H₂), 3.88 (m, 4H, C₅H₂), 6.98 (m, 4H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ [ppm] = 20.5, 50.1, 67.1, 116.1, 129.6, 129.8, 149.3; MS (EI): m/z [M⁺] calcd for C₁₁H₁₅NO: 177.13; found: 177.1.

4-(3,5-dimethoxyphenyl)morpholine 209f

The product was isolated as a white solid (51%) upon column chromatography with hexane/ethyl acetate 3:1 as an eluent.

¹H NMR (300 MHz, CDCl₃): δ [ppm] = 3.14 (m, 4H, C₅H₂), 3.78 (s, 3H, OCH₃), 3.84 (m, 4H, C₅H₂), 6.05 (m, 1H, Ar-H), 6.08 (m, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ [ppm] = 49.5, 55.3, 67.0, 92.0, 94.9, 153.4, 161.6; MS (EI): m/z [M⁺] calcd for C₁₂H₁₇NO₃: 223.1; found: 223.1.
2.6 References


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Chapter 3: Oxidative Functionalization of Tröger’s Base Derivatives

3.1 Introduction

Carbon-carbon bonds form the backbone of most organic compounds. Nevertheless, the reactivity profile of most organic molecules is often determined by the presence of heteroatoms—such as nitrogen, oxygen and sulphur—which are held in these molecules by carbon-heteroatom bonds. To illustrate this, heterocyclic compounds bearing C–N, C–O or C–S bonds have properties, significantly different from their all carbon analogues, which stem from the influence of carbon-heteroatom bond. Furthermore, several pharmaceuticals contain amine C–N bonds, and virtually all the known natural products contain either, ester or ketone C–O bonds. Apart from traditional methods, which often require functionalised starting materials, the direct conversion of C–H bonds to C–X bonds (X = N, O, etc.), is a much sought after methodology. Amines are perhaps one of the most interesting classes of organic molecules, and the cyclic variants are omnipresent motifs in natural products and industry-relevant structures. Naturally occurring molecules such as nicotine, coniine or morphine, drugs such as oxycodone, demethylphenidate and prasugrel too are examples of amines, however on closer inspection we do see that they contain substituted carbons adjacent to the amine nitrogen (Figure 3.1)

![Figure 3.1 Amines in nature and those used as medicines.](image)
3.1.1 Amine α-Functionalization

The direct formation of C–C, C–O, C–N bonds from normally torpid C–H bonds is a challenging area of organic synthesis. The functionalization of C–H bonds adjacent to nitrogen atoms is important due to the number of important chemical building blocks that can be formed in a single synthetic step, and accordingly the α-functionalization of tertiary amines has interested chemists for a long period of time. Several strategies have been developed as briefly considered further. The substituents may be introduced next to nitrogen atoms by α-deprotonation of an amine and subsequent reaction of the resulting α-amino anion with an electrophile, first described by Beak and Lee (Scheme 3.1).

![Scheme 3.1 α-Deprotonation and addition to electrophiles.]

Alternatively, α-amino radicals can be generated photochemically and coupled with another radical as shown in scheme 3.2.

![Scheme 3.2 Photoredox C–H arylation of amines]

In a related reaction, the alpha-amino radical generated by the action of tributyltin hydride and VAZO (Scheme 3.3) undergoes cyclization with a pendant olefin yielding the fused-indole product (d.r 6:1).

![Scheme 3.3 CH activation-cyclization. VAZO = 1,1'-azobis(cyclohexane-1-carbonitride).]
A great many strategies – electrochemical oxidation, chemical oxidants, transition metal, and visible light photoredox catalysis – have been developed to generate an α-amino cation, which can be trapped by a nucleophile. The tropylium ion oxidises the amine to yield the iminium cation that undergoes a salt metathesis to yield the nitrile analogue, which then collapses to generate the product (Scheme 3.4).  

![Scheme 3.4 Amine α-cyanation.](image)

Liang and co-workers, using a hypervalent iodine reagent as an oxidant, have developed a method that allows for diacetoxylation of tertiary amines (Scheme 3.5).

![Scheme 3.5 Diacetoxylation of 1-phenylpiperidine.](image)

In addition, a completely different method of α-functionalization of tertiary amines exploits transition-metal-catalyzed sp³ C–H activation (Scheme 3.6).

![Scheme 3.6 Transition metal catalysed amine α-arylation.](image)
3.1.2 Amine α-Functionalization of Tröger’s Base Analogues

Tröger’s base and its ethylene-bridged analogue are bicyclic tertiary diamines, and there are not too many methods in literature, which deal with the functionalization of their amine α-C–H bonds.\(^1\) Harmata and co-workers who deprotonated the alpha-amino position of TB with a strong base, and then subjected the lithiated species to several electrophiles (Scheme 3.7).\(^2\)

![Scheme 3.7 Alkylation of Tröger’s base.](image)

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>Yield</th>
<th>Electrophile</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCH(_2)Br</td>
<td>68</td>
<td>TMSCl</td>
<td>66</td>
</tr>
<tr>
<td>2-(3-bromopropyl)furan</td>
<td>75</td>
<td>MEMCl</td>
<td>84</td>
</tr>
<tr>
<td>allyl bromide</td>
<td>62</td>
<td>furfural</td>
<td>66</td>
</tr>
<tr>
<td>CH(_3)I</td>
<td>87</td>
<td>Ph(_2)CO</td>
<td>66</td>
</tr>
<tr>
<td>5-ido-1-pentene</td>
<td>76</td>
<td>iBuOCOCl</td>
<td>62</td>
</tr>
</tbody>
</table>

Furthermore, the use of Vilsmeier reagents as independently shown by the groups of Shridar\(^3\) and Try\(^4\) leads to the insertion of an amino functionality on the carbon between the two nitrogen atoms as shown in scheme 3.8. Interestingly, the ethylene-bridged analogue did not react at all.\(^5\)

![Scheme 3.8 Effect of Vilsmeier reagents on Tröger’s base.](image)

A combination of TiCl\(_4\) and aromatic aldehyde leads to the arylation of the carbon between the two nitrogen atoms, leaving the benzylic carbon untouched (Scheme 3.9).\(^6\)

![Scheme 3.9 Reaction of TiCl\(_4\) and benzaldehyde with Tröger’s base.](image)

Try and co-workers have developed a protocol for the introduction of spiro[4.5] lactone straps onto the Tröger’s base scaffold (Scheme 3.10).\(^7\)
More, recently Lacour and co-workers making use of carbenes and nitrenes, have synthesised amine α-functionalised ethylene-bridged Tröger’s base derivatives starting from Tröger’s base (Scheme 3.11).

Utilising DDQ as an oxidant, Lacour and co-workers have manage to transfer a two-carbon analogue to a one-carbon derivative under mild conditions via an extrusion of a CH₂ unit (Scheme 3.12).

In a KMnO₄ mediated oxidation, Wärnmark and co-workers have synthesised a Tröger’s base derived twisted bis-amide (Scheme 3.13).
3.2 Motivation

As a part of our research on the chemistry of Tröger’s base, I have explored the ethylene-bridged analogue – ethano Tröger’s base 301a, that was first synthesised by Hamada in 1996.21 In the course of developing phosphane ligands based on a Tröger’s base scaffold, we were interested in synthesising phosphanes based on the ethylene-bridged variant (Figure 3.2).

In contrast to Tröger’s base, for which there exist several methods to functionalise the aromatic rings, either by using pre-functionalised aniline moieties or by post-synthesis transformations, and to a lesser extent the bridge of the molecule, there exist a handful of methods to access functionalised ethano Tröger’s base derivatives.12 This paucity in methods to functionalise ethano Tröger’s base got us interested in exploring its chemistry.
3.3 NBS Promoted Oxygenation and Nitrogenation of Amine α-C–H bonds in Ethano Tröger’s base

Part of this subchapter has been reproduced in Pereira, R.; Otth, E.; Cvengroš, J. Eur. J. Org. Chem. 2015, 1674

3.3.1 Discovery

During the course of our research program in Tröger’s base chemistry we have attempted to functionalise the aromatic rings of ethano-Tröger’s base 301a by means of electrophilic bromination. However, the system proved to be completely unreactive to a variety of conditions and the introduction of a bromine atom to any of the aromatic positions was never observed. Interestingly, the exposure of 301a to an excess of N-bromosuccinimide (NBS) and a catalytic amount of palladium acetate in acetonitrile at 105 °C led to a formation of a new crystalline compound isolated in 24% yield. Its X-ray crystallographic analysis revealed that two bromine atoms have been introduced to both carbons of the ethano-bridge of 301a in a stereospecific fashion affording dibromide 302a (Scheme 3.14).

![Scheme 3.14 α-Functionalization of bicyclic tertiary amines. Distances between the aromatic para-carbon atoms and dihedral angles between the planes defined by the aromatic rings are given.](image)

During the subsequent optimization of the reaction conditions (vide infra), the presence of two additional by-products in significant amounts was observed. Besides 302a, we could thus isolate acetoxy-derivative 303a and imide 304a and their structures were
unambiguously confirmed by X-ray crystallography. These compounds were then also
detected under the conditions of the original experiment albeit only in trace amounts.
Interestingly, no functionalization of the benzylic positions has been observed. Compounds
\textbf{302a}, \textbf{303a} and \textbf{304a} are unusual examples of stable α-oxygen- or α-nitrogen-substituted
tertiary diamines. As the X-ray crystallographic analyses suggest, in all three cases the
carbon-bromine, carbon-oxygen and carbon-nitrogen bonds were formed in a
stereoselective fashion as the substituents exclusively occupy the positions above the
benzylic carbon atoms. The dihedral angles (89.4° for \textbf{302a}, 83.1° for \textbf{303a} and 85.1° for
\textbf{304a}, respectively) between the planes formed by the aromatic rings are in the lower range
of the values observed for the methano-bridged Tröger’s base analogues (84-113°). 22

3.3.2 Exploring the Reaction

This unusual functionalization event prompted us to inspect the reaction further. We
examined several conditions and made some valuable observations in order to optimize the
yield of the functionalised products as well as to clarify the reaction mechanism (Table 3.1).
The reaction can be carried out at lower temperatures and an almost complete conversion
was observed even at room temperature (Table 3.1, entries 2 and 3), but \textbf{302a} was formed
in low yields only. The screening further revealed that no conversion is observed without
NBS (Table 3.1, entry 4) and the use of 1 equivalent of NBS is not sufficient for a satisfactory
conversion of \textbf{301a} (Table 3.1, entry 5). The reaction proceeds even without palladium
acetate, but the reaction is slower, \textbf{302a} is observed only in trace amounts and \textbf{303a} and
\textbf{304a} were not detected (Table 3.1, entry 6). The presence of an additional amount of
acetate anion in the form of potassium acetate favours the formation of both the acetate
\textbf{303a} and imide \textbf{304a} (Table 3.1, entry 7). In that case, the loading of Pd(OAc)$_2$ can be
lowered to 15 mol% (Table 3.1, entry 8). However, at 10 mol% the conversion of \textbf{302a}
significantly drops (Table 3.1, entry 9). Alternatively, the presence of KOAc allows for the
lowering of the temperature to 25 °C (Table 3.1, entry 10). The solvent plays an important
role as high conversions towards the α-functionalised products were achieved only in
acetonitrile. The reaction could also be run in methylene chloride, albeit with lower yields
(Table 3.1, entries 11 and 12). Interestingly, a quantitative recovery of the starting material
was observed when the reaction was performed in carbon tetrachloride, a solvent typically
used for bromination with NBS (Table 3.1, entry 13).
Table 3.1 Optimization of the reaction conditions according to the transformation presented in Scheme 3.11.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>NBS [equiv]</th>
<th>Pd(OAc)\textsubscript{2} [mol%]</th>
<th>KOAc [equiv]</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>Conversion [%]</th>
<th>302a [%]</th>
<th>303a [%]</th>
<th>304a [%]</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>20</td>
<td>0</td>
<td>CH\textsubscript{3}CN</td>
<td>105</td>
<td>99</td>
<td>24</td>
<td>traces</td>
<td>traces</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>20</td>
<td>0</td>
<td>CH\textsubscript{3}CN</td>
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<td>99</td>
<td>22</td>
<td>traces</td>
<td>traces</td>
</tr>
<tr>
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<td>2</td>
<td>20</td>
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<td>CH\textsubscript{3}CN</td>
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<td>85</td>
<td>20</td>
<td>traces</td>
<td>traces</td>
</tr>
<tr>
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<td>0</td>
<td>20</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
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<td>20</td>
<td>0</td>
<td>CH\textsubscript{3}CN</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
<td>CH\textsubscript{3}CN</td>
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<td>5</td>
<td>37</td>
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<td>2</td>
<td>15</td>
<td>2</td>
<td>CH\textsubscript{3}CN</td>
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<td>20</td>
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<td>CH\textsubscript{3}CN</td>
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<td>21</td>
<td>30</td>
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<tr>
<td>11</td>
<td>2</td>
<td>20</td>
<td>2</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>82</td>
<td>63</td>
<td>15</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>20</td>
<td>2</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>25</td>
<td>25</td>
<td>22</td>
<td>traces</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>20</td>
<td>2</td>
<td>CCl\textsubscript{4}</td>
<td>82</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{a} All reactions were stirred for 18 h.\textsuperscript{b} Conversion based on recovery of 301\textsubscript{a} or determined by GC with respect to an internal standard (hexachloroethane). \textsuperscript{c} Isolated yields after column chromatography.

The results of the screening suggest that running the reaction in acetonitrile at 50 °C in the presence of potassium acetate would lead to the formation of 303\textsubscript{a} and 304\textsubscript{a} preferentially (Table 3.1, entry 7). However, both products are formed simultaneously and compete for the acetate. Despite extensive efforts, the dibromide 302\textsubscript{a} was always formed only in rather low yields, which implies that the reaction pathway leading to this product is only a minor one. Applying the optimized conditions we have screened different 2,8-disubstituted ethano-Tröger’s base derivatives. It has been noticed that electron-donating groups in these positions increase the reactivity of the system but have no significant influence on the ratio of 303 and 304 (Table 3.2). The reaction with the ethyl ester derivative 301\textsubscript{d} yielded only the imide 304\textsubscript{d} in a low yield of 21% after column chromatography.
Interestingly, our preliminary attempts with other diamines (e.g., 1,4-diazobicyclo[2.2.2]octane; DABCO) yielded mono- and dibrominated products as detected by GC–MS, but the isolation failed due to their instability. In addition to the screening efforts, we have carried out further experiments to understand the mechanism of this transformation (Scheme 3.15). The reaction was completely suppressed in the presence of TEMPO (2 equiv) under standard conditions [NBS (2 equiv), Pd(OAc)$_2$ (20 mol%) in methylene chloride at 82 °C or CH$_3$CN at 50 °C] hinting towards a radical mechanism. However, TEMPO-adducts in the reaction mixture were never detected. Interestingly, attempts to perform the reaction under conditions typical for radical processes (e.g. in the presence of AIBN as radical initiator) failed to deliver any of the three described products.

### Table 3.2 Scope of the NBS-Pd(OAc)$_2$ α-oxygenation and α-nitrogenation of bicyclic tertiary amines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Conversion [%]</th>
<th>Yield of 303 [%]$^a$</th>
<th>Yield of 304 [%]$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_3$</td>
<td>99</td>
<td>303a(37)</td>
<td>304a(40)</td>
</tr>
<tr>
<td>2</td>
<td>OMe</td>
<td>99</td>
<td>303b(49)</td>
<td>304b(48)</td>
</tr>
<tr>
<td>3</td>
<td>iPr</td>
<td>72</td>
<td>303c(20)</td>
<td>304c(26)</td>
</tr>
<tr>
<td>4</td>
<td>COOEt</td>
<td>64</td>
<td>303d(0)</td>
<td>304d(21)</td>
</tr>
</tbody>
</table>

$^a$Isolated yields after column-chromatography.
Scheme 3.15 Experiments directed towards clarifying the reaction mechanism.

In some of the screening experiments, we have detected and isolated minor amounts of the olefin 305a, which may serve as a direct precursor for the formation of the dibromide 302a (vide infra). We have also performed the transformation with enantiomerically pure (–)-301a and single diastereomers of 303a and 304a were obtained (confirmed by HPLC analysis). This result suggests that the carbon-carbon and carbon-nitrogen bridge-forming bonds remain intact during the process as the cleavage of one of these bonds will be accompanied by a rapid pyramidal inversion at the nitrogen centres resulting in racemization. When the reaction was carried out in propionitrile instead of acetonitrile, the acetopropionimide 306a was isolated in a yield of 27%. However, as no diacetoimide 304a was detected, we could unambiguously confirm that the nitrile acts as a reagent.

NMR studies showed that palladium does not coordinate to the nitrogen atoms. However, an interesting observation was made when the 1H NMR of the reaction mixture containing different amounts of NBS was recorded after 15-20 minutes (Figure 3.3). The proton resonances at 3.54 ppm, which correspond to the diastereotopic protons of the ethano-bridge of the molecule, lose their characteristic splitting pattern and manifest themselves as a sharp singlet with an integral value of four at a slightly downfield shift of 3.57 ppm. All other resonances are unaffected, except for a minor shift of the benzylic exo-protons. The
dramatic metamorphosis of the said signal points towards a rapid process, which makes the four bridge protons equivalent on the NMR time scale. We suspect that bromine-nitrogen bond in NBS homolytically cleaves yielding succinimidyl and bromine radical, which abstract a hydrogen radical from the ethano-bridge of 301a in a fast reversible fashion.

Based on our observations, we thus propose that the abstraction of the hydrogen radical by one of the radicals stemming from NBS yields A (Scheme 3.16). A subsequent abstraction of the second hydrogen radical affords 305a, which has indeed been observed in the reaction mixture. Dibromide 302a is then formed from 305a via a typical olefinic bromination with bromine, which is produced from the interaction of HBr and NBS. Alternatively, radical A is oxidized by the second equivalent of NBS to the carbocation intermediate B, which can be intercepted by a nucleophile.
The reaction of B with acetate anion thus yields 303a. B can also participate in a Ritter-type reaction with acetonitrile. Initially, the nitrilium cation C is formed which reacts with acetate to furnish intermediate D that rearranges to the imide 304a. Clearly, the mechanistic proposal does not reflect the role of palladium(II) acetate as all our attempts to clarify its function failed to deliver an indubitable proof. The activation of NBS by Pd(OAc)$_2$ as Lewis-acidic catalyst can be ruled out as a heterolytic cleavage of the nitrogen-bromine bond would be favoured in such case. More likely, palladium(II) acetate could activate the olefin 305a for the nucleophilic attack yielding an intermediate, which would furnish the product upon protodemetalation step. Although, the intermediacy of 305a towards 303a or 304a could not be confirmed by an independent experiment starting from 305a, it might be assumed that it was not possible to entirely simulate the original conditions of the reaction as when 301a was used as substrate.
In order to shed light on the stereoselectivity of the reaction, the proposed carbocation B merits a comment. The presence of the neighbouring nitrogen atom implies for the stabilization by its free electron pair but such explanation suffers from a serious drawback. The alignment of the empty p-orbital on the cationic carbon atom and the free electron pair on the nitrogen required for an effective orbital overlap is far from perfect and the resulting iminium intermediate would represent an anti-Bredt species (Scheme 3.17). This renders such proposal for the stabilization of the carbocation B highly unlikely. On the other hand, the fact that the reaction is more efficient when substrates with electron-rich arenes are employed opens the possibility that the aromatic system stabilizes B via a neighboring group participation given rise to a non-classical phenonium carbocation. Such stabilization would also clarify why the cation was never generated at the benzylic carbon atoms. Finally, the presence of such anchimeric assistance is also in accord with the observed stereoselectivity. The nucleophile (acetate or acetonitrile) thus attacks the carbocation selectively from the side opposite to the aromatic ring, which is involved in the stabilization. Similarly, in the bromination event the stabilizing effect would be extended to the bromonium cation.

Scheme 3.17 Considerations for the stabilization of the carbocation B and explanation of the stereoselectivity of the given transformations.

The bromide anion can attack only the carbon of the ethano-bridge, which is not directly interacting with the aromatic ring. In all cases the incoming substituents occupy the positions above the benzylic positions as it was observed in the X-ray crystal structures.
3.3.3 Conclusion

In conclusion, we have discovered a mild procedure for the α-oxygenation and α-nitrogenation of tertiary diamines via NBS-mediated oxidation. The reaction was carried out under mild conditions using NBS as oxidant along with Pd(OAc)₂ as catalyst. We have also shown that brominated α-functionalised amines can be prepared by this methodology. In addition a succinct mechanistic study was carried out, which suggested the possibility of a non-classical carbocation being involved a key-step of the mechanism. As a logical extension to this study, we are applying this Pd(OAc)₂-NBS mediated methodology to other tertiary amines and nucleophiles as considered further on in this chapter.
3.4 NBS Promoted Acetoxylation and Azidation of Amine α-C–H Bonds in Tröger’s Base Analogues

In the course of our research on Tröger’s base chemistry, we have developed a method to functionalise the bridge of ethano-Tröger’s base derivatives in a chemoselective and stereoselective manner. We showed that carbon-oxygen and carbon-nitrogen bonds could be formed next to the nitrogen centers via an acetoxylation or a Ritter-type reaction.\textsuperscript{22}

Herein, we present the utilisation of this protocol for the acetoxylation and azidation of methano-bridged Tröger’s base analogues.

3.4.1 Acetoxylation of Tröger’s Base Analogues

The use of 307a as a model system under the original conditions in the presence of two equivalents of N-bromosuccinimide (NBS), potassium acetate (KOAc) and a catalytic amount of palladium(II)acetate in acetonitrile at 50 °C resulted in the formation of mono- and diacetoxy Tröger’s base analogues 308a and 309a in 78% and 20% yield respectively (Scheme 3.18).

\[
\text{NBS (2 equiv) } \quad \text{Pd(OAc)}_2 \quad \text{(20 mol%) } \quad \text{KOAc (2 equiv)} \quad \text{CH}_3\text{CN (c = 0.1 M) } \quad 50 \degree \text{C, 18 h}
\]

\[
\begin{array}{ccc}
   & \text{307a} & \text{OAc} \\
\rightarrow & \text{308a} \quad 78\% & + \\
   & \text{309a} \quad 20\% & \\
\end{array}
\]

\textbf{Scheme 3.18} α-Acetoxylation of Tröger’s base. Yields refer to yield of isolated products after column chromatography.

To our delight, it was possible to grow crystals of 309a and a monoacetoxy derivative 308c (\textit{vide infra}), suitable for X-ray crystallographic analysis which indeed revealed that the acetoxylation occurred at the carbons between the aromatic systems and nitrogen leaving the methylene-bridge carbon untouched (Figure 3.4).

\textbf{Figure 3.4} ORTEP-III representation of the diacetoxyalted product \textit{rac-309a} (l) and monoacetoxyalted product \textit{rac-308c} (r). Irrelevant hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at 40% probability.
Moreover, the analysis disclosed the exo configuration of the carbon-oxygen bonds as a consequence of a better access to the Tröger’s base scaffold from its convex face. Although the results of the initial experiment were satisfactory (98% combined yield), we felt intrigued whether it is possible to control the selectivity of the reaction, and optimize the amounts of NBS, palladium(II)acetate and potassium acetate (Table 3.3). We have thus observed 50% conversion when a single equivalent of NBS was used (Table 3.3, entry 2) and no acetoxylation took place in the absence of NBS (Table 3.3, entry 3). The reaction proceeds even without palladium(II) acetate but the efficiency of the transformation is lower (Table 3.3, entry 4). Furthermore, a significant lowering of the palladium loading results in a dramatic decrease of the yield (Table 3.3, entry 5).

**Table 3.3** Screening of the reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from standard conditions</th>
<th>Conversion [%]</th>
<th><strong>308a</strong> [%]</th>
<th><strong>309a</strong> [%]</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>&gt;99</td>
<td>78 (78)</td>
<td>22 (20)</td>
</tr>
<tr>
<td>2</td>
<td>NBS [1 equiv]</td>
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</tr>
<tr>
<td>3</td>
<td>NBS [0 equiv]</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$ [0 mol%]</td>
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<td>15</td>
<td>1.5</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$ [10 mol%]</td>
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<td>41</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>KOAc [4 equiv]</td>
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<td>85</td>
<td>7</td>
</tr>
<tr>
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<td>43</td>
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<tr>
<td>8</td>
<td>80 °C</td>
<td>99</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>9</td>
<td>dark reaction</td>
<td>99</td>
<td>85</td>
<td>15</td>
</tr>
</tbody>
</table>

*a* Standard reaction conditions: **307a** (1 equiv), NBS (2 equiv), Pd(OAc)$_2$ (20 mol%), KOAc (2 equiv), CH$_3$CN (c = 0.1 M), 50 °C, 18 h, argon atmosphere. *b* Conversion and yield determined by GC with respect to an internal standard (DABCO). *c* In parentheses is isolated yield after flash chromatography.

