Charles University

Faculty of Science

Study programme: Chemistry

Branch of study: Chemistry

Daniel Čermák

Preparation of enantiomerically enriched triazolium salts suitable for catalysis

Příprava enantiomerně čistých triazoliových solí využitelných v katalýze

Bachelor's thesis

Supervisor: prof. RNDr. Jan Veselý, Ph.D.

Consultant: RNDr. Vojtěch Dočekal, Ph.D.

Prague, 2024

Prohlášení

Prohlašuji, že jsem tuto bakalářskou práci zpracoval samostatně, a že jsem uvedl všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze, 22. 5. 2024

Daniel Čermák

Acknowledgements

To begin with, I would like to thank my supervisor, prof. RNDr. Jan Veselý, Ph.D., for giving me the opportunity to join his Group of Asymmetric Synthesis and for his cooperation during the project's undertaking, as well as his ever-present joyful personality. Big thanks also go to my consultant, RNDr. Vojtěch Dočekal, Ph.D., who took me under his wing and guided me through every hurdle that came up during my chemical endeavours, whether during synthesis, or during writing. Next, I would like to thank all members of the group for the endless laughs and for generally creating a fantastic workplace atmosphere, which made me look forward to coming back to the lab each day. Special thanks go to RNDr. Michael Franc, Ph.D., Mgr. Ladislav Lóška, and Mgr. Martin Nigríni for their invaluable tips and their willingness to give advice whenever I was uncertain, especially in the early stages. I also cannot forget to mention my fume hood roommate, Bc. Adam Kurčina, who made me partake in many unforgettable discussions about chemical obscurities and existential topics.

To continue, I would like to give thanks to RNDr. Zdeněk Tošner, Ph.D. and Mgr. Filip Koucký for teaching me how to use the NMR machines, Mgr. Bohunka Šperlichová for the specific rotation measurements, and RNDr. Martin Štícha, Ph.D. for the mass spectrometry measurements.

Lastly, this list wouldn't be complete without me expressing gratitude to my family for their endless support, and my friends and those closest to me for always standing by my side and making my study years so far a wonderful experience.

Abstract

The subject of this work is the preparation of multiple chiral triazole-derived conjugate acids of *N*-heterocyclic carbenes (NHC), a class of covalent organocatalysts used in many stereoselective transformations. The NHC conjugate acids in question were prepared in the form of triazolium salts by multi-step syntheses starting from readily available natural compounds.

The prepared chiral triazolium salts were used as pre-catalysts in a chosen enantioselective spiroannulation reaction between a benzofuranone derivative and an α-bromoenal compound. Additionally, an alternative oxidative approach to the key azolium-dienolate intermediate was explored.

Keywords

Asymmetric synthesis, organocatalysis, *N*-heterocyclic carbene, triazole, azolium-dienolate, spiroannulation

Abstrakt

Tématem této práce byla příprava vybraných chirálních konjugovaných kyselin *N*-heterocyklických karbenů (NHC), které jako kovalentní organokatalyzátory nachází využití ve stereoselektivních reakcích. V této práci byly připraveny prekurzory těchto katalyzátorů, triazoliové soli, pomocí vícekrokové syntézy vycházející z dostupných chirálních přírodních sloučenin.

Tyto připravené chirální triazoliové soli byly použity jako katalyzátory ve vybrané enantioselektivní spiroanulační reakci mezi derivátem benzofuranonu a α-bromoenalem. Nad rámec cílů této práce byl zkoumán alternativní způsob generace klíčového azolium dienolátu s využitím přídavku oxidantu.

Klíčová slova

Asymetrická syntéza, organokatalýza, *N*-heterocyklický karben, triazol, azolium dienolát, spiroanulace

Table of contents

1. Introduction 8

1.1 Asymmetric methods in organic synthesis 8

1.2 *N*-Heterocyclic carbenes in organocatalysis 8

2. State of the art 11

2.1 Triazolium salts as NHC catalysts 11

2.2 Synthetic ways towards chiral triazolium salts 11

2.3 Selected organocatalytic transformations mediated by chiral NHC catalysts 16

3. Goals of the project 19

4. Results and discussion 20

4.1 Preparation of chiral NHC conjugate acids derived from both valine enantiomers 20

4.2 Preparation of chiral NHC pre-catalysts derived from D-camphor 21

4.3 Spiroannulation reaction 24

5. Experimental part 30

5.1 General remarks about the used procedures 30

5.2 General procedures 31

5.3 Synthesised compounds and related spectroscopic data 35

6. Conclusion 46

7. References 47

List of used acronyms and abbreviations

Ac	acetyl
Ada	adamantyl
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
CAM	ceric ammonium molybdate
DCE	1,2-dichloroethane
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DNPH	2,4-dinitrophenylhydrazine
dr	diastereomeric ratio
ee	enantiomeric excess
eq.	equivalent
ESI	electrospray ionisation
Et	ethyl
EWG	electron-withdrawing group
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Me	methyl
Mes	mesityl
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
n.d.	not defined
Ph	phenyl
Pr	propyl
THF	tetrahydrofuran
TLC	thin-layer chromatography

1. Introduction

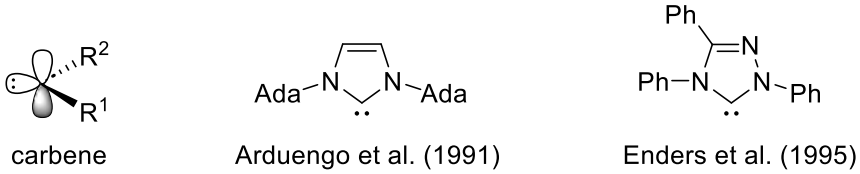
1.1 Asymmetric methods in organic synthesis

Stereochemistry is a crucial concept in medicinal chemistry, as it dictates the interaction of the compound with biological systems.[1] In chiral compounds especially, only one enantiomer may exhibit the desired activity. As the market preference for racemic drugs has steadily faded, enantiopure compounds are dominant as newly-designed drug candidates.[2] Therefore, the ever-more expanding pharmaceutical industry relies on the existence of a large library of synthetic procedures that provide access to optically pure compounds. In many cases, these procedures include the use of chiral catalysts, with chiral organocatalysts specifically being an attractive area of research.[3] In comparison to metal-based chiral catalysts, small organic molecules generally carry lower toxicity and environmental strain, while also being applicable to a larger substrate scope than enzymes.[4] In addition, starting materials for the preparations of organocatalysts are often derived from small chiral organic molecules, such as amino acids, alkaloids, and their derivatives, leading to lower costs.[3]

1.2 *N*-Heterocyclic carbenes in organocatalysis

1.2.1 Definition and chemical properties of *N*-heterocyclic carbenes

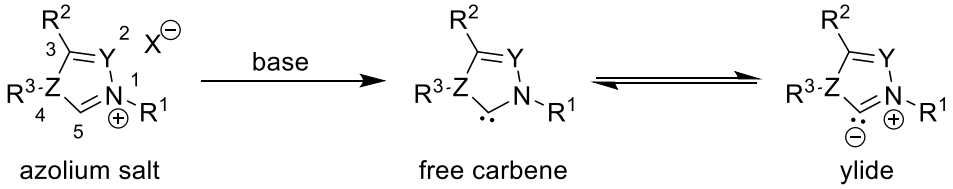
Carbenes are a chemical peculiarity, being carbon atoms with only six electrons present in their valence shell. These electrons are distributed into two σ-bonds and in most cases an sp^2-hybridised lone pair, complemented by an unoccupied *p*-orbital. An *N*-heterocyclic carbene (NHC) is defined as a species (Figure 1), where the carbene carbon is a part of a heterocyclic ring containing at least one nitrogen atom.[5] The field has experienced rapid evolution over the past thirty years, first set in motion by the preparation of the first bench-stable carbene prepared in 1991 by Arduengo et al.,[6] and the synthesis of the first commercially available NHC conjugate acid in 1995.[7]



carbene Arduengo et al. (1991) Enders et al. (1995)

Figure 1. Electronic structure of a carbene and the first stable synthesised carbenes.

The ability to store NHCs long-term in the form of their conjugate acids, azolium salts, has given the green light to explore and uncover the vast library of such compounds that can be prepared. In the reaction mixture, the free carbene can be regenerated from its conjugate acid through deprotonation by a mild base, such as triethylamine (Scheme 1).



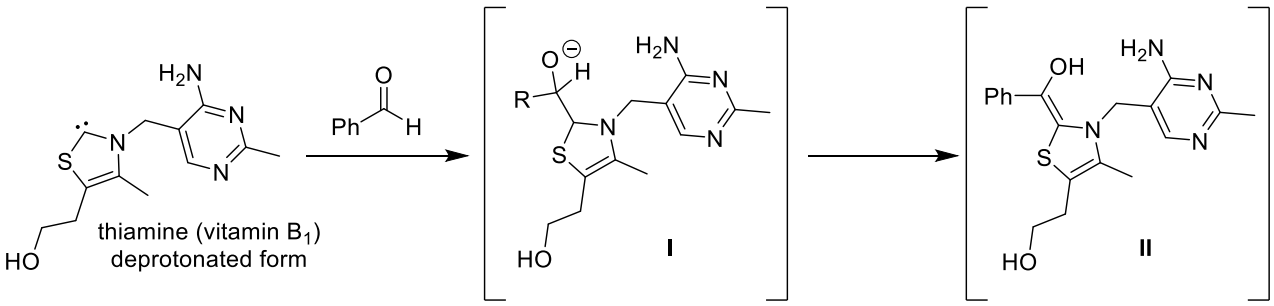
Scheme 1. Generation of the free carbene in the reaction environment.

The core heterocycle ring can be easily substituted, with the substituents ranging from simple aliphatic chains to complex polycyclic systems. However, the general trend is for the N^1 substituent to be aromatic, with *o*,*o*-disubstituted aryls being preferred, as they generally exhibit higher efficiency.[8] The 3 and 4 positions of the ring are usually incorporated into a ring system bearing chiral substituents. This makes the NHC compound itself chiral and allows the use of these compounds as chiral organocatalysts in asymmetric transformations.

The substitution patterns of the heterocyclic ring also have a profound effect on the reactivity and stereoselectivity of the catalyst, by affecting both the carbene's electronics and steric bulkiness. The heterocycle moiety brings much-needed stability both through aromaticity, and through the σ-electron withdrawing and π-electron donating effects of the heteroatoms. This relative stability makes these species strongly nucleophilic and potent σ-donors.[5]

1.2.2 Reactions catalysed by *N*-heterocyclic carbenes

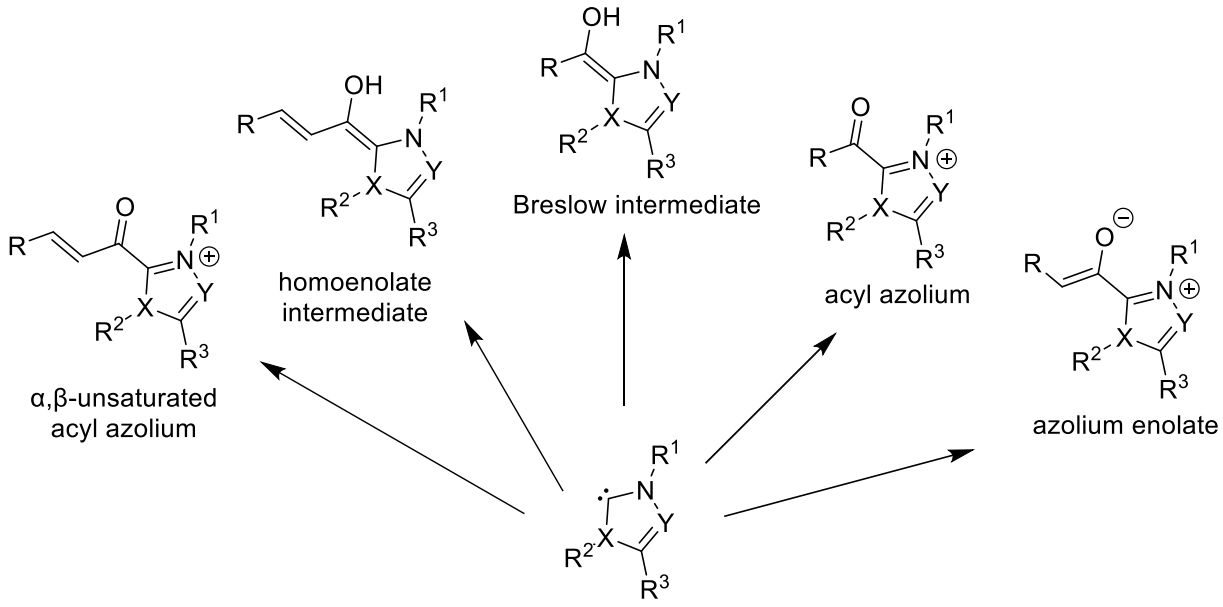
With their powerful σ-donating ability, (chiral) NHCs are mainly used to manifest (asymmetric) C-C (or C-heteroatom) forming reactions, such as the benzoin (acyloin) condensation.[9] Its similarity to biochemical processes catalysed by enzymes carrying the thiazole-derived cofactor triamine pyrophosphate is not by accident. As the thiazole moiety is highly unusual in nature, the physiological role of thiamine in biochemical processes was the subject of investigation. In 1958, following upon the observations of Jansen,[10] Breslow used the example of thiamine pyrophosphate to propose a mechanism for a thiazolium salt-catalysed benzoin condensation between two benzaldehyde molecules (Scheme 2).[11]



Scheme 2. Generation of the intermediate adduct **II**, as proposed by Breslow.

In this mechanism, the azolium salt is converted to the free carbene using a base, followed by the carbene lone pair performing a nucleophilic attack on the electron-deficient carbonyl carbon of the aldehyde. This forms the intermediate adduct **II** (now called the Breslow intermediate), which is notable for inversing polarity of the carbonyl group. This renders the carbonyl carbon nucleophilic, and capable of attacking another molecule. If, for example, the target is another aldehyde (acyloin condensation), an α-hydroxy ketone is formed,[12] while an attack on a Michael acceptor results in a 1,4-conjugate addition (Stetter reaction).[13] These reactions generally result in the formation of a new stereogenic centre.

The Breslow intermediate is just one of several key intermediates (overviewed in Scheme 3) formed in NHC-catalysed reactions. The nature of the intermediate is crucial to explain the product scope and stereoselectivity of the transformation and is mainly dependent on the type of substrate and catalyst used.[14] If the NHC catalyst is chiral, one isomer of the intermediate may be formed preferentially, forcing the electrophile upon the less hindered face, leading predominantly to one stereoisomer of the product.[5]



Scheme 3. Five distinct intermediates generated during NHC-catalysed reactions.

2. State of the art

2.1 Triazolium salts as NHC catalysts

Triazoles are aromatic, heterocyclic compounds, containing three nitrogen and two carbon atoms. It is therefore apparent, that two distinct isomers of triazole exist, those being 1,2,4-triazole and 1,2,3-triazole. While both isomer moieties can be found in synthesised biologically active compounds (Figure 2),[15] this work only focused on the chemistry of 1,2,4-triazoles. Therefore, any mentions of the terms *triazole* or *triazolium salt* will refer to this particular isomer.

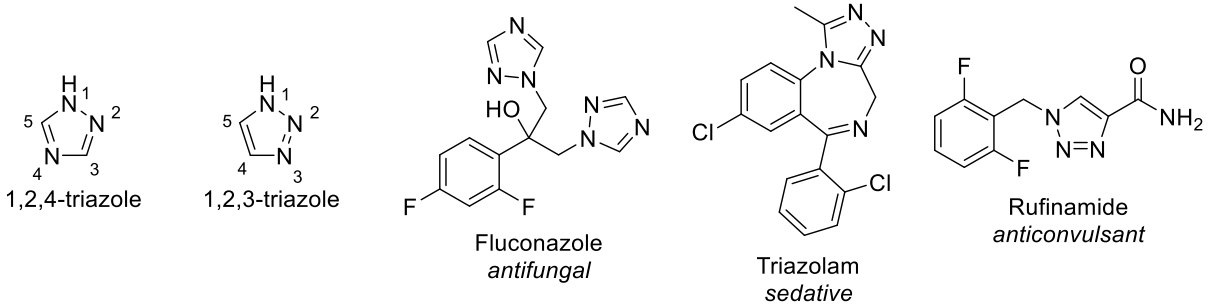
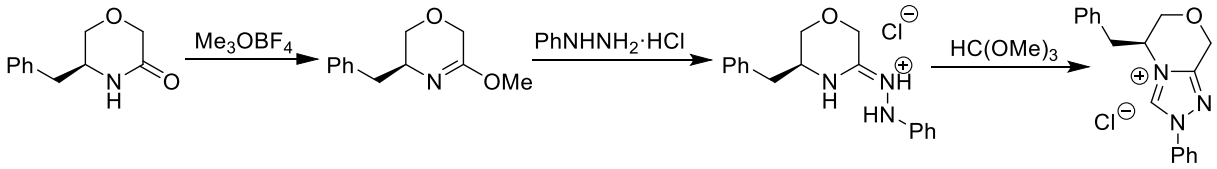


Figure 2. Both isomers of triazole and examples of triazole-containing biologically active compounds.

