# Organocatalytic Reduction of Imines with Trichlorosilane

UNIVERSITAS
CAROLINA


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Submitted to the Charles University in fulfilment of the requirements of the degree of Doctor of Philosophy

April 2024

# Declaration

I hereby declare that this thesis is my own work and efforts and that it has not been submitted anywhere for any award of another degree. I also undertake that any quotations or paraphrases from the published works of other people have been acknowledged. I am aware of the fact, that any potential use of the results published in this work, outside of the Charles University in Prague, is possible only with the official permission of the University. This work was supervised by Prof. Pavel Kočovský.

Kirill Popov

# Acknowledgements

I have been fortunate enough to perform my PhD study at the Charles University in Prague and receive a great deal of support throughout it. First and foremost, I would like to express my deepest gratitude to my supervisor Prof. Pavel Kočovský for encouraging, directing and inspiring me from the beginning to the finish of this unusual route.

I would like to thank my first supervisor, Prof Jana Roithová, under whose patient supervision I started my 1st year of PhD study and found my way further. Also, I am very grateful to my co-supervisor Dr. Petr Beier, for a great chance to perform my last steps on a PhD route in his laboratory, working together with his students, nice and welcoming people.

This project would not have been possible without financial support of the Charles University and Institute of Organic Chemistry and Biochemistry (IOCB).

I would like to express many thanks to Dr. Blanka Klepetářová at IOCB and her help with measuring X-ray crystal structures, Dr. Josef Cvačka and his group members for carrying out all the HRMS measurements at IOCB, Dr Michal Urban for carrying out all the IR experiments at the Charles University and Dr. Lucie Bednárová for measuring IR spectra at IOCB.

I would like to thank all my former and present colleagues - Anamarija, Mariarosa for their endless help me to adapt to totally new life in Prague and settle in, Olga, Norbert, Vladimir, David, Martin, Svatava, Anička, Lukáš, Olena and Mykyta. Moreover, I am grateful to all those musicians and DJ's whose music was the first aid kit for me during long hours of experiments and creating this dissertation.

And finally, my appreciation and love go to Nastya, my loving wife, who was with me together during this amazing and evocative way, sometimes long and challenging, as well as to my parents, brother and friends for believing in me and cheering me on, all the way.

# Abstrakt

Reduktivní aminace je základním kamenem syntézy aminů, klíčových molekul v přírodní i syntetické chemii, zejména ve farmaceutickém průmyslu. Reduktivní aminace zprostředkovaná trichlorosilanem se jeví jako obzvláště atraktivní metoda, která nabízí jednoduchost, účinnost a univerzálnost pro různé funkční skupiny. Tato práce se zabývá použitím a zdokonalením této metody s cílem rozšířit její využití, zejména se zaměřením na syntézu sloučenin snižujících hladinu cholesterolu na příkladu ezetimibu.

Výzkum začíná zkoumáním stability různých funkčních skupin za podmínek reduktivní aminace zprostředkované $HSiCl_3$ s dimethylformamidem jako katalyzátorem, čímž se vytváří základní představa o rozsahu reakce. Mezi identifikovanými stabilními funkčními skupinami je i pentafluorosulfanylový ($SF_5$) fragment, známý svými výraznými vlastnostmi a potenciálem v medicinální chemii. Výzkum se zabývá použitelností této metody na aldehydy a prochirální ketony, což ukazuje její všestrannost.

Na základě těchto poznatků studie směřuje k vývoji a použití asymetrické verze reduktivní aminace zaměřené na ezetimib a jeho analogy. Syntetická cesta zahrnuje katalytické využití dříve syntetizovaného chirálního katalyzátoru Kenamid ve spojení s trichlorsilanem, který nabízí výhody oproti tradičním metodikám z hlediska chemoselektivity a možnosti provádět reakce ve zvětšeném měřítku.

Kromě toho práce zkoumá strategické začlenění polyfluorovaných substituentů, jako je skupina $SF_5$, která je známá svými příznivými vlastnostmi při zvyšování chemické a metabolické stability. Zkoumáním sloučenin se skupinami $SF_5$ a $CF_3$ si studie klade za cíl optimalizovat syntetické cesty nejen k ezetimibu, ale také k jeho analogům, což může potenciálně zlepšit farmakokinetické profily. Předběžná biologická hodnocení syntetizovaných derivátů poskytují náhled na jejich potenciální farmakologickou účinnost, což otevírá cestu k dalšímu zkoumání při vývoji léčiv.

Celkově tato práce přispívá k rozvoji syntetických metodik ve farmaceutické chemii, přičemž její důsledky zasahují do širšího měřítka organické syntézy a objevování léčiv.

# Abstract

Reductive amination and its stepwise variant stands as a cornerstone in the synthesis of amines, crucial molecules in both natural and synthetic chemistry, especially in pharmaceutical industry. Trichlorosilane-mediated reductive amination emerges as a particularly attractive method, offering simplicity, efficacy, and versatility across various functional groups. This thesis explores the application and enhancement of this method, aiming to expand its utility, particularly focusing on the synthesis of cholesterol-lowering compounds exemplified by Ezetimibe.

The research begins with an investigation into the stability of diverse functional groups under $HSiCl_3$-mediated reductive amination conditions with dimethylformamide as a catalyst, establishing a fundamental understanding of the reaction scope. Among the stable functional groups identified is the pentafluorosulfanyl ($SF_5$) moiety, known for its distinct properties and potential in medicinal chemistry. The investigation delves into the applicability of this method to aldehydes and prochiral ketones, demonstrating its versatility.

Building upon this groundwork, the study progresses towards the development and application of an asymmetric version of reductive amination, targeting Ezetimibe and its analogues. The synthetic pathway involves the catalytic use of previously synthesized in our group chiral catalyst Kenamide in conjunction with trichlorosilane, offering advantages over traditional methodologies in terms of chemoselectivity and scalability.

Moreover, the thesis examines the strategic incorporation of polyfluorinated substituents, such as the $SF_5$ group, known for its beneficial properties in enhancing chemical and metabolic stability. By exploring compounds featuring the $SF_5$ and $CF_3$ groups, the study aims at optimization of synthetic routes not only to Ezetimibe, but also its analogues, potentially improving pharmacokinetic profiles. Preliminary biological evaluations of the synthesized derivatives provide insights into their potential pharmacological efficacy, paving the way for further exploration in drug development.

Overall, this thesis contributes to the advancement of synthetic methodologies in pharmaceutical chemistry, with implications extending to the broader scale of organic synthesis and drug discovery.

# List of abbreviations

| | |
|---|---|
| 9-BBN | 9-borabicyclo[3.3.1]nonane |
| Å | Ångström |
| Ac | acetyl |
| acac | acetylacetone |
| AI | artificial intelligence |
| APT | attached proton test |
| ATP | adenosine triphosphate |
| BINOL | 1,1′-bi-2-naphthol |
| BMS | borane-dimethyl sulfide |
| Boc | *tert*-butyloxycarbonyl |
| $Boc_2O$ | di-*tert*-butyl dicarbonate, Boc anhydride |
| BSA | *N,O*-bis-(trimethylsilyl)acetamide |
| CBS | Corey–Bakshi–Shibata (reaction, catalyst) |
| Cbz | benzyloxycarbonyl |
| CoA | coenzyme A |
| COD | cycloocta-1,5-diene |
| COSY | correlation spectroscopy |
| CVD | cardiovascular disease |
| d | doublet |
| DBN | 1,5-diazabicyclo[4.3.0]non-5-ene |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |

| | |
|---|---|
| DCC | *N*,*N*′-dicyclohexylcarbodiimide |
| DCE | dichloroethane |
| DCM | dichloromethane |
| DEPT | distortionless enhancement by polarization transfer |
| DFT | density functional theory |
| DHP | 3,4-dihydropyran |
| DIBAL-H | diisobutylaluminium hydride |
| DIPEA | *N*,*N*-diisopropylethylamine, Hünig's base |
| DMAc | *N,N*-dimethylacetamide (DMA) |
| DMAP | 4-dimethylaminopyridine |
| DMF | *N,N*-dimethylformamide |
| DMPU | *N,N*′-dimethylpropyleneurea |
| DMSO | dimethylsulfoxide |
| DPS | 2,2’-dipyridyldisulfide |
| EDCl | 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| equiv | equivalent |
| Fc | ferrocenyl |
| Gly | glycine |
| HBpin | pinacolborane, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane |
| HDL | high-density lipoprotein |
| HMBC | heteronuclear multiple bond coherence |
| HMDS | hexamethyldisilazane, bis(trimethylsilyl)amine |
| HMPA | hexamethylphosphoramide |

| | |
|---|---|
| HPLC | high-performance liquid chromatography |
| HRMS | high-resolution mass spectrometry |
| HSQC | heteronuclear single quantum coherence spectroscopy |
| Hz | Hertz |
| ImH | imidazole |
| IPA | isopropyl alcohol |
| IR | infrared |
| JohnPhos | (2-biphenyl)di-*tert*-butylphosphine |
| LC | liquid chromatography |
| LDA | lithium diisopropylamide |
| LDL | low-density lipoprotein |
| LiHMDS | lithium bis(trimethylsilyl)amide |
| Lys | lysine |
| m | multiplet |
| *m*CPBA | *meta*-chloroperoxybenzoic acid |
| MHz | megahertz |
| mg | milligram |
| mL | millilitre |
| mmol | millimole |
| MS | mass spectrometry |
| MS | molecular sieves |
| MTBE | methyl *tert*-butyl ether (*tert*-butyl methyl ether) |
| NBS | *N*-bromosuccinimide |

| | |
|---|---|
| NFP | *N*-formylpiperidine (1-formylpiperidine) |
| NMF | *N*-methylformamide |
| NMR | nuclear magnetic resonance |
| Nps | 2-nitrophenylsulfenyl |
| OAc | acetate |
| ORTEP | Oak Ridge thermal ellipsoid plot |
| p | pentet |
| PCC | pyridinium chlorochromate |
| pH | potential of hydrogen |
| Phe | phenylalanine |
| PhMe | toluene |
| PIC | products interaction complex |
| ppm | parts per million |
| PPTS | pyridinium *p*-toluenesulfonate |
| PTAB | trimethylphenylammonium tribromide |
| pTSA | *p*-toluenesulfonic acid or tosylic acid (PTSA, TsOH) |
| Py | pyridine |
| PyBOP | (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate |
| q | quadruplet |
| Rf | retardation factor |
| RIC | reactants interaction complex |
| rt | room temperature |
| s | singlet |

| | |
|---|---|
| SA | salicylic acid |
| salen | *N,N'*-ethylenebis(salicylimine) |
| Superhydride | lithium triethylborohydride, $LiEt_3BH$ |
| t | triplet |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBAI | tetra-*n*-butylammonium iodide |
| TBDMSCl | *tert*-butyldimethylsilyl chloride |
| TBHP | *tert*-butyl hydroperoxide (*t*BuOOH) |
| TBS | *tert*-butyldimethylsilyl (group, protection) |
| TCICA | trichloroisocyanuric acid |
| TEA | triethylamine |
| THF | tetrahydrofuran |
| TFA | trifluoroacetic acid |
| TLC | thin-layer chromatography |
| TMG | *N,N,N',N'*-tetramethylguanidine |
| TMS | tetramethylsilane |
| TMSCl | trimethylsilyl chloride |
| $t_R$ | retention time |
| TS | transition state |
| Ts | *p*-toluenesulfonyl, tosyl |
| XRD | X-ray diffraction |

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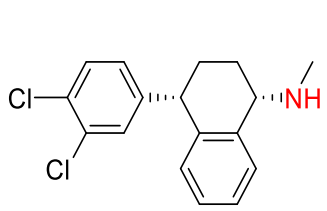
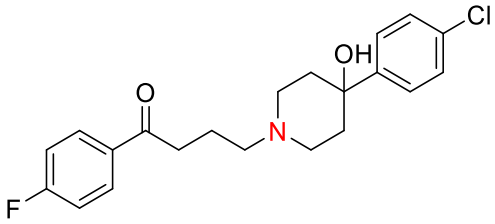
# Chapter I. Reductive amination

## Introduction

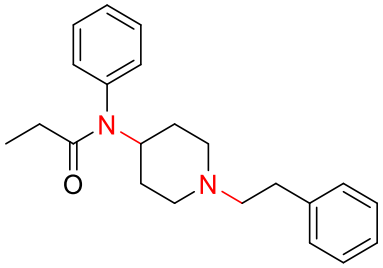
Reductive amination, as well as its stepwise variant, is one of the best known and used methods to make amines. Amines play a huge role in nature, as well as in the whole man-made chemical industry, such as medicinal, bio-, or pharmaceutical chemistry. Myriads of well-known drugs contain an amine moiety in their structures. Antidepressants, such as Zoloft (sertraline), Prozac (fluoxetine), Amitriptyline, Ritalin, and many other widely are available drugs for treating depression. Haloperidol, Thorazine (chlorpromazine), Loxapine, Clozapine, and other medicinal drugs are used to manage psychosis and as mood stabilizers in the treatment of bipolar disorder. Stimulants, analgesics (painkillers), sedatives as a large class of compounds, and antihistamines also contain an amino group. Antibiotics and antiviral drugs, antifungals and anthelminthics represent other examples. This is the reason why the synthesis of amines is one of the most valuable goals in organic chemistry in general.



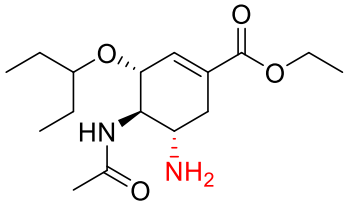

Sertraline



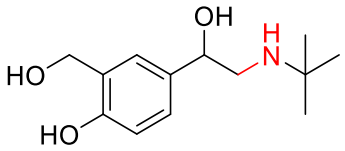

Haloperidol



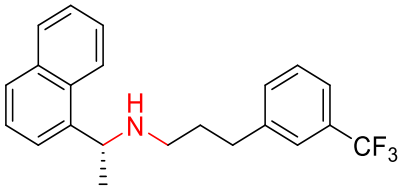

Fentanyl




Oseltamivir




Salbutamol




Cinacalcet

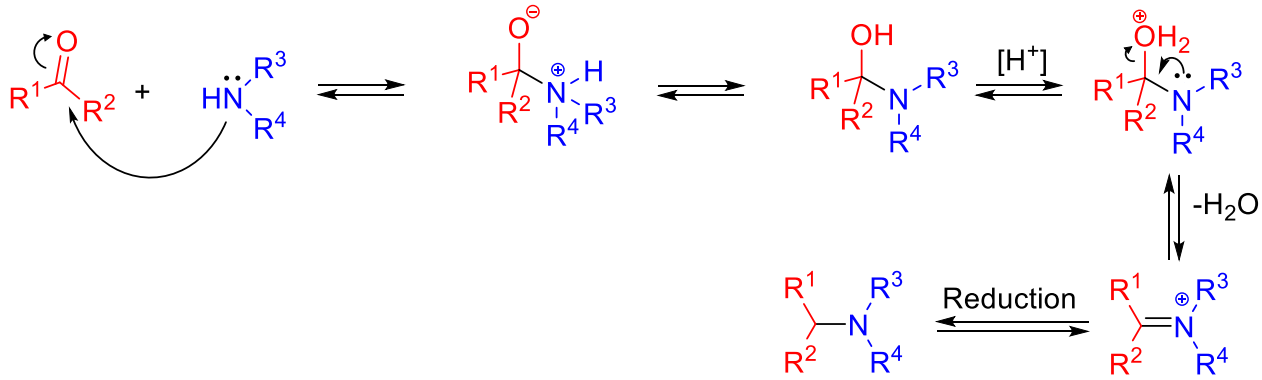
**Figure 1**. Examples of essential drugs with amino groups in the structure.

Since the beginning of modern organic chemistry, many pathways towards amines have been developed. For primary amines Gabriel synthesis, Delépine and Ritter reactions, based on

electrophilic alkylation, represent one of the main synthetic routes in the laboratory, complemented by nitrile reduction. Another group of reactions is based on rearrangement and formation of isocyanate intermediate, in particular Curtius and Hofmann rearrangements, and Schmidt reaction. However, there is a considerable disadvantage using these reactions – a need to use azides or hydrazoic acid, which limits their application. For secondary and tertiary amines, it is worth mentioning Mannich, Petasis, and Kabachnik-Fields reactions, which have been applied in the synthesis of natural compounds (peptides, nucleotides, alkaloids), especially in their asymmetric variants.

A particularly attractive method for amine synthesis is reductive amination. The method gained its role due to its easiness, effectiveness, and versatility towards many co-existing functional groups in substrates. Moreover, its low cost and high atom efficiency make it preferable for large scale industry (pharmaceutical, agrochemical and chemical). It was estimated by Roughley *et al.*,[1] that reductive amination is responsible for a quarter of C–N bond-forming reactions in pharmaceutical industry, being surpassed only by amide (peptide) formation.

Reductive amination, in a nutshell, is a method to construct a C–N bond starting from an aldehyde or ketone and an amine, proceeding through an imine intermediate. Since its appearance in organic chemistry, the most desired characteristics of reductive amination are its selectivity and versatility. Researchers are constantly looking for a method of a new C–N bond creation on the broadest scope of starting molecules, while having other functional groups untouched. Several methods of reductive amination were developed, as demonstrated below.

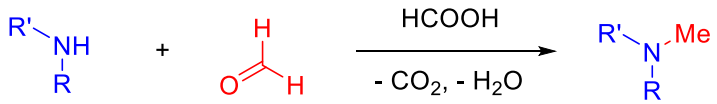



**Scheme 1.** Reductive amination – a general view.

# Reductive amination methods

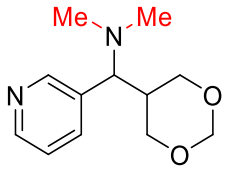
## Eschweiler-Clarke reaction

In the Eschweiler-Clarke reaction methylation of primary or secondary amines takes place using an excess of formaldehyde and formic acid. Whilst using the excess of the reactants, the reduction does not proceed to the formation of quaternary ammonium salts and halts at the formation of a tertiary amine. The reaction proceeds via an imine intermediate with formaldehyde, followed by reduction on the imine by formic acid and losing a $CO_2$ molecule; this makes the whole process irreversible. If a primary amine is used, the reaction continues and gives rise to a tertiary amine. As there is no way to form an imine from the tertiary amine, the reaction stops at this stage. The schematic process is depicted on **Scheme 2**.

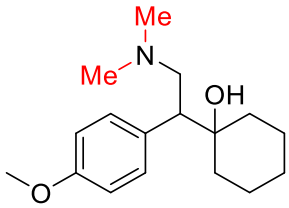



**Scheme 2.** Eschweiler-Clarke reaction.

Eschweiler-Clarke reaction was used for the synthesis of Doxpicomine[2] in the last step, allowing to retain the chiral center and to form a dimethylated amine. Another notable example is Venlafaxine,[3] where reduction of a hemiaminal gives a tertiary amine in excellent yields on a multigram scale.




Doxpicomine

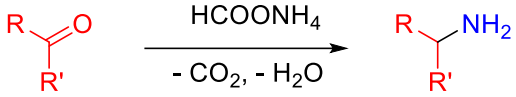



Venlafaxine

**Figure 2**. Doxpicomine and Venlafaxine structures.

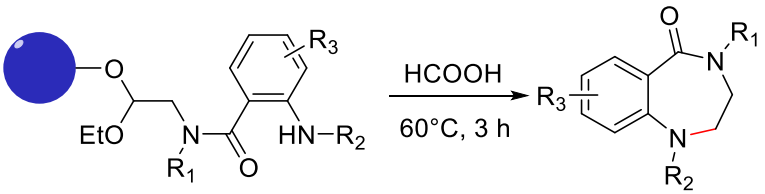
## Leuckart-Wallach reaction

Leuckart-Wallach reaction is a transformation of carbonyl compounds into amines by means of ammonium formate, formamide or primary/secondary amines in formic acid medium at elevated temperature. The reaction mechanism involves the formation of hemiaminal and protonation of hydroxyl, making it a good leaving group and generating an iminium ion intermediate. This intermediate is reduced by formic acid to the resulting amine with concurrent evolution of $CO_2$ what makes the last step irreversible.




**Scheme 3**. Leuckart-Wallach reaction scheme.

The Leuckart-Wallach reaction was used as a key step transformation by Park *et al.*[4] in the synthesis of a variety of substituted benzodiazepinones. The authors managed to cyclize *ortho*-substituted anilines with a side chain, tethered through acetals to resins with good to excellent yields and impressive purity. Formic acid plays a double role in this transformation. It cleaves the acetal forming a free aldehyde and plays the principal role in the following Leuckart-Wallach reaction with a substituted aniline as shown on **Scheme 4**.

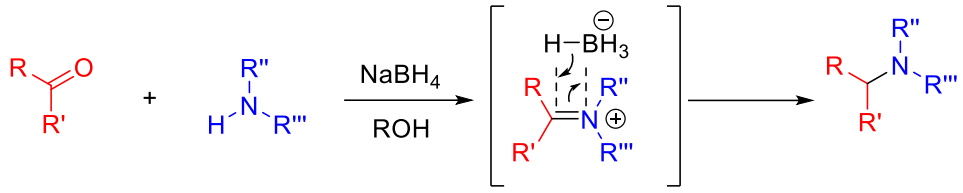



**Scheme 4.** Leuckart-Wallach reaction example.[4]

Another large group of reductive amination reactions consists of reactions catalyzed by noble metals, or reactions involving hydride sources, some of which are discussed below.

## Reductive amination using hydrides. $NaBH_4$

Reductive amination using sodium borohydride ($NaBH_4$) and its congeners is another widely used method. Typically, it is carried out[5] in alcoholic (methanol or ethanol) solvents under neutral conditions in a broad range of temperatures, from 0 °C to that of the refluxing solvents. In a recent review[6] the authors presented a comparison of various conditions for several most often used reductive amination procedures. Along with $NaBH_4$ they have found that addition of Ti(IV) compounds ($TiCl_4$ or $Ti(O^iPr)_4$) helps to form the Schiff base with its subsequent reduction. In most cases, it improves the yield of the resulting amine.




**Scheme 5.** An overview of $NaBH_4$-mediated reduction.

Besides reduction of imines, sodium borohydride ($NaBH_4$) serves as a gentle and chemoselective reducing agent for carbonyl functional groups. At an ambient temperature in hydroxylic solvents, it exhibits rapid reductive capabilities towards aldehydes and ketones, while demonstrating relative inertness towards various other functional groups, including epoxides, esters, lactones, carboxylic acid salts, nitriles, and nitro groups.

However, under certain conditions, sodium borohydride is prone to reduce mentioned functional groups and acting as a nonselective reductant. For instance, $NaBH_4$ displays a tendency to reduce α,β-unsaturated ketones in a 1,4-regioselective manner, yielding mixtures of both saturated alcohols and ketones.[7] In alcoholic solvents, additional formation of saturated β-alkoxy alcohols may occur as byproducts due to conjugate addition of the solvent.[8] It is worth noting that the selectivity of this reaction is not consistently high. When considering the reduction of carboxylic esters,[7,9] sodium borohydride typically exhibits a slow reaction rate. However, this reduction can be expedited by employing an excess of the reagent in methanolic or ethanolic solutions, particularly at room temperature or higher temperatures.[10]

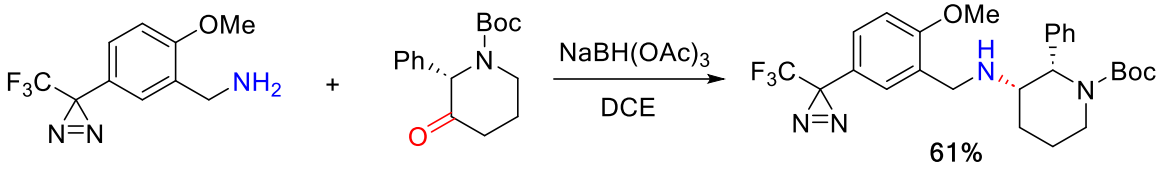
Summarizing, $NaBH_4$-mediated reductive amination has certain drawbacks, namely toxicity and its inflammable nature due to possible release of diborane and hydrogen, and a number of susceptible functional groups as shown before.

## Reductive amination using hydrides. $NaBH(OAc)_3$

One of the tools of choice in reductive amination reactions is $NaBH(OAc)_3$ that is prepared from sodium borohydride and acetic acid. In comparison with its parental compound, sodium triacetoxyborohydride is milder and more susceptible towards hydrolysis. For example, methanol is an inappropriate solvent for such reductions, while ethanol and isopropanol can still be used. However, $NaBH(OAc)_3$ is much more selective than $NaBH_4$, leaving most keto groups untouched, which makes it especially suitable for reductive amination. Nevertheless, it is essential to highlight a noteworthy exception to this general selectivity; α- and β-hydroxy ketones are found to undergo reduction to yield *anti*-configured diols, and this specific transformation is mediated by hydroxy-directed hydride transfer.[11–13] The reaction rate of an imine or enamine reduction is much higher than that of an aldehyde, so the reaction can be carried out in a one-pot manner without a competing formation of alcohol.

Despite all these advantages, the $NaBH(OAc)_3$ reductive amination has its own drawbacks. As it was already mentioned, it is susceptible towards hydrolysis and thus it should be used together with aprotic solvents such as toluene, THF, 1,4-dioxane, DCE or DCM. In some reactions it leads to a lack or decreased reactivity. For example, ammonium acetate is often used as an ammonia equivalent in reductive amination. While used in the aforementioned solvents, where it is poorly soluble, ammonium acetate forms almost quantitatively secondary amines with traces of intended primary ones. It happens due to better solubility and higher reactivity of the initially generated primary amine, which makes the process to continue. Last but not least, it should be mentioned that $NaBH(OAc)_3$ is about 3 times more expensive than $NaBH_4$ according to the actual Merck catalogue.

Eventually, there are examples of diastereocontrol due to steric effects or directing by a neighboring group.[14,15] An illustrative example of such diastereoselective reductive amination is depicted on **Scheme 6**.



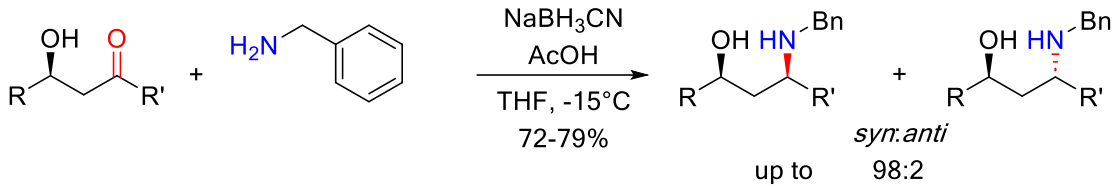

**Scheme 6.** $NaBH(OAc)_3$-mediated reductive amination.[15]

## Reductive amination using hydrides. $NaBH_3CN$

One of the most selective reducing agents is sodium cyanoborohydride ($NaBH_3CN$). Due to the presence of the electron-withdrawing cyano group it is less reactive than the parental $NaBH_4$. As described in a review,[16] the chemoselectivity of $NaBH_3CN$ varies with conditions – the choice of solvent and pH. When using slightly acidic or neutral conditions (pH > 5), only imines are reduced in protic, aprotic or ether solvents (usually MeOH). Other functional groups, such as nitriles, nitro groups, oximes, esters, lactones, epoxides, carbonyls, remain intact under these conditions. Usually, this method of reduction is used in a direct way when the carbonyl compound is mixed with the amine and the reducing agent without prior isolation of the imine or iminium salt as well as for other borohydrides. In especially difficult cases (poorly nucleophilic amines, hindered, and/or $CF_3$-substituted ketones) there is a way to greatly improve the yield by using a stepwise procedure, when imine or iminium compound are formed prior to the addition of sodium cyanoborohydride. This transformation might be carried out with $TiCl_4$ or $Ti(O^iPr)_4$.

Attention should be paid to the fact that $NaBH_3CN$ has one significant disadvantage comparing to other hydrides – $NaBH_4$ and $NaBH(OAc)_3$. It is toxic due to the presence of a cyano anion in the molecule. Thus, all necessary cautions should be taken as for any other inorganic cyanides. Another disadvantage is its cost. Sodium cyanoborohydride is about 6 times more expensive than sodium borohydride. It means that in some applications where the cost plays a significant role, this reagent will not be one of choice.

Similarly to sodium triacetoxyborohydride, $NaBH_3CN$ reductions might proceed with the control of diastereoselectivity when having bulky enough or coordinating neighboring functional groups as it is depicted on **Scheme 7**.[17]



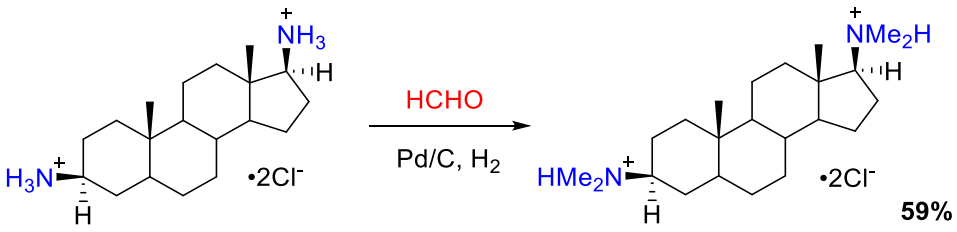

**Scheme 7.** An example of diastereoselective $NaBH_3CN$-mediated reduction.[17]

Concerning the limitations, it should be mentioned that in acidic environments (pH < 4), aldehydes and ketones undergo selective reduction to form alcohols.[18,19]

Eventually, $NaBH_3CN$-mediated reductive amination stays as a tool of choice in all cases, when the increased selectivity and lack of reactivity towards various functional groups play the paramount role despite its toxicity and high cost compared to other hydride sources.

## Noble metal-catalyzed reductive amination. Hydrogenation over Pd/C

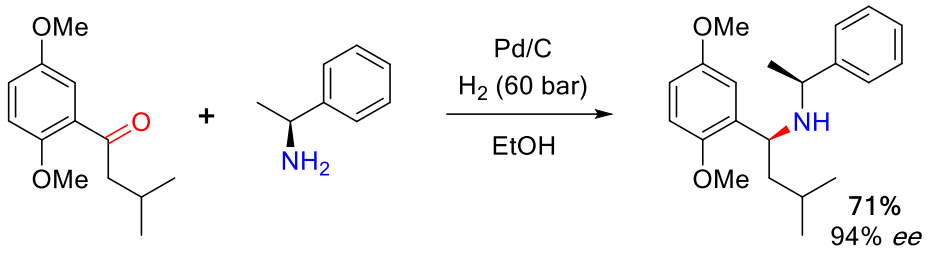
Another useful method for reductive amination is hydrogenation of a carbonyl compound and amine mixture, catalyzed by palladium on carbon in a protic solvent (methanol or ethanol) at an increased pressure of hydrogen.[20] An example of such a reaction is shown on **Scheme 8**. However, other functional groups, such as double and triple bonds,[21] azides,[22] diazo compounds,[23] nitro-[24] and cyano groups, and *N*-oxides can be hydrogenated along,[25] which represents a considerable limitation of this method in terms of selectivity. Pyridine and pyridinium derivatives are readily hydrogenated to produce piperidines.[26] Another possible issue is the hydrogenolysis of a benzyl group attached to an oxygen or nitrogen atom which is a commonly used protecting group in complex synthetic schemes. Several less reactive functional groups encompass ketones,[27] esters,[28] benzyl ethers[29] and epoxides[30] may add to the problem.




**Scheme 8.** An example of Pd/C catalyzed reductive excessive formylation.[20]

To conclude, the main disadvantages of using Pd/C for reductive amination are decreased chemoselectivity in comparison with other methods and lack of possibility to induce an enantioselective transformation.

Concerning the asymmetric reductive amination, Bringmann *et al*. reported using of α-methylbenzylamine as a chiral auxiliary, forming the products with high *de* ratio (**Scheme 9**).[31]




**Scheme 9**. Diastereoselective reduction with (*S*)-(-)-α-methylbenzylamine as a chiral auxiliary.[31]

## Noble metal-catalyzed reductive amination. Rh/CO

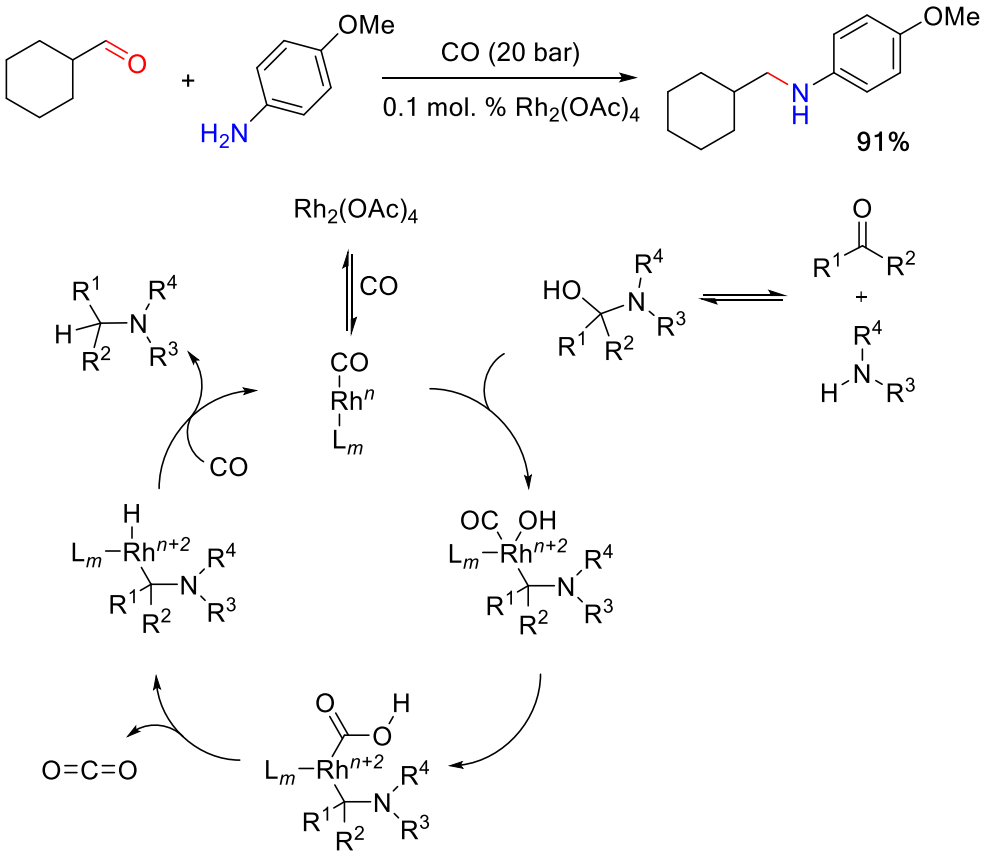
Dirhodium tetraacetate [$Rh_2(OAc)_4$] serves as the archetypical catalyst for the decomposition of diazocompounds, leading to the transient formation of rhodium-carbenoid intermediates. The latter species find broad application in carbene chemistry and creation a new C–C bond.[32]

However, [$Rh_2(OAc)_4$] applicability is not limited to carbenes and carbene chemistry. While used in particular conditions and with new reactants, it may participate in carbonylation or reductive amination reactions. One of those specific reagents is carbon monoxide.

While carbon monoxide (CO) traditionally serves as a one-carbon synthon in various syntheses, its toxic and potentially explosive nature has prompted exploration of less hazardous alternatives. Notably, formic acid has been harnessed to introduce the carboxylic acid moiety to alkenes, without the need for CO gas, in a $Rh_2(OAc)_4$-catalyzed reaction.[33]

However, on a laboratory scale a great deal of work has been carried out by List, leading to development of a new catalytic method for amines formation.[34] The authors describe the reaction between carbonyl compounds (both aldehydes and ketones, aliphatic and aromatic) and amines (again, aromatic and aliphatic, primary and secondary amines) under a pressure of carbon monoxide and catalyzed by $Rh_2(OAc)_4$. New amines were formed with good to excellent yields

(typically, exceeding 70%). Multigram-scale experiment afforded the secondary amine without diminution of yield. However, the cost of the catalyst and difficult removal of its leftovers from the product are prohibitive for large industrial use as well as the absence of reported induction of chirality. The reaction example and proposed mechanism are shown on **Scheme 10**.



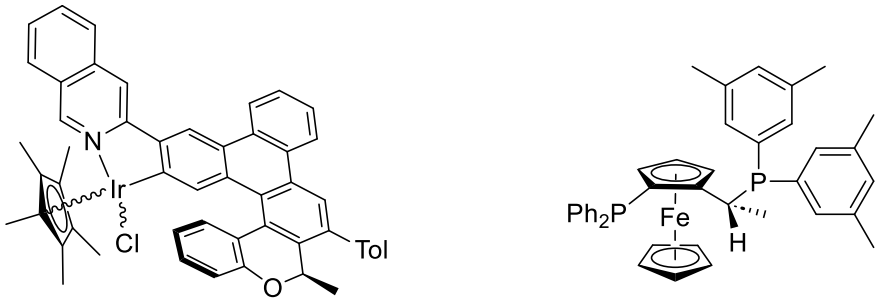

**Scheme 10.** Rh-catalyzed reductive amination and its plausible mechanism according to List *et al.*[34]

In summary, the Rhodium/Carbon Monoxide (Rh/CO) system might help in the construction of new C–N bonds from carbonyl compounds and amines in the case, when the toxicity of CO and need to work with high-pressure vessels is not an issue.

## Noble metals catalyzed reductive amination. Ir-catalyzed reduction

To complete the discussion about the noble metals-catalyzed reductive amination, the chiral version of reductive amination is also reachable by employing novel Ir-based catalysts with chiral

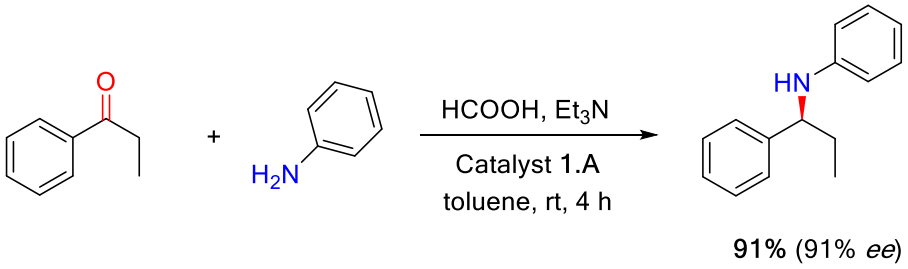
ligands. It was found by Stary *et al.*,[35] that helicenes could serve as ligands (**Figure 3, 1.A**) with helical chirality for Iridium atom allowing the asymmetric reduction of imines with formic acid (HCOOH) as a reductant. In their article the authors show that there are known only a few reports on enantioselective reactions with helically chiral organometallic helicenes.




1.A 1.B (Josiphos)

**Figure 3**. Catalysts and precatalysts structures: i) Ir-catalyst **1.A** by Stary *et al.*, ii) Josiphos **1.B**.

Under mild conditions the Starý's team method allows to get various α-substituted benzylamines in high yields (> 80%) and excellent enantioselectivity (up to 92% *ee*). An example of the reaction is depicted on **Scheme 11**.




**Scheme 11.** Reductive amination of propiophenone catalyzed by chiral Ir-catalyst **1.A**.

It is essential to highlight one of the most often used ligand in organic synthesis, Josiphos (**Figure 3, 1.B**), which was developed in the Togni's laboratory.[36] Its Ir complex became one of the most effective catalysts for the hydrogenation of the C=N bond, with numerous applications.[37–39] Moreover, Ir-Josiphos finds its practical employment on an industrial scale, namely in the production of one of the most important grass herbicides, Metolachlor. Historically, this substance was produced by catalytic reductive alkylation over palladium on carbon as a mixture of four stereoisomers. Later, it was found that almost all herbicidal activity (~ 95%) of Metolachlor is

caused by only two diastereomers. After this discovery, the new, Ir-Josiphos-mediated protocol, was introduced and has been actively used ever since.

There are a number of publications regarding the Ir-catalyzed asymmetric reductive amination. Thus, Mršić *et al*.[40] used a chiral complex generated from a BINOL-based ligand and $[Ir(COD)_2]BArF$,[41] for a high pressure enantioselective hydrogenation of prochiral ketimines. They achieved high yields and fascinating levels of enantioselectivity. More recently, Salomó and colleagues[42] reported on a high pressure hydrogenated acetophenone N-Aryl imines, catalyzed by Ir-MaxPHOX complex to attain high levels of enantioenrichment and conversion. Also noteworthy is the successful synthesis of enantioenriched debenz[*c*,*e*]azepines in 2019, in which Yang and co-workers used an intramolecular reductive amination process as the key step.[43] These unique 7-membered cyclic amines were constructed from aryl-bridged aminoketones on hydrogenation at 30 atm in the presence of a catalyst generated from $[Ir(COD)Cl]_2$ and DifluorPhos as a ligand, with $Ti(O^iPr)_4$ as an additive. In most cases the authors reached high yields and excellent enantioselectivity.

## Miscellaneous

A series of reports appeared on non-classical reductive amination reactions. There is a pioneering work on chiral Brønsted acid-based catalysis employing sterically hindered BINOL-derived acids released in 2005 by Rueping *et al*.[44] 10 years later, a number of chiral Brønsted acid-based catalysts were developed by List *et al*.,[45] showing their high efficiency in the synthesis of chiral secondary *N*-alkyl amines. Hantzsch esters as hydrogen source were employed in the protocol and the presence of $Boc_2O$ was required for ongoing reaction. Another attractive procedure was proposed in 2016 by Du and colleagues.[46] Here, the reductive amination was carried out in the presence of a so-called frustrated Lewis pair (FLP) and ammonia borane as a hydrogen source. The FLP is a combination of $H^{\delta-}$ and $H^{\delta+}$ incorporated Lewis acid and base. In this instance the frustrated Lewis pair consists of chiral Ellman's *tert*-butylsulfinamide and Piers' borane. The resulting *N*-substituted α-methyl benzylamines were obtained with excellent yields and levels of *ee*. A report by Speed and colleagues[47] describes the use of diazaphospholenes as chiral catalysts and pinacolborane (HBpin) as a hydride source for the reduction of selected ketimines. Secondary amines were thus obtained with good yields and moderate enantioselectivity.

In 2020, Gade *et al*.[48] employed a chiral Fe-complex as a catalyst. The authors showed that iron(II) alkyl complexes, carrying a specific pincer ligand act together with HBpin as a hydrogen source and reduce a series of ketinimines with good yields and levels of *ee*.

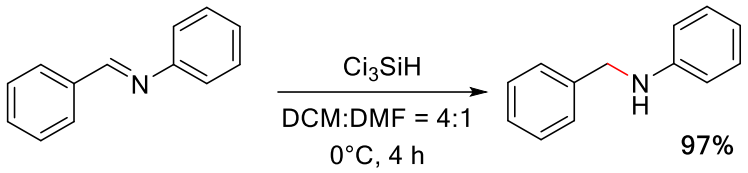
# $Cl_3SiH$-mediated reductive amination

## Historical overview

It has been known since 1970, that trichlorosilane has reducing properties. It was shown by Benkeser,[49] that mesitylene may be synthesized from the 3,5-dimethylbenzoic acid using $Ci_3SiH$ as a reductant. Authors have shown that aromatic carboxylic acids (or even dicarboxylic acids) in general may be reduced through the formation of benzyltrichlorosilane to methylbenzenes. The reaction usually gives good to excellent yields.

Next significant work was published by Kobayashi in 1996, who showed that reductive amination of aldehydes and ketones is possible under mild conditions with good to excellent yields by means of $Cl_3SiH$ in a $CH_2Cl_2$-DMF mixed solvent system (4:1).[50] This work where several aromatic/aliphatic aldehydes and primary amines were employed as substrates, introduced a new synthetic tool with advantages and drawbacks. Moreover, the reductive amination was carried out in two ways – direct and stepwise. In the first case, the aldehyde and the primary amine were mixed with some $MgSO_4$ in dichloromethane. The mixture was stirred for 1 hour at room temperature for an *in situ* formation of the imine, after which time the mixture was cooled to 0 °C and trichlorosilane (1.5 equiv) in DCM: DMF mixture was added dropwise. After a simple work up, the corresponding secondary amines were obtained with yields exceeding 74%.

In the case of the stepwise protocol, imines were first prepared and isolated, and then submitted to the reduction, with similar molar and solvents ratios, temperature, and times. It gave rise to the expected secondary amines with excellent yields (more than 86%). The example of a reaction is shown on **Scheme 12**.




**Scheme 12.** $Cl_3SiH$-mediated reductive amination by Kobayashi *et al*.[50]

Aldimines do not require any sophisticated catalysts as they are reduced into non-chiral secondary amines. Thus, DMF or other Lewis bases (DMSO, HMPA) might be more than sufficient for the $Cl_3SiH$-mediated reductive amination. However, the widely known carcinogenicity of hexamethylphosphoramide (HMPA) and the susceptibility of dimethylsulfoxide (DMSO) to reductions makes DMF the catalyst of choice for nonchiral imine reduction.

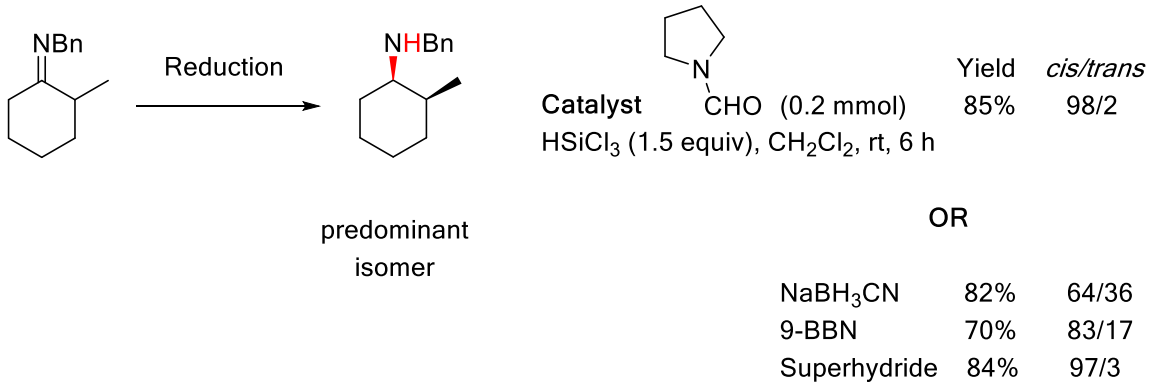
The game is being changed in the case of ketimines. DMF (and other possible Lewis bases) gives only racemic products in the case of prochiral ketones. As a result, the aim of performing an enantioselective version of the $Cl_3SiH$-mediated reductive amination presents a challenge.

Kobayashi's work inspired several groups worldwide, which set out to develop an asymmetric version of this reaction, suitable for ketimines. The obvious choice was to construct a chiral catalyst.

Matsumura and coworkers were the first to describe chiral analogs of DMF.[51] They explored *N*-formylpyrrolidine derivatives, with various substituents at position 2, and found that ketimines, mixed together with the starting ketones (1:1 ratio), could be selectively reduced in competitive reduction experiments, while other reducing agents such as $LiAlH_4$, DIBAL, $NaBH_4$ and $NaBH_3CN$ give mixed results, with dominating formation of alcohol. The same observation should be mentioned regarding compounds bearing several functional groups. Matsumura and coworkers have tried to reduce α-iminoesters and isolated the pure α-aminoester in an experiment with *N*-formylpyrrolidine with excellent yield. In the absence of the catalyst, incomplete reduction was observed, with 2/3 of the starting material. While using the same substrate and $NaBH_4$ as a reductant, authors observed a complex mixture of starting material, expected product and amino alcohol (the product of full reduction).

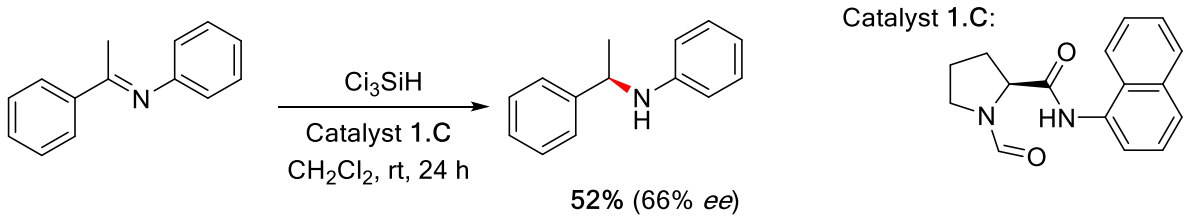
The authors have also demonstrated excellent diastereoselectivity in the reduction of imine derived from the 2-methyl cyclohexanone. With *N*-formylpyrrolidine, the imine was clearly reduced into

the amine with high *cis*/*trans* stereoselectivity (98:2). The result might be compared only with Superhydride reduction in terms of yield and stereoselective formation of the *cis* product. With other reductants (sodium cyanoborohydride and 9-BBN) the authors obtained significantly lower stereoselectivity (**Scheme 13**).




**Scheme 13**. *Cis/trans* selectivity of various reductants.

The most important discovery was that *N*-formylpyrrolidines with a chiral center close to the formyl group can promote the formation of optically active amines. Two different pyrrolidines were investigated, and enantiomeric excess was found to be up to 66% (**Scheme 14**). The authors[51] proposed a reduction pathway based on the observation that (*S*)-catalysts allowed to obtain (*R*)-enriched amines.




**Scheme 14.** The first enantioselective $HSiCl_3$-mediated reduction.

Working in this field, our group developed a several successful protocols and chiral catalysts for reductive amination.[52–55] Since the proline-based catalysts developed by Matsumura did not exhibit the highest enantioselectivities, our group resolved to exploit other amino acid scaffolds. L-valine turned out to be the most promising and a series of its derivatives was synthesized with the constant *N*-formyl group and various substituents in the carboxylic acid side. Those substituents were derived from various amines – aromatic and aliphatic, forming secondary and

tertiary amides. It was established that amides derived from aliphatic amines and secondary amines significantly decrease the yields and enantioselectivity. Screening eventually identified the aniline-type amides (**1.D-F**) as the catalyst of choice, surpassing the proline-derived catalysts in enantioselectivity. Of these, Kenamide (**1.E**) (with 3,5-dimethylaniline as a substituent from the carboxylic side) and Sigamide (**1.F**) (3,5-di-*tert*-butylaniline) were chosen by Aldrich for commercialization. These organocatalysts can be synthesized in 3 steps starting from the commercially available *N*-Boc-protected L-Valine (**Figure 4**).

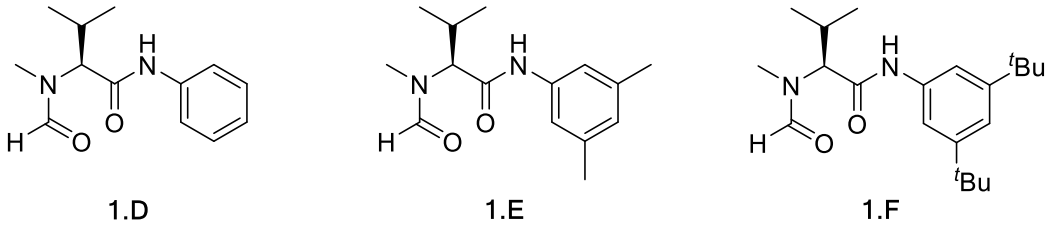



**Figure 4.** Simple anilide (**1.D**), Kenamide (**1.E**) and Sigamide (**1.F**).

Several papers were published with newly developed catalysts containing a chiral version of DMF derivatives.[56–58] Some of these structures are depicted in **Figure 5**.

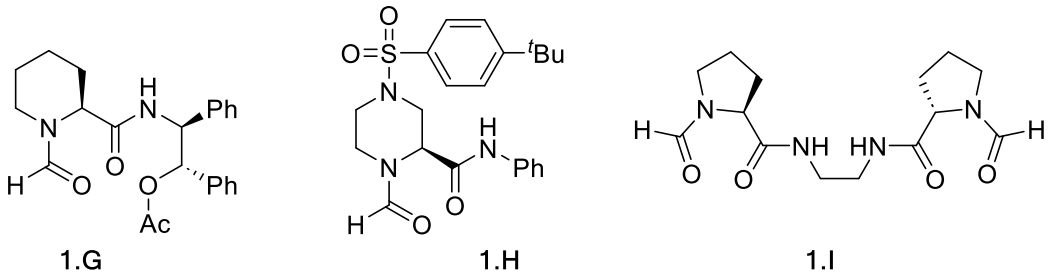



**Figure 5.** Piperidine- and piperazine-based chiral catalysts **1.G-I**.

Further investigations by the Matsumura's group led to the finding that *N*-picolinoylpyrrolidine derivatives could serve as catalysts in imine reduction.[59] Especially one example, with 1',1'-diphenylsubstituted chiral prolinol, was found to be a successful organocatalyst (**1.J**) with *ee* up to 80%. Matsumura and colleagues have found that some features are essential in the catalyst structure. It was found that picolinoyl residue should be 2-substituted for successful reduction. 3- and 4-picolinoyl substituted pyrrolidines were inefficient catalysts giving negligible yields. Further, the 1',1'-diphenylsubstituted chiral prolinol pattern was investigated. In comparison with a structure lacking the hydroxyl group (R = $CHPh_2$ instead of $CPh_2OH$) prolinol-based catalyst **1.J**

gives superior results in terms of enantioselectivity (73% *ee* of resulting amine vs. 13% *ee*). The structure of the most successful catalyst **1.J** is shown on the picture below (**Figure 6**).

Subsequent articles were dedicated to the synthesis and exploring of *N*-picolinoyl-based catalysts.[60,61] As discussed before, Matsumura with co-workers were the pioneers in introducing this motif in the design of chiral catalysts for reductive amination. Other authors followed their work and prepared more compounds with catalytic activity. Among them are compounds **1.K** and **1.L** based on chiral aminoalcohols,[60] on altered Matsumura's catalyst; the most notable examples are shown in **Figure 6**.

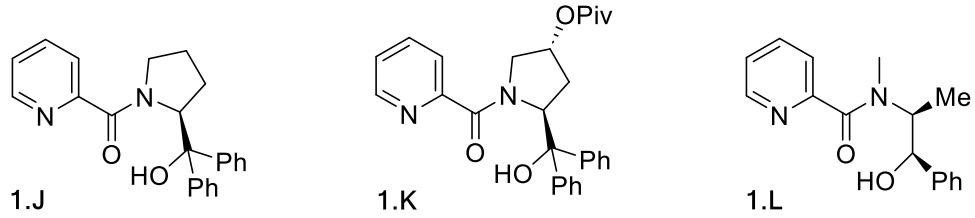



**Figure 6.** Matsumura's *N*-picolinoyl-based catalyst **1.J** and similar catalysts **1.K** and **1.L**.

In the following years, a new class of chiral catalysts bearing a chiral sulfonamide group was developed. Sun and coworkers[62–65] built catalysts with various chiral backbones (L-Proline, L-pipecolinic acid, L-Valine and L-Phenylalanine) but with the constant chiral sulfininamido group. The best results were attained with *N*-benzyl, *N*-alkyl and *N*-aryl ketimines. Structures of the catalysts **1.M-P** are shown in **Figure 7**.

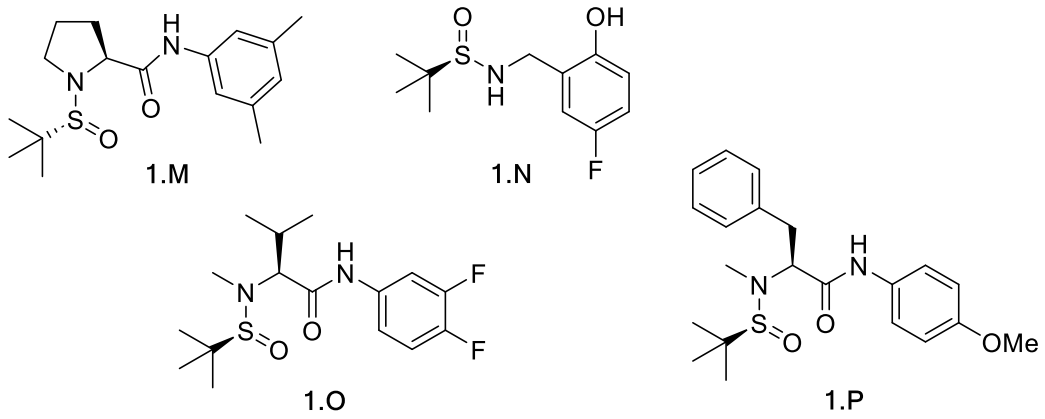


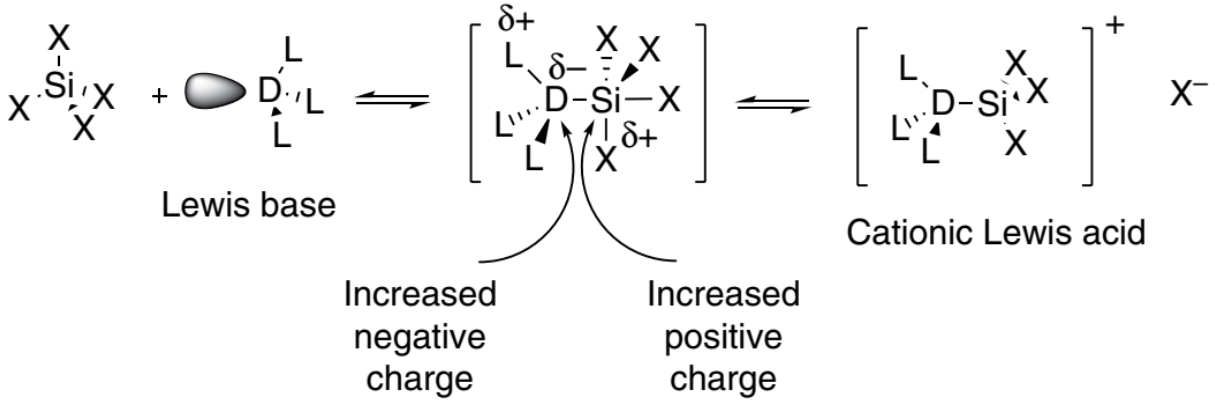

**Figure 7.** Chiral sulfonamide catalysts **1.M-P**.

## Mechanistic studies

Hypercoordinated silicon compounds have garnered significant attention since their initial discovery in the 19th century by J.L. Gay-Lussac, J.A. Thénard, and J. Davy, who reported the $SiF_4 \cdot 2NH_3$ complex.[66,67] Subsequently, over the past two centuries, numerous silicon species with penta-, hexa-, and hepta-coordination have been identified and extensively investigated.[68] Presently, it is well-documented that silicon can form more than the expected four bonds dictated by primary valency rules. This unique capacity has played a pivotal role in the advancement of enantioselective reactions involving various silicon-based Lewis acids.

Ordinarily, a silicon atom establishes bonds with just four atoms to fulfill its outer shell octet electron requirement. Nevertheless, under specific conditions, when a Lewis-acidic silicon species interacts with a Lewis base, it can give rise to a highly reactive adduct, contrary to the general principles of Lewis acid–base theory and predicted a more stable acid-base adduct, thus deviating from the "Lewis–Langmuir octet rule".

Various theories have been proposed to elucidate this distinctive behavior. One of the earliest theories involves a reconfiguration of the electron density surrounding the silicon atom, as depicted in Gutmann's semi-empirical analysis (**Scheme 15**).[69] Gutmann recognized that the formation of a dative bond between the Lewis base and the Lewis acidic silicon results in an overall augmentation of electron density on the acceptor component of the adduct. However, the distribution of this electron density is uneven among the constituent atoms, resulting in an enhancement of both nucleophilic and electrophilic characteristics. Consequently, the bonds in the newly formed adduct lengthen, leading to an expansion of the coordination sphere around the silicon atom. This electronic redistribution results in an increased electrophilicity of the central silicon atom and increased nucleophilicity of the peripheral ligands within the new complex.




**Scheme 15.** Lewis acid-Lewis base complexation by Gutmann.[69] Adopted from ref.[70]

Of the other theories, is worth mentioning the idea that the silicon atom participates in hypervalent bonding or expands its coordination sphere. In this scenario, the silicon 3p orbitals play a crucial role in forming one or two electron-rich, three-center, four-electron bonds. These hybrids were originally introduced by Pimentel, building upon earlier concepts formulated by Rundle.[71,72] According to this theory, the formation of penta- or hexacoordinate silicon species entails the creation of one or two three-center four-electron bonds, respectively. Each of these bonds involves one silicon p orbital and two p orbitals from the ligands contributing to the coordination (see **Figure 8**). A significant implication of this mechanism is the distinct behavior of ligand positions in penta- and hexacoordinated silicon species. In such cases, the σ-acceptor ligands tend to form "hypervalent" bonds, whereas the σ-donors preferentially establish conventional covalent bonds with the $sp^2$ orbitals (in penta-coordinate compounds) or *sp* orbitals (in hexa-coordinate compounds) of the silicon atom.

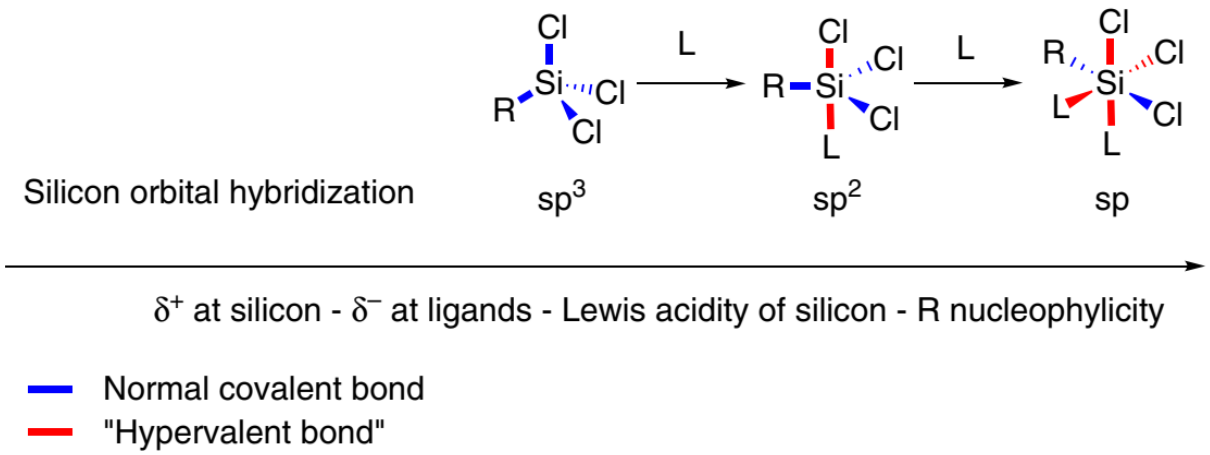
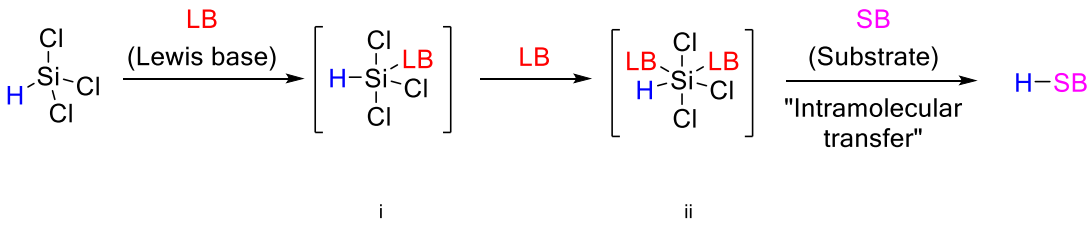



**Figure 8.** The hypervalent bonds result in an electron-rich character at the periphery of the ligands and an electron-deficient character at the central silicon atom. Adopted from ref.[70]

In general, hypercoordinate silicon species exhibit increased Lewis acidity, which allows them to coordinate and activate various substrates. When hypercoordinate silicon species **i** and **ii** form through the coordination of one or two Lewis bases (LBs), and in the absence of a nucleophilic substrate, the more thermodynamically favored silicon adduct **ii** (compared to **i**)[73,74] can undergo an intermolecular process referred to as "direct transfer." In this process, one of the peripheral ligands is transferred directly onto the substrate (**Scheme 16**).




**Scheme 16.** Hypercoordination of the central Si atom. Adopted from ref.[70]

Kobayashi *et al.*[50] performed a $^{29}$Si NMR analysis and identified the hypervalent silicon species by comparing and assigning signals of the $HSiCl_3$/DMF mixture and the reaction mixture with a carbonyl compound.

A few mechanisms were suggested for various catalysts (chiral or non-chiral) and computational studies were performed to model imine reduction. Thus, Schreiner in his work[75] used substituted *N*-formylproline as a model catalyst to study the mechanistic and structural aspects of imines reduction. Density functional theory (DFT) with the B3PW91 combination of functionals[76]

revealed that the catalyst not only coordinates to $HSiCl_3$, but also acts as a proton donor in the essential transitional structure. Transition structures were modeled employing *N*-methylformamide (NMF, **C4**) or *N*,*N*-dimethylformamide (DMF, **C5**) as a catalyst and aldimine **C2** as a substrate and showing a clear lower activation barrier in comparison with a route where the silicon atom of trichlorosilane **C1** coordinates with an imine nitrogen atom (see **Figure 9)**.

