Enantioselective Nucleophilic Dearomatization of Heteroarenes by Anion-Binding-Catalysis

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To my family

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1. Introduction

1.1 Anion Binding Catalysis

Asymmetric catalysis is one of the most important tools in organic synthesis to achieve enantiopure compounds. Depending on the targeted reaction and nature of the reactants, all the different types of chemical interactions between the substrates and catalysts can be utilized. In this regard covalent bonding (e.g. *via* enamine catalysis, metal complexes, etc.) and different types of non-covalent interactions, such as hydrogen-bonding or ion-pairing, must be mentioned. The latter relies on charged intermediates and reagents, and depending on their activation modes the catalytic approaches based on it can be divided in four fields: 1) chiral cation-directed catalysis, 2) cation-binding catalysis, 3) chiral anion-directed catalysis and 4) anion-binding catalysis (Figure 1a).[1] In general, reactivity and enantioselectivity can be introduced by forming a charged intermediate during the reaction. Interaction of these ionic intermediates with chiral neutral or charged catalysts has emerged as a powerful tool for catalytic enantioselective synthesis. The most prominent type of catalysts in this research area consist of bi- or multi-H-bond donor compounds such as (thio)ureas,[2] squaramides,[3] (macrocyclic)amides[4] or calixarenes,[5] which can bind anions like halides, cyanides, carboxylates, sulfates or phosphates through H-bonding (Figure 1b).

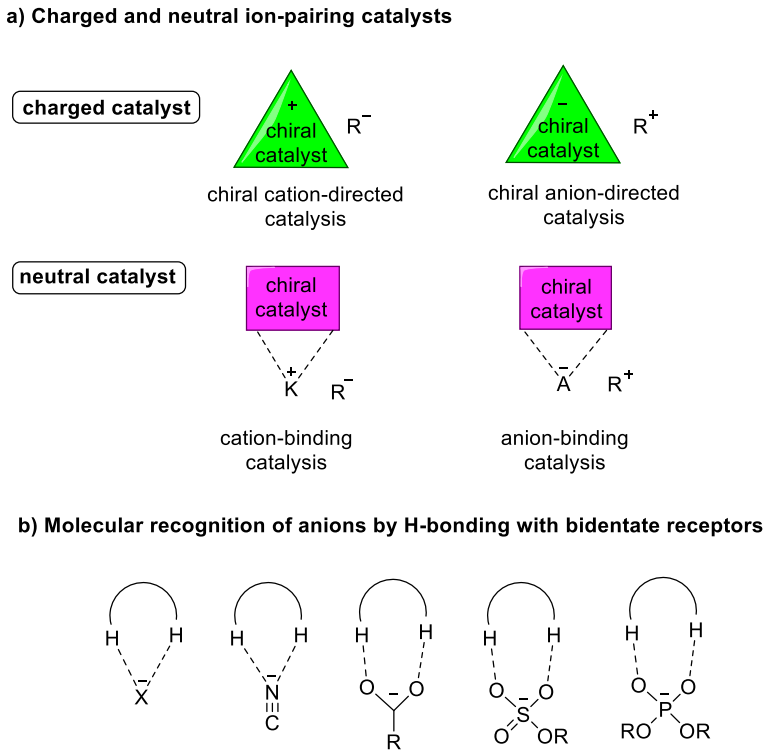
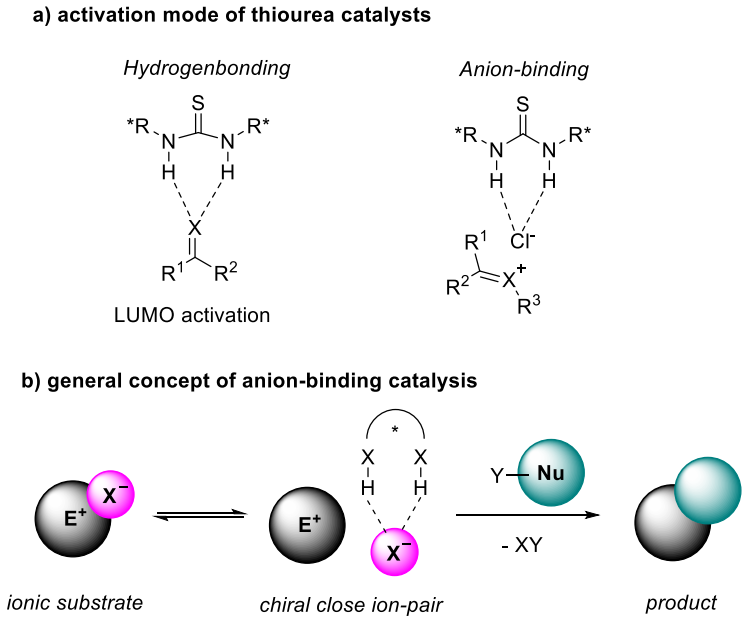


Figure 1 a) Charged and neutral ion-pairing activations, and b) molecular recognition of anions.

This thesis focuses on the so-called "anion-binding catalysis" approach that involves the non-covalent binding to an ion pair by a chiral, neutral catalyst. For that reason, the principle of anion-binding catalysis will be described more closely.

In general, anion-binding catalysis consists on the concept of ion pairs, which was described by Anslyn and Dougherty: "*An ion pair is defined to exist when a cation and anion are close enough in space that the energy associated with their electrostatic attraction is larger than the thermal energy (RT) available to separate them. This means that the ions stay associated longer than the time required for Brownian motion to separate non-interacting species.*"[6]

Finally, having a look at the development of anion-binding catalysis, it can be concluded that it was born from the more classical hydrogen bond-donor asymmetric catalysis. Thus, the ability of thioureas as privileged H-donor organocatalysts to activate neutral electrophiles through hydrogen bonding has been extensively exploited. However, it may have led in some cases to the misinterpretation of the mechanism (neutral H-donor *vs.* anion-binding catalysis), since this type of catalysts can indeed activate an *in situ* formed electrophilic intermediate by binding to its counter-anion (Scheme 1).[7]

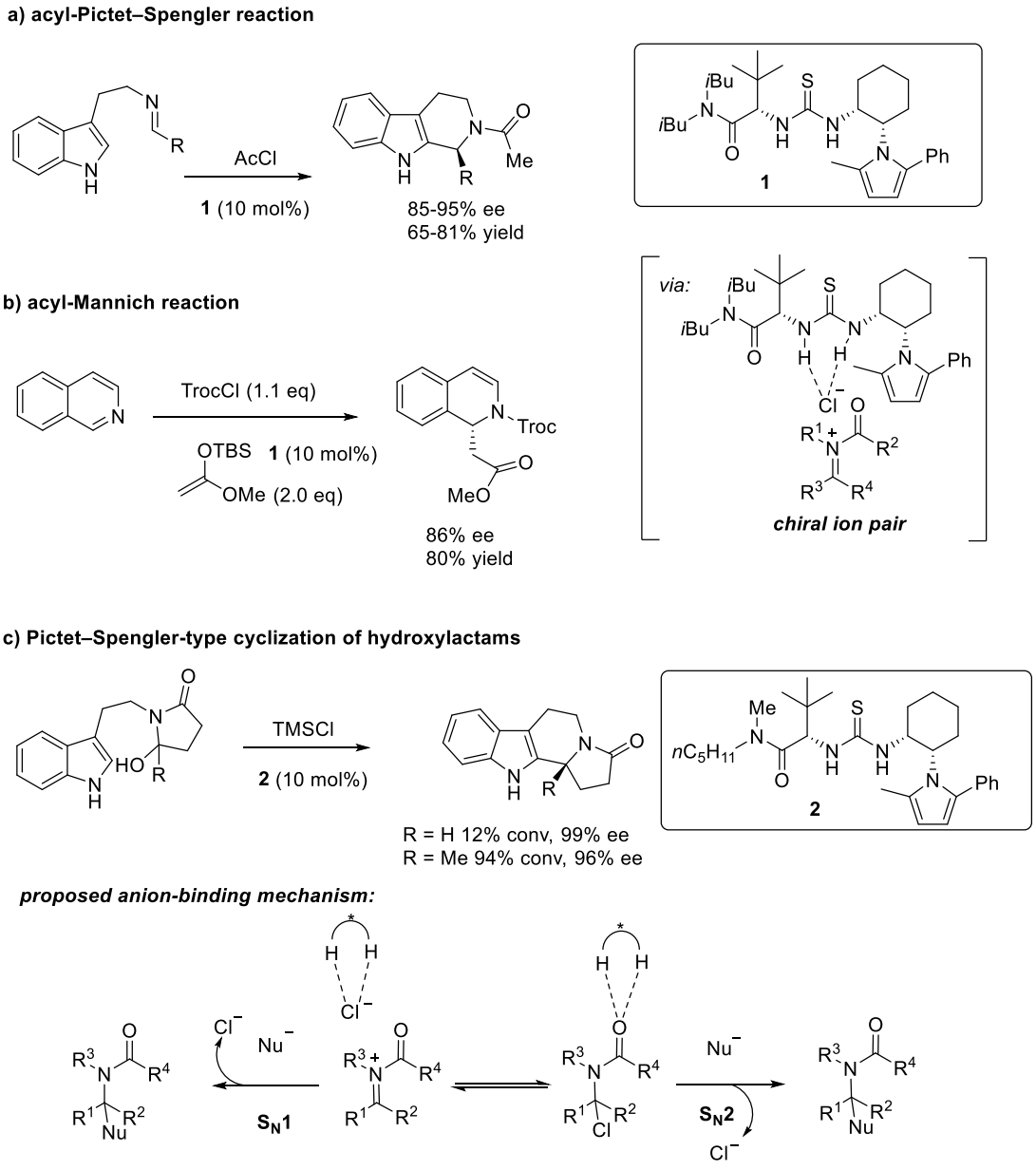


Scheme 1 Activation modes of thiourea catalysts and anion-binding catalysis.

In the following, key examples of anion-binding catalysis with various ionic species will be described. Since the field is huge, the examples of anion-binding catalysis implying heteroarenes as substrates will be emphasized.

1.1.1 Halide Binding

In 2004, Jacobsen reported on a thiourea-catalyzed acyl-Pictet–Spengler reaction of tryptamine with different aldehydes to give tetrahydro-β-carbolines in good yields and enantioselectivities.[8] First, an activation by hydrogen bonding of the neutral carbonyl moiety was postulated, which later was refuted. They demonstrated that their acyl-Pictet–Spengler reaction does involve the formation of the chiral ion-pair intermediate between catalyst **1** and the formed ionic intermediate upon acylation of the neutral imine (Scheme 2a). Subsequently, the enantiodifferentiation of prochiral *N*-acyliminium ions by chiral thiourea **1** could be applied in a Mannich-type reaction of isoquinolines (Scheme 2b).[9] To get a better insight into the nature of the substrate-catalyst interactions, ^{1}H NMR studies of the acyl-Pictet–Spengler type reaction with catalyst **2** were carried out. Therefore, *N*-acyl iminium ions were generated *in situ* by dehydration of hydroxylactams. In the presence of TMSCl as dehydrating reagent, the formation of the corresponding chlorolactam was fast and irreversible. A decrease of the conversion in the reaction was observed when the methyl substituent in alpha to the N-atom in the model substrate was replaced through a hydrogen atom. Due to this observation the possibility of an S_N2 could be eliminated and a S_N1 cyclization mechanism was postulated (Scheme 2c).[10]

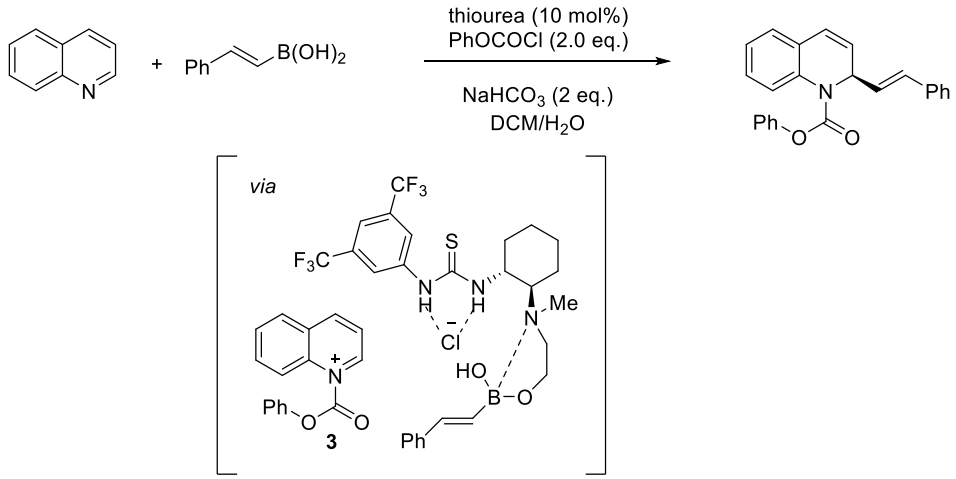


Scheme 2 Enantioselective thiourea-catalyzed a) acyl-Pictet-Spengler reaction; b) acyl-Mannich reactions proceeding *via N*-acyliminium ions; c) Pictet–Spengler-type cyclization of hydroxylactams and the proposed anion-binding mechanism.

Computational studies indicated that thiourea **2** was not bound to the carbonyl group due to the low Lewis basicity of the intermediates, but instead it is most plausible to be bound to the chlorine atom of the α-chloroamide. Furthermore, the thiourea catalyst **2** might assist the cleavage of the C-Cl bond with the formation of the resulting iminium ionic form. As it is depicted in Scheme 1, a close ion pair between the *N*-acyl iminium intermediate and the thiourea-chloride complex as chiral counteranion is formed, which is the responsible for the high chirality transfer of the reaction. The postulated anion-binding model found further support when the halide counterion and solvent effects were studied. Thus, a decrease in

enantioselectivity was observed with other halides (Br, 68% ee; I, < 5% ee) and polar solvents (MTBE, 97% ee; CH_2Cl_2, <5% ee). These experiments also agreed with a S_N1 mechanism. NMR-binding studies showed a 0.56 ppm downfield shift of the N-H protons of the thiourea when the catalyst was treated with a chloride source. This proofed a strong binding between the catalyst and the chloride anion. After these findings, intensive research directed to the exploration of new enantioselective transformations catalyzed by thioureas as anion-binders has been done.[11] Thus, the method has also been extended successfully to the regio- and enantioselective cyclization of pyrrole nucleophiles using the same thiourea catalyst **2**.[12] A rate acceleration due to increased substitution at the electrophilic center was observed, which also confirmed a S_N1 mechanism.

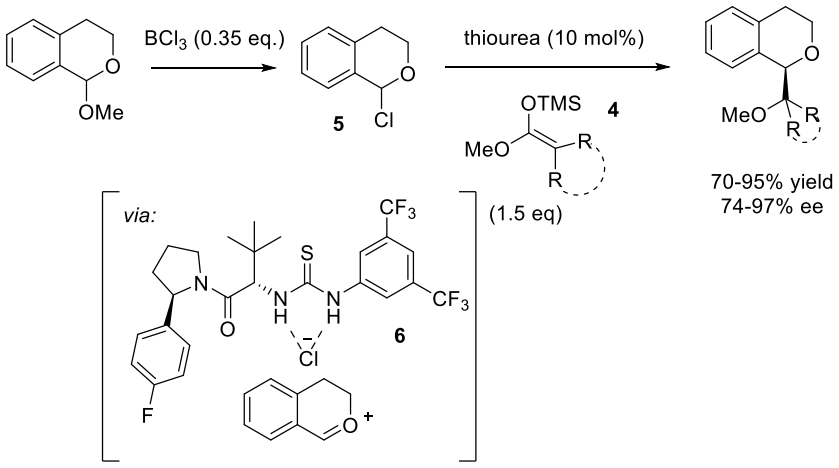
In 2007, Takemoto reported on the first asymmetric Petatis reaction catalyzed by a chiral bifunctional thiourea catalyst, which promotes the enantioselective addition of vinyl boronic acids to *in situ* generated *N*-acylquinolinium salts **3** (Scheme 3).[13] Although an activation of the substrate by H-bonding of the catalyst to the carbamate carbonyl group of substrate salt was proposed, an anion-binding mechanism is more likely to take place. Consequently, during the reaction, the 1,2-amino alcohol moiety of the catalyst formed a reactive boron-"ate" complex by chelating the boronic acid, while the thiourea moiety interacted with the *N*-acylquinolinium salt **3**.



Scheme 3 Thiourea-catalyzed enantioselective Petasis-type reaction of quinolines proceeding via *N*-acylquinolinium ions.

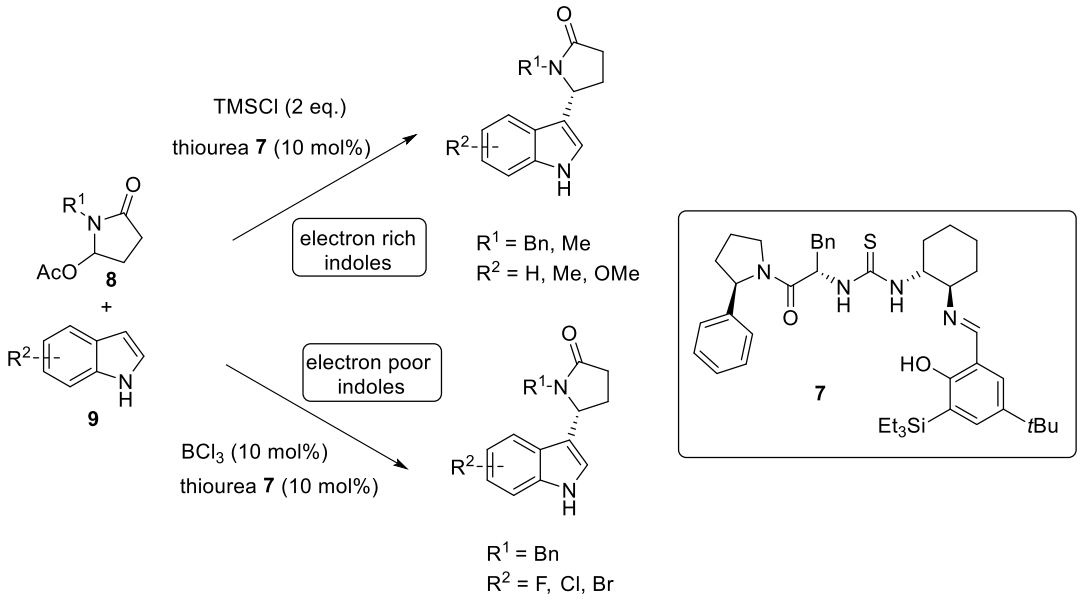
Later, Jacobsen and coworkers successfully applied the principle of asymmetric hydrogen-bond catalysis by anion binding to various cationic species, aside from iminium ions.[14] For example, the addition of silyl ketene acetals **4** to 1-chloroisochromanes **5** proceeded smoothly

with moderate to excellent yields and enantioselectivities (Scheme 4).[14b] The products were isolated in more than 50% yield and moderate to high enantioselectivities, which remained constant during the reaction, indicating that a dynamic kinetic resolution took place. Therefore, racemization of the chloroether starting material by thiourea-assisted chloride dissociation was required. Interestingly, the addition of *n*Bu_4NCl led to the inhibition of the reaction, indicating the binding of the chloride anions to the catalyst. This observation supported the concept of chloride binding catalysis. Due to poor enantioselectivities obtained in this reaction with the established catalyst **1**, the Jacobsen's group developed a new catalyst **6** with an additional aryl group at the amide unit.



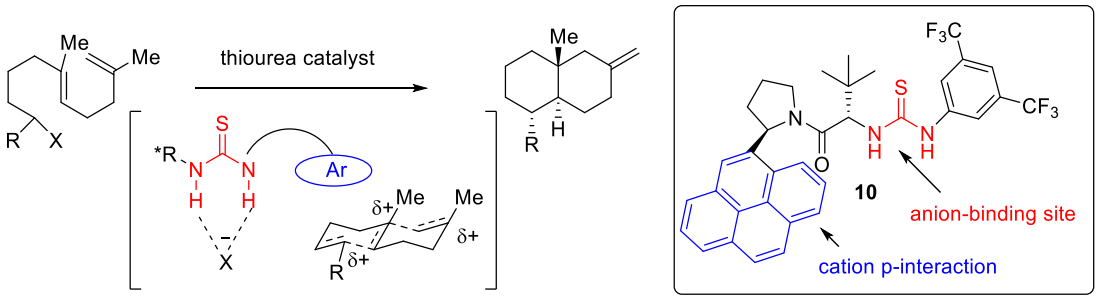
Scheme 4 Thiourea catalyzed additions to oxocarbenium ions.

After a longstanding two-years re-optimization of the catalyst structure to the newly designed thiourea catalyst **7**,[15] the same group was able to develop an intermolecular version of the reaction of acyloxylactams **8** with electron-rich and poor indoles **9** to form the corresponding substituted products with high enantioselectivities (Scheme 5).



Scheme 5 Intermolecular addition of indoles to cyclic *N*-acyliminium ions.

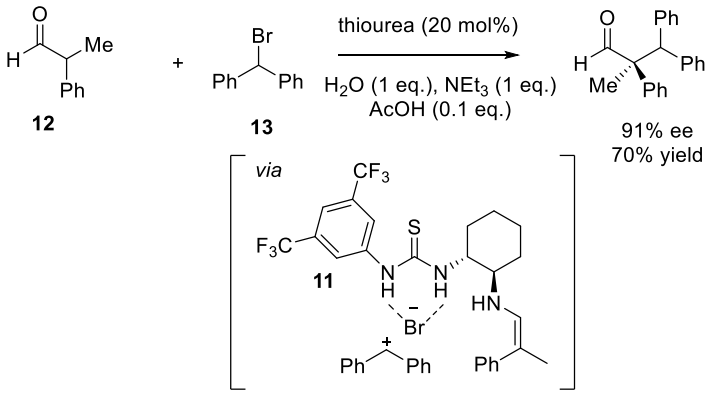
From these examples, it is already visible that catalyst design is not trivial and the different available thioureas are not generally applicable for every kind of reaction. From there on, huge efforts have been done in designing new catalyst systems with the aim of developing a general catalyst structure. These efforts have also led to a new concept of catalysts, which consists of the combination of two distinct recognition sites for both cationic and anionic moieties of the ionic substrate. Catalyst **10** was designed not only to bind a chloride anion within the thiourea moiety, but also to engage stabilizing cation π-interactions as a second fundamental recognition element (Scheme 6). This new concept was successfully employed in the cationic bicyclization of hydroxylactams to generate highly enantioenriched tetracycles.[16]



Scheme 6 Thiourea catalyst with two recognition sites.

Despite the well-established (thio)urea-chloride binding for halogen anion acceptor catalysis, bromide anions can also be used. A primary aminothiourea **11** was found to catalyze the enantioselective α-alkylation of α-branched aldehydes **12** with symmetrical

diarylbromomethanes **13** (Scheme 7).[14a] Since the thiourea catalyst **11** can also bind to the diarylbromomethane and promote a S_N2 type reaction, various mechanistic studies had to be performed. A normal secondary kinetic isotope effect for the benzhydryl proton indicated that the electrophilic carbon undergoes a rehybridization from sp^3 to sp^2 in the rate-determining transition state. A Hammett study proved that during the reaction a positive charge at the benzhydryl carbon in the transition state (p= -1.95) was developed. As a third study a competition experiment was performed by adding an equimolar amount of benzyl bromide to the catalytic reaction. The reaction showed a complete selectivity, in which only the alkylation of the bromodiphenylmethane was observed. These experiments led to the assumption that the reaction proceeded through a S_N1 mechanism as demonstrated in Scheme 6.



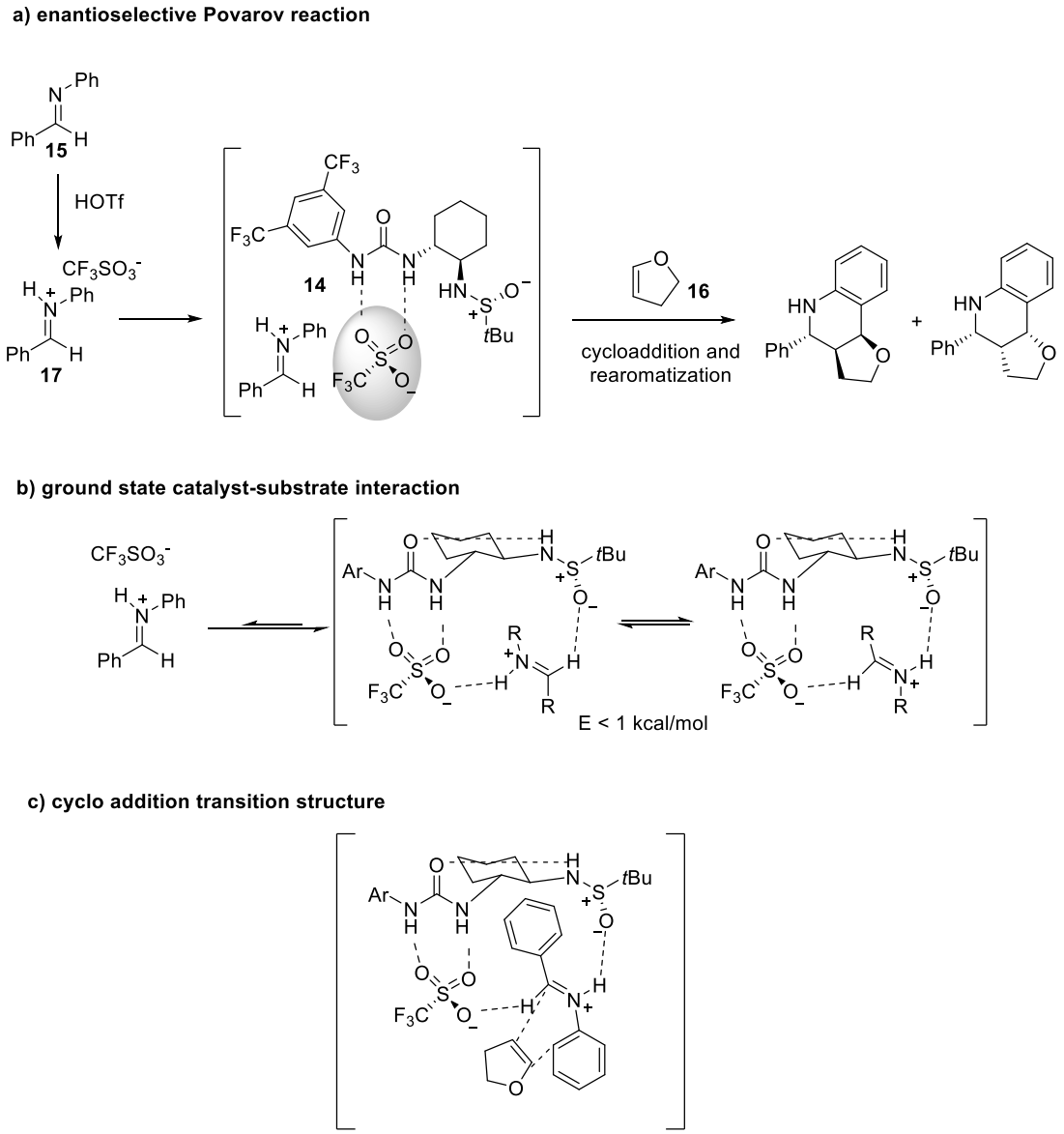
Scheme 7 Enantioselective, catalytic S_N1-type alkylation of aldehydes with benzhydryl cations.

Asymmetric chloride-binding hydrogen-bond catalysis has been applied successfully to several different classes of electrophiles. Additionally, taking bromide- and fluoride-[17] binding systems into account, ion-pairing catalysis using halide counterions presents a broad potential in asymmetric synthesis.

1.1.2 Sulfonate Anions

Besides the well-studied halide anions, sulfonate anions have gained increased interest in anion binding catalysis. In 2010, the first anion-binding-catalyzed enantioselective Povarov reaction was described by Jacobsen and coworkers.[18] They introduced the sulfonic acid/chiral urea catalytic system **14**, and an achiral sulfonic acid (TfOH) to promote the highly enantioselective [4+2]-cycloaddition of *N*-aryl imines **15** and electron rich olefins **16**. After the initial protonation of the imine to form a protonated iminium intermediate **17**, the urea catalyst **14** bind the sulfonate counter anion and a close ion pair between the formed catalyst-

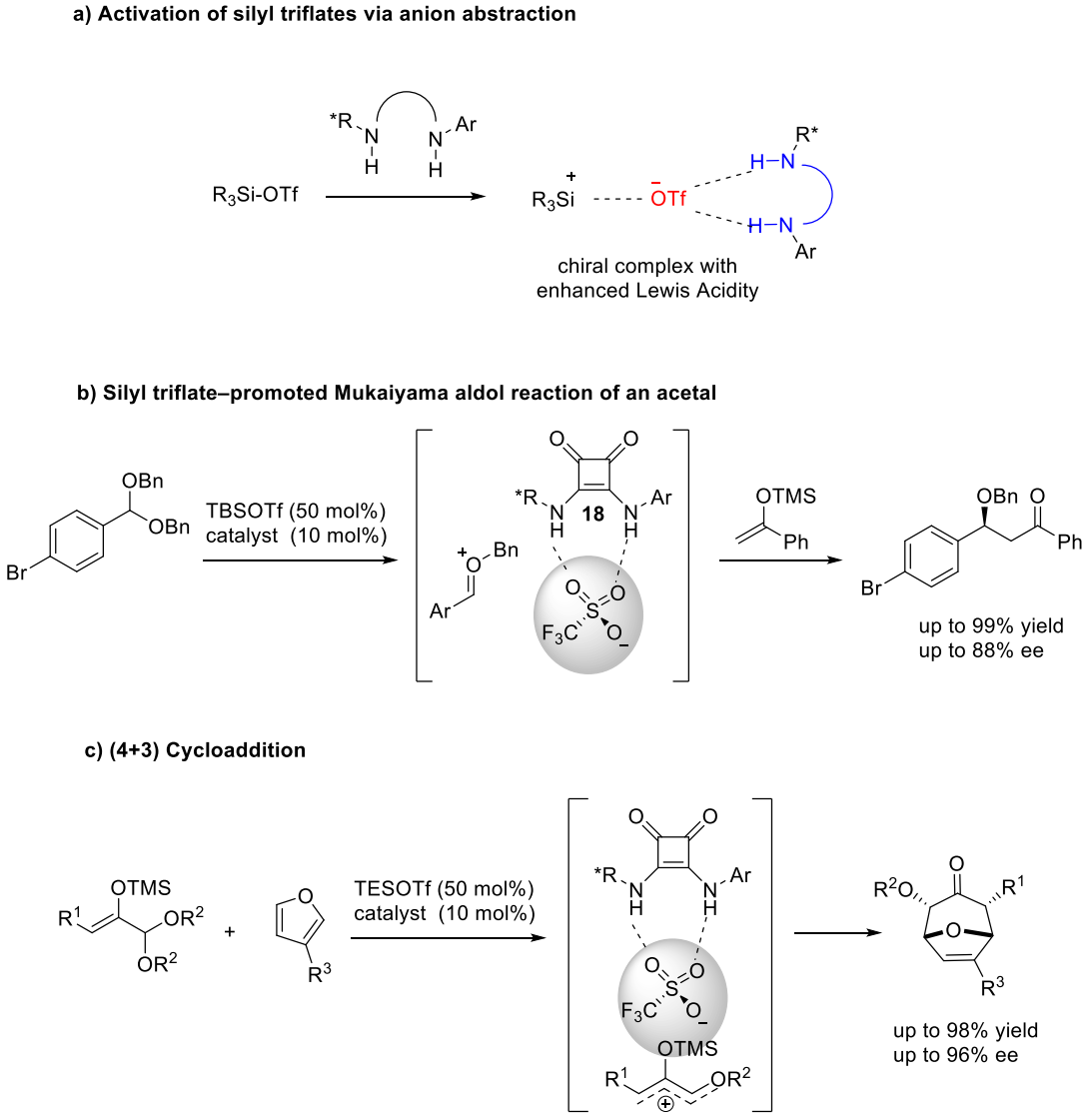
anion complex and the iminium substrate is formed (Scheme 8a). It was shown that both chiral moieties, the cyclohexyldiamino and the sulfonamide units, were crucial to obtain high enantioselectivities. Experimental and computational studies were carried out to get a better insight in the complex reaction system. With the bifunctional sulfonamide-urea catalyst **14**, a higher solubility of the protio-iminium sulfate, as well as a substantial decrease in the reaction rate, were observed. Thus, the decrease in reactivity led to the possibility of a higher stereoinduction control. Since the plain Brønsted acid-catalyzed reaction is several times faster, for the enantioselective version it must be guaranteed that no free triflic acid is available to promote the racemic pathway. Various data demonstrated that the high enantioselectivities were achieved because of the strong binding between the protio-iminium triflate **17** and the sulfinamido urea catalyst **14**. A large binding constant ($K = 9 \times 10^3\ M^{-1}$) was observed for the catalyst-protio-iminium sulfate complex. A dynamic structure was considered, consisting of electrostatic and hydrogen bond interactions (Scheme 8b). As it is shown in the proposed transition structure, the kinetic isotopic effect suggested a partial rehybridization of the ortho-carbon of the aniline in the rate-limiting step. This indicated a concerted, but highly asynchronous [4+2]-cycloaddition, followed by re-aromatization (Scheme 8c).



Scheme 8 a) Urea/strong Brønsted acid co-catalyzed enantioselective Povarov reaction (NBSA = *o*-nitrobenzenesulfonic acid); b) the ground state catalyst–substrate interactions; c) cycloaddition transition structure.

Recently, in 2017 Banik and Jacobsen published on a Lewis acid enhancement by hydrogen-bond donors for asymmetric catalysis.[19] A new mode of catalytic activation with chiral H-bond donors, which enables enantioselective reactions of relatively unreactive electrophiles, was introduced. In general, ureas, thioureas, squaramides and guanidinium ions show weak acidity and therefore require highly reactive electrophilic substrates to be effective. They proved that squaramide **18** can interact with silyl triflates by binding the triflate counterion to form a stable, yet highly Lewis acidic, complex (Scheme 9a). The silyl triflate-chiral squaramide combination promoted then the generation of oxocarbenium intermediates from acetal

substrates. Non-covalent interactions between the squaramide catalyst **18** and the oxocarbenium triflate can hence control the enantioselective addition of nucleophiles.



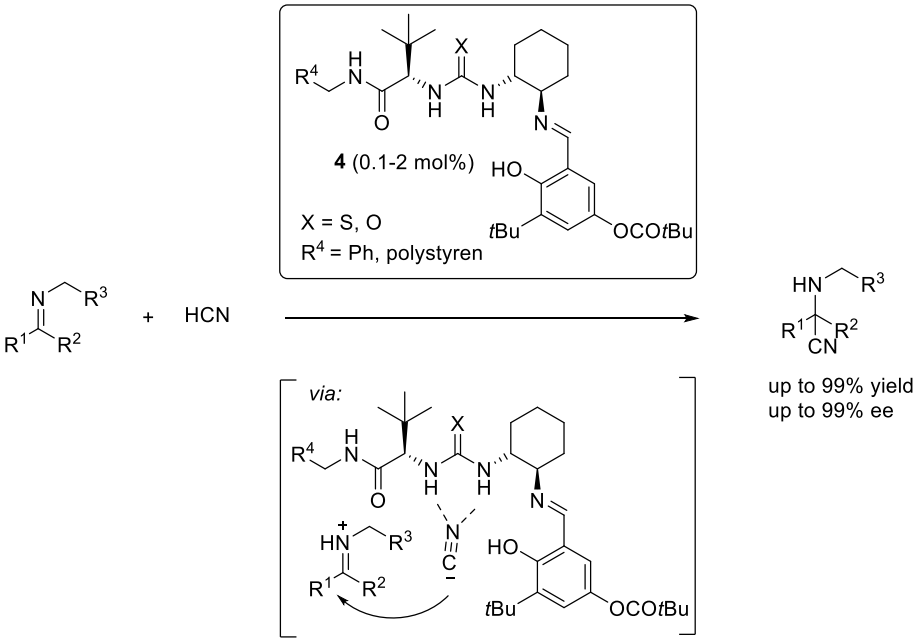
Scheme 9 a) Activation of silyl triflates *via* anion abstraction; b) Silyl triflate–promoted Mukaiyama aldol reaction of an acetal; c) [4+3]-Cycloaddition.

This activation principle was successfully applied to the generation of oxocarbenium ions from stable acetals for the Mukaiyama aldol reaction (Scheme 9b) and for highly demanding [4+3]-cycloadditions (Scheme 9c). Mechanistic studies for the [4+3]-cycloaddition were carried out to get a better insight in the catalytic mechanism. Kinetic data and titration experiments were consistent with a pre-equilibrium formation of a resting-state complex between the squaramide catalyst and TESOTf, displaying a 1:1 binding interaction between the catalyst and the anion.

Such type of detailed mechanistic studies[18-19] gave a better understanding of the stereochemical outcome of reactions controlled by non-covalent interaction between a catalyst and an ion pair intermediate.

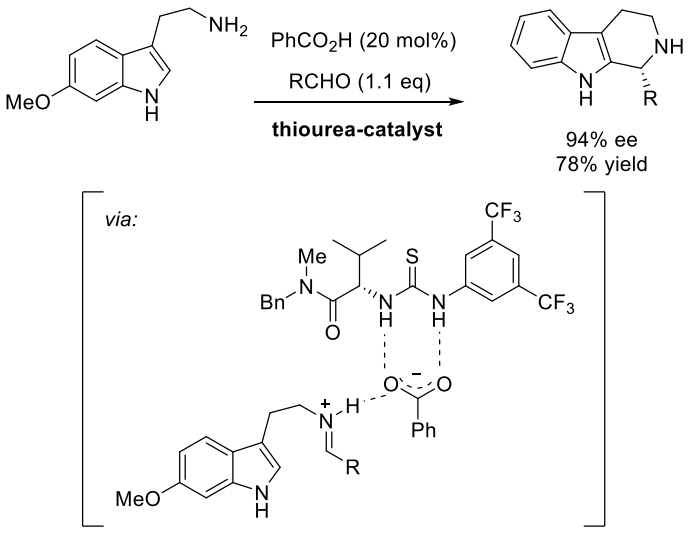
1.1.3 Cyanide and Carboxylate Anions

The use of cyanides as counterions in anion-binding catalysis was discovered by coincidence during the development of a metal-catalyzed enantioselective Strecker reaction of imines. It was found out that the reaction also proceeded without any metal. The group of Jacobsen then developed a thiourea-catalyzed asymmetric Strecker reaction, followed by extensive studies of their behavior (Scheme 10).[20]



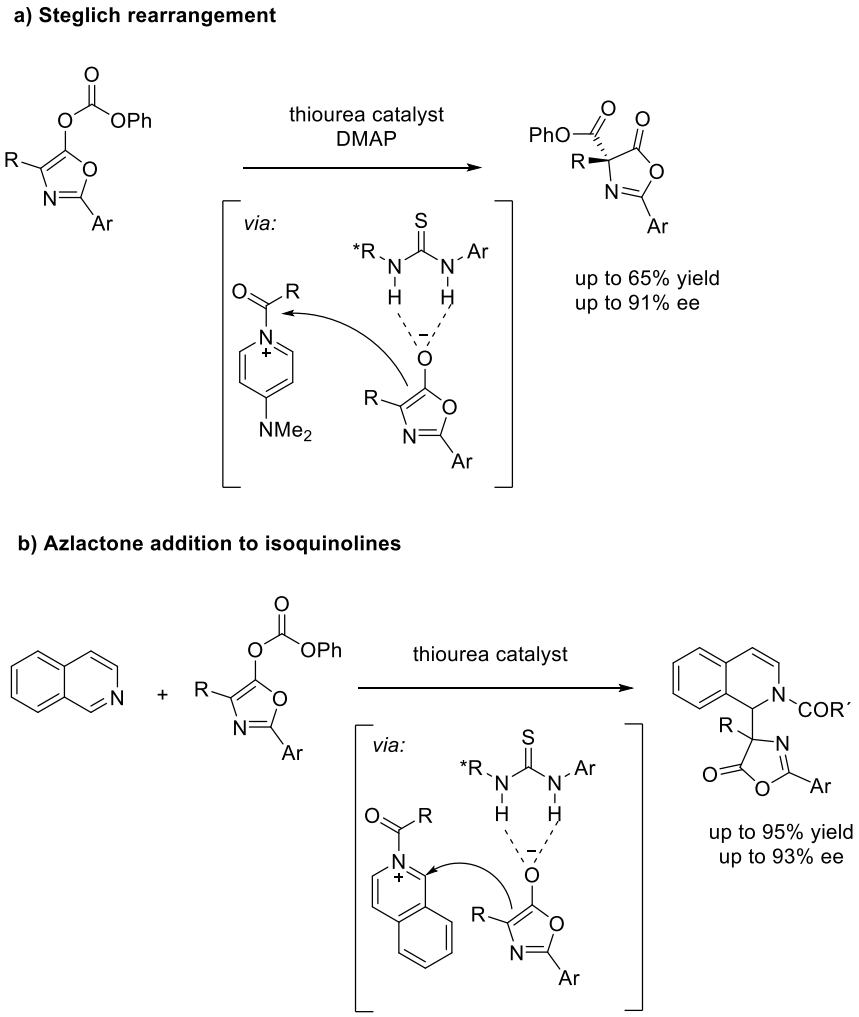
Scheme 10 (Thio)urea-catalyzed asymmetric Strecker reaction.

Like the sulfonate anions, carboxylates can also be efficiently bound by urea- and thiourea-based compounds in a bidentate fashion. Jacobsen and coworkers reported various protocols in this field. The reported enantioselective Pictet-Spengler[21] and iso-Pictet-Spengler[22] reactions with carboxylates as a counterion has contributed essentially to the further development in this area. The formation of a benzoate-iminium ion salt was proposed to be facilitated by hydrogen bonding of the thiourea catalyst (Scheme 11).



Scheme 11 Thiourea-catalyzed enantioselective Pictet-Spengler reaction.

In 2011, Seidel and his group developed an enantioselective version of the Steglich reaction by a rearrangement of O-acylated azalactones to the corresponding C-acylated compounds (Scheme 12a). Therefore, they employed a dual-catalysis approach by combining an achiral nucleophilic catalyst (DMAP) and a chiral anion-binding catalyst to provide α,α-disubstituted amino acid derivatives in a highly enantioselective fashion. By replacing the cocatalyst DMAP by isoquinoline they were able to synthesize highly functionalized enantioenriched α,β-diamio acid derivatives (Scheme 12b). The *in situ* formed acyl-isoquinolinium ion was attacked by the enolate at the 1-position of the isoquinoline ring yielding the desired products in high yield and enantioselectivities (up to 93% ee).[23]

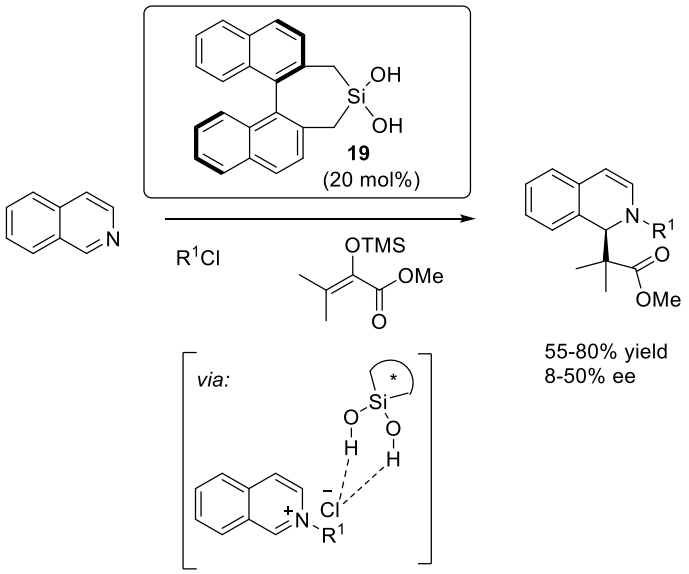


Scheme 12 a) Steglich rearrangement of O-acylated azalactones b) Azlactone addition to isoquinolines.

As it is demonstrated, the concept of anion-binding catalysis based on NH-bond donors represents an important field in organocatalysis and organic synthesis. Various publications and reviews can be found in literature,[3, 11, 24] whereby here only a few important works were presented.

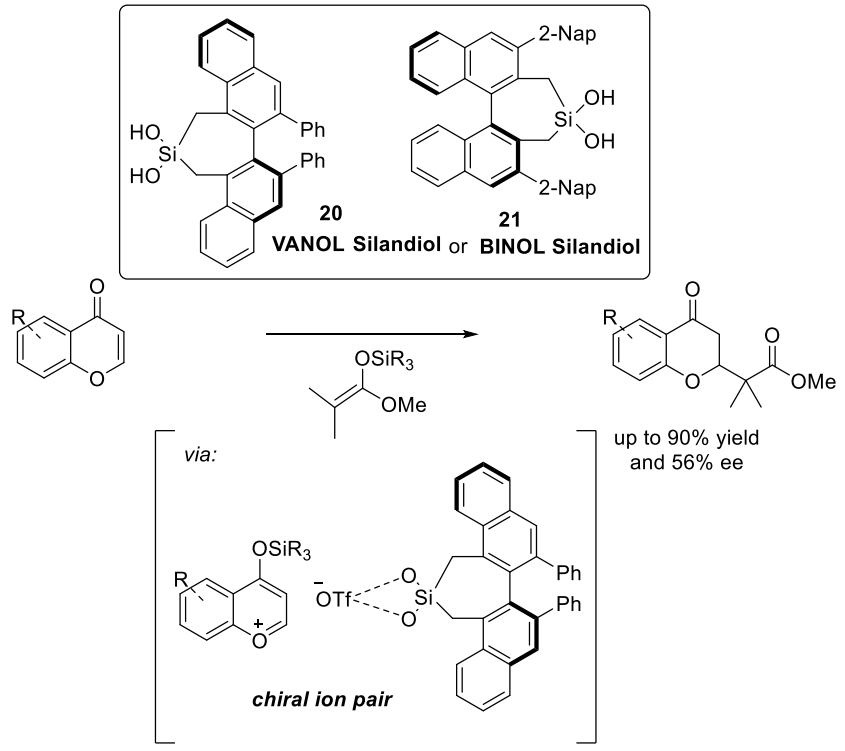
1.1.4 O-H Bond Donor Catalysts

As it can be seen in the previous sections, the enantioselective anion-binding catalysis is mostly dominated using (thio)urea-based catalysts. Alternatively, to (thio)ureas, in 2013 Mattson and co-workers found out that BINOL-based silanediols can not only act as hydrogen bond donors but could also be employed as catalysts in halide anion-binding catalysis. They applied a BINOL-based silanediol catalyst **19** in an enantioselective acyl-Mannich reaction with isoquinolines and obtained good yields and moderate enantioselectivities (up to 50% e.e., Scheme 13).[25]



Scheme 13 BINOL-based silanediol catalyst in an enantioselective acyl-Mannich reaction with isoquinolines.

In 2016, the same group reported a silanediol-catalyzed functionalization of chromenones.[26] They obtained promising levels of enantiocontrol (up to 56% e.e.) in the addition of silyl ketene acetals to benzopyrylium triflates. As it is shown in Scheme 14, silanediol catalyst **20** or **21** can bind the triflate anion and build a chiral ion pair. But still, in terms of enantioselectivity they could not reach the levels as with the well-established NH-based catalysts (50's *vs.* 90's e.e.).



Scheme 14 Silanediol-catalyzed chromenone functionalization.

The small amount of publications of alternative highly enantioselective anion-binding catalysts that are not NH-based demonstrates the difficulty in this field. The group of García Mancheño is dedicated to the development of a new class of anion binding catalysts based on the polarized C-H bonds of triazoles, aiming at opening a new field of C-H bonding. The earliest achievements reached in this field will be described in the following chapter.

1.2 Triazoles as Anion-Acceptors

1.2.1 From N-H to C-H

As mentioned above, the most common structures in anion-binding catalysis are N-H-based catalysts such as *e.g.* (thio)ureas, squaramides or guanidines. This is because of the strong bond polarity, which relies in the great difference between their electronegativities (H: 2.20 *vs.* N: 3.07). O-H-bonds also show potential as H-bond donors in anion-binding catalysis due to their even higher electronegativitiy difference (O: 3.50).[26-27] In contrast, the use of the less polarized C-H-bonds as hydrogen-donor moieties have been neglected, though they represent the most common bonds in organic molecules. Thus, some theoretical studies have shown that C-H bonds normally presents a binding strength of 50% of the N-H bonds.[28] However, in 2008 the groups of Flood,[29] Craig[30] and Hecht[31] published at almost the same time different triazole-based anion receptors able to coordinate to different anions in their cavity, showing a high selectivity for the chloride anion (Figure 2).

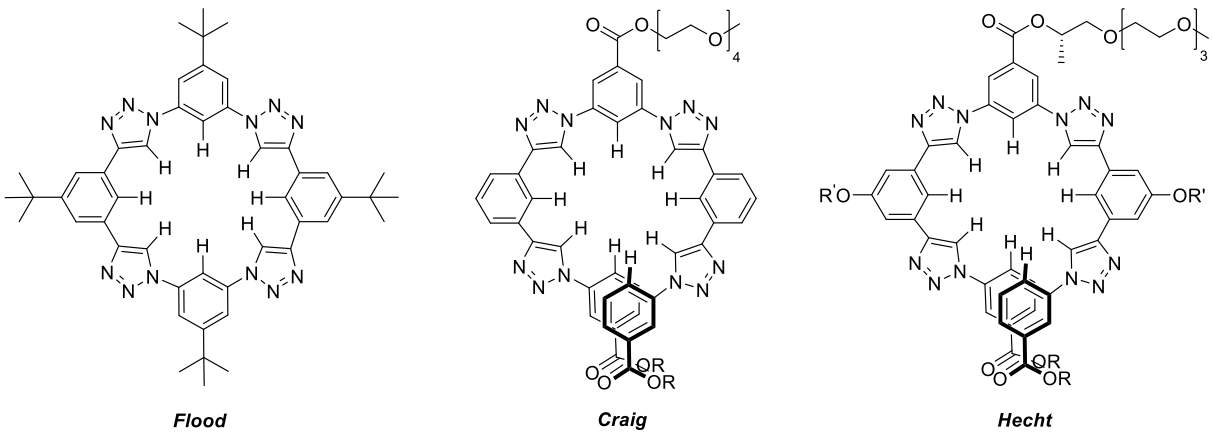


Figure 2 Triazole-acceptors developed by the groups of Flood, Craig, and Hecht.

Flood and coworkers designed triazolophane macrocycles bearing *tert*-butyl substituents at the backbone, which show a very high chloride anion affinity (K_a (1,3±0,3)·10^5 M^{-1}; ΔG= -7.0

kcal·mol^{-1} in CH_2Cl_2), even superior to N-H-based anion acceptors. Craig and Hecht developed two different foldamers, which adopt a helical conformation by binding to a chloride anion. Anion-binding studies suggested a comparable high binding constant to the chloride anion of K_a = 1.7·10^4 M^{-1} in acetone. Interestingly, all three groups utilized 1,4-disubstituted 1,2,3-triazoles as principal binding units in their systems. The triazole-moiety presents important characteristics such as a relative highly polarized C-H bond[32] and a large dipole moment (*e.g.* μ = 4.38 D) aligned with the C_5-H bond,[33] which emphasizes the polarization and a high acidity of its C-H bond (*e.g*. pKa = 27.8 in DMSO for 1-methyl-1*H*-1,2,3-triazole).[34] Additionally, triazoles are easy to synthesize by the well-established "click"-chemistry protocols using a Cu(I)-catalyzed azide-alkyne cycloaddition reaction (CuAAC) (Figure 3 a)).[35] Its polarized C-H bond, bearing an electropositive hydrogen atom, enables the formation of complexes with electronegative species such as anions (C-H···X$^-$) (Figure 3 b)).

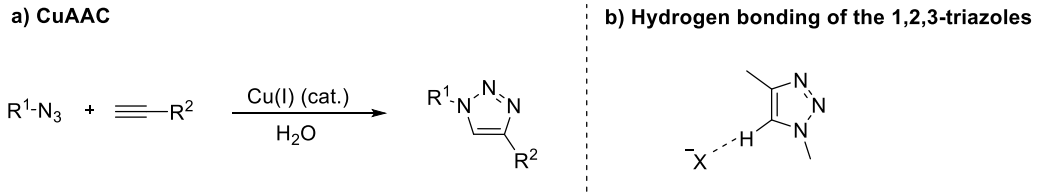


Figure 3 a) Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) and b) hydrogen bonding interaction.

Furthermore, Flood and coworkers found out that intramolecular hydrogen bonds between hydroxyl groups and the N_3-atom of the triazole led to a preorganized backbone, which enhance the affinities of the 1,2,3-triazole acceptors towards Cl$^-$ binding. Additionally, flexible aryl-triazole oligomers containing the same number or even more C-H bond donor units presented weaker binding constants compared to the rigid or rigidized structures (Figure 5).[36]

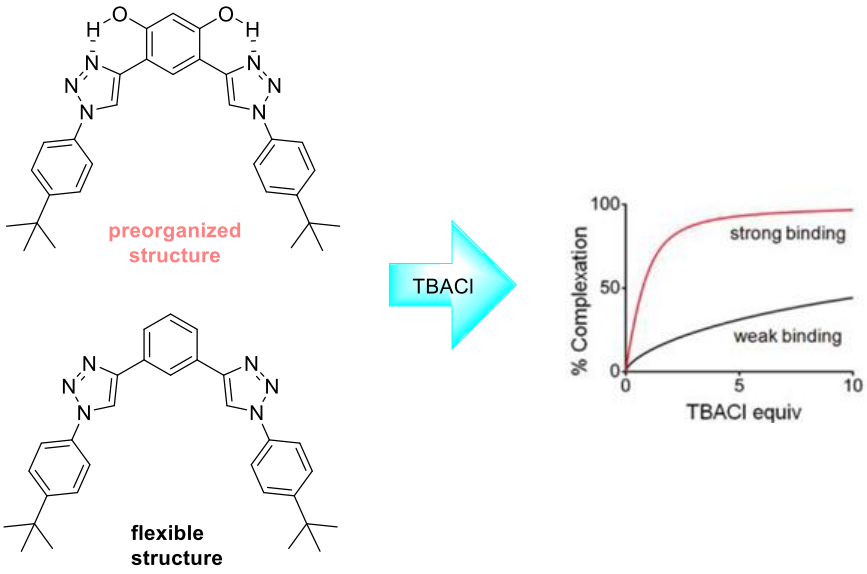


Figure 4 Chloride binding between preorganized and flexible 1,2,3-triazole structures.

1.2.2 "Click" Bis-Triazoles as Neutral C-H···Anion-Acceptor Organocatalysts

Considering the exceptional properties of triazoles, the unexplored function of the usually neglected 1,2,3-triazole as active group in organocatalysis was employed as a new valuable player to the field of anion-acceptor catalysis for the first time by our group.[37]

Firstly, to determine the binding constants (K), NMR titration studies of various new bistriazoles **BisTri** containing a 1,3-bistriazoylbenzene moiety were carried out (Figure 5a). While aliphatic substituents (**BisTri1**) led to a low binding constant, other bistriazoles, which bear different electronically varied aromatic substituents, showed enhanced binding affinities. Derivative **BisTri5**, bearing a 3,5-bis(trifluoromethyl)phenyl group, was identified as the best bistriazole chloride anion acceptor ($K_{a(acetone)}$ = 485 ± 56 M^{-1}). Its binding affinity was improved when THF was used as solvent ($K_{a(THF)}$ = 1417 ± 171 M^{-1}), whereas the use of DCM led to a notably lower binding constant ($K_{a(DCM)}$ = 108 ± 9 M^{-1}). The lower binding affinity of the **BisTri2** bearing an electronpoor perfluorophenyl substituents is in accordance with previous NMR-studies of thiourea catalysts by Schreiner *et al.*, which showed that the ortho-hydrogens of the 3,5-bis(trifluoromethyl)phenyl ring also participate in the binding to a chloride.[38]

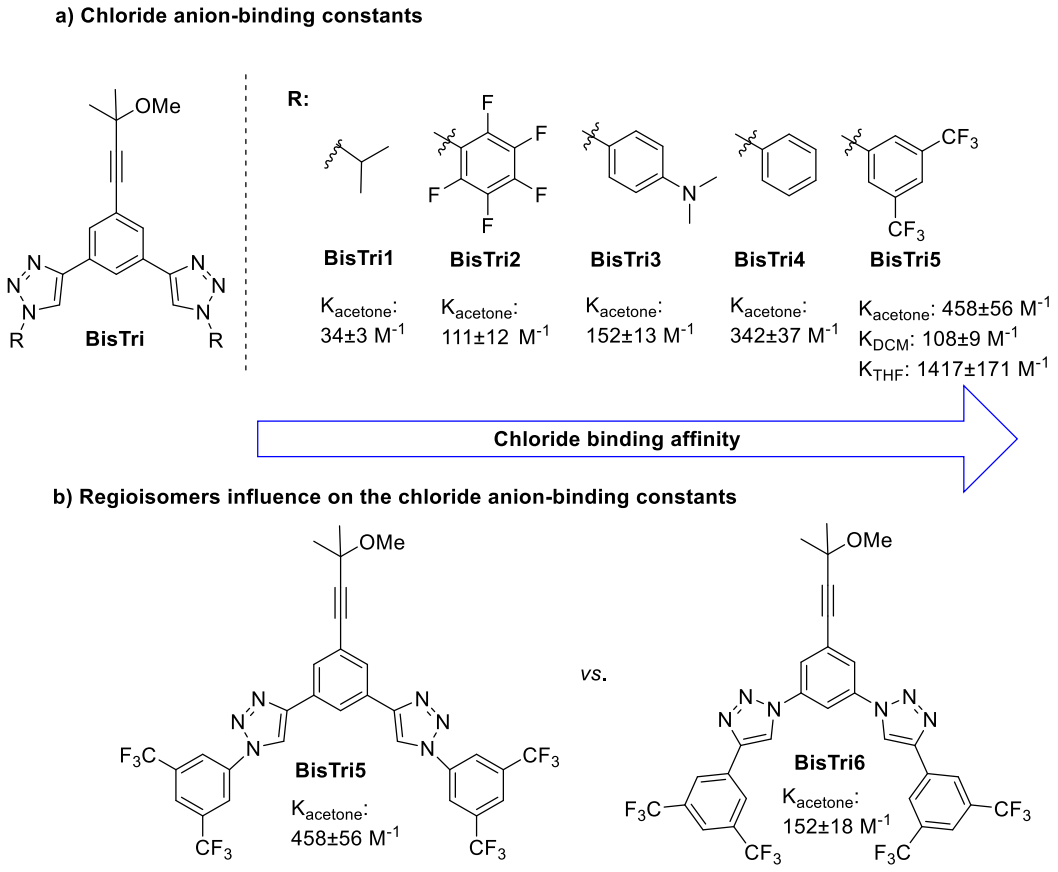
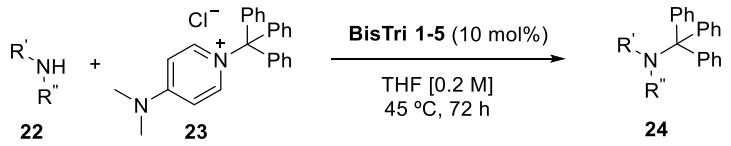


Figure 5 a) Chloride anion-binding constants: **BisTri 1-5** b) Regioisomers influence on the chloride anion-binding constants.

