Selective Transformations of Allylic Compounds and Enol Derivatives
– Synthesis of Fluorinated and Nitrogenated Scaffolds

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PhD Thesis

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Abstract

In this thesis, new synthetic methods to give access to molecules having fluorinated scaffolds and other polar functional groups have been developed. The methods give access to highly valuable organic compounds that may serve as building blocks in the synthesis of functionalized drug candidates. In particular, the present thesis describes four new protocols for the synthesis of such compounds starting from allylic substrates and enol derivatives, using metal- or organocatalysts.

In the introductory chapter (Chapter 1), the importance and the different approaches to catalysis are discussed. The structural features and reactivity of allylic substrates are presented, followed by an extensive description of the use of CO_2 as a building block in organic synthesis. In the final part of this chapter, the structure and common reactive pathways of hypervalent iodine(III) reagents are described.

In the second part (Chapter 2), a palladium-catalyzed allylic substitution method is designed to obtain 3-fluoropiperidines from 1,3-dicarbonyl compounds and allylic carbamates. The final products are further functionalized in a chemo- and diastereoselective manner. Additionally, the enantioselective version of this reaction is studied using chiral phosphoramidite ligands.

In the third chapter, an umpolung methodology for CO_2 fixation is explored in the coupling of silyl enol ethers with amines and CO_2 mediated by hypervalent iodine(III) reagents. The mechanism of this transformation is examined using DFT calculations and experimental results. Moreover, this protocol is extended to 1,3-dicarbonyl compounds, yielding α-carbamate-β-ketocarbonyl compounds.

The final part of this thesis (Chapter IV and V) describes the base-catalyzed stereospecific isomerization of allylic halides and amines. Catalytic amounts of a simple guanidine type base (TBD), are able to transfer the chirality during the isomerization reaction of chiral allylic substrates. In the case of allylic amines, the synthetic utility of the chiral enamine/imine intermediates derived from the isomerization reaction is extensively explored, designing a one-pot protocol for the stereospecific and diastereoselective synthesis of chiral γ-trifluoromethylated aliphatic amines with two non-consecutive stereogenic centers.

List of publications

This doctoral thesis is based on the following publications, which would be referred to in the text with Roman numerals **I-IV**. The contribution of the author in each publication is presented in Appendix A. Reprints of the publications were made with permission from the publishers.

Paper I

A Pd-Catalyzed [4+2] Annulation Approach to Fluorinated N-Heterocycles

Víctor García-Vázquez,‡ Larry Hoteite,‡ Christopher P. Lakeland,‡ David W. Watson and Joseph P. A. Harrity*

Org. Lett. **2021**, *23*, 2811-2815

Paper II

A General Method for alpha-Functionalization of Enol Derivatives through the Umpolung Cross-Nucleophile Coupling Mediated by a Single Iodine(III) Reagent

Víctor García-Vázquez,‡ Alba Carretero-Cerdán,‡ Amparo Sanz-Marco,‡ and Belén Martín-Matute*

ChemRxiv. Cambridge: Cambridge Open Engage; **2022***;* This content is a preprint and has not been peer-reviewed.

DOI: 10.26434/chemrxiv-2022-vbc0x (Preprint)

Paper III

Stereospecific Isomerization of Allylic Halides via Ion Pairs with Induced Non-Covalent Chirality

Samuel Martínez-Erro,‡ Víctor García-Vázquez,‡ Amparo Sanz-Marco and Belén Martín-Matute*

Org. Lett. **2020**, *22*, 4123-4128

Paper IV

Synthesis of α,γ-Chiral Trifluoromethylated Amines through the Stereospecific Isomerization of α-Chiral Allylic Amines

Víctor García-Vázquez,‡ Pablo Martínez-Pardo,‡ Alexandru Postole and Belén Martín-Matute*

ChemRxiv. Cambridge: Cambridge Open Engage; **2022**; This content is a preprint and has not been peer-reviewed.

DOI: 10.26434/chemrxiv-2022-4dbqm (Preprint)

‡ These authors contributed equally to the publication

Publications not included in this thesis:

Paper V

Unraveling the Mechanism of the Ir^{III}-Catalyzed Regiospecific Synthesis of α-Chlorocarbonyl Compounds from Allylic Alcohols
Man Li, Amparo Sanz-Marco, Samuel Martínez-Erro, Víctor García-Vázquez, Binh Khanh Mai, Jacob Fernández-Gallardo, Fahmi Himo and Belén Martín-Matute*
Chem. Eur. J. **2020**, *26*, 14978-14986.

List of Contributions

Paper I
Contributed equally to Larry Hoteite and Christopher P. Lakeland. Performed the optimization of the reaction conditions. Isolation and characterization of around 80% of the products of the substrate scope. Helped Christopher P. Lakeland with the synthetic transformations. Performed the chiral ligand screening in the enantioselective version of the reaction. Wrote the first draft of the manuscript and supporting information.

Paper II
Contributed equally to Alba Carretero-Cerdán in the experimental part reflected in the article. Amparo Sanz-Marco developed the concept, and together we performed the optimization. I performed the isolation and characterization of around 80% of the substrate scope presented in the thesis. I performed the mechanistic experimental studies, and Alba Carretero-Cerdán performed the computational analysis. I wrote the manuscript and the supporting information, with the exception of the DFT contributions.

Paper III
Contributed equally to Samuel Martinez-Erro. Participated in the synthesis of 60% of the starting materials. Performed around 30% of the substrate scope of the reaction. Performed the KIE studies. Participated in the study of the functionalization of the products. Participated in the writing of the manuscript and the supporting information.

Paper IV
Performed the major part of the optimization of the reaction conditions. Synthesis of the major part of the starting materials. Performed the isolation and characterization of around 90% of the compounds in the substrate scope. Participated in the synthesis of chiral enamide and α-cyano-γ-trifluoromethylated amines. Wrote the manuscript and contributed to the writing of the supporting information.

Previous documents based on this work

This thesis work has been performed at Stockholm University (home university) and at the University of Sheffield (host university) within the multi-partner Marie Skłodowska-Curie actions (MSCA) Innovative Training Network (ITN) European Joint Doctorate (EJD) "Catalytic Methods for Sustainable Synthesis. 'A Merged Experimental and Computational Approach" (CATMEC). Within this program, I aim to obtain a double PhD degree, from Stockholm University, Sweden and from the University of Sheffield, United Kingdom. Therefore, the content of this thesis manuscript will also be presented in the thesis defense (viva) at the University of Sheffield on the March 7th, 2022.

The content of this thesis is partly based on the author's half-time report presented on June 26th, 2020.

The introduction (Chapter 1) has been revised and updated with the current literature to cover the necessary background.

Chapter 2 was included in the half time report as a manuscript in preparation; for this thesis, it has been updated including a most detailed background of the project and taking into consideration the feedback received from the half-time presentation.

Chapter 3 was included in the half-time report as a manuscript in preparation; for this thesis, the background of the project has been changed and updated with recent literature. Moreover, here we present a larger scope and a mechanistic investigation.

Chapter 4 was included in the half-time report as a manuscript submitted; for this thesis, the background of the project has been modified and the application of vinyl chlorides has been studied.

Chapter 5 is entirely new.

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Abbreviations

Abbreviations and acronyms are in agreement with standards in the field.* Common abbreviations in this report and other non-conventional abbreviations are listed below.

Alk	Alkyl
BINAP	(2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl)
c.t.	Chirality transfer
COD	1,5-Cyclooctadiene
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dba	Dibenzylideneacetone
DIB	(Diacetoxyiodo)benzene
DIBAL-H	Diisobutylaluminum hydride
DMF	*N*,*N*-Dimethylformamide
DFT	Density-functional theory
d.r.	Diastereomeric ratio
dba	Dibenzylidene acetone
DAST	Diethylaminosulfur trifluoride
DMF	*N, N*-Dimethylformamide
DPE	1,1-Diphenylethylene
e.r.	Enantiomeric ratio
ee	Enantiomeric excess
EWG	Electron-withdrawing group
HTIB	[Hydroxy(tosyloxy)iodo]benzene
HPLC	High performance liquid chromatography
I.S.	Internal standard
KIE	Kinetic Isotope Effect
L	Ligand
LG	Leaving group
MTBD	7-Methyl-1,5,7-triazabicyclo(4.4.0)dec-5-ene
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
rds	Rate determining step
RT	Room temperature
TBS	*tert*-Butyldimethylsilyl
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TBAI	Tetra-*N*-butylammonium iodide
TBHP	*tert*-butylhydroperoxide

n-Pr	*n*-Propyl
$P_4{}^tBu$	(1-tert-Butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylidenamino]-2λ5,4λ5-catenadi(phosphazene)).
NMR	Nuclear magnetic resonance
n.d.	Not determined
S_N1	Unimolecular nucleophilic substitution
S_N2	Bimolecular nucleophilic substitution

*: Petronella, K.M. Abbreviations List, The ACS Guide to Scholarly Communication. 2020 (DOI: 10.1021/acsguide.50308)

Table of Contents

1. Introduction

1.1 Organic synthesis and drug discovery

The design and synthesis of novel organic molecules is of utmost importance for our society. Therefore, the development of synthetic methods to access these compounds constitutes a major field of research, where catalysis has played a pivotal role. Outstanding catalytic examples for the construction of C-C and C-heteroatom bonds include cross-coupling reactions,[1] C–H activations,[2] and metathesis reactions,[3] to name a few. These methods have been applied for the synthesis of chiral compounds (i.e. enantioselective catalysis).[4] New synthetic methods to access molecules bearing unprotected polar groups, such as amines or heterocycles,[5] or for the synthesis of fluorinated compounds in a selective manner[6] are still needed, to enable access to new drugs and other molecules with important activity (Figure 1).[7]

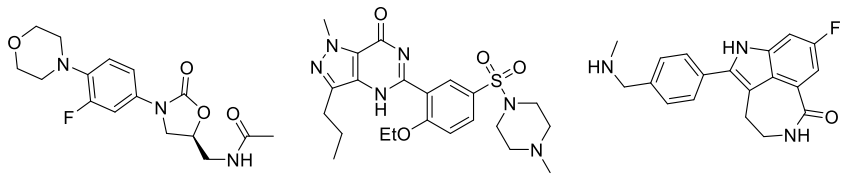


Figure 1. Representative synthetically challenging drug molecules containing nitrogen and fluorine atoms.

The concept of "Green Chemistry" was defined by Anastas and Warner as the development and application of chemical processes with the aim of reducing the use or generation of hazardous substances.[8, 9] They reported this definition together with twelve principles to be considered when sustainable synthetic applications are designed.[8, 9] In this work, we have considered these principles in the design and development of the new synthetic methods. Optimization has been done towards a minimum catalyst loadings, and the metal catalysts have been replaced by organocatalysts when possible. Atom-economy and the use of renewable feedstocks have been also considered in the work.

1.2 Catalysis

1.2.1 Catalysis in organic chemistry

As mentioned above, the development of more efficient and less environmentally hazardous methodologies for the synthesis of organic molecules has become a great challenge in organic chemistry. In this sense, catalysis plays a crucial role to reduce the amount of by-products formed

during chemical reactions, minimizing the reaction time and energy demand, while keeping an excellent selectivity.[10]

The activation energy is the energy required for a reaction to proceed. A catalyst is a substance that increases the rate of the reaction without modifying the standard Gibbs free energy (ΔG^0).[11] Catalysis can occur by diminishing the activation energy of the process, or by completely changing the reaction pathway through less energetically demanding intermediates (Figure 2). Catalysts are not modified over the reaction pathway and, as a result, they can be used in substoichiometric amounts.

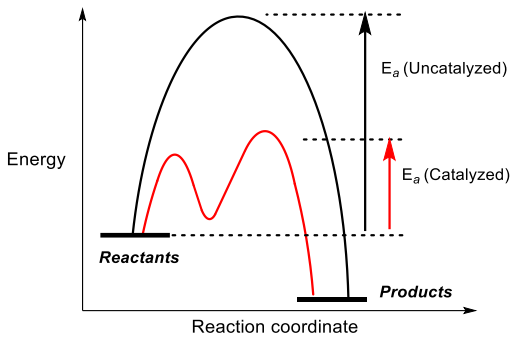


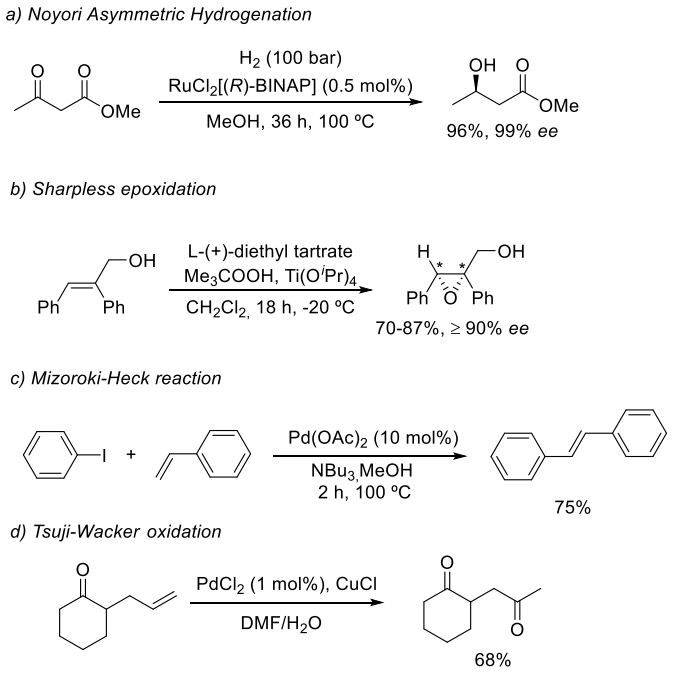
Figure 2. Energy profiles of uncatalyzed (black) and catalyzed (red) reactions.

Transition-metal catalysts have been extensively used in organic synthesis. Their ability to handle different oxidation states favors the coordination of the reagents and enables a wide number of possible catalytic cycles.[12] This results in new reaction pathways with lower activation energy and higher efficiency comparing to the uncatalyzed one. As a complement to transition-metal catalysis, organocatalysis has emerged as a powerful tool.[13] It consists in the use of small organic molecules to increase the rate of chemical reactions.[14] In parallel, catalysts can be classified as homogeneous or heterogeneous depending on the phase where it is possible to find the catalyst, reagents and products. Due to the ease of modification of organometallic compounds, a more rational design of homogeneous catalysts can be done in comparison to heterogeneous catalysis. However, their separation from the products or reactants of the reaction is difficult, making the recyclability of the catalyst highly inefficient and resulting in an unavoidable contamination of the products. Nevertheless, recent advances in the area of heterogeneous catalysis has resulted in catalytic systems being able to surpass the activity and/or selectivity of homogeneous counterparts.[15, 16] This has been done, to a large extent, due to advances in synthetic techniques allowing a controlled incorporation of the catalytic species on the solid phase.[17, 18] Furthermore, the

possibility to study the heterogeneous catalytic process *in operando*, enables understanding of their mode of action and thus contributes to develop improved versions.[19, 20] One of the main advantages of heterogeneous catalyst is the ease of recyclability, which enhances the sustainability of the process.[21]

1.2.2 Transition-metal catalysis and organocatalysis

The production of many of the commercialized chemicals rely on methods involving at least one catalytic step.[22] Transition-metal catalysts have become the most studied since the development of the Haber-Bosch process for the synthesis of ammonia from N_2 and H_2. This catalytic process enabled the synthesis of ammonia on a large scale, leading to an increment of the manufacture of fertilizers and a huge expansion of the human population.[23] Among other relevant examples we can find: Noyori´s asymmetric reduction of ketones (Scheme 1a);[24] Sharpless's asymmetric epoxidation of allylic alcohols promoted by titanium (Scheme 1b);[25] Pd-catalyzed coupling reactions, such as the Mizoroki-Heck reaction (Scheme 1c);[26, 27] or the Tsuji-Wacker's oxidation of olefins to carbonyl compounds (Scheme 1d).[28]

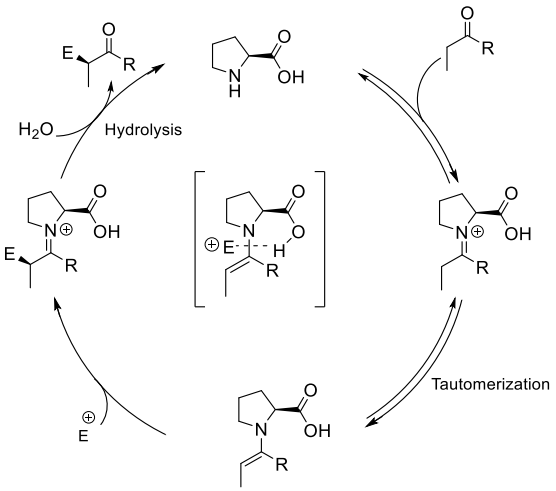


Scheme 1. Relevant examples of transition-metal catalyzed reactions.

The use of organocatalysts was firstly documented in the early 70s by Hajos and Parrish by using L-proline to mediate an asymmetric aldol condensation reaction.[29] Years later, two remarkable reports appeared simultaneously by the groups of List and MacMillan, one in the field of enamine catalysis,[30] and another in imine catalysis.[31] The field has evolved enormously since then.[32, 33]

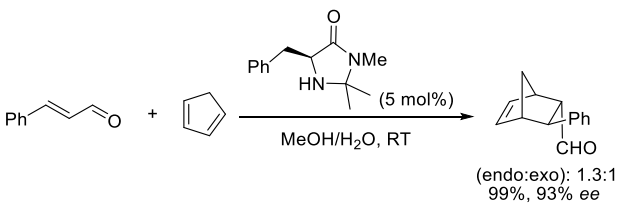
In the year 2021, the Nobel committee awarded the Nobel Prize to Benjamin List and David MacMillan for the development of asymmetric organocatalysis.

In enamine catalysis, an amine catalyst typically reacts with a ketone or an aldehyde, forming the enamine intermediate that interacts with an electrophilic partner, through hydrogen bonding or electrostatic interaction. Importantly, this might be used to get α-functionalized carbonyl compounds in an enantioselective way by using proline as catalyst (Scheme 2).[34]



Scheme 2. General mechanism for the proline enamine catalysis.

In the case of iminium catalysis, a secondary amine catalyst reacts with aldehydes resulting in the formation of the iminium intermediate that is highly activated towards nucleophilic attack. This reactivity is similar to the traditional Lewis acid catalysis where the lowest-unoccupied molecular orbital (LUMO) is activated. As in the case of enamine catalysis, chiral amine catalysts have been used to induce enantioselectivity (Scheme 3).[35]



Scheme 3. Organocatalyzed enantioselective Diels-Alder reaction.[31]

Hydrogen-bonding catalysis relies on the use of hydrogen bond interactions for the activation or stabilization of different key intermediates, electrophiles

or direct protonation with Brønsted acids.[36] N-Heterocyclic carbenes (NHCs) can be also used as organocatalysts in C–C, C–O and C–N bond formation reactions under mild conditions.[37] Another type of organocatalysis is phase transfer catalysis. Here, charged organic molecules are used as catalyst in reactions using two immiscible solvents.[38] More recently, Brønsted bases have been used as efficient organocatalysts for the activation of nucleophiles in asymmetric C–C and C–X bond formation reactions.[39]

Despite of the different activation modes, most of the organocatalytic reactions frequently involve the formation of ionic intermediates, also known as ion pairs. The design of cooperative ion pairs that can enhance the chemical efficiency or the selectivity of a certain reaction acting as precatalysts, catalysts or intermediates, has been defined as ion pairing organocatalysis.[40]

1.2.3 Cooperative ion pair organocatalysis

An ion pair has been defined as any unit formed by cationic and anionic species close in the space by Coulombic interactions.[41] However, in ion pairing catalysis both ions must participate in a cooperative process.[40] One of the first examples of these interactions in organocatalysis was reported by Wynberg and co-workers using chiral quaternary ammonium salts as catalysts in an enantioselective Michael addition reaction.[42] In this particular case, the ammonium salt enhances the reactivity of nucleophilic species and controls the enantioselectivity of the reaction, whereas the fluoride counteranion was demonstrated to play a crucial role as Brønsted base.

Charged organocatalysts such as quaternary ammonium salts or phosphonium salts have been widely studied in asymmetric ion-pairing catalysis. In those processes, the anion usually acts as the main activator of the reaction serving as Lewis/Brønsted base whereas the presence of the cation is responsible for the enantioselectivity (Figure 3a).[43-47] Another mode of action in ion-pairing catalysis relies on the cation playing the main role in the catalytic pathway. In most cases, this activation occurs through a complexation with pronucleophiles, resulting in stereoselective events by steric difference, or as electrophile shuttle (Figure 3b).[48-54] Neutral hydrogen bond donors such as chiral thioureas or squaramides have been also used as catalysts in ion-pairing catalysis. By taking advantage of their strong binding ability to anion intermediates, those catalysts play a main role in the enantioselective addition of nucleophiles to highly electrophilic moieties (Figure 3c).[55-57] More recently, the design of bifunctional ion pair catalysts has allowed the combination of those activation mechanisms enabling previously unexplored transformations.[58-62]

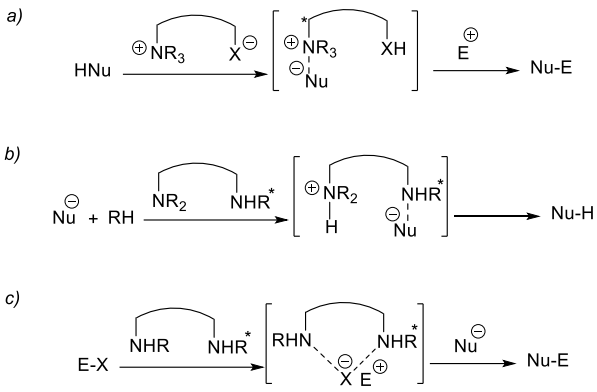


Figure 3. Examples of mode of actions in ion-pairing catalysis. a) Anion acting as Brønsted base. b) Cation acting in electrophile shuttle. c) Anion binding by hydrogen donors.

The group of Maruoka reported a enantioselective michael addition of silyl nitronates to unsaturated aldehydes catalyzed by a chiral ammonium bifluoride salt where the bifluoride anion acts as a Lewis base activator for the silyl nitronate, whereas the cationc ammonium salt is responsible for the high levels of enantioselectivity observed (**Figure 4**).[63]

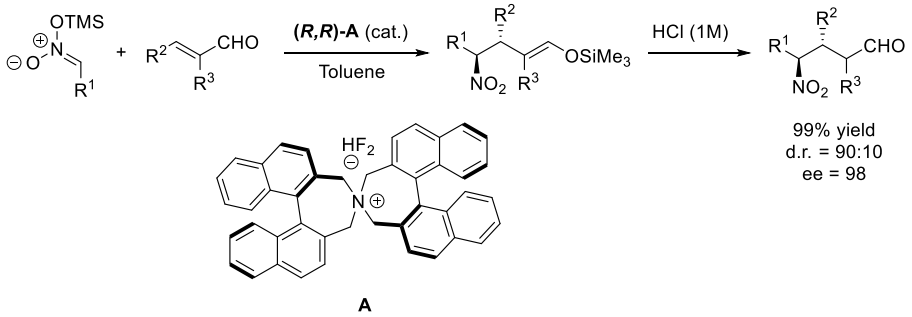


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Figure 4. Enantioselective michael addition of silyl nitronates to unsaturated aldehydes.[63]

More scarce are the examples where the anion acts as a Brønsted base. Tetraaminophosphonium salts have been used by the group of Ooi for the enantioselective conjugate addition of acyl anions to unsaturated ester surrogates. (**Figure 5**).[64]

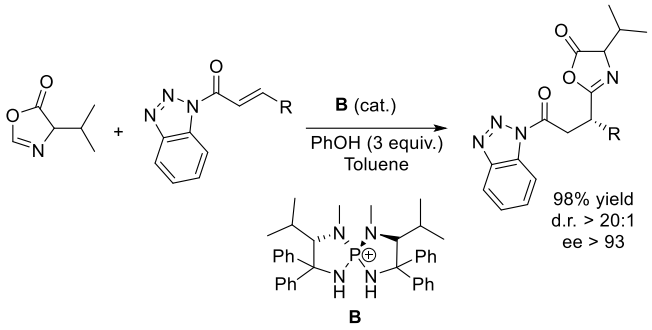


Figure 5. Enantioselective addition Michael addition to unsaturated ester surrogates catalyzed by tetraaminophosphonium salts.[64]

The catalytic processes where the cation is the main activator of the reaction is much less developed, and the role of the cation is less clear. A particular case where the cation acted as a proton shuttle was reported by Yamamoto and coworkers.[48] In this case, chiral *N*-trifyl sulfophosphoramides are used as catalyst in the presence of stoichiometric amounts of phenol (**Figure 6**).

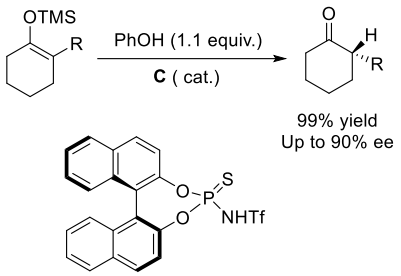


Figure 6. Enantioselective protonation of silyl enol ethers using phenol as proton shuttle.[48]

In this case, two possible mechanisms are proposed. The catalyst can directly protonate the silyl enol ether whereas the phenol assists the desilylation process or forms a little amount of a chiral anion of the catalyst that delivers the proton in an enantioselective manner.

More recently, anion-binding catalysis has arisen as an efficient manner for the enantioselective catalysis of processes controlled by anion species. This approach relies on the binding ability of hydrogen bond catalysts with unreactive anionic counterparts of the highly reactive cations in organic transformations. The group of Jacobsen have reported several examples of this strategy using thioureas or squaramide catalysts with outstanding levels of enantioselectivity.[65]

A particularly relevant example was reported by his group in 2018 when the first enantioselective S_N1 type reaction was catalyzed by a squaramide catalyst (**Figure 7**).[57] Extensive mechanistic investigations proved that the transformation followed the formation of a carbocation which is stabilized by the presence of a triflate anion in the proximity of the squaramide catalyst due to the formation of hidrogen-bonding interactions.

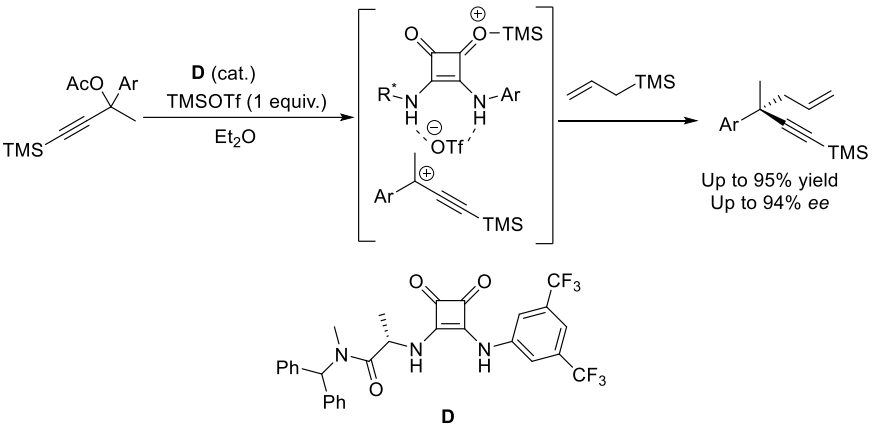


Figure 7. Enantioselective S_N1 type reaction catalyzed by squaramide D.

1.3 Allylic compounds

1.3.1 Relevance, structure and general reactivity

An allylic group is defined as an olefin bonded to a saturated carbon attached to a functional group or a carbon chain, giving to the molecule an interesting combination of structure and reactivity features. The olefin activates the functional group, making it susceptible to substitution reactions. Rearrangements are common among allylic substrates. For example, the Mislow-Evans rearrangement of allylic sulfoxides or the Ireland-Claisen rearrangement of allylic carboxylates have been used for the synthesis of complex molecules.[66, 67]

Allylic functionalities are present in a large number of natural and pharmaceutical compounds. Isopropenylpyrophosphate (Figure 4a) is an important intermediate in the biosynthesis of terpenes. Naloxone (Figure 4b), a drug used in intoxication by opioids, consists of an allylic amine in its structure, and several terpenes such as Nerol (Figure 4c), display allylic alcohols.

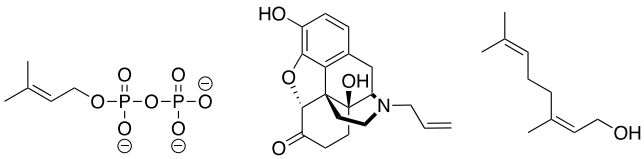
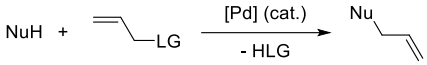


Figure 8. Relevant examples of natural and pharmaceutical compounds bearing allylic functionalities.

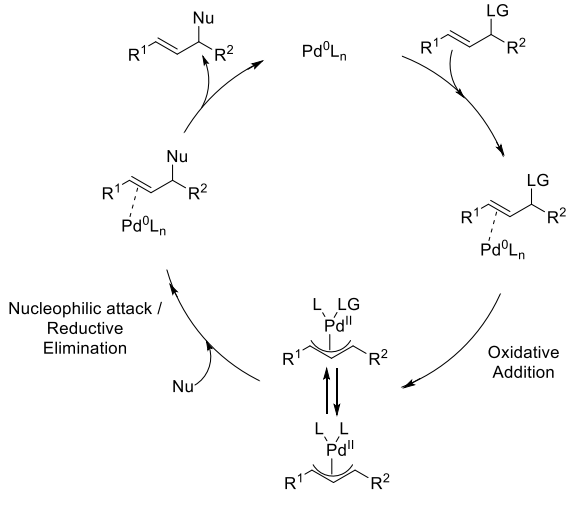
1.3.2 Transition metal-catalyzed allylic substitutions

Allylic substitutions occur upon reaction of an allylic system bearing a leaving group (LG), a metal catalyst and a nucleophile, resulting in formation of a new allylic compound (Scheme 4). This reaction is commonly known as the Tsuji-Trost reaction.[68, 69]



Scheme 4. General scheme of Pd-catalyzed allylic substitution reactions.

Mechanistically, the reaction starts with palladium(0) species and, after an oxidative addition step of the allylic system to palladium(0), an η^3-π-allyl palladium(II) complex is formed. Depending on the nature of the nucleophile, the bond-forming step takes places intramolecularly or intermolecularly. In the latter case, the nucleophilic attack takes place over the allylic carbon directly, with concomitant reduction of palladium (Figure 9a). The new allylic product is formed upon decoordination of the palladium(0) complex. If the nucleophile first coordinates to the Pd center, the cycle is then closed *via* a reductive elimination step, delivering the final product and regenerating palladium(0) (Figure 9b).[70]



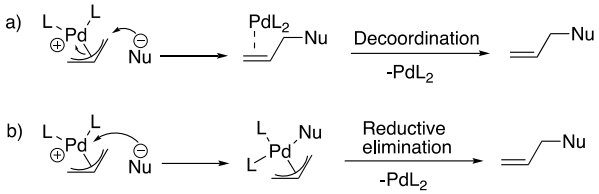


Figure 9. General mechanistic pathways for the nucleophilic attack in the Tsuji-Trost reaction.

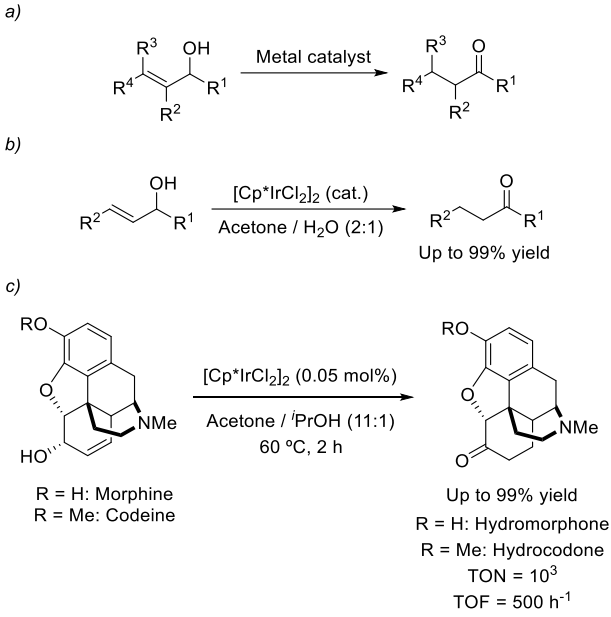
Chiral ligands bearing phosphorous, nitrogen and sulfur, or any combination of these atoms, have been widely used in allylic substitution reactions. This is due to their tunability, enabling the modification of their electronic and steric properties to result in high levels of enantioselectivity.[71, 72] Allylic substitution reactions have been focused on Pd catalysts due to the readily availability of compatible substrates and chiral ligands. However, other metals have also shown outstanding levels of regio- and enantioselectivity. In particular, Ir catalysts have their own unique features. For example, the use of chiral phosphoramidite ligands in the Ir-catalyzed allylic substitution reactions has resulted in a remarkable advance of this area of research.[73-75] Other metals such as Ni, Pt or Mo have been used for allylic substitution reactions with outstanding efficiency.[76]

1.3.3 Isomerization of allylic substrates

1.3.3.1 Transition-metal-catalyzed isomerization of allylic substrates

The thermal isomerization of the alkene in an allylic system is symmetrically allowed in accordance with the Woodward-Hoffmann rules as antarafacial [1,3]-sigmatropic hydrogen shift. However, it cannot take place without the action of a catalyst due to steric reasons.[77]

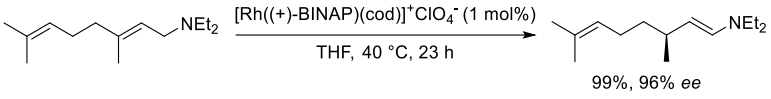
A relevant example is the direct isomerization of allylic alcohols into carbonyl compounds (Scheme 5a). In contrast to the traditional two-step oxidation / reduction (or *vice versa*) sequence, the direct catalyzed isomerization is an internal redox process that occurs with only the use of the catalyst. As such, stoichiometric oxidants and reductants are not needed, resulting in a highly atom-economic transformation.[78] Early reports for this transformation used $Fe(CO)_5$ as catalyst.[79] However, the slow reaction rates, narrow scope and low yields and selectivities limited its applicability. Since then, a number of new transition-metal catalysts able to enhance the efficiency of the reaction have been reported.[78, 80-82] Our group has contributed with the isomerization of primary and secondary allylic alcohols using a commercially available iridium(III) complex under very mild conditions in aqueous solvents (Scheme 5b).[83, 84] This protocol has been applied to the synthesis of pharmaceutically relevant organic compounds (Scheme 5c).[83]



Scheme 5. Metal-catalyzed isomerization of allylic alcohols.[83]

Allylic ethers and amines can also be isomerized using transition-metal catalysts. In those cases, one of the parameters that determines the efficiency of the catalyst is the selectivity of the new double bond.[85-90]

Asymmetric protocols for the isomerization of allylic alcohols, ethers and amines have been reported in the last decades. Starting from achiral allylic systems, and using chiral transition-metal complexes as catalysts, chiral vinyl products can be synthesized through a stereoselective reaction (Scheme 6).[80, 89, 90]



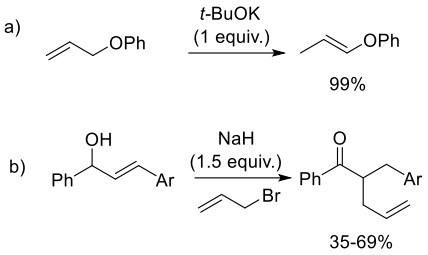
Scheme 6. Enantioselective Rh-catalyzed isomerization of allylic amines.[88]

An alternative approach to obtain enantiomerically enriched products from allylic systems is through stereospecific isomerization reactions. Starting from enantiopure starting materials, the catalyst is able to mediate the reaction with a concomitant transfer of chirality.[91-96]

1.3.3.2 Transition-metal-free isomerization of allylic substrates

Brønsted bases have been used in metal-free protocols for the isomerization of allylic substrates. Although the first example dates from 1928,[97] reports of this type of processes are very rare in the literature and usually require

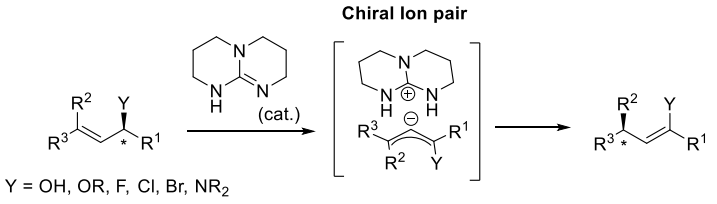
stoichiometric amounts of strong bases, resulting in a limited substrate scope due to poor functional group compatibility (Scheme 7).[98-101]



Scheme 7. Examples of base-promoted isomerization of allylic ethers and alcohols.[99, 101]

Only a few examples of a catalytic version of the reaction can be found in the literature. The group of Snyder reported an early example of isomerization of allylic amines using catalytic amounts of base for the transformation, although only tertiary amines yielded the desired enamine products.[102] A combination of phenanthroline and *t*-BuONa as catalyst was reported for the isomerization of allylic alcohols and amines through the formation of radical anions by the group of Tang.[103] Organic bases as DABCO have also been used for the transformation of primary allylic alcohols to the corresponding aldehydes.[104]

In 2016, the Martín-Matute group contributed significantly to the field by reporting the use of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as catalyst for the isomerization of allylic alcohols and ethers.[94] Importantly, when chiral allylic substrates were examined in the transformation, the chirality was transferred to the final product due to the formation of a chiral ion-pair intermediate resulting in a stereospecific isomerization (Scheme 8). Recently, we have applied this protocol to other allylic substrates such as allylic halides and allylic amines (Chapters IV and V).[95, 96]



Scheme 8. Base-catalyzed stereospecific isomerization of allylic substrates through the formation of chiral ion pairs.[94-96]

A similar protocol has been recently reported by the group of He.[105, 106] A combination of an asymmetric Ir-catalyzed allylic substitution reaction of allylic carbonates and amides or phenols with a DBU-mediated stereospecific

isomerization resulted in the synthesis of axially chiral substrates with excellent enantioselectivities and chirality transfer levels.

1.4 CO_2 fixation

1.4.1 CO_2 as a renewable source for chemical feedstock

Since the industrial revolution, the amount of CO_2 emissions has increased causing the rise of atmospheric temperature and climate changes. This is largely due to the combustion of fossil fuels as resource for the world energy demand.[107] The high abundance, non-toxicity and recyclability of CO_2 offers the possibility of using it as a one-carbon synthon for organic synthesis. Still, the thermodynamic stability of CO_2 makes its activation problematic and, as a consequence, the use of highly reactive substrates or harsh conditions is required for the use of CO_2 as a reagent in organic synthesis, limiting the applicability of the reported methodologies.[108, 109]

1.4.2 CO_2 in organic synthesis

Despite the thermodynamical stability of CO_2, its reactivity has been broadly explored over the last century.[109] CO_2 can react with highly electrophilic partners such as aziridines and epoxides in the presence of Lewis acid catalysts, leading to cyclic carbonates and carbamates.[108] The reaction of CO_2 with strong nucleophiles, such as organolithium and Grignard reagents results in the synthesis of carboxylic acids and derivatives with high efficiency.[110] Importantly, the number of transition-metal-catalyzed or organocatalyzed protocols for the use of carbon dioxide as building block has increased considerably over the last decade, giving access to a very broad variety of organic compounds accessible from CO_2 (Figure 10).[109, 111, 112]

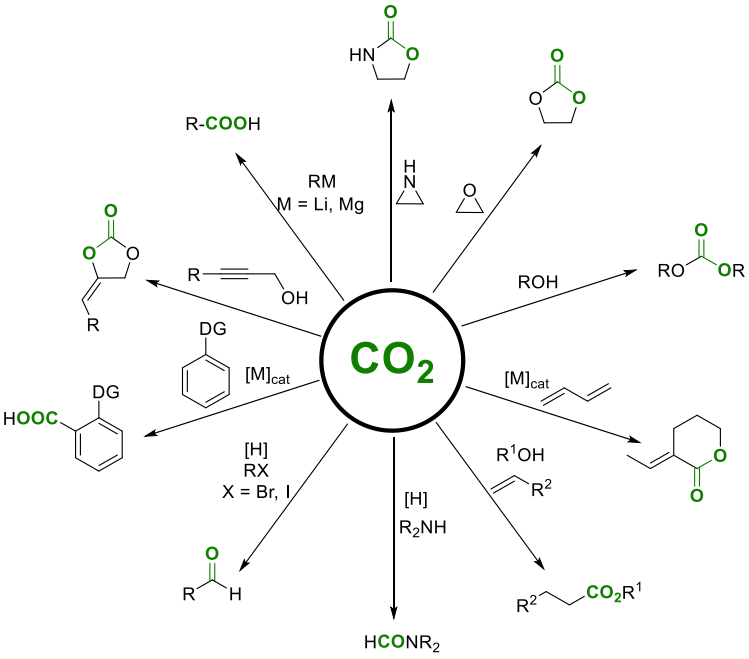
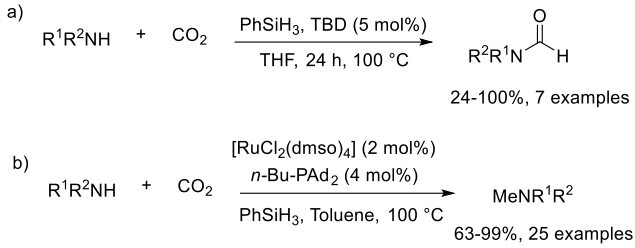


Figure 10. Relevant examples of organic reactions using CO_2 as building block.[109]

Among the different options for CO_2 valorization, the synthesis of cyclic carbonates and polycarbonates should be highlighted. Indeed, a large number of catalytic systems have been studied for this transformation, leading to its industrial application.[113, 114] While most of the works in the field require the use of high CO_2 pressure, the group of North reported the synthesis of cyclic carbonates using bimetallic aluminium(III) complexes at temperatures as low as 25 °C and under 1 bar of pressure.[115] The Martín-Matute group has recently contributed to this field using different heterogeneous catalysts.[116] In 2015, the group of Kleij reported an organocatalytic method for the synthesis of cyclic carbonates from oxiranes using tannic acid as catalyst in the presence of a halide salt that assists in the epoxide opening.[117]

Another important example in the use of CO_2 as a C_1 building block is the catalytic formylation or methylation of amines. In these cases, the coordination of amines to CO_2 promotes the C–N bond formation in a carbamate or urethane intermediate that facilitates the reduction. Cantat and co-workers reported an organocatalytic synthesis of formamides using TBD as the catalyst (Scheme 9a).[118] Ru complexes in combination with phosphine ligands have also been reported as efficient catalysts for *N*-methylation in the reductive coupling of CO_2 with both aliphatic and aromatic amines (Scheme 9b).[119]



Scheme 9. Catalytic reductive reactions of amines with CO_2.[118, 119]

The highly reactive organolithium and Grignard reagents react directly with CO_2 affording carboxylic acids.[110, 120] For less reactive carbon nucleophiles, such as C–B, C–halide or C–H, different metal catalysts based on Pd, Co, Ni, Ag and Cu have been used for their reactions with CO_2.[111]

Organic carbamates are widely used in agriculture, pharmaceuticals or for the synthesis of polyurethanes. However, the synthesis of carbamates relies on highly toxic and corrosive reagents or high-energy consuming processes, leading to the formation of more atmospheric CO_2, making the process inefficient. During the last decades, several groups have synthesized carbamates from CO_2. Importantly, metal-free protocols that use organic bases to enhance the reactivity of CO_2 have been recently reported.[121]

1.5 Hypervalent iodine(III) reagents

1.5.1 Structure and reactivity of hypervalent iodine compounds

The ability of an atom to exceed the number of valence electrons beyond the limits of the Lewis octet rules is known as hypervalency.[11] Hypervalency can occur among the compounds for the second and subsequent elements in groups 15-18 in the periodic table. In particular, hypervalent iodine compounds have been extensively studied in organic transformations. Common structures of hypervalent iodine reagents include I^{III}, I^{V} and I^{VII} compounds and have been employed as oxidants in several transformations.[122-124] Hypervalency of iodine have been explained by a molecular orbital description involving a three-center-four-electron bond (3c-4e, Figure 11). According to this description, in a L-I-L bond, one pair of bonding electrons are delocalized within the two ligands and, as a consequence, the central iodine atom is described with a partial positive charge while the ligands accumulate a partial negative charge.

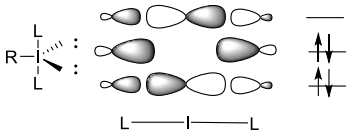


Figure 11. Molecular orbital description of a 3-center-4-electron bond in I^{III} molecules.

The reactivity of hypervalent iodine(III) reagents can be explained as a result of the 3c-4e bond. Because of the partial positive charge centered in the iodine atom, it reacts as an excellent electrophile. Nucleophiles react displacing one of the ligands and after an elimination step, the desired products are formed together with a reduced iodine(I) species. This can occur through a reductive elimination pathway or as a concerted coupling of the two ligands (Figure 12).[125]

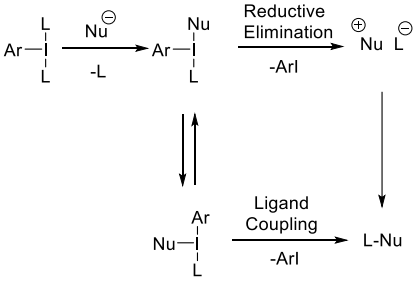


Figure 12. Description of reactivity of nucleophiles with hypervalent iodine(III) reagents.[125]

By taking advantage of this reactivity, it is possible to couple carbon nucleophiles with several functional groups such as halides,[126, 127] trifluoromethyl,[128] or oxygen- and nitrogen-containing molecules.[122, 129, 130] through the formation of enolonium intermediates. Importantly, inherent nucleophilic groups such as enol derivatives can react with other nucleophiles mediated by hypervalent iodine (III) reagents in an umpolung S_N2-type reaction. [126, 130-133] This type of reactivity has been recently defined as cross-coupling of nucleophiles and has been applied for the reaction of silyl enol ethers, ketones or dicarbonyl compounds with a large number of nucleophilic partners.[134]

1.6 Aim of this thesis

The aim of this thesis is to develop new organic transformations from allylic compounds and from enol derivatives mediated by transition-metal catalysts and by organocatalysts. The methods reported in this thesis complement and overcome some of the limitations of previously reported transformations. In particular, the focus is to have access to organic compounds bearing highly polar functional groups, including fluorinated

moieties. These compounds may serve for the synthesis of biologically active compounds.

3-Fluoropiperidines can be obtained following direct fluorination protocols or different metal-catalyzed processes such as reduction of fluorinated pyridines or aminofluorination. However, these protocols rely on stoichiometric amounts of toxic or expensive reagents. The first part of this work aims to develop a catalytic method for the synthesis of 3-fluoropiperidines under very mild conditions.

The synthesis of α-carbamoyl carbonyl compounds from CO_2 requires the use of high pressure of CO_2 and high temperatures. Moreover, only electrophilic partners have been reported for this transformation. In the third chapter, we aim to couple CO_2 with nucleophiles under very mild conditions using hypervalent iodine(III) reagents to mediate an umpolung transformation.

Stereospecific methodologies have been reported for the isomerization of allylic alcohols and ethers. However, other chiral allylic substrates such as halides or amines have not been isomerized with chirality transfer. In the last part of the thesis, our goal is to develop seminal protocols for the base-catalyzed stereospecific isomerization of allylic halides and amines using TBD as catalyst. Moreover, we aim to prove the synthetic utility of the methodology synthesizing highly valuable organic compounds from the isomerized chiral vinyl derivatives.

2. Synthesis of 3-fluoropiperidines through a Pd-catalyzed allylic substitution (Paper I)

2.1 Background of the project

3-Fluoropiperidines have been shown to improve the pharmacological properties of a number of biologically active compounds.[135-138] However, the amount of approaches for the synthesis of 3-fluoropiperidine scaffolds are scarce.[139-145] For example, direct fluorination of piperidone enol derivatives or deoxofluorination of alkoxypiperidine protocols have been recently reported (Figure 13a and b), but these reactions rely on the use of stoichiometric amounts of fluorinating reagents that decrease the atom economy of the process, moreover, high prefunctionalization is required to obtain the starting materials.[139-141] The intramolecular aminofluorination of olefins has arisen as a prevalent strategy for the synthesis of 3-fluoropiperidines using Pd catalysts or hypervalent iodine reagent to promote the reaction (Figure 13c). These strategies usually require the use of strong oxidizing agents in stoichiometric amounts.[142-144] More recently, the group of Glorius provided a diastereoselective method for the direct hydrogenation of fluoropyridines using Rh catalysis and yielding the desired 3-fluoropiperidines in high yield and diastereoselectivity (Figure 13d) although the use of high pressure of H_2 limits the operational simplicity.[145]

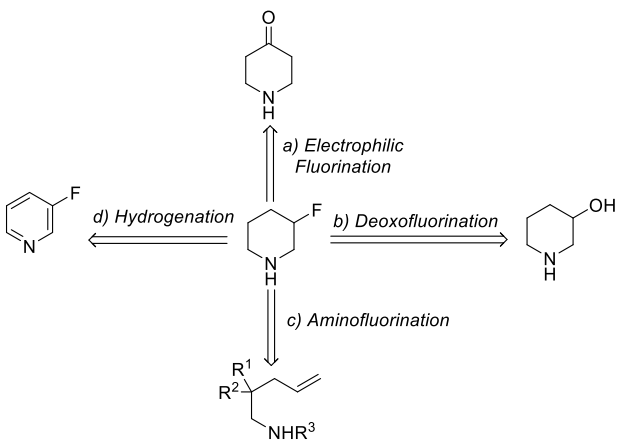
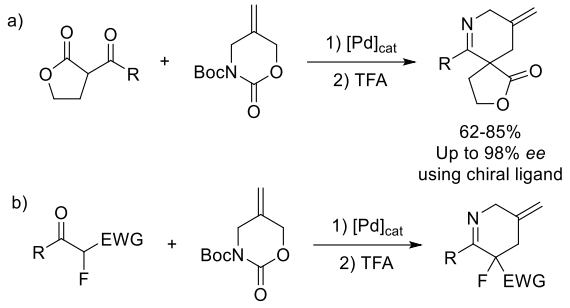


Figure 13. Synthetic routes to access 3-fluoropiperidines.

In 2016, the group of Harrity reported formal [4+2] annulation protocol for the synthesis of highly functionalized piperidines (Scheme 10a).[146] This strategy consisted in a Pd-catalyzed allylation/condensation sequence that led to the formation of piperidine imine scaffolds, which can be easily reduced to the desired highly functionalized piperidines in a diastereoselective manner.

Now, we envisioned the application of this protocol to the synthesis of 3-fluoropiperidines from readily available α-fluoro-β-ketoesters (Scheme 10b).

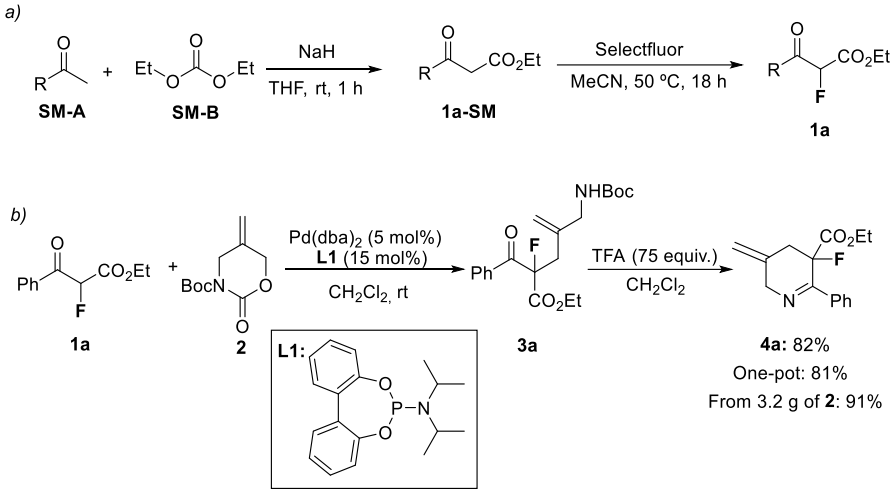


Scheme 10. a) Pd-catalyzed synthesis of quaternary substituted piperidine scaffolds. b) Our approach for the synthesis of 3-fluoropiperidines.[146]

2.2 Results and discussion

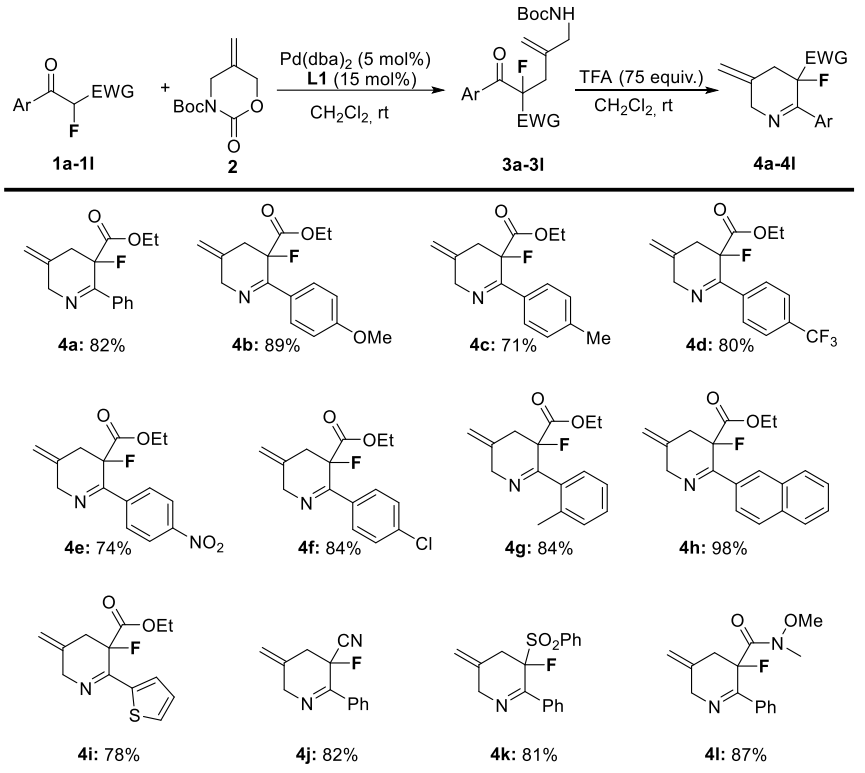
First, we synthesized a number of α-fluoro-β-ketoesters **1** from ketones and diethylcarbonate using Selectfluor as electrophilic fluorinating agent (Scheme 11a).

After slight modifications of the previously reported conditions for the Pd-catalyzed synthesis of piperidines, we found that α-fluoro-β-ketoester **1a** was successfully allylated by using carbamate **2** (2 equiv.), catalytic amounts of $Pd(dba)_2$ and the phosphoramidite ligand **L1** at room temperature. Phosphoramidite ligands have been notably reported to improve the efficiency of the catalytic system in Pd-catalyzed allylic substitution reactions.[147, 148] After treatment of intermediate **3a** with TFA, 3-fluoropiperidine imine **4a** was obtained in 82% yield. A similar yield was obtained following a one-pot procedure without isolation of intermediate **3a**. Notably, we were able to scale up the reaction to multigram quantities with excellent yield of the desired 3-fluoropiperidine imine scaffold (Scheme 11b).



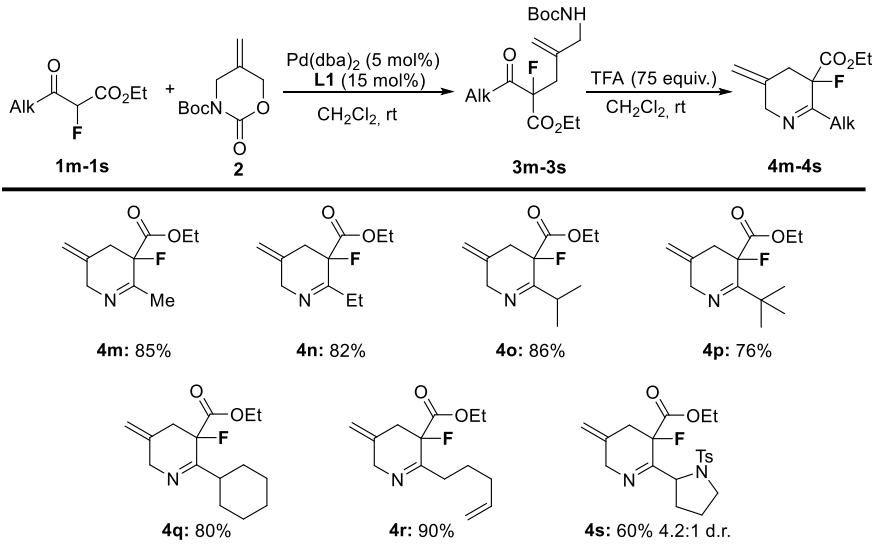
Scheme 11. a) Synthesis of starting materials **1**. b) Synthesis of 3-fluoropiperidine imine **4a** through Pd-catalyzed allylation.

With this efficient protocol in our hands, we evaluated the scope of the reaction by applying our optimized reaction conditions to a number of aryl substituted α-fluoro-β-ketoesters (Scheme 12). Electron-donating and electron-withdrawing groups at the *para* position of the aryl group were well tolerated and the piperidine imine derivatives were isolated in excellent yields in all the cases (**4b**-**4e**). Halide substituents gave also excellent results under our reaction conditions and *para*-chloro substituted **4f** was obtained in 84% isolated yield over two steps. Other substitution patterns at the aryl substituent of α-fluoro-β-ketoesters such as *ortho*-methyl substituted **1g** or naphtyl derivative **1h** yielded the desired products with high efficiency. Thiophenyl piperidine imine **4i** could also be isolated in good yield under our allylation/condensation conditions. Importantly, this protocol is not only limited to α-fluoro-β-ketoesters but other fluorinated compounds bearing different electron-withdrawing groups reacted smoothly. Therefore, cyano substituted piperidine imine **4j** was obtained in high yield. Sulphonyl derivative **4k** and the Weinreb amide substituted **4l** were also isolated in high yields, proving the high functional group compatibility of our synthetic methodology.



Scheme 12. Scope of Pd-catalyzed synthesis of 2-aryl-3-fluoropiperidine imines. Reaction conditions: **1** (0.3 mmol, 1.5 equiv.), **2** (0.2 mmol), $Pd(dba)_2$ (0.01 mmol, 5 mol %), **L1** (0.03 mmol, 15 mol %), CH_2Cl_2 (0.1 M), rt, 18 h under N_2 atmosphere. Isolated yields after two steps.

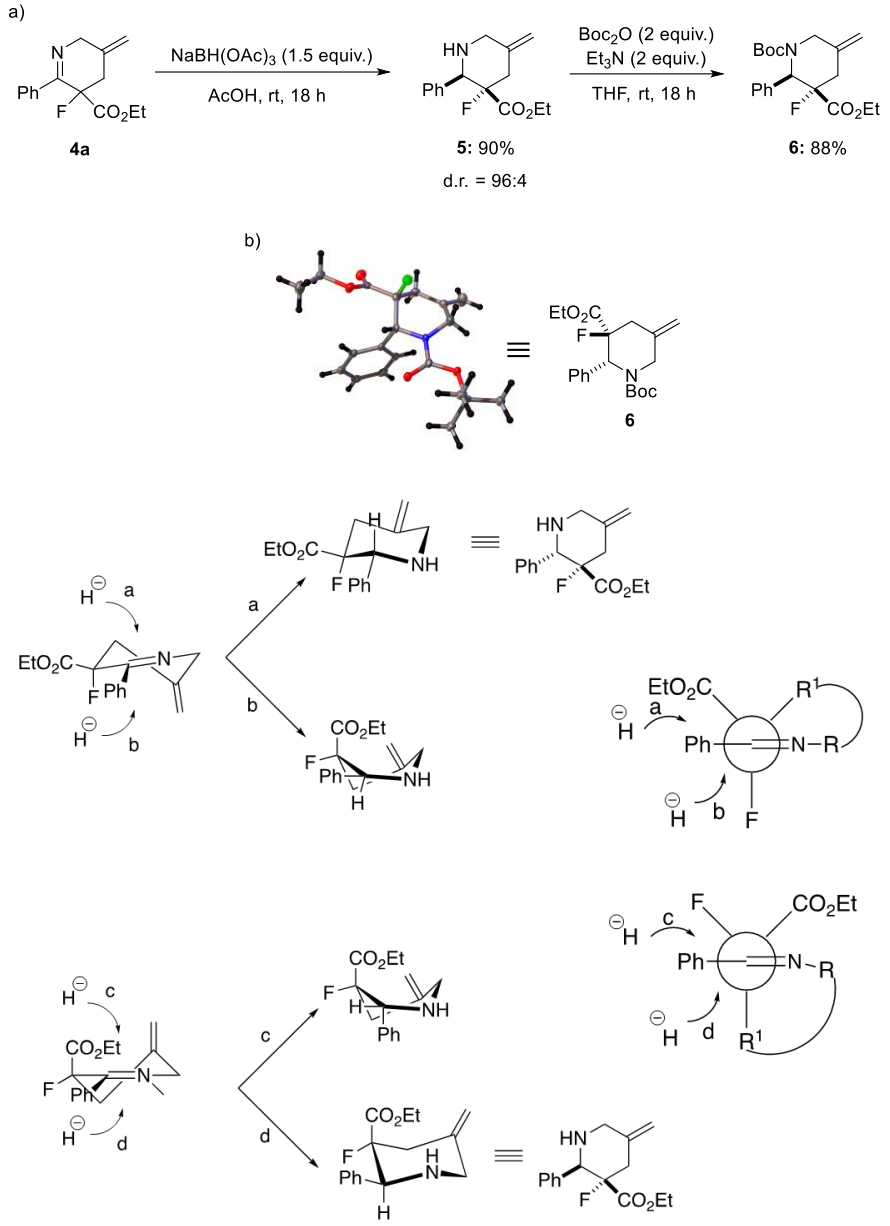
Remarkably, this method could be also applied to alkyl substituted α-fluoro-β-ketoesters with different degrees of substitution (1º, 2º and 3º) in a regioselective manner (Scheme 13) . Substrates bearing alkyl groups such as methyl, ethyl, isopropyl and *tert*-butyl afforded 3-fluoropiperidines **4m**-**4r** in excellent yields. In all the cases, the allylation occurred selectively at the most acidic position. Cyclohexyl derivative **4q** was obtained with high efficiency and alkyl chains bearing other functional groups such as alkenes were well tolerated, yielding the desired product in 90% yield (**4r**). The L-proline substituted α-fluoro-β-ketoester **1s** was evaluated under the reaction conditions, obtaining compound **4s** in good yield and with moderate diastereoselectivity (4.2:1).



Scheme 13. Scope of Pd-catalyzed synthesis of 2-alkyl-3-fluoropiperidine imines. Reaction conditions: **1** (0.3 mmol, 1.5 equiv.), **2** (0.2 mmol), $Pd(dba)_2$ (0.01 mmol, 5 mol %), **L1** (0.03 mmol, 15 mol %), CH_2Cl_2 (0.1 M), rt, 18 h under N_2 atmosphere. Isolated yields after two steps.