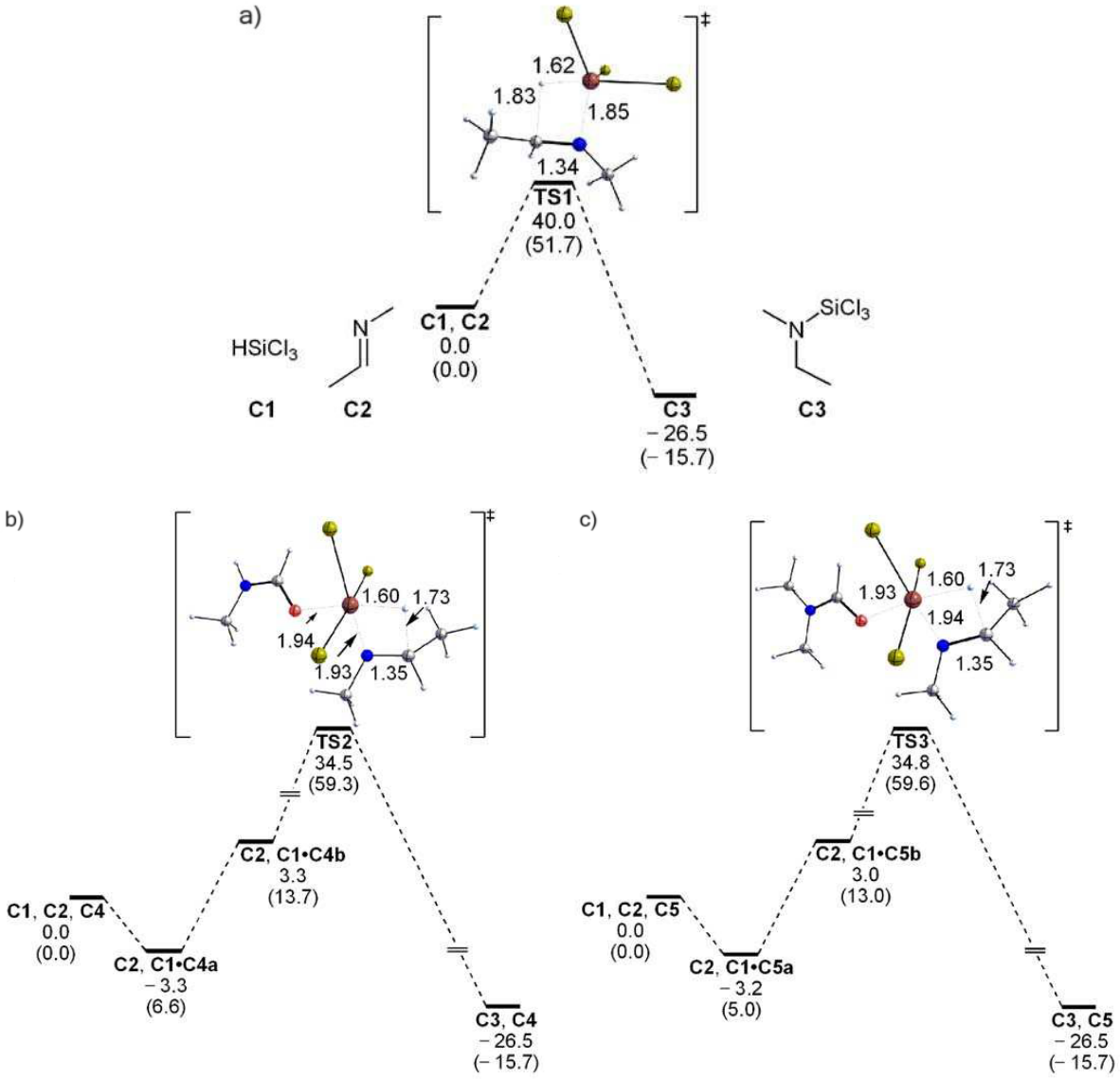
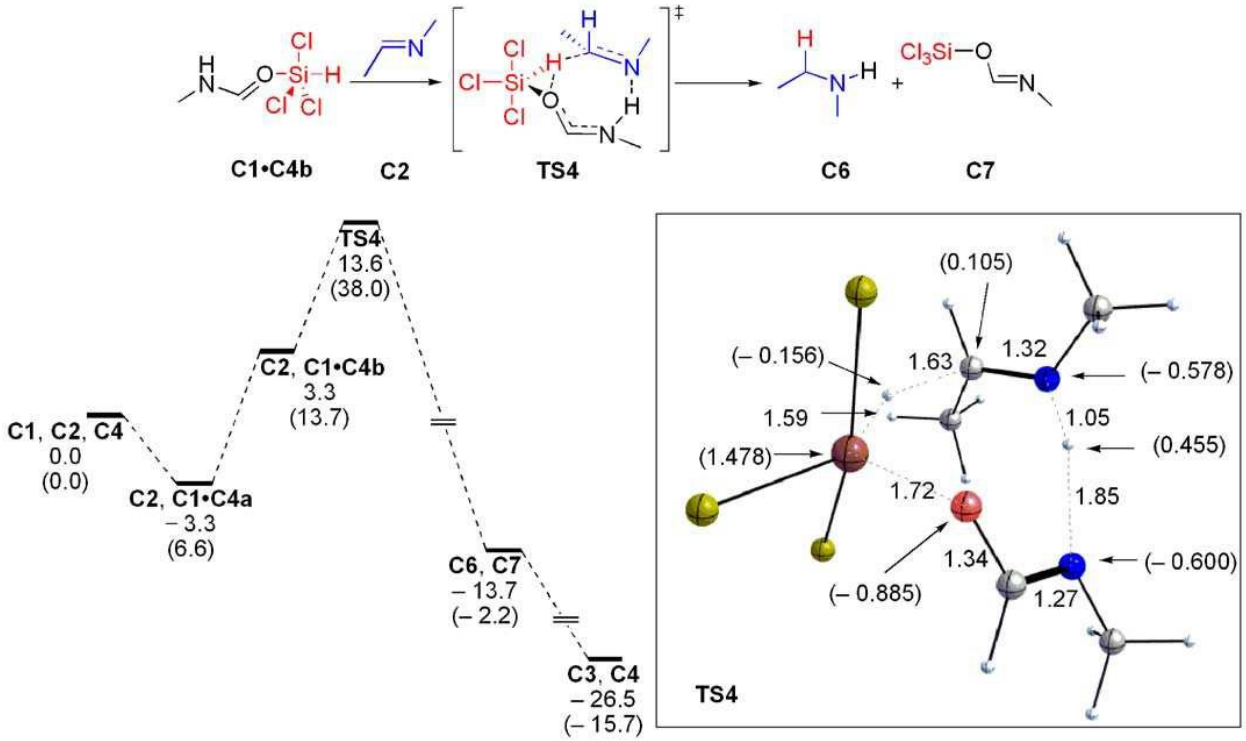



**Figure 9**. The potential energy hypersurfaces for a reaction of $HSiCl_3$ with an imine in the absence of a catalyst (**a**) and with the catalyst – NMF (**b**) or DMF (**c**). Copied from ref.[75]

Moreover, subsequent calculations showed that the presence of the NH proton of the amide group might play a crucial role in reductive amination. Indeed, the activation barrier is much lower when the hydrogen atom of the catalyst **C4** amido-group participates and binds the basic nitrogen atom of imine **C2** forming the transition state **TS4**. Thus, the whole transformation might be considered as a formal $H^+/H^-$ ionic pair addition onto a C=N bond (**Scheme 17**). Schreiner and colleagues assumed a similar pattern for the enantioselective reduction catalyzed by proline derivatives.




**Scheme 17.** The potential energy hypersurface for reduction of imine **C2** catalyzed by NMF through **TS4**. Copied from ref.[75]

This work was greatly supplemented in 2021 by Maciá *et al*.,[77] who synthesized new prolinamide-based organocatalysts and performed calculations, kinetic analyses, and other experimental work in order to shed more mechanistic light on the imine reduction with the aim to develop optimal catalysts. In the case of two catalysts of the 1st generation, **1.Q** and **1.R**, the ratio $k_2/k_1$ ($k_2$ is a kinetic constant for the catalysed reaction, $k_1$ is a constant for the uncatalyzed reaction) is laying in the range of 86-96 displaying almost 100 times higher reaction rate than the reaction rate for the uncatalyzed process. It means that a higher activity of the catalyst can significantly promote the asymmetric induction, while the uncatalyzed reaction, forming a racemate, will reduce this

process contribution. The 3rd explored catalyst, **1.S**, showed $k_2/k_1 = 16$ indicating lower catalytic activity. Interestingly, further experiments with the catalyst **1.S** revealed that the general activity and enantioselectivity is strongly influenced by the catalyst concentration and the substrate-to-catalyst ratio (**Figure 10**).

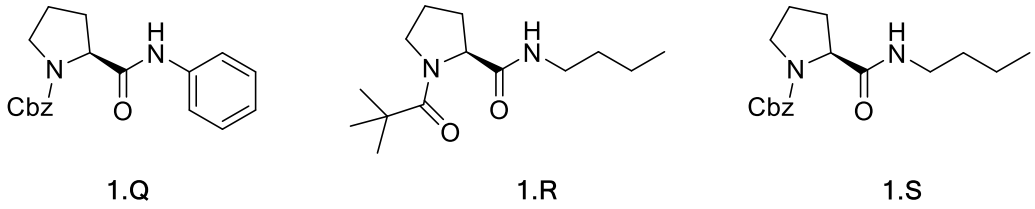
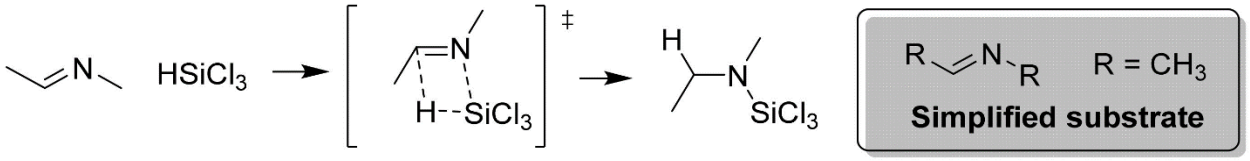


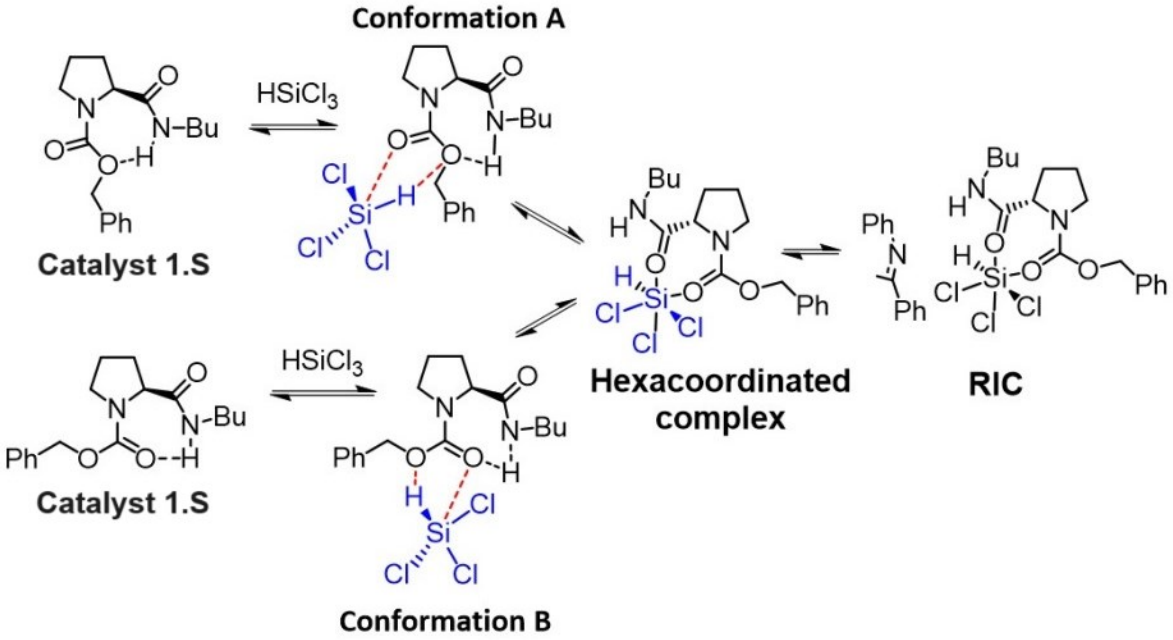

**Figure 10**. Structures of **1.Q-S** catalysts.

The initial DFT-based mechanistic investigation, employing simplified representations of both the imine and the catalyst, postulated a mechanism that involves the formations of a catalyst−$HSiCl_3$ complex capable of mediating a formal $H^+/H^-$ transfer to the C=N bond as mentioned earlier.[75] Building upon this precedent and aiming to discern the contributions of various structural elements, Maciá *et al*. opted for the expedient PM6 semi-empirical method.[78,79] This choice was made to enable the analysis of structures that more closely resemble their actual counterparts. These computational simulations were carried out employing the Gaussian 09 software package.[80] To validate the chosen computational approach, the authors initially examined the uncatalyzed reaction pathway utilizing the simplified imine model previously employed by Schreiner (*vide supra*). In this process (**Scheme 18**), the mixture involving the imine and $HSiCl_3$ subsequently evolves into a four-centered transition state (TS). During this transition, hydrogen is transferred from trichlorosilane to the carbon atom of the imine, leading to the formation of the products interaction complex (PIC). The computed energy barrier was found to be 40 kcal/mol, consistent with the results obtained through DFT calculations in Schreiner's work. Consequently, this computational methodology, which facilitates the exploration of the impacts of structural alterations in the catalyst, was deemed to be valid.




**Scheme 18**. Formation of products interaction complex (PIC) involving the imine and $HSiCl_3$.

This exploratory analysis extended to the conformational space of a model representing catalyst **1.S**, where the benzyl and butyl groups were simplified to methyl groups (**Figure 11**). This investigation employed the same imine model as depicted on **Scheme 18**. Consistent with the $^1$H-NMR spectrum displaying two amide NH signals of comparable intensities (Supplementary materials of Maciá's work), both potential intramolecular amide NH hydrogen bonds present in the Cbz derivatives were taken into consideration. Both configurations appeared amenable to interact with $HSiCl_3$ attaining **Conformation A** or **Conformation B**. Both these conformations form a hexacoordinate complex (**Scheme 19**) in which the silicon atom forms bonds with the two carbonyl oxygens of the catalyst, necessitating the disruption of the preexisting intramolecular hydrogen bonds, followed by emerging of reactant interaction complex with the imine (RIC).




**Scheme 19**. Formation of $HSiCl_3$-hexacoordinated complex with **1.S**. Copied from ref.[77]

The structural characteristics of this complex could vary depending on the spatial arrangement around the silicon atom (as depicted in **Figure 11**, **A**). Notably, configurations in which the hydrogen was situated in equatorial positions exhibited lower energy than those with the hydrogen in apical positions. Consequently, the transition state was exclusively assessed with configurations **C** and **D**. It is pertinent to note that an optimized geometry for the transition state was successfully obtained only with configuration **C** (as demonstrated in **Figure 11**, **B** and **C**).

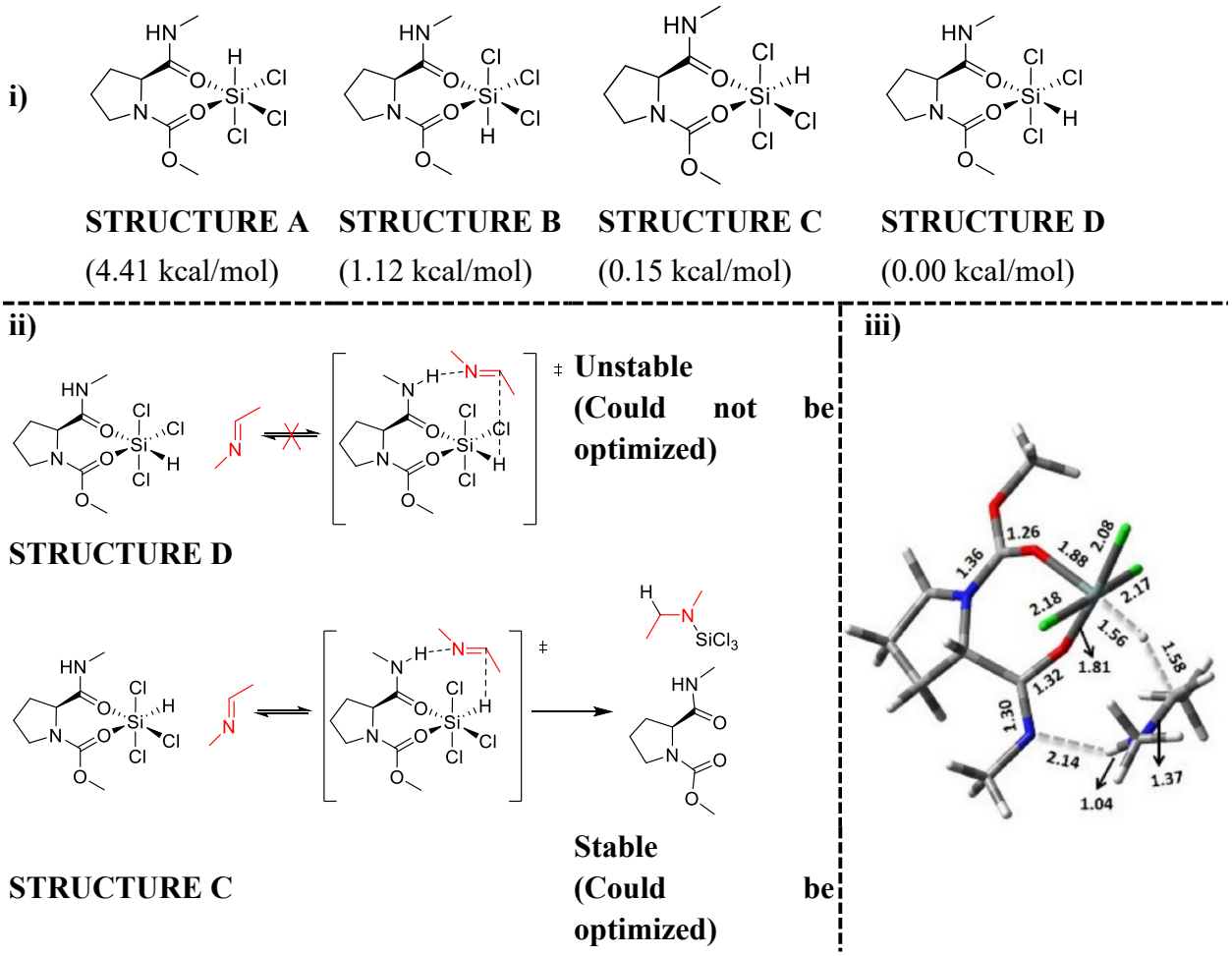
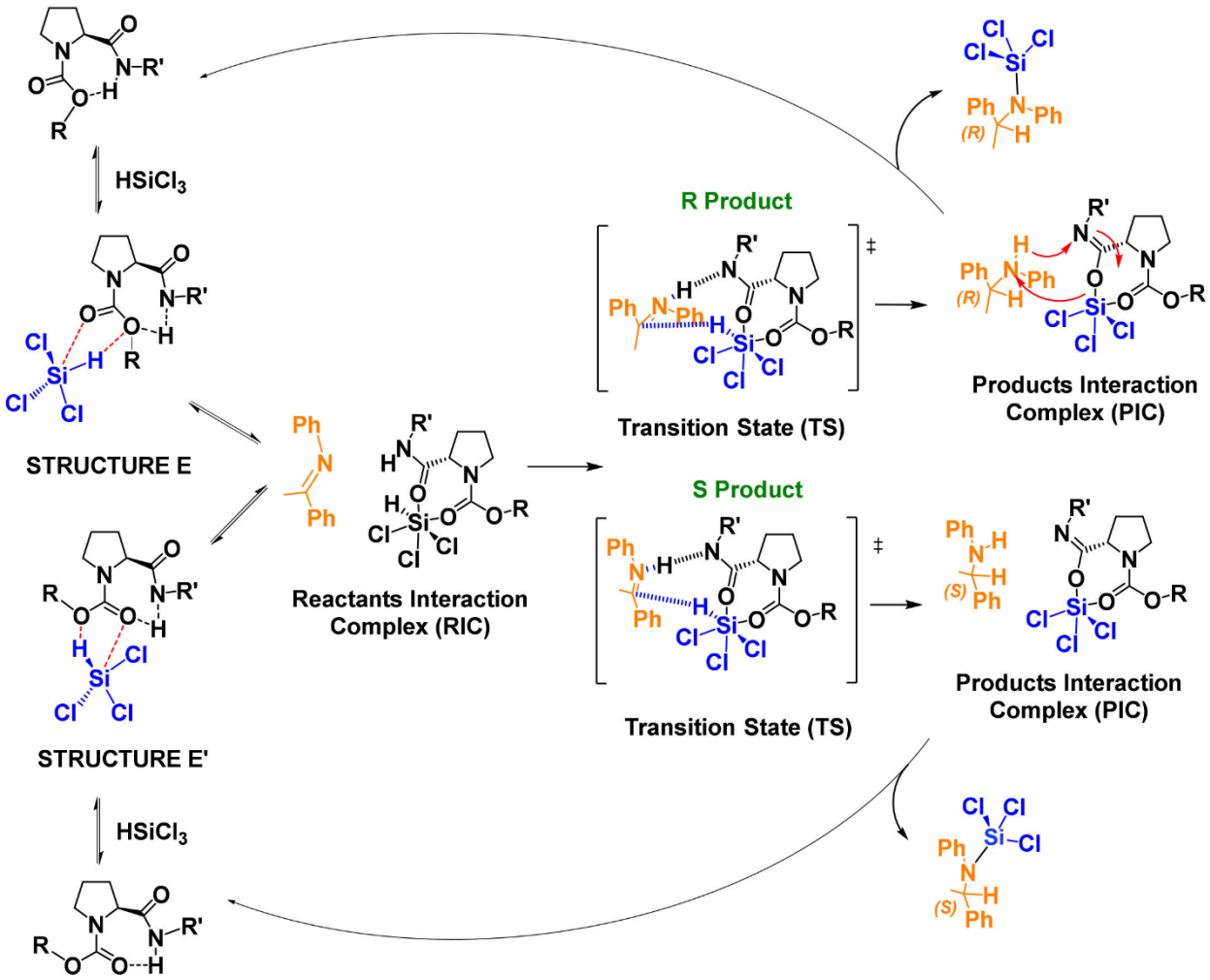



**Figure 11.** (**i**) Calculated structures and energy values for the catalyst– $HSiCl_3$ complex. (**ii**) Reaction pathways from **C** and **D** structures. (**iii**) Optimized geometry for the TS of the structure **C**. Adopted from ref.[77]

Henceforth, the comprehensive mechanistic pathway to be shown for *N*-carbamate-proline catalysts (as delineated on **Scheme 20**) entails an initial interaction between $HSiCl_3$ and the two feasible conformations of the *N*-carbamate-amide. This interaction results in the formation of weak

complexes, which subsequently evolve towards a shared Reactants Interaction Complex (RIC) in the presence of the imine. The Transition State (TS) that features a pivotal $N_{amide}\cdots NH\cdots N_{imine}$ interaction, leads to the establishment of a new amine N-H bond. Concurrently, the $Si\cdots H\cdots C_{imine}$ interaction promotes the creation of a C-H bond at the new stereogenic carbon atom of the amine. Additional supramolecular interactions, especially those involving aromatic rings, as proposed earlier,[81,82] may contribute to the stabilization of the TS and lowering the energy barrier. The TS evolves into the Products Interaction Complex (PIC), ultimately yielding the final product (the chiral amine-$SiCl_3$ complex), through a formal proton transfer from the amine to the **catalyst**-$SiCl_3$ complex. This catalytic cycle is then completed by regeneration of the catalyst.




**Scheme 20**. The general reaction mechanism for the hydrogenation of imine (orange) by $HSiCl_3$ in the presence of a catalyst – Lewis base. Copied from ref. [77]

Conclusions, made for simplified catalysts, were proven in a reasonable way for real compounds. Finally, Maciá *et al*. stated that the developed theoretical model was found to reproduce the experimental results.[77]

To date, this is the last available computational work concerning the working principles and the mechanism of reductive amination.

These computations support and validate the original proposal made by our group 20 years ago regarding the reduction of *N*-arylimines with the previously developed catalyst Kenamide **1.E**,[52] where the silicon atom is chelated by the two amide carbonyls. The central L-valine backbone with the bulky aryl substituent induces the required stereoselective reduction through the formation of a new amine N-H bond by interaction with amido NH group along with the creation of a new C-H bond (Si-H to C atom interaction) and carbon stereocenter (**Figure 12**).

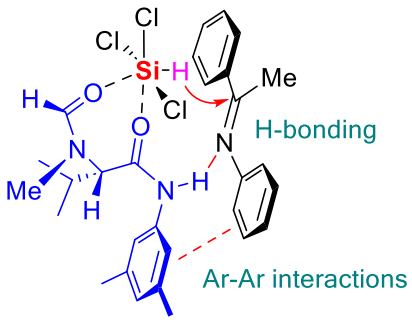



**Figure 12**. The proposed transition state (TS) in the enantioselective reduction of ketimine with help of Kenamide **1.E**.[52]

## Conclusions

To conclude this part of my thesis, the trichlorosilane-mediated reductive amination holds its significant role as the one of the most practical, well studied, environmentally friendly and non-expensive methods of a new C–N bond creation. The reaction conditions are mild, employing commonly available solvents such as toluene or dichloromethane along with dimethylformamide which serves as a Lewis base catalyst for such transformations. Moreover, a great deal of work was done by several groups, including our own, to prepare suitable chiral catalysts for further expanding of the reaction applicability area. As a rule of thumb, the reported catalysts have Lewis

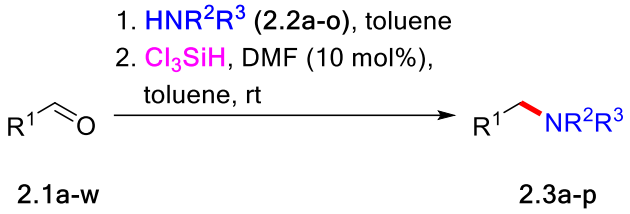
basic properties and resemble the simple DMF molecule. Employment of such catalysts allows to create new stereogenic carbon centers with excellent enantioselectivities, offering an advantage over the group of hydrides reducing agents ($NaBH_4$, $NaBH(OAc)_3$ or $NaBH_3CN$), Pd on carbon-based hydrogenation and traditional methods (Eschweiler-Clarke reaction, Leuckart-Wallach reaction) and attaining the methods based on precious metals catalysis (Ir, Rh) with complex chiral ligands. To date, there are still huge possibilities for further improvement and development of new molecules with catalytic activities as well as for exploration of the existing catalysts and expanding the limits of reductive amination reaction.

The latter point was one of aims during my doctoral study, which time I dedicated to research the scope and applicability of reductive amination for a broad range of functional groups and molecules under $HSiCl_3$-mediated reduction conditions. Results and experimental details will be covered in further chapters.

# Chapter II. Results and discussion

## Introduction

The previous work of our group[52–55] explored the $HSiCl_3$-mediated reductive amination using series of substrates, reaction conditions, ratios of reactants, solvents and catalysts. These efforts have led to the development of novel Lewis-basic organocatalysts, which represent one of the most catalyst classes in this area; two of these were commercialized by Aldrich under the names Kenamide and Sigamide. In general, these reactions proceed in toluene as a solvent of choice in two consecutive reactions. The first reaction, the imine formation, proceeds usually at room temperature, with a slight excess of amine to a carbonyl compound, and the water is absorbed by molecular sieves. These conditions allow to obtain the desired imine with mostly high yields within several hours (6-8 h). Other protocols of ketimines synthesis can also be used, especially for the less reactive substrates. The subsequent reduction can be carried out in the same flask but an optimized protocol recommends to first filter off the molecular sieves, before adding the catalyst, followed by an excess of trichlorosilane at 0 °C, and then leaving the mixture at rt overnight. Standard workup generates innocuous inorganic byproducts and the desired amines are typically obtained at high yields and enantioselectivities (≥90% *ee*). Schematically, the whole process applied to aldehydes is depicted on **Scheme 21**.




**Scheme 21**. Reductive amination of aldehydes with $Cl_3SiH$ catalyzed by DMF.

In spite of the success in asymmetric reactions, little was known about the tolerance of functional groups. It was therefore of interest to revisit the original Kobayashi's protocol,[50] now with DMF as a non-chiral catalyst rather than a stoichiometric activator (**Scheme 21**), find optimal conditions for the reductive amination (or its two-step version), and establish its scope.

Moreover, since reductive amination is very popular in industry, as highlighted in the **Introduction** part, we endeavored to extend the portfolio of aldehydes and amines to those that are particularly relevant to industrial needs, i.e., those containing various functional groups. To this end, we have selected a matrix of 18 representative aromatic, heteroaromatic, and aliphatic aldehydes with a variety of potentially reducible functional groups and an analogous matrix of 15 primary and secondary amines (**Figure 13**), which gives 270 theoretically possible combinations. Another member of the group investigated the application of this method in the synthesis of various heterocycles (*vide infra*).[83] For practical reasons, only representative combinations of aldehydes and amines (26 in total) were selected to establish the scope on a preparative scale (1 mmol and more), bearing in mind also possible solubility problems. Other sources of nucleophilic nitrogen were employed such as ammonia and various hydrazine derivatives. Several ketones were also selected for specific cases to complement the findings with aldehydes.

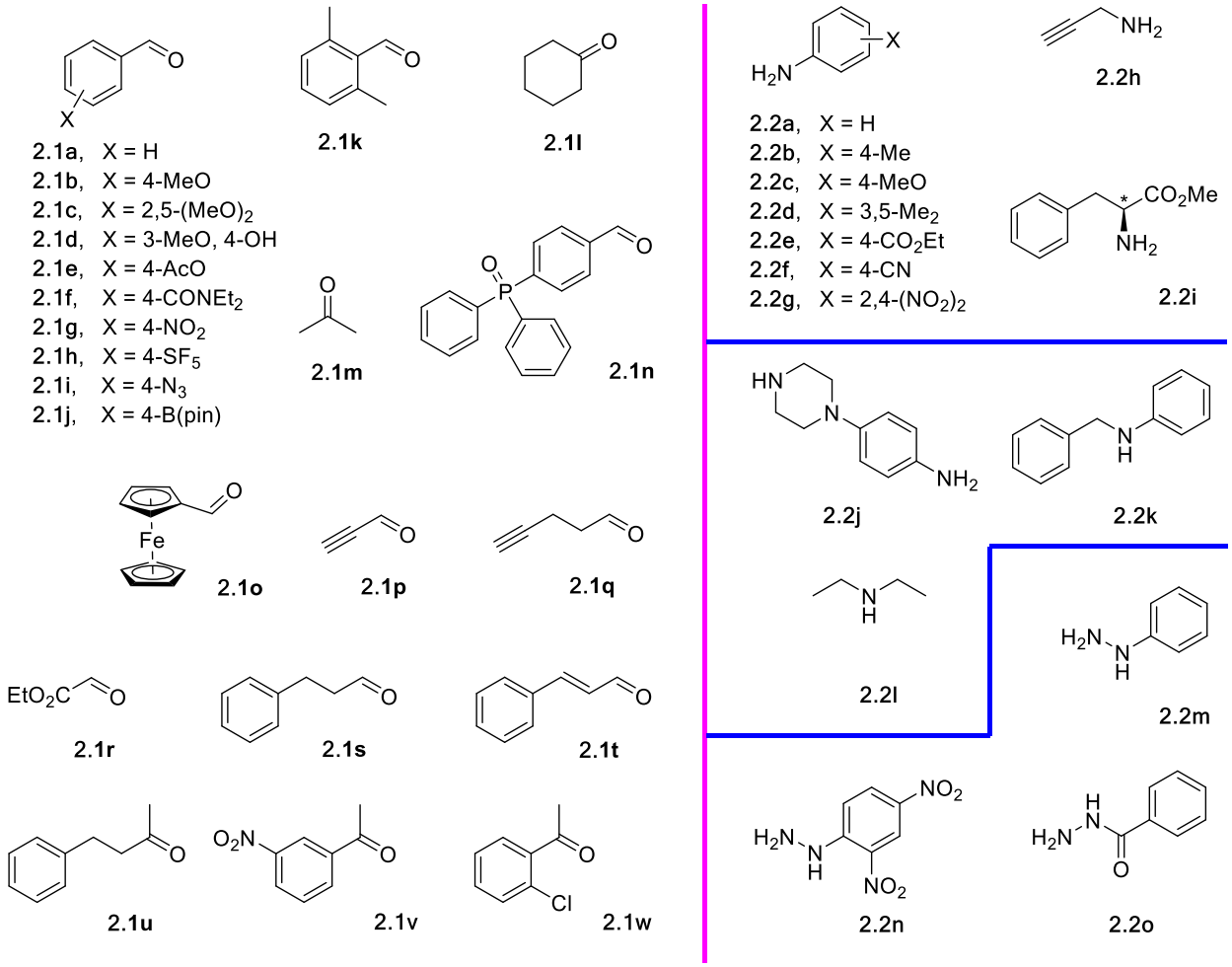



**Figure 13**. List of carbonyl compounds and amino compounds.

# Results

## Reductive amination of benzaldehyde and substituted aromatic aldehydes with primary and secondary amines

Our initial goal was to investigate the reactivity of simple benzaldehyde and its substituted congeners towards a variety of primary and secondary amines. Since asymmetric induction was not an issue in the case of aldimines, we explored the reactions with dimethylformamide as a catalyst. It should be mentioned that since other members of the group mostly carried out the experiments with aliphatic and heterocyclic amines, my research was dedicated to using series of

various aniline derivatives together with several aliphatic and unsaturated amines, mainly propargylamine. To investigate the influence of substituents and the behavior of the interfering or potentially reducible moieties, we have selected substituted benzaldehydes **2.1a**-**1j, 1k, 1n, 1o**. Additionally, a limited number of experiments were conducted with benzaldehyde itself (**2.1a**).

The imines were generated starting from the corresponding benzaldehyde and a slight excess of amine, in toluene or dichloromethane (depending on solubility of the starting compounds) and with molecular sieves as dehydrating agent. The whole reaction mixture was stirred at room temperature for several hours, usually 4-8 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). After the reaction was completed, the 2$^{nd}$ step was immediately set up without changing the solvent or evaporating the reaction mixture. The whole solution was filtered from molecular sieves into a new flask, the filtrate was charged with the catalyst (around 10 mol %) and cooled to 0 °C. The cooled reaction mixture was then treated with an excess of trichlorosilane. After the addition of reducing agent was completed, the mixture was allowed to warm to ambient temperature and stirred, usually overnight or up to 24 hours. Following the basic work-up procedure ($NaHCO_3$ saturated aqueous solution), the crude product was purified by silica gel column chromatography. This two-step sequence was successful in all instances, and the yields of the respective products (typically revolving around 90% at an almost quantitative conversion) are shown in **Figure 14**, where the new C−N bond is highlighted.

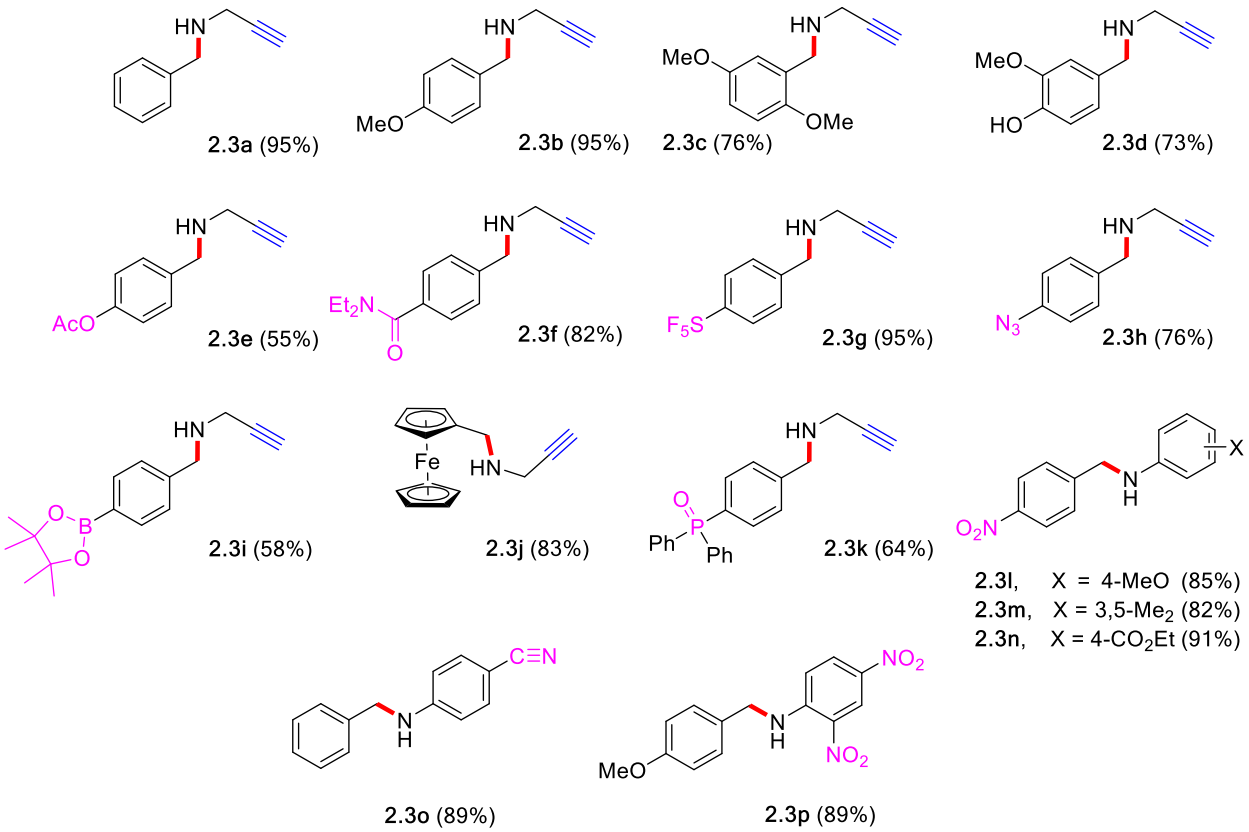



**Figure 14**. List of resulting secondary amines.

The presence of various functional groups in *ortho*-, *meta*- and *para*-positions hardly had any effect on the reductive amination, as illustrated by the high yields of resulting amines **2.3a-k**. The use of propargylamine gave the expected products with a terminal triple bond, which might find a broad application in click chemistry.

Among the functional groups remaining intact are ester, amide, nitro, nitrile, azide, $SF_5$, boronic esters and phosphine oxides, as it was demonstrated by the high yields of corresponding products **2.3a-k**. The ferrocene core of ferrocenecarboxaldehyde **2.1o** did not face any impact either, affording amine **2.3j**. The groups of especial interest are azido group, which brings an interesting applicability in click and pharmaceutical chemistry, pentafluorosulfanyl ($SF_5$) group, already discussed in the previous part, boronic esters as they open the pathway towards further functionalization *via* Suzuki coupling, and phosphine oxides, which may be present in various biologically active molecules and/or in ligands for organometallic catalysts. Among the newly prepared amines the one with a boronic ester group was obtained with a rather moderate yield. It

could be explained by the partial decomposition of a boronic ester moiety during the work-up procedure and/or during the column chromatography purification as it is prone to hydrolysis at low pH (the conversion of the starting aldehyde was quantitative, based on TLC).[84]

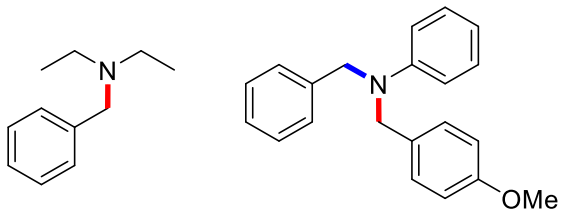
Besides successful experiments the failed attempts should also be mentioned. In one of those experiments we tried to obtain the corresponding secondary amine starting from propargylamine and 4-isothiocyanato-benzaldehyde. The latter aldehyde was synthesized according to protocols described in a 3-step procedure,[85] starting from 4-aminobenzaldehyde. However, the reaction failed to give the expected product. Instead, we isolated several compounds, two of which were identified as the corresponding thiourea and the 5-membered cyclic product of 1,3-dipolar cycloaddition. The screening of literature showed that it is a reported reaction giving a rise to N-substituted-5-methylene-1,3-thiazolidine-2-imines.[86] Using a tertiary amine might solve this problem and diminish the cyclization possibility but this was not pursued any further.

Interesting was the case of phosphine oxide benzaldehyde **2.1n**: while the P=O group is known to be reduced to the corresponding phosphine by a variety of silanes, including trichlorosilane ($HSiCl_3$) at elevated temperatures (>100 °C),[87] under our reductive amination conditions at rt it remained intact, and the resulting amine with phosphine oxide moiety **2.3k** was obtained in high yield.

Nitriles and nitro groups were also proven to stay firmly, allowing the formation of the corresponding amines **2.3o** and **2.3p** with these functional groups intact. In the case of **2.3p** even two nitro groups were present in the resulting amine.[88–92]

Eventually, the triple bond of propargylamine demonstrated an exceptional stability, showing no signs of its partial or full reduction. It was further confirmed by pent-4-ynal **2.1q** (*vide infra*). It helps us to claim the synthetic usefulness and selectivity of $HSiCl_3$-mediated reductive amination. On the other hand, the conjugated propynal **2.1p** proved problematic, as the attempted preparation of the corresponding imines was hampered by the competing 1,4-addition of the amine (in contrast to enal **2.1t**), so that further experimentation was abandoned. Another unsuccessful attempt was that with the sterically hindered 2,6-dimethyl benzaldehyde **2.1k**, due to its lack of reactivity with amines owing to the steric hindrance.

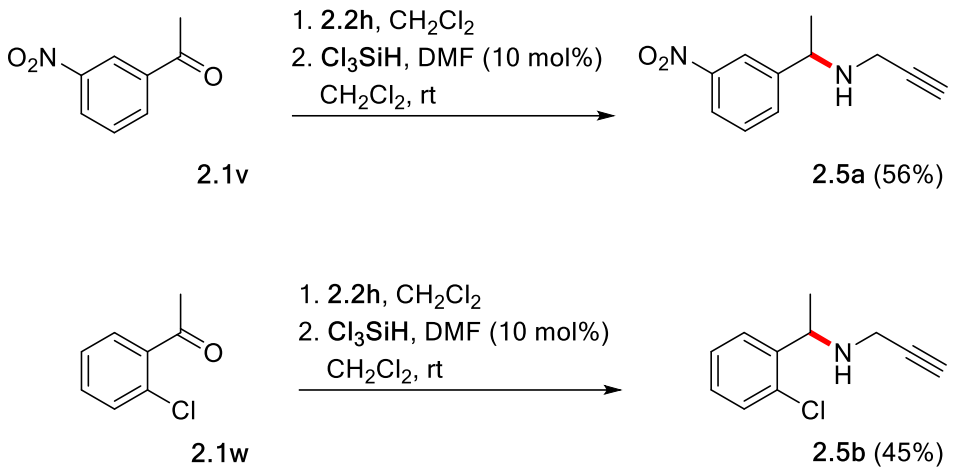
Secondary amines reacted in a similar way and produced the corresponding tertiary amines in high yields when combined with benzaldehydes. Diethylamine **2.2l** gives the corresponding tertiary amine **2.4a** in a respectable yield (92%) on reaction with benzaldehyde **2.1a**. Moreover, the secondary amine **2.2k**, resulting from the reductive amination of benzaldehyde **2.1a** with 1 equivalent of aniline **2.2a**, was used in the second alkylation, this time with anisaldehyde **2.1b**, and readily yielded the tertiary amine **2.4b** with three different moieties attached to the nitrogen atom (**Figure 15**).




2.4a (92%) 2.4b (97%)

**Figure 15**. Tertiary amines **2.4a** and **2.4b**.

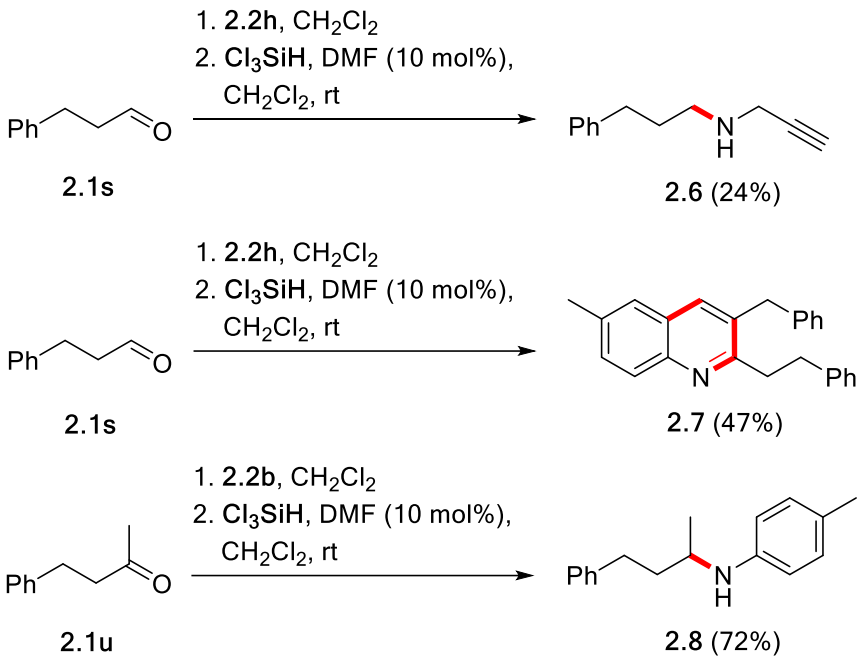
To broaden the scope to ketones, substituted acetophenones **2.1v** and **2.1w** were reacted with propargylamine **2.2h** under the same conditions – initial formation of the imine, followed by its reduction with trichlorosilane (2 equiv) in a presence of DMF (10 mol %) as a catalyst (**Scheme 22**). As expected, the formation of the corresponding imines proceeded slower than for the aldehydes and the overall conversion was lower. However, the reduction step did not show any significant effect related to the nature of a carbonyl compound. The expected racemic secondary amines **2.5a** and **2.5b** were isolated in moderate yields showing the great capability of dimethylformamide to catalyze reductive amination of ketones as for aldehydes.




**Scheme 22**. Reductive amination of substituted acetophenones.

## Enolizable Substrates

The readily enolizable aldehydes, which are also prone to generate the corresponding enamines when treated with primary or secondary amines, require special attention.[6] Therefore, dihydrocinnamyl aldehyde (**2.1s**) was chosen as a representative of this class to broaden the portfolio of our model compounds (**Scheme 23**). Amination of the latter aldehyde (**2.1s**) with propargylamine (**2.2h**) resulted in the formation of the expected amine (**2.6**) that was isolated from a complex product mixture in a rather low yield (24%), apparently due to the competing enamine formation. The same scenario is likely to be responsible for the rather low yield of pentyn-4-yl-substituted L-phenylalanine **2.10c** (*vide infra*). Standard treatment of aldehyde **2.1s** with *p*-toluidine (**2.2b**) (1 equiv), followed by reduction with $HSiCl_3$, catalyzed by DMF (10 mol %), gave rise to a mixture of several products, from which the major one, quinoline derivative **2.7** was isolated in 47% yield. Its formation obviously relies on the initial generation of an enamine intermediate, followed by an aldol reaction and subsequent attack at the aromatic ring, resulting in cyclization.[93–95]




**Scheme 23**. Reductive amination of readily enolizable substrates.

By contrast, these complications were not observed with the less readily enolizable α-substituted aldehydes, as observed by other members of the group in the case of cyclohexanecarboxaldehyde and 2-ethylbutanal, which gave the corresponding amination products in high yields. The corresponding ketone **2.1u**, which is also less prone to enamine formation, reacted readily to produce amine **2.8** in 72% yield.

The behavior of enolizable aldehydes also contrasts with that of the enolizable ketones, where enamine intervention was not observed either. Thus, ketones, such as PhCH=CHCOMe and especially β-keto esters $RCOCH(X)CO_2Et$, have been found to produce the corresponding amines on reduction with $HSiCl_3$, catalyzed by chiral congeners of DMF and related organocatalysts (exhibiting high levels of asymmetric induction) with no complication that could be expected when enamines played a role here.[55,96–99]

## Reductive Amination Resulting in the Formation of Polyalkylated Products

Most of the amines obtained above were produced from the primary amines, reacting in a 1:1 ratio to benzaldehyde (in fact, 1.05:1 ratio) and giving the secondary amines, products of monoalkylation. Double alkylation, i.e., the formation of tertiary amines from primary amines, which often accompanies the classical one-pot reductive amination mediated by $NaBH_4$ and its congeners,[100] has not been observed for $HSiCl_3$, except for the highly electrophilic *p*-nitrobenzaldehyde (**2.1g**), where minor quantities of double alkylated products were detected in several instances (*vide infra*). Therefore, it was of interest to find out whether a modification of the stoichiometry in our methodology could lead to double alkylated products, i.e., tertiary amines. We have selected a couple of representative examples, where the aldehyde-to-amine ratio was ≥ 2:1. Indeed, the one-pot reaction of 4 equivalents of benzaldehyde (**2.1a**) with 1 equivalent of amine **2.2f**, carried out in the presence of molecular sieves, followed by the reduction, produced the tertiary amine **2.9a** (85%). This result clearly demonstrates that double alkylation can be attained and that the process can be controlled by the stoichiometry in favor of either mono- or double-alkylation.

Finally, diamine **2.2j**, featuring both primary (aromatic) and secondary amino groups, was selected as a probe to unravel any selectivity. Initial experiments with 1 equivalent of *p*-nitrobenzaldehyde (**2.1g**) afforded a mixture of mono- and dialkylated products, indicating that there was no significant preference for either of the processes. On the other hand, with 3 equivalents of **2.1g**, full alkylation was attained, giving rise to the triple-alkylated product **2.9b** (**Figure 16**).

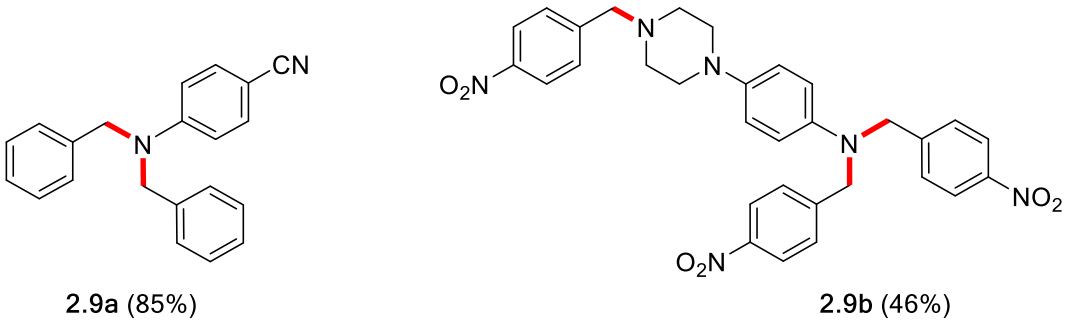
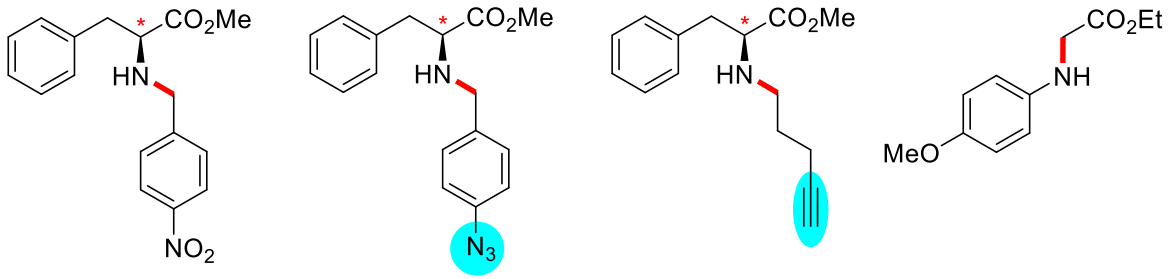



**Figure 16**. Polyalkylated products.

## Reductive Amination of Aldehydes with Amino Acids

Derivatization of amino acids is of significance for the investigation of their role in various life processes.[101] Since reductive amination has been frequently used for protein tagging,[102,103] it was of interest to briefly explore the applicability of our methodology for the preparation of *N*-alkylated amino acids, with a view of their potential incorporation into peptides or proteins.

Reductive amination of L-phenylalanine methyl ester (**2.2i**) with 1.1 equivalent of *p*-nitrobenzaldehyde (**2.1g**) was selected as a model example and found to proceed readily, giving a 5:1 mixture of the mono- and bis-alkylated products, apparently because of the enhanced reactivity of **2.1g** (compared with other aldehydes). Chromatographic separation afforded the pure monoalkylated product **2.10a** in 65% yield and with ≥96% *ee* (**Figure 17**), as revealed by chiral HPLC. The enantiopurity here and in the subsequent experiments was verified by comparison with authentic samples obtained from racemic phenylalanine. Indeed, retention of stereochemical integrity in this transformation is an important issue, since the imine intermediate (with a C=N group being generated in the α-position to the carbonyl)[104] is particularly prone to enolization and, therefore, racemization. However, under the conditions of our reaction, this does not seem to be a problem. The bisalkylation was almost entirely suppressed by using a 1.5:1 mixture of **2.2i** and **2.1g**, in which case the monoalkylated product **2.10a** was obtained again with ≥96% *ee* and with an excellent yield exceeding 92%.




**2.10a** (65%) **2.10b** (45%) **2.10c** (39%) **2.10d** (65%)

**Figure 17**. Products of reductive amination of aldehydes and amino acids with $HSiCl_3$ catalyzed by DMF.

In view of the potential of further functionalization of the amino acid derivatives by click chemistry, phenylalanine derivatives with an azido group (**2.10b**) and with a C≡C bond (**2.10c**) were then prepared in acceptable yields and high enantiopurity (≥96% *ee*) from L-phenylalanine

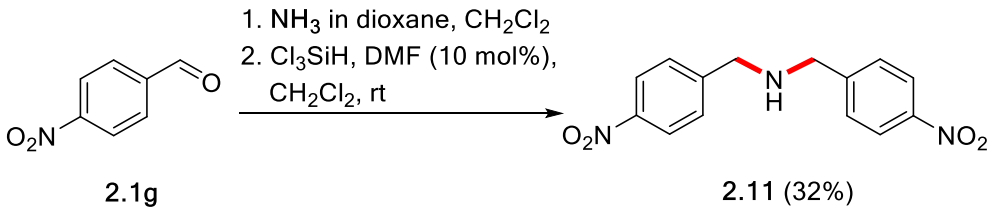
methyl ester (**2.2i**) and the respective aldehydes **2.1i** and **2.1q**. These experiments thus clearly demonstrate that the preparation of amino acid derivatives, amenable to further modification in biological environment, is a viable avenue. The rather low yield of **2.10c** apparently originates from the competing reactions of the readily enolizable aldehyde (*vide supra*).

It is worth noting that the L-phenylalanine methyl ester **2.2i** and its racemic counterpart were prepared with help of trimethylsilyl chloride (TMSCl) in methanolic solution with quantitative yields in a form of hydrochlorides. The method was reported by Li *et al*.[105]

Finally, the *N*-aryl glycine ester **2.10d** was prepared with good yield by reductive amination of ethyl gloxylate (**2.1r**) with anisidine (**2.2c**).[106]

## Ammonia

Although this study was primarily focused on the synthesis of secondary and tertiary amines from aldehydes and primary and secondary amines, respectively, it was of interest to briefly explore the feasibility of an analogous reaction using ammonia (**Scheme 24**). To this end, *p*-nitrobenzaldehyde (**2.1g**) was selected as a probe, combined with a dioxane solution of $NH_3$ (1.5 equiv). Under standard conditions, with $HSiCl_3$ (2 equiv) and DMF (10 mol %), the secondary amine **2.11** was obtained in 32% yield as the main product, together with some unreacted aldehyde and an intractable mixture of several other products. This experiment thus shows that, in principle, ammonia can extend the portfolio of this methodology, but a lot of optimization would be required.

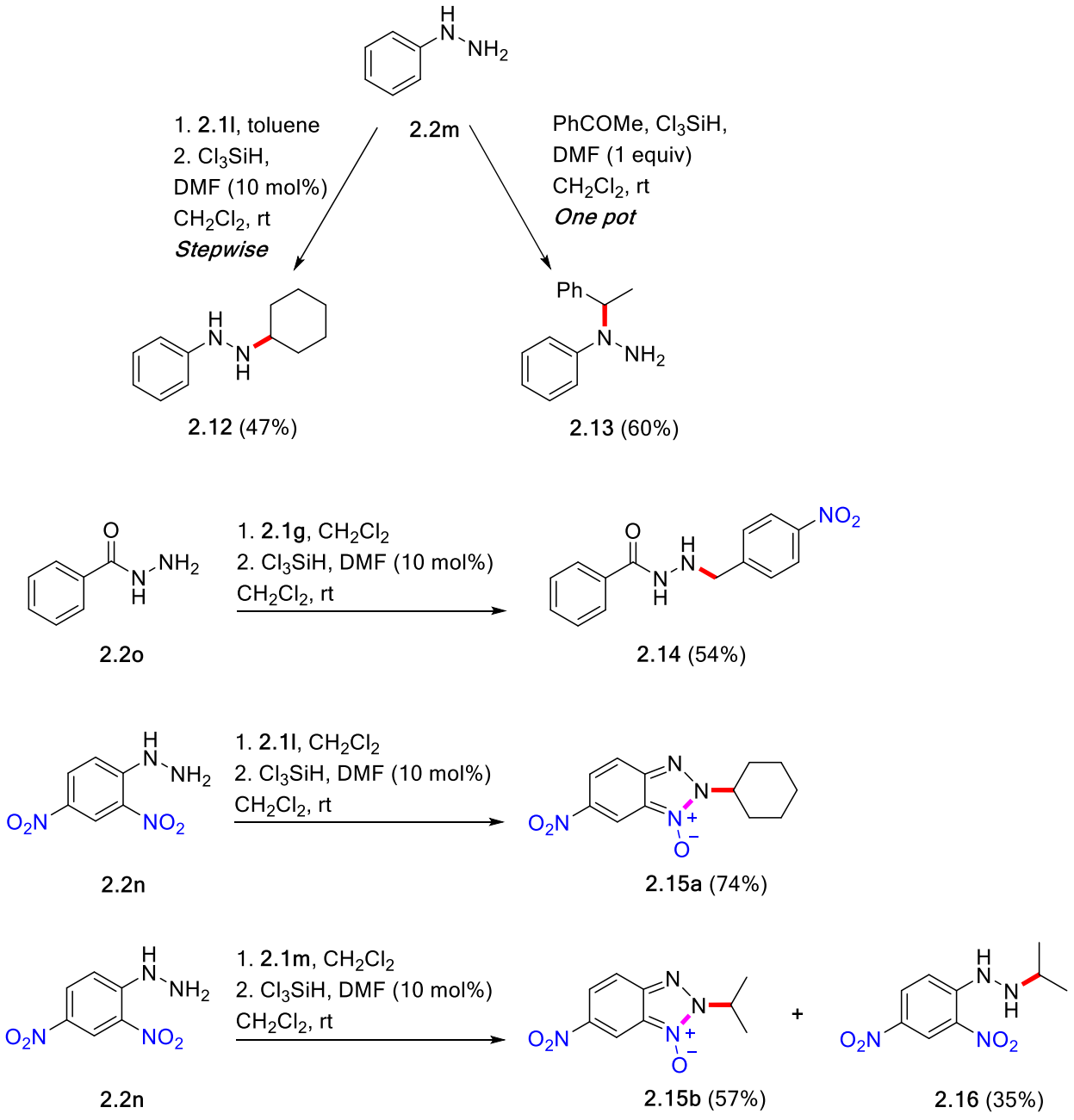



**Scheme 24**. Reductive amination using ammonia.

## Reductive Hydrazination

In view of the successful reductive amination, it was of interest to probe the analogous reductive hydrazination. To this end, phenylhydrazine (**2.2m**) and benzoic acid hydrazide (**2.2o**) were selected as representative examples (**Scheme 25**). When phenylhydrazone was first generated from its components **2.1l** and **2.2m** and then submitted to the reduction, the expected monoalkylated 1,2-disubstituted hydrazine derivative **2.12** was obtained in this two-step procedure. Interestingly, Sun *et al*. has demonstrated that when all components are mixed in one pot, as is the case of **2.2m** and acetophenone, $HSiCl_3$ apparently first coordinates the terminal nitrogen of **2.2m**, which results in the formation of the 1,1-disubstituted isomer **2.13**.[107] Hydrazide **2.2o** underwent the reaction at the unsubstituted nitrogen to afford the monoalkylated product **2.14** as expected.

An interesting reaction was observed with the once popular 2,4-dinitrophenylhydrazine (**2.2n**): The corresponding hydrazone, derived from cyclohexanone (**2.1l**), afforded the triazole *N*-oxide **2.15a** (74%) along with the expected *N*-cyclohexyl-2,4-dinitrophenylhydrazine (26%), on reduction with $HSiCl_3$, catalyzed by DMF (10 mol %), showing that while the isolated $NO_2$ is inert to the reduction (as in the case of **2.2o**), it may participate when located in the vicinity of the carbonyl/imine moiety. However, this behavior appears to be confined to the hydrazine series, since in the case of 2,4-dinitroaniline (**2.2g**) the *ortho*-$NO_2$ group remained intact (**2.1b** + **2.2g** → **2.3p**).




**Scheme 25**. Reductive amination with hydrazines as substrates.

Inspired by these results, we carried out several experiments employing the same 2,4-dinitrophenylhydrazine (**2.2n**) as a substrate and various ketones. We started from the simplest ketone, acetone **2.1m**, and after isolation and purification by column chromatography the corresponding substituted triazole *N*-oxide **2.15b** was obtained with very similar yield (74%). Then, we scaled up the method by 10 times and isolated both possible products – the major triazole

*N*-oxide **2.15b** with a slightly decreased yield (57%) and the minor 1,2-disubsituted hydrazine **2.16** in 35% yield. Moreover, we succeeded in crystallizing and growing a single crystal of triazole *N*-oxide **2.15b** suitable for XRD analysis. The ORTEP structure is presented in **Figure 18**. Additionally, we set up several experiments with more complex ketones such as camphor, *R*-(-)-carvone or acetophenone. However, these reactions were found to be unsuccessful, and the topic was not pursued further.

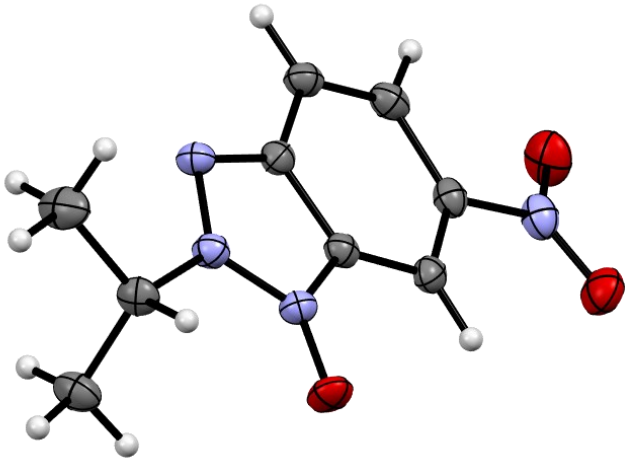
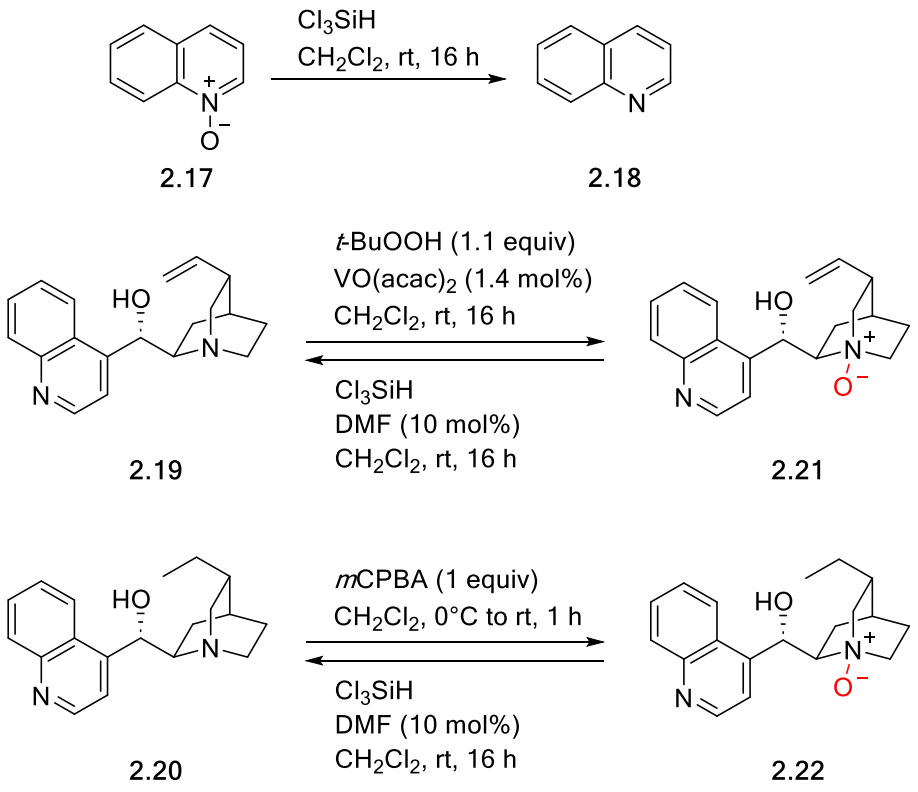


**Figure 18**. ORTEP (Mercury) diagram of **2.15b**.

## *N*-Oxide Reduction

One of the members of the group noticed that sulfoxides are reduced to sulfides.[83] Another observation was made about reduction of the *N*-oxide group during reductive amination of the *N*-oxide of picolinic aldehyde affording the corresponding amine with a pyridine core. This result suggests that $HSiCl_3$ could serve as an efficient reducing agent for *N*-oxides in general and thus broaden the portfolio of reagents available for this task,[108–110] many of which, however, may be less tolerant to functional groups. To demonstrate the preparative feasibility of this method, quinoline *N*-oxide (**2.17**) was quantitatively reduced to quinoline (**2.18**) on reaction with $HSiCl_3$, catalyzed by DMF (10 mol %) (**Scheme 26**). Since allylic trichlorosilanes $Cl_3SiCHCH=C(R)H$ are

known to be activated by Lewis bases,[111–115] especially by pyridine *N*-oxide-type catalysts, to transfer the allylic group,[116–119] it was of further interest to find whether $HSiCl_3$ itself could be activated in a similar way by the *N*-oxides. Indeed, this turned out to be the case, since quinoline *N*-oxide (**2.17**) was readily reduced even in the absence of DMF (in toluene at rt over 16 h) to give quinoline (**2.18**) in a quantitative yield. The substrate quinoline *N*-oxide can thus be regarded as a self-immolative catalyst.



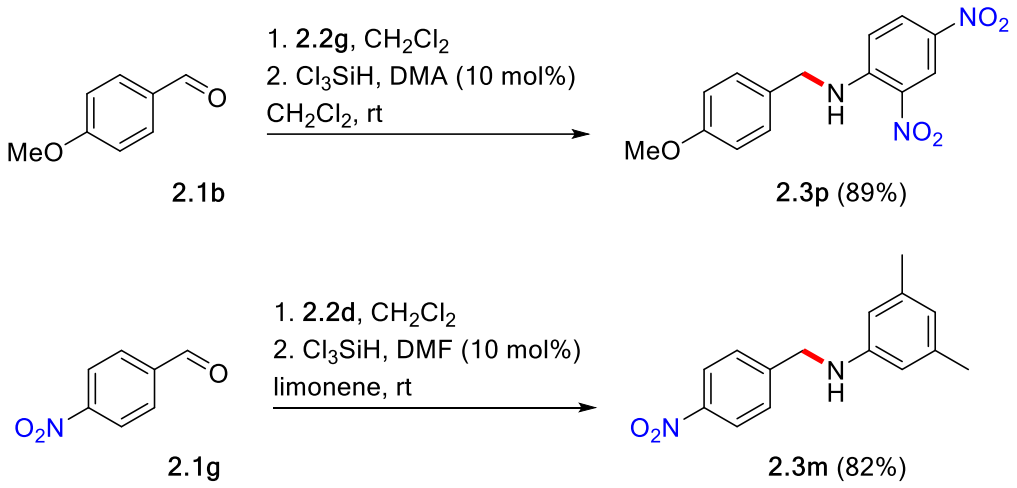

**Scheme 26**. Reduction of *N*-oxides with $HSiCl_3$.

We then addressed the question whether this reduction could be extended to *N*-oxides derived from non-aromatic tertiary amines. To this end, cinchonine (**2.19**) and dihydrocinchonine (**2.20**) were selected as representative examples with the view that *N*-oxidation would preferentially occur at the quinuclidine nitrogen. To prevent epoxidation of the vinyl group in the quinuclidine nucleus, the precautionary hydrogenation on Pd/C was performed using 1 atm of hydrogen to afford dihydrocinchonine (**2.20**) in excellent yield. The *N*-oxidation of **2.19** and **2.20** was performed in two parallel ways employing different oxidizing agents. Indeed, the required *N*-oxide (**2.21**) was readily prepared from **2.19** in a quantitative yield on the hydroxyl-directed oxidation with

*t*-BuOOH, catalyzed by $VO(acac)_2$.[120] The same *N*-oxide (**2.21**) was obtained quantitatively by oxidation of **2.19** with *meta*-chloroperbenzoic acid (*m*CPBA); interestingly, no epoxidation of the vinyl group was observed in this instance.[121] Oxidation of dihydrocinchonine **2.20** using *m*CPBA also proceeded uneventfully, affording *N*-oxide **2.22**. Reduction of **2.21** with $HSiCl_3$ (toluene, rt) turned out to be rather slow, affording a mixture of cinchonine (**2.19**) and the unreacted *N*-oxide **2.21** in ca. 2:3 ratio after 16 h, as revealed by a $^1H$ NMR spectrum of the crude mixture. The dihydrocinchonine *N*-oxide **2.22** behaved in a similar way. No much improvement was attained by carrying out the experiment in the presence of DMF (10 mol %): after 16 h at rt, the crude mixture still contained a 2:1 mixture of **2.19** and **2.21**. These experiments thus clearly demonstrate that while heteroaromatic *N*-oxides are reduced readily, this method is not suitable for their aliphatic counterparts.