Interestingly, the regioisomer of **BisTri5**, **BisTri6**, showed a significantly lower binding constant, which indicated that a specific disposition of the triazoles in the structure is necessary for an effective chloride binding (Figure 5b). Next, the binding affinity of the best acceptor **BisTri5** towards different anions was studied. Halide anions showed a decreasing binding from chloride to iodide: Cl^- (K_{THF} = 1417±171 M^{-1}) > Br^- (K_{THF} = 438±11 M^{-1}) > I^- (K_{THF} = 319±24 M^{-1}). In contrast, the weakly coordinating TfO^- and BF_4^- anions did not show any interaction with the acceptor. Due to a space limitation in the triazole cavity the binding affinity is obviously associated with the size and electronegativity of the anion. The bigger the anion, the weaker was the affinity to a halide. A clear anion selectivity of the **BisTri5** for a chloride anion was obtained in this screening.

The **BisTri5** was then applied to the alkylation of benzylamine **22** with 4-dimethylamino-*N*-triphenylmethyl-pyridinium chloride **23** as ionic electrophilic substrate (Scheme 15). This reaction was chosen as a model reaction to test the use of the new designed C-H bond-based neutral anion-acceptors as organocatalysts. The reaction was carried out with 10 mol% of **BisTri5** and various amines, yielding the corresponding amine **24** in good yields. Later, by

applying **BisTri1-5** to the reaction, the correlation of the binding affinity of the triazoles to their catalytic activity was confirmed: the higher the chloride binding affinity, the higher the yield.



Scheme 15 *N*-alkylation reaction catalyzed by **BisTri 1-5.**

1.2.3 From BisTriazoles to Chiral TetraTriazoles

The studies of BisTriazoles proved that simple C-H bonds can be effectively used for anion-binding catalysis.[37, 39] Nevertheless, the demand for the asymmetric version of C-H bond donors as anion-binding catalysts was still elusive. As a consequence, in 2014 our group was able to report for the first time on chiral helical oligotriazoles as a new class of anion-binding catalysts.[40] Based on the results with the **BisTri** catalysts, they designed extended, flexible structures with four triazole units (**TetraTri**) (Figure 6 a)). Under normal conditions in solution, the structure present an equilibrium between the linear and helical conformations. However, upon complexation to a chloride anion, a reinforced defined helical system was envisioned (Figure 6 b)).

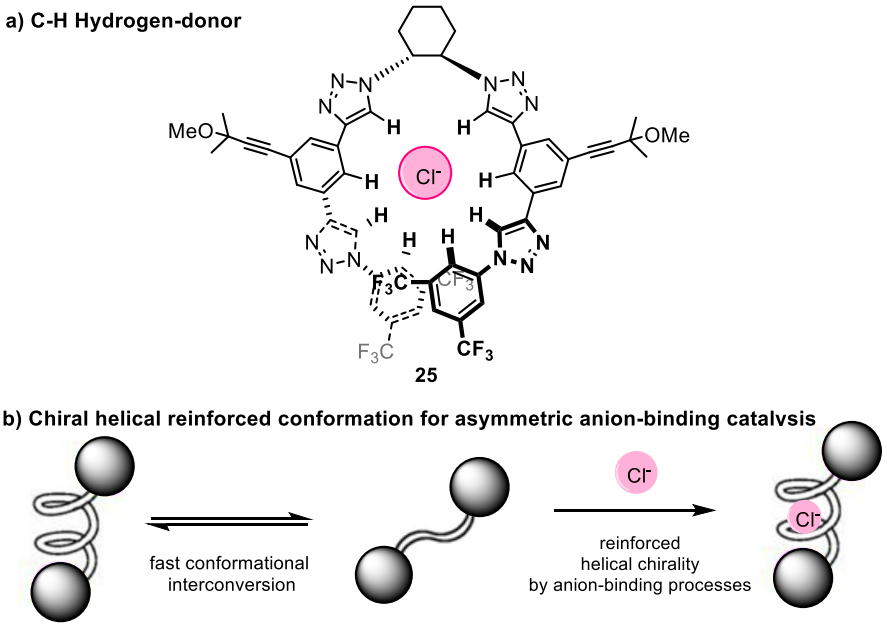


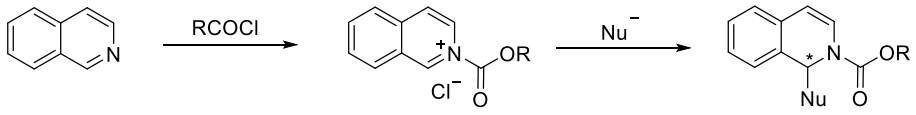
Figure 6 a) Designed triazole-based catalysts b) Chiral helical reinforced conformation for asymmetric anion-binding catalysis.

The fact of introducing another two triazole units into the system gave a few advantages. First, the binding affinities are much higher than the ones of the BisTriazoles and second, by enhancing the size of the catalyst, the system cannot adopt a fully planar geometry during binding the anion like in the case of the BisTriazoles. Instead, a helical geometry is formed like it is represented in Figure 6. By introducing the chirality into the TetraTriazole through a chiral *trans*-diamine backbone, the resulting C_2-symmetric TetraTriazole-anion complex during the reaction can then transfer its chirality information to a target molecule. The effective binding to a chloride anion was confirmed by CD (circular dicroism) titration of the tetrakistriazole catalyst **25** with tetrabutylammonium chloride (TBACl) as chloride anion source. A strong CD effect was observed when increasing the amount of TBACl. This led to the suggestion that various possible flexible open-chain conformers might be present in solution. However, upon addition and binding to a chloride anion a more rigid chiral helical catalyst-anion complex structure is formed, enhancing the population of the less thermodynamically stable catalyst's helical conformation.[31, 41]

This interesting catalyst system was then introduced in various enantioselective dearomatization reactions of heteroarenes. The progress and outcome of these studies will be described in the following sections.

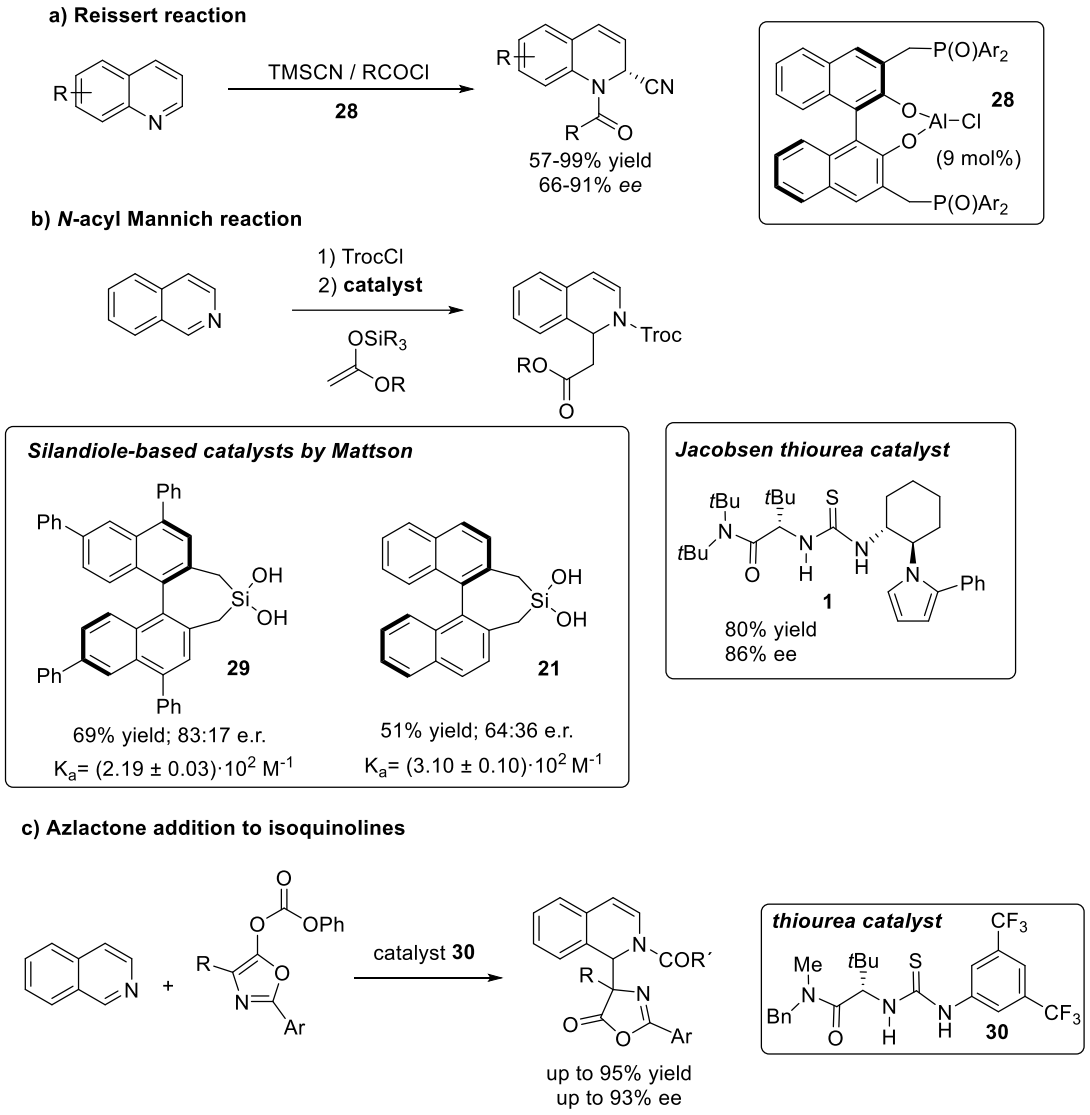
1.3 Preliminary Work on Enantioselective Dearomatization of *N*-Heteroarenes by Anion Binding Catalysis

Since enantioselective dearomatization reactions of heteroarenes represent a powerful tool for the synthesis of bioactive and synthetically valuable chiral heterocycles, there is a great interest on the development of new catalytic systems to obtain the desired structures. There are various approaches reported in literature for achieving enantioselective dearomatization reactions. Those depend on transition metal catalysis,[42] hydration methods,[43] cycloaddition reactions,[44] nucleophilic dearomatization[45] and the organocatalyzed dearomatization of heterocycles. Since our investigation interest relies on the organocatalytic dearomatization of nitrogen and oxygen containing heterocycles, this section should give an overview of the state-of-the-art in this field. An interesting dearomatization approach consists in the activation of an *N*-heteroarene employing an acylating agent to generate the corresponding *N*-acyl iminium species.[46] This intermediate could then react with a nucleophile, generating a new stereocenter (Scheme 16).



Scheme 16 Reissert-type reaction of isoquinolines.

Pioneer work was done by Shibasaki *et al*., in which a chiral BINOL-derived aluminium catalyst **28** was employed in the Reissert reaction of quinolines and isoquinolines, leading to the corresponding nitrile products in moderate to good enantioselectivities (66-91% e.e.) (Scheme 17a).[45b, 45c] This metal-catalyzed method was followed by the already mentioned work of Jacobsen and coworkers (Scheme 17b), which implied the thiourea organocatalyst **1** for the *N*-acyl-Mannich reaction of isoquinolines.[9] As shown before, the same *N*-acyl Mannich reaction was later carried out by Mattson *et al.*, employing silandioles **29** and **21** as anion-binding catalysts, leading to the desired products in moderate yields and enantioselectivities.[25] As a further example, the addition of azolactones to isoquinolines catalyzed by a thiourea catalyst **30** by Seidel *et al*. must be mentioned. The dearomatized isoquinoline derivatives were obtained in high yields and enantioselectivities (Scheme 17c).[23]

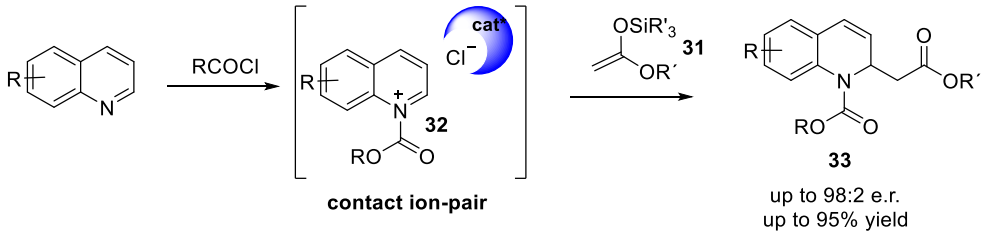


Scheme 17 Enantioselective dearomatization by a) Reissert reaction and b) *N*-acyl Mannich reaction c) Azolacton addition to isoquinolines

New entries for this type of catalytic dearomatization reactions were achieved with our novel chiral triazole-based catalysts, which allowed the extension different *N*-heteroarenes including the highly demanding pyridines. These methodologies are presented in more detailed the following sections.

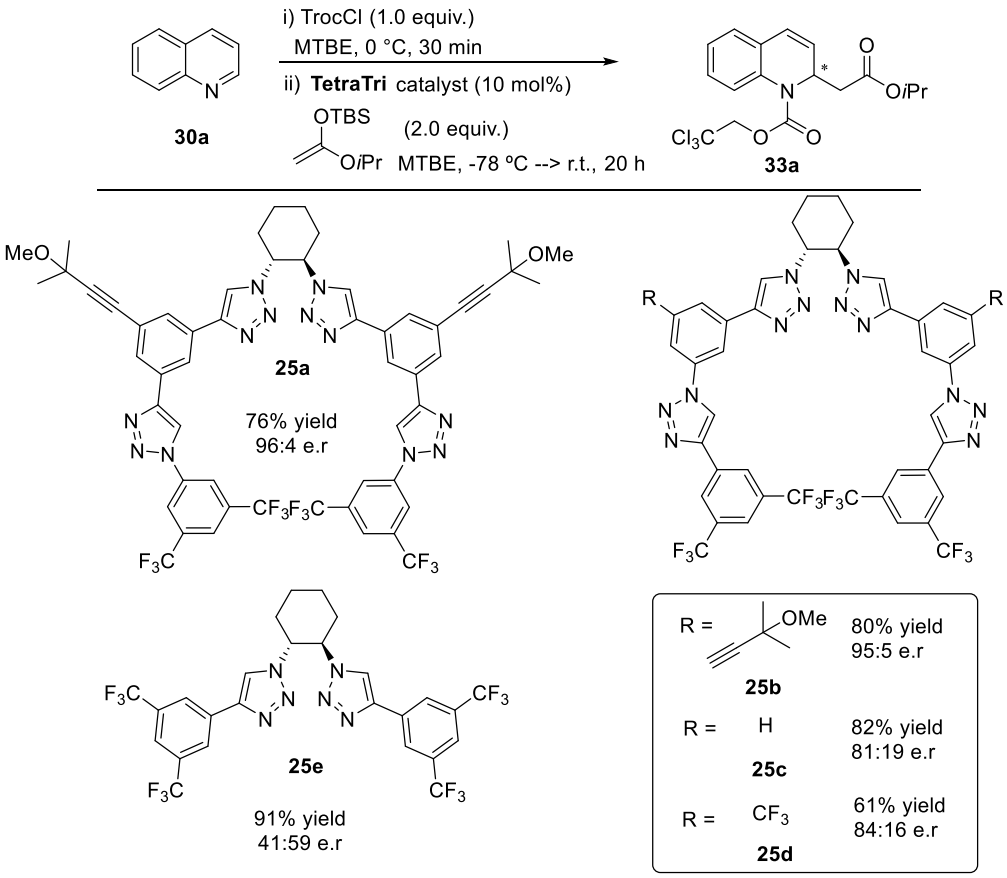
1.3.1 Dearomatization of Quinolines with Chiral Triazole Catalysts

1,2-Dihydroquinolines are important synthetic intermediates in the preparation of biological active compounds.[47] Therefore, and inspired by the seminal work of Jacobsen, the addition of silyl ketene acetals **31** to *N*-acyl iminium quinoline substrates **32** in the presence of catalytic amounts of chiral TetraTriazoles was carried out to obtain synthetically valuable 2-substituted chiral 1,2-dihydroquinolines **33** (Scheme 18).[40]



Scheme 18 Enantioselective dearomatization of quinolines by triazole-based anion-binding catalysis.

A catalyst screening of different triazole-based catalysts identified **25a** as the best catalyst in terms of enantioselecivity (96:4 e.r.) (Scheme 19).



Scheme 19 Screening of various triazole catalysts.

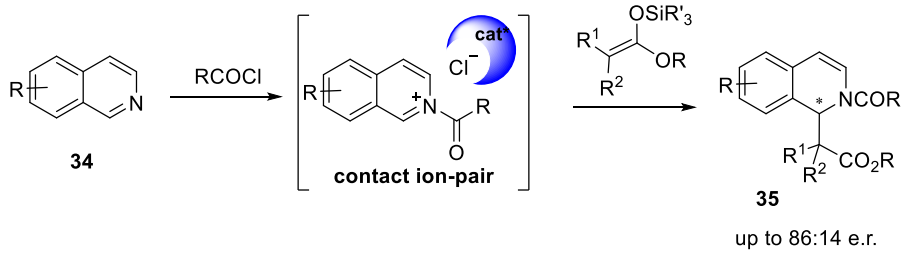
After an initial optimization of the reaction conditions this transformation was applied for a wide number of substituted substrates (>16 examples), leading to high enantioselectivities up to 98:2 e.r. in the final chiral product.

^{1}H-NMR titration and Circular dichroism (CD) titration of the catalyst (*R,R*)-**25** with either preformed quinolinium chloride or Bu_4NCl was carried out to get a better understanding of the activity of the **TetraTri** catalyst. ^{1}H-NMR titration consisted a clear downfield shift of the proton signals of the C–H bonds of the triazoles and therefore a cooperative H-bond to the

chloride anion can be suggested. By CD spectroscopy conformational changes of structures can be observed. The titration curve of a chloride anion to (*R,R*)-**25** (from Bu_4NCl) led to the assumption of a reinforced catalyst helical structure upon the coordination to a Cl^- anion.[40]

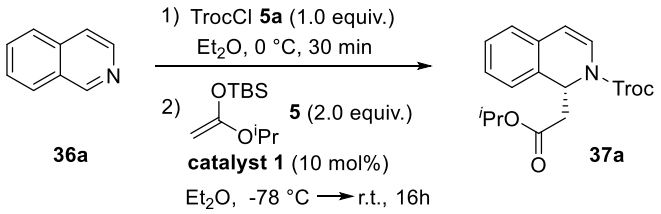
1.3.2 Dearomatization of Isoquinolines

The triazole-based catalysts **25** could be also applied successfully to the enantioselective dearomatization reaction of isoquinolines **34**, providing the desired products **35** in good yields and moderate to good enantioselectivities (Scheme 20).[48]

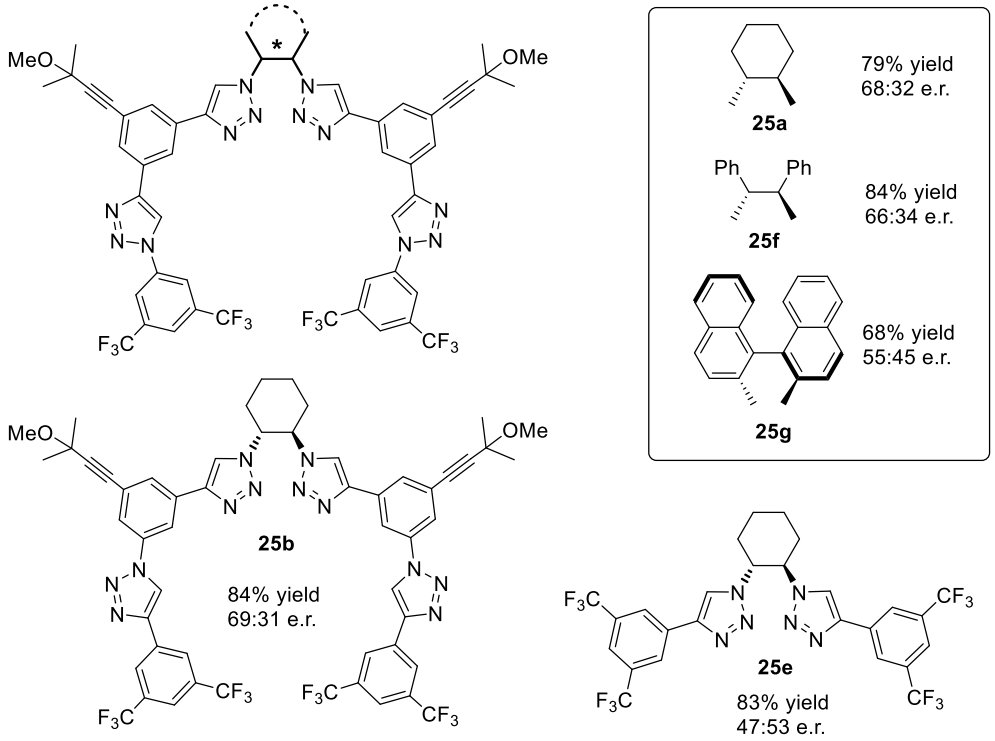


Scheme 20 Enantioselective *N*-acyl Mannich reaction of isoquinolines by triazole-based anion-binding catalysis.

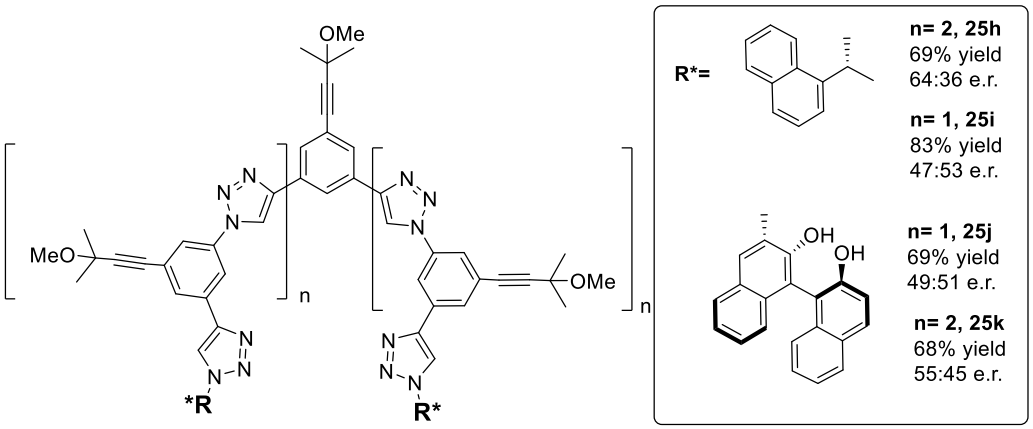
First, the focus was placed on a detailed catalyst screening. Different BisTriazoles and TetraTriazoles with chirality at the centered backbone, and TetraTriazoles and HexaTriazoles with chirality at the end-chain were tested. The catalysts bearing the chirality at the central backbone were clearly superior to the ones with chirality at the end-chain. Consequently, the highest enantioselectivities were induced by the catalysts **25a** and **25b** presenting four triazole and the chiral *trans*-(*R,R*)-1,2-diaminocyclohexane unit (aprox. 70:30 e.r., Scheme 21). After an optimization of the reaction conditions, various isoquinolines and silyl ketene acetal nucleophiles were successfully applied (14 examples, up to 86:14 e.r.).



a) BisTriazole and TetraTriazoles with chirality at the centered backbone



b) TetraTriazoles and HexaTriazoles with chirality at the end-chain



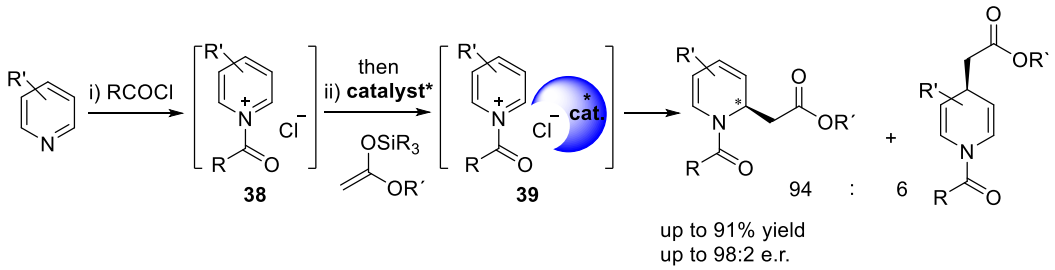
Scheme 21 Family of chiral triazole-based catalysts, with chiral moiety at a) the backbone and b) the end-chain.

To sum up, a straightforward and enantioselective method for the dearomatization of isoquinoline substrates employing triazole-based chiral catalysts was developed.

1.3.3. Dearomatization of Pyridines

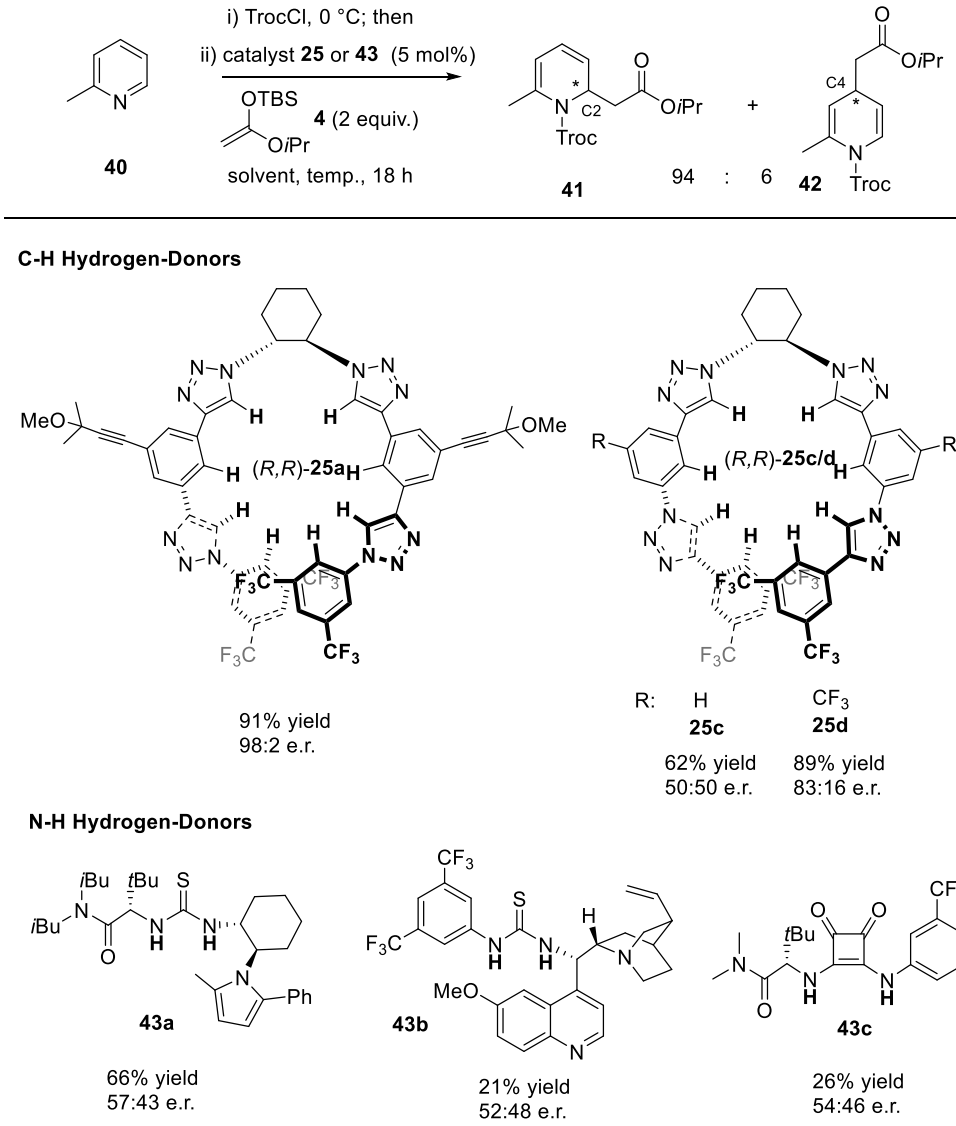
Partially hydrogenated pyridines and piperidine derivatives constitute an important class of compounds widely present in naturally occurring and synthetic substances with a broad bioactive spectrum.[49] Important characteristics of pyridines include their intrinsic electrophilic reactivity at both the C2 and the C4 position, which causes an important regioselectivity issue. Furthermore, upon nucleophilic attack, the aromaticity of the system will be completely broken due to the fact that no other aromatic ring is present like in the (iso)quinoline structures. For that reason, reports on this field are still rare and effective and selective catalytic processes are still challenging. The direct dearomatization of pyridines *via* the formation of their pyridinium salts represents the most efficient method for the synthesis of these kind of enantioenriched products.[45d, 50]

After the promising results with quinolines and isoquinolines, the dearomatization reaction of a more fascinating but also more challenging substrate: the pyridine was studied with the C-H-bond donor triazole catalyst developed in our group. Thus, we were able to report on a highly nucleophilic dearomatization reaction of pyridines with silyl ketene acetals. An effective chiral transfer to the final dihydropyridine product was achieved from the *in situ* formed chiral contact ion-pair **39** between the ionic intermediate **38** and the catalyst–anion complex (Scheme 22).[51]



Scheme 22 Asymmetric dearomatization of pyridines by triazole-based anion-binding catalysis.

After an initial optimization of the reaction using 2-picoline **40** as a model substrate, an excellent 94:6 regioselectivity towards the C2-addition product **41** was obtained. Moreover, the dearomatized product **41** presented an excellent enantiomeric ratio of 98:2. It was shown that our C-H-bond donor catalyst **25a** was superior to the more common N-H-donor catalysts such as thioureas (**43a/b**) or squaramides (**43c**), which led to lower regioselectivities in favor for the 1,4-addition product **42** and hardly no enantiomeric induction for both regioisomers (Scheme 23).



Scheme 23 Hydrogen donor catalysts tested in this study.

Interestingly, the regioisomeric outcome showed a high dependence on the substitution of the pyridine substrate. 2- and 4-substituted pyridines showed a preference for the formation of the 1,2-addition products, whereby a C3-substitution mainly gave the 1,4-addition product or a mixture of the 1,4- and the most crowded 1,2-addition products.

These reports showed the high potential of the C-H bonds of 1,2,3-triazoles for promoting highly enantioselective catalytic reactions. Therefore, the triazole-based anion-binding catalysts developed in our research group constitute alternative H-donor structures. The main part of this thesis deals with the discovery of new enantioselective transformations employing these triazole-based catalysts and it will be extensively discussed in the following chapters 2-4.

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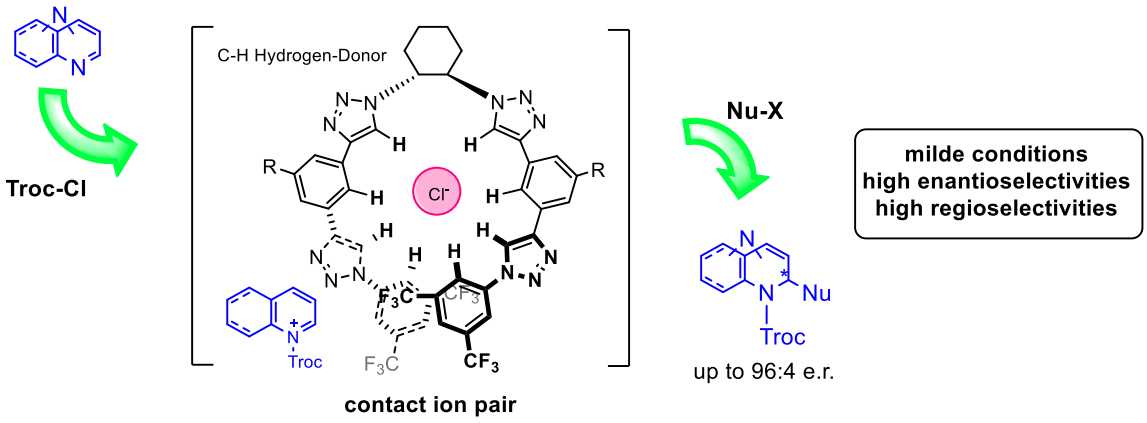
Chapter 2

2. Enantioselective Dearomatization of Diazarenes by Anion-Binding Catalysis



Abstract: The first anion-binding organocatalyzed enantioselective Reissert-type dearomatization of diazarenes has been developed. This reaction represents a synthetic challenge since diazarenes have various reactive sites. The use of a chiral tetrakistriazole as a C–H-based hydrogen-donor catalyst allowed the straightforward highly regio- and enantioselective synthesis of a variety of chiral diazaheterocycles

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Preliminary work for the dearomatization of diazarenes was already performed: Theresa Fischer, *Master Thesis, University of Regensburg* **2015**.

Author contribution:

Theresa Fischer:	80% of reproduced part: Initial optimization, catalyst screening, screening of the acylating agent and silyl ketene acetal, scope of the reaction with various diazarenes, 50% of the derivatization of **5a**
Julia Bamberger:	20% of the screening of the acylating agent (Table 3); 50% of the derivatization of **5a** (Scheme 6)
Olga García Mancheño:	corresponding author

2.1 Introduction

Chiral diazaheterocycles and their partial unsaturated derivatives are important naturally occurring substances and building blocks for the synthesis of bioactive compounds with a broad activity spectrum.[2] A few examples of relevant natural and synthetic bioactive di-nitrogen-containing chiral hetero- cycles are shown in Fig. 1.

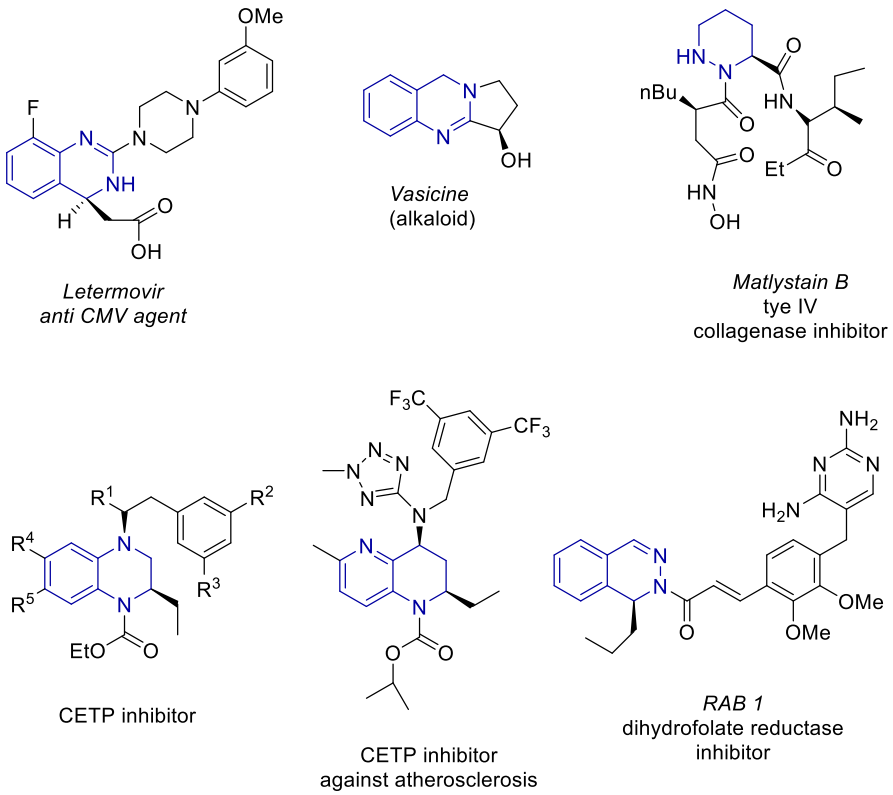
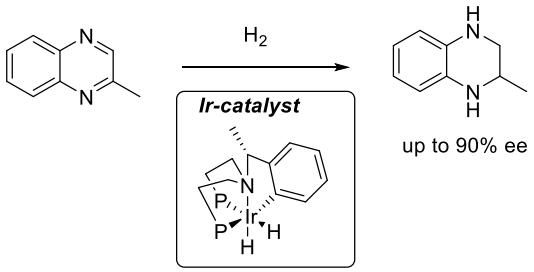


Figure 1 Representative dugs and bioactive pyridine-derived or di-*N*-heterocycles.

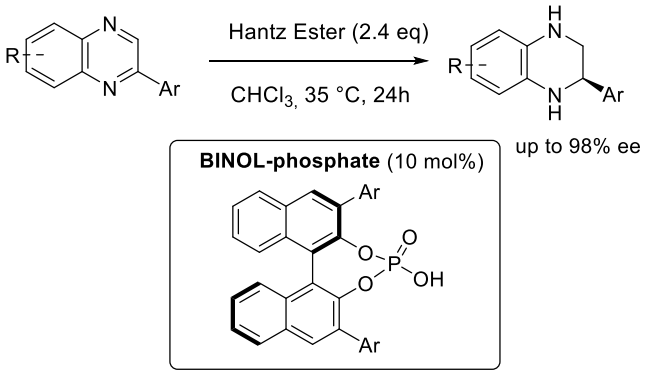
Among some interesting quinazoline derivatives, letermovir[3] is one of the top-selling antiviral drugs developed for the treatment of Cytomegalovirus infections and the alkaloid vasicine[4] is a cardiac-depressant. Moreover, based on a pyrazine moiety, matlystain B shows collagenase inhibitor properties.[5] Other di- or tetrahydrostructures based on diazarenes such as quinoxaline, naphthyridine or phthalazine present relevant biological activities such as CETP inhibition against atherosclerosis,[6] anti-dyslipidemia[7] or dihydrofolate reductase inhibition towards antibiotic-resistant Gram-positive bacteria.[8] Despite the great diversity of applications of chiral diazaheterocycles, there is still a demand of simple, mild and direct synthesis methods. Most of the common routes to chiral diazaheterocycles require long and tedious synthesis from chiral starting materials and normally involve the generation of at least one of the N-heterocyclic rings.[2] A more appealing and straightforward approach consists of

the enantioselective dearomatization of readily available diazarenes.[9] In this regard, the main method for inducing chirality relies on catalyzed asymmetric hydrogenation reactions of substituted azarenes,[10] for which several transition metal-catalyst systems consisting of rhodium, iridium or ruthenium complexes have been developed in the last past decades (Scheme 1).[10] A breakthrough in asymmetric hydrogenation of aromatics was done by Bianchini and his group in 1998. They reported on a hydrogenation of 2-methyl-quinoxaline catalyzed by a *ortho*-metalated dihydride iridium complex (Scheme 1). Later a lot of work was done in this field, yielding the dearomatized products in good enantioselectivities.[10]



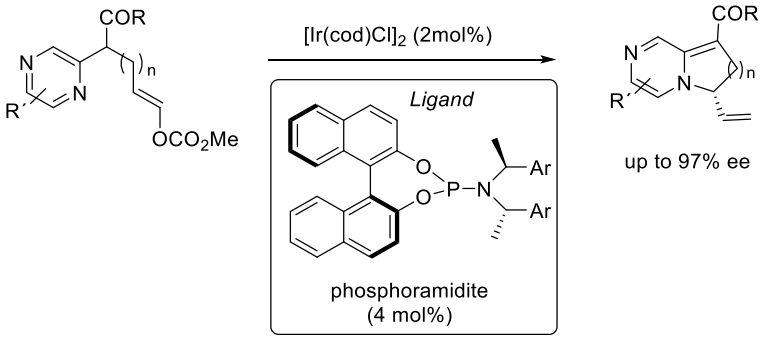
Scheme 1 Transition metal – catalyzed asymmetric hydrogenation of quinoxalines.

More recently, many efforts have been set to overcome the need of transition metals. Consequently, in 2010 Rueping *et al.* first developed an organocatalytic transfer hydrogenation approach to the synthesis of tetrahydroquinoxalines.[11] 2-Arylquinoxalines were hence reacted with Hantzsch esters upon activation with catalytic amounts of a chiral BINOL-phosphate as catalyst to provide the corresponding tetrahydroquinoxalines in good yields (73-98%) and excellent enantioselectivities (80-98% ee) (Scheme 2). However, applying these reaction conditions to alkyl-substituted quinoxalines resulted in lower enantioselectivities (up to 64% ee).



Scheme 2 Organocatalyzed asymmetric transfer hydrogenation of quinoxalines.

Besides asymmetric hydrogenation, the enantioselective nucleophilic addition to *N*-heteroarenes represents a powerful tool towards the dearomatization of such systems. Several methods based on this approach have been developed for mono *N*-heteroarenes,[9c, 12] however, to the best of our knowledge only one example for diazarenes has been described to date. The group of You reported an iridium-catalyzed intramolecular asymmetric allylic dearomatization reaction of pyrazines. 6,7-dihydropyrrolo[1,2-a]pyrazine derivatives were obtained with excellent yields (up to 95%) and enantioselectivity (up to 97% ee) (Scheme 3).[13]



Scheme 3 Asymmetric allylic dearomatization.

2.2 Objectives

In this chapter, we aimed at developing an efficient, highly regio- and enantioselective dearomatization methodology for diazarenes based on an anion-binding catalysis.

The fact that there are only scarce both metal- and organocatalytic enantioselective examples in this field could be explained due to the presence of a larger number of reactive sites of diazarenes and therefore the possible generation of a complex mixture of products, which makes the dearomatization of this type of compounds highly challenging (Figure 2).

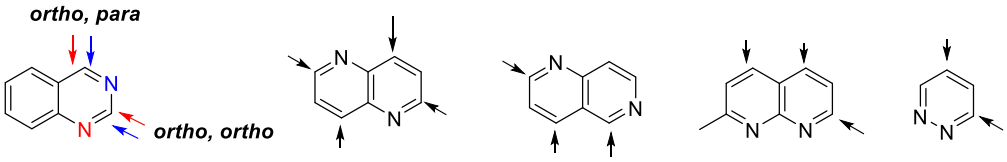
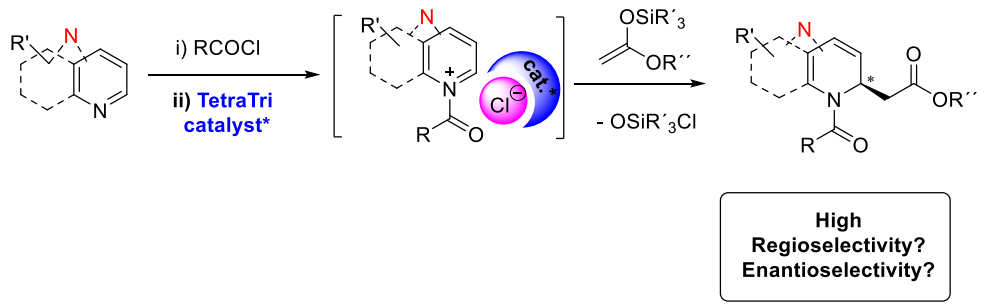


Figure 2 Reactive sites of diazarenes.

Recently, we have described the use of a family of triazole- based H-bond donors[14] as efficient anion-binding catalysts[14c, 15] for the asymmetric nucleophilic dearomatization of N-heteroarenes, such as isoquinolines, quinolines and pyridines.[16] Therefore, in order to accomplish our envisioned catalytic asymmetric synthesis of chiral diaza-heterocycles, we decided to explore these H-donor catalysts for the related dearomatization of various types of 6-membered ring-containing diazarenes (Scheme 4).



Scheme 4 Asymmetric dearomatization of diazarenes by anion-binding catalysis.

To achieve the main goal of this chapter, the following points will be addressed:

- Optimization of the reaction conditions: Screening of various chiral H-donor catalysts, acylating agents and the silyl ketene acetals
- Study of the scope of the reaction with various diazarenes
- Further derivatization reactions of the obtained chiral diaza-heterocycles

2.3 Results and Discussion

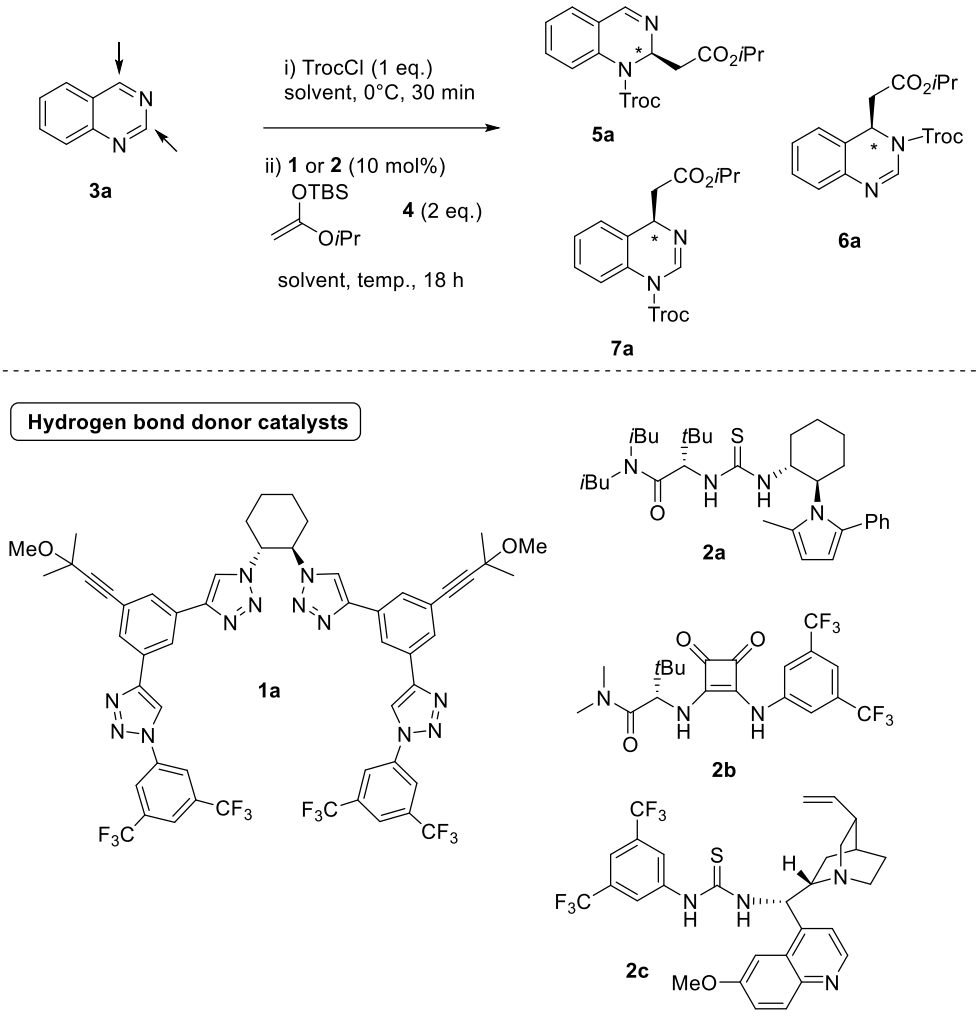
2.3.1 Initial Optimization Experiments

Our studies started with the optimization of the reaction of quinazoline (**3a**) as model substrate and with silyl ketene acetal **4a** as nucleophile (Table 1). Various chiral H-donor catalysts such as tetrakistriazole **1a**,[14] Jacobsen's thiourea **2a**,[16] squaramide **2b**[17] and bifunctional thiourea-cinchona alkaloid **2c**[18] were initially explored (entries 2-5). Following previously reported procedures,[14,16] the required ionic substrate, quinazolinium chloride salt, was generate *in situ* by acylating **3a** with 2,2,2-trichloroethyl chloroformate (TrocCl) in MTBE at 0 °C for 30 min. Subsequent addition of the H-donor catalyst **1** or **2** and **4a** at −78 °C (allowing the reaction mixture to warm up to room temperature overnight) delivered the dearomatized products **5-7**.

It is worth mentioning that there was an appreciable background reaction in the absence of a catalyst (entry 1, 56%). Fortunately, the heterocycle **5a** was formed regioselectively along with small amounts of **6a** (91:9, **5a**:**6a**) and not observing the formation of the other possible isomer **7a**. The catalytic reactions also showed a similar excellent regioselectivity towards **5a**. From the catalysts tested in this study (entries 2–5), the triazole-based H-donor **1a** proved to be the most efficient in terms of both reactivity and enantioselectivity. Thus, **5a** was obtained in 65% yield and 96:4 er (entry 2), whereas the other catalysts delivered the dearomatized product in significantly low yields (13–34%) and low to moderate enantiomeric inductions (45:55–61:39 er).

The change to other ethereal solvents such as Et_2O was not beneficial, hampering the enantioselectivity (84:16 er, entry 6). When the reaction was carried out at a continuous temperature of −78 °C, the same enantiomeric ratio (96:4 er, entry 7) was obtained. A similar procedure at −40 °C led to **5a** in a lower 86:14 er (entry 8). Lastly, the use of 5 mol% of catalyst **1a** provided an inferior chiral induction (91:9 er, entry 9). Therefore, 10 mol% of catalyst loading and a slow temperature gradient (from −78 °C to r.t.) were employed as optimal conditions for further studies.

Table 1 Optimization of the reaction with **3a** as a model substrate.[a]



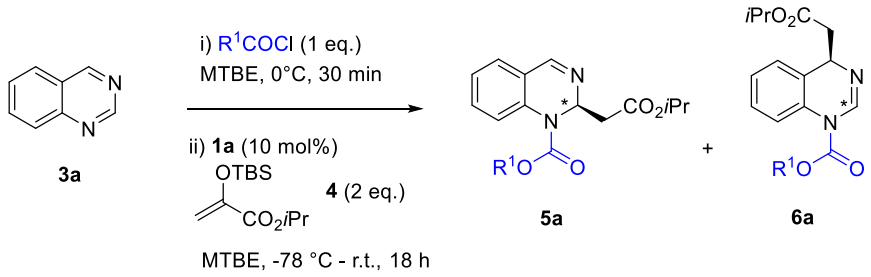
Entry	Catalyst	Solvent	T. (°C)	Yield (%)[b]	**5a:6a:7a**[c]	**5a**, e.r.[d]
1	--	MTBE	-78 - rt	56	91:9:--[e]	--
2	**1a**	MTBE	-78 - rt	65	92:8:--[e]	96:4
3	**2a**	MTBE	-78 - rt	34	92:8:--[e]	61:39
4	**2b**	MTBE	-78 - rt	21	92:8:--[e]	46:54
5	**2c**	MTBE	-78 - rt	13	92:8:--[e]	45:55
6	**1a**	Et_2O	-78 - rt	61	91:9:--[e]	84:16
7	**1a**	MTBE	-78	88	92:8:--[e]	96:4
8	**1a**	MTBE	-40	54	92:8:--[e]	86:14
9	**1a**	MTBE	-78 - rt	66	92:8:--[e]	91:9[f]

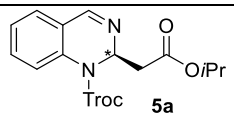
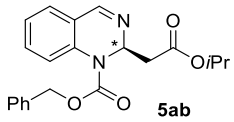
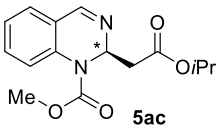
[a] Conditions: i) **3a** (1 eq.) and TrocCl (1 eq.) were stirred in the appropriate dry solvent at 0 °C for 30 min; then ii) catalyst **1** or **2** (10 mol%) and **4a** (2 eq.) were added at -78 °C and stirred for 18 h while allowing to reach slowly rt. [b] Isolated yield. [c] Isomeric ratios determined by ^{1}H-NMR of the crude reaction. [d] Enantiomeric ratios determined by chiral HPLC. [e] Isomer **7a** was not detected by NMR. [f] Reaction using 5 mol% of catalyst **1a**.

2.3.2 Screening of the Acylating Agent

The screening of the acylation reagents was next carried out (Table 2). Besides TrocCl (entry 1), benzylchloroformate (CbzCl) was successfully employed in the reaction. However higher yields could be obtained with this acylating agent (65% vs.71%) a significant drop from 96:4 e.r. with TrocCl to 60: 40 e.r. with CbzCl, in the enantioinduction was observed (entry 2). Methoxycarboxylic chloride could also be employed as acylating reagents (entry 3) but, an inseparable mixture of **5ac**, **6ac** and starting material **3a** was obtained which made analyzation of the yield and enantiomeric ratio impossible. Additionally, in terms of regioselectivitiy TrocCl was superior compared to methoxycarboxylic chloride (98:2 vs 84:16) and was therefore used as the acylating agent of choice in further studies.

Table 2 Screening of the acylating agent[a]



Entry	R^1COCl	Product **5**	Yield (%)[b]	**5a:6a** [c]	**5a**, e.r.[d]
1	TrocCl	 **5a**	65	98:2	96 :4
2	CbzCl	 **5ab**	71	n.d.	60:40
3	MeOCOCl	 **5ac**	n.d.[e]	84:16	n.d. [e]

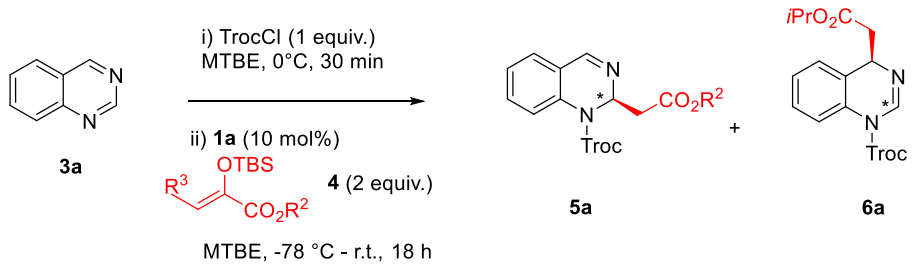
[a] Conditions: (i) **3a** (1 eq.) and R^1COCl (1 eq.) were stirred in dry MTBE at 0 °C for 30 min; then (ii) catalyst **1a** (10 mol%) and **4** (2 eq.) were added at −78 °C and stirred for 18 h while allowing to reach slowly rt. [b] Isolated yield. [c] Isomeric ratios **5**:**6** determined by ^1H–NMR of the crude reaction. [d] Enantiomeric ratios determined by chiral HPLC. [e] An inseparable mixture of **5ac**, **6ac** and staring material **3a**. n.d. = not determined

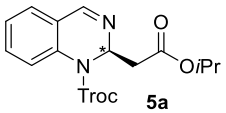
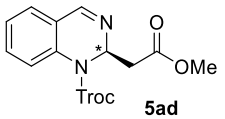
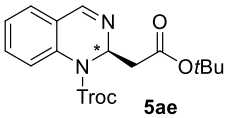
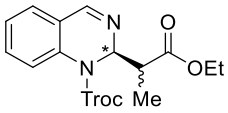
2.3.3 Screening of the Nucleophile Silyl Ketene Acetal

Having identified TrocCl as optimal acylating agent, the effect of the substitution at the silyl ketene acetals **4** on the reactivity and enantioselectivity of the reaction was investigated (Table 3). Silyl ketene acetals **4** derived from acetic acid presenting different substitution such

as the less hindered MeO (**4b**, entry 2) or the bulkier *t*BuO (**4c**, entry 3) groups, as well as a propionic acid derivative (**4d**, entry 4) were then explored. Moderate to good enantioselectivities were achieved (72:28 to 88:12 er), where the initial *i*PrO-substituted ketene acetal **4a** remained the most efficient nucleophile (entry 1).

Table 3 Screening of the silyl ketene acetal **4**[a]



Entry	**4**, R_2/R_3	Product **5**	Yield(%)[b]	**5a:6a** [c]	**5a**, e.r.[d]
1	^{i}Pr/H	 **5a**	65	98:2	96 :4
2	Me/H	 **5ad**	72	94:6	72 :28 (94:6)[e]
3	^{t}Bu/H	 **5ae**	62	95:5	83 :17 (95:5)[e]
4	Et/Me	 **5af**	91	>95:5 [5:1 dr][e]	88 :12 (major) 73 :27 (minor)

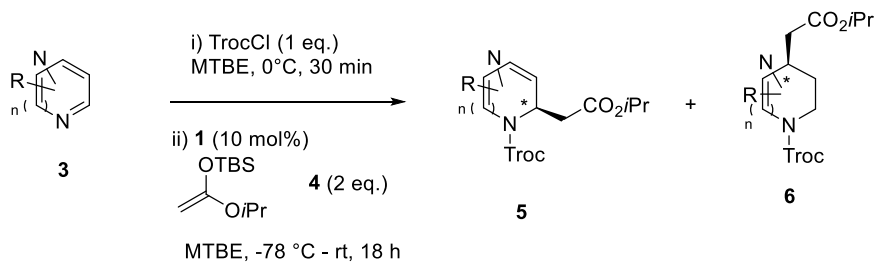
[a] Conditions: (i) **3a** (1 equiv.) and R^1COCl (1 equiv.) were stirred in dry MTBE at 0 °C for 30 min; then (ii) catalyst **1a** (10 mol%) and **4** (2 equiv.) were added at −78 °C and stirred for 18 h while allowing to reach slowly rt. [b] Isolated yield. [c] Isomeric ratios **5**:**6** determined by ^{1}H–NMR of the crude reaction. [d] Enantiomeric ratios determined by chiral HPLC. [e] Reaction with a 1:0.8 isomeric mixture of silyl ketene acetal **4d**. The diastereomeric ratio of **5af** was determined by ^{1}H-NMR of the crude reaction.