Counterintuitively, in an attempt to force the reaction towards the diacetate product **309a** using 4 equivalents of KOAc, the formation of the monoacetate product **308a** was favoured (Table 3.3, entry 6). An elevated temperature seems to be essential as the reaction at room temperature is rather sluggish (Table 3.3, entry 7). Interestingly, diacetate **309a** was formed only in trace amounts at 25 °C. On the other hand, the result of an experiment in acetonitrile at 80 °C proved almost indifferent compared to standard conditions (Table 3.3, entry 8). Finally, the exclusion of light had a minimal impact on the outcome of the reaction (Table
3.3, entry 9). Thus interestingly, the conditions optimized for the functionalization of the bridge of ethano-Tröger’s base proved the most effective also for the original Tröger’s base albeit different carbon-hydrogen bonds were functionalised. With optimized conditions in our hands, we set about exploring the limits of this methodology. We could thus show that a large variety of differently substituted Tröger’s base analogues undergo α-C-H oxygenation at the benzylic positions next to the nitrogen atoms (Scheme 3.19). Derivatives bearing electron-donating substituents tend to deliver a mixture of mono- and diacetoxylated products in high yields, wherein 308 was the predominant product (substrates 307b, 307c, 307d).

![Scheme 3.19 Substrate scope of the α-acetoxylation.](image)

However, in the case of tetramethyl-substituted derivative 307e the diacetate 309e was obtained exclusively. Interestingly, palladium did not undergo oxidative addition to carbon-halogen bonds and the halogen-containing substrates 307f-307j afforded the corresponding monoacetates 308f-308j. Only in the case of 307g the diacetate 309g was detected and isolated. On the other hand, the presence of electron-withdrawing groups attenuated the reactivity of the substrates, resulting in low (307k) or no yields (307l). Unfortunately, free amino groups on the TB-scaffold were not tolerated (substrate 307m).
3.4.2 Azidation of Tröger’s Base Analogues

We then turned our attention to other nucleophiles. Predictably other carboxylates can be employed in the reaction, albeit with lower yields of the corresponding products: sodium propionate furnished 28% of the monopropionate 308n and 7% of the dipropionate 309n (Figure 3.5).

Figure 3.5 Screening of nucleophiles as substitutes for KOAc. Yields refer to yield of isolated products after column chromatography. [Note: Pavol Ondrisek carried out all of these experiments]

Having shown that oxygen-nucleophiles worked well, we wanted to ascertain the range of heteroatoms that could be introduced into the benzylic positions via this methodology. Gratifyingly, after a series of disappointing results with various nucleophiles, we observed full conversion of the starting material to monoazide 310a (38%) and bisazide 311a (46%) with sodium azide as the nucleophile.

Scheme 3.20 Azidation reaction. Yields refer to yield of isolated products after column chromatography. [Note: Pavol Ondrisek carried out all of these experiments].
The azidation protocol proved to be as robust as the acetoxylation reaction, and a variety of Tröger’s base analogues could be transformed to the corresponding mono-and bisazides (Scheme 3.20).

3.4.3 Conclusion

In conclusion, we have extended the original procedure as described in section 3.3 to classical methano Tröger’s base derivatives. We have been able to α-oxygenate as well as azidate Tröger’s bases via this method. The reaction was carried out under mild conditions using NBS as oxidant along with Pd(OAc)$_2$ as catalyst, and we are able to make highly functionalised TB derivatives with relative ease.
3.5 KMnO₄ Mediated Functionalization of the Ethano-Tröger’s Base

Wärnmark and co-workers showed that potassium permanganate has been used to oxidize the benzylic C–H bonds of Tröger’s base (TB), 307 to yield a twisted bis-amide, rac-2,8-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine-6,12-dione, 312 in 28% yield (Scheme 3.13).²⁰ As a part of our research on Tröger’s base we have been developing methods to access functionalized derivatives of 301 and to this extent we have been able to oxygenate and nitrogenate the non-benzylic alpha-carbon atoms in 301a in a chemo- and stereoselective manner using palladium acetate, N-bromosuccinimide and potassium acetate (Scheme 3.14).

3.5.1 Reaction Scope

Here we would like to report the extension of a method developed by Wärnmark and co-worker to oxidize the benzylic C–H bond of 301a leaving the alpha amino C–H bond untouched to yield 301a (Scheme 3.21).

Optimization of the reaction conditions revealed that the original conditions were the best (Table 3.4, entry 1) and that nine equivalents of KMnO₄ and the phase transfer catalyst were required. The quality of the methylene chloride utilized did not affect the reaction at all. Furthermore, we could also run the reaction efficiently in acetonitrile (Table 3.4, entry 9). It must be noted that the bis-amide products are poorly soluble in most organic solvents, and only methylene chloride and pyridine were able to dissolve them sufficiently, nevertheless the separation of the products from the starting material is straightforward and the products belong to the rare class of medium-bridge lactams.
Table 3.4 Exploring the reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from standard conditions</th>
<th>Ratio 313a:301a</th>
<th>3a [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>90:10</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>0 equiv. of KMnO₄</td>
<td>0:100</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>0 equiv. of BnEt₃ NCl</td>
<td>0:100</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>3 equiv. of KMnO₄</td>
<td>10:90</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>6 equiv. of KMnO₄ at 25 °C</td>
<td>45:55</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>9 equiv. of KMnO₄ at 50 °C</td>
<td>0:100</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>3 equiv. of KMnO₄ in CH₂CN at 50 °C</td>
<td>30:70</td>
<td>ND</td>
</tr>
<tr>
<td>8</td>
<td>6 equiv. of KMnO₄ in CH₂CN at 50 °C</td>
<td>57:43</td>
<td>ND</td>
</tr>
<tr>
<td>9</td>
<td>9 equiv. of KMnO₄ in CH₂CN at 50 °C</td>
<td>86:14</td>
<td>46</td>
</tr>
<tr>
<td>10</td>
<td>9 equiv. of KMnO₄ in CH₂CN at 25 °C</td>
<td>03:97</td>
<td>ND</td>
</tr>
<tr>
<td>11</td>
<td>Toluene</td>
<td>0:100</td>
<td>-</td>
</tr>
</tbody>
</table>

Standard reaction conditions: 301a (1 equiv), KMnO₄ (9 equiv), BnEt₃ NCl (9 equiv), CH₂Cl₂ (c = 0.1 M), 50 °C, 18 h, open to air. Ratio determined by ¹H NMR. Isolated yield after flash chromatography.

Using the optimized conditions we have subjected different 2,8-disubstituted ETB derivatives successfully to this transformation. Electron-donating groups on the aromatic ring increase the reactivity of the system whereas electron-withdrawing groups inhibit the reaction (Table 3.5, entries 301b, 301c, 301d, 301e and 301f).

Table 3.5 Scope of the reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>R</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>301a</td>
<td>Me</td>
<td>313a</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>301b</td>
<td>OMe</td>
<td>313b</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>301e</td>
<td>Br</td>
<td>313e</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>301f</td>
<td>Cl</td>
<td>313f</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>301d</td>
<td>COOEt</td>
<td>313d</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>301j</td>
<td>Me,F</td>
<td>313j</td>
<td>0</td>
</tr>
</tbody>
</table>

Reaction conditions: 1a (1 equiv), KMnO₄ (9 equiv), BnEt₃ NCl (9 equiv), CH₂Cl₂ (c = 0.1 M), 50 °C, 18 h, open to air. Isolated yield after flash chromatography. 4,10-difluoro-2,8-dimethyl-6H,12H-5,11-ethanodibenzo [b,f] [1,5] diazocine was used.
Compound 301j merits a mention, as it is the first example of an ETB analogue bearing substituents ortho to the nitrogen atoms.

Scheme 3.22 Synthesis of the first 4,10-disubstituted ETB analogue 301j. ORTEP plot of 301j. Thermal ellipsoids are drawn at 50% probability.

This compound was synthesized via modified bridge replacement procedure wherein 307j was stirred with 1,2-dibromoethane and Li₂CO₃ in DMF at 125 °C for 72 hours to give 301j in 50% yield (Scheme 3.22). To our disappointment 301j did not react at all with potassium permanganate, suggesting that the electron withdrawing effect of the fluorine hampers the reaction which is consistent with the reduced yield when a chlorine or ester functionality is present on the aromatic ring (Table 3.5, entries 301d, 301e).

3.5.2 Structural Analysis

We next studied the structural properties of these bis-amides 313 via X-ray crystallography, and compared them with known twisted amides.

Figure 3.6 (Top left) Twisted amides 312 and 315 along with a planar amide 314. (Bottom left) Planar and Distorted geometries of amides. (Right) Twist-angle distribution of tertiary amides in the Cambridge Crystallographic Database (CCDB) on 8th December 2015. Data for 13000 structures.
To our delight we were able to grow suitable quality crystals for X-ray diffraction analysis (Figure 3.7).

![Figure 3.7 ORETTP plots of 313a and 313d. Thermal ellipsoids are drawn at 40% probability](image)

The twist angle $\tau$ of 313a, 313d and 316a (vide infra) are significantly twisted from planarity. The carbonyl groups are planar whilst the amine nitrogen is neither planar nor tetrahedral.

Relevant structural and spectroscopic parameters are compared in Table 3.6 with those of 1-methyl-2-piperidone 314 ($\tau = 2.5^\circ$), Tröger’s base derived amide 312 ($\tau = 43.7^\circ$) and 1-aza-2-adamantan-one 315 ($\tau = 90.5^\circ$).

**Table 3.6** Select structural and spectroscopic parameters.

<table>
<thead>
<tr>
<th></th>
<th>314</th>
<th>313a</th>
<th>313d</th>
<th>316a</th>
<th>312 \textsuperscript{20d}</th>
<th>315</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau(\text{\degree})$</td>
<td>2.5</td>
<td>29.8</td>
<td>-28.1</td>
<td>30.2</td>
<td>-43.7</td>
<td>90.5</td>
</tr>
<tr>
<td>Sum of bond angles at N(\degree)</td>
<td>358.9</td>
<td>344.5</td>
<td>344.4</td>
<td>346.3</td>
<td>333.0</td>
<td>325.7</td>
</tr>
<tr>
<td>Sum of bond angles at C=O (\degree)</td>
<td>359.9</td>
<td>359.8</td>
<td>359.8</td>
<td>359.7</td>
<td>359.8</td>
<td>359.9</td>
</tr>
<tr>
<td>Bond length C(O)–N (Å)</td>
<td>1.352</td>
<td>1.402</td>
<td>1.402</td>
<td>1.386</td>
<td>1.437</td>
<td>1.475</td>
</tr>
<tr>
<td>Bond length C=O (Å)</td>
<td>1.233</td>
<td>1.215</td>
<td>1.220</td>
<td>1.225</td>
<td>1.209</td>
<td>1.195</td>
</tr>
<tr>
<td>Distance O–O (Å)</td>
<td>na</td>
<td>3.52</td>
<td>3.42</td>
<td>3.95*</td>
<td>5.34</td>
<td>na</td>
</tr>
<tr>
<td>Distance N–N (Å)</td>
<td>na</td>
<td>2.66</td>
<td>2.66</td>
<td>2.66</td>
<td>2.39</td>
<td>na</td>
</tr>
<tr>
<td>Angle between aromatic rings $\Psi(\text{\degree})$</td>
<td>na</td>
<td>41.8</td>
<td>39.8</td>
<td>36.7</td>
<td>120.1</td>
<td>na</td>
</tr>
<tr>
<td>IR $\nu_{\text{C=O}}$ (cm$^{-1}$)</td>
<td>1653</td>
<td>1674</td>
<td>1666</td>
<td>1667</td>
<td>1694</td>
<td>1732</td>
</tr>
<tr>
<td>$^{13}$C NMR C=O (δ, ppm) (CDCl$_3$)</td>
<td>165.0</td>
<td>179.1</td>
<td>176.5</td>
<td>181.3</td>
<td>170.1</td>
<td>200.0</td>
</tr>
</tbody>
</table>

Note: O–O distance is between the two amide-oxygen atoms. N–N distance is between the two nitrogen atoms of the ring. * In 316a O–O distance is replaced by the O–N distance between the amide-oxygen atom and the carbon of the double bond.

The ETB derivatives 313a and 313d show C(O)–N and C=O bond lengths which are substantially longer and shorter respectively than those of 314 1-methyl-2-piperidone, a planar amide, but not as altered as Kirby's most twisted amide, 315. Twisted amides are known to exhibit abnormal infrared profiles wherein the $\nu_{\text{C=O}}$ stretches increase with an increase in $\tau$. 313a and 313d show IR absorption values which are in-between those of 314 and Wärnmark's twisted amide 312. The $^{13}$C NMR chemical shifts for the carbonyl carbon resonance are also susceptible to variations, although to a minor extent. Interestingly the $\delta^{13}$C (C=O) values (313a 179.1 ppm, 313d 176.8 ppm and 316a 181.1 ppm), are higher than those reported for Wärnmark's twisted amide [$\delta^{13}$C (C=O)= 170.1 ppm], wherein the $\tau$ is
greater at -43.7°. Furthermore, 313a, 313d and mono-amide 316a have the shallowest cavities and the longest C$_2$–C$_8$ distance of all known ETB and TB analogues.

3.5.3 Probing the Reactivity

We next turned our attention to probing the reactivity of the amide moiety in 313a; more specifically we wanted to ascertain whether the amide was significantly twisted to exhibit the amino-ketone behaviour that is associated with twisted amides.$^{25}$ We started with the Wittig-olefination, unfortunately 313a did not react with either (ethoxycarbonylmethylene)-triphenylphosphorane or methyltriphenylphosphonium bromide and were able recover the starting material in quantitative yield. Lawesson’s reagent too did not react with either of the carbonyl groups. At this point we accessed the use of the more oxophilic titanium-based reagents to functionalise the amide and to our delight with the Petasis reagent [Cp$_2$TiMe$_2$] we were able to olefinate the one of the C=O bonds to yield enamine 316a which was reduced to yield 318a (Scheme 3.23).

![Scheme 3.23](image)

**Scheme 3.23** Top): Reaction of 313a with the Petasis reagent [Cp$_2$TiMe$_2$] and reduction to yield the product 318a. Bottom): Bis-olefination under Takai’s conditions [Performed by Ján Cvengroš].

In an attempt to reduce the second amide group, we initially subjected 316a to the reaction with [Cp$_2$TiMe$_2$], unfortunately this did not yield the desired product. We then attempted to olefinate 313a under Takai’s conditions$^{26}$ and were able to obtain the bis-olefinated product 317a, unfortunately this compound was rather unstable. We, at this point in time were puzzled by the inertness of 313a, which did not undergo a Wittig-olefination that its one-carbon analogue 312a underwent with ease. Interestingly the close-proximity of the two amide-oxygen atoms (3.5 Å vs 5.3 Å seen in 312) might be responsible for the molecules
torpidity and thought it prudent to explore the reactivity of this twisted amide 313a with smaller nucleophiles.

**Figure 3.8** ORETP plots of 316a and 319a. Thermal ellipsoids are drawn at 40% probability

The reduction of the amide with LiAlH₄ afforded no product, and exclusively the starting material was recovered. Surprisingly, NaBH₄ when reacted with 313a in a mixture of methanol and methylene chloride yielded a product that at first seemed to contain a single amide and a single hemi-aminal moiety, however X-Ray crystallographic analysis revealed that the diazocine ring was cleaved during the reaction to yield 319a (Scheme 3.24).

Next we treated 313a with triflic anhydride (Tf₂O) in an attempt to generate a transient anti-bredt iminium, which would be alkylated with methylmagnesiumbromide to deliver the alpha-alkylated ETB derivative 320a. However, we observed along with uncharacterized degradation products, the formation of 1,2-addition product 321a in 52% isolated yield (Scheme 3.25).
Oxidative Functionalization of Trögers Base Derivatives

Scheme 3.25 1,2-addition of methylmagnesiumbromide to 313a.

3.5.4 Conclusion

In conclusion, we have utilized KMnO₄ as an oxidant for the selective α-oxygenation of ETB derivatives. Importantly, the benzylic positions are oxidized which is complementary to a method we have previously described wherein only the alkyl bridge is functionalised.

Scheme 3.26 Oxidant mediated site selectivity.

X-ray diffraction analysis revealed 313a and 313d to be examples of the relatively rare class of twisted bis-amides. In addition, they have the shallowest cavity of all TB and ETB analogues investigated till date. We have carried out a reactivity study on the amide and shown that this twist amide has a lower range of reactivity as compared to its analogue 312.
3.6 Experimental

3.6.1 General

All reactions were performed in dried apparatus with magnetic stirring under an inert atmosphere of argon or nitrogen. All solvents and chemicals were used as purchased unless stated otherwise. All NMR spectra were recorded on Bruker AV400, AVIII400, AVIIIHD 500 spectrometers. $^1$H and $^{13}$C NMR spectra are reported relative to external TMS as chemical shifts (δ) in parts per million (ppm). $^{19}$F NMR shifts are referenced relative to external CFCl$_3$ at 0.0 ppm. Coupling constants (J) are reported in units of hertz (Hz). The following abbreviations are used to describe multiplets: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), td (triplet of doublets), br (broad), aapd (apparent doublet), apt (apparent triplet). High-resolution mass spectra (HRMS, m/z) were recorded on a Bruker MicroTOF spectrometer using positive electrospray ionization (ESI) or on a Waters GC-TOF spectrometer using electron impact (EI). Infrared spectra were recorded as neat compounds using a Bruker Tensor 27 FT-IR spectrometer. Absorptions are reported in wavenumbers (cm$^{-1}$) and only peaks of interest are reported. Melting points of solids were measured on a Griffin apparatus and are uncorrected. IUPAC names were generated using ChemDraw Professional 15.0. All solvents were dried on a column of alumina prior to use. Thin layer chromatography (TLC) was performed using Merck aluminium-foil baked plates coated with Kieselgel 60 F245. The products were visualized using UV fluorescence (254 nm) or potassium permanganate stain. Flash column chromatography was performed over Merck silica gel C60 (40-60 μm) using eluent systems as described for each experiment. X-ray structure of 302a, 303a, 304a, 308c, 309a, 309c, 309e and 313j were measured on a Bruker APEX2 CCD area detector diffractometer with Mo-Kα radiation. Single crystal was coated at room temperature with perfluoroalkylether oil and mounted on a polymer pin. The structures were solved by direct methods in SHELXTL and successive interpretation of the difference Fourier maps, followed by full-matrix least-squares refinement (against F2). Low temperature (150 K) single-crystal X-ray diffraction data for 313a, 313e, 316a and 319a were collected using or an Oxford Diffraction (Agilent) SuperNova A diffractometer. Raw frame data were reduced using the instrument manufacturer supplied software CrysAlisPro. All structures could be solved ab initio using SuperFlip, and full-matrix least-squares refinement was carried out using CRYSTALS. All non-hydrogen atoms were refined using anisotropic displacement ellipsoids, and hydrogen atoms were visible in the difference map. Once the heavy atoms structure was complete, hydrogen atoms were positioned geometrically then refined separately using soft restraints prior to inclusion in the final refinement using a
riding model. CCDC 1009233 302a, CCDC 1009232 303a, CCDC 1009231 304a, CCDC 1013952 309a, CCDC 1013951 308c, CCDC 1013950 309c, CCDC 1013949 309e CCDC 1442060 313a CCDC 1442061 313f CCDC 1442062 316a CCDC 1442063 319a contain the supplementary crystallographic data for this chapter. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif and are also available in the supporting information for this chapter.
3.6.2 Synthesis

**Synthesis of 301a**

rac-2,8-Dimethyl-6,12-dihydro-5,11methanodibenzo [b,f] [1,5] diazocine, Tröger’s base, (10 g, 40 mmol) was stirred with Li$_2$CO$_3$ (14.7 g, 200 mmol) and 1,2-dibromoethane (15.5 mL, 33.8 g, 180 mmol) in DMF (75 mL) for 12 hours at 105 °C. The reaction was diluted with ethyl acetate (400 mL) and filtered hot over a pad of celite (10 cm x 5 cm). The pad was rinsed with boiling ethyl acetate (100 mL x 3). The organic solvents were removed on a rotatory evaporator at 80 °C. The residual slurry was diluted with ethyl acetate (100 mL) and then adsorbed onto silica gel (50 g). The solvents were removed under reduced pressure to give a free flowing powder, which was purified via flash chromatography [silica gel (200 g), ethyl acetate/hexane (20:80) to (35:65)] to give 301a (4.8 g, 45%) as a white solid.

**1H NMR** (300 MHz, CDCl$_3$): $\delta$ = 2.18 (s, 6H, CH$_3$), 3.58 (m, 4H, NCH$_2$CH$_2$N), 4.40 (d, $J$ = 17.2 Hz, 2H, endo-CH$_2$N), 4.56 (d, $J$ = 17.2 Hz, 2H, exo-CH$_2$N), 6.72 (s, 2H, Ar-H), 6.88 (d, $J$ = 8.0 Hz, 2H Ar-H), 7.01 (d, $J$ = 8.0 Hz, 2H Ar-H); **13C NMR** (75 MHz, CDCl$_3$): $\delta$ = 20.8, 55.1, 59.3, 127.7, 127.9, 129.3, 134.2, 136.6, 147.7; **MS** (EI); m/z [M]$^+$ calcd. for C$_{18}$H$_{26}$N$_2$: 264.1; found: 264.1.

**Synthesis of 301b**

rac-2,8-Dimethoxy-6,12-dihydro-5,11 methanodibenzo [b,f] [1,5] diazocine$^{29}$ (5.65 g, 20 mmol) was stirred with Li$_2$CO$_3$ (7.4 g, 100 mmol) and 1,2-dibromoethane (7.8 mL, 16.9 g, 90 mmol) in DMF (30 mL) for 12 hours at 105 °C. The reaction was diluted with ethyl acetate (100 mL) and filtered hot over a pad of celite (10 cm x 5 cm). The pad was rinsed with boiling ethyl acetate (100 mL x 3). The organic solvents were removed on a rotatory evaporator at 80 °C. The residual slurry was diluted with ethyl acetate (100 mL) and then adsorbed onto silica gel (10 g). The solvents were removed under reduced pressure to give a free flowing powder, which was purified via flash chromatography [silica gel (50 g), ethyl acetate/hexane (30:70) to (50:50)] to give 301b (2.95 g, 50%) as a white solid.

**1H NMR** (300 MHz, CDCl$_3$): $\delta$ = 3.56 (m, 4H, NCH$_2$CH$_2$N), 3.68 (s, 6H, OMe), 4.36 (d, $J$ = 17.2 Hz, 2H, endo-CH$_2$N), 4.54 (d, $J$ = 17.1 Hz, 2H, exo-CH$_2$N), 6.43 (d, $J$ = 2.9 Hz, 2H, Ar-H), 6.61 (dd, $J$ = 8.6, 2.9 Hz, 2H, Ar-H), 7.03 (d, $J$ = 8.6 Hz, 2H, Ar-H); **13C NMR** (75 MHz, CDCl$_3$): $\delta$ = 55.2, 55.3, 59.5, 112.8, 113.3, 128.9, 138.2, 143.2, 156.6; **MS** (EI); m/z [M]$^+$ calcd for C$_{18}$H$_{26}$N$_2$O$_2$: 296.1; found: 296.1.
Synthesis of 301c

rac-2,8-diisopropyl-6,12-dihydro-5,11 methanodibenzo [b,f] [1,5] diazocine\(^{30}\) (2 g, 6.5 mmol) was stirred with Li\(_2\)CO\(_3\) (2.42 g, 32.7 mmol) and 1,2-dibromoethane (2.6 mL, 5.5 g, 29.5 mmol) in DMF (10 mL) for 12 hours at 105 °C. The reaction was diluted with ethyl acetate (100 mL) and filtered hot over a pad of celite (10 cm × 5 cm). The pad was rinsed with boiling ethyl acetate (50 mL × 3). The organic solvents were removed on a rotatory evaporator at 80 °C. The residual slurry was diluted with ethyl acetate (100 mL) and then adsorbed on to silica gel (15 g). The solvents were removed under reduced pressure to give a free flowing powder, which was purified via flash chromatography [silica gel (40 g), ethyl acetate/hexane (30:70)] to give 301c (0.56 g, 27%) as a pale yellow powder.