## Green Conditions

In view of the potential toxicity of DMF, which can be metabolized to methyl isocyanate and thus presents an occupational hazard[122,123] and was recently banned in the EU for its wide use, it was desirable to replace it with dimethylacetamide (DMA),[107] its rather innocuous analogue. At the same time, we also attempted to replace toluene with limonene, as an environmentally even more acceptable equivalent.[124] Indeed, the reductive amination, using **2.1b** and **2.2g** and DMA as a catalyst (in $CH_2Cl_2$) proceeded well, giving rise to **2.3p** in 89% yield at full conversion. In a similar way, the reaction **2.1g** with **2.2d**, carried out in limonene (with DMF as a catalyst), exhibited full conversion, affording **2.3m** in 82% yield (**Scheme 27**). However, owing to the boiling point of limonene (176 °C), which is 66 °C higher than that of toluene, isolation of the product proved to be more cumbersome. Evaporation of this solvent under a high vacuum represents no substantial problem on a small scale, but for large scale operations it would be more convenient to isolate the resulting amine in the form of its salt. Furthermore, a number of people have developed allergy to limonene oxidation products, present, e.g., in certain soaps, washing powders, and other cosmetics, which makes this solvent rather more problematic than originally thought.




**Scheme 27**. Reductive amination in green conditions.

## Conclusions

Reductive amination of aldehydes with amines was achieved by using trichlorosilane as the stoichiometric reducing agent, catalyzed by dimethylformamide (10 mol %) or dimethylacetamide (DMA) in toluene or $CH_2Cl_2$ at room temperature in the presence of 4 Å molecular sieves (≤24 h). It is recommended that before the reduction step the molecular sieves be filtered off and $HSiCl_3$ (1.5 equiv) and DMF (10 mol %) be added to the filtrate. Aqueous workup with $NaHCO_3$, generating separable, innocuous inorganic materials (NaCl and silica), gives, in most cases, the corresponding amines in high purity. Potentially reducible functional groups, such as ester (**2.3e**,**n, 2.10d**), amide (**2.3f**), nitro groups (**2.3m-n,p, 2.9b, 2.10a, 2.11, 2.14, 2.15a-c**), nitriles (**2.3o, 2.9a**),[125] $SF_5$ (**2.3g**), and azide (**2.3h**) moieties, boronic esters (**2.3i**), double and triple bonds (**2.3a-k, 2.14c**), ferrocenyl nucleus (**2.3j**), and phosphine oxide (**2.3k**) remain intact under these conditions. On the other hand, my colleagues found that sulfoxides are reduced to the corresponding sulfides. Similarly, heteroaromatic and aliphatic *N*-oxides are reduced to the corresponding amine, whereas free carboxylic acids induce a gradual decomposition of the reagent, which generates a thick gel, difficult to handle. Conjugated aldimines undergo 1,2-reduction only, giving rise to allylic amines; no conjugate 1,4-reduction has been observed. *N*-Monoalkylation of amines has been selectively attained with a 1:1 aldehyde to amine ratio. On the other hand, with a ≥ 2:1 ratio, using the one-pot protocol, double alkylation was attained

(**2.9a**,**b**). *N*-Alkylation of α-amino acids was found to proceed essentially without racemization to afford practically enantiopure phenylalanine derivatives (**2.10a**−**c**). Derivatives **2.10b** and **2.10c** can be regarded as building blocks amenable to click chemistry and thus prone to application for biological systems. Analogous reductive hydrazination has also been attained (**2.12**, **2.14** and **2.15c**).

This reliable protocol offers significant advantages over the traditional methodologies based on borohydride reduction or catalytic hydrogenation, especially in terms of chemoselectivity. Owing to the experimental simplicity, the method is suitable for both parallel chemistry and preparative production of desired compounds on a larger scale. Solubility of some of the reacting partners appears to be the only limitation but can be attenuated by using a mixture of toluene/dichloromethane and DMF (up to 1:3) as a solvent (and catalyst) instead of pure toluene/$CH_2Cl_2$. A greener variant has also been developed, using dimethylacetamide as a catalyst and limonene as a solvent (instead of DMF and toluene).

This study was confined to aldimines, generated from aldehydes. However, it can be applied to ketones as well (even those that can be easily enolized, such as β-keto esters), as demonstrated with prochiral ketones **2.1u-w**, which are thus converted into chiral amines on the reaction catalyzed by chiral congeners of DMF and related organocatalysts.[51,52,55–59]

# Chapter III. Application of reductive amination

## Ezetimibe

### General info

Cholesterol is a crucial element in cellular physiology, and the regulation of overall cholesterol balance within the body is meticulously controlled.[126] Primary contributors to circulating levels of cholesterol in plasma encompass external cholesterol absorbed through the gastrointestinal tract and internally synthesized cholesterol, primarily originating in the liver. The malfunctioning of cholesterol regulation system may lead to dyslipidemia. Dyslipidemia (a metabolic disorder characterized by abnormally high or low levels of any or all lipids or lipoproteins in the blood) is widely recognized as a principal risk factor for atherosclerotic cardiovascular disease (CVD), with substantial evidence supporting hypercholesterolemia as a risk factor for ischemic cerebrovascular events.[127]

A recent survey conducted by the American Heart Association (AHA) revealed a notable deficiency in the understanding of high cholesterol as a significant risk factor for CVD, even among individuals at the highest risk for heart disease and stroke.[128] Moreover, individuals/patients often lack a comprehensive understanding that elevated levels of circulating cholesterol can result from increased cholesterol absorption, heightened cholesterol synthesis, or both. There exists a significant gap in comprehending the reciprocal contributions of these two pathways to overall cholesterol balance within the body.[129]

Cardiovascular diseases persist as the primary cause of mortality in the US and other "Western" societies, despite the success of statin drugs in reducing LDL (low-density lipoprotein) cholesterol. Consequently, identifying novel targets for pharmaceutical intervention aimed at lowering CVD risk has remained a high-priority focus of research spanning decades. Although statins primarily reduce LDL by diminishing endogenous cholesterol synthesis, an alternative strategy for preventing excessive cholesterol accumulation involves reducing the absorption of dietary cholesterol. This approach also prevents the reabsorption of biliary cholesterol, a substantial contributor to overall cholesterol metabolism, as a significant portion of biliary cholesterol

undergoes recirculation in the intestine. Several reviews on mechanisms of cholesterol and lipid absorption were published.[130–133]

While the liver has traditionally been viewed as the principal regulatory point for maintaining overall cholesterol balance within the body, recent years have seen a shift in focus towards the intestine, where cholesterol absorption occurs.[126,134] However, the biological mechanisms governing cholesterol homeostatic pathways in the intestine remain a subject of ongoing debate. Additionally, the extent of dietary cholesterol absorption influences endogenous cholesterol biosynthesis in the liver. This dietary impact on plasma cholesterol levels exhibits considerable variability in the general population, with genetic factors might be contributing to the wide interindividual variation in cholesterol absorption.[130] In 2009 Davis and Altmann[135] reported absorption efficiency for dietary cholesterol ranging from 29% to 80% among humans.

The quest for identification of intestinal cholesterol transporters has extended over many years, initially marked by a debate on whether the process is facilitated by proteins or not [136]. The pancreatic enzyme carboxyl ester lipase (CEL, also known as cholesterol esterase) was initially considered to be crucial to this process.[137] Substantial resources were dedicated by various companies to developing and testing compounds to inhibit CEL, yielding mixed results.[138] However, these efforts were abandoned in the mid-1990s after studies with gene-knockout mice demonstrated that the enzyme was significant solely for the absorption of cholesteryl ester, a minor component of dietary cholesterol present at very low levels in bile.[139,140] Intriguingly, CEL is also present in the liver, where it has been shown to impact HDL (high-density lipoprotein) metabolism.[141] Thus, CEL may ultimately play a crucial role in cholesterol metabolism and could potentially serve as a valuable drug target for the treatment of CVD.

## Cholesterol absorption and its factors

The absorption process of cholesterol, whether from dietary or biliary sources, involves multiple sequential steps, including emulsification, hydrolysis (of dietary esterified cholesterol) by lipases, solubilization in micelles, and uptake across the apical membrane of enterocytes.[142] Subsequent to absorption, cholesterol is mobilized into chylomicrons for secretion into the lymph and blood through the basolateral membrane of enterocytes.[143]

The biosynthesis of cholesterol in the liver is notably responsive to dietary cholesterol from the intestine, primarily through the chylomicron-remnant pathway. Intestinal cholesterol absorption is a complex process involving various determinants, such as transporters, converting and regulatory enzymes, and lipoproteins.[142]

Crucial proteins facilitating the transport of cholesterol/sterols across the intestinal lining encompass Niemann-Pick C1-like 1 (NPC1L1) protein, scavenger receptor BeI (SR-BI), fatty acid translocase CD36, adenosine-triphosphate (ATP)-binding cassette A1 (ABCA1), and the heterodimer adenosine-triphosphate (ATP)-binding cassette G5 and G8 (ABCG5/G8), responsible for mediating cholesterol efflux back to the intestinal lumen to limit cholesterol absorption.[130]

Masson *et al*.[144] investigated the distribution profiles of transporter proteins involved in cholesterol absorption along the human intestinal tract and identified the highest levels in the ileum for ABCA1, ABCG8, NPC1L1, and CD36, suggesting a significant role of the ileum in transporter-mediated cholesterol uptake.

Intestinal acyl-CoA:cholesterol acyltransferase (ACAT-2), also present in the liver, esterifies free cholesterol with palmitic or oleic acid. Early on, ACAT-2 was considered a potential target for inhibiting cholesterol absorption due to the esterification of most cholesterol in chylomicrons before secretion by enterocytes.[145,146] Similar to CEL, inhibitors of ACAT were developed and tested with mixed outcomes.[138,147] However, the significance of ACAT-2 was later confirmed by studies on gene-knockout mice, showing markedly reduced cholesterol absorption and atherosclerosis when fed a Western diet.[148] Progress in developing effective ACAT inhibitors has been slow, partly due to concerns about potential systemic effects resulting from the inhibition of the more widely expressed ACAT-1.[149] In spite of these challenges and mixed results in animal and clinical trials, interest persists in developing ACAT inhibitors, especially those selectively targeting ACAT-2.[150]

In 1997, Schering-Plough reported a significant inhibition of cholesterol absorption by a compound later named Ezetimibe (**Figure 19**). This compound was developed through the modification of known ACAT inhibitors, aiming to generate novel compounds with improved pharmacodynamics and pharmacokinetics.[151] Intensive structural optimization, guided by structure-activity relationship (SAR) studies and identification of its sites of metabolism, led to the final derivative (**Ezetimibe**), exhibiting a 50-fold increase in activity compared to the parent

β-lactam **SCH 48461**. The incorporation of fluorine atoms, known for blocking sites of metabolism, contributed to the improvement of pharmacokinetic and pharmacodynamic profiles. The fluorine was chosen because of its small size and oxidation-deactivating effect to halt P450-mediated aromatic hydroxylation.

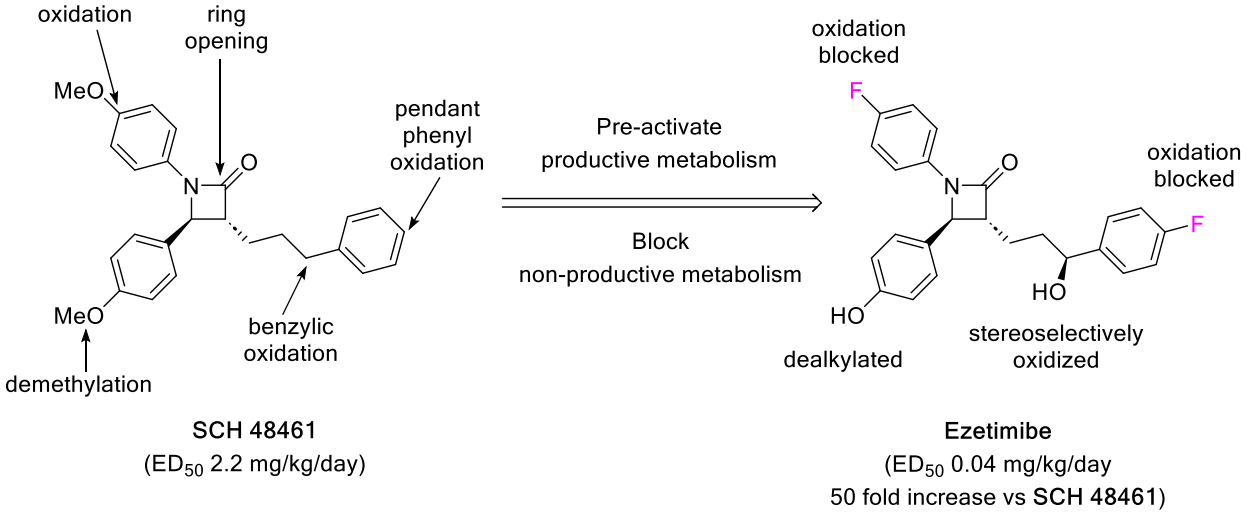



**Figure 19**. Structures of SCH 48461 and Ezetimibe.

Notably, while Ezetimibe effectively blocked absorption by up to 90%, it no longer acted as an effective ACAT inhibitor.[151] Subsequent studies utilizing database mining and gene-knockout mice identified NPC1L1 as the essential protein for cholesterol absorption and the likely target of Ezetimibe.[152,153] The development of Ezetimibe and the identification of its putative target gene marked significant breakthroughs in research on cholesterol and lipoprotein metabolism, as well as in the treatment of hypercholesterolemia and CVD. Ezetimibe (Zetia™) has gained widespread clinical use, particularly for patients with poor response to statins or intolerance to their side effects.[154]

## NPC1L1 in Cholesterol Absorption

The identification of NPC1L1 significantly contributed not only to the comprehension of intestinal cholesterol absorption but also to the understanding of overall cholesterol metabolism.[143] Prior to the discovery of Ezetimibe, an inhibitor of intestinal cholesterol absorption that reduces plasma LDL-cholesterol (LDL-C), the mechanism for cholesterol transport by an apically localized sterol

transporter was believed to be a passive diffusion. Altmann *et al*.[152] and Davis *et al*.[155] showed that NPC1L1 is a part of the ezetimibe-sensitive pathway, and that cholesterol uptake is a protein-mediated process.

NPC1L1 facilitates the cellular uptake of various sterols but exhibits a lower affinity for noncholesterol sterols (NCSs) such as plant sterols (PS) compared to cholesterol.[156] Moreover, this protein appears to have evolved at the apical membrane of enterocytes (and canalicular membrane of hepatocytes) to mediate cholesterol uptake, thereby protecting the body against fecal and biliary loss of cholesterol.[157] NPC1L1-dependent sterol uptake appears to be a clathrin-mediated endocytic process regulated by cellular cholesterol content.[143,158]

The study by Zhang *et al*.[159] revealed that NPC1L1 senses cholesterol through direct binding by its N-terminal domain. Subsequently, cholesterol may be transferred to the plasma membrane to form the NPC1L1-cholesterol membrane microdomain, which undergoes clathrin-mediated internalization/endocytosis. This process is followed by vesicle trafficking toward the endoplasmic reticulum (ER) for selective esterification via acyl-CoA cholesterol acyl transferase 2 (ACAT2), an ER membrane-localized enzyme. When intracellular cholesterol levels are low, NPC1L1 is recycled back to the proximity of the brush border, targeted for cholesterol absorption[156] (see **Figure 20**).

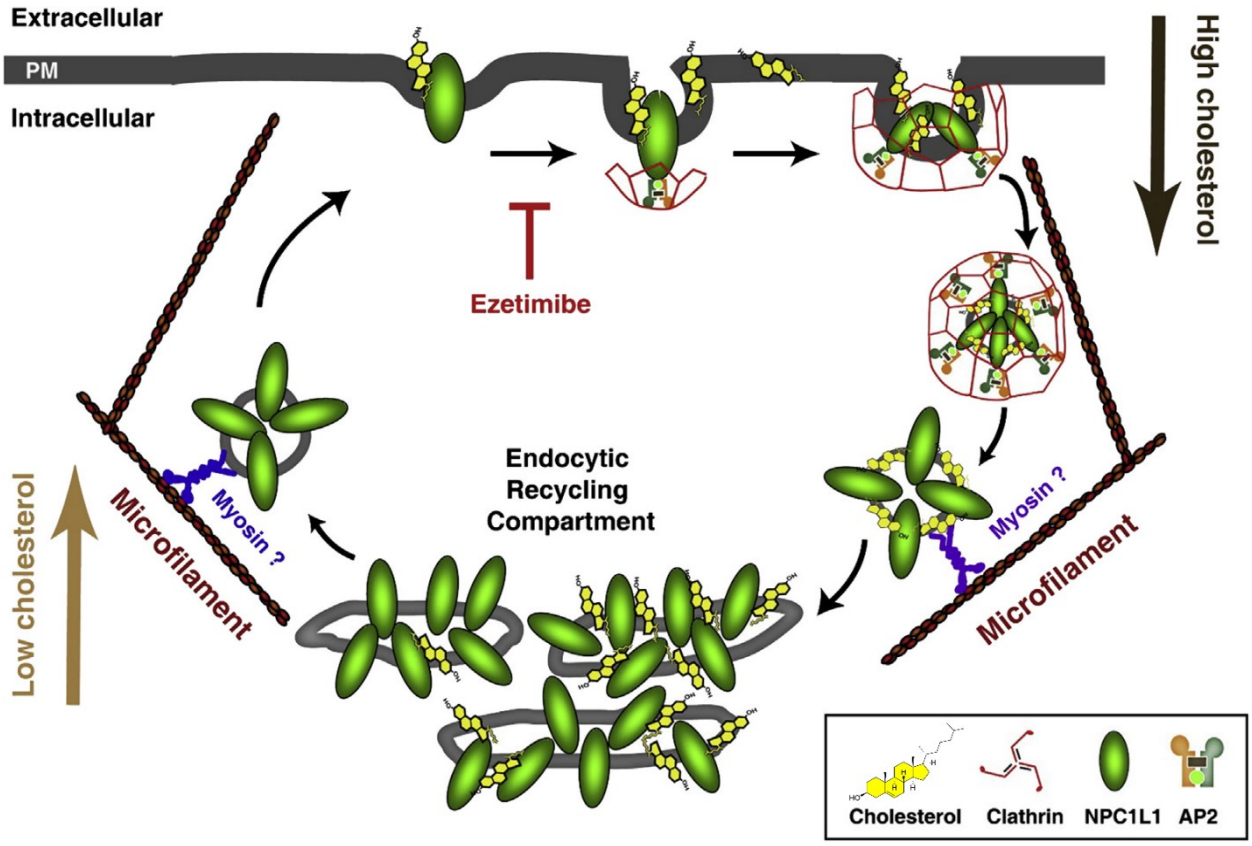



**Figure 20**. A model for NCP1L1-mediated cholesterol uptake. From Ref.[156]

The specificity of cholesterol binding may explain, at a molecular level, the selectivity of cholesterol absorption in the intestine. NPC1L1 competently mediates the absorbance of cholesterol but no other sterols.[156] Moreover, Zhang *et al*.[159] demonstrated that oxysterols (25- and 27-hydroxycholesterols) may be involved in regulating cholesterol uptake by competing with cholesterol for binding.

Accumulating evidence suggests that NPC1L1-dependent intestinal cholesterol absorption may be implicated in metabolic diseases, including insulin resistance, diabetes, and obesity, in addition to atherosclerotic coronary heart disease.[143]

A short statement by the Royal Pharmaceutical Society about Ezetimibe, published in British National Formulary 84, 2023[160], is cited below:

*CARDIOVASCULAR DISEASE PREVENTION*

Recommendations on cardiovascular disease (CVD) prevention are from the *National Institute for Health and Care Excellence (NICE)—Cardiovascular disease: risk assessment and reduction, including lipid modification guideline (CG181, 2016)*, and *Scottish Intercollegiate Guidelines Network (SIGN)—Risk estimation and the prevention of cardiovascular disease guideline (SIGN 149, 2017)*. *SIGN 149* uses strategies outlined by the *Joint British Society (JBS)—Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (2014)*.

All patients at any risk of CVD should be advised to make lifestyle modifications that may include beneficial changes to diet (such as increasing fruit and vegetable consumption, reducing saturated fat and dietary salt intake), increasing physical exercise, weight management, reducing alcohol consumption, and smoking cessation. An annual review should be considered to discuss lifestyle modification, medication adherence and risk factors. The frequency of review may be tailored to the individual.

Further preventative measures with drug treatment should be taken in individuals with a high risk of developing CVD (primary prevention), and to prevent recurrence of events in those with established CVD (secondary prevention).

SIGN (2017) recommends that ezetimibe and bile acid sequestrants such as colestyramine and colestipol hydrochloride only be considered for primary prevention in patients with an elevated cardiovascular risk in whom statin therapy is contra-indicated, and in patients with familial hypercholesterolaemia. However, NICE (2016) recommend that ezetimibe be considered for primary hypercholesterolaemia in line with National funding/access decisions for ezetimibe, and do not recommend bile acid sequestrants.

## Conclusion

Presently, Ezetimibe is accessible in the form of a generic pharmaceutical. In 2021, it ranked as the 92$^{nd}$ most frequently prescribed drug in the United States, with a prescription count exceeding

7.5 million.[161] As the expiration of patents approaches for various statins (and has already occurred for Ezetimibe), main pharmaceutical companies are actively exploring novel targets and compounds aimed at lowering plasma cholesterol levels and mitigating cardiovascular disease risk. Compounds bearing resemblance to Ezetimibe in both mechanism of action and pharmacokinetics are particularly attractive. Ezetimibe undergoes glucuronidation in the intestine (and liver), enhancing its effectiveness in lowering cholesterol absorption. This enhancement is attributed, at least in part, to the high affinity of the glucuronidated form for the intestinal brush border and its limited reabsorption following the initial pass through the enterohepatic circulation.[151] Consequently, there is a preference for compounds that exert their effects in the intestine and either remain unabsorbed, accumulate at the site of action, or demonstrate substantial efficacy at low systemic concentrations. This preference arises from the reduced risk of off-target effects, especially in cases where absorption does not occur.

## Ezetimibe synthesis

The potent biological activity, non-obvious structure and the presence of 3 stereocenters inspired the chemical community to seek ways to optimally and efficiently synthesize the Ezetimibe molecule. The existing methods towards Ezetimibe and its close analogues can be classified into several main types. They are depicted in **Figure 21**, on a network graph showing Ezetimibe and various synthetic routes with the key structures/intermediates and references.

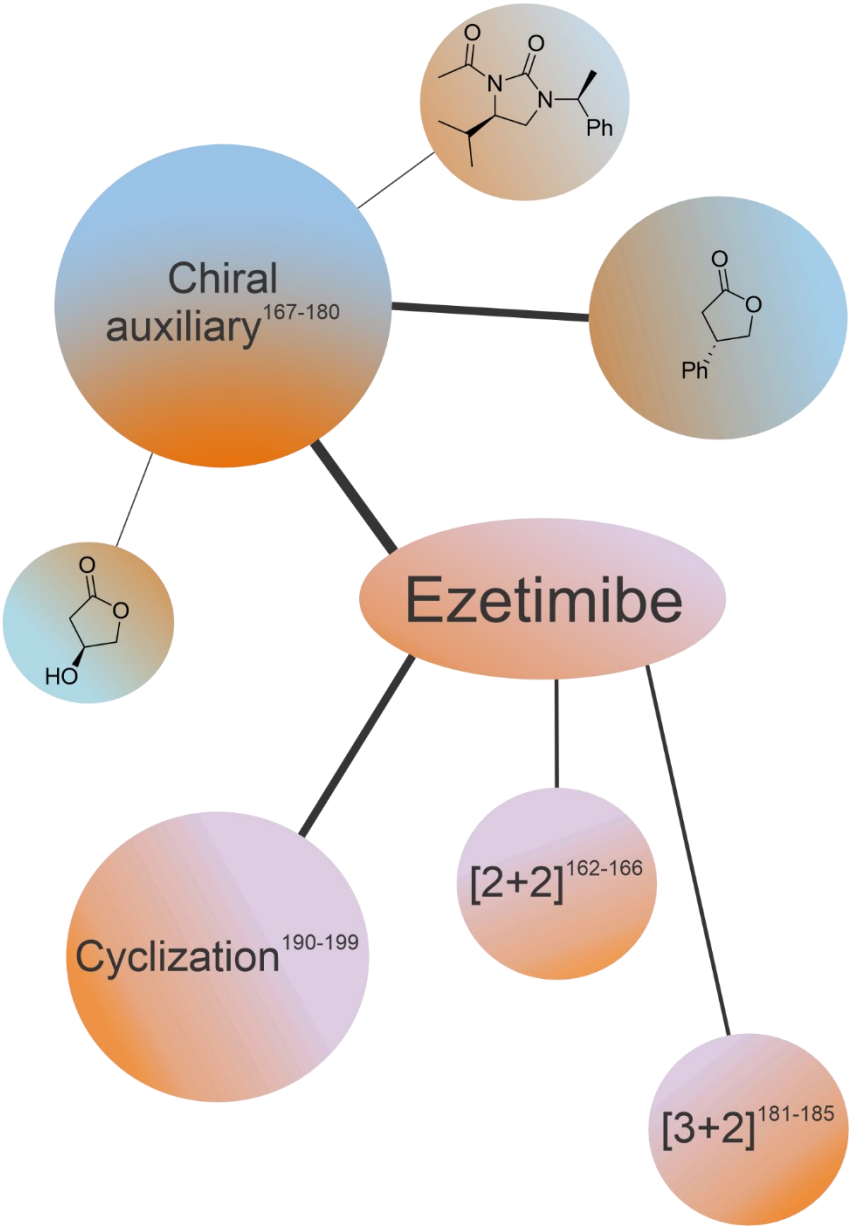
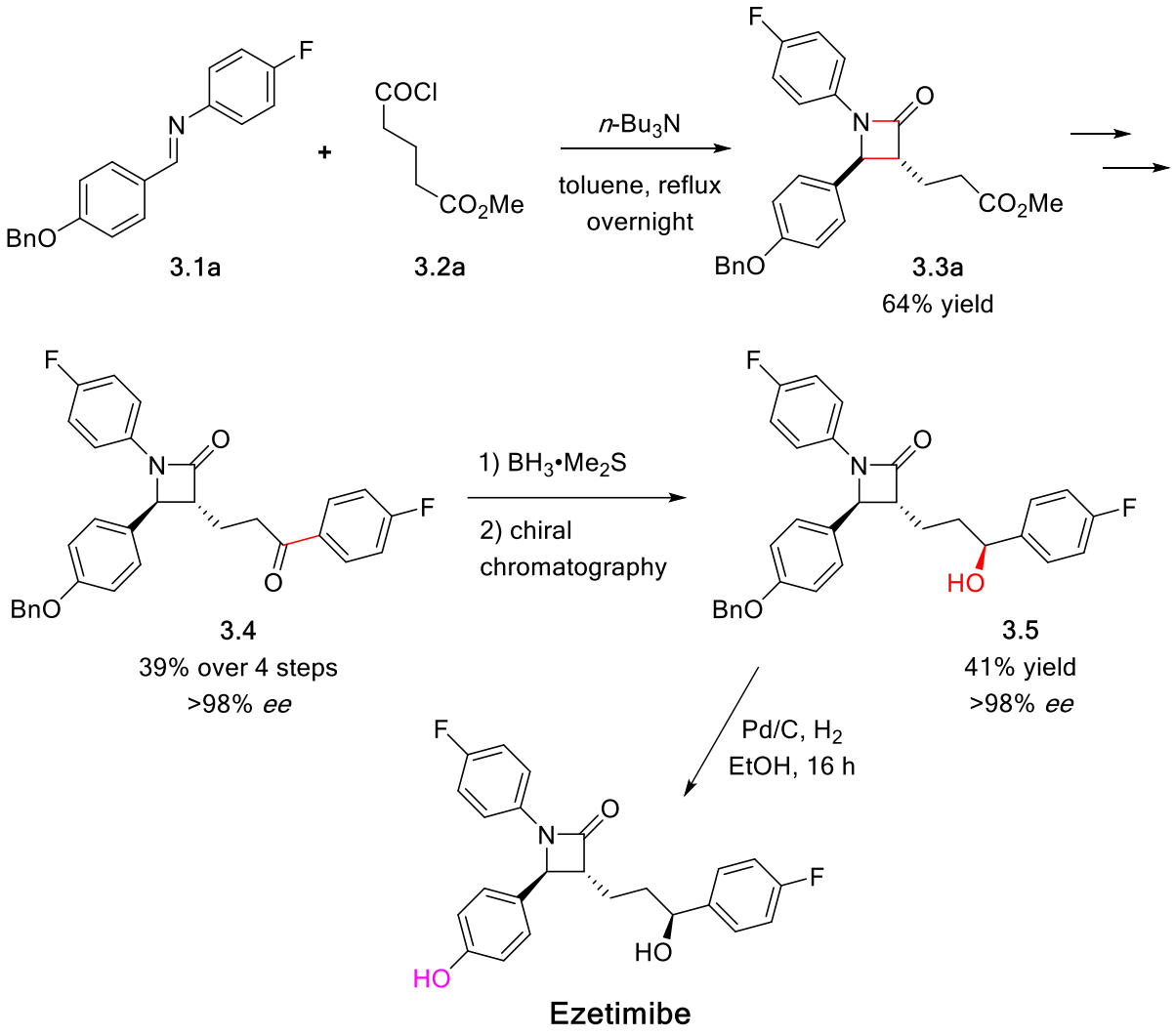



**Figure 21**. Ezetimibe and synthetic ways towards it.

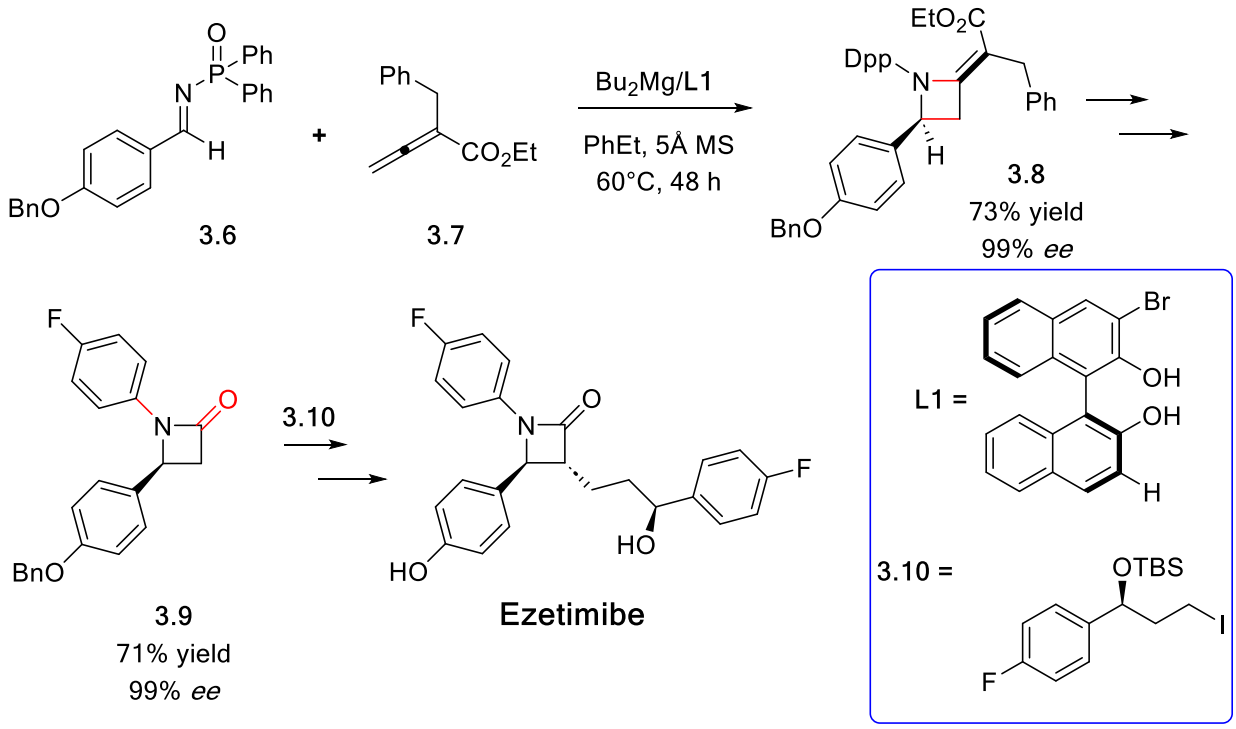
Historically, the first described method was the Staudinger-type synthesis which is a non-photochemical [2+2] cycloaddition between an imine and a ketene[162] though the base of these results has been built a few years before.[163] In the 1996 article the researchers from the Schering-Plough research institute described the synthesis of SCH 48461-(-) employing [2+2] cycloaddition method and its advantages in comparison with a previously published enolate-imine way[164,165] which gives a mixture of isomers and necessity to isolate the major *trans* isomer either by chromatography or crystallization. Back to the Ezetimibe synthesis,[162] the corresponding ketene was synthesized *in situ* from the acyl chloride **3.2a** in the presence of *n*-$Bu_3N$. As described, the cyclization works well in quite mild conditions and gives the expected β-lactam **3.3a** in good yield but as a racemate. The imine counterpart **3.1a** for [2+2] cyclization was synthesized using common azeotropic removal of water from the boiling mixture of *p*-fluoroaniline and the corresponding benzaldehyde. After chiral chromatography resolution the side chain of (3*R*,4*S*)-**3.3a** was modified in a couple of steps allowing the acyl chloride which was effectively coupled with the *para*-substituted arylzinc moiety under Negishi conditions ($Pd(PPh_3)_4$, THF). The resulting substituted β-lactam **3.4** with a ketone moiety was further reduced using Corey-Itsuno reaction ($BH_3$•$Me_2S$, BMS) followed by another chiral chromatography affording the desired (3'*S*)-diastereoisomer **3.5**. The last step was debenzylation of **3.5** with hydrogenolysis by Pd/C at high pressure (60 atm), which led to the desired Ezetimibe (**Scheme 28**).




**Scheme 28**. [2+2] synthesis of Ezetimibe according to a publication by Rosenblum *et al*.[162]

Interestingly, the [2+2] cyclization approach did not acquire much attention; instead, other pathways were sought (*vide infra*). However, in 2023 Wang *et al*. released an appealing work with a novel [2+2] route to Ezetimibe.[166] The key step here relies on an enantioselective [2+2] cyclization reaction between diphenylphosphinoyl (DPP)-imines and α-branched allenoates, affording chiral azetidines with high enantioselectivity. The reaction is catalysed by *in situ* generated Mg(II) complex generated from dibutylmagnesium and the monobromo-substituted BINOL ligand **L1**. With the highly enantioenriched azetidine **3.8** (73% yield, 99% *ee*) in hands, the authors converted it in 3 steps into the unsubstituted β-lactam **3.9** with retention of the stereochemical integrity. The authors indicated that latter lactam might be transformed into the

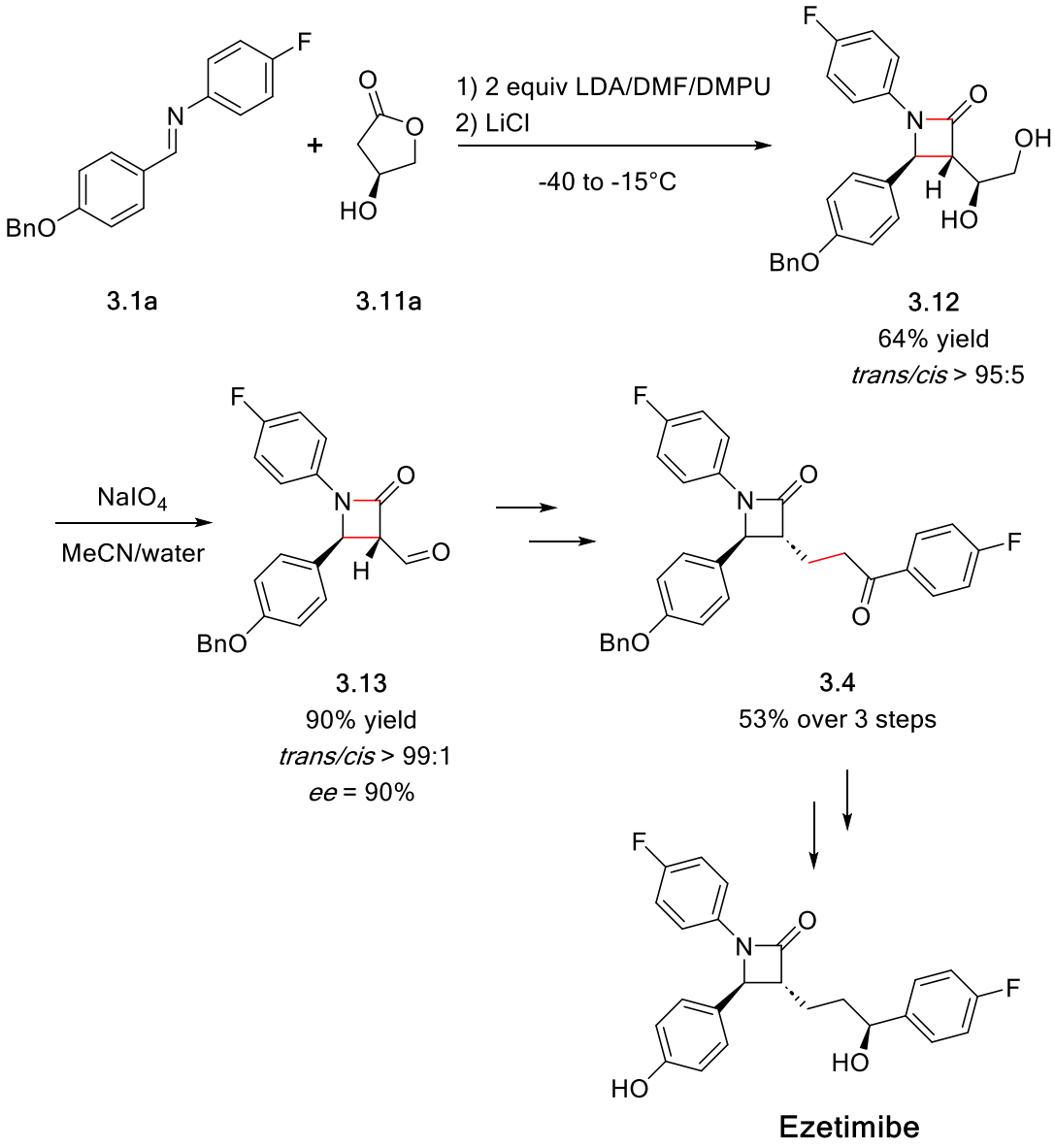
target Ezetimibe using the side chain precursor **3.10**, but did not perform the total synthesis (**Scheme 29**).




**Scheme 29**. Synthesis of a key intermediate **3.2.G** and proposed last steps by Wang *et al.*[166]

The next (and the largest) group of Ezetimibe syntheses is standing for using chiral auxiliaries. Based on the published data, the story started by the 1999 report,[167] in which the Schering-Plough group continued their colleagues' huge input (*vide supra*) and developed a novel method for the Ezetimibe synthesis. The novelty consists of the use of chiral (3)-3-hydroxy-γ-butyrolactone **3.11a**, which induced the formation of the C3' chiral center. According to this protocol, the easily available hydroxy-γ-lactone **3.11a** is treated with 2 equivalents of LDA forming the corresponding enolate which then reacts with the previously synthesized imine **3.1a** giving the expected product **3.12** with high *trans*/*cis* ratio (> 19:1). Subsequent transformations include the $NaIO_4$-mediated cleavage of a diol **3.12** forming an aldehyde **3.13**, followed by Mukaiyama aldol reaction with the enolate of 4-fluoroacetophenone. Dehydration of the arising alcohol, followed by selective hydrogenation of the double bond over Wilkinson's catalyst afforded the previously discussed ketone **3.4**,[162] which was reduced using the oxazaborolidine (CBS) catalyst, instead of the previously employed Corey-Itsuno conditions (**Scheme 30**). The chiral catalyst allowed to induce

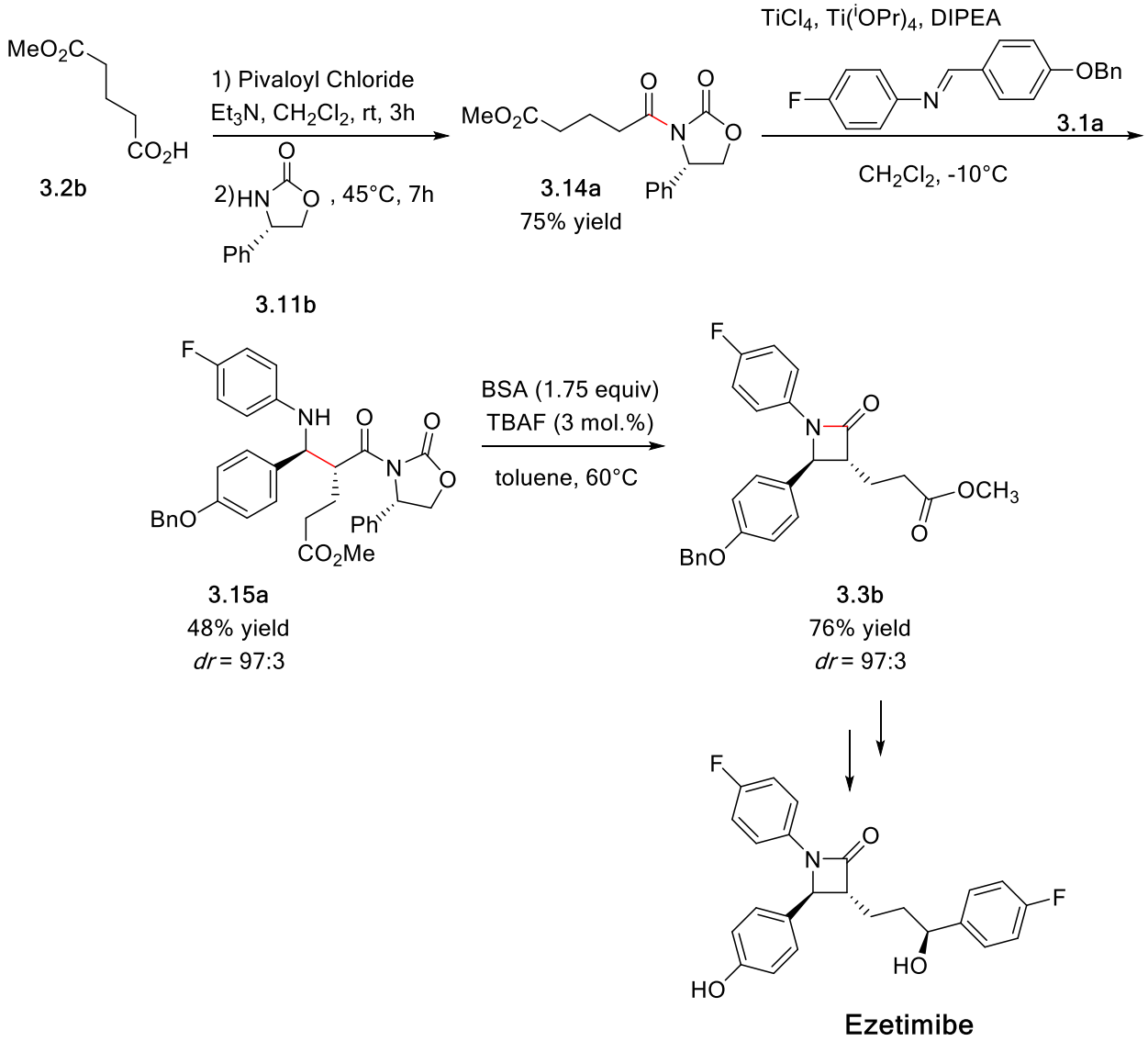
a new asymmetric center and omit the chiral chromatography separation step. Debenzylation is proceeded *via* hydrogenation over Pd/C and yielded desired Ezetimibe with a good yield and enantiopurity. This work introduced a wide practice to use chiral auxiliaries in future publications concerning Ezetimibe and its synthesis.




**Scheme 30**. Ezetimibe synthesis by means of chiral lactone in accordance with Wu.[167]

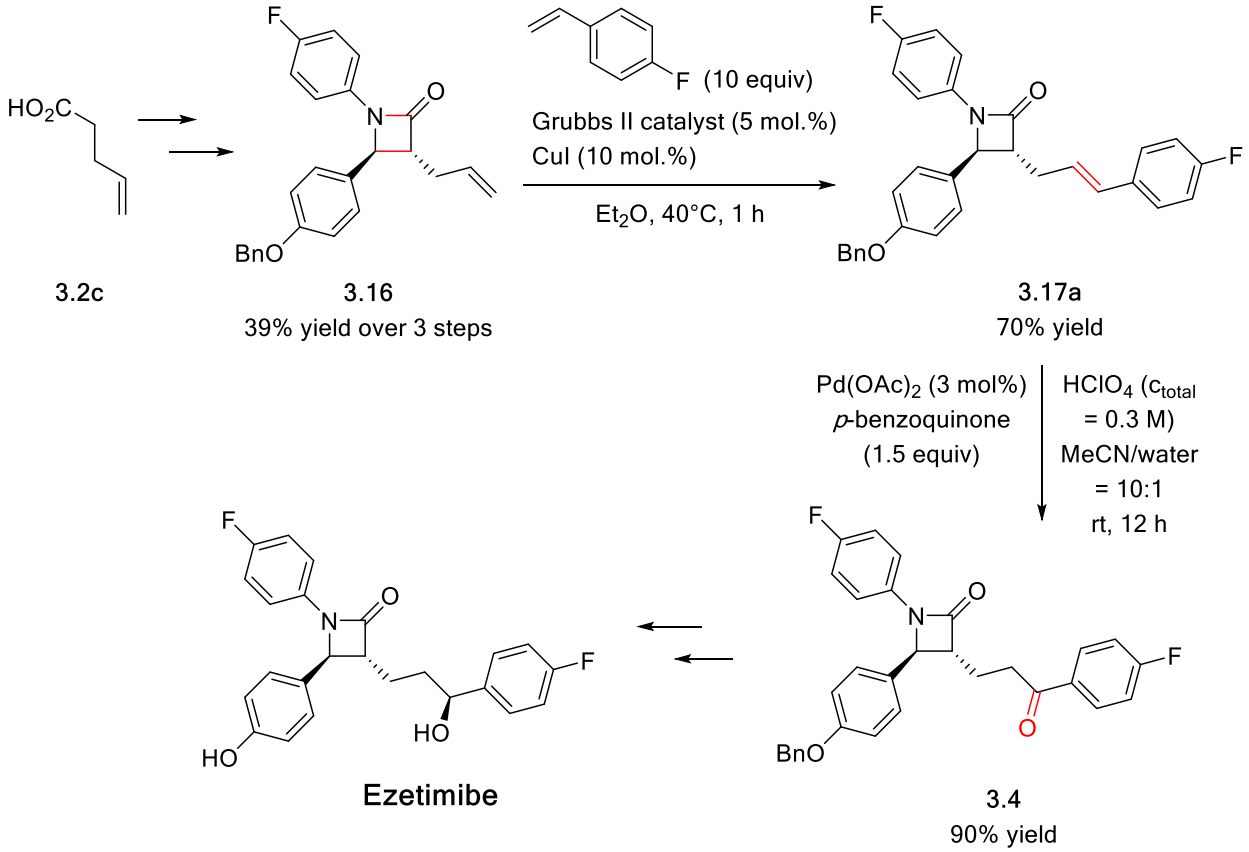
Shortly after the previous work, the new chiral auxiliary was arranged as a gold standard in Ezetimibe synthesis. The molecule of (*S*)-4-phenyl-2-oxazolidinone **3.11b** (Evans auxiliary) was found to be the perfect tool for creating an enantioenriched enolate and performing the reaction

with the previously mentioned imine **3.1a**. Here, the authors[168–170] used aliphatic or unsaturated 5-carbon molecules as workpieces and coupled them with chiral oxazolidinones, followed by enolate formation and addition to the imine **3.1a**. For instance, Sasikala[168] obtained the product **3.15** with excellent diastereoselectivity, which was then cyclized into **3.3b** by means of *N,O*-bis-(trimethylsilyl)acetamide (BSA) and tetrabutylammonium fluoride (TBAF) without degradation of enantiopurity (**Scheme 31**). Subsequent transformations of the side chain were similar to those described earlier.




**Scheme 31**. Ezetimibe synthesis using Evans auxiliary.[168]

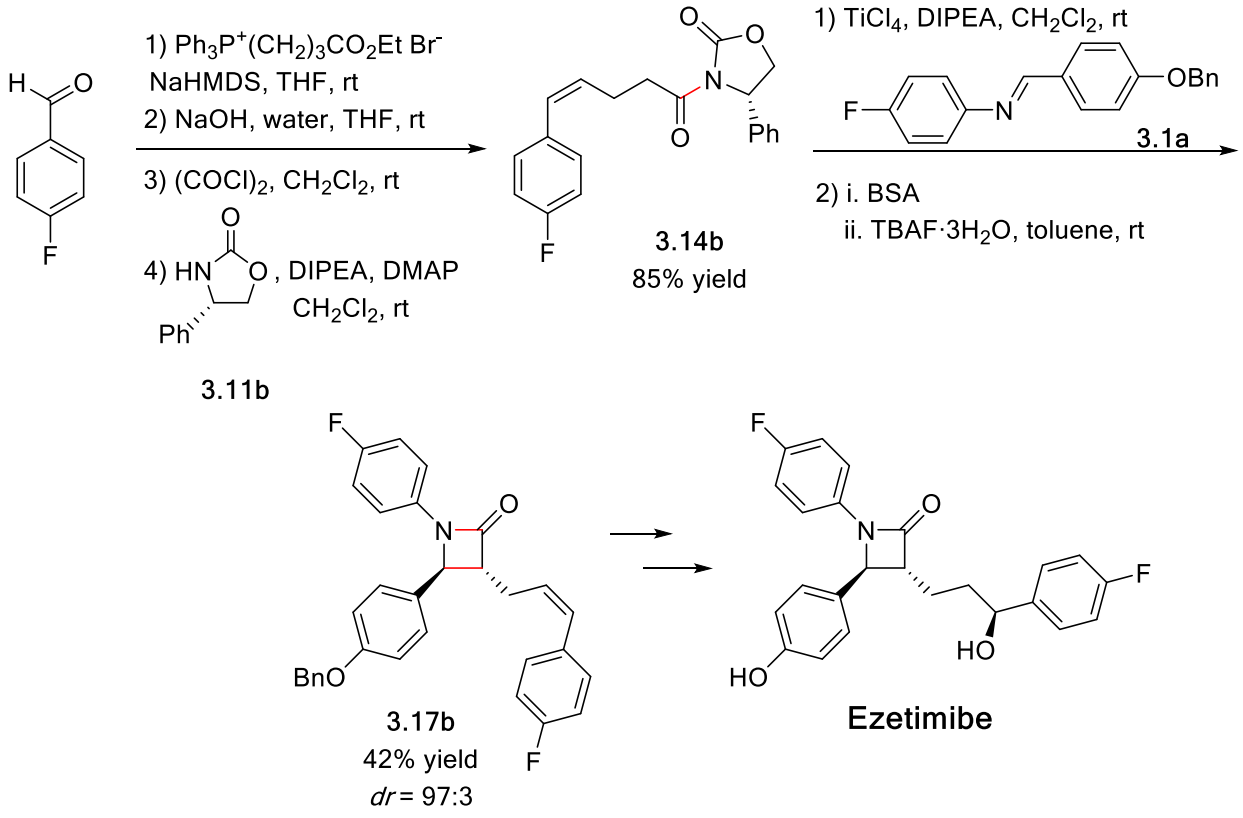
Interestingly, Lee *et al.*[170] suggested a modification of previous protocol, using pent-4-enoic acid **3.2c** as the initial acid, which was coupled with the Evans auxiliary, then treated with the imine **3.1a** and $TiCl_4$/DIPEA system similarly to **Scheme 31**, forming the product in a diastereoselective manner, and cyclized into a corresponding *trans*-substituted lactam **3.16** with the *exo* allyl group. After, the authors performed Grubbs'-catalyzed (2nd generation) metathesis reaction with *para*-F-substituted styrene. Formed β-lactam **3.17a** with a double bond in a side chain (70%) was quantitively converted into the previously discussed ketone **3.4** under Wacker-type oxidation conditions (**Scheme 32**). However, no meanings of enantiomeric purity were reported.




**Scheme 32**. Ezetimibe synthesis according to Lee *et al.*[170]

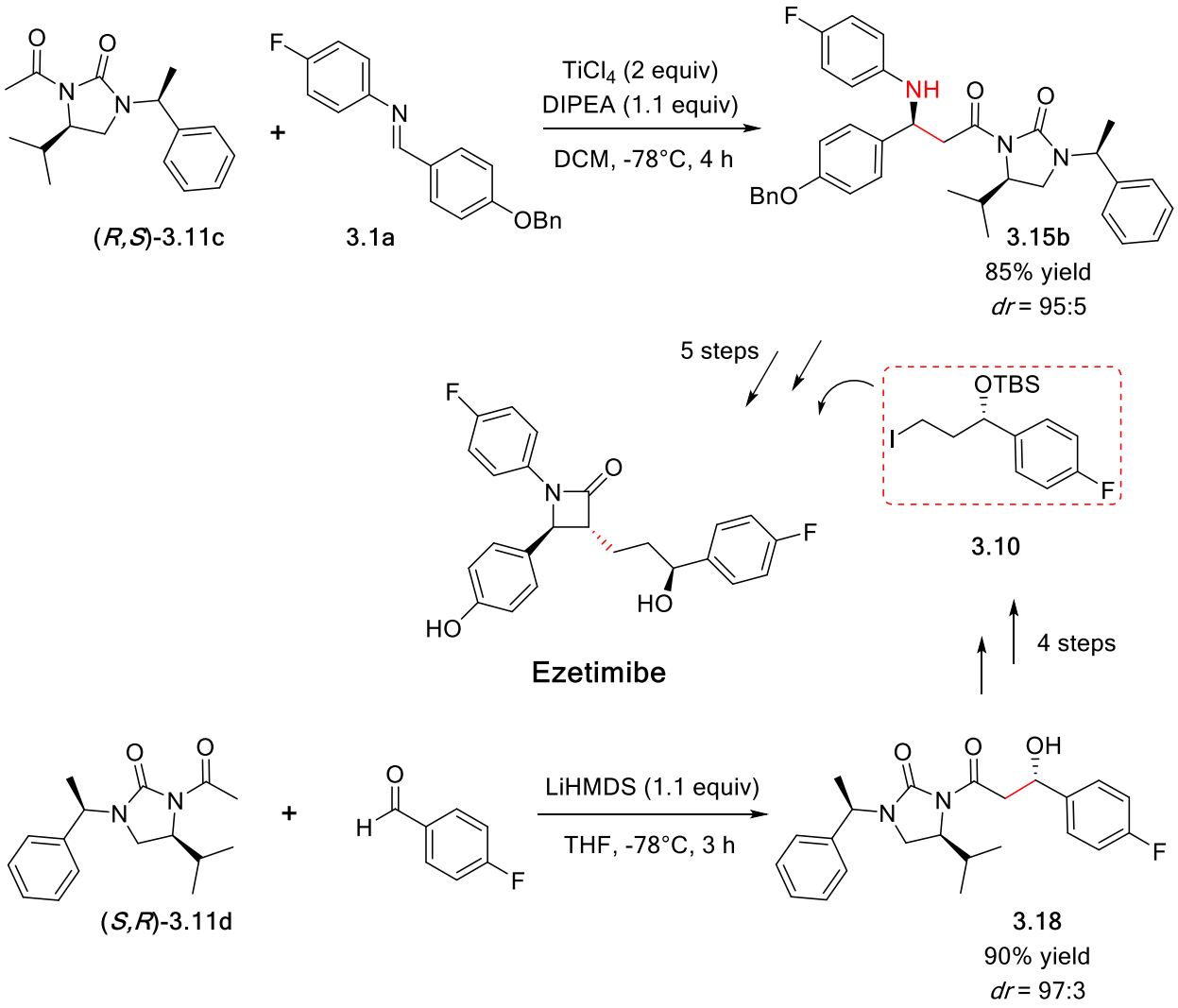
In a series of papers[171–178] the principle of aryl-substituted side chain employment was established. The principal scheme of transformations remains similar to those mentioned earlier. A *para*-substituted aryl with a side chain (5 carbons, in publications[173,174] containing the double bond in benzylic position), usually with an ester moiety, is turned into an acid or acid chloride coupled with chiral Evans auxiliary to form the corresponding asymmetric amide **3.14b**, for instance.[174]

Further addition to the imine **3.1a** and cyclization leads to the formation of the substituted β-lactam **3.17b** - a key precursor to Ezetimibe. The methods of creation of the 3rd stereocenter vary from the formation of the chiral alcohol during the initial steps,[171,172] even before the coupling with (*S*)-4-phenyl-2-oxazolidinone as in ref.,[178] to chiral Corey-Itsuno reduction of a keto-group in a very last stage,[174–177] similar to transformations reported by Wu *et al.*[167] or Lee.[170] Interestingly, Sova *et al.*[173,174] performed the total synthesis of Ezetimibe using (*Z*)-5-(4-fluorophenyl)pent-4-enoic acid (prepared from 4-fluorobenzaldehyde) as a key substance. Further oxidation of the substituted β-lactam **3.17b** *via* Wacker-type process and chiral reduction of the arising ketone using Corey-Itsuno protocol (**Scheme 33**). These authors claimed to have increased the total yield by more than 20% and improve the performance in Pd-catalyzed double bond oxidation (86% vs 70-80% yields for corresponding *E*-alkene in the patent literature[179]) along with the CBS-catalyzed ketone reduction (95% comparing to 42% yield in a patent[179]). Unfortunately, no indicated yields (absolute or percentage) could be found in that patent for the last 2 steps that makes the Sova's claims rather dubious.




**Scheme 33**. Ezetimibe synthesis by Sova *et al.*[174]

The idea of chiral auxiliary got further development by Goyal *et al*.,[180] who developed a new chiral imidazolidinones based on natural L-Valine and its enantiomer D-Valine. Thus, authors synthesized the unsubstituted and 3-methyl substituted β-lactams with high diastereoselectivity (for Ezetimibe unsubstituted β-lactam *trans*/*cis* ratio > 19:1) starting from *N*-acetylated (*R*)-4-isopropyl-1-[(*S*)-1-phenylethyl] imidazolidin-2-one (*R,S*)-**3.11c** and essential imine **3.1a**, followed by hydrolysis of intermediate **3.15b** and subsequent cyclization (**Scheme 34**). The side chain **3.10** bearing a protected hydroxyl group was synthesized from the opposite enantiomer of chiral auxiliary, i.e., *N*-acetylated (*S*)-4-isopropyl-1-[(*R*)-1-phenylethyl]imidazolidin-2-one (*S,R*)-**3.11d**, and attached to the β-lactam; all protecting groups (TBS and benzyl) were then removed during the last step. The authors claimed to have proved the final structure of Ezetimibe by means of several analytical methods (NMR, melting point, optical rotation and HRMS). Unfortunately, any chiral chromatography results regarding the unsubstituted β-lactams and following substances were not mentioned in the article. This fact makes it difficult to estimate the enantiopurity of compounds just from their optical rotation. Chiral chromatography was performed only for 3-methyl substituted lactams.

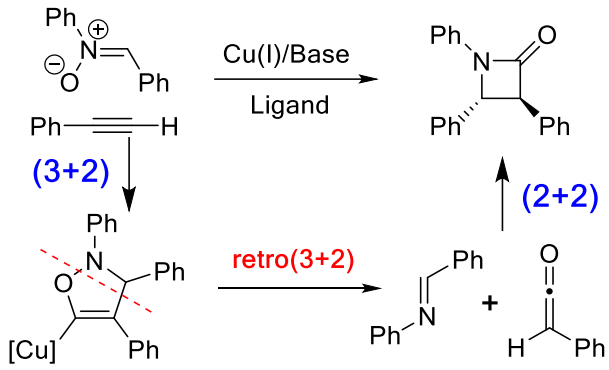



**Scheme 34**. Ezetimibe synthesis by Goyal *et al*.[180]

Next group of synthetic methods towards Ezetimibe is based on nitrone-olefine [3+2] cycloaddition reaction, a combination of a nitrone with an alkene or alkyne.[181–185] The majority of these methods of Ezetimibe synthesis rely on the Kinugasa reaction as the key step in the β-lactam ring formation. One report stands apart and will be outlined in detail in the next section.

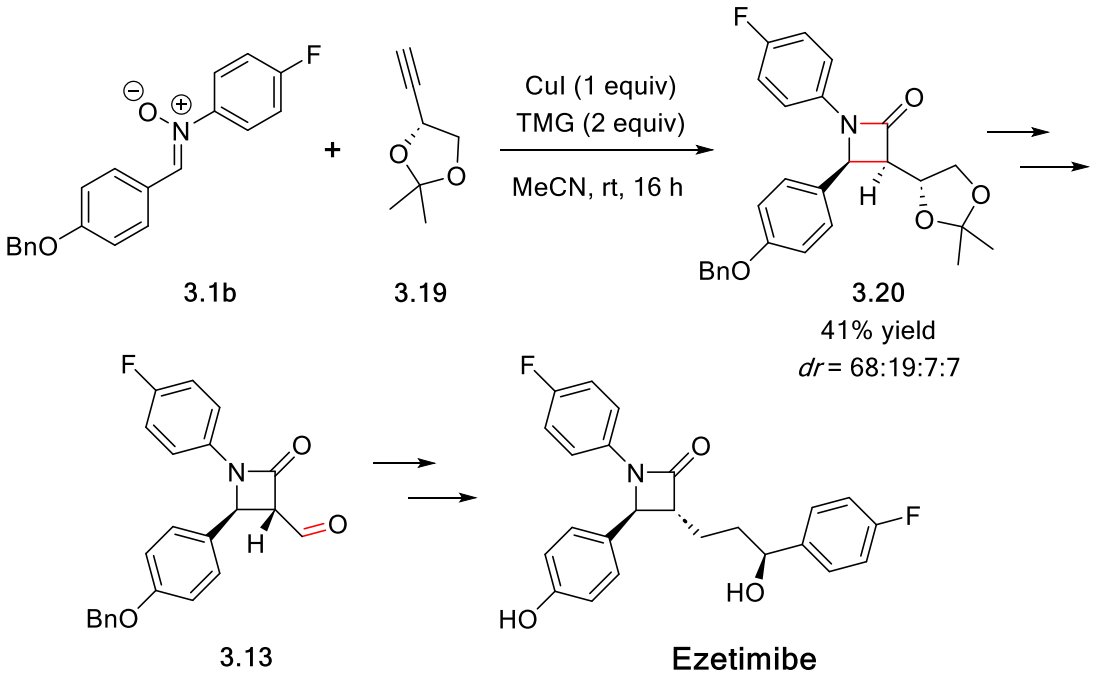
Kinugasa reaction is a [3+2] cycloaddition between a nitrone and copper acetylide, generated *in situ* from a terminal alkyne and a copper salt. This addition gives a 5-membered isooxazoline, which rearranges into a 4-membered lactam cycle concomitantly with copper atom extrusion.[186–189] Recently, Hein *et al*.[182] shed light on the mechanism with kinetic and mechanistic experiments. According to these authors (**Scheme 35**), the reaction proceeds via a cascade

involving [3+2] cycloaddition, [3+2] cycloreversion and terminating with a formal [2+2] cycloaddition known as the Staudinger synthesis (*vide supra*).



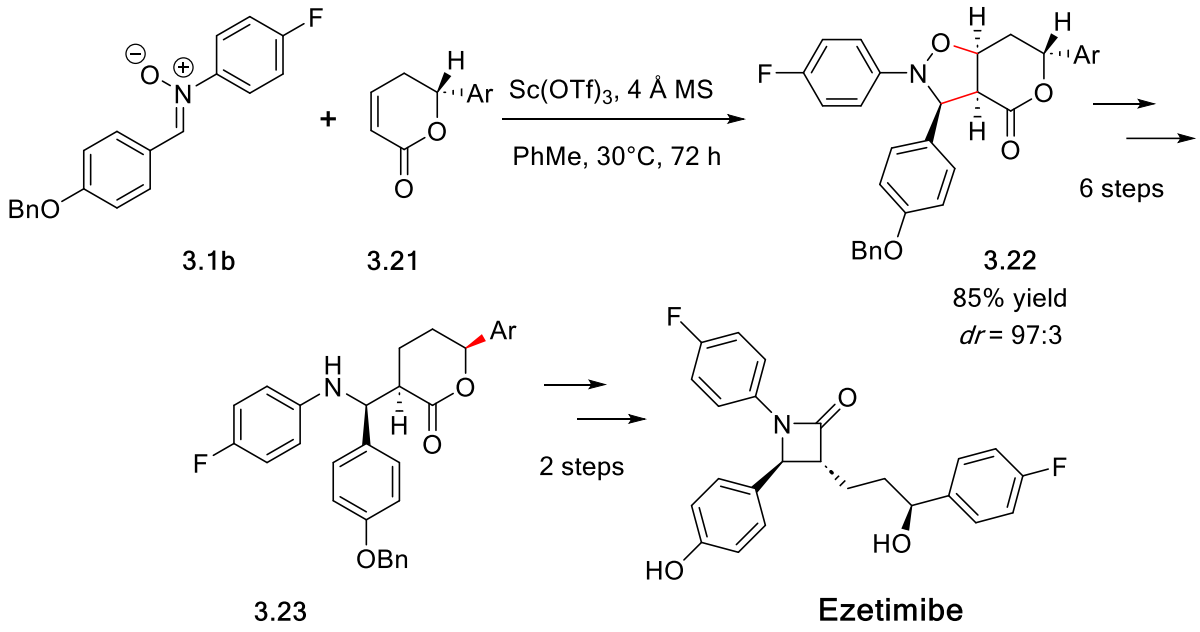

**Scheme 35**. A proposed mechanism of Kinugasa reaction by Hein *et al*.[182]

The most comprehensive work on [3+2] cycloaddition towards Ezetimibe was carried out by Chmielewski *et al*.[183,184] (**Scheme 36**). In these publications β-lactam **3.20** was constructed through Kinugasa reaction between the nitrone **3.1b** carrying *para*-benzyloxy- and *para*-fluorine-substituted phenyls (the nitrone **3.1b** derived from the imine **3.1a**) and the protected chiral diol **3.19** with a terminal triple bond. After deprotection the diol was oxidized by $NaIO_4$ to give the previously shown β-lactam **3.13** with a formyl moiety at position 3. Further transformations directly to Ezetimibe were inspired by the work of Wu.[167]



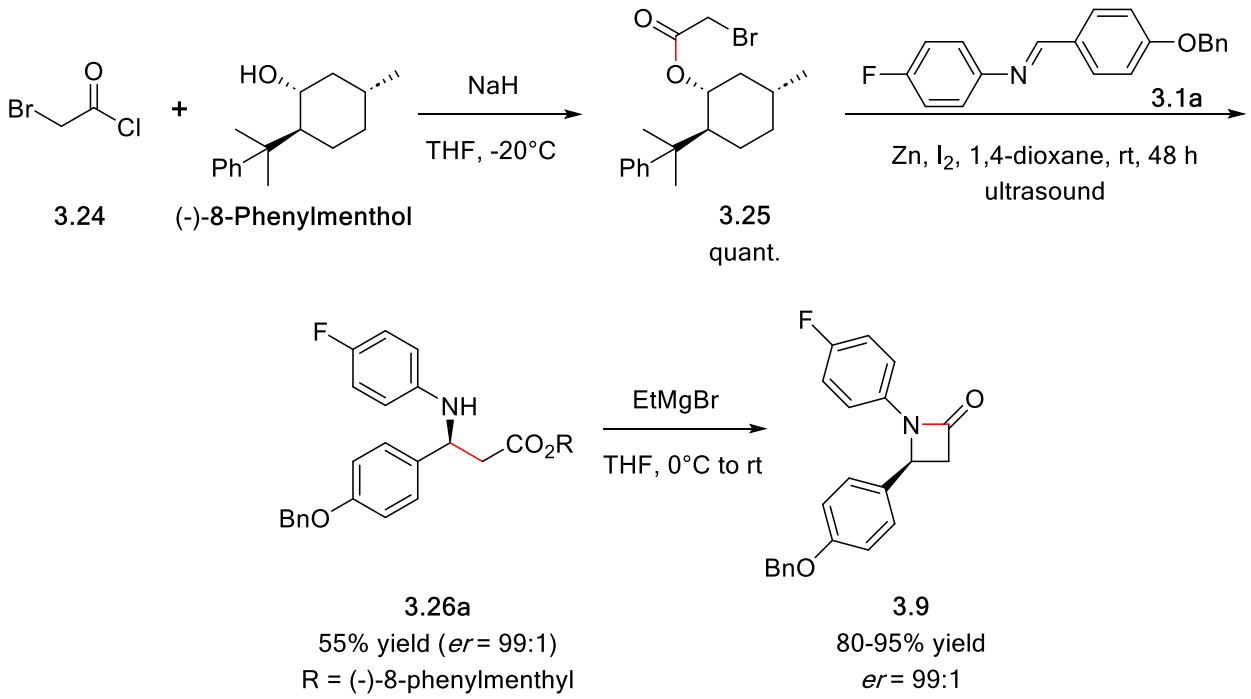

**Scheme 36**. Ezetimibe synthesis employing the Kinugasa reaction by Chmielewski *et al*.[184]

The stand-alone project[185] by the same authors was dedicated to the masterpiece synthesis of Ezetimibe using a novel sequence of chemical transformations. There should be brought up the Jacobsen asymmetric hetero-Diels-Alder reaction promoted by a salen-Cr(III) complex, allowing to obtain the chiral unsaturated lactone **3.21**, then Kinugasa reaction between this lactone **3.21** and nitrone **3.1b** forming a 5-membered *exo* cycloadduct **3.22** promoted by Lewis acid $Sc(OTf)_3$. Next, this cycloadduct was converted into the saturated 6-membered lactone **3.23** with a side chain containing an amine in several efficient transformations. The intermediate was cyclized into a β-lactam by a strong base (Grignard reagent) and the product was debenzylated in the very last step as usual (Pd/C under hydrogen atmosphere) to yield Ezetimibe (**Scheme 37**).



