Towards Novel Atropisomeric Triazole-Containing Organocatalysts

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UNIVERSITY OF BIRMINGHAM

A thesis submitted to

The University of Birmingham

for the degree of

DOCTOR OF PHILOSOPHY

School of Chemistry

College of Engineering and Physical Sciences

University of Birmingham

May 2021

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Acknowledgement

Whilst many people are to be thanked for having accompanied and supported me during this journey, firstly, I would like to express my gratitude to my supervisor, Prof. John Fossey, for having welcomed me in his group and having always been supportive throughout these years. Having allowed me to pursue my own ideas, he has given me the chance to push the boundaries of my knowledge, and, with his positive attitude, he has greatly helped me build my confidence as a scientist. I would also like to thank Dr Ben Buckley (University of Loughborough), my second supervisor, for the useful suggestions provided during our meetings, and Dr Andrew Leach (University of Manchester) for all the computational data provided.

Thanks also to all the members of the Fossey and the Davies group I have had the pleasure to meet and/or work with; I will always cherish the fun times we have shared over these past (and rather unlucky one might say) years. In particular, I would like to thank Huy, which has always been a reference for me, Yiming, for all the enthusiastic discussions about chemistry, Joe for having shared interminable days in the lab with me, and Alex, for having always had a hug ready when needed. A big thanks goes also to George (you really are a legend!), Will, and Harry for having helped proofread this thesis, along with Yiming and Joe.

I am also truly thankful to the analytical facility, in particular to Dr Cécile Le Duff for all the help with the NMR and the nice chats (and coffees!) I have enjoyed in her office, Dr Christopher Williams for the unbelievable number of mass spectra he has run for me over just a few months, Dr Allen Bowen for all the help with the GC and HPLC, and Dr Louise Male for having run the XRD for me.

Lastly, I would like to thank my partner Giorgio, my family and friends for their unconditional love and support. While I will never find the right words to express my gratitude, I know that without you this would have been much harder.

Abstract

Atropisomerism is a type of axial chirality displayed by compounds whose rotation is restricted about an axis. Atropisomeric compounds have shown unique properties in many fields, including drug discovery and catalysis. The vast majority of these compounds are six-membered biaryl or heterobiaryl ring derivatives, and atropisomeric species featuring smaller rings have received much less attention. Nonetheless, they have been successfully employed in numerous asymmetric transformations.

This thesis outlines the synthesis of a novel class of atropisomeric triazole-containing compounds whose potential applications lie within the organocatalytic realm. The experiments detailed in the following chapters will show the scope and limitations of different synthetic approaches, which led to defined syntheses of two distinct generations of triazoles and triazolium salts. Computational calculations, NMR spectroscopy and/or HPLC analyses will reveal that the rotation may be significantly restricted, thus in principle, allowing access to single atropisomers of these chiral compounds. Preliminary results in asymmetric organocatalysis will finally highlight their potential.

How to Read This Thesis

In this thesis, chiral axes are defined by heavy bonds coloured in red or, in some instances, in black. When a racemic or diastereomeric mixture of atropisomeric compounds is being depicted, the chiral axis is the only element highlighted, and no other indication of the spatial arrangement is given (**Figure I**).

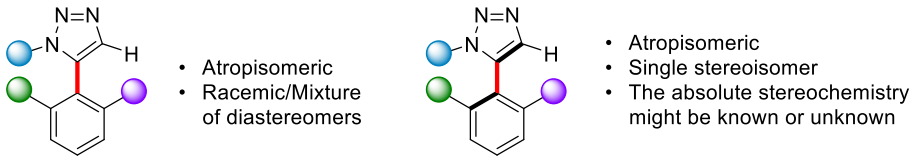


Figure I Notation used for racemic mixtures (left) and single stereoisomers (right)

When referring to a pure stereoisomer, the absolute configuration is used if known, and the compound is drawn accordingly, giving a representation of its tridimensionality using solid wedged and hashed wedged bonds. Where the absolute configuration is unknown, it has been arbitrarily chosen for clarity; the caption and/or the main text report whether this is the case. Single enantiomers whose absolute configuration is unknown will be distinguished by the sign of the $[\alpha]_D$. Stereoisomers differing only for the configuration of the chiral axis, and whose point chirality is the same, are labelled "single diastereoisomers and single enantiomers" in the experimental, to highlight that a stereomerically pure species is being reported.

Unless otherwise specified, all the calculated $\Delta G^{\ddagger}$ in this thesis are referred to the barrier of enantiomerisation, whether or not the explicit subscript ($\Delta G_e^{\ddagger}$) is present.

The bibliography is organised in the style of *Royal Society of Chemistry*.

Abbreviations

Å	Angstrom
ABSA	Acetamidobenzenesulfonyl Azide
AP	Affinity Purification
APCI	Atmospheric-Pressure Chemical Ionisation
Ar	Aromatic (generic)
ASAP	Atmospheric Solids Analysis Probe
aq.	Aqueous
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	2,2'-Dihydroxy-1,1'-binaphthyl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bz	Benzoyl
ca.	*Circa*
calc.	Calculated
cat.	Catalyst
CDC	Cross-Dehydrogenative Coupling
compd.	Compound
cond.	Conditions
conv.	Conversion
COD	Cyclooctadiene
CuAAC	Copper-Catalysed Azide-Alkyne Cycloaddition
Cy	Cyclohexyl

d	Distance between two given groups
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
de	Diastereomeric Excess
dec.	Decomposed
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
d.r.	Diastereomeric Ratio
E	*Entgegen*
ee	Enantiomeric Excess
e.g.	*exempli gratia*
EI	Electron Ionisation
ent-	Indicates one enantiomer of a certain compound
eq.	Equivalents
e.r.	Enantiomeric Ratio
ES *or* ESI	Electrospray Ionisation
Et	Ethyl
et al.	*et alia*
EtOAC	Ethyl Acetate
FTIR	Fourier-Transform Infrared Spectroscopy
g	Grams
h	Hours

HPLC	High-Performance Liquid Chromatography
HRMS	High-Resolution Mass Spectrometry
Hx	Hexane
i.e.	*id est*
IPA	Isopropyl Alcohol
*i*Pr	Isopropyl
IUPAC	International Union of Pure and Applied Chemistry
kcal	Kilocalorie
L	Ligand
M	Molar
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
min	Minutes
mol	Moles
m.p.	Melting Point
MW	Microwave
N	Normal
NaAsc	Sodium Ascorbate
NBS	*N*-Bromosuccinimide
*n*Bu	*normal*-Butyl
NFSI	*N*-Fluorobenzene Sulfonimide
NHC	*N*-Heterocyclic Carbene
NMI	*N*-Methylimidazole

NMP	*N*-Methyl-2-Pyrrolidone
NMR	Nuclear Magnet Resonance
obs.	Observed
Ph	Phenyl
ppm	parts per million
(A)PTC	(Asymmetric) Phase-Transfer Catalysis
quant.	Quantitative
q.v.	*quod vide*
rac.	Racemic
R_f	Retention Factor
R_t	Retention Time
rt	Room Temperature
S	Selectivity Factor
sat.	Saturated
S_N1	Nucleophilic Substitution (First Order)
S_N2	Nucleophilic Substitution (Second Order)
SPS	Solvent Purification System
t	Time
TBAF	Tetrabutylammonium Fluoride
TBS	tert-Butyldimethylsilyl Ether
*t*Bu	tertiary-Butyl
TCE	Tetrachloroethane
TEA	Triethylamine
Tf	Triflate

TFA	Trifluoroacetic Acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilane
TOF	Time of Flight
Troc	Trichloroethyl Chloroformate
TS	Transition State
UV	Ultraviolet
VT	Variable Temperature
v/v	Volume for Volume
w/v	Weight for Volume
XRD	X-Ray Diffractometry
Z	*Zusammen*

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1 Introduction

1.1 Axial Chirality and Atropisomerism

"Is it not evident that the property that certain molecules have, to diverge the plane of polarization has an immediate cause, or is at least closely related to the asymmetry of these molecules?"[1]

Although he was not the first to observe such a phenomenon, Pasteur was the first, in 1848, to relate the optical rotation of a molecule to its molecular structure: he had discovered molecular chirality. Chirality (from the Greek *chier*, "hand") is a fundamental property of certain molecules and, more in general, objects, and is ubiquitous. Structures that are not superimposable to their mirror image are defined as chiral; chiral structures therefore exist as two non-identical entities, called enantiomers. Stereoisomerism is often observed as a consequence of a sp^3 hybridised carbon or heteroatom (*e.g.* nitrogen or phosphorous) bearing four different substituents (**Figure 1a**). On a molecular level, however, chirality can arise not only from a stereogenic centre (point chirality) but also as a result of a chiral plane (planar chirality), a helix (helical chirality), or a chiral axis (axial chirality).

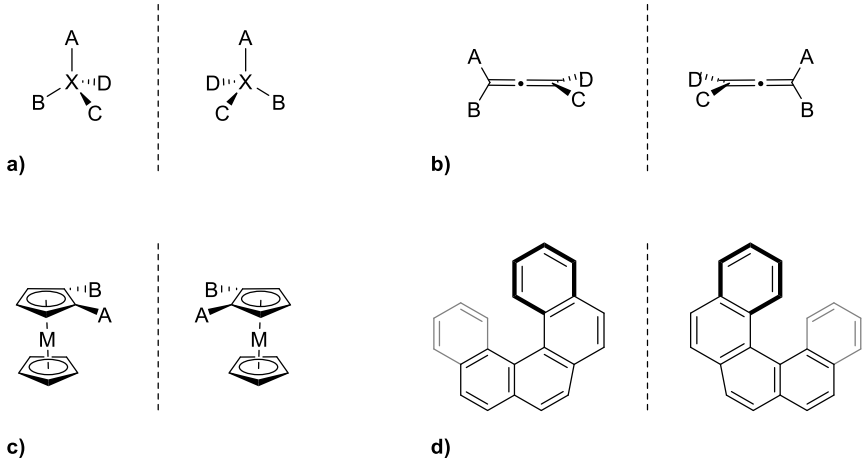


Figure 1 Type of chirality: **a)** Point chirality; **b)** Axial chirality; **c)** Planar chirality: **d)** Helical chirality.

Axial chirality was initially envisaged by Van t'Hoff in 1875 in regard to allenes[I] (**Figure 1b**),[2] and experimentally observed, in 1922 – almost fifty years later – by Christie and Kenner, who resolved the enantiomers of 6,6'-dinitro-2,2'-diphenic acid (**Figure 2a**).[3] The concept of axial chirality, in fact, expands beyond allenes and includes spiranes, aryl and non-aryl atropisomeric compounds. Whilst spiranes exhibit axially chirality in a way rather similar to allenes, atropisomerism (a term coined by Kuhn, from the Greek prefix *atropos*, "not turning") is a peculiar type of axial chirality that arises from restricted rotation about a single covalent bond. Given that atropisomers are conformational isomers, "atropisomerism" can have a broad meaning and under the appropriate conditions, almost all organic compounds could be defined atropisomeric. Oki proposed that the minimum requirement for two rotamers, *tropos*, to be *atropos*, is a half-life of 1000 s which, at room temperature, corresponds to a $\Delta G^{\ddagger}$ of *ca.* 22 kcal/mol.[4] By this definition, butane becomes atropisomeric at 53 K (**Figure 2b**)[5] however, such low temperatures would not be practical and it is common to refer to atropisomers as species that exist as stable rotamers and that can be isolated at room temperature.

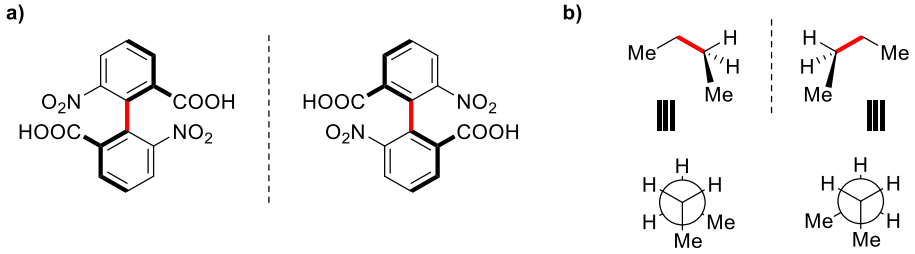


Figure 2 a) Atropisomerism in 6,6'-dinitro-2,2'-diphenic acid; **b)** Atropisomerism in butane (at low temperature).

In 2011, LaPlante *et al.* offered an alternative classification of atropisomers into three classes, based on their half-lives, extrapolated from the rotational barriers.[6]

[I] Axial chirality of allenes was proven by Maitland and Mills in 1935, six decades later.

- *Class I*: Compounds with rotational barriers between *ca.* 0-20 kcal/mol and rotation rates on the order of seconds or fractions of seconds. At room temperature, these compounds freely rotate and do not show any atropisomeric property.
- *Class II*: Compounds with rotational barriers between *ca.* 20-30 kcal/mol and rotation rates up to several months. These compounds exhibit delayed axial interconversion, consequently, they might exist as atropisomers and they can be isolated as single enantiomers. Nonetheless, their intermediate stability may pose a problem, especially in drug discovery.
- *Class III*: Compounds with rotational barriers greater than 30 kcal/mol and rotation rates on the order of years. These compounds are stable, and no axial interconversion is generally observed under normal conditions.

The absolute configuration of atropisomeric compounds can be described, using the Newman projection along the chiral axis, either according to the Cahn-Ingold-Prelog convention, as R_a and S_a, or, referring to the helicity, as *M* (minus) and *P* (plus). In this latter approach, the configuration is assigned following the rotation from the nearest to the furthest highest priority substituent (A and C in **Figure 3**).

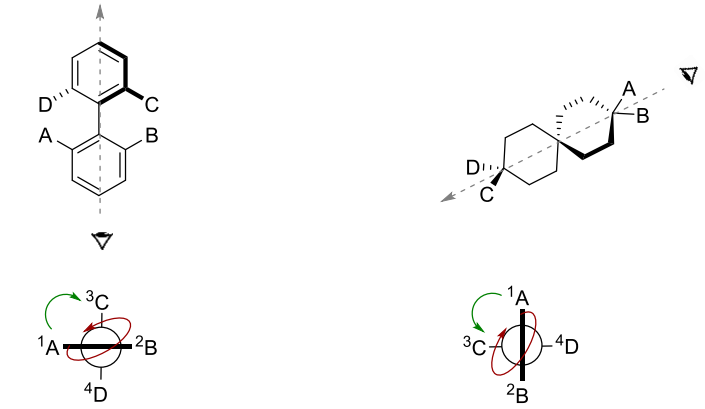


Figure 3 Assignment of absolute configuration in axially chiral compounds; the subscript *a* indicates axial chirality.

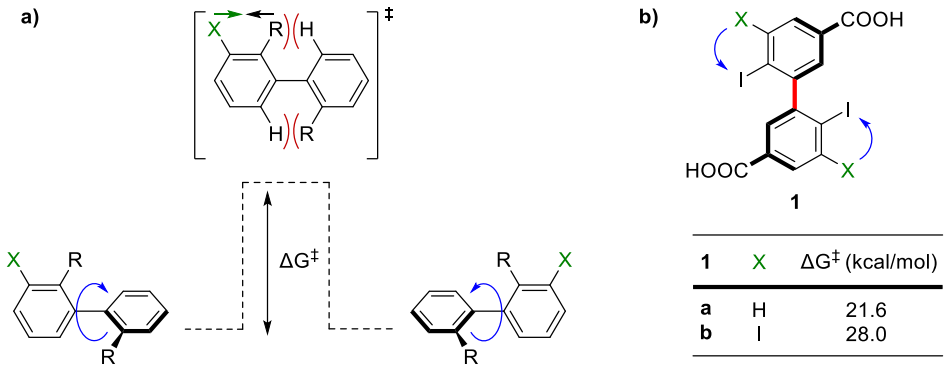
1.1.1 Configurational Stability

The occurrence of racemisation in atropisomeric compounds largely depends on the system being examined (*e.g.* bridged, heteroaryl, non-aryl, etc.), and it might involve transient bonds,[7] bond-breaking through chemical processes[8] or photochemical excitation.[9-11] Nonetheless, one of the major pathways of interconversion involves a simple rotation about the chiral axis. This is influenced by factors such as the degree of steric hindrance, the temperature or the solvent amongst others.[12] Seminal work by Adam *et al.* concluded that the rate of racemisation in enantiopure biaryl systems is mainly influenced by steric factors.[13] In 2005, Bringman added two more elements governing the configurational stability of axially chiral biaryls: *i)* the presence and nature (*i.e.* length and rigidity) of bridges; *ii)* the type of mechanism involved.[14] In non-bridged, biaryl atropisomers, the magnitude of the rotational barrier $\Delta G^{\ddagger}$ can often be rationalised in terms of *ortho*-substituents (number and size), size of the rings featured and nature of the heteroatom in the chiral axis C-X (if any are present).

Ortho-substituents to the chiral axis exert their influence through the steric repulsion experienced in the periplanar transition state, which is in turn related to the Van der Waals radii of the substituents so that, for instance, H < F < NMe_2 < Cl < CH_3 < Br < I < *i*Pr.[15] The number of *ortho*-substituents is also relevant and, whilst most of the tri- and tetra-*o*-substituted biaryls are generally conformationally stable, axially chiral biaryls with fewer than three substituents are not, unless bulky substituents (*e.g. tert*-butyl, isopropyl) are present.[5]

Meta-substituents can also be influential, especially if sterically demanding. This phenomenon, firstly observed by Chien *et al.* in 1934,[16] is known as the *buttressing effect* and it enhances the steric repulsion in the transition state, due to the *ortho*-substituents not being able to bend over (**Figure 4a**). For example, Rieger observed that both the experimental and the computed barrier to rotation in tetra-iodobiphenyl compound **1b** was about 6.4 kcal higher than the di-iodo

analogue **1a**, as a consequence of the buttressing effect of the iodine atoms in the 3-positions (**Figure 4b**).[17]



1	X	ΔG‡ (kcal/mol)
a	H	21.6
b	I	28.0

Figure 4 a) Buttressing effect. **b)** Buttressing effect in tetra-iododiphenyl dicarboxylic acid.

The size of the rings involved is also relevant, and atropisomeric biaryl and heterobiaryl systems featuring rings smaller than six atoms are conformationally less stable. In fact, as the size of the rings decreases, the distance between the *ortho*-substituents next to the chiral axis increases as a result of the reduced bond angle, alleviating the steric repulsion and thus lowering the barrier to rotation (**Figure 5**).[18]

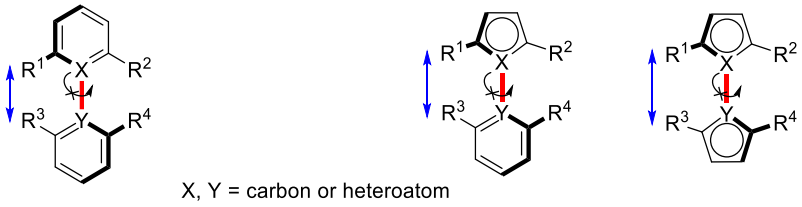
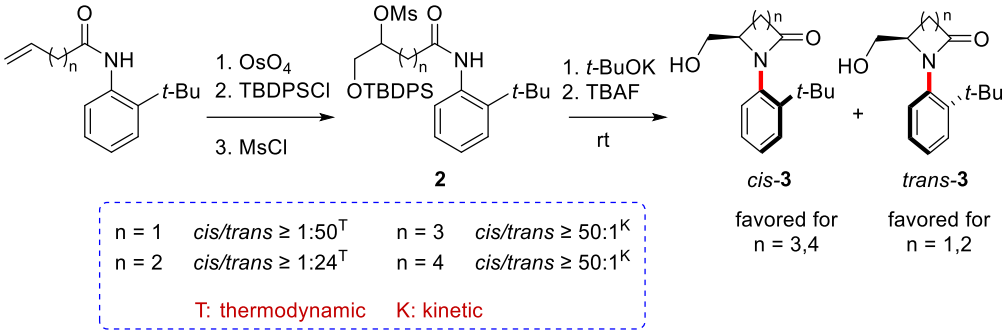


Figure 5 Reduced steric repulsion between *ortho*-substituent in atropisomers featuring one or two five-membered rings.

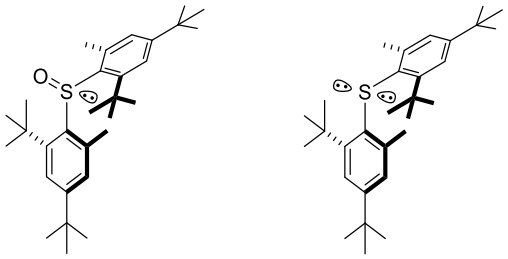
The different stereochemical outcomes reported by Taguchi and co-workers in the stereoselective synthesis of diastereomeric axially chiral lactams of different sizes provides an interesting example (**Scheme 1**).[19] Whilst in four- and five-membered lactams the *o-tert*-butyl functionality was in a *trans* orientation (thermodynamic product), in six- and seven-membered rings the same functionality was *cis* (kinetic product).



Scheme 1 Stereoselective synthesis of diastereomeric axially chiral lactams.

Mechanistic investigations of the reaction led the authors to conclude that in all cases the kinetic *cis* product was initially formed, regardless of the size of the lactam. However, as a result of an eased rotation about the chiral axis, four- and five-membered rings slowly converted to the more thermodynamically stable *trans* product.

Another important aspect that affects the magnitude of the rotational barrier is the nature of the heteroatom in the chiral axis C-X (*e.g.* N, O, S, P), if any are present.[12] This is due to the fact that the steric compression related to the bond length varies with different atoms, and it might considerably impact the racemisation barrier. An example is given by the different racemisation barriers of sulfoxide **4** and sulfide **5** reported by Clayden and co-workers.[20] The calculated barriers to rotation about the C-S revealed that, as a consequence of a shorter bond length, sulfide **5** racemised approximately three orders of magnitude slower than sulfoxide **4** (**Figure 6**).



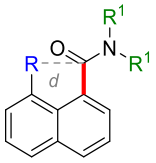
4
Sulfoxide

5
Sulfide

C-S bond length (pm)		$\tau_{1/2}$	$\Delta G^{\ddagger}$ (kcal/mol)
Sulfoxide	182.0	70 s	20.6 (17 °C)
Sulfide	179.4	14 h	24.1 (40 °C)

Figure 6 Bond lengths, half-lives and barriers to rotation in sulfoxide **4** and sulfide **5**.[20]

On occasions, other factors need to be taken into consideration. For instance, Clayden *et al.* reported that the rate of racemisation of atropisomeric 8-substituted 1-naphthamides was mainly governed by electronic properties, namely *peri*-interactions.[21] Crystal structures of the compounds analysed revealed shorter distances *d* between R and C=O when bonding interactions between the substituents in the 8-position and the amide carbonyl could take place (**Figure 7**).



R	**R^1**	*d* (pm)	$\tau_{1/2}$ (20 °C)	$\Delta G^{\ddagger}$ (kcal/mol)
H	*i*-Pr	290	1 s	17.8
CH_2NMe_2	*i*-Pr	289	960 s	21.8
NMe_2	*i*-Pr	276	27 h	24.4
OMe	*i*-Pr	262	12 d	25.8
NMe_2	Me	270	3 h	23.2

Figure 7 Calculated barrier to ration in 8-substituted 1-naphtamides.

As a result, a higher barrier to rotation was observed for 8-substituents with a superior ability to form a partial bond to the amide carbonyl group (*e.g.* NMe_2, OMe), even if smaller in size (*e.g.* CH_2NMe_2 *vs* OMe).

Similarly, Kitagawa and co-workers reported a series of C-N axially chiral aromatic anilines, whose barriers to rotation varied according to the electronic effect of the *para*-substituent on

the aryl group (**Figure 8a**).[22] In particular, electron withdrawing groups were found to be less inclined to racemise as a result of the resonance stabilisation energy of the nitrogen lone pair into the coplanar *para*-substituted phenyl ring. Density functional theory (DFT) calculations showed that the transition state adopts a twisted geometry that would cause a loss of named stabilisation energy and hence a higher barrier to rotation (**Figure 8b**).

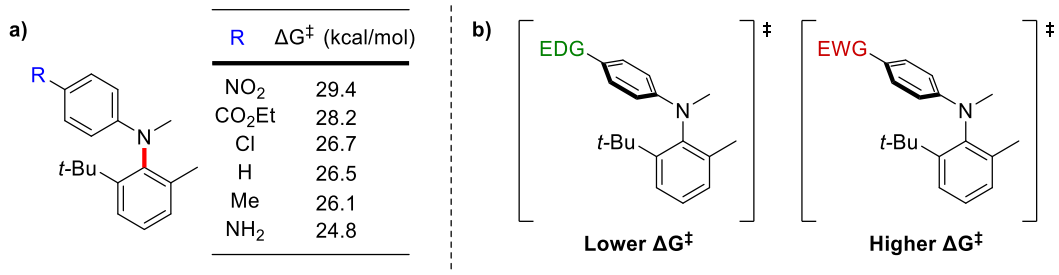
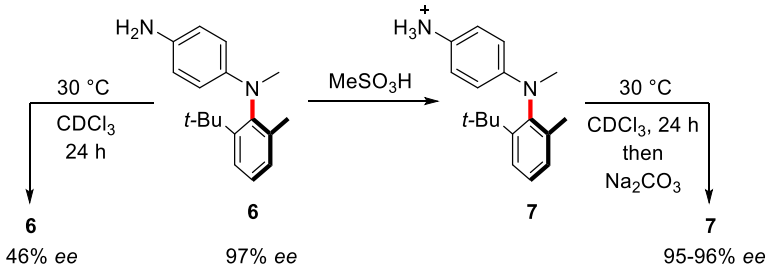


Figure 8 a) Electronic effect of the R group on the barriers to rotation. **b)** Representation of the computed transition states.

As a direct consequence, the same research group designed a proton "brake" in which the rate of racemisation of a given compound about the C-N chiral axis could be decelerated by protonation at the *para*-position, which could turn a strong electron donating group like NH_2 into an electron withdrawing $^{+}NH_3$ (**Scheme 2**).



Scheme 2 Proton brake: change of *ee* in **6** and **7**.[22]

1.2 Analytical Methods to Calculate Barriers to Rotation

Given their intrinsically dynamic nature, the determination of the barriers to rotation in atropisomers is of fundamental importance for developing novel catalysts, molecular gears or drugs displaying this type of chirality. Interconversion of stereoisomers with barriers to rotation

ranging between 4 and 24 kcal/mol can be studied by dynamic NMR spectroscopy (DNMR), whilst dynamic chromatography (*e.g.* DGC, DHPLC, DSFC) can be employed with more stable compounds.[23] As highlighted by Testa and co-workers in 1995, the configurational stability of a given compound can be investigated either at a macroscopic or microscopic level. The former refers to the irreversible formation of a racemic mixture, hence to *racemisation*, whereas the latter refers to the interconversion of enantiomers, or *enantiomerisation* (**Figure 9**).[24]

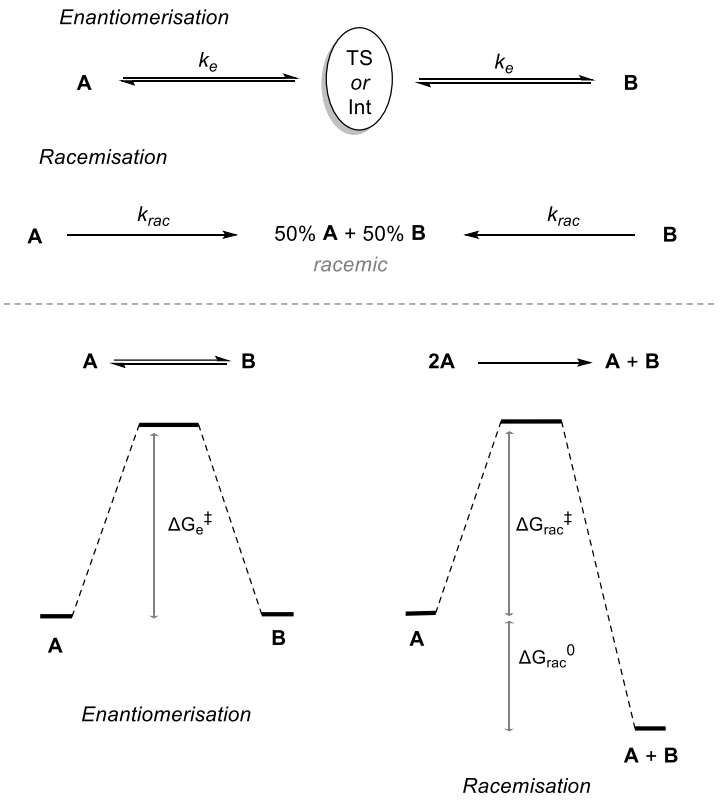


Figure 9 Schematic representation of enantiomerisation and racemisation (top); energy diagrams for enantiomerisation and racemisation (bottom).

Whilst the rate of racemisation and enantiomerisation are related (with the rate of enantiomerisation being half that of racemisation), when dealing with the configurational stability of chiral compounds it is crucial to distinguish the two, especially as it is the rate of

enantiomerisation k_e, rather than the rate of racemisation k_{rac}[II], that should be used to calculate the thermodynamic parameters $\Delta G_e^{\ddagger}$, $\Delta H_e^{\ddagger}$ and $\Delta S_e^{\ddagger}$.[25]

1.2.1 Dynamic NMR Spectroscopy

The advent of NMR spectroscopy, and the subsequent development of dynamic NMR techniques, considerably contributed to the study of atropisomeric compounds. At a microscopic level, if the interconversion rate between the stereoisomers is slow enough (10^{-1} – 10^{-2} s), two signals appear, whereas, if it is fast ($\gg 10^{-2}$ s) a time-averaged signal appears. The exchange rate is a function of the temperature, and information at various temperatures can easily be obtained by NMR spectroscopy. The simplest scenario is offered by a system where two nuclei give, at a certain temperature, two singlets which merge into a single time-averaged peak at the *coalescence* temperature T_c.(*e.g. N,N*-dimethylacetamide[26]) At this temperature, the rate of interconversion k_e and the free energy of activation $\Delta G^{\ddagger}$ will be given by:[27]

$$k_{e[T_c]} = \frac{\pi \Delta \nu}{\sqrt{2}} \qquad (\mathbf{1})$$

$$\Delta G_{e[T_c]}^{\ddagger} = 4.57 T_c \left[10.32 + log\left(\frac{T_c}{\Delta \nu}\right)\right] \qquad (\mathbf{2})$$

where $\Delta \nu$ is the difference in chemical shifts (in Hz) between the two signals in absence of exchange.[III] In the slightly more complex case where the nuclei interact with each other (*e.g.* tertiary aromatic amides[28]), the two equations become:[27]

$$k_{e[T_c]} = \pi \sqrt{\frac{\Delta \nu^2 + 6J^2}{2}} \qquad (\mathbf{3})$$

[II] Given that it corresponds to a macroscopic system, k_{rac} is determined experimentally as an erosion of *ee*.
[III] The free energy of activation is derived from the Eyring equation solved for $\Delta G^{\ddagger}$.

$$\Delta G^{\ddagger}_{e[T_c]} = 4.57 T_c \left[10.32 + log \left(\frac{T_c}{\sqrt{\Delta \nu^2 + 6J^2}} \right) \right] \quad (\mathbf{4})$$

where J is the coupling constant between the nuclei involved.

Although dynamic processes are usually studied by ^{1}H NMR spectroscopy, other spin-active nuclei (*e.g.* ^{19}F, ^{31}P, ^{13}C) serve the purpose equally well. This method, also known as the *coalescence method*, often suffers from limited accuracy due to difficulties in the determination of the exact temperature of the sample: errors of ±2 °C cause an error in $\Delta G^{\ddagger}$ up to 0.25 kcal/mol. Furthermore, although its inherent simplicity, the coalescence method is not applicable to compounds with convoluted NMR spectra possessing multiple coupling patterns. In these cases, accurate rotational barriers can be obtained by line shape analysis with custom programs, using mathematical simulations.[29, 30]

1.2.2 Dynamic Chromatography

Stereoisomers with barriers to rotation greater than 24 kcal/mol are better analysed *via* chromatographic methods. Compared to NMR spectroscopy, chromatographic time scales extend from seconds - for very short columns – to hours – for long columns and/or low flow rates. Depending on the enantiomerisation rate, three possible scenarios ought to be expected: *i)* two baseline-resolved peaks; *ii)* a plateau between the peaks, and *iii)* one single peak (no resolution).[23] In analogy to DNMR, the first case is observed when the racemisation is slow compared to the chromatographic time scale, whilst the latter arises when the interconversion is much faster than the timeframe of the resolution. In the simple case where separation of the two enantiomers is achieved, it is possible to calculate the rate of racemisation k_{rac} using the following equation:[25]

$$\ln[A]_t = -k_{rac} t + \ln[A]_0 \quad (\mathbf{5})$$

Where A is the enantiomer being studied, and $-k_{rac}$ is the (negative) slope of $\ln[A]_t$ plotted against the time t. The half-life, instead, is given by:[25]

$$t_{\frac{1}{2}} = \frac{\ln(2)}{k_{rac}} \quad (\mathbf{6})$$

As k_{rac} is twice k_e, the obtained k_{rac} can be used to calculate the rate of enantiomerisation k_e, needed for determining the thermodynamic parameters ($\Delta G_e^{\ddagger}$, $\Delta H_e^{\ddagger}$, $\Delta S_e^{\ddagger}$). In particular, the barrier of interconversion $\Delta G_e^{\ddagger}$, at the temperature T, will be:[25]

$$\Delta G_{e[T]}^{\ddagger} = RT\left[\ln\left(\frac{k_B T}{h}\right) - \ln(k_e)\right] \quad (\mathbf{7})$$

where R is the universal gas constant, k_B is the Boltzmann constant and T is the temperature in Kelvin.

Whilst dynamic chromatography can overcome some of the disadvantages of DNMR, it is not exempt from limitations itself. Among these, there are the lower limits of detection (*i.e.* lower sensitivity) and the fact that high temperatures are generally not tolerated by coated chiral columns.

1.3 Biaryl Atropisomers: from Nature to Catalysis

Several natural products exhibit axial chirality and many of them have shown potential medicinal applications.[31, 32] Relevant examples are listed in **Figure 10** and include the toxic Gossypol produced by the cotton plant of the *Gossypium* genus, which has shown possible applications as an anticancer and a male contraceptive agent in its more biologically active *(M)*-enantiomer;[33] Viriditoxin, identified as a component of numerous fungal extracts, known for its antibiotic activity[34] and more recently studied for its antitumoral activity against prostate

cancer;[35] the N,C2-linked bipyrrole Marinopyrrole A, isolated from marine streptomycetes with promising antimicrobial activity[36] as well as many others.

Furthermore, the need to explore a larger chemical space for drug candidates and the move away from classical flat aromatic scaffolds have led many pharmaceutical chemists to embrace axial chirality, and there are several examples of stable atropisomeric FDA-approved drugs, some of which are represented in **Figure 10**.

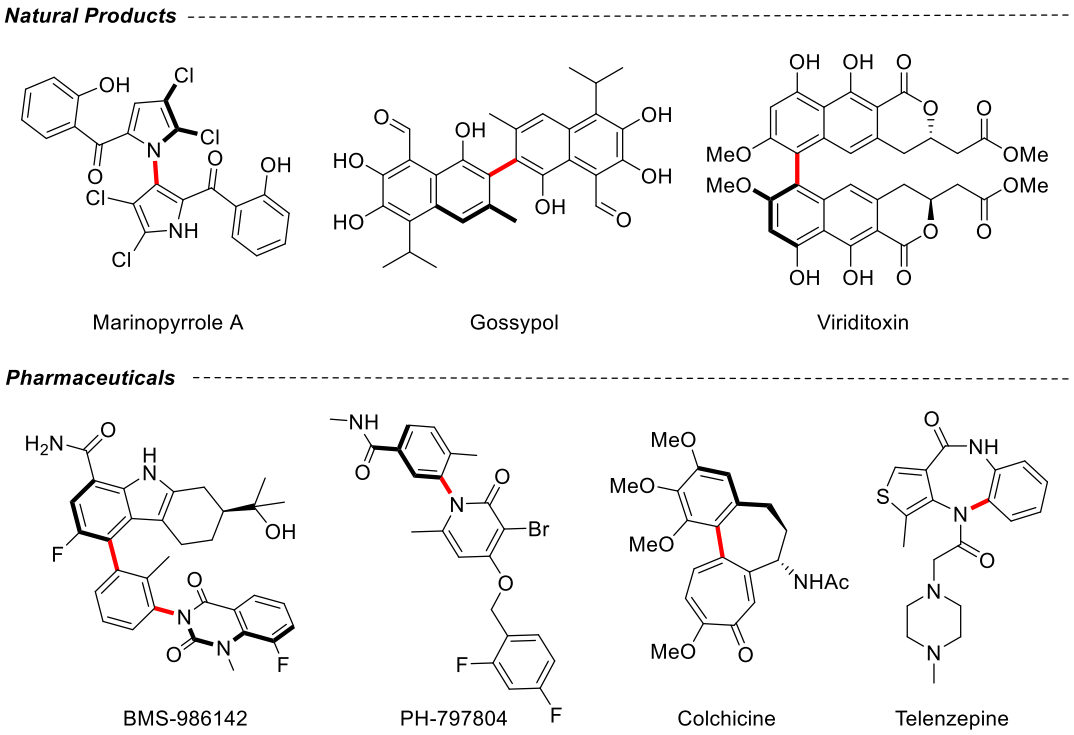


Figure 10 Selected examples of natural and pharmaceutical atropisomeric compounds.

Furthermore, in the last few decades, biaryl atropisomeric compounds have been successfully employed in a multitude of asymmetric transformations as ligands or organocatalysts. A major breakthrough in this area was the development of the atropisomeric diphosphine ligand BINAP **9** (**Figure 11**), prepared from BINOL **8** and firstly reported by Noyori and co-workers in 1980.[37]

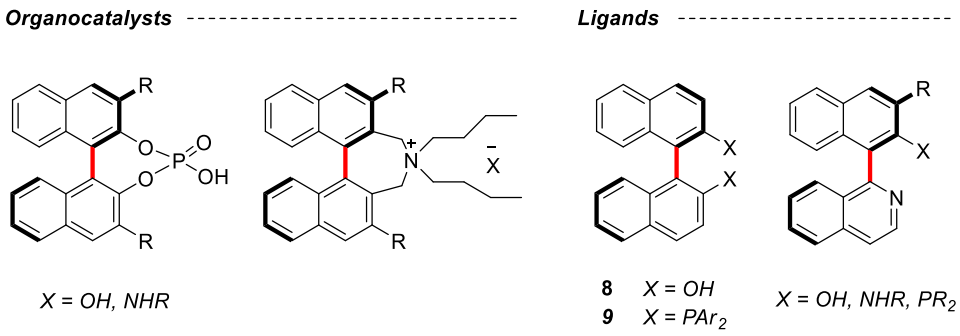
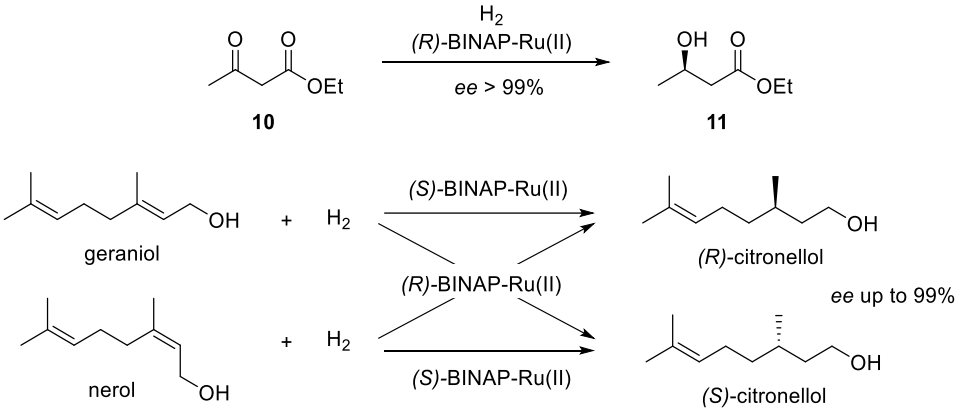


Figure 11 Selected examples of atropisomeric compounds used in catalysis.

BINAP was used in Ru-catalysed asymmetric hydrogenation of olefins and ketones (**Scheme 3**),[38] reaction that in 2001 earned Noyori, alongside Knowles and Sharpless, the Nobel Prize for Chemistry.



Scheme 3 Examples of Ru-catalysed asymmetric hydrogenations of olefins and ketones.[38]

Since then, many other atropisomeric catalysts and ligands based on the 1,1'-binaphthyl scaffold have been developed and employed in asymmetric catalysis and supramolecular chemistry with excellent results,[39-41] so that the 1,1-binaphthalene core is considered a "privileged" scaffold.[42, 43] Although the large majority of atropisomeric compounds employed in asymmetric catalysis belongs to the biaryl class, a variety of non-biaryl atropisomers has been developed over the years. Among these, aryl amides,[44, 45] ethers[46, 47] and anilides,[48] dienes[49, 50] and others,[20, 51-53] have found successful applications in catalysis,[12, 54] drug discovery,[55] medicinal[31] and supramolecular chemistry.[56, 57] However, this thesis is concerned

with the synthesis of atropisomers featuring five-membered rings with potential applications in asymmetric catalysis, henceforth the rest of the chapter will mainly focus on the applications in this area, referring to the relevant literature with a historical perspective.

1.3.1 Five-Membered Containing Atropisomers

Atropisomers featuring pentatomic rings are far less common than six-membered biaryls and heterobiaryls. The reason resides, as it was previously mentioned in *Section 1.1.1*, in the inherent lower stability of these compounds, which makes their design and, in certain cases, synthesis more challenging.[12, 18] Nonetheless, not only do they occur in nature (*e.g.* Marinopyrrole A in **Figure 10**) but many synthetic chemists have embraced the challenge, allowing them to access novel classes of chiral reagents, catalysts and ligands (to name a few) displaying either a C-C or a C-X heteronuclear chiral axis.

The very first synthesis of these compounds dates back to 1931, when Adam and Bock reported a series of C-N chiral *N*-aryl pyrroles, of which however they managed to resolve only one example (compound **12** in **Figure 12**).[58]

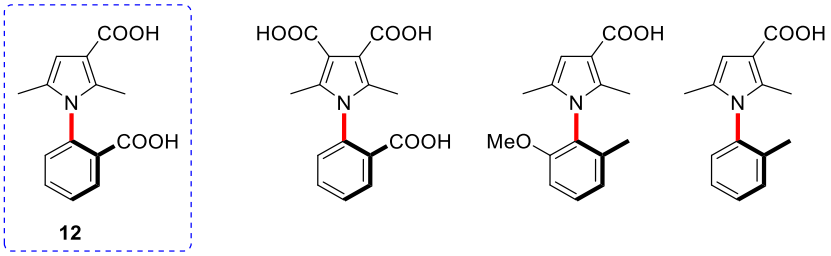
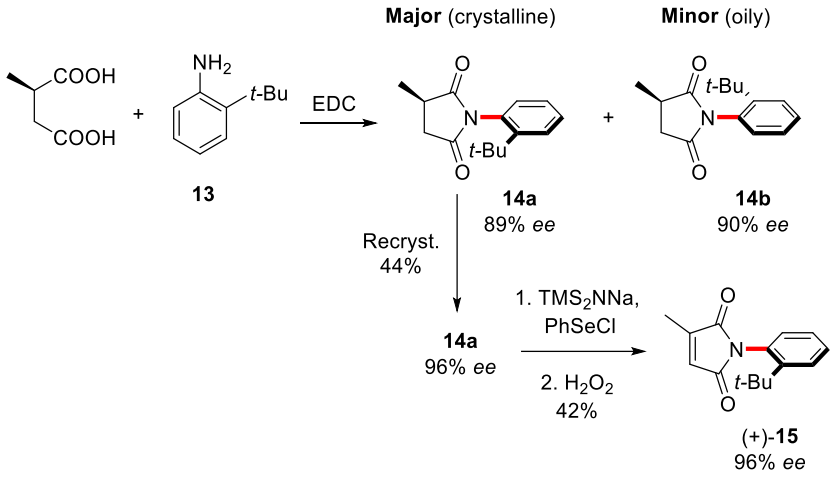


Figure 12 *N*-aryl pyrroles prepared by Adam and co-workers.[58]

Although numerous reports followed,[59-65] the interest for atropisomers containing five-membered rings remained purely academic for a long time, and more than sixty years passed before a first application was reported. Herein, a selection of examples of these compounds, grouped by application, is outlined.

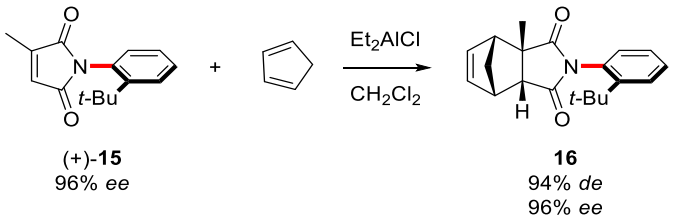
1.3.1.1 As Chiral Reagents

Following the seminal work of Curran *et al.*,[65] in 1998 Taguchi and co-workers reported the synthesis of atropisomeric maleimide **15**, prepared in high purity by oxidative selenoxide elimination of the corresponding diastereomeric succinimide **14a**, obtained from the primary aniline **13** and enantiopure *(R)*-2-methylsuccinic acid (**Scheme 4**).[66]



Scheme 4 Synthesis of highly enantiopure maleimide **15**.[66]

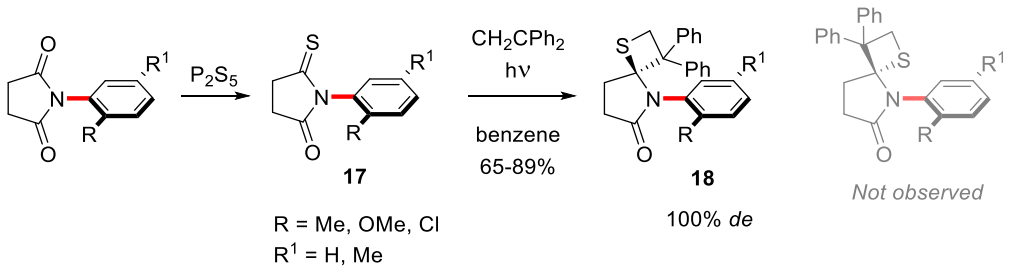
Atropisomeric maleimide **15** was used as a chiral starting material in a Lewis acid catalysed asymmetric Dies-Alder reaction, showing remarkable *endo* and diastereofacial selectivity (**Scheme 5**).



Scheme 5 Lewis acid catalysed asymmetric Dies-Alder reaction of atropisomeric maleimide and cyclopentadiene.[66]

Cycloadditions were also exploited by Sakamoto and co-workers, which in 2003 reported a high chemo-, regio- and diastereoselective [2+2] photocycloaddition of enantiopure

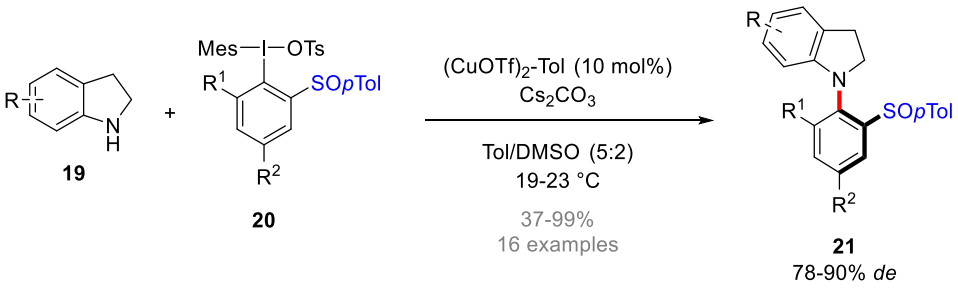
monothiosuccinimides **17** to 1,1-diphenylethylene, allowing access to spirothietanes **18** in good to excellent yield (**Scheme 6**).[67]



Scheme 6 Diastereoselective synthesis of spirothietanes **18**.[67]

As the authors reported, in all cases the addition was controlled by the *ortho*-substituent R, with the 1,1-diphenylethylene always adding from the opposite site, thus leading exclusively to one diastereoisomer (**Scheme 6**).

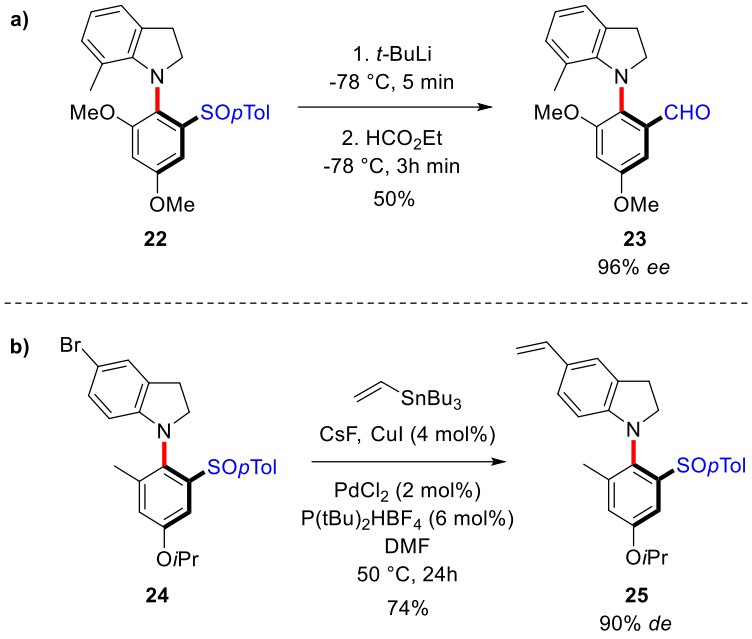
Another interesting, and more recent example is offered by the intermolecular atropodiastereoselective C-N cross-coupling of indolines **19** and optically pure chiral sulfoxide iodanes **20** reported by Wencel-Delord and Colobert (**Scheme 7**).[68]



Scheme 7 Atropodiastereoselective C-N cross-coupling.[68]

This reaction represents the first example of atroposelective intermolecular C-N cross-coupling. Furthermore, thanks to the considerable number of post-modifications that the sulfoxide moiety gives access to, along with its compatibility with halogenated substrates, this method allows a simple diversification of the atropisomeric C-N products, permitting, in principle, the synthesis of a large number of atropisomeric scaffolds. Examples of such diversification reported by the

same authors are shown in **Scheme 8** and include Li/sulfoxide exchange and Stille cross-coupling.



Scheme 8 Post-modifications of atropisomeric indolines. **a)** Sulfoxide/Lithium exchange; **b)** Stille cross-coupling.[68]

1.3.1.2 In Medicinal Chemistry and Drug-Discovery

Examples of pharmaceuticals featuring five-membered rings are rather limited, partially because it is only recently that medicinal chemists have started dealing with atropisomerism.[6] Among the atropisomerically stable FDA-approved drugs there is Lesinurad (**Figure 13A**), a urate transporter inhibitor patented in 2006,[69] and officially approved in 2015, under the trade name "Zurampic", as a drug for lowering uric acid levels in the blood of patients with gout.

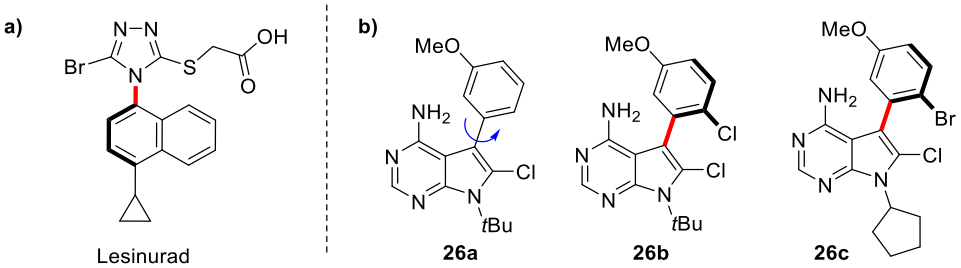
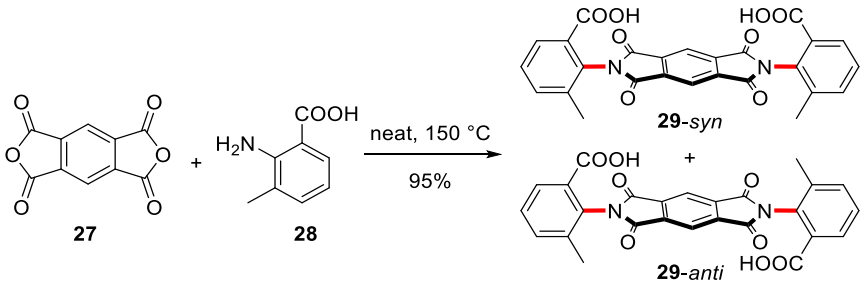


Figure 13 a) Lesinurad; **b)** Kinase inhibitors.

Another example is offered by pyrrolopyrimidines **26** in **Figure 13b**. Atropisomerism in compounds **26b** and **26c**, reported by Gustafson and co-workers, was used as an intentional and strategic rigidification of the pyrrolopyrimidine **26a**, which freely rotates at room temperature, aimed to improve target selectivity towards tyrosine kinases.[70] The authors reported different selectivity patterns between atropisomers and, despite the resultant potency being inferior, the selectivity was enhanced (*e.g.* compound **26b**-(*R*) inhibited 11% of the screened kinases, whilst **26a** inhibited 44%).

1.3.1.3 In Supramolecular and Material Chemistry

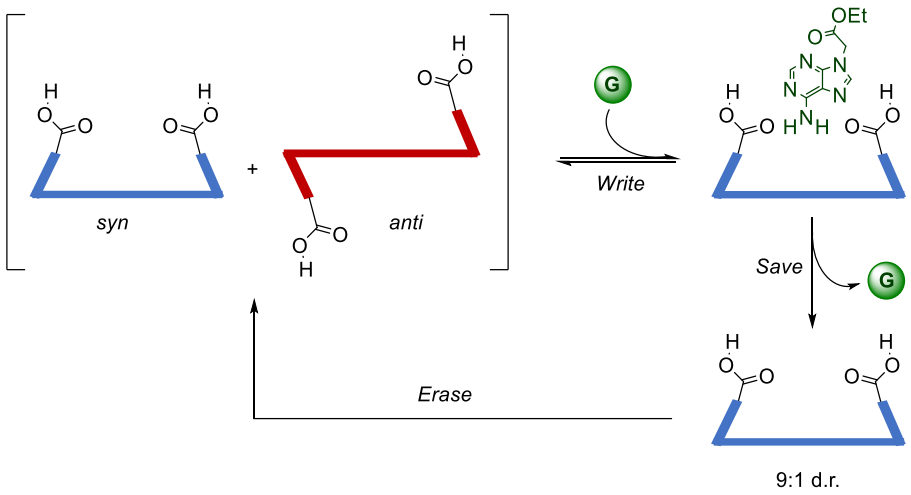
In 2005, Shimizu's group reported the synthesis of an atropisomeric receptor with "write", "save" and "erase" recognition properties.[71] The synthesis was easily achieved *via* condensation of 2-amino-3-methyl benzoic acid **28** with dianhydride **27** (**Scheme 9**).



Scheme 9 Atropisomeric diacids receptors **29**-*syn* and -*anti*.[71]

Stable at room temperature, with a $\Delta G^{\ddagger} = 29.4$ kcal/mol and a half-life of 10.9 days, the receptor showed conformational flexibility at higher temperatures, which allowed rotation and consequent coordination *via* hydrogen bonding to a guest molecule (*i.e.* ethyl adenine-9 acetate) when heated at 90 °C ("write"). Upon cooling back to room temperature, the guest molecule is released, and the conformation adopted is "saved", resulting in a considerable increase of diastereomeric ratio (up to 9:1 with 4 equivalents of **28**) in favour of the *syn* isomer. As the

process is entirely reversible, the host returned to its original state (1:1 d.r.) simply by heating in absence of the guest ("erase").



Scheme 10 Conformationally imprintable atropisomeric receptor reported by Shimizu's group.[71]

Another intriguing application involving a five-membered atropisomeric biheteroaromatic scaffold was reported by Sannicolò *et al.* in 2014.[72] Conversely to the typical approach for the design of chiral electroactive materials, which utilise an external chiral unit, Sannicolò's group prepared a new electroactive, inherently chiral poly-heterocyclic organic film, whose monomers are the optically pure atropisomeric 3,3'-bithianaphthene derivative **30** shown in **Figure 14**.

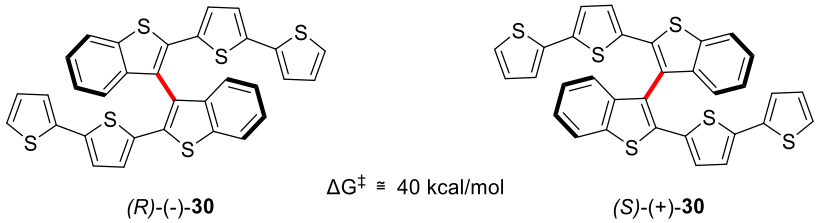
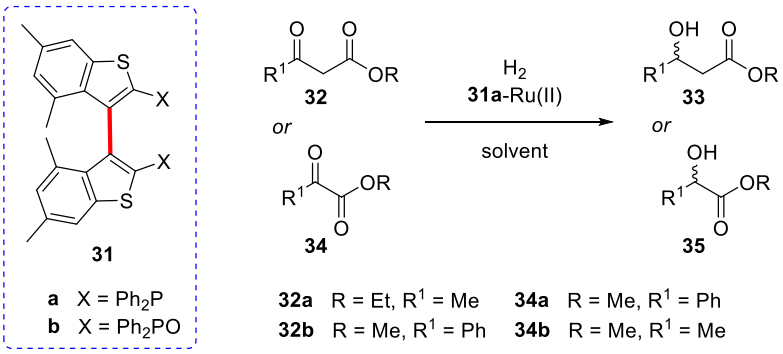


Figure 14 Atropisomeric monomers for chiral electroactive organic films reported by Sannicolò *et al.*[72]

In addition to the remarkable chiroptical properties shown, electrodes functionalised with said films, displayed outstanding enantioselective properties, allowing in principle applications in stereoselective electrocatalysis and electroanalysis.

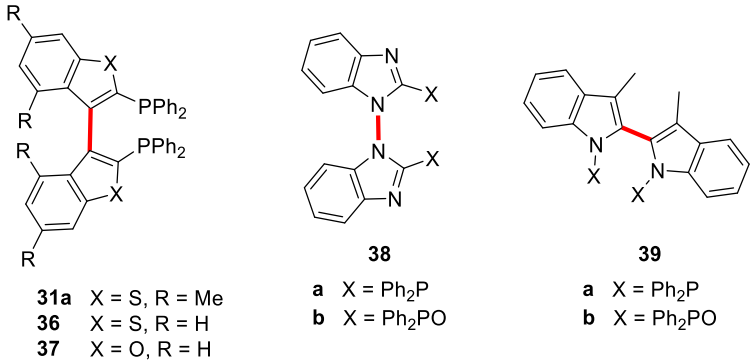
1.3.1.4 As Ligands for Metal Complexes

If not the most important, the application of atropisomers featuring pentatomic rings as ligands for metal-catalysed reactions is certainly the one that has most examples. One of the very first dates back to 1995, when Cesarotti and co-workers reported the synthesis of a novel class of pentatomic, atropisomeric diphosphine ligands for Ru-catalysed asymmetric hydrogenation of α and β-ketoesters (**Scheme 11**).[73]



Scheme 11 Ru-catalysed hydrogenation of α and β-ketoesters reported by Cesarotti *et al.*[73]

The novel bithiophenes diphosphine ligands **31** performed equally well (and even better with certain substrates) to the BINAP-Ru(II) reported by Noyori, under the same experimental conditions.[73] In the following years, the same group reported other heterocyclic variants of ligand **31a**. However, not all of them could be resolved at room temperature (*e.g.* compound **37** in **Figure 15**), proving that the choice of the heterocyclic system was a crucial factor to ensure configurational stability.[74, 75]



31a X = S, R = Me
36 X = S, R = H
37 X = O, R = H

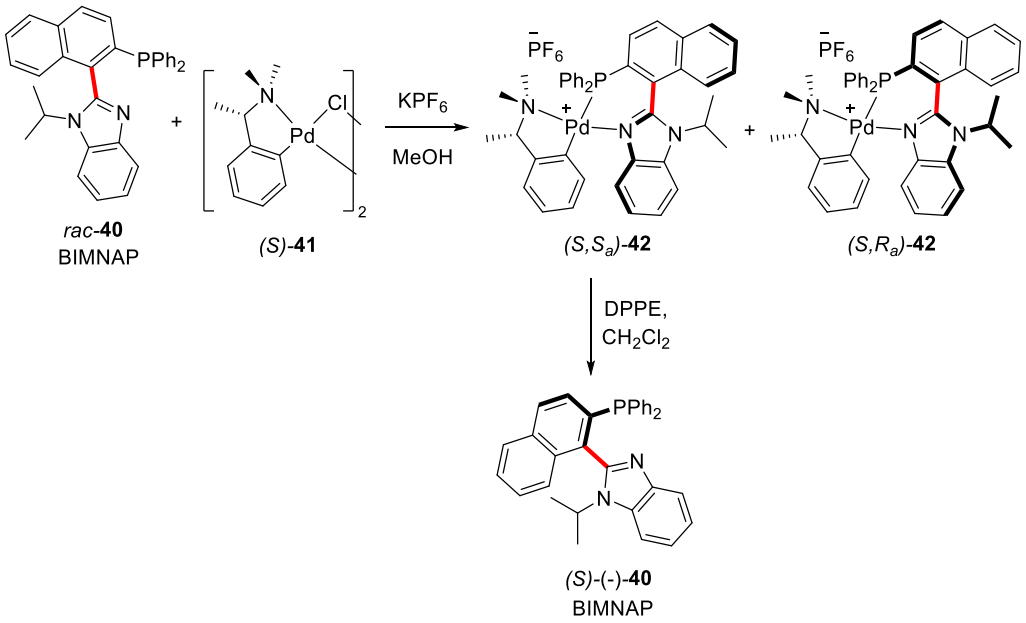
38
a X = Ph_2P
b X = Ph_2PO

39
a X = Ph_2P
b X = Ph_2PO

Figure 15 Atropisomeric heteroaromatic diphosphine ligands reported by Cesarotti *et al.*[74, 75]

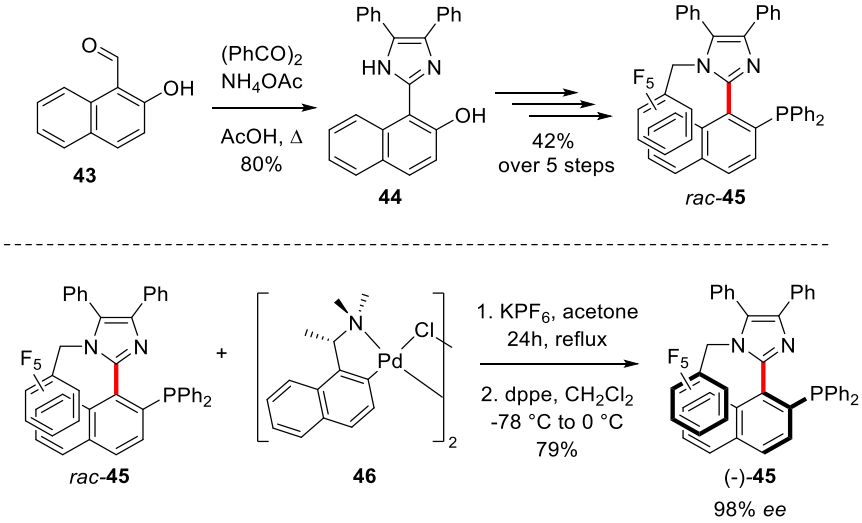
Interestingly, compounds **38a** (bimip) and **38b** (bimipo) represent one of the early examples of atropisomeric compounds featuring a N-N chiral axis and the first example of atropisomeric diphosphines with hindered rotation around a N-N chiral axis.[75] It is worth mentioning that, while they have found limited applications in asymmetric catalysis so far,[76] *N,N'*-bisazaheterocycles have gained a considerable importance given their pharmacological activity.[77] Furthermore, the new atropisomeric five-membered biheteroaromatic diphosphines reported represented an important step towards the development of phosphine ligands with tunable electronic proprieties (depending on the nature of the heteroatom).

Following these pioneering works, Altenbach and co-workers reported the first *P,N*-chelating ligand **40** (**Scheme 12**) featuring a five-membered ring.[78] Despite the compound being prepared in good yield and resolved into single enantiomers *via* fractional crystallisation of the corresponding diastereomeric Pd-complex **42**, no applications were reported by the authors.



Scheme 12 Resolution of BIMNAP *via* fractional crystallisation of the diastereomeric Pd-complex.[78]

An atropisomeric imidazole-based *P,N*-ligand that turned out to be remarkably good in several metal-catalysed reactions is StackPhos **45**, reported by Aponick and co-workers in 2013.[79] The synthesis of this ligand was achieved in six straightforward steps from the commercially available 2-hydroxy-1-naphthaldehyde **43** (**Scheme 13**). Of particular interest, is the concept behind the design of **45**: the authors hypothesised that, in spite of the presence of a five-membered ring, conformational stability could be achieved through stabilisation of the ground state, specifically by intramolecular π-stacking between the electron-poor pentafluorophenyl group and the electron-rich naphthalene ring.



Scheme 13 Synthesis and resolution of StackPhos **45**.[79]

The catalytic activity of (-)-**45** was initially tested in an asymmetric Cu-catalysed aldehyde-alkyne-amine A^3-coupling reaction, where it performed remarkably well with yields up to 95% and *ee* up to 97%,[79] and subsequently in a variety of other reactions. Among these, a Cu-catalysed quinoline alkynylation,[80] the synthesis of skipped diynes,[81] a conjugate alkyne addition to Meldrum's acids[82] and, recently, chromones.[83]. Despite its incredible success and efficacy, the resolution of StackPhos requires expensive resolving agents like **46** (**Scheme 13**). To address this drawback, the same Aponick and, independently Guiry reported the synthesis of a new class of phosphinoimidazoline (Phim) ligands **47** and **48** (**Figure 16**),[84, 85] where the imidazole core is replaced by a chiral imidazoline that acts as a built-in resolution unit, allowing an easy separation of the atropisomeric diastereoisomers by either chromatography or recrystallisation.

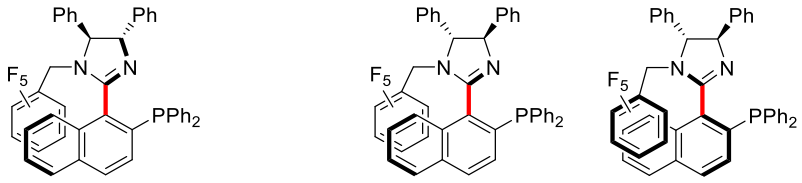
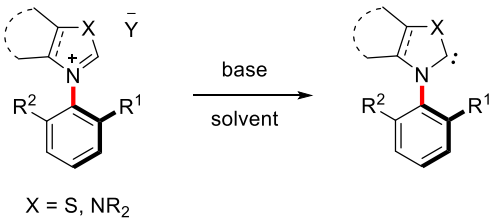


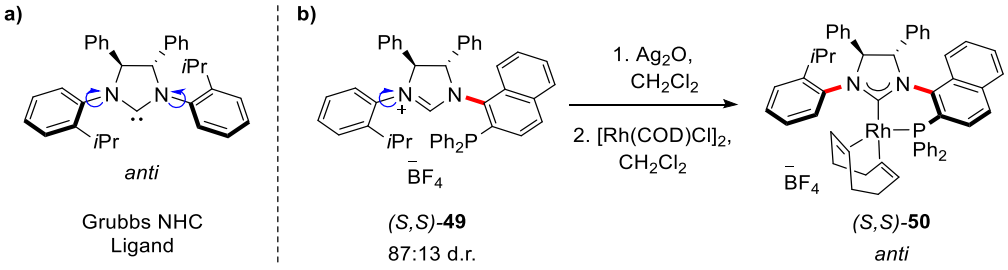
Figure 16 UCD-Phim **47** (Guiry)/StackPhim **48** (Aponick) ligands.[84, 85]

Another important family of atropisomers incorporating pentatomic rings is that of *N*-aryl(thio)azolium salts, which are precursors of *N*-heterocyclic carbenes (NHCs),[86] as shown in **Scheme 14**.



Scheme 14 Preparation of NHCs from corresponding (thio)azolium salts.

Following the seminal and independent work of Grubbs and Hoveyda in the field,[87, 88] Helmchen and Bappert reported the synthesis of the atropisomeric Rh-NHC complex **50** (**Scheme 15b**), obtained by transmetallation of the corresponding silver complex, prepared *in situ* from a mixture of diastereoisomers (87:13 d.r.) of imidazolium salt **49**.[89] Variable-temperature NMR studies confirmed that compound **49** was conformationally stable at room temperature, with coalescence observed at 135 °C, indicative of a high barrier to rotation about the C-N axis.

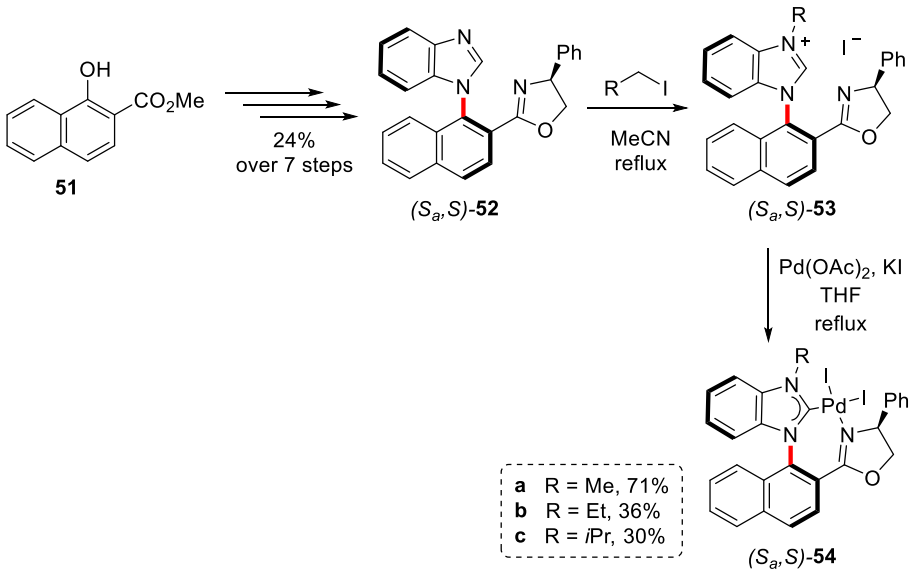


Scheme 15 a) Example of a Grubbs NHC ligand;[87] **b)** Preparation of Rh-NHC complex reported by Helmchen and Bappert.[89]

According to the authors, the ^{31}P NMR spectrum of compound **50** showed two isomers with an intensity ratio of 2:1, which were assumed to be atropisomers with respect to the C-N bond on the *i*Pr-substituted phenyl ring. The two isomers were confirmed to be stable at room

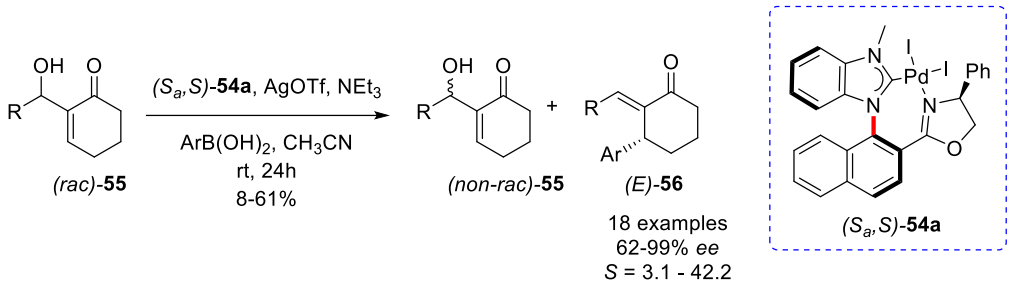
temperature and, despite not being separated, **50** was tested in Rh-catalysed hydrogenations of α, β-unsaturated esters and enamides with both high conversions and enantioselectivities.[89]

A different and more recent (but yet rather dated) example of NHC ligands, displaying an oxazoline unit, instead of a phosphine, was reported in 2011 by Wang and Shi.[90] The Pd-complexes **54** of these compounds were prepared in nine steps from commercially available compound **51** and isolated by column chromatography on silica gel as single diastereoisomers (**Scheme 16**).



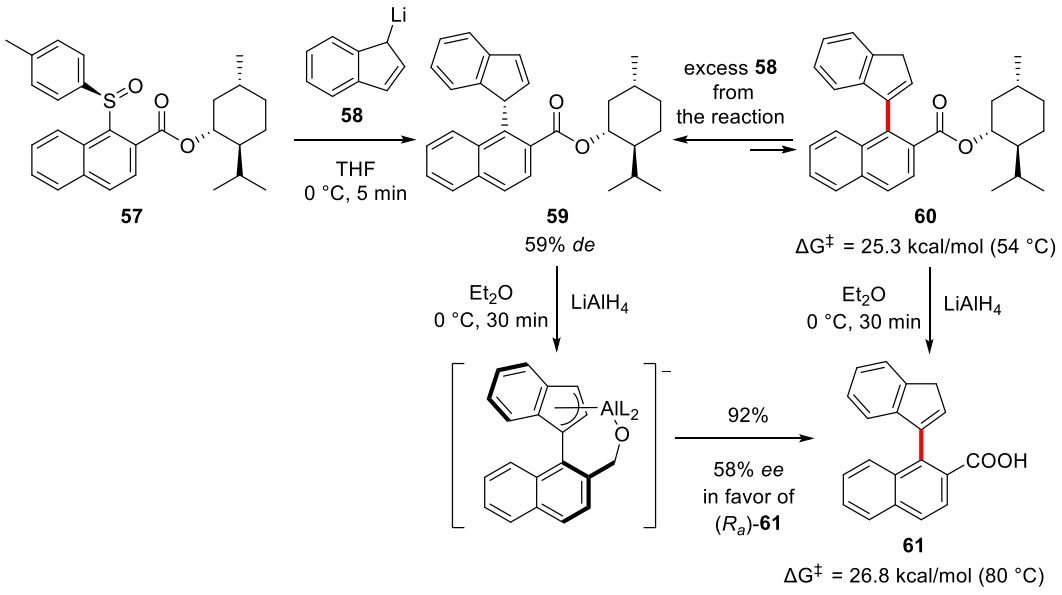
Scheme 16 Preparation of Pd-NHC ligands featuring an oxazoline unit, reported by Wang and Shi.[90]

Preliminary reaction screenings proved compound *(Sa,S)*-**54a** to be the most catalytically active, thus it was further investigated in a non-standard kinetic resolution of Morita-Baylis-Hillmann adducts **55** (**Scheme 17**), affording the corresponding products **56** with moderate to good yields and high enantioselectivities, with a selectivity factor up to 42.2.[90]



Scheme 17 Kinetic resolution of Morita-Baylis-Hilmann adducts **55** catalysed by Pd-complex **54a**, reported by Wang *et al*.[90]

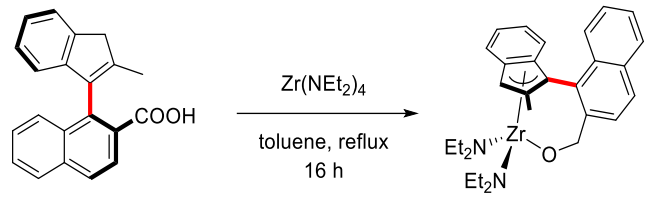
Two more examples are worth mentioning for their rather rare structural features. The first one is part of a series originally reported by Baker and co-workers in 1996, and it represents the first and only example of an atropisomeric compound featuring a non-heteroaromatic five-membered ring.[91] Compound **61** (**Scheme 18**), was prepared *via* central-to-axial chirality conversion, a class of transformation firstly hypothesised by Berson in 1955,[92] and demonstrated by Meyers almost thirty years later,[93] which still counts a fairly limited number of applications.[IV]



Scheme 18 Preparation of atropisomeric **61** *via* central-to-axial chirality conversion, as reported by Baker.[91]

[IV] Based on the number of papers published on the topic of "chirality conversion" in the period 2001-2020, according to Web of Science.

Using the sulfoxide auxiliary **57**, the authors accessed enantiomerically pure **61** either *via* the intermediate **60**, formed through the interconversion of **59** due to the excess of indenyllithium **58** or directly by treatment of **59** with $LiAlH_4$ (**Scheme 18**). Compound **61** proved to be highly stable, with a barrier to rotation of 26.8 kcal/mol at 80 °C, determined by HPLC analysis on chiral stationary phase.[91] Although no applications were reported for **61**, the 2-methylindenyl variant **62** was reported a few years later by the same group, and used to prepare the optically pure planar chiral Zr-complex **63** *via* an efficient axial-to-planar chirality conversion (**Scheme 19**).[94]



ent-**62**
99% *ee*

(P)-**63**
99% *ee*

Scheme 19 Preparation of the planar chiral Zr-complex **63** *via* axial-to-planar chirality conversion.[94]

Finally, it is worth mentioning the atropisomeric 5,5'-bistriazoles recently reported by Pericàs and Etayo.[95] This series of compounds represents one of the rare examples of atropisomeric compounds featuring a 1,2,3-triazole unit.[96-98] The synthesis of these compounds was easily achieved in one single step *via* a copper-catalysed azide-alkyne cycloaddition (CuAAC), originally reported by Meldal,[99] Fokin and Sharpless.[100] Configurational stability studies on these heterobiaryl atropisomers demonstrated that compounds like **64** (**Figure 17b**), displaying solely axial chirality were not stable enough, with a half-life of only 9 hours, whilst an axially and centrally chiral bistriazole like **65** proved to be stable under ambient conditions, with a half-life of *ca.* 201 days (**Figure 17b**).

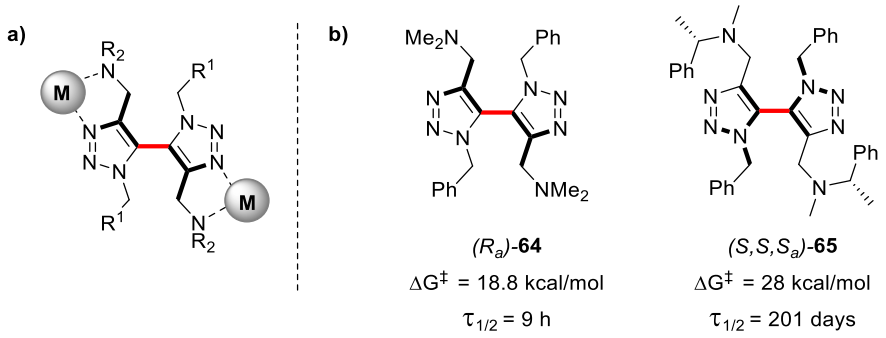
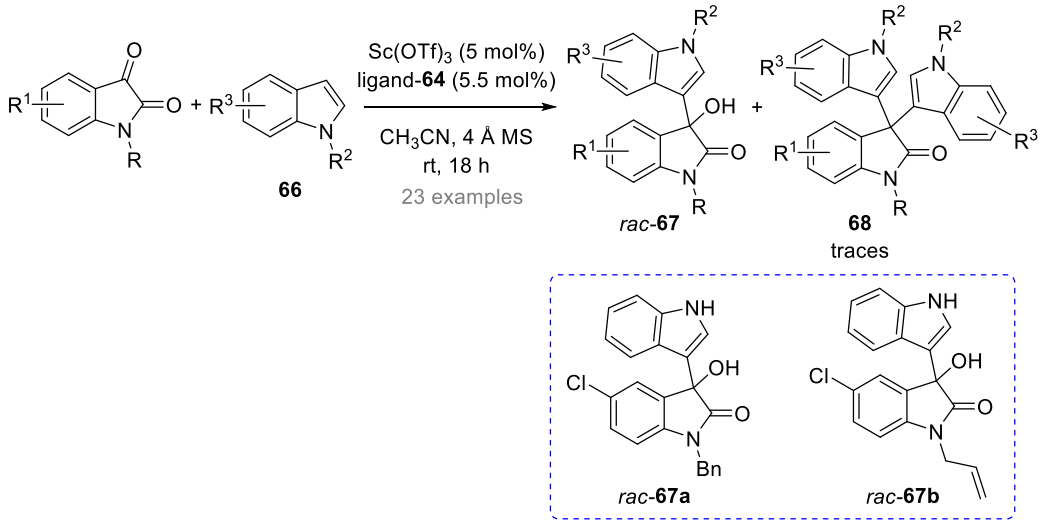


Figure 17 a) Ligand design; **b)** Conformational stability of atropisomeric 5-5'-bistriazoles **64** and **65**.[95]

Atropisomeric compound **64** was successfully employed in a highly chemoselective Sc-catalysed Friedel-Craft alkylation of indoles **66** with isatins (**Scheme 20**). Although the products **67a-b** were obtained racemic, the authors demonstrated that the reaction had a very broad substrate scope (with 23 examples prepared) and managed to synthesise **67a**, an oncology drug candidate, and **67b,** a novel regioisomer of a potent antimicrobial.[95]



Scheme 20 Sc-catalysed nucleophilic addition of indoles to isatins, performed with bistriazole **64** (**Figure 17**) as ligand.[95]

1.3.1.5 As Organocatalysts

Examples of atropisomeric organocatalysts featuring five-membered rings are scarce, and this is perhaps due to the fact that, although many novel strategies have emerged in the past years,[18,

[101, 102] the methods available are often limited to specific substrates, narrowing *de facto* the potential applications of the resulting chiral products.

One of the early applications in organocatalysis was reported by Bach's group in 2004, which demonstrated that, in principle, axially chiral *N*-arylthiazolium salts (*e.g.* **70** and **71** in **Figure 18**) could be employed as catalysts in nucleophilic aldehyde activations.[103]

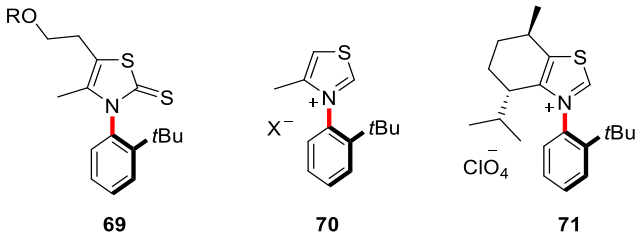
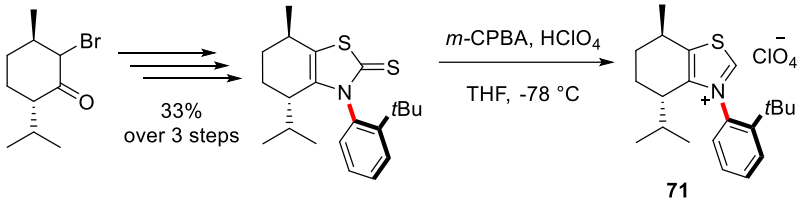


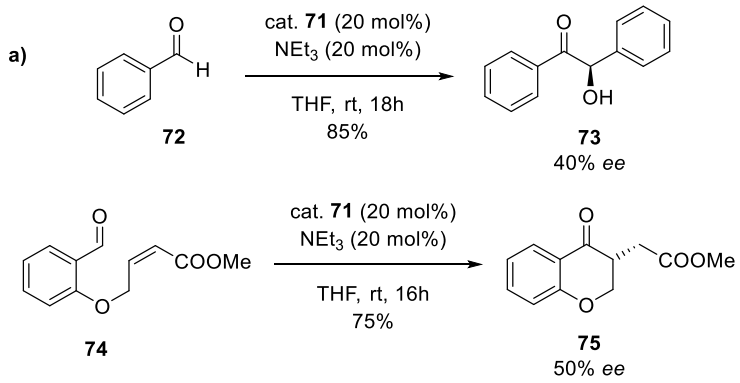
Figure 18 Chiral thiazole derivatives reported by Bach and co-workers.[103]

Their efforts to access compounds like **70** and **71** (**Figure 18**) led to a defined synthesis proceeding *via* oxidation of thiones like **69**. Particularly relevant in this regard is the synthesis of thiazolium **71**, obtained diastereomerically pure from α-bromo menthone, in four steps (**Scheme 21**).



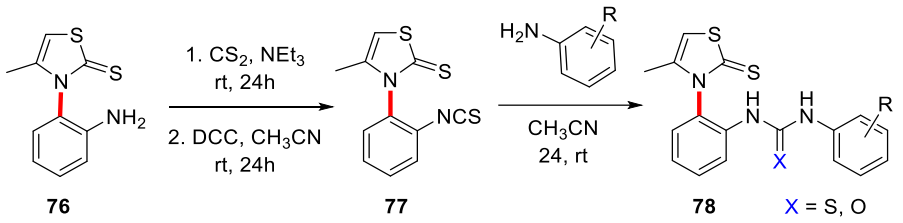
Scheme 21 Diastereoselective synthesis of thiazolium salts **71**.[103]

Catalytic screening conducted with compound **71** proved, at least in principle, its suitability as an organocatalyst in the benzoin condensation of benzaldehyde **72** (**Scheme 22a**), and in the intramolecular Stetter reaction of the α, β-unsaturated ester **74** (**Scheme 22b**). In both cases, optimal results were obtained with 20 mol% catalyst loading. However, although the yields achieved were overall good, the enantioselectivities were quite modest, with up to 40% *ee* attained in the benzoin condensation and 50% *ee* in the Stetter reaction.[103]



Scheme 22 Organocatalytic benzoin condensation and **b)** Stetter reaction catalysed by thiazolium salt **71**.[103]

A few years later, Roussel and co-workers reported a series of non-racemic atropisomeric (thio)ureas **78**, prepared in good overall yields starting from thione **76** (**Scheme 23**).[104]



Scheme 23 Synthesis of atropisomeric (thio)ureas **78** reported by Roussel and co-workers.[104]

Optically pure (thio)ureas were obtained through semi-preparative HPLC on chiral column, hence tested as anion receptors, where they showed modest binding affinities and discriminations towards selected amino-acids derivatives. The authors found that, contrary to what was expected on the basis of the NHs acidities in (thio)ureas, the association constants were higher for ureas rather than the corresponding thioureas. The explanation provided came from computational and experimental analyses, which proved that whilst thioureas adopted a (*Z,E*) conformation, ureas were pre-organised in a (*Z,Z*) conformation, suitable for a double hydrogen bond with the anions tested (**Figure 19**). In addition, it was found that thioureas engaged in an intramolecular hydrogen bond with the thiocarbonyl group of the heterocycle that, according to the authors, might contribute to a smaller association constant, as a consequence of the reduced availability of NH for binding.

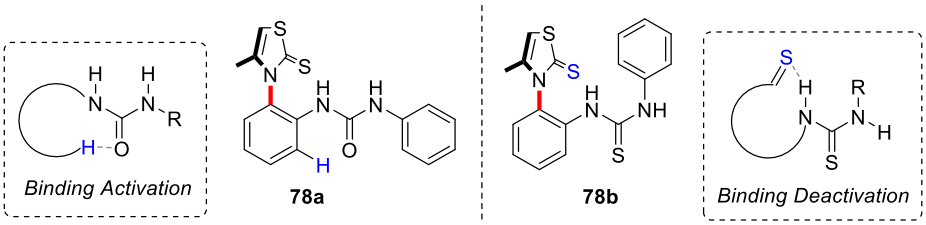


Figure 19 Conformation adopted and corresponding possible influence of intramolecular hydrogen bond on binding ability of urea **78a** and thiourea **78b**.

Based on this design, Steele *et al.*, in collaboration with Roussel, reported the new bifunctional atropisomeric thioureas **79**, as both a mixture of and the single diastereoisomers.[105]

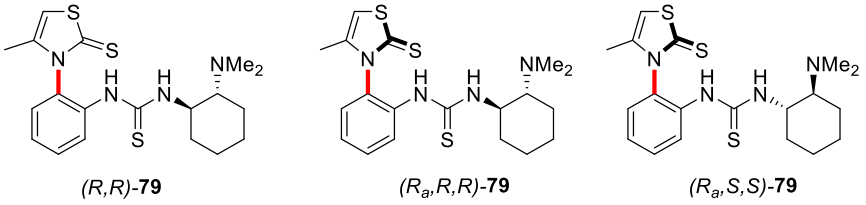
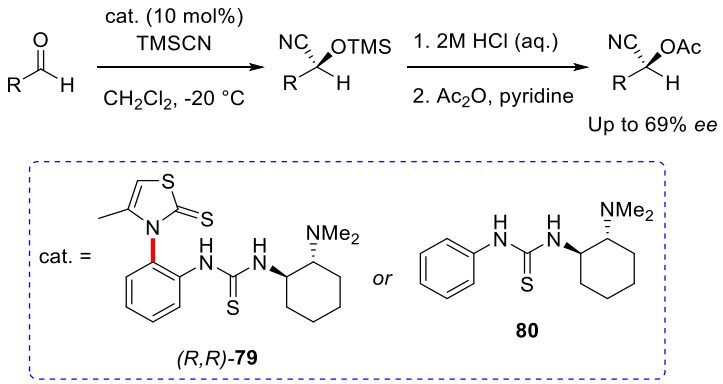


Figure 20 Atropisomeric thioureas reported by Steele *et al.*[105]

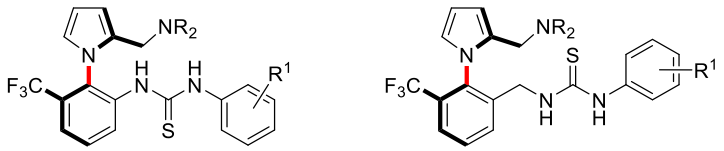
The compounds were tested as organocatalysts in an asymmetric cyanosilylation of aldehydes (**Scheme 24**). Optimal conditions were found to be the use of dichloromethane as a solvent at -20 °C, and branched aliphatic aldehydes giving the best overall results with up to quantitative yields and 69% enantiomeric excess.



Scheme 24 Asymmetric cyanosilylation catalysed by atropisomeric thiourea **79**.[105]

Interestingly, the catalytic screenings highlighted that *(R,R)*-**79** (**Figure 20**), the mixture of two diastereoisomers, gave better enantioselectivities than the single diastereoisomers *(R_a,R,R)*-**79**

and *(R_a,S,S)*-**79**, which was tentatively attributed to there being more than one molecule of thiourea in the transition state, resulting in a cooperative interaction. Furthermore, by comparison with urea **80** (**Scheme 24**), the authors were able to demonstrate that axial chirality was crucial to attaining good enantioselectivities. Indeed, under optimal conditions, thiourea **80** afforded poor 15% *ee*. Following these pioneering works, Faigl *et al.* recently reported a series of atropisomeric 1-phenylpyrrole-containing (thio)ureas **81** and **82** (**Figure 21**).[106]

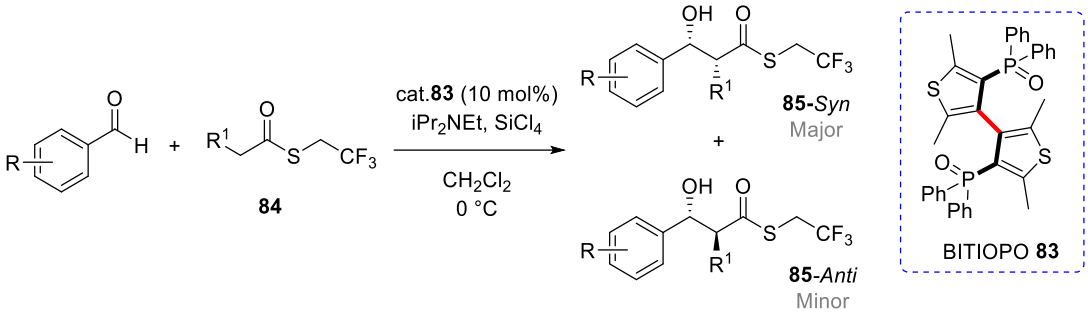


(R)-**81** *(S)*-**82**

Figure 21 Atropisomeric 1-phenylpyrrole-containing thioureas reported by Faigl *et al.*[106]

Although the preparation of these compounds was relatively straightforward, the asymmetric induction in the reaction tested, *i.e.* the Michael addition of 1,3-diketones to β-nitrostyrene, was modest, with 54% being the best *ee* achieved under optimised conditions. In addition, the authors found that the more rigid design of compounds **81** (containing a -CH_2- less) could attain higher asymmetric inductions, albeit at the expense of the yields.

Phosphine oxides represent another important class of compounds in organocatalysis. In this regard, the bis-thiophenyl phosphine oxides reported by Benaglia and co-workers are a successful example of atropisomeric organocatalysts featuring five-membered rings. Following their initial report in 2011,[107] the group published a remarkable first example of enantioselective crossed aldol addition of activated thioesters of type **84** to aldehydes catalysed by BITIOPO **83** (**Scheme 25**).[108]



Scheme 25 Organocatalytic enantioselective crossed aldol addition of activated thioesters to aldehydes.[108]

Optimal results were obtained in dichloromethane at 0 °C, indeed lower temperatures (-40 °C) were found to be detrimental, leading to excessively long reaction times and no better enantioselectivities. Notably, BITIOPO **83** showed a superior catalytic activity compared to BITIANPO **86,**[74] and BINAPO **87**,[109] in terms of both yields and enantioselectivities, highlighting the importance of the electronic properties of the chiral phosphine oxide.

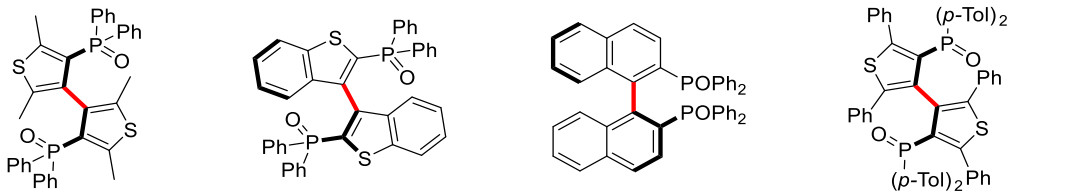


Figure 22 Atropisomeric phosphine oxides reported by Benaglia and co-workers.

Under fully optimised conditions, the methodology was expanded to a range of aromatic and heteroaromatic aldehydes as well as variously substituted trifluoroethyl thioesters, achieving high isolated yields, diastereo- and enantioselectivities (*i.e.* up to 98:2 *syn*/*anti* ratio and 95% *ee*). The observed stereoselectivity was rationalised on the basis of steric considerations, according to which the formation of the *syn* aldol (preferred isomer) proceeds *via* the chair-like transition state **A** where, conversely to **B**, the steric repulsion between the trifluoroethyl (R in **Figure 23**) and the phenyl group of the catalyst is minimised.

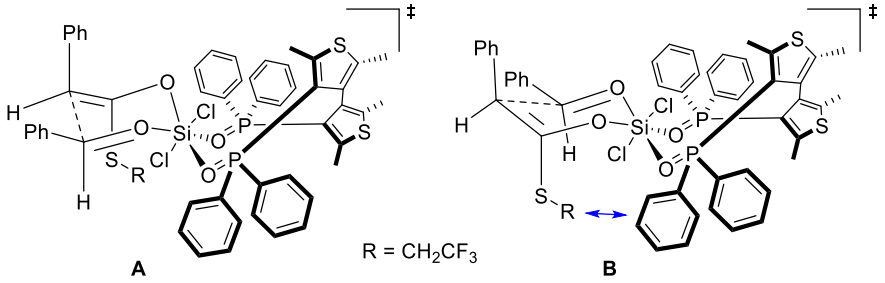
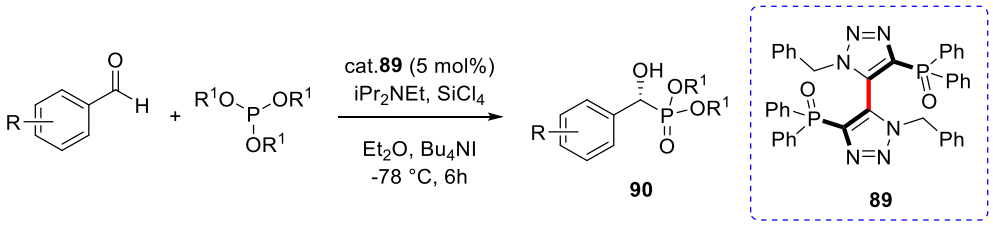


Figure 23 Proposed model of stereoselectivity in crossed aldol addition of activated thioesters to aldehydes.[108]

Recently, the same group has reported **88** (**Figure 22**), a variant of BITIOPO **83** featuring a tetra phenyl bis-thiophene scaffold and a tolyl substituted phosphine oxide functionality.[110] The performance of the catalyst was tested in a number of direct aldol reactions, and although its ability to promote them was proved, the stereocontrol achieved was overall lower compared to BITIOPO **83**, although its reactivity was superior with certain substrates.