2.3. Chemo- and diastereoselective functionalization of 3-fluoropiperidine imine scaffolds

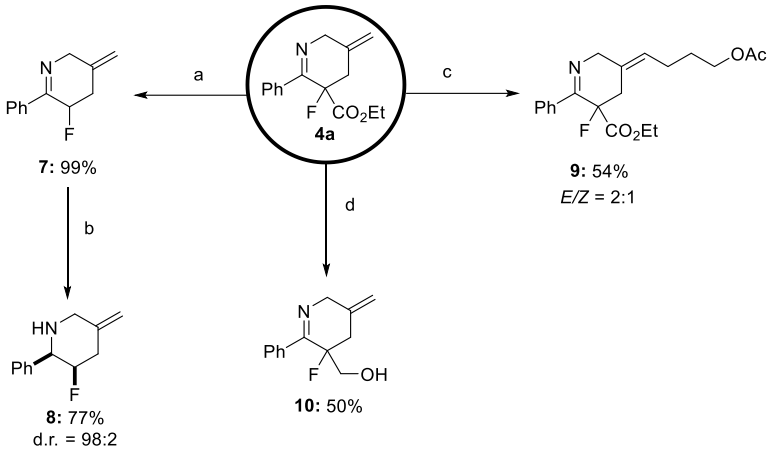
We next focused our efforts on the use of 3-fluoropiperidines as versatile building blocks in organic synthesis. First, the chemo- and diastereoselective reduction of the imine functional group of **4a** using $NaBH(OAc)_3$ in acetic acid yielded piperidine **5** with high yield and diastereoselectivity (Scheme 14a). Protection of **5** using di-*tert*-butyl dicarbonate gave compound **6** in high yield, which was used to determine the relative configuration of the major diastereomer using single crystal x-ray diffraction (Scheme 14b). The stereochemistry of compound **6** can be explained by the stereochemical model showed in Scheme 14b. Four possible attacks from the nucleophile, in this case a hydride, could be expected. However, two of them (**b** and **c**) lead to the formation of a twisted-boat intermediate, which is unfavourable in energy compared to the direct formation of a chair conformation. Although attacks **a** and **d** are possible, the latter is less sterically hindered due to the proximity of the nucleophile to a fluorine atom and not the bigger ester group present in nucleophilic attack **a**.



Scheme 14. a) Chemo- and diastereoselective reduction and Boc protection of **4a**. b) single crystal x-ray structure of **6**. CCDC: 2063492

The synthetic importance of all the functional groups in the piperidine imine scaffolds was then demonstrated in a series of chemo- and diastereoselective functionalization reactions (Scheme 15).[a]

[a] Experimental results obtained by Dr. Christopher Lakeland

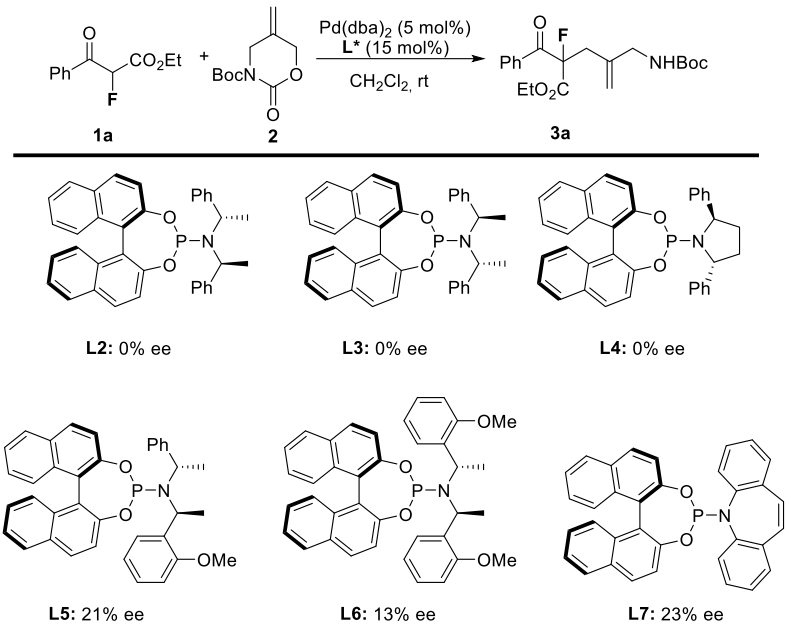


Scheme 15. Chemoselective functionalization of 3-fluoropiperidine imine **4a**. Reaction conditions: a) aq. HCl (15 equiv.), 100 °C, 1 h; b) $NaBH_4$ (2.0 equiv.), MeOH, 0 °C to rt, 18 h; c) Hoveyda-Grubbs 2nd Gen. (5 mol %), pent-4-en-1-yl acetate (3 equiv.), CH_2Cl_2, rt 18 h then reflux, 3 h. d) $LiAlH_4$ (2 equiv.), THF, rt, 3.5 h.

Using high amounts of concentrated HCl in aqueous media, we were able to obtain the decarboxylated 3-fluoropiperidine imine **7** in quantitative yield, which could then be reduced using $NaBH_4$ yielding piperidine **8** with 98:2 diastereoselectivity in 77% yield. To our delight, chemoselective functionalization of the exocyclic alkene was also achieved; thus, cross-metathesis formed compound **9**, although a 2:1 mixture of *E/Z* isomers was observed. An interesting selective reduction of the ester group to form compound **10** was achieved in 50% yield by using $LiAlH_4$. In this case, the relative configuration compound **8** has been elucidated by taking advantage of the *J* constants observed by NMR spectroscopy. In this particular case, the higher hyperconjugation observed in six-membered 3-fluoropiperidines when the fluorine atom appears in axial position explains the high diastereoselectivity observed.[149]

2.4 Enantioselective synthesis of 3-fluoropiperidines

After establishing chemo- and diastereoselective protocols for the functionalization of the 3-fluoropiperidine imine scaffolds we turned our attention to the development of an enantioselective version of the Pd-catalyzed allylation of α-fluoro-β-ketoesters using chiral phosphoramidite ligands under our reaction conditions (Scheme 16).



Scheme 16. Screening of chiral phosphoramidite ligands. Reaction conditions: **1a** (0.3 mmol), **2** (0.2 mmol), $Pd(dba)_2$ (0.01 mmol, 5 mol%), **L*** (0.03 mmol, 15 mol%), CH_2Cl_2 (0.1 M), rt, 18 h under N_2.

We first tested those phosphoramidite ligands that gave excellent enantioselectivities in in the previous project studied in the group.[146] However, only racemates of the allylated intermediate **3a** were observed with those chiral ligands (**L2**-**L4**). Modifying the electronic properties of the aryl substituents at the benzylic position showed to be beneficial and poor enantioselectivities were observed (**L5**-**L6**). Azepine based phosphoramidite ligand **L7** delivered the best enantioselectivity under our reaction conditions.

2.5 Conclusion

In this chapter, we have developed a method for the synthesis of 3-fluoropiperidines through a Pd-catalyzed allylation/condensation sequence.

A wide number of α-fluoro-β-ketoesters have been converted into the corresponding 3-fluoropiperidine imine scaffolds. Importantly, when other electron-withdrawing groups such as –CN, sulfone or Weinreb amides were tested, excellent yields were obtained proving the synthetic utility of the method for the synthesis of highly functionalized 3-fluoropiperidine imines.

A chemo- and diastereoselective functionalization of the fluoropiperidine imine **4a** have been developed with excellent yields and selectivities, proving that each functional group in **4a** may serve as a synthetic building block.

Finally, different chiral phosphoramidite ligands have been evaluated in the enantioselective synthesis of the allylated intermediate **3a**, reaching moderate enantiomeric excess.

3. Hypervalent iodine(III) mediated coupling of enol derivatives with CO_2 (Paper II)

3.1 Background of the project

Among the different reports in the last decade focusing on the use of CO_2 as C_1 building block in organic synthesis, the synthesis of organic carbamates has withdrawn an important part of the efforts from synthetic chemists due to their great chemical stability and unique conformational features.[150] Therefore, carbamates are present in a large number of biologically active compounds (Figure 14). [150]

Ethyl carbamate, also known as urethane, was commercialized as a chemotherapy agent until it was found to be toxic.[151] Other examples of carbamates with important properties are Aldicarb, a potent compound used as insecticide, or Felbamate,[152] widely used before the rise of benzodiazepines as anxiolytic.[153]

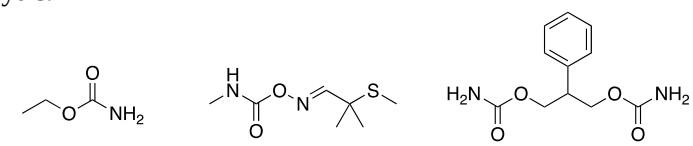
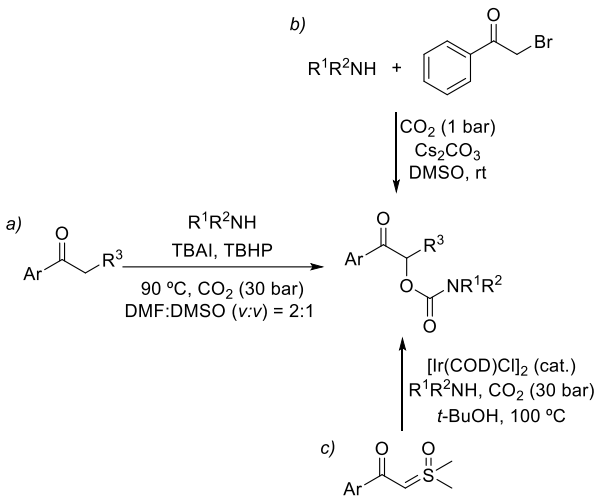


Figure 14. Relevant examples of organic carbamates.

Classic methods for the synthesis of organic carbamates include the carbonylation of amines and nitroaromatic scaffolds,[154, 155] the reaction of alcohols with isocyanates,[156] the Curtius rearrangement of acyl azides,[157, 158] or the Hofmann rearrangement of amides.[159] Moreover, carbamates can also be synthetized in a three component reaction using CO_2 and amines to generate a nucleophilic carbamate anion that can react with different electrophilic partners.[155]

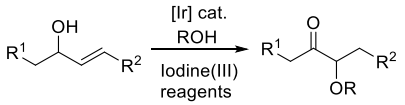
When it comes to the synthesis of α-carbamoyl carbonyl compounds an umpolung event is required due to the nucleophilic nature of the α carbon of enol derivatives. In this field, Jiang and co-workers described the efficient synthesis of carbamates *via* C(sp^3)–H oxidative coupling reaction catalyzed by *n*-Bu_4NI using *tert*-butyl hydroperoxide as an oxidant. This protocol afforded *O*-β-oxoalkyl carbamates in good yields from arylketones through a radical iodination/ nucleophilic substitution pathway (Scheme 17a).[160] In this report, high pressure of CO_2 and elevated temperature is required to obtain the desired products. Taking advantage of the nucleophilic nature of carbamate anions, the synthesis of phenacyl carbamates has been reported by the group of Zeitler starting from commercially available phenacyl bromide, although

the substrate is limited to one specific α-bromoketone (Scheme 17b).[161] An iridium-catalyzed three component reaction approach has recently been reported by Cheng and co-workers.[162] In this case, sulfonium ylides were used as starting materials to generate the desired α-carbamoyl compounds with high efficiency under 30 bar of CO_2 at high temperature (Scheme 17c).



Scheme 17. Reported strategies for the synthesis of α-carbamoyl carbonyl compounds.[160, 161, 162]

Hypervalent iodine(III) compounds have been used to invert the polarity of diverse nucleophiles, thus enabling an umpolung reaction.[163] In particular, the reaction of carbonyl compounds or enol derivatives with other various nucleophiles can be promoted by hypervalent iodine(III) compounds. Pioneering examples in the α-alkoxylation of ketones were reported during the 20th century.[130, 164, 165] More recently, relevant examples in the inversion of the polarity of enol derivatives by hypervalent iodine(III) reagents have been recently reported by different authors, using different nucleophiles and a larger substrate scope.[129, 131, 134, 166-168] On this subject, the Martín-Matute group described recently an unprecedented umpolung protocol for the synthesis of α-alkoxy ketones (Scheme 18) as single constitutional isomers and 3-(2*H*)-furanones from allylic alcohols catalyzed by iridium complexes.[132]

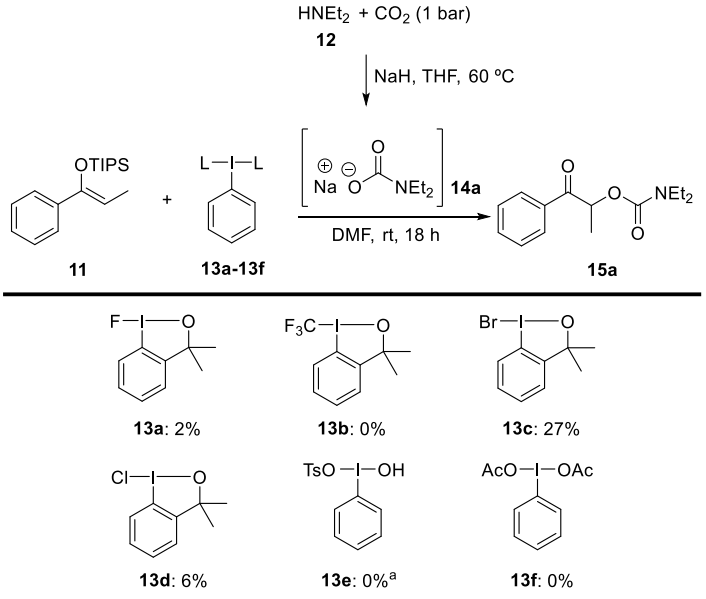


Scheme 18. Isomerization/ umpolung α-alkoxylation of allylic alcohols.

The goal in this chapter is to develop an umpolung strategy for the coupling of CO_2 with enol derivatives, mediated by iodine(III) reagents, for the synthesis of organic carbonates or carbamates.

3.2 Optimization of the reaction conditions

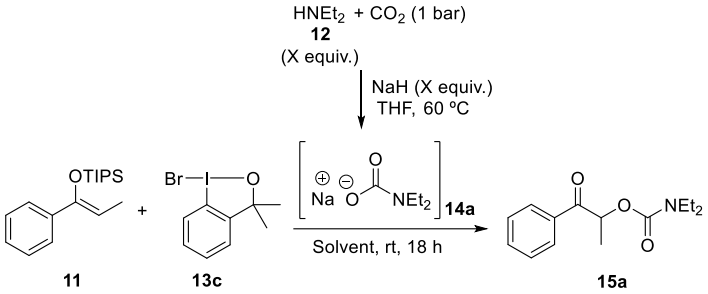
We started our investigations by screening different hypervalent iodine(III) reagents as mediators for the reaction of silyl enol ether **11** with an *in situ* generated carbamate (Scheme 19). Our general procedure for the formation of the carbamate anion (**14a**) was based on a previously reported procedure,[169] where an amine (in our case **12**) and CO_2 reacted together in the presence of NaH. First, we tested 1-fluoro-3,3-dimethyl-1,2-benziodoxole **13a**, obtaining only a small amount of the desired product in DMF. With 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (**13b**), the product **15a** was not detected. Using 1-bromo-3,3-dimethyl-1,2-benziodoxole (**13c**)**,** carbamate **15a** was formed in 27%. yield. No further improvement was observed when chlorinated hypervalent iodine **13d** was tested. Non-cyclic [hydroxy(tosyloxy)iodo]benzene (HTIB, **13e**) and (diacetoxyiodo)benzene (DIB, **13f**) were also evaluated, but they did not afford the desired product. With HTIB, a number of unidentified by-products where observed.[131]



Scheme 19. Screening of hypervalent iodine(III) reagents for the synthesis of α-carbamoyl compounds. Reaction conditions: **11** (0.1 mmol, 1 equiv.), NaH (0.3 mmol, 3 equiv.), **12** (0.2 mmol, 2 equiv.), CO_2 (1 bar), **13a**-**13f** (0.2 mmol, 2 equiv.), DMF (0.33 M), rt, 18 h. Yields determined by ^{1}H NMR using 2,3,5,6-tetrachloronitrobenzene as internal standard. [a]: Several by-products observed. α-hydroxyketone observed as the major product

Next, different reaction conditions were evaluated following the general procedure for the formation of carbamate anions (Table 1). Decreasing the amount of base from 3 equiv. to 1.5 equiv. resulted in a substantial increase of yield (Table 1, entries 1 – 3). Further decrease in the base loading had a negative effect (Table 1, entry 4). Diminishing the amount of **12** resulted in a significantly lower yield of carbamate **15a** (Table 1, entry 5).

Table 1. Optimization of the reaction conditions for the synthesis of carbamate **14a**.[a]



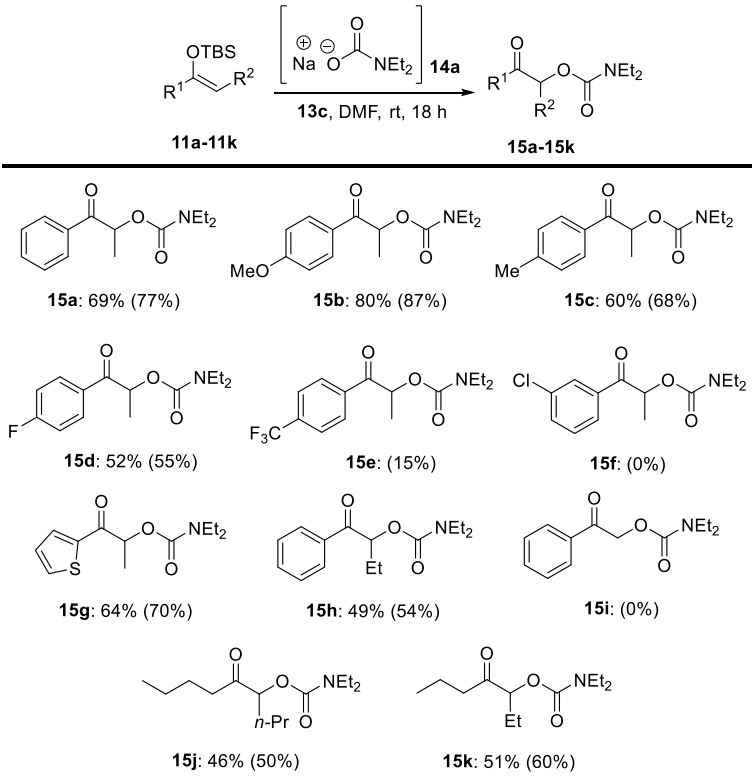
Entry	NaH (equiv.)	12 (equiv.)	13c (equiv.)	Solvent	Yield (%)[b]
1	3	2	1.2	DMF	27
2	2	2	1.2	DMF	43
3	1.5	2	1.2	DMF	59
4	1	2	1.2	DMF	51
5	1.5	1.5	1.2	DMF	43
6	1.5	2	1.5	DMF	68
7[c]	**1.5**	**2**	**1.5**	**DMF**	**77**
8[d]	1.5	2	1.5	DMF	55
9[c]	1.5	2	1.5	THF	-
10[c]	1.5	2	1.5	Toluene	-
11[c]	1.5	2	1.5	Acetone	-

[a]: Reactions were run using **11** (0.1 mmol, 0.33 M) in the corresponding solvent at rt for 18 h under CO_2 (1 bar). [b]: Yields determined by ^{1}H NMR spectroscopy using 2,3,5,6-tetrachloronitrobenzene as internal standard. [c]: With *tert*-butyldimethylsilyl enol ether. [d]: With trimethylsilyl enol ether.

Just increasing slightly the equivalents of bromobenzoiodoxole **13c**, we were able to obtain carbamate **15a** in 68% yield (Table 1, entry 6). The effect of the silyl group was next evaluated showing that the use of more sterically hindered groups positively affects the reaction, leading to the optimized reaction conditions (Table 1, entry 7). A trimethylsilyl enol ether derivative was also tested under those conditions, resulting in a significant decrease in the yield of the reaction (Table 1, entry 8). Other solvents were evaluated (Table 1, entries 9 – 11), but **15a** was only formed in DMF.

3.3 Substrate scope and limitations

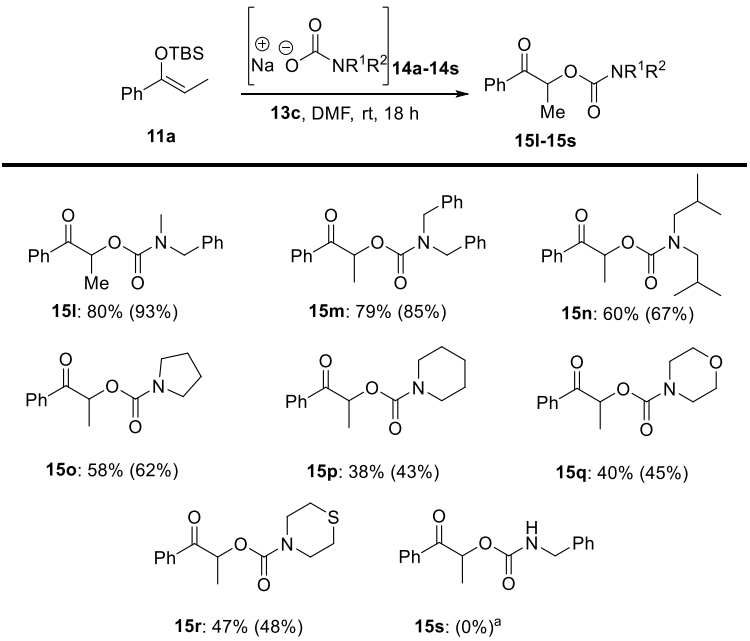
Next, we applied the general procedure for the formation of carbamate anion **14a** together with the optimized umpolung reaction conditions (Table 1, Entry 7) to a variety of silyl enol ethers (Scheme 20).



Scheme 20. Scope and limitations of enol ether nucleophiles. Unless otherwise noted and following the general procedure, **11a-11k** (0.1 mmol, 1 equiv.), **12** (0.2 mmol, 2 equiv.), **13c** (0.15 mmol, 1.5 equiv.), NaH (0.15 mmol, 1.5 equiv.), CO_2 (1 bar), DMF (0.33 M), rt, 18 h. Yields are isolated. Yield determined by ^{1}H NMR spectroscopy using 2,3,5,6-tetrachloronitrobenzene as internal standard in parentheses.

First, different substituents in the *para* position of the aryl group at R^1 were evaluated. Electron-donating substituted silyl enol ethers reacted smoothly yielding the desired α-carbamoyl carbonyl compounds in high yields (**15b**-**15c**). Although the *para*-fluorine derivative **11d** gave the corresponding product with high efficiency, its *para*-trifluoromethylated analogue **11e** had significantly lower reactivity, yielding **15e** in only 15% yield. Unfortunately, *meta*-chloro substituted **15f** could not be obtained under our reaction conditions. Thiophene substituted α-carbamate carbonyl compound **15g** was obtained in 64% yield. Similarly, ethyl substitution at R^2 was also well tolerated and carbamate **15h** was formed in 49% yield, although the non-substituted silyl enol ether **11i** did not react under the optimized conditions. Finally, alkyl substituted silyl enol ethers yielded the desired products in good yield (**15j** and **15k**). It is worth to mention that the only product observed was the desired α-carbamate carbonyl compounds (**15**), together with the starting silyl enol ethers (**11**).

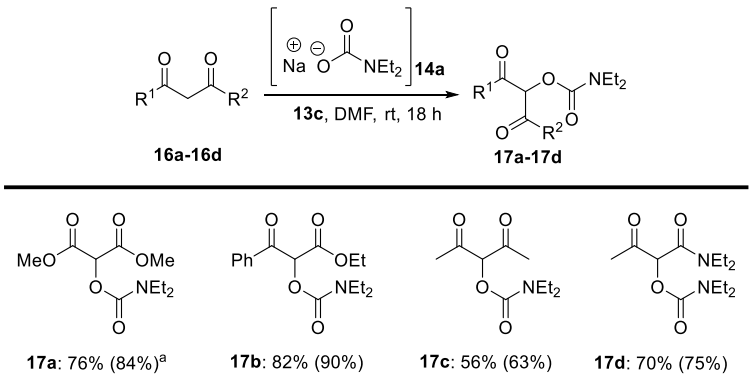
With these results in hand, we focused our efforts on evaluating how the nature of the amine affect the outcome of the reaction (Scheme 21).



Scheme 21. Scope and limitations of the amine nucleophile. Unless otherwise noted and following the general procedure, **11a** (0.1 mmol, 1 equiv.), **12l-12s** (0.2 mmol, 2 equiv.), **13c** (0.15 mmol, 1.5 equiv.), NaH (0.15 mmol, 1.5 equiv.), CO_2 (1 bar), DMF (0.33 M), rt, 18 h. Isolated yields. Yields determined by ^{1}H NMR spectroscopy using 2,3,5,6-tetrachloronitrobenzene as internal standard in parentheses. [a]: Various unidentified by-products obtained.

Different secondary amines bearing alkyl chains as substituents were evaluated under the optimized conditions obtaining good yields in all the cases (**14l**-**14n**). Heterocyclic amines were well tolerated, yielding the desired α-carbamoyl carbonyl compounds in moderate yields (**14o**-**14r**). However, when primary amines were tested, different by-products were observed, showing a limitation of this method.

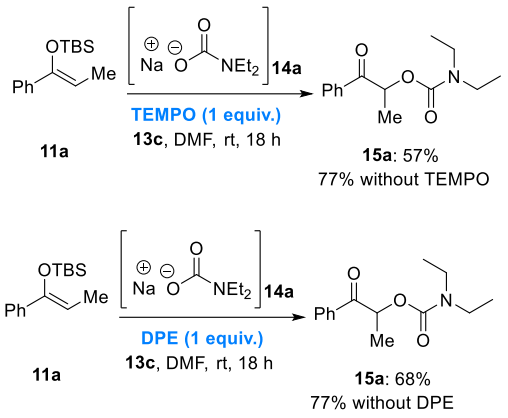
Finally, the hypervalent iodine(III) mediated coupling of CO_2 with nucleophiles was not only limited to silyl enol ethers. When different 1,3-carbonyl compounds were tested, the corresponding carbamates were obtained in good yields (Scheme 22). Malonate **16a** afforded carbamate **17a** in 76% yield. Ketoester **16b** and 1,3-diketone **16c were** also tolerated in the reaction conditions, and the corresponding carbamates were obtained in 82% and 56% isolated yield, respectively. Finally, the more challenging ketoamide **16d** reacted smoothly to provide α-carbamoyl carbonyl compound **17d** in 70% yield.



Scheme 22. Scope and limitations of 1,3-dicarbonyl nucleophiles: Unless otherwise noted and following the general procedure, **16a-16d** (0.1 mmol, 1 equiv.), **12a** (0.2 mmol, 2 equiv.), **13c** (0.15 mmol, 1.5 equiv.), NaH (0.15 mmol, 1.5 equiv.), CO_2 (1 bar), DMF (0.33 M), rt, 18 h. [a]: Instead of **13c**, 1-bromo-3,3-bis(trifluoromethyl)-1,3-dihydro-1λ-3-benzo[d]-[1,2]iodaoxole was used.

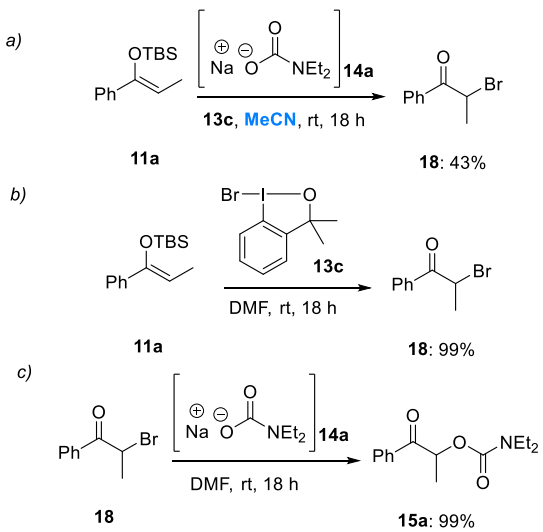
3.4 Mechanistic investigations

After the study of the scope and limitations of the reaction, we focused our attention on the study of the mechanism. First, we performed a series of control experiments adding different radical scavengers in stoichiometric amounts the optimal reaction conditions (Scheme 23). Addition of TEMPO or of diphenylethylene (DPE) did not affect the yields significantly, suggesting the absence of a radical pathway.[170]



Scheme 23. Radical trapping control experiments.

In an attempt to understand the dramatic effect of DMF in the reaction outcome, different polar non-protic solvents were tested. In particular in acetonitrile, only 2-bromo-1-phenylpropan-1-one (**18**) was observed (Scheme 24a). Moreover, when silyl enol ether **11a** was placed in DMF with benzoiodoxole **13c**, α-bromoketone (**18**) was isolated in 99% yield (Scheme 24b). Further, α-carbamoyl carbonyl compound **15a** was obtained in quantitative yield through nucleophilic substitution when α-bromoketone **18** was reacted with the *in situ* generated carbamate from diethyl amine and CO_2 (Scheme 24c). These experiments suggest a mechanistic pathway starting with an umpolung bromination of the enol derivatives, followed by a nucleophilic substitution reaction, yielding the desired carbamates.



Scheme 24. Control experiments.

The kinetic profile was obtained by determining the yield of **15a**, as well as that of α-bromoketone **18**, as the reaction proceeds (Figure 15).

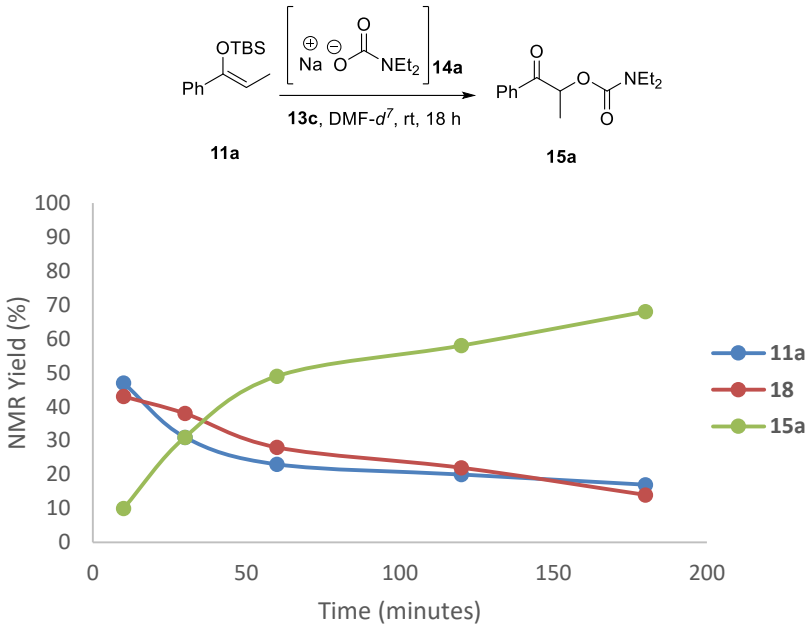


Figure 15. Reaction profile for the coupling of silyl enol ethers with CO_2.

After only 10 min. of reaction time, when the first NMR was recorded, the mixture is composed by 47% of remaining **11a**, 10% of final α-carbamoyl **15a**, together with 43% of α-bromoketone **18**. This is the highest concentration of the brominated intermediate detected. As the reaction proceeds, the concentration of **15a** increases steadily up to a yield ca. 50% after 60 min. The reaction rate decreases from this point, reaching the highest recorded yield of 68 % after 180 min. It can be concluded that α-bromoketone **18** is formed as an intermediate, which is then consumed via nucleophilic displacement of the bromide atom by the carbamate anion, affording product **15a**.

Combining the experimental results with preliminary DFT calculations,[b] we propose a mechanism which starts with the bromination of silyl enol ether **11a** (Figure 16). The bromination reaction may occur through an *O*-bound enolonium intermediate **Int 1** or a *C*-bound **Int 2**. Which of the enolonium intermediates is more stable seems to be dependent on the nature of the enol, as well as on the substituents present on the I^{III} reagent.[131,132] The final bromination takes place *via* reductive ligand coupling, this step is followed by an S_N2 type reaction yielding the desired α-carbamoyl carbonyl compound.

[b] Performed by Alba Carretero Cerdán.

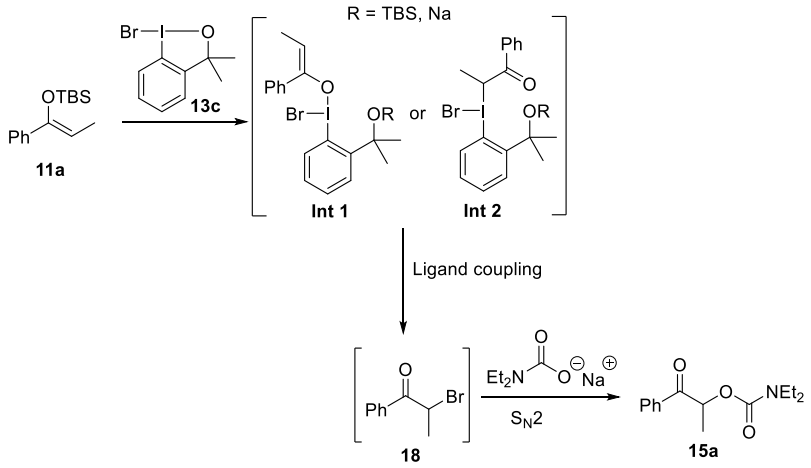


Figure 16. Proposed mechanism for the hypervalent iodine(III) coupling of enol derivatives with carbamates.

All our attempts to perform the reaction using other common brominating agents such as NBS or Br_2, resulted in complex mixtures of products. Therefore, **13c** exhibits a unique mild reactivity, yielding mono-brominated carbonyl compounds even under basic conditions.[171, 172]

The formation of highly reactive intermediates under very mild conditions for the umpolung functionalization of enol derivatives with other nucleophiles have been previously discussed by Maulide[173] and Jørgensen[174] among others, as an opportunity to unify the formation of α-substituted carbonyl compounds through nucleophile coupling reactions. Encouraged by our DFT calculations and the experimental results, other members in our research group have developed an umpolung bromination/nucleophilic substitution strategy for the coupling of enol derivatives with a large number of nucleophiles, being able to form C–C, C–O, C–N and C–S bonds under similar reaction conditions.

3.5 Conclusion

In this chapter, we have described a hypervalent iodine(III) mediated umpolung reaction between enol derivatives and carbamates generated from CO_2 and amines, which afford α-carbamoyl carbonyl compound.

Importantly, the reaction conditions have been optimized by studying the role of the substituents in the hypervalent iodine(III) reagent. A detailed optimization of the reagent's equivalents, silyl protecting group and solvent led to an efficient protocol for the coupling of CO_2 with silyl enol ethers.

The scope and limitations of the reaction have also been evaluated, showing that substrates with electron-donating groups at *para* position of the aryl

substituent reacted with higher yields than those with electron-withdrawing groups. Moreover, a large number of secondary amines can be used under our reaction conditions, whereas primary amines led to a mixture of different products. The reaction conditions can also be applied to 1,3-dicarbonyl compounds, without previous formation of the corresponding silyl enol ethers, yielding highly functionalized α-carbamoyl-1,3-dicarbonyl compounds.

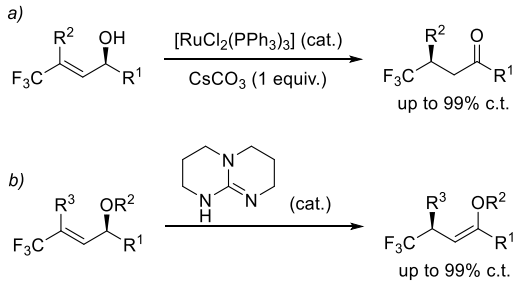
Finally, the mechanism of the reaction has been investigated experimentally in this thesis. Combined with the DFT studies performed within the group, it can be concluded that an umpolung mono-bromination mediated by the hypervalent iodine(III) reagent occurs first under the reaction conditions, which is followed by a subsequent nucleophilic substitution reaction affording α-carbamoyl carbonyl compounds.

4. Stereospecific isomerization of allylic halides via chiral ion pairs with induced non-covalent chirality (Paper III)

4.1 Background of the project

The stereospecific isomerization of allylic compounds has arisen as an alternative to the stereoselective protocols, which relies on the use of chiral catalysts. An early example of this strategy was proposed by Cahard in 2012 with the stereospecific isomerization of chiral γ-trifluoromethylated allylic alcohols using a non-chiral ruthenium complex as catalyst for the transformation (Scheme 25a).[91]

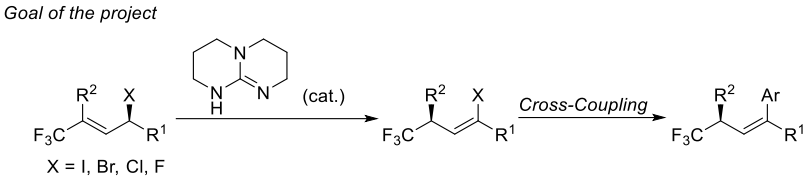
The Martín-Matute group has contributed to this field by developing a base-catalyzed stereospecific isomerization of γ-trifluoromethylated allylic alcohols and ethers using a guanidine-type base, 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) as catalyst (Scheme 25b).[94] The mechanism of the reaction was studied experimentally and by DFT calculations, which showed that formation of a tight ion pair intermediate, with induced non-covalent chirality, was the key for the chirality transfer.



Scheme 25. Stereospecific strategies for the isomerization of allylic alcohols and ethers.

With these outstanding results, our research interest has been focused on expanding the scope of the reaction to other allylic systems which may serve to introduce stereogenic centers in more complex molecules. In this regard, allylic halides appeared as suitable candidates, although reported isomerization examples are rare and limited only to allylic fluorides and no stereospecific examples have been previously reported.[175, 176] Vinyl halides, the products of the isomerization reaction, have been widely used as synthetic building blocks in organic synthesis. They can be used as electrophilic partners in C–C bond formation cross-coupling reactions.[177-179] Moreover, vinyl halides can be used to form other vinyl compounds through a vinylic substitution reaction[180] or olefin metathesis reactions.[181]

In this chapter, the main goal is to develop a protocol for the stereospecific isomerization of allylic halides. After synthesizing chiral allylic chlorides in an efficient manner, the base-catalyzed isomerization is studied. Finally, we aim to explore the synthetic opportunities of the vinyl halides obtained in the transformation in cross-coupling reactions (Scheme 26).



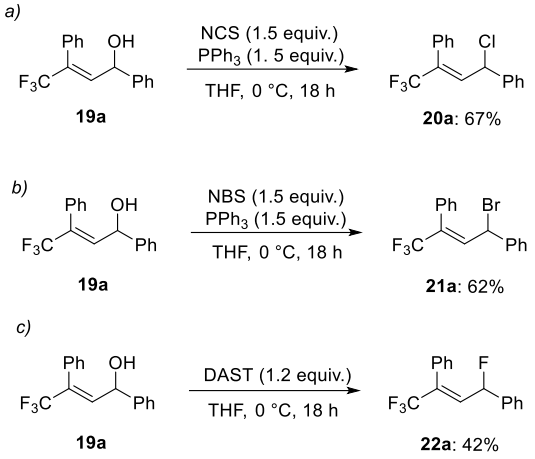
Scheme 26. Stereospecific isomerization of allylic halides and its application in cross-coupling reactions.

4.2 Regioselective synthesis of allylic halides and optimization of the isomerization reaction

Allylic chlorides can be easily accessed from allylic alcohols through substitution reactions using different chlorinating agents such as PCl_3, SO_2Cl or the combination of PPh_3 and CCl_4, also known as the Appel reaction.[182] However, the vast majority of these reported protocols present regioselectivity issues due to the competition of S_N1/S_N2 and $S_N1´/S_N2´$ pathways, resulting in a mixture of isomers which is difficult to separate.[183-185]

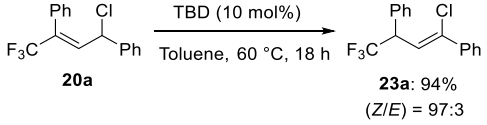
With these difficulties in mind, we focused our efforts in the regioselective synthesis of allylic chlorides from γ-trifluoromethylated allylic alcohols. Different chlorination conditions were evaluated using (*E*)-**19a** as model substrate. By using a combination of NCS/PPh_3 (1.5 equiv.) as deoxochlorinating agent in THF yielded (*E*)-**20a** in high yield and with excellent regioselectivity (Scheme 27a). Moreover, we were also able to access allylic bromides using this reaction conditions with similar results (Scheme 27b). Finally, following a reported procedure for deoxofluorination using DAST (diethylaminosulfur trifluoride) as fluorinating agent,[186] the synthesis of allylic fluoride **22a** was achieved in 45% yield as a single isomer (Scheme 27c).[c]

[c] Experiments performed by Dr. Samuel Martinez-Erro.



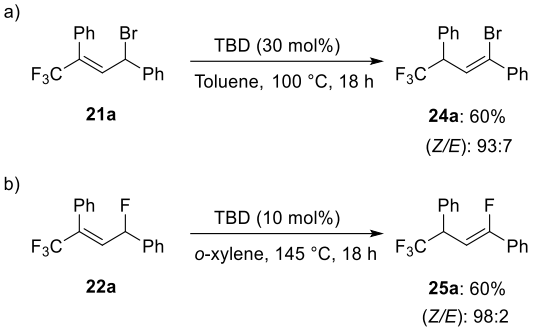
Scheme 27. Regioselective protocols for the synthesis of allylic halides.

After developing regioselective methods for the synthesis of allylic chlorides, bromides and fluorides, we turned our attention on the base-catalyzed isomerization of γ-trifluoromethylated allylic halides. Using (*E*)-allylic chloride **20a** as substrate, a large number of bases, solvents, and temperatures were evaluated. The conclusion of those experiments was that the corresponding vinyl chloride **23a** could be obtained using TBD as catalyst for the transformation in toluene at 60 ºC in quantitative yield and with excellent *Z*/*E* ratio (Scheme 28).[c]



Scheme 28. Base-catalyzed isomerization of allylic chloride **19a**.

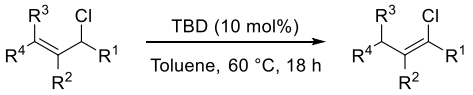
Small modifications were needed for the isomerization of allylic bromides and fluorides. In particular for allylic bromides, a higher amount of base was needed to avoid decomposition of the substrate. Allylic bromide **21a** was successfully isomerized into the corresponding vinyl bromide **24a** adding 30 mol% of TBD in toluene at 100 °C in 60% isolated yield (Scheme 29a). In the case of allylic fluoride **22a**, the amount of base was maintained to 10 mol% although a significant increase of the temperature to 145 °C in *o*-xylene was needed to achieve full conversion into the vinyl fluoride **25a** (Scheme 29b).



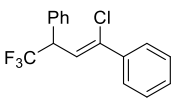
Scheme 29. Base-catalyzed isomerization of a) allylic bromides and b) allylic fluorides.

4.3 Substrate Scope

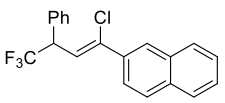
With the optimized conditions for the base-catalyzed isomerization of allylic halides in hand, we studied the opportunities of this protocol. First, a number of allylic chlorides were evaluated under the optimized reaction conditions (Scheme 30). Different allylic chlorides bearing an aromatic ring at R^1 were evaluated yielding the corresponding vinyl chloride smoothly even with a bulkier naphthyl substituent (**23b**). Both electron-withdrawing and electron-donating groups in *para* position of the aryl group gave good to excellent yields (**23c**-**23g**). However, a dramatic effect was observed when the aryl group was removed (**23h**-**23i**). An increase of the temperature and catalyst amount was needed to reach significantly lower conversion, showing a correlation between the pK_a of the proton in the α position to the halide and the efficiency of the reaction. Interestingly, an allylic chloride bearing a fluoride at R^2 was isomerized to **23j** in moderate yield and very poor *Z/E* ratio in comparison with the rest of substrates studied for this transformation. Substituents in the *para* position on the aryl group at R^3 did not show to have any major effect in the yield of the reaction and compounds **23k** and **23l** were successfully achieved in high yields. Not only aromatic rings were tolerated in this position, thus, **20m** and **20n** with a methyl and a hydrogen at R^3 were isomerized by TBD with very good yields. To our delight, not only γ-trifluoromethylated allylic chlorides could be isomerized, other electron-withdrawing groups such as sulfones, allylic chlorides (*E*)-**20o** and (*Z*)-**20o** provided the corresponding vinyl chloride products with excellent outcomes in yields and *Z*/*E* ratios. The geometry of the compounds **23** was determined by analogy with the previously reported isomerization of allylic ethers under very similar conditions. [94]



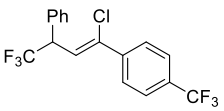
20a-20o **23a-23o**



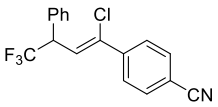
23a: 94%
(*Z*/*E*): 93:7



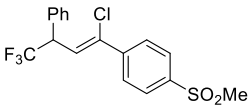
23b: 86%
(*Z*/*E*): 96:4



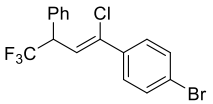
23c: 92%
(*Z*/*E*): 97:3



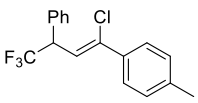
23d: 88%
(*Z*/*E*): 94:6



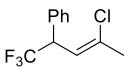
23e: 77%
(*Z*/*E*): 96:4



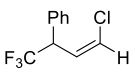
23f: 82%
(*Z*/*E*): 95:5



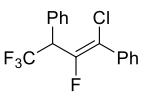
23g: 80%
(*Z*/*E*): 94:6



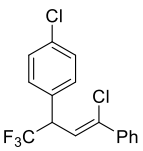
23h: 30%[a]
(*Z*/*E*): n.d.



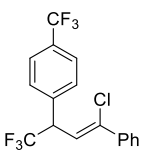
23i: 51%[a]
(*Z*/*E*): n.d.



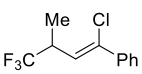
23j: 45%
(*Z*/*E*): 54:46



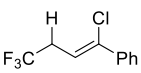
23k: 80%
(*Z*/*E*): 95:5



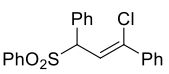
23l: 75%
(*Z*/*E*): 96:4



23m: 92%
(*Z*/*E*): 97:3



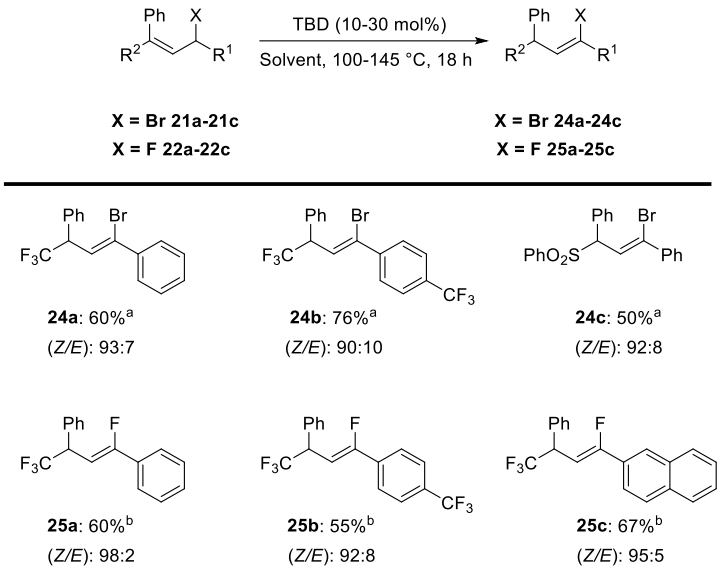
23n: 85%
(*Z*/*E*): 99:1



23o: From (*E*)-**20o**: 85%
(*Z*/*E*): 93:7
From (*Z*)-**20o**: 80%
(*E*/*Z*): 94:6

Scheme 30. Scope of the base-catalyzed isomerization of allylic chlorides. *Z*/*E* ratios determined by ^{19}F NMR or ^{1}H NMR spectroscopy. Isolated yields. Reaction conditions: **20a-20o** (0.1 mmol), TBD (0.01 mmol, 10 mol %), Toluene (0.1 M), 60 °C, 18 h. [a]: TBD (0.02 mmol, 20 mol %), 120 ºC, not isolated. n.d. = not determined

As mentioned above, our base-catalyzed isomerization protocol is not limited to only allylic chlorides. Allylic bromides and fluorides can also be isomerized using slightly modified reaction conditions (Scheme 31). Allylic bromide **21b** with a trifluoromethyl substituent at *para* position at R^1 was successfully converted to the corresponding synthetically useful vinyl bromide in high yield. As in the case of allylic chlorides, a γ-sulphonyl vinyl bromide could also be obtained in 50% yield and high *Z/E* ratio (**24c**). In the case of allylic fluorides, different substrates bearing aromatic rings at R^1 were transformed to γ-trifluoromethylated vinyl fluorides (**25a-25c**) in moderate yields.



Scheme 31. Scope of the base-catalyzed isomerization of allylic bromides and fluorides. *Z/E* ratios determined by ^{19}F NMR or ^{1}H NMR spectroscopy. [a]: **21a-21c** (0.1 mmol), TBD (0.03 mmol, 30 mol %), Toluene (0.1 M), 100 °C, 18 h. [b]: **22a-22c** (0.1 mmol), TBD (0.01 mmol, 10 mol %), *o*-Xylene (0.1 M), 145 °C, 18 h.

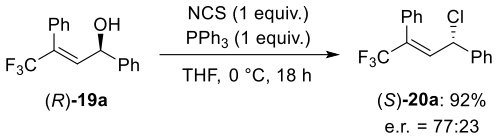
4.4 Stereospecific base-catalyzed isomerization of allylic chlorides

4.4.1 Synthesis of enantiomerically enriched allylic chlorides

The synthesis of chiral allylic compounds from other allylic substrates has been somehow limited metal-catalyzed allylic substitutions, requiring transition-metal catalysts and chiral ligands.[70, 71] The scope has been focused on accessing chiral allylic amines or chiral allylic ethers. In the case of allylic halides, the reported examples are limited to the synthesis of allylic fluorides, probably due to the higher stability of these in comparison to that of allylic chlorides, bromides or iodides under the reaction conditions.[187, 188] Moreover,

via S_N1-type reactions, racemization of allylic halides easily occur, which is due to the high stability of the allylic carbocation intermediates involved. This effect could be more pronounced for the γ-trifluoromethylated allylic halides that are the focus of this work, as these are not only allylic, but also benzylic, providing further stabilization to the carbocationic intermediates.[189]

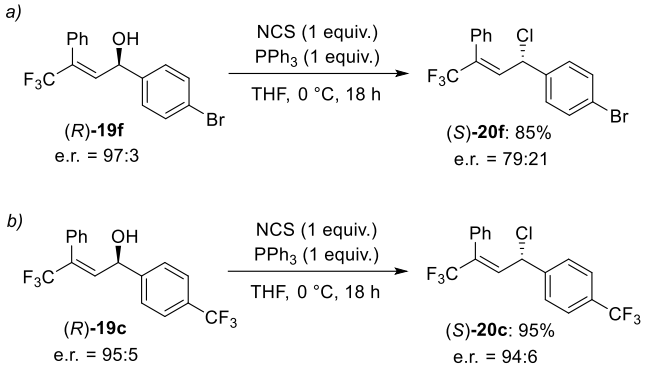
With these difficulties in mind, we optimized the S_N2-type reaction for the synthesis of allylic chlorides starting from enantiomerically enriched allylic alcohols. The Appel conditions previously used (*vide supra*, Scheme 27a) showed the competition between S_N2 and S_N1 pathways for the synthesis of allylic chlorides, resulting in moderate enantiomeric ratio (75:25). We were able to increase the enantiomeric ratio slightly to 77:23 by lowering the synthetic equivalents of chlorinating agent and triphenylphosphine (Scheme 32). Further optimization was attempted, by varying the chlorinating agents, phosphines, temperature and solvents, but all of these attempts failed in our hands.[c]



(*R*)-**19a** (*S*)-**20a**: 92%
e.r. = 77:23

Scheme 32. Optimized conditions for the synthesis of chiral allylic chloride (*S*)-**23a**. Reaction conditions: (*R*)-**19a** (0.1 mmol, 1 equiv.), NCS (0.1 mmol, 1 equiv.), PPh_3 (0.1 mmol, 1 equiv.) THF (1 mL, 0.1 M), 0 °C, 18 h. Enantiomeric ratio determined by chiral HPLC.

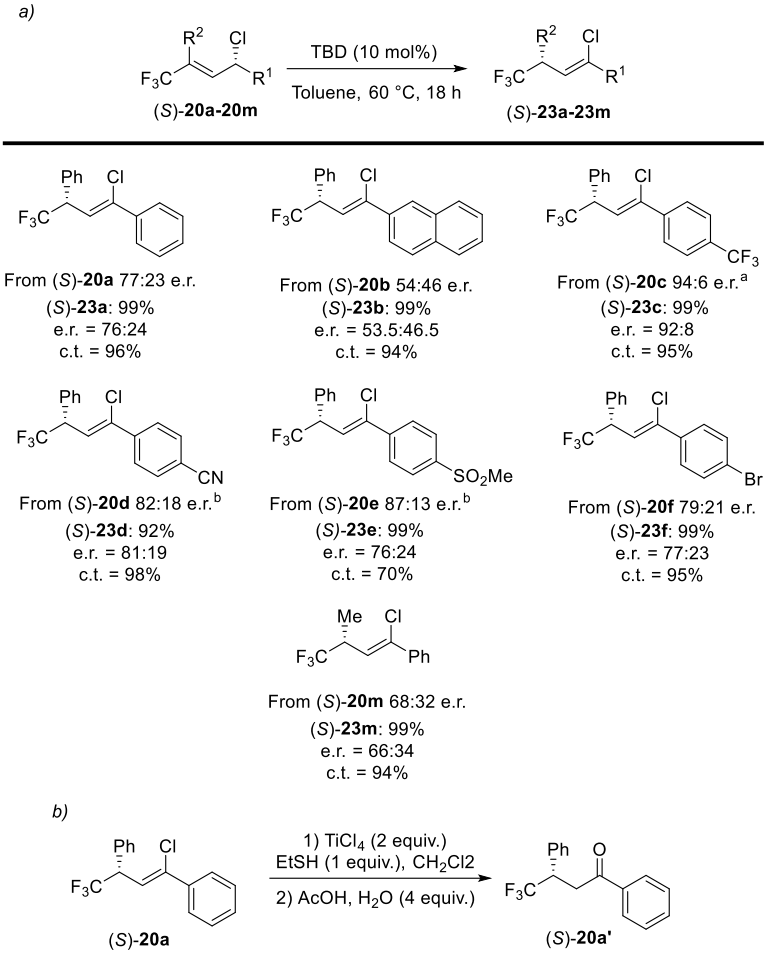
In spite of our efforts, only moderate enantiomeric ratios were obtained. In an attempt to obtain better results, we studied how the electronic properties of the substituents at the benzylic ring could affect the stability of the carbocation intermediate. First, *para*-bromo substituted allylic alcohol (*R*)-**19f** was subjected to our reaction conditions, showing slightly better results than in the case of the non-substituted derivative (Scheme 33a). To our delight, when an electron-withdrawing trifluoromethyl group was placed at *para* position of the aryl group (**19c**), a significant increase of the enantiomeric ratio was observed (Scheme 33b).



Scheme 33. Study of the electronic effect in the enantiomeric ratio obtained in the synthesis of chiral allylic chlorides. Reaction conditions: (*R*)-**19f** or (*R*)-**19c** (0.1 mmol, 1 equiv.), NCS (0.1 mmol, 1 equiv.), PPh_3 (0.1 mmol, 1 equiv.) THF (1 mL, 0.1 M), 0 ºC, 18 h. Enantiomeric ratio determined by chiral HPLC.

4.4.2 Stereospecific isomerization of enantiomerically enriched allylic chlorides

After using this method to synthesize a number of chiral allylic chlorides, we decided to test them in the base-catalyzed isomerization conditions to study chirality transfer (Scheme 34a). Importantly, different substituents at the *para* position of the aryl group at R^2 were well tolerated, and high levels of chirality transfer were obtained in all the cases. Although allylic chloride (*S*)-**20b** could only be obtained with poor enantiomeric ratio, due to the high stabilization of the corresponding carbocation, chiral vinyl chloride (*S*)-**23b** was obtained with excellent chirality transfer. Different electron-withdrawing groups such as cyano and trifluoromethyl were well tolerated and the corresponding chiral vinyl derivatives (*S*)-**23c** and (*S*)-**23d** were obtained with excellent enantiomeric ratios. With a more polar substituent, as sulfone (*S*)-**20e**, a significant decrease of the chirality transfer was observed. Importantly, other halides are tolerated under our reaction conditions and vinyl chloride (*S*)-**23f** was obtained with good enantiomeric ratio. Finally, an alkyl substituted allylic chloride was tested under the isomerization conditions leading to (*S*)-**23m** with moderate enantiomeric ratio. The absolute configuration of (*S*)-**23a** was determined by converting it into a previously reported ketone (*S*)-**20a'** (Scheme 34b).[94] The stereochemistry of the other products was assigned by analogy.

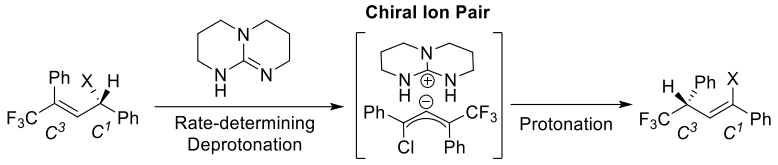


Scheme 34. Stereospecific base-catalyzed isomerization of enantiomerically enriched allylic chlorides. Yields measured by ^{19}F NMR [a]: 1 h, rt. [b]: 1 h, 0 ºC. c.t. = $(ee_{product}/ee_{SM})*100$

4.5 Mechanistic investigations

As the reaction conditions and experimental results were in accordance with those previously reported in the base-catalyzed isomerization of allylic alcohols,[94] we hypothesized that a similar mechanistic pathway was taking place in the case of allylic halides. To support this, we decided to perform deuterium labeling studies by subjecting a deuterated allylic halide **20a**-*d*[1] to the reaction conditions. The difference in the initial reaction rates of deuterated and non-deuterated allylic chlorides resulted in a KIE (kinetic isotope effect) of 5.4 ± 0.6, concluding that the rate determining step corresponds to the deprotonation of C^1–H by TBD.

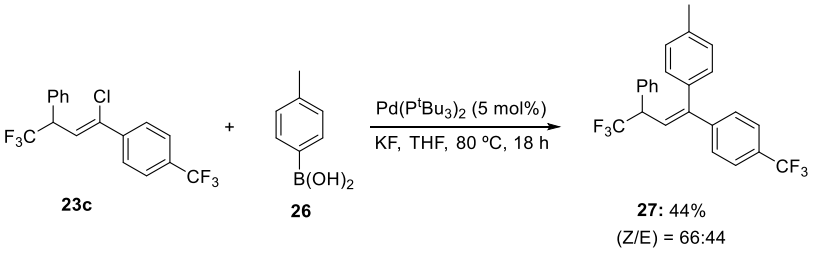
Merging this data with our preliminary knowledge about the TBD catalysis in the isomerization of allylic alcohols, we propose that after an interaction of the catalyst with the allylic halide, the rate determining deprotonation step occurs. Afterwards, an ion pair intermediate is formed with induced chirality through non-covalent interactions between the protonated base and the planar anionic allylic chloride, the stability of this ion pair is the key for the high levels of chirality transfer. Finally, after protonation and decoordination from the base, the vinyl halide is formed and the base is regenerated (Scheme 35).



Scheme 35. Proposed mechanism for the stereospecific isomerization of allylic halides.

4.6 Functionalization of vinyl chlorides

After developing a stereospecific protocol for the base-catalyzed isomerization of allylic chlorides, we focused our efforts on the functionalization of the vinyl chloride products. Different Pd-catalyzed cross-coupling reactions were tested but vinyl chloride **23a** remained unreacted, showing that the oxidative addition might be difficult with our substrates. Therefore, we selected a highly activated vinyl chloride (**23c**) as substrate for the Suzuki-Miyaura cross-coupling reaction following the reported conditions by Fu and co-workers.[177] Using $Pd(P^tBu_3)_2$ as catalyst, and KF as base, we were able to obtain allylic trifluoromethyl **27** in 44% yield and modest *Z/E* ratio (Scheme 36). Other functionalization such as epoxidation of vinyl chlorides were studied by other members of our group obtaining good yields and diastereoselectivities.



Scheme 36. Pd-catalyzed Suzuki-Miyaura cross-coupling of **23c** with *p*-tolylboronic acid. Reaction conditions: **23c** (0.1 mmol, 1 equiv.), **26** (0.11 mmol, 1.1 equiv.), $Pd(P^tBu_3)_2$ (0.005 mmol, 5 mol%), KF (0.33 mmol, 3.3 equiv.), THF (2 mL, 0.5 M), 80 ºC, 18 h.

4.7 Conclusion

The base-catalyzed stereospecific isomerization of allylic halides has been discussed in this chapter.

After developing a protocol for the synthesis of enantiomerically enriched allylic chlorides from chiral allylic alcohols, we have studied the stereospecific isomerization to vinyl chlorides, obtaining high levels of chirality transfer in all the cases.

Using kinetic isotope effect studies and with our previous knowledge about the isomerization reaction, we have proposed a mechanism that starts with a rate-determining deprotonation step that leads to the formation of an ion pair with induced non-covalent chirality. Keeping this ion pair tightly is the key for obtaining high levels of chirality transfer.

Finally, the synthetic opportunities of vinyl chlorides have been explored, and an allylic trifluoromethyl compound has been obtained through a Suzuki-Miyaura cross-coupling reaction.

5. Stereospecific and diastereoselective synthesis of chiral γ-trifluoromethylated aliphatic amines via chiral ion pairs with induced non-covalent chirality (Paper IV)

5.1 Background of the project

Aliphatic amines bearing at least one stereocenter in its structure are widely prominent substructures in natural products and pharmaceuticals.[190, 191] In particular, (chiral) γ-branched aliphatic amines represent an important subclass, as they are present in a large number of pharmaceuticals (Figure 17). In spite of their importance, synthetic methods for the preparation of γ-branched aliphatic amines are scarce in comparison to those focusing the stereocontrol on the α and β positions to the amine functional group.[191, 192]

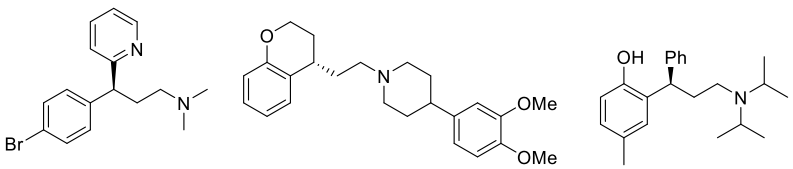
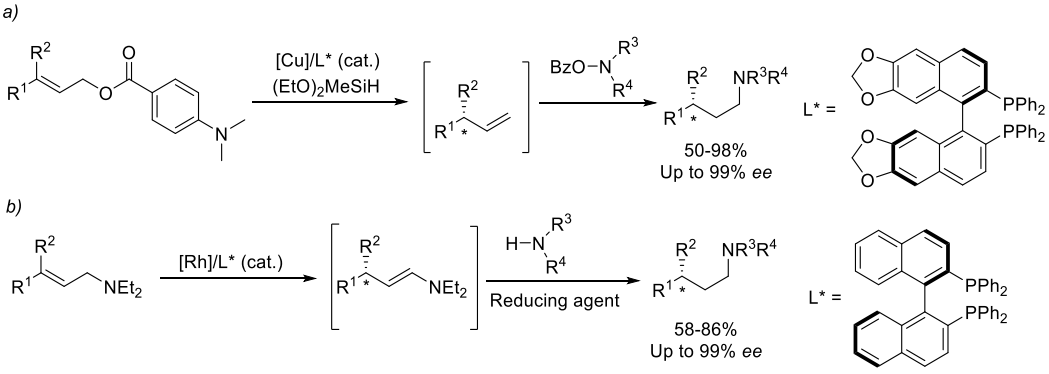


Figure 17. Relevant examples of chiral γ-branched aliphatic amines.

The group of Buchwald has recently reported a method for the synthesis of chiral γ-branched aliphatic amines via a Cu-catalyzed hydrocupration/β-alkoxide elimination of allylic esters, followed by an *anti*-Markovnikov hydroamination of the olefin intermediate (Scheme 37a).[193] Despite the excellent enantioselectivity, the method relies on the use of electrophilic amination reagents, limiting the substrate scope to the synthesis of tertiary amines.