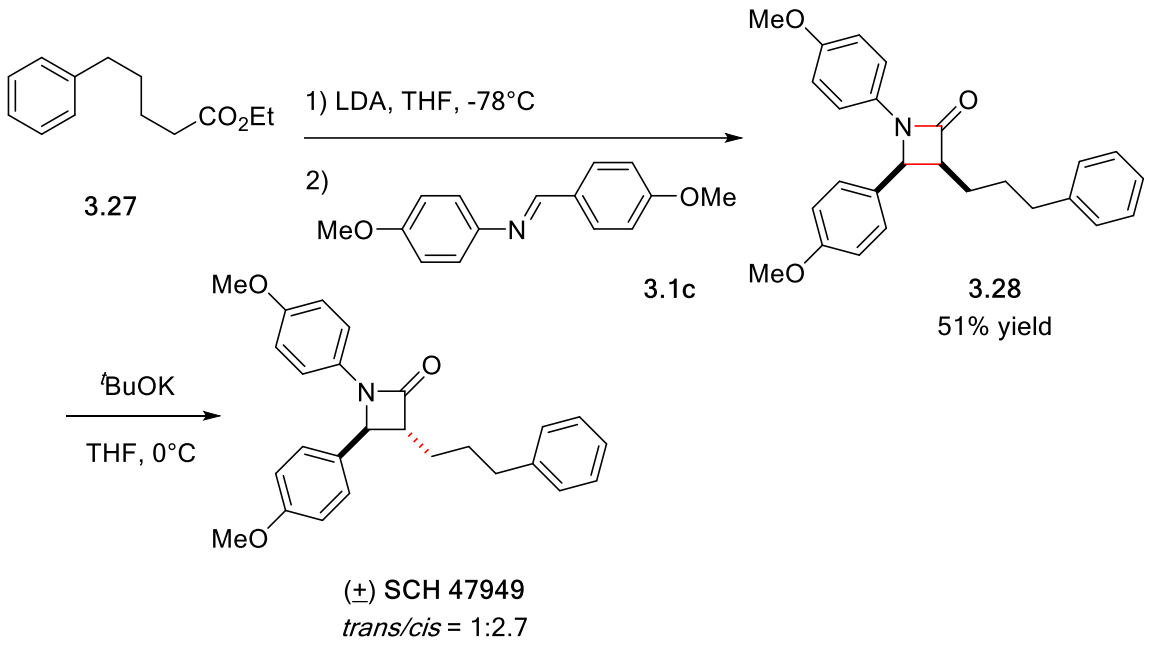

**Scheme 37**. Ezetimibe synthesis by Chmielewski *et al.*[185]. Ar = 4-F-$C_6H_4$.

Another approach to Ezetimibe involves chiral center creation in the intermediate product, followed by its cyclization. The pioneering work in the field of Ezetimibe and its predecessors was published in 1996 by chemists at Schering-Plough[190] based on their 1995 patent.[191] In this publication the authors considered the formation of unsubstituted 4-membered lactam cycle and its subsequent alkylation as another way towards the target molecule. While having already chiral unsubstituted β-lactam, these researchers estimated the chances of synthesizing a *trans* substituted product as reasonable. To perform this idea, they started using chiral alcohols and their esterification with bromoacetic acid derivative **3.24**. Next step was the Reformatsky reaction of synthesized bromoacetate **3.25** with the imine **3.1a**. It allowed to obtain the corresponding β-amino esters with moderate yields and good level of enantiomeric excess. The most prominent results in terms of *ee* were obtained while using (-)-*trans*-2-phenylcyclohexanol or (-)-8-phenylmentol (up to 98% *ee*). A further reaction was the cyclization of obtained β-amino ester **3.26a** into the β-lactam cycle **3.9** by treatment with Grignard reagent. The resulting cyclic β-lactam was used for the synthesis of **SCH 48461** analogues (**Scheme 38**).




**Scheme 38**. Synthesis of enantioenriched β-lactam **3.9**.[190]

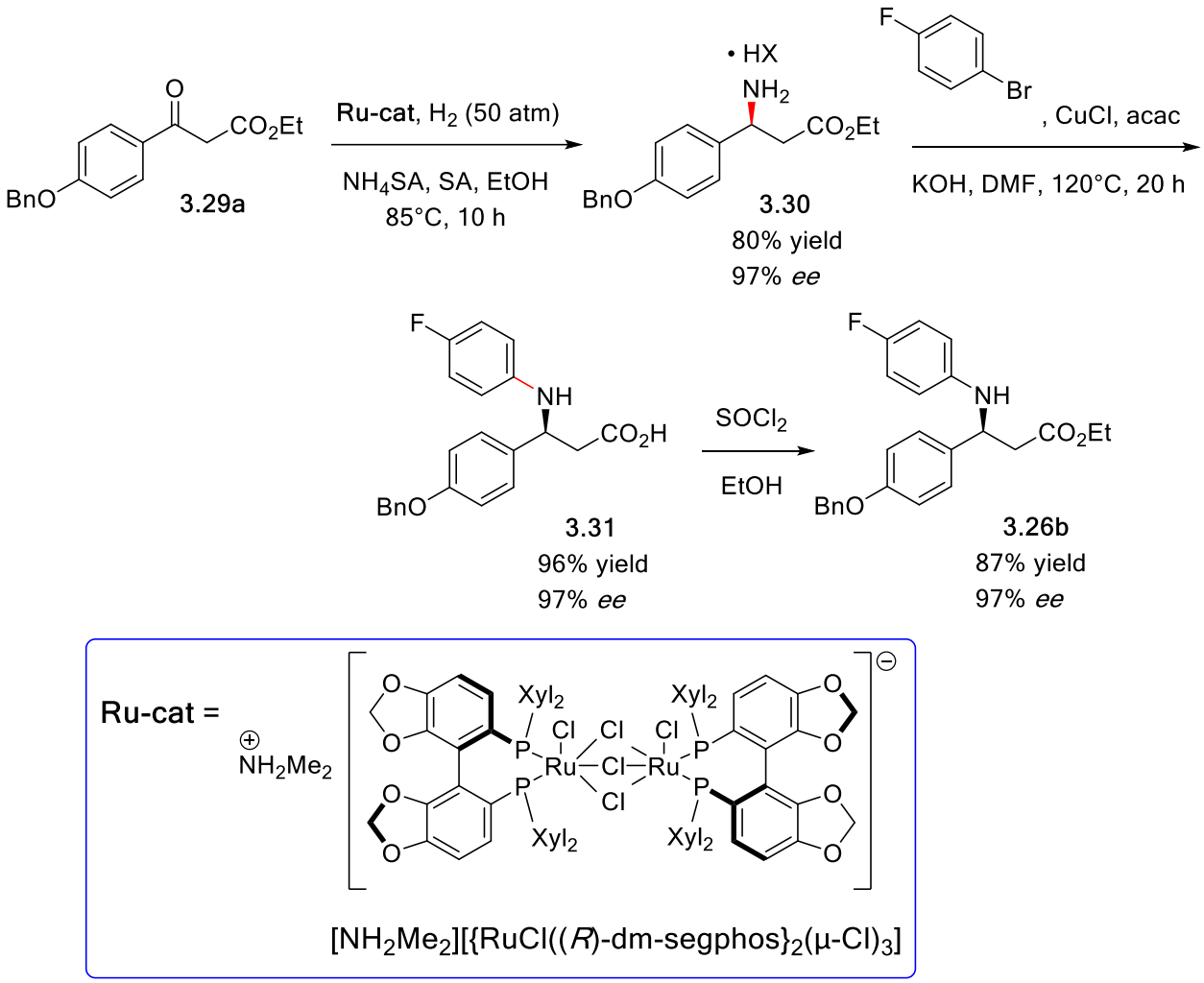
Here might be briefly mentioned one of the first methods in Ezetimibe analogues synthesis.[163] The formation of enolate from an ester **3.27** having α-CH or $CH_2$ group treated with a strong base (LDA) and its reaction with the imine **3.1c**. It leads to the cyclization of an intermediate when the electron pair of nucleophilic nitrogen atom attacks the ester group. This condensation predominantly gives a rise to the *cis*-substituted β-lactam **3.28** which requires further epimerization (**Scheme 39**) by treatment with a strong base ($^t$BuOK) and separation of enantiomers.




**Scheme 39**. Synthesis of (±) **SCH 47949** in accordance with work by Clader *et al*.[163]

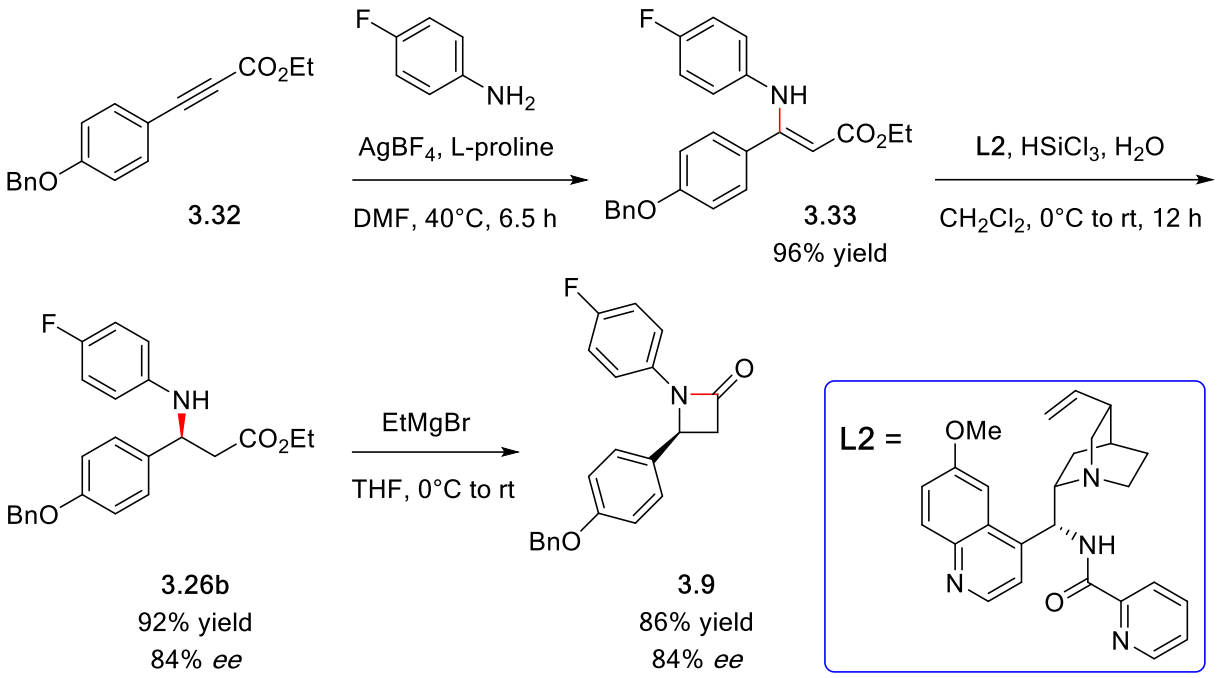
Other groups[192–199] focused on the construction of the chiral center by using chiral catalysts rather than chiral auxiliaries as it was in case of Shankar's work.[190] Busscher *et al*.[193] tried to create chiral β-amino esters from 1,3-keto esters and various anilines *via* hydrogenation catalyzed by chiral Ir complexes. The reaction took place, but the enantiomeric excess was not satisfactory. Thus, the researchers changed the strategy and performed the successful chiral amination of 1,3-keto ester **3.29a** with ammonium salicylate ($NH_4SA$) and chiral Ru complexes, which gave the corresponding β-amino ester **3.30** with an excellent level of enantioenrichment. Subsequent Ullmann-type coupling with substituted aryl bromide (**Scheme 40**) in the presence of copper (I) chloride as a catalyst and potassium hydroxide or potassium *tert*-butoxide as a base afforded **3.31** quantitatively. These bases were found to be superior to alkali metals carbonates, imidazole, or triethylamine, which tend to form cinnamic esters as the elimination byproducts. In another modification by Lange *et al*., the Cu-catalyzed *N*-arylation was carried out with 0.2 equivalents of acetylacetone (acac) as a ligand.[200] Notably, 1-bromo-4-fluorobenzene, which is 5 times less expensive than the corresponding iodide, was found to be sufficiently reactive. The resulting acid **3.31**, obtained with the retention of enantiopurity, was subjected to reesterification with ethanol and $SOCl_2$, giving the ethyl ester **3.26b** with the retention of stereointegrity. The authors clearly

stated that the resulting enantioenriched β-amino ester **3.26b** might be converted into the final molecule of Ezetimibe but did not complete the total synthesis by themselves.



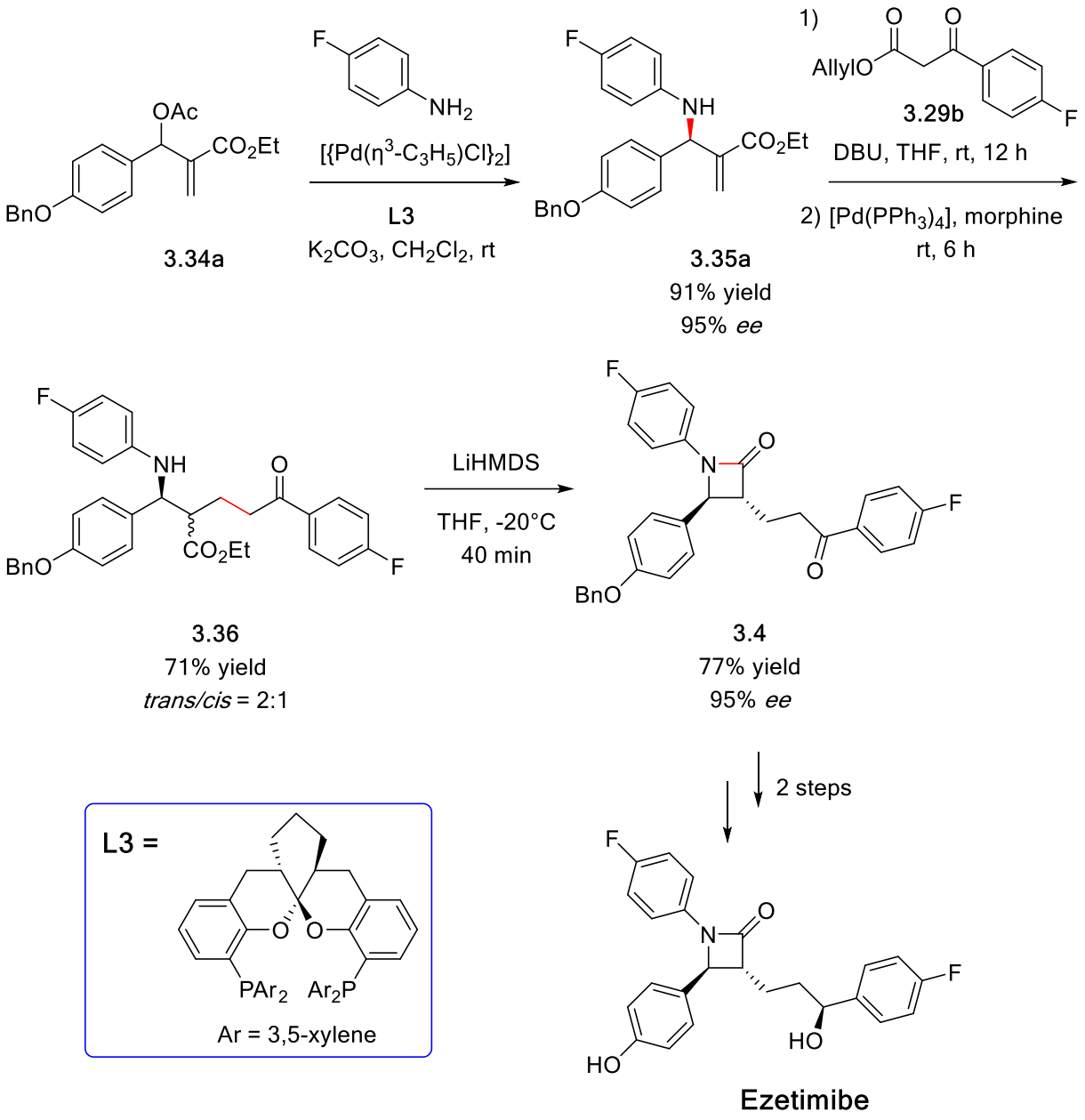

**Scheme 40**. Synthesis of chiral β-amino ester by Busscher *et al.*[193]

Another report[196] was dedicated to the synthesis of unsubstituted β-lactam **3.9** starting from 1,2-disubstituted acetylene **3.32** which upon $AgBF_4$-catalyzed reaction with the appropriate aniline gave the arylsubstituted enamine **3.33**. For the next step the authors used chiral cinchona-based catalyst **L2** and trichlorosilane as a reducing reagent, affording the β-amino ester **3.26b** with good *ee* and yield (**Scheme 41**). The latter aminoester **3.26b** was subjected to cyclization *via* Grignard reagent-mediated reaction resulting in the formation of the β-lactam **3.9**. The whole work ended with this step without performing the total Ezetimibe synthesis.




**Scheme 41**. Synthesis of a key intermediate **3.9** according to Lee's work.[196]

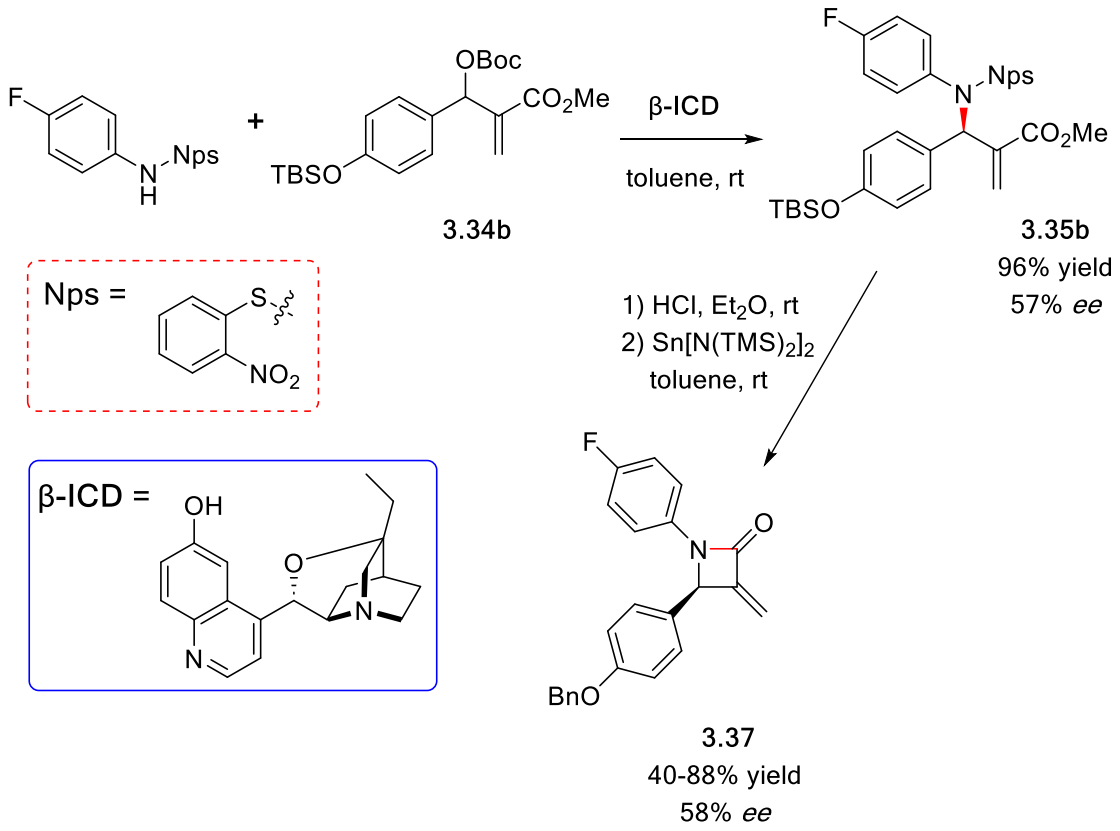
Several publications[194,197–199] have in common the idea of catalyzed enantioselective allylic amination of the racemic *O*-protected Morita-Baylis-Hillman (MBH) adducts and its further application in a total Ezetimibe synthesis. Ding *et al.*[194,198] employed aromatic spiroketal bisphosphines as ligands for Pd-catalyzed amination of MBH adducts (**3.34a**)[194] or monosubstituted allenes.[198] In both cases the expected chiral amines were synthesized with high enantioselectivity (up to 94% *ee*) and good yields. Further functionalization was relied on the reaction of certain allylic chiral amine **3.35a** with 1,3-keto ester **3.29b** under basic conditions affording the corresponding Michael adduct, which was further treated with [$Pd(PPh_3)_4$] to remove the allyloxycarbonyl group and give **3.36**. The latter product **3.36** was then cyclized under strong basic conditions giving the substituted β-lactam **3.4** with a keto group in a benzylic position with excellent enantioselectivity (**Scheme 42**). Although the researchers did not perform the rest of the total synthesis, they referred to known literature.




**Scheme 42**. Ezetimibe synthesis by Ding *et al.*[194]

Publications by Veselý[197] and Kotora[199] are complementary approaches to Ezetimibe synthesis. Veselý *et al.*[197] have found the way to organocatalyzed enantioselective allylic amination of the racemic O-protected Morita-Baylis-Hillman adducts (**Scheme 43**). β-Isocupreidine (β-**ICD**), prepared from natural quinidine in one step, was used as a chiral catalyst. The reaction was carried out under mild conditions, using toluene as a solvent, at room temperature for 2 days. Interestingly, the authors stated that it was optimal to use a Nps (2-nitrophenylsulfenyl) protecting group for

anilines rather than unprotected primary amines. They suggested that the challenging stereocontrol or reduced nucleophilicity may be the reason for worse reactivity of primary aromatic amines during experiments with unprotected aniline. The various *N*-protected α-allylic-β-amino esters thus obtained were deprotected and readily cyclized in the presence of Mukaiyama reagent with moderate to good yields. However, in the case of the Ezetimibe predecessor **3.35b**, which was obtained with a modest enantiomeric excess (57%), the procedure gave relatively poor yields and another protocol, with $Sn[N(TMS)_2]_2$ as a cyclizing agent, was used affording **3.37** in good to excellent yields (40-88%) while retaining enantioselectivity. The resulting 3-methylene-substituted lactam **3.37** might be considered as a valuable intermediate in Ezetimibe synthesis.




**Scheme 43**. Synthesis of a key intermediate of Ezetimibe according to Veselý *et al.*[197]

This approach was extended by functionalization of α-methylidene-β-lactams using cross-metathesis reaction catalyzed by Hoveyda-Grubbs 2$^{nd}$ generation catalyst, which gave a series of the corresponding 3-methylidene-substituted β-lactams in good yields. The double bond of freshly prepared lactams was hydrogenated over Pd/C catalyst forming a mixture of *cis*-configured

diastereoisomers (1:1), which were then epimerized in strongly alkaline medium (DBN) into the mixture of easily separable *trans*-substituted isomers. After the isolation of the desired diastereoisomer, its secondary alcohol moiety was deprotected (TBS-protection) in a very last step by using Olah reagent (HF/pyridine) allowing the desired Ezetimibe in high yield and level of enantioenrichment.[199]

Several miscellaneous works devoted to Ezetimibe are also worth mentioning. Thus, Toyota *et al*.[195] were interested in evaluating artificial intelligence (AI) capabilities to predict the total synthesis of Ezetimibe. Using a so-called SYNSUP system, developed by Bersohn[201] the researchers managed to choose a one-pot preparation of trans β-lactam cycle among 2,250 proposed synthetic routes. After modifying and optimizing the procedure they obtained the unsubstituted β-lactam for **SCH 47949** in good yield and claimed pure *trans* configuration and proposed the electrocyclic mechanism of reaction. Despite this, no measurements of absolute configuration or enantiomeric excess were provided. With the AI-predicted and synthesized 3-substituted β-lactam in hand, the authors carried out the total synthesis of **SCH 47949**.

Another work by Kyslík *et al*.[202] was dedicated to the possibility of diastereoselective reduction of the Ezetimibe precursor, corresponding ketone, by microorganisms. The authors found that the microbial strain *Rhodococcus fascians* MO22 converted up to 84% of the ketone (the isolated yield is 68%) or up to 63% of the protected ketone during 48 hours at 30 °C with excellent enantioselectivity (99.9% of *de*). This discovery might be especially useful in the pharmaceutical industry where the requirements of enantiomeric purity are the most demanding.

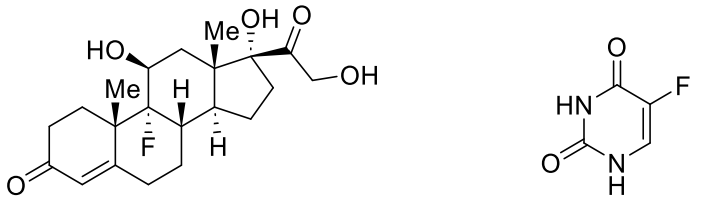
Moreover, a few papers[203,204] were published with results regarding the synthesis of Ezetimibe analogues. Thus, Xu *et al*.[204] synthesized a series of analogues with a reorganized order of substituents on the β-lactam cycle and evaluated their biological activity. For the arranging of the molecule central core Xu with colleagues used the classical [2 + 2] Staudinger synthesis and further modified the secondary amide into the tertiary one with the side chain having a preinstalled chiral alcohol moiety. After biological evaluation it was found that 3 of 4 newly developed Ezetimibe analogues have some activity in lowering the total cholesterol and LDL. The Liu's publication[203] revealed the structure of *trans*-4-$CF_3$ Zetia analogue which showed some level of inhibition of cholesterol absorption.

Carreira's group[205–207] glycosylated the phenolic group, echoing the glycuronide derivative of Ezetimibe that is formed as a metabolite in the intestine as shown by Van Heek *et al*.[208] Another variation concerned the β-lactam cycle, which was fully reduced to azetidine. The compounds thus obtained were tested in biological assays presenting some level of anticholesterol activity. Ritter *et al*.[206] synthesized several Ezetimibe-similar compounds with 5-membered heterocycles which were tested in biological assays. Among them, only oxazolidinone-containing structure showed a similar *in vitro* activity (19% inhibition) to Ezetimibe (16% inhibition).

In conclusion, many studies were conducted, and their results are published regarding the Ezetimibe synthesis itself and its analogues. A significant part of these publications might be grouped into several classes concerning the creation of 4-membered β-lactam cycle and inducing chirality. Such classification was done in previous pages and the idea of a novel synthesis of Ezetimibe popped up in our scientific group. The results of our efforts will be delivered further.

# Fluorine

Fluorine's unique chemical properties make it rare in biological compounds, with notable exceptions like inorganic fluorides beneficial for dental and bone health in mammals. Organofluorine compounds, found mainly in plants and microorganisms, such as monofluoroacetic acid, exhibit toxicity due to the inhibition of the citric acid cycle (Krebs cycle). Despite initial skepticism in the mid-20th century regarding incorporating fluorine into organic molecules, discoveries like fludrocortisone[209,210] and 5-fluorouracil (**Figure 22**) demonstrated significant pharmaceutical potential, leading to a paradigm shift in biological research.




Fludrocortisone 5-fluorouracil

**Figure 22.** Structures of fludrocortisone and 5-fluorouracil.

These discoveries prompted exploration into fluorine's role in drug design, with principles established for incorporating fluorine into biologically active compounds.[211] Fluorine's effects on organic compounds, including electronegativity, size, and lipophilicity, can profoundly influence chemical reactivity and biological properties. This understanding has led to the routine use of fluorine scans (a method in drug candidates development when F atom is systematically inserted at various positions of the molecule under exploration) in drug development to enhance therapeutic efficacy and pharmacological properties. It is known that alteration of lipophilicity might be performed with introduction not only F atoms, but also $CF_3$, $OCF_3$, $SCF_3$ and $SF_5$ groups. Together with amendment of lipophilicity conformational changes might appear due to steric bulkiness or electrostatic repulsion/attraction of new moieties.[212,213] Reviews[214–216] are valuable sources of fluorine-containing drugs data for researchers.

Approximately 25% of current drugs contain fluorine or fluorine-containing groups, with its incorporation contributing to properties like lipophilicity and metabolic stability, exemplified by

2023 top-selling pharmaceuticals like Rinvoq® (Upadacitinib), Paxlovid® (Nirmatrelvir), and Biktarvy® (**Figure 23**).[217]

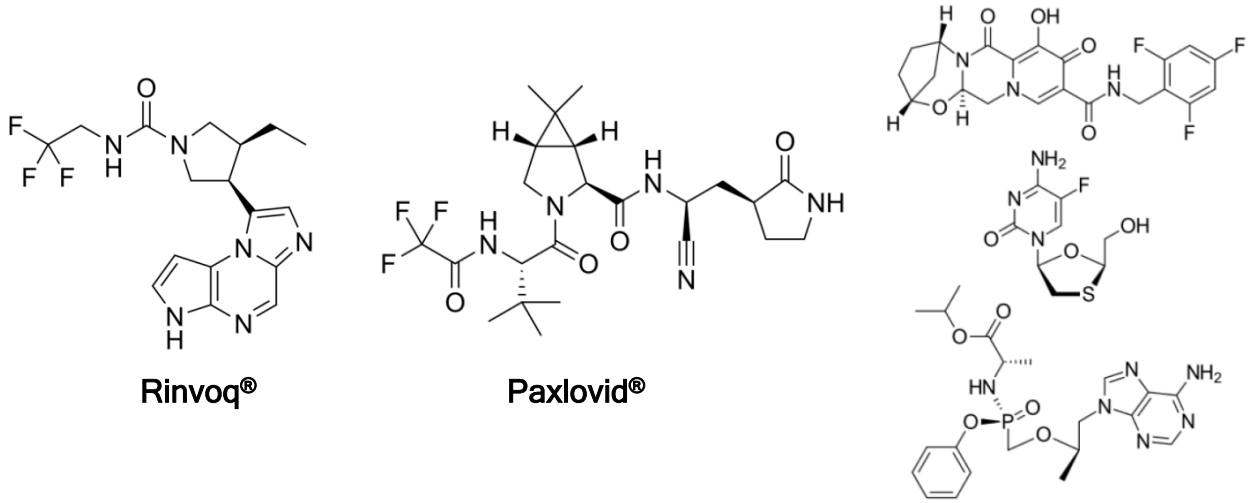



**Figure 23**. Structures of Rinvoq®, Paxlovid® and Biktarvy®.

Moreover, widely prescribed medications such as Prozac (fluoxetine), Lipitor® (atorvastatin), and Ciprobay (ciprofloxacin) contain fluorine, underlining its prevalence in successful drugs (see **Figure 24**). Lipitor, the most prescribed medicine in the US in 2021,[218] and the world's best-selling drug during its patented age,[219] highlight fluorine's significant role in pharmaceuticals. With over half of all statins on the market containing fluorine, the trend suggests a growing role for fluorine in medicinal chemistry, with expectations of more fluorinated drugs in the future.

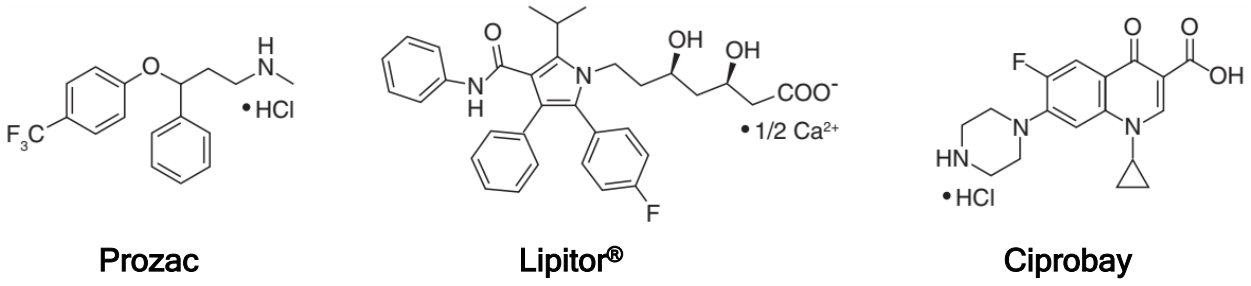



**Figure 24**. Prozac, Lipitor® and Ciprobay structures.

## $SF_5$

The perfluorinated substituent, pentafluorosulfanyl ($SF_5$) group, has garnered significant attention in recent decades due to its distinct properties.[220,221] Pentafluorosulfanyl ($SF_5$) compounds are organic derivatives of sulfur hexafluoride ($SF_6$). Both $SF_6$ and $SF_5$-compounds exhibit a hypervalent hexacoordinated state of the sulfur atom with an octahedral ligand geometry. The pentafluorosulfanyl group displays remarkable chemical stability, and compounds featuring this group often possess advantageous properties such as high thermal, chemical and hydrolytic stability, electronegativity, lipophilicity, and biological activity.[222] While some of these properties overlap with those of the trifluoromethyl group (**Figure 25**, **a** and **b**), to which $SF_5$ is often compared, the pentafluorosulfanyl group is not just exotic and "larger" version of $CF_3$ group or "super-$CF_3$ group" as it might be encountered in the literature.[223]

Currently, it is established that aromatic $SF_5$ compounds exhibit diminished aqueous solubility, increased hydrophobicity, and equivalent hydrolytic stability comparingly to their $CF_3$ counterparts. They exhibit resistance to strong Brønstedt acids and bases, remain stable under diverse hydrogenation conditions, and are amenable to participate in metal-catalyzed C−C coupling reactions. Conversely, $SF_5$ compounds, as their $CF_3$ analogs, display sensitivity to strong Lewis acids. Additionally, they might be reduced by some organometallic reagents, such as *n*-butyllithium.[224] Aromatic $SF_5$ compounds exhibit stability under physiological conditions,[225] yet there is currently a lack of knowledge regarding their toxicology and environmental destiny. Their relatively low solubility in water implies potential dissemination into soil, sediments, and biota, possibly showing them more prone to bioaccumulation. On the other hand, environmental investigations (photolytic fate in borate buffer at pH 8.5) reveal their degradation into water-soluble, nonfluorinated products.[226]

Pentafluorosulfanyl-containing compounds have been known for over half a century,[227] yet remained relatively underdeveloped for an extended period.[220,221] The limited availability of key building blocks hindered progress in the chemistry of $SF_5$-containing compounds. However, recent years have witnessed a renewed interest in this functional group. Synthetic methods for aliphatic $SF_5$-including compounds involve free radical addition of $SF_5Cl$ or $SF_5Br$ to unsaturated compounds (alkenes or alkynes),[228–230] while aromatic compounds with $SF_5$ group are obtained through Umemoto's two-step synthesis from diaryl disulfides or benzenethiols[231] or its Togni's

modification (trichloroisocyanuric acid (TCICA) is used instead of gaseous $Cl_2$),[232] or by reacting nitrophenyl disulfides with elemental fluorine.[233,234]

Over the past decade, the integration of the pentafluorosulfanyl ($SF_5$) group into biologically active molecules has demonstrated consistent success. There is a potential of the $SF_5$ group as a bioisosteric substitute for various substituents, namely $CF_3$, $^t$Bu, halogens, and $NO_2$ groups, on an aromatic ring. The $SF_5$ group has consistently exhibited promising utility as an analogue of the $CF_3$ group (*vide supra*), often surpassing the activities of $CF_3$ analogues in numerous substances.[235–240]

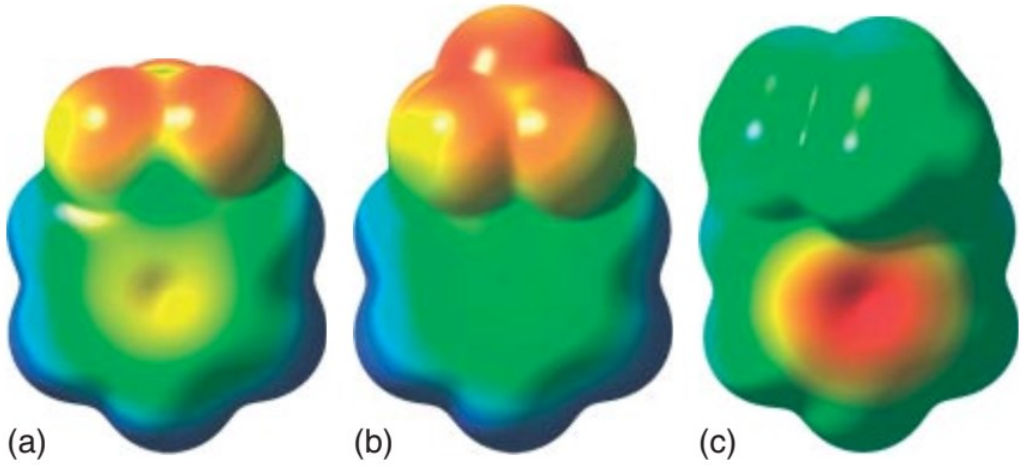



**Figure 25**. Electrostatic potentials mapped on the electron isodensity surface of $CF_3$- (**a**), $SF_5$- (**b**), and $^t$Bu-benzene (**c**). Red denotes negative and blue positive partial charges. Adopted from ref.[223]

In cases where the size and hydrophobicity are pivotal criteria, the pentafluorosulfanyl ($SF_5$) group emerges as an effective bioisosteric replacement for the *tert*-butyl group.[223] This substitution proves to be particularly advantageous when the metabolic stability of the *tert*-butyl group is a matter of concern.[240] However, caution is needed due to differences in electronic characteristics (electronegativity) between the two groups (**Figure 25**, **b** and **c**).

The electronic similarities between $SF_5$ and $NO_2$ groups justify their potential application as mutual bioisosteric replacements.[223,241] Nevertheless, the feasibility of this isosteric substitution is constrained by the larger size of the $SF_5$ group. In contrast to $CF_3$ and $^t$Bu moieties, limited

literature examples exist for nitro group replacements, highlighting the need for further investigation.[242,243]

Similar to halogens, the $SF_5$ group exhibits electronegativity and hydrophobicity. Numerous literature examples document the replacement of halogens with the $SF_5$ group, resulting in compounds that are equipotent or more potent.[240,244] Moreover, these replacements often yield compounds with enhanced selectivity and notable differences in physiochemical properties.[245]

In summary, the ligands featuring the $SF_5$ group, discussed in this section, sometimes exhibit potency equal to or greater than their $CF_3$, $^{i}$Bu, halogens, or $NO_2$ counterparts. The incorporation of the $SF_5$ group generally elevates the lipophilicity of the compounds, thereby augmenting membrane permeability. Notably, the introduction of the $SF_5$ group has the potential to enhance substances selectivity in some examples.

# Chapter IV. Results and discussion

## Introduction

In Part 1 part was described, in details, our investigation of the stability of various functional groups in $HSiCl_3$-mediated reductive amination reactions. Among the stable functional groups was the *p*-pentafluorosulfanyl ($SF_5$) moiety (**2.1h** + **2.2h** → **2.3g**). As also shown in the Introduction part, this group is highly stable towards various reagents – oxidants and reductants, Brønstedt bases and acids, and hydrogenating agents. However, strong Lewis acids or certain organometallic reagents do react with it, which had to be kept in mind in planning subsequent work.[224]

After having established the fundamentals of the reductive aminations with $HSiCl_3$, we aimed for its asymmetric version, focusing on Ezetimibe, a cholesterol-lowering drug. Most of known methods of Ezetimibe and its predecessor SCH 48461 were comprehensively covered in the Introduction part showing their advantages and drawbacks. Given its significance and challenges, particularly due to its multiple stereocenters, we aimed at developing a new synthetic approach to Ezetimibe (**4.1**) and its analogues **4.2**-**4.4** with $CF_3$ and $SF_5$ (**Figure 26**) moieties; preliminary biological evaluation of the new derivatives was also part of the plan.

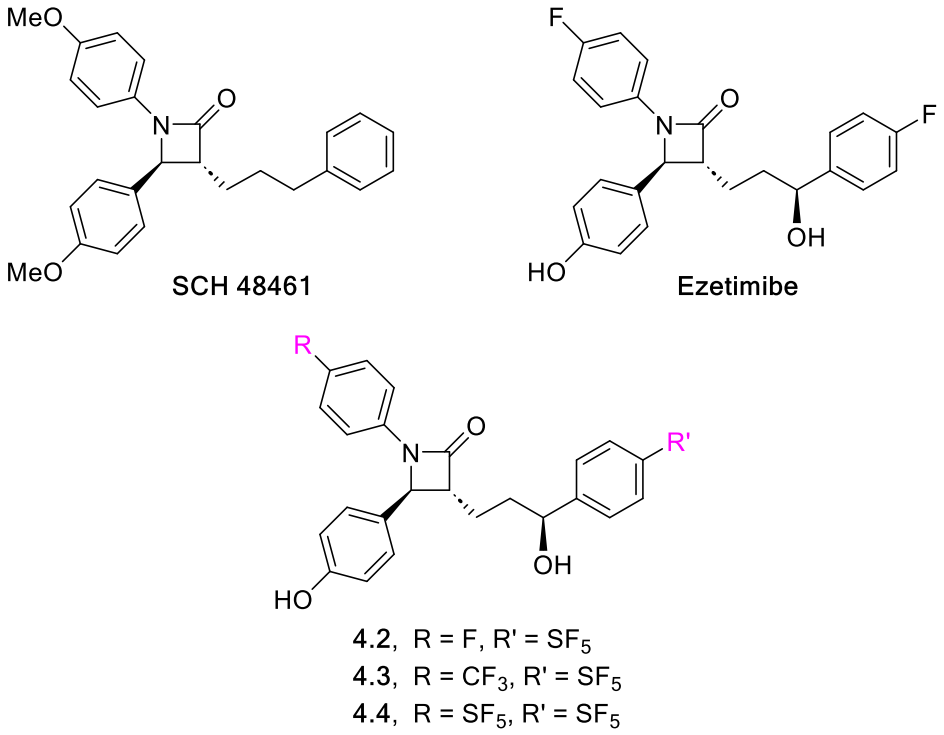
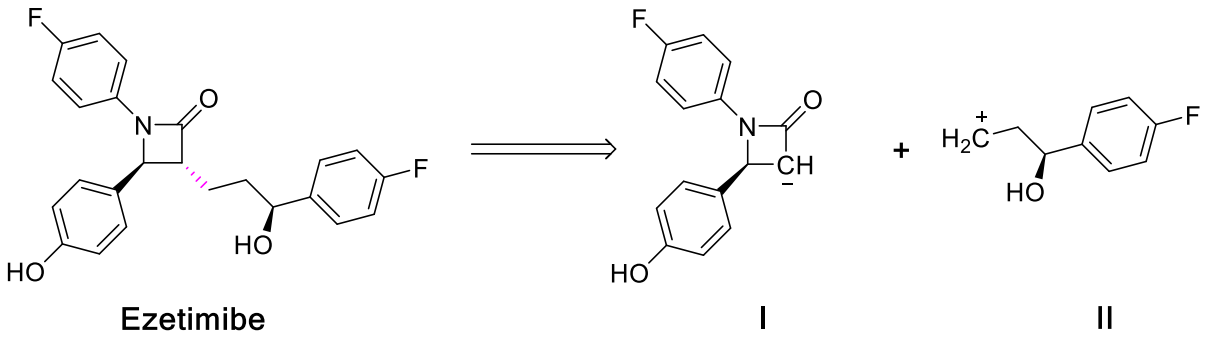



**Figure 26**. SCH 48461, Ezetimibe and its analogues.

## Retrosynthetic analysis

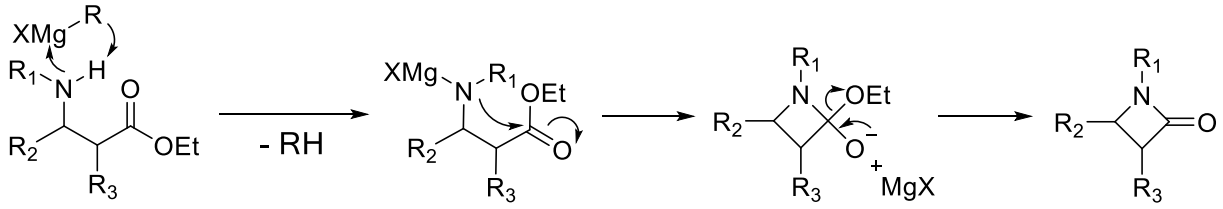
Retrosynthetic analysis of Ezetimibe suggests a disconnection into two principal building blocks, **I** and **II** (**Scheme 44**). Synthon **I**, featuring a β-lactam cycle with a chiral carbon, prompted reviewing available methods for β-lactam construction, notably the Staudinger synthesis and alternative strategies outlined in the Introduction.




**Scheme 44**. Retrosynthetic analysis of Ezetimibe.

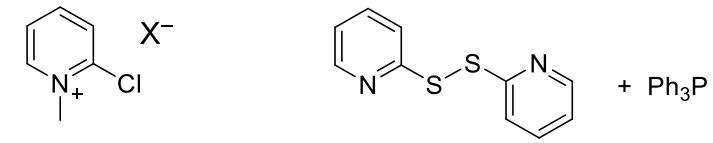
While the Staudinger [2 + 2] synthesis offered an attractive approach, its modest enantioselectivity outcome necessitated consideration of other methods. The Breckpot method and Mukaiyama's reagent emerged as viable alternatives, offering diverse routes to β-lactam synthesis with varying degrees of enantioselectivity and yield improvements.

The Breckpot method, developed by Breckpot in 1923,[246,247] relies on deprotonation of β-amino esters by a Grignard reagent, the resulting N−MgBr species then undergoes a 4-*exo-trig* ring closure to afford the desired β-lactam (**Scheme 45**). β-Lactams with or without substituents at positions 3, 4 or at N atom can be synthesized by variation of the starting β-amino ester.




**Scheme 45**. Breckpot synthesis of 4-membered β-lactam.

Another way to construct β-lactams is to cyclize β-amino acids using Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide **4.A**, **Figure 27**).[248,249] However, the original Mukaiyama's reagent only gives moderate yields, around 50%. Replacement of the nucleophilic iodide counterion with non-nucleophilic triflate (2-chloro-1-methylpyridinium iodide **4.B**, **Figure 27**) improved the yields quite dramatically (90%).[250] Another reagent, also referred to as Mukaiyama's reagent, as it was first reported by Mukaiyama in 1970,[251] has been further developed by Kobayashi.[252] This reagent is a mixture of triphenylphosphine ($PPh_3$) and 2,2'-dipyridyldisulfide (DPS) (**4.C**, **Figure 27**) in acetonitrile as a solvent allowing to synthesize β-lactams in good to excellent yields. Notably, racemization is largely suppressed in this reaction system.

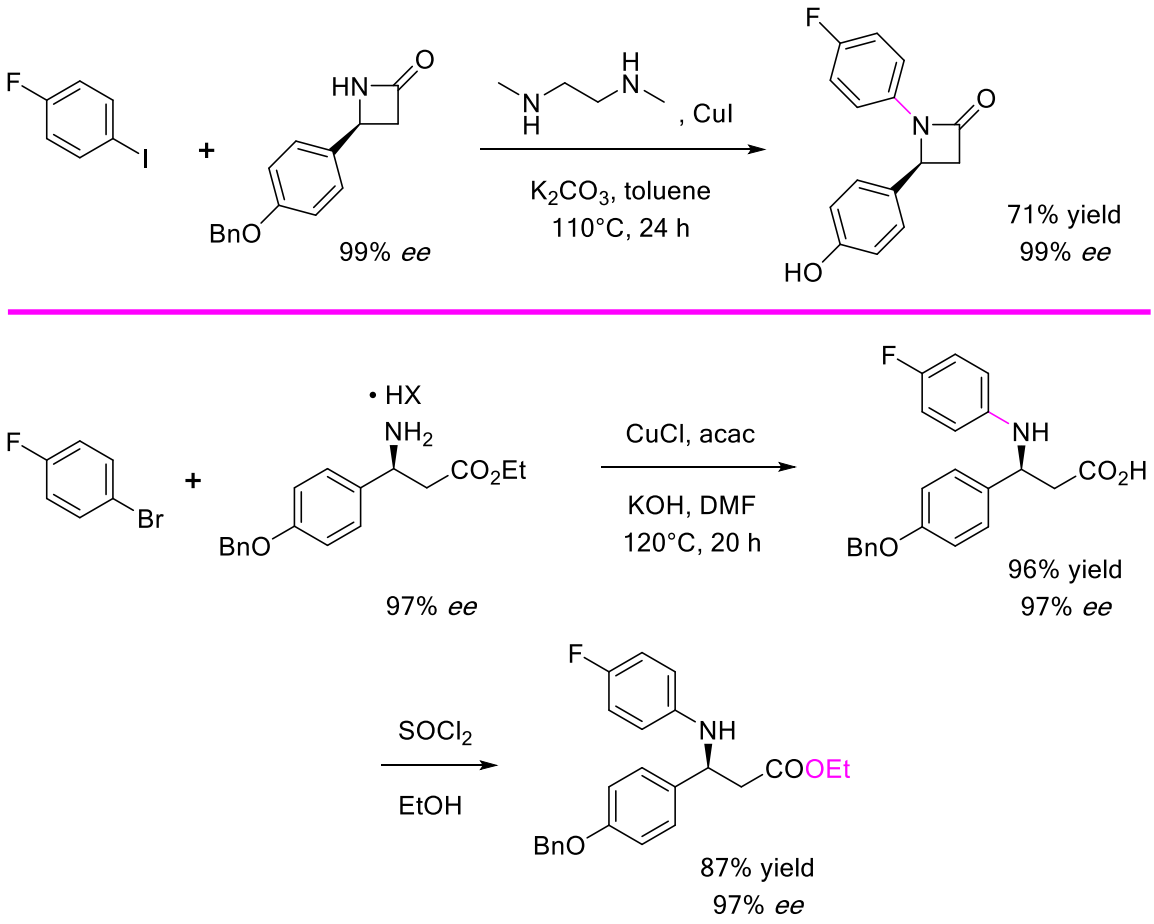



4.A, X = I
4.B, X = TfO

4.C

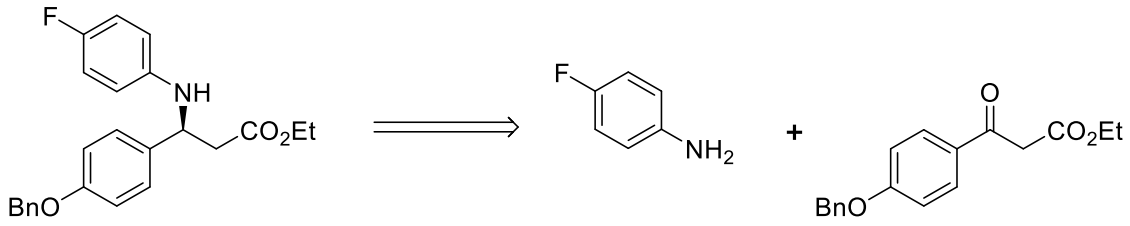
**Figure 27**. Mukaiyama's reagents.

A different strategy that relies on the Ullmann-type *N*-arylation of either β-lactams or esters of β-amino acids with Ar–I, was reported by Wang *et al*. and Busscher *et al*. (**Scheme 46**)[166,193] and covered in the **Introduction** part (*vide supra*). Since the enantiopurity of the starting β-lactam was preserved in the product, despite the rather harsh conditions, this strategy would seem to be quite attractive. Nevertheless, in view of the successful enantioselective synthesis of *N*-aryl β-amino acids directly from β-keto esters and the corresponding anilines, developed in our group earlier,[253] the *N*-arylation was not considered.



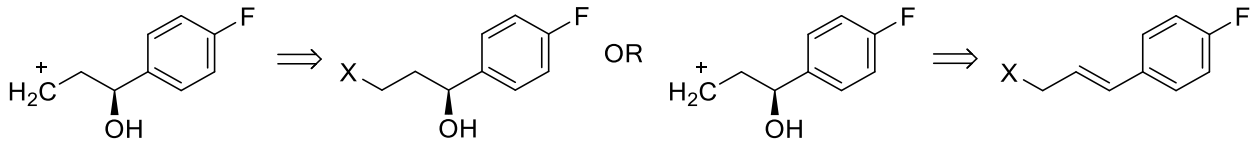

**Scheme 46**. Ullmann-type reactions by Wang *et al*.[166] and Busscher *et al*.[193]

Building upon our group's expertise in enantioselective reductive amination, we chose the Breckpot protocol for *N*-aryl β-lactam synthesis, employing a benzyl group for hydroxyl protection and a Claisen condensation for β-keto ester construction (**Scheme 47**).




**Scheme 47**. Retrosynthetic analysis of β-aminoester.

While having an apparently robust plan for the construction of the β-lactam core, the next goal to address was to find the best way for the introduction of the side chain. However, any building block containing the required benzylic hydroxyl group (**Scheme 48**) is likely to be prone to either ring closure on treatment with a nucleophile (e.g., the enolate of the β-lactam) or dehydration. Hence alkylating agents of this kind were excluded.




**Scheme 48**. Retrosynthetic analysis of the side chain.

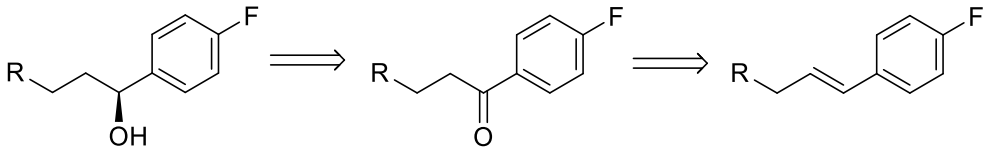
After evaluating different pathways, we opted for electrophilic alkylation prior to the introduction of the hydroxyl group. This would involve using a substituted allyl halide and subsequent side chain functionalization. While unsubstituted cinnamyl alcohol is readily available, its substituted analogs had to be synthesized.

However, the latter functionalization of the cinnamyl moiety would have to be enantioselective. Here, inspiration was drawn from the work of Hu *et al*.,[254] who developed a catalytic hydrosilylation of various mono- and 1,2-disubstituted alkenes. This process yielded racemic hydrosilylated products convertible into different derivatives, including alcohols, but was limited to (*Z*)-alkenes.

Another avenue considered was bromoacyloxylation reactions, wherein the double bond undergoes electrophilic bromination followed by nucleophilic opening of the intermediate bromonium ion with carboxylic acid. Ng *et al*.[255] and Ahmad *et al*.[256] achieved notable results using various nucleophiles (benzoate and acetate anions, respectively) and catalysts, with *anti*-stereoselectivity and correct regioselectivity.

Enantioselective bromoacyloxylation of selected alkenes was also investigated using various chiral organocatalysts (BINOL-derived phosphoric acids[257] or dimeric cinchona alkaloid $(DHQD)_2PHAL$[258]), albeit with mixed success in achieving enantiomeric excess. Mostly, *N*-bromosuccinimide or *N*-bromobenzamide served as the bromine source in these reactions.

Eventually, we considered a two-step oxidation-reduction approach for the enantioselective construction of benzylic-type alcohols. This would involve Wacker oxidation[259] of the double bond of **4.F** with the well-established $Pd(OAc)_2$/*p*-benzoquinone system to yield a ketone **4.E**, followed by stereoselective reduction using the Corey-Itsuno oxazoborolidine,[260] which should afford the enantioenriched benzylic alcohol **4.D** (**Scheme 49**).



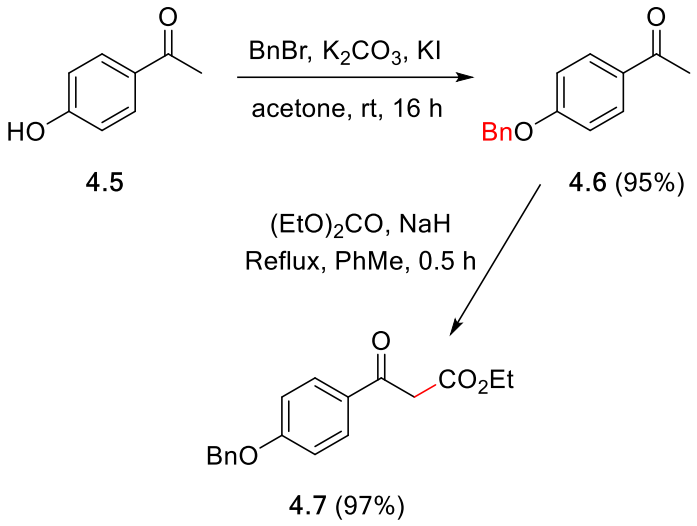

4.D 4.E 4.F

**Scheme 49**. Retrosynthetic analysis of the (*S*)-OH moiety.

# Total synthesis of Ezetimibe and its analogues

## Synthesis of the lactam core

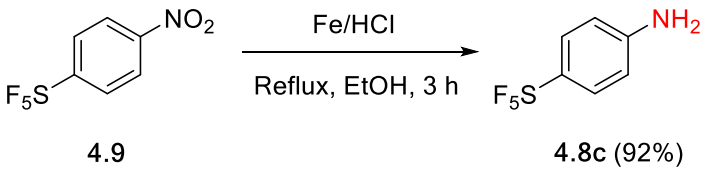
Benzylation of the commercially available 4-hydroxyacetophenone **4.5**[261] afforded the protected *O*-benzyl derivative **4.6**, which on Claisen condensation, using the Krapcho protocol,[262] was converted into the β-keto ester **4.7** (**Scheme 50**).




**Scheme 50**. Benzylation of 4-OH-acetophenone, followed by Claisen condensation.

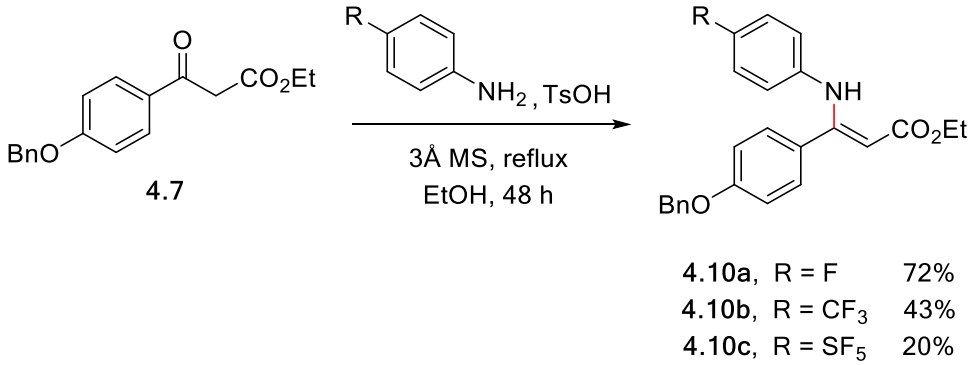
The next step required the conversion of β-keto ester **4.7** into the corresponding imine, that would be subsequently reduced to produce the desired β-amino ester. However, it is known that imines of that type exist mainly as the enamine tautomers. Nevertheless, previous work in our group demonstrated that the equilibration can be accelerated by acid and the imine, although a minor component in this equilibrium, can be reduced with $HSiCl_3$ in the presence of a chiral organocatalyst and thus continuously siphoned off. Of the available protocols for the generation of imines from ketones, discussed in Part 1, condensation of the keto ester **4.7** in an aromatic solvent with the amine upon an azeotropic removal of water[263] appeared particularly suitable. Eventually, we settled for a modification, in which a mixture of the β-keto ester **4.7**, amine (1.1 equiv), and a catalytic amount of *p*TSA in dry ethanol is heated at reflux.[253]

Three *para*-substituted anilines were selected for this study, namely 4-fluoroaniline (**4.8a**), 4-trifluormethyl aniline (**4.8b**), and 4-pentafluorosulfanyl aniline (**4.8c**). While the first two of this series are commercially available, the third one, still regarded as a rather exotic compound, was prepared by reduction of the commercially available nitro derivative (**4.9**).[264] A plethora of method for the reduction are available in the literature, such as catalytic hydrogenation over palladium on carbon[265] or Raney nickel,[266] reduction by sulfur anions in low oxidation states – $Na_2S_2O_4$,[267] $Na_2S$[268] or $(NH_4)HS$,[269] also by tin(II) chloride[270] and by metals (iron,[271–274] tin,[275] zinc[276]) in acidic media. Of these we chose a combination of iron powder and HCl, which on boiling in ethanol for 3 h afforded the desired aniline derivative **4.8c** in 92% yield on a multigram scale (**Scheme 51**).




**Scheme 51**. Reduction of 4-$SF_5$-nitrobenzene.

Initial experiments, where a mixture of the β-keto ester **4.7**, 4-pentafluorosulfanyl aniline **4.8c** (1.1 equiv), and a catalytic amount of *p*TSA in dry ethanol was heated at reflux for 1 day,[253] afforded the corresponding enamine **4.10c** in 10% yield. Addition of molecular sieves (3 Å) followed heating and reflux for another day improved to yield to 25-30% (**Scheme 52**). Alternative recommended procedures using $TiCl_4$[277] or PyBOP and imidazole[278] proved fruitless.




**Scheme 52**. Synthesis of enamines.

After this partial success, we focused on the preparation of the 4-F and 4-$CF_3$-aniline derivatives **4.10a** and **4.10b**. Here, an important observation was made: we noticed that the stirring bar actually grinded the molecular sieves to powder over the period of 24 h on heating to reflux. Therefore, in a new experiment, the reaction mixture was heated without stirring, which indeed improved the yields. Thus, the *p*-F-derivative **4.10a** and its $CF_3$ counterpart **4.10b** were obtained in >70% yield and 43% yield, respectively. It should be noted that during the column chromatography separation in all experiments formed enamines were eluted in the first fractions and easily separated. The following fractions contained an inseparable mixture of the unreacted β-keto-ester and aniline derivative. Submitting this mixture to the reaction again, provided more additional batches of **4.10a**, **4.10b** and **4.10c**, which in fact increased the overall yield.

## Synthesis of the organocatalyst Kenamide

The enantioselective reduction of enamines **4.10a**-**4.10c** required a chiral organocatalyst. Several of these were developed in the group previously, the most successful being Kenamide (**4.G**) and Sigamide (**Figure 28**).[52,53,279,280] Both are based on the natural L-Valine, in which the *N*-terminus is converted into *N*-methyl formamide, while the carboxyl terminus is in the form of anilide, differing in the 3,5-substituents. Their catalytic activity is practically the same, the enantioselectivity being only marginally higher with Sigamide. No sufficient quantity of any of these two catalysts was available within the group anymore, so that it had to be synthesized again. Since 3,5-dimethylaniline, a precursor for Kenamide, is about 35 times less expensive than 3,5-di-*tert*-butylaniline, we chose to prepare Kenamide for further experiments.

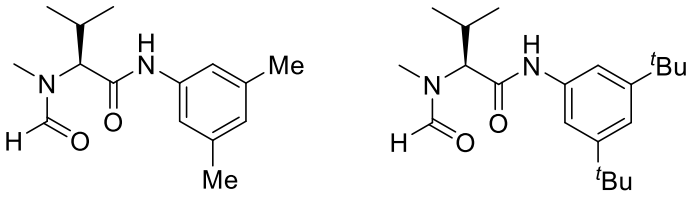
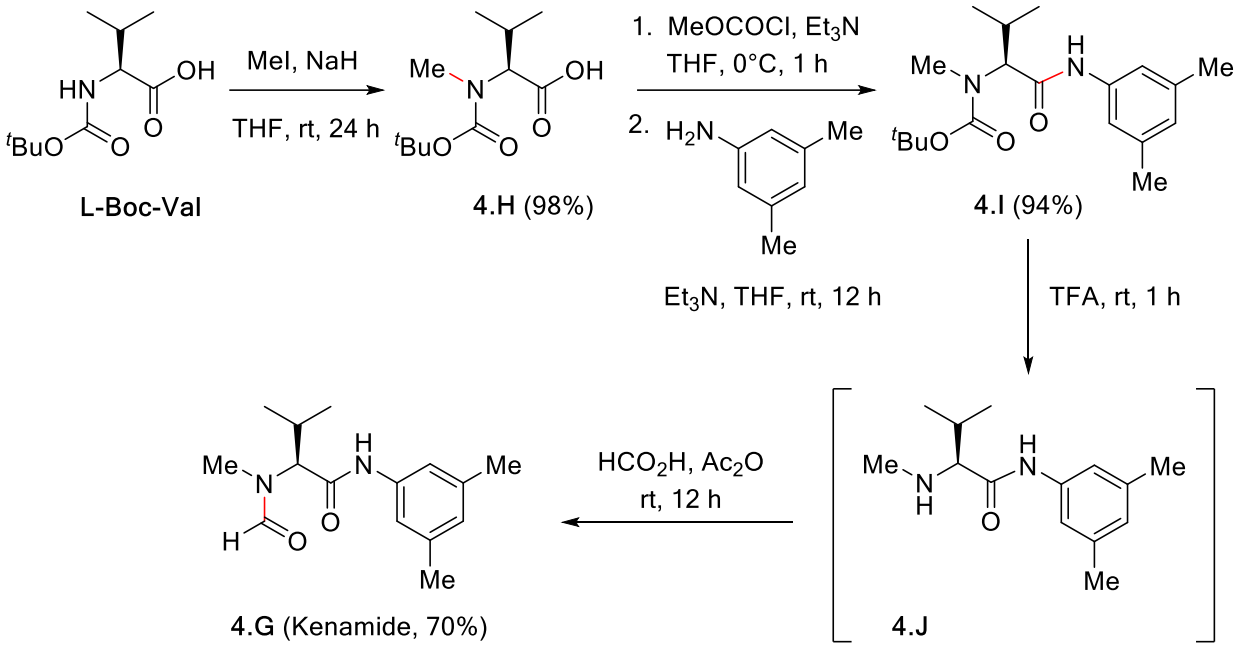



**Figure 28**. Kenamide (**4.G)** and Sigamide structures.

In the synthesis, we followed the original procedure, developed earlier in the group (**Scheme 53**).[53] The commercially available Boc-L-valine was first selectively *N*-methylated by iodomethane in the presence of sodium hydride in THF at room temperature over 24 hours. Notably, the order of addition of the individual reagents is the key to avoid a concomitant methylation of the carboxyl: the optimized protocol, based on mechanistic investigation,[281] requires that NaH is slowly added to the solution of Boc-L-valine and methyl iodide, not the other way around. The resulting *N*-methyl-Boc-L-valine (**4.H**), obtained in a quantitative yield was converted into amide **4.I** using a mixed-anhydride method, namely by treatment with methyl chloroformate at 0 °C, followed by addition of 3,5-dimethylaniline and stirring the mixture at rt overnight. The Boc group was then removed with trifluoroacetic acid (TFA) and the resulting amine **4.J** was treated at rt with a mixed anhydride, generated *in situ* by mixing formic acid and acetic anhydride. Purification by column chromatography afforded Kenamide (**4.G**) in a good yield over 3 synthetic steps (64% overall) and with retention of enantiopurity.