Similar in design, the bis-triazolyl phosphine oxides reported by Virieux and co-workers[96-98] offer another example. A few years after the first report of these compounds,[96] in 2017 the group disclosed the first application of compound **89** (**Scheme 26**) in asymmetric organocatalysis: a $SiCl_4$-mediated enantioselective Abramov phosphonylation of aldehydes with trialkyl phosphites.[97]

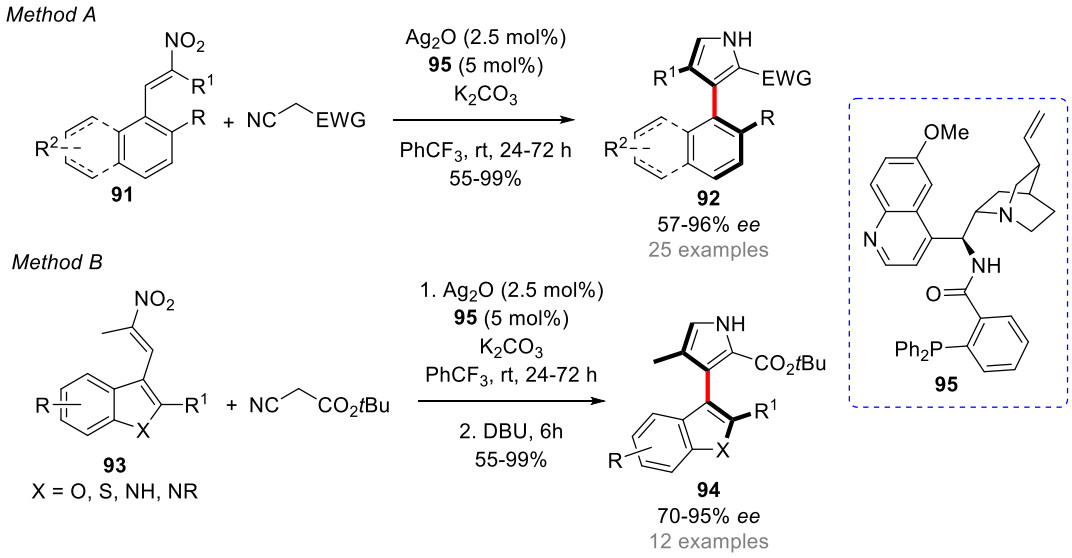


Scheme 26 Organocatalysed enantioselective Abramov phosphonylation of aldehydes with phosphites.[97]

The reaction showed a strong dependence on the solvent employed, with diethyl ether affording the best yields and enantioselectivities. Furthermore, it was found that the use of tetrabutylammonium iodide, significantly increased the catalytic activity of **89**. Under fully optimised conditions, the authors showed that a wide range of chiral α-hydroxyphosphonates

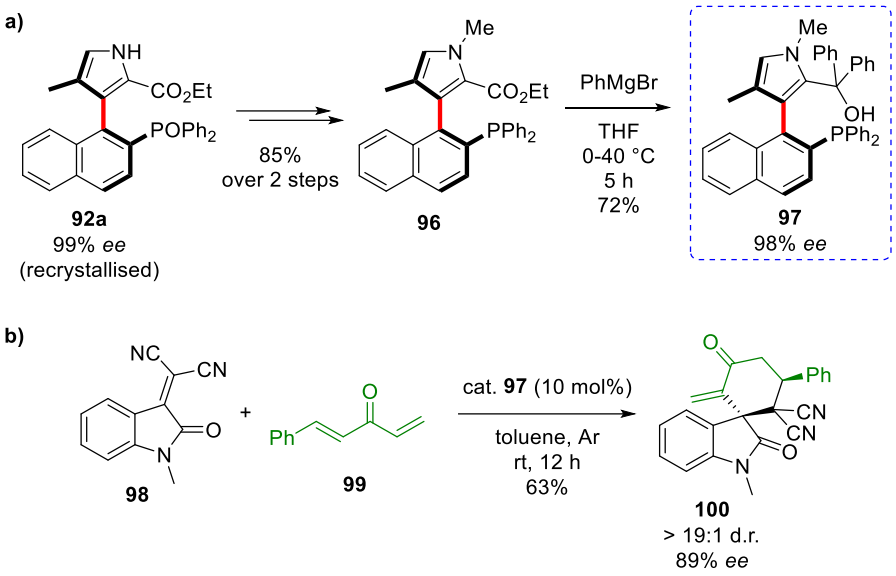
90 (**Scheme 26**) could be prepared in excellent isolated yields (up to 96%) and good enantioselectivities (up to 78% *ee*). Other applications of **89** include the enantioselective allylation of aldehydes and the asymmetric reductive crossed aldol reaction for the preparation of β-hydroxyl ketones.[98]

Finally, in 2019 He *et al.* reported an unprecedented atroposelective Barton-Zard reaction that afforded axially chiral (hetero)aryl pyrroles of type **92** and **94** in a straightforward manner with high yields and selectivities (**Scheme 27**).[111]



Scheme 27 Asymmetric Barton-Zard reaction for the construction of atropisomeric (hetero)aryl pyrroles.[111]

Apart from the elegance of the approach itself, the authors demonstrated the potential of the products obtained, transforming compound **92a** into the corresponding bifunctional phosphine **97** in three simple steps whilst fully retaining the optical purity (**Scheme 28a**). Phosphine **97** was then used as a Lewis base organocatalyst in a [4+2] cycloaddition of alkene **98** to dienone **99**, affording the spirooxindole product **100** in modest yield but high diastereo- and enantioselectivity (**Scheme 28b**).



Scheme 28 a) Synthesis of bifunctional phosphine **97**; **b)** Application in asymmetric [4+2] cycloaddition.[111]

1.4 1,2,3-Triazoles: An Overview

Triazoles are five-membered heterocyclic rings whose main skeleton contains three nitrogen and two carbon atoms. Depending on the relative positions of the nitrogen atoms, two sets of tautomeric isomers can be identified (**Figure 24**).

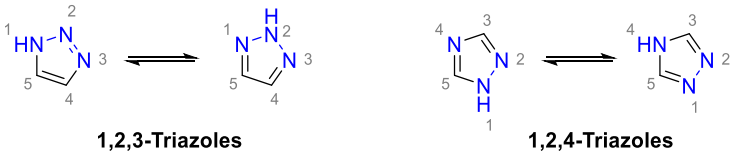


Figure 24 Isomers of triazoles.

Triazoles are aromatic: all the atoms are sp^2 hybridised and the 6π electrons are delocalised in the ring, conferring great stability.

A major breakthrough in the development of triazole chemistry came with the advent of "click chemistry". Coined and defined by Sharpless and co-workers in 2001,[112] the term "click" refers to reactions that are high yielding, stereo- and chemoselective, wide in scope and that proceed under simple reaction conditions (*i.e.* insensitive to oxygen and moisture) using benign solvents, and whose product(s) can ideally be isolated by nonchromatographic methods. As

Sharpless himself defined it, the Huisgen 1,3-dipolar cycloaddition of azides and alkynes is the "cream of the crop" of click reactions. In particular, the copper-catalysed variant of this reaction[99, 100] and the ruthenium-catalysed version[113] have allowed easy access to 1,4- and 1,5-disubstituted 1,2,3-triazoles respectively, contributing to the ubiquity of this scaffold in many areas of chemistry.[114-117] Given the considerable interest that triazoles have gained, numerous other metal-catalysed and metal-free synthetic approaches have emerged in the past few years, and a comprehensive review covering the literature spanning the last decade has recently been published.[118]

In addition to its simple preparation, the 1,2,3-triazole ring is an intriguing heterocycle with notable intrinsic properties. In medicinal chemistry, it is considered a bioisostere of amides, with the lone pairs on the nitrogen atoms mimicking those on the carbonyl oxygen and functioning as hydrogen-bond acceptors, and the highly polarised C-H bond acting as a hydrogen bond donor, analogously to the N-H bond in amides (**Figure 25**).[119]

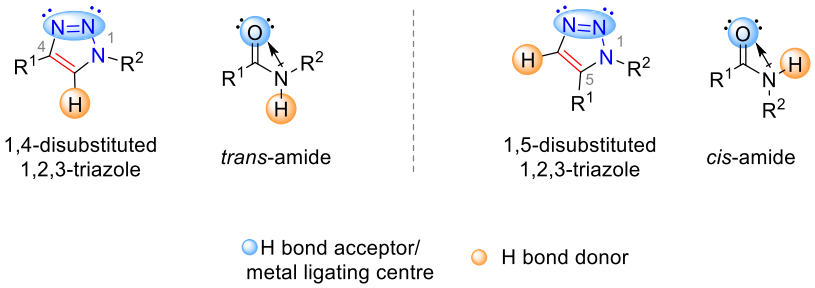
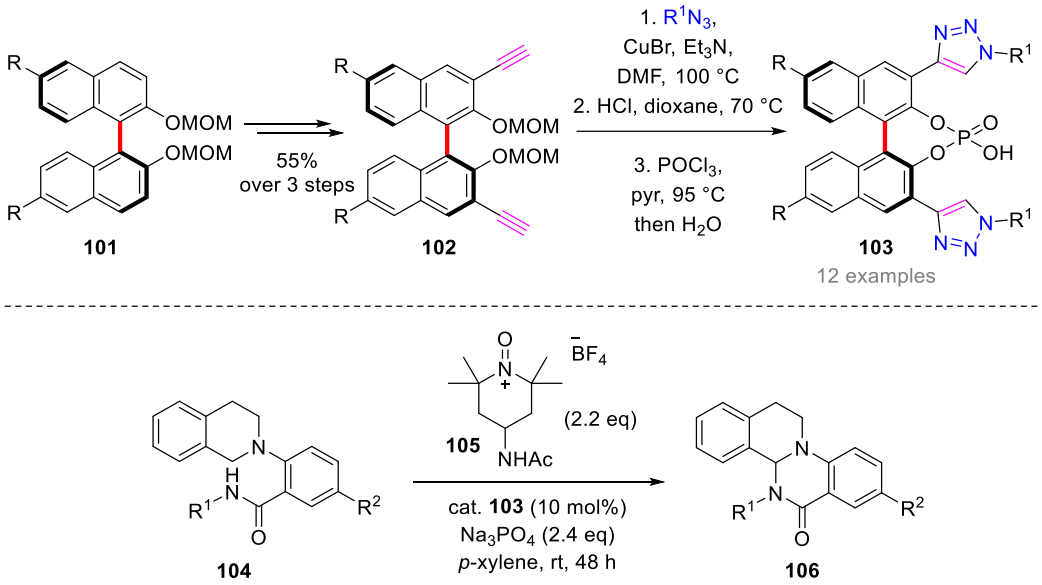


Figure 25 Intrinsic properties of 1,2,3-triazoles.

These features, in addition to its large dipole moment, allow numerous other possible intra- and intermolecular interactions such as coordination to metals and anions complexation, resulting in myriads of applications in supramolecular[120-122] and coordination chemistry,[123] medicinal chemistry,[121, 124] drug discovery,[125] and catalysis.[126, 127] Of particular interest for the purpose of this thesis are the applications of chiral 1,2,3-triazoles in asymmetric organocatalysis, which complement the previous section and will conclude the chapter.

1.4.1 Chiral 1,2,3-Triazoles in Asymmetric Organocatalysis

Taking advantage of the CuAAC, Toste and co-workers reported a library of 3,3'-triazolyl BINOL-derived phosphoric acids **103**, prepared using a simple synthetic protocol (**Scheme 29**).[128]



Scheme 29 Synthesis of Click-BINOL phosphoric acids and application in oxidative coupling reactions .[128]

The compounds were tested as bifunctional organocatalysts in enantioselective intramolecular cross-dehydrogenative coupling (CDC) of tetrahydroisoquinolines **104**, performing significantly better than conventional axially chiral phosphoric acids like those shown in **Figure 26a**. Furthermore, the pyrazolyl and imidazolyl isosteric analogues **107** and **108** (**Figure 26b**) achieved similar conversions but considerably lower enantioselectivities, suggesting that the electronic properties of the triazole substituents were pivotal to achieve high enantioselectivities.

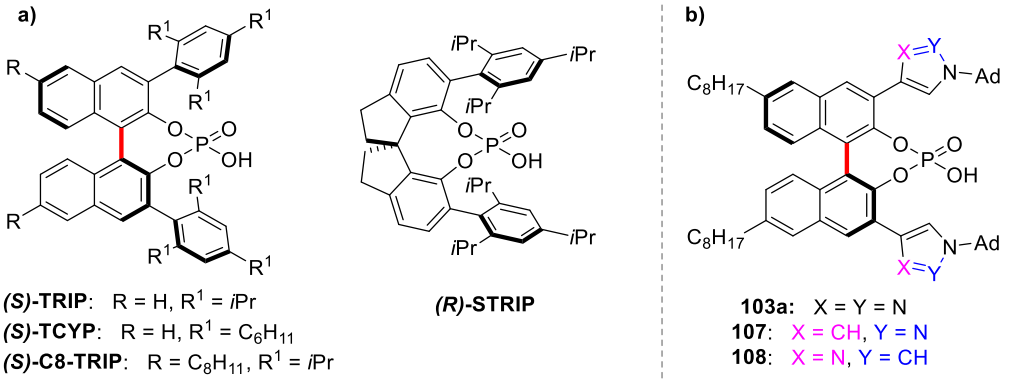
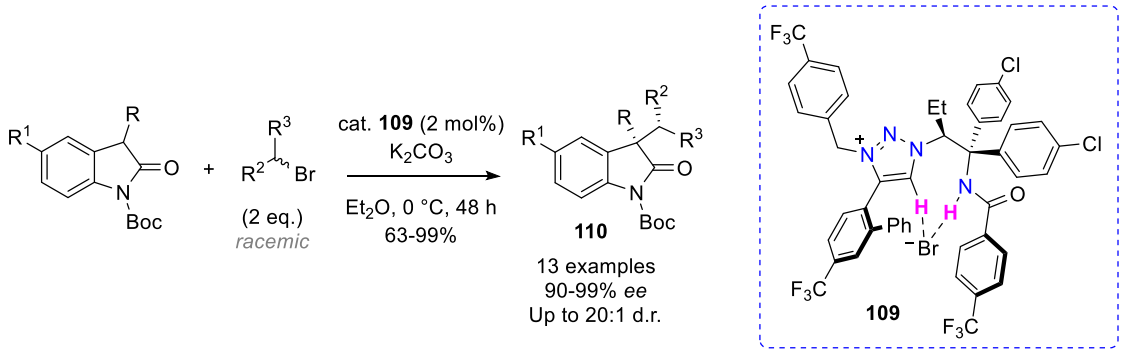


Figure 26 Phosphoric acids screened by Toste and co-workers as organocatalysts for enantioselective CDC amidation.

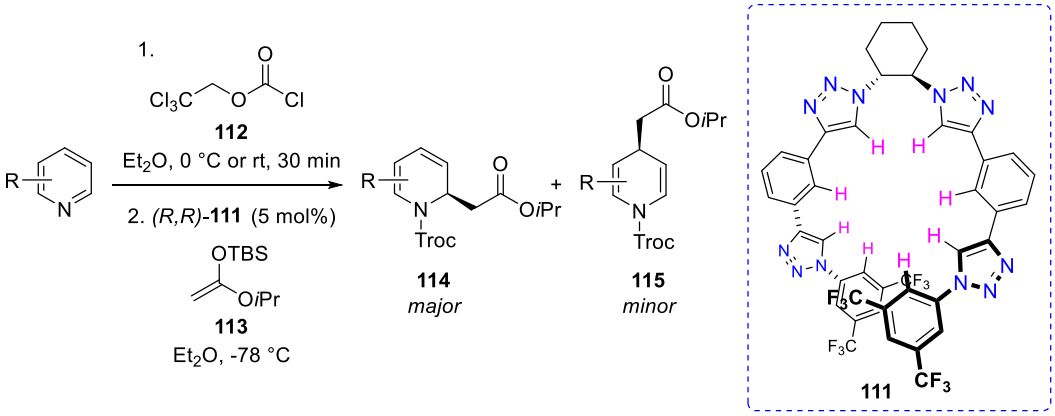
Asymmetric phase-transfer catalysis was also extensively exploited by Ooi's group, which reported a series of chiral 1,2,3-triazolium salts that were successfully employed in a variety of asymmetric reactions. Among these, a recent example is represented by the diastereo- and enantioselective alkylation of oxindoles with racemic secondary alkyl halides catalysed by triazolium salt **109** (**Scheme 30**).[129]



Scheme 30 Diastereo- and enantioselective alkylation of 3-substituted oxindoles with racemic secondary alkyl bromides.[129]

Under fully optimised conditions, the catalyst afforded good to excellent yields, and high diastereo- and enantioselectivies with a range of racemic alkyl bromides, although heteroaromatic substituents, small alkyl groups (*e.g.* Me, Et) and esters showed a pronounced decrease in diastereoselectivity. The scalability of the method was also proved, making the catalyst a remarkable tool for the asymmetric synthesis of compounds like **110**, featuring vicinal all-carbon quaternary or tertiary stereocentres. It is worth mentioning that, in a previous

publication, the authors had proven the importance of the double hydrogen-bonding interaction between the triazolium salt and the anion for achieving a high level of asymmetric induction.[130] Another important type of asymmetric ion-pairing catalysis involves neutral, rather than charged, catalysts. In this regard, the work of García Mancheño and co-workers has emerged. Among the numerous applications reported by her group, newly developed chiral helical oligotriazoles with C-H bond donor ability were employed as anion-binding organocatalysts in the first enantioselective nucleophilic dearomatization of pyridines (**Scheme 31**).[131]



Scheme 31 Enantioselective nucleophilic dearomatization of pyridines catalysed by oligotriazoles **77**.[131]

Similar to Toste's catalysts **103**, the novel tetratriazole-containing catalyst **111** performed better than other well-known N-H hydrogen-bond donor catalysts (**Figure 27**), promoting preferentially the formation of 1,2-dihydropyridines **114** (with few exceptions) up to 88% yield and 98% *ee*.

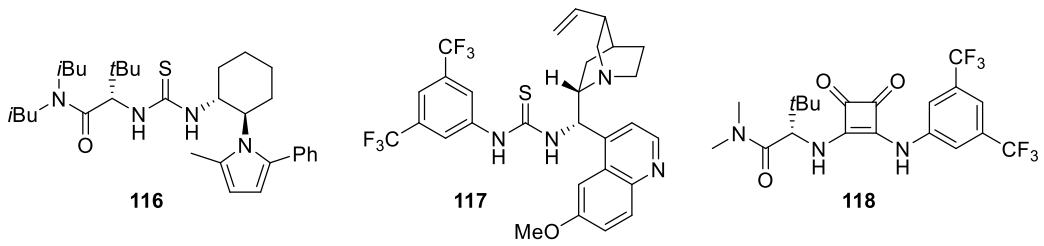


Figure 27 Known hydrogen-bond donor catalysts.

Noncovalent organocatalysis can also be enabled by halogen-bond donors, and in this regard, there are examples, although limited, of asymmetric reactions catalysed by compounds able to engage in different simultaneous interactions, including halogen bonds.[132, 133] None of these, however, include a triazole unit. Interestingly though, examples of chiral halotriazole-based compounds are known (*e.g.* **Figure 28**), and some of them have shown enantioselective recognition.[134-137] Nonetheless, no successful application in asymmetric organocatalysis has been found in the literature.

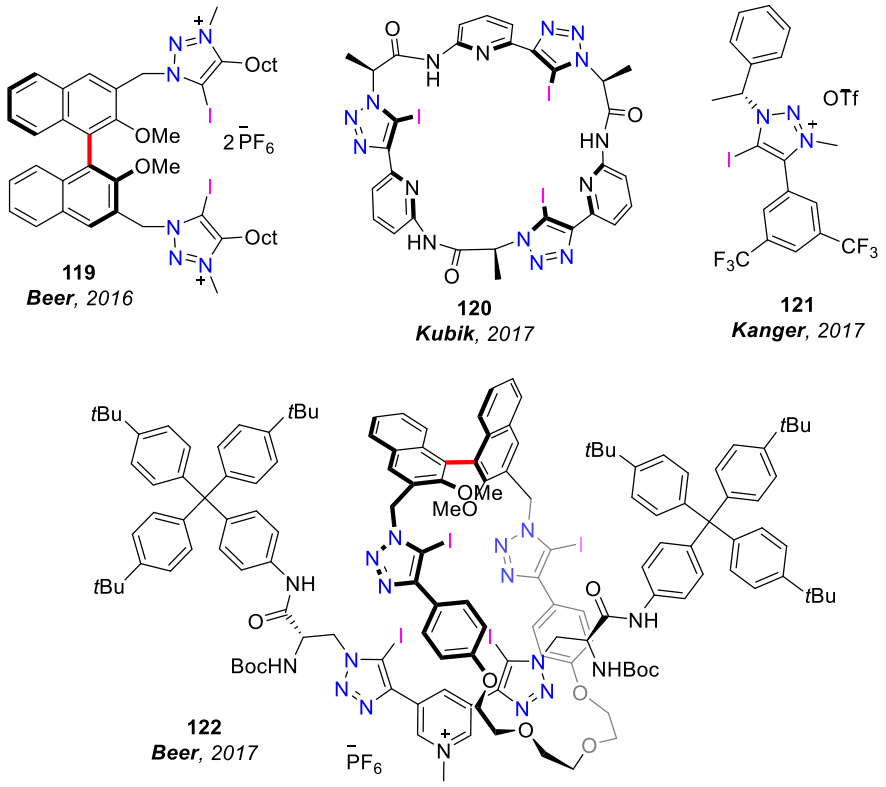
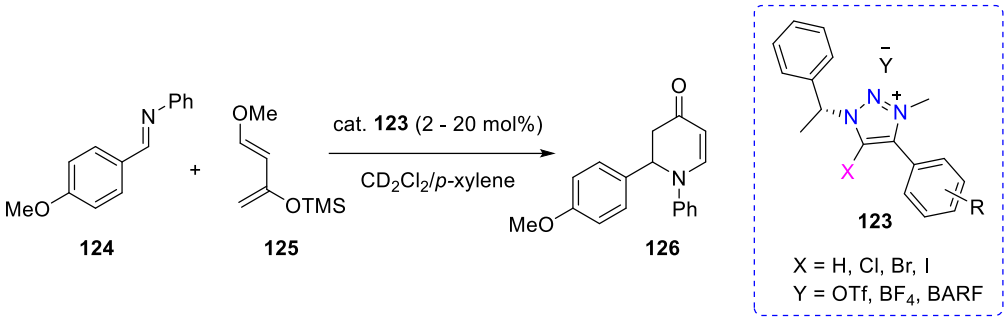


Figure 28 Selected examples of chiral iodotriazole-based halogen-bond donor organocatalysts.[134-137]

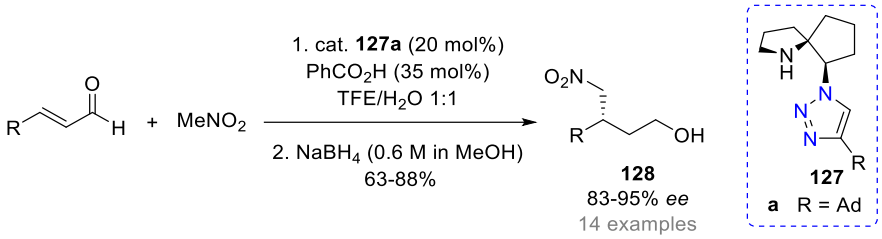
Kanger and co-workers, however, evaluated the catalytic performances of halo-1,2,3-triazolium salts **123** in a model organocatalytic aza Dies-Alder reaction (**Scheme 32**). Whilst no stereoselectivity was observed, the authors showed that the catalytic activity can be tuned by modifying the structure of the catalyst so that, for instance, a pentafluorophenyl substituent in the 4 position lowered the catalyst loading to 2 mol%, and both the choice of the halogen atom

X and the counterion significantly impacted the catalytic activity (albeit in an unusual and unpredictable way).[138]



Scheme 32 Model aza Dies-Alder reaction catalysed by halo-triazolium salts **123**.[138]

Lastly, it is worth mentioning the series of new spiropyrrolidine triazole catalysts **127**, reported by Liu *et al.* in 2015.[139] These compounds proved to be effective catalysts in the asymmetric Michael addition of nitromethane to α, β-unsaturated aldehydes (**Scheme 33**), promoting it *via* an iminium-type activation.



Scheme 33 Asymmetric Michael addition of nitromethane to α, β-unsaturated aldehydes catalysed by spiropyrrolidine triazole **127a**.[139]

Whilst all catalysts reported catalysed the reaction, the stereoselectivity was largely affected by the R substituent on the 4-position of the triazole, with the bulky adamantyl group affording the highest enantioselectivities (up to 95% *ee*), and hence chosen for further optimisations. Both (hetero)aromatic and aliphatic aldehydes were well tolerated, affording the desired products in moderate to excellent yields (*i.e.* 63-88%).

1.5 Summary

Atropisomerism is a peculiar type of axial chirality arising from restricted rotation around a single bond. The stability of these compounds is determined by the magnitude of the rotational barrier $\Delta G^{\ddagger}$, which is influenced by factors such as the degree of steric hindrance, the temperature, and the solvent. Atropisomeric compounds have shown unique properties in many areas of chemistry including supramolecular and material chemistry, drug discovery and catalysis.[12, 55, 140]

When compared to six-membered biaryl or heterobiaryl ring derivatives, atropisomeric compounds featuring five-membered rings have received much less attention. Nonetheless, these compounds have found numerous successful applications, especially as chiral ligands for metal-catalysed reactions. However, as it has been shown, examples in asymmetric organocatalysis are still rather limited, and in general, there is a distinct prevalence in the literature of catalysts based on substituted proline, the binaphthyl scaffold or cinchona alkaloids.[141, 142]

Among the applications referenced, atropisomeric compounds based on the 1,2,3-triazole core are of particular interest for the author of this thesis not only because 1,2,3-triazoles are generally easily accessible but, thanks to their unique properties, they allow a number of inter- and intramolecular interactions, which are key in numerous (organo)catalytic applications.

2 Aim

Despite the significant contributions towards the development of novel atropisomeric compounds featuring pentatomic rings, the design and synthesis of these compounds is still a challenge.

Given the considerable interest that our group has for the triazole core,[143-146] and the remarkable chiral recognition that atropisomers have shown, this project aims to synthesise a class of novel atropisomeric triazole-containing compounds that could combine the intriguing properties of the triazole motif with the hallmarks of axial chirality.

Existing synthetic strategies will be optimised *ad hoc* to access the desired atropisomeric compounds. The rotational barriers of said compounds will then be assessed through experimental and/or computational methods, demonstrating that the rotation about the chiral axis may be significantly restricted. The design will hence be validated in asymmetric catalysis, where these atropisomeric compounds will be tested as catalysts in a series of organocatalytic reactions taken from the existing literature.

3 First Generation Atropisomeric Triazoles

Previous work conducted in the Fossey group had proved that appropriately substituted 1,4-triazoles could engender atropisomerism upon alkylation. In particular, compound **129** (**Figure 29**) had shown remarkable stability at high temperatures, with the four diastereotopic protons not coalescing even at 100 °C in TCE-d_2, indicative of a highly restricted rotation on the NMR time scale.[147]

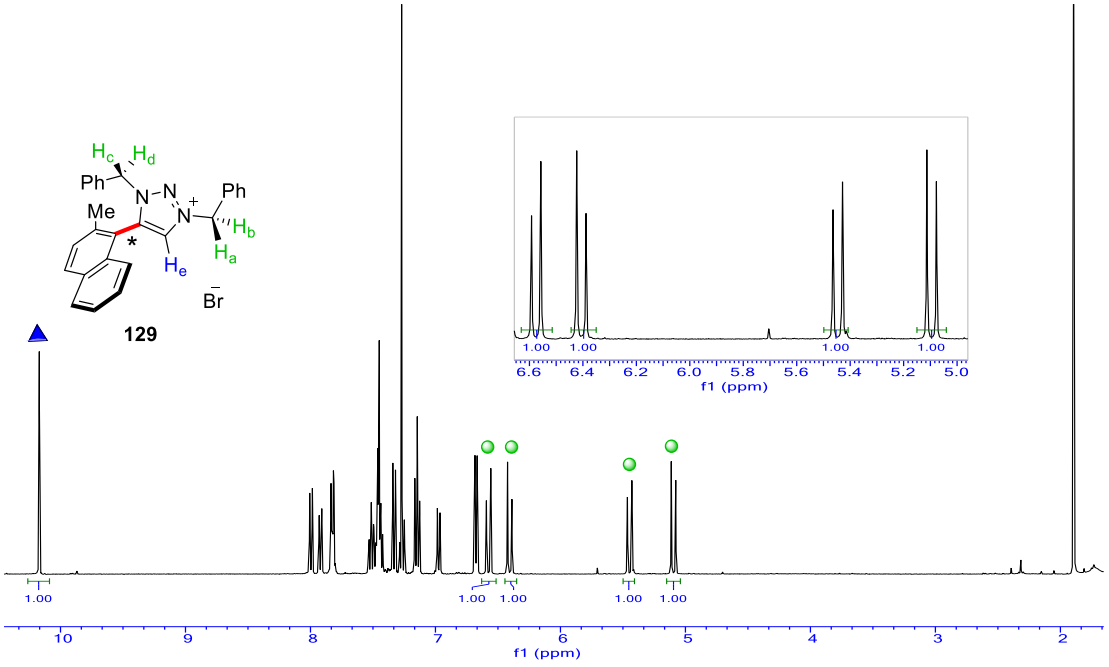
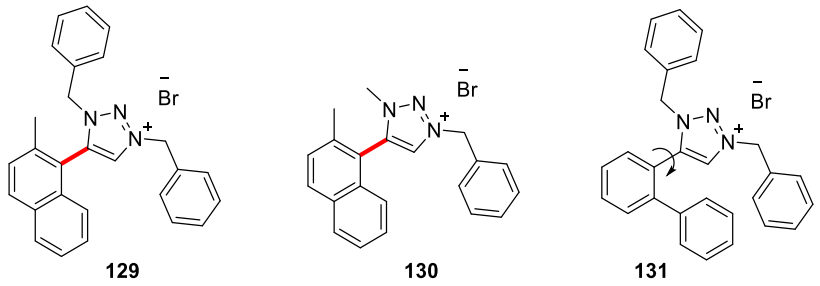


Figure 29 ^{1}H NMR spectrum of compound **129**; diastereotopic resonances are labelled with a green dot.

To define what steric requirements were needed to achieve atropisomerism, a small library of model compounds had been synthesised, showing that the *ortho* substituents of the aromatic ring at the C(4) of the triazole were key in this regard (**Figure 30**).



129 **130** **131**

Rotation restricted *Stable at RT*

Rotation restricted *Slowly rotating at RT*

Rotation not restricted *Freely rotating at RT*

Figure 30 Examples of previously synthesised triazolium salts, highlighting the importance of the *ortho* substituents.

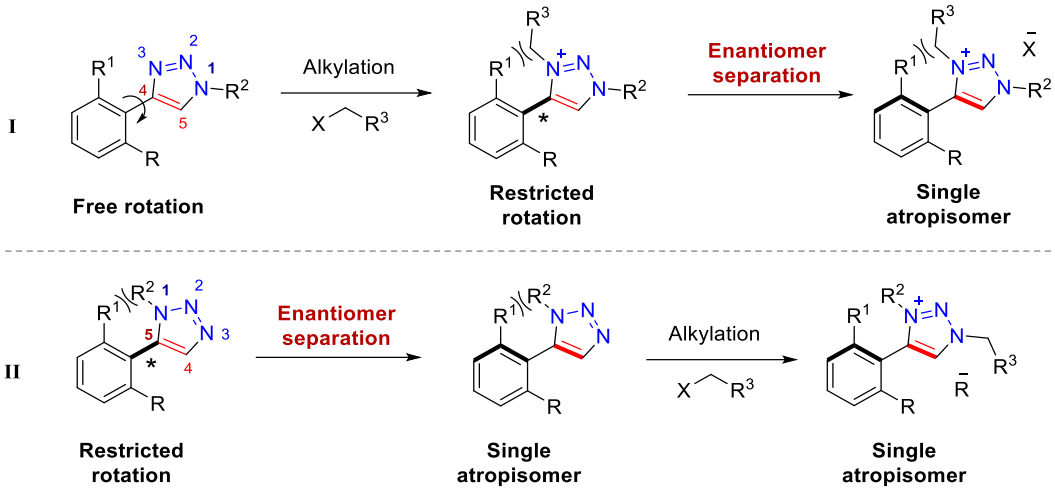
With this preliminary knowledge in hand, it was yet to be proven whether:

i. Access to the single enantiomers of such compounds was achievable.

ii. These compounds could be used as effective organocatalysts.

3.1 Synthetic Approaches

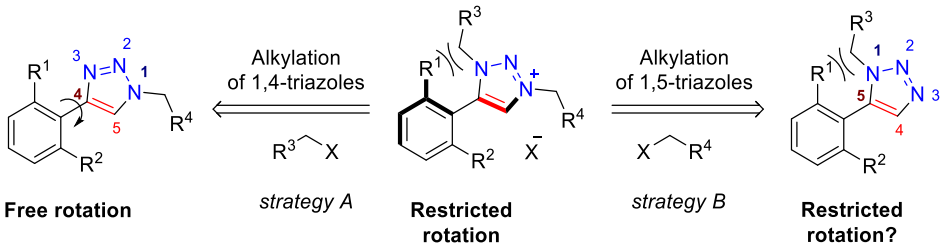
In order to lock the conformation in such systems, two approaches were taken (**Scheme 34**). Initially, similarly to what had been previously done in the Fossey group,[148] appropriately substituted 1,4-triazoles were subjected to *N*-alkylation, affording, in turn, the corresponding conformationally locked 1,3,4-trisubstituted triazolium salts. Later, it was hypothesised that using similar *ortho*-disubstituted alkynes, the rotation about the sp^2-sp^2 bond in a 1,5-disubstituted triazole could be restricted as a consequence of the steric congestion between the two R groups (R^1 and R^2 in **Scheme 34**). This hypothesis proved correct, and it will be discussed in the following pages.



Scheme 34 Resolution and alkylation in the two approaches. While approach **I** envisages the enantiomer separation as the last step, approach **II** sees it as the first.

These two approaches aimed to give the flexibility of resolving the single enantiomers at different stages, on either a charged species or a neutral one, and allow the functionalisation at two different positions of the triazole ring.

3.2 Resolution of Racemic Triazolium Salts



Scheme 35 Retrosynthetic approaches to atropisomeric triazolium salts.

Building upon work previously done within the group, the resolution of racemic triazolium salts was initially attempted by the alkylation of either 1,4- or 1,5-triazoles containing a 2-methylnaphthyl unit (**Figure 31**), which in the past had proven successful in restricting the rotation.

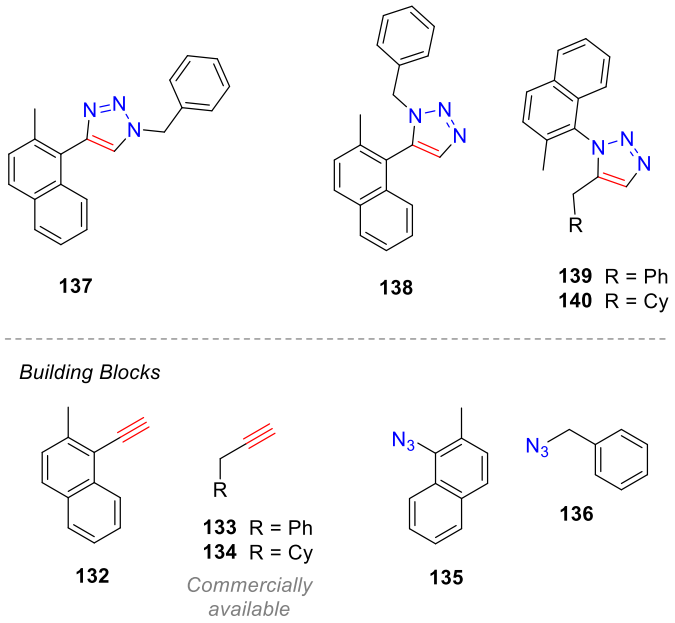
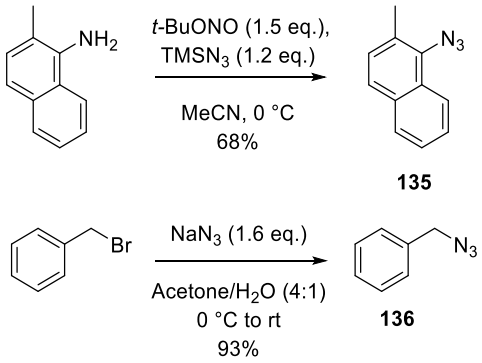


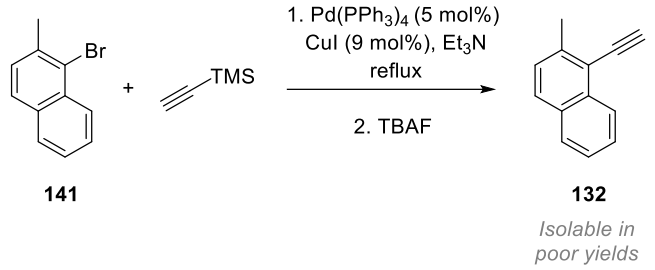
Figure 31 Structures of 1,4- and 1,5-triazoles incorporating a 2-methylnaphthyl unit used for alkylation.

Whilst the preparation of azides **135** and **136** proceeded smoothly (**Scheme 36**) *via* nucleophilic substitution with sodium azide (**136**) or diazonium salts from the corresponding aniline (**135**), preparation of alkyne **132** proved troublesome, in agreement to what had been previously reported within the group.



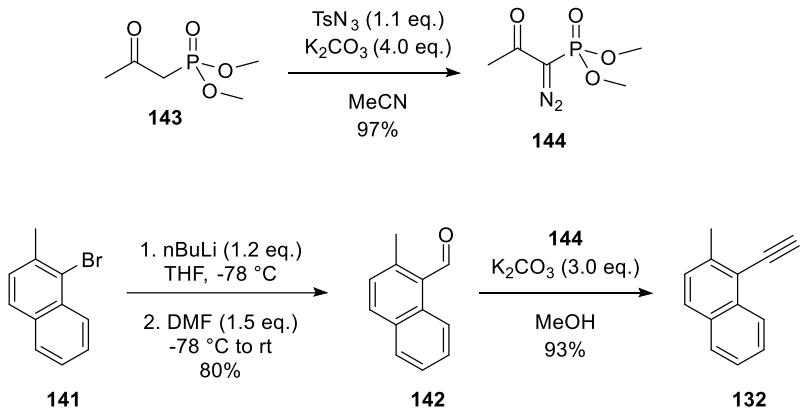
Scheme 36 Preparation of azide **135** and **136**.

Sonogashira cross-coupling with TMS acetylene and aryl bromide **141** (**Scheme 37**), under a number of conditions, produced a mixture of products difficult to separate, and attempts to proceed to the next steps with the crude material resulted in very poor overall yields.



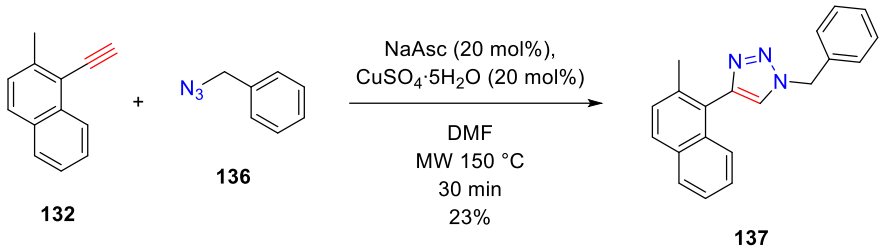
Scheme 37 Sonogashira cross-coupling of aryl bromide **141** with TMS acetylene and TMS deprotection. Variations from the conditions shown include: $Pd(PPh_3)_2Cl_2$ and PPh_3 in place of Pd-tetrakis; DIPEA, *i*Pr_2NH, or piperidine instead of Et_3N; THF or DMF as solvent; different catalyst loadings, temperatures and reaction times.

As an alternative procedure to cross-couplings, a Seyferth-Gilbert homologation with aldehyde **142** and the Bestmann-Ohira reagent **144** was attempted. The reaction was very effective and produced alkyne **132** in 93% yield from the corresponding aldehyde **142** (**Scheme 38**).



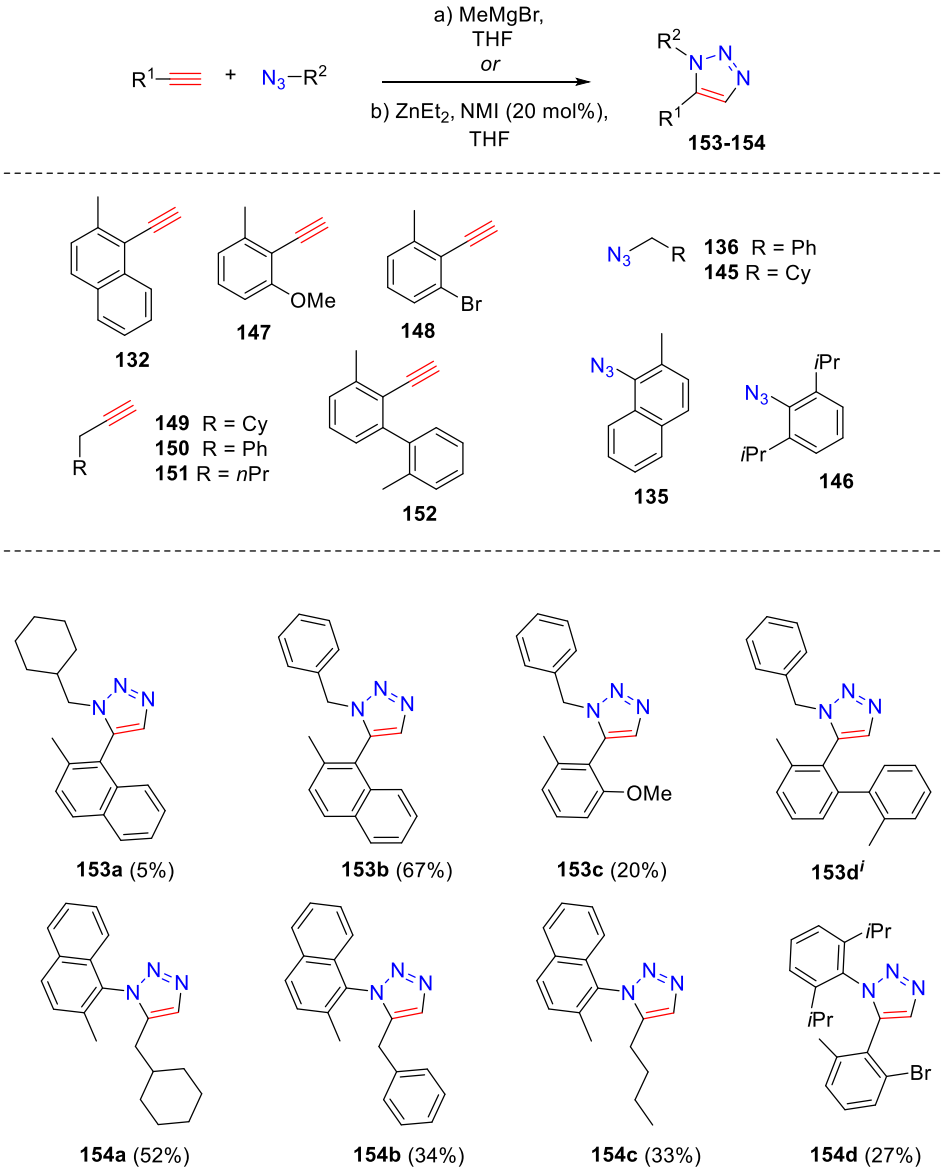
Scheme 38 Preparation of alkyne **132** with Bestmann-Ohira reagent **144**.

With the azides and alkyne starting materials in hand, the syntheses were carried forward. While the synthesis of the 1,4-triazole precursor was easily achieved *via* a copper catalysed azide-alkyne cycloaddition (**Scheme 39**), the synthesis of the corresponding 1,5-triazoles was unexpectedly challenging. In fact, although able to afford simple, unhindered triazoles, the complementary ruthenium[149] or nickel catalysed cycloadditions[150] failed to deliver the targeted compounds, in agreement with what has recently been reported by Mahadari *et al.* for the synthesis of sterically demanding 1,5-disubstituted 1,2,3-triazoles, where metal catalysed reactions led to no product being observed.[151]



Scheme 39 CuAAC of alkyne **132** and azide **136**.

Following the inability for ruthenium and nickel catalysed reactions to deliver the desired species, alternative approaches were sought. Regioselective access to 1,5-triazoles is also possible using stochiometric amounts of bases[152] or organometallic reagents including organomagnesium[153] or organozinc reagents.[154] These last two methods, in particular, allowed access to a library of eight variously substituted 1,5-triazoles (**Scheme 40**) and were found to be complementary. The former was more effective in delivering triazoles **153a-d**, bearing an aromatic moiety at the 5-position, whilst the latter was more effective for the synthesis of triazoles **154a-d**, bearing an aromatic moiety at the 1-position. Employing differently substituted aliphatic or aromatic alkynes and azides, restricted rotation about either the C-C or the C-N single bond was thus achieved.



Scheme 40 Library of 1,5-disubstituted triazoles prepared. Series **153a-d** using conditions *a*; series **154a-d** conditions *b*. *i)* Compound isolated in two fractions enriched in one diastereoisomers (1:1.73 d.r. and 1:1.59 d.r. ratio).

The generally low yields obtained were attributed to the steric congestion within the system, which was needed to achieve atropisomerism. Nonetheless, the methodology gave enough material for the main aim of analysing the atropisomeric characteristics to be achieved. Pleasingly, inspection of the ^{1}H NMR spectra of the compounds revealed (with few exceptions, *vide infra*) the expected diastereotopic splitting pattern relative to the benzylic -CH_2- protons that, being no longer magnetically equivalent (^{2}J = 14.5 Hz), resonate at different frequencies (**Figure 32**).

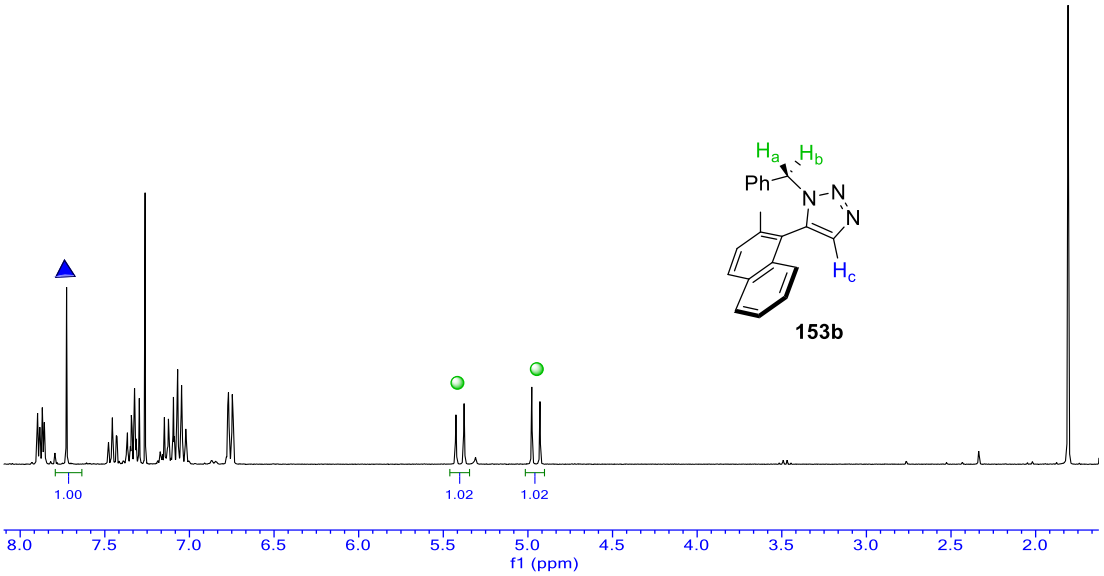


Figure 32 ^{1}H NMR spectrum of compound **153b**; diastereotopic resonances are labelled with a green dot.

In the case of compound **153d** a mixture of diastereomeric triazoles was isolated, suggesting that a double axially chiral compound had been formed; however, neither flash chromatography nor preparative TLC allowed separation of the two diastereoisomers.

Whilst all the compounds were designed to provide a straightforward verification of chirality *via* NMR spectroscopy, had the rotation been successfully restricted, this was not always the case. Contrary to expectations, compound **154a** did not show any diastereotopic splitting patterns on the ^{1}H NMR spectrum recorded in $CDCl_3$ at room temperature, conversely to its isomer **153a** and similarly to compound **154c** of the same series (**Figure 33**).

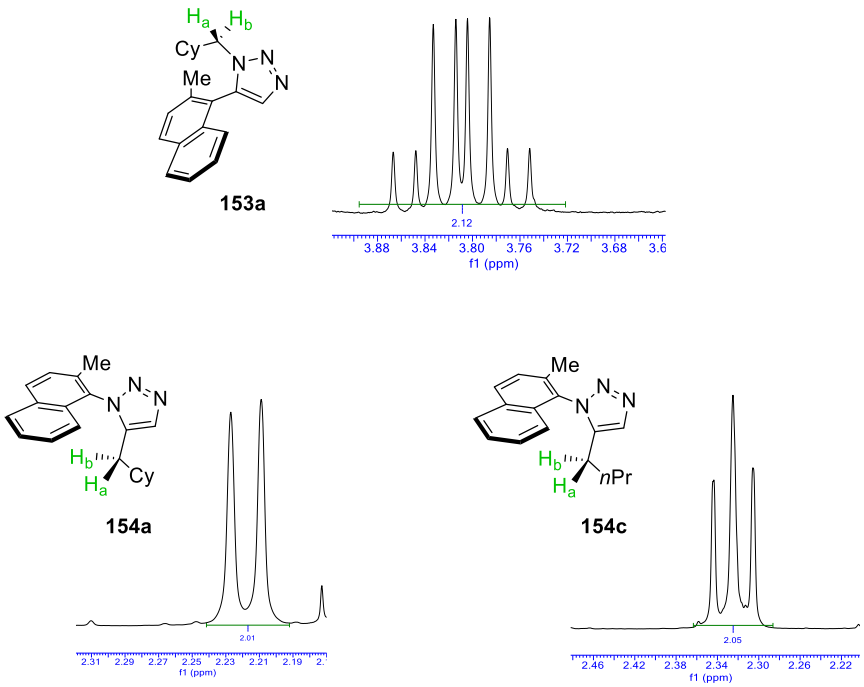


Figure 33 Comparison between the resonances of the *–CH₂–* protons in compound **153a** (top), displaying the characteristic diastereotopic splitting, and in compounds **154a** and **154c** (bottom), showing isochronism.

In case of compound **154a**, however, it was possible to detect the characteristic splitting at -35 °C (*q.v.* Section 8.2), in $CDCl_3$. Where accidental isochronism was observed, and the chirality could not be assessed by NMR, it was confirmed by analytical HPLC analysis using a mixture of water/acetonitrile as mobile phase, and Phenomenex Cellulose-1 as the chiral stationary phase, which revealed two sharp peaks consistent with the presence of stable enantiomers.

Having both 1,4- and 1,5-triazoles in hand, a small library of racemic triazolium salts was in turn prepared *via* alkylation of either species (**Figure 34**). The synthesis of diverse compounds intended to ensure that an array of triazolium salts could be studied, comparing yields and effectiveness of resolution, and successively screened in catalysis. In all cases, the alkylation proceeded smoothly, affording the desired triazolium salts in good yields refluxing in acetonitrile with an excess of the appropriate alkylating agent.

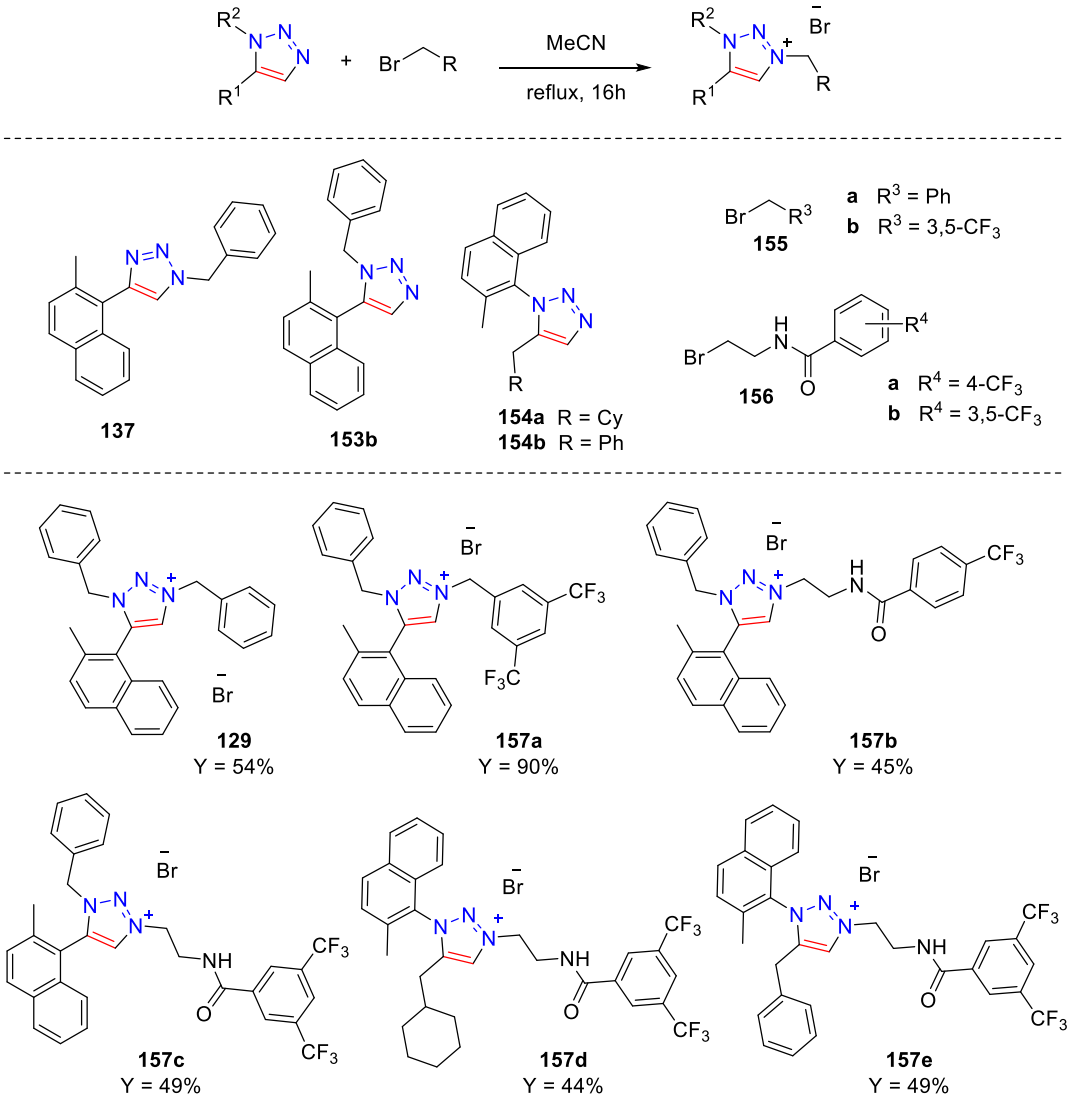
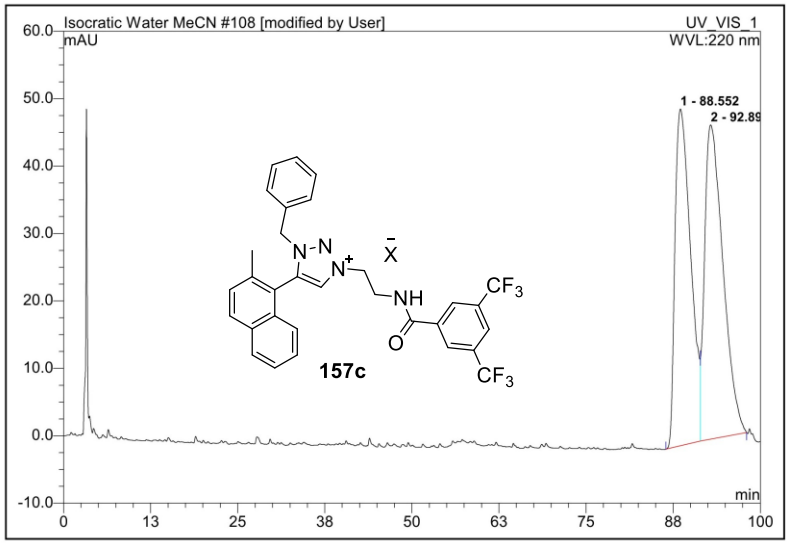


Figure 34 Atropisomeric triazolium salts prepared.

In particular, compounds **157b-e** were designed in analogy to the triazolium salts reported by Ooi's group, which have successfully been employed in numerous asymmetric transformations under phase-transfer conditions (*q.v.* page 73).[129, 130, 155-160]

Preparative HPLC on chiral stationary phase was initially explored as a convenient method to isolate both enantiomers in relatively large quantities. Unfortunately, chiral separation of triazolium salts proved to be incredibly challenging: cellulose (OD-H and OD-J) and amylose (AD-H and AD-J) columns were tested both in normal and reverse phase, affording very poorly resolved peaks, often with no baseline separation. The influence of the temperature and flow

rate was also evaluated, but no significant improvement was noticed. Changing the composition of the mobile phase, on the other hand, heavily influenced the outcome of the separation, with acetonitrile being a far superior solvent than methanol, and poorly solvated, hydrophobic counterions such as PF_6^- or BF_4^- significantly improving the peak shape (**Figure 35**), although never leading to well-resolved peaks.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	88.55	n.a.	49.952	129.729	47.59	n.a.	BM *
2	92.89	n.a.	46.600	142.859	52.41	n.a.	MB*
Total:			96.552	272.589	100.00	0.000	

Figure 35 Chiral HPLC trace of compound **157c**. Isocratic 45:55 MeCN/0.1 M KPF_6, Phenomenex Cellulose 1. X^- denotes either Br^- or PF_6^-.

Despite best efforts, baseline separation was rarely achieved, and attempts of obtaining enantiopure samples through an iterative process on a preparative column, under the same conditions, were also ineffective. Furthermore, where baseline separation was attainable, it was not possible to replicate the method on the preparative column due to the broadening of the peaks observed on a larger column.

Since it was concluded that the separation of atropisomeric triazolium salts into single enantiomers *via* HPLC was not feasible, separation of diastereomeric ion pairs was attempted. Compounds **160** were in turn prepared by precipitation of the corresponding silver halides

(**Figure 36**). The successful exchange was confirmed by ^{1}H NMR, which revealed a clear splitting of the triazolic proton due to the newly formed diastereomeric ion pairs, and, in the case of compounds **160c**, by ^{19}F NMR, which showed the presence of an extra peak relative to the CF_3 of the Mosher's acid.

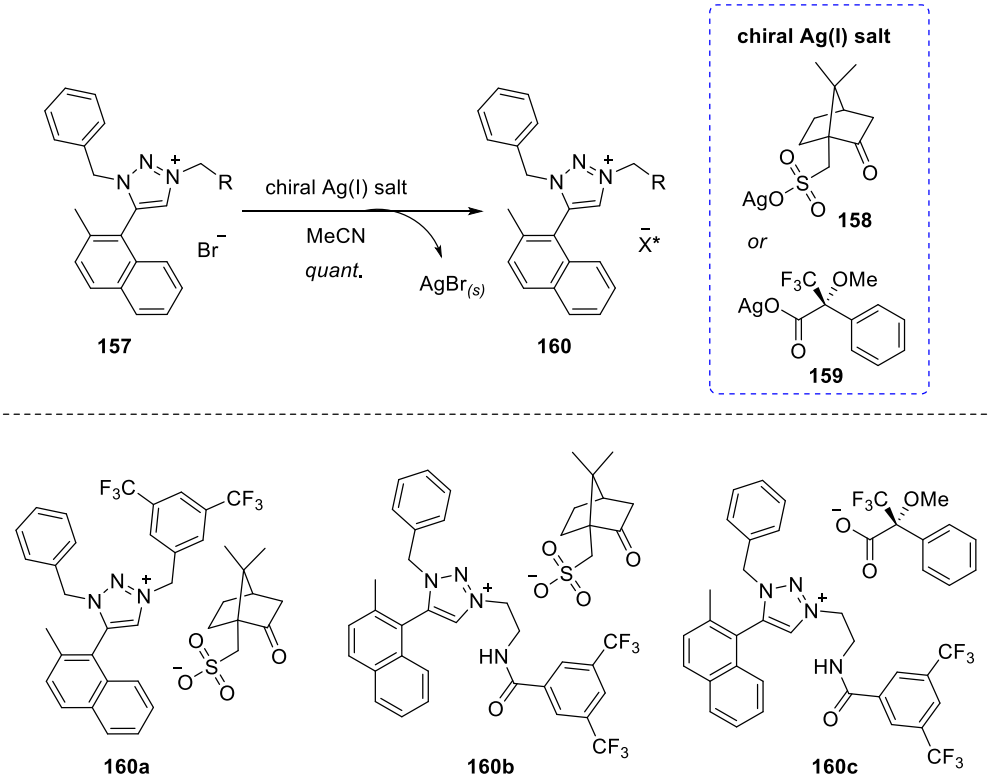
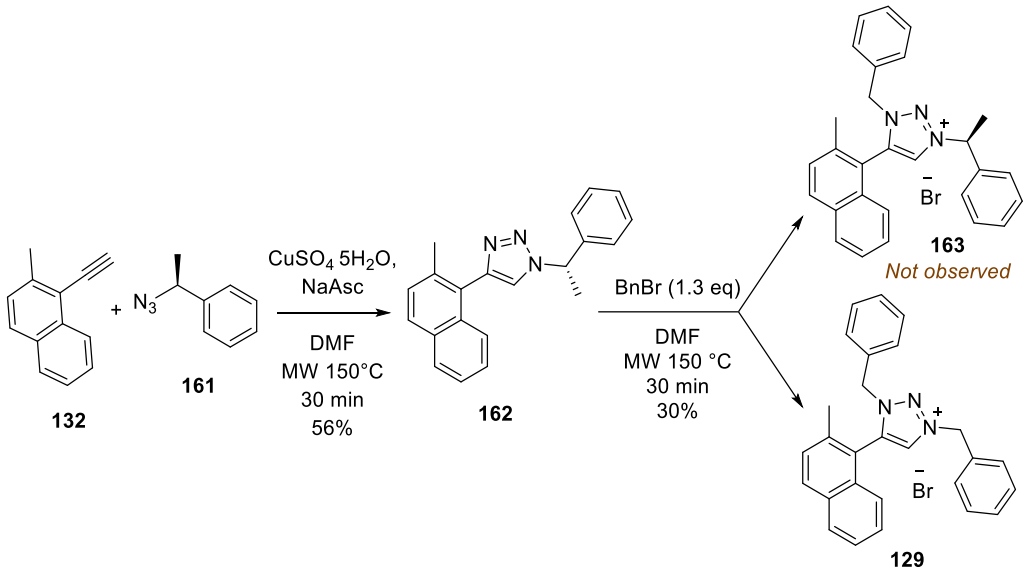


Figure 36 Diastereomeric ion pairs prepared.

To identify possible conditions for separation, an exhaustive approach was again employed. Flash chromatography on silica gel, using DCM/MeOH (isocratic or gradient) was found unfeasible for separation of such diastereomeric ion pairs. Similarly, preparative TLC run in normal and reverse phase, with or without additives, provided no better results. It was thought that, perhaps, solvation was keeping the two ions apart, disrupting the diastereoisomerism and consequently invalidating attempts at separation. Being that the chromatographic methods were completely ineffective, attention was directed towards recrystallisation. However, on a small scale, no successful result was obtained employing single solvents, multiple solvents, or slow

vapour diffusion. Whilst semi-crystalline solids were collected, assessment of the ^{1}H NMR did not show any diastereotopic enrichment.

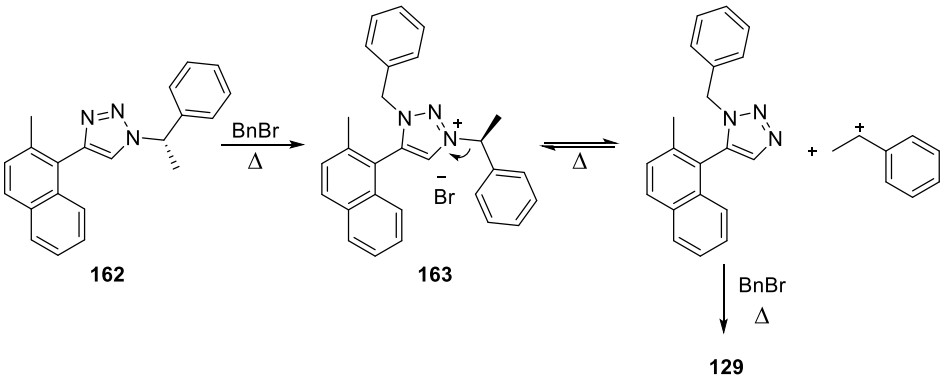
It was then questioned whether having a diastereomeric triazolium salt, rather than a diastereomeric ion pair, could aid the separation. To validate the hypothesis, compound **163** was targeted. 1-Ethynyl-2-methylnaphthalene **132** was treated with chiral azide **161** *via* a CuAAC under microwave irradiation, to afford triazole **162** in 56% yield. Benzyl bromide was then added and the triazole heated under microwave irradiation in DMF for 30 minutes (**Scheme 41**).



Scheme 41 CuAAC to from triazole **162**, followed by alkylation.

Upon inspection of the ^{1}H NMR spectrum of the isolated product, it was noticed that transalkylation had occurred, and triazolium **129** had been formed instead, in a 30% yield.

Although it was not observed, it is believed that compound **163** was indeed formed during the reaction. However, given the exceptional stability of secondary benzyl carbocations (stabilised by four resonance structures), the transalkylation occurred as a consequence of its elimination (that yielded the corresponding 1,5-triazole) and subsequent (re)alkylation with the remaining alkylating agent, which eventually garnered **129** (**Scheme 42**).



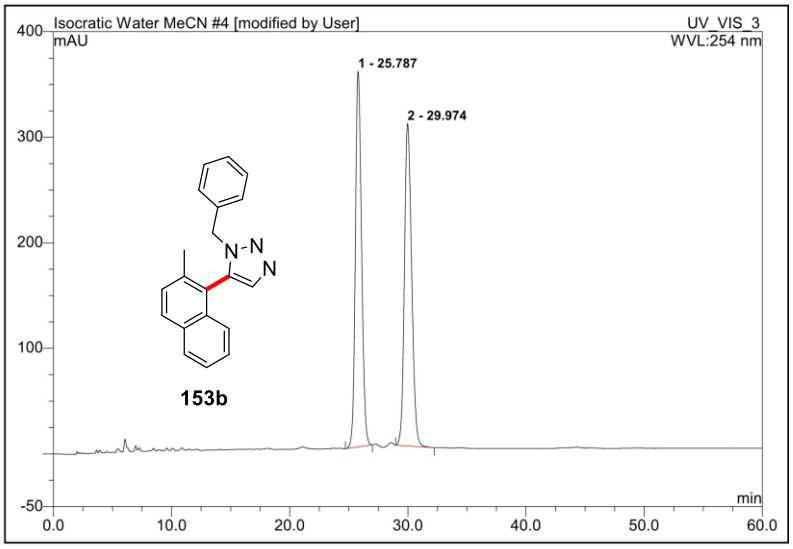
Scheme 42 Possible synthetic pathway for the formation of **129**.

As it was found that this phenomenon had already been documented in the literature for similar substrates where good leaving groups were garnishing the triazole,[161] the strategy was abandoned and the reaction not investigated any further.

Having exhausted all the possible options of resolution into single enantiomers, it was decided to pursue the second approach, which entailed the chiral HPLC separation of atropisomeric 1,5-triazoles, and their subsequent alkylation. It was reasoned that, given the lack of charge, resolution could be more easily achieved.

3.3 Resolution and Stability of Atropisomeric 1,5-Triazoles

Atropisomeric triazole **153b** was chosen to develop resolution conditions *via* HPLC. As anticipated, the separation of the two enantiomers was found to be straightforward, with the two atropisomers being separable in a mixture of 40:60 water/acetonitrile, using Phenomenex Cellulose-1 (OD-H) as the chiral stationary phase (**Figure 37**).



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25.79	n.a.	355.870	215.238	49.98	n.a.	BMB
2	29.97	n.a.	305.505	215.403	50.02	n.a.	BMB*
Total:			661.375	430.641	100.00	0.000	

Figure 37 Chiral HPLC trace of compound **153b**. Isocratic 40:60 water/MeCN, Phenomenex Cellulose 1.

Close inspection of the baseline revealed no "batman peak" (*i.e.* a plateau between two adjacent peaks), indicative of dynamic interconversion on column.[162] To begin investigating the stability of the atropisomer, variable-temperature (VT) ^{1}H NMR studies were conducted. The compound was dissolved in tetrachloroethane-d_2 (TCE) and a spectrum recorded every 10 °C up to 100 °C (**Figure 38**).

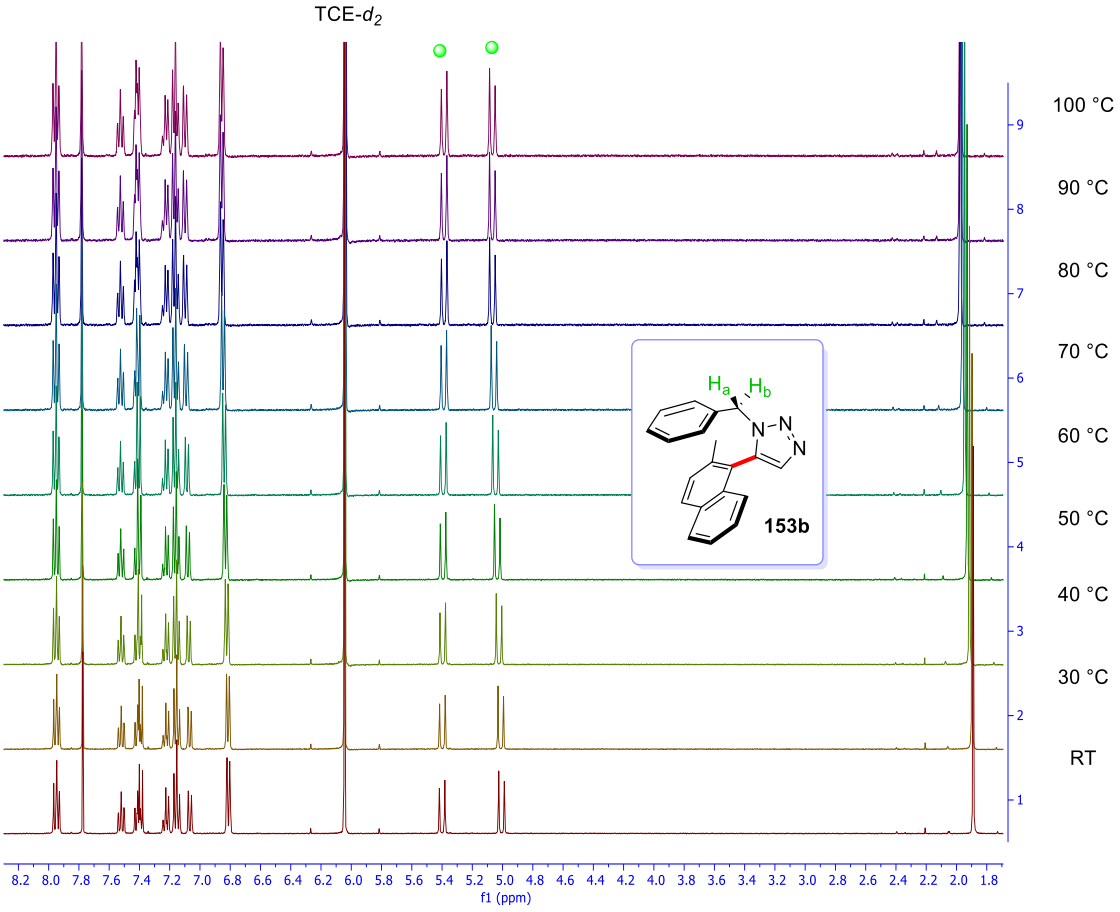


Figure 38 VT ^{1}H NMR study of compound **153b** from RT to 100 °C in TCE-d_2.

The two doublets for the diastereotopic benzylic protons H_a and H_b (green dots in **Figure 38**) did not coalesce even at 100 °C, suggesting that the rotation within the system was highly restricted and the atropisomeric scaffold was suitable to proceed with the alkylation to the triazolium salt.[V]

The effect of the solvent was also evaluated, and the same study was conducted in toluene-d_8. Similarly to what has been reported by Aponick's group in the case of StackPhos,[79] it was thought that intramolecular π-stacking interactions happening in solution could stabilise the conformation through stabilisation of the ground state. A non-polar aromatic solvent such as toluene was expected to disrupt said interactions, and hence indirectly estimate their putative

[V] At that point, the timespan of the reaction, which deeply compromised the envisioned outcome, had not been taken into consideration; this will be discussed in due course.

contribution to the overall stability. However, no difference was observed, and the peaks still did not coalesce at 100 °C, strongly suggesting that, if present, these non-covalent interactions were only marginally contributing to the stability.

Given the crystalline nature of triazole **153b**, additional structural insights were obtained by x-ray diffractometry on a single crystal of racemic **153b**, grown *via* slow evaporation of DCM in hexane (**Figure 39**).

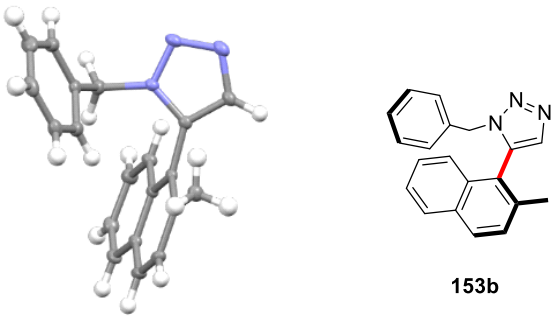


Figure 39 Crystal structure of triazole **153b**. Ellipsoids drawn at 50% probability level.

In agreement with the upfield shift of the *ortho*-aromatic protons in the phenyl ring on the ^{1}H NMR spectrum and the literature values,[163, 164] the compound displayed intramolecular edge-to-face π-stacking (centroid-centroid distance 5.448 Å) occurring between the naphthyl and the benzyl ring, and intermolecular off-set face-to-face stacking between naphthyl units.

The stability of the 1,5-triazoles was further studied using computational modelling. All the calculations were performed by Dr Andrew Leach (University of Manchester). Analyses of the rotation about either the C-C or C-N chiral axis showed, in general, a greater stability for the C-N chiral series. Compound **154a**, bearing a cyclohexyl substituent, was the most stable of all with a computed $\Delta G^{\ddagger}$ of 34.2 kcal·mol^{-1} and a corresponding half-life at room temperature on the order of millennia, stability comparable to that of BINOL.[165] From a steric point of view, there is no significant difference between the size of a lone pair and the size of a hydrogen atom,[166, 167] therefore the higher barriers to rotation of the C-N chiral series can be ascribed to

the C_{sp^2}-N_{sp^2} bond length, typically shorter than a C_{sp^2}-C_{sp^2} bond,[168] which decreases the distance between the naphthyl and the triazolic ring, consequently enhancing the repulsion between the *ortho* substituents in the transition states (**Figure 40**).

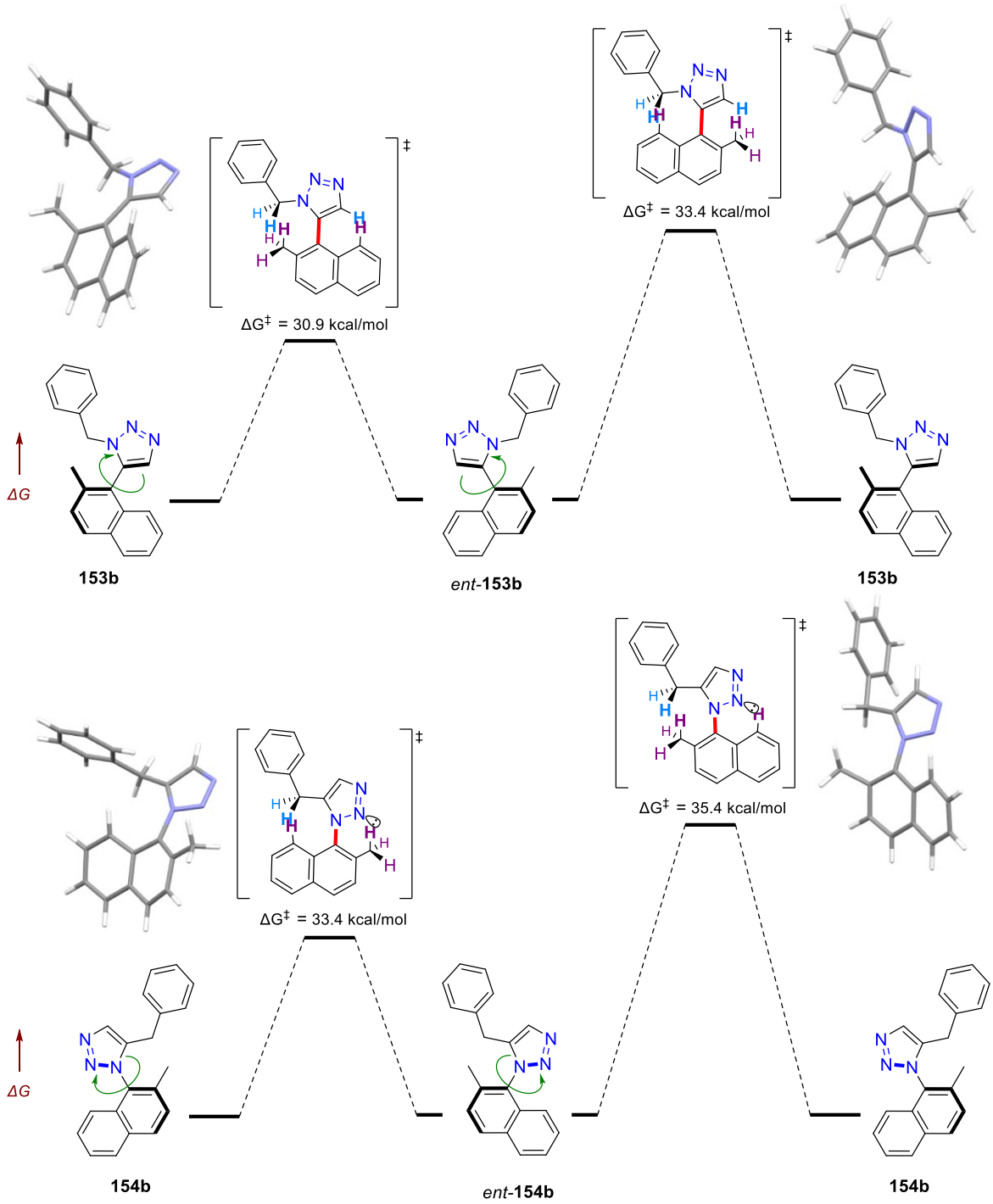


Figure 40 Energy level diagrams for the rotation about the chiral axis in **153b** and **154b**. 3D representations of the computed transition states are shown. Calculations are at the M06-2X/6-31+G* level of theory including solvation *via* the IEFPCM model and were performed using Gaussian09. Free energies at 298 K are computed using GoodVibes.

Evidence obtained by VT-NMR analysis (*vide supra*) had suggested that, if present, non-covalent interactions between aromatic rings were only marginally contributing to the stability, and accordingly, it was calculated that **154a**, **154b** and **154c** had similar $\Delta G^{\ddagger}$ (**Figure 41**).

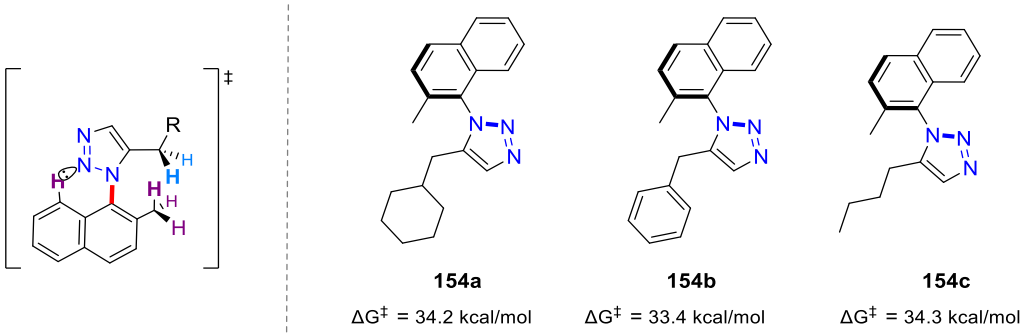


Figure 41 Computed barriers to rotation in **154a**, **154b** and **154c**.

It was found that compound **153c**, having an *ortho*-methoxy substituent, had a much lower barrier to rotation than **153b** of the same series, bearing the naphthyl group. This difference can be explained by considering the size and hybridisation of the oxygen atom. In fact, in addition to being smaller than a carbon atom, the lone pairs on the oxygen in **153c** point away (θ = 50° *ca.*) from both the H(4) in the triazolic ring and the benzylic protons, whereas in **153b** the hydrogen in the *peri* position points directly at them, being the carbons sp^2 hybridised, thus enhancing the steric repulsion in the transition state. As a result, the naphthyl and the triazolic ring significantly bend out of the plane of the C-C bond (chiral axis) to relieve the repulsion (**Figure 42**).

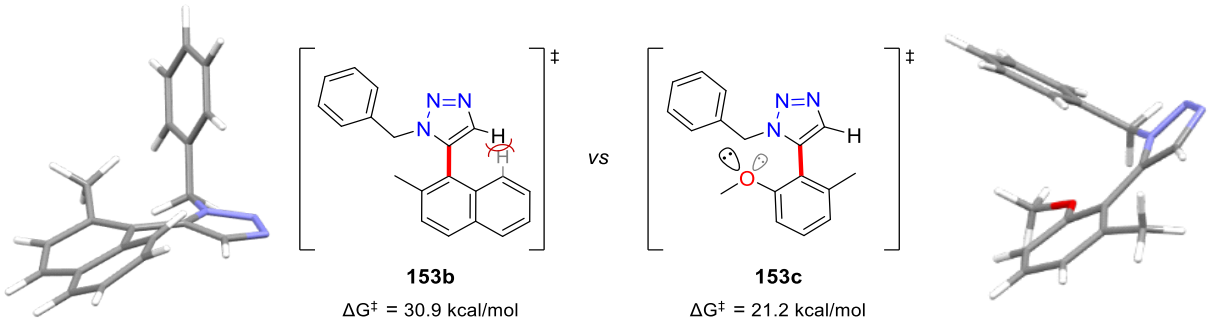
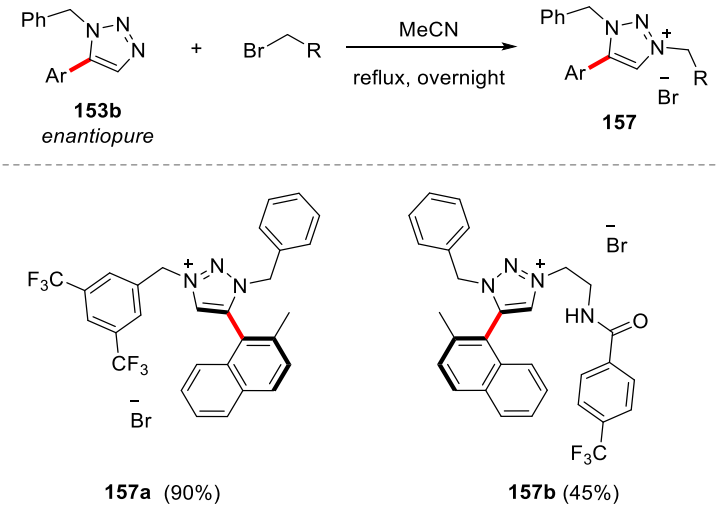


Figure 42 Comparison between transition states in **153b** and **153c**. 3D representations of the lowest energy computed transition states are shown.

Having determined the condition for separation, racemic triazole **153b** was subjected to preparative HPLC to afford both enantiomers in over 99% optical purity. These were further treated with an excess of the alkylating agent in acetonitrile at reflux to afford 1,2,3-triazolium salts **157a** and **157b** in moderate to high yields (**Scheme 43**).



Scheme 43 Synthesis of enantioenriched triazolium salts **157a** and **157b**. The absolute configuration of the compounds is unknown, and it has been arbitrarily chosen for clarity: compounds **157a** and **157b** have opposite configuration.

The enantiopurity of the final products was hence determined using two different approaches: the enantiopurity of compound **157a** was assessed by ^{1}H NMR analysis in $CDCl_3$, employing (*S*)-(+)-camphorsulfonate as a convenient chiral shift reagent, whereas the enantiopurity of compound **157b** was determined by HPLC using MeCN/20 mM aqueous ammonium formate and 0.1% triethylamine as an additive, and Phenomenex Cellulose-1 as the chiral stationary phase. Disappointingly, both methods confirmed that the stereochemical purity had been eroded during the alkylation step, delivering the triazolium salts in only 28% enantiopurity (**Figure 43**).

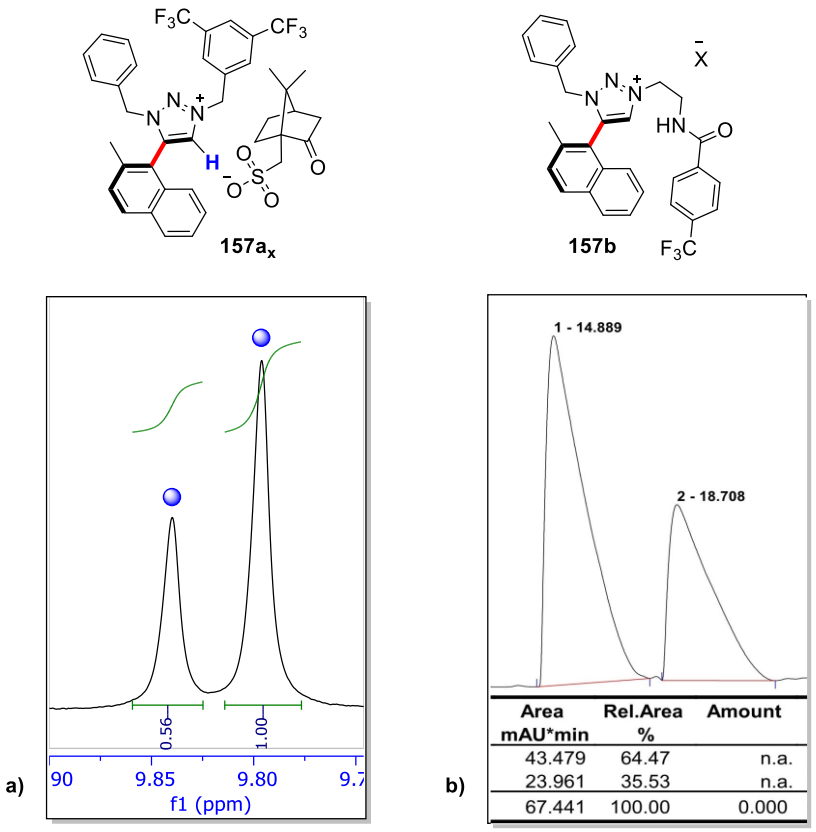


Figure 43 a) Detail of the ^{1}H NMR of compound **157a$_x$**; peaks relative to the protons in 5 position in the two diastereomeric ion pairs are shown. **b)** Chiral HPLC trace of compound **157b**; separation was performed on an OD-H column, isocratic MeCN/w. 20 mM NH_4HCO_2 + 0.1% TEA (40:60).

To further investigate these results, the barrier to rotation of triazole **153b** was experimentally determined by HPLC. Enantiopure (+)-**153b** obtained by preparative HPLC was dissolved in MeCN and the resulting solution heated at 70 °C throughout. Samples were collected at regular intervals, reinjected, and the erosion of the *ee* recorded.

As mentioned in Chapter 1 (*Equation 5*), plotting $ln\left(\frac{100}{e.e.}\right)$ against time gives k_{rac} as the slope. Using then *Equation 7*, $\Delta G_T^{\ddagger}$ can be determined. When the *ee* was plotted against time, a distinct exponential decay was observed (**Figure 44**).

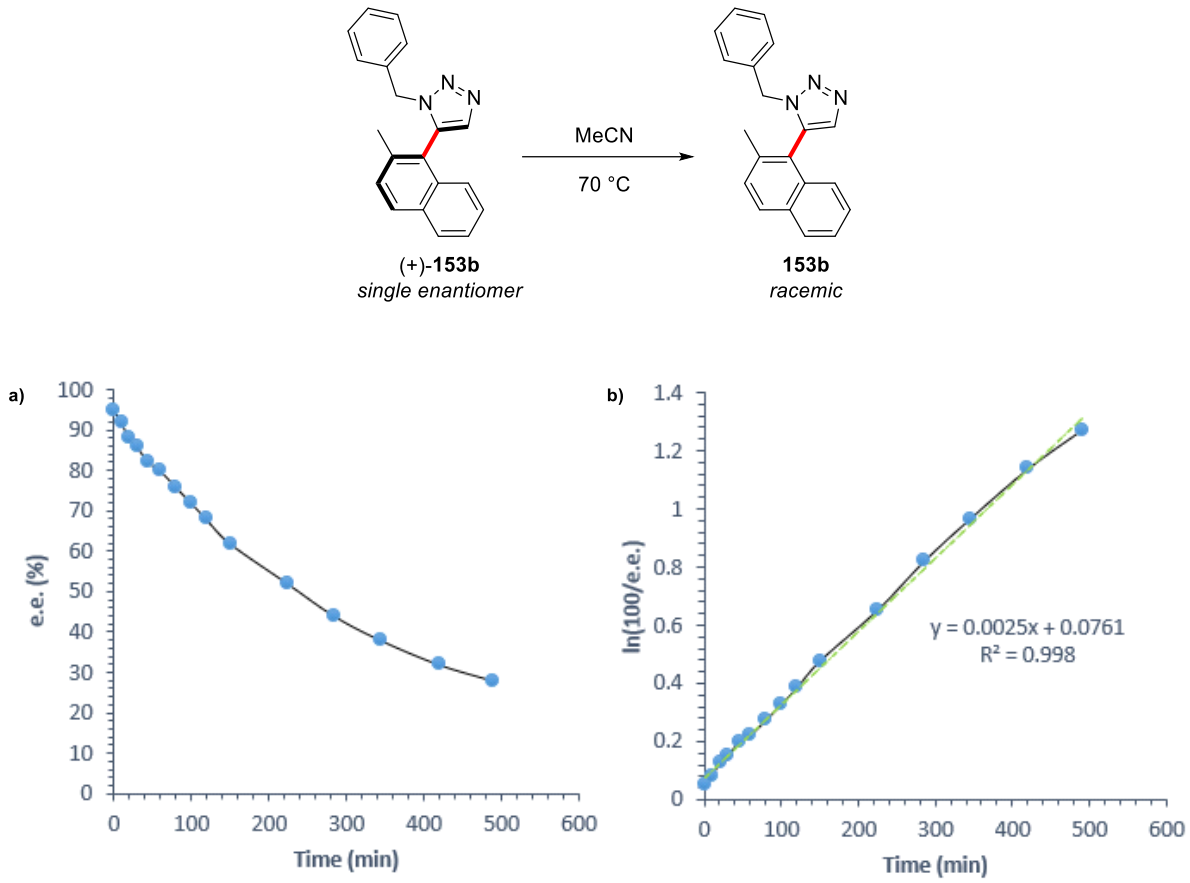


Figure 44 a) ee% decay of (+)-**153b** over time. **b)** ln(100/ee) over time. The absolute configuration of (+)-**153b** is unknown, and it has been arbitrarily chosen for clarity.

The half-life was calculated to be 4.6 hours, with a $\Delta G^{\ddagger}_{343}$ of 25.0 kcal·mol^{-1}, smaller than the computed value and too low to withstand the alkylation, requiring prolonged heating at 80 °C. In order to evaluate the conformational stability across the series originally reported (**Scheme 40**), the process was repeated for the regioisomeric triazole **154b**. However, data collected at 70 °C, over 8 hours, did not show the exponential decay observed for compound **153b**, rather a nearly horizontal line. The temperature was then increased to 80 °C, and data points were collected over 5 days. While the rotational barrier was found to be lower than the original computed value, the relative stability was proven correct and compound **154b** displayed a much higher stability than **153b**, with a $\Delta G^{\ddagger}_{353}$ of 29.0 kcal·mol^{-1} corresponding to a half-life of 24 days at 80 °C, and about 2.5 years at room temperature.

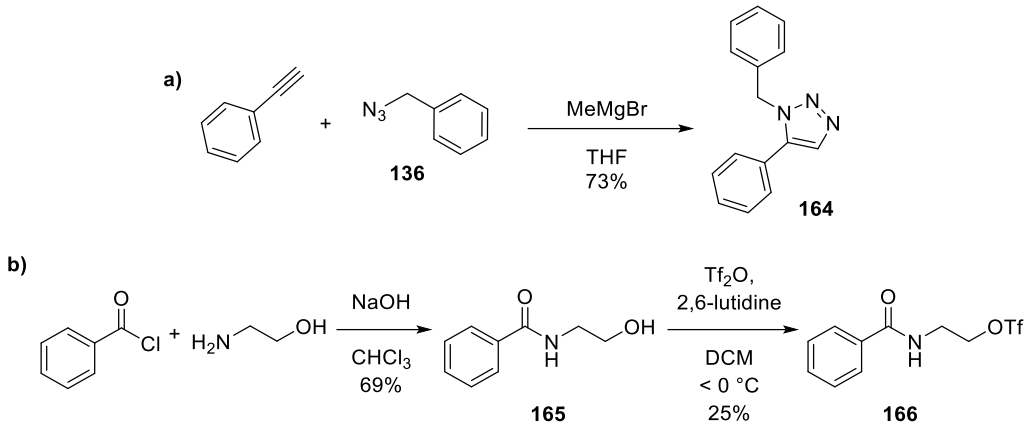
Having displayed an outstanding stability at the temperature needed for the alkylation, resolution of compound **154b** was attempted on a preparative chiral column. However, the broadening of the peaks observed on a large column, along with their deepened asymmetry, did not allow a complete separation of the peaks (due to the very poor resolution). Despite this, an enantiopure sample could be probably obtained through an iterative process, where the enantioenriched material gets reinjected into the column until optical purity is achieved. However, given the extensive HPLC work required for the resolution of these C-N chiral species, it was decided to focus the efforts into the development of a *N*-alkylation of 1,5-triazoles under milder conditions.

3.4 Studies Towards the *N*-alkylation of Triazoles at Room Temperature

Quaternisation of 1,2,3-triazoles to form triazolium salts generally requires forcing conditions, *i.e.* high temperatures and/or pressures. Nonetheless, there are instances in the literature of *N*-alkylation of pentatomic nitrogen-containing heterocycles, namely 1,4-disubstituted 1,2,3-triazoles,[169, 170] 1,5-disubstituted pyrazoles[171] and 1-substituted 1*H* imidazoles,[172] performed at room temperature. In all the reported examples, good to high yields were obtained within 18 hours, employing triflates as the alkylating agents.

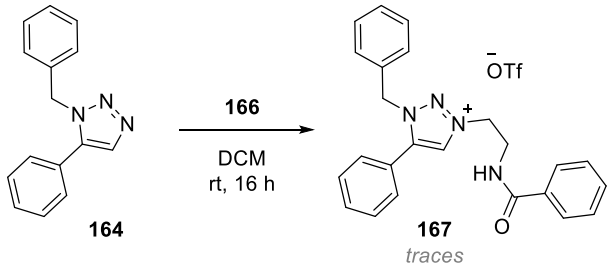
It was thought that similar conditions could be employed to alkylate the 1,5-triazoles synthesised at room temperature, thus averting the racemisation of the starting materials.

To test the hypothesis, a simple triazole **164** and alkylating triflate **166** were synthesised and used to conduct a preliminary investigation. Compound **164** was isolated in 73% yield from phenyl acetylene and benzyl azide **136** (**Scheme 44a**), whereas compound **166** was prepared in two steps in a poor 17% overall yield, largely due to the exceptional reactivity of primary alkyl triflates (**Scheme 44b**).[173]



Scheme 44 Synthesis of **a)** triazole **165** and **b)** alkyl triflate **166**.

Following the aforementioned literature,[169-172] quaternisation of triazole **164** at room temperature was initially attempted in dichloromethane. However, after approximately 16 hours the conversion registered[VI] was very poor, and only trace amounts of the desired compound were observed by ^{1}H NMR spectroscopy.



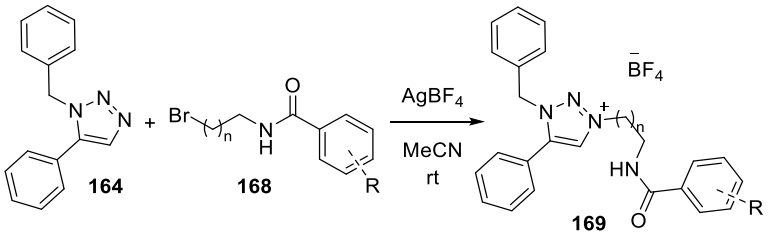
Scheme 45 Alkylation of **164** with alkyl triflate **167**, at room temperature.

The reaction was attempted again in other polar aprotic solvents (*i.e.* acetone, acetonitrile, diethyl ether), but no better results were obtained. As no other parameter could be varied, it was decided not to pursue this route further.

Seeking an alternative method, it was thought that, perhaps, the substrates could be forced to react taking advantage of the great affinity that silver has for halides, expedient documented in the literature for the alkylation of pyridine.[174]

[VI] Reaction monitored by TLC.