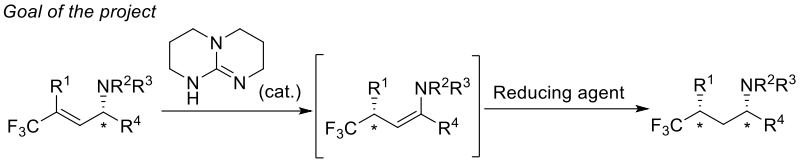
As mentioned above (Chapter 1) the transition metal-catalyzed isomerization of allylic amines or alcohols has been widely used to create new stereocenters in remote positions to ketones, aldehydes or enamines.[80, 81, 88-91] The group of Hull combined this strategy with a reductive amination protocol (Scheme 37b).[90] Starting from allylic diethyl amines, and using a rhodium catalyst, chiral enamine intermediates are formed *via* a redox-neutral isomerization process. Then, this chiral enamine reacts with other nucleophilic amines in the presence of a reducing agent, yielding chiral γ-branched primary and secondary amines with high enantioselectivities.[90] The chirality is induced by using chiral ligands, which are designed for every particular group of

substrates. This requires an important synthetic effort, resulting in a limited substrate scope.[194]



Scheme 37. Strategies for the synthesis of chiral γ-branched aliphatic amines.[90, 193]

In this chapter, we explore the synthesis of γ-trifluoromethylated aliphatic amines via a stereospecific isomerization/diastereoselective reduction strategy (Scheme 38). Importantly, we envision that with this method, we might access chiral aliphatic amines bearing two non-consecutive stereogenic carbons in the α and γ positions to the amine functional group. These scaffolds remain, to the best of our knowledge, unexplored.



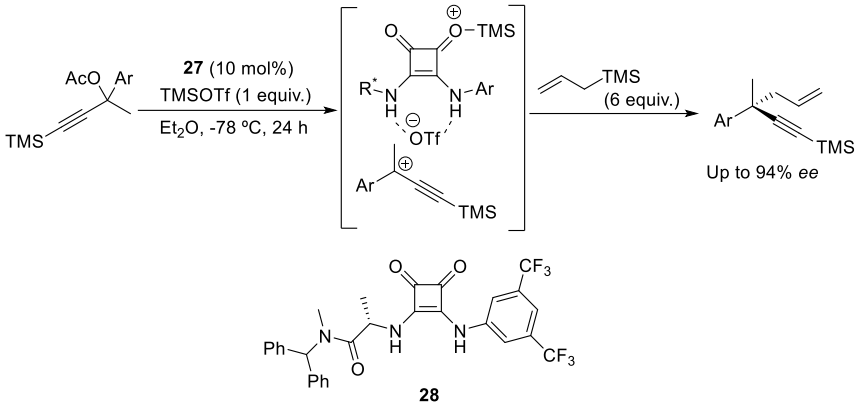
Scheme 38. Stereospecific and diastereoselective synthesis of γ-trifluoromethylated aliphatic amines.

5.2 Synthesis of chiral allylic amines

A direct approach for the synthesis of chiral allylic amines is the nucleophilic displacement of different leaving groups such as halides, mesylates or tosylates. However, as in the case of the synthesis of allylic chlorides (*vide supra*, Chapter 4), competitive reactions might lead to epimerization and the formation of undesired by-products. As expected, all our attempts to synthesize chiral allylic amines using nucleophilic substitution methods failed in our hands, resulting in poor yields and/or enantiomeric ratios.

The group of Jacobsen recently reported an enantioselective nucleophilic substitution of propargyl acetates with allyl silanes using hydrogen bonding

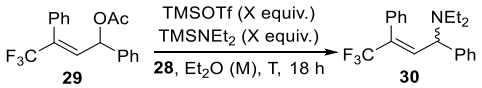
catalysis.[57] In this enantioselective S_N1 type reaction, a chiral ion pair is formed after the elimination of the acetyl group. This chiral ion pair controls the attack of the nucleophilic allyl silane, which occurs in an enantioselective manner (Scheme 39).



Scheme 39. Enantioselective S_N1 type reaction catalyzed by squaramide **28**.

Inspired by these results, we decided to test the enantioselective S_N1 reaction conditions on our tryfluoromethylated allylic systems aiming to synthesize chiral allylic amines (Table 2). Using the conditions described by Jacobsen and co-workers, the starting material was recovered both at −78 ºC and at room temperature (Table 2, entries 1 and 2). However, when the equivalents of TMSOTf were increased, 20% yield of the desired product was observed (Table 2, entry 3). Doubling up the concentration showed to be beneficial for the yield of the reaction, although **30** was obtained as a racemate (Table 2, entry 4). We next tested the reaction without the squaramide catalyst **28** (Table 2, entry 5), and a high yield of 77% of the desired product was obtained. This suggests that at room temperature, the background reaction is responsible for the low enantioselectivity. In an attempt to avoid this situation, we decreased the temperature of the reaction, but similar outcomes were observed in terms of enantiomeric excess, whereas the conversion decreased significantly (Table 2, entries 6 and 7).

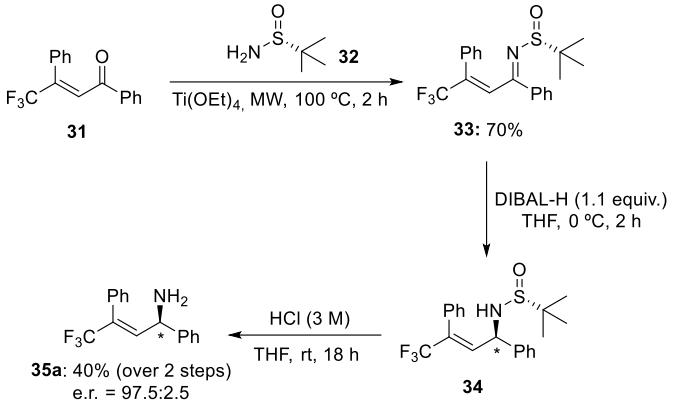
Table 2. Optimization studies of the enantioselective synthesis of allylic amines.[a]



Entry	TMSOTf (equiv.)	$TMSNEt_2$ (equiv.)	M (mol/L)	T (ºC)	Conv. (%)[b]	e.r.[c]
1	1	6	0.1	–78	-	n.d.
2	1	6	0.1	25	-	n.d.
3	2	6	0.1	25	20	n.d.
4	2	6	0.2	25	100	50:50
5[d]	2	6	0.2	25	77	n.d.
6	2	6	0.2	0	15	50:50
7	2	6	0.2	-78	-	n.d.

[a]: Reactions carried out using **29** (0.1 mmol). [b]: Conversion determined by ^1H NMR spectroscopy. [c]: e.r. determined by chiral HPLC analysis. d: Reaction performed without catalyst **28**.

We therefore decided to change our strategy for the synthesis of chiral trifluoromethylated allylic amines. Chiral sulfinamides have recently been used by the group of Guijarro for the synthesis of chiral sulfinyl imines in a microwave assisted protocol using $Ti(OEt)_4$.[195] When these conditions were applied to enone **31** (Scheme 40) and (*R*)-*tert*-butylsulfinamide (**32**), chiral sulfinyl imine **33** was obtained in 70%. Afterwards, a diastereoselective reduction of the imine using DIBAL-H as reducing agent, and subsequent deprotection of the chiral auxiliary, resulted in chiral γ-trifluoromethylated allylic amine **35a** in good yield over two steps with very high enantioselectivity.



Scheme 40. Synthesis of chiral allylic amines.

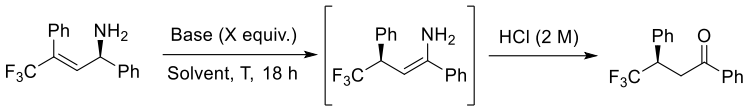
5.3 Optimization of the stereospecific isomerization/ diastereoselective reduction of allylic amines

After developing an enantioselective protocol for the synthesis of chiral trifluoromethylated allylic amines, we focused our efforts on the optimization of the stereospecific isomerization/diastereoselective protocol.

As a first approach, we studied the reaction conditions for the stereospecific isomerization of allylic amines (Table 3). To simplify the enantiomeric excess determination, we hydrolyzed the enamine/imine intermediates observed after the base-catalyzed isomerization reaction, obtaining the previously reported trifluoromethylated ketones (**37**) as products.[94]

First, different organic bases were evaluated in catalytic amounts at 120 ºC. As expected from our previous studies, TBD was able to catalyze the reaction with high efficiency in terms of yield and transfer of chirality (c.t.; Table 3, entry 1). 1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU) also yielded the desired product in catalytic amounts, but a significant decrease of the yield was observed (Table 3, entry 2). The N–H bond in TBD was proven to be crucial for the reaction to take place in catalytic amounts with high efficiency since 7-methyl-1,5,7-triazabicyclo(4.4.0)dec-5-ene (MTBD) only gave 17% yield of the desired product (Table 3, entry 3). The more basic phosphazene base P_4-*t*-Bu afforded only 7% yield of **37** (Table 3, entry 4).

Table 3. Optimization of the stereospecific isomerization of allylic amines.[a]



35a
Z/E = 92:8
ee = 95%

36

37

Entry	Base (equiv.)	Solvent	Temp. (ºC)	Yield (%)[b]	c.t. (%)[c]
1	TBD (0.1)	Toluene	120	>99	84
2	DBU (0.1)	Toluene	120	52	n.d.
3	MTBD (0.1)	Toluene	120	17	n.d.
4	P_4-*t*-Bu (0.1)	Toluene	120	7	n.d.
5	TBD (0.1)	Toluene	60	>99	88
6	TBD (0.1)	Toluene	25	0	n.d.
7	TBD (0.1)	HFIP	60	0	n.d.
8	TBD (0.1)	$CHCl_3$	60	11	n.d.
9	TBD (0.1)	Dioxane	60	>99	86
10	TBD (0.1)	EtOAc	60	>99	84
11	**TBD (0.05)**	**Toluene**	**60**	**>99**	**93**
12	TBD (0.025)	Toluene	60	45	n.d.

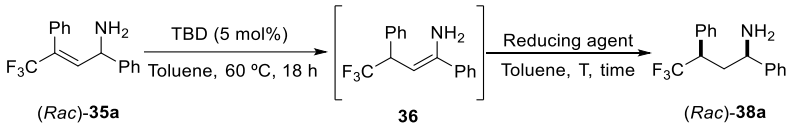
[a]: Reactions were run using **35a** (0.1 mmol). [b]: Yield of **37** determined by ^{19}F NMR spectroscopy. [c]: c.t. = ($ee_{product}/ee_{SM}$)*100 determined after hydrolysis into **37**.

Lowering the reaction temperature to 60 ºC did not have any dramatic effect in the yield nor on the enantiomeric ratio of the ketone (Table 3, entry 5). And when the temperature was decreased to room temperature, only the starting material was recovered (Table 3, entry 6). In polar solvents such as HFIP or $CHCl_3$ and at 60 ºC very low conversions where observed (Table 3,

entries 7 and 8). Dioxane and EtOAc could also be used as solvents in the transformation but not further improvement in the enantiomeric ratio of **36** was observed (Table 3, entries 9 and 10). Finally, we could lower the catalyst loading to 5 mol% with similar outcomes, but decreasing it even more had a negative effect in the yield of the reaction (Table 3, entries 11 and 12).

After establishing the optimal conditions for the stereospecific isomerization of allylic amines, we studied the one-pot isomerization/diastereoselective reduction of intermediate **36** (Table 4). We first tested different reducing procedures starting with $NaBH_4$, which yielded the desired product as a mixture of diastereomers (Table 4, entry 1). Using diisobutylaluminium hydride (DIBAL–H) as reducing agent at room temperature we were also able to identify amine **38** among different by-products with poor diastereoselectivity (Table 4, entry 2). Other reducing agents were tested at room temperature but none of them led to the formation of **38a** in synthetically useful yields (Table 4, entries 3, 4 and 5). Reducing the temperature to 0 ºC or −78 ºC using DIBAL–H as reducing agent resulted in a significant improvement in the diastereoselectivity and avoided completely the formation of by-products (Table 4, entries 6 and 7). Other hydride donor reagents were evaluated under our one-pot reaction conditions, although complex reaction mixtures were obtained in the case of L-Selectride (Table 4, entry 8) and poor diastereoselectivity in the case of lithium triethylborohydride (Super-hydride) (Table 4, entry 9). Decreasing the temperature even more to –90 ºC using DIBAL-H led to the optimized reaction conditions for the one pot isomerization/reduction protocol (Table 4, entry 10). Using less equivalents of DIBAL–H had a negative effect on the yield of the reaction (Table 4, entry 11).

Table 4. Optimization of the one pot isomerization / diastereoselective synthesis of γ-trifluoromethylated aliphatic amines.[a]



(*Rac*)-**35a** **36** (*Rac*)-**38a**

Entry	Reducing agent	Temp. (ºC)	Time (h)	Conversion (%)[b]	Yield (%)[b]	d.r.[b]
1[c]	$NaBH_4$	25	2	99	99	50:50
2	DIBAL-H	25	2	99[d]		58:42
3	$BH_3{\cdot}SMe_2$	25	18	0	0	-
4	$BH_3{\cdot}THF$	25	18	0	0	-
5	$Et_3SiH/B(C_6F_5)_3$	25	18	0	0	-
6	DIBAL-H	0	2	99	99	65:35
7	DIBAL-H	–78 ºC	2	99	99	70:30
8	L-Selectride	–78 ºC	2	99[d]	13	92:8
9	Super-hydride	–78 ºC	2	99	81	56:44
10	**DIBAL-H**	**–90 ºC**	**2**	**99**	**99% (83%)[e]**	**75:25**
11[f]	DIBAL-H	–90 ºC	2	99	10	-

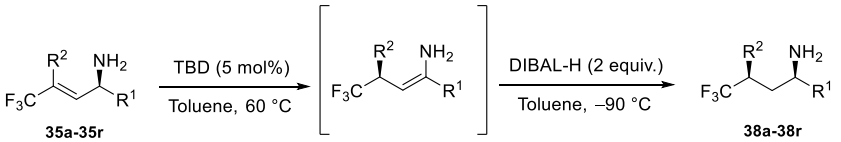
[a]: Reactions were run using **35a** (0.1 mmol) and 2 equiv. of reducing agent, toluene 0.02 M. [b]: Conversion yield and d.r. determined by ^{19}F NMR spectroscopy. [c]: Toluene:MeOH (1:1) used as solvent. d: Different by-products observed. [e]: Isolated yield in parentheses. [f]: 1 equiv. of DIBAL-H used, ketone **37** observed as the major product.

5.4 Scope of the synthesis of γ-trifluoromethylated aliphatic amines from chiral allylic amines

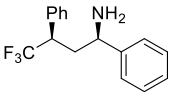
The best reaction conditions (Table 4, entry 10) were then applied to study the stereospecific isomerization / reduction of a variety of allylic amines (Scheme 41).

We then studied the effect of the substitution at R^2, *para* and *meta* substituted γ-trifluoromethylated aliphatic amines were obtained in high yield, good diastereoselectivities and a good chirality transfer (**38m**-**38o**). Thiophene substituted allylic amine **35n** yielded the desired product in quantitative yield and chirality transfer, although moderate diastereoselectivity was obtained. Disubstituted allylic amines could also be converted to γ-trifluoromethylated aliphatic amines under our reaction conditions (**38q**). Importantly, propargyl amine **35r** was transformed to the corresponding allylic amine under our reaction conditions in high yield and good *E*/*Z* ratios (**38r**).

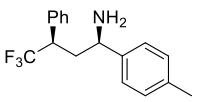
4-Methyl substituted allylic amine **35b** was also well tolerated and the desired chiral amine was obtained with high efficiency, although with a somehow less efficient chirality transfer. This is due to the lower *E*/*Z* ratio of the starting chiral allylic amine (**35b**). Both electron-donating and electron-withdrawing groups at *para* position at R^1 reacted smoothly, yielding chiral γ-trifluoromethylated aliphatic amines **38b**-**38e** in high yields, with excellent levels of chirality transfer, and good diastereoselectivities. Naphthyl substituted allylic amine **35f** was also converted into the desired aliphatic amine in 86% yield, 75:25 diastereomeric ratio, and, remarkably, with high transfer of chirality . *Meta* substitution was also nicely tolerated under the reaction conditions (**38g-38h**). A higher temperature was required for the isomerization of the *ortho* substituted allylic amine **35i** as a consequence of the higher steric hindrance in the deprotonation step. When the aryl substituent was replaced by an alkyl substituent (**35j**), only 8% yield was observed, even at an increased temperature of 120 ºC, due to the lower acidity of the transferred proton. However, non-substituted allylic amine **35k** was converted to its corresponding aliphatic amine in 60% yield.



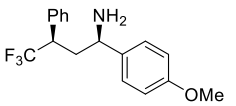
35a-35r **38a-38r**



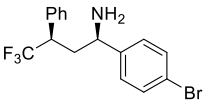
38a: From **35a** (*ee* = 95%, E/Z = 97:3): 83%, d.r. = 75:25, *ee* (major) = 90% c.t. = 95%



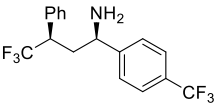
38b: From **35b** (*ee* = 90%, E/Z = 85:15): 90%, d.r. = 67:33, ee (major) = 70% c.t. = 78%



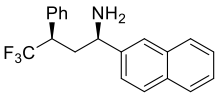
38c: From **35c** (*ee* = 90%, E/Z = 94:6): 68%[a], d.r. = 65:35, *ee* (major) = 85% c.t. = 94%



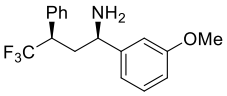
38d: From **35d** (*ee* = 94%, E/Z = 90:10): 73%, d.r. = 72:28, *ee* (major) = 86% c.t. = 91%



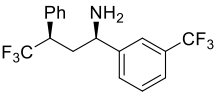
38e: From **35e** (*ee* = 95%, E/Z = 92:8): 54%, d.r. = 65:35, *ee* (major) = 87% c.t. = 92%



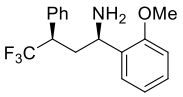
38f: From **35f** (*ee* = 97%, E/Z = 97:3): 87%, d.r. = 75:25, *ee* (major) = 94% c.t. = 97%



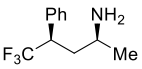
38g: From **35g** (*ee* = 93%, E/Z = 97:3): 99%[a], d.r. = 66:33, *ee* (major) = 88% c.t. = 95%



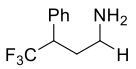
38h: From **35h** (*ee* = 94%, E/Z = 92:8): 80%, d.r. = 75:25, ee (major) = 80% c.t. = 85%



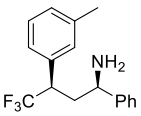
38i: From **35i** (*ee* = 75%, E/Z = 98:2): 42%[a], d.r. = 66:34, ee (major) =72% c.t. = 96%



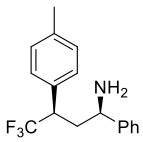
38j: From **35j** (E/Z = 97:3): 8%[a,b], d.r. = 75:25



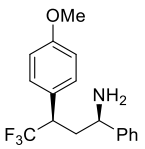
38k: From **35k** (E/Z = 98:2): 60%[a,b]



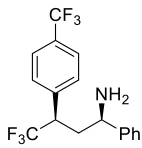
38l: From **35l** (*ee* = 92%, E/Z = 89:11): 75%, d.r. = 75:25, *ee* (major) = 83% c.t. = 90%



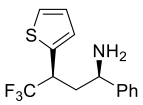
38m: From **35m** (*ee* = 91%, E/Z = 87:13): 90%, d.r. = 67:33, *ee* (major) = 70% c.t. = 77%



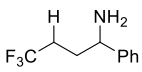
38n: From **35n** (*ee* = 91%, E/Z = 88:12): 73%, d.r. = 65:35, *ee* (major) = 81% c.t. = 89%



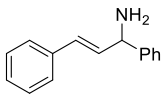
38o: From **35o** (*ee* = 94%, E/Z = 95:5): 55%, d.r. = 85:15, *ee* (major) = 70% c.t. = 74%



38p: From **35p** (*ee* = 95%, E/Z = 96:4): 99%, d.r. = 73:27, *ee* (major) = 90% c.t. = 95%



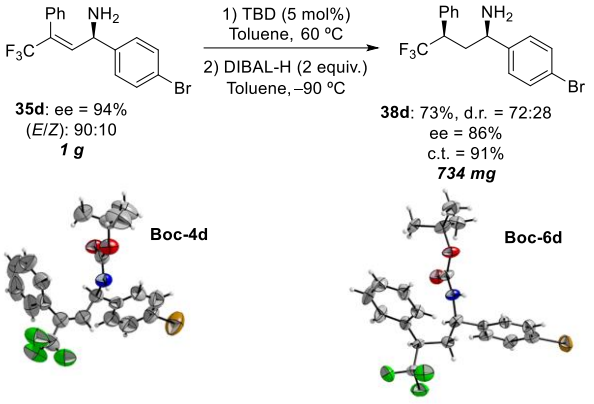
38q: From **35q** (E/Z = 98:2): 65%[a]



38r: 77%, E/Z = 70:30

Scheme 41. Scope of the stereospecific and diastereoselective synthesis of chiral γ-trifluoromethylated aliphatic amines. Reaction conditions: **35a-35r** (0.25 mmol, 1 equiv.), TBD (0.013 mmol, 0.05 equiv.), DIBAL-H (0.5 mmol, 2 equiv.), Toluene (0.02 M). c.t. = ($ee_{product}/ee_{SM}$)*100. Yield determined by ^{19}F NMR. a: Reaction performed at 120 ºC.

Moreover, the reaction can be carried out in gram-scale without observing a significant effect in the yield of the chirality transfer of the reaction (Scheme 42). The absolute configuration of allylic amine **35d** and its corresponding aliphatic amine **38d** was determined by x-ray single crystal analysis of their boc-protected analogues (Scheme 42).



Scheme 42. Determination of the absolute configuration of **4d** and **6d**.

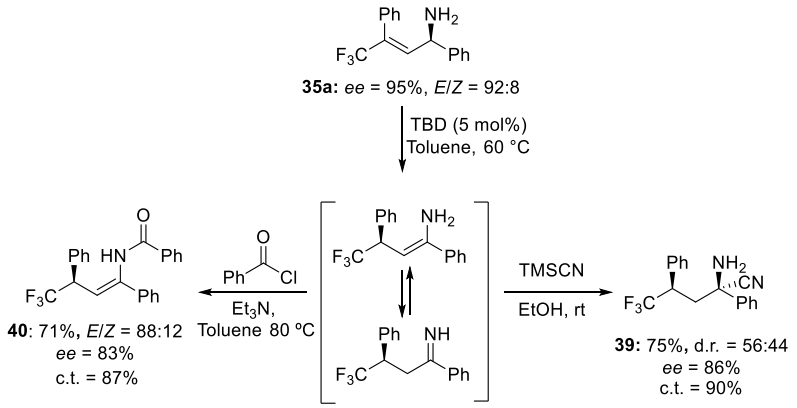
5.5 Enamine / Imine intermediates as chiral building blocks in organic synthesis

After developing a protocol for the synthesis of chiral γ-trifluoromethylated aliphatic amines, we focused our attention in the synthetic utility of the chiral enamine/imine intermediates of the stereospecific isomerization reaction (Scheme 43).

A Strecker type reaction was first evaluated (Scheme 43), by reacting the chiral enamine/imine intermediate with a cyanide source. This reaction yielded chiral α-cyano-γ-trifluoromethylated amine **39** in very high yield and good enantiomeric excess, although poor diastereoselectivity was obtained in this case. Our synthetic methodology represents an opportunity to obtain chiral γ-trifluoromethylated α-amino acids, that might serve for the formation of biologically active compounds, under very mild conditions.[196]

The enamine/imine intermediates formed after the stereospecific isomerization can react further not only with nucleophiles, but also with electrophiles. The nitrogen is the more nucleophilic center in the enamine/imine intermediates. Benzoyl chloride can be used to form enamide **40** in high yield and good enantiomeric excess. Enamides are valuable intermediates in synthetic organic chemistry, as they are resistant to hydrolysis

in addition to being important building blocks in transition metal-catalyzed reactions.[197]



Scheme 43. Stereospecific synthetic transformations from chiral allylic amines.

5.6 Conclusion

In this chapter, the stereospecific and diastereoselective synthesis of chiral γ-trifluoromethylated aliphatic amines has been discussed.

First, the enantioselective synthesis of chiral allylic amines has been developed in three steps, starting from readily available enones and a chiral sulfinamide as chiral auxiliary.

We have optimized the reaction conditions for the base-catalyzed stereospecific isomerization of allylic amines and their diastereoselective reduction to form chiral γ-trifluoromethylated aliphatic amines in a one-pot two steps protocol with excellent yields and moderate diastereoselectivities. Importantly, when chiral allylic amines have been subjected to our reaction conditions, excellent levels of chirality transfer have been obtained.

Finally, the synthetic opportunities of the chiral enamine/imine intermediates of the isomerization reaction have been explored. Using different protocols for their reaction with nucleophiles and electrophiles, the synthesis of chiral α-cyano-γ-trifluoromethylated amines and chiral enamides have been achieved in high yield and enantiomeric excess.

6. Concluding remarks

In the present thesis, four new methodologies for the transformation of allylic molecules and enol derivatives into highly functionalized organic compounds are described. Different approaches have been selected for the synthesis of molecules containing very polar functional groups, such as organic carbamates, primary amines, and fluorinated moieties, which are prominent in pharmaceutically active compounds.

First, a palladium-catalyzed allylic substitution reaction has been used for the synthesis of 3-fluoropiperidine imine scaffolds in a very efficient and regioselective manner. 3-Fluoropiperidine imines are important building blocks in organic synthesis, as they can be subjected to chemo- and diastereoselective functionalization. Different chiral phosphoramidite ligands have been tested under the reaction conditions, enabling the synthesis of enantiomerically enriched 3-fluoropiperidine imines with modest enantiomeric excess.

The reaction of silyl enol ethers with carbamate anions generated from CO_2 has been discussed in the second chapter of this thesis. As both reagents are nucelophiles, the reaction is only achieved through an umpolung strategy mediated by a hypervalent iodine(III) reagent. Only with 1-bromo-3,3-dimethyl-1,2-benziodoxole the desired products were observed. After optimizing the reaction conditions, different silyl enol ethers and amines have been tested yielding the desired carbamates in good yields. The method is not limited only to silyl enol ethers, but 1,3-dicarbonyl compounds can also react as nucleophiles to yield α-carbamate-β-ketoesters. The mechanism of the transformation, which relies on the formation of α-bromoketones and their nucleophilic substitution with other nucleophiles, has been studied experimentally in this thesis.

In Chapter IV, allylic chlorides, bromides and fluorides have been stereospecifically isomerized to the corresponding vinyl halides with high efficiency. After developing a method for the synthesis of chiral allylic chlorides, we have studied the chirality transfer over the isomerization reaction. The formation of a chiral ion pair after the deprotonation rate-determining step, is key for the high levels of transfer of chirality. Importantly, the synthetic utility of vinyl chlorides has been demonstrated by using them in a Suzuki-Miyaura cross-coupling reaction. In chapter V, this stereospecific protocol has been applied to chiral allylic amines. By reducing the enamine/imine intermediates in a diastereoselective manner, chiral γ-trifluoromethylated aliphatic amines have been obtained with high yield, and

high diastereoselectivity, as well as high enantioselectivity for the major isomer.

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Experimental procedures and characterization of novel compounds

General Methods

All reactions were carried out in flame-dried glassware equipped with a magnetic stir bar under nitrogen atmosphere, unless stated otherwise. Solvents were purified using a PureSolv MD purification system and transferred under nitrogen. A DrySyn block combined with a temperature probe was used as the heating source, where required. Infrared (IR) spectra were recorded on a Perkin Elmer Paragon FTIR spectrometer (vmax in cm-1). Samples were recorded neat as thin films. 1HNMR spectra were recorded on a Bruker AVIII HD 400 (400 MHz), Bruker AVI 400 (400 MHz) or Bruker AMX400 (400 MHz). Chemical shifts are reported in parts per million (ppm) from tetramethylsilane, using the residual protic solvent resonance as the internal reference: ($CHCl_3$: δ 7.26) unless otherwise stated. Data are reported as follows: chemical shift (integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz)). 13C-NMR spectra were recorded on a Bruker AVIII HD 400 (101 MHz), Bruker AVI 400 (101 MHz) or Bruker AMX-400 (101 MHz) with broadband proton decoupling. Chemical shifts are reported in ppm from trimethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.16). 19F-NMR spectra were recorded on a Bruker AV III HD 400 (377 MHz) and are uncorrected. High resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either a Micromass LCT operating in electrospray mode (TOF, ES+) or a Micromass Prospec operating in FAB (FAB+), EI (EI+) or CI (CI+) mode. Thin layer chromatography (TLC) was performed on aluminium-backed plates pre coated with silica (0.2 mm, Merck 60 F254) which were developed using standard visualizing agents: UV light or potassium permanganate. Flash chromatography was performed on silica gel (Merck 40- 63 µm). Melting points were recorded on Gallenkamp melting point apparatus and are uncorrected. Enantiomeric excesses were determined using HPLC analysis on an Agilent 1200-series instrument with an autosampler and UV detection and using Chiralcel OD-H, Chiralpak AD-H and IF and Phenomenex Lux Cellulose 5 columns. Optical rotations were recorded on a RUDOLPH AUTOPOL IV with an automatic polarimeter. Microwave reactions were performed in an Initiator Classic microwave reactor from Biotage.

Chapter 2 (Paper I)

General Procedures

General Procedure A (GPA)

To a suspension of sodium hydride (60% dispersion in mineral oil, 2.5 equiv.) in THF (0.5 M) under nitrogen was added ketone (1 equiv.) and diethyl carbonate (2.8 equiv.) and the resulting suspension heated to reflux until complete consumption of the ketone substrate. The reaction was then cooled to room temperature, diluted with AcOH (0.1 mL per mmol) and water (4 mL per mmol) and extracted with DCM (3 x 4 mL per mmol). The combined organic layers were then dried over anhydrous magnesium sulfate and concentrated under vacuum. The crude oil was then dissolved in acetonitrile (0.5 M) under nitrogen and selectfluor (1.2 equiv.) was added and the resulting mixture heated to 50 °C overnight. After cooling to room temperature the reaction was diluted with water (4 mL per mmol) and extracted with ethyl acetate (3 x 4 mL per mmol). The combined organic layers were then dried over anhydrous magnesium sulfate and

concentrated under vacuum. Purification by flash silica column chromatography (FCC) afforded the target fluorinated ketoesters.

General Procedure B (GPB)

To a solution of ethyl fluoroacetate (1 equiv.) and diphenylphosphinic chloride (1 equiv.) in dry THF (0.125 M) at -78 °C was added dropwise a solution of lithium bis(trimethylsilyl)amide (1.0 M in hexanes, 2 equiv.). After 10 minutes, the corresponding acyl chloride (1.1 equiv.) was added dropwise. The mixture was then stirred overnight at RT. After completion, the reaction was diluted with a saturated solution of ammonium chloride (4 mL per mmol) and extracted with ethyl acetate (3x 4 mL per mmol). The combined organic layers were then dried over anhydrous magnesium sulfate and concentrated under vacuum. Purification by flash silica column chromatography (FCC) afforded the target fluorinated ketoesters.

General Procedure C (GPC)

To a solution of the corresponding β-ketoester (1 equiv.) in MeCN (0.5 M) under nitrogen was added selectfluor (1.2 equiv.) and the resulting mixture heated to 50 °C overnight. After cooling to room temperature the reaction was diluted with water (4 mL per mmol) and extracted with ethyl acetate (3 x 4 mL per mmol). The combined organic layers were then dried over anhydrous magnesium sulfate and concentrated under vacuum. Purification by flash silica column chromatography (FCC) afforded the target fluorinated ketoesters.

General Procedure D (GPD)

Solution 1: To a solution of carboxylic acid (1.1 equiv.) in DCM (0.33 M) under nitrogen at 0 °C was added $(COCl)_2$ (1.1 equiv.) and 1 drop of DMF and the solution stirred at room temperature for 1.5 hours. The solvent was then removed under vacuum and the residue dissolved in THF (0.36 M) under nitrogen.

Solution 2: To a solution of ethyl fluoroacetate (1 equiv.) and diphenylphosphinic chloride (1 equiv.) in dry THF (0.2 M) at -78 °C was added dropwise a solution of lithium bis(trimethylsilyl)amide (1.0 M in hexanes, 3 equiv.). After 10 minutes **solution 1** was added dropwise and the reaction mixture was then allowed to warm to room temperature and stirred overnight. The mixture was then diluted with sat. NH4Cl (25 mL), extracted with EtOAc (4 x 25 mL) and the combined organic layers dried over anhydrous magnesium sulfate and concentrated under vacuum. Purification by flash silica column chromatography (FCC) afforded the target fluorinated ketoesters.

General Procedure E (GPE)

A flame-dried sealed tube was charged with $Pd(dba)_2$ (5 mol%), *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (15 mol%) and *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (1 equiv.) under nitrogen. Anhydrous CH_2Cl_2 (5 mL per mmol) was then added and the mixture stirred at room temperature for 10 minutes. A solution of ketoester (1.5 equiv.) in CH_2Cl_2 (5 mL per mmol) was then added and the reaction stirred at room temperature overnight. The reaction was then concentrated under vacuum and purified by flash silica column chromatography.

General Procedure F (GPF)

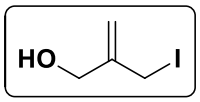
To a solution of allyation product (1 eq) in DCM (0.1M) was added TFA (75 equiv.) and the resulting mixture stirred at room temperature for 1.5 hours. The mixture was then basified to pH 8 using sat. $NaHCO_3$ and stirred for 45 minutes before extraction with DCM (3 x 25 mL). The combined organic layers were then dried over anhydrous magnesium sulfate and concentrated under vacuum to afford the title piperidines.

SCF_3-substituted starting materials **11a** - **11i** were synthesised in a single step from commercially available α-haloketones following reported procedure.[1]

NMR Data of Compounds

Substrates and Ligands

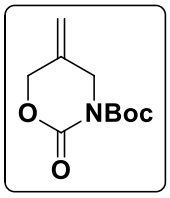
2-(iodomethyl)prop-2-en-1-ol (s1)[2]



To a solution of 2-methylene-1,3-propanediol (22.0 g, 250 mmol), triphenylphosphine (72.1 g, 275 mmol) and imidazole (18.7 g, 275 mmol) in a mixture of DCM (277 mL) and EtOAc (277 mL) at 0 °C under nitrogen was added iodine (63.4 g, 250 mmol) portionwise and the resulting mixture stirred at room temperature in the dark for 24 hours. The solvent was then removed under vacuum (**CAUTION**: alkylating agents) and the residue purified by FCC (gradient from 15-20% EtOAc in 40-60 petroleum ether) to afford 2-(iodomethyl)prop-2-en-1-ol (**s1**) as a yellow oil (28.2 g, 57%).

^{1}H NMR (400 MHz, CDCl3) δ 5.38 (dd, J= 1.5, 1.0 Hz, 1H), 5.23 (dd, J= 2.5, 1.5 Hz, 1H), 4.34 (d, J= 5.5 Hz, 2H), 4.00 (d, J= 1.0 Hz, 2H), 2.14 (t, J= 5.5 Hz, 1H); **^{13}C NMR (101 MHz, CDCl3)** δ 145.8, 114.2, 63.9, 5.8.

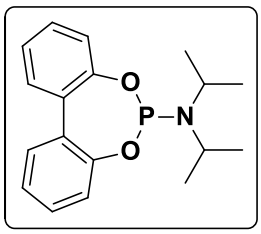
tert-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (2)[2]



To a suspension of silver cyanate (32.0 g, 214 mmol) in toluene (375 mL) under nitrogen was added 2-(iodomethyl)prop-2-en-1-ol (**s1**) (28.2 g, 142 mmol) in toluene (30 mL) and the resulting mixture heated at reflux for 24 hours. After cooling to room temperature the reaction was filtered through celite, the filter pad washed with Et_2O (3 x 100 mL) and the combined filtrates concentrated under vacuum. The crude solid and 4-dimethylaminopyridine (3.5 g, 28 mmol) were then dissolved in DCM (215 mL) under nitrogen and the resulting mixture cooled to 0 °C. Di-*tert*-butyl dicarbonate (62.0 g, 284 mmol) was then added slowly and the resulting mixture heated at 25 °C for 24 hours. Removal of the solvent under vacuum and purification by FCC (gradient from 20-25% EtOAc in 40-60 petroleum ether) afforded *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (**2**) as a colourless oil which converted to a white solid upon standing in the freezer (17.6 g, 58%).

^{1}H NMR (400 MHz, CDCl3) δ 5.18 (d, J = 6.0 Hz, 2H), 4.64 (s, 2H), 4.29 (t, J= 2.0 Hz, 2H), 1.52 (s, 9H); **^{13}C NMR (100 MHz, CDCl3)** δ152.0, 150.9, 134.7, 113.0, 83.9, 69.9, 48.7, 28.0.

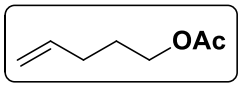
N,*N*-diisopropyldibenzo[d,f][1,3,2]dioxaphosphepin-6-amine (L1)[2]



To a flame-dried RBF containing THF (168 mL) at 0 °C under nitrogen was added PCl_3 (3.7 g, 27 mmol) dropwise over 15 minutes. Et_3N (14 g, 134 mmol) was then added dropwise over 15 minutes followed by the addition of diisopropylamine (2.7 g, 27 mmol) dropwise over 30 minutes. The resulting mixture was then warmed to room temperature and stirred for 3 hours before cooling to 0 °C. 2,2'-Biphenol (5.0 g, 27 mmol) was then added portionwise and the reaction mixture stirred at room temperature overnight. The volatiles were then removed under vacuum (**CAUTION**: toxic) and the resulting residue purified by FCC (gradient from 0-20% DCM in 40-60 petroleum ether) to afford *N*,*N*-diisopropyldibenzo[d,f][1,3,2]dioxaphosphepin-6-amine (**L1**) as a white solid (7.4 g, 87%).

^{1}H NMR (400 MHz, CDCl3) δ 7.46 (dd, J= 7.5, 1.5 Hz, 2H), 7.33 (td, J= 7.5, 1.5 Hz, 2H), 7.24 –7.16 (m, 4H), 3.58 –3.44 (dhept., 10.5 Hz, J= 7.0 Hz, 2H), 1.22 (d, J= 7.0 Hz, 12H); **^{13}C NMR (101 MHz, CDCl3)** δ 151.9 (d, *J* = 5.5 Hz), 131.0 (d, *J* = 3.0 Hz), 129.8, 129.1, 124.3, 122.3, 44.7 (d, *J* = 12.5 Hz), 24.6 (d, *J* = 8.0 Hz); **^{31}P NMR (162 MHz, $CDCl_3$)** δ 152.2 – 151.8 (m).

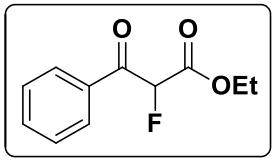
pent-4-en-1-yl acetate (s2)[3]



To a solution of 4-penten-1-ol (0.86 g, 10 mmol) and 4-dimethylaminopyridine (0.24 g, 2.0 mmol) in pyridine (20 mL) under nitrogen was added acetyl chloride (1.6 g, 20 mmol) and the resulting mixture heated at 40 °C for 4 hours. After cooling to room temperature the mixture was diluted with H_2O (10 mL) and sat. $NaHCO_3$ (10 mL) and extracted with Et_2O (4 x 25 mL). The combined organic layers were then washed with 5% $CuSO_4$ (8 x 10 mL) and 1.0 M HCl (3 x 25 mL) and dried over anhydrous $MgSO_4$. Removal of the volatiles under vacuum afforded pent-4-en-1-yl acetate (**s2**) (1.1 g, 84%)(CAUTION: stench).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H), 5.06 – 4.94 (m, 2H), 4.06 (t, *J* = 6.5 Hz, 2H), 2.11 (dd, *J* = 14.5, 7.5 Hz, 2H), 2.03 (s, 3H), 1.76 – 1.67 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.3, 137.6, 115.4, 64.0, 30.1, 27.9, 21.1.

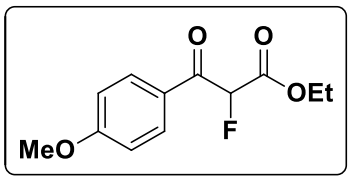
ethyl 2-fluoro-3-oxo-3-phenylpropanoate (1a)[4]



Following GPA using acetophenone (2.50 g, 21 mmol), diethylcarbonate (6.8 g, 58 mmol), sodium hydride (60% dispersion in mineral oil, 2.1 g, 52 mmol), selectfluor (8.8 g, 25 mmol) and acetic acid (2.5 mL) with FCC (10% EtOAc in 40-60 petroleum ether) afforded ethyl 2-fluoro-3-oxo-3-phenylpropanoate (**1a**) as a yellow oil (3.6 g, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 8.00 (m, 2H), 7.66 – 7.59 (m, 1H), 7.52 – 7.46 (m, 2H), 5.87 (d, *J* = 49.0 Hz, 1H), 4.34 – 4.22 (m, 2H), 1.24 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 189.6 (d, *J* = 20.0 Hz), 165.0 (d, *J* = 24.0 Hz), 134.63, 133.5 (d, *J* = 2.0 Hz), 129.6 (d, *J* = 3.5 Hz), 128.9, 90.1 (d, *J* = 197.5 Hz), 62.8, 14.0; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -190.4 (d, *J* = 49.0 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 2984, 1758, 1692, 1597, 1449, 1241, 1096, 1014 cm^{-1}.

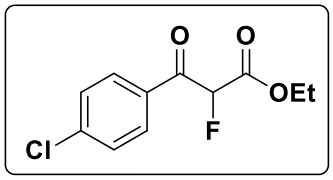
ethyl 2-fluoro-3-(4-methoxyphenyl)-3-oxopropanoate (1b)[5]



Following GPA using 4-methoxyacetophenone (1.5 g, 10 mmol), diethylcarbonate (3.3 g, 28 mmol), sodium hydride (60% dispersion in mineral oil, 1.0 g, 25 mmol), selectfluor (4.3 g, 12 mmol) and acetic acid (1 mL) with FCC (gradient from 0-10% EtOAc in 40-60 petroleum ether) afforded ethyl 2-fluoro-3-(4-methoxyphenyl)-3-oxopropanoate (**1b**) as an orange oil (1.8 g, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 8.00 (m, 2H), 6.97 – 6.93 (m, 2H), 5.81 (d, *J* = 49.0 Hz, 1H), 4.34 – 4.21 (m, 2H), 3.87 (s, 3H), 1.25 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 187.9 (d, *J* = 20.0 Hz), 165.3 (d, *J* = 24.5 Hz), 164.7, 132.1 (d, *J* = 3.5 Hz), 126.4 (d, *J* = 2.0 Hz), 114.2, 90.1 (d, *J* = 197.0 Hz), 62.7, 55.7, 14.0; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -189.6 (d, *J* = 49.0 Hz).

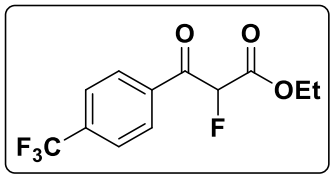
ethyl 2-fluoro-3-(4-chlorophenyl)-3-oxopropanoate (1f)[6]



Following GPB using ethyl fluoroacetate (0.53 g, 5 mmol), diphenylphosphinic chloride (1.7 g, 5 mmol), lithium bis(trimethylsilyl)amide (1 M solution in Hexane, 1.67 g, 10 mmol and 4-chlorobenzoyl chloride (0.96 g, 5.5 mmol) with FCC (gradient from 10-20% EtOAc in 40-60 petroleum ether) afforded ethyl 2-fluoro-3-(4-chlorophenyl)-3-oxopropanoate (**1c**) as a pale yellow oil (0.4 g, 33%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.94 (m, 2H), 7.53 – 7.41 (m, 2H), 5.81 (d, *J* = 49.0 Hz, 1H), 4.35 – 4.23 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 188.6 (d, *J* = 20.5 Hz), 164.8 (d, *J* = 24.0 Hz), 141.4, 131.7, 131.1 (d, *J* = 3.5 Hz), 129.4, 90.4 (d, *J* = 198.0 Hz), 63.0, 14.1; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -190.0 (d, *J* = 49.0 Hz).

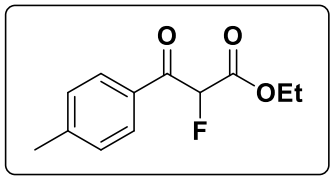
ethyl 2-fluoro-3-(4-trifluoromethylphenyl)-3-oxopropanoate (1d)



Following GPB using ethyl fluoroacetate (0.53 g, 5 mmol), diphenylphosphinic chloride (1.7 g, 5 mmol), lithium bis(trimethylsilyl)amide (1 M solution in Hexane, 1.67 g, 10 mmol and 4-trifluoromethylbenzoyl chloride (1.15 g, 5.5 mmol) with FCC (gradient from 10-20% EtOAc in 40-60 petroleum ether) afforded ethyl 2-fluoro-3-(4-trifluoromethylphenyl)-3-oxopropanoate (**1d**) as a yellow oil (0.43 g, 31%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H), 5.85 (d, *J* = 49.0 Hz, 1H), 4.34 – 4.26 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 189.1 (d, *J* = 21.0 Hz), 164.6 (d, *J* = 24.0 Hz), 135.9, 135.5, 130.0 (d, *J* = 4.0 Hz), 126.0 (dd, *J* = 7.0, 3.5 Hz), 123.3 (q, *J* = 273.0 Hz), 90.4 (d, *J* = 199.0 Hz), 63.1, 14.0; **^{19}F NMR (376 MHz, $CDCl_3$)**: δ -63.5, -190.5 (d, *J* = 49.0 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 2987, 1761, 1704, 1412, 1325, 1170, 1128, 1066, 889, 853 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{12}H_{11}F_4O_3$ (ES^+)($+H^+$): 279.0639. Found: 279.0647.

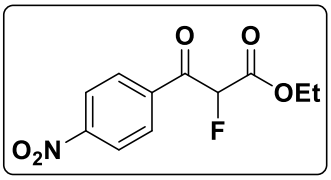
ethyl 2-fluoro-3-(4-methylphenyl)-3-oxopropanoate (1b)[7]



Following GPB using ethyl fluoroacetate (0.53 g, 5 mmol), diphenylphosphinic chloride (1.7 g, 5 mmol), lithium bis(trimethylsilyl)amide (1 M solution in Hexane, 1.67 g, 10 mmol and 4-methylbenzoyl chloride (0.85 g, 5.5 mmol) with FCC (gradient from 10-20% EtOAc in 40-60 petroleum ether) afforded ethyl 2-fluoro-3-(4-methylphenyl)-3-oxopropanoate (**1e**) as a colourless oil (0.60 g, 55%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.84 (d, *J* = 49.0 Hz, 1H), 4.35 – 4.23 (m, 2H), 2.42 (s, 3H), 1.25 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 189.2 (d, *J* = 20.0 Hz), 165.2 (d, *J* = 24.0 Hz), 145.9, 131.0, 129.8 (d, *J* = 3.5 Hz), 129.7, 90.2 (d, *J* = 197.4 Hz), 62.8, 22.0, 14.1; **^{19}F NMR (377 MHz, $CDCl_3$):** δ -190.2 (d, *J* = 49.0 Hz).

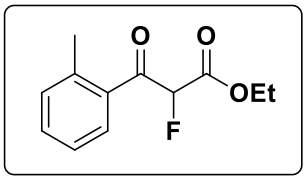
ethyl 2-fluoro-3-(4-nitrophenyl)-3-oxopropanoate (1e)[8]



Following GPB using ethyl fluoroacetate (0.53 g, 5 mmol), diphenylphosphinic chloride (1.7 g, 5 mmol), lithium bis(trimethylsilyl)amide (1 M solution in Hexane, 1.67 g, 10 mmol and 4-nitrobenzoyl chloride (1.0 g, 5.5 mmol) with FCC (gradient from 10-20% EtOAc in 40-60 petroleum ether) afforded ethyl 2-fluoro-3-(4-nitrophenyl)-3-oxopropanoate (**1f**) as a orange oil (0.35 g, 27%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, *J* = 9.0 Hz, 2H), 8.22 (d, *J* = 8.5 Hz, 2H), 5.84 (d, *J* = 49.0 Hz, 1H), 4.33 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 188.7 (d, *J* = 21.5 Hz), 164.3 (d, *J* = 24.0 Hz), 151.1, 137.8 (d, *J* = 2.5 Hz), 130.8 (d, *J* = 4.0 Hz), 124.1, 90.6 (d, *J* = 199.0 Hz), 63.3, 14.1; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -190.2 (d, *J* = 49.0 Hz).

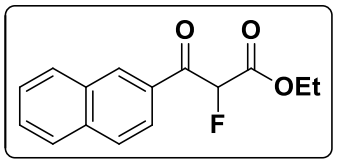
ethyl 2-fluoro-3-(2-methylphenyl)-3-oxopropanoate (1g)



Following GPB using ethyl fluoroacetate (0.53 g, 5 mmol), diphenylphosphinic chloride (1.7 g, 5 mmol), lithium bis(trimethylsilyl)amide (1 M solution in Hexane, 1.67 g, 10 mmol and 2-methylbenzoyl chloride (0.85 g, 5.5 mmol) with FCC (gradient from 10-20% EtOAc in 40-60 petroleum ether) afforded ethyl 2-fluoro-3-(2-methylphenyl)-3-oxopropanoate (**1g**) as a colourless oil (0.13 g, 11%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.70 (m, 1H), 7.46 – 7.40 (m, 1H), 7.31 – 7.26 (m, 2H), 5.82 (d, *J* = 49.0 Hz, 1H), 4.31 – 4.22 (m, 2H), 2.49 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 192.5 (d, *J* = 20.5 Hz), 164.9 (d, *J* = 24.0 Hz), 140.2, 133.3, 132.8, 132.2, 129.8 (d, *J* = 4.5 Hz), 125.7, 90.3 (d, *J* = 198.5 Hz), 62.6, 21.1, 13.9; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -189.2 (dd, *J* = 49.0, 2.0Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 2985, 1759, 1699, 1457, 1265, 1236, 1106, 1014, 735, 703 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{12}H_{14}FO_3$ (ES^+)($+H^+$): 225.0921 Found: 225.0922.

ethyl 2-fluoro-3-(naphthalen-2-yl)-3-oxopropanoate (1h)

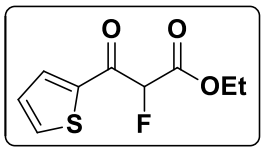


Following GPA using 2-acetylnaphthalene (0.85 g, 5 mmol), diethylcarbonate (1.7 g, 14 mmol), sodium hydride (60% dispersion in mineral oil, 0.50 g, 13 mmol), selectfluor (2.1 g, 6 mmol) and acetic acid (0.5 mL) with FCC (gradient from 20-50% DCM in 40-60 petroleum ether) afforded ethyl 2-fluoro-3-(naphthalen-2-yl)-3-oxopropanoate (**1h**) as a yellow oil (1.1 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.05 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.99 (dd, *J* = 8.0, 0.5 Hz, 1H), 7.94 – 7.86 (m, 2H), 7.64 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.58 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 5.99 (d, *J* = 49.0 Hz, 1H), 4.37 – 4.25 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)**

δ 189.5 (d, *J* = 20.0 Hz), 165.2 (d, *J* = 24.0 Hz), 136.2, 132.4 (d, *J* = 4.5 Hz), 130.8 (d, *J* = 2.0 Hz), 130.1, 129.5, 128.9, 128.0, 127.2, 124.3 (2C), 90.3 (d, *J* = 197.5 Hz), 62.85, 14.09; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -189.6 (d, *J* = 49.0 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 3061, 2983, 1759, 1687, 1626, 1467, 1256, 1229, 1188, 1097 1019 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{15}H_{13}FO_3$ (ES^+)($+H^+$): 261.0921. Found: 261.0926.

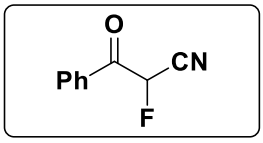
ethyl 2-fluoro-3-oxo-3-(thiophen-2-yl)propanoate (1i)[9]



Following GPA using 2-acetylthiophene (1.3 g, 10 mmol), diethylcarbonate (3.3 g, 28 mmol), sodium hydride (60% dispersion in mineral oil, 1.0 g, 25 mmol), selectfluor (4.3 g, 12 mmol) and acetic acid (1 mL) with FCC (gradient from 30-60% DCM in 40-60 petroleum ether) afforded ethyl 2-fluoro-3-oxo-3-(thiophen-2-yl)propanoate (**1i**) as an orange oil (1.7 g, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.99 (m, 1H), 7.79 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.18 (dd, *J* = 5.0, 4.0 Hz, 1H), 5.69 (d, *J* = 49.0 Hz, 1H), 4.36 – 4.23 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 182.5 (d, *J* = 22.0 Hz), 164.7 (d, *J* = 24.5 Hz), 139.6 (d, *J* = 3.0 Hz), 136.4, 135.5 (d, *J* = 7.0 Hz), 128.8, 90.6 (d, *J* = 199.0 Hz), 62.91, 14.06; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -189.2 (dd, *J* = 49.0, 1.5 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 3106, 2984, 1756, 1665, 1410, 1251, 1202, 1095, 1061, 1018 cm^{-1}.

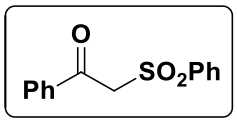
2-fluoro-3-oxo-3-phenylpropanenitrile (1j)[10]



Following GPB using ethyl fluoroacetonitrile (0.3 g, 5 mmol), diphenylphosphinic chloride (1.7 g, 5 mmol), lithium bis(trimethylsilyl)amide (1 M solution in Hexane, 1.67 g, 10 mmol and benzoyl chloride (0.77 g, 5.5 mmol) with FCC (gradient from 10-20% EtOAc in 40-60 petroleum ether) afforded 2-fluoro-3-oxo-3-phenylpropanenitrile (**1j**) as a yellow oil (0.3 g, 37%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.0 Hz, 2H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 2H), 6.14 (d, *J* = 46.7 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 184.9 (d, *J* = 20.0 Hz), 135.7, 131.7, 129.5, 129.4 (d, *J* = 3.0 Hz), 112.4 (d, *J* = 30.0 Hz), 79.7 (d, *J* = 197.2 Hz); **^{19}F NMR (377 MHz, $CDCl_3$)** δ -192.0 (d, *J* = 46.5 Hz).

1-phenyl-2-(phenylsulfonyl)ethanone (s3)[11]



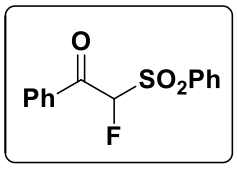
To a solution of acetophenone (1.2 g, 10 mmol) in THF (25 mL) under nitrogen at -78 °C was added LiHMDS (1.0 M in hexanes, 12 mL, 12 mmol) and the solution was stirred at -78 °C for 30 minutes. Acetic anhydride (2.0 g, 20 mmol) was then added and the resulting mixture was stirred for 30 minutes before being warmed to room temperature and stirred for a further 2 hours. The mixture was then diluted with sat. $NaHCO_3$ (30 mL) and extracted with EtOAc (4 x 30 mL). The combined organic layers were then washed with brine (30 mL), dried over anhydrous magnesium sulfate and concentrated under vacuum. The crude residue was then purified by FCC (gradient from 20-30% DCM in 40-60 petroleum ether).

The purified oil and sodium *p*-toluenesulfinate (1.5 g, 7.5 mmol) were then dissolved in MeCN (15 mL) and H_2O (4 mL) before the addition of iodine (1.6 g, 6.2 mmol). The resulting mixture was heated at 70 °C overnight and then cooled to room temperature and diluted with water (30 mL). The product was extracted with EtOAc (3 x 30 mL) and the combined organic layers dried over anhydrous magnesium sulfate and concentrated under vacuum. Purification by FCC (30%

EtOAc in 40-60 petroleum ether) afforded 1-phenyl-2-(phenylsulfonyl)ethanone (**s3**) as a yellow solid (1.1 g, 39%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.92 (m, 2H), 7.79 – 7.74 (m, 2H), 7.65 – 7.59 (m, 1H), 7.51 – 7.46 (m, 2H), 7.36 – 7.31 (m, 2H), 4.71 (s, 2H), 2.44 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 188.3, 145.5, 135.9, 135.9, 134.5, 130.0, 129.5, 129.0, 128.8, 63.7, 21.9.

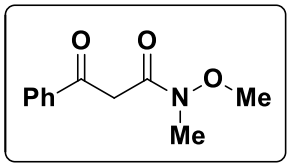
2-fluoro-1-phenyl-2-(phenylsulfonyl)ethanone (1k)[12]



To a solution of sodium hydride (60% dispersion in mineral oil, 73 mg, 1.8 mmol) in THF (3.6 mL) under nitrogen at 0 °C was added 1-phenyl-2-(phenylsulfonyl)ethanone (**s3**) (0.50 g, 1.8 mmol) in THF (3.6 mL) dropwise and the solution was stirred at 0 °C for 2 hours. Selectfluor (0.65 g, 1.8 mmol) was then added in 1 portion and the resulting mixture was stirred at room temperature overnight. The reaction mixture was then diluted with water (30 mL) and extracted with DCM (3 x 30mL). The combined organic layers were then washed with brine (30 mL), dried over anhydrous magnesium sulfate and concentrated under vacuum. Purification by FCC (gradient from 50-100% DCM in 40-60 petroleum ether) afforded 2-fluoro-1-phenyl-2-(phenylsulfonyl)ethanone (**1k**) as a white solid (0.37 g, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.5 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.71 – 7.65 (m, 1H), 7.56 – 7.50 (m, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 6.32 (d, *J* = 48.0 Hz, 1H), 2.47 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.7 (d, *J* = 17.5 Hz), 146.8, 135.1, 134.1, 131.6, 130.1, 130.0, 129.9 (d, *J* = 2.5 Hz), 128.9, 100.3 (d, *J* = 231.5 Hz), 21.9; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -179.6 (d, *J* = 48.0 Hz).

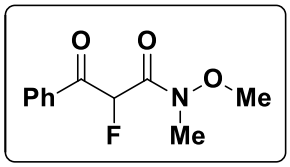
N-methoxy-*N*-methyl-3-oxo-3-phenylpropanamide (s4)[13]



To a solution of diisopropylamine (2.2 g, 21 mmol) in THF (29 mL) under nitrogen at -78 °C was added *n*-butyllithium (2.4 M in hexanes, 8.1 mL, 19 mmol) and the resulting solution stirred at -78 °C for 1 hour. A solution of *N*-methoxy-*N*-methylacetamide (1.0 g, 9.7 mmol) in THF (10 mL) was then added and the reaction mixture stirred for 1 hour before the addition of benzoyl chloride (1.4 g, 9.7 mmol). After stirring at -78 °C for 4 hours the mixture was warmed to room temperature, diluted with 1M HCl (50 mL) and extracted with EtOAc (4 x 40 mL). The combined organic layers were then dried over anhydrous magnesium sulfate and concentrated under vacuum. Purification by FCC (30% EtOAc in 40-60 petroleum ether) afforded *N*-methoxy-*N*-methyl-3-oxo-3-phenylpropanamide (**s4**) as an orange oil (1.8 g, 90%)(2:1, keto:enol).

<u>Keto:</u> ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.93 (m, 2H), 7.52 – 7.39 (m, 3H), 4.13 (s, 2H), 3.65 (s, 3H), 3.23 (s, 3H); **<u>Enol:</u> ^{1}H NMR (400 MHz, $CDCl_3$)** δ 14.26 (s, 1H), 7.84 – 7.77 (m, 2H), 7.62 – 7.55 (m, 2H), 7.50 – 7.39 (m, 1H), 6.08 (s, 1H), 3.75 (s, 3H), 3.26 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 193.6, 172.8, 171.6, 168.6, 136.4, 134.5, 133.7, 131.0, 128.8, 128.5, 126.1, 84.5, 61.6, 61.5, 44.6, 32.3, 32.1.

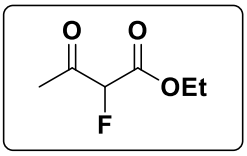
2-fluoro-*N*-methoxy-*N*-methyl-3-oxo-3-phenylpropanamide (1l)



Following GPC using *N*-methoxy-*N*-methyl-3-oxo-3-phenylpropanamide (**s4**) (1.4 g, 6.8 mmol) and selectfluor (2.9 g, 8.2 mmol) with FCC (gradient from 25-30% EtOAc in 40-60 petroleum ether) afforded 2-fluoro-*N*-methoxy-*N*-methyl-3-oxo-3-phenylpropanamide (**1l**) as a yellow oil (1.4 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 6.14 (d, *J* = 48.5 Hz, 1H), 3.64 (s, 3H), 3.23 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 190.2 (d, *J* = 20.5 Hz), 165.9 (d, *J* = 22.0 Hz), 134.4, 134.0, 129.4 (d, *J* = 3.0 Hz), 128.9, 90.0 (d, *J* = 190.5 Hz), 61.7, 32.6; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -190.9 (d, *J* = 48.5 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 3008, 2947, 1685, 1680, 1450, 1340, 1219, 1053, 972 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{11}H_{13}FNO_3$ (ES^+)(+H^+): 226.0874. Found: 226.0867.

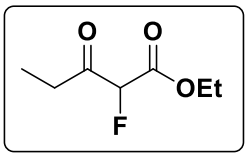
ethyl 2-fluoro-3-oxobutanoate (1m)[14]



Following GPC using ethyl 3-oxobutanoate (0.65 g, 5 mmol) and selectfluor (2.13 g, 6 mmol) with FCC (gradient from 10-20% EtOAc in 40-60 petroleum ether) afforded ethyl 2-fluoro-3-oxobutanoate (**1m**) as a colourless oil (0.5 g, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (d, *J* = 49.5 Hz, 1H), 4.34 – 4.27 (m, 2H), 2.34 (d, *J* = 4.0 Hz, 3H), 1.32 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 199.2 (d, *J* = 24.0 Hz), 164.1 (d, *J* = 24.0 Hz), 91.6 (d, *J* = 198.0 Hz), 62.9, 26.2, 14.1; **^{19}F NMR (377 MHz, $CDCl_3$):** δ -193.1 (dq, *J* = 49.5, 4.0 Hz).

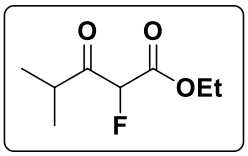
ethyl 2-fluoro-3-oxopentanoate (1n)[15]



Following GPC using ethyl 3-oxopentanoate (0.72 g, 5 mmol) and selectfluor (2.13 g, 6 mmol) with FCC (gradient from 10-20% EtOAc in 40-60 petroleum ether) afforded ethyl 2-fluoro-3-oxopentanoate (**1n**) as a colourless oil (0.7 g, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.21 (d, *J* = 49.5 Hz, 1H), 4.30 (q, *J* = 7.0 Hz, 2H), 2.81 – 2.61 (m, 2H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.10 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 202.0 (d, *J* = 23.0 Hz), 164.4 (d, *J* = 24.0 Hz), 91.4 (d, *J* = 198.5 Hz), 62.8, 32.0, 14.1, 6.9; **^{19}F NMR (376 MHz, $CDCl_3$)**: δ -195.1 (d, *J* = 49.4 Hz).