2.2 Synthetic ways towards chiral triazolium salts

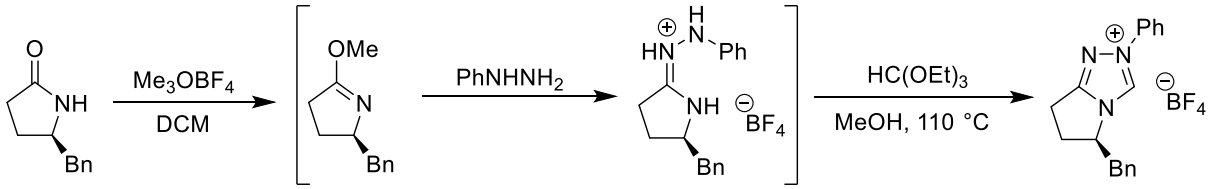
2.2.1 Triazolium salts from cyclic amides

The most important approach for preparing triazolium salts from a variety of chiral lactams is based on a three-step procedure, first described by Knight & Leeper in 1998 (Scheme 4).[16] The starting cyclic amide, a chiral morpholinone derivative in this case, is converted to an imino ether with the use of a powerful methylating agent (most often trimethyloxonium tetrafluoroborate, known as Meerwein's reagent). Then, an aryl hydrazine hydrochloride is added to the intermediate, which provides the nitrogen atoms for the future triazole ring, and the chloride counter-anion. The hydrazone is then formylated and subsequently cyclised by heating with triethyl orthoformate.

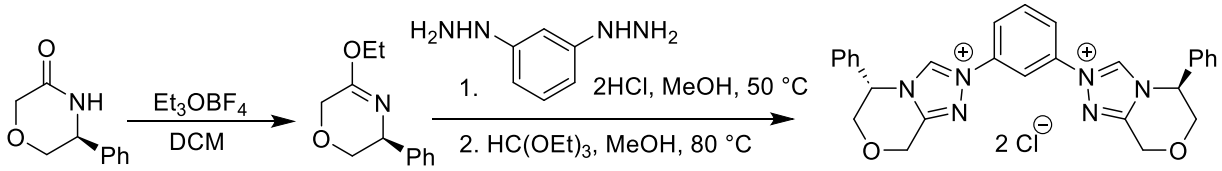


Scheme 4. The first approach to preparing triazolium salts from lactam compounds.

A few years later, Rovis and co-workers reported that the three-step reaction may be performed as a one-pot procedure (Scheme 5).[17] This procedure is applicable to a broad range of cyclic amides. It is also possible to prepare bis-bicyclic triazolium salts with this method, as shown by Ma and colleagues. They modified the procedure to accommodate a dihydrazine (*m*-phenylenedihydrazine) to achieve the product (Scheme 6).[18]



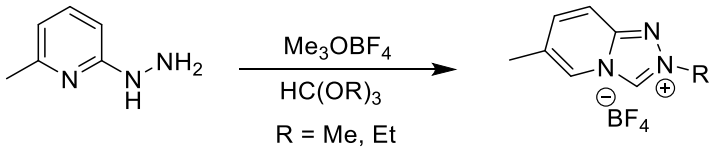
Scheme 5. A one-pot procedure for preparing triazolium salts from a lactam compound.



Scheme 6. Synthesis of a bis-bicyclic triazolium salt using an analogous procedure.

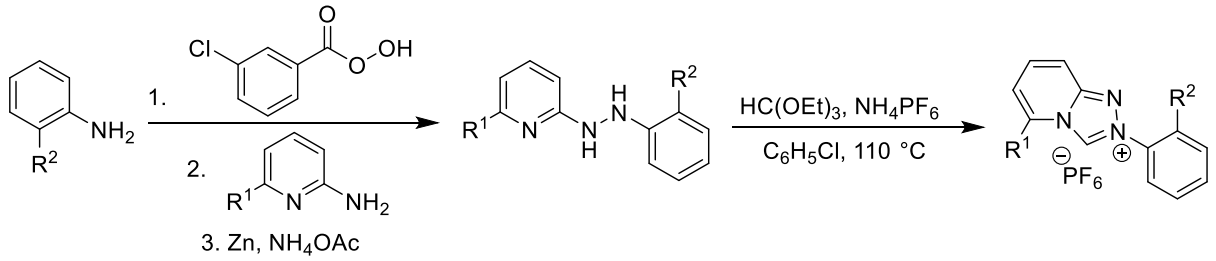
2.2.2 Pyrido-annulated triazolium salts

The question of whether the triazole ring can be a part of a larger, aromatic system of rings in the final molecule was answered by Ma et al. His group developed two methods of forming the triazole moiety from a pyridine backbone to create these kinds of salts.[19] The first method starts with 1-(pyridine-2-yl)hydrazine, which reacts with Meerwein's reagent and a trialkyl orthoformate (Scheme 7) to form the product. However, a large limitation of this method is the inability to attach an aryl substituent to the N^1 atom of the triazole ring, as the substituent on this atom comes from the trialkyl orthoformate used.



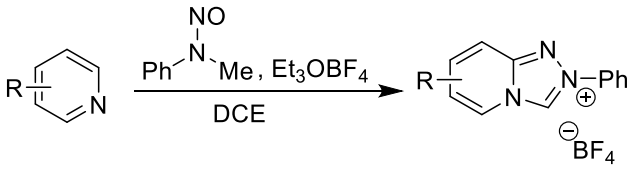
Scheme 7. Synthesis of pyrido-annulated triazolium salts bearing simple substituents.

Hence, a second method was also presented (Scheme 8), which avoids this constrain by treating an aniline derivative with *m*-chloroperoxybenzoic acid and then condensing the intermediate nitrosobenzene with a 2-aminopyridine derivative. The formed azo compound is then reduced with zinc and ammonium acetate to a hydrazone, which is then cyclised by heating with triethyl orthoformate and a counter-anion source. The substituted aniline ring therefore becomes the aromatic substituent on the N^1 atom of the triazole ring in the final compound.



Scheme 8. Preparation of more complex pyrido-annulated triazolium salts from substituted anilines and an aminopyridine derivative.

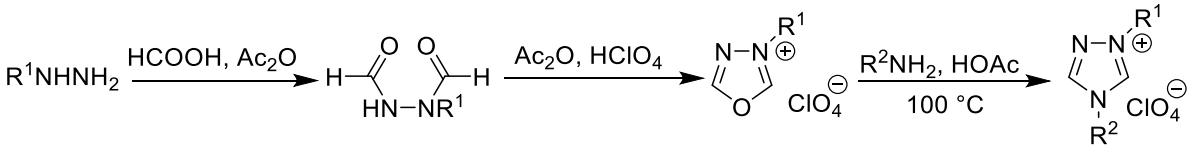
An alternative procedure was presented by Sigüenda et al. in 2009 (based on a method reported in 1969 by Eicher),[20,21] where various substituted pyridines are added to a flask charged with methyl-*N*-nitrosoaniline and Meerwein's reagent in dry DCE, leading to a similarly substituted compound (Scheme 9).



Scheme 9. Synthesis of pyrido-annulated triazolium salts with the use of nitrosoanilines.

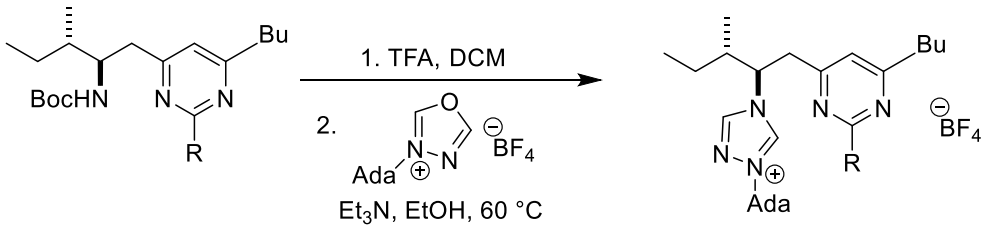
2.2.3 Triazolium salts from oxadiazole rings

Building upon a method first developed by Boyd et al.,[22] Enders et al. presented a method of accessing triazolium salts by a ring-opening-ring-closing reaction of a previously prepared oxadiazolium salt with a chiral primary amine (Scheme 10).[23] The oxadiazolium salt is prepared by reacting an alkyl or aryl hydrazine with formic acid and acetic anhydride. This intermediate is then condensed with the help of acetic anhydride and perchloric acid.



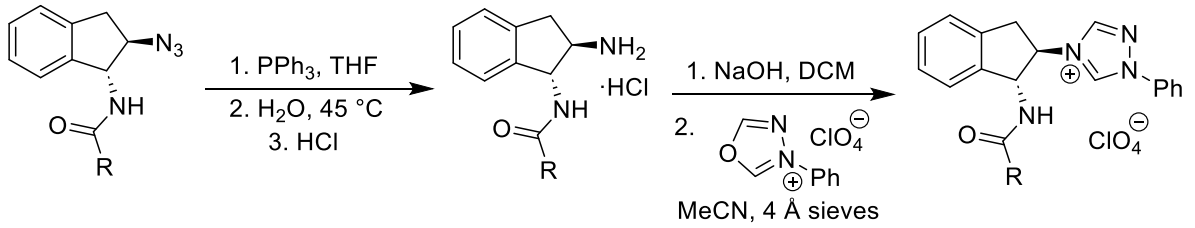
Scheme 10. Synthesis of triazolium salts from oxadiazolium compounds prepared from hydrazines.

The scope of primary amines, which may be used, is broad. In the work of Chen et al., a freshly de-protected primary amine is shown to react with an oxadiazolium tetrafluoroborate, prepared from 1-bromoadamantane, to provide a 1,4-disubstituted triazolium salt (Scheme 11).[24]



Scheme 11. Example of a triazolium salt preparation from a chiral primary amine and an oxadiazolium salt.

In a different body of work, O'Toole and Connon prepared a chiral primary amine hydrochloride from an azide via Staudinger reduction, followed by treatment with base and reaction with an oxadiazole to yield the triazolium product (Scheme 12).[25]

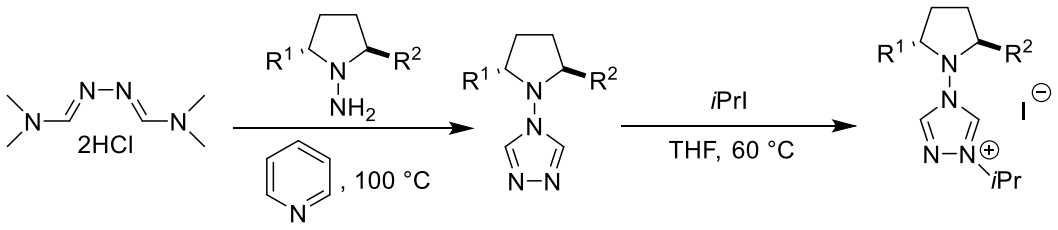


Scheme 12. Analogous synthesis of a triazolium salt from a chiral substituted aminoindane.

2.2.4 Other synthetic methods for the preparation of triazolium salts

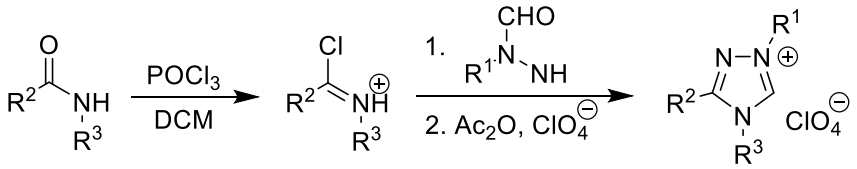
A piece of work published by Lassaletta et al. presents an alternative procedure of synthesising *N*-(dialkylamino)triazoles as precursors for their derived triazolium salts.[26] This procedure improves upon a previously reported method reported by Castellano et al., which dealt with the preparation of these compounds by reductive amination and subsequent alkylation of 4-amino-triazoles;[27] this method however proved unusable, if the introduction of more complex, chiral *N*-dialkylamino groups was desired.

The group therefore designed a process, in which chiral *N*,*N*-dialkylhydrazines react with *N*,*N*-dimethyl-formamidazine dihydrochloride in pyridine at 100 °C, leading to the formation of 4-(dialkylamino)triazoles (Scheme 13). These intermediates can then react with alkylating agents to alkylate the N^1 triazole atom selectively, and to provide the triazolium salt's counter-anion.



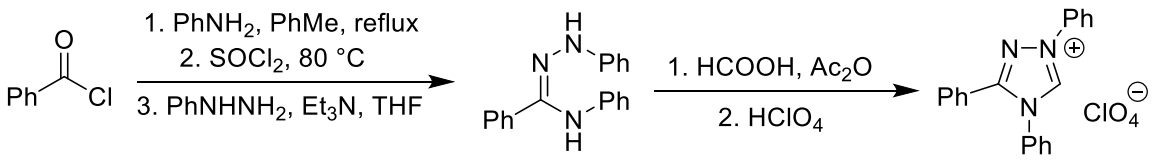
Scheme 13. Synthesis of dialkylaminotriazolium salts from chiral *N*,*N*-dialkylhydrazines.

Another procedure, stemming from imidoyl chlorides, was highlighted in a paper by Enders et al.[23] Here, the imidoyl chloride is freshly prepared by reacting an amide with phosphoryl chloride, and is afterwards mixed with an *N*-alkyl-*N*-formyl hydrazine in the presence of acetic anhydride and perchloric acid (Scheme 14). This sequence leads to the formation of 3,4-disubstituted-1-alkyl-triazolium perchlorates.



Scheme 14. Preparation of triazolium salts from imidoyl chlorides and *N*-alkyl-*N*-formylhydrazines.

Another way of preparing the salts is a multiple-step procedure originating from benzoyl chloride (Scheme 15).[28] At first, the chloride is condensed with aniline by refluxing in toluene, followed by the addition of thionyl chloride at 80 °C. The formed intermediate is then dissolved in THF, and condensed with phenylhydrazine in the presence of triethylamine, forming most of the ring's skeleton. Finally, to complete the triazole ring, formic acid, acetic anhydride, and perchloric acid are added, yielding the perchlorate salt.

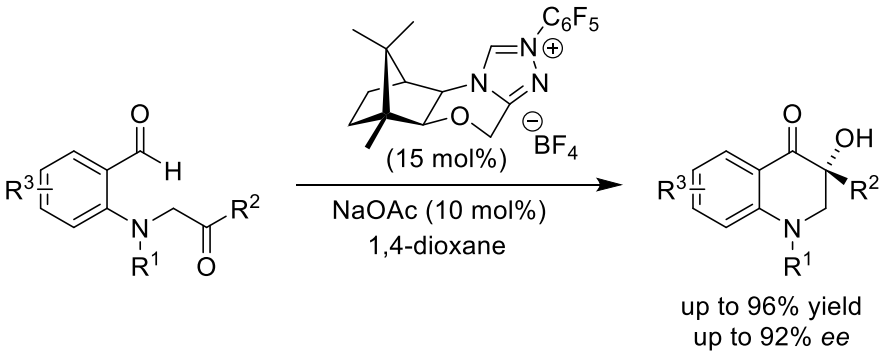


Scheme 15. Alternative procedure of preparing tri-substituted triazolium salts from benzoyl chloride.