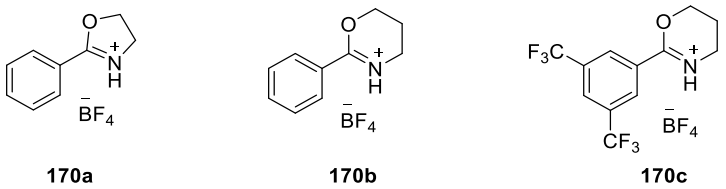
To investigate the reaction, model triazole **164** was treated with primary alkyl bromides **168** in acetonitrile, at room temperature, in presence of silver tetrafluoroborate (**Scheme 46**).



168/ 169	n	R
a	1	H
b	2	H
c	2	3,5-CF_3
d	1	3,5-CF_3

Scheme 46 Alkylation of **164** with alkyl bromides **168a-d**, in presence of $AgBF_4$.

Of the reactions tested, only alkyl bromide **168d** succeeded in delivering the corresponding triazolium salt (41% yield), whereas in all the other cases the major component was identified as the product derived from the self-cyclisation of the alkyl bromides.



170a **170b** **170c**

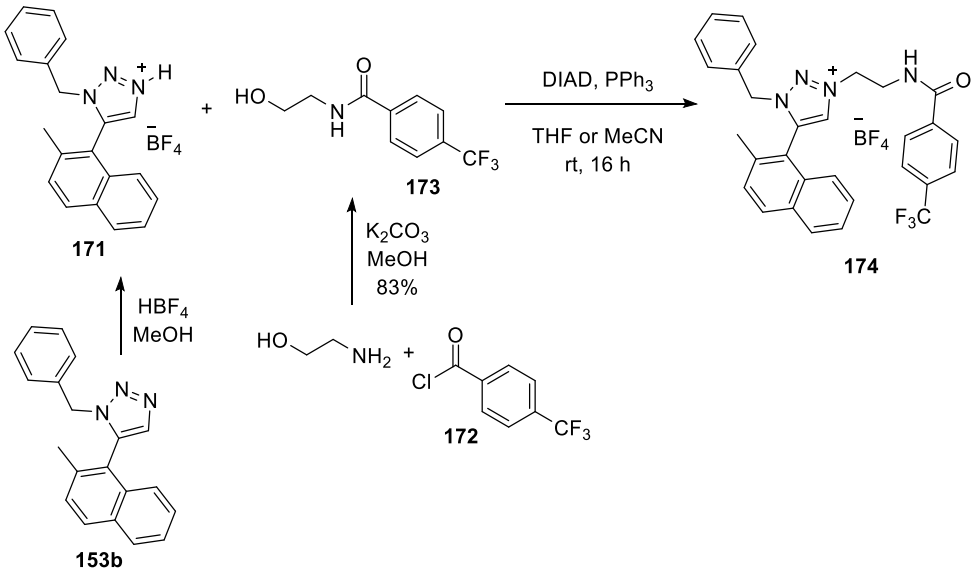
Figure 45 By-products of the N-alkylation of triazole **164** in presence of $AgBF_4$. The identity of the compounds was confirmed by NMR.

Kornblum *et al.* have demonstrated that the reaction of silver salts with alkyl halides proceeds *via* a concerted process involving a "pull" of the silver and a "push" of the anion (hence "pull-push" mechanism).[175, 176] The transition state possesses both S_N1 and S_N2 character, and the degree of its resemblance to one or the other varies with the structure of the halide. In general, the greater the S_N1 character, the greater the preference of the transition state for the atom with the higher electronegativity, and consequently, the greater the S_N2 character, the greater the preference for less electronegative atoms.

Apart from kinetic considerations, the formation of products **170** is also entropically favoured. In the reaction reported (**Scheme 46**), the N(3) of the triazolic ring and the O of the carbonyl compete in the substitution, and it is believed that a combination of kinetic and thermodynamic

factors favours the *O*-alkylation, with consequent formation of **170**. In this regard, alkyl bromide **168d** seems to represent an exception to the observed reactivity pattern that has not yet found a definite explanation.

Revisiting possible options for alkylations under mild conditions, it was thought that a Mitsunobu reaction could offer a solution. It was found that this strategy had successfully been employed by Bischoff's group for the quaternisation of pyridinium and imidazolium salts.[177, 178] Since the Mitsunobu reaction requires an acidic nucleophile (NuH), the authors reported a simple, yet remarkably efficient method for the *N*-alkylation of aromatic heterocycles under mild conditions, employing onium salts (rather than neutral species) as the nucleophilic starting materials. To test the viability of the method with triazoles, triazolium tetrafluoroborate **171** was treated with an excess of amido alcohol **173**, prepared in 83% yield from acyl chloride **172** and ethanolamine (**Scheme 47**).



Scheme 47 Quaternisation of triazole **153b** to form triazolium **174** *via* Mitsunobu reaction.

Under the conditions reported in the literature (5 eq. **173**, MeCN), it was not possible to observe any conversion by TLC. However, employing THF, a more common solvent in Mitsunobu reactions,[179] the desired compound **174** was isolated in *ca.*1:1 mixture with the amido alcohol

173. Inspection of the ^{1}H NMR revealed the unmistakable downfield shift[130] of the triazolic proton and a more subtle shift of the two diastereotopic protons H_a and H_b (**Figure 46**)

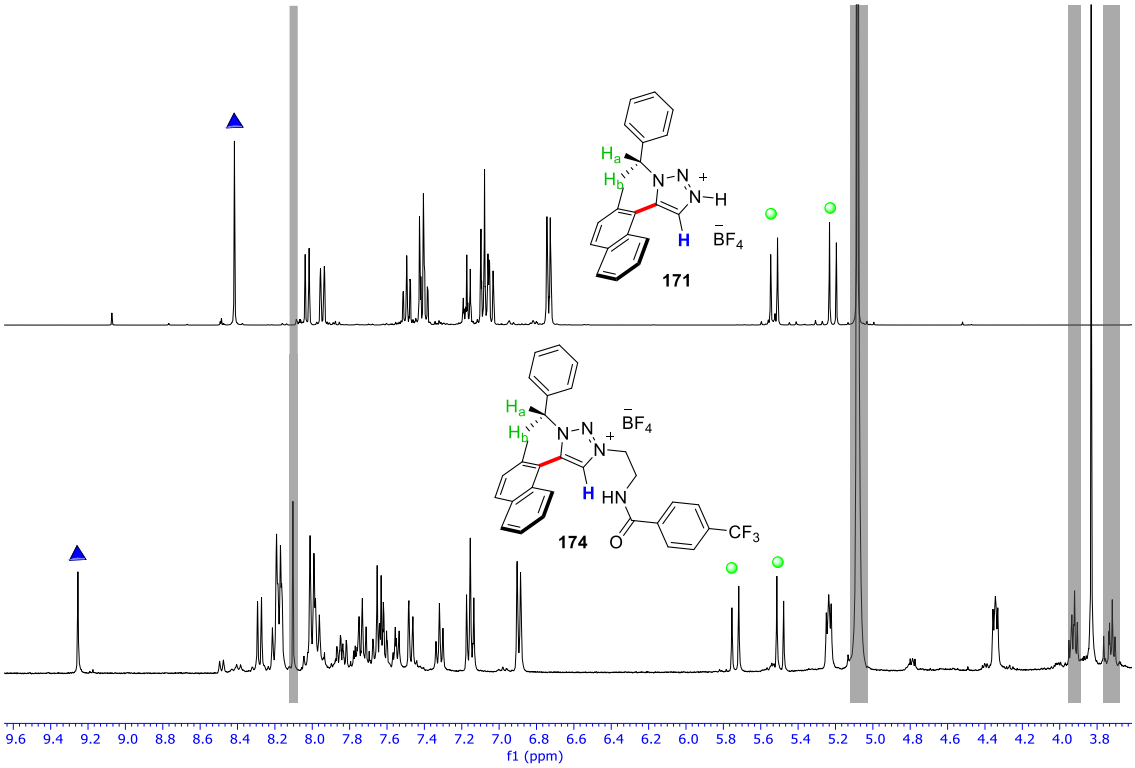


Figure 46 Overlaid ^{1}H NMR spectra of compounds **171** (starting material) and **174** (product) in MeOD. The two -CH_2- peaks (3.71 & 3.92 ppm) of the amido alcohol **173**, the residual H_2O (5.05 ppm) and $CHCl_3$ (8.10 ppm) have been greyed out for clarity.

^{19}F NMR spectroscopy provided further evidence that the alkylation had occurred. Indeed, inspection of the spectra revealed a shift of both the BF_4^- anion, characterised by the typical ^{11}B/^{10}B isotope effect,[180] and the CF_3 group (**Figure 47**).

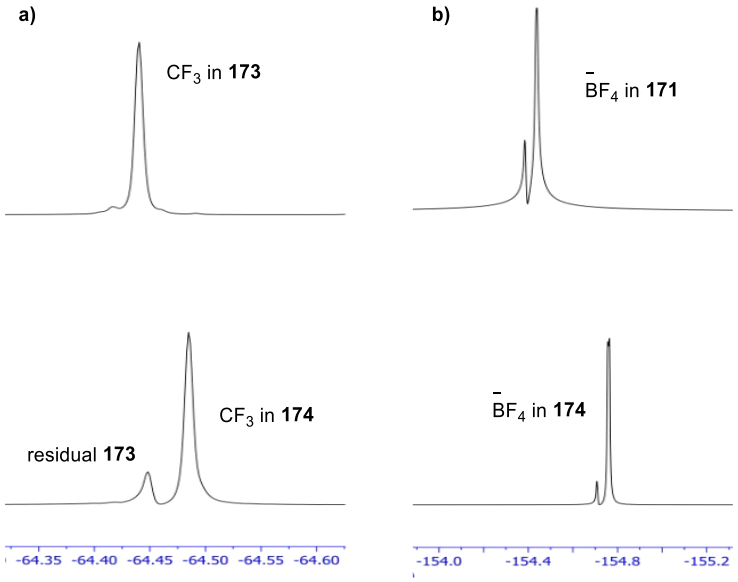
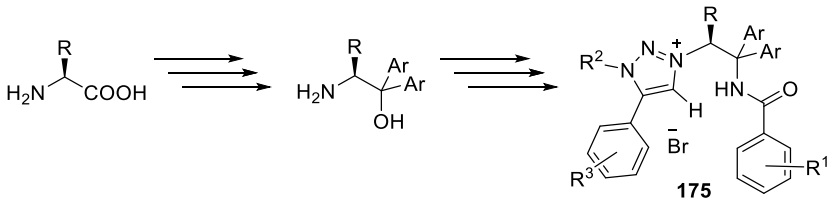


Figure 47 Overlaid ^{19}F NMR spectra of **a)** compound **173** and **174 b)** compound **171** and **174**.

Despite the promising result, time constraints within the laboratory did not allow further investigation of the reaction. However, the knowledge acquired will hopefully provide a good starting point for future work within the group.

3.5 Applications of Atropisomeric Triazolium Salts

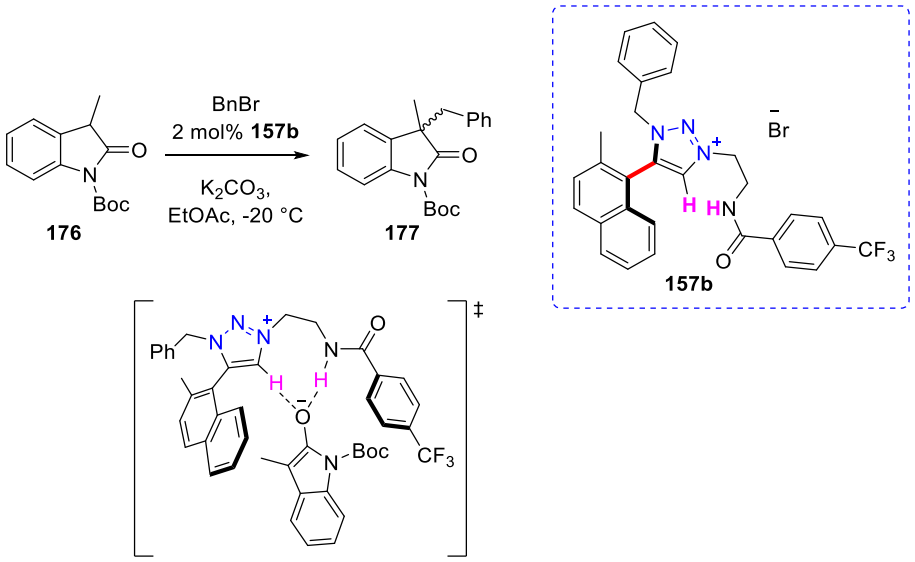
Thanks to the work of Ooi and co-workers, in the last decade, 1,2,3-triazolium salts of type **175**, derived from α-amino alcohols as chiral pools, have emerged as a new class of phase-transfer catalysts.[129, 130, 155, 156, 158-160, 181-183]



Scheme 48 Chiral triazolium salts reported by Ooi's group.

Introduce by Stark in 1971,[184] phase-transfer catalysis (PTC) involves the transfer across the interface of an anionic species, from an aqueous or solid inorganic phase to a liquid or gaseous

organic phase. PTC has many unique advantages such as the mild, green reaction conditions, the high yields generally observed, the possibility of conducting reactions between reactants that have no common solvent, and the substantial cost savings over more traditional synthetic methods due to its catalytic nature.[185] Over the past few decades, PTC has established itself as a versatile technique applicable in many areas of chemistry, including asymmetric synthesis.[186] In order to demonstrate, in principle, the feasibility of the atropisomeric triazolium salts synthesised to act as organocatalysts, it was decided to benchmark the reactivity of triazolium salt **157b** (obtained in 28% enantiopurity *via* thermal alkylation of the corresponding starting materials) against the alkylation of 3-methyl oxindole **176** under phase-transfer conditions. Following the conditions reported in the literature,[130] the reaction was performed in ethyl acetate, at -20 °C, with 2 mol% of **157b** and potassium carbonate as the base. The reaction achieved full conversion after 16 hours, and the product **177** was isolated in quantitative yield and a promising 14% enantioenrichment (**Scheme 49**), as determined by HPLC analysis on chiral stationary phase.



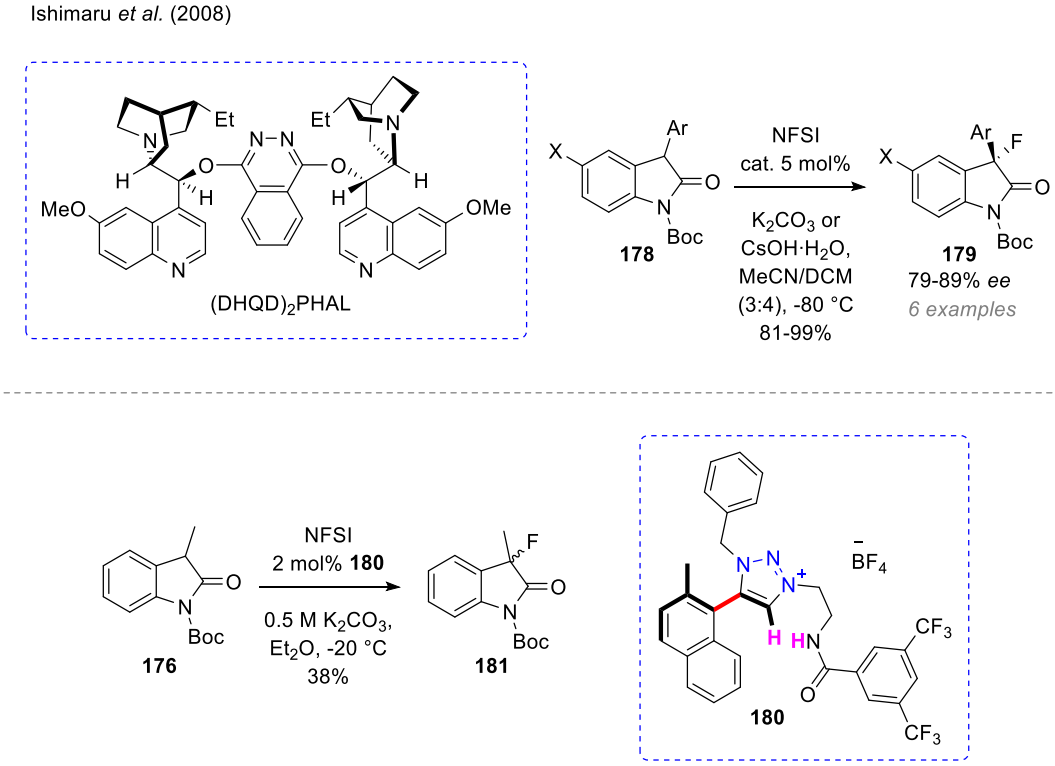
Scheme 49 Asymmetric alkylation of oxindole **176** catalysed by triazolium salt **157b**. The proposed transition state is shown. The absolute configuration of **157b** is unknown, and it has been arbitrarily chosen for clarity:

Given the intentional structural resemblance with the catalysts reported by Ooi and co-workers, it can be assumed that the reaction proceeds *via* the same mechanism, *i.e.* the C(5)-H and the NH (highlighted in pink in **Scheme 49**) coordinate to the prochiral enolate through a double hydrogen-bond interaction, with the C(4) and the amide substituents playing a crucial role in the stereodetermining step, being that these are located in the vicinity of the enolate in the transition state.[130]

Despite the influence of the chiral axis on the selectivity could not be evaluated without enantiopure **157b**, and a positive non-linear effect (NLE)[187] cannot be excluded, all in all, this preliminary result was considered encouraging and demonstrates, in principle, the potential of these atropisomeric compounds.

Furthermore, it was found that triazolium salts like **180** could also catalyse the fluorination of 3-substituted oxindoles under phase-transfer conditions (**Scheme 50b**). The construction of quaternary C-F bonds with defined stereochemistry is a reaction that has drawn the attention of synthetic chemists in recent years, mainly due to the enormous interest that fluorinated compounds have found in virtually every area of the chemical industry.[188] Since the development of bench-stable, easy-to-handle electrophilic fluorinating reagents (*e.g.* SelectFluor, NFSI) numerous catalytic enantioselective fluorination of nucleophilic substrates have been developed, yet this reaction is still rather challenging.[189] In particular, while the asymmetric fluorination of 3-substituted oxindoles under phase-transfer conditions has a literature precedent, the method appears to be limited to 3-aryl substituted substrates.[190, 191]

The reaction was performed in diethyl ether, at -15 °C, with 2 mol% of **180**[VII] and a 0.5 M aqueous solution of potassium carbonate as the base (**Scheme 50b**). Over 16 hours under these conditions, full conversion was not achieved, and the product was isolated in 38% yield.



Scheme 50 Asymmetric fluorination reported by Ishimaru *et al.*[190] (top) and asymmetric fluorination of oxindole **176** catalysed by triazolium salt **180** (bottom). The absolute configuration of **180** is unknown, and it has been arbitrarily chosen for clarity:

Although complete baseline separation on the chiral HPLC was not achieved[VIII], the chromatogram revealed that roughly 17% *ee* had been achieved. While the result is not optimal *per se*, and the reaction was never optimised, it demonstrates the general applicability of these atropisomeric compounds in organocatalysis, even for synthetically challenging reactions like fluorinations.

[VII] The enantiopurity of **180** has not been calculated; however, as it was prepared by a silver salt mediated alkylation of the corresponding triazole at room temperature, it was assumed enantiopure.
[VIII] In the literature successful chiral HPLC separation of **181** has been achieved in normal-phase; however, at the time when the experiment was performed, no suitable instrument for separations in normal-phase was available from the analytical facility.

3.6 Summary

For the synthesis of the compounds reported in this chapter, different strategies were explored. The first approach, described in *Section 3.1*, involved the synthesis of racemic 1,3,4-trisubstituted triazolium salts prepared *via* alkylation of either 1,4- or 1,5-triazoles. However, while separation conditions could be established in certain cases, the strategy did not prove overall viable, and the resolution into single enantiomers through chromatographic methods or recrystallisation of diastereomeric ion pairs could not be accomplished. Following the finding that restricted rotation could be achieved in appropriately substituted 1,5-triazoles, a different approach envisaging alkylation of the single enantiomer(s) of these species was explored, and a series of novel atropisomeric triazoles (**153**-**154**) was successfully prepared. The compounds showed remarkable stability, with computed barriers to rotation up to 34.3 kcal/mol and half-lives of millennia at room temperature.

While the resolution of these neutral compounds was easily achieved on a chiral column, the conditions needed for the alkylation step, given the poor nucleophilicity of the triazoles, led to partial racemisation, thus invalidating the strategy.

Changing the alkylating bromide(s) for a more electrophilic triflate, as reported in the literature for other nitrogen-containing aromatic compounds, was ineffective, and attempts of exploiting the insolubility of silver halides led preferentially to self-cyclisation (*O*-alkylation) of the alkylating agents. Performing a Mitsunobu reaction on the corresponding 1*H*-triazolium tetrafluoroborate salt, on the other hand, showed promising results. However, time constraints within the laboratory did not allow further investigations and/or optimisation of the reaction.

To demonstrate the potential of these species, an asymmetric alkylation of 3-substituted oxindoles under phase-transfer conditions was performed with enantioenriched triazolium salt

157b (28% ee) as the catalyst. The product isolated displayed 14% enantioenrichment, a result that can be considered overall encouraging. Indeed, even if it was not possible to determine the influence of the chiral axis on the selectivity, or exclude a positive non-linear effect, the reaction shows that, in principle, the catalyst can give rise to an appreciable level of asymmetric induction, even when not optically pure.

4 Second Generation Atropisomeric Triazoles

Given the difficulties encountered in the preparation of charged axially chiral compounds of the type presented in the previous chapter, it was decided to revisit the design of the compounds, still aiming to prepare a small library of these and explore potential application in asymmetric organocatalysis (**Figure 48**).

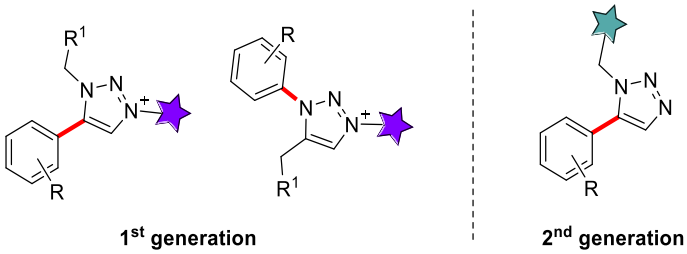


Figure 48 First and second generation atropisomeric triazole derivatives.

Given the considerable success that they have gained as organocatalysts over the past few decades, it was decided to embed a (thio)urea unit into the neutral 1,5-triazole scaffold.[192, 193] Due to their Lewis acidity and coordination properties, (thio)ureas have earned a central role in hydrogen-bond[194] and ion-pairing catalysis[131] (**Figure 49**), both of which have a generic mode of activation based on LUMO activation, *i.e.* the energy of the lowest unoccupied molecular orbital of the electrophile is lowered upon coordination to the catalyst.

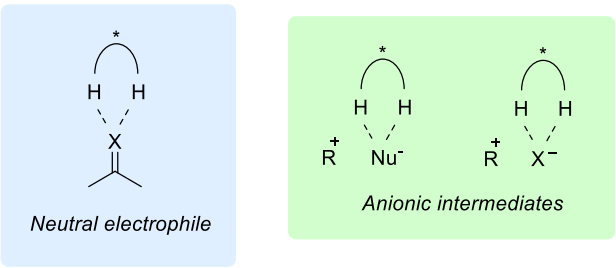
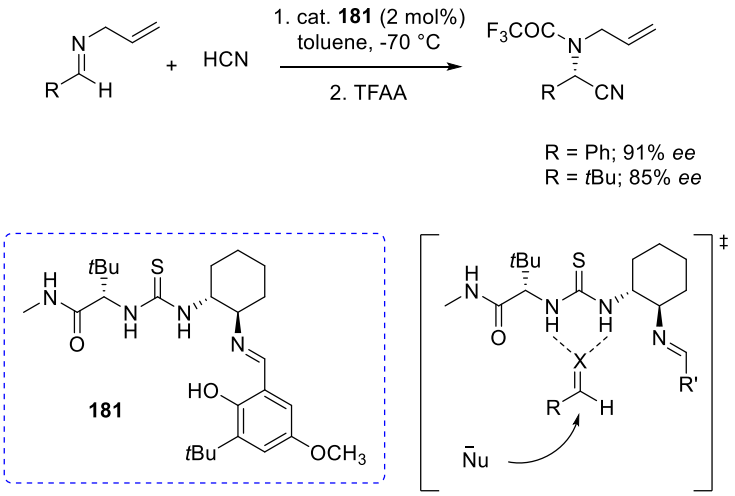


Figure 49 Hydrogen-bond catalysis (blue, left) *vs* ion-pairing catalysis (green, right).

- ***Hydrogen-bond catalysis***

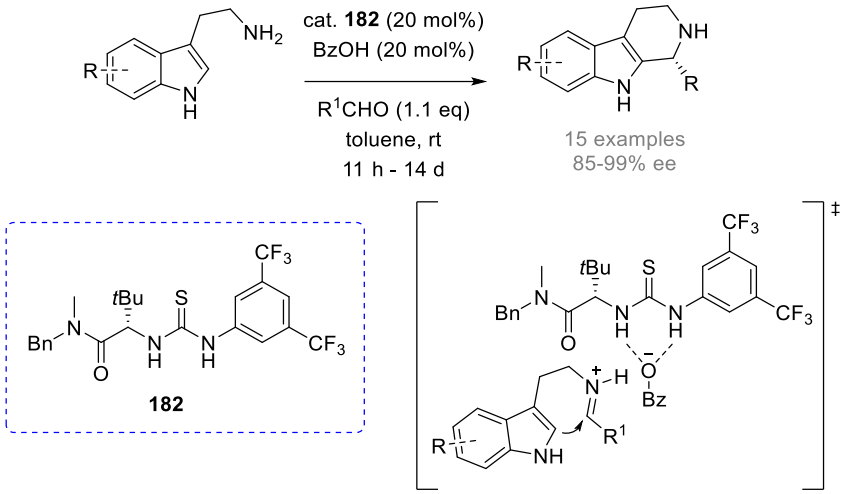
Enabled by small hydrogen-bond donors, hydrogen-bond catalysis entails the direct activation of neutral electrophiles (*e.g.* imines, carbonyls) *via* the simultaneous donation of two hydrogen bonds. Following the pioneering work of Jacobsen and co-workers, who reported an asymmetric variant of the Strecker reaction promoted by thiourea derivative **181** (**Scheme 51**),[195, 196] several asymmetric reactions based on this mechanism of activation have been developed, many of which are mediated by (thio)ureas derivatives.[197]



Scheme 51 Thiourea-catalysed asymmetric Strecker reaction.[195]

- ***Ion-pairing catalysis – Anion-binding catalysis***

More recently, Jacobsen and co-workers have demonstrated that chiral thioureas can bind anions and form transient ion-pairs.[198] These complexes function as chiral counterions, hence influencing the approach of nucleophiles to either face of the (transient) electrophile (*i.e.* the cation). An example of this mechanism of activation is given by the one-pot Pictet-Spengler reaction catalysed by thiourea **182**, reported by Jacobsen and co-workers (**Scheme 52**).[199]

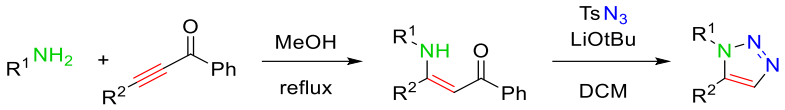


Scheme 52 One-pot Pictet-Spengler reaction catalysed by thiourea **182**.[199]

Key advantages of (thio)urea organocatalysts include, but are not limited to, their air and moisture stability, which generally translates into easier experimental setups, their nontoxicity, which increases the overall safety of the catalysis, and the possibility to recover and reuse the catalysts.[200] On the other hand, catalyst loadings are generally higher (10-20 mol%) and the catalytic rate accelerations relative to uncatalysed reactions are usually far less than the corresponding metal-catalysed reactions,[201] which means reaction times are generally longer (up to weeks). Nonetheless, thioureas have emerged in the field of organocatalysis as a convenient and versatile class of compounds.

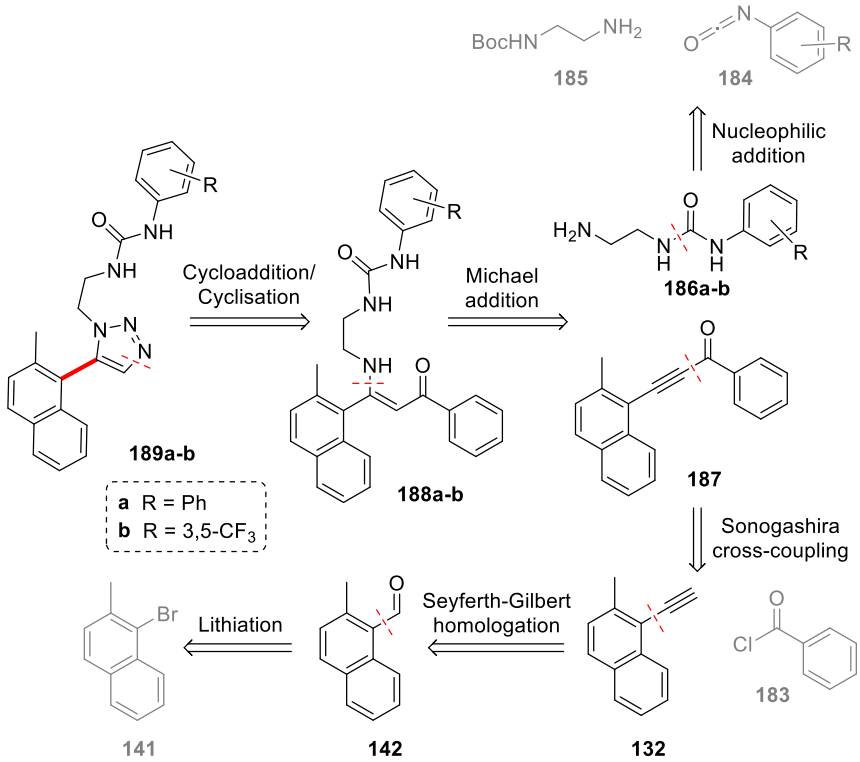
4.1 Substrate Selection and Synthetic Approach

The new design required an alternative synthetic strategy. In fact, due to substrate incompatibilities, using either the magnesium- or the zinc-mediated synthesis of 1,5-triazoles thus far employed was no longer feasible. A review of the literature allowed the identification of a metal-free regiospecific synthesis of 1,5-disubstituted triazoles (**Scheme 53**).[202]



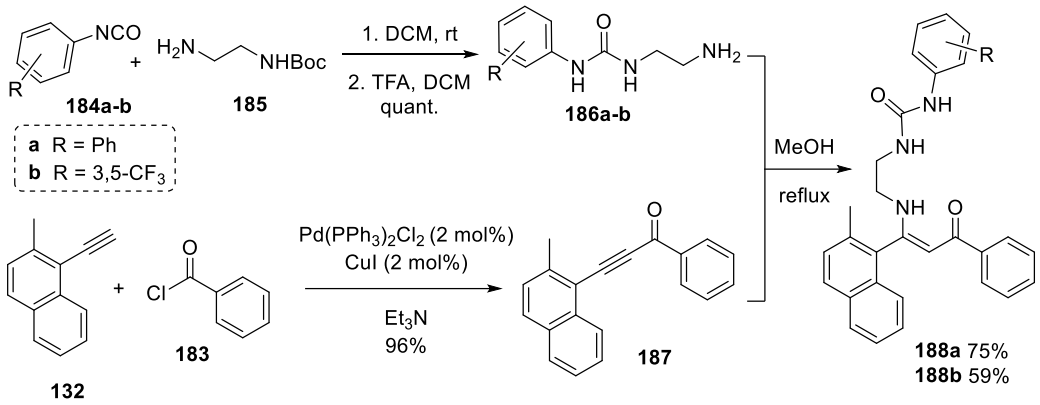
Scheme 53 Metal-free regiospecific synthesis of 1,5-triazoles.[202]

Whilst the reaction could be performed in one-pot, the two-step procedure was judged to be more cautious, and offered the advantage of allowing an easier identification of putative issues, should it not have proceeded as reported with the chosen substrates. To test the reaction, model compounds **189a** and **189b** were designed (**Scheme 54**). To minimise the number of linear steps, it was decided to disconnect the triazole ring first and proceed with a convergent sequence from commercially available starting materials **141** and **183** (**Scheme 54**).



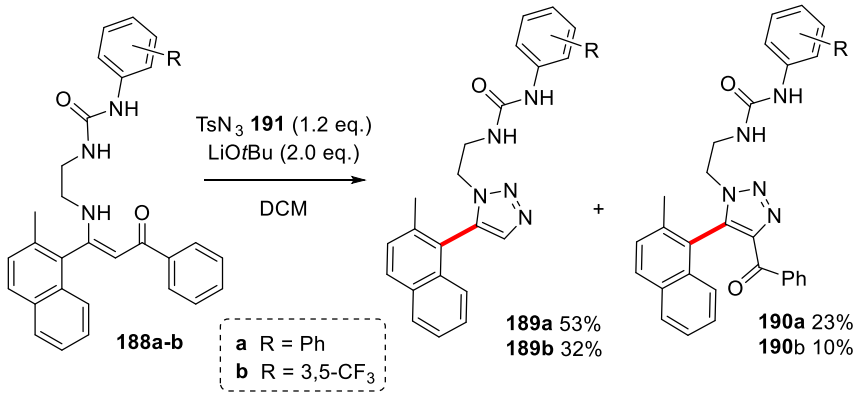
Scheme 54 Retrosynthetic sequence initially planned. Commercially available compounds have been greyed out.

The synthesis of 1**87** and **186** was straightforward, and enaminones **188a-b** were obtained in good overall yields of 75% and 59% respectively (**Scheme 55**).



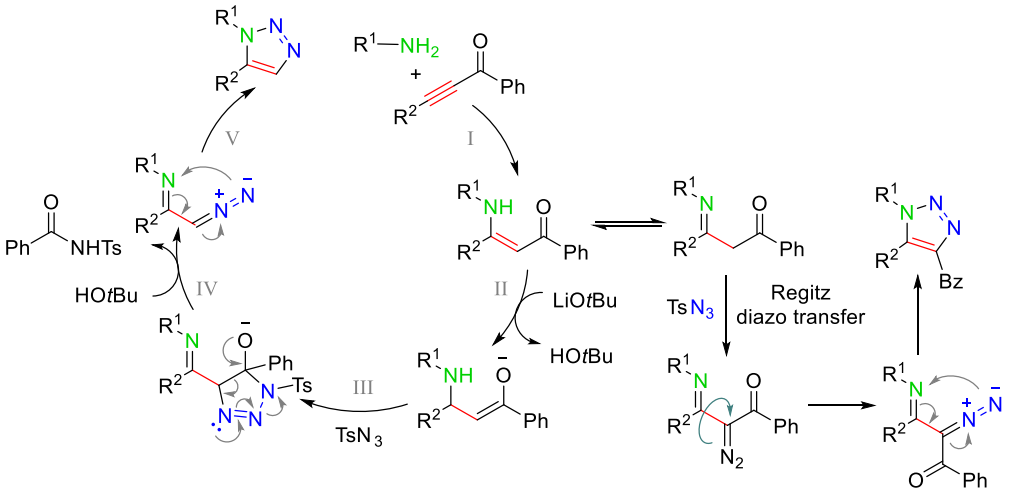
Scheme 55 Synthesis of enaminones **188** from **186** and **187**.

Following the literature, the cycloaddition of **188** with tosyl azide **191** to form triazoles **189** was set up in dichloromethane and lithium *tert*-butoxide as the base. **189a-b** were obtained in reasonable yields, however, in contrast to the original report, in both cases the by-products **190a-b** (**Scheme 56**) from the Regitz diazo transfer[203] were isolated in 10-23% yield, lowering the yields of the desired products.



Scheme 56 Metal-free synthesis of 1,5-disubstituted triazoles.

Similar by-products were reported by the authors only when the benzoyl group in the enaminones was replaced by an acetyl group, which being an electron donor, made the enolization step (II in **Scheme 57**) more difficult.[202]

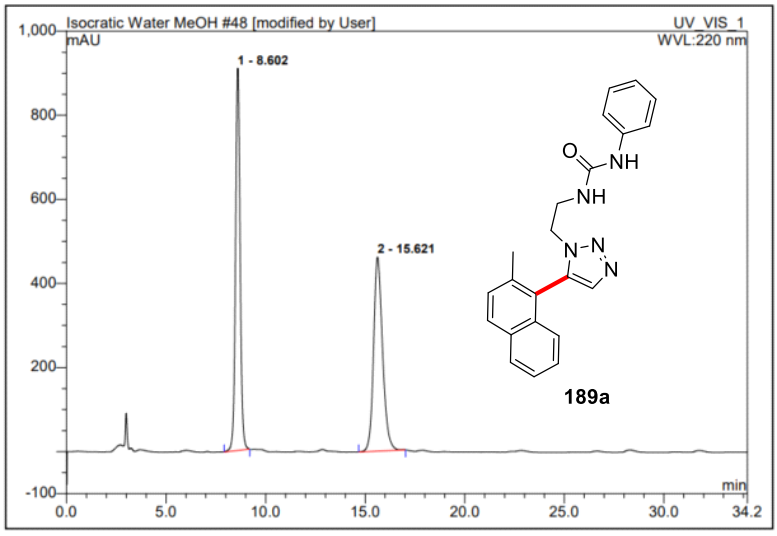


Scheme 57 Reaction pathway proposed by Cheng *et al.*,[202] and possible side path.

It was hypothesised that, with substrates **188a-b**, difficulties in the enolization step could be ascribed to the urea moiety, which could stabilise the enaminones produced in step I (**Scheme 57**) through multiple H-bonding with the carbonyl oxygen, and consequently shift the equilibrium towards them. Attempts of minimising the side product and optimising the yields resulted in shorter reaction times (2-3 hours even if full conversion was not achieved) and doubling the amount of the base.[IX]

Assessment of the achieved restricted rotation was done *via* HPLC, which showed an outstanding baseline separation between the two enantiomeric peaks ($\Delta R_t \approx 7$ minutes) in a mixture of 40:60 water/acetonitrile, and Phenomenex Cellulose-1 (OD-H) as the chiral stationary phase.

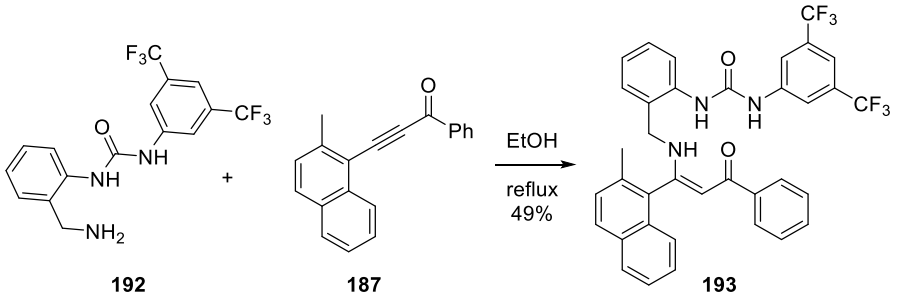
[IX] The reaction proceeds under heterogeneous conditions.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.60	n.a.	908.994	244.620	50.35	n.a.	BMB*
2	15.62	n.a.	461.874	241.235	49.65	n.a.	BMB*
Total:			1370.869	485.856	100.00	0.000	

Figure 50 Chiral HPLC trace of **189a**.

Having proved that the resolution into single enantiomers could be easily achieved, the preparation of **193** (**Scheme 58**), containing a more rigid benzyl linker (*i.e.* a more rigid moiety connecting the (thio)urea to the triazole ring), was attempted following the same synthetic sequence. Structural rigidity can help to provide well-defined chiral pockets, hence, in asymmetric catalysis, rigid structures are generally associated with higher enantioselectivities.[204-206] The synthesis of **193** was thus considered of value, not only to determine the effects of structural rigidity in future catalytic screenings but also to explore possible substrate limitations in the method used. **193** was isolated in 49% yield from propanone **187** and benzyl amine **192** (**Scheme 58**).



192 187 193

Scheme 58 Preparation of **193**.

Compound **193** displayed a locked conformation, which is believed to be a consequence of the strong intramolecular hydrogen bond formed between the heterodienic fragments of the (β-)enaminone, as already reported in the literature.[207-210] This interaction imparts rigidity to the system through the formation of a six-membered ring, therefore increasing the barrier to rotation about the C_{sp^2}-C_{sp^2} single bond (highlighted in red in **Figure 51**) between the aryl group and the enaminone double bond. Upon inspection of the ^{1}H NMR it was thus possible to observe two doublets relative to the diastereotopic benzylic protons. To assess the stability of **193**, VT ^{1}H NMR spectroscopic analysis was conducted. Compound **193** showed a remarkable stability in TCE-MeOD on the NMR timescale, and coalescence was not observed even at 100 °C (**Figure 51**).

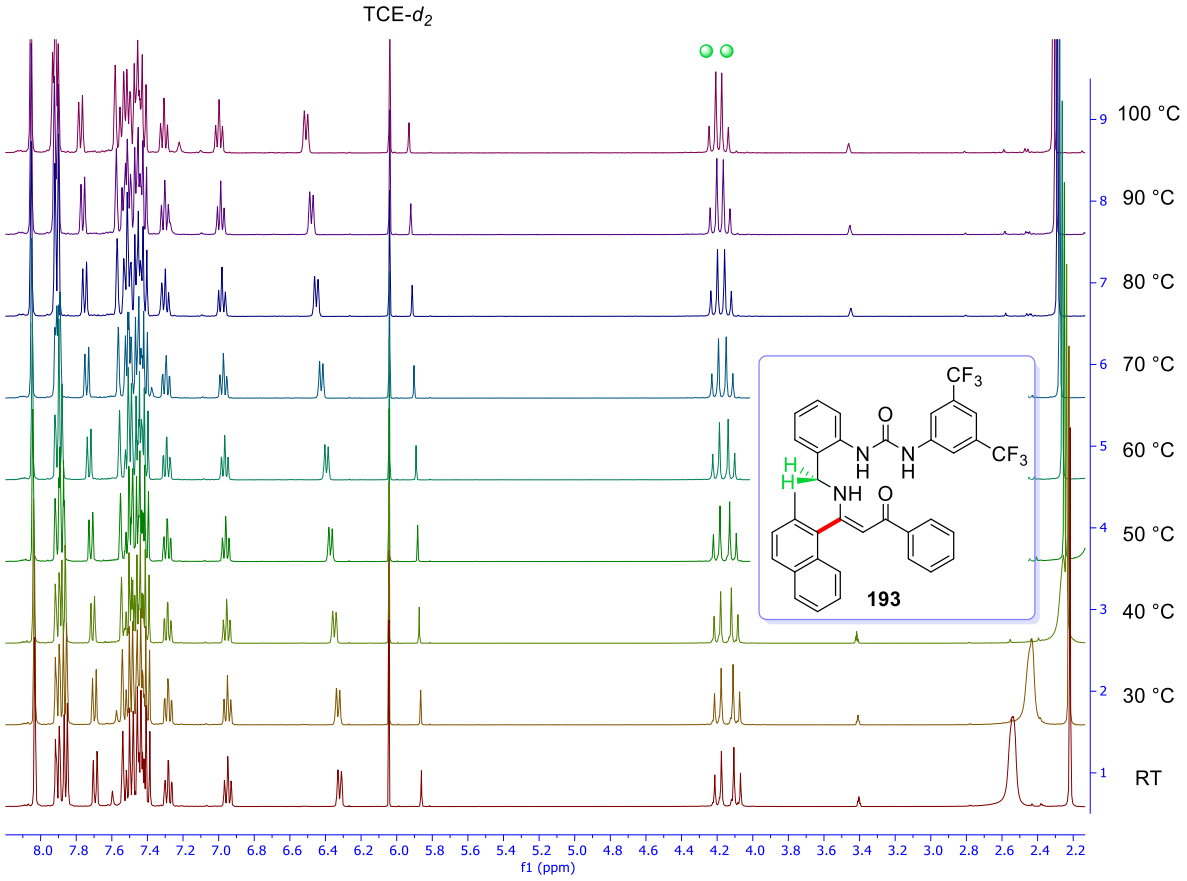
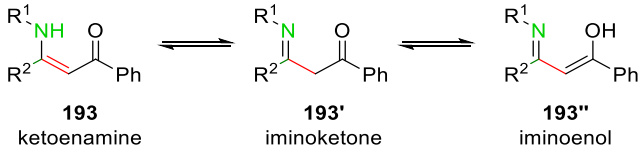


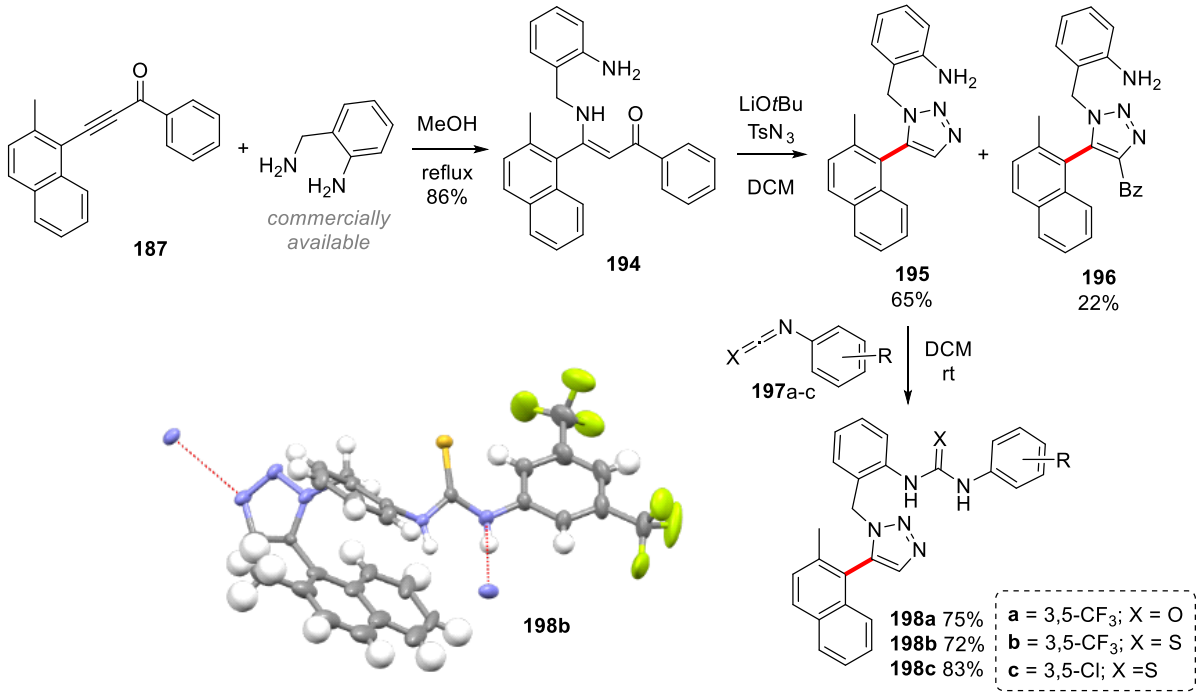
Figure 51 VT ^{1}H NMR study of compound **193** from RT to 100 °C.

The unforeseen conformational stability of **193** turned out to be a problem and all the attempts to form the corresponding triazole failed, even when the base was changed to the stronger sodium amide. The result can be rationalised as a consequence of the ketoenamine-iminoketone equilibrium (**Scheme 59**) completely shifted toward the ketoenamine form (*i.e.* **193**), which makes the enolization step (II in **Scheme 57**), and consequently the formation of the triazole, unfeasible.



Scheme 59 Tautomers of compound **193**.

To access compounds like **198** a new, divergent synthetic route envisaging the (thio)urea formation as the last step was planned. The sequence proved viable and compound **198a** was isolated in 35% yield over three steps from propinone **187** (**Scheme 60**).



Scheme 60 Synthesis of compounds **198**. The crystal structure of **198b** with ellipsoids drawn at 50% probability level is shown. The naphthyl ring is disordered over two positions; for clarity, only the major position is shown. The structure contains a molecule of chloroform which has been omitted.

To expand the library of potential catalysts, compounds of type **199** were thus designed (**Figure 52**). π-Surfaces were thought to potentially offer a greater selectivity in future catalysis, whereas electron withdrawing groups have been shown to improve the catalytic efficiency of (thio)urea, due to the reduction of the pK_a values (*i.e.* higher acidity) and a consequent enhancement of the H-bond donor ability.[211]

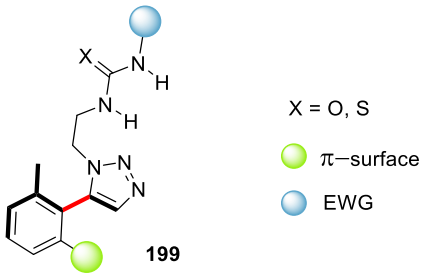
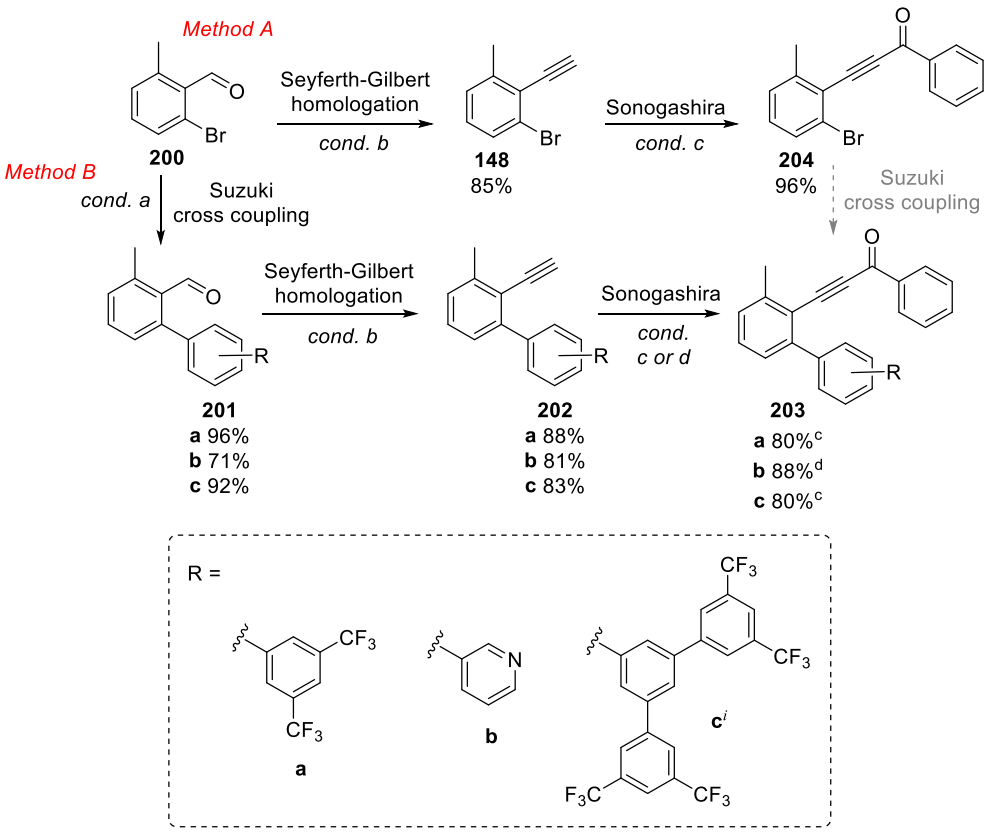


Figure 52 General structure of the triazole-containing (thio)ureas designed.

Starting from the common aldehyde **200**, propinones **203** were prepared in three steps following either *Method A* or *Method B* (**Scheme 61**).

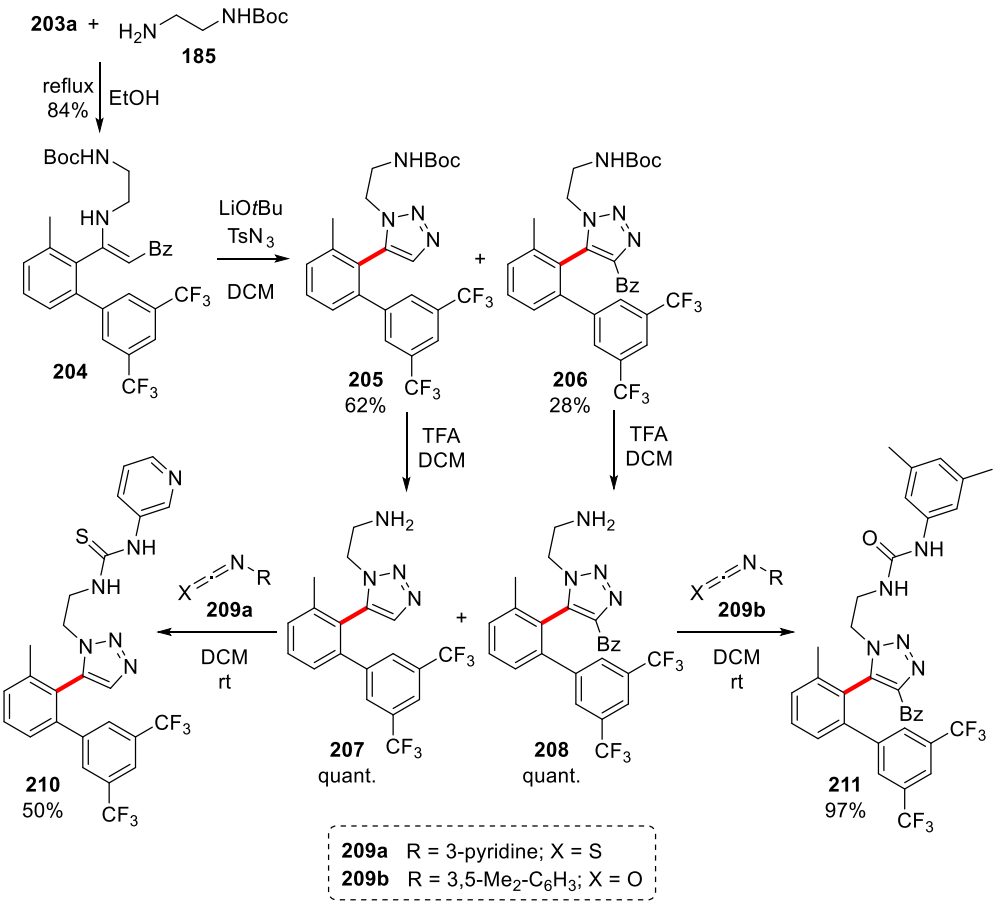


Scheme 61 Preparation of propinones **203** from aldehyde **200**. *a)* $RB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene/EtOH 1:1, 100 °C, 16 h; *b) p*-ABSA, K_2CO_3, MeOH, rt, 16 h; *c)* BzCl, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, rt, 16 h; *d)* BzCl, Pd/C (10 wt.%), Et_3N, toluene, 110 °C, 16 h. *i*) Corresponding boronic acid prepared in four steps from commercially available 1,3-dibromobenzene.

Method A, allowing access to a range of propinones from their common intermediate **204**, was initially deemed more convenient. However, the poor yields recorded in the final Suzuki cross-coupling step (especially in the synthesis of **203b** and **203c**) led to consider *Method B* that,

although divergent and overall lengthier, allowed the isolation of compounds **203a-c** in good overall yields (*i.e.* 54-68%).

To test whether the sequence previously used was feasible with a simple alkyl linker, propinone **203a** was treated with amine **185** to afford **204**, hence subjected to the cycloaddition/cyclisation with tosyl azide and lithium *tert*-butoxide to afford triazoles **205** and **206** in 62% and 28% yields respectively. Following the deprotection of the Boc group, **207** and **208** were treated with isocyanates **209a** and **209b**, to afford **210** and **211** in 50% and 97% yields respectively (**Scheme 62**).



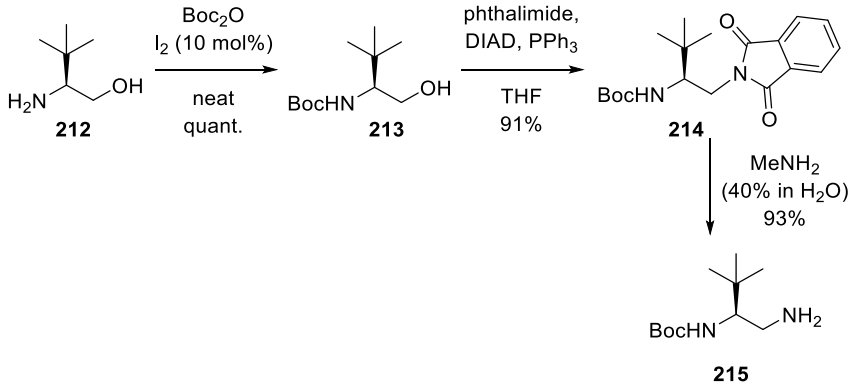
Scheme 62 Synthesis of compound **210** and **211**.

Having a small library of triazole-containing (thio)ureas available, resolution of enantiomers was attempted on a preparative scale. Whilst the isolation of the enantiomeric pairs **198a-c** was

easily achieved in a mixture of water/acetonitrile under isocratic conditions, on a Phenomenex Cellulose-1 column, compounds containing an alkyl linker could not be resolved, with the exception of **189a**. In all these cases, despite the exceptional separation between peaks displayed on the analytical column, the poor solubility of the compounds in MeCN/MeOH/EtOH/*i*PrOH (solvents compatible with the chiral stationary phase[X]) forced the use of large injection volumes that led to extreme peak broadening and poor sensitivity, which made the resolution of this type of compounds unachievable.

4.2 Diastereomeric Triazole-containing Thioureas

To circumvent the difficult resolution of compounds containing an alkyl liker (*e.g.* **210** and **211)** and, at the same time, minimise the use of preparative HPLC, the new chiral linker **215**, readily accessible from the corresponding α-amino alcohol, was prepared (**Scheme 63**).



Scheme 63 Preparation of chiral linker **215** from the corresponding amino alcohol **212**.

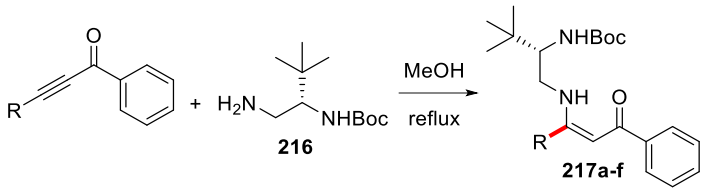
215 was reacted with propinones **187** (*Entry 2*), **203a-c** (*Entry 3-5*), **204** (*Entry 6*), and **216** (*Entry 1*) to afford pairs of diastereomeric enaminones **217a-f** (**Table 1**), derived by the high energy barriers to rotation arising from the strong intramolecular N-H•••O fragments, as already observed for **193** (*vide supra*). Diastereoselectivity was observed with propinones bearing

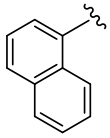
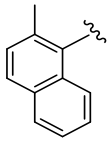
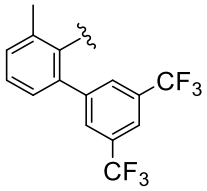
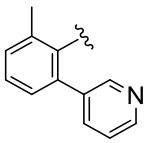
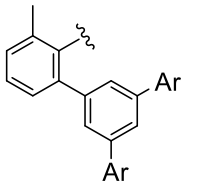
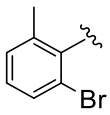
[X] Column manufacturer guide.

substituents with large π-surfaces (*e.g*. **228**-**229**). Separation of the diastereoisomers at this stage was not possible, except for **217f**, whose diastereoisomers (**217f** and **217f'**) were isolated in 43% and 45% yield (**Table 1**, *Entry 6*), and **217c**, whose major diastereoisomer was isolated in 60% yield[XI] (**Table 1**, *Entry 3*).

[XI] Minor diastereoisomer not isolated.

Table 1 Preparation of diastereomeric enaminones **217**. Where the two diastereoisomers were isolated, two yields are given; for a given compound, the prime symbol denotes the other diastereoisomer isolated. A diastereomeric ratio (d.r.) is given for compounds isolated as diastereomerically enriched mixtures; a 1:1 d.r. is intended in all remaining cases.



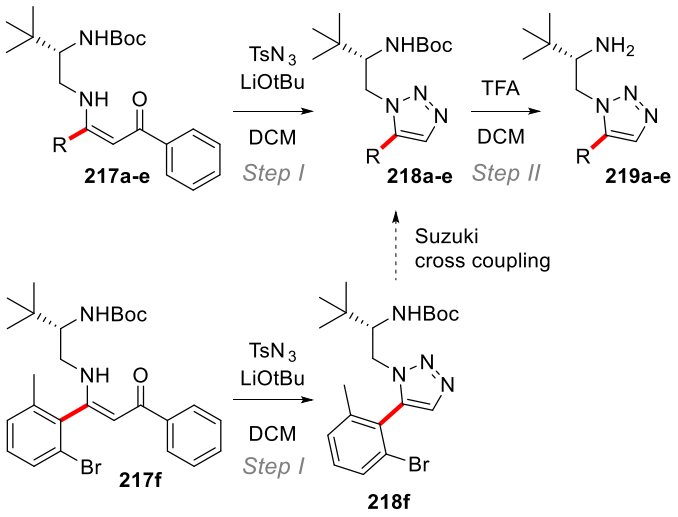
Entry	R	Product	Yield (%)
1		**217a**	68[i] (1:1 d.r.)
2		**217b**	81[i] (1:1 d.r.)
3		**217c** **217c'**	60 35[ii] (1:3.4 d.r.[iii])
4		**217d**	79[i, ii] (1:2.3 d.r.[iii])
5	 Ar = 3,5-$(CF_3)_2$-C_6H_3	**217e** **217e'**	23[ii] (1:4.0 d.r.[iii]) 31[ii] (1:5.5 d.r.[iii])
6		**217f** **217f'**	43 45

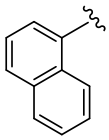
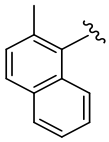
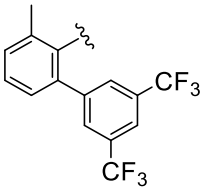
i) isolated yield after flash chromatography for the mixture of the two diastereoisomers; *ii)* mixture enriched in one diastereomer; *iii)* d.r. calculated by ^{1}H NMR.

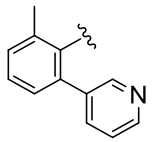
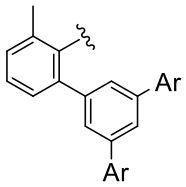
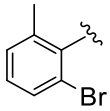
Compound **217a**, precursors of a non-atropisomeric triazole, was prepared to estimate the influence of the chiral axis on the selectivity in catalysis.

The enaminones were hence reacted, mainly as diastereomeric mixtures, to afford, following deprotection, the corresponding triazoles **219a-e** (**Table 2**).

Table 2 Preparation of triazoles **219** from enaminones **217**. Where the two diastereoisomers were isolated, two yields are given; for a given compound, the prime symbol denotes the other diastereoisomer isolated.



		Yields (%)	
Entry	**R**	**Step I**	**Step II**
1 (**a**)		49	99
2 (**b**)		47	99
(**b'**)		48	95
3 (**c**)		65[i]	99

4 (**d**)		41 (72)[ii]	Used as a crude in the next step
5 (**e**)	 Ar = 3,5-$(CF_3)_2$-C_6H_3	36[iii]	99
6 (**f**) (**f'**)		71[i] 88[i]	/

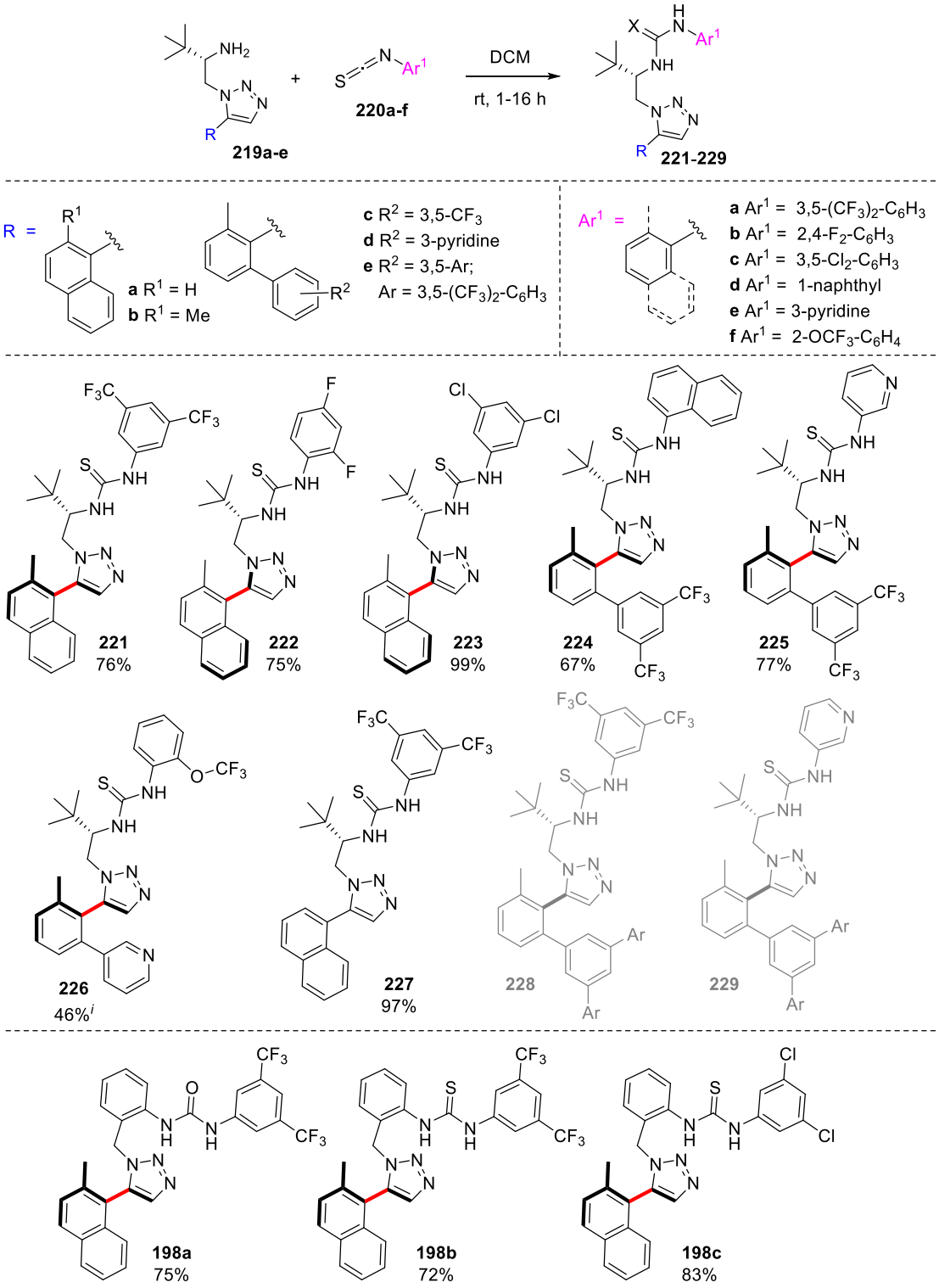
i) from diastereomerically pure starting material; *ii)* isolated yield after flash chromatography for the mixture of the two diastereoisomers; *iii)* only one diastereomer was isolated

Enaminone **217e**, containing a highly sterically demanding substituent, displayed the poorest reactivity and under the conditions employed the best yield recorded for **218e**, the only diastereomer isolated, was 36%.

The convergent route starting from **218f-f'** was also investigated, however, no better yields were recorded and, although more convenient, the method proved overall worse and limited with regard to certain substrates (*e.g*. preparation of **218d**).

Separation of the Boc-protected triazoles **218** was achieved by column chromatography on silica gel, in hexane/ethyl acetate. Where chromatographic separation was not possible (*i.e.* **218d**), the diastereoisomers were separated by fractional recrystallisation, albeit in this case the mass recovery was lower (**Table 2**, *Entry 4*).

Triazoles **219a-e** were subsequently reacted with a range of isothiocyanates **220a-f**, as previously done, to afford the corresponding thioureas **221-229** containing a triazole-core.



Scheme 64 Triazole-containing thioureas **221**-**229** prepared. The absolute configuration of the compounds is unknown, and it has been arbitrarily chosen for clarity; where different diastereoisomers were used, opposite configurations are shown. *i)* yield over two steps.

The bulky triazole **219e**, displayed low reactivity and even when reacted with **220a**, bearing electron withdrawing CF_3 groups, only a small amount of the desired product (**228**) was isolated.

4.3 Application in Organocatalysis

The new design raised the question of whether the triazole and the (thio)urea moiety could work synergistically in the molecular recognition process, through multiple hydrogen-bond interactions (**Figure 53**) and how, in a similar scenario, the chiral axis would impact the stereoselectivity.

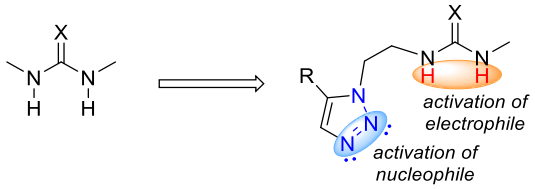


Figure 53 Hypothetical multiple H-bonding synergistic activation.

Several notable examples of "dual activation" catalysis can be found in the literature,[212-215] however, the majority of bifunctional thiourea catalysts entail the activation of the nucleophilic component of the reaction *via* deprotonation or nucleophilic catalysis by means of a vicinal basic functionality, which is generally a tertiary amine (**Figure 54**).

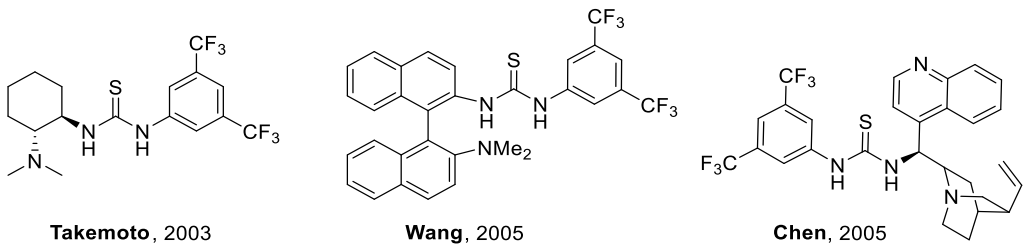


Figure 54 Selected examples of chiral bifunctional thioureas.[212, 215, 216]

Given the poor basicity of 1,2,3-triazoles[217] (pKa ≈ 1.1-1.2), a similar mechanism was not deemed likely. It was hypothesised that, perhaps, a more plausible interaction could be a

cooperative thiourea-Brønsted acid type catalysis,[218-220] mediated by the triazole ring. In this regard, a major reference came from the work of Zhang *et al.*,[221] who reported an enantioselective addition of TMS cyanide to aldehydes, promoted by a chiral bifunctional imidazole-thiourea catalyst in tandem with *meta*-bromo benzoic acid, the co-catalyst (**Figure 55a**).

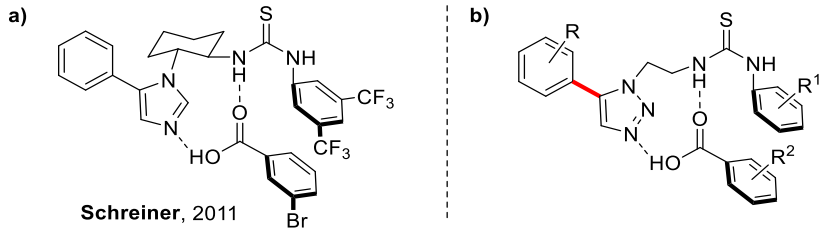


Figure 55 a) Cooperative imidazole-thiourea/m-Br benzoic acid catalytic system.[221] **b)** Hypothetical cooperative triazole-thiourea/benzoic acid derivative catalytic system.

A further question that was raised was whether the H-bond donor ability of the triazolic H(4) could activate the (thio)urea moiety through intramolecular H-bonding, similarly to what has already been reported in the literature (**Figure 56a**).[104, 222-224]

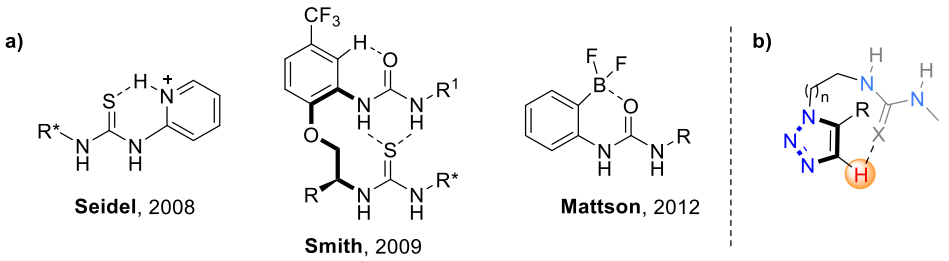
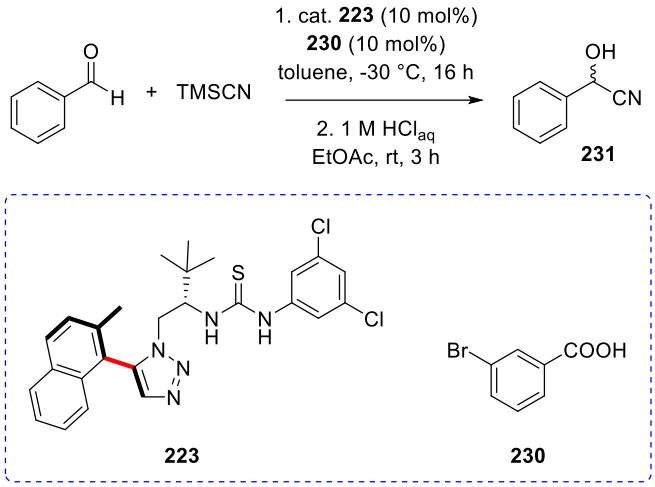


Figure 56 a) Selected examples of (thio)urea organocatalysts activated through an internal Brønsted acid.[222-224] **b)** Hypothetical internal activation of (thio)ureas containing a triazole unit.

To test the possibility of a cooperation between the triazole and the (thio)urea moiety, similarly to that which Zhang *et al.* reported,[221] it was decided to investigate the catalytic activity of **223**, bearing electron withdrawing chlorines. **223** was deemed suitable for the interaction sought and was available in larger quantities, for use in the asymmetric cyanosilylation of aldehydes with TMSCN. Following the conditions reported,[221] the reaction was performed under argon, in

anhydrous toluene at -30 °C, using benzaldehyde as the model substrate and 3-bromobenzoic acid **230** as cocatalyst (**Scheme 65**).



Scheme 65 Asymmetric addition of TMSCN to benzaldehyde. The absolute configuration of **223** is unknown, and it has been arbitrarily chosen for clarity.

Unfortunately, **223** displayed no catalytic activity and, under the conditions employed, no conversion was observed, even when the reaction time was extended to three days. A lack of catalytic activity was observed by Zhang *et al.* with oxazoline thioureas of type **232** (**Figure 57**), and it was rationalised as a drastically reduced binding ability of the thioureas due to the strong hydrogen-bonding interactions between the thiourea NH and the lone pair of the nitrogen of the oxazoline ring. This hypothesis was supported by ^{1}H NMR spectroscopy, displaying both the NH protons at rather low fields (13.3-8.7 ppm), and further validated by computational data. Binding deactivation caused by intramolecular hydrogen-bonding has also been reported by Roussel and co-workers[104] and it has been discussed already in Chapter 1 (**Figure 19**).

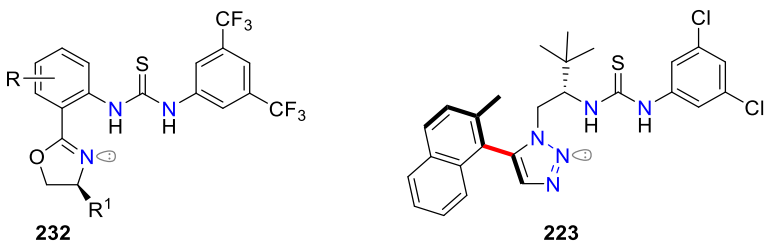


Figure 57 Comparison between **232**, reported by Zhang *et al.*,[221] and **223**.

^{1}H NMR spectroscopic analysis suggests that a similar scenario is plausible for **223**, being that the Δδ between the two NH protons is less than 2 ppm (**Figure 58**, bottom spectrum). Furthermore, the comparison between the ^{1}H NMR spectra of **223** and **219b**, the corresponding starting material, shows an appreciable downfield shift of the H(4) in the triazole ring (**Figure 58**), indicative of the deshielding given by intramolecular H-bonding.

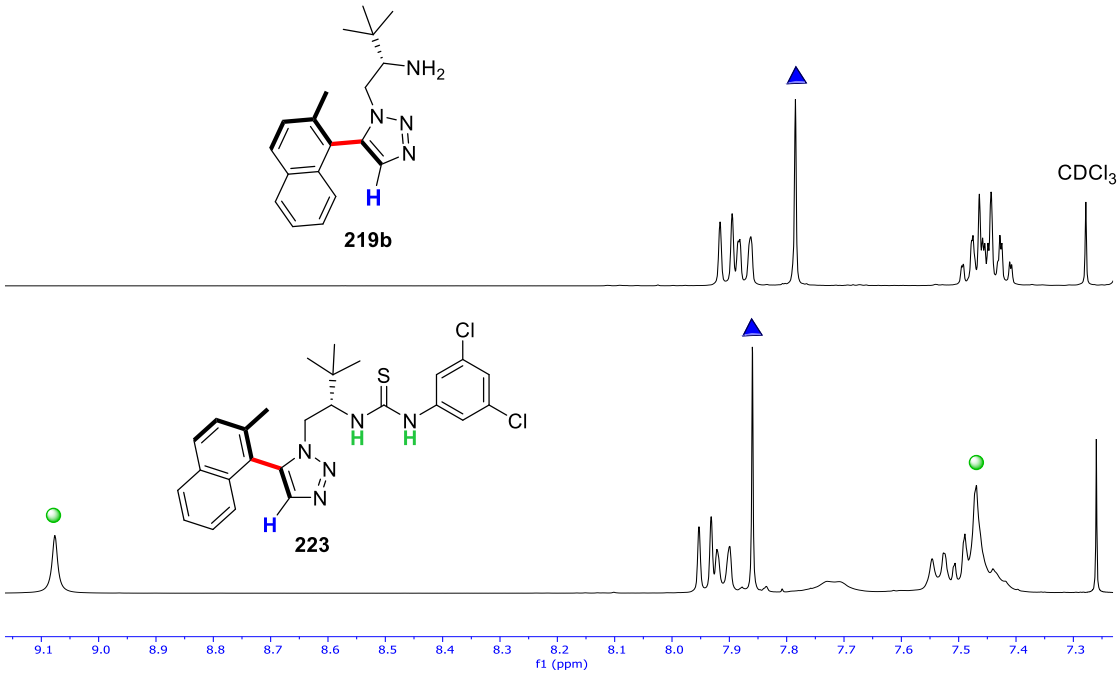


Figure 58 Overlaid ^{1}H NMR aromatic region of compounds **219b** and **223**. The absolute configuration of the compounds is unknown, and it has been arbitrarily chosen for clarity.

To corroborate that the catalysts could not engage in hydrogen-bonds with a benzoic acid derivative like **230**, a further NMR spectroscopy investigation was conducted. The ^{1}H NMR spectrum of a 1:1 mixture of **223** and 2,4,6-trimethylbenzoic acid[XII] in benzene-d_6 was recorded at room temperature, hence compared to the spectra of the two species involved measured individually in the same solvent. In agreement with the lack of catalytic activity observed, only subtle downfield shifts (0.01-0.05 ppm) were observed for the NH proton of the thiourea and

[XII] Chosen in place of **230** to simplify the spectrum, hence the analysis.

the H(4) in the triazole ring, supporting the experimental evidence that the type of cooperativity pursued was not achievable with similar catalysts.

Having excluded the possibility of a cooperative type of catalysis, it was decided to benchmark the catalytic activity against literature reactions catalysed by either mono- or bifunctional hydrogen-bonding catalysts. The strategy adopted aimed to identify a suitable reaction to then optimise by screening diverse reactions. It was expected that at least one reaction would stand-out during the screening, so that efforts could be focussed on the optimisation of that specific example. Given the large quantities of catalyst needed for the purpose, catalyst **227** (**Figure 59**), the one most readily available, was reprepared on a bigger scale and tested on eight different reactions adapted from the literature.[215, 225-232]

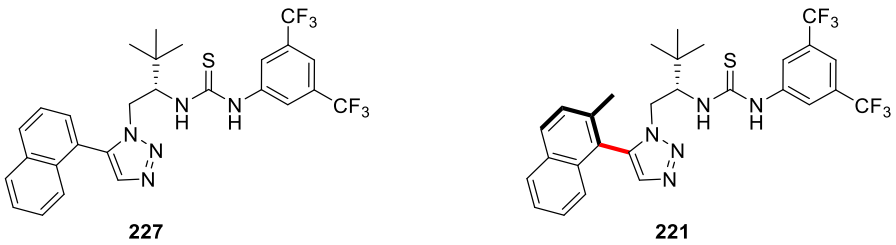
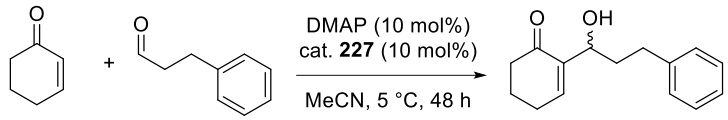
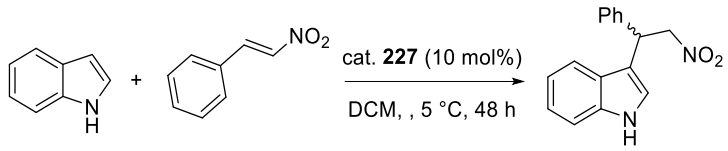
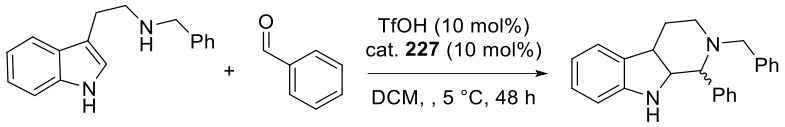
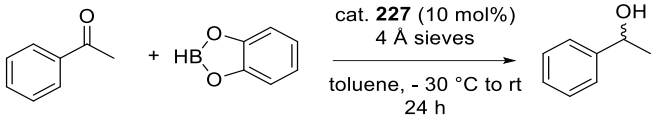
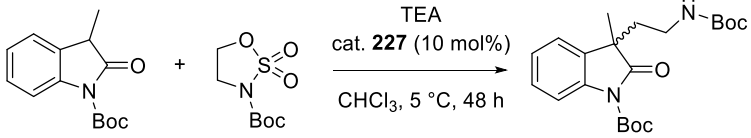
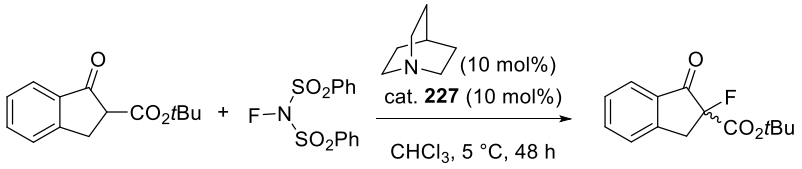
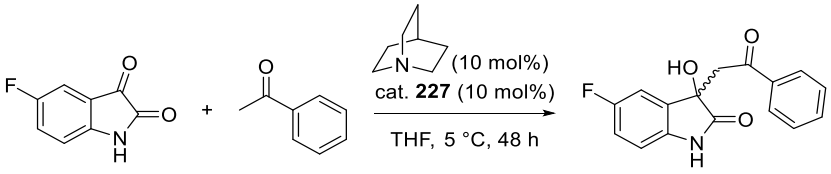
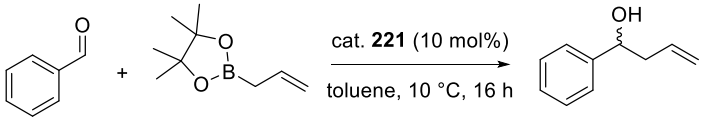


Figure 59 Model chiral catalyst **227** (point chirality only), used in the catalytic screenings, and corresponding atropisomeric catalyst **221**.

The reaction tested are shown in **Table 3** below.

Table 3 Reaction screening. All the reactions were performed in parallel with the corresponding uncatalysed version.

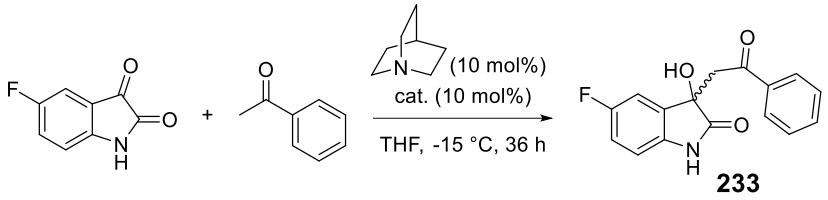
Entry	Reaction	Yield (%)[i]	e.r.[ii]
1		no conv.	/
2		no conv.	/
3		no conv.	/
4		traces	/
5		no conv.	/
6		22	50:50
7		82	47:53
8		54[iii]	51:49

i) isolated yield after chromatography; *ii)* determined by HPLC on chiral stationary phase; *iii)* catalysed by **221**.

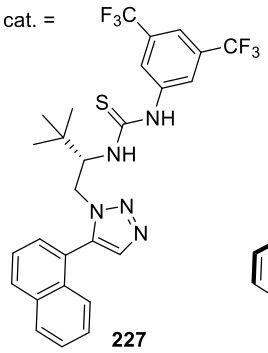
Of the reaction tested only *Entry 6*, fluorination of a β-keto ester,[231] *Entry 7*, aldol reaction,[226] and *Entry 8*, allylboration of benzaldehyde,[230] displayed an appreciable conversion under the conditions employed. However, in all cases, the isolated products were racemic or essentially racemic. Nonetheless, it is worth mentioning that, in most cases, it was possible to completely recover the catalyst from the reaction mixture.

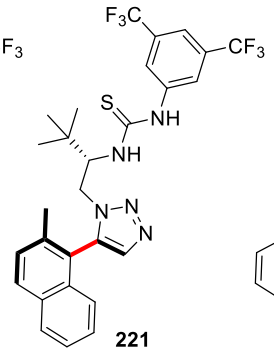
To gain insights into the catalytic activity of the catalyst(s) employed, it was decided to further investigate the aldol reaction (*Entry 7*). To determine the effect of the temperature on the outcome, the reaction was performed at -15 °C using catalysts **227**, **221**, **223**, **225**, and quenched after 36 hours (**Table 4**). The set of catalysts chosen aimed to assess the influence of the chiral axis on the selectivity by direct comparison between **221** and **227**, and, at the same time, start to investigate the structure-activity relationship of the catalysts.

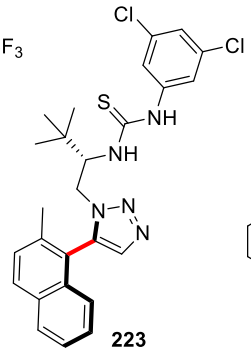
Table 4 Catalyst screening. All the catalysts employed are stereochemically pure.

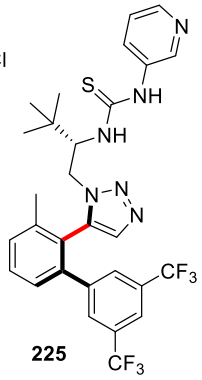


cat. =


227


221


223

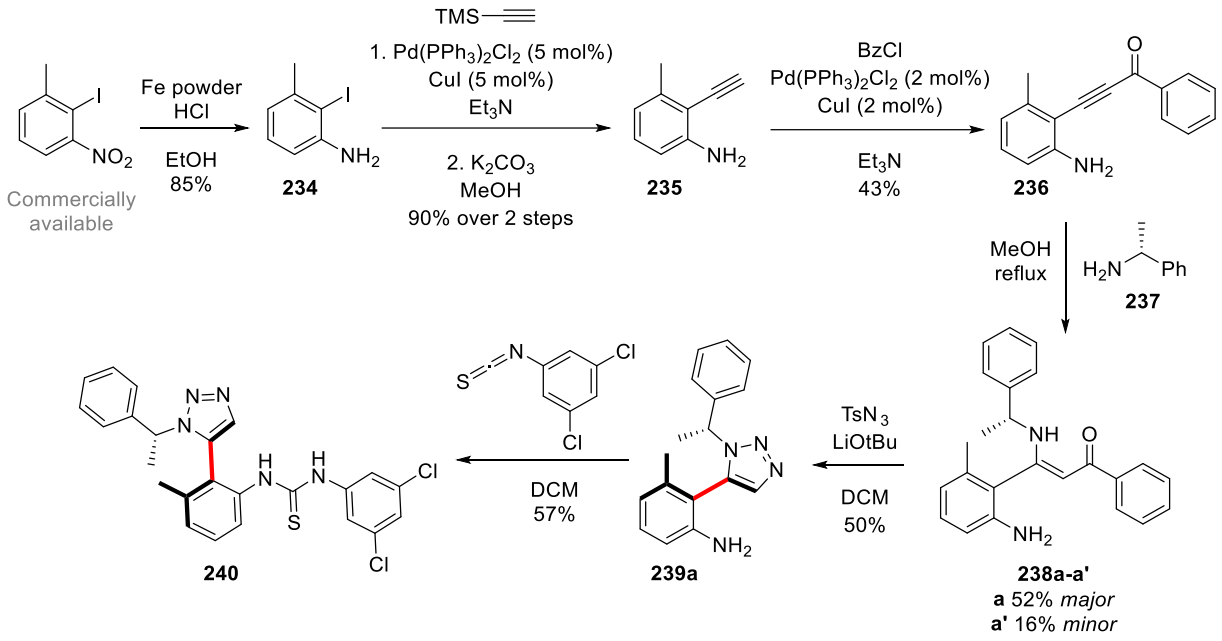

225

Entry	Catalyst	Yield (%)[i]	e.r.[ii]
1	**227**	30 (75)[iii]	47:53 (44:56)
2	**221**	35	45:55
3	**223**	38	44:56
4	**225**	33	48:52

i) isolated yield after chromatography; *ii)* determined by HPLC on chiral stationary phase; *iii)* isolated yield after 5 days

As expected, the yields recorded at -15 °C after 36 hours were all significantly lower than the yield previously recorded at 5 °C after 48 hours (**Table 3**, entry 7), however, the selectivities were roughly the same and, in general, quite low. Nonetheless, it was possible to observe a slight, yet coherent, increase in selectivity with the atropisomeric catalysts. The results obtained led to questioning whether having the chiral axis closer to the thiourea moiety, hence the coordination site, would have improved the asymmetric induction step. To test the hypothesis,

catalysts **240** was designed and prepared in six steps from commercially available 2-iodo-1-methyl-3-nitrobenzene (**Scheme 66**).



Scheme 66 Synthesis of thiourea **240**. The absolute configuration of the compound is unknown, and it has been arbitrarily chosen for clarity.

The reaction was thus set up under identical conditions and quenched after 41 hours. However, the e.r. measured was comparable to the ones previously observed (*i.e.* 54:46), and the yield was the lowest recorded, perhaps as a consequence of an increased rigidity.[106]

According to the original report,[226] the reaction proceeds through an enolate mechanism, *via* a transient ion pair. The ketone is hence deprotonated by the basic functionality embedded in the catalyst (*i.e.* quinuclidine), while the isatin coordinates to the thiourea moiety (**Figure 60**); steric effects in the transition state would then account for the observed selectivity.

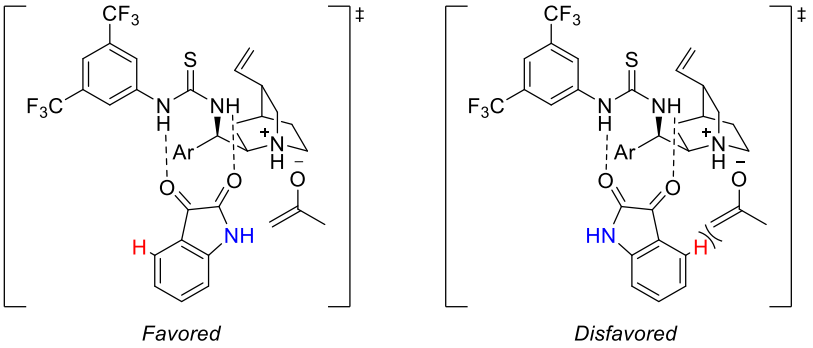


Figure 60 Transition states proposed by Guo *et al.*[226]

However, when the reaction was set up at room temperature with catalyst **221** without the base, it proceeded, although very slowly (14% yield after 4 days), but the product isolated displayed the same level of enantioenrichment, highlighting a flaw in the catalyst design. The thiourea moiety is the coordination site, where the catalysis happens and the chiral information is transferred. The low levels of asymmetric induction achieved suggest that the catalysts used might lack steric bulk, hence no significant preference for one of the enantiomers of the product is observed, being the transition states energetically similar (**Figure 61**).

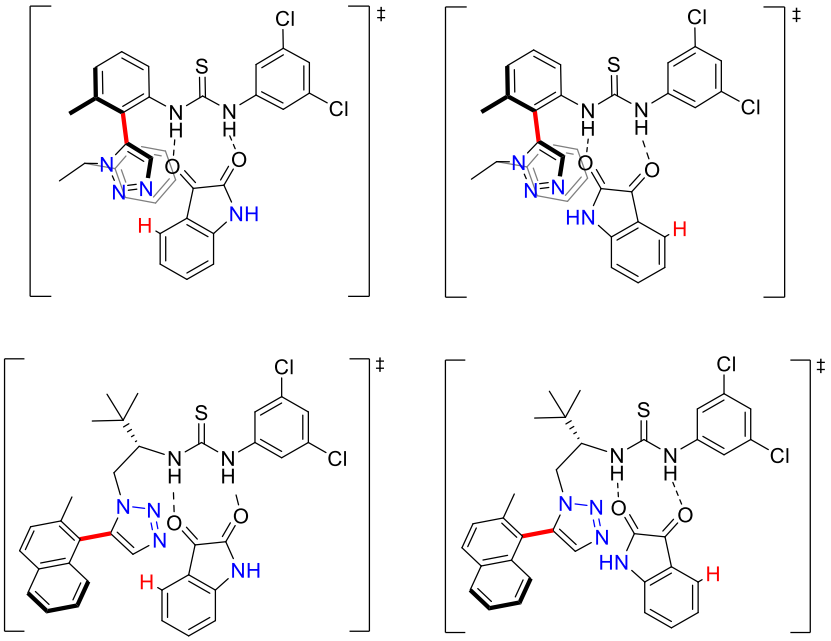


Figure 61 Possible TS with catalysts **240** (top) and **223** (bottom).

Furthermore, ion-pairing catalysis generally requires tight ion pairs to induce high stereoselectivity. Whilst the catalyst used in the literature could force the two reagents to be in proximity, being the basic functionality part of the catalyst backbone, this is not the case for the catalysts tested, where the base acts independently as the cocatalyst. As such, it is believed that better results could be obtained using a non-polar solvent (*e.g.* toluene) and/or an aromatic base (*e.g.* lutidine). Nonetheless, time constraints within the laboratory did not allow the testing of other conditions or catalysts such as **228** and **229**, which offered rather large π-surfaces that could enable enantiodifferentiation.

4.4 Summary

Given the practical difficulties encountered in the preparation of enantiopure triazolium salts and following the considerable success that thioureas have gained in organocatalysis, this chapter has described the synthesis of novel atropisomeric triazole-containing (thio)ureas and the preliminary results obtained in asymmetric organocatalysis.

Different synthetic sequences were considered, and it was found that the stability of the enaminone intermediates, given by the strong intramolecular N-H•••O, could hamper the subsequent steps. In particular, VT ^{1}H NMR spectroscopic analyses revealed that a benzyl linker could confer a remarkable stability, and compounds like **193** were shown to be stable to interconversion on the NMR time scale even at high temperatures (*i.e.* 100 °C).

To circumvent difficult and/or lengthy HPLC separations, a library of diastereomeric compounds, rather than purely atropisomeric ones, was prepared. Preliminary results obtained on the cyanosilylation of benzaldehyde, successfully catalysed in the literature by an imidazole thiourea catalyst and a benzoic acid derivative as cocatalyst, suggested that the cooperativity sought with Brønsted acids was not feasible with the triazole. Consequently, a set of reactions

taken from the literature were screened with a model chiral catalyst, aiming to find a reaction to further investigate. Of the ones chosen, however, only a few were effectively catalysed, whereas the rest did not show any appreciable conversion, albeit in most cases it was possible to completely recover the catalyst by simple column chromatography. The attempts of optimising the aldol reaction with isatin highlighted a flaw in the design. While the selectivity obtained with the atropisomeric catalysts were consistently higher than the model catalyst (lacking the chiral axis), with catalyst **223** being the best, the low selectivities recorded do not allow the assessment of the influence of the chiral axis on the outcome. However, the synthesis of atropisomeric functionalised triazoles is still of interest within the group, and it is hoped the observations outlined in this chapter will improve the catalytic performance of future compounds.

5 Conclusions and Future Work

This thesis has focussed on the synthesis of novel atropisomeric triazoles and triazolium salts for application in asymmetric organocatalysis, showing that – in spite of the lower conformational stability that generally characterises them – atropisomeric compounds featuring five-membered rings can be remarkably stable, even when one of the *ortho*-substituents is a simple hydrogen atom.