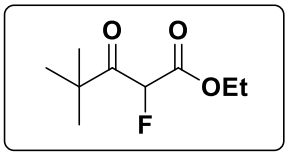
ethyl 2-fluoro-4-methyl-3-oxopentanoate (1o)[16]



Following GPC using ethyl 4-methyl-3-oxo-pentanoate (0.79 g, 5 mmol) and selectfluor (2.13 g, 6 mmol) with FCC (gradient from 10-20% EtOAc in 40-60 petroleum ether) afforded ethyl 2-fluoro-4-methyl-3-oxopentanoate (**1o**) as a colourless oil (0.62 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.29 (d, *J* = 49.0 Hz, 1H), 4.30 (q, *J* = 7.0 Hz, 2H), 3.16 – 3.05 (m, 1H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.15 (d, *J* = 3.5 Hz, 3H), 1.13 (d, *J* = 3.5 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 205.0 (d, *J* = 22.0 Hz), 164.5 (d, *J* = 24.0 Hz), 90.8 (d, *J* = 198.0 Hz), 62.7, 37.1, 17.9, 17.5, 14.1; **^{19}F NMR (376 MHz, $CDCl_3$)**: δ -195.7 (dd, *J* = 49.5, 2.5 Hz).

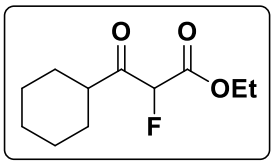
ethyl 2-fluoro-4,4-dimethyl-3-oxopentanoate (1p)



Following GPB using ethyl fluoroacetate (0.53 g, 5 mmol), diphenylphosphinic chloride (1.7 g, 5 mmol), lithium bis(trimethylsilyl)amide (1 M solution in Hexane, 1.67 g, 10 mmol and 4- 2,2-dimethylpropanoyl chloride (0.66 g, 5.5 mmol) with FCC (gradient from 10-20% EtOAc in 40-60 petroleum ether) afforded ethyl 2-fluoro-4,4-dimethyl-3-oxopentanoate (**1p**) as a yellow oil (0.43 g, 31%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.47 (d, *J* = 49.0 Hz, 1H), 4.30 (q, *J* = 7.0 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.25 (d, *J* = 1.0 Hz, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 205.3 (d, *J* = 18.0 Hz), 165.1 (d, *J* = 23.5 Hz), 89.3 (d, *J* = 198.0 Hz), 62.6, 44.7, 25.9 (d, *J* = 2.0 Hz), 14.2; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -190.6 (d, *J* = 49.0 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 2975, 1760, 1717, 1479, 1369, 1213, 1094, 1017, 939, 736 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_9H_{16}FO_3$ (ES^+)($+H^+$): 191.1078. Found: 191.1081.

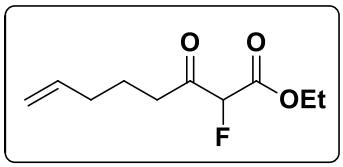
ethyl 3-cyclohexyl-2-fluoro-3-oxopropanoate (1q)



Following GPA using 1-cyclohexylethan-1-one (0.7 g, 5 mmol), diethylcarbonate (1.7 g, 14 mmol), sodium hydride (60% dispersion in mineral oil, 0.3 g, 12.5 mmol), selectfluor (2.13 g, 6 mmol) and acetic acid (0.5 mL) with FCC (10% EtOAc in 40-60 petroleum ether) afforded ethyl 3-cyclohexyl-2-fluoro-3-oxopropanoate (**1q**) as a colourless oil (0.52 g, 48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.26 (d, *J* = 49.5 Hz, 1H), 4.30 (q, *J* = 7.0 Hz, 2H), 2.96 – 2.77 (m, 1H), 1.96 – 1.59 (m, 6H), 1.45 – 1.16 (m, 7H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 203.8 (d, *J* = 21.5 Hz), 164.4 (d, *J* = 24.0 Hz), 90.7 (d, *J* = 197.5 Hz), 62.5, 46.5, 28.1, 27.6, 25.7, 25.5, 25.3, 14.0; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -195.7 (dd, *J* = 49.5, 3.0 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 2932, 2857, 1757, 1725, 1450, 1261, 1146, 1096, 1023, 993 cm^{-1}. **HRMS (ESI$^+$):** calculated for $C_{11}H_{18}FO_3$ (ES^+)($+H^+$): 217.1234 Found: 217.1233.

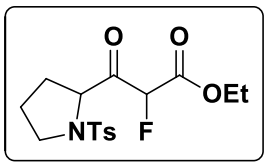
ethyl 2-fluoro-3-oxooct-7-enoate (1r)



Following GPD using hex-5-enoic acid (0.25 g, 2.2 mmol), $(COCl)_2$ (0.31 g, 2.4 mmol), ethyl fluoroacetate (0.21 g, 2.0 mmol), diphenylphosphinic chloride (0.47 g, 2.0 mmol) and LiHMDS (6.0 mL, 6.0 mmol) with FCC (gradient from 10-50% EtOAc in 40-60 petroleum ether) afforded ethyl 2-fluoro-3-oxooct-7-enoate (**1r**) as a yellow oil (95 mg, 24%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H), 5.18 (d, *J* = 49.5 Hz, 1H), 5.05 – 4.96 (m, 2H), 4.29 (q, *J* = 7.0 Hz, 2H), 2.75 – 2.59 (m, 2H), 2.07 (q, *J* = 7.0 Hz, 2H), 1.72 (p, *J* = 7.0 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 201.3 (d, *J* = 23.0 Hz), 164.3 (d, *J* = 24.0 Hz), 137.6, 115.8, 91.5 (d, *J* = 198.5 Hz), 62.8, 37.7, 32.9, 21.8, 14.1; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -194.8 (d, *J* = 49.5 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 2980, 2940, 1758, 1732, 1371, 1258, 1133, 1096, 1016 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{10}H_{16}FO_3$ (ES^+)($+H^+$): 203.1078. Found: 203.1080.

ethyl 2-fluoro-3-oxo-3-(1-tosylpyrrolidin-2-yl)propanoate (1s)

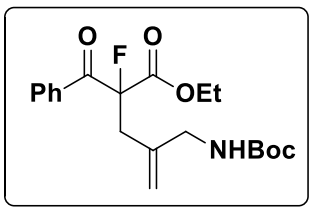


Following GPD using *N*-tosyl-*L*-proline (0.59 g, 2.2 mmol), $(COCl)_2$ (0.31 g, 2.4 mmol), ethyl fluoroacetate (0.21 g, 2.0 mmol), diphenylphosphinic chloride (0.47 g, 2.0 mmol) and LiHMDS (6.0 mL, 6.0 mmol) with FCC (20% EtOAc in 40-60 petroleum ether) afforded ethyl 2-fluoro-3-oxo-3-(1-tosylpyrrolidin-2-yl)propanoate (**1s**) as a yellow oil (0.24 g, 33%)(1:1 mixture of diastereoisomers).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.69 (m, 2H), 7.38 – 7.29 (m, 2H), 5.78 – 5.45 (m, 1H), 4.93 – 4.56 (m, 1H), 4.41 – 4.20 (m, 2H), 3.55 – 3.39 (m, 1H), 3.34 – 3.22 (m, 1H), 2.48 – 2.40 (m, 3H), 2.09 – 1.72 (m, 3H), 1.70 – 1.60 (m, 1H), 1.40 – 1.20 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 199.3 (d, *J* = 21.0 Hz), 198.9 (d, *J* = 21.0 Hz), 164.2 (d, *J* = 24.0 Hz), 164.2 (d, *J* = 23.0 Hz), 144.3, 144.2, 134.2, 134.1, 130.0, 129.8, 127.8, 127.7, 90.5 (d, *J* = 195.5 Hz), 90.4 (d, *J* = 195.5 Hz), 64.2 (2C), 63.1, 63.0, 49.0 (2C), 29.7 – 29.4 (m, 2C), 25.0 – 24.7 (m, 2C), 21.7 (2C), 14.1 (2C); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -197.4 – -197.7 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 2983, 1744, 1340, 1201, 1156, 1092, 1017 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{16}H_{21}FNO_5S$ (ES^+)($+H^+$): 358.1119. Found: 358.1118.

Allylation Products

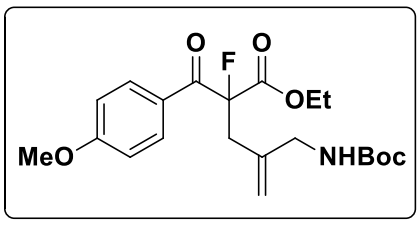
ethyl 2-benzoyl-4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoropent-4-enoate (3a)



Following GPE with ethyl 2-fluoro-3-oxo-3-phenylpropanoate (**1a**) (63 mg, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (20 % ethyl acetate in petroleum ether) afforded ethyl 2-benzoyl-4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoropent-4-enoate (**3a**) as a pale yellow oil (74 mg, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 5.14 (s, 1H), 5.03 (s, 1H), 4.77 (br, 1H), 4.35 – 4.16 (m, 2H), 3.76 (d, *J* = 4.0 Hz, 2H), 3.14 (dd, *J* = 33.0, 15.0 Hz, 1H), 2.97 (dd, *J* = 18.5, 15.5 Hz, 1H), 1.43 (s, 9H), 1.20 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 191.3 (d, *J* = 26.0 Hz), 167.1 (d, *J* = 26.0 Hz), 155.9, 139.8, 134.1, 133.8 (d, *J* = 3.0 Hz), 129.9 (d, *J* = 5.5 Hz), 128.8, 116.2, 100.0 (d, *J* = 200.0 Hz), 79.5, 62.9, 45.8, 38.2 (d, *J* = 20.5 Hz), 28.5, 14.1; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -157.6 (dd, *J* = 33.0, 18.5 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 2981, 2931, 1755, 1697, 1509, 1449, 1267, 1240, 1168, 908, 729, 694 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{20}H_{26}FNO_5Na$ (ES^+)($+Na^+$): 402.1687. Found: 402.1701.

ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(4-methoxybenzoyl)pent-4-enoate (3b)

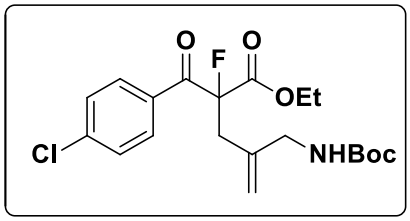


Following GPE with ethyl 2-fluoro-3-(4-methoxyphenyl)-3-oxopropanoate (**1b**) (72 mg, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (20 % ethyl acetate in petroleum ether) afforded ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(4-methoxybenzoyl)pent-4-enoate (**3b**) as an orange oil (78 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (dd, *J* = 9.0, 1.5 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 5.12 (s, 1H), 5.02 (s, 1H), 4.79 (br, 1H), 4.34 – 4.11 (m, 2H), 3.86 (s, 3H), 3.75 (s, 1H), 3.13 (dd, *J* = 34.0, 15.0 Hz, 1H), 2.94 (dd, *J* = 18.0, 15.5 Hz, 1H), 1.43 (s, 9H), 1.19 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz,**

$CDCl_3$) δ 189.4 (d, *J* = 25.0 Hz), 167.4 (d, *J* = 26.0 Hz), 164.3, 155.9, 139.9, 132.5 (d, *J* = 6.0 Hz), 126.5 (d, *J* = 3.5 Hz), 116.0, 114.1 (d, *J* = 20.0 Hz), 100.0 (d, *J* = 200.5 Hz), 79.5, 62.7, 55.6, 45.8, 38.2 (d, *J* = 20.5 Hz), 28.5, 14.1; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -156.9 (dd, *J* = 34.0, 18.0 Hz). **FTIR:** ν_{max}/cm^{-1} (neat) 2979, 1756, 1687, 1601, 1512, 1252, 1175, 1027, 848, 764 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{21}H_{28}FNO_6Na$ (ES^+)($+Na^+$): 432.1793. Found: 432.1799.

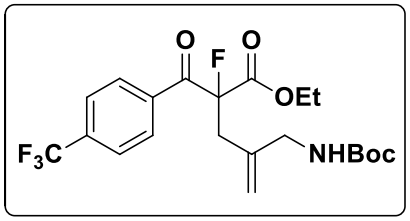
ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(4-chloromethylbenzoyl)pent-4-enoate (3f)



Following GPE with ethyl 2-fluoro-3-(4-chloromethylphenyl)-3-oxopropanoate (**1c**) (73 mg, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (20 % ethyl acetate in petroleum ether) afforded ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(4-chloromethylbenzoyl)pent-4-enoate (**3c**) as a colourless oil (74 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.44 – 7.39 (m, 2H), 5.13 (s, 1H), 5.02 (s, 1H), 4.76 (br, 1H), 4.31 – 4.14 (m, 2H), 3.74 (d, *J* = 5.0 Hz, 2H), 3.12 (dd, *J* = 33.0, 15.5 Hz, 1H), 2.95 (dd, *J* = 19.0, 15.5 Hz, 1H), 1.42 (s, 9H), 1.20 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 190.2 (d, *J* = 26.0 Hz), 166.8 (d, *J* = 26.0 Hz), 155.9, 140.8, 139.7, 132.0 (d, *J* = 3.5 Hz), 131.4 (d, *J* = 6.0 Hz), 129.2, 116.2, 100.0 (d, *J* = 200.0 Hz), 79.6, 63.0, 45.8, 38.1 (d, *J* = 20.5 Hz), 28.5, 14.1; **^{19}F NMR (377 MHz, $CDCl_3$):** δ -157.7 (dd, *J* = 33.0, 19.0 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 2925, 1752, 1700, 1589, 1275, 1261, 1170, 750 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{20}H_{25}ClFNO_5Na$ (ES^+)($+Na^+$): 436.1297 Found: 436.1312.

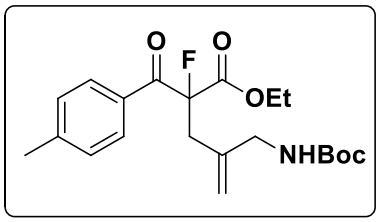
ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(4-trifluoromethylbenzoyl) pent-4-enoate (3d)



Following GPE with ethyl 2-fluoro-3-(4-trifluoromethylphenyl)-3-oxopropanoate (**1d**) (84 mg, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (20 % ethyl acetate in petroleum ether) afforded ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(4-trifluoromethylbenzoyl)pent-4-enoate (**3d**) as a pale yellow oil (76 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 2H), 5.14 (s, 1H), 5.03 (s, 1H), 4.76 (br, 1H), 4.29 – 4.13 (m, 2H), 3.75 (d, *J* = 5.5 Hz, 1H), 3.13 (dd, *J* = 32.5, 15.5 Hz, 1H), 2.97 (dd, *J* = 19.5, 15.5 Hz, 1H), 1.42 (s, 9H), 1.21 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 190.8 (d, *J* = 26.5 Hz), 166.6 (d, *J* = 26.0 Hz), 155.9, 139.6, 136.5, 135.2 (q, *J* = 33.0 Hz), 130.3 (d, *J* = 6.0 Hz), 125.8 (d, *J* = 3.5 Hz), 123.5 (q, *J* = 273.0 Hz), 116.3, 100.1 (d, *J* = 200.0 Hz), 79.6, 63.2, 45.8, 38.1 (d, *J* = 20.5 Hz), 28.5, 14.1; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -63.4 (s), -158.2 (dd, *J* = 32.5, 19.5 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 2986, 1758, 1715, 1638, 1409, 1325, 1314, 1124, 1115, 1066, 849, 701 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{21}H_{25}F_4NO_5Na$ (ES^+)($+Na^+$): 470.1561. Found: 470.1556.

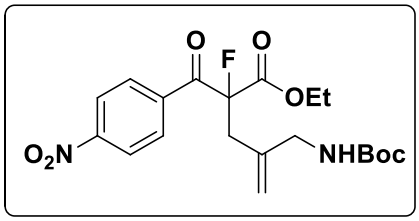
ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(4-methylbenzoyl)pent-4-enoate (3c)



Following GPE with ethyl 2-fluoro-3-(4-methylphenyl)-3-oxopropanoate (**1e**) (67 mg, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (20 % ethyl acetate in petroleum ether) afforded ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(4-methylbenzoyl)pent-4-enoate (**3e**) as a colourless oil (60 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.13 (s, 1H), 5.02 (s, 1H), 4.78 (br, 1H), 4.21 (tdd, *J* = 12.0, 7.0, 3.5 Hz, 2H), 3.75 (s, 2H), 3.13 (dd, *J* = 33.5, 15.5 Hz, 1H), 2.95 (dd, *J* = 18.0, 15.5 Hz, 1H), 2.40 (s, 3H), 1.43 (s, 9H), 1.19 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 190.7 (d, *J* = 25.5 Hz), 167.2 (d, *J* = 26.0 Hz), 155.9, 145.3, 139.9, 131.2 (d, *J* = 3.5 Hz), 130.1 (d, *J* = 5.5 Hz), 129.5, 116.0, 99.9 (d, *J* = 200.5 Hz), 79.5, 62.8, 45.8, 38.2 (d, *J* = 20.5 Hz), 28.5, 21.9, 14.1; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -157.3 (dd, *J* = 33.5, 18.5 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 2924, 1752, 1701, 1697, 1606, 1507, 1366, 1275, 1166, 1044, 764 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{21}H_{28}FNO_5Na$ (ES^+)($+Na^+$): 416.1844. Found: 416.1827.

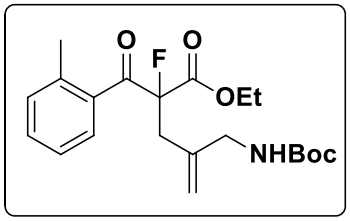
ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(4-nitrobenzoyl)pent-4-enoate (3e)



Following GPE with ethyl 2-fluoro-3-(4-nitrophenyl)-3-oxopropanoate (**1f**) (77 mg, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (20 % ethyl acetate in petroleum ether) afforded ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(4-nitrobenzoyl)pent-4-enoate (**3f**) as an orange oil (69 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.0 Hz, 2H), 8.18 (d, *J* = 8.5 Hz, 2H), 5.15 (s, 1H), 5.03 (s, 1H), 4.74 (br, 1H), 4.32 – 4.19 (m, 1H), 3.75 (d, *J* = 5.0 Hz, 2H), 3.13 (dd, *J* = 32.0, 15.0 Hz, 1H), 2.98 (dd, *J* = 20.0, 15.5 Hz, 1H), 1.43 (s, 9H), 1.23 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 190.7 (d, *J* = 27.0 Hz), 166.3 (d, *J* = 26.0 Hz), 155.9, 150.7, 139.4, 138.4 (d, *J* = 3.5 Hz), 131.0 (d, *J* = 6.0 Hz), 123.9, 116.4, 100.2 (d, *J* = 200.0 Hz), 79.7, 63.3 (d, *J* = 6.5 Hz), 45.8, 38.0 (d, *J* = 20.5 Hz), 28.5, 14.1; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -158.3 (dd, *J* = 32.0, 20.0 Hz).); **FTIR:** ν_{max}/cm^{-1} (neat) 3338, 1704, 1636, 1526, 1349, 1275, 1261, 1169,764, 750 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{20}H_{25}FN_2O_7Na$ (ES^+)($+Na^+$): 447.1538. Found: 447.1535.

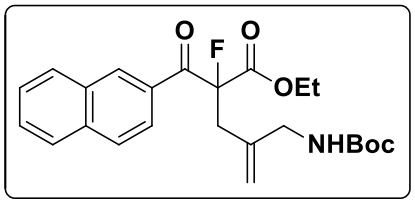
ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(2-methylbenzoyl)pent-4-enoate (3g)



Following GPE with ethyl 2-fluoro-3-(2-methylphenyl)-3-oxopropanoate (**1g**) (67 mg, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (20 % ethyl acetate in petroleum ether) afforded ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(2-methylbenzoyl)pent-4-enoate (**3g**) as a colourless oil (67 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (dd, *J* = 7.5, 3.0 Hz, 1H), 7.38 (td, *J* = 7.5, 1.0 Hz, 1H), 7.23 (dd, *J* = 15.0, 7.0 Hz, 2H), 5.13 (s, 1H), 5.05 (s, 1H), 4.77 (br, 1H), 4.25 (qd, *J* = 7.0, 2.0 Hz, 2H), 3.73 (d, *J* = 5.5 Hz, 2H), 3.14 – 2.95 (m, 2H), 2.41 (s, 3H), 1.43 (s, 9H), 1.24 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 195.4 (d, *J* = 27.0 Hz), 166.8 (d, *J* = 26.0 Hz), 155.9, 139.8, 139.3, 134.3, 132.1, 132.0, 129.0 (d, *J* = 9.0 Hz), 125.5, 116.1, 100.3 (d, *J* = 202.0 Hz), 79.5, 62.9, 45.8, 38.6 (d, *J* = 20.5 Hz), 28.5, 20.9, 14.1; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -158.1 (dd, *J* = 29.0, 22.0 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 2980, 2929, 1749, 1704, 1699, 1505, 1367, 1265, 1236, 1167, 1049, 735, 703 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{21}H_{28}FNO_5Na$ (ES^+)($+Na^+$): 416.1844. Found: 416.1864.

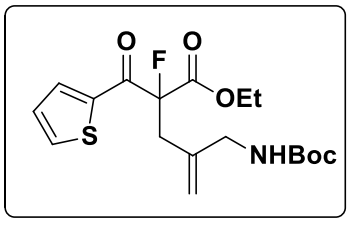
ethyl 2-(2-naphthoyl)-4-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluoropent-4-enoate (3h)



Following GPE using ethyl 2-fluoro-3-(naphthalen-2-yl)-3-oxopropanoate (**1h**) (78 mg, 0.30 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.20 mmol), $Pd(dba)_2$ (5.8 mg, 10 µmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (9.5 mg, 30 µmol) with FCC (50-100% DCM in 40-60 petroleum ether) afforded ethyl 2-(2-naphthoyl)-4-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluoropent-4-enoate (**3h**) as a yellow oil (86 mg, quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.03 (dt, *J* = 8.5, 1.5 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.87 (t, *J* = 8.5 Hz, 2H), 7.62 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.55 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 5.16 (s, 1H), 5.07 (s, 1H), 4.79 (br, 1H), 4.34 – 4.15 (m, 2H), 3.80 (br, 2H), 3.29 – 2.97 (m, 2H), 1.44 (s, 9H), 1.20 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 191.0 (d, *J* = 25.5 Hz), 167.2 (d, *J* = 26.0 Hz), 155.9, 139.9, 136.0, 132.4 (d, *J* = 8.0 Hz), 131.0 (2C), 130.3, 129.3, 128.6, 127.8, 127.1, 124.9 (d, *J* = 3.0 Hz), 116.1, 100.2 (d, *J* = 200.5 Hz), 62.9, 45.8, 38.3 (d, *J* = 20.5 Hz), 28.5 (3C), 14.1; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -156.8 (dd, *J* = 33.0, 18.5 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 3416, 2979, 1754, 1691, 1627, 1506, 1366, 1246, 1165, 909 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{24}H_{28}FNO_5Na$ (ES^+)($+Na^+$): 452.1844. Found: 452.1859.

ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(thiophene-2-carbonyl)pent-4-enoate (3i)

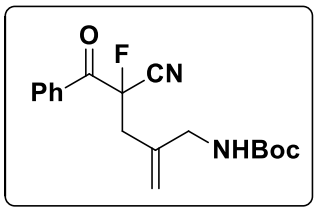


Following GPE with ethyl 2-fluoro-3-oxo-3-(thiophen-2-yl)propanoate (**1i**) (65 mg, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (20 % ethyl acetate in petroleum ether) afforded ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(thiophene-2-carbonyl)pent-4-enoate (**3i**) as an orange oil (63 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (t, *J* = 3.0 Hz, 1H), 7.73 (d, *J* = 5.0 Hz, 1H), 7.13 (t, *J* = 4.5 Hz, 1H), 5.12 (s, 1H), 5.04 (s, 1H), 4.78 (br, 1H), 4.29 – 4.15 (m, 2H), 3.74 (d, *J* = 5.0 Hz, 2H), 3.11 (dd, *J* = 32.0, 15.5 Hz, 1H), 2.95 (dd, *J* = 20.0, 15.5 Hz, 1H), 1.42 (s, 9H), 1.21 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 184.3 (d, *J* = 26.5 Hz), 166.5 (d, *J* = 26.5 Hz), 155.9, 139.6 (d, *J* = 4.5 Hz), 139.5, 136.1 (d, *J* = 2.0 Hz), 135.7 (d, *J* = 10.5 Hz), 128.8 (d, *J* = 1.5 Hz), 116.1, 100.0 (d, *J* = 200.5 Hz), 79.5, 62.9, 45.8, 37.8 (d, *J* = 20.0 Hz), 28.5, 14.1; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -158.3 (dd, *J* = 32.0, 20.0 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 2979, 1756, 1705, 1512, 1410, 1366, 1249, 1169, 1064,

911, 859, 732 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{18}H_{24}FNO_5SNa$ (ES^+)(+Na^+): 408.1251. Found: 408.1251.

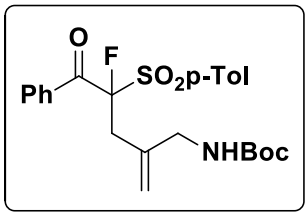
tert-butyl (4-cyano-4-fluoro-2-methylene-5-oxo-5-phenylpentyl)carbamate (3j)



Following GPE with α-fluoro-β-oxo-benzenepropanenitrile (**1j**) (49 mg, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (20 % ethyl acetate in petroleum ether) afforded *tert*-butyl (4-cyano-4-fluoro-2-methylene-5-oxo-5-phenylpentyl)carbamate (**3j**) as a colourless oil (58 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.0 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 5.33 (s, 1H), 5.23 (s, 1H), 4.79 (br, 1H), 3.90 – 3.73 (m, 2H), 3.13 – 2.93 (m, 2H), 1.44 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 188.6 (d, *J* = 24.5 Hz), 155.9, 137.8, 135.1, 131.9 (d, *J* = 3.5 Hz), 130.3 (d, *J* = 5.5 Hz), 129.1, 118.6, 114.7 (d, *J* = 34.0 Hz), 92.9 (d, *J* = 200.0 Hz), 79.9, 45.8, 40.2 (d, *J* = 22.0 Hz), 28.5; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -152.4 (dd, *J* = 30.0, 18.0 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 2986, 1758, 1715, 1638, 1409, 1325, 1314, 1124, 1115, 1066, 849, 701 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{18}H_{21}FN_2O_3Na$ (ES^+)(+Na^+): 355.1428. Found: 355.1443.

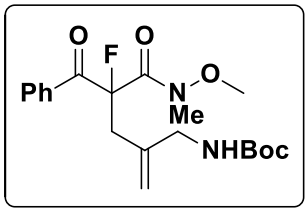
tert-butyl (4-fluoro-2-methylene-5-oxo-5-phenyl-4-tosylpentyl)carbamate (3k)



Following GPE using 2-fluoro-1-phenyl-2-(phenylsulfonyl)ethanone (**1k**) (88 mg, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (15 % ethyl acetate in petroleum ether) afforded *tert*-butyl (4-fluoro-2-methylene-5-oxo-5-phenyl-4-tosylpentyl)carbamate (**3k**) as a yellow oil (91 mg, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.69 (m, 4H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.36 – 7.27 (m, 4H), 5.03 (s, 1H), 4.92 (s, 1H), 4.67 (br, 1H), 3.61 – 3.53 (m, 2H), 3.45 (dd, *J* = 41.0, 15.0 Hz, 1H), 2.80 (dd, *J* = 14.5, 10.0 Hz, 1H), 2.40 (s, 3H), 1.38 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 193.0 (d, *J* = 24.5 Hz), 155.7, 146.7, 137.9, 135.5 (d, *J* = 4.0 Hz), 133.7, 131.3, 130.8, 130.0, 129.8 (d, *J* = 8.0 Hz), 128.3, 116.9, 112.9 (d, *J* = 240.0 Hz), 79.6, 45.8, 36.1 (d, *J* = 19.0 Hz), 28.4, 21.8; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -154.0 – -154.3 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 3356, 2977, 1686, 1651, 1523, 1334, 1288, 1249, 1150, 1072 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{24}H_{28}FNO_5SNa$ (ES^+)(+Na^+): 484.1564. Found: 484.1582.

tert-butyl (4-benzoyl-4-fluoro-5-(methoxy(methyl)amino)-2-methylene-5-oxopentyl)carbamate (3l)

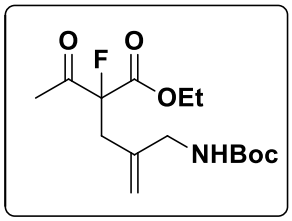


Following GPE using 2-fluoro-*N*-methoxy-*N*-methyl-3-oxo-3-phenylpropanamide (**1l**) (68 mg, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (15 % ethyl acetate in

petroleum ether) afforded *tert*-butyl (4-benzoyl-4-fluoro-5-(methoxy(methyl)amino)-2-methylene-5-oxopentyl)carbamate (**3l**) as a yellow oil (71 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.5 Hz, 2H), 7.60 – 7.53 (m, 1H), 7.49 – 7.41 (m, 2H), 5.07 (s, 1H), 4.91 (s, 1H), 4.83 (br, 1H), 3.76 (ddd, *J* = 21.5, 16.5, 6.0 Hz, 2H), 3.42 (s, 3H), 3.20 – 3.07 (m, 4H), 2.98 (dd, *J* = 27.0, 15.0 Hz, 1H), 1.43 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 192.3 (d, *J* = 24.5 Hz), 156.0, 139.9, 134.4, 133.6, 129.5 (d, *J* = 5.5 Hz), 128.7, 116.7, 100.2 (d, *J* = 198.0 Hz), 79.4, 61.4, 45.8, 38.4 (d, *J* = 21.0 Hz), 33.3, 28.5; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -154.4 – -154.7 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 3364, 2978, 2939, 1682, 1509, 1448, 1365, 1246, 1167, 986 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{20}H_{27}FN_2O_5Na$ (ES^+)(+Na^+): 417.1796. Found: 417.1808.

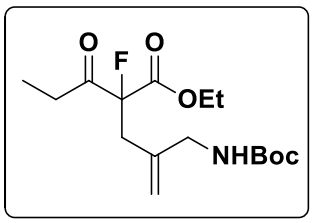
ethyl 2-acetyl-4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoropent-4-enoate (3m)



Following GPE with ethyl 2-fluoro-3-oxobutanoate (**1m**) (44 mg, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (15 % ethyl acetate in petroleum ether) afforded ethyl 2-acetyl-4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoropent-4-enoate (**3m**) as a colourless oil (56 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.10 (s, 1H), 4.99 (s, 1H), 4.73 (br, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 3.77 – 3.62 (m, 2H), 2.94 – 2.73 (m, 2H), 2.29 (d, *J* = 5.0 Hz, 3H), 1.43 (s, 9H), 1.28 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 201.7 (d, *J* = 29.5 Hz), 165.8 (d, *J* = 25.5 Hz), 155.9, 139.5, 115.8, 100.4 (d, *J* = 200.0 Hz), 79.6, 62.9, 45.8, 37.4 (d, *J* = 20.0 Hz), 28.5, 26.0, 14.1; **^{19}F NMR (377 MHz, $CDCl_3$):** δ -163.6 – -163.7 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 2979, 1755, 1716, 1514, 1367, 1248, 1169, 861 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{15}H_{24}FNO_5Na$ (ES^+)(+Na^+): 340.1531 Found: 340.1541.

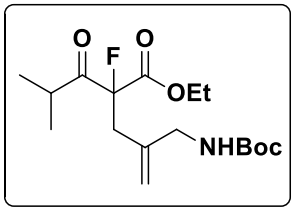
ethyl 4-({[(*tert*-butoxy)carbonyl]amino}methyl)-2-fluoro-2-propanoylpent-4-enoate (3n)



Following GPE with ethyl 2-fluoro-3-oxopentanoate (**1n**) (49 mg, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (15 % ethyl acetate in petroleum ether) afforded ethyl 4-({[(*tert*-butoxy)carbonyl]amino}methyl)-2-fluoro-2-propanoylpent-4-enoate (**3n**) as a pale yellow oil (55 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.09 (s, 1H), 4.98 (s, 1H), 4.72 (br, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 3.73 – 3.62 (m, 2H), 3.02 – 2.72 (m, 2H), 2.68 – 2.58 (m, 2H), 1.43 (s, 9H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.05 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 204.5 (d, *J* = 27.0 Hz), 166.0 (d, *J* = 25.5 Hz), 155.9, 139.6, 115.8, 100.6 (d, *J* = 199.5 Hz), 79.6, 62.8, 45.8, 37.6 (d, *J* = 20.0 Hz), 31.7, 28.5, 14.1, 7.1 (d, *J* = 2.0 Hz); **^{19}F NMR (376 MHz, $CDCl_3$)**: δ -165.8 – -166.1 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 2981, 1755, 1717, 1514, 1275, 1268, 1169, 764, 750 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{16}H_{26}FNO_5Na$ (ES^+)(+Na^+): 354.1687 Found: 354.1680.

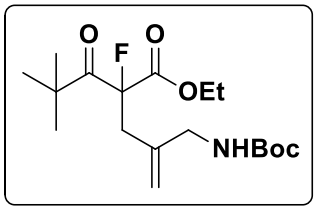
ethyl 4-({[(*tert*-butoxy)carbonyl]amino}methyl)-2-fluoro-2-(2-methylpropanoyl)pent-4-enoate (3o)



Following GPE with ethyl 2-fluoro-4-methyl-3-oxopentanoate (**1o**) (53 mg, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (15 % ethyl acetate in petroleum ether) afforded ethyl 4-({[(*tert*-butoxy)carbonyl]amino}methyl)-2-fluoro-2-(2-methylpropanoyl)pent-4-enoate (**3o**) as a colourless oil (63 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (s, 1H), 4.98 (s, 1H), 4.72 (br, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 3.78 – 3.61 (m, 2H), 3.20 – 3.07 (m, 1H), 2.90 (dd, *J* = 27.5, 15.0 Hz, 1H), 2.78 (dd, *J* = 23.5, 15.0 Hz, 1H), 1.43 (s, 9H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.12 – 1.05 (m, 6H); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 166.0 (d, *J* = 25.5 Hz), 155.8, 139.5, 115.8, 100.7 (d, *J* = 201.0 Hz), 79.4, 62.7, 45.7, 37.9 (d, *J* = 20.0 Hz), 36.3, 28.4, 18.5, 17.8, 14.0; **^{19}F NMR (376 MHz, $CDCl_3$)**: δ -167.1 – -167.4 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 2977, 1753, 1716, 1511, 1366, 1247, 1166, 1097, 1042, 909, 859 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{17}H_{28}FNO_5Na$ (ES^+)($+Na^+$): 368.1844. Found: 368.1829.

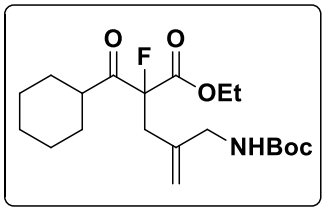
ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-(2,2-dimethylpropanoyl)-2-fluoropent-4-enoate (3p)



Following GPE with ethyl 2-fluoro-3-(2,2-dimethylpropanoyl)-3-oxopropanoate (**1p**) (57 mg, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (20 % ethyl acetate in petroleum ether) afforded ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-(2,2dimethylpropanoyl)-2-fluoropent-4-enoate (**3p**) as a colourless oil (58 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.09 (s, 1H), 4.99 (s, 1H), 4.74 (br, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 3.70 (d, *J* = 5.5 Hz, 2H), 2.93 (dd, *J* = 29.5, 15.0 Hz, 1H), 2.77 (dd, *J* = 21.5, 15.0 Hz, 1H), 1.43 (s, 9H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.20 (d, *J* = 1.5 Hz, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 206.7 (d, *J* = 25.5 Hz), 166.4 (d, *J* = 25.5 Hz), 155.9, 139.9, 116.1, 102.1 (d, *J* = 204.5 Hz), 79.5, 62.7, 45.8, 45.4 (d, *J* = 3.5 Hz), 39.3 (d, *J* = 20.5 Hz), 28.5, 26.4 (d, *J* = 4.5 Hz), 14.2; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -164.6 (dd, *J* = 28.5, 22.0 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 2928, 1716, 1696, 1576, 1367, 1275, 1260, 764 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{18}H_{30}FNO_5Na$ (ES^+)($+Na^+$): 382.2000 Found: 382.2014.

ethyl 4-({[(*tert*-butoxy)carbonyl]amino}methyl)-2-cyclohexanecarbonyl-2-fluoropent-4-enoate (3q)

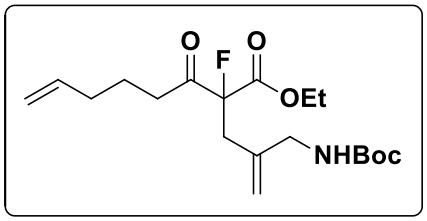


Following GPE with ethyl 3-cyclohexyl-2-fluoro-3-oxopropanoate (**1q**) (65 mg, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (15 % ethyl acetate in petroleum ether) afforded ethyl 4-({[(*tert*-butoxy)carbonyl]amino}methyl)-2-cyclohexanecarbonyl-2-fluoropent-4-enoate (**3q**) as a colourless oil (62 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.08 (s, 1H), 4.97 (s, 1H), 4.72 (br, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.69 (s, 2H), 2.96 – 2.67 (m, 3H), 1.86 – 1.62 (m, 6H), 1.42 (s, 9H), 1.35 – 1.20 (m, 7H); **^{13}C NMR (101**

MHz, $CDCl_3$) δ 206.4 (d, *J* = 25.0 Hz), 166.1 (d, *J* = 25.5 Hz), 155.9, 139.7, 115.9, 100.8 (d, *J* = 200.5 Hz), 79.6, 62.7, 46.1, 45.8, 37.9 (d, *J* = 20.5 Hz), 28.8 (d, *J* = 1.0 Hz), 28.5, 27.9 (d, *J* = 1.0 Hz), 25.7 (d, *J* = 4.5 Hz), 25.3, 14.2; **^{19}F NMR (376 MHz, $CDCl_3$)**: δ -167.1 – -167.4 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 2929, 1754, 1718, 1507, 1367, 1244, 1172 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{20}H_{32}FNO_5Na$ (ES^+)(+Na^+): 408.2157 Found: 408.2142.

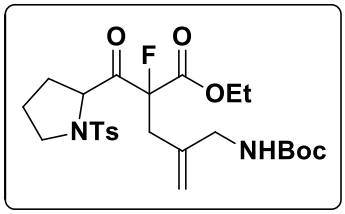
ethyl 2-(2-(((*tert*-butoxycarbonyl)amino)methyl)allyl)-2-fluoro-3-oxooct-7-enoate (3r)



Following GPE using ethyl 2-fluoro-3-oxooct-7-enoate (**1r**) (61 mg, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (15 % ethyl acetate in petroleum ether) afforded ethyl 2-(2-(((*tert*-butoxycarbonyl)amino)methyl)allyl)-2-fluoro-3-oxooct-7-enoate (**3r**) as a yellow oil (70 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H), 5.10 (s, 1H), 5.04 – 4.95 (m, 3H), 4.71 (s, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 3.78 – 3.61 (m, 2H), 2.90 (dd, *J* = 27.0, 15.5 Hz, 1H), 2.78 (dd, *J* = 24.0, 15.5 Hz, 1H), 2.68 – 2.62 (m, 2H), 2.05 (q, *J* = 7.5 Hz, 2H), 1.72 – 1.64 (m, 2H), 1.44 (s, 9H), 1.28 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 203.6 (d, *J* = 28.0 Hz), 165.9 (d, *J* = 25.5 Hz), 155.8, 139.5, 137.7, 115.7 (s, *J* = 17.0 Hz), 115.5, 100.5 (d, *J* = 200.0 Hz), 79.5, 62.8, 45.8, 37.5 (d, *J* = 20.0 Hz), 37.3, 32.8, 28.4, 21.9 (d, *J* = 2.0 Hz), 14.1; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -165.5 – -165.8 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 3411, 2978, 2933, 1754, 1716, 1510, 1366, 1245, 1165, 1048 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{19}H_{30}FNO_5Na$ (ES^+)(+Na^+): 394.2000. Found: 394.1991.

ethyl 4-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluoro-2-(1-tosylpyrrolidine-2-carbonyl)pent-4-enoate (3s)



Following GPE using ethyl 2-fluoro-3-oxo-3-(1-tosylpyrrolidin-2-yl)propanoate (**1s**) (0.11g, 0.3 mmol), *tert*-butyl 5-methylene-2-oxo-1,3-oxazinane-3-carboxylate (43 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol) and *N*,*N*-diisopropyldibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (10 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) with FCC (15 % ethyl acetate in petroleum ether) afforded ethyl 4-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluoro-2-(1-tosylpyrrolidine-2-carbonyl)pent-4-enoate (**3s**) as a yellow oil (76 mg, 72%)(4.2:1 mixture of diastereoisomers).

Major Isomer

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.65 (m, 2H), 7.35 – 7.29 (m, 2H), 5.11 (s, 1H), 5.04 (s, 1H), 4.78 (ddd, *J* = 9.0, 4.5, 2.5 Hz, 1H), 4.71 (br, 1H), 4.39 – 4.23 (m, 2H), 3.80 – 3.62 (m, 2H), 3.50 – 3.19 (m, 2H), 3.09 – 2.77 (m, 2H), 2.42 (s, 3H), 2.08 – 1.99 (m, 1H), 1.90 – 1.74 (m, 2H), 1.72 – 1.65 (m, 1H), 1.47 – 1.40 (m, 9H), 1.35 – 1.29 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 200.1 (d, *J* = 27.5 Hz), 165.1 (d, *J* = 26.0 Hz), 155.8, 143.8, 139.6, 134.8, 129.8, 127.5, 115.8, 101.3 (d, *J* = 196.5 Hz), 79.5, 63.5, 62.2, 48.6, 45.9, 37.0 (d, *J* = 19.5 Hz), 29.8, 28.4, 24.8, 21.6, 14.0.

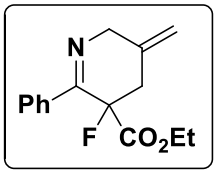
Minor Isomer

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.65 (m, 2H), 7.35 – 7.29 (m, 2H), 5.18 (s, 1H), 5.11 (s, 1H), 4.91 (br, 1H), 4.88 (ddd, *J* = 9.0, 4.5, 3.0 Hz, 1H), 4.39 – 4.23 (m, 2H), 3.80 – 3.62 (m, 2H), 3.50 – 3.19 (m, 2H), 3.09 – 2.77 (m, 2H), 2.42 (s, 3H), 2.08 – 1.99 (m, 1H), 1.90 – 1.74 (m, 2H), 1.72 – 1.65 (m, 1H), 1.47 – 1.40 (m, 9H), 1.35 – 1.29 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 200.1 (d, *J* = 27.5 Hz), 165.1 (d, *J* = 26.0 Hz), 156.0, 143.9, 138.7, 135.2, 129.8, 127.6, 116.1, 100.5 (d, *J* = 200.5 Hz), 79.5, 63.8, 63.1, 48.5, 45.8, 38.1 (d, *J* = 20.0 Hz), 29.5, 28.4, 24.5, 22.6, 14.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ -168.2 – -168.5 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 3405, 2979, 2932, 1745, 1704, 1509, 1448, 1349, 1248, 1157, 1097 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{25}H_{35}FN_2O_7SNa$ (ES^+)(+Na^+): 549.2041. Found: 549.2048.

Condensation Products

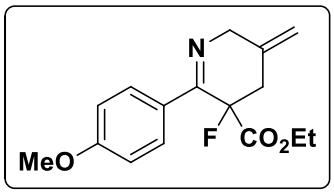
ethyl 3-fluoro-5-methylene-2-(phenyl)-3,4,5,6-tetrahydropyridine-3-carboxylate (4a)



Following GPF using ethyl 2-(phenyl)-4-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluoropent-4-enoate (**3a**) (74 mg, 0.19 mmol) and TFA (1.6 g, 14 mmol) afforded ethyl 3-fluoro-5-methylene-2-(phenyl)-3,4,5,6-tetrahydropyridine-3-carboxylate (**4a**) as a yellow oil (43 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.66 (m, 2H), 7.39 – 7.31 (m, 3H), 5.09 (s, 1H), 5.02 (s, 1H), 4.64 (dd, *J* = 20.5, 5.5 Hz, 1H), 4.53 (dd, *J* = 20.5, 5.5 Hz, 1H), 4.19 – 4.06 (m, 2H), 3.00 – 2.83 (m, 2H), 1.03 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.1 (d, *J* = 26.5 Hz), 160.3 (d, *J* = 18.5 Hz), 136.9, 136.3 (d, *J* = 3.5 Hz), 130.0, 128.4, 127.2 (d, *J* = 2.5 Hz), 112.6, 90.8 (d, *J* = 196.0 Hz), 62.3, 56.0, 39.5 (d, *J* = 24.0 Hz), 13.9; **^{19}F NMR (377 MHz, $CDCl_3$):** δ -146.5 – -146.7 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 2983, 1754, 1635, 1447, 1322, 1262, 1076, 1061, 856, 694 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{15}H_{17}FNO_2$ (ES^+)(+H^+): 262.1238. Found: 262.1240.

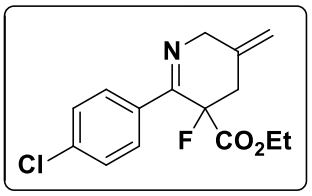
ethyl 3-fluoro-2-(4-methoxyphenyl)-5-methylidene-3,4,5,6-tetrahydropyridine-3-carboxylate (4b)



Following GPF 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(4-methoxybenzoyl)pent-4-enoate (**3b**) (78 mg, 0.18 mmol) and TFA (1.5 g, 13.5 mmol) afforded ethyl ethyl 3-fluoro-2-(4-methoxyphenyl)-5-methylidene-3,4,5,6-tetrahydropyridine-3-carboxylate (**4b**) as an orange oil (52 mg , 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (dd, *J* = 8.5, 1.0 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 5.07 (s, 1H), 5.00 (s, 1H), 4.60 (dd, *J* = 20.5, 5.0 Hz, 1H), 4.49 (dd, *J* = 20.5, 5.0 Hz, 1H), 4.15 (q, *J* = 7.0 Hz, 1H), 3.81 (s, 3H), 2.98 – 2.81 (m, 2H), 1.07 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.3 (d, *J* = 26.5 Hz), 161.1, 159.4 (d, *J* = 18.5 Hz), 136.6 (d, *J* = 4.0 Hz), 129.5, 128.9 (d, *J* = 3.0 Hz), 113.7, 112.4, 91.0 (d, *J* = 196.0 Hz), 62.3, 55.8, 55.4, 39.6 (d, *J* = 24.0 Hz), 14.0; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -146.4 – -146.6 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 2939, 1738, 1673, 1599, 1515, 1259, 1173, 1139, 1022, 838, 705 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{16}H_{19}FNO_3$ (ES^+)($+H^+$): 292.1343. Found: 292.1340.

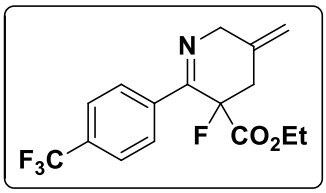
ethyl 3-fluoro-2-(4-chlorophenyl)-5-methylidene-3,4,5,6-tetrahydropyridine-3-carboxylate (4f)



Following GPF using 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(4-chlorobenzoyl)pent-4-enoate (**3c**) (74 mg, 0.18 mmol) and TFA (1.5 g, 13.5 mmol) afforded ethyl ethyl 3-fluoro-2-(4-chlorophenyl)-5-methylidene-3,4,5,6-tetrahydropyridine-3-carboxylate (**4c**) as a colourless oil (50 mg , 94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 – 7.63 (m, 2H), 7.35 – 7.30 (m, 2H), 5.10 (s, 1H), 5.02 (s, 1H), 4.63 (dd, *J* = 21.0, 5.5 Hz, 1H), 4.51 (dd, *J* = 21.0, 5.5 Hz, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 2.99 – 2.81 (m, 2H), 1.08 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.0 (d, *J* = 26.5 Hz), 159.2 (d, *J* = 18.5 Hz), 136.2, 136.0 (d, *J* = 3.5 Hz), 135.3, 128.7 (d, *J* = 3.0 Hz), 128.6, 112.8, 90.8 (d, *J* = 196.0 Hz), 62.5, 56.1, 39.5 (d, *J* = 24.0 Hz), 14.0; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -146.72 – -146.88 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 2986, 1757, 1600, 1521, 1349, 1275, 1065, 852, 750 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{15}H_{16}ClFNO_2$ (ES^+)($+H^+$): 296.0848. Found: 296.0855.

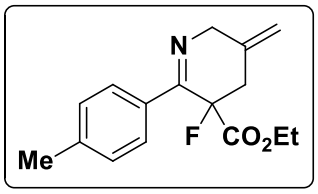
ethyl 3-fluoro-2-(4-trifluorophenyl)-5-methylidene-3,4,5,6-tetrahydropyridine-3-carboxylate (4d)



Following GPF using 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(4-trifluorobenzoyl)pent-4-enoate (**3d**) (76 mg, 0.17 mmol) and TFA (1.4 g, 12 mmol) afforded ethyl ethyl 3-fluoro-2-(4-trifluorophenyl)-5-methylidene-3,4,5,6-tetrahydropyridine-3-carboxylate (**4d**) as a pale yellow oil (50 mg , 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 0H), 5.12 (s, 1H), 5.04 (s, 1H), 4.67 (dd, *J* = 21.0, 5.5 Hz, 1H), 4.55 (dd, *J* = 21.0, 5.5 Hz, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 3.02 – 2.84 (m, 2H), 1.06 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.8 (d, *J* = 26.5 Hz), 159.3 (d, *J* = 19.0 Hz), 140.1, 135.8 (d, *J* = 3.5 Hz), 131.8 (q, *J* = 32.5 Hz), 127.7 (d, *J* = 3.0 Hz), 125.4 (q, *J* = 3.5 Hz), 123.6 (q, *J* = 272.5 Hz), 113.1, 90.7 (d, *J* = 196.0 Hz), 62.6, 56.2, 39.4 (d, *J* = 24.0 Hz), 13.9; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -62.87, -147.0 – -147.1; **FTIR:** ν_{max}/cm^{-1} (neat) 2986, 1758, 1638, 1325, 1315, 1267, 1166, 1124, 850 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{15}H_{16}ClFNO_2$ (ES^+)($+H^+$): 330.1112. Found: 330.1116.

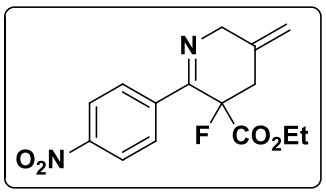
ethyl 3-fluoro-2-(4-methylphenyl)-5-methylidene-3,4,5,6-tetrahydropyridine-3-carboxylate (4c)



Following GPF using 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(4-methylbenzoyl)pent-4-enoate (**3e**) (60 mg, 0.15 mmol) and TFA (1.3 g, 11.4 mmol) afforded ethyl 3-fluoro-2-(4-methylphenyl)-5-methylidene-3,4,5,6-tetrahydropyridine-3-carboxylate (**4e**) as a yellow oil (39 mg , 94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 – 7.52 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 5.08 (s, 1H), 5.00 (d, *J* = 1.0 Hz, 1H), 4.62 (dd, *J* = 20.5, 5.5 Hz, 1H), 4.51 (dd, *J* = 20.5, 5.5 Hz, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.01 – 2.80 (m, 2H), 2.34 (s, 3H), 1.07 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.3 (d, *J* = 26.5 Hz), 160.1 (d, *J* = 18.5 Hz), 140.1, 136.5 (d, *J* = 3.5 Hz), 134.1, 129.1, 127.2 (d, *J* = 2.5 Hz), 112.4, 90.9 (d, *J* = 196.0 Hz), 62.3, 55.9, 39.6 (d, *J* = 24.0 Hz), 21.4, 13.9; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -146.54 – -146.70 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 2984, 1755, 1633, 1611, 1445, 1267, 1186, 1063, 827, 764 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{16}H_{19}FNO2$ (ES^+)($+H^+$): 276.1394. Found: 276.1403.

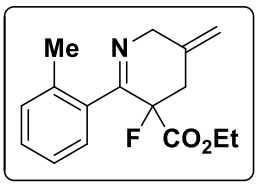
ethyl 3-fluoro-2-(4-nitrophenyl)-5-methylidene-3,4,5,6-tetrahydropyridine-3-carboxylate (4e)



Following GPF using 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(4-nitrobenzoyl)pent-4-enoate (**3f**) (69 mg, 0.16 mmol) and TFA (1.4 g, 12 mmol) afforded ethyl ethyl 3-fluoro-2-(4-nitrophenyl)-5-methylidene-3,4,5,6-tetrahydropyridine-3-carboxylate (**4f**) as a yellow oil (45 mg , 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 9.0 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 2H), 5.13 (s, 1H), 5.06 (s, 1H), 4.70 (dd, *J* = 21.0, 5.5 Hz, 1H), 4.58 (dd, *J* = 21.0, 5.5 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 3.04 – 2.84 (m, 2H), 1.09 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.6 (d, *J* = 26.5 Hz), 158.8 (d, *J* = 18.5 Hz), 148.7, 142.4, 135.5 (d, *J* = 4.0 Hz), 128.4 (d, *J* = 3.0 Hz), 123.6, 113.4, 90.7 (d, *J* = 196.5 Hz), 62.8, 56.4, 39.4 (d, *J* = 24.0 Hz), 14.0; **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -147.1 – -147.2 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 2986, 1755, 1738, 1599, 1519, 1347, 1193, 850, 701 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{15}H_{16}FN_2O_4$ (ES^+)($+H^+$): 307.1089. Found: 307.1098.

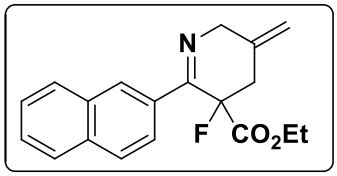
ethyl 3-fluoro-2-(4-methylphenyl)-5-methylidene-3,4,5,6-tetrahydropyridine-3-carboxylate (4g)



Following GPF using 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(2-methylbenzoyl)pent-4-enoate (**3g**) (67 mg, 0.18 mmol) and TFA (1.4 g, 12 mmol) afforded ethyl ethyl 3-fluoro-2-(2-methylphenyl)-5-methylidene-3,4,5,6-tetrahydropyridine-3-carboxylate (**4g**) as a colourless oil (46 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.06 (m, 4H), 5.12 (s, 1H), 5.04 (s, 1H), 4.69 – 4.51 (m, 2H), 4.13 – 3.97 (m, 2H), 3.13 – 2.81 (m, 2H), 2.34 (s, 3H), 1.04 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.5 (d, *J* = 26.5 Hz), 161.9 (d, *J* = 18.5 Hz), 136.8, 136.6, 136.0 (d, *J* = 3.0 Hz), 130.8, 128.9, 127.2 (d, *J* = 2.5 Hz), 125.5, 112.9, 91.1 (d, *J* = 195.5 Hz), 62.3, 55.7, 38.9 (d, *J* = 23.5 Hz), 19.9, 13.8; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -148.2 (ddt, *J* = 25.0, 15.5, 6.0 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 2981, 1760, 1645, 1445, 1245, 1075, 1064, 1009, 903, 888, 728 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{16}H_{19}FNO_2$ (ES^+)($+H^+$): 276.1394. Found: 276.1398.

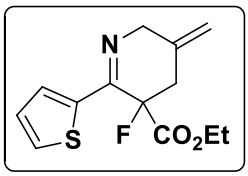
ethyl 3-fluoro-5-methylene-2-(naphthalen-2-yl)-3,4,5,6-tetrahydropyridine-3-carboxylate (4h)



Following GPF using ethyl 2-(2-naphthoyl)-4-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluoropent-4-enoate (**3h**) (80 mg, 0.19 mmol) and TFA (1.6 g, 14 mmol) afforded ethyl 3-fluoro-5-methylene-2-(naphthalen-2-yl)-3,4,5,6-tetrahydropyridine-3-carboxylate (**4h**) as a yellow oil (58 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.91 – 7.79 (m, 4H), 7.53 – 7.44 (m, 2H), 5.13 (s, 1H), 5.06 (s, 1H), 4.66 (qd, *J* = 20.5, 5.5 Hz, 2H), 4.19 – 4.06 (m, 2H), 3.06 – 2.90 (m, 2H), 1.01 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.3 (d, *J* = 26.5 Hz), 160.1 (d, *J* = 18.5 Hz), 136.3 (d, *J* = 3.5 Hz), 134.2, 134.1, 132.9, 129.1, 128.1, 127.7, 127.2 (d, *J* = 4.0 Hz), 127.1, 126.4, 124.6, 112.7, 91.0 (d, *J* = 196.5 Hz), 62.4, 56.2, 39.7 (d, *J* = 24.0 Hz), 13.9; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -146.02 (ddt, *J* = 22.6, 18.2, 5.2 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 3059, 2983, 2928, 1754, 1738, 1626, 1319, 1266, 1187, 1063 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{19}H_{19}FNO_2$ (ES^+)($+H^+$): 312.1394. Found: 312.1401.

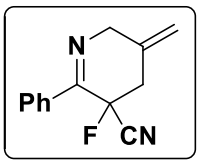
ethyl 3-fluoro-5-methylidene-2-(thiophen-2-yl)-3,4,5,6-tetrahydropyridine-3-carboxylate (4i)



Following GPF using ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoro-2-(thiophene-2-carbonyl)pent-4-enoate (**3i**) (63 mg, 0.18 mmol) and TFA (1.5 g, 13.5 mmol) afforded ethyl 3-fluoro-5-methylidene-2-(thiophen-2-yl)-3,4,5,6-tetrahydropyridine-3-carboxylate (**4i**) as an orange oil (46 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, *J* = 3.0 Hz, 1H), 7.35 (d, *J* = 5.0 Hz, 1H), 7.03 – 6.98 (m, 1H), 5.06 (s, 1H), 4.98 (s, 1H), 4.55 (dd, *J* = 20.5, 4.0 Hz, 1H), 4.46 (d, *J* = 20.5 Hz, 1H), 4.28 – 4.14 (m, 2H), 3.02 – 2.84 (m, 2H), 1.16 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.7 (d, *J* = 27.5 Hz), 155.4 (d, *J* = 20.5 Hz), 141.8 (d, *J* = 2.5 Hz), 136.4 (d, *J* = 5.5 Hz), 128.9, 128.5 (d, *J* = 7.0 Hz), 127.8, 112.6, 91.0 (d, *J* = 197.0 Hz), 62.6, 55.5, 39.6 (d, *J* = 24.0 Hz), 14.1; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -147.7 – -147.8 **FTIR:** ν_{max}/cm^{-1} (neat) 2984, 1753, 1622, 1429, 1285, 1189, 1065, 1008, 909, 694 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{13}H_{15}FNO_2S$ (ES^+)($+H^+$): 268.0802. Found: 268.0806.

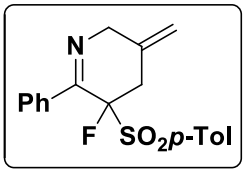
3-Fluoro-5-methylidene-2-phenyl-4,6-dihydropyridine-3-carbonitrile (4j)



Following GPF using *tert*-butyl *N*-[4-cyano-4-fluoro-4-(4-methoxybenzoyl)-2-methylidenebutyl]carbamate (**3j**) (58 mg, 0.16 mmol) and TFA (1.4 g, 12 mmol) afforded 3-fluoro-2-(4-methoxyphenyl)-5-methylidene-3,4,5,6-tetrahydropyridine -3-carboxylate (**4j**) as a yellow oil (34 mg , 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.0 Hz, 2H), 7.50 – 7.36 (m, 3H), 5.24 (s, 2H), 4.62 – 4.45 (m, 2H), 3.16 (t, *J* = 13.0 Hz, 1H), 3.03 (t, *J* = 13.0 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 157.8 (d, *J* = 22.0 Hz), 134.7, 134.2 (d, *J* = 5.5 Hz), 130.9, 128.6, 127.8 (d, *J* = 2.5 Hz), 116.0 (d, *J* = 35.0 Hz), 115.5, 84.0 (d, *J* = 196.0 Hz), 55.9, 40.9 (d, *J* = 23.5 Hz); **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -142.6 (t, *J* = 12.5 Hz);); **FTIR:** ν_{max}/cm^{-1} (neat) 2927, 2253, 1634, 1447, 1322, 1281, 1065, 906, 728 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{13}H_{12}FN_2$ (ES^+)($+Na^+$): 215.0979. Found: 215.0984.

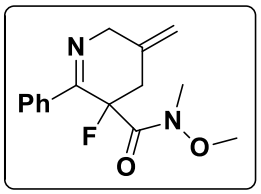
5-fluoro-3-methylene-6-phenyl-5-tosyl-2,3,4,5-tetrahydropyridine (4k)



Following GPF using *tert*-butyl (4-fluoro-2-methylene-5-oxo-5-phenyl-4-tosylpentyl)carbamate (**3k**) (85 mg, 0.18 mmol) and TFA (1.1g, 9.2 mmol) afforded 5-fluoro-3-methylene-6-phenyl-5-tosyl-2,3,4,5-tetrahydropyridine (**4k**) as a yellow oil (56 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.57 (m, 4H), 7.35 – 7.29 (m, 1H), 7.25 – 7.15 (m, 4H), 5.13 (s, 1H), 5.03 (s, 1H), 4.84 – 4.76 (m, 1H), 4.76 – 4.67 (m, 1H), 3.17 (dd, *J* = 15.5, 6.0 Hz, 1H), 2.94 – 2.82 (m, 1H), 2.39 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 159.9 (d, *J* = 18.0 Hz), 146.0, 136.6 (d, *J* = 3.0 Hz), 135.8 (d, *J* = 8.0 Hz), 131.5, 130.5, 129.8, 129.5, 129.1 (d, *J* = 5.5 Hz), 127.9, 112.4, 104.5 (d, *J* = 234.5 Hz), 55.9, 36.4 (d, *J* = 21.0 Hz), 21.8; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -141.5 – -141.6 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 3061, 2924, 1670, 1596, 1413, 1317, 1146 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{19}H_{19}FNO_2S$ (ES^+)($+H^+$): 344.1115. Found: 344.1121.

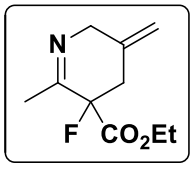
3-fluoro-*N*-methoxy-*N*-methyl-5-methylene-2-phenyl-3,4,5,6-tetrahydropyridine-3-carboxamide (4l)



Following GPF using *tert*-butyl (4-benzoyl-4-fluoro-5-(methoxy(methyl)amino)-2-methylene-5-oxopentyl)carbamate (**3l**) (71 mg, 0.18 mmol) and TFA (1.0 g, 9.0 mmol) afforded 3-fluoro-*N*-methoxy-*N*-methyl-5-methylene-2-phenyl-3,4,5,6-tetrahydropyridine-3-carboxamide (**4l**) as an orange oil (48 mg, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.77 (m, 2H), 7.46 – 7.31 (m, 3H), 5.08 (s, 1H), 5.01 (s, 1H), 4.62 (dd, *J* = 19.5, 5.0 Hz, 1H), 4.35 (dd, *J* = 19.5, 7.5 Hz, 1H), 3.44 (s, 3H), 3.14 – 2.94 (m, 4H), 2.83 (dd, *J* = 21.5, 14.5 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 159.8 (d, *J* = 19.5 Hz), 136.7, 136.1, 129.9, 128.3, 127.4 (d, *J* = 2.0 Hz), 112.4, 92.1 (d, *J* = 191.5 Hz), 60.9, 55.8, 38.5 (d, *J* = 24.5 Hz), 33.4; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -140.8 – -141.1 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 2939, 1677, 1631, 1446, 1380, 1064, 972 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{15}H_{18}FN_2O_2$ (ES^+)($+H^+$): 277.1347. Found: 277.1355.