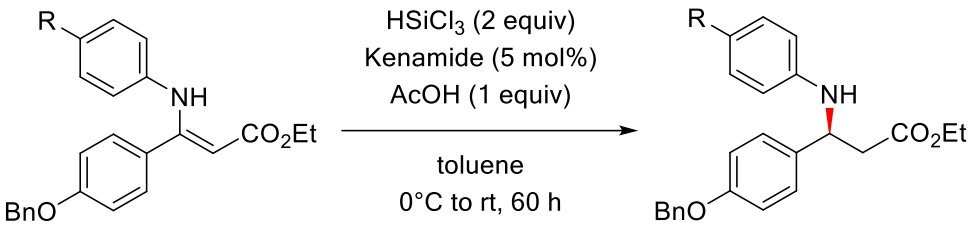



**Scheme 53**. Synthesis of Kenamide from Boc-L-Val.

## Reduction of enamines

With freshly prepared catalyst in hands, we could embark on the enantioselective reduction of enamines **4.10a**-**4.10c**. In addition, each reaction was to be carried out in a racemic version for comparison and determining the enantioselectivity.

For the racemic reduction we used DMF as a catalyst (10 mol %) in toluene, 2 equivalents of trichlorosilane as a reductant, and glacial acetic acid (1 equiv) to facilitate the enamine-imine equilibration. The reaction was usually left while stirring at rt for 2-3 days. The asymmetric variant was carried out with Kenamide as a catalyst (5 mol %) under the same conditions. The enantiopurity of the resulting β-amino esters **4.11a**, **4.11b** and **4.11c** was in the range of 78-92% *ee* (**Scheme 54**). The variation of the enantiomeric excess may be interpreted as a function of the steric bulk of the substituent R, but it would be premature to make this conclusion, since the electron-withdrawing effect may also play a role. The absolute configuration was established earlier for a closely related analogue[253] and was confirmed by the successful synthesis of the correct enantiomer of Ezetimibe (*vide infra*).




**4.10a**, R = F
**4.10b**, R = $CF_3$
**4.10c**, R = $SF_5$

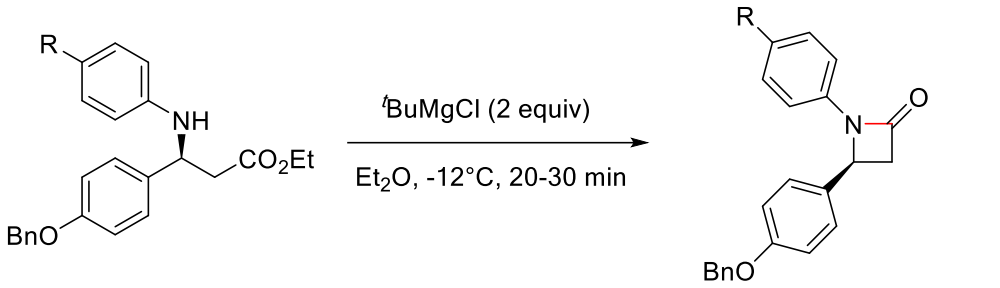
**4.11a**, R = F 83% (89%), 78% *ee*
**4.11b**, R = $CF_3$ 93% (97%), 86% *ee*
**4.11c**, R = $SF_5$ 87% (88%), 92% *ee*

**Scheme 54**. Reduction of enamines; racemic version was carried out with DMF in place of Kenamide and its yields are shown in parentheses.

## Cyclization of β-amino esters

At the next step we focused on the ring closure of the β-amino esters into the corresponding β-lactams. According to the protocol developed by Michaut *et al.*,[282] a solution of commercial MeMgBr (2 equiv) was added dropwise to an ethereal solution of the corresponding β-amino ester at -12 °C. During this addition, a sticky semi-solid material was formed, which partly clogged the magnetic stirrer in the case of all β-amino esters **4.11a**-**4.11c** (F-, $CF_3$- and $SF_5$-containing). Following completion of the reaction and a straightforward work-up procedure, purification was achieved using column chromatography. It is important to highlight that both the product and the starting β-amino ester exhibited similar Rf values, rendering their separation on a column challenging. Nevertheless, these initial trials gave satisfactory results, with good yields (65-70%) and the retention of enantiomeric purity.

Switching from MeMgBr to the bulkier *t*BuMgCl turned out to increase the yields >85% (after optimization) of the desired lactams **4.12a** and **4.12c** that were obtained, again, with full retention of the enantiopurity (**Scheme 55**). However, while the cyclization of **4.11a**, **4.11c** and their racemic counterparts proceeded smoothly, difficulty was encountered in the case of the $CF_3$-derivative **4.11b**. Here, after addition of 2 equivalents of *t*BuMgCl, the mixture turned dark and the yield of **4.12b** dropped to 35-40% in both enantiomerically enriched and racemic versions. Unfortunately, due to the time pressure and limited source of the starting material, no attempts could be made at improving the outcome.




| | | | |
|---|---|---|---|
| **4.11a**, R = F | | **4.12a**, R = F | 71% (86%) |
| **4.11b**, R = $CF_3$ | | **4.12b**, R = $CF_3$ | 35% (41%) |
| **4.11c**, R = $SF_5$ | | **4.12c**, R = $SF_5$ | 89% (77%) |

**Scheme 55**. Synthesis of β-lactams, yields of racemic versions are shown in parentheses.

Attempted crystallization of the $SF_5$-β-lactam **4.12c** (92% *ee*) from chloroform afforded a tiny amount of crystals, which turned out to be racemic **4.12c**, according to crystallographic analysis (**Figure 29**). This interesting result suggests that this procedure could be used for enhancing the enantiopurity of the enantiomerically enriched **4.12c**.

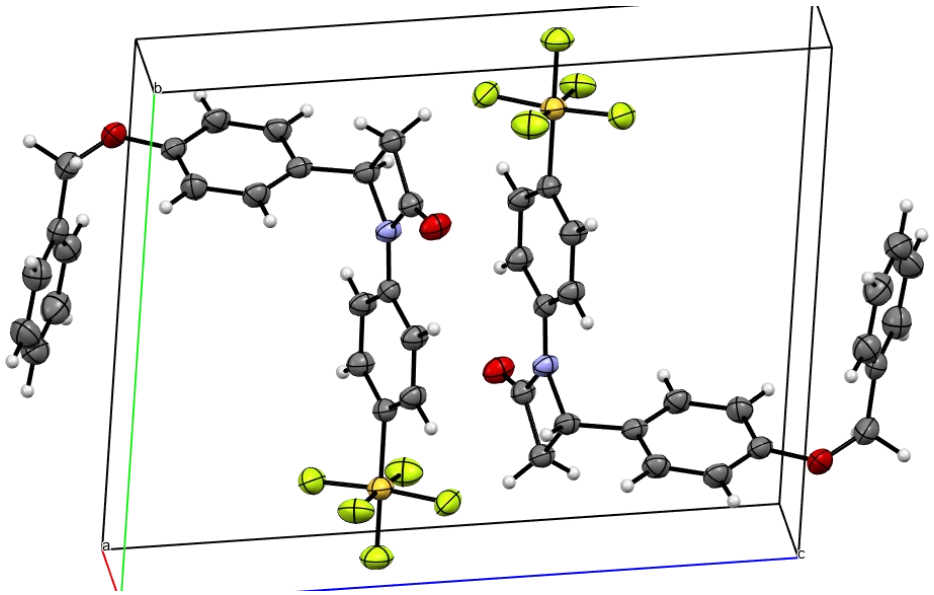


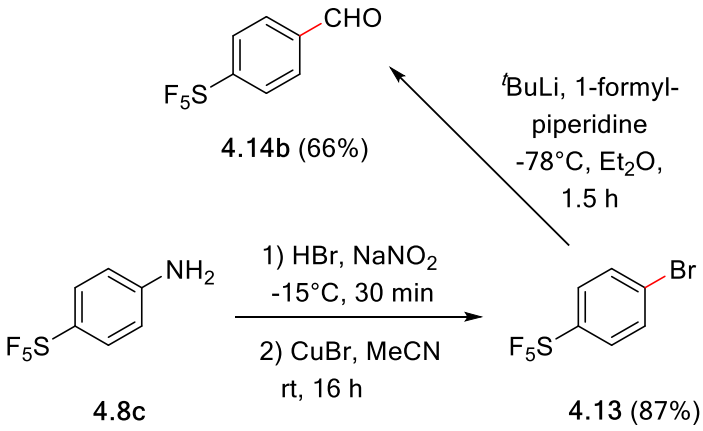
**Figure 29**. ORTEP diagram of racemic β-lactam (±)-**4.12c**.

## Synthesis of the side chain

The strategy for the construction and the appending the side chain was outlined in the introduction to this chapter (**Scheme 49**). We have opted for α-alkylation of the β-lactam with a cinnamyl moiety that would be subsequently functionalized to introduce the hydroxy group in a stereoselective manner. The required *p*-substituted cinnamyl derivatives would be prepared from the *p*-substituted benzaldehydes by Wittig olefination (*vide infra*).

While *p*-fluorobenzaldehyde (**4.14a**) is commercially available, its *p*-$SF_5$ analog **4.14b** was prepared by formylation of the bromo derivative **4.13**, which in turn was obtained from the aniline derivative **4.8c** as follows (**Scheme 56**). Diazotization of 4-($SF_5$)-aniline **4.8c** in acetonitrile, followed by the Sandmeyer reaction with CuBr[283] afforded bromide **4.13** (87%) as a substrate for formylation. It is pertinent to note that this classical protocol turned out to be superior to more recent modifications.[284,285]

For the formylation, we first used the conditions described by Zarantonello,[264] according to which bromide **4.13** was lithiated with *t*BuLi in ether at -78 °C, stirred for 1h and then 1-formylpiperidine (NFP) was added in small portions. After stirring at -78 °C for 30 min and then at rt for 4 h, the mixture was worked up and the crude product was purified by column chromatography to afford the pure aldehyde **4.14b** but in mere 30% yield. We then switched to a patented procedure,[286] which recommended shortening the stirring period during lithiation to 30 min (at -78 °C) and omitting the stirring at rt. Indeed, that procedure afforded the desired aldehyde **4.14b** in a much better yield (66%) on a >5 g scale.




**Scheme 56**. Two-step formylation of 4-($SF_5$)-aniline **4.7c**.

Olefination of aldehydes **4.13a** and **4.13b** was carried out by employing Wittig olefination. For the synthesis of corresponding cinnamyl esters we opted to utilize commercially available (carbethoxymethylene)triphenylphosphorane (ethyl (triphenylphosphoranylidene)acetate), as the ylide. According to a protocol outlined by West *et al*.,[287] we combined the solution of the corresponding benzaldehyde in $CH_2Cl_2$ with the ylide at rt and allowed it to stir overnight. In a case of both benzaldehydes, **4.14a** and **4.14b**, we successfully isolated cinnamyl esters **4.15a** and **4.15b** in yields revolving around 95% on a >10 g scale.

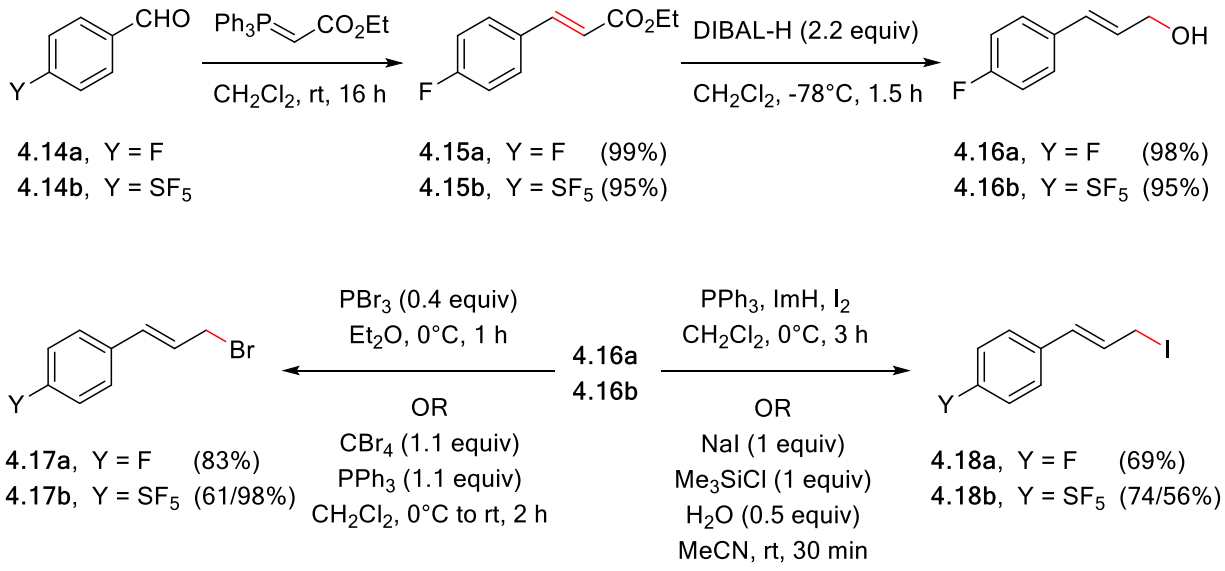
The subsequent transformation entailed the reduction of the freshly synthesized acrylates **4.15a** and **4.15b** to yield the corresponding cinnamyl alcohols **4.16a** and **4.16b**. Following a protocol from the same authors with minor adaptations, the solution of the corresponding acrylate in anhydrous $CH_2Cl_2$ was treated with 2.2 equivalents of commercial diisobutylaluminium hydride (DIBAL-H) solution at -78 °C for 1.5 h. After work-up and column chromatography purification (if needed), cinnamyl alcohols **4.16a** and **4.16b** were isolated in quantitative yields (95-98%) on a >10 g scale.

Resulting cinnamyl alcohols **4.16a** and **4.16b** necessitated conversion into the final electrophilic alkylating reagent. Reviewing literature, we observed Goyal's attempt[180] to use alkyl tosylates as alkylating agents for electrophilic alkylation of 4-membered β-lactam cycles at position 3, albeit unsuccessfully. Given this, we opted for direct halogenation of alcohols to generate bromides or iodides.

Several methods were explored. Initially, we pursued bromination of the synthesized cinnamyl alcohols employing the conventional method with $PBr_3$.[287,288] The reaction involved treating the ethereal solution of the corresponding cinnamyl alcohol with phosphorus tribromide (0.4 equiv) at 0 °C. Following work-up, products **4.17a** and **4.17b** were simply extracted with *n*-hexane, making the column chromatography unnecessary. However, yields of final bromides differed significantly. While 4-F-substituted product **4.17a** was isolated in high yield (83%), its $SF_5$-substituted counterpart **4.17b** was obtained in a moderate yield (61%). Thus, for $SF_5$-substituted cinnamyl alcohol **4.16b** we switched to another protocol,[289] namely Appel reaction, employing $CBr_4$ as a brominating agent, which proved to be very efficient and allowed to obtain bromide **4.17b** in a quantitative yield (98%) on a >5 g scale, albeit with the presence of unavoidable and inseparable

bromoform ($CHBr_3$) as a side product. Luckily, this compound does not interfere with any of our substances and might be chromatographically separated in the following steps.

In subsequent experiments, we sought the possibility to enhance the electrophilicity of the alkylating agent by preparing iodides. For this purpose, we adopted the well-described protocol of the Appel reaction by Xu *et al.*[290] A mixture of triphenylphosphine, imidazole, and iodine in $CH_2Cl_2$ was combined with the cinnamyl alcohols **4.16a** or **4.16b** at rt. Purification of the crude products using column chromatography with a highly non-polar eluent furnished the desired iodides **4.18a** and **4.18b** in a good yield (69-74%). Despite the promising results (74% yield) for the iodide **4.18b**, alternative protocol was considered,[291] though ultimately deemed less practical due to lower yields (56%) and cumbersome work-up procedures. The obtained iodides were promptly employed in subsequent transformations due to their noticeable degradation over several days. Although the exact cause of decomposition remains unclear, moisture and light sensitivity are plausible factors. All synthetic transformations are demonstrated on **Scheme 57**.



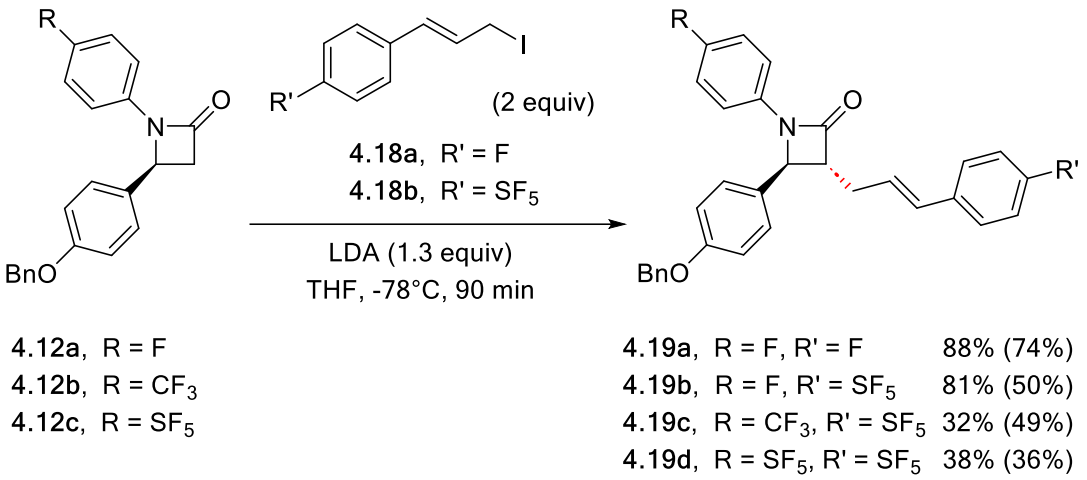

**Scheme 57**. Various synthetic paths towards cinnamyl bromides **4.17a**-**4.17b** and iodides **4.18a**-**4.18b**.

## Alkylation of β-lactams

Since the enolates derived from β-lactams are generally less reactive than expected,[190,292] strong electrophiles need to be employed, such as allylic halides. Therefore, we chose iodides **4.18a,b** rather than bromides **4.17a,b** expecting a better reactivity. Thus, β-lactams **4.12a-4.12c** were enolized with LDA (1.3 equiv) at -78 °C and the resulting enolates were alkylated with allylic iodides **4.18a,b** (or, in some cases, with bromides **4.17a,b**) (**Scheme 58**).

Alkylation of the *p*-F-substituted β-lactam **4.12a** with *p*-F-cinnamyl iodide **4.18a** proceeded readily, giving the expected product **4.19a** (88%) as a single diastereomer (>20:1 *dr*), as was assigned following analysis of its $^1$H NMR spectrum where a small coupling constant $J_{3,4}$ = 2.4 Hz between the protons on C(3) and C(4) was observed. Similar result was attained with racemic β-lactam **4.12a**. Alkylation of the same β-lactam **4.12a** with the *p*-$SF_5$-substituted cinnamyl bromide **4.17b** proceeded readily as well, giving rise to **4.19b** in 81% yield, again as a single diastereoisomer. It is pertinent to note that these results were attained with commercial LDA. In the initial experiments with LDA generated from *n*-BuLi and *i*$Pr_2NH$, the yield of **4.19b** was lower, presumably due to undesired side reactions of the pentafluorosulfanyl group with unreacted *n*-BuLi that were reported in the literature.[224]

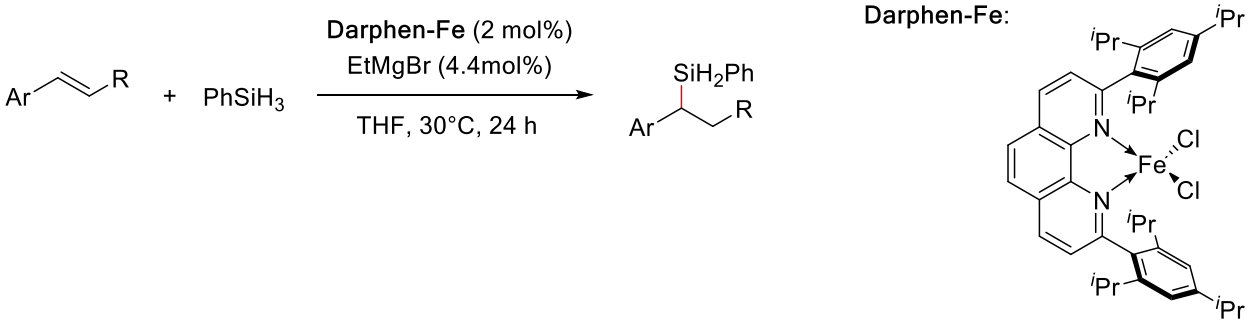
Alkylation of the remaining β-lactams **4.12b,c** with the *p*-$SF_5$ cinnamyl iodide **4.18b** or bromide **4.17b** gave the expected products **4.19c** and **4.19d** as single diastereoisomers ($J_{3,4}$ = 2.5-2.6 Hz), though in lower yields, presumably due to the effect of the electron-withdrawing effect of the *p*-substituents; the reactivity decreased in the order F > $CF_3$ > $SF_5$. Obviously, these transformations call for optimization.




**Scheme 58**. Alkylation of β-lactams. The yields in parentheses refer to the racemic compounds.

## Functionalization of the side chain

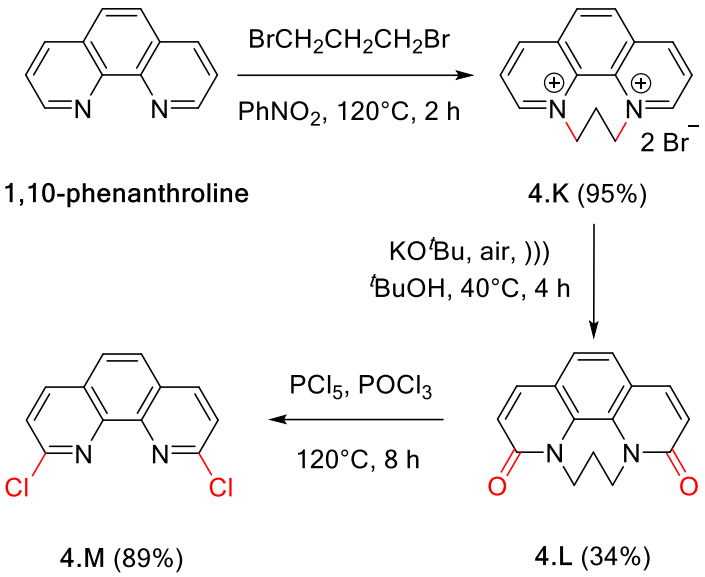
Ideally, enantioselective hydration of the alkylated β-lactams **4.19a-d**, proceeding in Markovnikov fashion, would deliver the desired Ezetimibe and its analogs in one step. Several approaches were considered, based on literature data. Thus, hydrosilylation reported by Hu,[254] employing Darphen-Fe catalyst, may seem promising, as the resulting product could be converted in the corresponding alcohol in an oxidation reaction that is known to proceed with retention of configuration.[293–295]




**Scheme 59**. Hydrosilylation of styrenes by Hu *et al*.

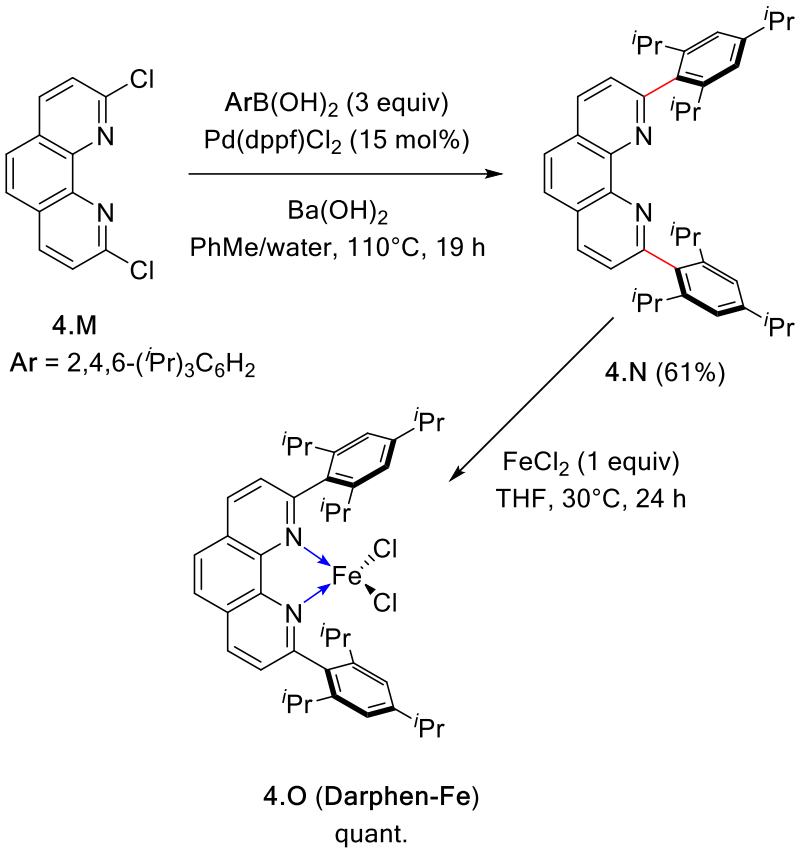
Although this iron(II)-catalyzed hydrosilylation was only developed as a racemic procedure, its enantioselective version could be envisaged. To verify the suitability of this methodology to Ezetimibe-like substrates, we resolved to first synthesize the catalyst. Several approaches to the ligand have been developed, starting with the preparation of 2,9-dichloro-1,10-phenanthroline

**4.M**. Of the existing methods,[296–300] we chose the most recent publication by Guo *et al.*[301] (**Scheme 60**): 1,10-phenanthroline was first alkylated with 1,3-dibromopropane and the resulting cyclic product **4.K** (95%) was oxidized with air in a strongly alkaline medium to afford dione **4.L** (30%). The latter product was then converted into the 2,9-dichloride **4.M** (89%) upon heating with a mixture of $PCl_5$ and $POCl_3$.




**Scheme 60**. Synthesis of 2,9-dichloro-1,10-phenanthroline **4.1.m**.

Suzuki-Miyaura coupling of dichloride **4.M** with an excess of (2,4,6-triisopropylphenyl)boronic acid afforded the desired ligand **4.N**, coordination of which with $FeCl_2$ gave the required Darphen-Fe complex **4.O**. The complex formation was carried out according to the published procedure in a glove-box, using the freshly prepared ligand, iron(II) chloride, and tetrahydrofuran, and allowing the mixture to stir at rt for 24 h. However, contrary to the expected outcome, no precipitation occurred and subsequent attempts to induce precipitation by evaporating the solvent and re-dissolving the residue in THF led to undesired color changes and the formation of brown solids, inconsistent with the reported catalyst appearance. In a repeated attempt, a crucial modification was implemented: upon completion of the chelation, the entire mixture was evaporated to dryness, resulting in the quantitative yield of the product **4.O**. The appearance of the synthesized Darphen-Fe **4.O** in this instance corresponded to that described in the literature.[254]



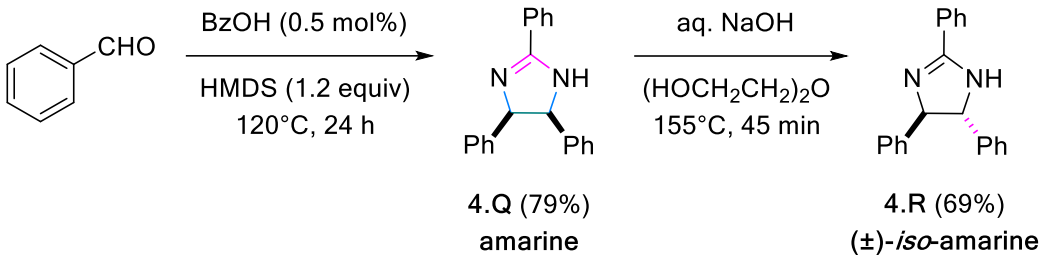

**Scheme 61**. Synthesis of Darphen-Fe **4.O**.

The hydrosilylation catalyzed by Darphen-Fe (**4.O**) was first attempted with *trans*-β-methylstyrene as a model substrate, which in turn was obtained by an iron(III)-catalyzed isomerization of allylstyrene.[302] However, the attempted silylation failed in our hands and so did the experiment using *trans*-anethole. Therefore, a different way of functionalization was investigated.

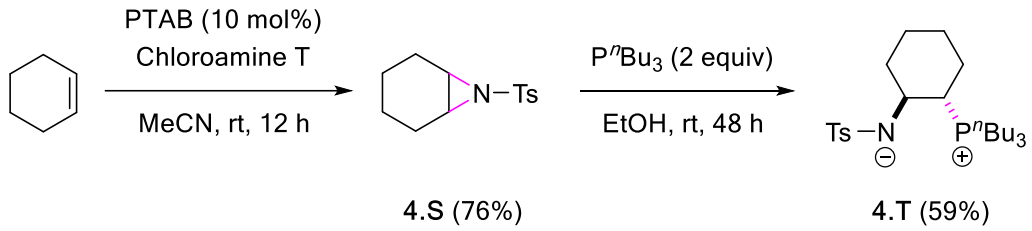
## Bromoacyloxylation

Since the hydrosilylation proved fruitless, we turned to electrophilic bromoacyloxylation, which is known to deliver an acyloxy group into the benzylic position.[255,256] Here, the desired Markovnikov-type regioselectivity can be enhanced by using (±)-*iso*-amarine **4.R**, as demonstrated with bromoacetoxylation of various 1,2-disubstituted trans-styrenes[256] with added diastereoselectivity. Since attempts at reproducing the microwave-assisted literature procedure[303]

for the synthesis of isomarine proved unsuccessful, a more conventional route[304,305] was followed: heating a mixture of benzaldehyde, HMDS, and a catalytic amount of benzoic acid, followed by a tedious workup afforded amarine **4.Q** (**Scheme 62**). Subsequent epimerization using NaOH at high temperature then produced the desired (±)-*iso*-amarine **4.R** in 69% yield.[305] Another molecule known to promote bromoacyloxylation is the bifunctional amide/phosphonium zwitterionic catalyst **4.T**.[255] Its synthesis was carried out according to the literature, which entailed a two-step process starting with commercially available compounds, namely cyclohexene, chloroamine-T, trimethylphenylammonium tribromide (PTAB) and tributylphosphine, culminating in the desired zwitterionic compound **4.T** with moderate yield and high purity (**Scheme 63**).

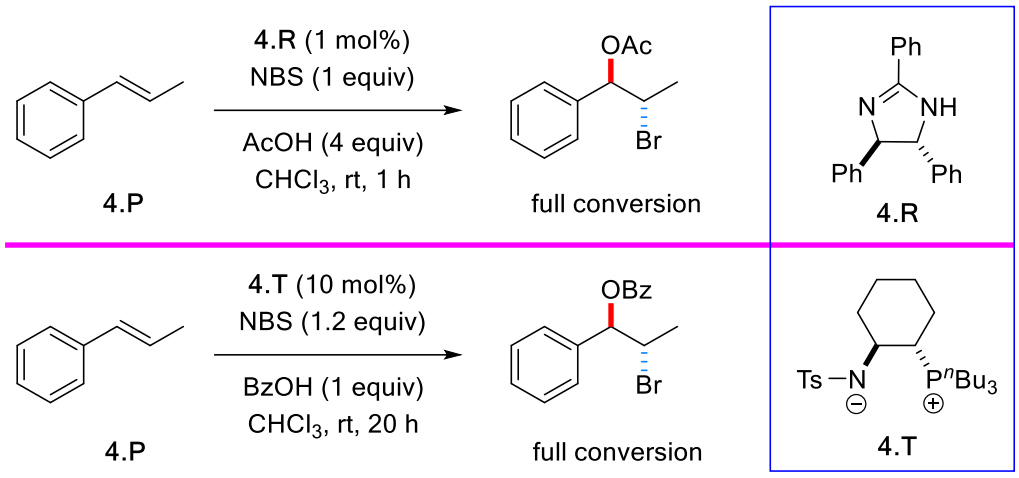



**Scheme 62**. Synthesis of (±)-*iso*-amarine **4.R**.




**Scheme 63**. Synthesis of a catalyst **4.T**.

With these two freshly prepared racemic catalysts in hand, experiments were carried out, employing *trans*-β-methylstyrene **4.P** as a model substrate (**Scheme 64**). Bromoacetoxylation using NBS and (±)-*iso*-amarine (**4.R**) as a catalyst afforded the *anti*-addition product as the sole product (full conversion) with the proper Markovnikov regioselectivity. Similarly, bromobenzoyloxylation, catalyzed by **4.T**, gave the expected product as a single diastereoisomer with full conversion of the starting material.




**Scheme 64**. Electrophilic bromoesterifications in accordance with literature.[255,256]

Since the enantioselective version of these successful reactions would require resolution of the catalysts **4.R** and **4.T** and further developmental work, the project was set aside for the time being and we focused on a yet another strategy.

## Wacker-type oxidation

The palladium-catalyzed Wacker oxidation of styrene-type molecules is known to proceed in the benzylic position to afford the corresponding acylarenes.[306] Hence, if applied to **4.19a-d**, it can be expected to produce the corresponding ketones, whose stereoselective reduction should deliver the desired Ezetimibe derivatives.

Initially, we adopted a patented protocol,[170] which utilized palladium(II) acetate as a catalyst alongside *p*-benzoquinone (1.5 equiv) in acetonitrile. In our hands, racemic **4.19b** afforded the expected ketone **4.20b** in a rather low yield (< 40%). In a similar way, enantiomerically enriched **4.19b** did produce the corresponding ketone but, again in a low yield; The diastereoisomeric purity remain intact in both instances. Hence, it was obvious that the Wacker oxidation required optimization.

Notably, instead of the reported degassing of the solvent using inert gas, we opted for a more efficient Freeze-Pump-Thaw procedure to achieve deoxygenation. The water used in the protocol was degassed in the same way.

Several modifications of the procedure have been reported for oxidation of anethole as a model olefin, which differ in the oxidizing agent (*p*-benzoquinone vs TBHP), added acid, solvent composition, and concentration (**Table 1**):[307–309] of these, Morandi's protocol (entry 3)[308] appeared most promising.

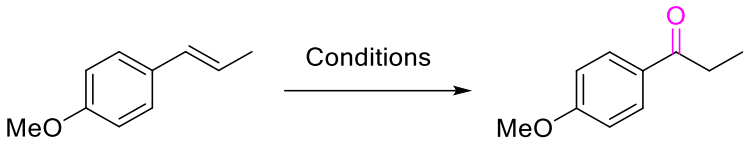
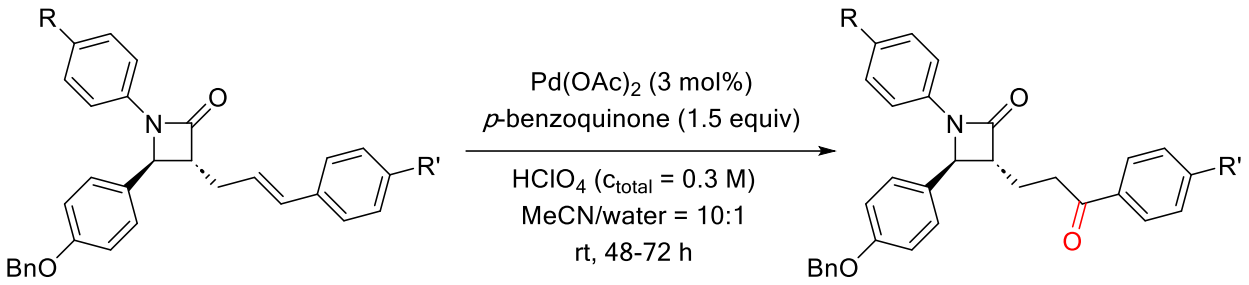



**Table 1**. Exploring of anethole Wacker oxidation.

| Entry | Conditions | Conversion |
|---|---|---|
| 1 | $Pd(OAc)_2$ (3 mol %), *p*-benzoquinone (1.5 equiv), $HClO_4$ ($c_{total}$ = 0.3 M), MeCN/water = 10:1, rt, 24 h | Incomplete[307] |
| 2 | $Pd(OAc)_2$ (3 mol %), *p*-benzoquinone (1.5 equiv), $HClO_4$ ($c_{total}$ = 0.3 M), MeCN/water = 10:1, rt, 24 h [(a)] | Incomplete[170] |
| 3 | $Pd(OAc)_2$ (5 mol %), *p*-benzoquinone (1 equiv), $HBF_4$ ($c_{total}$ = 0.27 M), DMA/MeCN/water = 3.5:3.5:1, rt, 16 h | Full[308] |
| 4 | $Pd(OAc)_2$ (5 mol %), TBHP (3 equiv), *p*TSA (1 equiv), MeCN, rt, 6 h | Incomplete[309] |

(a) Anethole was dissolved in a half of MeCN and added dropwise. Perchloric acid was added in two equal portions.

However, even this protocol proved rather inefficient in the case of β-lactams. Therefore, we turned to a protocol reported by Sova,[174] who recommended strictly air-free conditions. However, we could not see any improvement of the yield either. Moreover, we observed a further fall in the yield (~ 10%). It prompted us to move in the opposite direction and use no such rigorous oxygen exclusion. Indeed, we observed, at long last a substantial increase yields of the products (**Scheme 65**). The ketone intermediate toward original Ezetimibe (**4.20a**) was obtained in high yield (76%) and purity, as shown by NMR and chiral chromatography methods; its racemic version (80%) followed the suite. Somewhat lower yields were obtained in the remaining instances but the stereochemical integrity was preserved, showing that the minor modification of the established methodology of the Wacker oxidation paid off.



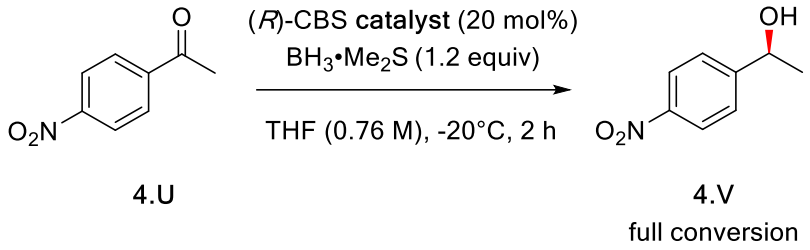

| | | | |
|---|---|---|---|
| **4.19a**, | R = F, R' = F | **4.20a**, R = F, R' = F | 76% (80%) |
| **4.19b**, | R = F, R' = $SF_5$ | **4.20b**, R = F, R' = $SF_5$ | 46% (58%) |
| **4.19c**, | R = $CF_3$, R' = $SF_5$ | **4.20c**, R = $CF_3$, R' = $SF_5$ | 40% (50%) |
| **4.19d**, | R = $SF_5$, R' = $SF_5$ | **4.20d**, R = $SF_5$, R' = $SF_5$ | 51% (43%) |

**Scheme 65**. General view of Wacker-type oxidation.

## Asymmetric reduction

To obtain the correct diastereoisomers by reduction of ketones **4.20a-d**, we chose the Corey-Itsuno method (also known as CBS reduction), as it has a reputation of proceeding with remarkably high stereoselectivity under mild conditions and of tolerance of a wide range of functional groups.[170,310–312]

Initial experiments were performed with a solid form of the (*R*)-Corey-Bakshi-Shibata catalyst in combination with a solution of borane-dimethylsulfide ($BH_3$•$Me_2S$, BMS) adduct in dichloromethane. Ketone **4.20b** along with its racemic counterpart with an F−$SF_5$ combination were used to test the condition. Their reduction, carried out in anhydrous THF at -20 °C, afforded the corresponding alcohol **4.21b** (and its analogue from (±)-**4.20b**) of the anticipated (*S*)-configuration,[170] but in modest yields and diastereomeric purity. Obviously, the experimental procedure required optimization. To this end, we employed 4'-nitroacetophenone **4.U** as a simple test substrate and explored various sources of the reagents (**Scheme 66**). From the tested forms of the catalyst, the 1 M solution in toluene proved to work most efficiently (**Table 2**) in terms of *ee* of the product **4.V** (in all cases conversion of the starting acetophenone **4.U** was complete).




**Scheme 66**. Test experiments employing 4'-nitroacetophenone.

**Table 2**. Exploring of various sources of the (*R*)-Corey-Bakshi-Shibata catalyst.

| **Form of catalyst** | **ee, %** |
|---|---|
| Solid, fresh stock | 76 |
| Solution, old bottle | 86 |
| Solution, fresh stock | 89 |

With these improvements, we could return to ketone **4.20b** and its racemic version. In order to maximize their quantity, alcohol **4.21b** (with (±)-**4.21b**) obtained in the initial experiments, were reoxidized to ketones **4.20b** and (±)-**4.20b** using PCC (Corey-Suggs reagent).

The asymmetric reduction of ketones **4.20a-d** was now performed with fresh reagents as follows (**Scheme 67**): the ketone and the (*R*)-CBS catalyst were dissolved in anhydrous THF and the solution was cooled to -20 °C. A solution of $BH_3$•$Me_2S$ in THF was then added dropwise and the mixture was stirred at -20 °C for 3-5 h. The resulting alcohols **4.21a-d** were obtained in good yields and with high level of diastereoselectivity (*dr* > 8:1) as shown by NMR spectroscopy (**Figure 30**, **Figure 31**). Here, signals at 4.55-4.60 ppm (C*H*-N) for the racemic substances ((±)-**4.21a-b**) exhibit two doublets of approximately similar areas referring to two diastereoisomers. On the other hand, integration of the signals for their scalemic counterparts (**4.21a-b**) corresponds to > 8:1 *dr*. Further, NMR results were corroborated by chiral HPLC, where the indicated substances **4.21a** and **4.21b** display product ratios of 90:5:4:1 and 87:7:5:1, respectively.

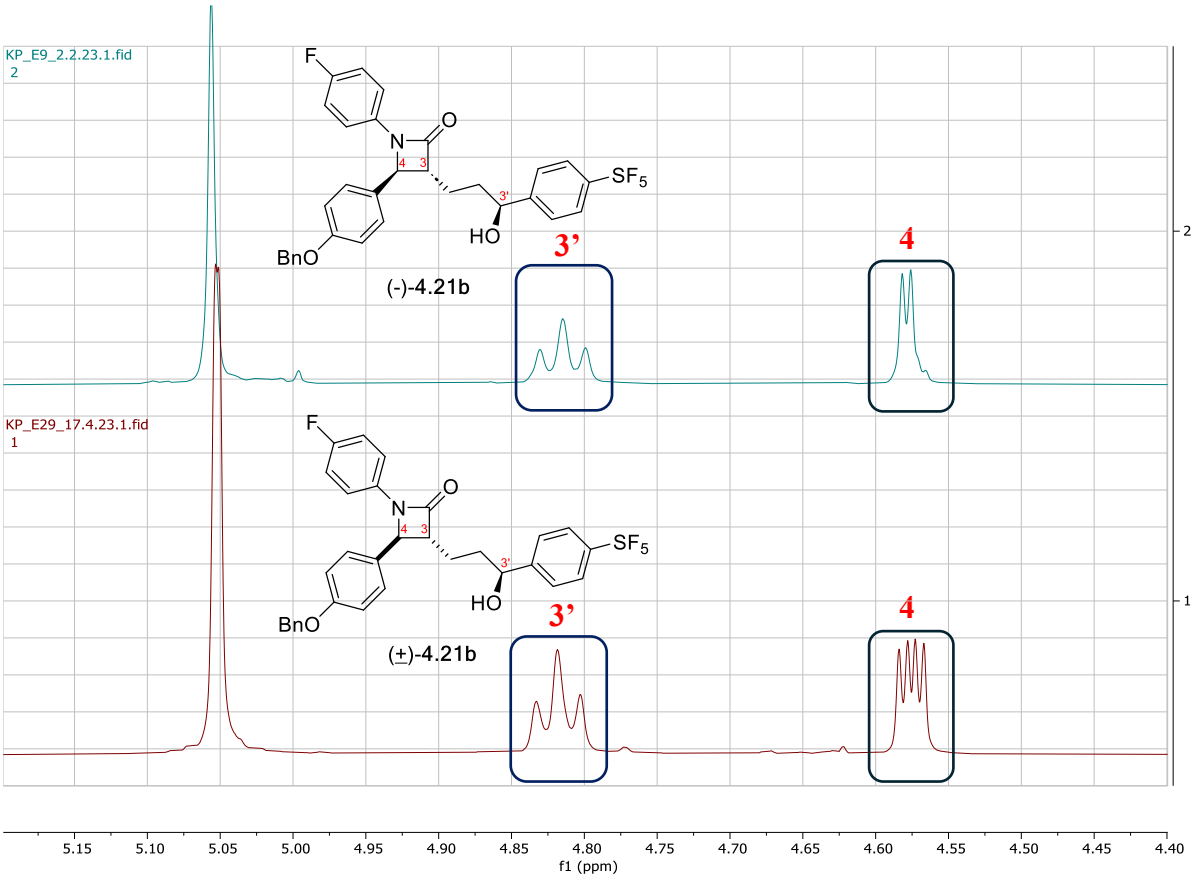



**Figure 30**. $^{1}$H NMR spectra (4.40-5.20 ppm) of enantioenriched (-)-**4.21b** and its counterpart (±)-**4.21b**.

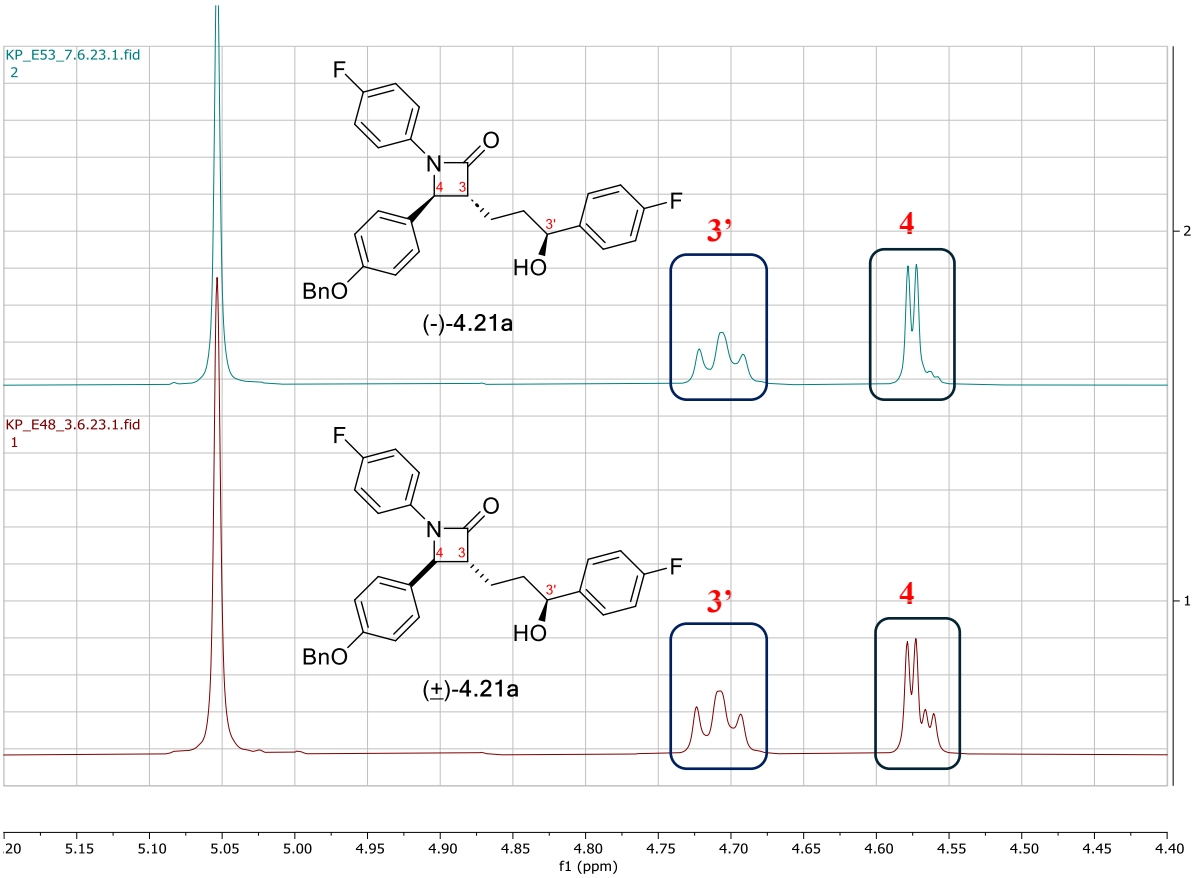
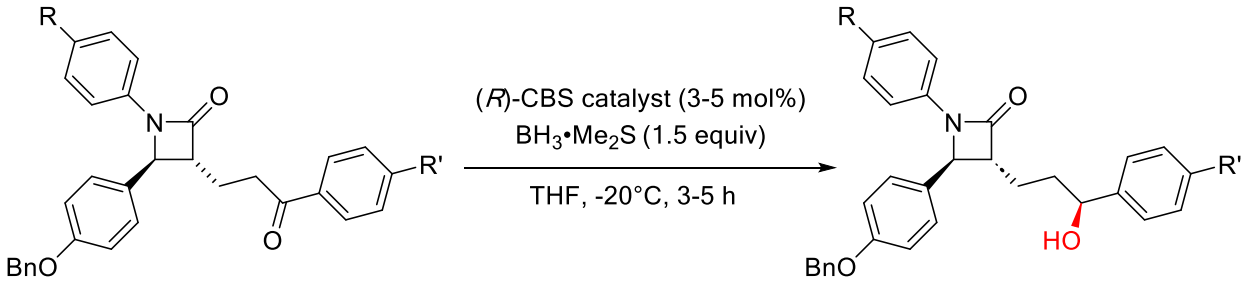



**Figure 31**. $^{1}$H NMR spectra (4.40-5.20 ppm) of enantioenriched (-)-**4.21a** and its counterpart (±)-**4.21a**.

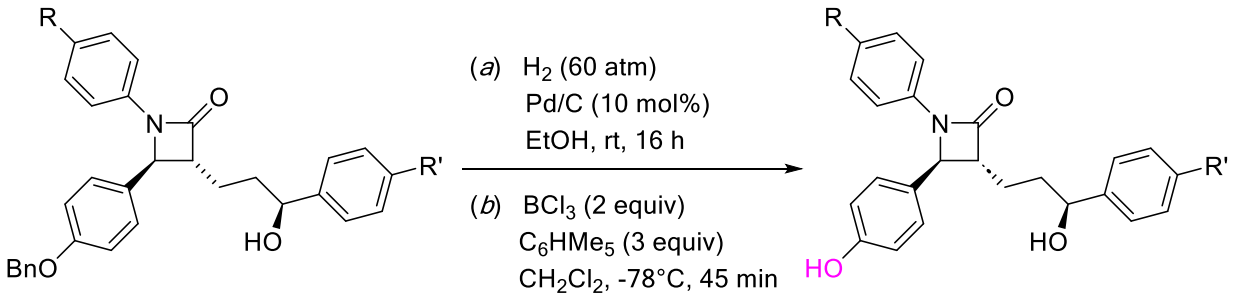



| | | | |
|---|---|---|---|
| **4.20a**, | R = F, R' = F | **4.21a**, | R = F, R' = F 51% (80%) |
| **4.20b**, | R = F, R' = $SF_5$ | **4.21b**, | R = F, R' = $SF_5$ 67% (66%) |
| **4.20c**, | R = $CF_3$, R' = $SF_5$ | **4.21c**, | R = $CF_3$, R' = $SF_5$ 93% (56%) |
| **4.20d**, | R = $SF_5$, R' = $SF_5$ | **4.21d**, | R = $SF_5$, R' = $SF_5$ 75% (64%) |

**Scheme 67**. Asymmetric reduction of ketone intermediates **4.20a-d**. The yields in parentheses refer to the racemic compounds.

## Debenzylation

Various methods exist for debenzylation of benzyl ethers.[170,313,314] Although hydrogenation over palladium hydroxide[170] failed, palladium on charcoal (10%)[313,314] as a catalyst and using high pressure of $H_2$ is known to deprotect **4.21a**, giving rise to Ezetimibe in 70-80% yield .[162,167,174,180,185] In analogy, our **4.21b** delivered the debenzylated product **4.2** in 82% yield. However, the same method proved unsuccessful with the $CF_3/SF_5$ and $SF_5/SF_5$ substrates **4.21c** and **4.21d**. Recognizing the limitations of traditional methods, we turned to Lewis acid-promoted debenzylation, namely that using $FeCl_3$[315] or $BCl_3$.[316] While the $FeCl_3$ method was found to be fruitless with our substrates, $BCl_3$ proved successful, producing **4.3** and **4.4** in 89% and 87% yields, respectively. The latter reactions were carried out in anhydrous $CH_2Cl_2$ at -78 °C in the presence of pentamethylbenzene (3 equiv) as a non-Lewis-basic cation scavenger that has a reputation of not lowering the Lewis acidity of $BCl_3$ (unlike other scavengers, such as $Me_2S$ or PhSMe).[316] However, when applied to the F/F derivative (**4.21a**), this method afforded the desired Ezetimibe **4.1** in mere 30% yield due a substantial side-reaction producing the corresponding chloride (50-55%) as results of hydroxyl substitution.




**4.21a**, R = F, R' = F
**4.21b**, R = F, R' = $SF_5$
**4.21c**, R = $CF_3$, R' = $SF_5$
**4.21d**, R = $SF_5$, R' = $SF_5$

**4.1**, R = F, R' = F — 30% (89:5:5:1)[b]
**4.2**, R = F, R' = $SF_5$ — 82% (87:9:4)[a]
**4.3**, R = $CF_3$, R' = $SF_5$ — 89% (80:8:8:4)[b]
**4.4**, R = $SF_5$, R' = $SF_5$ — 87% (87:10:3)[b]

**Scheme 68**. Debenzylation of benzyl ethers.

In conclusion, our study highlights the critical role of debenzylation in the synthesis of complex molecules and underscores the importance of method selection and optimization. While Lewis acid-promoted debenzylation emerged as a robust strategy for our polyfluorinated intermediates **4.21c** and **4.21d**, challenges persist in extending its applicability to over derivatives. The classical hydrogenation over Pd/C worked well for **4.21b**.

In this study, we successfully synthesized a series of polyfluorinated analogues **4.2**-**4.4** of the cholesterol-lowering drug Ezetimibe and fully characterized them by means of various analytical methods (NMR, MS, IR, optical rotation, HPLC etc.). Through a comprehensive exploration of synthetic methodologies and rigorous characterization techniques, we have elucidated key structural features and wish to evaluate their impact on biological function.

Several issues were encountered during our research and proved solvable after thorough research. For instance, we optimized the synthetic protocols for key intermediates (benzylated 4'-OH-acetophenone, corresponding β-keto ester, *para*-substituted $SF_5$-aniline etc.), allowing their straightforward isolation and purification. Next, the conditions of β-lactam cycles alkylation using various alkylating agents (bromide or iodides) and Wacker-type oxidation of the double bond at benzylic position were comprehensively explored and optimized in terms of yield and/or overall simplicity of the process. As the cherry on top, we prosperously employed the reductive amination reaction, which was previously deeply explored in our group, in the reduction of enamines together with creation a new asymmetric center in the molecule. It allowed us to perform the following transformations while retaining enantioenrichment.

Looking ahead, several promising directions for future research emerge from our findings. Firstly, further investigations are warranted to explore the possible alterations of new compounds structures, making them more lipophilic/hydrophilic or binding with additional auxiliaries. Additionally, *in vitro* and *in vivo* studies are essential to validate the biological potential of these compounds and assess their pharmacokinetic properties.

## Attempted characterization of the newly synthesized compounds

The crystal structure of Ezetimibe (**4.1**) is known.[185] However, our attempts at crystallization of the analogues **4.2**-**4.4**, employing various recommended techniques (including MeOH/water,[170] *i*PrOH/water[167] and heptane or *n*-hexane/MTBE mixtures,[167,185]) were unsuccessful. We then entered into a collaboration with M. J. Hall (Newcastle University), who has developed an Encapsulated Nanodroplet Crystallization (ENC) technique for growing single crystals of small organic molecules, which were then successfully applied to a wide range of compounds previously regarded as difficult to crystallize.[317] Unfortunately, the new compounds **4.2**-**4.4** proved quite

resistant to the attempts at crystallization (384 experiments with variation of 12 different solvents); only small single crystals or microcrystalline material was obtained in the case of **4.2**. Compounds **4.3** and **4.4** exhibited formation of only amorphous solids. The selected experimental data is shown in **Figure 32**, **Figure 33** and **Figure 34**.

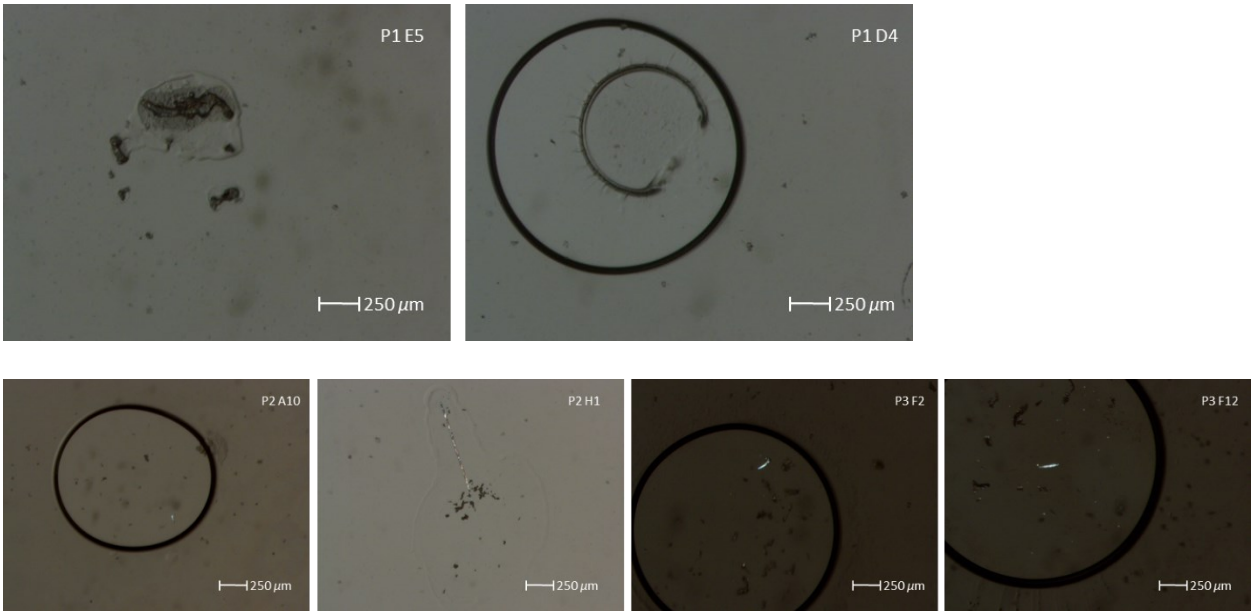



**Figure 32**. Pictures of compound **4.2**.

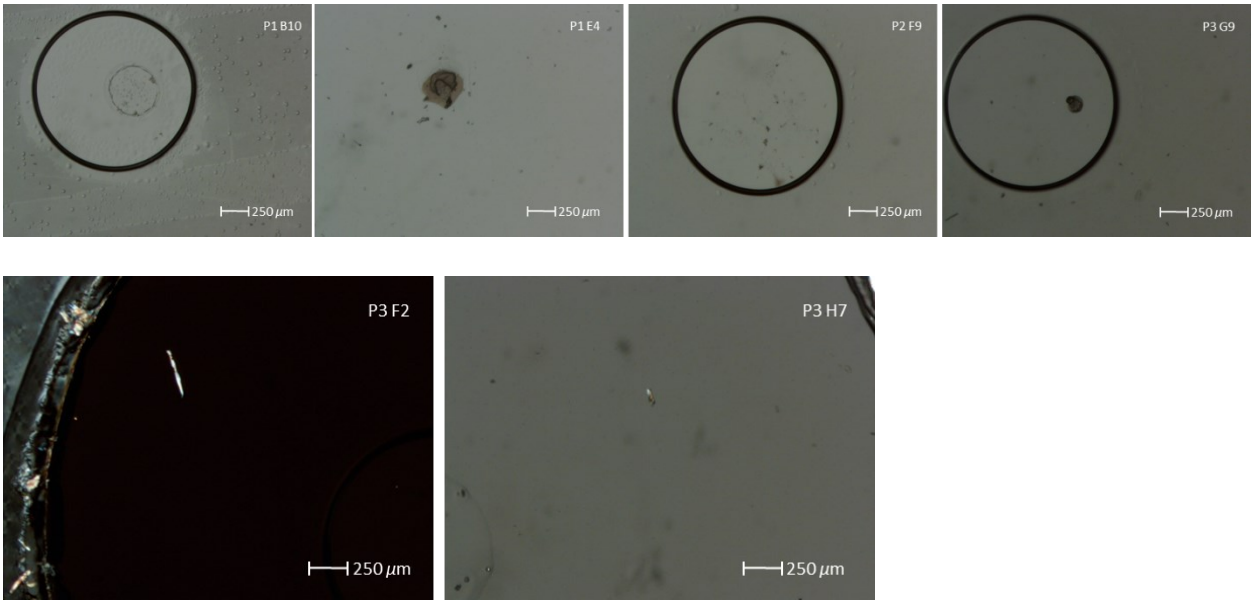



**Figure 33**. Pictures of compound **4.3**.

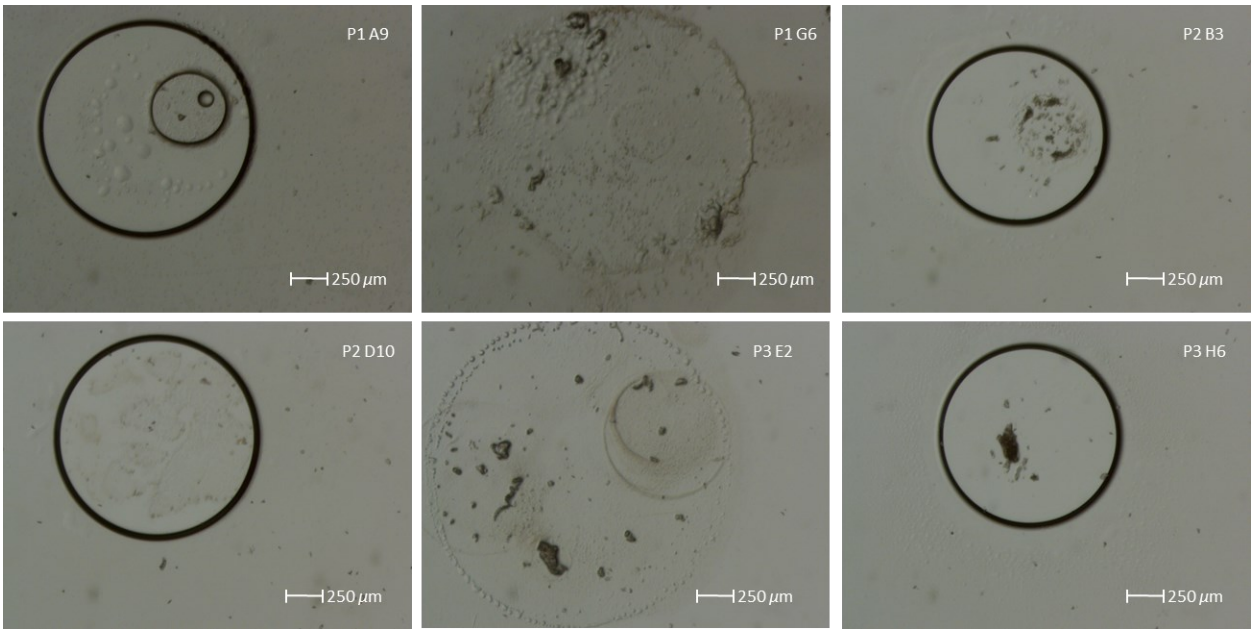



**Figure 34**. Pictures of compound **4.4**.

## Preliminary biological experiments

The initial stage toward evaluation of the new polyfluorinated Ezetimibe analogs **4.2**-**4.4** was carried out at IOCB and their contractor. The first step was to evaluate the metabolic stability in human hepatocytes.

The assay conditions involved incubating the compounds at 1 µM concentration in a solution with less than 0.1% DMSO, with subsequent sampling over 180 minutes. Control compounds, including testosterone, umbelliferone, and caffeine, were utilized to assess their buffer stability. High-throughput LC-MS/MS analysis, employing reverse-phase chromatography and protein precipitation with diclofenac as an internal standard, was employed for sample analysis.

The results of the metabolic stability assay were promising. Graphical representations revealed distinct patterns for each compound compared to control counterparts. Notably, compounds were classified based on their predicted *in vivo* hepatic clearance, with our synthesized molecules exhibiting varied behavior. Compound **4.2** displayed a metabolic stability profile akin to Ezetimibe but with a longer half-life (36.3 min vs 12.6 min) and slightly lower predicted hepatic clearance. Conversely, compounds **4.3** and **4.4** exhibited negligible clearance, suggesting potential metabolic

inertness due to the introduction of polyfluorinated moieties. The data is given (**Figure 35**, **Figure 36** and **Figure 37**).

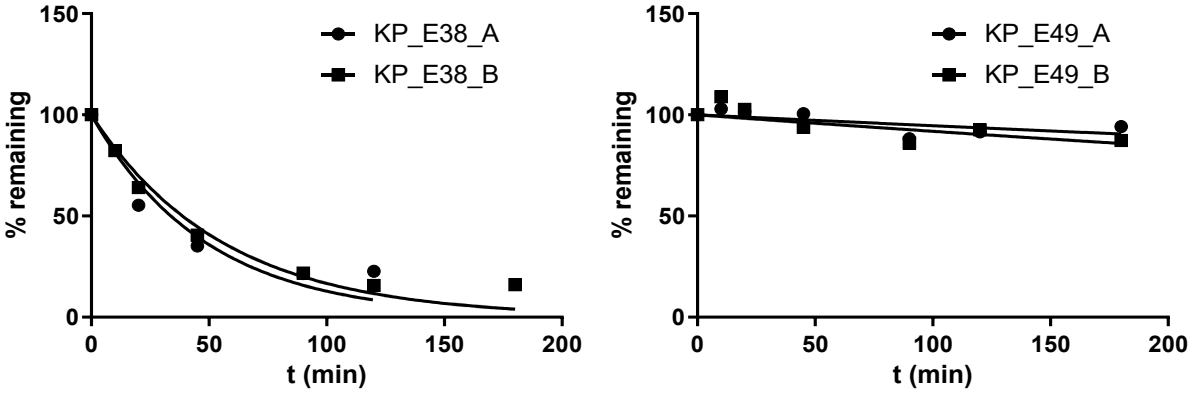



**Figure 35**. % Remaining - time dependencies for substrates i) **4.2** and ii) **4.3**.

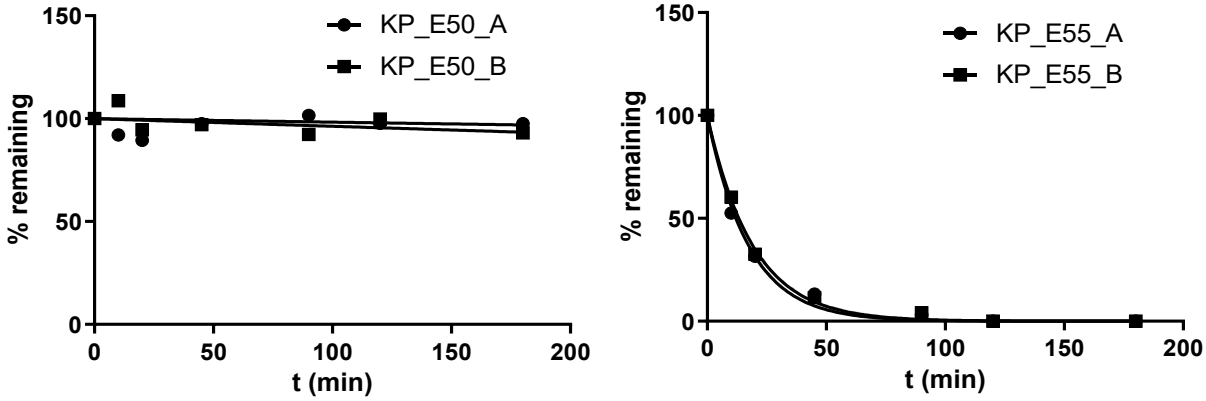



**Figure 36**. % Remaining - time dependencies for substrates i) **4.4** and ii) **Ezetimibe** (**4.1**).

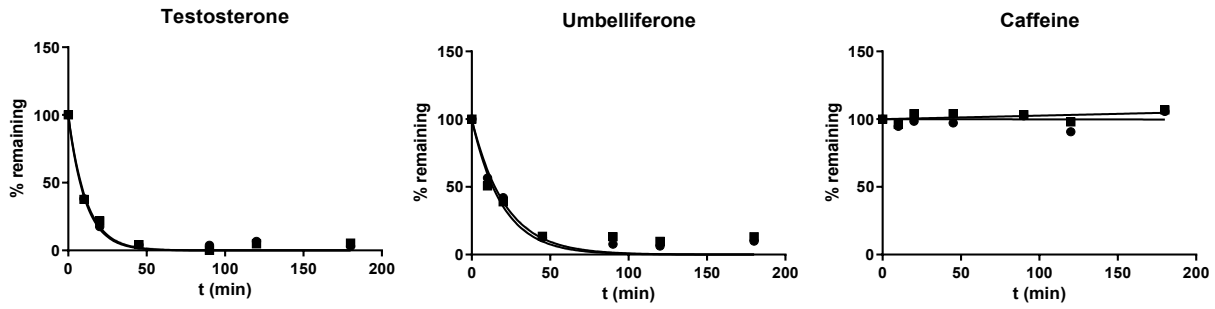



**Figure 37**. % Remaining - time dependencies for control substrates i) testosterone, ii) umbelliferone and iii) caffeine.