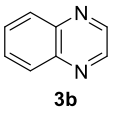
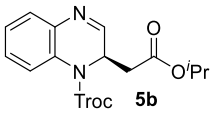
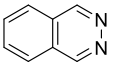
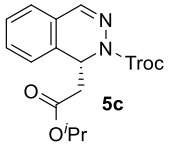
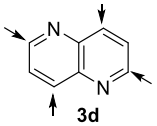
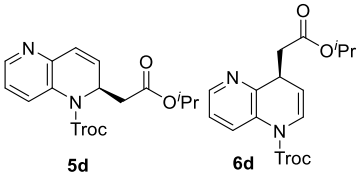
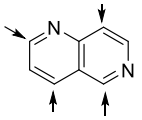
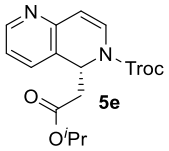
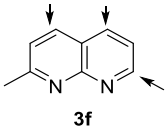
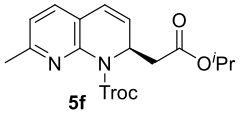
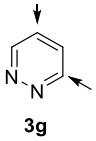
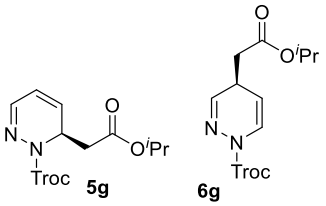
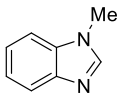
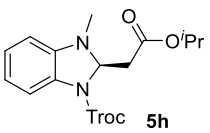
2.3.4 Scope of the Reaction with Various Diazarenes

Based on these results, the screening of the substrate scope was next carried out with catalyst **1a**, TrocCl, silyl ketene acetal **4a** and several representative, readily available mono- and bicyclic diazarenes in MTBE (Table 3). The study continued with the dearomatization of the analogous diazarene quinoxaline (**3b**), which also presents both nitrogen atoms in the same aromatic unit (entry 1). Although this substrate reminds of the structure of quinoline, only a complex mixture was obtained, in which the double addition of the TrocCl to both nitrogen

atoms could also be observed. The dearomatization of the highly symmetric phthalazine (**3c**), exhibiting only one equivalent reactive α-position, yielded compound **5c** in a good 93% yield and 76:24 enantiomeric ratio (entry 2).

Table 4. Scope of the reaction with various diazarenes[a]



Entry	Diazarene **3**	Products **5 / 6**	yield (%)[b] [**5**:**6**][c]	**5**, e.r.[d]	**6**, e.r.[d]
1	 **3b**	 **5b**	**5b**, Decomp.	--	--
2	 **3c**	 **5c**	**5c**, 93% (45%)[e]	76:24 (79:21)[e]	--
3	 **3d**	 **5d** **6d**	**5d**, 86% **6d**, 5% [95:5]	83:17	62:38
4	 **3e**	 **5e**	**5e**, 56%[f]	80:20	--
5	 **3f**	 **5f**	**5f**, 74% (38%)[e]	63:37 (61:39)[e]	--
6	 **3g**	 **5g** **6g**	**5g**, 87% **6g**, 6% [94:6]	73:27	52:48
7	 **3h**	 **5h**	**5h**, 72%,	66:34	--

[a] Conditions: (i) **3** (1 eq.) and TrocCl (1 eq.) were stirred in dry MTBE at 0 °C for 30 min; (ii) catalyst **1a** (10 mol%) and **4** (2 eq.) were added at −78 °C and stirred for 18 h while allowing to reach slowly rt. [b] Isolated yield. [c] Isomeric ratios determined by ^{1}H NMR. [d] Enantiomeric ratios determined by chiral HPLC. [e] Reaction at −78 °C in brackets. [f] Other possible isomers were not detected by NMR.

In the case of 1,5-naphthyridine (**3d**), which has one nitrogen atom in each ring, the challenge was again the control of the regioselectivity since both the C4 and C2 positions of each heteroaromatic ring are prone to nucleophilic addition (entry 3). A good regioselectivity of 95:5 was obtained in favor of the desired C2-addition product **5d**. After the separation from the minor 4-addition product **6d**, compound **5d** was obtained in an 86% yield and a good 83:17 enantiomeric ratio.

Next, 1,6-naphthyridine (**3e**) was explored as a substrate (entry 4). Since this compound contains both the quinoline and the isoquinoline unit, it was interesting to get a deeper understanding about the reactivity, regioselectivity and enantioselectivity of this type of mixed structure. Due to the higher intrinsic reactivity of the benzylic position within the isoquinoline core, a high regioselectivity could be expected. Consequently, **5e** was obtained as a single isomer and with high enantioselectivity (80:20 er).

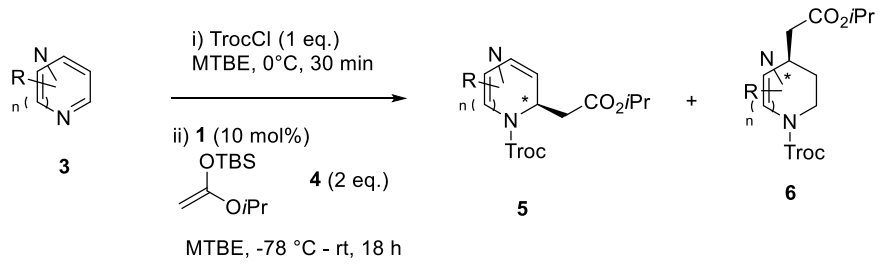
The reaction with methyl-substituted 1,8-naphthyridine (**3f**) proceeded smoothly, providing exclusively compound **5f** in a good 74% yield and a significantly lower enantioselectivity (63:37 er, entry 5). This unexpected result compared to other naphthyridines cannot be easily rationalized, since in the previous work the related monoazarene quinolines provided very high enantioselectivities for this type of reaction (typically >95:5 er).[15a]

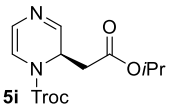
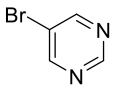
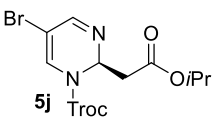
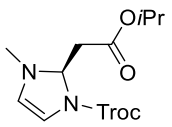
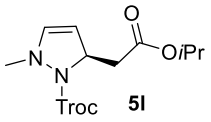
As the dearomatization of the bicyclic diazarenes showed a good performance and a moderate to excellent enantioselectivity, a more challenging six-membered monocyclic heteroarene was next explored. Pyridazine (**3g**) was again nicely enrolled in the catalytic dearomatization reaction, providing a good 93% overall yield and a 94:6 mixture of the 2- (**5g**) and 4-addition (**6g**) products (entry 6). Remarkably, an acceptable 73:27 enantiomeric ratio was obtained for the more interesting 2-addition product **5g**, whereas for the minor regioisomer **6g** an almost racemic compound was formed. This can be explained by the greater distance of the newly introduced stereocenter at the C4 with respect to the C2 position to the positive nitrogen present in the key ionic intermediate. Consequently, the catalyst-chloride anion complex should stay near the nitrogen atom and therefore, the chirality transfer might be more efficient in the adjacent C2-position.

Lastly, the reaction with a five membered diazarene was carried out. Thus, *N*-methyl benzimidazole provided the desired dearomatized heterocycle **5h** in a good yield and moderate enantioselectivity (72%, 66:34 er; entry 7).

The reaction with other diazarenes such as 6-membered ring pyrazine and 5-bromopyrimidine, or five-membered derivatives *N*-methyl imidazole and *N*-methyl pyrazole also proceeded. Unfortunately, the products showed a high instability and they could not be isolated pure, leading to a complex mixture of decomposition products (Table 5).

Table 5 Reaction with various 5- and 6-membered diazarenes.



Entry	Diazarene **3**	Products **5 / 6**	yield (%)[b] [**5**:**6**][c]	**5**, e.r.[d]	**6**, e.r.[d]
1	 **3i**	 **5i**	**5i**, Decomp.	--	--
2	 **3j**	 **5j**	**5j**, Decomp.	--	--
3	 **3k**	 **5k**	**5k**, Decomp.	--	--
4	 **3l**	 **5l**	**5l**, Decomp.	--	--

[a] Conditions: (i) **3** (1 eq.) and TrocCl (1 eq.) were stirred in dry MTBE at 0 °C for 30 min; (ii) catalyst **1a** (10 mol%) and **4** (2 eq.) were added at −78 °C and stirred for 18 h while allowing to reach slowly rt. [b] Isolated yield. [c] Isomeric ratios determined by ^{1}H NMR. [d] Enantiomeric ratios determined by chiral HPLC.

2.3.5 Absolute Configuration

Succeeding the reaction scope's study, we were interested in determining the absolute configuration of the obtained new C-stereocenters. Unfortunately, most of the products resulted oils, hampering obtaining crystals for their X-ray structural analysis. However, we could assume the same behavior of the catalyst (*R,R*)-**1a** as in the reactions of the related mono-azarenes. Thus, the absolute configuration (*R*) was assigned for the products **5** and **6** by

comparison with the one previously obtained for quinolines, pyridines and isoquinolines as substrates (Figure 3).[16]

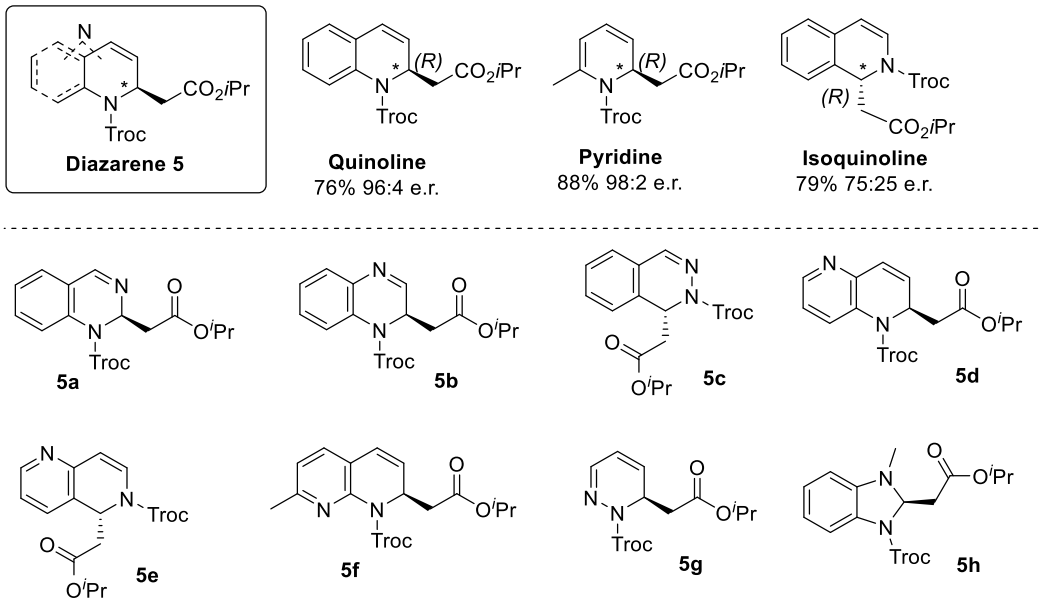
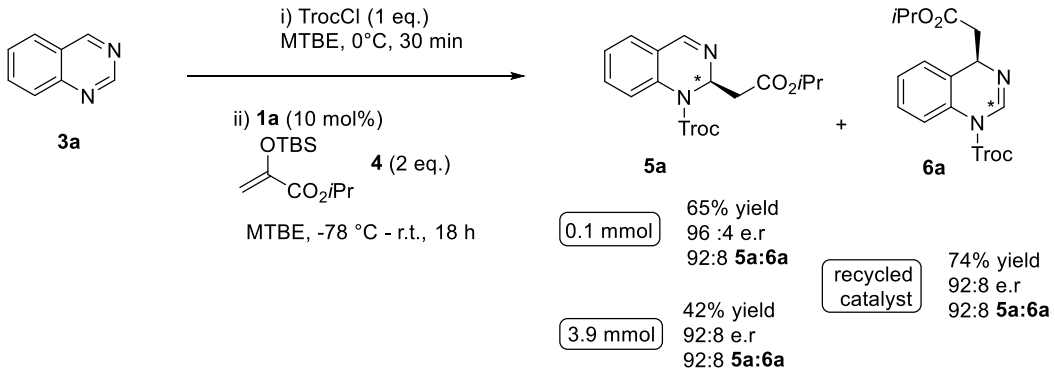


Figure 3 Absolute configuration of diazarenes, quinolines, pyridines and isoquinolines obtained with catalyst (*R,R*)-**1a**.

2.3.6 Scale-up Reaction and Catalyst Recycling

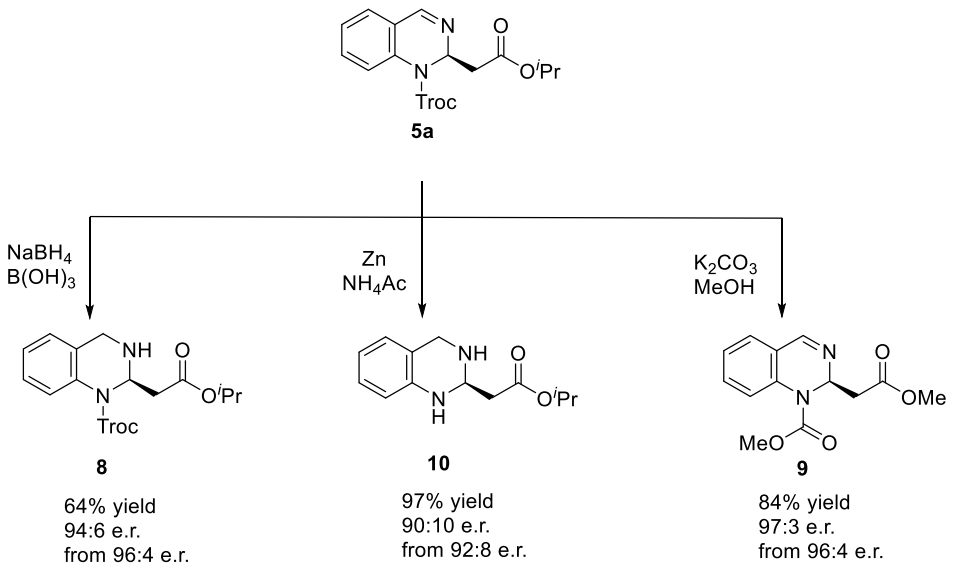
The developed methodology proved to be very robust, allowing the scaling up of the reactions. Consequently, the enantioselective dearomatization of the model substrate **3a** could be scaled-up to approximately 40 times (0.5 g scale) without any significant detriment of the enantioselectivity of the reaction (92:8 er vs. 96:4 er, 3.9 vs. 0.1 mmol scale; respectively). Moreover, the catalyst could be re-isolated in a good 74% yield and reused, delivering the same reactivity and stereochemical results (Scheme 5).



Scheme 5 Reaction scale-up and catalyst recycling.

2.3.7 Derivatization of Diazarene Compounds

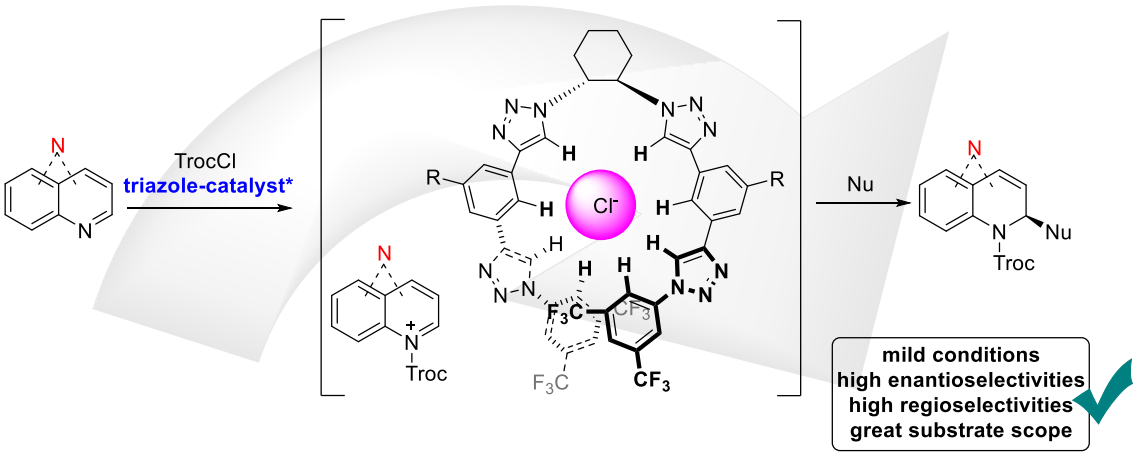
Finally, the synthetic utility of this method was demonstrated by the derivatization of **5a**. These reactions were carried out in cooperation with Julia Bamberger. Thus, the corresponding tetrahydroderivative **8** was synthesized by reduction with $NaBH_4$ in the presence of $B(OH)_3$.[17] The reduction of **5a** with common reduction procedures like Et_3SiH/TFA or the H_2–Pd/C system under various conditions did not occur or lead to decomposition products. The dimethyl derivative **9** by trans-esterification with *in situ* generated KOMe with K_2CO_3 in MeOH (Scheme 6). Moreover, the Troc protecting group could easily be removed from **5a** using Zn and NH_4OAc at room temperature, providing the corresponding *N*-deprotected product **10** in 97% yield.



Scheme 6 Derivatization of the quinazoline derivative **5a**.

2.4 Conclusion

In conclusion, the first enantioselective nucleophilic dearomatization of diazarenes under mild and metal free conditions, using an anion-binding organocatalysis approach has been developed. Tetrakistriazole-based H-bond donor catalysts were superior to the more common N-H-based hydrogen-bond donors, providing the corresponding products in high enantioselectivities up to 96:4 e.r. Furthermore, we overcame the regioselectivity problems, which are present in the diazarenes due to a larger number of reactive sites. By formation of a close chiral anion pair between the catalyst and the *in situ* generated *N*-acyldiazarene highly regioselective dearomatization products were obtained. The great substrate scope demonstrated that the reaction could be nicely enrolled into almost every kind of diazarene accepting various positions of the two nitrogen heteroatoms in the ring.



The absolute configuration was determined as (*R*) for the products **5** and **6** by comparison with the one previously reported dearomatized products of quinolines, pyridines and isoquinolines as substrates. Finally, the utility of the method was demonstrated by derivatizing the obtained dearomatized products. The rapid access to substituted chiral di- or tetrahydro diazaheterocycles by the new class of tetrakistriazole-based H-bond donor catalysts was clearly constituted.

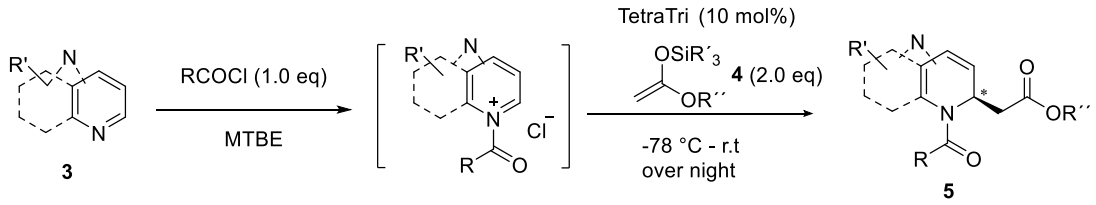
This work encouraged us to further investigate this kind of C-H-based chiral catalysts in reactions with other substrates or different nucleophiles such as the interesting phosphorous- or sulfur-nucleophiles.

2.5 Experimental Part

2.5.1 General Information and Analytical Techniques

^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ (reference signals: ^{1}H = 7.26 ppm, ^{13}C = 77.16 ppm) on a Bruker ARX-300 and a Varian AV-300, 400 or 600 MHz. Chemical shifts (δ) are given in ppm and spin–spin coupling constants (J) are given in Hz. Analytical thin layer chromatography was performed using silica gel 60 F254 and a solution of $KMnO_4$ served as the staining agent. Column chromatography was performed on silica gel 60 (0.040–0.063 mm). Exact masses (HRMS) were recorded on an Agilent Q-TOF 6540 UHD spectrometer using electro- spray (ES) or chemical (CI) ionization techniques. Chiral High-Pressure Liquid Chromatography (HPLC) analyses were per- formed on an Agilent 1200 series instrument.
MTBE and Et_2O were distilled and dried over Na. The catalysts **1a**[16] and **2a**–**c**,[17,18] and the silyl ketene acetals **4**,[16a,17] were prepared following the known literature procedures. The starting materials and other commercially available reagents were used without further purification.

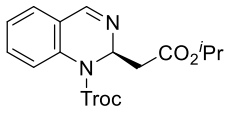
2.5.2 General Organocatalytic Procedure



The diazarene **3** (0.10 mmol, 1.0 eq.) was dissolved in freshly distilled anhydrous MTBE (1 mL, 0.1 M) and cooled to 0 °C. After the addition of 2,2,2-trichloroethyl chloroformate (14 µL, 0.10 mmol, 1.0 eq.), the reaction was stirred for 30 min at 0 °C and then cooled to −78 °C. Isopropyl TBS-ketene acetal **4a** (51 µL, 0.20 mmol, 2.0 eq.) and the catalyst **1a** (11.2 mg, 0.01 mmol, 10 mol%) were added and the reaction mixture was stirred overnight, which was allowed to warm slowly to room temperature during that time. The crude mixture was purified by flash column chromatography (petrol ether/EtOAc 10:1) to obtain the desired addition product.

2.5.3 Analytical Data for Compounds 5 and 6

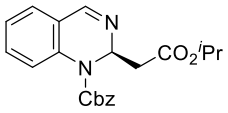
2,2,2-Trichloroethyl (*R*)-2-(2-isopropoxy-2-oxoethyl)quinazoline-1(2H)-carboxylate (5a).



Quinazoline (**3a**) (13.0 mg, 0.100 mmol, 1.0 eq.), TrocCl, catalysts **1a** and **4a** were added according to the general procedure, leading to a 98:2 mixture of **5a** and **6a**. The main product **5a** (26.5 mg, 0.065 mmol, 65%)

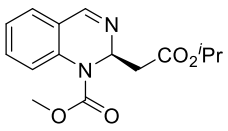
was isolated by column chromatography. The enantiomeric ratio was determined as 96:4 er by chiral HPLC [Chiralcel OJ-H, hexane/iPrOH (98:2), 1.0 mL min^{-1}, λ =300 nm: tr (minor): 14.0 min, tr (major): 22.2 min]. $[\alpha]_{589}^{20}$: −91.5 (c 0.1, $CHCl_3$). **^{1}H NMR** (400 MHz, CDCl3): δ 8.08 (s, 1H), 7.36–7.31 (m, 2H), 7.25–7.15 (m, 2H), 5.77–5.60 (m, 1H), 5.14–4.75 (m, 3H), 2.81–2.70 (m, 1H), 2.70–2.58 (m, 1H), 1.16 (d, *J* = 6.3 Hz, 3H), 1.13 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (100 MHz, CDCl3): δ 168.9, 150.8, 140.7, 138.7, 129.2, 127.7, 126.1, 126.2, 124.8, 94.3, 75.7, 68.6, 50.7, 41.8, 21.7, 21.6; **HRMS** (ESI): m/z calculated for $[C_{16}H_{18}Cl_3N_2O_4]$+: 407.0327; found 407.0333.

Benzyl (*R*)-2-(2-isopropoxy-2-oxoethyl)quinazoline-1(2H)-carboxylate (5ab).



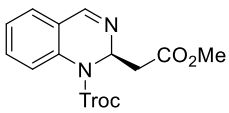
Quinazoline (**3a**) (13.0 mg, 0.100 mmol, 1.0 eq.), benzylchloroformate (14.2 µL, 0.100 mmol, 1.0 eq.), catalyst **1a** and **4a** were added according to the general procedure, leading to the desired product **5ab** (26.1 mg, 0.071 mmol, 71%). The enantiomeric ratio was determined as 60:40 er by chiral HPLC [Chiralcel OJ-H, hexane/iPrOH (98:2), 1.0 mL min^{-1}, λ = 300 nm: tr (minor): 26.6 min, tr (major): 38.2 min]. $[\alpha]_{589}^{20}$: −13.2 (c 0.1, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.44–7.35 (m, 5H), 7.32–7.28 (m, 2H), 7.19 (m, 2H), 5.66 (t, *J* = 6.3 Hz, 1H), 5.32 (d, *J* = 3.5 Hz, 2H), 4.97–4.84 (m, 1H), 2.63 (m, 2H), 1.14 (d, *J* = 5.9 Hz, 3H), 1.12 (d, *J* = 6.3 Hz, H); **^{13}C NMR** (100 MHz, $CDCl_3$): 169.1, 145.6, 141.8, 134.8, 129.1, 128.9, 128.8, 128.4, 127.4, 126.1, 125.9, 125.0, 69.0, 68.5, 50.5, 42.0, 29.7, 21.6; **HRMS** (ESI): m/z calculated for $[C_{21}H_{23}N_2O_4]$+: 367.1652; found 367.1658.

Methyl (*R*)-2-(2-isopropoxy-2-oxoethyl)quinazoline-1(2H)-carboxylate (5ac).



Quinazoline (**3a**) (13.0 mg, 0.100 mmol, 1.0 eq.), MeOCOCl (7.7 µL, 0.100 mmol, 1.0 eq.), catalyst **1a** and **4a** were added according to the general procedure, leading to an inseparable mixture of the desired product **5ac**, the 4-addition by-product **6ac** and the starting material.

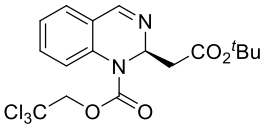
2,2,2-Trichloroethyl (*R*)-2-(2-methoxy-2-oxoethyl)quinazoline-1(2H)-carboxylate (5ad).



Quinazoline (**3a**) (13.0 mg, 0.100 mmol, 1.0 eq.), TrocCl, catalyst **1a** and the silyl ketene acetal **4b** (45.0 µL, 0.200 mmol, 2.0 eq.) were added according to the general procedure, leading to the desired product **5ad** (27.2 mg, 0.072 mmol, 72%). The enantiomeric ratio was determined as 72:28 er by chiral HPLC [Chiralcel OJ-H, hexane/iPrOH (98:2), 1.0 mL min^{-1}, λ = 300 nm: tr (minor): 28.0 min, tr (major): 36.7 min].

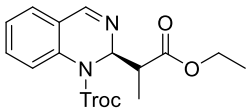
$[\alpha]_{589}^{20}$: −39.6 (c 0.1, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.29 (m, 2H), 7.20–7.08 (m, 2H), 5.65 (t, *J* = 6.2 Hz, 1H), 4.87 (s, 2H), 3.58 (s, 3H), 2.68 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.8, 147.1, 138.7, 129.3, 127.8, 126.4, 126.1, 124.8, 94.3, 75.7, 52.1, 50.7, 29.7; **HRMS** (ESI): m/z calculated for $[C_{14}H_{14}Cl_3N_2O_4]$+: 379.0014; found 379.0019.

2,2,2-Trichloroethyl (*R*)-2-(2-(tert-butoxy)-2-oxoethyl)quinazoline-1(2H)-carboxylate (5ae).



Quinazoline (**3a**) (13.0 mg, 0.100 mmol, 1.0 eq.), TrocCl, catalyst **1a** and the silyl ketene acetal **4c** (54.0 µL, 0.200 mmol, 2.0 eq.) were added according to the general procedure, leading to the desired product **5ae** (26.2 mg, 0.062 mmol, 62%). The enantiomeric ratio was determined as 83:17 er by chiral HPLC [Chiralcel OJ-H, hexane/iPrOH (98:2), 1.0 mL min^{-1}, λ = 300 nm: tr (minor): 13.90 min, tr (major): 21.4 min]. $[\alpha]_{589}^{20}$: −1.7 (c 0.1, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.36–7.30 (m, 2H), 7.24–7.16 (m, 2H), 5.62 (t, *J* = 11.8, 1H), 4.91 (s, 2H), 2.80–2.53 (m, 2H), 1.35 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.6, 150.9, 138.7, 129.2, 127.7, 126.3, 124.9, 94.4, 81.5, 75.7, 50.8, 40.9, 27.9; **HRMS** (ESI): m/z calculated for $[C_{17}H_{20}Cl_3N_2O_4]$+: 421.0483; found 421.0487.

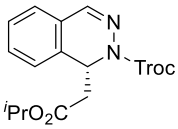
2,2,2-Trichloroethyl (*R*)-2-(1-ethoxy-1-oxopropan-2-yl)quinazoline-1(2H)-carboxylate (5af).



Quinazoline (**3a**) (26.0 mg, 0.20 mmol, 1.0 eq.), TrocCl, catalyst **1a** and the silyl ketene acetal **4d** (150.0 µL, 0.20 mmol, 2.0 equiv.; 1:0.8 E/Z mixture) were added according to the general procedure, leading to the desired product **5af** (74.5 mg, 0.18 mmol, 91%) as a 5:1 mixture of diastereomers. The enantiomeric ratio was determined as 88:12 er for the major diastereoisomer and 73:27 for the minor diastereoisomer by chiral HPLC [Chiralcel OD-H, hexane/iPrOH (95:5), 1.0 mL min^{-1}, λ = 290 nm: major isomer: tr (minor): 9.23 min, tr (major): 16.54 min; minor: tr (minor): 7.78 min, tr (major): 11.76 min]. **^{1}H NMR** (300 MHz, $CDCl_3$) (major): δ 8.13 (s, 1H), 7.33 (d, *J* = 3.9 Hz, 2H), 7.21 (m, 1H), 7.02 (d, *J* = 7.3 Hz, 1H), 5.70 (bs, 1H), 5.03–4.79 (m, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.89 (bs, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.99 (d, *J* = 7.1 Hz, 3H); **^{1}H NMR** (300 MHz, $CDCl_3$) (minor): δ 8.11 (s, 1H), 7.33 (d, *J* = 3.9 Hz, 2H), 7.21 (m, 1H), 7.12 (d, *J* =7.5 Hz, 1H), 5.54 (bs, 1H), 5.03–4.77 (m, 2H), 4.07–3.95 (m, 2H), 2.80–2.69 (m, 1H), 1.15 (t, *J* = 4.5 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.8, 172.2, 172.1, 151.4, 141.3, 139.4, 129.3, 129.2, 127.6,

126.6, 126.5, 126.2, 126.1, 94.3, 75.8, 75.7, 61.1, 55.3, 46.6, 24.0, 14.2, 14.0; **HRMS** (ESI): m/z calculated for $[C_{16}H_{18}Cl_3N_2O_4]$+: 407.0327; found 407.0329.

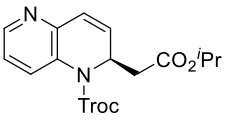
2,2,2-Trichloroethyl (*R*)-1-(2-isopropoxy-2-oxoethyl)phthalazine-2(1H)-carboxylate (5c)



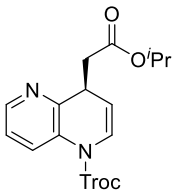
Phthalazine (**3c**) (13.0 mg, 0.100 mmol, 1.0 eq.), TrocCl, catalysts **1a** and **4a** were added according to the general procedure, leading to the desired product **5c** (38 mg, 0.093 mmol, 93%). The enantiomeric ratio was determined as 76:24 er by chiral HPLC [Chiralcel OD-H, hexane/iPrOH (99 :1), 1.0 mL min^{-1}, λ = 290 nm: tr (minor): 44.4 min, tr (major): 46.8 min]. $[\boldsymbol{\alpha}]_{\boldsymbol{589}}^{\boldsymbol{20}}$: −145.0 (c 0.1, CHCl3). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.81 (bs, 1H), 7.56–7.38 (m, 2H), 7.36–7.29 (m, 2H), 5.97 (t, *J* = 7.1 Hz, 1H), 5.12–5.00 (m, 1H), 4.94 (sept, *J* = 6.3 Hz, 1H), 4.90–4.81 (m, 1H), 2.83–2.50 (m, 2H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.11 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 168.9, 145.1, 144.2, 132.4, 132.0, 128.9, 126.5, 126.3, 123.2, 95.0, 75.6, 68.5, 50.7, 39.5, 21.7, 21.7; **HRMS** (ESI): m/z calculated for $[C_{16}H_{18}Cl_3N_2O_4]$+: 407.0327; found 407.0333.

2,2,2-Trichloroethyl (*R*)-2-(2-isopropoxy-2-oxoethyl)-1,5-naphthyridine-1(2H)-carboxylate (5d) and 2,2,2-trichloroethyl 4-(2-isopropoxy-2-oxoethyl)-1,5-naphthyridine-1(4H)-carboxylate (6d)

1,5-Naphthyridine (**3d**) (13.0 mg, 0.100 mmol, 1.0 eq.), TrocCl (13.8 µL, 0.100 mmol, 1.0 eq.), **1a** (11.2 mg, 0.010 mmol, 10 mol%) and the silyl ketene acetal **4** (51.0 µL, 0.200 mmol, 2.0 equiv.) were added according to the general procedure, leading to a 6:1 mixture of **5d** and **6d**. The mixture of isomers were separated and isolated by flash column chromatography (petrol ether/EtOAc 10:1) to yield the 2-addition product **5d** (35.6 mg, 0.087 mmol, 87%) and the 4-addition **6d** (2.0 mg, 0.005 mmol, 5%).

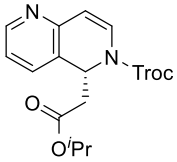


5d: The enantiomeric ratio of was detemined as 83:17 e.r. by chiral HPLC [Chiralcel OD-H, hexane/*i*PrOH (98:2), 1.0 mL min^{-1}, λ= 280 nm: *t*r (minor): 13.8 min, *t*r (major): 29.7 min]. $[\boldsymbol{\alpha}]_{\boldsymbol{589}}^{\boldsymbol{20}}$: -147.2 (*c* 0.1, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.33 (d, *J* = 4.6 Hz, 1H), 8.01 (bs, 1H), 7.19 (dd, *J* = 8.3, 4.8 Hz, 1H), 6.75 (d, *J* = 9.9 Hz, 1H), 6.43 (dd, *J* = 9.8, 5.8 Hz, 1H), 5.53 (dd, *J* = 13.4, 6.9 Hz, 1H), 5.01 (bs, 1H), 4.97 (sept, *J* = 6.3 Hz, 1H), 4.72 (bs, 1H), 2.60-2.40 (m, 2H), 1.17 (d, *J* = 8.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.1, 152.0, 145.7, 132.3, 127.3, 122.5, 94.8, 75.6, 68.5, 50.2, 38.9, 21.8, 21.7; **HRMS** (ESI): *m/z* calculated for $[C_{16}H_{18}Cl_3N_2O_4]^+$: 407.0327; found 407.0332.



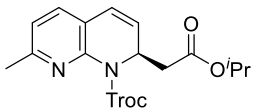
6d: The enantiomeric ratio of was detemined as 62:38 e.r. by chiral HPLC [Chiralcel OD-H, hexane/*i*PrOH (98:2), 1.0 mL/min, λ= 230 nm: *t*r (minor): 8.9 min, *t*r (major): 9.7 min]. $[\alpha]_{589}^{20}$: +4.8 (*c* 0.1, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.43 (d, *J* = 8.5 Hz, 1H), 8.37 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.21 (dd, *J* = 8.4, 4.6 Hz, 1H), 7.07 (dd, *J* = 8.0, 0.9 Hz, 1H), 5.50 (dd, *J* = 8.0, 4.5 Hz, 1H), 5.03 (sept., *J* = 6.3 Hz, 1H), 4.94 (d, *J* = 11.9 Hz (AB system), 1H), 4.80 (d, *J* = 11.9 Hz (AB system), 1H), 4.04 (dt, *J* = 9.2, 4.6 Hz, 1H), 2.92 (dd, *J* = 15.7, 5.1 Hz, 1H), 2.64 (dd, *J* = 15.7, 8.9 Hz, 1H), 1.21 (d, *J* = 6.3 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.0, 150.6, 150.5, 148.6, 146.0, 128.5, 124.7, 121.8, 113.1, 94.7, 75.6, 67.9, 40.9, 36.7, 21.8; **HRMS** (ESI): *m/z* calculated for $[C_{16}H_{18}Cl_3N_2O_4]^+$: 407.0327; found 407.0331.

2,2,2-Trichloroethyl (*R*)-5-(2-isopropoxy-2-oxoethyl)-1,6-naphthyridine-6(5H)-carboxylate (5e)



1,6-Naphthyridine (**3e**) (13.0 mg, 0.100 mmol, 1.0 eq.), TrocCl (13.8 µL, 0.100 mmol, 1.0 eq.), **1a** (11.2 mg, 0.010 mmol, 10 mol%) and the silyl ketene acetal **4** (51.0 µL, 0.200 mmol, 2.0 eq.) were added according to the general procedure, leading to a 1:1.6 mixture of rotamers of the titled product (23.0 mg, 0.056 mmol, 56%). The enantiomeric ratio was detemined as 80:20 e.r. by chiral HPLC [Chiralcel OJ-H, hexane/*i*PrOH (98:2), 1.0 mL/min, λ= 290 nm: *t*r (minor): 15.8 min, *t*r (major): 23.2 min]. $[\alpha]_{589}^{20}$: -65.0 (*c* 0.1, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.45 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.21 – 7.14 (m, 1H), 7.13 – 7.04(m, 1H), 6.21 (d, *J* = 8.1 Hz, 1H, minor rotamer), 6.16 (d, J = 8.0 Hz, 1H, major rotamer), 5.86 (dd, *J* = 7.5, 6.3 Hz, 1H), 5.07 – 4.86 (m, 2H), 4.78 (bd, *J* = 15.2, 1H), 2.94 – 2.58 (m, 2H), 1.22 – 1.07 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 169.2, 150.8, 149.3, 134.4, 129.3, 129.2, 128.2, 126.5, 126.4, 122.03, 121.8, 111.0, 94.9, 75.8, 68.6, 52.9, 40.4, 39.6, 21.8; **HRMS** (ESI): *m/z* calculated for $[C_{16}H_{18}Cl_3N_2O_4]^+$: 407.0327; found 407.0334.

2,2,2-Trichloroethyl (*R*)-2-(2-isopropoxy-2-oxoethyl)-7-methyl-1,8-naphthyridine-1(2H)-carboxylate (5f)

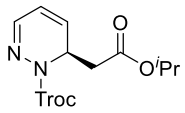


2-Methyl-1,8-naphthyridine (**3f**) (14.4 mg, 0.100 mmol, 1.0 eq.), TrocCl (13.8 µL, 0.100 mmol, 1.0 eq.), **1a** (11.2 mg, 0.010 mmol, 10 mol%) and the silyl ketene acetal **4** (51.0 µL, 0.200 mmol, 2.0 eq.) were added according to the general

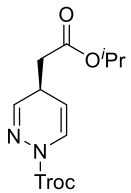
procedure, leading to the desired product (31.0 mg, 0.074 mmol, 74%). The enantiomeric ratio was determined as 63:37 e.r. by chiral HPLC [Chiralcel OD-H, hexane/*i*PrOH (98:2), 1.0 mL min^{-1}, λ= 290 nm: *t*r (minor): 13.4 min, *t*r (major): 22.1 min]. $[\boldsymbol{\alpha}]_{\mathbf{589}}^{\mathbf{20}}$: +4.0 (*c* 0.1, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.31 (d, *J* = 7.6 Hz, 1H), 6.94 (dd, *J* = 7.7, 0.4 Hz, 1H), 6.47 (d, *J* = 9.5 Hz, 1H), 6.16 (dd, *J* = 9.5, 5.8 Hz, 1H), 5.51 (dt, *J* = 10.0, 5.5 Hz, 1H), 5.05 – 4.92 (m, 1H), 4.99 (d, *J* = 11.9 Hz, 1H), 4.72 (d, *J* = 11.9 Hz, 1H), 2.64 (dd, *J* = 15.3, 5.3 Hz, 1H), 2.51 (s, 3H), 2.48 (dd, *J* = 15.3, 9.7 Hz, 1H), 1.22 (d, *J* = 6.7 Hz, 3H), 1.19 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 169.3, 156.7, 152.1, 146.6, 134.4, 128.3, 124.1, 120.4, 119.2, 94.9, 75.7, 68.3, 51.2, 39.3, 24.3, 21.8; **HRMS** (ESI): *m/z* calculated for $[C_{17}H_{20}Cl_3N_2O_4]^+$: 421.0483; found 421.0486.

2,2,2-Trichloroethyl (*R*)-6-(2-isopropoxy-2-oxoethyl)pyridazine-1(6H)-carboxylate (5g) and 2,2,2-trichloroethyl 4-(2-isopropoxy-2-oxoethyl)pyridazine-1(4H)-carboxylate (6g)

Pyridazine (**3g**) (7.3 mg, 0.100 mmol, 1.0 eq.), TrocCl (13.8 µL, 0.100 mmol, 1.0 eq.), **1a** (11.2 mg, 0.010 mmol, 10 mol%) and the silyl ketene acetal **4** (51.0 µL, 0.200 mmol, 2.0 eq.) were added according to the general procedure, leading to the 2-addition product **5g** (31.0 mg, 0.087 mmol, 87%) and the 4-addition product **6g** (4.0 mg, 0.011 mmol, 11%).

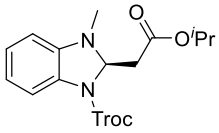


5g: The enantiomeric ratio of the main product was detemined as 73:27 e.r. by chiral HPLC [Chiralcel OJ-H, hexane/*i*PrOH (98:2), 1.0 mL min^{-1}, λ= 300 nm: *t*r (minor): 15.3 min, *t*r (major): 18.2 min]. $[\boldsymbol{\alpha}]_{\mathbf{589}}^{\mathbf{20}}$: -245.0 (*c* 0.1, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.24 (bs, 1H), 6.39 (ddd, *J* = 9.6, 6.1, 1.7 Hz, 1H), 5.97 (dd, *J* = 9.7, 3.2 Hz, 1H), 5.43 – 5.23 (m, 1H), 5.16 – 4.61 (m, 3H), 2.83 – 2.30 (m, 2H), 1.22 (d, *J* = 6.3 Hz, 6H); **^{13}C NMR** (75 MHz, acetone-D_6): δ 168.9, 152.7, 141.4, 132.0, 117.4, 95.0, 75.5, 68.5, 47.8, 38.1, 21.8; **HRMS** (ESI): *m/z* calculated for $[C_{12}H_{16}Cl_3N_2O_4]^+$: 357.0175; found 357.0175.



6g: The enantiomeric ratio was determined as 52:48 e.r. by chiral HPLC [Chiralcel OJ-H, hexane/*i*PrOH (98:2), 1.0 mL min^{-1}, λ= 230 nm: *t*r (minor): 17.8 min, *t*r (major): 19.9 min]. $[\boldsymbol{\alpha}]_{\mathbf{589}}^{\mathbf{20}}$: -2.0 (*c* 0.1, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.06 (d, *J* = 8.4 Hz, 1H), 7.02 (bs, 1H), 5.18 – 4.95 (m, 2H), 4.92 (s, 2H), 3.46 – 3.27 (m, 1H), 2.53 (dd, *J* = 16.1, 6.9 Hz, 1H), 2.43 (dd, *J* = 16.1, 7.3 Hz, 1H) 1.24 (d, *J* = 6.2 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 169.9, 154.0, 142.7, 123.2, 94.7, 75.5, 68.6, 39.7, 28.8, 21.8; **HRMS** (ESI): *m/z* calculated for $[C_{12}H_{16}Cl_3N_2O_4]^+$: 357.0175; found 357.0183.

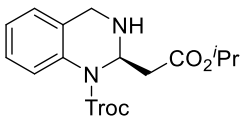
2,2,2-Trichloroethy 2-(2-isopropoxy-2-oxoethyl)-3-methyl-2,3-dihydro-(1H)-benzo[d] imidazole-1-carboxylate (5f)



1-Methylbenzimidazole (**3f**) (13.2 mg, 0.100 mmol, 1.0 eq.), TrocCl (13.8 µL, 0.100 mmol, 1.0 eq.), **1a** (11.2 mg, 0.010 mmol, 10 mol%) and the silyl ketene acetal **4** (51.0 µL, 0.200 mmol, 2.0 eq.) were added according to the general procedure, leading to the desired product (29.4 mg, 0.072 mmol, 72%).The enantiomeric ratio was detemined as 66:34 e.r. by chiral HPLC [Chiralcel OJ-H, hexane/*i*PrOH (99:2), 1.0 mL min^{-1}, λ= 300 nm: *t*r (minor): 10.5 min, *t*r (major): 12.0 min]. (Note: instable compound. Partial decomposition occurred during the structural analysis). $[\alpha]_{589}^{20}$: -12.7 (*c* 0.1, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.62-7.39 (m, 1H), 6.94 (dd, *J* = 7.7, 6.9 Hz, 1H), 6.71 (bd, *J* = 7.0 Hz, 1H), 6.48 (d, *J* = 7.7 Hz, 1H), 5.79 (bd, *J* = 9.8 Hz, 1H), 5.15-4.68 (m, 3H), 2.92 (s, 5H), 1.14 (d, *J* = 6.3 Hz, 3H), 1.08 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.3, 149.2, 142.3, 124.6, 118.9, 118.7, 114.1, 109.9, 107.3, 78.8, 78.3, 75.7, 75.0, 68.4, 40.3, 38.9, 34.7, 34.2, 21.8, 21.7; **HRMS** (ESI): *m/z* calculated for $[C_{16}H_{20}Cl_3N_2O_4]^+$: 409.0483; found 409.0480.

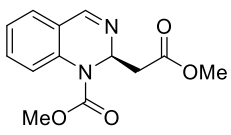
2.5.4 Derivatization of 5a

2,2,2-Trichloroethyl(*R*)-2-(2-isopropoxy-2-oxoethyl)-3,4-dihydroquinazoline-1(2H)-carboxylate (8)



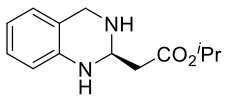
To a solution of **5a** (0.1 mmol, 40 mg, 1 eq.) in anhydrous MeOH (1mL) at 0 °C, $B(OH)_3$ (0.2 mmol, 12.2 mg, 2 eq.) and $NaBH_4$ (0.2 mmol, 7.2 mg, 2 eq.) were added slowly and stirred for 1 h at room temperature. The reaction mixture was quenched with H_2O (2 mL), filtered and washed with EtOAc (3 x3 mL). Purification by solid phase extraction (MeOH:Et_3N 50:1) yielded the desired product **8** (26 mg, 0.064 mmol, 64%). $[\alpha]_{589}^{20}$: -4.6 (*c* 0.1, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.09 (t, *J* = 7.2 Hz, 2H), 6.82 (t, *J* = 7.1 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.64 (t, *J* = 6.9 Hz, 1H), 5.22 (d, *J* = 12.1 Hz, 1H), 5.00 (m, 1H), 4.77 (s, 1H), 4.43 (m, 1H), 2.84 (bs, 2H), 1.23 (d, *J* = 6.2 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 169.7, 152.8, 141.8, 128.1, 127.6, 122.9, 120.0, 117.4, 95.3, 75.3, 68.4, 51.4, 42.6, 29.7, 21.8; **HRMS** (ESI): *m/z* calculated for $[C_{16}H_{19}Cl_3N_2Na\ O_4]^+$: 431.0303; found 431.0300.

Methyl (*R*)-2-(2-methoxy-2-oxoethyl)quinazoline-1(2H)-carboxylate (9)



A mixture of **5a** (20.0 mg, 0.05 mmol, 1 eq.) and K_2CO_3 (35.0 mg, 0.25 mmol, 5 eq.) in anhydrous MeOH (1mL) was stirred for 1 h at room temperature. After that time H_2O (1 mL) was added, the mixture extracted with $CHCl_3$ (3 x 3 mL), washed with brine (3 x 3 mL) and the crude product was dried over $NaSO_4$. Purification by column chromatography (petrol ether/EtOAc 5:1) yielded the desired product **9** (11.0 mg, 0.04 mmol, 84%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.72 (bs, 1H), 7.45 (td, *J* = 7.5, 1.4 Hz, 1H), 7.41 – 7.36 (td, *J* = 7.5, 1.2 Hz, 1H), 7.32 – 7.25 (m, 2H), 6.01 – 5.88 (bm, 1H), 3.91 (s, 3H), 3.62 (s, 3H), 2.69 (dd, *J* = 14.5, 5.8 Hz, 1H), 2.63 (dd, *J* = 14.5, 8.2 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.1, 154.4, 143.1, 132.4, 131.9, 128.8, 126.3, 126.0, 123.5, 76.7, 54.0, 51.9, 39.1; **HRMS** (ESI): *m/z* calculated for $[C_{13}H_{15}N_2O_4]^+$: 263.1026; found 263.1021. $[\alpha]_{589}^{20}$: -18.8 (*c* 0.1, $CHCl_3$).

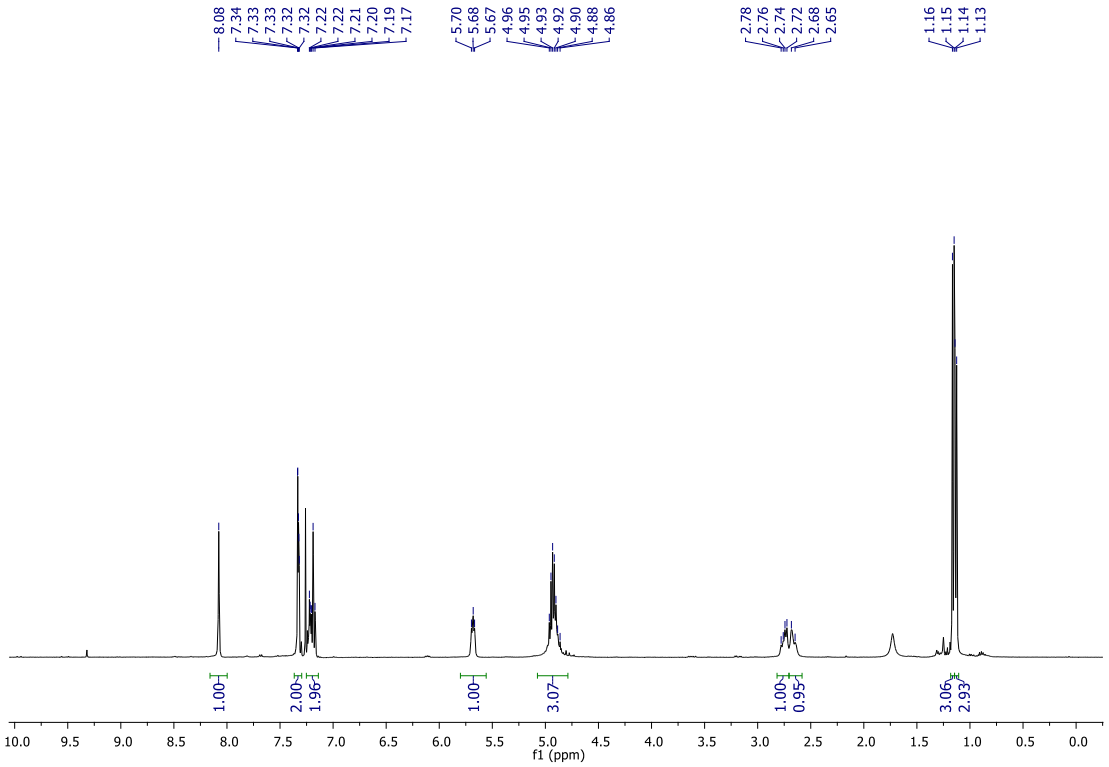
Isopropyl (*R*)-2-(1,2,3,4-tetrahydroquinazolin-2-yl)acetate (10)

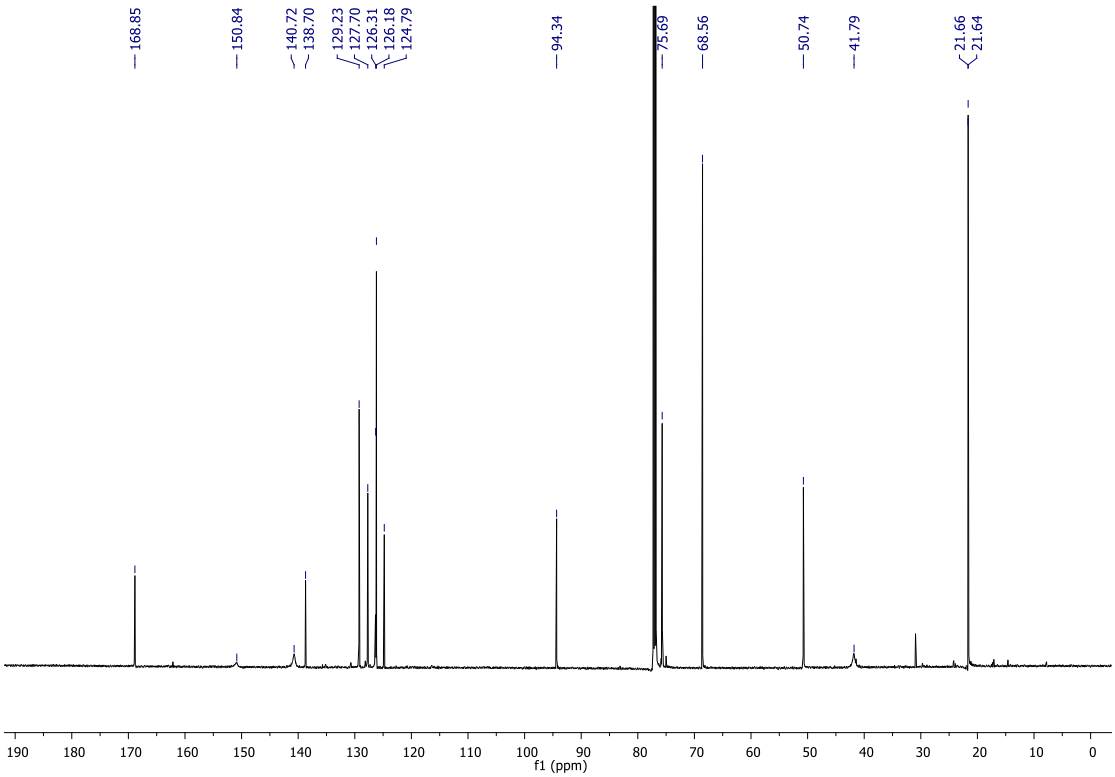


A mixture of **5a** (20.0 mg, 0.05 mmol, 1 eq.) and Zn-powder (34.0 mg, 0.05 mmol, 10 eq.) in NH_4OAc (1.0 M)/THF (1/3; 1mL) was stirred for 16 h at room temperature. After that time sat. aq. K_2CO_3 solution (1 mL) was added, extracted with $CHCl_3$ (3 x 3 mL) and dried over $NaSO_4$ to yield the desired product **10** (11.0 mg, 0.04 mmol, 84%).

The enantiomeric ratio was determined as 90:10 er by chiral HPLC [Chiralpack AD, hexane/iPrOH (90:10), 1.0 mL min^{-1}, λ = 280 nm: tr (major): 8.6 min, tr (minor): 9.7 min]. $[\alpha]_{589}^{20}$: +16.8 (c 0.1, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.25 – 7.12 (m, 2H), 7.04 (m, 2H), 6.96 – 6.82 (m, 1H), 5.06 (s, 1H), 5.18 – 4.30 (m, 3H), 2.88 (dd, *J* = 16.8, 10.0 Hz, 1H), 2.59 (dd, *J* = 16.8, 3.2 Hz, 1H), 1.27 – 1.22 (d, *J* = 6.3, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.2, 146.7, 140.5, 128.6, 125.7, 125.0, 123.4, 123.2, 68.6, 49.0, 44.1, 21.8; **HRMS** (APCI): m/z calculated for $[C_{13}H_{16}N_2O_2]^+$: 233.1285, found. 233.1290.