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.15\) (d, \(J = 6.9\) Hz, 12H, iPr), 2.75 (hept, \(J = 6.9\) Hz, 1H, iPr), 3.41 (m, 4H, NCH\(_2\)CH\(_2\)N), 4.43 (d, \(J = 17.5\) Hz, 2H, endo-CH\(_2\)N), 4.58 (d, \(J = 17.5\) Hz, 2H, exo-CH\(_2\)N), 6.75 (s, 2H, Ar-H), 6.93 (d, \(J = 8.1\) Hz, 2H, Ar-H), 7.04 (d, \(J = 8.1\) Hz, 2H, Ar-H); \(^{13}\)C NMR (75MHz, CDCl\(_3\)): \(\delta = 23.9, 24.1, 33.4, 55.1, 59.4, 125.1, 126.6, 127.9, 136.7, 145.1, 147.9\).

HRMS (EI); m/z [M\(^+\)] calc. for C\(_{22}\)H\(_{28}\)N\(_2\): 320.2252; found 320.2247. **MP = 113 °C.**

Synthesis of 301d

rac-diethyl 6,12-dihydro-5,11-ethanodibenzo [b,f] [1,5] diazocine-2,8-dicarboxylate,\(^{31}\) (2 g, 5.45 mmol) was stirred with Li\(_2\)CO\(_3\) (2.02 g, 27.3 mmol) and 1,2-dibromoethane (2.1 mL, 4.6 g, 24.6 mmol) in DMF (10 mL) for 48 hours at 110 °C. The reaction was diluted with ethyl acetate (100mL) and filtered hot over a pad of celite (10 cm × 5 cm). The pad was rinsed with boiling ethyl acetate (50 mL x 3). The organic solvents were removed on a rotatory evaporator at 80 °C. The residual slurry was diluted with ethyl acetate (100 mL) and then adsorbed onto silica gel (15 g). The solvents were removed under reduced pressure to give a free flowing powder, which was purified via flash chromatography [silica gel (40 g), ethyl acetate/hexane (30:70) to (50:50)] followed by recrystallization from benzene to give 301d (0.760g, 37%) as a pale yellow powder.

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.32\) (t, \(J = 7.1\) Hz, CH\(_2\)), 3.61 (m, 4H, NCH\(_2\)CH\(_2\)N), 4.27 (q, \(J = 7.1\) Hz, 4H, CH\(_2\)), 4.53 (d, \(J = 17.3\) Hz, 2H, endo-CH\(_2\)N), 4.64 (d, \(J = 17.3\) Hz, 2H, exo-CH\(_2\)N), 7.12 (d, \(J = 8.2\) Hz, 2H, Ar-H), 7.61 (d, \(J = 1.8\) Hz, 2H, Ar-H); 7.71 (dd, \(J = 8.2, 1.8\) Hz, 2H, Ar-H); \(^{13}\)C NMR (75MHz, CDCl\(_3\)): \(\delta = 14.4, 54.4, 58.9, 60.8, 126.9, 128.0, 128.8, 130.6, 136.2, 154.9, 163.2; HRMS (EI); m/z [M\(^+\)] calc. for C\(_{22}\)H\(_{28}\)N\(_2\)O\(_4\): 380.1736; found 380.1730; **MP = 152 °C.**
Oxidative Functionalization of Tröger’s Base Derivatives

Synthesis of 302a

A 100 mL J. Young flask was charged with 301a (264 mg, 1 mmol), Pd(OAc)$_2$ (44.9 mg, 0.2 mmol, 20 mol%) and NBS (356 mg, 2 mmol, 2 equiv). The flask was evacuated and refilled with argon. Dry acetonitrile (10 mL) was injected, the flask was sealed and allowed to stir at 105 °C for 18 hours. The crude reaction was adsorbed onto celite and purified via column chromatography [silica gel (15 g), ethyl acetate/hexane (30:70) containing 0.5% Et$_3$N] to give 302a (85 mg, 23%) as a white solid.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta =$ 2.21 (s, 6H, CH$_3$), 4.27 (d, $J =$ 17.8 Hz, 2H, endo-CH$_2$N), 5.05 (d, $J =$ 17.8 Hz, 2H exo-CH$_2$N), 5.78 (s, 2H, NCHBrCHBrN), 6.78 (s, 2H, Ar-H), 6.94 (d, $J =$ 8.1 Hz, 2H Ar-H), 7.03 (d, $J =$ 8.1 Hz, 2H Ar-H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$): $\delta =$ 21.0, 53.8, 80.7, 127.8, 128.8, 129.2, 134.8, 136.6, 143.2; HRMS (MALDI): m/z [M+H]$^+$ calcd for C$_{18}$H$_{19}$N$_2$Br$_2$: 420.9910; found: 420.9908; MP = 175 °C.

Synthesis of 303a and 304a

A 20 mL J. Young flask was charged with 301a (264 mg, 1 mmol), Pd(OAc)$_2$ (44.9 mg, 0.2 mmol, 20 mol%), KOAc (196 mg, 2 mmol) and NBS (356 mg, 2 mmol, 2 equiv). The flask was evacuated and refilled with argon. Dry acetonitrile (10 mL) was injected, the flask was sealed and allowed to stir at 50 °C for 18 hours. The crude reaction was adsorbed onto celite and then purified via column chromatography [silica gel (15 g), ethyl acetate/hexane (30:70) containing 0.5% Et$_3$N] to give 303a (120 mg, 37%) as a white solid and 304a (145 mg, 40%) as a white solid.

Note: (20mg, 7%) 305a was also isolated as a white solid.

303a

$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta =$ 2.09 (s, 3H, OCOCH$_3$), 2.17 (s, 3H, CH$_3$), 2.19 (s, 3H, CH$_3$), 3.49 (dd, $J =$ 14.3, 10.5 Hz, 1H, NCH$_2$CHOAcN), 3.78 (dd, $J =$ 14.7, 5.5 Hz, 1H, NCH$_2$CHOAcN), 4.12 (d, $J =$ 17.3 Hz, 1H, CH$_2$N), 4.35 (d, $J =$ 17.3 Hz, 1H, CH$_2$N), 4.61 (d, $J =$ 17.3 Hz, 1H, CH$_2$N), 4.80 (d, $J =$ 17.3 Hz, 1H, CH$_2$N), 5.86 (dd, $J =$ 10.2, 5.7 Hz, 1H, NCH$_2$CHOAcN), 6.73 (brs, 2H, Ar-H), 6.88 (dd, $J =$ 7.9, 1.7 Hz, 1H, Ar-H), 6.93 (dd, $J =$ 7.9, 1.7 Hz, 1H, Ar-H), 6.97-6.99 (m, 1H, Ar-H), 7.01 (d, $J =$ 8.0 Hz, 1H, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 20.9, 20.96, 21.5, 53.8, 57.2, 59.7, 85.1, 127.3, 128.2, 128.3, 128.4, 129.1, 129.2, 134.7, 135.2, 135.5, 137.1, 143.7, 147.1, 169.9; HRMS (MALDI): m/z [M+H]$^+$ calcd for C$_{20}$H$_{23}$N$_2$O$_2$: 323.1754; found: 323.1756; MP = 72 °C.
Synthesis of (+)-304 containing 0.5% Et purified via column chromatography [silica gel (15 g), ethyl acetate/hexane (30:70)] and allowed to stir at 50 °C for 18 hours. The crude reaction adsorbed onto celite and then evacuated and refilled with argon. Dry acetonitrile (10 mL) was injected, the flask was sealed and allowed to stir at 50 °C for 18 hours. The crude reaction adsorbed onto celite and then purified via column chromatography [silica gel (15 g), ethyl acetate/hexane (30:70) containing 0.5% Et₂N] to give (+)-304a, [α]₀⁺ = +294.3 (c = 0.1, CHCl₃), (118 mg, 37%) and (+)-304a, [α]₀⁺ = +189.7 (c = 0.1, CHCl₃), (140 mg, 40%) as single diastereomers.

Synthesis of 306a

A 20 mL J. Young flask was charged with 301a (264 mg, 1 mmol), Pd(OAc)₂ (44.9 mg, 0.2 mmol, 20 mol%), KOAc (196 mg, 2 mmol) and NBS (356 mg, 2 mmol, 2 equiv). The flask was evacuated and refilled with argon. Dry propionitrile (10 mL) was injected, the flask

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**304a**

![Structure of 304a]

**1H NMR** (400 MHz, CDCl₃): δ = 2.16 (s, 3H, CH₃), 2.18 (s, 3H, CH₃), 2.27 (s, 6H, NCOCH₃), 3.72 (dd, J = 14.5, 5.7 Hz, 1H, NCH₂CHNacN), 4.10 (d, J = 17.6 Hz, 1H, NCH₂), 4.41 (m, 1H, NCH₂CHNacN), 4.43 (d, J = 17.6 Hz, 1H, CH₂N), 4.56 (d, J = 17.3 Hz, 1H, CH₂N), 5.16 (m, 1H, NCH₂CHNacN), 5.19 (d, J = 17.3 Hz, 1H, CH₂N), 6.67 (s, 1H, Ar-H), 6.71 (s, 1H, Ar-H), 6.84 (dd, J = 8.0, 1.9 Hz, 1H, Ar-H), 6.9 (dd, J = 8.0, 1.9 Hz, 1H, Ar-H), 6.96 (d, J = 8.1 Hz, 1H, Ar-H), 6.99 (d, J = 8.1 Hz, 1H, Ar-H), 7.03 (d, J = 8.1 Hz, 2H, Ar-H); **13C NMR** (100 MHz, CDCl₃): δ = 20.91, 20.94, 26.6, 55.1, 55.4, 58.9, 75.51, 127.3, 127.6, 127.9, 128.6, 129.1, 129.4, 134.6, 135.2, 135.9, 136.2, 146.1, 146.6, 175.9; **MS (MALDI); m/z [M+H]+** calcd for C₂₂H₂₈N₂O₂: 364.2020; found: 364.2013; **MP = 172 °C.**

**305a**

(Despite multiple purifications by flash chromatography, the product is contaminated by minor amounts of impurities.)

![Structure of 305a]

**1H NMR** (400 MHz, CDCl₃): δ = 2.21 (s, 6H, CH₃), 4.27 (d, J = 17.8 Hz, 2H, CH₂N), 5.04 (d, J = 17.8 Hz, 2H, CH₂N), 5.78 (s, 2H, NCHCN), 6.78 (s, 2H, Ar-H), 6.94 (d, J = 8.1 Hz, 2H, Ar-H), 7.03 (d, J = 8.1 Hz, 2H, Ar-H); **13C NMR** (75 MHz, CD₂Cl₂): δ = 21.0, 53.8, 80.7, 127.7, 128.8, 129.2 1346, 136.6, 143.2.

**HRMS (ESI); m/z [M+H]+** calcd for C₁₉H₁₉N₂: 263.1543; found: 263.1541; **MP = 210 °C.**

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Synthesis of (+)-303a and (+)-304a

A 20 mL J. Young flask was charged with (S,S)-301a (264 mg, 1 mmol), Pd(OAc)₂ (44.9 mg, 0.2 mmol, 20 mol%), KOAc (196 mg, 2 mmol) and NBS (356 mg, 2 mmol, 2 equiv). The flask was evacuated and refilled with argon. Dry acetonitrile (10 mL) was injected, the flask was sealed and allowed to stir at 50 °C for 18 hours. The crude reaction adsorbed onto celite and then purified via column chromatography [silica gel (15 g), ethyl acetate/hexane (30:70) containing 0.5% Et₂N] to give (+)-303a, [α]₀⁺ = +294.3 (c = 0.1, CHCl₃), (118 mg, 37%) and (+)-304a, [α]₀⁺ = +189.7 (c = 0.1, CHCl₃), (140 mg, 40%) as single diastereomers.

Synthesis of 306a

A 20 mL J. Young flask was charged with 301a (264 mg, 1 mmol), Pd(OAc)₂ (44.9 mg, 0.2 mmol, 20 mol%), KOAc (196 mg, 2 mmol) and NBS (356 mg, 2 mmol, 2 equiv). The flask was evacuated and refilled with argon. Dry propionitrile (10 mL) was injected, the flask
was sealed and allowed to stir at 50 °C for 18 hours. The crude reaction was adsorbed onto celite and then purified via column chromatography [silica gel (15 g), ethyl acetate/hexane (30:70) containing 0.5% Et₃N] to give 306a (102 mg, 27%) as a white solid.

**1H NMR (400 MHz, CDCl₃):** δ = 1.13 (t, J = 7.3 Hz, 3H, NCOCH₂CH₃), 2.16 (s, 3H, CH₃), 2.19 (s, 3H, CH₃), 2.23 (s, 3H, NCOCH₃), 2.43 (m, 2H, NCOCH₂CH₃), 3.75 (dd, J = 14.4, 5.7 Hz, 1H, NCH₂CHNACPrN), 4.08 (d, J = 17.5 Hz, 1H, NCH₂), 4.26 (dd, J = 14.3, 11.2 Hz, 1H, NCH₂CHNACPrN), 4.43 (d, J = 17.5 Hz 1H, NCH₂), 4.57 (d, J = 17.5 Hz 1H, CH₂N), 5.20 (m, 2H), 6.67 (s, 1H, Ar-H), 6.72 (s, 1H, Ar-H), 6.84 (d, J = 8.0 Hz, 1H, Ar-H), 6.9 (d, J = 8.0 Hz, 1H, Ar-H), 6.95 (d, J = 4.8 Hz, 1H, Ar-H), 6.98 (d, J = 8.1 Hz, 1H, Ar-H); **13C NMR (100 MHz, CDCl₃):** δ = 9.5, 20.90, 20.95, 26.0, 32.2, 54.8, 55.7, 59.0, 75.1, 127.3, 127.6, 127.9, 128.5, 129.1, 129.3, 134.5, 135.2, 135.9, 136.4, 146.0, 146.7, 175.3, 180.4; **HRMS (ESI):** m/z [M+H]+ calcd. for C₃₃H₃₈N₂O₂: 378.2176; found: 378.2178; **MP = 177 °C.**

**Synthesis of 303b and 304b**

A 20 ml J. Young flask was charged with 301b (296 mg, 1 mmol), Pd(OAc)₂ (44.9 mg, 0.2 mmol, 20 mol%), KOAc (196 mg, 2 mmol) and NBS (356 mg, 2 mmol, 2 equiv). The flask was evacuated and refilled with argon. Dry acetonitrile (10 ml) was injected, the flask was sealed and allowed to stir at 50 °C for 18 hours. The crude reaction was adsorbed onto celite and then purified via column chromatography [silica gel (15 g), ethyl acetate/hexane (1:1) containing 0.5% Et₃N] to give 303b (173 mg, 49%) as a white solid and 304b (189 mg, 48%) as a white solid.

**303b**

**1H NMR (300 MHz, CDCl₃):** δ = 2.12 (s, 3H, OCOCH₃), 3.46 (dd, J = 14.3, 10.3 Hz, 1H, NCH₂CHOAcN), 3.68 (s, 6H, OCH₃), 3.83 (dd, J = 14.5, 5.6 Hz, 1H, NCH₂CHOAcN), 4.13 (d, J = 17.4 Hz, 1H, CH₂N), 4.34 (d, J = 17.4 Hz, 1H, CH₂N), 4.60 (d, J = 17.3 Hz, 1H, CH₂N), 4.82 (d, J = 17.5 Hz, 1H, CH₂N), 5.92 (dd, J = 9.9, 5.7 Hz, 1H, NCH₂CHOAcN), 6.41 (brs, 2H, Ar-H), 6.64 (m, 2H, Ar-H), 7.01 (d, J = 8.7 Hz, 1H, Ar-H), 7.11 (d, J = 8.6 Hz, 1H, Ar-H); **13C NMR (75 MHz, CDCl₃):** δ = 21.5, 54.0, 55.4, 57.4, 59.9, 85.4, 113.01, 113.04, 113.07, 113.3, 128.6, 129.5, 136.8, 138.8, 139.2, 142.7, 156.8, 145.4, 169.9; **HRMS (ESI):** m/z [M+H]+ calcd. for C₂₀H₂₃N₂O₄: 355.1652; found: 355.1647; **MP = 80 °C.**
Oxidative Functionalization of Trögers Base Derivatives

304b

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.27 (s, 6H, NCOCH$_3$), 3.65 (s, 3H, OCH$_3$), 3.67 (m, 1H, NCH$_3$CH$_2$N), 3.68 (s, 3H, OCH$_3$), 4.08 (d, $J$ = 17.5 Hz, 1H, CH$_2$N), 4.41 (d, $J$ = 17.5 Hz, 1H, CH$_2$N), 4.43 (m, 1H, NCH$_2$CHOAcN), 4.56 (d, $J$ = 17.5 Hz, 1H, CH$_2$N), 5.13 (dd, $J$ = 9.9, 5.7 Hz, 1H, NCH$_3$CHOAcN), 5.21 (d, $J$ = 17.3 Hz, 1H, NCH$_2$CHOAcN), 6.38 (d, $J$ = 3.0 Hz, 1H, Ar-H), 6.42 (d, $J$ = 3.0 Hz, 1H, Ar-H), 6.60 (dd, $J$ = 3.0, 8.8 Hz, 1H, Ar-H), 7.00 (d, $J$ = 8.8 Hz, 1H, Ar-H), 7.04 (d, $J$ = 8.8 Hz, 1H, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 21.5, 54.0, 55.4, 57.4, 59.9, 85.4, 113.01, 113.04, 113.07, 113.3, 128.6, 129.5, 136.8, 138.8, 139.2, 142.7, 156.8, 145.4, 145.4, 169.9; HRMS (ESI): m/z [M+H]$^+$ calcd. for C$_{22}$H$_{26}$N$_3$O$_4$: 396.1918; found: 396.1918; MP = 192 °C.

Synthesis of 303c and 304c

A 20 mL J. Young flask was charged with 301c (213 mg, 0.66 mmol), Pd(OAc)$_2$ (29.6 mg, 0.13 mmol, 20 mol%), KOAc (130 mg, 1.33 mmol) and NBS (236 mg, 1.33 mmol, 2 equiv). The flask was evacuated and refilled with argon. Dry acetonitrile (7 mL) was injected, the flask was sealed and allowed to stir at 50 °C for 18 hours. The crude reaction was adsorbed onto celite and then purified via column chromatography [silica gel (15 g), ethyl acetate/hexane (0:1 to 30:70)] to give 303c (50 mg, 20%) as a white solid and 304c (72 mg, 26%) as a white solid. Note: 1c (60 mg) was recovered from the reaction.

303c

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.14 (d, $J$ = 6.9 Hz, 12H, CH(CH$_3$)$_2$), 2.12 (s, 3H, CH$_3$), 2.75 (m, 2H, CH(CH$_3$)$_2$), 3.49 (dd, $J$ =14.4, 10.3 Hz, 1H, NCH$_3$CH$_2$N), 3.85 (dd, $J$ =14.4, 5.7 Hz, 1H, NCH$_2$CHOAc), 4.22 (d, $J$ = 17.7 Hz, 1H, CH$_2$N), 4.42 (d, $J$ = 17.4 Hz, 1H, CH$_2$N), 4.65 (d, $J$ = 17.4 Hz, 1H, CH$_2$N), 4.87 (d, $J$ = 17.5 Hz, 1H, CH$_2$N), 5.94 (dd, $J$ =14.4, 5.7 Hz, 1H, NCH$_2$CHOAc), 6.73 (d, $J$ = 1.7 Hz, 1H, Ar-H), 6.73 (d, $J$ = 1.7 Hz, 1H, Ar-H), 6.97 (m, 2H, Ar-H), 7.03 (d, $J$ = 8.1 Hz, 1H, Ar-H), 7.12 (d, $J$ = 8.1 Hz, 1H, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 21.5, 23.9, 24.1, 24.13, 33.41, 33.48, 53.7, 57.0, 59.5, 85.2, 125.2, 125.4, 126.3, 126.4, 127.4, 128.3, 135.2, 137.0, 143.7, 145.4, 146.1, 147.2, 170.0; HRMS (ESI): m/z [M+H]$^+$ calcd for C$_{22}$H$_{31}$O$_2$N$_2$: 379.2380; found: 379.2374; MP = 77 °C.
304c

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.13$ (m, 12H, CH(CH$_3$)$_2$), 2.27 (s, 3H, CH$_2$CONCOCH$_3$), 2.74 (m, 2H, CH(CH$_3$)$_2$), 3.70 (dd, $J = 14.4$, 5.8 Hz, 1H, NCH$_2$CHNAc), 4.13 (d, $J = 17.6$ Hz, 1H, CH$_2$N), 4.41 (dd, $J = 14.3$, 11.2 Hz, 1H, NCH$_2$CHNAc), 4.47 (d, $J = 17.6$ Hz, 1H, CH$_2$N), 4.59 (d, $J = 17.6$ Hz, 1H, CH$_2$N), 5.14 (dd, $J = 11.4$, 5.8 Hz, 1H, NCH$_2$CHNAc), 5.20 (d, $J = 17.6$ Hz, 1H, CH$_2$N), 6.71 (s, 1H Ar-H), 6.74 (s, 1H, Ar-H), 6.92 (m, 2H, Ar-H), 7.03 (m, 2H, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 23.83$, 23.87, 24.0, 24.1, 26.7, 33.3, 33.4, 55.0, 55.2, 58.8 75.4, 124.8, 125.6, 126.4, 126.5 127.3, 127.6, 135.8, 136.1, 145.3, 145.8, 146.0, 146.7, 176.0; HRMS (ESI); m/z [M+H]$^+$ calcd. for C$_{26}$H$_{34}$O$_2$N$_3$: 420.2646; found: 420.2641; MP = 173 °C.

Synthesis of 304d

A 20 mL J. Young flask was charged with 301d (380mg, 1 mmol), Pd(OAc)$_2$ (44.9 mg, 0.2 mmol, 20 mol%), KOAc (196 mg, 2 mmol) and NBS (356 mg, 2 mmol, 2 equiv). The flask was evacuated and refilled with argon. Dry acetonitrile (10 mL) was injected, the flask was sealed and allowed to stir at 50 °C for 18 hours. The crude reaction was adsorbed onto celite and purified via column chromatography [silica gel (15 g), ethyl acetate/hexane (10:90 to 30:70)] to give 304d (100 mg, 21%) as a white solid. Note: 301d (135 mg) was recovered from the reaction.

$^1$H NMR (400 MHz, CDCl$_3$, 298K): $\delta = 1.31$ (t, $J = 7.1$ Hz, 3H, CH$_2$CH$_3$), 1.32 (t, $J = 7.1$ Hz, 3H, CH$_2$CH$_3$), 2.26 (s, 6H, NCOCH$_3$), 3.71 (dd, $J = 14.5$, 5.6 Hz, 4H, NCH$_2$CHNOAcN), 4.28 (m, 5H; 4H, CH$_2$CH$_3$ & 1H, NCH$_2$), 4.55 (dd, $J = 14.6$, 11.3 Hz, 1H, NCH$_2$CHNOAcN), 4.59 (d, $J = 17.7$ Hz, 1H, CH$_2$N), 4.67 (d, $J = 17.6$ Hz, 1H, CH$_2$N), 5.23 (m, 1H, NCH$_2$CHNOAcN), 5.38 (d, $J = 17.7$ Hz, 1H, CH$_2$N), 7.11 (d, $J = 8.3$ Hz, 1H, Ar-H), 7.16 (d, $J = 8.3$ Hz, 1H, Ar-H), 7.58 (d, $J = 2.0$ Hz, 1H, Ar-H), 7.64 (d, $J = 2.0$ Hz, 1H, Ar-H), 7.71 (dd, $J = 8.3$ Hz, 2.0 Hz, 1H, Ar-H), 7.77 (dd, $J = 8.3$ Hz, 2.0 Hz, 1H, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$, 298K): $\delta = 14.4$, 26.5, 54.7, 54.9, 58.6, 60.9, 61.1, 74.5, 127.3, 127.7, 127.90, 127.99, 128.8, 129.3, 130.4, 130.6, 135.6, 135.8, 153.2, 153.6, 165.9, 166.1, 175.6; HRMS (ESI); m/z [M+H]$^+$ calcd. for C$_{26}$H$_{34}$O$_2$N$_3$: 480.2129, found 480.2124; MP = 170° C.
Synthesis of 307g

A 250 mL round bottomed flask was charged with trifluoroacetic acid (40 mL) and cooled to -15 °C and 4-bromo-3,5-dimethyl aniline (4.0 g, 20 mmol) and paraformaldehyde (1.21 g, 40 mmol) were added portionwise. The reaction was allowed to reach room temperature and then stirred for 48 hours more, after which it was poured into ice and then neutralized with NH₃ (aq. 25%). The white precipitate formed was collected and then dissolved in methylene chloride (100 mL). The organic phase was rinsed with water (25 mL) and then brine (25 mL × 2) and finally dried over MgSO₄. The solvents were evaporated and the residue was crystalized from boiling EtOAc (400 mL) to yield 2,8-dibromo-1,3,7,9-tetramethyl-6H,12H-5,11-methanodibenzo [b,f] [1,5]diazocine 307g as white crystals (3.75 g, 86%).

