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New Vinylogous Mannich-Type Reactions with Fluorinated Imines

Tesis Doctoral con Mención Internacional

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CERTIFICAN:

Que la presente Tesis Doctoral, titulada "**New Vinylogous-Type Reactions with Fluorinated Imines**", ha sido realizada bajo su dirección en el Departamento de Química Orgánica de la Universitat de València, por el licenciado en Química **Alvaro Sanz Vidal**, y autorizan su presentación para que sea calificada como Tesis Doctoral.

Valencia, Julio 2021

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Resumen

Los compuestos organofluorados juegan un papel relevante en química médica. Aproximadamente, el 25% de los fármacos que están actualmente en el mercado contienen al menos un átomo de flúor, lo que nos indica su extraordinaria importancia. Es un elemento de pequeño tamaño y alta electronegatividad, que una vez incorporado en la estructura del fármaco, mejora sus propiedades farmacocinéticas y fisicoquímicas, tales como la estabilidad metabólica o la lipofilia, lo que permite una mayor permeabilidad en las membranas celulares. Adicionalmente, la especie radioactiva de 18-F está emergiendo como un elemento clave en el diagnóstico por imagen, mediante la Tomografía de Emisión de Positrones (PET). Desde el descubrimiento de las propiedades antitumorales del 5-fluorouracilo, este elemento ha jugado un papel clave en el descubrimiento de nuevos fármacos, y ha estado siempre presente en los programas de química médica.

Sin embargo, los enlaces C-F son prácticamente desconocidos en la naturaleza, y eso indica que todos los compuestos organofluorados han de ser sintetizados en el laboratorio. Hasta la fecha, se han desarrollado una gran variedad de metodologías que permiten acceder a este tipo de compuestos que de forma general se pueden englobar en dos tipos. El primero consiste en una incorporación tardía de los átomos de flúor en las moléculas objetivo mediante el uso de reactivos de fluoración, que pueden ser tanto electrofílicos como nucleofílicos. La segunda forma general de acceder a este tipo de compuestos consiste en el empleo de lo que se denominan "building blocks fluorados". Son moléculas pequeñas que contienen átomos de flúor que se emplean como sillares para la generación de moléculas más complejas.

La presente Tesis Doctoral se centra en el desarrollo de nuevas metodologías que permitan acceder a nuevos esqueletos orgánicos fluorados, cuyo desarrollo tiene importantes implicaciones en química médica, como hemos indicado previamente. Específicamente, esta Tesis se enmarca en este segundo tipo de metodologías antes mencionado, que conlleva el empleo de moléculas fluoradas pequeñas, iminas fluoradas, que se han utilizado como sustratos para la creación de nuevas moléculas

fluoradas más complejas. Para ello, emplearemos un tipo de transformaciones, las reacciones de Mannich vinílogas, que hasta la fecha se han utilizado escasamente con sustratos fluorados. Los resultados obtenidos se recogen en los tres capítulos que se indican a continuación.

Capítulo 1: **Reacciones tipo Povarov con iminoésteres fluorados y furanos como donores vinílogos.**

Las reacciones de tipo aza-Friedel-Crafts asimétricas con iminas fluoradas conduce a la formación de aminas fluoradas enantiomericamente enriquecidas de forma sencilla. Estos compuestos son de gran importancia en química médica, sobre todo por tu atenuada basicidad inducida por el efecto electronegativo de los átomos de flúor.

Cuando esta reacción de lleva a cabo sobre iminoésteres como componente imínico del proceso, a pesar de la elevada electrofilia del carbono imínico por la presencia de dos sustituyentes electrón-atractores, ejemplos de la versión enantioselectiva son extraordinariamente escasos y suelen estar siempre involucrados los indoles como componentes heterocíclicos. Esto nos motivó a estudiar este tipo de procesos con otro tipo de heterociclos, específicamente los furanos.

La adición de estos a aldiminas fluoradas había sido descrita mediante catálisis con sales de oro. Por tanto, decidimos evaluar este proceso con imino ésteres con sales de oro como catalizadores. La serendipia en química juega un rol muy importante en el descubrimiento de nuevas transformaciones, y veremos que a lo largo de la presente memoria está presente varias veces en los resultados presentados. En este caso, no se obtuvo el producto esperado de alquilación de Friedel-Crafts, sino que tuvo lugar un proceso tándem Povarov/Friedel Crafts que condujo a la formación de derivados de furoquinolina fluorados con generación simultánea de cuatro estereocentros. Además de poseer la estructura heterocíclica antes mencionada, presente en varios compuestos con diversas actividades biológicas, estos compuestos constituyen una nueva familia de alfa-amino ácidos fluorados cíclicos.

La reacción transcurre de forma general con buenos rendimientos y diastereoselectividades moderadas. Sin embargo, el comportamiento cromatográfico de las mezclas ha permitido separar fácilmente el diastereoisómero mayoritario en todos los casos, proporcionando utilidad sintética a la metodología desarrollada.

En cuanto al alcance del proceso, éste es compatible con una gran variedad de imino ésteres fluorados, con distintas cadenas perfluoroalquílicas y una gran variedad de sustituyentes anclados al nitrógeno. Sin embargo, el alcance en lo que se refiere al furano tiene más limitaciones. Aunque se han conseguido buenos resultados con una gran variedad de ellos, hay sustratos que sorprendentemente no han dado resultados positivos, como son el 2-metoxifurano y el 2-trimetilsililoxifurano, dado en efecto electrón donor de los sustituyentes.

El transcurso de la reacción puede racionalizarse a través de una adición de Mannich vinílоga del furano sobre el imino éster, y un posterior ataque de la posición orto del sustituyente aromático del imino éster. La rearomatización del sistema genera el producto tipo Povarov. Este producto contiene una unidad dihidrofurano, que en presencia de la sal de oro isomeriza a la correspondiente sal de iminio susceptible de ser atacada por un segundo equivalente de furano. Aparentemente este último paso de la reacción tándem es el que hace viable el proceso, probablemente por su naturaleza irreversible.

***Capítulo 2:* Adiciones asimétricas de tipo Mannich-vinílоga de dicianoalquenos a sulfinil iminas fluoradas**

El segundo capítulo de la presente tesis doctoral se centra en el estudio de la reacción de Mannich vinílоga de α,α-dicianoalquenos como donores vinílogos y fluoroalquil sulfinil iminas como electrófilos.

Los dicianoalquenos son conocidos desde tiempos ancestrales por sus propiedades como aceptores de Michael. Sin embargo, esta tendencia ha cambiado desde el trabajo seminal de Jorgensen y Deng en 2005. Ambos autores encontraron que cuando estos compuestos poseen hidrógenos en posición gamma, pueden actuar como donores vinílogos frente a una gran variedad de electrófilos. Una de las reacciones más destacadas es con compuestos imínicos en presencia de varios catalizadores quirales, tanto métalicos como orgánicos. De esta manera, estos compuestos experimentan la reacción de Mannich vinílogа de manera enantioselectiva. Sin embargo, a pesar del desarrollo de este tipo de metodologías, no existían ejemplos en la bibliografía de esta reacción con iminas fluoradas. Esto nos llevó a evaluar la viabilidad de este proceso.

Los intentos iniciales fueron infructuosos, bien con imino ésteres o con aldiminas fluoradas. El cambio de tendencia se produjo cuando se emplearon N-sulfinil iminas como fuente electrófila. Estos compuestos ya habían mostrado su extraordinaria utilidad en la formación de una gran variedad de aminas fluoradas quirales mediante la adición sobre estas de una gran variedad de nucleófilos. Los dicianoalquenos se adicionaron a estas sulfinil iminas fluoradas con excelentes rendimientos y diastereoselectividades en presencia de terc-butóxido potásico como base. La reacción transcurre con una gran variedad de restos perfluoroalquilados en la función imina además de una gran variedad de diciano alquenos.

Este tipo de iminas fluoradas habían sido utilizadas por el Prof. Fen Lin-Qing en reacciones de tipo Mannich vinílogа, pero utilizando otro tipo de donores vinílogos. Un estudio detallado del proceso indicó que en nuestro caso se producía una diastereoselectividad contraria a los ejemplos antes mencionados. Esto indicaba claramente que el proceso tenía lugar con un transcurso estereoquímico distinto. En este contexto, habitualmente la estereoquímica de las adiciones de nucleófilos a sulfinil iminas fluoradas se racionaliza mediante un modelo de Felkin-Anh no quelado. Parece claro que para que se produzca una inversión de la configuración en el nuevo estereocentro generado en el proceso, es necesario que este tenga lugar por un mecanismo distinto, en este caso, a través de un modelo quelado. De esta manera, mediante la propuesta de un estado de transición de 6-miembros en el cual anión de potasio generado forma un quelato con el nitrógeno de la sulfinil imina, la adición ha de tener lugar por la cara contraria del grupo voluminoso del sulfóxido. Una prueba adicional que va en esta dirección es la reacción con disolventes polares como acetonitrilo o acetona, que dificultarían la formación de este quelato. Experimentalmente se observa que tiene lugar un descenso drástico de la diastereoselectividad.

Una de las características de la función diciano alqueno es que es susceptible de realizar derivatizaciones posteriores de las moléculas formadas. De hecho, son equivalentes sintéticos de la función cetona. Por otra parte, pueden ser hidrogenados o incluso pueden actuar en procesos de tipo Michael.

En este caso, previamente a todas estas transformaciones, el grupo sulfóxido se oxidó a la correspondiente sulfona. De esta forma, se puede eliminar la función dicianoalqueno para regenerar la cetona de partida. De la misma forma, se puede eliminar la función sulfinilo para generar las correspondientes aminas quirales. Otra reacción hatibualmente efectuada en este tipo de compuestos es la hidrogenación del doble enlace. Este proceso resultó más complejo de lo esperado, probablemente por la influencia de la unidad trifluorometilo. Finalmente, en un reactor de hidrogenación en condiciones de flujo (H-Cube) fue posible llevar a cabo esta hidrogenación que transcurría con una hidrogenación parcial de uno de los grupos ciano.

La última derivatización que se llevó a cabo fue un estudio de las reacciones de alquilación de los compuestos que proceden de dicianoalquenos no sustituidos en posición gamma. De esta forma, se encontraron condiciones que permitieron llevar a cabo una alquilación regioselectiva del dicianoalqueno, dando lugar al producto de alquilación gamma en presencia de NaH como base y al producto de alquilación alfa en presencia del fosfaceno P2-Et como base.

Capítulo 3: **Síntesis de trifluorometil arenos mediante reacción de dicianoalquenos y sulfinil iminas conjugadas fluoradas**

En el tercer capítulo se describe el estudio de la reacción de dicianoalquenos con iminas fluoradas conjugadas. Al igual que ocurría en el capítulo anterior, este tipo de reacciones vinílogas no había sido evaluado con anterioridad. En este caso, el proceso supone un reto mayor, ya que pueden aparecer problemas de regioselectividad tanto en el donor vinílogo como en el aceptor, donde puede tener lugar una adición 1,2 o 1,4. Los antecedentes bibliográficos de adiciones nucleófilas a sulfinil iminas fluoradas conjugadas indicaban que en todos los casos tiene lugar una adición 1,2. El objetivo inicial de este proyecto era modificar este tipo de reactividad mediante el uso de nucleófilos más blandos como es el caso de los dicianoalquenos a través de la posición gamma.

De nuevo, la serendipia entra en juego en este capítulo, ya que la reacción de dicianoalquenos a fluoroalquil sulfinil iminas fluoradas conjugadas conduce a la inesperada formación de los correspondientes trifluorometil arenos en un proceso de cicloaromatización con perdida final de las funciones sulfinil amina y diciano.

La unidad trifluorometil areno es una estructura aromática de gran importancia, ya que constituye un motivo recurrente en numerosos productos biológicamente activos y conocidos fármacos como el Januvia (sitagliptina), Celebrex (celecobix) o Prozac (Fluoxetina). Por esta razón, se han dedicado muchos esfuerzos para desarrollar metodologías sintéticas que permitan acceder a este tipo de compuestos. La gran mayoría de las metodologías descritas para acceder a este tipo de compuestos involucran una reacción de trifluorometilación aromática, mediante reactivos nucleofílicos o electrofílicos a partir de precursores que contienen halógenos, sales de diazonio, o ácidos borónicos entre otros. Casi todos ellos conllevan el uso de metales. Una metodología alternativa la constituyen los procesos de tipo Diels-Alder, aunque ha sido poco desarrollada dados los problemas de regioselectividad que muestran estos procesos. Un estudio bibliográfico más detallado indica que ejemplos de la formación de este tipo de compuestos mediante la generación simultánea del anillo aromático han sido muy escasos. La metodología desarrollada en este capítulo permite acceder a sistemas policíclicos que contienen la unidad trifluorometilareno, de forma sencilla mediante una creación de novo del anillo aromático.

El estudio de estas reacciones tuvo lugar inicialmente con iminas fluoradas con sustituyentes aromáticos en el nitrógeno tales como PMP (p-metoxifenilo) pero todas las bases ensayadas fueron infructuosas. De nuevo, la tendencia cambió con el uso de las sulfinil iminas de Ellman. En este caso, en presencia de DBU tuvo lugar un proceso de cicloaromatización que condujo a los productos aromáticos con buenos rendimientos. El estudio del alcance de la reacción nos permitió determinar que la función terc-butil sulfinil imina es clave en el proceso, ya que cualquier cambio en esa posición se traducía en el fallo del proceso. Por otro lado, una gran variedad de diciano alquenos como fuente vinílogа y de sulfinil iminas conjugadas fueron compatibles con el proceso.

Una posible explicación de la reacción de cicloaromatización comenzaría por una adición 1,4- de la posición gamma del dicianoalqueno sobre la sulfinil imina fluorada conjugada. Posteriormente, para formar el esqueleto del anillo aromático es necesario que tenga lugar ahora una adición alfa 1,2- del dicianoalqueno sobre la función imínica resultante. Esto nos permitiría explicar la conectividad de los productos finales. A partir de aquí, la aromatización conllevaría la pérdida de la función dicianoalqueno y de la función sulfinil amina. Ambos casos tienen precedentes en la literatura. La reacción de dicianoalquenos sobre cetonas conjugadas tiene lugar con una ciclación final y pérdida de la función dicianoalqueno mediante una beta-eliminación que generaría un doble enlace. El otro doble enlace restante tiene que formarse con la pérdida de la sulfinil amina, proceso que ha sido descrito recientemente por otros autores, aunque en un proceso distinto.

De esta forma, es importante señalar que este proceso se iniciaría con una adición gamma 1,4- del dicianoalqueno sobre la sulfinil imina conjugada, lo que constituye el primer ejemplo descrito en la bibliografía. De la misma forma, una doble adición alfa y gamma de un dicianoalqueno con pérdida final de la función diciano tampoco tiene precedentes en la literatura.

Abstract

The present doctoral thesis is devoted to the study of the vinylogous Mannich reaction with fluorinated imines and imino esters as electrophilic counterparts. Initially, furanes were the vinylogous donors of choice, and fluorinated imino esters the acceptors. In a second stage, dicyanoalkenes were used as vinylogous donors with fluorinated sulfinyl imines and finally, the reactivity of these dicyanoalkenes with fluorinated conjugated sulfinyl imines was evaluated.

In Chapter 1, the reaction of substituted furanes with fluorinated imino esters in the presence of gold salts give rise to a new family of fluorinated furoquinolines in good yields and moderate diastereoselectivities. This serendipitous finding involved a tandem Povarov-type reaction/formal Friedel Crafts reaction with the participation of two equivalents of the furane counterpart.