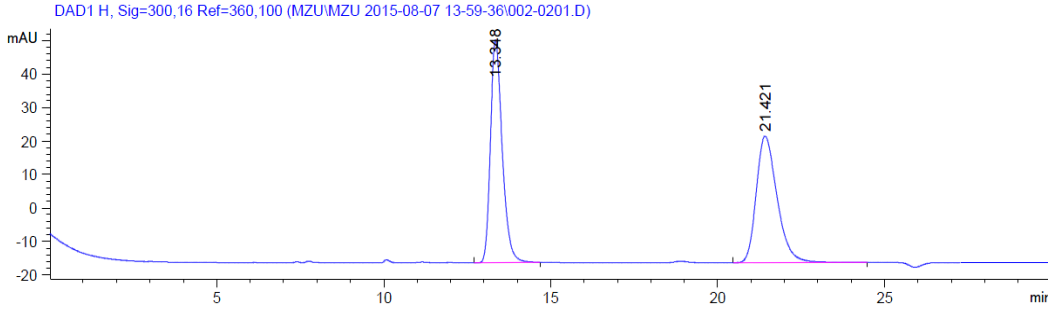
2.5.5 Representative Spectra and HPLC Chromatograms of 5a





Chiral-phase HPLC: OJ-H; Hex/^{i}PrOH 98:2 (λ = 300 nm)

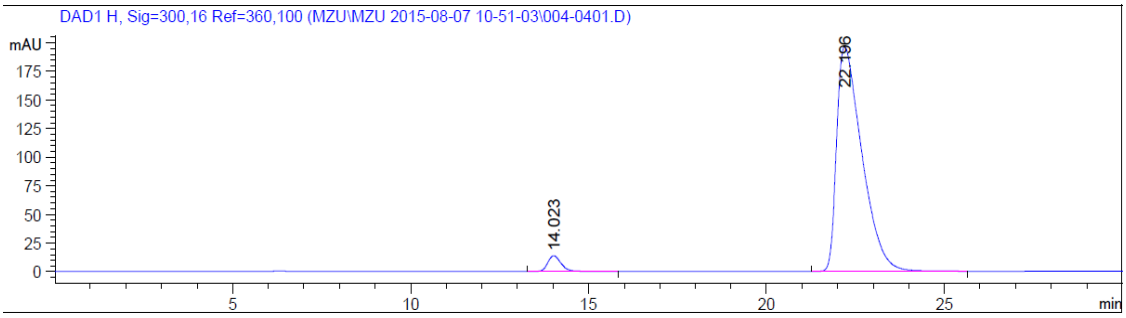
racemic:



Signal 5: DAD1 H, Sig=300,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.348	BB	0.3737	1628.41760	66.50849	49.8369
2	21.421	BB	0.6597	1639.07910	37.81224	50.1631

enantioselective:



Signal 4: DAD1 H, Sig=300,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.023	BB	0.3966	362.53653	13.97744	3.6026
2	22.196	BB	0.7472	9700.76172	196.74654	96.3974

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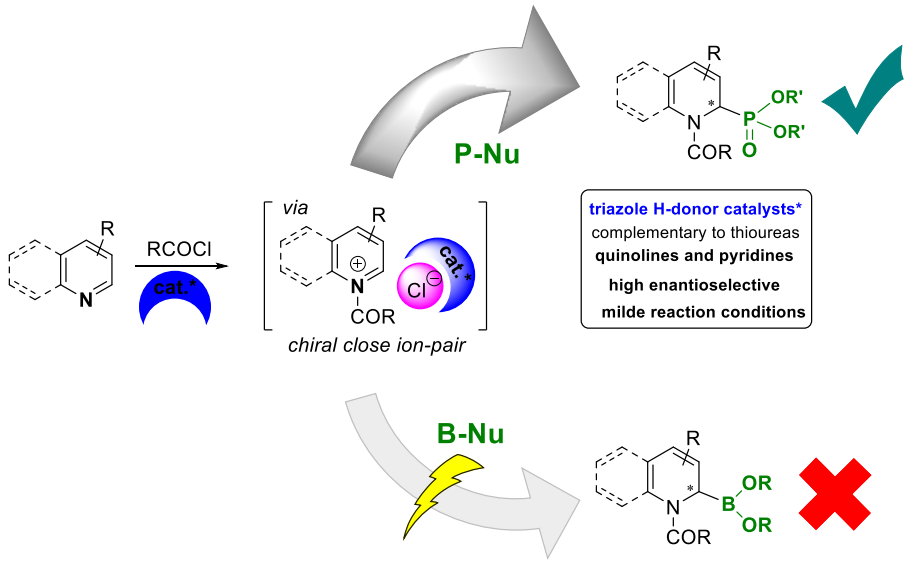
Chapter 3

3. Triazole-Based Anion-Binding Catalysis for the Enantioselective Dearomatization of *N*-Heteroarenes with Different Nucleophiles



Abstract: The first enantioselective synthesis of chiral heterocyclic α-amino phosphonates by nucleophilic dearomatization of quinolines and pyridines using an anion-binding organocatalysis approach is described. Chiral tetrakistriazoles were employed as efficient hydrogen-bond donor catalysts by the formation of a chiral close ion-pair with the *in situ* formed *N*-acyl salts with Troc-chloride and subsequent treatment with various phosphorous nucleophiles, such as silyl protected dialkyl phosphites and trialkylphosphites. Thus, the corresponding products were obtained in complete or high regioselectivities and up to 97:3 e.r. for quinolines or up to 87:13 e.r. for the more demanding pyridine substrates. This method allows the rapid access to substituted chiral cyclic α-amino phosphonates, which can easily further be transform into phosphonic acid derivatives. Introducing boron-nucleophiles in the same reaction was not successful and did not lead to any new discovery.

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Author contribution:

Theresa Fischer:	80% of reproduced part Initial optimization, catalyst screening, 80% of the scope of the reaction with various diazarenes, derivatization of **4/5**
Qui Nhi Duong:	20% Scope of the reaction with various diazarenes
Olga García Mancheño:	corresponding author

3.1 Triazole-Based Anion-Binding Catalysis for the Enantioselective Dearomatization of *N*-Heteroarenes with P-Nucleophiles

3.1.1 Introduction

Chiral α-aminophosphonic acid derivatives are important bioactive structures in the pharmaceutical and medicinal industry, as well as valuable building blocks in organic synthesis.[2] Few examples of relevant bioactive chiral α-aminophosphonic acid derivatives are shown in Figure 1. Thus, surrogates of α-amino acids, (*e.g.* of L-ornithine or pipecolic acid), have been extendedly exploited as more robust units.[3] Moreover, several structures based on an α-aminophosphonic acid moiety such as dufulin,[4] show pesticide activity. Other interesting derivatives are cyclic α-aminophosphonates, which present a broad biological spectrum such as antiobiotics[5] or proteinases inhibitors.[6]

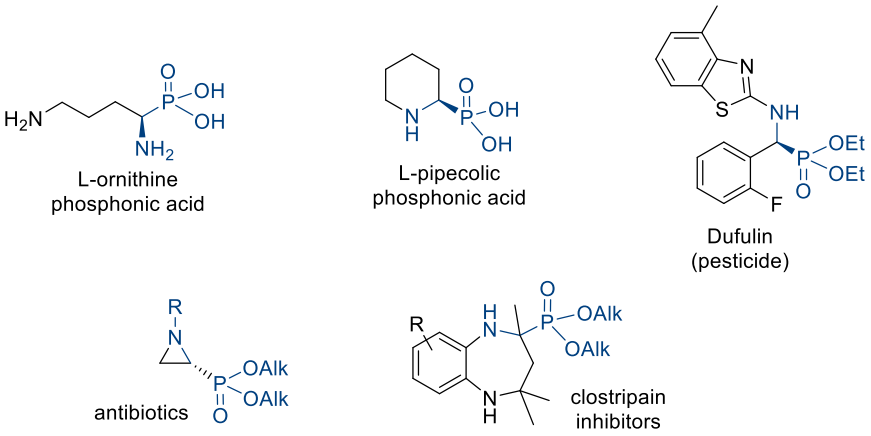
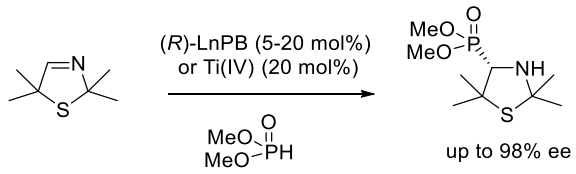


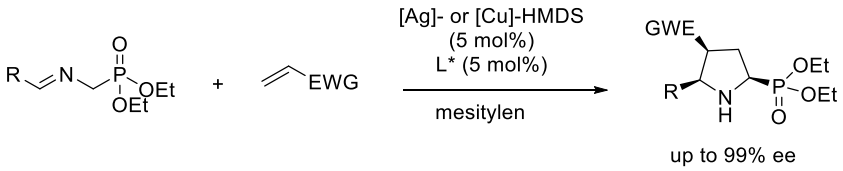
Figure 1 Representative bioactive α-aminophosphonic acid derivatives.

Several methods for the synthesis of α-aminophosphonic acid derivatives have been reported.[7] However, only scarce asymmetric approaches to cyclic α-aminophosphonic acids are available and most of them rely on metal catalysis. For example in 1998, a catalytic enantioselective hydrophosphonylation of cyclic imines catalyzed by chiral heterobimetallic lanthanoid complexes was reported by the group of Shikasaki (Scheme 1).[8] They demonstrated an asymmetric approach to cyclic *R*-aminophosphonates using thiazolines as the imine model component and a heterobimetallic (*R*)-LnPB-catalyst (Ln = lanthanoid metal, P = potassium, B = (*R*)-binaphthol) for the hydrophosphonylation of the C=N double bond with up to 98% enantiomeric excess and 98% yield.



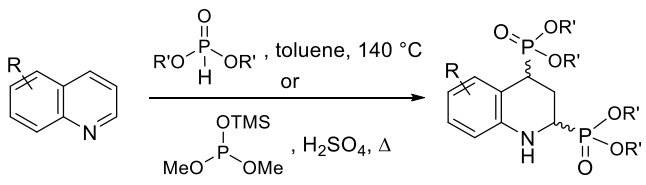
Scheme 1 Enantioselective hydrophosphonylation catalyzed by (*R*)-LnPB or Ti(IV) complexes.

More recently, in 2015 Kobayashi and his group described a catalytic asymmetric *endo*-selective [3+2]-cycloaddition reaction of Schiff bases of α-aminophosphonates with olefins, obtaining cyclic α-aminophosphonic acids in high yields (up to 90%) and enantioselectivities (up to 99% ee) (Scheme 2).[9] They introduced a [Ag]- or [Cu]-amide catalyst bearing a chiral ligand to control the endo- and enantioselectivity.



Scheme 2 Catalytic asymmetric endo-selective [3+2]-cycloaddition reaction between olefins and Schiff bases of α-aminophosphonates.

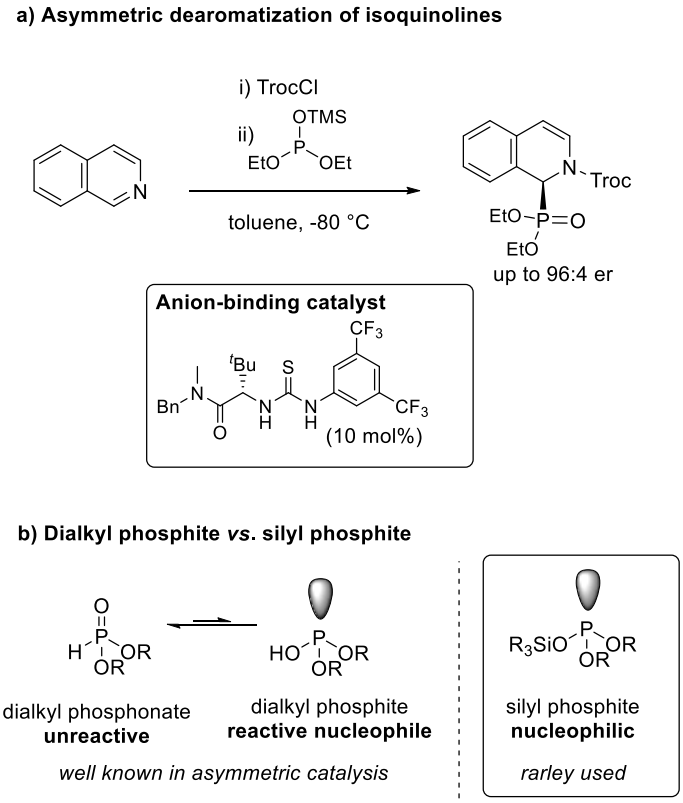
A different interesting and highly straightforward approach for the formation of aza-heterocyclic phosphonic acid derivatives consists in the dearomatization of readily available *N*-heteroarenes with phosphorous nucleophiles (Scheme 3).[10] However, besides few examples of the racemic addition of phosphites to the *N*-acyl salts,[11] most of the common metal-free routes to α-aminophosphonic acids from heteroarenes require harsh temperature and acidic conditions, hampering the development of selective and asymmetric versions (Scheme 3).[12]



Scheme 3 Nucleophilic dearomatization of quinolines.

In this regard, the Mukherjee's group recently reported on a thiourea-based anion-binding-catalyzed[13],[14] asymmetric dearomatization of isoquinolines by acylation and subsequent reaction with trimethylsilyl-substituted phosphites (Scheme 4 a).[15] They showed that by

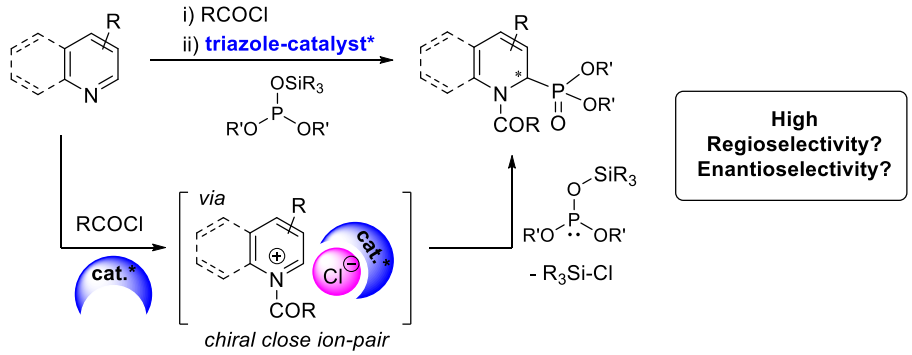
anion-binding catalysis cyclic α-aminophosphonates could be synthesized in excellent yields with moderate to high enantioselectivities (up to 94% ee). Instead of the popular dialkyl- or trialkylphosphites, they used the less common silyl esters of dialkyl phosphonates (silyl phosphites) as nucleophiles which showed high reactivity (Scheme 4 b).[16] In 2015, the group of List introduced this class of nucleophiles in a catalytic enantioselective Abramov reaction.[10f] However, apart from these two examples, the use of silyl phosphites in asymmetric synthesis remains rare.



Scheme 4 Thiourea-based anion-binding-catalyzed asymmetric dearomatization of isoquinolines.

3.1.2 Objectives

Inspired by the work of Mukherjee and based on the observed superior performance of our recently developed triazole-based chiral H-donor catalyst[17] with the more challenging substrates quinolines and pyridines,[18] we decided to explore the enantioselective dearomatization of these heteroarenes with phosphorous nucleophiles (Scheme 5).



Scheme 5 Triazole-based anion-binding catalysis for the enantioselective dearomatization of *N*-heteroarenes with P-nucleophiles.

The key step is the formation of a chiral close ion-pair between an *in situ* generated *N*-acyl salt and the triazole catalyst-chloride anion complex, which is responsible for the chirality transfer to the product.

To achieve high regio- and enantioselectivities and to get a deeper insight in the operating modes of our catalyst, the following steps will be performed:

- Initial optimization of the reaction with quinoline and different P-nucleophiles
- Scope of the reaction with various quinoline and pyridine derivatives
- Study other phosphorous nucleophiles of different nature
- Further derivatization reactions of the chiral aminophosphonates

3.1.3 Results and Discussion

3.1.3.1 Initial Optimization

For our first studies, the reaction of quinoline (**2a**) as substrate, TrocCl as acylating agent and diethyl(trimethylsilyl)phosphite (**3a**) as phosphorous nucleophile was chosen as model transformation (Table 1). The study was initially carried out in the presence of triazole-**1a**, which proofed to be the best catalyst in the dearomatization of quinolines and pyridines with silyl ketene acetals.[16] Several aprotic solvents such as ethers (MTBE, Et_2O or THF, entries 1-3) and aromatics (toluene, ethylbenzene or cumene, entries 4-6) were tested at low temperatures (-90 to -80 °C). Although this type of triazole catalysts generally provides the best enantiomeric inductions in ethereal solvents, **1a** showed a higher performance in aromatic solvents with this type of nucleophile (up to 92:8 e.r.). Consequently, toluene was chosen as solvent for further optimization studies. The effect of the substitution at the phosphite **3** was then evaluated (entries 7-12). While the substitution at the silyl group did not significantly affect to the reaction outcome, the nature of the alkoxy groups was determining. Thus, alkylic chains were well suitable, from which the *n*-butyl group provided the best enantioselectivity of 94:6 e.r. (entry 8). On the other hand, aromatic rests such as phenyl were not tolerated, being not reactive under the employed conditions (entry 10). Other triazole-based chiral H-donor catalysts such as regioisomeric tetrakistriazoles **1a'**, **1b** and **1c**, and bistriazole **1d** were next explored (entries 13-16, Figure 2). As expected, the tetrakistriazoles **1a**-**1c** were superior to the chiral bistriazole **1d**. Moreover, the same high enantioselectivity (94:6 e.r.) was observed with the catalysts **1a** and **1c**. However, due to the more simplicity in the synthesis of **1a**, this catalyst was chosen as the ideal structure. Finally, no loss of catalyst efficiency was obtained by decreasing it's loading to 5 or even 2.5 mol%, both resulting in the same high 95:5 e.r. (entries 17-18). The reaction could also be scaled up 10 times (to 1 mmol scale), maintaining the high levels of reactivity and enantioselectivity (entry 18, in brackets).

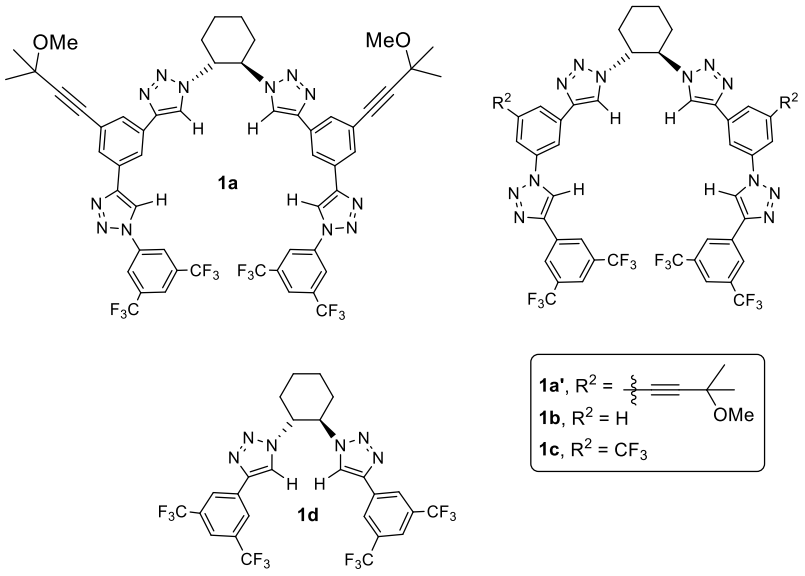
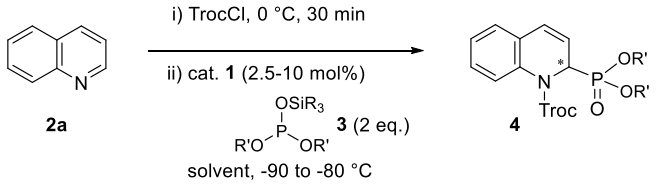


Figure 2 Catalysts tested in model reaction.

Table 1. Optimization of the reaction conditions with quinoline (**2a**).[a]



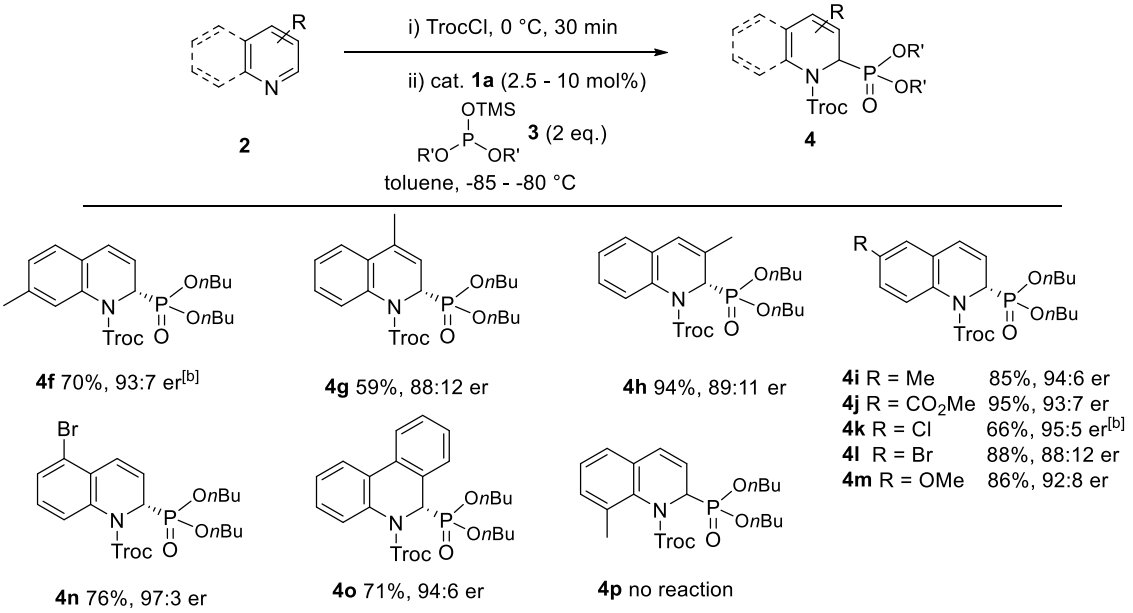
Entry	Cat. **1** (mol%)	R_3Si, R' (**3**)	Solvent	**4**, yield (%)[b]	e.r. [c]
1	**1a** (10)	TMS, Et (**3a**)	MTBE	**4a**, 98	85:15
2	**1a** (10)	TMS, Et (**3a**)	Et_2O	**4a**, 64	81:19
3	**1a** (10)	TMS, Et (**3a**)	THF	**4a**, 99	63:37
4	**1a** (10)	TMS, Et (**3a**)	toluene	**4a**, 99	90:10
5	**1a** (10)	TMS, Et (**3a**)	EtC_6H_5	**4a**, 89	92:8
6	**1a** (10)	TMS, Et (**3a**)	cumene	**4a**, 94	86:14
7	**1a** (10)	TMS, Me (**3b**)	toluene	**4b**, 99	90:10
8	**1a** (10)	TMS, *n*Bu (**3c**)	toluene	**4c**, 94	94:6
9	**1a** (10)	TMS, *i*Pr (**3d**)	toluene	**4d**, 95	90:10
10	**1a** (10)	TMS, Ph (**3e**)	toluene	**4e**, ---	---
11	**1a** (10)	TBS, *n*Bu (**3f**)	toluene	**4c**, 80	91:9
12	**1a** (10)	DMPS, *n*Bu (**3h**)	toluene	**4c**, 78	92:8
13	**1a'** (10)	TMS, *n*Bu (**3c**)	toluene	**4c**, 92	92:8
14	**1b** (10)	TMS, *n*Bu (**3c**)	toluene	**4c**, 97	82:18
15	**1c** (10)	TMS, *n*Bu (**3c**)	toluene	**4c**, 92	94:6
16	**1d** (10)	TMS, *n*Bu (**3c**)	toluene	**4c**, 90	69:31
17	**1a** (5.0)	TMS, *n*Bu (**3c**)	toluene	**4c**, 85	95:5
18	**1a** (2.5)	TMS, *n*Bu (**3c**)	toluene	**4c**, 86(87) [d]	95:5 (92:8)[d]

[a] Conditions: i) **2a** (0.1 mmol, 1.0 eq.) and TrocCl (1.0 eq.) in the corresponding solvent at 0 °C, 30 min; then ii) at -90 °C, the catalyst **1** and nucleophile **3** (2.0 eq.) were added and stirred for 18 h (-90 to -80 °C overnight). [b] Isolated yields. [c] E.r. determined by chiral HPLC. [d] 1 mmol scale reaction in brackets.

3.1.3.2 Scope of the Reaction with Various Quinoline and Pyridine Derivatives

The screening of the substrate scope with catalyst **1a** was next carried out (Table 2). Together with Qui-Nhi Duong, a variety of substituted quinolines were explored using 2.5 or 5 mol% of **1a**. The method showed to be general, tolerating both electron donating and withdrawing groups, as well as substitution at nearly every position (**4f** – **4o**) except for postion C8 of the quinoline core (**4p**). In all the cases, the products were obtained with good to excellent yields and enantioselectivities (up to 97:3 e.r.). Furthermore, polycyclic systems such as phenanthridine could be enrolled in the reaction, leading to the corresponding α-aminophosphonate **4o** in a high enantiomeric ratio of 94:6. In this case, although the same enantioselectivity was obtained, 5 mol% of **1a** was employed to achieve a higher yield (**4o**, 71% vs. 30% with 2.5 mol%). Moreover, it is worthy to mention that the reaction proceeded with complete regioselectivity towards the 2-addition products, with exception of 7-methyl (**4f**) and 6-chloroquinoline (**4k**), in which the formation of the 4-addition products was also observed. For those cases, moisture could be responsible for the formation of some 4-addition product. Generally, under incompletely dry conditions, a loss of reactivity and regioselectivity was observed.

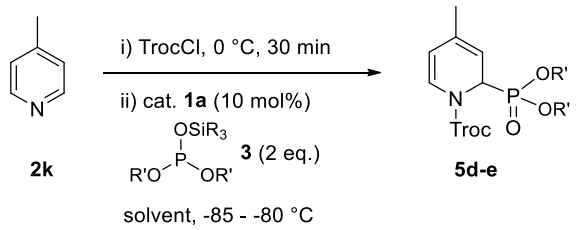
Table 2 Scope of various quinoline derivatives.[a]



[a] Conditions: i) **2** (1.0 eq.) and TrocCl (1.0 eq.) in toluene or MTBE at -80 °C, 30 min; then ii) at -85 °C, the catalyst **1a** (10 mol%) and **3** (2.0 eq.) were added and stirred for 18 h (-85 to -80 °C overnight). Isolated yields are shown. E.r. determined by chiral HPLC. [b] Concomitant formation of the 4-addition product (see the experimental part for details).

Based on the good results obtained with quinolines, the more demanding pyridines were subsequently investigated. Since the pyridine structure acts different as the quinolines, due to full dearomatization of the ring, a re-optimization of the reaction conditions had to be carried out. 4-Methylpyridine (**2k**) and 10 mol% of catalyst **1a** were used to test different solvents, phosphites and reaction times (Table 3). First, a solvent screening was carried out using **3a** as a nucleophile (entries 1-6). Under various etheral and aromatic solvents, MTBE and toluene proofed to be the best yielding high yields (81%) and enantioselectivities around 80:20 e.r. (entries 1-2). Later, a screening of nucleophiles was done, whereby both, MTBE and toluene was used as a solvent. Furthermore, the reaction time was extended to 36 h to improve the yield and the enantioselective outcome (entries 7-15). Under the tested nucleophiles, it was observed that greater steric hinderance lead to higher enantioinduction. Thus, alkylic chains were well suitable, from which the *n*-butyl group in MTBE provided the best enantioselectivity of 81:19 e.r. (entry 11). On the other hand, the methyl goup did not lead to any conversion of the product (entry 8; 12). Additionally, the extension of the reaction time did not really enhance the enantioselective outcome, but a drop in yield was observed.
Since we did not get a clear information about the behavior of the pyridine derivatives under the reaction conditions, a short re-optimization for 3-methylpyridine (**2j**) was next carried out (Table 4).

Table 3 Re-optimization-screening for 4-methylpyridine (**2k**)[a]

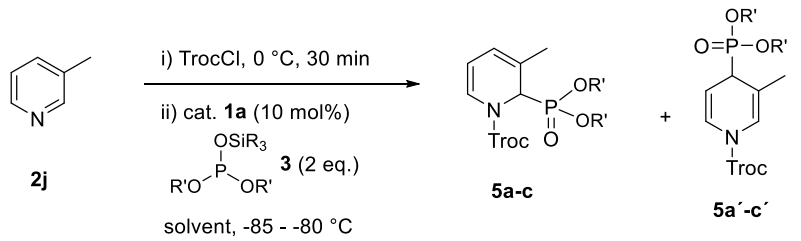


Entry	R_3Si, R' (**3**)	Solvent	t [h]	Yield [%][b]	e.r.[c]
1	TMS, Et (**3a**)	MTBE	18	81	78:22
2	TMS, Et (**3a**)	toluene	18	81	82:18
3	TMS, Et (**3a**)	DCM	18	21	52:48
4	TMS, Et (**3a**)	Et_2O	18	55	78:22
5	TMS, Et (**3a**)	cumene	18	49	58:42
6	TMS, Et (**3a**)	EtC_6H_5	18	30	62:38
7	TMS, Et (**3a**)	MTBE	36	52	77:23
8	TMS, Me (**3b**)	MTBE	36	-	-
10	TMS, *i*Pr (**3d**)	MTBE	36	94	76:24
11	TMS, *n*Bu (**3c**)	MTBE	36	67	81:19
12	TMS, Me (**3b**)	toluene	36	-	-
13	TMS, Et (**3a**)	toluene	36	36	69:31
14	TMS, *i*Pr (**3d**)	toluene	36	66	75:25
15	TMS, *n*Bu (**3c**)	toluene	36	15	65:35

[a] Conditions: i) 4-Methylpyridine (**2k**) (0.1 mmol, 1.0 eq.) and TrocCl (1.0 eq.) in the corresponding solvent at 0 °C, 30 min; then ii) at -90 °C, the catalyst **1a** and nucleophile **3** (2.0 eq.) were added and stirred for 18 h at -90 to -80 °C. [b] Isolated yields. [c] E.r. determined by chiral HPLC.

Since 3-methylpyridine (**2j**) consists of two reactive sites, the C2 and the C4 position we were interested to see if the reaction conditions have a great influence on regioselectivities. Testing various solvents (entries 1-6), once more, MTBE and toluene proofed to be the best solvents for this reaction yielding the same enantiomeric ratios (83:17 e.r.) of the 2-addition product **5a** (entries1-2). However, toluene was superior in terms of regioselectivity, only yielding the 2-addition product **5a,** whereas in MTBE the 4-addition product **5a´**was formed in 11% yield and a moderate enantiomeric ratio (63:37 e.r.). Changing the ethyl group of the nucleophile to a *n*-butyl or a *iso*-propyl group (entries 7-10), similar enantiomeric ratios were obtained, whereby *n*-butyl phosphite in toluene gave **5b** in high yield (84%), complete regioselectivity and good enantioselectivity (85:15 e.r.) (entry 8).

Table 4 Re-optimization-screening for 3-methylpyridine (**2j**)[a]

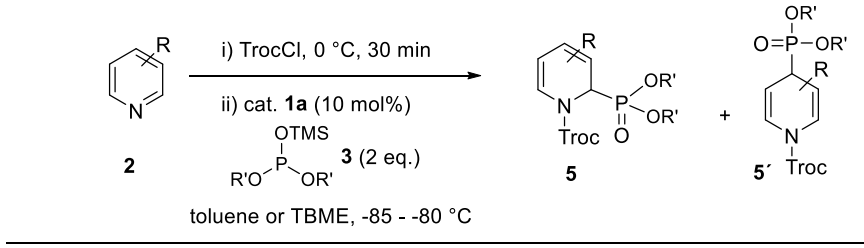


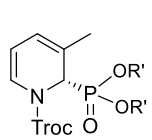
Entry	R_3Si, R′ (**3**)	Solvent	Product [%] **5** (**5´**)[b]	e.r. [c] **5** (**5´**)
1	TMS, Et (**3a**)	MTBE	**5a** 81 (11)	83:17 (63:37)
2	TMS, Et (**3a**)	toluene	**5a** 89 (-)	83:17 (-)
3	TMS, Et (**3a**)	DCM	**5a** 52 (19)	52:48 (51:49)
4	TMS, Et (**3a**)	Et_2O	**5a** 37 (27)	61:39
5	TMS, Et (**3a**)	THF	**5a** 37 (22)	74:26
6	TMS, Et (**3a**)	hexane	**5a** 56 (19)	45:55
7	TMS, *n*-Bu (**3b**)	MTBE	**5b** 76 (-)	80:20 (-)
8	TMS, *n*-Bu (**3b**)	toluene	**5b** 84 (-)	85:15 (-)
9	TMS, *i*-Pr (**3c**)	MTBE	**5c** 26 (41)	77:23 (-)
10	TMS, i-Pr (**3c**)	toluene	**5c** 88 (7)	81:19 (73:27)

[a] Conditions: i) 3-Methylpyridine (**2j**) (0.1 mmol, 1.0 eq.) and TrocCl (1.0 eq.) in the corresponding solvent at 0 °C, 30 min; then ii) at -90 °C, the catalyst **1a** and nucleophile **3** (2.0 eq.) were added and stirred for 18 h at -90 to -80 °C. [b] Isolated yields. [c] E.r. determined by chiral HPLC.

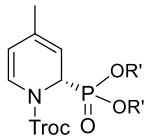
The scope of various pyridine derivatives was then carried out using toluene or MTBE as solvent and 10 mol% of **1a** as catalyst (Table 5). The regioselectivities (mixtures of 2-/4-addition) and the enantioselectivities were uniformly lower as for the quinoline substrates. However, considering the more challenging nature of pyridines, the obtained results are the state-of-the-art for this heteroarenes. In this regard, products **5a**, **5b**, **5c** and **5h** were obtained in good yields and enantioselectivities (up to 85:15 e.r.) but regioselectivity was not complete. On the other hand, with products **5d-g** no 4-addition product, but good enantioselectivities (up to 82:18 e.r.) were observed. Furthermore, it was shown that substitution in every position of the pyridine was tolerated yielding the desired products in good regio- and enantioselectivities and moderate to high yields.

Table 5 Scope of various pyridine derivatives. [a]

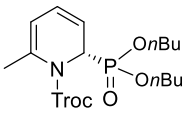




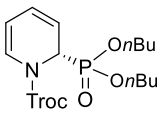
5a R' = Et 89%, 83:17 er[b]
5b R' = Bu 84%, 85:15 er[b]
5c R' = *i*Pr 88%, 81:19 er[b]



5d R' = Et 81%, 82:18 er
5e R' = Bu 67%, 81:19 er
5f R' = *i*Pr 94%, 76:24 er



5g 78%, 85:15 er

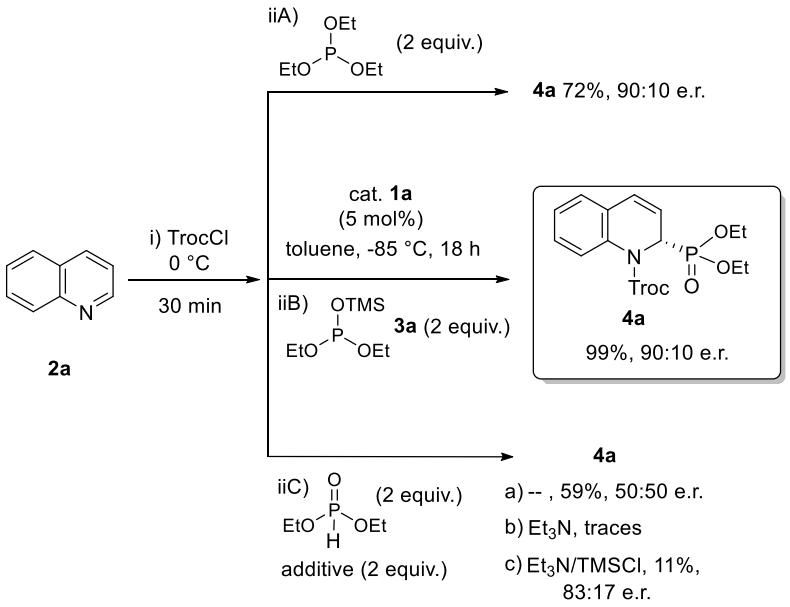


5h 94%, 80:20 er[b]

[a] Conditions: i) **2** (1.0 eq.) and TrocCl (1.0 eq.) in toluene or MTBE at -80 °C, 30 min; then ii) at -85 °C, the catalyst **1a** (10 mol%) and **3** (2.0 eq.) were added and stirred for 18 h at -85 to -80 °C. See the experimental part for the exact conditions for each substrate. Isolated yields are shown. E.r. determined by chiral HPLC. [b] Concomitant formation of the 4-addition product **5´** (see experimental part for details).

3.1.3.3 Application of Other Phosphorous Nucleophiles

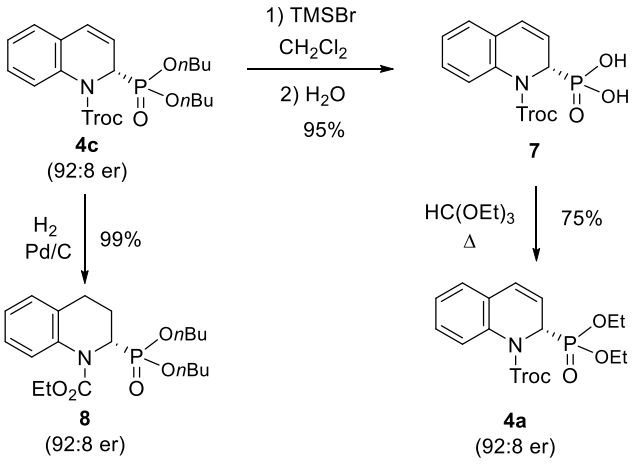
The possibility of employing other phosphorous nucleophiles of different nature was next explored (Scheme 6). First, the reactivity of a trialkylphosphite and a non-protected dialkylphosphite was compared to the corresponding silylated phosphite **3**. Triethylphosphite worked well, providing the product in good yield (72% *vs.* 99%) and same enantioselectivity (90:10 e.r.) (Scheme 6, iiA). On the other hand, the less nucleophilic dialkylphosphite[19] showed a lower reactivity and led to a racemic product (Scheme 6, iiC) a)). Moreover, when the corresponding phosphite anion was generated *in situ* under standard conditions using Et_3N as base, no reaction was observed (Scheme 6, iiC) b)). The *in situ* formation and reaction of TMS-phosphite delivered the product in only 11% and a significant lower enantioselectivity (83:17 *vs.* 90:10 e.r.) (Scheme 6, iiC) c)).



Scheme 6 Application of other phosphorous nucleophiles.

3.1.3.4 Derivatization of the Chiral Aminophosphonates

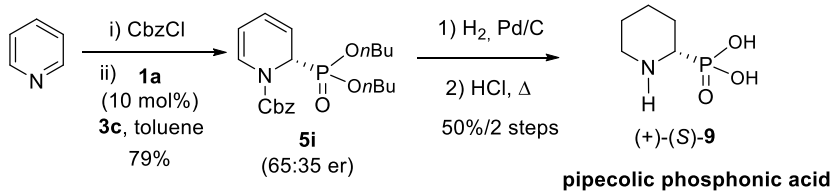
Finally, the applicability of the method was illustrated by the derivatization of the formed chiral α-aminophosphonates **4** and **5** (Scheme 7). Thus, the corresponding phosphonic acid **7** was easily obtained by treatment of **4c** with TMSBr. This reaction preceded without loss of enantiopurity, which could be determined after re-esterification with ethyl orthoester. Moreover, **4c** could also be hydrogenated to provide the tetrahydroquinoline derivative **8**.



Scheme 7 Derivatization of the chiral α- aminophosphonates.

To assign the absolute configuration of the phosphonates **4**/**5**, the reaction of pyridine with CbzCl was performed. Although a lower asymmetric induction was observed with this acylating agent (65:35 e.r.), it permitted the straightforward synthesis of pipecolic phosphonic

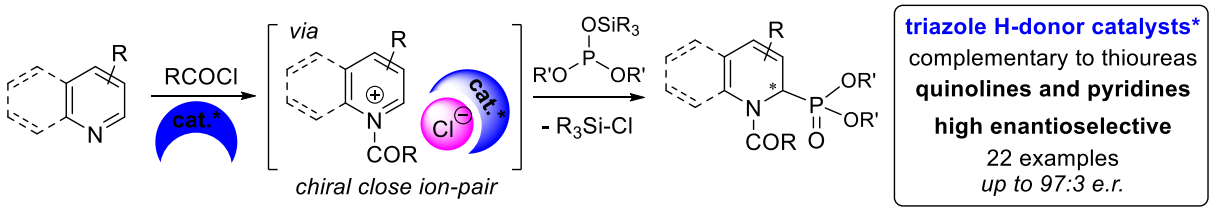
acid **9** by hydrogenation and phosphonate hydrolysis (Scheme 8). Consequently, the absolute configuration was determined to be (*S*) by comparison of the optical rotation with the reported literature (*R*)-**9** [α] : −4.5 (c 1.0, (1 M NaOH)).[20]



Scheme 8 Determination of the absolute configuration.

3.1.4 Conclusion

In conclusion, the first enantioselective synthesis of chiral cyclic α-aminophosphonic acid derivatives by nucleophilic dearomatization of quinolines and pyridines using an anion-binding organocatalysis approach has been developed.



Tetrakistriazole-based H-bond donor catalysts were highly effective with both silyl-protected dialkyl- and trialkylphosphites as nucleophiles, providing the corresponding products in complete or high regioselectivities, and up to 97:3 e.r. for quinolines or up to 89:11e.r. for the more demanding pyridine substrates. This method allows for easy access to substituted chiral cyclic α-amino phosphonates, which can be further transformed into other phosphonic acid derivatives.

3.1.5 References

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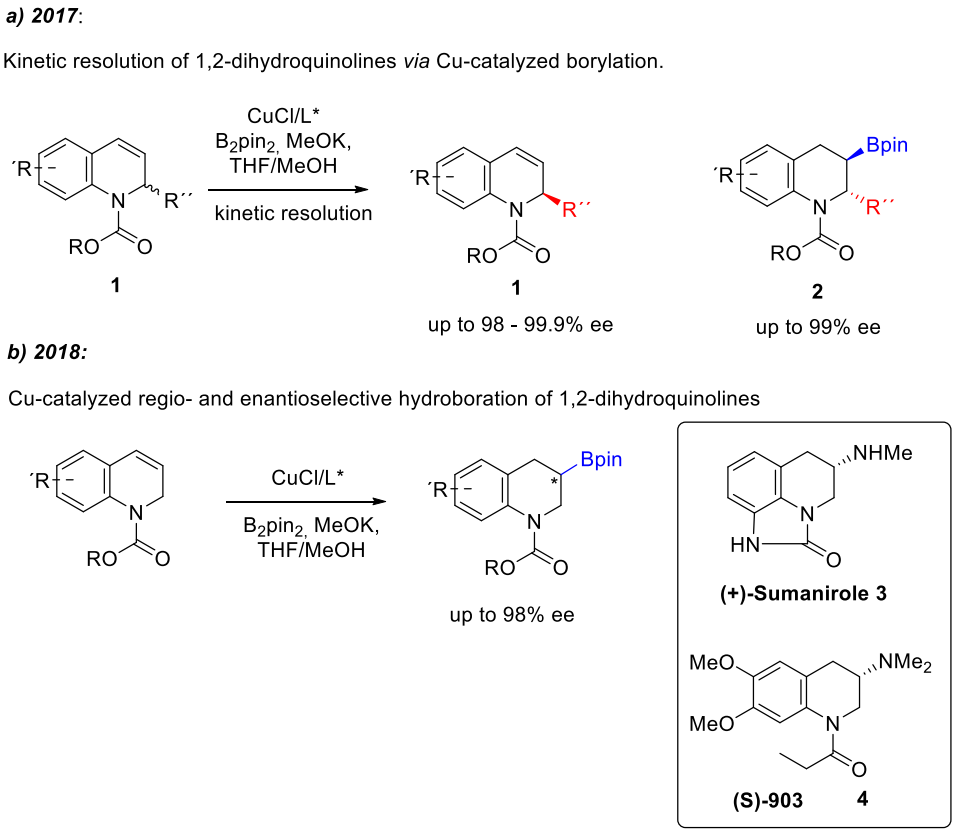
3.2 Triazole-Based Anion-Binding Catalysis for the Enantioselective Dearomatization of *N*-Heteroarenes with Boron-Nucleophiles

3.2.1 Introduction

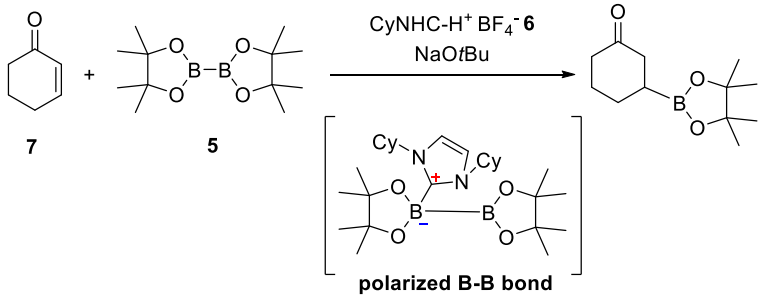
As we demonstrated in our group, dearomatization reactions have emerged as powerful tools to convert planar aromatic compounds into several of three dimensional, highly functionalized cyclic products.[1] Recently, dearomative borylation involving *N*-heteroarenes has gained increasing attention as it can provide saturated or partially saturated borylated *N*-heterocycles that present important building blocks for organic synthesis and bioactive products.[2] The development of an enantioselective C-B bond-forming dearomatization reaction would provide an attractive and complementary approach for the synthesis of complex, functionalized cyclic molecules in combination with the stereospecific transformation of a stereogenic C-B bond. In the last years, Cu-catalyzed hydroborations of unsaturated C-C bonds has gained of interest, leading to the development of a large number of reported methods in this field by famous groups like Tsuji,[3] Tortosa,[4] Feringa[5] or Hartwig.[6] Moreover, Ito *et al.* made an outstanding work on the hydroboration of N-heterocyclic substrates and published high enantioselective Cu-catalyzed hydroboration of indoles,[7] pyridines[8] and dihydroquinolines derivatives[9] *via* an strategy based on a sequential dearomatization/borylation reaction.

However, due to their archetypal Lewis acid character, common routes to organoboranes rely on the reactivity of boron as an electrophile. Therefore, besides hydroborylation reactions with boranes, a main challenge in this field is the formation of the required boron-nucleophile for direct additions. Recently, the group of Zhang reported on a kinetic resolution of racemic 2-substituted 1,2-dihydroquinolines **1** *via* asymmetric Cu-catalyzed borylation with kinetic selectivity factors of up to 569 (Scheme 1a).[2c] Under mild conditions, a variety of chiral 3-boryl-1,2,3,4-tetrahydroquinolines **2** containing two vicinal stereogenic centers and the unreacted 2-substituted 1,2-dihydroquinolines **1** were afforded in high yields with up to 99% ee and dr > 99:1, and over 98% ee values, respectively. This year, the same group published an enantioselective synthesis of boryl tetrahydroquinolines *via* Cu-catalyzed hydroboration (Scheme 1b).[2d] They were also able to apply this strategy in the enantioselective synthesis of the potential agent sumanirole **3** for the treatment of Parkinson's disease and of the positive inotropic agent (*S*)-903 **4** (Scheme1).



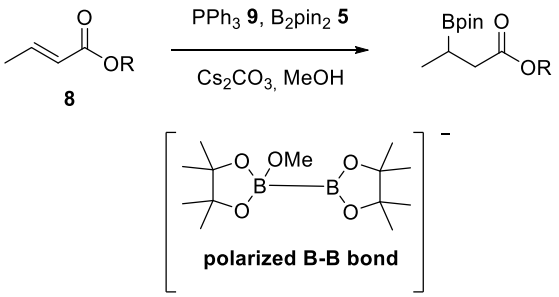
Scheme1 Cu-catalyzed hydroboration of 1,2-dihydroquinolines.

Recently, a few methods have been reported on the metal-free formation of boron-nucleophiles. Hoveyda *et al*. postulated that a neutral, intermolecular Lewis base adduct of B_2pin_2 **5** and a N-heterocycliccarbene (NHC) **6** can act as a boron-nucleophile in the NHC-catalyzed β-borylation of α,β-unsaturated ketones **7** (Scheme 2).[10] This constitutes a novel organocatalytic process distinct from those previously reported involving Cu-catalysis.[11] Due to mechanistic studies, 10 mol% of carbene can activate the diboron reagent (B_2pin_2) **5** by nucleophilic attack at one of the boron atoms and formation of a boronate species.



Scheme 2 NHC-catalyzed borylation reported by Hoveyda *et al*.

Almost simultaneously the group of Fernandez described a method for the synthesis of β-borated carbonyl compounds by reacting B_2pin_2 **5** with α,β-unsaturated esters **8** in the presence of a phosphine catalyst **9**. The reaction is not only metal-free, but also only requires simple additives such as MeOH, an inorganic base and a phosphine like triphenylphosphine to create a nucleophilic boron-species (Scheme 3).[13]

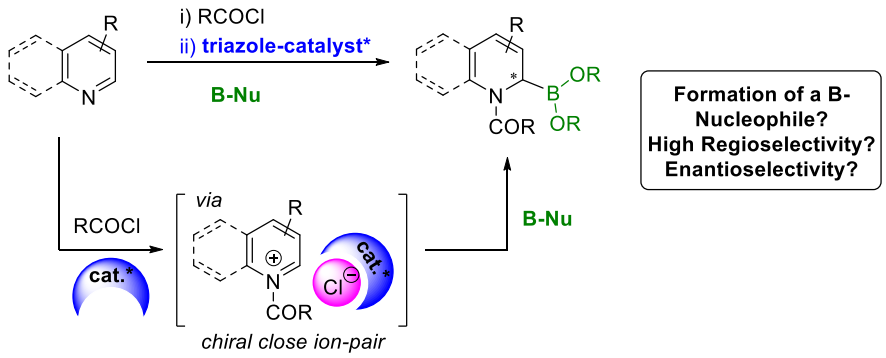


Scheme 3 Phosphine-mediated catalytic β-boration of α,β-unsaturated esters with B_2pin_2.

3.2.2 Objectives

Inspired by the recent work of enantioselective hydroboration of 1,2-dihydroquinolines, the new approaches towards nucleophilic boron-reagents and our expertise in triazole-based anion-binding catalysis for enantioselective dearomatization of *N*-heteroarenes[1] we aimed at combining these stratgeties and developing a new methodology based on the enantioselective dearomatization of *N*-Heteroarenes by triazole-based anion-binding catalysis with boron-nucleophiles.

The previous work in this field with *N*-heterocycles is limited to 1,2-dihydroquinolines substrates that must be first gained by reduction of the corresponding quinolines, Therefore, we envisioned to overcome this restraint by introducing the boron-nucleophile into a previously *in situ* generated *N*-acyl salt. Consequently, the triazole catalyst would bind the ionic substrate, forming a chiral close ion-pair that would be responsible for the chirality transfer to the final product (Scheme 4).



Scheme 4 Triazole-based anion-binding catalyzed enantioselective dearomatization of *N*-heteroarenes with B-nucleophiles.

To achieve the main goal of this chapter, the following points will be addressed:

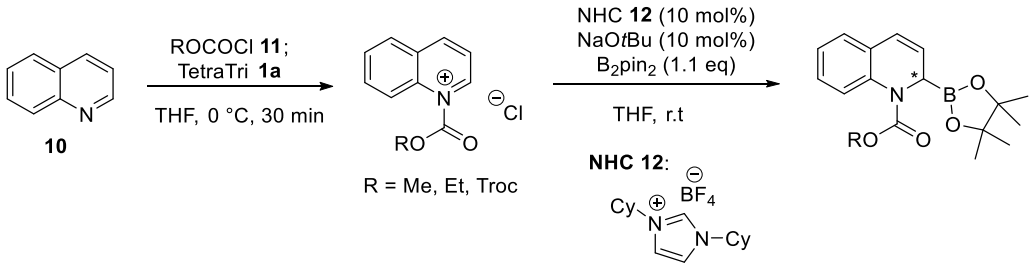
- Optimization of the borylation reaction conditions under metal-free conditions
- Optimization of the Cu-catalyzed borylation with quinoline as model substrate
- Study of the scope of the reaction with different N-heteroarenes

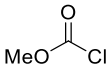
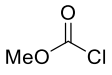
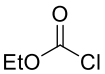
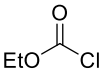
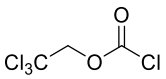
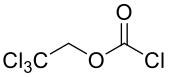
3.2.3 Results and Discussion

3.2.3.1 Metal-free Borylations

To achieve a complete metal-free asymmetric dearomatization of *N*-heteroarenes with boron-nucleophiles, initial attempts were carried out following the recently published reaction conditions from Hoveyda.[10a] Therefore, quinoline **10** was used as a model substrate and an acylating agent **12** was added at 0 °C to form the *N*-acyl salt.[12] *N*-Heterocyclic carbene **12** served as catalysts to polarize the B-B bond of the bis(pinacolato)diboron **5**. All steps were carried out in an Ar-filled glove box to avoid any decomposition of the *in situ* generated reactive boron reagent by moisture or oxygen. Unfortunately, neither by changing the acylating agent (entries 1-5), nor by adding additives like MeOH (entry 6) afforded any conversion. Pure quinoline starting material **10** was isolated, which pointed to the fact that the nucleophilic boron-species was not formed.

Table 1 Initial Optimization of the dearomatization of quinoline promoted by N-heterocyclic carbenes.[a]

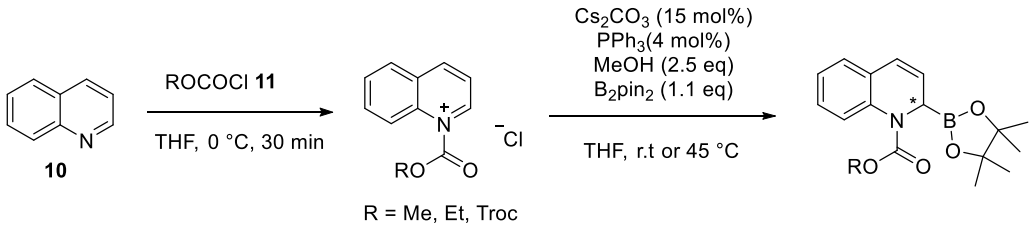


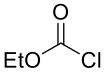
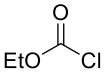
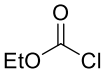
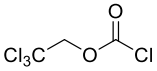
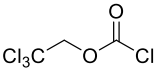
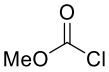
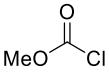
Entry	Acylating reagent **11**	Additive	TetraTri **1a**	Conversion (%)
1		-	-	-
2		-	10 mol%	-
3		-	-	-
4		-	10 mol%	-
5		-	-	-
6		MeOH	-	-

[a] Conditions: i) Quinoline **10** (1.0 eq.) and acylating agent (1.0 eq.) in THF at 0 °C, 30 min; then ii) the catalyst **1a** (10 mol%), NHC (10 mol%), NaO*t*Bu (10 mol%) and B_2pin_2 (1.1 eq.) were added and stirred for 18 h. All steps were carried out in an Ar-filled glovebox.

In a next step, a phosphine-based catalytic system was used to form the nucleophilic boron-species. Therefore, we followed the reported reaction conditions of the group of Fernandez using triphenyl phosphine, MeOH and the cesium carbonate base as additives (Table 2).[13] The acylating agent **11**, additives and temperature were screened, but unfortunately without any success. No conversion of the quinoline starting material could be observed.

Table 2 Initial optimization of the dearomatization of quinoline promoted by a phosphine-based catalyst.[a]



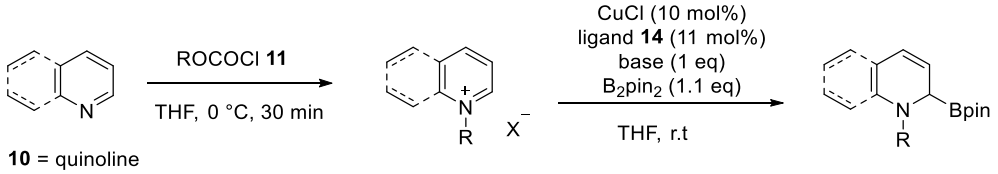
Entry	Acylating reagent **11**	P-catalyst	Temp [°C]	Conversion (%)
1		-	45	-
2		PPh_3	45	-
3		PPh_3	r.t.	-
4		PPh_3	r.t.	-
5		PPh_3	60	-
6		-	60	-
7		PPh_3	60	-

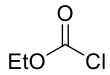
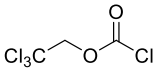
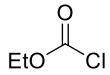
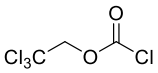
[a] Conditions: i) Quinoline **10** (1.0 eq.) and acylating agent (1.0 eq.) in THF at 0 °C, 30 min; then ii) the phosphine catalyst (10 mol%), Cs_2CO_3 (10 mol%), MeOH (2.5 eq.) and B_2pin_2 (1.1 eq.) were added and stirred for 18 h. All steps were carried out in an Ar-filled glovebox.

3.2.3.2 Cu(I)-Catalyzed Borylations

Since all our attempts of a full metal-free dearomatization of quinolines did not gave any satisfactory result, we decided to change to a Cu(I)-catalyzed formation of the boron-nucleophile. With the knowledge of our cooperation partner Mariola Tortosa (U.A.M., Spain) in boron chemistry, we introduced a catalytic Cu(I) species (CuCl) and screened various reaction conditions (Table 3).[4, 14]

Table 3 Initial optimization of the Cu(I)-catalyzed dearomatization of quinoline and pyridine.[a]



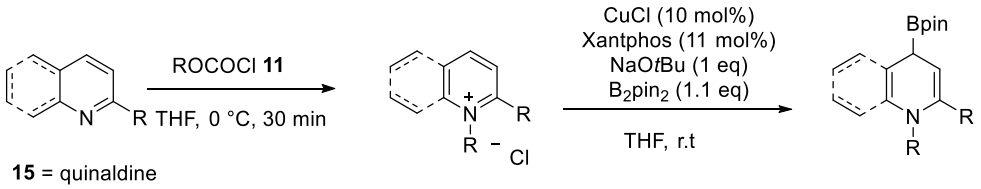
Entry	substrate	Acylating reagent **11**	Ligand **14**	Base	conversion (%)
1	**13**		xantphos	NaO*t*Bu	decomp
2	**13**		xantphos	NaO*t*Bu	decomp
3	**13**	MeOTf	PCy_3	NaO*t*Bu	decomp
4	**13**	MeOTf	PCy_3	MgO*t*Bu	decomp
5	**13**	MeOTf	PCy_3	NaOMe	decomp
6	**10**		xantphos	NaO*t*Bu	decomp
7	**10**		xantphos	NaO*t*Bu	decomp
8	**10**	MeOTf	PCy_3	NaOMe	-
9	**10**	MeOTf	PCy_3	LiO*t*Bu	-
10	**10**	MeOTf	PCy_3	NaO*t*Bu	-

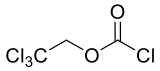
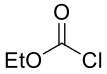
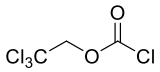
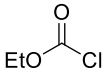
[a] Conditions: i) substrate (1.0 eq.) and acylating agent **11** (1.0 eq.) in THF at 0°C, 30 min; then ii) a solution of CuCl (10 mol%), ligand (11 mol%), base (1.0 eq.) and B_2pin_2 (1.1 eq.) was added to the *N*-acyl salt and stirred for 18 h. All steps were carried out in an Ar-filled glovebox.