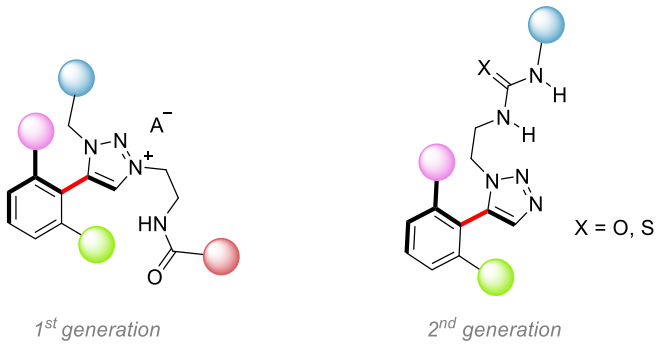


Figure 62 First *vs* second generation atropisomeric triazole-containing compounds.

In doing so, it has laid the groundwork for the development of a new class of atropisomeric triazole-containing organocatalysts, nonetheless, further work is needed in this direction. It is believed that three main areas, in particular, need to be addressed.

5.1 Alkylation of 1,5-Triazoles and Application in Organocatalysis

While Ooi and co-workers have extensively proved the value of 1,2,3-triazolium salts in asymmetric phase-transfer catalysis,[129, 130, 155, 156, 158-160, 181-183] access to these compounds is still limited and generally requires several steps. In this regard, *Chapter 3* outlines a new strategy that, in principle, allows access to atropisomerically pure materials in three simple steps. However, the sequence still requires further optimisation, in particular of the alkylation step at room temperature. Good preliminary results were obtained with a Mitsunobu reaction, and

future work would be to optimise the reaction conditions to increase the isolated yields to synthetically relevant levels. With an optimised reaction in hand, the synthesis of diverse atropisomerically pure compounds could easily proceed *via* alkylation in one, single step. Further screening of the catalysts, based on the preliminary results obtained, would then elucidate the influence exerted by the chiral axis on the selectivity and unveil the full potential of the compounds.

5.2 Asymmetric Synthesis of 1,5-Triazoles

Resolution into single enantiomers by chiral HPLC, however, represents a drawback of the route designed. Chiral columns are expensive and, in addition to the cost, developing a separation method is generally a time-consuming task with no guarantees of general applicability, as different compounds of the same type might require different chiral stationary phases. For this reason, further work in the area would be to develop an asymmetric synthesis of the 1,5-triazoles reported. At present, the asymmetric synthesis of atropisomeric species featuring five-membered rings still represents a real challenge, and only a few strategies, generally limited to specific substrates, are currently available in the literature.[101, 111, 233-237]. In this regard, the introduction of a chiral ligand for lithium (*e.g.* sparteine) or zinc (*e.g.* amino alcohols or salen ligands) might offer a simple solution worth further investigations.

5.3 Anion-Binding Catalysis

While *Chapter 4* has presented a new route allowing access to atropisomeric functionalised triazoles, the preliminary results obtained in catalysis suggest that the design of the compounds needs to be revisited. The general mechanism of catalysis with thioureas is based on LUMO activation, where the energy of the lowest unoccupied molecular orbital of the electrophile is lowered either upon direct coordination of the neutral electrophilic species to the catalyst or

following the formation of an ion-pair with the anionic species coordinated to the catalyst. As such, to enhance the transfer of the chiral information, the steric bulk around the coordination site, *i.e.* the thiourea, needs to be increased. In this respect, preparing catalysts **228**-**229**, containing sterically demanding aryl substituents, on a useful scale and testing them in catalysis would provide insights into the structural modifications needed.

6 Experimental

6.1 General Information

Unless otherwise noted, commercially available solvents and reagents were purchased from suppliers and used without any further purification. Where anhydrous solvents were required, they were dried using a Solvent Purification System (SPS). Anhydrous MeOH was dried over 3 Å molecular sieves at least three days prior to use. Degassed solvents were prepared by the purging method, bubbling argon through the specified solvent for 30 to 60 minutes. Room temperature refers to 20-25 °C. 0 °C were obtained using an ice/water bath, -78 °C using a dry ice/acetone bath. All the other temperatures below room temperature were obtained using a Julabo FT902 immersion cooler with an external temperature probe placed in a solution of ethylene glycol/water (1:1, v/v), or a Julabo F25-ME recirculating chiller equipped with an Asynt DrySyn Snowstorm reactor. Microwave heated reactions were conducted, where specified, using a *CEM Discover S* microwave reaction heating system. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60 F254 plates. TLC plates were visualised by either UV light with 254 nm/365 nm or by staining with an appropriate dip. Column chromatography was carried out using a Combiflash R*f* 200i (stationary phase silica). Chromatograms were recorded at two wavelengths (254 nm and 280 nm). NMR spectra were recorded using a Bruker AVIII300 (at 300 MHz for ^{1}H, 282 MHz for ^{19}F, 121 MHz for ^{31}P), a Bruker AVIII400 or AvanceNeo 400 (at 400 MHz for ^{1}H, 377 MHz for ^{19}F, 128 MHz for ^{11}B, and 101 MHz for ^{13}C). All the ^{13}C NMR spectra were obtained proton-decoupled. VT-^{1}H NMR spectra were recorded at the temperature stated on a Bruker AvanceNeo equipped with a temperature probe at 400 MHz. Chemical shifts (δ) are reported in ppm relative to TMS (δ 0.00) or the residual non-deuterated peak of the solvent stated. ^{19}F NMR chemical shifts are indirectly

referenced to $CFCl_3$ (δ 0.00). The spectra of compounds reported as "mixture of diastereoisomers" list peaks and multiplicities as they appear, *i.e.* belonging to both stereoisomers. All coupling constants (*J*) are reported in Hertz (Hz). Multiplicities of the signals are abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (sextet), hept (heptet), m (multiplet). The abbreviations app and br denote apparent and broad, respectively. Infrared spectra were recorded on a Perkin-Elmer Spectrum 100 FT-IR spectrometer using an ATR attachment; selected frequencies (ν_{max}) are reported in wavenumbers (cm^{-1}). Mass spectra were recorded in either positive or negative mode, using a Waters GCT Premier, a Waters LCT or a Waters Xevo G2-XS spectrometer equipped with a Time of Flight (TOF) detector, under conditions of electrospray ionisation (ES), electron ionisation (EI), atmospheric pressure chemical ionisation (APCI), atmospheric solids analysis probe (ASAP) or affinity purification (AP). All the spectrometers run with Waters MassLynx (v4.1) software, which reports both the calculated and measured mass values as neutrals; the HRMS for all compounds, therefore, reports the mass of neutral species. Melting points were measured using a Stuart digital (SMP10) or analogue (SMP1) melting point apparatus and are uncorrected. Specific rotations were recorded at 589 nm (sodium D line) on a Bellingham Stanley ADP450 Polarimeter with a Peltier temperature control. Concentrations are reported in g/100 mL. The X-ray crystal structures were determined using an Agilent SuperNova X-ray diffractometer with an Atlas detector (wavelength 1.5418 Å). HPLC analysis was carried out using a *Shimadzu LC2010 HPLC* system fitted with an appropriate column (ø 4.6 mm × 25 mm) and mobile phase. Chromatograms were recorded using the solvent system stated at two or four UV wavelengths (220, 254, 280, and 365nm). Retention times (R_t) are reported in minutes; flow rates of the eluent are reported in $mL \cdot min^{-1}$.

6.2 General Procedures

General Procedure A: Preparation of azides

Warning! Azides are known to be potentially explosive and appropriate caution should be taken.

A solution of sodium azide (1.6 eq.) in water (2.0 M) was added dropwise to a cooled solution of the appropriate primary chloride or bromide (1.0 eq.) in acetone (0.4 M) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 8-12 hours. Water (25 mL) was added, and the reaction mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic fractions were washed with water (3 × 15 mL) and brine (15 mL), dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure. The desired azides were obtained sufficiently pure to be used without further purification.

General Procedure B: Preparation of aryl azides

Warning! Azides are known to be potentially explosive and appropriate caution should be taken.

tert-Butyl nitrite (1.5 eq.) was added dropwise to a cooled solution of the appropriate aniline (1.0 eq.) and azidotrimethylsilane (1.2 eq.) in acetonitrile (0.3 M) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 16 hours. The solvent was removed under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-100% Hx/EtOAc).

General Procedure C: Synthesis of aldehydes

Adapted from a literature procedure.[238] In an oven-dried two neck round bottom flask, 2-bromo-6-methylbenzaldehyde **200** (1.0 eq.), the appropriate boronic acid (1.1 eq.), and tetrakis(triphenylphosphine)palladium(0) (5 mol%) were dissolved in a degassed solution of toluene/ethanol (1:1, v/v, 0.05 M). The flask was evacuated and backfilled with argon three

times, then sodium carbonate (2.5 eq.) was added. A waterless condenser was mounted, and the reaction stirred at 100 °C for 12-18 hours under argon protection. Upon completion, the mixture was filtered through a pad of celite and concentrated under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-100% Hx/EtOAc).

General Procedure D: Synthesis of alkynes

In an oven-dried two-neck round bottom flask, the appropriate aldehyde (1.0 eq.) was dissolved in anhydrous MeOH (0.3 M) under a constant flow of argon. To this solution, potassium carbonate (3.0 eq.) was added, followed by dimethyl-1-diazo-2-oxopropylphosphonate **144** (1.5 eq.). The resulting mixture was stirred at room temperature for 16-24 hours. Water (25 mL) was added, and the reaction mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic fractions were washed with aqueous sodium bicarbonate (0.1 M, 25 mL) and brine (25 mL), dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure. The desired product was obtained sufficiently pure to be used without further purification.

General procedure E: Synthesis of 1,4-disubstituted triazoles using MW irradiation

Adapted from a literature procedure.[239] In a microwave tube, 1-ethynyl-2-methylnaphthalene **132** (1.0 eq.), sodium ascorbate (20 mol%) and $CuSO_4 \cdot 5H_2O$ (20 mol%) were dissolved in dimethylformamide (0.2 M). The appropriate azide (1.0 eq.) was added, and the resulting solution was subjected to microwave irradiation at 150 °C for 30 minutes. Diethyl ether (10 mL) was added, and the reaction mixture was washed with water (3 x 10 mL) and brine (10 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-100% Hx/EtOAc).

General procedure F: Synthesis of 1,5-disubstituted triazoles **153** using Grignard's reagents

Adapted from a literature procedure.[153] In an oven-dried two-neck round bottom flask, the appropriate alkyne (1.0 eq.) was dissolved in tetrahydrofuran (1.3 M) under a constant flow of argon. To this solution, methyl magnesium bromide (3.0 M in hexane, 1.2 eq.) was added dropwise. The resulting solution was heated to 50 °C for 15 minutes, then allowed to cool down to room temperature. At this point, the appropriate azide (1.0 eq.) was added dropwise and the reaction was stirred at room temperature until full consumption of the starting material. Saturated ammonium chloride in water (15 mL) was added to quench the unreacted methyl magnesium bromide, and the reaction mixture extracted with ethyl acetate (3 × 15 mL). The combined organic fractions were washed with brine, dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure. The obtained crude residue was purified by automated flash column chromatography (0-100% Hx/EtOAc).

General Procedure G: Synthesis of 1,5-disubstituted triazoles **154** using organozinc reagents

Adapted from a literature procedure.[154] In an oven-dried two-neck round bottom flask, the appropriate azide (1.0 eq.) and alkyne (1.2 eq.), and *N*-methylimidazole (20 mol%) were dissolved in tetrahydrofuran (1.5 mL). To this solution, diethyl zinc (1.0 M in hexane, 3.0 eq.) was added dropwise over 5 minutes, and the reaction mixture was stirred at room temperature until full consumption of the starting material. Saturated ammonium chloride in water (15 mL) was added to quench the unreacted diethyl zinc, and the reaction mixture extracted with ethyl acetate (3 × 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure. The obtained crude residue was purified by automated flash column chromatography (0-100% Hx/EtOAc).

General Procedure H: Preparation of benzamides

The appropriate alcohol, amine or ammonium salt (1.0 eq.) was added to a solution of the appropriate acyl chloride or acid anhydride (1.1 eq.) in dichloromethane (0.2 M) cooled to 0 °C. Triethylamine (1.1 eq. with amines and alcohols, 2.5 eq. with ammonium salts) was added dropwise and the resulting solution was stirred at room temperature for 6-16 hours. The solvent was removed under reduced pressure and the residue redissolved in diethyl ether (25 mL). The solution was transferred to a separating funnel, and the organic layer was washed with water (3 × 20 mL) and brine (20 mL), dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure to afford a crude residue that was purified either by recrystallisation or automated flash column chromatography (20-100% Hx/EtOAc).

General Procedure I: Synthesis of 1,3,4-trisubstituted triazolium salts

The appropriate alkyl bromide (1.5 eq.) and 1,4- or 1,5-disubstituted triazole (1.0 eq.) were dissolved in acetonitrile (0.2 M), and the resulting solution was heated at reflux for 12-16 hours. Acetonitrile was removed under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-20% DCM/MeOH).

General Procedure J: Synthesis of ynones

Method A: Adapted from a literature procedure.[240] The appropriate alkyne (1.0 eq.), benzoyl chloride (1.3 eq.), palladium(II)bis(triphenylphosphine) dichloride (2 mol%), and copper(I) iodide (2 mol%) were dissolved in degassed triethylamine (0.1 M). The reaction mixture was stirred at room temperature until full consumption of the starting material, at which point it was filtered through a pad of celite. The filtrate was concentrated under reduced pressure, redissolved in ethyl acetate (25 mL), washed with water (3 × 20 mL) and brine (25 mL), dried

over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-100% Hx/EtOAc).

Method B: Adapted from a literature procedure.[241] In an oven-dried round bottom flask, the appropriate alkyne (1.0 eq.) was dissolved in anhydrous toluene (1.0 M) under a stream of argon. 10 wt.% Pd/C (1 mol%) was added and the reaction stirred under argon for 15 minutes. To this mixture, a solution of benzoyl chloride in anhydrous toluene (1.2 M, 1.2 eq.) was added dropwise over 5 minutes. The resulting mixture was stirred at reflux under argon for 16 hours, at which point it was filtered through a pad of celite and concentrated under reduced pressure to afford a crude residue that was purified by automated flash column (0-100% Hx/EtOAc).

General Procedure K: Synthesis of thioureas

The appropriate iso(thio)cyanate (1.0 eq) was added dropwise to a solution of the appropriate amine (1.0 eq.) in dichloromethane (0.3 M) at room temperature. The resulting solution was stirred at room temperature until full consumption of the starting material, at which point it was concentrated under reduced pressure to afford a crude residue that was either used without further purification or purified by automated flash column chromatography (0-100% Hx/EtOAc).

General Procedure L: Boc-deprotection

Trifluoroacetic acid (25.0 eq.) was added to a solution of the appropriate Boc-protected substrate (1.0 eq.) in dichloromethane (0.2 M). After 4-6 hours, the solution was concentrated under reduced pressure and the crude residue redissolved in ethyl acetate (15 mL). Saturated aqueous sodium carbonate (15 mL) was added, and the biphasic mixture stirred vigorously for 15 minutes. The mixture was transferred to a separating funnel, and the organic layer was

washed with a 1 M aqueous solution of sodium hydroxide (3 × 20 mL), water (10 mL) and brine (15 mL), dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure. The desired products were either used without further purification or purified by automated flash column chromatography (0-100% Hx/EtOAc).

General Procedure M: Synthesis of enaminones

The appropriate ynone (1.0 eq.) and amine (1.1 eq.) were dissolved in methanol or ethanol and stirred at reflux for 12-16 hours. The solution was concentrated under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-100% Hx/EtOAc).

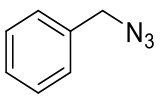
General Procedure N: Metal-free synthesis of 1,5-disubstituted triazoles

Adapted from a literature procedure.[202] Tosyl azide **191** (1.2 eq.) and lithium *tert*-butoxide (4.3 eq.) were added to a solution of the appropriate enaminone (1.0 eq.) in dichloromethane (0.25 M). The resulting mixture was stirred at room temperature for 2-4 hours, at which point it was concentrated under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-100% Hx/EtOAc).

6.3 Characterisation Data of Compounds

6.3.1 Data for *Chapter 3*

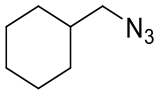
Benzyl azide 136



Prepared from benzyl bromide, following the *General Procedure A*, on a 17.00 mmol scale. The title compound was obtained as a colourless oil in 93% yield (2.103 g, 15.77 mmol). Data

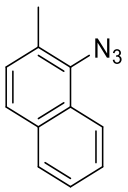
in agreement with the reported literature values.[242] Additional spectroscopic characterisation is provided. **IR** (neat) ν_{max} (cm^{-1}) 3033, 2090; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.48 – 7.30 (5H, m), 4.34 (2H, s). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 135.4, 128.8, 128.3, 128.2, 54.8. **MS** (EI^+) *m/z* 133.1 $[M]^+$.

(Azidomethyl) cyclohexane 145



Prepared from (bromomethyl)cyclohexane, following the *General Procedure A*, on a 3.60 mmol scale. The title compound was obtained as a pale yellow oil in 92% yield (0.463 g, 3.33 mmol). Data in agreement with the reported literature values.[243] Additional spectroscopic characterisation is provided. **IR** (neat) ν_{max} (cm^{-1}) 2924, 2854, 2093; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.11 (2 H, d, *J* 6.7), 1.82 – 1.64 (5 H, m), 1.62 – 1.47 (1 H, m), 1.35 – 1.11 (3 H, m), 1.04 – 0.87 (2 H, m). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 58.1, 38.1, 30.6, 26.2, 25.7. **MS** (EI^+) *m/z* 139.1 $[M]^+$.

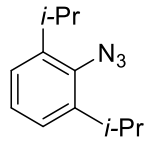
1-Azido-2-methylnaphtalene 135



Prepared from 2-methylnaphthalen-1-amine, following the *General Procedure B*, on a 6.36 mmol scale. The title compound was obtained as a deep red oil in 68% yield (0.797 g, 4.35 mmol). Data in agreement with the reported literature values.[244] Additional spectroscopic characterisation is provided. **IR** (neat) ν_{max} (cm^{-1}) 3053, 2924, 2101; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.16 (1 H, d, *J* 9.5), 7.80 (1 H, d, *J* 7.9), 7.63 (1 H, d, *J* 8.4), 7.59 – 7.41 (2 H, m),

7.28 (1 H, d, *J* 8.4), 2.58 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 133.2, 133.0, 129.2, 128.7, 128.2, 127.9, 126.6, 126.0, 125.8, 122.5, 18.1. **MS** (EI^+) *m/z* 183.2 $[M]^+$.

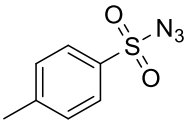
2-Azido-1,3-diisopropylbenzene 146



Prepared from 2,6-diisopropylaniline, following the *General Procedure B*, on a 5.00 mmol scale. The title compound was obtained as a pale yellow oil in 96% yield (0.972 g, 4.78 mmol). Data in agreement with the reported literature values.[245] **IR** (neat) ν_{max} (cm^{-1}) 2964, 2931, 2871, 2122, 2097; **^{1}H NMR** (400 MHz, $CDCl_3$): 7.22 – 7.11 (3 H, m), 3.36 (2 H, hept, *J* 6.8), 1.27 (12 H, d, *J* 6.9). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.1, 135.3, 126.8, 123.9, 28.8, 23.5. **MS** (EI^+) *m/z* 175.1 $[M-2N]^+$.

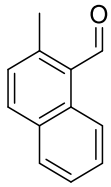
4-Methylbenzenesulfonyl azide 191

Caution: Highly toxic compound, handle in a well ventilated fumehood.



Prepared from 4-toluenesulfonyl chloride, following the *General Procedure A*, on a 21.00 mmol scale. The title compound was obtained as a white solid in 95% yield (3.932 g, 19.95 mmol). Data in agreement with the reported literature values.[246] **IR** (neat) ν_{max} (cm^{-1}) 2121, 1595, 1366, 1161; **^{1}H NMR** (400 MHz, $CDCl_3$): 7.85 (2 H, d, *J* 8.4), 7.41 (2 H, d, *J* 8.0), 2.49 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 146.2, 135.5, 130.3, 127.6, 21.8. **MS** (EI^+) *m/z* 197.2 $[M]^+$.

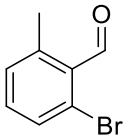
2-Methyl-1-naphthaldehyde 142



Adapted from a literature procedure.[247] In an oven-dried two-neck round bottom flask, *n*-Butyl lithium (2.5 M in hexane, 12.5 mL, 31.00 mmol) was added dropwise, under a stream of argon, to a solution of 1-bromo-2-methylnaphthalene (4.0 mL, 26.00 mmol) in tetrahydrofuran (50 mL) cooled to -78 °C. The resulting solution was stirred at -78 °C for 2 hours, at which point dimethylformamide (3.0 mL, 39.00 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for an additional 12 hours. Saturated ammonium chloride in water (25 mL) was added to quench the unreacted *n*-butyl lithium, and the reaction mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure. The obtained crude residue was purified by automated flash column chromatography (0-20% Hx/EtOAc).

The title compound was obtained as a pale yellow solid in 80% yield (3.530 g, 20.74 mmol). Data in agreement with the reported literature values.[247, 248] **IR** (neat) ν_{max} (cm^{-1}) 3332, 3107, 2880, 2777, 1671, 1593; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 10.96 (1 H, s), 8.97 (1 H, d, *J* 8.6), 7.93 (1 H, d, *J* 8.4), 7.83 (1 H, d, *J* 8.1), 7.61 (1 H, t, *J* 8.5), 7.50 (1 H, t, *J* 7.5), 7.33 (1 H, d, *J* 8.4), 2.81 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.3, 142.6, 134.3, 132.5, 131.5, 129.8, 128.8, 128.44, 128.41, 126.0, 124.4, 20.1. **MS** (EI^+) *m/z* 170.1 $[M]^+$.

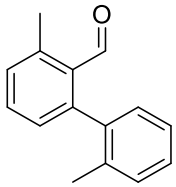
2-Bromo-6-methylbenzaldehyde 200



Adapted from a literature procedure.[249] A round bottom flask was charged with 2-methylbenzaldehyde (2.9 mL, 25.00 mmol), *N*-bromo succinimide (5.403 g, 30.00 mmol), 4-bromo-2-(trifluoromethyl)aniline (702 µL, 4.58 mmol), and palladium(II) acetate (0.561 g, 2.50 mmol). A premixed solution of DCE:TFA (5:1, v/v, 180 mL) was added, the flask was flushed with argon, sealed and the resulting mixture was stirred at 60 °C for 24 hours. The reaction mixture was cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated under reduced pressure, redissolved in ethyl acetate (80 mL) and transferred to a separating funnel, where the organic layer was washed with saturated aqueous sodium carbonate (3 × 30 mL) and brine (15 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-20% Hx/EtOAc).

The title compound was obtained as a colourless crystalline solid in 62% yield (3.106 g, 15.95 mmol). Data in agreement with the reported literature values.[249] **IR** (neat) ν_{max} (cm^{-1}) 2929, 2864, 1693, 1590, 1451; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.53 (1 H, s), 7.52 (1 H, d, *J* 7.8), 7.27 (1 H, app t, *J* 7.7), 7.21 (1 H, d, *J* 7.6), 2.58 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 194.6, 142.7, 133.6, 131.8, 131.7, 131.4, 128.3, 21.2. **MS** (EI^+) *m/z* 198.0 $[M]^+$, 200.0 $[M+2]^+$.

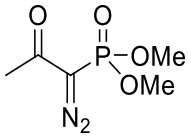
2',3-Dimethyl-[1,1'-biphenyl]-2-carbaldehyde 241



2-Bromo-6-methylbenzaldehyde **142** (0.150 g, 0.75 mmol), *o*-tolylboronic acid (0.150 g, 1.10 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.018 g, 0.02 mmol) were dissolved in anhydrous toluene (2.0 mL). Degassed aqueous sodium carbonate (1.0 M, 1.72 mmol) was added and the resulting solution heated at 100 °C for 16 hours. Upon completion, the reaction mixture was cooled down to room temperature and extracted with ethyl acetate (3 × 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure. The obtained crude residue was purified by automated flash column chromatography (0-20% Hx/EtOAc).

The title compound was obtained as a colourless oil in 91% yield (0.144 g, 0.68 mmol). $\mathbf{R_f}$ = 0.70 (20% EtOAc/Hx); **IR** (neat) ν_{max} (cm^{-1}) 3060, 3021, 2858, 2760, 1736, 1692, 1588, 1464; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.85 (1 H, s), 7.44 (1 H, t, *J* 7.6), 7.32 – 7.19 (4 H, m), 7.14 (1 H, dd, *J* 7.5, 1.5), 7.10 (1 H, ddd, *J* 7.5, 1.4, 0.7), 2.67 (3 H, s), 2.08 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 194.4, 147.2, 140.2, 138.7, 136.1, 132.5, 132.3, 131.2, 130.1, 130.0, 128.5, 128.1, 125.7, 21.7, 20.4. **MS** ($ASAP^+$) *m/z* 211.1 $[M+H]^+$; **HRMS** ($ASAP^+$) calc. 211.1123 $[C_{15}H_{15}O]$, obs. 211.1130.

Dimethyl-1-diazo-2-oxopropylphosphonate 144

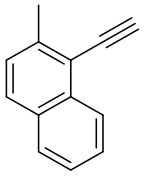


Adapted from a literature procedure.[250] In an oven-dried two-neck round bottom flask, 4-acetamidobenzenesulfonyl azide (7.000 g, 29.16 mmol) was dissolved in anhydrous acetonitrile

(81 mL) under a constant flow of argon. Anhydrous potassium carbonate (13.440 g, 97.22 mmol) was added and the resulting mixture was cooled to 0 °C. Dimethyl (2-oxopropyl)phosphonate (4 mL, 24.30 mmol) was added dropwise, and the reaction mixture was stirred at 0 °C for 16 hours. Diethyl ether (100 mL) was added, and the reaction mixture was filtered through a pad of celite. The filtrate was concentrated under reduced pressure to afford a crude residue that was used without any further purification.

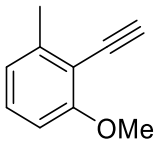
The title compound was obtained as a yellow oil in 93% yield (4.342 g, 22.60 mmol). Data in agreement with the reported literature values.[251] Additional spectroscopic characterisation is provided. **IR** (neat) ν_{max} (cm^{-1}) 2120, 1655, 1260; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.85 (6 H, d, $^{3}J_{HP}$ 11.9), 2.28 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 189.87 (d, $^{2}J_{CP}$ 13.1), 127.98 (d, $^{1}J_{CP}$ 325.8), 53.58 (d, $^{2}J_{CP}$ 5.6), 27.14. **^{31}P NMR** (162 MHz, $CDCl_3$): δ 14.3 (hept, $^{3}J_{PH}$ 12.1 Hz). **MS** (ES^+) *m/z* 192.0 $[M]^+$,165.0 $[M\text{-}N_2]^+$.

1-Ethynyl-2-methylnaphthalene 132



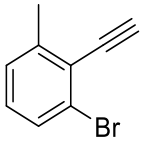
Prepared from 2-methyl-1-naphthaldehyde **142**, following the *General Procedure D*, on a 8.81 mmol scale. The title compound was obtained as a pale pink oil in 93% yield (1.370 g, 8.24 mmol). Data in agreement with the reported literature values.[146, 252] **IR** (neat) ν_{max} (cm^{-1}) 3291, 3054, 2919, 2098, 1508; **^{1}H NMR** (300 MHz, $CDCl_3$): 8.35 (1 H, d, *J* 8.4), 7.80 (1 H, d, *J* 8.1), 7.75 (1 H, d, *J* 8.4), 7.60 – 7.51 (1 H, m), 7.50 – 7.41 (1 H, m), 7.34 (1 H, d, *J* 8.4), 3.71 (1 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 140.2, 133.9, 131.4, 128.6, 128.1, 127.9, 126.9, 125.8, 125.5, 118.2, 86.3, 80.6, 21.3. **MS** (EI^+) *m/z* 166.1 $[M]^+$.

2-Ethynyl-1-methoxy-3-methylbenzene 147



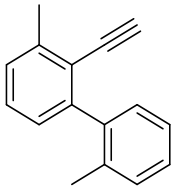
Prepared from 2-methoxy-6-methylbenzaldehyde, following the *General Procedure D*, on a 1.00 mmol scale. The title compound was obtained as a pale yellow oil in 58% yield (0.084 g, 0.58 mmol). Data in agreement with the reported literature values.[252] **IR** (neat) ν_{max} (cm^{-1}) 3293, 2961, 2092, 1556, 1450; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.20 (1 H, dd, *J* 8.3, 7.7), 6.83 (1 H, dt, *J* 7.7, 0.9), 6.73 (1 H, d, *J* 8.4), 3.89 (3 H, s), 3.55 (1 H, s), 2.44 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.9, 143.0, 129.3, 121.9, 111.1, 107.7, 85.4, 78.8, 55.9, 20.7. **MS** (EI^+) *m/z* 146.1 $[M]^+$.

1-Bromo-2-ethynyl-3-methylbenzene 148



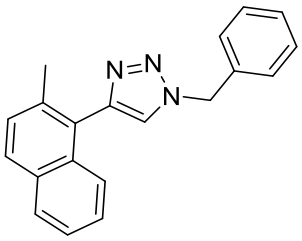
Prepared from 2-bromo-6-methylbenzaldehyde **200**, following the *General Procedure D*, on a 5.02 mmol scale. The title compound was obtained as a colourless oil in 79% yield (0.771 g, 3.95 mmol). Data in agreement with the reported literature values.[253] **IR** (neat) ν_{max} (cm^{-1}) 3293, 2961, 2092, 1556, 1450; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 (1 H, dd, *J* 7.9, 0.7), 7.16 (1 H, dd, *J* 7.6, 0.7), 7.08 (1 H, t, *J* 7.8), 3.60 (1 H, s), 2.49 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.4, 129.7, 129.4, 128.2, 126.0, 124.1, 86.0, 80.8, 21.6. **MS** (EI^+) *m/z* 194.0 $[M]^+$, 196.0 $[M+2]^+$, 115.1 $[M-Br]^+$.

2-Ethynyl-2',3-dimethyl-1,1'-biphenyl 152



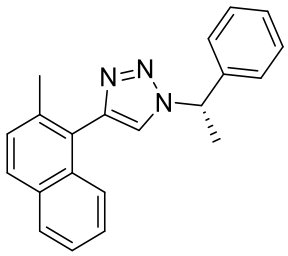
Prepared from 2',3-dimethyl-[1,1'-biphenyl]-2-carbaldehyde **241**, following the *General Procedure D*, on a 3.60 mmol scale. The title compound was obtained as a colourless oil in 64% yield (0.478 g, 2.32 mmol); $\mathbf{R_f}$ = 0.81 (20% EtOAc/Hx); **IR** (neat) ν_{max} (cm^{-1}) 3283, 3059, 3018, 2950, 2103, 1464; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.17 – 7.13 (3 H, m), 7.12 – 7.06 (3 H, m), 6.94 (1 H, dd, *J* 7.5, 1.7), 2.99 (1 H, s), 2.41 (3 H, s), 2.06 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.2, 140.1, 139.9, 135.0, 128.6, 128.4, 127.0, 127.0, 126.4, 125.8, 124.2, 120.5, 83.2, 80.1, 20.1, 18.9. **MS** (EI^+) *m/z* 206.1 $[M]^+$; **HRMS** (EI^+) calc. 206.1096 [$C_{16}H_{14}$], obs. 206.1087.

1-Benzyl-4-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazole 137



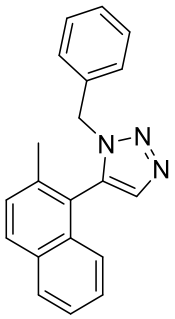
Prepared from 1-ethynyl-2-methylnaphthalene **132** and benzyl azide **136**, following the *General Procedure E*, on a 1.00 mmol scale. The title compound was obtained as an off-white solid in 23% yield (0.068 g, 0.23 mmol). Data in agreement with those previously reported within the group.[148] **IR** (neat) ν_{max} (cm^{-1}) 3104, 3065, 3047, 2927, 2898, 1506, 1457; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (1 H, m), 7.80 (1 H, d, *J* 8.4), 7.53 (1 H, ddd, *J* 7.9, 1.8, 0.8), 7.53 (1 H, s), 7.46 – 7.33 (8 H, m), 5.70 (2 H, s), 2.32 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.1, 135.7, 134.9, 133.3, 132.0, 129.2, 128.8, 128.7, 128.6, 128.0, 127.9, 126.3, 125.3, 125.0, 123.5, 54.3, 20.9. **MS** ES^+ *m/z* 300.1 $[M+H]^+$, 322.1 $[M+Na]^+$.

(*S*)-4-(2-methylnaphthalen-1-yl)-1-(1-phenylethyl)-1*H*-1,2,3-triazole 162



Prepared from 1-ethynyl-2-methylnaphthalene **132** and (*S*)-(1-azidoethyl)benzene, following the *General Procedure E*, on a 0.53 mmol scale. The title compound was obtained as a white solid in 57% yield (0.101 g, 0.30 mmol). **m.p.** 69-71 °C; **IR** (neat) ν_{max} (cm^{-1}) 3144, 3054, 2984, 2936, 2865, 1506, 1454; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 – 7.77 (1 H, m), 7.80 (1 H, d, *J* 8.4), 7.53 (1 H, ddd, *J* 7.5, 2.1, 0.8), 7.50 (1 H, s), 7.47 – 7.30 (8 H, m), 5.97 (1 H, q, *J* 7.1), 2.31 (3 H, s), 2.12 (3 H, d, *J* 7.1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.6, 140.3, 135.7, 133.4, 132.0, 129.1, 128.7, 128.5, 127.9, 126.5, 126.4, 126.3, 125.3, 124.9, 122.5, 60.4, 21.6, 20.9. **MS** ES^+ *m/z* 314.2 $[M+H]^+$. **HRMS** (ES^+) calc. 314.1657 [$C_{21}H_{20}N_3$], obs. 314.1659.

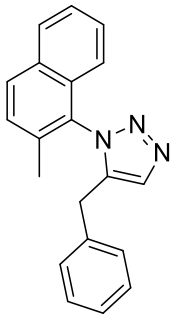
1-Benzyl-5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazole 153b



Prepared from 1-ethynyl-2-methylnaphthalene **132** and benzyl azide **136**, following the *General Procedure F*, on a 0.62 mmol scale. The title compound was obtained as an off-white solid in 67% yield (0.125 g, 0.42 mmol). **m.p.** 101 – 103 °C. **IR** (neat) ν_{max} (cm^{-1}) 3055, 3039, 1506, 1456. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.88 (1 H, d, *J* 8.5), 7.87 (1 H, app dt, *J* 8.1, 0.5), 7.73 (1 H, s), 7.46 (1 H, ddd, *J* 8.1, 6.9, 1.1), 7.34 (1 H, ddd, *J* 8.2, 6.9, 1.5), 7.31 (1 H, d, *J*

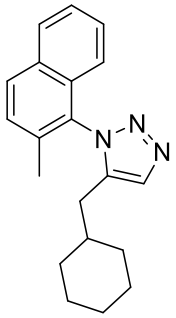
8.5), 7.19 – 7.01 (4 H, m), 6.76 (2 H, d, *J* 7.1), 5.40 (1 H, d, *J* 14.4), 4.95 (1 H, d, *J* 14.6), 1.81 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.3, 134.9, 134.6, 134.2, 132.6, 131.7, 130.0, 128.4, 128.3, 128.2, 128.2, 127.2, 125.6, 124.3, 122.1, 52.5, 20.0 (17 of the 18 expected signals are observed). **MS (**ES^+) *m/z* 300.1 $[M+H]^+$. **HRMS** (ES^+) calc. 300.1501 [$C_{20}H_{18}N_3$], obs. 300.1503. **HPLC** (Phenomenex Cellulose-1, 50% MeCN/H_2O, 1.0 mL/min, λ = 254 nm) R_{t1} = 25.79 min, R_{t2} = 29.97 min. **$[\alpha]_D$** = +69.39° (*c* = 1.0, $CHCl_3$, peak 1); -69.12° (*c* = 1.0, $CHCl_3$, peak 2).

(*rac*)-5-Benzyl-1-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazole 154b



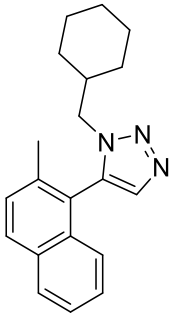
Prepared from 1-azido-2-methylnaphthalene **135** and prop-2-yn-1-yl benzene, following the *General Procedure G*, on a 1.00 mmol scale. The title compound was obtained as a brown oil in 34% yield (0.101 g, 0.34 mmol). **R_f** = 0.29 (30% EtOAc/Hx); **IR** (neat) ν_{max} (cm^{-1}) 3060, 3028, 2923, 1601, 1508, 1455; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.92 (1 H, d, *J* 8.5), 7.89 (1 H, dt, *J* 8.3, 0.9), 7.72 (1 H, t, *J* 0.8), 7.47 (1 H, ddd, *J* 8.2, 6.9, 1.2), 7.40 (1 H, ddd, *J* 8.3, 6.9, 1.3), 7.37 (1 H, d, *J* 8.4), 7.13 – 7.11 (3 H, m), 6.87 (1 H, dq, *J* 8.4, 0.9), 6.82 – 6.79 (2 H, m), 3.75 (1 H, d, *J* 16.0), 3.55 (1 H, d, *J* 15.9), 1.90 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 139.0, 135.9, 134.7, 132.7, 132.5, 130.5, 130.4, 130.1, 128.7, 128.5, 128.3, 128.0, 127.9, 127.0, 126.1, 121.6, 29.7, 17.4. **MS (**ES^+) *m/z* 300.1 $[M+H]^+$. **HRMS** (ES^+) calc. 300.1501 [$C_{20}H_{18}N_3$], obs. 300.1505. **HPLC** (Phenomenex Cellulose-1, 50% MeCN/H_2O, 1.0 mL/min, λ = 280 nm) R_{t1} = 30.04 min, R_{t2} = 31.90 min

(*rac*)-5-(Cyclohexylmethyl)-1-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazole 154a



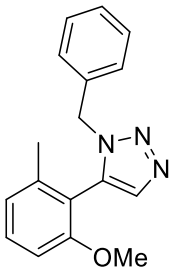
Prepared from 1-azido-2-methylnaphthalene **135** and prop-2-yn-1-ylcyclohexane, following the *General Procedure G*, on a 1.60 mmol scale. The title compound was obtained as a light brown solid in 52% yield (0.252 g, 0.82 mmol). **m.p.** 104 – 105 °C. **IR** (neat) ν_{max} (cm^{-1}) 3055, 2957, 2930, 2871, 1509, 1448; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.95 (1 H, d, *J* 8.5), 7.90 (1 H, d, *J* 8.1), 7.74 (1 H, s), 7.50 (1 H, ddd, *J* 8.1, 6.9, 1.2), 7.48 (1 H, d, *J* 8.5), 7.44 (1 H, ddd, *J* 8.2, 6.9, 1.3), 6.91 (1 H, dq, *J* 8.4, 0.9), 2.22 (2 H, d, *J* 7.3), 2.15 (3 H, s), 1.65 – 1.54 (5 H, m), 1.46 – 1.35 (1 H, m), 1.17 – 1.00 (3 H, m), 0.91 – 0.69 (2 H, m). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 139.0, 135.9, 134.7, 132.7, 132.5, 130.5, 130.4, 130.1, 128.7, 128.5, 128.3, 128.0, 127.9, 127.0, 126.1, 121.6, 29.7, 17.4. **MS (**ES^+) *m/z* 306.2 $[M+H]^+$. **HRMS** (ES^+) calc. 306.1970 $[C_{20}H_{24}N_3]^+$, obs. 306.1968. **HPLC** (Phenomenex Cellulose-1, 50% MeCN/H_2O, 1.0 mL/min, λ = 280 nm) R_{t1} = 44.11 min, R_{t2} = 46.11 min

(*rac*)-1-(Cyclohexylmethyl)-5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazole 153a



Prepared from 3-(2-methylnaphthalen-1-yl)-1-phenylprop-2-yn-1-one **187** and cyclohexylmethanamine, following the *General Procedure N,* on a 1.06 mmol scale. The title compound was obtained as a pale yellow solid in 67% yield (0.217 g, 0.71 mmol). **m.p.** 66 – 67 °C **IR** (neat) ν_{max} (cm^{-1}) 3055, 2924, 2851, 2105, 1507, 1449; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.92 – 7.85 (2 H, m), 7.71 (1 H, s), 7.49 – 7.38 (3 H, m), 7.19 (1 H, d, *J* 8.3), 3.84 (1 H, dd, *J* 13.5, 7.6), 3.78 (1 H, dd, *J* 13.6, 7.5), 2.24 (3 H, s), 1.80 – 1.66 (1 H, m), 1.61 – 1.51 (3 H, m), 1.43 (2 H, app t, *J* 10.9), 1.10 – 0.96 (3 H, m), 0.82 – 0.65 (2 H, m). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 136.6, 134.8, 134.4, 132.8, 131.9, 130.0, 128.4, 128.3, 127.1, 125.7, 124.5, 122.5, 54.2, 37.8, 30.4, 26.0, 25.4, 20.4. **MS (**ES^+) *m/z* 306.2 $[M+H]^+$. **HRMS** (ES^+) calc. 306.1970 [$C_{20}H_{24}N_3$], obs. 306.1977.

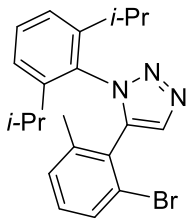
(*rac*)-1-Benzyl-5-(2-methoxy-6-methylphenyl)-1*H*-1,2,3-triazole 153c



Prepared from 2-ethynyl-1-methoxy-3-methylbenzene **147** and benzyl azide **136**, following the *General Procedure F*, on a 0.60 mmol scale. The title compound was obtained as a light brown solid in 20% yield (0.033 g, 0.11 mmol). **m.p.** 131 – 133 °C. **IR** (neat) ν_{max} (cm^{-1}) 2941, 2841, 1583, 1472; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.57 (1 H, s), 7.31 (1 H, t, *J* 8.0), 7.21 – 7.13 (3 H,

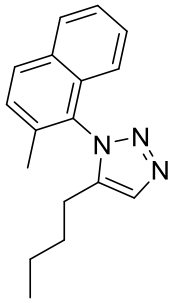
m), 6.93 (2 H, dd, *J* 7.7, 1.5), 6.79 (2 H, t, *J* 8.1), 5.42 (1 H, d, *J* 14.7), 5.14 (1 H, d, *J* 14.7), 3.61 (3 H, s), 1.70 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.5, 140.0, 135.0, 134.3, 133.0, 130.9, 128.4, 128.1, 128.0, 122.4, 115.3, 108.1, 55.4, 52.3, 19.6. **MS (**ES^+) *m/z* 280.1 $[M+H]^+$. **HRMS** (ES^+) calc. 280.1450 [$C_{17}H_{18}N_3O$], obs. 280.1455

(*rac*)-5-(2-Bromo-6-methylphenyl)-1-(2,6-diisopropylphenyl)-1*H*-1,2,3-triazole 154d



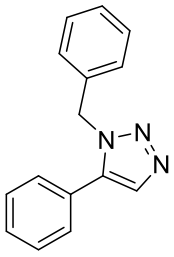
Prepared from 1-bromo-2-ethynyl-3-methylbenzene **148** and 2-azido-1,3-diisopropylbenzene **146**, following the *General procedure G,* on a 0.97 mmol scale. The title compound was obtained as a light brown solid in 27% yield (0.104 g, 0.26 mmol). **m.p**. 188 – 190 °C. **IR** (neat) ν_{max} (cm^{-1}) 2964, 2930, 2869, 1447; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (1 H, s), 7.51 (1 H, dd, *J* 7.7, 1.6), 7.40 (1 H, t, *J* 7.8), 7.26 (2 H, dd, *J* 8.1, 1.1), 7.15 – 7.03 (3 H, m), 2.61 (1 H, hept, *J* 6.6), 2.25 (1 H, hept, *J* 6.7), 1.94 (3 H, s), 1.30 (3 H, d, *J* 6.7), 1.09 (3 H, d, *J* 6.8), 1.01 (3 H, d, *J* 6.8), 0.69 (3 H, d, *J* 6.8). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.2, 145.8, 140.4, 136.9, 136.0, 132.4, 131.2, 130.6, 130.4, 129.5, 127.5, 126.0, 124.3, 124.1, 29.3, 28.4, 27.0, 25.7, 22.0, 21.8, 21.5. **MS (**ES^+) *m/z* 398.1 $[M]^+$, 400.1 $[M+2]^+$. **HRMS** (ES^+) calc. 398.1232 [$C_{21}H_{25}N_3Br$], obs. 398.1230.

(*rac*)-5-Butyl-1-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazole 154c



Prepared from 1-azido-2-methylnaphthalene **135** and hex-1-yne, following the *General procedure G*, on a 1.00 mmol scale. The title compound was obtained as a deep red oil in 33% yield (0.087 g, 0.33 mmol). $\mathbf{R_f}$ = 0.38 (30% EtOAc/Hx); **IR** (neat) ν_{max} (cm^{-1}) 2923, 2850, 1509, 1448; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.93 (1 H, d, *J* 8.5), 7.89 (1 H, d, *J* 8.0), 7.76 (1 H, s), 7.51 – 7.40 (3 H, m), 6.91 (1 H, d, *J* 8.3), 2.32 (2 H, t, *J* 7.5), 2.15 (3 H, s), 1.48 (2 H, app p, *J* 7.6), 1.23 (2 H, app h, *J* 7.3), 0.77 (3 H, t, *J* 7.4). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 139.9, 134.2, 132.5, 131.8, 130.6, 130.3, 130.2, 128.3, 128.0, 127.8, 126.1, 121.8, 29.9, 22.7, 22.1, 17.6, 13.6. **MS (**ES^+) *m/z* 266.2 $[M+H]^+$. **HRMS** (ES^+) calc. 266.1657 [$C_{17}H_{20}N_3$], obs. 266.1662. **HPLC** (Phenomenex Cellulose-1, 50% MeCN/H_2O, 1.0 mL/min, λ = 280 nm) R_{t1} = 19.95 min, R_{t2} = 20.68 min.

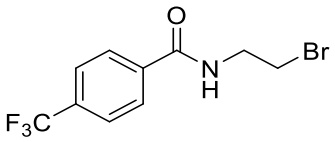
1-Benzyl-5-phenyl-1*H*-1,2,3-triazole 164



Prepared from phenylacetylene and benzyl azide **136**, following the *General Procedure F*, on a 7.51 mmol scale. The title compound was obtained as a white solid in 73% yield (1.293 g, 5.50 mmol). Data in agreement with the reported literature values.[254] **IR** (neat) ν_{max} (cm^{-1}) 3063, 3032, 2944, 1493, 1455; **^{1}H NMR** (300 MHz, $CDCl_3$): 7.73 (1 H, s), 7.48 – 7.36 (3 H, m), 7.32

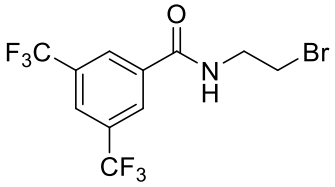
– 7.21 (5 H, m), 7.13 – 6.98 (2 H, m), 5.54 (2 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 138.2, 135.5, 133.3, 129.5, 129.0, 128.9, 128.8, 128.2, 127.2, 126.9, 51.8. **MS** (EI^+) *m/z* 236.1 $[M+H]^+$.

***N*-(2-Bromoethyl)-4-(trifluoromethyl)benzamide 156a**



Prepared from 4-(trifluoromethyl)benzoyl chloride and 2-bromoethylamine hydrobromide, following the *General procedure H*, on a 3.06 mmol scale. The title compound was obtained as a white solid in 72% yield (0.652 g, 2.20 mmol). **m.p**. 108 – 110 °C.; **IR** (neat) ν_{max} (cm^{-1}) 3294, 1640, 1544, 1327; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.91 (2 H, d, *J* 8.1), 7.73 (2 H, d, *J* 8.1), 6.56 (1 H, br s), 3.91 (2 H, q, *J* 5.8), 3.63 (2 H, t, *J* 5.7). **^{19}F NMR** (377 MHz, $CDCl_3$) -63.00. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.42, 137.29, 133.49 (q, $^2J_{CF}$ 32.7), 127.53, 125.72 (q, $^3J_{CF}$ 3.8), 123.61 (q, $^1J_{CF}$ 272.8), 41.58, 32.29. **MS** (ES^+) *m/z* 296.0 $[M]^+$, 298.0 $[M+2]^+$. **HRMS** (ES^+) calc. 295.9898 [$C_{10}H_{10}BrF_3NO$], obs. 295.9905.

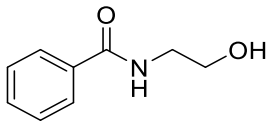
***N*-(2-Bromoethyl)-3,5-bis(trifluoromethyl)benzamide 156b**



Prepared from 3,5-bis(trifluoromethyl)benzoyl chloride and 2-bromoethylamine hydrobromide, following the *General procedure H*, on a 2.76 mmol scale. The title compound was obtained as colourless crystals in 90% yield (0.908 g, 2.49 mmol). **m.p**. 97 – 99 °C.; **IR** (neat) ν_{max} (cm^{-1}) 3318, 3099, 1644, 1558, 1271; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.24 (2 H, s), 8.01 (1 H, s), 7.12 (1 H, br s), 3.91 (2 H, q, *J* 5.8), 3.61 (2 H, t, *J* 5.8). **^{19}F NMR** (377 MHz, $CDCl_3$) -63.03. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.0, 136.1, 132.3 (q, $^2J_{CF}$ 34.0), 127.4 (q,

$^{3}J_{CF}$ 3.6), 125.3 (app h, $^{3}J_{CF}$ 3.7), 122.8 (q, $^{1}J_{CF}$ 273.0), 42.0, 31.6. **MS (**ES^{+}) *m/z* 364.0 [M]$^{+}$, 366.0 [M+2]$^{+}$. **HRMS** (ES^{+}) calc. 363.9772 [$C_{10}H_9BrF_6NO$], obs. 363.9771.

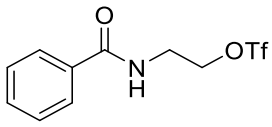
_N_-(2-Hydroxyethyl)benzamide 165



Ethanolamine (950 µL, 15.66 mmol) was dissolved in a mixture of diethyl ether/saturated aqueous sodium bicarbonate (80 mL, 1:1, v/v). Benzoyl chloride (2.7 mL, 10.81 mmol) was added, and the resulting mixture vigorously stirred at room temperature for 16 hours. The organic layer was collected, dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (20-100% Hx/EtOAc).

The title compound was obtained as a white solid in 69% yield (1.232 g, 7.46 mmol). Data in agreement with the reported literature values.[255] **IR** (neat) ν_{max} (cm^{-1}) 3294, 2940, 2878, 1635, 1538; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.73 (2 H, d, *J* 8.0), 7.43 (1 H, t, *J* 7.0), 7.39 – 7.28 (3 H, m), 4.28 (1 H, br s), 3.78 – 3.65 (2 H, m), 3.52 (2 H, t, *J* 5.4). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.9, 134.0, 131.6, 128.5, 127.0, 61.6, 42.8. **MS (**ES^{+}) *m/z* 166.1 [M+H]$^{+}$, 188.1 [M+Na]$^{+}$.

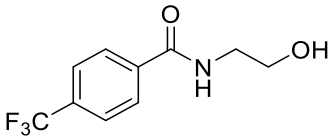
2-Benzamidoethyl trifluoromethanesulfonate 166



Prepared from *N*-(2-hydroxyethyl)benzamide **165** and triflic anhydride on a 0.60 mmol scale, following a modified version of the *General procedure H* with 2,6-lutidine in place of triethylamine and anhydrous dichloromethane. The title compound was obtained as a white solid in 25% yield (0.045 g, 0.15mmol). **m.p**. 75 – 76 °C. **IR** (neat) ν_{max} (cm^{-1}) 3210, 2965,

2895, 1694, 1456, 1373; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 8.01 (2 H, m), 7.63 – 7.56 (1 H, m), 7.49 – 7.43 (2 H, m), 5.64 (1 H, br s), 4.51 – 4.46 (2 H, m), 3.69 (2 H, td, *J* 5.1, 0.8). **^{19}F NMR** (377 MHz, $CDCl_3$) -77.42. **^{13}C NMR** (101 MHz, CDCl3) 166.7, 133.7, 129.8, 129.0, 128.6, 119.6 (q, $^{1}J_{CF}$ 320.9), 63.5, 43.8. **MS (**ASAP$^+$) *m/z* 298.0 $[M]^+$. **HRMS** (ASAP$^+$) calc. 298.0361 [$C_{10}H_{11}NO_4SF_3$], obs. 298.0357.

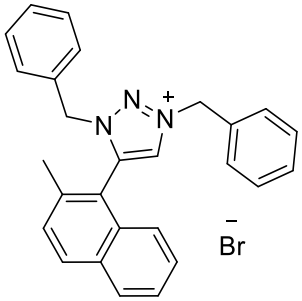
_N_-(2-Hydroxyethyl)-4-(trifluromethyl)benzamide 173



4-(Trifluoromethyl)benzoyl chloride (1.0 mL, 6.73 mmol) was added to a mixture of ethanolamine (370 μL, 6.11 mmol) and potassium carbonate (0.930 g, 6.73 mmol) in methanol (30 mL) cooled to 0 °C. The resulting mixture was vigorously stirred at room temperature for 16 hours, at which point it was filtered and concentrated under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (20-100% Hx/EtOAc).

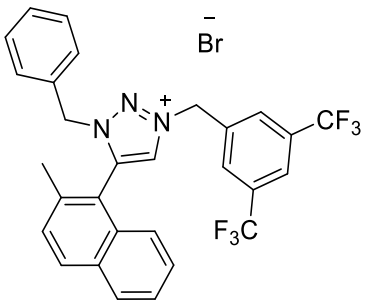
The title compound was obtained as a white solid in 83% yield (1.302 g, 4.82 mmol). Data in agreement with the reported literature values.[255] **IR** (neat) ν_{max} (cm^{-1}) 3299, 2973, 2893, 1639, 1551, 1319; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 (2 H, d, *J* 8.1), 7.67 (2 H, d, *J* 8.1), 7.21 (1 H, br s), 3.80 (2 H, t, *J* 5.1), 3.61 (2 H, q, *J* 5.5), 1.87 (1 H, br s). **^{19}F NMR** (377 MHz, $CDCl_3$) -63.04. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.26, 137.46, 133.29 (q, $^{2}J_{CF}$ 32.7), 127.52, 125.57 (q, $^{3}J_{CF}$ 3.8), 123.62 (q, $^{1}J_{CF}$ 272.3), 61.49, 42.72. **MS (**ES$^+$) *m/z* 234.1 $[M+H]^+$, 256.1 $[M+Na]^+$.

(*rac*)-1,3-Dibenzyl-4-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-3-ium bromide 129



Prepared from 1-benzyl-4-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazole **137** and benzyl bromide, following the *General procedure I*, on a 0.19 mmol scale. The title compound was obtained as an off-white solid in 54% yield (0.048 g, 0.10 mmol). Data in agreement with those previously reported within the group.[148] **IR** (neat) ν_{max} (cm^{-1}) 3034, 2927, 2855, 1457; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.17 (1 H, s), 8.00 (1 H, d, *J* 8.5), 7.92 (1 H, d, *J* 8.1), 7.87 – 7.79 (2 H, m), 7.51 (1 H, ddd, *J* 8.2, 6.9, 1.2), 7.48 – 7.40 (3 H, m), 7.33 (1 H, d, *J* 8.5), 7.30 – 7.23 (2 H, m), 7.22 – 7.10 (2 H, m), 6.97 (1 H, app dq, *J* 8.3, 0.9), 6.74 – 6.65 (2 H, m), 6.57 (1 H, d, *J* 13.9), 6.41 (1 H, d, *J* 14.0), 5.45 (1 H, d, *J* 14.2), 5.10 (1 H, d, *J* 14.3), 1.89 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 139.8, 139.1, 132.5, 132.5, 132.2, 131.7, 131.5, 130.1, 129.9, 129.8, 129.4, 129.1, 128.9, 128.7, 128.3, 126.4, 123.0, 116.4, 57.9, 55.7, 20.5. **MS (**ES^+) *m/z* 390.2 $[M]^+$.

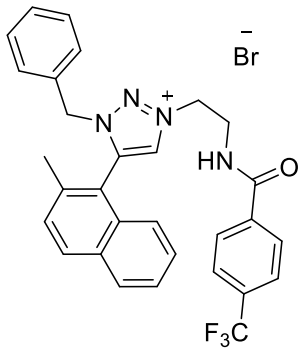
1-Benzyl-3-(3,5-bis(trifluoromethyl)benzyl)-5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-3-ium bromide 157a (*non-rac*)



Prepared from (+)-1-benzyl-5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazole **153b** and 1-(bromomethyl)-3,5-bis(trifluoromethyl)benzene, following the *General procedure I*, on a 0.19

mmol scale. The title compound was obtained in 28% ee (^{1}H NMR) as a pale yellow solid in 90% yield (0.104 g, 0.17 mmol). **m.p**. 85 – 88 °C. **IR** (neat) ν_{max} (cm^{-1}) 3033, 1626, 1377, 1279; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.34 (1 H, s), 8.23 (2 H, s), 7.97 (1 H, d, *J* 8.5), 7.93 (1 H, s), 7.88 (1 H, d, *J* 7.6), 7.51 – 7.39 (2 H, m), 7.30 (1 H, d, *J* 8.5), 7.25 (1 H, t, *J* 7.5), 7.18 (1 H, d, *J* 7.9), 7.12 (2 H, t, *J* 7.7), 6.87 (1 H, d, *J* 14.5), 6.76 (1 H, d, *J* 14.5), 6.66 (2 H, d, *J* 7.9), 5.47 (1 H, d, *J* 14.3), 5.10 (1 H, d, *J* 14.3), 1.87 (3 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -62.79. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.1, 138.91, 138.90, 134.8, 133.0, 132.6 (q, $^2J_{CF}$ 33.8), 132.5, 131.6, 131.4, 130.0 (q, $^3J_{CF}$ 3.5), 129.9, 129.2, 128.8, 128.7, 128.7, 128.2, 126.4, 123.6 (hept, $^3J_{CF}$ 3.6), 123.3, 122.9 (q, $^1J_{CF}$ 273.1), 116.1, 56.2, 55.9, 20.4. **MS (**ES$^+$) *m/z* 526.2 [M]$^+$. **HRMS** (ES$^+$) calc. 526.1718 [$C_{29}H_{22}N_3F_6$], obs. 526.1729.

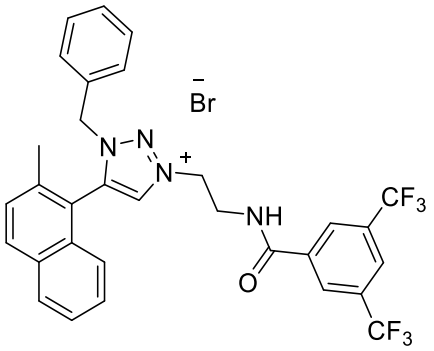
1-Benzyl-5-(2-methylnaphthalen-1-yl)-3-(2-(4-(trifluoromethyl)benzamido)ethyl)-1*H*-1,2,3-triazol-3-ium bromide 157b (*non-rac*)



Prepared from (-)-1-benzyl-5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazole **153b** and *N*-(2-bromoethyl)-4-(trifluoromethyl)benzamide **156a**, following the *General procedure I*, on a 0.13 mmol scale. The title compound was obtained in 28% ee (HPLC) as a pale yellow solid in 45% yield (0.035 g, 0.06 mmol). **m.p**. 55 – 58 °C. **IR** (neat) ν_{max} (cm^{-1}) 3234, 3044, 1661, 1542, 1328; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.44 (1 H, s), 9.30 (1 H, t, *J* 6.1), 8.28 (2 H, d, *J* 8.1), 7.94 (1 H, d, *J* 8.5), 7.86 (1 H, d, *J* 8.2), 7.61 (2 H, d, *J* 8.2), 7.45 (1 H, ddd, *J* 8.1, 6.9, 1.1), 7.31 –

7.19 (3 H, m), 7.15 – 7.03 (3 H, m), 6.71 (2 H, d, *J* 7.3), 5.55 (1 H, ddd, *J* 13.3, 7.1, 4.1), 5.48 (1 H, d, *J* 14.3), 5.42 (1 H, ddd, *J* 13.4, 6.3, 3.9), 5.11 (1 H, d, *J* 14.3), 4.39 – 4.21 (2 H, m), 1.68 (3 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -63.06. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.6, 139.9, 138.7, 135.9, 133.2 (q, $^2J_{CF}$ 32.6), 132.5, 132.3, 131.6, 131.5, 129.8, 129.0, 128.8, 128.7, 128.5, 128.4, 128.1, 126.4, 125.4 (q, $^3J_{CF}$ 3.8), 123.7 (q, $^1J_{CF}$ 272.5), 123.1, 116.1, 56.0, 53.8, 39.3, 20.1. **MS** (ES^+) *m/z* 515.2 $[M]^+$. **HRMS** (ES^+) calc. 515.2059 [$C_{30}H_{26}N_4OF_3$], obs. 515.2072. **HPLC** (Phenomenex Cellulose-1, 40% MeCN/20 mM NH_4CO_2 + 0.1% TEA, 1.0 mL/min, λ = 280 nm) R_t (major) = 14.89 min, R_t (minor) = 18.71 min.

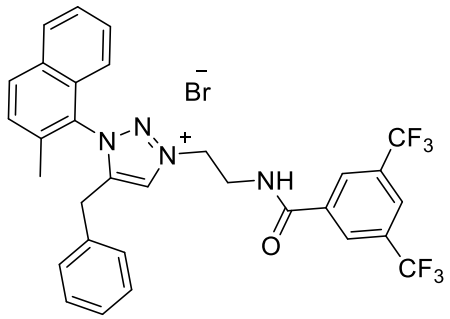
(*rac*)-1-Benzyl-3-(2-(3,5-bis(trifluoromethyl)benzamido)ethyl)-5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-3-ium bromide 157c



Prepared from 1-benzyl-5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazole **153b** and *N*-(2-bromoethyl)-3,5-bis(trifluoromethyl)benzamide **156b**, following the *General procedure I*, on a 0.26 mmol scale. The title compound was obtained as a white solid in 49% yield (0.085 g, 0.13 mmol). **m.p**. 49 – 52 °C. **IR** (neat) ν_{max} (cm^{-1}) 3240, 3054, 1663, 1278; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.76 (1 H, t, *J* 6.0), 9.50 (1 H, s), 8.68 (2 H, s), 7.94 (1 H, d, *J* 8.5), 7.89 (1 H, s), 7.86 (1 H, d, *J* 7.4), 7.49 – 7.37 (3 H, m), 7.25 (1 H, dd, *J* 8.3, 1.1), 7.24 (1 H, d, *J* 8.5), 7.20 (1 H, dt, *J* 7.6, 1.2), 7.15 – 7.05 (2 H, m), 6.70 (2 H, d, *J* 7.0), 5.59 – 5.50 (1 H, m), 5.50 (1 H, d, *J* 14.4), 5.44 – 5.35 (1 H, m), 5.09 (1 H, d, *J* 14.4), 4.33 – 4.20 (2 H, m), 1.72 (3 H, s). **^{19}F NMR**

(377 MHz, $CDCl_3$) -62.85. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.9, 139.9, 138.7, 134.9, 132.4, 132.3, 131.7 (q, $^2J_{CF}$ 33.9), 131.6, 131.5, 129.9, 129.7, 128.9, 128.8, 128.7, 128.6, 128.5 (q, $^3J_{CF}$ 2.9), 128.1, 126.4, 125.0 (app h, $^3J_{CF}$ 3.3), 123.2, 123.0 (q, $^1J_{CF}$ 273.1), 116.2, 55.9, 54.0, 39.6, 20.1. **MS** (ES^+) *m/z* 583.2 $[M]^+$. **HRMS** (ES^+) calc. 583.1933[$C_{31}H_{25}N_4OF_6$], obs. 583.1945.

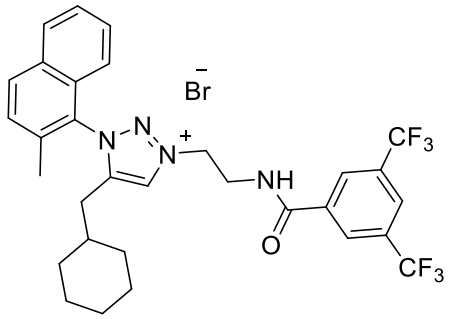
(*rac*)-5-Benzyl-3-(2-(3,5-bis(trifluoromethyl)benzamido)ethyl)-1-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-3-ium bromide 157e



Prepared from 5-benzyl-1-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazole **154b** and *N*-(2-bromoethyl)-3,5-bis(trifluoromethyl)benzamide **156b**, following the *General procedure I*, on a 0.66 mmol scale. The title compound was obtained as a light brown solid in 49% yield (0.215 g, 0.32 mmol). **m.p**. 61 – 63 °C. **IR** (neat) ν_{max} (cm^{-1}) 3199, 3052, 2204, 1663, 1277; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.97 (1 H, s), 9.75 (1 H, t, *J* 5.9), 8.69 (2 H, s), 8.02 (1 H, d, *J* 8.5), 7.94 (1 H, s), 7.92 (1 H, s), 7.56 (1 H, ddd, *J* 8.2, 6.9, 1.3), 7.51 (1 H, ddd, *J* 8.3, 6.9, 1.5), 7.33 (1 H, d, *J* 8.5), 7.19 (1 H, d, *J* 8.3), 7.04 (1 H, tt, *J* 7.5, 1.4), 6.97 (2 H, t, *J* 7.4), 6.70 (2 H, d, *J* 7.3), 5.44 (2 H, app q, *J* 5.8), 4.34 (2 H, app p, *J* 5.8), 4.06 (1 H, d, *J* 16.0), 3.68 (1 H, d, *J* 16.1), 1.82 (3 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -62.60. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.0, 145.3, 135.1, 134.9, 132.6, 132.3, 132.2, 131.7 (q, $^2J_{CF}$ 33.6), 131.2, 129.5, 128.7, 128.5, 128.4 (q, $^3J_{CF}$ 3.2), 128.4, 127.9, 127.8, 127.1, 127.0, 125.1 (app h, $^3J_{CF}$ 3.5), 123.1 (q, $^1J_{CF}$ 271.7),

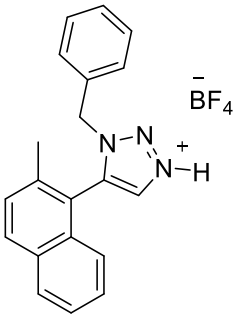
120.5, 53.9, 39.6, 29.9, 17.2 (25 of the 26 expected signals are observed). **MS (**ES^+) *m/z* 583.2 $[M]^+$. **HRMS** (ES^+) calc. 583.1933[$C_{31}H_{25}N_4OF_6$], obs. 583.1949.

(*rac*)-3-(2-(3,5-Bis(trifluoromethyl)benzamido)ethyl)-5-(cyclohexylmethyl)-1-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-3-ium bromide 157d



Prepared from 5-(cyclohexylmethyl)-1-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazole **154a** and *N*-(2-bromoethyl)-3,5-bis(trifluoromethyl)benzamide **156b**, following the *General procedure I*, on a 0.33 mmol scale. The title compound was obtained as a white solid in 44% yield (0.097 g, 0.15 mmol). **m.p**. 63 – 66 °C. **IR** (neat) ν_{max} (cm^{-1}) 3211, 3052, 2929, 2855, 1664, 1277; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.86 (1 H, s), 9.75 (1 H, t, *J* 5.8), 8.76 (2 H, s), 8.09 (1 H, d, *J* 8.5), 8.00 – 7.94 (1 H, m), 7.97 (1 H, s), 7.60 (1 H, d, *J* 3.8), 7.64 – 7.56 (1 H, m), 7.52 (1 H, d, *J* 8.5), 7.10 (1 H, d, *J* 7.6), 5.49 (2 H, app q, *J* 5.3), 4.32 (2 H, app q, *J* 5.5), 2.30 (2 H, d, *J* 7.0), 2.21 (3 H, s), 1.58 – 1.32 (6 H, m), 1.04 – 0.81 (3 H, m), 0.73 – 0.45 (2 H, m). **^{19}F NMR** (377 MHz, $CDCl_3$) -62.64. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.1, 145.5, 135.2, 134.4, 132.6, 132.3, 131.8 (q, $^2J_{CF}$ 33.8), 131.0, 129.4, 128.8, 128.5, 128.4, 128.0, 127.2, 127.1, 125.1 (app h, $^3J_{CF}$ 2.6), 123.9 (q, $^1J_{CF}$ 273.1), 120.6, 54.0, 39.7, 36.1, 32.6, 31.1, 25.5, 25.4, 17.6. **MS (**ES^+) *m/z* 589.2 $[M]^+$. **HRMS** (ES^+) calc. 589.2402 [$C_{31}H_{31}N_4OF_6$], obs. 583.2411.

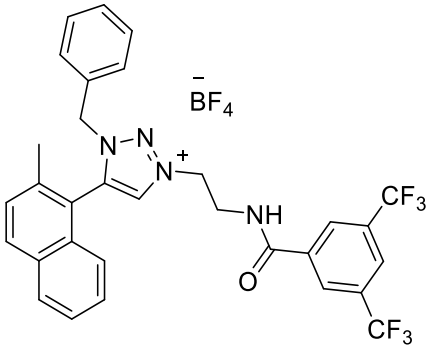
1-Benzyl-5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-3-ium tetrafluoroborate 171



Tetrafluoroboric acid (48wt. % H_2O, 30 μL, 0.28 mmol) was added to a solution of 1-benzyl-5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazole **153b** (0.0084 g, .28 mmol) in methanol (1.50 mL) cooled to 0 °C. The resulting solution was stirred at room temperature for 1 hour, at which point it was concentrated under reduced pressure to afford a crude residue that was used without further purification.

The title compound was obtained as a colourless oil in 99% yield (0.107 g, 0.28 mmol). **R_f** = 0.27 (20% MeOH/DCM); **IR** (neat) ν_{max} (cm^{-1}) 3546, 3154, 1625, 1591, 1051, 1026; **^{1}H NMR** (400 MHz, MeOD) δ 8.44 (1 H, s), 8.05 (1 H, d, *J* 8.4), 7.96 (1 H, d, *J* 8.2), 7.51 (1 H, ddd, *J* 8.2, 6.9, 1.2), 7.43 (1 H, d, *J* 8.4), 7.44 – 7.39 (1 H, m), 7.23 – 7.17 (1 H, m), 7.11 (2 H, dt, *J* 7.8, 1.7), 7.09 – 7.04 (1 H, m), 6.75 (2 H, d, *J* 7.3), 5.55 (1 H, d, *J* 14.7), 5.23 (1 H, d, *J* 14.7), 1.92 (3 H, s). **^{19}F NMR** (377 MHz, MeOD) -154.38 ($^{10}BF_4$), -154.44 ($^{11}BF_4$). **^{13}C NMR** (101 MHz, MeOD) δ 138.1, 137.6, 132.3, 132.1, 131.9, 131.3, 131.2, 128.6, 128.4, 128.3, 128.2, 128.0, 127.6, 125.7, 123.3, 118.6, 54.1, 18.8. **MS (**ES^+) *m/z* 300.1 $[M]^+$. **HRMS** (ES^+) calc. 300.1501 [$C_{20}H_{18}N_3$], obs. 300.1507.

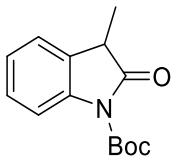
1-Benzyl-3-(2-(3,5-bis(trifluoromethyl)benzamido)ethyl)-5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-3-ium tetrafluoroborate 180



Silver tetrafluoroborate (0.039 g, 0.20 mmol) was added to a solution of (+)-1-benzyl-5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazole **153b** (0.020 g, 0.07 mmol) in acetonitrile (150 μL), under a stream of argon. To this mixture, a solution of *N*-(2-bromoethyl)-3,5-bis(trifluoromethyl)benzamide **156b** (0.073 g, 0.20 mmol) in acetonitrile (300 μL) was added dropwise over 1 hour with a syringe pump. The reaction mixture was filtered through a pad of celite and concentrated under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-20% MeOH/DCM).

The title compound was obtained as a white solid in 28% yield (0.012 g, 0.02 mmol). **m.p**. 47 – 50 °C. **IR** (neat) ν_{max} (cm^{-1}) 3397, 2927, 2860, 1671, 1279; **^{1}H NMR** (400 MHz, $CDCl_3$) 9.17 (1 H, t, *J* 6.0), 8.93 (1 H, s), 8.48 (2 H, s), 7.91 (1 H, d, *J* 8.6), 7.88 (1 H, s), 7.85 (1 H, d, *J* 7.7), 7.48 – 7.37 (2 H, m), 7.24 – 7.17 (3 H, m), 7.08 (2 H, t, *J* 7.7), 6.69 (2 H, d, *J* 7.2), 5.48 (1 H, d, *J* 14.4), 5.28 (1 H, ddd, *J* 13.7, 6.3, 4.4), 5.20 (1 H, ddd, *J* 13.7, 5.9, 4.1), 5.07 (1 H, d, *J* 14.5), 4.28 – 4.16 (2 H, m), 1.69 (3 H, s). **^{19}F NMR** (282 MHz, $CDCl_3$) -62.85, -150.83 ($^{10}BF_4$), -150.88 ($^{11}BF_4$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.2, 140.1, 138.8, 135.0, 132.3, 132.3, 132.1, 131.8 (q, $^{2}J_{CF}$ 34.1), 131.6, 130.0, 129.7, 128.9, 128.8, 128.6, 128.2 (q, $^{3}J_{CF}$ 3.5), 128.1, 126.4, 125.0 (app h, $^{3}J_{CF}$ 3.3), 123.1, 123.0 (q, $^{1}J_{CF}$ 273.0), 116.3, 55.9, 54.1, 39.8, 19.8. **MS** (ES^+) *m/z* 583.2 $[M]^+$. **HRMS** (ES^+) calc. 583.1933 [$C_{31}H_{25}N_4OF_6$], obs. 583.1946.

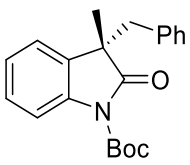
***tert*-Butyl 3-methyl-2-oxoindoline-1-carboxylate 176**



In an oven-dried two-neck round bottom flask, a solution of 3-methyl-2-oxindole (1.000 g, 6.79 mmol) in anhydrous tetrahydrofuran (20 ml) was cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 0.331 g, 8.28 mmol) was added portion wise under a stream of argon. When the gas production ceased, a solution of di-*tert*-butyl dicarbonate (1.800 g, 8.28 mmol) in tetrahydrofuran (10 mL) was added dropwise, and the resulting mixture stirred at 0 °C for 6 hours. The reaction was quenched with saturated aqueous ammonium chloride (20 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic fractions were washed with brine (25mL), dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-100% Hx/EtOAc).

The title compound was obtained as a colourless oil in 65% yield (1.091 g, 4.42 mmol). Data in agreement with the reported literature values.[256] **IR** (neat) ν_{max} (cm^{-1}) 2980, 2935, 1765, 1726; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81 (1 H, d, *J* 8.2), 7.34 – 7.25 (1 H, m), 7.24 (1 H, d, *J* 7.4), 7.16 (1 H, t, *J* 7.4), 3.56 (1 H, q, *J* 7.6), 1.65 (9 H, s), 1.52 (3 H, d, *J* 7.6). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 176.9, 149.3, 139.7, 129.4, 128.1, 124.3, 123.4, 115.0, 84.3, 41.1, 28.1, 16.0. **MS** (ES^+) *m/z* 270.1 $[M+Na]^+$.

***tert*-Butyl (*S*)-3-benzyl-3-methyl-2-oxoindoline-1-carboxylate 177**

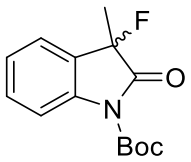


Adapted from a literature procedure.[130] A solution of enantioenriched 1-benzyl-5-(2-methylnaphthalen-1-yl)-3-(2-(4-(trifluoromethyl)benzamido)ethyl)-1*H*-1,2,3-triazol-3-ium

bromide **157b** (0.002 g, 2 mol%), *N*-Boc oxindole **176** (0.049 g, 0.20 mmol), and benzyl bromide (30 μL, 0.24 mmol) in anhydrous ethyl acetate (600 μL) was cooled to -20 °C. Potassium carbonate (0.070 g, 0.50 mmol) was added, and the resulting mixture stirred at -20 °C for 12 hours, at which point the solvent was removed under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-100% Hx/EtOAc).

The title compound was obtained as a white solid in 99% yield (0.069 g, 0.20 mmol) and 43:57 enantiomeric ratio. Data in agreement with the reported literature values.[130] **IR** (neat) ν_{max} (cm^{-1}) 3032, 2980, 2932, 1764, 1731; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.61 (1 H, d, *J* 7.7), 7.28 – 7.17 (1 H, m), 7.16 – 7.00 (5 H, m), 6.83 (2 H, dd, *J* 7.7, 1.9), 3.15 (1 H, d, *J* 13.0), 3.00 (1 H, d, *J* 13.0), 1.57 (9 H, s), 1.52 (3 H, s). **HRMS** (ES^+) calc. 360.1576 [$C_{21}H_{23}NO_3Na$], obs. 360.1575. **HPLC** (Phenomenex Cellulose-1, 1% *i*PrOH/Hx, 0.5 mL/min, λ = 254 nm) R_t (minor) = 10.00 min, R_t (major) = 10.68 min.

***tert*-Butyl-3-fluoro-3-methyl-2-oxoindoline-1-carboxylate 181** (*non-rac*)



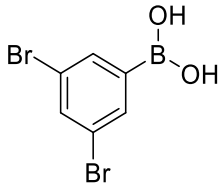
Aqueous solution of potassium carbonate (0.5 M, 1.0 mL, 0.50 mmol) was added to a solution of 1-benzyl-3-(2-(3,5-bis(trifluoromethyl)benzamido)ethyl)-5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-3-ium tetrafluoroborate **180** (0.003 g, 2 mol%) and *N*-Boc oxindole **176** (0.049 g, 0.20 mmol) in diethyl ether (2.0 mL). The resulting mixture was vigorously stirred for 15 minutes, hence cooled to-20 °C. *N*-fluorobenzenesulfonimide (0.070 g, 0.22 mmol) was added in one portion and the reaction mixture stirred at -20 °C for 16 hours, at which point it was transferred to a separating funnel and extracted with ethyl acetate (3 × 5 mL). The combined

organic fractions were washed with brine (5 mL), dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-100% Hx/EtOAc).

The title compound was obtained as a white solid in 38% yield (0.020 g, 0.01 mmol) and 41:59 enantiomeric ratio. Data in agreement with the reported literature values.[256] **IR** (neat) ν_{max} (cm^{-1}) 2982, 2928, 2860, 1734; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 (1 H, d, *J* 8.1), 7.50 – 7.38 (2 H, m), 7.22 (1 H, dt, *J* 7.5, 1.0), 1.79 (3 H, d, $^3J_{HF}$ 21.6), 1.65 (9 H, s). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -144.96 (q, $^3J_{FH}$ 22.4). **HRMS** (ES^+) calc. 288.1012 [$C_{14}H_{16}NO_3FNa$], obs. 288.1018. **HPLC** (Phenomenex Cellulose-1, 38% MeCN/H_2O, 1.0 mL/min, λ = 220 nm) R_t (minor) = 46.78 min, R_t (major) = 48.67 min.

6.3.2 Data for *Chapter 4*

(3,5-Dibromophenyl)boronic acid 242

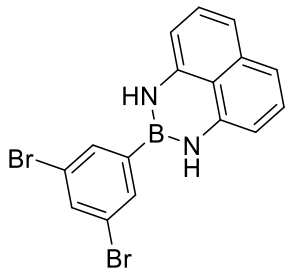


Adapted from a literature procedure.[257] In an Ace round-bottom pressure flask, 1,3-dibromobenzene (1.2 mL, 10.00 mmol), bis(pinacolato)diboron, (2.180 g, 8.60 mmol), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.006 g, 0.2 mol%), and (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (0.006 g, 0.1 mol%), were dissolved in anhydrous tetrahydrofuran (10.0 mL). The flask was flushed with argon, sealed, and heated at 80 °C for 16 hours. The reaction mixture was allowed to cool to room temperature and diluted with water (4.0 mL). Sodium perchlorate (3.200 g, 14.90 mmol) was added, and the resulting mixture stirred for 15 minutes. Aqueous

acid chloride (1.0 M, 10 mL) was added, and the reaction stirred for additional 4 hours, at which point it was transferred to a separating funnel and extracted with ethyl acetate (3 × 25 mL). The combined organic fractions were washed with brine (25mL), dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure to afford a crude residue that was washed with hexane (3 × 25 mL) to afford the pure boronic acid.

The title compound was obtained as a beige powder in 75% yield (2.101 g, 7.51 mmol). **m.p**. >300 °C. **IR** (neat) ν_{max} (cm^{-1}) 3063, 3020, 1405, 1327, 747. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (2 H, br s), 7.72 – 7.67 (3 H, m). **^{11}B NMR** (128 MHz, $CDCl_3$) 27.26. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.4, 135.1, 122.8 (3 of the 4 expected signals are observed). **MS (**ES^-) *m/z* 279 $[M-H]^-$. **HRMS** (ES^-) calc. 275.8707 [$C_6H_4{}^{10}BO_2Br_2$], obs. 275.8712.

2-(3,5-Dibromophenyl)-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborinine 243

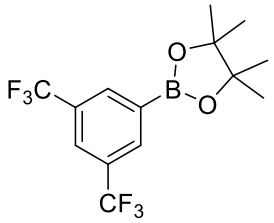


Following a literature procedure,[258] (3,5-dibromophenyl)boronic acid **242** (0.882 g, 3.15 mmol) and 1,8-diaminonaphthalene (0.550 g, 3.47 mmol) were dissolved in toluene (21 mL) and the resulting solution heated to 100 °C for 15 minutes. The solution was allowed to cool to room temperature, diluted with a 10% solution of ethyl acetate in hexane (100 mL), filtered through a short silica pad and concentrated under reduced pressure to afford the desired product.

The title compound was obtained as a light brown solid in 93% yield (1.181 g, 2.94 mmol). Data in agreement with the reported literature values.[258] **IR** (neat) ν_{max} (cm^{-1}) 3434, 1601, 1509, 1402. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (1 H, t, *J* 1.8), 7.67 (2 H, d, *J* 1.8), 7.15 (1 H, d, *J* 7.2), 7.13 (1 H, d, *J* 7.2), 7.08 (2 H, dd, *J* 8.4, 1.1), 6.42 (2 H, dd, *J* 7.2, 1.1), 5.93 (2 H, br s).

^{11}B NMR (128 MHz, $CDCl_3$) 28.92. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.4, 136.3, 135.5, 133.0, 127.6, 123.5, 120.0, 118.4, 106.4. **HRMS** (ES^+) calc. 398.9418 [$C_{16}H_{11}{}^{10}BN_2Br_2$], obs. 398.9404.

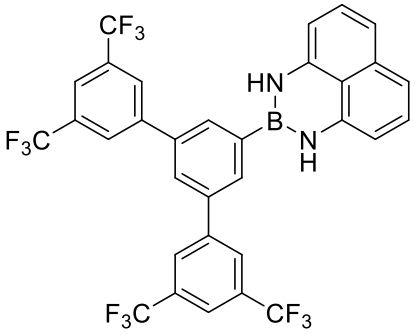
2-(3,5-Bis-trifluoromethyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane 244



3,5-Bis(trifluoromethyl)phenylboronic acid (5.000 g, 19.40 mmol), pinacol (2.290 g. 19.40 mmol) were dissolved in diethyl ether (28 mL). Magnesium sulphate (2.330 g, 19.40 mmol) was added, and the resulting mixture stirred at room temperature for 16 hours, at which point it was filtered and concentrated under reduced pressure to afford the desired product.

The title compound was obtained as a white solid in quantitative yield (6.587 g, 19.37 mmol). Data in agreement with the reported literature values.[259] **IR** (neat) ν_{max} (cm^{-1}) 2984, 2937, 1618, 1308, 1276, 1127. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.24 (2 H, s), 7.95 (1 H, s), 1.38 (12 H, s). **^{19}F NMR** (282 MHz, $CDCl_3$) -62.89. **HRMS** ($ASAP^+$) calc. 340.1184 [$C_{14}H_{16}O_2F_6{}^{10}B$], obs. 340.1176.

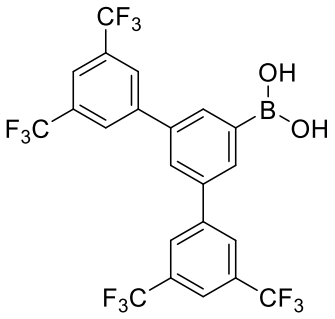
2-(3,3'',5,5''-Tetrakis(trifluoromethyl)-[1,1':3',1''-terphenyl]-5'-yl)-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborinine 245



Adapted from a literature procedure.[260] In an Ace round-bottom pressure flask, diazaborinine **243** (0.919 g, 2.29 mmol), boronic ester **244** (1.720 g, 4.80 mmol), SPhos (0.090 g, 10 mol%) and palladium(II) acetate (0.025 g, 5 mol%) were dissolved in a degassed solution of tetrahydrofuran (23 mL). Potassium phosphate tribasic (1.460 g, 3.00 mmol) was added, the flask was flushed with argon, sealed, and heated at 90 °C for 24 hours. Upon completion, the mixture was filtered through a pad of celite and concentrated under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-100% Hx/EtOAc).

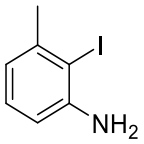
The title compound was obtained as a dark green solid in 91% yield (1.402 g, 2.10 mmol). **m.p**. 243-245 °C. **IR** (neat) ν_{max} (cm^{-1}) 3441, 3060, 2936, 1602, 1365, 1275. **^{1}H NMR** 8.10 (4 H, s), 7.95 (2 H, s), 7.89 (2 H, d, *J* 1.8), 7.83 (1 H, t, *J* 1.8), 7.18 (1 H, d, *J* 7.2), 7.16 (1 H, d, *J* 7.2), 7.10 (2 H, dd, *J* 8.4, 1.0), 6.50 (2 H, dd, *J* 7.2, 1.1), 6.12 (2 H, br s). **^{19}F NMR** (282 MHz, $CDCl_3$) -62.68. **^{11}B NMR** (128 MHz, $CDCl_3$) 29.59. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.7, 140.5, 139.6, 136.3, 132.5 (q, $^{2}J_{CF}$ 33.3), 130.9, 128.0, 127.7, 127.6 (q, $^{3}J_{CF}$ 2.9), 123.3 (q, $^{1}J_{CF}$ 272.9), 121.6 (app h, $^{3}J_{CF}$ 3.9), 120.0, 118.4, 106.4 (14 of the 15 expected signals are observed). **MS (**ES^+) *m/z* 668.1 $[M]^+$. **HRMS** (ES^+) calc. 667.1329 [$C_{32}H_{17}{}^{10}BN_2F_{12}$], obs. 667.1337.

(3,3'',5,5''-Tetrakis(trifluoromethyl)-[1,1':3',1''-terphenyl]-5'-yl)boronic acid 246



Following a literature procedure,[260] diazaborinine **245** (1.400 g, 2.09 mmol) was dissolved in tetrahydrofuran (42 mL). Aqueous hydrochloric acid (5.0 M, 5.0 mL, 25.00 mmol) was added and the resulting solution stirred at room temperature for 8 hours. Aqueous hydrochloric acid (3.0 M, 50.0 mL) was added, the mixture filtered through a pad of celite, and the filtrate extracted with diethyl ether (3 × 25 mL). The combined organic fractions were washed with brine (25mL), dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure to afford a crude product (1.140 g, 2.09 mmol) that was used in the subsequent step without any further purification.

2-Iodo-3-methylaniline 234

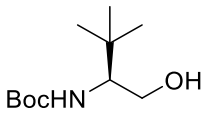


Iron powder (2.630 g, 47.14 mmol) was added to a solution of 2-iodo-3-nitrotoluene (2.000 g, 7.60 mmol) in ethanol (25 mL). Concentrated hydrochloric acid (37%, 785 μL, 9.12 mmol) was added and the resulting mixture stirred at reflux for 6 hours. Sodium carbonate was added portion wise until the gas production ceased, at which point the mixture was filtered through a pad of celite and concentrated under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-100% Hx/EtOAc).

The title compound was obtained as a brown solid in 85% yield (1.503 g, 6.45 mmol). Data in agreement with the reported literature values.[261] **IR** (neat) ν_{max} (cm^{-1}) 3395, 3295, 3149, 1611,

1462. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.00 (1 H, t, *J* 7.7), 6.64 (1 H, ddq, *J* 7.4, 1.6, 0.7), 6.57 (1 H, ddt, *J* 8.1, 1.6, 0.5), 4.08 (2 H, br s), 2.41 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.1, 142.5, 128.5, 119.6, 111.9, 91.6, 29.3. **HRMS** (AP^+) calc. 233.9780 [$C_7H_9N^{127}I$], obs. 233.9786.

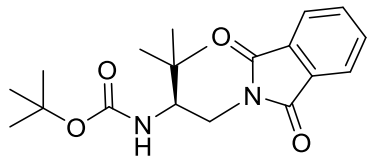
tert-Butyl (*S*)-(1-hydroxy-3,3-dimethylbutan-2-yl)carbamate 213



Following a literature procedure,[262] iodine (0.433 g, 10 mol%) was added to a mixture of L-*tert*-leucinol (2.000 g, 17.07 mmol) and di-*tert*-butyl dicarbonate (3.720 g, 17.07 mmol) and the resulting mixture was stirred neat at room temperature for 16 hours. Diethyl ether (25 mL) was added, and the reaction mixture was washed with an aqueous solution of sodium thiosulphate (5%, 20 mL), a saturated aqueous solution of sodium bicarbonate (20 mL), and brine (20 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure to afford the pure product.

The title compound was obtained as a white solid in 95% yield (3.531 g, 16.25 mmol). Data in agreement with the reported literature values.[262] **IR** (neat) ν_{max} (cm^{-1}) 3366, 3253, 2962, 1680. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.71 (1 H, br s), 3.83 (1 H, m), 3.56 – 3.40 (2 H, m), 2.45 (1 H, br s), 1.46 (9 H, s), 0.94 (9 H, s). **HRMS** (AS^+) calc. 240.1576 [$C_{11}H_{23}NO_3Na$], obs. 240.1586. **$[\alpha]_D$** = -6.93° (*c* = 1.0, $CHCl_3$).

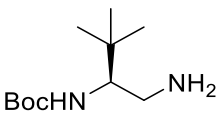
tert-Butyl (*S*)-(1-(1,3-dioxoisoindolin-2-yl)-3,3-dimethylbutan-2-yl)carbamate 214



Diisopropyl azodicarboxylate (3.5 mL, 17.50 mmol) was added dropwise, under a stream of argon, to a solution of triphenylphosphine (5.510 g, 21.00 mmol), *tert*-butyl (*S*)-(1-hydroxy-3,3-dimethylbutan-2-yl)carbamate **213** (1.520 g, 7.00 mmol) and phthalimide (1.550 g, 10.51 mmol) in tetrahydrofuran (50 mL) cooled to 0 °C. The reaction mixture was allowed to warm to room temperature and stirred until full consumption of the starting material, at which point it was concentrated under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-100% Hx/EtOAc).

The title compound was obtained as a white solid in 91% yield (2.201 g, 6.35 mmol). Data in agreement with the reported literature values.[263] **IR** (neat) ν_{max} (cm^{-1}) 3365, 3253, 2967, 1774, 1713. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (2 H, dd, *J* 5.4, 3.1), 7.68 (2 H, dd, *J* 5.5, 3.0), 4.47 (1 H, d, *J* 10.3), 3.85 (1 H, dd, *J* 12.5, 3.3), 3.80 (1 H, dd, *J* 10.7, 3.2), 3.63 (1 H, td, *J* 12.4, 1.5), 1.12 (9 H, s), 1.03 (9 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.5, 156.0, 133.7, 132.2, 123.1, 79.0, 57.5, 38.6, 33.7, 27.9, 26.5. **HRMS** (ES^+) calc. 369.1790 [$C_{19}H_{26}N_2O_4Na$], obs. 369.1801. **$[\alpha]_D$** = +51.00° (*c* = 0.5, $CHCl_3$).

tert-Butyl (*S*)-(1-amino-3,3-dimethylbutan-2-yl)carbamate 215

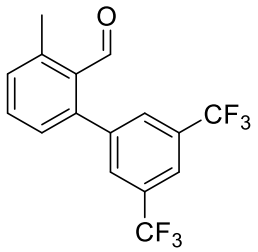


Carbamate **214** (2.201 g, 6.35 mmol) was dissolved in an aqueous solution of methylamine (40 wt. %, 65 mL) and the resulting mixture was stirred at room temperature for 16 hours. The solvent was removed under reduced pressure and the residue redissolved in ethyl acetate (25 mL). The solution was transferred to a separating funnel, and the organic layer was washed

with brine (20 mL), dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure to afford the desired product sufficiently pure to be used without further purification.

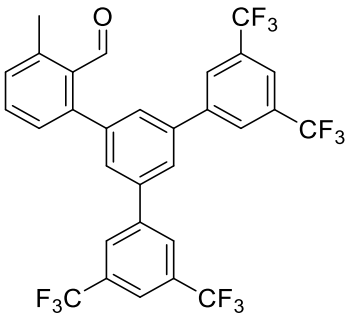
The title compound was obtained as a pale yellow solid in 93% yield (1.278 g, 5.91 mmol). Data in agreement with the reported literature values.[263] Additional spectroscopic characterisation is reported. **IR** (neat) ν_{max} (cm^{-1}) 3258, 2965, 2971, 1699, 1172. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.52 (1 H, d, *J* 10.4), 3.34 (1 H, td, *J* 10.4, 3.2), 2.96 (1 H, dd, *J* 13.3, 3.3), 2.41 (1 H, dd, *J* 13.3, 10.4), 1.55 (2 H, br s), 1.45 (9 H, s), 0.91 (9 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.8, 79.2, 62.5, 42.5, 34.2, 28.4, 26.6. **HRMS** (ES^+) calc. 217.1916 [$C_{11}H_{25}N_2O_2$], obs. 217.1926. **$[\alpha]_D$** = +10.03° (*c* = 0.5, $CHCl_3$).

Methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde 201a



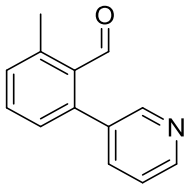
Prepared from 2-bromo-6-methylbenzaldehyde **200** and 3,5-bis(trifluoromethyl)phenylboronic acid, following the *General Procedure C*, on a 5.02 mmol scale. The title compound was obtained as a yellow solid in 96% yield (1.613 g, 4.82 mmol). **m.p.** 44 – 46 °C. **IR** (neat) ν_{max} (cm^{-1}) 3067, 2935, 2858, 2761, 1695, 1277. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.04 (1 H, s), 7.94 (1 H, s), 7.79 (2 H, s), 7.54 (1 H, t, *J* 7.6), 7.39 (1 H, ddt, *J* 7.7, 1.2, 0.6), 7.23 (1 H, ddd, *J* 7.6, 1.2, 0.6), 2.69 (3 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$): δ -62.80. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.6, 143.2, 141.6, 141.1, 132.7, 132.6, 132.3, 131.7 (q, $^{2}J_{CF}$ 33.6), 129.7 (q, $^{3}J_{CF}$ 4.2), 128.8, 123.1 (q, $^{1}J_{CF}$ 272.4), 121.7 (app p, $^{3}J_{CF}$ 3.7), 21.2. **MS (**$ASAP^+$) *m/z* 333.1 $[M+H]^+$. **HRMS** ($ASAP^+$) calc. 333.0714 [$C_{16}H_{11}OF_6$], obs. 333.0718.

5'-(3,5-Bis(trifluoromethyl)phenyl)-3-methyl-3'',5''-bis(trifluoromethyl)-[1,1':3',1''-terphenyl]-2-carbaldehyde 201c



Prepared from 2-bromo-6-methylbenzaldehyde **200** and (3,3'',5,5''-tetrakis(trifluoromethyl)-[1,1':3',1''-terphenyl]-5'-yl)boronic acid **246**, following the *General Procedure C*, on a 1.72 mmol scale. The title compound was obtained as a white solid in 92% yield (0.985 g, 1.59 mmol). **m.p.** 145 – 147 °C. **IR** (neat) ν_{max} (cm^{-1}) 3075, 2863, 2762, 2761, 1697, 1366, 1274. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.15 (1 H, s), 8.08 (4 H, s), 7.94 (2 H, s), 7.83 (1 H, t, *J* 1.7), 7.65 (2 H, d, *J* 1.7), 7.57 (1 H, t, *J* 7.6), 7.38 (2 H, t, *J* 7.8), 2.71 (3 H, s).**^{19}F NMR** (377 MHz, $CDCl_3$): δ -62.78. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.5, 145.1, 142.1, 141.7, 140.8, 139.8, 132.62, 132.5 (q, $^{2}J_{CF}$ 33.4), 132.1, 129.1, 128.7, 127.6 (q, $^{3}J_{CF}$ 3.8), 125.7, 123.2 (q, $^{1}J_{CF}$ 273.3), 121.9, 121.8 (app h, $^{3}J_{CF}$ 3.6), 21.4. **MS (**ASAP^{+}) *m/z* 621.1 $[M+H]^{+}$. **HRMS** (ASAP^{+}) calc. 621.1088 [$C_{30}H_{17}OF_{12}$], obs. 621.1096.

