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Development of Metal-Free Methodologies for the Synthesis of Biologically Relevant Compounds

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by

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G. Goebel, "Development of Novel Hypervalent Iodine Catalysts for Asymmetric α-Functionalization of Ketones", *Bachelor Thesis*, **2019**

dedicated to my family and my partner

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Abstract

The establishment of novel concepts for metal-free transformations in modern synthetic chemistry is in high demand. For decades, synthetic chemists were relying on transition metal catalysis to accomplish important classes of organic reactions. However, nowadays the need of society towards more sustainable and greener chemistry is higher than ever. Therefore, metal-free strategies can provide an environmentally benign and economical solution for the synthesis of simple building blocks to access "target molecules".

In the present thesis, the development of novel metal free methodologies for the construction of biologically interesting nitrogen-containing molecules (chapter 3) as well as for asymmetric oxidative transformations (chapter 4) has been studied.

The modular synthesis of 1,6-dihydropyridine scaffolds has been investigated in a metal-free manner. To achieve this, a combination of vinyliminophospharenes and ketones in an aza-Wittig/6π-electrocyclization sequence was employed. The transformation proceeded *via* the generation of an azatriene, the key intermediate in the reaction sequence, which would further cyclize in a 6pi electron disrotatory mode. A wide variety of unprecedented 1,6-dihydropyridines with quaternary centers was obtained with yields up to 97%, due to the high functional group tolerance of the method. Further structural modifications on the 1,6-dihydropyridine scaffold through hydrogenation and Diels-Alder reaction allowed a facile access to the corresponding tetrahydropyridine, piperidine and isoquinuclidine moieties. Furthermore, the development of an asymmetric variant of this methodology was attempted using various chiral Brønsted acids which resulted in 1,6-dihydropyridines with poor enantioselectivities.

In the second part of the thesis, the reactivity and stereoselectivity of chiral hypervalent iodine(III) reagents in asymmetric oxidative transformations were explored. These compounds are well-known substitutes for transition metal-catalyzed reactions. Therefore, the rational design and rapid synthesis of a series of reported and novel C_2-symmetric iodoarenes endowed with different chiral features was accomplished. To evaluate both the catalytic activity and the asymmetry-inducing ability of the synthesized iodoarenes, they were applied in enantioselective α-functionalization of carbonyl compounds and specifically in the α-tosyloxylation of propiophenone and ethyl 2-methylacetoacetate, and lactonization of 4-benzoylbutyric acid. Even though, they proved to be

able to catalyze these oxidative transformations yielding the products in moderate to good yields, their ability to exert stereocontrol was inadequate.

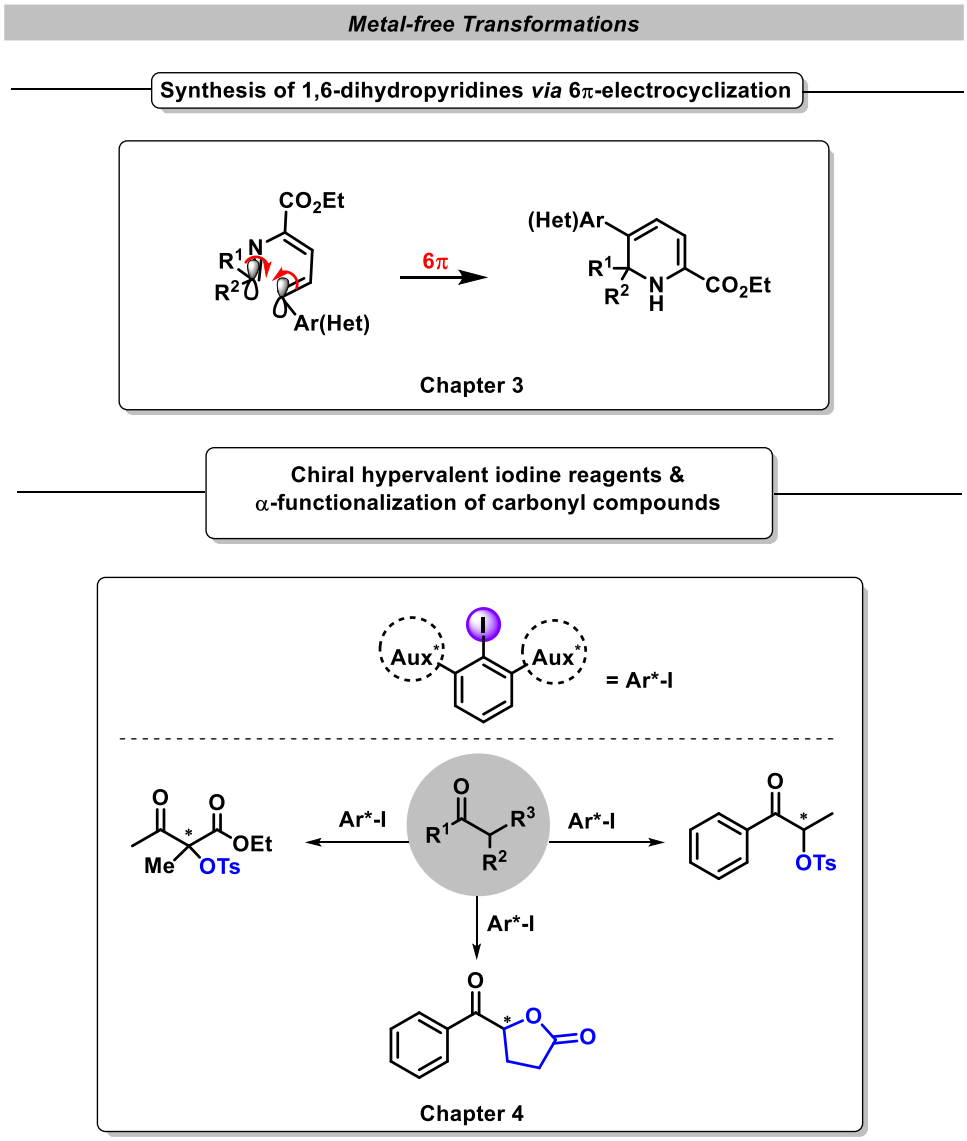


Figure 1. Overview of the projects described in the thesis.

Zusammenfassung

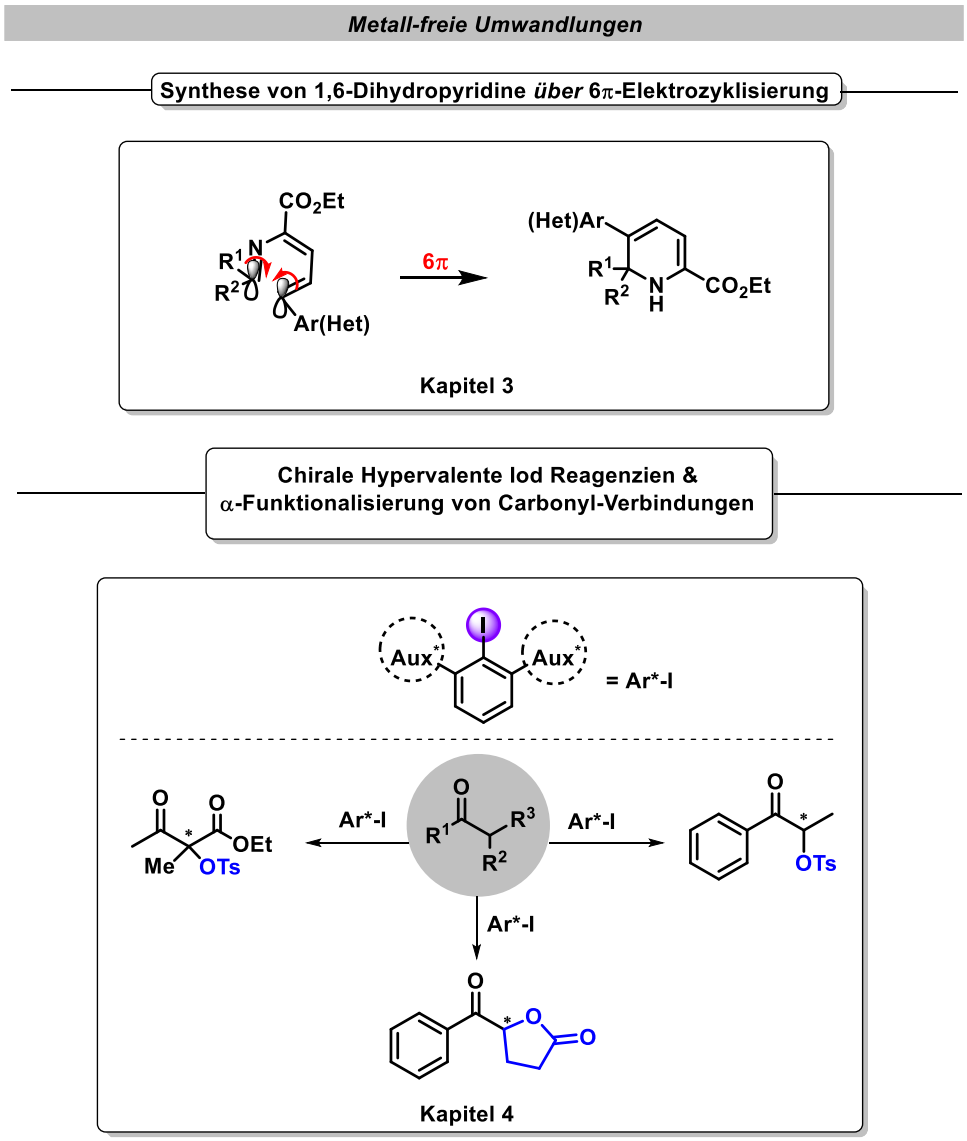
Die Entwicklung von neuen Konzepten für metallfreie Umwandlungen in der modernen Synthese-Chemie ist sehr gefragt. Jahrzehntelang insistierten Synthesechemiker auf die Katalyse von Übergangsmetallen, um wichtige Klassen organischer Reaktionen durchzuführen. Heutzutage ist das Bedürfnis der Gesellschaft nach einer nachhaltigeren und umweltfreundlicheren Chemie jedoch größer denn je. Daher können metallfreie Strategien eine umweltfreundliche und wirtschaftliche Lösung für die Synthese einfacher Bausteine darstellen, um Zugang zu "Zielmolekülen" zu erhalten.

In der vorliegenden Arbeit wurde die Entwicklung neuartiger metallfreier Methoden für die Herstellung biologisch relevanter stickstoffhaltiger Moleküle (Kapitel 3) sowie für asymmetrische oxidative Transformationen (Kapitel 4) untersucht.

Die modulare Synthese von 1,6-Dihydropyridin-Gerüsten wurde über eine metallfreie Methode untersucht. Dazu wurden Vinyliminophospharene und Ketone in einer Aza-Wittig/6π-Elektrozyklisierungssequenz eingesetzt. Die Umwandlung verlief über die Bildung eines Aza-Triens, ein Schlüsselintermediat in der Reaktionssequenz, das über einen 6π-disrotatorischen Verlauf weiter zyklisiert. Aufgrund der hohen Toleranz von funktionellen Gruppen dieser Methode, wurde eine große Vielfalt an neuen 1,6- Dihydropyridinen mit quaternären Zentren mit einer Ausbeute von bis 97% erhalten. Weitere strukturelle Modifikationen am 1,6-Dihydropyridin-Gerüst durch Hydrierung und Diels-Alder-Reaktion ermöglichten einen einfachen Zugang zu den entsprechenden Tetrahydropyridinen, Piperidinen und Isochinolidinen. Schließlich wurde die Entwicklung einer asymmetrischen Variante dieser Methode unter Verwendung von verschiedenen chiralen Brønsted-Säuren versucht, die zu 1,6-Dihydropyridinen mit niedrigen Enantioselektivitäten führten.

Im zweiten Teil der Arbeit wurden die Reaktivität und Stereoselektivität von chiralen hypervalenten Iod(III)-Reagenzien in der asymmetrischen oxidativen Umwandlungen untersucht. Diese Verbindungen sind bekannte Alternativen für Übergangsmetall-katalysierte Reaktionen. Ein strukturelles Design sowie eine vereinfachte Synthese von neuartigen C2-symmetrischen Iodoarenen mit verschiedenen chiralen Eigenschaften wurde durchgeführt. Um sowohl die katalytische Aktivität als auch die Asymmetrie-induzierende Fähigkeit der synthetisierten

Jodarene zu bewerten, wurden diese in einer enantioselektiven α-Funktionalisierung von Carbonylverbindungen wie der α-Tosyloxylierung von Propiophenon und Ethyl-2-Methylacetoacetat sowie der Lactonisierung von 4-Benzoylbuttersäure angewendet. Obwohl diese sich als fähig erwiesen, die oxidativen Umwandlungen zur Produkt Bildung zu katalysieren, war das Potential bezüglich der Stereokontrolle nicht ausreichend.



Figur 2. Übersicht der in der Thesis thematisierten Projekte.

Chapter 1. Introduction to Electrocyclic Reactions

1 Introduction

1.1 General considerations about electrocyclic transformations

Electrocyclic transformations fall into the class of pericyclic reactions. In 1965, Woodward and Hoffmann defined them as the formation of a new σ-bond between the ends of an open-chain conjugated system containing *k* π-electrons (*k* = 4, 6, 8, 10), and *vice versa*.[1]

Electrocyclizations can take place under thermal or photochemical conditions, through two possible modes defined as *conrotatory* and *disrotatory*. The two terms were coined for the description of the relative motion of bond rotation engaged in the electrocyclic ring-opening/closure process. Specifically, the term *conrotatory* is used when the terminal groups bonded to the forming or breaking bond rotate in the same direction (either both clockwise or both counterclockwise). In contrast, the *disrotatory* mode represents the rotation of those groups in opposite directions (one clockwise and one counterclockwise).[1] The significance of the electrocyclic reactions is based on their high stereospecificity. To explain how these reactions proceed in such a stereospecific manner, Woodward and Hoffmann, formulated a set of rules, the orbital symmetry rules. The basic concept behind them is that the symmetry properties of the highest occupied molecular orbital (HOMO) of the reacting system control the reaction´s stereochemistry.[1] In 4n systems like 1,3-dienes, the HOMOs have opposite phases at the terminal atoms. In 4n+2 systems like trienes, the HOMOs have same phase at the terminal atoms. Therefore, this suggests that electrocyclic reactions of 4n π-electron systems will occur by conrotatory mode, while reactions involving (4n+2) π-electron systems will take place *via* the disrotatory motion. In the case of photoinitiated electrocyclic transformations, the promotion of one electron from the HOMO of the reacting system to the lowest unoccupied molecular orbital (LUMO) reverses the terminal symmetry relationships and therefore the stereospecificity (Figure 1.1).[1-2]

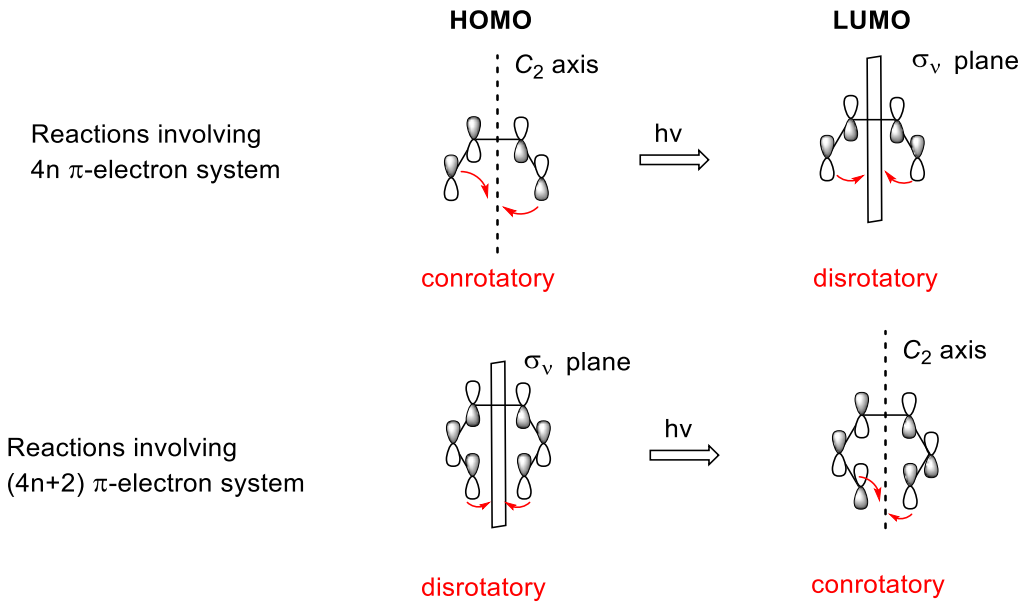
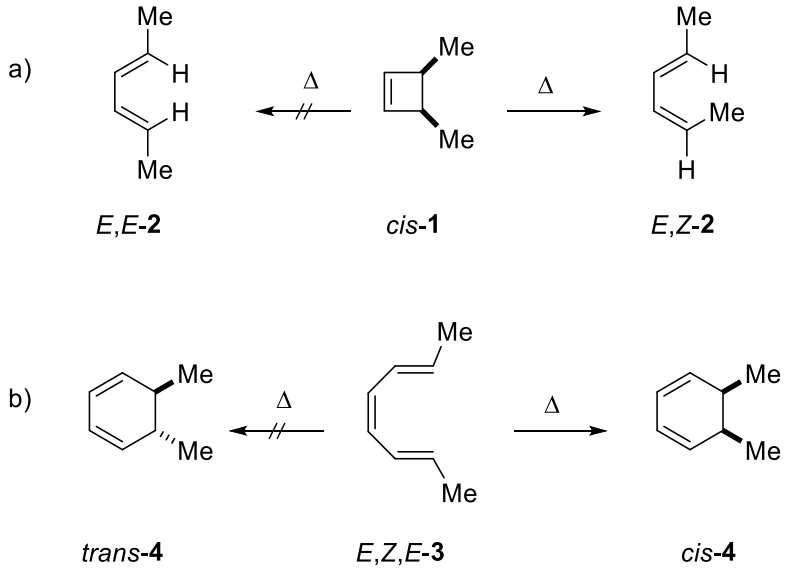


Figure 1.1. The Woodward − Hoffman rules

The stereospecificity of thermal electrocyclic reactions is illustrated with two simple examples in Scheme 1. In the first case, the thermal ring opening of *cis*-3,4-dimethylcyclobutene **1** results to the formation of *E*,*Z*-2,4-hexadiene **2** (Scheme 1.1a).[3] The second example depicts the conversion of *E*,*Z*,*E*-2,4,6-octatriene **3** only to *cis*- 5,6-dimethyl-1,3-cyclohexadiene **4** (Scheme 1.1b).[4]

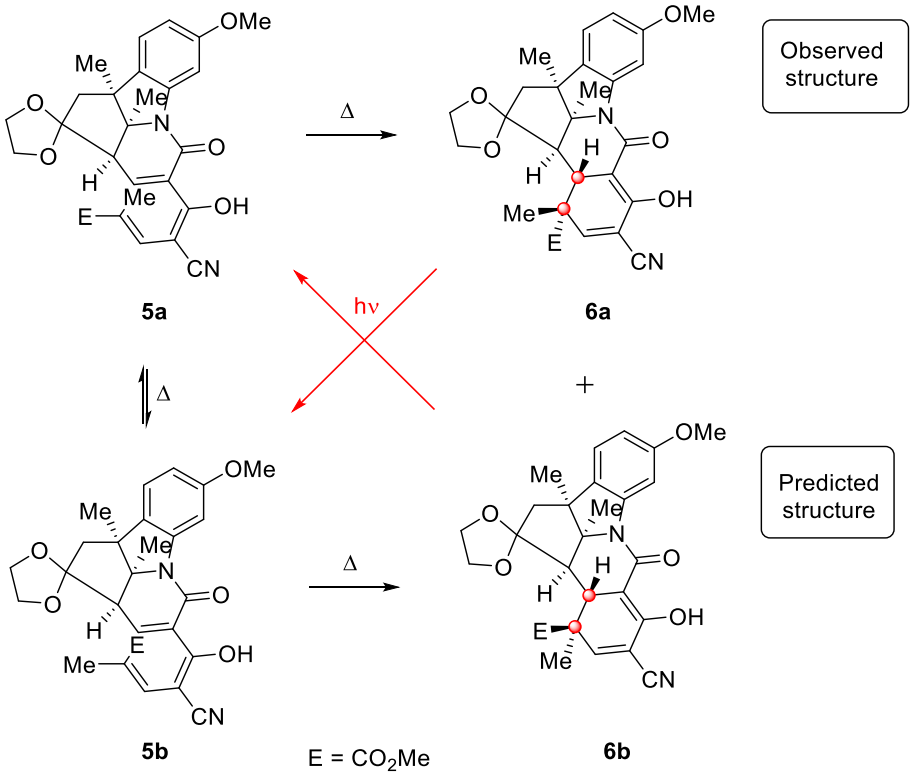


Scheme 1.1. Representative examples of thermal electrocyclizations. a) Thermal *conrotatory* ring opening of 4n π-electron system. b) Thermal *disrotatory* electrocyclization of (4n+2) π-electron system.

1.2 Genesis of the orbital symmetry rules

Upon a brief discussion on the half-century-old symmetry rules introduced by Woodward and Hoffman, it is interesting to mention how the theory was developed.

Woodward became really interested in the so-called "no-mechanism" reactions[5] during his lab´s research efforts on the total synthesis of vitamin B_{12}[6]. Initially, they synthesized fragment **5a** with the plan to perform an intramolecular Michael addition that would lead to the formation of a new 6-member ring. Unfortunately, the reaction did not take place upon treatment with base; the ring closure occurred upon melting of cyano-enol **5a**, resulting to a mixture of diastereomers **6a** and **6b**. After careful investigation of the reaction, they concluded that the presence of the mixture was due to the thermal isomerization of the fragment **5a** and that in fact the electrocyclization reactions were stereospecific. Additionally, when the cyclized products **6a** and **6b** were irradiated, they reformed the olefins **5b** and **5a** accordingly**,** in a reverse geometry to that from which they were generated (Scheme 1.2).[7] These unexpected results in combination with some "unexplained" reactions led to his collaboration with the theoretical-computational chemist, Roard Hoffmann, and therefore the *Conservation of Orbital Symmetry* was proposed.[8]

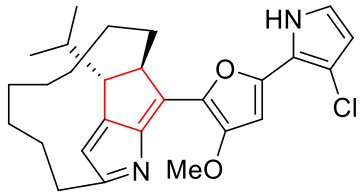


Scheme 1.2. Electrocyclization during vitamin B_{12} total synthesis by Woodward.

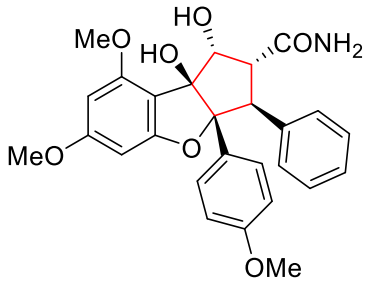
Since the mechanism and stereochemistry of electrocyclic reactions were elucidated[1], they have developed into powerful and practical synthetic tools to rapidly access structurally complex and diverse molecules.[9] However, when compared to other pericyclic reactions, such as cycloadditions and sigmatropic rearrangements[10] as well as their asymmetric versions[11] that have been widely studied, electrocyclizations are not fully exploited yet. Main reasons for this might be the high temperatures that often required to ignite those transformations and challenges related to the design and preparation of precursors.[9a, 9c, 9d, 12] Also, general methods for the asymmetric catalysis of electrocyclizations are limited and so the chances for exerting stereocontrol.

1.3 4π-Electrocyclization reactions

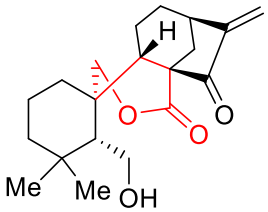
Among the various types of electrocyclic reactions, 4π-electrocyclization is one of the most investigated. Many interesting polycyclic molecules with prominent biological activities have been accessed by employing this strategy as the key synthetic step, some of which are shown in Figure 1.2.[13]



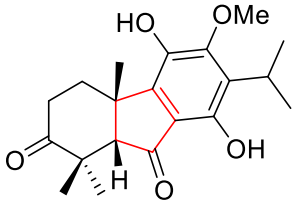
roseophillin, (7)
Flynn, 2012



rocaglamide, (8)
Frontier, 2012



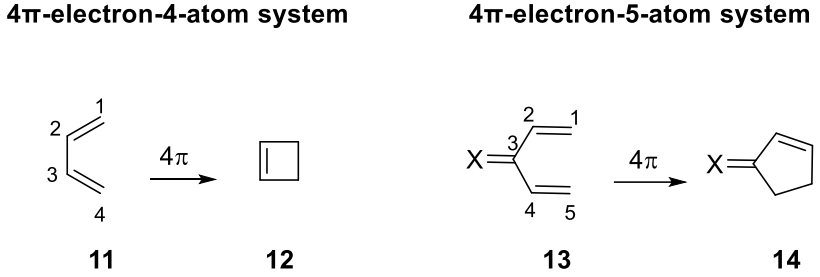
sculponeatin N, (9)
Thomson, 2014



taiwaniaquinol F, (10)
Bisai, 2015

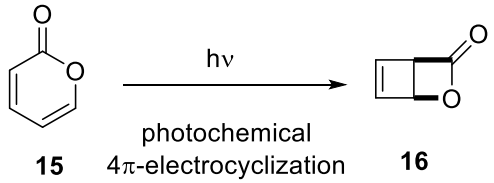
Figure 1.2. Selected examples of natural products synthesized *via* 4π-electrocyclization strategy.

Thermal 4π-electrocyclizations can occur under a conrotatory mode while the photochemical ones under a disrotatory motion. Furthermore, depending on the number of atoms and π electrons engaged in the process, they can also be classified into 4π-electron-4-atom and 4π-electron-5-atom electrocyclizations (Scheme 1.3). In general, the first type of 4π-electrocyclizations results to substituted cyclobutene motifs while the latter to highly functionalized five-membered carbocycles. [9e, 14]



Scheme 1.3. General representation of 4π-electron-4-atom and 4π-electron-5-atom electrocyclization.

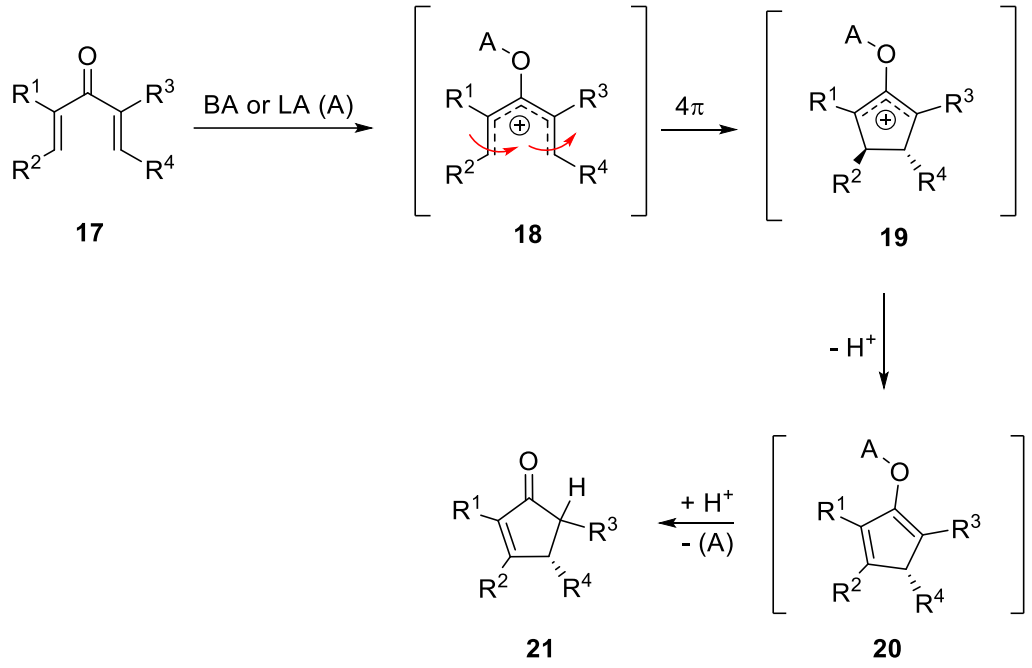
An illustrative example of 4π-electron-4-atom disrotatory photo-electrocyclization is the synthesis of cyclobutene lactones **16** starting from 2-pyrone derivatives **15** (Scheme 1.4). The strategy was first introduced by Corey in 1964,[15] and since then many groups harnessed this method to access valuable starting materials for further transformations.[16]



Scheme 1.4. Synthesis of cyclobutene lactones **16** from 2-pyrone **15** *via* a photochemical 4π-electrocyclization process.

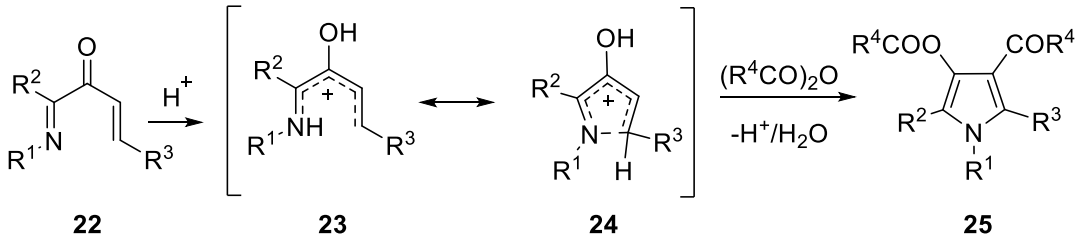
1.3.1 Nazarov (4π) cyclization

One of the most known 4π-electron-5-atom type electrocyclic process is the so-called Nazarov cyclization.[17] In its classic version, a pentadienyl cation **18** (resulted from a Brønsted or Lewis acid activation of divinyl ketones **17**) is cyclized to give cyclopentenones **21** (Scheme 1.5) [18]



Scheme 1.5. Representation of classic Nazarov cyclization.

Apart from the conventional Nazarov cyclization, several modifications have been established.[19] Among others, aza-Nazarov reaction is particularly useful since it gives access to 5-membered nitrogen-containing heterocycles.[20] As an example, the synthesis of substituted pyrroles **25** can be achieved from imines **22** *via* cationic intermediates **23** and **24** (Scheme 1.6).[21]

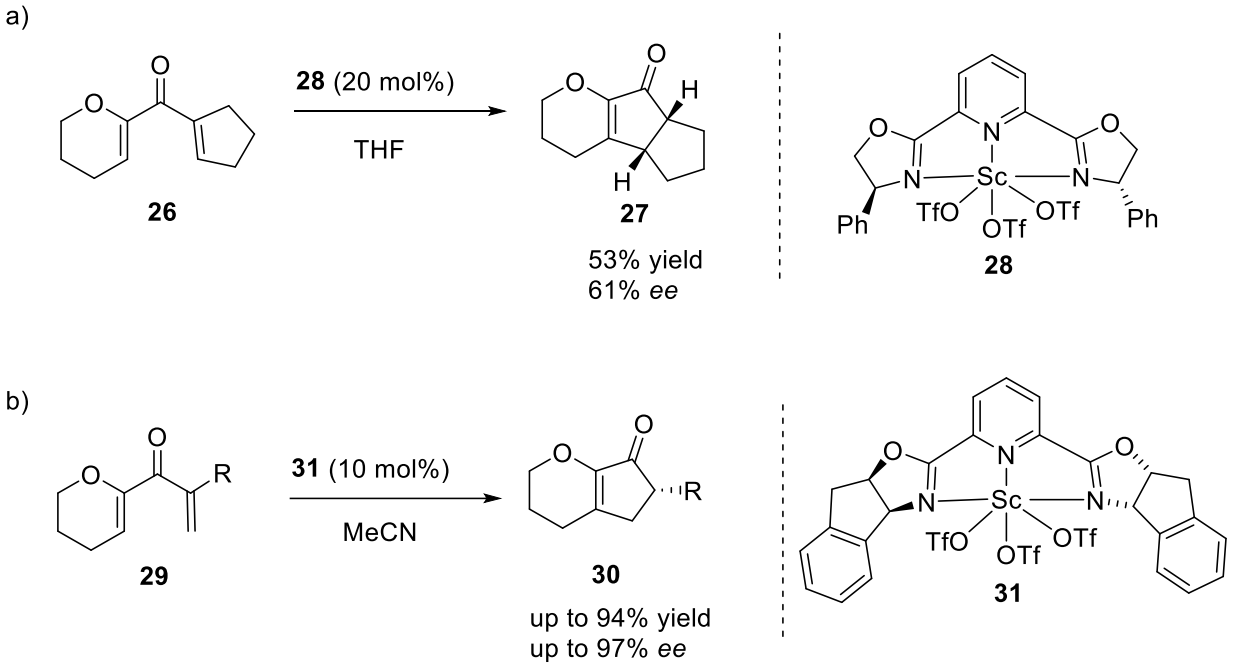


Scheme 1.6. Representation of aza-Nazarov cyclization.

1.3.2 Asymmetric Nazarov (4π) cyclization

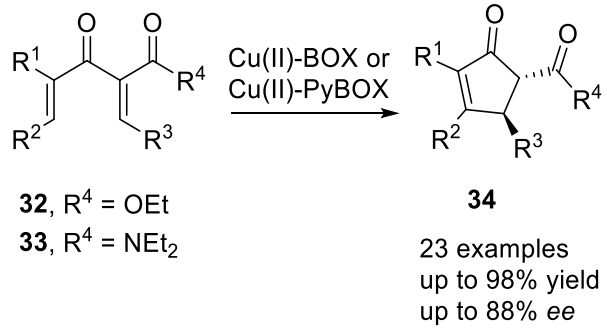
The high importance of five-membered rings as synthetic building blocks for the assembly of natural products and biological relevant compounds, led to the development of asymmetric versions of the Nazarov reaction. One of the first catalytic asymmetric examples of Nazarov cyclization was reported by Trauner and co-workers in 2003. They envisioned that the bidentate binding properties of substrates type **26** along with their high reactivity could lead to stereo-

induction. The use of a chiral scandium triflate PyBOX complex **28** transformed the α-oxygenated dienone **26** to product **27** in moderate yield and enantioselectivity (Scheme 1.7a).[22] One year later, the same group achieved excellent enantioselectivities of this transformation when utilizing indane-PyBOX complex **31** (Scheme 1.7b).[23]



Scheme 1.7. First examples of catalytic asymmetric Nazarov cyclization by Trauner *et al.*

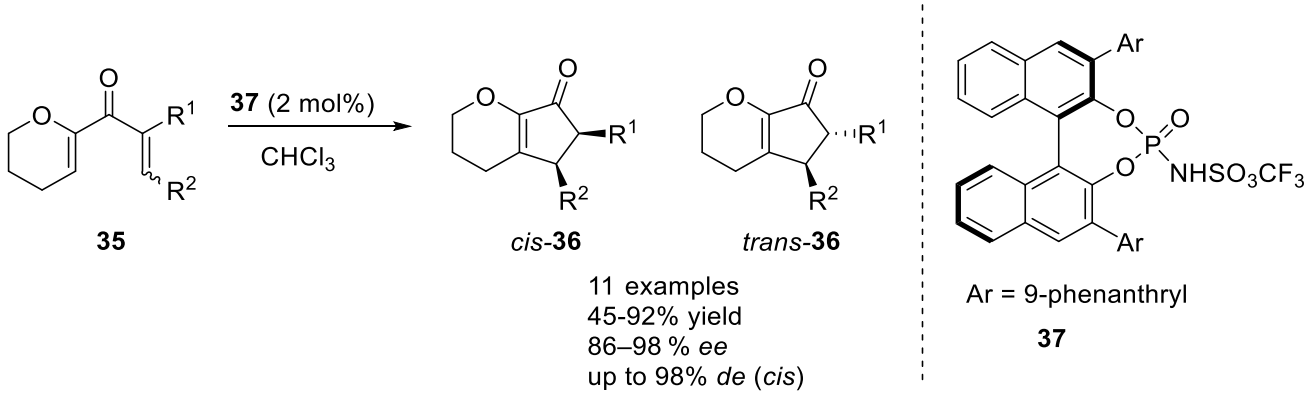
Concomitant with Trauner´s work, Aggarwal and his co-workers reported another asymmetric version of Nazarov cyclization. Employing stoichiometric amounts of copper(II)-BOX and copper(II)-PyBOX complexes promoted the cyclization of both divinyl keto-esters **32** and keto-amides **33** with good levels of enantioselectivity (Scheme 1.8).[24]



Scheme 1.8. Asymmetric Nazarov cyclization promoted by copper(II)-bisoxazoline Lewis acid complexes.

Later on, several other Lewis acidic metals, e.g. Ni(II)-complexes, and chiral ligands were identified as catalysts for the asymmetric Nazarov cyclization.[25]

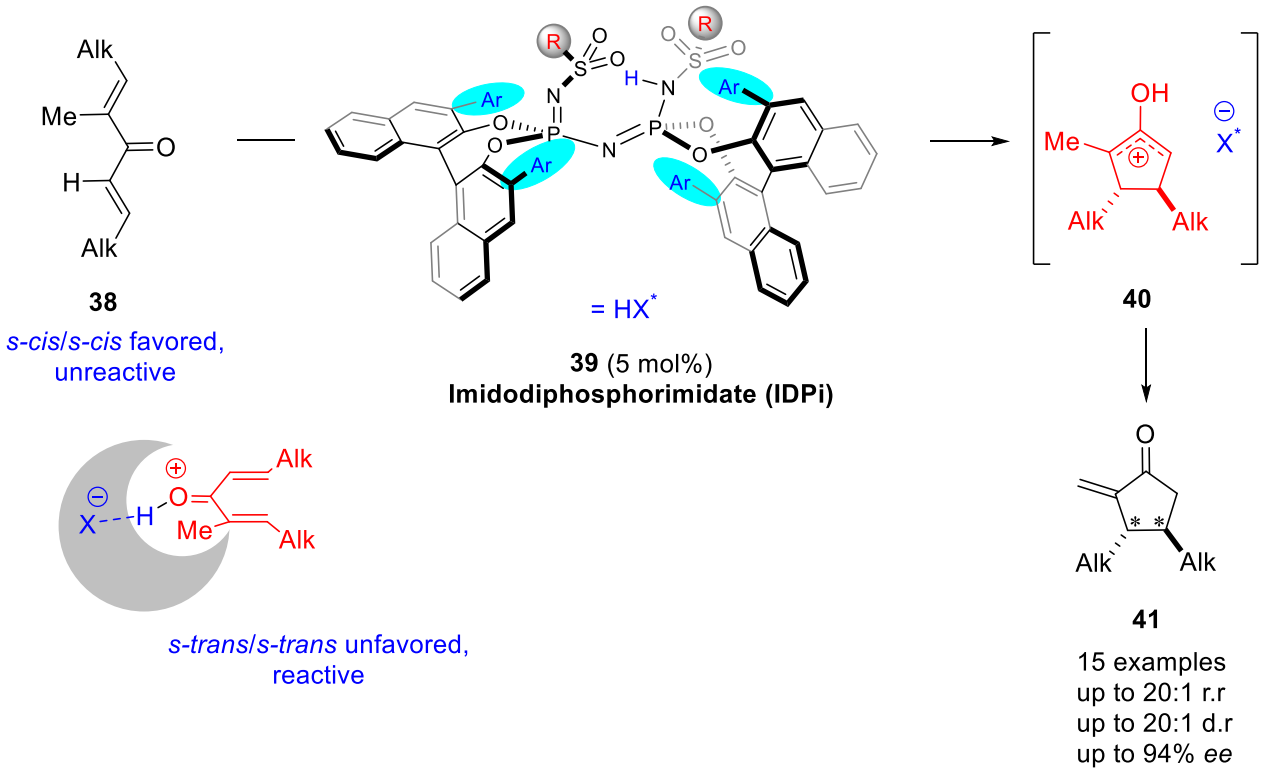
In 2007, Rueping *et al.* demonstrated the first organocatalytic enantioselective Nazarov reaction by employing a chiral BINOL-derived Brønsted acid in a very low catalyst loading.[26] This strategy enabled the access to highly enantioselective cyclopentenones **36** from various dienones **35** (Scheme 1.9).



Scheme 1.9. First organocatalytic asymmetric Nazarov cyclization.

Interestingly, this reaction provided selectively *cis*-products whereas similar reported metal-catalyzed transformations led to the formation of *trans*-cyclopentenones.[22-25]

Very recently, List *et al.* reported a successful employment of their new class of chiral Brønsted acids (imidodiphosphorimidates, (IDPis)) with highly acidic profile and confinement, in asymmetric Nazarov cyclization of simple, aliphatic divinyl ketones **38**.[27] Catalyst **39** successfully induced chirality and enabled the conversion of **38** to its "cyclization-reactive" conformer, resulting to the formation of cyclopentenones **41** in high levels of regio-, diastereo- and enantioselectivities (Scheme 1.10).



Scheme 1.10. Catalytic asymmetric Nazarov cyclization of simple divinyl ketones enabled by IDPis.

Based on the aforementioned examples and the extensive literature not presented here, it becomes clear that the catalytic methods and their asymmetric variants for the Nazarov cyclization are now well-established. Thus, they could pave the way for the development of catalytic modes for other types of electrocyclization, in particular 6π-electrocyclic transformations which are the main focus of the work presented in this thesis.

1.4 6π-Electrocyclization reactions

6π-Electrocyclic reactions are categorized in three types: the pentadienyl anion **A**, triene **B**, and heptatrienyl cation type **C** (Figure 1.3).[28] The transformation of 1,3,5-hexatriene to 1,3-cyclohexadiene (middle reaction of Figure 1.3) represents a thermal disrotatory 6π-electrocyclization in its simplest form.[29] However, this type of reactions usually requires temperatures as high as 130-200 °C to take place. This is a big concern when comes to the use of 6π-electrocyclization as synthetic strategy of choice for the construction of complex, delicate molecules with multiple functional groups. To improve the reaction conditions associated to the high temperatures, efforts have been made to increase the rate of those transformations. Studies

have shown that the electrocyclization energy barriers can be lower by incorporating proper substituents and/or replacing carbon atoms with heteroatoms into the 6π-system of trienes.

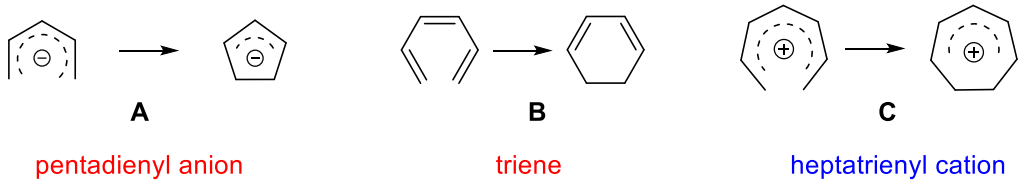
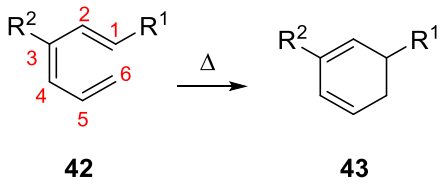


Figure 1.3. Types of 6π-electrocyclization.

1.4.1 The role of precursors

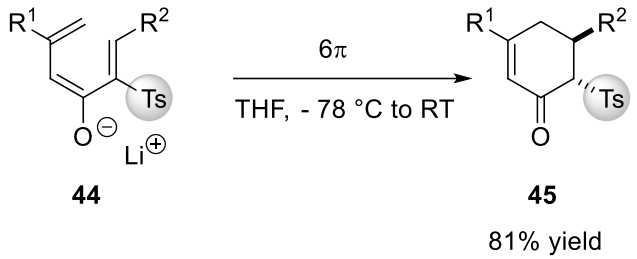
In 1964, Lewis and Steiner performed kinetic studies on the 6π-electrocyclic ring closure of 1,3,5-hexatriene **42** (R^1, R^2 = H) and they found out that the activation energy for this process is 29.9 ± 0.5 kcal/mol.[30] Later, Spangler and colleagues investigated how a series of substituents in different positions of the hexatriene system could affect the reaction rate of the 6π-electrocyclization. Based on experimental results, they demonstrated that alkyl and vinyl groups in 3-position that are not in proximity of the reaction center increase the cyclization rate while the same substituents located in 1-position show a similar trend in a rather less extent (Scheme 1.11). The effects of the substituents are based on electronic as well as steric effects.[31]



R^1, R^2 = H, Me, Et, *i*-Pr, *i*-Bu, CH_2=CH

Scheme 1.11. Substituent effect on the 6π-electrocyclization rate.

In the same context, Tang *et. al* observed interestingly that introducing an electron-withdrawing group (sulfonyl) at the 2-position of 3-oxido hexatrienes **44** (generated from the corresponding α-lithiated α,β-unsaturated sulfones and cyclobutenones) results to a significant decrease of the activation energy of the process and thus it can occur under milder conditions (Scheme 1.12).[32]



44 **45**

81% yield

Scheme 1.12. Low-temperature 6π-electrocyclization by Tang *et al.*

Many theoretical studies have also been carried out to examine how different substituents in different positions of the triene system influence the electrocyclization rate. They showed that a variety of electron-withdrawing groups such as methyl-ester, sulfonyl, nitro, and dimethylaminomethylene at the C2-position could significantly facilitate the ring closure by decreasing the activation barriers by 17-25 kcal/mol. Being located at C1-, C5-, or C4-position, they could still lower the activation energy but only by 0.3 to 6.6 kcal/mol. [29, 33] Additionally, the captodative effect (stabilization of intermediates by the synergy of electron-withdrawing/electron-donating groups)[34] on 6π-electrocyclization of hexatrienes has been computationally investigated by Guo *et al.*[35] It was found that strategic installment of both electron-acceptor and electron-donor substituents could lower the activation barriers by up to 10 kcal/mol compared to their parent hexatrienes (Figure 1.4).[35] All these results were in good agreement with the experimental findings.

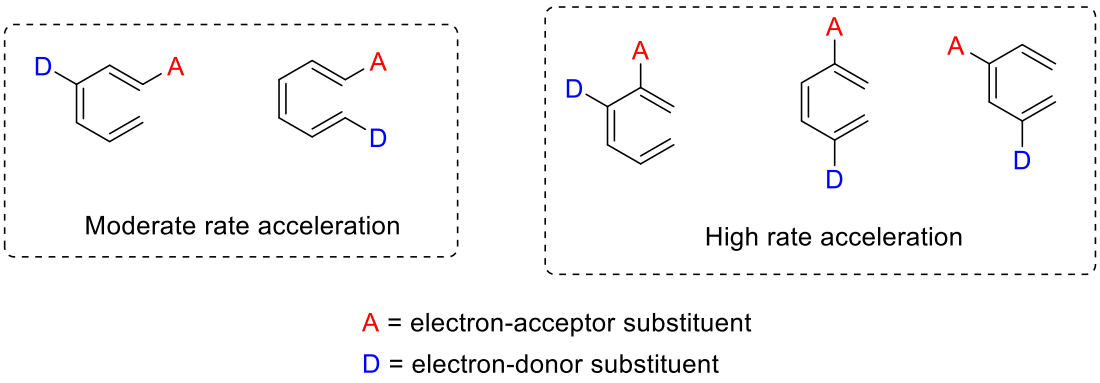
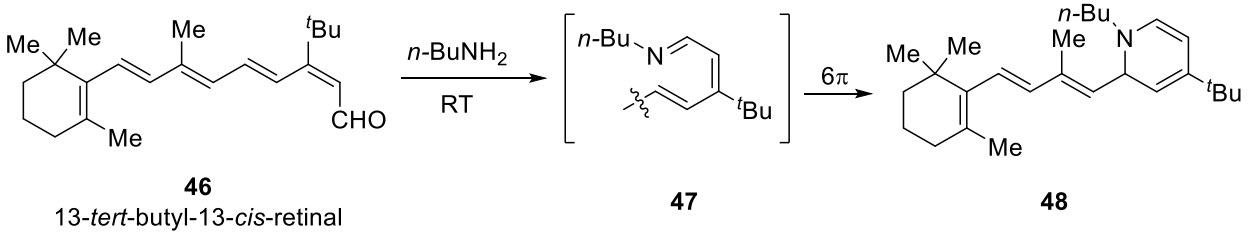


Figure 1.4. The captodative effect on 6π-electrocyclizations of 1,3,5-hexatrienes.

Furthermore, it has been observed that replacement of a carbon-atom with a heteroatom in the triene system results to 6π-electrocyclizations that can occur under milder conditions and shorter reaction times. Thermal electrocyclizations of simple azatrienes (nitrogen-containing analogues of

all-carbon trienes) found to have lower activation energies in about 5–10 kcal/ mol than those of the conventional all-carbon trienes. In 1989, Okamura and co-workers reported that the reaction between 13-*tert*-butyl-13-*cis*-retinal **46** and *n*-butylamine solely yielded the 6π-electrocyclized product **48** at ambient temperature (Scheme 1.13).[36]



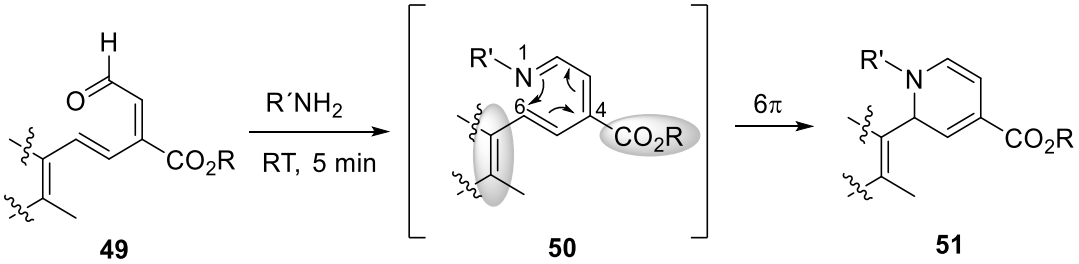
46
13-*tert*-butyl-13-*cis*-retinal

47

48

Scheme 1.13. Formation of **48** *via* a condensation/6π electrocyclization process of **46** and *n*-butylamine.

Later on, extensive structure-reactivity studies[37] revealed that incorporation of an electron-donating or electron-withdrawing substituent at the end of the 1-azatriene further accelerates the process. Inspired by their earlier reports[36-38], they also examined the 6π-electrocyclization of disubstituted 1-azatrienes and found that a combination of C4-carbonyl and C6-alkenyl groups in an *in situ* formed azatriene **50** can significantly increase the reaction rate (Scheme 1.14).[39]



49

50

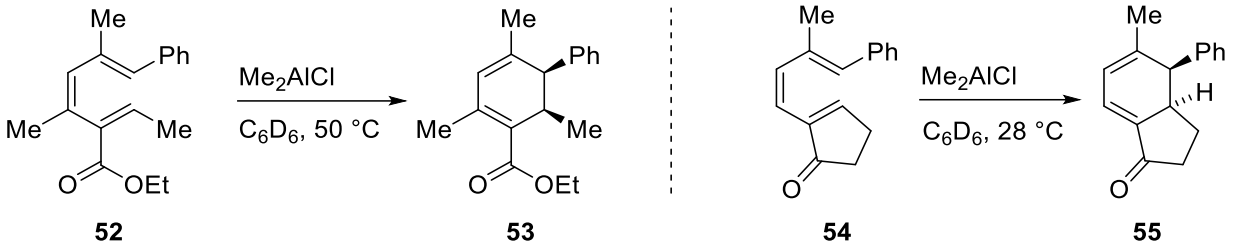
51

Scheme 1.14. Substituent effect on 6π-azaelectrocyclization.