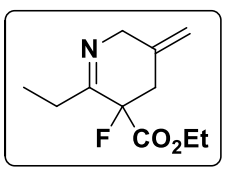
ethyl 2-methyl-3-fluoro-5-methylidene-4,6-dihydropyridine-3-carboxylate (4m)



Following GPF using ethyl 2-acetyl-4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-fluoropent-4-enoate (**3m**) (56 mg, 0.18 mmol) and TFA (1.5 g, 13.5 mmol) afforded ethyl 2-methyl-3-fluoro-5-methylidene-4,6-dihydropyridine-3-carboxylate (**4m**) as a yellow oil (32 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.99 (d, *J* = 1.0 Hz, 1H), 4.92 (s, 1H), 4.36 – 4.14 (m, 4H), 2.91 (t, *J* = 14.0 Hz, 1H), 2.78 – 2.65 (m, 1H), 2.05 (dd, *J* = 3.5, 2.0 Hz, 3H), 1.29 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.3 (d, *J* = 27.5 Hz), 161.6 (d, *J* = 21.0 Hz), 136.8 (d, *J* = 6.0 Hz), 112.4, 91.7 (d, *J* = 193.5 Hz), 62.5, 55.3, 38.5 (d, *J* = 23.5 Hz), 21.5, 14.2; **^{19}F NMR (377 MHz, $CDCl_3$):** δ -152.5 – -152.9 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 2984, 1756, 1739, 1668, 1442, 1370, 1278, 1183, 1072, 1041, 903, 759 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{10}H_{15}FNO_2$ (ES^+)($+H^+$): 200.1081. Found: 200.1083.

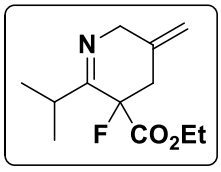
ethyl 2-ethyl-3-fluoro-5-methylidene-4,6-dihydropyridine-3-carboxylate (4n)



Following GPF using ethyl 4-({[(*tert*-butoxy)carbonyl]amino}methyl)-2-fluoro-2-propanoylpent-4-enoate (**3n**) (52 mg, 0.16 mmol) and TFA (1.4 g, 12 mmol) afforded ethyl 2-ethyl-3-fluoro-5-methylidene-4,6-dihydropyridine-3-carboxylate (**4n**) as a colourless oil (32 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.98 (s, 1H), 4.90 (s, 1H), 4.42 – 4.15 (m, 4H), 2.90 (t, *J* = 14.0 Hz, 1H), 2.78 – 2.65 (m, 1H), 2.51 – 2.38 (m, 1H), 2.34 – 2.19 (m, 1H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.09 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.6 (d, *J* = 27.0 Hz), 165.0 (d, *J* = 20.5 Hz), 137.1 (d, *J* = 6.0 Hz), 112.0, 91.8 (d, *J* = 194.0 Hz), 62.4, 55.2, 38.7 (d, *J* = 23.5 Hz), 27.4, 14.2, 10.2; **^{19}F NMR (377 MHz, $CDCl_3$):** δ -153.4 – -153.8 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 2981, 1756, 1738, 1665, 1446, 1369, 1274, 1178, 1067, 999, 901, 856 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{11}H_{17}FNO_2$ (ES^+)($+H^+$): 214.1238. Found: 214.1248.

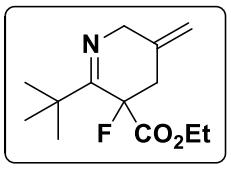
ethyl 3-fluoro-5-methylidene-2-(propan-2-yl)-3,4,5,6-tetrahydropyridine-3-carboxylate (4o)



Following GPF using ethyl 4-({[(*tert*-butoxy)carbonyl]amino}methyl)-2-fluoro-2-propanoylpent-4-enoate (**3o**) (63 mg, 0.18 mmol) and TFA (1.5 g, 13.5 mmol) afforded ethyl 3-fluoro-5-methylidene-2-(propan-2-yl)-3,4,5,6-tetrahydropyridine-3-carboxylate (**4o**) as a colourless oil (32 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.97 (d, *J* = 1.0 Hz, 1H), 4.89 (s, 1H), 4.43 – 4.16 (m, 4H), 2.87 (dd, *J* = 13.5, 13.0 Hz, 1H), 2.76 – 2.63 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.12 (dd, *J* = 6.7, 0.5 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.1 (d, *J* = 20.0 Hz), 168.7 (d, *J* = 27.5 Hz), 137.3 (d, *J* = 6.5 Hz), 111.8, 92.3 (d, *J* = 193.5 Hz), 62.3, 55.2, 39.2 (d, *J* = 23.5 Hz), 32.8, 21.2 (d, *J* = 37.5 Hz), 14.2; **^{19}F NMR (376 MHz, $CDCl_3$)**: δ -154.7 – -154.8 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 2975, 1755, 1661, 1446, 1272, 1222, 1072, 1011, 901, 855 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{12}H_{19}FNO_2$ (ES^+)($+H^+$): 228.1394. Found: 228.1396.

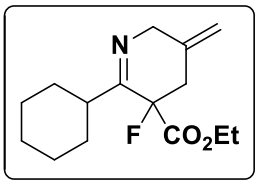
ethyl 2-tert-butyl-3-fluoro-5-methylidene-4,6-dihydropyridine-3-carboxylate (4p)



Following GPF using ethyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}-2-(2,2-dimethylpropanoyl)-2-fluoropent-4-enoate (**3p**) (58 mg, 0.16 mmol) and TFA (1.4 g, 12 mmol) afforded ethyl 2-tert-butyl-3-fluoro-5-methylidene-4,6-dihydropyridine-3-carboxylate (**4p**) as a yellow oil (37 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.94 (s, 1H), 4.84 (s, 1H), 4.45 – 4.28 (m, 2H), 4.27 – 4.13 (m, 2H), 2.85 – 2.67 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.18 (d, *J* = 1.0 Hz, 9H; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.5 (d, *J* = 18.5 Hz), 168.8 (d, *J* = 26.0 Hz), 138.1 (d, *J* = 9.0 Hz), 111.2, 93.5 (d, *J* = 199.0 Hz), 62.2, 55.1, 40.6 (d, *J* = 24.0 Hz), 29.8, 28.8 (d, *J* = 3.5 Hz), 14.2; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -154.7 – -154.9 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 2960, 1754, 1725, 1690, 1574, 1545, 1367, 1273, 1202, 1090, 855, 840 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{13}H_{21}FNO_2$ (ES^+)($+H^+$): 242.1551. Found: 242.1555.

ethyl 2-cyclohexyl-3-fluoro-5-methylidene-3,4,5,6-tetrahydropyridine-3-carboxylate (4q)

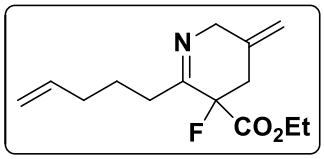


Following GPF using ethyl 4-({[(*tert*-butoxy)carbonyl]amino}methyl)-2-cyclohexanecarbonyl-2-fluoropent-4-enoate (**3q**) (62 mg, 0.16 mmol) and TFA (1.4 g, 12 mmol) afforded ethyl 2-cyclohexyl-3-fluoro-5-methylidene-3,4,5,6-tetrahydropyridine-3-carboxylate (**4q**) as a pale yellow oil (41 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.97 (s, 1H), 4.89 (s, 1H), 4.45 – 4.18 (m, 4H), 2.87 (t, *J* = 13.5 Hz, 1H), 2.75 – 2.62 (m, 1H), 2.36 (t, *J* = 10.5 Hz, 1H), 1.90 – 1.60 (m, 5H), 1.48 – 1.12 (m, 8H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.7 (d, *J* = 27.5 Hz), 168.3 (d, *J* = 20.0 Hz), 137.2 (d, *J* = 6.5 Hz), 111.9, 92.2 (d, *J* = 194.0 Hz), 62.3, 55.2, 42.9, 39.1 (d, *J* = 23.5 Hz), 31.7, 31.2, 26.4, 26.3, 26.0, 14.3; **^{19}F**

NMR (376 MHz, $CDCl_3$): δ -154.4– -154.6 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 2930, 2853, 1756, 1659, 1668, 1448, 1273, 1075, 1010, 897 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{15}H_{23}FNO_2$ (ES^+)($+H^+$): 268.1707. Found: 268.1710.

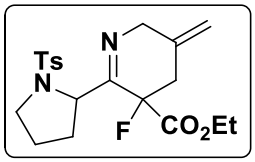
ethyl 3-fluoro-5-methylene-2-(pent-4-en-1-yl)-3,4,5,6-tetrahydropyridine-3-carboxylate (4r)



Following GPF using ethyl 2-(2-(((*tert*-butoxycarbonyl)amino)methyl)allyl)-2-fluoro-3-oxooct-7-enoate (**3r**) (70 mg, 0.19 mmol) and TFA (1.07 g, 9.4 mmol) afforded ethyl 3-fluoro-5-methylene-2-(pent-4-en-1-yl)-3,4,5,6-tetrahydropyridine-3-carboxylate (**4r**) as a yellow oil (47 mg, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H), 5.03 – 4.87 (m, 4H), 4.41 – 4.17 (m, 4H), 2.89 (t, *J* = 14.0 Hz, 1H), 2.76 – 2.64 (m, 1H), 2.44 – 2.33 (m, 1H), 2.31 – 2.21 (m, 1H), 2.10 – 2.02 (m, 2H), 1.73 – 1.62 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.5 (d, *J* = 27.5 Hz), 163.9 (d, *J* = 20.5 Hz), 138.4, 137.0 (d, *J* = 6.0 Hz), 115.0, 112.1, 91.9 (d, *J* = 194.0 Hz), 62.4, 55.2 (d, *J* = 1.0 Hz), 38.7 (d, *J* = 23.5 Hz), 33.6, 33.4, 25.1, 14.2; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -153.45 – -153.7 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 3078, 2980, 2936, 1756, 1738, 1665, 1272, 1177, 1066, 906 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{14}H_{21}FNO_2$ (ES^+)($+H^+$): 254.1551. Found: 254.1555.

ethyl 3-fluoro-5-methylene-2-(1-tosylpyrrolidin-2-yl)-3,4,5,6-tetrahydropyridine-3-carboxylate (4s)



Following GPF using ethyl 4-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluoro-2-(1-tosylpyrrolidine-2-carbonyl)pent-4-enoate (**3s**) (76 mg, 0.14 mmol) and TFA (0.82 g, 7.2 mmol) afforded ethyl 3-fluoro-5-methylene-2-(1-tosylpyrrolidin-2-yl)-3,4,5,6-tetrahydropyridine-3-carboxylate (**4s**) as a yellow oil (56 mg, 68%) (4.1:1 mixture of diastereoisomers).

Major Isomer

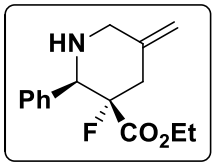
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.65 (m, 1H), 7.33 – 7.25 (m, 1H), 4.97 (s, 1H), 4.92 (s, 1H), 4.65 – 4.48 (m, 1H), 4.43 – 4.20 (m, 2H), 3.54 – 3.25 (m, 1H), 3.02 – 2.89 (m, 1H), 2.79 – 2.55 (m, 1H), 2.41 (s, 2H), 1.98 – 1.80 (m, 2H), 1.68 – 1.55 (m, 1H), 1.34 – 1.28 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.8 (d, *J* = 28.0 Hz), 163.8 (d, *J* = 20.0 Hz), 143.2, 136.9 (d, *J* = 7.5 Hz), 135.7, 129.6, 127.6, 111.9, 91.4 (d, *J* = 192.0 Hz), 63.0, 60.6, 54.7, 48.7, 38.7 (d, *J* = 22.5 Hz), 32.0, 24.2, 21.6, 14.1; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -154.0 – -154.2 (m).

Minor Isomer

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.65 (m, 1H), 7.33 – 7.25 (m, 1H), 4.97 (s, 1H), 4.92 (s, 1H), 4.65 – 4.48 (m, 1H), 4.43 – 4.20 (m, 2H), 3.54 – 3.25 (m, 1H), 3.02 – 2.89 (m, 1H), 2.79 – 2.55 (m, 1H), 2.41 (s, 2H), 1.98 – 1.80 (m, 2H), 1.68 – 1.55 (m, 1H), 1.34 – 1.28 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.9 (d, *J* = 27.5 Hz), 164.1 (d, *J* = 19.5 Hz), 143.5, 136.9 (d, *J* = 7.5 Hz), 135.7, 129.7, 127.9, 112.1, 91.1 (d, *J* = 194.5 Hz), 62.7, 60.6, 55.0, 49.6, 39.4 (d, *J* = 23.0 Hz), 32.0, 24.3, 22.6, 14.1; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -153.1 – -153.2 (m).

FTIR: ν_{max}/cm^{-1} (neat) 3423, 2982, 1748, 1668, 1339, 1156, 1091, 1010 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{20}H_{26}FN_2O_4S$ (ES^+)($+H^+$): 409.1592. Found: 409.1601.

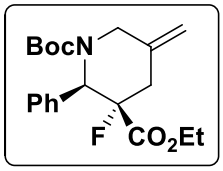
(2*R*,3*S*)-ethyl 3-fluoro-5-methylene-2-phenylpiperidine-3-carboxylate (5)



To a solution of $NaBH(OAc)_3$ (0.24 g, 1.15 mmol) in acetic acid (1.5 mL) under nitrogen was added 3-fluoro-5-methylene-2-(phenyl)-3,4,5,6-tetrahydropyridine-3-carboxylate (**4a**) (0.20 g, 0.77 mmol) and the resulting mixture stirred at 20 °C overnight. The mixture was then diluted with sat. $NaHCO_3$ (10 mL) and extracted with EtOAc (5 x 10 mL). The combined organic layers were then dried over anhydrous $MgSO_4$, concentrated under vacuum and the residue purified by FCC (50% EtOAc in 40-60 petroleum ether) to afford (2R,3S)-ethyl 3-fluoro-5-methylene-2-phenylpiperidine-3-carboxylate (**5**) as a yellow oil (0.18 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 5H), 4.97 – 4.93 (m, 1H), 4.81 (s, 1H), 4.08 – 3.96 (m, 3H), 3.70 – 3.64 (m, 1H), 3.41 (d, *J* = 14.5 Hz, 1H), 2.99 – 2.92 (m, 1H), 2.80 – 2.69 (m, 1H), 2.49 (br, 1H), 1.02 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.4 (d, *J* = 24.5 Hz), 141.7 (d, *J* = 8.5 Hz), 137.1, 128.2, 128.0, 127.5 (d, *J* = 1.5 Hz), 111.4, 94.4 (d, *J* = 200.0 Hz), 65.2, 65.0, 61.5 (d, *J* = 27.5 Hz), 52.1, 42.5 (d, *J* = 23.0 Hz), 14.0; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -149.7 (ddd, *J* = 11.0, 7.5, 3.0 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 2983, 1724, 1466, 1372, 1228, 1192, 1072, 1040 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{15}H_{19}FNO_2$ (ES$^+$)(+H$^+$): 264.1394. Found: 264.1396.

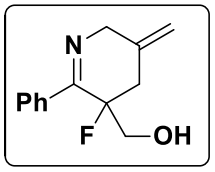
(2*R*,3*S*)-1-*tert*-butyl 3-ethyl 3-fluoro-5-methylene-2-phenylpiperidine-1,3-dicarboxylate (6)



To a solution of (2R,3S)-ethyl 3-fluoro-5-methylene-2-phenylpiperidine-3-carboxylate (**5**) (0.18 g, 0.68 mmol) in THF (3.9 mL) under nitrogen was added Et3N (0.16 g, 1.5 mmol) and di-*tert*-butyl dicarbonate (0.34 g, 1.5 mmol) and the resulting mixture stirred at room temperature overnight. The reaction was then diluted with H_2O (20 mL) and extracted with DCM (4 x 20 mL). The combined organic layers were then dried over anhydrous $MgSO_4$, concentrated under vacuum and purified by FCC (4% EtOAc in 40-60 petroleum ether) to afford (2R,3S)-1-*tert*-butyl 3-ethyl 3-fluoro-5-methylene-2-phenylpiperidine-1,3-dicarboxylate (**6**) as a colourless oil (0.22 g, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 5H), 5.43 (br, 1H), 5.15 (s, 1H), 5.01 (s, 1H), 4.56 – 4.42 (m, 1H), 4.11 – 3.89 (m, 3H), 3.16 (dd, *J* = 43.5, 16.5 Hz, 1H), 2.84 – 2.72 (m, 1H), 1.34 (br, 9H), 1.04 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.2 (d, *J* = 23.0 Hz), 154.9, 141.1, 136.4, 128.5, 128.1, 128.0, 114.0, 94.8 (d, *J* = 189.5 Hz), 80.6, 79.3, 62.0, 46.0, 34.3 (d, *J* = 23.0 Hz), 28.2, 13.6; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -149.2 (dt, *J* = 42.0, 13.0 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 2979, 2933, 1747, 1694, 1455, 1392, 1367, 1275, 1253, 1157, 1106, 1060, 1011. 895, 858, 756, 700; HRMS (ESI+): calculated for $C_{20}H_{26}FNO_4Na$ (ES+)(+Na$^+$): 386.1738. Found: 386.1747.

(3-fluoro-5-methylene-2-phenyl-3,4,5,6-tetrahydropyridin-3-yl)methanol (7)

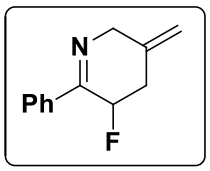


To a suspension of $LiAlH_4$ (15 mg, 0.38 mmol) in THF (2 mL) under nitrogen was added 3-fluoro-5-methylene-2-(phenyl)-3,4,5,6-tetrahydropyridine-3-carboxylate (**4a**) (50 mg, 0.19 mmol) in THF (2 mL) and the resulting mixture stirred at 20 °C for 3 hours. H_2O (0.2 mL) was then added dropwise and the reaction stirred for 15 minutes before the addition of anhydrous $MgSO_4$. After 10 minutes the reaction mixture was filtered through celite and the volatiles removed under vacuum. Purification by FCC (30% EtOAc in 40-60 petroleum ether) afforded (3-fluoro-5-methylene-2-phenyl-3,4,5,6-tetrahydropyridin-3-yl)methanol (**7**) as a yellow oil (21 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.5 Hz, 2H), 7.43 – 7.33 (m, 3H), 5.04 (s, 2H), 4.61 – 4.52 (m, 1H), 4.40 (d, *J* = 20.5 Hz, 1H), 3.90 – 3.82 (m, 1H), 3.65 (dd, *J* = 25.5, 12.5 Hz, 1H), 3.06 (t, *J* =

13.0 Hz, 1H), 2.69 (t, *J* = 14.2 Hz, 1H), 2.02 (s, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.6 (d, *J* = 18.5 Hz), 139.1 (d, *J* = 8.0 Hz), 137.5, 129.7, 128.3, 128.3, 111.9, 95.6 (d, *J* = 184.5 Hz), 64.9 (d, *J* = 26.0 Hz), 56.5, 37.0 (d, *J* = 23.5 Hz); **^{19}F NMR (377 MHz, $CDCl_3$)** δ -155.8 – -156.0 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 3241, 2926, 1628, 1445, 1325, 1090, 1011, 902 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{13}H_{15}FNO$ (ES^+)($+H^+$): 220.1132. Found: 220.1136.

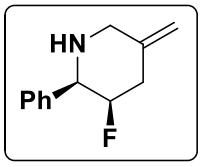
5-fluoro-3-methylene-6-phenyl-2,3,4,5-tetrahydropyridine (8)



To a pressure tube containing 3-fluoro-5-methylene-2-(phenyl)-3,4,5,6-tetrahydropyridine-3-carboxylate (**4a**) (50 mg, 0.19 mmol) was added aq. HCl (6.0 M, 0.48 mL) and the resulting mixture heated at 100 °C for 1.5 h. After cooling to room temperature the reaction was basified to pH 8 with sat. $NaHCO_3$ and extracted with EtOAc (3 x 25 mL). The combined organic layers were then dried over anhydrous $MgSO_4$ and concentrated under vacuum to afford 5-fluoro-3-methylene-6-phenyl-2,3,4,5-tetrahydropyridine (**8**) as a yellow oil (0.38 g, quant.)(**CAUTION**: this compound decomposes by eliminating HF under prolonged heating (>30 °C) under vacuum).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.79 (m, 2H), 7.45 – 7.39 (m, 3H), 5.53 (dt, *J* = 48.5, 5.0 Hz, 1H), 5.07 (s, 1H), 5.03 (s, 1H), 4.55 (dd, *J* = 20.5, 5.5 Hz, 1H), 4.45 (dd, *J* = 20.5, 5.5 Hz, 1H), 2.90 – 2.70 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.7 (d, *J* = 16.5 Hz), 137.7 (d, *J* = 4.0 Hz), 137.3, 130.3, 128.5, 127.0 (d, *J* = 1.5 Hz), 112.0, 84.5 (d, *J* = 177.5 Hz), 56.3 (d, *J* = 2.0 Hz), 35.7 (d, *J* = 22.0 Hz); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -170.5 – -170.9 (m); **FTIR:** ν_{max}/cm^{-1} (neat) 3061, 2923, 1632, 1447, 1319, 1015, 899 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{12}H_{13}FN$ (ES^+)($+H^+$): 190.1027. Found: 190.1034.

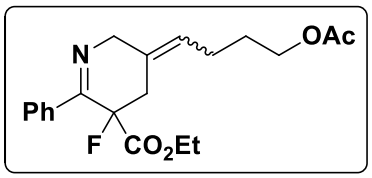
(2R,3R)-3-fluoro-5-methylene-2-phenylpiperidine (9)



To a solution of 5-fluoro-3-methylene-6-phenyl-2,3,4,5-tetrahydropyridine (**8**) (50 mg, 0.26 mmol) in MeOH (0.52 mL) under nitrogen at 0 °C was added $NaBH_4$ (20 mg, 0.52 mmol) and the resulting mixture warmed to room temperature and stirred overnight. The reaction was then diluted with $NaHCO_3$ (10 mL) and extracted with EtOAc (5 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, concentrated under vacuum and the residue purified by FCC (40% EtOAc in 40-60 petroleum ether) to afford (2R,3R)-3-fluoro-5-methylene-2-phenylpiperidine (**9**) as a white solid (39 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, 5H), 4.97 – 4.79 (m, 3H), 3.87 (d, *J* = 30.0 Hz, 1H), 3.63 (dd, *J* = 14.0, 1.5 Hz, 1H), 3.46 (d, *J* = 14.0 Hz, 1H), 2.84 – 2.75 (m, 1H), 2.56 (dd, *J* = 45.0, 15.0 Hz, 1H), 1.93 (s, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 140.3, 140.0 128.5, 127.6, 127.2, 112.1, 90.4 (d, *J* = 178.5 Hz), 62.7 (d, *J* = 19.0 Hz), 53.1, 38.9 (d, *J* = 23.5 Hz); **^{19}F NMR (377 MHz, $CDCl_3$)** δ -197.47 (dddd, *J* = 48.5, 45.0, 30.0, 11.0 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 3291, 2937, 1656, 1467, 1261, 1100, 1022 cm^{-1}; **HRMS (ESI^+):** calculated for $C_{12}H_{15}FN$ (ES^+)($+H^+$): 192.1183. Found: 192.1186.

ethyl 5-(4-acetoxybutylidene)-3-fluoro-2-phenyl-3,4,5,6-tetrahydropyridine-3-carboxylate (10)



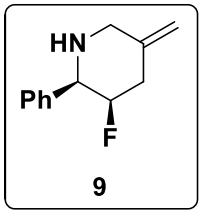
To a solution of Hoveyda-Grubbs Catalyst® 2nd Generation (6.0 mg, 9.6 µmol (5 mol%) in anhydrous, degassed DCM (0.76 mL) was added 3-fluoro-5-methylene-2-(phenyl)-3,4,5,6-tetrahydropyridine-3-carboxylate (**4a**) (50 mg, 0.19 mmol) and pent-4-en-1-yl acetate (**s2**) (68 mg, 0.57 mmol) and the resulting mixture stirred at 25 °C overnight (open to nitrogen). DCM (0.76 mL) was then added and the reaction mixture heated at reflux for 4 hours (sealed). Removal of the volatiles under vacuum and purification by FCC (20% EtOAc in 40-60 petroleum ether) afforded ethyl 5-(4-acetoxybutylidene)-3-fluoro-2-phenyl-3,4,5,6-tetrahydropyridine-3-carboxylate (**11**) as an orange oil (38 mg, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.63 (m, 2H), 7.43 – 7.30 (m, 3H), 5.59 (t, *J* = 7.0 Hz, 1H, **minor**), 5.36 (t, *J* = 7.5 Hz, 1H, **major**), 4.81 – 4.41 (m, 2H), 4.21 – 4.00 (m, 4H), 3.08 – 2.76 (m, 2H), 2.25 – 2.11 (m, 2H), 2.09 – 2.02 (m, 3H), 1.78 – 1.65 (m, 2H), 1.08 – 0.98 (m, 2H); **^{19}F NMR (377 MHz, $CDCl_3$)** δ -145.47 (ddt, *J* = 24.0, 18.0, 6.0 Hz, **minor**), -147.72 (ddt, *J* = 21.3, 16.5, 4.9 Hz, **major**); **FTIR:** ν_{max}/cm^{-1} (neat) 2962, 1733, 1637, 1447, 1367, 1236, 1041 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{20}H_{25}FNO_4$ (ES^+)($+H^+$): 362.1762. Found: 362.1774.

^{13}C NMR MAJOR (101 MHz, $CDCl_3$) δ 171.3, 169.2 (d, *J* = 27.0 Hz), 160.9 (d, *J* = 18.5 Hz), 136.9, 128.4, 127.4, 127.3, 127.2, 126.8, 90.8 (d, *J* = 195.5 Hz), 63.7, 62.3, 51.3, 40.4 (d, *J* = 24.0 Hz), 28.4, 23.7, 21.1, 13.9.

^{13}C NMR MINOR (101 MHz, $CDCl_3$) δ 171.3, 169.4 (d, *J* = 26.5 Hz), 160.0 (d, *J* = 18.0 Hz), 137.0, 130.0, 127.4, 127.2, 127.2, 126.4, 90.8 (d, *J* = 195.5 Hz), 63.8, 62.4, 57.6, 34.0 (d, *J* = 24.0 Hz), 28.6, 23.4, 21.1, 13.8.

Stereochemical Assignment of 9



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, 5H), 4.97 – 4.79 (m, 3H), 3.87 (d, *J* = 30.0 Hz, 1H), 3.63 (dd, *J* = 14.0, 1.5 Hz, 1H), 3.46 (d, *J* = 14.0 Hz, 1H), 2.84 – 2.75 (m, 1H), 2.56 (dd, *J* = 45.0, 15.0 Hz, 1H), 1.93 (s, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 140.3, 140.0 128.5, 127.6, 127.2, 112.1, 90.4 (d, *J* = 178.5 Hz), 62.7 (d, *J* = 19.0 Hz), 53.1, 38.9 (d, *J* = 23.5 Hz); **^{19}F NMR (377 MHz, $CDCl_3$)** δ -197.47 (dddd, *J* = 48.5, 45.0, 30.0, 11.0 Hz); **FTIR:** ν_{max}/cm^{-1} (neat) 3291, 2937, 1656, 1467, 1261, 1100, 1022 cm^{-1}; **HRMS (ESI$^+$):** calculated for $C_{12}H_{15}FN$ (ES^+)($+H^+$): 192.1183. Found: 192.1186.

The assignment of **9** as containing a relative *cis*-stereochemistry between the fluorine atom and phenyl ring is made on the basis of the magnitude of the proton-fluorine coupling constants in the ^{1}H and ^{19}F NMR spectra. Examination of the current literature reveals a clear trend between molecular conformation and the magnitude of proton-fluorine coupling constants within six membered rings.[17-21] Typically, geminal ($^{2}J_{F\text{-}H}$) and *trans*-diaxial ($^{3}J_{F(ax)\text{-}H(ax)}$) couplings are much larger than the corresponding axial-equatorial ($^{3}J_{F(ax)\text{-}H(eq)}$ or $^{3}J_{F(eq)\text{-}H(ax)}$) and equatorial-equatorial ($^{3}J_{F(eq)\text{-}H(eq)}$) couplings (Figure S1). In the case of **9**, 4 different 3-Dimensional conformations are possible (Scheme S1). Analysis of the ^{1}H and ^{19}F NMR spectra of **9** indicates that there is a geminal coupling (48.5 Hz), 2 *trans*-diaxial couplings (45.0 and 30.0 Hz) and one axial-equatorial or equatorial-equatorial coupling (11.0 Hz). Given that only conformation **B1** would give rise to NMR spectra matching the observed spectra, we assigned the fluorine atom and phenyl ring in **9** in a *cis*-relationship relative to one another.

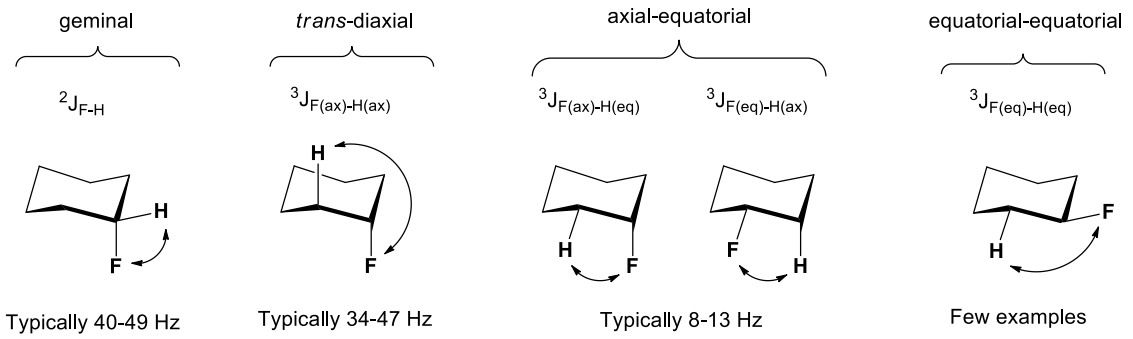
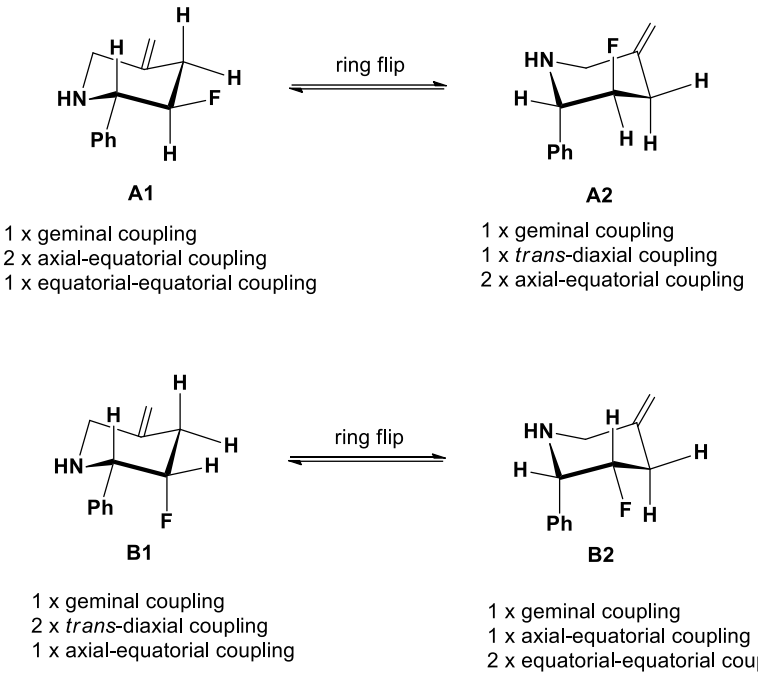


Figure S1 – Typical ranges for proton-fluorine coupling constants reported in the chemical literature



Scheme S1 – Possible conformations of **9** and their associated proton-fluorine couplings

X-Ray Structure for compound 6

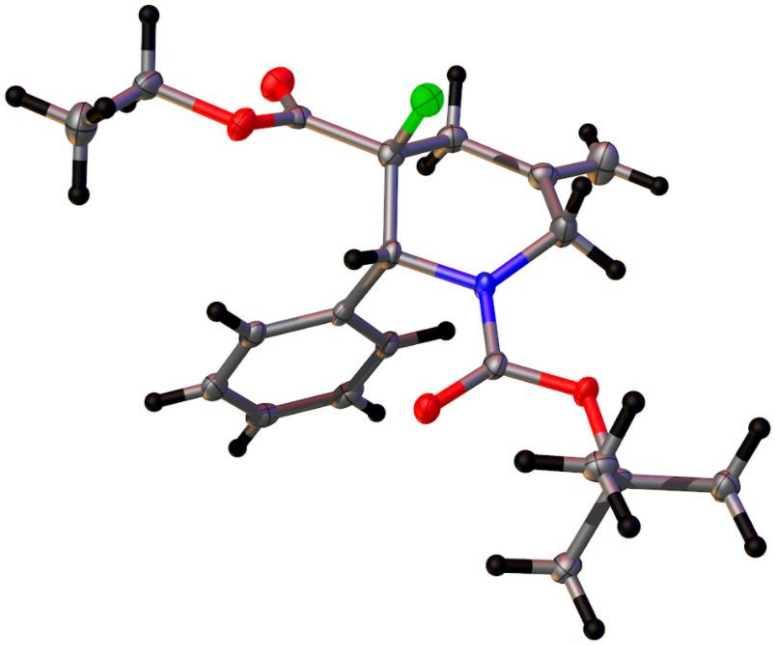


Figure 1. X-Ray Structure for compound **6**. Flack parameter = 0.8(5).

X-Ray Structure for compound 13a

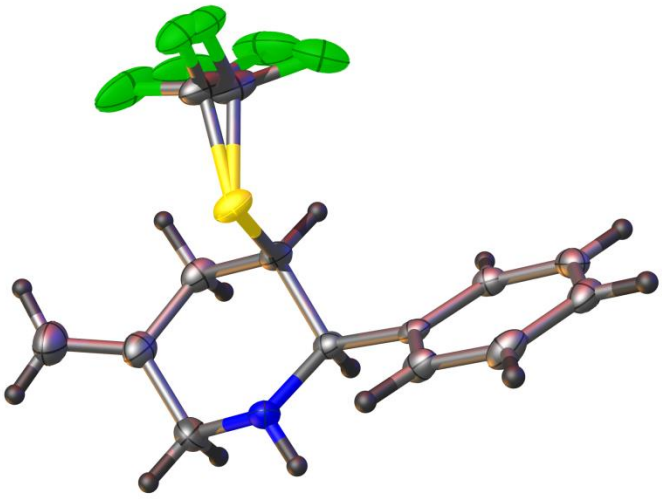


Figure 2. X-Ray Structure for compound **13a.**

X-Ray Structure for compound 13e

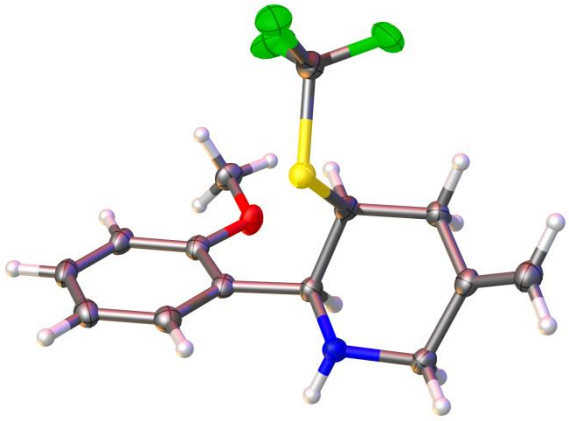


Figure 2. X-Ray Structure for compound **13e.**

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Chapter 3 (Paper II)

General procedure for the synthesis of silyl enol ethers (GPA)

To a solution of the corresponding ketone (4 mmol, 1 equiv.) in MeCN (0.5 M) under an argon atmosphere, *tert*-butyldimethylsilyl chloride (730 mg, 5.2 mmol, 1.3 equiv.), sodium iodide (558 mg, 4 mmol, 1 equiv.) and triethylamine (0.5 mL, 4 mmol, 1 equiv.) were added at 0 °C. The reaction mixture was then warmed up to room temperature and stirred for additional 18 h. The mixture was then quenched using NH_4Cl (8 mL), extracted with EtOAc (3x 10 mL), washed with brine (30 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The silyl enol (**1**) ethers were isolated by flash column chromatography (FCC) using silica gel as stationary phase and a mixture of pentane:EtOAc (99:1).

General procedure for the synthesis of organic carbamates (GPB)

To a suspension of NaH (60% in mineral oil, 6 mg, 0.15 mmol,1.5 equiv.) in THF (0.5 M) under an atmosphere of argon, diethylamine (24 µL, 0.2 mmol, 2 equiv.) was added, and the mixture was stirred at 60 °C for 1 h. The reaction was then cooled to –20 °C and CO_2 was bubbled for 30 min. After warming the mixture to room temperature (2-3 minutes), 1-bromo-3,3-dimethyl-1,3-dihydro-1λ3-benzo[d][1,2]iodaoxole (51 mg, 0.15 mmol, 1.5 equiv.), the silyl enol ether (**1**, 0.1 mmol, 1 equiv.) and DMF (0.33 M) were added slowly and the reaction mixture was stirred at room temperature for 18 h. After completion, the crude was extracted with EtOAc (3 x 1 mL) and the organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The products were isolated by flash column chromatography (FCC) using silica gel as stationary phase and a gradient of DCM:MeOH as eluent (0 to 2% of MeOH)

General procedure for the synthesis of α-substituted ketones (GPC)

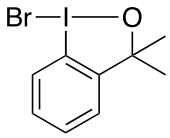
1-Bromo-3,3-dimethyl-1,3-dihydro-1λ3-benzo[d][1,2]iodaoxole (**2c**, 0.15 mmol, 1.5 equiv.), the nucleophile (0.2 mmol, 2 equiv.) and NaH (0.15 mmol, 1.5 equiv. 60% in mineral oil) were placed in a pressure tube. The tube was sealed with a teflon cap. A solution of (*Z*)-*tert*-butyldimethyl((1-phenylprop-1-en-1-yl)oxy)silane (**1a**, 0.1 mmol, 1 equiv.) in DMF (1 mL, 0.1M) was then added under an atmosphere of argon. The mixture was stirred overnight (18 h) at room temperature. The final mixture was extracted with EtOAc (3 x 5 mL), dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. The products were purified by flash column chromatography (FCC) using silica gel as stationary phase and a mixture of pentane:EtOAc as eluent (10 to 100% EtOAc).

General procedure for the synthesis of α-substituted ketones: one-pot two steps procedure (GPD)

(*Z*)-*tert*-Butyldimethyl((1-phenylprop-1-en-1-yl)oxy)silane (**1a**, 0.1 mmol, 1 equiv.) and 1-bromo-3,3-dimethyl-1,3-dihydro-1λ3-benzo[d][1,2]iodaoxole (**2c**, 0.15 mmol, 1.5 equiv.) were placed in a pressure tube sealed with a teflon cap. The tube was flashed with argon, and DMF (0.5 mL, 0.2M) was added. The mixture was stirred overnight (18 h) at room temperature. After 18 h, α-bromoketone **9** is formed quantitatively, as confirmed by TLC and NMR. Then a suspension of the nucleophile (0.2 mmol, 2 equiv.) and NaH (0.15 mmol, 1.5 equiv., 60% in mineral oil) in DMF (0.5 mL, 0.2M) is transferred with a syringe to the sealed tube. The mixture is stirred at room temperature for additional 4 h, and the mixture is then extracted with EtOAc (3 x 5 mL) and dried with $MgSO_4$. The solvent was evaporated under reduced pressure. The products were purified by flash column chromatography using silica gel as stationary phase and a mixture of pentane:EtOAc as eluent (10 to 100%) EtOAc.

Characterization of compounds

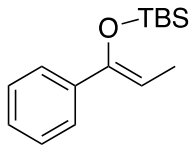
Synthesis of 1-bromo-3,3-dimethyl-1,3-dihydro-1λ3-benzo[d][1,2]iodaoxole (13c)



The title compound was synthesized following a reported procedure using NBS (1.63 g, 9.16 mmol) and 2-(2-iodophenyl)propan-2-ol (2 g, 7.64 mmol) in $CHCl_3$ (25 mL). The final compound was isolated as bright yellow crystals (1.6 g, 60% isolated yield). The physical and spectroscopic data agreed with the described in the literature. **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 8.19 – 7.90 (m, 1H), 7.69 – 7.50 (m, 2H), 7.27 – 7.06 (m, 1H), 1.58 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 149.8, 131.1, 130.4, 129.3, 112.0, 84.2, 29.2.

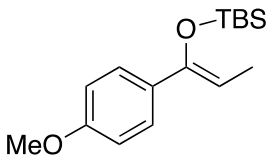
For complete characterization see: C. Braddock, G. Cansell, S. A. Hermitage, A. J. P. White, *Chem. Commun.* **2006**, *13*, 1442-1444.

(*Z*)-*tert*-butyldimethyl((1-phenylprop-1-en-1-yl)oxy)silane (11a)



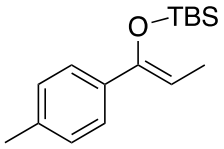
The title compound was synthesized according to the GPA using propiophenone (4 mmol, 536 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a mixture of pentane:EtOAc (99:1) as a colorless oil (794 mg, 80% isolated yield). **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 7.45 – 7.41 (m, 2H), 7.31 – 7.21 (m, 3H), 5.20 (q, *J* = 7.0 Hz, 1H), 1.74 (d, *J* = 7.0 Hz, 3H), 0.99 (s, 9H), -0.03 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 150.1, 139.6, 128.0, 127.3, 125.8, 106.4, 26.1, 18.4, 11.9, -4.0.

(*Z*)-*tert*-butyl((1-(4-methoxyphenyl)prop-1-en-1-yl)oxy)dimethylsilane (11b)



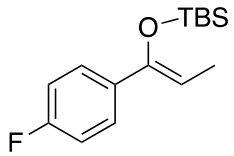
The title compound was synthesized according to the GPA using 1-(4-methoxyphenyl)propan-1-one (4 mmol, 656 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a mixture of pentane:EtOAc (99:1) as a colorless oil (1113 mg, 99% isolated yield). **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 7.35 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 5.08 (q, *J* = 7.0 Hz, 1H), 3.80 (s, 3H) 1.71 (d, *J* = 7.0 Hz, 3H), 0.99 (s, 9H), -0.04 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 158.9, 149.9, 131.7, 126.9, 113.2, 104.3, 55.2, 25.9, 18.4, 11.7, - 4.0.

(*Z*)-*tert*-butyldimethyl((1-(p-tolyl)prop-1-en-1-yl)oxy)silane (11c)



The title compound was synthesized according to the GPA using 1-(p-tolyl)propan-1-one (4 mmol, 592 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a mixture of pentane:EtOAc (99:1) as a colorless oil (891 mg, 85% isolated yield). **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 7.32 (d, *J* = 8.0 Hz, 2H), 7.10 – 7.07 (m, 2H), 5.15 (q, *J* = 7.0 Hz, 1H), 2.33 (s, 3H) 1.72 (d, *J* = 7.0 Hz, 3H), 0.99 (s, 9H), - 0.04 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 150.2, 137.0, 136.9, 128.6, 125.6, 105.0, 25.9, 21.1, 18.4, 11.7, -4.0

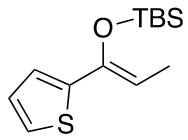
(*Z*)-*tert*-butyl((1-(4-fluorophenyl)prop-1-en-1-yl)oxy)dimethylsilane (11d)



The title compound was synthesized according to the GPA using 1-(4-fluorophenyl)propan-1-one (4 mmol, 608 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a mixture of pentane:EtOAc (99:1) as a colorless oil (820 mg, 77% isolated yield). **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 7.57 – 7.28 (m, 2H), 7.00 – 6.93 (m, 2H), 5.13 (q, *J* = 7.0 Hz, 1H), 1.72 (d, *J* = 7.0 Hz, 3H), 0.98 (s, 9H), -0.05 (s, 6H). **^{13}C NMR (100 MHz,**

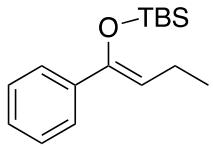
$CDCl_3$-*d*) δ 162.2 (d, *J* = 246.0 Hz), 149.3, 136.0 (d, *J* = 3.0 Hz), 127.3 (d, *J* = 8.0 Hz), 114.7 (d, *J* = 21.5 Hz), 105.7, 25.8, 18.3, 11.7, -4.0

(*Z*)-*tert*-butyldimethyl((1-(thiophen-2-yl)prop-1-en-1-yl)oxy)silane (11g)



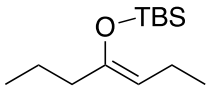
The title compound was synthesized according to the GPA using 1-(thiophen-2-yl)propan-1-one (4 mmol, 560 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a mixture of pentane:EtOAc (99:1) as a colorless oil (671 mg, 68% isolated yield). **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 7.10 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.01 (dd, *J* = 3.5, 1.5 Hz, 1H), 6.92 (dd, *J* = 5.0, 1.0 Hz, 1H), 5.24 (q, *J* = 7.0 Hz, 1H), 1.71 (d, *J* = 7.0 Hz, 3H), 1.01 (s, 9H), 0.07 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 144.7, 143.6, 126.8, 125.5, 123.1, 105.6, 25.9, 18.4, 11.7, -3.9.

(*Z*)-*tert*-butyldimethyl((1-phenylbut-1-en-1-yl)oxy)silane (11h)



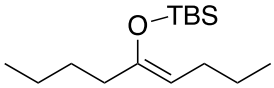
The title compound was synthesized according to the GPA using 1-phenylbutan-1-one (4 mmol, 592 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a mixture of pentane:EtOAc (99:1) as a colorless oil (859 mg, 82% isolated yield). **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 7.46 – 7.41 (m, 2H), 7.32 – 7.25 (m, 3H), 5.09 (q, *J* = 7.0 Hz, 1H), 2.22 (p, *J* = 7.5 Hz, 2H) 1.03 (t, *J* = 7.5 Hz, 3H), 0.99 (s, 9H), -0.04 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 148.7, 139.8, 128.3, 127.9, 125.8, 113.8, 25.9, 19.5, 18.3, 14.25, -4.1.

(*Z*)-*tert*-butyl(hept-3-en-4-yloxy)dimethylsilane (11j)



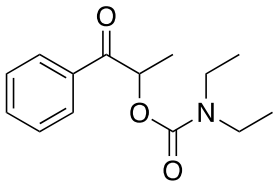
The title compound was synthesized according to the GPA using heptan-4-one (4 mmol, 456 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a mixture of pentane:EtOAc (99:1) as a colorless oil (456 mg, 50% isolated yield). **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 4.43(t, *J* = 7.0 Hz, 1H), 2.19 – 1.89 (m, 4H), 1.55 – 1.38 (m, 2H), 0.97 (s, 9H),), 0.93 – 0.88 (m, 6H) 0.14 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 149.6, 109.9, 38.7, 25.8, 20.3, 18.6, 18.3, 14.5, 13.7, -4.1.

(*Z*)-*tert*-butyldimethyl(non-4-en-5-yloxy)silane (11k)



The title compound was synthesized according to the GPA using nonan-5-one (4 mmol, 568 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a mixture of pentane:EtOAc (99:1) as a colorless oil (450 mg, 44% isolated yield). **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 4.41(t, *J* = 7.0 Hz, 1H), 2.06 – 1.87 (m, 4H), 1.49 – 1.39 (m, 2H), 1.37 – 1.26 (m, 4H), 0.94 (s, 9H),), 0.87 (t, *J* = 8.0 Hz, 6H) 0.11 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 150.4, 107.7, 36.3, 31.0, 29.4, 27.4, 25.9, 25.6, 23.1, 22.3, 18.3, 14.0, - 4.0.

1-Oxo-1-phenylpropan-2-yl diethylcarbamate (15a)

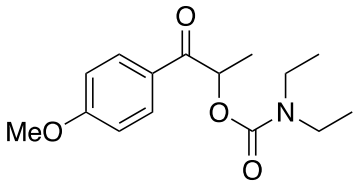


The title compound was synthesized according to the GPB using (*Z*)-*tert*-butyldimethyl((1-phenylprop-1-en-1-yl)oxy)silane (0.1 mmol, 25 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a gradient of DCM:MeOH as eluent (0 to 2% of MeOH) as a colorless oil (17 mg, 69% isolated yield). **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 8.03 – 7.87

(m, 2H), 7.62 – 7.51 (m, 1H), 7.50 – 7.40 (m, 2H), 5.95 (q, *J* = 7.0 Hz, 1H), 3.31 (brs, 4H), 1.51 (d, *J* = 7.0 Hz, 3H), 1.17 – 1.09 (m, 6H). **^{13}C NMR (100 MHz, CDCl$_3$-*d*)** δ 198.3, 155.2, 135.0, 133.4, 128.8, 128.6, 71.7, 42.1, 41.6, 17.4, 14.1, 13.6.

For complete characterization see: Y. Peng, J. Liu, C. Qi, G. Yuan, J. Li, H. Jiang, *Chem. Commun*., **2017**, *53*, 2665-2668.

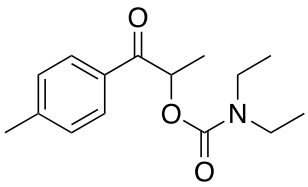
1-(4-Methoxyphenyl)-1-oxopropan-2-yl diethylcarbamate (15b)



The title compound was synthesized according to the GPB using (*Z*)-*tert*-butyl((1-(4-methoxyphenyl)prop-1-en-1-yl)oxy)dimethylsilane (0.1 mmol, 28 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a gradient of DCM:MeOH as eluent (0 to 2% of MeOH) as a colorless oil (22 mg, 80% isolated yield). **^{1}H NMR (400 MHz, CDCl$_3$-*d*)** δ 8.05 – 7.78 (m, 2H), 7.04 – 6.78 (m, 2H), 5.93 (q, *J* = 7.0 Hz, 1H), 3.86 (s, 3H), 3.31 (brs, 4H), 1.49 (d, *J* = 7.0 Hz, 3H), 1.23 – 0.87 (m, 6H). **^{13}C NMR (100 MHz, CDCl$_3$-*d*)** δ 196.6, 163.8, 155.3, 131.0, 127.8, 114.0, 71.4, 55.6, 42.1, 41.6, 17.6, 14.1, 13.6.

For complete characterization see: Y. Peng, J. Liu, C. Qi, G. Yuan, J. Li, H. Jiang, *Chem. Commun*., **2017**, *53*, 2665-2668.

1-Oxo-1-(*p*-tolyl)propan-2-yl diethylcarbamate (15c)

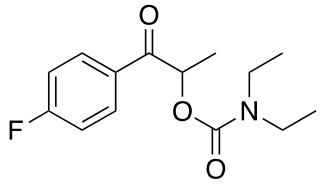


The title compound was synthesized according to the GPB using (*Z*)-*tert*-butyldimethyl((1-(p-tolyl)prop-1-en-1-yl)oxy)silane (0.1 mmol, 26 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a gradient of DCM:MeOH as eluent (0 to 2% of MeOH) as a

colorless oil (16 mg, 60% isolated yield). **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 8.00 – 7.75 (m, 2H), 7.27 – 7.24 (d, *J* = 6.4 Hz, 2H), 5.94 (q, *J* = 7.0 Hz, 1H), 3.32 (brs, 4H), 2.40 (s, 3H), 1.49 (d, *J* = 7.0 Hz, 3H), 1.22 – 0.97 (m, 6H). **^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 197.8, 155.2, 144.2, 132.3, 129.4, 128.9, 128.7, 71.6, 42.0, 41.6, 21.8, 17.4, 14.0, 13.6.

For complete characterization see: Y. Peng, J. Liu, C. Qi, G. Yuan, J. Li, H. Jiang, *Chem. Commun*., **2017**, *53*, 2665-2668.

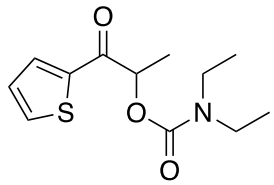
1-(4-fluorophenyl)-1-oxopropan-2-yl diethylcarbamate (15d)



The title compound was synthesized according to the GPB using (*Z*)-*tert*-butyldimethyl((1-(4-fluorophenyl)prop-1-en-oxy)silane (0.1 mmol, 26 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a gradient of DCM:MeOH as eluent (0 to 2% of MeOH) as a colorless oil (14 mg, 52% isolated yield). **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 7.99 (dd, *J* = 9.0, 5.5 Hz) 2H), 7.22 – 7.05 (m, 2H), 5.89 (q, *J* = 7.0 Hz, 1H), 3.45 – 3.11 (m, 4H), 1.50 (d, *J* = 7.0 Hz, 3H), 1.13 (dt, *J* = 15.5, 7.0 Hz, 6H).**^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 196.6, 165.8 (d, *J* = 255.0 Hz), 155.0, 131.2 (d, *J* = 3.0 Hz), 131.2 (d, *J* = 9.5 Hz), 115.8 (d, *J* = 22.0 Hz), 71.4, 42.0, 41.5, 17.1, 14.0, 13.4. **^{19}F NMR (376 MHz, $CDCl_3$-d)** δ – 104.7 (s).

For complete characterization see: Y. Peng, J. Liu, C. Qi, G. Yuan, J. Li, H. Jiang, *Chem. Commun*., **2017**, *53*, 2665-2668.

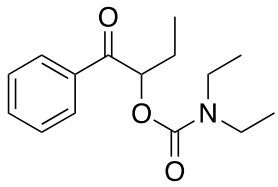
1-oxo-1-(thiophen-2-yl)propan-2-yl diethylcarbamate (15g)



The title compound was synthesized according to the GPB using (*Z*)-*tert*-butyldimethyl((1-(thiophen-2-yl)prop-1-en-1-yl)oxy)silane (0.1 mmol, 25 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a gradient of DCM:MeOH as eluent (0 to 2% of MeOH) as a colorless oil (16 mg, 64% isolated yield). **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 7.81 (dd, *J* = 3.5, 1.0 Hz) 1H), 7.66 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.14 (dd, *J* = 5.0, 4.0 Hz, 1H), 5.73 (q, *J* = 7.0 Hz, 1H), 3.40 – 3.20 (m, 4H), 1.55 (d, *J* = 7.0 Hz, 3H), 1.23 – 1.08 (m, 6H).**^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 190.8, 155.0, 140.9, 134.0, 132.5, 128.1, 72.5, 42.0, 41.5, 25.7, 17.7, 14.0, 13.4.

For complete characterization see: Y. Peng, J. Liu, C. Qi, G. Yuan, J. Li, H. Jiang, *Chem. Commun*., **2017**, *53*, 2665-2668.

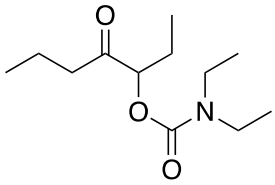
1-oxo-1-phenylbutan-2-yl diethylcarbamate (15h)



The title compound was synthesized according to the GPB using (*Z*)-*tert*-butyldimethyl((1-phenylbut-1-en-1-yl)oxy)silane (0.1 mmol, 26 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a gradient of DCM:MeOH as eluent (0 to 2% of MeOH) as a colorless oil (13 mg, 49% isolated yield). **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 7.96 (dd, *J* = 8.5, 1.5 Hz) 1H), 7.61– 7.52 (m, 1H), 7.51 – 7.42 (m, 1H), 5.80 (dd, *J* = 8.1, 4.4 Hz, 1H), 3.48 – 3.20 (m, 4H), 2.03 – 1.76 (m, 2H), 1.24 – 1.06 (m, 6H), 1.03 (d, *J* = 7.5 Hz, 3H).**^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 197.9, 155.4, 135.4, 133.2, 128.7, 128.5, 76.5, 42.1, 41.7, 24.9, 14.1, 13.5, 10.0.

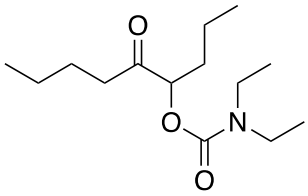
For complete characterization see: Y. Peng, J. Liu, C. Qi, G. Yuan, J. Li, H. Jiang, *Chem. Commun*., **2017**, *53*, 2665-2668.

4-oxoheptan-3-yl diethylcarbamate (15j)



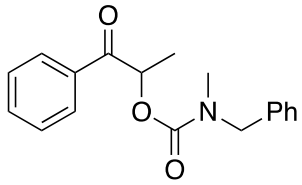
The title compound was synthesized according to the GPB using (*Z*)-*tert*-butyl(hept-3-en-4-yloxy)dimethylsilane (0.1 mmol, 23 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a gradient of DCM:MeOH as eluent (0 to 2% of MeOH) as a colorless oil (12 mg, 51% isolated yield). **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 4.90 (dd, *J* = 8.0, 4.5 Hz, 1H), 3.38 – 3.25 (m, 4H), 2.66 – 2.31 (m, 2H), 1.89 – 1.70 (m, 2H), 1.62 (q, *J* = 7.5 Hz, 2H), 1.21 – 1.11 (m, 6H), 0.98 (t, *J* = 7.5 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H).**^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 208.8, 155.3, 79.9, 42.1, 41.5, 40.6, 24.2, 16.6, 14.2, 13.8, 13.5, 9.8. **FTIR** $\nu_{max/cm}^{-1}$ (neat) 2964, 1748, 1707, 1428, 1269, 1236, 1160, 1021, 763. **HRMS (ESI):** m/z calculated for $[C_{12}H_{23}NO_3Na]^+$: 252.1570; found: 252.1583.

5-oxononan-4-yl diethylcarbamate (15k)



The title compound was synthesized according to the GPB using (*Z*)-*tert*-butyldimethyl(non-4-en-5-yloxy)silane (0.1 mmol, 26 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a gradient of DCM:MeOH as eluent (0 to 2% of MeOH) as a colorless oil (12 mg, 46% isolated yield). **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 4.94 (dd, *J* = 7.5, 5.5 Hz, 1H), 3.43 – 3.26 (m, 4H), 2.56 – 2.34 (m, 2H), 1.76 – 1.65 (m, 2H), 1.65 – 1.52 (m, 2H), 1.47 – 1.38 (m, 2H), 1.35 – 1.26 (m, 2H), 1.21 – 1.07 (m, 6H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H).**^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 209.1, 155.4, 78.8, 42.0, 41.5, 38.2, 32.9, 25.7, 25.2, 22.4, 18.7, 14.1, 13.9, 13.8, 13.5. **FTIR** $\nu_{max/cm}^{-1}$ (neat) 2967, 2875, 2032, 1697, 1425, 1171. **HRMS (ESI):** m/z calculated for $[C_{14}H_{27}NO_3Na]^+$: 280.1883; found 280.1883.

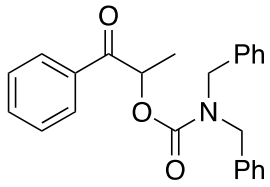
1-oxo-1-phenylpropan-2-yl benzyl(methyl)carbamate (5l)



The title compound was synthesized according to the GPB using (*Z*)-*tert*-butyldimethyl((1-phenylprop-1-en-1-yl)oxy)silane (0.1 mmol, 25 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a gradient of DCM:MeOH as eluent (0 to 2% of MeOH) as a colorless oil (24 mg, 80% isolated yield). **^{1}H NMR (400 MHz, CDCl$_3$-*d*)** δ 8.00 (d, *J* = 7.5 Hz, 2H), 7.64 – 7.58 (m, 1H), 7.55 – 7.46 (m, 2H), 7.41 – 7.30 (m, 4H), 7.23 (d, *J* = 7.5 Hz, 1H), 6.01 (dq, *J* = 14.0, 7.0 Hz, 1H), 4.68 – 4.44 (m, 2H), 2.94 – 2.88 (two singlets, rotamers, 3H) 1.56 (dd, *J* = 14.5, 7.0 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$-*d*)** δ 198.0, 197.9, 156.1, 155.6, 137.2, 134.8, 133.4, 128.8, 128.6, 128.5, 127.7, 127.6, 127.4, 127.4, 72.4, 72.2, 52.6, 52.5, 34.2, 33.7, 17.3, 17.2.

For complete characterization see: Y. Peng, J. Liu, C. Qi, G. Yuan, J. Li, H. Jiang, *Chem. Commun*., **2017**, *53*, 2665-2668.

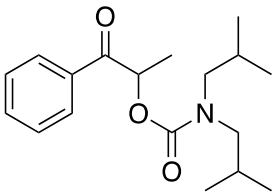
1-oxo-1-phenylpropan-2-yl dibenzylcarbamate (15m)



The title compound was synthesized according to the GPB using (*Z*)-*tert*-butyldimethyl((1-phenylprop-1-en-1-yl)oxy)silane (0.1 mmol, 25 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a gradient of DCM:MeOH as eluent (0 to 2% of MeOH) as a colorless oil (29 mg, 79% isolated yield). **^{1}H NMR (400 MHz, CDCl$_3$-*d*)** δ 8.01 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.64 – 7.56 (m, 1H), 7.54 – 7.45 (m, 2H), 7.42 – 7.23 (m, 10H), 6.06 (q, *J* = 7.0 Hz, 1H), 4.46 (dd, *J* = 22.5, 7.5 Hz, 4H), 1.57 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$-*d*)** δ 197.8, 156.0, 137.1, 137.0, 134.8, 133.3, 128.8, 128.6, 128.6, 128.0, 127.9, 127.5, 126.7, 72.6, 49.3, 29.2, 17.2.

For complete characterization see: Y. Peng, J. Liu, C. Qi, G. Yuan, J. Li, H. Jiang, *Chem. Commun*., **2017**, *53*, 2665-2668.

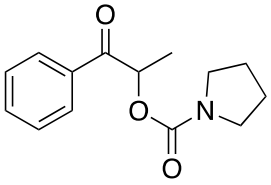
1-oxo-1-phenylpropan-2-yl diisobutylcarbamate (15n)



The title compound was synthesized according to the GPB using (*Z*)-*tert*-butyldimethyl((1-phenylprop-1-en-1-yl)oxy)silane (0.1 mmol, 25 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a gradient of DCM:MeOH as eluent (0 to 2% of MeOH) as a colorless oil (18 mg, 60% isolated yield). **^{1}H NMR (400 MHz, CDCl$_3$-*d*)** δ 7.98 – 7.91 (m, 2H), 7.58 – 7.52 (m, 1H), 7.48 – 7.41 (m, 2H), 5.93 (q, *J* = 7.0 Hz, 1H), 3.22– 2.95 (m, 4H), 1.96 (tt, *J* = 14.0, 7.0 Hz, 2H), 1.50 (d, *J* = 7.0 Hz, 3H), 0.93– 0.77 (m, 12H). **^{13}C NMR (100 MHz, CDCl$_3$-*d*)** δ 198.1, 155.9, 134.9, 133.2, 128.6, 128.5, 71.7, 55.2, 54.8, 27.4, 26.9, 20.2, 20.1, 20.0, 19.9, 17.1.

For complete characterization see: Y. Peng, J. Liu, C. Qi, G. Yuan, J. Li, H. Jiang, *Chem. Commun*., **2017**, *53*, 2665-2668.

1-oxo-1-phenylpropan-2-yl pyrrolidine-1-carboxylate (15o)

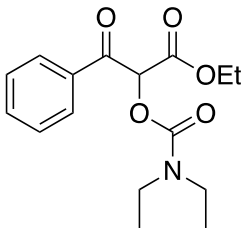


The title compound was synthesized according to the GPB using (*Z*)-*tert*-butyldimethyl((1-phenylprop-1-en-1-yl)oxy)silane (0.1 mmol, 25 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a gradient of DCM:MeOH as eluent (0 to 2% of MeOH) as a colorless oil (14 mg, 58% isolated yield). **^{1}H NMR (400 MHz, CDCl$_3$-*d*)** δ 7.97 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.60 – 7.54 (m, 1H), 7.50 – 7.43 (m, 2H), 5.94 (q, *J* = 7.0 Hz, 1H), 3.56

– 3.24 (m, 4H), 1.97–1.80 (m, 4H), 1.51 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 198.2, 154.2, 134.8, 133.3, 128.6, 128.6, 71.5, 46.2, 45.9, 25.7, 24.9, 17.3.