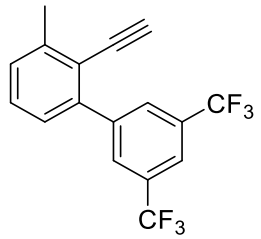
2-Methyl-6-(pyridin-3-yl)benzaldehyde 201b



Prepared from 2-bromo-6-methylbenzaldehyde **200** and 3-pyridinylboronic acid, following the *General Procedure C*, on a 7.54 mmol scale. The title compound was obtained as a pale yellow oil in 71% yield (1.056 g, 5.35 mmol). $\mathbf{R_f}$ = 0.20 (30% EtOAc/Hx); **IR** (neat) ν_{max} (cm^{-1}) 2966,

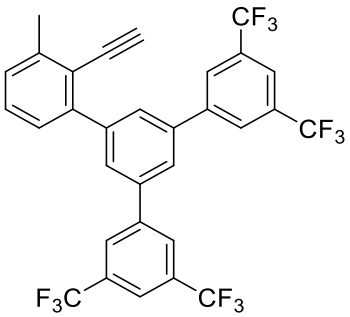
2855, 2758, 2761, 1685, 1586. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.03 (1 H, s), 8.67 (1 H, dd, *J* 4.9, 1.7), 8.63 (1 H, dd, *J* 2.4, 0.9), 7.67 (1 H, ddd, *J* 7.8, 2.3, 1.7), 7.52 (1 H, t, *J* 7.6), 7.39 (1 H, ddd, *J* 7.8, 4.9, 0.9), 7.35 (1 H, ddt, *J* 7.7, 1.4, 0.7), 7.25 (1 H, ddd, *J* 7.6, 1.3, 0.6), 2.68 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.4, 150.1, 149.2, 143.0, 140.7, 137.2, 134.8, 132.6, 132.6, 132.0, 128.9, 123.0, 21.4. **MS (**ES^+) *m/z* 198.1 $[M+H]^+$. **HRMS** (ES^+) calc. 198.0919 [$C_{13}H_{12}NO$], obs. 198.0924.

2-Ethynyl-3-methyl-3',5'-bis(trifluoromethyl)-1,1'-biphenyl 202a



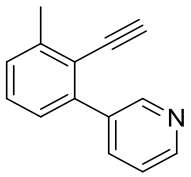
Prepared from 3-methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde **201a**, following the *General Procedure D*, on a 4.83 mmol scale. The title compound was obtained as a white solid in 88% yield (1.391 g, 4.23 mmol). **m.p.** 41 – 43 °C. **IR** (neat) ν_{max} (cm^{-1}) 3311, 3178, 1274. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.05 (2 H, s), 7.87 (1 H, s), 7.35 (1 H, t, *J* 7.6), 7.31 (1 H, ddd, *J* 7.7, 1.6, 0.7), 7.21 (1 H, ddd, *J* 7.3, 1.6, 0.7), 3.31 (1 H, s), 2.54 (3 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$): δ -62.84. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.6, 142.5, 141.7, 131.2 (q, $^{2}J_{CF}$ 33.3), 129.7, 129.6 (q, $^{3}J_{CF}$ 3.7), 128.8, 126.7, 123.4 (q, $^{1}J_{CF}$ 273.0), 121.1 (app p, $^{3}J_{CF}$ 3.9), 120.5, 86.0, 80.5, 21.3. **MS (**EI^+) *m/z* 328.1 $[M]^+$. **HRMS** (EI^+) calc. 328.0687 [$C_{17}H_{10}F_6$], obs. 328.0703.

5'-(3,5-Bis(trifluoromethyl)phenyl)-2-ethynyl-3-methyl-3'',5''-bis(trifluoromethyl)-1,1':3',1''-terphenyl 202c



Prepared from 5'-(3,5-bis(trifluoromethyl)phenyl)-3-methyl-3",5"-bis(trifluoromethyl)-[1,1':3',1"-terphenyl]-2-carbaldehyde **201c**, following the *General Procedure D*, on a 1.53 mmol scale. The title compound was obtained as a white solid in 83% yield (0.779 g, 1.26 mmol). **m.p.** 162 – 164 °C. **IR** (neat) ν_{max} (cm^{-1}) 3307, 2988, 1365, 1274, 1125. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.11 (4 H, s), 7.93 (2 H, s), 7.90 (2 H, d, *J* 1.7), 7.76 (1 H, t, *J* 1.7), 7.38 (1 H, dd, *J* 8.2, 7.0), 7.33 (1 H, dd, *J* 1.4, 0.7), 7.31 (1 H, td, *J* 1.8, 0.7), 3.38 (1 H, s), 2.58 (3 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$): δ -62.79. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.2, 142.9, 142.8, 142.5, 139.2, 132.4 (q, $^{2}J_{CF}$ 33.4), 129.3, 128.9, 128.8, 127.5 (q, $^{3}J_{CF}$ 4.1), 126.8, 125.0, 123.3 (q, $^{1}J_{CF}$ 272.8), 121.53 (app h, $^{3}J_{CF}$ 3.9), 120.52, 85.4, 81.6, 21.4. **MS (**AP^-) *m/z* 616.1 $[M]^-$. **HRMS** (AP^-) calc. 615.0982 [$C_{31}H_{15}F_{12}$], obs. 615.0991.

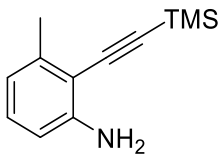
3-(2-Ethynyl-3-methylphenyl)pyridine 202b



Prepared from 2-methyl-6-(pyridin-3-yl)benzaldehyde **201b**, following the *General Procedure D*, on a 2.89 mmol scale. The title compound was obtained as a blue oil in 81% yield (0.445 g, 2.35 mmol). **R_f** = 0.32 (30% EtOAc/Hx); **IR** (neat) ν_{max} (cm^{-1}) 3290, 3030, 2099, 2761, 1463, 1403. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.79 (1 H, dd, *J* 2.3, 0.9), 8.60 (1 H, dd, *J* 4.9, 1.7), 7.89 (1 H, ddd, *J* 7.9, 2.3, 1.7), 7.36 – 7.33 (1 H, m), 7.31 (1 H, d, *J* 7.4), 7.27 (1 H, ddd, *J* 7.7, 1.5,

0.7), 7.18 (1 H, dd, *J* 7.4, 0.8), 3.28 (1 H, s), 2.53 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.0, 148.5, 142.2, 141.2, 136.6, 136.4, 129.1, 128.6, 126.9, 122.7, 120.8, 85.4, 81.0, 21.3. **MS (**AP^+) *m/z* 194.1 $[M+H]^+$. **HRMS** (AP^+) calc. 194.0970 [$C_{14}H_{12}N$], obs. 194.0974.

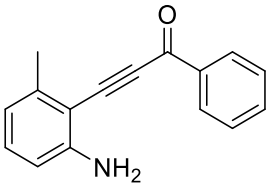
3-Methyl-2-((trimethylsilyl)ethynyl)aniline 247



2-Iodo-3-methylaniline **234** (1.000 g, 4.29 mmol), trimethylsilylacetylene (1.2 mL, 8.58 mmol), palladium(II)bis(triphenylphosphine) dichloride (0.147 g, 5 mol%), and copper(I) iodide (0.040 g, 5 mol%) were dissolved in degassed triethylamine (86.0 mL). The reaction mixture was stirred at 60 °C for 12 hours, at which point it was filtered through a pad of celite. The filtrate was concentrated under reduced pressure, redissolved in ethyl acetate (25 mL), washed with water (3 × 20 mL) and brine (25 mL), dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-10% Hx/EtOAc).

The title compound was obtained as a brown oil in 92% yield (0.801 g, 3.95 mmol). $\mathbf{R_f}$ = 0.51 (20% EtOAc/Hx); **IR** (neat) ν_{max} (cm^{-1}) 3480, 3383, 3036, 2959, 2898, 2142, 1611, 1470, 861, 840. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.86 (1 H, t, *J* 7.8), 6.43 (1 H, d, *J* 7.5), 6.39 (1 H, d, *J* 8.1), 4.09 (2 H, br s), 2.24 (3 H, s), 0.14 (9 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.1, 141.0, 128.8, 118.6, 111.2, 107.9, 103.6, 100.5, 20.6, 0.0. *Expected ions not observed by mass spectrometry.*

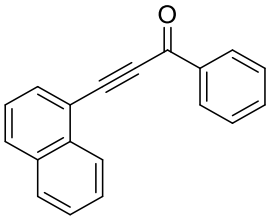
3-(2-Amino-6-methylphenyl)-1-phenylprop-2-yn-1-one 236



Step I: Potassium carbonate (1.040 g, 7.52 mmol) was added to a solution of 3-methyl-2-((trimethylsilyl)ethynyl)aniline **247** (0.765 g, 3.76 mmol) in methanol (4.7 mL). The resulting solution was stirred at room temperature for 12 hours, at which point it was filtered and concentrated under reduced pressure to afford the crude 2-ethynyl-3-methylaniline **235**, which was used without further purification.

Step II: 2-Ethynyl-3-methylaniline **235** was treated with benzoyl chloride according to the *General Procedure J (Method A)*. The title compound was obtained as an orange solid in 43% yield (0.378 g, 1.60 mmol). **m.p.** 103 – 105 °C. **IR** (neat) ν_{max} (cm^{-1}) 3340, 3323, 3210, 2170, 1634; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.26 – 8.19 (2 H, m), 7.63 (1 H, tt, *J* 7.4, 1.3), 7.57 – 7.48 (2 H, m), 7.13 (1 H, dd, *J* 8.2, 7.4), 6.62 (1 H, dt, *J* 7.5, 0.9), 6.58 (1 H, d, *J* 8.2), 4.56 (2 H, br s), 2.53 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 177.9, 151.0, 143.0, 137.2, 133.9, 132.0, 129.5, 128.7, 119.1, 112.0, 104.3, 97.5, 90.2, 21.3. **MS** (ES^+) *m/z* 236.1 $[M+H]^+$; **HRMS** (ES^+) calc. 236.1075 [$C_{16}H_{14}NO$], obs. 236.1075.

3-(Naphthalen-1-yl)-1-phenylprop-2-yn-1-one 248

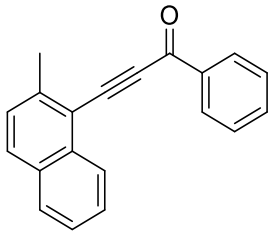


Step I: Tetrabutylammonium fluoride (1.0 M in THF, 1.1 mL, 10.70 mmol) was added dropwise to a solution of 1-(trimethylsilyl)naphthalene (2.000 g, 8.91 mmol) in tetrahydrofuran (30 mL) cooled to 0 °C, and the resulting solution stirred for 3 hours. Saturated ammonium chloride in

water (20 mL) was added, and the reaction mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic fractions were washed with brine (20 mL), dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure to afford the crude 1-ethynylnaphthalene, which was used without further purification.

Step II: 1-Ethynylnaphthalene was treated with benzoyl chloride according to the *General Procedure J (Method B)*. The title compound was obtained as an off-white solid in 73% yield (1.665 g, 6.50 mmol). Data in agreement with the reported literature values.[264] **IR** (neat) ν_{max} (cm^{-1}) 3060, 2186, 1636; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.42 (1 H, dq, *J* 8.4, 1.0), 8.35 – 8.28 (2 H, m), 7.97 (1 H, d, *J* 8.2), 7.95 (1 H, dd, *J* 7.2, 1.2), 7.90 (1 H, dt, *J* 8.2, 0.6), 7.69 – 7.62 (2 H, m), 7.60 – 7.48 (4 H, m). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 178.0, 137.1, 134.2, 133.7, 133.2, 133.1, 131.5, 129.7, 128.8, 128.6, 127.8, 127.0, 125.9, 125.2, 117.8, 91.7, 91.5. **HRMS** (ES^+) calc. 257.0966 [$C_{19}H_{13}O$], obs. 257.0970.

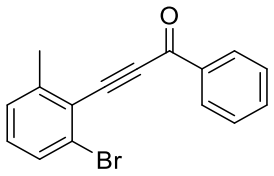
3-(2-Methylnaphthalen-1-yl)-1-phenylprop-2-yn-1-one 249



Prepared from 1-ethynyl-2-methylnaphthalene **132**, following the *General Procedure J (Method A)*, on a 2.78 mmol scale. The title compound was obtained as a yellow powder in 96% yield (0.719 g, 2.66 mmol); **m.p.** 80 – 81 °C. **IR** (neat) ν_{max} (cm^{-1}) 3056, 2921, 2854, 2177, 1633. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.39 (1 H, d, *J* 8.3), 8.34 – 8.29 (2 H, m), 7.83 (2 H, dd, *J* 8.1, 4.9), 7.68 – 7.56 (1 H, m), 7.58 – 7.45 (2 H, m), 7.38 (1 H, dd, *J* 8.4, 1.8), 2.77 (1 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.1, 142.8, 137.3, 134.1, 131.5, 130.9, 130.6, 129.6, 128.8,

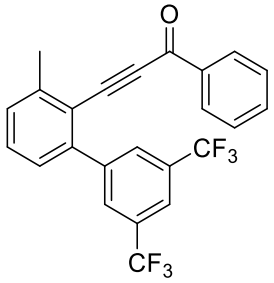
128.4, 128.0, 127.8, 126.1, 125.6, 116.3, 96.2, 90.5, 21.7. **MS** (ES^+) *m/z* 271.1 $[M+H]^+$; **HRMS** (ES^+) calc. 271.1123 [$C_{20}H_{15}O$], obs. 271.1125.

3-(2-Bromo-6-methylphenyl)-1-phenylprop-2-yn-1-one 204



Prepared from 1-bromo-2-ethynyl-3-methylbenzene **200**, following the *General Procedure J (Method A)*, on a 3.28 mmol scale. The title compound was obtained as a white powder in 96% yield (0.940 g, 3.14 mmol); **m.p.** 100 – 101 °C. **IR** (neat) ν_{max} (cm^{-1}) 3058, 2972, 2194, 1636. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.33 (2 H, dd, *J* 8.4, 1.3), 7.64 (1 H, t, *J* 7.4), 7.57 – 7.46 (3 H, m), 7.25 – 7.16 (2 H, m), 2.60 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.8, 145.1, 137.0, 134.2, 131.3, 130.1, 129.9, 128.7, 128.6, 127.2, 122.5, 94.5, 89.6, 21.7. **MS** (ES^+) *m/z* 299.0 $[M+H]^+$, 301.0 $[(M+H)+2]^+$; **HRMS** (ES^+) calc. 299.0072 [$C_{16}H_{12}OBr$], obs. 299.0078.

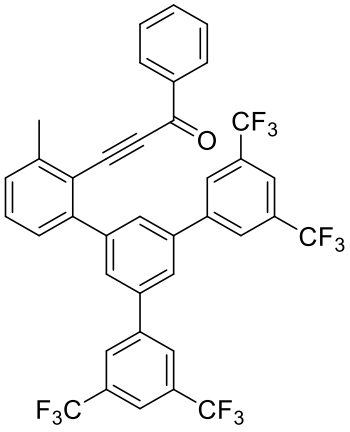
3-(3-Methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-1-phenylprop-2-yn-1-one 203a



Prepared from 2-ethynyl-3-methyl-3',5'-bis(trifluoromethyl)-1,1'-biphenyl **202a**, following the *General Procedure J (Method B)*, on a 2.73 mmol scale. The title compound was obtained as a yellow powder in 80% yield (0.949 g, 2.19 mmol); **m.p.** 98 – 100 °C. **IR** (neat) ν_{max} (cm^{-1}) 3061, 2928, 2190, 1635. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.04 (2 H, s), 7.91 (1 H, s), 7.73 (2 H,

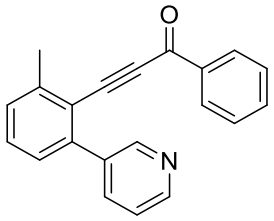
dd, *J* 8.4, 1.3), 7.61 – 7.48 (2 H, m), 7.47 (1 H, d, *J* 7.6), 7.40 (1 H, d, *J* 7.7), 7.36 – 7.27 (3 H, m), 2.68 (3 H, s). **^{19}F NMR** (282 MHz, $CDCl_3$) -62.80. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.4, 144.1, 143.1, 142.4, 136.6, 134.0, 131.7 (q, $^{2}J_{CF}$ 33.4), 130.7, 130.1, 129.6 (q, $^{3}J_{CF}$ 3.6), 129.2, 128.5, 127.0, 123.2 (q, $^{1}J_{CF}$ 273.3), 121.6 (hept, $^{3}J_{CF}$ 3.8), 119.0, 94.8, 89.6, 21.4. **MS** (ES^+) *m/z* 433.1 $[M+H]^+$; **HRMS** (ES^+) calc. 433.1027 $[C_{24}H_{15}OF_6]$, obs. 433.1022.

3-(5'-(3,5-Bis(trifluoromethyl)phenyl)-3-methyl-3'',5''-bis(trifluoromethyl)-[1,1':3',1''-terphenyl]-2-yl)-1-phenylprop-2-yn-1-one 203c



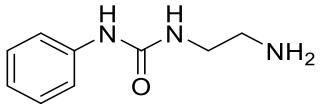
Prepared from alkyne **202c**, following the *General Procedure J (Method B)*, on a 0.30 mmol scale. The title compound was obtained as a white powder in 80% yield (0.173 g, 0.24 mmol); **m.p.** 161 – 163 °C. **IR** (neat) ν_{max} (cm^{-1}) 3065, 2927, 2190, 1639. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (4 H, s), 7.90 (2 H, s), 7.86 (1 H, d, *J* 1.7), 7.83 (1 H, d, *J* 1.3), 7.81 (1 H, d, *J* 1.4), 7.77 (1 H, t, *J* 1.8), 7.57 – 7.43 (3 H, m), 7.41 (1 H, d, *J* 3.1), 7.39 (1 H, d, *J* 3.3), 7.24 (1 H, d, *J* 7.4), 7.22 (1 H, d, *J* 7.4), 2.72 (3 H, s). **^{19}F NMR** (282 MHz, $CDCl_3$) -62.74. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.4, 145.0, 143.9, 142.7, 142.4, 139.8, 136.8, 133.9, 132.4 (q, $^{2}J_{CF}$ 33.4), 130.8, 129.6, 129.3, 128.9, 128.4, 127.6 (q, $^{3}J_{CF}$ 4.5), 127.2, 125.6, 123.2 (q, $^{1}J_{CF}$ 273.0), 121.6 (app h, $^{3}J_{CF}$ 3.6), 118.9, 94.6, 90.7, 21.5. **MS** (ES^+) *m/z* 721.1 $[M+H]^+$; **HRMS** (ES^+) calc. 721.1401 $[C_{38}H_{21}OF_{12}]$, obs. 721.1407.

3-(2-Methyl-6-(pyridin-3-yl)phenyl)-1-phenylprop-2-yn-1-one 203b



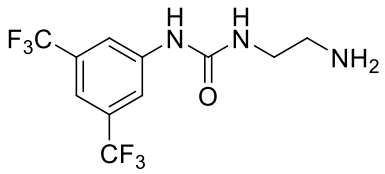
Prepared from 3-(2-ethynyl-3-methylphenyl)pyridine **202b**, following the *General Procedure J (Method A)*, on a 4.08 mmol scale. The title compound was obtained as a white powder in 88% yield (1.073 g, 3.61 mmol); **m.p.** 126 – 128 °C. **IR** (neat) ν_{max} (cm^{-1}) 3059, 2973, 2186, 1633. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.83 (1 H, s), 8.70 (1 H, s), 7.94 (1 H, dt, *J* 8.1, 1.5), 7.77 (2 H, dd, *J* 8.3, 1.3), 7.55 (1 H, ddt, *J* 8.7, 7.1, 1.3), 7.46 (1 H, app t, *J* 7.7), 7.43 – 7.32 (4 H, m), 7.28 (1 H, d, *J* 7.9), 2.67 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.6, 149.8, 148.9, 144.0, 142.6, 136.9, 136.7, 134.0, 130.6, 129.6, 129.4, 128.5, 127.1, 126.3, 123.1, 119.2, 94.4, 90.4, 21.4. **MS** (ES^+) *m/z* 298.1 $[M+H]^+$; **HRMS** (ES^+) calc. 298.1232 [$C_{21}H_{16}NO$], obs. 298.1240.

1-(2-Aminoethyl)-3-phenylurea 186a



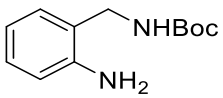
Prepared from phenyl isocyanate and *N*-Boc-ethylenediamine, following *General Procedure K* (step I) and *General Procedure L (*step II), on a 1.59 mmol scale. The title compound was obtained as a white powder in 93% yield over two steps (0.265 g, 1.48 mmol). **m.p.** 153 – 155 °C. **IR** (neat) ν_{max} (cm^{-1}) 3321, 2933, 2100, 1650, 1557. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36 – 7.25 (4 H, m), 7.10 (1 H, tt, *J* 7.1, 1.9), 6.98 (1 H, br s), 5.47 (1 H, t, *J* 5.4), 3.50 – 3.34 (4 H, m). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.0, 138.2, 129.4, 124.2, 121.4, 51.5, 39.7. **MS** (ES^+) *m/z* 180.1 $[M+H]^+$; **HRMS** (ES^+) calc. 180.1137 [$C_9H_{14}N_3O$], obs. 180.1140.

1-(2-Aminoethyl)-3-(3,5-bis(trifluoromethyl)phenyl)urea 186b



Prepared from 3,5-bis(trifluoromethyl)phenyl isocyanate and *N*-Boc-ethylenediamine, following *General Procedure K* (step I) and *General Procedure L (*step II), on a 2.40 mmol scale. The title compound was obtained as a white powder in 96% yield over two steps (0.726 g, 2.30 mmol). **m.p.** 165 – 167 °C. **IR** (neat) ν_{max} (cm^{-1}) 3330, 3068, 1673, 1571. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.98 (1 H, br s), 7.82 (2 H, s), 7.39 (1 H, s), 6.26 (1 H, t, *J* 5.7), 3.31 (2 H, app q, *J* 5.2), 2.86 (2 H, t, *J* 5.6), 2.55 (2 H, br s). **^{19}F NMR** (377 MHz, $CDCl_3$) -63.29. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.4, 141.2, 131.9 (q, $^{2}J_{CF}$ 33.1), 123.2 (q, $^{1}J_{CF}$ 272.6), 118.1 (q, $^{3}J_{CF}$ 3.7), 115.2 (hept, $^{3}J_{CF}$ 3.4), 42.4, 41.8. **MS** ($ASAP^+$) *m/z* 316.1 $[M+H]^+$; **HRMS** ($ASAP^+$) calc. 316.0885 [$C_{11}H_{12}N_3OF_6$], obs. 316.0891.

***tert*-Butyl (2-aminobenzyl)carbamate 250**

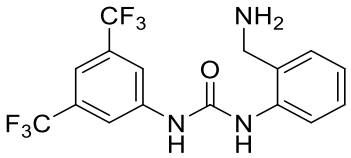


A solution of 2-(aminomethyl)aniline (1.000 g, 8.18 mmol) in dichloromethane (14 mL) was added dropwise to a solution of di-*tert*-butyl dicarbonate (1.780 g, 8.18 mmol) in dichloromethane (14 mL), under a stream of argon. The resulting solution was stirred for 12 hours, at which point the solvent was removed under reduced pressure to afford a crude residue that was purified by recrystallisation (DCM/Hx).

The title compound was obtained as colourless crystals in quantitative yield (1.812 g, 8.15 mmol). Data in agreement with the reported literature values.[265] **IR** (neat) ν_{max} (cm^{-1}) 3420, 3357, 2976, 2937, 2891, 1669, 1498. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.10 (1 H, td, *J* 7.8, 1.6),

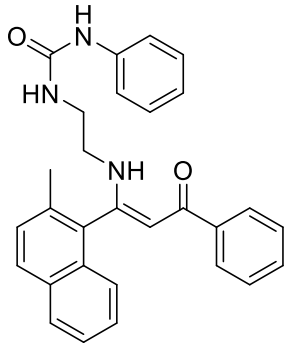
7.02 (1 H, dd, *J* 7.9, 1.6), 6.73 – 6.61 (2 H, m), 4.78 (1 H, br s), 4.24 (2 H, d, *J* 6.2), 4.22 (2 H, br s), 1.45 (9 H, s). **HRMS** (ES^+) calc. 223.1447 [$C_{12}H_{19}N_2O$], obs. 223.1451.

1-(2-(Aminomethyl)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl)urea 192



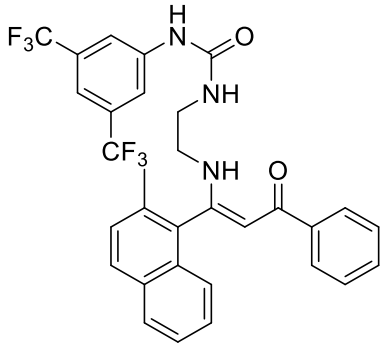
Prepared from 3,5-bis(trifluoromethyl)phenyl isocyanate and *tert*-Butyl (2-aminobenzyl)carbamate **250**, following *General Procedure K* (step I) and *General Procedure L (*step II), on a 3.28 mmol scale. The title compound was obtained as a white powder in 82% yield over two steps (1.015 g, 2.69 mmol). **m.p.** 83 – 86 °C. **IR** (neat) ν_{max} (cm^{-1}) 3297, 3110, 1665, 1572, 1540, 1386. **^{1}H NMR** (300 MHz, MeOD): δ 8.10 (2 H, s), 7.66 (1 H, dd, *J* 8.0, 1.3), 7.53 (1 H, s), 7.33 (1 H, dd, *J* 7.5, 1.6), 7.27 (2 H, td, *J* 7.7, 1.7), 7.13 (1 H, td, *J* 7.5, 1.3), 3.87 (2 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -63.00. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.5, 143.3, 137.7, 135.4, 133.2 (q, $^2J_{CF}$ 33.1), 130.0, 128.79, 125.9, 125.1, 124.9 (q, $^1J_{CF}$ 271.9), 119.4 (q, $^3J_{CF}$ 4.5), 115.8 (hept, $^3J_{CF}$ 3.7), 44.1. **MS** (ES^+) *m/z* 378.1 $[M+H]^+$; **HRMS** (ES^+) calc. 378.1041 [$C_{16}H_{14}N_3OF_6$], obs. 378.1049.

(*Z*)-1-(2-((1-(2-Methylnaphthalen-1-yl)-3-oxo-3-phenylprop-1-en-1-yl)amino)ethyl)-3-phenylurea 188a



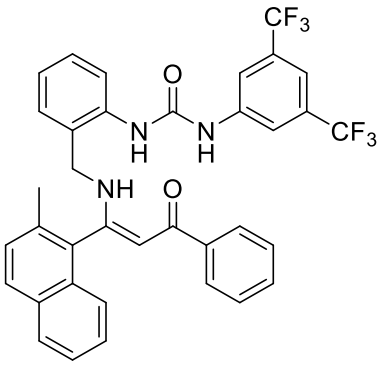
Prepared from ynone **187** and 1-(2-aminoethyl)-3-phenylurea **186a**, following the *General Procedure M*, on a 0.99 mmol scale. The title compound was obtained as a white powder in 91% yield (0.530 g, 0.90 mmol). **m.p.** 42 – 45 °C. **IR** (neat) ν_{max} (cm^{-1}) 3325, 3056, 2924, 2863, 1653, 1547. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.83 (1 H, t, *J* 6.0), 7.86 – 7.76 (5 H, m), 7.46 – 7.39 (3 H, m), 7.38 – 7.30 (4 H, m), 7.24 – 7.16 (4 H, m), 6.98 (1 H, tt, *J* 7.0, 1.5), 5.81 (1 H, s), 5.76 (1 H, t, *J* 5.8), 3.29 – 3.16 (1 H, m), 3.16 – 3.07 (1 H, m), 3.04 (1 H, t, *J* 7.3), 2.98 (1 H, dtd, *J* 13.3, 6.1, 4.3), 2.42 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 188.8, 165.6, 155.9, 140.0, 138.8, 132.8, 131.7, 130.9, 130.6, 130.4, 129.1, 129.0, 128.4, 128.3, 128.2, 127.2, 127.1, 125.6, 124.6, 123.1, 120.2, 94.0, 44.4, 40.3, 19.8. **MS** (ES^+) *m/z* 450.2 $[M+H]^+$; **HRMS** (ES^+) calc. 450.2182 [$C_{29}H_{28}N_3O_2$], obs. 450.2195.

(*Z*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(2-((1-(2-methylnaphthalen-1-yl)-3-oxo-3-phenylprop-1-en-1-yl)amino)ethyl)urea 188b



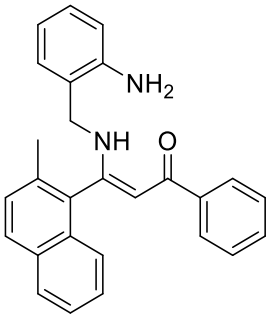
Prepared from ynone **187** and 1-(2-aminoethyl)-3-(3,5-bis(trifluoromethyl)phenyl)urea **186b**, following the *General Procedure M*, on a 0.63 mmol scale. The title compound was obtained as a pale yellow powder in 60% yield (0.220 g, 0.38 mmol). **m.p.** 68 – 71 °C. **IR** (neat) ν_{max} (cm^{-1}) 3367, 3057, 1709, 1668, 1568. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 12.03 (1 H, t, *J* 5.6), 8.34 (1 H, s), 7.84 – 7.74 (3 H, m), 7.69 (2 H, d, *J* 7.0), 7.57 (2 H, s), 7.42 – 7.36 (2 H, m), 7.34 (1 H, d, *J* 8.6), 7.29 (1 H, d, *J* 7.3), 7.27 – 7.20 (3 H, m), 6.57 (1 H, t, *J* 5.3), 5.80 (1 H, s), 3.37 – 3.13 (3 H, m), 3.15 – 2.97 (1 H, m), 2.42 (3 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -63.06. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 188.6, 165.9, 154.1, 139.7, 138.9, 131.8, 130.7, 130.7 (q, $^{2}J_{CF}$ 33.1), 130.3, 129.4, 128.9, 128.4, 127.5, 127.4, 127.3, 126.4, 125.9, 124.8, 123.3, 122.2 (q, $^{1}J_{CF}$ 272.7), 116.4 (q, $^{3}J_{CF}$ 3.5), 114.1 (hept, $^{3}J_{CF}$ 3.3), 93.7, 42.9, 39.3, 18.7. **MS** (ES^+) *m/z* 586.2 $[M+H]^+$; **HRMS** (ES^+) calc. 586.1929 [$C_{31}H_{26}N_3O_2F_6$], obs. 586.1927.

(*Z*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(2-(((1-(2-methylnaphthalen-1-yl)-3-oxo-3-phenylprop-1-en-1-yl)amino)methyl)phenyl)urea 193



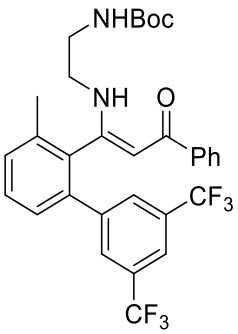
Prepared from ynone **187** and amino urea **192**, following the *General Procedure M*, on a 2.15 mmol scale. The title compound was obtained as colourless crystals in 49% yield (0.689 g, 1.06 mmol). **m.p.** 239 – 240 °C. **IR** (neat) ν_{max} (cm^{-1}) 3282, 3113, 3052, 1677, 1555, 1525. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.03 (2 H, s), 7.86 (2 H, d, *J* 8.3), 7.81 (2 H, dd, *J* 8.3, 1.4), 7.67 (1 H, d, *J* 8.4), 7.50 (1 H, s), 7.49 – 7.32 (7 H, m), 7.24 (1 H, td, *J* 7.7, 1.5), 6.88 (1 H, td, *J* 7.5, 1.2), 6.24 (1 H, d, *J* 7.6), 5.80 (1 H, s), 4.18 (1 H, d, *J* 14.7), 4.09 (1 H, d, *J* 14.7), 2.62 (1 H, br s), 2.20 (3 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -63.12. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 189.0, 166.0, 153.5, 141.1, 139.7, 135.6, 133.4, 132.4, 132.0 (q, $^{2}J_{CF}$ 33.2), 131.6, 131.3, 130.4, 130.1, 129.9, 129.3, 128.9, 128.4, 128.1, 127.2, 126.9, 126.6, 126.0, 125.7, 124.5, 123.3 (q, $^{1}J_{CF}$ 273.0), 118.2 (q, $^{3}J_{CF}$ 3.4), 115.3 (hept, $^{3}J_{CF}$ 4.0), 94.3, 46.2, 19.6. **MS** (ES^+) *m/z* 648.2 $[M+H]^+$; **HRMS** (ES^+) calc. 648.2086 [$C_{36}H_{28}N_3O_2F_6$], obs. 648.2093.

(*Z*)-3-((2-Aminobenzyl)amino)-3-(2-methylnaphthalen-1-yl)-1-phenylprop-2-en-1-one 194



Prepared from ynone **187** and 2-(aminomethyl)aniline, following the *General Procedure M*, on a 2.11 mmol scale. The title compound was obtained as a yellow foam in 87% yield (0.717 g, 1.83 mmol). **m.p.** 57 – 60 °C. **IR** (neat) ν_{max} (cm^{-1}) 3448, 3352, 3052, 2921, 1621, 1553, 1539. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.86 (1 H, t, *J* 4.5), 7.93 – 7.82 (5 H, m), 7.48 (1 H, d, *J* 9.7), 7.48 (1 H, dd, *J* 3.1, 1.4), 7.44 – 7.33 (4 H, m), 7.04 (1 H, td, *J* 7.7, 1.6), 6.74 (1 H, dd, *J* 8.0, 1.6), 6.62 (1 H, td, *J* 7.5, 7.1, 1.2), 6.61 (1 H, d, *J* 7.7), 5.87 (1 H, s), 3.99 (1 H, dd, *J* 14.8, 5.7), 3.95 (1 H, dd, *J* 14.8, 5.7), 3.60 (2 H, br s), 2.41 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 188.8, 164.6, 144.4, 140.0, 133.3, 131.7, 130.9, 130.8, 130.7, 129.7, 129.0, 128.9, 128.5, 128.2, 128.1, 127.2, 127.2, 125.7, 124.8, 121.7, 118.9, 116.3, 94.0, 45.3, 19.9. **MS** (ES^+) *m/z* 393.2 $[M+H]^+$; **HRMS** (ES^+) calc. 393.1967 [$C_{27}H_{25}N_2O$], obs. 393.1961.

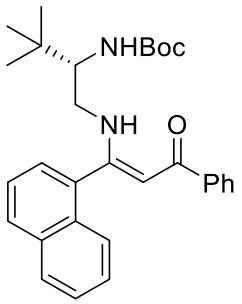
tert-Butyl (*Z*)-(2-((1-(3-methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-3-oxo-3-phenylprop-1-en-1-yl)amino)ethyl)carbamate 240



Prepared from ynone **203a** and *N*-Boc-ethylenediamine, following the *General Procedure M*, on a 1.29 mmol scale. The title compound was obtained as yellow foam in 84% yield (0.642 g,

1.07 mmol). **m.p.** 96 – 98 °C. **IR** (neat) ν_{max} (cm^{-1}) 3322, 2979, 2932, 2869, 1710, 1278. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.28 (1 H, t, *J* 5.9), 7.92 (2 H, s), 7.81 (1 H, s), 7.77 (2 H, dt, *J* 6.6, 1.4), 7.47 – 7.41 (2 H, m), 7.41 – 7.36 (3 H, m), 7.26 (1 H, dd, *J* 7.7, 1.2), 5.75 (1 H, s), 4.81 (1 H, t, *J* 6.0), 3.26 – 3.16 (1 H, m), 3.11 – 2.92 (2 H, m), 2.81 (1 H, dt, *J* 13.3, 5.1), 2.42 (3 H, s), 1.40 (9 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -62.85. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 188.5, 163.5, 155.6, 142.3, 140.0, 137.3, 136.4, 133.2, 131.4 (q, $^2J_{CF}$ 33.8), 131.0, 130.9, 129.5, 129.1 (q, $^3J_{CF}$ 2.6), 128.3, 127.4, 126.9, 123.2 (q, $^1J_{CF}$ 272.8), 121.3 (hept, $^3J_{CF}$ 3.5), 95.3, 79.7, 44.5, 40.6, 28.3, 19.9. **MS** (ES^+) *m/z* 593.2 $[M+H]^+$; **HRMS** (ES^+) calc. 593.2239 [$C_{31}H_{31}N_2O_3F_6$], obs. 593.2252.

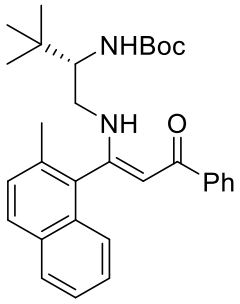
***tert*-Butyl (*S,Z*)-(3,3-dimethyl-1-((1-(naphthalen-1-yl)-3-oxo-3-phenylprop-1-en-1-yl)amino)butan-2-yl)carbamate 217a** *(mixture of diastereoisomers)*



Prepared from ynone **248** and *tert*-butyl (*S*)-(1-amino-3,3-dimethylbutan-2-yl)carbamate **216**, following the *General Procedure M*, on a 1.87 mmol scale. The title compound was isolated as an inseparable mixture of diastereoisomers (d.r. 1:1), as a yellow foam in 76% yield (0.676 g, 1.43 mmol). **R_f** = 0.48 (30% EtOAc/Hx); **IR** (neat) ν_{max} (cm^{-1}) 3252, 3135, 2960, 1700, 1574. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.73 – 11.58 (2 H, m), 8.11 – 8.04 (1 H, m), 8.03 – 7.96 (1 H, m), 7.95 – 7.80 (8 H, m), 7.69 (1 H, dd, *J* 7.0, 1.3), 7.62 – 7.46 (7 H, m), 7.43 – 7.30 (6 H, m), 5.88 (1 H, s), 5.86 (1 H, s), 4.45 (1 H, d, *J* 10.7), 4.42 (1 H, d, *J* 10.3), 3.52 (1 H, app td, *J* 10.5, 10.0, 3.4), 3.45 (1 H, app td, *J* 10.5, 9.8, 3.7), 3.22 (1 H, ddd, *J* 13.8, 6.7, 3.6), 3.09 (1 H, ddd,

J 14.0, 8.4, 3.8), 2.79 (2 H, app dddd, *J* 16.2, 13.9, 9.9, 5.6), 1.49 (9 H, s), 1.45 (9 H, s), 0.61 (9 H, s), 0.60 (9 H, s).. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 188.43, 188.38, 165.5, 165.0, 156.1, 155.9, 140.31, 140.28, 133.3, 133.21, 133.16, 132.9, 130.6, 130.5, 130.3, 129.5, 129.4, 128.5, 128.3, 128.1, 127.4, 127.1, 126.6, 126.5, 126.4, 126.2, 125.7, 125.5, 125.3, 125.1, 125.0, 94.7, 94.4, 79.51, 79.45, 59.4, 59.1, 45.1, 44.7, 33.8, 33.7, 28.5, 28.4, 26.2, 26.1 (45 of the 48 total expected signals are observed). **MS** (AP^+) *m/z* 473.3 $[M+H]^+$; **HRMS** (AP^+) calc. 473.2804 [$C_{30}H_{37}N_2O_3$], obs. 473.2792.

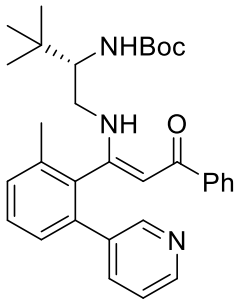
***tert*-Butyl (*S,Z*)-(3,3-dimethyl-1-((1-(2-methylnaphthalen-1-yl)-3-oxo-3-phenylprop-1-en-1-yl)amino)butan-2-yl)carbamate 217b** *(mixture of diastereoisomers)*



Prepared from ynone **249** and *tert*-butyl (*S*)-(1-amino-3,3-dimethylbutan-2-yl)carbamate **216**, following the *General Procedure M*, on a 0.91 mmol scale. The title compound was isolated as an inseparable mixture of diastereoisomers (d.r. 1:1), as a yellow foam in 81% yield (0.360 g, 0.74 mmol). $\mathbf{R_f}$ = 0.48 (30% EtOAc/Hx);. **IR** (neat) ν_{max} (cm^{-1}) 3320, 3056, 2965, 1699, 1574. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.83 (1 H, br s), 11.78 (1 H, br s), 7.98 (1 H, d, *J* 8.4), 7.88 – 7.85 (5 H, m), 7.82 (4 H, dt, *J* 8.3, 2.8), 7.56 (1 H, ddd, *J* 8.4, 6.8, 1.4), 7.51 – 7.44 (3 H, m), 7.42 – 7.34 (8 H, m), 5.79 (1 H, s), 5.78 (1 H, s), 4.43 (1 H, d, *J* 10.5), 4.38 (1 H, d, *J* 10.5), 3.53 (1 H, td, *J* 10.2, 3.6), 3.44 (1 H, td, *J* 10.0, 3.4), 3.11 (1 H, ddd, *J* 13.8, 7.1, 3.6), 3.04 (1 H, ddd, *J* 13.8, 8.2, 3.4), 2.80 (1 H, ddd, *J* 13.9, 9.5, 4.4), 2.72 (1 H, ddd, *J* 13.8, 9.9, 5.5), 2.54 (3 H, s), 2.47 (3 H, s), 1.49 (9 H, s), 1.48 (9 H, s), 0.65 (9 H, s), 0.57 (9 H, s). **^{13}C NMR** (101

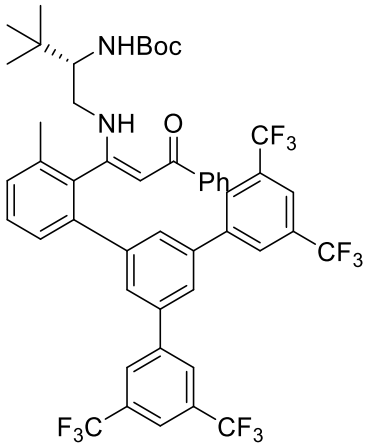
MHz, $CDCl_3$) δ 188.3, 188.2, 164.34, 164.29, 156.0, 155.8, 140.3, 133.4, 132.7, 131.7, 131.6, 130.9, 130.8, 130.7, 130.6, 128.9, 128.8, 128.6, 128.2, 128.1, 127.8, 127.2, 127.14, 127.06, 125.7, 125.6, 125.5, 124.9, 93.7, 93.6, 79.53, 79.46, 59.1, 58.7, 44.8, 44.6, 34.0, 28.4, 26.2, 26.1, 20.2, 19.9 (42 of the 50 total expected signals are observed). **MS** (ES^+) *m/z* 487.3 $[M+H]^+$; **HRMS** (ES^+) calc. 487.2961 [$C_{31}H_{39}N_2O_3$], obs. 487.2972.

***tert*-Butyl (*S,Z*)-(3,3-dimethyl-1-((1-(2-methyl-6-(pyridin-3-yl)phenyl)-3-oxo-3-phenylprop-1-en-1-yl)amino)butan-2-yl)carbamate 217d** *(mixture of diastereoisomers)*



Prepared from ynone **203b** and *tert*-butyl (*S*)-(1-amino-3,3-dimethylbutan-2-yl)carbamate **216**, following the *General Procedure M*, on a 0.49 mmol scale. The title compound was isolated as an inseparable mixture of diastereoisomers (d.r. 1:2.3), as a pale yellow foam in 79% yield (0.193 g, 0.39 mmol). $\mathbf{R_f}$ = 0.11 (30% EtOAc/Hx); **IR** (neat) ν_{max} (cm^{-1}) 3282, 2966, 2875, 1702, 1574. *Only the NMR data for the major diastereomer is reported.* **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.44 (1 H, t, *J* 3.8), 8.63 (1 H, d, *J* 2.3), 8.54 (1 H, dd, *J* 4.8, 1.6), 7.85 – 7.82 (2 H, m), 7.43 – 7.36 (6 H, m), 7.26 – 7.22 (2 H, m), 5.82 (1 H, s), 4.24 (1 H, d, *J* 10.5), 3.38 (1 H, app td, *J* 10.1, 3.4), 3.04 (1 H, ddd, *J* 13.7, 8.5, 3.6), 2.49 (3 H, s), 2.55 – 2.46 (1 H, m), 1.44 (9 H, s), 0.72 (9 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 187.2, 163.4, 155.8, 149.4, 148.8, 140.2, 136.7, 136.5, 136.2, 136.1, 136.0, 133.4, 130.6, 129.3, 128.2, 127.5, 127.1, 123.0, 94.9, 79.5, 58.7, 44.3, 34.0, 28.4, 26.2, 20.4. **MS** (ES^+) *m/z* 514.3 $[M+H]^+$; **HRMS** (ES^+) calc. 514.3070 [$C_{32}H_{40}N_3O_3$], obs. 514.3082.

***tert*-Butyl (*S*,*Z*)-(1-((1-(5'-(3,5-bis(trifluoromethyl)phenyl)-3-methyl-3'',5''-bis(trifluoromethyl)-[1,1':3',1''-terphenyl]-2-yl)-3-oxo-3-phenylprop-1-en-1-yl)amino)-3,3-dimethylbutan-2-yl)carbamate 217e/217e'**

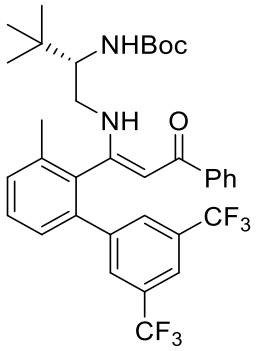


Prepared from ynone **203c** and *tert*-butyl (*S*)-(1-amino-3,3-dimethylbutan-2-yl)carbamate **216**, following the *General Procedure M*, on a 0.80 mmol scale. Two diastereomerically enriched fractions (**217e** and **217e'**) of the title compound were isolated in 54% overall yield.

<u>*Fraction 1*</u> (**217e**) Isolated as a khaki green foam in 23% yield (0.174 g, 0.19 mmol, d.r. 1:4.0). **R_f** = 0.71 (30% EtOAc/Hx); **IR** (neat) ν_{max} (cm^{-1}) 2968, 1702, 1575, 1366, 1276. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.50 (1 H, t, *J* 3.5), 7.98 (4 H, s), 7.87 (2 H, s), 7.75 (2 H, s), 7.69 (1 H, s), 7.47 (1 H, app t, *J* 7.6), 7.41 (2 H, d, *J* 6.7), 7.37 (2 H, d, *J* 7.2), 7.31 (3 H, app q, *J* 7.0), 5.88 (1 H, s), 4.22 (1 H, d, *J* 10.4), 3.44 (1 H, td, *J* 9.8, 3.7), 3.18 (1 H, ddd, *J* 12.8, 8.4, 3.8), 2.64 (1 H, ddd, *J* 12.9, 9.4, 3.5), 2.52 (3 H, s), 1.39 (9 H, s), 0.71 (9 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -62.83. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 187.6, 163.6, 155.8, 142.8, 142.4, 139.9, 139.5, 138.8, 136.7, 133.3, 132.4 (q, $^2J_{CF}$ 33.6), 130.7, 129.4, 128.4, 128.1, 127.4 (q, $^3J_{CF}$ 3.0), 127.4, 126.9, 126.8, 125.4, 123.2 (q, $^1J_{CF}$ 272.9), 121.6 (hept, $^3J_{CF}$ 3.7), 95.0, 79.6, 58.6, 44.4, 34.0, 3.2, 26.2 20.4. **MS** (ES^+) *m/z* 937.3 $[M+H]^+$; **HRMS** (ES^+) calc. 937.3239 [$C_{49}H_{45}N_2O_3F_{12}$], obs. 937.3265.

Fraction 2 (**217e'**) Isolated as a light brown foam in 31% yield (0.234 g, 0.25 mmol, d.r. 1:5.5). **R_f** = 0.66 (30% EtOAc/Hx); **IR** (neat) ν_{max} (cm^{-1}) 2968, 1702, 1575, 1366, 1276. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.46 (1 H, t, *J* 5.9), 7.99 (4 H, s), 7.83 (2 H, s), 7.76 (2 H, s), 7.71 (1 H, s), 7.52 – 7.44 (1 H, m), 7.44 – 7.34 (4 H, m), 7.35 – 7.27 (3 H, m), 5.91 (1 H, s), 4.21 (1 H, d, *J* 10.3), 3.08 (1 H, td, *J* 10.4, 3.8), 3.01 – 2.90 (1 H, m), 2.70 (1 H, ddd, *J* 13.8, 10.4, 4.9), 2.44 (3 H, s), 1.35 (9 H, s), 0.62 (9 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -62.81. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 188.0, 162.7, 155.8, 142.4, 140.3, 137.2, 136.8, 133.4, 133.3, 131.4 (q, $^2J_{CF}$ 33.2), 131.1, 131.0, 130.6, 129.4, 129.2 (q, $^3J_{CF}$ 2.7), 129.1, 128.1, 127.3, 127.1, 126.9, 121.8 (q, $^1J_{CF}$ 273.0), 121.2 (hept, $^3J_{CF}$ 3.6), 95.3, 79.6, 58.5, 44.3, 34.0, 28.3, 26.2, 20.3. **MS** (ES^+) *m/z* 937.3 $[M+H]^+$; **HRMS** (ES^+) calc. 937.3239 [$C_{49}H_{45}N_2O_3F_{12}$], obs. 937.3265.

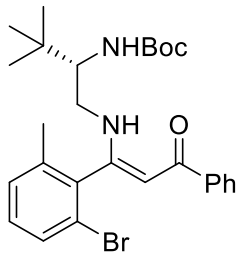
tert*-Butyl (*S,Z*)-(3,3-dimethyl-1-((1-(3-methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-3-oxo-3-phenylprop-1-en-1-yl)amino)butan-2-yl)carbamate 217c** ***(*single diastereoisomer and single enantiomer)*



Prepared from ynone **203a** and *tert*-butyl (*S*)-(1-amino-3,3-dimethylbutan-2-yl)carbamate **216**, following the *General Procedure M*, on a 1.07 mmol scale. A single diastereoisomer (and single enantiomer) of the title compound was isolated as a pale yellow foam in 60% yield (0.417 g, 0.64 mmol). **m.p.** 63 – 65 °C. **IR** (neat) ν_{max} (cm^{-1}) 3064, 2967, 2875, 1702, 1575, 1276. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.30 (1 H, dd, *J* 9.3, 3.3), 7.92 (2 H, s), 7.81 (1 H, s), 7.78 (2 H,

dt, *J* 6.6, 1.6), 7.50 – 7.32 (6 H, m), 7.24 (1 H, dd, *J* 7.2, 1.4), 5.79 (1 H, s), 4.32 (1 H, d, *J* 10.4), 3.38 (1 H, td, *J* 9.9, 3.8), 2.99 (1 H, ddd, *J* 13.1, 8.8, 3.8), 2.49 (3 H, s), 1.43 (9 H, s), 0.72 (9 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -62.91. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 188.0, 162.7, 155.8, 142.4, 140.3, 137.2, 136.8, 133.2, 131.4 (q, $^2J_{CF}$ 33.3), 131.1, 130.6, 129.4, 129.2 (q, $^3J_{CF}$ 2.9), 128.1, 127.1, 126.9, 123.2 (q, $^1J_{CF}$ 272.3), 121.3 (hept, $^3J_{CF}$ 3.5), 95.3, 79.6, 58.5, 44.3, 34.0, 28.3, 26.2, 20.3. **MS** (ES^+) *m/z* 649.3 $[M+H]^+$; **HRMS** (ES^+) calc. 649.2865 [$C_{35}H_{39}N_2O_3F_6$], obs. 649.2889. **$[\alpha]_D$** = -38.50° (*c* = 0.5, $CHCl_3$)

(-)-*tert*-Butyl (*S,Z*)-(1-((1-(2-bromo-6-methylphenyl)-3-oxo-3-phenylprop-1-en-1-yl)amino)-3,3-dimethylbutan-2-yl)carbamate 217f/217f'



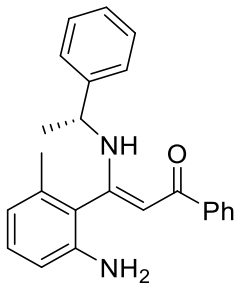
Prepared from ynone **204** and *tert*-butyl (*S*)-(1-amino-3,3-dimethylbutan-2-yl)carbamate **216**, following the *General Procedure M*, on a 1.85 mmol scale. The two single diastereoisomers (**217f** and **217f'**, both single enantiomers) were isolated in 88% overall yield.

<u>*Fraction 1*</u> (**217f**) Isolated as a white foam in 43% yield (0.408 g, 0.79 mmol). **R_f** = 0.61 (30% EtOAc/Hx); **m.p.** 153 – 155 °C. **IR** (neat) ν_{max} (cm^{-1}) 3293, 2964, 2875, 1699, 1576. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.56 (1 H, t, *J* 5.9), 7.87 (2 H, dt, *J* 6.5, 1.4), 7.47 (1 H, d, *J* 7.7), 7.42 – 7.32 (3 H, m), 7.24 (1 H, d, *J* 7.6), 7.17 (1 H, t, *J* 7.8), 5.66 (1 H, s), 4.77 (1 H, d, *J* 10.5), 3.49 (1 H, td, *J* 10.0, 3.6), 3.17 (1 H, ddd, *J* 13.9, 7.6, 3.7), 2.98 (1 H, ddd, *J* 14.0, 9.7, 4.5), 2.43 (3 H, s), 1.46 (9 H, s), 0.78 (9 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 188.6, 163.8, 156.1, 140.2, 138.4, 135.6, 130.7, 130.1, 130.1, 129.5, 128.1, 127.1, 121.9, 92.4, 79.4, 58.7, 44.4, 34.2, 28.4,

26.3, 20.5. **MS** (ES^+) *m/z* 515.2 $[M+H]^+$, 517.2 $[(M+H)+2]^+$; **HRMS** (ES^+) calc. 515.1909 $[C_{27}H_{36}N_2O_3Br]$, obs. 515.1924. $[\alpha]_D$ = -115.75° (*c* = 0.7, $CHCl_3$)

Fraction 2 (**217f'**) Isolated as a white foam in 45% yield (0.431 g, 0.84 mmol). R_f = 0.52 (30% EtOAc/Hx); **m.p.** 78 – 80 °C. **IR** (neat) ν_{max} (cm^{-1}) 3270, 2965, 2871, 1698, 1576. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.57 (1 H, t, *J* 6.0), 7.87 (2 H, dt, *J* 7.1, 1.5), 7.51 – 7.43 (1 H, m), 7.43 – 7.31 (3 H, m), 7.25 – 7.10 (2 H, m), 5.65 (1 H, s), 4.58 (1 H, d, *J* 10.3), 3.71 (1 H, ddd, *J* 10.3, 8.7, 3.7), 3.22 (1 H, ddd, *J* 13.6, 7.6, 3.7), 2.90 (1 H, ddd, *J* 13.5, 8.7, 4.6), 2.35 (3 H, s), 1.47 (9 H, s), 0.87 (9 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 188.7, 163.7, 155.8, 140.2, 137.9, 135.8, 130.7, 130.3, 130.1, 129.2, 128.1, 127.1, 122.1, 92.4, 79.4, 58.6, 45.0, 34.4, 28.4, 26.5, 20.3. **MS** (ES^+) *m/z* 515.2 $[M+H]^+$, 517.2 $[(M+H)+2]^+$; **HRMS** (ES^+) calc. 515.1909 $[C_{27}H_{36}N_2O_3Br]$, obs. 515.1922. $[\alpha]_D$ = -48.48° (*c* = 0.7, $CHCl_3$)

(*R,Z*)-3-(2-Amino-6-methylphenyl)-1-phenyl-3-((1-phenylethyl)amino)prop-2-en-1-one 238a/238a'



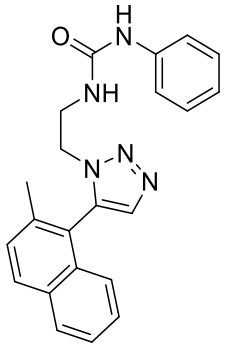
Prepared from ynone **236** and (*R*)-(+)-1-phenylethylamine, following the *General Procedure M*, on a 1.53 mmol scale. The two single diastereoisomers (**238a** and **238a'**, both single enantiomers) were isolated in 68% overall yield.

Fraction 1 (**238a**) Isolated as an orange powder in 52% yield (0.295 g, 0.83 mmol). R_f = 0.55 (20% EtOAc/Hx); **m.p.** 164 – 166 °C. **IR** (neat) ν_{max} (cm^{-1}) 3461, 3361, 2977, 2927, 2173,

1591, 1563. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.95 (1 H, d, *J* 9.1), 7.89 (2 H, dd, *J* 8.1, 1.7), 7.43 – 7.36 (4 H, m), 7.27 – 7.20 (1 H, m), 7.18 – 7.14 (2 H, m), 7.08 (2 H, app t, *J* 7.8), 6.69 (1 H, d, *J* 7.5), 6.44 (1 H, d, *J* 8.0), 5.77 (1 H, s), 4.32 (1 H, dq, *J* 9.2, 6.9), 3.24 (2 H, br s), 2.33 (3 H, s), 1.53 (3 H, d, *J* 6.9). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 188.6, 163.8, 156.1, 140.2, 138.4, 135.6, 130.7, 130.1, 130.1, 129.5, 128.1, 127.1, 121.9, 92.4, 79.4, 58.7, 44.4, 34.2, 28.4, 26.3, 20.5. **MS** (ES^+) *m/z* 357.2 $[M+H]^+$; **HRMS** (ES^+) calc. 357.1967 [$C_{24}H_{25}N_2O$], obs. 357.1977. **$[\alpha]_D$** = -371.75° (*c* = 1.0, $CHCl_3$)

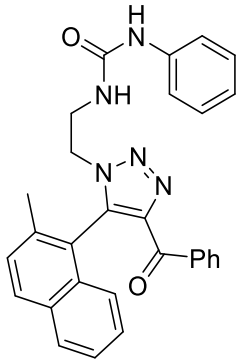
<u>*Fraction 2*</u> (**238a'**) Isolated as an orange powder in 16% yield (0.085 g, 0.24 mmol). **R_f** = 0.45 (20% EtOAc/Hx); **m.p.** 105 – 106 °C. **IR** (neat) ν_{max} (cm^{-1}) 3470, 3351, 3007, 2927, 2173, 1591, 1564. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.95 (1 H, d, *J* 9.0), 7.90 (2 H, dd, *J* 8.1, 1.6), 7.45 – 7.35 (4 H, m), 7.29 – 7.17 (3 H, m), 7.10 – 7.06 (2 H, m), 6.62 (1 H, d, *J* 8.0), 6.51 (1 H, d, *J* 7.6), 5.74 (1 H, s), 4.36 (1 H, dq, *J* 9.0, 6.8), 3.88 (2 H, br s), 1.67 (3 H, s), 1.57 (3 H, d, *J* 6.8). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.4, 163.9, 144.9, 144.2, 141.1, 137.9, 132.1, 130.8, 129.7, 129.4, 128.3, 128.2, 127.2, 122.3, 121.1, 113.8, 93.5, 55.5, 25.9, 20.4. **MS** (ES^+) *m/z* 357.2 $[M+H]^+$; **HRMS** (ES^+) calc. 357.1967 [$C_{24}H_{25}N_2O$], obs. 357.1975. **$[\alpha]_D$** = -323.41° (*c* = 0.8, $CHCl_3$)

1-(2-(5-(2-Methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-1-yl)ethyl)-3-phenylurea 189a



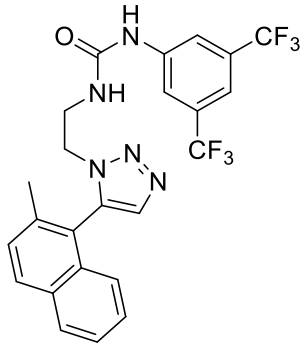
Prepared from enaminone **188a** on a 0.30 mmol scale, following a modified version of the *General procedure N* with 2.0 eq. of lithium *tert*-butoxide.[202] The title compound was obtained as a white solid in 53% yield (0.058 g, 0.16 mmol). **m.p.** 175 – 177 °C. **IR** (neat) ν_{max} (cm^{-1}) 3330, 3057, 2922, 2852, 1685, 1593, 1564, 1167. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.89 (1 H, d, *J* 8.5), 7.84 (1 H, d, *J* 7.5), 7.74 (1 H, s), 7.42 (1 H, ddd, *J* 8.2, 6.8, 1.4), 7.42 (1 H, d, *J* 8.5), 7.37 (1 H, ddd, *J* 8.3, 6.8, 1.5), 7.29 – 7.20 (5 H, m), 7.13 (1 H, d, *J* 8.3), 6.98 (1 H, tt, *J* 7.2, 1.6), 6.03 (1 H, t, *J* 5.6), 4.16 – 4.01 (2 H, m), 3.62 (2 H, ddd, *J* 6.2, 4.6, 1.3), 2.21 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.6, 139.1, 136.8, 135.9, 134.2, 132.7, 131.9, 130.4, 128.9, 128.4, 127.4, 125.8, 123.9, 122.5, 121.3, 119.3, 119.1, 48.3, 38.9, 20.2. **MS** (ES^+) *m/z* 372.2 $[M+H]^+$; **HRMS** (ES^+) calc. 372.1824 [$C_{22}H_{22}N_5O$], obs. 372.1830. **HPLC** (Phenomenex Cellulose-1, 60% MeCN/H_2O, 1.0 mL/min, λ = 220 nm) R_{t1} = 8.60 min, R_{t2} = 15.62 min. **$[\alpha]_D$** = +18.94° (*c* = 0.5, $CHCl_3$, peak 1); -19.11° (*c* = 0.5, $CHCl_3$, peak 2).

(*rac*)-1-(2-(4-Benzoyl-5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-1-yl)ethyl)-3-phenylurea 190a



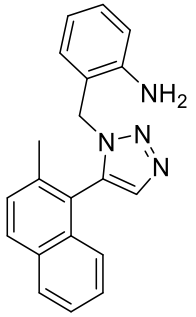
Prepared from enaminone **188a** on a 0.30 mmol scale, following a modified version of the *General procedure N* with 2.0 eq. of lithium *tert*-butoxide.[202] The title compound was obtained as a white solid in 23% yield (0.033 g, 0.07 mmol). **m.p.** dec. 240 °C. **IR** (neat) ν_{max} (cm^{-1}) 3341, 3356, 2925, 2855, 1651, 1546, 1564. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.05 (2 H, dd, *J* 8.2, 1.1), 7.85 – 7.76 (2 H, m), 7.44 (1 H, tt, *J* 7.4, 1.2), 7.36 (1 H, td, *J* 7.4, 1.4), 7.33 – 7.26 (4 H, m), 7.23 – 7.13 (4 H, m), 7.06 (1 H, dd, *J* 7.9, 1.0), 7.03 – 6.93 (2 H, m), 5.91 (1 H, t, *J* 5.8), 4.14 (2 H, t, *J* 4.7), 3.73 – 3.65 (2 H, m), 2.16 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 186.4, 155.2, 145.0, 140.3, 138.5, 136.7, 136.7, 133.1, 132.0, 131.9, 130.6, 130.1, 129.0, 128.7, 128.4, 128.1, 127.6, 125.7, 123.4, 123.3, 121.1, 120.2, 48.6, 39.3, 20.2. **MS** (ES^+) *m/z* 476.2 $[M+H]^+$; **HRMS** (ES^+) calc. 476.2087 [$C_{29}H_{26}N_5O_2$], obs. 476.2098.

(*rac*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(2-(5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-1-yl)ethyl)urea 189b



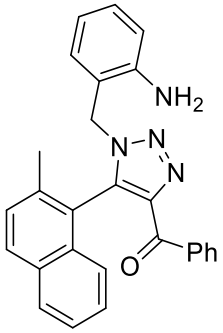
Prepared from enaminone **188b** on a 0.37 mmol scale, following a modified version of the *General procedure N* with 2.0 eq. of lithium *tert*-butoxide.[202] The title compound was obtained as a white solid in 32% yield (0.060 g, 0.12 mmol). **m.p.** 203 – 205 °C. **IR** (neat) ν_{max} (cm^{-1}) 3364, 3292, 3095, 3057, 1687, 1568, 1274. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.88 (1 H, s), 7.93 (1 H, d, *J* 8.5), 7.86 – 7.82 (1 H, m), 7.80 (1 H, s), 7.79 (2 H, s), 7.46 (1 H, d, *J* 8.5), 7.39 (1 H, s), 7.36 (2 H, ddd, *J* 8.8, 6.3, 1.8), 7.24 – 7.18 (1 H, m), 6.69 (1 H, t, *J* 5.9), 4.35 – 4.18 (2 H, m), 3.78 – 3.58 (2 H, m), 2.27 (3 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -63.06. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.2, 136.8, 136.8, 134.2, 132.6, 132.0, 131.8 (q, $^{2}J_{CF}$ 33.1), 130.8, 129.5, 128.6, 128.4, 127.5, 125.8, 123.6, 123.3 (q, $^{1}J_{CF}$ 272.6), 120.6, 117.6 (q, $^{3}J_{CF}$ 3.7), 115.0 (hept, $^{3}J_{CF}$ 3.5), 48.1, 39.1, 20.3. **MS** (ES^+) *m/z* 508.2 $[M+H]^+$, 530.1 $[M+Na]^+$; **HRMS** (ES^+) calc. 508.1572 [$C_{24}H_{20}N_5OF_6$], obs. 508.1581. **HPLC** (Phenomenex Cellulose-1, 50% MeCN/H_2O, 1.0 mL/min, λ = 254 nm) R_{t1} = 22.64 min, R_{t2} = 26.96 min.

(*rac*)-2-((5-(2-Methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-1-yl)methyl)aniline 195



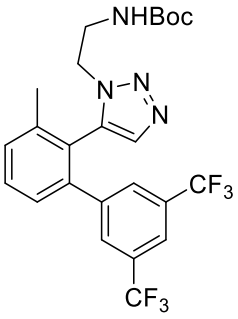
Prepared from enaminone **194** on a 1.78 mmol scale, following a modified version of the *General procedure N* with 2.0 eq. of lithium *tert*-butoxide.[202] The title compound was obtained as a yellow solid in 65% yield (0.362 g, 1.15 mmol). **m.p.** 141 – 143 °C. **IR** (neat) ν_{max} (cm^{-1}) 3455, 3367, 3065, 2936, 2252, 1634, 906. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.92 (1 H, d, *J* 8.1), 7.89 (1 H, dt, *J* 7.8, 1.1), 7.71 (1 H, s), 7.47 (1 H, ddd, *J* 8.2, 7.0, 1.2), 7.37 (1 H, ddd, *J* 7.9, 7.0, 1.4), 7.35 (1 H, d, *J* 8.2), 7.05 (1 H, dq, *J* 8.4, 1.0), 6.96 (1 H, td, *J* 7.8, 1.5), 6.56 (1 H, dd, *J* 8.0, 1.0), 6.24 (1 H, td, *J* 7.6, 1.4), 5.78 (1 H, dd, *J* 7.5, 1.5), 5.35 (1 H, d, *J* 14.6), 4.86 (1 H, br s, *J* 14.6), 4.41 (2 H, br s), 1.82 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.4, 137.6, 135.0, 134.7, 132.7, 131.8, 130.9, 130.1, 129.9, 128.3, 128.3, 127.3, 125.7, 124.2, 122.0, 118.2, 117.5, 116.3, 50.1, 20.0. **MS** (ES^+) *m/z* 315.2 $[M+H]^+$; **HRMS** (ES^+) calc. 315.1610 [$C_{20}H_{19}N_4$], obs. 315.1616. **HPLC** (Phenomenex Cellulose-1, 60% MeCN/H_2O, 1.0 mL/min, λ = 254 nm) R_{t1} = 12.70 min, R_{t2} = 15.49 min.

(*rac*)-(1-(2-Aminobenzyl)-5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone 196



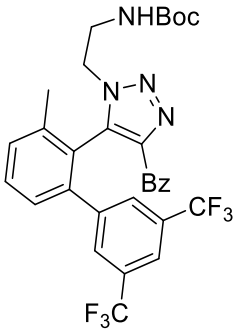
Prepared from enaminone **194** on a 1.78 mmol scale, following a modified version of the *General procedure N* with 2.0 eq. of lithium *tert*-butoxide.[202] The title compound was obtained as an orange solid in 22% yield (0.165 g, 0.39 mmol). **m.p.** 143 – 145 °C. **IR** (neat) ν_{max} (cm^{-1}) 3451, 3368, 3059, 2919, 2123, 1653, 1652, 904. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.32 (1 H, d, *J* 8.1), 8.32 (1 H, d, *J* 8.9), 7.95 (1 H, d, *J* 8.5), 7.91 (1 H, d, *J* 8.4), 7.56 (1 H, tt, *J* 7.2, 1.3), 7.51 – 7.30 (5 H, m), 7.06 – 6.94 (2 H, m), 6.60 (1 H, dd, *J* 8.2, 1.0), 6.30 (1 H, td, *J* 7.4, 1.1), 5.81 (1 H, dd, *J* 7.6, 1.4), 5.39 (1 H, d, *J* 14.5), 4.86 (1 H, d, *J* 14.6), 4.39 (2 H, s), 1.83 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 185.6, 146.2, 145.3, 139.8, 137.5, 136.9, 133.0, 131.9, 131.7, 131.2, 130.6, 130.3, 130.2, 128.6, 128.4, 128.3, 127.5, 125.6, 123.5, 121.7, 117.8, 117.6, 116.5, 50.2, 19.9. **MS** (ES^+) *m/z* 419.2 $[M+H]^+$; **HRMS** (ES^+) calc. 419.1872 [$C_{20}H_{19}N_4O$], obs. 419.1871.

tert-Butyl (2-(5-(3-methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-1*H*-1,2,3-triazol-1-yl)ethyl)carbamate 205



Prepared from enaminone **204** on a 1.42 mmol scale, following a modified version of the *General procedure N* with 2.0 eq. of lithium *tert*-butoxide.[202] The title compound was obtained as a pale yellow solid in 62% yield (0.453 g, 0.88 mmol). **m.p.** 124 – 127 °C. **IR** (neat) ν_{max} (cm^{-1}) 3349, 2980, 1716, 1279. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75 (1 H, d, *J* 32.4), 7.63 (1 H, s), 7.55 (2 H, s), 7.53 (1 H, t, *J* 7.6), 7.43 (1 H, d, *J* 7.6), 7.34 (1 H, dd, *J* 7.5, 1.3), 4.97 (1 H, t, *J* 5.0), 3.84 (1 H, ddd, *J* 12.8, 7.3, 4.9), 3.65 (1 H, dt, *J* 13.7, 4.8), 3.52 – 3.43 (2 H, m), 2.17 (3 H, s), 1.36 (9 H, s). **^{19}F NMR** (282 MHz, $CDCl_3$) -62.95. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.6, 142.1, 139.9, 139.3, 134.9, 134.6, 131.7 (q, $^{2}J_{CF}$ 33.5), 131.1, 130.6, 129.0 (q, $^{3}J_{CF}$ 3.1), 127.8, 124.6, 122.9 (q, $^{1}J_{CF}$ 273.0), 121.2 (hept, $^{3}J_{CF}$ 3.9), 79.8, 47.6, 39.5, 28.2, 20.4. **MS** (ES^+) *m/z* 515.2 $[M+H]^+$; **HRMS** (ES^+) calc. 515.1882 [$C_{24}H_{25}N_4O_2F_6$], obs. 515.1893.

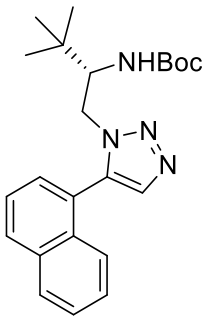
(*rac*)-*tert*-Butyl (2-(4-benzoyl-5-(3-methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-1*H*-1,2,3-triazol-1-yl)ethyl)carbamate 206



Prepared from enaminone **204** on a 1.42 mmol scale, following a modified version of the *General procedure N* with 2.0 eq. of lithium *tert*-butoxide.[202] The title compound was obtained

as a pale yellow solid in 28% yield (0.244 g, 0.39 mmol). **m.p.** 108 – 110 °C. **IR** (neat) ν_{max} (cm^{-1}) 3356, 2981, 1715, 1713, 1278. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.24 (2 H, dd, *J* 8.4, 1.3), 7.68 (1 H, s), 7.62 (2 H, s), 7.60 – 7.41 (5 H, m), 7.34 (1 H, dd, *J* 7.6, 1.1), 4.90 (1 H, t, *J* 4.9), 3.87 (1 H, dt, *J* 12.7, 6.1), 3.73 (1 H, dt, *J* 13.7, 4.9), 3.51 (2 H, app q, *J* 5.7), 2.12 (3 H, s), 1.38 (9 H, s). **^{19}F NMR** (282 MHz, $CDCl_3$) -62.96. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 186.4, 155.5, 145.4, 142.1, 140.2, 139.3, 138.7, 136.5, 133.4, 131.6 (q, $^{2}J_{CF}$ 33.6), 131.0, 130.7, 130.5, 128.8 (q, $^{3}J_{CF}$ 3.2), 128.3, 127.6, 124.8, 122.0 (q, $^{1}J_{CF}$ 273.1), 121.3 (hept, $^{3}J_{CF}$ 2.7), 80.0, 47.8, 39.4, 28.2, 20.1. **MS** (ES^+) *m/z* 619.2 $[M+H]^+$; **HRMS** (ES^+) calc. 619.2144 [$C_{31}H_{29}N_4O_3F_6$], obs. 619.2158.

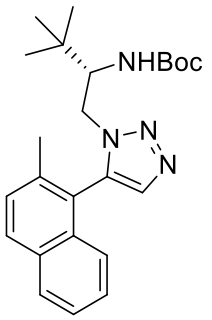
(+)-*tert*-Butyl (*S*)-(3,3-dimethyl-1-(5-(naphthalen-1-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-yl)carbamate 218a



Prepared from enaminone **217a**, following the *General Procedure N*, on a 0.63 mmol scale. The title compound was obtained as a pale yellow foam in 49% yield (0.121 g, 0.31 mmol). **m.p.** 87 – 89 °C. **IR** (neat) ν_{max} (cm^{-1}) 3311, 2967, 1699, 1160. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.00 (1 H, d, *J* 8.2), 7.94 (1 H, d, *J* 7.9), 7.77 (1 H, s), 7.70 (1 H, d, *J* 6.8), 7.62 (1 H, t, *J* 7.6), 7.59 – 7.47 (3 H, m), 7.44 (1 H, d, *J* 7.6), 4.67 (1 H, d, *J* 12.5), 4.18 (1 H, br d, *J* 8.0), 3.56 – 3.47 (1 H, m), 1.37 (9 H, s), 0.60 (9 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.7, 136.0, 134.4, 133.5, 131.7, 130.3, 129.5, 128.6, 127.4, 126.6, 125.3, 124.6, 124.2, 79.4, 58.6, 49.3, 33.7, 28.3,

25.9. **MS** (ES^+) *m/z* 395.2 $[M+H]^+$, 418.2 $[M+Na]^+$; **HRMS** (ES^+) calc. 395.2447 $[C_{23}H_{31}N_4O_2]$, obs. 395.2445. $[\alpha]_D$ = +79.22° (*c* = 1.0, $CHCl_3$)

***tert*-Butyl (*S*)-(3,3-dimethyl-1-(5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-yl)carbamate 218b/218b'**



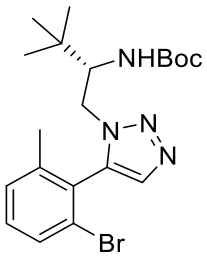
Prepared from enaminone **217b**, following the *General Procedure N*, on a 1.02 mmol scale. The two single diastereoisomers (**218b** and **218b'**, both single enantiomers) were isolated in 95% overall yield.

<u>*Fraction 1*</u> (**218b**) Isolated as a white foam in 47% yield (0.196 g, 0.48 mmol). R_f = 0.21 (20% EtOAc/Hx); **m.p.** 189 – 190 °C. **IR** (neat) ν_{max} (cm^{-1}) 3296, 3056, 2965, 2871, 1713, 1694, 1172. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.93 – 7.83 (2 H, m), 7.77 (1 H, s), 7.49 (1 H, d, *J* 8.4), 7.46 (2 H, ddd, *J* 7.9, 5.7, 1.7), 7.12 (1 H, d, *J* 7.5), 4.62 (1 H, d, *J* 10.2), 4.07 (1 H, dd, *J* 14.1, 10.3), 4.01 (1 H, dd, *J* 14.1, 3.6), 3.30 (1 H, td, *J* 10.3, 3.5), 2.41 (3 H, s), 1.37 (9 H, s), 0.51 (9 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.6, 137.8, 134.7, 134.4, 132.1, 131.9, 130.0, 128.9, 128.5, 127.4, 125.5, 123.9, 121.7, 79.4, 58.6, 49.1, 34.1, 28.3, 25.7, 20.6. **MS** (ES^+) *m/z* 409.3 $[M+H]^+$; **HRMS** (ES^+) calc. 409.2604 $[C_{24}H_{33}N_4O_2]$, obs. 409.2607. $[\alpha]_D$ = +100.55° (*c* = 1.0, $CHCl_3$)

<u>*Fraction 2*</u> (**218b'**) Isolated as a white foam in 48% yield (0.200 g, 0.49 mmol). R_f = 0.12 (20% EtOAc/Hx); **m.p.** 115 – 117 °C. **IR** (neat) ν_{max} (cm^{-1}) 3305, 3060, 2966, 2871, 1693, 727. **^{1}H**

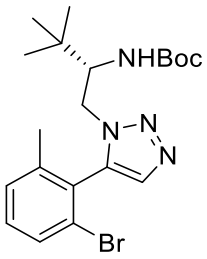
NMR (400 MHz, $CDCl_3$): δ 7.90 (1 H, d, *J* 8.4), 7.86 (1 H, dd, *J* 7.3, 1.8), 7.73 (1 H, s), 7.56 – 7.47 (2 H, m), 7.46 – 7.39 (2 H, m), 4.67 (1 H, d, *J* 10.3), 4.07 (1 H, dd, *J* 14.1, 2.9), 3.95 (1 H, dd, *J* 14.0, 10.1), 3.46 (1 H, td, *J* 10.2, 2.8), 2.22 (3 H, s), 1.41 (9 H, s), 0.55 (9 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.5, 136.2, 134.8, 134.2, 132.9, 131.8, 130.1, 128.1, 127.9, 127.5, 126.0, 125.6, 122.3, 79.4, 58.6, 48.8, 34.1, 28.4, 25.9, 20.4. **MS** (ES^+) *m/z* 409.3 $[M+H]^+$; **HRMS** (ES^+) calc. 409.2604 $[C_{24}H_{33}N_4O_2]$, obs. 409.2612. **$[\alpha]_D$** = +12.28° (*c* = 1.0, $CHCl_3$)

***tert*-Butyl (*S*)-(1-(5-(2-bromo-6-methylphenyl)-1*H*-1,2,3-triazol-1-yl)-3,3-dimethylbutan-2-yl)carbamate 218f** *(single diastereoisomer and single enantiomer)*



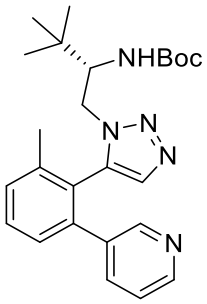
Prepared from enaminone **217f**, following the *General Procedure N*, on a 0.41 mmol scale. The title compound was obtained as a pale yellow powder in 71% yield (0.128 g, 0.29 mmol). **m.p.** 164 – 166 °C. **IR** (neat) ν_{max} (cm^{-1}) 3300, 2966, 1693, 1171. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.65 (1 H, s), 7.54 (1 H, d, *J* 7.9), 7.33 (1 H, d, *J* 7.5), 7.25 (1 H, t, *J* 7.8), 4.78 (1 H, d, *J* 10.1), 4.33 (1 H, dd, *J* 14.4, 3.0), 4.22 (1 H, dd, *J* 14.4, 11.1), 3.26 (1 H, td, *J* 10.7, 2.9), 2.28 (3 H, s), 1.34 (9 H, s), 0.74 (9 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.7, 141.9, 134.9, 133.7, 131.3, 130.4, 129.8, 127.5, 124.5, 79.4, 58.7, 49.3, 34.3, 28.2, 25.9, 21.0. **MS** (ES^+) *m/z* 437.2 $[M+H]^+$, 439.2 $[(M+H)+2]^+$; **HRMS** (ES^+) calc. 437.1552 $[C_{20}H_{30}N_4O_2Br]$, obs. 437.1542. **$[\alpha]_D$** = +76.87° (*c* = 1.0, $CHCl_3$)

***tert*-Butyl (*S*)-(1-(5-(2-bromo-6-methylphenyl)-1*H*-1,2,3-triazol-1-yl)-3,3-dimethylbutan-2-yl)carbamate 218f'** *(single diastereoisomer and single enantiomer)*



Prepared from enaminone **217f'**, following the *General Procedure N*, on a 0.36 mmol scale. The title compound was obtained as a pale yellow powder in 88% yield (0.138 g, 0.32 mmol). **m.p.** 137 – 139 °C. **IR** (neat) ν_{max} (cm^{-1}) 3293, 2968, 1713, 1699, 1166. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.63 (1 H, s), 7.33 – 7.27 (2 H, m), 7.25 (1 H, d, *J* 7.7), 4.69 (1 H, d, *J* 8.8), 4.29 (1 H, dd, *J* 11.8, 7.8), 4.01 – 3.86 (2 H, m), 2.12 (3 H, s), 1.37 (9 H, s), 0.82 (9 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.3, 140.6, 135.9, 133.4, 131.3, 130.8, 129.4, 127.8, 125.6, 79.4, 58.6, 48.8, 34.8, 28.3, 26.2, 20.9. **MS** (ES^+) *m/z* 437.2 $[M+H]^+$, 439.2 $[(M+H)+2]^+$; **HRMS** (ES^+) calc. 437.1552 [$C_{20}H_{30}N_4O_2Br$], obs. 437.1565. **$[\alpha]_D$** = -15.93° (*c* = 1.0, $CHCl_3$)

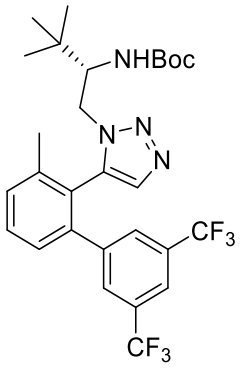
***tert*-Butyl (*S*)-(3,3-dimethyl-1-(5-(2-methyl-6-(pyridin-3-yl)phenyl)-1*H*-1,2,3-triazol-1-yl)butan-2-yl)carbamate 218d** *(single diastereoisomer and single enantiomer)*



Prepared from enaminone **217d** following the *General Procedure N*, on a 1.55 mmol scale. A diastereomerically enriched fraction was isolated in 1:1.83 d.r. and 72% yield. A single diastereoisomer (and single enantiomer) was isolated by recrystallisation (DCM/Hx) on a 0.46 mmol scale.

The title compound was obtained as colourless crystals in 41% yield (0.082 g, 0.19 mmol). **m.p.** 155 – 156 °C. **IR** (neat) ν_{max} (cm^{-1}) 3215, 3036, 2972, 2873, 1706, 1174. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.57 (1 H, d, *J* 2.3), 8.49 (1 H, dd, *J* 4.8, 1.8), 7.83 (1 H, s), 7.55 – 7.42 (2 H, m), 7.34 (1 H, d, *J* 7.4), 7.27 (1 H, dt, *J* 8.0, 2.0), 7.11 (1 H, dd, *J* 8.0, 4.8), 4.56 (1 H, d, *J* 10.1), 3.72 – 3.58 (2 H, m), 3.08 (1 H, td, *J* 10.3, 3.9), 2.36 (3 H, s), 1.31 (9 H, s), 0.66 (9 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.5, 149.3, 148.8, 140.3, 138.0, 135.9, 135.8, 135.6, 133.7, 131.0, 130.4, 127.8, 124.5, 123.1, 79.3, 58.4, 48.4, 34.2, 28.2, 25.9, 20.7. **MS** (ES^+) *m/z* 436.3 $[M+H]^+$; **HRMS** (ES^+) calc. 436.2713 [$C_{25}H_{34}N_5O_2$], obs. 436.2711. **$[\alpha]_D$** = +19.04° (*c* = 0.4, $CHCl_3$)

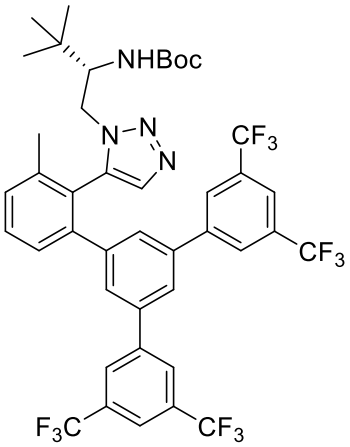
***tert*-Butyl (*S*)-(3,3-dimethyl-1-(5-(3-methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-yl)carbamate 218c** *(single diastereoisomer and single enantiomer)*



Prepared from enaminone **217c**, following the *General Procedure N*, on a 0.60 mmol scale. The title compound was obtained as a yellow foam in 65% yield (0.221 g, 0.39 mmol). **m.p.** 55 – 57 °C. **IR** (neat) ν_{max} (cm^{-1}) 3290, 2968, 1698, 1278. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84 (1 H, s), 7.76 (1 H, s), 7.57 (2 H, s), 7.56 – 7.48 (2 H, m), 7.36 (1 H, dd, *J* 7.4, 1.3), 4.51 (1 H, d, *J* 10.2), 3.65 (1 H, dd, *J* 14.1, 11.5), 3.53 (1 H, dd, *J* 13.6, 2.9), 3.08 (1 H, ddd, *J* 11.2, 10.1, 3.0), 2.36 (3 H, s), 1.31 (9 H, s), 0.66 (9 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -63.08. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.5, 142.2, 140.6, 138.6, 135.6, 133.3, 131.9 (q, $^2J_{CF}$ 33.6), 131.6, 130.6,

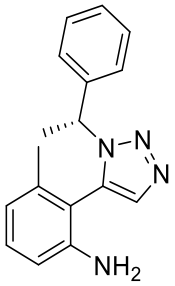
128.9 (q, $^{3}J_{CF}$ 3.0), 127.6, 124.4, 122.9 (q, $^{1}J_{CF}$ 272.6), 121.2 (hept, $^{3}J_{CF}$ 4.1), 79.5, 58.2, 48.3, 34.2, 28.2, 25.9, 20.7. **MS** (ES^+) *m/z* 571.3 $[M+H]^+$; **HRMS** (ES^+) calc. 571.2508 [$C_{28}H_{33}N_4O_2F_6$], obs. 571.2524. $[\alpha]_D$ = +10.53° (*c* = 1.0, $CHCl_3$)

***tert*-Butyl (*S*)-(1-(5-(5'-(3,5-bis(trifluoromethyl)phenyl)-3-methyl-3'',5''-bis(trifluoromethyl)-[1,1':3',1''-terphenyl]-2-yl)-1*H*-1,2,3-triazol-1-yl)-3,3-dimethylbutan-2-yl)carbamate 218e** *(single diastereoisomer and single enantiomer)*



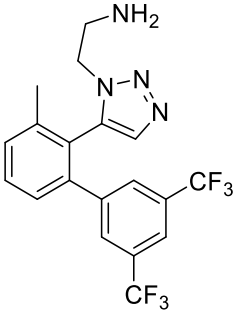
Prepared from enaminone **217e**, following the *General Procedure N*, on a 0.15 mmol scale. The title compound was obtained as a yellow foam in 36% yield (0.041 g, 0.05 mmol). **m.p.** 76 – 78 °C. **IR** (neat) ν_{max} (cm^{-1}) 2969, 1717, 1367, 1278, 1133. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.92 (2 H, s), 7.90 (1 H, s), 7.88 (4 H, s), 7.62 (1 H, t, *J* 1.7), 7.58 – 7.43 (3 H, m), 7.41 (2 H, d, *J* 1.7), 4.47 (1 H, d, *J* 10.1), 3.89 – 3.67 (2 H, m), 3.18 (1 H, td, *J* 10.4, 3.7), 2.39 (3 H, s), 1.30 (9 H, s), 0.70 (9 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -62.77. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.0, 142.3, 141.9, 141.5, 139.8, 139.3, 135.1, 132.3 (q, $^{2}J_{CF}$ 33.4), 130.6, 130.4, 128.6, 128.3, 127.6 (q, $^{3}J_{CF}$ 2.8), 127.4, 125.6, 124.8, 122.4 (q, $^{1}J_{CF}$ 273.0), 121.6 (hept, $^{3}J_{CF}$ 3.1), 79.2, 58.2, 48.1, 34.4, 28.1, 26.0, 20.7. **MS** (ES^+) *m/z* 859.3 $[M+H]^+$; **HRMS** (ES^+) calc. 859.2881 [$C_{42}H_{39}N_4O_2F_{12}$], obs. 859.2904. $[\alpha]_D$ = +12.33° (*c* = 1.0, $CHCl_3$)

(*R*)-3-Methyl-2-(1-(1-phenylethyl)-1*H*-1,2,3-triazol-5-yl)aniline 239a



Prepared from enaminone **238a'**, following the *General Procedure N*, on a 0.71 mmol scale. The title compound was obtained as a light brown solid in 50% yield (0.098 g, 0.35 mmol). **m.p.** 167 – 170 °C. **IR** (neat) ν_{max} (cm^{-1}) 3368, 3327, 3070, 2987, 2985, 1469, 1166. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (1 H, s), 7.24 – 7.16 (3 H, m), 7.15 (1 H, t, *J* 7.8), 7.10 – 7.01 (2 H, m), 6.66 (1 H, d, *J* 8.0), 6.55 (1 H, d, *J* 7.5), 5.26 (1 H, q, *J* 7.1), 3.46 (2 H, br s), 2.04 (3 H, d, *J* 7.1), 1.35 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.3, 140.5, 139.8, 133.9, 133.0, 130.7, 128.5, 128.0, 126.6, 120.1, 112.8, 111.7, 58.8, 21.9, 19.6. **MS** (ES^+) *m/z* 279.2 $[M+H]^+$; **HRMS** (ES^+) calc. 279.1610 [$C_{17}H_{19}N_4$], obs. 279.1617. **$[\alpha]_D$** = +23.03° (*c* = 0.8, $CHCl_3$).

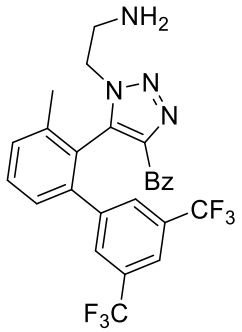
2-(5-(3-Methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-1*H*-1,2,3-triazol-1-yl)ethan-1-amine 207



Prepared from *N*-Boc-1*H*-1,2,3-triazole **205**, following the *General Procedure L*, on a 0.82 mmol scale. The title compound was obtained as a pale yellow oil in 99% yield (0.336 g, 0.81 mmol). **R_f** = 0.36 (5% MeOH/DCM). **IR** (neat) ν_{max} (cm^{-1}) 3385, 2948, 1378, 1275, 1129. **^{1}H**

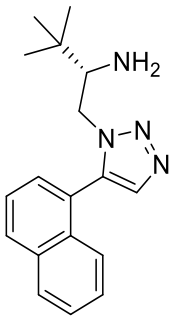
NMR (400 MHz, $CDCl_3$): δ 7.75 (1 H, s), 7.60 (1 H, s), 7.60 (2 H, s), 7.53 (1 H, t, *J* 7.7), 7.44 (1 H, ddd, *J* 7.7, 1.4, 0.7), 7.34 (1 H, ddd, *J* 7.7, 1.4, 0.7), 3.80 (1 H, ddd, *J* 13.5, 6.3, 5.6), 3.72 (1 H, ddd, *J* 13.5, 6.7, 5.6), 3.10 – 2.90 (2 H, m), 2.17 (3 H, s), 1.34 (2 H, br s). **^{19}F NMR** (377 MHz, $CDCl_3$) -63.14. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.1, 140.0, 139.4, 134.6, 134.6, 131.6 (q, $^{2}J_{CF}$ 33.3), 131.0, 130.5, 129.1 (q, $^{3}J_{CF}$ 3.0), 127.8, 125.0, 123.0 (q, $^{1}J_{CF}$ 272.7), 121.2 (hept, $^{3}J_{CF}$ 3.7), 50.7, 41.1, 20.5. **MS** (ES^+) *m/z* 415.1 $[M+H]^+$; **HRMS** (ES^+) calc. 415.1357 $[C_{19}H_{17}N_4F_6]$, obs. 415.1354.

(1-(2-Aminoethyl)-5-(3-methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone 208



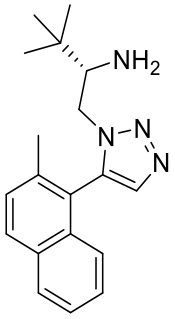
Prepared from *N*-Boc-1*H*-1,2,3-triazole **206**, following the *General Procedure L*, on a 0.32 mmol scale. The title compound was obtained as a yellow/brown solid in 99% yield (0.164 g, 0.32 mmol). **m.p.** 35 – 38 °C. **IR** (neat) ν_{max} (cm^{-1}) 3071, 2930, 2860, 1652, 1276, 1130. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.22 (2 H, dd, *J* 8.4, 1.4), 7.67 (3 H, s), 7.64 – 7.43 (5 H, m), 7.34 (1 H, dd, *J* 7.8, 1.0), 3.80 (2 H, td, *J* 6.1, 1.8), 3.05 (2 H, h, *J* 7.3), 2.13 (3 H, s), 1.26 (2 H, br s). **^{19}F NMR** (282 MHz, $CDCl_3$) -62.94. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 186.5, 145.3, 142.2, 139.9, 139.4, 138.8, 136.5, 133.3, 131.5 (q, $^{2}J_{CF}$ 33.6), 131.0, 130.6, 130.5, 129.0 (q, $^{3}J_{CF}$ 3.0), 128.3, 127.6, 125.1, 122.9 (q, $^{1}J_{CF}$ 273.0), 121.2 (hept, $^{3}J_{CF}$ 3.9), 50.8, 40.8, 20.2. **MS** (ES^+) *m/z* 519.2 $[M+H]^+$; **HRMS** (ES^+) calc. 519.1620 $[C_{26}H_{21}N_4OF_6]$, obs. 519.1631.

(*S*)-3,3-Dimethyl-1-(5-(naphthalen-1-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-amine 219a



Prepared from *N*-Boc-1*H*-1,2,3-triazole **218a**, following the *General Procedure L*, on a 0.25 mmol scale. The title compound was obtained as a colourless oil in 99% yield (0.074 g, 0.25 mmol). **R_f =** 0.35 (10% MeOH/DCM). **IR** (neat) ν_{max} (cm^{-1}) 3055, 2960, 2869, 732. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.00 (1 H, d, *J* 8.3), 7.94 (1 H, d, *J* 7.9), 7.83 (1 H, s), 7.62 – 7.50 (2 H, m), 7.52 – 7.43 (3 H, m), 4.26 (1 H, d, *J* 13.6), 3.97 (1 H, dd, *J* 13.5, 10.5), 2.65 (1 H, dd, *J* 10.4, 2.1), 1.49 (2 H, br s), 0.63 (9 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.1, 134.6, 133.6, 131.9, 130.4, 128.8, 128.7, 127.4, 126.7, 125.1, 124.6, 124.4, 60.4, 51.6, 33.6, 25.7. **MS** (ES^+) *m/z* 295.2 $[M+H]^+$; **HRMS** (ES^+) calc. 295.1923 [$C_{18}H_{23}N_4$], obs. 295.1924. **$[\alpha]_D$** = +10.09° (*c* = 0.7, $CHCl_3$).

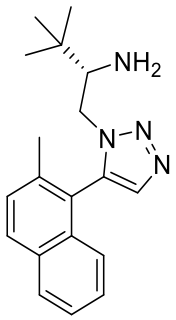
(*S*)-3,3-Dimethyl-1-(5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-amine 219b *(single diastereoisomer and single enantiomer)*



Prepared from *N*-Boc-1*H*-1,2,3-triazole **218b**, following the *General Procedure L*, on a 0.18 mmol scale. The title compound was obtained as a colourless oil in 99% yield (0.055 g, 0.18

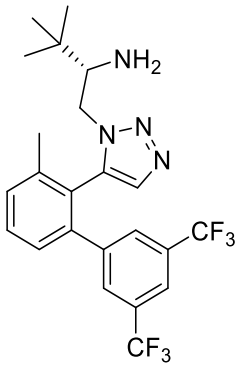
mmol). **R_f** = 0.23 (10% MeOH/DCM). **IR** (neat) ν_{max} (cm^{-1}) 3388, 3385, 2959, 2871, 730. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.91 (1 H, d, *J* 8.5), 7.88 (1 H, d, *J* 8.2), 7.79 (1 H, s), 7.52 – 7.40 (3 H, m), 7.17 (1 H, d, *J* 8.2), 4.02 (1 H, dd, *J* 13.7, 2.1), 3.87 (1 H, dd, *J* 13.6, 10.3), 2.55 (1 H, dd, *J* 10.2, 2.1), 2.28 (3 H, s), 1.35 (2 H, br s), 0.59 (9 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.7, 134.7, 132.5, 131.9, 130.1, 128.4, 128.3, 128.3, 127.4, 125.7, 124.2, 122.3, 60.4, 51.8, 33.5, 25.6, 20.6. **MS** (ES^+) *m/z* 309.2 $[M+H]^+$, 331.2 $[M+Na]^+$. **HRMS** (ES^+) calc. 331.1899 [$C_{19}H_{24}N_4Na$], obs. 331.1899. **$[\alpha]_D$** = +61.30° (*c* = 1.0, $CHCl_3$).