Further exploration into compound behavior was conducted through cell permeability assays using Caco-2 cells and talinolol and diclofenac as control substances. Despite employing various concentrations and experimental conditions, including the use of P-gp inhibitor Elacridar, none of the new compounds **4.2**-**4.4** exhibited measurable efflux ratios or significant permeability coefficients. This outcome contrasts starkly with the expected behavior and poses a significant challenge in the evaluation of these compounds' biological activity. The observed low permeability values for both our compounds and Ezetimibe underscore the complexity of their cellular transport mechanisms.

In summary, while our synthesized compounds showed promising metabolic stability, their poor cell permeability presents a significant hurdle in their biological evaluation. Future research efforts will focus on elucidating the underlying mechanisms governing compound permeability and exploring alternative strategies to enhance their bioavailability and efficacy.

# Chapter V. Experimental part

## Reductive amination. General methods

Melting points were determined on a Kofler block and are uncorrected. The NMR spectra were recorded for $CDCl_3$ solutions, $^1H$ at 400 MHz, $^{13}C$ at 100.6 MHz with chloroform, chloroform-d (δ 7.26, $^1H$; δ 77.16, $^{13}C$) or TMS as internal standard unless otherwise indicated, and $^{19}F$ at 376.5 MHz (with δ 0.00 for $CCl_3F$) were used as internal standards unless otherwise indicated. Another solvents for NMR spectra were DMSO-$d_6$ ($^1H$ at 400 MHz, $^{13}C$ at 100.6 MHz; DMSO-$d_5$, δ 2.50, $^1H$; δ 39.52, $^{13}C$ as internal standard), deuterated methanol $CD_3OD$ ($^1H$ at 400 MHz, $^{13}C$ at 100.6 MHz; $CD_2HOD$, δ 3.31, $^1H$; δ 49.00, $^{13}C$ as internal standard) and deuterium oxide $D_2O$ ($^1H$ at 400 MHz, $^{13}C$ at 100.6 MHz; HOD, δ 4.79, $^1H$ as internal standard). Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded for a thin film of $CHCl_3$ solutions between NaCl plates [or KBr tablets (neat)]. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation; some spectra were also obtained by using electrospray technique (ESI) with nitrogen as drying and nebulizer gas with quadrupole or TOF detection. HRMS spectra were obtained using LC/MS-ESI technique with quadrupole TOF detection. Chiral HPLC analysis was performed on Daicel Chiralpak IA, IB, IC, AD, ODH columns with a spectrophotometric detector; the samples containing optically active material were compared with racemates. Optical rotation measurement was performed using automatic polarimeters at a wavelength of 589 nm (sodium D line) and as solvent was used $CHCl_3$. Some reactions, when needed, were performed under an atmosphere of dry, oxygen-free argon in oven-dried glassware twice evacuated and filled with the argon. Solvents and solutions were transferred by syringe-septum technique. Solvents for the reactions were of reagent grade and were dried as follows: toluene, THF and diethyl ether was distilled from sodium and stored under argon; $CHCl_3$, acetonitrile, DMF, ethanol and dichloromethane (Acroseal$^{TM}$, extra dry or anhydrous, over molecular sieves) were obtained from Acros Organics and tested prior to use. Aniline and *p*-anisidine were distilled prior to use. Petroleum ether (PE) refers to the fraction boiling in the range of 40−60 °C, EtOAc refers to ethyl acetate, MeOH refers to methanol, AcOH refers to acetic acid, TsOH refers to *p*-toluenesulfonic acid, and MS refers to molecular sieves. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR

spectrum and are not optimized. Conversions were determined from $^1$H NMR spectra of crude products before purification. The identity of the products prepared by different methods was checked by comparison of their NMR, IR, and MS data and by the TLC behavior. Heating of reaction mixtures was provided by an oil bath, unless stated otherwise. Cooling to subzero temperatures was provided by Julabo FT902 FT Immersion Cooler combined with an ethanol bath or dry ice/acetone bath. The starting compounds were purchased from Sigma-Aldrich, Acros Organics, Alfa Aesar, Strem Chemicals and Fluorochem companies.

Aldehydic amide **2.1f** was obtained from the acid 4-(O═CH)$C_6H_4CO_2H$ on reaction with $Et_2NH$ mediated by EDC.[318] Azido aldehyde **2.1i** was prepared in two ways: (a) From 4-$NO_2C_6H_4CHO$ (**2.1g**), which was first reacted with ethylene glycol and the resulting acetal was reduced with $NaBH_4/NiCl_2$ to afford the corresponding amine.[319] Subsequent diazotation with $NaNO_2$ and $H_2SO_4$ (conc.) in AcOH, followed by a reaction with $NaN_3$ and final dilution with water, furnished **2.1i** in 61% overall yield.[319] An alternative reduction of the acetal-protected 4-$NO_2C_6H_4CHO$ with $HSiCl_3$, catalyzed by $Et_3N$,[89] and followed by deprotection, was also successful. (b) Direct ipso-substitution reaction of 4-$NO_2C_6H_4CHO$ (**2.1g**) with $NaN_3$ (2 equiv) in HMPA at rt overnight[320] afforded **2.1i** in one step in 71% yield and is thus preferred. The phosphine oxide aldehyde **2.1n** was prepared from 4-Br-$C_6H_4CHO$, whose acetal (with ethylene glycol) was converted into the corresponding Grignard reagent (using the Knochel turbo protocol[321]), which was then treated with $Ph_2P(O)Cl$. Subsequent acetal hydrolysis afforded **2.1n** in 90% overall yield.[322] 4-Pentynal **2.1q** was obtained from 4-pentynol in 90% yield on Swern oxidation with $(COCl)_2$, DMSO, and $Et_3N$.[323]

**Procedure A: General Method for the Generation of Imines using Molecular Sieves.**

Molecular sieves (4 Å; 0.5−1.0 g) were added to a solution of the aldehyde (1.00 mmol; 1 equiv) and the corresponding amine (1.05 mmol; 1.05 equiv) in anhydrous toluene or $CH_2Cl_2$ (5 mL) and the reaction mixture was stirred at room temperature for 4−8 h while monitoring the progress by TLC. The sieves were then filtered off and the filtrate was used immediately for the reduction (samples were taken for the characterization of new imines).

**Procedure B: General Method for the Generation of Imines from Poorly Soluble Heteroaromatic Amines using Molecular Sieves.**

Anhydrous DMF (up to 5 mL) was added dropwise to a suspension of a heteroaromatic amine (1.05 mmol; 1.05 equiv) in anhydrous $CH_2Cl_2$ (5 mL) while stirring vigorously until the amine had dissolved completely. Activated 4 Å molecular sieves (1 g) were added to the clear solution in one portion. The corresponding aldehyde (1.00 mmol; 1 equiv) was then added dropwise via a Hamilton syringe and the reaction mixture was stirred at room temperature for 12−24 h while monitoring the progress by TLC. The molecular sieves were then promptly filtered off through a short pad of sand and Celite and the filtrate was used immediately for the reduction.

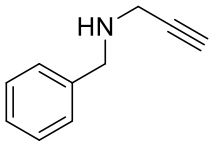
**Procedure C: General Dean−Stark Method for the Generation of Imines.**

A solution of the aldehyde (1.0 mmol; 1 equiv), amine (1.05 mmol, 1.05 equiv) in anhydrous toluene (25 mL) was heated under reflux (oil bath) with a Dean−Stark trap for 10 h, then cooled and concentrated under reduced pressure. The imine solution thus generated was used directly for the reduction experiment. Note that with aldehydes, there was no need to use an acid catalyst.

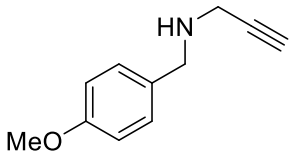
**Procedure D: General Method for the Reduction of Imines.**

Trichlorosilane (202 µL, 2.0 mmol, 2 equiv) was added dropwise to a cooled solution (0 °C) of the *in situ* generated imine (1.0 mmol, 1 equiv) and dimethylformamide (7.5 µL, 0.1 equiv) in anhydrous toluene or $CH_2Cl_2$ (5 mL) under an argon atmosphere and the reaction mixture was allowed to stir at room temperature (15−20 °C) for 16 h (unless otherwise stated). The reaction mixture was then diluted with ethyl acetate (5 mL), quenched with a saturated aqueous solution of $NaHCO_3$ (20 mL), stirred for 10-15 minutes and filtered through a short pad of sand and Celite. The layers were separated, the aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with water (2 × 15 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by flash chromatography on a silica gel column (2.0 × 7.0 cm) with a petroleum ether−ethyl acetate mixture (98:2 to 85:15). The yields are given in **Figures 15-18** and **Schemes 22-27**. The identity of the known amines was established by comparison of their spectral data with those available in the literature and/or by comparison of their characteristics with those of authentic samples. New compounds were fully characterized by spectral and analytical methods.

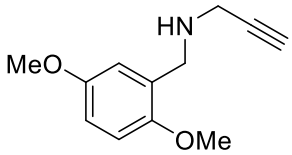
# List of compounds



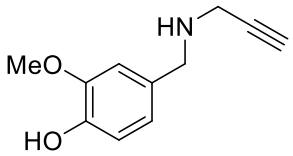

***N*-Propargylbenzylamine** (**2.3a**).[324] Obtained from **2.1a** and **2.2h** using procedure A, followed by E: Yellow oil (142 mg, 95% yield): $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.57 (s, 1H), 2.28 (t, J = 2.4 Hz, 1H), 3.46 (d, J = 2.4 Hz, 2H), 3.91 (s, 2H), 7.40−7.25 (m, 5H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 37.5 ($CH_2$), 52.4 ($CH_2$), 71.7 (CH), 82.2 (C), 127.3 (CH), 128.5 (2 × CH), 128.6 (2 × CH), 139.5 (C); IR (NaCl) ν 3291, 2836, 2101, 734, 698 $cm^{-1}$; MS (ESI) m/z (%) 146 ($MH^+$, 100), 129 (83); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{10}H_{11}N$ 146.0959, found 146.0970.



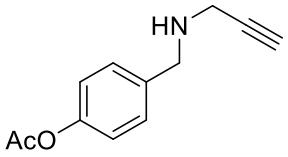

***N*-(4-Methoxybenzyl)-2-propyn-1-ylamine** (**2.3b**).[325] Obtained from **2.1b** and **2.2h** using procedure A, followed by E. Yellow oil (172 mg, 95% yield): $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 1H), 2.28 (t, J = 2.4 Hz, 1H), 3.43 (d, J = 2.5 Hz, 2H), 3.81 (s, 3H), 3.84 (s, 2H), 6.88 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 37.3 ($CH_2$), 51.7 ($CH_2$), 55.4 ($CH_3$), 71.6 (CH), 82.2 (C), 113.9 (2 × CH), 129.7 (2 × CH), 131.6 (C), 158.9 (C) in accordance with the literature data. IR (NaCl) ν 3290, 2062, 1251, 1105, 816, 638 $cm^{-1}$; MS (ESI) m/z (%) 176 ($MH^+$, 7), 121 (100); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{11}H_{13}NO$ 176.1065, found 176.1062.



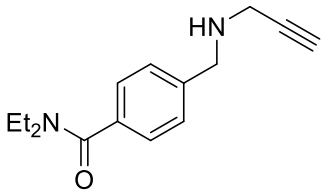

***N*-(2,5-Dimethoxybenzyl)-2-propyn-1-ylamine** (**2.3c**). A new compound.[83] Obtained from **2.1c** and **2.2h** using procedure A, followed by E: Yellow oil (125 mg, 76% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.91 (s, 1H), 2.26 (t, J = 2.4 Hz, 1H), 3.44 (d, J = 2.4 Hz, 2H), 3.78 (s, 3H), 3.81 (s, 3H), 3.86 (s, 2H), 6.84−6.75 (m, 2H), 6.89 (d, J = 2.7 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 37.6 ($CH_2$), 48.1 ($CH_2$), 55.8 ($CH_3$), 56.0 ($CH_3$), 71.5 (CH), 82.3 (C), 111.3 (CH), 112.7 (CH), 116.3 (CH), 128.7 (C), 152.0 (C), 153.6 (C); IR (NaCl) ν 3291, 2101, 1228, 1180, 1048, 875, 803 $cm^{-1}$; MS (ESI) m/z (%) 206 ($M^{\bullet+}$, 92), 151 (44), 144 (23); HRMS (CI/isobutene, M + $H^+$) m/z $[M + H]^+$ calcd for $C_{12}H_{16}NO_2$ 206.1176, found 206.1183.




***N*-(4-Hydroxy-3-methoxybenzyl)-2-propyn-1-ylamine** (**2.3d**). A new compound.[83] Obtained from **2.1d** and **2.2h** using a procedure A ($CH_2Cl_2$ instead of toluene), followed by modified E as well: Dark-pink solid (112 mg, 73% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 1H), 3.44 (d, J = 1.9 Hz, 2H),3.83 (s, 2H),3.88 (s, 3H),6.83 (d, J = 8.0 Hz, 1H),6.87 (d, J = 8.0 Hz, 1H), 6.91 (s, 1H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 37.3 ($CH_2$), 52.3 ($CH_2$), 56.0 ($CH_3$), 71.8 (CH), 82.1 (C), 111.2 (CH), 114.4 (CH), 121.5 (CH), 131.2 (C), 145.1 (C), 146.8 (C); IR (NaCl) ν 3306, 3249, 2107, 1592, 1266, 1242, 1159, 1129, 1093, 1033, 857, 815 cm$^{-1}$; MS (ESI) m/z (%) 192 ($M^{\bullet+}$, 16), 137 (100), 122 (68); HRMS (CI/isobutene, M + $H^+$) m/z $[M + H]^+$ calcd for $C_{11}H_{14}NO_2$ 192.1020, found 192.1027.

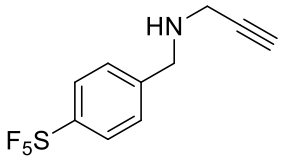



***N*-(4-Acetoxybenzyl)-2-propyn-1-ylamine** (**2.3e**). A new compound.[83] Obtained from **2.1e** and **2.2h** using procedure A, followed by E; column chromatography first eluted the unreacted imine intermediate (32 mg, 20% yield), followed by 10a, which was obtained as a yellow oil (89 mg, 55% yield): $^1$H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 1H), 2.28 (t, J = 2.3 Hz, 1H), 2.31 (s, 3H), 3.45 (d, J = 2.3 Hz, 2H), 3.90 (s, 2H), 7.06 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 21.3 ($CH_2$), 37.4 ($CH_2$), 51.7 ($CH_3$), 71.9 (CH), 82.0 (C), 121.7 (2 × CH), 129.6 (2 × CH), 137.0 (C), 149.9 (C), 169.7 (C); IR (NaCl) ν 3288, 2110, 1751, 1222, 1186, 1105, 1018, 911, 854 cm$^{-1}$; MS (ESI) m/z (%) 204 ($M^{\bullet+}$, 48), 149 (22), 107 (100); HRMS (CI/isobutene) m/z $[M + H]^+$ calcd for $C_{12}H_{14}NO_2$ 204.1020, found 204.1024.

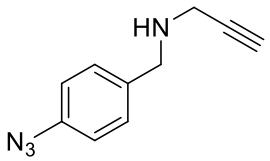



**4-(*N*-(2-Propynyl)aminomethyl)-*N′*,*N′*-diethylbenzamide** (**2.3f**). A new compound.[83] Obtained from **2.1f** and **2.2h** using a procedure A, followed by E ($CH_2Cl_2$ instead of toluene): Yellow oil (122 mg, 82% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.25 (s, 3H), 2.28 (s, 1H),2.50 (s, 1H), 3.26 (s, 2H), 3.48−3.37 (m, 2H), 3.55 (s, 2H), 3.92 (s, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 7.9 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 13.0 ($CH_3$), 14.3 ($CH_3$), 37.3 ($CH_2$), 39.4 ($CH_2$), 43.4 ($CH_2$), 51.9 ($CH_2$), 72.1 (CH), 81.7 (C), 126.6 (CH), 128.6 (CH), 136.3 (C), 140.3 (C), 171.3 (C); IR (NaCl) ν 3288, 3222, 2108, 1625, 1222, 1093, 1021, 848 cm$^{-1}$;

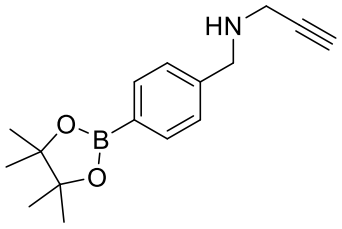
MS (ESI) m/z (%) 245 ($M^{\bullet+}$, 100), 144 (35), 153 (24); HRMS (CI/isobutene) m/z $[M + H]^+$ calcd for $C_{15}H_{21}N_2O$ 245.1649, found 245.1656.



***N*-(4-(Pentafluoro-λ6-sulfanyl)benzyl)-2-propyn-1-ylamine** (**2.3g**). A new compound.[83] Obtained from **2.1h** and **2.2h** using procedure A, followed by E ($CH_2Cl_2$ instead of toluene): Yellowish oil (214 mg, 95% yield); $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.64 (s, 1H), 2.29 (t, J = 2.4 Hz, 1H), 3.45 (d, J = 2.4 Hz, 2H), 3.97 (s, 2H), 7.48 (d, J = 8.3 Hz, 2H), 7.73 (d, J = 8.7 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 37.5 ($CH_2$), 51.3 ($CH_2$), 72.1 (CH), 81.7 (C), 126.1−126.2 (2 × CH), 128.6 (2 × CH), 143.6 (C), 153.0 (C); $^{19}F$ NMR (376 MHz, $CDCl_3$) δ 63.02 (d, J = 149.9 Hz, 4F), 85.81−83.83 (m, 1F); IR (NaCl) ν 3309, 2107, 1099, 839 $cm^{-1}$; MS (ESI) m/z (%) 272 ($MH^+$, 6), 153 (14), 146 (100), 144 (17); HRMS (CI/isobutene) m/z $[M + H]^+$ calcd for $C_{10}H_{11}F_5NS$ 272.0527, found 272.0533.

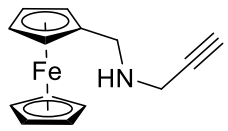


***N*-(4-Azidobenzyl)-2-propyn-1-ylamine** (**2.3h**). A new compound.[83] Obtained from **2.1i** and **2.2h** using procedure A, followed by E ($CH_2Cl_2$ instead of toluene): Orange oil (113 mg, 76% yield); $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.63 (s, 1H), 2.28 (s, 1H), 3.43 (s, 2H), 3.88 (s, 2H), 7.01 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 37.3 ($CH_2$), 51.7 ($CH_2$), 71.8 (CH), 82.0 (C), 119.1 (2 × CH), 130.0 (2 × CH), 136.3 (C), 139.0 (C); IR (NaCl) ν 3291, 2110, 1607, 911, 833 $cm^{-1}$; MS (ESI) m/z (%) 187 ($MH^+$, 4), 173 (12), 153 (39), 146 (76), 144 (100); HRMS (CI/isobutene) m/z $[M + H]^+$ calcd for $C_{10}H_{11}N_4$ 187.0979, found 187.0986.

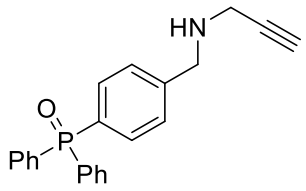


***N*-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)prop-2-yn-1-amine** (**2.3i**). A new compound.[83] Obtained from **2.1j** and **2.2h** using procedure A, followed by E ($CH_2Cl_2$ instead of toluene): Off-white solid (156 mg, 58% yield): $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 12H), 1.79 (s, 1H), 2.26 (s, 1H), 3.42 (d, J = 2.4 Hz, 2H), 3.90 (s, 2H), 7.35 (d, J = 7.5 Hz, 2H), 7.78 (d, J = 7.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ

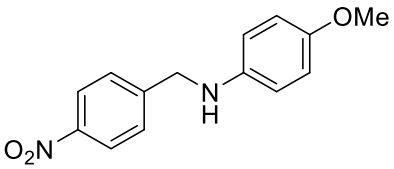
25.1 (4 × $CH_3$), 37.6 ($CH_2$), 52.5 ($CH_2$), 72.0 (CH), 82.2 (C), 84.0 (2 × C), 128.0 (2 × CH), 135.3 (2 × CH), 142.8 (2 × C); IR (NaCl) ν 3333, 3159, 2977, 2095, 1141, 1090, 961, 857 $cm^{-1}$; MS (CI) m/z (%) 272 ($MH^+$, 100), 217 (100), 159 (23), 135 (54), 117 (47); HRMS (CI/isobutene) m/z [M + H]$^+$ calcd for $C_{16}H_{23}BNO_2$ 272.1811, found 272.1825.



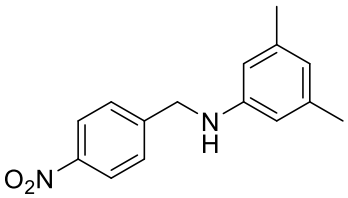

**[(Prop-2-yn-1-ylamino)methyl]ferrocene** (**2.3j**). A new compound.[83] Obtained from **2.1o** and **2.2h** using procedure A, followed by E ($CH_2Cl_2$ instead of toluene): Red-brown oil (211 mg, 83% yield): $^1$H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 1H), 2.26 (t, J = 2.4 Hz, 1H), 3.44 (d, J = 2.5 Hz, 2H), 3.59 (s, 2H), 4.11 (t, J = 1.8 Hz, 2H), 4.13 (s, 5H), 4.20 (t, J = 1.9 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 37.8 ($CH_2$), 47.6 ($CH_2$), 68.1 (2 × CH), 68.6 (2 × CH), 68.7 (C of Cp), 71.7 (CH), 82.5 (C), 86.3 (C); IR (NaCl) ν 3294, 3091, 2104, 1234, 1105, 908, 815, 504, 486 $cm^{-1}$; MS (ESI) m/z (%) 253 ($M^{\bullet+}$, 54), 199 (100), 153 (15); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{14}H_{15}FeN$ 253.0543, found 253.0556.



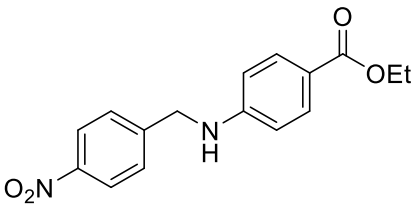

**Diphenyl(4-((prop-2-yn-1-ylamino)methyl)phenyl)phosphine oxide** (**2.3k**). A new compound.[83] Obtained from **2.1n** and **2.2h** using procedure A, followed by E ($CH_2Cl_2$ instead of toluene). Yellowish oil (221 mg, 64%): $^1$H NMR (400 MHz, $CDCl_3$) δ 1.67 (s, 1H), 2.26 (t, J = 2.4 Hz, 1H), 3.42 (d, J = 2.4 Hz, 2H), 3.94 (s, 2H), 7.45 (tdd, J = 7.1, 3.0, 1.9 Hz, 6H), 7.54 (td, J = 7.2, 1.5 Hz, 2H), 7.59−7.71 (m, 6H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 37.7 ($CH_2$), 52.0 ($CH_2$), 72.1 (CH), 82.0 (C), 128.7 (d, J = 12.4 Hz, 2 × CH), 128.7 (d, J = 12.4 Hz, 4 × CH), 131.5 (d, J = 105.0 Hz, 2 × C), 132.2 (d, J = 2.8 Hz, 2 × CH), 132.3 (d, J = 10.0 Hz, 4 × CH), 132.5 (d, J = 10.3 Hz, 2 × CH), 133.4 (C), 143.87 (d, J = 2.8 Hz, C); $^{31}$P NMR (162 MHz, $CDCl_3$) δ 28.88 (p, J = 12.1 Hz); IR (NaCl) ν 3291, 2101, 1183, 1117, 725, $cm^{-1}$; MS (CI) m/z (%) 346 ($MH^+$, 100), 306 (81), 292 (26), 201 (36); HRMS (CI) m/z: [M + Na]$^+$ calcd for $C_{22}H_{20}NNaOP$ 368.1170, found 368.1174.



**4-Methoxy-*N*-(4′-nitrobenzyl)aniline** (**2.3l**).[326,327] Obtained from **2.1g** and **2.2c** using procedure A followed by E: Yellow solid (220 mg, 85% yield); mp 96−98 °C (EtOAc−hexane; lit[**87**][327] gives 97−98 °C); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.99 (bs, NH), 4.43 (s, 2H), 6.54 (d, J = 9.0, 2H), 6.77 (d, J = 9.5, 2H), 7.54 (d, J = 9.0, 2H), 8.19 (d, J = 8.5, 2H); $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 48.9 ($CH_2$), 56.2 ($CH_3$), 114.6 (CH), 115.4 (CH), 124.3 (CH), 128.2 (CH), 141.9 (C), 147.6 (C), 148.2 (C), 153.0 (C); IR (neat) 3445, 2987, 1605, 1515, 1422, 1347, 1265 cm$^{-1}$; MS (EI) m/z (%) 259 ($MH^+$, 100), 227 (18), 124 (22); HRMS (CI) m/z $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_3$ 259.1079, found 259.1084.

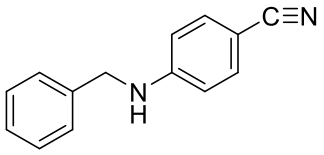


***N*-(4-Nitrobenzyl)-3,5-dimethyl-aniline** (**2.3m**). A new compound.[83] Obtained from **2.1g** and **2.2d** using modified procedure A ((*R*)-(+)-limonene as a solvent), followed by modified E ((*R*)-(+)-limonene as a solvent). Orange solid (210 mg, 82% yield): $^{1}$H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 6H), 4.12 (s, 1H), 4.44 (s, 2H), 6.22 (s, 2H), 6.41 (s, 1H), 7.51 (d, J = 9.0 Hz, 2H), 8.16 (d, J = 8.7 Hz, 2H); $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 21.7 (2 × $CH_3$), 47.9 ($CH_2$), 111.1 (2 × CH), 120.5 (CH), 124.1 (2 × CH), 127.9 (2 × CH), 139.4 (2 × C), 147.4 (C), 147.8 (C), 148.1 (C); IR (NaCl) ν 3393, 1604, 1344, 821 cm$^{-1}$; MS (CI) m/z (%) 257 ($MH^+$, 100), 121 (100), 106 (78); HRMS (CI/ isobutene) m/z $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_2$ 257.1280, found 257.1297.

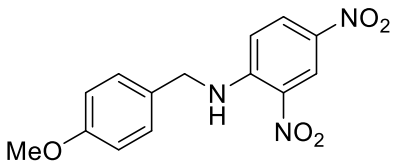


**Ethyl *N*-(4-Nitrobenzyl)-4-aminobenzoate** (**2.3n**). A new compound.[83] Obtained from **2.1g** and **2.2e** using procedure A followed by E ($CH_2Cl_2$ instead of toluene): Yellowish amorphous solid (321 mg, 91% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J = 7.1 Hz, 3H), 4.30 (q, J = 7.1 Hz, 2H), 4.53 (s, 2H), 4.77 (s, 1H), 6.55 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 7.86 (d, J = 8.8 Hz, 2H), 8.18 (d, J = 8.8 Hz, 2H); $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 14.5 ($CH_3$), 47.1 ($CH_2$), 60.5 ($CH_2$), 111.9 (2 × CH), 119.9 (C), 124.1 (2 × CH), 127.8 (2 × CH), 131.7 (2 × CH), 146.5 (C), 147.4 (C), 151.1 (C), 166.8 (C); IR (NaCl) ν 3357, 2983, 1734, 1523, 1344, 1282, 1176, 1124 cm$^{-1}$; MS (ESI) m/z (%) 301 ($MH^+$, 100), 255

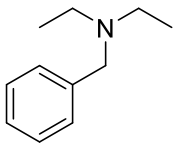
(28), 229 (16), 165(5); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{16}N_2O_4$ 301.1183, found 301.1182.



**4-(Benzylamino)benzonitrile** (**2.3o**).[328] Obtained from **2.1a** and **2.2f** using procedure A followed by E: Yellow solid (185 mg, 89% yield); Mp 74−76 °C (AcOEt−hexane; lit[**91**] gives 74.9−75.6 °C); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.36 (d, J = 5.0 Hz, 2H), 4.66 (s, 1H), 6.58 (d, J = 8.8 Hz, 2H), 7.26−7.37 (m, 5H), 7.39 (d, J = 8.8 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 47.6 ($CH_2$), 99.1 (C), 112.5 (2 × CH), 120.5 (C), 127.4 (2 × CH), 127.8 (CH), 129.0 (2 × CH), 133.8 (2 × CH), 138.0 (C), 151.2 (C); IR (neat) ν 3347, 2206, 1604, 1452, 1339, 1170, 824 $cm^{-1}$; MS (EI) *m/z* (%) 208 ($M^{\bullet+}$, 64), 91 (100), 82 (75); HRMS (EI) *m/z* $[M]^+$ calcd for $C_{14}H_{12}N_2$ 208.0995, found 208.1004.

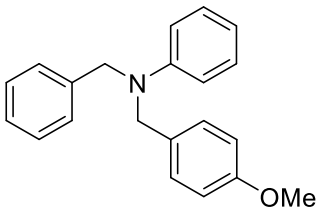


***N*-(4-Methoxybenzyl)-2,4-dinitroaniline** (**2.3p**).[329] Obtained from **2.1b** and **2.2g** using procedure A ($CH_2Cl_2$ instead of toluene), followed by modified E (DMA instead of DMF). A bright yellow solid (269 mg, 89% yield): $^1$H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 4.57 (d, J = 5.5 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.95 (s, 1H), 7.27 (d, J = 8.7 Hz, 2H), 8.23 (ddd, J = 9.4, 2.7, 0.7 Hz, 1H), 8.82 (t, J = 5.5 Hz, 1H), 9.13 (d, J = 2.7 Hz, 1H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 47.4 ($CH_2$), 55.6 ($CH_3$), 114.7 (CH), 114.9 (2 × CH), 124.4 (CH), 127.7 (C), 128.8 (2 × CH), 130.6 (CH), 130.9 (C), 136.6 (C), 148.4 (C), 159.9 (C); IR (NaCl) ν 3379, 1585, 1334, 1244, 1140, 1012, 744, $cm^{-1}$; MS (ESI) m/z (%) 304 ($MH^+$, 12), 280 (27), 241 (32), 121 (100); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{13}N_3O_5$ 304.0923, found 304.0924.

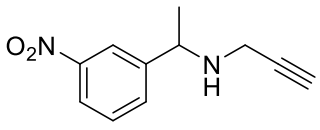


***N*-Benzyl-*N*,*N*-diethylamine** (**2.4a**).[330] Obtained from **2.1a** and **2.2l** using procedure A, followed by E: Yellow oil (155 mg, 92% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J = 6.9 Hz, 6H), 2.45 (br q, J = 6.9 Hz, 4H), 3.52 (s, 2H), 7.24 (m, 5H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 11.3 (2 × $CH_3$), 46.3 (2 × $CH_2$), 57.1 ($CH_2$), 126.9 (CH), 128.1 (2 × CH), 129.1 (2 × CH), 138.8 (C); IR (NaCl) ν 2968, 1454, 1384, 1249, 1025, $cm^{-1}$;

MS (CI) *m/z* (%) 164 ($MH^+$, 100), 150 (26), 136 (68), 107 (28); HRMS (CI) *m/z* $[M + H]^+$ calcd for $C_{11}H_{18}N$ 164.1434, found 164.1434.

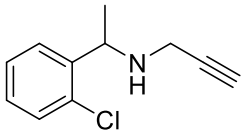



***N*-Benzyl-*N*-(4-methoxybenzyl)aniline (2.4b)**.[331] Anisaldehyde (**2.1b**) (225 μL, 1.84 mmol) and dry DMF (145 μL, 1.87 mmol) were added in one portion to a solution of *N*-benzylidenaniline (**2.2k**) (333 mg, 1.82 mmol) in dry toluene (20 mL) under argon. The mixture was cooled to 0 °C, trichlorosilane (930 μL, 9.15 mmol) was added in one portion, and the mixture was then stirred at 0 °C temperature for 2 h. Ethyl acetate (20 mL) was then added in one portion, followed by a saturated aqueous solution of $NaHCO_3$ dropwise, still at 0 °C, while stirring vigorously. The solid white precipitate was filtered off on a short pad of sand, which was then eluted with another portion of ethyl acetate (20 mL). The organic layer was separated and washed with water (20 mL, 2×) and brine (20 mL), dried ($Na_2SO_4$), and concentrated *in vacuo*. The crude product was purified by flash chromatography on a short column of silica gel (15 g), using a mixture of *n*-hexane and ethyl acetate (20:1) as an eluent (Rf = 0.38, stains visualized by UV) to afford **2.4b** (536 mg, 97% yield) as a viscous oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 4.62 (s, 2H), 4.65 (s, 2H), 6.73 (tt, J = 7.3 Hz, 1.0 Hz, 1H), 6.78 (dd, J = 8.9 Hz, 1.0 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 7.20 (td, J = 7.2 Hz, 1.1 Hz, 4H), 7.27−7.32 (m, 3H), 7.36 (m, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 53.7 ($CH_2$), 54.1 ($CH_2$), 55.4 ($CH_3$), 112.7 (2 × CH), 114.2 (2 × CH), 116.8 (CH), 126.8 (2 × CH), 127.0 (CH), 128.0 (2 × CH), 128.7 (2 × CH), 129.3 (2 × CH), 130.6 (C), 138.8 (C), 149.4 (C), 158.7 (C); IR (NaCl) ν 3028, 1246, 1173, 1034, $cm^{-1}$; MS (EI) *m/z* (%) 304 ($M^{\bullet+}$, 100), 182 (62), 121 (100); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{21}H_{21}NNaO$ 326.1516, found 326.1507.

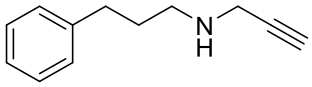



***N*-[1-(3-nitrophenyl)ethyl]prop-2-yn-1-amine (2.5a)**. A new compound. Obtained from **2.1v** and **2.2h** using procedure A, followed by E ($CH_2Cl_2$ instead of toluene): Yellow oil (95 mg, 0.46 mmol, 56% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.38 (d, J = 6.6 Hz, 3H), 1.62 (s, 1H), 2.23 (t, J = 2.4 Hz, 1H), 3.12 (dd, J = 17.3, 2.4 Hz, 1H), 3.40 (dd, J = 17.3, 2.5 Hz, 1H), 4.17 (q, J = 6.6 Hz, 1H), 7.49 (t, J = 7.9 Hz, 1H), 7.71 (dt, J = 7.7, 1.4 Hz, 1H), 8.11 (ddd, J = 8.1, 2.4, 1.1 Hz, 1H), 8.23 (t, J =

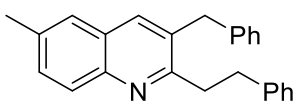
2.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 24.3 ($CH_3$), 36.0 ($CH_2$), 55.8 (CH), 71.9 (CH), 81.7 (C), 122.1 (CH), 122.5 (CH), 129.6 (CH), 133.4 (CH), 147.1 (C), 148.7 (C); IR (NaCl) ν 3285, 2968, 2926, 1527, 1350, 1117, 914, 740 $cm^{-1}$; HRMS (CI) m/z $[M + H]^+$ calcd for $C_{11}H_{13}N_2O_2$ 205.0977, found 205. 0975.



***N*-[1-(2-chlorophenyl)ethyl]prop-2-yn-1-amine** (**2.5b**). A new compound. Obtained from **2.1w** and **2.2h** using procedure A, followed by E ($CH_2Cl_2$ instead of toluene): Yellow oil (70 mg, 0.36 mmol, 45% yield); $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 1.34 (d, J = 6.6 Hz, 3H), 1.67 (s, 1H), 2.21 (t, J = 2.5 Hz, 1H), 3.21 (dd, J = 17.0, 2.4 Hz, 1H), 3.35 (dd, J = 17.0, 2.5 Hz, 1H), 4.51 (q, J = 6.6 Hz, 1H), 7.17 (td, J = 7.6, 1.8 Hz, 1H), 7.26 (td, J = 7.3, 1.4 Hz, 1H), 7.33 (dd, J = 7.9, 1.4 Hz, 1H), 7.53 (dd, J = 7.8, 1.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 22.6 ($CH_3$), 36.1 ($CH_2$), 52.8 (CH), 71.5 (CH), 82.2 (C), 127.3 (CH), 127.5 (CH), 128.1 (CH), 129.8 (CH), 133.5 (C), 141.7 (C); IR (NaCl) ν 3294, 2968, 2929, 1655, 1440, 1120, 1036, 755 $cm^{-1}$; HRMS (CI) m/z $[M + H]^+$ calcd for $C_{11}H_{13}ClN$ 194.0737, found 194. 0734.

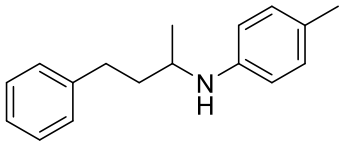


***N*-(3-Phenylpropyl)prop-2-yn-1-amine** (**2.6**).[332] Obtained from **2.1s** and **2.2h** using procedure A, followed by E ($CH_2Cl_2$ instead of toluene): Yellow oil (84 mg, 0.49 mmol, 24% yield); $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 1H), 1.73−1.88 (m, 2H), 2.20 (t, J = 2.4 Hz, 1H), 2.62−2.71 (m, 2H), 2.72 (t, J = 7.1 Hz, 2H), 3.41 (d, J = 2.5 Hz, 2H), 7.18 (d, J = 7.4 Hz, 3H), 7.24−7.31 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 31.5 ($CH_2$), 33.6 ($CH_2$), 38.2 ($CH_2$), 48.2 ($CH_2$), 71.3 (CH), 82.3 (C), 125.9 (CH), 128.4 (2 × CH), 128.4 (2 × CH), 142.1 (C); IR (NaCl) ν 3290, 2931, 2856, 1603, 1454, 746, 700 $cm^{-1}$; MS (ESI) m/z (%) 174 ($MH^+$, 100), 134 (2), 119 (4); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{15}N$ 174.1277, found 174.1282.

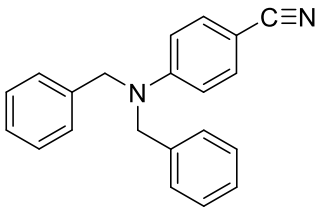


**3-Benzyl-6-methyl-2-phenethylquinoline** (**2.7**).[93,94] Obtained from **2.1s** and **2.2b** using procedure A, followed by E ($CH_2Cl_2$ instead of toluene): White crystals (84.4 mg, 0.25 mmol, 47% yield), mp 127.5 − 129.5 °C (lit[93,94] gives

124−126 °C); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H), 2.98−3.11 (m, 2H), 3.12−3.26 (m, 2H), 4.05 (s, 2H), 7.09 (d, J = 6.9 Hz, 2H), 7.14 (dd, J = 8.2, 1.5 Hz, 2H), 7.17−7.22 (m, 1H), 7.22−7.26 (m, 3H), 7.26−7.33 (m, 2H), 7.47 (s, 1H), 7.49 (dd, J = 8.5, 2.0 Hz, 1H), 7.65 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H); $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 21.7 ($CH_3$), 35.5 ($CH_2$), 37.8 ($CH_2$), 38.8 ($CH_2$), 126.0 (CH), 126.2 (CH), 126.6 (CH), 127.3 (C), 128.4 (CH), 128.5 (2 × CH), 128.7 (2 × CH), 128.8 (2 × CH), 129.0 (2 × CH), 131.2 (CH), 132.5 (C), 135.8 (C), 136.0 (CH), 139.6 (C), 142.2 (C), 145.6 (C), 160.4 (C); IR (NaCl) ν 3020, 2916, 1601, 1493, 1356, 1186, 1132, 825, 754, 698 $cm^{-1}$; MS (ESI) m/z (%) 338 ($MH^+$, 100), 246 (55), 232 (17); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{25}H_{23}N$ 338.1903, found 338.1918.

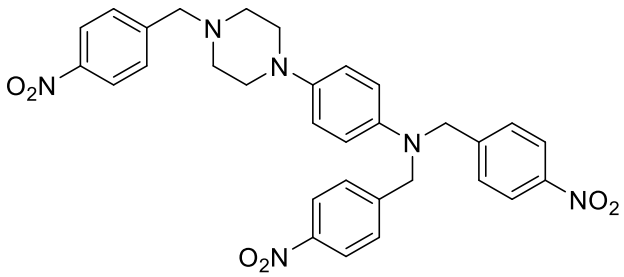


**4-Methyl-*N*-(4-phenylbutan-2-yl)aniline** (**2.8**).[333] Obtained from **2.1u**[334] and **2.2b** using procedure A, followed by E ($CH_2Cl_2$ instead of toluene): Yellowish oil (175 mg, 0.73 mmol, 72% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J = 6.3 Hz, 3H), 1.74 (dtd, J = 13.8, 7.8, 6.2 Hz, 1H), 1.86 (dtd, J = 14.3, 7.5, 6.4 Hz, 1H), 2.22 (s, 3H), 2.71 (t, J = 7.9 Hz, 2H), 3.25 (s, 1H), 3.44 (p, J = 6.3 Hz, 1H), 6.45 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 7.8 Hz, 2H), 7.13−7.21 (m, 3H), 7.23−7.31 (m, 2H); $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 20.5 ($CH_3$), 21.0 ($CH_3$), 32.6 ($CH_2$), 39.0 (CH), 48.3 ($CH_2$), 113.6 (2 × CH), 125.9 (CH), 126.3 (C), 128.5 (2 × CH), 128.6 (2 × CH), 129.9 (2 × CH), 142.2 (C), 145.4 (C); IR (NaCl) ν 3398, 2920, 2860, 1616, 1520, 1454, 808, 748, 700 $cm^{-1}$; MS (ESI) m/z (%) 240 ($MH^+$, 100), 198 (1), 133 (2), 108 (29); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{21}N$ 240.1747, found 240.1749.

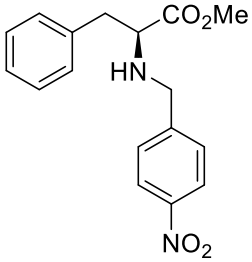


**4-Dibenzylamino-benzonitrile** (**2.9a**).[335] Obtained from **2.1a** and **2.2f** using procedure A, followed by procedure E with the following quantities: **2.1a** (0.5 mL, 4.9 mmol), **2.2f** (118 mg, 1.0 mmol), 4 Å molecular sieves (400 mg), $Cl_3SiH$ (0.5 mL, 4.9 mmol), DMF (7 µL, 0.1 mmol) and toluene (2 mL). The residue was purified by column chromatography on silica gel with a *n*-hexane − ethyl acetate mixture (10:1) to afford **2.9a** (254 mg, 85% yield): mp 113−115 °C (AcOEt−hexane); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 4.72 (s, 4H), 6.72 (d, J = 9.1 Hz, 2H), 7.21 (dd, J = 6.9 Hz, 1.5 Hz, 4H), 7.27−7.33 (m, 2H), 7.33−7.39 (m, 4H), 7.41 (d, J = 9.0 Hz, 2H);

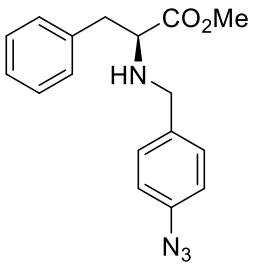
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 54.2 (2 × $CH_2$), 98.6 (C), 112.2 (2 × CH), 120.5 (C), 126.4 (4 × CH), 127.6 (2 × CH), 129.1 (4 × CH), 133.8 (2 × CH), 136.9 (2 × C), 152.0 (C); IR (Neat) ν 2897, 2205, 1450, 1356, $cm^{-1}$; MS (EI) *m/z* (%) 298 ($M^{\bullet+}$, 90), 207 (33), 179 (40), 91 (100); HRMS (EI) *m/z* $[M]^+$ calcd for $C_{21}H_{18}N_2$ 298.1465, found 298.1471.



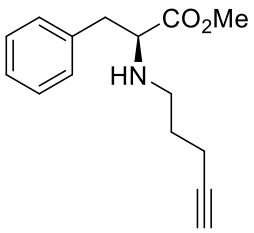
***N,N*-Bis(4-nitrobenzyl)-4-(4-(4-nitrobenzyl)piperazin-1-yl)aniline** (**2.9b**). A new compound.[83] Obtained from **2.1g** and **2.2j** using modified procedure B (3 equiv of 4-nitrobenzaldehyde were used), followed by F. A reddish-brown solid (268 mg, 46% yield): $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 2.55−2.67 (m, 4H), 3.00−3.13 (m, 4H), 3.65 (s, 2H), 4.58 (s, 4H), 6.65 (d, J = 9.1 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 7.42 (d, J = 8.8 Hz, 4H), 7.53 (d, J = 8.8 Hz, 2H), 8.18 (dd, J = 8.8, 2.1 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 50.6 (2 × $CH_2$), 53.6 (2 × $CH_2$), 55.6 (2 × $CH_2$), 62.4 ($CH_2$), 115.4 (2 × CH), 118.6 (2 × CH), 123.9 (2 × CH), 124.3 (4 × CH), 128.0 (4 × CH), 129.9 (2 × CH), 142.4 (C), 144.6 (C), 146.7 (3 × C), 147.6 (3 × C); IR (NaCl) ν 1515, 1344, 1231 $cm^{-1}$; MS (CI) m/z (%) 583 ($MH^+$, 100), 448 (95), 292 (27), 136 (70), 106 (28); HRMS (CI/isobutene) m/z $[M + H]^+$ calcd for $C_{31}H_{31}N_6O_6$ 583.2300, found 583.2307.



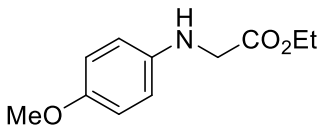
**Methyl (*S*)-*N*-(4-Nitrobenzyl)-phenylalaninate** (**2.10a**).[336] Obtained from 4-nitrobenzaldehyde (**2.1g**) and L-phenylalanine methyl ester (**2.2i**) using a procedure A, followed by a procedure E ($CH_2Cl_2$ instead of toluene) to afford the product as a yellow oil (146.7 mg, 65% yield): $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 1H), 2.80−3.20 (m, 2H), 3.49 (s, 1H), 3.71 (s, 4H), 3.97 (d, J = 13.7 Hz, 1H), 7.19 (d, J = 6.9 Hz, 2H), 7.23−7.34 (m, 3H), 7.36 (d, J = 7.4 Hz, 2H), 8.11 (d, J = 8.2 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 39.9 ($CH_2$), 51.3 (CH), 52.1 ($CH_2$), 62.2 ($CH_3$), 123.7 (2 × CH), 127.1 (CH), 128.7 (2 × CH), 128.8 (2 × CH), 129.5 (2 × CH), 137.3 (C), 147.3 (C), 147.7 (C), 174.9 (C); IR (NaCl) ν 3339, 1736, 1604, 1344, 1201, 1015, 851, 743 $cm^{-1}$; MS (ESI) m/z (%) 315 ($MH^+$, 75), 146 (40), 144 (100), 130 (30); HRMS (CI/isobutene) m/z $[M + H]^+$ calcd for $C_{17}H_{19}N_2O_4$ 315.1340, found 315.1348.



**Methyl (*S*)-*N*-(4-Azidobenzyl)-phenylalaninate** (**2.10b**). A new compound.[83] Obtained from **2.1i** and **2.2i** using procedure A, followed by E ($CH_2Cl_2$ instead of toluene) to afford the product as a red oil (113 mg, 45% yield): $^1$H NMR (400 MHz, $CDCl_3$) δ 1.82 (s, 1H), 2.92 (dd, J = 13.5, 7.4 Hz, 1H), 2.97 (dd, J = 13.5, 6.4 Hz, 1H), 3.50 (dd, J = 7.4, 6.4 Hz, 1H), 3.58 (d, J = 13.3 Hz, 1H), 3.65 (s, 3H), 3.78 (d, J = 13.4 Hz, 1H), 6.92 (d, J = 8.5 Hz, 2H), 7.12−7.17 (m, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.20−7.31 (m, 3H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 39.7 ($CH_2$), 51.6 ($CH_2$), 52.0 (CH), 62.2 ($CH_3$), 119.2 (2 × CH), 127.0 (CH), 128.7 (2 × CH), 129.5 (2 × CH), 129.8 (2 × CH), 136.8 (C), 137.6 (C), 139.0 (C), 175.3 (C); IR (NaCl) ν 3321, 2107, 1736, 1204, 1018 cm$^{-1}$; MS (CI) m/z (%) 312 ($MH^+$, 100), 283 (99), 223 (16), 189 (28); HRMS (CI/isobutene) m/z $[M + H]^+$ calcd for $C_{17}H_{19}N_4O_2$ 311.1498, found 311.1514.

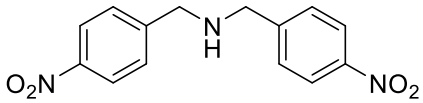


**Methyl (*S*)-*N*-(Pent-4-yn-1-yl)-phenylalaninate** (**2.10c**).[337] Obtained from **2.1q** and **2.2i** using a procedure A, followed by E ($CH_2Cl_2$ instead of toluene): Orange oil (96 mg, 39% yield): $^1$H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 1H), 1.63 (p, J = 7.0 Hz, 2H), 1.91 (t, J = 2.7 Hz, 1H), 2.19 (td, J = 7.1, 2.7 Hz, 2H), 2.55 (dt, J = 11.5, 7.0 Hz, 1H), 2.71 (dt, J = 11.5, 6.9 Hz, 1H), 2.94 (d, J = 6.9 Hz, 2H), 3.51 (t, J = 6.9 Hz, 1H), 3.64 (s, 3H), 7.12−7.33 (m, 5H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 16.4 ($CH_2$), 29.0 ($CH_2$), 40.0 ($CH_2$), 47.1 ($CH_2$), 51.9 (CH), 63.3 ($CH_3$), 68.8 (CH), 84.3 (C), 127.0 (CH), 128.7 (2 × CH), 129.5 (2 × CH), 137.6 (C), 175.7 (C); IR (NaCl) ν 3306, 3285, 2113, 1739, 1207, 1015, 746 cm$^{-1}$; MS (ESI) m/z (%) 246 ($MH^+$, 100), 186 (97), 121 (23); HRMS (CI/ isobutene) m/z $[M + H]^+$ calcd for $C_{15}H_{20}NO_2$ 246.1484, found 246.1482.

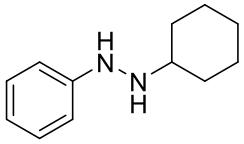


**Ethyl *N*-(4-Methoxyphenyl)glycinate** (**2.10d**).[338] Obtained from **2.1r** and **2.2c** using procedure A, followed by E ($CH_2Cl_2$ instead of toluene). Brownish solid (136 mg, 65% yield): $^1$H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 3.74 (s, 3H), 3.85 (s, 2H), 4.03 (s, 1H), 4.23 (q, J = 7.2 Hz, 2H), 6.55−6.61 (m, 2H), 6.75−6.82 (m, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 14.5 ($CH_3$), 47.1 ($CH_2$), 56.0 ($CH_3$), 61.5 ($CH_2$), 114.7 (2 × CH), 115.2 (2 × CH), 141.6 (C), 152.9 (C), 171.7 (C); IR (NaCl) ν

3383, 1732, 1213, 1146, 1024, 824, $cm^{-1}$; MS (ESI) m/z (%) 210 ($MH^+$, 100), 136 (100), 123 (56), 108 (46); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{11}H_{15}NO_3$ 210.1120, found 210.1126.

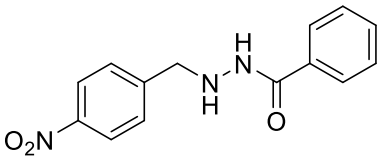


**Di(4-nitrobenzyl)amine** (**2.11**).[339] Molecular sieves (4 Å; 0.5−1.0 g) were added to a solution of **2.1g** (1.00 mmol; 1 equiv) and the ammonia solution (1.5 mmol; 3 mL, 1.5 equiv; 0.5 M in dioxane) in anhydrous $CH_2Cl_2$ (5 mL) and the mixture was stirred at room temperature for 8 h while monitoring the progress by TLC. The sieves were then filtered off and the filtrate was used immediately for the reduction. Trichlorosilane (202 μL, 2.0 mmol, 2 equiv) was added dropwise to a cooled solution (0 °C) of the *in situ* generated imine (1.0 mmol, 1 equiv) and dimethylformamide (7.5 μL, 0.1 equiv) in anhydrous $CH_2Cl_2$ (2 mL) under an argon atmosphere and the mixture was allowed to stir at ambient temperature overnight. The reaction mixture was then diluted with ethyl acetate (5 mL), quenched with a saturated aqueous solution of $NaHCO_3$ (20 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with water (2 × 15 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$, and evaporated to dryness. The crude product was purified by chromatography on a column of silica gel (∼15 g) with a mixture of $CH_2Cl_2$, MeOH, and $NH_3$ (92:7.5:0.5) to give the secondary amine **2.11** as the main product (48 mg, 0.17 mmol, 32% yield) as a yellow oil solidifying on standing: $^1H$ NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 4H), 7.55 (d, J = 8.7 Hz, 4H), 8.19 (d, J = 8.7 Hz, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 52.5 (2 × $CH_2$), 123.8 (2 × CH), 128.8 (2 × CH), 147.3 (C), 147.7 (C); IR (NaCl) ν 3535, 2924, 2850, 1597, 1512, 1344, 1107, 852 $cm^{-1}$; MS (ESI) m/z (%) 288 ($MH^+$, 100), 136 (16), 106 (10); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{13}N_3O_4$ 288.0979, found 288.0970.

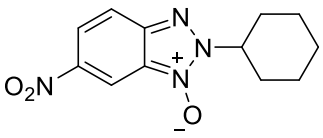


**1-Cyclohexyl-2-phenylhydrazine** (**2.12**).[14] Obtained from **2.1l** and **2.2m** using procedure A, followed by E ($CH_2Cl_2$ instead of toluene): Bright-yellow oil (89 mg, 47% yield): $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.27−1.53 (m, 4H), 1.77 (dd, J = 11.7, 4.0 Hz, 2H), 1.87 (q, J = 6.4, 5.4 Hz, 4H), 1.91−2.00 (m, 2H), 3.69 (p, J = 7.3 Hz, 1H), 7.36−7.56 (m, 3H), 7.69 (d, J = 7.1 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 24.4 (2 × $CH_2$), 25.7 ($CH_2$), 30.9 (2 × $CH_2$), 76.7 (CH), 122.1 (2 × CH), 129.0 (2 × CH), 130.2 (CH), 152.3

(C); IR (NaCl) ν 3062, 2931, 1595, 1450, 764, 690 $cm^{-1}$; MS (ESI) m/z (%) 191 ($MH^+$, 17), 174 (100), 132 (47); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{18}N_2$ 191.1538, found 191.1541.

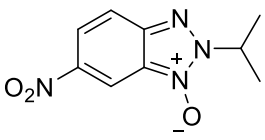


***N′*-(4-Nitrobenzyl)benzoic Acid Hydrazide** (**2.14**). A new compound.[83] Obtained from **2.1g** and **2.2o** using procedure A, followed by E ($CH_2Cl_2$ instead of toluene): Yellow solid (244 mg; 87% yield); mp 162−166 °C (crystallized from *i*-PrOH; 131 mg, 54% yield); $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 4.14 (d, J = 5.0 Hz, 2H), 5.75 (q, J = 5.3 Hz, 1H), 7.46 (dt, J = 31.0, 7.3 Hz, 3H), 7.67 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 7.0 Hz, 2H), 8.18 (d, J = 8.6 Hz, 2H), 10.03 (d, J = 5.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-$d_6$) δ 54.5 ($CH_2$), 123.9 (2 × CH), 127.7 (2 × CH), 129.0 (2 × CH), 130.2 (2 × CH), 132.0 (CH), 133.8 (C), 147.2 (C), 147.8 (C), 166.5 (C); IR (NaCl) ν 3273, 3231, 1637, 1601, 1323, 899, 806 $cm^{-1}$; MS (CI) m/z (%) 272 ($MH^+$, 100), 151 (13), 105 (14), 136 (11); HRMS (CI/isobutene) m/z $[M + H]^+$ calcd for $C_{14}H_{14}N_3O_3$ 272.1025, found 272.1034.



**2-Cyclohexyl-6-nitro-2*H*-benzo[*d*][1,2,3]triazole 1-Oxide** (**2.15a**).[340] Obtained from **2.1l** and **2.2n** using the following procedure. Concentrated $H_2SO_4$ (0.4 mL) was added to a slurry of **2.2n** (201 mg, 1 mmol, 1 equiv) in methanol (4 mL), followed by a solution of cyclohexanone **2.1l** (198 mg, 2 mmol, 2 equiv) in methanol (1 mL); formation of the corresponding hydrazone was observed immediately. The mixture was stirred at room temperature for 15 min and the precipitated product was isolated by filtration. The precipitate was washed with a small amount of cold MeOH and dried *in vacuo*, yielding the hydrazone (240 mg, 0.86 mmol, 86%) as a yellow solid. Reduction, using procedure E ($CH_2Cl_2$ instead of toluene), gave a crude product that was purified by column chromatography on silica gel (∼15 g) with a benzene−$CH_2Cl_2$ mixture (1:1) to afford the *N*-oxide **2.15a** as bright-yellow crystals (168 mg, 0.64 mmol, 74%), mp 111−113 °C (benzene-$CH_2Cl_2$) (lit[340] gives 120−122 °C): $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.38 (tt, J = 12.8, 3.6 Hz, 1H), 1.56 (dtdd, J = 16.0, 12.9, 5.3, 2.3 Hz, 2H), 1.82 (dqd, J = 13.6, 3.4, 1.7 Hz, 1H), 1.85−1.97 (m, 2H), 1.96−2.07 (m, 2H), 2.16−2.26 (m, 2H), 5.23 (tt, J = 11.3, 3.9 Hz, 1H), 7.85 (dd, J = 9.5, 0.7 Hz, 1H), 8.22 (dd, J = 9.5, 2.2 Hz, 1H), 8.81 (dd, J = 2.1, 0.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 25.1 ($CH_2$), 25.1 (2 × $CH_2$), 31.1 (2 × $CH_2$), 59.0 (CH), 112.7 (CH), 120.5 (CH), 122.5 (CH), 125.0 (C),

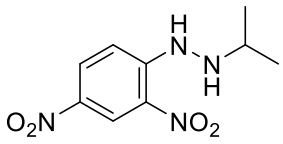
141.4 (C), 145.3 (C); IR (NaCl) ν 3100, 2956. 2935. 2854, 1619, 1329, 1269, 1156, 899 $cm^{-1}$; MS (ESI) m/z (%) 263 ($MH^+$, 100), 233 (13), 181 (99); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{14}N_4O_3$ 263.1139, found 263.1156.



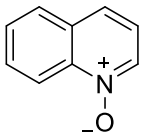
**2-Isopropyl-6-nitro-2*H*-benzo[*d*][1,2,3]triazole 1-Oxide (2.15b)**.[340] Obtained from **2.1m** and **2.2n** using the following procedure. Concentrated $H_2SO_4$ (0.4 mL) was added to a slurry of **2.2n** (201 mg, 1 mmol, 1 equiv) in methanol (4 mL), followed by a solution of acetone **2.1m** (116 mg, 2 mmol, 2 equiv) in methanol (1 mL); formation of the corresponding yellow hydrazone was observed immediately. The mixture was stirred at room temperature for 15 min, placed into a freezer overnight and the precipitated product was isolated by filtration. The precipitate was washed with a small amount of cold MeOH and dried *in vacuo*, yielding the hydrazone (191 mg, 0.8 mmol, 80%) as a yellow crystalline solid. Reduction, using procedure E ($CH_2Cl_2$ instead of toluene), gave a crude product that was purified by automated flash chromatography system purification on silica gel (~10 g) with a *n*-hexane – ethyl acetate mixture (7:1 to 6:1) to afford the *N*-oxide **2.15b** as greenish crystals (131 mg, 0.59 mmol, 74 %), mp 137-139 °C (benzene-$CH_2Cl_2$) (lit[340] gives 151−153 °C): $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.64 (d, J = 6.7 Hz, 6H), 5.53 (hept, J = 6.7 Hz, 1H), 7.84 (dd, J = 9.5, 0.7 Hz, 1H), 8.19 (dd, J = 9.5, 2.1 Hz, 1H), 8.76 (dd, J = 2.2, 0.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 20.7 (2 × $CH_3$), 52.7 (CH), 112.7 (CH), 120.6 (CH), 122.6 (CH), 124.8 (C), 141.4 (C), 145.3 (C); IR ($CHCl_3$) ν 2994, 1530, 1502, 1346, 1149, 819 $cm^{-1}$; MS (APCI) m/z (%) 223 ($MH^+$, 88), 181 (100), 124 (3); HRMS (APCI) m/z $[M + H]^+$ calcd for $C_9H_{11}N_4O_3$ 223.0824, found 223.0826.

**Multigram scale experiment**. All amounts were multiplied by 10 times. Concentrated $H_2SO_4$ (4 mL) was added to a slurry of **2.2n** (2.0 g, 10 mmol, 1 equiv) in methanol (40 mL), followed by a solution of acetone (1.47 mL, 20 mmol, 2 equiv) in methanol (10 mL); formation of the corresponding yellow hydrazone was observed immediately. The mixture was stirred at room temperature for 15 min, placed into a freezer overnight and the precipitated product was isolated by filtration. The precipitate was washed with a small amount of cold MeOH and dried *in vacuo*, yielding the hydrazone (2.1 g, 8.8 mmol, 87%) as a yellow crystalline solid. Reduction, using procedure E ($CH_2Cl_2$ instead of toluene), gave a crude mixture that was purified by automated

flash chromatography system purification on silica gel (~120 g) with a *n*-hexane – ethyl acetate mixture (100:0 to 85:15) to afford the N-oxide **2.15b** as greenish crystals (1.11 g, 5 mmol, 57 %).

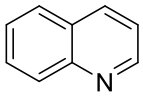


**1-(2,4-Dinitrophenyl)-2-isopropylhydrazine** (**2.16**).[340] Obtained from **2.1m** and **2.2n** using the following procedure. Concentrated $H_2SO_4$ (4 mL) was added a slurry of **2.2n** (2.0 g, 10 mmol, 1 equiv) in methanol (40 mL), followed by a solution of acetone (1.47 mL, 20 mmol, 2 equiv) in methanol (10 mL); formation of the corresponding yellow hydrazone was observed immediately. The mixture was stirred at room temperature for 15 min, placed into a freezer overnight and the precipitated product was isolated by filtration. The precipitate was washed with a small amount of cold MeOH and dried *in vacuo*, yielding the hydrazone (2.1 g, 8.8 mmol, 87%) as a yellow crystalline solid. Reduction, using procedure E ($CH_2Cl_2$ instead of toluene), gave a crude mixture that was purified by automated flash chromatography system purification on silica gel (~120 g) with a *n*-hexane – ethyl acetate mixture (100:0 to 85:15) to afford the corresponding hydrazine **2.16** as brick red crystals (0.74 g, 3.1 mmol, 35 %). Mp 102-104 °C (benzene-$CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, $J$ = 6.4 Hz, 6H), 3.21 (hept, $J$ = 6.3 Hz, 1H), 3.80 (s, 1H), 7.83 (d, $J$ = 9.7 Hz, 1H), 8.20 (ddd, $J$ = 9.6, 2.6, 0.9 Hz, 1H), 9.03 (d, $J$ = 2.6 Hz, 1H), 9.33 (s, 1H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 20.7 (2 × $CH_3$), 52.5 (CH), 116.3 (CH), 124.0 (CH), 129.0 (C), 130.1 (CH), 136.8 (C), 150.8 (C); MS (APCI) m/z (%) 241 ($MH^+$, 39), 223 ($MH^+$, 83), 181 (100), 124 (9); IR ($CHCl_3$) ν 3339, 1621, 1524, 1336, 1313, 924 cm$^{-1}$; HRMS (APCI) m/z $[M + H]^+$ calcd for $C_9H_{13}N_4O_4$ 241.0931, found 241.0931.

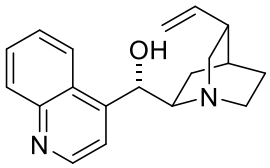


**Quinoline *N*-Oxide** (**2.17**).[341] *m*-CPBA (524 mg, 1.2 equiv) was added to a 0.2 M solution of quinoline (323 mg, 1.0 equiv) in dry in $CH_2Cl_2$ (12.5 mL) and the mixture was stirred at ambient temperature overnight. Triphenylphosphine (0.5 equiv) was then added and the mixture was stirred for another 4 h after which time the mixture was evaporated *in vacuo* to dryness and the residue was purified by chromatography on a silica gel column (~15 g) with a mixture of EtOAc and MeOH (9:1) yielding the *N*-oxide **2.17** (370 mg, quant) as an off-white solid: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.27 − 7.35 (m, 1H), 7.65 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.72−7.81 (m, 2H), 7.88 (dd, J = 8.1, 1.4 Hz, 1H), 8.57 (dd, J = 6.0, 1.1 Hz, 1H), 8.76 (d, J =

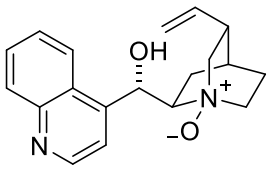
8.5 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 119.8 (CH), 121.0 (CH), 126.4 (CH), 128.2 (CH), 128.9 (CH), 130.6 (CH), 130.6 (CH), 135.8 (C), 141.5 (C).



**Quinoline** (**2.18**). Trichlorosilane (2 equiv) was added to a solution of quinoline *N*-oxide **2.17** (1 equiv) in $CH_2Cl_2$ (5 mL) at 0 °C and the mixture was stirred at rt overnight (ca. 16 h). The reaction was quenched with a saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with EtOAc (3×). The combined organic phase was washed with brine, dried with $Na_2SO_4$, and concentrated *in vacuo* to afford pure quinoline **2.18** (170 mg, 98% yield).



**Cinchonine** (**2.19**). Obtained by reduction of its *N*-oxide (**2.21**). Trichlorosilane (1.1 equiv) was added to a solution of **2.21** (0.37 mmol) in $CH_2Cl_2$ (1.5 mL) with or without addition of catalytic amount of DMF (10 mol %) at 0 °C, the mixture was allowed to warm to rt and left while stirring overnight (ca. 16 h). The reaction was quenched with sat $NaHCO_3$ and the product was extracted in EtOAc (3×). The combined organic phase was washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo* to give the crude product that was characterized by $^{1}H$ NMR spectroscopy, which revealed a mixture of **2.19** and **2.21** in ca. 2:3 ratio for the experiment carried out in the absence of DMF and 2:1 in its presence.