¹H NMR (300 MHz, CDCl₃): δ [ppm] = 2.20 (s, 6H, CH₃), 2.36 (s, 6H, CH₃), 4.14 (d, J = 16.9 Hz, 2H, ArCH₂N), 4.19 (s, 2H, NCH₂N), 4.52 (d, J = 16.9 Hz, 2H, ArCH₂N), 6.93 (s, 2H, Ar-H);

¹³C NMR (75 MHz, CDCl₃): δ [ppm] = 18.5, 24.2, 58.3, 65.7, 123.0, 124.8, 124.9, 135.3, 137.3, 137.3, 146.9; IR (ATR, neat): 1/λ [cm⁻¹] = 2971, 2946, 2920, 2902, 2852 1736, 1533, 1451, 1370, 1277, 1266, 1189, 1211, 1094, 1011, 971, 908, 841, 772, 708, 675; HRMS (ESI) m/z [M+H]⁺: calcd. for C₁₅H₂₁N₂Br₂: 435.0066, found: 435.0065; MP = 247 °C.

General procedure for the preparation of monoacetoxylated (308) and bisacetoxylated (309) products

A 20 mL J. Young flask was charged with the Tröger’s base analogue 307 (1 mmol), Pd(OAc)₂ (44.5 mg, 0.2 mmol, 20 mol%), NBS (356 mg, 2 mmol) and KOAc (196 mg, 2 mmol). The flask was evacuated and refilled with argon (3 times). Dry acetonitrile (10 mL) was injected after which the flask was sealed and allowed to stir at 50 °C for 18 hours. The crude reaction was adsorbed onto celite and purified via flash chromatography.

Synthesis of 308a and 309a

Compounds 308a and 309a were synthesized according to the GP with rac-2,8-dimethyl-6,12-dihydro-5,11-methanodibenzo[b,f][1,5]diazocine, Tröger’s base 307a (250 mg, 1 mmol) or (−)-2,8-dimethyl-6,12-dihydro-5,11- methanodibenzo[b,f][1,5]diazocine, Tröger’s base (−)-1a (250 mg, 1 mmol) as the starting material. Purification via flash chromatography [silica gel (particle size: 20-40 μm) (40 g), ethyl acetate/hexane (02:97) to (18:82)] yielded 308a (240 mg, 78%) or (−)-309a (220 mg, 72%) as a white solid and 308a (73 mg, 20%) or (−)-309a (76 mg, 21%) as a white solid.
Oxidative Functionalization of Trögers Base Derivatives

308a

\[ \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{)}: } \delta \text{ [ppm] = 2.23 (s, 3H, CH}_3\text{), 2.24 (s, 3H, CH}_3\text{), 2.26 (s, 3H, CH}_3\text{), 4.12 (d, } J = 16.7 \text{ Hz, 1H, ArCH}_2\text{N), 4.26 (d, } J = 12.8 \text{ Hz, 1H, NCH}_2\text{N), 4.53 (dd, } J = 12.8, 1.7 \text{ Hz, 1H, NCH}_2\text{N), 4.67 (d, } J = 16.7 \text{ Hz, 1H, ArCH}_2\text{N), 6.45 (s, 6.40, 1H, HCOAc), 6.71 (s, 1H, Ar-H), 6.95 (s, 1H, Ar-H), 7.01 (m, 1H, Ar-H), 7.10 (d, } J = 1.2 \text{ Hz, 2H, Ar-H) 7.33 (d, } J = 8.2 \text{ Hz 1H, Ar-H); } \text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3\text{)}: } \delta \text{ [ppm] = 20.8, 20.9, 21.6, 56.9, 62.0, 84.6, 124.6, 124.84, 124.88, 127.4, 127.48, 128.5, 129.1, 130.5, 133.9, 141.7, 145.8, 170.4; } \text{IR (ATR, neat): 1/\lambda [cm}^{-1}\text{] = 2967, 1742, 1489, 1359, 1338, 1206, 1139, 1122, 971, 953,880, 834, 799, 774, 635, 618; HRMS (ESI) m/z [M+Na]^+: } \text{calcd. for C}_{21}\text{H}_{28}\text{N}_2\text{O}_4\text{: 309.1598, found: 309.1597; MP = 187 °C; } [\alpha]_D^{20} = -187.5 (c = 0.1, CHCl}_3\text{).}

309a

\[ \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{)}: } \delta \text{ [ppm] = 2.24 (s, 6H, CH}_3\text{), 2.25 (s, 6H, OCOCH}_3\text{), 4.45 (s, 2H, NCH}_2\text{N), 6.40 (s, 2H, OCHNCH}_2\text{NCHO), 6.91 (s, 2H, Ar-H), 7.12 (d, } J = 8.2 \text{ Hz, 1H, Ar-H), 7.39 (s, } J = 8.2 \text{ Hz, 2H, Ar-H); } \text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3\text{)}: } \delta \text{ [ppm] = 20.9, 21.7, 57.4, 83.2, 124.6, 125.0, 129.2, 130.9, 134.8, 142.1, 170.5; } \text{IR (ATR, neat): 1/\lambda [cm}^{-1}\text{] = 3019, 2979, 1722, 1495, 1374, 1362, 1225, 1112, 1017, 950, 927, 840, 799, 740, 728, 664, 654; HRMS (ESI) m/z [M+Na]^+: } \text{calcd. for C}_{21}\text{H}_{28}\text{N}_2\text{NaO}_4\text{: 389.1472, found: 389.1477; MP = 187 °C; } [\alpha]_D^{20} = -259.6 (c = 0.1, CHCl}_3\text{).}

Synthesis of 308b and 309b

Compounds 308b and 309b were synthesized according to the GP with rac-2,8-diisopropyl-6,12-dihydro-5,11-methanodibenzo[b,f][1,5]diazocine, 307b (306 mg, 1 mmol) as the starting material. Purification via flash chromatography [silica gel (particle size: 20-40 μm) (40 g), ethyl acetate/hexane (02:97) to (18:82)] yielded 308b (240 mg, 72%) as a white solid and 309b (73 mg, 28%) as a white solid.

308b

\[ \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{)}: } \delta \text{ [ppm] = 0.82-1.33 (m, 12H, CH(CH}_3\text{)j), 2.25 (s, 3H, OCOCH}_3\text{), 2.81 (dt, } J = 13.9, 6.9 \text{ Hz, 2H, CH(CH}_3\text{)j) 4.15 (d, } J = 16.5 \text{ Hz, 1H, ArCH}_2\text{N), 4.26 (dd, } J = 12.8, 1.1 \text{ Hz, 1H, NCH}_2\text{N), 4.52 (dd, } J = 12.8, 1.7 \text{ Hz, 1H, NCH}_2\text{N), 4.71 (d, } J = 16.7 \text{ Hz, 1H, ArCH}_2\text{N), 6.47 (s, 1H, HCOAc), 6.75 (d, } J = 2.0 \text{ Hz, 1H, Ar-H), 6.98 (d, } J = 2.0 \text{ Hz, 1H, Ar-H), 7.07 (dd, } J = 8.3, 2.1 \text{ Hz, 1H, Ar-H),}

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7.16 (m, 2H, Ar-H) 7.37 (d, J = 8.3 Hz, 1H, Ar-H); \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) [ppm] = 21.7, 23.9, 24.03, 24.06, 24.1, 33.64, 33.67, 56.9, 62.0, 84.6, 124.6, 124.8, 124.9, 125.0, 125.9, 126.5, 127.5, 127.8, 142.1, 144.8, 145.3, 146.2, 170.5; IR (ATR, neat): \(1/\lambda\) [cm\(^{-1}\)] = 2956, 2866, 1730, 1614, 1491, 1460, 1364, 1313, 1212, 1199, 1178, 1170, 1010, 971, 952, 859, 838, 771, 732, 660, 614; HRMS (ESI) \(m/z\) [M+H]\(^+\): calcd. for \(\text{C}_{23}\text{H}_{29}\text{N}_{2}\text{O}_2\): 365.2224, found: 365.2217; MP = 217 °C.

309b

\(1^1\text{H}\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) [ppm] = 1.19 (dd, \(J = 6.9, 1.7\) Hz, 12H, CH(CH\(_3\))\(_2\), 2.25 (s, 6H, OCOCH\(_3\)), 2.82 (hept, \(J = 6.9\) Hz, 2H, CH(CH\(_3\))\(_2\)), 4.45 (s, 2H, NCH\(_2\)), 6.42 (s, 2H, OCHNCH\(_2\)NCHO), 6.94 (d, \(J = 2.2\) Hz, 2H, Ar-H), 7.19 (dd, \(J = 8.2, 2.1\) Hz, 2H, Ar-H), 7.44 (d, \(J = 8.2\) Hz, 2H, Ar-H); \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) [ppm] = 21.7, 23.8, 24.1, 33.7, 57.4, 83.2, 124.8 125.0, 126.5, 128.3, 142.5, 145.7, 170.6; IR (ATR, neat): \(1/\lambda\) [cm\(^{-1}\)] = 2962, 2870, 1736, 1493, 1372, 1259, 1159, 1009, 833, 774, 732, 718, 664, 646, 634; HRMS (ESI) \(m/z\) [M+Na]\(^+\): calcd. for \(\text{C}_{25}\text{H}_{30}\text{N}_{2}\text{O}_4\): 445.2098, found: 445.2098; MP = 188 °C.

Synthesis of 308c and 309c

Compounds 308c and 309c were synthesized according to the GP with rac-2,8-dimethoxy-6,12-dihydro-5,11-methanobenzo[\(b,f\)][1,5]diazocine, 307c (282 mg, 1 mmol) as the starting material. Purification via flash chromatography [silica gel (particle size: 20-40 \(\mu\)m) (40 g), ethyl acetate/hexane (05:95) to (30:70)] yielded 308c (250 mg, 73%) as a white solid and 309c (110 mg, 27%) as a white solid.

308c

\(1^1\text{H}\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) [ppm] = 2.22 (s, 3H, OCOCH\(_3\)), 3.70 (s, 3H, OCH\(_3\)), 3.72 (s, 3H, OCH\(_3\)), 4.07 (d, \(J = 16.7\) Hz, 1H, ArCH\(_2\)N), 4.23 (d, \(J = 12.8\) Hz, 1H, NCH\(_2\)N), 4.49 (dd, \(J = 12.8, 1.6\) Hz, 1H, NCH\(_2\)N), 4.65 (d, \(J = 16.8\) Hz, 1H, ArCH\(_2\)N), 6.38 (s, 2H, HCOAc), 6.41 (d, \(J = 2.9\) Hz, 1H, Ar-H), 6.62 (dd, \(J = 2.9\) Hz, 1H, Ar-H), 6.76 (dd, \(J = 8.8, 2.9\) Hz, 1H, Ar-H), 6.87 (dd, \(J = 8.8, 2.9\) Hz, 1H, Ar-H), 7.12(d, \(J = 8.8\) Hz, 1H, Ar-H), 7.34 (d, \(J = 8.8\) Hz, 1H, Ar-H); \(^{13}\text{C}\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) [ppm] = 21.7, 55.4, 55.6, 57.1, 62.2, 84.8, 111.2, 112.1, 114.2, 117.1, 125.7, 125.9, 126.1, 128.7, 137.2, 141.3, 156.3, 156.8, 170.5; IR (ATR, neat): \(1/\lambda\) [cm\(^{-1}\)] = 2972, 2946, 2903, 1738, 1611, 1492, 1451, 1319, 1122, 1109, 1031, 973, 965, 938, 841, 930, 773, 728, 709, 658; HRMS (ESI) \(m/z\) [M+H]\(^+\): calcd. for \(\text{C}_{19}\text{H}_{21}\text{N}_{2}\text{O}_4\): 341.1496, found: 341.1498; MP = 123 °C.
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309c

![Image of 309c]

\[ ^1H \text{NMR} (300 \text{ MHz, CDCl}_3): \delta \text{ [ppm]} = 2.22 \text{ (s, 6H, OCOCH}_3), 3.72 \text{ (s, 6H, OCH}_3), 4.42 \text{ (s, 2H, NCH}_2N), 6.35 \text{ (s, 2H, OCHNCH}_3NCHO), 6.59 \text{ (d, } J = 2.9 \text{ Hz, 2H, Ar-H)}, 6.89 \text{ (dd, } J = 8.9, 2.9 \text{ Hz, 2H, Ar-H)}, 7.42 \text{ (d, } J = 8.9 \text{ Hz, 2H, Ar-H}); ^13C \text{NMR} (75 \text{ MHz, CDCl}_3): \delta \text{ [ppm]} = 21.7, 55.6, 57.7, 83.3, 112.4, 117.2, 126.0, 126.06, 137.7, 156.9, 170.5; \text{IR (ATR, neat): } 1/\lambda \text{ [cm}^{-1}] = 2971, 2946, 2920, 2840, 1739, 1612, 1492, 1389, 1364, 1277, 1207, 150, 1137, 1064, 963, 870, 894, 828, 803, 735, 628; \text{HRMS (ESI) } m/z [M+Na]^+: \text{calcd. for } C_{21}H_{22}N_2NaO}_6: 421.1370, \text{found: } 421.1368; \text{MP} = 174 \degree C. \]

Synthesis of 308f

Compound 308f was synthesized according to the GP with rac-2,8-dichloro-6,12-dihydro-5,11-methanodibenzo[\text{b,f}][1,5]diazocine, 307f (290 mg, 1 mmol) as the starting material. Purification via flash chromatography [silica gel (particle size: 20-40 μm) (40 g), ethyl acetate/hexane (05:95) to (35:65)] yielded 308f (270 mg, 78%) as a white solid along with an unreacted 1f (50 mg, 15%). No bisacetate 309f was detected.

308f

\[ ^1H \text{NMR} (300 \text{ MHz, CDCl}_3): \delta \text{ [ppm]} = 2.35 \text{ (s, 3H, OCOCH}_3), 4.21 \text{ (d, } J = 16.7 \text{ Hz, 1H, ArCH}_2N), 4.32 \text{ (d, } J = 13.0 \text{ Hz, 1H, NCH}_2N), 4.57 \text{ (dd, } J = 13.0, 1.8 \text{ Hz, 1H, NCH}_2N), 4.78 \text{ (d, } J = 16.9 \text{ Hz, 1H, ArCH}_2N), 6.47 \text{ (s, CHOAc, 1H)}, 7.01 \text{ (d, } J = 2.4 \text{ Hz, 1H, Ar-H}), 7.24 \text{ (m, 2H, Ar-H)}, 7.29 \text{ (m, 1H, Ar-H)}, 7.37 \text{ (dd, } J = 8.5, 2.3 \text{ Hz, 1H, Ar-H}), 7.49 \text{ (d, } J = 8.6 \text{ Hz, 1H, Ar-H}); ^13C \text{NMR} (75 \text{ MHz, CDCl}_3): \delta \text{ [ppm]} = 21.5, 56.6, 61.6, 83.9, 126.3, 126.4, 126.5, 126.9, 128.2, 128.7, 129.2, 129.5, 130.0, 130.2, 124.6, 146.6, 170.3; \text{IR (ATR, neat): } 1/\lambda \text{ [cm}^{-1}] = 3156, 2964, 2899, 1732, 1491, 1474, 1321, 1413, 1193, 1145, 1014, 980,960, 893, 825, 772, 725, 655; \text{HRMS (ESI) } m/z [M+H]^+: \text{calcd. for } C_{17}H_{16}Cl_2N_2O}_2: 349.0505, \text{found: } 349.0509; \text{MP} = 156 \degree C. \]

Synthesis of 308h

Compound 308h was synthesized according to the GP with rac-4,10-dibromo-2,8-dimethyl-6,12-dihydro-5,11-methanodibenzo[\text{b,f}][1,5]diazocine 307h (408 mg, 1.0 mmol) as the starting material. Purification via flash chromatography [silica gel (particle size: 20-40 μm) (40 g), ethyl acetate/hexane (03:97) to (13:87)] to give 308h (400 mg, 86%) as a white solid along with an unreacted 307h (20 mg, 5%). No bisacetate 309h was detected.
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308h

\(^{1}\text{H NMR}\) (300 MHz, CDCl\textsubscript{3}): δ [ppm] = 2.21 (s, 3H, OCOCH\textsubscript{3}), 2.22 (burs, 6H, CH\textsubscript{3}), 4.27 (d, J = 17.4 Hz, 1H, ArCH\textsubscript{2}N), 4.33 (d, J = 13.3 Hz, 1H, NCH\textsubscript{3}N), 4.54 (d, J = 17.4 Hz, 1H, ArCH\textsubscript{2}N), 4.67 (dd, J = 13.3, 1.7 Hz, 1H, NCH\textsubscript{3}N), 6.72 (s, 2H, two overlapping peaks of HCO\textsubscript{Ac} and Ar-H), 7.12 (s, 1H, Ar-H), 7.29 (s, 1H, Ar-H), 7.38 (d, J = 1.5 Hz, 1H, Ar-H); \(^{13}\text{C NMR}\) (125 MHz, CDCl\textsubscript{3}): δ [ppm] = 20.70, 20.71, 54.07, 63.52, 81.22, 119.3, 119.6, 127.0, 128.6, 128.9, 130.7, 132.3, 134.4, 136.2, 138.4, 141.9, 169.8; IR (ATR, neat): 1/λ [cm\textsuperscript{-1}] = 2919, 1736, 1475, 1460, 1434, 1370, 1224, 1125, 1070, 977, 949, 935, 917, 852, 773, 749, 678, 645; HRMS (ESI) m/z [M+H]\textsuperscript{+}: calcd. for C\textsubscript{19}H\textsubscript{19}N\textsubscript{2}O\textsubscript{2}Br\textsubscript{2}: 464.9808; found: 464.9801; \textit{MP} = 173 °C.

Synthesis of 308j

Compound 308j was synthesized according to the GP with \textit{rac}-4,10-difluoro-2,8-dimethyl-6,12-dihydro-5,11-methanodibenzo[\textit{b,f}][1,5]diazocine, 307j (286 mg, 1 mmol) as the starting material. Purification via flash chromatography [silica gel (particle size: 20-40 μm) (40 g), ethyl acetate/hexane (00:100) to (15:85)] yielded a 1:1 mixture, determined via \(^{19}\text{F NMR}\), of 307j and 308j (270 mg) as a white solid along with a single fraction of pure 308j (13 mg, 4%). No bisacetate 309j was detected.

308j

\(^{1}\text{H NMR}\) (400 MHz, CDCl\textsubscript{3}): δ [ppm] = 2.21 (s, 3H, CH\textsubscript{3}), 2.22 (s, 3H, CH\textsubscript{3}), 2.24 (s, 3H, OCOCH\textsubscript{3}), 4.13 (d, J = 17.2 Hz, 1H, ArCH\textsubscript{2}N), 4.24 (d, J = 13.0 Hz, 1H, NCH\textsubscript{3}N), 4.57 (d, J = 17.4 Hz, 1H, ArCH\textsubscript{2}N), 4.61 (dd, J = 13.1, 1.1 Hz, 1H, NCH\textsubscript{3}N), 6.53 (s, 1H, HCO\textsubscript{Ac}), 6.59 (s, 1H, Ar-H), 6.77 (d, J = 11.4 Hz, 1H, Ar-H), 6.82 (s, 1H, Ar-H), 6.86 (d, J = 11.6 Hz, 1H, Ar-H); \(^{13}\text{C NMR}\) (100 MHz, CDCl\textsubscript{3}): δ [ppm] = 21.03 (d, J = 1.4 Hz), 21.06 (d, J = 1.4 Hz), 21.53, 54.1, 62.5, 80.4, 115.1 (d, J = 19.1 Hz), 116.9 (d, J = 18.9 Hz), 122.9 (d, J = 3.2 Hz), 124.6 (d, J = 3.3 Hz), 127.7 (d, J = 3.0 Hz), 128.3 (d, J = 12.9 Hz), 129.9 (d, J = 2.8 Hz), 132.5 (d, J = 12.5 Hz), 135.2 (d, J = 7.8 Hz), 135.9 (d, J = 7.7 Hz), 154.4 (d, J = 24.3 Hz), 156.9 (d, J = 26.0 Hz), 169.6; \(^{19}\text{F NMR}\) (376 MHz, CDCl\textsubscript{3}): δ [ppm] = -125.5, -127.6; IR (ATR, neat): 1/λ [cm\textsuperscript{-1}] = 2924, 1752, 1483, 1455, 1318, 1201, 1136, 1121, 1050, 1012, 959, 917, 852, 803, 761, 701, 662, 638; HRMS (ESI) m/z [M+H]\textsuperscript{+}: calcd. for C\textsubscript{19}H\textsubscript{19}F\textsubscript{2}N\textsubscript{2}O\textsubscript{2}: 345.1409, found: 345.1405; \textit{MP} = 173 °C.
Synthesis of 308k

Compound 308k was synthesized according to the GP with rac-diethyl 6,12-dihydro-5,11-methanodibenzo[b,f][1,5]diazocine-2,8-dicarboxylate, 307k (366 mg, 1 mmol) as the starting material. Purification via flash chromatography [silica gel (particle size: 20-40 μm) (40 g), ethyl acetate/hexane (05:95) to (35:65)] yielded 308k (185 mg, 44%) as a white solid along with an unreacted 307k (195 mg, 54%).

308k

Synthesis of 313a

A 50 mL round bottomed flask fitted with a water cooled reflux condenser was charged with 2,8-dimethyl-6H,12H-5,11-ethanodibenzo[b,f][1,5]diazocine 301a (0.528 g, 2.0 mmol), KMnO₄ (2.84 g, 18.0 mmol, 9.0 equiv) and BnEt₃NCl (4.08 g, 18.0 mmol, 9.0 equiv). HPLC grade methylene chloride (20 mL) was added and then the reaction was allowed to stir at 50 °C for 18 hours. The flask was cooled to 0 °C and then a saturated aqueous solution of NaHSO₃ was added (30 mL) until the reaction turned white and biphasic. The reaction was diluted with methylene chloride (20 mL) and phases were separated and the aqueous phase was extracted with methylene chloride (75 mL × 2). The combined organic phase was rinsed with water (20 mL × 2) and then with brine (20 mL × 2). The organic volatiles were removed under reduced pressure and then dried under high vacuum to yield an orange powder that was purified via column chromatography [silica gel (particle size: 20-40 μm) (15 g); 5% ethyl acetate in methylene chloride] to yield 2,8-dimethyl-6H,12H-
5,11-ethanodibenzo[b,f][1,5]diazocine-6,12-dione 313a as a white powder with a faint yellow tinge (271 mg, 47%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ [ppm] = 2.40 (s, 6H, CH$_3$), 3.39 (m, 2H, NCH$_2$CH$_2$N), 3.75 (m, 2H, NCH$_2$CH$_2$N), 7.32 (d, $J = 7.9$ Hz, 2H, Ar-H), 7.38 (dd, $J = 1.8$ Hz, 2H, Ar-H), 7.46 (d, $J = 1.8$ Hz, 2H, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ [ppm] = 21.3, 49.7, 128.5, 130.0, 134.0, 135.7, 139.8, 140.1, 179.1

IR (ATR, neat): $\nu$ [cm$^{-1}$] = 2962, 1674, 1655, 1478, 1346, 1305, 1284, 1192, 1028, 1012, 850, 843, 742, 654; HRMS (ESI): m/z [M+H]$^+$ calcd for C$_{18}$H$_{17}$N$_2$O$_4$: 325.1183; found: 325.1184; MP = 245 °C (decomposes).

Synthesis of 313b

A 50 mL round bottomed flask fitted with a water cooled reflux condenser was charged with 2,8-dimethoxy-6H,12H-5,11-ethanodibenzo[b,f][1,5]diazocine 301b (0.592 g, 2.0 mmol), KMnO$_4$ (2.846 g, 18.0 mmol, 9.0 equiv) and BnEt$_2$NCl (4.086 g, 18.0 mmol, 9.0 equiv). HPLC methylene chloride (20 mL) was added and then the reaction was allowed to stir at 50 °C for 18 hours. The flask was cooled to 0 °C and then a saturated aqueous solution of NaHSO$_3$ was added (30 mL) until the reaction turned white and biphasic. The reaction was diluted with methylene chloride (20 mL) and phases were separated and the aqueous phase was extracted with methylene chloride (75 mL x 2). The combined organic phase was rinsed with water (20 mL x 2) and then with brine (20 mL x 2). The organic volatiles were removed under reduced pressure and then dried under high vacuum to yield an orange powder that was purified via column chromatography [silica gel (particle size: 20-40 μm) (15 g); 7.5% ethyl acetate in methylene chloride] to yield 2,8-dimethoxy-6H,12H-5,11-ethanodibenzo[b,f][1,5]diazocine-6,12-dione 313b as a white powder with a faint yellow tinge (337 mg, 52%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ [ppm] = 3.39 (m, 2H, NCH$_2$CH$_2$N), 3.72 (m, 2H, NCH$_2$CH$_2$N), 3.83 (s, 6H, OCH$_3$), 7.07 (dd, $J = 8.6$, 3.0 Hz, 2H, Ar-H), 7.15 (d, $J = 3.0$ Hz, 2H, Ar-H), 7.35 (d, $J = 8.6$ Hz, 2H, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ [ppm] = 49.8, 55.9, 113.8, 119.2, 129.8, 135.2, 136.8, 160.1, 178.7; IR (ATR, neat): $\nu$ [cm$^{-1}$] = 2942, 1683, 1666, 1478, 1346, 1305, 1284, 1192, 1028, 1012, 850, 843, 742, 654; HRMS (ESI): m/z [M+H]$^+$ calcd for C$_{18}$H$_{17}$N$_2$O$_4$: 325.1183; found: 325.1184; MP = 245 °C (decomposes).