1.4.2 Catalysis of 6π-electrocyclizations

The catalytic versions of 6π-electrocyclizations has been only recently reported. Bergman, Trauner and co-workers reported the first experimental one.[40] Taking into account the pre-existing literature, they proposed that a Lewis acid could be coordinated to an electron-withdrawing substituent placed in the C2-position of an hexatriene resulting to the decrease of the energy barrier. After careful investigations supported by both computational and experimental studies, they have shown that an up to 55-fold rate acceleration towards the electrocyclization of the substrates **52** and **54** could be achieved, in the presence of dimethylaluminum chloride (Me_2AlCl)

(Scheme 1.15). In order to expand the scope of 2-substituted hexatriene substrates **52** and **54**, 2-formyl hexatrienes were also examined. However, these substrates proved to be incompatible with this approach.[41]

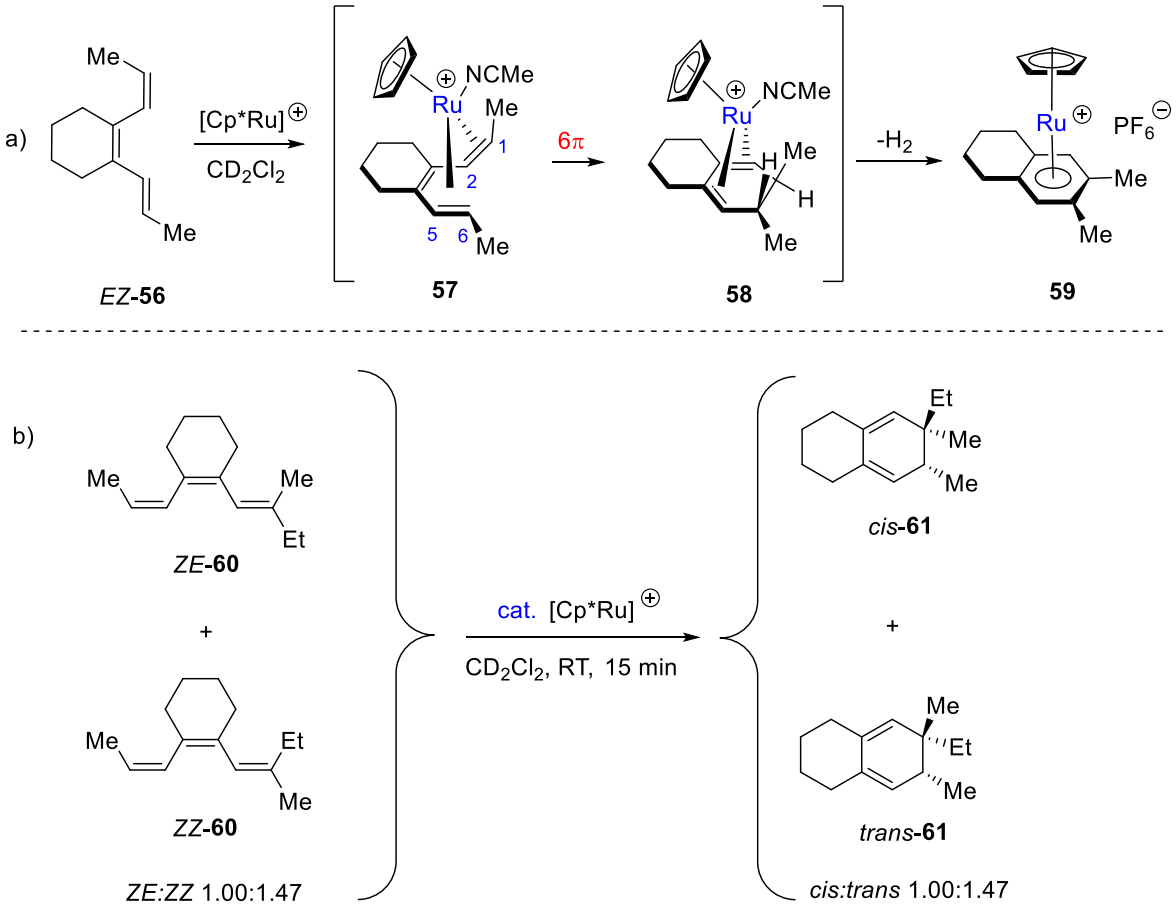


52 **53** **54** **55**

Scheme 1.15. Lewis acid-catalyzed 6π-electrocyclization reported by Bergman & Trauner *et al.*

Another approach for a catalytic 6π-electrocyclic reaction based on metal-π-electron interactions was also accomplished. In 1995, a theoretical study by Jiao and Schleyer predicted that l,3-*cis*-5-hexatriene can rapidly cyclize to 1,3-cyclohexadiene when metal cations are present.[42] Specifically, it was proposed that the activation energy can be decreased by more than 10 kcal/mol through a Li^+ complexation that electrostatically stabilizes the transition state.[42]

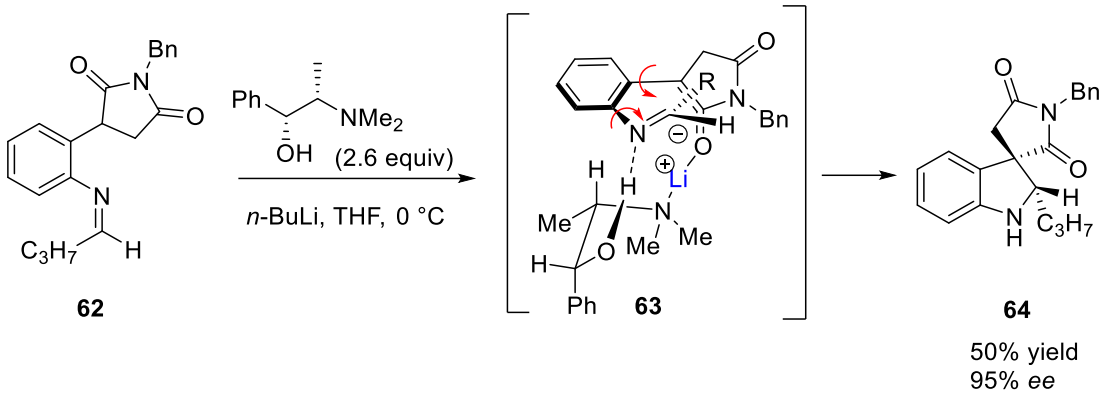
Recently, Rheingold *et. al* described the first experimental ruthenium-promoted 6π-electrocyclic ring closure of unfunctionalized trienes.[43] Treatment of triene **56** with precatalyst $[(C_5H_5)Ru(MeCN)_3]PF_6$ led to the formation of a stable ruthenium-arene complex **59** through a 6π-electrocyclization followed by dehydrogenation (Scheme 1.16a). Intensive kinetic and NMR studies revealed that triene acts as a π-electron donor ligand generating a η^6-triene complex (in presence of acetonitrile a η^4-triene complex is generated) as intermediate. In the presence of a quaternary carbon in the terminal position of the triene system **60**, the dehydrogenation of the cyclohexadiene-intermediate is avoided. Thus, the product **61** of the ruthenium-mediated stereospecific 6π-electrocyclization is obtained (Scheme 1.16b).



Scheme 1.16. Ruthenium-catalyzed 6π-electrocyclizations of trienes a) in absence b) in presence of terminal quaternary carbon in the terminal position of the triene.

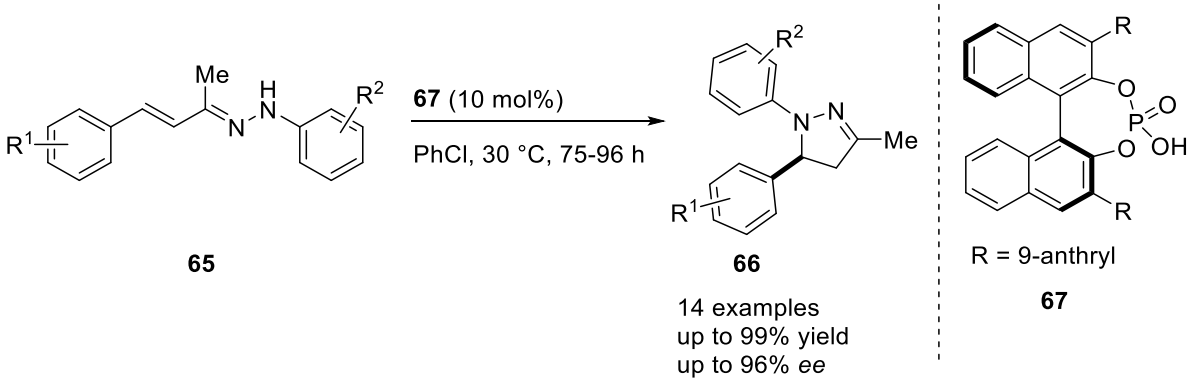
1.4.3 Asymmetric catalysis of 6π-electrocyclizations

The stereochemical outcome of asymmetric 6π-electrocyclizations is highly depended on the rotational preference of the orbitals, known as torquoselectivity,[44] which can be controlled in two possible ways; either by electronic or steric blocking of one of the enantiotopic faces of the involved 6π system.[9b] Early studies on enantioselective electrocyclizations were demonstrated in a series of reports by Speckamp and co-workers.[45] They reported that [1,5]-electrocyclization of azapentadienyl anions (generated from azomethines **62**) can take place in the presence of a mixture of *N*-methylephedrine and *n*-BuLi which results in enantioenriched indolines **64** (Scheme 1.17).[45b] In a suggested model of the transition state, the hydroxy group of the chiral alcohol interacts with the nitrogen of the azomethine *via* a hydrogen bond while its tertiary amine is linked to the enolate oxygen through a Li^+. In this way, the enolate oxygen and azomethine are organized in a helical conformation which generates the *cis*-product.



Scheme 1.17. Enantioselective synthesis of spiro-indolines **64** *via* [1,5]-electrocyclization of azomethines.

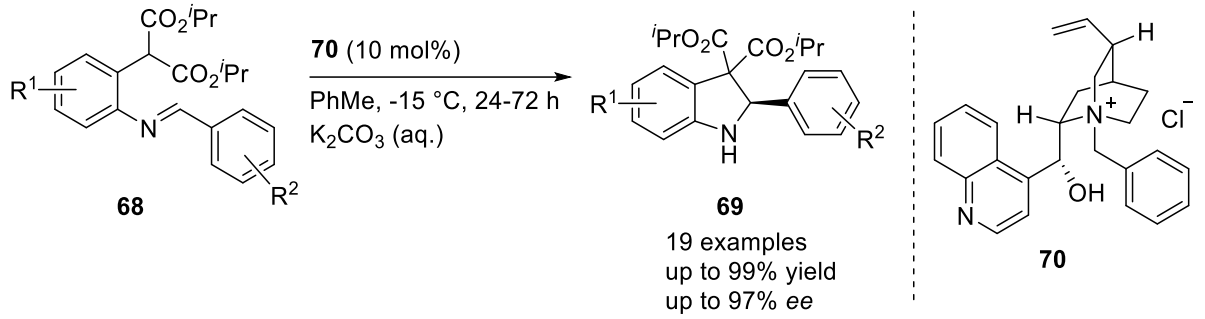
In 2009, List and Müller reported an organocatalytic asymmetric method for the 6π-electrocyclization of α,β-unsaturated aryl hydrazones **65** to pyrazolines **66** in excellent yields and enantioselectivities (Scheme 1.18).[46] A chiral BINOL-derived phosphoric acid was used to catalyze the process which proved to be suitable for a wide range of hydrazones bearing substituents with different electronic properties. The reaction could also be performed in one-step, starting directly from enones and phenylhydrazines without a negative effect on the enantioselectivities.



Scheme 1.18. Chiral Brønsted-acid catalyzed enantioselective electrocyclization of α,β-unsaturated aryl hydrazones.

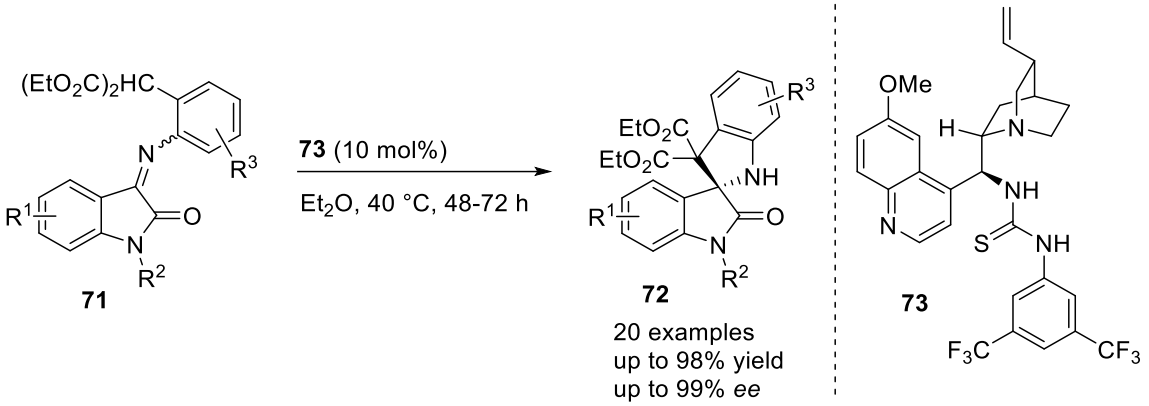
In a similar work, Smith and co-workers demonstrated an asymmetric electrocyclization of benzaldimines **68** to functionalized indolines **69** using chiral cinchona alkaloid-derived ammonium salts **70** as catalysts (Scheme 1.19).[47] By employing the tight ion-pairing strategy, the chiral counterion could block one face of the aza-pentadienyl anion (generated from the benzaldimine **68**) and thus induce chirality in the final products **69**. This reaction could also occur in a one-pot

fashion using aniline derivatives and aldehydes as substrates and maintaining both the high yields and levels of enantioselectivity.



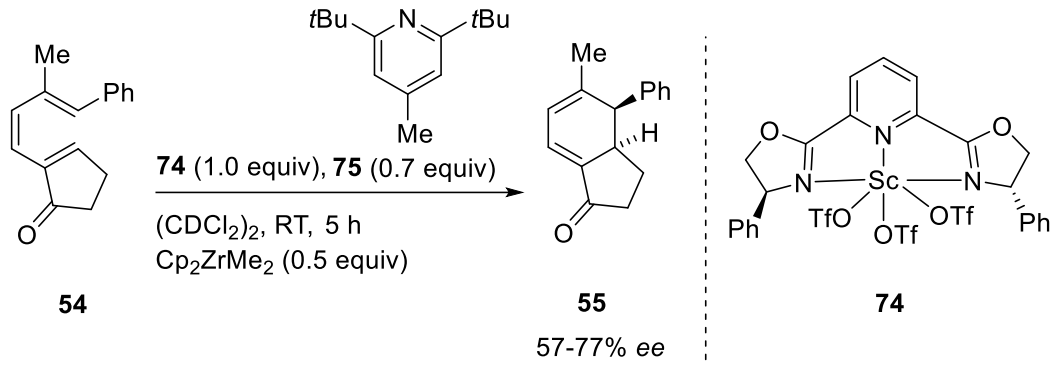
Scheme 1.19. Asymmetric electrocyclization of benzaldimines **68** under phase-transfer catalysis.

Inspired by the pioneering works of List[46] and Smith[47] on catalytic asymmetric [1,5]-electrocyclizations, Zhou *et al.* described in their paper of an enantioselective triple relay catalysis[48], a key step that involves an asymmetric 6π-electrocyclization of ketimines **71** to oxindole-based spirocyclic indolines **72**, catalyzed by a quinine-derived bifunctional thiourea (Scheme 1.20).



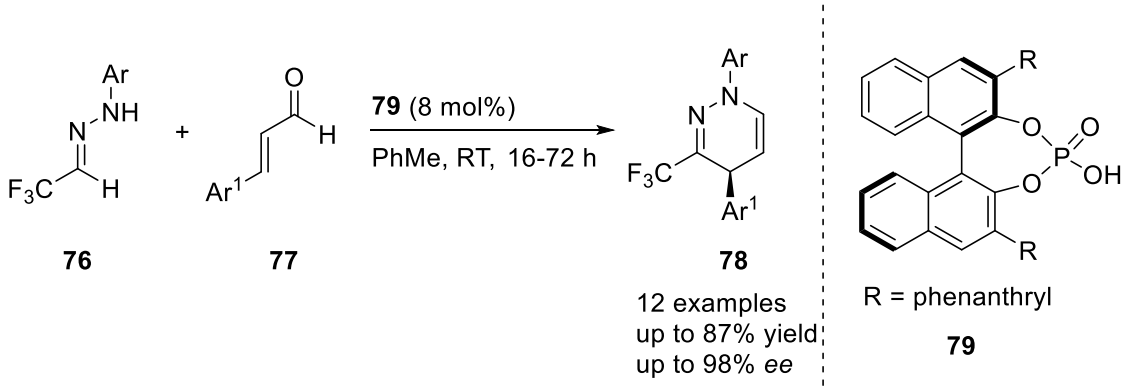
Scheme 1.20. Asymmetric 6π-electrocyclization of functionalized ketimines.[48]

The first example of enantioselective Lewis-acid catalyzed carba-6π-electrocyclization was reported by Trauner and co-workers[41], as a continuation of their earlier report.[40] The authors showed that an all-carbon hexatriene system, substituted in the 2-position with a carbonyl group **54**, could be cyclized to product **55** with moderate levels of enantioselectivity (57–77%) in the presence of a chiral scandium triflate PyBOX complex **74**, catalyst that was also used for the asymmetric Nazarov reaction[22], 2,6-di-*tert*-butyl-4-methylpyridine **75** and dimethylzirconocene in deuterated 1,1,2,2-tetrachloroethane solvent (Scheme 1.21).



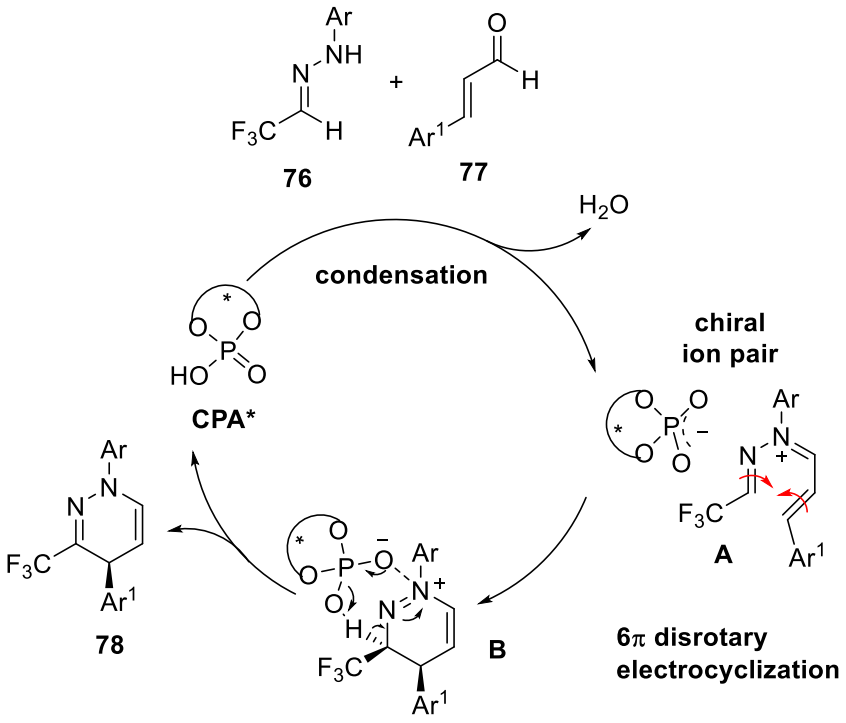
Scheme 1.21. Enantioselective Lewis-acid catalyzed carba-6π-electrocyclization.

In 2013, the group of Rueping described an asymmetric Brønsted-acid catalyzed condensation/6π-electrocyclization of *N*-aryl hydrazones **76** and α,β-unsaturated aldehydes **77** to 1,4-dihydropyridazines **78** (Scheme 1.22).[49] This protocol could tolerate a wide range of α,β-unsaturated aldehydes bearing electronically different groups and it could be performed at ambient temperature.



Scheme 1.22. Asymmetric Brønsted-acid catalyzed condensation/ 6π-electrocyclization for the synthesis of dihydropyridazines **78**.

Regarding the reaction´s mechanism (Scheme 1.23), it was proposed that the chiral Brønsted acid initially promotes the condensation of **76** and **77** upon which an ion-pair **A**, comprised of the hydrozonium cation and the chiral acid anion, is formed. Subsequently, intermediate **B** is generated by a 6π disrotatory electrocyclic reaction. The chiral counter anion controls the stereochemical result by shielding one of the two faces of the delocalized 6π system. Deprotonation of intermediate **B** generates the chiral phosphoric acid (CPA*) and the final asymmetric product **78**.



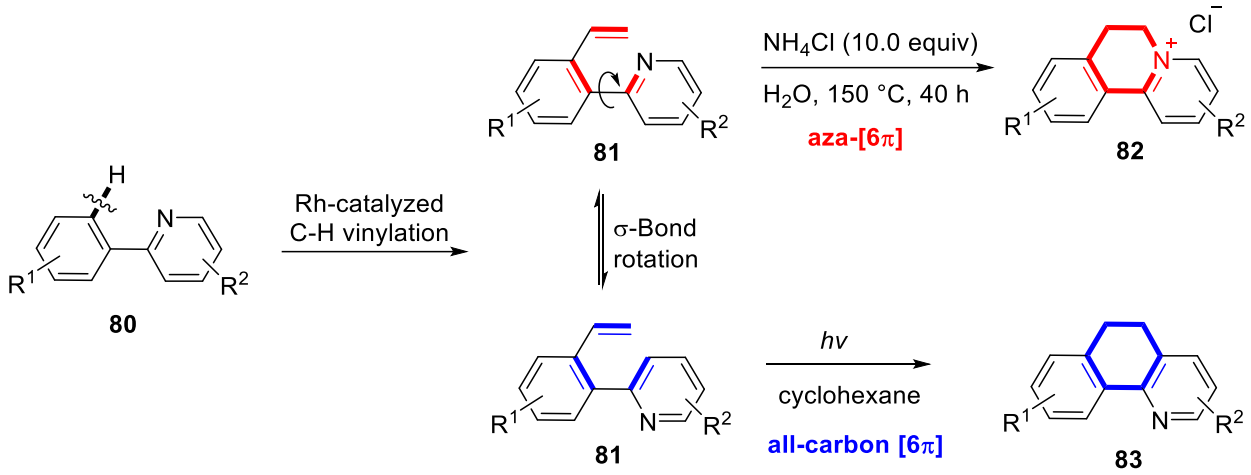
Scheme 1.23. Proposed mechanism for the Brønsted-acid catalyzed condensation/ 6π-electrocyclization reaction.

1.4.4 Examples of 6π-electrocyclization-mediated syntheses

Over the past few years, 6π-electrocyclic transformations and especially those of heteroaromatic triene systems are progressively being involved in the synthesis of valuable building blocks found in numerous natural products, drugs, and biologically active compounds. Among the main reasons that led to this increase in their synthetic utility, other than their efficiency and atom-economy, were the rationalization of the design and engineering of triene precursors in order to cyclize easier as well as the establishment of metal-catalyzed protocols to conveniently access them. Thus, a selection of recent examples is presented.

Polyheterocycles containing quaternary pyridinium salts can have a wide range of applications from dyes to supramolecular chemistry.[50] Very recently, Hu and Zhang developed two switchable 6π-electrocyclizations that could selectively afford dihydropyridoisoquinoliniums **82** or dihydrobenzoquinolines **83**, solely depending on external factors and not on the substrates (Scheme 1.24).[51] The precursors **81** were prepared from 2-phenylpyridines **80** and vinyl borates through a Rh-catalyzed oxidative C−H vinylation. In the presence of NH_4Cl and under thermal conditions, the triene system would cyclize to give exclusively compound **82** while the absence of

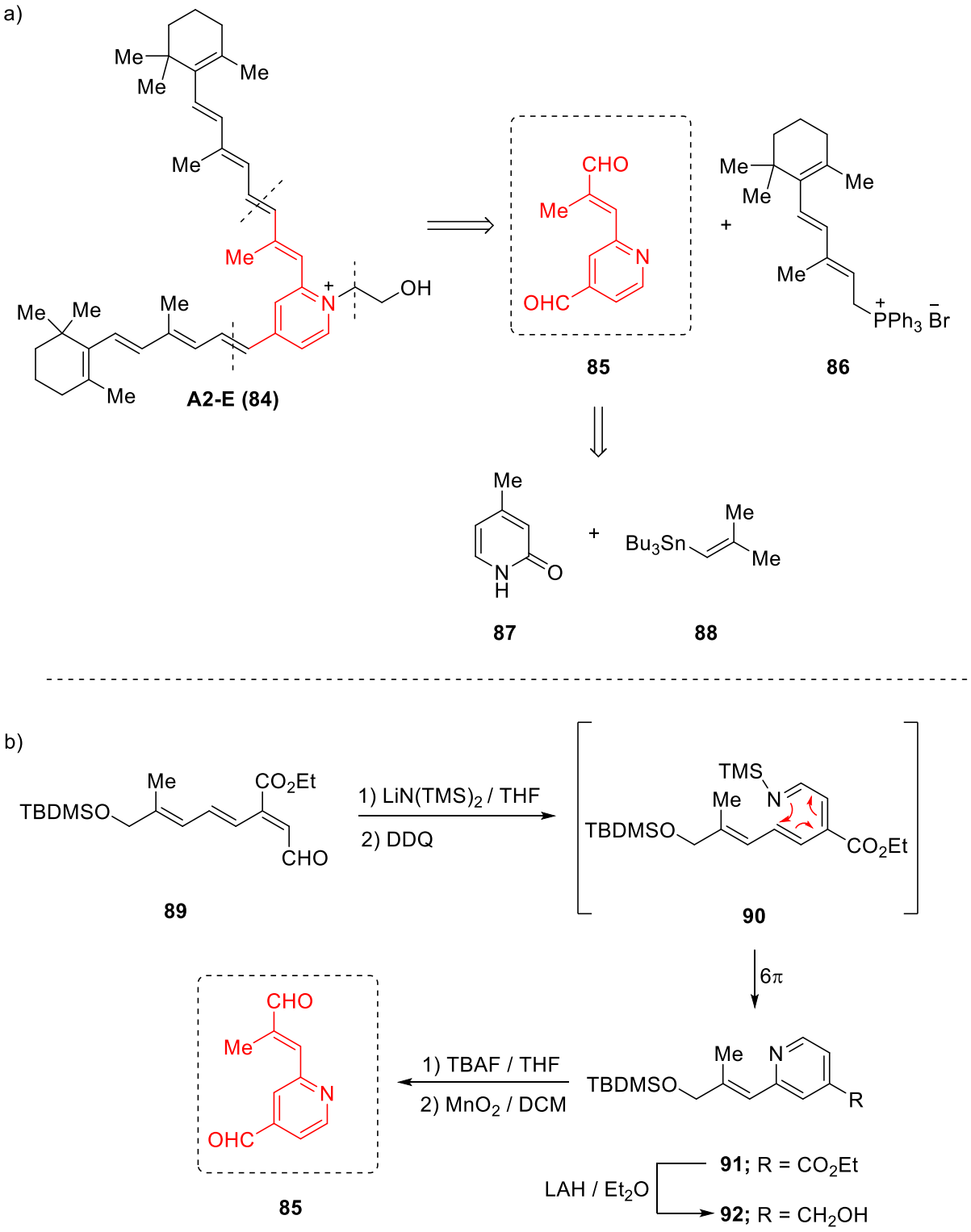
additive and photochemical conditions would favor the all-carbon cyclization, thus the formation of product **83**.



Scheme 1.24. Switchable 6π-electrocyclizations to access dihydropyridoisoquinoliniums **82** and dihydrobenzoquinolines **83**.

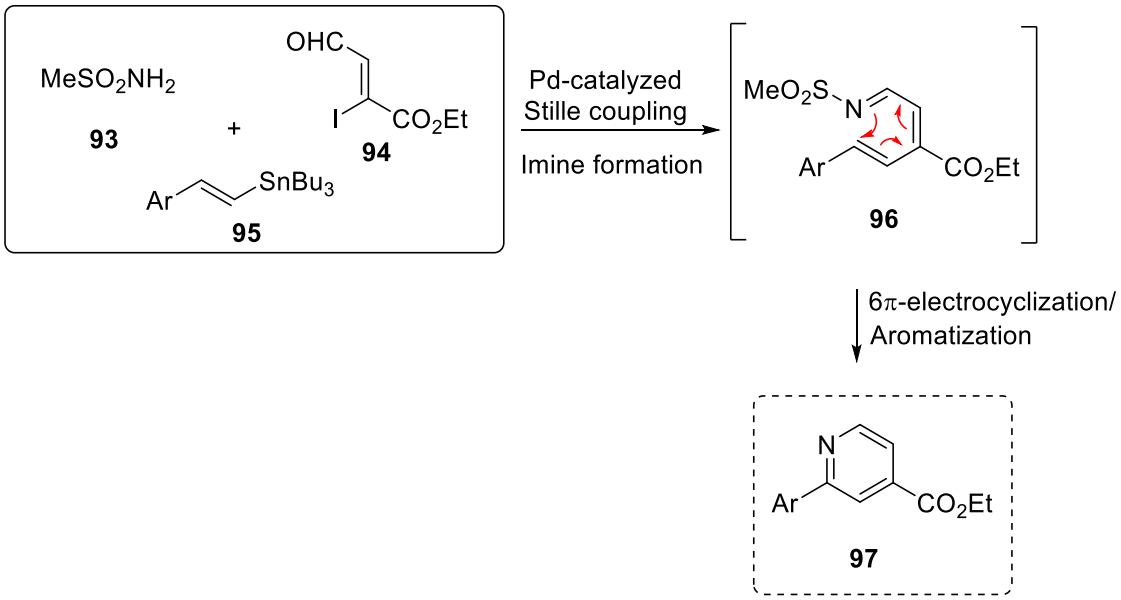
6π-Electrocyclizations are also employed in the synthesis of substituted pyridines which are leading structural components in various fields such as medicinal chemistry.[52]

The structure of the pyridinium bis-retinoid, "A2-E", an ocular age pigment and one of the main components of lipofuscin, was determined by the group of Nakanishi in 1996.[53] The importance of "A2-E" relies on its possible involvement in various age-related eye diseases such as age-related macular degeneration (AMD), the most common cause of vision loss in the elderly population.[54] One year later, the same group achieved the total synthesis of "A2-E" in a convergent fashion by employing a double-Wittig olefination of compound **85** with the triphenyl phosphonium ylide **86** and a subsequent alkylation at the nitrogen of the pyridine ring (Scheme 1.25a).[55] 4-Methyl-2-pyridone **87** was used as the starting material which upon oxidation of the methyl group and Stille-coupling with organostannane **88** resulted to the key bis-aldehyde **85**. In 2000, Tanaka and Katsumura reported a revised synthesis of "A2-E" where they focused on the preparation of the key compound **85** by employing Peterson olefination of (*E*)-3-carbonyl-2,4,6-trienal **89**, followed by a 6π-electrocyclization/oxidation sequence. A final TBDMS-group deprotection and oxidation afforded the desired substituted pyridine (Scheme 1.25b).[56]



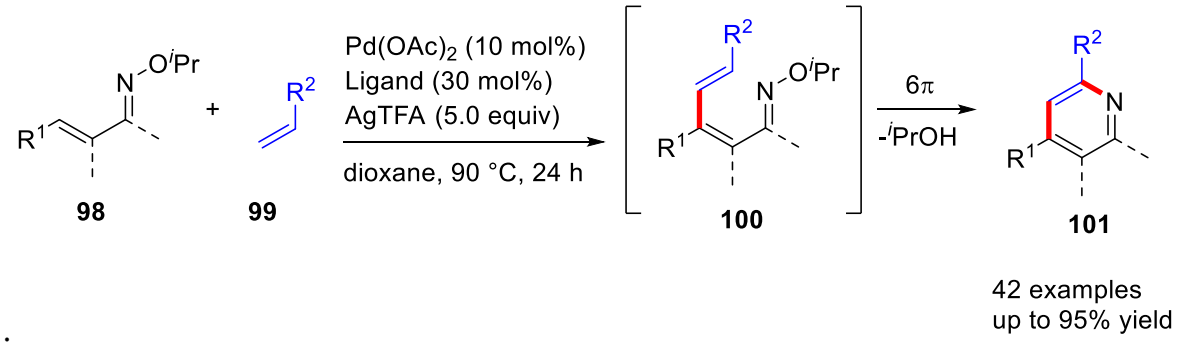
Scheme 1.25. Synthesis of A2-E a) *via* key intermediate **85** as reported by Nakanishi *et al.* b) *via* key intermediate **85** as reported by Katsumura *et al.*

Later on, Tanaka and Katsumura further developed a more general, one-pot protocol for the synthesis of 2,4-disubstituted pyridines **97** which could be also applied to solid-phase synthesis.[57] Particularly, this protocol involved a Pd-catalyzed Stille coupling / imine formation / 6π-electrocyclization sequence, followed by aromatization (Scheme 1.26).[57b]



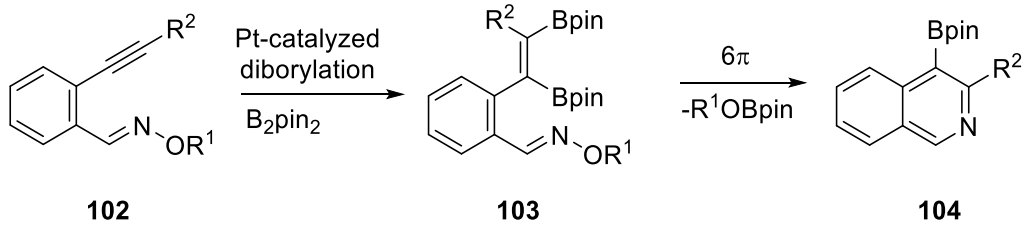
Scheme 1.26. One-pot pyridine synthesis from three components *via* 6π-electrocyclization.

Recently, a novel synthetic method for the generation of multi-substituted pyridines was accomplished by Tamura and co-workers.[58] In this work, high regioselectivity was achieved by the combination of a Pd-catalyzed C−H functionalization of α,β-unsaturated oximes **98** with various alkenes **99** and 6π-electrocyclization of the formed azatriene system **100** to afford **101** (Scheme 1.27). The scope of the strategy proved to be broad and applicable to both symmetrical and unsymmetrical oximes. Regarding the mechanism, a ligand-controlled β-selective C−H activation occurs, followed by a Heck-type coupling with an external olefin generating the precursor for the 6π-electrocyclization. This protocol overcomes selectivity limitations of Rh-catalyzed approaches for the construction of highly substituted pyridines.



Scheme 1.27. Pd-catalyzed C−H alkenylation/aza-6π electrocyclization process for the synthesis of substituted pyridines **101**.

In 2016, Harrity and colleagues demonstrated the synthesis of various functionalized isoquinolines in a two-step process, consisting of a diboration and an electrocyclization reaction.[59] Starting from alkyne-substituted oximes **102**, a Pt-catalyzed diboration on the alkyne moiety takes place leading to the formation of the diboron-substituted triene **103** which subsequently undergoes 6π-electrocyclization. During this process, a selective elimination of one of the two boronate-units proceeds resulting in the final product **104** (Scheme 1.28). Notably, this strategy could be also performed in one-pot fashion when aliphatic substrates were used to form pyridine-based derivatives.

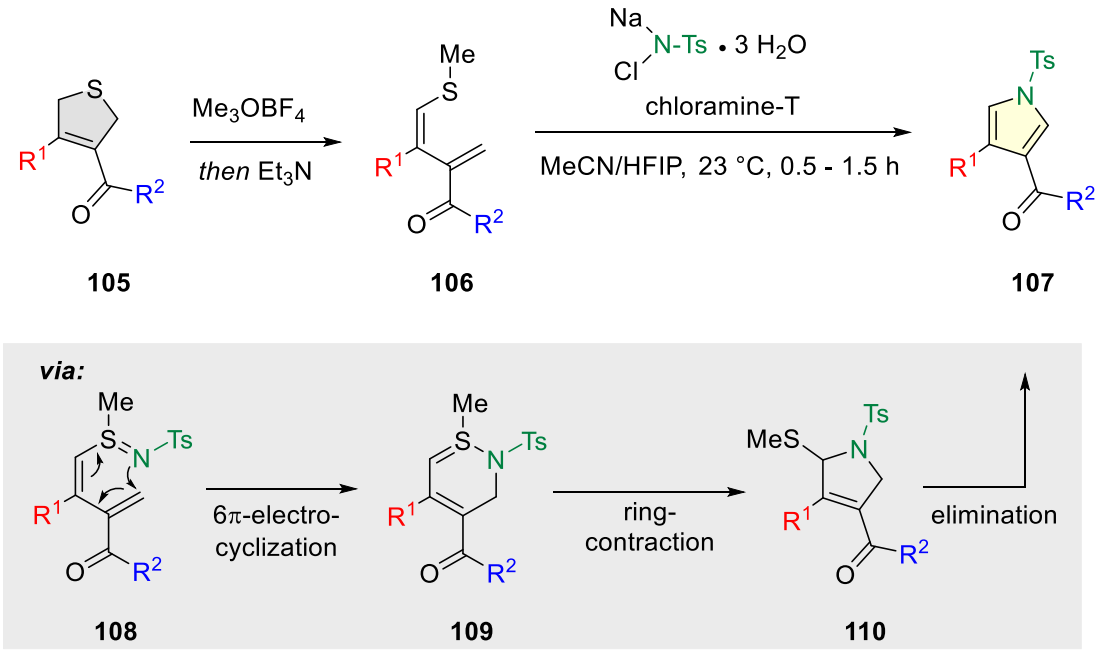


Scheme 1.28. Diboration/6π-electrocyclization process for the synthesis of functionalized isoquinolines **104**.[59]

Although, the 6π-azaelectrocyclization has been mainly employed in the synthesis of 6-membered ring *N*-containing heterocycles, it has also been used as a key synthetic step to access 5-membered rings and particularly pyrroles. The value of pyrroles lies on their presence as lead structures in many biologically active compounds and approved drugs.[60]

Very recently, Magauer *et al.* established a modular 6π-electrocyclization/ring contraction/elimination sequence as a powerful strategy to access those scaffolds.[61] In this context, treatment of readily available 2,5-dihydrothiophenes **105** with Me_3OBF_4 causes the ring-opening of the heterocycle to provide 1,3-dienes **106** which can be converted to the corresponding

pyrroles **107** upon addition of chloramine-T trihydrate under mild conditions (Scheme 1.29). DFT calculations revealed that the reaction proceeds through the formation of sulfilimines **108** followed by 6π-electrocyclization to furnish **109**, an uninterrupted process of ring-contraction (**110**) and final aromatization.



Scheme 1.29. Synthesis of poly-substituted pyrroles **107** from 2,5-dihydrothiophenes **105** *via* 6π-electrocyclization as a key step.

Moreover, 6π-electrocyclizations can be utilized in the construction of more complex molecules such as polycyclic-containing natural products. Pyrido[4,3-b]carbazole alkaloids have attracted the interest of synthetic chemists due to their wide range of biological activities.[62] Representative examples of this class of alkaloids are ellipticine[63] and olivacine[64] which have been extracted from several plants[65] (Figure 1.5).

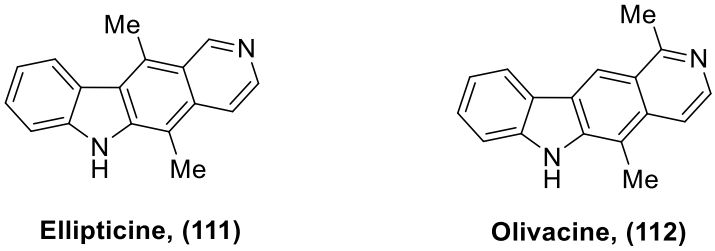
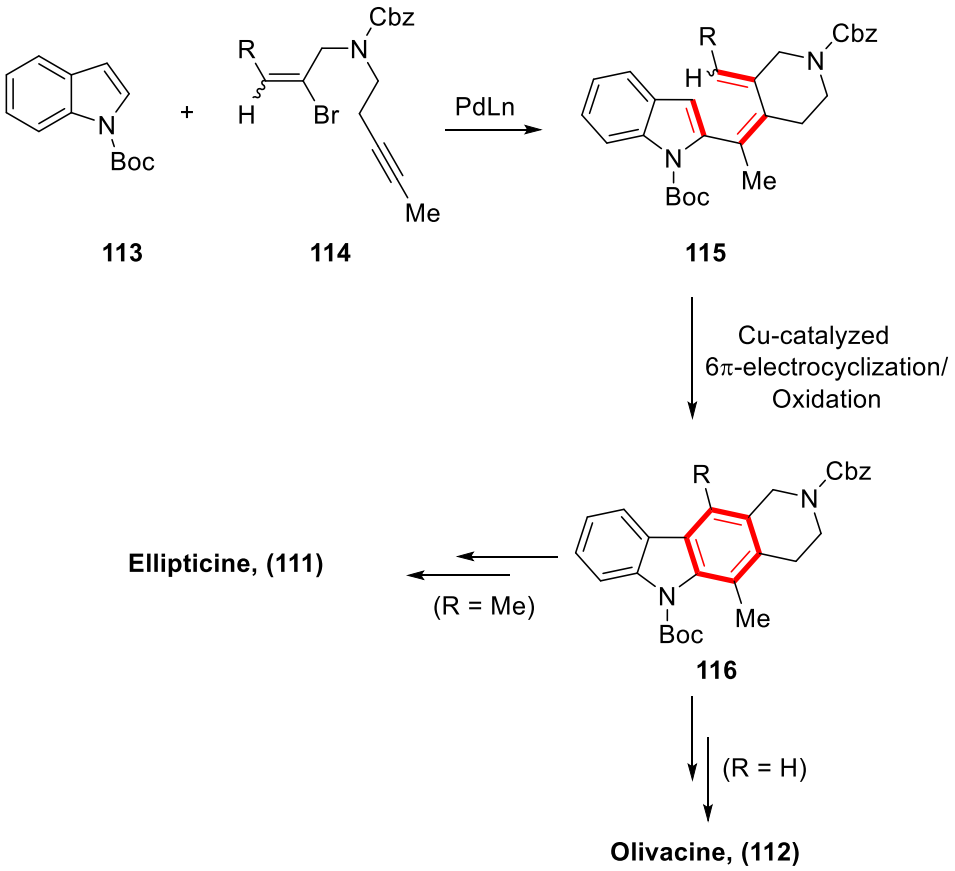


Figure 1.5. Representative examples of pyrido[4,3-b]carbazole alkaloids.

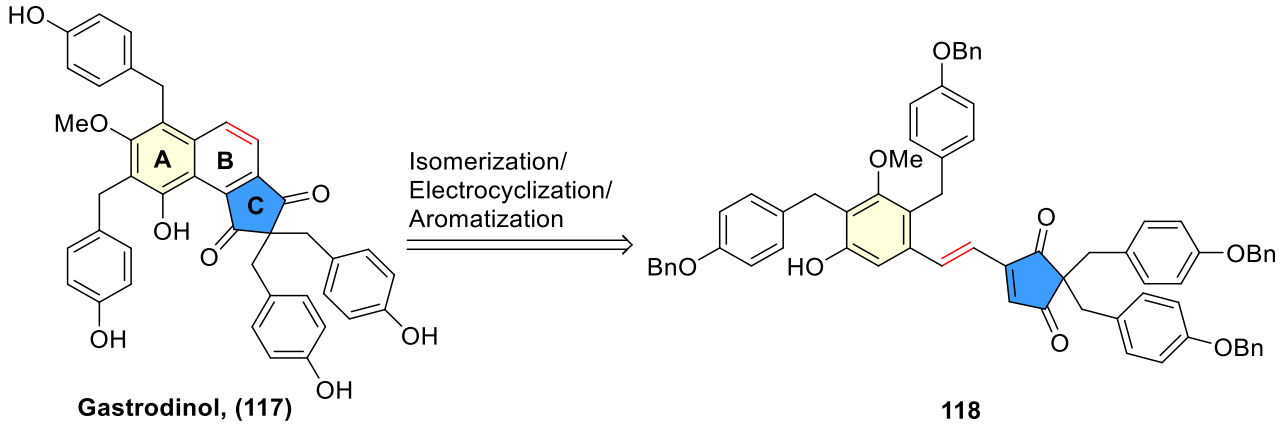
A facile synthetic route for their construction has been proposed by Ishikura *et al.* which involved a Cu-catalyzed 6π-electrocyclization step of an indole-based triene system (Scheme 1.30).[66] The precursor **115** for the electrocyclization was acquired by a cascade cyclization/cross-coupling mediated by palladium catalyst. Upon experimental studies, it was found that the conformation of the substituted terminal olefin of the indole-based triene **115** is crucial for the reaction´s outcome. Ring-closure of the (*E*)-isomer could proceed smoothly in the presence of $(CuOTf)_2$·toluene and at ambient temperature while in the case of (*Z*)-conformer, the cyclized product **116** was not observed. This could be explained by its highly flexible behavior that could inhibit the cyclization. These fused-carbazoles **116** could be further transformed to enable access to ellipticine **111** and olivacine **112** (Scheme 1.30).



Scheme 1.30. Cu-catalyzed 6π-electrocyclization towards the construction of pyrido[4,3-b]carbazole alkaloids **116**.

Another recent example of the employment of 6π-electrocyclization as a strategy towards the total synthesis of natural products was demonstrated by Hu, Zhou and co-workers.[67] Gastrodinol, a natural product isolated from the plant *Gastrodia elata* (Orchidaceae), possesses a fused tricyclic

ring system that consists of a naphthalene moiety attached to a 1,3- cyclopentanedione ring.[68] In their proposed retrosynthetic analysis (Scheme 1.31), the construction of the multi-substituted ring B could be achieved through a photoinduced 6π-electrocyclization of compound **118** followed by aromatization. The choice of this strategy is related to its high success in the assembly of complex molecules containing fused rings.[69]



Gastrodinol, (117) **118**

Scheme 1.31. Synthesis of Gastrodinol *via* 6π-electrocyclization of **118**.

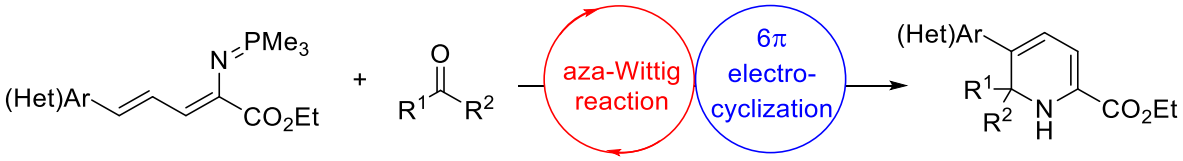
Although, the list of examples described above was by no means exhaustive, it has as main purpose to exhibit the potential of 6π-electrocyclizations as efficient and atom-economic transformations that can lead to various heterocyclic compounds.

Chapter 2. Aim of the Thesis

2 Aim of the Thesis

Modern chemistry is driven by the need to provide greener solutions in many aspects of society and science such as medicine, biology, biotechnology, pharmaceutical industry, and agriculture. This can be achieved by minimizing the use and generation of hazardous substances and thus the environmental impact. As such, catalysis plays a crucial role since traditional metal catalysis has been successfully employed in organic synthesis. However, the continuous demand for scarce, precious metals raises concerns for both the economy and the environment. To overcome these problems, alternative, metal-free synthetic strategies can be employed.

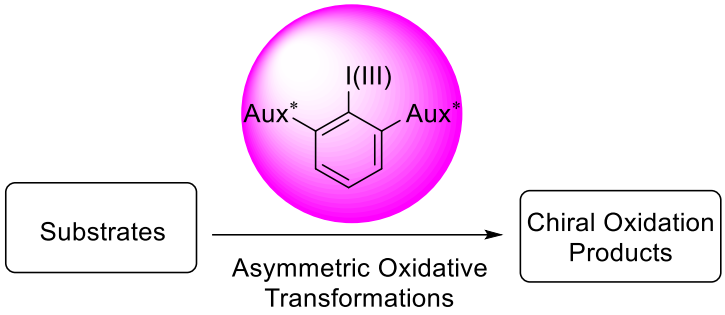
In this context, the aim of the first part of this thesis is the development, optimization and establishment of a novel, metal-free synthetic method to access nitrogen-containing heterocycles, particularly, 1,6-dihydropyridines. Therefore, a cascade aza-Wittig/6π-electrocyclization process employing easily accessible vinyliminophosphoranes and ketones is proposed for the construction of 1,6-dihydropyridine scaffolds with a quaternary center (Scheme 2.1). Optimization studies on the reaction conditions will be performed and the scope of the method will be examined. Furthermore, the reaction mechanism and the synthetic utility of the obtained products will be investigated. Intrigued by the challenges involved in exerting stereocontrol in 6π-electrocyclic transformations and the limited, available enantioselective examples, the asymmetric variant of this method will also be studied using various chiral organocatalysts.



Scheme 2.1. Cascade aza-Wittig/6π-electrocyclization process to access 1,6-dihydropyridines.

In the second part of this thesis, the design and synthesis of a library that contains both reported and novel chiral hypervalent iodoarenes is planned. Due to the continuous interest in environmentally benign synthetic solutions, also in the field of asymmetric synthesis, hypervalent iodine-mediated transformations have emerged as a promising alternative to transition metal-catalyzed reactions. In this context, the synthesized novel chiral hypervalent iodine reagents will be employed in a series of enantioselective oxidative transformations and both their catalytic

activity, and the asymmetry-inducing ability will be evaluated with respect of those already reported (Scheme 2.2).



Scheme 2.2. Schematic representation of hypervalent iodine mediated asymmetric oxidative transformations.

Chapter 3. Synthesis of 1,6-Dihydropyridines *via* a Cascade aza-Wittig/6π-Electrocyclization Process

(Parts of this chapter have already been published: Vasiliki Polychronidou, Anna Krupp, Carsten Strohmann, and Andrey P. Antonchick, *Org. Lett.*, **2021**, *23*, 6024–6029.)