A variety of parameters were tested, but none of the applied conditions led to the desired product. In the case of using pyridine as a substrate, only decomposition was observed (entries 1-5), while quinoline gave either decomposition or no conversion (entries 6-10). Since the formation of the *N*-acyl salt was visible in all cases, we imagine a high intrinsic instability of the 2-addition product. Therefore, we tried to block the 2-position of the substrate to force a

4-addition of the boron-nucleophile. Unfortunately, the employed 2-substituted substrates did not give any conversion (entries 1-4, Table 4)

Table 4 Initial optimization of the Cu(I)-catalyzed dearomatization of quinaldine and 2-phenylpyridine.[a]



Entry	substrate	Acylating reagent **11**	conversion (%)
1	**15**		-
2	**15**		-
3	**16**		-
4	**16**		-

[a] Conditions: i) substrate (1.0 eq.) and acylating agent (1.0 eq.) in THF at 0 °C, 30 min; then ii) a solution of CuCl (10 mol%), xantphos (11 mol%), NaO*t*Bu (1.0 eq.) and B_2pin_2 (1.1 eq.) was added to the N-acyl salt and stirred for 18 h. All steps were carried out in an Ar-filled glovebox.

3.2.4 Conclusion

To sum up the obtained results, all our efforts were not successful, and we could not achieve the addition of a boron-nucleophile to a *N*-heteroarene under different dearomatization reaction conditions. It turned out that our original idea was more complex than what we first thought, most probably due to the intrinsic unstable nature of the targeted N,B-products. Therefore, extensive studies will further be required in order to achieve the aims of this project.

3.2.5 References

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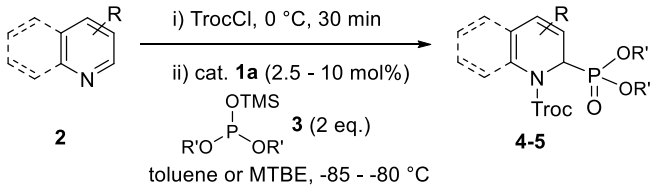
3.3 Experimental part

3.3.1 General Information

^{1}H, **^{13}C** and **^{31}P NMR** spectra were recorded in $CDCl_3$ (reference signals:[1] ^{1}H = 7.26 ppm, ^{13}C = 77.16 ppm, $CDCl_3$) on a *Bruker Advance* 300 or 400 MHz. Chemical shifts (δ) are given in ppm and spin-spin coupling constants (J) are given in Hz. Analytical thin layer chromatography was performed using silica gel 60 F_{254} and a solution of $KMnO_4$ or phosphomolybdic acid served as staining agent. Column chromatography was performed on silica gel 60 (0.040-0.063 mm). Exact masses (HRMS) were recorded on an *Agilent Q-TOF 6540 UHD* spectrometer (samples in CH_3OH as solvent) using electrospray (ESI) or electron (EI) ionization techniques. Chiral High-Pressure Liquid Chromatography (HPLC) analyses were performed on an Agilent 1200 series instrument.

CH_2Cl_2 and Et_3N were distilled over CaH_2. THF, toluene, MTBE and Et_2O were distilled and dried over Na. The different silyl-phosphites **3** were prepared following known literature procedures.[2] Other solvents and commercially available reagents were used without further purification.

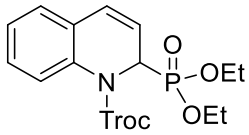
3.3.2 General Procedure for the Catalytic Dearomatization Reaction



The quinoline or pyridine derivative **2** (0.1 mmol, 1.0 eq.) was dissolved in the corresponding anhydrous solvent (1 mL, 0.1 M) and cooled to 0 °C. After the addition of TrocCl (13.8 µL, 0.1 mmol, 1.0 eq.), the reaction was stirred for 30 min at 0 °C and then cooled to - 85 °C. The phosphite **3** (0.2 mmol, 2 eq) and the catalyst **1a** (2.5 to 10 mol%) were added and the resulting mixture was stirred overnight at – 80 °C. Purification by flash column chromatography (petroleum ether/EtOAc) yielded the crude product, which was stirred in NaOH (2 M, 1.0 mL) for 30 min. The organic phase was washed again with NaOH (2 M, 3 x 1 mL) to remove the remaining phosphite, dried over $MgSO_4$, and concentrated in vacuo to obtain the desired product.

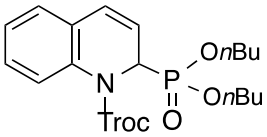
3.3.3 Analytical Data for Compounds 4

2,2,2-Trichloroethyl 2-(di-ethoxyphosphoryl)quinoline-1(2*H*)-carboxylate (4a)



Quinoline (**2a**) (11.8 µL, 0.1 mmol, 1.0 eq.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (11.0 mg, 0.01 mmol, 10 mol%) and diethyl(trimethylsilyl) phosphite (**3a**) (44.4 µL, 0.2 mmol, 2.0 eq.) were reacted in ethylbenzene according to the general procedure. The desired product **4a** (39.4 mg, 0.089 mmol, 89%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as slight pale yellow oil. The enantiomeric ratio was found to be 92:8 by chiral HPLC (Chiralpak IA, Hex/^{i}PrOH 95:5, 1.0 mL/min, λ=300 nm: *t*r (minor): 17.3 min, *t*r (major): 16.3 min. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.17 (s, 1H), 7.04 (q, *J* = 7.3 Hz, 2H), 6.56 (dd, *J* = 9.4, 5.5 Hz, 1H), 6.05 (s, 1H), 5.59 (d, *J* = 20.1 Hz, 1H), 5.04 (d, *J* = 64.8 Hz, 1H), 4.60 (d, *J* = 62.4 Hz, 1H), 3.78 (s, 4H), 1.13 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 152.7, 134.3, 129.3, 128.0, 127.5, 126.5, 125.6, 123.1, 95.0, 76.0, 63.2 (d, *J* = 6.9 Hz), 62.9 (d, *J* = 6.9 Hz), 51.7 (d, *J* = 153.5 Hz), 16.3 (d, *J* = 5.9 Hz), 16.1 (d, *J* = 5.9 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$): δ 19.06 (s, minor rotamer), 18.19 (s, major rotamer); **HRMS** (ESI): *m/z* calculated for $[C_{16}H_{20}Cl_3NO_5P]^+$: 442.0139, found 442.0147.

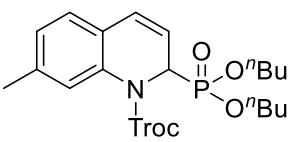
2,2,2-Trichloroethyl 2-(dibutoxyphosphoryl)quinoline-1(2*H*)-carboxylate (**4c**)



Quinoline (**2a**) (11.8 µL, 0.1 mmol, 1.0 equ.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (2.8 mg, 0.0025 mmol, 2.5 mol%) and dibutyl(trimethylsilyl) phosphite (**3c**) (44.4 µL, 0.2 mmol, 2.0 eq.) were reacted in toluene according to the general procedure. The desired product **4c** (42.8 mg, 0.086 mmol, 86%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as slight pale yellow oil. The enantiomeric ratio was determined as 95:5 e.r. by chiral HPLC [Chiralpak IA, hexane/*i*PrOH (95:5), 1.0 mL/min, λ= 300 nm: *t*r (major): 14.6 min, *t*r (minor): 15.5 min]. *Scale-up reaction:* Quinoline (118.2 µL, 1.0 mmol, 1.0 equiv.), TrocCl (142.0 µL, 1.0 mmol, 1.0 equiv.), **1a** (28.0 mg, 2.5 mol%) and phosphite **3c** (440 µL, 2.0 mmol, 2.0 equiv.) were reacted in toluene for 26 h according to the general procedure. The desired product **4c** (433.3 mg, 0,87 mmol, 87%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as slight pale yellow oil. The enantiomeric ratio was detemined as 92:8 e.r. by chiral HPLC [Chiralpak IA, hexane/*i*PrOH (95:5), 1.0 mL/min, λ= 300 nm: *t*r (major): 14.6 min, *t*r (minor): 15.5 min].

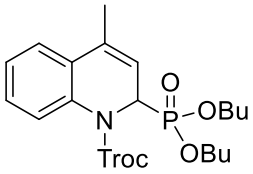
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80- 7.55 (bs, 1H), 7.23 b(s, 1H), 7.17 – 7.04 (m, 2H), 6.61 (dd, *J* = 9.5, 5.3 Hz, 1H), 6.12 (bs, 1H), 5.66 (bd, *J* = 17.6 Hz, 1H), 5.25 - 4.90 (m, 1H), 4.80 - 4.45 (m, 1H), 4.08 – 3.82 (m, 3H), 3.76 (dq, *J* = 9.9, 6.5 Hz, 1H), 1.57 – 1.44 (m, 2H), 1.37 – 1.22 (m, 4H), 1.17 – 1.00 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.78 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.6 (bs), 135.2, 133.1 (bs), 126.8 (bs), 126.4 (d, *J* = 4.1 Hz), 125.5 (d, *J* = 2.0 Hz), 125.3 (bs), 124.4 (bs), 123.1 (bs), 122.1 (bs), 121.0 (bs), 93.9, 74.9 (bs), 65.7 (bs), 65.4 (d, *J* = 6.7 Hz), 50.6 (d, *J* = 153.4 Hz), 31.4 (d, *J* = 6.0 Hz), 31.2 (d, *J* = 6.1 Hz), 17.5 (d, *J* = 12.6 Hz), 12.5 (d, *J* = 6.3 Hz). **^{31}P NMR** (121 MHz, $CDCl_3$) δ 18.40; **HRMS** (ESI): *m/z* calculated for $[C_{20}H_{28}Cl_3NO_5P]^+$: 498.0765; found 498.0773.

2,2,2-Trichloroethyl 2-(dibutoxyphosphoryl)-7-methylquinoline-1(2H)-carboxylate (4f)



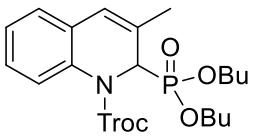
7-Methylquinoline (**2b**) (13.4 µL, 0.1 mmol, 1.0 eq.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (5.6 mg, 0.005 mmol, 5.0 mol%) and phosphite **3c** (44.4 µL, 0.2 mmol, 2.0 eq.) were reacted in toluene according to the general procedure leading to a mixture of **4f** and regioisomer **4f'** (5:1). An inseparable mixture of 2-addition **4f** and 4-addition **4f'** (36.0 mg, 0.070 mmol, 70%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as slight pale yellow oil. The enantiomeric ratio was detemined as 97:3 e.r. by chiral HPLC [Chiralpak IA, hexane/*i*PrOH (95:5), 1.0 mL/min, λ= 300 nm: *t*r (major): 15.6 min, *t*r (minor): 16.6 min]. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 (bs, 1H, 2-add + 1H, 4-add), 7.11 (t, *J* = 7.3 Hz, 1H, 4-add), 6.99 – 6.88 (q, *J* = 7.7 Hz , 2H, 2-add + 1 H 4-add), 6.81 (dd, *J* = 9.7, 5.4 Hz, 1H, 4-add), 6.51 (dd, *J* = 9.5, 5.4 Hz, 1H, 2-add), 6.16 (bs, 1H, 4-add), 6.04 (bs, 1H, 2-add), 5.57 (bd, *J* = 20.4 Hz, 1H, 2-add + 1H, 4-add), 5.30 – 4.90 (m, 1H, 2-add + 1H, 4-add), 4.80 – 4.35 (m, 1H, 2-add + 1H, 4-add), 4.05 – 3.66 (m, 5H, 2-add + 4 H, 4-add), 2.25 (d, *J* = 3.2 Hz, 3H, 2-add), 1.58 – 1.46 (m, 2H, 2-add), 1.35 – 1.22 (m, 4H), 1.14 – 1.01 (m, 2H, 2-add), 0.81 (t, *J* = 7.3 Hz, 3H, 2-add), 0.71 (t, *J* = 7.3 Hz, 3H, 2-add); **^{13}C NMR** (75 MHz, $CDCl_3$) (major product of 2-add) δ 152.6, 138.0, 133.8, 127.7, 127.2, 126.3, 126.1, 125.9, 124.8, 124.7, 121.7, 95.0, 76.0, 66.5 (dd, *J* = 18.9, 7.4 Hz), 51.5 (d, *J* = 153.2 Hz), 32.3 (dd, *J* = 11.3, 6.1 Hz), 18.5 (d, *J* = 12.1 Hz), 13.5 (d, *J* = 6.1 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$) δ 18.62.; **HRMS** (ESI): *m/z* calculated for $[C_{21}H_{30}Cl_3NO_5P]^+$: 512.0922; found 512.0926.

2,2,2-Trichloroethyl 2-(dibutoxyphosphoryl)-4-methylquinoline-1(2*H*)-carboxylate (4g)



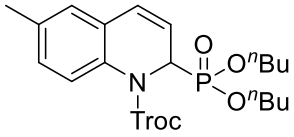
4-Methylquinoline (**2c**) (13.2 µL, 0.1 mmol, 1.0 eq.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (2.8 mg, 0.0025 mmol, 2.5 mol%) and phosphite **3c** (50.0 µL, 0.2 mmol, 2.0 eq.) were reacted in toluene according to the general procedure. The desired product **4g** (30.0 mg, 0.059 mmol, 59%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as a colourless oil. The enantiomeric ratio was found to be 90:10 by chiral HPLC (Chiralpak OD-H, Hex/^{i}PrOH 95:5, 1.0 mL/min, λ =300 nm: *t*r (minor): 7.9 min, *t*r (major): 7.4 min. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.61 (bs, 1H), 7.25 (s, 1H), 7.24 – 7.12 (m, 2H), 5.92 (s, 1H), 5.58 (d, *J* = 18.0 Hz, 1H), 5.11 (d, *J* = 55.5 Hz, 1H), 4.60 (d, *J* = 64.2 Hz, 1H), 4.02 – 3.64 (m, 4H), 2.11 (d, *J* = 5.5 Hz, 3H), 1.61 – 1.43 (m, 2H), 1.35 – 1.20 (m, 4H), 1.14 – 0.97 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.77 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 152.4, 134.9, 133.3, 130.3, 129.1, 127.8, 126.6, 125.3, 123.3, 119.4, 95.0, 75.8, 66.4, 51.3 (d, *J* = 156.8 Hz), 32.5 (d, *J* = 6.0 Hz), 32.3 (d, *J* = 6.1 Hz), 18.6 (d, *J* = 5.8 Hz), 18.5 (d, *J* = 5.5 Hz), 13.6 (d, *J* = 6.1 Hz).; **^{31}P NMR** (121 MHz, $CDCl_3$): δ 18.93; **HRMS** (ESI): *m/z* calculated for $[C_{21}H_{30}Cl_3NO_6P]^+$: 512.0922, found 512.0922.

2,2,2-Trichloroethyl 2-(dibutoxyphosphoryl)-3-methylquinoline-1(2H)-carboxylate (4h)



3-Methylquinoline (**2d**) (13.4 µL, 0.1 mmol, 1.0 eq.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (11.0 mg, 0.01 mmol, 10 mol%) and phosphite **3c** (50.0 µL, 0.2 mmol, 2.0 eq.) were reacted in toluene according to the general procedure. The desired product **4h** (48.6 mg, 0.094 mmol, 94%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as a colourless oil. The enantiomeric ratio was found to be 89:11 by chiral HPLC (Chiralpak IA, Hex/^{i}PrOH 95:5, 1.0 mL/min, λ =300 nm: *t*r (minor): 10.5 min, *t*r (major): 11.4 min. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.73 – 7.52 (m, 1H), 7.16 (s, 1H), 7.08 (td, *J* = 7.4, 1.2 Hz, 1H), 7.02 (d, *J* = 7.3 Hz, 1H), 6.35 (d, *J* = 4.7 Hz, 1H), 5.43 (d, *J* = 20.9 Hz, 1H), 5.15 (d, *J* = 58.9, 11.8 Hz, 1H), 4.60 (dd, *J* = 58.6, 10.8 Hz, 1H), 4.06 – 3.61 (m, *J* = 13.1, 9.8, 6.3 Hz, 4H), 2.12 (s, 3H), 1.62 – 1.42 (m, 2H), 1.39 - 1.18 (m, 4H), 1.15 – 0.99 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.76 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 152.4, 133.2, 128.5 (d, *J* = 3.9 Hz), 126.8, 125.6, 125.4, 124.9, 123.5, 95.0, 75.9, 66.5, 66.3, 55.4 (d, *J* = 148.6 Hz), 32.4 (d, *J* = 5.9 Hz), 32.2 (d, *J* = 6.2 Hz), 21.7, 18.5 (d, *J* = 17.3 Hz), 13.5 (d, *J* = 8.9 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$): δ 18.92; **HRMS** (ESI): *m/z* calculated for $[C_{21}H_{30}Cl_3NO_6P]^+$: 512.0922, found 512.0919.

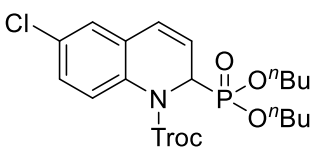
2,2,2-Trichloroethyl 2-(dibutoxyphosphoryl)-6-methylquinoline-1(2H)-carboxylate (4i)



6-Methylquinoline (**2e**) (13.4 µL, 0.1 mmol, 1.0 eq.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (5.6 mg, 0.005 mmol, 5.0 mol%) and phosphite **3c** (44.4 µL, 0.2 mmol, 2.0 eq.) were reacted in toluene according to the general procedure. The desired product **4i** (43.6 mg, 0.085 mmol, 85%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as slight pale yellow oil. The enantiomeric ratio was determined as 94:6 e.r. by chiral HPLC [Chiralpak IA, hexane/*i*PrOH (95:5), 1.0 mL/min, λ= 300 nm: *t*r (major): 13.8 min, *t*r (minor): 15.8 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.60 – 7.40 (m, 1H), 7.03 (bd, *J* = 7.3 Hz, 1H), 6.89 (s, 1H), 6.56 (dd, *J* = 9.5, 5.4 Hz, 1H), 6.09 (bs, 1H), 5.64 (bd, *J* = 20.7 Hz, 1H), 5.25 – 4.90 (m, 1H), 4.80 – 4.40 (t, *J* = 36.2 Hz, 1H), 4.11 – 3.68 (m, 4H), 1.67 – 1.41 (m, 2H), 1.41 – 1.19 (m, 4H), 1.16 – 1.00 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.77 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.8, 135.1, 131.6, 128.5, 128.0, 127.2 (d, *J* = 4.1 Hz), 127.0 (d, *J* = 2.0 Hz), 125.1, 123.0, 95.0, 75.8, 67.09 – 66.01 (m), 51.6 (d, *J* = 153.2 Hz), 32.3 (dd, *J* = 10.1, 6.1 Hz), 20.8 (s), 18.5 (d, *J* = 10.8 Hz), 13.5 (d, *J* = 5.4 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$) δ 18.53; **HRMS** (ESI): *m/z* calculated for $[C_{21}H_{30}Cl_3NO_5P]^+$: 512.0922; found 512.0917.

2,2,2-Trichloroethyl 6-chloro-2-(dibutoxyphosphoryl)quinoline-1(2H)-carboxylate (4k)

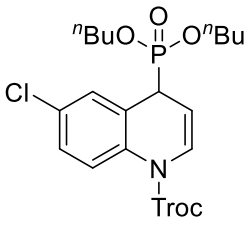
6-Chloroquinoline (**2f**) (16.3 mg, 0.1 mmol, 1.0 eq.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (5.6 mg, 5.0 mol%) and phosphite **3c** (44.4 µL, 0.2 mmol, 2.0 eq.) were reacted in toluene according to the general procedure leading to a mixture of 2.6:1 of **4k** and regioisomer **4k'**. The desired product **4k** (35.0 mg, 0.066 mmol, 66%) and the regioisomer **4k'** (14.0 mg, 0.026 mmol, 26%) were isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as slight pale yellow oil.



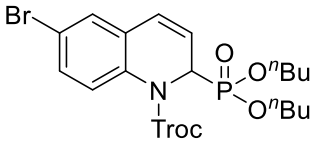
4k: The enantiomeric ratio was determined as 95:5 e.r. by chiral HPLC [Chiralpak IA, hexane/*i*PrOH (95:5), 1.0 mL/min, λ= 300 nm: *t*r (major): 14.6 min, *t*r (minor): 15.5 min]. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.53 (bs, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 2.1 Hz, 1H), 6.54 (dd, *J* = 9.5, 5.4 Hz, 1H), 6.16 (bs, 1H), 5.64 (d, *J* = 19.1 Hz, 1H), 5.09 (m, 1H), 4.60 (m, 1H), 4.12 – 3.77 (m, 4H), 1.60 – 1.40 (m, 2H), 1.38 – 1.23 (m, 4H), 1.16 – 1.02 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.81 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 152.2, 133.2, 131.1 – 130.2 (m, *J* = 14.5, 10.0 Hz), 129.2

(dd, *J* = 16.5, 3.1 Hz), 128.0 – 126.5 (m, *J* = 8.3 Hz), 124.9 – 124.5 (m), 123.4, 118.7 – 118.3 (m), 94.7, 75.9 (d, *J* = 5.1 Hz), 66.5 (d, *J* = 6.7 Hz), 65.5 (d, *J* = 5.9 Hz), 51.5 (d, *J* = 153.6 Hz), 32.3 (dd, *J* = 7.4, 6.3 Hz), 18.5 (d, *J* = 8.1 Hz), 13.6 (d, *J* = 4.1 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$): δ 18.07; **HRMS** (ESI): *m/z* calculated for $[C_{20}H_{27}Cl_4NO_5P]^+$: 532.0375; found 532.0382.

4k': The enantiomeric ratio was determined as 50:50 e.r. by chiral HPLC [Chiralpak IA, hexane/*i*PrOH (95:5), 1.0 mL/min, λ= 300 nm: *t*r (major): 10.5 min, *t*r (minor): 11.5 min]. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.63 (bs, 1H), 7.16 (bs, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.35 (d, *J* = 4.3 Hz, 1H), 5.43 (d, *J* = 20.5 Hz, 1H), 5.15 (m, 1H), 4.57 (m, 1H), 4.00 – 3.64 (m, 3H), 1.57 – 1.49 (m, 2H), 1.34 – 1.23 (m, 4H), 1.15 – 1.00 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H) 0.77 (t, *J* = 7.2, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 152.6, 141.5, 128.5, 126.8, 125.5 (d, *J* = 25.8 Hz), 124.8, 123.9 – 123.2 (m), 94.8, 76.0 – 75.4 (m), 65.5 (d, *J* = 6.0 Hz), 32.6 – 32.2 (m), 23.8, 21.7, 18.6 (d, *J* = 8.7 Hz), 13.5 (d, *J* = 5.5 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$): δ 17.90 - 17.7 (m); **HRMS** (ESI): *m/z* calculated for $[C_{20}H_{27}Cl_4NO_5P]^+$: 532.0375; found 532.0998.

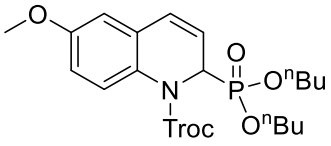


2,2,2-Trichloroethyl 6-bromo-2-(dibutoxyphosphoryl)quinoline-1(2H)-carboxylate (4l)



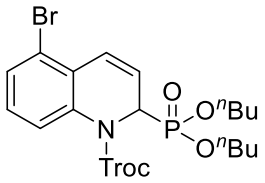
6-Bromoquinoline (**2g**) (20.1 mg, 0.1 mmol, 1.0 eq.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (2.8 mg, 2.5 mol%) and phosphite **3c** (44.4 µL, 0.2 mmol, 2.0 eq.) were reacted in toluene according to the general procedure. The desired product **4l** (51.0 mg, 0.088 mmol, 88%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as slight pale yellow oil. The enantiomeric ratio was determined as 88:12 e.r. by chiral HPLC [Chiralpak IA, hexane/*i*PrOH (95:5), 1.0 mL/min, λ= 300 nm: *t*r (major): 15.4 min, *t*r (minor): 16.5 min]. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.53 (bs, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 2.1 Hz, 1H), 6.54 (dd, *J* = 9.5, 5.4 Hz, 1H), 6.16 (bs, 1H), 5.64 (d, *J* = 19.1 Hz, 1H), 5.09 (m, 1H), 4.60 (m, 1H), 4.12 – 3.77 (m, 4H), 1.60 – 1.40 (m, 2H), 1.38 – 1.23 (m, 4H), 1.16 – 1.02 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.81 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 152.2, 133.3 – 132.8 (m), 130.7 – 130.4 (m), 129.2 (dd, *J* = 16.5, 3.1 Hz), 128.0 – 126.5 (m), 124.9 – 124.5 (m), 123.4, 118.4, 94.7, 76.2 – 74.4 (m), 69.0 – 66.1 (m), 65.5 (d, *J* = 5.9 Hz), 51.6 (d, *J* = 153.6 Hz), 32.4 (dd, *J* = 7.4, 6.3 Hz), 18.6 (d, *J* = 8.1 Hz), 13.6 (d, *J* = 4.1 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$): δ 18.07; **HRMS** (ESI): *m/z* calculated for $[C_{20}H_{27}BrCl_3NO_5P]^+$: 575.9870; found 575.9870.

2,2,2-Trichloroethyl 2-(dibutoxyphosphoryl)-6-methoxyquinoline-1(2*H*)-carboxylate (4m)



6-Methoxyquinoline (**2h**) (13.8 µL, 0.1 mmol, 1.0 eq.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (5.6 mg, 0.005 mmol, 5.0 mol%) and phosphite **3c** (50.0 µL, 0.2 mmol, 2.0 eq.) were reacted in toluene according to the general procedure. The desired product **4m** (45.7 mg, 0.086 mmol, 86%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as a colourless oil. The enantiomeric ratio was found to be 92:8 by chiral HPLC (Chiralpak IA, Hex/^{i}PrOH 95:5, 1.0 mL/min, λ =300 nm: *t*r (minor): 20.9 min, *t*r (major): 19.7 min. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.62-7.34 (m, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.62 (d, *J* = 2.8 Hz, 1H), 6.57 (dd, *J* = 9.5, 5.4 Hz, 1H), 6.07 (s, 1H), 5.65 – 5.49 (m, 1H), 5.03 (dd, *J* = 61.1, 11.4 Hz, 1H), 4.55 (dd, *J* = 62.8, 11.1 Hz, 1H), 4.06 – 3.73 (m, 4H), 3.72 (s, 3H), 1.53 – 1.36 (m, 2H), 1.32-1.16 (m, 4H), 1.03 (d, *J* = 6.8 Hz, 2H), 0.81 (t, *J* = 7.2 Hz, 3H), 0.72 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 157.1 (d, *J* = 5.7 Hz), 152.4 (d, *J* = 5.7 Hz), 128.4, 127.8, 126.4, 123.8, 113.1, 110.3, 94.98, 75.9, 66.5-66.4 (m), 55.4, 51.7 (d, *J* = 153.0 Hz), 32.4 (dd, *J* = 11.1, 6.1 Hz), 18.5 (d, *J* = 13.4 Hz), 13.5 (d, *J* = 8.2 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$): δ 18.48; **HRMS** (ESI): *m/z* calculated for $[C_{21}H_{30}Cl_3NO_6P]^+$: 528.0864, found 528.0871.

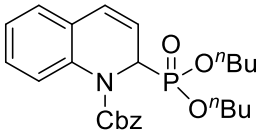
2,2,2-Trichloroethyl 5-bromo-2-(dibutoxyphosphoryl)quinoline-1(2H)-carboxylate (4n)



5-Bromoquinoline (**2i**) (14.8 µL, 0.1 mmol, 1.0 eq.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (2.8 mg, 2.5 mol%) and phosphite **3c** (44.4 µL, 0.2 mmol, 2.0 eq.) were reacted in toluene according to the general procedure. The desired product **4n** (44.0 mg, 0.076 mmol, 76%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as slight pale yellow oil. The enantiomeric ratio was detemined as 97:3 e.r. by chiral HPLC [Chiralpak IA, hexane/*i*PrOH (95:5), 1.0 mL/min, λ= 300 nm: *t*r (major): 15.6 min, *t*r (minor): 16.6 min]. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.57 (bs, 1H), 7.37 (d, *J* = 8.1Hz, 1H), 7.09 (t, *J* = 7.9 Hz, 1H), 7.00 (dd, *J* = 9.8, 5.4 Hz, 1H), 6.25 (q, *J* = 4.7 Hz, 1H), 5.75 – 5.55 (d, *J* = 19.8 Hz 1H), 5.16 - 4.55 (m, 2H), 4.12 – 3.72 (m, 4H), 1.58 – 1.44 (m, 2H), 1.35 – 1.29 (m, 4H), 1.20 – 1.00 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.80 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 152.3, 129.58 - 129.53 (m), 128.5 - 128.3 (m), 127.1 (d, *J* = 4.2 Hz), 126.9 - 126.8 (m) , 121.3 (d, *J* = 2.7 Hz), 94.7, 75.97 - 75.92 (m), 66.9 - 66.5 (m), 51.3 (d, *J* =153.3 Hz), 32.4 (dd, *J* = 14.6, 6.1 Hz), 18.6 (d, *J* = 15.0 Hz),

13.6 (d, *J* = 6.6 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$): δ 17.85; **HRMS** (ESI): *m/z* calculated for $[C_{20}H_{27}BrCl_3NO_5P]^+$: 575.9870; found 575.9865.

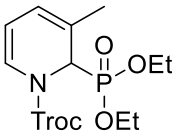
Benzyl 2-(dibutoxyphosphoryl)quinoline-1(2H)-carboxylate (**4p**)



Quinoline (**2a**) (11.8 µL, 0.1 mmol, 1.0 eq.), CbzCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (2.8 mg, 2.5 mol%) and phosphite **3c** (44.4 µL, 0.2 mmol, 2.0 eq.) were reacted in toluene according to the general procedure. The desired product **4p** (37.5 mg, 0.082 mmol, 82%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as slight pale yellow oil. The enantiomeric ratio was determined as 79:21 e.r. by chiral HPLC [Chiralpak IA, hexane/*i*PrOH (95:5), 1.0 mL/min, λ= 300 nm: *t*r (major): 25.8 min, *t*r (minor): 19.6 min]. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.43 – 7.31 (m, 5H), 7.19 (bs, 1H), 7.10 – 7.01 (m, 2H), 6.58 (dd, *J* = 9.5, 5.5 Hz, 1H), 6.07 (bs, 1H), 5.65 (bs, 1H), 5.25 (d, *J* = 24.9 Hz, 2H), 3.95 – 3.63 (m, 4H), 1.32 – 1.22 (m, 8H), 0.88 (t, *J* = 7.6 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 157.3, 135.7, 128.5, 128.3, 128.1 (d, *J* = 1.8 Hz), 128.0 (d, *J* = 2.4 Hz), 127.9, 127.3, 126.4 (d, *J* = 2.1 Hz), 124.8 (d, *J* = 6.2 Hz), 32.3 (dd, *J* = 10.1, 6.1 Hz), 31.6, 25.4, 22.7, 18.5 (d, *J* = 10.1 Hz), 13.6 (d, *J* = 6.0 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$): δ 18.93.

3.3.4 Analytical Data for Compounds 5

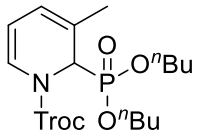
2,2,2-Trichloroethyl 2-(diethoxyphosphoryl)-3-methylpyridine-1(2H)-carboxylate (5a)



3-Picoline (**2j**) (10.0 µL, 0.1 mmol, 1.0 eq.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (11.0 mg, 0.01 mmol, 10 mol%) and phosphite **3a** (44.4 µL, 0.2 mmol, 2.0 eq.) were reacted in toluene according to the general procedure. The desired product **5a** (36.0 mg, 0.089 mmol, 89%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as slight pale yellow oil. The enantiomeric ratio was determined as 87:13 e.r. by chiral HPLC [Chiralpak IC, hexane/*i*PrOH (80:20), 1.0 mL/min, λ= 300 nm: *t*r (major): 10.2 min, *t*r (minor): 9.5 min]. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.71 (t, *J* = 6.0 Hz, 1H), 5.82 (t, *J* = 5.8 Hz, 1H), 5.53 – 5.35 (m, 1H), 5.14 (d, *J* = 16.8 Hz, 1H), 4.94 (dd, *J* = 34.1, 11.9 Hz, 1H), 4.71 (dd, *J* = 34.8, 11.9 Hz, 1H), 4.20 – 4.04 (m, 4H), 1.97 (d, *J* = 3.4 Hz, 3H), 1.31 – 1.26 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 151.8 (d, *J* = 1.0 Hz, minor), 151.4 (d, *J* = 1.8 Hz, major), 137.7, 130.7, 130.1, 128.5, 126.5 (d, *J* = 4.3 Hz, major), 126.0 (d, *J* = 4.3 Hz, minor), 124.3, 123.3 (d, *J* = 1.5 Hz), 122.1 (d, *J* = 1.6 Hz), 120.2 (d, *J* = 9.5 Hz, minor), 119.7 (d, *J* = 9.6 Hz, major), 94.8 (s, major), 94.7 (s, minor), 75.5, 63.0 (d, *J* = 7.1 Hz, major), 62.6 (d, *J* = 6.3 Hz,

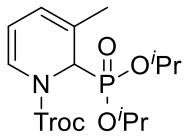
minor), 55.6 (d, *J* = 74.2 Hz, minor), 54.8 (d, *J* = 148.7 Hz, major), 28.2, 21.65 (d, *J* = 2.7 Hz, minor), 21.5 (d, *J* = 2.6 Hz, major), 16.5 (d, *J* = 5.5 Hz, minor), 16.4 (d, *J* = 6.2 Hz, major); **^{31}P NMR** (121 MHz, $CDCl_3$) δ 19.86; **HRMS** (ESI): *m/z* calculated for $[C_{13}H_{20}Cl_3NO_5P + MeOH]^+$: 438.0401; found 438.0032.

2,2,2-Trichloroethyl 2-(dibutoxyphosphoryl)-3-methylpyridine-1(2H)-carboxylate (5b)



3-Picoline (**2j**) (10.0 µL, 0.1 mmol, 1.0 eq.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (11.0 mg, 0.01 mmol, 10 mol%) and phosphite **3c** (44.4 µL, 0.2 mmol, 2.0 eq.) were reacted in toluene according to the general procedure. The desired product **5b** (39.0 mg, 0.084 mmol, 84%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as slight pale yellow oil. The enantiomeric ratio was determined as 85:15 e.r. by chiral HPLC [Chiralpak IA, hexane/*i*PrOH (95:5), 1.0 mL/min, λ= 300 nm: *t*r (major): 9.9 min, *t*r (minor): 9.3 min]. **^{1}H NMR** (300 MHz, $CDCl_3$): δ ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (m, 1H), 5.82 (m, 1H), 5.51 – 5.34 (m, 1H), 5.14 (d, *J* = 16.9 Hz, 1H), 5.06 – 4.83 (dd, $J_{P\text{-}H}$, $J_{H\text{-}H}$ = 52.6, 11.8 1H), 4.80 – 4.57 (dd $J_{P\text{-}H}$, $J_{H\text{-}H}$ = 12.12, 1H), 4.15 – 3.95 (m, 4H), 1.97 (d, *J* = 3.6 Hz, 3H), 1.65 – 1.55 (m, 4H), 1.43 – 1.31 (m, 4H), 0.91 (t, *J* = 7.4 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 151.4 (d, *J* = 1.7 Hz), 126.6 (d, *J* = 4.2 Hz), 122.1, 119.7 (d, *J* = 9.9 Hz), 109.0 (d, *J* = 3.08 Hz), 94.8, 93.8, 75.6, 66.5 (d, *J* = 7.5 Hz), 66.2 (d, *J* = 6.6 Hz), 55.8, 53.8, 32.6 - 32.5 (m), 23.8, 21.5, 18.6 (d, *J* = 1.2 Hz), 13.6 (d, *J* = 2.0 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$) δ 20.00; **HRMS** (ESI): *m/z* calculated for $[C_{17}H_{28}Cl_3NO_5P + MeOH]^+$: 478.1078; found 478.0716.

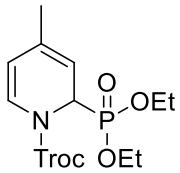
2,2,2-Trichloroethyl 2-(diisopropoxyphosphoryl)-3-methylpyridine-1(2H)-carboxylate (5c)



3-Picoline (**2j**) (10.0 µL, 0.1 mmol, 1.0 eq.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (11.0 mg, 0.01 mmol, 10 mol%) and phosphite **3d** (44.4 µL, 0.2 mmol, 2.0 eq.) were reacted in toluene according to the general procedure leading to a mixture of 12.5:1 of **5c** and regioisomer **5c'**. The desired product **5c** (38.2 mg, 0.088 mmol, 88%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as slight pale yellow oil. The enantiomeric ratio was determined as 81:19 e.r. by chiral HPLC [Chiralpak IA, hexane/*i*PrOH (98:2), 1.0 mL/min, λ= 300 nm: *t*r (major): 14.7 min, *t*r (minor): 13.8 min]. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.71 (t, *J* = 6.7 Hz, 1H), 5.82 (dd, *J* = 12.6, 6.4 Hz, 1H), 5.49 – 5.32 (m, 1H), 5.16 – 5.04 (m, 1H), 4.87 – 4.75 (m, 2H), 4.74 – 4.56 (m, 2H), 1.96 (d, *J* = 3.3 Hz, 3H), 1.34 – 1.25 (m, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 147.9, 146.0, 130.1, 128.6 (d, *J*

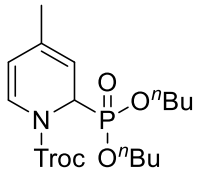
= 24.8 Hz), 124.1 (d, *J* = 55.7 Hz), 122.1 (s), 119.8 (d, *J* = 80.4), 118.0, 113.4, 94.8, 75.3, 70.8 (d, *J* = 5.7 Hz), 51.7, 28.2, 23.9 (dd, *J* = 20.0, 4.5 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$): δ 18.52-18.12 (m); **HRMS** (ESI): *m/z* calculated for $[C_{15}H_{24}Cl_3NO_5P]^+$: 434.0433; found 434.0452.

2,2,2-Trichloroethyl 2-(diethoxyphosphoryl)-4-methylpyridine-1(2H)-carboxylate (5d)



4-Picoline (**2k**) (10.0 µL, 0.1 mmol, 1.0 eq.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (11.0 mg, 0.01 mmol, 10 mol%) and phosphite **3a** (44.4 µL, 0.2 mmol, 2.0 eq.) were reacted in toluene according to the general procedure. The desired product **5d** (33.0 mg, 0.081 mmol, 81%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as slight pale yellow oil. The enantiomeric ratio was determined as 82:18 e.r. by chiral HPLC [Chiralpak IC, hexane/*i*PrOH (80:20), 1.0 mL/min, λ= 300 nm: *tr* (major): 11.5 min, *tr* (minor): 19.8 min]. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.78 (t, *J* = 8.9 Hz, 1H), 5.38 (d, *J* = 4.8 Hz, 1H), 5.36 – 5.20 (m, 2H), 4.96 (dd, *J* = 44.8, 11.9 Hz, 1H), 4.68 (dd, *J* = 51.0, 11.9 Hz, 1H), 4.29 – 3.93 (m, 4H), 1.85 – 1.77 (m, 3H), 1.29 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 152.4, 151.2, 133.5, 131.5, 125.5, 124.3, 111.7 (d, *J* = 3.5 Hz), 111.0 (d, *J* = 5.5 Hz), 75.5, 63.2 - 62.7 (m), 51.0 (d, *J* = 151.6 Hz), 20.5, 16.5 (d, *J* = 10.5 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$): δ 18.86 (d, *J* = 28.6 Hz); **HRMS** (ESI): *m/z* calculated for $[C_{13}H_{20}Cl_3NO_5P]^+$: 406.0139; found 406.0108.

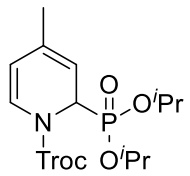
2,2,2-Trichloroethyl 2-(dibutoxyphosphoryl)-4-methylpyridine-1(2H)-carboxylate (5e)



4-Picoline (**2k**) (10.0 µL, 0.1 mmol, 1.0 e.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (11.0 mg, 0.01 mmol, 10 mol%) and phosphite **3c** (44.4 µL, 0.2 mmol, 2.0 eq.) were reacted in MTBE according to the general procedure. The desired product x (31.0 mg, 0.067 mmol, 67%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as slight pale yellow oil. The enantiomeric ratio was determined as 81:19 e.r. by chiral HPLC [Chiralpak IC, hexane/*i*PrOH (90:10), 1.0 mL/min, λ= 300 nm: *tr* (major): 14.1 min, *tr* (minor): 22.4 min]. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.88 – 6.63 (m, 1H), 5.37 (s, 1H), 5.29 (dd, *J* = 14.5, 7.5 Hz, 1H), 5.08 – 4.54 (m, 3H), 4.20 – 3.89 (m, 4H), 1.80 (d, *J* = 5.8 Hz, 3H), 1.70 – 1.50 (m, 4H), 1.43 – 1.30 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 151.2, 133.1, 132.6 (d, *J* = 9.7 Hz), 125.9 – 125.5 (m), 125.4, 124.2, 111.6 (d, *J* = 3.6 Hz), 111.1 (d, *J* = 5.4 Hz), 94.8, 75.5, 66.4 (dd, *J* = 25.8, 7.2 Hz), 65.4 (d, *J* = 6.0 Hz), 50.9 (d, *J* = 153.8 Hz), 32.9 – 31.9 (m), 20.5 (d, *J* = 3.2 Hz), 18.6 (d, *J* = 3.6

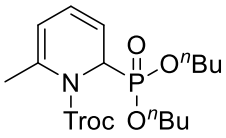
Hz), 13.5 (d, *J* = 4.9 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$): δ 19.33 (m) **HRMS** (ESI): *m/z* calculated for $[C_{17}H_{28}Cl_3NO_5P + MeOH - O]^+$: 478.1078; found 478.0715.

2,2,2-Trichloroethyl 2-(diisopropoxyphosphoryl)-4-methylpyridine-1(2H)-carboxylate (5f)



4-Picoline (**2k**) (10.0 µL, 0.1 mmol, 1.0 eq.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (11.0 mg, 0.01 mmol, 10 mol%) and phosphite **3d** (44.4 µL, 0.2 mmol, 2.0 eq.) were reacted in MTBE according to the general procedure. The desired product x (40.7 mg, 0.094 mmol, 94%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as slight pale yellow oil. The enantiomeric ratio was determined as 76:24 e.r. by chiral HPLC [Chiralpak IC, hexane/*i*PrOH (90:10), 1.0 mL/min, λ= 300 nm: *t*r (major): 9.0 min, *t*r (minor): 10.7 min]. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.71 (t, *J* = 6.7 Hz, 1H), 5.88 – 5.75 (m, 1H), 5.52 – 5.30 (m, 1H), 5.20 – 5.01 (m, 1H), 4.81 (d, *J* = 2.2 Hz, 1H), 4.78 – 4.55 (m, 3H), 1.96 (d, *J* = 3.6, 3H), 1.34 – 1.25 (m, 12H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 150.4, 125.9 (d, *J* = 4.3 Hz), 122.1, 121.1, 118.9 (d, *J* = 9.6 Hz), 118.5 (d, *J* = 9.7 Hz), 108.2 (d, *J* = 3.8 Hz), 93.8, 74.6, 70.5 (dd, *J* = 20.9, 7.4 Hz), 54.7 (d, *J* = 151.2 Hz), 23.3 (d, *J* = 3.0 Hz), 23.2 (d, *J* = 2.8 Hz), 22.8 – 22.6 (m), 20.5 (d, *J* = 2.7 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$) δ 18.23; **HRMS** (ESI): *m/z* calculated for $[C_{15}H_{23}Cl_3NO_5P + Na]^+$: 456.0272; found 456.0275.

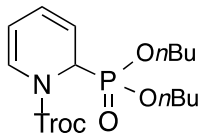
2,2,2-Trichloroethyl 2-(dibutoxyphosphoryl)-6-methylpyridine-1(2H)-carboxylate (5g)



2-Picoline (**2l**) (10.0 µL, 0.1 mmol, 1.0 eq.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (11.0 mg, 0.01 mmol, 10 mol%) and phosphite **3c** (44.4 µL, 0.2 mmol, 2.0 eq.) were reacted in toluene according to the general procedure. The desired product **5g** (36.0 mg, 0.078 mmol, 78%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as a colourless oil. The enantiomeric ratio was determined as 85:15 e.r. by chiral HPLC [Chiralpak IA, hexane/*i*PrOH (90:10), 1.0 mL/min, λ= 300 nm: *t*r (major): 12.4 min, *t*r (minor): 31.0 min]. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.13 – 5.95 (m, 1H), 5.81 – 5.66 (m, 1H), 5.61 – 5.36 (m, 2H), 5.22 – 4.94 (m, 2H), 4.13 – 3.98 (m, *J* = 16.7, 13.7, 6.6, 3.4 Hz, 4H), 2.25 (s, 3H), 1.66 – 1.57 (m, 4H), 1.41 – 1.33 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 145.4 (d, *J* = 154.3 Hz), 144.2 – 143.2 (m), 137.4, 133.6 – 133.4 (m), 132.9 (d, *J* = 51.5 Hz), 132.1 (d, *J* = 44.9 Hz), 127.1 – 125.9 (m), 125.1 (d, *J* = 127.3 Hz), 122.4, 122.3 (d, *J* = 29.7 Hz), 121.9 (dd, *J* = 78.0, 40.9 Hz), 119.9, 118.7, 116.5, 114.0

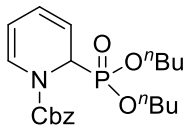
(d, *J* = 4.3 Hz), 94.8, 75.9 – 75.3 (m, *J* = 22.0 Hz), 67.3 – 66.0 (m), 64.3, 51.4 (d, *J* = 153. Hz), 32.6 (dd, *J* = 8.2, 5. Hz), 24.5, 18.6, 13.6 (d, *J* = 1.7 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$): δ 19.40; **HRMS** (ESI): *m/z* calculated for $[C_{17}H_{28}Cl_3NO_5P]^+$: 462.0765; found 462.0729.

2,2,2-Trichloroethyl 2-(dibutoxyphosphoryl)pyridine-1(2*H*)-carboxylate (**5h**)



Pyridine (**2m**) (8.0 µL, 0.1 mmol, 1.0 eq.), TrocCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (11.0 mg, 0.01 mmol, 10 mol%) and phosphite **3c** (44.4 µL, 0.2 mmol, 2.0 eq.) were reacted in toluene according to the general procedure leading to a mixture of 11:1 of **5h** and regioisomer **5h'**. The desired product **5h** (42.0 mg, 0.094 mmol, 94%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as a colourless oil. The enantiomeric ratio was determined as 80:20 e.r. by chiral HPLC [Chiralpak IA, hexane/*i*PrOH (95:5), 1.0 mL/min, λ= 300 nm: *t*r (major): 11.7 min, *t*r (minor): 12.4 min]. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.86 – 6.73 (m, 1H), 6.19 – 5.94 (m, 1H), 5.75 – 5.61 (m, 1H), 5.56 – 5.24 (m, 2H), 4.98 (dd, *J* = 58.4, 11.9 Hz, 1H), 4.67 (dd, *J* = 60.6, 11.9 Hz, 1H), 4.22 – 3.92 (m, 4H), 1.69 – 1.53 (m, 4H), 1.45 – 1.28 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 6.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 150.8 (s, minor), 150.3 (d, *J* = 1.9 Hz, major), 125.1 – 124.9 (m), 123.9 (d, *J* = 1.3 Hz), 123.7 (d, *J* = 9.7 Hz, minor), 123.1 (d, *J* = 9.7 Hz, major), 115.7 (d, *J* = 5.4 Hz, major), 115.2 (d, *J* = 5.4 Hz, minor), 107.6 (d, *J* = 3.7 Hz, minor), 107.2 (d, *J* = 3.8 Hz, major),93.8 (s, major), 93.7 (s, minor), 74.6 (s), 66.3 – 65.3 (m), 50.3 (d, *J* = 153.5 Hz, minor), 49.8 (d, *J* = 153.8 Hz, major), 32.0 – 31.1 (m), 17.6 (s), 12.6 (d, *J* = 2.3 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$): δ 18.57; **HRMS** (ESI): *m/z* calculated for $[C_{16}H_{26}Cl_3NO_5P]^+$: 448.0609; found 448.0600.

Benzyl 2-(dibutoxyphosphoryl)pyridine-1(2H)-carboxylate (5i)

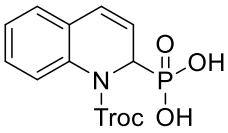


Pyridine (**2m**) (8.0 µL, 0.1 mmol, 1.0 eq.), CbzCl (14.2 µL, 0.1 mmol, 1.0 eq.), **1a** (11.0 mg, 0.01 mmol, 10 mol%) and phosphite **3c** (44.4 µL, 0.2 mmol, 2.0 eq.) were reacted in toluene according to the general procedure leading to a mixture of 4:1 of **5i** and regioisomer **5i'**. The desired product **5i** (32.0 mg, 0.079 mmol, 79%) was isolated by flash column chromatography (petroleum ether/ethyl acetate, 7:3) as a colourless yellow oil. The enantiomeric ratio was determined as 65:35 e.r. by chiral HPLC [Chiralpak IA, hexane/*i*PrOH (95:5), 1.0 mL/min, λ= 300 nm: *t*r (major): 17.4 min, *t*r (minor): 15.7 min]. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.44 – 7.32 (m, 5H), 6.80 (dd, *J* = 37.7, 7.6 Hz, 1H), 6.17 – 5.94 (m, 1H), 5.72 – 5.53 (m, 1H), 5.42 (dd, *J* = 16.8, 6.4 Hz, 1H), 5.35 – 5.26 (m, 1H), 5.25 –

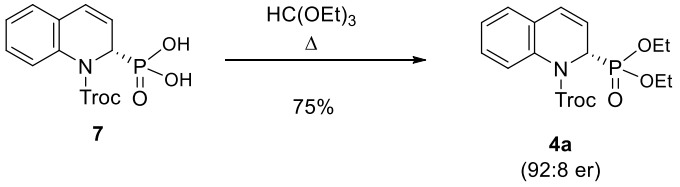
5.12 (m, 2H), 4.10 – 3.83 (m, 4H), 1.63 – 1.53 (m, 4H), 1.31 – 1.22 (m, 4H), 0.94 – 0.87 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 149.4, 135.7, 128.5, 128.1 (d, *J* = 1.8 Hz), 127.8, 126.4 (d, *J* = 2.1 Hz), 124.8 (d, *J* = 6.2 Hz), 68.3, 66.3 (d, *J* = 7.0 Hz), 32.9 – 30.6 (m), 25.3, 22.7, 18.5 (d, *J* = 10.1 Hz), 13.5 (d, *J* = 6.0 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$): δ 19.27

3.3.5 Derivatization of Phosphonates 4/5:

(1-((2,2,2-Trichloroethoxy)carbonyl)-1,2-dihydroquinolin-2-yl)phosphonic acid (7)

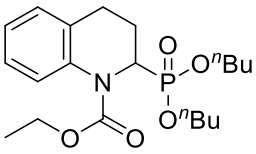


4a (30 mg, 0.060 mmol, 1.0 eq.; 92:8 e.r.) was dissolved in anhydrous DCM (1 mL) and cooled to 0 °C. Bromotrimethylsilane (20 µL, 0.180 mmol, 3.0 eq.) was added and the reaction mixture was stirred overnight at room temperature. After the addition of H_2O (1 mL), solvent and water were removed in vacuo to obtain the desired product **7** (22 mg, 0.057 mmol, 95%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.55 (bs, 1H), 7.17 (bs, 1H), 7.11 – 6.85 (m, 2H), 6.54 (bs, 1H), 5.97 (bs, 1H), 5.49 (bd, *J* = 18.0 Hz, 1H), 5.04 (bs, 1H), 4.56 (bs, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 152.1, 133.5, 128.2, 127.5, 127.4, 126.7, 126.7, 126.0, 125.0, 124.9, 124.8, 122.3, 94.3, 75.5, 52.9, 50.8; **^{31}P NMR** (121 MHz, $CDCl_3$): δ 12.37; **HRMS** (ESI): *m/z* calculated for $[C_{12}H_{12}Cl_3NO_5P]^+$: 385.9513; found 385.9513.



To determine the enantiomeric ratio, the acid was again esterified. Therefore, **7** (22 mg, 0.057 mmol, 95%) was dissolved in $CH(OEt)_3$ (1 mL) and stirred at 145 °C for 3 h. The reaction mixture was cooled to r.t. and solvent was evaporated in vacuo. The brown oil was dissolved in EtOAc, washed with brine and concentrated in vacuo to obtain the desired product **4a** (19 mg, 0.043 mmol, 75%) as a brown oil. The enantiomeric ratio was determined as 92:8 e.r. by chiral HPLC [Chiralpak IA, hexane/*i*PrOH (95:5), 1.0 mL/min, λ= 300 nm: *t*r (major): 16.3 min, *t*r (minor): 17.3 min].

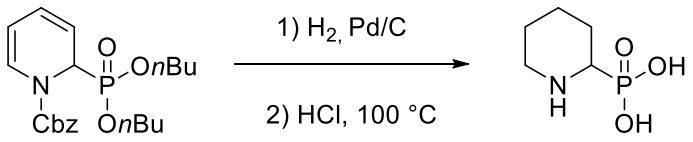
Ethyl 2-(dibutoxyphosphoryl)-3,4-dihydroquinoline-1(2H)-carboxylate (8)



4c (264.0 mg, 0.53 mmol, 1 eq.; 92:8 e.r.) was dissolved in MeOH (5 mL) and Pd/C (5.3 mg, 0.05 mmol, 10 mol%) was added. The reaction mixture was stirred overnight in an autoclave (10 bar, r.t.) and the

product **8** (198.5 mg, 0.5 mmol, 99%) was obtained by filtration through celite. The enantiomeric ratio was determined as 92:8 e.r. by chiral HPLC [Chiralpak IA, hexane/*i*PrOH (95:5), 1.0 mL/min, λ= 300 nm: *t*r (major): 14.3 min, *t*r (minor): 15.3 min]. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.50 (dd, *J* = 13.4 Hz, *J* = 7.8 Hz, 1H), 7.23 – 6.98 (m, 3H), 5.11 – 4.93 (m, 1H), 4.38 – 4.08 (m, 2H), 4.06 – 3.79 (m, 4H), 2.90 – 2.76 (m, 1H), 2.72 – 2.55 (m, 1H), 2.53 – 2.35 (m, 1H), 2.28 – 2.01 (m, 1H), 1.59 – 1.50 (m, 2H), 1.41 – 1.26 (m, 7H), 1.19 – 1.04 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.84 – 0.76 (m, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 153.8, 136.1, 126.5, 125.1 (t, *J* = 17.3 Hz), 123.8, 68.8, 67.6, 65.1 (d, *J* = 6.6 Hz), 64.6 (d, *J* = 7.6 Hz), 61.4, 48.0 (d, *J* = 158.0 Hz), 31.4 (dd, *J* = 13.6, 6.2 Hz), 29.3, 24.5, 17.6 (d, *J* = 13.4 Hz), 13.4, 12.6 (d, *J* = 7.7 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$): δ 24.65, 23.90; **HRMS** (ESI): *m/z* calculated for $[C_{20}H_{33}NO_5P]^+$: 398.2091; found 398.2095. The enantiomeric ratio was detemined as 92:8 e.r. by chiral HPLC [Chiralpak IA, hexane/*i*PrOH (95:5), 1.0 mL/min, λ= 300 nm: *t*r (major): 14.3 min, *t*r (minor): 15.3 min].