Synthesis of 313e
A 100 mL round bottomed flask fitted with a water cooled reflux condenser was charged with 2,8-dibromo-6H,12H-5,11-ethanodibenzo[bf] [1,5] diazocine 307e (1.57 g, 4.0 mmol), KMnO₄ (5.69 g, 36.0 mmol, 9 equiv) and BnEt₃NCl (8.2 g, 36.0 mmol, 9 equiv). HPLC grade methylene chloride was added and then the reaction was allowed to stir at 50 °C for 18 hours. The flask was cooled to 0 °C and then a saturated aqueous solution of NaHSO₃ was added (60 mL) until the reaction turned white and biphasic. The reaction was diluted with methylene chloride (40 mL) and phases were separated and the aqueous phase was extracted with methylene chloride (100 mL × 2). The combined organic phase was rinsed with water (30 mL × 2) and then with brine (30 mL × 2). The organic volatiles were removed under reduced pressure and then dried under high vacuum to yield an orange powder that was purified via column chromatography (silica gel (particle size: 20-40 μm) (25 g); 7.5% ethyl acetate in methylene chloride) to yield 2,8-dibromo-6H,12H-5,11-ethanodibenzo[bf][1,5]diazocine-6,12-dione as a pale yellow powder 313e (500 mg, 30%).

1H NMR (400 MHz, CDCl₃): δ [ppm] = 3.44 (m, 2H, NCH₂CH₃N), 3.77 (m, 2H, NCH₂CH₂N), 7.34 (d, J = 8.3 Hz, 2H, Ar-H), 7.73 (dd, J = 8.3, 2.3 Hz, 2H, Ar-H), 7.80 (d, J = 2.3 Hz, 2H, Ar-H); 13C NMR (100 MHz, DMSO-d6): δ [ppm] = 39.52, 48.57, 121.97, 130.88, 131.79, 135.89, 137.44, 141.21, 176.39; IR (ATR, neat): ν [cm⁻¹] = 1676, 1659, 1403, 1335, 1182, 1119, 1015, 844, 779, 720, 664, 643; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₂H₁₂Br₂N₂O₂: 420.9182; found: 420.9183; MP = 314 °C (decomposes).

Synthesis of 313f

A 50 mL round bottomed flask fitted with a water cooled reflux condenser was charged with 2,8-dichloro-6H,12H-5,11-ethanodibenzo[bf][1,5] diazocine 307f (0.61 g, 2.0 mmol), KMnO₄ (2.84 g, 18.0 mmol, 9.0 equiv) and BnEt₃NCl (4.08 g, 18.0 mmol, 9.0 equiv). HPLC grade methylene chloride (20 mL) was added and then the reaction was allowed to stir at 50 °C for 18 hours. The flask was cooled to 0 °C and then a saturated aqueous solution of NaHSO₃ was added (30 mL) until the reaction turned white and biphasic. The reaction was diluted with methylene chloride (20 mL) and phases were separated and the aqueous phase was extracted with methylene chloride (75 mL × 2). The combined organic phase was rinsed with water (20 mL × 2) and then with brine (20 mL × 2). The organic volatiles were removed under reduced pressure and then dried under high vacuum to yield a brown powder that was purified via column chromatography (silica gel (particle
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size: 20-40 μm) (15 g); 5% ethyl acetate in methylene chloride to yield 2,8-dichloro-6H,12H-5,11-ethanodibenzo[b,f][1,5]diazocine-6,12-dione 313f as a white powder (200 mg, 30%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) [ppm] = 3.48 (m, 2H, NCH\(_2\)CH\(_2\)N), 3.71 (m, 2H, NCH\(_2\)CH\(_2\)N), 7.40 (d, \(J = 8.3\) Hz, 2H, Ar-H), 7.57 (dd, \(J = 8.3, 2.4\) Hz, 2H, Ar-H), 7.65 (d, \(J = 2.4\) Hz, 2H, Ar-H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) [ppm] = 49.3, 129.8, 130.3, 135.8, 137.1, 140.7, 176.9; IR (ATR, neat): \(\nu\) [cm\(^{-1}\)] = 1666, 1658, 1457, 1466, 1408, 1342, 1334, 1220, 1184, 852, 793, 727, 675, 651, 631; HRMS (ESI): m/z [M+H]+ calcd for C\(_{16}\)H\(_{15}\)Cl\(_2\)O\(_2\): 333.0192, found: 333.0197; MP = 278 °C (decomposes).

Synthesis of 316a

A 100 mL pressure tube under argon was charged with 313a (292 mg, 1.0 mmol) and dry methylene chloride (20 mL), after which a solution (0.23M in toluene) of Cp\(_2\)TiMe\(_2\) (13.5 mL, 3.0 mmol) was injected. The reaction was warmed to 70 °C and allowed to stir for 18 hours. The reaction was cooled to room temperature and diluted with methylene chloride (20 mL) and then rinsed with water (15 mL). The organic phase was then dried over MgSO\(_4\). The volatiles were removed under reduced pressure and then purified via flash chromatography [silica gel (particle size: 20-40 μm) (15 g); ethyl acetate/pentane 10/90 to 30/70] to yield 2,8-dimethyl-12-methylene-6H,12H-5,11-ethanodibenzo[b,f][1,5]diazocin-6-one 316a as a tan solid (72 mg, 25%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) [ppm] = 2.37 (s, 3H, CH\(_3\)), 2.38 (s, 3H, CH\(_3\)), 3.13 (m, 1H, NCH\(_2\)CH\(_2\)N), 3.29 (m, 1H, NCH\(_2\)CH\(_2\)N), 3.39 (m, 1H, NCH\(_2\)CH\(_2\)N), 3.64 (m, 1H, NCH\(_2\)CH\(_2\)N), 4.59 (s, 1H, NC=CH\(_2\)), 4.65 (s, 1H, NC=CH\(_2\)), 7.22 (m, 2H, Ar-H), 7.25 (m, 2H, Ar-H), 7.30 (m, 1H, Ar-H), 7.48 (s, 1H, Ar-H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) [ppm] = 21.6, 21.4, 49.1, 50.6, 105.3, 128.2, 128.7, 129.6, 130.0, 130.9, 133.4, 135.6, 137.9, 138.3, 138.8, 146.8, 155.5, 179.9; HRMS (ESI) m/z [M+H]+ calcd. for C\(_{19}\)H\(_{19}\)N\(_2\)O: 291.1491, found: 291.1492; MP = 125 °C

Synthesis of 318a

A 250 mL round bottomed flask was charged with 316a (500 mg, 1.72 mmol) and Pd/C (10%) (183 mg, 0.172 mmol, 10 mol%). The flask was evacuated and refilled with nitrogen (3x). Dry MeOH (75 mL) was injected after which a balloon filled with hydrogen was introduced and the reaction was stirred for 90 minutes. The hydrogen was vented, and the reaction was filtered through a celite plug (2 cm × 3 cm) after which it was purified via column chromatography [silica gel (particle size: 20-40 μm) (25 g); ethyl acetate/methylene chloride
0/100 to 5/95]) to yield rac-2,8,12-trimethyl-6H,12H-5,11-ethanodibenzo[b,f][1,5]diazocin-6-one 318a as a white solid (375 mg, 75%).

\^1H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) [ppm] = 1.01 (d, \(J = 7.5\) Hz, 3H, NCH\textsubscript{3}), 2.28 (s, 3H, CH\textsubscript{3}), 2.32 (s, 3H, CH\textsubscript{3}), 3.09 (m, 1H, NCH\textsubscript{2}CH\textsubscript{2}N), 3.24 (m, 2H, NCH\textsubscript{2}CH\textsubscript{2}N), 3.55 (m, 1H, NCH\textsubscript{2}CH\textsubscript{2}N), 4.66 (t, \(J = 7.5\) Hz, 1H, NCH\textsubscript{3}), 6.88 (s, 1H, Ar-H), 7.04 (dd, \(J = 7.8, 1.9\) Hz, 2H, Ar-H), 7.22 (m, 2H, Ar-H), 7.44 (d, \(J = 2.0\) Hz, 1H, Ar-H); \(^{13}C\) NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) [ppm] = 21.1, 21.3, 48.9, 51.2, 63.4, 77.1, 128.9, 129.1, 129.3, 129.9, 131.9, 133.7, 137.0, 137.9, 138.1, 138.4, 143.1, 144.4, 181.3; HRMS (ESI) m/z [M+H]\(^+\) calc. for C\textsubscript{19}H\textsubscript{17}N\textsubscript{2}O: 293.1648, found: 293.1647; MP = 115 °C

**Synthesis of 319a**

A dry 50 mL round bottomed flask under nitrogen was charged with 313a (292 mg, 1.0 mmol), NaBH\textsubscript{4} (228 mg, 6.0 mmol), methanol (10 mL) and methylene chloride (40 mL). The reaction was stirred under a nitrogen atmosphere for 24 hours after which it was quenched with NH\textsubscript{2}Cl (sat. aq.) (10 mL). The reaction was diluted with methylene chloride (50 mL) and the phases were separated. The aqueous phase was extracted with methylene chloride (25 mL x 2). The combined methylene chloride phases were rinsed with water (25 mL x 2) dried over MgSO\textsubscript{4} and then purified via column chromatography [silica gel (particle size: 20-40 \(\mu\)m) (25 g); acetate/pentane 50/50] to yield 4-(2-(hydroxymethyl)-4-methylphenyl)-7-methyl-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one 319a as a white solid (250 mg, 89%).

\(^1H\) NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) [ppm] = 2.29 (s, 3H, CH\textsubscript{3}), 2.38 (s, 3H, CH\textsubscript{3}), 3.64 (m, 2H, NCH\textsubscript{2}CH\textsubscript{2}N), 3.88 (m, 2H, NCH\textsubscript{2}CH\textsubscript{2}N), 4.49 (d, \(J = 12.0\) Hz, 1H, NCHOH), 4.62 (d, \(J = 12.0\) Hz, 1H, NCHOH), 6.65 (d, \(J = 8.1\) Hz, 1H, Ar-H), 7.11 (d, \(J = 7.9\) Hz, 1H, Ar-H), 7.13 (dd, \(J = 9.4, 1.3\) Hz, 1H, Ar-H), 7.21 (dd, \(J = 8.0, 1.5\) Hz, 1H, Ar-H), 7.62 (d, \(J = 1.5\) Hz, 1H, Ar-H), 7.33 (d, \(J = 1.7\) Hz, 1H, Ar-H); \(^{13}C\) NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) [ppm] = 20.5, 21.1, 49.8, 50.2, 62.6, 119.9, 123.8, 126.2, 130.3, 131.8, 131.9, 133.9, 137.9, 138.2, 139.5, 142.6, 171.5; HRMS (EI) m/z [M]+ calc. for C\textsubscript{19}H\textsubscript{17}N\textsubscript{2}O: 296.1525, found: 296.1529; MP = 105-108 °C

**Synthesis of 321a**

A dry 50 mL flask under nitrogen was charged with 313a (73 mg, 0.25 mmol, 1.0 equiv) and 2,6-Di-tert-butyl-4-methylpyridine (123 mg, 0.6 mmol, 2.4 equiv). Dry methylene chloride (10 mL) was injected and the contents were stirred at room temperature until a clear solution resulted [Gentle heating was required]. The flask was cooled to -78 °C in a dry ice-acetone bath, and then Tf\textsubscript{2}O (170
mg, 0.1 mL, 0.6 mmol) was injected dropwise over five minutes. After 45 minutes at -78 °C, MeMgBr (0.5 mL, 1.5 mmol, 3M in Et₂O) was injected and the reaction was stirred at -78 °C for 90 minutes after which it was allowed to reach room temperature over the course of an hour. The reaction was quenched with a saturated solution of NH₄Cl (5mL), and then diluted with methylene chloride (30 mL). The phases were separated and the aqueous phase was extracted with methylene chloride (15 mL x 2). The combined methylene chloride phases were rinsed with water (15 mL × 2) dried over MgSO₄ and then purified via column chromatography [silica gel (particle size: 20-40 μm) (5 g); acetate/pentane 5/95] to yield 1,1'-(ethane-1,2-diylbis(azanediyl))bis(5-methyl-2,1-phenylene))bis(ethan-1-one) **321a** as a viscous yellow oil (42 mg, 52%)

**¹H NMR** (400 MHz, CDCl₃): δ [ppm] = 2.19 (s, 6H, CH₃), 2.49 (s, 6H, CH₃), 3.43 (m, 4H NCH₂CH₂N), 6.60 (d, J = 8.6 Hz, 2H, Ar-H), 7.12 (dd, J = 8.6, 2.0 Hz, 2H, Ar-H), 7.46 (s, 2H, Ar-H), 8.76 (brs, 2H, NH). **¹³C NMR** (100 MHz, CDCl₃): δ [ppm] = 49.1, 50.1, 61.6, 111.7, 121.3, 122.1, 122.8, 128.1, 132.5, 133.6, 134.8, 135.9, 140.2, 144.3, 169.5; **IR (ATR, neat)**: ν [cm⁻¹] = 3278 (N-H), 1630 (C=O); **MS (ESI)**: m/z [M]+ calcd for C₂₀H₂₅N₂O₂: 325.2; found: 325.2.
3.6.3 NMR Spectra

Variation of Pd(OAc)$_2$ with 301a

$^1$H NMR (400 MHz, CD$_2$Cl$_2$) of 301a (1 equiv) and Pd(OAc)$_2$ (0.5 to 2.0 equiv) at 298 K

Zoom from 5.0 to 3.0 ppm.
Variation of NBS with 301a.

$^1$H NMR (400 MHz, CD$_2$Cl$_2$) of 301a (1 equiv) and NBS (0.5 to 2.0 equiv) at 298 K

Zoom from 5.0 to 3.0 ppm.
Variation of NBS with Pd(OAc)$_2$ and 301a
$^1$H NMR (400 MHz, CD$_2$Cl$_2$) of 301a (1 equiv), Pd(OAc)$_2$ (0.2 equiv) and NBS (0.5 to 2.0 equiv) at 298 K.
Variation of temperature with NBS, Pd(OAc)$_2$ and 301a

Variable temperature $^1$H NMR (400 MHz, CD$_2$Cl$_2$) of 301a (1 equiv), Pd(OAc)$_2$ (0.2 equiv) and NBS (2.0 equiv).

Zoom from 5.0 ppm to 3.0 ppm.
3.6.4 X-Ray Data

ORTEP-III representation of the diacetoxylated product \textit{rac}-309c and monoacetoxylated product \textit{rac}-309e. Irrelevant hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at 40% probability.
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Oxidative Functionalization of Trögers Base Derivatives
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<td>0.9996 and 0.9367</td>
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<td>Full-matrix least-squares on F²</td>
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<td>1.044</td>
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<td>C_{16}H_{10}Cl_{2}N_{2}O_{2}</td>
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<td>M_r</td>
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<td>0.31 and -0.33</td>
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<td>(\text{C}<em>{18}\text{H}</em>{20}\text{N}<em>{2}\text{O}</em>{2})</td>
</tr>
<tr>
<td>Mr.</td>
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<td>296.37</td>
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<td>150</td>
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<td>P21/c</td>
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<td>10.6272(2), 90</td>
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<td>0.680</td>
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<td>632</td>
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<td>99.7</td>
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<td>31065</td>
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<td>multi-scan</td>
<td>multi-scan</td>
</tr>
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<td>Max. and min. transmission</td>
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<td>3182 / 0 / 199</td>
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<td>0.43 and -0.29</td>
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3.7 References


Chapter 4: An Ethano-Tröger’s Base Derived Electrophilic Fluorinating Reagent

Part of this chapter has been reproduced in Pereira, R.; Woltenshulme, W.; Sandford, G.; Claridge, T.D.W.; Gouverneur, V.; Cvengroš, J. Chem. Commun., 2016, 52, 1606.

4.1 Introduction

4.1.1 Fluorine in Organic Chemistry

Fluorinated organic molecules play an integral role in pharmaceuticals, agrochemicals, materials and PET tracers. Today approximately 25% of all drugs on the market contain fluorine; a number that has risen from 2% in 1970. The consequence of fluorine on molecular properties boils down to the nature of the C–F bond. The high electronegativity of fluorine ($\chi = 3.98$; Pauling electronegativity) results in the C–F bond being polarized with most of the electron density on the fluorine. The unequal electron density distribution leads to columbic attraction between C$^{5+}$ and F$^{6-}$ which is responsible for the high C–F bond strength. As a consequence of this polarized covalent bond between carbon and fluorine, the C–F moiety exhibits attractive interactions with hydrogen-bond donors, other fluorinated compounds, carbonyl and different polar functional groups. From a medicinal chemistry perspective the polarized nature of the C–F bond cause changes in physical, chemical and physiological properties of an organic molecule such as the modulation of $pK_a$ values of functional groups in the vicinity of the fluorine or alteration of the lipophilicity profile of the molecule. It may also have an impact on conformational changes in molecules and increase their stability towards enzymatic oxidation.

Fluorine is the thirteenth most abundant element in the earth’s crust, yet the number of fluorinated natural products is negligible compared to those with other halogen (Cl, Br, I)–bearing natural products. The difficulties encountered in carbon-fluorine bond synthesis can be ascribed to fluorine’s high electronegativity, the oxidizing nature of elemental fluorine ($E_{ox} = -3.06$ V) and the high energy of hydration of the fluoride ion (117 kcal/mol). From a conceptual point of view apart from a radical pathway, there exist broadly two methods to introduce fluorine into an organic molecule, i.e. nucleophilic and electrophilic fluorination. The former introduces fluorine via an “F” source such as alkali metal fluoride salts, tetra- $N$-butyl ammonium fluoride (TBAF), SF$_4$, $N$,$N$-diethylaminosulfur trifluoride (DAST) and BF$_3$ (Fig.4.1). At the other end of the spectrum electrophilic fluorinating reagents such as F$_2$, XeF$_2$ and the milder N-F based reagents such as the N-fluoropyridinium salts, NFSI and Selectfluor are sources of formal “F” (Figure 4.2).
4.1.2 Fluorinating Reagents

Due to the meagre number of naturally occurring fluorinated organic compounds, fluorinated building blocks are accessed synthetically. The simplest fluorinating reagent that one could conceive is \( F_2 \) gas itself, however its highly reactive nature makes it extremely difficult to handle safely in a standard laboratory setting without special equipment and handling techniques. Whilst fluorine gas can be employed to fluorinate substrates, the precautions needed limits its use to a few specialised research centres, thereby limiting its applicability in most chemistry laboratories. Instead, fluorine is routinely used in laboratories in the guise of a fluorinating reagent, which allows for a much safer handling, and in certain cases bespoke reactivity. From a conceptual point of view, fluorinating reagents can be divided into two main classes – nucleophilic and electrophilic. The progress made in recent years in the field of modern organofluorine chemistry indicates that the nature of the fluorine source is critical for a particular fluorination process to succeed. This observation stands true for nucleophilic and electrophilic fluorination, and this independently of the activation manifold applied to induce C-F bond formation. Much research has therefore focused on the development of new reagents for late stage fluorination, thereby allowing for milder and functional group tolerant methodologies.

4.1.2.1 Nucleophilic Fluorinating Reagents

In a prototypical nucleophilic fluorination reaction, the substrate acts as the electrophile whilst a fluoride anion behaves as the nucleophile. The perceived simplicity of nucleophilic fluorinating reagents does not always translate into straightforward reactivity due to low solubility in commonly used organic solvents and the inherent basicity of fluoride. The simplest nucleophilic source of fluorine is hydrogen fluoride (HF). Over the years reagents have been developed as either tamed sources: \( \text{Et}_3\text{N} \) and HF/pyridine, or latent sources: \( \text{N,N-diethylaminosulfur trifluoride} \) (DAST), \( \text{bis(2-methoxyethyl)aminosulfur trifluoride} \) (DeoxoFluor), \( \text{morpholinodifluorosulfinium tetrafluoroborate} \) (XtalFluor-E), \( \text{morpholinodifluorosulfinium tetrafluoroborate} \) (XtalFluor-M), all of hydrogen fluoride. The metal fluoride salts (\( \text{KHF}_2 \), \( \text{CuF}_2 \), \( \text{KF} \), \( \text{AgF}_2 \)) along with the tetraalkylammonium salts such as \( \text{teta-n-butyl ammonium fluoride} \) (TBAF), anhydrous TBAF, and alcohol-coordinated TBAF are widely used in organic synthesis. Sulphur tetrafluoride (\( \text{SF}_4 \)), boron trifluoride (\( \text{BF}_3 \)), tetrafluoroboric acid \( \text{HBF}_4 \) and the hypervalent \( p \)-iodotoluene difluoride, all have been used as nucleophilic sources of fluorine in organic synthesis.
Figure 4.1 Nucleophilic fluorinating reagents.

4.1.2.2 Electrophilic Fluorinating Reagents
Fluorine gas is the simplest and most reactive source of electrophilic fluorine. The high reactivity is attributed to the small size of $F_2$, so that there is a large repulsion perceived between the lone pairs on both the fluorine atoms, thereby weakening the $F-F$ bond and creating a very reactive species. This weak bond, coupled with the high bond enthalpy fluorine exhibits with many other elements, such as hydrogen, carbon and silicon, allows $F_2$ to react, potentially explosively, with almost any material. Over the years several research groups have worked towards the development of electrophilic fluorinating reagents. Examples include $\text{XeF}_2$, perchloryl fluoride ($\text{ClO}_3F$) or the O–F reagents, such as trifluoromethyl hypofluorite($\text{CF}_3\text{OF}$), acyl and perfluoroacyl hypofluorites. However most of these regents are scarcely less reactive than fluorine gas and several of them are explosive liquids that require specialized handling techniques. It was not until the appearance of safe and easy to handle N–F reagents that revolutionised the field of electrophilic fluorination. The N-fluoropyridinium salts introduced by the group of Umemoto are easily handled crystalline solids that are routinely used in organofluorine chemistry. A significant advantage of this system is that the electronics of pyridine rings can be easily tuned by introducing suitable functional groups. The sulfonamide motif was used by Barnette to develop a fluorinating reagent for carbanions. Differding developed the stable and practical $N$-fluorobis(phenyl)sulfonimide (NFSI), and DesMarteau and co-workers developed the highly reactive $N$-fluorobis[[trifluoromethyl]sulfonyl] imide, based on the sulphonimide motif. Perhaps the greatest contribution to the N–F class of reagents was
made by Eric Banks, with the development of 1-chloromethyl-4-fluoro-1,4-diazeniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (Selectfluor or F-TEDA-BF₄). This compound over the past 25 years has established itself as a stable, non-hygroscopic, reactive, solid crystalline electrophilic fluorinating reagent. Chiral electrophilic reagents have been recently introduced by the groups of Gouverneur and Shibata based on the backbone of Selectfluor and NFSI.

4.1.3 Reactivity of Electrophilic Fluorinating Reagents

The relative reactivity of N–F electrophilic fluorinating reagents have been experimentally analysed by electrochemical methods, nuclear magnetic resonance and pKₐ methods, and via competitive halogenation. These methods are considered in the following section, and as with any methodology, each has merits and limitations.

4.1.3.1 Electrochemical Methods

Electrochemical methods to analyse the N–F bond in electrophilic fluorinating reagents utilize cyclic voltammetry to arrive at peak (reduction) potentials. In all cases the reduction peak is the only peak observed due to the irreversible reduction of the N–F bond. Gilicinski et al. reason that whether the mechanism of electrophilic fluorination is a single electron transfer or a nucleophilic displacement, there is essentially a reduction of the reagent. Accordingly the reactivity of electrophilic fluorinating reagents (with a specific nucleophile)
may correlate with the redox potentials, with the most oxidizing reagent having the greatest fluorinating power.