2.3 Selected organocatalytic transformations mediated by chiral NHC catalysts

The use of chiral triazolium salts as conjugated acids of active NHC catalysts evolved from experiments involving thiazolium-based NHCs in asymmetric benzoin condensations, which were carried out with poor to moderate yields and enantioselectivity.[29,30] This led to the development of analogous NHC catalysts based on triazole, immediately providing better results.[16,31] Following these observations, more and more chiral NHC catalysts, based on compounds such as amino acids, aminoindane, or camphor, have been successfully synthesised and used in the following years.[32]

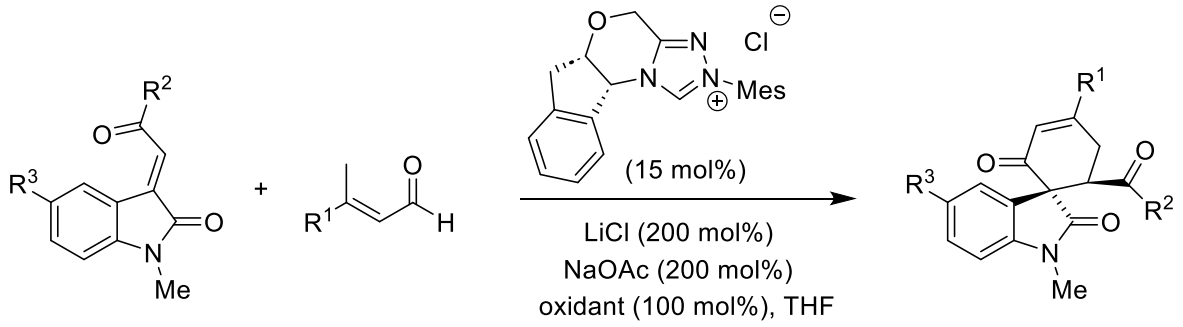
Of course, these NHC catalysts can be applied to the usual umpolung transformations of aldehydes, briefly overviewed in Section 1.2.2. Such an example is an asymmetric intramolecular acyloin condensation performed by You et al., using catalysis with an NHC generated from a camphor-derived triazolium salt (Scheme 16).[33]



Scheme 16. Example of an NHC-catalysed asymmetric intramolecular acyloin condensation.

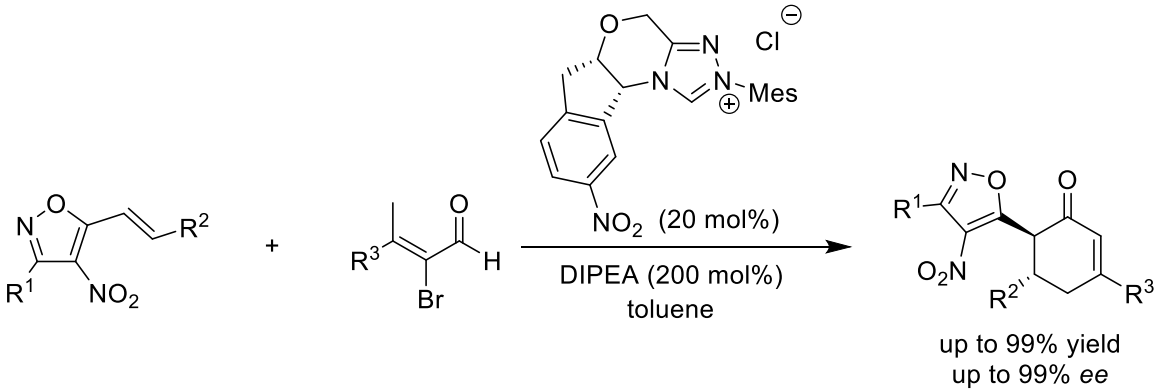
However, an increased amount of attention has also been paid to designing NHC-catalysed asymmetric cycloaddition and annulation reactions. Such reactions are valuable, as they provide access to many different ring skeletons that may be useful in various syntheses of pharmaceuticals and biologically active compounds. These include, but are not limited to, derivatives of (spiro)indoles, quinolines, (benzo)furans, lactones, and pyrazoles.[14]

A particular method of preparing chiral cyclohexenones falls in this category. The reaction proceeds by generating an azolium-dienolate intermediate from an *α*,*β*-unsaturated aldehyde via *in situ* oxidation by an external oxidant. This intermediate can then attack a different substrate containing a polarised double bond, to complete the formal [4+2] cycloaddition, creating two stereogenic centres in the process. An example of such a transformation is the synthesis of a chiral spiroindole derivative by Liu et al. (Scheme 17).[34]



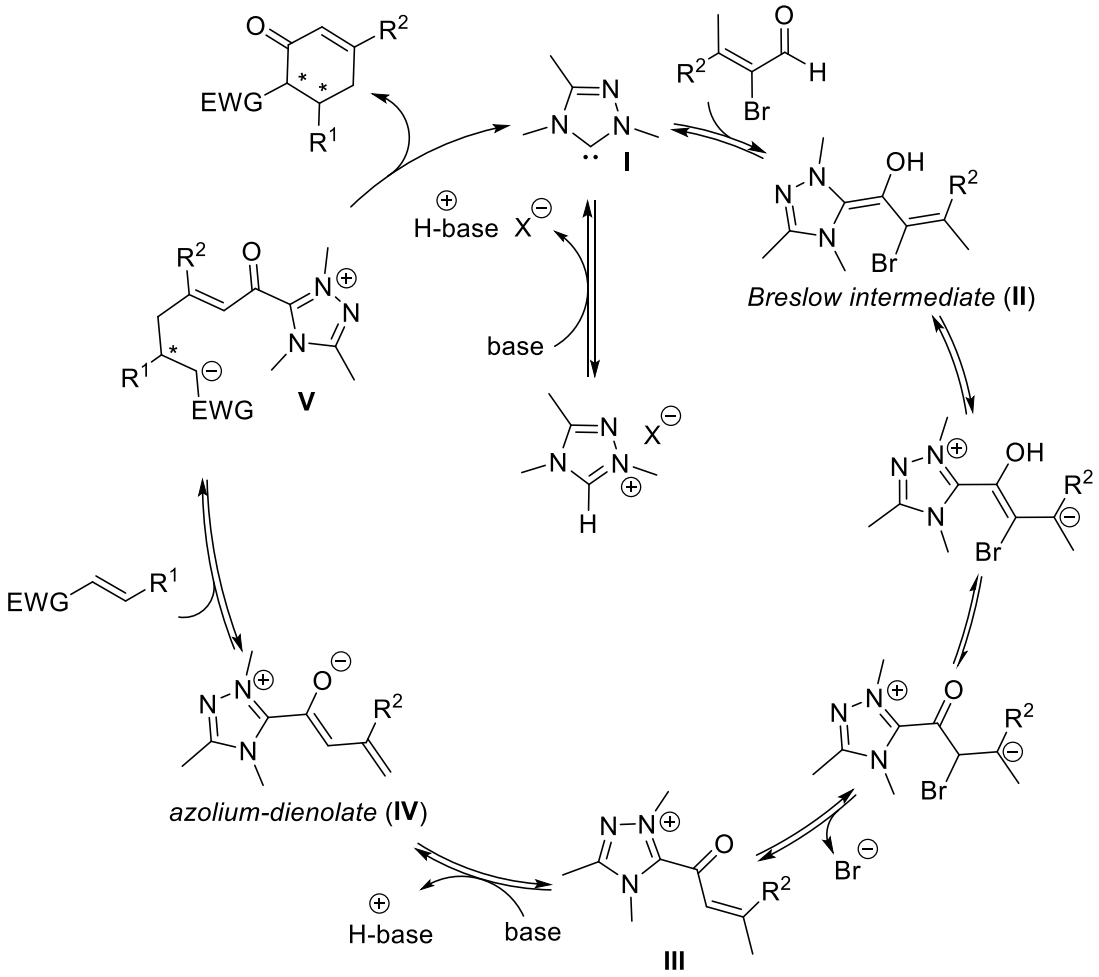
Scheme 17. Asymmetric [4+2] cycloaddition of an enal and a chiral spiroindole derivative.

However, as has been shown, it is also possible to prepare these compounds without the use of an external oxidant, by reacting electron-deficient alkenes with an *α*-bromo-*α*,*β*-unsaturated aldehyde. For example, this tactic has been used in the synthesis of chiral cyclohexenones from substituted nitroisooxazoles by Lóška et al. (Scheme 18).[35]



Scheme 18. NHC-catalysed asymmetric synthesis of chiral cyclohexenones from nitroisooxazole derivatives.

The assumed mechanism of these transformations is overviewed in Scheme 19. First, the carbene lone pair attacks the carbonyl group of the *α*-bromoenal, forming the Breslow intermediate **II**. Upon tautomerization, the *α*-bromine atom acts as a leaving group, forming the azolium intermediate **III**, which is then deprotonated to yield the azolium-dienolate **IV**. The electron-rich *γ*-carbon atom can then attack the double bond of the electron-deficient alkene substrate to form **V**. This intermediate then undergoes cyclisation via an intramolecular nucleophilic attack to yield the chiral cyclohexenone compound.



Scheme 19. Plausible mechanism of the key intermediate generation *in situ* and subsequent formation of the product.

3. Goals of the project

The main objective of this project was the synthesis of selected chiral NHC conjugate acids, all containing a triazolium moiety, from readily available, small molecules. These compounds would then be used in a model asymmetric reaction to showcase their catalytic ability. The project can therefore be divided into the following steps:

a) Preparation of two chiral NHC conjugate acids derived from both enantiomers of the essential amino acid valine.

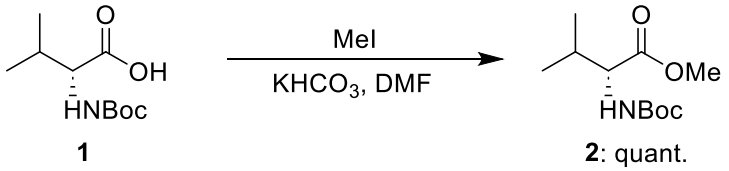
b) Preparation of two chiral NHC conjugate acids derived from the naturally-occuring compound D-camphor, with the final compounds differing in the aryl group bonded to the triazolium ring.

c) Use of the prepared NHC conjugate acids as organocatalysts in a selected enantioselective reaction, and comparison to previously tested NHC catalysts.

4. Results and discussion

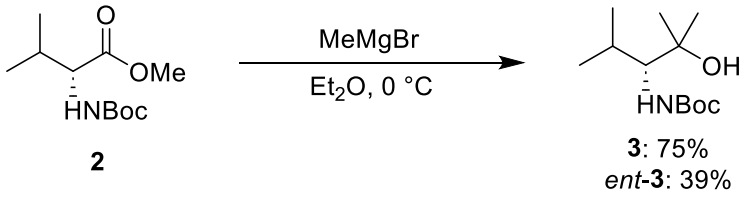
4.1 Preparation of chiral NHC conjugate acids derived from both valine enantiomers

As the Boc-protected derivative (**1**) of the essential α-amino acid valine is readily available for purchase, it was chosen as the starting material for the following steps. The first step of the synthesis was an esterification using methyl iodide in the presence of a weak base (Scheme 20),[36] which afforded Boc-D-valine methyl ester (**2**) in quantitative yield. The *ent*-**2** compound was commercially available.



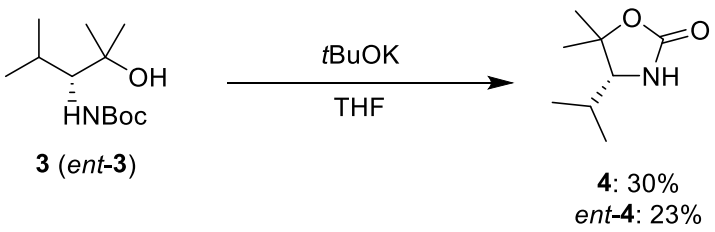
Scheme 20. Preparation of the Boc-valine methyl ester.

The ester functional group of of **2** (*ent*-**2**) was converted into the tertiary alcohol **3** (*ent*-**3**) by a Grignard reaction with methyl magnesium bromide (Scheme 21).[37] The reaction proceeded with acceptable yields (75 and 39%), and the product was used immediately for the next step. Interestingly, *ent*-**3** was prepared in a noticeably lower yield, despite the use of the same reaction procedure.



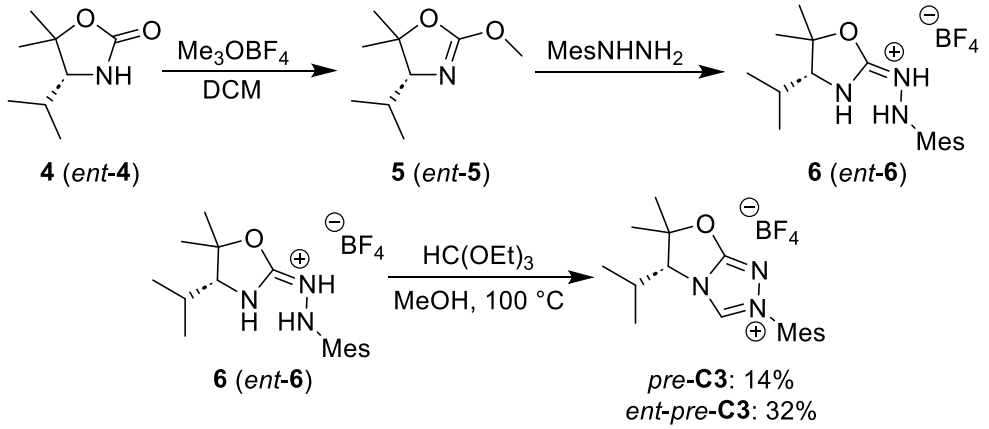
Scheme 21. Preparation of the tertiary alcohol intermediate.

The Grignard products **3** and *ent*-**3** were cyclised into oxazolidinones **4** and *ent*-**4**, respectively, using potassium *tert*-butoxide as a base (Scheme 22).[37] The cyclisation step proved to be troublesome, with yields of 30% (for **4**) and 23% (for *ent*-**4**). It was hypothesised that the cyclic products **4** and *ent*-**4** may have a high affinity for the water phase during extraction, or that some losses may have occurred during evaporation because of the compound's volatility.



Scheme 22. Preparation of the cyclic oxazolidinone derivative.

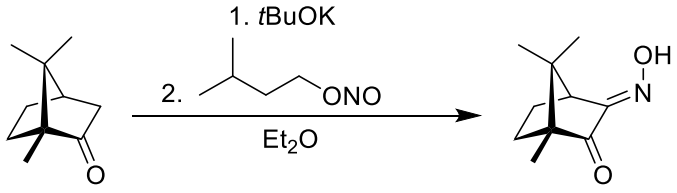
The oxazolidinones **4** and *ent*-**4** were then converted into the triazolium salt pre-catalyst by a three step procedure (Scheme 23).[37] The carbonyl oxygen was methylated by Meerwein's reagent, forming the imino ether intermediate **5** (*ent*-**5**), to which was then added freshly prepared mesityhydrazine. The formed intermediate **6** (*ent*-**6**) was then converted into the triazolium salt product *pre*-**C3** (*ent-pre*-**C3**) by refluxing with triethyl orthoformate in MeOH. The differences in yield (14% and 32%) could be attributed to the purification required to afford the pre-catalysts in sufficient purity, which differed for *pre*-**C3** and *ent-pre*-**C3**.



Scheme 23. Three-step preparation of the valine-derived NHC conjugate acids.

4.2 Preparation of chiral NHC pre-catalysts derived from D-camphor

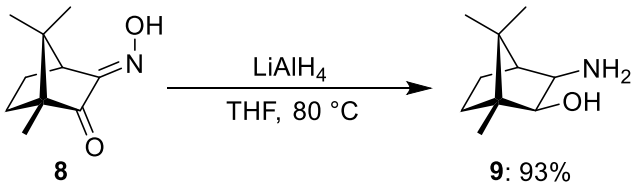
The starting material for this synthesis was D-camphor (**7**), an enantiopure natural compound easily available for purchase. In the first step, the D-camphor was deprotonated in the α-position by potassium *tert*-butoxide and subsequently turned into mainly the *E*-isomer of the oxime **8** (*dr* = 9:1) by adding isopentyl nitrite (Scheme 24).[37] The reaction proceeded with a high yield of 92%.



7 **8**: 92%

Scheme 24. Preparation of the D-camphor oxime derivative.

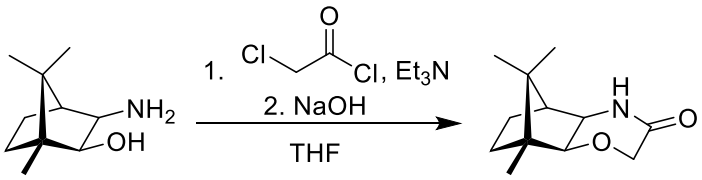
The oxime **8** was then converted into an amino alcohol **9** via reduction with lithium aluminium hydride (Scheme 25),[37] in a reaction which heavily favoured the formation of the *syn*-stereoisomer of **9** (*dr* = 17:1). The reaction ended up going ahead with an excellent yield of 93%.



8 **9**: 93%

Scheme 25. Preparation of the *syn*-aminoisoborneol intermediate.