3 Synthesis of 1,6-Dihydropyridines *via* a Cascade aza-Wittig/6π-Electrocyclization Process

3.1 Introduction

Dihydropyridines (DHPs) are six-membered ring, *N*-containing heterocycles which study began with their first synthesis reported by Arthur Hantzsch in 1881.[70] There are five possible isomeric structures.[71] Among them, the 1,4- and 1,2-isomers (Figure 3.1) exhibit the highest stability, therefore they are the most frequently found. The structural motif of 1,4-DHPs is prevalent in a wide variety of compounds with high pharmaceutical and biological importance (Figure 3.1)[72] and there are several synthetic strategies available in order to access them.[72c, 73] On the other hand, the biological annotation of molecules bearing the 1,2- or 1,6-DHP (depending on their substitution pattern) scaffold is relatively less investigated.[74] 1,2- DHPs have mainly received attention for their potential to serve as versatile synthetic intermediates for the construction of several alkaloids[75] and other drugs[76] (Figure 3.1). In general, their high reactivity renders them prone to various chemical transformations resulting in the formation of diverse azacycles.[76b, 77]

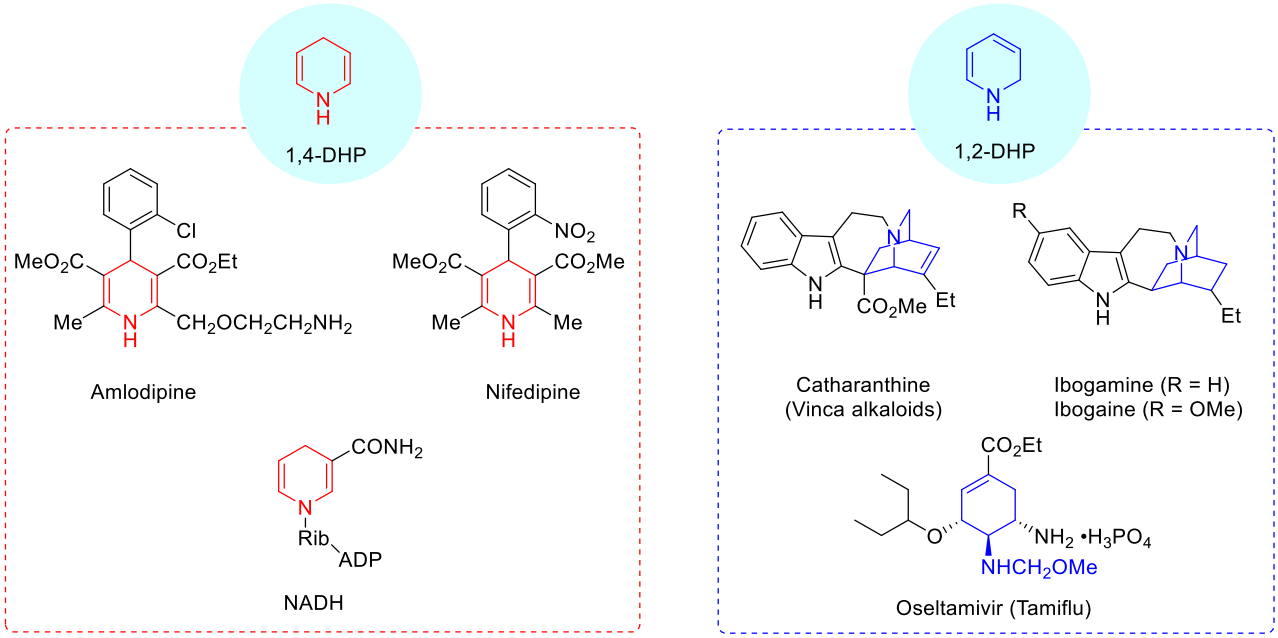
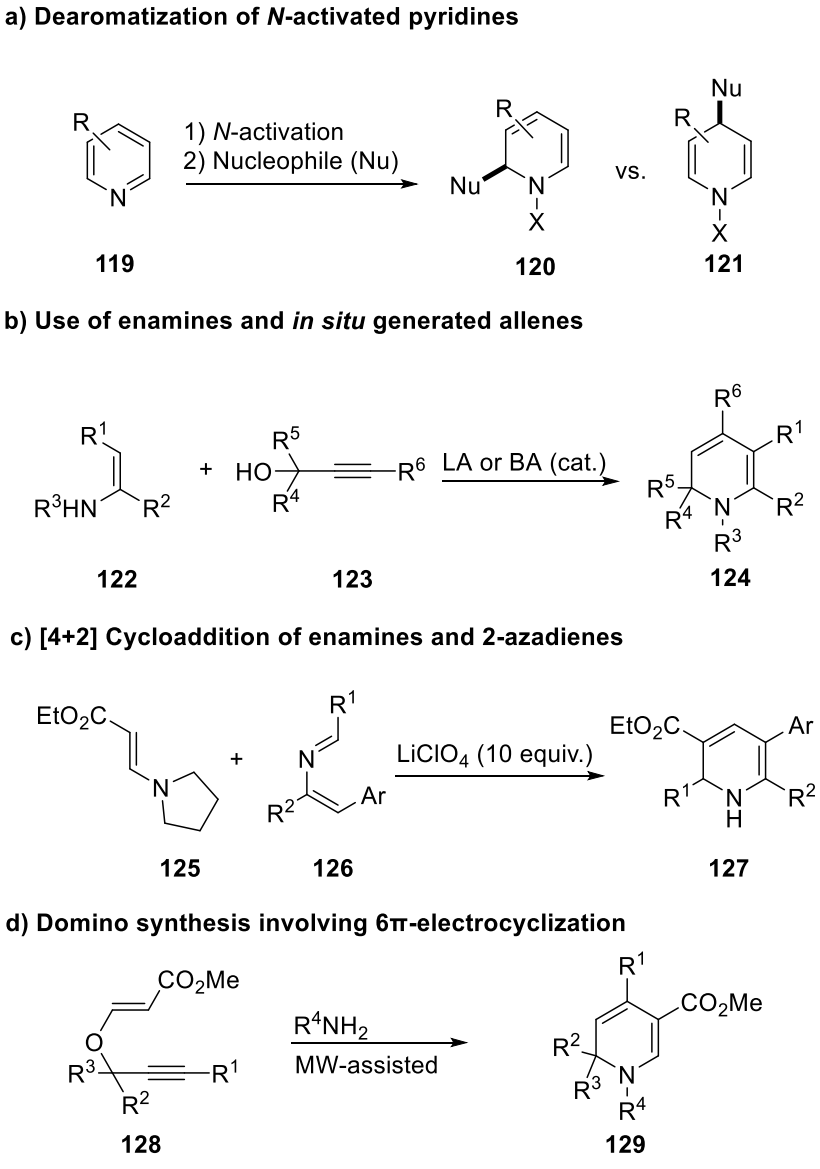


Figure 3.1. Structures of 1,4- and 1,2-DHPs and selected examples accessible from DHPs.

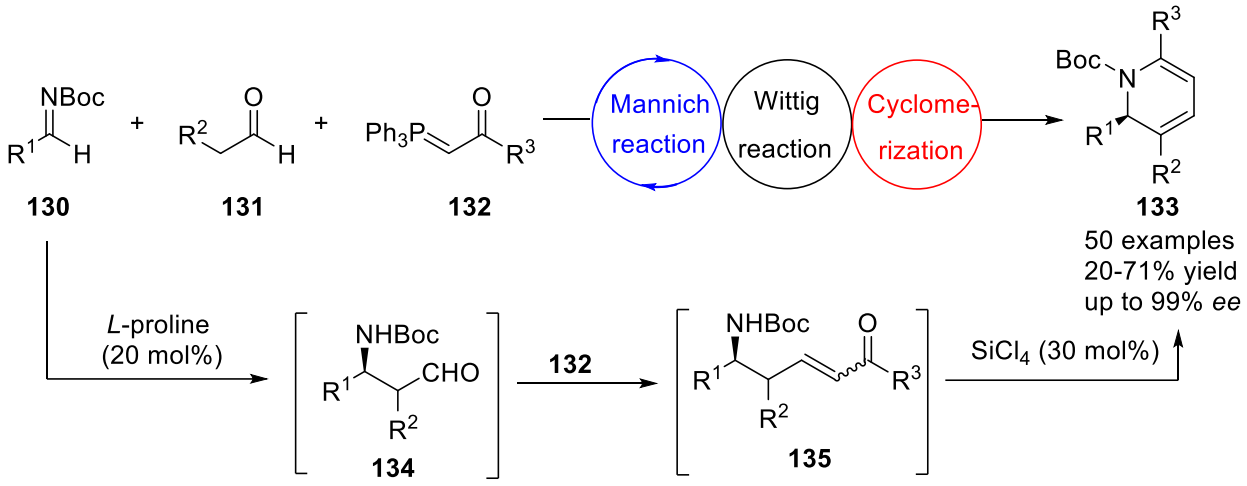
Several synthetic methodologies have been established for the generation of the 1,2-DHP scaffold. A common synthetic strategy includes the dearomatization of activated pyridines mediated by a

nucleophilic addition (Scheme 3.1a).[73f, 78] Very recently, a new method that allows access to both 1,4- and 1,2-dihydropyridines *via* dearomatization of readily available pyridines with amine borane reagent was reported by Glorius *et al*.[73c] Its selectivity towards 1,4- or 1,2-dihydropyridines was controlled by the substitution pattern of the pyridine motifs. In addition, transition-metal catalyzed processes as an alternative approach for the synthesis of 1,2-dihydropyridines proved to be beneficial as well.[77d, 79] 1,2-DHPs could be also accessed from the reaction of enamines with alkynes promoted by Lewis[80] or Brønsted[81] acids which enable the *in situ* formation of allene species as key intermediates (Scheme 3.1b).



Scheme 3.1. Synthetic strategies for the synthesis of 1,2-dihydropyridines.

Undoubtedly, pericyclic reactions play a pivotal role in the synthesis of this class of compounds. A simple and convenient Diels-Alder reaction of 2-azadienes with enamines which affords multi-substituted 1,2-dihydropyridines was described by Palacios *et al.*(Scheme 3.1c).[82] Furthermore, domino reactions involving 6π-electrocyclization of 1-azatrienes constitute a common synthetic route to 1,2-dihydropyridines with high degree of structural diversity. In particular, Tejedor and co-workers successfully demonstrated a metal-free protocol which consists of a microwave-assisted reaction sequence leading to substituted 1,2-dihydropyridine-3-carboxylates (Scheme 3.1d).[71, 83] The transformation is initiated by Claisen rearrangement of propargyl vinyl ethers which further undergo a [1,3]-hydride shift to yield 2,4-dienals followed by imine formation and a subsequent ring closure. Regarding the asymmetric synthesis of 1,2-dihydropyridines, there is a shortage of available methods, limited to the stereoselective dearomatization of pyridinium species by nucleophiles.[78c, 84] Only recently, Yu, Zhou *et al.* accomplished the synthesis of enantioenriched and structurally diverse 1,2-dihydropyridines in a modular approach employing a chiral organocatalyst (Scheme 3.2).[85]



Scheme 3.2. Organocatalytic Mannich/Wittig/cycloisomerization sequence to chiral 1,2-dihydropyridines **133**.

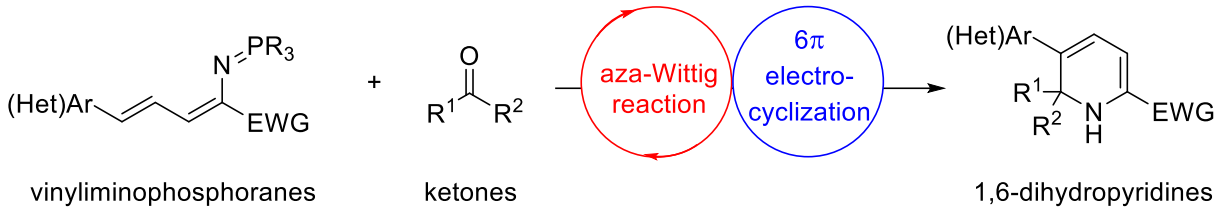
Generally, the generation of 1,2-DHPs and their derivatives bearing quaternary and spiro structural motifs in a metal-free fashion is challenging and in high demand. In addition, introduction of a simple fluorine atom or fluorinated functional groups into these motifs can have a great impact on their physicochemical and biological properties. One of the major effects of fluorine due to its strong electronegativity is the modulation of the p*K*a of functional groups in proximity. Changes in p*K*a of a molecule can influence its lipophilicity and subsequently its affinity, bioavailability,

and solubility.[86] In addition, the replacement of a C–H bond with a C–F bond can improve the metabolic stability of a compound. This is associated with the strong nature of C–F bond which can resist the attack by Cytochrome P450 monooxygenases, preventing in that way the oxidative metabolism. Fluorination can also cause conformational changes in a molecule due to van der Waals interactions of fluorine with other substituents.[86] Those features have been extensively exploited in medicinal chemistry[86-87], agrochemistry[88], and materials science[89]. It is interesting that in recent years organofluorine compounds represent about 20% of all the marketed drugs[87c, 90] and *ca.* 50% of all the agrochemicals[88c, 91]. Among those, trifluoromethyl-substituted pyridines are key structural motifs in active ingredients of agrochemical and pharmaceutical products.[92]

3.2 Project design

The design strategy to develop a novel, metal-free and efficient methodology for the synthesis of 1,2-dihydropyridines evolved from the notion that the corresponding azacycles could be generated *via* a ring closure. 6π-Electrocyclization of azatrienes is a common approach to accomplish the synthesis of these scaffolds. Although, this specific strategy entails challenges that are usually associated with the design and preparation of highly functionalized, requisite precursors in an efficient and practical manner. Up to date, the synthesis of azatriene platforms is mainly realized by two synthetic avenues, either treating primary amine functionalities with 2,4-dienals or from vinylogous amides coupled with α, β-unsaturated iminium salts.[36, 39, 71, 79c, 79d, 83]

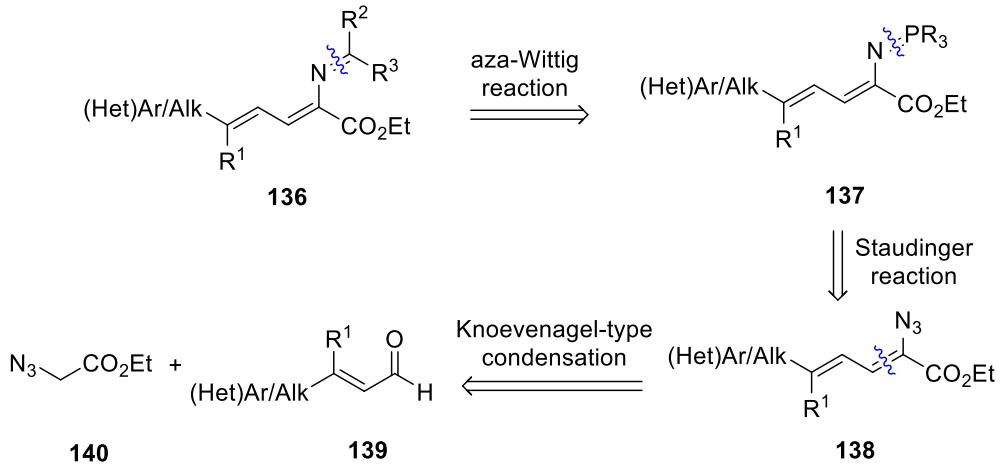
However, *N*-vinylic phosphazenes which display similar reactivity with phosphonium ylides towards carbonyl compounds, they have been proved to be valuable precursors for the construction of 2-azahexa- 1,3,5-trienes, as described by Palacios and co-workers.[93] It was envisioned that the high synthetic potential of *N*-vinylic λ^5-phosphazenes could be utilized for the development of a new method that would lead to the desired structural motifs. In parallel, organofluorine units could be introduced in the 1,2-DHP scaffold through the carbonyl reaction partners (Scheme 3.3).



Scheme 3.3. Reaction development for the modular synthesis of 1,6-dihydropyridines.

3.2.1 Retrosynthesis of aza-hexatriene precursor

As the azatriene substrate is one of the key components that determines the success of the transformation, it had to be rationally designed. It was proposed that the requisite precursor **136** could be *in situ* formed from *N*-vinylic phosphazenes **137** and carbonyl compounds *via* an aza-Wittig reaction.[94] The corresponding phosphazenes **137** could arise from a Staudinger reaction[95] of azido-acrylates[96] **138** and phosphine reagents upon nitrogen evolution. Also, previous experimental and theoretical studies, that have been extensively discussed in the introduction part, suggested that the presence of suitable substituents on the azatriene backbone can affect the rate of 6π-electrocyclization. Therefore, the general hexatriene skeleton was assembled according to the key disconnections, illustrated in Scheme 3.4.

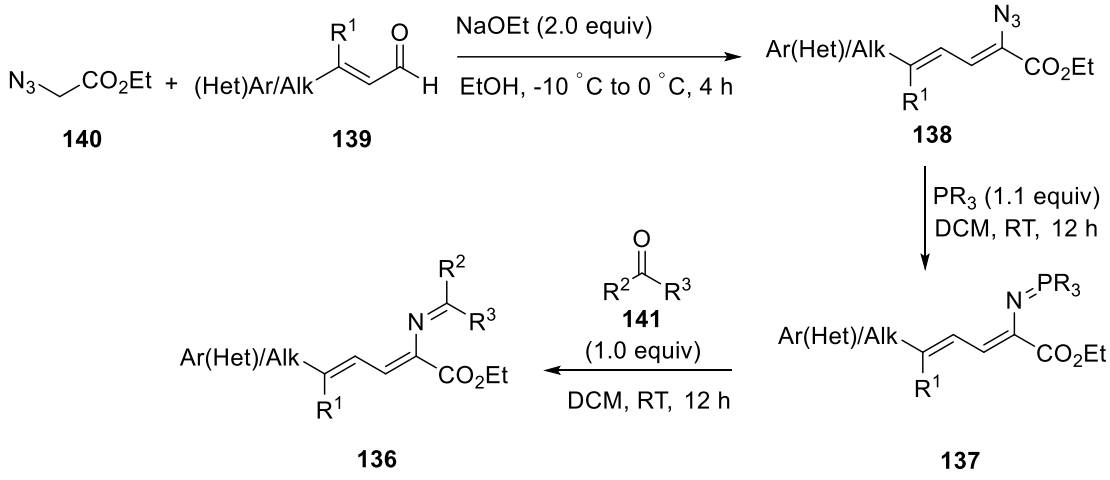


Scheme 3.4. Retrosynthetic analysis for the preparation of aza-hexatrienes **136**.

3.2.2 Synthesis of aza-hexatriene precursor

According to the retrosynthetic plan, the first step was the preparation of azido-acrylates. Following a method reported by Moody and co-workers,[96] the requisite vinyl azides **138** were prepared in one step upon condensation of ethyl azidoacetate[97] **140** with a series of readily available cinnamaldehydes **139** in the presence of a solution of sodium ethoxide in ethanol. In a next step, the corresponding azido-acrylates **138** were subjected to a Staudinger reaction by treatment with phosphine reagents to afford the *N*-vinylic phosphazenes **137** in quantitative yields. Finally, they were used without further purification, in an aza-Wittig reaction with activated ketones **141** in order to yield the desired precursors **136** (Scheme 3.5). It should be noted that this

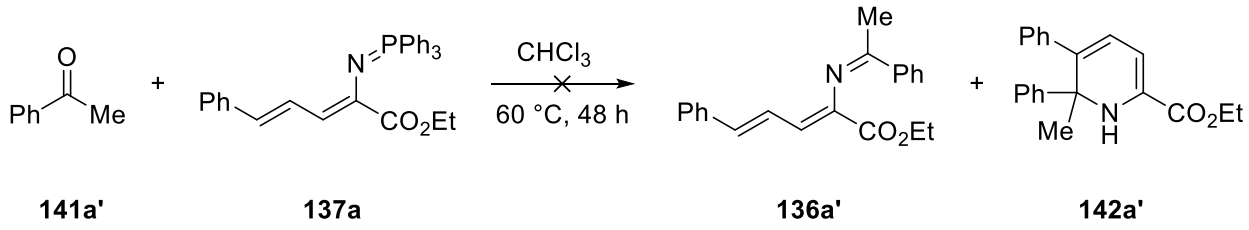
transformation is highly depended on the electronic properties of the phosphorus which is determined by its substituents.



Scheme 3.5. General synthetic route of aza-hexatrienes **136**.

3.3 Initial results and optimization

To prove the hypothesis that 1,2-dihydropyridines could be formed through a 6π-electrocyclization of an *in situ* generated aza-hexatriene **136a'**, initially a reaction between acetophenone **141a'** and *N*-vinylic- λ5-phosphazene **137a** bearing a triphenylphosphine substituent was tested (Scheme 3.6). However, neither the formation of the azatriene **136a'** nor the desired cyclized product **142a'** were detected. Instead, decomposition of **137a** and unreacted ketone **141a'** was observed.

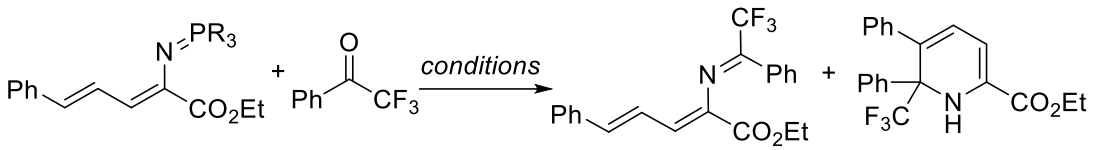


Scheme 3.6. Test reaction between acetophenone **141a'** and phosphazene **137a**.

It was assumed that enhancing the electrophilicity of the carbonyl group by introducing an electron-withdrawing group in the ketone moiety could allow the reaction to take place. A more electrophilic ketone in combination with a suitable substitution on the phosphorus atom of the phosphazene could facilitate the aza-Witting reaction. Thus, 2,2,2-trifluoroacetophenone **141a** and phosphazene **137a** were chosen as template for the reaction design.

Screening studies started with altering the phosphorus substituents of the vinyliminiphosphorane **137a** and modifying parameters such as solvent, temperature and reaction time. As illustrated in Table 3.1, treatment of 2,2,2-trifluoroacetophenone **141a** with triphenylphosphine substituent-containing phosphazene in ambient temperature and using dichloromethane as solvent, resulted in the formation of only linear imine **136a** in low yield (entry 1). The low yield indicates that the corresponding aza-Wittig reaction did not proceed smoothly. This is associated with the substituent on the phosphorus atom that affects the reactivity of the *N*-vinylic- λ5-phosphazene.[98] The triphenyl group decreases the electron density of the phosphorus atom, thus leading to a nitrogen with lower nucleophilic profile. By replacing one phenyl group with methyl substituent enhanced reactivity was observed that significantly improved the yield of the acyclic azatriene even in shorter reaction time (entry 2). Excellent yields of **136a** were obtained when trimethyl-phosphine containing vinyliminophosphorane was used (entries 3-4). However, when the reaction was performed at room temperature, the cyclized product **142a** was not detected regardless the reaction time (entry 4). A change in the solvent system, from dichloromethane to chloroform allowed the reaction to proceed in higher temperature (40 °C), yielding the desired product **142a** but in low yield (entry 5). A further increase in the reaction temperature (60 °C) and using the triphenyl-phosphine substituted vinyliminophosphorane, led to the formation of **142a** in still low yield (entry 6) due to the electronic reasons described above. Gratifyingly, when vinyliminophosphorane bearing the trimethyl phosphine substituent was employed, the dihydropyridine scaffold **142a** was obtained in 84% yield (entry 7). Further increase of the temperature and switching to toluene and chlorobenzene as solvents did not affect significantly the yield of the reaction.

Table 3.1. Representative conditions for the optimization of the aza-Wittig/6π-electrocyclization sequence[a].

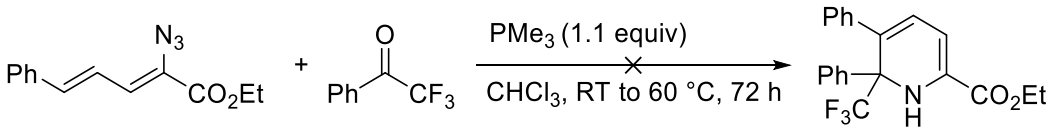


137a **141a** **136a** **142a**

Entry	PR_3	Solvent [0.1 M]	Temp. (°C)	Time (h)	Yield (%)[b] **136a**	Yield (%)[b] **142a**
1	PPh_3	DCM	RT	72	20	--
2	PPh_2Me	DCM	RT	48	70	--
3	PMe_3	DCM	RT	12	92	--
4	PMe_3	DCM	RT	96	92	--
5	PMe_3	$CHCl_3$	40	72	70	25
6	PPh_3	$CHCl_3$	60	72	25	30
7	**PMe_3**	**$CHCl_3$**	**60**	**72**	**--**	**84**
8	PMe_3	PhMe	110	72	--	80
9	PMe_3	PhCl	130	72	--	83

[a]Reaction conditions: **137a** (0.15 mmol, 1.0 equiv) and **141a** (0.15 mmol, 1.0 equiv) were stirred in solvent [0.1 M] at given temperature for given time. [b]Isolated yield.

After having conducted the screening studies, it was evaluated whether a direct protocol can be employed to access the desired product in one-pot fashion overriding the preparation of vinyliminophosphoranes. A reaction using vinyl azide **138a**, trimethyl phosphine, and ketone **141a** was performed. However, the desired product **142a** was not observed (Scheme 3.7).

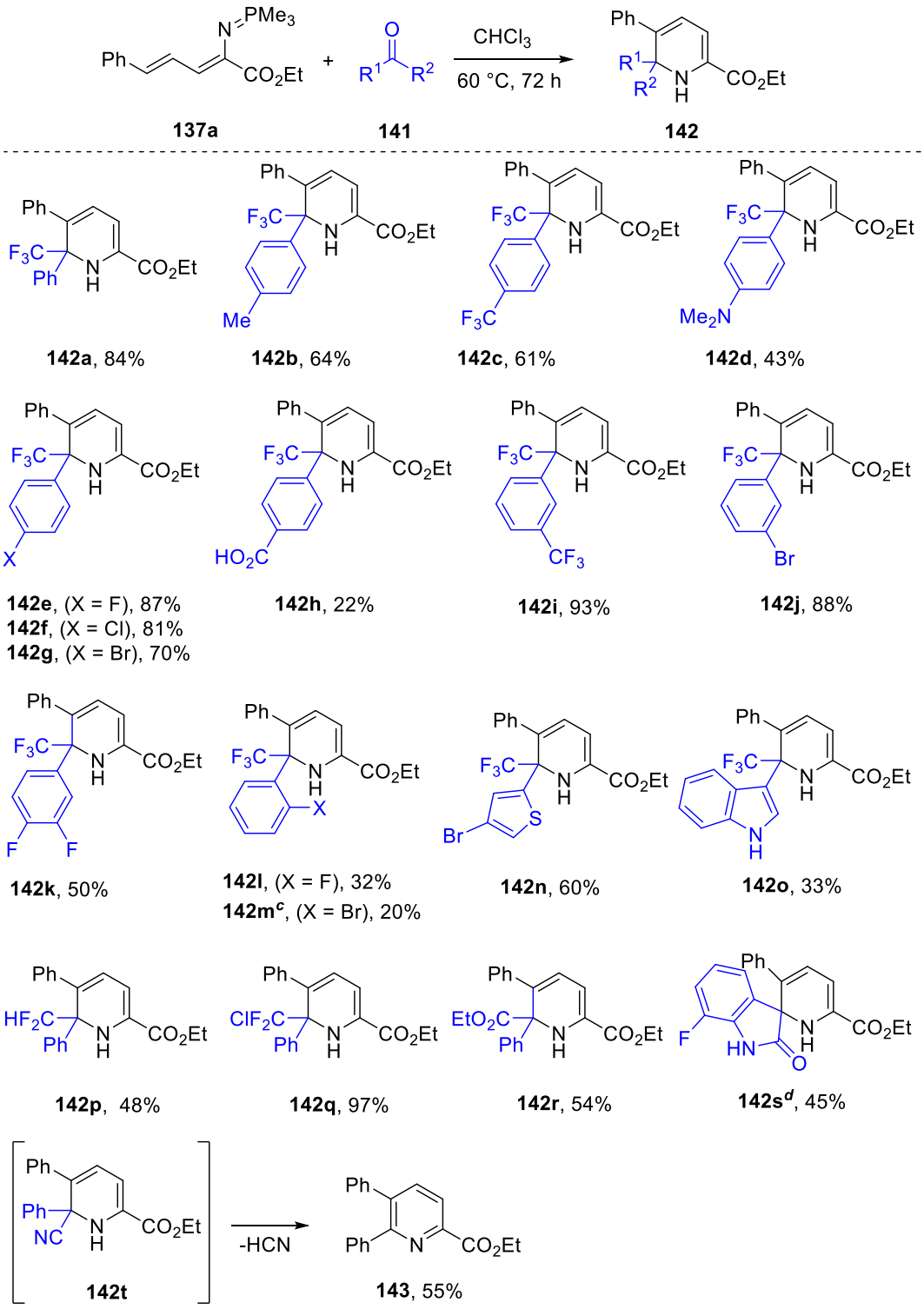


138a (1.0 equiv) **141a** (1.0 equiv) **142a**

Scheme 3.7. Unsuccessful attempt towards the one-pot synthesis of **142a**.

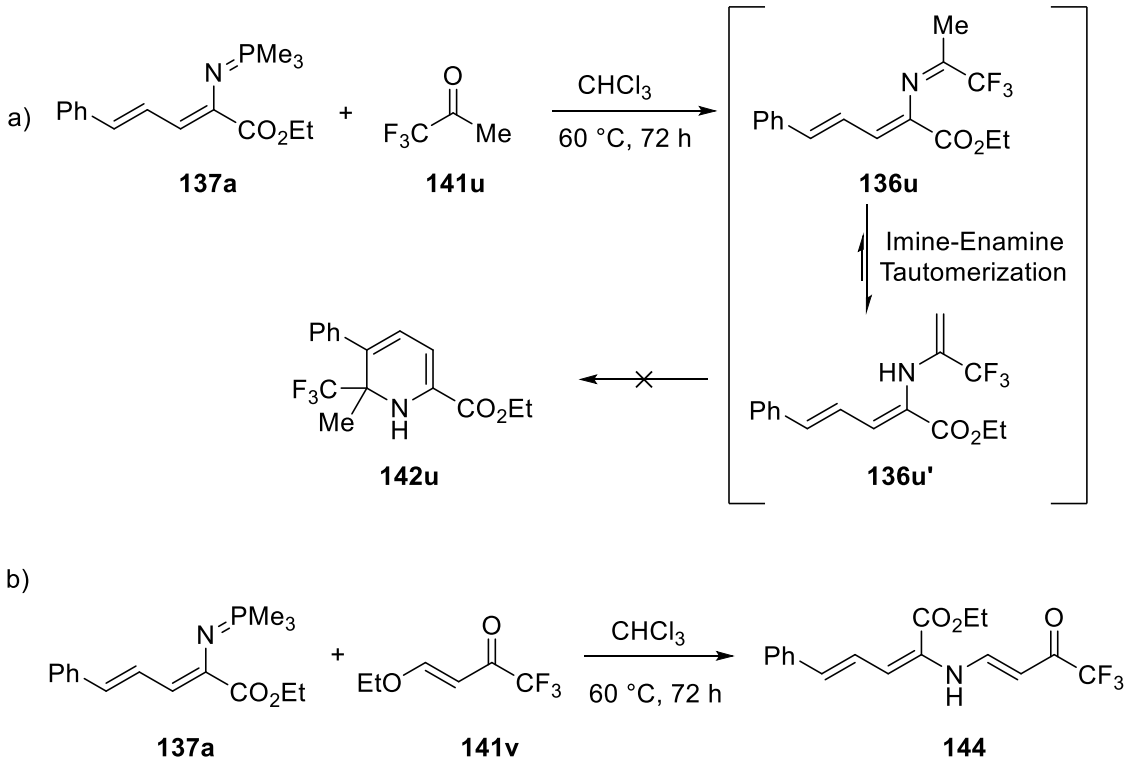
3.4 Scope of ketones and vinyliminophosphoranes

Having the optimal reaction conditions in hand, the scope, and limitations of the aza-Wittig/6π-electrocyclization sequence were studied. Initially, the scope of readily available ketones with different substitution pattern on the aryl group was investigated in a systematic manner (Scheme 3.8). Electron-donating or electron-withdrawing substituents placed on the *meta*- and/or *para*-position of the aryl group of ketones were well tolerated and the desired products (**142a-142k**) were obtained in moderate to excellent yields (22-93%). A significant decrease in the reaction yields were observed when *ortho*-substituted ketones were used as substrates. It was reasoned that the steric influence of the *ortho*-substituent could lead to unfavorable interactions. Nevertheless, a smaller atom (fluorine substituent) in *ortho*-position resulted in product **142l** with 34% yield. Whereas, switching to bromine substituent, the steric demand was further increased and only traces of the cyclized product **142m** were detected as the reaction stopped at the stage of the acyclic imine. In order to overcome this limitation, alternative conditions were adopted. The isolated azatriene was subjected to higher temperature in toluene as solvent affording the cyclized product **142m** in 20% yield. In addition, the scope was rapidly extended to ketones with heteroaryl-substituents which reacted to provide the corresponding products **142n** and **142o** with 33 and 60% yield, respectively. Ketones containing different electron-withdrawing groups other than trifluoromethyl such as difluoromethyl, chlorodifluoromethyl, ethoxycarbonyl and cyano could also be utilized in this method without having any noticeable effect on the reaction yield (48-97%). However, in latter case the cyano-substituted 1,6-dihydropyridine **142t** was rapidly converted to pyridine **143** upon spontaneous elimination of hydrogen cyanide (Scheme 3.8). Remarkably, highly activated ketones such as isatins have emerged as suitable reaction partners for this method, providing the useful dihydropyridine-based spirooxindole **142s** with 45% yield. It should be noted that the cyclized product was obtained as an inseparable mixture with its non-cyclized intermediate. Attempts to force the undesired intermediate from this mixture to ring closure failed.



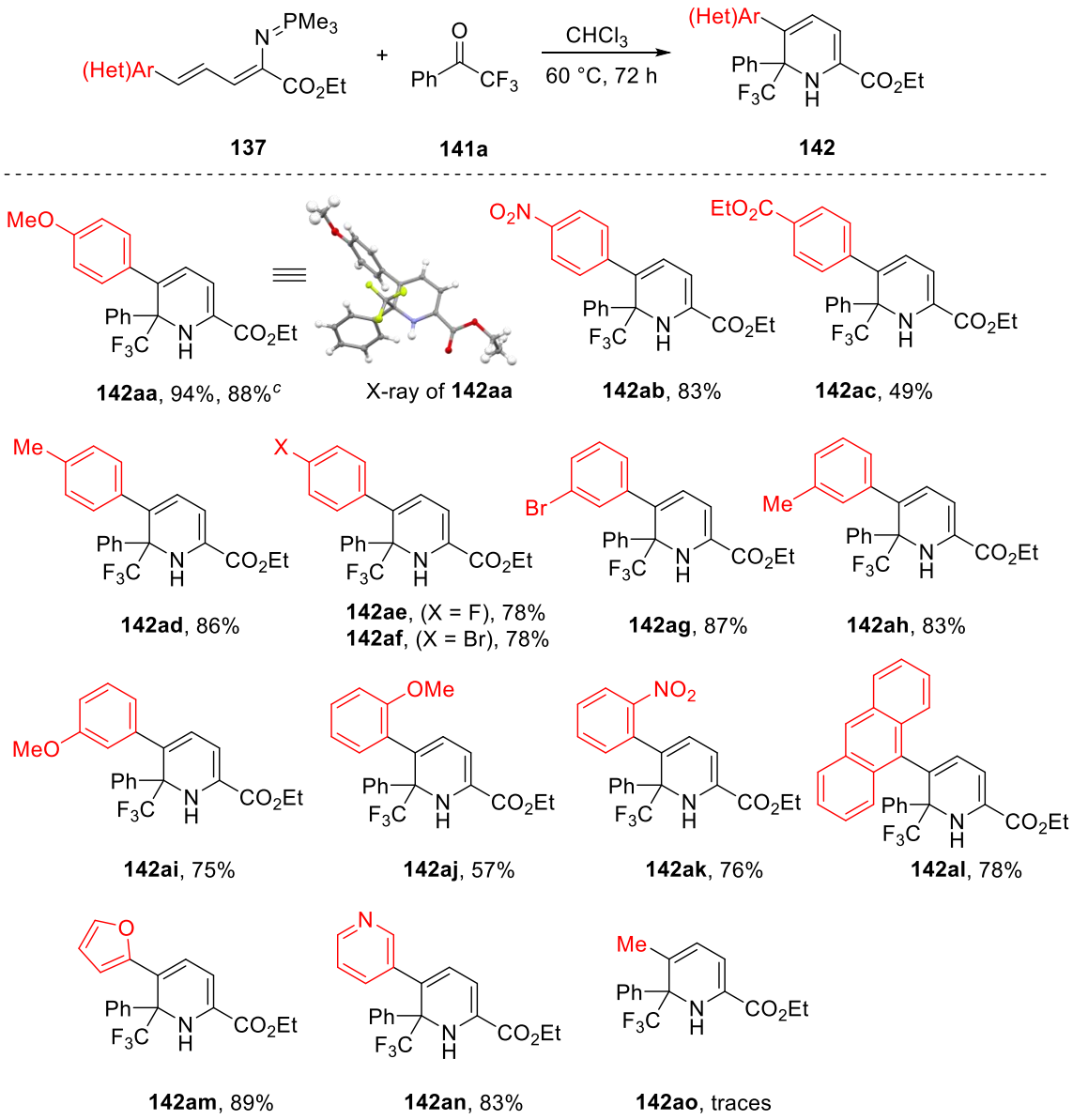
Scheme 3.8. Substrate scope with different ketones. [a]Reaction conditions: **137a** (0.15 mmol), **141** (0.15 mmol), in $CHCl_3$ [0.1 M] were stirred at 60 °C for 72 h. [b]Isolated yield. [c]Reaction was conducted by heating the corresponding isolated non-cyclized product in toluene, at 110 °C for 72 h. [d]Isolated as inseparable mixture with the intermediate acyclic imine in a ratio of 4:1.

It was found that an important limitation of the scope was the use of aliphatic ketones such as 1,1,1-trifluoroacetone **141u**, as the reaction was confronted with imine-enamine tautomerization and therefore restricting the ring closure (Scheme 3.9a). By employing an α, β-unsaturated ketone **141v**, a competitive 1,4-addition took place, preventing the formation of the azatriene precursor and therefore its cyclization to the desired product (Scheme 3.9b).



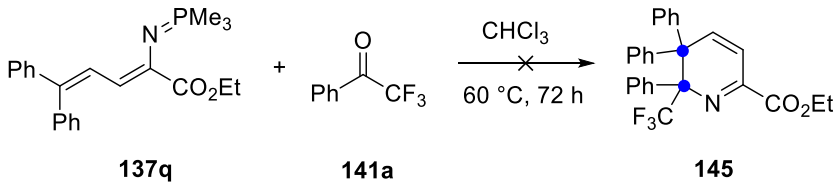
Scheme 3.9. Limitations of the scope a) by enamine formation b) competitive 1,4-addition.

To further unlock the potential of the developed method, its compatibility with a wide range of vinyliminiphosphoranes was tested. Pleasingly, the scope in respect of those proved to be broad as well, allowing a further expansion of the chemical space. Vinyliminiphosphoranes with *ortho*-, *meta*-, and *para*-substituents on the aryl ring were highly compatible regardless their electronic properties. In particular, both electron-rich and electron-poor substituents did not affect the yields (49-94%) of the corresponding products **142aa-142al** (Scheme 3.10). Additionally, the structure of compound **142aa** was determined by X-Ray analysis. Switching to heterocycle-containing substrates, high levels of reactivity were still observed, delivering the products **142am** and **142an** in very good yields (83-89%). However, when alkyl-substituted vinyliminiphosphorane was employed, the reactivity dropped significantly, yielding the product **142ao** only in traces.



Scheme 3.10. Substrate scope with different vinyliminophosphoranes. [a]Reaction conditions: **137** (0.15 mmol), **141a** (0.15 mmol), in $CHCl_3$ [0.1 M] were stirred at 60 °C for 72 h. [b]Isolated yield. [c]Isolated yield for 1.00 mmol scale.

Also, by further increasing the degree of substitution on the terminal double bond of the phosphazene **137q**, no cyclization occurred (Scheme 3.11). Deviation from the standard conditions such as increase of the reaction temperature at 110 °C and change of the solvent to toluene wasn't successful. The failure of the ring closure is assumed to be related to steric factors or the stability of the cyclized product itself as the [1,5]-hydride shift, the reaction´s driving force, is blocked.

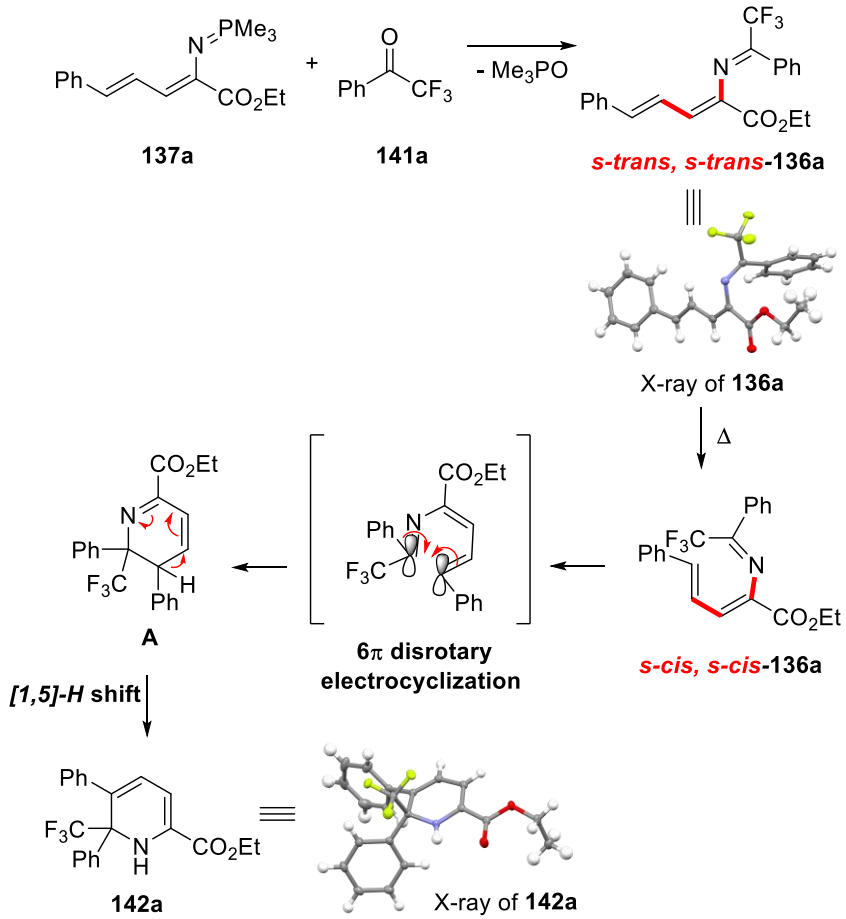


Scheme 3.11. Attempt for generation of dihydropyridine **145** with two quaternary carbon centers.

Finally, the scalability of the method was evaluated by performing the reaction in 1.00 mmol scale. No significant impact on the reaction outcome was observed.

3.5 Mechanistic considerations

In the light of the obtained results and based on the previous reports[79f, 93], a reasonable reaction mechanism could be suggested (Scheme 3.12). Initially, azatriene **136a** is generated by an aza-Wittig reaction of the vinyliminophospharene **137a** and ketone **141a** through a sequence of imine formation and trimethyl phosphine oxide elimination.

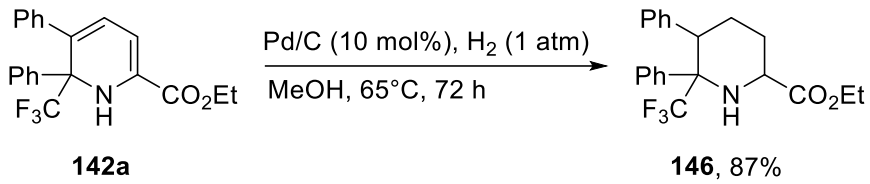


Scheme 3.12. Proposed reaction mechanism for the aza-Wittig/6π-electrocyclization sequence.

X-ray analysis of the isolated imine **136a** revealed that it has an *s-trans*, *s-trans* configuration which cannot undergo 6π-electrocyclization. This can be enabled upon conversion of the *s-trans*, *s-trans* conformer to the "cyclization-reactive" *s-cis*, *s-cis* conformer **136a** *via* bond rotation. The "reactive" conformer, which is higher in energy and thermodynamically less favored, requires thermal conditions to be formed. Once this prerequisite is fulfilled, a 6π-electrocyclization in a *disrotatory* mode takes place affording intermediate **A**. Finally, subsequent [1,5]-hydride shift affords the desired 1,6-dihydropyridine scaffold **142a**.

3.6 Synthetic utility of the 1,6-dihydropyridine scaffolds

To stress the synthetic value of the developed method, several product transformations were explored. First, the obtained multi-substituted 1,6-dihydropyridines could be exploited for the rapid generation of piperidines *via* reduction of both double bonds. Substrate **142a** was subjected to hydrogenation in the presence of Pd/C catalyst to deliver the corresponding piperidine **146** as a single diastereomer (Scheme 3.13).

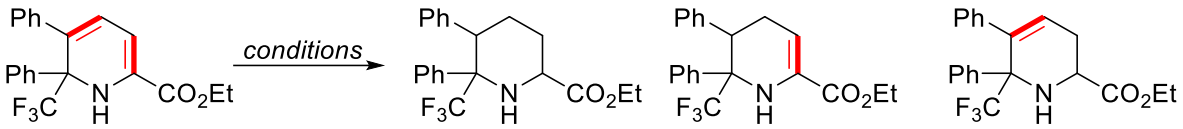


142a **146**, 87%

Scheme 3.13. Synthesis of piperidine **146** by hydrogenation of **142a**.

As **142a** contains two double bonds which might differ in reactivity, it was interesting to explore whether it was possible to selectively reduce one of them in order to obtain the corresponding tetrahydropyridine. Thus, substrate **142a** was treated with catalyst Pd/C in ambient temperature and hydrogen atmosphere while the progress of the reaction was monitored over the time (Table 3.2). Upon completion of 96 h only piperidine **146** was observed (entry 1). By decreasing the reaction time to 36 h and 22 h respectively, a mixture of mono-reduced product **147a** and **146** in a ratio of 5:1 was observed in both cases (entries 2-3). Gratifyingly, isolation of pure tetrahydropyridine **147a** was achieved in a reaction time of 12 h. Further attempts to selectively obtain compound **147b** by thiourea-catalyzed transfer hydrogenation were unsuccessful (entries 5-6). In general, the critical parameter to control the reduction of one double bond of compound **142a** over its full reduction was the reaction time.

Table 3.2. Condition screening for selective hydrogenation of **142a**.[a]



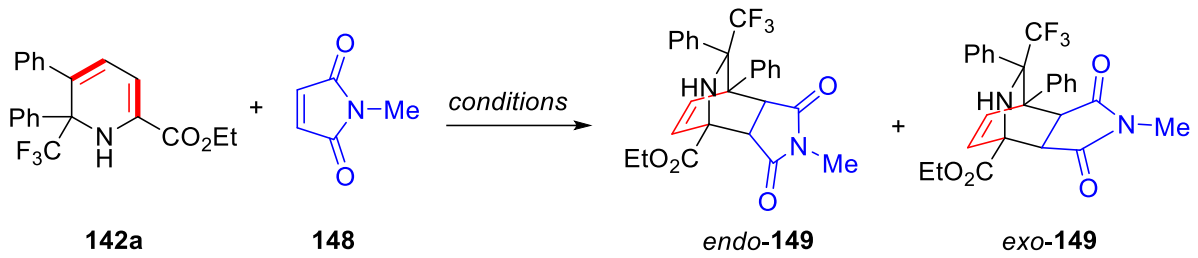
142a **146** **147a** **147b**

Entry	Catalyst	Temp. (°C)	Time (h)	Product ratio	Yield (%)[b]
1	Pd/C (10 mol%)	RT	96	only **146**	77
2	Pd/C (10 mol%)	RT	36	**147a**/**146** (5:1)	66[c]
3	Pd/C (10 mol%)	RT	22	**147a**/**146** (5:1)	72[c]
4	Pd/C (10 mol%)	RT	12	only **147a**	84
5	Hantzsch ester (1.2 equiv), Schreiner′s thiourea catalyst (20 mol%)	RT	48	--	--
6	Hantzsch ester (1.2 equiv), Schreiner′s thiourea catalyst (20 mol%)	40	72	--	--

[a]Reaction conditions: **142a** (0.05 mmol) was stirred in PhMe [0.05M] at given temperature for given time. [b]Isolated yield. [c]Calculated yield for main product.

As it was previously mentioned, 1,6-dihydropyridines can serve as cyclic azadienes in Diels-Alder reactions providing access to the valuable scaffold of isoquinuclidine. Therefore, diene **142a** and *N*-methylmaleimide **148** as dienophile were chosen as the model substrates for this transformation. Different reaction conditions were screened to accomplish the formation of the bridged ring **149** (Table 3.3). Initially, the reaction was performed in the absence of additives. Changing the solvents and gradually increasing the temperature and reaction time did not result in product formation **149**, instead the starting material **142a** was fully recovered (entries 1-3). In an attempt to decrease the energy gap between the HOMO and LUMO of the reaction partners, Lewis acids were employed. In the presence of catalytic amounts of $Mg(NTf_2)_2$ in ambient temperature as well as at 65 °C, no reaction occurred (entries 4-5). A similar trend was observed by employing stoichiometric amounts of $ZnCl_2$ (entries 6-7). Traces of the desired product were detected when switching to a relatively strong Lewis acid, $BF_3{\cdot}Et_2O$ at room temperature (entry 8). It was speculated that an increase of the temperature could enhance the product formation. Indeed, when the reaction was performed at 50 °C, the product could be isolated albeit in very low yield (entry 9). Characterization by ^{1}H NMR revealed that the product was obtained as a mixture of *endo*/*exo* (1.6:1).

Table 3.3. Condition screening for Diels-Alder reaction of **142a** and *N*-methylmaleimide **148**.[a]



142a **148** ***endo*-149** ***exo*-149**

Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	*endo*/*exo*-Product ratio	Yield (%)[b]
1	--	DCM	RT	24	--	--
2	--	$CHCl_3$	65	72	--	--
3	--	PhMe	110	72	--	--
4	$Mg(NTf_2)_2$ (10 mol%)	DCM	RT	24	--	--
5	$Mg(NTf_2)_2$ (10 mol%)	$CHCl_3$	65	72	--	--
6	$ZnCl_2$ (1.1 equiv)	DCM	RT	24	--	--
7	$ZnCl_2$ (1.1 equiv)	$CHCl_3$	65	48	--	--
8	$BF_3{\cdot}Et_2O$ (10 mol%)	DCM	RT	24	--	traces
9	$BF_3{\cdot}Et_2O$ (10 mol%)	DCM	50	72	1.6:1[c]	13

[a]Reaction conditions: **142a** (0.1 mmol, 1.0 equiv) and **148** (0.11 mmol,1.1 equiv) were stirred in solvent [0.1 M] at given temperature for given time. [b]Isolated yield. [c]Determined by ^1H NMR.