Table 4.1 Peak reduction potentials of selected electrophilic fluorinating reagents.  

<table>
<thead>
<tr>
<th>No.</th>
<th>Reagent</th>
<th>(E_{\text{p, red}}) (CH(_3)CN, V vs SCE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(N)-fluoro-bis[trifluoromethylsulfonyl]imide [DesMarteau reagent]</td>
<td>+0.18</td>
</tr>
<tr>
<td>2</td>
<td>1-chloromethyl-4-fluoro-1,4-diazaoniabicyclo-[2.2.2]octane bis tetrafluoroborate [Selectfluor (^{\text{TM}})]</td>
<td>-0.04</td>
</tr>
<tr>
<td>3</td>
<td>1-fluoro-4-methyl-1,4-diazaoniabicyclo-[2.2.2]octane bistetrafluoroborate [Selectfluor II (^{\text{TM}})]</td>
<td>-0.09</td>
</tr>
<tr>
<td>4</td>
<td>(N)-fluoropyridinium pyridine heptafluorodiborate</td>
<td>-0.34</td>
</tr>
<tr>
<td>5</td>
<td>(N)-fluoroquinuclidinium triflate</td>
<td>-0.37</td>
</tr>
<tr>
<td>6</td>
<td>(N)-fluoropyridinium triflate</td>
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</tr>
<tr>
<td>7</td>
<td>(N)-fluorocollidine triflate</td>
<td>-0.73</td>
</tr>
<tr>
<td>8</td>
<td>(N)-fluoro-benzenesulphonamide (NFSI)</td>
<td>-0.78</td>
</tr>
<tr>
<td>9</td>
<td>(N)-methyl-(N)-fluoro-p-toluenesulphonamide</td>
<td>-2.10</td>
</tr>
<tr>
<td>10</td>
<td>(N)-propyl-(N)-fluoro-p-toluenesulphonamide</td>
<td>-2.20</td>
</tr>
</tbody>
</table>

The peak reduction potentials mirrored the order of observed chemical reactivity. For example, the DesMarteau reagent (Table 4.1, entry 1) is the most reactive of the electrophilic fluorinating reagents, being able to fluorinating benzene at room temperature (50% conversion in 18 hours\(^{39}\)) and correspondingly has the highest peak reduction potential \((E_p)\) of +0.18 V. Comparatively, Selectfluor is less reactive and fails to fluorinate benzene at room temperature; however, it fluorinates the more reactive anisole (72% conversion at 40 °C in 6 hours).\(^{44}\) The analogous Selectfluor II derivative is less reactive, taking 13 hours to achieve the same level of conversion.\(^{44}\) This reactivity does fit well with the electrochemical data, which shows Selectfluor to be slightly more reactive than Selectfluor II (Table 4.1, entry 2 vs entry 3). \(N\)-fluoropyridinium triflate with a reduction peak potential of −0.47 V (Table 4.1, entry 6) reacts with anisole under more forcing conditions to give a 72% conversion in DCE at 120 °C after 18 hours.\(^{36c}\) The Barnette reagents (Table 4.1, entries 9 and 10) will only react with aromatic carbanions as envisaged by their very low peak reduction potentials.\(^{37}\) Whilst the data offers useful qualitative information about the reagents investigated, the absolute values of the reduction potentials are interesting. To illustrate, Selectfluor will oxidise iodide and bromide (but not chloride) at room temperature to the elements. However, the \(E^+\) value for aqueous bromide oxidation is +0.846 V versus the standard calomel electrode and therefore it is clear that Selectfluor is a much stronger oxidizing agent than is indicated by the non-aqueous electrochemical \(E_{\text{p, red}}\) value of -0.04 V versus the standard calomel electrode. Fainzil’berg et al., performed a similar study, albeit on fewer reagents, but using a
rotating disk electrode rather than the stationary electrode used in the first report.\textsuperscript{45} Their data fitted the same trend but this time showed Selectfluor to have a higher electrode potential (+0.33 V). The value is still considerably less than for the oxidation of bromide. Similarly, a study by Evan’s and co-workers demonstrated that it was not possible to measure the reverse peak potential due to an irreversible reduction of the N–F bond. This is perhaps not too surprising given the enormous energy price of oxidizing fluoride to F\textsuperscript{−}. However, taken together these works have nicely shown that the more reactive fluorinating reagents have higher reduction potentials, which is consistent with other studies on reactivity. In conclusion, the standard reduction potentials (or peak reduction potentials where appropriate) are very useful guides to the reactivity of an N–F reagent.

4.1.3.2 $^{19}$F NMR Techniques and $pK_a$

Studying the electronic environment around the N-F bond via NMR presents an alternative approach to the electrochemical ordering of a series of N-F reagents. Umemoto and co-workers carried out a study correlating the $^{19}$F chemical shifts of a series of N-fluoropyridinium salts with reactivity.\textsuperscript{46} Accordingly an electron-poor environment, which would correspond to an increased reactivity, should cause a downfield shift in the NMR ($^{19}$F), i.e. a more positive chemical shift. Furthermore, the electron-poor pyridine would be expected to be a strong acid (or a weak base). From the findings of Umemoto et al., an ordering of pyridinium class of N–F reagents can be established as illustrated below (Figure 4.3). Also one sees that the reactivity does increase with decreasing $pK_a$ values of the corresponding pyridines.\textsuperscript{47}

![Figure 4.3 Ordering of N-fluoropyridinium reagents. a) ref 47a; b) ref 47b; c) ref 47c; d) ref 47d; e) ref 47e.](image-url)

Their key findings showed that (a) the $^{19}$F NMR shifts of N-fluoropyridinium salts are independent of the nature of the counter ion, and thus the compounds are completely ionic. (b) Secondly, there is a general trend of increasing chemical shift i.e. more positive $^{19}$F ($\delta$) ppm values, with increasing fluorinating power but with several anomalies. (c) With non-alkyl alpha substituents, the fluorinating power is not related to the $^{19}$F NMR shift but is still
correlated to the pKₐ’s of the corresponding pyridines. The increasing chemical shift with increasing fluorinating power trend holds well except for those reagents bearing ortho-substituents. Highlighting this anomaly, the reagents derived from 2,6-dichloropyridine (31.7 ppm) and pentachloropyridine (48 ppm) display a chemical shift that would suggest a less powerful reagent than pyridine (48.4 ppm) itself. Clearly, this is not the case and leads one to the conclusion that for ortho-substituents the through space effect on the chemical shift has a greater effect than electronic effects caused by the nature of the ring. Another source of results inconsistent with the general trend is observed in reagents bearing electron-donating groups at the 4-position. The effect of this substitution pattern is to cause a significant upfield shift in the ¹⁹F NMR, more than would be expected by considering the observed reactivity or the pKₐ of the relevant pyridine.

Figure 4.4 Effect of electron-donating groups at the 4-position. ¹⁹F NMR values from ref 36a. pKₐ values from ref 47c.

For example, the reagent derived from 4-methoxypyridine exhibits a significantly altered ¹⁹F NMR resonance value, compared to those reagents derived from 4-methyl pyridine and pyridine (Figure 4.4) The deviation from the trend can be explained for these compounds by considering the difference between an N-protonated pyridinium species and an N-fluoropyridinium species. In the case of the N-fluoro compound, we would expect a much larger resonance contribution from the electron-releasing group at the para position due to the high electronegativity of fluorine on the nitrogen atom. Consequently, the nitrogen is much more stabilised than pKₐ values would suggest and hence the deviation from the trend.

Figure 4.5 N-fluoroquinoid resonance stabilisation.

However, in general where the chemical shift value proves to be unreliable it is possible to use the pKₐ value to order the reactivity. In the series of reagents described in figure 4.3 the highly reactive chlorinated examples have an anomalous chemical shift due to the consequence of ortho substitution but their respective pKₐ values are representative of their high reactivity. Misleading information can also come from the pKₐ values, when steric effects are significant. For example, 2,6-di-tert-butylpyridine has an abnormally low pKₐ
value, which is attributed to the favourable release of steric clashing upon dissociation of the acid in a dynamic protonation/deprotonation system. However, dissociation of an N–F bond does not occur in the same way and so we should expect the fluorine to experience a similar chemical shift to that of the corresponding dimethyl compound. Indeed, this was the case with the 2,6-di-tert-butylpyridinium reagent was found to have a chemical shift of +23.1 ppm, compared to the +24.8 ppm shift of 2,6-lutidine. This evidence suggests that pyridines substituted with alkyl groups at the ortho position follow the general trend, but other substitution was not supported. In conclusion, ordering of reagents on electronic terms using the chemical shift of the fluorine and the pKₐ of the corresponding acid can be a very useful method for pyridinium type salts.

4.1.3.3 Competitive Halogenation

An experimental method of measuring the chemical reactivity of various N–F reagents was disclosed by Togni and co-workers.⁴⁸ They used a competition reaction between electrophilic fluorinating reagents and N-chlorosuccinimide to determine the relative reactivity of a range of reagents. A β-ketoester with a chiral Lewis acid catalyst was chosen as the model reaction (Scheme 4.1).

![Scheme 4.1 Competitive halogenation between N–F reagents and N-Chlorosuccinimide.](image)

The halogenation reactions were performed in the presence of 1 equivalent of N-chlorosuccinimide (NCS) and 1 equivalent of electrophilic fluorinating reagent. After full consumption of the starting β-ketoester, the amounts of fluorinated and chlorinated product were determined by HPLC. They reasoned that the rate of the chlorination reaction (k_Cl) should be independent of the fluorination reaction (k_F) and so the molar ratio of the two products is a relative measure of the rate of fluorination with a specific N-F reagent, as described by the equation 4.1.
An Ethano-Tröger’s Base Derived Electrophilic Fluorinating Reagent

\[
k_{rel} = \frac{k_F}{k_{Cl}} = \frac{n_F}{n_{Cl}}
\]

**Equation 4.1** Relative rate of reaction for fluorinating reagents is proportional to molar ratio of two products.

Where the rate constants \( k_{F/Cl} \) represents the rates of fluorination/chlorination, and the parameters \( n_{F/Cl} \) are the molar amounts of fluorination/chlorination products formed. The results of the competition reactions are displayed below (Table 4.2). In preliminary reactions the authors showed that the electrophilic fluorinating reagents did not react with NCS under the reaction conditions.

**Table 4.2** Results of competitive halogenation of the model β-ketoester.

<table>
<thead>
<tr>
<th>Fluorinating reagent</th>
<th>Fluorinated product [%]</th>
<th>Chlorinated product [%]</th>
<th>( k_{rel} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectfluor</td>
<td>73</td>
<td>27</td>
<td>2.72</td>
</tr>
<tr>
<td>Accufluor</td>
<td>65</td>
<td>35</td>
<td>1.84</td>
</tr>
<tr>
<td>2,6-dichloro-1-fluoropyridium</td>
<td>13</td>
<td>87</td>
<td>0.15</td>
</tr>
<tr>
<td>tetrafluoroborate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synfluor</td>
<td>6</td>
<td>94</td>
<td>0.06</td>
</tr>
<tr>
<td>NFSI</td>
<td>4</td>
<td>96</td>
<td>0.04</td>
</tr>
<tr>
<td>( N )-fluoro-perfluoropiperidine</td>
<td>3</td>
<td>97</td>
<td>0.03</td>
</tr>
</tbody>
</table>

The results shown in table 4.2 are in accordance with the ordering of N–F reagents done by electrochemical as well as \(^{19}\)F NMR and \( pK_a \) methods.

**4.1.4 On Electrophilic Fluorine**

In electrophilic fluorinating compounds the traditional role of fluorine as a nucleophile is reversed. In essence by using the term ‘electrophilic fluorine’ we suggest that the moiety to which fluorine is delivered must have a greater propensity to gain electrons than fluorine, which intuitively seems to be incorrect since fluorine is the most electronegative element in the periodic table. Elemental fluorine is potentially a source of \( F^+ \) radicals, \( F^- \) ions and cationic fluorine, \( F^+ \). The energetics for the formation of the three species in gas phase is as shown below:\(^{49}\)

\[
\begin{align*}
F_2 & \quad \text{Homolytic} \quad 2F^- \quad \Delta H^\circ = 37.9 \text{ kcal/mol} \\
F_2 & \quad \text{Heterolytic} \quad F^+ \cdot F^- \quad \Delta H^\circ = 420.4 - 59.3 = 361.1 \text{ kcal/mol}
\end{align*}
\]

**Figure 4.6** Homolytic and heterolytic cleavage of \( F_2 \).
As seen, the homolytic cleavage is much more facile than the formation of \( F^+ \) in the gas phase, and the radical reactions of \( F_2 \) tend to dominate at room temperatures or higher. Whilst \( F^+ \) radicals and \( F^- \) ions have been well documented in literature, \( F^+ \) has only been detected spectroscopically in the gas phase. There are no known \( F^+ X^- \) salts, and the cations such as \( XeF^+, N_2F^+ \) and \( NF_4^+ \) are viewed as stabilized forms of ‘positive fluorine’. The concept of certain compounds being able to furnish a positive fluorine atom has been a matter of great debate. Barton and co-workers, whilst working with \( CF_3OF \) noted that the direct aromatic fluorination would only be possible if fluoroxytrifluoromethane were able to furnish a fluorine cation. Cartwright and Woolf in their report suggested the reluctance of chemists to accept ‘positive fluorine’, stemmed from the way electronegativity was understood. They believe that the models to describe electronegativity are derived from the atomic or molecular properties of simple molecules such as hydrogen fluoride, and cannot be used predictively to describe a situation wherein fluorine is a part of a complex molecule, especially when fluorine is a part of a delocalized-electron system as then inductive effect of fluorine is easily overcome by the mesomeric effect. To bolster their argument they cited the weakening of aromatic carboxylic acids bearing \( \omega \)- and \( \rho \)-fluorine substitution; \( CF_3O^+ F \) polarity to explain aromatic fluorinations even though fluorine is formally more electronegative than the \( CF_3 \) group; the increasing Lewis acidity of boron trihalides from \( BF_3 \) to \( BL_3 \).

Christe in his rebuttal to Cartwrights and Woolf's report, utilizing the reaction of perfluoropropene with hypofluorous perchloric anhydride suggested that the product spread indicates a rather weaker polarisation of the O–F bond is not strongly polarized and the observed regioselectivity is likely to be a consequence of steric factors and not electronic with the larger \( OCIO_3 \) moiety being directed away by the \( CF_3 \) group.

\[
\text{Scheme 4.2 Fluorination of perfluoropropene.}
\]

He further went on to suggest that fluorine being the most electronegative element cannot exhibit such polarization \([CF_3O^+ F] \), and that it was only logical to expect fluorine, as the most electronegative element, to be the most electronegative group, with all other groups bearing increasing numbers of fluorine atoms asymptotically reaching the electronegativity of fluorine.
In a subsequent publication, Cartwright and Wolf retorted\(^4^9\) that the formal positive charge on fluorine, following heterolysis of an F–F bond, could be stabilized using the formation of a tetrafluoroammonium salt. Using a relatively strong Lewis acid, to promote heterolysis and loss of fluoride, and a weak Lewis base (as a strong Lewis base would simply interact with the Lewis acid) an electron deficient fluorine atom can be obtained. If half of the fluorine becomes fluoride, then by a charge-balance argument, the other half must be ‘positive fluorine’ (Scheme 4.3).

\[
\text{Scheme 4.3 Fluorination of trifluoroamine.}
\]

However, this was rebuffed by Christie using the example of the reaction of lithium hydride with molecular fluorine. Going by the logic purported by Cartwright and Woolf, the fluorine in the HF formed in scheme 4.4 would have to be positive, and clearly this could never be the case.\(^5^4\)

\[
\text{Scheme 4.4 Fluorination of LiH.}
\]

Cartwright and Woolf, countering the product spread in scheme 4.2, suggested that the low temperatures and choice of olefin favour a nucleophilic attack, thereby leaving an inductively stabilised carbanion, rather than an electrophilic substitution. Responding to the argument that fluorine is the most electronegative element and can never show a positive polarity when combined with another group, they say that arguments based on electronegativity differences in such complex molecules where the electronegativity differences are small or where fluorine is a part of delocalized system and back bonding can occur, must be made with great care. They also allude to the fact that the picture may not be so clear, as perchloryl fluoride can furnish both electrophilic fluorine and electrophilic ClO\(_3\). To highlight this, benzene will react with perchloryl fluoride under Friedel-Craft conditions to yield perchloryl benzene but 3,5-dimethoxyphenol in pyridine will be fluorinated to give both 2- and 4-fluoro products. The authors concluded by suggesting that the differences between Christie’s views and their own were possibly semantic. For example, Christie had recognized NF\(_4^+\) as an electrophilic fluorinating reagent but not as stabilised ‘positive fluorine.’ Cartwright and Woolf would identify this as stabilised ‘positive fluorine’ but would still agree that “F” would have an enormous affinity for an electron, exceeding that of even a proton. Thus a bare “F” would no more exist under ordinary conditions than would a bare proton.
Whilst there is clearly significant debate in the literature about what ‘positive fluorine’ is and how it is defined, there is little doubt that however the X–F bond behaves prior to the bond breaking event, it does, in fact, deliver electrophilic fluorination products. However, the exact mechanism by which this occurs is too shrouded in mystery and has been keenly debated in the fluorochemistry community. The notion of an electrophilic source of highly electronegative elements or groups is very interesting and an area that has been hugely exploited in the recent decades in fluorochemistry – the prime example being the hypervalent iodine reagents, which have been used as sources of CF$_3$.$^{55}$

4.1.5 Mechanism of Fluorination with N–F reagents: S$_N$2 or SET?
The N-fluoropyridiniums introduced by Umemoto and F-TEDA-BF$_4$ by Banks have revolutionised the field of electrophilic fluorination, and several other reagents have been developed over the past years. However, the nature of the fluorination reaction with N–F reagents has been a subject of debate ever since their introduction. Two possible pathways have been postulated: a single-electron transfer (SET) or nucleophilic S$_N$2 substitution.$^{56}$

As shown in above (Scheme 4.5), both SET and S$_N$2 pathways can lead to identical products, in this case via a fluorinated carbocation. Eric Banks and co-workers in their studies with Selectfluor initially suggested a S$_N$2 process$^{57}$ but later came to a conclusion that a substrate-dependent mechanistic continuum could be operational.$^{44}$ Differding and co-workers conducted experiments$^{58}$ using a radical clock to detect the presence of intermediate radical species. In the first instance, they took a carbanion substrate that would be susceptible to rearrangement, should the radical pathway be operating. However, with all fluorinating reagents tested the rearranged fluorinated cyclised product C was not observed; the protonated-rearranged product D was only observed in small amounts (~10%) when xenon difluoride was used.
In the majority of cases only the two products of direct fluorination were observed, resulting in either mono A or difluorination B. It was rationalised that the difluorinated product could arise from further deprotonation by excess base or by unreacted enolate. It was rationalised, from this observation, that oxidation of the enolate was not occurring as otherwise the fluorinated-rearranged product would have been detected. In an independent reaction, tributyltin hydride was added to the α-bromo-citronellic ester derivative and the rearranged protonated product was recovered in high yield, demonstrating that if radicals were present the cyclised product would be expected (Scheme 4.7).

This experiment ruled out the possibility of free-radicals to give the fluorinated product, whereas it suggested the proto-rearranged product does in fact arise from a free radical pathway. However, it does not rule out the possibility of a SET mechanism since the cyclization of a 5-hexenyl radical has been shown to occur at a rate of approximately $1 \times 10^6$ s$^{-1}$, and the absolute rate constant for the reaction of atomic fluorine (F') with a solvent is between $10^9$ and $10^{11}$ s$^{-1}$, some four to six orders of magnitude faster than the fastest possible closing of a 5-hexenyl radical. It is possible that the radical enolate is formed, which is followed by a fast in cage recombination to give the fluorinated product. Umemoto, in 1990, provided considerable experimental evidence to support an electron transfer mechanism when studying various N-fluoropyridinium salts. They found that N-fluoropyridinium salts reacted with Grignard reagents to yield the corresponding fluorinated...
products, whilst the organolithiums did not react. It was suggested that this is due to the fact that Grignard reactions are known to involve a one-electron transfer mechanism. However, Holm and Crossland showed that Grignard reagents can also react by an S_N2 mechanism.\textsuperscript{61} Furthermore, Yamataka \textit{et al.} reported that organolithium reagents react almost exclusively by SET. They suggested that the rate-determining step is the electron transfer, unlike for Grignard reagents, in which case the recombination of the radicals is the rate-determining step.\textsuperscript{62} If both studies are taken together, one possible interpretation of the finding of Umemoto \textit{et al.} is that the transition state for the SET reaction with organolithium compounds occurs in such an early phase of the reaction that F\textsuperscript{−} reacts with the solvent preferentially, with no formation of the desired product. Stronger evidence for the SET pathway came from the work of Umemoto \textit{et. al.} who observed the reaction between N-fluropyridinium triflate and 2-napthol initially turned orange and then the colour disappeared as the reaction proceeded. They ascribed the colour to the formation of a π complex between the substrate and the reagent.\textsuperscript{36c}

\begin{center}
\begin{tabular}{c}
\includegraphics[width=\textwidth]{Scheme4.8.png}
\end{tabular}
\end{center}

\textit{Scheme 4.8} Electrophilic fluorination via a π complex.

Despite extensive research probing the possible reaction mechanisms of N–F reagents, a definitive answer has not been found and may remain undiscovered as a result of the difficulty of assessing these ultra fast reactions.
4.2 Motivation

Prior work in the Gouverneur laboratories had lead to the development of chiral electrophilic fluorinating reagents that are based on a 1,4-diazabicyclo[2.2.2]octane (DABCO) structure—chiral Selectfluor. Employing these reagents, they have successfully performed enantioselective fluorocyclizations on prochiral indene derivatives using a pendant carbon nucleophile (Scheme 4.9), which could not be carried out using a combination of Selectfluor and a chiral Brønsted acid.

![Scheme 4.9 Chiral Selectfluor type reagents (top); Fluorocarbocyclisation (bottom).](image)

In the field of fluorine chemistry nitrogen atoms have played an important role, *viz.* the N–F fluorinating reagents. In this regard the ethylene-bridged Tröger’s base (ETB) and its analogues are attractive candidates for transformation into N–F reagents, due to their $C_2$ symmetry and concave Λ-shape. Furthermore, ETB and DABCO do have a certain degree of similarity, and it would make an interesting study to see the effects of aromatic rings fused to the larger diaza-bicyclo ring structure on reactivity, *i.e.* N–F reagents based on ETB versus Selectfluor. Additionally, since ETB belongs to the $C_2$ point group and can be easily resolved, we would have access to an enantiopure fluorinating reagent.

![Figure 4.7 Ethano-Tröger’s base (left) and DABCO (right).](image)
4.3 Synthetic Chemistry

4.3.1 Reagent Synthesis

The synthesis of 403 was investigated with a study in racemic series. Modifying a literature procedure, the treatment of (±)-ETB with a large excess of methyl iodide in a mixture of MeOH/CH₂Cl₂ afforded the desired monoquaternised iodide salt, which was then subjected to ion metathesis with AgOTf to afford 402, isolated in 70% yield over two steps (Scheme 4.10).

The validation and optimisation of the critical fluorination step was carried out with 402. The reaction was monitored by ¹⁹F NMR spectroscopy (Table 4.3).

**Table 4.3 Optimisation of the fluorination of 402**

| No. | F Source | Equiv | Temp. [°C] | Conversion [%]
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>XeF₂</td>
<td>1</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>XeF₂</td>
<td>1</td>
<td>80</td>
<td>0*</td>
</tr>
<tr>
<td>3</td>
<td>F₂</td>
<td>2</td>
<td>-35</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>F₂</td>
<td>2</td>
<td>-35</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>F₂</td>
<td>2</td>
<td>-35</td>
<td>0*</td>
</tr>
<tr>
<td>6</td>
<td>F₂</td>
<td>2</td>
<td>-10</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>F₂</td>
<td>2</td>
<td>0</td>
<td>0*</td>
</tr>
<tr>
<td>8</td>
<td>405</td>
<td>1</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>406</td>
<td>1</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>404</td>
<td>1</td>
<td>25</td>
<td>55</td>
</tr>
<tr>
<td>11</td>
<td>404</td>
<td>1</td>
<td>-35</td>
<td>&gt; 95</td>
</tr>
</tbody>
</table>

XeF₂, F₂ and a series of commercially available N–F reagents were tested for their ability to transfer fluorine onto 402. These experiments also gave information on relative reactivity. XeF₂ and F₂ are atom economical reagents, and have the advantage to facilitate post-fluorination purification since no organic co-product is produced upon fluorine transfer. Regrettably, we found that these reagents were not suitable for the synthesis of 403. XeF₂ did not react at room temperature or at 40 °C and led to decomposition at 80 °C. Similarly, F₂ (10% in N₂) led to decomposition at 0 °C, or returned unreacted starting material at −10 °C or −35 °C. No fluorine transfer took place upon treatment of 402 with a single equivalent of Selectfluor 405 or N-fluoro-2,6-dichloropyridinium triflate 406 in acetonitrile at room temperature, suggesting that these known N–F reagents would be less reactive than 403. Pleasingly, the more reactive N-fluoro-2,3,4,5,6-pentachloropyridinium triflate 404 gave 55% of 403 when the reaction was performed at ambient temperature. Significant improvement was observed when the reaction temperature was lowered to −35 °C. Under these conditions, the pyridinium salt fully transferred F⁻ on to 402. Stability studies indicate that decomposition was taking place when a solution of 403 in acetonitrile was left at room temperature for eight hours or more. As a result, the reagent is best prepared immediately before use. Therefore, the optimized procedure for the synthesis of 403 consists of treating a solution of 402 (43 mg, 0.1 mmol, 1 equiv) in dry CH₃CN (1 mL) with a slurry of N-fluoro-2,3,4,5,6-pentachloropyridinium triflate 404 (1 equiv) in dry CH₃CN (1 mL) at −35 °C. The resulting solution is composed of the novel N–F reagent 403 and an equimolar amount of 2,3,4,5,6-pentachloropyridine.