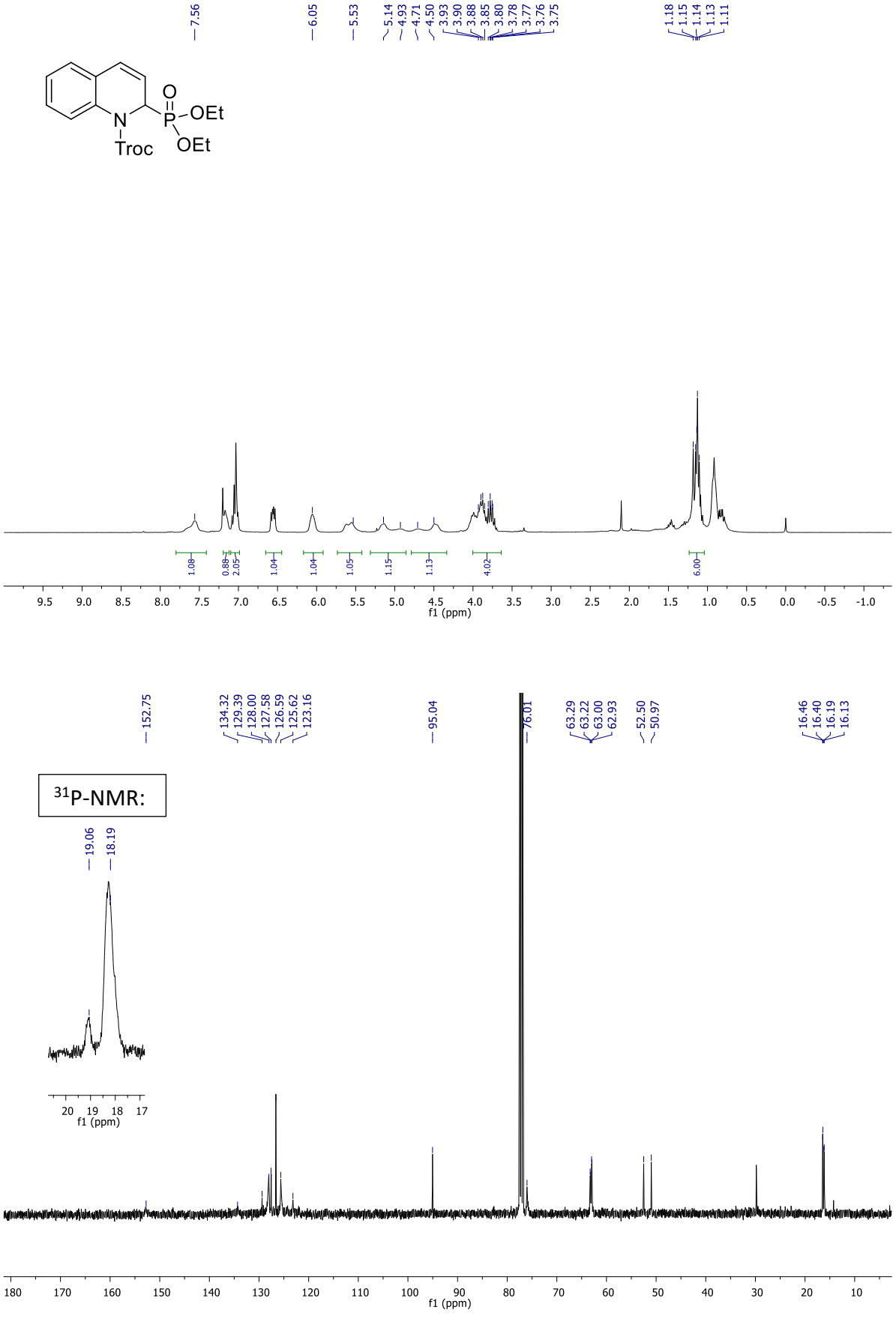
Piperidin-2-ylphosphonic acid (9) [3]



5i **9**

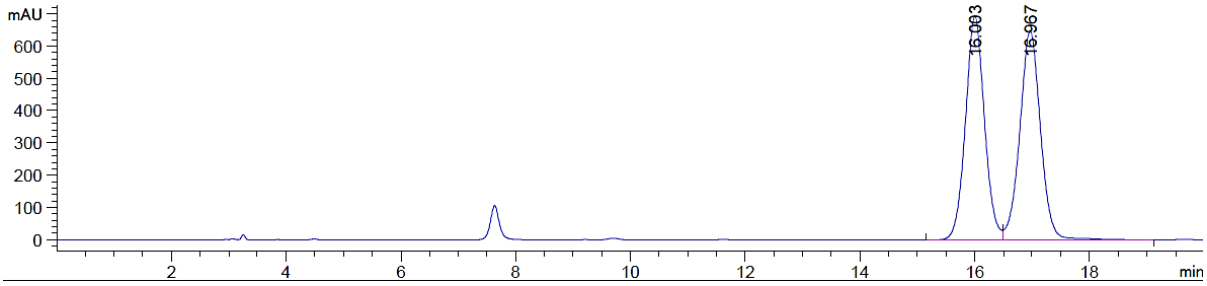
5i (50 mg, 0.12 mmol, 1 eq.) and Pd/C (1.1 mg, 10 mol%) were dissolved in MeOH (1 mL) and stirred overnight in an autoclave (10 bar) at room temperature. The reaction mixture was filtered through celite to remove the Pd-catalyst, and the crude product was directly dissolved in HCl (6 M, 1mL) and stirred at 100 °C for 3 h. After cooling to room temperature, volatiles were removed under reduced pressure and the crude product was dissolved again in a small amount of MeOH and dropped into Et_2O to obtain the desired product as a pale yellow solid (5 mg, 0.03 mmol, 25%). Moreover, further 5 mg of **9** were recovered from the MeOH-Et_2O solution (combined 50% yield/2 steps). $[\alpha]_{589}^{20}$: +2.7 (*c* 0.1, NaOH 1M); $[\alpha]_{589}^{20}$: +2.6 (*c* 0.1, CD_3OD); Lit.[3b] [(-)-(*R*)-**9** $[\alpha]_{589}^{20}$: -4.5 (c 1.0, 1M NaOH)]. **^{1}H NMR** (300 MHz, CD_3OD): δ 3.98 (dd, *J* = 13.9, 6.8 Hz, 1H), 3.22 (d, *J* = 13.9 Hz, 1H), 2.99 (t, *J* = 12.4 Hz, 1H), 2.14 (t, *J* = 13.3 Hz, 1H), 1.88 (d, *J* = 13.1 Hz, 2H), 1.71 – 1.60 (m, 2H), 1.52 – 1.37 (m, 1H); **^{31}P NMR** (162 MHz, CD_3OD): δ 13.69.

3.1.4.5 Representative Spectra and HPLC Chromatograms of 4a and 5a



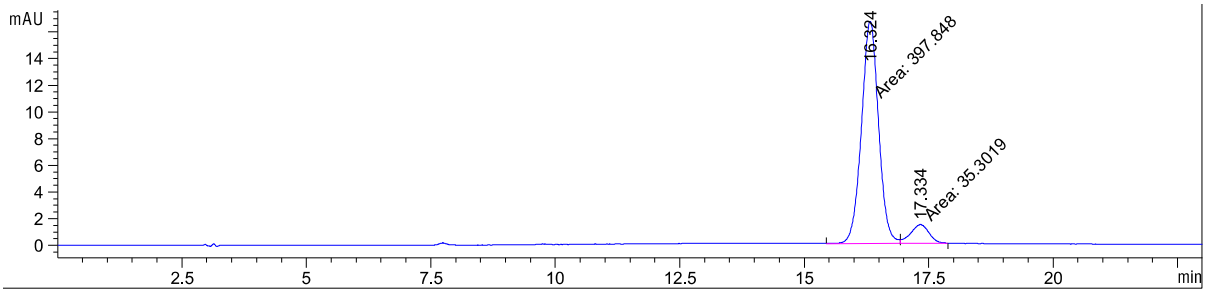
Chiral-phase HPLC: IA; Hex/^{i}PrOH 95:5, F = 1 mL/min (λ = 300 nm)

racemic:

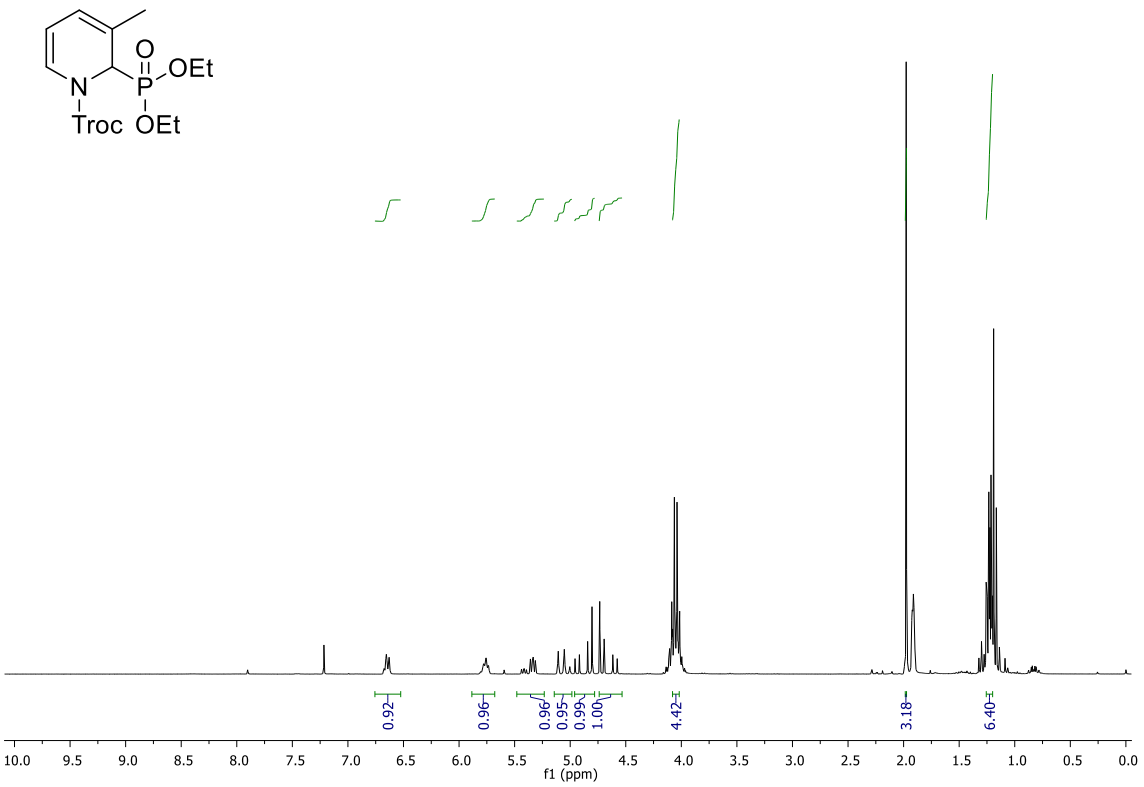


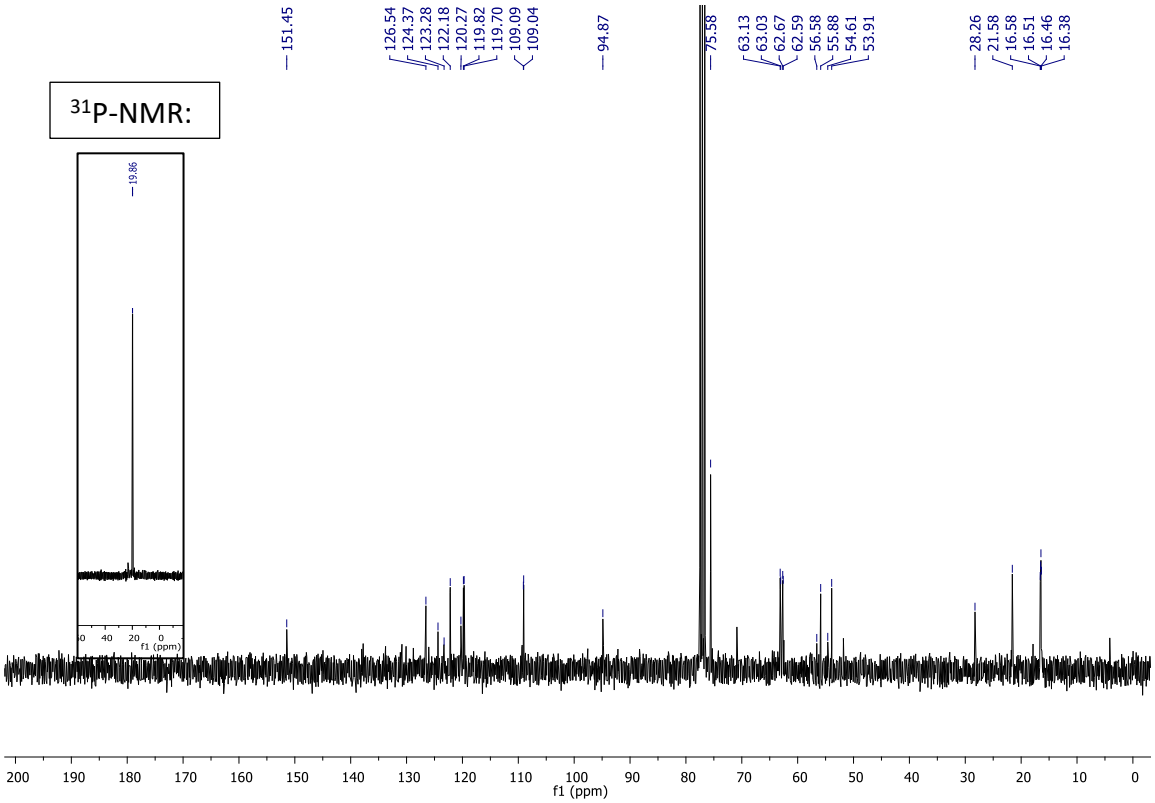
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.003	BV	0.3499	1.59212e4	693.31519	49.5165
2	16.967	VB	0.3807	1.62322e4	647.06104	50.4835

enantioselective:



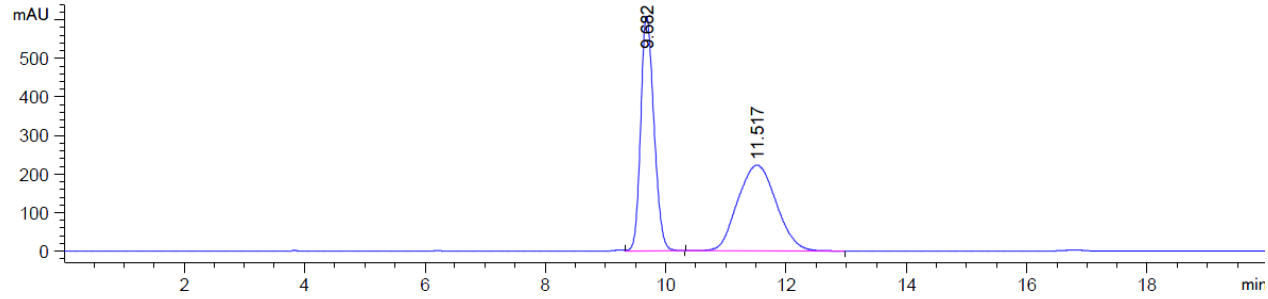
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.324	MF	0.3980	397.84839	16.65875	91.8500
2	17.334	FM	0.4218	35.30189	1.39503	8.1500


O
OEt
N
P
Troc OEt
0.92
0.96
0.96
0.95
0.99
1.00
4.42
3.18
6.40
f1 (ppm)


151.45
126.54
124.37
123.28
122.18
120.27
119.82
119.70
109.09
109.04
94.87
75.58
63.13
63.03
62.67
62.59
56.58
55.88
54.61
53.91
28.26
21.58
16.58
16.51
16.46
16.38
31P-NMR:
19.86
f1 (ppm)

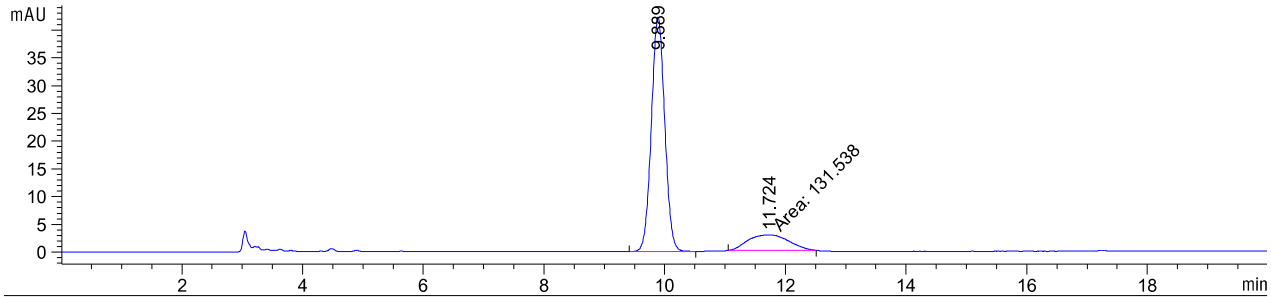
Chiral-phase HPLC: IC; Hex/^{i}PrOH 80:20 (λ = 300 nm)

racemic:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.682	MM	0.2625	1.82887e4	1161.25647	49.0459
2	11.523	MM	0.7519	1.90003e4	421.14157	50.9541

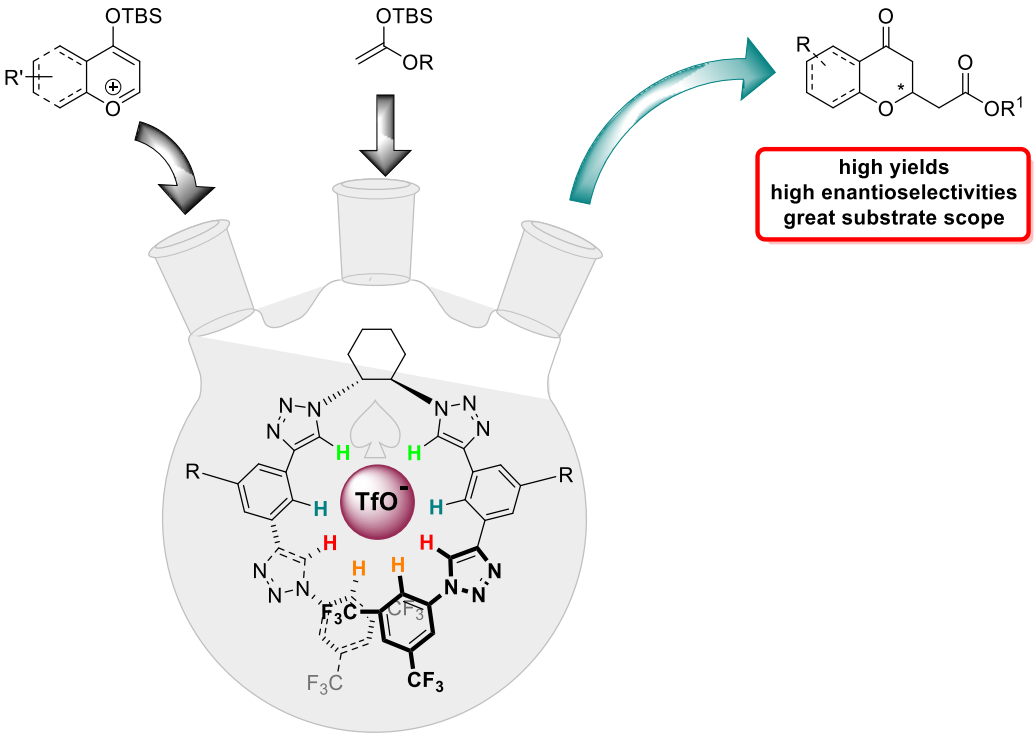
enantioselective:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.889	BB	0.2397	650.58734	42.23640	83.1820
2	11.724	MM	0.7827	131.53767	2.80100	16.8180

Chapter 4

4. Highly Enantioselective Nucleophilic Dearomatization of Pyrylium Derivatives



Abstract: A general and highly enantioselective catalytic synthesis of 2-alkyl substituted oxygen heterocycles by nucleophilic dearomatization of pyrylium triflate derivatives with silyl ketene acetals is described. The use of chiral triazoles as anion-binding catalysts, able to form a close ion-pair with the substrates, was crucial to achieve both high conversions and chirality transfer. Thus, this method provides a simple access to chiral chromanones and dihydropyranones in excellent enantioselectivities from the corresponding 4-(benzo)pyranones. Kinetic, binding and computational studies were performed, suggesting a high order complexation of the catalyst with the triflate anions to form the active catalytic species.

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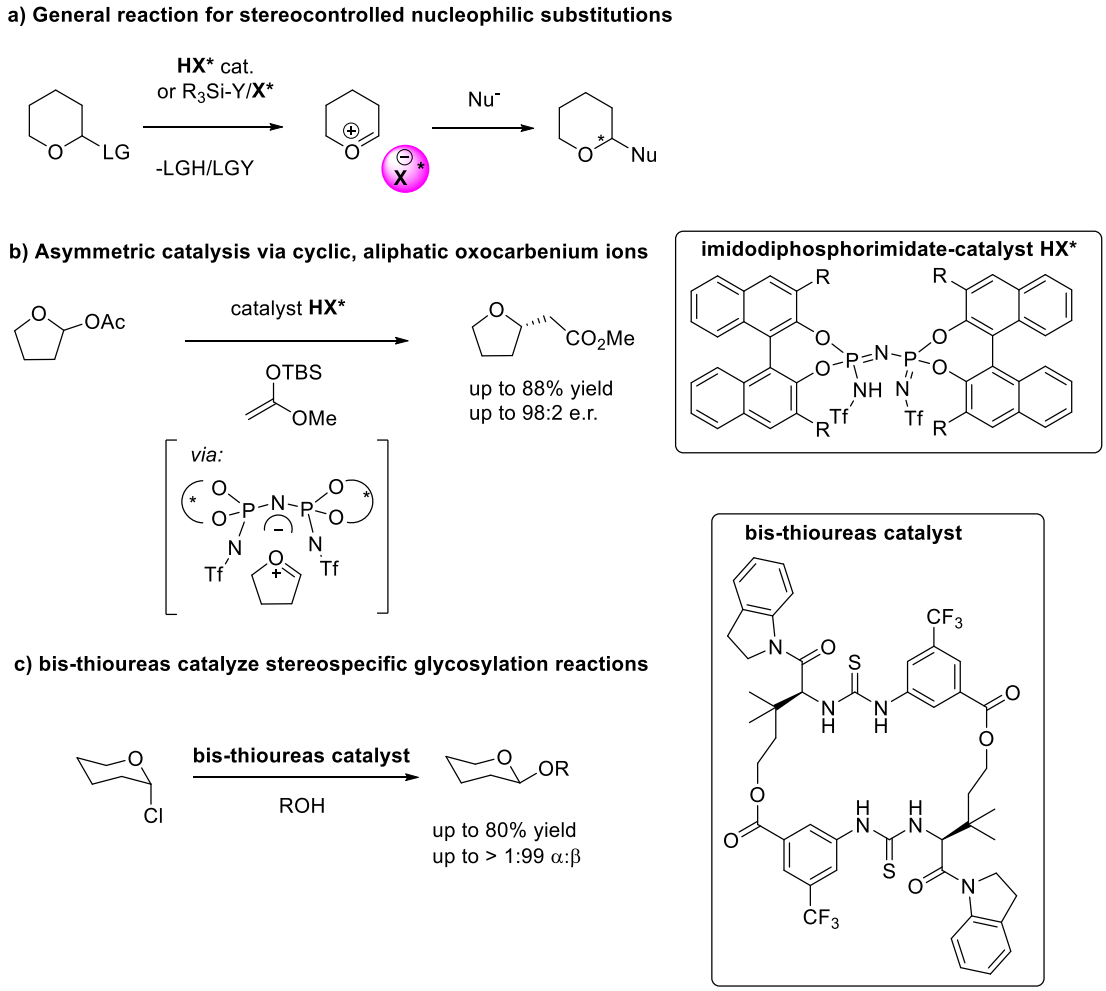
Author contribution:

Theresa Fischer:	90% of reproduced part Initial optimization, catalyst screening, scope of the reaction with various silyl ketene acetals and 4-chromone derivatives, synthetic applicability and determination of the absolute configuration
Julia Bamberger and Melania Gómez Martínez:	Scope of the reaction with various pyrone derivatives
Olga García Mancheño:	corresponding author

4.1 Introduction

Oxygen-containing chiral heterocycles are essential moieties commonly found in bioactive compounds and natural products.[1] Owing to their synthetic significance, many efforts for the development of catalytic asymmetric methodologies have been made.[2] Most of the described methods rely however on cyclization reactions from linear compounds[2c] or oxygen-containing leaving groups alpha to the O-atom in cyclic systems[2e, 2g] to form *in situ* the reactive oxonium species. In 2017, important breakthroughs in this area through cyclic oxonium ion intermediates engaging asymmetric organocatalysis have been achieved by List[3] and Jacobsen.[4] In both cases, the method relies as well on the employment of a leaving group alpha to the oxygen atom to form *in situ* the active oxonium species from lactols (LG = OAc) and sugars (LG = Cl) (Scheme 1).



Scheme 1 Standard LG-approach for asymmetric nucleophilic addition to oxocarbenium ions.

List and co-workers introduced an imidodiphosphorimidate (IDPi) catalyst in the stereocontrolled nucleophilic substitution reaction with various oxygen heterocycles, including tetrahydrofuranes, tetrahydropyranes, oxepanes, chromanes, and dihydrobenzofuranes (Scheme 1a). They obtained excellent enantioselectivities by reacting the corresponding lactol acetates with silyl ketene acetals. Mechanistic studies confirmed pairing between a non-stabilized, aliphatic, cyclic oxocarbenium ion intermediate and the chiral counter anion (Scheme 1b).[3] In the same year, Jacobsen reported on a macrocyclic bis-thiourea derivative that catalyzes α-configured glycosyl electrophiles, which are transformed to β-O-glycosidic linkages by means of invertive substitution. (Scheme 1c).[4]

Alternatively, an interesting approach for the synthesis of chiral oxygen-heterocycles is based on catalyzed enantioselective nucleophilic dearomatization reactions[5] of pyrylium-type derivatives.[6] However, the targeted electrophilic pyrylium salts present some intrinsic reactivity and selectivity challenges (Figure 1). Pyrylium and benzopyrylium salts comprise an oxonium ion (–C=O$^+$–), which is stabilized by aromaticity and is therefore less reactive than a non-conjugated oxocarbenium ion. Additionally, in most cases the reaction of pyrylium salts leads mainly to the ring-opening products, which has been extensively exploited in synthesis (*e.g.* to form the corresponding pyridine derivatives).[7] Moreover, compared to the related *N*-heteroarene salts (–C=NR$^+$–), the asymmetric reactions of pyrylium salts are more challenging since it is not possible to fine-tune the stereoelectronic properties close to the reactive C2-site by introducing the appropriate rest "R" at the heteroatom.

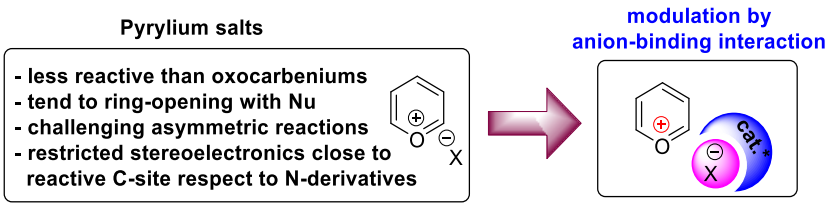
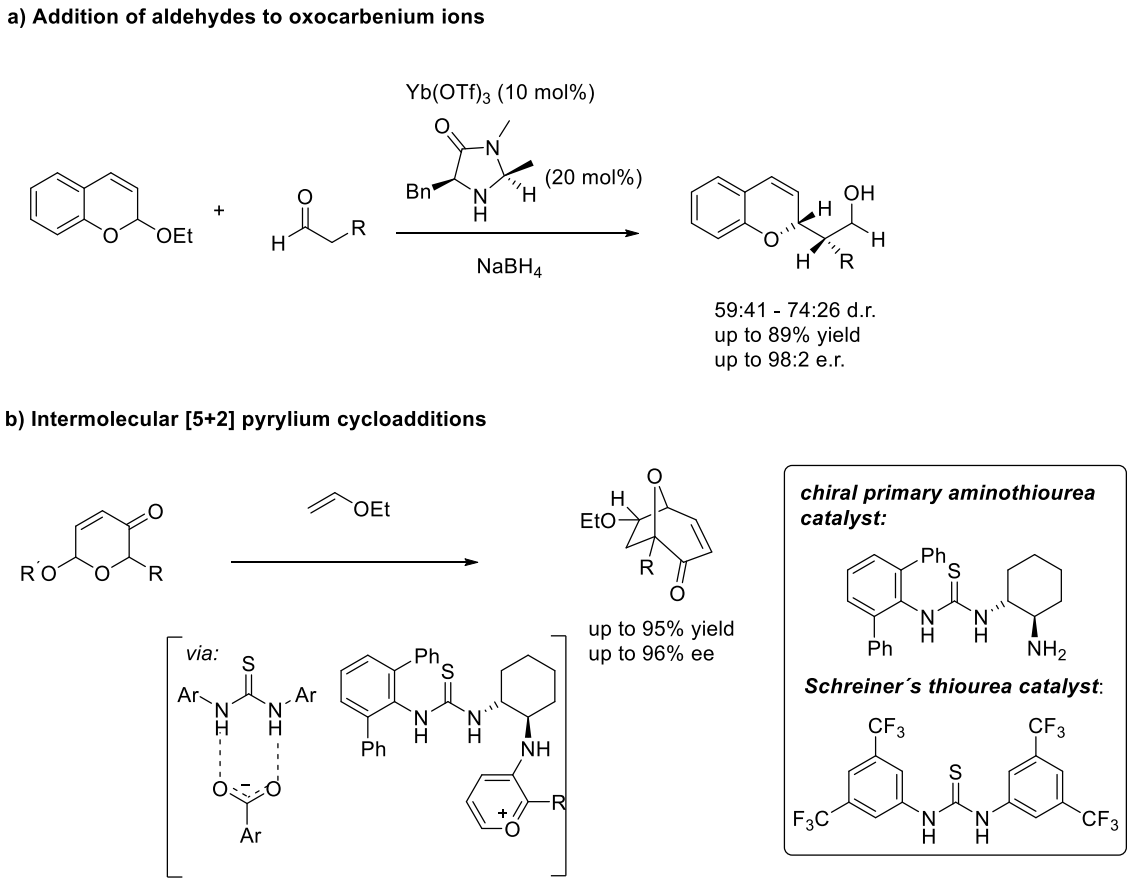


Figure 1 Reactivity challenges of electrophilic pyrylium salts.

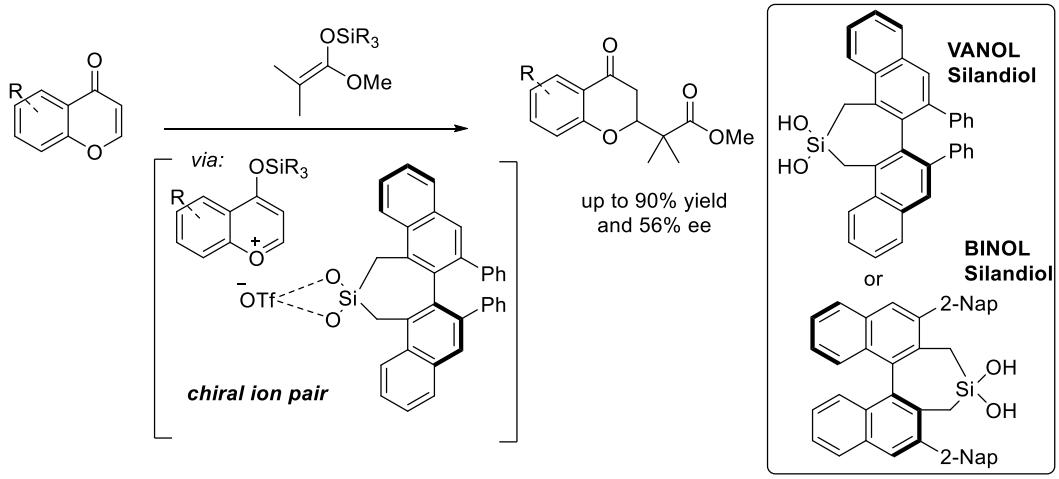
Besides the pioneer enantioselective work employing metal catalysis,[8] only few efficient organocatalytic approaches for such enantioselective dearomatizations have been reported for stereocontrolled nucleophilic substitutions[9] or [5+2]-cyclization[10] reactions on pyrylium derivatives (Scheme 2). In this regard, Rueping and his group described a synergistic catalytic system for the asymmetric addition of aldehydes to *in situ* generated prochiral oxocarbenium ions yielding the desired products in high enantiomeric ratios and moderate diastereomeric

ratios (Scheme 2a).[9a] An example for an intermolecular [5+2] pyrylium cycloaddition was given by Jacobsen, who introduced a dual catalyst system consisting of the achiral *Schreiner´s* thiourea catalyst and a chiral primary aminothiourea. Covalent aminocatalysis is responsible for the chirality transfer to the desired cyclic products and *Schreiner´s* thiourea catalyst for the anion binding.(Scheme 2b).[10a]



Scheme 2 a) Asymmetric nucleophilic substitutions and b) [5+2]-cyclization of pyrylium derivatives.

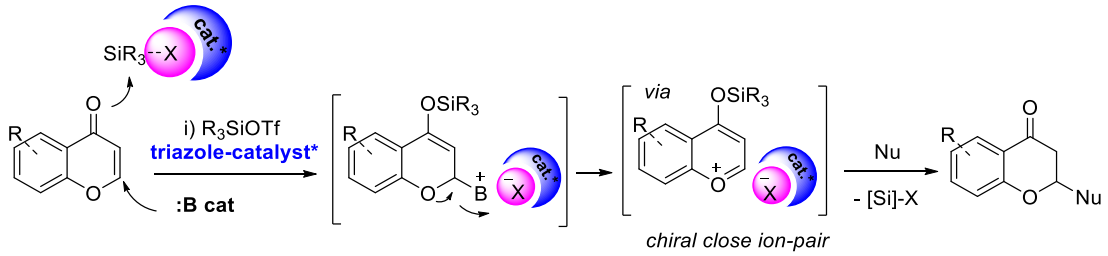
Consequently, divergent approaches towards highly enantioselective methods under mild and metal-free conditions from different type of simple cyclic starting materials, such as chromones, are still greatly demanded.[11] In this regard, the group of Mattson developed a silanediol-catalyzed functionalization of simple chromenones (Scheme 3).[11] Due to moderate enantioinductions reached with this kind of catalysts, the development of a general and simple method is still needed.



Scheme 3 Silanediol-catalyzed chromenone functionalization.

4.2 Objectives

As it is already demonstrated in the chapters before, along with the popular N-H and O-H hydrogen bond donors, the less common 1,2,3-triazole-based C-H bond donors have revealed enormous potential in dearomatization reactions.[12] For instance, the chiral TetrakisTriazole catalysts recently developed by our group have shown excellent results in the dearomatization of various demanding heteroarenes such as quinolines,[12b, 12e] isoquinolines,[12d] diazarenes[12a] and pyridines[12b, 12c] upon prior *N*-acylation to the corresponding salt. We envisioned to overcome some of the current reactivity and enantioselectivity issues of the related O-heteroarenes with our highly active triazole-based H-donor catalysts by forming a chiral contact ion-pair between an *in situ* generated pyrylium ion and the corresponding catalyst-counterion complex (Scheme 4). Moreover, the catalyst is anticipated to further facilitate the *in situ* formation of the pyrylium substrates from the corresponding neutral 4-pyrones by activation of the silylating agent for the enolization step.



Scheme 4 Enantioselective nucleophilic dearomatization of pyrylium derivatives.

To achieve a highly enantioselective dearomatization reaction of pyrylium derivatives and to get a better insight into the anion-binding ability of our triazole catalysts, the following points will be carried out in cooperation with Julia Bamberger and Melania Gómez Martínez:

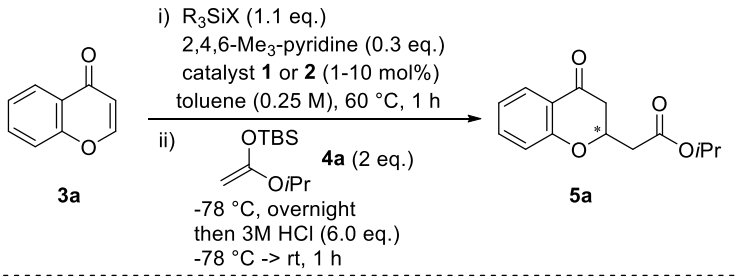
- Optimization of the reaction conditions: Screening of various chiral H-donor catalysts, solvents and silylating agents
- Study of the scope of the reaction with various silyl ketene acetals, 4-chromone and 4-pyrone derivatives
- Illustration of the synthetic applicability of the catalytic method by further derivatization of the obtained chiral products

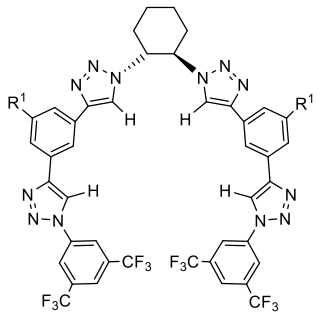
4.3 Results and Discussion

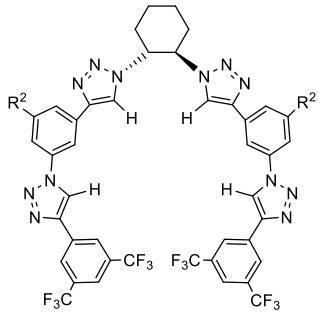
4.3.1 Optimization Screening

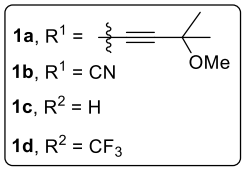
We started our studies with the one-pot reaction between commercial available 4*H*-chromen-4-one (**3a**) as model substrate and silyl ketene acetal **4a** as nucleophile at -78 °C to provide enantioenriched 2-substitued chromanone **5a** (Table 1). The active benzopyrylium-ion species was previously formed *in situ* by treatment with a silyl derivative (R_3SiX) in the presence of 10 mol% of the H-donor catalyst and catalytic amounts of 2,4,6-collidine at 60 °C. Bulkier 2,6-di-*tert*-butyl-4-methylpyridine or less hindered 2-picoline led to no improvement or provided lower conversions. The change from chloride to bromide to triflate trimethylsilane led to a notable higher conversion (from 32 to 72%) and enantioselectivity (from 64:36 to 87:13 e.r., entries 1-3). A screening of various triflate derivatives such as TESOTf, TIPSOTf and TBSOTf (entry 3-6) identified TBSOTf as the most active silyl derivative with yields up to 92% and a promising enantiomeric ratio of 91:9 (entry 6). Various C-H-based triazole **1**,[12] N-H-based thiourea[13] and squaramide[14] **2** catalysts were tested (Table 1), leading to the product **5a** in moderate to excellent yields and a broad range of enantioselectivities from almost racemic to high (entries 8-13). Among the tested catalysts, the triazole **1a** and **1b** showed the highest performance, providing **5a** in a promising 91:9 e.r. when using TBSOTf as silylating reagent (entry 3). Same e.r., but within a lower yield, was observed when adding catalyst **1a** in the second step. Compared to the N-H-based thiourea and squaramide catalysts **2**, all the C-H-based triazole catalysts **1a-d** were superior in terms of enantioselectivitiy.

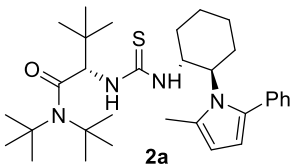
Table 1 Screening of silylating derivatives and various catalysts with **3a** as a model substrate.[a]

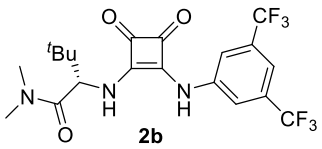


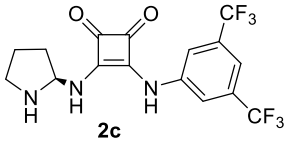










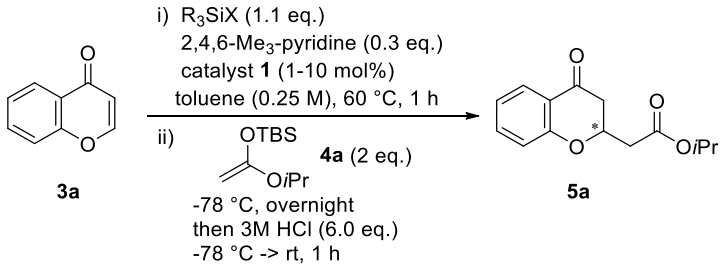


entry	Catalyst (mol%)	R_3SiX	yield (%)[b]	**5a**, e.r.[c]
1	(*R,R*)-**1a** (10)	TMSCl	32	64:36
2	(*R,R*)-**1a** (10)	TMSBr	70	71:29
3	(*R,R*)-**1a** (10)	TMSOTf	72	87:13
4	(*R,R*)-**1a** (10)	TESOTf	87	84:16
5	(*R,R*)-**1a** (10)	TIPSOTf	88	81:19
6	(*R,R*)-**1a** (10)	TBSOTf	92	91:9
7	(*R,R*)-**1a** (10)	TBSCl	10	72:28
8	(*R,R*)-**1b** (10)	TBSOTf	82	91:9
9	(*R,R*)-**1c** (10)	TBSOTf	92	78:22
10	(*R,R*)-**1d** (10)	TBSOTf	70	85:13
11	**2a** (10)	TBSOTf	82	57:43
12	**2b** (10)	TBSOTf	59	51:49
13	**2c** (10)	TBSOTf	58	50:50
14	--	TBSOTf	85	50:50

[a] Conditions: i) **3** (1 eq.) R_3SiX (1.1 eq.) and catalyst in toluene (0.25 M) at 60 °C, 1h; ii) at -78 °C, **4a** (2 eq.) was added and stirred overnight. [b] Isolated yield. [c] Enantiomeric ratios determined by chiral HPLC using a Diacel Chiralcel IG column.

In a next screening, different solvents, catalyst loadings and additional bulky silylating derivatives (R_3SiX) were tested (Table 2).

Table 2 Further optimization of the reaction with **3a** as a model substrate.[a]



entry	(*R,R*)-**1a** (X mol%)	solvent	R_3SiX	yield (%)[b]	**5a**, e.r.[c]
1	10	cumene	TBSOTf	95	80:20
2	10	ethylbenzene	TBSOTf	88	91:9
3	10	Et_2O	TBSOTf	82	89:11
4	10	MTBE	TBSOTf	15	73:27
5	10	toluene	TBSOTf	92	76:24[d]
6	5	toluene	TBSOTf	92	98:2
7	2.5	toluene	TBSOTf	88	96:4
8	1	toluene	TBSOTf	90	97:3
9	1	toluene	TBSCl	15	93:7
10	1	toluene	TMSOMs	32	97:3
11	1	toluene	$Ph_2tBuSiOTf$	95	54:46
12	1	toluene	$(tBu)_2iBuSiOTf$	96	82:18

[a] Conditions: i) **3** (1 eq.) R_3SiX (1.1 eq.) and catalyst in the appropriate solvent (0.25 M) at 60 °C, 1h; ii) at -78 °C, **4**a (2 eq.) was added and stirred overnight. [b] Isolated yield. [c] Enantiomeric ratios determined by chiral HPLC using a Diacel Chiralcel IG column. [d] Reaction at a 0.10 M concentration.

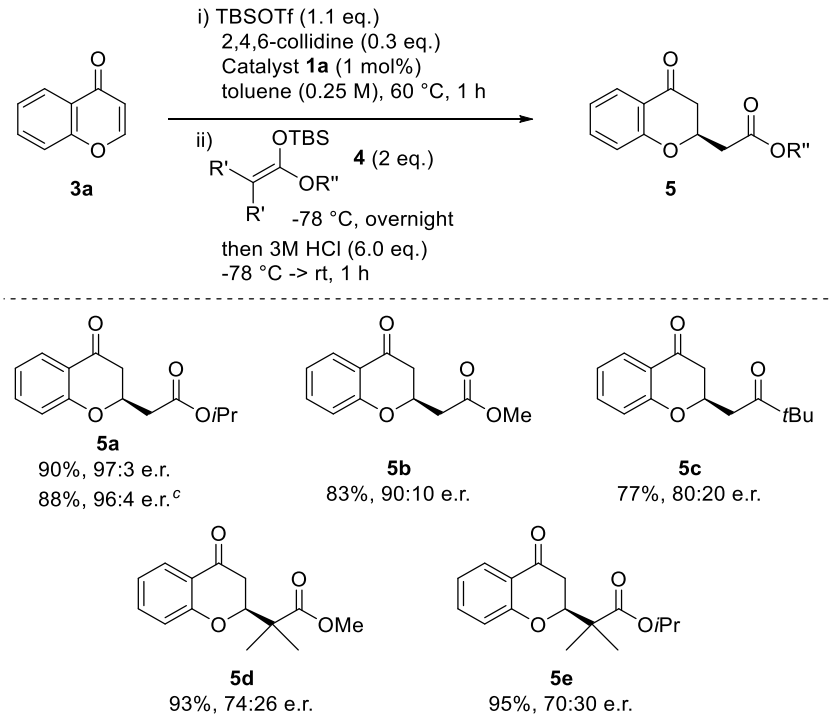
First, different etheral and aromatic solvents were tested (entries 1-4), from which toluene aroused as the optimal choice. When the reaction was carried out in a more diluted media (0.10 M vs. 0.25 M), a drop in enantioselectivity was observed (entry 5). We were pleased to see that a decrease of the catalyst loading to 5%, 2.5% and 1% had no crucial influence on the yield and provided a notably improved enantioselectivity to 98:2, 96:4 and 97:3 e.r., respectively (entries 6-8). For this reason, our following investigations were carried out with a 1 mol% catalyst loading. Furthermore, the use of other silylating agents than TBSOTf such as

TBSCl and TMSOMs or $Ph_2tBuSiOTf$ and $(tBu)_2iBuSiOTf$ provided **5a** in considerable low yields (entries 9-10) or enantioselectivities (entries 11-12).

4.3.2 Screening of the Scope of the Reaction

With the optimal conditions in hand, [TBSOTf, 2,4,6-collidine and catalyst **1a** (1 mol%) in toluene], the scope of the reaction was then investigated. Various silyl ketene acetals **4** were first tested in the reaction with chromone **3a** (Table 3). It is worthy to note that the reaction with **4a** could be scaled up to 1 mmol without significant detriment on the yield or enantioselectivity (**5a**, 88%, 96:4 e.r.). Moreover, a slightly change on the nucleophile's substitution showed a great influence on the enantioselectivity outcome. Whereas the methylester derivative **4b** still provided the product **5b** with a high enantiopurity (90:10 e.r.), the reaction with more sterically hindered nucleophiles such as **4c-e** proceeded smoothly but showed only a moderate chirality transfer.

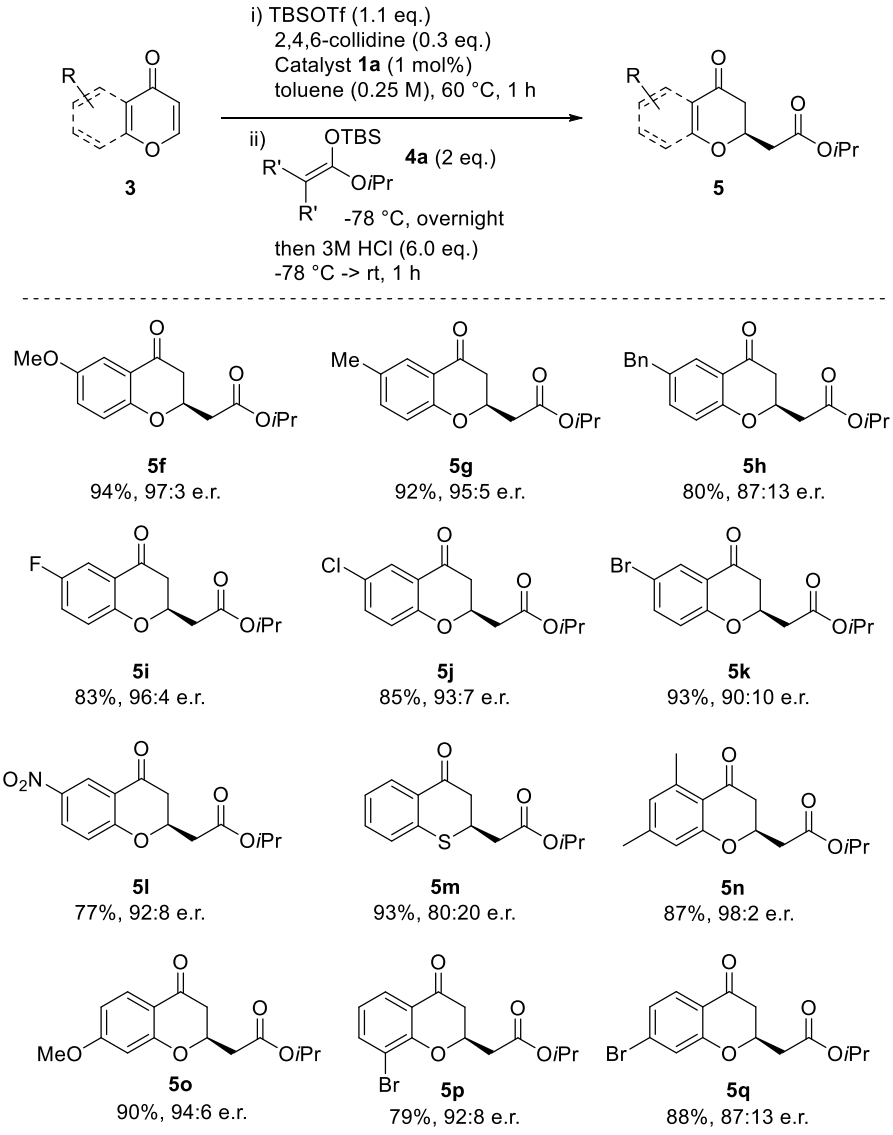
Table 3 Screening of the scope of the reaction with different silyl ketene acetals **4**. [a],[b]



[a] Conditions: i) **3** (1.0 eq.), TBSOTf (1.1 eq.), 2,4,6-collidine (0.3 eq.) and **1a** (1 mol%) in toluene, 1 h at 60 °C; ii) at -78 °C, **4** (2 eq.) was added and stirred overnight. [b] Isolated yields; enantiomeric ratios determined by chiral HPLC. [c] Reaction on a 1 mmol scale using 1.2 equiv. of **4a**.

Different substituted 4-chromones **3** were next examined (Table 4). Electron donating (**5f-h**) and withdrawing groups (**5i-l**) at the C6-position were well tolerated providing high yields and good to excellent enantioselectivities (up to 97:3 e.r.). Substituents at the C7- and C8-position led to the products **5o-q** in similar high enantioselectivities (up to 94:6 e.r.). One of the best results was obtained with the 5,7-dimethyl substituted substrate, obtaining **5m** in 98:2 e.r. Additionally, thiochromone was effectively enrolled in this reaction too, providing the corresponding thiochromane **5m** (80:20 e.r.).

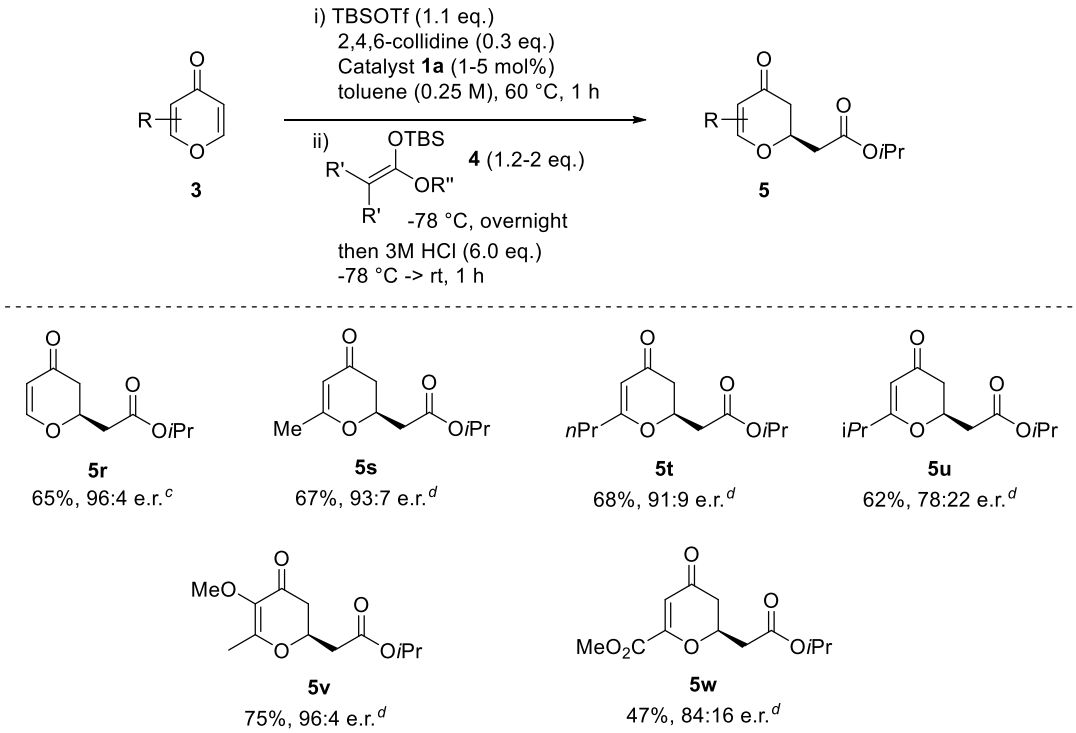
Table 4 Screening of the scope of the reaction of 4-chromones. [a],[b]



[a] Conditions: i) **3** (1.0 eq.), TBSOTf (1.1 eq.), 2,4,6-collidine (0.3 eq.) and **1a** (1 mol%) in toluene, 1 h at 60 °C; ii) at -78 °C, **4a** (2 eq.) was added and stirred overnight. [b] Isolated yields; enantiomeric ratios determined by chiral HPLC.

Finally, Julia Bamberger and Melania Gómez Martínez could confirm the great feasibility of the catalytic system by the effective reaction with the more challenging 4-pyrones (Table 5).

Table 5 Screening of the scope of the reaction of 4-pyrones. [a]- [b]

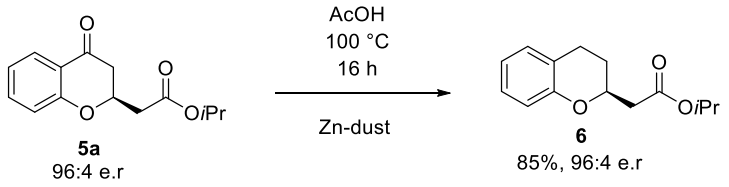


[a] Conditions: i) **3** (1.0 eq.), TBSOTf (1.1 eq.), 2,4,6-collidine (0.3 eq.) and **1a** (1 mol%) in toluene, 1 h at 60 °C; ii) at -78 °C, **4a** (2 eq.) was added and stirred overnight. [b] Isolated yields; enantiomeric ratios determined by chiral HPLC. [c] Reaction using 1.2 eq. of **4a**. [d] Reaction using 5 mol% of **1a**.

Though it was also possible to carry out the reaction with 4-pyrone (**3r**) in the presence of 1 mol% of catalyst (**5r**, 96:4 e.r.), the use of 5 mol% of **1a** generally led to the best results with this type of substrates in terms of both yield and enantioselectivity. Whereas the reaction of electron deficient (2-CO_2Me, **3w**) and bulky substituted (2-*i*Pr, **3u**) pyrones proceeded with moderate chirality transfer; good to excellent enantioselectivities were obtained with 2-alkyl substituted derivatives, leading to the products **5s-t** and **5v** with up to 96:4 e.r.

4.3.3 Synthetic Application

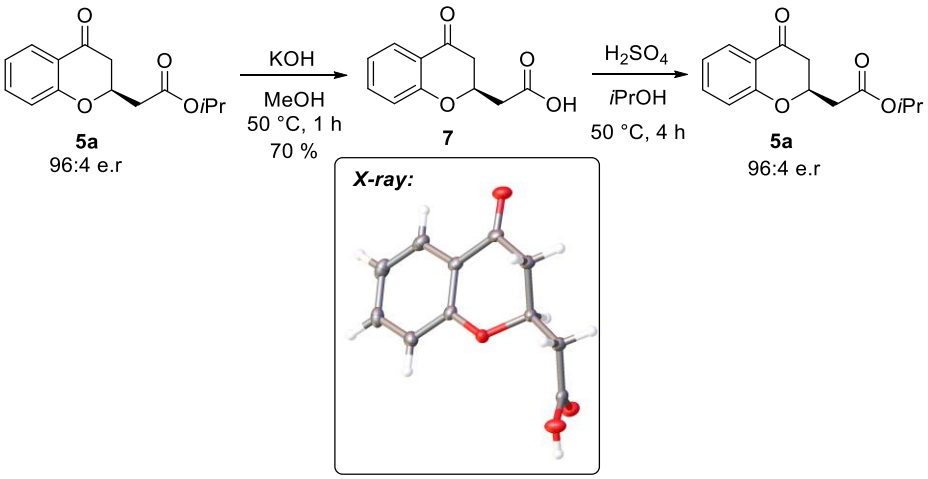
The synthetic applicability of this methodology was next demonstrated by derivatization of the chiral products **5** (Scheme 5). Thus, **5a** easily transformed to chromane derivative **6** in one step by a Clemmensen reduction with Zn in AcOH. The reaction proceeded without loss of enantiopurity, which was confirmed by chiral HPLC analysis of **6** (Scheme 5).



Scheme 5 Derivatization of products **5a** by Clemmensen reduction.

4.3.4 Absolut Configuration

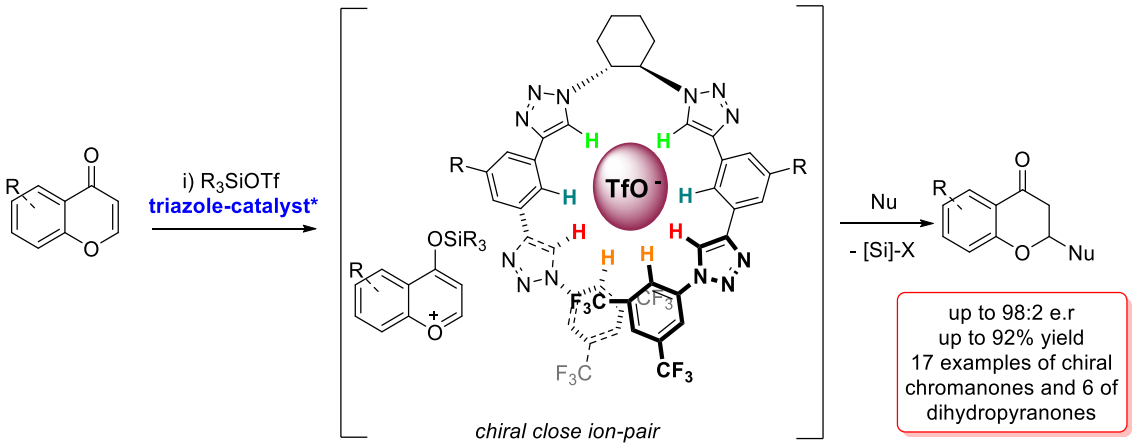
After the reaction scope's study, determining the absolute configuration of the obtained new C-stereocenters was of interest. Unfortunately, most of the products resulted as oils, hampering obtaining crystals for their X-ray structural analysis. However, alkaline hydrolysis of **5a** led to the corresponding acid **7**, which allowed crystallization followed by X-ray analysis of **7** to determine the absolute configuration as (*S*) at the new stereocenter formed during the catalytic reaction (Scheme 6). HPLC-analysis after re-esterification of **7** with *i*PrOH to compound **5a** confirmed that the process proceeded without loss of enantiopurity (96:4 e.r.)