In Chapter 2, the asymmetric vinylogous Mannich reaction of dicyanoalkenes with fluorinated sulfinyl imines was developed. The process takes place with excellent levels of diastereoselectivity affording final products as single diasteroisomers. Finally, a derivatization of the finals products was performed, including elimination of the dicyanomoiety, elimination of the chiral auxiliary, hydrogenation and alkylation.

Finally, in Chapter 3, a novel tandem cycloaromatization protocol was identified in a serendipitous manner. The reaction of dicyanoalkenes with fluorinated sulfinyl imines rendered the corresponding trifluoromethyl arenes in good yields, very important compounds in medicinal chemistry. The reaction involved a formal [3+3] formal cycloaddition with concomitant elimination of the sulfinyl amine and dicyano moieties, process with no precedents in the literature.

List of abbreviations

[O]	oxidant
Å	ångströms
Ac	acetyl
AMY	Azomethine Ylide
aq	aqueous
Ar	aryl
atm	atmospheres
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOX	bisoxazoline
br	broad
Bu	butyl
Bz	benzoyl
CAN	cerium ammonium nitrate
cat.	catalyst
Cbz	benzyloxycarbonyl
CM	cross metathesis
Conv.	conversion
Cy	cyclohexyl
δ	chemical shift
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	density functional theory
DMF	*N,N*-dimethyl formamide
DMSO	dimethyl sulfoxide
DOS	diversity-oriented synthesis
dr	diastereomeric ratio

E	electrophile
e.g.	for example
ee	enantiomeric excess
equiv	equivalents
er	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl
EWG	electron-withdrawing group
FCA	Friedel-Crafts Alkylation
FG	functional group
FMO	Frontier Molecular Orbital
g	grams
gem	geminal
h	hours
HG-II	second generation Hoveyda-Grubbs catalyst
HIV	human immunodeficiency vir-us
HOESY	(Two-dimensional) Heteronuclear Overhauser Effect
HOMO	Highest Occupied Molecular Orbital
HPLC	high-performance liquid chro-matography
HQN-NH$_2$	9-amino-(9-deoxy)*epi*-hydroquinine
HRMS	high-resolution mass spectro-metry
HTS	High-Throughput Screening
Hz	Hertz
IBA	Indolizidine-based alkaloids
i.e.	in other words
INCR	Intramolecular Nitrone Cycloaddition Reaction
***i*-Pr**	isopropyl
L	ligand
LUMO	Lowest Occupied Molecular Orbital
m	*meta*
M	molar
m	multiplet

Me	methyl
mg	milligram
min	minutes
mmol	millimole
mL	millilitre
mp	melting point
Ms	mesyl, methanesulfonyl
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
N	normal
NCI	Non-Covalent Interactions
NME	new molecular entity
NMR	nuclear magnetic resonance
Nu	nucleophile
o	*ortho*
°C	degrees Celsius
p	*para*
PCC	pyridinium chlorochromate
Pent	pentyl
P_2Et	phosphazene superbase
Ph	phenyl
ppm	parts per million
q	quartet
QTOF	quadrupole time-of-flight
r.t.	room temperature
RCM	ring-closing metathesis
R^F	fluorine-containing substitute-nt
s	singlet
sat	saturated
SM	starting material
SOMO	Single Occupied Molecular Orbital
t	triplet

***t*-Bu**	*tert*-butyl
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TIPS	triisopropyl silyl
TMS	trimethyl silyl
TRIP	2,4,6-tri(isopropyl)phenyl
Ts	tosyl, toluenesulfonyl
TS	transition state
UV	ultraviolet
µwaves	microwave irradiation

Summary

General Introduction

General Objetcives

Chapter 1

Chapter2

Chapter 3

Bibliography

General Introduction

I.1. Fluorine in Organic and Medicinal Chemistry

Within the pharmaceutical industry, the number of new drugs introduced into the market has been clearly reduced compared to the investment set aside for that aim (Figure I.1). The generation of *new chemical entities* (NCEs, i.e. original structural skeletons capable of interacting with a therapeutic target) is currently one of the most important bottlenecks along the drug discovery process. Arguably, the design of new synthetic methodologies leading to the generation of diverse molecular scaffolds represents one of the most significant goals of chemical research.

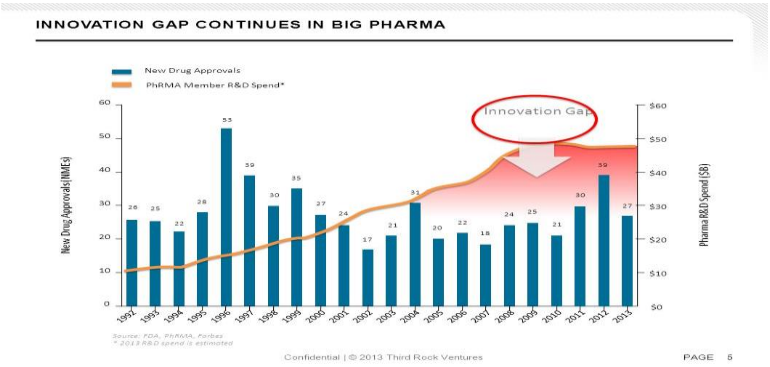

Figure I.1. Marketed drugs *vs* R&D investments over the last years (1992-2013).

Among this new molecular scaffolds, over the past few decades, fluorinated organic entities have gain considerable attention in organic and medicinal chemistry. It is well known that up to 20% of the marketed drugs[1] contain fluorine atoms in their structures (Figure I.2). For instance, Fluoxetine (*Prozac*©)[2] used in depression treatments, Efavirenz (*Sustiva*©)[3] as reverse transcriptase inhibitor in HIV treatments, Fluticasone (*Seretide*©)

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[1] (a) J. Wang; M. Sánchez-Roselló; J. L. Aceña; C. del Pozo; A. E. Sorochinsky; S. Fustero; V. A. Soloshonok; H. Liu, *Chem. Rev.,* **2014,** *114*, 2432-2506; (b) Y. Zhou; J. Wang; Z. Gu; S. Wang; W. Zhu; J. L. Aceña; V. A. Soloshonok; K. Izawa; H. Liu, *Chem. Rev.,* **2016,** *116*, 422-518; (c) S. Purser; P. R. Moore; S. Swallow; V. Gouverneur, *Chem. Soc. Rev.,* **2008,** *37*, 320-330; (d) H. Mei; J. Han; S. Fustero; M. Medio-Simon; D. M. Sedgwick; C. Santi; R. Ruzziconi; V. A. Soloshonok, *Chem. Eur. J.,* **2019,** *25*, 11797-11819; (e) J.-P. Bégué; D. Bonnet-Delpon, *J. Fluorine Chem.,* **2006,** *127*, 992-1012; (f) C. Isanbor; D. O'Hagan, *J. Fluorine Chem.,* **2006,** *127*, 303-319; (g) K. L. Kirk, *J. Fluorine Chem.,* **2006,** *127*, 1013-1029; (h) W. K. Hagmann, *J. Med. Chem.,* **2008,** *51*, 4359-4369.

[2] B. S. Molloy, K., US 4018895, **1997**.

[3] M. Patel; S. S. Ko; R. J. McHugh; J. A. Markwalder; A. S. Srivastava; B. C. Cordova; R. M. Klabe; S. Erickson-Viitanen; G. L. Trainor; S. P. Seitz, *Bioor. Med. Chem. Let.,* **1999,** *9*, 2805-2810.

by GSK or Rosuvastatin (*Crestor*©) developed by AstraZeneca, for cholesterol reduction treatments, have been in the worldwide top-ten selling drugs in the late years (Figure I.3). The beneficial effect that fluorine substitution may have on the pharmacological and pharmacokinetic properties of lead molecules has been demonstrated.[4] Arguably, fluorine has played a "key" role in the growth and development of medicinal chemistry, providing great advances in drug discovery.

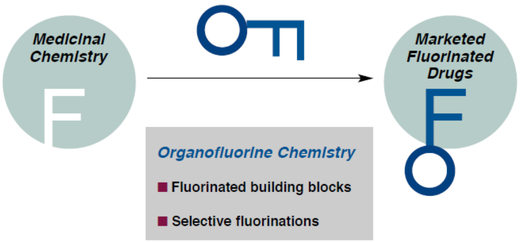

Figure I.2. The "key" role of fluorine in Medicinal Chemistry.

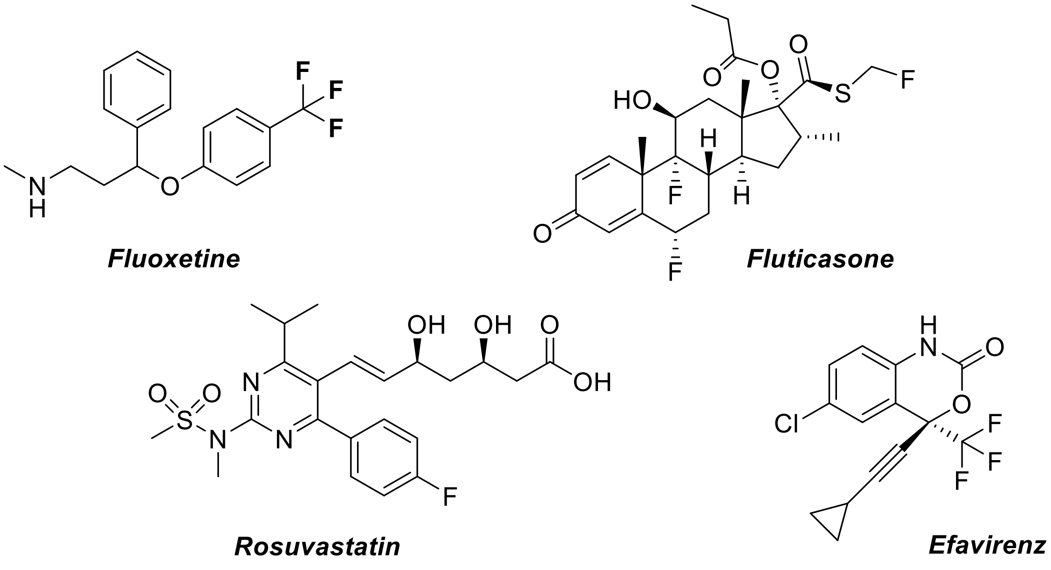

Figure I.3. Top-selling fluorinated drugs.

Fluorine is the most electronegative element in the periodic table, and it possesses a moderate size, which confers to the C-F bond a highly polarised character. As a result, the electronic distribution is affected, changing the acid-base properties of adjoining functional groups, its reactivity or even the whole molecule stability.[5] Another

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[4] K. Müller; C. Faeh; F. Diederich, *Science,* **2007,** *317*, 1881-1886.

[5] (a) R. E. Banks; B. E. Smart; J. C. Tatlow, *Organofluorine Chemistry, Principles and Commercial Applications*. **1994**; (b) D. O'Hagan, *Chem. Soc. Rev.,* **2008,** *37*, 308-319.

peculiarity of fluorinated moieties, consequence of its high electronic density is their capacity to establish hydrogen-bonds. Moreover, the Van der Waals radius of the fluorine atom is similar enough to hydrogen, allowing the exchange between them without a significant increase of steric hindrance.

As a result, biological properties of molecules, including lipophilicity, bioavailability and metabolic stability, can be modulated by the introduction of fluorine atoms.[5b,6] The beneficial effect of fluorine substitution has not been restricted to medicinal chemistry, finding increasing applications in other industrial areas such as agrochemistry and material sciences.

More specifically, the introduction of fluorine into molecules with biological activity could cause effects such as:

a) ***Biological mechanisms blocked through hydrogen bonding interactions***. Drugs activity depends on their binding to an enzyme through hydrogen bonds. The substitution of some hydrogen atoms by fluorine can intensify this substrate-enzyme binding, blocking its metabolism and preventing the natural enzyme mechanism. A great example of that is the *5-Fluorourcil* (antitumor agent), which inhibits the *Thymidylate Synthase* by means of an irreversible bonding between substrate and enzyme, impeding the formation of *thymidylic acid*, DNA essential component.

b) ***Peptidic bonds stabilisation***, as a consequence of the effect of the fluorine in the reactivity of adjacent functional groups, achieving a delay on enzymatic degradation. For instance, *4-fluoroglutamic acid* has been employed in the synthesis of antitumor *Methotrexate*, in which the presence of fluorine increases the acidity of the contiguous carboxylic acid and stabilises the peptidic bond with the enzyme. This more stabilised bond confers stability to the substrate-enzyme system, allowing lower doses for its administration and reducing the toxicity.

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[6] (a) Q. A. Huchet; B. Kuhn; B. Wagner; N. A. Kratochwil; H. Fischer; M. Kansy; D. Zimmerli; E. M. Carreira; K. Müller, *J. Med. Chem.,* **2015,** *58*, 9041-9060; (b) E. P. Gillis; K. J. Eastman; M. D. Hill; D. J. Donnelly; N. A. Meanwell, *J. Med. Chem.,* **2015,** *58*, 8315-8359.

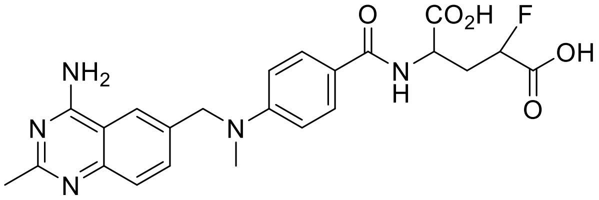

Figure I.4. Methotrexate.

c) Increase of lipophilicity and bioavailability. Controlling lipophilicity has shown to be essential for improving the prospect of drug candidates. Therefore, it has been suggested that successful drug development is associated with keeping the molecular lipophilicity of the drug candidates within optimal boundaries during the affinity optimization process. Incorporation of fluorine into drug molecules is a commonly used tactic to modulate lipophilicity.[7] Whereas it is still frequently stated that fluorination increases lipophilicity, this is typically limited to aromatic substrates, and the influence of aliphatic fluorination on lipophilicity is more complex.[8] In general, the ability of fluorine to maintain low lipophilicity levels while increasing molecular weight is regarded as one of the keys to a successful drug-discovery program.

This property focuses its significance in drugs acting in Central Nervous System. Increasing lipophilicity of some compound facilitates them to surpass the blood-brain barrier. It englobes most antidepressants, like *Fluoxetine* (Figure I.3).

Despite fluorine is the 13th most abundant element in the Earth's crust, its presence in natural organic molecules is highly limited,[9] and most of fluorinated organic molecules are synthetic. For that reason, the study and development of new methodologies to access fluorine-containing organic structures is at the forefront of chemical research.

Two different strategies are commonly used in the development of new protocols to access new fluorinated organic molecules. On the one hand, the use of either nucleophilic, electrophilic or radical reagents to selectively incorporate fluorine atoms

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[7] B. Linclau; Z. Wang; G. Compain; V. Paumelle; C. Q. Fontenelle; N. Wells; A. Weymouth-Wilson, *Angew. Chem. Int. Ed.,* **2016,** *55*, 674-678.

[8] (a) B. Jeffries; Z. Wang; H. R. Felstead; J.-Y. Le Questel; J. S. Scott; E. Chiarparin; J. Graton; B. Linclau, *J. Med. Chem.,* **2020,** *63*, 1002-1031; (b) J. St-Gelais; M. Bouchard; V. Denavit; D. Giguère, *J. Org. Chem.,* **2019,** *84*, 8509-8522.