**Cinchonine *N*-Oxide** (**2.21**).[342] Method A. A solution of *t*-BuOOH in decane (1 mmol) was added dropwise to a mixture of cinchonine **2.19** (1 mmol) and $VO(acac)_2$[343] (1.4 mol %) in dry $CH_2Cl_2$ (3 mL) and the resulting slurry was stirred overnight at rt (ca. 16 h). The mixture that became a transparent colorless solution was directly loaded on the top of a silica gel column (~15 g) ($CH_2Cl_2$−MeOH = 10:1, $R_f$ = 0.28) to give the product **2.21**[344] as an off-white solid foam (308 mg, 95%). $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 1.21−1.31 (m, 1H), 1.83 (dd, J = 11.2, 9.0 Hz, 1H), 1.91 (s, 1H), 1.93−2.05 (m, 1H), 2.67−2.86 (m, 2H), 3.22 (dq, J = 22.5, 12.7, 11.8 Hz, 2H), 3.32−3.50 (m, 2H), 4.81 (ddd, J = 12.0, 8.1, 2.6 Hz, 1H), 5.14−5.28 (m, 2H), 6.17 (ddd, J = 17.1, 10.4, 7.5

Hz, 1H), 7.01 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 7.20 (s, 1H), 7.51 (ddd, J = 8.3, 6.9, 1.2 Hz, 1H), 7.89 (dd, J = 4.4, 0.7 Hz, 1H), 7.93 (d, J = 7.9 Hz, 1H), 8.05 (dd, J = 8.5, 1.3 Hz, 1H), 8.89 (d, J = 4.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 20.7, 26.9, 28.0, 41.6, 63.3, 63.8, 65.9, 73.1, 117.0, 119.7, 123.2, 125.4, 126.9, 129.0, 130.2, 137.8, 148.1, 149.4, 150.6; IR (NaCl) ν 3508, 2993, 1373, 1165, 947, 866, 762 $cm^{-1}$; MS (CI) m/z (%) 311 ($MH^+$, 100), 203 (58), 156 (99); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{23}N_2O_2$ 311.170, found 311.1758.

Method B. A solution of *m*-CPBA (1 mmol) in $CH_2Cl_2$ (3 mL) was added dropwise to a stirred suspension of cinchonine **2.19** (1 mmol) in $CH_2Cl_2$ (9 mL) at 0 °C, the mixture was allowed to warm to rt and then stirred for 1 h. The mixture was then washed with sat. $NaHCO_3$, the organic layer was dried over $Na_2SO_4$, and concentrated *in vacuo* to give the pure product **2.21** as a white foam (304 mg, 97%).

## Ezetimibe project. General methods

*p*-$SF_5$-aniline **4.8c** was obtained in 92% yield from *p*-$SF_5$-nitrobenzene **4.9** by reduction with Fe in acidic solution.[264] The experiment was repeated several times and on multigram scales, with consistent yield and sufficient level of purity for further use without need of column chromatography. Analytically pure sample was prepared by recrystallization from EtOH/water mixture. *p*-$SF_5$-bromobenzene **4.13** was synthesized in two ways: (a) From *p*-$SF_5$-aniline **4.8c**, which was treated with *tert*-butyl nitrite ($^t$BuONO) and $CuBr_2$ in acetonitrile.[264] This method allowed us to obtain *p*-$SF_5$-bromobenzene **4.13** with a moderate yield (76%), although with non-sufficient level of purity (some impurities weren't separated even after column chromatography with pure *n*-hexane as an eluent). (b) From *p*-$SF_5$-aniline **4.8c**, which was first reacted with $NaNO_2$/HBr mixture and to the resulting diazonium salt suspension was added CuBr.[283] The procedure gave the expected *p*-$SF_5$-bromobenzene **4.13** with an excellent yield (87%) and high level of purity after column chromatography. Benzylation of 4-hydroxyacetophenone **4.5** was performed in accordance with ref.,[261] mixing the starting 4-hydroxyacetophenone **4.5** with an excess of benzyl bromide, $K_2CO_3$ and small amount of KI in acetone. The benzylated product **4.6** was obtained with a quantitative yield after recrystallization from *n*-hexane. Preparation of β-ketoester **4.7** was performed by the treatment of **4.6** with NaH and diethyl carbonate in boiling toluene.[262] The product **4.7** was isolated with a quantitative yield and sufficient level of purity without need in column chromatography. *p*-$SF_5$-benzaldehyde **4.14b** was prepared from *p*-$SF_5$-bromobenzene **4.13**, which was treated with $^t$BuLi solution at -78 °C with following addition of N-formylpiperidine as a formylating agent.[286] The resulting substituted benzaldehyde **4.14b** was obtained with a good yield (66%) after column chromatography purification.

**Procedure E: General method for the synthesis of substituted ethyl cinnamates *via* Wittig reaction**

A solution of corresponding substituted benzaldehyde (1 equiv) in $CH_2Cl_2$ (10 mL/g ArCHO) was treated with ethyl 2-(triphenyl-λ5-phosphanylidene)acetate (1.05 equiv). The reaction mixture was stirred at room temperature overnight, concentrated *in vacuo*, the residue was treated with a mixture of *n*-Hexane/$Et_2O$ = 9:1 (20 mL/g ArCHO) and stirred for 30 min, filtered and the filtrate was evaporated. The resulting oil was purified by silica gel column chromatography with a *n*-hexane – ethyl acetate mixture (6:1). The yields are given in a description of certain experiments.

**Procedure F: General method for the reduction of substituted ethyl cinnamates with DIBAL-H solution**

A solution of α,β-unsaturated ester (1 equiv) in anhydrous $CH_2Cl_2$ (0.25 M) was cooled to -78 °C and treated with DIBAL-H solution (25% ωt in PhMe ≈ 1.5 M, 2.2 equiv) in a dropwise manner. The reductant was added in two equal portions (the second portion 10 minutes after the first one). The resulting mixture was stirred for 1.5 h at the same temperature, then quenched with aqueous NaOH (10% ωt, equal volume). The mixture was allowed to warm to an ambient temperature, the layers were separated, and the aqueous fraction was extracted with $CH_2Cl_2$ (3×), the combined organic extracts were washed with 2 M aqueous HCl (equal to NaOH volume). brine, dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography with a *n*-hexane – ethyl acetate mixture (1:1).

**Procedure G: General method for bromination of substituted cinnamyl alcohols**

A solution of allylic alcohol (1 equiv) in $Et_2O$ (0.33 M) was cooled to 0 °C and treated with $PBr_3$ (0.4 equiv) in the darkness and stirred for 1 h, the reaction was quenched by the dropwise addition of aqueous saturated $NaHCO_3$ (equal volume), the mixture was allowed to warm to rt. The layers were then separated, the aqueous layer extracted with $Et_2O$ (2×), the combined organic layers washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give allylic bromides, which were used directly.

**Procedure H: General method for bromination of substituted cinnamyl alcohols**

The corresponding cinnamyl alcohol (1 equiv) and $CBr_4$ (1.1 equiv) were dissolved in $CH_2Cl_2$ (1.1 M) and cooled to 0 °C. $PPh_3$ (1.1. equiv) was added *via* the powder funnel in portions over 30 minutes with vigorous stirring. Upon addition of the phosphine, the solution was stirred for an additional 2 h at room temperature. The mixture was concentrated to a brown oil and quickly added to *n*-hexane (~ 3 × RM volume) under stirring. The white precipitate of phosphine oxide was filtered, and the remaining solution was passed through a short pad of silica. The solvent was evaporated to give the product which was of sufficient purity for further use.

**Procedure I: General method for iodination of substituted cinnamyl alcohols**

A round-bottomed flask was charged with $PPh_3$ (1 equiv), imidazole (1 equiv) and $CH_2Cl_2$ (0.33 M). Iodine (1 equiv) was added in small portions to the stirring solution. After 30 minutes,

the flask was wrapped in an aluminium foil and placed in an ice bath, followed by slow addition of cinnamyl alcohol (1 equiv) solution in $CH_2Cl_2$ (0.5 M). After the reaction was complete (~ 30 min), the mixture was filtered through a plug of silica, which was then washed with a *n*-hexane ethyl acetate mixture (10:1, 2–3×). The combined solution was concentrated *in vacuo* and purified by flash column chromatography with a *n*-hexane – ethyl acetate mixture (96:4).

**Procedure J: General method for iodination of substituted cinnamyl alcohols**

$Me_3SiCl$ (1 equiv), water (0.5 equiv), and then the corresponding cinnamyl alcohol (1 equiv) were added slowly to an efficiently stirred solution of NaI (1 equiv) in acetonitrile (0.67 M). The mixture was allowed to react at room temperature for 30 minutes. After quenching with water (3 × RM volume), the product was extracted with $Et_2O$ (3×). The ether layer was washed with 10% aqueous $Na_2S_2O_3$ (1.3 – 1.5 × RM volume), dried over $MgSO_4$ and evaporated to dryness. The crude product was purified using short flash chromatography with pure *n*-hexane as an eluent.

**Procedure K: General method for enamine synthesis**

A solution of β-ketoester **27** (1 equiv), corresponding aniline (1.1 equiv) and *para*-toluenesulfonic acid monohydrate (10 mol %) in dry EtOH (1 M) was heated to reflux for 24 h under an inert atmosphere, then 3Å molecular sieves (1 g/4 mmol β-ketoester) were added and the mixture was refluxed for additional 24 h. The magnetic stirrer was off during this period of time. The cooled reaction mixture was filtered through a pad of Celite and the pad was washed with $CH_2Cl_2$. Filtrate was evaporated to dryness, redissolved in $CH_2Cl_2$ and washed with water. The organic phase was dried ($Na_2SO_4$), filtered and evaporated. The crude product was purified by silica gel column chromatography with a *n*-hexane – ethyl acetate mixture (100:0 to 96:4).

**Procedure L: General method for asymmetric reduction of enamines with trichlorosilane**

A solution of the corresponding enamine (1 equiv) and a chiral catalyst Kenamide (5 mol %) in dry toluene (0.1 M) was pre-cooled to 0 °C and glacial acetic acid (1 equiv) was added, followed by dropwise addition of trichlorosilane (2 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 60 h, after which time a saturated aqueous solution of $NaHCO_3$ was added to quench the reaction (pH control). The mixture was extracted with EtOAc (3×), the organic phase was washed with brine and dried over $Na_2SO_4$. Concentration *in vacuo*, followed by

automated flash chromatography system purification or silica gel column chromatography with a *n*-hexane – ethyl acetate mixture (100:0 to 90:10) afforded the product.

**Procedure M: General method for racemic reduction of enamines with trichlorosilane**

A solution of the corresponding enamine (1 equiv) and DMF as a non-chiral Lewis base catalyst (0.1 equiv) in dry toluene (0.1 M) was pre-cooled to 0 °C and glacial acetic acid (1 equiv) was added, followed by dropwise addition of trichlorosilane (2 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 60 h, after which time a saturated aqueous solution of $NaHCO_3$ was added to quench the reaction (pH control). The mixture was extracted with EtOAc (3×), the organic phase was washed with brine and dried over $Na_2SO_4$. Concentration *in vacuo*, followed by automated flash chromatography system purification or silica gel column chromatography with a *n*-hexane – ethyl acetate mixture (100:0 to 90:10) afforded the product.

**Procedure N: General method for synthesis of 4-membered β-lactams**

A solution of *tert*-butylmagnesium halide (chloride or bromide, 2 equiv) was added slowly to a cold solution of the corresponding β-amino ester (1 equiv) in anhydrous diethyl ether (0.1 M) at -12 °C. The reaction mixture was allowed to stir for another 15-20 min at the same temperature, after which time a saturated aqueous solution of $NH_4Cl$ (pH control) was added to quench the reaction. The mixture was extracted with EtOAc (3×), the combined organic phase was dried over $Na_2SO_4$. Evaporation in vacuum and subsequent automated flash chromatography system purification or silica gel column chromatography with a *n*-hexane – ethyl acetate mixture (100:0 to 88:12) afforded the product.

**Procedure O: General method for alkylation of β-lactams**

To a stirred solution of corresponding lactam (1 equiv) in dry THF (0.045 M) the solution of commercial LDA (20% ωt in THF/PhEt/Hept ≈ 1.5 M, 1.3 equiv) was added dropwise at -78 °C and the mixture was stirred for 30 minutes at the same. The solution of corresponding cinnamyl halide (1.85 equiv) in dry THF (0.34 M) was then added dropwise and the reaction mixture was stirred for another 90 minutes at -78 °C. After indicated time, the reaction mixture was quenched by an addition of saturated aqueous $NH_4Cl$ (1.3 – 1.5 × RM volume), allowed to warm to room temperature and extracted with EtOAc (3×). The organic phase was dried over $Na_2SO_4$ and evaporated to dryness. The crude product was purified by automated flash chromatography system

purification or silica gel column chromatography with a *n*-hexane – ethyl acetate mixture (9:1 to 5:1).

**Procedure P: General method for Wacker-type oxidation of alkylated β-lactams**

$Pd(OAc)_2$ (3 mol %), *p*-benzoquinone (1.5 equiv) and 70% $HClO_4$ (70 μL/mmol) were added to acetonitrile ($V_1 = V_2$, $C_{total} \approx 0.2$ M). Next, water (0.5 mL/mmol) was added thereto, followed by vigorous stirring of the reaction mixture for another 5 min. Then, a solution of the corresponding alkylated lactam (1 equiv) in equal amount of acetonitrile ($V_2 = V_1$, $C_{total} \approx 0.2$ M) was added dropwise. The reaction mixture was stirred for 4 h, after which time the second portion of 70% $HClO_4$ (70 μL/mmol, $C_{total} \approx 0.3$ M) was added, and the whole mixture was stirred for 72 h at ambient temperature. The reaction was quenched with water (60 mL) and brine (30 mL), extracted with EtOAc (25 mL, 3×) and washed with brine. The organic phase was dried over $Na_2SO_4$ and evaporated to dryness. The crude product was purified by automated flash chromatography system purification or silica gel column chromatography with a *n*-hexane – ethyl acetate mixture (9:1 to 4:1).

**Procedure Q: General method for chiral reduction of ketone moieties in alkylated β-lactams**

A (*R*)-methyl-CBS catalyst (20 mol %. 1 M solution in toluene) and the corresponding ketone (1 equiv) were dissolved in anhydrous THF (0.63 M) and then stirred at -20 °C for 5 minutes. Subsequently, a BMS complex solution (2 M solution in THF, 1.2 equiv) was added dropwise thereto at the rate 0.44 mL/h, after which time the reaction mixture was stirred for another 3 h at -20 °C. The reaction was terminated with MeOH (equal volume), acidified with an excess of 1 M HCl (50 mL) and extracted with EtOAc (25 mL, 3×). The organic phase was dried over $Na_2SO_4$, filtered and concentrated. The crude product was purified by automated flash chromatography system purification or silica gel column chromatography with a *n*-hexane – ethyl acetate mixture (9:1 to 2:1).

**Procedure R: General method for chiral reduction of ketone moieties in alkylated β-lactams**

In a round-bottomed flask with a stirrer bar the corresponding lactam (1 equiv) was dissolved in $CH_2Cl_2$ (0.21 M). To the resulting solution at -20 °C were added sequentially an (*R*)-methyl-

CBS catalyst (10 mol %. 1 M solution in toluene) and a BMS complex solution (1 equiv) over 2 h at -20 °C. The reaction mixture was allowed to warm to 0 °C for 1 h and terminated with MeOH (until hydrogen evolution ceases), acidified with an excess of 1 M HCl (50 mL) and extracted with EtOAc (25 mL, 3×). The organic phase was dried over $Na_2SO_4$, filtered and concentrated. The crude product was purified by automated flash chromatography system purification or silica gel column chromatography with a *n*-hexane – ethyl acetate mixture (6:1 to 3:1).

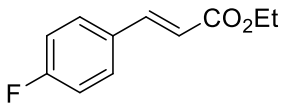
**Procedure S: General method for removal of benzylic protection by Pd/C hydrogenolysis**

An autoclave glass tube equipped with a magnetic stirrer bar was charged with the corresponding substrate (1 equiv) dissolved in EtOH (0.05 M). A catalyst Pd/C (10% ωt, 8 mol %) was added to the mixture and the hydrogenator was purged several times with hydrogen. Subsequently, a high pressure of hydrogen (60 atm) was maintained, and the reaction mixture was stirred at room temperature overnight. After hydrogen removal by purging with an inert gas, the reaction mixture was filtered through a short pad of Celite, eluted with EtOAc and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography with a *n*-hexane – ethyl acetate mixture (2:1).

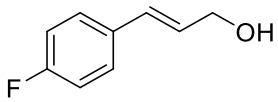
**Procedure T: General method for removal of benzylic protection by treatment with $BCl_3$**

A 2 mL vial equipped with a stirrer bar was charged with the corresponding lactam (1 equiv), pentamethylbenzene (3 equiv) and anhydrous $CH_2Cl_2$ (0.2 M). The reaction mixture was cooled to -78 °C and 1 M solution $BCl_3$ in $CH_2Cl_2$ (2 equiv) was added dropwise over 5 min. After stirring for 45 min at the same temperature, the reaction mixture was quenched with the mixture $CHCl_3$/MeOH = 10:1 (equal to $BCl_3$ solution volume) at -78 °C and warmed to room temperature. The solution was concentrated on a rotary evaporator and remaining crude product was purified by silica gel column chromatography with a *n*-hexane – ethyl acetate mixture (2:1).

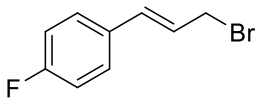
# List of compounds



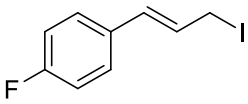

**Ethyl (*E*)-3-(4-fluorophenyl)acrylate** (**4.15a**).[345] Obtained from commercially available 4-fluorobenzaldehyde **4.14a** and ethyl 2-(triphenyl-λ5-phosphanylidene)acetate using procedure E: Colorless oil (4.04 g, 99% yield, E/Z ratio = 95:5); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.1 Hz, 3H), 4.25 (q, *J* = 7.1 Hz, 2H), 6.34 (dd, *J* = 16.0, 0.6 Hz, 1H), 7.00 – 7.10 (m, 2H), 7.45 – 7.53 (m, 2H), 7.63 (d, *J* = 16.0 Hz, 1H); $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 14.41 ($CH_3$), 60.63 ($CH_2$), 116.11 (d, *J* = 22.0 Hz, 2 × CH), 118.14 (d, *J* = 2.3 Hz, CH), 129.99 (d, *J* = 8.5 Hz, 2 × CH), 130.82 (d, *J* = 3.4 Hz, C), 143.34 (CH), 163.95 (d, *J* = 251.0 Hz, C), 166.94 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -109.76 (ddd, *J* = 14.1, 8.7, 5.3 Hz).



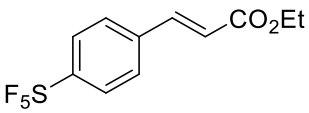

**(*E*)-3-(4-Fluorophenyl)-2-propen-1-ol** (**4.16a**).[346] Obtained from **4.15a** using procedure F: White amorphous solid (3.12 g, 98% yield, E/Z ratio = 95:5); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 1H), 4.32 (ddd, *J* = 5.7, 1.5, 0.4 Hz, 2H), 6.28 (dtd, *J* = 15.9, 5.7, 0.6 Hz, 1H), 6.58 (dt, *J* = 15.9, 1.6 Hz, 1H), 7.00 (t, J = 8.7 Hz, 2H), 7.34 (dd, J = 8.7, 5.5 Hz, 2H); $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 63.7, 115.6 (d, J = 21.6 Hz), 128.1 (d, J = 8.1 Hz), 128.4 (d, J = 2.3 Hz), 130.1, 133.0 (d, J = 3.4 Hz), 162.5 (d, J = 246.7 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -114.33 (ddd, *J* = 14.3, 8.9, 5.5 Hz).



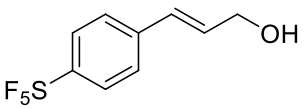

**(*E*)-1-(3-Bromoprop-1-en-1-yl)-4-fluorobenzene** (**4.17a**).[347] Obtained from **4.16a** using procedure G: White amorphous solid (0.47 g, 83% yield, E/Z ratio = 95:5); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 4.15 (dd, J = 7.8, 1.0 Hz, 2H), 6.32 (dt, J = 15.7, 7.8 Hz, 1H), 6.61 (d, J = 15.6 Hz, 1H), 7.02 (t, J = 8.7 Hz, 2H), 7.36 (dd, J = 8.7, 5.4 Hz, 2H); $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 33.4, 115.8 (d, J = 21.7 Hz), 125.1 (d, J = 2.3 Hz), 128.5 (d, J = 8.1 Hz), 132.1 (d, J = 3.2 Hz), 133.5, 162.9 (d, J = 248.1 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -113.05 (tt, J = 8.6, 5.3 Hz).



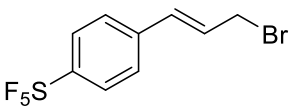
**1-Fluoro-4-[(1*E*)-3-iodo-1-propen-1-yl]benzene** (**4.18a**).[290] Obtained from **4.16a** using procedure I: Yellow amorphous solid (2.36 g, 69% yield, E/Z ratio = 95:5); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 4.10 (dd, *J* = 8.1, 0.9 Hz, 2H), 6.35 (dtd, *J* = 15.5, 8.2, 0.6 Hz, 1H), 6.56 (d, *J* = 15.5 Hz, 1H), 6.97 – 7.05 (m, 2H), 7.30 – 7.37 (m, 2H); $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 6.70 ($CH_2$), 115.77 (d, *J* = 21.8 Hz, 2 × CH), 126.82 (d, *J* = 2.3 Hz, CH), 128.33 (d, *J* = 8.1 Hz, 2 × CH), 132.07 (CH), 132.23 (d, *J* = 3.4 Hz, C), 162.77 (d, *J* = 248.1 Hz, C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -113.26 (ddd, *J* = 13.8, 8.8, 5.3 Hz).



**Ethyl (*E*)-3-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)acrylate** (**4.15b**). A new compound. Obtained from **4.14b** and ethyl 2-(triphenyl-λ5-phosphanylidene)acetate using procedure E: Yellowish oil (9.47 g, 95% yield, E/Z ratio = 95:5); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.1 Hz, 3H), 4.28 (q, *J* = 7.1 Hz, 2H), 6.49 (d, *J* = 16.0 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 16.0 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 2H). $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 14.35 ($CH_3$), 61.00 ($CH_2$), 121.73 (CH), 126.71 (p, *J* = 4.7 Hz, 2 × CH), 128.13 (2 × CH), 137.77 (C), 141.98 (CH), 154.54 (t, *J* = 18.1 Hz, C), 166.33 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ 62.60 (d, *J* = 150.1 Hz), 82.89 – 84.54 (m).

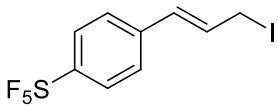


**(*E*)-3-(4-(Pentafluoro-λ$^6$-sulfanyl)phenyl)-2-propen-1-ol** (**4.16b**). A new compound. Obtained from **4.15b** using procedure F: Yellow oil solidifying on standing (7.73 g, 95% yield, E/Z ratio = 95:5); mp 45-47 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.95 (s, 1H), 4.36 (dd, *J* = 5.2, 1.7 Hz, 2H), 6.44 (dt, *J* = 15.9, 5.2 Hz, 1H), 6.64 (dt, *J* = 16.0, 1.8 Hz, 1H), 7.41 (dt, *J* = 8.8, 1.1 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H); $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 63.27 ($CH_2$), 126.39 (p, *J* = 4.7 Hz, 2 × CH) 126.49 (2 × CH), 128.60 (CH), 132.25 (CH), 140.17 (C), 152.76 (t, *J* = 18.1 Hz, C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ 62.97 (d, *J* = 149.9 Hz), 83.89 – 85.81 (m); HRMS-EI: *m/z* $[M^{\bullet}]^+$ calcld for $C_9H_9OF_5S$: 260.0289; found: 260.0289.

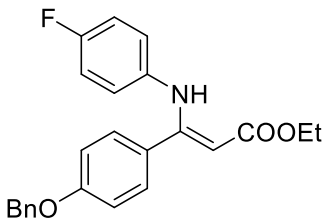


**(*E*)-1-(3-Bromoprop-1-en-1-yl)-4-(pentafluoro-λ$^6$-sulfanyl)benzene** (**4.17b**). A new compound. Obtained from **4.16b** in two ways: (a) Using procedure G: Slightly yellow oil solidifying on standing (0.37 g, 61% yield, E/Z ratio = 95:5) (b)

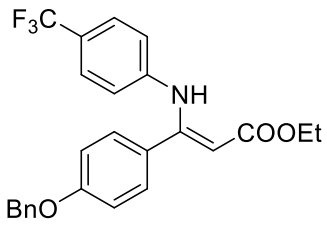
Using procedure H: Slightly yellow oil solidifying on standing (9.4 g, 98% yield, E/Z ratio = 95:5); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 4.15 (dd, *J* = 7.6, 1.0 Hz, 2H), 6.42 – 6.54 (m, 1H), 6.65 (d, *J* = 15.7 Hz, 1H), 7.44 (d, *J* = 8.9 Hz, 2H), 7.71 (d, *J* = 8.9 Hz, 2H); $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 32.25 ($CH_2$), 126.48 (p, *J* = 4.7 Hz, 2 × CH), 126.85 (2 × CH), 128.79 (CH), 132.31 (CH), 139.22 (C), 153.38 (t, *J* = 18.1 Hz, C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ 62.90 (d, *J* = 150.5 Hz), 83.47 – 85.57 (m).



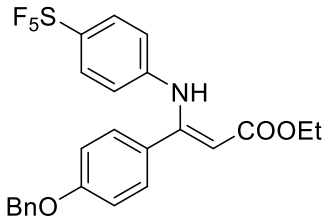

**(*E*)-1-(3-Iodoprop-1-en-1-yl)-4-(pentafluoro-λ$^{6}$-sulfanyl)benzene** (**4.18b**). A new compound. Prepared from **4.16b** in two ways: (a) Using procedure I: Yellow amorphous solid (1.37 g, 74% yield, E/Z ratio = 95:5) (b) Using procedure J: Yellow amorphous solid (2.09 g, 56% yield, E/Z ratio = 95:5); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 4.09 (dd, *J* = 7.2, 0.9 Hz, 2H), 6.47 – 6.57 (m, 1H), 6.59 (d, *J* = 15.6 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H); $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 5.01 ($CH_2$), 126.49 (p, *J* = 4.8 Hz, 2 × CH), 126.69 (2 × CH), 130.55 (CH), 130.94 (CH), 139.35 (C), 153.24 (t, *J* = 18.1 Hz, C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ 62.91 (d, *J* = 149.9 Hz), 83.48 – 85.78 (m).



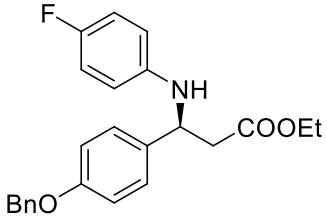

**Ethyl (Z)-3-(4-(benzyloxy)phenyl)-3-((4-fluorophenyl)amino) acrylate** (**4.10a**).[193] Obtained from commercially available 4-fluoroaniline **4.8a** and **4.7** using procedure K: Yellowish oil (8.15 g, 72% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.1 Hz, 3H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.99 (s, 1H), 5.05 (s, 2H), 6.63 – 6.71 (m, 2H), 6.76 – 6.84 (m, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.31 – 7.46 (m, 5H), 10.22 (s, 1H); $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 14.66 ($CH_3$), 59.38 ($CH_2$), 70.16 ($CH_2$), 90.45 (CH), 114.85 (2 × CH), 115.49 (d, *J* = 22.7 Hz, 2 × CH), 124.13 (d, *J* = 8.0 Hz, 2 × CH), 127.65 (2 × CH), 128.20 (C), 128.25 (CH), 128.74 (2 × CH), 129.88 (2 × CH), 136.59 (C), 136.91 (d, *J* = 2.7 Hz, C), 159.00 (d, *J* = 242.5 Hz, C). 159.14 (C), 159.92 (C), 170.37 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -120.02 (tt, *J* = 8.6, 4.7 Hz).




**Ethyl (Z)-3-(4-(benzyloxy)phenyl)-3-((4-(trifluoromethyl)phenyl) amino)acrylate** (**4.10b**). A new compound. Obtained from commercially available 4-(trifluoromethyl)aniline **4.8b** and **4.7** using procedure K: Yellow oil (5.7 g, 43% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.1 Hz, 3H), 4.23 (q, *J* = 7.1 Hz, 2H), 5.08 (s, 2H), 5.10 (s, 1H), 6.71 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.32 – 7.46 (m, 7H), 10.37 (s, 1H); $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 14.58 ($CH_3$), 59.67 ($CH_2$), 70.21 ($CH_2$), 93.23 (CH), 115.16 (2 × CH), 120.98 (2 × CH), 124.17 (q, *J* = 32.7 Hz, C), 124.40 (d, *J* = 271.4 Hz, C), 126.01 (q, *J* = 3.8 Hz, 2 × CH), 127.67 (2 × CH), 127.90 (C), 128.29 (CH), 128.76 (2 × CH), 129.62 (2 × CH), 136.52 (C), 144.09 (C), 157.59 (C), 160.24 (C), 170.04 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -61.84.

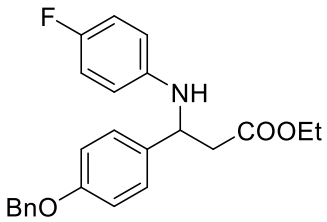



**Ethyl (Z)-3-(4-(benzyloxy)phenyl)-3-((4-(pentafluoro-λ$^{6}$-sulfanyl) phenyl)amino)acrylate** (**4.10c**). A new compound. Obtained from **4.8c** and **4.7** using procedure K: Yellowish oil (4.02 g, 20% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.2 Hz, 3H), 4.24 (q, *J* = 7.1 Hz, 2H), 5.09 (s, 2H), 5.13 (s, 1H), 6.65 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.35 – 7.50 (m, 7H), 10.39 (s, 1H); $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 14.57 ($CH_3$), 59.80 ($CH_2$), 70.25 ($CH_2$), 93.99 (CH), 115.30 (2 × CH), 120.07 (2 × CH), 126.76 (p, *J* = 4.6 Hz, 2 × CH), 127.70 (2 × CH), 128.34 (CH), 128.79 (2 × CH), 129.57 (2 × CH), 136.47 (C), 143.75 (C), 147.72 (t, *J* = 17.4 Hz, C), 157.20 (C), 160.35 (C), 169.97 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ 63.91 (d, *J* = 150.0 Hz), 86.01 (p, *J* = 150.3).

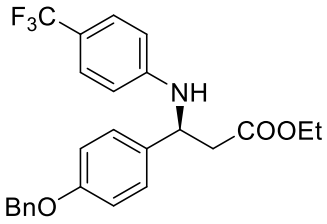



**Ethyl (*S*)-3-(4-(benzyloxy)phenyl)-3-((4-fluorophenyl)amino) propanoate** (**4.11a**).[193] Obtained from **4.10a** using procedure L: Yellow oil solidifying on standing (3.4 g, 83% yield); $[\alpha]_D^{20}$ -1.6 (c = 0.619, $CHCl_3$); chiral HPLC: IA column, Heptane/*i*PrOH = 90/10; $\tau_{minor}$ = 11.733 min, $\tau_{major}$ = 13.648 min, *ee* = 78%; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.1 Hz, 3H), 2.76 (d, *J* = 1.2 Hz, 1H), 2.77 (s, 1H), 4.11 (qd, *J* = 7.2, 0.7 Hz, 2H), 4.43 (s, 1H), 4.71 (t, *J* = 6.7 Hz, 1H), 5.04 (s, 2H), 6.45 – 6.54 (m, 2H), 6.77 – 6.86 (m, 2H),

6.94 (d, $J$ = 8.7 Hz, 2H), 7.28 (d, $J$ = 8.3 Hz, 3H), 7.30 – 7.45 (m, 5H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 14.28 ($CH_3$), 43.06 ($CH_2$), 55.24 (CH), 60.89 ($CH_2$), 70.17 ($CH_2$), 114.78 (d, $J$ = 7.4 Hz, 2 × CH), 115.20 (2 × CH), 115.68 (d, $J$ = 22.2 Hz, 2 × CH), 127.50 (2 × CH), 127.62 (2 × CH), 128.12 (CH), 128.71 (2 × CH), 134.42 (C), 137.08 (C), 143.35 (d, $J$ = 2.0 Hz, C), 156.09 (d, $J$ = 235.5 Hz, C), 158.31 (C), 171.34 (C); $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -127.58 (tt, $J$ = 8.6, 4.4 Hz).

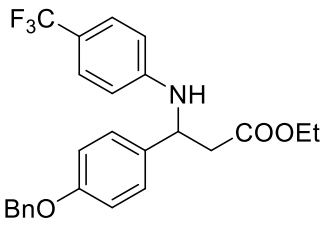



**Ethyl 3-(4-(benzyloxy)phenyl)-3-((4-fluorophenyl)amino) propanoate** (±)-(**4.11a**).[193] Obtained from **4.10a** using procedure M: Yellow oil solidifying on standing (3.66 g, 89% yield); chiral HPLC: IA column, Heptane/*i*PrOH = 90/10; $\tau_1$ = 11.739 min, $\tau_2$ = 13.661 min, *ee* = 0%; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 1.20 (t, $J$ = 7.1 Hz, 3H), 2.76 (d, $J$ = 1.2 Hz, 1H), 2.77 (s, 1H), 4.11 (qd, $J$ = 7.2, 0.7 Hz, 2H), 4.43 (s, 1H), 4.71 (t, $J$ = 6.7 Hz, 1H), 5.04 (s, 2H), 6.45 – 6.54 (m, 2H), 6.77 – 6.86 (m, 2H), 6.94 (d, $J$ = 8.7 Hz, 2H), 7.28 (d, $J$ = 8.3 Hz, 3H), 7.30 – 7.45 (m, 5H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 14.28 ($CH_3$), 43.06 ($CH_2$), 55.24 (CH), 60.89 ($CH_2$), 70.17 ($CH_2$), 114.78 (d, $J$ = 7.4 Hz, 2 × CH), 115.20 (2 × CH), 115.68 (d, $J$ = 22.2 Hz, 2 × CH), 127.50 (2 × CH), 127.62 (2 × CH), 128.12 (CH), 128.71 (2 × CH), 134.42 (C), 137.08 (C), 143.35 (d, $J$ = 2.0 Hz, C), 156.09 (d, $J$ = 235.5 Hz, C), 158.31 (C), 171.34 (C); $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -127.58 (tt, $J$ = 8.6, 4.4 Hz).

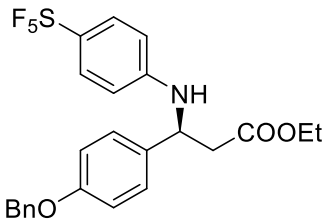



**Ethyl (*S*)-3-(4-(benzyloxy)phenyl)-3-((4-(trifluoromethyl) phenyl)amino)propanoate** (**4.11b**). A new compound. Obtained from **4.10b** using procedure L: Yellowish oil solidifying on standing (2.69 g, 93% yield); mp 79-81 °C (*n*-hexane-EtOAc); $[\alpha]_D^{25}$ -59.3 (c = 0.70, $CHCl_3$); chiral HPLC: IA column, Heptane/*i*PrOH = 90/10; $\tau_{minor}$ = 10.823 min, $\tau_{major}$ = 13.788 min, *ee* = 87%; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 1.21 (t, $J$ = 7.2 Hz, 3H), 2.79 (dd, $J$ = 14.2, 6.9 Hz, 1H), 2.84 (dd, $J$ = 14.2, 5.1 Hz, 1H), 4.13 (qd, $J$ = 7.2, 1.0 Hz, 2H), 4.83 (s, 1H), 4.98 (s, 1H), 5.05 (s, 2H), 6.58 (d, $J$ = 8.9 Hz, 2H), 6.96 (d, $J$ = 8.7 Hz, 2H), 7.28 (d, $J$ = 8.6 Hz, 2H), 7.31 – 7.47 (m, 7H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 14.23 ($CH_3$), 42.79 ($CH_2$), 54.17 (CH), 61.02 ($CH_2$), 70.17 ($CH_2$), 112.89 (2 × CH), 115.31 (2 × CH), 119.31 (q, $J$ = 32.5 Hz, C), 125.02 (d, $J$ = 270.3 Hz, C), 126.61 (q, $J$ = 3.8 Hz, 2

× CH), 127.40 (2 × CH), 127.61 (2 × CH), 128.13 (CH), 128.71 (2 × CH), 133.61 (C), 137.01 (C), 149.46 (C), 158.44 (C), 171.11 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -61.04; HRMS-ESI: *m/z* [M + Na]$^+$ calcld for $C_{25}H_{24}O_3NF_3Na$: 466.1601; found: 466.1596.

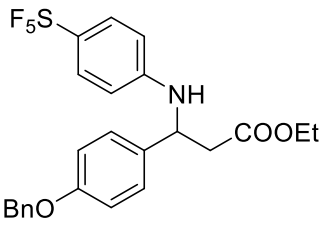



**Ethyl 3-(4-(benzyloxy)phenyl)-3-((4-(trifluoromethyl)phenyl) amino)propanoate** (±)-(**4.11b**). A new compound. Obtained from **4.10b** using procedure M: Yellowish oil solidifying on standing (2.78 g, 97% yield); mp 75-77 °C (*n*-hexane-EtOAc); chiral HPLC: IA column, Heptane/*i*PrOH = 90/10; $\tau_1$ = 10.845 min, $\tau_2$ = 13.810 min, *ee* = 0%; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.2 Hz, 3H), 2.78 (dd, *J* = 14.3, 6.9 Hz, 1H), 2.81 – 2.87 (m, 1H), 4.13 (qd, *J* = 7.2, 1.0 Hz, 2H), 4.83 (t, *J* = 6.6 Hz, 1H), 4.98 (s, 1H), 5.05 (s, 2H), 6.58 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.31 – 7.47 (m, 7H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 14.24 ($CH_3$), 42.79 ($CH_2$), 54.18 (CH), 61.02 ($CH_2$), 70.17 ($CH_2$), 112.89 (2 × CH), 115.31 (2 × CH), 119.32 (q, *J* = 32.5 Hz, C), 125.02 (d, *J* = 270.3 Hz, C), 126.62 (q, *J* = 3.7 Hz, 2 × CH), 127.41 (2 × CH), 127.61 (2 × CH), 128.13 (CH), 128.72 (2 × CH), 133.61 (C), 137.01 (C), 149.46 (C), 158.44 (C), 171.11 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -61.05; HRMS-ESI: *m/z* [M + Na]$^+$ calcld for $C_{25}H_{24}O_3NF_3Na$: 466.1601; found: 466.1596.

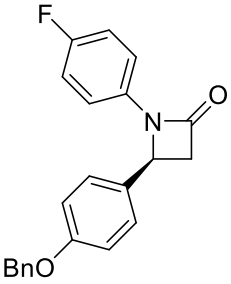



**Ethyl (*S*)-3-(4-(benzyloxy)phenyl)-3-((4-(pentafluoro-λ$^6$-sulfanyl)phenyl)amino)propanoate** (**4.11c**). A new compound. Obtained from **4.10c** using procedure L: White amorphous solid (2.15 g, 95% yield); $[\alpha]_D^{25}$ -22.2 (c = 0.45, $CHCl_3$); chiral HPLC: IA column, Heptane/*i*PrOH = 90/10; $\tau_{minor}$ = 13.800 min, $\tau_{major}$ = 19.112 min, *ee* = 91%; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.1 Hz, 3H), 2.77 (dd, *J* = 14.9, 7.6 Hz, 1H), 2.83 (dd, *J* = 14.9, 5.4 Hz, 1H), 4.12 (qd, *J* = 7.1, 1.2 Hz, 2H), 4.79 (dt, *J* = 7.6, 5.8 Hz, 1H), 5.04 (s, 2H), 5.07 (s, 1H), 6.49 (d, *J* = 9.1 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.31 – 7.44 (m, 5H), 7.47 (d, *J* = 9.1 Hz, 3H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 14.25 ($CH_3$), 42.74 ($CH_2$), 54.21 (CH), 61.10 ($CH_2$), 70.21 ($CH_2$), 112.10 (2 × CH), 115.39 (2 × CH), 127.33 - 127.42 (4 × CH), 127.63 (2 × CH), 128.17(CH), 128.74 (2 × CH), 133.32 (C), 136.98 (C), 143.90 (t, *J* = 17.2 Hz, C), 148.94 (C), 158.53 (C), 171.07 (C); $^{19}$F NMR (377 MHz,

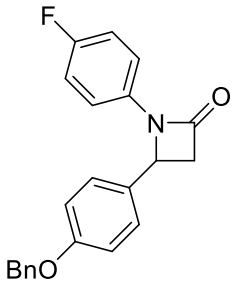
$CDCl_3$) δ 64.74 (d, *J* = 149.9 Hz), 87.04 – 88.87 (m); HRMS-ESI: *m/z* $[M + Na]^+$ calcld for $C_{24}H_{24}O_3NF_5NaS$: 524.1289; found: 524.1281.



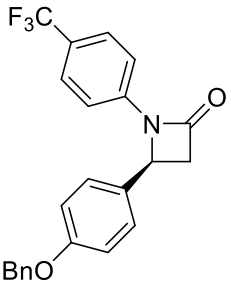

**Ethyl 3-(4-(benzyloxy)phenyl)-3-((4-(pentafluoro-λ⁶-sulfanyl) phenyl)amino)propanoate** (±)-(**4.11c**). A new compound. Obtained from **4.10c** using procedure M: White solid (1.51 g, 86% yield); mp 81-83 °C (*n*-hexane-EtOAc); chiral HPLC: IA column, Heptane/*i*PrOH = 90/10; $\tau_1$ = 13.928 min, $\tau_2$ = 19.065 min, *ee* = 0%; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.1 Hz, 3H), 2.77 (dd, *J* = 14.9, 7.6 Hz, 1H), 2.83 (dd, *J* = 14.9, 5.4 Hz, 1H), 4.12 (qd, *J* = 7.1, 1.2 Hz, 2H), 4.79 (dt, *J* = 7.6, 5.8 Hz, 1H), 5.04 (s, 2H), 5.07 (s, 1H), 6.49 (d, *J* = 9.1 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.31 – 7.44 (m, 5H), 7.47 (d, *J* = 9.1 Hz, 3H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 14.25 ($CH_3$), 42.74 ($CH_2$), 54.21 (CH), 61.10 ($CH_2$), 70.21 ($CH_2$), 112.10 (2 × CH), 115.39 (2 × CH), 127.33 - 127.42 (4 × CH), 127.63 (2 × CH), 128.17(CH), 128.74 (2 × CH), 133.32 (C), 136.98 (C), 143.90 (t, *J* = 17.2 Hz, C), 148.94 (C), 158.53 (C), 171.07 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ 64.74 (d, *J* = 149.9 Hz), 87.04 – 88.87 (m); HRMS-ESI: *m/z* $[M + Na]^+$ calcld for $C_{24}H_{24}O_3NF_5NaS$: 524.1289; found: 524.1281.



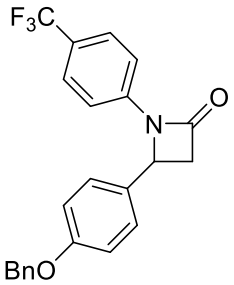

**(*S*)-4-(4-(Benzyloxy)phenyl)-1-(4-fluorophenyl)azetidin-2-one** (**4.12a**).[166] Obtained from **4.11a** using procedure N: White solid (1.05 g, 79% yield); mp 129-131 °C (*n*-hexane-EtOAc); $[\alpha]_D^{20}$ -69.8 (c = 0.322, $CHCl_3$); chiral HPLC: IA column, Heptane/*i*PrOH = 90/10; $\tau_{minor}$ = 10.962 min, $\tau_{major}$ = 12.782 min, *ee* = 74%; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.93 (dd, *J* = 15.2, 2.6 Hz, 1H), 3.53 (dd, *J* = 15.1, 5.6 Hz, 1H), 4.94 (dd, *J* = 5.6, 2.6 Hz, 1H), 5.06 (s, 2H), 6.89 – 6.96 (m, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 7.24 – 7.27 (m, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.31 – 7.45 (m, 5H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 47.38 ($CH_2$), 54.06 (CH), 70.24 ($CH_2$), 115.65 (2 × CH), 115.92 (d, *J* = 22.6 Hz, 2 × CH), 118.37 (d, *J* = 7.8 Hz, 2 × CH), 127.37 (2 × CH), 127.61 (2 × CH), 128.23 (CH), 128.77 (2 × CH), 130.16 (C), 134.23 (d, *J* = 2.6 Hz, C), 136.79 (C), 159.08 (d, *J* = 243.2 Hz, C), 159.20 (C), 164.58 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -118.17 (tt, *J* = 8.6, 4.7 Hz).



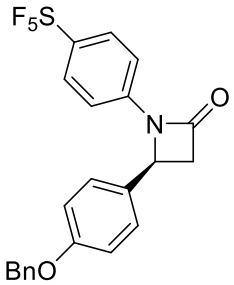
**4-(4-(Benzyloxy)phenyl)-1-(4-fluorophenyl)azetidin-2-one** (±)-(**4.12a**).[348] Obtained from (±)-**4.11a** using procedure N: Off-white solid (1.41 g, 93% yield); mp 149-151 °C (*n*-hexane-EtOAc); chiral HPLC: IA column, Heptane/*i*PrOH = 90/10; $\tau_1$ = 10.882 min, $\tau_2$ = 12.691 min, *ee* = 0%; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.93 (dd, *J* = 15.2, 2.6 Hz, 1H), 3.53 (dd, *J* = 15.1, 5.6 Hz, 1H), 4.94 (dd, *J* = 5.6, 2.6 Hz, 1H), 5.06 (s, 2H), 6.89 – 6.96 (m, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 7.24 – 7.27 (m, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.31 – 7.45 (m, 5H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 47.38 ($CH_2$), 54.06 (CH), 70.24 ($CH_2$), 115.65 (2 × CH), 115.92 (d, *J* = 22.6 Hz, 2 × CH), 118.37 (d, *J* = 7.8 Hz, 2 × CH), 127.37 (2 × CH), 127.61 (2 × CH), 128.23 (CH), 128.77 (2 × CH), 130.16 (C), 134.23 (d, *J* = 2.6 Hz, C), 136.79 (C), 159.08 (d, *J* = 243.2 Hz, C), 159.20 (C), 164.58 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -118.17 (tt, *J* = 8.6, 4.7 Hz).



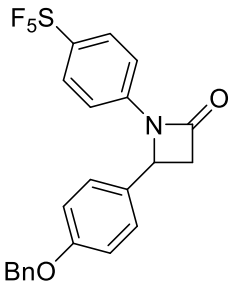
**(*S*)-4-(4-(Benzyloxy)phenyl)-1-(4-(trifluoromethyl)phenyl)azetidin-2-one** (**4.12b**). A new compound. Obtained from **4.11b** using procedure N: Bright yellow solid (0.84 g, 35% yield); mp 116-118 °C (*n*-hexane-EtOAc); $[\alpha]_D^{25}$ -70.0 (c = 0.60, $CHCl_3$); chiral HPLC: IA column, Heptane/*i*PrOH = 90/10; $\tau_{minor}$ = 10.790 min, $\tau_{major}$ = 11.607 min, *ee* = 87%; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.98 (dd, *J* = 15.4, 2.7 Hz, 1H), 3.58 (dd, *J* = 15.4, 5.7 Hz, 1H), 5.00 (dd, *J* = 5.7, 2.8 Hz, 1H), 5.06 (s, 2H), 7.00 (d, *J* = 8.7 Hz, 2H), 7.27 – 7.46 (m, 9H), 7.49 (d, *J* = 8.6 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 47.55 ($CH_2$), 54.13 (CH), 70.24 ($CH_2$), 115.74 (2 × CH), 116.76 (2 × CH), 124.16 (d, *J* = 271.4 Hz, C), 125.62 (q, *J* = 32.7 Hz, C), 126.45 (q, *J* = 4.0 Hz, 2 × CH), 127.34 (2 × CH), 127.60 (2 × CH), 128.24 (CH), 128.76 (2 × CH), 129.74 (C), 136.74 (C), 140.55 (C), 159.31 (C), 165.13 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -62.06; HRMS-ESI: *m/z* $[M + Na]^+$ calcld for $C_{23}H_{18}O_2NF_3Na$: 420.1182; found: 420.1181.



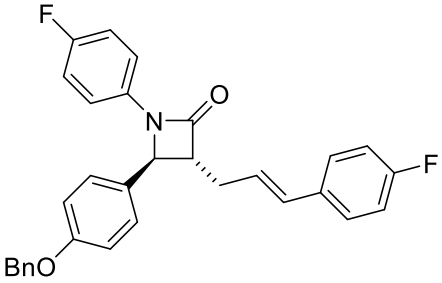
**4-(4-(Benzyloxy)phenyl)-1-(4-(trifluoromethyl)phenyl)azetidin-2-one** (±)-(**4.12b**). A new compound. Obtained from (±)-**4.11b** using procedure N: Yellowish solid (1.01 g, 41% yield); mp 146-148 °C (*n*-hexane-EtOAc); chiral HPLC: IA column, Heptane/*i*PrOH = 90/10; $\tau_1$ = 10.857 min, $\tau_2$ = 11.680 min, *ee* = 0%; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.99 (dd, *J* = 15.4, 2.8 Hz, 1H), 3.58 (dd, *J* = 15.4, 5.8 Hz, 1H), 5.00 (dd, *J* = 5.8, 2.7 Hz, 1H), 5.06 (s, 2H), 7.00 (d, *J* = 8.7 Hz, 2H), 7.27 – 7.45 (m, 9H), 7.50 (d, *J* = 8.3 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 47.56 ($CH_2$), 54.15 (CH), 70.26 ($CH_2$), 115.75 (2 × CH), 116.77 (2 × CH), 124.17 (d, *J* = 271.4 Hz, C), 125.64 (q, *J* = 32.8 Hz, C), 126.46 (q, *J* = 3.7 Hz, 2 × CH), 127.34 (2 × CH), 127.61 (2 × CH), 128.25 (CH), 128.77 (2 × CH), 129.75 (C), 136.74 (C), 140.56 (C), 159.32 (C), 165.14 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -62.07; HRMS-ESI: *m/z* $[M + Na]^+$ calcld for $C_{23}H_{18}O_2NF_3Na$: 420.1182; found: 420.1181.



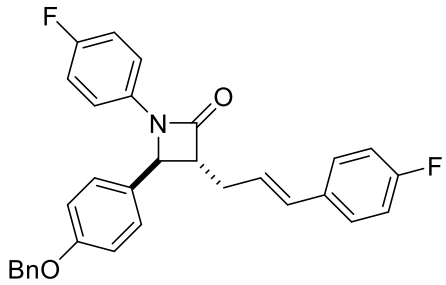
**(*S*)-4-(4-(Benzyloxy)phenyl)-1-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl) azetidin-2-one** (**4.12c**). A new compound. Obtained from **4.11c** using procedure N: White solid (1.51 g, 83% yield); mp 116-118 °C (*n*-hexane-EtOAc); $[\alpha]_D^{25}$ -82.0 (c = 0.50, $CHCl_3$); chiral HPLC: IC column, Heptane/*i*PrOH = 97/3; $\tau_{minor}$ = 20.414 min, $\tau_{major}$ = 21.742 min, *ee* = 91%; $^1$H NMR (400 MHz, $CDCl_3$) δ 3.00 (dd, *J* = 15.5, 2.8 Hz, 1H), 3.59 (dd, *J* = 15.5, 5.8 Hz, 1H), 5.00 (dd, *J* = 5.7, 2.8 Hz, 1H), 5.07 (s, 2H), 7.00 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 3H), 7.31 – 7.45 (m, 7H), 7.62 (d, *J* = 9.1 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 47.73 ($CH_2$), 54.28 (CH), 70.29 ($CH_2$), 115.83 (2 × CH), 116.41 (2 × CH), 127.27 (p, *J* = 4.6 Hz, 2 × CH), 127.36 (2 × CH), 127.63 (2 × CH), 128.29 (CH), 128.80 (2 × CH), 129.52 (C), 136.72 (C), 140.09 (C), 148.99 (t, *J* = 17.2 Hz, C), 159.41 (C), 165.16 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ 63.54 (d, *J* = 150.1 Hz), 83.98 – 86.32 (m); HRMS-ESI: *m/z* $[M + Na]^+$ calcld for $C_{22}H_{18}O_2NF_5NaS$: 478.0871; found: 478.0866.



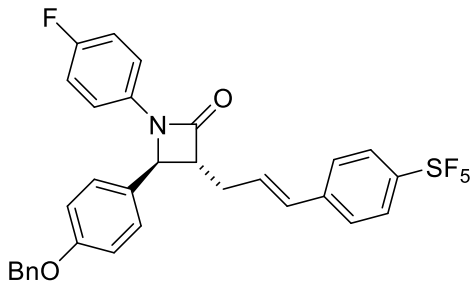
**4-(4-(Benzyloxy)phenyl)-1-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl) azetidin-2-one** (±)-(**4.12c**). A new compound. Obtained from (±)-**4.11c** using procedure N: White solid (1.05 g, 77% yield); mp 148-150 °C (*n*-hexane-EtOAc); chiral HPLC: IC column, Heptane/*i*PrOH = 97/3; $\tau_1$ = 20.097 min, $\tau_2$ = 21.425 min, *ee* = 0%; $^1$H NMR (400 MHz, $CDCl_3$) δ 3.00 (dd, *J* = 15.5, 2.8 Hz, 1H), 3.59 (dd, *J* = 15.5, 5.8 Hz, 1H), 5.00 (dd, *J* = 5.7, 2.8 Hz, 1H), 5.07 (s, 2H), 7.00 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 3H), 7.31 – 7.45 (m, 7H), 7.62 (d, *J* = 9.1 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 47.73 ($CH_2$), 54.28 (CH), 70.29 ($CH_2$), 115.83 (2 × CH), 116.41 (2 × CH), 127.27 (p, *J* = 4.6 Hz, 2 × CH), 127.36 (2 × CH), 127.63 (2 × CH), 128.29 (CH), 128.80 (2 × CH), 129.52 (C), 136.72 (C), 140.09 (C), 148.99 (t, *J* = 17.2 Hz, C), 159.41 (C), 165.16 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ 63.54 (d, *J* = 150.1 Hz), 83.98 – 86.32 (m); HRMS-ESI: *m/z* $[M + Na]^+$ calcld for $C_{22}H_{18}O_2NF_5NaS$: 478.0871; found: 478.0866.



**(3*R*,4*S*)-4-(4-(Benzyloxy)phenyl)-1-(4-fluorophenyl)-3-((*E*)-3-(4-fluorophenyl)allyl)azetidin-2-one** (**4.19a**).[349,350] Obtained from **4.12a** and **4.18a** using procedure O: Yellow oil (855 mg, 88% yield); chiral HPLC: IA column, Heptane/*i*PrOH = 80/20; $\tau_{minor}$ = 9.113 min, $\tau_{major}$ = 18.456 min, *er* = 11:89, *ee* = 78%; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.71 (dddd, *J* = 15.1, 9.1, 7.3, 1.4 Hz, 1H), 2.87 (dtd, *J* = 15.2, 5.8, 1.6 Hz, 1H), 3.27 (ddd, *J* = 9.4, 5.4, 2.4 Hz, 1H), 4.67 (d, *J* = 2.4 Hz, 1H), 5.06 (s, 2H), 6.16 (ddd, *J* = 15.8, 7.3, 6.3 Hz, 1H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.90 – 7.03 (m, 6H), 7.22 – 7.30 (m, 6H), 7.31 – 7.46 (m, 5H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 32.12 ($CH_2$), 59.98 (CH), 60.58 (CH), 70.21 ($CH_2$), 115.60 (d, *J* = 21.5 Hz, 2 × CH), 115.63 (2 × CH), 115.94 (d, *J* = 22.7 Hz, 2 × CH), 118.54 (d, *J* = 7.8 Hz, 2 × CH), 125.43 (d, *J* = 2.3 Hz, CH), 127.39 (2 × CH), 127.60 (2 × CH), 127.77 (d, *J* = 8.0 Hz, 2 × CH), 128.24 (CH), 128.76 (2 × CH), 129.71 (C), 131.48 (CH), 133.20 (d, *J* = 3.3 Hz, C), 134.04 (d, *J* = 2.6 Hz, C), 136.76 (C), 159.10 (d, *J* = 243.4 Hz, C), 159.14 (C), 162.34 (d, *J* = 246.7 Hz, C), 166.95 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -118.04 (tt, *J* = 8.7, 4.7 Hz), -114.59 (ddd, *J* = 14.1, 8.8, 5.4 Hz); HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{31}H_{26}O_2NF_2$: 482.1926; found: 482.1923.

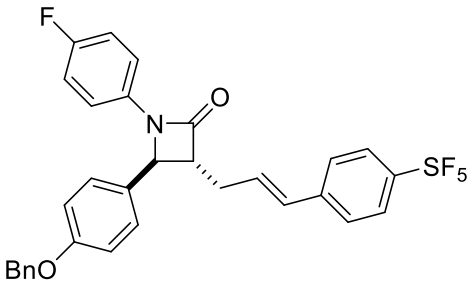


**(*3R*,4S**)-4-(4-(Benzyloxy)phenyl)-1-(4-fluorophenyl)-3-((*E*)3-(4-fluorophenyl)allyl)azetidin-2-one** (±)-(**4.19a**).[351,352] Obtained from (±)-**4.12a** and **4.18a** using procedure O: Yellow oil (718 mg, 74% yield); chiral HPLC: IA column, Heptane/*i*PrOH = 80/20; $\tau_1$ = 9.180 min, $\tau_2$ = 18.598 min, *er* = 50:50, *ee* = 0%, $^1$H NMR (400 MHz, $CDCl_3$) δ 2.71 (dddd, *J* = 15.1, 9.1, 7.3, 1.4 Hz, 1H), 2.87 (dtd, *J* = 15.2, 5.8, 1.6 Hz, 1H), 3.27 (ddd, *J* = 9.4, 5.4, 2.4 Hz, 1H), 4.67 (d, *J* = 2.4 Hz, 1H), 5.06 (s, 2H), 6.16 (ddd, *J* = 15.8, 7.3, 6.3 Hz, 1H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.90 – 7.03 (m, 6H), 7.22 – 7.30 (m, 6H), 7.31 – 7.46 (m, 5H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 32.12 ($CH_2$), 59.98 (CH), 60.58 (CH), 70.21 ($CH_2$), 115.60 (d, *J* = 21.5 Hz, 2 × CH), 115.63 (2 × CH), 115.94 (d, *J* = 22.7 Hz, 2 × CH), 118.54 (d, *J* = 7.8 Hz, 2 × CH), 125.43 (d, *J* = 2.3 Hz, CH), 127.39 (2 × CH), 127.60 (2 × CH), 127.77 (d, *J* = 8.0 Hz, 2 × CH), 128.24 (CH), 128.76 (2 × CH), 129.71 (C), 131.48 (CH), 133.20 (d, *J* = 3.3 Hz, C), 134.04 (d, *J* = 2.6 Hz, C), 136.76 (C), 159.10 (d, *J* = 243.4 Hz, C), 159.14 (C), 162.34 (d, *J* = 246.7 Hz, C), 166.95 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -118.04 (tt, *J* = 8.7, 4.7 Hz), -114.59 (ddd, *J* = 14.1, 8.8, 5.4 Hz); HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{31}H_{26}O_2NF_2$: 482.1926; found: 482.1923.

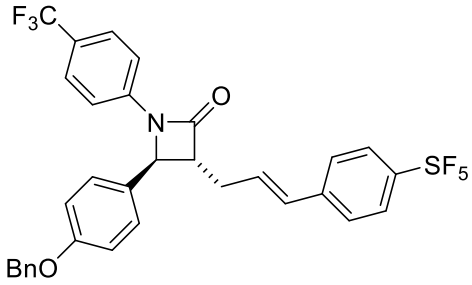


**(3*R*,4*S*)-4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-3-((*E*)-3-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)allyl) azetidin-2-one** (**4.19b**). A new compound. Obtained from **4.12a** and **4.17b** using procedure O: Yellow oil (954 mg, 81% yield); $[\alpha]_D^{25}$ -7.8 (c = 0.71, $CHCl_3$); chiral HPLC: IA column, Heptane/*i*PrOH = 80/20; $\tau_{minor}$ = 10.817 min, $\tau_{major}$ = 21.822 min, *ee* = 78%; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.69 – 2.82 (m, 1H), 2.91 (dtd, *J* = 15.3, 5.8, 1.5 Hz, 1H), 3.30 (ddd, *J* = 9.2, 5.7, 2.4 Hz, 1H), 4.66 (d, *J* = 2.4 Hz, 1H), 5.07 (s, 2H), 6.37 (ddd, *J* = 15.9, 7.1, 5.9 Hz, 1H), 6.50 (d, *J* = 16.1 Hz, 1H), 6.94 (dd, *J* = 9.2, 8.3 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 7.26 (tt, *J* = 9.0, 2.6 Hz, 4H), 7.32 – 7.46 (m, 7H), 7.68 (d, *J* = 8.8 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 32.18 ($CH_2$), 59.68 (CH), 60.69 (CH), 70.23 ($CH_2$), 115.73 (2 × CH), 115.98 (d, *J* = 22.7 Hz, 2 × CH), 118.57 (d, *J* = 7.9 Hz, 2 × CH), 126.25 (2 × CH), 126.41 (t, *J* = 4.7 Hz, 2 × CH), 127.39 (2 × CH), 127.59 (2 × CH), 128.25 (CH), 128.78 (2 × CH), 129.47 (CH), 129.54 (C), 130.76 (CH), 133.98 (d, *J* = 2.8 Hz, C), 136.75 (C), 140.26

(C), 152.78 (t, $J$ = 17.2 Hz, C), 159.17 (d, $J$ = 243.5 Hz, C), 159.25 (C), 166.67 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ -117.85 (tt, $J$ = 8.5, 4.7 Hz), 63.07 (d, $J$ = 149.3 Hz), 84.97 (p, $J$ = 149.9 Hz); HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{31}H_{26}O_2NF_6S$: 590.1583; found: 590.1577.

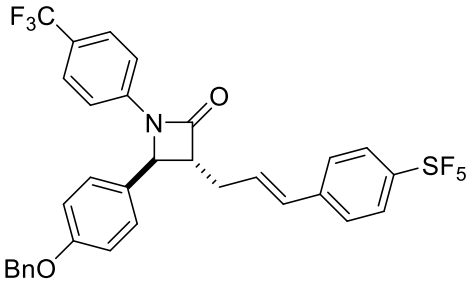



**(*3R*,4S**)-4-(4-(Benzyloxy)phenyl)-1-(4-fluorophenyl)-3-((*E*)-3-(4-(pentafluoro-λ$^6$-sulfanyl) phenyl)allyl)azetidin-2-one** (±)-(**4.19b**). A new compound. Obtained from (±)-**4.12a** and **4.18b** using procedure O: Yellow oil (660 mg, 56% yield); chiral HPLC: IA column, Heptane/*i*PrOH = 80/20; $\tau_1$ = 10.837 min, $\tau_2$ = 21.892 min, *ee* = 0%; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.69 – 2.82 (m, 1H), 2.91 (dtd, $J$ = 15.3, 5.8, 1.5 Hz, 1H), 3.30 (ddd, $J$ = 9.2, 5.7, 2.4 Hz, 1H), 4.66 (d, $J$ = 2.4 Hz, 1H), 5.07 (s, 2H), 6.37 (ddd, $J$ = 15.9, 7.1, 5.9 Hz, 1H), 6.50 (d, $J$ = 16.1 Hz, 1H), 6.94 (dd, $J$ = 9.2, 8.3 Hz, 2H), 6.98 (d, $J$ = 8.7 Hz, 2H), 7.26 (tt, $J$ = 9.0, 2.6 Hz, 4H), 7.32 – 7.46 (m, 7H), 7.68 (d, $J$ = 8.8 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 32.18 ($CH_2$), 59.68 (CH), 60.69 (CH), 70.23 ($CH_2$), 115.73 (2 × CH), 115.98 (d, $J$ = 22.7 Hz, 2 × CH), 118.57 (d, $J$ = 7.9 Hz, 2 × CH), 126.25 (2 × CH), 126.41 (t, $J$ = 4.7 Hz, 2 × CH), 127.39 (2 × CH), 127.59 (2 × CH), 128.25 (CH), 128.78 (2 × CH), 129.47 (CH), 129.54 (C), 130.76 (CH), 133.98 (d, $J$ = 2.8 Hz, C), 136.75 (C), 140.26 (C), 152.79 (t, $J$ = 17.2 Hz, C), 159.17 (d, $J$ = 243.5 Hz, C), 159.25 (C), 166.67 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ -117.85 (tt, $J$ = 8.5, 4.7 Hz), 63.07 (d, $J$ = 149.3 Hz), 84.97 (p, $J$ = 149.9 Hz); HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{31}H_{26}O_2NF_6S$: 590.1583; found: 590.1577.

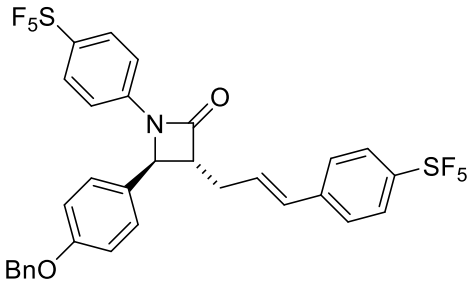



**(3*R*,4*S*)-4-(4-(Benzyloxy)phenyl)-1-(4-(trifluoromethyl)phenyl)-3-((*E*)-3-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)allyl)azetidin-2-one** (**4.19c**). A new compound. Obtained from **4.12b** and **4.17b** using procedure O: Yellow foam (420 mg, 32% yield); $[\alpha]_D^{20}$ -9.0 (c = 0.336, $CHCl_3$); chiral HPLC: IC column, Heptane/*i*PrOH = 97/3; $\tau_{minor}$ = 10.537 min, $\tau_{major}$ = 11.161 min, *ee* = 86%; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.71 – 2.84 (m, 1H), 2.92 (dtd, $J$ = 15.4, 5.9, 1.6 Hz, 1H), 3.35 (ddd, $J$ = 9.1, 5.7, 2.5 Hz,

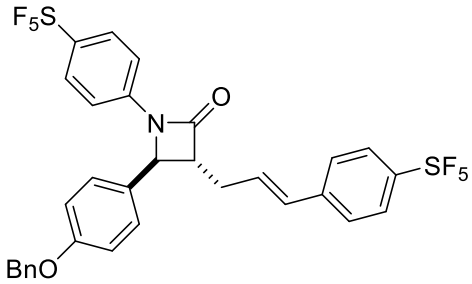
1H), 4.72 (d, *J* = 2.5 Hz, 1H), 5.07 (s, 2H), 6.36 (ddd, *J* = 15.9, 7.2, 6.0 Hz, 1H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.31 – 7.45 (m, 9H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 32.13 ($CH_2$), 59.90 (CH), 60.75 (CH), 70.26 ($CH_2$), 115.84 (2 × CH), 117.01 (2 × CH), 124.15 (d, *J* = 271.5 Hz, C), 125.83 (d, *J* = 32.8 Hz, C), 126.28 (2 × CH), 126.45 (q, *J* = 3.7 Hz, 2 × CH), 126.49 (p, *J* = 4.8 Hz, 2 × CH), 127.36 (2 × CH), 127.60 (2 × CH), 128.28 (CH), 128.79 (2 × CH), 129.16 (CH), 129.16 (C), 130.96 (CH), 136.71 (C), 140.18 (C), 140.37 (C), 152.93 (t, *J* = 16.9 Hz, C), 159.38 (C), 167.30 (C); $^{19}F$ NMR (377 MHz, $CDCl_3$) δ -62.11, 63.03 (d, *J* = 149.8 Hz), 84.87 (p, *J* = 150.2 Hz); HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{32}H_{26}O_2NF_8S$: 640.1551; found: 640.1554.