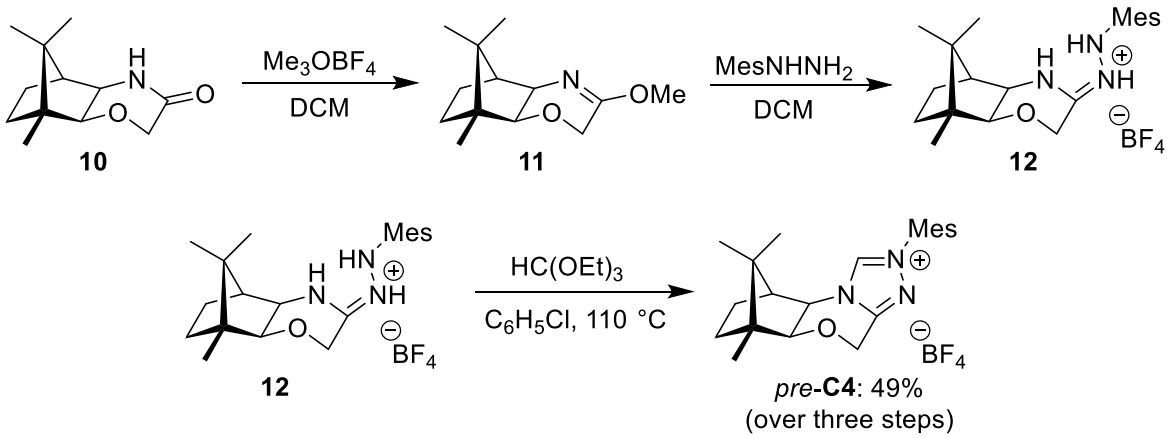
The amino alcohol product **9** was then immediately used for the subsequent two-step cyclisation. First, the amine was turned into an amide by the amidation of chloroacetyl chloride, and the six-membered lactam cycle was then fused by an intramolecular S_N2 substitution promoted by a base (Scheme 26).[37,38] After some necessary optimisations of the reaction conditions (base, reaction time, temperature), full conversion of the amide in the substitution reaction prompted by a solution of hydroxide was observed after 5 days. In the end, the morpholinone product **10** was yielded in an acceptable yield of 35%.



9 **10**: 35% (over two steps)

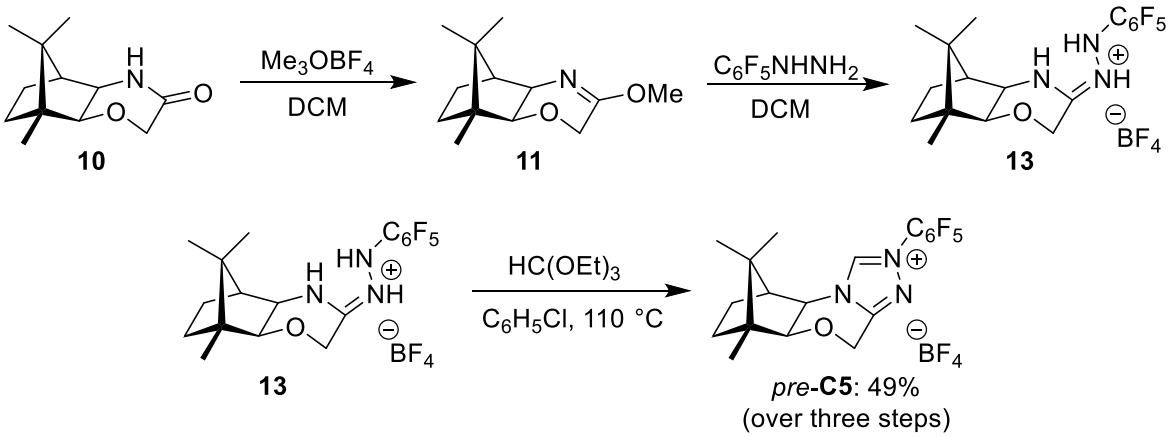
Scheme 26. Preparation of the cyclic morpholinone derivative.

To prepare the first camphor-derived pre-catalyst (*pre*-**C4**), Meerwein's reagent was added to the morpholinone **10** in dry DCM to create the imino ether **11**, to which was then added freshly prepared mesityl hydrazine. Subsequently, the hydrazone **12** was cyclised into the triazolium salt *pre*-**C4** by refluxing with triethyl orthoformate in chlorobenzene (Scheme 27).[39] The total yield for these three steps was a respectable 49%.



Scheme 27. Preparation of the mesityl-substituted camphor-derived NHC conjugate acid.

The second of the camphor-derived pre-catalysts (*pre*-**C5**) was prepared using a very similar procedure, with the only difference being the use of pentafluorophenylhydrazine as the aryl hydrazine (Scheme 28).[39] The procedure was also made slightly easier, due to pentafluorophenylhydrazine being a shelf-stable solid, meaning that it can be directly added to the reaction mixture. In the end, the pre-catalyst *pre*-**C5** was generated from the three-step reaction in a 49% yield.

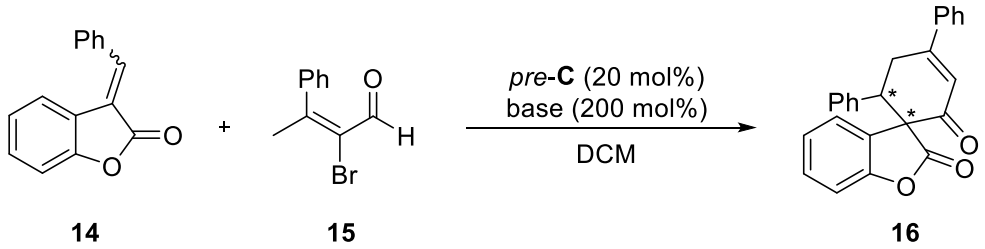


Scheme 28. Preparation of the pentafluorobenzyl-substituted camphor-derived NHC conjugate acid.

4.3 Spiroannulation reaction

4.3.1 Motivation for the selected substrates

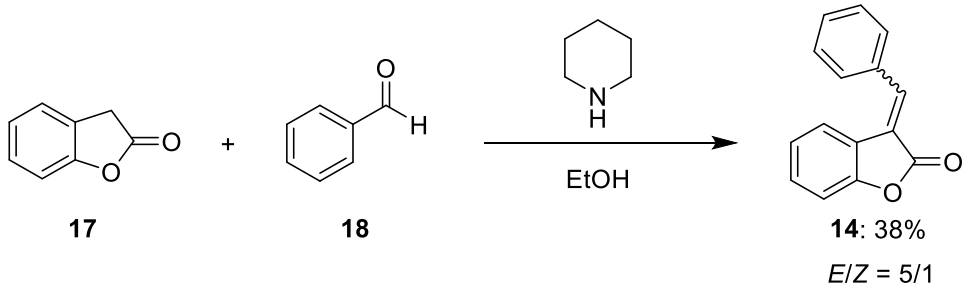
A chiral NHC-catalysed asymmetric spiroannulation reaction of benzylidene-3-benzofuran-2(3*H*)-one (**14**) and (*E*)-2-bromo-3-phenylbut-2-enal (**15**) was chosen as the model reaction for the catalyst screening. The inspiration for this reaction came from the ongoing research in our group, focused on the synthesis of spirocyclic derivatives of various heterocycles. Compounds based on oxygen-containing heterocycles, such as benzofuranone, are often a part of biologically active structures.[40] Exploring transformations leading to these compounds could, therefore, be of significance in novel drug development.



Scheme 29. Overview of the selected model reaction.

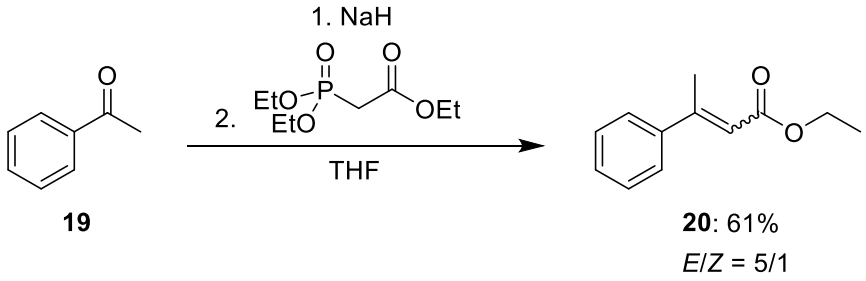
4.3.2 Preparation of the starting compounds

The benzylidene starting material **14** was prepared from 2-coumaranone (**17**) in a one-step reaction by Knoevenagel condensation with benzaldehyde (**18**) in the presence of piperidine (Scheme 30).[41] The reaction ran without issue, however, multiple washes with a sodium bisulfite solution were required to remove all residual benzaldehyde, leading to a yield of 38%.



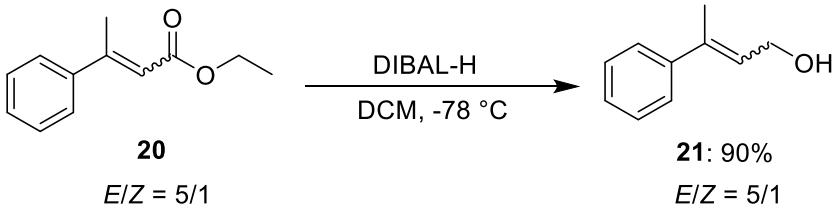
Scheme 30. Preparation of the benzylidene benzofuranone derivative starting material.

The α-bromo enal **15** was prepared in a four-step synthesis starting from acetophenone (**19**).[35] In the first step, the ketone was converted to an α,β-unsaturated ester **20** by the Horner-Wadsworth-Emmons reaction, using a phosphonate-stabilised carbanion created by the deprotonation of triethyl phosphonoacetate by sodium hydride (Scheme 31). Resulting from this reaction was the ester product **20** as a 5/1 mix of *E*/*Z* isomers in a 61% yield.



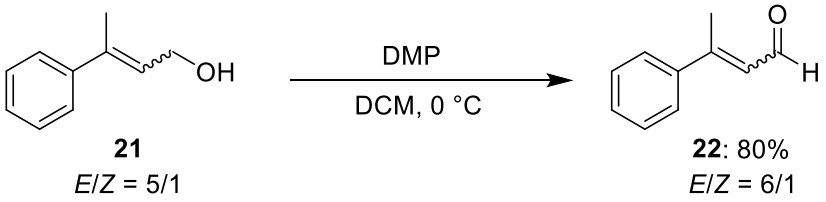
Scheme 31. Preparation of the α,β-unsaturated ester from acetophenone.

The ester product **20** from the previous step was then converted into an alcohol **21** via reduction with DIBAL-H (Scheme 32),[35] again yielding a 5/1 mix of *E*/*Z* isomers, in a yield of 90%.



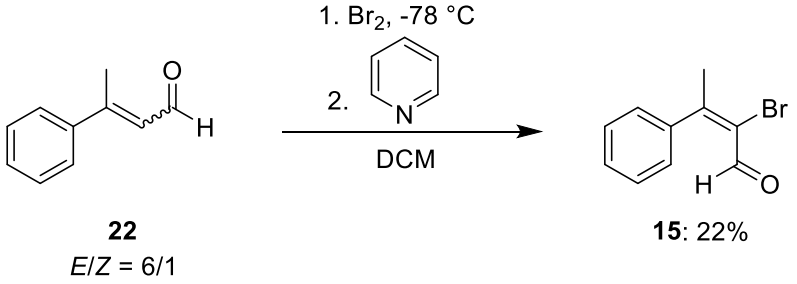
Scheme 32. Preparation of the alcohol by a reduction of the α,β-unsaturated ester.

In the next step (Scheme 33), the alcohol **21** was converted into an aldehyde **22** by gentle oxidation with Dess-Martin periodinane (DMP).[35] The *E*/*Z* isomers could be separated to a small degree during column chromatography, so the product was afforded as a 6/1 mixture of *E*/*Z* isomers in an 80% yield. Due to the significant instability of the aldehyde product **22**, degrading over time to a carboxylic acid, it was used immediately for the next step.



Scheme 33. Preparation of the α,β-unsaturated aldehyde.

For the final step of the synthesis of the α-bromoenal starting material **15**, the aldehyde product **22** from the previous step was reacted with bromine in dry DCM at -78 °C, followed by the addition of pyridine, which prompted an elimination of the formed dibromo-substituted intermediate to yield almost exclusively the *E*-isomer of the final product **15** in a 22% yield.



22
E/*Z* = 6/1

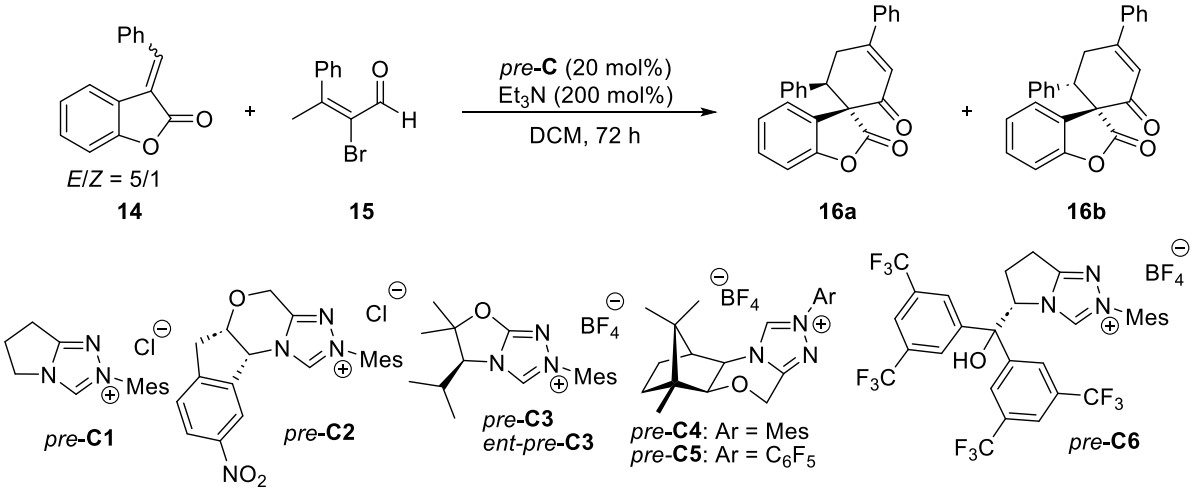
15: 22%

Scheme 34. Preparation of the α-bromoenal starting material.

4.3.3 Results of the catalyst screening

In addition to the four previously prepared NHC conjugate acids (*pre*-**C3**, *ent-pre*-**C3**, *ent*-**C4**, *ent*-**C5**), two additional NHC pre-catalysts were used as benchmarks. An achiral NHC (*pre*-**C1**) was tested to highlight the expected increased enantioselectivity when using chiral NHCs. An aminoindanone-derived NHC (*pre*-**C2**), which had shown great catalytic activity in the nitrooaxazole reaction shown in Section 2.3 (Scheme 18) was also studied. To round off the scope of studied catalysts, a bi-functional NHC pre-catalyst containing a tertiary alcohol group (*pre*-**C6**) was also tested. It was hypothesised that the catalytic ability could be improved due to H-bond formation with an intermediate, leading to a more rigid transition state.

Table 1. Overview of the model reaction outcomes based on the used NHC precursor.



Entry[a]	*pre*-Catalyst	Conversion	*Dr*[b]	Comb. yield (%)[c]	*Ee* (%)[d]
1	*pre*-**C1**	full	1.0/1.9	70	0/0
2	*pre*-**C2**	full	4.5/1.0	66	86/52
3	*pre*-**C3**	not full	3.7/1.0	24	55/45
4	*ent-pre*-**C3**	not full	3.8/1.0	37	-48/-55
5	*pre*-**C4**	no	n.d.	traces	n.d.
6	*pre*-**C5**	no	n.d.	traces	n.d.
7	*pre*-**C6**	not full	4.0/1.0	36	95/82

[a] Reactions were conducted with **14** (0.10 mmol), substrate **15** (0.15 mmol), Et_3N (0.20 mmol), and selected *pre*-**Catalyst** (20 mol%) in DCM (1.0 ml, 0.1 M) at room temperature. [b] Ratio of the diastereomers **16a** and **16b** as determined by ^1H NMR of the crude reaction mixture. [c] Isolated yield after column chromatography. [d] Determined by chiral HPLC analysis.