[9] (a) D.-Z. Liu; J.-K. Liu, *Nat. Prod. Bioprosp.,* **2013,** *3*, 161-206; (b) D. B. Harper; D. O'Hagan, *Nat. Prod. Rep.,* **1994,** *11*, 123-133; (c) N. Jaivel; C. Uvarani; R. Rajesh; D. Velmurugan; P. Marimuthu, *J. Nat. Prod.,* **2015,** *78*, 343-343.

into specific positions of an organic framework.[10] This strategy is usually more challenging, given the chemoselectivity handicap. Among the nucleophilic reagents, DAST[11] and Deoxofluor,[12] besides more recently developed PhenoFluor[13] and PyFluor,[14] are commonly employed in deoxyfluorination reactions, converting alcohols and carbonyls into fluorinated motif and trimethyl(trifluoromethyl)silane ($TMSCF_3$; Ruppert-Prakash reagent)[15] efficiently performs trifluoromethylation reactions (Figure I.5).

Electrophilic fluorination reactions are also feasible with reagents such as N-fluorobenzenesulfonimide (NFSI)[16], 1-chloromethyl-4-fluorodiazoniobicyclo[2.2.2]octane bis(tetra-fluoroborate) (Selectfluor)[17] or selective trifluoromethylating reagents like hypervalent iodine compounds (Togni's reagent) (Figure I.5).[18]

However, while electrophilic and nucleophilic fluorinations have been extensively developed over the last century, practical methods for selective radical fluorination were clearly underdeveloped. Some elegant solutions using free radical strategy have been reported, but electrophilic fluorinating agents such as Selectfluor or NFSI were employed as fluorine atom transfer reagents by electron transfer reactions.[19]

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[10] (a) J.-A. Ma; S. Li, *Org. Chem. Front.,* **2014,** *1*, 712-715; (b) V. Bizet; T. Besset; J. A. Ma; D. Cahard, *Curr. Top. Med. Chem.,* **2014,** *14*, 901-940; (c) X. Yang; T. Wu; R. J. Phipps; F. D. Toste, *Chem. Rev.,* **2015,** *115*, 826-870; (d) P. A. Champagne; J. Desroches; J. D. Hamel; M. Vandamme; J. F. Paquin, *Chem. Rev.,* **2015,** *115*, 9073-9174.

[11] (a) W. J. Middleton; E. M. Bingham, *J. Org. Chem.,* **1980,** *45*, 2883-2887; (b) W. J. Middleton, *J. Org. Chem.,* **1975,** *40*, 574-578.

[12] (a) Y. R. Mirzaei; B. Twamley; J. M. Shreeve, *J. Org. Chem.,* **2002,** *67*, 9340-9345; (b) G. S. Lal; G. P. Pez; R. J. Pesaresi; F. M. Prozonic, *Chem. Commun.,* **1999**, 215-216.

[13] F. Sladojevich; S. I. Arlow; P. Tang; T. Ritter, *J. Am. Chem. Soc.,* **2013,** *135*, 2470-2473.

[14] M. K. Nielsen; C. R. Ugaz; W. Li; A. G. Doyle, *J. Am. Chem. Soc.,* **2015,** *137*, 9571-9574.

[15] (a) I. Ruppert; K. Schlich; W. Volbach, *Tetrahedron Lett.,* **1984,** *25*, 2195-2198; (b) R. Krishnamurti; D. R. Bellew; G. K. S. Prakash, *J. Org. Chem.,* **1991,** *56*, 984-989; (c) G. K. S. Prakash; A. K. Yudin, *Chem. Rev.,* **1997,** *97*, 757-786.

[16] P. Kirsch, *Modern Fluoroorganic Chemistry*. Wiley-VCH: **2004**.

[17] R. E. Banks, *J. Fluorine Chem.,* **1998,** *87*, 1-17.

[18] P. Eisenberger; S. Gischig; A. Togni, *Chem. Eur. J.,* **2006,** *12*, 2579-2586.

[19] (a) B. Lantaño; A. Postigo, *Organic & Biomolecular Chemistry,* **2017,** *15*, 9954-9973; (b) M. P. Sibi; Y. Landais, *Angew. Chem. Int. Ed.,* **2013,** *52*, 3570-3572.

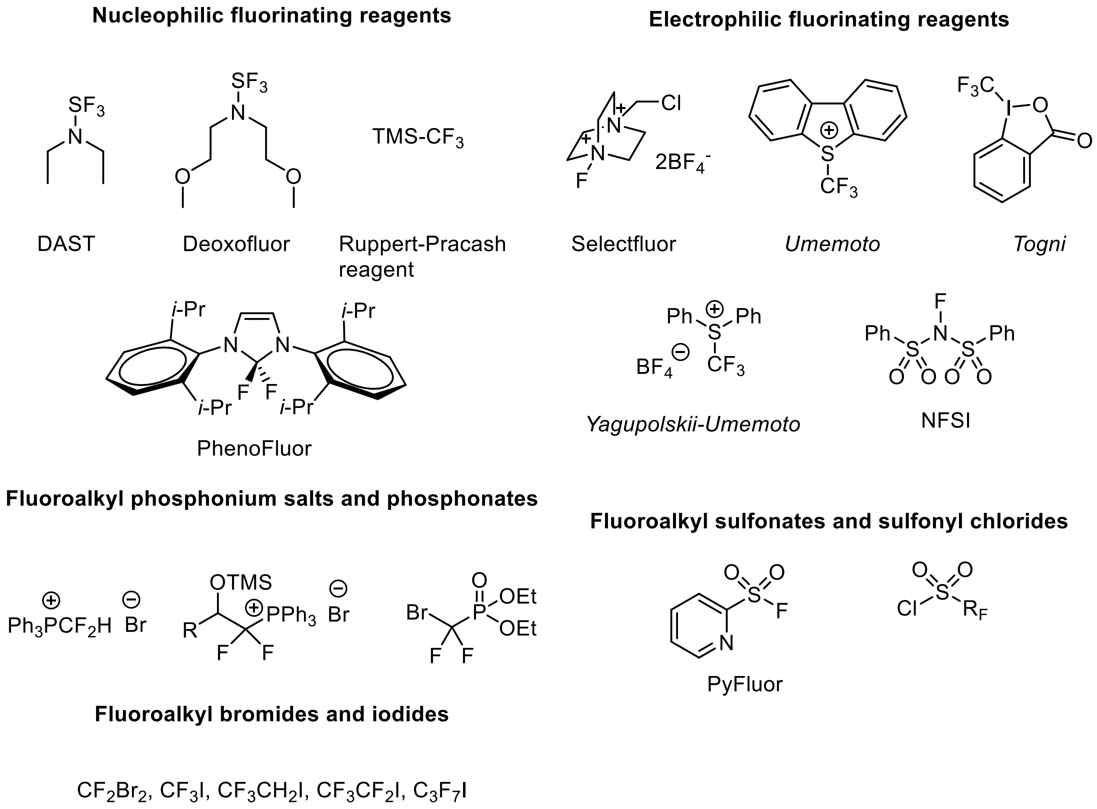

Figure I.5. Different fluorinating reagents.

With the advent of the photoredox catalysis this scenario changed dramatically.[20] The photoredox catalysis methodology has proven to be especially well-suited for the generation of fluoroalkyl radicals. Thus, the direct generation of electron-deficient carbon-centered fluoroalkyl radical intermediates by means of commonly employed ruthenium- or iridium-based photocatalysts become in the last few years a fundamental tool for the late stage incorporation of fluorinated moieties into organic molecules. Numerous publications in the last four years demonstrate the impressive research activity in this area.[21] A wide variety of fluorinated radical precursors such us fluoroalkyl phosphonium salts and phosphonates, fluoroalkyl halides and fluoroalkyl sulfonates and sulfonyl chlorides among others (Figure I.5) have been reported to date, since commonly used photocatalysts usually have potential as one-electron reductants strong enough to reduce those precursors, resulting in the generation of the corresponding radicals which

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[20] A breakthrough in this field was due to the development by MacMillan and You of the $[Ru(bpy)_3]Cl_2$ photocatalyst: (a) M. A. Ischay; M. E. Anzovino; J. Du; T. P. Yoon, *J. Am. Chem. Soc.,* **2008,** *130*, 12886-12887; (b) D. A. Nicewicz; D. W. C. MacMillan, *Science,* **2008,** *322*, 77-80.

[21] Recent reviews: (a) T. Chatterjee; N. Iqbal; Y. You; E. J. Cho, *Acc Chem Res,* **2016,** *49*, 2284-2294; (b) A. Arora; J. D. Weaver, *Acc. Chem. Res,* **2016,** *49*, 2273-2283.

will then participate in effective and selective fluoroalkylation reactions under mild reaction conditions.

On the other hand, a more versatile strategy is based on the use of simple fluorine-containing entities as building blocks,[22] constructing the new molecule around these fluorinated scaffolds. Although standard experimental procedures are applicable, the presence of fluorine may lead to unexpected reactivity or selectivity issues in comparison with their non-fluorinated counterparts. However, this strategy has been proved, in general, more prosperous than direct fluorination, since it displays a higher range of reactivity and functional groups tolerance.

In order to consider a small molecule as a potential building block it must be easily available, stable, easy to prepare on a relatively large scale and multifunctional for its use in different syntheses. Among others, fluorinated imidoyl halides, imines, acrylic acid derivatives, alkynes, nitriles and 1,3-diketones feature these properties (Figure I.6); with most of them being widely used for the preparation of nitrogen-containing organofluorine compounds.

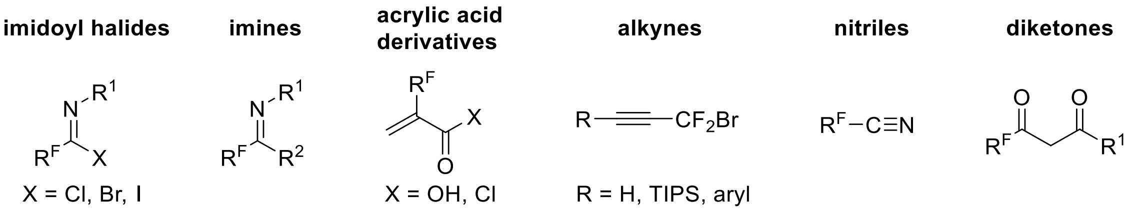

Figure I.6. Fluorinated building blocks.

Most of the molecules in nature contain nitrogen atoms. Therefore, the employment of fluorinated building blocks incorporating nitrogen to the final structure has become a highly useful tool in the late years for the preparation of new fluorinated compounds with potential biological and medicinal applications. For instance, fluorinated α- and β-

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[22] (a) S. Fustero; J. F. Sanz-Cervera; J. L. Aceña; M. Sánchez-Roselló, *Synlett,* **2009,** *2009*, 525-549; (b) W. Dmowski, *J. Fluorine Chem.,* **2012,** *142*, 6-13; (c) W. Dmowski, *J. Fluorine Chem.,* **2011,** *132*, 504-511; (d) M. C. Pacheco; S. Purser; V. Gouverneur, *Chem. Rev.,* **2008,** *108*, 1943-1981; (e) M. F. Kuehnel; D. Lentz; T. Braun, *Angew. Chem. Int. Ed.,* **2013,** *52*, 3328-3348.

aminoalcohols and amino acids have biological properties that makes them versatile intermediates in organic synthesis.[23]

In this context, one of the most popular building blocks for the preparation of fluorinated nitrogen-containing scaffolds are the fluorinated imines. The popularity of this family of building blocks remains in the high reactivity profile they show in different reaction pathways. Hence, florinated imines will define one of the scientific pillars of this thesis.

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[23] (a) S. Fustero; J.-F. Sanz-Cervera; C. del Pozo; Aceña; J.-L., Nitrogen-Containing Organofluorine Compounds Through Metathesis Reactions, In Current Fluoroorganic Chemistry: New Synthetic Directions, Technologies, Materials, and Biological Applications. In *ACS Symposium Series* Soloshonok, V.; Mikami, K.; Yamazaki, T.; Welch, J. T.; Honek, J., Eds., Eds. American Chemical Society: Washington DC: **2007**; pp 54–68; (b) S. Fustero; J.-F. Sanz-Cervera; C. del Pozo; Aceña; J.-L., Nitrogen-Containing Organofluorine Compounds Through Metathesis Reactions, In Current Fluoroorganic Chemistry: New Synthetic Directions, Technologies, Materials, and Biological Applications. In *ACS Symposium Series*, Soloshonok, V.; Mikami, K.; Yamazaki, T.; Welch, J. T.; Honek, J., Eds., Eds. American Chemical Society: Washington DC: **2007**; pp 54–68.

I.2. Fluorinated Imines

Fluorine-containing imines are commonly prepared from the corresponding fluorinated carbonyl precursors through condensation with substituted amines. Given the electron-withdrawing character of fluorine, substitution at the α-position enhances the electrophilicity of the carbon-nitrogen double bond as compared to their non-fluorinated counterparts. Hence, the addition of a wide range of nucleophilic reagents to fluoroalkyl-substituted imines is an efficient method for preparing fluorinated amines, even in an asymmetric fashion.[24]

For the sake of a better understanding of this thesis, we will divide the whole family of fluorinated imines in three different groups depending on the nature of the substituents at the iminic carbon.

I.2.1. Fluorinated α-imino esters

They represent a highly versatile group of imines, principally because of the great electrophilicity that an ester group, together with a fluorinated moiety, ascribes to the iminic carbon, disclosing the addition of a wide range of soft nucleophiles.

To the best of our knowledge, only a few methodologies have been described to prepare this type of imines. Uneyama and co-workers reported a palladium-catalysed alkoxycarbonylation of imidoyl iodides to give fluorinated α-imino esters under mild conditions (Scheme I.1, left).[25] In addition, these imines can be prepared from fluorinated α-keto esters via an aza-Wittig reaction,[26] avoiding the employment of transition metals and CO. Likewise, the condensation of carbamates[27] or amines[28] with trifluoropiruvates gives access to fluorinated imino esters in a straightforward manner

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[24] (a) J. P. Begue; D. Bonnet-Delpon; B. Crousse; J. Legros, *Chem Soc Rev,* **2005,** *34*, 562-572; (b) A. Roy; F. Gosselin; P. D. O'Shea; C.-Y. Chen, *J. Org. Chem.,* **2006,** *71*, 4320-4323; (c) V. L. Truong; M. S. Menard; I. Dion, *Org. Lett.,* **2007,** *9*, 683-695; (d) C. Lauzon; A. B. Charette, *Org. Lett.,* **2006,** *8*, 2743-2745.