**(*3R*,4S**)-4-(4-(Benzyloxy)phenyl)-1-(4-(trifluoromethyl)phenyl)-3-((*E*)-3-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)allyl)azetidin-2-one** (±)-(**4.19c**). A new compound. Obtained from (±)-**4.12b** and **4.18b** using procedure O: Yellow foam (452 mg, 49% yield); chiral HPLC: IC column, Heptane/*i*PrOH = 97/3; $\tau_1$ = 10.544 min, $\tau_2$ = 11.167 min, *ee* = 0%; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 2.77 (dddd, *J* = 15.1, 8.9, 7.2, 1.3 Hz, 1H), 2.92 (dtd, *J* = 15.3, 5.8, 1.5 Hz, 1H), 3.35 (ddd, *J* = 9.2, 5.7, 2.5 Hz, 1H), 4.72 (d, *J* = 2.5 Hz, 1H), 5.07 (s, 2H), 6.36 (ddd, *J* = 15.9, 7.2, 6.0 Hz, 1H), 6.51 (d, *J* = 16.1 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.33 – 7.46 (m, 9H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 32.13 ($CH_2$), 59.90 (CH), 60.74 (CH), 70.27 ($CH_2$), 115.84 (2 × CH), 117.01 (2 × CH), 124.15 (d, *J* = 271.3 Hz, C), 125.83 (d, *J* = 32.9 Hz, C), 126.28 (2 × CH), 126.45 (q, *J* = 3.7 Hz, 2 × CH), 126.49 (p, *J* = 4.8 Hz, 2 × CH), 127.36 (2 × CH), 127.60 (2 × CH), 128.28 (CH), 128.80 (2 × CH), 129.16 (CH), 129.16 (C), 130.97 (CH), 136.71 (C), 140.17 (C), 140.37 (C), 152.86 (t, *J* = 17.2 Hz, C), 159.38 (C), 167.29 (C); $^{19}F$ NMR (377 MHz, $CDCl_3$) δ -62.11, 63.02 (d, *J* = 149.8 Hz), 84.86 (p, *J* = 150.0 Hz); HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{32}H_{26}O_2NF_8S$: 640.1551; found: 640.1554.

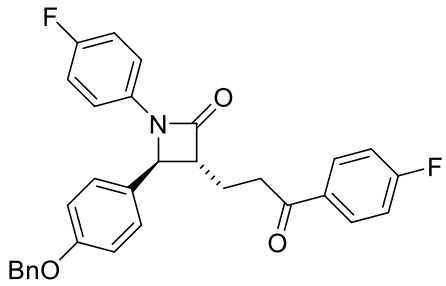



**(3*R*,4*S*)-4-(4-(Benzyloxy)phenyl)-1-(4-(pentafluoro-λ⁶-sulfanyl)phenyl)-3-((*E*)-3-(4-(pentafluoro-λ⁶-sulfanyl)phenyl)allyl)azetidin-2-one** (**4.19d**). A new compound. Obtained from **4.12c** and **4.17b** using procedure O: Yellow oil (536 mg, 38% yield); $[\alpha]_D^{20}$ -4.4 (c = 0.302, $CHCl_3$); chiral HPLC: IA column, Heptane/*i*PrOH = 80/20; $\tau_{minor}$ = 12.919 min, $\tau_{major}$ = 24.776 min, *ee* = 84%; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.73 – 2.85 (m, 1H), 2.87 – 2.99 (m, 1H), 3.38 (ddd, *J* = 9.1, 5.8, 2.6 Hz, 1H), 4.72 (d, *J* = 2.5 Hz, 1H), 5.09 (s, 2H), 6.37 (ddd, *J* = 15.8, 7.1, 5.9 Hz, 1H), 6.52 (d, *J* = 15.9 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 7.32 – 7.47 (m, 9H), 7.64 (d, *J* = 9.2 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 32.09 ($CH_2$), 60.07 (CH), 60.83 (CH), 70.27 ($CH_2$), 115.91 (2 × CH), 116.64 (2 × CH), 126.29 (2 × CH), 126.45 (t, *J* = 4.7 Hz, 2 × CH), 127.30 (t, *J* = 4.7 Hz, 2 × CH), 127.37 (2 × CH), 127.59 (2 × CH), 128.30 (CH), 128.80 (2 × CH), 128.92 (C), 129.00 (CH), 131.04 (CH), 136.68 (C), 139.89 (C), 140.12 (C), 149.11 (t, *J* = 17.2 Hz, C), 152.88 (t, *J* = 17.2 Hz, C), 159.45 (C), 167.32 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ 63.03 (d, *J* = 149.3 Hz), 63.53 (d, *J* = 149.9 Hz), 84.85 (p, *J* = 150.8 Hz), 85.09 (p, *J* = 150.2 Hz); HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{31}H_{26}O_2NF_{10}S$: 698.1240; found: 698.1237.

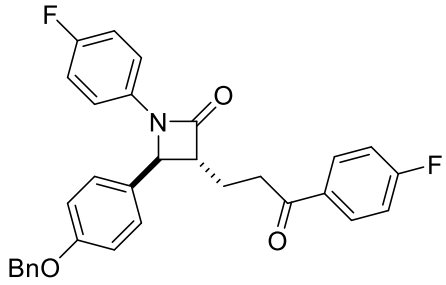



***(3R*,4S*)*-4-(4-(Benzyloxy)phenyl)-1-(4-(pentafluoro-λ⁶-sulfanyl)phenyl)-3-((*E*)-3-(4-( pentafluoro-λ⁶-sulfanyl)phenyl)allyl)azetidin-2-one** (±)-(**4.19d**). A new compound. Obtained from (±)-**4.12c** and **4.17b** using procedure O: Yellow foam (557 mg, 36% yield); chiral HPLC: IA column, Heptane/*i*PrOH = 80/20; $\tau_1$ = 12.343 min, $\tau_2$ = 22.372 min, *ee* = 0%; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.77 (dddd, *J* = 15.3, 9.0, 7.3, 1.3 Hz, 1H), 2.92 (dtd, *J* = 15.4, 5.9, 1.6 Hz, 1H), 3.37 (ddd, *J* = 9.1, 5.8, 2.6 Hz, 1H), 4.71 (d, *J* = 2.6 Hz, 1H), 5.07 (s, 2H), 6.36 (ddd, *J* = 15.9, 7.2, 6.0 Hz, 1H), 6.51 (d, *J* = 16.1 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.47 (m, 9H), 7.63 (d, *J* = 9.2 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 32.09 ($CH_2$), 60.06 (CH), 60.82 (CH), 70.28 ($CH_2$), 115.91 (2 × CH), 116.64 (2 × CH), 126.29 (2 × CH), 126.45 (p, *J* = 4.8 Hz, 2 × CH), 127.29 (p, *J* = 4.8 Hz, 2 × CH), 127.37 (2 × CH), 127.60 (2 × CH), 128.30 (CH), 128.80 (2 × CH), 128.92

(C), 129.00 (CH), 131.04 (CH), 136.67 (C), 139.89 (C), 140.13 (C), 149.10 (t, $J$ = 17.2 Hz, C), 152.87 (t, $J$ = 17.2 Hz, C), 159.45 (C), 167.32 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ 63.02 (d, $J$ = 149.8 Hz), 63.52 (d, $J$ = 150.0 Hz), 84.84 (p, $J$ = 150.4 Hz), 85.08 (p, $J$ = 150.5 Hz); HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{31}H_{26}O_2NF_{10}S$: 698.1240; found: 698.1237.

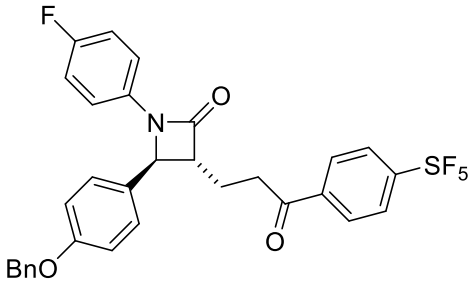



**(3*R*,4*S*)-4-[4-(Benzyloxy)phenyl]-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-oxopropyl]azetidin-2-one** (**4.20a**).[162,179] Obtained from **4.19a** using procedure P: Orange oil (600 mg, 76% yield); $[\alpha]_D^{20}$ +6.9 (c = 0.460, $CHCl_3$) (lit.[174] $[\alpha]_D^{20}$ +4.9 (c = 1.00, MeOH)); chiral HPLC: IC column, Heptane/*i*PrOH = 70/30; $\tau_{minor}$ = 11.335 min, $\tau_{major}$ = 12.707 min, *er* = 11:89, *ee* = 78%; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.27 (dtd, $J$ = 14.0, 8.4, 5.6 Hz, 1H), 2.40 (ddt, $J$ = 13.9, 8.3, 6.9 Hz, 1H), 3.09 – 3.22 (m, 2H), 3.29 (ddd, $J$ = 17.6, 8.3, 5.6 Hz, 1H), 4.68 (d, $J$ = 2.4 Hz, 1H), 5.05 (s, 2H), 6.89 – 6.99 (m, 4H), 7.09 – 7.16 (m, 2H), 7.22 – 7.29 (m, 4H), 7.30 – 7.45 (m, 5H), 7.96 – 8.02 (m, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 23.32 ($CH_2$), 35.67 ($CH_2$), 59.92 (CH), 61.25 (CH), 70.22 ($CH_2$), 115.64 (2 × CH), 115.80 (d, $J$ = 6.7 Hz, 2 × CH), 116.02 (d, $J$ = 7.4 Hz, 2 × CH), 118.55 (d, $J$ = 7.8 Hz, 2 × CH), 127.35 (2 × CH), 127.60 (2 × CH), 128.23 (CH), 128.77 (2 × CH), 129.62 (C), 130.84 (d, $J$ = 9.3 Hz, 2 × CH), 133.20 (d, $J$ = 3.0 Hz, C), 134.01 (d, $J$ = 2.7 Hz, C), 136.77 (C), 159.10 (d, $J$ = 243.3 Hz, C), 159.19 (C), 165.95 (d, $J$ = 254.9 Hz, C), 167.37 (C), 197.48 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -118.02 (tt, $J$ = 8.6, 4.6 Hz), -104.91 (ddd, $J$ = 13.7, 8.4, 5.3 Hz); HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{31}H_{26}O_3NF_2$: 498.1875; found: 498.1874.

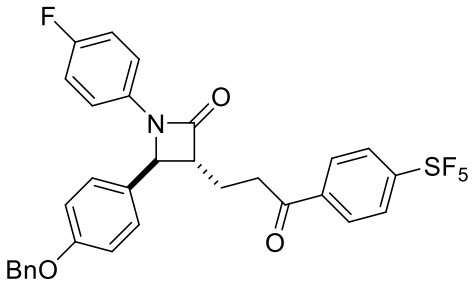



***(3R*,4S*)*-4-(4-(Benzyloxy)-phenyl)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-oxopropyl)azetidin-2-one** (±)-(**4.20a**).[179] Obtained from (±)-**4.19a** using procedure P: Dark yellow oil (545 mg, 80% yield); chiral HPLC: IC column, Heptane/*i*PrOH = 70/30; $\tau_1$ = 11.353 min, $\tau_2$ = 12.738 min, *er* = 50:50, *ee* = 0%; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.27 (dtd, $J$ = 14.0, 8.4, 5.6 Hz, 1H), 2.40 (ddt, $J$ = 13.9, 8.3, 6.9 Hz, 1H), 3.09 – 3.22 (m, 2H), 3.29 (ddd, $J$ =

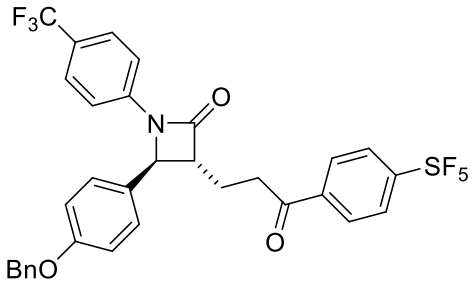
17.6, 8.3, 5.6 Hz, 1H), 4.68 (d, *J* = 2.4 Hz, 1H), 5.05 (s, 2H), 6.89 – 6.99 (m, 4H), 7.09 – 7.16 (m, 2H), 7.22 – 7.29 (m, 4H), 7.30 – 7.45 (m, 5H), 7.96 – 8.02 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 23.32 ($CH_2$), 35.67 ($CH_2$), 59.92 (CH), 61.25 (CH), 70.22 ($CH_2$), 115.64 (2 × CH), 115.80 (d, *J* = 6.7 Hz, 2 × CH), 116.02 (d, *J* = 7.4 Hz, 2 × CH), 118.55 (d, *J* = 7.8 Hz, 2 × CH), 127.35 (2 × CH), 127.60 (2 × CH), 128.23 (CH), 128.77 (2 × CH), 129.62 (C), 130.84 (d, *J* = 9.3 Hz, 2 × CH), 133.20 (d, *J* = 3.0 Hz, C), 134.01 (d, *J* = 2.7 Hz, C), 136.77 (C), 159.10 (d, *J* = 243.3 Hz, C), 159.19 (C), 165.95 (d, *J* = 254.9 Hz, C), 167.37 (C), 197.48 (C); $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -118.02 (tt, *J* = 8.6, 4.6 Hz), -104.91 (ddd, *J* = 13.7, 8.4, 5.3 Hz); HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{31}H_{26}O_3NF_2$: 498.1875; found: 498.1874.




**(3*R*,4*S*)-4-[4-(Benzyloxy)phenyl]-1-(4-fluorophenyl)-3-[3-(4-(pentafluoro-λ⁶-sulfanyl)phenyl)-3-oxopropyl]azetidin-2-one** (**4.20b**). A new compound. Obtained from **4.19b** using procedure P: Pink foam (316 mg, 46% yield); chiral HPLC: IC column, Heptane/*i*PrOH = 80/20; $\tau_{minor}$ = 9.477 min, $\tau_{major}$ = 10.729 min, *ee* = 79%; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 2.29 (dtd, *J* = 14.2, 8.5, 5.6 Hz, 1H), 2.42 (ddt, *J* = 13.7, 8.2, 6.8 Hz, 1H), 3.17 (tt, *J* = 6.9, 2.4 Hz, 1H), 3.23 (dd, *J* = 8.2, 6.7 Hz, 1H), 3.35 (ddd, *J* = 17.9, 8.2, 5.6 Hz, 1H), 4.68 (d, *J* = 2.4 Hz, 1H), 5.05 (s, 2H), 6.94 (dd, *J* = 9.1, 8.3 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 7.21 – 7.30 (m, 4H), 7.30 – 7.47 (m, 5H), 7.85 (d, *J* = 8.9 Hz, 2H), 8.04 (d, *J* = 9.1 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 23.15 ($CH_2$), 36.12 ($CH_2$), 59.67 (CH), 61.32 (CH), 70.24 ($CH_2$), 115.71 (2 × CH), 115.98 (d, *J* = 22.7 Hz, 2 × CH), 118.59 (d, *J* = 7.8 Hz, 2 × CH), 126.65 (t, *J* = 4.7 Hz, 2 × CH), 127.36 (2 × CH), 127.60 (2 × CH), 128.25 (CH), 128.61 (2 × CH), 128.78 (2 × CH), 129.50 (C), 133.96 (d, *J* = 2.6 Hz, C), 136.76 (C), 138.87 (C), 156.97 (t, *J* = 18.1 Hz, C), 159.17 (d, *J* = 243.3 Hz, C), 159.27 (C), 167.25 (C), 197.63 (C); $^{19}F$ NMR (377 MHz, $CDCl_3$) δ -117.88 (tt, *J* = 8.4, 4.6 Hz), 62.39 (d, *J* = 149.9 Hz), 82.77 (p, *J* = 149.9 Hz); IR (neat, KBr) 1741 (s, C=O, amide), 1695 (m, C=O, ketone), 857 (s, $SF_5$) $cm^{-1}$; HRMS-ESI: *m/z* $[M + Na]^+$ calcld for $C_{31}H_{25}O_3NF_6NaS$: 628.1352; found: 628.1347.

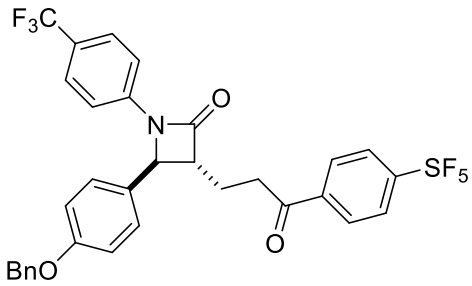


**(*3R*,4S**)-4-(4-(Benzyloxy)-phenyl)-1-(4-fluorophenyl)-3-(3-(4-(pentafluoro-λ$^6$-sulfanyl) phenyl)-3-oxopropyl)azetidin-2-one** (±)-(**4.20b**). A new compound. Obtained from (±)-**4.19b** using procedure P: Red oil (201 mg, 58% yield); chiral HPLC: IC column, Heptane/*i*PrOH = 80/20; $\tau_1$ = 9.813 min, $\tau_2$ = 11.301 min, *ee* = 0%; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.29 (dtd, *J* = 14.2, 8.5, 5.6 Hz, 1H), 2.42 (ddt, *J* = 13.7, 8.2, 6.8 Hz, 1H), 3.17 (tt, *J* = 6.9, 2.4 Hz, 1H), 3.23 (dd, *J* = 8.2, 6.7 Hz, 1H), 3.35 (ddd, *J* = 17.9, 8.2, 5.6 Hz, 1H), 4.68 (d, *J* = 2.4 Hz, 1H), 5.05 (s, 2H), 6.94 (dd, *J* = 9.1, 8.3 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 7.21 – 7.30 (m, 4H), 7.30 – 7.47 (m, 5H), 7.85 (d, *J* = 8.9 Hz, 2H), 8.04 (d, *J* = 9.1 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 23.15 ($CH_2$), 36.12 ($CH_2$), 59.67 (CH), 61.32 (CH), 70.24 ($CH_2$), 115.71 (2 × CH), 115.98 (d, *J* = 22.7 Hz, 2 × CH), 118.59 (d, *J* = 7.8 Hz, 2 × CH), 126.65 (t, *J* = 4.7 Hz, 2 × CH), 127.36 (2 × CH), 127.60 (2 × CH), 128.25 (CH), 128.61 (2 × CH), 128.78 (2 × CH), 129.50 (C), 133.96 (d, *J* = 2.6 Hz, C), 136.76 (C), 138.87 (C), 157.05 (t, *J* = 18.1 Hz, C), 159.17 (d, *J* = 243.3 Hz, C), 159.27 (C), 167.25 (C), 197.63 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ -117.88 (tt, *J* = 8.4, 4.6 Hz), 62.39 (d, *J* = 149.9 Hz), 82.77 (p, *J* = 149.9 Hz); IR (neat, KBr) 1741 (s, C=O, amide), 1695 (m, C=O, ketone), 857 (s, $SF_5$) cm$^{-1}$; HRMS-ESI: *m/z* $[M + Na]^+$ calcld for $C_{31}H_{25}O_3NF_6NaS$: 628.1352; found: 628.1347.

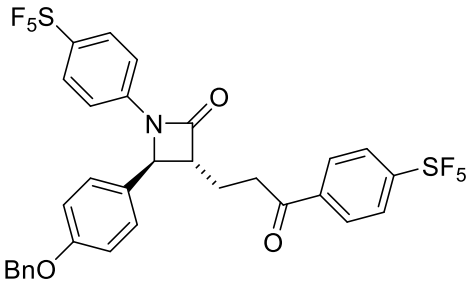


**(3*R*,4*S*)-4-[4-(Benzyloxy)phenyl]-1-(4-(trifluoromethyl)phenyl)-3-[3-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)-3-oxopropyl]azetidin-2-one** (**4.20c**). A new compound. Obtained from **4.19c** using procedure P: Red oil (151 mg, 40% yield); chiral HPLC: IC column, Heptane/*i*PrOH = 90/10; $\tau_{minor}$ = 10.500 min, $\tau_{major}$ = 12.665 min, *er* = 7:93, *ee* = 86%; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.31 (dtd, *J* = 14.1, 8.2, 5.6 Hz, 1H), 2.44 (ddt, *J* = 13.9, 8.1, 7.0 Hz, 1H), 3.22 (tdd, *J* = 10.0, 7.4, 5.6 Hz, 2H), 3.35 (ddd, *J* = 17.9, 8.0, 5.6 Hz, 1H), 4.74 (d, *J* = 2.5 Hz, 1H), 5.05 (s, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 7.26 – 7.30 (m, 2H), 7.31 – 7.45 (m, 7H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.9 Hz, 2H), 8.04 (d, *J* = 8.5 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 23.09 ($CH_2$), 36.08 ($CH_2$), 59.89 (CH), 61.41 (CH), 70.27 ($CH_2$), 115.80 (2 × CH), 117.01 (2 × CH), 124.14 (q, *J* = 271.8 Hz, C), 125.82 (q, *J* = 32.8 Hz, C), 126.52

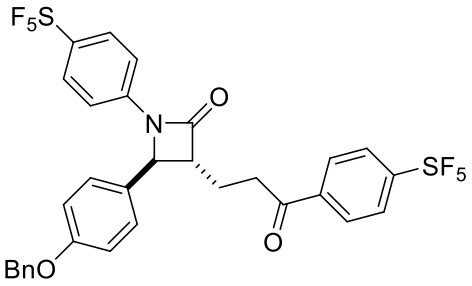
(q, $J$ = 3.9 Hz, 2 × CH), 126.69 (p, $J$ = 4.6 Hz, 2 × CH), 127.33 (2 × CH), 127.62 (2 × CH), 128.29 (CH), 128.61 (2 × CH), 128.80 (2 × CH), 129.12 (C), 136.70 (C), 138.81 (C), 140.35 (C), 157.11 (t, $J$ = 17.2 Hz, C), 159.38 (C), 167.89 (C), 197.51 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -62.12, 62.36 (d, $J$ = 150.3 Hz), 82.70 (p, $J$ = 150.5 Hz); IR (neat, KBr) 1750 (s, C=O, amide), 1695 (m, C=O, ketone), 1325 (s, $CF_3$), 857 (s, $SF_5$) cm$^{-1}$; HRMS-ESI: *m/z* [M + H]$^+$ calcld for $C_{32}H_{26}O_3NF_8S$: 656.1500; found: 656.1506.




**(*3R*,4S**)-4-(4-(Benzyloxy)-phenyl)-1-(4-(trifluoromethyl)phenyl)-3-(3-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)-3-oxopropyl)azetidin-2-one** (±)-(**4.20c**). A new compound. Obtained from (±)-**4.19c** using procedure P: Red foamy oil (222 mg, 50% yield); chiral HPLC: IC column, Heptane/*i*PrOH = 90/10; $\tau_1$ = 10.493 min, $\tau_2$ = 12.666 min, *ee* = 0%; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.31 (dtd, $J$ = 14.1, 8.2, 5.6 Hz, 1H), 2.44 (ddt, $J$ = 13.9, 8.1, 7.0 Hz, 1H), 3.22 (tdd, $J$ = 10.0, 7.4, 5.6 Hz, 2H), 3.35 (ddd, $J$ = 17.9, 8.0, 5.6 Hz, 1H), 4.74 (d, $J$ = 2.5 Hz, 1H), 5.05 (s, 2H), 6.98 (d, $J$ = 8.7 Hz, 2H), 7.26 – 7.30 (m, 2H), 7.31 – 7.45 (m, 7H), 7.50 (d, $J$ = 8.4 Hz, 2H), 7.86 (d, $J$ = 8.9 Hz, 2H), 8.04 (d, $J$ = 8.5 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 23.09 ($CH_2$), 36.08 ($CH_2$), 59.89 (CH), 61.41 (CH), 70.27 ($CH_2$), 115.80 (2 × CH), 117.01 (2 × CH), 124.14 (q, $J$ = 271.8 Hz, C), 125.82 (q, $J$ = 32.8 Hz, C), 126.52 (q, $J$ = 3.9 Hz, 2 × CH), 126.69 (p, $J$ = 4.6 Hz, 2 × CH), 127.33 (2 × CH), 127.62 (2 × CH), 128.29 (CH), 128.61 (2 × CH), 128.80 (2 × CH), 129.12 (C), 136.70 (C), 138.81 (C), 140.35 (C), 157.11 (t, $J$ = 17.2 Hz, C), 159.38 (C), 167.89 (C), 197.51 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -62.12, 62.36 (d, $J$ = 150.3 Hz), 82.70 (p, $J$ = 150.5 Hz); IR (neat, KBr) 1750 (s, C=O, amide), 1695 (m, C=O, ketone), 1325 (s, $CF_3$), 857 (s, $SF_5$) cm$^{-1}$; HRMS-ESI: *m/z* [M + H]$^+$ calcld for $C_{32}H_{26}O_3NF_8S$: 656.1500; found: 656.1506.

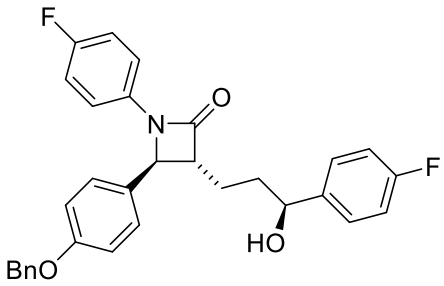


**(3*R*,4*S*)-4-[4-(Benzyloxy)phenyl]-1-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)-3-[3-(4-(pentafluoro-λ$^6$-sulfanyl) phenyl)-3-oxopropyl]azetidin-2-one** (**4.20d**). A new compound. Obtained from **4.19d** using procedure P: Pinkish foam (105 mg, 51% yield); $[\alpha]_D^{20}$ -2.1 (c = 0.298, $CHCl_3$); chiral HPLC: IC column, Heptane/*i*PrOH = 80/20; $\tau_{minor}$ = 6.996 min, $\tau_{major}$ = 7.946 min, *er* = 7:93, *ee* = 87%; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.30 (dtd, *J* = 14.2, 8.0, 5.7 Hz, 1H), 2.43 (dq, *J* = 14.6, 7.2 Hz, 1H), 3.15 – 3.28 (m, 2H), 3.34 (ddd, *J* = 18.0, 7.9, 5.6 Hz, 1H), 4.74 (d, *J* = 2.6 Hz, 1H), 5.05 (s, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.29 – 7.45 (m, 7H), 7.62 (d, *J* = 9.2 Hz, 2H), 7.86 (d, *J* = 8.9 Hz, 2H), 8.03 (d, *J* = 8.5 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 23.04 ($CH_2$), 36.07 ($CH_2$), 60.05 (CH), 61.53 (CH), 70.27 ($CH_2$), 115.86 (2 × CH), 116.64 (2 × CH), 126.69 (p, *J* = 4.7 Hz, 2 × CH), 127.27 (p, *J* = 4.6 Hz, 2 × CH), 127.35 (2 × CH), 127.62 (2 × CH), 128.30 (CH), 128.60 (2 × CH), 128.80 (2 × CH), 128.88 (C), 136.66 (C), 138.79 (C), 139.87 (C), 149.09 (t, *J* = 17.2 Hz, C), 157.13 (t, *J* = 17.2 Hz, C), 159.45 (C), 167.94 (C), 197.46 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ 62.35 (d, *J* = 150.2 Hz), 63.49 (d, *J* = 150.1 Hz), 82.68 (p, *J* = 150.5 Hz), 85.04 (p, *J* = 150.6 Hz); IR (neat, KBr) 1751 (s, C=O, amide), 1695 (m, C=O, ketone), 857 (s, $SF_5$) cm$^{-1}$; HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{31}H_{26}O_3NF_{10}S_2$: 714.1189; found: 714.1188.

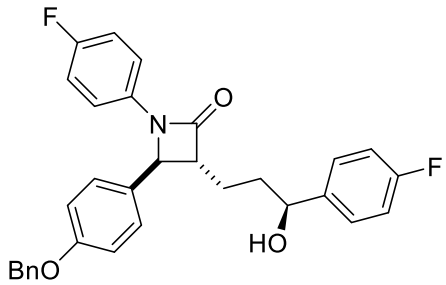


**(*3R*,4S**)-4-(4-(Benzyloxy)-phenyl)-1-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)-3-(3-(4-(pentafluoro-λ$^6$-sulfanyl) phenyl)-3-oxopropyl)azetidin-2-one** (±)-(**4.20d**). A new compound. Obtained from (±)-**4.19d** using procedure P: Pinkish foam (136 mg, 43% yield); chiral HPLC: IC column, Heptane/*i*PrOH = 80/20; $\tau_1$ = 6.985 min, $\tau_2$ = 7.934 min, *ee* = 0%; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.30 (dtd, *J* = 14.2, 8.0, 5.7 Hz, 1H), 2.43 (dq, *J* = 14.6, 7.2 Hz, 1H), 3.15 – 3.28 (m, 2H), 3.34 (ddd, *J* = 18.0, 7.9, 5.6 Hz, 1H), 4.74 (d, *J* = 2.6 Hz, 1H), 5.05 (s, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.29 – 7.45 (m, 7H), 7.62 (d, *J* = 9.2 Hz, 2H), 7.86 (d, *J* = 8.9 Hz, 2H), 8.03 (d, *J* = 8.5 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 23.04 ($CH_2$), 36.07 ($CH_2$), 60.05 (CH), 61.53 (CH), 70.27 ($CH_2$), 115.86 (2 × CH), 116.64 (2 × CH), 126.69 (p, *J* = 4.7 Hz, 2 × CH), 127.27 (p, *J* = 4.6 Hz, 2 × CH), 127.35 (2 × CH),

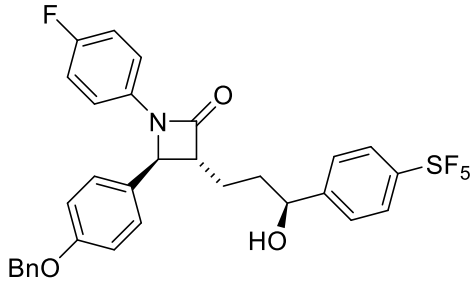
127.62 (2 × CH), 128.30 (CH), 128.60 (2 × CH), 128.80 (2 × CH), 128.88 (C), 136.66 (C), 138.79 (C), 139.87 (C), 149.09 (t, *J* = 17.2 Hz, C), 157.13 (t, *J* = 17.2 Hz, C), 159.45 (C), 167.94 (C), 197.46 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ 62.35 (d, *J* = 150.2 Hz), 63.49 (d, *J* = 150.1 Hz), 82.68 (p, *J* = 150.5 Hz), 85.04 (p, *J* = 150.6 Hz); IR (neat, KBr) 1751 (s, C=O, amide), 1695 (m, C=O, ketone), 857 (s, $SF_5$) $cm^{-1}$; HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{31}H_{26}O_3NF_{10}S_2$: 714.1189; found: 714.1188.




**(*3R,4S*)-4-(4-(Benzyloxy)phenyl)-1-(4-fluorophenyl)-3-((*S*)-3-(4-fluorophenyl)-3-hydroxypropyl)azetidin-2-one** (**4.21a**).[167] Obtained from **4.20a** using procedure R: White viscous oil (450 mg, 80% yield); $[\alpha]_D^{20}$ -31.0 (c = 0.316, $CHCl_3$) (lit.[174] $[\alpha]_D^{20}$ -15.8 (c = 1.00, MeOH)); chiral HPLC: ADH column, Heptane/*i*PrOH = 70/30; $\tau_{minor}$ = 13.252 min, $\tau_{minor}$ = 15.883 min, $\tau_{major}$ = 20.250 min, $\tau_{minor}$ = 25.718 min, *dr* = 1:5:90:4; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.81 – 2.04 (m, 4H), 2.42 (s, 1H), 3.08 (td, *J* = 7.4, 2.4 Hz, 1H), 4.58 (d, *J* = 2.4 Hz, 1H), 4.71 (t, *J* = 6.0 Hz, 1H), 5.05 (s, 2H), 6.88 – 6.95 (m, 2H), 6.95 – 7.05 (m, 4H), 7.20 – 7.26 (m, 4H), 7.26 – 7.31 (m, 2H), 7.31 – 7.45 (m, 5H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 25.13 ($CH_2$), 36.74 ($CH_2$), 60.41 (CH), 61.22 (CH), 70.23 ($CH_2$), 73.18 (CH), 115.46 (d, *J* = 21.3 Hz, 2 × CH), 115.66 (2 × CH), 115.93 (d, *J* = 22.7 Hz, 2 × CH), 118.53 (d, *J* = 7.8 Hz, 2 × CH), 127.30 (2 × CH), 127.51 (d, *J* = 8.1 Hz, 2 × CH), 127.60 (2 × CH), 128.25 (CH), 128.77 (2 × CH), 129.74 (C), 134.00 (d, *J* = 2.7 Hz, C), 136.76 (C), 140.20 (d, *J* = 3.2 Hz, C), 159.10 (d, *J* = 243.4 Hz, C), 159.17 (C), 162.30 (d, *J* = 245.6 Hz, C), 167.80 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -118.03 (tt, *J* = 8.6, 4.7 Hz), -114.89 (ddd, *J* = 14.1, 8.9, 5.4 Hz); HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{31}H_{28}O_3NF_2$: 500.2032; found: 500.2030.

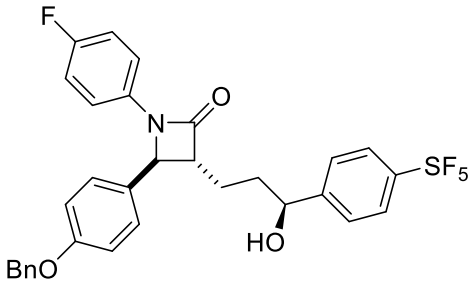


**(*3R*,4S**)-4-(4-(Benzyloxy)phenyl)-1-(4-fluorophenyl)-3-((*S*)-3-(4-fluorophenyl)-3-hydroxypropyl)azetidin-2-one** (±)-(**4.21a**).[353] Obtained from (±)-**4.20a** using procedure Q: Pinkish foam (251 mg, 51% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.81 – 2.04 (m, 4H), 2.42 (s, 1H), 3.08 (td, *J* = 7.4, 2.4 Hz, 1H), 4.58 (d, *J* = 2.4 Hz, 1H), 4.71 (t, *J* = 6.0 Hz, 1H), 5.05 (s, 2H), 6.88 – 6.95 (m, 2H), 6.95 – 7.05 (m, 4H), 7.20 – 7.26 (m, 4H), 7.26 – 7.31 (m, 2H), 7.31 – 7.45 (m, 5H); $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 25.13 ($CH_2$), 36.74 ($CH_2$), 60.41 (CH), 61.22 (CH), 70.23 ($CH_2$), 73.18 (CH), 115.46 (d, *J* = 21.3 Hz, 2 × CH), 115.66 (2 × CH), 115.93 (d, *J* = 22.7 Hz, 2 × CH), 118.53 (d, *J* = 7.8 Hz, 2 × CH), 127.30 (2 × CH), 127.51 (d, *J* = 8.1 Hz, 2 × CH), 127.60 (2 × CH), 128.25 (CH), 128.77 (2 × CH), 129.74 (C), 134.00 (d, *J* = 2.7 Hz, C), 136.76 (C), 140.20 (d, *J* = 3.2 Hz, C), 159.10 (d, *J* = 243.4 Hz, C), 159.17 (C), 162.30 (d, *J* = 245.6 Hz, C), 167.80 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -118.03 (tt, *J* = 8.6, 4.7 Hz), -114.89 (ddd, *J* = 14.1, 8.9, 5.4 Hz); HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{31}H_{28}O_3NF_2$: 500.2032; found: 500.2030.

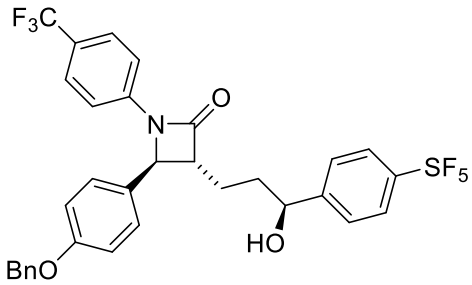


**(*3R,4S*)-4-(4-(Benzyloxy)phenyl)-1-(4-fluorophenyl)-3-((*S*)-3-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)-3-hydroxypropyl)azetidin-2-one** (**4.21b**). A new compound. Obtained from **4.20b** using procedure Q: White foamy oil (182 mg, 67% yield); $[\alpha]_D^{20}$ -16.5 (c = 0.439, $CHCl_3$); chiral HPLC: ADH column, Heptane/*i*PrOH = 70/30; $\tau_{minor}$ = 10.320 min, $\tau_{minor}$ = 11.552 min, $\tau_{major}$ = 15.282 min, $\tau_{minor}$ = 21.146 min, *dr* = 1:5:87:7; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.91 (ddd, *J* = 8.9, 6.6, 5.0 Hz, 2H), 2.01 (t, *J* = 7.8 Hz, 2H), 2.74 (s, 1H), 3.10 (td, *J* = 7.6, 2.4 Hz, 1H), 4.58 (d, *J* = 2.4 Hz, 1H), 4.81 (t, *J* = 6.3 Hz, 1H), 5.06 (s, 2H), 6.90 – 6.96 (m, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 7.23 (td, *J* = 5.3, 3.5 Hz, 3H), 7.31 – 7.46 (m, 8H), 7.71 (d, *J* = 8.8 Hz, 2H); $^{13}$C{$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 24.82 ($CH_2$), 36.81 ($CH_2$), 60.29 (CH), 61.28 (CH), 70.27 ($CH_2$), 72.53 (CH), 115.75 (2 × CH), 115.99 (d, *J* = 22.7 Hz, 2 × CH), 118.60 (d, *J* = 7.7 Hz, 2 × CH), 126.06 (2 × CH), 126.29 (t, *J* = 4.4 Hz, 2 × CH), 127.32 (2 × CH), 127.60 (2 × CH), 128.27 (CH), 128.79 (2 × CH), 129.58 (C), 133.93 (d, *J* = 2.6 Hz, C), 136.76 (C), 148.39 (C), 153.11 (t, *J* = 17.2 Hz, C), 159.20 (d, *J* = 243.6 Hz, C), 159.28 (C), 167.86 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ -117.82 (tt, *J* = 8.6, 4.7 Hz), 63.05 (d, *J* = 149.9

Hz), 83.79 – 85.63 (m); HRMS-ESI: *m/z* [M + H]$^+$ calcld for $C_{31}H_{28}O_3NF_6S$: 608.1687; found: 608.1685.

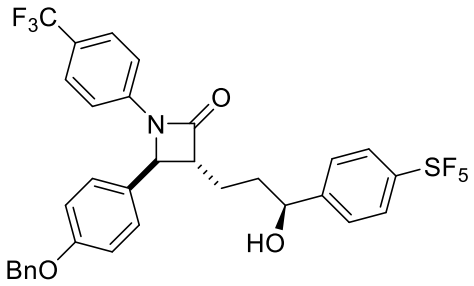



**(*3R*,4S**)-4-(4-(Benzyloxy)phenyl)-1-(4-fluorophenyl)-3-((*S*)-3-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)-3-hydroxypropyl)azetidin-2-one** (±)-(**4.21b**). A new compound. Obtained from (±)-**4.20b** using procedure Q: Brownish oil (158 mg, 66% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.91 (ddd, *J* = 8.9, 6.6, 5.0 Hz, 2H), 2.01 (t, *J* = 7.8 Hz, 2H), 2.74 (s, 1H), 3.10 (td, *J* = 7.6, 2.4 Hz, 1H), 4.58 (d, *J* = 2.4 Hz, 1H), 4.81 (t, *J* = 6.3 Hz, 1H), 5.06 (s, 2H), 6.90 – 6.96 (m, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 7.23 (td, *J* = 5.3, 3.5 Hz, 3H), 7.31 – 7.46 (m, 8H), 7.71 (d, *J* = 8.8 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 24.82 ($CH_2$), 36.81 ($CH_2$), 60.29 (CH), 61.28 (CH), 70.27 ($CH_2$), 72.53 (CH), 115.75 (2 × CH), 115.99 (d, *J* = 22.7 Hz, 2 × CH), 118.60 (d, *J* = 7.7 Hz, 2 × CH), 126.06 (2 × CH), 126.29 (t, *J* = 4.4 Hz, 2 × CH), 127.32 (2 × CH), 127.60 (2 × CH), 128.27 (CH), 128.79 (2 × CH), 129.58 (C), 133.93 (d, *J* = 2.6 Hz, C), 136.76 (C), 148.39 (C), 153.11 (t, *J* = 17.2 Hz, C), 159.20 (d, *J* = 243.6 Hz, C), 159.28 (C), 167.86 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ -117.82 (tt, *J* = 8.6, 4.7 Hz). 63.02 (d, *J* = 149.6 Hz), 84.68 (pd, *J* = 150.1, 10.8 Hz); HRMS-ESI: *m/z* [M + H]$^+$ calcld for $C_{31}H_{28}O_3NF_6S$: 608.1687; found: 608.1685.

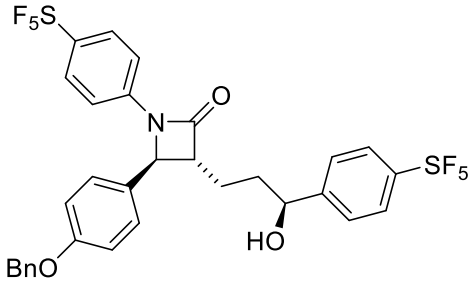



**(*3R,4S*)-4-(4-(Benzyloxy)phenyl)-1-(4-(trifluoromethyl) phenyl)-3-((*S*)-3-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)-3-hydroxypropyl)azetidin-2-one** (**4.21c**). A new compound. Obtained from **4.20c** using procedure Q: Pink oil (120 mg, 93% yield); chiral HPLC: ADH column, Heptane/*i*PrOH = 70/30; $\tau_{minor}$ = 11.507 min, $\tau_{major}$ = 15.176 min, $\tau_{minor}$ = 20.985 min, *dr* = 4:88:8; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.86 – 1.97 (m, 2H), 1.97 – 2.09 (m, 2H), 3.15 (td, *J* = 7.6, 2.5 Hz, 1H), 4.64 (d, *J* = 2.6 Hz, 1H), 4.82 (t, *J* = 6.3 Hz, 1H), 5.06 (s, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.31 – 7.46 (m, 9H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.9 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 24.88 ($CH_2$), 36.73 ($CH_2$),

60.53 (CH), 61.31 (CH), 70.27 ($CH_2$), 72.64 (CH), 115.83 (2 × CH), 117.00 (2 × CH), 124.13 (q, $J$ = 271.7 Hz, C), 125.84 (q, $J$ = 33.1 Hz, C), 126.06 (2 × CH), 126.35 (p, $J$ = 4.7 Hz, 2 × CH), 126.51 (q, $J$ = 3.9 Hz, 2 × CH), 127.29 (2 × CH), 127.62 (2 × CH), 128.30 (CH), 128.81 (2 × CH), 129.22 (C), 136.70 (C), 140.34 (C), 148.26 (C), 153.18 (t, $J$ = 17.5 Hz, C), 159.37 (C), 168.40 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -62.13, 63.01 (d, $J$ = 150.0 Hz), 84.63 (p, $J$ = 150.0 Hz); HRMS-ESI: *m/z* [M - H]$^-$ calcld for $C_{32}H_{26}O_3NF_8S$: 656.1511; found: 656.1508.

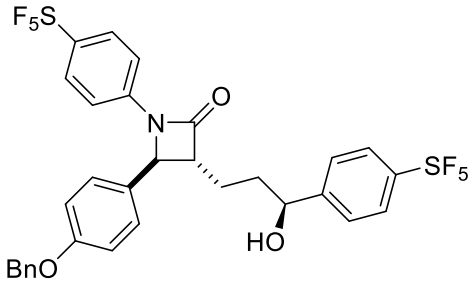



**(*3R*,4S**)-4-(4-(Benzyloxy)phenyl)-1-(4-(trifluoromethyl)phenyl)-3-((*S*)-3-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)-3-hydroxypropyl)azetidin-2-one** (±)-(**4.21c**). A new compound. Obtained from (±)-**4.20c** using procedure Q: Pinkish foam (106 mg, 56% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.86 – 1.99 (m, 2H), 1.99 – 2.09 (m, 2H), 3.16 (qd, $J$ = 8.5, 2.5 Hz, 1H), 4.64 (dd, $J$ = 3.8, 2.5 Hz, 1H), 4.82 (t, $J$ = 6.4 Hz, 1H), 5.06 (s, 2H), 6.98 (d, $J$ = 8.8 Hz, 2H), 7.26 (d, $J$ = 8.7 Hz, 2H), 7.31 – 7.46 (m, 9H), 7.46 – 7.53 (m, 2H), 7.69 – 7.76 (m, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 24.88 ($CH_2$), 36.73 ($CH_2$), 60.53 (CH), 61.31 (CH), 70.27 ($CH_2$), 72.64 (CH), 115.83 (2 × CH), 117.00 (2 × CH), 124.13 (q, $J$ = 271.7 Hz, C), 125.84 (q, $J$ = 33.1 Hz, C), 126.06 (2 × CH), 126.35 (p, $J$ = 4.7 Hz, 2 × CH), 126.51 (q, $J$ = 3.9 Hz, 2 × CH), 127.29 (2 × CH), 127.62 (2 × CH), 128.30 (CH), 128.81 (2 × CH), 129.22 (C), 136.70 (C), 140.34 (C), 148.26 (C), 153.18 (t, $J$ = 17.5 Hz, C), 159.37 (C), 168.40 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -62.13, 63.01 (d, $J$ = 150.0 Hz), 84.63 (p, $J$ = 150.0 Hz); HRMS-ESI: *m/z* [M - H]$^-$ calcld for $C_{32}H_{26}O_3NF_8S$: 656.1511; found: 656.1508.

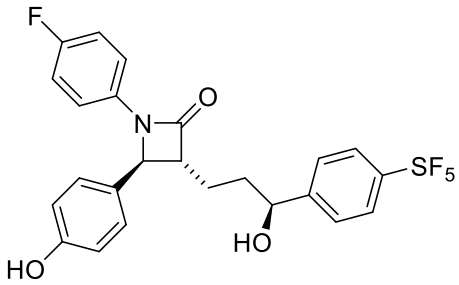



**(*3R,4S*)-4-(4-(Benzyloxy)phenyl)-1-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)-3-((*S*)-3-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)-3-hydroxypropyl)azetidin-2-one** (**4.21d**). A new compound. Obtained from **4.20d** using procedure Q: Reddish foam (155 mg, 75% yield); chiral HPLC: ADH column, Heptane/*i*PrOH = 70/30; $\tau_{major}$ = 16.711 min, $\tau_{minor}$ = 20.251 min, $\tau_{minor}$ = 25.328 min, *dr* = 92:2:6; $^1$H NMR (400 MHz, $CDCl_3$) δ

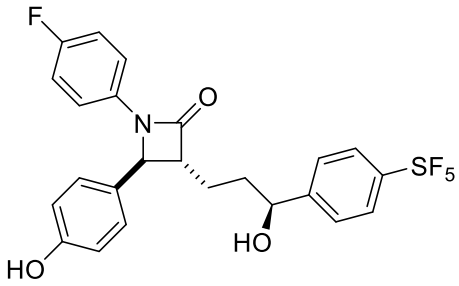
1.87 – 1.95 (m, 2H), 1.98 – 2.07 (m, 2H), 3.16 (td, *J* = 7.6, 2.6 Hz, 1H), 4.63 (d, *J* = 2.6 Hz, 1H), 4.81 (t, *J* = 6.3 Hz, 1H), 5.06 (s, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 9.2 Hz, 2H), 7.33 – 7.46 (m, 7H), 7.62 (d, *J* = 9.2 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 24.86 ($CH_2$), 36.67 ($CH_2$), 60.68 (CH), 61.40 (CH), 70.28 ($CH_2$), 72.65 (CH), 115.89 (2 × CH), 116.63 (2 × CH), 126.05 (2 × CH), 126.35 (p, *J* = 4.6 Hz, 2 × CH), 127.29 (2 × CH), 127.30 (p, *J* = 4.6 Hz, 2 × CH), 127.61 (2 × CH), 128.31 (CH), 128.81 (2 × CH), 128.98 (C), 136.66 (C), 139.86 (C), 148.21 (C), 149.09 (t, *J* = 17.5 Hz, C), 153.18 (t, *J* = 17.5 Hz, C), 159.44 (C), 168.43 (C); $^{19}F$ NMR (377 MHz, $CDCl_3$) δ 63.00 (d, *J* = 149.4 Hz), 63.49 (d, *J* = 150.1 Hz), 83.77 – 85.87 (m); HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{31}H_{28}O_3NF_{10}S_2$: 716.1345; found: 716.1343.




**(*3R*,4S**)-4-(4-(Benzyloxy)phenyl)-1-(4-(pentafluoro-λ⁶-sulfanyl)phenyl)-3-((*S*)-3-(4-(pentafluoro-λ⁶-sulfanyl)phenyl)-3-hydroxypropyl)azetidin-2-one** (±)-(**4.21d**). A new compound. Obtained from (±)-**4.20d** using procedure Q: Red oil (166 mg, 64% yield); $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 1.85 – 2.08 (m, 4H), 3.18 (dtd, *J* = 16.4, 7.3, 2.5 Hz, 1H), 4.63 (dd, *J* = 3.8, 2.6 Hz, 1H), 4.82 (t, *J* = 6.5 Hz, 1H), 5.06 (s, 2H), 6.99 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.28 – 7.33 (m, 2H), 7.33 – 7.46 (m, 7H), 7.61 (dd, *J* = 9.2, 2.8 Hz, 2H), 7.73 (dd, *J* = 8.8, 3.0 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 24.86 ($CH_2$), 36.67 ($CH_2$), 60.68 (CH), 61.40 (CH), 70.28 ($CH_2$), 72.65 (CH), 115.89 (2 × CH), 116.63 (2 × CH), 126.05 (2 × CH), 126.35 (p, *J* = 4.6 Hz, 2 × CH), 127.29 (2 × CH), 127.30 (p, *J* = 4.6 Hz, 2 × CH), 127.61 (2 × CH), 128.31 (CH), 128.81 (2 × CH), 128.98 (C), 136.66 (C), 139.86 (C), 148.21 (C), 149.09 (t, *J* = 17.5 Hz, C), 153.18 (t, *J* = 17.5 Hz, C), 159.44 (C), 168.43 (C); $^{19}F$ NMR (377 MHz, $CDCl_3$) δ 63.00 (d, *J* = 149.4 Hz), 63.49 (d, *J* = 150.1 Hz), 83.77 – 85.87 (m); HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{31}H_{28}O_3NF_{10}S_2$: 716.1345; found: 716.1343.

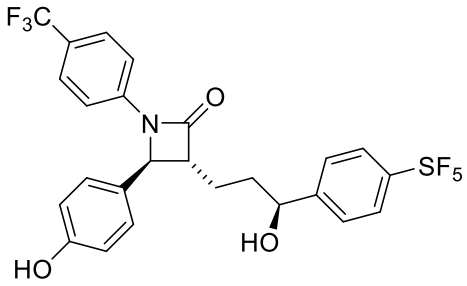



**(*3R,4S*)-1-(4-Fluorophenyl)-3-((*S*)-3-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl)azetidin-2-one** (**4.2**). A new compound. Obtained from **4.21b** using procedure S: White foam (118 mg, 82% yield); mp 80-85 °C (*n*-hexane-EtOAc); $[\alpha]_D^{20}$ -21.5 (c = 0.366, $CHCl_3$); chiral HPLC: IC column, Heptane/*i*PrOH = 93/7; $\tau_{major}$ = 16.289 min, $\tau_{minor}$ = 17.842 min, $\tau_{minor}$ = 21.302 min, *dr* = 87:9:4; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.85 – 1.95 (m, 2H), 1.97 – 2.05 (m, 2H), 2.84 (s, 1H), 3.08 (td, *J* = 7.6, 2.4 Hz, 1H), 4.56 (d, *J* = 2.4 Hz, 1H), 4.80 (t, *J* = 6.2 Hz, 1H), 5.83 (s, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.87 – 6.97 (m, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.22 (ddd, *J* = 8.8, 4.4, 2.1 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 24.81 ($CH_2$), 36.69 ($CH_2$), 60.17 (CH), 61.37 (CH), 72.66 (CH), 116.02 (d, *J* = 22.7 Hz, 2 × CH), 116.35 (2 × CH), 118.68 (d, *J* = 7.8 Hz, 2 × CH), 126.06 (2 × CH), 126.31 (p, *J* = 4.6 Hz, 2 × CH), 127.49 (2 × CH), 129.11 (C), 133.76 (d, *J* = 2.9 Hz, C), 148.20 (C), 153.13 (t, *J* = 17.1 Hz, C), 156.41 (C), 159.26 (d, *J* = 243.9 Hz, C), 168.16 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -117.53 (tt, *J* = 8.5, 4.6 Hz), 63.02 (d, *J* = 149.9 Hz), 84.69 (p, *J* = 150.4 Hz); HRMS-ESI: *m/z* [M - H]$^-$ calcld for $C_{24}H_{20}O_3NF_6S$: 516.1074; found: 516.1078.

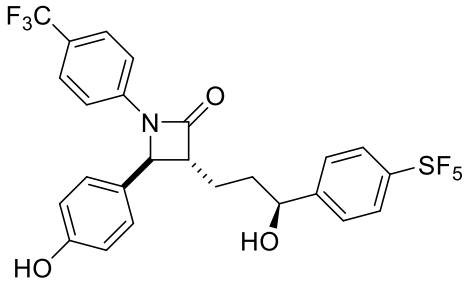



**(*3R*,4S**)-1-(4-Fluorophenyl)-3-((*S*)-3-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl)azetidin-2-one** (±)-(**4.2**). A new compound. Obtained from (±)-**4.21b** using procedure S: Grey foam (114 mg, 96% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.85 – 1.95 (m, 2H), 1.97 – 2.05 (m, 2H), 2.84 (s, 1H), 3.08 (td, *J* = 7.6, 2.4 Hz, 1H), 4.56 (d, *J* = 2.4 Hz, 1H), 4.81 (t, *J* = 6.2 Hz, 1H), 5.67 (s, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.87 – 6.97 (m, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.22 (ddd, *J* = 8.8, 4.4, 2.1 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 24.81 ($CH_2$), 36.69 ($CH_2$), 60.17 (CH), 61.37 (CH), 72.66 (CH), 116.02 (d, *J* = 22.7 Hz, 2 × CH), 116.35 (2 × CH), 118.68 (d, *J* = 7.8 Hz, 2 × CH), 126.06 (2 × CH), 126.31 (p, *J* = 4.6 Hz, 2 × CH), 127.49 (2 × CH), 129.11 (C), 133.76 (d, *J* = 2.9 Hz, C), 148.20 (C), 153.13 (t, *J* = 17.1 Hz, C), 156.41 (C), 159.26 (d, *J* = 243.9 Hz, C), 168.16 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -117.53 (tt, *J*

= 8.5, 4.6 Hz), 63.02 (d, *J* = 149.9 Hz), 84.69 (p, *J* = 150.4 Hz); HRMS-ESI: *m/z* [M - H]$^-$ calcld for $C_{24}H_{20}O_3NF_6S$: 516.1074; found: 516.1078.

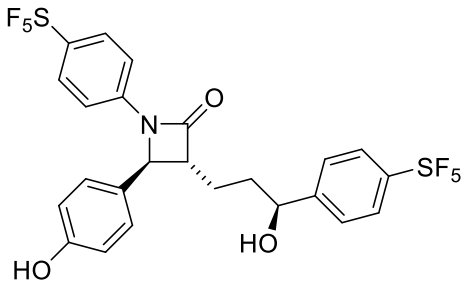


**(*3R,4S*)-1-(4-(Trifluoromethyl)phenyl)-3-((*S*)-3-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl)azetidin-2-one** (**4.3**). A new compound. Obtained from **4.21c** using procedure T: Pinkish foam (91 mg, 89% yield); mp 84-88 °C (*n*-hexane-EtOAc); $[\alpha]_D^{20}$ -27.7 (c = 0.321, $CHCl_3$); chiral HPLC: ADH column, Heptane/*i*PrOH = 85/15; $\tau_{minor}$ = 20.089 min, $\tau_{major}$ = 21.533 min, $\tau_{minor}$ = 24.934 min, $\tau_{minor}$ = 27.570 min, *dr* = 8:80:4:8; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.87 – 1.95 (m, 2H), 1.98 – 2.07 (m, 2H), 2.69 (s, 1H), 3.13 (td, *J* = 7.6, 2.5 Hz, 1H), 4.63 (d, *J* = 2.4 Hz, 1H), 4.81 (t, *J* = 6.2 Hz, 1H), 5.75 (s, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.9 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.71 (d, *J* = 8.8 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 24.84 ($CH_2$), 36.60 ($CH_2$), 60.42 (CH), 61.37 (CH), 72.73 (CH), 116.44 (2 × CH), 117.06 (2 × CH), 124.08 (q, *J* = 271.7 Hz, C), 125.98 (q, *J* = 33.0 Hz, C), 126.05 (2 × CH), 126.35 (p, *J* = 4.7 Hz, 2 × CH), 126.51 (q, *J* = 3.8 Hz, 2 × CH), 127.46 (2 × CH), 128.83 (C), 140.20 (C), 148.11 (C), 153.19 (t, *J* = 17.4 Hz, C), 156.48 (C), 168.70 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -62.16, 63.00 (d, *J* = 149.8 Hz), 84.62 (p, *J* = 150.2 Hz); HRMS-ESI: *m/z* [M - H]$^-$ calcld for $C_{25}H_{20}O_3NF_8S$: 566.1031; found: 566.1036.

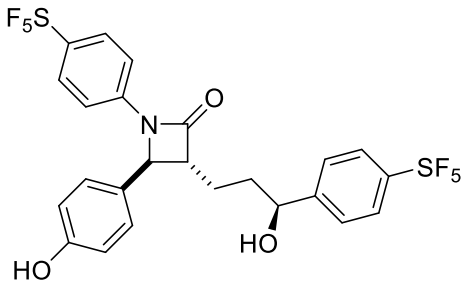


**(*3R*,4S**)-1-(4-(Trifluoromethyl)phenyl)-3-((*S*)-3-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl)azetidin-2-one** (±)-(**4.3**). A new compound. Obtained from (±)-**4.21c** using procedure T: Off-white foam (73 mg, 92% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.87 – 1.95 (m, 2H), 1.98 – 2.07 (m, 2H), 2.69 (s, 1H), 3.13 (td, *J* = 7.6, 2.5 Hz, 1H), 4.63 (d, *J* = 2.4 Hz, 1H), 4.81 (t, *J* = 6.2 Hz, 1H), 5.75 (s, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.9 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.71 (d, *J* = 8.8 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 24.84

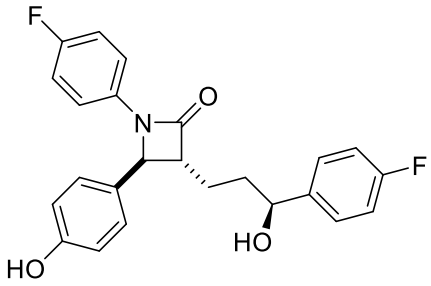
($CH_2$), 36.60 ($CH_2$), 60.42 (CH), 61.37 (CH), 72.73 (CH), 116.44 (2 × CH), 117.06 (2 × CH), 124.08 (q, $J$ = 271.7 Hz, C), 125.98 (q, $J$ = 33.0 Hz, C), 126.05 (2 × CH), 126.35 (p, $J$ = 4.7 Hz, 2 × CH), 126.51 (q, $J$ = 3.8 Hz, 2 × CH), 127.46 (2 × CH), 128.83 (C), 140.20 (C), 148.11 (C), 153.19 (t, $J$ = 17.4 Hz, C), 156.48 (C), 168.70 (C); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -62.16, 63.00 (d, $J$ = 149.8 Hz), 84.62 (p, $J$ = 150.2 Hz); HRMS-ESI: *m/z* [M - H]$^-$ calcld for $C_{25}H_{20}O_3NF_8S$: 566.1031; found: 566.1036.



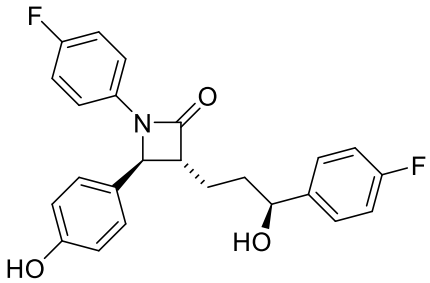

**(*3R,4S*)-1-(4-(Pentafluoro-λ$^6$-sulfanyl)phenyl)-3-((*S*)-3-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl)azetidin-2-one** (**4.4**). A new compound. Obtained from **4.21d** using procedure T: Pinkish solid (116 mg, 87% yield); mp 147-149 °C (*n*-hexane-EtOAc); $[\alpha]_D^{20}$ -22.5 (c = 0.329, MeOH); chiral HPLC: IC column, Heptane/*i*PrOH = 93/7; $\tau_{major}$ = 9.966 min, $\tau_{minor}$ = 10.878 min, $\tau_{minor}$ = 12.898 min, *dr* = 87:10:3; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.86 – 1.96 (m, 2H), 1.99 – 2.07 (m, 2H), 2.52 (s, 1H), 3.15 (td, $J$ = 7.6, 2.5 Hz, 1H), 4.62 (d, $J$ = 2.5 Hz, 1H), 4.81 (t, $J$ = 6.3 Hz, 1H), 5.44 (s, 1H), 6.85 (d, $J$ = 8.5 Hz, 2H), 7.20 (d, $J$ = 8.7 Hz, 2H), 7.30 (d, $J$ = 8.7 Hz, 2H), 7.41 (d, $J$ = 8.3 Hz, 2H), 7.61 (d, $J$ = 9.3 Hz, 2H), 7.72 (d, $J$ = 8.9 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 24.86 ($CH_2$), 36.61 ($CH_2$), 60.65 (CH), 61.44 (CH), 72.74 (CH), 116.49 (2 × CH), 116.66 (2 × CH), 126.05 (2 × CH), 126.37 (p, $J$ = 4.7 Hz, 2 × CH), 127.30 (p, $J$ = 4.7 Hz, 2 × CH), 127.49 (2 × CH), 128.78 (C), 139.78 (C), 148.12 (C), 149.16 (t, $J$ = 17.4 Hz, C), 153.22 (t, $J$ = 17.4 Hz, C), 156.45 (C), 168.57 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ 62.99 (d, $J$ = 149.7 Hz), 63.46 (d, $J$ = 149.8 Hz), 83.77 – 85.79 (m); HRMS-ESI: *m/z* [M + H]$^+$ calcld for $C_{24}H_{22}O_3NF_{10}S_2$: 626.0876; found: 626.0881.



**(*3R*,4S**)-1-(4-(Pentafluoro-λ$^6$-sulfanyl)phenyl)-3-((*S*)-3-(4-(pentafluoro-λ$^6$-sulfanyl)phenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl)azetidin-2-one** (±)-(**4.4**). A new compound. Obtained from (±)-**4.21d** using procedure T: Pink solid (99 mg, 83% yield); mp 85-90 °C (*n*-hexane-EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.86 – 1.96 (m, 2H), 1.99 – 2.07 (m, 2H), 2.52 (s, 1H), 3.15 (td, *J* = 7.6, 2.5 Hz, 1H), 4.62 (d, *J* = 2.5 Hz, 1H), 4.81 (t, *J* = 6.3 Hz, 1H), 5.44 (s, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 9.3 Hz, 2H), 7.72 (d, *J* = 8.9 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 24.86 ($CH_2$), 36.61 ($CH_2$), 60.65 (CH), 61.44 (CH), 72.74 (CH), 116.49 (2 × CH), 116.66 (2 × CH), 126.05 (2 × CH), 126.37 (p, *J* = 4.7 Hz, 2 × CH), 127.30 (p, *J* = 4.7 Hz, 2 × CH), 127.49 (2 × CH), 128.78 (C), 139.78 (C), 148.12 (C), 149.16 (t, *J* = 17.4 Hz, C), 153.22 (t, *J* = 17.4 Hz, C), 156.45 (C), 168.57 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ 62.99 (d, *J* = 149.7 Hz), 63.46 (d, *J* = 149.8 Hz), 83.77 – 85.79 (m); HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{24}H_{22}O_3NF_{10}S_2$: 626.0876; found: 626.0881.



**(*3R*,4S**)-1-(4-fluorophenyl)-3-((*S*)-3-(4-fluorophenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl)azetidin-2-one** (±)-(**4.1**).[354] Obtained from (±)-**4.21a** using procedure T: Off-white foam (50 mg, 29% yield); $^1$H NMR (401 MHz, $CDCl_3$) δ 1.92 (tddd, *J* = 15.7, 11.1, 6.4, 2.9 Hz, 4H), 2.57 (s, 1H), 3.05 (td, *J* = 7.4, 2.3 Hz, 1H), 4.56 (d, *J* = 2.3 Hz, 1H), 4.69 (dd, *J* = 7.1, 4.9 Hz, 1H), 6.01 (s, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.87 – 6.95 (m, 2H), 6.95 – 7.03 (m, 2H), 7.16 (d, *J* = 8.6 Hz, 2H), 7.19 – 7.29 (m, 4H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 25.13 ($CH_2$), 36.60 ($CH_2$), 60.29 (CH), 61.36 (CH), 73.36 (CH), 115.52 (d, *J* = 21.4 Hz, 2 × CH), 115.98 (d, *J* = 22.6 Hz, 2 × CH), 116.32 (2 × CH), 118.64 (d, *J* = 7.9 Hz, 2 × CH), 127.46 (2 × CH), 127.54 (d, *J* = 7.9 Hz, 2 × CH), 129.17 (C), 133.84 (d, *J* = 2.6 Hz, C), 139.97 (d, *J* = 3.0 Hz, C), 156.42 (C), 159.20 (d, *J* = 243.7 Hz, C), 162.34 (d, *J* = 245.8 Hz, C), 168.16 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ -117.70 (tt, *J* = 8.3, 4.7 Hz), -114.74 (tt, *J* = 8.6, 5.3 Hz); HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{24}H_{22}O_3NF_2$: 410.1562; found: 410.1558.



**Ezetimibe**

**Ezetimibe** (**4.1**).[162] Obtained from **4.21a** using procedure T: White foam (107 mg, 30% yield); $[\alpha]_D^{20}$ -28.2 (c = 0.296, $CHCl_3$) (lit.[355] $[\alpha]_D^{22}$ -33.9 (c = 3.00, MeOH), lit.[356] $[\alpha]_D^{20}$ -27.5 (c is unknown, MeOH)); chiral HPLC: IC column, Heptane/*i*PrOH = 90/10; $\tau_{major}$ = 16.563 min, $\tau_{minor}$ = 20.215 min, $\tau_{minor}$ = 24.047 min, $\tau_{minor}$ = 28.134 min, *dr* = 89:5:5:1; $^1$H NMR (401 MHz, $CDCl_3$) δ 1.92 (tddd, *J* = 15.7, 11.1, 6.4, 2.9 Hz, 4H), 2.57 (s, 1H), 3.05 (td, *J* = 7.4, 2.3 Hz, 1H), 4.56 (d, *J* = 2.3 Hz, 1H), 4.69 (dd, *J* = 7.1, 4.9 Hz, 1H), 6.01 (s, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.87 – 6.95 (m, 2H), 6.95 – 7.03 (m, 2H), 7.16 (d, *J* = 8.6 Hz, 2H), 7.19 – 7.29 (m, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 25.13 ($CH_2$), 36.60 ($CH_2$), 60.29 (CH), 61.36 (CH), 73.36 (CH), 115.52 (d, *J* = 21.4 Hz, 2 × CH), 115.98 (d, *J* = 22.6 Hz, 2 × CH), 116.32 (2 × CH), 118.64 (d, *J* = 7.9 Hz, 2 × CH), 127.46 (2 × CH), 127.54 (d, *J* = 7.9 Hz, 2 × CH), 129.17 (C), 133.84 (d, *J* = 2.6 Hz, C), 139.97 (d, *J* = 3.0 Hz, C), 156.42 (C), 159.20 (d, *J* = 243.7 Hz, C), 162.34 (d, *J* = 245.8 Hz, C), 168.16 (C); $^{19}$F NMR (377 MHz, $CDCl_3$) δ -117.70 (tt, *J* = 8.3, 4.7 Hz), -114.74 (tt, *J* = 8.6, 5.3 Hz); HRMS-ESI: *m/z* $[M + H]^+$ calcld for $C_{24}H_{22}O_3NF_2$: 410.1562; found: 410.1558.

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