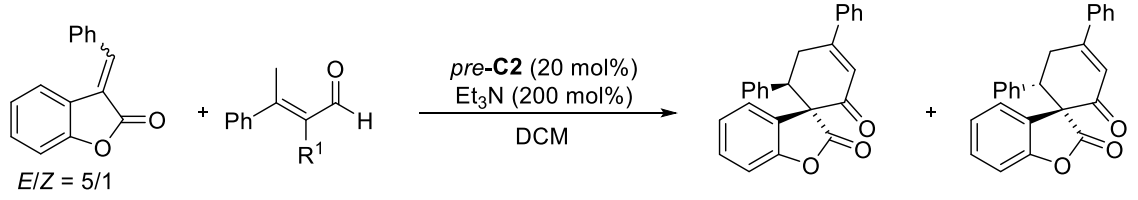
As anticipated, the model reaction using the achiral *pre*-**C1** provided racemic mixtures of the **16a** and **16b** diastereomers (entry **1**), which were necessary for further determination of enantioselectivity using chiral HPLC. Enantiomeric excess (*ee*) was measured for all reactions, as the use of a chiral NHC catalyst should preferentially yield one enantiomer of both diastereomers **16a** and **16b**. The model reaction conducted in the presence of *pre*-**C2** (entry **2**) led to the best overall results (*dr* = 4.5/1.0, *ee* = 86%/52%). The valine-derived NHCs *pre*-**C3** and *ent-pre*-**C3** (entries **3** & **4**) showed a modest amount of enantiocontrol, although with relatively poor yields (24% and 37%). However, the *dr* (3.7/1.0 and 3.8/1.0) was comparable with the better-performing catalysts. As is evident, the NHCs derived from camphor (*pre*-**C4** and *pre*-**C5**, entries **5** & **6**) did not illicit any catalytic activity, with only traces of product being detected via TLC. Interesting stereocontrol (*dr* = 4.0/1.0, *ee* = 95%/82%) was observed in the model reaction catalysed by the bifunctional *pre*-**C6** (entry **7**), albeit in a low yield of 36%.

4.3.4 Other methods of accessing the azolium-dienolate intermediate

To compare the viability of the prior method to an oxidative approach, an additional experiment was carried out. In contrast to the previous experiment, the aldehyde compound **22** was used as the second substrate in the presence of an external oxidant. Furthermore, the NHC catalyst of choice was *pre*-**C2** for every reaction, as it provided the best overall results in the previous experiment. Additionally, all reactions were run until full conversion of **14** had been achieved, or until 48 h of reaction time had passed. Finally, an oxidant was present in the reaction mixture to facilitate the generation of the key azolium-dienolate intermediate.

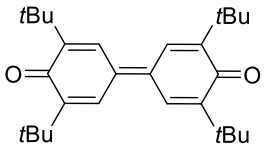
In total, four reactions were performed, differing in the applied oxidant. Three reactions were run with either Kharasch oxidant (DQ), manganese dioxide, or a catalytic amount of DQ in excess manganese dioxide as the oxidative source, whereas one reaction was run under electrochemical conditions.[42]

Table 2. Overview of the model reaction outcomes based on the used oxidative conditions.



Entry[a]	R^1	Oxidant	Time (h)	*Dr*[b]	Comb. yield (%)[c]	*Ee* (%)[d]
1	Br	none	72	4.5/1.0	66	86/52
2	H	DQ (150 mol%)	16	4.8/1.0	94	95/55
3	H	MnO_2 (150 mol%)	24	5.0/1.0	51	96/60
4	H	DQ/MnO_2 (10/500 mol%)	24	4.8/1.0	45	97/60
5	H	electrochemical[e]	48	1.0/1.0	20	94/61

[a] Reactions were conducted with **14** (0.10 mmol), substrate **22** (0.15 mmol), Et_3N (0.20 mmol), and *pre*-**C2** (20 mol%) in DCM (1.0 ml, 0.1 M) at room temperature. [b] Ratio of the diastereomers **16a** and **16b** as determined by ^1H NMR of the crude reaction mixture, with the exception of entries **3** through **5**, where *dr* was determined by ^1H NMR of the isolated reaction mixture. [c] Isolated yield after column chromatography. [d] Determined by chiral HPLC analysis. [e] Electrochemical oxidation. Standard conditions: Pt anode, Pt cathode and reaction was conducted with **14** (0.20 mmol), **22** (0.30 mmol), *n*-Bu_4NI (0.20 mmol), Et_3N (0.40 mmol), and *pre*-**C2** (20 mol%) in DCM (2.0 ml, 0.1 M) in constant current of 1.0 mA in IKA ElectraSyn 2.0 at room temperature.



DQ oxidant

Apart from the electrochemical approach (entry **5**), which led to the formation of a multitude of side products, the oxidative conditions led to overall improvements in product stereoselectivity (entries **2** through **4**) compared to the original procedure (entry **1**). This is apparent in the increased *dr* (up to 5.0/1.0) and *ee* (up to 97%/60%) values compared to the previous experiment. In addition to this, the model reaction using just DQ as the oxidant (entry **2**) proceeded with an excellent yield (94%), which was also complemented by the shortest reaction time of 16 h. In comparison, the model reactions using manganese dioxide as the oxidant (entries **3** & **4**) proceeded with noticeably lower yields.

5. Experimental part

5.1 General remarks about the used procedures

Reactions, which required to be run in anhydrous conditions, were ran in vessels which were first evacuated under reduced pressure generated by a Lavat VR 1,5/21 **oil vacuum pump**, and then refilled with inert gas (argon). Excess solvents were removed under reduced pressure via a Heidolph Hei-VAP Core **rotary evaporator**. When necessary, final products were dried under reduced pressure created by an oil vacuum pump, until constant mass was reached.

Reaction conversion, as well as product purity, was monitored by **thin-layer chromatography** (TLC), with the use of Kieselgel 60 F_{254} (Merck) plates. The spots were then visualised either under UV, generated by the UV lamp CAMAG UV Cabinet 2 (λ = 254 nm, 366 nm), or by using TLC stains, followed by heating to 100 – 200 °C by a heat gun. The TLC stains that were used include: **CAM** – ceric ammonium molybdate, preparing by dissolving phosphomolybdenic acid (25 g) and ammonium cerium(IV) sulfate dihydrate (10 g) in a sulphuric acid solution (1.2 M, 1 l), **$KMnO_4$** – prepared by dissolving potassium permanganate (3 g) and potassium carbonate (20 g) in water (300 ml), with the solution being made alkaline by the addition of a sodium hydroxide solution (5% w/w, 5 ml), **DNPH** – prepared by dissolving 2-4-dinitrophenylhydrazine in water (20 ml) and sulphuric acid (96% w/w, 15 ml), followed by the addition of ethanol (50 ml).

Column chromatography was used for product separation, with Fluka 60 (40-63 μm) silica gel serving as the stationary phase, and freshly distilled solvents serving as the mobile phase. For filtrating thick slurries under reduced pressure, Celite® 545 was used.

Multiple techniques were used for the characterisation of prepared compounds. **Nuclear magnetic resonance** (NMR) was performed on a Bruker AVANCE III 400 machine, with ^{1}H spectra being measured at a frequency of 400 MHz, and ^{13}C spectra being measured at a frequency of 101 MHz. Chemical shifts were referenced to the protons or carbon atoms of the used deuterated solvent (chloroform-*d*, δ_H = 7.26 ppm, δ_C = 77.16 ppm).

To confirm the molecular mass of the prepared compound, **high-resolution mass spectrometry** (HRMS) was performed by the dissolution of the compound in methanol, and subsequent measurement on a Q-TOP COMPACT BRUKER machine, with ESI being used as the ionisation method.

To measure **specific rotation** ($[\alpha]_D^{20}$), of the prepared product, an AUTOMATIC POLARIMETER Autopol III machine was used. The concentration, measured in g/100 ml, is listed for each compound separately, with the special rotation being measured in the units 10^{-1} deg · cm^2 · g^{-1}.

Enantiomeric excess (*ee*) was measured by HPLC analysis on a Shimadzu LC20AD machine, equipped with an SPD-M20A spectrophotometric detector, and a Daicel Chiralpak® IH chiral stationary phase. The samples were prepared by dissolving the measured product in *i*-PrOH.

5.2 General procedures

5.2.1 General procedure I: Preparation of 4-isopropyl -5,5-dimethyloxazolidin-2-ones

The corresponding oxazolidinones (**4** and *ent*-**4**) were prepared by a modified literature procedure.[37]

A round-bottom flask was charged with a magnetic stirring bar and the corresponding Boc-valine methyl ester (1.0 eq.). The flask was evacuated under reduced pressure and refilled with argon. Then, the starting material was dissolved in anhydrous Et_2O (0.5 M with respect to ester) and cooled to 0 °C (ice/water cooling bath). At this temperature, a solution of methylmagnesium bromide (3.0 M in Et_2O, 3.2 eq.) was added dropwise to the stirred solution of ester. After all the Grignard reagent was added, the flask was removed from the cooling bath, and the mixture was left to stir at ambient temperature overnight. Once the starting ester was no longer detected by thin-layer chromatography (TLC), the reaction was quenched by dropwise addition of ice-cold water (40 ml for 50 mmol of ester). The resulting heterogeneous mixture was filtered through a short pad of Celite®, and the biphasic filtrate was separated, followed by extraction of the water layer with EtOAc (3 × 50 ml, for 50 mmol of ester). The combined organic phases were washed with brine (1 × 50 ml, for 50 mmol of ester) and dried under anhydrous $MgSO_4$. After filtration of the solid, the fitrate was concentrated under reduced pressure, yielding the virtually pure (according to NMR) tertiary alcohol **3** (*ent*-**3**). The crude product was used immediately for the next step without further purification.

A round-bottom flask was charged with a magnetic stirring bar and the corresponding crude alcohol **3** (1.0 eq.). The flask was evacuated under reduced pressure and refilled with argon. Afterwards, the alcohol was dissolved in anhydrous THF (0.2 M with respect to alcohol),

and the resulting solution was cooled to 0 °C (ice/water cooling bath). Upon cooling, potassium *tert*-butoxide (1.1 eq.) was added in small doses, and the reaction mixture was left to stir for 2-3 h at this temperature. Once the starting alcohol was no longer detected by TLC, the reaction mixture was concentrated under reduced pressure. The remaining solids were dissolved in EtOAc (250 ml for 35 mmol of alcohol), and the solution was very swiftly washed with ice-cold dilute hydrochloric acid (0.1 M, 1 × 50 ml for 35 mmol of alcohol), brine (1 × 50 ml for 35 mmol of alcohol), and then dried under anhydrous $MgSO_4$. After filtration of the solid, the filtrate was concentrated under reduced pressure. The oxazolidinone product (**4**, *ent*-**4**) was then isolated by column chromatography using hexane/EtOAc (1:1) as the mobile phase.

5.2.2 General procedure II: Preparation of valine-derived NHC conjugate acids

The corresponding NHC pre-catalysts (*pre*-**C3** and *ent-pre*-**C3**) were prepared according to a modified literature procedure.[37]

A small flask was charged with a magnetic stirring bar and the desired enantiomer of compound **4** (1.0 eq.). The flask was evacuated under reduced and refilled with argon. The starting material was then dissolved in anhydrous DCM (0.2 M with respect to oxazolidinone), and trimethyloxonoium tetrafluoroborate (1.1 eq.) was added to the stirred solution of oxazolidione. The reaction was left to run overnight at ambient temperature, until it was determined by ^{1}H NMR that almost all the starting material had been converted to the intermediate. Afterwards, freshly prepared mesitylhydrazine (1.5 eq.) was added to the reaction mixture. The mixture was left to stir overnight at ambient temperature. Once ^{1}H NMR confirmed full conversion to the second intermediate, the reaction mixture was concentrated under reduced pressure, and the remaining solids were re-dissolved in a few millilitres of anhydrous MeOH. Triethyl orthoformate (15.0 eq.) was then added to the flask, and the mixture was heated to 100 °C and left to reflux, until full conversion had been achieved, according to ^{1}H NMR (16-36 h). The reaction mixture was concentrated under reduced pressure, and the crude pre-catalyst was isolated by column chromatography, using a hexane/EtOAc polarity gradient (2:1 – 1:2) as the mobile phase. To remove residual impurities from the pre-catalyst, a second column chromatography was done, using DCM/acetone (20:1) as the mobile phase. The pure pre-catalyst (*pre*-**C3**, *ent-pre*-**C3**) was then transferred to a vial and dried under reduced pressure.

5.2.3 General procedure III: Preparation of camphor-derived NHC conjugate acids

The corresponding NHC pre-catalysts (*pre*-**C4** and *pre*-**C5**) were prepared according to a modified literature procedure.[39]

A small flask was charged with a magnetic stirring bar and compound **10** (1.0 eq.). The flask was evacuated under reduced pressure and refilled with argon. Afterwards, the starting material was dissolved in anhydrous THF (62.5 mM with respect to morpholinone), followed by the addition of trimethyloxonium tetrafluoroborate (1.2 eq.) The reaction mixture was left to stir overnight at ambient temperature until ^{1}H NMR showed almost full conversion to the intermediate. The corresponding arylhydrazine (1.5 eq.) was then added to the reaction mixture, which was left to stir overnight at ambient temperature. After this time, the previous intermediate was no longer detected by ^{1}H NMR, and the reaction mixture was therefore concentrated under reduced pressure. The remaining solids were dissolved in chlorobenzene (20 ml for every 2.5 mmol of morpholinone), and triethyl orthoformate (6.3 eq.) was subsequently added to the solution. The reaction mixture was then heated to 110 °C and left to stir at this temperature overnight, until the previous intermediate was no longer detected by ^{1}H NMR. The reaction mixture was concentrated under reduced pressure, and crude pre-catalyst was then isolated by column chromatography, using DCM/acetone (20:1) as the mobile phase. The pure pre-catalyst (*pre*-**C4**, *pre*-**C5**) was then transferred to a vial and dried under reduced pressure.

5.2.4 General procedure IV: Preparation of the benzofuranone spiro-derivative

5.2.4.1 General procedure IVa: Use of the *α*-bromoenal 18 as a starting material

A 4 ml vial was charged with a small magnetic stirring bar and compound **14** (22.2 mg, 0.10 mmol, 1.0 eq.), compound **15** (33.8 mg, 0.15 mmol, 1.5 eq.), and the corresponding *pre*-**Catalyst** (0.02 mmol, 0.2 eq.). The vial contents were dissolved in anhydrous DCM (1 ml, 0.1 M), and finally, triethylamine (28 µl, 0.20 mmol, 2.0 eq.) was added to initiate the reaction. The reaction mixture was left to stir for 72 h at room temperature, with the conversion of the starting materials being monitored by TLC. Once the indicated time had passed, the solvent was removed under reduced pressure. The crude product was purified via column chromatography, using a hexane/EtOAc polarity gradient (12:1 – 8:1) as the mobile phase.

5.2.4.2 General procedure IVb: Use of the enal 25 as a starting material

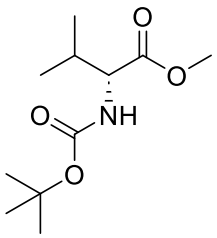
A 4 ml vial was charged with a small magnetic stirring bar and compound **14** (22.2 mg, 0.10 mmol, 1.0 eq.), compound **22** (21.9 mg, 0.15 mmol, 1.5 eq.), *pre*-**C2** (8.3 mg, 0.02 mmol, 0.2 eq.), and the corresponding oxidant (0.15 mmol, in the case of a combination of oxidants 0.01 mmol DQ + 0.50 mmol MnO_2). The vial contents were dissolved in anhydrous DCM (1 ml, 0.1 M), and finally, triethylamine (28 µl, 0.20 mmol, 2.0 eq.) was added to initiate the reaction. The reaction mixture was left to stir at room temperature, until full conversion of the starting material **14** was observed by TLC (16 – 24 h). After this time, the solvent was removed under reduced pressure. The crude product was purified via column chromatography, using a hexane/EtOAc polarity gradient (12:1 – 8:1) as the mobile phase.

5.2.4.3 General procedure IVc: Electrochemical variation

A 5 ml ElectraSyn vial was charged with a magnetic stirring bar and compound **14** (44.4 mg, 0.20 mmol, 1.0 eq.), compound **22** (43.9 mg, 0.30 mmol, 1.5 eq.), *pre*-**C2** (16.5 mg, 0.04 mmol, 0.2 eq.), tetra-*n*-butylammonium iodide (73.9 mg, 0.20 mmol, 1.0 eq.), triethylamine (56 µl, 0.40 mmol, 2.0 eq.), and anhydrous DCM (2 ml, 0.1 M). A rubber cap fitted with a Pt cathode and a Pt anode was inserted into the ElectraSyn vial, and the vial was then connected to the ElectraSyn 2.0 electrochemistry kit. The stirred reaction mixture was electrolysed under a constant current of 1.0 mA for 48 h at room temperature. After this time, TLC had shown continued presence of the starting material **14**, however there was no more remaining enal **22** due to decomposition. Therefore, the solvent was removed under reduced pressure, and the product was purified via column chromatography, using a hexane/EtOAc polarity gradient (12:1 – 8:1) as the mobile phase.