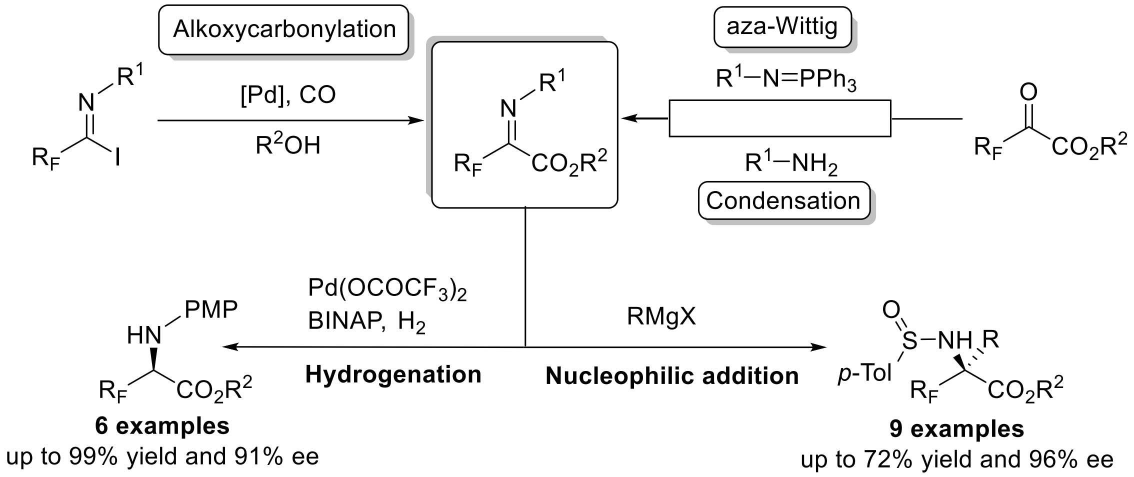
[25] (a) H. Amii; Y. Kishikawa; K. Kageyama; K. Uneyama, *J. Org. Chem.,* **2000,** *65*, 3404-3408; (b) H. Watanabe; Y. Hashizume; K. Uneyama, *Tetrahedron Lett.,* **1992,** *33*, 4333-4336.

[26] A. Asensio; P. Bravo; M. Crucianelli; A. Farina; S. Fustero; J. G. Soler; S. V. Meille; W. Panzeri; F. Viani; A. Volonterio; M. Zanda, *Eur. J. Org. Chem.,* **2001,** 1449-1458.

[27] N. Osipov; A. S. Golubev; N. Sewald; T. Michel; A. F. Kolomiets; A. V. Fokin; K. Burger, *J. Org. Chem.,* **1996,** *61*, 7521-7528.

[28] (a) M. Abid; L. Teixeira; B. Török, *Org. Lett.,* **2008,** *10*, 933-935; (b) G. Chaume; M.-C. Van Severen; S. Marinkovic; T. Brigaud, *Org. Lett.,* **2006,** *8*, 6123-6126.

(Scheme I.1, right), although in this case the methodology is restricted to trifluoromethyl imines.



Scheme I.1. Synthesis and reactivity of fluorinated α-imino esters.

These fluorinated α-imino esters entail a great versatility for the synthesis of different biologically relevant structures. For instance, they are valuable synthetic intermediates for the preparation of β-fluorinated α-amino acids by asymmetric hydrogenation, as Uneyama and co-workers reported (Scheme I.1, down).[29] They are also a convenient source of chiral quaternary α-fluoroalkyl-substituted amino acids. Such interesting molecules are usually achieved using chiral protecting groups on the nitrogen atom to control the stereoselective nucleophilic addition to the iminic carbon. Fustero and co-workers reported the preparation of enantiopure trifluoromethyl-containing amino acids starting from α-trifluoromethyl imino esters (Scheme I.1, down).[20]

I.2.2. Fluorinated aldimines

A different class of fluorinated building blocks, with reduced electrophilicity as compared to α-imino esters are fluorinated aldimines. However, these type of imines are also useful building blocks in the design and synthesis of fluorinated amines and α-amino acids.[30]

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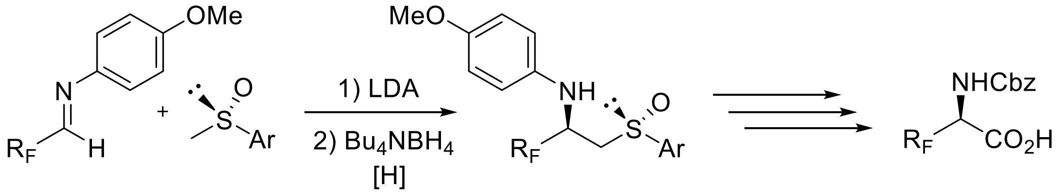
[29] H. Abe; H. Amii; K. Uneyama, *Org. Lett.,* **2001,** *3*, 313-315.

[30] (a) H. Mei; C. Xie; J. Han; V. A. Soloshonok, *Eur. J. Org. Chem.,* **2016,** *2016*, 5917-5932; (b) P. Bravo; M. Guidetti; F. Viani; M. Zanda; A. L. Markovsky; A. E. Sorochinsky; I. V. Soloshonok; V. A. Soloshonok, *Tetrahedron,* **1998,** *54*, 12789-12806.

A great example of this is the enantioselective synthesis of α-fluoroalkyl amino acids reported by our research group in 2001.[31] Starting from the corresponding fluorinated aldimine and, after a few steps, the desired amino acids bearing a fluorinated moiety in the α-position were successfully achieved with high levels of enantioselectivity by intramolecular π-stacking interactions of 1-naphthylsulfinyl (Ar) and *N*-aryl groups (Scheme I.2).



Scheme I.2. Enantioselective synthesis of α-fluoroalkyl amino acids by Fustero.

In particular, *N-tert*-butylsulfynil imines, inspired by the seminal work of Ellman,[32] which possess remarkable stereo-controlling properties and increased reactivity, can be used for the selective and efficient installation of α-trifluoromethyl aminoalkyl moieties. As demonstrated by numerous research groups,[33] trifluoromethyl-aldimines easily react with virtually any type of nucleophiles, being great reaction partners for Baylis-Hillman and Friedel-Crafts reactions, among others, affording fluorinated nitrogen-containing compounds with excellent yields and diastereoselectivities.

I.2.3. Fluorinated ketimines

Fluorinated ketimines, (usually prepared by an aza-Wittig reaction of the fluorinated alkyl ketones and iminophosphoranes, as described above in Scheme 1), are also common precursors for the synthesis of fluorine-containing interesting scaffolds. The presence of an aromatic or an alkyl moiety in the iminic carbon considerably reduces its electrophilicity, narrowing down the realm of different nucleophilic reagents allowed

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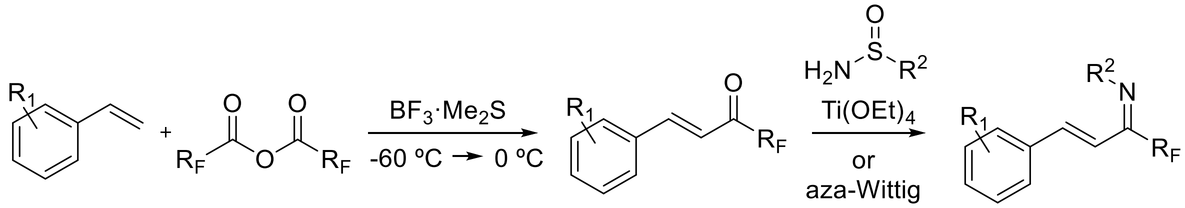
[31] S. Fustero; A. Navarro; B. Pina; J. G. Soler; A. Bartolomé; A. Asensio; A. Simón; P. Bravo; G. Fronza; A. Volonterio; M. Zanda, *Org. Lett.,* **2001,** *3*, 2621-2624.

[32] (a) J. A. Ellman; T. D. Owens; T. P. Tang, *Acc. Chem. Res.,* **2002,** *35*, 984-995; (b) M. T. Robak; M. A. Herbage; J. A. Ellman, *Chem. Rev.,* **2010,** *110*, 3600-3740.

[33] (a) H. Mei; C. Xie; J. Han; V. A. Soloshonok, *Eur. J. Org. Chem.,* **2016,** *2016*, 5917-5932; (b) J. Liu; J. Hu, *Fut. Med. Chem.,* **2009,** *1*, 875-888; (c) A. E. Sorochinsky; V. A. Soloshonok, *J. Fluorine Chem.,* **2010,** *131*, 127-139; (d) L. Wu; C. Xie; J. Zhou; H. Mei; V. A. Soloshonok; J. Han; Y. Pan, *J. Fluorine Chem.,* **2015,** *170*, 57-65; (e) S. Fioravanti, *Tetrahedron,* **2016,** *72*, 4449-4489.

for the addition into the imine. However, the addition of a wide variety of nucleophiles to these types of imines have been described.[34]

Despite the high versatility of those fluorinated building blocks, the use of conjugated fluorinated ketimines lagged behind, and only a few reports regarding its reactivity have been published to date. They can be prepared from the corresponding fluorinated conjugated ketones, in turn prepared by addition of styrene to fluorine-containing anhydrides. Condensation with sulfinamides or aza-Wittig reaction with the corresponding phosphazene give access to the conjugated imines, as depicted in Scheme I.3.



Scheme I.3. General procedure for the synthesis of fluorinated conjugated imines.

This family of imines, less studied than its non-conjugated analogues, possesses several peculiarities that makes them highly interesting. The electronic conjugation of the imine displays a new reactive site against nucleophilic reagents, enhancing the synthetic possibilities for the use of these imines as versatile building blocks. They will be treated in more detail in chapter 3 of the present work.

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[34] For recent examples of the use of fluorinated ketimines, see: (a) M.-W. Chen; Q. Yang; Z. Deng; Y. Zhou; Q. Ding; Y. Peng, *J. Org. Chem.,* **2018,** *83*, 8688-8694; (b) M. Urban; M. Franc; M. Hofmanová; I. Císařová; J. Veselý, *Org. Biomol. Chem.,* **2017,** *15*, 9071-9076; (c) M.-W. Chen; B. Wu; Z.-P. Chen; L. Shi; Y.-G. Zhou, *Org. Lett.,* **2016,** *18*, 4650-4653; (d) M.-W. Chen; X. Mao; Y. Ji; J. Yuan; Z. Deng; Y. Peng, *Tetrahedron Lett.,* **2019,** *60*, 151280.

I.3. The vinilogous Mannich Reaction

The Mannich reaction has been thoroughly studied over the years, with countless applications and variants granting it as an efficient and useful tool in organic synthesis. Mannich-type reactions have been widely employed in the past years for the formation of fluorinated α-amino acid derivatives and other fluoroalkyl amines from imines. For instance, fluoro-substituted imines are common Mannich acceptors for the synthesis of fluorinated β-amino carbonyl compounds.[35]

Its vinylogous counterpart, i.e. the conjugate extension of the nucleophilic addition of carbon enolates to imines or iminium salts, has attracted ever-increasing attention in recent years, with outstanding results in both methodology- and target-oriented endeavours.[36]

Since the vinylogous Mannich reaction (VMR) constitutes, together with fluorinated imines, the two pillars of the present dissertation, we will describe this transformation in more detail. We will focus specifically in the asymmetric version of the VMR.[37] In this context, and due to the great variety of possible VMRs, we will categorise them focusing on the nature of the different pronucleophiles employed, namely 2-silyloxyfurans and 2-silyloxypyrroles (section **I.3.1.**), acyclic silyl dienolates (section **I.3.2.**), γ-butenolides and butyrolactams (section **I.3.3.**) or α,α-dicyanoolefins (section **I.3.4.**).

I.3.1. Reactions with 2-silyloxyfurans and 2-silyloxypirroles.

One of the main challenges in the development of VMRs lies in achieving high levels of γ-regioselectivity over α-addition. In this regard, 2-silyloxyfurans entail a very useful group of pronucleophiles due to the more electronically favoured γ-carbon addition in comparison to the reaction through the α-carbon.[38]

In this context, Hoveyda and Snapper designed a practical protocol for the Ag-catalysed enantioselective VMR of aryl-substituted aldimines and 2-trimethylsilyloxyfurans

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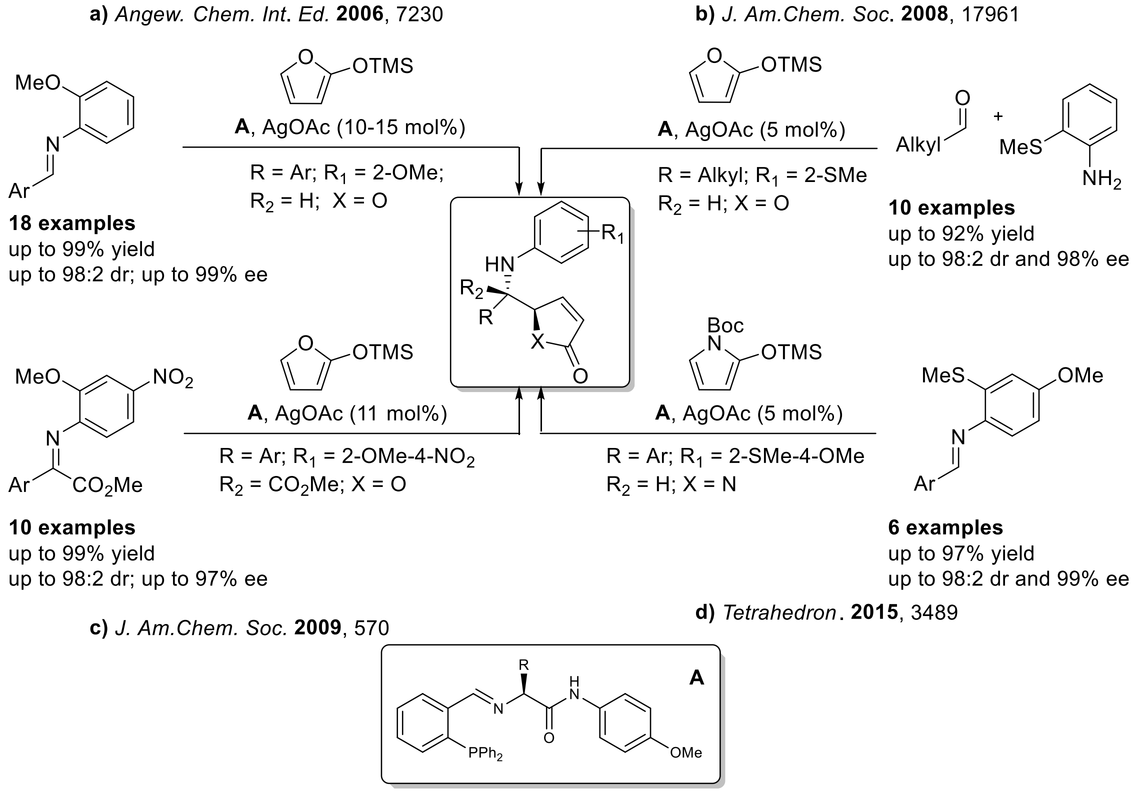
[35] S. Fustero; B. Pina; E. Salavert; A. Navarro; M. C. Ramírez de Arellano; A. S. Fuentes, *J. Org. Chem.,* **2002,** *67*, 4667-4679.

[36] (a) S. F. Martin, *Acc. Chem. Res.,* **2002,** *35*, 895-904; (b) S. K. Bur; S. F. Martin, *Tetrahedron,* **2001,** *57*, 3221-3242.

[37] For a recent review, see: M. S. Roselló; C. del Pozo; S. Fustero, *Synthesis,* **2016,** *48*, 2553-2571.

[38] G. Casiraghi; F. Zanardi; L. Battistini; G. Rassu, *Synlett,* **2009,** *2009*, 1525-1542.

(Scheme I.4, **a**), yielding the corresponding *anti*-γ-butenolide derivatives in very good yields, complete diastereocontrol and high enantioselectivities.[39] The great selectivity of their protocol relayed in the use of chiral imino phosphine-type ligands, which directs the nucleophilic attack by coordination with both the imine (through the silver metallic center) and the trimethysilyloxy group (through the carbonyl moiety).



Scheme I.4. Enantioselective Ag-catalysed VMRs by Hoveyda.