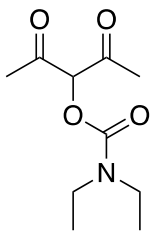
For complete characterization see: Y. Peng, J. Liu, C. Qi, G. Yuan, J. Li, H. Jiang, *Chem. Commun*., **2017**, *53*, 2665-2668.

ethyl 2-((diethylcarbamoyl)oxy)-3-oxo-3-phenylpropanoate (17b)



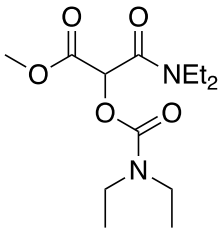
The title compound was synthesized according to the GPB using ethyl 3-oxo-3-phenylpropanoate (0.1 mmol, 19 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a gradient of DCM:MeOH as eluent (0 to 2% of MeOH) as a colorless oil (28 mg, 82% isolated yield) as a 1.3:1 keto/enol mixture. **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 8.11 – 8.05 (m, 2H, enol tautomer), 8.11 – 8.05 (m, 2H, keto tautomer), 7.65 – 7.53 (m, 1H, keto tautomer, 1H, enol tautomer), 7.52– 7.42 (m, 2H, keto tautomer, 2H, enol tautomer), 6.43 (s, 1H, keto tautomer), 4.33 (dq, *J* = 7.0, 2.0 Hz, 2H, enol tautomer), 4.25 (dq, *J* = 7.0, 2.5 Hz, 2H, keto tautomer) 3.39 – 3.18 (m, 4H, keto tautomer, 4H, enol tautomer), 1.37 – 0.98 (m, 9H, keto tautomer, 9H, enol tautomer). **^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 190.9, 185.9, 166.1, 164.1, 153.9, 151.0, 134.5, 133.9, 133.5, 132.3, 129.9, 129.2, 128.6, 128.3, 87.5, 74.8, 63.7, 62.1, 42.4, 42.4, 41.9, 41.7, 14.1, 13.9, 13.9, 13.7, 13.3, 13.0. **FTIR** $\nu_{max/cm}^{-1}$ (neat) 2978, 2929, 2073, 1706, 1596, 1448, 1401, 1133, 1024, 698. **HRMS (ESI):** m/z calculated for $[C_{16}H_{21}NO_5Na]^+$: 330.1312; found: 330.1327

2,4-dioxopentan-3-yl diethylcarbamate (17c)



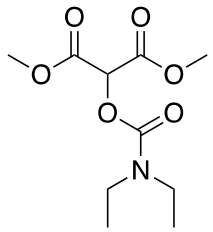
The title compound was synthesized according to the GPB using pentane-2,4-dione (0.1 mmol, 10 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a gradient of DCM:MeOH as eluent (0 to 2% of MeOH) as a colorless oil (12 mg, 56% isolated yield) as a 2.7:1 keto/enol mixture. **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 14.36 (s, 1H, enol tautomer), 5.49 (s, 1H, keto tautomer), 3.49 – 3.26 (m, 4H, keto tautomer, 4H, enol tautomer), 2.29 (s, 6H, keto tautomer), 2.04 (s, 6H, enol tautomer) 1.31 – 1.09 (m, 6H, keto tautomer, 6H, enol tautomer). **^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 200.2, 185.3, 153.9, 153.8, 128.7, 85.5, 77.3, 42.6, 42.4, 41.9, 41.8, 27.4, 20.8, 14.4, 14.0, 13.5, 13.4. **FTIR** $\nu_{max/cm}^{-1}$ (neat) 2973, 2928, 2496, 2360, 1726, 1700, 1635, 1424, 1270, 1078, 763. **HRMS (ESI):** m/z calculated for $[C_{10}H_{17}NO_4Na]^+$: 238.1050; found: 238.1045

methyl 3-(diethylamino)-2-((diethylcarbamoyl)oxy)-3-oxopropanoate (17d)



The title compound was synthesized according to the GPB using methyl 3-(diethylamino)-3-oxopropanoate (0.1 mmol, 17 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a gradient of DCM:MeOH as eluent (0 to 2% of MeOH) as a colorless oil (20 mg, 68% isolated yield). **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 5.88 (s, 1H), 3.80 (s, 1H), 3.53 – 3.28 (m, 8H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.14 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 167.0, 164.0, 154.1, 70.6, 52.7, 42.3, 42.1, 41.7, 40.6, 14.2, 13.9, 13.3, 12.6. **FTIR** $\nu_{max/cm}^{-1}$ (neat) 2956, 1748, 1707, 1428, 1269, 1236, 1160, 1021, 763. **HRMS (ESI):** m/z calculated for $[C_{13}H_{24}N_2O_5Na]^+$: 311.1577; found: 311.1559.

dimethyl 2-((diethylcarbamoyl)oxy)malonate (17a)

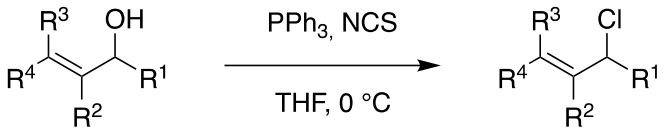


The title compound was synthesized according to the GPB using dimethyl malonate (0.1 mmol, 13 mg) as substrate. The final compound was isolated by flash column chromatography (FCC) using silica gel as stationary phase and a gradient of DCM:MeOH as eluent (0 to 2% of MeOH) as a colorless oil (19 mg, 78% isolated yield). **^{1}H NMR (400 MHz, $CDCl_3$-*d*)** δ 5.61 (s, 1H), 3.83 (s, 1H), 3.44 – 3.27 (m, 4H), 1.21 (t, *J* = 7.0 Hz, 3H), 1.15 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$-*d*)** δ 165.8, 153.9, 72.1, 53.2, 42.5, 41.9, 14.0, 13.4. **FTIR** $\nu_{max/cm}^{-1}$ (neat) 2954, 2923, 1733, 1435, 1254, 700. **HRMS (ESI):** m/z calculated for $[C_{10}H_{17}NO_6Na]^+$: 270.0948; found: 270.0977.

Chapter 4 (Paper III)

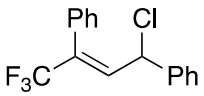
Optimization studies

General procedure for the synthesis of allylic chlorides 20a-o.



PPh_3 and NCS (1.5 equiv.) were added to a solution of the corresponding allylic alcohol (1 equiv.) in dry THF (0.1 M) at 0 °C. The mixture was warmed to room temperature overnight and petroleum ether (5 mL per mmol of substrate) was added and stirred for 15 min. The resulting suspension was filtered and evaporated under reduced pressure. The resulting residue was purified using silica chromatography employing petroleum ether as eluent and yielding the desired allylic chlorides as pure products.

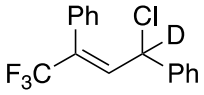
(*E*)-(1-chloro-4,4,4-trifluorobut-2-ene-1,3-diyl)dibenzene (20a)



The title compound was synthesized according to the above procedure using (*E*)-4,4,4-trifluoro-1,3-diphenylbut-2-en-1-ol (1 mmol, 278 mg) as substrate. The final compound was isolated as a colorless oil (199 mg, 67% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.46 (m, 3H), 7.40–7.33 (m, 3H), 7.31–7.29 (m, 4H), 6.77 (dq, *J* = 10.6, 1.5 Hz, 1H), 5.30 (d, *J* = 10.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 138.8, 134.4 (q, *J* = 6 Hz), 131.8 (q, *J* = 30 Hz), 130.7, 129.6, 129.2, 129.1, 129.1, 129.0, 127.2, 123.0 (q, *J* = 274 Hz), 57.5. **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 66.51 (s). **HPLC:** CHIRALCEL OJ-H, flow rate 1.0 mL/min, isohexane/isopropanol (90/10) τ_{minor} (*R*) = 4.27 min. τ_{major} (*S*) = 7.21 min. **$[\alpha]_D^{20}$** +10 (c 0.1, $CHCl_3$, *e.r.* 77:23).

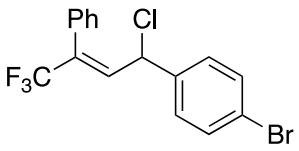
(*E*)-(1-chloro-4,4,4-trifluorobut-2-ene-1,3-diyl-1-*d*)dibenzene (20a-*d*)



The title compound was synthesized according to the above procedure using (*E*)-4,4,4-trifluoro-1,3-diphenylbut-2-en-1-d-1-ol (1 mmol, 279 mg) as substrate. The final compound was isolated as a colorless oil (188 mg, 63% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.45 (m, 3H), 7.40–7.29 (m, 7H), 6.76 (s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 138.8, 134.3 (q, *J* = 6 Hz), 131.8 (q, *J* = 31 Hz), 130.7, 129.6, 129.2, 129.1, 129.0, 127.2, 126.3, 123.0 (q, *J* = 274 Hz), 57.2 (t, *J* = 25 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 66.51 (s).

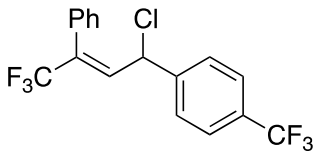
(*E*)-1-Bromo-4-(1-chloro-4,4,4-trifluoro-3-phenylbut-2-en-1-yl)benzene (20f)



The title compound was synthesized according to the above procedure using (*E*)-1-(4-bromophenyl)-4,4,4-trifluoro-3-phenylbut-2-en-1-ol (1 mmol, 357 mg) as substrate. The final compound was isolated as a colorless oil (301 mg, 80% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.49 (m, 2H), 7.48–7.45 (m, 3H), 7.30–7.26 (m, 2H), 7.20–7.18 (m, 2H), 6.70 (dq, *J* = 10.6, 1.6 Hz, 1H), 5.25 (d, *J* = 10.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 137.9, 133.8 (q, *J* = 6 Hz), 132.4, 132.3 (q, *J* = 30 Hz), 130.5, 129.7, 129.4, 129.0, 128.9, 123.2, 122.9 (q, *J* = 274 Hz), 56.7. **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 66.60 (s). **HPLC:** CHIRALCEL OD-H, flow rate 1.0 mL/min, isohexane/isopropanol (100/0) τ_{minor} (*R*) = 13.05 min. τ_{major} (*S*) = 13.50 min. **$[\alpha]_D^{20}$** +24 (c 0.1, $CHCl_3$, *e.r.* 79:21).

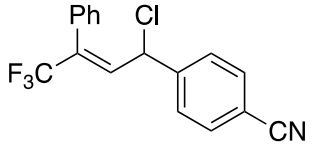
(*E*)-1-(1-chloro-4,4,4-trifluoro-3-phenylbut-2-en-1-yl)-4-(trifluoromethyl)benzene (20c)



The title compound was synthesized according to the above procedure using (*E*)-4,4,4-trifluoro-3-phenyl-1-(4-(trifluoromethyl)phenyl)but-2-en-1-ol (1 mmol, 356 mg) as substrate. The final compound was isolated as a colorless oil (296 mg, 81% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.2 Hz, 2H), 7.49–7.47 (m, 3H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.30–7.26 (m, 2H), 6.71 (dq, *J* = 10.5, 1.4 Hz, 1H), 5.33 (d, *J* = 10.5 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 142.7, 133.6 (q, *J* = 6 Hz), 132.9 (q, *J* = 31 Hz), 131.2 (q, *J* = 33 Hz), 130.4, 129.8, 129.4, 129.1, 127.6, 126.2 (q, *J* = 4 Hz), 123.8 (q, *J* = 272 Hz), 122.8 (q, *J* = 274 Hz), 56.5. **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 62.81 (s, 3F), – 66.68 (s, 3F). **HPLC:** CHIRALCEL OD-H, flow rate 0.5 mL/min, isohexane/isopropanol (100/0) τ_{minor} (*R*) = 10.17 min. τ_{major} (*S*) = 10.60 min. **$[\alpha]_D^{20}$** +22 (c 0.1, $CHCl_3$, *e.r.* 94:6).

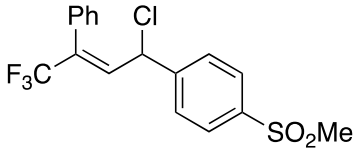
(*E*)-4-(1-chloro-4,4,4-trifluoro-3-phenylbut-2-en-1-yl)benzonitrile (20d)



The title compound was synthesized according to the above procedure using ((*E*)-4-(4,4,4-trifluoro-1-hydroxy-3-phenylbut-2-en-1-yl)benzonitrile (1 mmol, 303 mg) as substrate. The final compound was isolated as a colorless oil (229 mg, 71% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.59 (m, 2H), 7.50–7.46 (m, 3H), 7.45–7.40 (m, 2H), 7.30-7.26 (m, 2H), 6.66 (dd, *J* = 10.5, 1.6 Hz, 1H), 5.31 (d, *J* = 10.5 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 143.7, 133.4 (q, *J* = 31 Hz), 133.1 (q, *J* = 6 Hz), 133.0, 130.3, 129.9, 129.3, 129.2, 128.0, 122.8 (q, *J* = 274 Hz), 125.6, 113.0, 56.3. **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 66.72 (s). **HPLC:** CHIRALCEL AD-H, flow rate 1.0 mL/min, isohexane/isopropanol (95/5) τ_{major} (*S*) = 5.18 min. τ_{minor} (*R*) = 5.44 min. **$[\alpha]_D^{20}$** +38 (c 0.1, $CHCl_3$, *e.r.* 82:18).

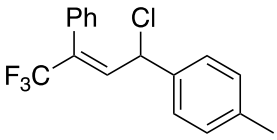
(*E*)-1-(1-chloro-4,4,4-trifluoro-3-phenylbut-2-en-1-yl)-4-(methylsulfonyl)benzene (20e)



The title compound was synthesized according to the above procedure using (*E*)-4,4,4-trifluoro-1-(4-(methylsulfonyl)phenyl)-3-phenylbut-2-en-1-ol (1 mmol, 356 mg) as substrate. The final compound was isolated as a colorless oil (296 mg, 79% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–7.87 (m, 2H), 7.61–7.43 (m, 5H), 7.34–7.27 (m, 2H), 6.69 (dd, *J* = 10.5, 1.6 Hz, 1H), 5.35 (d, *J* = 10.5 Hz, 1H), 3.06 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 144.7, 141.2, 133.5, 133.2 (q, *J* = 6 Hz), 130.3, 129.9, 129.4, 129.2, 128.4, 128.3, 122.8 (q, *J* = 271 Hz), 56.2, 44.6. **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 66.71 (s). **HPLC:** CHIRALCEL OD-H, flow rate 1.0 mL/min, isohexane/isopropanol (90/10) τ_{major} (*S*) = 13.48 min. τ_{minor} (*R*) = 14.24 min. **$[\alpha]_D^{20}$** +12 (c 0.1, $CHCl_3$, *e.r.* 87:13).

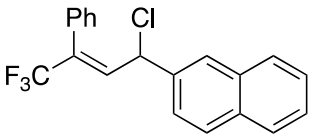
(*E*)-1-(1-chloro-4,4,4-trifluoro-3-phenylbut-2-en-1-yl)-4-methylbenzene (20g)



The title compound was synthesized according to the above procedure using (*E*)-4,4,4-trifluoro-3-phenyl-1-(p-tolyl)but-2-en-1-ol (1 mmol, 292 mg) as substrate. The final compound was isolated as a colorless oil (215 mg, 69% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.45 (m, 3H), 7.30–7.28 (m, 2H), 7.22–7.16 (m, 4H), 6.77 (dq, *J* = 10.6, 1.6 Hz, 1H), 5.25 (d, *J* = 10.6 Hz, 1H), 2.36 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 139.1, 136.0, 134.5 (q, *J* = 6 Hz), 130.7, 129.8, 129.6, 129.5, 128.9, 127.1, 126.3, 123.1 (q, *J* = 274 Hz), 57.5, 21.3. **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 66.47 (s).

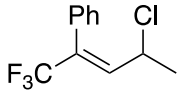
(*E*)-2-(1-chloro-4,4,4-trifluoro-3-phenylbut-2-en-1-yl)naphthalene (20b)



The title compound was synthesized according to the above procedure using (*E*)-4,4,4-trifluoro-1-(naphthalen-2-yl)-3-phenylbut-2-en-1-ol (1 mmol, 328 mg) as substrate. The final compound was isolated as a white solid (246 mg, 71% isolated yield) (m.p. = 87–88°C).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.81 (m, 3H), 7.71 (s, 1H), 7.53–7.47 (m, 6H), 7.35–7.32 (m, 2H), 6.90 (dq, *J* = 10.6, 1.3 Hz, 1H), 5.48 (d, *J* = 10.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 136.1, 134.2 (q, *J* = 6 Hz), 133.5, 133.2, 132.0 (q, *J* = 31 Hz), 130.7, 129.6, 129.3, 129.0, 128.3, 127.9, 127.1, 127.0, 126.9, 126.3, 124.6, 123.0 (q, *J* = 274 Hz), 57.8. **^{19}F NMR (376 MHz, $CDCl_3$)** δ − 66.45 (s). **HPLC:** CHIRALCEL OD-H, flow rate 1.0 mL/min, isohexane/isopropanol (100/0) τ_{minor} (*R*) = 15.23 min. τ_{major} (*S*) = 16.76 min.

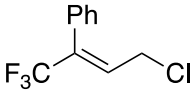
(*E*)-(4-chloro-1,1,1-trifluoropent-2-en-2-yl)benzene (20h)



The title compound was synthesized according to the above procedure using (*E*)-5,5,5-trifluoro-4-phenylpent-3-en-2-ol (1 mmol, 216 mg) as substrate. The final compound was isolated as a colorless oil (169 mg, 69% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.43 (m, 3H), 7.30–7.28 (m, 2H), 6.46 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.39 (dp, *J* = 13.1, 6.6 Hz, 1H), 1.57 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 136.4 (q, *J* = 6 Hz), 131.8 (q, *J* = 30 Hz), 130.9, 129.4, 129.3, 128.9, 123.1 (q, *J* = 274 Hz), 52.1, 25.0. **^{19}F NMR (376 MHz, $CDCl_3$)** δ − 66.56 (s).

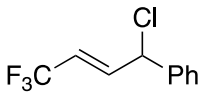
(*E*)-(4-chloro-1,1,1-trifluorobut-2-en-2-yl)benzene (20i)



The title compound was synthesized according to the above procedure using (*E*)-4,4,4-trifluoro-3-phenylbut-2-en-1-ol (1 mmol, 202 mg) as substrate. The final compound was isolated as a colorless oil (177 mg, 80% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.42 (m, 3H), 7.30–7.28 (m, 2H), 6.58-6.54 (m, 1H), 3.95 (dp, *J* = 7.8, 1.5 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 134.7 (q, *J* = 30 Hz), 130.9 (q, *J* = 6 Hz), 130.6, 129.4, 128.9, 125.7, 122.9 (q, *J* = 274 Hz), 39.3. **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 64.52 (s).

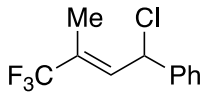
(*E*)-(1-chloro-4,4,4-trifluorobut-2-en-1-yl)benzene (20n)



The title compound was synthesized according to the above procedure using (E)-4,4,4-trifluoro-1-phenylbut-2-en-1-ol (1 mmol, 202 mg) as substrate. The final compound was isolated as a colorless oil (133 mg, 60% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.34 (m, 5H), 6.70–6.64 (m, 1H), 6.00–5.91 (m, 1H), 5.53–5.51 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 138.8 (q, *J* = 6 Hz), 138.2, 129.3, 129.2, 127.6, 122.8 (q, *J* = 270 Hz), 127.1 (q, *J* = 34 Hz), 60.0. **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 64.15 (d, *J* = 6 Hz).

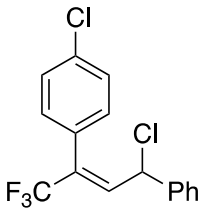
(*E*)-(1-chloro-4,4,4-trifluoro-3-methylbut-2-en-1-yl)benzene (20m)



The title compound was synthesized according to the above procedure using (*E*)-4,4,4-trifluoro-3-methyl-1-phenylbut-2-en-1-ol (1 mmol, 216 mg) as substrate. The final compound was isolated as a colorless oil (167 mg, 71% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.34 (m, 5H), 6.52 (dp, *J* = 9.9, 1.6 Hz, 1H), 5.68 (dd, *J* = 10.0, 1.2 Hz, 1H), 1.96 (d, *J* = 1.5 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 139.2, 132.4 (q, *J* = 6 Hz), 129.2, 129.1, 127.2, 127.1 (q, *J* = 30 Hz), 123.8 (q, *J* = 273 Hz), 56.6, 11.1 (q, *J* = 1 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 70.01 (s). **HPLC:** CHIRALCEL AD-H, flow rate 1.0 mL/min, isohexane/isopropanol (100/0) τ_{minor} (*R*) = 4.71 min. τ_{major} (*S*) = 4.86 min. **$[\alpha]_D^{20}$** +4 (c 0.1, $CHCl_3$, *e.r.* 68:32).

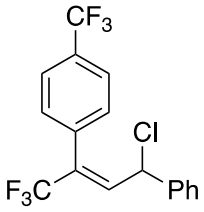
(*E*)-1-chloro-4-(4-chloro-1,1,1-trifluoro-4-phenylbut-2-en-2-yl)benzene (20k)



The title compound was synthesized according to the above procedure using (*E*)-3-(4-chlorophenyl)-4,4,4-trifluoro-1-phenylbut-2-en-1-ol (1 mmol, 313 mg) as substrate. The final compound was isolated as a colorless oil (258 mg, 78% isolated yield).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48–7.44 (m, 2H), 7.42–7.30 (m, 5H), 7.26–7.24 (m, 2H), 6.79 (dd, *J* = 10.7, 1.6 Hz, 1H), 5.25 (d, *J* = 10.7 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 138. 5, 135.9, 134.9 (q, *J* = 6 Hz), 131.0, 129.4, 129.3, 129.2, 129.0, 127.2, 122.8 (q, *J* = 274 Hz), 57.2. **^{19}F NMR (376 MHz, CDCl$_3$)** δ – 66.53 (s).

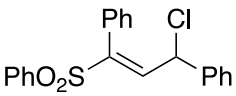
(*E*)-1-(4-Chloro-1,1,1-trifluoro-4-phenylbut-2-en-2-yl)-4-(trifluoromethyl)benzene (20l)



The title compound was synthesized according to the above procedure using (*E*)-4,4,4-trifluoro-1-phenyl-3-(4-(trifluoromethyl)phenyl)but-2-en-1-ol (1 mmol, 346 mg) as substrate. The final compound was isolated as a colorless oil (336 mg, 92% isolated yield).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.42–7.30 (m, 5H), 6.84 (dd, *J* = 10.7, 1.6 Hz, 1H), 5.20 (d, *J* = 10.7 Hz, 1H).**^{13}C NMR (100 MHz, CDCl$_3$)** δ 138. 3, 135.3 (q, *J* = 6 Hz), 134.3, 131.9 (q, *J* = 33 Hz), 130.4 (q, *J* = 31 Hz), 130.4, 130.1, 129.3, 127.2, 126.0 (q, *J* = 4 Hz), 123.9 (q, *J* = 272 Hz), 122.7 (q, *J* = 274 Hz), 57.1. **^{19}F NMR (376 MHz, CDCl$_3$)** δ – 66.34 (s, 3F), – 62.81 (s, 3F).

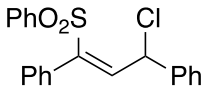
(*E*)-(3-chloro-1-(phenylsulfonyl)prop-1-ene-1,3-diyl)dibenzene ((*E*)-20o)



The title compound was synthesized according to the above procedure using (*E*)-1,3-diphenyl-3-(phenylsulfonyl)prop-2-en-1-ol (1 mmol, 350 mg) as substrate. The final compound was isolated as a colorless oil (185 mg, 50% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.52 (m, 3H), 7.46 (d, *J* = 10.7 Hz, 1H), 7.43–7.29 (m, 10H), 7.06–7.01 (m, 2H), 5.17 (d, *J* = 10.7 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 143.2, 138.3, 138.1, 138.0, 133.7, 130.4, 129.9, 129.3, 129.2, 129.2, 129.0, 128.8, 128.7, 127.3, 57.6.

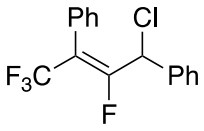
(*Z*)-(3-chloro-1-(phenylsulfonyl)prop-1-ene-1,3-diyl)dibenzene ((*Z*)-20o)



The title compound was synthesized according to the above procedure using (*Z*)-1,3-diphenyl-3-(phenylsulfonyl)prop-2-en-1-ol (1 mmol, 350 mg) as substrate. The final compound was isolated as a colorless oil (233 mg, 63% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.58 (m, 3H), 7.56–7.51 (m, 1H), 7.44–7.36 (m, 5H), 7.34–7.27 (m, 3H), 7.25–7.21 (m, 2H), 7.18–7.15 (m, 2H), 6.45 (d, *J* = 10.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 141.9, 140.7, 139.5, 139.0, 134.2, 133.8, 130.2, 129.3, 129.2, 129.04, 129.03, 128.2, 128.1, 127.6, 55.3.

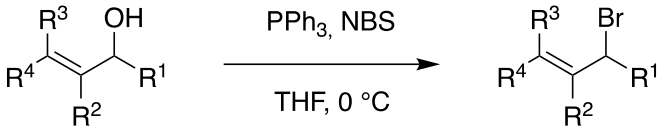
(*Z*)-(1-chloro-2,4,4,4-tetrafluorobut-2-ene-1,3-diyl)dibenzene (20j)



The title compound was synthesized according to the above procedure using (*Z*)-2,4,4,4-tetrafluoro-1,3-diphenylbut-2-en-1-ol (1 mmol, 296 mg) as substrate. The final compound was isolated as a colorless oil (214 mg, 68% isolated yield).

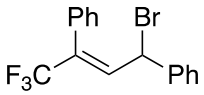
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.48 (m, 3H), 7.40–7.35 (m, 7H), 5.37 (d, *J* = 27.2 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.2 (dq, *J* = 281, 3 Hz), 134.9, 130.1 (d, *J* = 3 Hz), 129.8, 129.3, 129.1, 128.8, 127.65, 127.64, 122.1 (d, *J* = 274 Hz), 113.5 (dq, *J* = 33, 10 Hz), 56.0 (d, *J* = 24 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ −59.50 (d, *J* = 24 Hz, 3F), −109.72 (dq, *J* = 26, 24 Hz, 1F).

<u>General procedure for the synthesis of allylic bromides 21a-c</u>



PPh_3 and NBS (1.5 equiv.) were added to a solution of the corresponding allylic alcohol (1 equiv.) in dry THF (0.1 M) at 0 °C. The mixture was warmed to room temperature overnight and petroleum ether (5 mL per mmol of substrate) was added and stirred for 15 min. The resulting suspension was filtered and evaporated under reduced pressure. The final product was purified using silica chromatography doped with NEt_3 (1%) employing petroleum ether as eluent yielding the desired allylic bromides.

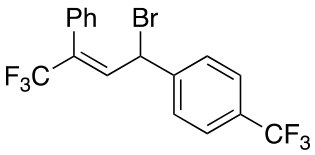
(*E*)-(1-bromo-4,4,4-trifluorobut-2-ene-1,3-diyl)dibenzene (21a)



The title compound was synthesized according to the above procedure using (*E*)-4,4,4-trifluoro-1,3-diphenylbut-2-en-1-ol (1 mmol, 278 mg) as substrate. The final compound was isolated as a yellow oil (276 mg, 81% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.46 (m, 3H), 7.37–7.28 (m, 7H), 6.98 (dq, *J* = 11.0, 1.6 Hz, 1H), 5.41 (d, *J* = 11 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 139.0, 134.3 (q, *J* = 6 Hz), 130.8 (q, *J* = 30 Hz), 129.5, 129.3, 129.2, 129.1, 129.0, 127.6, 126.9, 123.0 (q, *J* = 274 Hz), 47.7. **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 66.41 (s).

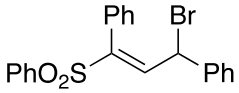
(*E*)-1-(1-bromo-4,4,4-trifluoro-3-phenylbut-2-en-1-yl)-4-(trifluoromethyl)benzene (21b)



The title compound was synthesized according to the above procedure using (*E*)-4,4,4-trifluoro-3-phenyl-1-(4-(trifluoromethyl)phenyl)but-2-en-1-ol (1 mmol, 346 mg) as substrate. The final compound was isolated as a yellow oil (226 mg, 56% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.59 (m, 2H), 7.53–7.44 (m, 5H), 7.32–7.27 (m, 2H), 6.93 (dq, *J* = 11.1, 1.6 Hz, 1H), 5.42 (d, *J* = 11.1 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 142.9, 133.5 (q, *J* = 6 Hz), 132.0 (q, *J* = 31 Hz), 131.2 (q, *J* = 33 Hz), 130.4, 129.8, 129.2, 129.1, 128.0, 126.3 (q, *J* = 4 Hz), 123.8 (q, *J* = 272 Hz), 122.9 (q, *J* = 274 Hz), 46.0. **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 66.57 (s, 3F), – 62.84 (s, 3F).

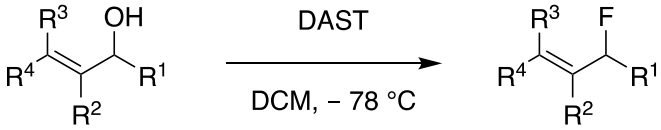
(*E*)-(3-bromo-1-(phenylsulfonyl)prop-1-ene-1,3-diyl)dibenzene (21c)



The title compound was synthesized according to the above procedure using (*E*)-1,3-diphenyl-3-(phenylsulfonyl)prop-2-en-1-ol (1 mmol, 350 mg) as substrate. The final compound was isolated as a yellow oil (155 mg, 35% isolated yield).

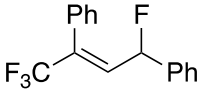
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 11.2 Hz, 1H), 7.60–7.50 (m, 3H), 7.45–7.29 (m, 10H), 7.11–7.01 (m, 2H), 5.28 (d, *J* = 11.3 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 142.2, 138.3, 138.2, 138.2, 133.7, 130.2, 129.8, 129.3, 129.3, 129.2, 129.0, 128.8, 128.7, 127.7, 47.6.

General procedure for the synthesis of allylic fluorides 22a-c.



To a solution of the corresponding allylic alcohol (1 equiv.) in dry DCM (0.1 M) at -78 °C, DAST (1 equiv.) was added carefully dropwise. The reaction was warmed to room temperature overnight and quenched with a saturated solution of $NaHCO_3$. The mixture was extracted with DCM (3 x 5 mL per mmol of substrate), dried with $MgSO_4$ and the solvent was reduced under vacuum. The final product was purified using silica chromatography employing petroleum ether as eluent.

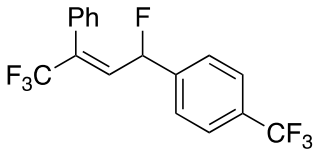
(*E*)-(1-fluoro-4,4,4-trifluorobut-2-ene-1,3-diyl)dibenzene (22a)



The title compound was synthesized according to the above procedure using (*E*)-4,4,4-trifluoro-1,3-diphenylbut-2-en-1-ol (1 mmol, 278 mg) as substrate. The final compound was isolated as a yellow oil (126 mg, 45% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.44 (m, 3H), 7.40–7.38 (m, 3H), 7.30–7.24 (m, 4H), 6.70 (tq, *J* = 9.3, 1.5 Hz, 1H), 5.75 (d, *J* = 47.2, 9.3 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 137.8 (d, *J* = 22 Hz), 135.0–134.7 (m), 132.7 (dq, J = 27, 5 Hz), 130.8, 129.7 (d, *J* = 2 Hz), 129.5, 129.3 (d, *J* = 2 Hz), 129.0, 128.8, 126.3 (d, *J* = 5 Hz), 123.0 (q, *J* = 274 Hz), 89.26 (d, *J* = 166 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ –66.84 (s, 3F), –166.0 (d, *J* = 47 Hz, 1F).

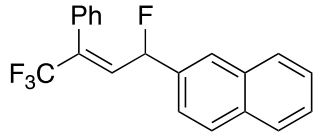
(*E*)-1-(1,4,4,4-tetrafluoro-3-phenylbut-2-en-1-yl)-4-(trifluoromethyl)benzene (22b)



The title compound was synthesized according to the above procedure using (*E*)-4,4,4-trifluoro-3-phenyl-1-(4-(trifluoromethyl)phenyl)but-2-en-1-ol (1 mmol, 346 mg) as substrate. The final compound was isolated as a yellow oil (209 mg, 60% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.50–7.49 (m, 3H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.35–7.32 (m, 2H), 6.68 (td, *J* = 9.2 Hz, 1.4 Hz, 1H), 5.86 (dd, *J* = 47.2, 9.2Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 141.7 (d, *J* = 22 Hz), 136.6–135.6 (m), 132.0 (dq, *J* = 26, 5 Hz), 131.4 (dq, *J* = 33, 2 Hz), 130.6 (d, *J* = 2 Hz), 129.8, 129.6 (d, *J* = 2 Hz), 129.0, 126.4 (d, *J* = 6 Hz), 126.0 (q, *J* = 4 Hz), 124.0 (d, *J* = 272 Hz), 122.8 (d, *J* = 274 Hz), 88.5 (d, *J* = 168 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ –62.84 (s, 3F), –67.07 (d, *J* = 4 Hz, 3F),–170.07 (ddd, *J* = 47, 9, 4 Hz, 1F).

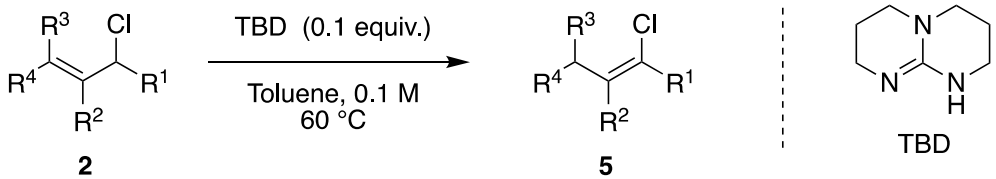
(*E*)-2-(1,4,4,4-tetrafluoro-3-phenylbut-2-en-1-yl)naphthalene (22c)



The title compound was synthesized according to the above procedure using (*E*)-4,4,4-trifluoro-1-(naphthalen-2-yl)-3-phenylbut-2-en-1-ol (1 mmol, 328 mg) as substrate. The final compound was isolated as a yellow oil (89 mg, 27% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.83 (m, 3H), 7.68 (s, 1H), 7.55–7.52 (m, 2H), 7.49–7.45 (m, 3H), 7.40–7.38 (m, 1H), 7.34–7.32 (m, 2H), 6.82 (tq, *J* = 9.3, 1.4 Hz, 1H), 5.75 (d, *J* = 47.4, 9.3 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 135.1 (q, *J* = 22 Hz), 133.7, 133.2, 132.8–132.5 (m), 130.8, 129.7, 129.7, 129.6, 129.1, 128.9, 128.3, 127.9, 127.0, 126.8, 125.8 (d, *J* = 7 Hz), 123.5 (d, *J* = 7 Hz), 122.9 (q, *J* = 274 Hz), 89.5 (d, *J* = 166 Hz).

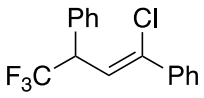
General procedure for the base-catalyzed isomerization of allylic chlorides 23a-n



2 **5**

The corresponding allylic chloride (0.18 mmol, 1 equiv.) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (2.5 mg, 0.018 mmol, 0.1 equiv.) were placed in a pressure tube and toluene was added (1.8 mL). The mixture was then stirred at 60 °C overnight. The reaction was quenched with H_2O (2 mL) and extracted with EtOAc (3 x 5 mL). The solvent was removed under reduced pressure yielding the desired vinyl chloride.

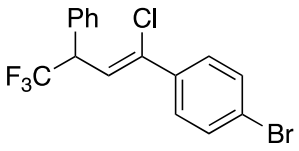
(*Z*)-(1-chloro-4,4,4-trifluorobut-1-ene-1,3-diyl)dibenzene (23a)



The title compound was synthesized according to the above procedure using (*E*)-(1-chloro-4,4,4-trifluorobut-2-ene-1,3-diyl)dibenzene as substrate. The final compound was isolated as a colorless oil with 94% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.60 (m, 2H), 7.44–7.37 (m, 8H), 6.52 (d, *J* = 9.0 Hz, 1H), 4.79–4.70 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 138.1, 137.2, 134.1, 129.6, 129.2, 129.0, 128.60, 128.55, 126.9, 126.0 (q, *J* = 280 Hz), 120.3 (q, *J* = 3 Hz), 50.5 (q, *J* = 28 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 69.02 (d, *J* = 9.0 Hz). **HRMS (APCI):** m/z calcd for [$C_{16}H_{12}F_3Cl$]: 296.0574; found: 296.0579. **HPLC:** CHIRALCEL OJ-H, flow rate 1.0 mL/min, isohexane/isopropanol (90/10) τ_{minor} (*R*) = 6.38 min. τ_{major} (*S*) = 7.11 min. **$[\alpha]_D^{20}$** –4 (c 0.1, $CHCl_3$, *e.r.* 76:24).

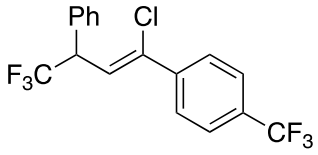
(*Z*)-1-bromo-4-(1-chloro-4,4,4-trifluoro-3-phenylbut-1-en-1-yl)benzene (23f)



The title compound was synthesized according to the above procedure using (*E*)-1-bromo-4-(1-chloro-4,4,4-trifluoro-3-phenylbut-2-en-1-yl)benzene as substrate. The final compound was isolated as a colorless oil with 82% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.50 (m, 2H), 7.47–7.45 (m, 2H), 7.40–7.36 (m, 5H), 6.49 (d, *J* = 9.0 Hz, 1H), 4.74–4.65 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 137.0, 136.2, 133.8, 131.8, 129.2, 129.1, 128.7, 128.4, 125.9 (q, *J* = 280 Hz), 123.8, 120.9 (q, *J* = 3 Hz), 50.6 (q, *J* = 28 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 69.00 (d, *J* = 9.0 Hz).**GCMS (EI):** for [$C_{16}H_{11}BrClF_3$]; found: 374.0. **HPLC:** CHIRALCEL OJ-H, flow rate 1.0 mL/min, isohexane/isopropanol (90/10) τ_{major} (*S*) = 8.82 min. τ_{minor} (*R*) = 10.37 min. **$[\alpha]_D^{20}$** –6 (c 0.1, $CHCl_3$, *e.r.* 77:23).

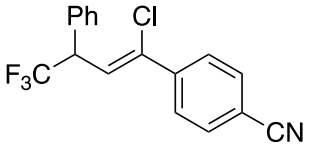
(*Z*)-1-(1-chloro-4,4,4-trifluoro-3-phenylbut-1-en-1-yl)-4-(trifluoromethyl)benzene (23c)



The title compound was synthesized according to the above procedure using (*E*)-1-(1-chloro-4,4,4-trifluoro-3-phenylbut-2-en-1-yl)-4-(trifluoromethyl)benzene as substrate. The final compound was isolated as a colorless oil with 92% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 8.3 Hz,2H), 7.41–7.37 (m, 5H), 6.58 (d, *J* = 9.0 Hz, 1H), 4.76–4.67 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 140.5, 136.7, 133.6, 131.5 (q, *J* = 33 Hz), 129.2, 129.1, 128.8, 127.3, 125.8 (q, *J* = 280 Hz), 125.6 (q, *J* = 4 Hz), 123.9 (q, *J* = 272 Hz), 122.5 (q, *J* = 3 Hz), 50.6 (q, *J* = 29 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 62.91 (s, 3F), – 69.00 (d, *J* = 9.0 Hz, 3F). **GCMS (EI):** for [$C_{17}H_{11}ClF_6$]; found: 364.1. **HPLC:** CHIRALCEL OD-H, flow rate 0.5 mL/min, isohexane/isopropanol (100/0) τ_{major} (*S*) = 16.10 min. τ_{minor} (*R*) = 17.73 min. **$[\alpha]_D^{20}$** –8 (c 0.1, $CHCl_3$, *e.r.* 92:8).

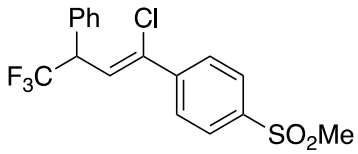
(*Z*)-4-(1-chloro-4,4,4-trifluoro-3-phenylbut-1-en-1-yl)benzonitrile (23d)



The title compound was synthesized according to the above procedure using (*E*)-4-(1-chloro-4,4,4-trifluoro-3-phenylbut-2-en-1-yl)benzonitrile as substrate. The final compound was isolated as a colorless oil with 88% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 9.0 Hz, 2H), 7.67 (d, *J* = 9.0 Hz, 2H), 7.41–7.38 (m, 5H), 6.61 (d, *J* = 9.0 Hz, 1H), 4.76–4.66 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 141.2, 136.3, 133.4, 132.4, 129.2, 129.1, 128.8, 127.5, 126.8 (q, *J* = 271 Hz), 123.4 (d, *J* = 3 Hz), 118.3, 113.2, 50.7 (q, J = 29 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 69.00 (d, *J* = 9.0 Hz). **GCMS (EI):** for [$C_{17}H_{11}ClF_3N$]; found: 321.1. **HPLC:** CHIRALCEL OD-H, flow rate 1.0 mL/min, isohexane/isopropanol (90/10) τ_{major} (*S*) = 5.81 min. τ_{minor} (*R*) = 6.34 min. **$[\alpha]_D^{20}$** –8 (c 0.1, $CHCl_3$, *e.r.* 81:19).

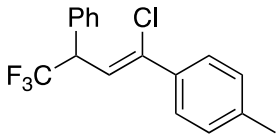
(*Z*)-1-(1-chloro-4,4,4-trifluoro-3-phenylbut-1-en-1-yl)-4-(methylsulfonyl)benzene (23e)



The title compound was synthesized according to the above procedure using (*E*)-1-(1-chloro-4,4,4-trifluoro-3-phenylbut-2-en-1-yl)-4-(methylsulfonyl)benzene as substrate. The final compound was isolated as a colorless oil with 77% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 9.0 Hz, 2H), 7.79 (d, *J* = 9.0 Hz, 2H), 7.41–7.38 (m, 5H), 6.64 (d, *J* = 9.3 Hz, 1H), 4.77–4.68 (m, 1H), 3.06 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 142.2, 141.2, 136.2, 133.4, 129.1, 128.8, 128.3, 127.8, 125.7 (q, *J* = 280 Hz), 125.4, 123.6 (q, *J* = 3 Hz), 50.7 (q, *J* = 29 Hz), 44.6. **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 68.90 (d, *J* = 9.0 Hz). **GCMS (EI):** for [$C_{17}H_{14}ClF_3O_2S$]; found: 374.1. **HPLC:** CHIRALCEL OD-H, flow rate 1.0 mL/min, isohexane/isopropanol (80/20) τ_{major} (*S*) = 13.60 min. τ_{minor} (*R*) = 19.01 min. **$[\alpha]_D^{20}$** –4 (c 0.1, $CHCl_3$, *e.r.* 76:24).

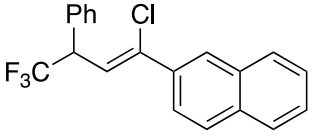
(*Z*)-1-(1-chloro-4,4,4-trifluoro-3-phenylbut-1-en-1-yl)-4-methylbenzene (23g)



The title compound was synthesized according to the above procedure using (*E*)-1-(1-chloro-4,4,4-trifluoro-3-phenylbut-2-en-1-yl)-4-methylbenzene as substrate. The final compound was isolated as a colorless oil with 80% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.3 Hz, 2H), 7.42–7.35 (m, 5H), 7.18 (d, *J* = 8.3 Hz, 2H), 6.46 (d, *J* = 9.0 Hz, 1H), 4.76–4.67 (m, 1H), 2.37 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 139.7, 138.1, 134.5, 134.2, 129.3, 129.2, 129.0, 128.5, 126.8, 126.0 (q, *J* = 280 Hz), 119.4 (q, *J* = 2 Hz), 50.5 (q, *J* = 28 Hz), 21.3. **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 69.06 (d, *J* = 9.0 Hz). **GCMS (EI):** for [$C_{17}H_{14}ClF_3$]; found: 310.1.

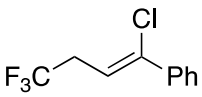
(*Z*)-2-(1-chloro-4,4,4-trifluoro-3-phenylbut-1-en-1-yl)naphthalene (23f)



The title compound was synthesized according to the above procedure using (*E*)-2-(1-chloro-4,4,4-trifluoro-3-phenylbut-2-en-1-yl)naphthalene as substrate. The final compound was isolated as a white solid with 86% isolated yield (m.p. = 108–109°C).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.89–7.82 (m, 3H), 7.70–7.68 (m, 1H), 7.54–7.50 (m, 2H), 7.46–7.37 (m, 5H), 6.64 (d, *J* = 9.0, 1H), 4.83–4.47 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 138.2, 134.4, 134.1, 133.7, 133.0, 129.2, 129.0, 128.7, 128.6, 128.3, 127.7, 127.2, 126.9, 126.8, 126.4 (q, *J* = 280 Hz), 123.9, 120.7 (q, *J* = 3 Hz), 50.7 (q, *J* = 28 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 68.96 (d, *J* = 9 Hz). **GCMS (EI):** for [$C_{20}H_{14}ClF_3$]; found: 346.1. **HPLC:** CHIRALCEL OD-H, flow rate 1.0 mL/min, isohexane/isopropanol (100/0) τ_{minor} (*R*) = 32.77 min. τ_{major} (*S*) = 42.49 min.

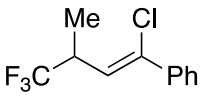
(*Z*)-(1-chloro-4,4,4-trifluorobut-1-en-1-yl)benzene (23n)



The title compound was synthesized according to the above procedure using (*E*)-(1-chloro-4,4,4-trifluorobut-2-en-1-yl)benzene as substrate. The final compound was isolated as a colorless oil with 85% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.58 (m, 2H), 7.40–7.37 (m, 3H), 6.12 (t, *J* = 6.8 Hz, 1H), 3.25 (qd, *J* = 10.7, 6.8 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 138.6, 137.2, 129.5, 128.6, 126.8, 125.9 (q, *J* = 277 Hz), 115.2 (q, *J* = 4 Hz), 34.9 (q, *J* = 30 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ –65.61 (t, *J* = 11.0 Hz). **GCMS (EI):** for [$C_{10}H_8ClF_3$]; found: 220.0.

(*Z*)-(1-chloro-4,4,4-trifluoro-3-methylbut-1-en-1-yl)benzene (23m)

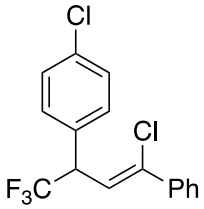


The title compound was synthesized according to the above procedure using (*E*)-(1-chloro-4,4,4-trifluoro-3-methylbut-2-en-1-yl)benzene as substrate. The final compound was isolated as a colorless oil with 92% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.57 (m, 2H), 7.40–7.36 (m, 3H), 6.05 (d, *J* = 9.0 Hz, 1H), 3.67–3.56 (m, 1H), 1.32 (d, *J* = 7 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 137.3, 132.3, 129.4, 128.6, 127.1 (d, *J* = 279 Hz), 126.8, 122.1 (q, *J* = 3 Hz), 39.7 (q, *J* = 28 Hz), 13.3 (q, *J* = 3

Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ −72.24 (d, *J* = 9.0 Hz). **HPLC:** CHIRALCEL OD-H, flow rate 1.0 mL/min, isohexane/isopropanol (100/0) τ_{major} (*S*) = 6.45 min. τ_{minor} (*R*) = 7.57 min. **$[\alpha]_D^{20}$** −3 (c 0.1, $CHCl_3$, *e.r.* 66:34).

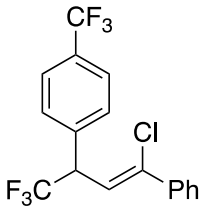
(*Z*)-1-chloro-4-(4-chloro-1,1,1-trifluoro-4-phenylbut-3-en-2-yl)benzene (23k)



The title compound was synthesized according to the above procedure using (*E*)-1-chloro-4-(4-chloro-1,1,1-trifluoro-4-phenylbut-2-en-2-yl)benzene as substrate. The final compound was isolated as a colorless oil with 80% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.61 (m, 2H), 7.43–7.36 (m, 7H), 6.54–6.49 (m, 1H), 4.81–4.69 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 138.7, 137.0, 134.6, 132.5, 130.5, 129.7, 129.2, 128.58 (q, *J* = 280 Hz), 128.60, 126.9, 119.7, 50.0 (q, *J* = 29 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ −69.11 (d, *J* = 9.0 Hz). **GCMS (EI):** for [$C_{16}H_{11}Cl_2F_3$]; found: 330.1.

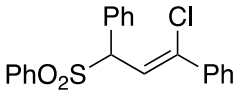
(*Z*)-1-(4-chloro-1,1,1-trifluoro-4-phenylbut-3-en-2-yl)-4-(trifluoromethyl)benzene (23l)



The title compound was synthesized according to the above procedure using (*E*)-1-(4-Chloro-1,1,1-trifluoro-4-phenylbut-2-en-2-yl)-4-(trifluoromethyl)benzene as substrate. The final compound was isolated as a colorless oil with 75% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.63–7.60 (m, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.43–7.38 (m, 3H), 6.51 (d, *J* = 9.0 Hz, 1H), 4.85–3.76 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 139.1, 138.0, 136.9, 130.9 (q, *J* = 33 Hz), 129.8, 129.7, 128.7, 126.9, 126.0 (q, *J* = 4 Hz), 119.3 (q, *J* = 3 Hz), 124.3 (q, *J* = 280 Hz), 124.0 (q, *J* = 272 Hz), 50.4 (q, *J* = 29 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ −62.78 (s, 3H), −68.94 (d, *J* = 9.0 Hz). **GCMS (EI):** for [$C_{17}H_{11}ClF_6$]; found: 364.2.

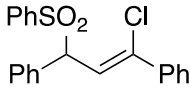
(*Z*)-(1-chloro-3-(phenylsulfonyl)prop-1-ene-1,3-diyl)dibenzene ((*Z*)-23o)



The title compound was synthesized according to the above procedure using (*E*)-(3-chloro-1-(phenylsulfonyl)prop-1-ene-1,3-diyl)dibenzene as substrate. The final compound was isolated as a colorless oil with 85% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.79 (m, 2H), 7.63–7.59 (m, 1H), 7.52–7.43 (m, 6H), 7.38–7.36 (m, 6H), 6.63 (d, *J* = 10.3 Hz, 1H), 5.44 (d, *J* = 10.3 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 139.6, 137.8, 137.0, 134.0, 131.3, 130.1, 129.8, 129.3, 129.28, 129.1, 129.0, 128.6, 126.9, 118.6, 71.6. **GCMS (EI):** for [$C_{21}H_{17}ClO_2S$]; found: 368.2.

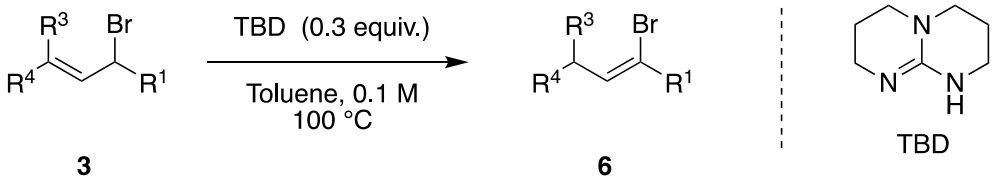
(*E*)-(1-chloro-3-(phenylsulfonyl)prop-1-ene-1,3-diyl)dibenzene ((*E*)-23o)



The title compound was synthesized according to the above procedure using (*Z*)-(3-chloro-1-(phenylsulfonyl)prop-1-ene-1,3-diyl)dibenzene as substrate. The final compound was isolated as a colorless oil with 80% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.63–7.59 (m, 1H), 7.52–7.47 (m, 4H), 7.45–7.42 (m, 2H), 7.38–7.36 (m, 6H), 6.63 (d, *J* = 10.3 Hz, 1H), 5.43 (d, *J* = 10.3 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 139.5, 137.7, 136.9, 133.9, 131.2, 130.0, 129.7, 129.2, 129.2, 128.9, 128.5, 128.1, 126.8, 118.5, 71.5.

General procedure for the base-catalyzed isomerization of allylic bromides 24a-c

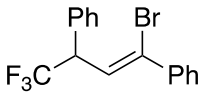


3 **6**

The corresponding allylic bromide (0.18 mmol, 1 equiv.) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (7.5 mg, 0.054 mmol, 0.3 equiv.) were placed in a pressure tube and toluene was added (1.8 mL). The mixture was then stirred at 100 °C overnight. The reaction

was quenched with H_2O (2 mL) and extracted with EtOAc (3 x 5 mL). The solvent was removed under reduced pressure yielding the desired vinyl bromide.

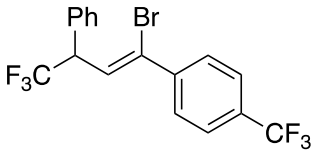
(*Z*)-(1-bromo-4,4,4-trifluorobut-1-ene-1,3-diyl)dibenzene (24a)



The title compound was synthesized according to the above procedure using (*E*)-(1-bromo-4,4,4-trifluorobut-2-ene-1,3-diyl)dibenzene as substrate. The final compound was isolated as a colorless oil with 60% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.53 (m, 2H), 7.40–7.35 (m, 8H), 6.60 (d, *J* = 9.0 Hz, 1H), 4.71–4.62 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 139.1, 133.9, 130.9, 129.5, 129.3, 129.0, 128.6, 128.5, 127.9, 125.9 (q, *J* = 280Hz), 124.2 (q, *J* = 3 Hz), 53.3 (q, *J* = 28Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 69.02 (d, *J* = 9.0 Hz). **GCMS (EI):** for [$C_{16}H_{12}BrF_3$]; found: 340.0.

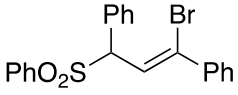
(*Z*)-1-(1-bromo-4,4,4-trifluoro-3-phenylbut-1-en-1-yl)-4-(trifluoromethyl)benzene (24b)



The title compound was synthesized according to the above procedure using (*E*)-1-(1-bromo-4,4,4-trifluoro-3-phenylbut-2-en-1-yl)-4-(trifluoromethyl)benzene as substrate. The final compound was isolated as a colorless oil with 76% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.3 Hz,2H), 7.41–7.37 (m, 5H), 6.67 (d, *J* = 9.0 Hz, 1H), 4.71–4.62 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 142.4, 133.5, 132.3 (q, J = 10 Hz), 131.4 (d, *J* = 33 Hz), 129.2, 129.1, 128.8, 128.3, 126.27 (d, *J* = 3 Hz), 125.75 (q, *J* = 280 Hz), 125.59 (q, *J* = 4 Hz), 123.90 (q, *J* = 272 Hz), 53.3 (q, *J* = 29 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ –62.79 (s, 3F), –68.87 (d, *J* = 9.0 Hz).

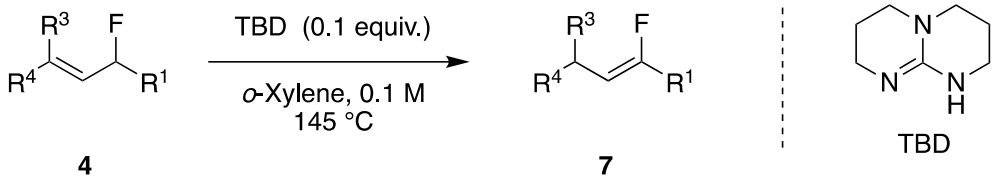
(*Z*)-(1-bromo-3-(phenylsulfonyl)prop-1-ene-1,3-diyl)dibenzene (24c)



The title compound was synthesized according to the above procedure using (*E*)-(3-bromo-1-(phenylsulfonyl)prop-1-ene-1,3-diyl)dibenzene as substrate. The final compound was isolated as a colorless oil with 50% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.81 (m, 2H), 7.47–7.42 (m, 4H), 7.38–7.31 (m, 9H), 6.71 (d, *J* = 10.2 Hz, 1H), 5.40 (d, *J* = 10.2 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 138.9, 137.9, 134.0, 132.6, 131.1, 130.1, 129.7, 129.3, 129.1, 129.02, 129.00, 128.6, 127.8, 122.6, 74.3.

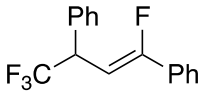
General procedure for the base-catalyzed isomerization of allylic fluorides 25a-c



4 **7**

The corresponding allylic fluoride (0.18 mmol, 1 equiv.) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (2.5 mg, 0.018 mmol, 0.1 equiv.) were placed in a pressure tube and *o*-xylene was added (1.8 mL). The mixture was then stirred at 145 °C overnight. The reaction was quenched with H_2O (2 mL) and extracted with EtOAc (3 x 5 mL). The solvent was removed under reduced pressure yielding the desired vinyl fluoride.

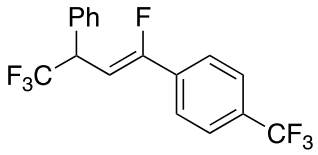
(*Z*)-(1-fluoro-4,4,4-trifluorobut-1-ene-1,3-diyl)dibenzene (25a)



The title compound was synthesized according to the above procedure using (*E*)-(1-fluoro-4,4,4-trifluorobut-2-ene-1,3-diyl)dibenzene as substrate. The final compound was isolated as a colorless oil with 60% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.54 (m, 2H), 7.43–7.35 (m, 8H), 5.79 (dd, *J* = 34.0, 10.0 Hz, 1H), 4.71–4.62 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.6 (d, *J* = 254 Hz), 134.7, 131.3 (d, *J* = 28 Hz), 129.9, 129.0, 128.9, 128.80 (q, *J* = 280 Hz), 128.72 (d, *J* = 2 Hz), 128.5, 124.7 (d, *J* = 7 Hz), 99.5 (dd, *J* = 16, 3 Hz), 45.8 (dq, *J* = 29, 6 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ –69.56 (dd, *J* = 9.2, 2.5 Hz, 3F), –113.88 (dd, J = 34.60, 2.5 Hz, 1F). **GCMS (EI):** for [$C_{16}H_{12}F_4$]; found: 280.1.

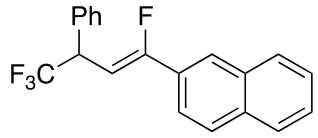
(*Z*)-1-(1-fluoro-4,4,4-trifluoro-3-phenylbut-1-en-1-yl)-4-(trifluoromethyl)benzene (25b)



The title compound was synthesized according to the above procedure using (*E*)-1-(1-chloro-4,4,4-trifluoro-3-phenylbut-2-en-1-yl)-4-(trifluoromethyl)benzene as substrate. The final compound was isolated as a colorless oil with 55% isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.59 (m, 4H), 7.44–7.26 (m, 5H), 5.92 (dd, *J* = 33.2, 10.0 Hz, 1H), 4.74–4.65 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.3 (d, *J* = 254 Hz), 134.6 (d, *J* = 30 Hz), 134.3, 131.7 (q, *J* = 33 Hz), 129.1, 128.9, 128.7, 128.5 (q, *J* = 258 Hz), 125.8–125.7 (m), 125.0 (d, *J* = 7 Hz), 123.9 (q, *J* = 272 Hz), 101.9 (dd, *J* = 16, 3 Hz), 45.9 (dq, *J* = 29, 6 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ – 62.9 (s, 3F), –69.48 (dd, *J* = 9.0, 2.5 Hz, 3F), –114.2 (d, *J* = 35.4, 1F). **GCMS (EI):** for [$C_{17}H_{11}F_7$]; found: 348.1.

(*Z*)-2-(1-fluoro-4,4,4-trifluoro-3-phenylbut-1-en-1-yl)naphthalene (25c)



The title compound was synthesized according to the above procedure using (*E*)-2-(1-fluoro-4,4,4-trifluoro-3-phenylbut-2-en-1-yl)naphthalene as substrate. The final compound was isolated as a white solid with 67% isolated yield.

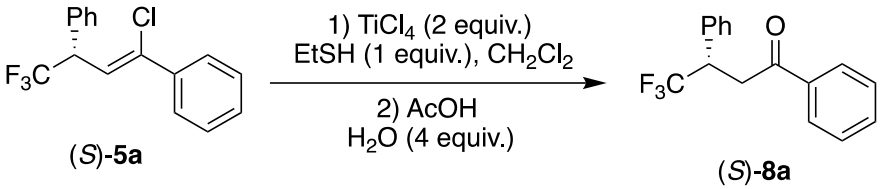
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.88–7.83 (m, 3H), 7.62 (d, *J* = 9 Hz, 1H), 7.54–7.50 (m, 2H), 7.46 (d, *J* = 8.0, 2H), 7.45–7.36 (m, 3H), 5.92 (dd, *J* = 34.0, 10.0 Hz, 1H), 4.78–4.68 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.6 (d, *J* = 254 Hz), 134.8, 133.8, 133.0, 129.02, 128.96, 128.7, 128.61–128.58 (m), 128.5, 128.30 (q, *J* = 250 Hz), 128.33, 127.8, 127.2, 126.9, 124.4 (d, *J* = 7.0 Hz), 121.9 (d, *J* = 7 Hz), 100.1 (dq, *J* = 16, 3 Hz), 45.9 (dq, *J* = 28, 6 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)** δ –69.47 (dd, *J* = 9.0, 2.4 Hz, 3F), –114.00 (dd, *J* = 34.0, 2.4 Hz, 1F). **GCMS (EI):** for [$C_{20}H_{14}F_4$]; found: 330.1.

Determination of the absolute configuration of 23a

The absolute configuration of **23a** was determined by performing its transformation to the corresponding β-trifluoromethylated ketone. The hydrolysis was accomplished using a modified literature procedure. Vinyl chloride **23a** (1 equiv.) was added to a mixture of EtSH (1 equiv.) and

$TiCl_4$ (2 equiv.) in DCM (0.3 M of **23a**) at rt and the reaction was stirred overnight. After that, AcOH (0.3 M of **23a)** and H_2O (4 equiv) were added and the mixture stirred for 3h. The reaction was then quenched with a saturated solution of $NaHCO_3$, extracted with DCM (3 x 5 mL), dried with $MgSO_4$ and the solvent was reduced under vacuum. The final ketone was purified using silica chromatography employing petroleum ether and ethyl acetate as eluents.

The pure final ketone was analysed and the data was compared to that reported in the literature. **HPLC**: CHIRALCEL OD-H, flow rate 1.0 mL/min, isohexane/isopropanol (95/05) τ_{major} (*S*) = 5.0 min. τ_{minor} (*R*) = 6.4 min. and $[\alpha]_D^{20}$ –12 (c 0.66, $CHCl_3$). It was concluded that the ketone had a (*S*) configuration so the starting material 5a had to have the same (S) configuration. The rest of the vinyl chlorides were assigned by analogy.



Scheme S1. Conversion of (*S*)-**5a** to saturated ketone (*S*)-**18a**

Mechanistic Investigations: Kinetic Isotope Effect

The Kinetic isotope effect of the TBD-catalyzed isomerization of allylic halides was calculated by performing parallel reactions with non-deuterated allylic chloride **2a** and deuterated compound **2a**-*d*. Individual reactions were run according to the general procedure and stopped at certain times. The resulted KIE was 5.4 ± 0.6 (figure S1 and S2).