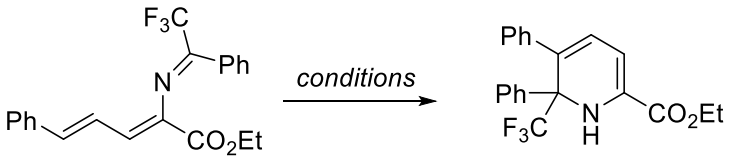
Considering the electron-withdrawing effect of the CO_2Et group on the diene scaffold **142a**, it was hypothesized that the diene might be electron-poor and thus it could undergo an inverse-electron demand aza-Diels-Alder reaction.[99] Based on this assumption, diene **142a** was subjected to reactions with electron-rich dienophiles such as ethyl vinyl ether and 2,3-dihydrofuran (2,3-DHF). However, no product formation was noticed after varying the reaction parameters.

3.7 Investigation of the asymmetric 6π-electrocyclization

To extend the studies of 6π-electrocyclization to an asymmetric transformation, it was first investigated whether it is possible to initiate the reaction at lower temperatures (< 60 °C) with the

assistance of a Lewis or Brønsted acid. It is well-known that generally elevated temperatures have a negative effect on the enantioselective outcome in most asymmetric reactions.[100]

Table 3.4. Condition screening for LA or BA-catalyzed 6π-electrocyclization of **136a**.



136a **142a**

Entry	Catalyst (10 mol%)	Time (h)	Yield (%)[b]
1	TfOH	20 min	16
2	Tf_2NH	72	traces
3	TFA	72	traces
4	$TsOH{\cdot}H_2O$	72	traces
5	$(CuOTf)_2$	72	--
6	$Sc(OTf)_3$	72	--
7	$Yb(OTf)_3$	72	--
8	$Zn(OTf)_2$	72	--
9	$Mg(NTf_2)_2$	72	--

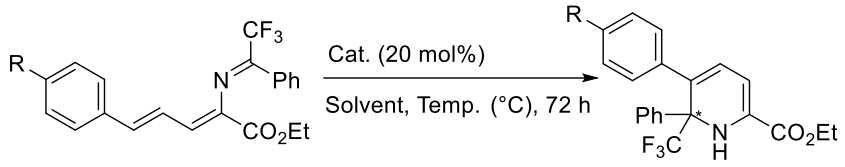
[a]Reaction conditions: **136a** (0.025 mmol, 1.0 equiv) was stirred in DCM [0.1 M] at ambient temperature for given time. [b]Isolated yield. [c]Reaction was carried out at 40 °C.

In order to establish a catalytic method for the 6π-electrocyclization, azatriene **136a** was chosen as model substrate in an effort to eliminate any perturbations derived from the tandem aza-Wittig/6π-electrocyclization process. Initial screening started with the employment of strong Brønsted acids. When the reaction was performed in the presence of catalytic amounts of trifluoromethanesulfonic acid (TfOH), the cyclized product was formed at ambient temperature, albeit in low yield (16%) (Table 3.4, entry 1). Due to the highly acidic nature of TfOH, a competition of substrate´s decomposition **136a** and product formation **142a** was observed over the course of the reaction. The use of different Brønsted acids did not lead to better results (entries 2-4). Switching to Lewis acids as catalysts, the reaction did not take place while substrate **136a** was recovered in all cases (entries 5-9).

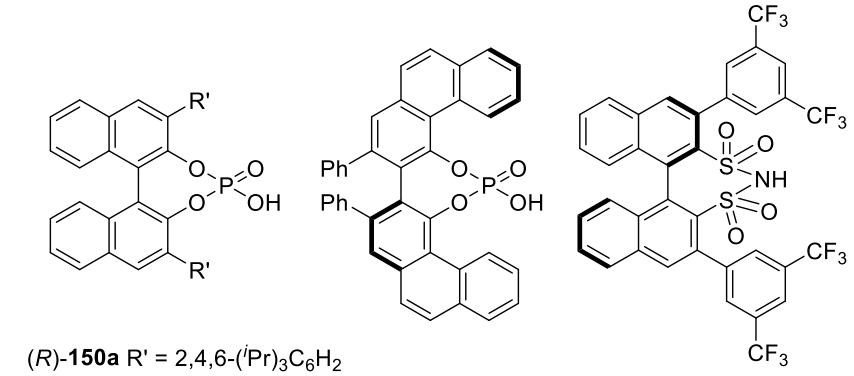
The potential of TfOH to initiate the 6π-electrocyclization at ambient temperature could create an opportunity to explore this transformation in an asymmetric fashion. Therefore, the performance of several chiral Brønsted acids, a well-known strategy for inducing asymmetry in pericyclic reactions[101], was evaluated. Specifically, the enantioselective electrocyclic ring closure of substrate **136ab** was studied in the presence of various phosphoric acids (**150** and **151**) endowed with axial chirality and chiral disulfonimide **152** (Table 3.5). Under the standard reaction conditions, the presence of chiral Brønsted acids did not affect the product formation with the reaction yields ranging from 70-90%. In terms of enantioselectivity, chiral phosphoric acids **150a-150d** and **151** resulted in the cyclized product with low enantiomeric excess (3-16%, entries 1-4 and 8). A promising increase in the enantioselectivity was noticed (24%, entry 5) by changing the substituent on the binol phosphate catalyst to phenanthryl group ((*R*)-**150e**). This can be explained by an enhanced shielding of one π face of the 6π delocalized system derived by the chiral Brønsted acid counter anion as described in previous works (see Scheme 1.19).[46, 49] Maintaining the same catalytic system ((*R*)-**150e**), the influence of the temperature on the stereochemical outcome was also examined. Interestingly, when performing the reaction at 50 °C, the enantioselectivity was slightly improved to 34% while the yield dropped down to 40% (entry 6). However, only traces of product were detected when an even lower temperature was attempted (entry 7). Finally, switching to chiral disulfonimide **152**, almost no enantio-induction was observed (entry 9).

To exclude that the low enantioselectivity is related to this specific substrate, further investigation was conducted using azatriene **136ac** and the chiral phosphoric acids (*R*)-**150d** and (*R*)-**150e** which exhibited good performance in the initial screening (Table 3.5). In addition, the effect of different solvents was studied which revealed that chlorinated solvents provide better selectivity over the non-chlorinated ones. In general, the poor levels of enantioselectivity in this transformation might be associated with the competing background reaction as the electrocyclic ring closure of the azatrienes can even proceed without any additives at high temperatures (≥50 °C).

Table 3.5. Condition screening for the asymmetric 6π-electrocyclization of **136** with chiral Brønsted acids.



136 **142**



(*R*)-**150a** R' = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$
(*S*)-**150b** R' = 3,5-(CF$_3$)$_2$C$_6$H$_3$
(*R*)-**150c** R' = SiPh$_3$
(*R*)-**150d** R'= 9-Anthracenyl
(*R*)-**150e** R' = 9-Phenanthryl

151 **152**

Entry	**136** (R)	Catalyst	Solvent	Temp. (°C)	Yield (%)[b]	*ee* (%)[c]
1	NO_2	(*R*)-**150a**	$CHCl_3$	60	90	5
2	NO_2	(*S*)-**150b**	$CHCl_3$	60	88	3
3	NO_2	(*R*)-**150c**	$CHCl_3$	60	90	16
4	NO_2	(*R*)-**150d**	$CHCl_3$	60	70	13
5	NO_2	(*R*)-**150e**	$CHCl_3$	60	75	24
6	NO_2	(*R*)-**150e**	$CHCl_3$	50	40	34
7	NO_2	(*R*)-**150e**	$CHCl_3$	30	traces	n.d.[d]
8	NO_2	**151**	$CHCl_3$	60	80	3
9	NO_2	**152**	$CHCl_3$	60	85	2
10	CO_2Et	(*R*)-**150d**	$CHCl_3$	60	42	14
11	CO_2Et	(*R*)-**150d**	PhCl	60	42	14
12	CO_2Et	(*R*)-**150d**	PhMe	60	41	10
13	CO_2Et	(*R*)-**150d**	MeCN	60	40	2
14	CO_2Et	(*R*)-**150e**	$CHCl_3$	60	40	8

[a]Reaction conditions: **136** (0.025 mmol, 1.0 equiv) in solvent [0.1 M] using 20 mol% of chiral catalyst for 72 h. [b]Isolated yield. [c]Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase. [d]n.d. = not determined.

3.8 Conclusion

In summary, a novel and metal-free method has been developed that allows access to a variety of 1,6-dihydropyridines with quaternary and spiro motifs *via* a domino aza-Wittig/6π-electrocyclization sequence. The protocol could take place under mild conditions and exhibited high functional group tolerance as well as operational simplicity. The obtained 1,6-dihydropyridines could undergo further transformations providing new chemotypes with potential biological and pharmacological activities. In addition, efforts have been made for the development of an asymmetric variant of this method which unfortunately resulted in products with inadequate levels of enantioselectivity.

Chapter 4. Preparation and Synthetic Applications of Novel Hypervalent Iodine Reagents

(Parts of this chapter have already been published: G. Goebel, "Development of Novel Hypervalent Iodine Catalysts for Asymmetric α-Functionalization of Ketones", Bachelor Thesis, 2019)

4 Preparation and Synthetic Applications of Novel Hypervalent Iodine Reagents

4.1 Introduction

In 1811, the industrial chemist B. Courtois isolated iodine from the ash of seaweed for the first time.[102] The name of iodine originates from the Greek term "violet-colored" which mirrors the distinctive purple color of its vapor and it was given by J. L. Gay Lussac in 1813.[103] Iodine is typically found in monovalent compounds, having an oxidation state of -1.[102] However, being the largest, both most polarizable and electropositive element of the halogen family can form stable multivalent compounds as well.[102]

In 1886, the first hypervalent iodine(III) compound, dichloroiodobenzene ($PhICl_2$), was synthesized from iodobenzene and chlorine gas by the German chemist C. Willgerodt.[104] Since then, numerous multivalent organoiodine compounds have been prepared. Some well-established and frequently used hypervalent iodine reagents are illustrated in Figure 4.1.[105] Depending on iodine´s oxidation state, they can be classified into iodine(III) and iodine(V) compounds, also known as λ^3-iodanes and λ^5-iodanes, respectively[102, 106] (Figure 4.1). The λ^3-iodanes are usually arranged in a trigonal bipyramidal geometry in which the aryl group (Ar) is oriented in the equatorial position, while the heteroatom ligands (L) occupy the apical positions (Figure 4.1, **A**).[106b] The linear bond L-I-L which can be explained by a three-center-four-electron (3c-4e) model[107], represents the hypervalent bond and it is responsible for the high electrophilic character of the hypervalent iodine compounds in chemical transformations.[106b] On the other hand, λ^5-iodanes possess a square bipyramidal geometry with the aryl group and the free electron pair located in the apex while the four heteroatom ligands (L) in the basal positions (Figure 4.1, **B**).[106b] The high interest towards those compounds derives from their both special features and reactivity. In particular, hypervalent iodine reagents are relatively inexpensive, nontoxic, environmentally benign oxidants with high stability towards atmospheric oxygen and moisture, and easy handling.[105a, 108] Also, they can be a good alternative to transition metal derivatives since they have similar structure and reactivity.[106b] Therefore, hypervalent iodine reagents can induce various "transition-metal-like" transformations, in particular oxidative reactions[109], carbon-carbon[110] or carbon-heteroatom bond formations[111] in a "metal-free" manner.[105a, 108]

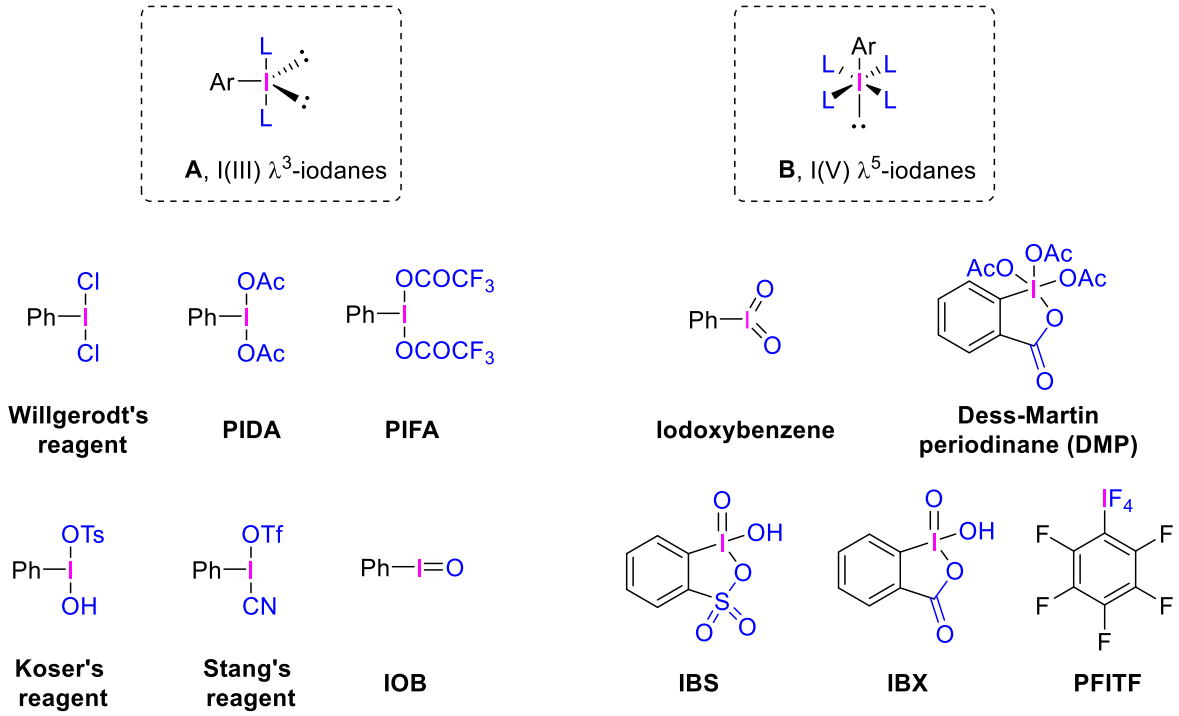


Figure 4.1. Representative examples of hypervalent iodine reagents.

4.1.1 Chiral hypervalent iodine reagents in enantioselective synthesis

Over the last decades, the application of polyvalent organoiodine compounds has been extended in asymmetric synthesis due to their potential in a plethora of asymmetric organocatalytic transformations[105a, 108, 112] and natural product synthesis.[113] The earliest example of chiral hypervalent iodine(III) reagent was a diphenyliodonium tartrate which was reported by Pribam[114] in 1907 without revealing the exact structure. It is assumed that this chiral λ^3-iodane which chirality was confirmed by optical rotation, possesses one of the structures illustrated in Figure 4.2.[105a]

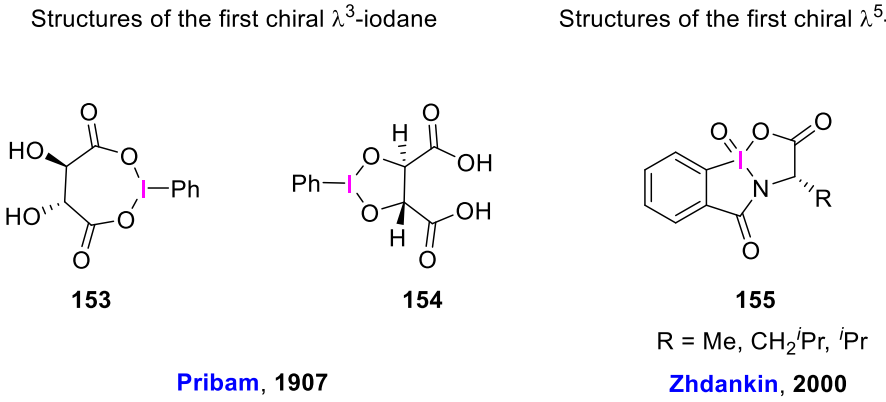


Figure 4.2. Structures of the first chiral hypervalent iodine(III) and iodine(V) compounds.

Interestingly, almost one century later, the synthesis of the first chiral λ^5-iodanes derived from amino acids was described by Zhdankin *et al.* (Figure 4.2).[115] Great progress has been made in the design and development of chiral hypervalent iodine compounds, ever since. Initially, chiral iodoarenes with preformed iodine(III) centers were mainly used in stoichiometric amounts to promote the corresponding reactions. However, in an effort to establish their catalytic versions and to facilitate the process in terms of economy and practicability, the *in situ* generation of chiral iodoarenes(III) from the corresponding iodine(I) precursors was explored.[112a] In that way, the additional step of their pre-oxidation and purification could be prevented. In the course of this program, numerous chiral iodoarenes have been prepared which can be clustered in four different types based on the chirality that they are endowed with (Figure 4.3).[105a]

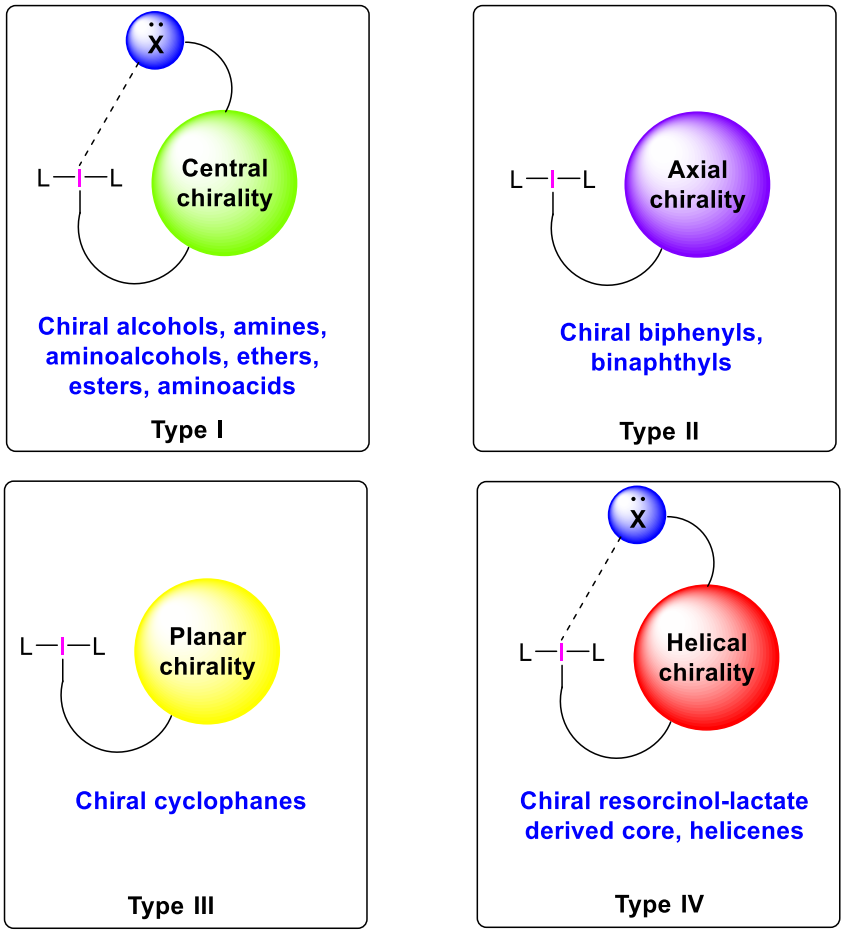
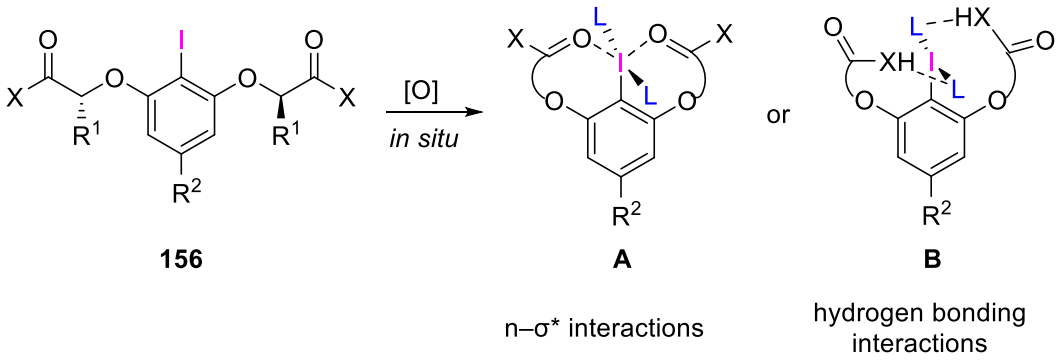


Figure 4.3. Different types of chirality installed in hypervalent iodine compounds. Reprinted from ref.[105a] Copyright (2019) American Chemical Society.

Type I represents the family of iodine(I) compounds with central chirality derived from the carbon segment with stereogenic centers. In this regard, many chiral functionalities have been installed

e.g. alcohols, amines, and more which display coordinative properties to stabilize the formed intermediate during the reaction course. In the case of **Type II** and **Type III**, axial and planar chirality features have been introduced in the structure of the catalyst in order to control the stereoselectivity. In the latter type (**Type IV**), the group of chiral iodine(I) compounds is endowed with helical chirality[116] around the iodine atom. These catalysts are predominant in various oxidative transformations due to their high success rate in enantio-induction. Fujita[117] and Ishihara[118] were the first to present this strategy in their pioneering works in 2010. Specifically, they demonstrated the synthesis of resorcinol-based iodine(I) compounds **156** with flexible chiral lactate moieties in C2 position. Their unique performance is highly associated with the generation of an effective chiral pocket from the intramolecular n–σ* interactions of the carbonyl group and the oxidized iodine (**A**, Scheme 4.1). Alternatively, other potential, noncovalent intramolecular interactions such as hydrogen-bonding between the subfunctional group (X) of the catalyst and the iodine(III) ligands (L) or π-π interactions of aromatic residues can also contribute to a three-dimensional folding, thus leading to a helical structure (**B**, Scheme 4.1).[105a, 112a, 118a]



Scheme 4.1. Structural arrangements in resorcinol/lactate-based iodoarenes.

Apart from the various chiral features installed in the organoiodine(I) compounds, different types of structural symmetry have been also examined in the architecture of those reagents. At present, the known chiral iodoarene precursors possess either C_1- or C_2-symmetry[119] with the latter being the most successful in terms of stereoselectivity in numerous asymmetric oxidative transformations. Some representative examples of reported precatalysts of hypervalent organoiodine(III) compounds are illustrated in Figure 4.4.[105a, 112c, 119] A brief overview of the enantioselective catalytic potential of those compounds in some selected reactions will also be discussed below.

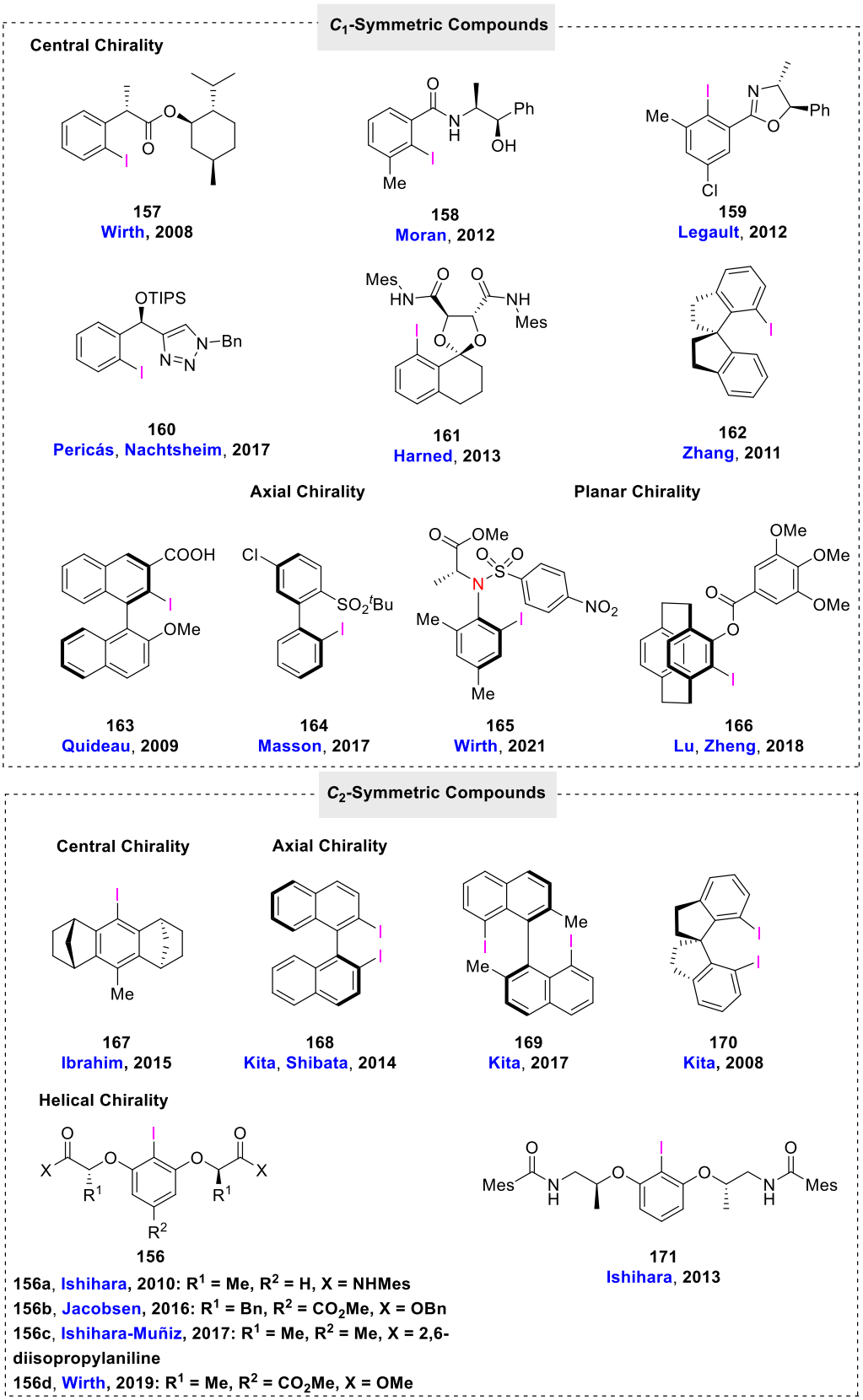
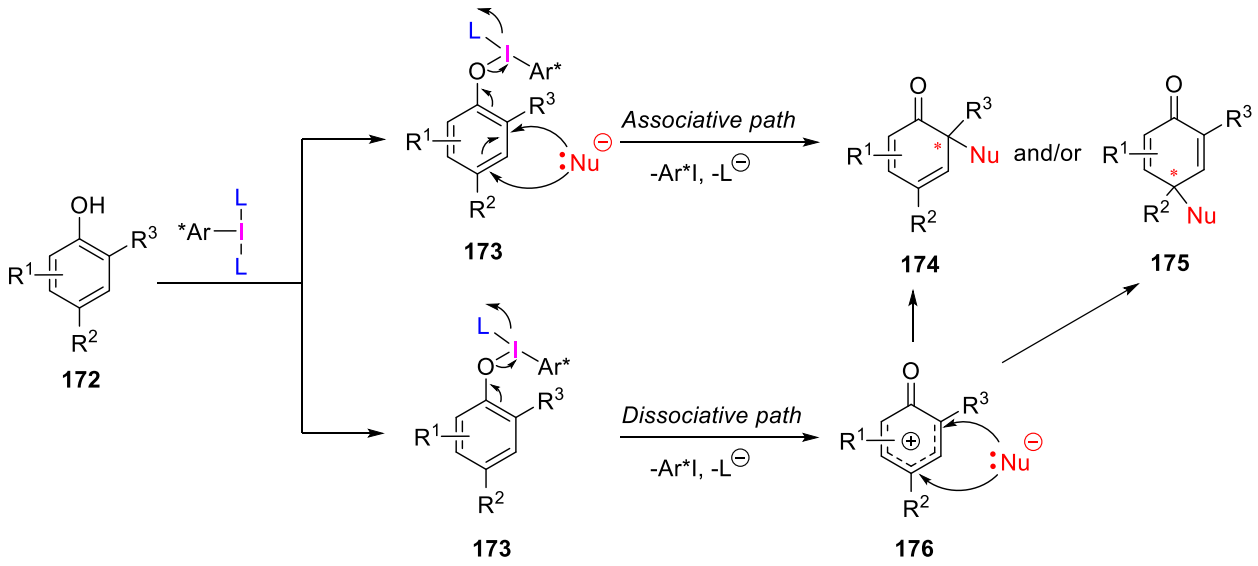


Figure 4.4. Representative C_1 & C_2-symmetric structures of chiral iodoarene(I) precursors.

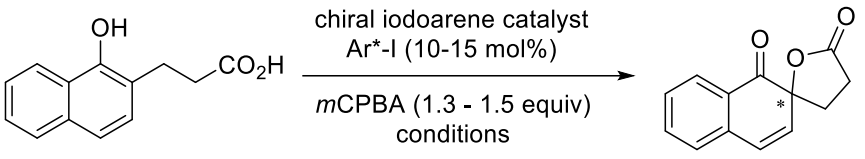
4.1.1.1 Catalytic oxidative dearomatization of phenols and derivatives

The enantioselective dearomatization of phenols and derivatives has been well-studied as it is a reaction of great interest, especially in the synthesis of complex molecules. It represents one of the first and most popular chiral hypervalent iodine(III) catalyzed transformations.[120] The process is initiated by an *in situ* generated chiral iodine(III) catalyst upon oxidation with *m*CPBA, followed by a ligand exchange with the phenol **172** which leads to intermediate **173** (Scheme 4.2). At this point, the reaction can proceed *via* two putative mechanistic pathways: a) the associative path where the nucleophile can directly attack the intermediate **173** in a S_N2' fashion or b) the dissociative path where the organoiodine(III) moiety is directly fragmentized from **173** leading to the formation of the corresponding phenoxenium ion **176** that can be captured by the nucleophile. In the latter case, there is a lack of stereocontrol. Therefore, reaction conditions that force towards the associative path are necessary in order to induce asymmetry.

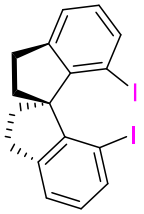
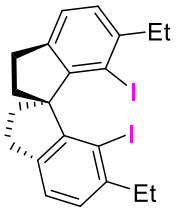
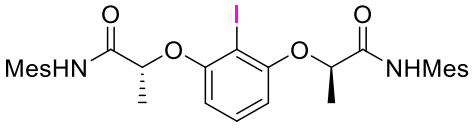
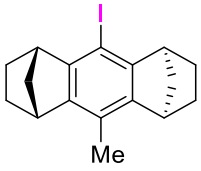
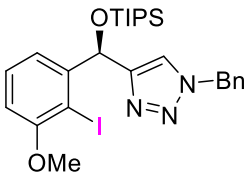


Scheme 4.2. Possible mechanistic pathways for the hypervalent iodine(III)-catalyzed asymmetric dearomatization of phenols.

One of the earliest examples of oxidative dearomatization of phenols in an enantioselective fashion, in the presence of catalytic amounts of chiral hypervalent iodine(III) reagents was demonstrated by Kita *et al.* in 2008.[121] In this work, the rigid C_2-symmetric catalyst **170** with the axial chirality was employed and the product **178** was obtained from the naphtholcarboxylic acid **177** in 65% *ee* (Scheme 4.3). A significant improvement in the enantioselectivity (up to 92% *ee*) was achieved by introducing *ortho* substituents on the spirobiindane scaffold (catalyst **170a**).[122]



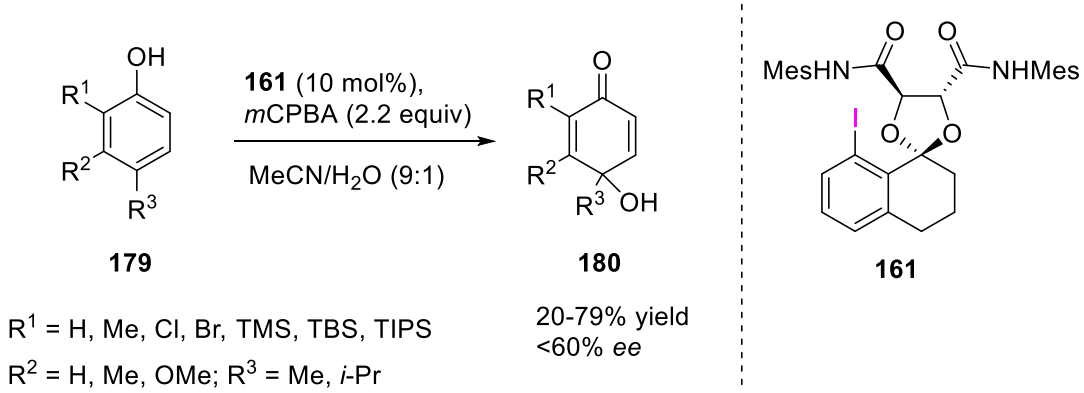
177 **178**

chiral iodoarene catalyst (Ar*-I)	Result & Conditions
 **170**	68% yield, 65% *ee* (**170** (15 mol%), DCM, 0 °C, 3 h)
 **170a**	83% yield, 87% *ee* (**170a** (10 mol%), $CHCl_3$, 0 °C, 8 h) 56% yield, 92% *ee* (**170a** (15 mol%), $CHCl_3$-hexane, 0 °C, 10 h)
 **156a**	60% yield, 92% *ee* (**156a** (15 mol%), $CHCl_3$, 0 °C, 18 h) 65% yield, 90% *ee* (**156a** (15 mol%), $CHCl_3$-$MeNO_2$, 0 °C, 5 h)
 **167**	36% yield, 40% *ee* (**167** (10 mol%), $CHCl_3$, 0 °C, 19 h)
 **160a**	85% yield, 99% *ee* (**160a** (10 mol%), DCM/$CHCl_3$ + 6 equiv EtOH, -10 °C, 32 h)

Scheme 4.3. Catalytic enantioselective oxidative dearomatization of naphtholcarboxylic acid **177** with different chiral iodoarene catalysts.

In 2010, Ishihara and co-workers investigated the performance of a novel chiral lactate-based iodosylarene catalyst **156a** in the oxidative spirolactonization of **177** by maintaining the same reaction conditions as established by Kita. Excellent enantioselectivities (up to 92% *ee*) and good yields were reported for the corresponding transformation (Scheme 4.3).[118] In 2015, Ibrahim *et al*. described the design and synthesis of a chiral octahydrodimethanoanthracene-based iodoarene(I) **167** and its application in Kita´s spirolactonization of phenolic derivative **177**, although resulting in lower yields and enantioselectivities.[123] The group of Nachtsheim, developed recently a "second generation" of their triazole-containing chiral iodoarene (I) catalyst **160**[124] by introducing *ortho*-substituents at the aryl iodide.[125] Chiral iodoarene(I) **160a** proved to be a highly reactive catalyst in this spirolactonization affording the spirocyclized product **178** in very good yield (85%) and excellent level of enantioselectivity (99% *ee*) (Scheme 4.3).

Although, high levels of stereocontrol have been reported for the spirolactonization of **177**, intermolecular dearomatization of phenols **179** to access enantioenriched para-quinols **180** proved to be more challenging. Harned *et al.* reported the synthesis of *para*-hydroxy phenols in low to good yields (20-79%) and enantioselectivities up to 60% by employing a series of novel chiral catalysts with 8-iodotetralone core such as **161** (Scheme 4.4).[126]

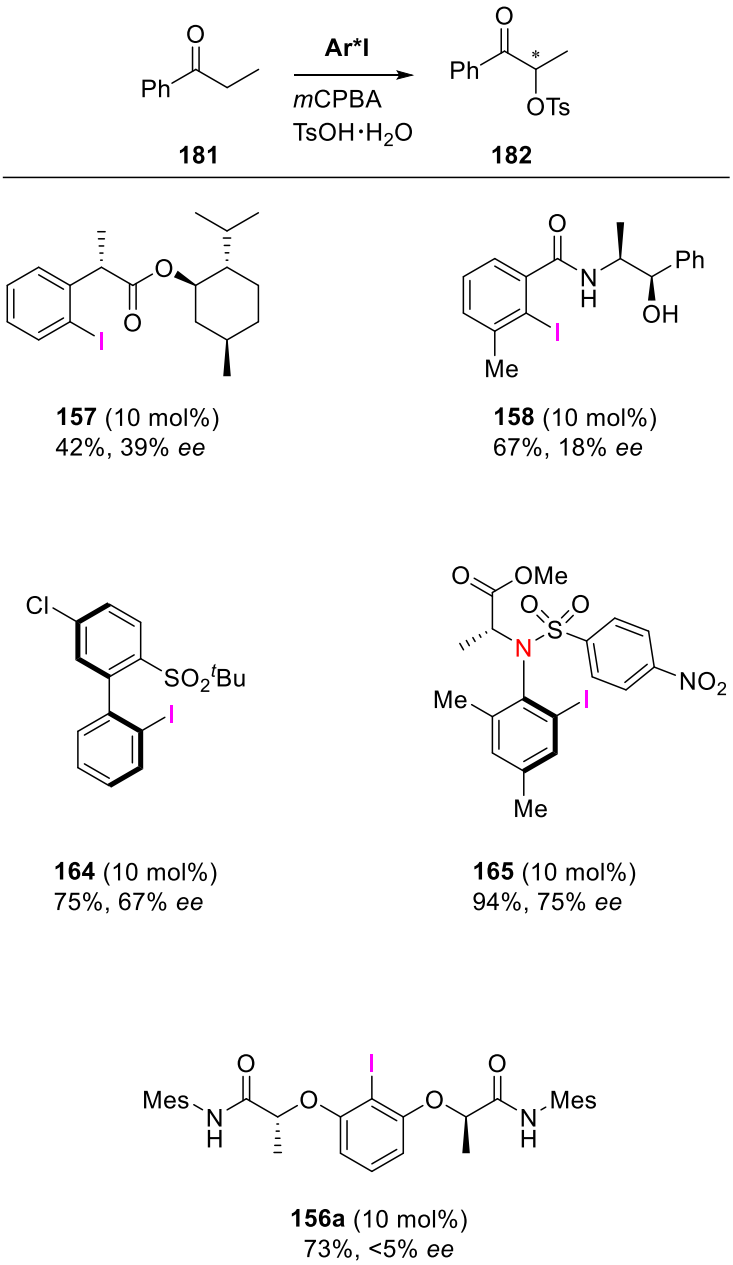


Scheme 4.4. Enantioselective intermolecular dearomatization of phenols **179** with chiral Iodoarene catalyst **161**.

4.1.1.2 α-Functionalization of carbonyl compounds

Chiral hypervalent iodine(III) compounds have been further applied as catalysts in the field of asymmetric α-functionalization of carbonyl compounds. Several functional groups including sulfonyl[127], phosphoryloxy[127] and acetoxy[128] have been installed in the α-position of carbonyl derivatives.

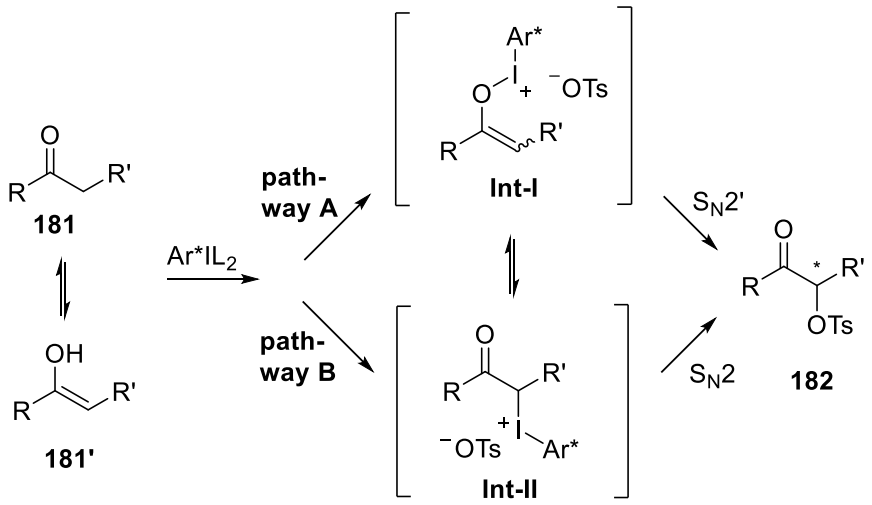
The α-oxytosylation of ketones is considered the first asymmetric catalytic transformation in the presence of hypervalent iodine reagents as reported by Wirth *et al* in 2007.[129] Since then, several types of chiral iodoarenes have been designed in order to improve the stereochemical outcome of this transformation. Wirth and his research team continued their efforts on this topic by synthesizing different C_1-symmetric iodoarenes with central chirality but disappointingly the reported enantioselectivities were very low.[130] In case of their ester-based precatalyst **157** (Scheme 4.5), a slight improvement in the enantioselectivity was observed (39% *ee*). This could be reasoned by the additional chiral center on the ester, derived from the menthol moiety.[131] Moran and co-workers also described the synthesis of chiral iodoarenes from simple reactions such as amidation (pre-catalyst **158**) and tested them in the α-oxytosylation of propiophenone without particular success in terms of enantioselectivity (18% *ee*).[132] Very recently, Wirth *et al*. reported significantly higher levels of enantioselectivity (75% *ee*) by employing a new class of C-N axially chiral iodoarenes such as pre-catalyst **165**.[133] Other C_1-symmetric iodoarenes with axial chirality such as **164** provided α-tosyloxylated propiophenone **182** in both respectable yield and enantioselectivity (75%, 67% *ee*) as described by Leroux and Masson.[127] Surprisingly, the employment of Ishihara´s catalyst **156a** in this transformation resulted in very low enantioselectivity (<5%) despite its usual superior performance.[134]



Scheme 4.5. Asymmetric catalytic α-tosyloxylation of propiophenone with different chiral iodoarene catalysts.

The difficulties to achieve adequate levels of enantioselectivity in this transformation is highly associated with its mechanism. Many studies have been performed in order to elucidate it.[134-135] The reaction can take place *via* two possible mechanistically distinct modes (path **A** and path **B** in Scheme 4.6).Initially, the chiral iodine(I) pre-catalyst is converted to the chiral Koser derivative upon reaction with *m*CPBA and TsOH·H_2O. In pathway **A**, the chiral iodine(III) catalyst forms a complex **Int-I** with the enolic form of the substrate followed by an S_N2' reaction with tosylate to

deliver the final product **182**. Alternatively, in pathway **B**, the chiral iodine(III) catalyst is bound to the α-carbon of the ketone **Int-II** which is subsequently substituted by the tosylate anion *via* a direct S_N2 reaction resulting in the same product. Considering both possible mechanistic pathways, enantioselectivity could be introduced either during the formation of the enol complex **Int-I** or at the stage where alkyl iodane intermediate **Int-II** is being generated. The low stereoselectivity that is frequently observed for this transformation can be ascribed to two main reasons: 1) racemization can occur through equilibration of the intermediates **Int-I** and **Int-II**[133] or 2) in case that the reaction follows pathway **A** as reported by Beaulieu and Legault[135a], the chiral catalyst is remoted from the prochiral center.



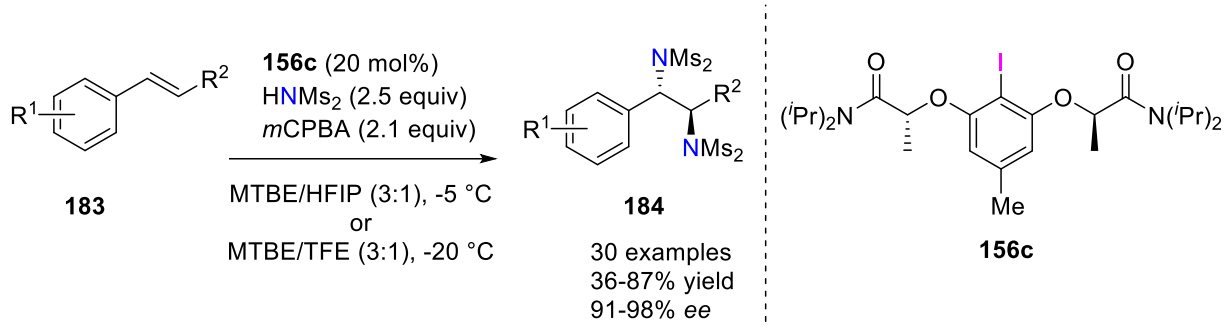
Scheme 4.6. Mechanistic insights of the asymmetric hypervalent iodine-mediated α-oxytosylation of ketones.

4.1.1.3 Difunctionalization of olefines

Enantioselective difunctionalization of olefines is of high interest in organic synthesis as it enables the rapid conversion of simple π-systems to chiral molecules with multiple reactive centers. A very convenient strategy to activate C–C double bonds is by employing hypervalent iodine(III) reagents. The coordination of the electrophilic iodine atom of these reagents to the π-system of alkenes renders them susceptible to nucleophilic attacks. In this context, several asymmetric hypervalent-iodine mediated difunctionalizations of alkenes have been accomplished up to date such as aminations and fluorinations.

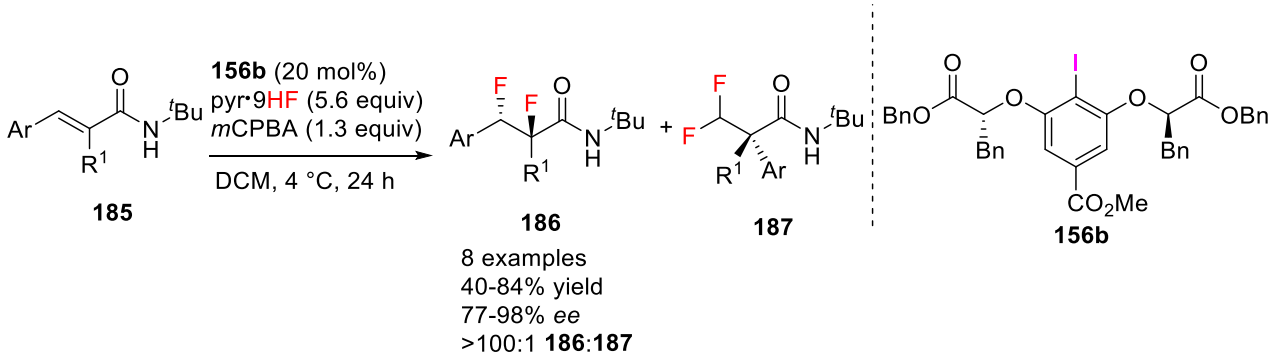
An asymmetric protocol for the vicinal diamination of styrenes **183** was reported by Muñiz and co-workers in 2017.[136] In this work, the transformation was catalyzed by an *in situ* generated C_2-

symmetric hypervalent iodine(III) catalyst **156c** and bismesylimide was used as a nitrogen source. The formation of chiral vicinal diamines **184** in good yields and excellent enantioselectivities was enabled by this strategy (Scheme 4.7).



Scheme 4.7. Enantioselective hypervalent iodine(III) catalyzed vicinal diamination of styrenes **183**.

In the context of hypervalent iodine(III)-catalyzed fluorination of olefines, Jacobsen *et al.* described one of the first attempts for asymmetric 1,2-difluorination of alkenes in 2016.[137] In their protocol, a nucleophilic fluoride source along with *m*CPBA as the oxidant for the generation of the active chiral iodine(III) species were utilized for the conversion of cinnamamide **185** to 1,2-difluorinated compound **186**. In 2019, the same group unlocked the potential of this method by further extending the reaction scope and successfully suppressing the competing 1,1-difluorination that leads to the formation of products **187.** The favorable formation of 1,2-difluorinated products was achieved upon enhancement of the anchimeric assistance with the installation of a *tert*-butyl group on the amide moiety (Scheme 4.8).[138]



Scheme 4.8. Asymmetric vicinal difluorination of cinnamamides **185** by chiral hypervalent iodine(III) catalyst **156b**.

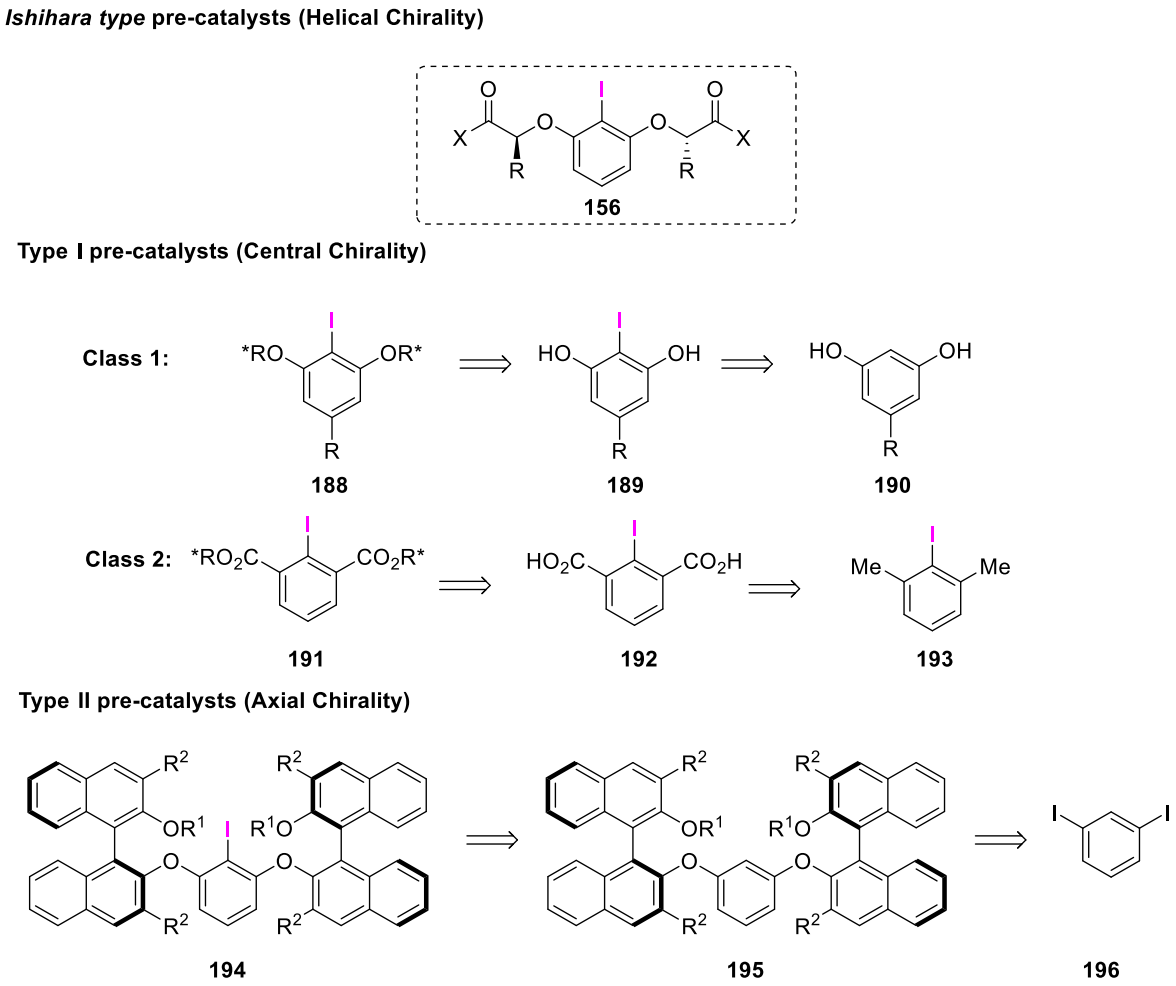
Concomitant to Jacobsen´s work, Gilmour and his research team also reported the vicinal difluorination of styrenes with different substitution patterns using a slight modified protocol where *m*CPBA is replaced by Selectfluor as the oxidizing agent.[139]

The potential of chiral hypervalent iodine reagents (III) is not restricted to the transformations mentioned above. They have found also wide applications in other type of reactions including oxidation of sulfur compounds[140], and oxidative rearrangements[141] that are not highlighted in the present thesis.