(*S*)-3,3-Dimethyl-1-(5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-amine 219b' *(single diastereoisomer and single enantiomer)*



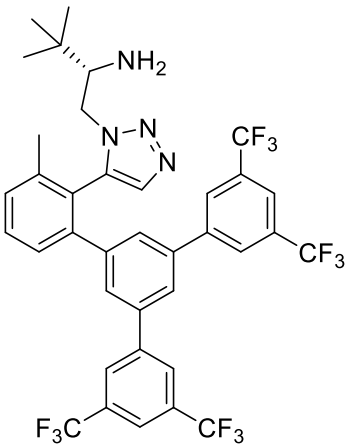
Prepared from *N*-Boc-1*H*-1,2,3-triazole **218b'**, following the *General Procedure L*, on a 0.13 mmol scale. The title compound was obtained as a colourless oil in 95% yield (0.038 g, 0.12 mmol). **R_f** = 0.23 (10% MeOH/DCM). **IR** (neat) ν_{max} (cm^{-1}) 3384, 3381, 2959, 2871, 816. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.91 (1 H, d, *J* 8.5), 7.87 (1 H, d, *J* 8.0), 7.79 (1 H, s), 7.52 – 7.38 (3 H, m), 7.21 (1 H, d, *J* 8.3), 4.02 (1 H, dd, *J* 13.6, 2.0), 3.84 (1 H, dd, *J* 13.6, 10.2), 2.52 (1 H, dd, *J* 10.3, 2.0), 2.25 (3 H, s), 1.38 (2 H, br s), 0.53 (9 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.5, 134.9, 134.5, 133.0, 131.8, 130.1, 128.4, 128.3, 127.2, 125.7, 124.4, 122.4, 60.1, 51.4, 33.4, 25.5, 20.4. **MS** ($ASAP^+$) *m/z* 309.2 $[M+H]^+$. **HRMS** ($ASAP^+$) calc. 309.2079 [$C_{19}H_{25}N_4$], obs. 309.2084. **$[\alpha]_D$** = -2.77° (*c* = 1.0, $CHCl_3$).

(*S*)-3,3-Dimethyl-1-(5-(3-methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-amine 219c *(single diastereoisomer and single enantiomer)*



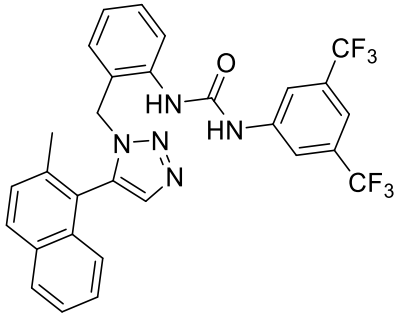
Prepared from *N*-Boc-1*H*-1,2,3-triazole **218c**, following the *General Procedure L*, on a 0.33 mmol scale. The title compound was obtained as a colourless oil in 99% yield (0.155 g, 0.33 mmol). **R_f** = 0.56 (10% MeOH/DCM). **IR** (neat) ν_{max} (cm^{-1}) 2956, 2923, 2855, 1277, 1136. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75 (1 H, s), 7.69 (1 H, s), 7.67 (2 H, s), 7.55 (1 H, t, *J* 7.7), 7.46 (1 H, d, *J* 7.6), 7.37 (1 H, d, *J* 7.6), 3.75 (1 H, dd, *J* 13.5, 2.2), 3.52 (1 H, dd, *J* 13.5, 10.5), 2.54 (1 H, dd, *J* 10.5, 2.1), 2.19 (3 H, s), 1.26 (2 H, br s), 0.74 (9 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -62.95. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.1, 139.6, 139.3, 135.1, 134.1, 131.6 (q, $^2J_{CF}$ 33.6), 131.0, 130.6, 129.2 (q, $^3J_{CF}$ 2.3), 127.8, 125.1, 122.2 (q, $^1J_{CF}$ 272.7), 121.2 (hept, $^3J_{CF}$ 3.7), 59.9, 51.2, 33.6, 25.7, 20.6. **MS** (ES^+) *m/z* 471.2 $[M+H]^+$; **HRMS** (ES^+) calc. 471.1983 [$C_{23}H_{25}N_4F_6$], obs. 471.1993. **$[\alpha]_D$** = +40.44° (*c* = 0.5, $CHCl_3$).

(*S*)-1-(5-(5'-(3,5-Bis(trifluoromethyl)phenyl)-3-methyl-3'',5''-bis(trifluoromethyl)-[1,1':3',1''-terphenyl]-2-yl)-1*H*-1,2,3-triazol-1-yl)-3,3-dimethylbutan-2-amine 219e *(single diastereoisomer and single enantiomer)*



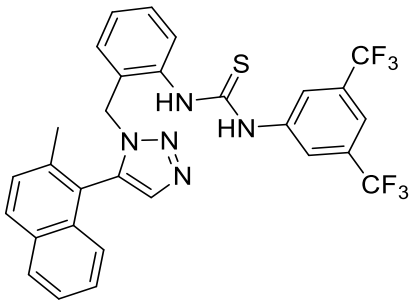
Prepared from *N*-Boc-1*H*-1,2,3-triazole **218e**, following the *General Procedure L*, on a 0.07 mmol scale. The title compound was obtained as a white powder in 99% yield (0.053 g, 0.07 mmol). **m.p.** 148 – 151 °C. **IR** (neat) ν_{max} (cm^{-1}) 3071, 2963, 2868, 2855, 1275, 1127. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.93 (4 H, s), 7.91 (2 H, s), 7.75 (1 H, s), 7.66 – 7.60 (1 H, m), 7.55 (1 H, t, *J* 7.6), 7.50 – 7.41 (3 H, m), 7.40 (1 H, d, *J* 1.7), 7.39 (1 H, d, *J* 1.7), 3.76 (1 H, dd, *J* 13.6, 2.9), 3.69 (1 H, dd, *J* 13.5, 10.0), 2.89 (2 H, br s), 2.24 (3 H, s), 0.76 (9 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -62.74. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.4, 142.1, 141.3, 139.7, 139.2, 135.55, 135.1, 132.4 (q, $^{2}J_{CF}$ 33.5), 130.6, 130.4, 128.4, 127.9, 127.5 (q, $^{3}J_{CF}$ 3.1), 125.3, 124.9, 123.2 (q, $^{1}J_{CF}$ 273.5), 121.8 (hept, $^{3}J_{CF}$ 3.1), 59.3, 50.7, 33.5, 25.9, 20.7. **MS** (ES^+) *m/z* 759.2 $[M+H]^+$; **HRMS** (ES^+) calc. 759.2357 [$C_{37}H_{31}N_4F_{12}$], obs. 759.2336. **$[\alpha]_D$** = +15.51° (*c* = 0.5, $CHCl_3$).

1-(3,5-Bis(trifluoromethyl)phenyl)-3-(2-((5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-1-yl)methyl)phenyl)urea 198a



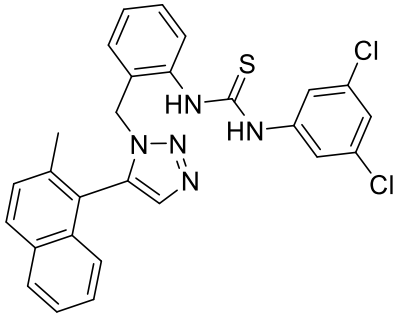
Prepared from 1*H*-1,2,3-triazole **195** and 3,5-bis(trifluoromethyl)phenyl isocyanate, following the *General Procedure K*, on a 0.54 mmol scale. The title compound was obtained as colourless crystals in 75% yield (0.231 g, 0.41 mmol). **m.p.** 203 – 206 °C. **IR** (neat) ν_{max} (cm^{-1}) 3345, 3058, 1705, 1276, 1128. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.08 (1 H, br s), 8.53 (1 H, br s), 8.08 (2 H, s), 7.97 (1 H, d, *J* 8.4), 7.92 (1 H, d, *J* 8.1), 7.74 (1 H, s), 7.70 (1 H, ddd, *J* 8.2, 4.2, 1.2), 7.55 – 7.46 (2 H, m), 7.42 (1 H, d, *J* 8.5), 7.38 (1 H, ddd, *J* 8.3, 6.9, 1.3), 7.23 (1 H, td, *J* 7.8, 1.6), 6.99 (1 H, d, *J* 8.4), 6.71 (1 H, td, *J* 7.5, 1.2), 6.08 (1 H, dt, *J* 7.6, 1.5), 5.32 (1 H, d, *J* 14.6), 5.02 (1 H, d, *J* 14.4), 1.94 (3 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -63.04. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.0, 141.2, 141.1, 137.4, 137.3, 137.2, 135.7, 134.6, 132.5, 132.0 (q, $^{2}J_{CF}$ 33.2), 131.8, 130.7, 130.7, 130.0, 128.5, 128.3, 127.6, 125.9, 125.2, 124.4, 123.9, 123.4 (q, $^{1}J_{CF}$ 272.6), 121.0, 118.4 (q, $^{3}J_{CF}$ 3.6), 115.5 (hept, $^{3}J_{CF}$ 3.7), 49.7, 20.1 (25 of the 26 expected signals are observed). **MS** (ES^+) *m/z* 570.2 $[M+H]^+$; **HRMS** (ES^+) calc. 570.1729 [$C_{29}H_{22}N_5OF_6$], obs. 570.1738. **HPLC** (Phenomenex Cellulose-1, 55% MeCN/H_2O, 1.0 mL/min, λ = 220 nm) R_{t1} = 38.07 min, R_{t2} = 44.03 min. **$[\alpha]_D$** = +8.59° (*c* = 1.0, $CHCl_3$, peak 1); -8.45° (*c* = 1.0, $CHCl_3$, peak 2).

1-(3,5-Bis(trifluoromethyl)phenyl)-3-(2-((5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-1-yl)methyl)phenyl)thiourea 198b



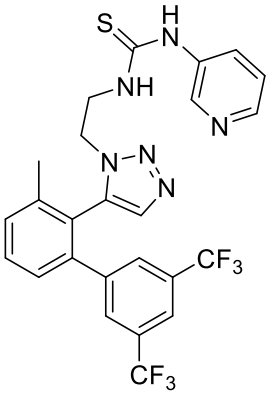
Prepared from 1*H*-1,2,3-triazole **195** and 3,5-bis(trifluoromethyl)phenyl isothiocyanate, following the *General Procedure K*, on a 0.54 mmol scale. The title compound was obtained as colourless crystals in 72% yield (0.228 g, 0.39 mmol). **m.p.** 167 – 168 °C. **IR** (neat) ν_{max} (cm^{-1}) 3323, 3057, 1631, 1276, 1127. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.92 (1 H, br s), 8.63 (1 H, br s), 8.14 (2 H, s), 7.96 (1 H, d, *J* 8.5), 7.91 (1 H, d, *J* 8.1), 7.69 (1 H, s), 7.66 (1 H, s), 7.49 (1 H, ddd, *J* 8.1, 6.9, 1.1), 7.45 (1 H, d, *J* 8.5), 7.42 – 7.37 (2 H, m), 7.31 (1 H, td, *J* 7.7, 1.5), 7.04 (2 H, d, *J* 8.1), 6.56 (1 H, d, *J* 7.7), 5.27 (1 H, d, *J* 14.5), 5.12 (1 H, d, *J* 14.4), 2.06 (3 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -62.87. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.3, 140.5, 137.6, 137.2, 135.7, 134.2, 132.5, 131.8, 131.7 (q, $^{2}J_{CF}$ 33.4), 131.0, 131.0, 130.7, 130.1, 129.4, 128.5, 128.3, 127.8, 127.6, 126.0, 123.9, 123.1 (q, $^{1}J_{CF}$ 272.9), 122.9 (q, $^{3}J_{CF}$ 3.4), 121.1, 118.3 (hept, $^{3}J_{CF}$ 3.6), 49.5, 20.2. **MS** (ES^+) *m/z* 586.1 $[M+H]^+$; **HRMS** (ES^+) calc. 586.1500 [$C_{29}H_{22}N_5SF_6$], obs. 586.1511. **HPLC** (Phenomenex Cellulose-1, 60% MeCN/H_2O, 1.0 mL/min, λ = 220 nm) R_{t1} = 21.56 min, R_{t2} = 24.34 min. **$[\alpha]_D$** = +10.53° (*c* = 0.5, $CHCl_3$, peak 1); -10.25° (*c* = 0.5, $CHCl_3$, peak 2).

1-(3,5-Dichlorophenyl)-3-(2-((5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-1-yl)methyl)phenyl)thiourea 198c



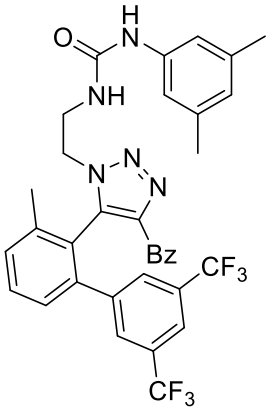
Prepared from 1*H*-1,2,3-triazole **195** and 3,5-dichlorophenyl isothiocyanate, following the *General Procedure K*, on a 0.32 mmol scale. The title compound was obtained as a white powder in 83% yield (0.137 g, 0.26 mmol). **m.p.** dec. 200 °C. **IR** (neat) ν_{max} (cm^{-1}) 3312, 3007, 1588, 1508, 727. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.07 (1 H, br s), 8.76 (1 H, br s), 7.93 (1 H, d, *J* 8.5), 7.89 (1 H, d, *J* 8.0), 7.64 (1 H, s), 7.51 (2 H, d, *J* 1.8), 7.48 (1 H, ddd, *J* 8.1, 6.8, 1.2), 7.42 (1 H, d, *J* 8.5), 7.40 – 7.32 (2 H, m), 7.26 (1 H, td, *J* 7.7, 1.5), 7.19 (1 H, t, *J* 1.9), 7.00 (1 H, d, *J* 8.1), 6.96 (1 H, td, *J* 7.5, 1.1), 6.45 (1 H, d, *J* 7.5), 5.23 (1 H, d, *J* 14.4), 5.08 (1 H, d, *J* 14.4), 2.03 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.0, 140.0, 137.6, 137.2, 135.2, 135.1, 134.3, 132.6, 131.8, 130.9, 130.8, 130.6, 129.9, 129.2, 128.4, 128.3, 127.6, 127.6, 125.9, 125.8, 124.1, 122.3, 121.4, 49.0, 20.3. **MS** (ES^+) *m/z* 518.1 $[M+H]^+$, 520.1 $[(M+H)+2]^+$, 522.1 $[(M+H)+4]^+$; **HRMS** (ES^+) calc. 518.0973 [$C_{27}H_{22}N_5SCl_2$], obs. 518.0984. **HPLC** (Phenomenex Cellulose-1, 60% MeCN/H_2O, 1.0 mL/min, λ = 220 nm) R_{t1} = 29.37 min, R_{t2} = 33.33 min. **$[\alpha]_D$** = +12.60° (*c* = 1.0, $CHCl_3$, peak 1); -12.74° (*c* = 1.0, $CHCl_3$, peak 2).

1-(2-(5-(3-Methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-1*H*-1,2,3-triazol-1-yl)ethyl)-3-(pyridin-3-yl)thiourea 210



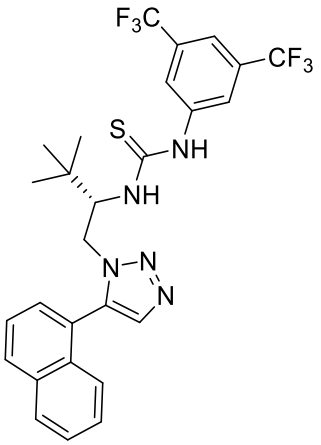
Prepared from 1*H*-1,2,3-triazole **207** and 3-pyridyl isothiocyanate, following the *General Procedure K*, on a 0.24 mmol scale. The title compound was obtained as a white powder in 50% yield (0.066 g, 0.12 mmol). **m.p.** 74 – 75 °C. **IR** (neat) ν_{max} (cm^{-1}) 3307, 3054, 1530, 1276, 1132. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.27 (1 H, br s), 8.49 (1 H, d, *J* 2.6), 8.35 (1 H, d, *J* 4.7), 7.95 (1 H, d, *J* 8.2), 7.72 (1 H, s), 7.64 – 7.50 (5 H, m), 7.43 (1 H, d, *J* 7.8), 7.35 (1 H, d, *J* 7.7), 7.29 – 7.25 (1 H, m), 4.23 (1 H, ddd, *J* 13.1, 7.9, 4.5), 4.16 – 4.06 (1 H, m), 3.94 – 3.84 (1 H, m), 3.79 (1 H, dt, *J* 13.5, 4.9), 2.14 (3 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -62.91. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 182.0, 146.3, 145.1, 142.0, 139.8, 139.4, 135.7, 135.2, 134.5, 131.7, 131.6 (q, $^{2}J_{CF}$ 33.5), 131.2, 130.9, 129.0 (q, $^{3}J_{CF}$ 3.7), 127.9, 123.9, 123.6, 122.9 (q, $^{1}J_{CF}$ 273.0), 121.2 (hept, $^{3}J_{CF}$ 3.7), 46.6, 43.0, 20.3. **MS** (ES^+) *m/z* 551.1 $[M+H]^+$; **HRMS** (ES^+) calc. 551.1453 [$C_{25}H_{21}N_6SF_6$], obs. 551.1460.

1-(2-(4-Benzoyl-5-(3-methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-1*H*-1,2,3-triazol-1-yl)ethyl)-3-(3,5-dimethylphenyl)urea 211



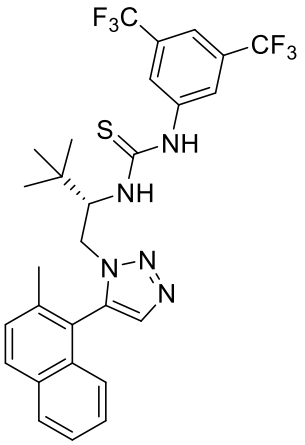
Prepared from 1*H*-1,2,3-triazole **208** and 3,5-dimethylphenyl isothiocyanate, following the *General Procedure K*, on a 0.40 mmol scale. The title compound was obtained as a white powder in 97% yield (0.260 g, 0.39 mmol). **m.p.** 223 – 225 °C. **IR** (neat) ν_{max} (cm^{-1}) 3342, 3060, 1707, 1276, 1128. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.16 (2 H, dd, *J* 8.2, 1.1), 7.68 (1 H, s), 7.62 (2 H, s), 7.66 – 7.57 (1 H, m), 7.54 (1 H, t, *J* 7.7), 7.54 – 7.45 (2 H, m), 7.40 (1 H, dt, *J* 7.7, 1.1), 7.34 (1 H, d, *J* 7.6), 7.17 (1 H, br s), 6.86 (2 H, s), 6.68 (1 H, s), 5.78 (1 H, t, *J* 5.9), 3.98 (1 H, ddd, *J* 13.8, 7.9, 4.1), 3.76 (1 H, ddd, *J* 13.8, 5.7, 4.1), 3.69 – 3.56 (1 H, m), 3.59 – 3.46 (1 H, m), 2.26 (6 H, s), 2.08 (3 H, s). **^{19}F NMR** (377 MHz, Acetone) -63.40. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 186.5, 155.6, 145.2, 142.2, 140.3, 139.2, 138.7, 138.6, 136.4, 133.4, 131.6 (q, $^{2}J_{CF}$ 33.6), 131.1, 130.8, 130.4, 128.8 (q, $^{3}J_{CF}$ 2.9), 128.3, 127.6, 125.1, 124.4, 122.9 (q, $^{1}J_{CF}$ 272.8), 121.2 (hept, $^{3}J_{CF}$ 3.6), 117.9, 117.7, 48.1, 38.5, 21.3, 19.9. **MS** (ES^+) *m/z* 666.2 $[M+H]^+$; **HRMS** (ES^+) calc. 666.2304 [$C_{35}H_{30}N_5OF_6$], obs. 666.2312.

(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(3,3-dimethyl-1-(5-(naphthalen-1-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-yl)thiourea 227



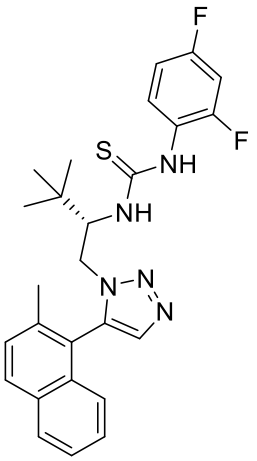
Prepared from 1*H*-1,2,3-triazole **219a** and 3,5-bis(trifluoromethyl)phenyl isothiocyanate, following the *General Procedure K*, on a 0.25 mmol scale. The title compound was obtained as a white powder in 97% yield (0.137 g, 0.24 mmol). **m.p.** 204 – 205 °C. **IR** (neat) ν_{max} (cm^{-1}) 3333, 2962, 1544, 1275, 1117. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.68 (1 H, br s), 8.11 (2 H, s), 8.09 (1 H, d, *J* 8.5), 8.07 – 7.98 (3 H, m), 7.93 (1 H, s), 7.72 (1 H, t, *J* 7.7), 7.65 – 7.42 (3 H, m), 7.35 (1 H, br s), 4.89 – 4.77 (1 H, m), 4.57 – 4.39 (2 H, m), 0.71 (9 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -63.00. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.6, 140.8, 137.8, 134.9, 133.6, 131.5, 131.0, 130.8 (q, $^{2}J_{CF}$ 33.6), 129.0, 127.7, 126.8, 125.5, 123.1 (q, $^{1}J_{CF}$ 272.5), 122.7, 121.0 (q, $^{3}J_{CF}$ 2.6), 117.0 (hept, $^{3}J_{CF}$ 3.2), 61.3, 49.5, 34.8, 26.1 (20 of the 22 expected signals are observed). **MS** (ES^+) *m/z* 566.2 $[M]^+$; **HRMS** (ES^+) calc. 566.1813 [$C_{27}H_{25}N_5SF_6$], obs. 566.1810. **$[\alpha]_D$** = +129.36° (*c* = 1.0, $CHCl_3$).

(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(3,3-dimethyl-1-(5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-yl)thiourea 221 *(single diastereoisomer and single enantiomer)*



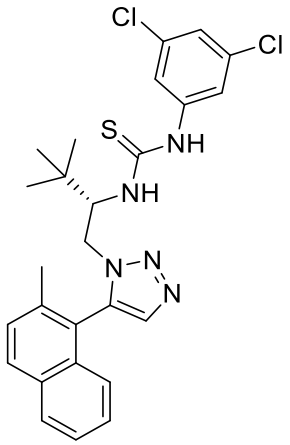
Prepared from 1*H*-1,2,3-triazole **219b** and 3,5-bis(trifluoromethyl)phenyl isothiocyanate, following the *General Procedure K*, on a 0.12 mmol scale. The title compound was obtained as a white powder in 76% yield (0.053 g, 0.09 mmol). **m.p.** 190 – 191 °C. **IR** (neat) ν_{max} (cm^{-1}) 3339, 2965, 2085, 1542, 1276, 1126. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.66 (1 H, br s), 8.18 (2 H, s), 8.09 (1 H, d, *J* 9.3), 7.96 (1 H, d, *J* 8.4), 7.91 (1 H, d, *J* 8.1), 7.90 (1 H, s), 7.81 (1 H, d, *J* 7.6), 7.65 (1 H, t, *J* 7.8), 7.57 (1 H, t, *J* 7.3), 7.47 (1 H, d, *J* 8.5), 7.42 (1 H, br s), 4.68 (1 H, dt, *J* 10.4, 5.4), 4.31 – 4.22 (2 H, m), 2.23 (3 H, s), 0.59 (9 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -62.96. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.5, 140.8, 136.6, 135.9, 134.5, 132.7, 131.9, 131.2 (q, $^{2}J_{CF}$ 32.6), 130.8, 128.0, 126.4, 126.3, 123.2 (q, $^{1}J_{CF}$ 272.8), 121.2, 121.1, 117.1, 61.4, 48.6, 34.9, 26.0, 20.2. (21 of the 23 expected signals are observed). **MS** (ES^+) *m/z* 580.2 $[M+H]^+$; **HRMS** (ES^+) calc. 580.1970 [$C_{28}H_{28}N_5SF_6$], obs. 580.1956. **$[\alpha]_D$** = +97.51° (*c* = 0.5, $CHCl_3$).

(*S*)-1-(2,4-Difluorophenyl)-3-(3,3-dimethyl-1-(5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-yl)thiourea 222 *(single diastereoisomer and single enantiomer)*



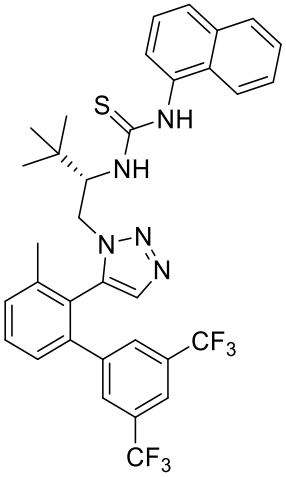
Prepared from 1*H*-1,2,3-triazole **219b'** and 2,6-difluorophenyl isothiocyanate, following the *General Procedure K*, on a 0.20 mmol scale. The title compound was obtained as an orange powder in 75% yield (0.072 g, 0.15 mmol). **m.p.** 186 – 187 °C. **IR** (neat) ν_{max} (cm^{-1}) 3311, 2964, 2086, 1508, 1260. **^{1}H NMR** (400 MHz, MeOD): δ 7.87 (1 H, d, *J* 8.5), 7.83 (1 H, dd, *J* 8.0, 1.4), 7.76 – 7.64 (1 H, m), 7.71 (1 H, s), 7.44 (1 H, d, *J* 8.5), 7.37 (1 H, ddd, *J* 8.1, 6.9, 1.3), 7.31 (1 H, ddd, *J* 8.3, 6.9, 1.5), 7.01 (1 H, d, *J* 8.3), 6.90 (1 H, ddd, *J* 10.5, 8.7, 2.8), 6.83 (1 H, dddd, *J* 9.3, 8.1, 2.9, 1.5), 4.46 (1 H, dd, *J* 9.3, 2.8), 4.11 (1 H, dd, *J* 14.3, 9.3), 4.05 (1 H, dd, *J* 14.3, 2.9), 2.41 (3 H, s), 0.51 (9 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -111.38, -118.42. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 182.7, 160.8 (dd, $^{1,3}J_{CF}$ 248.0, 9.6), 156.6 (dd, $^{1,3}J_{CF}$ 250.2, 12.0), 138.2, 135.2, 134.5, 132.2, 131.9, 130.2, 129.4 (dd, $^{3}J_{CF}$ 9.8, 9.4), 128.9, 128.6, 127.4, 125.1, 123.8, 121.0, 111.3 (d, $^{2}J_{CF}$ 22.3), 111.3 (d, $^{2}J_{CF}$ 24.0), 104.4 (dd, $^{2}J_{CF}$ 27.8, 24.3), 62.3, 48.5, 35.0, 26.1. **MS** (ES^+) *m/z* 480.2 $[M+H]^+$; **HRMS** (ES^+) calc. 480.2033 [$C_{26}H_{28}N_5SF_2$], obs. 480.2034. **$[\alpha]_D$** = +65.10° (*c* = 1.0, $CHCl_3$).

(*S*)-1-(3,5-Dichlorophenyl)-3-(3,3-dimethyl-1-(5-(2-methylnaphthalen-1-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-yl)thiourea 223 *(single diastereoisomer and single enantiomer)*



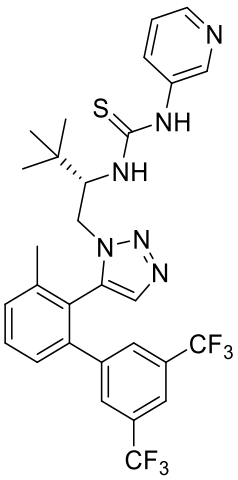
Prepared from 1*H*-1,2,3-triazole **219b'** and 3,5-dichlorophenyl isothiocyanate, following the *General Procedure K*, on a 0.10 mmol scale. The title compound was obtained as a white powder in 99% yield (0.051 g, 0.10 mmol). **m.p.** 178 – 180 °C. **IR** (neat) ν_{max} (cm^{-1}) 3330, 2965, 1594, 1537, 1265, 734. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.08 (1 H, s), 7.94 (1 H, d, *J* 8.4), 7.91 (1 H, d, *J* 9.4), 7.86 (1 H, s), 7.72 (1 H, d, *J* 9.5), 7.57 – 7.40 (5 H, m), 7.06 (1 H, s), 7.05 (1 H, s), 4.61 (1 H, td, *J* 9.7, 2.9), 4.35 – 4.24 (1 H, m), 4.21 (1 H, dd, *J* 14.0, 2.8), 2.59 (3 H, s), 0.63 (9 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.4, 140.4, 138.4, 135.8, 134.8, 134.7, 132.1, 131.9, 130.4, 129.0, 128.7, 127.5, 125.6, 124.8, 123.5, 121.2, 120.7, 62.0, 48.9, 35.1, 26.2, 21.7. **MS** (ES^+) *m/z* 512.1 $[M+H]^+$, 514.1 $[(M+H)+2]^+$, 516.1 $[(M+H)+4]^+$. **HRMS** (ES^+) calc. 512.1442 [$C_{26}H_{28}N_5SCl_2$], obs. 512.1440. **$[\alpha]_D$** = +152.35° (*c* = 1.0, $CHCl_3$).

(*S*)-1-(3,3-Dimethyl-1-(5-(3-methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-yl)-3-(naphthalen-1-yl)thiourea 224 *(single diastereoisomer and single enantiomer)*



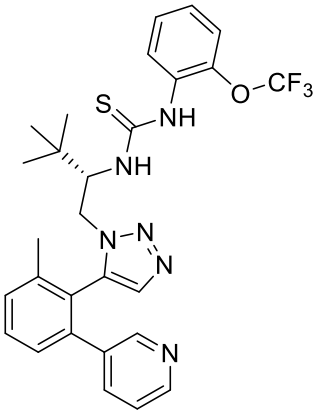
Prepared from 1*H*-1,2,3-triazole **219c** and 1-naphthyl isothiocyanate, following the *General Procedure K*, on a 0.17 mmol scale. The title compound was obtained as an off-white powder in 67% yield (0.075 g, 0.11 mmol). **m.p.** 107 – 109 °C. **IR** (neat) ν_{max} (cm^{-1}) 3305, 2967, 1534, 1277, 1135. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.03 (1 H, br s), 7.97 (1 H, d, *J* 8.0), 7.88 (2 H, d, *J* 7.6), 7.83 (1 H, s), 7.68 (1 H, s), 7.62 – 7.43 (8 H, m), 7.31 (1 H, dd, *J* 7.1, 1.9), 5.91 (1 H, br s), 4.31 (1 H, td, *J* 10.3, 3.0), 3.62 (1 H, dd, *J* 14.3, 3.1), 3.39 (1 H, dd, *J* 14.3, 10.5), 2.48 (3 H, s), 0.51 (9 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -63.09. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 182.2, 142.3, 140.9, 138.8, 135.3, 134.5, 133.7, 131.8 (q, $^{2}J_{CF}$ 33.4), 131.7, 131.2, 130.5, 130.2, 129.2, 128.9 (q, $^{3}J_{CF}$ 2.6), 128.4, 127.6, 127.4, 127.0, 126.3, 125.9, 124.2, 122.8 (q, $^{1}J_{CF}$ 272.9), 122.7, 121.0 (hept, $^{3}J_{CF}$ 3.4), 62.3, 47.4, 34.8, 26.0, 21.6. **MS** (ES^+) *m/z* 656.2 $[M+H]^+$; **HRMS** (ES^+) calc. 656.2283 [$C_{34}H_{32}N_5SF_6$], obs. 656.2275. **$[\alpha]_D$** = +52.91° (*c* = 1.0, $CHCl_3$).

(*S*)-1-(3,3-Dimethyl-1-(5-(3-methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-yl)-3-(pyridin-3-yl)thiourea 225 *(single diastereoisomer and single enantiomer)*



Prepared from 1*H*-1,2,3-triazole **219c** and 3-pyridyl isothiocyanate, following the *General Procedure K*, on a 0.17 mmol scale. The title compound was obtained as an off-white powder in 77% yield (0.079 g, 0.13 mmol). **m.p.** 127 – 130 °C. **IR** (neat) ν_{max} (cm^{-1}) 3321, 2963, 1541, 1277, 1135. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.20 (1 H, br s), 8.47 (1 H, d, *J* 2.6), 8.19 – 8.13 (1 H, m), 7.91 (1 H, s), 7.86 (1 H, ddd, *J* 8.2, 2.6, 1.5), 7.73 (1 H, s), 7.58 (2 H, s), 7.60 – 7.51 (2 H, m), 7.47 (1 H, br s), 7.37 (1 H, dd, *J* 7.2, 1.8), 6.94 (1 H, dd, *J* 7.9, 4.5), 4.46 (1 H, td, *J* 10.6, 2.2), 3.82 (1 H, dd, *J* 14.1, 2.4), 3.45 (1 H, dd, *J* 14.0, 11.0), 2.56 (3 H, s), 0.59 (9 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) - 63.16. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 182.2, 145.2, 144.6, 142.4, 141.1, 138.8, 135.7, 135.5, 134.9, 132.0, 131.9 (q, $^{2}J_{CF}$ 33.6), 131.0, 130.6, 128.9 (q, $^{3}J_{CF}$ 3.2), 127.7, 123.4, 122.8, 122.8 (q, $^{1}J_{CF}$ 272.8), 121.0 (hept, $^{3}J_{CF}$ 3.1), 61.2, 48.2, 34.9, 25.8, 21.7. **MS** (ES^+) *m/z* 607.2 $[M+H]^+$; **HRMS** (ES^+) calc. 607.2079 [$C_{29}H_{29}N_6SF_6$], obs. 607.2077. **$[\alpha]_D$** = +74.24° (*c* = 0.5, $CHCl_3$).

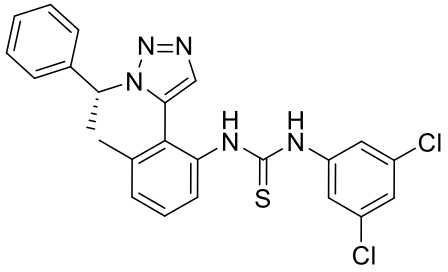
(*S*)-1-(3,3-Dimethyl-1-(5-(2-methyl-6-(pyridin-3-yl)phenyl)-1*H*-1,2,3-triazol-1-yl)butan-2-yl)-3-(2-(trifluoromethoxy)phenyl)thiourea 226 *(single diastereoisomer and single enantiomer)*



Step I: N-Boc-1*H*-1,2,3-triazole **219d** was deprotected, following the *General Procedure L*, on a 0.19 mmol scale. The crude product was obtained as a colourless oil (0.067 g), which was used without further purification.

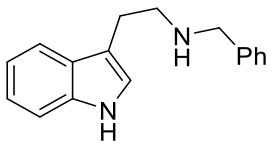
Step II: 1*H*-1,2,3-triazole from *Step I* was treated with 2-(trifluoromethoxy)phenyl isothiocyanate according to the *General Procedure K*, on a 0.19 mmol scale. The title compound was obtained as an off-white powder in 46% yield (0.048 g, 0.09 mmol). **m.p.** 154 – 155 °C. **IR** (neat) ν_{max} (cm^{-1}) 3371, 3251, 2934, 1584, 1528, 1237, 1135. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.55 (1 H, dd, *J* 2.4, 0.9), 8.47 (1 H, dd, *J* 5.0, 1.6), 8.17 (1 H, br s), 7.83 (1 H, br s), 7.70 (1 H, dd, *J* 7.4, 2.1), 7.52 (1 H, t, *J* 7.6), 7.47 (1 H, d, *J* 6.3), 7.34 (1 H, dd, *J* 7.5, 1.5), 7.32 – 7.20 (4 H, m), 7.09 (1 H, dd, *J* 8.0, 4.8), 6.78 (1 H, d, *J* 9.8), 4.39 (1 H, td, *J* 10.3, 2.8), 3.80 (1 H, dd, *J* 14.4, 2.9), 3.59 (1 H, dd, *J* 14.3, 10.7), 2.48 (3 H, s), 0.64 (9 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) -57.87. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 182.1, 149.3, 148.7, 142.9, 140.7, 138.1, 136.0, 135.9, 135.5, 134.6, 131.2, 130.5, 129.9, 128.6, 127.9, 127.6, 124.0, 123.1, 121.9, 120.4 (q, $^{1}J_{CF}$ 258.9), 62.2, 47.5, 35.2, 29.7, 26.1. **MS** (ES^+) *m/z* 555.2 $[M+H]^+$; **HRMS** (ES^+) calc. 555.2154 [$C_{28}H_{30}N_6OF_3S$], obs. 555.2169. **$[\alpha]_D$** = +46.12° (*c* = 1.0, $CHCl_3$).

(*R*)-1-(3,5-Dichlorophenyl)-3-(3-methyl-2-(1-(1-phenylethyl)-1*H*-1,2,3-triazol-5-yl)phenyl)thiourea 240 *(single diastereoisomer and single enantiomer)*



Prepared from 1*H*-1,2,3-triazole **239a** and 3,5-dichlorophenyl isothiocyanate, following the *General Procedure K*, on a 0.29 mmol scale. The title compound was obtained as an off-white powder in 57% yield (0.080 g, 0.17 mmol). **m.p.** 138 – 140 °C. **IR** (neat) ν_{max} (cm^{-1}) 3317, 2936, 1694, 1523. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.83 (1 H, br s), 9.27 (1 H, br s), 8.04 (1 H, d, *J* 7.9), 7.90 (2 H, d, *J* 1.9), 7.49 (1 H, t, *J* 8.0), 7.39 (1 H, s), 7.18 (1 H, t, *J* 1.9), 7.17 – 7.10 (3 H, m), 7.05 (1 H, dt, *J* 7.7, 1.1), 6.92 (2 H, dd, *J* 7.7, 1.9), 5.71 (1 H, q, *J* 7.0), 2.07 (3 H, d, *J* 7.1), 1.44 (3 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.2, 141.2, 139.7, 139.0, 137.9, 134.7, 134.6, 133.4, 129.9, 128.8, 128.2, 127.7, 127.1, 126.4, 125.1, 122.2, 120.5, 59.3, 20.8, 19.7. **MS** (ES^+) *m/z* 482.1 $[M+H]^+$, 486.1 $[(M+H)+2]^+$, 488.1 $[(M+H)+4]^+$. **HRMS** (ES^+) calc. 482.0973 [$C_{24}H_{22}N_5SCl_2$], obs. 482.0976. **$[\alpha]_D$** = -143.77° (*c* = 1.0, $CHCl_3$).

_N_-Benzyl-2-(1*H*-indol-3-yl)ethan-1-amine 251

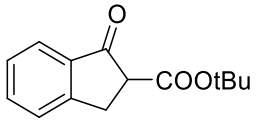


Following a literature procedure,[266] a solution of tryptamine (0.500 g, 3.12 mmol) and benzaldehyde (350 μL, 3.43 mmol) in methanol (18 mL) was stirred at room temperature for 3 hours. Sodium borohydride (0.177 g, 4.68 mmol) was added in one portion, and the resulting mixture was stirred for 1 hour, at which point the solvent was reduced under reduced pressure. Water (20 mL) was added, and the mixture extracted with ethyl acetate (3 × 20 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous magnesium

sulphate, filtered, and concentrated under reduced pressure to afford a crude product that was purified by automated flash column chromatography (30-100% Hx/EtOAc).

The title compound was obtained as a light brown oil in 90% yield (0.703 g, 2.81 mmol). Data in agreement with the reported literature values.[266] **IR** (neat) ν_{max} (cm^{-1}) 3411, 2917, 2840, 1454; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.11 (1 H, br s), 7.61 (1 H, ddt, *J* 7.8, 1.5, 0.8), 7.40 – 7.28 (3 H, m), 7.26 – 7.21 (3 H, m), 7.18 (1 H, ddd, *J* 8.1, 7.0, 1.3), 7.10 (1 H, ddd, *J* 8.0, 7.0, 1.2), 6.98 (1 H, d, *J* 2.3), 3.81 (2 H, s), 2.99 (4 H, s), 1.62 (1 H, br s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.3, 142.6, 134.3, 132.5, 131.5, 129.8, 128.8, 128.44, 128.41, 126.0, 124.4, 20.1. **HRMS** (ES^+) calc. 251.1548 [$C_{17}H_{19}N_2$], obs. 251.1551.

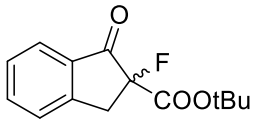
***tert*-Butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate 252**



Following a literature procedure,[267] a solution of indanone (1.000 g, 7.56 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 0.218 g, 9.10 mmol) in anhydrous tetrahydrofuran (10 mL), and the mixture refluxed for 10 minutes. A solution of *tert*-butyl pyrrole-1-carboxylate (1.6 mL, 9.10 mmol) in anhydrous tetrahydrofuran (3.0 mL) was added dropwise, and the resulting black solution was stirred at reflux for 16 hours, at which point it cooled to 0 °C. An aqueous solution of hydrochloric acid (1.0 M, 15 mL) was added, and the mixture extracted with ethyl acetate (3 × 20 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure to afford a crude product that was purified by automated flash column chromatography (0-20% Hx/EtOAc).

The title compound was obtained as light brown oil in 81% yield (1.430 g, 6.12 mmol). Data in agreement with the reported literature values.[267] **IR** (neat) ν_{max} (cm^{-1}) 2979, 2932, 1733, 1708, 1145; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.76 (1 H, dt, *J* 7.7, 1.0), 7.61 (1 H, td, *J* 7.4, 1.2), 7.50 (1 H, dt, *J* 7.7, 1.0), 7.39 (1 H, t, *J* 7.5), 3.62 (1 H, dd, *J* 8.2, 4.0), 3.50 (1 H, dd, *J* 17.3, 3.9), 3.34 (1 H, dd, *J* 17.2, 8.2), 1.49 (9 H, s). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.1, 168.4, 153.7, 135.5, 135.2, 127.7, 126.5, 124.6, 82.1, 54.4, 30.3, 28.0. **HRMS** (ES^+) calc. 255.0997 [$C_{16}H_{16}O_3Na$], obs. 255.1002.

***tert*-Butyl 2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate 253**

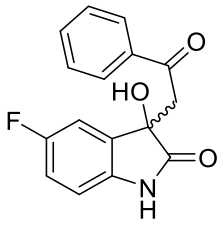


A solution of indanone **252** (0.046 g, 0.20 mmol), quinuclidine (0.002 g, 10 mol%) and triazole **227** (0.011 g, 10 mol%) in chloroform (1.0 mL) was stirred for 10 minutes at room temperature, hence cooled to 5 °C. *N*-Fluorobenzenesulfonimide (0.076 g, 0.24 mmol) was added, and the resulting mixture stirred at 5 °C for 48 hours. Saturated aqueous ammonium chloride (2 mL) was added, and the mixture extracted with ethyl acetate (3 × 5 mL). The combined organic fractions were washed with brine (5mL), dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-30% Hx/EtOAc).

The title compound was obtained as a pale yellow oil in 22% yield (0.011 g, 0.04 mmol) and 50:50 enantiomeric ratio. Data in agreement with the reported literature values.[268] **IR** (neat) ν_{max} (cm^{-1}) 2981, 2940, 1758, 1718, 1152; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.83 (1 H, dd, *J* 7.8, 1.2), 7.69 (1 H, td, *J* 7.5, 1.3), 7.54 – 7.40 (2 H, m), 3.73 (1 H, dd, *J* 17.5, 10.8), 3.40 (1 H, dd, *J* 22.8, 17.6), 1.43 (9 H, s). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -163.95 (dd, *J* 23.4, 11.0). **MS** (ES^+) *m/z* 268.1 $[M+NH_4]^+$; **HRMS** (ES^+) calc. 268.1349 [$C_{14}H_{19}NO_3F$], obs. 268.1352. **HPLC**

(Phenomenex Cellulose-3, 40% MeCN/H_2O, 1.0 mL/min, λ = 220 nm) R_t = 11.27 min, R_t = 12.75 min.

5-Fluoro-3-hydroxy-3-(2-oxo-2-phenylethyl)indolin-2-one 254 (*non-rac*)

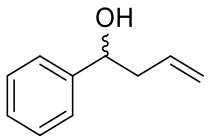


Adapted from a literature procedure.[226] A solution of 5-fluoroisatin (0.033 g, 0.20 mmol), quinuclidine (0.002 g, 10 mol%) and triazole **227** (0.011 g, 10 mol%) in tetrahydrofuran (4.0 mL) was stirred for 10 minutes at room temperature, hence cooled to 5 °C. Acetophenone (233 μL, 2.00 mmol) was added, and the resulting mixture stirred at 5 °C for 48 hours. Saturated aqueous ammonium chloride (2 mL) was added, and the mixture extracted with ethyl acetate (3 × 5 mL). The combined organic fractions were washed with brine (5mL), dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-50% Hx/EtOAc).

The title compound was obtained as a white solid in 82% yield (0.047 g, 0.16 mmol) and 47:53 enantiomeric ratio. Data in agreement with the reported literature values.[226] **IR** (neat) ν_{max} (cm^{-1}) 3330, 2924, 1717, 1683, 1489; **^{1}H NMR** (400 MHz, DMSO): δ 10.32 (1 H, br s), 7.93 – 7.82 (2 H, m), 7.63 (1 H, tt, *J* 7.4, 1.1), 7.51 (2 H, t, *J* 7.8), 7.23 (1 H, dd, *J* 8.2, 2.7), 7.00 (1 H, ddd, *J* 9.7, 8.4, 2.7), 6.81 (1 H, dd, *J* 8.4, 4.3), 6.22 (1 H, s), 4.13 (1 H, d, *J* 17.8), 3.64 (1 H, d, *J* 17.8). **^{13}C NMR** (101 MHz, DMSO) δ 197.0, 178.8, 158.3 (d, $^1J_{CF}$ 236.2), 139.6, 136.5, 134.1 (d, $^3J_{CF}$ 7.8), 134.0, 129.2, 128.4, 115.4 (d, $^2J_{CF}$ 23.2), 112.1 (d, $^2J_{CF}$ 24.5), 110.5 (d, $^3J_{CF}$ 7.8), 73.7, 46.2. **MS** (ES^+) *m/z* 308.1 $[M+Na]^+$; **HRMS** (ES^+) calc. 308.0699 [$C_{16}H_{12}NO_3Na$], obs.

308.0707. **HPLC** (Phenomenex Cellulose-3, 20% MeCN/H_2O, 1.0 mL/min, λ = 254 nm) R_t (major) = 23.32 min, R_t (minor) = 31.88 min.

1-Phenylbut-3-en-1-ol 255



Adapted from a literature procedure.[230] In an oven-dried two-neck round-bottom flask, allylboronic acid pinacol ester (45 μL, 0.24 mmol) was added dropwise, under a stream of argon, to a solution of benzaldehyde (20 μL, 0.20 mmol) and triazole **221** (0.012 g, 10 mol%) in anhydrous toluene (4.0 mL), cooled to 0 °C. The resulting solution was stirred for 16 hours at 10 °C, at which point the solvent was removed under reduced pressure to afford a crude residue that was purified by automated flash column chromatography (0-50% Hx/EtOAc).

The title compound was obtained as a colourless oil in 54% yield (0.016 g, 0.11 mmol) and 51:49 enantiomeric ratio. Data in agreement with the reported literature values.[269] **R_f** = 0.31 (25% EtOAc/Hx). **IR** (neat) ν_{max} (cm^{-1}) 3372, 3376, 3030, 2908, 1641, 1455, 700; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.40 – 7.30 (4 H, m), 7.32 – 7.27 (1 H, m), 5.82 (1 H, dddd, *J* 17.0, 10.2, 7.5, 6.7), 5.23 – 5.09 (2 H, m), 4.74 (1 H, ddd, *J* 7.8, 5.2, 2.6), 2.63 – 2.43 (2 H, m), 2.05 (1 H, br s). **MS** (CI^+) *m/z* 166.1 $[M+NH_4]^+$; **HRMS** (CI^+) calc. 166.1232 [$C_{10}H_{16}NO$], obs. 166.1230. **HPLC** (Phenomenex Cellulose-1, 30% MeCN/H_2O, 1.0 mL/min, λ = 220 nm) R_t (major) = 19.81 min, R_t (minor) = 22.36 min.

6.4 Computational Calculations

6.4.1 Computational Methods

Density Functional Theory (DFT) calculations were performed by Dr Andrew Leach (University of Manchester) with Gaussian09[270] using Truhlar's M06-2X hybrid meta GGA functional[271] and Pople's 6-31+G* split valence basis set.[272] Stationary points were optimized with default optimisation criteria, tight SCF convergence and ultrafine grid for numerical integration. Solvation by acetonitrile (MeCN) was described by a continuum description using the IEFPCM approach.[273] High-precision harmonic frequencies for vibrational modes were computed from the Hessian and characterised minima and transition states. Reported energies are free energies at 298 K calculated using default settings in Gaussian09.

6.4.2 Absolute Energies and Cartesian Coordinates

- *Ground States*

	M062X/6-31+G* in MeCN				
Compd.	**E_0 (au)**	**ZPE (au)**	**H (au)**	**TS (au)**	**G(t) (au)**
153a	-939.471951	0.398415	-939.451671	-0.071047	-939.522718
153b	-935.931918	0.327664	-935.912903	-0.066541	-935.979444
153c	-896.842018	0.313508	-896.822902	-0.068393	-896.891295
154a	-939.470238	0.397689	-939.449971	-0.068875	-939.518846
154b	-935.932198	0.327451	-935.913240	-0.065511	-935.978751
154c	-822.842476	0.331232	-822.823418	-0.067544	-822.890962

153a *CC_NAPHTHYL_Cy*

C	2.98119	0.25545	-1.98239
C	3.22401	-0.99754	-1.53722
C	2.64332	-1.46172	-0.32759
C	1.80433	-0.59728	0.4023
C	1.56069	0.73094	-0.09541
C	2.14044	1.15065	-1.26248
H	3.53686	-3.41779	-0.41818
H	3.43287	0.59823	-2.89718
H	3.86515	-1.65821	-2.09465
C	2.89064	-2.77289	0.15176
C	1.22559	-1.08673	1.6053
C	1.47834	-2.35072	2.04023
C	2.3246	-3.21059	1.30627
H	0.58451	-0.4468	2.18023
H	1.03064	-2.69972	2.95387
H	2.51618	-4.20634	1.66444
C	0.66815	1.63811	0.67306
C	0.86316	2.33636	1.82667
H	1.73669	2.3978	2.43967
N	-0.6057	1.93794	0.33799
N	-1.13187	2.76747	1.22015
N	-0.26733	3.01449	2.11445
C	1.95772	2.53721	-1.83741
H	1.37795	2.49962	-2.7562
H	1.46194	3.20962	-1.15238
H	2.9233	2.96557	-2.08662
C	-1.42278	1.45633	-0.76647
H	-2.1973	2.19872	-0.90426
H	-0.80653	1.44177	-1.65547
C	-2.03545	0.07142	-0.53494
C	-2.97661	0.03329	0.67606
C	-2.7721	-0.3811	-1.80404
H	-1.22049	-0.62756	-0.35555
C	-3.60537	-1.35158	0.85336
H	-3.76363	0.77424	0.53985
H	-2.44364	0.31721	1.577
C	-3.40803	-1.76304	-1.63021
H	-3.54957	0.34415	-2.04529
H	-2.08576	-0.39502	-2.64791
C	-4.33419	-1.80668	-0.41282
H	-4.29084	-1.3382	1.69632
H	-2.82518	-2.07132	1.09814
H	-3.95513	-2.03245	-2.52972
H	-2.62068	-2.50569	-1.51035
H	-4.72898	-2.81049	-0.27979
H	-5.18992	-1.15587	-0.58836

153b *CC_NAPHTHYL_BENZYL*

C	-3.32536	-0.14156	-1.36518
C	-3.30285	1.15493	-0.98226
C	-2.34544	1.61705	-0.04102

C	-1.4122	0.70319	0.48455
C	-1.45294	-0.66799	0.0537
C	-2.39599	-1.08708	-0.84579
H	-3.03792	3.65572	-0.03118
H	-4.06095	-0.48031	-2.07408
H	-4.01701	1.8526	-1.38441
C	-2.31622	2.97081	0.37933
C	-0.46388	1.18058	1.4289
C	-0.45866	2.4846	1.81428
C	-1.39758	3.39722	1.28438
H	0.25885	0.50262	1.84059
H	0.26888	2.82662	2.52862
H	-1.38052	4.4251	1.60041
C	-0.48333	-1.63604	0.63121
C	-0.53691	-2.4156	1.7471
H	-1.30395	-2.48198	2.48841
N	0.69738	-1.97471	0.07178
N	1.31052	-2.89032	0.79965
N	0.58593	-3.16219	1.8039
C	-2.50957	-2.5107	-1.34227
H	-2.22753	-2.57106	-2.39047
H	-1.88807	-3.19695	-0.7861
H	-3.53718	-2.85198	-1.26716
C	1.34174	-1.47068	-1.13213
H	1.92302	-2.29513	-1.52156
H	0.5673	-1.23571	-1.84787
C	2.22382	-0.2608	-0.89711
C	3.30485	-0.33355	-0.02314
C	1.9829	0.92368	-1.57483
C	4.12331	0.76406	0.16729
H	3.49846	-1.24845	0.50809
C	2.80673	2.02442	-1.38766
H	1.14561	0.99581	-2.24739
C	3.87696	1.94661	-0.51641
H	4.95568	0.69757	0.84549
H	2.60588	2.93822	-1.91829
H	4.5164	2.79887	-0.36797

153c *CC_NAPHTHYL_OMe*

C	3.15812	-1.58561	-0.96435
C	2.57796	-2.66931	-0.33702
C	1.52448	-2.50521	0.54605
C	1.04754	-1.2272	0.79929
C	1.62376	-0.11992	0.16411
C	2.68842	-0.29885	-0.71927
H	3.97839	-1.73332	-1.64333
H	2.94858	-3.66054	-0.53184
C	1.08814	1.23375	0.45088
C	1.40874	2.16293	1.39221
H	2.13983	2.11297	2.17008
N	0.10792	1.83221	-0.25662
N	-0.14422	3.03667	0.22478

N	0.62556	3.24683	1.20998
C	3.33964	0.88214	-1.40354
H	2.62854	1.43834	-2.00564
H	3.75278	1.57461	-0.67878
H	4.14093	0.55194	-2.05287
C	-0.6737	1.33052	-1.37301
H	-1.00666	2.20666	-1.91283
H	-0.01577	0.7672	-2.0199
C	-1.85924	0.47621	-0.9684
C	-2.78288	0.93673	-0.03535
C	-2.06016	-0.76	-1.5619
C	-3.88448	0.16914	0.29399
H	-2.6338	1.89327	0.43263
C	-3.16872	-1.52932	-1.23604
H	-1.34998	-1.13076	-2.2812
C	-4.0821	-1.06656	-0.30691
H	-4.59266	0.53565	1.01615
H	-3.31305	-2.48557	-1.70759
H	-4.94277	-1.65969	-0.05207
H	1.09197	-3.36122	1.02533
O	0.03981	-0.95869	1.64274
C	-0.70276	-2.00063	2.21518
H	-0.09235	-2.60255	2.88094
H	-1.48903	-1.52752	2.78338
H	-1.14492	-2.63278	1.45305

154a *CN_NAPHTHYL_Cy*

C	2.81036	-0.09015	-2.09289
C	2.91687	-1.34678	-1.6043
C	2.35605	-1.68882	-0.34472
C	1.6763	-0.69865	0.38799
C	1.57567	0.61502	-0.17034
C	2.13083	0.93365	-1.37312
H	2.9852	-3.7479	-0.38247
H	3.25005	0.15724	-3.04323
H	3.43655	-2.10399	-2.16522
C	2.46196	-2.99908	0.1864
C	1.11764	-1.04442	1.647
C	1.23379	-2.31078	2.12896
C	1.91425	-3.30549	1.39109
H	0.61542	-0.29434	2.22629
H	0.8095	-2.55837	3.08571
H	1.99821	-4.30082	1.78953
N	0.5425	2.97256	2.12563
C	2.08603	2.31856	-1.97307
H	1.4064	2.35216	-2.82047
H	1.77499	3.06484	-1.2567
H	3.07007	2.59247	-2.33797
C	-1.34671	1.60408	-0.72382
H	-2.10504	2.37287	-0.83928
H	-0.7986	1.56717	-1.65937
N	0.84234	1.59886	0.5604

N	1.38519	2.17194	1.63159
C	-0.58978	2.93758	1.38465
C	-0.4218	2.04697	0.37118
H	-1.43941	3.54157	1.6216
C	-2.03493	0.24402	-0.49574
C	-2.96814	0.25223	0.72244
C	-2.8085	-0.17226	-1.75479
H	-1.26161	-0.50149	-0.32145
C	-3.67041	-1.09577	0.90875
H	-3.71832	1.03282	0.58982
H	-2.41309	0.50528	1.62012
C	-3.51609	-1.51813	-1.57517
H	-3.54728	0.59438	-1.99039
H	-2.13115	-0.22262	-2.60423
C	-4.43337	-1.51234	-0.35042
H	-4.34674	-1.04447	1.75788
H	-2.92747	-1.8553	1.14817
H	-4.08431	-1.75892	-2.46983
H	-2.76891	-2.30208	-1.4608
H	-4.87991	-2.49351	-0.21224
H	-5.25493	-0.81709	-0.51941

154b *CN_NAPHTHYL_BENZYL*

C	3.06813	-0.63457	-1.46639
C	2.72821	-1.87556	-1.04233
C	1.74224	-2.05993	-0.03914
C	1.10563	-0.92821	0.50402
C	1.47464	0.35856	0.01047
C	2.44438	0.52647	-0.93382
H	1.88224	-4.20941	0.0122
H	3.82962	-0.51213	-2.21613
H	3.21587	-2.74055	-1.45736
C	1.39055	-3.35035	0.43468
C	0.13487	-1.1124	1.52414
C	-0.17848	-2.36082	1.95825
C	0.45462	-3.49912	1.40654
H	-0.34804	-0.25643	1.95377
H	-0.91508	-2.48787	2.73133
H	0.19274	-4.47912	1.7638
N	0.61555	3.12592	1.88388
C	2.86906	1.88705	-1.4347
H	2.25626	2.20369	-2.27494
H	2.79308	2.63929	-0.66176
H	3.89683	1.85556	-1.77633
C	-1.04612	1.82246	-1.13096
H	-1.54755	2.72358	-1.46926
H	-0.37649	1.52259	-1.9285
C	-2.07843	0.72781	-0.90476
C	-3.08771	0.88748	0.03994
C	-2.05076	-0.4352	-1.65913
C	-4.04348	-0.09447	0.22417
H	-3.12315	1.78199	0.63744

C	-3.00812	-1.42231	-1.47606
H	-1.27481	-0.57891	-2.39092
C	-4.00668	-1.25504	-0.53481
H	-4.81745	0.04505	0.95836
H	-2.96787	-2.31986	-2.06765
H	-4.74974	-2.01935	-0.39086
N	0.82231	1.50817	0.55453
N	1.31518	2.10326	1.63657
C	-0.36069	3.23106	0.95237
C	-0.24353	2.1933	0.08249
H	-1.06771	4.03307	0.96219

154c *CN_NAPHTHYL_BUTYL*

C	2.24211	-1.22133	2.05
C	3.01741	-0.14231	1.78935
C	2.78887	0.66019	0.64086
C	1.73337	0.31933	-0.22509
C	0.9264	-0.81346	0.09827
C	1.16393	-1.58513	1.19601
H	4.40079	2.04013	1.01128
H	2.43625	-1.82567	2.9185
H	3.82646	0.1147	2.45081
C	3.59707	1.78668	0.34201
C	1.51797	1.10929	-1.38565
C	2.31079	2.18264	-1.64536
C	3.36449	2.53162	-0.76954
H	0.73205	0.84355	-2.06671
H	2.14114	2.77074	-2.52973
H	3.98125	3.38406	-0.99179
N	-1.10546	-2.05165	-2.40122
C	0.32826	-2.79306	1.5463
H	-0.45604	-2.52799	2.25101
H	-0.13473	-3.22976	0.67311
H	0.94503	-3.55008	2.0169
C	-1.94297	0.27469	0.33324
H	-1.78732	-0.16228	1.31648
H	-1.33891	1.17799	0.30566
N	-0.16645	-1.12634	-0.76526
N	-0.00122	-1.94892	-1.79728
C	-2.03131	-1.28636	-1.77412
C	-1.44085	-0.67778	-0.71081
H	-3.03886	-1.22777	-2.12375
C	-3.41898	0.63596	0.1596
H	-3.56948	1.07657	-0.82326
H	-4.01928	-0.27049	0.18982
C	-3.91235	1.60765	1.23228
H	-3.30846	2.51242	1.20446
H	-3.75888	1.16769	2.21577
C	-5.38558	1.97557	1.06581
H	-5.70653	2.66504	1.84017
H	-5.56535	2.44975	0.10508
H	-6.019	1.09482	1.12336

- *Transition States*

Compd.		M062X/6-31+G* in MeCN				
		E_0 (au)	**ZPE (au)**	**H (au)**	**TS (au)**	**G(t) (au)**
153a	TS1	-939.424860	0.399468	-939.406058	0.063978	-939.470036
	TS2	-939.427432	0.399829	-939.408761	0.063606	-939.472367
153b	TS1	-935.880889	0.328500	-935.863122	0.063051	-935.926173
	TS2	-935.885842	0.329200	-935.868328	0.061874	-935.930202
153c	TS1	-896.803038	0.315728	-896.785593	0.062674	-896.848267
	TS2	-896.813720	0.315599	-896.796490	0.061084	-896.857574
154a	TS1	-939.415358	0.398637	-939.396517	0.064107	-939.460624
	TS2	-939.418757	0.398450	-939.399907	0.064411	-939.464318
154b	TS1	-935.876555	0.327761	-935.858679	0.063675	-935.922354
	TS2	-935.880471	0.327884	-935.862741	0.062699	-935.925440
154c	TS1	-822.792825	0.332041	-822.775516	0.060724	-822.836240
	TS2	-939.415358	0.398637	-939.396517	0.064107	-939.460624

153a TS1 *CC_NAPHTHYL_Cy*

C	1.65618	-2.48365	0.36026	C	2.89722	0.01625	0.146
C	2.91342	-2.42521	-0.11511	C	1.51515	-0.05668	0.62059
C	3.57661	-1.17587	-0.20149	C	0.95501	-1.30985	0.74126
C				H	5.39175	-2.07873	-0.90461

H	1.15986	-3.43121	0.47752
H	3.4372	-3.31868	-0.40599
C	4.92115	-1.14551	-0.64849
C	3.65426	1.21307	0.0163
C	4.94875	1.21689	-0.40612
C	5.60516	0.02127	-0.74903
H	3.22362	2.15448	0.25146
H	5.47274	2.15343	-0.47942
H	6.62661	0.03713	-1.0842
C	0.64158	1.17067	0.60099
C	0.94	2.50665	0.49305
H	1.79012	3.04186	0.84394
N	-0.64779	1.15757	0.07736
N	-1.04814	2.38596	-0.19442
N	-0.12703	3.2021	0.0704
C	-0.28868	-1.57189	1.57103
H	-0.76839	-0.66786	1.90943
H	-1.01597	-2.18752	1.05493
H	0.01992	-2.12183	2.45546
C	-1.43914	0.14196	-0.63918
H	-1.5336	0.50731	-1.65387
H	-0.8565	-0.75925	-0.687
C	-2.84105	-0.15119	-0.08192
C	-3.81646	1.03247	-0.17989
C	-3.41038	-1.36494	-0.83763
H	-2.75235	-0.41888	0.96729
C	-5.21621	0.64992	0.31049
H	-3.87291	1.3638	-1.21595
H	-3.44447	1.8746	0.3874
C	-4.81183	-1.74586	-0.35424
H	-3.45044	-1.13296	-1.90196
H	-2.74429	-2.21891	-0.73497
C	-5.77471	-0.56083	-0.43797
H	-5.88392	1.50004	0.20041
H	-5.17595	0.42561	1.3761
H	-5.18732	-2.58131	-0.93924
H	-4.75375	-2.09014	0.67761
H	-6.7463	-0.83859	-0.03781
H	-5.93116	-0.29773	-1.48335

153a TS2 *CC_NAPHTHYL_Cy*

C	2.08958	-2.56353	-0.44108
C	3.40794	-2.23234	-0.53461
	3.81776	-0.9377	-0.11486
C	2.82536	0.02526	0.22464
C	1.4151	-0.25761	-0.04011
C	1.0719	-1.60543	-0.14729
H	5.92362	-1.38732	-0.24785
H	1.77174	-3.58954	-0.61259
H	4.15582	-2.96586	-0.82448
C	5.19428	-0.6443	0.0659
C	3.27538	1.16864	0.94234

C	4.61406	1.4097	1.16061
C	5.59581	0.522	0.6706
H	2.55297	1.82932	1.40407
H	4.91065	2.2797	1.73902
H	6.65002	0.73275	0.82213
C	0.53494	0.92419	-0.29798
C	-0.85826	0.90515	-0.40483
H	-1.54214	0.07644	-0.40352
N	0.78433	2.2813	-0.2306
N	-0.35239	2.98285	-0.31629
N	-1.34377	2.16015	-0.42562
C	-0.2704	-2.23251	0.14542
H	-0.96748	-1.54583	0.61645
H	-0.73399	-2.68979	-0.73467
H	-0.09289	-3.04314	0.86062
C	1.95659	3.12128	0.04455
H	1.58045	3.93393	0.67224
H	2.65063	2.54758	0.65165
C	2.61481	3.71907	-1.20511
C	1.73577	4.7752	-1.88848
C	3.96614	4.32582	-0.80542
H	2.79249	2.9196	-1.93949
C	2.45254	5.40347	-3.08734
H	1.4898	5.55971	-1.15615
H	0.78649	4.3309	-2.2052
C	4.68005	4.95966	-2.00143
H	3.79311	5.09282	-0.0349
H	4.60457	3.55823	-0.34995
C	3.79722	6.00833	-2.68023
H	1.8113	6.1668	-3.54293
H	2.61986	4.63167	-3.85266
H	5.62721	5.40535	-1.67702
H	4.93021	4.17231	-2.72734
H	4.30742	6.42776	-3.55499
H	3.62236	6.83995	-1.98215

153b TS1 *CC_NAPHTHYL_BENZYL*

C	12.266	6.709	8.703
C	11.99297	8.05303	8.82812
H	11.77617	8.62546	8.1292
C	12.99868	5.01937	10.47486
H	13.5987	4.62803	9.82045
H	12.24156	4.42235	10.57937
C	13.71843	5.14247	11.79463
C	15.01025	5.66149	11.84835
H	15.43303	5.93247	11.06625
C	15.66918	5.77582	13.06587
H	16.52296	6.14341	13.09987
C	15.05446	5.34233	14.23151
H	15.50328	5.39845	15.04488
C	13.77376	4.82652	14.18522
H	13.35896	4.5419	14.96692

C	13.10233	4.73143	12.972
H	12.23713	4.39127	12.9469
C	12.299	5.778	7.555
C	12.091	6.249	6.267
C	12.228	5.343	5.184
H	12.097	5.653	4.317
C	12.547	4.033	5.373
H	12.637	3.471	4.638
C	12.742	3.515	6.678
C	12.599	4.394	7.79
C	12.77	3.857	9.092
H	12.665	4.41	9.832
C	13.09	2.535	9.276
H	13.183	2.199	10.139
C	13.277	1.682	8.167
H	13.521	0.794	8.298
C	13.099	2.163	6.899
H	13.214	1.594	6.173
C	11.757	7.681	5.952
H	10.826	7.752	5.73
H	12.287	7.977	5.208
H	11.946	8.23	6.718
N	12.52507	6.31652	9.9784
N	12.41931	7.35024	10.84083
N	12.08856	8.41017	10.13692

153b TS2 *CC_NAPHTHYL_BENZYL*

C	-1.35154	2.4875	0.24343
C	-2.65371	2.45116	-0.09303
C	-3.34889	1.21622	-0.08971
C	-2.66065	0.01424	0.20021
C	-1.23345	0.06236	0.51644
C	-0.63521	1.30356	0.5621
H	-5.21075	2.14941	-0.60628
H	-0.82651	3.42537	0.29377
H	-3.18702	3.35277	-0.33791
C	-4.73438	1.20971	-0.38724
C	-3.45218	-1.16676	0.17769
C	-4.78501	-1.14755	-0.10064
C	-5.44941	0.05716	-0.39253
H	-3.01893	-2.11348	0.38567
H	-5.33399	-2.07256	-0.09738
H	-6.50144	0.05932	-0.61421
C	-0.39558	-1.18499	0.41755
C	-0.72361	-2.51739	0.35696
H	-1.54343	-3.03564	0.794
N	0.83157	-1.20144	-0.23348
N	1.18888	-2.43911	-0.52937
N	0.28576	-3.2349	-0.16287
C	0.70009	1.55358	1.23972
H	1.21835	0.65152	1.52043
H	1.36762	2.16202	0.64158

H	0.4995	2.10616	2.15323
C	1.58506	-0.21072	-1.00276
H	1.65083	-0.61134	-2.00564
H	1.00525	0.69245	-1.06545
C	2.98992	0.08292	-0.50638
C	3.63852	-0.67988	0.45166
C	3.66642	1.15354	-1.08372
C	4.93585	-0.36762	0.83378
H	3.1438	-1.52237	0.89499
C	4.96013	1.4613	-0.70624
H	3.1773	1.75175	-1.83515
C	5.60053	0.70009	0.25992
H	5.42539	-0.96839	1.57992
H	5.46666	2.29352	-1.16259
H	6.60646	0.93719	0.55775

153c TS1 *CC_NAPHTHYL_OMe*

C	1.92211	-2.69902	-0.29326
C	3.28202	-2.52997	-0.31486
C	3.81207	-1.29579	0.0114
C	2.97467	-0.22389	0.26231
C	1.55652	-0.33207	0.1708
C	1.06317	-1.6357	-0.02245
H	1.4964	-3.67631	-0.43792
H	3.93622	-3.35634	-0.52878
C	0.78719	0.94715	-0.03412
C	1.28046	2.2278	-0.13549
H	2.21932	2.61258	0.16821
N	-0.47168	1.1044	-0.5841
N	-0.68774	2.37685	-0.88886
N	0.33627	3.05345	-0.61518
C	-0.34442	-2.06042	0.36141
H	-0.93188	-1.25974	0.77571
H	-0.89486	-2.51942	-0.4519
H	-0.25039	-2.81094	1.139
C	-1.46952	0.23234	-1.19632
H	-1.73157	0.71936	-2.12484
H	-1.00977	-0.70295	-1.45711
C	-2.73872	0.0239	-0.3904
C	-3.05371	0.78286	0.72558
C	-3.64255	-0.94093	-0.82512
C	-4.2473	0.57103	1.40179
H	-2.37803	1.54473	1.06503
C	-4.83294	-1.14865	-0.15409
H	-3.41408	-1.53389	-1.69561
C	-5.13881	-0.39215	0.96751
H	-4.47767	1.16716	2.26714
H	-5.51975	-1.89958	-0.50316
H	-6.06344	-0.55247	1.49308
H	4.87494	-1.17349	0.05765
O	3.47933	0.97012	0.6141
C	4.86096	1.17248	0.73497

H	5.3711	1.01132	-0.20856
H	4.9837	2.20332	1.03295
H	5.2899	0.52906	1.49544

153c TS2 *CC_NAPHTHYL_OMe*

C	-1.72567	2.75514	-0.39425
C	-2.97826	2.67922	0.18625
C	-3.49564	1.4316	0.48721
C	-2.74712	0.27981	0.23667
C	-1.41609	0.32164	-0.30263
C	-0.94844	1.61843	-0.65635
H	-1.32427	3.72544	-0.66768
H	-3.55524	3.57645	0.38813
C	-0.68002	-0.98991	-0.41587
C	0.58067	-1.17835	-0.99778
H	1.23577	-0.46699	-1.45568
N	-0.98601	-2.28737	-0.02071
N	0.00646	-3.13271	-0.35162
N	0.94591	-2.47296	-0.93328
C	0.34309	1.93758	-1.36592
H	1.22357	1.62581	-0.80566
H	0.36241	1.49909	-2.36693
H	0.42002	3.01835	-1.49738
C	-2.14744	-3.05722	0.43836
H	-1.70989	-3.98685	0.80779
H	-2.6264	-2.58001	1.28376
C	-3.12342	-3.37784	-0.67494
C	-2.84758	-3.09679	-2.01358
C	-4.32927	-4.00474	-0.34151
C	-3.76906	-3.43414	-3.00727
H	-1.9147	-2.61198	-2.29083
C	-5.24641	-4.34384	-1.33256
H	-4.55154	-4.22227	0.70135
C	-4.96872	-4.05763	-2.67121
H	-3.54419	-3.20804	-4.04552
H	-6.17949	-4.82832	-1.06028
H	-5.68489	-4.31894	-3.44453
H	-4.48579	1.35084	0.91532
O	-3.29544	-0.92936	0.5003
C	-4.62378	-1.02073	0.99292
H	-5.33525	-0.58183	0.28655
H	-4.82019	-2.08774	1.09485
H	-4.71661	-0.53668	1.97001

154a TS1 *CC_NAPHTHYL_Cy*

C	1.7054	-2.51776	0.10577
C	2.98212	-2.39263	-0.29635
C	3.62091	-1.12885	-0.22273
C	2.90069	0.02431	0.17629
C	1.47686	-0.12985	0.47569
C	0.94001	-1.39193	0.50752
H	5.49957	-1.94686	-0.85824

H	1.23098	-3.48331	0.13343
H	3.54655	-3.24719	-0.62462
C	5.00058	-1.0489	-0.53816
C	3.6666	1.22111	0.31452
C	4.99741	1.25857	0.02825
C	5.68313	0.11689	-0.42355
H	3.20063	2.10951	0.66653
H	5.53015	2.1839	0.15825
H	6.7319	0.16741	-0.65624
N	0.32331	3.0756	-0.06585
C	-0.32956	-1.72776	1.2672
H	-0.82213	-0.85401	1.66072
H	-1.03826	-2.30653	0.68816
H	-0.04039	-2.33904	2.11708
C	-1.58767	0.06098	-0.791
H	-1.80525	0.40447	-1.79817
H	-1.07381	-0.87798	-0.91805
N	0.57434	1.01203	0.43123
N	1.12281	2.23631	0.40067
C	-0.79124	2.42656	-0.46411
C	-0.65262	1.10384	-0.22235
H	-1.59612	2.93641	-0.94686
C	-2.94528	-0.16333	-0.0864
C	-3.8341	1.08918	-0.07088
C	-3.68459	-1.32056	-0.77732
H	-2.77322	-0.44779	0.94759
C	-5.19943	0.8128	0.5665
H	-3.98114	1.43791	-1.09377
H	-3.34186	1.89096	0.46805
C	-5.05021	-1.60039	-0.14491
H	-3.82087	-1.07456	-1.83053
H	-3.07612	-2.22141	-0.74968
C	-5.92389	-0.34528	-0.12101
H	-5.80823	1.71213	0.53031
H	-5.06107	0.5754	1.62052
H	-5.5505	-2.39831	-0.68719
H	-4.90784	-1.95902	0.87372
H	-6.86501	-0.55199	0.3815
H	-6.17182	-0.05975	-1.1426

154a TS2 *CC_NAPHTHYL_Cy*

C	2.11398	-2.56507	-0.456
C	3.43201	-2.23108	-0.42493
C	3.79633	-0.92452	-0.007
C	2.7869	0.06054	0.21197
C	1.41048	-0.26884	-0.15755
C	1.0693	-1.60864	-0.27867
H	5.89718	-1.40713	0.05097
H	1.81417	-3.59439	-0.63712
H	4.20652	-2.96868	-0.61599
C	5.15937	-0.64135	0.27738
C	3.20441	1.23752	0.9057

C	4.52334	1.4602	1.2289
C	5.52991	0.53825	0.87013
H	2.47269	1.96399	1.22009
H	4.78546	2.35904	1.77936
H	6.57115	0.74172	1.10134
N	-1.55942	1.466	-0.72551
C	-0.29095	-2.24561	-0.12582
H	-1.01388	-1.59097	0.34873
H	-0.69417	-2.62629	-1.06876
H	-0.16363	-3.11021	0.53343
C	1.53462	3.24337	0.05724
H	2.48696	2.80555	-0.26656
H	1.41816	4.14647	-0.536
N	0.49087	0.83104	-0.43559
N	-0.7894	0.43933	-0.68074
C	-0.81493	2.56639	-0.48288
C	0.4965	2.20952	-0.27328
H	-1.24167	3.55881	-0.44322
C	1.66915	3.56338	1.56223
C	2.94762	4.35325	1.86885
C	0.43788	4.3395	2.04392
H	1.731	2.62468	2.13372
C	3.0481	4.70157	3.35591
H	2.94124	5.28175	1.27638
H	3.82995	3.78183	1.55829
C	0.53482	4.6998	3.52819
H	0.34929	5.26071	1.44712
H	-0.47079	3.75241	1.85499
C	1.81734	5.47876	3.8278
H	3.96088	5.27898	3.54288
H	3.13488	3.77275	3.93832
H	-0.34559	5.27837	3.83079
H	0.52726	3.77452	4.12247
H	1.88966	5.69617	4.89978
H	1.78183	6.44661	3.30677

154b TS1 *CN_NAPHTHYL_BENZ*

C	-0.6157	-3.9239	0.47808
H	-1.46425	-4.03577	-0.19473
H	-0.97132	-3.88911	1.51042
C	0.31244	-5.10048	0.29987
C	0.48868	-5.66488	-0.96586
H	-0.02353	-5.23189	-1.82243
C	1.31935	-6.77016	-1.13508
H	1.45133	-7.20109	-2.1233
C	1.9735	-7.32653	-0.03407
H	2.61854	-8.19077	-0.16357
C	1.79055	-6.77435	1.23339
H	2.29208	-7.20703	2.09404
C	0.96054	-5.6656	1.39864
H	0.82059	-5.23326	2.38681
C	-1.79354	-0.72377	-0.18959

C	-2.90501	-1.5718	-0.13006
C	-4.15456	-1.06381	0.32976
H	-4.97841	-1.76662	0.42799
C	-4.32144	0.24109	0.69185
H	-5.25759	0.59421	1.11631
C	-3.2955	1.17402	0.38802
C	-2.0653	0.70462	-0.16158
C	-1.24878	1.68142	-0.7878
H	-0.4483	1.35998	-1.43411
C	-1.52383	3.02838	-0.70777
H	-0.88273	3.73614	-1.22529
C	-2.65209	3.48838	0.00502
H	-2.85072	4.55232	0.09037
C	-3.53504	2.5677	0.51445
H	-4.46215	2.88892	0.98319
C	-2.94838	-3.02497	-0.55364
H	-3.88489	-3.18454	-1.09693
H	-2.95993	-3.71421	0.29828
H	-2.12414	-3.29893	-1.21317
N	1.78781	-1.52486	-0.36456
N	-0.43931	-1.35531	-0.09726
N	0.73366	-0.69616	-0.46026
C	0.03064	-2.62888	0.16308
C	1.35879	-2.68628	0.01271
H	1.96701	-3.55106	0.17743

154b TS2 *CN_NAPHTHYL_BENZ*

C	4.04841	-0.32029	0.27345
C	3.72914	-1.56507	-0.13347
C	2.3626	-1.93006	-0.20118
C	1.38595	-0.93571	0.00424
C	1.79115	0.45359	0.05785
C	3.08373	0.72073	0.45444
H	2.7361	-4.01876	-0.53699
H	5.0788	-0.06869	0.44782
H	4.4907	-2.30519	-0.30349
C	1.97632	-3.28882	-0.31805
C	0.08219	-1.38525	0.33455
C	-0.25581	-2.70258	0.28723
C	0.69192	-3.67197	-0.09965
H	-0.63905	-0.68573	0.69725
H	-1.24942	-3.00244	0.56802
H	0.40972	-4.70761	-0.16505
N	0.48532	3.5821	-0.45064
C	3.66628	2.01997	0.97955
H	3.82783	2.74622	0.19398
H	3.02692	2.48343	1.71495
H	4.61957	1.79835	1.4462
C	-1.39052	0.5776	-1.27068
H	-1.74897	1.04265	-2.18377
H	-0.88437	-0.32138	-1.58311
C	-2.61731	0.21947	-0.43863

C	-3.01699	0.93588	0.67951
C	-3.40093	-0.85528	-0.85421
C	-4.17057	0.58496	1.36909
H	-2.43385	1.77083	1.02164
C	-4.55126	-1.20247	-0.1716
H	-3.10463	-1.4244	-1.71922
C	-4.9414	-0.48139	0.94797
H	-4.4614	1.15171	2.23602
H	-5.14228	-2.03541	-0.51004
H	-5.83475	-0.7512	1.48266
N	0.79163	1.50622	-0.02663
N	1.30361	2.75066	-0.00298
C	-0.602	2.91328	-0.88867
C	-0.42525	1.58739	-0.69442
H	-1.42875	3.41093	-1.34911

154c TS1 *CN_NAPHTHYL_Bu*

C	1.06175	-2.4976	0.4612
C	2.18612	-2.36327	-0.26336
C	2.75877	-1.07796	-0.44031
C	2.10584	0.07784	0.0538
C	0.81589	-0.09768	0.72041
C	0.36733	-1.37013	0.97466
H	4.45405	-1.87925	-1.48269
H	0.65985	-3.47318	0.67296
H	2.69024	-3.22243	-0.66874
C	4.00626	-0.9766	-1.10521
C	2.81571	1.30743	-0.0912
C	4.02575	1.36741	-0.71329
C	4.63291	0.21738	-1.24843
H	2.40716	2.20427	0.3081
H	4.52429	2.31754	-0.7884
H	5.58371	0.2849	-1.74647
N	-0.62373	3.01566	0.31403
C	-0.64418	-1.69949	2.06002
H	-1.05664	-0.82262	2.53471
H	-1.4528	-2.33129	1.71321
H	-0.11333	-2.25395	2.82813
C	-2.42548	-0.15596	0.33432
H	-1.89307	-0.97131	-0.14063
H	-2.79001	-0.52494	1.28415
N	-0.12079	1.00719	0.83408
N	0.32443	2.2483	0.58416
C	-1.76527	2.29328	0.27513
C	-1.47891	0.99742	0.53084
H	-2.69901	2.74338	0.02252
C	-3.63604	0.20709	-0.534
H	-4.21962	0.98592	-0.04994
H	-3.29814	0.61171	-1.48409
C	-4.53748	-1.00335	-0.78445
H	-4.86718	-1.41378	0.16825
H	-3.96189	-1.78709	-1.27309

C	-5.75798	-0.66465	-1.63859
H	-6.37663	-1.54138	-1.80184
H	-6.37451	0.09103	-1.16001
H	-5.46181	-0.28237	-2.61125

154c TS2 *CN_NAPHTHYL_Bu*

C	1.54764	-2.589	-0.23157
C	2.79572	-2.19497	-0.6063
C	3.18728	-0.85253	-0.36883
C	2.22548	0.09537	0.09022
C	0.82532	-0.31492	0.15387
C	0.54369	-1.67446	0.2075
H	5.24333	-1.22861	-0.90192
H	1.27347	-3.64039	-0.26832
H	3.52241	-2.90744	-0.98669
C	4.55427	-0.48809	-0.50362
C	2.74678	1.33184	0.58018
C	4.08547	1.63664	0.49825
C	5.0029	0.74129	-0.09541
H	2.08736	2.04052	1.05637
H	4.43812	2.57958	0.90588
H	6.05183	1.0076	-0.18435
N	-2.24168	1.30645	0.46159
C	-0.66444	-2.35797	0.80603
H	-1.16417	-1.73979	1.54609
H	-1.38842	-2.70614	0.06562
H	-0.29913	-3.2451	1.33151
C	0.87229	3.1552	-0.10561
H	1.66925	2.94515	0.61045
H	1.31224	3.13735	-1.10612
N	-0.18712	0.73366	0.10602
N	-1.44396	0.3042	0.40363
C	-1.53138	2.43526	0.2341
C	-0.20818	2.11973	0.03025
H	-1.99391	3.40962	0.2574
C	0.36228	4.57578	0.15609
H	-0.42199	4.8346	-0.5669
H	-0.08866	4.63315	1.15531
C	1.49403	5.59712	0.04894
H	1.93897	5.54135	-0.95321
H	2.289	5.33369	0.75901
C	1.01313	7.02097	0.31964
H	1.83184	7.74183	0.23231
H	0.23168	7.31088	-0.39183
H	0.59495	7.10603	1.32885

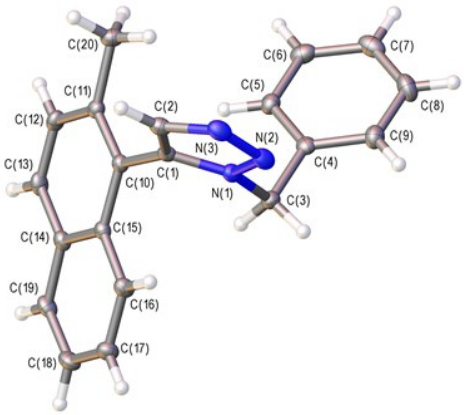
6.5 X-Ray Crystallography

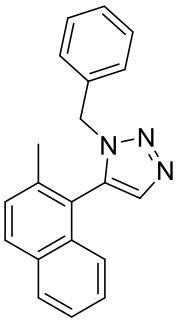
6.5.1 X-Ray Crystallography Methods

A suitable crystal was selected and measured on an Agilent SuperNova diffractometer using an Atlas detector. The crystal was kept at 100.00(10) K during data collection. Using Olex2,[274] the structure was solved with the ShelXT[275] structure solution program using using Intrinsic Phasing and refined with the ShelXL[276] refinement package Least Squares minimisation.. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on the equivalent isotropic displacement parameter (U_{eq}) of the parent atom.

6.5.2 Crystal Data

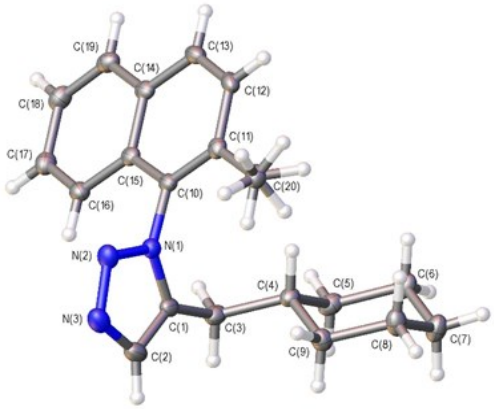
153b (*rac*)

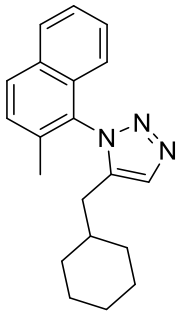




$C_{20}H_{17}N_3$ (M = 299.36 g/mol): monoclinic, space group C2/c (no. 15), a = 24.0885(9) Å, b = 9.0300(3) Å, c = 14.2334(5) Å, β = 101.643(3)°, V = 3032.33(19) Å^3, Z = 8, T = 100.00(10) K, μ(MoKα) = 0.079 mm^{-1}, *Dcalc* = 1.311 g/cm^3, 17439 reflections measured (6.87° ≤ 2Θ ≤ 58.8°), 3840 unique (R_{int} = 0.0232, R_{sigma} = 0.0200) which were used in all calculations. The final R_1 was 0.0417 (I > 2σ(I)) and wR_2 was 0.1123 (all data).

154a (*rac*)

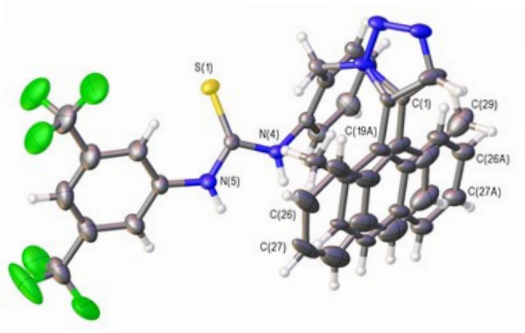


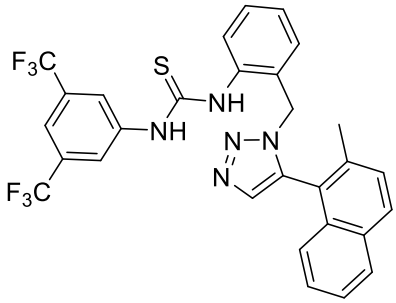


$C_{20}H_{23}N_3$ (M =305.41 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 11.2157(6) Å, b = 13.1072(5) Å, c = 12.3803(7) Å, β = 116.226(7)°, V = 1632.63(17) Å^3, Z = 4, T = 100.01(10) K, μ(CuKα) = 0.571 mm^{-1}, *Dcalc* = 1.243 g/cm^3, 6411 reflections measured (8.79° ≤ 2Θ ≤ 145.578°), 3163 unique (R_{int} = 0.0244, R_{sigma} = 0.0279) which were used in all calculations. The final R_1 was 0.0384 (I > 2σ(I)) and wR_2 was 0.1005 (all data).

The methyl hydrogen atoms bonded to C(20) are disordered over two positions at a refined percentage occupancy ratio of 51.8 (19) : 48.2 (19). These, and all other hydrogen atoms in the structure, were fixed as riding models with the isotropic thermal parameters (U_{iso}) based on the U_{eq} of the parent atom.

198b (*rac*)





$C_{30}H_{22}Cl_3F_6N_5S$ (M =704.93 g/mol): orthorhombic, space group Pbca (no. 61), a = 17.2172(4) Å, b = 13.8332(3) Å, c = 25.7251(7) Å, V = 6126.9(3) Å^3, Z = 8, T = 100.01(10) K, μ(CuKα) =

3.950 mm^{-1}, *Dcalc* = 1.528 g/cm^3, 15729 reflections measured ($6.872° \leq 2\Theta \leq 145.912°$), 5950 unique ($R_{int}$ = 0.0296, R_{sigma} = 0.0272) which were used in all calculations. The final R_1 was 0.0781 ($I > 2\sigma(I)$) and wR_2 was 0.2192 (all data).

The structure contains a molecule of chloroform (omitted for clarity). The fused ring system C(1)-C(19) – C(29) / C(1A)-C(19A) – C(29A) is disordered over two positions at a refined percentage occupancy ratio of 55.4 (6) : 44.6 (6). The hydrogen atoms bonded to N(4) and N(5) were located in the electron density and freely refined. All remaining hydrogen atoms were fixed as riding models with the isotropic thermal parameters (U_{iso}) based on the U_{eq} of the parent atom.

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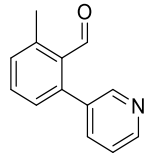
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8 Appendices

8.1 Representative NMR Spectra

8.1.1 Representative NMR Spectra for Aldehydes



201b

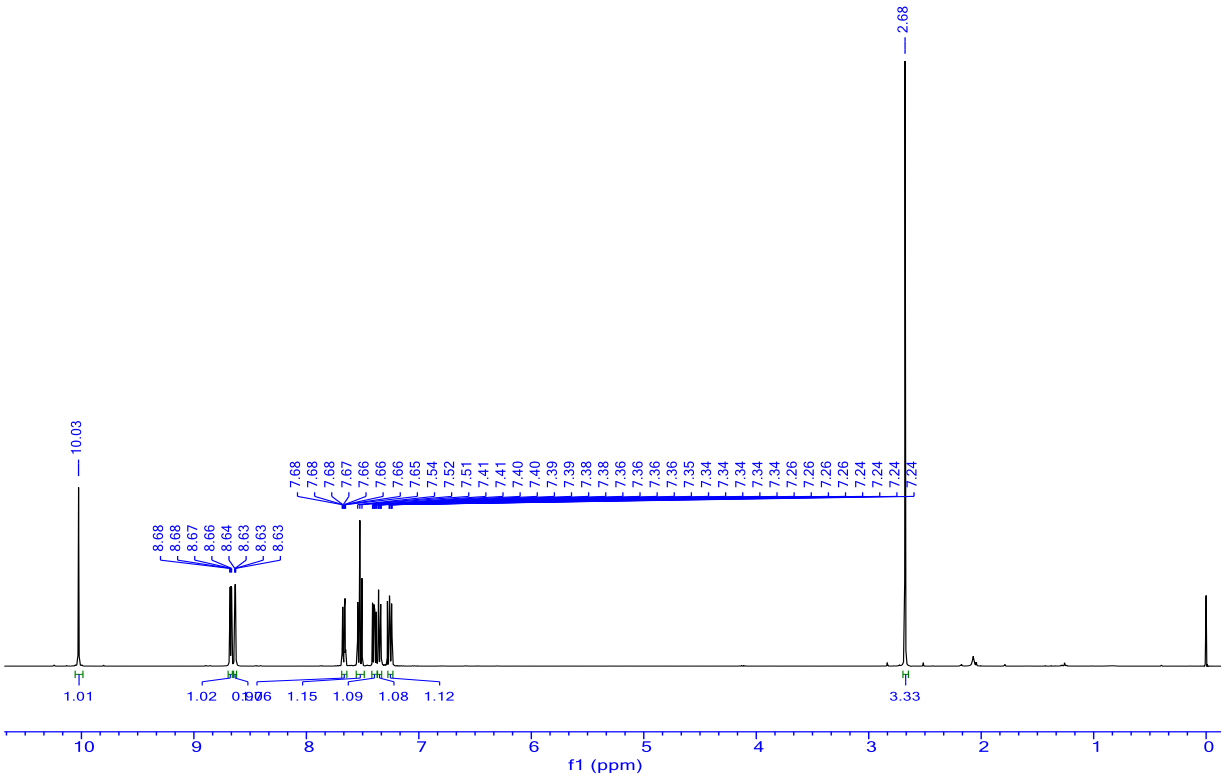


Figure 63 ^{1}H NMR spectrum of aldehyde **201b**.

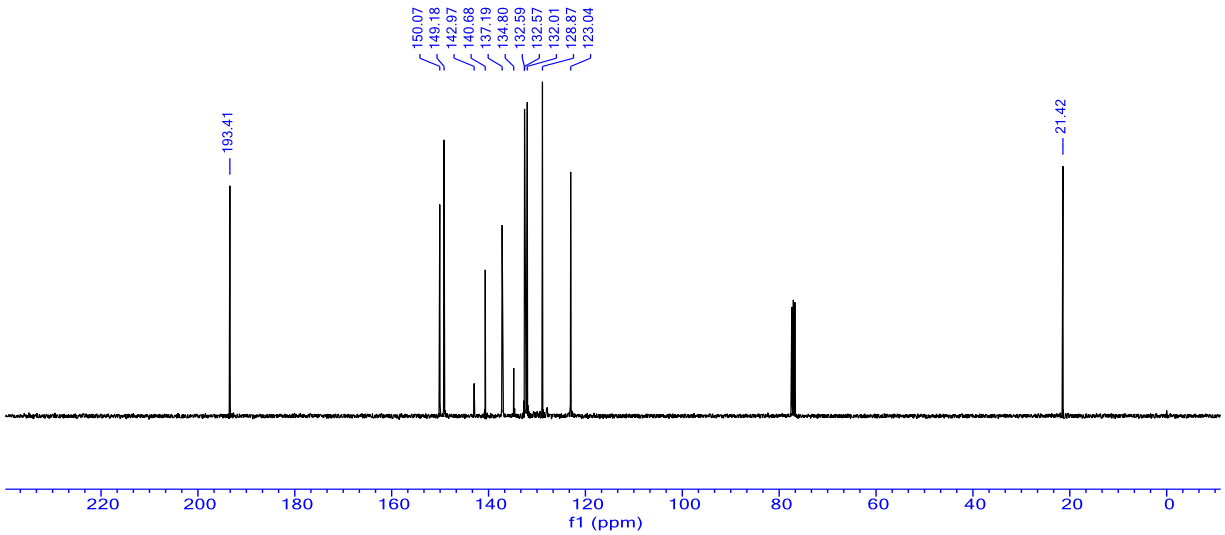


Figure 64 ^{13}C NMR spectrum of aldehyde **201b**.