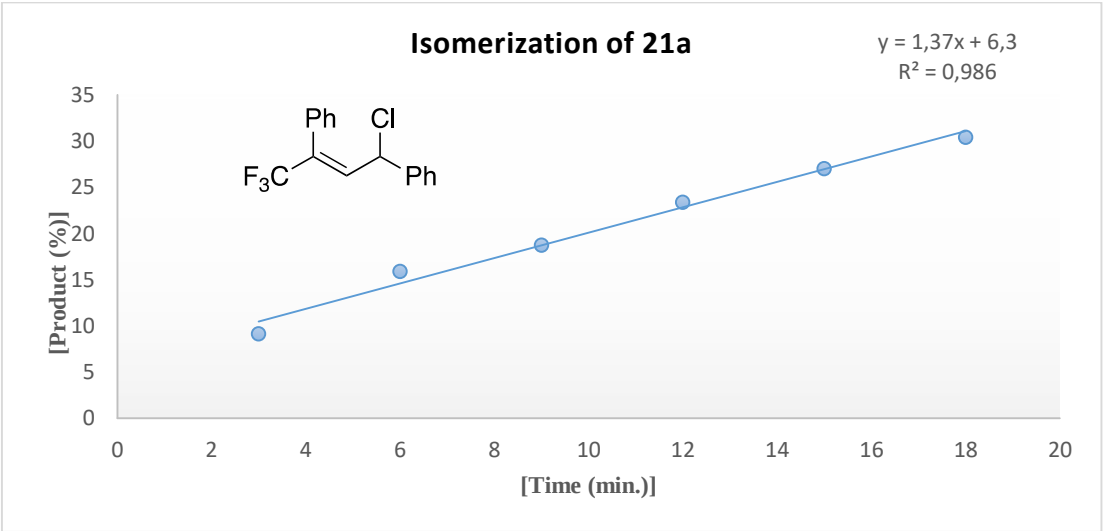


Figure S1. Kinetic profile of the isomerization of allylic halide **12a**.

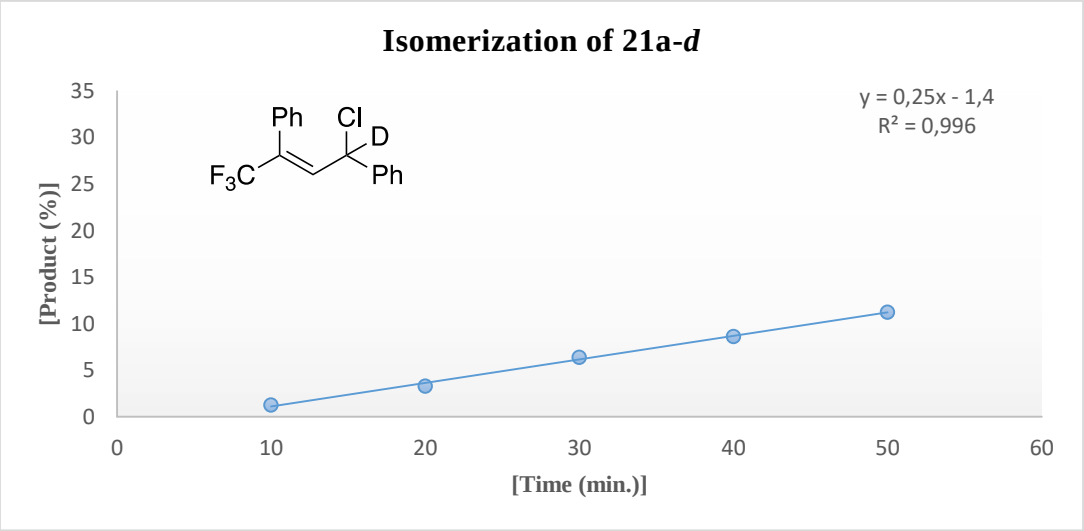


Figure S2. Kinetic profile of the isomerization of allylic halide **12a-*d***.

[1] a) Hanessian, S.; Ponpipom, M. M.; Lavalle, P. Procedures for the direct replacement of primary hydroxyl groups in carbohydrates by halogen. *Carbohydr. Res.* **1972**, *24*, 45–56; b) Jaseer, E. A.; Naidu, A. B.; Kumar, S. S.; Rao, R. K.; Thakur, K, G.; Sekar, G. Highly stereoselective chlorination of β-substituted cyclic alcohols using PPh_3-NCS: factors that control the stereoselectivty. *Chem. Commun.* **2007**, *8*, 867–869.

[1] Pacheco, M. C.; Purser, S.; Gouverneur, V. The Chemistry of Propargylic and Allylic Fluorides. *Chem. Rev.* **2008**, *108*, 1943–1981.

[1] Mukaiyama, T.; Imamoto, T.; Kobayashi, S. A convenient method for the hydrolysis of vinyl chlorides to ketones. *Chemistry letters*, **1973**, *2*, 261–264.

[1] a) V Bizet, V., Pannecoucke, X., Renaud, J.-L., Cahard, D. Ruthenium-Catalyzed Redox Isomerization of Trifluoromethylated Allylic Alcohols: Mechanistic Evidence for an Enantiospeficic Pathway. *Angew. Chem., Int. Ed.*, **51**, 6467−6470 (2012); b) Martinez-Erro, S., Sanz-Marco, A., Bermejo Gómez, A., Vázquez-Romero, A., Ahlquist, M. S. G., Martín-Matute, B. Base-Catalyzed Stereospecific Isomerization of Electron-Deficient Allylic Alcohols and Ethers through Ion-Pairing. *J. Am. Chem. Soc.* **138**, 13408–13414 (2016).

Chapter 5 (Paper IV)

General procedures

A Synthesis of allylic amines 35

The corresponding enone (5 mmol, 1 equiv.) was placed on a sealed MW vial with (*R*)-(+)-2-methyl-2-propanesulfinamide (7.5 mmol, 1.5 equiv.) and titanium(IV) ethoxide (10 mmol, 2 equiv.) and the reaction was stirred at 100 °C for 2 h under neat conditions in the MW reactor. After completion of the reaction, the resulting imine was purified with FCC (pentane:EtOAc 9:1) to afford the pure imine. The imine was dissolved in THF (1M) and the mixture was cooled to 0 °C, then DIBAL-H (5.5 mmol, 1.1 equiv.) was added dropwise. After the reaction was completed, a mixture THF:HCl 3M (50 mL, 1:1 *v/v*, 0.1M) was added and the reaction was stirred overnight at room temperature. The mixture was then basified adding NaOH (2M) slowly until reach pH = 14. The aqueous layer was extracted with EtOAc (3x100 mL), the organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the amine was purified by FCC (pentane:EtOAc 8:2 to 6:4) to afford the pure allylic amines.

(*rac*)-**4** were obtained using the same protocol with (*rac*)-2-methyl-2-propanesulfinamide.

B Amine protection

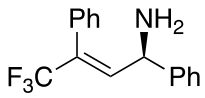
To a solution of the corresponding amine (0.3 mmol, 1 equiv.) in $CHCl_3$ (3 mL, 0.1 M) at 0 °C a solution of di-*tert*-butyl dicarbonate (0.36 mmol, 1.2 equiv.) in $CHCl_3$ (3mL, 0.1 M) was added and the reaction was stirred overnight. Then, the protected amine was purified by FCC (pentane:EtOAc 97:3 to 9:1) to obtain the desired compounds.

C Isomerization and reduction of the allylic amines 38

The allylic amine (0.25 mmol, 1 equiv.) and TBD (0.012 or 0.025 mmol, 5 or 10 mol %) were charged on a pressure vial and purged with Ar. Dry Toluene (12.5 mL, 0.02 M) was added and the reaction mixture was stirred for 18 h at 60 or 120 °C on an oil bath. Then, the reaction mixture was allowed to reach room temperature and cooled to -90 °C. DIBAL-H (0.5 mmol, 2 equiv.) was added and stirred at that temperature for an additional 4 h. The reaction was allowed to reach room temperature and a solution of Rochelle's salt was added and stirred for additional 30 min, the aqueous layer was extracted with EtOAc (3x15 mL), the organic layers were dried over $MgSO_4$, the solvent was removed under reduced pressure. The crude was then purified by FCC (pentane:EtOAc 7:3 to 0:1) to afford the pure amine.

Characterization of allylic amines 35 and 35'

(*R*,*E*)-4,4,4-Trifluoro-1,3-diphenylbut-2-en-1-amine (35a)



The title compound was obtained following GPA from (*R*,*E*)-4,4,4-trifluoro-1,3-diphenylbut-2-en-1-one (4.0 g, 14.5 mmol). The allylic amine was purified by FCC (pentane:EtOAc 7:3) as a yellow oil in 42% yield over 3 steps (1.69 g, 6.1 mmol).

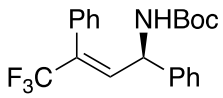
^{1}H NMR (400 MHz. $CDCl_3$) δ 7.44 – 7.41 (m, 3H), 7.37 – 7.33 (m, 2H), 7.30 – 7.27 (m, 5H), 6.55 (dq, J = 9.5, 1.5 Hz, 1H), 4.48 (d, J = 9.5 Hz, 1H), 1.55 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 139.0 (Cq, J_{CF} = 5.0 Hz), 131.7, 130.5 (Cq, J_{CF} = 30.0 Hz), 129.6, 128.82, 128.80, 128.5, 127.6, 126.4, 123.3 (Cq, J_{CF} = 273.5 Hz), 53.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.24 (s, CF_3).

HRMS (ESI) *m/z*: Fragmentation observed: 261.0906 $[M - NH_2]^+$ corresponding to $C_{16}H_{12}F_3^+$, $C_{16}H_{12}F_3^+$ requires 261.0886.

tert-Butyl (*R*,*E*)-(4,4,4-trifluoro-1,3-diphenylbut-2-en-1-yl)carbamate (35a')



The title compound was obtained following GPB from (*R*,*E*)-4,4,4-trifluoro-1,3-diphenylbut-2-en-1-amine (100.0 mg, 0.36 mmol). The protected allylic amine was purified by FCC (pentane:EtOAc 95:5) as a white solid in 73% (100.0 mg, 0.26 mmol).

The enantiomeric excess (minor isomer: nd, major isomer 95%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, (**1*R*,*E***) (major diastereomer): minor enantiomer t_r = 10.2 min, major enantiomer, t_r = 7.6 min.

$[\alpha]_D^{25}$: – 55.2 (c 1.00, $CHCl_3$, for the diastereomer mixture, d.r.: 97:3).

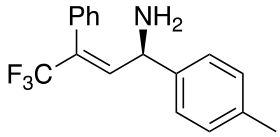
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.39 (m, 3H), 7.33 – 7.27 (m, 5H), 7.17 – 7.15 (m, 2H), 6.54 (dd, *J* = 9.5, 2.0 Hz, 1H), 5.21 (bs, 1H), 4.96 (d, *J* = 7.5 Hz, 1H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 140.2, 135.3 (Cq, J_{CF} = 5.0 Hz), 132.3, 131.1, 129.5, 128.92, 128.89, 128.5, 127.9, 126.6, 123.2 (Cq, J_{CF} = 273.4 Hz), 80.0, 52.6, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.28 (s, CF_3).

HRMS (ESI) *m/z*: 400.1474 $[M+Na]^+$, $C_{21}H_{22}F_3NNaO_2^+$ requires 400.1495.

(*R*,*E*)-4,4,4-Trifluoro-3-phenyl-1-(*p*-tolyl)but-2-en-1-amine (35b)



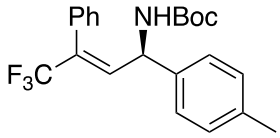
The title compound was obtained following GPA from (*R*,*E*)-4,4,4-trifluoro-3-phenyl-1-(*p*-tolyl)but-2-en-1-one (1.3 g, 4.5 mmol). The allylic amine was purified by FCC (pentane:EtOAc 7:3) as a yellow oil in 40% yield over 3 steps (0.52 g, 1.8 mmol).

^{1}H NMR (400 MHz. $CDCl_3$) δ 7.43 – 7.40 (m, 3H), 7.34 – 7.32 (m, 1H), 7.28-7.25 (m, 2H); 7.16 (s, 3H), 6.53 (dq, *J* = 10.0, 1.5 Hz, 1H), 4,44 (d, *J* = 10.0 Hz, 1H), 2.35 (s, 3H), 1.51 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 139.1 (Cq, J_{CF} = 5.0 Hz), 137.4, 131.7, 129.6, 129.5, 128.8, 128.5, 128.2, 126.6, 123.3 (Cq, J_{CF} = 273.0 Hz), 52.8, 21.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.21 (s, CF_3).

***tert*-Butyl (*R*,*E*)-(4,4,4-trifluoro-3-phenyl-1-(*p*-tolyl)but-2-en-1-yl)carbamate (35b')**



The title compound was obtained following GPB from (*R*,*E*)-4,4,4-trifluoro-3-phenyl-1-(*p*-tolyl)but-2-en-1-amine (58.3 mg, 0.20 mmol). The protected allylic amine was purified by FCC (pentane:EtOAc 95:5) as a white solid in 74% (57.9 mg, 0.15 mmol).

The enantiomeric excess (minor isomer: 96%, major isomer 90%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, (**1*R*,*Z***) (minor diastereomer): minor enantiomer, t_r = 13.0 min, major enantiomer, t_r = 9.6 min, (**1*R*,*E***) (major diastereomer): minor enantiomer t_r = 6.0 min, major enantiomer, t_r = 5.5 min.

$[\alpha]_D^{25}$: – 49.9 (c 0.85, $CHCl_3$, for the diastereomer mixture, d.r.: 84:16).

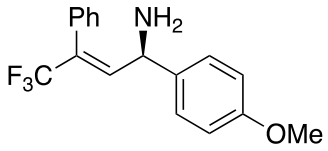
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 3H), 7.28 – 7.25 (m, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.53 (dd, *J* = 9.5, 1.5 Hz, 1H), 5.16 (bs, 1H), 4.91 (d, *J* = 7.5 Hz, 1H), 2.34 (s, 3H), 1.42 (bs, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 137.7, 137.2, 135.5 (Cq, J_{CF} = 5.0 Hz), 131.2, 129.63, 129.57, 128.9, 128.5, 128.3, 126.5, 123.2 (Cq, J_{CF} = 273.5 Hz), 79.9, 52.4, 28.3, 21.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.22 (s, CF_3).

HRMS (ESI) *m/z*: 414.1619 $[M+Na]^+$, $C_{22}H_{24}F_3NNaO_2^+$ requires 414.1651.

(*R*,*E*)-4,4,4-Trifluoro-1-(4-methoxyphenyl)-3-phenylbut-2-en-1-amine (35c)



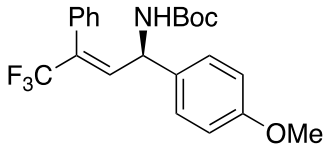
The title compound was obtained following GPA from (*R*,*E*)-4,4,4-trifluoro-1-(4-methoxyphenyl)-3-phenylbut-2-en-1-one (1.3 g, 4.2 mmol). The allylic amine was purified by FCC (pentane:EtOAc 7:3) as a yellow oil in 31% yield over 3 steps (0.4 g, 1.3 mmol).

^{1}H NMR (400 MHz. $CDCl_3$) δ 7.43 – 7.41 (m, 3H), 7.27 – 7.24 (m, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.52 (dq, J = 9.6, 1.6 Hz, 1H), 4.42 (d, *J* = 9.6 Hz, 1H), 3.80 (s, 3H), 1.50 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 139.3 (Cq, J_{CF} = 5.0 Hz), 135.0, 131.8, 130.1 (J_{CF} = 30.0 Hz) 129.7, 128.8, 128.5, 127.5, 123.3 (Cq, J_{CF} = 273.5 Hz), 114.2, 55.3, 52.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.20 (s, CF_3).

***tert*-Butyl (*R*,*E*)-(4,4,4-trifluoro-1-(4-methoxyphenyl)-3-phenylbut-2-en-1-yl)carbamate (35c')**



The title compound was obtained following GPB from (*R*,*E*)-4,4,4-trifluoro-1-(4-methoxyphenyl)-3-phenylbut-2-en-1-amine (61.5 mg, 0.20 mmol). The protected allylic amine was purified by FCC (pentane:EtOAc 95:5) as a white solid in 66% (53.8 mg, 0.13 mmol).

The enantiomeric excess (minor isomer: nd, major isomer 94%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, (**1*R*,*E***) (major diastereomer): minor enantiomer t_r = 8.4 min, major enantiomer, t_r = 7.8 min.

$[\alpha]_D^{25}$: – 74.6 (c 1.01, $CHCl_3$, for the diastereomer mixture, d.r.: 94:6).

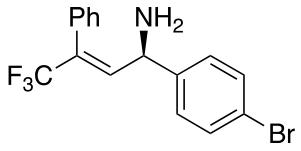
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.35 (m, 3H), 7.27 – 7.25 (m, 2H), 7.06 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 6.52 (dq, *J* = 9.5, 1.5 Hz, 1H), 5.13 (bs, 1H), 4.88 (d, *J* = 7.5 Hz, 1H), 3.79 (s, 3H), 1.41 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 154.5, 135.6 (Cq, J_{CF} = 5.5 Hz), 132.3 131.2, 129.5, 128.9, 128.4, 127.8, 127.3, 123.2 (Cq, J_{CF} = 273.5 Hz), 114.3, 79.9, 55.2, 52.1, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.20 (s, CF_3).

HRMS (ESI) *m/z*: 430.1606 $[M+Na]^+$, $C_{22}H_{24}F_3NNaO_3^+$ requires 430.1600.

(*R*,*E*)-1-(4-Bromophenyl)-4,4,4-trifluoro-3-phenylbut-2-en-1-amine (35d)



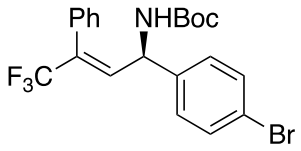
The title compound was obtained following GPA from (*R*,*E*)-1-(4-bromophenyl)-4,4,4-trifluoro-3-phenylbut-2-en-1-one (5.0 g, 14.1 mmol). The allylic amine was purified by FCC (pentane:EtOAc 7:3) as a yellow oil in 55% yield over 3 steps (2.7 g, 7.7 mmol).

^{1}H NMR (400 MHz. $CDCl_3$) δ 7.47 – 7.42 (m, 5H), 7.26 – 7.23 (m, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.47 (dd, *J* = 9.7, 1.7 Hz, 1H), 4.44 (d, *J* = 9.7 Hz, 1H), 1.51 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 138.5 (Cq, J_{CF} = 5.5 Hz), 131.9, 131.5, 129.5, 128.9, 128.6, 128.2, 127.2, 123.1 (Cq, J_{CF} = 273.5 Hz), 119.0, 52.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.37 (s, CF_3).

***tert*-Butyl (*R*,*E*)-(1-(4-bromophenyl)-4,4,4-trifluoro-3-phenylbut-2-en-1-yl)carbamate (35d')**



The title compound was obtained following GPB from (*R*,*E*)-1-(4-bromophenyl)-4,4,4-trifluoro-3-phenylbut-2-en-1-amine (71.2 mg, 0.20 mmol). The protected allylic amine was purified by FCC (pentane:EtOAc 95:5) as a white solid in 90% (82.3 mg, 0.18 mmol) [m.p.: 110 – 112 °C].

The enantiomeric excess (minor isomer: 92, major isomer 97%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, (**1*R*,*Z***) (minor diastereomer): minor enantiomer, t_r = 16.8 min, major enantiomer, t_r = 12.7 min, (**1*R*,*E***) (major diastereomer): minor enantiomer t_r = 7.6 min, major enantiomer, t_r = 6.8 min.

$[\alpha]_D^{25}$: – 96.8 (c 1.00, $CHCl_3$, for the diastereomer mixture, d.r.: 90:10).

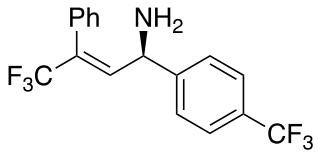
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.41 – 7.40 (m, 3H), 7.26 – 7.24 (m, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.47 (d, *J* = 9.0 Hz, 1H), 5.15 (bs, 1H), 4.97 (bs, 1H), 1.40 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 139.3, 134.5 (Cq, J_{CF} = 5.5 Hz), 132.1, 132.0, 130.9, 129.4, 129.1, 128.6, 128.2, 123.0 (Cq, J_{CF} = 273.6 Hz), 121.8, 80.2, 52.2, 28.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.38 (s, CF_3).

HRMS (ESI) *m/z*: 480.0637 $[M+Na]^+$, $C_{21}H_{21}BrF_3NNaO_2^+$ requires 480.0580.

(*R*,*E*)-4,4,4-Trifluoro-3-phenyl-1-(4-(trifluoromethyl)phenyl)but-2-en-1-amine (35e)



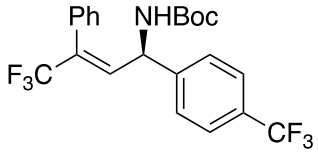
The title compound was obtained following GPA from (*E*)-4,4,4-trifluoro-3-phenyl-1-(4-(trifluoromethyl)phenyl)but-2-en-1-one (3.7 g, 10.8 mmol). The allylic amine was purified by FCC (pentane:EtOAc 7:3) as a yellow oil in 54% yield over 3 steps (2.0 g, 5.8 mmol).

^{1}H NMR (400 MHz. $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.46 – 7.44 (m, 3H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.27 (m, 2H), 6.50 (dd, *J* = 9.5, 1.5 Hz, 1H), 4.55 (d, *J* = 9.5 Hz, 1H), 1.56 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 138.2, (Cq, J_{CF} = 5.0 Hz), 131.5 (J_{CF} = 30.0 Hz), 131.4, 129.9 (J_{CF} = 32.4 Hz), 129.5, 129.0, 128.7, 126.9, 125.7 (Cq, J_{CF} = 4.0 Hz), 124.0 (Cq, J_{CF} = 272.0 Hz), 123.1 (Cq, J_{CF} = 273.5 Hz), 52.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.55 (s, CF_3), – 66.46 (s, CF_3).

***tert*-Butyl (*R*,*E*)-(4,4,4-trifluoro-3-phenyl-1-(4-(trifluoromethyl)phenyl)but-2-en-1-yl)carbamate (35e')**



The title compound was obtained following GPB from (*R*,*E*)-4,4,4-trifluoro-3-phenyl-1-(4-(trifluoromethyl)phenyl)but-2-en-1-amine (86.3 mg, 0.25 mmol). The protected allylic amine was purified by FCC (pentane:EtOAc 95:5) as a white solid in 88% (98.1 mg, 0.22 mmol).

The enantiomeric excess (minor isomer: nd, major isomer 95%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, (**1*R*,*E***) (major diastereomer): minor enantiomer t_r = 7.7 min, major enantiomer, t_r = 13.9 min.

$[\alpha]_D^{25}$: – 63.1 (c 0.99, $CHCl_3$, for the diastereomer mixture, d.r.: 91:9).

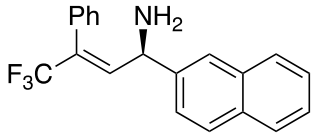
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.44 – 7.72 (m, 3H), 7.30 – 7.26 (m, 4H), 6.51 (dd, *J* = 9.5, 1.5 Hz, 1H), 5.28 (bs, 1H), 5.04 (bs, 1H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 144.3, 134.1 (Cq, J_{CF} = 5.5 Hz), 130.8, 130.1 (Cq, J_{CF} = 32.5 Hz), 129.4, 129.2, 128.7, 128.3 (Cq, J_{CF} = 32.2 Hz), 126.9, 125.9 (Cq, J_{CF} = 4.0 Hz), 123.9 (Cq, J_{CF} = 272.0 Hz), 123.0 (Cq, J_{CF} = 273.5 Hz), 80.4, 52.3, 28.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 62.64 (s, CF_3), – 66.50 (s, CF_3).

HRMS (ESI) *m/z*: 468.1336 $[M+Na]^+$, $C_{22}H_{21}F_6NNaO_2^+$ requires 468.1369.

(*R*,*E*)-4,4,4-Trifluoro-1-(naphthalen-2-yl)-3-phenylbut-2-en-1-amine (35f)



The title compound was obtained following GPA from (*E*)-4,4,4-trifluoro-1-(naphthalen-2-yl)-3-phenylbut-2-en-1-one (2.3 g, 7.1 mmol). The allylic amine was purified by FCC (pentane:EtOAc 7:3) as a yellow oil in 35% yield over 3 steps (0.8 g, 2.4 mmol).

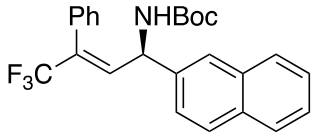
^{1}H NMR (400 MHz. $CDCl_3$) δ 7.85 – 7.82 (m, 3H), 7.72 (s, 1H), 7.53 – 7.49 (m, 2H), 7.47 – 7.45 (m, 3H), 7.43 – 7.38 (m, 1H), 7.33 – 7.32 (m, 2H), 6.65 (dd, *J* = 9.7, 1.7 Hz, 1H), 4.66 (d, *J* = 9.7 Hz, 1H), 1.69 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 138.9 (Cq, *J* = 5.2 Hz), 133.4, 132.9, 131.7, 130.8 (*J* = 30.0 Hz), 129.7, 128.9, 128.6, 127.9, 127.6, 127.3, 126.3, 126.0, 124.9, 124.7, 123.2 (*J* = 273.5 Hz), 53.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.16 (s, CF3).

HRMS (ESI) *m/z*: Fragmentation observed: 311.0988 $[M - NH_2]^+$ corresponding to $C_{20}H_{14}F_3^+$, $C_{20}H_{14}F_3^+$ requires 311.1042.

***tert*-Butyl (*R*,*E*)-(4,4,4-trifluoro-1-(naphthalen-2-yl)-3-phenylbut-2-en-1-yl)carbamate (35f')**



The title compound was obtained following GPB from (*R*,*E*)-4,4,4-trifluoro-1-(naphthalen-2-yl)-3-phenylbut-2-en-1-amine (60.0 mg, 0.18 mmol). The protected allylic amine was purified by FCC (pentane:EtOAc 95:5) as a white solid in 83% (65.2 mg, 0.15 mmol).

The enantiomeric excess (minor isomer: nd, major isomer 97%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, (**1*R*,*E***) (major diastereomer): minor enantiomer t_r = 13.7 min, major enantiomer, t_r = 9.6 min.

$[\alpha]_D^{25}$: – 176.8 (c 1.00, $CHCl_3$, for the diastereomer mixture, d.r.: 97:3).

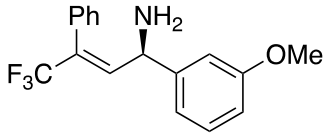
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.79 (m, 3H), 7.58 (s, 1H), 7.51 – 7.49 (m, 2H), 7.41 – 7.38 (m, 3H), 7.30 – 7.26 (m, 3H), 6.64 (d, *J* = 9.2 Hz, 1H), 5.38 (bs, 1H), 5.04 (d, *J* = 7.6 Hz, 1H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 137.6, 135.2 (Cq, *J* = 5.7 Hz), 133.3, 132.9, 131.1, 129.6, 129.0, 128.9, 128.6, 127.9, 127.6, 126.4, 126.3, 125.4, 124.5, 123.2 (Cq, *J* = 273.5 Hz), 80.0, 52.8, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.20 (s, CF_3).

HRMS (ESI) *m/z*: 450.1653 $[M+Na]^+$, $C_{25}H_{24}F_3NNaO_2^+$ requires 450.1651.

(*R*,*E*)-4,4,4-Trifluoro-1-(3-methoxyphenyl)-3-phenylbut-2-en-1-amine (35g)



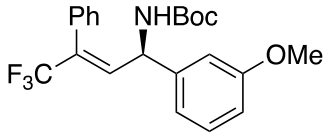
The title compound was obtained following GPA from (*E*)-4,4,4-trifluoro-1-(3-methoxyphenyl)-3-phenylbut-2-en-1-one (2.2 g, 7.2 mmol). The allylic amine was purified by FCC (pentane:EtOAc 7:3) as a yellow oil in 54% yield over 3 steps (1.2 g, 3.9 mmol).

^{1}H NMR (400 MHz. $CDCl_3$) δ 7.45 – 7.44 (m, 3H), 7.32 – 7.26 (m, 3H), 6.88 – 6.83 (m, 3H), 6.55 (dq, *J* = 9.9, 1.6 Hz, 1H), 4.47 (d, *J* = 9.9 Hz, 1H), 3.82 (s, 3H), 1.54 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 144.4, 138.9 (Cq, J_{CF} = 5.2 Hz), 131.6, 130.5 (Cq, J_{CF} = 30.0 Hz), 129.8, 129.6, 128.8, 128.5, 123.2 (Cq, J_{CF} = 273.3 Hz), 118.6, 112.9, 112.1, 55.2, 53.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.20 (s, CF_3).

***tert*-Butyl (*R*,*E*)-(4,4,4-trifluoro-1-(3-methoxyphenyl)-3-phenylbut-2-en-1-yl)carbamate (35g')**



The title compound was obtained following GPB from (*R*,*E*)-4,4,4-trifluoro-1-(3-methoxyphenyl)-3-phenylbut-2-en-1-amine (76.8 mg, 0.25 mmol). The protected allylic amine was purified by FCC (pentane:EtOAc 95:5) as a white solid in 91% (92.5 mg, 0.23 mmol).

The enantiomeric excess (minor isomer: nd, major isomer 94%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, (**1*R*,*E***) (major diastereomer): minor enantiomer t_r = 8.0 min, major enantiomer, t_r = 6.6 min.

$[\alpha]_D^{25}$: – 36.4 (c 0.77, $CHCl_3$, for the diastereomer mixture, d.r.: 97:3).

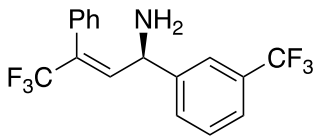
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 3H), 7.28 – 7.22 (m, 3H), 6.81 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.74 (d, *J* = 7.7 Hz, 1H), 6.67 (s, 1H), 6.50 (dd, *J* = 9.3, 1.9, 1H), 5.16 (bs, 1H), 4.93 (d, *J* = 7.4 Hz, 1H), 3.77 (s, 3H), 1.41 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 154.5, 141.7, 135.2 (Cq, J_{CF} = 5.3 Hz), 131.1, 130.0, 129.6, 128.9, 128.5, 123.1 (Cq, J_{CF} = 273.6 Hz), 119.1, 118.6, 113.2, 112.4, 79.9, 55.2, 52.6, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.28 (s, CF_3).

HRMS (ESI) *m/z*: 430.1595 $[M+Na]^+$, $C_{22}H_{24}F_3NNaO_3^+$ requires 430.1600.

(*R*,*E*)-4,4,4-Trifluoro-3-phenyl-1-(3-(trifluoromethyl)phenyl)but-2-en-1-amine (35h)



The title compound was obtained following GPA from (*E*)-4,4,4-trifluoro-3-phenyl-1-(3-(trifluoromethyl)phenyl)but-2-en-1-one (1.2 g, 3.5 mmol). The allylic amine was purified by FCC (pentane:EtOAc 7:3) as a yellow oil in 66% yield over 3 steps (0.8 g, 2.3 mmol).

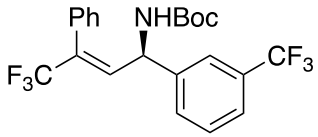
^{1}H NMR (400 MHz. $CDCl_3$) δ 7.57 – 7.53 (m, 2H), 7.45 – 7.44 (m, 5H), 7.26 – 7.25 (m, 2H), 6.49 (dd, *J* = 9.6, 1.7 Hz, 1H), 4.55 (d, *J* = 9.6, 1H), 1.54 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 138.3 (Cq, J_{CF} = 5.2 Hz), 131.5 (Cq, J_{CF} = 30.3 Hz), 131.4, 131.1 (J_{CF} = 32.3 Hz), 130.0, 129.5, 129.2, 129.1, 128.7, 124.5 (J_{CF} = 3.8 Hz), 123.4 (J_{CF} = 3.8 Hz), 124.0 (J_{CF} = 272.4 Hz), 123.1 (J_{CF} = 273.4 Hz), 52.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 62.65 (s, CF3), – 66.50 (s, CF3).

HRMS (ESI) *m/z*: Fragmentation observed: 329.0884 $[M - NH_2]^+$ corresponding to $C_{17}H_{11}F_6^+$, $C_{17}H_{11}F_6^+$ requires 329.0759.

tert-Butyl (*R*,*E*)-(4,4,4-trifluoro-3-phenyl-1-(3-(trifluoromethyl)phenyl)but-2-en-1-yl)carbamate (35h')



The title compound was obtained following GPB from (*R*,*E*)-4,4,4-trifluoro-3-phenyl-1-(3-(trifluoromethyl)phenyl)but-2-en-1-amine (86.3 mg, 0.25 mmol). The protected allylic amine was purified by FCC (pentane:EtOAc 95:5) as a white solid in 91% (93.5 mg, 0.21 mmol).

The enantiomeric excess (minor isomer: 99%, major isomer 94%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, (**1*R*,*Z***) (minor diastereomer): minor enantiomer, t_r = 13.3 min, major enantiomer, t_r = 9.1 min, (**1*R*,*E***) (major diastereomer): minor enantiomer t_r = 6.5 min, major enantiomer, t_r = 5.6 min.

$[\alpha]_D^{25}$: – 50.8 (c 1.00, $CHCl_3$, for the diastereomer mixture, d.r.: 92:8).

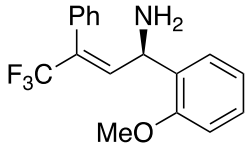
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.42 – 7.41 (m, 3H), 7.28 – 7.25 (m, 4H), 6.49 (d, *J* = 9.3 Hz, 1H), 5.25 (bs, 1H), 5.00 (bs, 1H), 1.41 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 144.3, 134.1 (Cq, J_{CF} = 5.4 Hz), 130.8, 130.1 (Cq, J_{CF} = 32.4 Hz), 129.4, 129.2, 128.7, 128.3 (Cq, J_{CF} = 3.7 Hz), 126.92, 126.85, 125.9 (Cq, J_{CF} = 3.7 Hz), 123.3 (Cq, J_{CF} = 3.8 Hz), 122.9 (Cq, J_{CF} = 273.6 Hz), 80.4, 52.3, 28.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 62.73(s, CF_3), – 66.54 (s, CF_3).

HRMS (ESI) *m/z*: 468.1364 $[M+Na]^+$, $C_{22}H_{21}F_6NNaO_2^+$ requires 468.1369.

(*R*,*E*)-4,4,4-Trifluoro-1-(2-methoxyphenyl)-3-phenylbut-2-en-1-amine (35i)



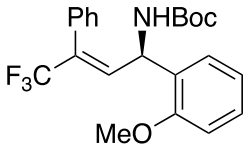
The title compound was obtained following GPA from (*E*)-4,4,4-trifluoro-1-(2-methoxyphenyl)-3-phenylbut-2-en-1-one (2.7 g, 8.7 mmol). The allylic amine was purified by FCC (pentane:EtOAc 7:3) as a yellow oil in 49% yield over 3 steps (1.3 g, 4.26 mmol).

^{1}H NMR (400 MHz. $CDCl_3$) δ 7.41 – 7.39 (m, 3H), 7.24 – 7.23 (m, 3H), 7.07 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.76 (dd, *J* = 9.6, 1,2 Hz, 1H), 4.54 (d, *J* = 9.7 Hz, 1H), 3.79 (s, 3H), 1.77 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 138.5 (Cq, J_{CF} = 5.3 Hz), 132.0, 131.1, 130.1 (Cq, J_{CF} = 29.7 Hz), 129.8, 128.63, 128.57, 128.3, 127.8, 123.5 (Cq, J_{CF} = 273.3 Hz), 120.9, 110.9, 55.1, 50.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.06 (S, CF_3).

***tert*-Butyl (*R*,*E*)-(4,4,4-trifluoro-1-(2-methoxyphenyl)-3-phenylbut-2-en-1-yl)carbamate (35i')**



The title compound was obtained following GPB from (*R*,*E*)-4,4,4-trifluoro-1-(2-methoxyphenyl)-3-phenylbut-2-en-1-amine (76.8 mg, 0.25 mmol). The protected allylic amine was purified by FCC (pentane:EtOAc 95:5) as a white solid in 99% (100.5 mg, 0.25 mmol).

The enantiomeric excess (minor isomer: 94%, major isomer 75%) was determined by HPLC (CHIRACEL® IC), hexane/iPrOH 98/2, 1 mL/min, (**1*R*,*Z***) (minor diastereomer): minor enantiomer, t_r = 12.8 min, major enantiomer, t_r = 10.9 min, (**1*R*,*E***) (major diastereomer): minor enantiomer tr = 9.3 min, major enantiomer, tr = 8.6 min.

$[\alpha]_D^{25}$: – 24.3 (c 0.76, $CHCl_3$, for the diastereomer mixture, d.r.: 97:3).

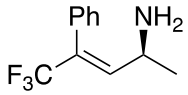
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.40 (m, 3H), 7.24 – 7.20 (m, 3H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.82 – 6.75 (m, 3H), 5.59 (bs, 1H), 5.30 (bs, 1H), 3.84 (s, 3H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 154.4, 136.0, 131.4, 131.2 (Cq, J_{CF} = 30.1 Hz), 129.8, 129.2, 128.7, 128.3, 127.9, 123.3 (Cq, J_{CF} = 273.3 Hz), 120.9, 111.1, 79.5, 55.3, 51.5, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.40 (s, CF_3).

HRMS (ESI) *m/z*: 430.1595 $[M+Na]^+$, $C_{22}H_{24}F_3NNaO_3^+$ requires 430.1600.

(*S*,*E*)-5,5,5-Trifluoro-4-phenylpent-3-en-2-amine (35j)



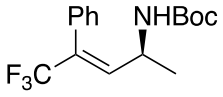
The title compound was obtained following GPA from (*E*)-5,5,5-trifluoro-4-phenylpent-3-en-2-one (2.0 g, 9.3 mmol). The allylic amine was purified by FCC (pentane:EtOAc 7:3) as a yellow oil in 30% yield over 3 steps (0.6 g, 2.8 mmol).

^{1}H NMR (400 MHz. $CDCl_3$) δ 7.41 – 7.37 (m, 3H), 7.24 – 7.22 (m, 2H), 6.26 (dq, *J* = 9.5, 1.6Hz, 1H), 3.44 (dt, *J* = 13.1, 6.6 Hz, 1H), 1.31 (bs, 2H), 1.14 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3 (Cq, J_{CF} = 5.1 Hz), 131.9, 129.8 (Cq, J_{CF} = 29.9 Hz), 129.5, 128.6, 128.5, 123.3 (Cq, J_{CF} = 273.1 Hz), 44.8, 23.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.30 (s, CF_3).

***tert*-Butyl (*S*,*E*)-(5,5,5-Trifluoro-4-phenylpent-3-en-2-yl)carbamate (35j')**



The title compound was obtained following GPB from (*S*,*E*)-5,5,5-trifluoro-4-phenylpent-3-en-2-amine (53.8 mg, 0.25 mmol). The protected allylic amine was purified by FCC (pentane:EtOAc 95:5) as a white solid in 99% (69.4 mg, 0.22 mmol).

The enantiomeric excess (minor isomer: nd, major isomer 28%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, (**1*S*,*E***) (major diastereomer): minor enantiomer t_r = 9.17 min, major enantiomer, t_r = 6.85 min.

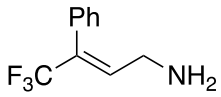
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.39 (m, 3H), 7.32 – 7.31 (m, 2H), 6.25 (d, *J* = 8.8 Hz, 1H), 4.47 (bs, 1H), 4.17 (bs, 1H), 1.42 (s, 9H), 1.14 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 137.9, 131.4, 129.5, 128.7, 128.5, 127.2, 123.2 (Cq, J_{CF} = 273.2 Hz), 44.9, 28.3, 21.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.46 (s, CF_3).

HRMS (ESI) *m/z*: 338.1360 $[M+Na]^+$, $C_{16}H_{20}F_3NNaO_2^+$ requires 338.1338.

(*E*)-4,4,4-Trifluoro-3-phenylbut-2-en-1-amine (35k)



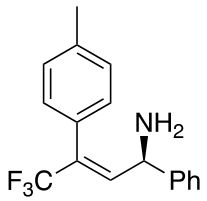
The title compound was obtained following GPA from (*E*)-4,4,4-trifluoro-3-phenylbut-2-enal (0.7 g, 3.5 mmol). The allylic amine was purified by FCC (pentane:EtOAc 7:3) as a yellow oil in 49% yield over 3 steps (0.35 g, 1.7 mmol).

^{1}H NMR (400 MHz. $CDCl_3$) δ 7.42 – 7.38 (m, 3H), 7.24 – 7.22 (m, 2H), 6.47 (t, *J* = 6.7 Hz, 1H), 3.27 (dd, *J* = 6.9, 2.2 Hz, 2H), 1.25 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0 (Cq, J_{CF} = 5.3 Hz), 131.7, 131.3 (Cq, J_{CF} = 29.6 Hz), 129.4, 128.7, 128.5, 123.3 (Cq, J_{CF} = 273.1 Hz), 39.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.01 (s, CF_3).

(*R*,*E*)-4,4,4-Trifluoro-1-phenyl-3-(*p*-tolyl)but-2-en-1-amine (35l)



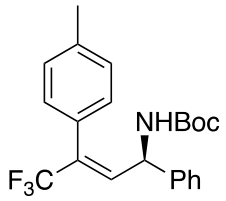
The title compound was obtained following GPA from (*E*)-4,4,4-trifluoro-1-phenyl-3-(*p*-tolyl)but-2-en-1-one (1.6 g, 5.5 mmol). The allylic amine was purified by FCC (pentane:EtOAc 7:3) as a yellow oil in 56% yield over 3 steps (0.9 g, 3.1 mmol).

^{1}H NMR (400 MHz. $CDCl_3$) δ 7.34 – 7.33 (m, 2H), 7.30 – 7.27 (m, 3H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 6.51 (dd, *J* = 9.8, 1.7 Hz, 1H), 4.50 (d, *J* = 9.8 Hz, 1H), 2.40 (s, 3H), 1.56 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 138.8 (Cq, J_{CF} = 5.2 Hz), 138.7, 130.5 (Cq, J_{CF} = 29.8 Hz), 129.5, 129.2, 128.8, 128.7, 127.6, 126.4, 123.3 (Cq, J_{CF} = 273.3 Hz), 53.0, 21.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.30 (s, CF_3).

***tert*-Butyl (*R*,*E*)-(4,4,4-trifluoro-1-phenyl-3-(*p*-tolyl)but-2-en-1-yl)carbamate (35l')**



The title compound was obtained following GPB from (*R*,*E*)-4,4,4-trifluoro-1-phenyl-3-(*p*-tolyl)but-2-en-1-amine (72.8 mg, 0.25 mmol). The protected allylic amine was purified by FCC (pentane:EtOAc 95:5) as a white solid in 99% (93.2 mg, 0.24 mmol).

The enantiomeric excess (minor isomer: nd, major isomer 90%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, (**1*R*,*E***) (major diastereomer): minor enantiomer t_r = 6.9 min, major enantiomer, t_r = 5.4 min.

$[\alpha]_D^{25}$: – 53.1 (c 0.98, $CHCl_3$, for the diastereomer mixture, d.r.: 87:13).

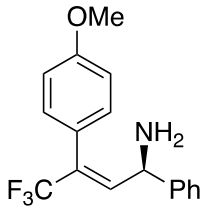
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 3H), 7.21 – 7.15 (m, 6H), 6.49 (dq, *J* = 9.4, 1.6 Hz, 1H), 5.22 (bs, 1H), 4.90 (d, *J* = 7.2 Hz, 1H), 2.38 (s, 3H), 1.41 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 140.3, 138.8, 134.9 (Cq, J_{CF} = 4.7 Hz), 129.4, 129.2, 128.9, 128.1, 127.9, 126.5, 123.2 (Cq, J_{CF} = 273.6 Hz), 80.0, 52.6, 28.3, 21.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.32 (s, CF_3).

HRMS (ESI) *m/z*: 414.1623 $[M+Na]^+$, $C_{22}H_{24}F_3NNaO_2^+$ requires 414.1651.

(*R*,*E*)-4,4,4-Trifluoro-3-(4-methoxyphenyl)-1-phenylbut-2-en-1-amine (35m)



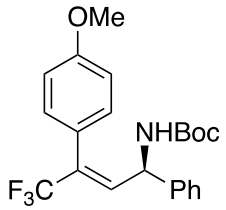
The title compound was obtained following GPA from (*E*)-4,4,4-trifluoro-3-(4-methoxyphenyl)-1-phenylbut-2-en-1-one (1.6 g, 5.5 mmol). The allylic amine was purified by FCC (pentane:EtOAc 7:3) as a yellow oil in 56% yield over 3 steps (0.9 g, 3.1 mmol).

^{1}H NMR (400 MHz. $CDCl_3$) δ 7.37 – 7.33 (m, 2H), 7.29 – 7.27 (m, 3H), 7.19 (d, *J* = 8.6 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 6.51 (d, *J* = 9.7, 1.5 Hz, 1H), 4.50 (d, *J* = 9.7 Hz, 1H), 3.85 (s, 3H), 1.55 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 143.0, 138.9 (Cq, *J* = 5.1 Hz), 130.9, 130.1 (Cq, *J* = 29.9 Hz), 128.8, 127.6, 126.4, 123.7, 123.4 (Cq, *J* = 273.3 Hz), 113.9, 55.2, 53.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.40 (s, CF_3).

***tert*-Butyl (*R*,*E*)-(4,4,4-trifluoro-3-(4-methoxyphenyl)-1-phenylbut-2-en-1-yl)carbamate (35m')**



The title compound was obtained following GPB from (*R*,*E*)-4,4,4-trifluoro-3-(4-methoxyphenyl)-1-phenylbut-2-en-1-amine (76.8 mg, 0.25 mmol). The protected allylic amine was purified by FCC (pentane:EtOAc 95:5) as a white solid in 99% (86.2 mg, 0.21 mmol).

The enantiomeric excess (minor isomer: 98%, major isomer 93%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, (**1*R*,*Z***) (minor diastereomer): minor enantiomer, t_r = 19.5 min, major enantiomer, t_r = 12.0 min, (**1*R*,*E***) (major diastereomer): minor enantiomer t_r = 8.4 min, major enantiomer, t_r = 6.3 min.

$[\alpha]_D^{25}$: – 60.0 (c 0.98, $CHCl_3$, for the diastereomer mixture, d.r.: 88:12).

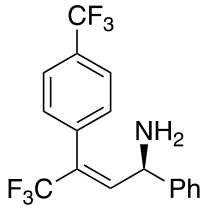
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 4H), 7.21 – 7.17 (m, 3H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.50 (d, *J* = 9.2 Hz, 1H), 5.24 (bs, 1H), 5.04 (bs, 1H), 3.82 (s, 3H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 154.5, 140.3, 135.1 (Cq, J_{CF} = 5.5 Hz), 130.8, 128.9, 127.8, 127.3, 126.5, 123.2 (Cq, J_{CF} = 273.5 Hz), 123.2, 113.9, 79.9, 55.1, 52.6, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.36 (s, CF_3).

HRMS (ESI) *m/z*: 430.1562 $[M+Na]^+$, $C_{21}H_{22}F_3NNaO_2^+$ requires 430.1600.

(*R*,*E*)-4,4,4-Trifluoro-1-phenyl-3-(4-(trifluoromethyl)phenyl)but-2-en-1-amine (35n)



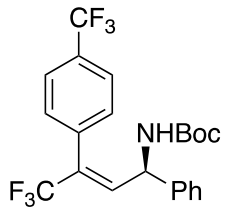
The title compound was obtained following GPA from (*E*)-4,4,4-trifluoro-1-phenyl-3-(4-(trifluoromethyl)phenyl)but-2-en-1-one (0.8 g, 2.3 mmol). The allylic amine was purified by FCC (pentane:EtOAc 7:3) as a yellow oil in 52% yield over 3 steps (0.4 g, 1.2 mmol).

^{1}H NMR (400 MHz. $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.45 – 7.44 (m, 3H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.26 (m, 2H), 6.50 (dd, *J* = 9.7, 1.7 Hz, 1H), 4.55 (d, *J* = 9.7 Hz, 1H), 1.56 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 138.2 (Cq, J_{CF} = 5.2 Hz), 131.5 (Cq, J_{CF} = 30.2 Hz), 131.4, 129.9 (Cq, J_{CF} = 32.5 Hz), 129.5, 129.0, 128.7, 126.9, 125.7 (Cq, J_{CF} = 3.8 Hz), 124.0 (Cq, J_{CF} = 272.0 Hz), 123.1 (Cq, J_{CF} = 273.4 Hz), 52.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.55 (s, CF_3), – 66.46 (s, CF_3).

***tert*-Butyl (*R*,*E*)-(4,4,4-trifluoro-1-phenyl-3-(4-(trifluoromethyl)phenyl)but-2-en-1-yl)carbamate (35n')**



The title compound was obtained following GPB from (*R*,*E*)-4,4,4-trifluoro-1-phenyl-3-(4-(trifluoromethyl)phenyl)but-2-en-1-amine (86.3 mg, 0.25 mmol). The protected allylic amine was purified by FCC (pentane:EtOAc 95:5) as a white solid in 82% (91.3 mg, 0.21 mmol).

The enantiomeric excess (minor isomer: nd, major isomer 94%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, (**1*R*,*E***) (major diastereomer): minor enantiomer t_r = 6.9 min, major enantiomer, t_r = 5.1 min.

$[\alpha]_D^{25}$: – 32.8 (c 0.78, $CHCl_3$, for the diastereomer mixture, d.r.: 95:5).

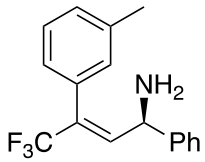
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 2H), 7.36 – 7.30 (m, 3H), 7.15 – 7.12 (m, 2H), 6.61 (dd, *J* = 9.4, 1.8 Hz, 1H), 5.13 (bs, 1H), 4.90 (d, *J* = 7.4 Hz, 1H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 139.5, 136.6 (Cq, J_{CF} = 4.4 Hz), 134.9, 131.13 (Cq, J_{CF} = 32.5 Hz), 131.06 (Cq, J_{CF} = 30.3 Hz), 130.2, 129.1, 128.2, 126.6, 125.5 (Cq, J_{CF} = 3.8 Hz), 123.9 (Cq, J_{CF} = 272.3 Hz), 122.8 (Cq, J_{CF} = 273.5 Hz), 80.2, 52.7, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 62.85 (s, CF_3), – 66.14 (s, CF_3).

HRMS (ESI) *m/z*: 468.1369 $[M+Na]^+$, $C_{22}H_{21}F_6NNaO_2^+$ requires 468.1369.

(*R*,*E*)-4,4,4-Trifluoro-1-phenyl-3-(*m*-tolyl)but-2-en-1-amine (35o)



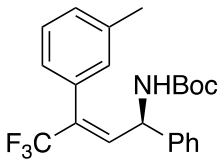
The title compound was obtained following GPA from (*E*)-4,4,4-trifluoro-1-phenyl-3-(*m*-tolyl)but-2-en-1-one (2.0 g, 6.9 mmol). The allylic amine was purified by FCC (pentane:EtOAc 7:3) as a yellow oil in 50% yield over 3 steps (1.0 g, 3.4 mmol).

^{1}H NMR (400 MHz. $CDCl_3$) δ 7.38 – 7.27 (m, 6H), 7.25 – 7.23 (m, 1H), 7.08 – 7.06 (m, 2H), 6.53 (dq, *J* = 9.7, 1.6 Hz, 1H), 4.49 (d, *J* = 9.7 Hz, 1H), 2.39 (s, 3H), 1.56 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 138.8 (Cq, J_{CF} = 5.2 Hz), 138.2, 131.6, 130.6 (Cq, J_{CF} = 29.9 Hz), 130.2, 129.6, 128.8, 128,4, 127.6, 126.7, 126.5, 123.3 (Cq, J_{CF} = 273.3 Hz), 53.0, 21.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.18 (s, CF_3).

***tert*-Butyl (*R*,*E*)-(4,4,4-trifluoro-1-phenyl-3-(*m*-tolyl)but-2-en-1-yl)carbamate (35o')**



The title compound was obtained following GPB from (*R*,*E*)-4,4,4-trifluoro-1-phenyl-3-(4-(trifluoromethyl)phenyl)but-2-en-1-amine (72.8 mg, 0.25 mmol). The protected allylic amine was purified by FCC (pentane:EtOAc 95:5) as a white solid in 94% (92.3 mg, 0.24 mmol).

The enantiomeric excess (minor isomer: 93%, major isomer 89%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, (**1*R*,*Z***) (minor diastereomer): minor enantiomer, t_r = 9.92 min, major enantiomer, t_r = 6.87 min, (**1*R*,*E***) (major diastereomer): minor enantiomer t_r = 5.78 min, major enantiomer, t_r = 4.93 min.

$[\alpha]_D^{25}$: – 54.2 (c 1.00, $CHCl_3$, for the diastereomer mixture, d.r.: 89:11).

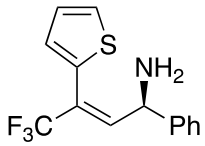
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 4H), 7.22 – 7. 20 (m, 1H), 7.17 – 7.15 (m, 2H), 7.08 – 7.05 (m, 2H), 6.52 (dd, *J* = 9.3, 1.9 Hz, 1H), 5.21 (bs, 1H), 4.99 (d, *J* = 7.6 Hz, 1H), 2.35 (s, 3H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 140.4, 138.1, 135.1, 132.4 (Cq, J_{CF} = 29.7 Hz), 131.0, 130.2, 129.7, 128.8, 128.3, 127.8, 126.6, 126.5, 123.2 (Cq, J_{CF} = 273.5 Hz), 80.0, 52.6, 28.3, 21.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.16 (s, CF_3).

HRMS (ESI) *m/z*: 414.1652 $[M+Na]^+$, $C_{21}H_{22}F_3NNaO_2^+$ requires 414.1651.

(*R*,*Z*)-4,4,4-Trifluoro-1-phenyl-3-(thiophen-2-yl)but-2-en-1-amine (35p)



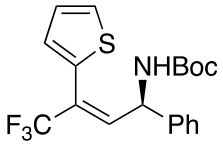
The title compound was obtained following GPA from (*Z*)-4,4,4-trifluoro-1-phenyl-3-(thiophen-2-yl)but-2-en-1-one (1.5 g, 5.3 mmol). The allylic amine was purified by FCC (pentane:EtOAc 7:3) as a yellow oil in 47% yield over 3 steps (0.7 g, 2.5 mmol).

^{1}H NMR (400 MHz. $CDCl_3$) δ 7.44 (d, *J* = 4.8 Hz, 1H), 7.40 – 7.29 (m, 5H), 7.11 – 7.09 (m, 2H), 6.62 (d, *J* = 9.7 Hz, 1H), 4.80 (d, *J* = 9.7 Hz, 1H), 1.60 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 141.3 (Cq, J_{CF} = 4.9 Hz), 130.9, 129.5, 128.8, 127.7, 127.5, 127.2, 126.5, 123.7 (Cq, J_{CF} = 31.2 Hz), 122.7 (Cq, J_{CF} = 273.5 Hz), 53.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.58 (s, CF_3).

***tert*-Butyl (R,Z)-(4,4,4-trifluoro-1-phenyl-3-(thiophen-2-yl)but-2-en-1-yl)carbamate (35p')**



The title compound was obtained following GPB from (*R*,*E*)-4,4,4-trifluoro-1-phenyl-3-(4-(trifluoromethyl)phenyl)but-2-en-1-amine (70.8 mg, 0.25 mmol). The protected allylic amine was purified by FCC (pentane:EtOAc 95:5) as a white solid in 98% (94.4 mg, 0.24 mmol).

The enantiomeric excess (minor isomer: nd, major isomer 95%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, (**1*R*,*E***) (major diastereomer): minor enantiomer t_r = 9.2 min, major enantiomer, t_r = 7.3 min.

$[\alpha]_D^{25}$: – 49.5 (c 1.00, $CHCl_3$, for the diastereomer mixture, d.r.: 96:4).

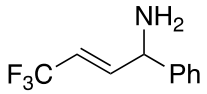
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.38 – 7.28 (m, 3H), 7.24 – 7.23 (m, 2H), 7.09 (bs, 1H), 7.06 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.58 (dd, *J* = 9.2, 0.8 Hz, 1H), 5.52 (bs, 1H), 4.95 (dd, *J* = 7.7 Hz, 1H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 139.9, 137.0 (Cq, J_{CF} = 5.5 Hz), 130.4, 129.8, 129.0, 128.1, 127.8, 127.1, 126.7, 126.6, 122.7 (Cq, J_{CF} = 273.9 Hz), 80.2, 52.7, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 65.51 (s, CF_3).

HRMS (ESI) *m/z*: 406.1024 $[M+Na]^+$, $C_{19}H_{20}F_3NNaO_2S^+$ requires 406.1059.

4,4,4-Trifluoro-1-phenylbut-2-en-1-amine (35q)



The title compound was obtained following GPA from (*E*)-4,4,4-trifluoro-1-phenylbut-2-en-1-one (0.7 g, 3.5 mmol). The allylic amine was purified by FCC (pentane:EtOAc 7:3) as a yellow oil in 33% yield over 3 steps (0.3 g, 1.2 mmol).

^{1}H NMR (400 MHz. $CDCl_3$) δ 7.39 – 7.36 (m, 2H), 7.32 – 7.29 (m, 3H), 6.55 (ddq, *J* = 15.7, 5.5, 2.1 Hz, 1H), 5.92 (dqd, *J* = 15.7, 6.4, 1,7 Hz, 1H), 4.65 (dp, *J* = 4.5, 2.2 Hz, 1H), 1.59 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3 (Cq, J_{CF} = 6.1 Hz), 142.3, 128.9, 127.9, 126.7, 123.3 (Cq, J_{CF} = 269.4 Hz), 117.6 (Cq, J_{CF} = 33.4 Hz), 56.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 63.79 (dt, *J* = 6.4, 2.1 Hz, CF_3).

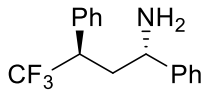
Characterization of amines 38 and 38'

HRMS of **38a-38q** could not be obtained due to decomposition of the compounds. Instead, the HRMS of the **38a'-6p'** (protected amines) are reported. **38q** HRMS could not be given, a fragmentation is observed. HPLC analysis and α values of **38a-38p** is not reported here. Instead, the HPLC analysis and α values of **38a'-38p'** is reported.

4,4,4-Trifluoro-1,3-diphenylbutan-1-amine (38a)

The titled compound was obtained following GPC from **35a** (69.3 mg, 0.25 mmol) as a colourless oil (83% NMR yield). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4). The diastereomers were obtained in a ratio 75:25 in 80% isolated yield. Minor diastereomer **(1*S*,3*R*)-38a** isolated 20 mg (0.07 mmol) 28% yield, major diastereomer **(1*R*,3*R*)-38a** isolated 36 mg (0.13 mmol) 52% yield.

Minor diastereomer (configuration 1*S*, 3*R*)-38a

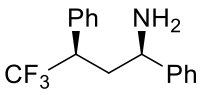


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 5H), 7.32 – 7.30 (m, 2H), 7.24 – 7.19 (m, 3H), 3.79 – 3.71 (m, 1H), 3.56 (t, *J* = 7.6 Hz, 1H), 2.24 – 2.50 (m, 2H), 1.40 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 134.4 (Cq, J_{CF} = 2,1 Hz), 129.2, 128.8, 128.7, 128.3, 127.2, 125.7, 124.3 (Cq, J_{CF} = 272.8 Hz), 52.5, 47.3 (Cq, J_{CF} = 26.7 Hz), 38.3 (Cq, J_{CF} = 2.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ – 69.47 (d, *J* = 9.7 Hz, CF_3).

Major diastereomer (configuration 1*R*, 3*R*)-38a



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 5H), 7.32 – 7.28 (m, 1H), 7.24 – 7.22 (m, 2H), 7.19 – 7.17 (m, 2H), 3.65 – 3.61 (m, 1H), 3.04 – 2.93 (m, 1H), 2.39 – 2.32 (m, 2H), 1.52 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 134.3 (Cq, J_{CF} = 2.0 Hz), 129.2, 128.8, 128.7, 128.3, 127.7, 126.8 (Cq, J_{CF} = 278.0 Hz), 126.6, 53.6, 47.4 (Cq, J_{CF} = 26.8 Hz), 37.9.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 69.91 (d, *J* = 9.5 Hz, CF_3).

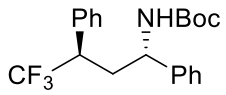
HRMS (ESI) *m/z*: 280.1336 $[M+H]^+$, $C_{16}H_{17}F_3N^+$ requires 280.1308.

***tert*-Butyl 4,4,4-trifluoro-1,3-diphenylbutyl)carbamate (38a')**

The titled compound was obtained following GPB from **35a** and purified by FCC using (pentane:EtOAc 95:5). Minor diastereomer **(1*S*,3*R*)-38a'**, isolated yield 57% (15.1 mg, 0.04 mmol) from 20 mg (0.07 mmol) of **(1*S*,3*R*)-38a**. Major diastereomer **(1*R*,3*R*)-38a'**, isolated yield 72% (34.1 mg, 0.09 mmol) from 36 mg (0.13 mmol) of **(1*R*,3*R*)-38a**.

The enantiomeric excess (minor isomer: 94%, major isomer 90%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, λ = 210 nm, **1*S*,3*R*** (minor diastereomer): minor enantiomer, t_r = 7.2 min, major enantiomer, t_r = 5.9 min, **1*R*,3*R*** (major diastereomer): minor enantiomer t_r = 6.1 min, major enantiomer, t_r = 7.8 min.

Minor diastereomer (configuration 1*S*, 3*R*)-38a'



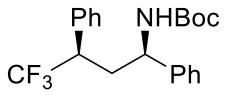
$[\alpha]_D^{25}$: – 5.4 (c 0.5, $CHCl_3$, ee 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (*Rotamers are observed*) 7.38 – 7.29 (m, 8H), 7.16 – 7.14 (m, 2H), 4.99 – 4.76 (m, 1H), 4.50 – 4.28 (m, 1H), 3.47 (bs, 1H), 2.39 – 2.31 (m, 2H), 1.44 – 1.27 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 142.2, 134.0, 129.1, 128.8, 128.7, 128.3, 127.5, 126,9 (Cq, J_{CF} = 279.9 Hz), 125.9, 79.7, 51.5, 47.3 (Cq, J_{CF} = 26.7 Hz), 36.8, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 69.31 (d, *J* = 9.7 Hz, CF_3).

Major diastereomer (configuration 1*R*, 3*R*)-38a'



$[\alpha]_D^{25}$: – 1.4 (c 0.71, $CHCl_3$, *ee* 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 6H), 7.23 – 7.21 (m, 2H), 7.13 – 7.11 (m, 2H), 4.71 (d, *J* = 6.3 Hz, 1H), 4.36 (bs, 1H), 3.00 – 2.89 (m, 1H), 2.62 (bs, 1H), 2.35 (ddd, *J* = 13.7, 10.3, 3.6 Hz, 1H), 1.37 (bs, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 140.3, 133.3 (Cq, J_{CF} = 2.1 Hz), 129.3, 129.0, 128.8, 128.5, 128.1, 126.6 (Cq, J_{CF} = 278.0 Hz), 126.8, 79.6, 53.0, 47.2 (Cq, J_{CF} = 27.9 Hz), 34.6, 28.3.

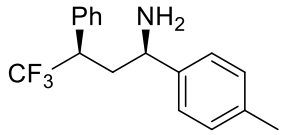
^{19}F NMR (376 MHz, $CDCl_3$) δ – 70.20 (bs, CF_3).

HRMS (ESI) *m/z*: 402.1647 $[M+Na]^+$, $C_{21}H_{24}F_3NNaO_2^+$ requires 402.1651.

4,4,4-Trifluoro-3-phenyl-1-(*p*-tolyl)butan-1-amine (38b)

The titled compound was obtained following GPC from **35b** (72.8 mg, 0.25 mmol) as a colourless oil (90% NMR yield). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4). The diastereomers were obtained in a ratio 67:33 in 61% yield. Minor diastereomer could not be purified. Major diastereomer **(1*R*,3*R*)-38b** isolated 45 mg (0.15 mmol) 61% yield.