Two years later, the same authors reported a three-component version of this Ag-catalysed enantioselective VMR over alkyl-substituted aldimines, derived from *ortho*-thiomethyl substituted anilines (Scheme I.4, **b**).[40] More challenging imines as *N*-aryl imino esters were also subjected to the asymmetric VMR with 2-TMS-silyloxyfurans, achieving the corresponding γ-butenolides in good yields and great levels of enantioselectivity, with the crucial role of a *p*-nitro group in the N-aryl moiety.[41] The authors demonstrated that the presence of this specific electron-withdrawing

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[39] E. L. Carswell; M. L. Snapper; A. H. Hoveyda, *Angew. Chem. Int. Ed.,* **2006,** *45*, 7230-7233.

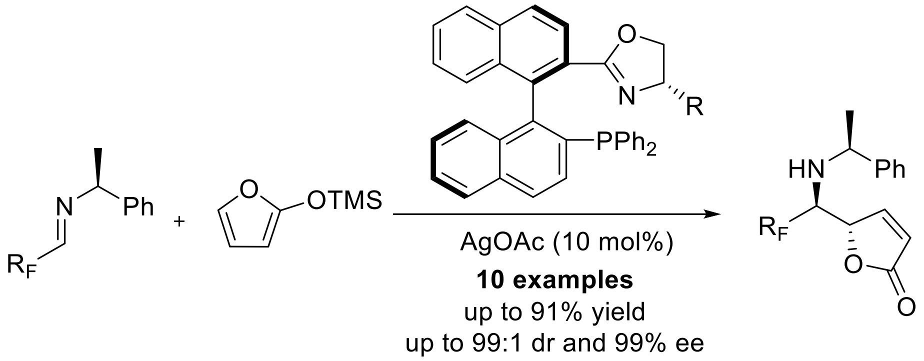
[40] H. Mandai; K. Mandai; M. L. Snapper; A. H. Hoveyda, *J. Am. Chem. Soc.,* **2008,** *130*, 17961-17969.

[41] L. C. Wieland; E. M. Vieira; M. L. Snapper; A. H. Hoveyda, *J. Am. Chem. Soc.,* **2009,** *131*, 570-576.

substituent was traduced into an improvement of yield, diastereo- and enantioselectivity (Scheme I.4, **c**).

More recently, Hoveyda and co-workers successfully performed an enantioselective VMR using 2-silyloxypyrroles as nucleophiles over substituted aldimines under similar conditions (Scheme I.4, **d**). These transformations occurred with high diastereo- and enantioselectivity and they also showed complete site-selectivity for the γ- *vs* the α-addition (Scheme I.4, **d**).[42]

A completely different catalytic system for the asymmetric VMR of aldimines with 2-trimethylsilyloxyfuran was designed by Shi and co-workers in 2009. Silver acetate in combination with axially chiral phosphine-Schiff-base-type ligands were found to catalyse this reaction with excellent enantioselectivity.[43] The procedure also tolerated the employment of fluorinated aldimines, achieving fluorinated VMR products in high yields, diastereoselectivities and enantiomeric excesses (Scheme I.5).[44]



Scheme I.5. Enantioselective Ag-catalysed VMR by Shi.

Organocatalysed-VMRs have also been reported in the last decades. Akiyama and co-workers developed a Brønsted acid catalysed asymmetric VMR in 2004 using chiral BINOL-derived phosphoric acids. The reaction of aromatic and aliphatic aldimines with trimethylsilyloxyfuran in good yields and high levels of diastereo- and enantioselectivity.[45] In this particular case, the *ortho*-substitution on the aryl ring as a

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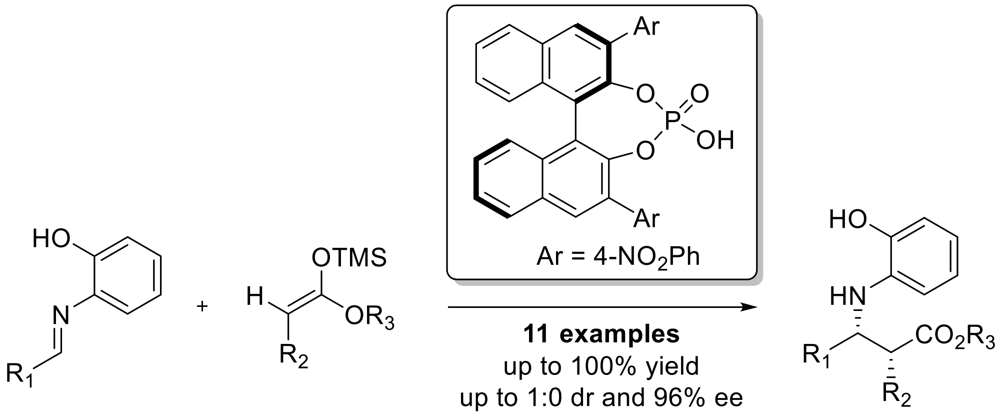
[42] D. L. Silverio; P. Fu; E. L. Carswell; M. L. Snapper; A. H. Hoveyda, *Tetrahedron Lett.,* **2015,** *56*, 3489-3493.

[43] (a) H.-P. Deng; Y. Wei; M. Shi, *Adv. Synth. Catal.,* **2009,** *351*, 2897-2902; (b) Z.-L. Yuan; J.-J. Jiang; M. Shi, *Tetrahedron,* **2009,** *65*, 6001-6007.

[44] Q.-Y. Zhao; Z.-L. Yuan; M. Shi, *Adv. Synth. Catal.,* **2011,** *353*, 637-643.

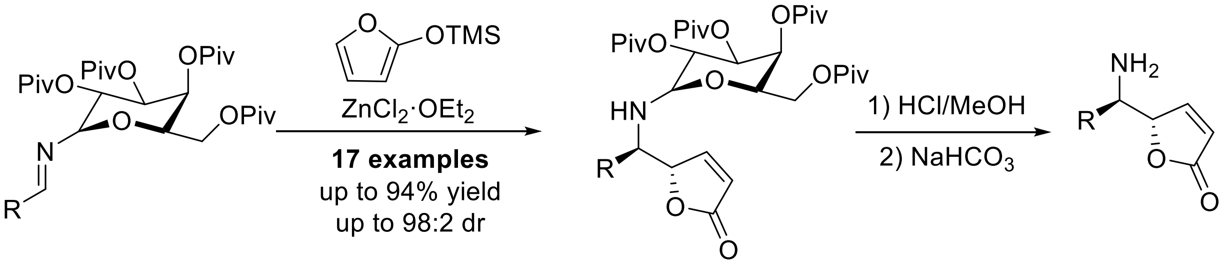
[45] T. Akiyama; J. Itoh; K. Yokota; K. Fuchibe, *Angew. Chem. Int. Ed.,* **2004,** *43*, 1566-1568.

second binding point through the phosphoryl oxygen of the catalyst was critical to afford high levels of enantioselectivity.



Scheme I.6. Organocatalysed VMR by Akiyama.

In addition, several examples of asymmetric VMRs using chiral auxiliaries have been reported. The first example was reported by Miao and Chen in 2011. Using *O*-pivaloyl *D*-galactosylamine as a chiral template (Scheme I.7), the reaction of different aldimines with trimethylsilyloxyfuran rapidly proceeded to generate the corresponding γ-butenolide derivatives with good diastereomeric excesses.[46]



Scheme I.7. Chiral auxiliary assisted VMR by Miao and Chen.

Using the Ellman's *N*-*tert*-butansulfinamide auxiliary, Huang and co-workers published in 2011 the stereoselective addition of TBS-furan to chiral *tert*-butylsulfinyl imines. The reaction occurred at -78 °C to provide a series of butenolides in great yields and diastereoselectivities (Scheme I.8).[47]

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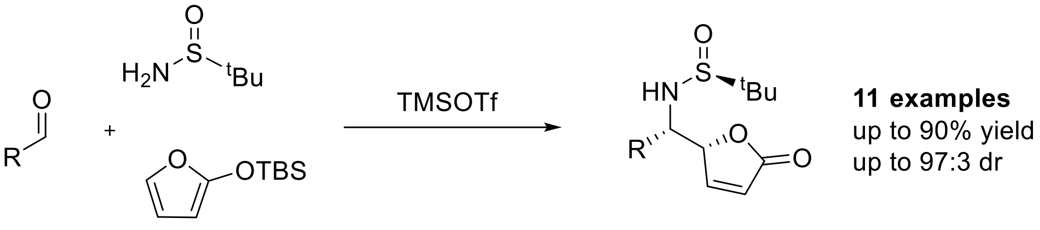
[46] J. Yu; Z. Miao; R. Chen, *Org. Biomol. Chem.,* **2011,** *9*, 1756-1762.

[47] S.-T. Ruan; J.-M. Luo; Y. Du; P.-Q. Huang, *Org. Lett.,* **2011,** *13*, 4938-4941.

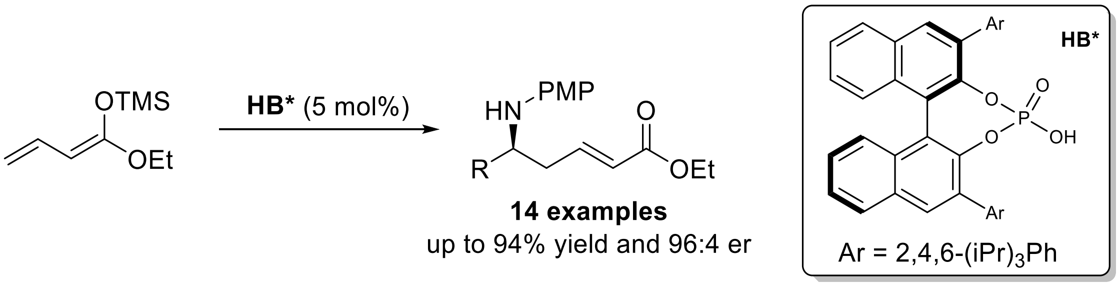


Scheme I.8. Ellman's chiral auxiliary-assisted diastereoselective VMR by Huang.

I.3.2. Reactions with acyclic silyl dienolates.

Acyclic silyl dienolates may lead to mixtures of α- and γ-addition products, thus imposing regioselectivity issues to these processes. Several types of catalytic systems have been successfully developed for the addition of acyclic silyl dienolates to imines, also in an enantioselective fashion.

In 2008, Schneider described an asymmetric VMR using a chiral BINOL-derived phosphoric acid as the catalyst. The addition of ester-derived silyl dienolates to aldimines proceeded with complete γ-site regioselectivity, leading to the corresponding vinilogous Mannich products in good yields and enantioselectivities.[48] Later on, they could extend the procedure to alkyl-substituted imines (Scheme I.9).[49]



Scheme I.9. Chiral Phosphoric acid-catalysed enantioselective VMR by Schneider.

List and co-workers used binaphtyl-derived chiral disulfonimides to synthesise δ-amino-β-keto esters from silyloxydienes and *N*-Boc-protected aromatic and heteroaromatic aldimines.[50] The methodology described proceeded with great yields and

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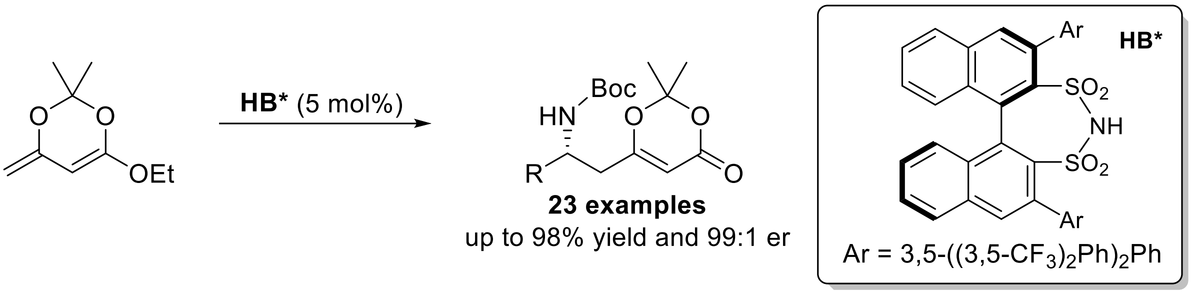
[48] (a) M. Sickert; C. Schneider, *Angew. Chem. Int. Ed.,* **2008,** *47*, 3631-3634; (b) M. Sickert; F. Abels; M. Lang; J. Sieler; C. Birkemeyer; C. Schneider, *Chem. Eur. J.,* **2010,** *16*, 2806-2818.

[49] F. Abels; C. Schneider, *Synthesis,* **2011,** *2011*, 4050-4058.

[50] Q. Wang; M. van Gemmeren; B. List, *Angew. Chem. Int. Ed.,* **2014,** *53*, 13592-13595.

enantioselectivities, providing with useful enantioenriched building blocks (Scheme I.10).



Scheme I.10. Disulfonamide-catalysed asymmetric VMR by List.

Several examples involving the use of TM complexes have also been recently described. We could highlight those reported by Carretero and Liu, both performing asymmetric versions of the VMR with silyloxydienes using copper and scandium complexes, respectively. The success of the procedure developed by Carretero and co-workers relayed on the combination of a Cu(I) species with chiral phosphine Fesulphos to catalyze the addition of acyclic dienes to sulfonyl aldimines, yielding α,β-unsaturated γ-amino carbonyl derivatives with high yields and enantioselectivities and complete γ-site regiocontrol (Scheme I.11, **a**).[51] On the other hand, Liu and Feng developed a three-component approach involving silyl dienol ether, aldehydes and 2-aminophenol using a chiral *N,N′*-dioxide-scandium(III) complex as the catalyst to access δ-amino-α,β-unsaturated esters in great yields and enantioselectivities (Scheme I.11, **b**).[52]

The combination of Lewis acids and chiral auxiliaries has also been employed in the development of highly regio- and diastereoselective VMRs. Liu, Chen and co-workers found conditions to carry out a regiodivergent VMR depending on the nature of the Lewis acid employed as catalyst.[53] Whereas AgOTf or Zn(OTf)$_2$ led to the desired products with complete γ-selectivity, α-regioisomers could be access in the presence of AgOCOCF$_3$ or AgOAc (Scheme I.11, **c**).

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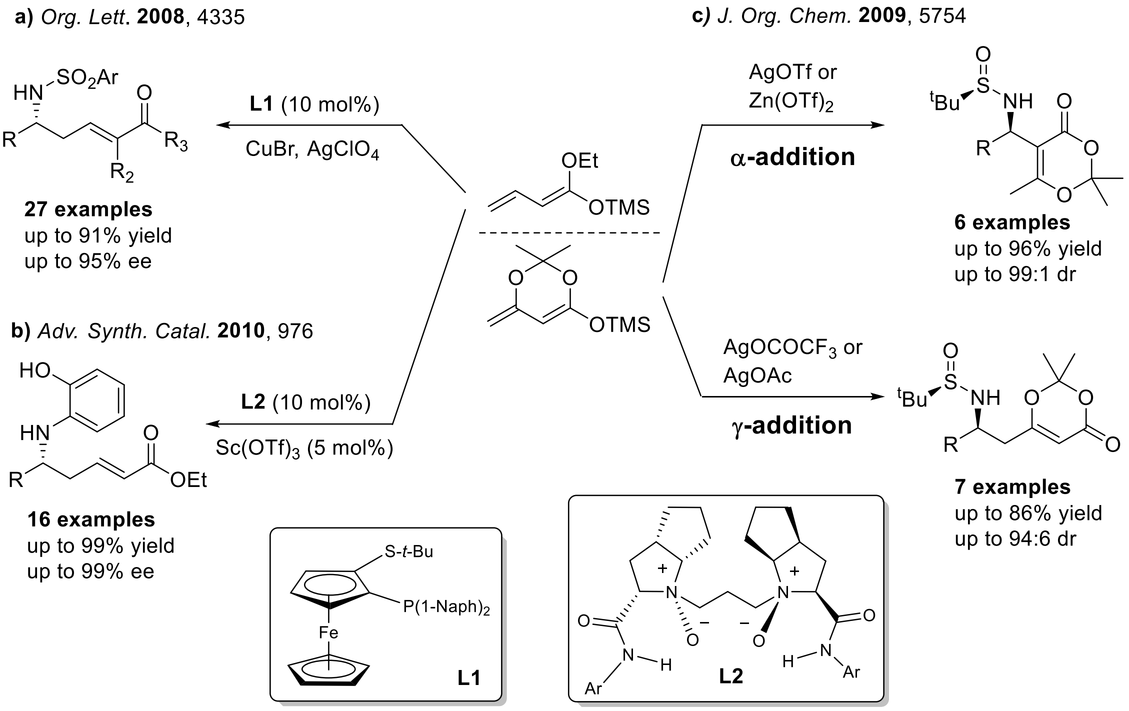
[51] A. Salvador González; R. Gómez Arrayás; M. Rodríguez Rivero; J. C. Carretero, *Org. Lett.,* **2008,** *10*, 4335-4337.