Scheme 6 Determination of the absolute configuration.

4.4 Conclusion and Outlook

To sum up, a highly enantioselective catalytic method towards valuable 2-alkyl substituted oxygen heterocycles by nucleophilic dearomatization of pyrylium derivatives with silyl ketene acetals using chiral triazoles as anion-binding catalysts has been developed. The robustness and high activity of the catalyst **1a** allows its presence along the different steps in the one-pot process without detriment on the reaction outcome, as well as the use of low catalytic loadings (1-5 mol%). Moreover, the reaction scope probed to be very broad, providing a simple access to the targeted chiral chromanones and dihydropyrones in enantioselectivities up to 98:2 e.r and 96:4 e.r, respectively.



The discovery that our TetraTri catalyst can bind not only halide but also triflate anions in its cavity and opens new possibilities of transformations. It would be interesting applying this catalytic system for example into the stereospecific glycosylation reaction for the synthesis of carbohydrates.

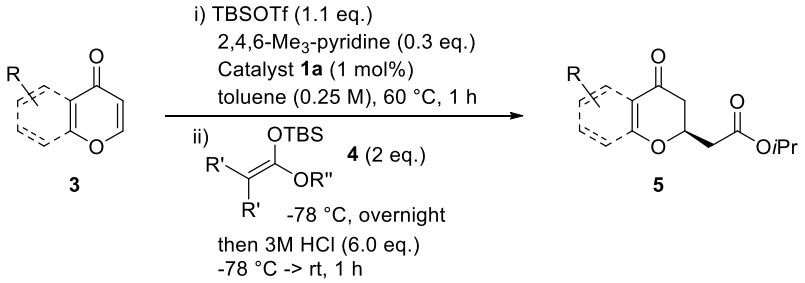
4.5 Experimental Part

4.5.1 General Information and Analytical Techniques

^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded in acetone-D_6 and $CDCl_3$ (reference signal:[15] ^{1}H = 2.05 ppm, ^{13}C = 29.84 ppm, acetone-D_6; ^{1}H = 7.26 ppm, ^{13}C = 77.16 ppm, $CDCl_3$) on a *Bruker Advance* 300 or 400 MHz. Chemical shifts (δ) are given in ppm and spin-spin coupling constants (J) are given in Hz. Analytical thin layer chromatography was performed using silica gel 60 F254 and a solution of $KMnO_4$ or phosphomolybdic acid served as staining agent. Column chromatography was performed on silica gel 60 (0.040-0.063 mm). Exact masses (HRMS) were performed using electrospray ionization techniques (ESI+) and recorded on an *Agilent Q-TOF 6540 UHD* or a *Bruker Daltonics MicroTof* spectrometer. Optical rotations $[\alpha]_{589}^{20}$ were measured on a Perkin Elmer 241 Polarimeter. Chiral High Pressure Liquid Chromatography (HPLC) analyses were performed on a 1200 series Agilent or SFC-LC Agilent using a chiral chiralpack IG or AD column.

Et_3N was distilled over CaH_2; and MTBE, THF, Et_2O, toluene, cumene and ethylbenzene were distilled and dried over sodium. The triazole catalysts **1**,[12e] NH-catalysts **2**,[16] silyl ketene acetals **4a-e**,[17] (thio)chromenones **3h**, and **3n** and **3m**[11] were prepared following literature known procedures. Other solvents and commercially available reagents were used without further purification.

4.5.2 General Procedure for the Organocatalytic Reaction



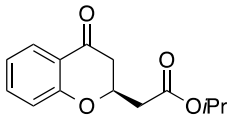
Derivative **3** (0.10 mmol, 1.0 eq.), 2,4,6-trimethylpyridine (4 μL, 0.03 mmol, 0.3 eq.) and catalyst **1a** (1.1 mg, 0.001 mmol, 1 mol%) were dissolved in dry toluene (0.4 mL, 0.25 M) and after the addition of TBSOTf (25 μL, 0.11 mmol, 1.1 eq.) the reaction mixture was stirred for 1 h at 60 °C and cooled to -78 °C afterwards. The silyl ketene acetal **4** (0.20 mmol, 2.0 eq.) was added and the reaction mixture was stirred at -78 °C overnight. 3 M HCl (6.0 eq.) was added and the mixture was allowed to warm to room temperature for one hour. The solution was

diluted with water (5 mL), extracted with ethyl acetate (3 x 10 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using petrol ether/EA (5:1) to afford the desired product.

The racemic versions were prepared without catalyst, following the general procedure described above.

4.5.3 Analytical Data for Compounds 5

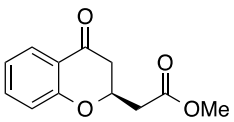
Isopropyl (*S*)-2-(4-oxochroman-2-yl)acetate (5a)



According to the general procedure, the reaction of **3a** (15.0 mg, 0.100 mmol, 1.0 eq.) with **4a** (51 μL, 0.200 mmol, 2.0 eq.) led after flash column chromatography (PE/EtOAc 5:1) to the desired product **5a** (22.8 mg, 0.092 mmol, 92%) as a pale yellow oil. The enantiomeric ratio was determined as 97:3 e.r. (98:2 e.r. when using 5 mol% of **1a** catalyst) by chiral HPLC (Chiralcel IG, hexane/*i*PrOH (80:20) 1.0 mL/min, λ= 254 nm): *t*r (minor): 8.5 min, *t*r (major): 11.7 min.). $[\boldsymbol{\alpha}]_{\mathbf{589}}^{\mathbf{20}}$: +38.72 (*c* 0.9, $CHCl_3$) (98:2 e.r.). ^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm = 7.89 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.53 – 7.43 (m, 1H), 7.07 – 7.00 (m, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 5.09 (hept., *J* = 6.2 Hz, 1H), 4.91 (dtd, *J* = 8.7, 7.2, 5.7 Hz, 1H), 2.89 (dd, *J* = 15.6, 7.4 Hz, 1H), 2.80 (s, 1H), 2.77 (d, *J* = 2.0 Hz, 1H), 2.69 (dd, *J* = 15.6, 5.7 Hz, 1H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.26 (d, *J* = 6.3 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm = 191.4, 169.0, 161.1, 136.1, 126.9, 121.6, 120.9, 117.9, 74.3, 68.5, 42.4, 40.3, 21.8, 21.7; HRMS (EI): *m/z* calculated for $[C_{14}H_{16}O_4]^+$: 248.10431, found 248.10456.

The scale up reaction of **3a** (150.0 mg, 1.0 mmol) using 1 mol% of **1a** and 1.2 equiv. of **4a** of led to the desired product 5a in 88% yield and the enantiomeric ratio of 96:4 e.r.

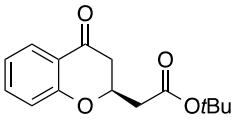
Methyl (*S*)-2-(4-oxochroman-2-yl)acetate (5b)



According to the general procedure, the reaction of **3a** (15 mg, 0.10 mmol, 1.0 eq.) with **4b** (51 μL, 0.20 mmol, 2 eq.) led after flash column chromatography (PE/EtOAc 5:1) to the desired product **5b** (18 mg, 0.083 mmol, 83%) as a pale yellow oil. The enantiomeric ratio was determined as 90:10 e.r. by chiral HPLC (Chiralcel IG, hexane/*i*PrOH (80:20) 1.0 mL/min, λ= 254 nm): *t*r (minor): 13.6 min, *t*r (major): 25.6 min.). $[\boldsymbol{\alpha}]_{\mathbf{589}}^{\mathbf{20}}$: + 16.31 (*c* 0.8, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.88 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.44 - 7.50 (m, 1H), 7.05 – 7.00 (m, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 4.95 – 4.87 (m, 1H), 3.75 (s, 3H), 2.94 (dd, *J* = 15.9, 7.3 Hz, 1H), 2.80 (s, 1H), 2.78 (d, *J* = 2.1 Hz, 1H), 2.74 (dd, *J* = 15.9, 5.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ/ppm = 191.4, 170.0, 161.1,

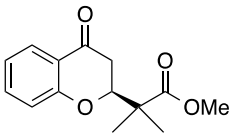
136.1, 127.0, 121.7, 120.8, 118.0, 74.1, 74.1, 52.1, 42.5, 39.7; HRMS (EI): *m/z* calculated for $[C_{12}H_{12}O_4]^+$: 220.07301, found 220.07261.

tert-Butyl (_S_)-2-(4-oxochroman-2-yl)acetate (5c)



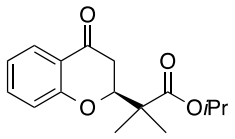
According to the general procedure, the reaction of **3a** (15 mg, 0.10 mmol, 1.0 eq.) with **4c** (54 μL, 0.20 mmol, 2 eq.) led after flash column chromatography (PE/EtOAc 5:1) to the desired product **5c** (20.2 mg, 0.077 mmol, 77%) as a pale yellow oil. The enantiomeric ratio was determined as 80:20 e.r. by chiral HPLC (Chiralcel IG, hexane/*i*PrOH (80:20) 1.0 mL/min, λ= 254 nm): *t*r (minor): 7.1 min, *t*r (major): 10.1 min.). $[\alpha]_{589}^{20}$: + 12.19 (*c* 0.5, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 8.12 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.71 (ddd, *J* = 8.8, 7.2, 1.8 Hz, 1H), 7.29 – 7.23 (m, 1H), 7.19 (d, *J* = 8.4, 1H), 5.15 – 5.06 (m, 1H), 3.07 (dd, *J* = 15.5, 7.4 Hz, 1H), 3.02 (s, 1H), 3.00 (d, *J* = 4.9 Hz, 1H), 2.88 (dd, *J* = 15.5, 5.8 Hz, 1H), 1.72 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ/ppm = 191.6, 168.8, 161.2, 136.1, 127.0, 121.6, 120.9, 118.0, 81.5, 74.5, 42.5, 41.3, 28.1; HRMS (EI): *m/z* calculated for $[C_{15}H_{18}O_4]^+$: 262.11996, found 262.12020.

Methyl (_S_)-2-methyl-2-(4-oxochroman-2-yl)propanoate (5d)



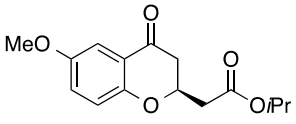
According to the general procedure, the reaction of **3a** (15 mg, 0.10 mmol, 1.0 eq.) with **4d** (41 μL, 0.20 mmol, 2 eq.) led after flash column chromatography (PE/EtOAc 5:1) to the desired product **5d** (23 mg, 0.093 mmol, 93%) as a pale yellow oil. The enantiomeric ratio was determined as 74:26 e.r. by chiral HPLC (Chiralcel IG, hexane/*i*PrOH (80:20) 1.0 mL/min, λ= 254 nm): *t*r (minor): 8.0 min, *t*r (major): 9.2 min.). $[\alpha]_{589}^{20}$: + 6.48 (*c* 0.5, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm 7.83 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.47 – 7.38 (m, 1H), 7.00 – 6.94 (m, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 4.61 (dd, *J* = 14.1, 2.6 Hz, 1H), 3.69 (s, 3H), 2.75 (dd, *J* = 16.5, 14.1 Hz, 1H), 2.56 (dd, *J* = 16.5, 2.6 Hz, 1H), 1.33 (s, 3H), 1.24 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ/ppm = 192.3, 175.5, 161.6, 136.0, 127.0, 121.5, 120.8, 117.9, 81.7, 52.3, 46.2, 38.4, 20.8, 20.6; HRMS (EI): *m/z* calculated for $[C_{14}H_{16}O_4]^+$: 248.10431, found 248.10460.

Isopropyl (*S*)-2-methyl-2-(4-oxochroman-2-yl)propanoate (5e)



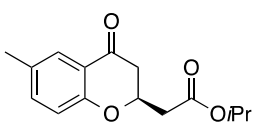
According to the general procedure, the reaction of **3a** (15 mg, 0.10 mmol, 1.0 eq.) with **4e** (58 μL, 0.20 mmol, 2 eq.) led after flash column chromatography (PE/EtOAc 5:1) to the desired product **5e** (26.2 mg, 0.095 mmol, 95%) as a pale yellow oil. The enantiomeric ratio was determined as 70:30 e.r. by chiral HPLC (Chiralcel IG, hexane/*i*PrOH (80:20) 1.0 mL/min, λ= 254 nm): *t*r (minor): 5.8 min, *t*r (major): 7.4 min.). $[\boldsymbol{\alpha}]_{\boldsymbol{589}}^{\boldsymbol{20}}$: + 2.04 (*c* 0.5, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm 7.87 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.46 (ddd, *J* = 8.5, 7.2, 1.8 Hz, 1H), 7.06 – 6.97 (m, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 5.06 (hept, *J* = 6.3 Hz, 1H), 4.66 (dd, *J* = 14.1, 2.6 Hz, 1H), 2.78 (dd, *J* = 16.5, 14.1 Hz, 1H), 2.60 (dd, *J* = 16.5, 2.6 Hz, 1H), 1.35 (s, 3H), 1.27 – 1.16 (m, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ/ppm = 192.4, 174.5, 161.7, 136.0, 127.0, 121.4, 120.9, 117.8, 81.9, 68.3, 46.0, 38.3, 21.7, 20.8, 20.2; HRMS (EI): *m/z* calculated for $[C_{16}H_{20}O_4]^+$: 276.13561, found 276.13505.

Isopropyl (*S*)-2-(6-methoxy-4-oxochroman-2-yl)acetate (5f)



According to the general procedure, the reaction of **3f** (18 mg, 0.10 mmol, 1.0 eq.) with **4a** (51 μL, 0.20 mmol, 2 eq.) led after flash column chromatography (PE/EtOAc 5:1) to the desired product **5f** (26 mg, 0.094 mmol, 94%) as a pale yellow oil. The enantiomeric ratio was determined as 97:3 e.r. by chiral HPLC (Chiralcel IG, hexane/*i*PrOH (80:20) 1.0 mL/min, λ= 254 nm): *t*r (minor): 9.3 min, *t*r (major): 16.2 min.). $[\boldsymbol{\alpha}]_{\boldsymbol{589}}^{\boldsymbol{20}}$: + 25.57 (*c* 0.8, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm = 7.30 (d, *J* = 3.2 Hz, 1H), 7.08 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 1H), 5.08 (hept, *J* = 6.3 Hz, 1H), 4.93 – 4.78 (m, 1H), 3.80 (s, 3H), 2.87 (dd, *J* = 15.6, 7.4 Hz, 1H), 2.77 (s, 1H), 2.74 (d, *J* = 2.9 Hz, 1H), 2.72 – 2.63 (m, 1H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.26 (d, *J* = 6.3 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm = 191.6, 169.1, 155.9, 154.2, 125.3, 120.7, 119.3, 107.3, 74.4, 68.5, 55.8, 42.5, 40.4, 21.8, 21.7; HRMS (EI): *m/z* calculated for $[C_{15}H_{18}O_5]^+$: 278.11488, found 278.11498.

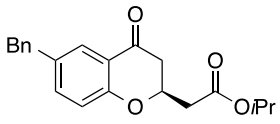
Isopropyl (*S*)-2-(6-methyl-4-oxochroman-2-yl)acetate (5g)



According to the general procedure, the reaction of **3g** (16 mg, 0.10 mmol, 1.0 eq.) with **4a** (51 μL, 0.20 mmol, 2 eq.) led after flash column chromatography (PE/EtOAc 5:1) to the desired product **5g** (24 mg, 0.092 mmol, 92%) as a pale yellow oil. The enantiomeric ratio was determined as 95:5 e.r. by chiral HPLC (Chiralcel IG, hexane/*i*PrOH (80:20) 1.0 mL/min, λ= 254 nm): *t*r (minor): 8.4 min,

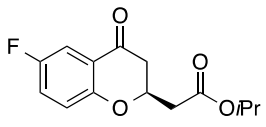
*t*r (major): 12.0 min.). $[\alpha]_{589}^{20}$: + 17.10 (*c* 1.00, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm = 7.67 (d, *J* = 1.8 Hz, 1H), 7.28 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 5.08 (hept, *J* = 6.3 Hz, 1H), 4.93 – 4.79 (m, 1H), 2.87 (dd, *J* = 15.6, 7.4 Hz, 1H), 2.76 (s, 1H), 2.74 (d, *J* = 2.1 Hz, 1H), 2.67 (dd, *J* = 15.6, 5.7 Hz, 1H), 2.30 (s, 3H), 1.27 (d, *J* = 6.2 Hz, 3H), 1.26 (d, *J* = 6.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm = 191.7, 169.1, 159.3, 137.2, 131.1, 126.6, 120.5, 117.7, 74.2, 68.5, 42.6, 40.4, 29.7, 21.8, 21.7, 20.4; HRMS (EI): *m/z* calculated for $[C_{15}H_{18}O_4]^+$: 262.11996, found 262.11925.

Isopropyl (*S*)-2-(6-benzyl-4-oxochroman-2-yl)acetate (5h)



According to the general procedure, the reaction of **3h** (24 mg, 0.10 mmol, 1.0 eq.) with **4a** (51 μL, 0.20 mmol, 2 eq.) led after flash column chromatography (PE/EtOAc 5:1) to the desired product **5h** (27 mg, 0.08 mmol, 80%) as a dark yellow oil. The enantiomeric ratio was determined as 87:13 e.r. by chiral HPLC (Chiralcel IG, hexane/*i*PrOH (80:20) 1.0 mL/min, λ= 254 nm): *t*r (minor): 10.2 min, *t*r (major): 13.7 min.). $[\alpha]_{589}^{20}$: + 11.07 (*c* 0.75, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.74 (d, *J* = 2.1 Hz, 1H), 7.30 (d, *J* = 2.1 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 7.3 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 1H), 5.08 (hept, *J* = 6.2 Hz, 1H), 4.92 – 4.83 (m, 1H), 3.93 (s, 2H), 2.87 (dd, *J* = 15.6, 7.4 Hz, 1H), 2.76 (s, 1H), 2.75 (d, *J* = 2.9 Hz, 1H), 2.67 (dd, *J* = 15.6, 5.6 Hz, 1H), 1.27 (d, *J* = 6.1 Hz, 3H), 1.26 (d, *J* = 6.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ/ppm = 191.6, 169.1, 159.7, 140.6, 136.9, 134.6, 128.8, 128.6, 126.6, 126.3, 120.6, 118.1, 74.3, 68.6, 42.5, 41.0, 40.4, 25.3, 21.8, 21.7; HRMS (EI): *m/z* calculated for $[C_{21}H_{22}O_4]^+$: 338.15126, found 338.15152.

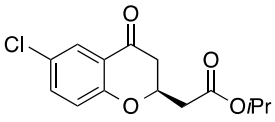
Isopropyl (*S*)-2-(6-fluoro-4-oxochroman-2-yl)acetate (5i)



According to the general procedure, the reaction of **3i** (16.0 mg, 0.10 mmol, 1.0 eq.) with **4a** (51 μL, 0.20 mmol, 2 eq.) led after flash column chromatography (PE/EtOAc 5:1) to the desired product **5i** (22.6 mg, 0.083 mmol, 83%) as a pale yellow oil. The enantiomeric ratio was determined as 96:4 e.r. by chiral HPLC (Chiralcel IG, hexane/*i*PrOH (80:20) 1.0 mL/min, λ= 230 nm): *t*r (minor): 7.4 min, *t*r (major): 10.1 min.). $[\alpha]_{589}^{20}$: +32.95 (*c* 1.05, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm = 7.54 (dd, *J* = 8.2, 3.2 Hz, 1H), 7.20 (ddd, *J* = 9.0, 7.8, 3.2 Hz, 1H), 6.95 (dd, *J* = 9.1, 4.2 Hz, 1H), 5.09 (hept, *J* = 6.2 Hz, 1H), 4.93 – 4.83 (m, 1H), 2.88 (dd, *J* = 15.7, 7.4 Hz, 1H), 2.79 (d, *J* = 2.0 Hz,

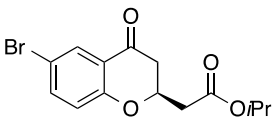
1H), 2.77 (d, *J* = 8.2 Hz, 1H), 2.69 (dd, *J* = 15.7, 5.7 Hz, 1H), 1.27 (d, *J* = 6.1 Hz, 3H), 1.26 (d, *J* = 6.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm = 190.7, 169.0, 157.5 (d, J_{CF} = 242.0 Hz), 157.4, 123.6 (d, J_{CF} = 24.4 Hz), 121.3, 119.6 (d, J_{CF} = 7.6 Hz), 112.1 - 111.9 (d, J_{CF} = 23.3 Hz), 74.5, 68.7, 42.2, 40.3, 21.8, 21.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -121.54; HRMS (EI): *m/z* calculated for $[C_{14}H_{15}FO_4]^+$: 266.09375, found 266.09425. The scale up reaction of **3i** (160.0 mg, 1.0 mmol) of led to the desired product **5i** in 76% yield and the same enantiomeric ratio of 96:4 e.r.

Isopropyl (*S*)-2-(6-chloro-4-oxochroman-2-yl)acetate (5j)



According to the general procedure, the reaction of **3j** (18 mg, 0.10 mmol, 1.0 eq.) with **4a** (51 μL, 0.20 mmol, 2 eq.) led after flash column chromatography (PE/EtOAc 5:1) to the desired product **5j** (23.7 mg, 0.085 mmol, 85%) as a yellow oil. The enantiomeric ratio was determined as 93:7 e.r. by chiral HPLC (Chiralcel IG, hexane/*i*PrOH (80:20) 1.0 mL/min, λ= 254 nm): *t*r (minor): 8.0 min, *t*r (major): 11.8 min.). $[\boldsymbol{\alpha}]_{\boldsymbol{589}}^{\boldsymbol{20}}$: + 21.16 (*c* 0.75, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.84 (d, *J* = 2.6 Hz, 1H), 7.41 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 5.09 (hept, *J* = 6.3 Hz, 1H), 4.96 – 4.81 (m, 1H), 2.88 (dd, *J* = 15.7, 7.4 Hz, 1H), 2.79 (d, *J* = 1.9 Hz, 1H), 2.77 (d, *J* = 7.9 Hz, 1H), 2.69 (dd, *J* = 15.8, 5.7 Hz, 1H), 1.27 (d, *J* = 6.2 Hz, 3H), 1.26 (d, *J* = 6.2 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ/ppm = 190.3, 168.9, 159.6, 136.0, 127.2, 126.4, 121.7, 119.7, 74.5, 68.7, 42.2, 40.2, 21.8, 21.7; HRMS (EI): *m/z* calculated for $[C_{14}H_{15}ClO_4]^+$: 282.06534, found 282.06469.

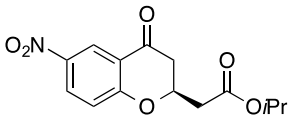
Isopropyl (*S*)-2-(6-bromo-4-oxochroman-2-yl)acetate (5k)



According to the general procedure, the reaction of **3k** (22.5 mg, 0.10 mmol, 1.0 eq.) with **4a** (51 μL, 0.20 mmol, 2 eq.) led after flash column chromatography (PE/EtOAc 5:1) to the desired product **5k** (27.3 mg, 0.085 mmol, 85%) as a pale yellow oil. The enantiomeric ratio was determined as 90:10 e.r. by chiral HPLC (Chiralcel IG, hexane/*i*PrOH (80:20) 1.0 mL/min, λ= 254 nm): *t*r (minor): 8.7 min, *t*r (major): 13.8 min.). $[\boldsymbol{\alpha}]_{\boldsymbol{589}}^{\boldsymbol{20}}$: + 19.36 (*c* 0.75, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm = 7.99 (d, *J* = 2.5 Hz, 1H), 7.55 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 5.09 (hept, *J* = 6.3 Hz, 1H), 4.89 (ddt, *J* = 10.2, 7.4, 5.6 Hz, 1H), 2.88 (dd, *J* = 15.8, 7.4 Hz, 1H), 2.79 (s, 1H), 2.77 (d, *J* = 5.3 Hz, 1H), 2.69 (dd, *J* = 15.8, 5.7 Hz, 1H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.26 (d, *J* = 6.3 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm = 190.2, 168.9, 160.0, 138.7, 129.5, 122.1,

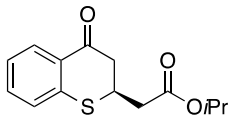
120.0, 114.4, 74.5, 68.7, 42.1, 40.2, 21.8, 21.7; HRMS (EI): *m/z* calculated for $[C_{14}H_{15}BrO_4]^+$: 326.01482, found 326.01416.

Isopropyl (*S*)-2-(6-nitro-4-oxochroman-2-yl)acetate (5l)



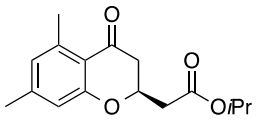
According to the general procedure, the reaction of **3l** (19.2 mg, 0.10 mmol, 1.0 eq.) with **4a** (51 μL, 0.20 mmol, 2 eq.) led after flash column chromatography (PE/EtOAc 5:1) to the desired product **5l** (22.4 mg, 0.077 mmol, 77%) as a dark yellow oil. The enantiomeric ratio was determined as 92:8 e.r. by chiral HPLC (Chiralcel IG, hexane/*i*PrOH (80:20) 1.0 mL/min, λ= 254 nm): *t*r (minor): 18.7 min, *t*r (major): 24.7 min.). $[\boldsymbol{\alpha}]_{\boldsymbol{589}}^{\boldsymbol{20}}$: + 46.48 (*c* 0.5, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 8.78 (d, *J* = 2.8 Hz, 1H), 8.34 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.10 (d, *J* = 9.1 Hz, 1H), 5.12 (hept, *J* = 6.3 Hz, 1H), 5.06 – 4.96 (m, 1H), 2.95 (dd, *J* = 10.1, 5.9 Hz, 1H), 2.91 – 2.84 (m, 2H), 2.75 (dd, *J* = 16.5, 5.6 Hz, 1H), 1.29 (d, *J* = 4.0 Hz, 3H), 1.27 (d, *J* = 4.0 Hz, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ/ppm = 189.21, 168.51, 164.92, 142.33, 130.44, 123.64, 120.39, 119.33, 75.25, 68.96, 41.85, 39.93, 29.71, 21.81, 21.79, 14.13; HRMS (EI): *m/z* calculated for $[C_{14}H_{15}NO_6]^+$: 293.08939, found 293.08920.

Isopropyl (*S*)-2-(4-oxothiochroman-2-yl)acetate (5m)



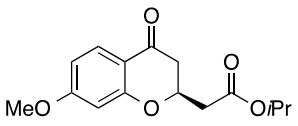
According to the general procedure, the reaction of **3m** (16 mg, 0.10 mmol, 1.0 eq.) with **4a** (51 μL, 0.20 mmol, 2 eq.) led after flash column chromatography (PE/EtOAc 5:1) to the desired product **5m** (24.7 mg, 0.093 mmol, 93%) as a pale yellow oil. The enantiomeric ratio was determined as 80:20 e.r. by chiral HPLC (Chiralcel IG, hexane/*i*PrOH (80:20) 1.0 mL/min, λ= 254 nm): *t*r (minor): 8.6 min, *t*r (major): 11.2 min.). $[\boldsymbol{\alpha}]_{\boldsymbol{589}}^{\boldsymbol{20}}$: + 32.66 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 8.09 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.46 – 7.31 (m, 1H), 7.28 – 7.15 (m, 2H), 5.05 (hept, *J* = 6.3 Hz, 1H), 3.99 – 3.87 (m, 1H), 3.13 (dd, *J* = 16.5, 3.6 Hz, 1H), 2.86 (dd, *J* = 16.5, 8.9 Hz, 1H), 2.77 – 2.60 (m, 2H), 1.24 (s, 3H), 1.22 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ/ppm = 193.5, 169.5, 140.5, 133.7, 130.4, 129.0, 127.8, 125.2, 68.7, 45.2, 39.3, 37.2, 21.8, 21.7; HRMS (EI): *m/z* calculated for $[C_{14}H_{16}O_3S]^+$: 264.08147, found 264.08088.

Isopropyl (*S*)-2-(5,7-dimethyl-4-oxochroman-2-yl)acetate (5n)



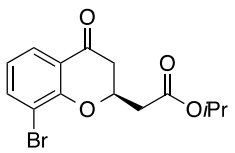
According to the general procedure, the reaction of **3n** (17.4 mg, 0.10 mmol, 1.0 eq.) with **4a** (51 μL, 0.20 mmol, 2 eq.) led after flash column chromatography (PE/EtOAc 5:1) to the desired product **5n** (24.1 mg, 0.087 mmol, 87%) as a yellow oil. The enantiomeric ratio was determined as 98:2 e.r. by chiral HPLC (Chiralcel IG, hexane/*i*PrOH (80:20) 1.0 mL/min, λ= 254 nm): *t*r (minor): 7.3 min, *t*r (major): 9.7 min.). $[\boldsymbol{\alpha}]_{\boldsymbol{589}}^{\boldsymbol{20}}$: + 14.81 (*c* 0.75, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 6.62 (s, 2H), 5.08 (hept, *J* = 6.3 Hz, 1H), 4.88 – 4.76 (m, 1H), 2.83 (dd, *J* = 15.5, 7.5 Hz, 1H), 2.73 (d, *J* = 1.5 Hz, 1H), 2.71 (s, 1H), 2.64 (dd, *J* = 15.5, 5.6 Hz, 1H), 2.59 (s, 3H), 2.28 (s, 3H), 1.27 (d, *J* = 5.3 Hz, 3H), 1.26 (d, *J* = 5.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ/ppm = 192.5, 169.2, 162.3, 146.0, 141.9, 126.1, 117.2, 116.0, 73.5, 68.5, 43.9, 40.4, 22.7, 21.9, 21.8, 21.6; HRMS (EI): *m/z* calculated for $[C_{16}H_{20}O_4]^+$: 276.13561, found 276.13617.

Isopropyl (*S*)-2-(7-methoxy-4-oxochroman-2-yl)acetate (5o)



According to the general procedure, the reaction of **3o** (17.6 mg, 0.10 mmol, 1.0 eq.) with **4a** (51 μL, 0.20 mmol, 2 eq.) led after flash column chromatography (PE/EtOAc 5:1) to the desired product **5o** (25.1 mg, 0.090 mmol, 90%) as a pale yellow oil. The enantiomeric ratio was determined as 94:6 e.r. by chiral HPLC (Chiralcel IG, hexane/*i*PrOH (80:20) 1.0 mL/min, λ= 254 nm): *t*r (minor): 16.6 min, *t*r (major): 23.9 min.). $[\boldsymbol{\alpha}]_{\boldsymbol{589}}^{\boldsymbol{20}}$: + 14.81 (*c* 0.75, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm = 7.82 (d, *J* = 8.8 Hz, 1H), 6.58 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 5.09 (hept, *J* = 6.3 Hz, 1H), 4.96 – 4.80 (m, 1H), 3.82 (s, 3H), 2.87 (dd, *J* = 15.7, 7.5 Hz, 1H), 2.72 (d, *J* = 7.5 Hz, 2H), 2.71 – 2.63 (dd, *J* = 15.7, 5.4 Hz, 1H), 1.28 (d, *J* = 6.2 Hz, 3H), 1.26 (d, *J* = 6.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ/ppm = 190.1, 169.1, 166.1, 163.1, 128.7, 114.8, 110.2, 100.8, 74.6, 68.6, 55.7, 42.2, 40.4, 21.8, 21.7; HRMS (EI): *m/z* calculated for $[C_{15}H_{18}O_5]^+$: 278.11488, found 278.11452.

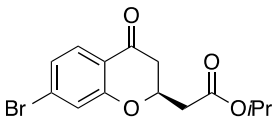
Isopropyl (*S*)-2-(8-bromo-4-oxochroman-2-yl)acetate (5p)



According to the general procedure, the reaction of **3p** (22.5 mg, 0.10 mmol, 1.0 eq.) with **4a** (51 μL, 0.20 mmol, 2 eq.) led after flash column chromatography (PE/EtOAc 5:1) to the desired product **5p** (28.1 mg, 0.086 mmol, 86%) as a dark yellow oil. The enantiomeric ratio was determined as 92:8 e.r.

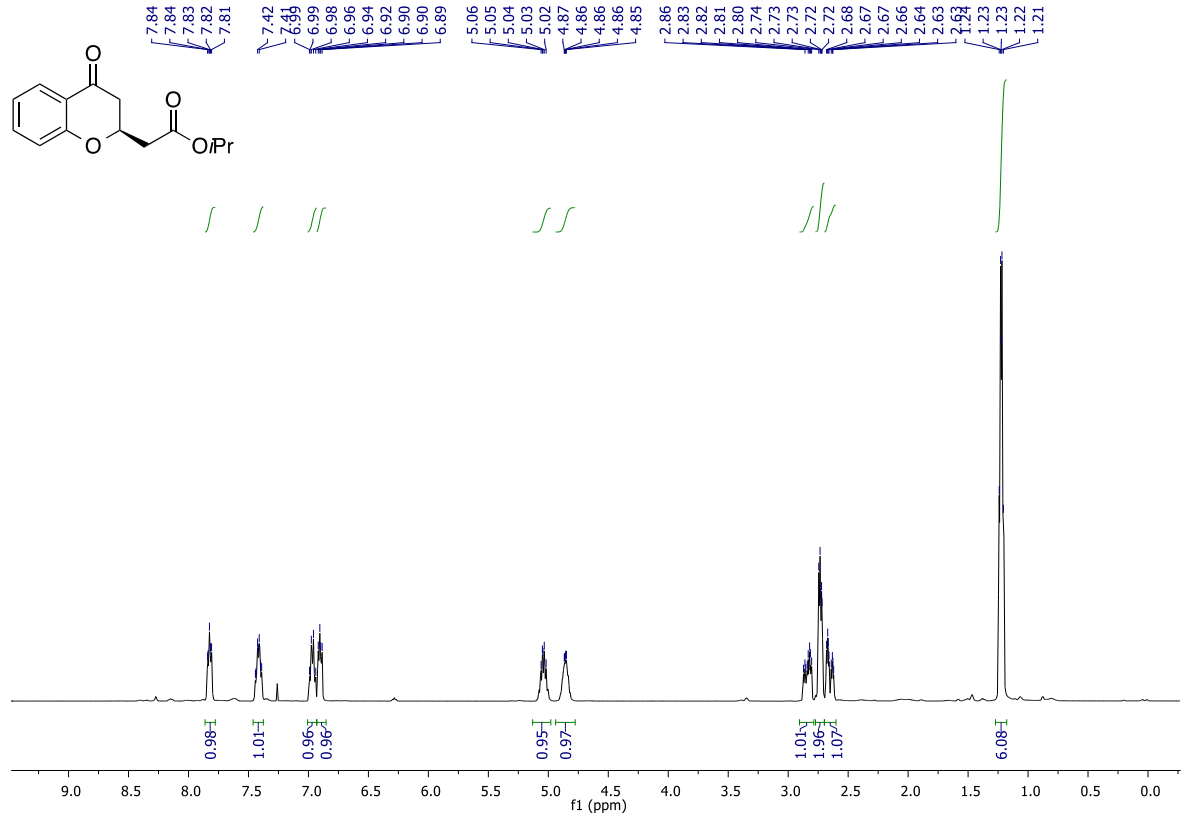
by chiral HPLC (Chiralcel IG, hexane/*i*PrOH (80:20) 1.0 mL/min, λ= 254 nm): *t*r (minor): 3.7 min, *t*r (major): 7.9 min.). $[\boldsymbol{\alpha}]_{\boldsymbol{589}}^{\boldsymbol{20}}$: + 22.08 (*c* 0.75, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm = 7.85 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 6.92 (t, *J* = 7.8 Hz, 1H), 5.10 (hept, *J* = 6.2 Hz, 1H), 4.99 (dt, *J* = 11.5, 5.2 Hz, 1H), 2.97 (dd, *J* = 15.6, 7.6 Hz, 1H), 2.89 – 2.78 (m, 2H), 2.74 (dd, *J* = 15.6, 5.6 Hz, 1H), 1.29 (d, *J* = 6.1 Hz, 3H), 1.27 (d, *J* = 6.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ/ppm = 190.6, 168.8, 157.6, 139.4, 126.4, 122.3, 122.1, 111.8, 75.2, 68.8, 42.1, 40.3, 21.9, 21.8; HRMS (EI): *m/z* calculated for $[C_{14}H_{15}BrO_4]^+$: 327.02400, found 327.02430.

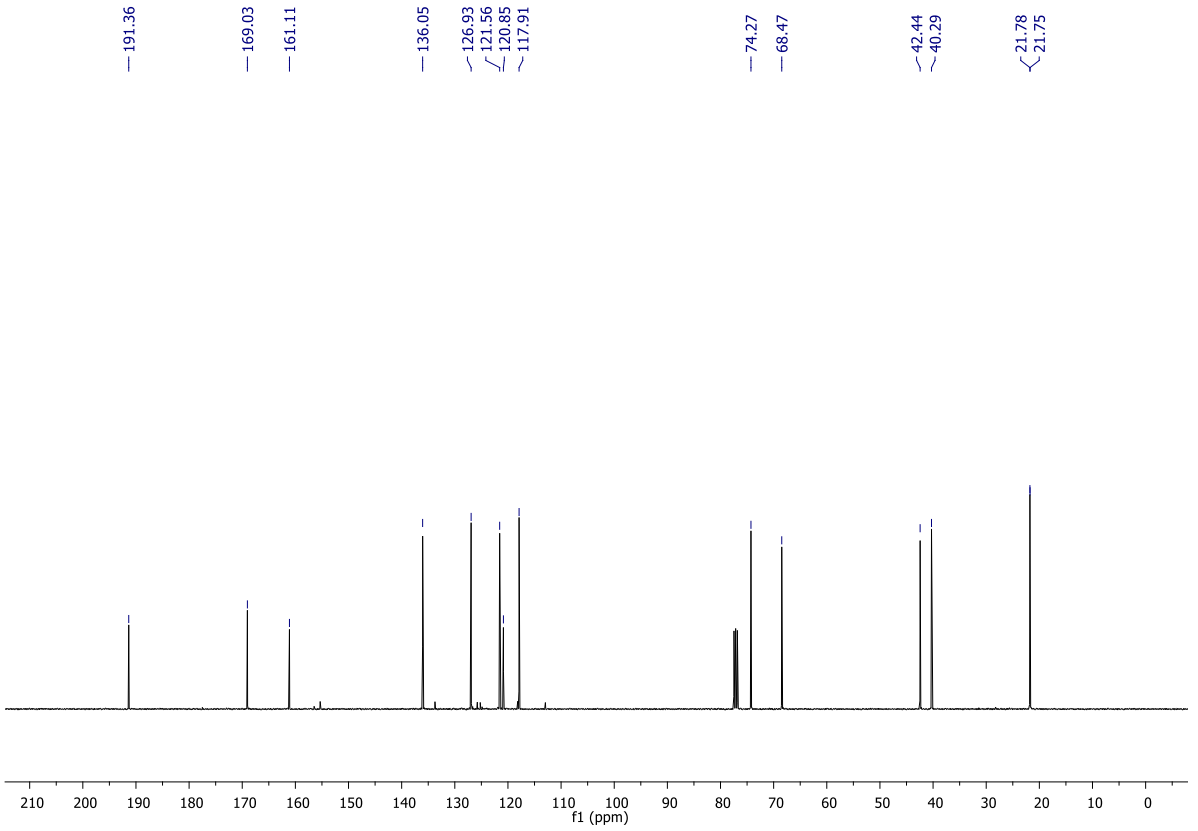
Isopropyl (*S*)-2-(7-bromo-4-oxochroman-2-yl)acetate (5q)



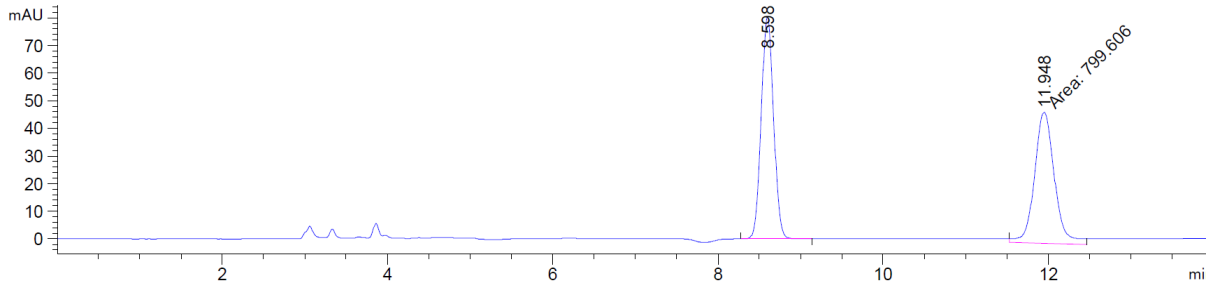
According to the general procedure, the reaction of **3q** (22.5 mg, 0.10 mmol, 1.0 eq.) with **4a** (51 μL, 0.20 mmol, 2 eq.) led after flash column chromatography (PE/EtOAc 5:1) to the desired product **5q** (28.7 mg, 0.088 mmol, 88%) as a yellow oil. The enantiomeric ratio was determined as 87:13 e.r. by chiral HPLC (Chiralcel IG, hexane/*i*PrOH (80:20) 1.0 mL/min, λ= 254 nm): *t*r (minor): 9.3 min, *t*r (major): 14.5 min.). $[\boldsymbol{\alpha}]_{\boldsymbol{589}}^{\boldsymbol{20}}$: + 21.82 (*c* 1.00, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ/ppm = 7.73 (d, *J* = 8.8 Hz, 1H), 7.19 – 7.12 (m, 2H), 5.08 (hept, *J* = 6.3 Hz, 1H), 4.97 – 4.84 (m, 1H), 2.87 (dd, *J* = 15.8, 7.4 Hz, 1H), 2.78 (s, 1H), 2.76 (d, *J* = 3.7 Hz, 1H), 2.68 (dd, *J* = 15.8, 5.6 Hz, 1H), 1.28 (d, *J* = 6.1 Hz, 3H), 1.26 (d, *J* = 6.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ/ppm = 190.5, 168.8, 161.3, 130.5, 128.2, 125.3, 121.2, 119.8, 74.8, 68.7, 42.3, 40.2, 21.8, 21.7; HRMS (EI): *m/z* calculated for $[C_{14}H_{15}BrO_4]^+$: 326.01482, found 326.01405.

4.5.4 Representative Spectra and HPLC Chromatograms of 5a



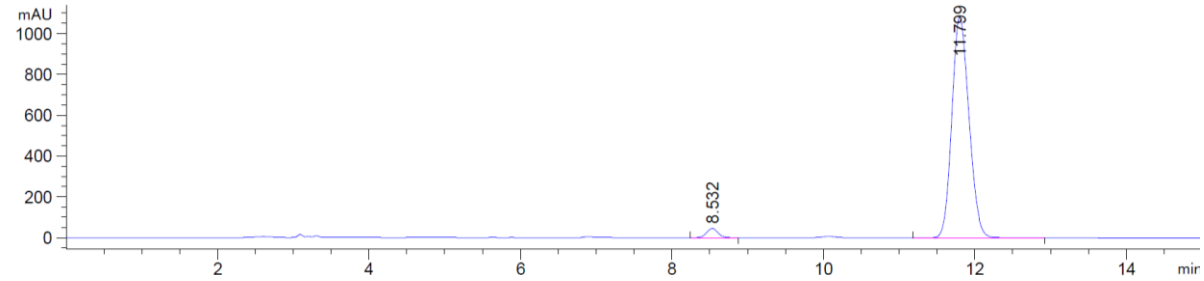


Chiral-phase HPLC: IG; Hex/^{i}PrOH 80:20, F = 1 mL/min (λ = 254 nm)
racemic:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.598	BB	0.1629	835.32294	80.57641	51.0923
2	11.948	MM	0.2810	799.60596	47.42349	48.9077

enantioselective:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.531	BB	0.1589	118.72321	11.64795	2.3913
2	11.799	MM	0.2701	4846.13867	299.05646	97.6087

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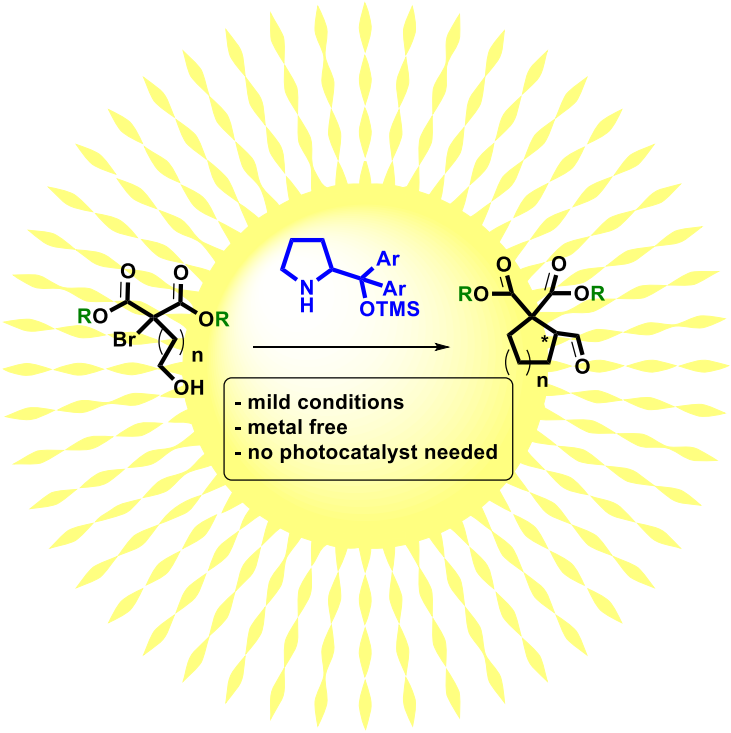
Chapter 5

Research stay abroad

5. Intramolecular α-Alkylation of Aldehydes *via* Photoredox Catalysis



Abstract: This project describes a methodological study carried out to develop a new intramolecular photocatalyzed enantioselective α-alkylation of aldehydes. To achieve this goal in asymmetric fashion, we have used an organocatalytic approach to create the new stereogenic carbons. Different tests have been performed with the corresponding previously-synthesized alkylbromo-aldehydes. Several variables, such as the aminocatalysts, photocatalysts, light sources, solvents or concentrations, have been evaluated aiming at achieving high yields and enantiomeric excesses.

This project was carried out in the chemistry department *Departamento de Química Orgánica de la Facultad de Ciencias de la Universidad Autónoma de Madrid* under the supervision of Prof. Dr. José Alemán Lara during a research stay of 5 months (February 2017 – July 2017).

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5.1 Introduction

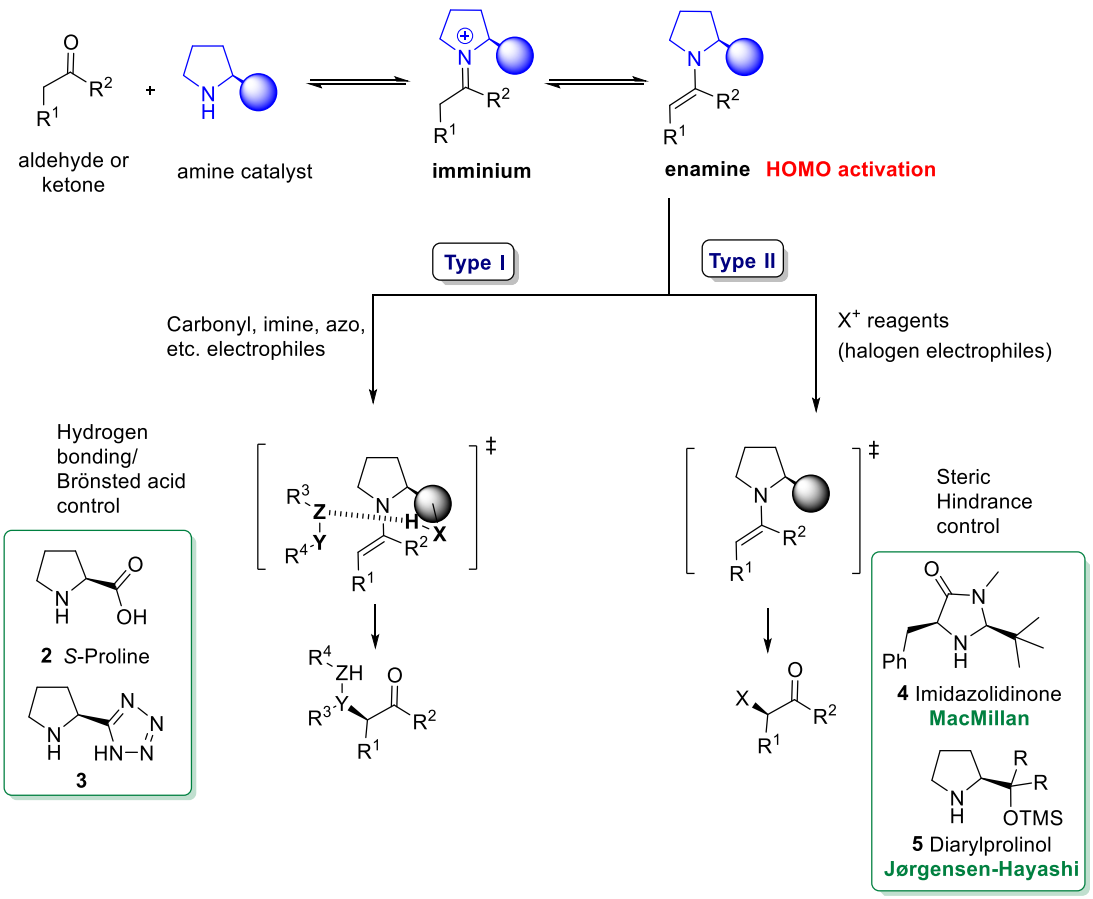
5.1.1 Enamine Catalysis

Although the early examples of amino acid catalyzed enantioselective reactions were known since 1971,[1] enamine catalysis was rediscovered in the late 90's, becoming one of the main pillars for the further advance of the field of organocatalysis. Accordingly, in 2000 Barbas III, Lerner and List used independently the natural amino acid (*S*)-proline to catalyze the intermolecular aldol reaction between aldehydes and ketones.[2] Since then, enamine catalysis and the development of new and more efficient organocatalysts gained huge interest. In this mode of activation, an amine-containing catalyst (typically a secondary amine) activates a carbonyl-containing substrate that has an α-acidic proton, which permits the iminium-enamine tautomery (Scheme 1). If the catalyst has an additional functionality, it acts as a bifunctional catalyst (*e.g.* activating the reaction partner through hydrogen bonding or it can also bear a photocatalytic moiety, which will be described later in this chapter). This mode of activation has been employed in a wide variety of enantioselective α-functionalization reactions.[3]

In general, two different types of catalysts can be differentiated. Type I, a catalyst like (*S*)-proline that contains a hydrogen bond donor to orient the attack of the nucleophile. They are used for aldol, Mannich, α-amination reactions, etc.

Type II, a catalyst that contains a bulky group, which pre-orient the attack of the nucleophile by blocking one face. Well established catalysts are the MacMillan imidazolidinones of type **4** and the Hayashi-Jørgensen diarylprolinol silyl ethers of type **5**. They can be employed for α-halogenation as well as some conjugate addition reactions.

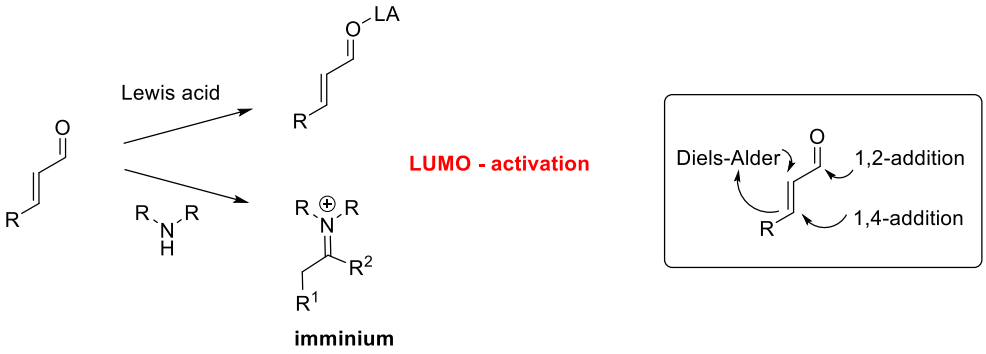
In this work we focused more on the type II catalyst.



Scheme 1. Enamine catalysis mechanism.

5.1.2 Iminium Catalysis

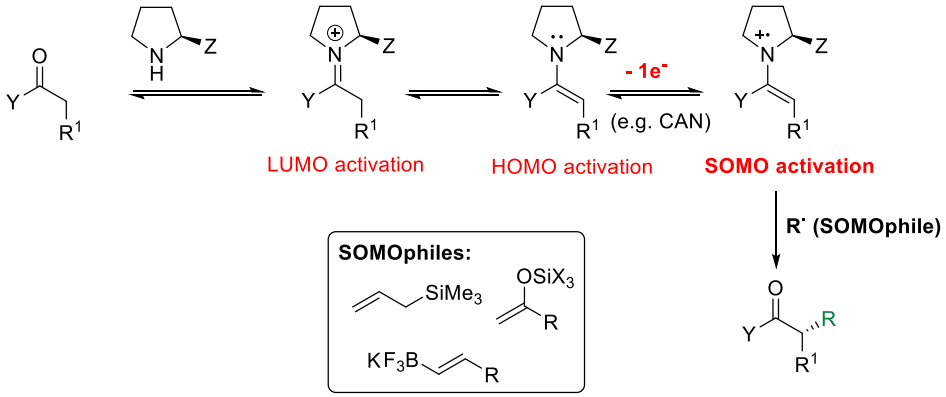
Depending on the reaction conditions, α,β-unsaturated carbonyl compounds can undergo nucleophilic 1,2-additions, 1,4-addition reactions or Diels-Alder reactions. For these transformations, a catalyst is used to lower the energy of the LUMO orbitals of the carbonyl group and therefore enhancing its electrophilic character. Traditionally a Lewis acid has been used to coordinate to the oxygen atom of the carbonyl group. In 2000, MacMillan introduced the concept of iminium catalysis, which relies on the use of a chiral secondary amine to form an iminium ion that is analogue to a Lewis acid activated carbonyl-containing compound (Scheme 2).[4] This approach has widespread use for various reactions such as cycloadditions, Friedel-Crafts alkylations and 1,4-addition reactions.[5] The most famous organocatalysts are the MacMillan imidazolidinones (**4** in Scheme **1**) and the Jørgensen-Hayashi diaryl prolinols (e.g. **5**, R = Ph or 3,5-$(CF_3)_2$Ph), which present an orthogonal reactivity.



Scheme 2. The fundamentals of iminium catalysis.

5.1.3 SOMO Catalysis

Recently, catalysis based on single electron oxidation of transiently produced, electron-rich enamines has introduced a new mode of activation termed SOMO (Single Occupied Molecular Orbital) organocatalysis. This activation mode was introduced by the MacMillan group, and is based on the idea of an electron-rich enamine, which can be oxidized to a reactive radical cation with three π-electrons. Thereby, the radical electron occupies the SOMO orbital. This reactive substrate can readily react at its α-position with a wide range of soft nucleophiles (SOMO-philes), with the subsequent alkylation of the substrate (Scheme 3). The reactivity of the activated enamine differs from its typical reactivity, leading to a wide range of possible transformations that are complementary to the enamine catalysis. This strategy represents a useful methodology for the α-functionalization of carbonyl compounds.[6]



Scheme 3. General mechanism of the SOMO catalysis.

5.1.4 Photocatalysis

In the last years, photocatalysis emerged as a useful tool for achieving transformations that were not feasible till date under standard thermal conditions. In the presence of light, certain photoactive compounds can accelerate reactions catalytically. The use of visible light could hence facilitate the synthesis of valuable molecules, while represents a cheap, clean and inexhaustible source of energy.[7] In this field, two different types of photoactivation must be differentiated:

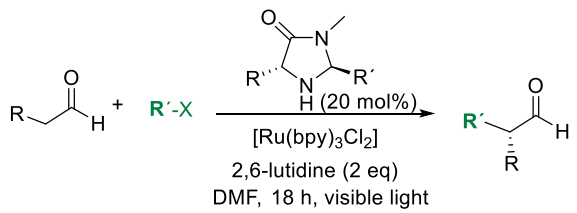
1) the photosensitization, which is the transfer of energy, and

2) the photoredox induction, which is the transfer of electrons.

In general, metal complexes are used in photoredox catalysis to perform electron transfer processes to organic substrates through the irradiation by visible light. Those catalysts in their excited state, reached by the absorption of light, can act as oxidants or reductants, depending on substrates and the reaction conditions employed.[8]

5.1.5 Merging Photoredox Catalysis with Organocatalysis

In 2008, MacMillan combined for the first time organocatalysis and photocatalysis and solved many of the still present issues in the asymmetric alkylation of aldehydes (Scheme 4). He used $[Ru(bpy)_3Cl_2]$ as photocatalyst and a imidazolidinone as organocatalyst. The *in situ* formed chiral enamines could then catch the radicals, which were generated in the photoredox cycle. The combination of these two methods presents a perfect technique to activate and react molecules *via* the corresponding generated radicals. It was found that these radical species give higher yields and enantiomeric excesses, the greater the electron withdrawing nature of α-bromocarbon is.[9]

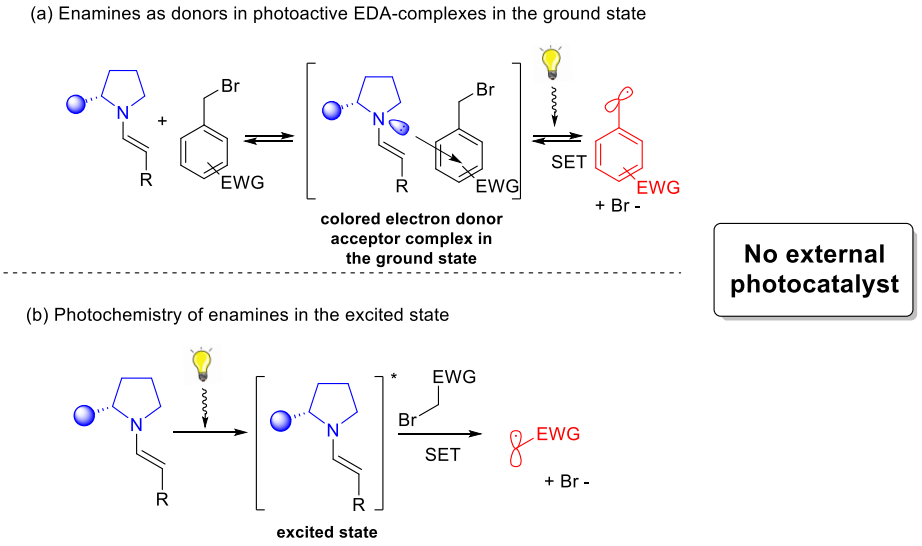


Scheme 4 Asymmetric α-alkylation of aldehydes by MacMillan.