5.3 Synthesised compounds and related spectroscopic data

Boc-D-valine methyl ester (2)

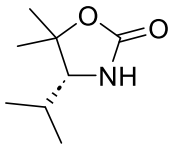


Compound **2** was prepared according to a modified procedure available in literature.[36]

A 250 ml round-bottom flask was charged with a magnetic stirring bar and Boc-D-valine (10.0 g, 46.0 mmol, 1.0 eq.), which was then dissolved in DMF (75 ml). Potassium bicarbonate (9.21 g, 92.0 mmol, 2.0 eq.) was added to the stirred solution, followed by addition of methyl iodide (4.6 ml, 73.6 mmol, 1.6 eq.). The mixture was left to stir at ambient temperature for 5 h, until the starting compound was no longer detected by TLC. At this point, the reaction was quenched by the addition of water (75 ml), the organic phase was separated, and the water phase was extracted with EtOAc (3 × 80 ml). The combined organic phases were washed with brine (1 × 50 ml) and dried with anhydrous $MgSO_4$. After filtration of the solid, the filtrate was concentrated under reduced pressure, and then co-distilled with $CHCl_3$ to afford **2** (10.7 g, quantitative yield) as a brown oil.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -9.8 ($CHCl_3$, *c* = 0.54). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.04 (d, *J* = 9.1 Hz, 1H), 4.22 (dd, *J* = 9.3, 4.9 Hz, 1H), 3.74 (s, 3H), 2.20 – 2.06 (m, 1H), 1.45 (s, 9H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.0, 155.8, 79.9, 58.7, 52.1, 31.4, 28.4, 19.1, 17.7 ppm. **MS (ESI+):** Calculated *m*/*z* for $C_{11}H_{21}NNaO_4$ $[M+Na]^+$: 254.1363, found: 254.1364. The obtained data is consistent with data previously reported in literature.[43]

(*R*)-4-Isopropyl -5,5-dimethyloxazolidin-2-one (4)

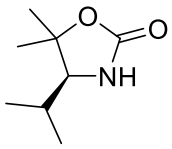


The compound **4** was prepared from compound **2** (10.6 g, 45.8 mmol) according to procedure **I** to afford **4** (1.57 g, 30%, over two steps) as an amorphous orange solid.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -11.0 ($CHCl_3$, *c* = 0.40). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.24 (s, 1H), 3.18 (d, *J* = 8.6 Hz, 1H), 1.83 (dp, *J* = 8.7, 6.6 Hz, 1H), 1.48 (s, 3H), 1.38 (s, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H) ppm. ^{13}C **NMR** (101 MHz, $CDCl_3$) δ 159.1, 84.0, 68.5, 28.7, 28.6, 21.4,

20.1, 20.1 ppm. **MS (ESI+):** Calculated *m*/*z* for $C_8H_{15}NNaO_2$ $[M+Na]^+$: 180.0995, found: 180.0995. The obtained data is consistent with data previously reported in literature.[37]

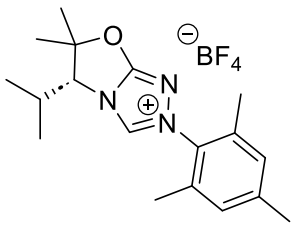
(*S*)-4-Isopropyl -5,5-dimethyloxazolidin-2-one (*ent*-4)



The compound *ent*-**4** was prepared from an impure mixture of Boc-L-valine methyl ester (27.3 g, 118.1 mmol) according to procedure **I** to afford *ent*-**4** (1.47 g, 23%, over two steps) as an amorphous off-white solid.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +11.0 ($CHCl_3$, *c* = 0.37). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.67 (s, 1H), 3.18 (d, *J* = 8.6 Hz, 1H), 1.84 (dp, *J* = 8.7, 6.6 Hz, 1H), 1.49 (s, 3H), 1.39 (s, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H) ppm. **^{13}C NMR, one quaternary carbon not visible** (101 MHz, $CDCl_3$) δ 84.0, 68.4, 28.7, 28.7, 21.5, 20.2, 20.1 ppm. **MS (ESI+):** Calculated *m*/*z* for $C_8H_{15}NNaO_2$ $[M+Na]^+$: 180.0995, found: 180.0997. The obtained data is consistent with data previously reported in literature.[37]

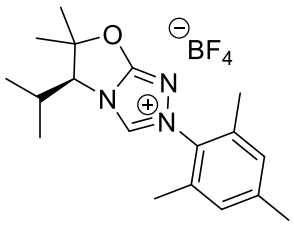
(*R*)-5-Isopropyl-6,6-dimethyl-2-(2,4,6-trimethyl)phenyl-5,6-dihydrooxazolo[2,3-c][1,2,4] triazol-2-ium tetrafluoroborate (*pre*-C3)



Compound *pre*-**C3** was prepared from compound **4** (1.0 g, 6.36 mmol) according to procedure **II** to afford *pre*-**C3** (0.34 g, 14%, over three steps) as an amorphous amber solid. Compared to procedure **II**, additional column chromatography was performed to further purify the product, using hexane/EtOAc (1:3) as the mobile phase.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +29.2 ($CHCl_3$, *c* = 0.45). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.01 (s, 2H), 5.00 (d, *J* = 3.1 Hz, 1H), 2.36 (s, 4H), 2.14 (s, 6H), 1.84 (s, 3H), 1.78 (s, 3H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.8, 142.5, 140.3, 135.4, 131.8, 129.8, 104.4, 71.8, 28.5, 28.5, 21.9, 21.4, 20.7, 17.2, 16.7 ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -151.00 – -151.08 (m) ppm. **MS (ESI+):** Calculated *m*/*z* for $C_{18}H_{26}N_3O$ $[M–BF_4]^+$: 300.2070, found: 300.2070. The obtained data is consistent with data previously reported in literature.[44]

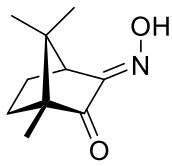
(*S*)-5-Isopropyl-6,6-dimethyl-2-(2,4,6-trimethylphenyl)-5,6-dihydrooxazolo[2,3-c][1,2,4] triazol-2-ium tetrafluoroborate (*ent-pre*-C3)



Compound *ent-pre*-**C3** was prepared from compound *ent*-**4** (0.4 g, 2.54 mmol) according to procedure **II** to afford *ent-pre*-**C3** (0.32 g, 32%, over three steps) as an amorphous dark green solid.

$[\alpha]_D^{20}$ = -23.1 ($CHCl_3$, *c* = 0.46). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.01 (s, 2H), 5.01 (d, *J* = 2.9 Hz, 1H), 2.36 (s, 4H), 2.14 (s, 6H), 1.84 (s, 3H), 1.78 (s, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.8, 142.5, 140.3, 135.5, 131.8, 129.9, 104.4, 71.8, 28.6, 28.6, 21.9, 21.4, 20.7, 17.3, 16.7 ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -150.97 – -151.06 (m) ppm. **MS (ESI+):** Calculated *m*/*z* for $C_{18}H_{26}N_3O$ $[M–BF_4]^+$: 300.2070, found: 300.2067. The obtained data is consistent with data previously reported in literature.[44]

(*E*)-(1*R*)-3-Hydroxyimino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (8)



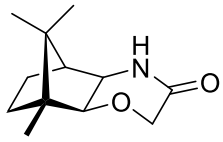
Compound **9** was prepared according to a modified procedure available in literature.[37]

A 500 ml round-bottom flask was charged with a magnetic stirring bar and potassium *tert*-butoxide (14.7 g, 82.0 mmol, 1.25 eq.). The flask was evacuated under reduced pressure and refilled with argon. The solid *tert*-butoxide was then suspended in anhydrous Et_2O (100 ml), and the resulting suspension was cooled to -40 °C (acetone/dry ice cooling bath). This was followed by preparing a solution of D-camphor (10.0 g, 65.6 mmol, 1.0 eq.) in anhydrous Et_2O (32 ml), which was then slowly added to the reaction mixture. Once added, the reaction mixture was left to stir for 1 h at ambient temperature. The flask was then re-cooled to -40 °C (acetone/dry ice cooling bath), and isopentyl nitrite (17.6 ml, 131.2 mmol, 2.0 eq.) was added dropwise to the stirred solution. The reaction mixture was left to stir overnight at ambient temperature. After this time, no more starting material was detected by TLC, therefore the reaction was quenched with water (50 ml). The two phases were separated, and the organic phase was extracted with water (2 × 50 ml). The collected aqueous phases were acidified with concentrated hydrochloric acid (35% *w*/*w*, 5 ml) until the solution had reached pH = 3, forming a precipitate. The precipitate was re-dissolved by the addition of DCM (50 ml), and the phases

were separated, with the water phase being extracted with DCM (2 × 50 ml). The combined organic phases were subsequently washed with a saturated sodium bicarbonate solution (1 × 20 ml), followed by water (1 × 20 ml) and brine (1 × 20 ml). The resulting solution was dried under anhydrous $MgSO_4$, and after filtration of the solid, the filtrate was concentrated under reduced pressure to yield the pure title product **8** (11.0 g, 92%) as an amorphous bright yellow solid.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +159.6 ($CHCl_3$, *c* = 0.47). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.25 (d, *J* = 4.5 Hz, 1H), 2.09 – 1.99 (m, 1H), 1.82 – 1.73 (m, 1H), 1.61 – 1.53 (m, 2H), 1.02 (s, 3H), 0.99 (s, 3H), 0.87 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.4, 159.9, 58.7, 46.8, 45.0, 30.8, 23.9, 20.8, 17.8, 9.1 ppm. **MS (ESI+):** Calculated *m*/*z* for $C_{10}H_{15}NNaO_2$ $[M+Na]^+$: 204.0995, found: 204.0997. The obtained data is consistent with data previously reported in literature.[45]

(1*R*,2*S*,7*R*,8*S*)-(+)-1,11,11-Trimethyl-3-oxa-6-aza-tricyclo-[6.2.1.0(2,7)]undecan-5-one (10)



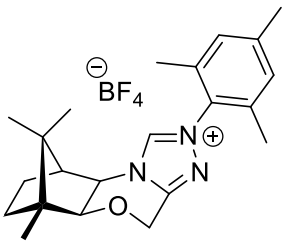
Compound **10** was prepared according to a modified procedure available in literature.[37,38]

A 250 ml round-bottom flask was charged with a magnetic stirring bar and the oxime compound **8** (10.0 g, 55.2 mmol, 1.0 eq.). The flask was evacuated under reduced pressure and refilled with argon. The solid oxime was dissolved in anhydrous THF (30 ml), and the formed solution was cooled to 0 °C (ice/water cooling bath). Once cooled, lithium aluminium hydride (5.92 g, 165.6 mmol, 3.0 eq.) was added in small batches to the stirred solution over the course of 45 min. After addition of the hydride and removal of the flask from the ice bath, the reaction mixture started to rapidly heat, which was dealt with by re-cooling to 0 °C (ice/water cooling bath) and diluting the reaction mixture with additional anhydrous THF (50 ml). The reaction was then heated to 80 °C to reflux, and was left to stir for 1 h, at which point there was no more starting material detected by TLC. After being cooled down to ambient temperature, the reaction was quenched very slowly with EtOAc (5 ml), water (5 ml), and a dilute sodium hydroxide solution (1 M, 50 ml). The resulting thick slurry was filtered through a short pad of Celite®, and the filtrate was concentrated under reduced pressure to afford the aminoisoborneol **9** (8.67 g, 93%). The crude product was immediately used for the next step without further purification.

For the following step, a 500 ml round-bottom flask was charged with a magnetic stirring bar and the aminoisoborneol **9** (4.00 g, 23.6 mmol, 1.0 eq.). The flask was evacuated under reduced pressure, and then refilled with argon. The starting material was then dissolved in anhydrous THF (160 ml), which was followed by the addition of triethylamine (3.32 ml, 23.6 mmol, 1.0 eq.). Upon cooling the solution down to 0 °C (ice/water cooling bath), chloroacetyl chloride (2.1 ml, 26.0 mmol, 1.1 eq.) was added dropwise to the reaction mixture. The reaction was then let to stir at ambient temperature for 4 h, at which point no more starting material was present, as determined by TLC. Thus, the reaction was cooled to 0 °C (ice/water cooling bath), and dilute sodium hydroxide solution (2 M, 80 ml, 141.8 mmol, 6.0 eq.) was added to the reaction mixture. The reaction was left to stir for a further 5 d at ambient temperature, with conversion of the intermediate being watched by ^{1}H NMR. Afterwards, the organic phase was separated, and the water phase was extracted with EtOAc (3 × 80 ml). The combined organic phases were then washed with brine (1 × 75 ml) and dried under anhydrous $MgSO_4$. After filtration of the solid, the filtrate was concentrated under reduced pressure. Column chromatography, using hexane/EtOAc (1:3) as the mobile phase, afforded the morpholinone **10** (1.72 g, 35%, over two steps) as an amorphous glittery white solid.

$[\alpha]_D^{20}$ = +93.5 ($CHCl_3$, *c* = 0.39). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.01 (s, 1H), 4.13 (d, *J* = 15.5 Hz, 1H), 3.78 (d, *J* = 15.5 Hz, 1H), 3.66 (d, *J* = 7.1 Hz, 1H), 3.37 (dd, *J* = 7.1, 1.1 Hz, 1H), 1.81 – 1.69 (m, 2H), 1.63 – 1.52 (m, 1H), 1.12 (s, 3H), 1.10 – 1.00 (m, 2H), 0.99 (s, 3H), 0.85 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 84.0, 66.5, 58.7, 50.9, 33.1, 26.0, 22.2, 20.7, 11.3 ppm. **MS (ESI+):** Calculated *m/z* for $C_{12}H_{19}NNaO_2$ $[M+Na]^+$: 232.1308, found: 232.1309. The obtained data is consistent with data previously reported in literature.[37]

(5a*S*,6*R*,9*S*,9a*R*)-6,11,11-Trimethyl-2-(2,4,6-trimethylphenyl)-5a,6,7,8,9,9a-hexahydro-4H-6,9-methano-benzo[b][1,2,4]triazolo[4,3-d][1,4]oxazin-2-ium tetrafluoroborate (*pre*-C4)

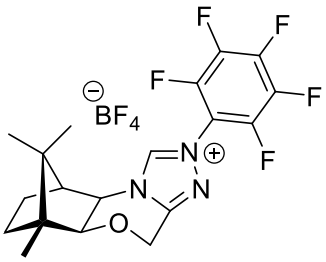


Compound *pre*-**C4** was prepared from compound **10** (0.5 g, 2.39 mmol) according to procedure **III** to afford *pre*-**C4** (0.51 g, 49%, over three steps) as an amorphous amber solid.

$[\alpha]_D^{20}$ = +17.3 ($CHCl_3$, *c* = 0.41). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.01 (s, 2H), 5.06 (d, *J* = 14.9 Hz, 1H), 4.70 (d, *J* = 14.9 Hz, 1H), 4.60 (d, *J* = 7.0 Hz,

1H), 4.13 (d, *J* = 6.8 Hz, 1H), 2.62 (d, *J* = 4.6 Hz, 1H), 2.37 (s, 3H), 2.04 (s, 6H), 1.92 (ddd, *J* = 17.5, 12.5, 4.7 Hz, 1H), 1.65 (td, *J* = 12.7, 3.9 Hz, 1H), 1.41 (ddd, *J* = 13.3, 9.3, 4.0 Hz, 1H), 1.25 (ddd, *J* = 13.8, 9.3, 4.8 Hz, 1H), 1.04 (s, 3H), 0.89 (s, 3H), 0.68 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* 151.2, 143.4, 142.3, 129.9, 84.3, 61.0, 58.9, 50.7, 50.0, 48.4, 32.8, 25.5, 21.4, 21.3, 20.4, 17.2, 11.2 ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) *δ* -151.84 – -151.93 (m) ppm. **MS (ESI+):** Calculated *m*/*z* for $C_{22}H_{30}N_3O$ $[M–BF_4]^+$: 352.2383, found: 352.2383. The obtained data is consistent with data previously reported in literature.[39]

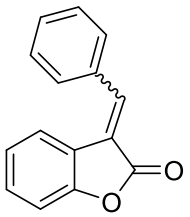
(5a*S*,6*R*,9*S*,9a*R*)-6,11,11-Trimethyl-2-(2,3,4,5,6-pentafluorophenyl)-5a,6,7,8,9,9a-hexahyd-4H-6,9-methano-benzo[b][1,2,4]triazolo[4,3-d][1,4]oxazin-2-ium tetrafluoroborate (*pre*-C5)



Compound *pre*-**C5** was prepared from compound **10** (0.5 g, 2.39 mmol) according to procedure **III** to afford *pre*-**C5** (0.57 g, 49%, over three steps) as an amorphous pale pink solid.