4.2 Results and discussion

4.2.1 Design strategy for the synthesis of novel chiral iodoarenes

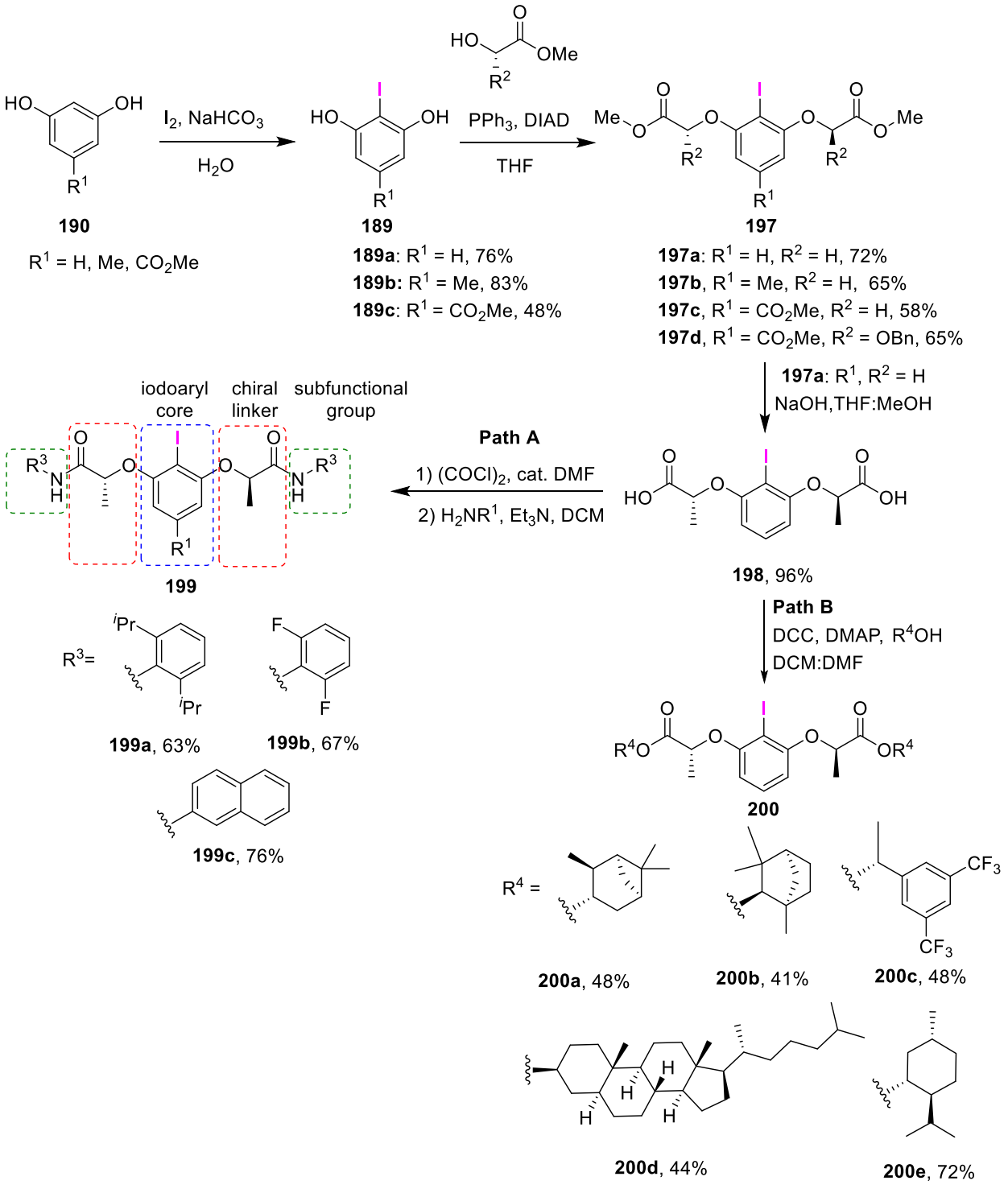
The structural design of chiral iodoarenes in terms of chirality and symmetry is of high importance for asymmetric transformations. It has been observed that even minor modifications on the iodoarene core can have a great impact on the stereochemical outcome. In this context, it was envisioned the generation of a library consisting of easily accessible, novel chiral iodoarenes with structural diversity. The possibility of a modular and robust synthetic plan using inexpensive and readily available chiral sources was considered. In addition, the focus was turned on the synthesis of C_2-symmetric scaffolds which is related to their known superior performance. For this purpose, three different types of catalysts were investigated. Initially, *Ishihara type* catalysts along with their structural analogues were synthesized, following the reported procedures.[117-118] Catalysts **Type I** with central chirality could be easily obtained in two simple synthetic steps starting from commercially available materials. In both cases, the chirality can be introduced from enantiopure, readily available alcohols *via* a Mitsunobu or esterification reaction, respectively. The synthesis of catalysts **194** endowed with axial chirality (**Type II**) could be accomplished from a double Ullmann coupling of 1,3-diiodobenzene and mono-protected (*R*)-BINOL, followed by selective iodination.



Scheme 4.9. Design of novel chiral iodoarenes.

4.2.2 Synthesis of novel chiral hypervalent iodine reagents

The preparation of the library commenced with the synthesis of *Ishihara type* pre-catalysts and their structural analogues. In general, the structure of the pre-catalyst can be divided into three fundamental units: the iodoaryl core, a linker as the chiral source and the additional subfunctional groups. The first synthetic step was the formation of the iodoaryl core by electrophilic iodination of resorcinol derivatives **190** using molecular iodine (Scheme 4.10). A double Mitsunobu reaction[142] of the obtained iodoresorcinol derivatives **189** and methyl *L*-lactate or methyl *L*-3-phenyllactate attached the chiral linker to the iodoaryl core thus giving access to compounds **197** which could be also used as pre-catalysts. Upon hydrolysis of the methyl esters (compound **198**), two different synthetic pathways could be followed leading to the introduction of different subfunctionalities.



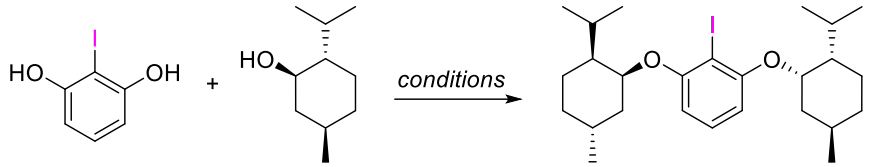
Scheme 4.10. Sequential synthesis of *Ishihara´s type* pre-catalysts.

In path **A**, lactamide derivatives **199** were generated *via* formation of acyl chloride followed by its coupling with aniline derivatives bearing both electron-donating and electron withdrawing groups. The final compounds (**199a**-**199c**) were obtained in moderate yields (63-76%) (Scheme 4.10). In

path **B**, a Steglich esterification[143] was followed in order to introduce additional stereogenic centers to the linker unit that derived from a variety of chiral alcohols affording the esterification products (**200a**-**200e**) in moderate yields (41-48%).

To rapidly expand the library of pre-catalysts, a different synthetic approach was performed that gave access to two structural classes of pre-catalysts **Type I**. In the first case, the chiral auxiliary was attached to the iodoarene core *via* an ether bond upon a double Mitsunobu reaction. Initially, iodoresorcinol **189a** and (−)-menthol **201** were used for the generation of pre-catalyst **188a** by following the same protocol as for the preparation of iodoarenes **197**. Unfortunately, this procedure afforded traces of the desired compound. Optimizing the reaction conditions by employing a different solvent system and changing the activating reagent from diisopropyl azodicarboxylate (DIAD) to di-*tert*-butyl azodicarboxylate (DBAD) delivered the chiral iodoarene **188a** in sufficient quantities for further testing (Table 4.1).

Table 4.1. Optimization of Mitsunobu reaction for the synthesis of **188a**.[a]



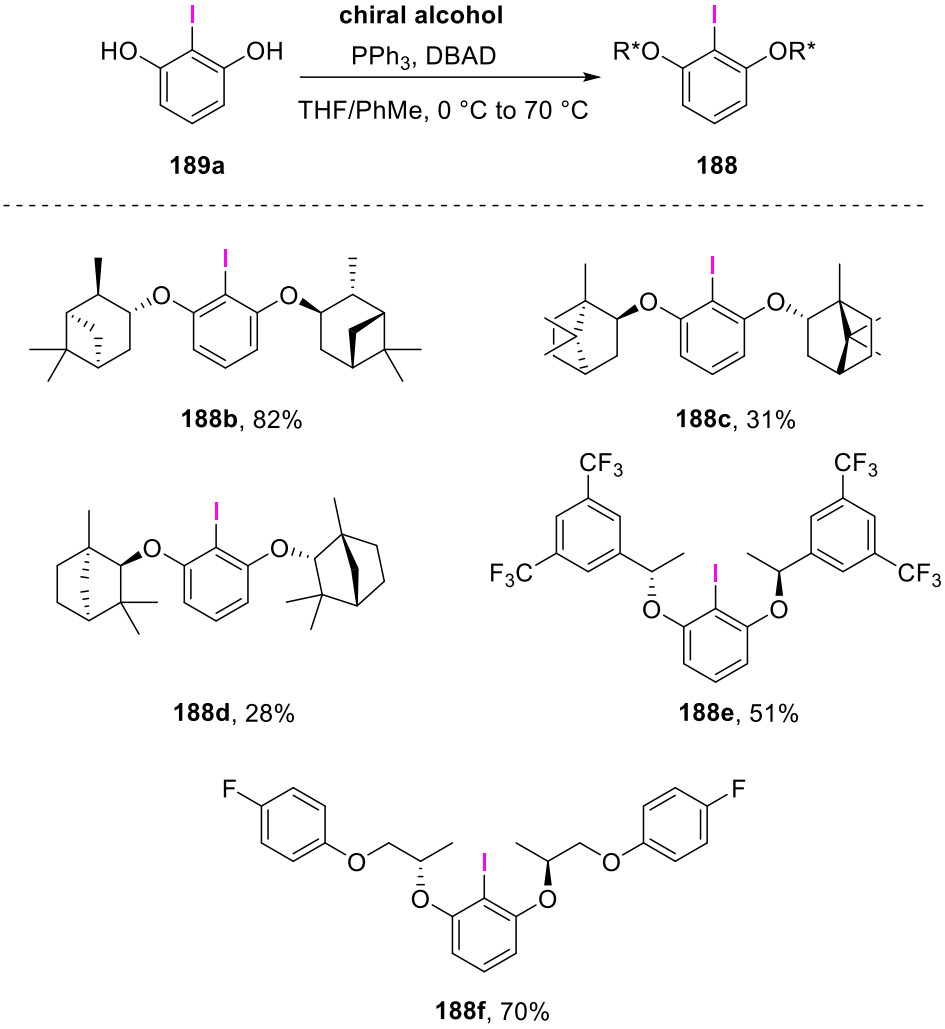
189a **201** **188a**

Entry	Azodicarboxylate (x equiv)	PPh_3 (y equiv)	Solvent	Time (h)/ Temp. (°C)	Yield (%)[b]
1	DIAD (2.3)	2.7	THF	24/RT then 24/70	traces
2	DIAD (4.6)	5.4	THF	24/RT then 24/70	3
3	DBAD (2.3)	2.7	THF:PhMe (1:1)	48/RT then 48/60	6
4	DBAD (4.6)	5.4	THF:PhMe (1:1)	24/RT then 70/70	16
5	**DBAD (6.6)**	**7.4**	**THF:PhMe (1:1)**	**24/RT then 48/70**	**20**

[a]Reaction conditions: iodoresorcinol **189a** (0.42 mmol, 1.0 equiv) and (−)-menthol **201** (1.86 mmol, 4.4 equiv) were stirred in solvent [0.4 M] for given time and temperature. [b]Isolated yield.

Having the optimized conditions in hand, five more examples of those pre-catalysts were rapidly prepared using enantiopure alcohols (Scheme 4.11). Bicyclic monoterpenoids such as fenchol and borneol resulted in relatively low yields (28-31%), similar to what have been observed in the case

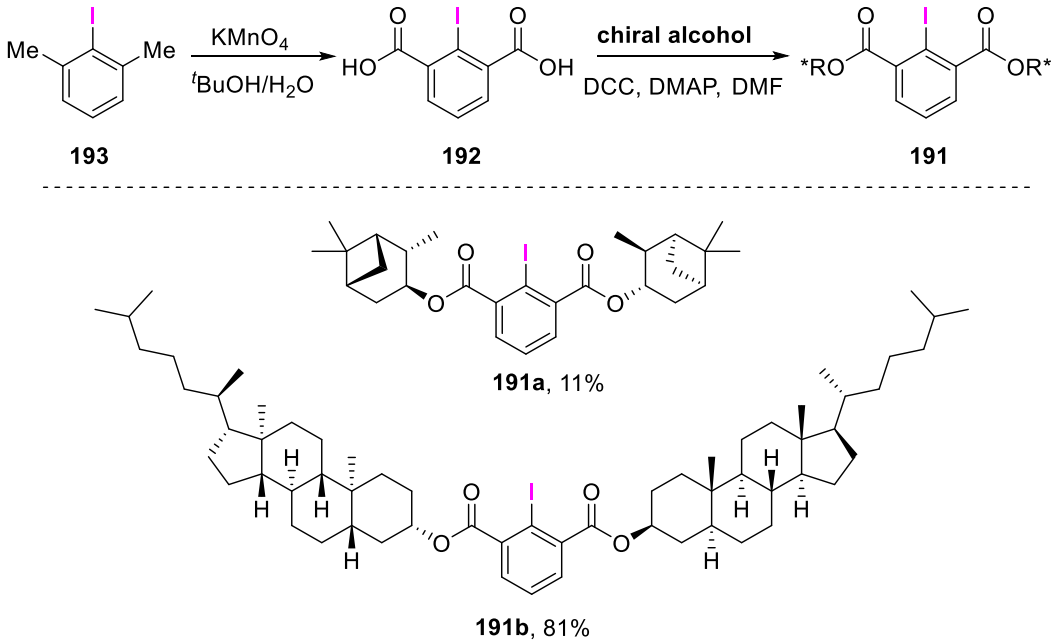
of menthol. Surprisingly, in the case of isopinocampheol, the corresponding chiral iodoarene **188b** has been isolated in significantly higher yield (82%). The coupling of chiral alcohols containing fluorinated aromatic rings delivered the pre-catalysts **188e** and **188f** in 51% and 70% yield, respectively.



Scheme 4.11. Structures of synthesized **Type I** pre-catalysts *via* Mitsunobu reaction with chiral alcohols.

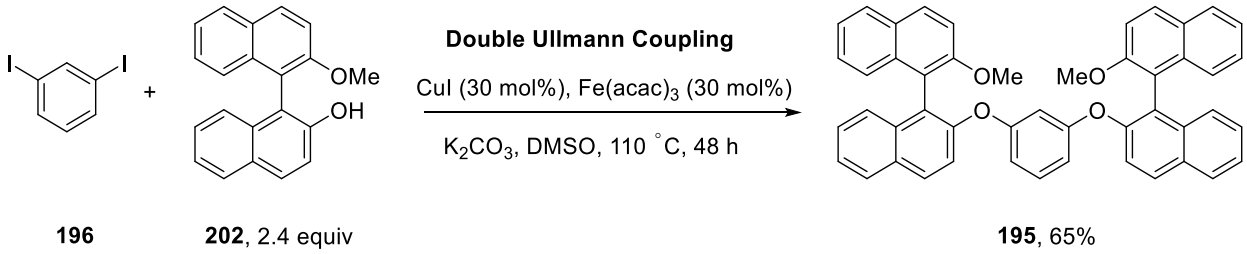
In the second family class of pre-catalysts **Type I**, the iodoarene core **193** was connected to the chiral auxiliary through an ester functionality upon an esterification reaction. The synthesis of those pre-catalysts was accomplished in two synthetic steps. Initially, oxidation of 2-iodo-1,3-dimethylbenzene **193** generated 1,3-dicarboxylic acid derivative **192**. Subsequently, reaction with a variety of chiral alcohols *via* a Steglich esterification furnished the corresponding chiral pre-catalysts **191**. Employment of isopinocampheol afforded the chiral iodoarene **191a** in low yield

(11%) while the polycyclic β-cholestanol resulted in the formation of compound **191b** with higher yield (81%) (Scheme 4.12).



Scheme 4.12. Structures of synthesized **Type I** pre-catalysts *via* esterification of **192** with chiral alcohols.

Finally, inspired by previous works of Quideau *et al.*[144] among others on the synthesis and application of binaphthylic iodanes, it was envisioned the preparation of a series of rare C_2-symmetrical axial chiral precatalysts. The synthesis commenced with mono-methylation of (*R*)-BINOL **202** which further subjected to a double Ullmann coupling with 1,3-diiodobenzene **196**. The reaction proceeded smoothly and the bis-binaphthylic benzene scaffold **195** was obtained in 65% yield (Scheme 4.13).

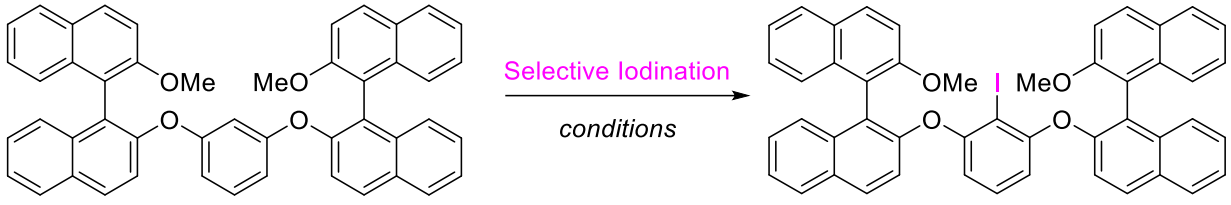


Scheme 4.13. Synthesis of bis-binaphthylic benzene scaffold **195** *via* double Ullmann coupling reaction.

The critical step in this reaction sequence was the selective iodination on the benzene core **195** to afford the desired iodoarene reagent. Several attempts for the regioselective installation of iodine have been made. Initially, a directed *ortho*-metalation approach was followed to generate the

aryllithium intermediate which could attack the electrophilic iodine (entry 1, Table 4.2). Unfortunately, this strategy was confronted with regioselectivity problems. Additionally, a direct aromatic iodination using *N*-iodosuccinimide (NIS) in combination with catalytic amounts of trifluoroacetic acid (TFA) which significantly enhances the electrophilic nature of iodine led to an inseparable mixture of regioisomers as well (entry 2, Table 4.2). Due to the synthetic limitations, the completion of the preparation of pre-catalysts **Type II** could not be accomplished.

Table 4.2. Attempts on the selective iodination of compound **195**.



195 **194**

Entry	Conditions	Observation
1	*n*-BuLi (1.0 equiv), I_2 (1.0 equiv.) THF, -78 °C to RT	Complex mixture of reaction products
2	NIS (1.1 equiv), TFA (30 mol%) MeCN, RT	Inseparable mixture of regioisomers

4.3 Performance evaluation of the synthesized chiral hypervalent iodine reagents in α-functionalization of carbonyl compounds

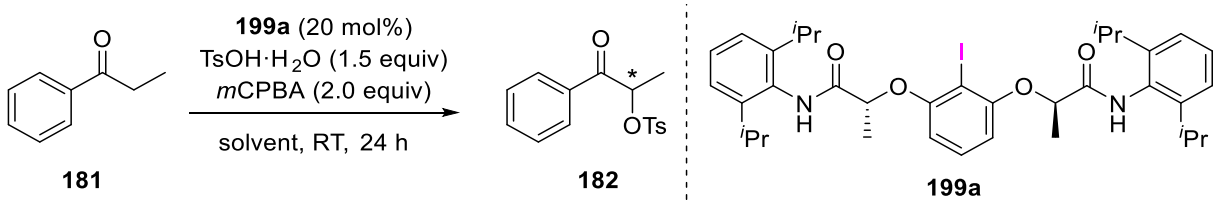
Having the library of the synthesized chiral iodoarenes in hand, their potential on enantioinduction was investigated in a series of known asymmetric transformations based on the α-functionalization of ketones such as α-tosyloxylation and lactonization.

4.3.1 Asymmetric α-tosyloxylation of ketones

α-Tosyloxylation of ketones represents one of the first applications of chiral hypervalent iodine reagents as reported by Wirth and co-workers in 1997[145] and the first example on catalytic approach of those reagents was described one decade later.[129] Since then, numerous efforts to design efficient chiral aryl iodide catalysts for this specific transformation mainly resulted in insignificant asymmetric induction.

Based on a reported procedure[146], propiophenone **181** was chosen as the model substrate, the corresponding synthesized chiral iodoarene as pre-catalyst, *m*-chloroperbenzoic acid (*m*CPBA, 2.0 equiv.) as the stoichiometric oxidant and *p*-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$, 1.5 equiv.) as the nucleophilic source. The study commenced with the screening of different solvents in presence of the reported pre-catalyst **199a** (Table 4.3) which was successfully applied in α-oxygenation of ketones in a previous report.[128] In general, the screened solvents were compatible with this transformation and afforded the α-oxygenated product **182** in moderate yields. The best result in terms of yield for **182** was obtained when the reaction was performed in acetonitrile (entry 1) while no conversion was observed in DMF (entry 6). However, in all cases poor levels of enantioselectivity were obtained, regardless the solvent system. Solvents such as acetonitrile, chloroform, and dichloroethane afforded compound **182** with very low enantiomeric excess (entries 1-2, and 10). The stereochemical outcome followed a similar trend in 1,4-dioxane, ethyl acetate and toluene (entries 4, 7 and 9).

Table 4.3. Solvent screening for the asymmetric α-oxytosylation of propiophenone **181** with catalyst **199a**.[a]

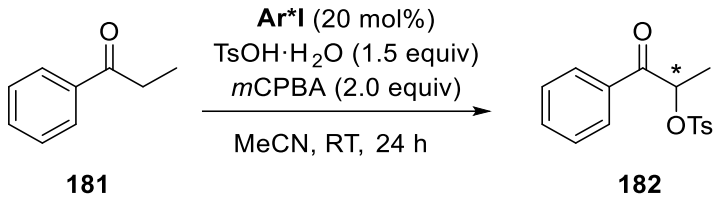


Entry	Solvent	Yield (%)[b]	*ee* (%)[c]
1	**MeCN**	**64**	**3**
2	$CHCl_3$	51	1
3	THF	11	19
4	1,4-Dioxane	32	5
5	Et_2O	32	10
6	DMF	--	--
7	EtOAc	38	3
8	Cyclohexane	31	18
9	PhMe	23	3
10	DCE	20	2
11	HFIP	27	7

[a]Reaction conditions: propiophenone **181** (0.04 mmol, 1.0 equiv), **199a** (0.007 mmol, 20 mol%), *m*CPBA (0.07 mmol, 2.0 equiv) and $TsOH{\cdot}H_2O$ (0.06 mmol, 1.5 equiv) were stirred in solvent (1.0 mL) at room temperature for 24 h. [b]Isolated yield. [c]Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase.

Slightly improved enantioselectivities (18% and 19% *ee*) were realized in polar aprotic solvent (THF, entry 3) as well as in the non-polar (cyclohexane, entry 8), albeit in lower yields. As the reaction proceeded smoothly in acetonitrile, the enantioselective α-tosyloxylation of propiophenone was further explored in this solvent employing the rest of the synthesized chiral iodoarenes. The catalyst screening (Table 4.4) revealed that catalytic amounts (20 mol%) of the majority of chiral iodoarenes led to the formation of product **182** in moderate yields except in the case of pre-catalysts **188b**, **188c**, **188d**, and **191b** (entries 15-17 and 19) that only low yields were obtained.

Table 4.4. Screening of pre-catalysts in the enantioselective α-tosyloxylation of propiophenone **181**.[a]



181 **182**

Entry	Pre-catalyst (Ar*I)	Yield (%)[b]	*ee* (%)[c]
1	**197a**	49	37
2	**197b**	37	24
3	**197c**	49	46
4	**197d**	**56**	**52**
5	**199a**	64	3
6	**199b**	39	10
7	**199c**	48	11
8	**200a**	51	37
9	**200b**	60	40
10	**200c**	54	45
11	**200d**	45	22
12	**200e**	63	35
13	**188a**	34	4
14	**188f**	24	23
15	**188b**	16	2
16	**188c**	18	n.d.[d]
17	**188d**	7	2
18	**188e**	53	28
19	**191b**	16	5
20	**191a**	46	n.d.[d]

[a]Reaction conditions: propiophenone **181** (0.04 mmol, 1.0 equiv), **Ar*I** (0.007 mmol, 20 mol%), *m*CPBA (0.07 mmol, 2.0 equiv) and $TsOH·H_2O$ (0.06 mmol, 1.5 equiv) were stirred in MeCN (1.0 mL) at room temperature for 24 h. [b]Isolated yield. [c]Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase. [d]n.d. = not determined.

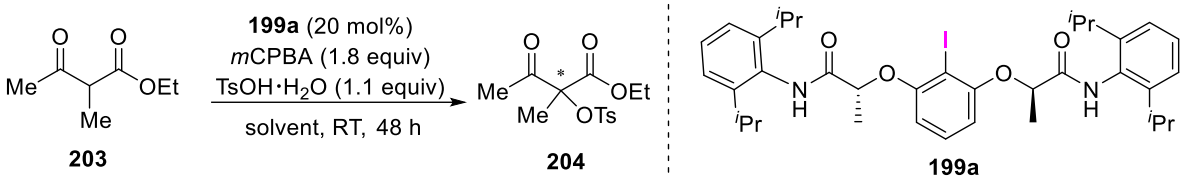
Ishihara type pre-catalysts with the terminal methyl ester **197a**-**197d** resulted in the α-tosyloxy ketone **182** in moderate enantioselectivities (24-54% *ee*) (entries 1-4). By employing the pre-catalysts **199a**-**199c** with the amide subfunctionality, a significant decrease in the enantioselectivities was noticed as the product was obtained in less than 11% *ee* (entries 5-7). Moderate enantioselectivities were also observed for *Ishihara type* pre-catalysts endowed with additional chiral auxiliaries (entries 8-12). Switching to pre-catalysts **Type I 188a**-**188f** and **191a**-**191b** which exhibit a central chirality, the obtained enantioselectivities were poor (entries 13-20). Even no asymmetry was induced in case of catalysts **188c** and **191a** (entries 16 and 20). Overall, the best result was obtained with pre-catalyst **197d**, although the enantioselectivity did not exceed 52% *ee*.

4.3.2 Asymmetric α-tosyloxylation of β-keto esters

In 2016, Xiong and Coeffard *et al.*[147] described the enantioselective α-oxidation of β-keto esters catalyzed by chiral C_2-symmetric iodoarenes to generate compounds which contain a quaternary center. Although, even upon optimization of the catalytic system and reaction conditions, the transformation was confronted with both moderate yields and enantioselectivities. For these reasons, the transformation was a good candidate for further studies with respect to higher enantioselectivities.

In this context, the asymmetric α-tosyloxylation of ethyl 2-methylacetoacetate **203** was explored in the presence of catalytic amounts of the synthesized chiral iodoarenes. Initially, the solvent effect was investigated in the presence of chiral pre-catalyst **199a** (Table 4.5). The solvent screening indicated that low to moderate yields were obtained in chlorinated solvents (entries 2-4). No significant changes were observed by changing to ethereal solvents (entries 6-7) except for tetrahydrofuran which yielded traces of the desired product (entry 5).

Table 4.5. Solvent screening for the asymmetric α-oxytosylation of ethyl 2-methylacetoacetate **203** with catalyst **199a**.[a]



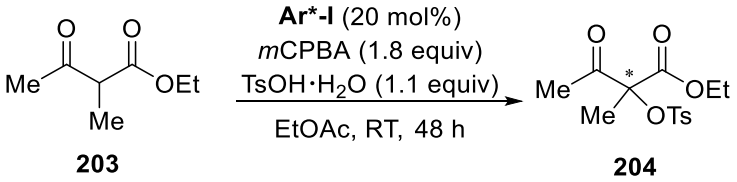
Entry	Solvent	Yield (%)[b]	*ee* (%)[c]
1	MeCN	56	7
2	DCM	37	16
3	DCE	43	18
4	$CHCl_3$	19	7
5	THF	traces	n.d.[d]
6	Et_2O	35	23
7	1,4-Dioxane	48	10
8	DMF	--	--
9	$MeNO_2$	79	9
10	EtOAc	60	35
11	PhMe	20	2
12	HFIP	--	--

[a]Reaction conditions: ethyl 2-methylacetoacetate **203** (0.03 mmol, 1.0 equiv), **199a** (0.007 mmol, 20 mol%), *m*CPBA (0.06 mmol, 1.8 equiv) and $TsOH·H_2O$ (0.04 mmol, 1.1 equiv) were stirred in solvent (1.0 mL) at room temperature for 48 h. [b]Isolated yield. [c]Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase.[d]n.d. = not determined.

While DMF, toluene and HFIP proved to be detrimental to the formation of product **204** (entries 8,11 and 12), ethyl acetate and nitromethane (entries 9-10) afforded the product in good yields with the latter one being the best (79%). However, poor enantioselectivities were observed through the solvent screening. While most of the solvents afforded the product in lower than 25% *ee*, a noticeable increase in enantioselectivity (35% *ee*) was observed in ethyl acetate (entry 10) which subsequently was chosen as the solvent for further screening.

The pre-catalyst screening for the asymmetric α-tosyloxylation of ethyl 2-methylacetoacetate **203** indicated that most of them showed both very low reactivity and selectivity for this transformation (Table 4.6).

Table 4.6. Screening of pre-catalysts in the asymmetric α-tosyloxylation of ethyl 2-methylacetoacetate **203**.[a]



203 **204**

Entry	Pre-catalyst (Ar*I)	Yield (%)[b]	*ee* (%)[c]
1	**199b**	**50**	**18**
2	**199c**	44	n.d.[d]
3	**188a**	--	--
4	**200e**	72	8
5	**188f**	55	5
6	**188b**	--	--
7	**188c**	--	--
8	**188d**	--	--
9	**188e**	41	n.d.[d]
10	**191b**	traces	n.d.[d]
11	**191a**	traces	n.d.[d]

[a]Reaction conditions: ethyl 2-methylacetoacetate **203** (0.07 mmol, 1.0 equiv), **Ar*I** (0.013 mmol, 20 mol%), *m*CPBA (0.12 mmol, 1.8 equiv) and $TsOH{\cdot}H_2O$ (0.07 mmol, 1.1 equiv) were stirred in EtOAc (1.0 mL) at room temperature for 48 h. [b]Isolated yield. [c]Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase. [d]n.d. = not determined.

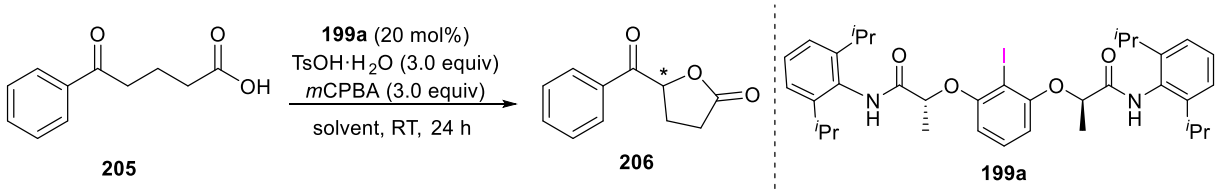
Among the *Ishihara type* pre-catalysts, **199b**, **199c** and **200e** could catalyze the reaction with satisfying yields (50-72%), albeit in low enantioselectivities (entries 1-2 and 4). In case of **Type I** pre-catalysts endowed with central chirality, only two of them (**188f** and **188e**) showed catalytic activity affording the product **204** in moderate yields (41-55%) but poor enantioselectivities (entries 5 and 9). In general, the yields achieved for this transformation were in good accordance with those previously reported but the enantioselectivities observed with the synthesized catalysts were lower.

4.3.3 Asymmetric lactonization of keto acids

Some selected chiral iodoarenes from the library were assessed as catalysts in the asymmetric lactonization of 5-oxo-5-phenylpentanoic acid **205**. This transformation was previously investigated by several groups with the group of Moran[132] and Nachtsheim[125] to report independently the best results in terms of enantioselectivity (51% *ee* and 81% *ee*, respectively). Since in all previous studies C_1-symmetric chiral iodoarenes have been employed, it was interesting to examine the performance of C_2-symmetric ones.

Following the procedure by Moran *et al.*[132], the screening commenced by examining the influence of different solvents in the presence of catalytic amounts of pre-catalyst **199a**. The result of the solvent screening (Table 4.7) shows that all the solvent systems led to the formation of the cyclized product **206** in moderate to excellent yields. In chlorinated solvents such as chloroform and dichloroethane (entries 3 and 11) substrate **206** was obtained in excellent yields (95%). Surprisingly, in dichloromethane a decrease in the yield (58%) was observed (entry 2). However, in terms of enantioselectivity, the results were not as satisfying. The highest levels of enantioselectivity that could be obtained were 17% *ee* in solvent THF (entry 4) and 12% *ee* in cyclohexane (entry 8) while in the rest cases were even lower.

Table 4.7. Solvent screening for the asymmetric lactonization of 5-oxo-5-phenylpentanoic acid **205** with catalyst **199a**.[a]

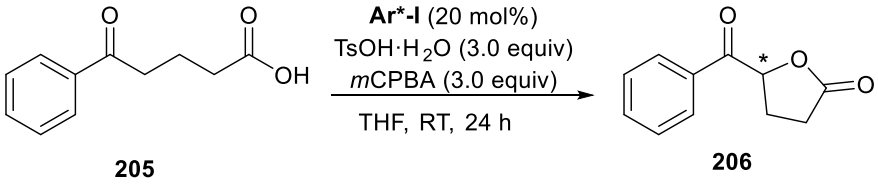


Entry	Solvent	Yield (%)[b]	*ee* (%)[c]
1	MeCN	42	1
2	DCM	58	3
3	$CHCl_3$	95	1
4	**THF**	**45**	**17**
5	1,4-Dioxane	63	8
6	Et_2O	74	9
7	EtOAc	87	3
8	Cyclohexane	92	12
9	PhMe	89	3
10	HFIP	39	4
11	DCE	95	3

[a]Reaction conditions: 5-oxo-5-phenylpentanoic acid **205** (0.03 mmol, 1.0 equiv), **199a** (5.0 μmol, 20 mol%), *m*CPBA (0.07 mmol, 3.0 equiv) and $TsOH·H_2O$ (0.07 mmol, 3.0 equiv) were stirred in solvent (1.0 mL) at room temperature for 24 h. [b]Isolated yield. [c]Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase.

Upon the solvent screening and selecting THF as the solvent of choice, some chiral iodoarenes were selected in order to test their properties in this transformation (Table 4.8).

Table 4.8. Screening of pre-catalysts in the asymmetric lactonization of 5-oxo-5-phenylpentanoic acid **205**.[a]



Entry	Pre-catalyst (Ar*I)	Yield (%)[b]	*ee* (%)[c]
1	**199b**	**76**	**15**
2	**199c**	--	--
3	**200e**	18	11
4	**188a**	68	n.d.[d]

[a]Reaction conditions: 5-oxo-5-phenylpentanoic acid **205** (0.03 mmol, 1.0 equiv), **Ar*-I** (5.0 μmol, 20 mol%), *m*CPBA (0.07 mmol, 3.0 equiv) and $TsOH \cdot H_2O$ (0.07 mmol, 3.0 equiv) were stirred in THF (1.0 mL) at room temperature for 24 h. [b]Isolated yield. [c]Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase. [d]n.d. = not determined.

In a similar trend with catalyst **199a**, catalyst **199b** afforded the cyclized product in good yield (76%) and relatively low enantioselectivity (15%, entry 1). Surprisingly, when catalyst **199c** which shares similar structural features with the previous two, was employed, the reaction did not take place (entry 2). In the presence of catalyst **200e**, a significant decrease in the yield was observed (18%) while the enantioselectivity remained low (11% *ee*). Finally, catalyst **Type I** (**188a**) could catalyze the reaction affording the product **206** in moderate yield (68%), however, no induction was observed.

4.4 Conclusion

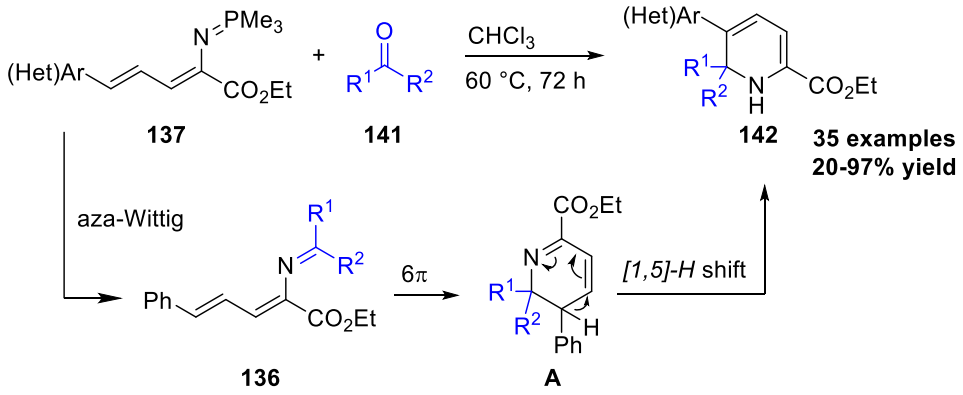
In conclusion, the generation of a library of 20 chiral iodoarenes was accomplished. The catalysts could be classified according to their structural and chirality properties into two distinct types: *Ishihara type* catalysts and **Type I** with central chirality. The preparation of **Type II** catalysts endowed with axial chirality was unsuccessful due to the failing attempts to introduce the iodine in the desired position. The performance of the synthesized chiral iodoarenes to induce asymmetry was evaluated in a series of reported transformations and compared with previous results. Unfortunately, in all cases even if the catalysts exhibited reactivity, the selectivity was low to moderate.

Chapter 5. Summary

5 Summary

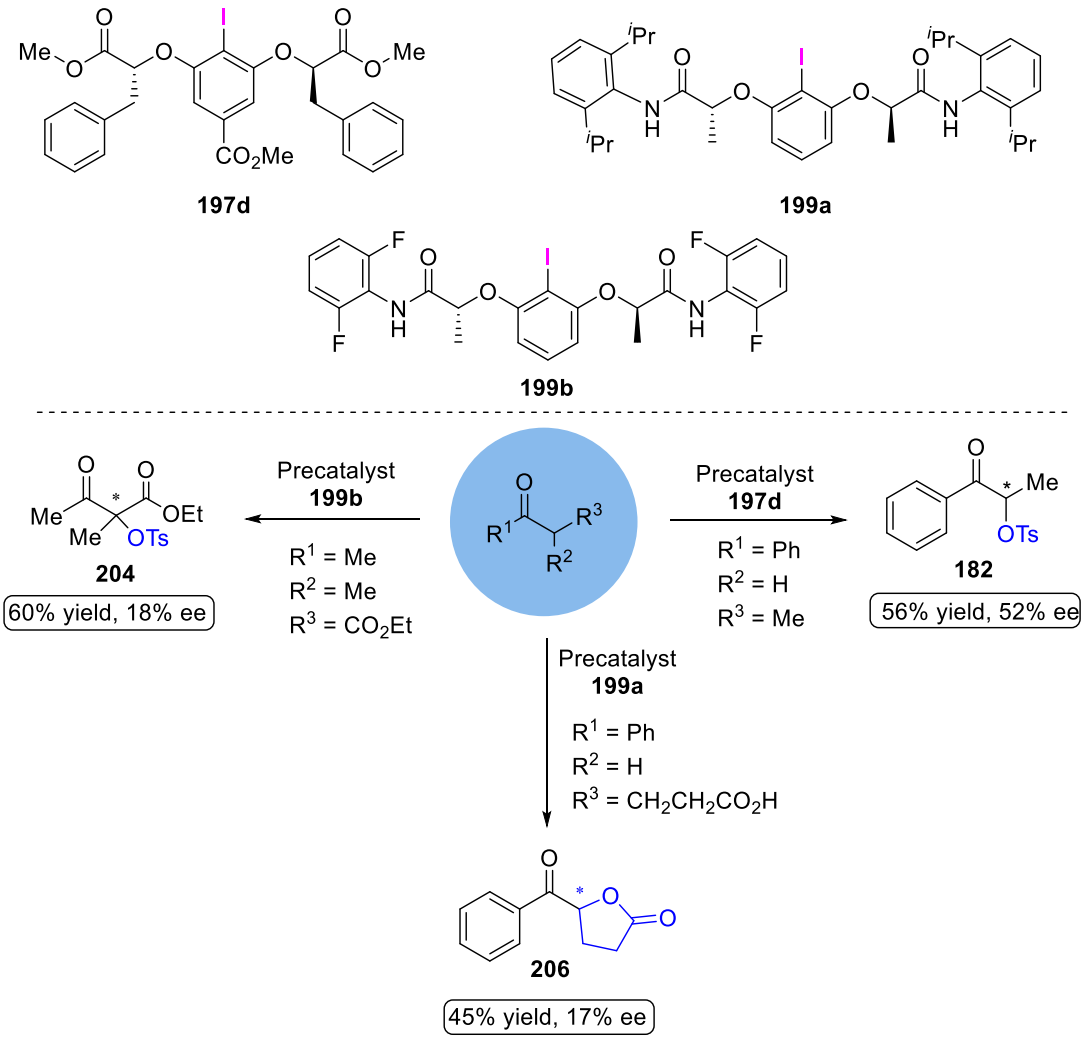
Over the last decades, the development of novel synthetic procedures that comply with the need for economical and sustainable solutions have gained significant interest. Even though, transition metal catalysis has found wide applications in various organic transformations, it is usually confronted with toxicity and cost intensive problems. A promising alternative to overcome these limitations are metal-free strategies. 6π-Electrocyclizations are known transformations to proceed under meta-free conditions giving access to complex molecular scaffolds in an atom economical and efficient way.

A cascade aza-Wittig/6π-electrocyclization process of readily available vinyliminophosphoranes **137** and ketones **141** for the construction of multi-substituted 1,6-dihydropyridines **142** containing a stereogenic center was systemically optimized and established under metal-free conditions (Scheme 5.1). The wide scope of this method has been demonstrated by employing a series of vinyliminophosphoranes **137** and ketones **141** with different substitution patterns which resulted in 1,6-dihydropyridines with up to 97% yield. Furthermore, a putative mechanism was proposed where an azatriene **136** as the key-intermediate undergoes a temperature-mediated disrotatory 6π-electrocyclization, followed by [1,5]-hydride shift. To examine the synthetic utility of the obtained compounds of this operational friendly aza-Witting/6π-electrocyclization sequence, they were subjected to further transformations. Subsequently, hydrogenation and Diels-Alder reaction gave access to diverse, valuable scaffolds. Finally, the asymmetric organocatalytic version of the established methodology has been studied with different chiral Brønsted acids and resulted in 1,6-dihydropyridines with low enantioselectivities.



Scheme 5.1. Synthesis of multi-substituted 1,6-dihydropyridines **142** *via* an aza-Wittig/6π-electrocyclization sequence.

Hypervalent iodine reagents are known organic surrogates for transition metal-catalyzed oxidative transformations. Their attractiveness is highly associated with their eco-friendly character, low cost, and toxicity. The systematic design of chiral hypervalent iodine compounds further expanded their application in the field of asymmetric synthesis. Based on this, in the second part of this thesis the generation of a series of easily accessible chiral iodoarenes and their evaluation in selected oxidative transformations were studied. Overall, 20 chiral iodoarenes (with 14 being novel) have been prepared in moderate yields *via* newly established, short reaction sequences. These chiral iodoarenes can be clustered in different types according to their structural features. Furthermore, their performance in enantioselective synthesis, and particularly, in three well-established oxidative transformations of carbonyl compounds was studied by tuning several reaction parameters. In general, even though the chiral iodoarenes were able to catalyze the reactions yielding the final products in moderate to good yields, no high enantioselectivities were achieved (Scheme 5.2).



Scheme 5.2. Application of chiral iodoarenes in asymmetric α-functionalization of ketones.

Chapter 6. Experimental Section

6 Experimental Section

6.1 General methods and materials

Reagents and solvents

Commercially available chemicals were purchased from *Sigma-Aldrich*, *Acros Organics*, *Alfa Aesar*, *VWR* Germany, *ABCR* and *TCI* Germany. Unless otherwise noted, all commercially available compounds and solvents were used as received and without further purifications. Dry solvents were purchased from *Acros* or *Sigma Aldrich* and used without further treatment. Solvents for chromatography were technical grade. Oxygen and/or moisture sensitive solutions were transferred using syringes and cannulas.

Chromatography

Analytical thin-layer chromatography (TLC) was performed on *Merck* silica gel aluminum plates with F-254 indicator, visualized by irradiation with UV light (254 nm) or staining with $KMnO_4$-solution (1.5 g $KMnO_4$, 10 g K_2CO_3, 1.25 mL 10% NaOH in 150 mL H_2O). Column chromatography was performed using silica gel *Merck 60* (particle size 0.040 - 0.063 mm). Solvent mixtures are understood as volume/volume.

Nuclear magnetic resonance spectroscopy (NMR)

^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR were recorded on a *Bruker DRX400* (400 MHz), *Bruker DRX500* (500 MHz), *INOVA500* (500 MHz) and *Bruker DRX700* (700 MHz) using CD_2Cl_2, $CDCl_3$, DMSO-d_6, or CD_3OD as solvent. Data are reported in the following order: chemical shift (δ) values are reported in ppm with the solvent resonance as internal standard (CD_2Cl_2: δ = 5.32 ppm for ^{1}H, δ = 53.84 ppm for ^{13}C; $CDCl_3$: δ = 7.26 ppm for ^{1}H, δ = 77.16 ppm for ^{13}C; DMSO-d_6: δ = 2.50 ppm for ^{1}H, δ = 39.52 ppm for ^{13}C; CD_3OD: δ = 3.31 ppm for ^{1}H, δ = 49.00 ppm for ^{13}C); multiplicities are indicated br s (broadened singlet), s (singlet), d (doublet), t (triplet), q (quartet) m (multiplet); coupling constants (*J*) are given in Hertz (Hz).

Fourier transform infrared spectroscopy (FT-IR)

Fourier transform infrared spectroscopy (FT-IR) spectra were obtained with a Bruker Tensor 27 spectrometer (ATR, neat) and are reported in terms of frequency of absorption (cm^{-1}).

Mass spectrometry

Low resolution mass spectra (MS-EI, 70 eV) were collected using an *Agilent Technologies 7890A GC-System* (column: HP-5MS, 30 m × 0.250 mm × 0.25 μm) equipped with an *Agilent Technologies 5975C inert XL MSD* with *Triple-Axis Detector*.

Low resolution mass spectra (MS-ESI) were collected using a *Waters Corp. LC-MS system* (column: LC reverse phase CC Nucleodur C4 Gravity, 5 μm from Macherey-Nagel) equipped with an *UV-Waters 2487 Dual Absorbance Detector* and *Waters Micromass ZQ 2000 ESCI+ Multi-Mode-Ionization MS-Detector*.

High resolution mass spectra were recorded on a *LTQ Orbitrap* mass spectrometer coupled to an *Acceka HPLC-System* (HPLC column: Hypersyl GOLD, 50 mm x 1 mm, particle size 1.9 μm, ionization method: electron spray ionization).

The enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase column (CHIRALCEL IC; eluent: (*iso*-hexane / *i*-PrOH); 4.6 mm x 250 mm, particle size 5 μm). The chiral HPLC methods were calibrated with the corresponding racemic mixtures.

Optical rotations

Optical rotations were measured in a Schmidt + Haensch Polartronic HH8 polarimeter equipped with a sodium lamp source (589 nm) and were reported as follows: $[\alpha]_D^{T\,°C}$ (c = g/100 mL, solvent).