4.3.2 Characterization of the Reagent

The relative instability and the difficulties encountered upon isolation and purification of 403 did not allow for the analysis of a single crystal by X-ray crystallography. The theoretical and experimentally measured HR-ESI spectra of 403 are in excellent agreement showing a parent peak at m/z 149.0917 and m/z 149.0918, respectively. To help characterize the N–F bond in particular, we performed 1D¹⁹F NMR and 2D¹⁹F–¹⁵N heteronuclear correlation experiments with 403 (Figure 4.8). From this, we observe a¹⁴N/¹⁵N one-bond isotope shift⁶⁴ Δδ equal to 0.27ppm. Similar experiments were performed with Selectfluor bis(tetrafluoroborate) 405 and the two chiral analogues 407 and 408; for completeness, we also performed these measurements on the N-fluoropyridiniums 404, 406, 409 and 410. All of the N–F reagents in this NMR study, as expected, do exhibit the characteristic one-bond
isotope shift (See experimental section 4.4.3 for further details). Table 4.4 assembles the $^{19}$F and $^{15}$N chemical shifts for these compounds. Nitrogen chemical shifts clearly reflect the differing hybridization states of the nitrogen in the [NF]$^{2+}$ and [NF]$^+$ compound groups, but otherwise exhibit little variation within each series. The $^{19}$F chemical shifts show a more pronounced difference for compound 403 specifically, which exhibited a very high shift of +103 ppm for the N–F group. This is well above the corresponding signals recorded for Selectfluor bis(triflate) and its derivatives, and the [NF]$^+$ reagents that typically range from 30 ppm to 50 ppm$^{15d,40}$ as considered further below.

![Figure 4.8 2D $^{19}$F-$^{15}$N HSQC of 403 (0.1 mM) in CD$_3$CN at 298K. $^{15}$N (60.8 MHz) & $^{19}$F (565.2 MHz). $^{19}$F $\Delta\delta$($^{14}$N-$^{15}$N) = 0.27 ppm.](image)

<table>
<thead>
<tr>
<th>[NF]$^{2+}$ Reagent</th>
<th>403</th>
<th>405</th>
<th>407</th>
<th>408</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{19}$F NMR (ppm)</td>
<td>+103.6</td>
<td>+48.1</td>
<td>+36.7</td>
<td>+36.0</td>
</tr>
<tr>
<td>$^{15}$N NMR (ppm)</td>
<td>+188</td>
<td>+177</td>
<td>+182</td>
<td>+183</td>
</tr>
<tr>
<td>$^1J_{FN}$ (Hz)$^a$</td>
<td>70</td>
<td>85</td>
<td>90</td>
<td>91</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>[NF]$^+$ Reagent</th>
<th>404</th>
<th>406</th>
<th>409</th>
<th>410</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{19}$F NMR (ppm)</td>
<td>+46.2</td>
<td>+30.2</td>
<td>+46.9</td>
<td>+15.9</td>
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<tr>
<td>$^{15}$N NMR (ppm)</td>
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<td>+256</td>
<td>+260</td>
<td>+259</td>
</tr>
<tr>
<td>$^1J_{FN}$ (Hz)$^a$</td>
<td>140</td>
<td>145</td>
<td>130</td>
<td>125</td>
</tr>
</tbody>
</table>

$^a$ Although not determined, the sign of these coupling constants are expected to be negative due to the negative magnetogyric ratio of $^{15}$N. The chemical shifts are relative to external NH$_3$ ($^{15}$N) and CFCl$_3$ ($^{19}$F) at 0.0 ppm.
We also measured $^{1}J_{FN}$ couplings constants to further characterise the N–F bond (Table 4.4). In the literature, experimental measurements of two-bond $^{19}\text{F}-^{15}\text{N}$ spin-spin coupling constants across N-H...F hydrogen bonds ($^{2}J_{FN}$) are available, due primarily to the work of Limbach and co-workers. These have also been reported for complexes with F-H...N and N-H...F hydrogen bonds. The directly recorded $^{1}J_{FN}$ coupling constant of 405 is in agreement with a literature precedent. To the best of our knowledge, the values of other reagents reported here are the first measurements of $^{1}J_{FN}$ coupling constants of electrophilic N–F reagents. These magnitudes principally reflect the nitrogen hybridization state in the two compound classes, increasing with greater s-character. We note that compound 403 shows the smallest $^{1}J_{FN}$ value, although the limited data set makes meaningful comparisons difficult.

4.3.3 Probing the Reactivity of the Reagent

With regard to the notably greater fluorine chemical shift of 403, previous studies have suggested that $^{19}\text{F}$ NMR shifts of N–F reagents correlate with reactivity for a series of structurally related reagents; for the dicationic [NF]$^{2+}$ type reagents, this trend would suggest that 403 is more reactive than Selectfluor and could therefore serve as a reagent to prepare Selectfluor from its monoquaternized precursor. Experimentally, we found that fluorine transfer from 403 to 411 was complete after 5 minutes at room temperature in acetonitrile (Scheme 4.11).

We probed next the ability of 403 to transfer F$^{-}$ onto substrates other than the Selectfluor precursor 411. Scheme 4.12 presents selected fluorination processes, and compare the reaction conditions and yields with data obtained from the literature for Selectfluor bis(tetrafluoroborate) 405 and when available for $N$-fluoro-2,3,4,5,6-pentachloropyridinium triflate 404. The fluorination reactions of benzene, fluorobenzene and anisole were successful and overall required shorter reaction times with 403 compared to 405. The ortho/para-ratios of the fluorinated products of anisole and fluorobenzene by 403 and 405 are similar suggesting a similar mode of reactivity. The reactivity profile of N–F reagents 403 and 404 is more similar. Styrene derivatives underwent fluorination in the presence of 403 and acetic acid giving the products of fluoroacetoxylation in good yields.
Additional experiments demonstrate that the ethylene-bridged Tröger based reagent 403 does not react with less activated alkenes, for example cyclohexene. This result defines the limitation of the novel N–F reagent 403 in term of reactivity.

A) Fluorination of aromatics

<table>
<thead>
<tr>
<th>R</th>
<th>F⁺ source</th>
<th>Temp [°C]</th>
<th>Time [h]</th>
<th>Yield [%]</th>
<th>α [%]</th>
<th>ρ [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>403a</td>
<td>40</td>
<td>6</td>
<td>85</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>404b</td>
<td>Reflux</td>
<td>2</td>
<td>48</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>405c</td>
<td>Reflux</td>
<td>20</td>
<td>83</td>
<td>—</td>
<td>—</td>
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<tr>
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B) Fluorination of styrenes

Scheme 4.12 A) Fluorination of arenes: a Arène (4 equiv), 403 (1.5 equiv), CH₂CN. b Data from reference 36c; substrate (excess), 404 (1.0 equiv) in CH₂Cl₂. c Data from reference 53; arene (2.8 equiv), 405 (1.4 equiv), TFOH (3 mL) in refluxing CH₂Cl₂. d Data from reference 36c; substrate (co-solvent), 404 (1 equiv), CH₂Cl₂. e Yields determined by ¹⁹F NMR spectroscopy using 1-fluoro-4-nitrobenzene as internal standard. B) Fluorination of styrenes: styrene (1 mmol, 1 equiv), 403 (1 equiv), CH₃COOH (0.04 M), 10 °C, 30 mins. Yields refer to product isolated after silica gel chromatography.

Having successfully synthesized and characterized reagent 403, we wanted to ascertain its potential in asymmetric fluorocarbocyclizations by comparing it with the results obtained with the chiral Selectfluor analogue as described by Gouverneur and co-workers.⁴⁰ We first tested the racemic reagent, which was prepared by an in situ fluorine transfer from N-fluoro-pentachloropyridinium triflate and validated its reactivity using the most electron-poor substrate; the 4-nitrobenzenesulfonyl protected aniline 416 (Scheme 4.13). To our delight we were able to observe excellent reactivity, delivering the desired product in excellent yield (95% via ¹⁹F NMR, using 1-fluoro-3-nitrobenzene as an internal standard).

Scheme 4.13 Fluorocarbocyclisation of 416
Having determined this new class of reagents as suitable candidates for fluorocarbocyclizations we proceeded to investigate the enantiopure variant to assess enantiocontrol. ETB was resolved into its (+)-(S,S) enantiomer (99% ee) following a literature procedure, and then this was treated with a large excess of methyl iodide in a mixture of MeOH/CH₂Cl₂ afforded the desired monoquaternized iodide salt, which was then subjected to ion metathesis with AgOTf to afford (−)-402 isolated in 70% yield over two steps. This was then treated with a single equivalent of 404 in acetonitrile at −35 °C to generate the active enantiopure reagent (Scheme 4.14).

Scheme 4.14 Synthesis of enantiopure 403.

The fluorocarbocyclization of 416 was assessed with enantiopure 403 at room as well as at the lowest possible temperature permitted by the solvent, in this case nitromethane. It must be noted that the reagent is soluble only in acetonitrile and nitromethane.

Table 4.5 Asymmetric fluorocarbocyclization mediated by (5R,11S)-403.

<table>
<thead>
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<th>Temp [°C]</th>
<th>Yield [%]b</th>
<th>ee [%]b</th>
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<tr>
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<tr>
<td>3</td>
<td>−25</td>
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<td>20</td>
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</table>

a Yield determined by 19F NMR, using 1-fluoro-3-nitrobenzene as an internal standard. b Determined by chiral phase HPLC Chiralpak IC. c Isolated after column chromatography.

With the knowledge that the fluorocarbocyclisation works the best with nitromethane or 1,4-dioxane as the solvent, we performed the fluorocarbocyclisations in nitromethane. The reaction at −25 °C yielded, the same enantiomeric excess values as when the reaction was run at room temperature suggesting that the fluorination reaction is extremely quick and that the ETB moiety is not sterically demanding enough to exercise better enantiocontrol (Table 4.5).

The fluorolactonization of double bond bearing pendant carboxylic acids was another reaction of interest. Unfortunately we were never able to obtain any fluorocyclized product
either with aromatic or aliphatic carboxylic acids. Nevertheless in the course of this study, it became apparent that 403 does not tolerate base, except for sodium hydrogen carbonate. Both caesium and sodium carbonate degrade the reagent within a few minutes at room temperature. In the case of Et$_3$N, its N-fluorination was observed.

4.4 Conclusions

In summary, the novel N–F reagent 403 derived from the ethylene-bridged Tröger base has been prepared and characterised. This reagent was found to be a competent F$^+$ source, more reactive than Selectfluor, and of similar reactivity to N-fluoropentachloropyridinium triflate. This reagent was able to fluorinate aromatics in good yields, under mild reaction conditions and short times. Furthermore, the fluoracetoxylation of styrene derivatives was accomplished with high yields under mild reaction conditions. Moreover, we present the first $^{1}$J$_{FN}$ coupling constants for eight N–F reagents inclusive of 403, a set of data serving as a new signature for the N–F bond. In the limited data set we do a correlation between the coupling constant and observed reactivity. Furthermore, utilising the C$_2$ symmetry of ETB$_i$, in a preliminary study, we have shown that 403 can be used to mediate enantoselective fluorocarbocyclizations with prochiral indene derivatives. Further optimisation of 403 is called for to improve enantiocontrol in the fluorocarbocyclization reaction, and to this extent we have explored the functionalization of ETB derivatives (Chapter 3).
4.5 Experimental

4.5.1 General

All reactions were performed in dried apparatus with magnetic stirring under an inert atmosphere of argon or nitrogen. All solvents and chemicals were used as purchased unless stated otherwise. All NMR spectra were recorded on Bruker AV400, AVIII400, AVIIIHD 500 or AVIIIHD 600 spectrometers. $^1$H and $^{13}$C NMR spectra are reported relative to external TMS as chemical shifts (δ) in parts per million (ppm). $^{15}$N shifts are referenced relative to external NH$_3$ and the $^{19}$F NMR shifts are referenced relative to external CFCl$_3$ at 0.0 ppm. $^{15}$N-$^{19}$F HMQC spectra were recorded at 600 MHz ($^{1}$H) using a N$_2$-cooled broadband Prodigy cryoprobe with the $^{1}$H channel tuned to $^{19}$F. These HMQC experiments were optimised for $^J$FN values of either 60 or 150 Hz. Coupling constants ($J$) are reported in units of hertz (Hz). The following abbreviations are used to describe multiplets: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), td (triplet of doublets), br (broad), aapd (apparent doublet), apt (apparent triplet). High-resolution mass spectra (HRMS, m/z) were recorded on a Bruker MicroTOF spectrometer using positive electrospray ionization (ESI) or on a Waters GC-TOF spectrometer using electron impact (EI). Infrared spectra were recorded as neat compounds using a Bruker Tensor 27 FT-IR spectrometer. Absorptions are reported in wavenumbers (cm$^{-1}$) and only peaks of interest are reported. Melting points of solids were measured on a Griffin apparatus and are uncorrected. IUPAC names were generated using ChemDraw Professional 15.0. All solvents were dried on a column of alumina prior to use. Thin layer chromatography (TLC) was performed using Merck aluminium-foil baked plates coated with Kieselgel 60 F245. The products were visualized using UV fluorescence (254 nm) or potassium permanganate stain. Flash column chromatography was performed over Merck silica gel C60 (40-60 μm) using eluent systems as described for each experiment.
4.5.2 Synthesis

Compounds 401, 404, 407 and 408 were prepared according to published methods while 405, 406, 409 and 410 were bought from Sigma-Aldrich.

Synthesis of 402

Following a modified literature procedure, rac-2,8-Dimethyl-6,12-dihydro-5,11-ethanodibenzo[b,f][1,5]diazocine, ethano-Tröger’s base, 401 (5 g, 18.9 mmol) was stirred with CH$_3$I (14.7 g, 189.0 mmol, 10 equiv) in methylene chloride (20 mL) and methanol (60 mL) for 24 hours at 25 °C. The solvents were removed under reduced pressure and the sticky residue was scratched with $n$-pentane (100 mL) until an off-white solid was formed. The solid was filtered-off and rinsed with acetone (50 mL × 3) to get rid off the unreacted 401. The solvents were removed under reduced pressure to give a free flowing powder of 2,5,8-trimethyl-5,12-dihydro-6H-5,11-ethanodibenzo[b,f][1,5]diazocin-5-ium iodide (5.45 g, 71%, 13.4 mmol) that was suspended in acetone (100 mL) and then treated in the dark with AgOTf (3.44 g, 13.4 mmol, 1.0 equiv) and stirred overnight. The silver iodide was filtered-off over a celite plug, and the filtrate was evaporated under reduced pressure to yield a sticky solid that was re-dissolved in acetonitrile and then evaporated to yield a stick solid that was scratched with $n$-pentane (100 mL) until an off-white solid formed which was filtered-off, finely powdered and then dried under high-vacuum overnight to yield rac-2,5,8-trimethyl-5,12-dihydro-6H-5,11-ethanodibenzo[b,f][1,5]diazocin-5-ium trifluoromethanesulfonate 402 as an off-white powder (5.67 g, 99%).

$^1$H NMR (500 MHz, CD$_3$CN): δ [ppm] = 2.15 (s, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$), 3.68 (dd, $J = 15.8$, 5.1 Hz, 1H, NCH$_2$CH$_2$N), 3.78 (td, $J = 14.9$, 12.8, 5.3 Hz, 1H, NCH$_2$CH$_2$N), 3.84 (s, 3H, NCH$_3$), 4.17 (dd, $J = 14.1$, 5.5 Hz, 1H, NCH$_2$CH$_2$N), 4.50 (d, $J = 17.5$ Hz, 1H, endo-CH$_2$N), 4.59 (td, $J = 13.3$, 12.8, 5.5 Hz, 1H, exo-CH$_2$N), 4.68 (d, $J = 15.6$ Hz, 1H, endo-CH$_3$NMe), 4.78 (d, $J = 17.5$ Hz, 1H, exo-CH$_2$N), 5.45 (d, $J = 15.5$ Hz, 1H, exo-CH$_3$NMe), 6.79 (s, 1H, Ar-H), 6.97 (s, 1H, Ar-H), 7.05 (s, 2H, Ar-H), 7.17 (d, $J = 8.7$ Hz, 1H Ar-H), 7.62 (d, $J = 8.7$ Hz, 1H Ar-H); $^{13}$C NMR (125 MHz, CD$_3$CN): δ [ppm] = 20.4, 20.6, 49.6, 59.7, 60.3, 69.8, 71.2, 122.4, 128.2, 128.9, 130.4, 131.0, 131.8, 132.6, 134.9, 136.5, 141.9, 142.4, 146.3; $^{19}$F NMR (125 MHz, CD$_3$CN): δ [ppm] = -79.3; MP = 152 °C
An Ethano-Tröger’s Base Derived Electrophilic Fluorinating Reagent

Synthesis of 403

In a dry vial fitted with a stirring bar and rubber septum under nitrogen, 402 (42.8 mg, 1.0 mmol) was dissolved in dry CD$_3$CN (1.0 mL) and then cooled to -35 °C. To this was added a cooled (0-5 °C) slurry of 2,3,4,5,6-pentachloro-1-fluoropyridin-1-ium trifluoromethanesulfonate 404 (44.0 mg, 1.05 mmol, 1.05 equiv) in dry CD$_3$CN (1.0 mL) keeping the reaction temperature below -35 °C. The reaction was allowed to reach room temperature over 15 minutes and then the clear pale yellow solution containing rac-5-fluoro-2,8,11-trimethyl-5,6,11,12-tetrahydro-5,11-ethanodibenzo[b,f][1,5]diazocine-5,11-diium trifluoromethanesulfonate was utilized in reactions or for $^1$H, $^{13}$C, $^{15}$N and $^{19}$F NMR and high-resolution mass spectrometry analyses.

$^1$H NMR (500 MHz, CD$_3$CN): δ [ppm] = 2.27 (s, 3H, CH$_3$), 2.31 (s, 3H, CH$_3$), 4.10 (s, 3H, NCH$_3$), 4.74 (appd, $J = 15.7$ Hz, 1H, FNC$_2$H$_2$NMe), 4.94 (m, 1H, FNC$_2$H$_2$NMe), 5.13 (d, $J = 16.0$ Hz, 1H, endo-CH$_2$NMe), 5.45 (m, 2H, FNC$_2$H$_2$NMe), 5.69 (d, $J = 16.0$ Hz, 1H, exo-CH$_2$NMe), 5.81 (appdd, $J = 17.6$, 15.1 Hz, 1H, endo-CH$_2$NF), 6.44 (d, $J = 14.5$ Hz, 1H, exo-CH$_2$NF), 7.15 (s, 1H, Ar-H), 7.16 (s, 1H, Ar-H), 7.46 (d, $J = 8.7$ Hz, 1H, Ar-H), 7.53 (d, $J = 8.7$ Hz, 1H, Ar-H), 7.80 (d, $J = 8.7$ Hz, 1H, Ar-H), 7.89 (d, $J = 8.7$ Hz, 1H, Ar-H); $^{13}$C NMR (100 MHz, CD$_3$CN): δ [ppm] = 20.5, 21.0, 59.9, 60.05 (d, $J = 8.6$ Hz), 65.7 (d, $J = 18.2$ Hz), 70.9, 75.4 (d, $J = 23.0$ Hz), 121.5 (d, $J = 12.2$ Hz), 122.6 (d, $J = 6.5$ Hz), 123.3, 123.4, 132.9, 133.79, 133.87, 134.3, 139.5 (d, $J = 18.7$ Hz), 140.6, 143.9, 146.7; $^{19}$F NMR (377 MHz, CD$_3$CN): δ [ppm] = +103.6 (N–F), -79.3 (OTf); HRMS (ESI); m/z [M-2OTf]$^+$ calcld. for C$_{19}$H$_{17}$FN$_2$: 149.0917; found: 149.0917.

Fluorination of aromatics

General Procedure

Following a literature protocol, to a solution of the aromatic compound (0.4 mmol) as a co-solvent in acetonitrile (1.0 mL) was added a stock solution of the fluorinating reagent 403 (2mL, 0.15 mmol, 1.5 equiv) at 0°C and then run at the indicated temperature and time after which (0.1 mmol, 0.1 equiv, 0.2 mL) of a stock solution of 1-fluoro-4-nitrobenzene (143.1 mg) in CD$_3$CN (2.0 mL) was added. The crude reaction (0.4 mL) was diluted with 0.2 mL CD$_3$CN and was analyzed via $^{19}$F NMR (using 1-Fluoro-4-nitrobenzene as an internal standard) and high-resolution GCMS.
Fluoroanisole

Fluoroanisole Deviating from the general procedure 403 (1.0 equiv) was used and the reaction was run at 0 °C for 1 hour.

$^{19}$F NMR (377 MHz, CH$_3$CN/CD$_3$CN): $\delta$ [ppm] = -137.4 (55%) [o-fluoroanisole (lit. 136.3 in CDCl$_3$]$^{68}$], -126.3 (30%) [p-fluoroanisole (lit. 125.1 in CDCl$_3$]$^{68}$]; HRMS (EI); m/z [M]$^+$ calcd. for C$_7$H$_7$FO: 126.0481; found: 126.0480.

Fluorobenzene

Following the general procedure, the reaction was run at 40 °C for 6 hours.

$^{19}$F NMR (377 MHz, CH$_3$CN/CD$_3$CN): $\delta$ [ppm] = -114.8 ppm (85%) [monofluorobenzene (lit. -113.7 in CDCl$_3$]$^{68}$ Authentic sample from Sigma-Aldrich -114.8 ppm in CD$_3$CN]; HRMS (EI); m/z [M]$^+$ calcd. for C$_6$H$_5$F: 96.0375 found: 96.0401.

Difluorobenzene

Following the general procedure, the reaction was run at 40 °C for 6 hours.

$^{19}$F NMR (377 MHz, CH$_3$CN/CD$_3$CN): $\delta$ [ppm] = -140.7 ppm (29%) [1,2-difluorobenzene (lit. -139.2 in CDCl$_3$]$^{68}$], -121.1 (60%) [1,4-difluorobenzene (lit. -120.3 in CDCl$_3$]$^4$]; HRMS (EI); m/z [M]$^+$ calcd. for C$_6$H$_4$F$_2$: 114.0281 found: 114.0306.