$[\alpha]_D^{20}$ = +30.9 ($CHCl_3$, *c* = 0.47). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 10.16 (s, 1H), 5.04 (d, *J* = 14.9 Hz, 1H), 4.75 (d, *J* = 15.0 Hz, 1H), 4.56 (d, *J* = 7.0 Hz, 1H), 4.14 (d, *J* = 7.0 Hz, 1H), 2.47 (d, *J* = 4.6 Hz, 1H), 1.97 (tt, *J* = 13.1, 4.7 Hz, 1H), 1.67 (td, *J* = 12.7, 3.9 Hz, 1H), 1.38 (ddd, *J* = 13.0, 9.3, 3.8 Hz, 1H), 1.33 – 1.22 (m, 1H), 1.03 (s, 3H), 0.91 (s, 3H), 0.64 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* 152.4, 145.6, 84.1, 61.2, 58.8, 50.4, 49.8, 48.6, 32.6, 25.4, 21.2, 20.0, 11.1 ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) *δ* -144.96 – -145.14 (m), -145.88 (tt, *J* = 21.5, 4.1 Hz), -152.56 – -152.66 (m), -158.80 – -158.98 (m) ppm. **MS (ESI+):** Calculated *m*/*z* for $C_{19}H_{19}F_5N_3O$ $[M–BF_4]^+$: 400.1443, found: 400.1446. The obtained data is consistent with data previously reported in literature.[39]

(*E*/*Z*)-3-Benzylidenebenzofuran-2(3*H*)-one (14)



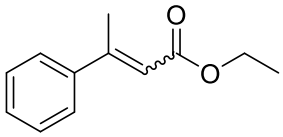
Compound **14** was prepared according to a modified procedure available in literature.[41]

A 100 ml flask was charged with a magnetic stirring bar and benzofuran-2(3*H*)-one (1.0 g, 7.46 mmol, 1.0 eq.). The starting material was dissolved in EtOH (20 ml), and benzaldehyde (0.75 ml, 7.46 mmol, 1.0 eq.) was then added to the stirred solution along with piperidine (74 µl, 0.75 mmol, 0.1 eq.). The reaction was left to stir overnight at

ambient temperature. After this time, the reaction mixture was concentrated under reduced pressure, and the remaining solids were dissolved in $CHCl_3$ (25 ml). To remove all residual benzaldehyde, saturated sodium bisulfite solution (20 ml) was added to the solution, and the resulting biphasic system was left to stir vigorously for 30 min. Afterwards, the water phase was discarded, and the stirring procedure was repeated three more times, each time with additional saturated sodium bisulfite solution (20 ml). Once no more benzaldehyde was detected in the mixture by TLC, the organic phase was dried under anhydrous $MgSO_4$. The solids were filtered out, and the filtrate was concentrated under reduced pressure. Column chromatography, using hexane/EtOAc (12:1) as the mobile phase, yielded the title product **14** (0.63 g, 38%) as a 5/1 *E*/*Z* mixture of isomers (determined by ^{1}H NMR), in the form of an amorphous neon yellow solid.

^{1}H NMR, *E*-isomer (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.73 (ddd, J = 7.8, 1.3, 0.6 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.54 – 7.44 (m, 3H), 7.35 (td, J = 7.8, 1.3 Hz, 1H), 7.15 (dt, J = 8.1, 0.9 Hz, 1H), 7.04 (td, J = 7.7, 1.1 Hz, 1H) ppm. **^{1}H NMR, *Z*-isomer** (400 MHz, $CDCl_3$) δ 8.22 – 8.16 (m, 2H), 7.64 (s, 1H), 7.55 (ddd, J = 7.7, 1.3, 0.6 Hz, 1H), 7.18 (td, J = 7.6, 1.0 Hz, 1H), 7.11 (dt, J = 8.0, 0.9 Hz, 1H) ppm. **^{13}C NMR, *E*-isomer** (101 MHz, $CDCl_3$) δ 169.1, 154.7, 141.1, 134.2, 131.1, 130.7, 129.5, 129.0, 123.8, 122.9, 122.5, 122.0, 111.4 ppm. **^{13}C NMR, *Z*-isomer** (101 MHz, $CDCl_3$) δ 140.5, 132.1, 131.5, 130.0, 128.7, 123.9, 119.6, 111.0 ppm. **MS (ESI+):** Calculated *m*/*z* for $C_{15}H_{11}O_2$ $[M+H]^+$: 223.0754, found: 223.0756. The obtained data is consistent with data previously reported in literature.[46]

(*E*/*Z*)-Ethyl 3-phenylbut-2-enoate (20)



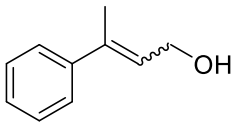
Compound **20** was prepared according to a modified procedure available in literature.[35]

A 100 ml flask was charged with a magnetic stirring bar, evacuated under reduced pressure, and refilled with argon. Next, anhydrous THF (20 ml) was added to the flask, followed by sodium hydride (60% *w*/*w* in mineral oil, 0.15 g, 6.24 mmol, 1.5 eq.). The formed suspension was cooled to 0 °C (ice/water cooling bath), and thereafter, triethyl phosphonoacetate (1.41 ml, 7.07 mmol, 1.7 eq.) was added dropwise. After removing from the cooling bath, acetophenone (0.5 ml, 4.16 mmol, 1.0 eq.) dissolved in anhydrous THF (5 ml) was added to the reaction mixture. The reaction was left to stir at ambient temperature overnight, until TLC showed no

more presence of starting material. The reaction was quenched by addition of water (10 ml), followed by separation of the two phases, and extraction of the water phase with EtOAc (3 × 10 ml). The combined organic phases were dried under anhydrous $MgSO_4$, followed by filtration of the solid, and concentration of the filtrate under reduced pressure. Column chromatography, using hexane/EtOAc (10:1) as the mobile phase, yielded the pure ester product **20** (0.48 g, 61%) as a 5/1 mixture of *E*/*Z* isomers (determined by ^{1}H NMR), in the form of a colourless oil.

^{1}H NMR, *E*-isomer (400 MHz, $CDCl_3$) δ 7.51 – 7.44 (m, 2H), 7.41 – 7.34 (m, 3H), 6.14 (q, J = 1.3 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.58 (d, J = 1.3 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H) ppm. **^{1}H NMR, *Z*-isomer** (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 3H), 7.22 – 7.18 (m, 2H), 5.91 (q, J = 1.5 Hz, 1H), 4.00 (q, J = 7.2 Hz, 2H), 2.18 (d, J = 1.5 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR, *E*-isomer** (101 MHz, $CDCl_3$) δ 167.0, 155.7, 142.4, 129.1, 128.6, 126.5, 117.4, 60.0, 18.1, 14.5 ppm. **^{13}C NMR, *Z*-isomer** (101 MHz, $CDCl_3$) δ 128.0, 127.9, 127.0, 117.9, 59.9, 27.3, 14.1 ppm. **MS (ESI+):** Calculated *m*/*z* for $C_{12}H_{14}NaO_2$ $[M+Na]^+$: 213.0886, found: 213.0891. The obtained data is consistent with data previously reported in literature.[47]

(*E*/*Z*)-3-Phenylbut-2-en-1-ol (21)



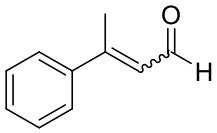
Compound **21** was prepared according to a modified procedure available in literature.[35]

A 500 ml round-bottom flask was charged with a magnetic stirring bar and the ester compound **20** (4.75 g, 25.0 mmol, 1.0 eq.). The flask was evacuated under reduced pressure and refilled with argon, with the ester then being dissolved in anhydrous DCM (70 ml). Upon cooling the solution to -78 °C (acetone/dry ice cooling bath), a solution of DIBAL-H (25% *w*/*w* in toluene, 35.5 ml, 62.4 mmol, 2.5 eq.) was added dropwise. After the addition, the reaction mixture was left to stir for 1 h at -78 °C. At this point, TLC had detected that some starting material was still left in the mixture, and so additional DIBAL-H solution (7 ml, 12.5 mmol, 0.5 eq.) was added. After another 10 min of stirring at -78 °C, the reaction was removed from the cooling bath and quenched with water (30 ml), turning the liquid mixture into a gel. The gel was loosened by the slow addition of a dilute sodium hydroxide solution (2 M, 50 ml), followed by 30 min of stirring. The organic phase was then separated, and the water phase was extracted with DCM (3 × 100 ml). The combined organic phases were dried

under anhydrous $MgSO_4$, and after filtering out the solid, the filtrate was concentrated under reduced pressure. Column chromatography, using a hexane/EtOAc polarity gradient (3:1 – pure EtOAc) as the mobile phase, afforded the alcohol product **21** (3.33 g, 90%) as a 5/1 mixture of *E*/*Z* isomers (determined by ^{1}H NMR), in the form of a colourless oil.

^{1}H NMR, *E*-isomer (400 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 2H), 7.37 – 7.30 (m, 2H), 7.30 – 7.24 (m, 1H), 5.98 (tq, J = 6.7, 1.4 Hz, 1H), 4.37 (dt, J = 6.7, 0.9 Hz, 2H), 2.09 (dd, J = 1.4, 0.8 Hz, 3H), 1.55 (s, 1H) ppm. **^{1}H NMR, *Z*-isomer** (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (3H, protons hidden under majority isomer signal), 7.20 – 7.16 (m, 2H), 5.75 – 5.69 (m, 1H), 4.10 – 4.06 (m, 2H), 2.09 (3H, protons hidden under majority isomer signal) ppm. **^{13}C NMR, *E*-isomer** (101 MHz, $CDCl_3$) δ 143.0, 138.1, 128.4, 127.4, 126.6, 125.9, 60.1, 16.2 ppm. **^{13}C NMR, *Z*-isomer** (101 MHz, $CDCl_3$) δ 140.9, 140.4, 128.3, 127.9, 127.3, 126.2, 60.4, 25.5 ppm. **MS (ESI-):** Calculated *m*/*z* for $C_{10}H_{11}O$ $[M-H]^-$: 147.0804, found: 147.0805. The obtained data is consistent with data previously reported in literature.[48,49]

(*E*/*Z*)-3-Phenylbut-2-enal (22)

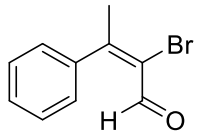


Compound **22** was prepared according to a modified procedure available in literature.[35]

A 250 ml round-bottom flask was charged with a magnetic stirring bar and the alcohol **21** (2.62 g, 17.7 mmol, 1.0 eq.). The flask was then evacuated under reduced pressure and was refilled with argon. The alcohol was then dissolved in anhydrous DCM (60 ml), and the reaction mixture was cooled to 0 °C (ice/water cooling bath). At this temperature, Dess-Martin periodinane (8.25 g, 19.5 mmol, 1.1 eq.) was added to the reaction mixture, and the milky solution was left to stir for 40 min, followed by 1 h of stirring at ambient temperature. As no more starting material was detected by TLC, two thirds of the solvent were removed under reduced pressure. The remaining crude solution was mixed with a few spoonfuls of silica gel and was then concentrated under reduced pressure. The formed solids were immediately transferred on top of the stationary phase for column chromatography, which was performed with hexane/EtOAc (10:1) as the mobile phase. This yielded the unstable aldehyde product **22** (2.06 g, 80%) as a 6/1 mixture of *E*/*Z* isomers (determined by ^{1}H NMR), in the form of a colourless oil.

^{1}H NMR, *E*-isomer (400 MHz, $CDCl_3$) δ 10.19 (d, J = 7.8 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.45 – 7.39 (m, 3H), 6.40 (dq, J = 7.9, 1.3 Hz, 1H), 2.58 (d, J = 1.3 Hz, 3H) ppm. **^{13}C NMR, *E*-isomer** (101 MHz, $CDCl_3$) δ 191.4, 157.8, 140.7, 130.2, 128.9, 127.4, 126.4, 16.6 ppm. **MS (ESI+):** Calculated m/z for $C_{10}H_{11}O$ $[M+H]^+$: 147.0804, found: 147.0807. The obtained data is consistent with data previously reported in literature.[50]

(*E*)-2-Bromo-3-phenylbut-2-enal (15)

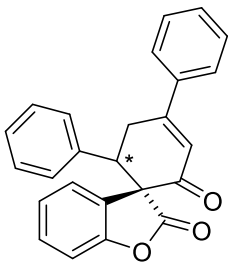


Compound **15** was prepared according to a modified procedure available in literature.[35]

A 100 ml flask was charged with a magnetic stirring bar and the enal **22** (2.06 g, 14.1 mmol, 1.0 eq.). The flask was evacuated under reduced pressure and refilled with argon. Afterwards, anhydrous DCM (40 ml) was added to the enal, and the solution was cooled to -78 °C (acetone/dry ice cooling bath). Bromine (0.87 ml, 16.9 mmol, 1.2 eq.) was then added to the solution dropwise, and the reaction mixture was left to stir at -78 °C for 1 h. After TLC showed full conversion of the starting material, pyridine (4.56 ml, 56.4 mmol, 4.0 eq.) was slowly added to the reaction mixture. Afterwards, the flask was taken out of the cooling bath, and the reaction was left to stir for 1 h at ambient temperature. As the intermediate was no longer detected by TLC, the reaction mixture was washed with a sodium thiosulfate solution (2 × 50 ml). After separating the phases, the water phase was extracted with DCM (3 × 50 ml), and the combined organic phases were dried with $MgSO_4$. After filtration of the solid, the filtrate was concentrated under reduced pressure. The crude product was isolated by column chromatography, using hexane/EtOAc (30:1) as the mobile phase, yielding the mostly pure α-bromoenal. To remove the remaining impurities, another column chromatography was performed, again using hexane/EtOAc (30:1) as the mobile phase. This yielded compound **15** (0.70 g, 22%) as the *E*-isomer (determined by ^{1}H NMR), in the form of a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.47 – 7.38 (m, 3H), 7.32 – 7.24 (m, 2H), 2.54 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 185.1, 161.6, 138.8, 129.6, 128.8, 128.6, 126.4, 28.2 ppm. **MS (ESI+):** Calculated m/z for $C_{10}H_{10}BrO$ $[M+H]^+$: 224.9910, found: 224.9910. The obtained data is consistent with data previously reported in literature.[35]

(3*S*,6'*R*/*S*)-4',6'-Diphenyl-2*H*-spiro[benzofuran-3,1'-cyclohexan]-3'-ene-2,2'-dione (16a/16b)



Compound **16** was prepared according to a procedure **IVb**, using DQ (61.3 mg, 0.15 mmol) as the oxidant, yielding a mix of diastereomers **16a**/**16b** (34.2 mg, 94% combined yield) as an amorphous off-white solid. The title compound was isolated as a poorly separable mixture of diastereomers (*dr* = 4.8/1.0).

95%/55% *ee* (**16a**/**16b**), enantiomeric excesses of the diastereomeric products were determined by HPLC using a Chiralpak® IH column (heptane/*i*-PrOH – 60:40, flow rate = 1.0 ml/min, λ = 289 nm), for **16a**: t_R = 19.4 min (major), t_R = 32.2 min (minor); for **16b**: t_R = 16.1 min (major), t_R = 9.7 min (minor).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -93.2 ($CHCl_3$, *c* = 0.39). **^{1}H NMR, 16a isomer** (400 MHz, $CDCl_3$) δ 7.74 – 7.66 (m, 2H), 7.55 – 7.45 (m, 3H), 7.32 (ddt, J = 8.5, 3.6, 1.4 Hz, 2H), 7.21 – 7.11 (m, 4H), 6.98 (dd, J = 8.5, 1.1 Hz, 1H), 6.96 – 6.92 (m, 2H), 6.74 (d, J = 2.2 Hz, 1H), 4.20 (dd, J = 11.9, 4.8 Hz, 1H), 3.54 (ddd, J = 19.0, 11.9, 2.4 Hz, 1H), 3.26 (dd, J = 19.0, 4.9 Hz, 1H) ppm. **^{13}C NMR, 16a isomer** (101 MHz, $CDCl_3$) δ 191.9, 173.6, 159.9, 153.8, 137.3, 136.8, 131.3, 130.3, 129.3, 128.7, 128.4, 126.5, 124.3, 124.1, 123.3, 111.9, 64.6, 47.0, 31.8 ppm. **MS (ESI+):** Calculated *m*/*z* for $C_{25}H_{19}O_3$ $[M+H]^+$: 367.1329, found: 367.1326. The obtained data is consistent with data previously reported in literature.[51]

6. Conclusion

This bachelor's thesis was concerned with the preparation of four distinct triazole-containing NHC conjugate acids, derived from chiral natural precursors, valine and D-camphor. The suggested conjugate acids were successfully prepared in high purity, with yields ranging from 14 – 49% for the final step. The yields were higher for the camphor-derived pre-catalysts, potentially being explained by the slightly different conditions used during cyclisation with triethyl orthoformate in the very last step, and only one column chromatography being required to purify the product.