Major diastereomer (configuration 1*R*, 3*R*)-38b



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.35 (m, 3H), 7.23 – 7.22 (m, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 2H), 3.57 (dd, *J* = 8.7, 6.4 Hz, 1H), 3.02 – 2.91 (m, 1H), 2.36 – 2.31 (m, 5H), 1.51 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 137.3, 134.4 (q, *J* = 2.1 Hz), 129.5, 129.2, 128.7, 128.3, 126.8 (q, *J* = 278.0 Hz), 126.5, 53.3, 47.4 (Cq, J_{CF} = 26.8 Hz), 37.9, 21.1.

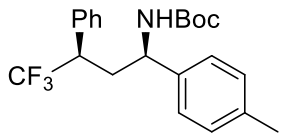
^{19}F NMR (376 MHz, $CDCl_3$) δ – 69.91 (d, *J* = 9.5 Hz, CF_3).

***tert*-Butyl (4,4,4-trifluoro-3-phenyl-1-(*p*-tolyl)butyl)carbamate (38b')**

The titled compound was obtained following GPB from **38b** and purified by FCC using (pentane:EtOAc 95:5). Major diastereomer **(1*R*,3*R*)-38b'**, isolated yield 56% (32.4 mg, 0.09 mmol) from 45 mg (0.15 mmol) of **38b**.

The enantiomeric excess (minor isomer: nd, major isomer 67%) was determined by HPLC (CHIRALPAK® IF), hexane/iPrOH 98/2, 1 mL/min, λ = 210 nm, **1*R*,3*R*** (major diastereomer): minor enantiomer tr = 7.1 min, major enantiomer, tr = 6.5 min.

Major diastereomer (configuration 1*R*, 3*R*)-38b'



$[\alpha]_D^{25}$: – 7.8 (c 0.63, $CHCl_3$, *ee* 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 3H), 7.26 – 7.23 (m, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.00 (d, *J* = 7.8 Hz, 2H), 4.68 (bs, 1H), 4.31 (bs, 1H), 2.99 – 2.88 (m, 1H), 2.62 (bs, 1H), 2.36 – 2.29 (m, 4H), 1.37 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 137.8, 137.3, 133.4, 130.8, 129.6, 129.3, 128.8, 128.4, 126.7, 126.65 (Cq, *J* = 279.8 Hz), 79.5, 52.7, 47.2 (Cq, *J* = 26.9 Hz), 34.6, 28.3, 21.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 70.18 (bs, CF_3).

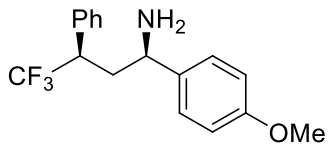
HRMS (ESI) *m/z*: 416.1871 $[M+Na]^+$, $C_{22}H_{26}F_3NNaO_2^+$ requires 416.1871.

4,4,4-Trifluoro-1-(4-methoxyphenyl)-3-phenylbutan-1-amine (38c)

The titled compound was obtained following GPC from **35c** (76.8 mg, 0.25 mmol) as a colourless oil (68% NMR yield). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4).

The diastereomers were obtained in a ratio 65:35 in 35% yield. Minor diastereomer could not be purified. Major diastereomer **(1*R*,3*R*)-38c** isolated 27 mg (0.09 mmol) 35% yield.

Major diastereomer (configuration 1*R*, 3*R*)-38c



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 3H), 7.23 – 7.21 (m, 2H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 3.82 (s, 3H), 3.57 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.94 (ddq, *J* = 14.2, 9.6, 4.8 Hz, 1H), 2.34 (m, 2H), 1.50 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 136.3, 134.3 (Cq, *J* = 1.9 Hz), 129.2, 128.7, 128.3, 127.7, 126.8 (Cq, *J* = 279.7 Hz), 114.2, 55.3, 52.9, 47.4 (Cq, *J* = 26.8 Hz), 38.0.

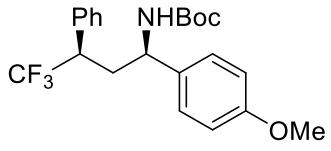
^{19}F NMR (376 MHz, $CDCl_3$) δ – 69.92 (d, *J* = 9.5 Hz, CF_3).

***tert*-Butyl (4,4,4-trifluoro-1-(4-methoxyphenyl)-3-phenylbutyl)carbamate (38c')**

The titled compound was obtained following GPB from **38c** and purified by FCC using (pentane:EtOAc 95:5). Major diastereomer **(1*R*,3*R*)-38c'**, isolated yield 85% (30.0 mg, 0.08 mmol) from 27 mg (0.15 mmol) of **38c**.

The enantiomeric excess (minor isomer: nd, major isomer 90%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, λ = 210 nm, **1*R*,3*R*** (major diastereomer): minor enantiomer t_r = 9.2 min, major enantiomer, t_r = 10.4 min.

Major diastereomer (configuration 1*R*, 3*R*)-38c'



$[\alpha]_D^{25}$: – 16.8 (c 0.70, $CHCl_3$, *ee* 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 3H), 7.22 – 7.02 (m, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.88 7.03 (d, *J* = 8.5 Hz, 2H), 4.65 (bs, 1H), 4.28 (bs, 1H), 3.82 (s, 3H), 2.97 – 2.87 (m, 1H), 2.62 (bs, 1H), 2.30 (ddd, *J* = 13.6, 10.7, 3.3 Hz, 1H), 1.37 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 154.6, 133.3, 132.3, 129.3, 128.8, 128.4, 128.0, 126.7 (Cq, *J* = 279.6 Hz), 114.3, 79.6, 55.3, 52.3, 47.2 (Cq, *J* = 26.4 Hz), 34.5, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 70.18 (d, *J* = 9.3 Hz, CF_3).

HRMS (ESI) *m/z*: 432.1757 $[M+Na]^+$, $C_{22}H_{26}F_3NNaO_3^+$ requires 432.1785.

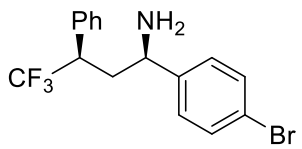
1-(4-Bromophenyl)-4,4,4-trifluoro-3-phenylbutan-1-amine (38d)

The titled compound was obtained following GPC from **35d** (89 mg, 0.25 mmol) as a colourless oil (67% NMR yield). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4). The diastereomers were obtained in a ratio 74:26 in 67% yield. Minor diastereomer could not be purified. Major diastereomer **(1*R*,3*R*)-38d** isolated 39.6 mg (0.09 mmol) 44% yield.

Reaction 1g scale

The titled compound was obtained following GPC from **35d** (1.0 g, 2.81 mmol) as a colourless oil (73% NMR yield). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4). The diastereomers were obtained in a ratio 70:30 in 68% yield. Minor diastereomer could not be purified. Major diastereomer **(1*R*,3*R*)-38d** isolated 387.5 mg (1.08 mmol) 38% yield.

Major diastereomer (configuration 1*R*, 3*R*)-38d



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.36 (m, 3H), 7.22 – 7.20 (m, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 3.62 (dd, *J* = 9.7, 5.3 Hz, 1H), 2.94 (ddp, *J* = 18.6, 9.5, 4.8, 4.3 Hz, 1H), 2.31 (dqt, *J* = 23.0, 9.5, 4.7 Hz, 1H), 1.51 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 134.0 (Cq, *J* = 2.0 Hz), 131.9, 129.1, 128.8, 128.41, 128.37, 126.6 (Cq, *J* = 279.8 Hz), 121.4, 53.1, 47.3 (q, *J* = 26.9 Hz), 38.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 69.98 (d, *J* = 9.5 Hz, CF_3).

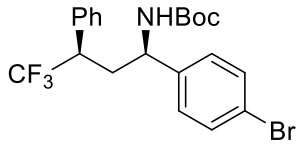
***tert*-Butyl (1-(4-bromophenyl)-4,4,4-trifluoro-3-phenylbutyl)carbamate (38d')**

The titled compound was obtained following GPB from **38d** and purified by FCC using (pentane:EtOAc 95:5). Major diastereomer **(1*R*,3*R*)-38d'**, isolated yield 91% (46.1 mg, 0.10 mmol) from 39.6 mg (0.11 mmol) of **38d**.

The titled compound was obtained following GPB from **38d** and purified by FCC using (pentane:EtOAc 95:5). Major diastereomer **(1*R*,3*R*)-38d'**, isolated yield 87% (432.1 mg, 0.94 mmol) from 387.5 mg (1.08 mmol) of **38d**.

The enantiomeric excess (minor isomer: nd, major isomer 86%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, λ = 210 nm, **1*R*,3*R*** (major diastereomer): minor enantiomer t_r = 9.0 min, major enantiomer, t_r = 12.4 min.

Major diastereomer (configuration 1*R*, 3*R*)-6d'



$[\alpha]_D^{25}$: – 37.1 (c 0.93, $CHCl_3$, *ee* 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.41 – 7.37 (m, 3H), 7.22 – 7.20 (m, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 4.70 (d, *J* = 7.4 Hz, 1H), 4.32 (bs, 1H), 2.92 (dtd, *J* = 18.3, 9.2, 4.6 Hz, 1H), 2.55 (bs, 1H), 2.30 (ddd, *J* = 13.7, 10.2, 3.6 Hz, 1H), 1.36 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 139.6, 133.1, 132.1, 129.2, 128.9, 128.6, 128.5, 126.5 (Cq, *J* = 279.8 Hz), 121.9, 79.9, 52.4, 47.15 (Cq, *J* = 29.4 Hz), 34.6, 28.3.

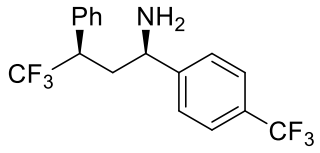
^{19}F NMR (376 MHz, $CDCl_3$) δ – 70.22 (d, *J* = 9.2 Hz, CF_3).

HRMS (ESI) *m/z*: 480.0733 $[M+Na]^+$, $C_{21}H_{23}F_3BrNNaO_2^+$ requires 480.0756.

4,4,4-Trifluoro-3-phenyl-1-(4-(trifluoromethyl)phenyl)butan-1-amine (38e)

The titled compound was obtained following GPC from **35e** (86.3 mg, 0.25 mmol) as a colourless oil (60% NMR yield). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4). The diastereomers were obtained in a ratio 65:35 in 54% yield. Minor diastereomer could not be purified. Major diastereomer **(1*R*,3*R*)-38e** isolated 28.0 mg (0.08 mmol) 32% yield.

Major diastereomer (configuration 1*R*, 3*R*)-38e



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.40 – 7.37 (m, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.23 – 7.21 (m, 2H), 3.75 (dd, *J* = 8.8, 6.1 Hz, 1H), 2.97 (pd, *J* = 9.4, 5.3 Hz, 1H), 2.42 – 2.30 (m, 2H), 1.54 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 134.0 (Cq, *J* = 1.8 Hz), 130.0 (Cq, *J* = 32.4 Hz), 129.1, 128.9, 128.5, 127.0, 126.6, 125.8 (Cq, *J* = 3.7 Hz), 124.0 (d, *J* = 272.1 Hz), 53.3, 47.3 (d, *J* = 27.1 Hz), 37.9.

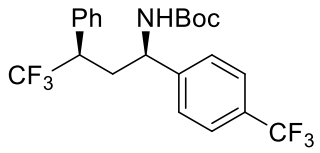
^{19}F NMR (376 MHz, $CDCl_3$) δ – 62.51 (s, CF_3), – 70.00 (d, *J* = 9.2 Hz, CF_3).

***tert*-Butyl (4,4,4-trifluoro-3-phenyl-1-(4-(trifluoromethyl)phenyl)butyl)carbamate (38e')**

The titled compound was obtained following GPB from **38e** and purified by FCC using (pentane:EtOAc 95:5). Major diastereomer **(1*R*,3*R*)-38e'**, isolated yield 78% (27.8 mg, 0.106 mmol) from 28.0 mg (0.08 mmol) of **38e**.

The enantiomeric excess (minor isomer: nd, major isomer 87%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, λ = 210 nm, **1*R*,3*R*** (major diastereomer): minor enantiomer t_r = 10.8 min, major enantiomer, t_r = 7.8 min.

Major diastereomer (configuration 1*R*, 3*R*)-38e'



$[\alpha]_D^{25}$: – 16.0 (c 0.45, $CHCl_3$, *ee* 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.42 – 7.38 (m, 3H), 7.26 – 7.21 (m, 4H), 4.75 (d, *J* = 7.5 Hz, 1H), 4.46 (bs, 1H), 2.95 (dtd, *J* = 18.4, 9.2, 3.7 Hz, 1H), 2.56 (bs, 1H), 2.36 (ddd, *J* = 13.6, 9.7, 3.8 Hz, 1H), 1.36 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 144.8, 133.2, 130.3 (Cq, *J* = 32.6 Hz), 129.1, 129.0, 128.7, 127.1, 126.4 (d, *J* = 279.8 Hz), 125.9 (Cq, *J* = 3.6 Hz), 123.9 (d, *J* = 272.1 Hz), 80.0, 52.7, 47.2 (Cq, *J* = 27.8 Hz), 34.8, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 62.56 (s, CF3), – 70.23 (bs, CF_3).

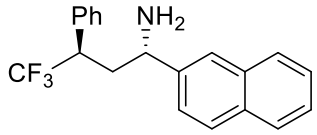
HRMS (ESI) *m/z*: 470.1551 $[M+Na]^+$, $C_{22}H_{23}F_6NNaO_2^+$ requires 470.1525.

4,4,4-Trifluoro-1-(naphthalen-2-yl)-3-phenylbutan-1-amine (38f)

The titled compound was obtained following GPC from **35f** (81.8 mg, 0.25 mmol) as a colourless oil (86% NMR yield). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4).

The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4). The diastereomers were obtained in a ratio 75:25 in 87% yield. Minor diastereomer **(1*S*,3*R*)-38f** isolated 23 mg (0.07 mmol) 28 % yiled. Major diastereomer **(1*R*,3*R*)-38f** isolated 46.0 mg (0.14 mmol) 56% yield.

Minor diastereomer (configuration 1*S*, 3*R*)-38f

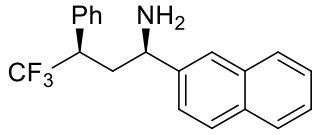


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 3H), 7.64 (s, 1H), 7.50 – 7.46 (m, 2H), 7.41 – 7.37 (m, 5H), 7.33 (dd, *J* = 8.6, 1.8 Hz, 1H), 3.82 – 3.73 (m, 2H), 2.32 (dd, *J* = 8.2, 6.5 Hz, 2H), 1.49 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 134.5 (Cq, *J* = 2.0 Hz), 133.4, 132.3, 129.2, 128.8, 128.5, 128.3, 127.7, 127.6, 126.2, 125.8, 124.2, 124.1, 52.6, 47.3 (Cq, *J* = 26.7 Hz), 38.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 69.39 (d, *J* = 9.6 Hz, CF_3).

Major diastereomer (configuration 1*R*, 3*R*)-38f



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.79 (m, 3H), 7.53 – 7.48 (m, 3H), 7.41 – 7.38 (m, 4H), 7.26 – 7.23 (m, 2H), 3.81 (t, *J* = 7.5 Hz, 1H), 2.99 (pd, *J* = 9.3, 6.6 Hz, 1H), 2.45 (dd, *J* = 8.4, 6.7 Hz, 2H), 1.61 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 134.3 (Cq, *J* = 1.9 Hz), 133.3, 133.0, 129.2, 128.9, 128.7, 128.3, 127.8, 127.7, 126.7 (Cq, *J* = 279.8 Hz), 126.3, 126.0, 125.8, 124.1, 53.7, 47.4 (Cq, *J* = 26.8 Hz), 37.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 69.93 (d, *J* = 9.6 Hz, CF_3).

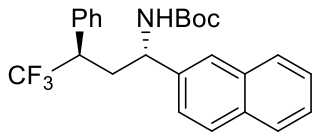
HRMS (ESI) *m/z*: 330.1482 $[M+H]^+$, $C_{20}H_{19}F_3N^+$ requires 330.1464.

***tert*-Butyl (4,4,4-trifluoro-1-(naphthalen-2-yl)-3-phenylbutyl)carbamate (38f')**

The titled compound was obtained following GPB from **38f** and purified by FCC using (pentane:EtOAc 95:5). Minor diastereomer **(1*S*,3*R*)-38f'**, isolated yield 25% (7.5 mg, 0.06 mmol) from 23.0 mg (0.08 mmol) of **5f**. Major diastereomer **(1*R*,3*R*)-38f'**, isolated yield 55% (33.1 mg, 0.08 mmol) from 46.0 mg (0.14 mmol) of **28f**.

The enantiomeric excess (minor isomer: 93%, major isomer 95%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, λ = 210 nm, **1*S*,3*R*** (minor diastereomer): minor enantiomer, t_r = 21.5 min, major enantiomer, t_r = 16.7 min, **1*R*,3*R*** (major diastereomer): minor enantiomer t_r = 13.2 min, major enantiomer, t_r = 10.9 min.

Minor diastereomer (configuration 1*S*, 3*R*)-38f'



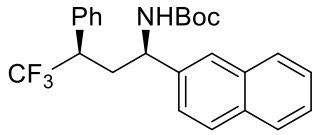
$[\alpha]_D^{25}$: – 21.0 (c 0.20, $CHCl_3$, *ee* 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.77 (m, 3H), 7.60 (s, 1H), 7.49 – 7.46 (m, 2H), 7.38 – 7.34 (m, 5H), 7.26 – 7.25 (m, 1H), 5.00 – 4.85 (m, 1H), 4.66 – 4.43 (m, 1H), 3.51 (bs, 1H), 2.46 – 2.40 (m, 2H), 1.44 – 1.27 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 139.5, 134.0, 133.3, 132.7, 129.1, 128.9, 128.6, 128.5, 127.8, 127.6, 126.9 (Cq, *J* = 278.0 Hz), 126.3, 126.0, 125.5, 124.5, 124.2, 79.8, 51.7, 47.4 (Cq, *J* = 27.0 Hz), 36.6, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 69.25 (d, *J* = 9.6 Hz, CF_3).

Major diastereomer (configuration 1*R*, 3*R*)-38f'



$[\alpha]_D^{25}$: – 43.5 (c 1.00, $CHCl_3$, *ee* 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.84 (m, 2H), 7.80 – 7.78 (m, 1H), 7.52 – 7.50 (m, 3H), 7.40 – 7.39 (m, 3H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.23 – 7.21 (m, 2H), 4.86 (d, *J* = 6.6 Hz, 1H), 4.54 (bs, 1H), 2.95 (ddt, *J* = 18.5, 12.7, 6.3 Hz, 1H), 2.68 (bs, 1H), 2.46 (ddd, *J* = 13.7, 10.2, 3.6 Hz, 1H), 1.37 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 137.6, 133.3, 133.2, 133.0, 129.3, 129.0, 128.8, 128.5, 128.0, 127.9, 127.7, 126.6 (Cq, *J* = 279.9 Hz), 126.4, 126.2, 124.1, 79.6, 53.1, 47.2 (Cq, *J* = 26.7 Hz), 35.5, 28.3.

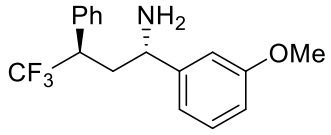
^{19}F NMR (376 MHz, $CDCl_3$) δ – 70.16 (s, CF_3).

HRMS (ESI) *m/z*: 452.1826 $[M+Na]^+$, $C_{25}H_{26}F_3NNaO_2^+$ requires 452.1808.

4,4,4-Trifluoro-1-(3-methoxyphenyl)-3-phenylbutan-1-amine (38g)

The titled compound was obtained following GPC from **35g** (76.8 mg, 0.25 mmol) as a colourless oil (99% NMR yield). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4). The diastereomers were obtained in a ratio 66:33 in 99% yield. Minor diastereomer **(1*S*,3*R*)-38g** isolated 24 mg (0.08 mmol) 31 % yiled. Major diastereomer **(1*R*,3*R*)-38g** isolated 48.0 mg (0.16 mmol) 62% yield.

Minor diastereomer (configuration 1*S*, 3*R*)-38g

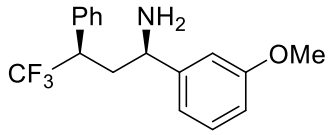


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 5H), 7.23 (t, *J* = 7.9 Hz, 1H), 6.80 – 6.73 (m, 3H), 3.80 (s, 3H), 3.75 – 3.51 (m, 1H), 2.23 – 2.19 (m, 2H), 1.49 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 148.2, 134.4 (Cq, *J* = 1.9 Hz), 129.7, 129.2, 128.8, 128.3, 127.1 (Cq, *J* = 279.6 Hz), 118.0, 112.2, 111.7, 55.2, 52.5, 47.3 (Cq, *J* = 26.7 Hz), 38.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 69.47 (d, *J* = 9.6 Hz, CF_3).

Major diastereomer (configuration 1*R*, 3*R*)-38g



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 3H), 7.29 – 7.23 (m, 3H), 6.84 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.71 (bs, 1H), 3.81 (s, 3H), 3.61 – 3.58 (m, 1H), 3.06 – 2.95 (m, 1H), 2.36 – 2.32 (m, 2H), 1.68 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 146.0, 134.3 (Cq, *J* = 1.9 Hz), 129.9, 129.2, 128.7, 128.1, 126.7 (Cq, *J* = 279.7 Hz), 118.8, 113.1, 112.1, 55.2, 53.6, 47.3 (Cq, *J* = 26.8 Hz), 37.8.

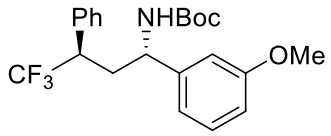
^{19}F NMR (376 MHz, $CDCl_3$) δ – 69.92 (d, *J* = 9.6 Hz, CF_3).

***tert*-Butyl (4,4,4-trifluoro-1-(3-methoxyphenyl)-3-phenylbutyl)carbamate (38g')**

The titled compound was obtained following GPB from **38g** and purified by FCC using (pentane:EtOAc 95:5). Minor diastereomer **(1*S*,3*R*)-38g'**, isolated yield 60% (19.7 mg, 0.05 mmol) from 24.0 mg (0.08 mmol) of **38g**. Major diastereomer **(1*R*,3*R*)-38g'**, isolated yield 88% (57.7 mg, 0.14 mmol) from 48.0 mg (0.16 mmol) of **38g**.

The enantiomeric excess (minor isomer: 86%, major isomer 89%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, λ = 210 nm, **1*R*,3*R*** (major diastereomer): minor enantiomer t_r = 9.5 min, major enantiomer, t_r = 7.7 min.

Minor diastereomer (configuration 1*S*, 3*R*)-38g'



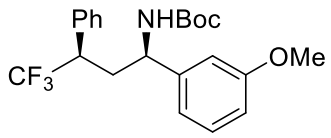
$[\alpha]_D^{25}$: – 43.5 (c 1.00, $CHCl_3$, *ee* 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.37 (m, 3H), 7.31 – 7.30 (m, 2H), 7.22 (t, *J* = 7.9 Hz, 1H), 6.78 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.74 (d, *J* = 7.7 Hz, 1H), 6.68 (s, 1H), 4.71 (d, *J* = 9.3 Hz, 1H), 4.41 (bs, 1H), 3.77 (s, 3H), 3.46 (bs, 1H), 2.37 – 2.27 (m, 2H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 154.9, 143.9, 134,0, 129.8, 129.1, 128.8, 128.5, 126.9 (Cq, *J* = 279.3 Hz), 118.1, 112.7, 112.0, 79.7, 55.2, 51.5, 47.3 (Cq, *J* = 27.0 Hz), 36.7, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 69.31 (d, *J* = 9.5 Hz, CF_3).

Major diastereomer (configuration 1*R*, 3*R*)-38g'



$[\alpha]_D^{25}$: – 0.8 (c 1.00, $CHCl_3$, *ee* 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 3H), 7.29 – 7.23 (m, 3H), 6.85 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.72 (d, *J* = 7.5 Hz, 1H), 6.63 (s, 1H), 4.74 (d, *J* = 7.3 Hz, 1H), 4.33 (bs, 1H), 3.78 (s, 3H), 2.97 (ddt, *J* = 18.7, 12.6, 6.3 Hz, 1H), 2.62 (bs, 1H), 2.33 (ddd, *J* = 13.7, 10.3, 3.5 Hz, 1H), 1.38 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 154.7, 141.9, 133.3, 130.1, 129.3, 128.8, 128.5, 126.6 (Cq, *J* = 279.8 Hz), 118.8, 113.5, 112.5, 79.6, 55.2, 52.9, 47.1 (Cq, *J* = 26.8 Hz), 35.6, 28.3.

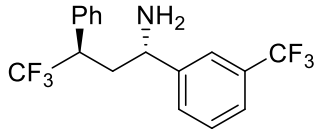
^{19}F NMR (376 MHz, $CDCl_3$) δ – 70.19 (s, CF_3).

HRMS (ESI) *m/z*: 432.1761 $[M+Na]^+$, $C_{22}H_{26}F_3NNaO_3^+$ requires 432.1757.

4,4,4-Trifluoro-3-phenyl-1-(3-(trifluoromethyl)phenyl)butan-1-amine (38h)

The titled compound was obtained following GPC from **35h** (86.3 mg, 0.25 mmol) as a colourless oil (80% NMR yield). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4). The diastereomers were obtained in a ratio 75:25 in 80% yield. Minor diastereomer **(1*S*,3*R*)-38h** isolated 15 mg (0.04 mmol) 17 % yiled. Major diastereomer **(1*R*,3*R*)-38h** isolated 45.0 mg (0.13 mmol) 52% yield.

Minor diastereomer (configuration 1*S*, 3*R*)-38h



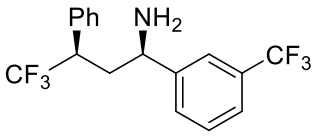
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.6 Hz, 1H), 7.45 – 7.33 (m, 8H), 3.77 – 3.67 (m, 1H), 3.65 – 3.61 (m, 1H), 2.24 – 2.20 (m, 2H), 1.51 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 134.0 (Cq, *J* = 1.9 Hz), 131.0 (Cq, *J* = 32.1 Hz), 129.3, 129.1, 128.9, 128.6, 128.4, 127.0 (Cq, *J* = 276.8 Hz), 126.7 (Cq, *J* = 279.6 Hz), 124.1 (Cq, *J* = 3.8 Hz), 122.6 (Cq, *J* = 3.8 Hz), 52.4, 47.3 (Cq, *J* = 26.9 Hz), 38.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 62.59 (s, CF_3), – 69.54 (d, *J* = 9.6 Hz, CF_3).

HRMS (ESI) *m/z*: 348.1137 $[M+H]^+$, $C_{17}H_{16}F_6N^+$ requires 348.1181.

Major diastereomer (configuration 1*R*, 3*R*)-38h



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.42 – 7.36 (m, 5H), 7.22 – 7.20 (m, 2H), 3.76 (dd, *J* = 9.2, 5.6 Hz, 1H), 2.96 (pd, *J* = 9.4, 4.7 Hz, 1H), 2.42 – 2.29 (m, 2H), 1.56 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 134.0 (Cq, *J* = 1.9 Hz), 131.0 (Cq, *J* = 32.2 Hz), 129.9, 129.3, 129.1, 128.9, 128.5, 126.6 (d, *J* = 279.8 Hz), 124.0 (Cq, *J* = 272.3 Hz), 124.6 (Cq, *J* = 3.8 Hz), 123.7 (Cq, *J* = 3.8 Hz), 53.4, 47.3 (Cq, *J* = 26.9 Hz), 38.0.

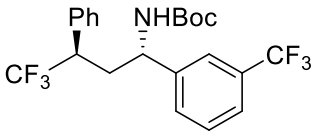
^{19}F NMR (376 MHz, $CDCl_3$) δ – 62.67 (s, CF_3), – 69.99 (d, *J* = 9.4 Hz, CF_3).

***tert*-Butyl (4,4,4-trifluoro-3-phenyl-1-(3-(trifluoromethyl)phenyl)butyl)carbamate (38h')**

The titled compound was obtained following GPB from **38h** and purified by FCC using (pentane:EtOAc 95:5). Minor diastereomer **(1*S*,3*R*)-38h'**, isolated yield 96% (17.1 mg, 0.04 mmol) from 15.0 mg (0.04 mmol) of **6h**. Major diastereomer **(1*R*,3*R*)-38h'**, isolated yield 93% (54.1 mg, 0.12 mmol) from 45.0 mg (0.13 mmol) of **38h**.

The enantiomeric excess (minor isomer: 77%, major isomer 90%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, λ = 210 nm, **1*S*,3*R*** (minor diastereomer): minor enantiomer, t_r = 7.6 min, major enantiomer, t_r = 10.8 min, **1*R*,3*R*** (major diastereomer): minor enantiomer t_r = 16.5 min, major enantiomer, t_r = 10.3 min.

Minor diastereomer (configuration 1*S*, 3*R*)-38h'



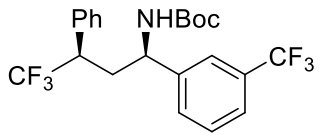
$[\alpha]_D^{25}$: – 9.9 (c 0.63, $CHCl_3$, *ee* 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.7 Hz, 1H), 7.44 – 7.26 (m, 8H), 4.77 (bs, 1H), 4.51 (bs, 1H), 3.48 (bs, 1H), 2.37 – 2.27 (m, 2H), 1.43 – 1.26 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 143.4, 133.5, 131.1 (Cq, *J* = 27.6 Hz), 129.54, 129.47, 129.23, 129.16, 129.0, 128.7, 124.4 (Cq, *J* = 3.7 Hz), 122.6, 80.2, 51.3, 47.4 (Cq, *J* = 27.6 Hz), 36.5, 28.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 62.66 (s, CF_3), – 69.38 (d, *J* = 9.5 Hz, CF_3).

Major diastereomer (configuration 1*R*, 3*R*)-38h'



$[\alpha]_D^{25}$: – 7.8 (c 0.90, $CHCl_3$, *ee* 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.40 – 7.33 (m, 5H), 7.21 – 7.20 (m, 2H), 4.76 (d, *J* = 7.4 Hz, 1H), 4.46 (bs, 1H), 2.99 – 2.88 (m, 1H), 2.56 (bs, 1H), 2.35 (ddd, *J* = 13.6, 9.6, 3.9 Hz, 1H), 1.36 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 141.8, 133.1, 131.18 (Cq, *J* = 32.3 Hz), 130.0, 129.5, 129.0, 128.7, 127.8, 126.44 (Cq, *J* = 279.9 Hz), 124.86 (Cq, *J* = 3.6 Hz), 123.9 (d, *J* = 272.5 Hz), 123.7, 80.0, 52.9, 47.2 (d, *J* = 25.8 Hz), 34.9, 28.2.

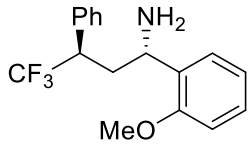
^{19}F NMR (376 MHz, $CDCl_3$) δ – 62.70 (s, CF_3), 70.22 (s, CF_3).

HRMS (ESI) *m/z*: 470.1531 $[M+Na]^+$, $C_{22}H_{23}F_6NNaO_2^+$ requires 470.1525.

4,4,4-Trifluoro-1-(2-methoxyphenyl)-3-phenylbutan-1-amine (38i)

The titled compound was obtained following GPC from **35i** (76.8 mg, 0.25 mmol) as a colourless oil (78% NMR yield). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4). The diastereomers were obtained in a ratio 66:34 in 56% yield. Minor diastereomer **(1*S*,3*R*)-38i** isolated 18.6 mg (0.06 mmol) 24 % yiled. Major diastereomer **(1*R*,3*R*)-38i** isolated 20.2 mg (0.17 mmol) 26% yield.

Minor diastereomer (configuration 1*S*, 3*R*)-38i

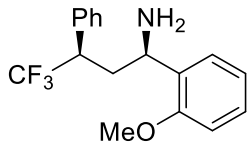


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 5H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 3.85 – 3.73 (m, 5H), 2.32 – 2.19 (m, 2H), 1.59 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 134.5 (Cq, *J* = 1.9 Hz), 134.4, 129.5, 128.4, 128.0, 127.9, 127.3 (Cq, *J* = 277.6 Hz), 126.1, 120.6, 110.6, 55.0, 48.6, 47.3 (q, *J* = 26.5 Hz), 35.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 69.58 (d, *J* = 9.7 Hz, CF_3).

Major diastereomer (configuration 1*R*, 3*R*)-38i



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 3H), 7.27 – 7.19 (m, 3H), 6.97 – 6.88 (m, 3H), 3.81 – 3.74 (m, 4H), 3.02 (pd, *J* = 9.8, 3.7 Hz, 1H), 2.63 (ddd, *J* = 13.6, 9.8, 3.8 Hz, 1H), 2.32 (ddd, *J* = 13.5, 11.1, 5.5 Hz, 1H), 1.83 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 134.7 (Cq, *J* = 1.8 Hz), 131.9, 129.3, 128.5, 128.4, 128.1, 126.9 (Cq, *J* = 277.7 Hz), 120.7, 111.0, 55.1, 50.8, 47.8 (Cq, *J* = 26.6 Hz), 35.9.

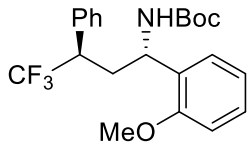
^{19}F NMR (376 MHz, $CDCl_3$) δ – 69.84 (d, *J* = 9.4 Hz, CF_3).

***tert*-Butyl (4,4,4-trifluoro-1-(2-methoxyphenyl)-3-phenylbutyl)carbamate (38i')**

The titled compound was obtained following GPB from **38i** and purified by FCC using (pentane:EtOAc 95:5). Minor diastereomer **(1*S*,3*R*)-38i'**, isolated yield 84% (20.6 mg, 0.05 mmol) from 18.6 mg (0.06 mmol) of **38i**. Major diastereomer **(1*R*,3*R*)-38i'**, isolated yield 89% (25.5 mg, 0.06 mmol) from 20.2 mg (0.07 mmol) of **38i**.

The enantiomeric excess (minor isomer: 69%, major isomer 72%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, λ = 210 nm, **1*S*,3*R*** (minor diastereomer): minor enantiomer, tr = 7.9 min, major enantiomer, tr = 7.3 min, **1*R*,3*R*** (major diastereomer): minor enantiomer tr = 9.6 min, major enantiomer, tr = 8.6 min.

Minor diastereomer (configuration 1*S*, 3*R*)-38i'



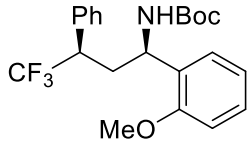
$[\alpha]_D^{25}$: – 26.9 (c 0.70, $CHCl_3$, *ee* 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (*Rotamers are observed*) 7.40 – 7.28 (m, 5H), 7.20 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.87 – 6.80 (m, 2H), 5.33 (d, *J* = 10.0 Hz, 1H), 4.59 (td, *J* = 10.2, 3.7 Hz, 1H), 3.78, 3.52 – 3.40 (m, 1H), 2.48 – 2.42 (m, 1H), 2.30 – 2.23 (m, 1H), 1.43 – 1.26 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8. 155.0, 134.1, 129.8, 129.4, 128.6, 128.5, 128.2, 127.9, 120.7, 110.9, 79.3, 55.1, 47.5 (Cq, *J* = 28.2 Hz), 35.3, 28.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 69.43 (d, *J* = 9.8 Hz, CF_3).

Major diastereomer (configuration 1*R*, 3*R*)-38i'



$[\alpha]_D^{25}$: +8.7 (c 0.50, $CHCl_3$, *ee* 72%).

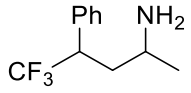
^{1}H NMR (400 MHz, $CDCl_3$) (*Rotamers are observed*) δ 7.39 – 7.34 (m, 3H), 7.30 – 7.26 (m, 1H), 7.22 – 7.21 (m, 2H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.86 (t, *J* = 7.4 Hz, 1H), 6.79 (d, *J* = 7.0 Hz, 1H), 5.42 (d, *J* = 8.7 Hz, 1H), 4.57 (q, *J* = 8.8 Hz, 1H), 3.86 (s, 3H), 2.95 – 2.86 (m, 1H), 2.65 – 2.59 (m, 1H), 2.60 – 2.42 (m, 1H), 1.39 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 154.9, 133.6, 130.0, 129.4, 129.1, 128.6, 128.3, 127.4, 126.8 (Cq, *J* = 279.9 Hz), 120.7, 111.1, 79.2, 55.3, 51.7, 47.6 (q, *J* = 27.0 Hz), 33.1, 28.4.

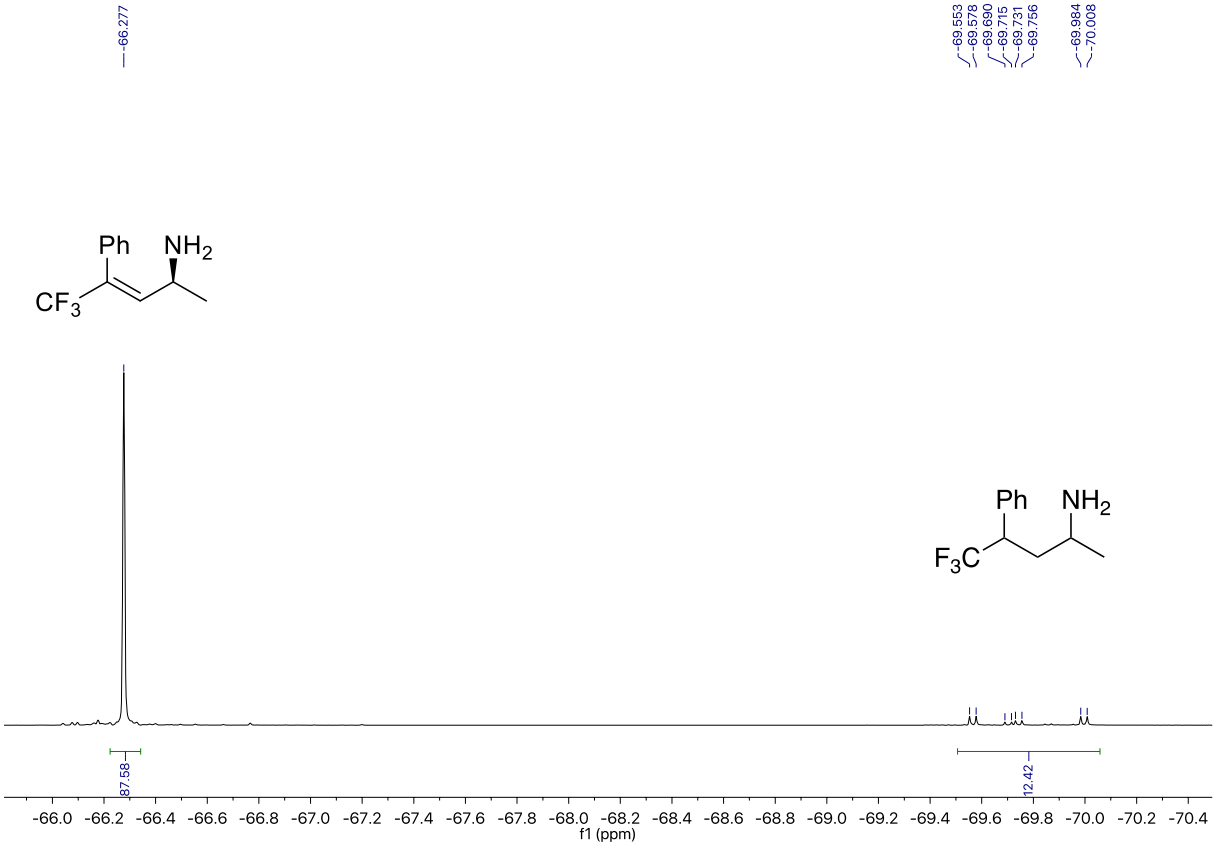
^{19}F NMR (376 MHz, $CDCl_3$) δ – 70.28 (d, *J* = 9.5 Hz, CF_3).

HRMS (ESI) *m/z*: 432.1736 $[M+Na]^+$, $C_{22}H_{26}F_3NNaO_3^+$ requires 432.1757.

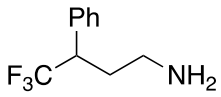
5,5,5-Trifluoro-4-phenylpentan-2-amine (38j)



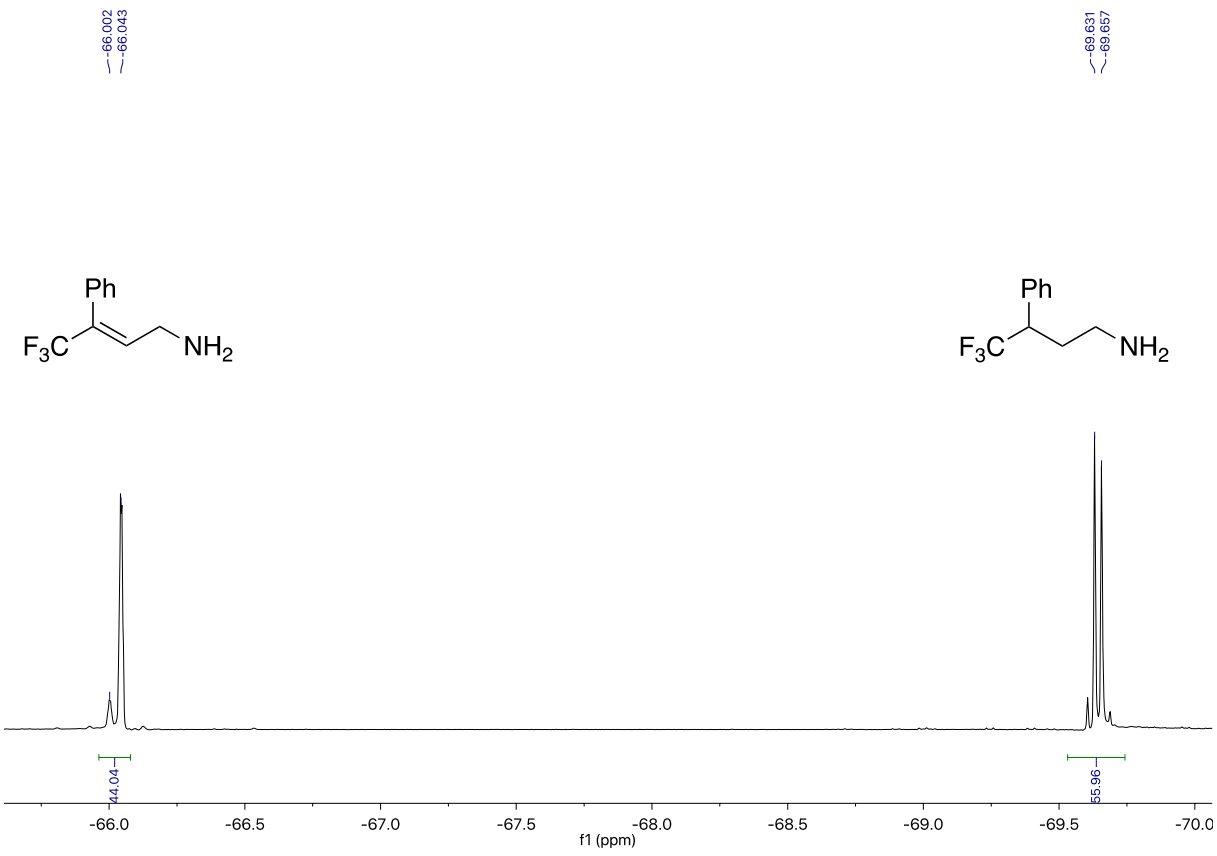
The final compound was not isolated due to low conversion. Conversion to the mixture of E and Z diastereomers was determined by integration of the CF_3 of both starting material and product by ^{19}F NMR (Shown below). ^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.28 (s, CF_3, Allylic amine **4j**), – 69.55 - – 70.01 (d, CF_3, diastereomeric mixture of **6j**).



4,4,4-Trifluoro-3-phenylbutan-1-amine (38k)



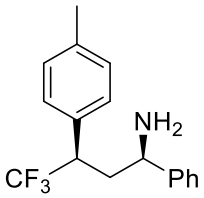
The final compound could not be separated from the starting material. The conversion to the mixture of E and Z diastereomers was determined by integration of the CF_3 of both starting material and product by ^{19}F NMR (Shown below). ^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.00 - – 66.04 (s, CF_3, Allylic amine **4k**), – 69.63 - – 69.66 (s, CF_3, **6k**).



4,4,4-Trifluoro-1-phenyl-3-(*p*-tolyl)butan-1-amine (38l)

The titled compound was obtained following GPC from **35l** (72.8 mg, 0.25 mmol) as a colourless oil (90% NMR yield). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4). The diastereomers were obtained in a ratio 67:33 in 90% yield. Minor diastereomer could not be isolated. Major diastereomer **(1*R*,3*R*)-38l** isolated 44.0 mg (0.15 mmol) 60% yield.

Major diastereomer (configuration 1*R*, 3*R*)-38l



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 3H), 7.19 – 7.17 (m, 4H), 7.11 (d, *J* = 7.9 Hz, 2H), 3.64 – 3.61 (m, 1H), 2.93 (dq, *J* = 18.5, 9.3 Hz, 1H), 2.37 (s, 3H), 2.35 – 2.31 (m, 2H), 1.55 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 138.1, 131.22 (Cq, *J* = 1.9 Hz), 129.4, 129.0, 128.8, 127.7, 126.6, 126.8 (Cq, *J* = 279.7 Hz), 53.6, 47.0 (Cq, *J* = 26.8 Hz), 37.9, 21.1.

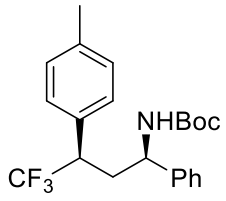
^{19}F NMR (376 MHz, $CDCl_3$) δ – 70.09 (d, *J* = 9.6 Hz, CF_3).

***tert*-Butyl (4,4,4-trifluoro-1-phenyl-3-(*p*-tolyl)butyl)carbamate (38l')**

The titled compound was obtained following GPB from **38l** and purified by FCC using (pentane:EtOAc 95:5). Major diastereomer **(1*R*,3*R*)-38l'**, isolated yield 87% (51.3 mg, 0.13 mmol) from 44.0 mg (0.15 mmol) of **38l**.

The enantiomeric excess (minor isomer: nd, major isomer 70%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, λ = 210 nm, **1*R*,3*R*** (major diastereomer): minor enantiomer t_r = 6.9 min, major enantiomer, t_r = 5.1 min.

Major diastereomer (configuration 1*R*, 3*R*)-38l'



$[\alpha]_D^{25}$: – 15.8 (c 0.70, $CHCl_3$, *ee* 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 3H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.13 – 7.10 (m, 4H), 4.72 (d, *J* = 6.5 Hz, 1H), 4.35 (bs, 1H), 2.95 – 2.85 (m, 1H), 2.59 (bs, 1H), 2.37 – 2.29 (m, 4H), 1.38 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 140.4, 138.2, 130.2, 129.5, 129.1, 128.9, 128.0, 126.8, 126.7 (Cq, *J* = 279.7 Hz), 79.5, 52.9, 46.7 (Cq, *J* = 27.4 Hz), 34.7, 28.3, 21.1.

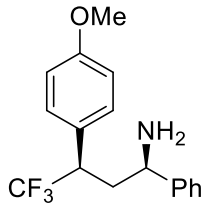
^{19}F NMR (376 MHz, $CDCl_3$) δ – 70.33 (d, *J* = 9.4 Hz, CF_3).

HRMS (ESI) *m/z*: 416.1871 $[M+Na]^+$, $C_{22}H_{26}F_3NNaO_2^+$ requires 416.1808.

4,4,4-Trifluoro-3-(4-methoxyphenyl)-1-phenylbutan-1-amine (38m)

The titled compound was obtained following GPC from **35m** (76.8 mg, 0.25 mmol) as a colourless oil (73% NMR yield). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4). The diastereomers were obtained in a ratio 65:35 in 73% yield. Minor diastereomer could not be isolated. Major diastereomer **(1*R*,3*R*)-38m** isolated 35.0 mg (0.11 mmol) 45% yield.

Major diastereomer (configuration 1*R*, 3*R*)-38m



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 2H), 7.31 – 7.27 (m, 1H), 7.18 – 7.13 (m, 4H), 6.90 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 3.64 – 3.61 (m, 1H), 2.96 – 2.85 (m, 1H), 2.33 – 2.30 (m, 2H), 1.62 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 144.4, 130.2, 128.8, 127.7, 126.8 (Cq, *J* = 278.0 Hz), 126.6, 126.2 (Cq, *J* = 2.2 Hz), 114.1, 55.2, 53.6, 46.6 (Cq, *J* = 26.9 Hz), 37.9.

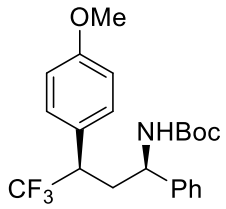
^{19}F NMR (376 MHz, $CDCl_3$) δ – 70.34 (d, *J* = 9.4 Hz, CF_3).

***tert*-Butyl (4,4,4-trifluoro-3-(4-methoxyphenyl)-1-phenylbutyl)carbamate (38m')**

The titled compound was obtained following GPB from **38m** and purified by FCC using (pentane:EtOAc 95:5). Major diastereomer **(1*R*,3*R*)-38m'**, isolated yield 64% (28.8 mg, 0.07 mmol) from 35.0 mg (0.11 mmol) of **38m**.

The enantiomeric excess (minor isomer: nd, major isomer 81%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, λ = 210 nm, **1*R*,3*R*** (major diastereomer): minor enantiomer t_r = 10.4 min, major enantiomer, t_r = 6.9 min.

Major diastereomer (configuration 1*R*, 3*R*)-38m'



$[\alpha]_D^{25}$: – 22.9 (c 0.85, $CHCl_3$, *ee* 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 3H), 7.15 – 7.11 (m, 4H), 6.91 (d, *J* = 8.6 Hz, 2H), 4.72 (d, *J* = 4.8 Hz, 1H), 4.34 (bs, 1H), 3.83 (s, 3H), 2.92 – 2.28 (m, 1H), 2.59 (bs, 1H), 2.31 (ddd, *J* = 13.6, 10.6, 3.4 Hz, 1H), 1.38 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 154.7, 140.3, 130.3, 129.0, 128.1, 126.9, 126.7 (Cq, *J* = 279.7 Hz), 125.1, 114.2, 79.5, 55.2, 52.9, 46.3 (Cq, *J* = 26.4 Hz), 34.6, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 70.58 (s, CF_3).

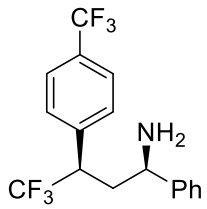
HRMS (ESI) *m/z*: 432.1764 $[M+Na]^+$, $C_{22}H_{26}F_3NNaO_3^+$ requires 432.1757.

4,4,4-Trifluoro-1-phenyl-3-(4-(trifluoromethyl)phenyl)butan-1-amine (38n)

The titled compound was obtained following GPC from **35n** (86.3 mg, 0.25 mmol) as a colourless oil (55% NMR yield). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4).

The diastereomers were obtained in a ratio 85:15 in 55% yield. Minor diastereomer could not be isolated. Major diastereomer **(1*R*,3*R*)-38n** isolated 37.0 mg (0.11 mmol) 43% yield.

Major diastereomer (configuration 1*R*, 3*R*)-38n



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.38 – 7.29 (m, 5H), 7.15 (d, *J* = 7.3 Hz, 2H), 3.60 (dd, *J* = 9.1, 6.0 Hz, 1H), 3.09 (pd, *J* = 9.4, 4.9 Hz, 1H), 2.43 – 2.31 (m, 2H), 1.56 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 134.0, 130.0 (Cq, *J* = 32.4 Hz), 129.1, 128.9, 128.5, 127.0, 126.6 (Cq, J_{CF} = 279.8 Hz), 125.8 (Cq, J_{CF} = 3.7 Hz), 124.0 (Cq, J_{CF} = 272.0 Hz), 53.3, 47.3, 37.9.

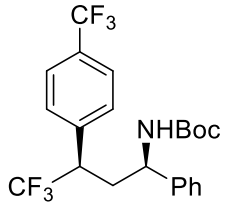
^{19}F NMR (376 MHz, $CDCl_3$) δ – 62.71 (s, CF_3), – 69.73 (d, *J* = 9.1 Hz, CF_3).

***tert*-Butyl (4,4,4-trifluoro-1-phenyl-3-(4-(trifluoromethyl)phenyl)butyl)carbamate (38n')**

The titled compound was obtained following GPB from **38n** and purified by FCC using (pentane:EtOAc 95:5). Major diastereomer **(1*R*,3*R*)-38n'**, isolated yield 82% (40.4 mg, 0.09 mmol) from 37.0 mg (0.11 mmol) of **38n**.

The enantiomeric excess (minor isomer: nd, major isomer 70%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, λ = 210 nm, **1*R*,3*R*** (major diastereomer): minor enantiomer t_r = 9.0 min, major enantiomer, t_r = 6.1 min.

Major diastereomer (configuration 1*R*, 3*R*)-38n'



$[\alpha]_D^{25}$: – 1.8 (c 0.55, $CHCl_3$, *ee* 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.1 Hz, 2H), 7.39 – 7.33 (m, 5H), 7.11 (dd, *J* = 7.8, 1.7 Hz, 2H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.31 (bs, 1H), 3.02 (ddq, *J* = 18.2, 9.1, 4.5, 3.4 Hz, 1H), 2.69 (bs, 1H), 2.39 (ddd, *J* = 13.7, 10.3, 3.5 Hz, 1H), 1.38 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 139.8, 137.4, 130.8 (Cq, *J* = 32.6 Hz), 129.8, 129.2, 128.4, 126.8, 126.2 (Cq, *J* = 278.0 Hz), 125.8 (Cq, *J* = 3.7 Hz), 123.9 (Cq, *J* = 272.2 Hz), 79.8, 53.0, 47.1 (Cq, *J* = 27.2 Hz), 34.2, 28.3.

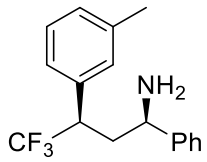
^{19}F NMR (376 MHz, $CDCl_3$) δ – 62.73 (s, CF_3), – 70.09 (d, *J* = 8.7 Hz, CF_3).

HRMS (ESI) *m/z*: 470.1548 $[M+Na]^+$, $C_{22}H_{23}F_6NNaO_2^+$ requires 470.1525.

4,4,4-Trifluoro-1-phenyl-3-(*m*-tolyl)butan-1-amine (38o)

The titled compound was obtained following GPC from **35o** (72.8 mg, 0.25 mmol) as a colourless oil (81% NMR yield). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4). The diastereomers were obtained in a ratio 75:25 in 75% yield. Minor diastereomer could not be isolated. Major diastereomer **(1*R*,3*R*)-38o** isolated 39.0 mg (0.13 mmol) 53% yield.

Major diastereomer (configuration 1*R*, 3*R*)-38o



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 2H), 7.31 – 7.29 (m, 1H), 7.28 – 7.24 (m, 1H), 7.19 – 7.16 (m, 3H), 7.04 – 7.00 (m, 2H), 3.63 (dd, *J* = 8.2, 6.8 Hz, 1H), 2.95 (dq, *J* = 18.6, 9.4 Hz, 1H), 2.37 (s, 3H), 2.35 – 2.32 (m, 2H), 1.62 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 138.4, 134.3 (Cq, *J* = 1.9 Hz), 129.7, 129.0, 128.8, 128.5, 128.2, 127.7, 126.8 (Cq, *J* = 278.0 Hz), 126.6, 126.4, 53.6, 47.3 (Cq, *J* = 26.7 Hz), 38.0, 21.4.

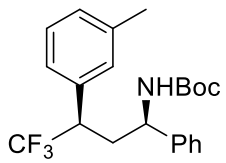
^{19}F NMR (376 MHz, $CDCl_3$) δ – 69.83 (d, *J* = 9.5 Hz, CF_3).

***tert*-Butyl (4,4,4-trifluoro-1-phenyl-3-(*m*-tolyl)butyl)carbamate (38o')**

The titled compound was obtained following GPB from **38o** and purified by FCC using (pentane:EtOAc 95:5). Major diastereomer **(1*R*,3*R*)-38o'**, isolated yield 71% (36.3 mg, 0.09 mmol) from 39.0 mg (0.11 mmol) of **38o**.

The enantiomeric excess (minor isomer: nd, major isomer 83%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, λ = 210 nm, **1*R*,3*R*** (major diastereomer): minor enantiomer t_r = 6.8 min, major enantiomer, t_r = 5.2 min.

Major diastereomer (configuration 1*R*, 3*R*)-38o'



$[\alpha]_D^{25}$: – 1.1 (c 0.90, $CHCl_3$, *ee* 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 3H), 7.27 – 7.25 (m, 1H), 7.18 – 7.13 (m, 3H), 7.03 (d, *J* = 7.7 Hz, 1H), 6.99 (s, 1H), 4.70 (bs, 1H), 4.38 (bs, 1H), 2.98 – 2.88 (m, 1H), 2.55 (bs, 1H), 2.37 – 2.31 (m, 4H), 1.37 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 140.6, 138.4, 133.4, 130.0, 129.2, 128.7, 128.0, 126.8, 126.2, 79.5, 53.0, 47.0, 35.0, 28.3, 21.4.

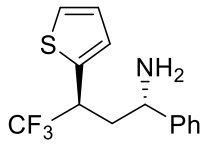
^{19}F NMR (376 MHz, $CDCl_3$) δ – 70.06 (s, CF_3).

HRMS (ESI) *m/z*: 416.1803 $[M+Na]^+$, $C_{22}H_{26}F_3NNaO_2^+$ requires 416.1808.

4,4,4-Trifluoro-1-phenyl-3-(thiophen-2-yl)butan-1-amine (38p)

The titled compound was obtained following GPC from **35p** (72.8 mg, 0.25 mmol) as a colourless oil (99% NMR yield). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4). The diastereomers were obtained in a ratio 73:27 in 99% yield. Minor diastereomer **(1*S*,3*S*)-38p** isolated 19.0 mg (0.07 mmol) 27% yield. Major diastereomer **(1*R*,3*S*)-38p** isolated 46.0 mg (0.16 mmol) 64% yield.

Minor diastereomer (configuration 1*S*, 3*S*)-38p

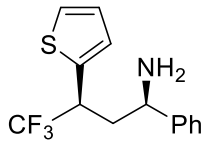


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 3H), 7.26 – 7.22 (m, 3H), 7.09 (d, *J* = 2.9 Hz, 1H), 7.05 (dd, *J* = 5.1, 3.5 Hz, 1H), 4.12 (dqd, *J* = 10.8, 9.2, 4.1 Hz, 1H), 3.67 (dd, *J* = 10.2, 4.1 Hz, 1H), 2.24 – 2.11 (m, 2H), 1.51 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 136.34 (Cq, *J* = 2.1 Hz), 128.7, 127.9, 127.2, 127.0, 126.3 (Cq, *J* = 279.5 Hz), 125.7, 125.6, 52.4, 42.8 (Cq, *J* = 28.4 Hz), 39.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 70.67 (d, *J* = 8.9 Hz, CF_3).

Major diastereomer (configuration 1*R*, 3*S*)-38p



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 4H), 7.24 – 7.22 (m, 2H), 7.03 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.96 (d, *J* = 3.3 Hz, 1H), 3.75 (dd, *J* = 10.0, 5.1 Hz, 1H), 3.28 (dtt, *J* = 17.8, 8.9, 4.5 Hz, 1H), 2.40 – 2.25 (m, 2H), 1.58 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 136.4 (q, *J* = 2.0 Hz), 128.9, 127.8, 127.7, 127.3, 126.9, 125.9 (Cq, *J* = 279.7 Hz), 125.7, 53.6, 42.9 (q, *J* = 28.5 Hz), 39.3.

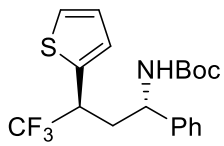
^{19}F NMR (376 MHz, $CDCl_3$) δ – 71.09 (d, *J* = 8.9 Hz, CF_3).

***tert*-Butyl (4,4,4-trifluoro-1-phenyl-3-(thiophen-2-yl)butyl)carbamate (38p')**

The titled compound was obtained following GPB from **38p** and purified by FCC using (pentane:EtOAc 95:5). Minor diastereomer **(1*S*,3*R*)-38p'**, isolated yield 99% (27.0 mg, 0.07 mmol) from 19.0 mg (0.07 mmol) of **38p**. Major diastereomer **(1*R*,3S)-38p'**, isolated yield 65% (40.1 mg, 0.10 mmol) from 46.0 mg (0.16 mmol) of **38p**.

The enantiomeric excess (minor isomer: 86%, major isomer 90%) was determined by HPLC (CHIRACEL® OD–H), hexane/iPrOH 98/2, 1 mL/min, λ = 210 nm, **1*S*,3*S*** (minor diastereomer): minor enantiomer, t_r = 6.1 min, major enantiomer, t_r = 7.5 min, **1*R*,3*S*** (major diastereomer): minor enantiomer t_r = 8.3 min, major enantiomer, t_r = 6.1 min.

Minor diastereomer (configuration 1*S*, 3*S*)-38p'



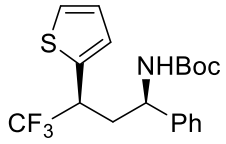
$[\alpha]_D^{25}$: – 37.0 (c 0.30, $CHCl_3$, *ee* 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 3H), 7.27 – 7.24 (m, 1H), 7.19 (d, *J* = 7.3 Hz, 1H), 7.06 – 7.04 (m, 2H), 4.77 (d, *J* = 9.4 Hz, 1H), 4.60 (bs, 1H), 3.83 (bs, 1H), 2.35 (t, *J* = 11.2 Hz, 1H), 2.25 (t, *J* = 11.5 Hz, 1H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 142.1, 135.6 (Cq, *J* = 2.0 Hz), 128.8, 128.5, 127.5, 127.0, 126.0, 125.8, 79.8, 51.5, 42.9 (Cq, *J* = 28.3 Hz), 38.2, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 70.63 (d, *J* = 9.0, CF_3).

Major diastereomer (configuration 1*R*, 3*S*)-38p'



$[\alpha]_D^{25}$: +5.3 (c 0.94, $CHCl_3$, *ee* 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 4H), 7.18 (d, *J* = 7.2 Hz, 2H), 7.05 – 7.00 (m, 2H), 4.75 (d, *J* = 4.8 H, 1H), 4.49 (bs, 1H), 3.24 (tt, *J* = 11.9, 8.8 Hz, 1H), 2.55 (bs, 1H), 2.37 (ddd, *J* = 13.5, 10.3, 3.3 Hz, 1H), 1.38 (s, 9H).

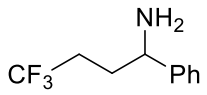
^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 140.2, 135.2, 129.1, 128.2, 127.9, 127.2, 127.0, 126.8, 126.0, 125.8 (Cq, *J* = 279.8 Hz), 79.7, 53.0, 42.6 (Cq, *J* = 28.7 Hz), 36.0, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ – 71.25 (d, *J* = 8.9 Hz, CF_3).

HRMS (ESI) *m/z*: 408.1197 $[M+Na]^+$, $C_{19}H_{22}F_3NNaO_2S^+$requires 408.1216.

4,4,4-Trifluoro-1-phenylbutan-1-amine (38q)

The titled compound was obtained following GPC from **35q** (50.3 mg, 0.25 mmol) as a colourless oil (99% NMR yield). The diastereomers were purified by FCC using (pentane:EtOAc 8:2 to 6:4).



Isolated yield 86% (40.1 mg, 0.22 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 2H), 7.29 – 7.25 (m, 3H), 3.94 (t, *J* = 6.8 Hz, 1H), 2.19 – 1.87 (m, 4H), 1.50 (bs. 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 128.8, 127.4, 127.2 (Cq, *J* = 274.3 Hz), 126.1, 55.1, 31.4 (Cq, *J* = 2.5 Hz), 30.86 (Cq, *J* = 28.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ – 66.19 (t, *J* = 10.7 Hz, CF_3).

HRMS (ESI) *m/z*: 187.0735 $[M+H]^+$, $C_{10}H_{10}F_3^+$ requires 187.0729.