Fluoro-acetoxylation of styrene derivatives

Synthesis of 412 A dry 50 mL flask was charged with 402 (428.5mg, 1.0 mmol) and dry acetonitrile (8.0 mL) and stirred at −35 °C. To this was added 404 (419.4mg, 1.0 mmol, 1.0 equiv) in dry acetonitrile (8.0 mL) and stirred at −35 °C for 10 minutes under argon. The turbid suspension was then allowed to reach 0 °C and upon doing so the suspension turned into a clear pale yellow solution which was then added over 15 minutes into a solution of styrene (104 mg, 1.0 mmol, 1.0 equiv) in glacial acetic acid (40 mL) at 10 °C. The reaction was stirred at 10 °C for 30 minutes and then quenched into a saturated solution of sodium bicarbonate, extracted with diethyl ether (75 mL × 3). The organic phase was rinsed with water (30 mL × 2) and then with brine (30 mL) before being dried over MgSO$_4$. The compound was purified via column chromatography (silica gel (20g), diethyl
ether/pentane (1:10)] to yield 2-fluoro-1-phenylethyl acetate 412 (141 mg, 77%) as a clear oil. The spectral data (1H and 19F) match a literature precedent.36c

\[\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\): } & \delta [ppm] = 2.14 (s, 3H, OCH}_3), 4.58 (dm, J = 48.0 Hz, 2H, CH}_2F), 4.73 (ddd, J = 16.5, 7.5, 3.4 Hz, 1H, CHOAc), 7.37 (m, 5H, Ar-H); \\
\text{13C NMR (100 MHz, CDCl}_3\): } & \delta [ppm] = 21.1, 74.1 (d, J = 20 Hz), 84.2 (d, J = 179 Hz), 126.9, 128.79, 128.85, 135.4 (d, J = 20 Hz), 170.1; \\
\text{19F NMR (377 MHz, CDCl}_3\): } & \delta [ppm] = -223.8 (td, J = 48.0, 16.5 Hz); \\
\text{IR (ATR, neat): } & \nu [cm^{-1}] = 1736 (C=O); \\
\text{MS (ESI): } & m/z [M+Na]^+ \text{ calcd. for C}_{10}H_{11}FO_2Na: 205.06; \text{ found: 205.1.}
\end{align*}\]

Synthesis of 413

A dry 50 mL flask was charged with 402 (428.5 mg, 1.0 mmol) and dry acetonitrile (8.0 mL) and stirred at −35 °C. To this was added 404 (419.4 mg, 1.0 mmol, 1.0 equiv) in dry acetonitrile (8.0 mL) and stirred at −35 °C for 10 minutes under argon. The turbid suspension was then allowed to reach 0 °C and upon doing so the suspension turned into a clear pale yellow solution which was then added over 15 minutes into a solution of 4-methylstyrene (118.1 mg, 1.0 mmol, 1.0 equiv) in glacial acetic acid (40 mL) at 10 °C. The reaction was stirred at 10 °C for 30 minutes and then quenched into a saturated solution of sodium bicarbonate, extracted with diethyl ether (75 mL × 3). The organic phase was rinsed with water (30 mL × 2) and then with brine (30 mL) before being dried over MgSO4. The compound was purified via column chromatography [silica gel (20g), diethyl ether/pentane (1:10)] to yield 2-fluoro-1-(p-tolyl)ethyl acetate 413 (159 mg, 81%) as a clear oil.

\[\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\): } & \delta [ppm] = 2.10 (s, 3H, OCH}_3), 2.32 (s, 3H, CH}_3), 4.52 (dm, J = 47.3 Hz, 2H, CH}_2F)), 5.98 (ddd, J = 16.0, 7.6, 3.4 Hz, 1H, CHOAc), 7.15 (d, J = 8.0 Hz, 2H, Ar-H), 7.22 (d, J = 8.0 Hz, 2H, Ar-H); \\
\text{13C NMR (100 MHz, CDCl}_3\): } & \delta [ppm] = 21.2, 21.3, 74.1 (d, J = 20.0 Hz), 84.3 (d, J = 179.1 Hz), 126.9, 129.5, 132.5 (d, J = 7.0 Hz), 138.8, 170.1; \\
\text{19F NMR (376 MHz, CDCl}_3\): } & \delta [ppm] = -223.47 (td, J = 47.3, 16.0 Hz); \\
\text{IR (ATR, neat): } & \nu [cm^{-1}] = 1742 (C=O). \\
\text{HRMS (ESI): } & m/z [M+Na]^+ \text{ calcd. for C}_{11}H_{13}FNaO_2: 219.0791; \text{ found: 219.0793.}
\end{align*}\]

Synthesis of 414

A dry 50 mL flask was charged with 402 (428.5 mg, 1.0 mmol) and dry acetonitrile (8.0 mL) and stirred at −35 °C. To this was added 404 (419.4 mg, 1.0 mmol, 1.0 equiv) in dry acetonitrile (8.0 mL) and stirred at −35 °C for 10 minutes under argon. The turbid suspension was then allowed to reach 0 °C and upon doing so the suspension turned into a clear pale yellow solution which was then added over 15 minutes into a solution of 4-bromostyrene (183.1 mg, 1.0 mmol, 1.0 equiv) in glacial acetic acid (40 mL) at 10 °C. The reaction was stirred at 10 °C for 30 minutes and then quenched into a saturated solution of sodium bicarbonate, extracted with diethyl ether (75 mL × 3). The organic phase was rinsed with water (30 mL × 2) and then with brine (30 mL) before being dried over MgSO4. The compound was purified via column chromatography [silica gel (20g), diethyl ether/pentane (1:10)] to yield 2-fluoro-1-(p-tolyl)ethyl acetate 413 (159 mg, 81%) as a clear oil.

\[\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\): } & \delta [ppm] = 2.10 (s, 3H, OCH}_3), 2.32 (s, 3H, CH}_3), 4.52 (dm, J = 47.3 Hz, 2H, CH}_2F)), 5.98 (ddd, J = 16.0, 7.6, 3.4 Hz, 1H, CHOAc), 7.15 (d, J = 8.0 Hz, 2H, Ar-H), 7.22 (d, J = 8.0 Hz, 2H, Ar-H); \\
\text{13C NMR (100 MHz, CDCl}_3\): } & \delta [ppm] = 21.2, 21.3, 74.1 (d, J = 20.0 Hz), 84.3 (d, J = 179.1 Hz), 126.9, 129.5, 132.5 (d, J = 7.0 Hz), 138.8, 170.1; \\
\text{19F NMR (376 MHz, CDCl}_3\): } & \delta [ppm] = -223.47 (td, J = 47.3, 16.0 Hz); \\
\text{IR (ATR, neat): } & \nu [cm^{-1}] = 1742 (C=O). \\
\text{HRMS (ESI): } & m/z [M+Na]^+ \text{ calcd. for C}_{11}H_{13}FNaO_2: 219.0791; \text{ found: 219.0793.}
\end{align*}\]
acid (40 mL) at 10 °C. The reaction was stirred at 10 °C for 30 minutes and then quenched into a saturated solution of sodium bicarbonate, extracted with diethyl ether (75 mL × 3). The organic phase was rinsed with water (30 mL × 2) and then with brine (30 mL) before being dried over MgSO₄. The compound was purified via column chromatography [silica gel (15g), diethyl ether/pentane (1:10)] to yield 1-(4-bromophenyl)-2-fluoroethyl acetate 414 (196mg, 75%) as a clear oil.

¹H NMR (400 MHz, CDCl₃): δ [ppm] = 2.10 (s, 3H, OCH₃), 4.51 (dm, J = 47 Hz, 2H, CH₂F), 5.92 (ddd, J = 16.9, 6.9, 3.7 Hz, 1H, CHOAc), 7.20 (m, 2H, Ar-H), 7.47 (m, 2H, Ar-H); ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 21.1, 73.5 (d, J = 20.0 Hz), 83.8 (d, J = 179.0 Hz), 123.0, 128.7, 132.1, 134.6 (d, J = 6.5 Hz), 170.1; ¹⁹F NMR (377 MHz CDCl₃): δ [ppm] = -224.9 (td, J = 47.1, 16.9 Hz).

IR (ATR, neat): ν [cm⁻¹] = 1738 (C=O); HRMS (ESI): m/z [M+Na]+ calcd. for C₁₉H₁₆BrFNaO₂: 282.97404; found: 282.97416.

Synthesis of 415

A dry 50 mL flask was charged with 402 (428.5mg, 1.0 mmol) and dry acetonitrile (8.0 mL) and stirred at -35 °C. To this was added 404 (419.4mg, 1.0 mmol, 1.0 equiv) in dry acetonitrile (8.0 mL) and stirred at -35 °C for 10 minutes under argon. The turbid suspension was then allowed to reach 0 °C and upon doing so the suspension turned into a clear pale yellow solution which was then added over 15 minutes into a solution of 2-chlorostyrene (138.6 mg, 1.0 mmol, 1.0 equiv) in glacial acetic acid (40 mL) at 10 °C. The reaction was stirred at 10 °C for 30 minutes and then quenched into a saturated solution of sodium bicarbonate, extracted with diethyl ether (75 mL × 3). The organic phase was rinsed with water (30 mL × 2) and then with brine (30 mL) before being dried over MgSO₄. The compound was purified via column chromatography [silica gel (20g), diethyl ether/pentane (1:10)] to yield 1-(2-chlorophenyl)-2-fluoroethyl acetate 415 (100 mg, 46%) as a clear oil.

¹H NMR (400 MHz, CDCl₃): δ [ppm] = 2.11 (s, 3H, OCH₃), 4.52 (m, 2H, CH₂F), 6.35 (ddd, J = 18.6, 6.8, 2.8 Hz, 1H, CHOAc), 7.21 (m, 2H, Ar-H), 7.31 (m, 1H, Ar-H), 7.37 (m, 1H, Ar-H).

¹³C NMR (100 MHz CDCl₃): δ [ppm] = 21.1, 71.3 (d, J = 19.9 Hz), 82.9 (d, J = 179.6 Hz), 127.2, 128.1, 129.8, 132.4, 133.2 (d, J = 6.5 Hz), 169.80; ¹⁹F NMR (377 MHz CDCl₃): δ [ppm] = -224.27 (td, J = 47.0, 18.6 Hz); IR (ATR, neat): ν [cm⁻¹] = 1743 (C=O); HRMS (ESI): m/z [M+Na]+ calcd. for C₁₉H₁₆ClFNaO₂: 239.0245; found: 239.0247.
Synthesis of 417

A dry 10 mL vial was charged with 402 (102.8 mg, 0.24 mmol, 1.2 equiv) and dry nitromethane (2 mL) and stirred at -30 °C. To this was added 404 (100.6 mg, 0.24 mmol, 1.2 equiv) in dry nitromethane (3 mL) and stirred at -30 °C for 10 minutes under argon. The turbid suspension was then allowed to reach 0-5 °C and upon doing so the suspension turned into a clear pale yellow solution.

35⁴⁰ (95 mg, 0.2 mmol, 1.0 equiv) was dissolved in nitromethane (2.0 mL) in a 20 mL screw-top vial and a few activated 3Å molecular sieves. The solution was left for 3 hours before NaHCO₃ (50 mg, 0.6 mmol, 3.0 equiv) was added and the reaction was cooled to -25 °C. To this solution was added fluorinating reagent (5 mL, 1.2 equiv, 0.24 mmol) at 0°C was added dropwise over 10 minutes keeping the reaction temperature a -25 °C.

The reaction was stirred at -25 °C 60 minutes before being filtered through a pipette of celite and eluted with ethyl acetate. The filtrate was concentrated in vacuo and purified directly by column chromatography [silica gel, EtOAc/PetEther (1/10)] to yield 6a-fluoro-2-isopropyl-7,7-dimethyl-5-tosyl-6,6a,7,11b-tetrahydro-5H-indeno[2,1-c]quinoline 417 as an oil. The analytics match reference 40.

¹H NMR (400 MHz, CDCl₃): δ = 1.27 (d, J = 6.2 Hz, 3H), 1.28 (d, J = 6.2 Hz, 3H), 1.34 (d, J = 3.3 Hz, 3H), 1.37 (s, 3H), 2.36 (s, 3H), 2.92 (sept, J = 6.2 Hz, 1H), 3.23 (dd, J = 37.5 Hz, J = 14.9 Hz, 1H), 4.31 (d, J = 15.4 Hz, 1H), 4.77 (ddd, J = 14.9 Hz, J = 10.5 Hz, J = 1.4 Hz, 1H), 7.06-7.28 (m, 8H), 7.66 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.6 Hz, 1H); ¹³C NMR (100.6 MHz, CDCl₃): δ = 20.8, 21.6, 24.0, 24.1, 24.4 (d, J = 9.2 Hz), 33.4, 46.7 (d, J = 20.6 Hz), 47.6 (d, J = 22.2 Hz), 47.9 (d, J = 20.6 Hz), 100.9 (d, J = 199.5 Hz), 121.8, 122.3, 124.0, 125.5, 126.4, 127.2, 127.7 (d, J = 2.6 Hz), 128.1, 128.1, 129.1, 133.0, 136.9, 139.4 (d, J = 8.7 Hz), 143.3, 144.9, 147.7 (d, J = 4.4 Hz);

¹⁹F NMR (376.6 MHz, CDCl₃): δ = -170.4 (m, 1F); HPLC Chiralpak IA, 95/5 hexanes/isopropanol, 1 mL/min, 13.8 min + 15.9 min, sample dissolved in EtOAc/hexane 1:9. 

Trace of 417 on a Chiralpak IA, 95/5 hexanes/isopropanol, 1 mL/min, 13.8 min + 15.9 min, sample dissolved in EtOAc/hexane 1:9.
An Ethano-Tröger’s Base Derived Electrophilic Fluorinating Reagent

HPLC trace of 417 after column chromatography

4.5.3 $^{14}$N/$^{15}$N One-Bond Isotope Shift [$^{19}$F $^\Delta\delta^{^{14}N-^{15}N}$]

<table>
<thead>
<tr>
<th>No</th>
<th>Compound</th>
<th>$^{19}$F $^\Delta\delta^{^{14}N-^{15}N}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>403</td>
<td>0.27 ppm</td>
</tr>
<tr>
<td>2</td>
<td>405</td>
<td>0.21 ppm</td>
</tr>
<tr>
<td>3</td>
<td>407</td>
<td>0.20 ppm</td>
</tr>
<tr>
<td>4</td>
<td>408</td>
<td>0.20 ppm</td>
</tr>
<tr>
<td>5</td>
<td>404</td>
<td>0.18 ppm</td>
</tr>
<tr>
<td>6</td>
<td>406</td>
<td>0.12 ppm</td>
</tr>
<tr>
<td>7</td>
<td>409</td>
<td>0.19 ppm</td>
</tr>
<tr>
<td>8</td>
<td>410</td>
<td>0.18 ppm</td>
</tr>
</tbody>
</table>

Conditions: $^{15}$N-$^{19}$F HMQC [$^{15}$N (60.8 MHz) & $^{19}$F (565.2 MHz) CD3CN, 298K]
4.5.4 NMR Spectra

$^1$H NMR (500 MHz, CD$_3$CN, 298K) of 403

![NMR Spectrum 1H](image)

$^{19}$F NMR (377 MHz, CD$_3$CN, 298K) of 403

![NMR Spectrum 19F](image)
An Ethano-Tröger’s Base Derived Electrophilic Fluorinating Reagent

$^1$H–$^1$H COSY (500 MHz, CD$_3$CN, 298K) of 403

Note: Since 3 was generated in situ; there are three residual peaks of pentachloropyridine in the $^{13}$C NMR (100 MHz, CD$_3$CN, 298K) spectrum (see below for a comparison).
**15N-19F HMQC Spectra**

All 2D 15N-19F HMQC spectra were recorded in the presence of 19F decoupling (the use of HMQC over HSQC was favoured as this avoids potential signal loss through the use of inversion pulses on 19F). In the figures below these are shown in trace (a) with the conventional 1H-coupled 19F spectra shown above. 1D versions of the 15N-19F HMQC experiment were also collected in the absence of 19F decoupling to enable measurement of the one-bond 19F-15N coupling constants (1JFN) with high resolution. Traces (b) show the 2D HMQC again but with the corresponding 1D HMQC spectrum shown above, thus revealing the reported 1JFN doublets and subject to the one-bond isotope shifts defined above.
An Ethano-Tröger’s Base Derived Electrophilic Fluorinating Reagent

$^{15}$N-$^{19}$F HMQC [$^{15}$N (60.8 MHz) & $^{19}$F (565.2 MHz) CD$_3$CN, 298K] of 403

a) Without showing the splitting of the $^{19}$F peak by $^{15}$N

![Graph](image)

b) Showing the splitting of the $^{19}$F peak by $^{15}$N

![Graph](image)
$^{15}\text{N}$-$^{19}\text{F}$ HMQC ($^{15}\text{N}$ (60.8 MHz) & $^{19}\text{F}$ (565.2 MHz) CD$_3$CN, 298K) of 405

a) Without showing the splitting of the $^{19}\text{F}$ peak by $^{15}\text{N}$

b) Showing the splitting of the $^{19}\text{F}$ peak by $^{15}\text{N}$
An Ethano-Tröger’s Base Derived Electrophilic Fluorinating Reagent

$^{15}\text{N}-^{19}\text{F}$ HMQC [$^{15}\text{N}$ (60.8 MHz) & $^{19}\text{F}$ (565.2 MHz) CD$_3$CN, 298 K] of 407

a) Without showing the splitting of the $^{19}\text{F}$ peak by $^{15}\text{N}$

b) Showing the splitting of the $^{19}\text{F}$ peak by $^{15}\text{N}$
$^{15}\text{N}$-$^{19}\text{F}$ HMQC [$^{15}\text{N}$ (60.8 MHz) & $^{19}\text{F}$ (565.2 MHz) CD$_3$CN, 298K] of 408

a) Without showing the splitting of the $^{19}\text{F}$ peak by $^{15}\text{N}$

b) Showing the splitting of the $^{19}\text{F}$ peak by $^{15}\text{N}$
$^{15}$N-$^{19}$F HMQC [$^{15}$N (60.8 MHz) & $^{19}$F (565.2 MHz) CD$_3$CN, 298K] of 404

a) Without showing the splitting of the $^{19}$F peak by $^{15}$N

b) Showing the splitting of the $^{19}$F peak by $^{15}$N
$^{15}\text{N}-^{19}\text{F} \text{ HMQC} [^{15}\text{N} \text{ (60.8 MHz)} \& \text{ } ^{19}\text{F} \text{ (565.2 MHz)} \text{ CD$_3$CN, 298K}] \text{ of 406}$

a) Without showing the splitting of the $^{19}\text{F}$ peak by $^{15}\text{N}$

b) Showing the splitting of the $^{19}\text{F}$ peak by $^{15}\text{N}$
\[ ^{15}\text{N} - ^{19}\text{F} \text{ HMQC} \left[ ^{15}\text{N} (60.8 \text{ MHz}) \& ^{19}\text{F} (565.2 \text{ MHz}) \right] \text{ CD}_3\text{CN, 298K} \] of 409

a) Without showing the splitting of the \(^{19}\text{F} \) peak by \(^{15}\text{N} \)

b) Showing the splitting of the \(^{19}\text{F} \) peak by \(^{15}\text{N} \)
$^{15}\text{N}-^{19}\text{F}$ HMQC [${}^{15}\text{N}$ (60.8 MHz) & ${}^{19}\text{F}$ (565.2 MHz) CD$_3$CN, 298K] of 410

a) Without showing the splitting of the $^{19}\text{F}$ peak by $^{15}\text{N}$

b) Showing the splitting of the $^{19}\text{F}$ peak by $^{15}\text{N}$
4.6 References

(13) Hutchinson, J.; Sandford, G. In Organofluorine Chemistry; Chambers, R., Ed.; Springer Berlin Heidelberg, 1997; Vol. 193.
Chapter 5: Conclusions and Outlook

Over the course of this thesis I have utilized the Tröger’s base (TB) as a scaffold for phosphorous ligands, developed a method to oxidatively functionalize TB derivatives, and synthesized an electrophilic fluorinating reagent based on the ethylene bridge Tröger’s base analogue.

We have developed a modular two-step synthetic route to novel TB derived C$_2$-symmetric bis(phosphane) ligands. The studies showed that position of the phosphorus moiety significantly affects the catalytic activity, with the ligands bearing the phosphane para to the nitrogen atom being more active.

We have shown that these ligands form a versatile catalytic system with Pd(OAc)$_2$ for Suzuki–Miyaura cross-coupling and Buchwald–Hartwig amination reactions of aryl bromides and chlorides. In the course of developing phosphane ligands based on a Tröger’s base scaffold, we were interested in synthesising phosphanes based on the ethylene-bridged variant.

A literature survey showed that there were no methods available to functionalize the ethylene-bridge Tröger’s base analogue (ETB), and in the course of attempting to brominate the ortho positions of the ETB we have discovered a mild procedure for the α-oxygenation and α-nitrogenation of tertiary diamines via an NBS-mediated oxidation. The reaction was carried out under mild conditions using NBS as oxidant along with Pd(OAc)$_2$ as catalyst.

Furthermore, we successfully extended this procedure to Tröger’s base analogues where we could acetoxylate as well as azidate the benzylic positions.
We have successfully expanded the reaction scope of the KMnO₄ mediated oxidation developed by Wärnmark to ETB derivatives.

Crystallography studies showed that these ETB derived bis-amides belonged to a rare class of twisted amides, with twist angle ($\tau$) values of 29°.

Continuing with our studies on ETB, a novel electrophilic N–F reagent derived from the ethylene-bridged Tröger base has bee prepared and characterized.

This reagent was found to be a competent F⁺ source, more reactive than Selectfluor, and of similar reactivity to N-fluoropentachloropyridinium triflate. This reagent was able to fluorinate aromatics in good yields, under mild reaction conditions and short times. Furthermore, the fluoracetoxylation of styrene derivatives was accomplished with high yields under mild reaction conditions. Finally, a brief study showed that an enantiopure fluorinating reagent derived from ETB was able to fluorocarbocyclize an indene derivative bearing a pendant carbon nucleophile, albeit the enantioselectivity was only modest.
In the future, the one promising avenue would be to introduce functional handles next to the nitrogen atoms of ETB so as to assert steric control in the fluorocarbocyclizaton reactions. Additionally, utilizing the high reactivity of this fluorinating reagent in late stage fluorinations is another potential avenue to explore.

The synthesis of the ethylene bridged Tröger’s base derived ortho phosphane has remained elusive. Building on the synthesis of the ortho fluorinated ETB, the synthesis of the brominated derivative should be explored. Alternatively routes to activate the torpid C–F bond does present an exciting challenge.

The exact roles of NBS and palladium in the NBS-Pd(OAc)$_2$ mediated oxygenation and nitrogenation of TB and ETB derivatives needs to be studied further so as to get a clearer understanding of the reaction, thereby allowing use to expand the scope of this transformation.

Also, exploring strategies to activate the carbonyl moiety of the ETB derived twisted amides would be an interesting avenue to explore. More specifically, building on the titanium mediated olefination to initially access the bis-olefin and then to generate ETB derivatives with substituents that could allow us to access the inside of the diazocine cavity.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>Ac</td>
<td>Acyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyl carbamaate</td>
</tr>
<tr>
<td>BSA</td>
<td>Bis(trimethylsilyl)acetamide</td>
</tr>
<tr>
<td>Calcd</td>
<td>Calculated</td>
</tr>
<tr>
<td>cod</td>
<td>Cyclooctadiene</td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>DAST</td>
<td>N,N-diethylaminosulfur trifluoride</td>
</tr>
<tr>
<td>Dbu</td>
<td>Dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicycloundec-7-ene</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-Dichloroethane</td>
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<tr>
<td>DCM</td>
<td>Dichloromethane</td>
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<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-1,4-benzoquinone</td>
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<tr>
<td>DFT</td>
<td>Density functional theory</td>
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<tr>
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<td>N,N'-dimethylformamide</td>
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<tr>
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<td>Deoxyribonucleic acid</td>
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<tr>
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<td>Electron ionisation</td>
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<td>Electrospray ionisation</td>
</tr>
<tr>
<td>equiv</td>
<td>Equivalents</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>ETB</td>
<td>Ethylene-bridged Tröger's base</td>
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<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>GC</td>
<td>Gas chromatography</td>
</tr>
<tr>
<td>HFIP</td>
<td>Hexafluoroisopropanol</td>
</tr>
<tr>
<td>HPLC</td>
<td>High-performance liquid chromatography</td>
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<tr>
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<td>High-resolution mass spectrometry</td>
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<td>iBu</td>
<td>Isobutyl</td>
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<tr>
<td>iPr</td>
<td>Isopropyl</td>
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<tr>
<td>IR</td>
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<tr>
<td>LHMDS</td>
<td>Lithium bis(trimethylsilyl)amide</td>
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<tr>
<td>MP</td>
<td>Melting point</td>
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<tr>
<td>MALDI</td>
<td>Matrix-assisted LASER desorption ionisation</td>
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<tr>
<td>Abbreviation</td>
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<tr>
<td>Me</td>
<td>Methyl</td>
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<tr>
<td>MeCN</td>
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<td>Methanesulphonic acid</td>
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<td>NBS</td>
<td>N-bromosuccinimide</td>
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<tr>
<td>nBuLi</td>
<td>n-Butyl lithium</td>
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<tr>
<td>NMR</td>
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<tr>
<td>NFSI</td>
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<tr>
<td>ORTEP</td>
<td>Oak ridge thermal ellipsoid plot</td>
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<tr>
<td>OTf</td>
<td>Triflate, trifluoromethanesulfonate</td>
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<td>Selectfluor</td>
<td>1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2] octan bis (tetra fluoroborate)</td>
</tr>
<tr>
<td>SET</td>
<td>Single electron transfer</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
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<tr>
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<td>Tröger’s base</td>
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<td>tert-Butyl</td>
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<td>Tetrahydrofuran</td>
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<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
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<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
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