X-ray analysis

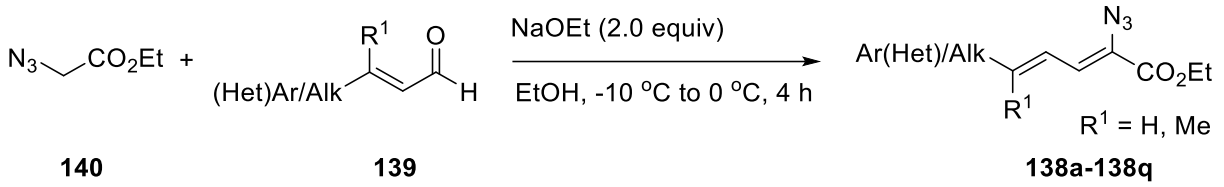
The crystal structures of compounds **136a**, **136b**, **142a** and **142aa** was determined using the *Bruker D8 Venture* four-circle diffractometer equipped with a *PHOTON II* CPAD detector by *Bruker AXS GmbH*. The X-ray radiation was generated by the *IμS* microfocus source Mo (λ = 0.71073 Å) from *Incoatec GmbH* equipped with HELIOS mirror optics and a single-hole collimator by *Bruker AXS GmbH*. The selected single crystal of **136a**, **136b**, **142a** and **142aa** were covered with an inert oil (perfluoropolyalkyl ether) and mounted on the *MicroMount* from *MiTeGen*. The APEX 3 Suite (v.2018.7-2) software integrated with SAINT (integration) and SADABS (adsorption correction) programs by *Bruker AXS GmbH* were used for data collection. The processing and finalization of the crystal structure were performed using the Olex2 program.[148] The crystal structures were solved by the ShelXT[149] structure solution program using the Intrinsic Phasing option, which

were further refined by the ShelXL[150] refinement package using Least Squares minimization. The non-hydrogen atoms were anisotropically refined. The C-bound H atoms were placed in geometrically calculated positions, and a fixed isotropic displacement parameter was assigned to each atom according to the riding-model: C–H = 0.95–1.00 Å with *U*iso(H) = 1.5*U*eq (CH3) and 1.2*U*eq (CH_2, CH) for other hydrogen atoms. The N-bound hydrogen atoms on N1, N2, N3 and N4 were located on the Difference-Fourier-Map and refined independently in every structure. The crystallographic data for the structures of **136a**, **136b**, **142a** and **142aa** has been published as supplementary publication number 2060066 (**136a**), 2081540 (**136b**) 2046825 (**142a**), 2046566 (**142aa**) in the Cambridge Crystallographic Data Centre. A copy of these data can be obtained for free by applying to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK, fax: 144-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

6.2 Experimental part for the synthesis of 1,6-dihydropyridines *via* a cascade aza-Wittig/6π-electrocyclization process

6.2.1 General procedures

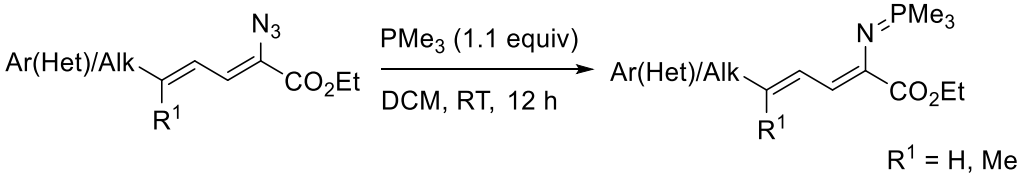
General procedure A for the preparation of vinyl azides



140 **139** **138a-138q**

A solution of ethyl azidoacetate (2.2 equiv) and α, β-unsaturated aldehydes (1.0 equiv) in anhydrous ethanol [3 M] were added dropwise to a well-stirred solution containing sodium ethoxide (21 wt % solution in ethanol, 2.2 equiv) in anhydrous ethanol [2.5 M] at -10 °C under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 4 h. After reaction completion, the mixture was diluted with water. The phases were separated, and the resulting aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuum. The crude reaction mixture was purified by means of short silica-gel column chromatography (eluent system: *n*-pentane – ethyl acetate) to afford the pure vinyl azides (**138a-138q**).

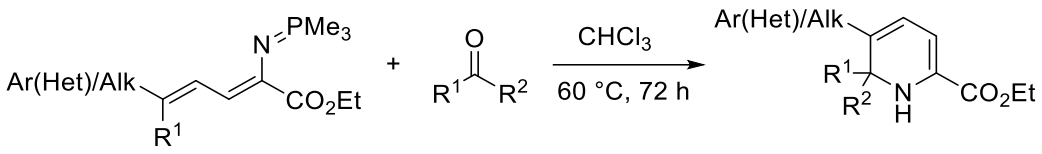
General procedure B for the preparation of vinyliminophosphoranes



138a-138q **137a-137q**

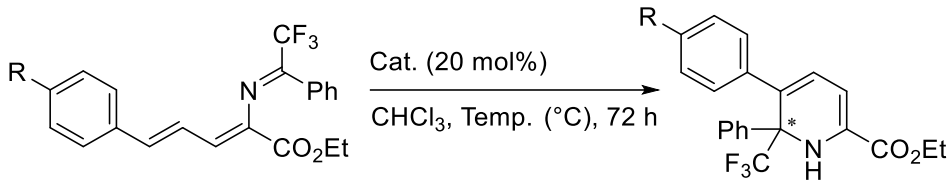
A solution of the corresponding vinyl azide (**138a-138q**) (1.0 equiv) in anhydrous dichloromethane [0.4 M] was added dropwise to a solution of trimethylphosphine (1 M solution in toluene, 1.1 equiv) in anhydrous dichloromethane [0.2 M] at room temperature and stirred for 12 h. Upon reaction completion, the solvent was removed under reduced pressure. The compounds **137a-137q** were used without further purification.

General procedure C for the synthesis 1,6-dihydropyridine-3-carboxylates



To a 5.0 mL screw-capped seal tube were successively added a solution of compound **137** (0.15 mmol, 1.0 equiv) in anhydrous chloroform [0.1 M] and the respective ketone **141** (0.15 mmol, 1.0 equiv). Then, the tube was sealed, and the resulting mixture was stirred vigorously at 60 °C (oil bath) till almost full consumption of imine, monitored by TLC analysis. Upon reaction completion, the solvent was evaporated, and the resulting crude was purified by means of short silica-gel column chromatography (eluent system: *n*-pentane - ethyl acetate) to afford the pure product **142**.

General procedure D for the asymmetric synthesis of 1,6-dihydropyridine-3-carboxylates



To a 2.0 mL screw-capped glass tube were successively added the corresponding acyclic imine **136** (10 mg, 0.024 mmol, 1.0 equiv.) and the corresponding catalyst (0.005 mmol, 20 mol%) in chloroform [0.1 M]. Then the tube was sealed, and the resulting mixture was stirred vigorously at 60 °C (oil bath) till almost full consumption of imine by TLC analysis. Upon reaction completion, the solvent was evaporated, and the resulting crude was purified by means of short silica-gel column chromatography (eluent system: *n*-pentane - ethyl acetate) and analyzed by HPLC on a chiral stationary phase.

1.00 mmol Scale reaction protocol for the synthesis of compound 142aa

To a 50.0 mL round-bottom flask, were successively added a solution of compound **137b** (378.1 mg, 1.0 mmol, 1.0 equiv) in anhydrous chloroform (10.0 mL) and 2,2,2-trifluoroacetophenone (141.84 μL, 1.0 mmol, 1.0 equiv). Then the flask was equipped with a findenser, and the resulting mixture was stirred vigorously at 60 °C (oil bath). Upon reaction completion as monitored by TLC,

the solvent was evaporated and the resulting crude was purified by means of short silica-gel column chromatography (eluent: 2% ethyl acetate in *n*-pentane) to afford the pure product as yellow amorphous solid (354.2 mg, 0.88 mmol, 88%).

One-pot reaction protocol for the synthesis of compound 142a

To a 5.0 mL screw-capped seal tube were successively added compound **138a** (50.0 mg, 0.21 mmol, 1.0 equiv) and trimethylphospine (1 M solution in toluene, 226.1 μL, 0.23 mmol, 1.1 equiv) and dissolved in anhydrous chloroform (2.0 mL). After stirring for 5 min at room temperature, 2,2,2-trifluoroacetophenone (29.1 μL, 0.21 mmol, 1.0 equiv) was added and the reaction mixture was heated up to 60 °C (oil bath). The reaction as monitored by TLC and GC-MS analysis did not lead to the formation of product **142a**.

Procedures for the hydrogenation of compound 142a

Synthesis of compound 146. A solution of substrate **142a** (0.08 mmol, 28.0 mg, 1.0 equiv.) in methanol [0.05 M] was treated with Pd/C (50-100 wt.%) (0.01 mmol, 8.1 mg, 10 mol%) and then the reaction mixture was saturated with hydrogen gas (two cycles). The solution was then stirred at 65 °C (oil bath) under hydrogen atmosphere for 72 h. The reaction was filtered through celite and washed with methanol (2 × 5 mL). Evaporation of the solvent afforded the expected product **146** (17.5 mg, 0.05 mmol, 87% yield).

Synthesis of compound 147a. A solution of substrate **142a** (0.05 mmol, 20.0 mg, 1.0 equiv.) in toluene [0.05 M] was treated with Pd/C (50-100 wt.%) (0.005 mmol, 5.7 mg, 10 mol%) and then the reaction mixture was saturated with hydrogen gas (two cycles). The solution was then stirred at room temperature under hydrogen atmosphere for 12 h. The reaction was filtered through celite and washed with methanol (2 × 5 mL). Evaporation of the solvent afforded the expected product **147a** (17.0 mg, 0.045 mmol, 84% yield).

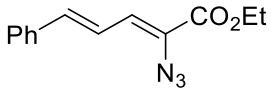
Procedure for the synthesis of bridged ring 149 *via* Diels-Alder reaction

1,6-Dihydropyridine **142a** (37.3 mg, 0.10 mmol, 1.0 equiv) was placed in a sealable glass vessel, equipped with a stir bar, in an inert argon atmosphere. To the reaction vessel were added *N*-methylmaleimide (12.6 mg, 0.11 mmol, 1.1 equiv) and $BF_3 \cdot Et_2O$ (1.26 μL, 0.010 mmol, 10 mol%) and they were dissolved in 1.0 mL of DCM. The reaction vessel was then sealed, and the mixture was stirred at ambient temperature. Upon reaction completion (monitored by TLC), the solvent

was removed in *vacuo*. The resulting residue was purified by column chromatography on silica gel (*n*-pentane/ ethyl acetate 5:1) to afford the product as light brown solid (6.2 mg, 0.013 mmol, 13%).

6.2.2 Physical data of compounds

6.2.2.1 Physical data of vinyl azides



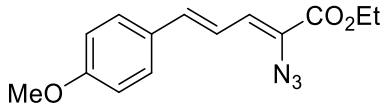
Ethyl (2*Z*, 4*E*) -2-azido-5-phenylpenta-2,4-dienoate (138a)

The general procedure A was followed and purification by column chromatography (2% ethyl acetate in *n*-pentane) afforded **138a** as a light-yellow solid, (1.7 g, 7.1 mmol, 47% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 2H), 7.31 – 7.25 (m, 2H), 7.25 – 7.19 (m, 1H), 7.10 (dd, *J* = 15.7, 11.2 Hz, 1H), 6.79 – 6.64 (m, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 139.1, 136.5, 129.1, 128.9, 127.4, 127.0, 125.9, 122.4, 62.1, 14.4 ppm.

The analytical data were in good accordance with those reported in the literature.[151]



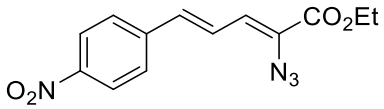
Ethyl (2*Z*, 4*E*) -2-azido-5-(4-methoxyphenyl) penta-2,4-dienoate (138b)

The general procedure A was followed and purification by column chromatography (4% ethyl acetate in *n*-pentane) afforded **138b** as a light-yellow solid, (1.0 g, 3.8 mmol, 31% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.7 Hz, 2H), 6.96 (dd, *J* = 15.6, 11.3 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.73 – 6.62 (m, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 160.5, 138.9, 129.4, 128.9, 127.7, 124.7, 120.3, 114.4, 62.0, 55.5, 14.4 ppm.

The analytical data were in good accordance with those reported in the literature.[152]



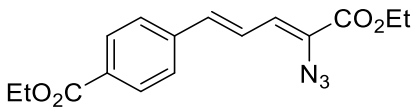
Ethyl (2*Z*,4*E*) -2-azido-5-(4-nitrophenyl) penta-2,4-dienoate (138c)

The general procedure A was followed and purification by column chromatography (4% ethyl acetate in *n*-pentane) afforded **138c** as a bright orange solid, (1.0 g, 3.5 mmol, 32% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.31 (dd, *J* = 15.7, 11.2 Hz, 1H), 6.83 (d, *J* = 15.7 Hz, 1H), 6.72 (d, *J* = 11.1 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9, 142.8, 135.6, 128.4, 127.7, 126.5, 125.0, 124.7, 124.3, 62.5, 14.3 ppm.

The analytical data were in good accordance with those reported in the literature.[152b, 153]



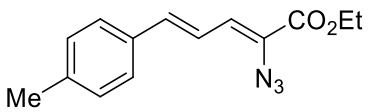
Ethyl 4-((1*E*, 3*Z*) -4-azido-5-ethoxy-5-oxopenta-1,3-dien-1-yl) benzoate (138d)

The general procedure A was followed and purification by column chromatography (4% ethyl acetate in *n*-pentane) afforded **138d** as a bright orange solid, (0.94 g, 3.0 mmol, 28% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.37 – 7.16 (m, 1H), 6.84 (s, 1H), 6.74 (dd, *J* = 11.3, 0.9 Hz, 1H), 4.36 (dq, *J* = 18.5, 7.1 Hz, 4H), 1.39 (dt, *J* = 9.3, 7.1 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 163.1, 140.7, 137.5, 130.4, 130.2, 127.1, 127.1, 126.0, 124.6, 62.3, 61.2, 14.5, 14.3 ppm.

HRMS (ESI): calcd. for $[M+H-N_2]^+$ $C_{16}H_{18}NO_4$ = 288.1230; found 288.1235.



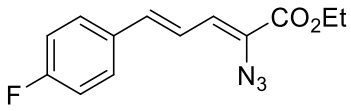
Ethyl (2*Z*, 4*E*) -2-azido-5-(p-tolyl) penta-2,4-dienoate (138e)

The general procedure A was followed and purification by column chromatography (2% ethyl acetate in *n*-pentane) afforded **138e** as a light-yellow solid, (1.9 g, 7.5 mmol, 58% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.13 – 7.05 (m, 1H), 6.79 (d, *J* = 15.7 Hz, 1H), 6.75 (dd, *J* = 11.3, 0.9 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.36 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2, 139.2, 139.1, 133.7, 129.6, 127.2, 125.2, 121.3, 77.3, 61.9, 21.4, 14.3 ppm.

The analytical data were in good accordance with those reported in the literature.[154]



Ethyl (2*Z*, 4*E*)-2-azido-5-(4-fluorophenyl) penta-2,4-dienoate (138f)

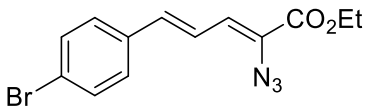
The general procedure A was followed and purification by column chromatography (2% ethyl acetate in *n*-pentane) afforded **138f** as a light-yellow solid, (1.2 g, 4.6 mmol, 36% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.15 – 7.00 (m, 3H), 6.84 – 6.69 (m, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2, 163.2 (d, J_{CF} = 249.8 Hz), 137.6, 132.8 (d, J_{CF} = 3.4 Hz), 129.0 (d, J_{CF}= 8.2 Hz), 126.7, 125.9, 122.1 (d, J_{CF} = 2.5 Hz), 116.0 (d, J_{CF} = 21.8 Hz), 62.2, 14.4 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -111.64 (s, 1F) ppm.

HRMS (ESI): calcd. for $[M+H-N_2]^+$ $C_{13}H_{13}FNO_2$ = 284.0925; found 284.0925.



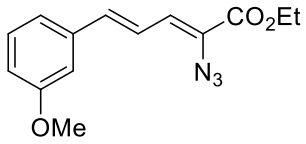
Ethyl (2*Z*, 4*E*)-2-azido-5-(4-bromophenyl) penta-2,4-dienoate (138g)

The general procedure A was followed and purification by column chromatography (2% ethyl acetate in *n*-pentane) afforded **138g** as a light-yellow solid, (1.3 g, 4.0 mmol, 44% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.15 (dd, *J* = 15.6, 11.3 Hz, 1H), 6.79 – 6.66 (m, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2, 137.5, 135.5, 132.1 (2C), 128.7 (2C), 126.4, 123.0, 62.2, 14.3 ppm.

The analytical data were in good accordance with those reported in the literature.[152a, 155]



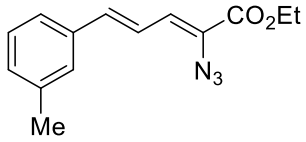
Ethyl (2*Z*, 4*E*)-2-azido-5-(3-methoxyphenyl) penta-2,4-dienoate (138h)

The general procedure A was followed and purification by column chromatography (4% ethyl acetate in *n*-pentane) afforded **138h** as a light-yellow solid, (1.3 g, 4.8 mmol, 41% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 1H), 7.14 (dd, *J* = 15.7, 11.2 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 2.1 Hz, 1H), 6.85 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.81 – 6.70 (m, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 160.0, 138.9, 137.9, 129.9, 126.8, 125.9, 122.6, 120.2, 114.9, 112.2, 62.0, 50.5, 14.3 ppm.

HRMS (ESI): calcd. for $[M+H-N_2]^+$ $C_{14}H_{16}NO_3$ = 246.1125; found 246.1125.



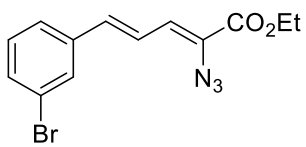
Ethyl (2*Z*, 4*E*)-2-azido-5-(m-tolyl) penta-2,4-dienoate (138i)

The general procedure A was followed and purification by column chromatography (2% ethyl acetate in *n*-pentane) afforded **138i** as a light-yellow solid, (1.2 g, 4.7 mmol, 36% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 3H), 7.19 – 7.10 (m, 2H), 6.79 (d, *J* = 15.7 Hz, 1H), 6.75 (dd, *J* = 11.2, 0.7 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.37 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.30, 139.29, 138.55, 136.44, 129.96, 128.82, 127.91, 127.13, 125.62, 124.70, 122.17, 62.10, 21.50, 14.35 ppm.

The analytical data were in good accordance with the methyl-ester derivative, reported in the literature.[152a]



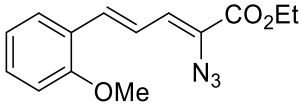
Ethyl (2*Z*, 4*E*) -2-azido-5-(3-bromophenyl) penta-2,4-dienoate (138j)

The general procedure A was followed and purification by column chromatography (2% ethyl acetate in *n*-pentane) afforded **138j** as a light-yellow solid, (0.85 g, 2.6 mmol, 29% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (t, *J* = 1.8 Hz, 1H), 7.44 – 7.35 (m, 2H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.19 – 7.10 (m, 1H), 6.73 (d, *J* = 3.8 Hz, 1H), 6.70 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.1, 138.7, 137.0, 131.8, 130.4, 130.0, 126.8, 126.1, 125.9, 123.7, 123.1, 62.3, 14.3 ppm.

HRMS (ESI): calcd. for $[M+H-N_2]^+$ $C_{13}H_{13}{}^{79}BrNO_2$ = 294.0124; found 294.0126, calcd. for $[M+H-N_2]^+$ $C_{13}H_{13}{}^{81}BrNO_2$ = 296.0104; found 296.0106 $C_{13}H_{13}{}^{81}BrNO_2$ = 296.0104; found 296.0106.



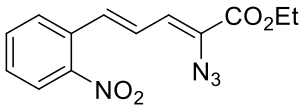
Ethyl (2*Z*, 4*E*)-2-azido-5-(2-methoxyphenyl) penta-2,4-dienoate (138k)

The general procedure A was followed and purification by column chromatography (4% ethyl acetate in *n*-pentane) afforded **138k** as a light-yellow solid, (1.7 g, 6.3 mmol, 52% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.29 – 7.21 (m, 1H), 7.06 – 6.99 (m, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.86 (dd, *J* = 7.2, 3.0 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 157.5, 134.1, 130.3, 128.1, 127.4, 125.5, 125.1, 122.7, 120.9, 111.1, 62.0, 55.7, 14.4 ppm.

The analytical data were in good accordance with those reported in the literature.[151]



Ethyl (2*Z*, 4*E*) -2-azido-5-(2-nitrophenyl) penta-2,4-dienoate (138l)

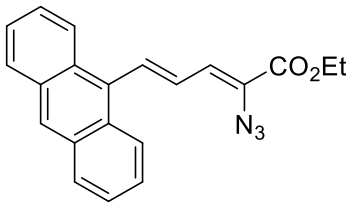
The general procedure A was followed and purification by column chromatography (4% ethyl acetate in *n*-pentane) afforded **138l** as a light-yellow solid, (0.90 g, 3.1 mmol, 28% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.75 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.60 (td, *J* = 7.7, 1.4 Hz, 1H), 7.44 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H), 7.30 (d, *J* = 15.6 Hz, 1H), 7.16 (dd,

J = 15.6, 11.0 Hz, 1H), 6.76 (dd, *J* = 11.1, 0.8 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9, 148.2, 133.3, 132.6, 132.0, 129.1, 128.4, 128.0, 127.0, 125.4, 125.0, 62.4, 14.3 ppm.

The analytical data were in good accordance with those reported in the literature.[151]



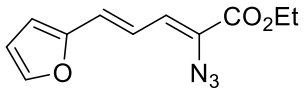
Ethyl (2*Z*, 4*E*)-5-(anthracen-9-yl)-2-azidopenta-2,4-dienoate (138m)

The general procedure A was followed and purification by column chromatography (2% ethyl acetate in *n*-pentane) afforded **138m** as a bright orange solid, (0.62 g, 1.8 mmol, 21% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.30 – 8.19 (m, 2H), 8.06 – 7.96 (m, 3H), 7.74 (d, *J* = 15.4 Hz, 1H), 7.53 – 7.46 (m, 4H), 7.16 – 6.95 (m, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 135.5, 131.5, 131.4, 131.2, 129.6, 129.0, 128.6, 127.7, 126.5, 126.2, 125.6, 125.4, 62.3, 14.4 ppm.

HRMS (ESI): calcd. for $[M+H-N_2]^+$ $C_{21}H_{18}NO_2$ = 316.1332; found 316.1333.



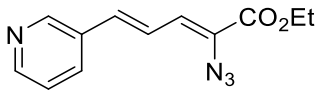
Ethyl (2*Z*, 4*E*)-2-azido-5-(furan-2-yl) penta-2,4-dienoate (138n)

The general procedure A was followed and purification by column chromatography (2% ethyl acetate in *n*-pentane) afforded **138n** as a light-yellow solid, (1.9 g, 8.2 mmol, 51% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.03 (dd, *J* = 15.6, 11.5 Hz, 1H), 6.68 (dd, *J* = 11.6, 0.9 Hz, 1H), 6.59 (d, *J* = 15.6 Hz, 1H), 6.43 (td, *J* = 4.0, 3.4, 2.5 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2, 152.8, 143.8, 126.5, 125.7, 125.5, 120.8, 112.3, 111.7, 62.1, 14.3 ppm.

The analytical data were in good accordance with those reported in the literature.[151]



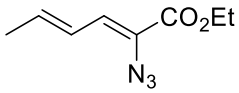
Ethyl (2*Z*, 4*E*)-2-azido-5-(pyridin-3-yl) penta-2,4-dienoate (138o)

The general procedure A was followed and purification by column chromatography (10% ethyl acetate in *n*-pentane) afforded **138o** as a bright orange solid, (0.70 g, 2.9 mmol, 19% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 1.7 Hz, 1H), 8.51 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.83 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.30 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.22 (dd, *J* = 15.8, 11.2 Hz, 1H), 6.82 – 6.56 (m, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.0, 149.5, 149.1, 134.6, 133.3, 132.4, 127.1, 125.7, 124.4, 123.9, 62.3, 14.3 ppm.

The analytical data were in good accordance with the methyl-ester derivative, reported in the literature.[156]



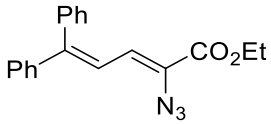
Ethyl (2*Z*, 4*E*) -2-azidohexa-2,4-dienoate (138p)

The general procedure A was followed and purification by column chromatography (10% ethyl acetate in *n*-pentane) afforded **138p** as a light-yellow oil, (2.0 g, 11.0 mmol, 39% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (d, *J* = 11.1 Hz, 1H), 6.49 – 6.39 (m, 1H), 6.12 – 6.02 (m, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.86 (dd, *J* = 6.9, 1.7 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 138.4, 127.4, 125.9, 123.9, 61.9, 19.1, 14.3 ppm.

The analytical data were in good accordance with those reported in the literature.[151]



Ethyl (*Z*)-2-azido-5,5-diphenylpenta-2,4-dienoate (138q)

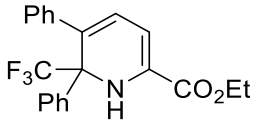
The general procedure A was followed and purification by column chromatography (1% ethyl acetate in *n*-pentane) afforded **138q** as a yellow solid, (660 mg, 2.1 mmol, 43% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 3H), 7.32 (s, 5H), 7.23 (d, *J* = 2.2 Hz, 1H), 7.21 (d, *J* = 1.6 Hz, 1H), 7.09 (d, *J* = 11.6 Hz, 1H), 6.69 (d, *J* = 11.6 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 149.7, 141.6, 138.9, 130.7, 128.5, 128.4, 124.7, 121.2, 62.0, 14.2 ppm.

The analytical data were in good accordance with those reported in the literature.[155]

6.2.2.2 Physical data of 1,6-dihydropyridines-3-carboxylates



Ethyl 5,6-diphenyl-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142a)

Prepared according to the general procedure C. The product was isolated as yellow amorphous solid (45 mg, 0.12 mmol, 84% yield) (eluent: 1% EtOAc in *n*-pentane).

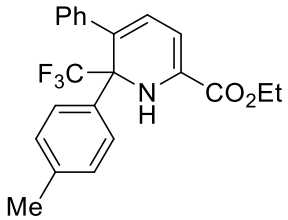
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.42 – 7.33 (m, 3H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 2H), 6.74 (d, *J* = 7.2 Hz, 2H), 6.35 (d, *J* = 6.5 Hz, 1H), 6.00 (dd, *J* = 6.5, 1.8 Hz, 1H), 5.06 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 140.7, 139.4, 130.5, 129.3, 128.7, 128.6, 128.1 (q, J_{CF} = 2.2 Hz, 2C), 127.6, 127.5, 127.0, 124.7, 100.9, 68.7 (q, J_{CF} = 27.5 Hz), 61.8, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.16 (s, 3F) ppm.

FT-IR: ṽ = 3342, 1706, 1638, 1462, 1449, 1392, 1372, 1273, 1204, 1170, 1091, 1044, 1028, 1001 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{21}H_{19}F_3NO_2$ = 374.1362; found 374.1365.



Ethyl 5-phenyl-6-(*p*-tolyl)-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142b)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (36 mg, 0.09 mmol, 64%) (eluent: 1% EtOAc in *n*-pentane).

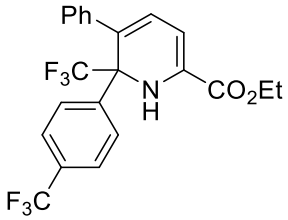
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.9 Hz, 2H), 7.21 – 7.12 (m, 3H), 7.09 (t, *J* = 7.4 Hz, 2H), 6.77 (d, *J* = 7.2 Hz, 2H), 6.33 (d, *J* = 6.5 Hz, 1H), 5.98 (dd, *J* = 6.5, 1.8 Hz, 1H), 5.02 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 2.38 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 139.5, 138.6, 137.9, 130.5, 129.4, 129.3 (d, J_{CF} = 3.5 Hz), 128.0 (q, J_{CF} = 2.2 Hz, 2C), 127.6, 127.5 (d, J_{CF} = 6.5 Hz), 127.3, 124.4, 100.9, 68.5 (q, J_{CF} = 27.4 Hz), 61.7, 21.2, 14.3 ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ -73.09 (s, 3F) ppm.

FT-IR: ῦ = 3353, 1704, 1638, 1496, 1443, 1375, 1274, 1254, 1171, 1160, 1149, 1079, 1037, 1005 cm^{-1}.

HRMS (ESI): calcd for $[M+H]^+$ $C_{22}H_{21}F_3NO_2$ = 388.1518; found 388.1521.



Ethyl 5-phenyl-6-(trifluoromethyl)-6-(4-(trifluoromethyl) phenyl)-1,6-dihydropyridine-2-carboxylate (142c)

Prepared according to the general procedure C. The product was isolated as yellow amorphous solid (39 mg, 0.09 mmol, 61%) (eluent: 1% EtOAc in *n*-pentane).

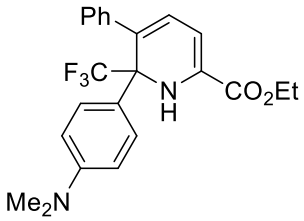
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.22 – 7.15 (m, 1H), 7.11 (t, *J* = 7.5 Hz, 2H), 6.76 (d, *J* = 7.3 Hz, 2H), 6.38 (d, *J* = 6.5 Hz, 1H), 6.03 (dd, *J* = 6.4, 1.8 Hz, 1H), 5.10 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 144.1, 138.8, 130.8 (q, J_{CF} = 32.6 Hz), 130.6, 129.2, 128.7, 128.5 (q, J_{CF} = 2.4 Hz,), 128.2, 127.8 (d, J_{CF} = 1.9 Hz), 127.0 (d, J_{CF} = 54.4 Hz), 125.5 (q, J_{CF} = 3.8 Hz), 124.7 (d, J_{CF} = 73.1 Hz), 122.8, 101.4, 68.5 (q, J_{CF} = 28.2, 28.6 Hz), 62.0, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) -62.73 (s, 3F), -72.99 (s, 3F) ppm.

FT-IR: ῦ = 3320, 1695, 1637, 1497, 1414, 1395, 1379, 1330, 1318, 1282, 1205, 1170, 1118, 1001 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{22}H_{18}F_6NO_2$ = 442.1236; found 442.1232.



Ethyl 6-(4-(dimethylamino) phenyl)-5-phenyl-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142d)

Prepared according to general procedure C. The product was isolated as orange amorphous solid (26 mg, 0.06 mmol, 43%) (eluent: 20% EtOAc in *n*-pentane).

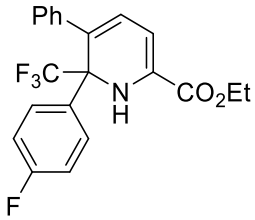
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.5 Hz, 2H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 2H), 6.80 (d, *J* = 7.2 Hz, 2H), 6.73 (bs, 2H), 6.31 (d, *J* = 6.5 Hz, 1H), 5.96 (dd, *J* = 6.4, 1.8 Hz, 1H), 4.99 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.00 (s, 6H), 1.33 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.6, 139.8, 130.4, 129.8, 129.3, 128.9, 127.6, 127.3, 127.1, 127.1, 124.7, 112.0, 111.0, 100.7, 68.3 (q, J_{CF} = 27.4 Hz), 61.7, 40.6, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.02 (s, 3F) ppm.

FT-IR: ṽ = 3348, 1700, 1637, 1609, 1525, 1484, 1448, 1370, 1281, 1258, 1217, 1099, 1040, 1006 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{23}H_{24}F_3N_2O_2$ = 417.1784; found 417.1781.



Ethyl 6-(4-fluorophenyl)-5-phenyl-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142e)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (50 mg, 0.13 mmol, 87%) (eluent: 1% EtOAc in *n*-pentane).

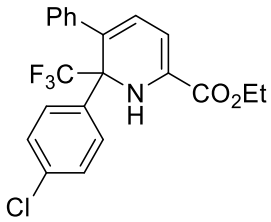
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.7, 5.2 Hz, 2H), 7.22 – 7.15 (m, 1H), 7.13 – 7.03 (m, 4H), 6.75 (d, *J* = 7.4 Hz, 2H), 6.34 (d, *J* = 6.5 Hz, 1H), 6.00 (dd, *J* = 6.5, 1.8 Hz, 1H), 5.06 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6 (d, J_{CF} = 249.0 Hz), 163.5, 139.2, 136.6 (d, J_{CF} = 3.5 Hz), 130.5, 130.1 (dd, J_{CF} = 8.3, 2.4 Hz), 129.3, 129.1, 127.7, 127.6, 126.9, 124.6, 115.5 (d, J_{CF} = 21.4 Hz), 101.1, 68.2 (q, J_{CF} = 27.6 Hz), 61.9, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.41 (s, 3F), -112.99 (s, 1F) ppm.

FT-IR: ṽ = 3356, 1701, 1637, 1595, 1498, 1473, 1442, 1376, 1275, 1258, 1242, 1170, 1129, 1103 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{21}H_{18}F_4NO_2$ = 392.1268; found 392.1268.



Ethyl 6-(4-chlorophenyl) -5-phenyl-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142f)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (48 mg, 0.12 mmol, 81%) (eluent: 1% EtOAc in *n*-pentane).

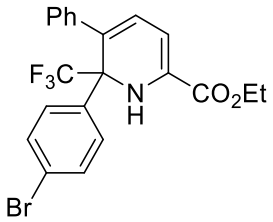
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.33 (m, 2H), 7.21 – 7.15 (m, 1H), 7.11 (t, *J* = 7.5 Hz, 2H), 6.77 (d, *J* = 7.3 Hz, 2H), 6.35 (d, *J* = 6.5 Hz, 1H), 6.00 (dd, *J* = 6.5, 1.8 Hz, 1H), 5.04 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 139.1 (d, J_{CF} = 8.8 Hz), 134.8, 130.5, 129.5 (q, J_{CF} = 2.4 Hz), 129.3, 128.9, 128.8, 127.9, 127.8, 127.7, 126.8, 124.5, 101.2, 68.3 (q, J_{CF} = 27.9 Hz), 61.9, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.20 (s, 3F) ppm.

FT-IR: ṽ = 3399, 3335, 1702, 1638, 1595, 1493, 1443, 1393, 1373, 1283, 1256, 1156, 1034, 1013 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{21}H_{18}{}^{35}ClF_3NO_2$ = 408.0972; found 408.0972; calcd. for $[M+H]^+$ $C_{21}H_{18}{}^{37}ClF_3NO_2$ = 410.0943; found 410.0942.



Ethyl 6-(4-bromophenyl)-5-phenyl-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142g)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (46 mg, 0.10 mmol, 70%) (eluent: 1% EtOAc in *n*-pentane).

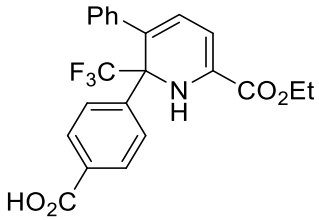
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.43 (m, 4H), 7.22 – 7.15 (m, 1H), 7.12 (t, *J* = 7.5 Hz, 2H), 6.77 (d, *J* = 7.2 Hz, 2H), 6.35 (d, *J* = 6.5 Hz, 1H), 6.00 (dd, *J* = 6.4, 1.8 Hz, 1H), 5.05 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 139.3 (d, J_{CF} = 75.3 Hz), 131.7, 130.5, 129.8 (q, J_{CF} = 2.3 Hz), 129.3, 128.8, 127.9, 127.8, 127.7, 126.8, 124.5, 123.1, 101.2, 68.4 (q, J_{CF} = 27.7 Hz), 61.9, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.13 (s, 3F) ppm.

FT-IR: ṽ = 3399, 3335, 1702, 1638, 1595, 1493, 1443, 1393, 1373, 1283, 1156, 1095, 1077, 1013 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{21}H_{18}{}^{79}BrF_3NO_2$ = 452.0467; found 452.0464; calcd. for $[M+H]^+$ $C_{21}H_{18}{}^{81}BrF_3NO_2$ = 454.0447; found 454.0443.



4-(6-(ethoxycarbonyl)-3-phenyl-2-(trifluoromethyl)-1,2-dihydropyridin-2-yl)benzoic acid (142h)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (14 mg, 0.03 mmol, 22%).

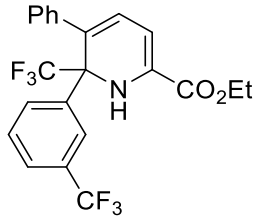
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.7 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.12 – 7.07 (m, 1H), 7.02 (t, *J* = 7.4 Hz, 2H), 6.69 (d, *J* = 7.2 Hz, 2H), 6.31 (d, *J* = 6.5 Hz, 1H), 5.95 (dd, *J* = 6.5, 1.8 Hz, 1H), 5.03 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 163.3, 145.7, 138.7, 130.5, 130.2, 129.3, 129.1, 128.6, 128.2, 128.2, 128.0, 127.7, 127.6, 101.2, 68.6 (d, *J*CF = 27.7 Hz), 61.8, 14.2 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.08 (s, 3F) ppm.

FT-IR: ṽ = 3345, 2926, 1693, 1637, 1612, 1578, 1497, 1473, 1424, 1377, 1283, 1246, 1207, 1173, 1161, 1152, 1126, 1071, 1034, 1019, 1001, 971, 927, 891, 817 cm^{-1}.

HRMS (ESI): $[M+H]^+$ calcd. $C_{22}H_{19}F_3NO_4$ m/z 418.12607, found 418.12595.



Ethyl 5-phenyl-6-(trifluoromethyl)-6-(3-(trifluoromethyl) phenyl)-1,6-dihydropyridine-2-carboxylate (142i)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (60 mg, 0.14 mmol, 93%) (eluent: 1% EtOAc in *n*-pentane).

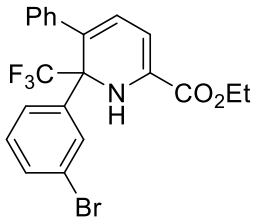
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.22 – 7.14 (m, 1H), 7.10 (t, *J* = 7.4 Hz, 2H), 6.72 (d, *J* = 7.3 Hz, 2H), 6.37 (d, *J* = 6.5 Hz, 1H), 6.04 (dd, *J* = 6.5, 1.8 Hz, 1H), 5.12 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 140.1 (d, J_{CF} = 257.1 Hz), 131.4, 131.0 (d, J_{CF} = 32.5 Hz), 130.7, 129.3, 129.1, 128.7, 128.2, 127.8, 127.8, 127.2, 125.5 (q, J_{CF} = 3.6 Hz), 125.3, 124.3, 122.6, 101.5, 68.4 (q, J_{CF} = 28.0 Hz), 62.0, 14.3 ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ -62.68 (s, 3F), -73.45 (s, 3F) ppm.

FT-IR: ṽ = 3339, 1702, 1643, 1486, 1441, 1392, 1375, 1332, 1285, 1239, 1151, 1099, 1072, 1001 cm^{-1}.

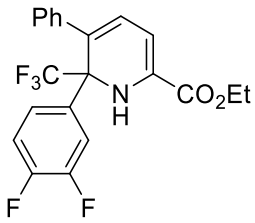
HRMS (ESI): calcd. for $[M+H]^+$ $C_{22}H_{18}F_6NO_2$ = 442.1236; found 442.1233.



Ethyl 6-(3-bromophenyl) -5-phenyl-6-(trifluoromethyl) -1,6-dihydropyridine-2-carboxylate (142j)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (58 mg, 0.13 mmol, 88%) (eluent: 1% EtOAc in *n*-pentane).

^{1}H NMR (500 MHz, $CDCl_3$) 7.86 (s, 1H), 7.57 (t, *J* = 7.7 Hz, 2H), 7.36 – 7.29 (m, 1H), 7.28 – 7.23 (m, 1H), 7.19 (t, *J* = 7.5 Hz, 2H), 6.84 (d, *J* = 7.3 Hz, 2H), 6.43 (d, *J* = 6.5 Hz, 1H), 6.08 (dd, *J* = 6.4, 1.8 Hz, 1H), 5.15 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 142.6, 138.9, 131.9, 131.5 (d, J_{CF} = 2.4 Hz), 130.5, 130.0, 129.3, 128.8, 128.0, 127.8, 127.7, 126.5 (d, J_{CF} = 2.3 Hz), 124.4, 122.9, 101.2, 68.4 (q, J_{CF} = 27.7 Hz), 61.9, 14.3 ppm.
^{19}F NMR (470 MHz, $CDCl_3$) δ -73.08 (s, 3F) ppm.
FT-IR: ṽ = 3336, 1688, 1638, 1566, 1496, 1394, 1377, 1274, 1257, 1152, 1098, 1078, 1040, 1015 cm^{-1}.
HRMS (ESI): calcd. for $[M+H]^+$ $C_{21}H_{18}{}^{79}BrF_3NO_2$ = 452.0467; found 452.0465, calcd. for $[M+H]^+$ $C_{21}H_{18}{}^{81}BrF_3NO_2$ = 454.0447; found 454.0443.



Ethyl 6-(3,4-difluorophenyl)-5-phenyl-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142k)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (30 mg, 0.07 mmol, 50%) (eluent: 1% EtOAc in *n*-pentane).

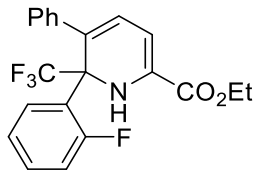
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (m, *J* = 11.8, 7.4, 2.4 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 7.22 – 7.09 (m, 4H), 6.77 (d, *J* = 7.3 Hz, 2H), 6.35 (d, *J* = 6.5 Hz, 1H), 6.01 (dd, *J* = 6.5, 1.8 Hz, 1H), 5.07 (s, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.4, 150.2 (dd, J_{CF} = 223.7, 12.6 Hz), 150.2 (dd, J_{CF} = 277.0, 12.6 Hz), 138.8, 137.5 (t, J_{CF} = 4.2 Hz), 130.5, 129.2, 128.7, 128.0, 127.9, 126.5, 124.6, 124.3, 117.9 (d, J_{CF} = 19.5 Hz), 117.3 (d, J_{CF} = 17.2 Hz), 101.4, 68.1 (q, J_{CF} = 27.7 Hz), 62.0, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.39 (s, 3F), -135.89 – -136.10 (m, 1F), -136.99 – -137.19 (m, 1F) ppm.

FT-IR: ṽ = 3330, 1696, 1639, 1515, 1494, 1443, 1423, 1277, 1214, 1167, 1070, 1050, 1035, 1001 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{21}H_{17}F_5NO_2$ = 410.1174; found 410.1172.



Ethyl 6-(2-fluorophenyl)-5-phenyl-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142l)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (18 mg, 0.05 mmol, 32%) (eluent: 1% EtOAc in *n*-pentane).

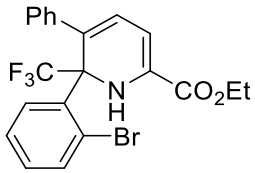
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.32 (m, 2H), 7.19 – 7.02 (m, 5H), 6.92 (d, *J* = 7.3 Hz, 2H), 6.40 (d, *J* = 6.6 Hz, 1H), 6.00 (dd, *J* = 6.6, 1.9 Hz, 1H), 4.99 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 162.2 (d, J_{CF} = 253.6 Hz), 139.1, 131.2 (d, J_{CF} = 9.1 Hz), 130.9, 128.9, 128.0, 127.8, 127.5, 127.2 (d, J_{CF} = 7.3 Hz), 126.5, 124.2, 123.6 (d, J_{CF} = 3.9 Hz), 117.7, 117.5, 101.2, 67.1 (q, J_{CF} = 28.3 Hz), 61.8, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -74.00 (s, 3F), -106.74 (s, 1F) ppm.

FT-IR: ṽ = 3164, 3002, 1443, 1375, 1038, 918 cm^{-1}.

HRMS (ESI): calcd for $[M+H]^+$. $C_{21}H_{18}F_4NO_2$ = 392.1268; found 392.1267.



Ethyl 6-(2-bromophenyl)-5-phenyl-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142m)

Following the general procedure C, the intermediate acyclic imine was isolated as the major product. To obtain the desired cyclized product, the imine was dissolved in toluene and heated at 110 °C (oil bath) for 72 h. The cyclized product was isolated as yellow amorphous solid (9.2 mg, 0.02 mmol, 20%) (eluent: 1% EtOAc in *n*-pentane).

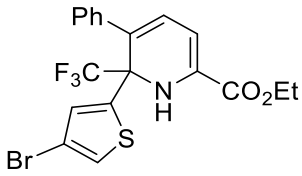
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.29 – 7.24 (m, 2H), 7.21 (td, *J* = 7.6, 1.6 Hz, 1H), 7.14 – 7.09 (m, 1H), 7.05 (t, *J* = 7.5 Hz, 2H), 6.84 – 6.76 (m, 2H), 6.40 (d, *J* = 6.7 Hz, 1H), 6.03 (dd, *J* = 6.7, 1.9 Hz, 1H), 4.67 (s, 1H), 4.30 (qt, *J* = 7.4, 3.7 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 139.2, 136.9, 136.6, 131.3, 130.3, 129.7, 129.0, 129.0, 128.9, 127.7, 127.3, 126.9, 126.7, 124.5, 101.1, 70.2 (d, J_{CF} = 27.8 Hz), 61.8, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -54.22 (s, 3F) ppm.

FT-IR: ṽ = 3356, 1701, 1637, 1595, 1498, 1442, 1376, 1275, 1196, 1170, 1150, 1129, 1103, 1027 cm^{-1}.

HRMS (ESI): calcd for $[M+H]^+$. $C_{21}H_{18}{}^{79}BrF_3NO_2$ = 452.0468; found 452.0464; calcd. for $[M+H]^+$ $C_{21}H_{18}{}^{81}BrF_3NO_2$ = 454.0447; found 454.0443.



Ethyl 6-(4-bromothiophen-2-yl)-5-phenyl-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142n)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (40 mg, 0.09 mmol, 60%) (eluent: 1% EtOAc in *n*-pentane).

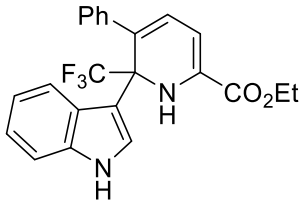
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 1.4 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.19 (t, *J* = 7.4 Hz, 2H), 6.86 (d, *J* = 7.3 Hz, 3H), 6.29 (d, *J* = 6.4 Hz, 1H), 6.08 (dd, *J* = 6.4, 1.7 Hz, 1H), 5.36 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2, 145.4, 138.3, 129.9 (d, J_{CF} = 107.6 Hz), 129.3, 129.0 (q, J_{CF} = 2.7 Hz), 128.0, 127.8, 127.7, 126.1, 124.9, 123.8, 109.9, 102.6, 66.2 (q, J_{CF} = 29.1 Hz), 62.0, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -75.56 (s, 3F) ppm.

FT-IR: ṽ = 3357, 3115, 1685, 1629, 1524, 1487, 1393, 1337, 1285, 1253, 1207, 1149, 1029, 1012 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{19}H_{16}{}^{79}BrF_3NO_2S$ = 458.0032; found 458.0028; calcd. for $[M+H]^+$ $C_{19}H_{16}{}^{81}BrF_3NO_2S$ = 460.0011; found 460.0006.



Ethyl 6-(1H-indol-3-yl)-5-phenyl-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142o)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (20 mg, 0.05 mmol, 33%).

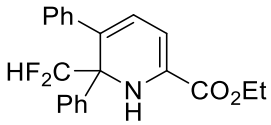
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.17 – 7.12 (m, 1H), 7.10 – 7.05 (m, 2H), 6.99 (t, *J* = 7.7 Hz, 2H), 6.67 (dd, *J* = 8.3, 1.1 Hz, 2H), 6.39 (d, *J* = 6.6 Hz, 1H), 6.06 (dd, *J* = 6.5, 1.9 Hz, 1H), 4.92 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 139.9, 136.1, 131.0, 129.1, 128.1, 127.8, 127.4, 127.2, 127.2,124.5, 122.9, 121.8 (q, *J*CF = 3.2 Hz), 121.1, 120.6, 114.9, 111.5, 100.4, 65.3 (q, *J*CF = 28.7 Hz), 61.7, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -77.47 (s, 3F) ppm.

FT-IR: ṽ = 3415, 2911, 1701, 1634, 1489, 1458, 1421, 1390, 1376, 1338, 1279, 1256, 1243, 1180, 1158, 1137, 1111, 1089, 1035, 1012, 967, 903, 895, 886, 874, 836, 813 cm^{-1}.

HRMS (ESI): $[M+H]^+$ calcd. $C_{23}H_{20}F_3N_2O_2$ m/z 413.14714, found. 413.14702.



Ethyl 6-(difluoromethyl)-5,6-diphenyl-1,6-dihydropyridine-2-carboxylate (142p)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (25 mg, 0.07 mmol, 48%) (eluent: 1% EtOAc in *n*-pentane).

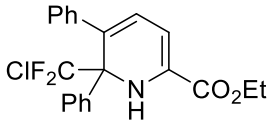
^{1}H NMR (500 MHz, CDCl$_3$) δ 7.58 – 7.49 (m, 2H), 7.41 – 7.31 (m, 3H), 7.22 – 7.12 (m, 3H), 6.92 – 6.88 (m, 2H), 6.38 – 6.13 (m, 2H), 5.95 (dd, *J* = 6.4, 1.7 Hz, 1H), 5.10 (s, 1H), 4.27 (qd, *J* = 7.1, 4.7 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, CDCl$_3$) δ 163.7, 141.8, 138.7, 131.0, 130.8, 128.8, 128.4 (d, J_{CF} = 76.6 Hz), 128.1 (d, J_{CF} = 87.2 Hz), 127.4, 125.9, 116.5, 114.5, 112.5, 101.0, 65.9 (t, J_{CF} = 18.9 Hz), 61.7, 14.3 ppm.

^{19}F NMR (470 MHz, CDCl$_3$) δ -125.61 (dd, J_{FF} = 276.8, 54.7 Hz, 1F), -134.70 (dd, J_{FF} = 276.8, 54.6 Hz, 1F) ppm.

FT-IR: ṽ = 3409, 1704, 1676, 1637, 1492, 1447, 1372, 1278, 1151, 1111, 1071, 1032, 953, 904, 861 cm^{-1}.

HRMS (ESI): calcd for [M+H]$^+$. $C_{21}H_{20}F_2NO_2$ = 356.1457; found 356.1459.



Ethyl 6-(chlorodifluoromethyl)-5,6-diphenyl-1,6-dihydropyridine-2-carboxylate (142q)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (55.3 mg, 0.14 mmol, 97%) (eluent: 1% EtOAc in *n*-pentane).

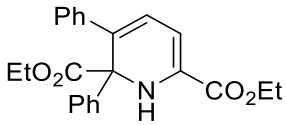
^{1}H NMR (500 MHz, CDCl$_3$) δ 7.63 – 7.58 (m, 2H), 7.40 – 7.34 (m, 3H), 7.16 – 7.10 (m, 1H), 7.05 (t, *J* = 7.7 Hz, 2H), 6.58 (d, *J* = 7.0 Hz, 2H), 6.27 (d, *J* = 6.5 Hz, 1H), 5.99 (dd, *J* = 6.5, 1.9 Hz, 1H), 5.27 (s, 1H), 4.32 (qd, *J* = 7.1, 2.2 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, CDCl$_3$) δ 163.7, 141.7, 139.9, 130.8, 129.7, 128.7, 128.6, 128.3, 127.6 (d, J_{CF} = 78.0 Hz), 127.4, 125.8 (dd, J_{CF} = 7.1, 3.7 Hz), 119.5, 110.7, 100.5, 72.74 (t, J_{CF} = 23.2 Hz), 61.8, 14.4 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -55.51, -83.18 (dd, *J*FF = 163.1 Hz, 23.3 Hz, 1F), -60.84, -90.56 (dd, *J*FF = 162.9 Hz, 23.3 Hz, 1F) ppm.

FT-IR: ṽ = 3343, 3058, 1701, 1637, 1494, 1467, 1390, 1372, 1292, 1256, 1174, 1084, 1049, 1011 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{21}H_{19}{}^{35}ClF_2NO_2$ = 390.1067; found .390.1068; calcd. for $[M+H]^+$ $C_{21}H_{19}{}^{37}ClF_2NO_2$ = 392.1037; found 392.1038.