[52] Q. Zhang; Y. Hui; X. Zhou; L. Lin; X. Liu; X. Feng, *Adv. Synth. Catal.,* **2010,** *352*, 976-980.

[53] C.-L. Gu; L. Liu; D. Wang; Y.-J. Chen, *J. Org. Chem.,* **2009,** *74*, 5754-5757.



Scheme I.11. Lewis acid-catalysed regiodivergent VMR by Carretero, Liu and Chen.

I.3.3. Reactions with γ-butenolides and γ-butyrolactams.

γ-Butenolides and related compounds have been widely used as pronucleophiles in vinilogous Mannich reactions given the presence of the γ-butenolide skeleton in several natural products and bioactive compounds (Figure I.7).[54]

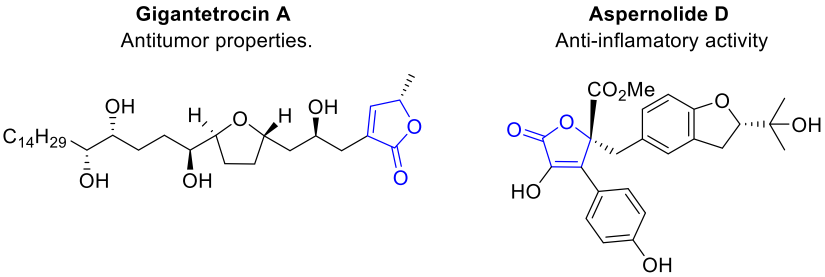


Figure I.7. Bioactive butenolide-containing compounds.

Two different catalytic strategies have been described to react these substrates with imines in an asymmetric manner. In one hand, Shibasaki and Matsunaga employed a Schiff base in conjunction with Lewis acids to promote the addition of γ-butenolides onto phosphinoyl imines (Scheme I.12). The catalytic system enhanced the selectivity of

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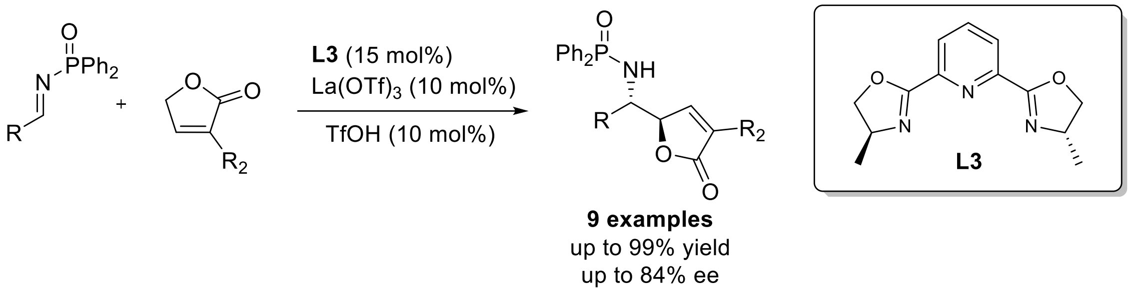
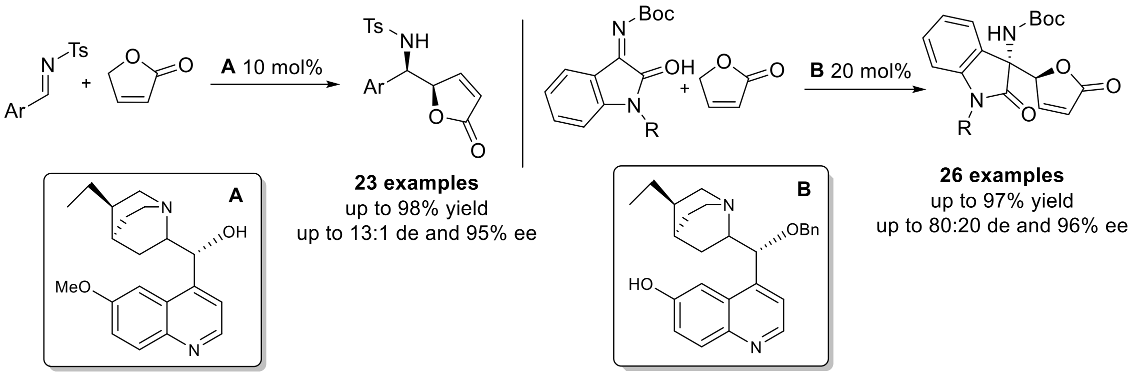
[54] (a) P. Nuclear; D. Sommit; N. Boonyuen; K. Pudhom, *Chem. & Pharm. Bull.*, **2010,** *58*, 1221-1223; (b) Y.-F. Liu; S.-Y. Cai; X.-M. Hao; F. Cao; H.-J. Zhu, *Chem. Nat. Comp.*, **2018,** *54*, 402-404.

the reaction by coordinating both, the γ-butenolide nucleophile (through the carbonyl moiety) and the *N*-diphenylphosphinoyl imines (through the phosphinoyl group).[55]



Scheme I.12. La-catalysed stereoselective VMR by Shibasaki.

On the other hand, organocatalytic processes have also been described in the late years. Namely, an asymmetric VMR of aryl aldimines with unsaturated γ-butyrolactams was performed by Xu, Wang and co-workers in 2012. The corresponding γ-butenolide derivatives were obtained in good yields and high levels of enantioselectivity using a quinine derivative as catalyst (Scheme I.13, left).[56] Similarly, Wang and co-workers designed a VMR involving γ-butenolides and *N*-Boc ketimines derived from isatines. This reaction is catalysed by a similar quinidine-derived catalyst, which activates simultaneously the γ-butenolides through the tertiary amino group and the isatin-derived electrophile through the hydroxyl group (Scheme I.13, right).[57]



Scheme I.13. Organocatalysed stereoselective VMRs by Wang.

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[55] A. Yamaguchi; S. Matsunaga; M. Shibasaki, *Org. Lett.,* **2008,** *10*, 2319-2322.

[56] Y.-L. Guo; J.-F. Bai; L. Peng; L.-L. Wang; L.-N. Jia; X.-Y. Luo; F. Tian; X.-Y. Xu; L.-X. Wang, *J. Org. Chem.,* **2012,** *77*, 8338-8343.

[57] Y. Guo; Y. Zhang; L. Qi; F. Tian; L. Wang, *RSC Adv.,* **2014,** *4*, 27286-27289.

I.3.4. Reactions with α,α-dicyanoolefins.

α,α-Dicyanoolefins, introduced by Jørgensen and Deng in 2007, are well known electrophiles, given their enhanced electrophilic character imparted by the cyano substituents. If one enolizable site is available, α,α-dicyanoalkenes can act as nucleophiles through the γ-position, acting as excellent vinylogous donors.

In 2007, Jørgensen reported the addition of dicyanoalkylidenes to *N*-acyl aromatic imines in the presence of phase-transfer catalyst **I**. This strategy provided the desired vinilogous products in good yields and enantioselectivities, with nearly complete levels of diastereoselectivity (Scheme I.14, **a**).[58] Independently, Chen and co-workers used thiourea-type hydrogen-bond donors as organocatalysts for the enantioselective VMR of dicyanoalkenes with *N*-Boc protected aromatic aldimines (Scheme I.14, **b**).[59]

Zhou demonstrated in 2009 that these type of VMRs with dicyanoolefins could also be catalysed by TM complexes. They reacted the aforementioned alkylidenes with aryl aldimines in the presence of silver acetate and chiral ferrocenyl ligands, yielding the corresponding products in good yields and stereoselectivities (Scheme I.14, **c**).[60]

It was not until this year when Chen and co-workers disclosed the very first VMR with dicyanoalkenes and non-aromatic imines. They found that such a process could be catalysed by a catalyst integrating a BINOL and a cinchona-derived alkaloid (Scheme I.14, **d**).[61] The authors were able to selectively obtain adducts *syn* and *anti*, depending on the absolute configuration of the catalyst employed for the VMR.

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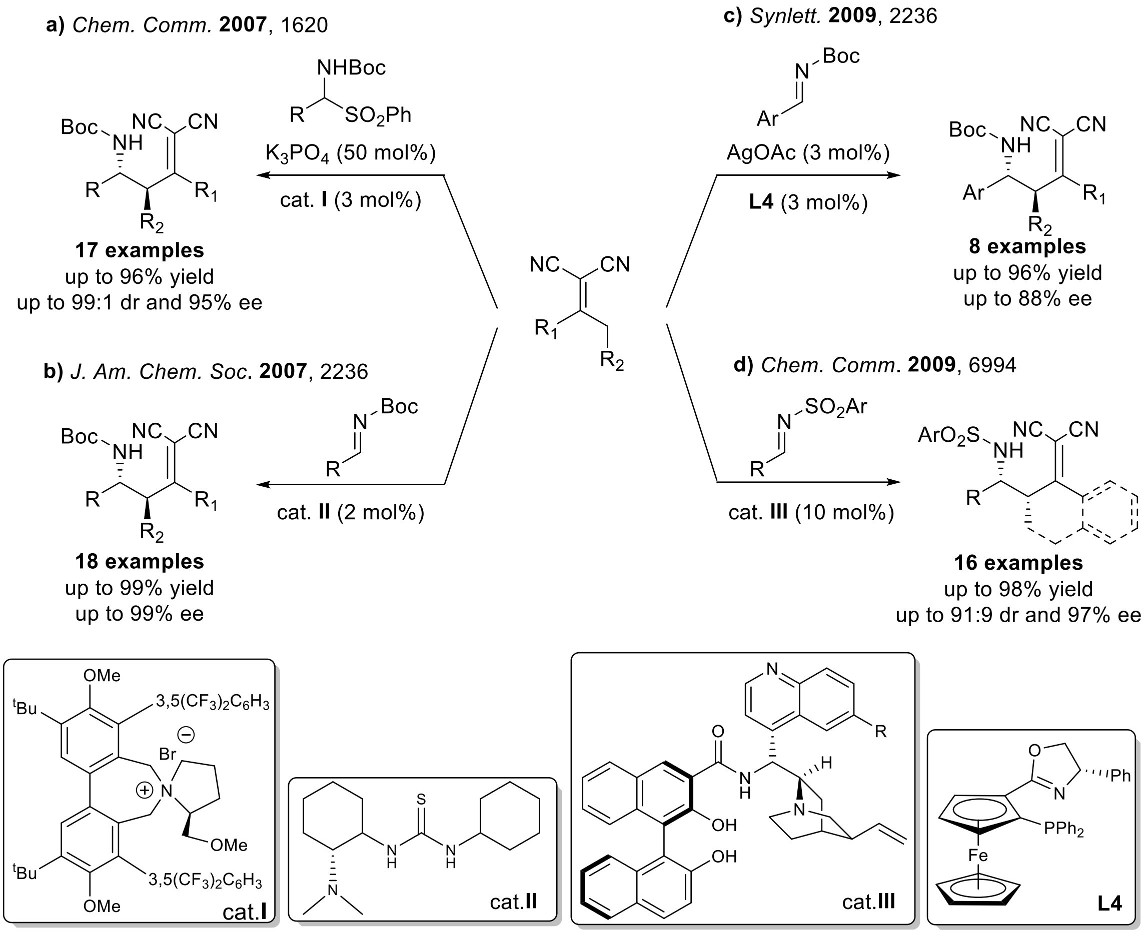
[58] B. Niess; K. A. Jørgensen, *Chem. Commun.,* **2007**, 1620-1622.

[59] T.-Y. Liu; H.-L. Cui; J. Long; B.-J. Li; Y. Wu; L.-S. Ding; Y.-C. Chen, *J. Am. Chem. Soc.,* **2007,** *129*, 1878-1879.

[60] Q.-A. Chen; W. Zeng; D.-W. Wang; Y.-G. Zhou, *Synlett,* **2009,** 2236-2241.

[61] X.-F. Xiong; Z.-J. Jia; W. Du; K. Jiang; T.-Y. Liu; Y.-C. Chen, *Chem. Commun.,* **2009**, 6994-6996.



Scheme I.14. VMRs with dicyanoalkenes.

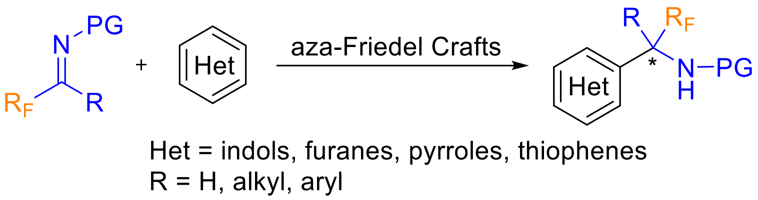
Despite the wide variety of vinilogous donors and imines used in asymmetric VMR, the use of fluorinated imines lagged behind. In the case of dicyano olefins, the use of fluorinated imines as partners was unprecedented to date. Therefore, the main objectives of this dissertation, as is detailed below, is to explore the use of different types of fluorinated imines in vinilogous Mannich-type reactions.

General Objectives

As indicated above, the objectives of this work entail a common task, the survey of new vinilogous-Mannich type reactions using fluorinated imines and iminoesters as fluorinated building blocks.

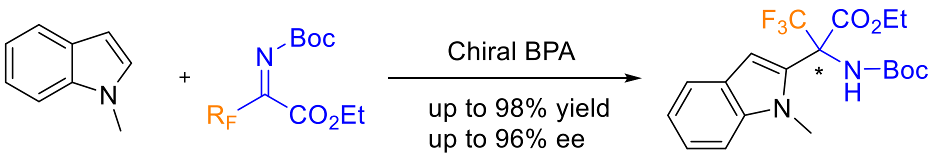
The detailed objetives are summarized below:

1. The aza-Friedel-Crafts reaction have been described with a wide variety of fluorinated imines, giving rise in the asymmetric version to the corresponding chiral fluorinated amines (Scheme I.15).[28,62]



Scheme I.15. Chiral fluorinated amines through aza-Friedel Crafts reaction.

The use of fluorinated iminoesters as imine parters will render fluorinated α-amino acids. However, as far as we know, only one example of addition of indoles to N-Boc trifluoromethyl esters have been described, using chiral binol phosphoric acids as catalyst (Scheme I.16).[63]



Scheme I.16. Chiral fluorinated amines from fluorinated iminoesters and indoles.

The initial goal of our research was to extend this process to other types of heterocycles, such as furanes.