8.1.2 Representative NMR Spectra for Alkynes

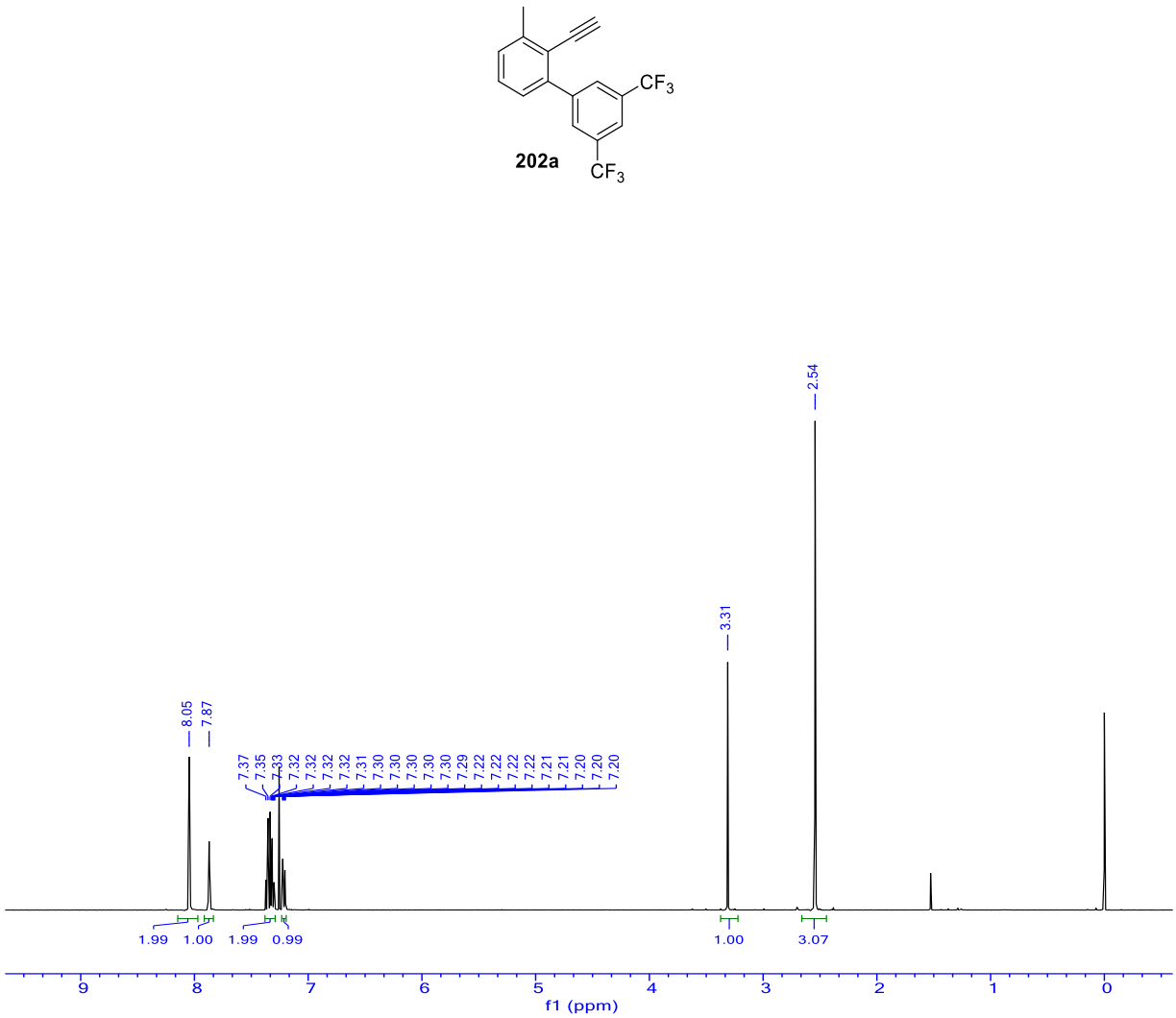


Figure 65 ^{1}H NMR spectrum of alkyne **202a**.

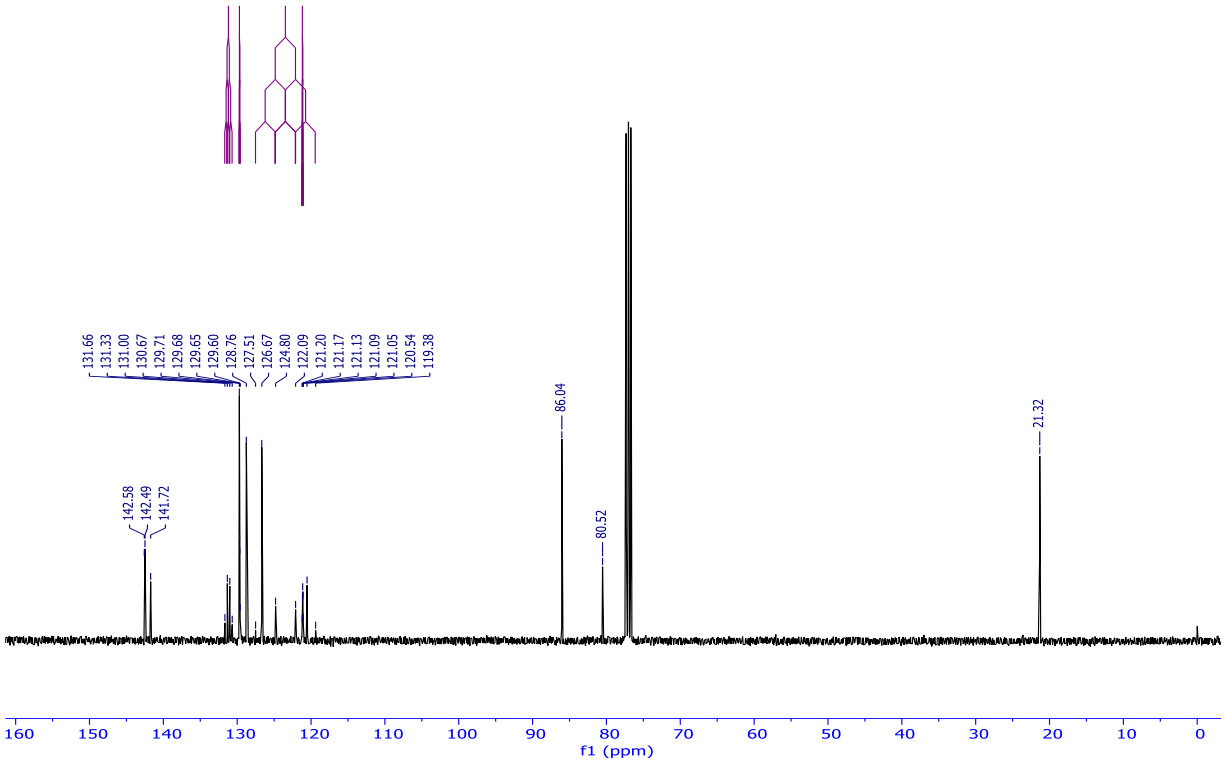


Figure 66 ^{13}C NMR spectrum of alkyne **202a**. The *J*'s tree is shown in purple.

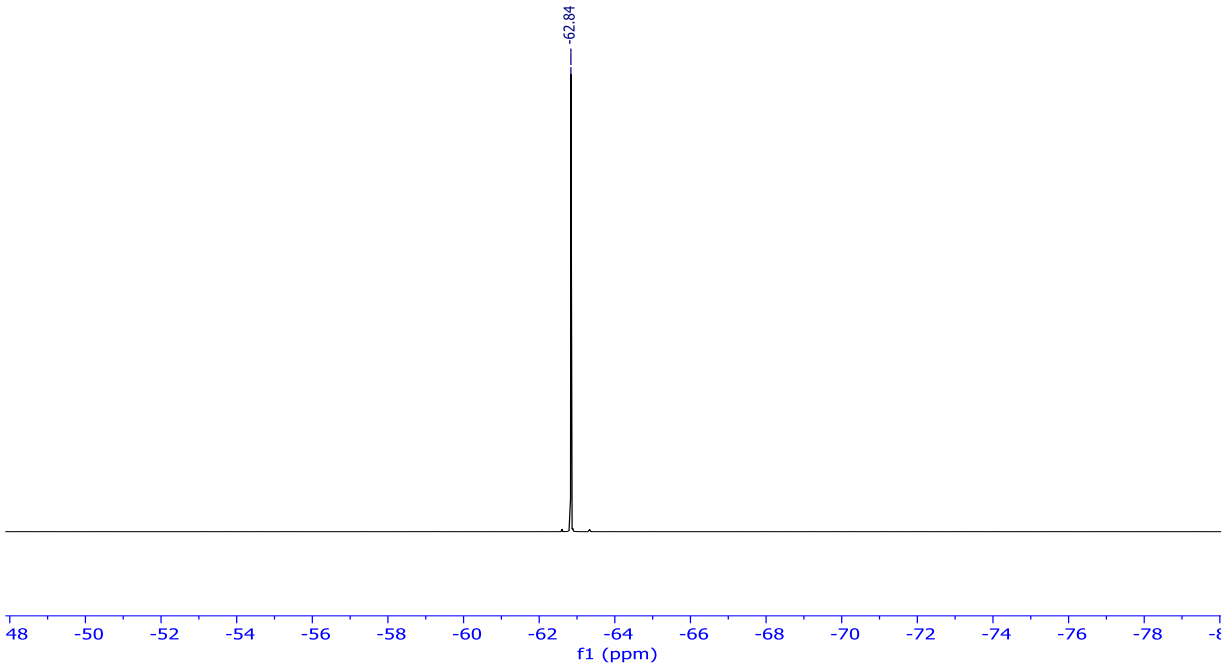
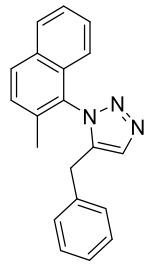


Figure 67 ^{19}F NMR spectrum of alkyne **202a**.

8.1.3 Representative NMR Spectra for Atropisomeric 1,5-Triazoles



154b

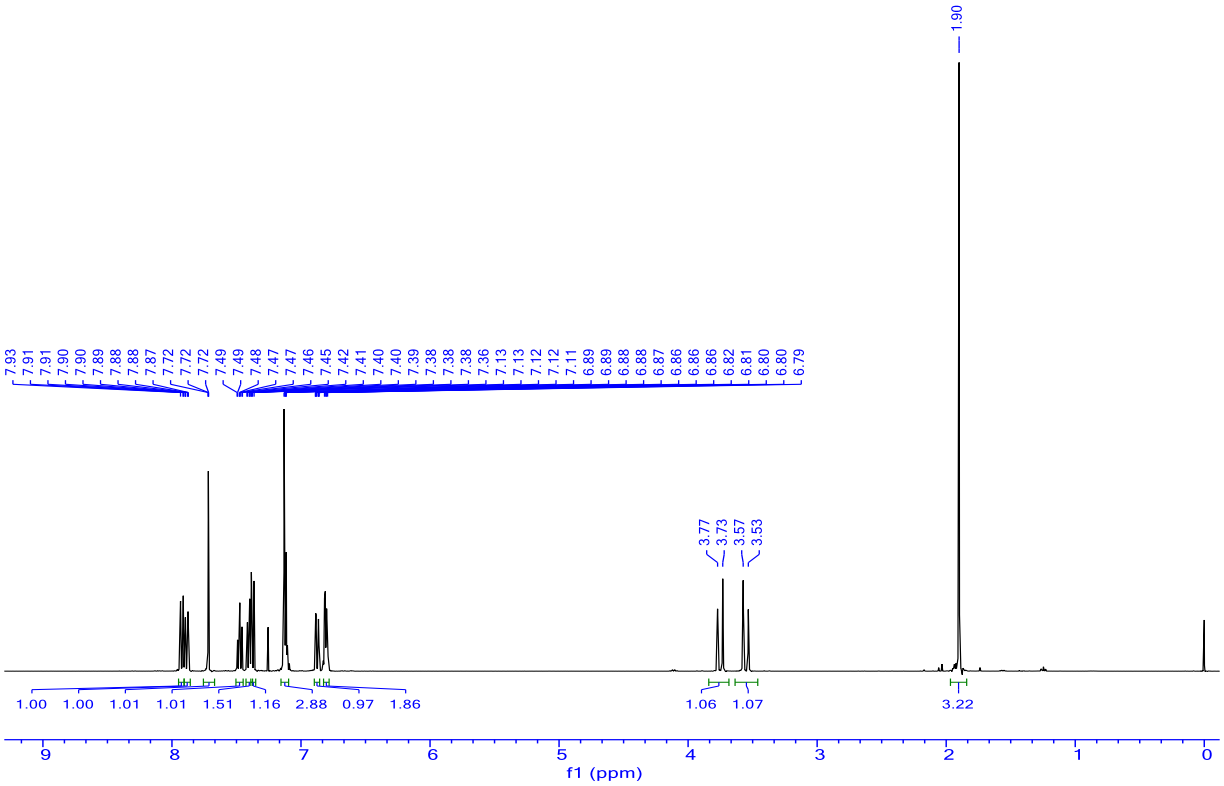


Figure 68 ^{1}H NMR spectrum of 1,5-triazole **154b**.

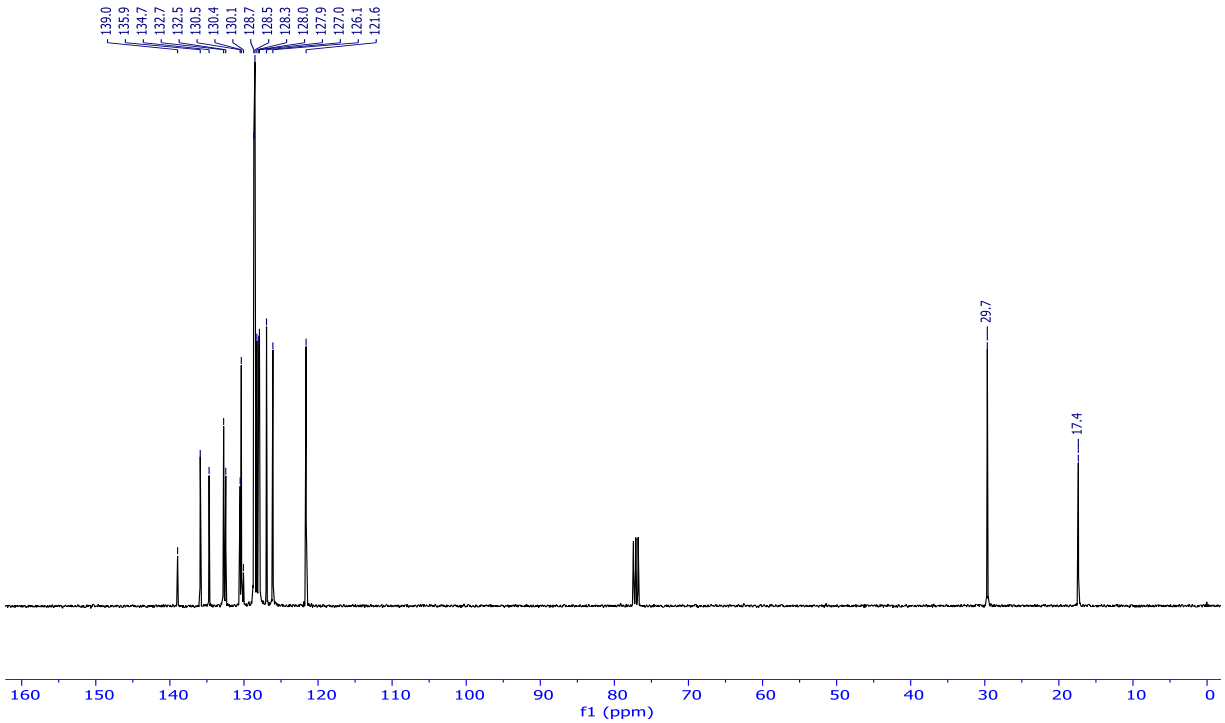
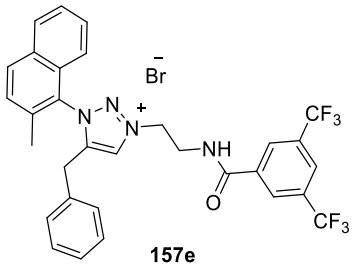


Figure 69 ^{13}C NMR spectrum of 1,5-triazole **154b**.

8.1.4 Representative NMR Spectra for Atropisomeric Triazolium Salts



157e

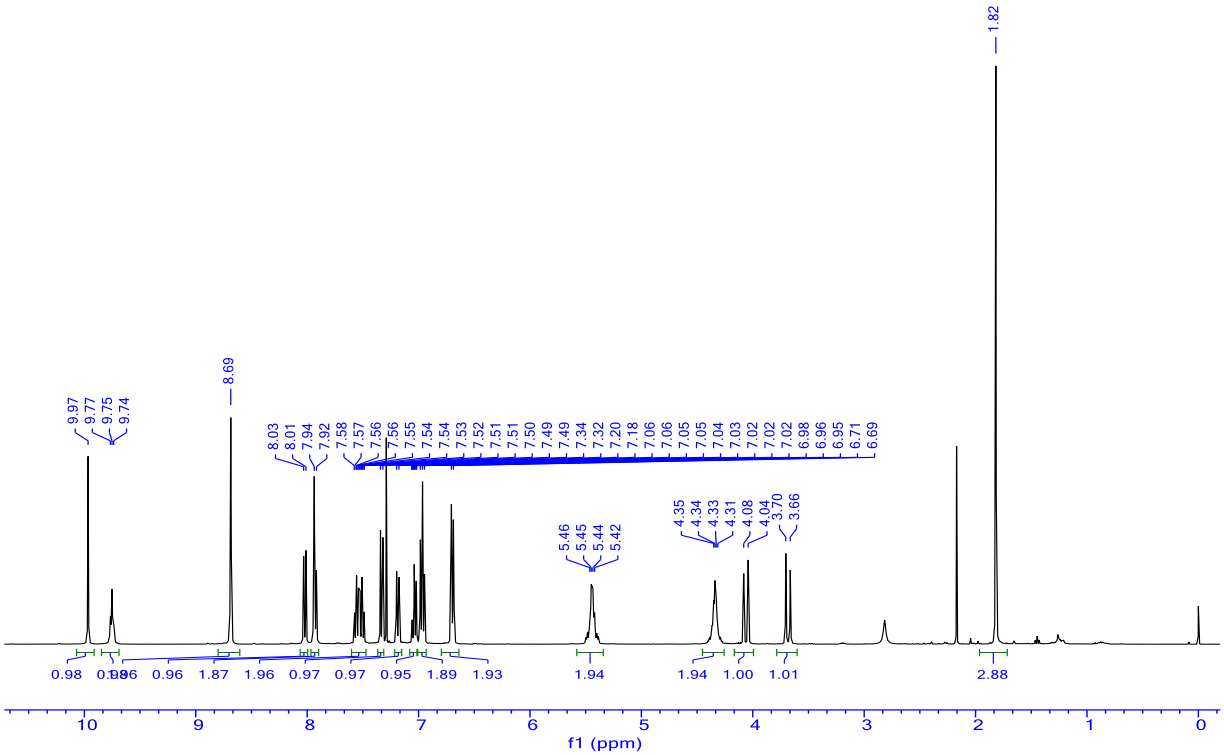


Figure 70 ^{1}H NMR spectrum of triazolium salt **157e**.

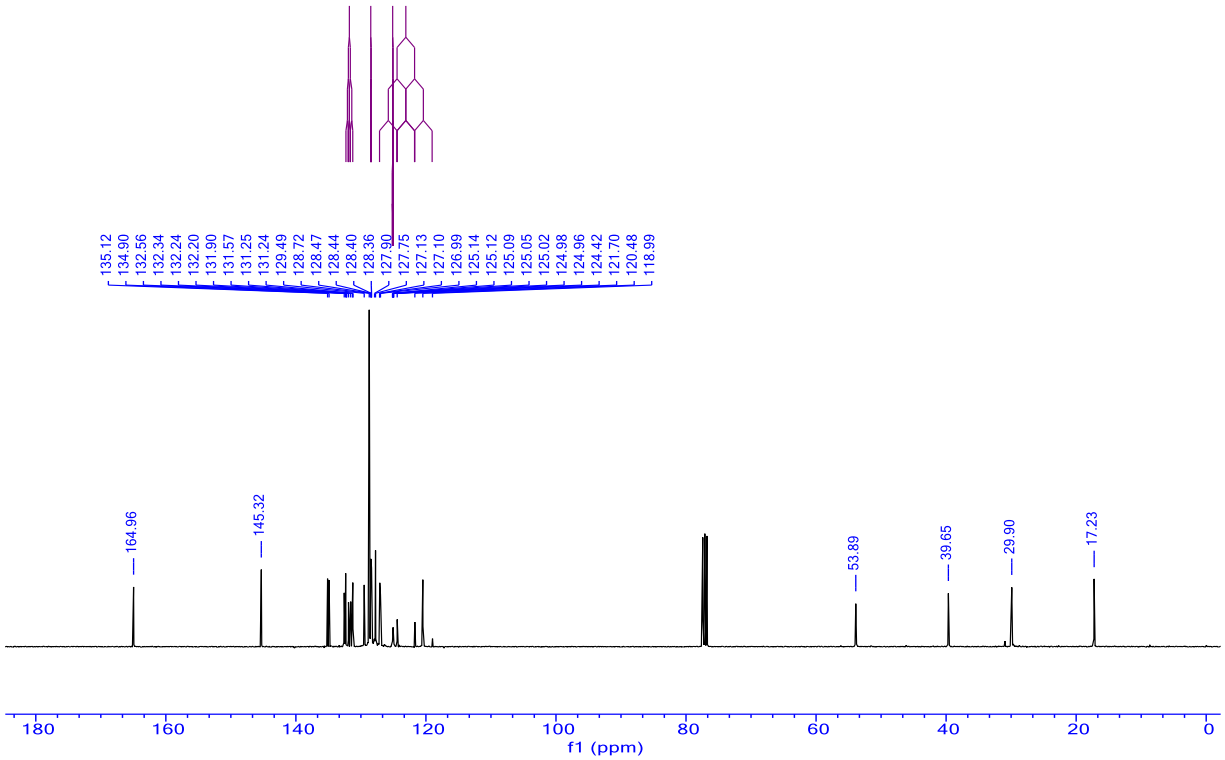


Figure 71 ^{13}C NMR spectrum of triazolium salt **157e**. The *J*'s tree is shown in purple.

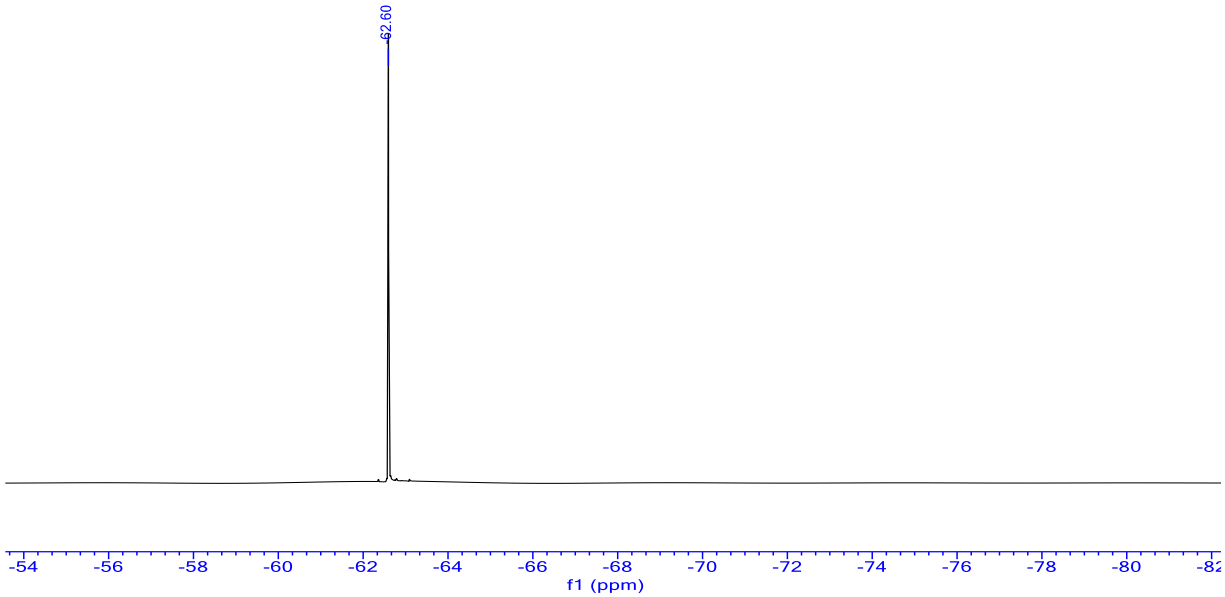
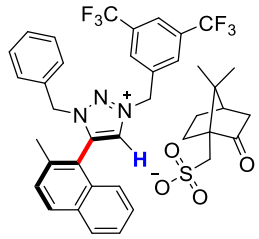


Figure 72 ^{19}F NMR spectrum of triazolium salt **157e**.

6.1.4.1 Determination of Enantiopurity of Triazolium Salt 157a *via* ^{1}H NMR



157a$_x$

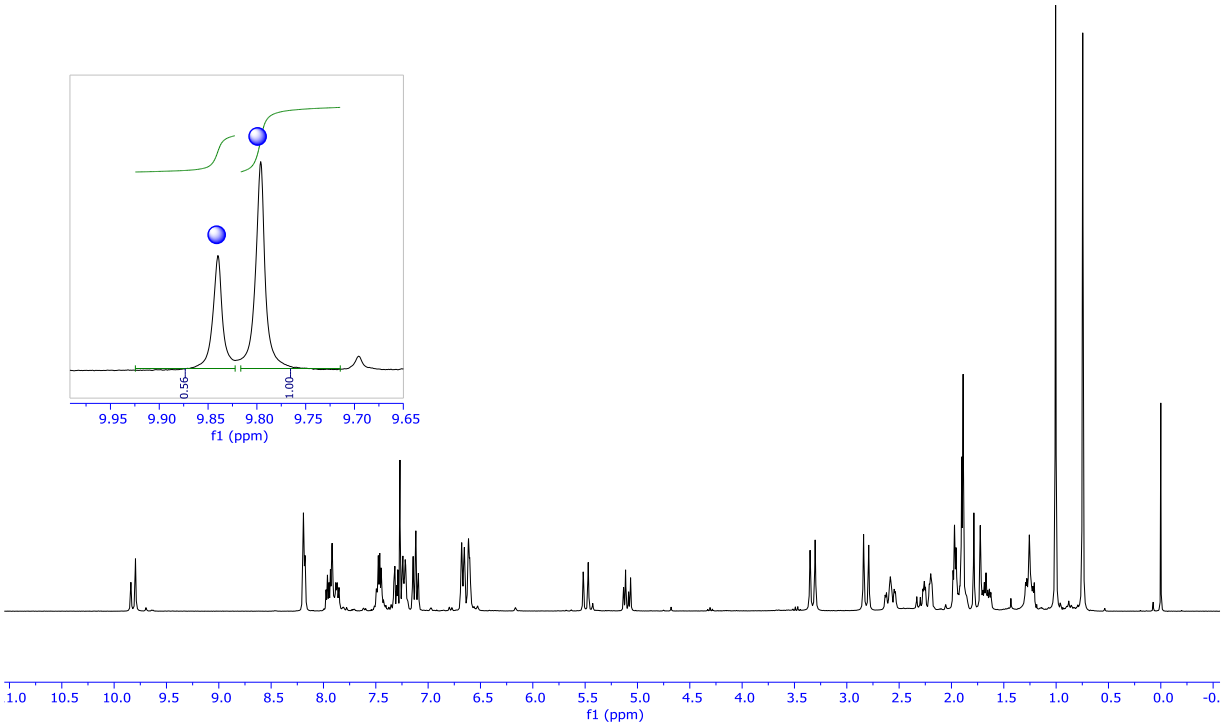
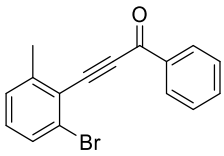


Figure 73 ^{1}H NMR spectrum of triazolium salt **157a$_x$**.

8.1.5 Representative NMR Spectra for Propinones



204

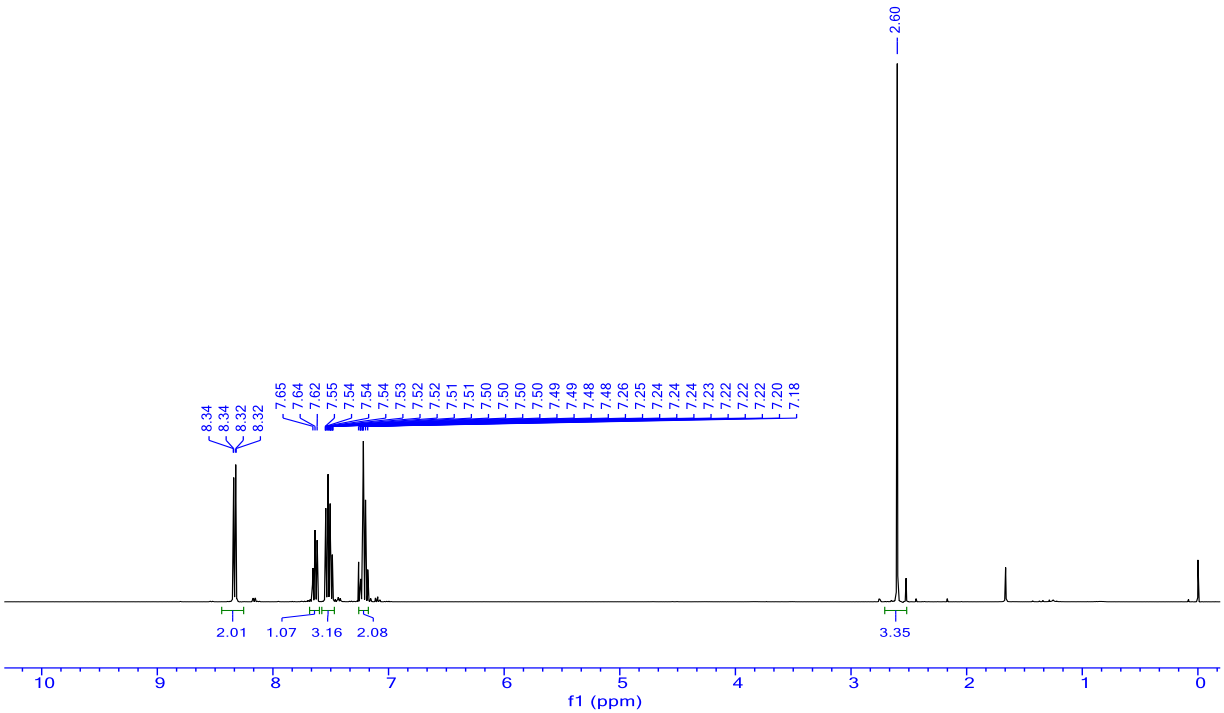


Figure 74 ^{1}H NMR spectrum of propinone **204**.

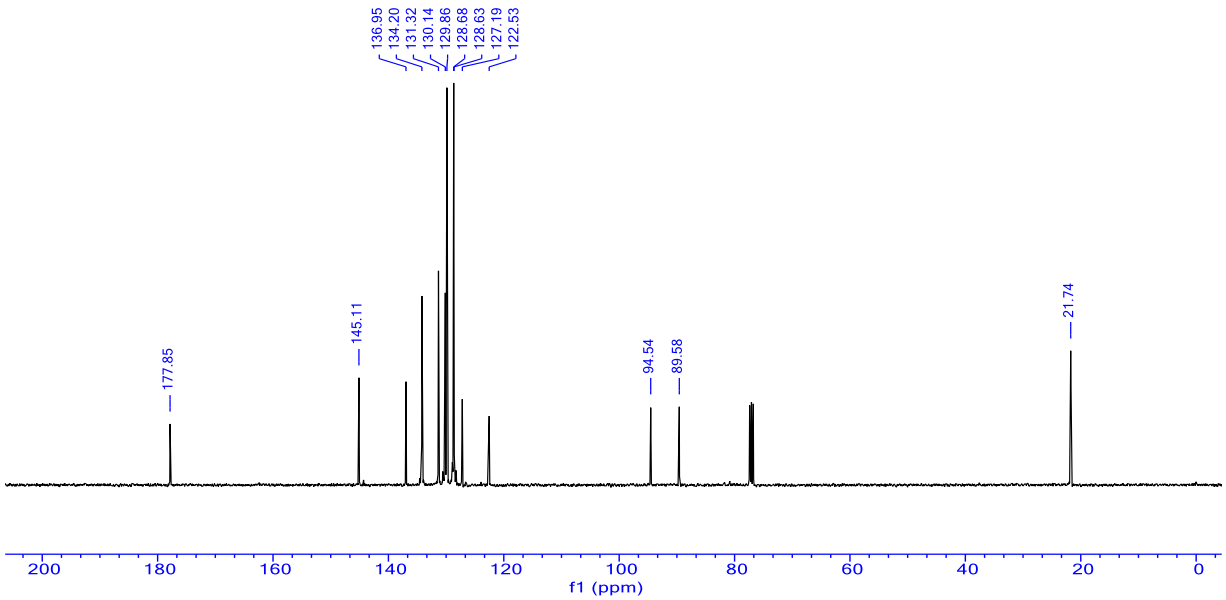
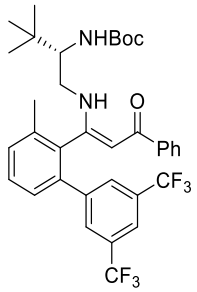


Figure 75 ^{13}C NMR spectrum of propinone **204**

8.1.6 Representative NMR Spectra for Enaminones



217c

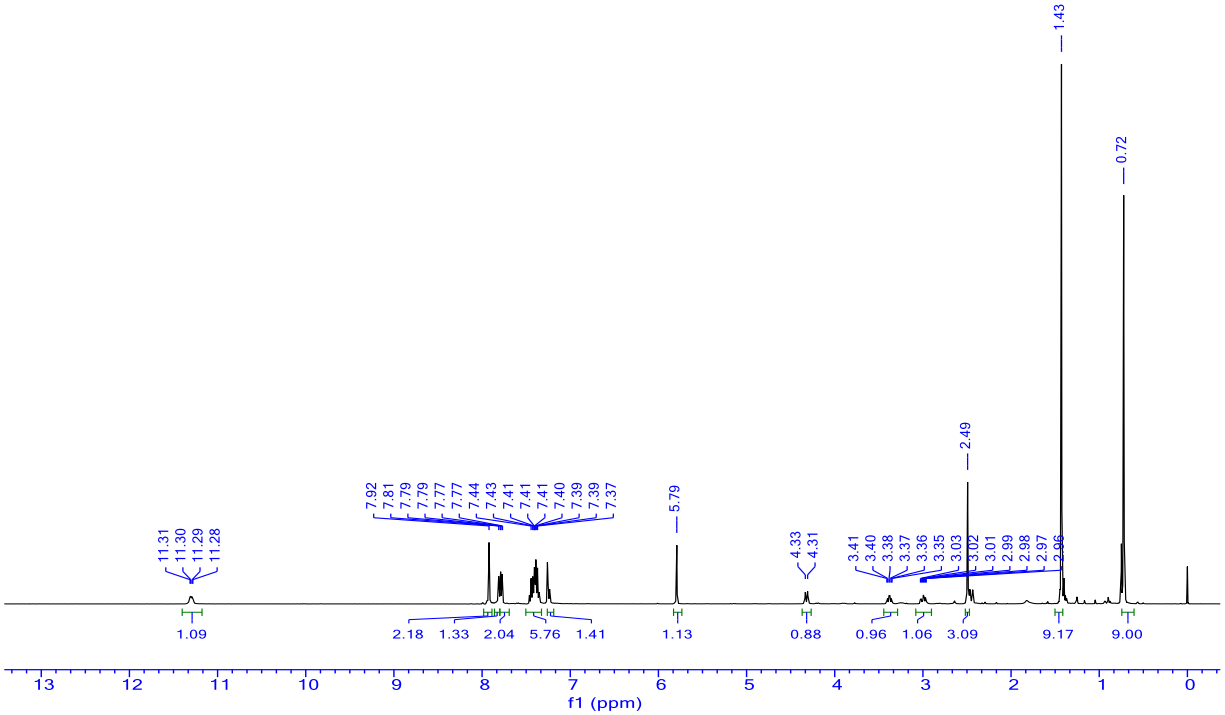


Figure 76 ^{1}H NMR spectrum of enaminone **217c**.

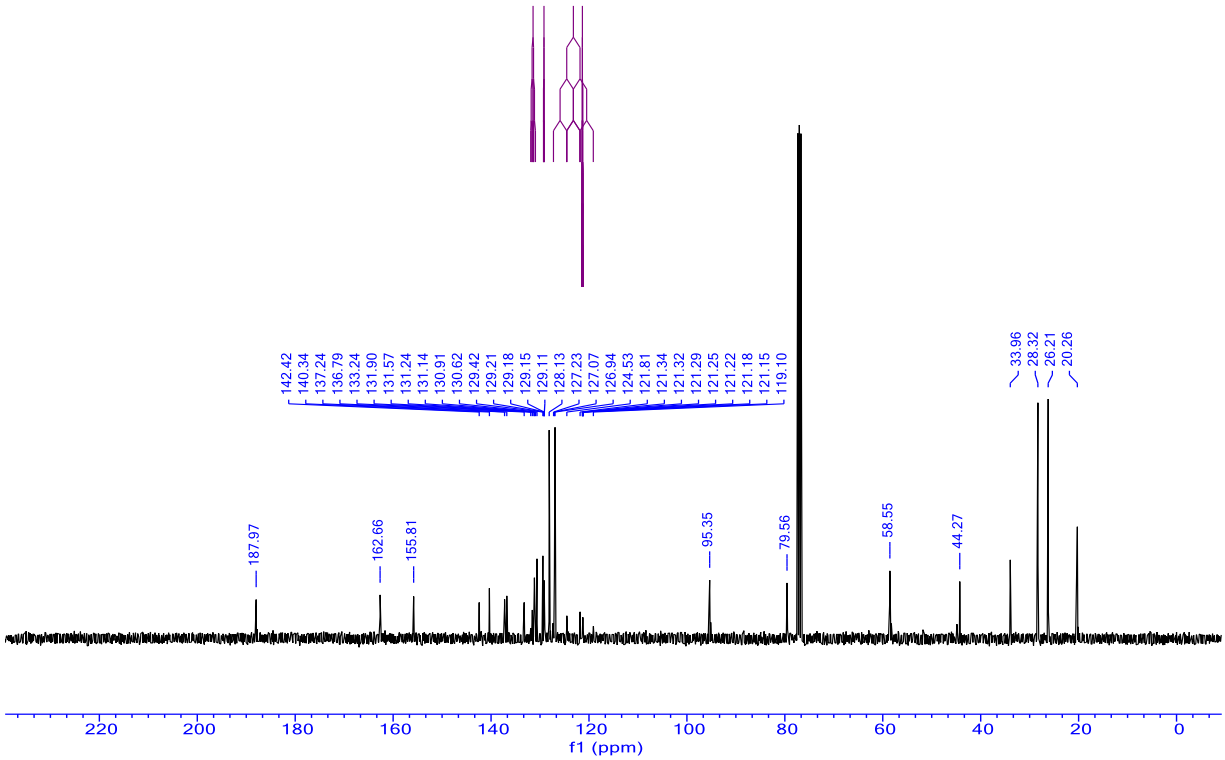


Figure 77 ^{13}C NMR spectrum of enaminone **217c**. The *J*'s tree is shown in purple.

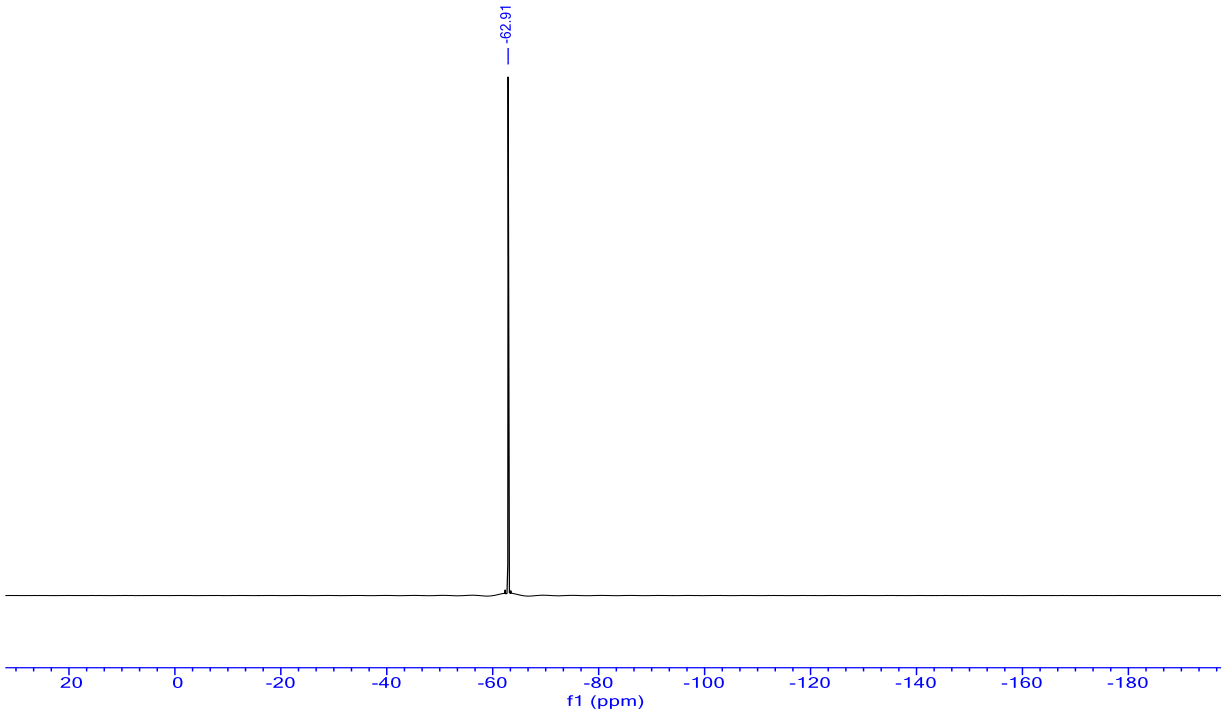


Figure 78 ^{19}F NMR spectrum of enaminone **217c**.

8.1.7 Representative NMR Spectra for Triazole-containing (Thio)Ureas

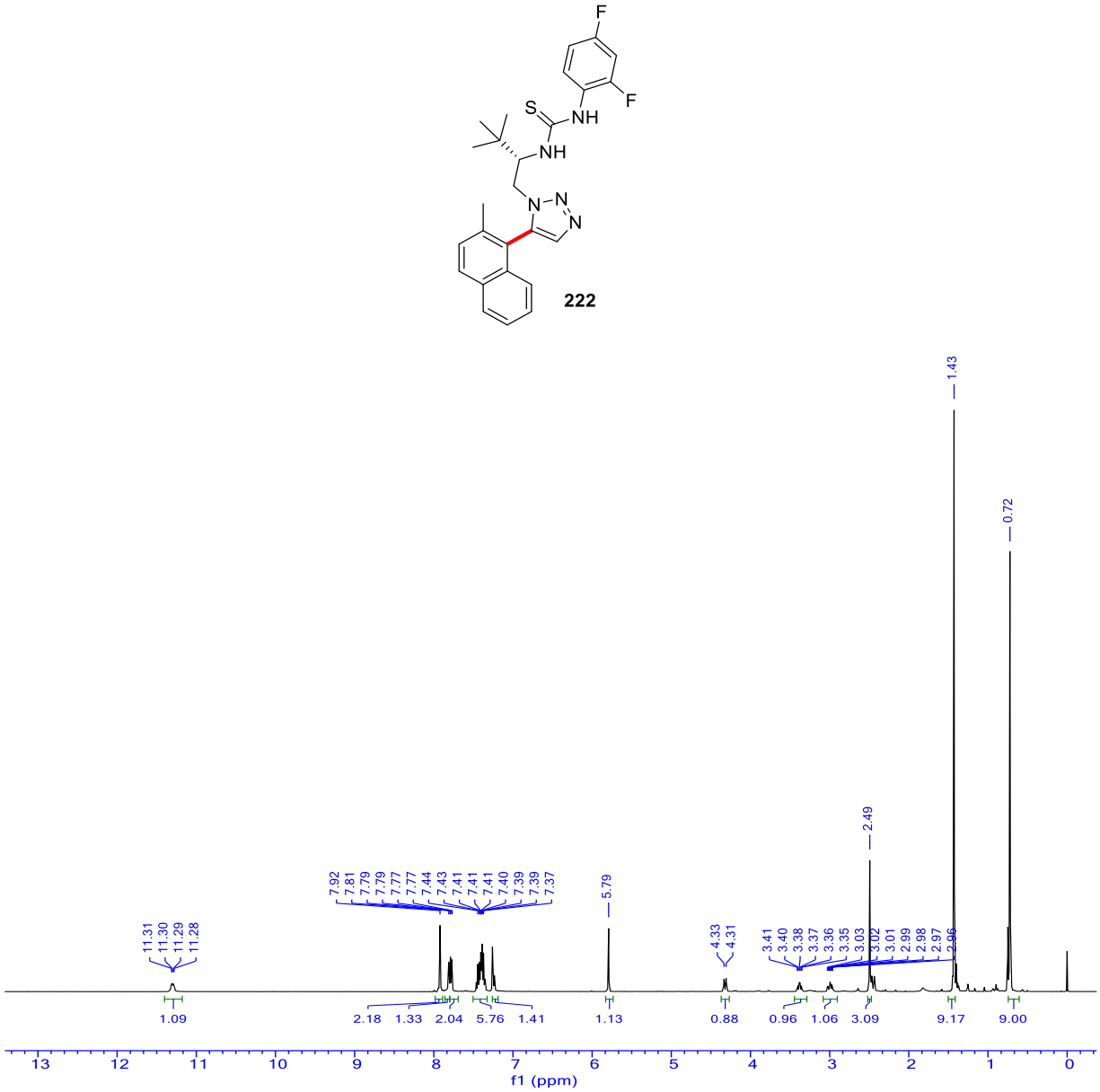


Figure 79 ^{1}H NMR spectrum of triazole-containing thiourea **222**.

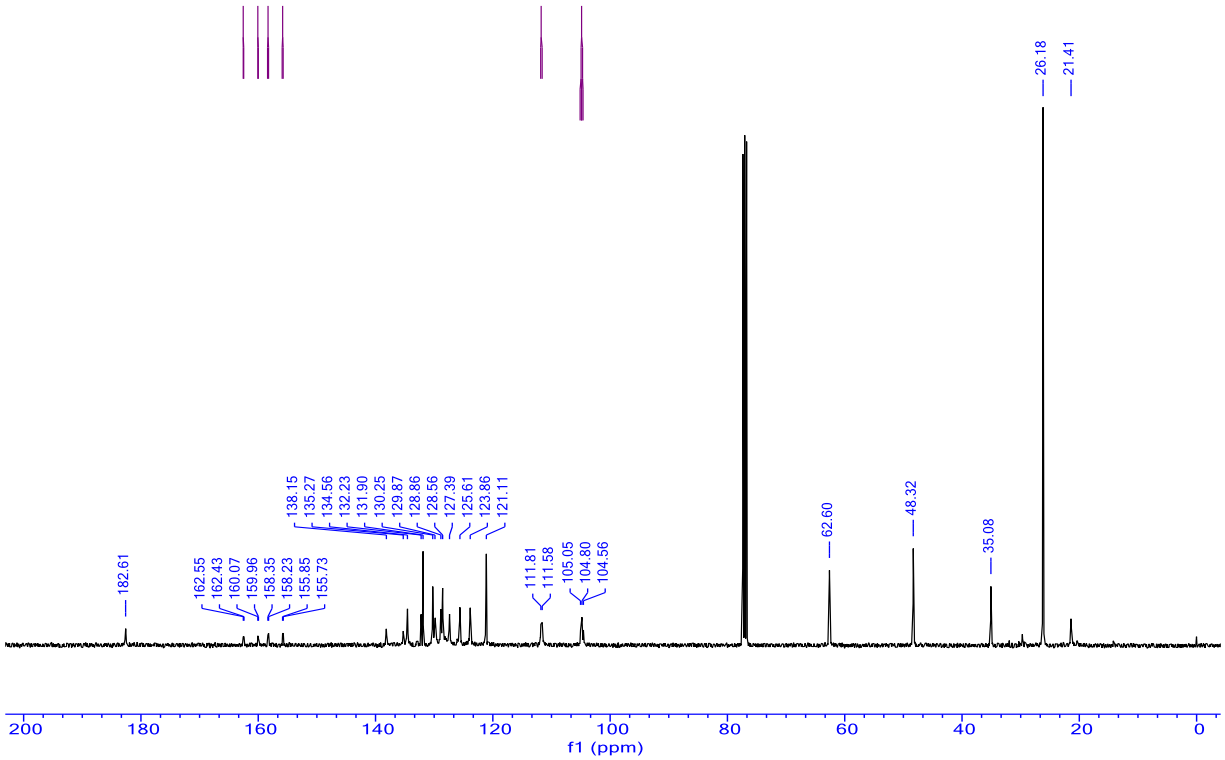


Figure 80 ^{13}C NMR spectrum of triazole-containing thiourea **222**. The *J*'s tree is shown in purple.

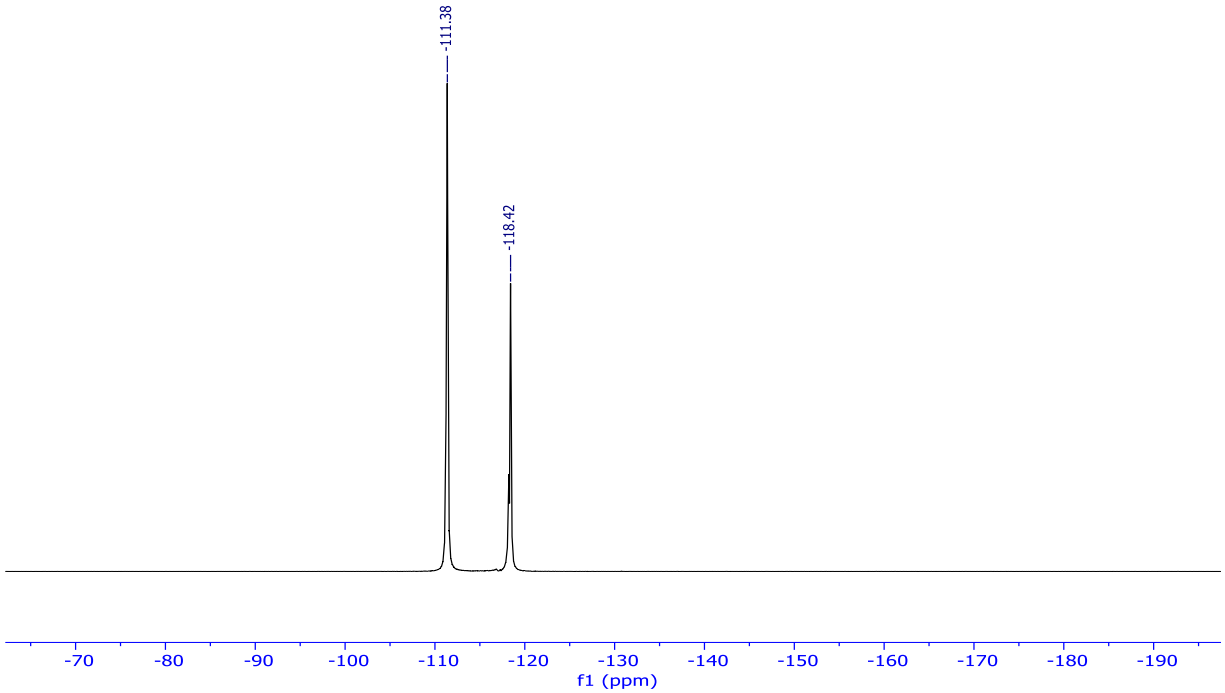


Figure 81 ^{19}F NMR spectrum of triazole-containing thiourea **222**.

8.2 Variable-Temperature (VT) ^{1}H NMR spectra

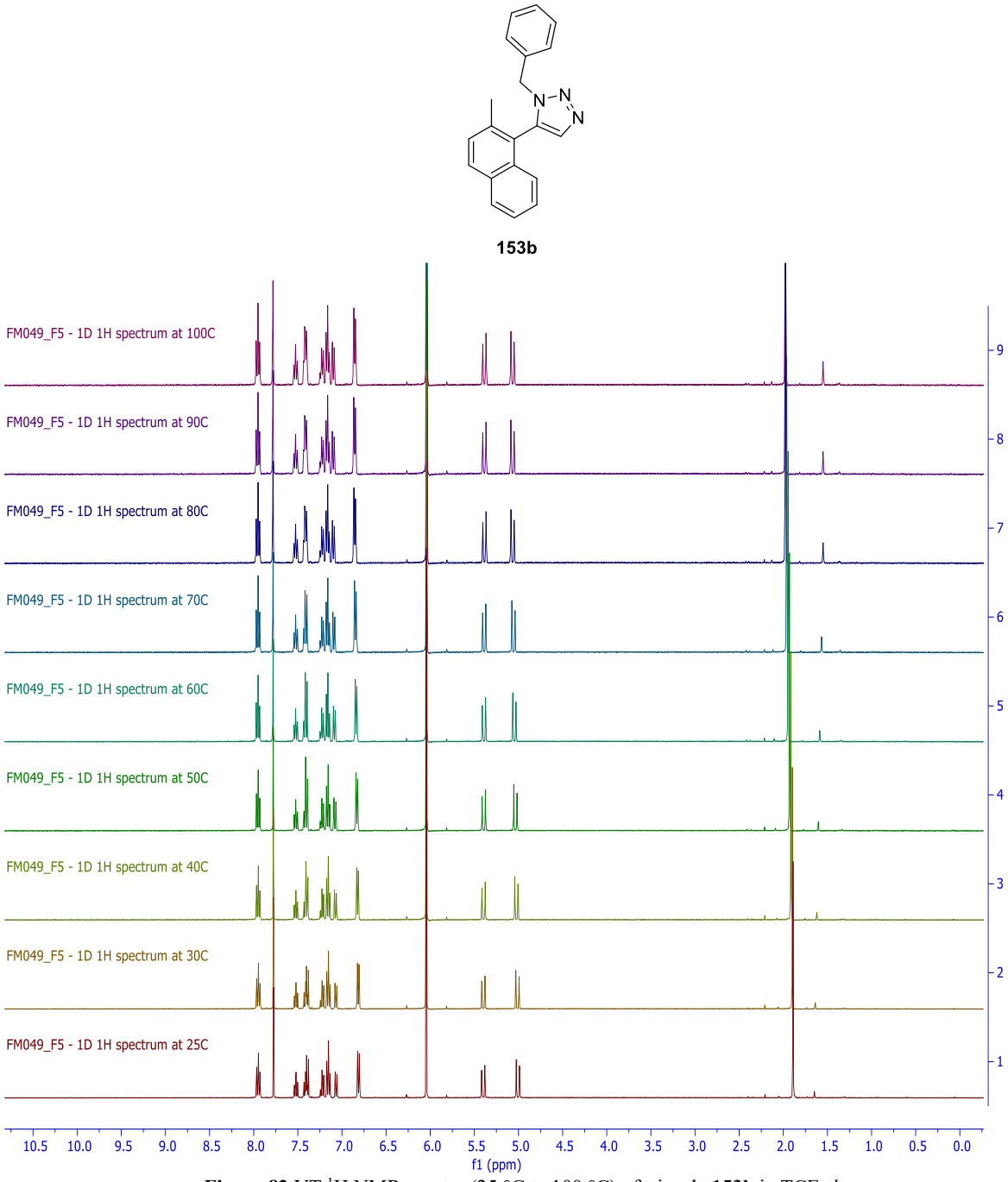


Figure 82 VT ^{1}H NMR spectra (25 °C to 100 °C) of triazole **153b** in TCE-d_2.

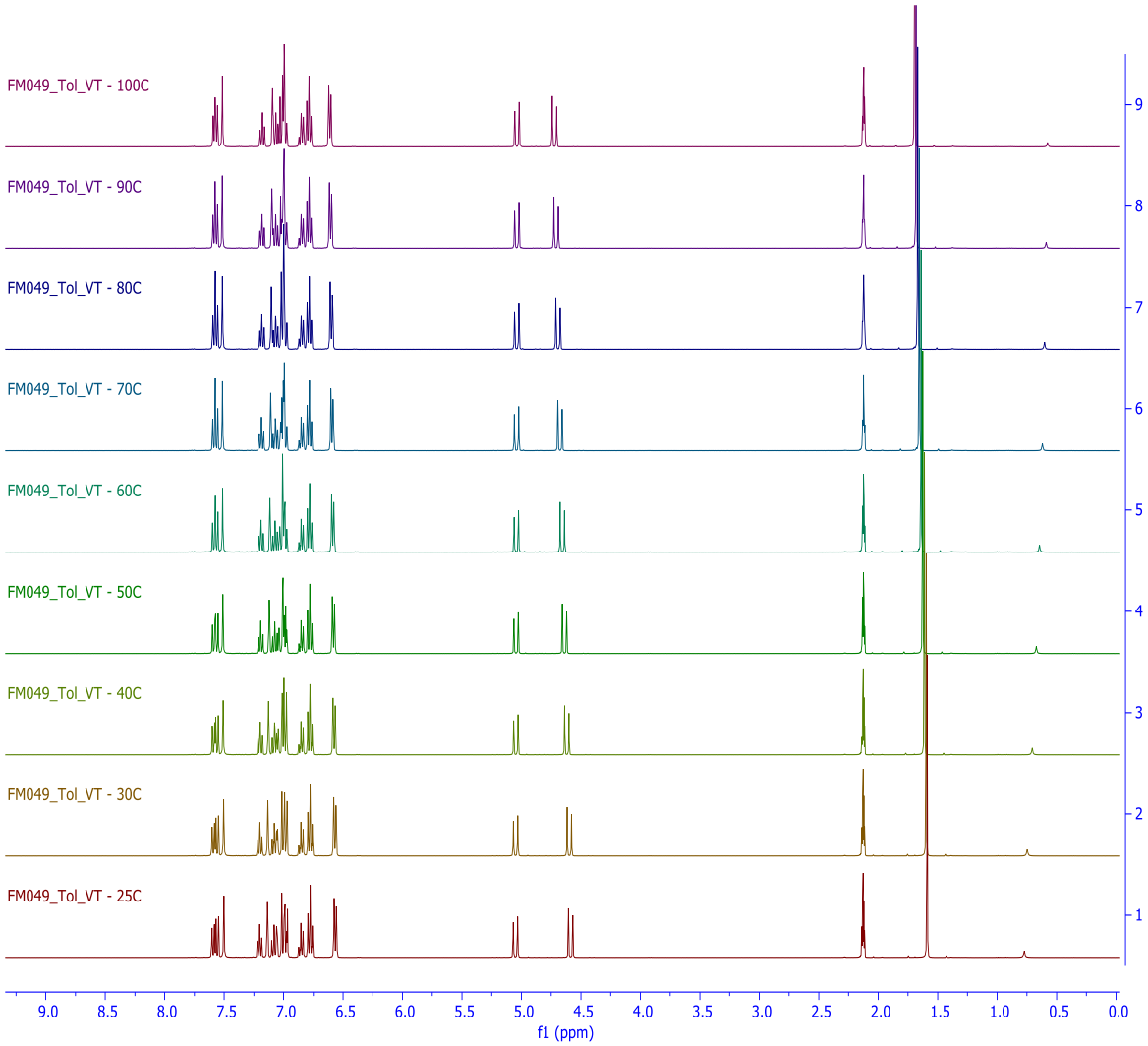


Figure 83 VT ^{1}H NMR spectra (25 °C to 100 °C) of triazole **153b** in toluene-d_8.

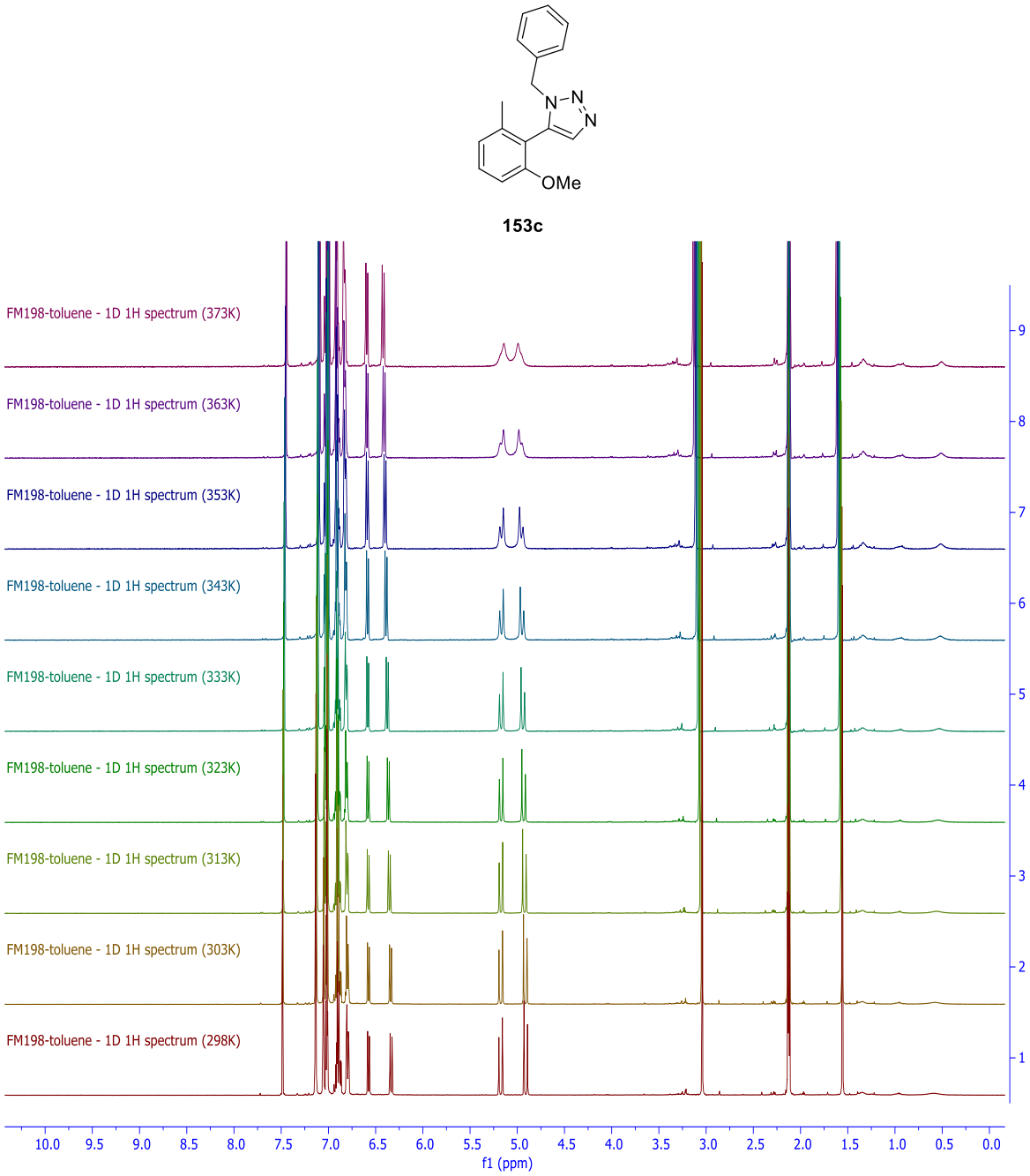


Figure 84 VT ^{1}H NMR spectra (25 °C to 100 °C) of triazole **153c** in toluene-*d*$_8$.

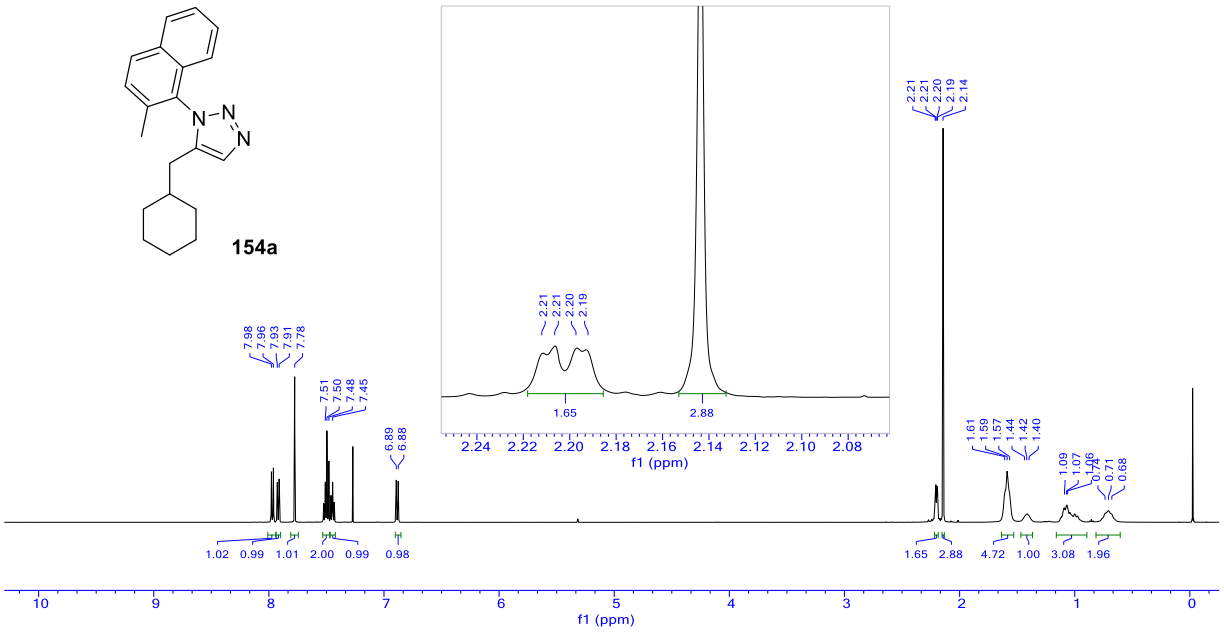


Figure 85 [1]H NMR spectrum of triazole **154a** in chloroform-*d* at -35 °C. The diastereomeric splitting pattern can be observed.

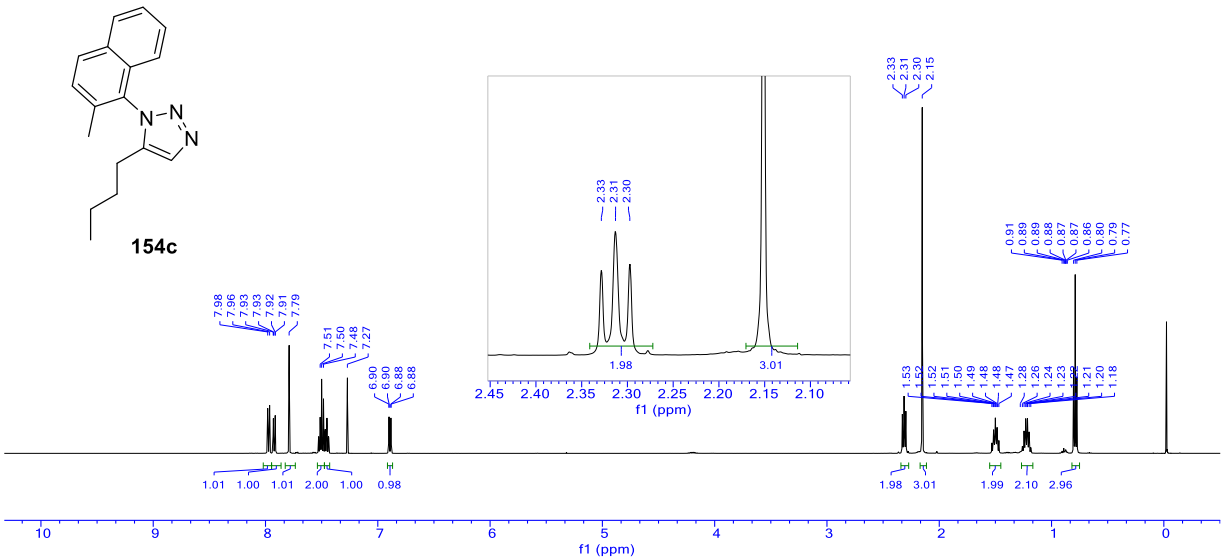


Figure 86 [1]H NMR spectrum of triazole **154c** in chloroform-*d* at -35 °C. No diastereomeric splitting pattern can be observed.

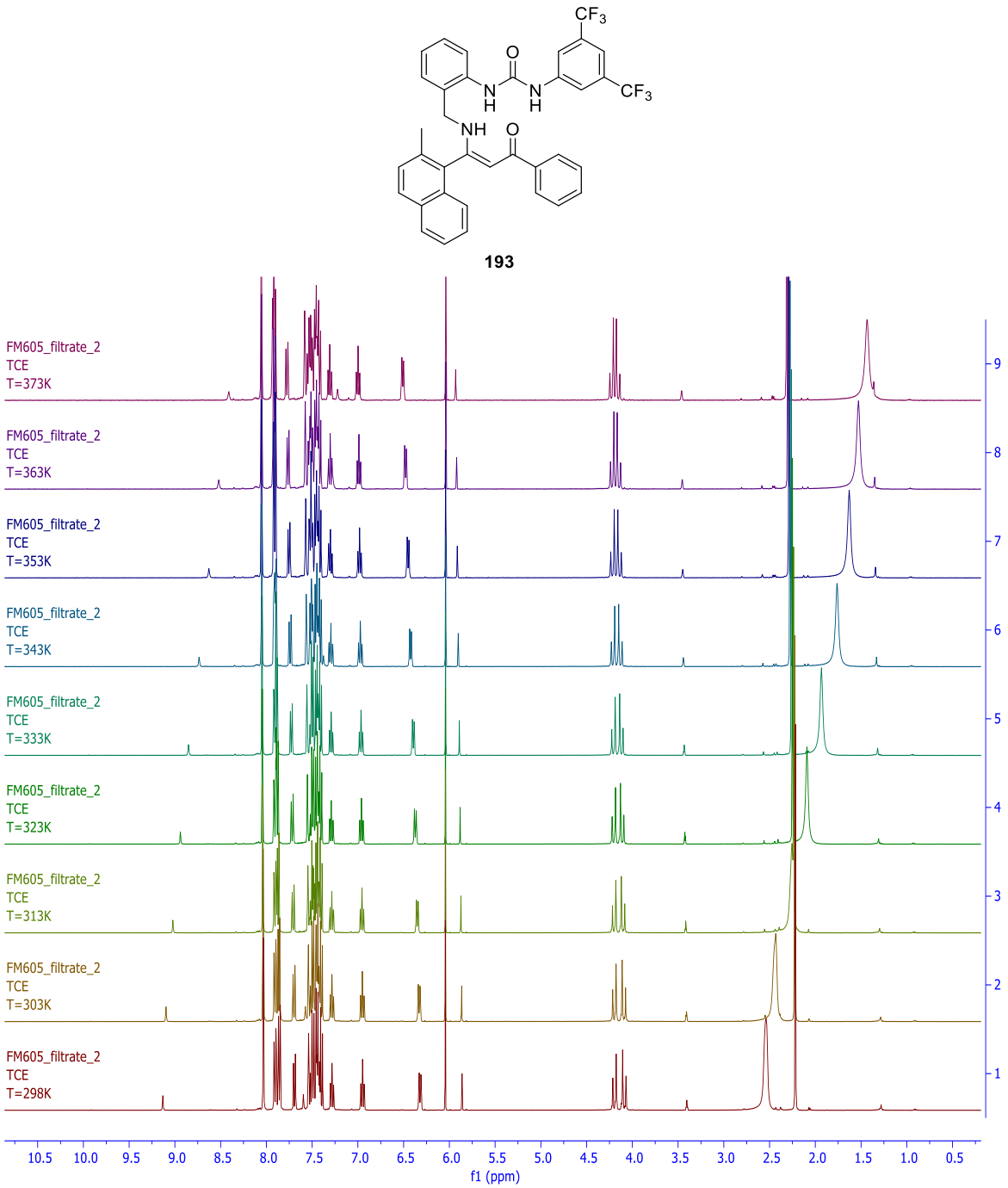
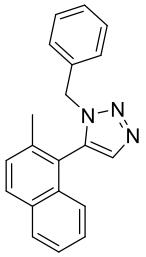


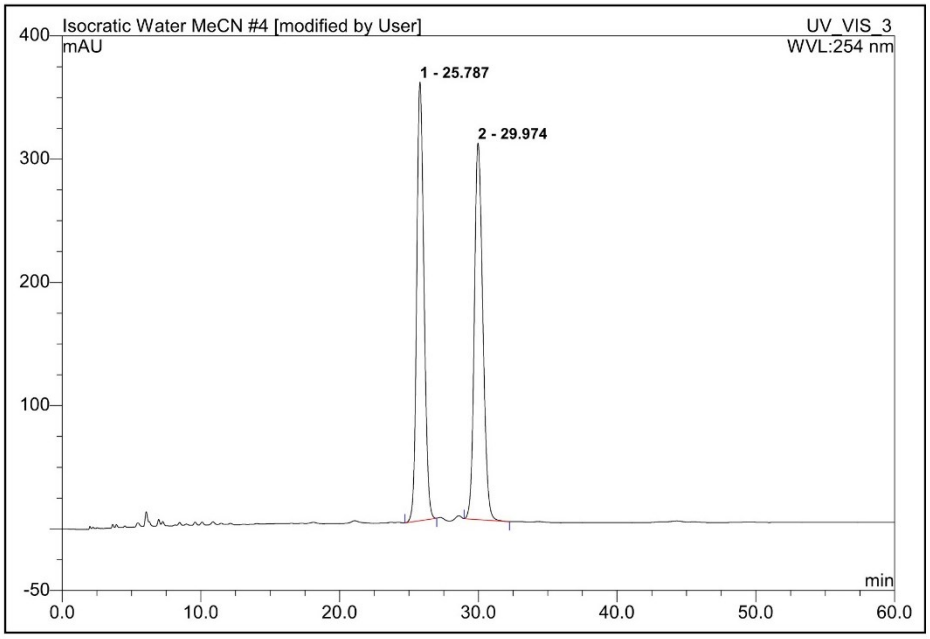
Figure 87 VT ^{1}H NMR spectra (25 °C to 100 °C) of enaminone **193** in a mixture of deuterated chloroform and methanol.

8.3 HPLC Chromatograms

8.3.1 HPLC Chromatograms of Atropisomeric 1,2,3-Triazoles in *Chapter 3*

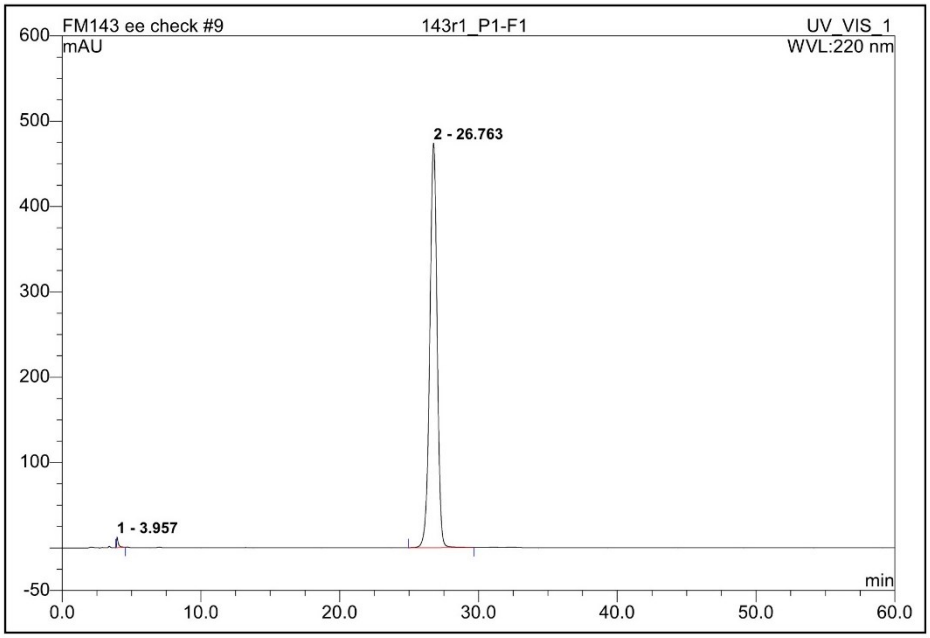


153b

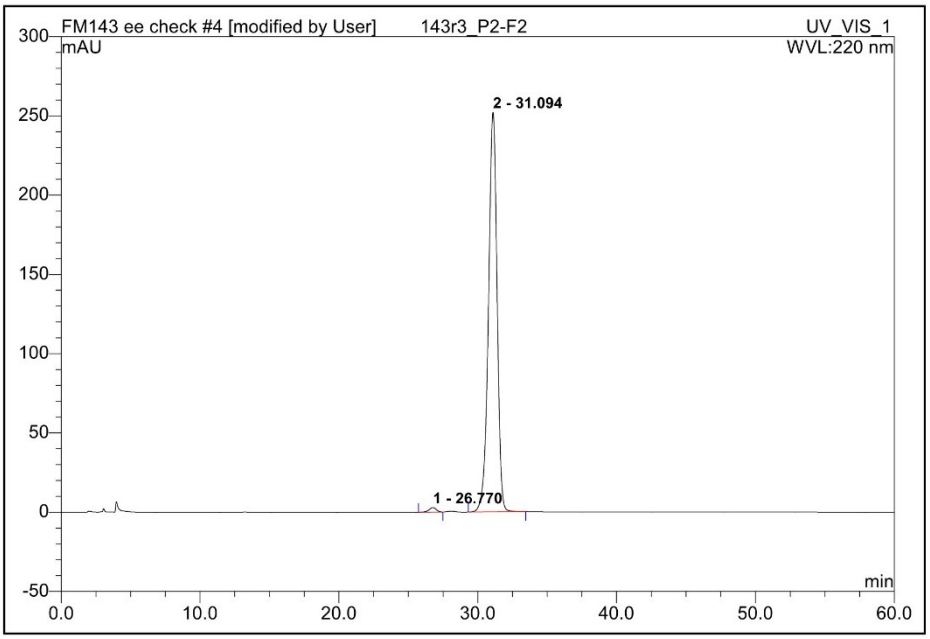


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25.79	n.a.	355.870	215.238	49.98	n.a.	BMB
2	29.97	n.a.	305.505	215.403	50.02	n.a.	BMB*
Total:			661.375	430.641	100.00	0.000	

Figure 88 HPLC chromatogram of racemic triazole **153b**. 50:50 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.

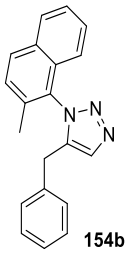


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	3.96	n.a.	12.482	1.794	0.62	n.a.	BMB
2	26.76	n.a.	473.807	289.157	99.38	n.a.	BMB
Total:			486.289	290.951	100.00	0.000	

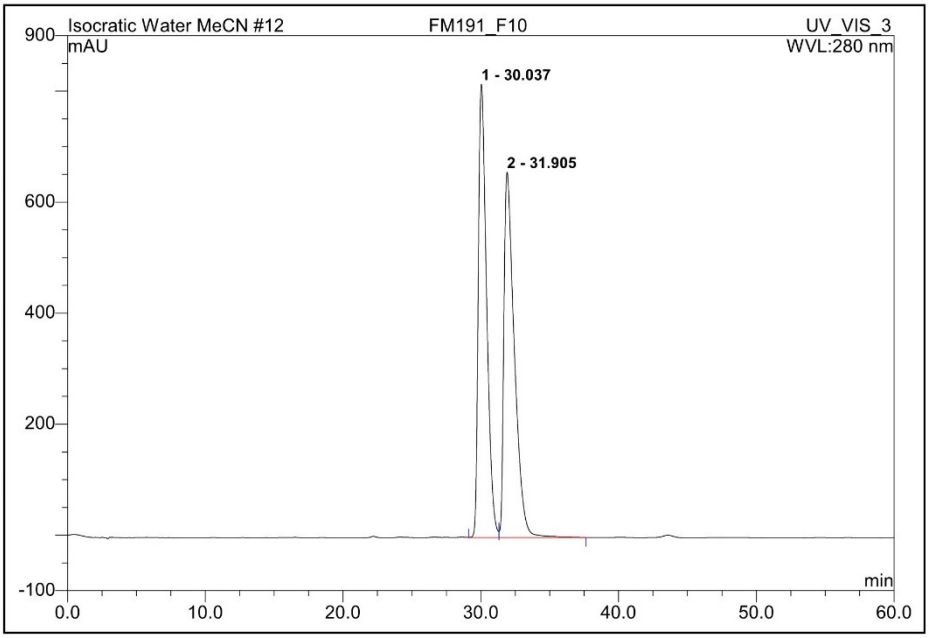


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	26.77	n.a.	2.871	1.712	0.94	n.a.	BMB
2	31.09	n.a.	252.137	181.175	99.06	n.a.	BMB
Total:			255.008	182.887	100.00	0.000	

Figure 89 HPLC chromatograms of enantiopure triazole **153b** (peak 1, top; peak 2, bottom). 50:50 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.

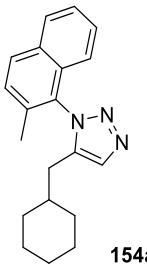


154b

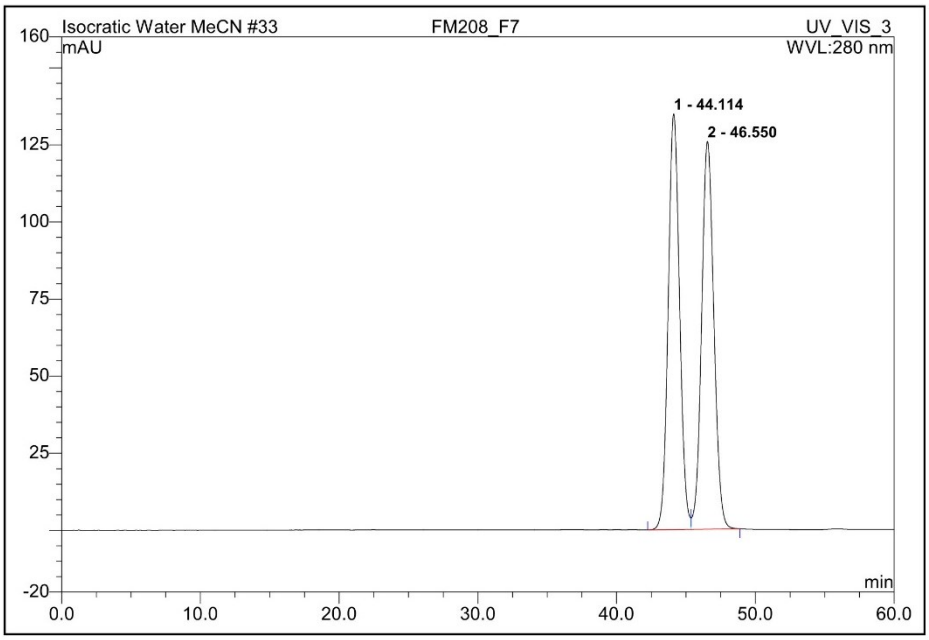


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	30.04	n.a.	816.577	571.002	49.47	n.a.	BM
2	31.90	n.a.	658.333	583.295	50.53	n.a.	MB
Total:			1474.910	1154.297	100.00	0.000	

Figure 90 HPLC chromatogram of racemic triazole **154b**. 50:50 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.

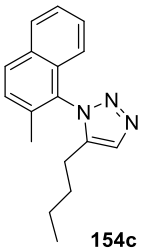


154a

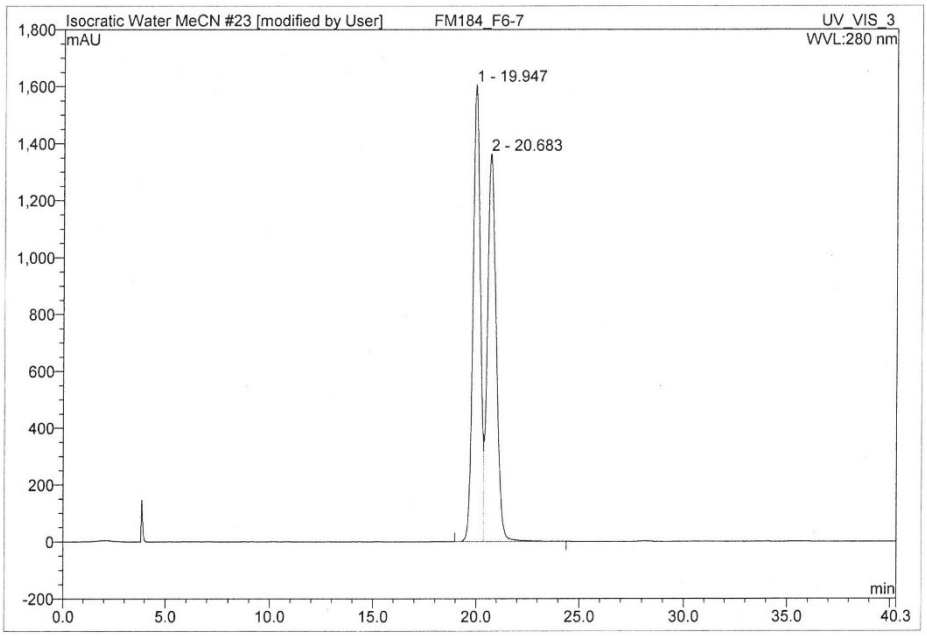


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	44.11	n.a.	134.812	128.447	49.95	n.a.	BM
2	46.55	n.a.	125.759	128.714	50.05	n.a.	MB
Total:			260.571	257.161	100.00	0.000	

Figure 91 HPLC chromatogram of racemic triazole **154a**. 50:50 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.

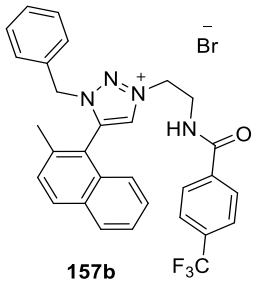


154c

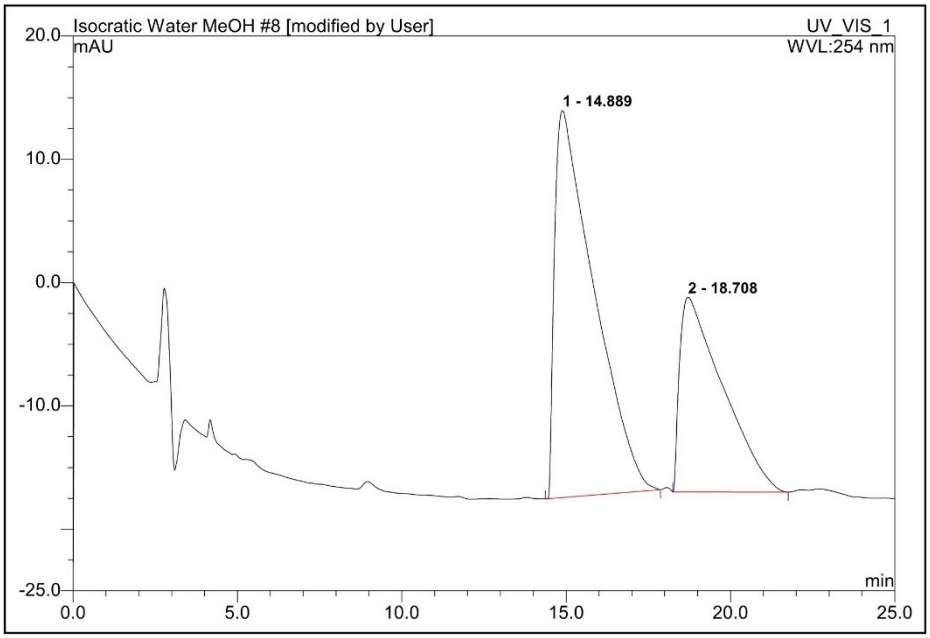


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	19.95	n.a.	1605.741	668.951	49.12	n.a.	BM
2	20.68	n.a.	1362.991	692.806	50.88	n.a.	MB
Total:			2968.732	1361.758	100.00	0.000	

Figure 92 HPLC chromatogram of racemic triazole **154c**. 50:50 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.



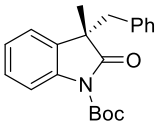
157b



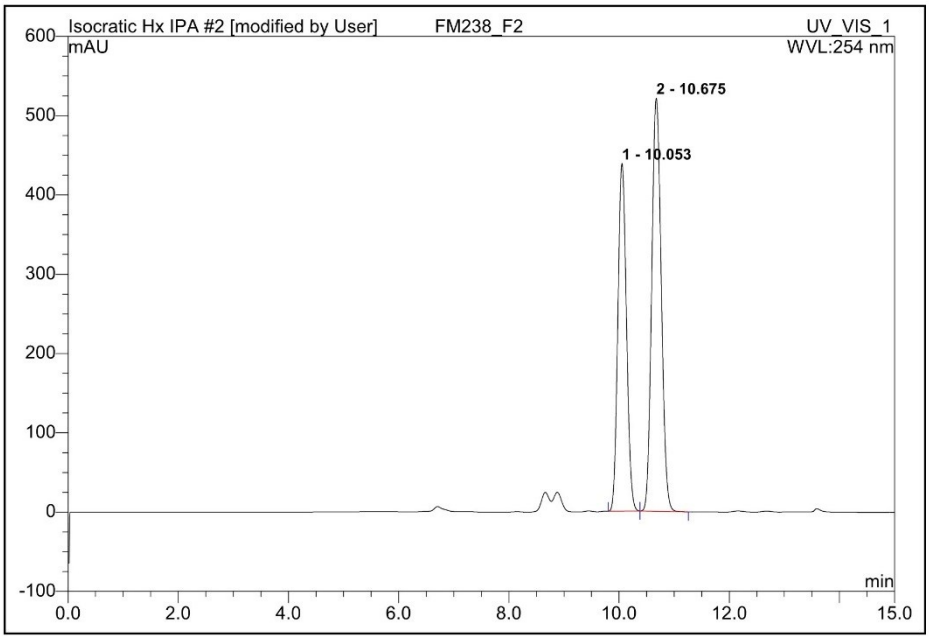
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.89	n.a.	31.402	43.479	64.47	n.a.	BMB*
2	18.71	n.a.	15.777	23.961	35.53	n.a.	BMB*
Total:			47.180	67.441	100.00	0.000	

Figure 93 HPLC chromatogram of enantioenriched triazolium salt **157b**. 60:40 (v/v) 20 mM NH_4HCO_2 + 0.1% TEA/MeCN, 1 mL/min; Phenomenex Cellulose-1.

8.3.2 HPLC Chromatograms of Preliminary Organocatalysis in *Chapter 3*

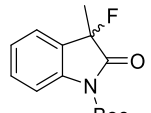


177

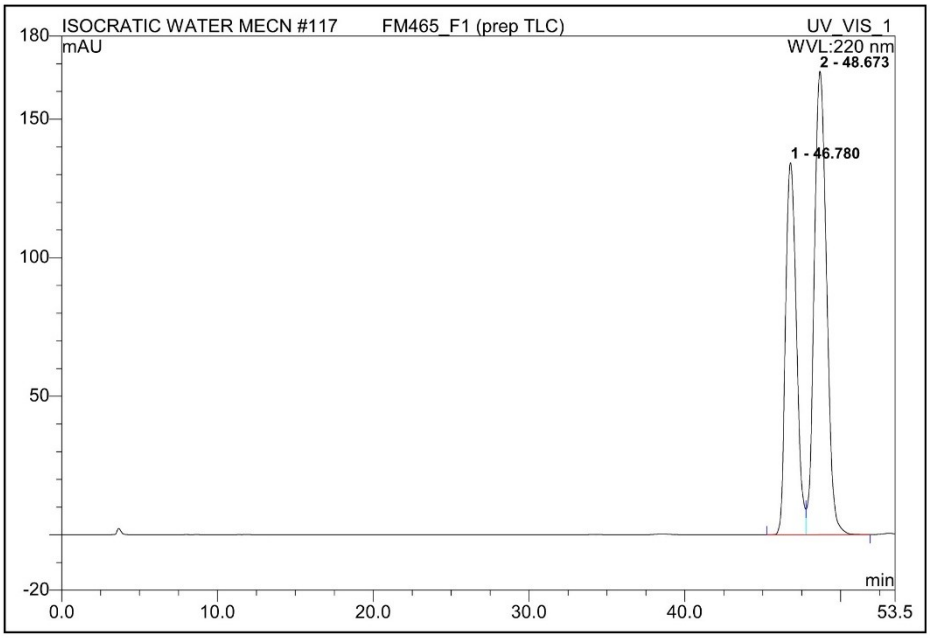


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Type
1	10.05	n.a.	438.379	78.902	43.06	n.a.	BMB*
2	10.68	n.a.	520.993	104.347	56.94	n.a.	BMB
Total:			959.372	183.249	100.00	0.000	

Figure 94 HPLC chromatogram of enantioenriched alkylated oxindole **177**. 5:95 (v/v) IPA/Hx, 1 mL/min; Phenomenex Cellulose-1.[130]



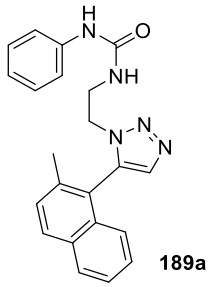
181



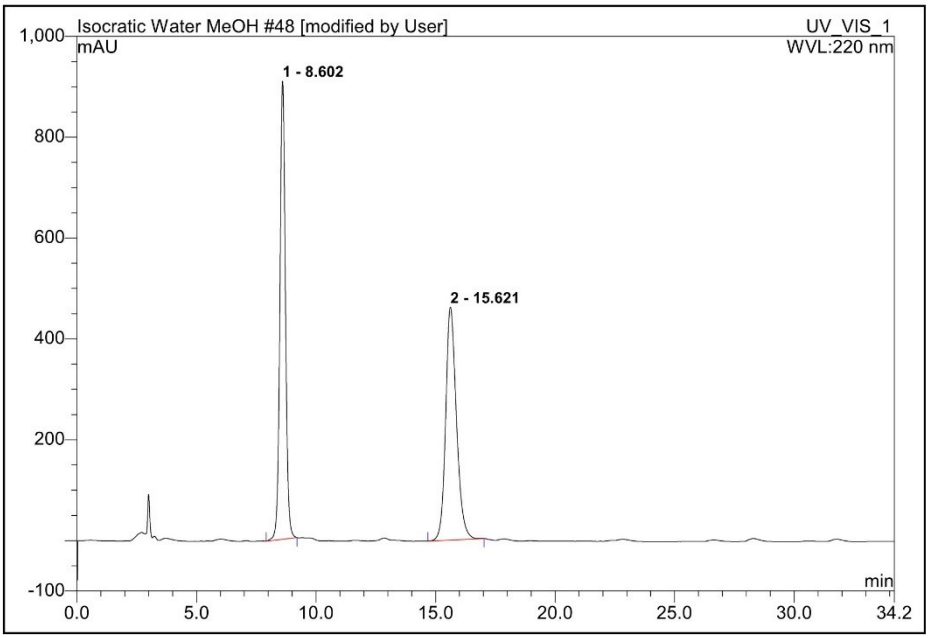
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	46.78	n.a.	134.324	109.034	41.45	n.a.	BM
2	48.67	n.a.	167.270	153.993	58.55	n.a.	MB
Total:			301.594	263.028	100.00	0.000	

Figure 95 HPLC chromatogram of enantioenriched fluorinated oxindole **181**. 62:38 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.

8.3.3 HPLC Chromatograms of Triazole-containing (Thio)Ureas in *Chapter 4*

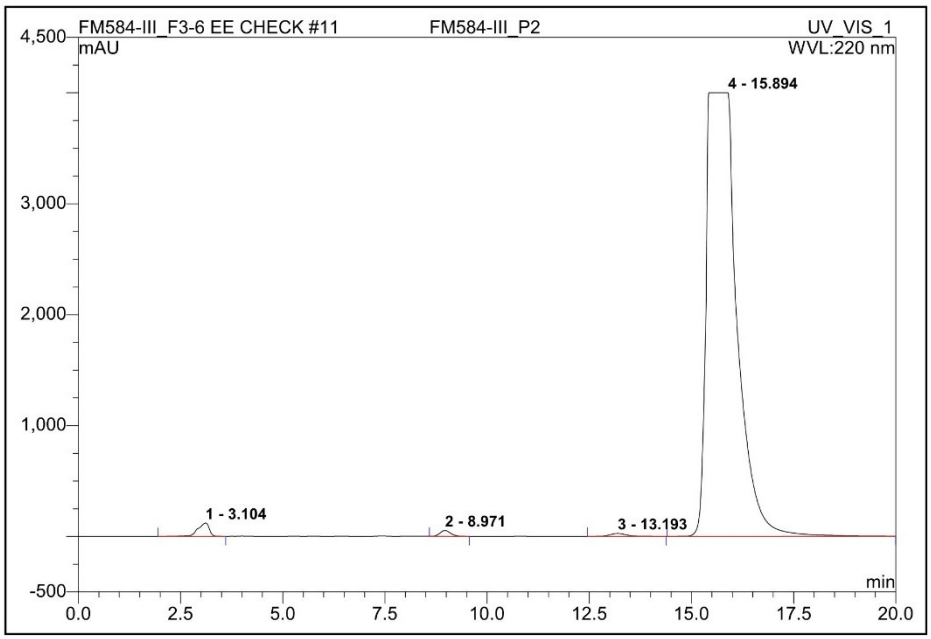


189a



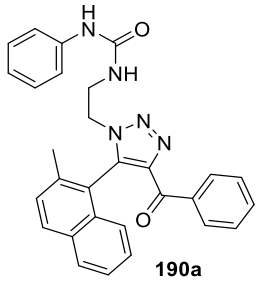
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.60	n.a.	908.994	244.620	50.35	n.a.	BMB*
2	15.62	n.a.	461.874	241.235	49.65	n.a.	BMB*
Total:			1370.869	485.856	100.00	0.000	

Figure 96 HPLC chromatogram of racemic thiourea **189a**. 40:60 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.