Diethyl 2,3-diphenyl-1,2-dihydropyridine-2,6-dicarboxylate (142r)

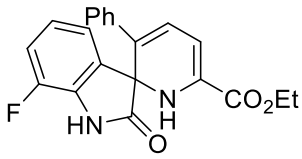
Prepared according to general procedure C. The product was isolated as orange amorphous solid (29.8 mg, 0.08 mmol, 54%) (eluent: 10% EtOAc in *n*-pentane).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 2H), 7.23 – 7.19 (m, 3H), 7.15 – 7.12 (m, 2H), 7.09 – 7.05 (m, 3H), 6.41 (d, *J* = 6.2 Hz, 1H), 6.25 (d, *J* = 6.2 Hz, 1H), 5.51 (s, 1H), 4.38 – 4.20 (m, 4H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.7, 163.6, 140.5, 139.2, 133.5, 132.7, 129.2, 128.4, 128.2, 128.1, 127.5, 127.0, 124.4, 105.9, 69.5, 61.8, 61.5, 14.4, 14.3.

FT-IR: ṽ = 3391, 1731, 1703, 1624, 1447, 1390, 1370, 1275, 1261, 1227, 1155, 1104, 1018, 942 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{23}H_{24}NO_4$ = 378.1700; found 378.1701.



Ethyl 7-fluoro-2-oxo-3'-phenyl-1'H-spiro[indoline-3,2'-pyridine]-6'-carboxylate (142s)

Prepared according to general procedure C. The product was isolated as orange amorphous solid (24 mg, 0.07 mmol, 45%, inseparable mixture with the intermediate acyclic imine, 4:1 ratio of product vs. intermediate) after purification by column chromatography (eluent: 8% EtOAc in *n*-pentane) and preparative TLC (eluent: 15% EtOAc in *n*-pentane).

(Product is mixture with intermediate acyclic imine. Signals are reported for main product.)

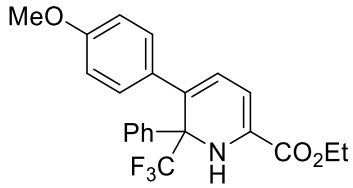
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.59 (dd, *J* = 8.1, 1.3 Hz, 2H), 7.48 – 7.40 (m, 3H), 7.12 (d, *J* = 3.9 Hz, 1H), 7.01 – 6.94 (m, 1H), 6.91 – 6.80 (m, 1H), 6.58 (d, *J* = 7.4 Hz, 1H), 6.37 (d, *J* = 3.9 Hz, 1H), 5.86 (s, 1H), 4.03 (qq, *J* = 10.8, 7.1 Hz, 1H), , 1.15 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 160.8, 148.0, 146.1, 144.1, 131.5, 131.1, 129.7, 129.2, 129.1, 127.4, 123.1 (d, J_{CF} = 5.4 Hz), 119.6, 118.0 (d, J_{CF} = 3.2 Hz), 116.1 (d, J_{CF} = 17.3 Hz), 110.2, 60.2, 59.2 (d, J_{CF} = 3.5 Hz), 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -134.5 (dd, *J* = 9.9, 4.7 Hz, 1F) ppm.

FT-IR: ṽ = 3257, 1747, 1669, 1605, 1460, 1400, 1323, 1252, 1228, 1198, 1088, 1019, 908, 819 cm^{-1}.

HRMS (ESI): calcd for $[M+H]^+$. $C_{21}H_{18}FN_2O_3$ = 365.1296, found 365.1300.



Ethyl 5-(4-methoxyphenyl)-6-phenyl-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142aa)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (50 mg, 0.12 mmol, 94%) (eluent: 2% EtOAc in *n*-pentane).

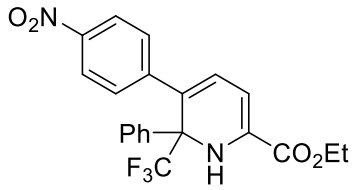
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.4 Hz, 2H), 7.45 – 7.33 (m, 3H), 6.75 – 6.65 (m, 2H), 6.65 – 6.57 (m, 2H), 6.32 (d, *J* = 6.5 Hz, 1H), 5.99 (dd, *J* = 6.5, 1.9 Hz, 1H), 5.08 – 4.90 (m, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 158.9, 140.7, 131.7, 130.3, 130.1, 128.8, 128.5, 128.5, 128.0 (q, J_{CF} = 2.3 Hz), 126.9, 124.6, 112.9, 101.1, 68.5 (q, J_{CF} = 27.3 Hz), 61.6, 55.1, 14.2 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -72.98 (s, 3F) ppm.

FT-IR: ṽ = 3339, 1706, 1638, 1607, 1572, 1493, 1443, 1388, 1276, 1258, 1242, 1207, 1069, 1006 cm^{-1}.

HRMS (ESI): calcd for $[M+H]^+$. $C_{22}H_{21}F_3NO_3$ = 404.1468, found 404.1465.



Ethyl 5-(4-nitrophenyl) -6-phenyl-6-(trifluoromethyl) -1,6-dihydropyridine-2-carboxylate (142ab)

Prepared according to general procedure C. The product was isolated as orange amorphous solid (44 mg, 0.11 mmol, 83%) (eluent: 2% EtOAc in *n*-pentane).

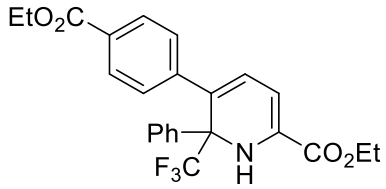
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.82 (m, 2H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.47 – 7.35 (m, 3H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.44 (d, *J* = 6.6 Hz, 1H), 6.00 (dd, *J* = 6.6, 1.9 Hz, 1H), 5.16 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.1, 146.9, 146.2, 140.2, 131.7, 130.0, 129.6, 129.2, 128.9, 128.1 (d, J_{CF} = 2.3 Hz), 126.9, 126.3, 124.6, 122.9, 100.1, 68.6 (d, J_{CF} = 27.8 Hz), 62.1, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.90 (s, 3F) ppm.

FT-IR: ṽ = 3343, 1698, 1633, 1593, 1515, 1493, 1452, 1280, 1212, 1151, 1106, 1072, 1046, 1030 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{21}H_{18}F_3N_2O_4$ m/z 419.1213; found 419.1212.



Ethyl 5-(4-(ethoxycarbonyl) phenyl) -6-phenyl-6-(trifluoromethyl) -1,6-dihydropyridine-2-carboxylate (142ac)

Prepared according to general procedure C. The product was isolated as a yellow amorphous solid (30 mg, 0.07 mmol, 49%) (eluent: 2% EtOAc in *n*-pentane).

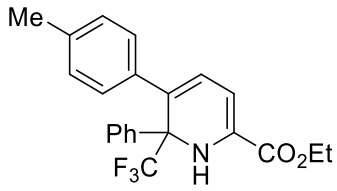
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 7.3 Hz, 2H), 7.44 – 7.37 (m, 3H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.39 (d, *J* = 6.5 Hz, 1H), 5.99 (dd, *J* = 6.5, 1.9 Hz, 1H), 5.09 (s, 1H), 4.30 (dq, *J* = 10.8, 7.1 Hz, 4H), 1.34 (td, *J* = 7.1, 1.2 Hz, 6H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4, 163.3, 144.0, 140.5, 131.1, 129.3, 129.2, 128.9, 128.9, 128.7, 128.5, 128.2 (d, J_{CF} = 2.2 Hz), 127.9, 125.8 (d, J_{CF} = 291.6 Hz), 100.6, 68.6 (q, J_{CF} = 27.8 Hz)., 61.9, 61.0, 14.4, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.61 (s, 3F) ppm.

FT-IR: ῦ = 3329, 1714, 1704, 1631, 1607, 1491, 1451, 1377, 1283, 1246, 1205, 1158, 1108, 1026 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{24}H_{23}F_3NO_4$ = 446.1574; found 446.1574.



Ethyl 6-phenyl-5-(p-tolyl) -6-(trifluoromethyl) -1,6-dihydropyridine-2-carboxylate (142ad)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (46 mg, 0.12 mmol, 86%) (eluent: 1% EtOAc in *n*-pentane).

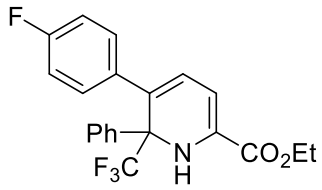
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.5 Hz, 2H), 7.43 – 7.32 (m, 3H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.64 (d, *J* = 8.2 Hz, 2H), 6.34 (d, *J* = 6.5 Hz, 1H), 6.00 (dd, *J* = 6.5, 1.8 Hz, 1H), 5.05 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 2.25 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 140.8, 137.3, 136.5, 130.3, 129.3, 129.1, 128.6, 128.5, 128.4, 128.1 (d, J_{CF} = 2.3 Hz), 127.3, 125.9 (d, J_{CF} = 291.2 Hz), 101.1, 68.7 (q, J_{CF} = 27.4 Hz), 61.7, 21.2, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.01 (s, 3F) ppm.

FT-IR: ῦ = 3353, 1704, 1637, 1501, 1477, 1449, 1379, 1255, 1204, 1191, 1178, 1147, 1118, 1022 cm^{-1}.

HRMS (ESI): calcd for $[M+H]^+$. $C_{22}H_{21}F_3NO_2$ = 388.1519; found 388.1521.



Ethyl 5-(4-fluorophenyl) -6-phenyl-6-(trifluoromethyl) -1,6-dihydropyridine-2-carboxylate (142ae)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (49 mg, 0.13 mmol, 78%) (eluent: 1% EtOAc in *n*-pentane).

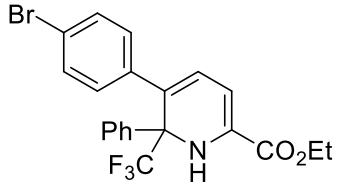
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.5 Hz, 2H), 7.48 – 7.33 (m, 3H), 6.83 – 6.72 (m, 2H), 6.72 – 6.59 (m, 2H), 6.31 (d, *J* = 6.5 Hz, 1H), 5.98 (dd, *J* = 6.5, 1.8 Hz, 1H), 5.08 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 162.2 (d, *J*CF = 247.0 Hz), 140.6, 135.4, 135.3, 131.0 (d, J_{CF} = 8.0 Hz), 130.7, 128.8, 128.6, 128.1 (t, J_{CF} = 2.4 Hz), 127.8, 125.8 (d, J_{CF} = 291.4 Hz), 114.6 (d, J_{CF} = 21.3 Hz), 100.7, 68.6 (q, J_{CF} = 27.5 Hz), 61.8, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.37 (s, 3F), -114.73 (s, 1F) ppm.

FT-IR: ṽ = 3344, 1697, 1633, 1594, 1505, 1394, 1375, 1283, 1254, 1219, 1175, 1162, 1069, 1016 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{21}H_{18}F_4NO_2$ = 392.1268; found 392.1266.



Ethyl 5-(4-bromophenyl) -6-phenyl-6-(trifluoromethyl) -1,6-dihydropyridine-2-carboxylate (142af)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (48 mg, 0.11 mmol, 78%) (eluent: 1% EtOAc in *n*-pentane).

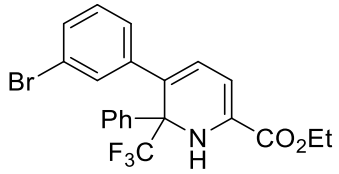
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.4 Hz, 2H), 7.39 (m, 3H), 7.22 – 7.16 (m, 2H), 6.62 – 6.50 (m, 2H), 6.32 (d, *J* = 6.5 Hz, 1H), 5.97 (dd, *J* = 6.5, 1.8 Hz, 1H), 5.07 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) 163.4, 140.5, 138.3, 130.9, 130.8, 128.9, 128.7, 128.1 (d, J_{CF} = 2.4 Hz), 128.0, 127.8, 127.0, 124.7, 121.7, 100.6, 68.5 (q, J_{CF} = 27.6 Hz), 61.9, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.50 (s, 3F) ppm.

FT-IR: ṽ = 3340, 1712, 1639, 1503, 1484, 1449, 1378, 1203, 1176, 1158, 1148, 1108, 1018, 1010 cm^{-1}.

HRMS (ESI): calcd for $[M+H]^+$. $C_{21}H_{18}{}^{79}BrF_3NO_2$ = 452.0468; found 452.0465; calcd. for $[M+H]^+$ $C_{21}H_{18}{}^{81}BrF_3NO_2$ = 454.0447; found 454.0443.



Ethyl 5-(3-bromophenyl)-6-phenyl-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142ag)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (45 mg, 0.10 mmol, 87%) (eluent: 1% EtOAc in *n*-pentane).

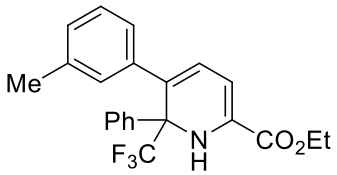
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.2 Hz, 2H), 7.46 – 7.34 (m, 3H), 7.28 (d, *J* = 1.0 Hz, 1H), 6.92 (t, *J* = 7.9 Hz, 1H), 6.83 (t, *J* = 1.9 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.33 (d, *J* = 6.5 Hz, 1H), 5.97 (dd, *J* = 6.5, 1.9 Hz, 1H), 5.09 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 141.4, 140.4, 132.3, 131.1, 130.4, 129.0 (d, J_{CF} = 15.7 Hz), 128.7, 128.3, 128.2 (q, J_{CF} = 2.3 Hz), 127.9, 127.5, 127.0, 124.7, 121.6, 100.5, 68.5 (q, J_{CF} = 27.7 Hz), 61.9, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.78 (s, 3F) ppm.

FT-IR: ṽ = 3348, 1792, 1702, 1639, 1590, 1555, 1440, 1376, 1282, 1208, 1148, 1074, 1018, 1003 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{21}H_{18}{}^{79}BrF_3NO_2$ = 452.0475; found 452.0467; calcd. for $[M+H]^+$ $C_{21}H_{18}{}^{81}BrF_3NO_2$ = 454.0447; found 454.0445.



Ethyl 6-phenyl-5-(m-tolyl)-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142ah)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (45 mg, 0.12 mmol, 83%) (eluent: 1% EtOAc in *n*-pentane).

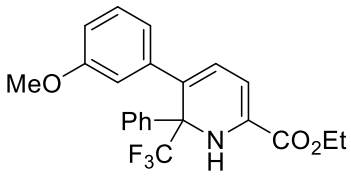
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.5 Hz, 2H), 7.44 – 7.35 (m, 3H), 6.98-6.93 (m, 2H), 6.53 (s, 1H), 6.49 (d, *J* = 6.7 Hz, 1H), 6.33 (d, *J* = 6.5 Hz, 1H), 5.99 (dd, *J* = 6.4, 1.8 Hz, 1H), 5.06 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 2.16 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 140.8, 139.3, 137.1, 130.5, 130.1, 129.5, 128.6, 129.5, 128.2, 127.4, 127.4, 127.0, 126.3, 124.7, 101.0, 68.7 (q, J_{CF} = 27.3 Hz), 61.8, 21.4, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.31 (s, 3F) ppm.

FT-IR: ῦ = 3337, 1699, 1626, 1493, 1465, 1451, 1374, 1285, 1210, 1187, 1093, 1074, 1027, 1003 cm^{-1}.

HRMS (ESI): calcd for $[M+H]^+$. $C_{22}H_{21}F_3NO_2$ = 388.1519; found 388.1519.



Ethyl 5-(3-methoxyphenyl) -6-phenyl-6-(trifluoromethyl) -1,6-dihydropyridine-2-carboxylate (142ai)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (40 mg, 0.10 mmol, 75%) (eluent: 2% EtOAc in *n*-pentane).

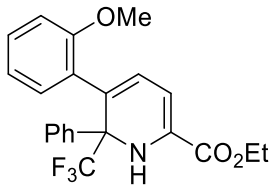
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.45 – 7.33 (m, 3H), 7.01 (t, *J* = 8.0 Hz, 1H), 6.70 (ddd, *J* = 8.3, 2.6, 0.8 Hz, 1H), 6.42 (d, *J* = 7.8 Hz, 1H), 6.36 (d, *J* = 6.5 Hz, 1H), 6.24 – 6.13 (m, 1H), 5.98 (dd, *J* = 6.5, 1.9 Hz, 1H), 5.05 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.52 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 158.6, 141.0, 140.7, 130.6, 129.0, 128.9, 128.7, 128.6, 128.6, 128.2 (d, J_{CF} = 2.1 Hz), 127.6, 122.0, 114.3, 113.6, 100.7, 61.8, 55.0, 38.9, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.47 (s, 3F) ppm.

FT-IR: ṽ = 3346, 2963, 1708, 1633, 1595, 1493, 1377, 1266, 1217, 1204, 1153, 1083, 1028, 1002, cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{22}H_{21}F_3NO_3$ = 404.1468; found 404.1467.



Ethyl 5-(2-methoxyphenyl)-6-phenyl-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142aj)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (36 mg, 0.09 mmol, 57%) (eluent: 2% EtOAc in *n*-pentane).

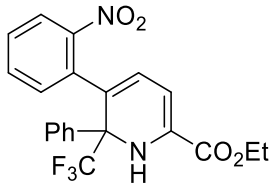
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.37 (m, 2H), 7.26 – 7.23 (m, 3H), 7.15 – 7.10 (m, 1H), 6.67 (td, *J* = 7.4, 1.1 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 2H), 6.15 (d, *J* = 6.4 Hz, 1H), 5.98 (dd, *J* = 6.4, 1.8 Hz, 1H), 5.10 (s, 1H), 4.29 (qd, *J* = 7.1, 1.1 Hz, 2H), 3.33 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.7, 157.4, 139.8, 131.8, 131.3, 129.0, 128.4, 128.1, 127.9 (d, J_{CF} = 2.5 Hz), 127.8, 127.5, 125.3, 125.2, 119.4, 110.3, 101.1, 68.0 (q, J_{CF} = 27.4 Hz), 61.7, 55.1, 14.4 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -75.55 (s, 3F) ppm.

FT-IR: ṽ = 3342, 1698, 1630, 1595, 1578, 1495, 1463, 1392, 1273, 1230, 1152, 1116, 1054, 1023 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+C_{22}H_{21}F_3NO_3$ = 404.1468; found 404.1466.



Ethyl 5-(2-nitrophenyl) -6-phenyl-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142ak)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (47 mg, 0.11 mmol, 76%) (eluent: 2% EtOAc in *n*-pentane).

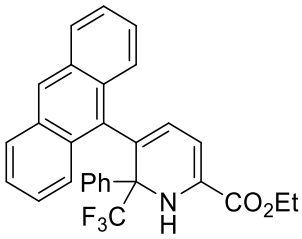
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.32 – 7.20 (m, 7H), 6.91 (s, 1H), 6.26 (d, *J* = 6.5 Hz, 1H), 5.99 (dd, *J* = 6.5, 1.8 Hz, 1H), 5.16 (s, 1H), 4.26 (qd, *J* = 7.1, 3.2 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 149.6, 137.7, 133.4, 133.1, 132.4, 131.6, 130.0, 128.7 (d, J_{CF} = 20.4 Hz), 128.5, 128.0 (d, J_{CF} = 2.5 Hz), 127.6, 125.2, 123.9, 121.9, 101.1, 67.7 (q, J_{CF} = 27.7 Hz), 62.0, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -75.89 (s, 3F) ppm.

FT-IR: ṽ = 3337, 1701, 1634, 1570, 1523, 1451, 1373, 1341, 1275, 1209, 1173, 1145, 1065, 1024 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{21}H_{18}F_3N_2O_4$ = 419.1213; found 419.1210.



Ethyl 5-(anthracen-9-yl)-6-phenyl-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142al)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (40 mg, 0.09 mmol, 78%) (eluent: 1% EtOAc in *n*-pentane).

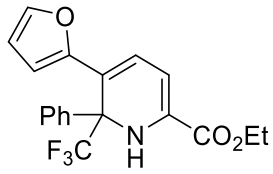
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 – 8.31 (m, 2H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.59 – 7.44 (m, 2H), 7.27 (d, *J* = 9.5 Hz, 1H), 7.17 – 7.07 (m, 1H), 6.93 – 6.86 (m, 3H), 6.83 – 6.72 (m, 3H), 6.53 (d, *J* = 6.2 Hz, 1H), 6.27 (dd, *J* = 6.2, 1.8 Hz, 1H), 5.53 (s, 1H), 4.44 (qd, *J* = 7.2, 5.3 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9, 136.2, 133.0, 132.1, 131.5, 131.2, 130.7 (d, J_{CF} = 53.4 Hz), 128.6, 127.8, 127.8 (d, J_{CF} = 2.5 Hz), 127.6, 127.4, 127.4, 127.1 (d, J_{CF} = 2.8 Hz), 126.7, 125.5, 125.2, 124.7, 124.4 (d, J_{CF} = 26.5 Hz), 101.9, 67.1 (q, J_{CF} = 27.6 Hz) 62.1, 14.4 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -75.79 (s, 3F) ppm.

FT-IR: ṽ = 3337, 3048, 1697, 1624, 1487, 1460, 1391, 1369, 1302, 1278, 1155, 1095, 1059, 1006 cm^{-1}.

HRMS (ESI): calcd for $[M+H]^+$ $C_{29}H_{23}F_3NO_2$ = 474.1675; found 474.1670.



Ethyl 5-(furan-2-yl)-6-phenyl-6-(trifluoromethyl)-1,6-dihydropyridine-2-carboxylate (142am)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (49 mg, 0.14 mmol, 89%) (eluent: 1% EtOAc in *n*-pentane).

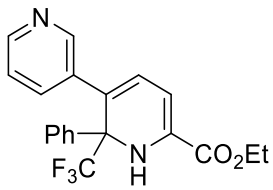
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.40 – 7.31 (m, 3H), 7.22 (d, *J* = 1.8 Hz, 1H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.10 (dd, *J* = 3.5, 1.8 Hz, 1H), 6.07 (dd, *J* = 7.0, 2.0 Hz, 1H), 5.27 (d, *J* = 3.5 Hz, 1H), 4.92 (s, 1H), 4.27 (qd, *J* = 7.1, 1.3 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2, 151.3, 141.5, 140.7, 130.2, 128.8 (d, J_{CF} = 2.3 Hz), 128.7, 128.3, 126.5 (d, J_{CF} = 293.7 Hz), 123.6, 117.1, 111.7, 110.2 (d, J_{CF} = 2.1 Hz), 101.4, 66.7 (q, J_{CF} = 28.6 Hz), 61.8, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -74.67 (s, 3F) ppm.

FT-IR: ṽ = 3321, 1703, 1627, 1545, 1577, 1402, 1375, 1277, 1208, 1174, 1105, 1074, 1026, 1013 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{19}H_{17}F_3NO_3$ = 364.1155; found 364.1156.



Ethyl 2-phenyl-2-(trifluoromethyl)-1,2-dihydro-[3,3'-bipyridine]-6-carboxylate (142an)

Prepared according to general procedure C. The product was isolated as yellow amorphous solid (45 mg, 0.12 mmol, 83%) (eluent: 5% EtOAc in *n*-pentane).

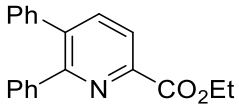
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.07 (s, 1H), 7.58 (d, *J* = 7.5 Hz, 2H), 7.43 – 7.34 (m, 3H), 6.97 (dd, *J* = 8.1, 4.8 Hz, 1H), 6.89 – 6.82 (m, 1H), 6.36 (d, *J* = 6.6 Hz, 1H), 5.99 (dd, *J* = 6.5, 1.9 Hz, 1H), 5.13 (s, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 149.7, 148.2, 140.2, 136.5, 135.4, 131.4, 129.1, 128.9, 128.8, 128.2 (d, J_{CF} = 2.3 Hz), 125.8 (d, J_{CF} = 291.7 Hz), 125.0, 122.4, 100.3, 68.4 (q, J_{CF} = 27.7 Hz), 62.0, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.99 (s, 3F) ppm.

FT-IR: ṽ = 2981, 1744, 1709, 1682, 1636, 1476, 1449, 1373, 1260, 1155, 1073, 1045, 1024, 1011 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{20}H_{18}F_3N_2O_2$ = 375.1315; found 375.1321.



Ethyl 5,6-diphenylpicolinate (143)

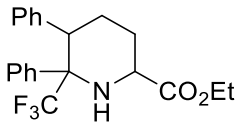
Prepared according to general procedure C from vinyliminophosphorane **137a** and benzoyl cyanide upon spontaneous elimination of hydrogen cyanide. The product was isolated as yellow amorphous solid (24 mg, 0.08 mmol, 55%) (eluent: 5% EtOAc in *n*-pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.37 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.27 – 7.23 (m, 3H), 7.23 – 7.18 (m, 3H), 7.17 – 7.11 (m, 2H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 157.6, 147.1, 139.5 (2C), 139.4, 139.3, 130.3, 129.5, 128.6, 128.3, 128.1, 127.9, 123.5, 62.0, 14.5 ppm.

The analytical data were in good accordance with those reported in the literature.[93]

6.2.2.3 Physical data of compounds 103, 104a and 106



Ethyl 5,6-diphenyl-6-(trifluoromethyl) piperidine-2-carboxylate (146)

^{1}H NMR (500 MHz, $CDCl_3$) δ7.73 (d, *J* = 7.5 Hz, 2H), 7.67 (d, *J* = 7.9 Hz, 2H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.42 – 7.38 (m, 1H), 7.38 – 7.31 (m, 2H), 7.32 – 7.28 (m, 1H), 4.29 (q, *J* = 7.1 Hz, 2H),

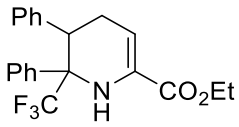
3.80 (dd, *J* = 4.8, 2.9 Hz, 1H), 3.74 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.14 – 2.02 (m, 1H), 1.91 – 1.79 (m, 1H), 1.72 – 1.60 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 141.4, 135.6, 130.6, 129.0, 128.5, 128.4, 128.0, 127.0, 125.5 (d, J_{CF} = 285.5 Hz), 66.4 (q, J_{CF} = 25.5 Hz), 61.4, 52.8, 41.8, 27.3, 22.0, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -72.79 (s, 3F) ppm.

FT-IR: ṽ = 2939, 2253, 1731, 1494, 1446, 1372, 1341, 1280, 1263, 1234, 1187, 1156, 1083, 1032 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ calcd. $C_{21}H_{23}F_3NO_2$ m/z 378.1675; found 378.1679.



Ethyl 5,6-diphenyl-6-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-2-carboxylate (147a)

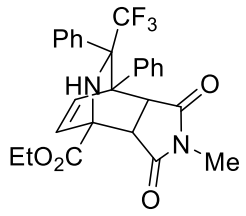
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.6 Hz, 2H), 7.44 – 7.36 (m, 3H), 7.34 – 7.27 (m, 5H), 5.85 (t, *J* = 4.2 Hz, 1H), 5.12 (s, 1H), 4.37 (m, 2H), 3.76 (d, *J* = 4.7 Hz, 1H), 2.29 – 2.15 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.8, 141.2, 138.5, 131.9, 129.1, 129.0, 128.6, 128.2, 127.3, 126.7, 124.4, 107.8, 65.4 (q, J_{CF} = 26.1 Hz), 61.7, 42.7, 28.2, 14. ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -71.48 (s, 3F) ppm.

FT-IR: ṽ = 3398, 1705, 1655, 1478, 1447, 1374, 1283, 1271, 1242, 1213, 1172, 1152, 1109, 1018 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ calcd. $C_{21}H_{21}F_3NO_2$ m/z 376.1519; found 376.1525.



(major *endo*-product)

Ethyl (3*aR*, 4*S*, 7*aS*, 8*S*)-2-methyl-1,3-dioxo-7,8-diphenyl-8-(trifluoromethyl)-1,2,3,3*a*,7,7*a*-hexahydro-4H-4,7-(epiminomethano) isoindole-4-carboxylate (149)

(Product is obtained as *endo*/*exo*-mixture. Signals are reported for the major product.)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (t, *J* = 7.8 Hz, 2H), 7.38 (dd, *J* = 7.8, 2.7 Hz, 3H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 2H), 6.76 (dd, *J* = 7.1, 4.6 Hz, 2H), 6.03 (d, *J* = 40.3 Hz, 2H), 5.14 (s, 1H), 4.35 – 4.24 (m, 2H), 3.16 – 3.06 (m, 1H), 3.04 (s, 3H), 2.67 – 2.56 (m, 1H), 1.32 (t, *J* = 3.7 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 176.5, 162.4, 139.8, 139.4, 138.4, 130.3 129.2 (m), 128.9, 128.7, 128.6, 128.2, 128.0 (d, *J* = 18.0 Hz) 127.9, 127.8, 95.4, 62.4, 36.6, 36.0, 29.9, 25.3, 25.2, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.35 (s, 3F) ppm.

FT-IR: $\tilde{\nu}$ = 3334, 2922, 1698, 1439, 1374, 1261, 1171, 1149, 1116, 1008, 962, 929 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ calcd. $C_{26}H_{24}F_3N_2O_4$ m/z 485.1683; found 485.1683.

6.2.3 Crystal data of compounds 136a, 136b, 142a and 142aa

Crystal structure for compound 136a

CCDC Number: 2060066

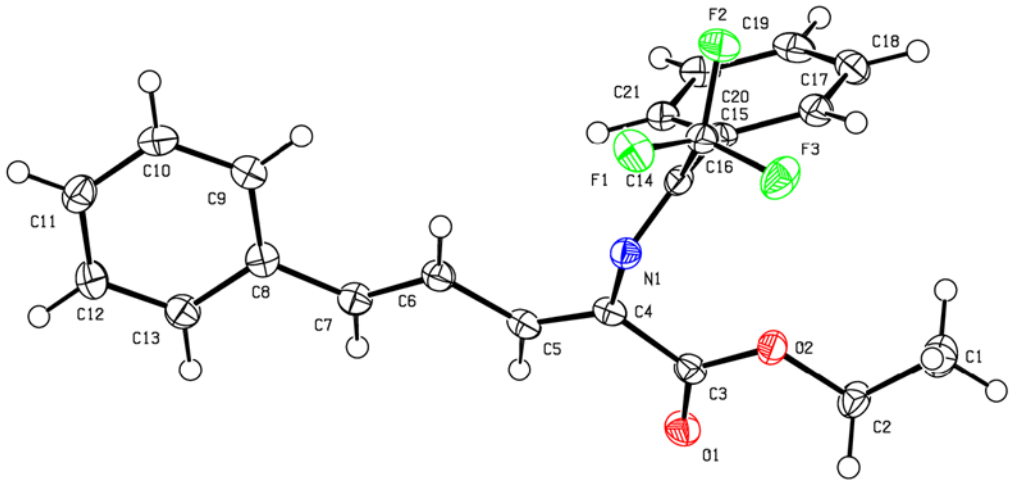


Figure 6.1. Ortep plot of the molecular structure in the crystal of compound **136a**.[157] The displacement ellipsoids are drawn at the 50% probability level. Co-crystallized solvent has been omitted for clarity.

Table 6.1. Crystallographic data of compound **136a**.

Compound	136a
Empirical formula	$C_{21}H_{18}F_3NO_2$
Formula weight	373.36
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	15.4189(10)
b/Å	13.2984(9)
c/Å	8.8308(5)
α/°	90
β/°	98.773(2)
γ/°	90
Volume/Å^3	1789.5(2)
Z	4
ρ_{calc}g/cm^3	1.386
μ/mm^{-1}	0.110
F(000)	776.0

Crystal size/mm^3	0.121 × 0.116 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.066 to 52.74
Index ranges	–19 ≤ h ≤ 19, –16 ≤ k ≤ 16, –11 ≤ l ≤ 11
Reflections collected	27328
Independent reflections	3655 [R_{int} = 0.0978, R_{sigma} = 0.0512]
Data/restraints/parameters	3655/0/245
Goodness-of-fit on F^2	1.069
Final *R* indexes [I>=2σ (I)]	R_1 = 0.0489, wR_2 = 0.0962
Final *R* indexes [all data]	R_1 = 0.0842, wR_2 = 0.1145
Largest diff. peak/hole / e Å^{-3}	0.22/-0.26
Flack parameter	–

Crystal structure for compound 136b

CCDC Number: 2081540

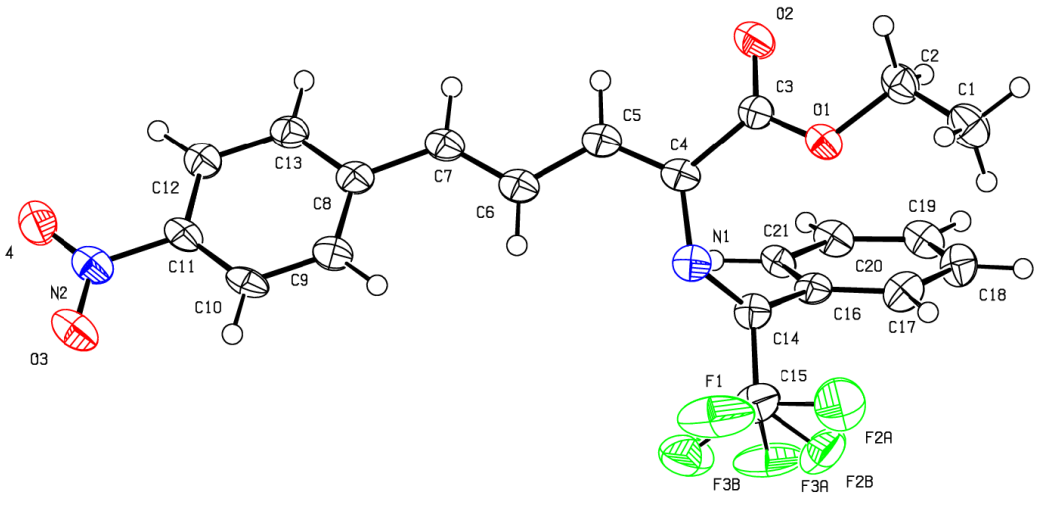


Figure 6.2. Ortep plot of the molecular structure in the crystal of compound **136b**.[157] The displacement ellipsoids are drawn at the 50% probability level. Co-crystallized solvent has been omitted for clarity.

Table 6.2. Crystallographic data of compound **136b**.

Compound	**136b**
Empirical formula	$C_{21}H_{17}F_3N_2O_4$
Formula weight	418.36
Temperature/K	100.0
Crystal system	Triclinic
Space group	*P*-1
a/Å	7.6686(17)
b/Å	8.2975(19)
c/Å	17.313(4)
α/°	89.757(8)
β/°	78.124(8)
γ/°	65.124(7)
Volume/Å^3	973.8(4)
Z	2
ρ_{calc}g/cm^3	1.427
μ/mm^{-1}	0.118
F(000)	432.0
Crystal size/mm^3	0.238 × 0.147 × 0.074
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.436 to 52.884
Index ranges	$-9 \le h \le 9$, $-10 \le k \le 10$, $-21 \le l \le 21$
Reflections collected	21521
Independent reflections	3982 [R_{int} = 0.1023, R_{sigma} = 0.0743]
Data/restraints/parameters	3982/0/306
Goodness-of-fit on F^2	1.108
Final *R* indexes [I>=2σ (I)]	R_1 = 0.0974, wR_2 = 0.2314
Final *R* indexes [all data]	R_1 = 0.1401, wR_2 = 0.2511
Largest diff. peak/hole / e Å^{-3}	0.41/–0.48
Flack parameter	–

Crystal structure for compound 142a

CCDC Number: 2046825

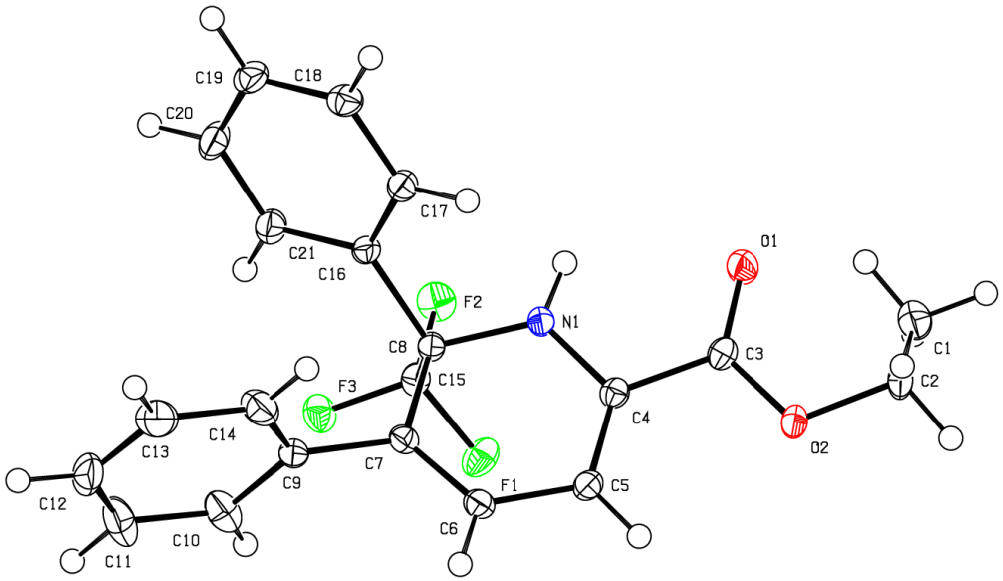


Figure 6.3. Ortep plot of the molecular structure in the crystal of compound **142a**.[157] The displacement ellipsoids are drawn at the 50% probability level.

Table 6.3. Crystallographic data of compound **142a**.

Compound	**142a**
Empirical formula	$C_{21}H_{18}F_3NO_2$
Formula weight	373.36
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	14.6948(6)
b/Å	6.2081(3)
c/Å	19.2023(8)
α/°	90
β/°	99.111(2)
γ/°	90
Volume/Å^3	1729.66(13)
Z	4
ρ_{calc}g/cm^3	1.434
μ/mm^{-1}	0.114

F(000)	776.0
Crystal size/mm^3	0.209 × 0.139 × 0.091
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.492 to 60
Index ranges	–20 ≤ h ≤ 20, –8 ≤ k ≤ 8, –27 ≤ l ≤ 21
Reflections collected	34035
Independent reflections	5056 [R_{int} = 0.0626, R_{sigma} = 0.0406]
Data/restraints/parameters	5056/0/249
Goodness-of-fit on F^2	1.034
Final *R* indexes [I>=2σ (I)]	R_1 = 0.0476, wR_2 = 0.0989
Final *R* indexes [all data]	R_1 = 0.0743, wR_2 = 0.1128
Largest diff. peak/hole / e Å^{-3}	0.34/–0.27
Flack parameter	–

Crystal structure for compound 142aa

CCDC Number: 2046566

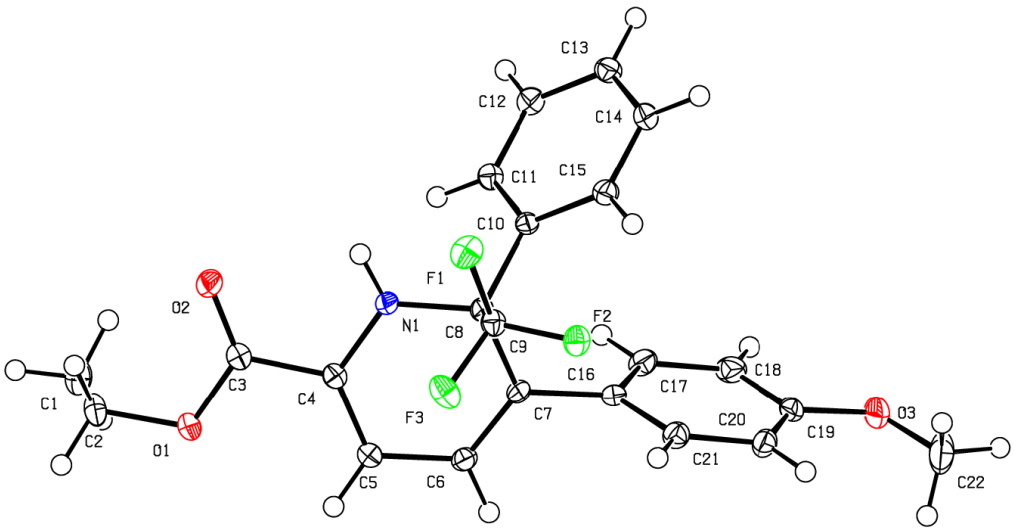


Figure 6.4. Ortep plot of the molecular structure in the crystal of compound **142aa**.[157] The displacement ellipsoids are drawn at the 50% probability level.

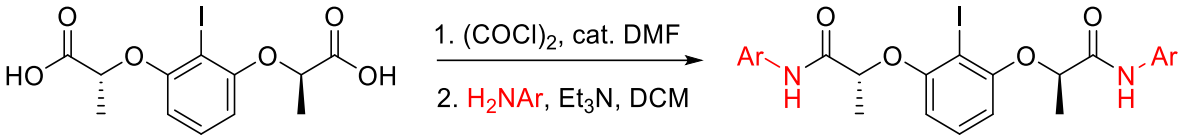
Table 6.4. Crystallographic data of compound **142aa**.

Compound	**142aa**
Empirical formula	$C_{22}H_{20}F_3NO_3$
Formula weight	403.39
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	14.374(3)
b/Å	6.0868(7)
c/Å	21.363(3)
α/°	90
β/°	92.254(8)
γ/°	90
Volume/Å^3	1861.2(5)
Z	4
ρ_{calc}g/cm^3	1.440
μ/mm^{-1}	0.115
F(000)	840.0
Crystal size/mm^3	0.275 × 0.168 × 0.118
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.692 to 59.996
Index ranges	$-20 \leq h \leq 20$, $-8 \leq k \leq 8$, $-29 \leq l \leq 30$
Reflections collected	20668
Independent reflections	5406 [R_{int} = 0.0306, R_{sigma} = 0.0284]
Data/restraints/parameters	5426/0/268
Goodness-of-fit on F^2	1.050
Final R indexes [I>=2σ (I)]	R_1 = 0.0422, wR_2 = 0.0994
Final R indexes [all data]	R_1 = 0.0527, wR_2 = 0.1077
Largest diff. peak/hole / e Å^{-3}	0.43/–0.27
Flack parameter	–

6.3 Experimental part for the preparation and synthetic applications of novel hypervalent iodine reagents

6.3.1 Synthesis and characterization of hypervalent iodine reagents

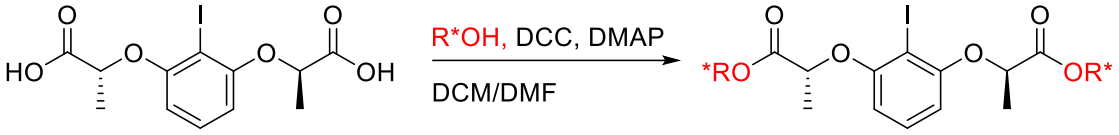
General procedure A:



198 **199**

Compound **198** (1.0 equiv) was suspended in dry DCM under an argon atmosphere. After addition of oxalyl chloride (3.5 equiv) and a catalytic amount of DMF, the reaction mixture was stirred for 3 h at room temperature and then concentrated in *vacuo*. The crude product was dissolved in dry DCM under an argon atmosphere and the aniline derivative (4.0 equiv) as well as Et_3N (4.0 equiv) were added. The reaction mixture was stirred for 16 h at room temperature and quenched by the addition of aqueous HCl (3 M). After extraction with DCM, the combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel column chromatography afforded the pure product.

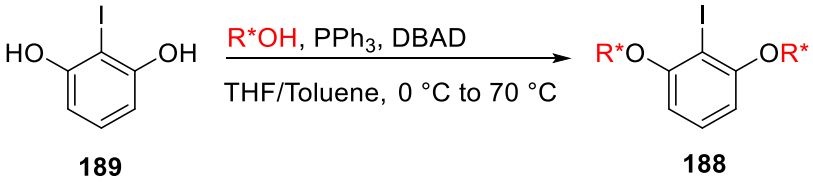
General procedure B:



198 **200**

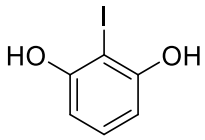
Following the Steglich esterification procedure[143], to a stirred solution of compound **198** (1.0 equiv) in dry DCM and dry DMF was added DMAP (1.1 equiv) and the corresponding chiral alcohol (2.5 equiv). DCC (2.2 equiv) was added to the reaction mixture at 0 °C, which was then stirred for 5 min at 0°C and 48 h at 20°C. Upon reaction completion, precipitated urea was filtered off and the filtrate evaporated down in *vacuo*. The DCM solution was then washed twice with 0.5M HCl and with saturated $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was removed by evaporation and the ester was isolated by a short silica gel column.

General procedure C:



189 **188**

Di-*tert*-butyl azodicarboxylate (DBAD) (6.6 equiv) dissolved in THF was added dropwise *via* syringe over 30 min to a stirred suspension of **189** (1.0 equiv), triphenylphosphine (7.4 equiv), and the corresponding chiral alcohol (6.4 equiv) in THF/toluene (1:1) at 0 °C. Since DBAD decomposes when warmed, the reaction temperature was maintained below 10 °C during the addition of this reagent at which time a slight exothermic reaction occurred. The reaction mixture was then allowed to warm to room temperature and stirred for 24 h. Afterwards, the temperature was increased to 70 °C and the reaction mixture was stirred for 48 h. Upon reaction completion, the crude mixture was concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/n-pentane) to give the desired product.



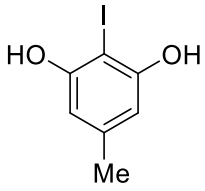
2-Iodobenzene-1,3-diol (189a)

Following a procedure by Muñiz *et al.*[158], resorcinol (5.0 g, 44.0 mmol, 1.0 equiv) was dissolved in 35 mL of H_2O. After cooling to 0 °C, iodine (12.0 g, 47.0 mmol, 1.1 equiv) was added followed by a slow addition of $NaHCO_3$ (4.2 g, 50.0 mmol, 1.1 equiv). The resulting reaction mixture was stirred for 10 min at 0 °C and then allowed to warm to room temperature over a period of 20 min. The reaction was then quenched by addition of saturated aqueous $Na_2S_2O_3$ solution. After extraction with EtOAc, the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification by recrystallization from ice cold $CHCl_3$ afforded pure product. The compound was obtained as an off-white solid (8.1 g, 34.2 mmol, 76%).

^{1}H NMR (500 MHz, DMSO) δ 10.06 (s, 2H), 6.93 (t, *J* = 8.0 Hz, 1H), 6.34 ppm (d, *J* = 8.0 Hz, 2H) ppm.

^{13}C NMR (126 MHz, DMSO) δ 158.5, 129.7, 106.2, 75.6 ppm.

Analytical data in agreement with literature.[158]



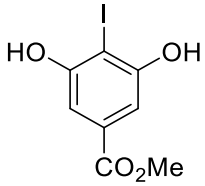
2-Iodo-5-methylbenzene-1,3-diol (189b)

Following a modified procedure by Kim *et al.*[159], 5-methyl resorcinol (5.0 g, 40.0 mmol, 1.0 equiv) was dissolved in 60 mL of H_2O/THF (1:1). After cooling to 0 °C, iodine (19.8 g, 78.0 mmol, 2.0 equiv) was added followed by a slow addition of $NaHCO_3$ (9.9 g, 117.0 mmol, 3.0 equiv). The reaction mixture was stirred at 0 °C for 1 h and was subsequently diluted with Et_2O (20ml). A saturated aqueous $Na_2S_2O_3$ solution was added slowly. The mixture was allowed to warm to ambient temperature and was stirred for 30 min until the effervescence had ceased. The mixture was extracted with Et_2O, and the combined organic phases were dried over $MgSO_4$. The solvent was removed in vacuo and the crude product was purified by column chromatography (9:1 n-pentane/EtOAc) to afford the pure product as white solid (8.1 g, 32.5 mmol, 83%).

^{1}H NMR (600 MHz, CD_3OD) δ 6.20 (s, 2H), 2.17 (s, 3H) ppm.

^{13}C NMR (151 MHz, CD_3OD) δ 158.9, 140.9, 107.9, 71.5, 21.2 ppm.

Analytical data in agreement with literature.[158]



Methyl 3,5-dihydroxy-4-iodobenzoate (189c)

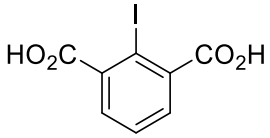
Following a modified procedure by Berliner *et al.*[160], methyl 3,5-dihydroxybenzoate (6.0 g, 35.0 mmol, 1.0 equiv) was dissolved in 70 mL of H_2O/THF (1:1). After cooling to 0 °C, iodine (17.6 g, 69.0 mmol, 2.0 equiv) was added followed by a slow addition of $NaHCO_3$ (8.8 g, 104.0 mmol, 3.0 equiv). The reaction mixture was stirred at 0 °C for 1 h and was subsequently diluted with Et_2O (40 ml). A saturated aqueous $Na_2S_2O_3$ solution was added slowly. The mixture was allowed to warm to ambient temperature and was stirred 30 min until the gas evolution ceased.

The mixture was extracted with Et_2O, and the combined organic phases were dried over $MgSO_4$. The solvent was removed in vacuo and the solid residue was taken up in MeOH (50 ml). To the stirred solution, H_2O (50 ml) was added slowly, and the resulting off-white precipitate was collected *via* filtration. The crude product was washed with a mixture of MeOH/H_2O (1:1). The mother liquor was stored at -20 °C in order to precipitate additional substance. The product was obtained as a bright yellow solid (4.9 g, 16.6 mmol, 48%).

^{1}H NMR (500 MHz, DMSO) δ 10.54 (s, 2H), 6.93 (s, 2H), 3.80 (s, 3H) ppm.

^{13}C NMR (126 MHz, DMSO) δ 166.0, 158.3, 130.6, 105.9, 81.9, 52.2, 40.0, 39.9, 39.7, 39.5, 39.4, 39.2, 39.0 ppm.

Analytical data in agreement with literature.[160]



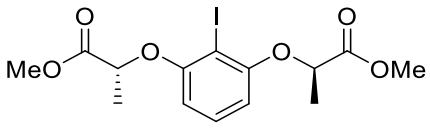
2-iodoisophthalic acid (192)

Following a modified procedure by Patureau *et al*.[161], 2-iodo-1,3-dimethylbenzene (1.0 g, 4.2 mmol, 1.0 equiv) was dissolved in 30 mL of *t*-BuOH/ H_2O (1:1). Then, the first portion of $KMnO_4$ (2.0 g, 12.5 mmol, 3.0 equiv) was added. The mixture was refluxed for 24 h, followed addition of the second portion of $KMnO_4$ (2.0 g, 12.5 mmol, 3.0 equiv). After refluxing for 48 h, the reaction was stopped, and the mixture was filtered while hot and acidified with HCl (5 N). The reaction was extracted with EtOAc, dried over $MgSO_4$ and the solvent was evaporated in the vacuo. The product was obtained as white solid (1.1 g, 3.7 mmol, 88%).