Since then, other groups like Melchiorre,[10] Zeitler[11] and Cozzi[12] investigated different methods for the α-alkylation of aldehydes with various cooperative systems. In general, those are assembled by an aminocatalyst and an organic or inorganic photocatalyst. MacMillan has

been very active in this field, publishing various key papers on the topic like the first α-trifluormethylation and α-perfluoroalkylation of aldehydes.[13]

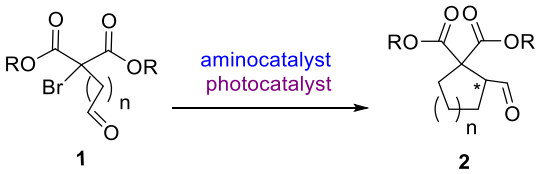
In 2015, Melchiorre published two strategies of α-alkylation without employing additional photocatalysts.[10b] He found out that the *in situ* generated enamines were able to form a photon-absorbing Electron Donor - Acceptor complex (EDA) with electron-deficient benzyl and phenacyl bromides. These EDA complexes could absorb visible light and trigger a photocatalytic reaction (Scheme 5a). Nevertheless, the reactions were limited to strong deactivated benzylic halides. More recently, Melchiorre described that some nucleophilic enamines can photo-reduce species and induce the photo-organocatalytical process (Scheme 5b).



Scheme 5. Strategies of the α-alkylation of aldehydes carried out by Melchiorre *et al*.

5.2 Objectives

As mentioned above, several methods for the intermolecular α-alkylation of aldehydes with electron-deficient groups such as α-trifluoromethylation,[13] α-benzylation,[14] α-amination[15] and α-cyanoalkylation[16] have been described in the literature. Inspired by the work of MacMillan and Melchiorre among many others, and in order to combine the knowledge of the group of José Alemán on the fields of organo- and photocatalysis, we decided to go one step further and investigate the enantioselective intramolecular alkylation of aldehydes. A mild and straightforward synthesis of this kind of enantioenriched molecules would open a new way to access chiral cyclic compounds of different ring sizes (Scheme 6).



Scheme 6 General reaction scheme of the intramolecular α-alkylation of aldehydes.

To achieve our goal in an asymmetric fashion, we will make use of an organocatalytic approach to create the new stereogenic carbons. Different tests will be performed with previously synthesized alkylbromo-containing aldehydes, in which several variables such as the aminocatalyst, photocatalyst, light source and wavelength, solvent or concentration will be evaluated to achieve optimal yields and high enantiomeric excesses.

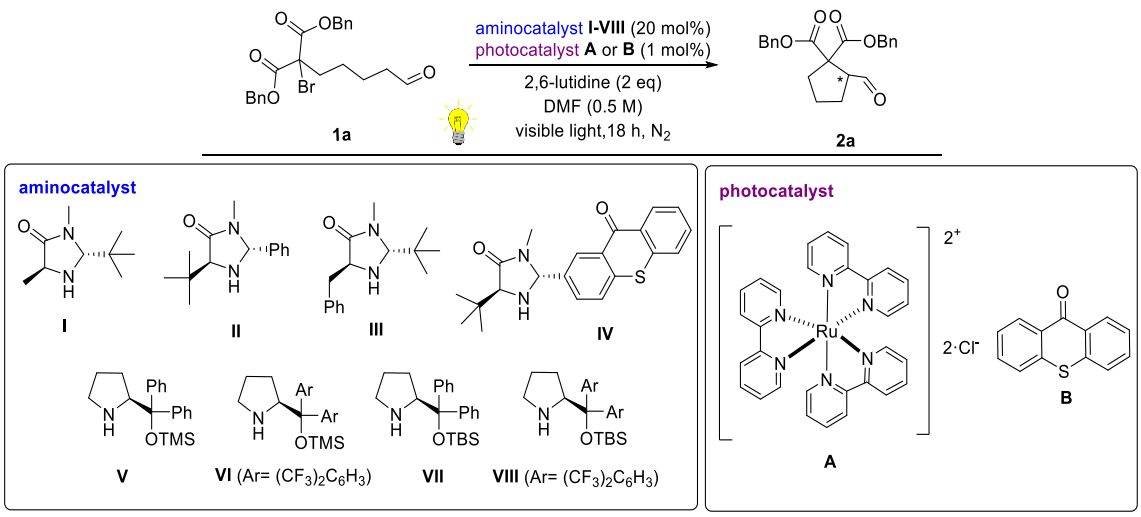
For this type of reaction, a cooperative mechanism with two catalytical cycles is proposed: a organocatalytic and a photocatalytic cycle. Nevertheless, Melchiorre published a mechanism for the intramolecular α-alkylation of aldehydes, where it seems to be possible that the photocatalyst is not required. Therefore, different reactions will be carried out to confirm this allegation.

5.3 Results and Discussion

5.3.1. Optimization of the Catalyst

To get a better insight in the reaction requirements, an optimization of the reaction conditions with different organo- and photocatalysts was carried out. These results are presented in Table 1. Initially, a blank reaction with aminocatalyst **I** and without light was performed, which did not yield any product (entry 1). Following the work of MacMillan, a cooperative system of aminocatalyst **I** and Ru-photocatalyst **A** was introduced to the reaction giving a complex mixture of decomposition products (entry 2). By changing the Ru-photocatalyst to the organophotocatalyst **B**, the desired product **2** was obtained in a moderate yield and enantioselectivity (entry 3). Next, a screening of different aminocatalysts was carried out (entries 4 - 8). However, the change from the MacMillan type catalyst (entry 4) to the Jørgensen-Hayashi type catalysts (**V-VIII**) gave no significant change in the yield and enantiopurity. This behavior can be traced back to the fact that the reaction already works without any aminocatalyst, which was confirmed by the formation of the product **2** in a 18% yield in the reaction using exclusively thioxanthene as a photocatalyst (entry 10). Thus, the thioxanthene is obviously able to reduce the bromo-species, which then could react with the enol present in the reaction medium. Consequently, an aminocatalyst is not needed then for obtaining the product and no enantiomeric induction would be seen. The group of José Alemán recently developed on a bifunctional photocatalyst (**IV**), which consists of the combination of an aminocatalytic- and a photocatalytic moiety and already proofed to work well in alkylation reactions of aldehydes. This bifunctional photocatalyst was next employed in the reaction, but unfortunately did not lead to any enantiomeric induction (entry 9). The need of an aminocatalyst was indicated in entry 11, where the reaction was carried out without any catalyst, yielding the product in only 10% yield. On the other hand, this try confirmed our fear of a background reaction, which would lower the enantiomeric excess. Thinking about the latest work of Melchiorre in this field, we decided to carry out the reaction without an additional photocatalyst and fortunately, we achieved better results. A screening of the different aminocatalyst (entries 12-17) showed that the Jørgensen-Hayashi type catalysts (entries 14-17) gave the best results in terms of both yield and enantioselectivity. Then, a promising enantiomeric ratio up to 75:25 with catalyst **VI** was obtained (entry 15).

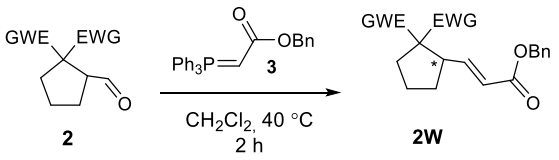
Table 1. Optimization of the reaction conditions and screening of various amino- and photocatalysts.[a]



Entry	Aminocatalyst	Photocatalyst	Conv.[%]	e.r.[b]
1	**rac-I**	-	-	-
2	**I**	**A**	-	-
3	**I**	**B**	38	40:60
4	**III**	**B**	54	55:45
5	**V**	**B**	52	40:60
6	**VI**	**B**	43	61:39
7	**VII**	**B**	54	50:50
8	**VIII**	**B**	52	50:50
9	**IV**	-	42	50:50
10[c]	-	**B**	18	50:50
11[c]	-	-	10	-
12	**I**	-	72	63:37
13	**II**	-	13	n.d.
14	**V**	-	100	67:34
15	**VI**	-	50	75:25
16	**VII**	-	100	47:53
17	**VIII**	-	92	70:30

[a] Conditions: organocatalyst (0.02 mmol, 20 mol %), **1a** (0.1 mmol, 1.0 eq.), and/or photocatalyst (0.001 mmol, 1 mol%), 2,6-lutidine (0.2 mmol, 2 eq.) in 0.2 mL of DMF under visible light irradiation (23 W) at room temperature and N_2-atmosphere. [b] The enantiomeric ratio of product **2a** was determined by chiral HPLC on the derivatization product **2Wa** from a subsequent Wittig reaction**.** [c] Reaction carried out in the absence of an aminocatalyst.

Since the direct determination of the enantiomeric ratio by HPLC or GC analysis was not possible with aldehyde **2a,** a further derivatization by a Wittig reaction was necessary. Therefore, benzyl(triphenylphosphoranylidene)acetate **3** was used as a Wittig reagent, forming, together with **2** the derivatized product **2W** after two hours in full conversion (Scheme 7).

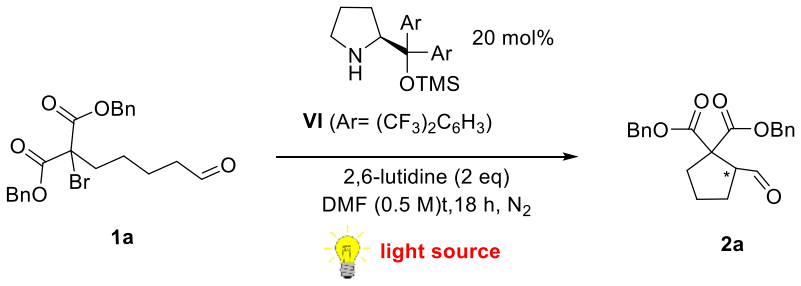


Scheme 7 General reaction scheme of the Wittig derivatization of aldehyde **2**.

5.3.2 Optimization of the Light Source

In a next step, different light sources were employed to see their influence on the reaction. With the optimized reaction conditions in hand (catalyst **VI** and DMF as a solvent), parallel reactions were carried out with four different wavelengths ranging from UV to white light (Table 3.2).

Table 2. Optimization of the light source**.** [a; b]



Entry	Light (λ_{max}, nm)	Conversion[%]	e.r.[b]
1	white	50	75:25
2	green (540)	100	61:39
3	blue (450)	90	65:35
4	UV (385)	100	55:45

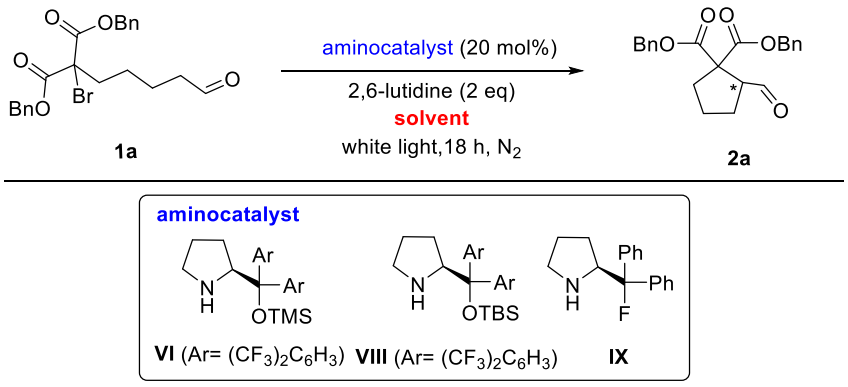
[a] Conditions: organocatalyst **IV** (0.02 mmol, 20 mol %), **1a** (0.1 mmol, 1.0 eq.), 2,6-lutidine (0.2 mmol, 2 eq.) in 0.2 mL of DMF at room temperature and N_2-atmosphere using different light sources as indicated. [b] To determine the enantiomeric ratio of product **2a** a derivatization with a Wittig reagent to **2Wa** was necessary**.**

It was observed that other wavelengths than white light improved the conversion to product **2** (90-100% vs. only 50%), but also a degradation of the enantiomeric induction was detected. Using green light (λ_{max} = 540 nm, P = 0.4 W, entry 2), a full conversion but an inferior 61:39 enantiomeric ratio was obtained. Employing a minor wavelength (blue light, λ_{max} = 450 nm, P = 0.4 W, entry 3), the conversion was also up to 90%, but no increase of the enantiomeric excess was achieved. UV light (λ_{max} = 385 nm, P = 0.4 W, entry 4) gave the lowest enantiomeric ratio, however full conversion was observed. Finally, we could conclude that the white light was the best light source in regard of enantiomeric induction (up to 75:25 e.r.).

5.3.3 Solvent Screening

Next, the solvent and concentration effects on the reaction were studied. First, other polar aprotic solvents like acetonitrile and DMSO were tested (entries 2 and 3), leading to a similar enantiomeric ratio but higher conversions than DMF (entry 1). In DCM, a higher enantiomeric induction and conversion were observed (entry 4), which turned out to be slightly enhanced in a more concentrated reaction media (0.25 M; 86:14 e.r., entry 5). Polar protic solvents like MeOH gave less satisfactory results (entry 6). Apolar solvents like MTBE (entry 7), hexane (entries 8 and 9) or cyclohexane (entries 10 and 11) gave improved results than the polar aprotic solvents but were not superior compared to DCM. Finally, aromatic solvents in different concentrations were tested (entries 12-19). In respect to the best results obtained till now in DCM shown in entry 5 (86:14 e.r.), *p*-xylene gave a better enantiomeric ratio of 87:13 (entry 12), whereas trifluorotoluene led to low enantioselectivity (60:40, entry 13). The highest enantiomeric ratio of 90:10 was obtained with toluene as a solvent and a concentration of 0.5 M (entry 14). To improve the conversion with toluene, the same reaction was carried out with a prolonged reaction time of three days. Unfortunately, a high detriment on the enantioinduction leading to almost a racemic mixture was observed (entry 15). To evaluate the solvent effects within other catalysts, different Jørgensen-Hayashi type catalysts were employed in the reaction with toluene as most promising solvent. However, no improvement of the enantiomeric excess took placed (entries 18 and 19).

Table 3. Optimization of solvent and concentration.[a]



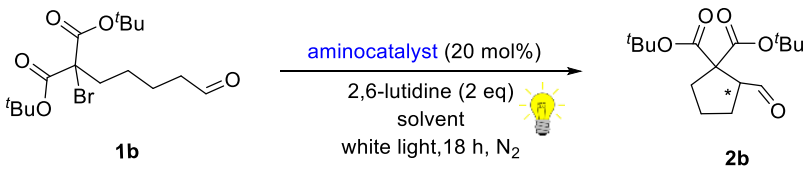
Entry	Aminocatalyst	Solvent	c [M]	Conversion [%]	e.r.[b]
1	**VI**	DMF	0.5	50	75:25
2	**VI**	CH_3CN	0.5	100	70:30
3	**VI**	DMSO	0.5	95	75:25
4	**VI**	CH_2Cl_2	0.5	93	83:17
5	**VI**	CH_2Cl_2	0.25	100	86:14
6	**VI**	CH_3OH	0.5	85	68:32
7	**VI**	MTBE	0.5	50	81:19
8	**VI**	hexane	0.5	60	67:33
9	**VI**	hexane	0.25	42	n.d
10	**VI**	cyclohexane	0.5	60	75:25
11	**VI**	cyclohexane	0.25	20	80:20
12	**VI**	*p*-xylene	0.5	50	87:13
13	**VI**	trifluorotoluene	0.5	100	60:40
14	**VI**	toluene	0.5	55	90:10
15[c]	**VI**	toluene	0.5	82	55:45[c]
16	**VI**	toluene	0.25	43	88:12
17	**VI**	toluene	1	72	70:30
18	**VIII**	toluene	0.5	66	70:30
19	**IX**	toluene	0.5	100	45:55

[a] Conditions: organocatalyst (0.02 mmol, 20 mol %), **1a** (0.1 mmol, 1.0 eq.), 2,6-lutidine (0.2 mmol, 2 eq.) in 0.2 mL of DMF at room temperature and N_2-atmosphere using different light sources as indicated. [b] To determine the enantiomeric ratio of product **2a** a derivatization with a Wittig reagent to **2Wa** was necessary**.** [c] The reaction was stirred for 3 days.

5.3.4 Reaction with Aldehydes 1b, 1c and 1d

With the optimized reaction conditions for aldehyde **1a** in hand, we decided to study the reaction with different aldehydes. In aldehyde **1b** the benzyl group of the esters moieties at the malonate unit was changed to a *tert*-butyl group to enhance the steric hindrance aiming at further improve the enantiomeric induction. First, the reaction was carried out with the best conditions from aldehyde **1a**, but surprisingly no reaction was observed (entry 1). Thus, an optimization of the reaction conditions for aldehyde **1b** was carried out (Table 4). When the reaction was performed for three days, low yield and moderate enantiomeric induction of 75:25 e.r. was recorded (entry 2). The conversion of the reaction could be improved dramatically by changing the catalyst from **VI** to **V**, though suffering from a drop in enantiomeric induction (25:65 e.r., entry 3). Following experiments changing the solvent or catalyst did not give a better result (entries 4-8).

Table 4. Modification of the electron withdrawing group and optimization of the reaction conditions.[a]

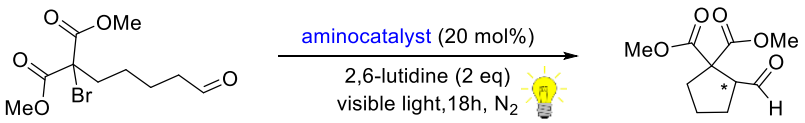


Entry	Aminocatalyst	Solvent	Conv.[%]	e.r.[b]
1	**VI**	toluene	n.r	-
2	**VI**	toluene	10	75:25[c]
3	**V**	toluene	76	35:65
4	**VI**	CH_2Cl_2	10	n.d
5	**VI**	MTBE	n.r	-
6	**VI**	DMF	30	50:50
7	**VI**	DMF	36	50:50
8	**V**	DMF	73	40:60

[a] Conditions: organocatalyst (0.02 mmol, 20 mol%), **1b** (0.1 mmol, 1.0 eq.), 2,6-lutidine (0.2 mmol, 2 eq.) in 0.2 mL of solvent at room temperature and N_2-atmosphere under visible light irradiation (23W). [b] To determine the enantiomeric ratio of product **2b** a derivatization with a Wittig reagent to **2Wb** was necessary. [c] The reaction was stirred for 3 days.

Since the enantiomeric ratio was not improved by a greater steric hinderance in the electron-withdrawing ester group of aldehyde **1b** we changed to a methyl substituent for further investigations. Therefore, aldehyde **1c** was synthesized bearing methyl instead of the *tert*-butyl ester groups. To our delight, the reaction worked smoothly with full conversion to the desired cyclic product **2c**. Unfortunately, we were not able to separate the two enantiomers by chiral HPLC to measure the enantiomeric ratio. All attempts with different methods and various chiral columns on HPLC, SFC and GC measurements were unsuccessful.

Table 5. Modification of the electron withdrawing group.[a]



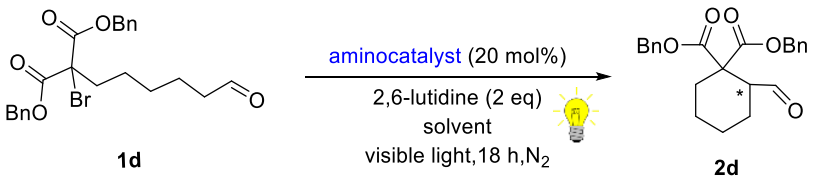
1c **2c**

Entry	Aminocatalyst	Solvent	Conv.[%]	e.r.[b]
1	**rac-I**	toluene	100	n.d
2	**VI**	DMF	100	n.d[c]

[a] Conditions: organocatalyst (0.02 mmol, 20 mol%), **1b** (0.1 mmol, 1.0 eq.), 2,6-lutidine (0.2 mmol, 2 eq.) in 0.2 mL of solvent at room temperature and N_2-atmosphere under visible light irradiation (23W). [b] The enantiomeric ratio of product **2c** could not be determined by chiral HPLC or GC. [c] The reaction was stirred for 3 days.

Since the changes on the ester groups of the malonate unit did not lead to the identification of any reactivity or enantioselectivity trend, we decided to vary the length of the alkyl chain to create a six-membered ring instead of a five-membered ring. Unfortunately, all our tries to achieve the product failed and no conversion was observed (Table 6).

Table 6. Modification of the length of the alkyl chain.[a]



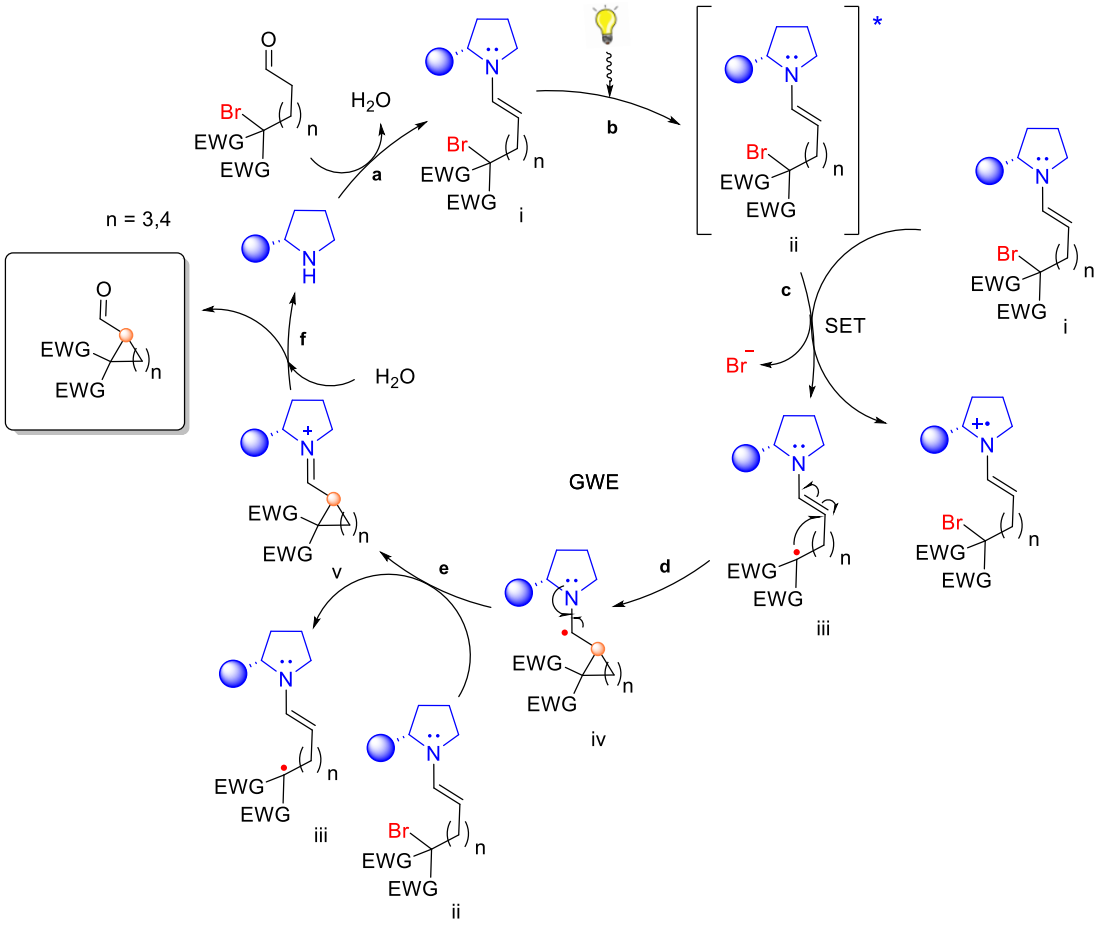
Entry	Aminocatalyst	Solvent	Conv.[%]	e.r.[b]
1	**rac-I**	DMF	n.r	-
2[b]	**rac-I**	DMF	n.r	-
3	**VI**	DMF	n.r	-
4	**V**	DMF	decomposition	
5[c]	**VI**	DMF	3	-
6	**VI**	CH_2Cl_2	n.r	-
7	**VI**	toluene	n.r	-
8[c]	**VI**	toluene	n.r	-

[a] Conditions: organocatalyst (0.02 mmol, 20 mol%), **1d** (0.1 mmol, 1.0 eq.), 2,6-lutidine (0.2 mmol, 2 eq.) in 0.2 mL of solvent at room temperature and N_2-atmosphere under visible light irradiation (23W). [b] The reaction was stirred for 6 days. [c] The reaction was stirred for 3 days.

5.3 Mechanistic Proposal

Based on the obtained results, we propose a possible mechanism depicted in Scheme 7. We supposed that the enamine **i** is able to absorb light and reach the excited state. In a first step, the corresponding aldehyde condensates with the aminocatalyst (**a**) followed by the absorption of visible light of the formed enamine from its ground state (**b**). The excited state enamine **ii** is then able to form a radical by reductive debromination (**c**). In this case, the excited state enamine **ii** acts as a photoindicator triggering the formation of the radical **iii** by a single electron transfer (SET). The enamine **i** is then used as a scarifying species, being oxidized ($E^{o} \simeq 2.0$ V) to reduce intermediate **ii** and to form the key C-centered radical **iii**. Next, **iii** reacts intramolecularly with the enamine group present in the molecule (**d**), forming a new C-C bond. Subsequently, the formed amino-radical **iv** is oxidized by the enamine **ii** (**e**), leading to the iminium intermediate **v.** Finally, hydrolysis of the iminium ion gives the α-alkylated aldehyde product and the recycled aminocatalyst (**f**).

2,6-Lutidine was necessary for the neutralization of the formed acid HBr, which would provoke the enolization of the aldehyde and the enantioselectivity loss.



Scheme 7 Proposed mechanism.

5.4 Conclusion

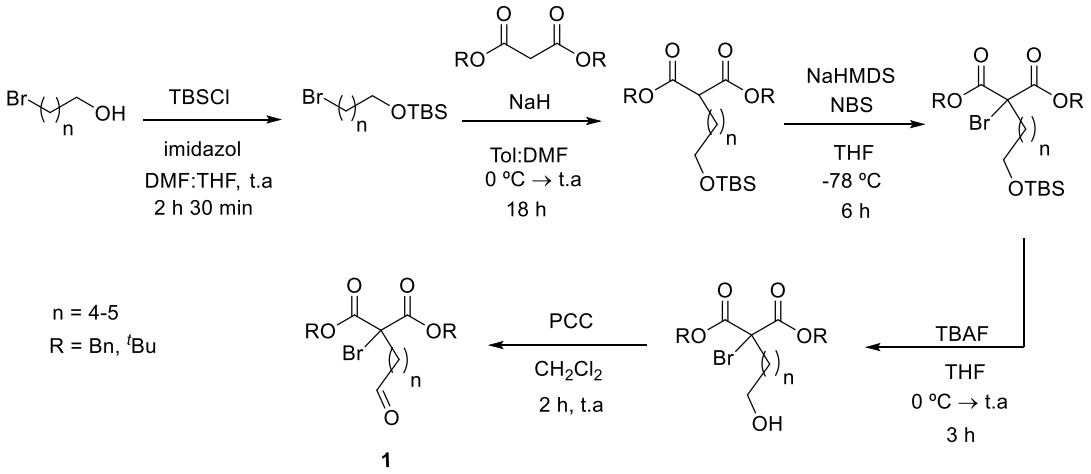
In conclusion, we have developed a new method for the intramolecular α-alkylation of aldehydes without the use of an additional metallic or organic photocatalyst. Despite some good results with the enantioselective cyclization of aldehyde **1a**, the found reaction conditions could not be applied to other substrates. For most of the cases, only low yields or enantioselectivities were obtained. Also, the reproducibility of the results was challenging and possess a lot of problems. Although a thorough study and various optimizations were carried out, until now, no solution for these issues was found.

5.5 Experimental Part

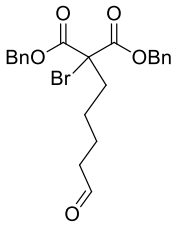
5.5.1 Synthesis of the Starting Material

Aldehydes **1** were prepared in 5 steps, following a literature known procedure from the corresponding malonate.[17]

General procedure for the synthesis of the starting material:

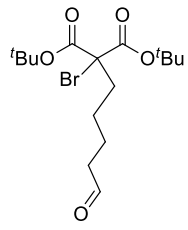


Dibenzyl 2-bromo-2-(5-oxopentyl)malonate (1a)



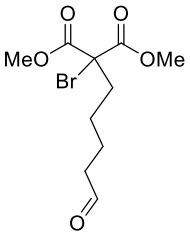
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.63 (d, *J* = 1.6 Hz, 1H), 7.33 – 7.17 (m, 10H), 5.11 (d, *J* = 5.0 Hz, 4H), 2.28 (td, *J* = 7.4, 1.6 Hz, 2H), 2.25-2.16 (m, 2H), 1.59-1.46 (m, 2H), 1.33-1.20 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 201.7, 166.4, 134.7, 128.6, 128.53, 128.3, 68.5, 67.1, 43.3, 37.9, 24.7, 21.5. **HRMS (ESI$^+$)**: *m/z* calculated for $C_{22}H_{27}NO_5Br$ $[M+NH_4]^+$ 464.1067; found: 464.1092.

Di-*tert*-butyl 2-bromo-2-(5-oxopentyl)malonate (1b)



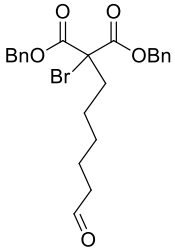
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.77 (d, *J* = 1.6 Hz, 1H), 2.47 (t, *J* = 7.2 Hz, 2H), 2.24 – 2.14 (m, 2H), 1.75 – 1.62 (m, 2H), 1.60 – 1.54 (m, 2H), 1.48 (s, 18H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 201.8, 165.7, 83.5, 65.8, 43.5, 37.8, 27.7, 24.7, 21.7. **HRMS (ESI$^+$)**: *m/z* calculated for $C_{16}H_{28}BrO_5$ $[M+H]^+$ 379.1115; found: 379.1092.

Dimethyl 2-bromo-2-(5-oxopentyl)malonate (1c)



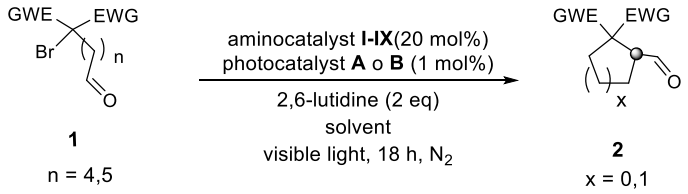
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (t, J = 1.3 Hz, 1H), 3.78 (s, 2H), 2.48 – 2.40 (m, 1H), 2.28 – 2.20 (m, 1H), 1.71 – 1.57 (m, 1H), 1.46 – 1.35 (m, 1H).

Dibenzyl 2-bromo-2-(6-oxohexyl)malonate (1d)



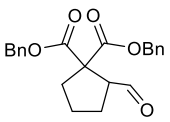
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.72 (d, *J* = 1.5 Hz, 1H), 7.36 – 7.26 (m, 10H), 5.18 (d, *J* = 5.4 Hz, 4H), 2.34 (td, *J* = 8.6, 4.3 Hz), 2.29 – 2.19 (m, 2H), 1.64 – 1.44 (m, 2H), 1.41 – 1.20 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 202.2, 166.5, 134.7, 128.6, 128.3, 128.2, 68.5, 63.1, 43.5, 37.9, 28.5, 24.9, 21.6. **HRMS (ESI$^+$)**: *m/z* calculated for $C_{23}H_{29}BrO_5N$ $[M+NH_4]^+$ 478.1224; found: 478.1258.

5.5.2 Organocatalytic Cyclization Reaction



In a crimp top vial, the corresponding aldehyde **1a-c** (0.05 mmol, 1.0 eq.), the photocatalyst (0.0005 mmol, 1 mol%) the aminocatalyst (0.01 mmol, 20 mol%) and 2,6-lutidine (0.1 mmol, 2.0 eq.) were dissolved in the described solvent. The vial was sealed, and three cycles of *Freeze Pump Thaw* were carried out. The reaction mixture was than irradiated with white light for 18 h while stirred. The temperature was regulated with a ventilator to avoid heating of the reaction by the lamp. The solvent was removed under reduced pressure and the conversion was determined by NMR on the crude reaction. Purification by flash column chromatography (cyclohexane/EtOAc 10:1) yielded the desired product as yellow oil.

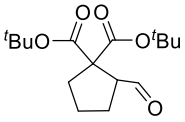
Dibenzyl 2-formylcyclopentane-1,1-dicarboxylate (2a)



^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.70 (d, *J* = 1.6 Hz, 1H), 7.38 – 7.26 (m, 10H), 5.24 – 5.12 (s, 4H), 2.41 – 2.24 (t, *J* = 7.4, 1.6 Hz, 3H), 1.60 (m, 2H), 1.41-1.29 (m, 2H). **^{13}C NMR** (75 MHz**,** $CDCl_3$): δ = 199.9, 165.3, 128.7, 128.6, 128.5, 128.2,

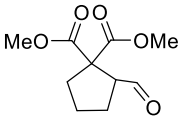
67.8, 57.7, 53.6, 34.8, 29.8, 22.8. **HRMS (ESI$^+$)**: *m/z* calculated for $C_{22}H_{23}O_5$ $[M+H]^+$ 367.1540; found: 367.1557.

Di-*tert*-butyl 2-formylcyclopentane-1,1-dicarboxylate (2b)



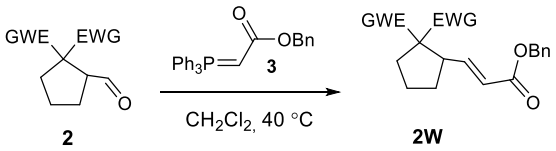
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.82 (d, *J* = 0.9 Hz, 1H), 3.08 (td, *J* = 8.6, 0.9 Hz, 1H), 2.35 - 2.09 (m, 2H), 1.96 (td, *J* = 8.6, 5.7 Hz, 2H), 1.81 – 1.63 (m, 1H), 1.48 (s, 9H), 1.43 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 200.7, 170.4, 169.4, 82.6, 82.2, 64.2, 57.6, 34.7, 29.9, 28.0, 27.9, 22.7. **HRMS (ESI$^+$):** m/z calculated for $C_{16}H_{27}O_5$ $[M+H]^+$ 299.1853; found: 299.1861.

Dimethyl 2-formylcyclopentane-1,1-dicarboxylate (2c)



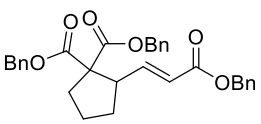
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H), 3.81 (s, *J* = 3.2 Hz, 5H), 3.75 (s, 1H), 2.52 – 2.42 (m, 2H), 2.33 – 2.22 (m, *J* = 10.0, 6.3 Hz, 2H), 1.71 – 1.65 (m, 2H).

5.5.3 Derivatization of the Aldehyde to the Wittig Product



To determine the enantiomeric ratio of the cyclic product, it was necessary to perform a derivatization to achieve a separation of the enantiomers in the chiral column of the HPLC. Product **2** (0.01 mmol, 1.0 eq.) and the Wittig-ylide **3** (0.02 mmol, 2.0 eq.) were dissolved in DCM (1.5 mL) and stirred for 2 h at 40 °C. Purification by flash column chromatography (cyclohexane/EtOAc 10:1) yielded the desired product.

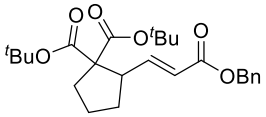
Dibenzyl (E)-2-(3-(benzyloxy)-3-oxoprop-1-en-1-yl)cyclopentane-1,1-dicarboxylate (2Wa)



^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 5.1 Hz, 5H), 7.33-7.14 (m, 10H), 7.01 (dd, *J* = 15.6, 7.99 Hz, 1H), 5.86 (dd, *J* = 15.6, 1.3 Hz, 1H), 5.12 (d, *J* = 9.0 Hz, 4H), 5.09-4.89 (m, 2H), 3.37 (m, 1H), 2.53 (m, 1H), 2.23-2.07 (m, 1H), 1.84-2.02 (m, 2H), 1.77-1.64 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 171.4, 170.1, 166.0, 147.9, 136.2, 135.5, 128.7, 128.7, 128.6, 128.4, 128.3, 128.2, 122.3, 67.4, 66.2, 64.3, 48.8, 34.4, 30.6, 29.8, 23.3. **HRMS (ESI+)**: m/z calculated for $C_{31}H_{34}NO_6$ $[M+NH_4]^+$ 516.2381;

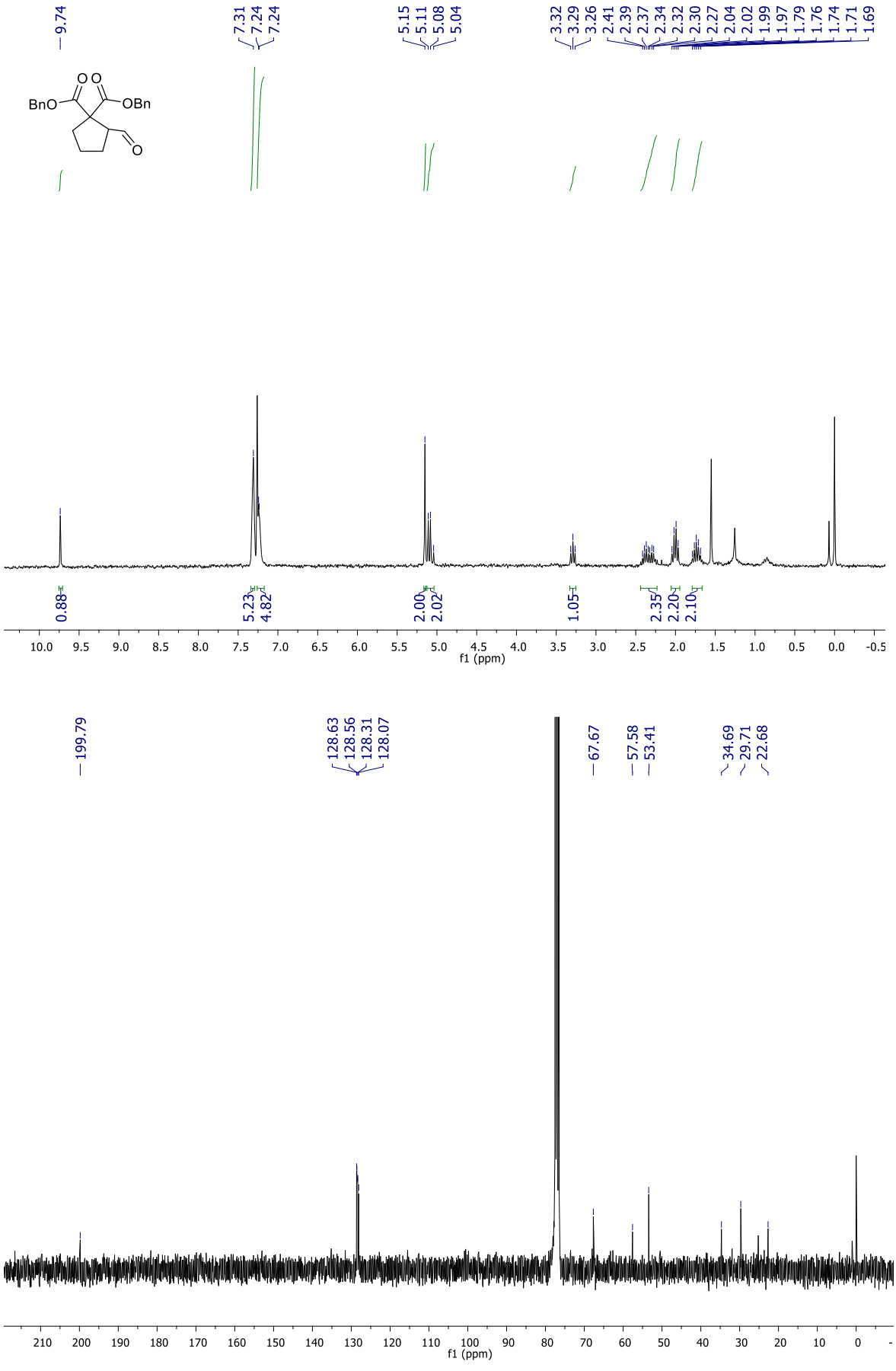
found: 516.2379. The enantiomeric ratio was determined as 90:10 e.r. by chiral SFC [Chiralpak IA, CO2/MeOH (90:10), 2.0 mL/min, λ= 300 nm: tr (major): 7.7 min, tr (minor): 8.1 min].

Di-*tert*-butyl (E)-2-(3-(benzyloxy)-3-oxoprop-1-en-1-yl)cyclopentane-1,1-dicarboxylate (2Wb).



^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 – 7.31 (m, 5H), 7.04 (dd, *J* = 15.7, 7.8 Hz, 1H), 5.89 (dd, *J* = 15.7, 1.4 Hz, 1H), 5.17 (s, 2H), 3.21 – 3.31 (m, 1H), 2.48 – 2.36 (m, 1H), 2.02 – 1.91 (m, 2H), 1.90 – 1.81 (m, 1H), 1.60 – 1.51 (m, 2H), 1.44 (s, 9H), 1.35 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 170.9, 170.6, 166.4, 149.4, 136.2, 128.6, 128.5, 128.3, 121.4, 81.9, 81.4, 66.2, 65.1, 48.1, 30.4, 29.9, 28.0, 27.9, 23.3. **HRMS (ESI^{+})**: m/z calculated for $C_{25}H_{38}O_6N$ $[M+NH_4]^+$ 448.2694; found: 498.2740. The enantiomeric ratio was determined as 75:25 e.r. by chiral SFC [Chiralpak IG, CO_2/MeOH (90:10), 2.0 mL/min, λ= 300 nm: tr (major): 2.4 min, tr (minor): 2.3 min].

5.5.4 Representative Spectra of 2a



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Chapter 6

6. Summary

Chiral heterocycles are ubiquitous structures in natural and synthetic molecules, but chemists are still struggling to develop general, convenient and mild methods for a direct synthesis of these products. Therefore, important work has been done in the field of anion-binding thiourea-catalyzed dearomatization reactions of heteroarenes by applying chiral thiourea catalysts. In this regard, the group of Olga García Mancheño developed a new class of triazole based C-H bond anion-binding catalysts. These catalysts were successfully applied into asymmetric dearomatization reactions of quinolines, isoquinolines and pyridines.

The main aim of this PhD was the development of novel asymmetric dearomatization reactions with the TetraTri catalysts showing their broad synthetic application spectrum.

In **Chapter 2**, the first anion-binding organocatalyzed enantioselective Reissert-type dearomatization of diazarenes has been developed. Due to various reactive sites in the diazarene structures, the reaction presents regioselectivity issues and is therefore highly challenging. Fortunately, the use of a chiral tetrakistriazole as a C–H-based hydrogen-donor catalyst allowed the straightforward highly regio- and enantioselective synthesis of a variety of chiral diazaheterocycles.

In **Chapter 3**, phosphorous nucleophiles were further explored. We could describe the first enantioselective synthesis of chiral heterocyclic α-amino phosphonates by nucleophilic dearomatization of quinolines and pyridines using an anion-binding organocatalysis approach. Chiral tetrakistriazoles were employed as efficient hydrogen-bond donor catalysts. The corresponding products were obtained in complete or high regioselectivities and up to 97:3 e.r. for quinolines or up to 87:13 e.r. for the more demanding pyridine substrates. This method allows the rapid access to substituted chiral cyclic α-amino phosphonates, which can easily further be transformed into phosphonic acid derivatives. Introducing boron-nucleophiles in the same reaction was not successful and did not lead to any new discovery.

In **Chapter 4**, we changed from the nitrogen-containing heteroarenes to the more challenging oxygen-containing heterocycles. A general and highly enantioselective catalytic synthesis of 2-alkyl substituted oxygen heterocycles by nucleophilic dearomatization of pyrylium triflate derivatives with silyl ketene acetals has been developed. The use of chiral triazoles as anion-binding catalysts, able to form a close ion-pair with the substrates, was crucial to achieve both high conversions and chirality transfer. Thus, this method provides a simple access to chiral chromanones and dihydropyranones in excellent enantioselectivities from the corresponding 4-(benzo)pyranones.

Besides the main theme of my thesis, in **chapter 5** the project of my stay abroad at the *Universidad Autonoma de Madrid* was described. A novel intramolecular photocatalyzed enantioselective α-alkylation of aldehydes was developed, yielding the desired product in good yield and enantioselectivity. Due to reproducibility issues and a limited applicability of the substrate scope, no further investigations were done.

Asymmetrische, dearomatisierte Heteroarene sind weitverbreitete Strukturmotive in natürlich vorkommenden oder synthetisch hergestellten Molekülen. Trotz ihrer großen Bedeutung, wird immer noch nach allgemein geeigneten und milden Methoden gesucht, diese Produkte direkt herzustellen. In diesem Zusammenhang entwickelten sich wichtige Dearomatisierungsreaktionen, die durch Anionbindungskatalyse mit Thioharnstoffkatalysatoren Chiralität in das finale Produkt einbringen können. Die Gruppe von Olga García Mancheño entwickelte eine neue Klasse von Anionbindungskatalysatoren, die Triazole basierten C-H Bindungskatalysatoren. Diese Katalysatorsysteme wurden erfolgreich in asymmetrische Dearomatisierungsreaktionen von Chinolinen, Isochinolinen und Pyridinen eingesetzt.

In dieser Arbeit wird ein breites Anwendungsgebiet dieser TetraTri Katalysatoren in verschiedenen Dearomatisierungsreaktionen präsentiert.

In **Kapitel 2** wurde die erste enantioselektive, anionbindungskatalysierte Reissert-artige Dearomatisierungsreaktion mit Diazarenen dargestellt. Auf Grund mehrerer reaktiver Zentren in der Diazarenstruktur, bringt die Reaktion einige Regioselektivitätsprobleme mit sich und ist somit sehr anspruchsvoll. Glücklicherweise konnten wir durch den Einsatz unseres chiralen C-H basierender Wasserstoffbrückenbindungskatalysator TetraTri die direkte Synthese von hoch regio- und enantioselektiven chiralen Diazaheterozyklen erreichen.

In **Kapitel 3** wurden Phosphornukleophile untersucht. Wir konnten die erste enantioselektive Synthese von chiralen heterozyklischen α-Aminophosphonaten durch nukleophile Dearomatisierung von Chinolinen und Pyridinen mit einem Anionbindungsansatz beschreiben. Chirale Tetrakistriazole wurden als effiziente Wasserstoffbindungskatalysatoren eingesetzt. Die entstandenen Produkte zeigten komplette oder hohe Regioselektivitäten und bis zu 97:3 e.r. für Chinoline und bis zu 87:13 e.r. für die schwierigeren Pyridine. Die Methode stellt einen schnellen Zugang zu chiralen, substituierten, zyklischen α-Aminophosphonaten dar, welche weiter zu ihren Phosphorsäurederivaten umgewandelt werden können. In die gleiche Reaktion sollten Bornukleophile eingesetzt werden. Es konnten jedoch keine Ergebnisse erzielt werden.

In **Kapitel 4,** wurden anstatt der Stickstoffheterozyklen Sauerstoffheterozyklen als Substrate verwendet. Eine allgemeingültige, hoch enantioselektive, katalytische Synthese von 2-alkylsubstituierten Sauerstoffheterozyklen durch nukleophile Dearomatisierung von Pyryliumtriflatderivativen mit Silylketenacetalen wurde dargestellt. Ausschlaggebend für den

hohen Umsatz und Chiralitätstransfer war die Bildung eines engen Ionenpaars zwischen dem chiralen Triazolkatalysator und dem Substrat. Folglich stellt diese Methode einen einfachen Zugang zu chiralen Chromanonen und Dihydropyranone mit exzellenten Enantioselektivitäten dar.

Neben dem Hauptthema meiner Doktorarbeit, wurde in **Kapitel 5** das Projekt meines Forschungsaufenthaltes an der *Universidad Autonoma de Madrid* beschrieben. Eine neue intramolekulare fotokatalysierte enantioselektive α-Alkylierung von Aldehyden wurde entwickelt. Obwohl eines der gewünschten Produkte in guten Ausbeuten und Enantioselekivitäten erhalten wurde, konnten auf Grund von Reproduzierbarkeitsproblemen, und einer stark limitierten Anwendbarkeit auf andere Substrate keine weiteren Forschungsergebnisse erreicht werden.

Chapter 7

7. Appendix

6.1 List of Abbreviations

[α]	specific rotation
aq.	aqueous
Ar	aryl
BINOL	1,1′-Bi-2-naphthol
Bn	benzyl
$B(OH)_3$	boric acid
B_2pin_2	Bis(pinacolato)diboron
Bu	butyl
CbzCl	Carboxybenzylchlorid
CD	Circular Dichroism
$CDCl_3$	Chloroform-d
CETP	Cholesteryl ester transfer protein
CI	chemical ionization
Conv.	Conversion
CuAAC	copper(I)-catalyzed alkyne-azide cycloaddition
Cy	cyclohexyl
d	doublet (NMR)
δ	chemical shift
DCM	dichloromthene
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EI	electron impact ionization (MS)
eq.	equivalent
e.r.	enantiomeric ratio
ESI	electrospray ionization (MS)
Et	ethyl
Et_2O	diethyl ether
Et_3N	triethyl amine
Et_3SiH	triethylsilane
EtOAc	ethyl acetate
FID	flame ionization detector (GC)
GC	gas chromatography
h	hour(s)
hept	heptet (NMR)
HPLC	High-performance liquid chromatography
HR	high resolution (MS)
Hz	hertz (NMR)
i	*iso*
***i*PrOH**	*iso*-propanol
J	coupling constant
K_2CO_3	potassium carbonate
$KMNO_4$	potassium permanganate
[M]	mol per liter
M	metal
m	multiplet (NMR); medium (IR)
Me	methyl
MeOH	methanol
MeOTf	methyl triflate
min.	minute(s)
mL	milliliter
MS	mass spectrometry
MTBE	Methyl *tert*-butyl ether

m/z	mass to charge ratio (MS)	**s**	singlet (NMR)
NBSA	nitrobenzene sulfonic acid	**sat.**	saturated
NMR	nuclear magnetic resonance	**sext**	sextet (NMR)
Nu	nucleophile	**t**	triplet (NMR)
Pd/C	palladium on active carbon	***t***	*tert*
Ph	phenyl	**t_R**	retention time
ppm	parts per million	**TBACl**	Tetramethylammonium chloride
Pr	propyl		
q	quartet (^{1}H-NMR); quaternary carbon (^{13}C-NMR)	**Temp.**	temperature
		TFA	trifluoroacetic acid
		THF	tetrahydrofuran
quin	quintet (NMR)	**TLC**	thin layer chromatography
rac	racemic	**Xantphos**	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
r.t.	room temperature		

6.2 Acknowledgements

My sincere thanks go to Prof. Dr. Olga García Mancheño for providing me with this very interesting and diversified project and for all her professional support during the whole process of the project. I could not imagine any better “Doktormama”. Thanks a lot for giving me the opportunity to carry out almost half of my thesis in Madrid and the possibility to learn new ways of working and living.

I want to give my special thanks to Prof. Dr. José Alemán for inviting me to work in his group in Spain and for all his help to get my life started there. Above all I want to thank him for his open door whenever I needed support and for all the fruitful discussions and explanations.

Furthermore, I thank Prof. Dr. Frank-Michael Matysik for doing the third examiner in my thesis, and Prof. Dr. Julia Rehbein for the chairwoman in my defence.

I want to thank iPUR, ERASMUS plus and GDCh for the financial support during all my stays abroad and conferences.

I also want to thank the AK García where I always found support with every matter I had. I want to thank them for the nice times we spent together at work as well as the time after. Especially my lab partner Mustafa Uygur brightened up some busy days with his very special and unique humor.
Furthermore, I want to thank my “amigos de españa” for the warm welcome, all their continuous help and an always friendly atmosphere.

Moreover, I want to give my thanks to all my friends for their company in any part of life and for the great experiences we had together with and beyond the chemistry. Particularly I want to thank my “Skifahren-Gruppe” who made the last 8 years extraordinary.

My very special thanks go to Julia Bamberger my “Dr. Stinki”. Without her love and support I would not be at this point in my life. Words alone cannot express what I owe her for her love and encouragement in the last 8 years.

I want to thank my fiancé Erick for his unconditional love and for showing me the world with different eyes. It’s a special gift finding someone like you in life.

My deepest thanks go to my family for their love, care, help and never-ending support during my whole life. My special thanks go to my parents and Nini, who were there for me in every time of my life

Danke

6.3 Curriculum Vitae

Theresa Fischer

Personal Data

Birthday:	12.04.1990
Birthplace:	Prien am Chiemsee, Germany
Nationality	German

Education

12/18:	planned PhD defence at the University of Regensburg
03/18 – 12/18:	Doctoral Thesis at the University of Münster, Institute of Organic Chemistry in the working group of Prof. Dr. Olga García Mancheño "*Enantioselective Nucleophilic Dearomatization of Heteroarenes by Anion-Binding-Catalysis*"
12/15 – 02/18:	Doctoral Thesis at the University of Regensburg, Institute of Organic Chemistry in the working group of Prof. Dr. Olga García Mancheño
10/13 – 09/15:	M.Sc. Chemistry at the University of Regensburg Master thesis in the working group of Prof. Dr. Olga García Mancheño, Institute of Organic Chemistry, University of Regensburg. "*Novel Hydrogen-Donor Organocatalysts for Enantioselective Sulfoxidation and Heteroarene-Dearomatization Reactions"*
10/10 – 07/13:	B.Sc. Chemistry at the University of Regensburg Bachelor thesis in the working group of Prof. Dr. Burkhard König, Institute of Organic Chemistry, University of Regensburg. "*Synthese von photoschaltbaren Aminosäuredithienylmaleimiden"*
09/00 – 06/09:	Abitur (A-level) at the Ludwig Thoma Gymnasium Prien am Chiemsee

Fellowships

03/17 – 05/17: iPUR fellowship for the stay abroad in Madrid (UAM)

04/18 – 08/18: ERASMUS plus fellowship for the stay abroad in Madrid (UAM)

06/16; 09/17/18: Conference travel fellowships from the GDCh

Congress contributions and other presentations

2018: "*Highly Enantioselective Chromenone Functionalization by Anion Binding Catalysis*" (poster), 21. Lecture Conference ORCHEM, Berlin, Germany.

2017: *"Triazole-Based Anion-Binding Catalysis for the Enantioselective Dearomatization of N-Heteroarenes with P-Nucleophiles"* (poster), 26th ISHC Congress, Regensburg, Germany.

2017: *"Triazole-Based Anion-Binding Catalysis for the Enantioselective Dearomatization of N-Heteroarenes with P-Nucleophiles"* (poster), GDCh-Wissenschaftsforum Chemie, Berlin, Germany.

2016: *"Asymmetric dearomatization of diazarenes by anion-binding catalysis"* (poster), 20. Lecture Conference ORCHEM, Weimar, Germany.

2016: *"Asymmetric nucleophilic dearomatization of diazarenes by anion-binding catalysis"* (poster), 17th Tetrahedron Symposium, Sitges, Spain.

2015: *"Organocatalysis and Oxidative C-H Bond Functionalization"* (oral presentation), Weihnachtssymposium Chemie 2015, Regensburg, Germany.

Research Stays

02/17 – 08/17: 6-month research stay in Madrid, Spain (Universidad Autonoma de Madrid) under the supervision of Prof. Dr. José Alemán.

04/18 – 08/18: 4-month research stay in Madrid, Spain (Universidad Autonoma de Madrid) under the supervision of Prof. Dr. Mariola Tortosa.

6.4 List of Publications

1) Olga García Mancheño, Soeren Asmus, Mercedes Zurro, **Theresa Fischer**; "Highly Enantioselective Nucleophilic Dearomatization of Pyridines by Anion-Binding Catalysis" *Angewandte Chemie, International Edition* **2015**, *54* (30), 8823-8827

2) **Theresa Fischer**, Julia Bamberger, Olga García Mancheño; "Asymmetric Nucleophilic Dearomatization of Diazarenes by Anion-Binding Catalysis" *Organic and Biomolecular Chemistry* **2016**, *14* (24), 5794-5802.

3) **Theresa Fischer**, Qhi Nhi Duong, Olga García Mancheño; "Triazole-based Anion-binding Catalysis for the Enantioselective Dearomatization of *N*-Heteroarenes with P-Nucleophiles" *Chem. Eur. J.* **2017**, *23,* 5983-5987.

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6.5 Eidesstattliche Erklärung

(1) Ich erkläre hiermit an Eides statt, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus anderen Quellen direkt oder indirekt übernommenen Daten und Konzepte sind unter Angabe des Literaturzitats gekennzeichnet.

(2) Bei der Auswahl und Auswertung haben mir die in den jeweiligen Kapiteln aufgeführten Personen in der beschriebenen Art und Weise unentgeldlich geholfen.

(3) Weitere Personen waren an der inhaltlich-materiellen Herstellung der vorliegenden Arbeit nicht beteiligt. Insbesondere habe ich hierfür nicht die entgeltliche Hilfe eines Promotionsberaters oder anderer Personen in Anspruch genommen. Niemand hat von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen.

(4) Die Arbeit wurde bisher weder im In- noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

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Theresa Fischer