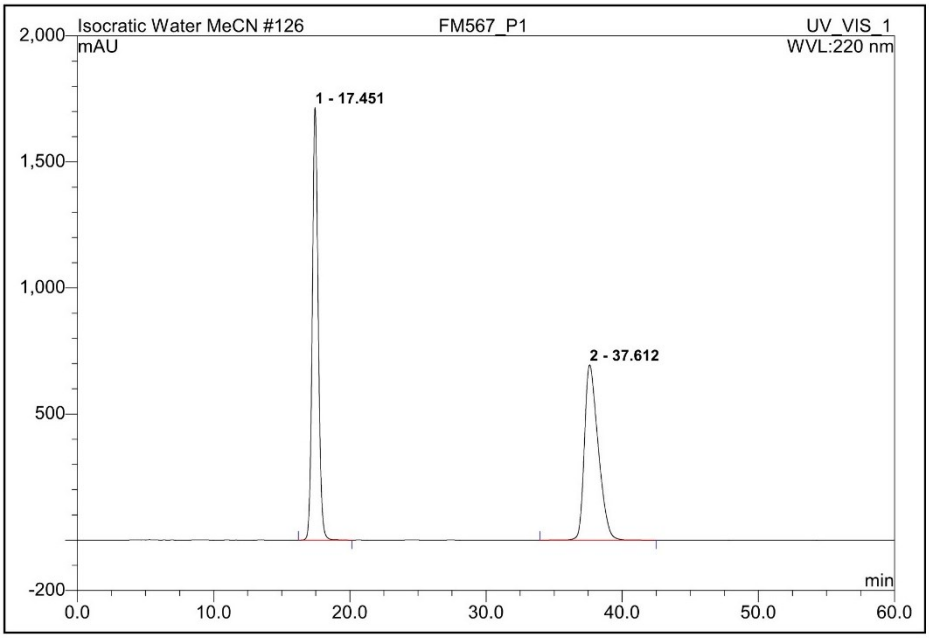


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	3.10	n.a.	120.228	40.124	1.13	n.a.	BMB
2	8.97	n.a.	52.926	16.042	0.45	n.a.	BMB
3	13.19	n.a.	27.195	13.076	0.37	n.a.	BMB
4	15.89	n.a.	3999.956	3472.295	98.04	n.a.	BMB
Total:			4200.305	3541.537	100.00	0.000	

Figure 97 HPLC chromatogram of enantiopure thiourea **189a** (peak 2). 40:60 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.

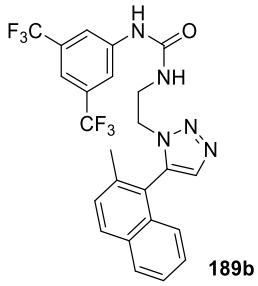


190a

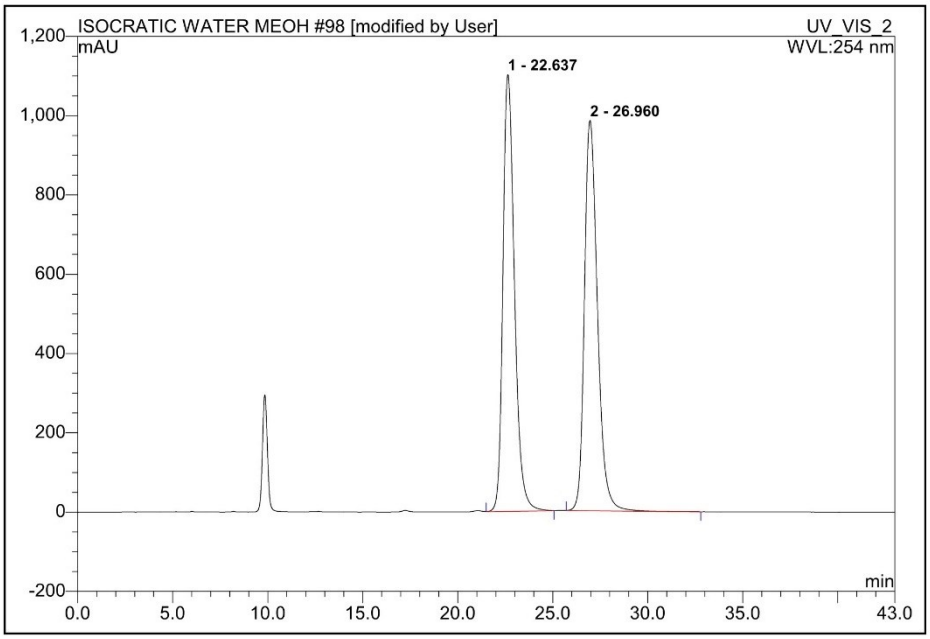


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17.45	n.a.	1715.329	867.812	51.56	n.a.	BMB
2	37.61	n.a.	695.118	815.352	48.44	n.a.	BMB
Total:			2410.447	1683.164	100.00	0.000	

Figure 98 HPLC chromatogram of racemic thiourea **190a**. 40:60 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.

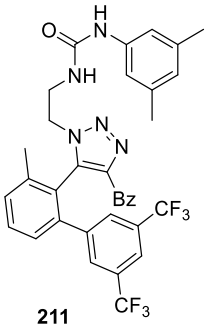


189b

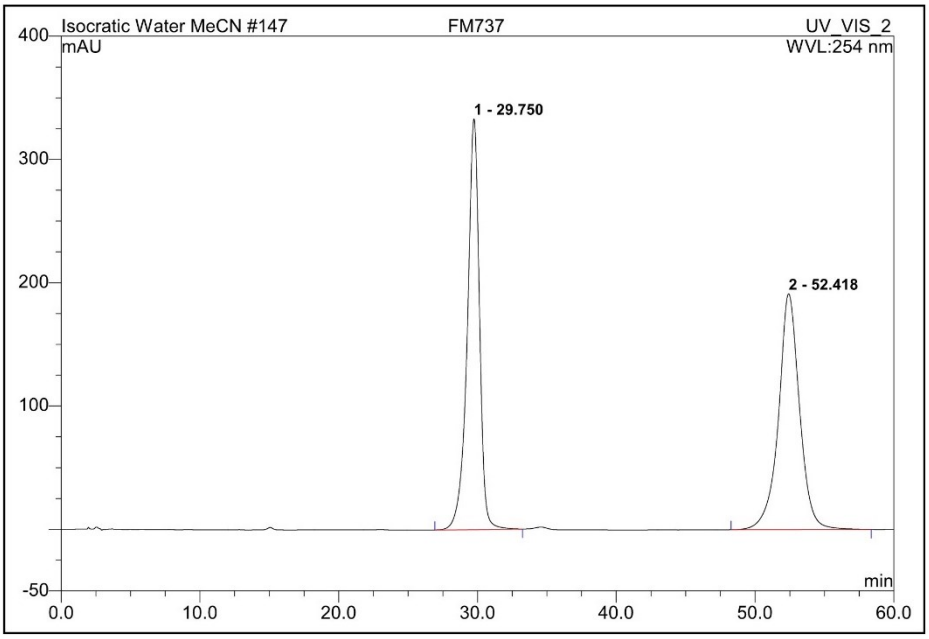


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	22.64	n.a.	1101.919	774.252	49.84	n.a.	BMB*
2	26.96	n.a.	984.365	779.314	50.16	n.a.	BMB*
Total:			2086.283	1553.565	100.00	0.000	

Figure 99 HPLC chromatogram of racemic thiourea **189b**. 50:50 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.

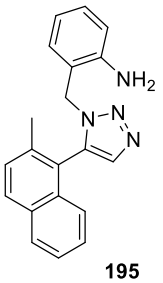


211

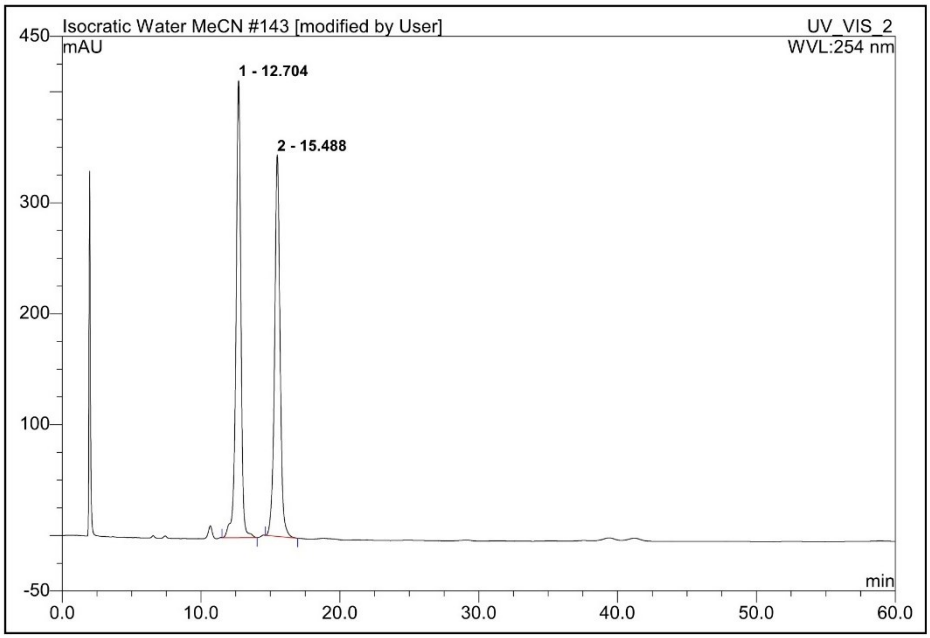


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	29.75	n.a.	333.279	338.276	50.10	n.a.	BMB
2	52.42	n.a.	191.256	336.990	49.90	n.a.	BMB
Total:			524.535	675.266	100.00	0.000	

Figure 100 HPLC chromatogram of racemic thiourea **211**. 40:60 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.

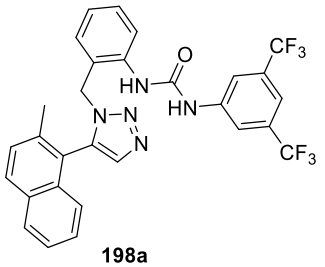


195

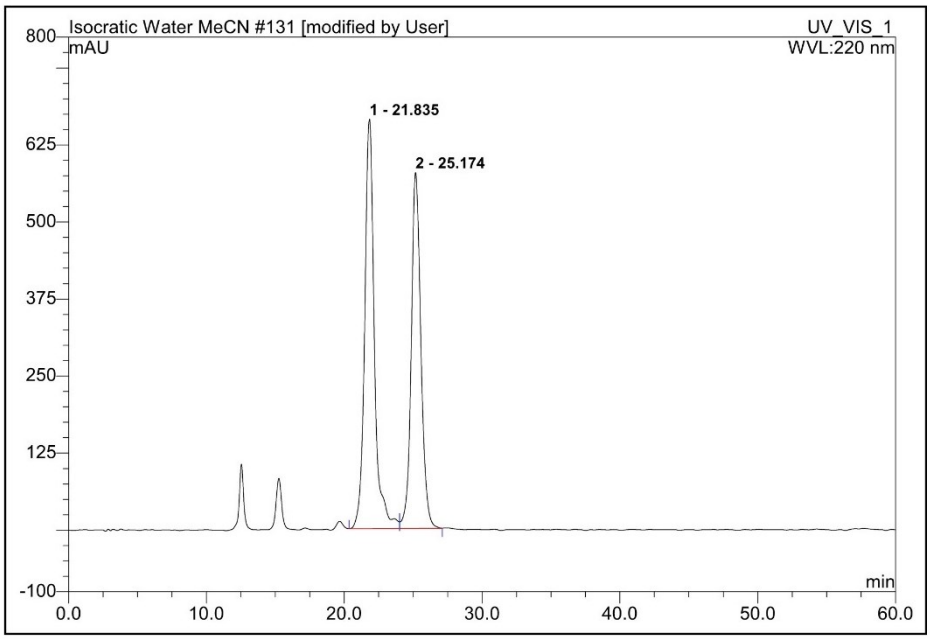


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.70	n.a.	412.306	168.227	51.92	n.a.	BMB
2	15.49	n.a.	343.957	155.797	48.08	n.a.	BMB
Total:			756.263	324.023	100.00	0.000	

Figure 101 HPLC chromatogram of racemic triazole **195**. 40:60 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.

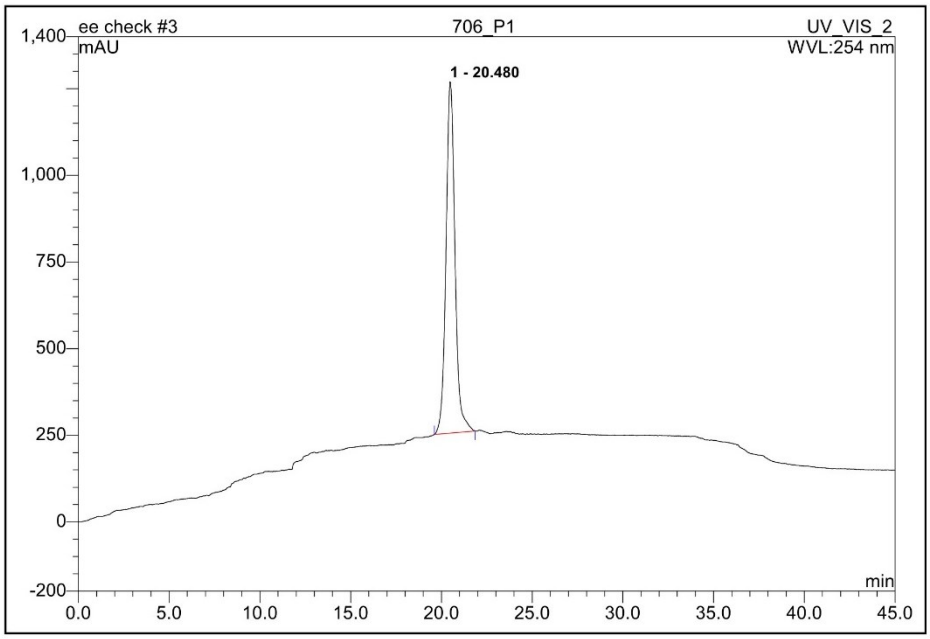


198a

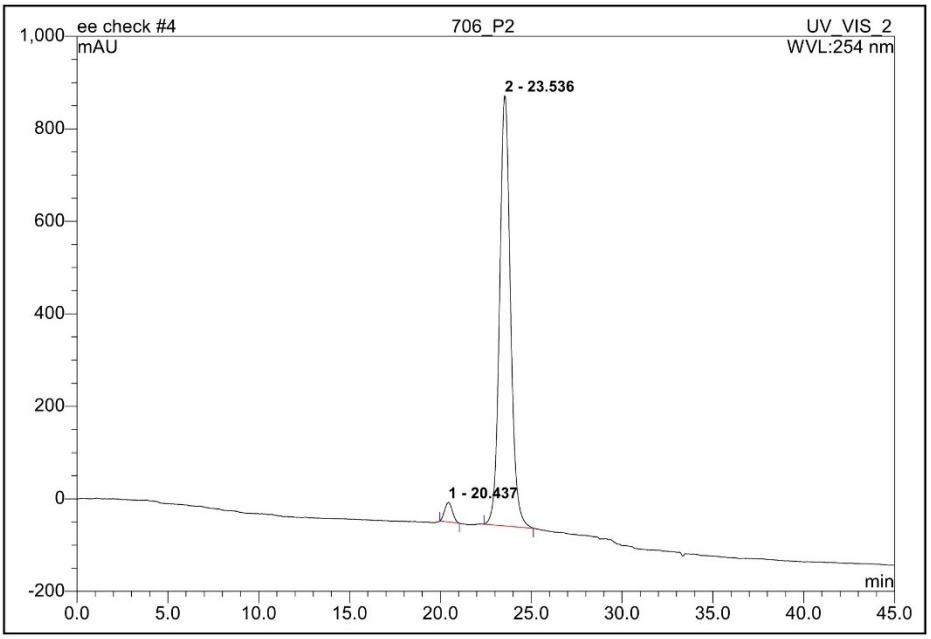


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	21.84	n.a.	664.440	541.793	53.64	n.a.	BM *
2	25.17	n.a.	577.483	468.349	46.36	n.a.	MB*
Total:			1241.923	1010.142	100.00	0.000	

Figure 102 HPLC chromatogram of racemic urea **198a**. 40:60 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.

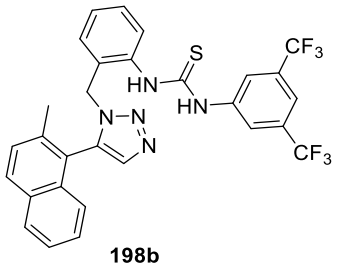


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20.48	n.a.	1014.643	582.633	100.00	n.a.	BMB
Total:			1014.643	582.633	100.00	0.000	

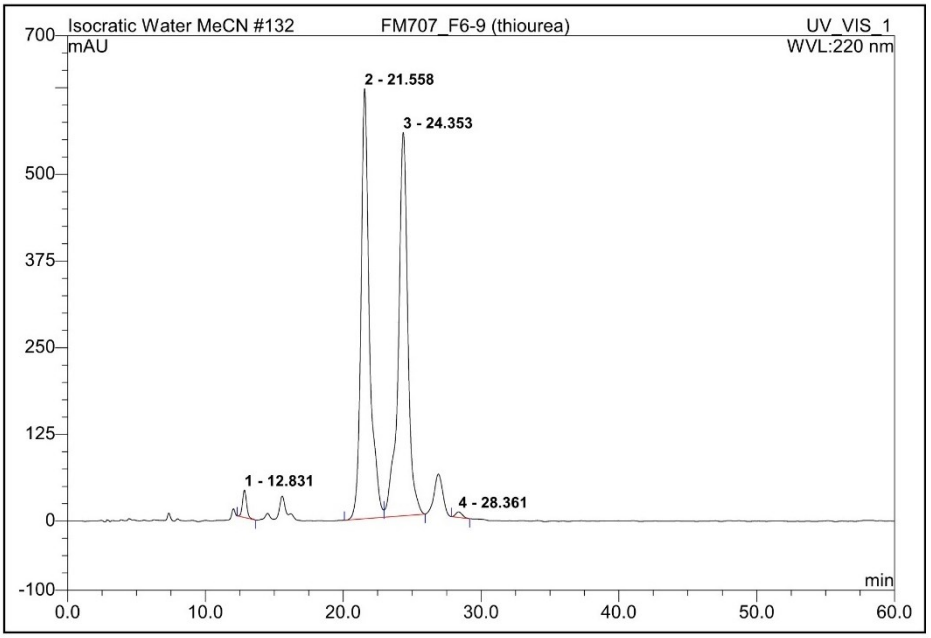


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20.44	n.a.	42.574	21.227	3.18	n.a.	BMB
2	23.54	n.a.	929.818	646.495	96.82	n.a.	BMB
Total:			972.392	667.722	100.00	0.000	

Figure 103 HPLC chromatograms of enantiopure (peak 1, top) and enantioenriched (peak 2, bottom) urea **198a**. 40:60 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.

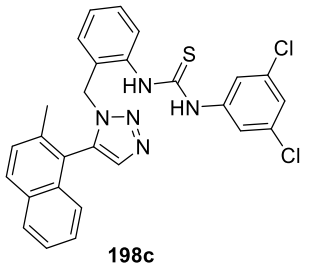


198b

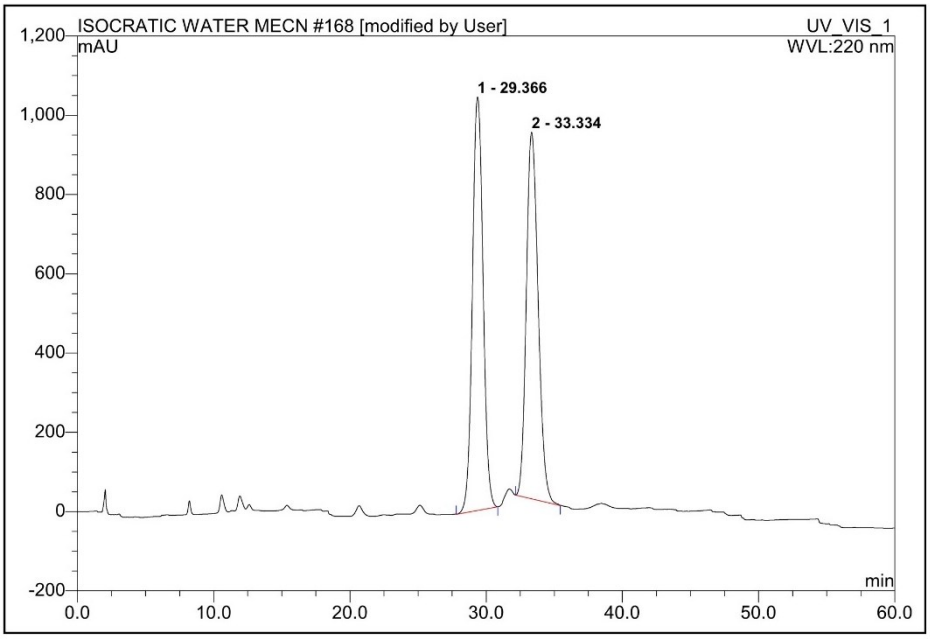


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.83	n.a.	39.525	13.873	1.53	n.a.	BMB
2	21.56	n.a.	620.378	442.053	48.87	n.a.	BM
3	24.35	n.a.	553.054	444.182	49.11	n.a.	MB
4	28.36	n.a.	7.996	4.376	0.48	n.a.	BMB
Total:			1220.953	904.484	100.00	0.000	

Figure 104 HPLC chromatogram of racemic thiourea **198b**. 40:60 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.

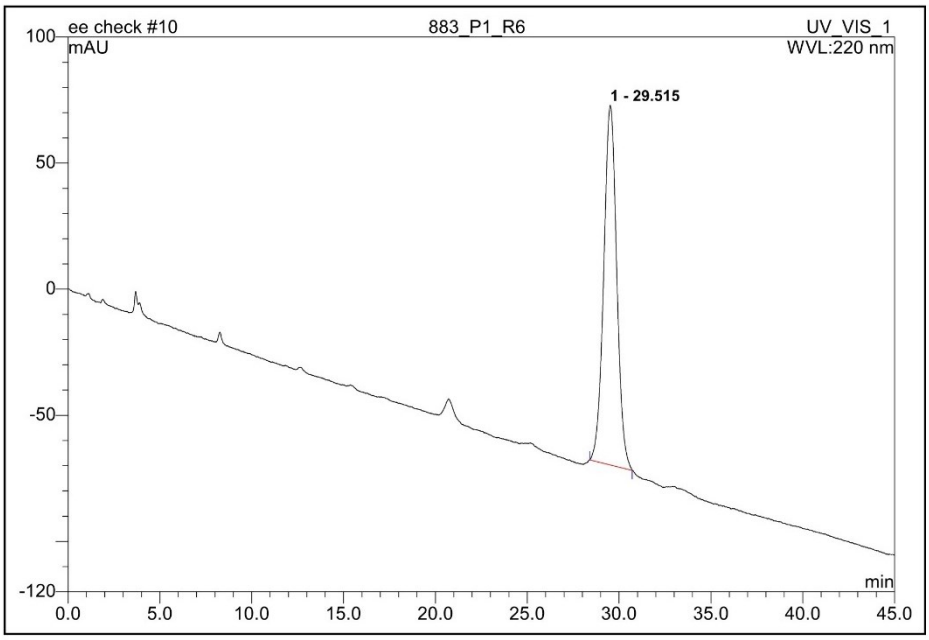


198c

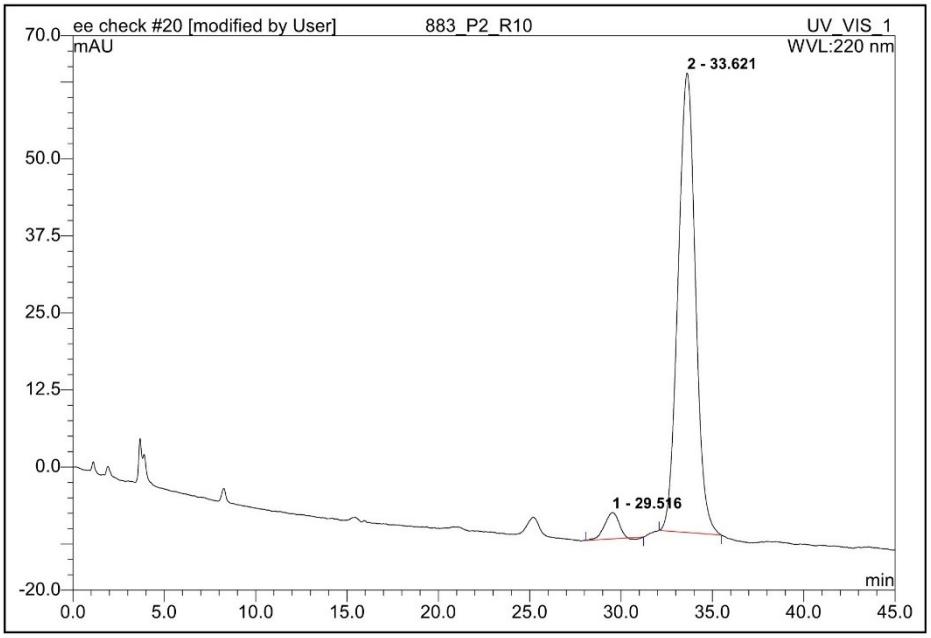


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	29.37	n.a.	1043.523	945.069	50.48	n.a.	BMB*
2	33.33	n.a.	925.083	927.229	49.52	n.a.	BMB*
Total:			1968.606	1872.298	100.00	0.000	

Figure 105 HPLC chromatogram of racemic thiourea **198c**. 40:60 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.



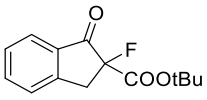
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	29.51	n.a.	142.664	116.927	100.00	n.a.	BMB
Total:			142.664	116.927	100.00	0.000	



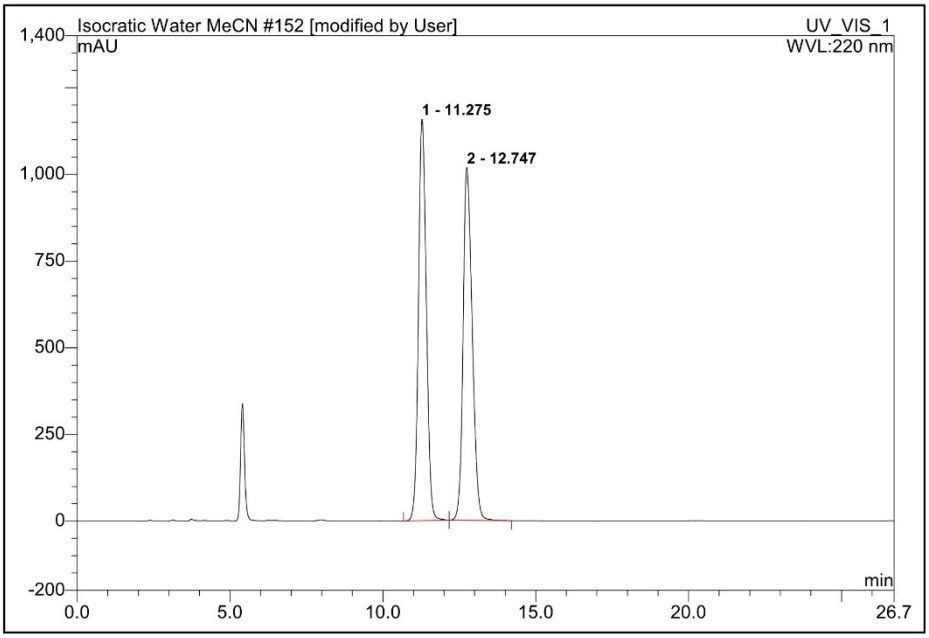
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	29.52	n.a.	4.284	3.730	4.33	n.a.	BMB*
2	33.62	n.a.	74.592	82.359	95.67	n.a.	BMB
Total:			78.876	86.089	100.00	0.000	

Figure 106 HPLC chromatograms of enantiopure thiourea **198c** (peak 1, top; peak 2, bottom). 40:60 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.

8.3.4 HPLC Chromatograms of Preliminary Organocatalysis in *Chapter 4*

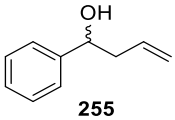


253

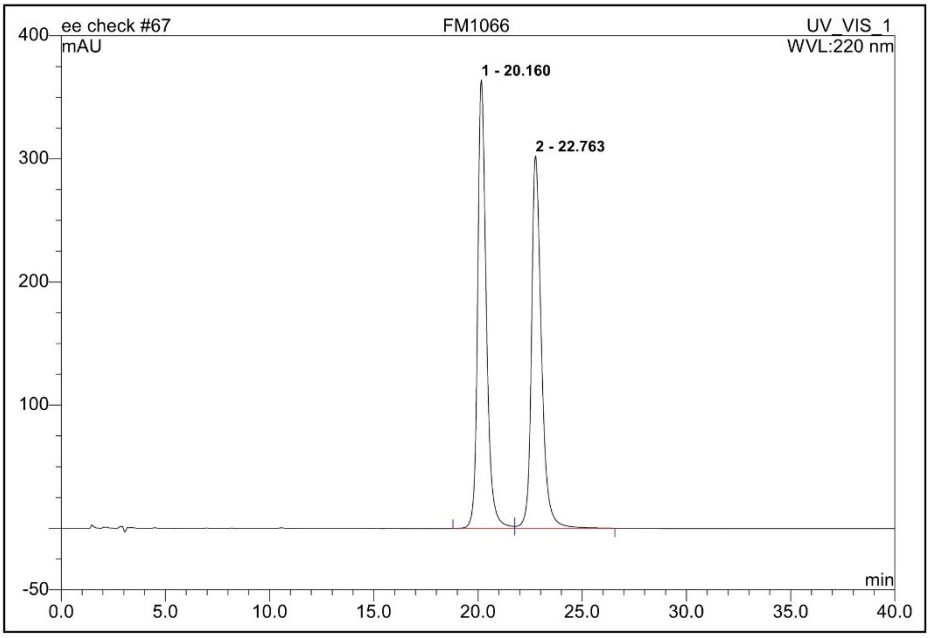


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.27	n.a.	1157.629	346.505	49.66	n.a.	BMb*
2	12.75	n.a.	1017.511	351.236	50.34	n.a.	bMB
Total:			2175.140	697.742	100.00	0.000	

Figure 107 HPLC chromatogram of fluorinated indanone **253**. 80:20 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-3.

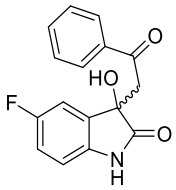


255

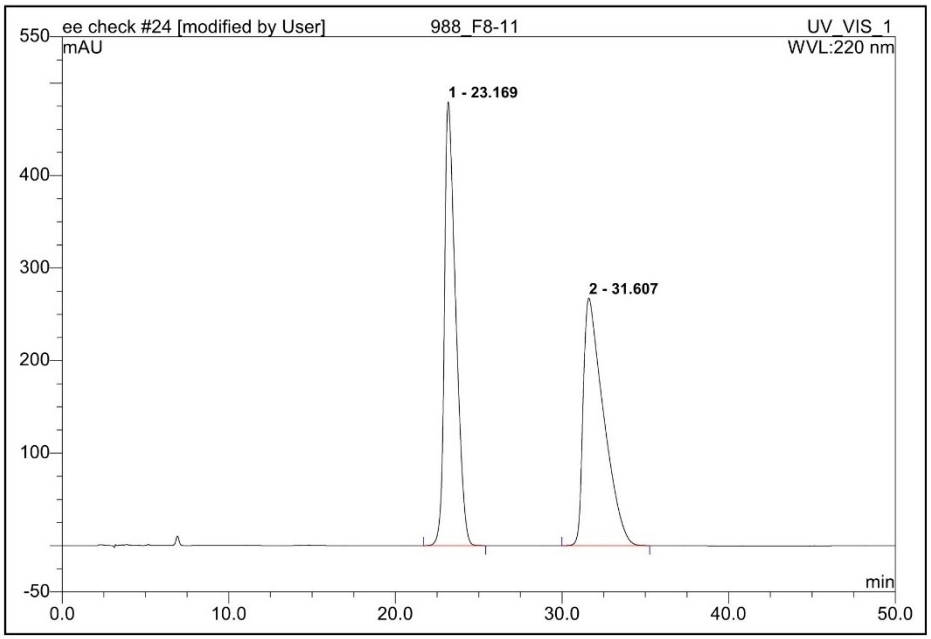


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20.16	n.a.	364.245	175.620	51.09	n.a.	BM
2	22.76	n.a.	302.611	168.112	48.91	n.a.	MB
Total:			666.856	343.732	100.00	0.000	

Figure 108 HPLC chromatogram of allyl alcohol **255**. 70:30 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-1.

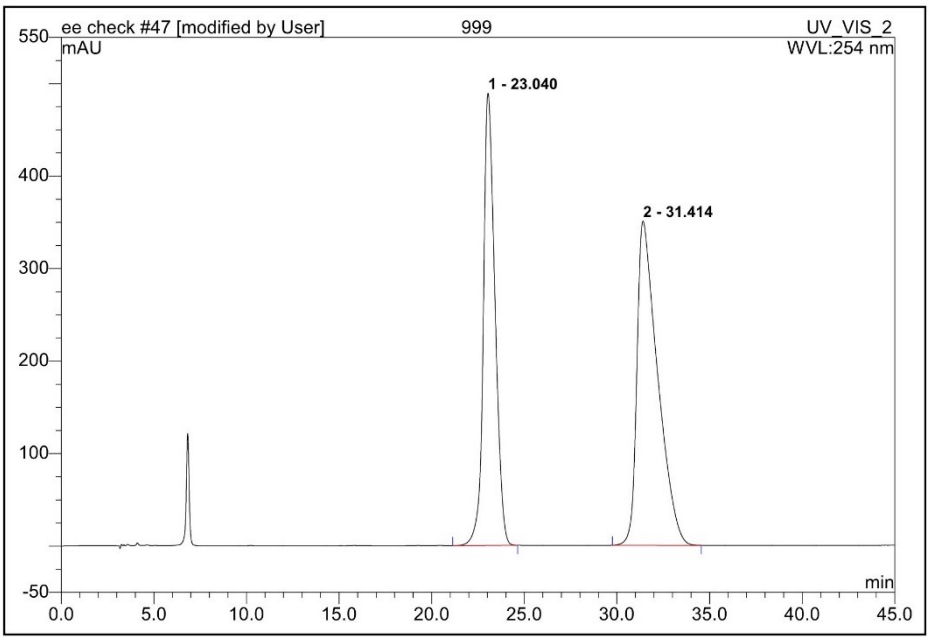


254



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	23.17	n.a.	479.897	378.008	49.88	n.a.	BMB
2	31.61	n.a.	267.588	379.864	50.12	n.a.	BMB
Total:			747.485	757.872	100.00	0.000	

Figure 109 HPLC chromatogram of racemic isatin derivative **254**. 80:20 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-3.



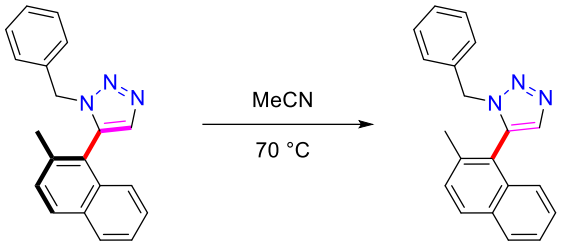
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	23.04	n.a.	488.959	356.660	44.00	n.a.	BMB
2	31.41	n.a.	350.450	453.903	56.00	n.a.	BMB
Total:			839.409	810.563	100.00	0.000	

Figure 110 HPLC chromatogram of enantioenriched isatin derivative **254**. 80:20 (v/v) H_2O/MeCN, 1 mL/min; Phenomenex Cellulose-3.

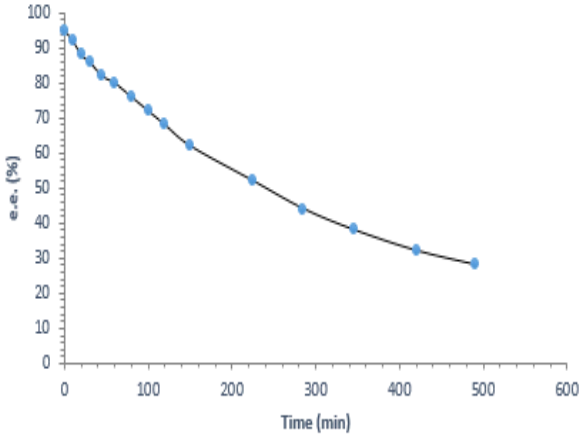
8.4 Experimental Barriers to Rotation

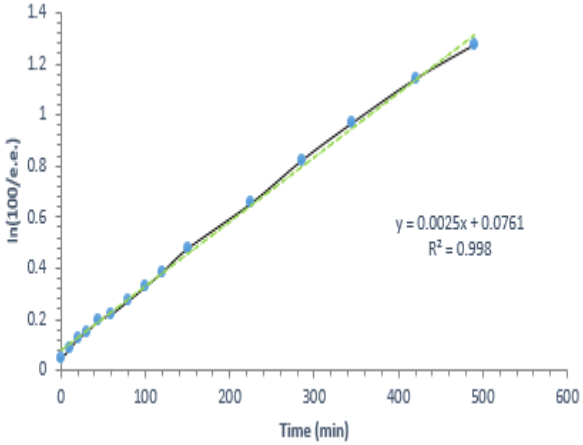
Enantioenriched materials of regioisomeric triazoles **153b** and **154b** were obtained *via* preparative HPLC on chiral stationary phase (Phenomenex Lux Cellulose-1, MeCN/H_2O). For each compound, *ca.* 10 mg were redissolved in acetonitrile (1.5 mL). The resulting solution was heated to 70 °C (**153b**) or 80 °C (**154b**) and kept at the temperature stated throughout the duration of the experiment. Samples were collected periodically and diluted with acetonitrile at room temperature (concentration unknown), hence directly injected into HPLC. Barriers to rotations were calculated measuring the erosion of the ee% registered over time.

8.4.1 Rotational barrier of 153b



Enantioenriched *Racemic*





Time (min)	ee %	log(100/ee)
0	95	0.051293294
10	92	0.083381609
20	88	0.127833372
30	86	0.15082289
45	82	0.198450939
60	80	0.223143551
80	76	0.274436846
100	72	0.328504067
120	68	0.385662481
150	62	0.478035801
225	52	0.653926467
285	44	0.820980552
345	38	0.967584026
420	32	1.139434283
490	28	1.272965676

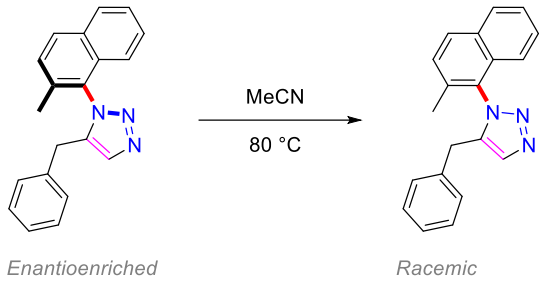
$$ln\left(\frac{100}{ee}\right) = k_{rac} \times t + ln\left(\frac{100}{ee_{t=0}}\right)$$

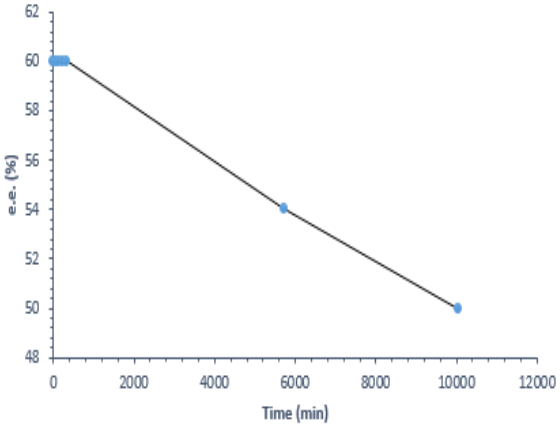
$$k_{ent} = \frac{1}{2}k_{rac} = \frac{1}{2}slope = 0.00125$$

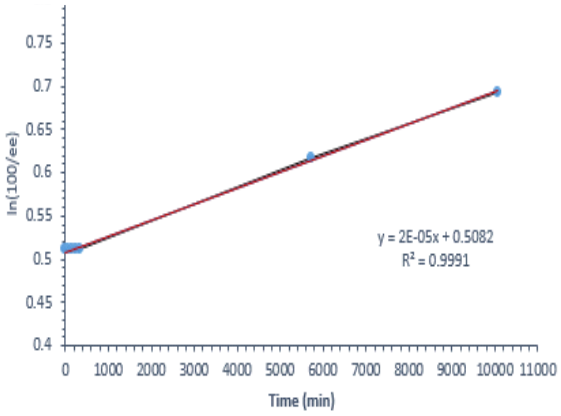
$$\Delta G^{\ddagger} = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) \mathrm{RT} = 104079.6964\ \mathrm{J \cdot mol^{-1}} = 24.98\ \mathrm{kcal \cdot mol^{-1}}$$

$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 277.26\ \mathrm{min} = 4.6\ \mathrm{h}$$

8.4.2 Rotational barrier of 154b







Time (min)	ee %	log(100/ee)
0	60	0.510825624
57	60	0.510825624
130	60	0.510825624
224	60	0.510825624
344	60	0.510825624
5735	54	0.616186139
10055	50	0.693147181

$$ln\left(\frac{100}{ee}\right) = k_{rac} \times t + \ln\left(\frac{100}{ee_{t=0}}\right)$$

$$k_{ent} = \frac{1}{2}k_{rac} = \frac{1}{2}slope = 0.00001$$

$$\Delta G^{\ddagger} = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) \mathrm{RT} = 120728.8732\ \mathrm{J \cdot mol^{-1}} = 28.97\ \mathrm{kcal \cdot mol^{-1}}$$

$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 34657.36\ \mathrm{min} = 577.6\ \mathrm{h}$$

8.5 X-Ray Crystallography Tables

8.5.1 Crystallographic Data for 153b

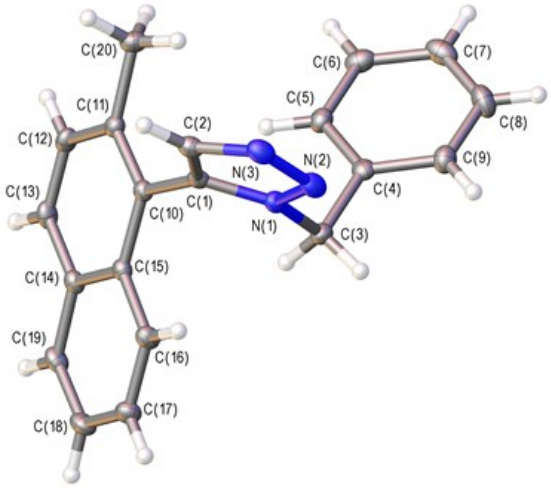


Table 5 Crystal data and structure refinement for **153b**.

Empirical formula	$C_{20}H_{17}N_3$
Formula weight	299.36
Temperature/K	100.00(10)
Crystal system	monoclinic
Space group	C2/c
a/Å	24.0885(9)
b/Å	9.0300(3)
c/Å	14.2334(5)
α/°	90
β/°	101.643(3)
γ/°	90
Volume/Å^3	3032.33(19)
Z	8

ρ_{calc}g/cm^3	1.311
μ/mm^{-1}	0.079
F(000)	1264.0
Crystal size/mm^3	0.294 × 0.238 × 0.147
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.87 to 58.8
Index ranges	$-33 \leq h \leq 33$, $-12 \leq k \leq 11$, $-18 \leq l \leq 19$
Reflections collected	17439
Independent reflections	3840 [R_{int} = 0.0232, R_{sigma} = 0.0200]
Data/restraints/parameters	3840/0/209
Goodness-of-fit on F^2	1.053
Final R indexes [I>=2σ (I)]	R_1 = 0.0417, wR_2 = 0.1087
Final R indexes [all data]	R_1 = 0.0465, wR_2 = 0.1123
Largest diff. peak/hole / e Å^{-3}	0.36/-0.23

Table 6 Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **153b**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
C1	5836.6(5)	7429.2(12)	6242.7(8)	13.8(2)
C2	5472.7(5)	8231.0(13)	6678.7(8)	16.6(2)
C3	6919.4(5)	7367.4(13)	6600.1(8)	17.0(2)
C4	7153.5(5)	8515.0(13)	6015.0(8)	16.0(2)
C5	6943.3(5)	8632.8(14)	5031.2(8)	18.5(2)
C6	7159.0(5)	9692.6(15)	4494.5(9)	21.9(3)
C7	7595.5(6)	10616.2(15)	4933.2(10)	24.9(3)
C8	7805.8(6)	10504.5(15)	5908.3(10)	25.9(3)
C9	7584.5(5)	9462.9(14)	6450.3(9)	20.6(2)
C10	5751.8(4)	6398.6(12)	5419.3(8)	13.2(2)
C11	5555.3(5)	6920.0(13)	4495.6(8)	14.7(2)
C12	5519.9(5)	5916.5(14)	3718.6(8)	17.3(2)
C13	5668.2(5)	4466.3(14)	3854.5(8)	17.9(2)
C14	5860.9(5)	3892.2(13)	4790.0(8)	15.1(2)
C15	5896.5(4)	4865.6(12)	5588.0(8)	13.6(2)
C16	6079.1(5)	4271.2(13)	6521.8(8)	16.9(2)
C17	6227.5(5)	2807.7(14)	6654.3(9)	19.7(2)
C18	6210.5(5)	1862.5(13)	5858.4(9)	20.1(2)
C19	6028.1(5)	2395.2(13)	4949.1(9)	18.5(2)
C20	5390.0(5)	8506.6(13)	4269.7(9)	19.6(2)
N1	6357.4(4)	7773.0(11)	6766.8(7)	14.9(2)
N2	6319.1(5)	8726.1(11)	7481.5(7)	19.0(2)
N3	5778.0(5)	9001.3(12)	7429.4(7)	19.8(2)

Table 7 Anisotropic Displacement Parameters ($Å^2×10^3$) for **153b**. The Anisotropic displacement factor exponent takes the form: $-2π^2[h^2a^{*2}U_{11}+2hka*b*U_{12}+…]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	16.7(5)	12.3(5)	12.9(5)	2.1(4)	4.1(4)	0.1(4)
C2	20.6(5)	14.4(5)	16.5(5)	0.9(4)	7.4(4)	1.3(4)
C3	15.5(5)	16.0(5)	19.0(5)	0.8(4)	1.9(4)	1.4(4)
C4	14.4(5)	14.7(5)	19.2(5)	-0.5(4)	4.3(4)	3.0(4)
C5	15.2(5)	20.3(6)	19.6(6)	-1.1(4)	2.4(4)	1.3(4)
C6	21.5(6)	25.1(6)	20.0(6)	4.2(5)	6.6(4)	6.9(5)
C7	27.3(6)	18.5(6)	33.1(7)	2.6(5)	16.6(5)	1.7(5)
C8	23.9(6)	22.7(6)	33.4(7)	-6.4(5)	10.8(5)	-7.5(5)
C9	18.4(5)	22.4(6)	20.7(6)	-4.2(5)	3.7(4)	-1.1(5)
C10	12.7(5)	13.6(5)	13.8(5)	-1.1(4)	3.9(4)	-0.7(4)
C11	12.9(5)	16.7(5)	14.7(5)	1.0(4)	3.2(4)	-0.8(4)
C12	16.6(5)	23.0(6)	11.7(5)	0.2(4)	1.5(4)	-2.5(4)
C13	19.6(5)	20.7(6)	13.9(5)	-4.9(4)	4.6(4)	-5.7(4)
C14	15.4(5)	14.7(5)	16.1(5)	-1.9(4)	5.6(4)	-2.7(4)
C15	13.3(5)	14.0(5)	14.2(5)	-1.1(4)	4.4(4)	-1.7(4)
C16	21.2(5)	15.7(5)	14.4(5)	-0.7(4)	5.2(4)	-1.2(4)
C17	23.5(6)	17.5(6)	18.3(5)	3.1(4)	4.7(4)	-0.1(5)
C18	23.0(6)	12.4(5)	26.0(6)	0.1(4)	7.3(5)	0.5(4)
C19	21.4(6)	14.3(5)	21.3(6)	-4.8(4)	8.1(4)	-2.9(4)
C20	21.7(6)	18.3(6)	18.6(5)	3.4(4)	3.7(4)	3.2(5)
N1	18.6(5)	13.7(5)	12.6(4)	-1.6(3)	3.6(3)	-0.2(4)
N2	26.9(5)	16.3(5)	14.6(5)	-3.0(4)	6.1(4)	-1.0(4)
N3	27.4(5)	16.5(5)	17.6(5)	-1.0(4)	9.5(4)	0.3(4)

Table 8 Bond Lengths for **153b**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C2	1.3775(15)	C10	C15	1.4359(15)
C1	C10	1.4780(15)	C11	C12	1.4189(16)
C1	N1	1.3598(15)	C11	C20	1.5043(16)
C2	N3	1.3599(16)	C12	C13	1.3609(18)
C3	C4	1.5084(16)	C13	C14	1.4169(16)
C3	N1	1.4672(15)	C14	C15	1.4250(15)
C4	C5	1.3937(16)	C14	C19	1.4156(17)
C4	C9	1.3910(17)	C15	C16	1.4185(15)
C5	C6	1.3890(17)	C16	C17	1.3721(17)
C6	C7	1.3878(19)	C17	C18	1.4123(17)
C7	C8	1.382(2)	C18	C19	1.3676(17)
C8	C9	1.3891(18)	N1	N2	1.3497(13)
C10	C11	1.3868(15)	N2	N3	1.3140(15)

Table 9 Bond Angles for **153b**.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C2	C1	C10	133.59(11)	C12	C11	C20	118.03(10)
N1	C1	C2	103.49(10)	C13	C12	C11	122.07(11)
N1	C1	C10	122.91(10)	C12	C13	C14	120.83(10)
N3	C2	C1	109.29(10)	C13	C14	C15	118.62(10)
N1	C3	C4	112.20(9)	C19	C14	C13	121.89(10)
C5	C4	C3	120.44(10)	C19	C14	C15	119.48(10)
C9	C4	C3	120.37(10)	C14	C15	C10	119.20(10)
C9	C4	C5	119.19(11)	C16	C15	C10	122.71(10)
C6	C5	C4	120.32(11)	C16	C15	C14	118.09(10)
C7	C6	C5	120.01(12)	C17	C16	C15	121.07(11)
C8	C7	C6	119.93(12)	C16	C17	C18	120.48(11)
C7	C8	C9	120.21(12)	C19	C18	C17	119.89(11)
C8	C9	C4	120.32(12)	C18	C19	C14	120.93(11)
C11	C10	C1	120.27(10)	C1	N1	C3	129.30(10)
C11	C10	C15	120.71(10)	N2	N1	C1	111.30(9)
C15	C10	C1	118.97(9)	N2	N1	C3	119.13(9)
C10	C11	C12	118.52(11)	N3	N2	N1	107.22(9)
C10	C11	C20	123.43(10)	N2	N3	C2	108.70(10)

Table 10 Torsion Angles for **153b**.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C1	C2	N3	N2	0.37(13)	C10	C15	C16	C17	-178.34(11)
C1	C10	C11	C12	175.35(10)	C11	C10	C15	C14	2.86(15)
C1	C10	C11	C20	-3.16(16)	C11	C10	C15	C16	-177.62(10)
C1	C10	C15	C14	-174.75(10)	C11	C12	C13	C14	0.63(17)
C1	C10	C15	C16	4.76(16)	C12	C13	C14	C15	0.01(17)
C1	N1	N2	N3	0.23(13)	C12	C13	C14	C19	-178.74(11)
C2	C1	C10	C11	68.89(17)	C13	C14	C15	C10	-1.70(15)
C2	C1	C10	C15	-113.48(14)	C13	C14	C15	C16	178.76(10)
C2	C1	N1	C3	-173.86(11)	C13	C14	C19	C18	-179.71(11)
C2	C1	N1	N2	0.00(12)	C14	C15	C16	C17	1.18(17)
C3	C4	C5	C6	179.87(11)	C15	C10	C11	C12	-2.23(16)
C3	C4	C9	C8	179.03(11)	C15	C10	C11	C20	179.26(10)
C3	N1	N2	N3	174.79(10)	C15	C14	C19	C18	1.55(17)
C4	C3	N1	C1	91.69(14)	C15	C16	C17	C18	1.07(18)
C4	C3	N1	N2	-81.76(12)	C16	C17	C18	C19	-2.04(18)
C4	C5	C6	C7	1.59(18)	C17	C18	C19	C14	0.71(18)
C5	C4	C9	C8	-0.59(18)	C19	C14	C15	C10	177.07(10)
C5	C6	C7	C8	-1.57(19)	C19	C14	C15	C16	-2.47(16)
C6	C7	C8	C9	0.5(2)	C20	C11	C12	C13	179.08(11)
C7	C8	C9	C4	0.61(19)	N1	C1	C2	N3	-0.22(12)
C9	C4	C5	C6	-0.51(17)	N1	C1	C10	C11	-111.80(12)
C10	C1	C2	N3	179.18(11)	N1	C1	C10	C15	65.82(14)
C10	C1	N1	C3	6.66(18)	N1	C3	C4	C5	-74.90(13)
C10	C1	N1	N2	-179.48(10)	N1	C3	C4	C9	105.49(12)

C10	C11	C12	C13	0.49(17)	N1	N2	N3	C2	-0.36(12)

Table 11 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **153b**.

Atom	*x*	*y*	*z*	U(eq)
H2	5079.91	8243.55	6489.51	20
H3A	6893.87	6424.07	6268.06	20
H3B	7178	7248.7	7212.78	20
H5	6657.25	7998.9	4732.67	22
H6	7010.85	9783.19	3841.17	26
H7	7746.29	11309.57	4571.26	30
H8	8096.39	11128.63	6202.75	31
H9	7725.24	9399.12	7107.33	25
H12	5391.23	6260.64	3096.91	21
H13	5642.68	3844.25	3326.79	21
H16	6098.56	4883.41	7052.91	20
H17	6340.16	2435.42	7272.68	24
H18	6323.06	879.4	5952.58	24
H19	6013.71	1765.24	4427.81	22
H20A	4984.36	8584.59	4110.07	29
H20B	5546.36	8834.3	3736.18	29
H20C	5533.66	9113.54	4818.7	29

8.5.2 Crystallographic Data for 154a

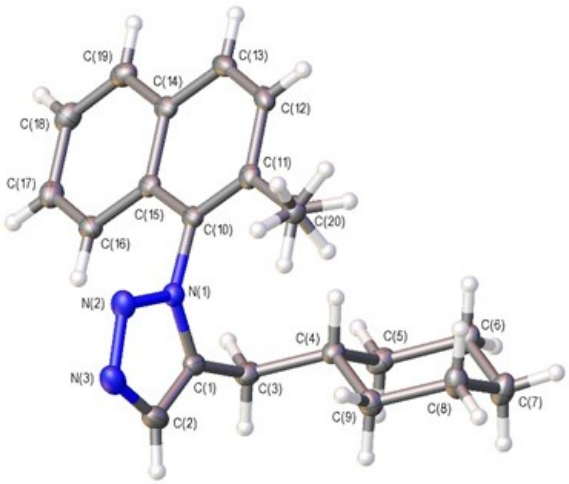


Table 12 Crystal data and structure refinement for **154a**.

Empirical formula	$C_{20}H_{23}N_3$

Formula weight	305.41
Temperature/K	100.01(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.2157(6)
b/Å	13.1072(5)
c/Å	12.3803(7)
α/°	90
β/°	116.226(7)
γ/°	90
Volume/Å^3	1632.63(17)
Z	4
ρ_{calc}g/cm^3	1.243
μ/mm^{-1}	0.571
F(000)	656.0
Crystal size/mm^3	0.195 × 0.183 × 0.101
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.79 to 145.578
Index ranges	$-8 \leq h \leq 13$, $-14 \leq k \leq 16$, $-15 \leq l \leq 10$
Reflections collected	6411
Independent reflections	3163 [R_{int} = 0.0244, R_{sigma} = 0.0279]
Data/restraints/parameters	3163/0/210
Goodness-of-fit on F^2	1.044
Final R indexes [I>=2σ (I)]	R_1 = 0.0384, wR_2 = 0.0935
Final R indexes [all data]	R_1 = 0.0454, wR_2 = 0.1005
Largest diff. peak/hole / e Å^{-3}	0.23/-0.29

Table 13 Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **154a**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
C(1)	7921.3(12)	3296.4(9)	3549.4(11)	19.5(3)
C(2)	8960.1(13)	2710.6(10)	4325.6(13)	25.1(3)
C(3)	7280.4(12)	3397.8(10)	2209.9(11)	21.3(3)
C(4)	7495.5(12)	4424.9(9)	1724.2(11)	18.7(3)
C(5)	6734.3(12)	4443.7(10)	345.4(11)	22.9(3)
C(6)	6902.0(13)	5459.9(11)	-168.9(11)	25.5(3)
C(7)	8372.9(13)	5681.2(12)	213.0(12)	27.4(3)
C(8)	9154.5(13)	5659.3(11)	1584.7(12)	25.2(3)
C(9)	8968.5(12)	4647.9(10)	2106.3(11)	22.0(3)
C(10)	6443.8(12)	4504.9(9)	3998.6(10)	17.2(2)
C(11)	6680.9(12)	5538.6(10)	4114.2(10)	19.1(3)
C(12)	5577.6(13)	6192.2(10)	3853.2(11)	21.5(3)
C(13)	4327.5(13)	5815.9(10)	3504.1(11)	21.7(3)
C(14)	4077.7(12)	4753.5(10)	3380.5(10)	19.0(3)
C(15)	5159.1(12)	4075.4(9)	3631.9(10)	17.1(2)
C(16)	4910.0(12)	3012.3(10)	3514.4(11)	20.0(3)
C(17)	3647.1(13)	2645.9(10)	3145.9(11)	22.9(3)

C(18)	2569.7(13)	3316.4(11)	2886.0(11)	24.1(3)
C(19)	2784.8(12)	4344.8(11)	3012.2(11)	22.4(3)
C(20)	8047.5(13)	5983.3(10)	4518.8(12)	23.7(3)
N(1)	7535.4(10)	3812.9(8)	4293.3(9)	18.3(2)
N(2)	8295.8(10)	3552.2(9)	5470.1(10)	23.7(2)
N(3)	9168.1(11)	2880.2(9)	5479.7(11)	27.3(3)

Table 14 Anisotropic Displacement Parameters ($Å^2×10^3$) for FM486_F8-10. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	21.7(6)	13.9(6)	27.2(6)	-0.4(5)	14.8(5)	-1.2(4)
C(2)	23.3(6)	18.7(6)	36.4(7)	2.3(5)	16.1(6)	3.0(5)
C(3)	24.1(6)	19.1(6)	24.7(6)	-4.4(5)	14.5(5)	-2.5(5)
C(4)	21.2(6)	18.4(6)	18.8(6)	-1.9(4)	11.1(5)	-0.6(5)
C(5)	21.1(6)	28.1(7)	20.2(6)	-5.8(5)	9.8(5)	-3.6(5)
C(6)	23.8(6)	34.9(8)	16.5(6)	1.2(5)	7.7(5)	-1.1(5)
C(7)	25.9(7)	33.9(8)	23.3(6)	5.8(5)	11.6(5)	-2.8(6)
C(8)	21.3(6)	26.2(7)	24.1(6)	5.2(5)	6.3(5)	-3.9(5)
C(9)	21.0(6)	21.4(6)	21.8(6)	2.3(5)	7.8(5)	-0.2(5)
C(10)	21.4(6)	17.8(6)	14.5(5)	1.7(4)	9.8(4)	3.1(5)
C(11)	25.3(6)	19.7(6)	14.2(5)	0.3(4)	10.4(5)	-0.9(5)
C(12)	33.6(7)	15.4(6)	19.4(6)	1.7(5)	15.3(5)	2.0(5)
C(13)	29.1(6)	19.4(6)	19.5(6)	3.4(5)	13.3(5)	7.9(5)
C(14)	23.9(6)	21.4(6)	13.3(5)	1.6(4)	9.8(5)	3.8(5)
C(15)	21.3(6)	19.4(6)	12.0(5)	0.7(4)	8.6(4)	1.7(5)
C(16)	24.3(6)	18.9(6)	19.1(6)	0.2(5)	11.6(5)	1.8(5)
C(17)	29.7(7)	20.3(6)	22.1(6)	-2.8(5)	14.4(5)	-4.0(5)
C(18)	20.7(6)	31.6(7)	20.6(6)	-1.2(5)	9.7(5)	-3.8(5)
C(19)	20.9(6)	28.8(7)	18.3(6)	2.6(5)	9.5(5)	5.1(5)
C(20)	28.0(7)	22.0(6)	22.7(6)	-0.3(5)	12.7(5)	-4.0(5)
N(1)	19.2(5)	18.2(5)	18.1(5)	2.6(4)	8.8(4)	1.4(4)
N(2)	22.0(5)	25.7(6)	21.5(5)	6.5(4)	8.0(4)	2.2(4)
N(3)	22.9(5)	25.0(6)	32.9(6)	8.4(5)	11.2(5)	3.5(4)

Table 15 Bond Lengths for **154a**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C(1)	C(2)	1.3714(18)	C(10)	N(1)	1.4352(15)
C(1)	C(3)	1.4936(17)	C(11)	C(12)	1.4199(18)
C(1)	N(1)	1.3587(16)	C(11)	C(20)	1.5038(17)
C(2)	N(3)	1.3605(19)	C(12)	C(13)	1.3639(19)
C(3)	C(4)	1.5364(17)	C(13)	C(14)	1.4153(18)
C(4)	C(5)	1.5347(17)	C(14)	C(15)	1.4227(17)
C(4)	C(9)	1.5323(17)	C(14)	C(19)	1.4189(18)
C(5)	C(6)	1.5234(19)	C(15)	C(16)	1.4160(17)
C(6)	C(7)	1.5297(18)	C(16)	C(17)	1.3688(18)

C(7)	C(8)	1.5290(18)	C(17)	C(18)	1.4115(19)
C(8)	C(9)	1.5288(18)	C(18)	C(19)	1.366(2)
C(10)	C(11)	1.3759(17)	N(1)	N(2)	1.3670(15)
C(10)	C(15)	1.4217(17)	N(2)	N(3)	1.3126(16)

Table 16 Bond Angles for **154a**.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C(2)	C(1)	C(3)	132.12(12)	C(12)	C(11)	C(20)	119.96(11)
N(1)	C(1)	C(2)	103.33(11)	C(13)	C(12)	C(11)	121.63(12)
N(1)	C(1)	C(3)	124.54(11)	C(12)	C(13)	C(14)	121.11(12)
N(3)	C(2)	C(1)	110.04(12)	C(13)	C(14)	C(15)	118.83(11)
C(1)	C(3)	C(4)	115.51(10)	C(13)	C(14)	C(19)	122.11(12)
C(5)	C(4)	C(3)	110.06(10)	C(19)	C(14)	C(15)	119.06(12)
C(9)	C(4)	C(3)	112.37(10)	C(10)	C(15)	C(14)	117.92(11)
C(9)	C(4)	C(5)	109.53(10)	C(16)	C(15)	C(10)	123.27(11)
C(6)	C(5)	C(4)	111.60(10)	C(16)	C(15)	C(14)	118.81(11)
C(5)	C(6)	C(7)	110.62(11)	C(17)	C(16)	C(15)	120.50(12)
C(8)	C(7)	C(6)	110.51(10)	C(16)	C(17)	C(18)	120.87(12)
C(9)	C(8)	C(7)	111.54(11)	C(19)	C(18)	C(17)	119.88(12)
C(8)	C(9)	C(4)	111.39(10)	C(18)	C(19)	C(14)	120.87(12)
C(11)	C(10)	C(15)	123.03(11)	C(1)	N(1)	C(10)	129.35(10)
C(11)	C(10)	N(1)	119.47(11)	C(1)	N(1)	N(2)	111.24(10)
C(15)	C(10)	N(1)	117.47(11)	N(2)	N(1)	C(10)	119.29(10)
C(10)	C(11)	C(12)	117.48(11)	N(3)	N(2)	N(1)	106.79(10)
C(10)	C(11)	C(20)	122.54(11)	N(2)	N(3)	C(2)	108.60(11)

Table 17 Hydrogen Atom Coordinates ($Å \times 10^4$) and Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **154a**.

Atom	x	y	z	U(eq)
H(2)	9450.56	2263.11	4096.5	30
H(3A)	6332.23	3289.79	1914.13	26
H(3B)	7616.49	2859.61	1881.16	26
H(4)	7139.79	4966.16	2045.1	22
H(5A)	7055.77	3897.81	14.03	27
H(5B)	5797.77	4324.94	107.56	27
H(6A)	6523.37	6001.96	115.2	31
H(6B)	6428.5	5440.55	-1040.66	31
H(7A)	8730.82	5174.9	-135.69	33
H(7B)	8465.1	6346.29	-85.44	33
H(8A)	10091.12	5760.23	1807.75	30
H(8B)	8859.58	6214.81	1925.56	30
H(9A)	9438.04	4673.74	2978.08	26
H(9B)	9348.63	4099.79	1832.19	26
H(12)	5710.65	6894.18	3922.06	26
H(13)	3627.47	6265.03	3344.56	26
H(16)	5609.68	2559.5	3689.05	24

H(17)	3497	1946.08	3065.74	28
H(18)	1715	3058.58	2629.19	29
H(19)	2074.53	4782.7	2854.75	27
H(20A)	8355.34	6249.49	5319.69	36
H(20B)	8014.63	6522.93	3982.06	36
H(20C)	8644.92	5461.2	4512.83	36
H(20D)	8651.62	5660.24	5253.87	36
H(20E)	8020.68	6702.74	4651.5	36
H(20F)	8342.59	5870.66	3909.2	36

Table 18 Atomic Occupancy for **154a**.

Atom	Occupancy	Atom	Occupancy	Atom	Occupancy
H(20A)	0.518(19)	H(20B)	0.518(19)	H(20C)	0.518(19)
H(20D)	0.482(19)	H(20E)	0.482(19)	H(20F)	0.482(19)

8.5.3 Crystallographic Data for 198b

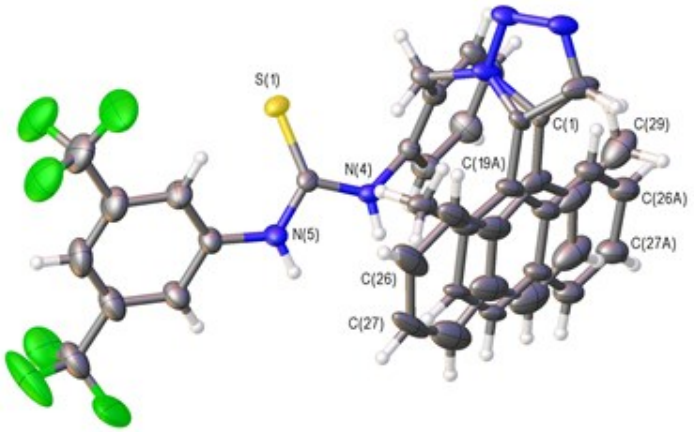


Table 19 Crystal data and structure refinement for **198b**.

Empirical formula	$C_{30}H_{22}Cl_3F_6N_5S$
Formula weight	704.93
Temperature/K	100.01(10)
Crystal system	orthorhombic
Space group	Pbca
a/Å	17.2172(4)
b/Å	13.8332(3)
c/Å	25.7251(7)
α/°	90
β/°	90
γ/°	90

Volume/Å^3	6126.9(3)
Z	8
ρ_{calc}g/cm^3	1.528
μ/mm^{-1}	3.950
F(000)	2864.0
Crystal size/mm^3	0.267 × 0.245 × 0.179
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.872 to 145.912
Index ranges	-12 ≤ h ≤ 20, -10 ≤ k ≤ 16, -31 ≤ l ≤ 27
Reflections collected	15729
Independent reflections	5950 [R_{int} = 0.0296, R_{sigma} = 0.0272]
Data/restraints/parameters	5950/269/525
Goodness-of-fit on F^2	1.056
Final R indexes [I>=2σ (I)]	R_1 = 0.0781, wR_2 = 0.2079
Final R indexes [all data]	R_1 = 0.0876, wR_2 = 0.2192
Largest diff. peak/hole / e Å^{-3}	1.09/-0.8

Table 20 Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **198b**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
C(1)	7979(5)	6141(7)	7882(3)	21.5(17)
C(1A)	7995(6)	6122(8)	7660(5)	24(2)
C(2)	8703(2)	6462(3)	7943(2)	56.6(13)
C(3)	7553.9(18)	4501(2)	7444.9(13)	28.9(7)
C(4)	6944.6(15)	4295(2)	7850.7(13)	26.8(6)
C(5)	6157.8(15)	4464(2)	7768.5(12)	25.2(6)
C(6)	5625(2)	4358(3)	8169.6(11)	33.5(7)
C(7)	5874(2)	4053(3)	8657.1(12)	43.0(9)
C(8)	6647(2)	3843(3)	8739.2(13)	41.1(9)
C(9)	7179.1(18)	3962(2)	8337.6(12)	34.3(8)
C(10)	5843.4(16)	4264(2)	6840.1(12)	24.0(6)
C(11)	5176.5(19)	4285(3)	5986.0(13)	31.6(7)
C(12)	5707(2)	3804(3)	5668.1(14)	38.1(8)
C(13)	5464(3)	3456(3)	5188.4(16)	49.4(10)
C(14)	4719(3)	3578(4)	5013.1(17)	54.0(11)
C(15)	4197(2)	4073(3)	5326.6(16)	46.7(10)
C(16)	4419(2)	4424(3)	5808.9(14)	37.8(8)
C(17)	6024(3)	2895(4)	4857.4(19)	62.0(13)
C(18)	3373(3)	4171(4)	5149.5(18)	58.1(12)
C(19)	7193(4)	6574(5)	7911(4)	43.3(14)
C(20)	6849(5)	6689(6)	8390(5)	56.3(16)
C(21)	6124(5)	7039(6)	8467(5)	66.2(17)
C(22)	5731(6)	7294(6)	8026(5)	68.1(18)
C(23)	6044(3)	7213(5)	7513(5)	62.1(16)
C(24)	6792(3)	6844(5)	7468(5)	51.5(14)
C(25)	7137(5)	6743(6)	6960(3)	53.7(17)
C(26)	6744(5)	6994(6)	6507(3)	68.5(18)

C(27)	5902(4)	7388(5)	6624(3)	68.8(19)
C(28)	5602(5)	7486(6)	7124(3)	75.9(19)
C(29)	7239(5)	6407(7)	8880(4)	63.1(18)
C(19A)	7214(5)	6575(6)	7622(4)	34.4(12)
C(20A)	6904(5)	6786(7)	7140(4)	33.7(12)
C(21A)	6130(4)	7205(5)	7135(4)	32.1(12)
C(22A)	5717(4)	7373(6)	7594(4)	33.8(12)
C(23A)	6037(4)	7137(6)	8082(4)	36.6(12)
C(24A)	6782(4)	6749(6)	8088(4)	35.9(11)
C(25A)	7085(5)	6525(7)	8558(3)	38.6(13)
C(26A)	6681(5)	6640(6)	9022(3)	42.8(13)
C(27A)	5924(5)	7007(6)	8993(3)	44.3(13)
C(28A)	5609(5)	7257(6)	8513(3)	41.6(13)
C(29A)	7292(5)	6557(6)	6642(4)	36.6(14)
F(1)	6754(2)	2976(3)	5006.8(14)	95.3(13)
F(2)	5991(2)	3168(2)	4358.8(11)	76.1(9)
F(3)	5862(2)	1943(2)	4857.8(12)	83.9(11)
F(4)	3018(2)	4927(3)	5353(2)	115.2(17)
F(5)	3317.5(19)	4243(4)	4635.8(12)	109.0(16)
F(6)	2941.3(16)	3431(3)	5272.6(14)	79.7(10)
N(1)	8118.8(15)	5212.7(19)	7639.3(12)	30.9(6)
N(2)	8866.3(15)	4973(2)	7700.5(12)	30.3(6)
N(3)	9226.4(16)	5739(2)	7883.0(13)	34.9(7)
N(4)	5860.4(14)	4796.6(19)	7282.8(10)	23.0(5)
N(5)	5374.0(15)	4673(2)	6471.7(11)	28.3(6)
S(1)	6335.5(5)	3234.2(6)	6773.4(3)	31.9(2)
C(101)	8538(3)	5054(4)	5657.1(19)	62.5(13)
Cl(11)	7908.9(9)	4322.8(11)	6035.4(6)	74.5(4)
Cl(12)	9127.2(10)	5774.4(14)	6049.7(7)	92.0(6)
Cl(13)	9105.4(11)	4370.6(19)	5251.0(8)	110.4(7)

Table 21 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **198b**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	23(3)	19(3)	22(4)	-3(4)	-4(4)	1(2)
C(1A)	19(4)	19(4)	34(6)	3(5)	-11(5)	-3(3)
C(2)	22.0(17)	21.9(17)	126(4)	-5(2)	-10(2)	-2.0(14)
C(3)	18.4(14)	26.4(14)	41.8(17)	5.3(13)	-4.4(13)	-5.4(12)
C(4)	24.2(15)	20.6(14)	35.5(16)	2.6(12)	-3.4(13)	-4.1(11)
C(5)	23.5(14)	22.2(14)	30.0(16)	0.6(12)	-3.5(12)	-2.7(12)
C(6)	27.6(16)	36.4(18)	36.4(18)	4.3(14)	2.4(14)	-0.6(14)
C(7)	41(2)	49(2)	39(2)	9.7(17)	3.6(16)	-5.6(17)
C(8)	46(2)	40.8(19)	36.2(19)	13.2(16)	-8.7(16)	-9.4(17)
C(9)	30.3(16)	27.6(16)	45.0(19)	5.4(14)	-10.9(15)	-4.5(13)
C(10)	15.1(13)	24.5(14)	32.3(15)	-3.7(12)	0.1(11)	-3.5(11)
C(11)	24.2(16)	37.4(17)	33.1(17)	-6.5(14)	-1.3(13)	-1.7(13)
C(12)	29.6(17)	47(2)	38.2(19)	-10.1(16)	3.2(15)	2.0(15)
C(13)	51(2)	58(3)	39(2)	-14.8(18)	4.5(18)	-1(2)
C(14)	57(3)	66(3)	39(2)	-16(2)	-5.7(19)	-12(2)

C(15)	36(2)	64(3)	40(2)	-3.8(18)	-8.4(17)	-10.3(18)
C(16)	26.6(17)	50(2)	36.6(19)	-3.7(16)	-2.7(14)	-0.3(15)
C(17)	76(3)	66(3)	44(2)	-22(2)	10(2)	4(3)
C(18)	42(2)	83(3)	49(2)	-4(2)	-17(2)	-8(2)
C(19)	23(2)	17(2)	90(3)	-7(3)	-1(3)	-4(2)
C(20)	35(3)	33(3)	101(4)	-18(3)	16(3)	-7(2)
C(21)	43(3)	40(3)	116(4)	-19(3)	20(3)	-6(3)
C(22)	42(3)	31(3)	131(4)	-9(3)	2(3)	-8(3)
C(23)	38(3)	24(3)	124(4)	5(3)	-20(3)	-6(2)
C(24)	32(2)	18(2)	105(4)	4(3)	-18(3)	-6(2)
C(25)	44(3)	23(3)	95(4)	11(3)	-36(3)	-7(3)
C(26)	62(3)	35(3)	109(4)	21(3)	-53(3)	-17(3)
C(27)	54(3)	27(3)	125(4)	23(3)	-63(3)	-11(2)
C(28)	52(3)	34(3)	142(4)	14(3)	-41(3)	-9(3)
C(29)	52(4)	50(4)	87(4)	-22(4)	24(3)	-10(3)
C(19A)	21(2)	20.9(19)	62(3)	3.4(19)	-15.3(19)	1.0(16)
C(20A)	19.8(19)	19.5(18)	62(3)	3.4(19)	-14.7(19)	1.3(16)
C(21A)	18(2)	17.2(19)	61(3)	2.9(19)	-17.8(19)	2.5(16)
C(22A)	19.9(19)	19.5(19)	62(3)	1.4(18)	-16.6(19)	2.7(16)
C(23A)	22.7(18)	24.7(18)	62(2)	1.9(17)	-14.6(18)	2.9(15)
C(24A)	22.7(18)	23.8(18)	61(2)	2.9(17)	-14.4(18)	1.4(15)
C(25A)	26(2)	28(2)	62(3)	3(2)	-12.7(19)	2.8(18)
C(26A)	31(2)	34(2)	64(3)	1(2)	-9(2)	3.1(18)
C(27A)	31(2)	36(2)	66(3)	0(2)	-6(2)	3.3(18)
C(28A)	27(2)	32(2)	66(3)	-0.3(19)	-8.5(19)	3.6(17)
C(29A)	25(2)	22(2)	64(3)	4(2)	-10(2)	-1(2)
F(1)	67(2)	141(3)	78(2)	-55(2)	9.6(17)	34(2)
F(2)	106(3)	78(2)	44.3(15)	-12.1(13)	23.4(15)	7.4(18)
F(3)	136(3)	64.8(19)	50.7(16)	-13.1(14)	22.0(18)	16.6(19)
F(4)	68(2)	97(3)	181(4)	-42(3)	-84(3)	26.8(19)
F(5)	56.8(19)	218(5)	52.3(17)	23(2)	-27.2(15)	-24(2)
F(6)	39.2(15)	107(3)	93(2)	0(2)	-2.9(14)	-21.3(16)
N(1)	14.9(12)	23.0(13)	54.9(18)	8.1(12)	-6.6(12)	-1.5(10)
N(2)	14.3(11)	28.7(14)	47.8(16)	4.0(12)	-4.0(11)	1.3(10)
N(3)	18.3(13)	24.3(13)	62.1(19)	5.2(13)	-7.5(13)	0.4(10)
N(4)	17.3(11)	21.3(12)	30.5(13)	0.1(10)	-1.5(10)	2.5(10)
N(5)	20.0(12)	33.3(14)	31.6(14)	-6.2(11)	-0.7(11)	5.8(11)
S(1)	23.0(4)	26.3(4)	46.5(5)	-8.8(3)	-2.8(3)	5.6(3)
C(101)	45(2)	87(4)	56(3)	17(3)	-7(2)	-5(2)
Cl(11)	76.6(9)	73.9(9)	73.0(8)	15.5(6)	3.2(7)	-20.2(7)
Cl(12)	85.6(11)	108.1(13)	82.4(10)	21.0(9)	-26.6(8)	-35.4(9)
Cl(13)	72.8(10)	160(2)	98.4(13)	-23.9(13)	19.0(9)	-2.2(11)

Table 22 Bond Lengths for **198b.**

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C(1)	C(2)	1.333(10)	C(18)	F(5)	1.329(6)
C(1)	C(19)	1.482(12)	C(18)	F(6)	1.304(6)
C(1)	N(1)	1.448(9)	C(19)	C(20)	1.376(10)
C(1A)	C(2)	1.496(11)	C(19)	C(24)	1.383(13)

C(1A)	C(19A)	1.488(14)	C(20)	C(21)	1.354(12)
C(1A)	N(1)	1.277(12)	C(20)	C(29)	1.479(12)
C(2)	N(3)	1.355(5)	C(21)	C(22)	1.366(12)
C(3)	C(4)	1.507(4)	C(22)	C(23)	1.430(17)
C(3)	N(1)	1.471(4)	C(23)	C(24)	1.391(2)
C(4)	C(5)	1.391(2)	C(23)	C(28)	1.313(14)
C(4)	C(9)	1.395(5)	C(24)	C(25)	1.442(13)
C(5)	C(6)	1.388(5)	C(25)	C(26)	1.391(2)
C(5)	N(4)	1.427(4)	C(26)	C(27)	1.579(13)
C(6)	C(7)	1.391(2)	C(27)	C(28)	1.391(2)
C(7)	C(8)	1.379(5)	C(19A)	C(20A)	1.381(10)
C(8)	C(9)	1.391(2)	C(19A)	C(24A)	1.431(14)
C(10)	N(4)	1.357(4)	C(20A)	C(21A)	1.453(10)
C(10)	N(5)	1.368(4)	C(20A)	C(29A)	1.480(12)
C(10)	S(1)	1.666(3)	C(21A)	C(22A)	1.397(11)
C(11)	C(12)	1.395(5)	C(22A)	C(23A)	1.410(13)
C(11)	C(16)	1.395(5)	C(23A)	C(24A)	1.391(3)
C(11)	N(5)	1.402(4)	C(23A)	C(28A)	1.341(14)
C(12)	C(13)	1.389(5)	C(24A)	C(25A)	1.353(13)
C(13)	C(14)	1.371(7)	C(25A)	C(26A)	1.390(3)
C(13)	C(17)	1.503(6)	C(26A)	C(27A)	1.401(11)
C(14)	C(15)	1.389(7)	C(27A)	C(28A)	1.391(3)
C(15)	C(16)	1.386(5)	N(1)	N(2)	1.338(4)
C(15)	C(18)	1.496(6)	N(2)	N(3)	1.315(4)
C(17)	F(1)	1.319(6)	C(101)	Cl(11)	1.773(5)
C(17)	F(2)	1.338(6)	C(101)	Cl(12)	1.744(6)
C(17)	F(3)	1.346(6)	C(101)	Cl(13)	1.714(6)
C(18)	F(4)	1.320(7)			

Table 23 Bond Angles for **198b.**

Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
C(2)	C(1)	C(19)	135.6(7)	C(20)	C(19)	C(24)	119.5(8)
C(2)	C(1)	N(1)	101.0(6)	C(24)	C(19)	C(1)	121.5(8)
N(1)	C(1)	C(19)	122.1(7)	C(19)	C(20)	C(29)	122.5(8)
C(19A)	C(1A)	C(2)	129.5(9)	C(21)	C(20)	C(19)	124.7(11)
N(1)	C(1A)	C(2)	101.2(7)	C(21)	C(20)	C(29)	112.8(9)
N(1)	C(1A)	C(19A)	124.3(9)	C(20)	C(21)	C(22)	115.3(10)
C(1)	C(2)	N(3)	111.3(5)	C(21)	C(22)	C(23)	124.0(9)
N(3)	C(2)	C(1A)	104.7(6)	C(24)	C(23)	C(22)	117.0(10)
N(1)	C(3)	C(4)	110.6(3)	C(28)	C(23)	C(22)	117.6(7)
C(5)	C(4)	C(3)	122.8(3)	C(28)	C(23)	C(24)	125.4(11)
C(5)	C(4)	C(9)	118.3(3)	C(19)	C(24)	C(23)	119.5(9)
C(9)	C(4)	C(3)	118.9(2)	C(19)	C(24)	C(25)	121.1(6)
C(4)	C(5)	N(4)	122.5(3)	C(23)	C(24)	C(25)	119.4(10)
C(6)	C(5)	C(4)	120.9(3)	C(26)	C(25)	C(24)	122.4(9)
C(6)	C(5)	N(4)	116.6(2)	C(25)	C(26)	C(27)	111.9(8)
C(5)	C(6)	C(7)	119.9(3)	C(28)	C(27)	C(26)	123.4(7)
C(8)	C(7)	C(6)	119.9(3)	C(23)	C(28)	C(27)	117.6(8)
C(7)	C(8)	C(9)	119.8(3)	C(20A)	C(19A)	C(1A)	119.9(9)

C(8)	C(9)	C(4)	121.0(3)	C(20A)	C(19A)	C(24A)	121.0(8)
N(4)	C(10)	N(5)	111.7(3)	C(24A)	C(19A)	C(1A)	119.0(8)
N(4)	C(10)	S(1)	122.7(2)	C(19A)	C(20A)	C(21A)	116.5(9)
N(5)	C(10)	S(1)	125.6(2)	C(19A)	C(20A)	C(29A)	123.9(8)
C(12)	C(11)	C(16)	119.2(3)	C(21A)	C(20A)	C(29A)	119.5(7)
C(12)	C(11)	N(5)	123.1(3)	C(22A)	C(21A)	C(20A)	121.7(8)
C(16)	C(11)	N(5)	117.7(3)	C(21A)	C(22A)	C(23A)	121.1(7)
C(13)	C(12)	C(11)	119.3(4)	C(24A)	C(23A)	C(22A)	117.3(9)
C(12)	C(13)	C(17)	119.3(4)	C(28A)	C(23A)	C(22A)	119.6(6)
C(14)	C(13)	C(12)	122.1(4)	C(28A)	C(23A)	C(24A)	123.0(9)
C(14)	C(13)	C(17)	118.5(4)	C(23A)	C(24A)	C(19A)	122.4(9)
C(13)	C(14)	C(15)	118.4(4)	C(25A)	C(24A)	C(19A)	120.7(6)
C(14)	C(15)	C(18)	118.8(4)	C(25A)	C(24A)	C(23A)	117.0(10)
C(16)	C(15)	C(14)	120.9(4)	C(24A)	C(25A)	C(26A)	123.2(9)
C(16)	C(15)	C(18)	120.1(4)	C(25A)	C(26A)	C(27A)	117.4(8)
C(15)	C(16)	C(11)	120.1(4)	C(28A)	C(27A)	C(26A)	120.0(8)
F(1)	C(17)	C(13)	113.7(4)	C(23A)	C(28A)	C(27A)	119.3(8)
F(1)	C(17)	F(2)	107.2(5)	C(1)	N(1)	C(3)	129.0(4)
F(1)	C(17)	F(3)	106.3(5)	C(1A)	N(1)	C(3)	124.3(5)
F(2)	C(17)	C(13)	111.7(5)	C(1A)	N(1)	N(2)	113.5(5)
F(2)	C(17)	F(3)	105.5(4)	N(2)	N(1)	C(1)	109.2(4)
F(3)	C(17)	C(13)	111.8(4)	N(2)	N(1)	C(3)	120.7(3)
F(4)	C(18)	C(15)	113.0(4)	N(3)	N(2)	N(1)	107.2(3)
F(4)	C(18)	F(5)	107.7(5)	N(2)	N(3)	C(2)	108.8(3)
F(5)	C(18)	C(15)	112.2(4)	C(10)	N(4)	C(5)	124.6(3)
F(6)	C(18)	C(15)	113.2(4)	C(10)	N(5)	C(11)	127.1(3)
F(6)	C(18)	F(4)	105.2(4)	Cl(12)	C(101)	Cl(11)	111.3(3)
F(6)	C(18)	F(5)	105.0(4)	Cl(13)	C(101)	Cl(11)	111.6(3)
C(20)	C(19)	C(1)	119.0(8)	Cl(13)	C(101)	Cl(12)	109.7(3)

Table 24 Torsion Angles for **198b.**

A	**B**	**C**	**D**	**Angle/°**	**A**	**B**	**C**	**D**	**Angle/°**
C(1)	C(2)	N(3)	N(2)	9.9(7)	C(19)	C(1)	N(1)	C(3)	-7.8(10)
C(1)	C(19)	C(20)	C(21)	-177.4(8)	C(19)	C(1)	N(1)	N(2)	-175.7(7)
C(1)	C(19)	C(20)	C(29)	0.7(11)	C(19)	C(20)	C(21)	C(22)	-0.6(12)
C(1)	C(19)	C(24)	C(23)	177.6(7)	C(19)	C(24)	C(25)	C(26)	178.9(7)
C(1)	C(19)	C(24)	C(25)	-2.0(10)	C(20)	C(19)	C(24)	C(23)	-1.1(10)
C(1)	N(1)	N(2)	N(3)	-10.2(5)	C(20)	C(19)	C(24)	C(25)	179.4(7)
C(1A)	C(2)	N(3)	N(2)	-12.6(7)	C(20)	C(21)	C(22)	C(23)	-0.4(12)
C(1A)	C(19A)	C(20A)	C(21A)	178.5(8)	C(21)	C(22)	C(23)	C(24)	0.5(12)
C(1A)	C(19A)	C(20A)	C(29A)	2.2(14)	C(21)	C(22)	C(23)	C(28)	-179.9(8)
C(1A)	C(19A)	C(24A)	C(23A)	-177.6(9)	C(22)	C(23)	C(24)	C(19)	0.2(10)
C(1A)	C(19A)	C(24A)	C(25A)	1.4(12)	C(22)	C(23)	C(24)	C(25)	179.8(7)
C(1A)	N(1)	N(2)	N(3)	14.3(7)	C(22)	C(23)	C(28)	C(27)	-178.7(7)
C(2)	C(1)	C(19)	C(20)	-81.6(12)	C(23)	C(24)	C(25)	C(26)	-0.6(11)
C(2)	C(1)	C(19)	C(24)	99.8(11)	C(24)	C(19)	C(20)	C(21)	1.3(12)
C(2)	C(1)	N(1)	C(3)	-176.8(4)	C(24)	C(19)	C(20)	C(29)	179.4(7)
C(2)	C(1)	N(1)	N(2)	15.3(7)	C(24)	C(23)	C(28)	C(27)	0.8(12)
C(2)	C(1A)	C(19A)	C(20A)	123.5(11)	C(24)	C(25)	C(26)	C(27)	0.0(10)
C(2)	C(1A)	C(19A)	C(24A)	-59.0(14)	C(25)	C(26)	C(27)	C(28)	1.1(10)

C(2)	C(1A)	N(1)	C(3)	173.3(4)	C(26)	C(27)	C(28)	C(23)	-1.5(12)
C(2)	C(1A)	N(1)	N(2)	-20.9(9)	C(28)	C(23)	C(24)	C(19)	-179.3(7)
C(3)	C(4)	C(5)	C(6)	-173.3(3)	C(28)	C(23)	C(24)	C(25)	0.3(11)
C(3)	C(4)	C(5)	N(4)	3.5(5)	C(29)	C(20)	C(21)	C(22)	-178.8(7)
C(3)	C(4)	C(9)	C(8)	174.2(3)	C(19A)	C(1A)	C(2)	N(3)	175.1(10)
C(3)	N(1)	N(2)	N(3)	-179.3(3)	C(19A)	C(1A)	N(1)	C(3)	16.3(14)
C(4)	C(3)	N(1)	C(1)	-50.0(6)	C(19A)	C(1A)	N(1)	N(2)	-177.8(8)
C(4)	C(3)	N(1)	C(1A)	-78.4(8)	C(19A)	C(20A)	C(21A)	C(22A)	-0.9(12)
C(4)	C(3)	N(1)	N(2)	116.7(3)	C(19A)	C(24A)	C(25A)	C(26A)	-177.2(8)
C(4)	C(5)	C(6)	C(7)	-1.9(5)	C(20A)	C(19A)	C(24A)	C(23A)	-0.1(13)
C(4)	C(5)	N(4)	C(10)	69.2(4)	C(20A)	C(19A)	C(24A)	C(25A)	178.8(9)
C(5)	C(4)	C(9)	C(8)	-3.0(5)	C(20A)	C(21A)	C(22A)	C(23A)	-0.2(12)
C(5)	C(6)	C(7)	C(8)	-0.9(6)	C(21A)	C(22A)	C(23A)	C(24A)	1.1(12)
C(6)	C(5)	N(4)	C(10)	-113.9(3)	C(21A)	C(22A)	C(23A)	C(28A)	-176.2(8)
C(6)	C(7)	C(8)	C(9)	1.7(6)	C(22A)	C(23A)	C(24A)	C(19A)	-1.0(13)
C(7)	C(8)	C(9)	C(4)	0.3(6)	C(22A)	C(23A)	C(24A)	C(25A)	-180.0(8)
C(9)	C(4)	C(5)	C(6)	3.8(5)	C(22A)	C(23A)	C(28A)	C(27A)	178.9(8)
C(9)	C(4)	C(5)	N(4)	-179.4(3)	C(23A)	C(24A)	C(25A)	C(26A)	1.8(14)
C(11)	C(12)	C(13)	C(14)	0.6(7)	C(24A)	C(19A)	C(20A)	C(21A)	1.0(13)
C(11)	C(12)	C(13)	C(17)	-176.9(4)	C(24A)	C(19A)	C(20A)	C(29A)	-175.2(8)
C(12)	C(11)	C(16)	C(15)	1.1(6)	C(24A)	C(23A)	C(28A)	C(27A)	1.7(14)
C(12)	C(11)	N(5)	C(10)	-40.7(5)	C(24A)	C(25A)	C(26A)	C(27A)	0.0(14)
C(12)	C(13)	C(14)	C(15)	0.6(7)	C(25A)	C(26A)	C(27A)	C(28A)	-1.1(13)
C(12)	C(13)	C(17)	F(1)	-14.8(7)	C(26A)	C(27A)	C(28A)	C(23A)	0.3(13)
C(12)	C(13)	C(17)	F(2)	-136.3(5)	C(28A)	C(23A)	C(24A)	C(19A)	176.3(8)
C(12)	C(13)	C(17)	F(3)	105.7(5)	C(28A)	C(23A)	C(24A)	C(25A)	-2.7(13)
C(13)	C(14)	C(15)	C(16)	-1.0(7)	C(29A)	C(20A)	C(21A)	C(22A)	175.6(8)
C(13)	C(14)	C(15)	C(18)	-177.3(5)	N(1)	C(1)	C(2)	N(3)	-14.9(7)
C(14)	C(13)	C(17)	F(1)	167.6(5)	N(1)	C(1)	C(19)	C(20)	114.0(8)
C(14)	C(13)	C(17)	F(2)	46.0(7)	N(1)	C(1)	C(19)	C(24)	-64.6(10)
C(14)	C(13)	C(17)	F(3)	-72.0(6)	N(1)	C(1A)	C(2)	N(3)	20.0(9)
C(14)	C(15)	C(16)	C(11)	0.1(7)	N(1)	C(1A)	C(19A)	C(20A)	-86.4(13)
C(14)	C(15)	C(18)	F(4)	-155.4(5)	N(1)	C(1A)	C(19A)	C(24A)	91.1(12)
C(14)	C(15)	C(18)	F(5)	-33.5(7)	N(1)	C(3)	C(4)	C(5)	120.0(3)
C(14)	C(15)	C(18)	F(6)	85.2(6)	N(1)	C(3)	C(4)	C(9)	-57.1(4)
C(16)	C(11)	C(12)	C(13)	-1.5(6)	N(1)	N(2)	N(3)	C(2)	0.7(5)
C(16)	C(11)	N(5)	C(10)	141.9(3)	N(4)	C(5)	C(6)	C(7)	-178.9(3)
C(16)	C(15)	C(18)	F(4)	28.2(7)	N(4)	C(10)	N(5)	C(11)	-174.9(3)
C(16)	C(15)	C(18)	F(5)	150.1(5)	N(5)	C(10)	N(4)	C(5)	166.0(3)
C(16)	C(15)	C(18)	F(6)	-91.2(6)	N(5)	C(11)	C(12)	C(13)	-178.9(4)
C(17)	C(13)	C(14)	C(15)	178.2(5)	N(5)	C(11)	C(16)	C(15)	178.7(4)
C(18)	C(15)	C(16)	C(11)	176.4(4)	S(1)	C(10)	N(4)	C(5)	-13.3(4)
C(19)	C(1)	C(2)	N(3)	178.5(9)	S(1)	C(10)	N(5)	C(11)	4.4(5)

Table 25 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **198b.**

Atom	***x***	***y***	***z***	**U(eq)**
H(2B)	8769.04	7041.16	8121.53	68
H(2A)	8832.35	7099.75	8018.13	68
H(3A)	7820.99	3906.94	7355.28	35
H(3B)	7307.04	4749.01	7133.24	35
H(6)	5102.77	4491.53	8112.34	40

H(7)	5518.68	3991	8927.49	52
H(8)	6812.07	3622.58	9062.32	49
H(9)	7699.5	3816.26	8394.61	41
H(12)	6217.83	3717.08	5776.24	46
H(14)	4566.42	3334.29	4691.99	65
H(16)	4062.09	4753.62	6014.82	45
H(21)	5908.06	7101.91	8796.69	79
H(22)	5229.41	7534.24	8062.18	82
H(25)	7639.21	6501.67	6934.36	64
H(26)	6953.01	6936.41	6175.4	82
H(27)	5589.45	7564.81	6344.93	83
H(28)	5107.6	7734.38	7179.73	91
H(29A)	7676.69	6002.52	8802.56	95
H(29B)	6879.94	6059.76	9095.91	95
H(29C)	7412.2	6976.63	9058.78	95
H(21A)	5903.25	7365.3	6818.4	39
H(22A)	5223.83	7644.3	7576.97	41
H(25A)	7588.1	6281.71	8571.56	46
H(26A)	6904.77	6479.43	9339.47	51
H(27A)	5631.48	7084.09	9293.87	53
H(28A)	5108.05	7503.56	8491.55	50
H(29D)	7842.77	6512.44	6696.18	55
H(29E)	7185.15	7058.37	6393.74	55
H(29F)	7101.27	5951.41	6511.61	55
H(4)	5520(20)	5250(30)	7313(14)	24(9)
H(5)	5070(20)	5140(30)	6576(16)	34(10)
H(101)	8217.51	5481.47	5442.1	75

Table 26 Atomic Occupancy for **198b.**

Atom	***Occupancy***	**Atom**	***Occupancy***	**Atom**	***Occupancy***
C(1)	0.554(6)	C(1A)	0.446(6)	H(2B)	0.446(6)
H(2A)	0.554(6)	C(19)	0.554(6)	C(20)	0.554(6)
C(21)	0.554(6)	H(21)	0.554(6)	C(22)	0.554(6)
H(22)	0.554(6)	C(23)	0.554(6)	C(24)	0.554(6)
C(25)	0.554(6)	H(25)	0.554(6)	C(26)	0.554(6)
H(26)	0.554(6)	C(27)	0.554(6)	H(27)	0.554(6)
C(28)	0.554(6)	H(28)	0.554(6)	C(29)	0.554(6)
H(29A)	0.554(6)	H(29B)	0.554(6)	H(29C)	0.554(6)
C(19A)	0.446(6)	C(20A)	0.446(6)	C(21A)	0.446(6)
H(21A)	0.446(6)	C(22A)	0.446(6)	H(22A)	0.446(6)
C(23A)	0.446(6)	C(24A)	0.446(6)	C(25A)	0.446(6)
H(25A)	0.446(6)	C(26A)	0.446(6)	H(26A)	0.446(6)
C(27A)	0.446(6)	H(27A)	0.446(6)	C(28A)	0.446(6)
H(28A)	0.446(6)	C(29A)	0.446(6)	H(29D)	0.446(6)
H(29E)	0.446(6)	H(29F)	0.446(6		