^{1}H NMR (700 MHz, DMSO) δ 13.47 (brs, 2H), 7.57 (d, *J* = 7.5 Hz, 2H), 7.51 (d, *J* = 7.5 Hz, 1H) ppm.

^{13}C NMR (176 MHz, DMSO) δ 169.3, 141.2, 129.6, 128.3, 91.1 ppm.

Analytical data in agreement with literature.[161]



Dimethyl 2,2'-((2-iodo-1,3-phenylene) bis(oxy)) (2*R*, 2'*R*)-dipropionate (197a)

Following a procedure by Fujita *et al*.[117], 2-iodobenzene-1,3-diol (2.0 g, 8.5 mmol, 1.0 equiv) was dissolved in dry THF (28 mL) under argon atmosphere. After addition of methyl (*S*)-lactate (2.0 g, 18.6 mmol, 2.2 equiv), triphenylphosphine (5.7 g, 19.5 mmol, 2.3 equiv) and diisopropyl-azodicarboxylate (4.2 g, 20.3 mmol, 2.4 equiv) at 0 °C, the reaction was allowed to warm to room temperature and stirred for 16 h. After reaction completion, the mixture was concentrated under reduced pressure. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc 5:1) as a white solid (2.5 g, 6.1 mmol, 72%).

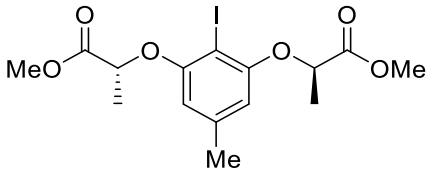
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (t, *J* = 8.3 Hz, 1H), 6.30 (d, *J* = 8.3 Hz, 2H), 4.70 (q, *J* = 6.8 Hz, 2H), 3.68 (s, 6H), 1.64 (d, *J* = 6.8 Hz, 6H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 158.3, 129.7, 106.9, 80.6, 74.2, 52.4, 18.7 ppm.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{14}H_{18}O_6I$ = 409.0143; found 409.0146.

$[\alpha]_D^{20}$: -12.75° (c = 1.00, $CHCl_3$)

Analytical data in agreement with literature.[117]



Dimethyl 2,2'-((2-iodo-5-methyl-1,3-phenylene) bis(oxy)) (2*R*, 2'*R*)-dipropionate (197b)

As described for the synthesis of **197a**, 2-iodo-5-methylbenzene-1,3-diol (8.0 g, 32.0 mmol, 1.0 equiv) was dissolved in dry THF (120 mL) under argon atmosphere. After addition of methyl (*S*)-lactate (7.5 g, 70.0 mmol, 2.2 equiv), triphenylphosphine (19.5 g, 73.6 mmol, 2.3 equiv) and diisopropyl-azodicarboxylate (15.8 g, 76.8 mmol, 2.4 equiv) at 0 °C, the reaction was allowed to warm to room temperature and stirred for 16 h. After reaction completion, the mixture was concentrated under reduced pressure. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc 5:1) as a white solid (8.8 g, 20.8 mmol, 65%).

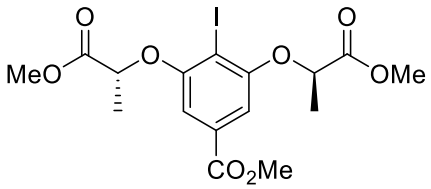
^{1}H NMR (500 MHz, DMSO) δ 6.31 (s, 2H), 4.99 (q, *J* = 6.8 Hz, 2H), 3.68 (s, 6H), 2.21 (s, 3H), 1.54 (d, *J* = 6.8 Hz, 6H) ppm.

^{13}C NMR (126 MHz, DMSO) δ 171.6, 157.3, 139.9, 107.5, 76.1, 72.9, 52.2, 21.4, 18.4 ppm.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{15}H_{20}O_6I$ = 423.0299; found 423.0301.

$[\alpha]_D^{20}$: +139.60° (c = 1.00, $CHCl_3$)

Analytical data in agreement with literature.[162]



Dimethyl 2,2'-((2-iodo-5-(methoxycarbonyl)-1,3-phenylene) bis(oxy)) (2*R*, 2'*R*)-dipropionate (197c)

As described for the synthesis of **197a**, methyl 3,5-dihydroxy-4-iodobenzoate (0.8 g, 2.7 mmol, 1.0 equiv) was dissolved in dry THF (10 mL) under argon atmosphere. After addition of methyl (*S*)-lactate (0.6 g, 5.9 mmol, 2.2 equiv), triphenylphosphine (1.7 g, 6.2 mmol, 2.3 equiv) and di-*tert*-butyl- azodicarboxylate (1.5 g, 6.5 mmol, 2.4 equiv) at 0 °C, the reaction was allowed to warm to room temperature and stirred for 20 h. After reaction completion, the mixture was concentrated under reduced pressure. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc 5:1) as a white solid (0.8g, 1.6 mmol, 58%).

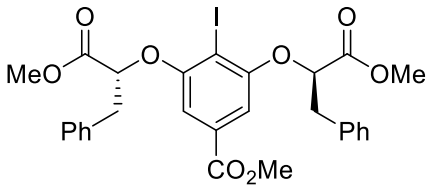
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (s, 2H), 4.88 (q, *J* = 6.8 Hz, 2H), 3.88 (s, 3H), 3.76 (s, 6H), 1.71 (d, *J* = 6.8 Hz, 6H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 166.2, 158.3, 131.9, 107.4, 87.5, 74.2, 52.6, 18.6 ppm.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{16}H_{20}O_8I$ = 467.0197; found 467.0198.

$[\alpha]_D^{20}$: +8.80° (c = 1.00, $CHCl_3$)

Analytical data in agreement with literature.[163]



Dimethyl 2,2'-((2-iodo-5-(methoxycarbonyl)-1,3-phenylene) bis(oxy)) (2*R*, 2'*R*)-bis(3-phenylpropanoate) (197d)

Following a procedure by Gilmour *et al.*[164], diisopropyl-azodicarboxylate (7.9 g, 38.3 mmol, 2.3 equiv) was added dropwise *via* syringe over 30 minutes to a stirred suspension of methyl 3,5-dihydroxy-4-iodobenzoate (5.0 g, 16.7 mmol, 1.0 equiv), triphenylphosphine (11.9 g, 45.0 mmol, 2.7 equiv), and (*S*)-methyl-2-hydroxy-3-phenylpropanoate (6.6 g, 35.0 mmol, 2.1 equiv) in THF (60 mL) at 0 °C. The reaction mixture was warmed to room temperature. After 12 hours, the

reaction mixture was concentrated under reduced pressure. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc 5:1) as a white solid (6.7 g, 10.8 mmol, 65%).

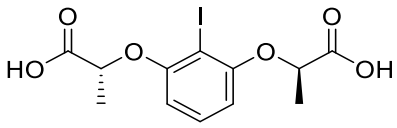
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.1 Hz, 4H), 7.30 (t, *J* = 7.4 Hz, 4H), 7.23 (d, *J* = 7.4 Hz, 2H), 6.86 (s, 2H), 4.92 (dd, *J* = 7.8, 4.7 Hz, 2H), 3.83 (s, 3H), 3.68 (s, 6H), 3.38 – 3.28 (m, 4H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 166.4, 158.4, 156.8, 136.3, 131.9, 130.3, 128.8, 127.5, 106.7, 79.0, 70.5, 52.8, 39.4 ppm.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{28}H_{28}O_8I$ = 619.0823; found 619.0827.

$[\alpha]_D^{20}$: +75.00° (c = 1.00, $CHCl_3$)

Analytical data in agreement with literature.[139]



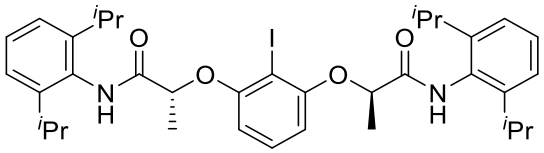
(2*R*, 2'*R*)-2,2'-((2-iodo-1,3-phenylene) bis(oxy)) propionic acid (198)

Following a procedure by Ishihara *et al*.[118b], dimethyl 2,2'-((2-iodo-1,3-phenylene) bis(oxy)) (2*R*, 2'*R*)-dipropionate (2.5 g, 6.1 mmol, 1.0 equiv) was dissolved in 32 mL of THF/MeOH (1:1). After addition of aqueous NaOH (2 M, 5.6 equiv), the reaction mixture was stirred for 6 h at room temperature and then was acidified with aqueous HCl (3 M). After extraction with EtOAc the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure affording the pure product as a white solid (2.3 g, 5.9 mmol, 96%).

^{1}H NMR (500 MHz, DMSO) δ 13.06 (s, 2H), 7.22 (t, *J* = 8.3 Hz, 1H), 6.43 (d, *J* = 8.4 Hz, 2H), 4.86 (q, *J* = 6.7 Hz, 2H), 1.55 ppm (d, *J* = 6.7 Hz, 6H) ppm.

^{13}C NMR (126 MHz, DMSO) δ 173.2, 158.2, 130.1, 106.4, 80.0, 73.2, 18.8 ppm.

Analytical data in agreement with literature.[118b]



(2*R*, 2'*R*)-2,2'-((2-iodo-1,3-phenylene) bis(oxy)) bis(N-(2,6-diisopropylphenyl) propanamide) (199a)

Prepared according to the general procedure A. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc/DCM 8:1:1) as a light-yellow solid (1.1 g, 1.5 mmol, 63%).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.87 (s, 2H), 7.33 (t, *J* = 8.3 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 4H), 6.65 (d, *J* = 8.3 Hz, 2H), 4.97 (q, *J* = 6.7 Hz, 2H), 2.96 – 2.77 (m, 4H), 1.69 (d, *J* = 6.6 Hz, 6H), 1.12 – 0.92 (m, 24H) ppm.

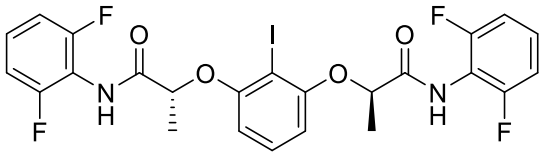
^{13}C NMR (126 MHz, CD_2Cl_2) δ 171.2, 157.6, 147.1, 131.2, 131.0, 129.0, 124.0, 107.7, 80.9, 76.7, 29.1, 23.9, 19.0 ppm.

FT-IR: $\tilde{\nu}$ = 3243, 2960, 1666, 1587, 1509, 1461, 1361, 1252, 1189, 1138, 1097, 1067, 1022, 941 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{36}H_{48}O_4N_2I$: 699.2653 found: 699.2656.

$[\alpha]_D^{20}$: -61.60° (c = 1.00, CH_2Cl_2)

Analytical data in agreement with literature.[165]



(2*R*, 2'*R*) -2,2'-((2-iodo-1,3-phenylene) bis(oxy)) bis(N-(2,6-difluorophenyl) propanamide) (199b)

Prepared according to the general procedure A. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc/DCM 8:1:1) as a yellow solid (0.42 g, 0.69 mmol, 65%).

^{1}H NMR (500 MHz, $CDCl_3$) 8.27 (s, 2H), 7.35 (t, *J* = 8.2 Hz, 1H), 7.28 – 7.17 (m, 2H), 6.98 (t, *J* = 7.9 Hz, 4H), 6.63 (d, *J* = 8.3 Hz, 2H), 5.00 (q, *J* = 6.7 Hz, 2H), 1.78 (d, *J* = 6.7 Hz, 6H) ppm.

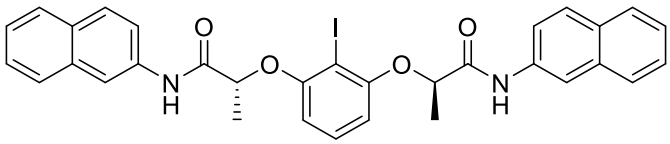
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 159.0 (d, J_{CF} = 4.7 Hz), 157.0 (d, J_{CF} = 4.7 Hz), 130.8, 128.1 (t, J_{CF} = 9.7 Hz), 113.2 (t, J_{CF} = 16.4 Hz), 112.0 (dd, J_{CF} = 19.3, 4.3 Hz), 107.6, 81.03, 76.4, 18.6 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -117.42 (q, J = 6.9 Hz, 4F) ppm.

FT-IR: $\tilde{\nu}$ = 3215, 2985, 1682, 1624, 1589, 1530, 1462, 1375, 1287, 1241, 1138, 1097, 1006, 924 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{24}H_{20}O_4N_2F_4I$: 603.0398 found: 603.0402.

$[\alpha]_D^{20}$: -107.60° (c = 1.00, CH_2Cl_2)



(2*R*, 2'*R*) -2,2'-((2-iodo-1,3-phenylene) bis(oxy)) bis(N-(naphthalen-2-yl) propanamide) (199c)

Prepared according to the general procedure A. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc/DCM 8:1:1) as a light brown solid (0.13 g, 0.19 mmol, 76%).

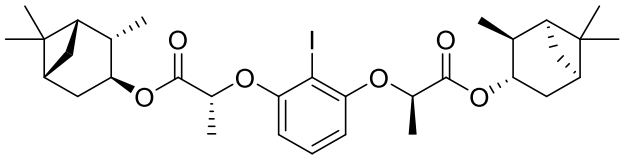
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (s, 2H), 8.38 (d, J = 2.1 Hz, 2H), 7.82 (dd, J = 16.2, 8.4 Hz, 6H), 7.61 (dd, J = 8.8, 2.2 Hz, 2H), 7.53 – 7.46 (m, 2H), 7.46 – 7.40 (m, 2H), 7.35 (t, J = 8.3 Hz, 1H), 6.64 (d, J = 8.3 Hz, 2H), 5.01 (q, J = 6.7 Hz, 2H), 1.80 (d, J = 6.7 Hz, 6H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) 169.2, 156.9, 134.8, 133.9, 131.0, 131.0, 129.1, 127.9, 127.7, 126.8, 125.4, 119.8, 116.8, 107.4, 81.0, 77.4, 77.2, 76.9, 76.3, 18.5 ppm.

FT-IR: $\tilde{\nu}$ = 3406, 2971, 2361, 1691, 1583, 1531, 1499, 1457, 1392, 1359, 1231, 1174, 1101, 1018, 956 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{32}H_{28}O_4N_2I$: 631.1088 found: 631.1091.

$[\alpha]_D^{20}$: -255.60° (c = 1.00, CH_2Cl_2)



Bis ((1*S*, 2*S*, 3*S*, 5*R*)-2,6,6-trimethylbicyclo [3.1.1] heptan-3-yl) 2,2'-((2-iodo-1,3-phenylene) bis(oxy)) (2*R*, 2'*R*)-dipropionate (200a)

Prepared according to the general procedure B. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc 9:1) as a colorless oil (0.25 g, 0.38 mmol, 48%).

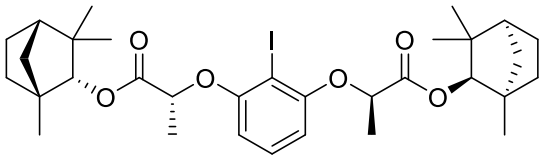
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (t, *J* = 8.3 Hz, 1H), 6.39 (d, *J* = 8.3 Hz, 2H), 5.08 (dt, *J* = 9.4, 4.4 Hz, 2H), 4.78 (q, *J* = 6.8 Hz, 2H), 2.52 - 2.46 (m, 2H), 2.34 – 2.29 (m, 2H), 2.18 – 2.13 (m, 2H), 1.87 – 1.84 (m, 2H), 1.82 – 1.79 (m, 2H), 1.70 (d, *J* = 6.8 Hz, 6H), 1.46 (dd, *J* = 4.2, 2.8 Hz, 1H), 1.43 (dd, *J* = 4.2, 2.8 Hz, 1H), 1.20 (s, 6H), 1.08 (d, *J* = 7.5 Hz, 6H), 0.94 (s, 1H), 0.92 (s, 7H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 158.5, 129.5, 107.0, 81.0, 75.3, 74.4, 47.5, 43.5, 41.2, 38.3, 35.6, 33.5, 27.5, 23.9, 20.6, 18.6 ppm.

FT-IR: $\tilde{\nu}$ = 2926, 2163, 1737, 1589, 1459, 1373, 1254, 1220, 1201, 1180, 1136, 1106, 1071, 1020, 972, 933, 900 cm^{-1}.

HRMS (ESI): calcd. for $[M+Na]^+$ $C_{32}H_{45}O_6INa$: 675.2153 found: 675.2157.

$[\alpha]_D^{20}$: +160.00° (c = 1.00, $CHCl_3$)



Bis ((1*R*, 2*R*, 4*S*)-1,3,3-trimethylbicyclo [2.2.1] heptan-2-yl) 2,2'-((2-iodo-1,3-phenylene) bis(oxy)) (2*R*, 2'*R*)-dipropionate (200b)

Prepared according to the general procedure B. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc 9:1) as a white solid (0.22 g, 0.32 mmol, 41%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (t, *J* = 8.3 Hz, 1H), 6.38 (d, *J* = 8.3 Hz, 2H), 4.83 (q, *J* = 6.7 Hz, 2H), 4.41 (d, *J* = 1.9 Hz, 2H), 1.71 (d, *J* = 6.8 Hz, 6H), 1.69 – 1.55 (m, 8H), 1.47 – 1.38 (m,

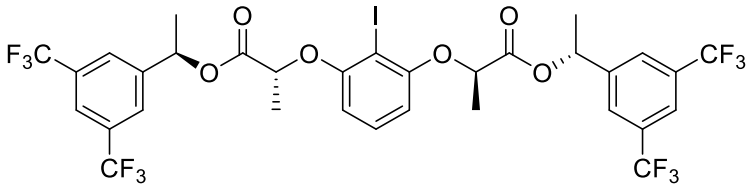
2H), 1.18 (dd, *J* = 10.3, 1.4 Hz, 2H), 1.12 – 1.08 (m, 2H), 1.05 (d, *J* = 2.1 Hz, 12H), 0.59 (s, 6H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 158.3, 129.5, 106.5, 87.4, 77.5, 77.2, 76.8, 74.0, 48.6, 48.4, 41.4, 39.5, 29.8, 26.7, 25.9, 20.3, 19.5, 19.0 ppm.

FT-IR: $\tilde{\nu}$ = 2947, 2166, 1748, 1588, 1459, 1377, 1320, 1253, 1202, 1179, 1134, 1110, 1067, 1034, 1018, 1003 cm^{-1}.

HRMS (ESI): calcd. for $[M+Na]^+$ $C_{32}H_{45}O_6INa$: 675.2153 found: 675.2158.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +147.83° (c = 1.00, $CHCl_3$)



Bis((*R*)-1-(3,5-bis(trifluoromethyl)phenyl) ethyl) 2,2'-((2-iodo-1,3-phenylene) bis(oxy)) (2*R*, 2'*R*)-dipropionate (200c)

Prepared according to the general procedure B. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc 9:1) as a colorless oil (0.32 g, 0.38 mmol, 48%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 2H), 7.63 (s, 4H), 6.95 (t, *J* = 8.3 Hz, 1H), 6.24 (d, *J* = 8.3 Hz, 2H), 5.98 (q, *J* = 6.6 Hz, 2H), 4.84 (q, *J* = 6.8 Hz, 2H), 1.73 (d, *J* = 6.8 Hz, 6H), 1.60 (d, *J* = 6.8 Hz, 6H) ppm.

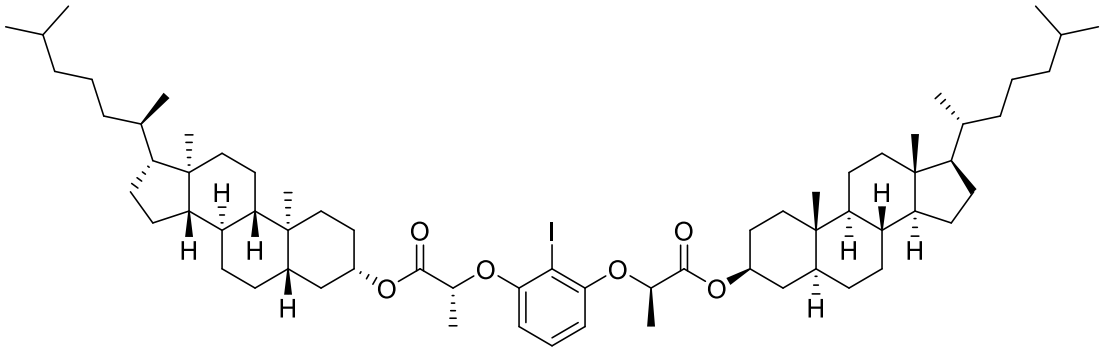
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 158.1, 143.6, 132.0 (q, J_{CF} = 33.4 Hz), 129.6, 126.3, 124.3, 122.1 (q, J_{CF} = 3.7 Hz), 106.1, 79.6, 73.8, 72.1, 22.2, 18.5 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -62.88 (s, 12F) ppm.

FT-IR: $\tilde{\nu}$ = 2992, 1753, 1626, 1590, 1464, 1384, 1378, 1338, 1317, 1302, 1278, 1259, 1181, 1129, 1103, 1076, 1014, 916 cm^{1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{32}H_{26}O_6F_{12}I$: 861.0577 found: 861.0571.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$: +149.17° (c = 1.00, $CHCl_3$)



Bis ((3*S*, 5*S*, 8*R*, 9*S*, 10*S*, 13*R*, 14*S*, 17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl) hexadecahydro-1H-cyclopenta[a]phenanthren-3-yl) 2,2'-((2-iodo-1,3-phenylene) bis(oxy)) (2*R*, 2'*R*)-dipropionate (200d)

Prepared according to the general procedure B. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc 7:1) as a white solid (0.39 g, 0.35 mmol, 44%).

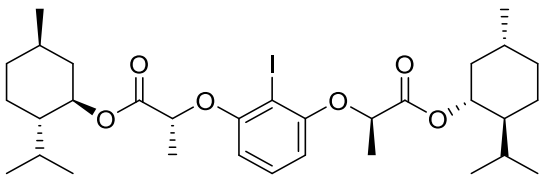
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 (t, *J* = 8.3 Hz, 1H), 6.36 (d, *J* = 8.3 Hz, 2H), 4.77 – 4.67 (m, 4H), 1.95 (dt, *J* = 12.3, 3.0 Hz, 2H), 1.83 – 1.77 (m, 2H), 1.71 – 1.61 (m, 12H), 1.61 – 1.48 (m, 8H), 1.47 – 1.18 (m, 24H), 1.17 – 0.93 (m, 20H), 0.89 (d, *J* = 6.5 Hz, 6H), 0.86 (dd, *J* = 6.6, 2.8 Hz, 12H), 0.80 (s, 6H), 0.64 (s, 6H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4, 158.5, 129.5, 107.2, 81.1, 75.0, 74.6, 56.5, 56.4, 54.3, 44.8, 42.7, 40.1, 39.7, 36.8, 36.3, 35.9, 35.6, 35.6, 34.0, 32.1, 28.7, 28.4, 28.2, 27.3, 24.3, 24.0, 23.0, 22.7, 21.3, 18.8, 18.7, 12.4, 12.2 ppm.

FT-IR: $\tilde{\nu}$ = 2928, 2349, 2005, 1761, 1735, 1585, 1459, 1380, 1276, 1251, 1176, 1129, 1106, 1063, 1023, 1006, 902 cm^{1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{66}H_{106}O_6I$: 1121.7029 found: 1121.7037.

$[\alpha]_D^{20}$: -2.90° (c = 1.00, $CHCl_3$)



Bis ((1*R*, 2*S*, 5*R*) -2-isopropyl-5-methylcyclohexyl) 2,2'-((2-iodo-1,3-phenylene) bis(oxy)) (2*R*, 2'*R*) -dipropionate (200e)

Prepared according to the general procedure B. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc 7:1) as colorless oil (0.60 g, 0.92 mmol, 72%).

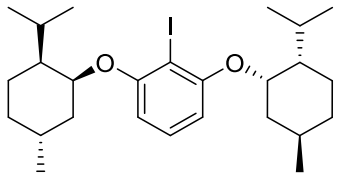
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (t, *J* = 8.3 Hz, 1H), 6.35 (d, *J* = 8.3 Hz, 2H), 4.75 (q, *J* = 6.7 Hz, 2H), 4.62 (td, *J* = 10.9, 4.4 Hz, 2H), 2.02 – 1.94 (m, 2H), 1.69 (d, *J* = 6.7 Hz, 6H), 1.50 – 1.29 (m, 6H), 1.41 – 1.29 (m, 4H), 1.05 – 0.92 (m, 4H), 0.89 (d, *J* = 6.6 Hz, 6H), 0.87 – 0.79 (m, 2H), 0.72 (d, *J* = 7.0 Hz, 6H), 0.53 (d, *J* = 6.9 Hz, 6H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 158.7, 129.9, 106.6, 80.5, 75.8, 74.7, 47.0, 40.8, 34.5, 31.7, 25.9, 23.3, 22.4, 21.2, 19.0, 16.0 ppm.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{32}H_{50}O_6I$: 657.2647 found: 657.2653.

$[\alpha]_D^{20}$: -61.54° (c = 1.00, $CHCl_3$)

Analytical data in agreement with literature.[162]



(1*S*, 1'*S*, 2*S*, 2'*S*, 4*R*, 4'*R*)-2,2'-((2-iodo-1,3-phenylene) bis(oxy)) bis(1-isopropyl-4-methylcyclohexane) (188a)

Prepared according to the general procedure C. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc 10:1) as a colorless oil (0.044 g, 0.086 mmol, 20%).

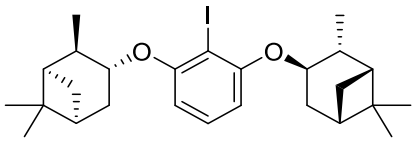
^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.17 (t, *J* = 8.3 Hz, 1H), 6.42 (d, *J* = 8.3 Hz, 2H), 4.76 – 4.72 (m, 2H), 2.08 – 1.99 (m, 2H), 1.85 – 1.67 (m, 10H), 1.09 – 0.97 (m, 6H), 0.95 (d, *J* = 6.6 Hz, 6H), 0.84 (d, *J* = 6.6 Hz, 6H), 0.81 (d, *J* = 6.6 Hz, 6H) ppm.

^{13}C NMR (126 MHz, CD_2Cl_2) δ 158.4, 130.1, 104.6, 80.4, 74.4, 48.5, 37.8, 35.6, 29.9, 26.9, 25.7, 22.6, 21.5, 21.2 ppm.

FT-IR: $\tilde{\nu}$ = 2927, 1586, 1564, 1459, 1441, 1382, 1368, 1337, 1281, 1250, 1243, 1220, 1201, 1149, 1104, 1070, 1016, 991, 958, 915 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{26}H_{42}O_2I$: 513.2224 found: 513.2220.

$[\alpha]_D^{20}$: -12.75° (c = 1.00, $CHCl_3$)



(1*R*, 1'*R*, 2*R*, 2'*R*, 3*R*, 3'*R*, 5*S*, 5'*S*)-3,3'-((2-iodo-1,3-phenylene) bis(oxy)) bis (2,6,6-trimethylbicyclo [3.1.1] heptane) (188b)

Prepared according to the general procedure C. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc 10:1) as a white solid (0.18 g, 0.35 mmol, 82%).

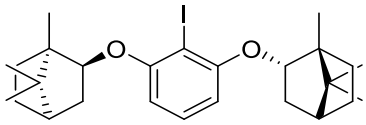
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (t, *J* = 8.2 Hz, 1H), 6.36 (d, *J* = 8.3 Hz, 2H), 4.90 (td, *J* = 9.8, 4.5 Hz, 2H), 2.81 – 2.67 (m, 2H), 2.62 – 2.50 (m, 2H), 2.39 – 2.26 (m, 2H), 2.13 – 2.03 (m, 2H), 1.94 (d, *J* = 5.7 Hz, 4H), 1.24 – 1.17 (m, 18H), 1.07 (d, *J* = 9.9 Hz, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 129.4, 104.9, 79.4, 71.2, 48.0, 40.6, 40.4, 38.9, 35.9, 31.0, 27.9, 22.4, 16.9 ppm.

FT-IR: $\tilde{\nu}$ = 2907, 2158, 2034, 1978, 1737, 1583, 1457, 1381, 1366, 1342, 1276, 1245, 1180, 1124, 1102, 1069, 1018, 965, 931, 908 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{26}H_{38}O_2I$: 509.1911 found: 509.1906.

$[\alpha]_D^{20}$: +102.33° (c = 1.00, $CHCl_3$)



(1*R*, 1'*R*, 2*S*, 2'*S*, 4*S*, 4'*S*)-2,2'-((2-iodo-1,3-phenylene) bis(oxy)) bis (1,7,7-trimethylbicyclo [2.2.1] heptane) (188c)

Prepared according to the general procedure C. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc 10:1) as a white solid (0.08 g, 0.16 mmol, 31%).

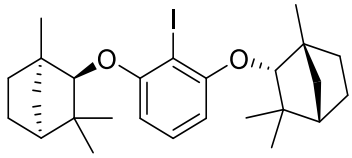
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.13 (t, *J* = 8.2 Hz, 1H), 6.34 (d, *J* = 8.2 Hz, 2H), 4.06 (t, *J* = 5.4 Hz, 2H), 1.85 (d, *J* = 6.5 Hz, 4H), 1.79 – 1.72 (m, 4H), 1.66 – 1.53 (m, 4H), 1.29 – 1.24 (m, 2H), 1.16 (s, 6H), 1.10 (s, 6H), 0.89 (s, 6H) ppm.

^{13}C NMR (176 MHz, $CDCl_3$) δ 158.3, 129.3, 104.6, 85.7, 78.9, 49.7, 47.3, 45.5, 39.8, 34.2, 27.5, 21.1, 20.5, 12.6 ppm.

FT-IR: $\tilde{\nu}$ = 2931, 2349, 2123, 2030, 1999, 1596, 1580, 1454, 1388, 1287, 1253, 1110, 1084, 1068, 1036, 1018 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{26}H_{38}O_2I$: 509.1911 found: 509.1906.

$[\alpha]_D^{20}$: +274.00° (c = 1.00, $CHCl_3$)



(1*R*, 1'*R*, 2*R*, 2'*R*, 4*S*, 4'*S*)-2,2'-((2-iodo-1,3-phenylene) bis(oxy)) bis (1,3,3-trimethylbicyclo [2.2.1] heptane) (188d)

Prepared according to the general procedure C. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc 10:1) as a white solid (0.07 g, 0.14 mmol, 28%).

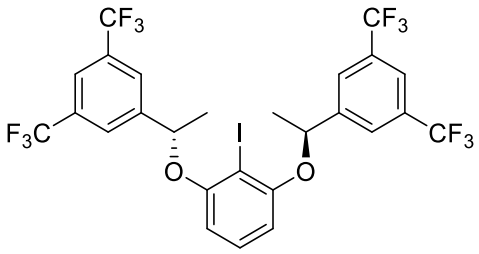
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (t, *J* = 8.2 Hz, 1H), 6.31 (d, *J* = 8.2 Hz, 2H), 3.68 (s, 2H), 2.14 – 2.01 (m, 2H), 1.71 (s, 2H), 1.68 – 1.61 (m, 2H), 1.50 – 1.39 (m, 4H), 1.18 (m, 14H), 1.13 (d, *J* = 10.0 Hz, 2H), 0.90 (s, 6H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 129.1, 103.9, 91.6, 78.2, 49.8, 49.2, 44.3, 41.8, 33.6, 26.6, 25.8, 23.9, 18.2 ppm.

FT-IR: $\tilde{\nu}$ = 2957, 1581, 1455, 1387, 1376, 1365, 1324, 1295, 1254, 1247, 1213, 1086, 1068, 1019, 962, 934, 904 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{26}H_{38}O_2I$: 509.1911 found: 509.1906.

$[\alpha]_D^{20}$: +111.20° (c = 1.00, $CHCl_3$)



5,5'-((1*S*, 1'*S*) -((2-iodo-1,3-phenylene) bis(oxy)) bis(ethane-1,1-diyl)) bis(1,3-bis(trifluoromethyl)benzene) (188e)

Prepared according to the general procedure C. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc 10:1) as a white solid (0.15 g, 0.21 mmol, 51%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 4H), 7.82 (s, 2H), 7.07 (t, *J* = 8.3 Hz, 1H), 6.34 (d, *J* = 8.3 Hz, 2H), 5.51 (q, *J* = 6.5 Hz, 2H), 1.73 (d, *J* = 6.5 Hz, 6H) ppm.

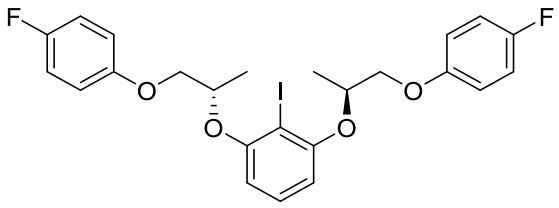
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.7, 145.5, 132.2 (q, J_{CF}= 33.5 Hz), 129.8, 126.6, 126.2 (d, J_{CF} = 4.0 Hz), 124.5, 122.3, 121.9 (p, J_{CF} = 3.7 Hz), 120.1, 107.8, 81.8, 76.6, 24.1 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -62.84 (s, 12F) ppm.

FT-IR: $\tilde{\nu}$ = 2987, 1624, 1584, 1466, 1457, 1384, 1374, 1338, 1318, 1277, 1251, 1171, 1115, 1093, 1053, 1023, 899 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{26}H_{18}O_2F_{12}I$: 717.0154 found: 717.0148.

$[\alpha]_D^{20}$: +138.71° (c = 1.00, $CHCl_3$)



4,4'-(((2*S*, 2'*S*) -((2-iodo-1,3-phenylene) bis(oxy)) bis(propane-2,1-diyl)) bis(oxy)) bis(fluorobenzene) (188f)

Prepared according to the general procedure C. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc 10:1) as a colorless oil (0.19 g, 0.35 mmol, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (t, *J* = 8.2 Hz, 1H), 7.03 – 6.93 (m, 4H), 6.92 – 6.83 (m, 4H), 6.63 (d, *J* = 8.2 Hz, 2H), 4.76 (m, 2H), 4.22 (dd, *J* = 9.7, 5.8 Hz, 2H), 4.04 (dd, *J* = 9.7, 5.8 Hz, 2H), 1.50 (d, *J* = 6.4 Hz, 6H) ppm.

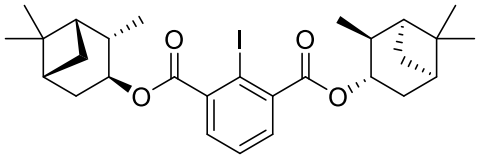
^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 157.5 (d, J_{CF} = 238.4 Hz), 154.9 (d, J_{CF} = 2.2 Hz), 129.6, 116.0 (d, J_{CF} = 7.5 Hz), 115.8 (d, J_{CF} = 7.5 Hz), 108.3, 83.3, 74.8, 71.8, 17.5 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ -123.47 (m, 2F) ppm.

FT-IR: $\tilde{\nu}$ = 2978, 2053, 1857, 1584, 1503, 1456, 1378, 1354, 1291, 1241, 1207, 1155, 1116, 1092, 1053, 1021, 1007, 996, 940, 910 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{24}H_{24}O_4F_2I$: 541.0682 found: 541.0677.

$[\alpha]_D^{20}$: +45.38° (c = 1.00, $CHCl_3$)



Bis ((1*S*, 2*S*, 3*S*, 5*R*)-2,6,6-trimethylbicyclo [3.1.1] heptan-3-yl) 2-iodoisophthalate (191a)

Prepared according to the general procedure B using 2-iodoisophthalic acid **192** and 3-pinanol. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc 5:1) as a white solid (0.02 g, 0.04 mmol, 11%).

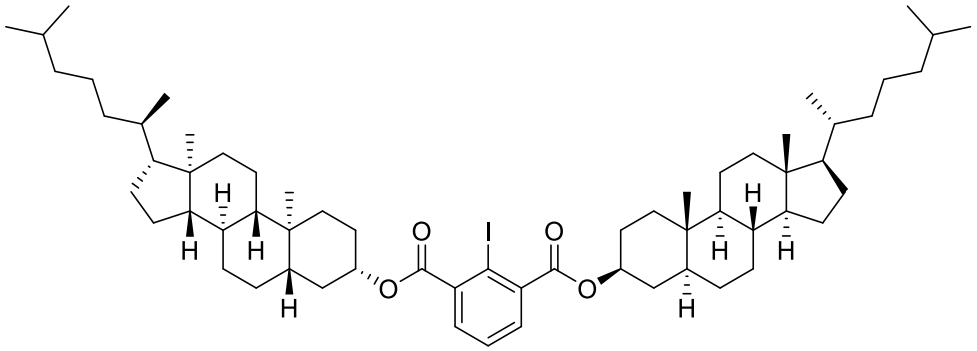
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.6 Hz, 2H), 7.44 (dd, *J* = 8.1, 7.2 Hz, 1H), 5.34 (dt, *J* = 9.4, 4.4 Hz, 2H), 2.76 – 2.70 (m, 2H), 2.42 – 2.38 (m, 2H), 2.36 – 2.30 (m, 2H), 2.04 – 1.77 (m, 6H), 1.25 (s, 6H), 1.21 (d, *J* = 7.4 Hz, 6H), 1.13 (d, *J* = 10.0 Hz, 2H), 1.01 (s, 6H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 140.5, 130.9, 128.1, 91.4, 76.6, 47.7, 43.5, 41.4, 38.5, 35.8, 33.6, 27.5, 24.0, 20.9 ppm.

FT-IR: $\tilde{\nu}$ = 2912, 2350, 2118, 1988, 1716, 1468, 1449, 1281, 1253, 1201, 1151, 1125, 1089, 1032, 979, 940, 897cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{28}H_{38}O_4I$: 565.1809 found: 565.1803.

$[\alpha]_D^{20}$: +32.14° (c = 1.00, $CHCl_3$)



Bis((3*S*, 5*S*, 8*R*, 9*S*, 10*S*, 13*R*, 14*S*, 17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl) hexadecahydro-1H-cyclopenta[a]phenanthren-3-yl) 2-iodoisophthalate (191b)

Prepared according to the general procedure B, using 2-iodoisophthalic acid **192** and β-cholestanol. Purification by silica gel column chromatography afforded the pure product (eluent system: *n*-pentane/EtOAc 10:1) as a white solid (0.57 g, 0.55 mmol, 81%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.5 Hz, 2H), 7.46 (dd, *J* = 8.1, 7.1 Hz, 1H), 5.32 (s, 2H), 2.01 – 1.89 (m, 4H), 1.84 – 1.43 (m, 22H), 1.37 – 1.16 (m, 18H), 1.16 – 0.94 (m, 16H), 0.89 (d, *J* = 6.6 Hz, 6H), 0.86 (dd, *J* = 6.6, 2.4 Hz, 12H), 0.83 (s, 6H), 0.77 – 0.69 (m, 2H), 0.65 (s, 6H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 140.6, 130.8, 128.1, 91.4, 72.8, 56.6, 56.4, 54.2, 42.7, 40.3, 40.1, 39.6, 36.3, 36.0, 35.9, 35.6, 33.2, 32.9, 32.1, 28.5, 28.4, 28.2, 26.2, 24.3, 24.0, 23.0, 22.7, 20.9, 18.8, 12.2, 11.6 ppm.

FT-IR: $\tilde{\nu}$ = 2926, 2363, 2236, 2206, 2169, 2155, 2064, 2045, 2039, 2030, 2010, 1992, 1962, 1737, 1457, 1246, 1063, 1019 cm^{-1}.

HRMS (ESI): calcd. for $[M+H]^+$ $C_{62}H_{98}O_4I$: 1033.6504 found: 1033.6504

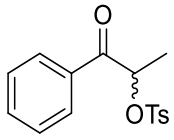
$[\alpha]_D^{20}$: +25.80° (c = 1.00, $CHCl_3$)

6.3.2 General procedures for α-functionalization of carbonyl compounds

6.3.2.1 General procedure for racemic α-tosyloxylation of propiophenone

Following a procedure by Togo *et al*.[166], to a solution of propiophenone (100.0 mg, 0.74 mmol, 1.0 equiv) in MeCN (5 mL) were added iodobenzene (15.36 mg, 0.07 mmol, 10 mol%), TsOH•H_2O (156.7 mg, 0.81 mmol, 1.1 equiv) and *m*CPBA (77% purity, 181.9 mg, 0.81 mmol, 1.1 equiv). The mixture was stirred for 5 h at 50 °C under argon atmosphere. After the reaction was completed the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted

with DCM. The organic layer was dried over $MgSO_4$. After the removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (eluent system: 5 to 20% EtOAc in *n*-pentane) to give the pure product as a brownish solid (126.0 mg, 0.41 mmol, 56%).



1-oxo-1-phenylpropan-2-yl 4-methylbenzenesulfonate (182)

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.78 – 7.74 (m, 2H), 7.68 – 7.63 (m, 2H), 7.56 – 7.50 (m, 1H), 7.42 – 7.36 (m, 2H), 7.26 – 7.19 (m, 2H), 5.65 (q, *J* = 7.0 Hz, 1H), 2.33 (s, 3H), 1.46 ppm (d, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, CD_2Cl_2) δ 194.7, 145.4, 133.9, 133.7, 133.4, 129.9, 128.8, 128.6, 127.8, 77.4, 21.4, 18.6 ppm.

HPLC conditions: CHIRALPAK IC column, *iso*-propanol/ *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1}, enantiomer 1: t_R = 35.73 min; enantiomer 2: t_R = 45.37 min (racemic).

The analytical data were in good accordance with those reported in the literature.[166]

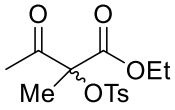
6.3.2.2 General procedure for asymmetric α-tosyloxylation of propiophenone

To a stirred solution of iodine(I)-catalyst (20 mol%) in MeCN (1 mL, 0.04 M) were added *m*CPBA (77% purity, 16.5 mg, 0.07 mmol, 2.0 equiv) and TsOH•H_2O (10.7 mg, 0.06 mmol, 1.5 equiv) followed by propiophenone (5.0 mg, 0.04 mmol, 1.0 equiv) and the mixture was stirred at room temperature for 24 h. Upon reaction completion, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution and extracted with DCM. The organic layer was dried with anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (eluent system: 5 to 20% EtOAc in *n*-pentane).

6.3.2.3 General procedure for racemic α-tosyloxylation of ethyl 2-methylacetoacetate

In an oven-dried flask equipped with a stir bar were placed ethyl 2-methylacetoacetate (52.6 mg, 0.35 mmol, 1.0 equiv), iodobenzene (14.44 mg, 0.07 mmol, 20 mol%), TsOH•H_2O (73.7 mg, 0.38 mmol, 1.1 equiv) and trifluoroacetic acid (79.7 µL, 1.04 mmol, 3.0 equiv) in $CHCl_3$ (1.5 mL) under an inert atmosphere. *m*CPBA (77% purity, 139.9 mg, 0.62 mmol, 1.8 equiv) was then added at 0

°C and the reaction mixture was stirred for 48 h. After the reaction was completed, the reaction mixture was poured into saturated aqueous $Na_2S_2O_3$ solution and a saturated aqueous $NaHCO_3$ solution and extracted with DCM. The organic layer was dried over $MgSO_4$. Upon removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (eluent system: 5 to 10% EtOAc in *n*-pentane) to give the pure product as colorless oil (56.2 mg, 0.18 mmol, 52%).



Ethyl 2-methyl-3-oxo-2-(tosyloxy) butanoate (204)

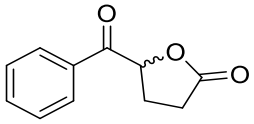
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 4.36 – 4.14 (m, 2H), 2.44 (s, 3H), 2.30 (s, 3H), 1.85 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 200.7, 166.6, 145.3, 135.1, 129.9, 127.7, 90.6, 63.0, 25.4, 21.8, 20.2, 14.0 ppm.
HPLC conditions: CHIRALPAK IC column, *iso*-propanol/ *iso*-hexane = 15/85, flow rate = 0.5 mL min^{-1}, enantiomer 1: t_R = 27.71 min; enantiomer 2: t_R = 32.97 min (racemic).
The analytical data were in good accordance with those reported in the literature.[147]

6.3.2.4 General procedure for asymmetric α-tosyloxylation of ethyl 2-methylacetoacetate

In an oven-dried flask equipped with a stir bar were placed ethyl 2-methylacetoacetate (5.0 mg, 0.03 mmol, 1.0 equiv), iodine(I)-catalyst (20 mol%), $TsOH•H_2O$ (7.0 mg, 0.04 mmol, 1.1 equiv) in EtOAc (0.5 mL) under an inert atmosphere. *m*CPBA (77% purity, 13.3 mg, 0.06 mmol, 1.8 equiv) was then added at 0 °C and the reaction mixture was stirred for 48 h. After the reaction was completed, the reaction mixture was poured into saturated aqueous $Na_2S_2O_3$ solution and a saturated aqueous $NaHCO_3$ solution and extracted with DCM. The organic layer was dried over $MgSO_4$. Upon removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (eluent system: 5 to 10% EtOAc in *n*-pentane) to give the pure product as colorless oil.

6.3.2.5 General procedure for racemic lactonization of 4-benzoylbutyric acid

To a stirring mixture of 4-benzoylbutyric acid (100.0 mg, 0.49 mmol, 1.0 equiv), iodobenzene (10.29 mg, 0.05 mmol, 10 mol%) and TsOH•H_2O (19.09 mg, 0.10 mmol, 20 mol%) in CH_3NO_2 (12 mL) was added *m*CPBA portion wise (77% purity, 132.9 mg, 0.59 mmol, 1.2 equiv per hour up to 265.8 mg, 1.19 mmol, 2.4 equiv) at 50 °C. After the reaction was completed, CH_3NO_2 was evaporated. The residue was dissolved in DCM, washed with aqueous $NaHCO_3$ and the aqueous layers were extracted with DCM twice. The organic layer was dried over anhydrous $MgSO_4$, and the solvents were removed in vacuo. The residue was purified by silica gel column chromatography (eluent system: 10 to 30% EtOAc in *n*-pentane) to give the pure product as a white solid (42.9 mg, 0.22 mmol, 45%).



5-benzoyldihydrofuran-2(3H)-one (206)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.86 (m, 2H), 7.62 – 7.53 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 5.82 – 5.58 (m, 1H), 2.75 – 2.29 (m, 4H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 194.3, 176.3, 134.4, 133.6, 129.1, 128.8, 78.3, 26.9, 25.0 ppm.

HPLC conditions: CHIRALPAK IC column, *iso*-propanol/ *iso*-hexane = 60/40, flow rate = 0.5 mL min^{-1}, enantiomer 1: t_R = 34.74 min; enantiomer 2: t_R = 44.18 min (racemic).

The analytical data were in good accordance with those reported in the literature.[167]

6.3.2.6 General procedure for asymmetric lactonization of 4-benzoylbutyric acid

4-Benzoylbutyric acid (5.0 mg, 0.02 mmol, 1.0 equiv) was added to a solution of iodine(I)-catalyst (20 mol%), *m*CPBA (77% purity, 16.6 mg, 0.07 mmol, 3.0 equiv) and TsOH•H_2O (14.3 mg, 0.07 mmol, 3.0 equiv) in THF (1.0 mL) at room temperature. The solution was stirred for 24 h and then was quenched by the addition of a saturated aqueous $Na_2S_2O_3$ solution, extracted with DCM, washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (eluent system: 10 to 30% EtOAc in *n*-pentane) to give the product.

Chapter 7. Appendix

7 List of Abbreviations

$[\alpha]$	specific rotation
AMD	age-related macular degeneration
BOX	bis(oxazoline)
calc.	calculated
CPA	chiral phosphoric acid
d.r.	diastereomeric ratio
DBAD	di-tert-butyl azodicarboxylate
DCC	*N, N′*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	density-functional-theory
DHP	dihydropyridine
DIAD	di-*iso*-propyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
e.r.	enantiomeric ratio
EDG	electron-donating group
ee	enantiomeric excess
equiv.	equivalent
Et	ethyl
et al.	*et alii* (and others)
EtOAc	ethyl acetate
EWG	electron-withdrawing group
FT-IR	Fourier-transform infrared spectroscopy
h	hours
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HI	hypervalent iodine
HOMO	highest occupied molecular orbital

HPLC	high performance liquid chromatography
HR-MS	high resolution mass spectrometry
IBS	2-iodoxybenzenesulfonic acid
IBX	2-iodoxybenzoic acid
IDPis	imidodiphosphorimidates
IOB	iodosylbenzene
^{i}Pr	*iso*-propyl
LAH	lithium aluminium hydride
LC/MS	liquid chromatography-mass spectrometry
LUMO	lowest Unoccupied Molecular Orbital
m/z	mass-to-charge ratio
*m*CPBA	meta-chloroperoxybenzoic acid
Me	methyl
Me_2AlCl	dimethylaluminum chloride
Me_3OBF_4	trimethyloxonium tetrafluoroborate
MeCN	acetonitrile
min	minutes
MW	molecular weight
n-BuLi	*n*-butyllithium
NMR	nuclear magnetic resonance
Nu	nucleophile
OTs	tosylate
PFITF	pentafluorophenyliodine tetrafluoride
Ph	phenyl
PhMe	toluene
PIDA	iodosobenzene diacetate
PIFA	iodosobenzene bis(trifluoroacetate)
ppm	parts per million
rr	regiomeric ratio
RT	room temperature
TBDMS	*tert*-butyldimethylsilyl ether

^{t}Bu	*tert*-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TsOH	toluenesulfonic acid

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Πάντα στον νου σου να 'χεις την Ιθάκη.
Το φθάσιμον εκεί είν' ο προορισμός σου.
Αλλά μη βιάζεις το ταξίδι διόλου.
Καλύτερα χρόνια πολλά να διαρκέσει·
και γέρος πια ν' αράξεις στο νησί,
πλούσιος με όσα κέρδισες στον δρόμο,
μη προσδοκώντας πλούτη να σε δώσει η Ιθάκη.

Η Ιθάκη σ' έδωσε τ' ωραίο ταξίδι.
Χωρίς αυτήν δεν θα 'βγαινες στον δρόμο.
Άλλα δεν έχει να σε δώσει πια.
Κι αν πτωχική την βρεις, η Ιθάκη δεν σε γέλασε.
Έτσι σοφός που έγινες, με τόση πείρα,
ήδη θα το κατάλαβες οι Ιθάκες τι σημαίνουν.

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Patent

Kahmann R.; Ludwig N.; Reißmann S.; Münch K.; Sievers S.; Lampe P.; Bischoff M.; Thoma A.; **Polychronidou V.**; Antonchick A. "Novel Antifungal Compounds", European Patent, Application No. EP21154940, filled: 03.02.2021.

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