These NHC precursors were then subject to being used as catalysts in a spiroannulation reaction between a benzylidene benzofuranone derivative and an α-bromoenal. In total, seven NHC precursors were tested, with an aminoindanone-derived NHC precursor performing the best in terms of both the isolated yield and the reaction stereocontrol.

Additionally, other approaches to generating the key azolium-dienolate intermediate present in this reaction were investigated on an analogous spiroannulation reaction. The key intermediate was generated from an aldehyde substrate oxidatively, either through an external oxidant, or by electrochemical means.

7. References

(1) Sekhon B. Exploiting the Power of Stereochemistry in Drugs: An Overview of Racemic and Enantiopure Drugs. *J. Mod. Med. Chem.* **2013**, 10–36. https://doi.org/10.12970/2308-8044.2013.01.01.2.

(2) McVicker, R. U.; O'Boyle, N. M. Chirality of New Drug Approvals (2013-2022): Trends and Perspectives. *J. Med. Chem.* **2024**, *67*, 2305–2320. https://doi.org/10.1021/acs.jmedchem.3c02239.

(3) Han, B.; He, X. H.; Liu, Y. Q.; He, G.; Peng, C.; Li, J. L. Asymmetric Organocatalysis: An Enabling Technology for Medicinal Chemistry. *Chem. Soc. Rev*. **2021**, *50*, 1522–1586. https://doi.org/10.1039/d0cs00196a.

(4) Reyes, E.; Prieto, L.; Milelli, A. Asymmetric Organocatalysis: A Survival Guide to Medicinal Chemists. *Molecules* **2022**, *28*, 271. https://doi.org/10.3390/molecules28010271.

(5) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An Overview of N-Heterocyclic Carbenes. *Nature* **2014**, *510*, 485–496. https://doi.org/10.1038/nature13384.

(6) Arduengo, A. J.; Harlow, R. L.; Kline, M. A Stable Crystalline Carbene. *J. Am. Chem. Soc.* **1991**, *113*, 361–363. https://doi.org/10.1021/ja00001a054.

(7) Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J. -P; Ebel, K.; Brode, S. Preparation, Structure, and Reactivity of 1,3,4-Triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene, a New Stable Carbene. *Angew. Chem. Int. Ed.* **1995**, *34*, 1021–1023. https://doi.org/10.1002/anie.199510211.

(8) Mahatthananchai, J.; Bode, J. W. The Effect of the N-Mesityl Group in NHC-Catalyzed Reactions. *Chem. Sci.* **2012**, *3*, 192–197. https://doi.org/10.1039/c1sc00397f.

(9) Hollóczki, O.; Kelemen, Z.; Nyulászi, L. On the Organocatalytic Activity of N-Heterocyclic Carbenes: Role of Sulfur in Thiamine. *J. Org. Chem.* **2012**, *77*, 6014–6022. https://doi.org/10.1021/jo300745e.

(10) Jansen, B. C. P. The Physiology of Thiamine. *Vitam. Horm.* **1949**, *7*, 83–110. https://doi.org/10.1016/S0083-6729(08)60825-0.

(11) Breslow, R. On the Mechanism of Thiamine Action. IV. Evidence from Studies on Model Systems. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726. https://doi.org/10.1021/ja01547a064.

(12) Menon, R. S.; Biju, A. T.; Nair, V. Recent Advances in N-Heterocyclic Carbene (NHC)-Catalysed Benzoin Reactions. *Beilstein J. Org. Chem.* **2016**, *12*, 444–461. https://doi.org/10.3762/bjoc.12.47.

(13) Heravi, M. M.; Zadsirjan, V.; Kafshdarzadeh, K.; Amiri, Z. Recent Advances in Stetter Reaction and Related Chemistry: An Update. *Asian J. Org. Chem.* **2020**, *9*, 1999–2034. https://doi.org/10.1002/ajoc.202000378.

(14) Li, M. M.; Chen, X.; Deng, Y.; Lu, J. Recent Advances of N-Heterocyclic Carbenes in the Applications of Constructing Carbo- And Heterocyclic Frameworks with Potential Biological Activity. *RSC Adv.* **2021**, *11*, 38060–38078. https://doi.org/10.1039/d1ra06155k.

(15) Holm, S. C.; Straub, B. F. Synthesis of N-Substituted 1,2,4-Triazoles. a Review. *Org. Prep. Proced. Int.* **2011**, *43*, 319–347. https://doi.org/10.1080/00304948.2011.593999.

(16) Knight, R. L.; Leeper, F. J. Comparison of Chiral Thiazolium and Triazolium Salts as Asymmetric Catalysts for the Benzoin Condensation. *J. Chem. Soc., Perkin Trans. 1* **1998**, *12*, 1891–1894. https://doi.org/10.1039/a803635g.

(17) Kerr, M. S.; Read De Alaniz, J.; Rovis, T. An Efficient Synthesis of Achiral and Chiral 1,2,4-Triazolium Salts: Bench Stable Precursors for N-Heterocyclic Carbenes. *J. Org. Chem.* **2005**, *70*, 5725–5728. https://doi.org/10.1021/jo050645n.

(18) Ma, Y.; Wei, S.; Wu, J.; Yang, F.; Liu, B.; Lan, J.; Yang, S.; You, J. From Mono-Triazolium Salt to Bis-Triazolium Salt: Improvement of the Asymmetric Intermolecular Benzoin Condensation. *Adv. Synth. Catal.* **2008**, *350*, 2645–2651. https://doi.org/10.1002/adsc.200800371.

(19) Ma, Y.; Wei, S.; Lan, J.; Wang, J.; Xie, R.; You, J. Pyrido[1,2-a][1,2,4]Triazol-3-Ylidenes as a New Family of Stable Annulated N-Heterocyclic Carbenes: Synthesis, Reactivity, and Their Application in Coordination Chemistry and Organocatalysis. *J. Org. Chem.* **2008**, *73*, 8256–8264. https://doi.org/10.1021/jo801349d.

(20) Iglesias-Sigüenza, J.; Ros, A.; Díez, E.; Alcarazo, M.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. Synthesis, Structure and Properties of [1,2,4]Triazolo[4,3-a]Pyridin-3-Ylidene Rhodium and Palladium Complexes. *Dalton Trans.* **2009**, *35*, 7113–7120. https://doi.org/10.1039/b907043e.

(21) Eicher, T.; Hünig, S.; Hansen, H. Alkoxy-Diazenium-Salze, III. Acyldiazene Durch Reaktion Mit Carboxylaten. *Chem. Ber.* **1969**, *102*, 2889–2899. https://doi.org/10.1002/cber.19691020903.

(22) Boyd, G. V.; Summers, A. J. H. The Action of Amines on 1,3,4-Oxadiazolium Salts. *J. Chem. Soc. C* **1971**, *0*, 409–414. https://doi.org/10.1039/j39710000409.

(23) Enders, D.; Gielen, H. Synthesis of Chiral Triazolinylidene and Imidazolinylidene Transition Metal Complexes and First Application in Asymmetric Catalysis. *J. Organomet. Chem.* **2001**, *617–618*, 70–80. https://doi.org/10.1016/S0022-328X(00)00600-8.

(24) Chen, D.; Reibenspies, J.; Burgess, K. New Optically Active N-Heterocyclic Carbene Complexes for Hydrogenation: A Tale with an Atropisomeric Twist. *Organometallics* **2007**, *26*, 855–859. https://doi.org/10.1021/om061013.

(25) O'Toole, S. E.; Connon, S. J. The Enantioselective Benzoin Condensation Promoted by Chiral Triazolium Precatalysts: Stereochemical Control via Hydrogen Bonding. *Org. Biomol. Chem.* **2009**, *7*, 3584–3593. https://doi.org/10.1039/b908517c.

(26) Ros, A.; Alcarazo, M.; Iglesias-Sigüenza, J.; Díez, E.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. Stereoselective Synthesis of Rhodium(I) 4-(Dialkylamino)Triazol-5-Ylidene Complexes. *Organometallics* **2008**, *27*, 4555–4564. https://doi.org/10.1021/om800533g.

(27) Castellano, S.; Stefancich, G.; Musiu, C.; Colla, P. La. A New Class of Antifungal Agents. Synthesis and Antimycotic Activity of Disubstituted N-Azolylamines. *Arch. Pharm.* **2000**, *333*, 299–304. https://doi.org/10.1002/1521-4184(20009)333:9<299::AID-ARDP299>3.0.CO;2-F.

(28) Enders, D.; Breuer, K.; Kallfass, U.; Balensiefer, T. Preparation and Application of 1,3,4-Triphenyl-4,5-Dihydro-1H-1,2,4-Triazol-5-Ylidene, A Stable Carbene. *Synthesis* **2003**, *2003*, 1292–1295. https://doi.org/10.1055/s-2003-39409.

(29) Martí, J.; Castells J.; López-Calahorra, F. Introduction to a Rational Design of Chiral Thiazolium Salts. *Tetrahedron Lett.* **1993**, *34*, 521–524. https://doi.org/10.1016/0040-4039(93)85117-F.

(30) Gerhard, A. U.; Leeper, F. J. Synthesis of and Asymmetric Induction by Chiral Polycyclic Thiazolium Salts. *Tetrahedron Lett.* **1997**, *38*, 3615–3618. https://doi.org/10.1016/s0040-4039(97)00682-5.

(31) Enders, D.; Breuer, K.; Teles, J. H. 105. A Novel Asymmetric Benzoin Reaction Catalyzed by a Chiral Triazolium Salt: Preliminary Communication. *Helv. Chim. Acta* **1996**, *79*, 1217–1221. https://doi.org/10.1002/hlca.19960790427.

(32) Benhamou, L.; Chardon, E.; Lavigne, G.; Bellemin-Laponnaz, S.; César, V. Synthetic Routes to N-Heterocyclic Carbene Precursors. *Chem. Rev.* **2011**, *111*, 2705–2733. https://doi.org/10.1021/cr100328e.

(33) Jia, M. Q.; You, S. L. N-Heterocyclic Carbene-Catalyzed Enantioselective Intramolecular N-Tethered Aldehyde-Ketone Benzoin Reactions. *ACS Catal.* **2013**, *3*, 622–624. https://doi.org/10.1021/cs4000014.

(34) Yao, H.; Zhou, Y.; Chen, X.; Zhang, P.; Xu, J.; Liu, H. N-Heterocyclic Carbene Catalytic [4 + 2] Cyclization of 3-Alkylenyloxindoles with Enals: Γ-Carbon Activation for Enantioselective Assembly of Spirocarbocyclic Oxindoles. *J. Org. Chem.* **2016**, *81*, 8888–8899. https://doi.org/10.1021/acs.joc.6b01596.

(35) Lóška, L.; Dočekal, V.; Císařová, I.; Veselý, J. Stereoselective N-Heterocyclic-Carbene-Catalyzed Formal [4 + 2] Cycloaddition: Access to Chiral Heterocyclic Cyclohexenones. *Org. Lett.* **2023**, *25*, 174–178. https://doi.org/10.1021/acs.orglett.2c04021.

(36) Hamada, Y.; Shibata, M.; Sugiura, T.; Kato, S.; Shioiri, T. New Methods and Reagents in Organic Synthesis. 67. A General Synthesis of Derivatives of Optically Pure 2-(l-Aminoalkyl)Thiazole-4-Carboxylic Acids. *J. Org. Chem.* **1987**, *52*, 1252–1255. https://doi.org/10.1021/jo00383a014.

(37) Campbell, C. D.; Concellón, C.; Smith, A. D. Catalytic Enantioselective Steglich Rearrangements Using Chiral N-Heterocyclic Carbenes. *Tetrahedron Asymmetry* **2011**, *22*, 797–811. https://doi.org/10.1016/j.tetasy.2011.04.001.

(38) Periasamy, M.; Sanjeevakumar, N.; Reddy, P. O. Convenient Methods to Access Chiral Camphanyl Amine Derivatives by Sodium Borohydride Reduction of D-(–)-Camphorquinone Imines. *Synthesis* **2012**, *44*, 3185–3190. https://doi.org/10.1055/s-0032-1317012.

(39) Li, Y.; Feng, Z.; You, S. L. D-Camphor-Derived Triazolium Salts for Catalytic Intramolecular Crossed Aldehyde–Ketone Benzoin Reactions. *Chem. Commun.* **2008**, *19*, 2263–2265. https://doi.org/10.1039/b801004h.

(40) Cossy, J.; Guérinot, A. Natural Products Containing Oxygen Heterocycles—Synthetic Advances Between 1990 and 2015. *Adv. Heterocycl. Chem.* **2016**, *119*, 107–142. https://doi.org/10.1016/bs.aihch.2016.03.002.

(41) Dočekal, V.; Formánek, B.; Císařová, I.; Veselý, J. A Formal [4 + 2] Cycloaddition of Sulfur-Containing Alkylidene Heterocycles with Allenic Compounds. *Org. Chem. Front.* **2019**, *6*, 3259–3263. https://doi.org/10.1039/c9qo00886a.

(42) Zhou, P.; Li, W.; Lan, J.; Zhu, T. Electroredox Carbene Organocatalysis with Iodide as Promoter. *Nat. Commun.* **2022**, *13*, 1–9. https://doi.org/10.1038/s41467-022-31453-7.

(43) Burkhardt, I.; Lauterbach, L.; Brock, N. L.; Dickschat, J. S. Chemical Differentiation of Three DMSP Lyases from the Marine Roseobacter Group. *Org. Biomol. Chem.* **2017**, *15*, 4432–4439. https://doi.org/10.1039/c7ob00913e.

(44) Lóška, L. Enantioselektívna Syntéza Chirálnych Cyklohexenónov Pomocou NHC Katalýzy. Diploma Thesis, Charles University, **2021**.

(45) Ruppenthal, S.; Brückner, R. Asymmetric Sulfinylations of N-Methylephedrine-Modified Tri- or Tetraalkyl Zincates by Symmetric Diaryl Sulfoxides. *Eur. J. Org. Chem.* **2018**, *2018*, 2518–2530. https://doi.org/10.1002/ejoc.201701603.

(46) Sahani, R. L.; Patil, M. D.; Wagh, S. B.; Liu, R. S. Catalytic Transformations of Alkynes into Either α-Alkoxy or α-Aryl Enolates: Mannich Reactions by Cooperative Catalysis and Evidence for Nucleophile-Directed Chemoselectivity. *Angew. Chem. Int. Ed.* **2018**, *57*, 14878–14882. https://doi.org/10.1002/anie.201806883.

(47) Wei, Y.-M.; Ma, X.-D.; Wang, L.; Duan, X.-F.; Li, R.; Chemcomm, /; Communication, C. Iron-Catalyzed Stereospecific Arylation of Enol Tosylates Using Grignard Reagents. *Chem. Commun.* **2020**, *56*, 1101–1104. https://doi.org/10.1039/c9cc09522e.

(48) Jäger, C.; Haase, M.; Koschorreck, K.; Urlacher, V. B.; Deska, J. Aerobic C−N Bond Formation through Enzymatic Nitroso-Ene-Type Reactions. *Angew. Chem. Int. Ed.* **2023**, *62*, e202213671. https://doi.org/10.1002/anie.202213671.

(49) Zhou, X.; Zhang, G.; Huang, R.; Huang, H. Palladium-Catalyzed Allyl-Allyl Reductive Coupling of Allylamines or Allylic Alcohols with H_2 as Sole Reductant. *Org. Lett.* **2021**, *23*, 365–369. https://doi.org/10.1021/acs.orglett.0c03865.

(50) Ghosh, B.; Harariya, M. S.; Mukherjee, S. Catalytic Enantioselective de Novo Construction of Chiral Arenes through Desymmetrizing Oxidative [4+2]-Cycloaddition. *Angew. Chem. Int. Ed.* **2022**, *61*, e202204523. https://doi.org/10.1002/anie.202204523.

(51) Lóška, L.; Dočekal, V.; Čermák, D.; Petrželová, S.; Pour, M.; Císařová, I.; Konečná, K.; Janďourek, O.; Veselý, J. Stereoselective N-Heterocyclic-Carbene-Catalyzed Spiroannulation as an Access towards Spirobenzofuranone-Fused Cyclohexenones. *ChemRxiv* **2024**. https://doi.org/10.26434/chemrxiv-2024-sfxq8.