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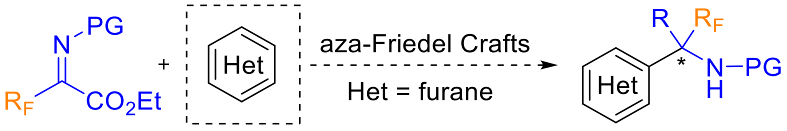
[62] For diastereoselective addition to trifluoromethyl imines, see: D. O'Hagan, *J. Fluorine Chem.,* **2010,** *131*, 1071-1081.

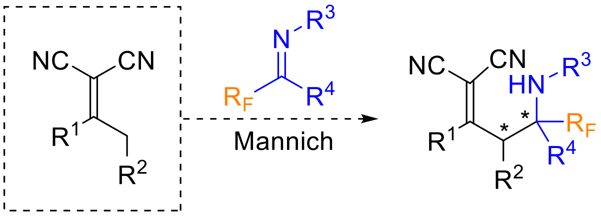
[63] R. Husmann; E. Sugiono; S. Mersmann; G. Raabe; M. Rueping; C. Bolm, *Org. Lett.,* **2011,** *13*, 1044-1047.



Scheme I.17. Aza-Friedel Craft reaction with fluorinated iminoesters and furanes.

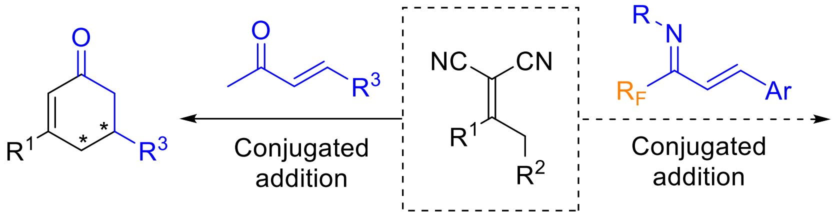
During the study of this process with furanes we found a serendipitious process, were the furane acts as a vinilogous donor in a Povarov-type process. The details of this study will be included in *"Chapter 1"*.

2. As we have mentioned before, dicyanoalkenes are excellent vinilogous donors when they have an enolizable position at that site. However, this reaction was unprecedented with fluorinated imines. Therefore, the second aim of this work was the study of the VMR of dicyanoalkenes with several different fluorinated imines.



Scheme I.18. VMR with dicyanoalkenes and fluorinated imines.

3. Dicyanoalkenes also react with conjugated ketones, in a formal Robinson-annulation process, to render cyclohexanones with two chiral centers. However, the reaction with conjugated imines was not reported to date. As we have mentioned in the introduction, the reactivity of conjugated fluorinated imines was scarcely explored. Thefore, we envisioned the possibility of evaluate the reaction of dicyanoalkenes with these fluorinated conjugated imines.



Scheme I.19. Novel conjugated addition of dicyanoalkenes to fluorinated imines aproach.

Again, this study led us to a serendipitous finding, were a cycloaromatization process took place to render polycyclic trifluoroarenes. The details will be described in *"Chapter 3"*.

» Chapter 1 «

Povarov type reactions with fluorinated imino esters and furans as vinylogous donors

1.1. Introduction

1.1.1. Quinoline derivatives as interesting scaffolds.

Quinoline or 1-aza-naphtalene was first extracted in 1834 from coal, which still is the main source for commercially available quinoline nowadays. The quinoline scaffold is present in the structure of many natural products,[64] marketed drugs and agrochemicals. Diverse natural products with antimalarial properties as quinine (extracted from *Cinchona Officinalis*)[65] or anticancer compounds as camptothecin[66] and exatecan (also extracted from different natural sources) include the quinoline scaffold in their structure (Figure 1.1).

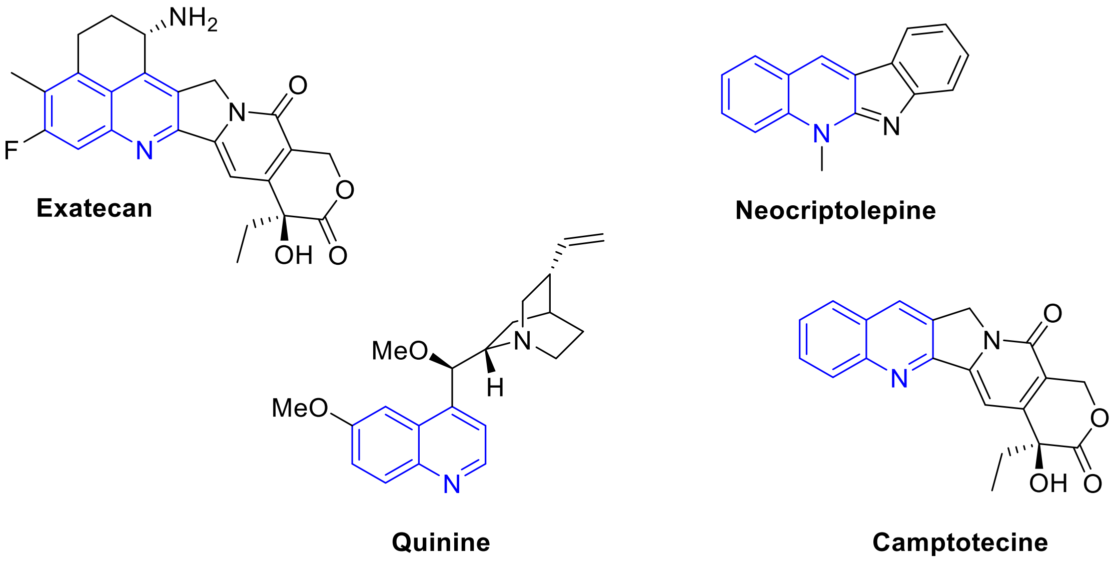


Figure 1.1. Bioactive quinoline-containing structures.

Among its partially hydrogenated derivatives, tetrahydroquinoline-type structures have gained increasing interest over the past decades due to its widespread presence in different products with high biological and pharmaceutical interest.[67] For instance, helquinoline (isolated from *Janibacter Limosus* in 2004) showed important antibiotic

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[64] J. P. Michael, *Nat. Prod. Rep.,* **2008,** *25*, 166-187.

[65] J. Achan; A. O. Talisuna; A. Erhart; A. Yeka; J. K. Tibenderana; F. N. Baliraine; P. J. Rosenthal; U. D'Alessandro, *Malaria J.,* **2011,** *10*, 144.

[66] M. E. Wall; M. C. Wani; C. E. Cook; K. H. Palmer; A. T. McPhail; G. A. Sim, *J. Am. Chem. Soc.,* **1966,** *88*, 3888-3890.

[67] N. B. Perry; J. W. Blunt; M. H. G. Munro; T. Higa; R. Sakai, *J. Org. Chem.,* **1988,** *53*, 4127-4128.

properties, whereas cuspareine (firstly extracted from *Galipea Officinalis*) possesses cytotoxic and anti-bacterial attributes (Figure 1.2).[68]

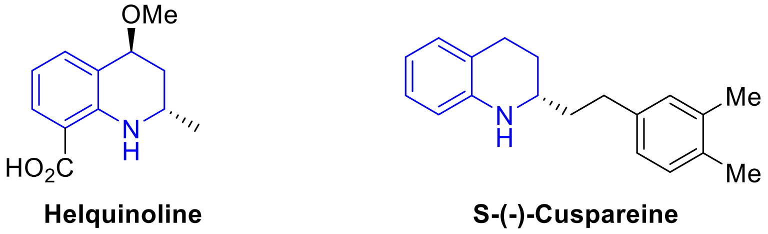
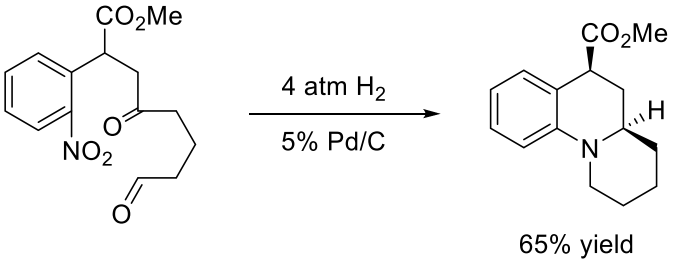


Figure 1.2. Bioactive tetrahydroquinolines.

Given the great biological and pharmaceutical importance of this family of products,[69] many synthetic protocols have been designed, optimised and implemented over the years in order to access different families of these substructures.[70]

Bunce early disclosed in 2001 a procedure involving a palladium-catalysed reduction-reductive amination sequence to prepare 5- and 6-member ring-fused tetrahydroquinolines in a straightforward manner (Scheme 1.1).[71] The tricyclic products were obtained diastereomerically pure from nitro aryl compounds in excellent yields. According to the author's hypothesis, the diastereoselectivity results from steric hindrance created by the ester group which directs the hydrogenation to the opposite face of the molecule.



Scheme 1.1. Preparation of tricyclic tratrahydroquinoline derivatives by Bunce.

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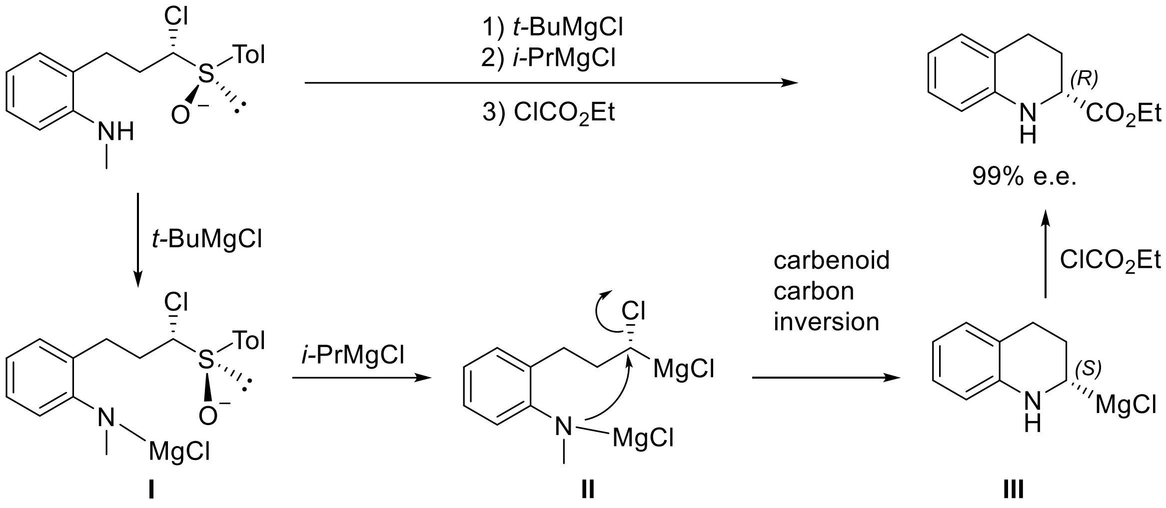
[68] G. M. Staub; J. B. Gloer; D. T. Wicklow; P. F. Dowd, *J. Am. Chem. Soc.,* **1992,** *114*, 1015-1017.

[69] (a) O. Afzal; S. Kumar; M. R. Haider; M. R. Ali; R. Kumar; M. Jaggi; S. Bawa, *Eur. J. Med. Chem.,* **2015,** *97*, 871-910; (b) S. Singh; G. Kaur; V. Mangla; M. K. Gupta, *J. Enz. Inh. & Med. Chem.,* **2015,** *30*, 492-504.

[70] (a) V. Sridharan; P. A. Suryavanshi; J. C. Menéndez, *Chem. Rev.,* **2011,** *111*, 7157-7259; (b) B. Nammalwar; R. A. Bunce, *Molecules,* **2014**, 204-232; (c) K.-i. Fujita; K. Yamamoto; R. Yamaguchi, *Org. Lett.,* **2002,** *4*, 2691-2694.

[71] R. A. Bunce; D. M. Herron; L. B. Johnson; S. V. Kotturi, *J. Org. Chem.,* **2001,** *66*, 2822-2827.

In 2009, Tsuyosi and co-workers reported the asymmetric synthesis of tetrahydroquinoline-type α-amino acid derivatives by an intramolecular nucleophilic substitution reaction of an aryl amine and a chiral sulfoxide, through a magnesium carbenoid intermediate (Scheme 1.2).[72] The key intramolecular cyclisation of **II** proceeds with inversion of the carbenoid carbon to afford α-amino carbanion **III** with *(S)*-absolute configuration. Finally, the anion was trapped by ethyl chloroformate with retention of configuration to afford the amino acid derivatives.



Scheme 1.2. Synthesis of enantiopure tetrahydroquinolines by Tsuyosi.

More recently, in 2012, Gillaizeau developed a domino approach to obtain nitrogen-fused tetrahydroquinoline frameworks from commercially available enamides and benzyl azides. The authors were able to prepare various types of these nitrogen-fused tetrahydroquinoline scaffolds in good yields under mild conditions, using triflic acid in toluene (Scheme 1.3).[73] After protonation of the azide, a rearrangement takes place to form an iminium ion with concomitant loss of molecular nitrogen. Then, the nucleophilic attack of the enamide to this iminium intermediate **II** generates acyclic intermediate **III**, which undergoes a cyclisation to yield polycyclic tetrahydroquinolines.

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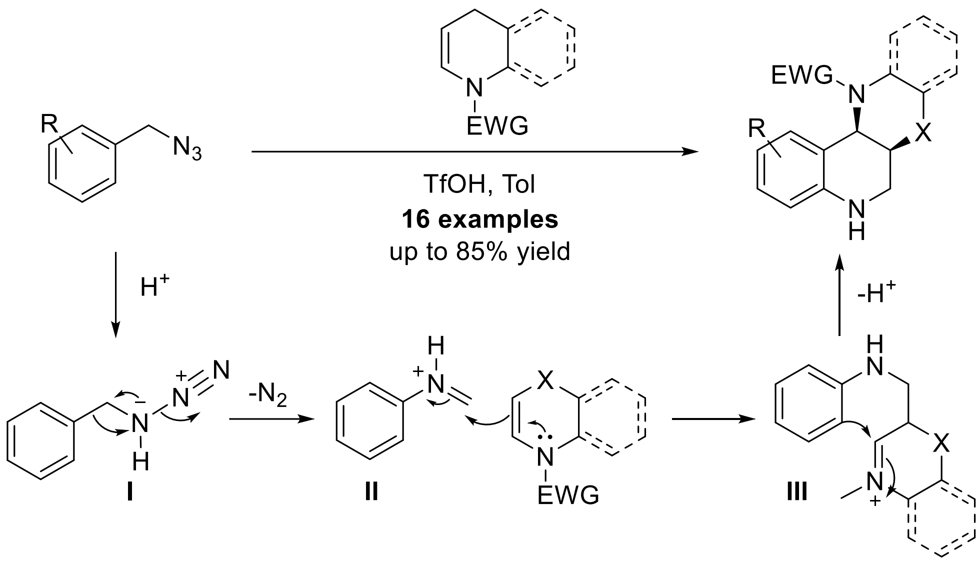
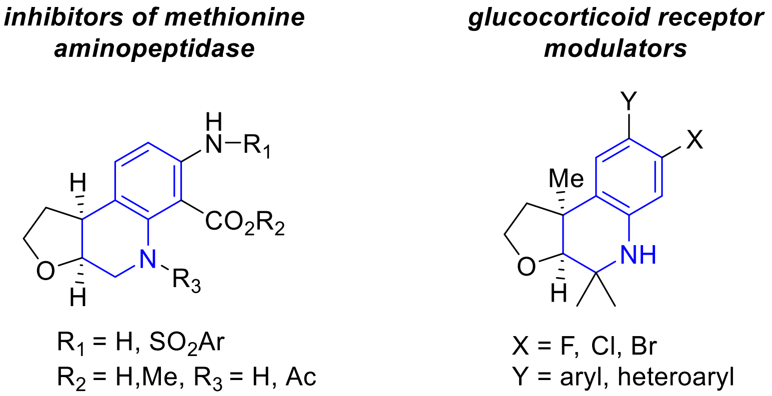
[72] S. Mitsunaga; T. Ohbayashi; S. Sugiyama; T. Saitou; M. Tadokoro; T. Satoh, *Tetrahedron: Asymm.,* **2009,** *20*, 1697-1708.

[73] N. Gigant; I. Gillaizeau, *Org. Lett.,* **2012,** *14*, 4622-4625.



Scheme 1.3. Synthesis of nitrogen-fused tetrahydroquinolines by Gallaizeau.

In particular, tetrahydrofuran-fused tetrahydroquinolines have recently been disclosed as inhibitors of methionyl amino peptidase and as glucocorticoid receptor modulators, being potential therapeutic agents for the treatment of liver disorders and obesity (Figure 1.3).[74]



R_1 = H, SO_2Ar
R_2 = H,Me, R_3 = H, Ac

X = F, Cl, Br
Y = aryl, heteroaryl

Figure 1.3. Bioactive tetrahydrofuran-fused tetrahydroquinolines.

Besides different patents published on these pharmaceutically useful tetrahydroquinolines, several procedures have been described for the synthesis of tetrahydrofuran-fused tetrahydroquinolines. For instance, in 2009 Mohan and co-workers disclosed a highly efficient Bi-catalysed methodology using different

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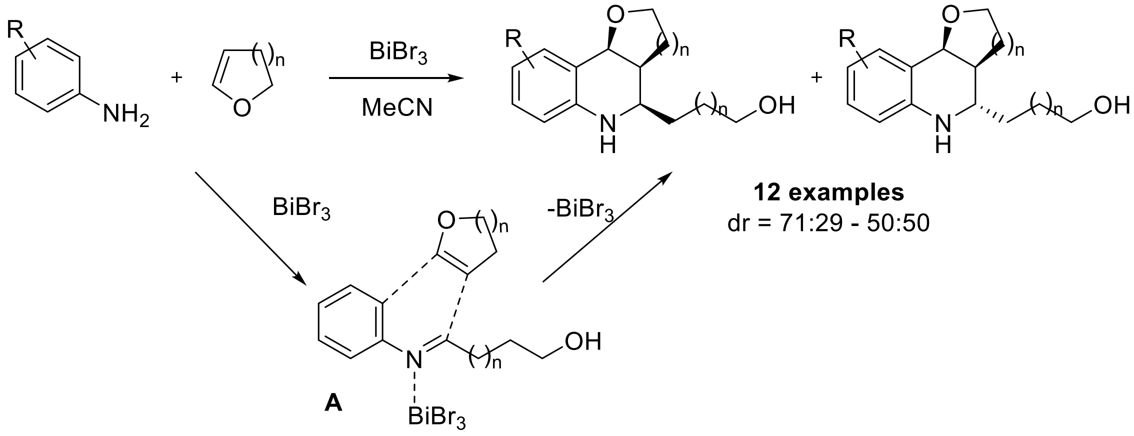
[74] (a) S. C. Mary; H. D., Joan; T. P., David; R. Zahler, Partially saturated tricyclic compounds and methods of making and using same, WO/2012/154676, 15/11/2012, **2012**; (b) T. Hughes, Methods of treating livers diseases, WO/2014/071368, 08/05/2014, **2014**.

substituted anilines and cyclic enol ethers as starting materials (Scheme 1.4). The authors obtained the corresponding tetrahydrofuran- and tetrahydropyran-fused tetrahydroquinolines in great yields as a mixture of diastereoisomers (Scheme 1.4).[75] The arylamines reacted with one equivalent of the enol ether to give the corresponding *N*-arylimines **A**, which underwent [4 + 2] cycloaddition with a second equivalent of the enol ether in the presence of $BiBr_3$ to afford tetrahydroquinolines as diastereomeric mixtures.



Scheme 1.4. Synthesis of tetrahydrofuran- and tetrahydropyran-fused tetrahydroquinolines by Mohan.

1.1.2. Tandem procedures: looking for chemical efficiency.

Tandem reactions allow multiple transformations with only one reaction set and no need of intermediates purification

These procedures have been frequently employed as high efficient strategies for the synthesis of natural products with biological activity or pharmaceutical interest.[76] In general, these methodologies allow complex synthetic transformations with great efficiency using relatively simple starting materials. Among other benefits, tandem reactions usually stand out for its great atom economy, selectivity and reduced waste, making them perfect examples of “Green Chemistry”.[60]

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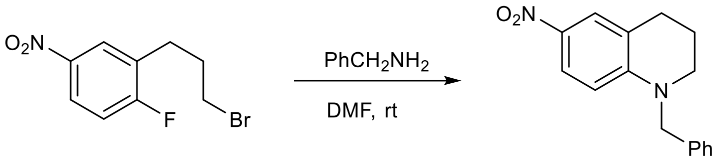
[75] J. L. Rogers; J. J. Ernat; H. Yung; R. S. Mohan, *Catal. Commun.,* **2009**, *10*, 625.

[76] K. C. Nicolaou; D. J. Edmonds; P. G. Bulger, *Angew. Chem. Int. Ed.,* **2006,** *45*, 7134-7186.

In particular, diverse tandem methodologies have been designed to synthesise tetrahydroquinoline-like structures. For a clear understanding of these reactions, we will categorise them depending on the nature of the transformations they promote.

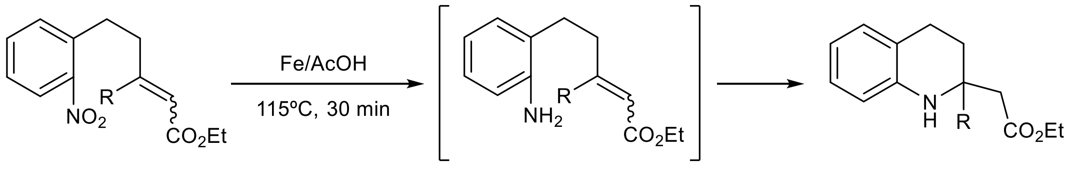
Reduction/oxidation reactions followed by a cyclisation configures a straightforward methodology to generate tetrahydroquinolines. The procedure designed by Bunce and co-workers[64] allowed the direct formation of disubstituted tetrahydroquinolines in good yields and diastereoselectivities (see Scheme 1.1).

Aromatic nucleophilic substitutions also promote great transformations in an easy manner. After an S_N2 attack of benzylamine over the dihalogenated starting material, an intramolecular S_NAr with fluorine elimination gives rise to electron-deficient tetrahydroquinolines in great yields (Scheme 1.5).[77] This method is amenable for the preparation of different size rings with great results and under mild conditions.[78]



Scheme 1.5. Tetrahydroquinoline synthesis by S_NAr.

Transition metal iniciated tandem processes have also been well studied. The reduction of a nitroaryl compound to the corresponding aniline, allowed Bunce and co-workers to synthesise, through a *6-exo-trig* Michael addition to the acrylate moiety, various substituted tetrahydroquinolines in good yields (Scheme 1.6).[79]



Scheme 1.6. Transition Metal iniciated tetrahydroquinoline synthesis.

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[77] R. A. Bunce; T. Nago; N. Sonobe; L. M. Slaughter, *J. Het. Chem.,* **2008,** *45*, 551-557.

[78] R. A. Bunce; E. J. Lee, *J. Het. Chem.,* **2010,** *47*, 1176-1182.

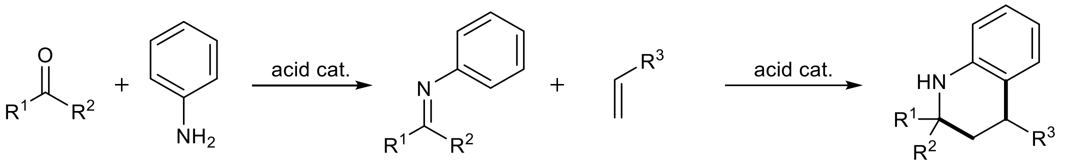
[79] R. A. Bunce; D. M. Herron; M. L. Ackerman, *J. Org. Chem.,* **2000,** *65*, 2847-2850.

Acid catalysed rearrangement/cyclisation processes allowed Gillaizeau and co-workers in 2012 to synthesise heterocyclic-fused tetrahydroquinolines from benzyl azides in great yields and diastereoselectivities (see Scheme 1.3).[66]

Within all these transformations, and to light up the path that leads this work, it is worth to highlight the last group of them, those catalysed by acids. In particular, the three component reaction between anilines, aldehydes and activated olefins to give tetrahydroquinolines, the so called Povarov reaction.

1.1.3. The Povarov reaction.

The acid-catalised inverse electron-demanding formal [4+2] cycloaddition reaction between *N*-arylimines and electron-rich dienophiles to give tetrahydroquinolines, also referred to as an aza-Diels-Alder reaction, was firstly developed by the Russian chemist Povarov in the 1960s, and is now popularly known as the Povarov reaction (Scheme 1.7).[80] The reaction can also be performed in a three-component fashion using the *in situ* generated *N*-arylimines starting from suitable arylamines and aldehydes.



Scheme 1.7. The Povarov reaction.

The Povarov reaction can be catalyzed by a wide variety of either Lewis and Brønsted acids, and the enantioselective version allows for the simultaneous generation of multiple stereocenters. Moreover, the reaction permits a huge diversity in substrate selection, allowing the use of electron-rich and electron-deficient arylamines and aldehydes, in combination with different dienophiles, including vinyl ethers, vinyl sulfides, silyl enol ethers, vinyl enamides, enamines, alkenes, and alkynes.[81] Povarov reactions are generally diastereoselective protocols.

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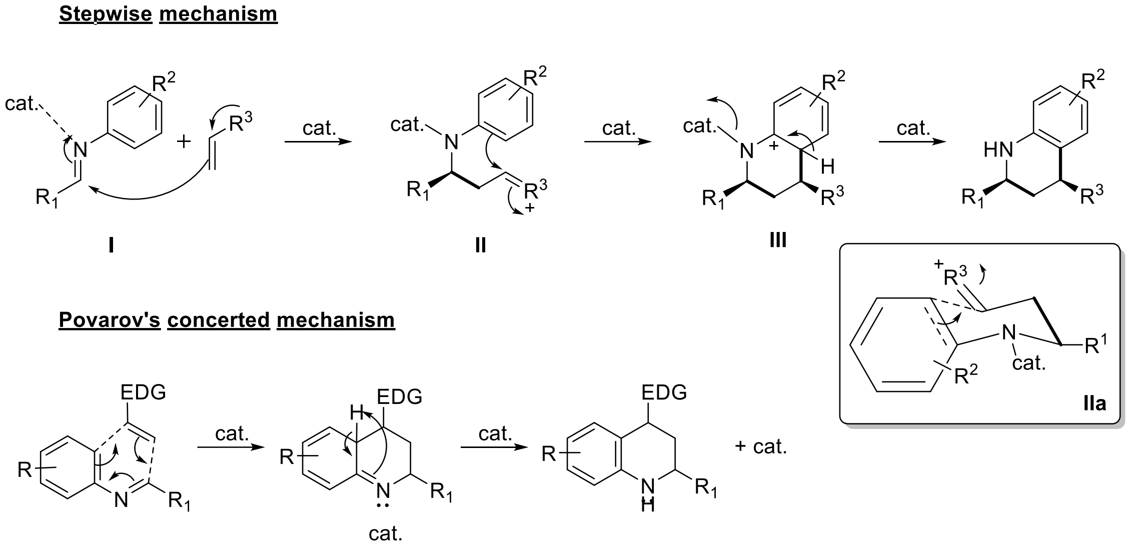
[80] L. S. Povarov, *Rus. Chem. Rev.,* **1967,** *36*, 656-670.

[81] V. V. Kouznetsov, *Tetrahedron,* **2009,** *65*, 2721-2750.

As regards to the mechanism, it is nowadays proved that the Povarov reaction is a stepwise reaction, proceeding through cationic intermediate **II** (Scheme 1.8), rather than a concerted protocol, as believed in the past.[82]



Scheme 1.8. Mechanism of the Povarov reaction.

After the acid-catalysed condensation of the aryl amine and the aldehyde to form imine **I**, viniligous Mannich addition of the dienophile to the imine results in oxonium intermediate **II**. The following Friedel-Craft cyclisation leads to intermediate **III**, which after rearomatisation results in the corresponding tetrahydroquinoline.[72]

The origin of the diastereoselectivity of these reactions could be rationalised based on the absolute configuration of the oxonium intermediate **II**. The major *cis* tetrahydroquinoline **III** may be derived from the less-hindered chair-like transition state **IIa**, where R^1 and R^3 occupy equatorial positions, avoiding 1,3-diaxial interactions (Scheme 1.8).

The modularity, the atom economy and the straightforward molecular complexity generation are remarkable aspects of Povarov's reaction, as illustrated by the numerous publications on this matter along the last decades.

Among the Brønsted acid-catalysed Povarov reactions, Zhu and co-workers disclosed in 2009 a three-component protocol to synthesise polysubstituted enantiomerically

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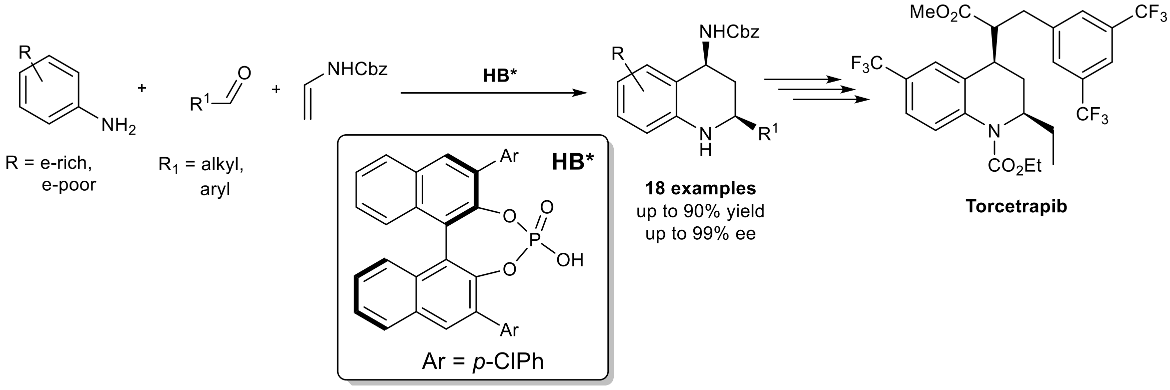
[82] D. Bello; R. Ramón; R. Lavilla, *Curr. Org. Chem.,* **2010,** *14*, 332-356.

enriched tetrahydroquinolines in an efficient manner (Scheme 1.9).[83] The authors employed a chiral BINOL-derived phosphoric acid to induce chirality in a procedure that tolerates the utilisation of electron-rich, -neutral and -poor anilines, and both aliphatic and aromatic aldehydes. Remarkably, this method was applied to the synthesis of Torcetrapib (an anti-cholesterol drug) in a four-steps reaction sequence.



Scheme 1.9. Chiral phosphoric acid-catalysed enantioselective Povarov reaction by Zhu.

In order to broaden the generality of this reaction, Gong and co-workers introduced styrenes as dienophiles in an organocatalytic asymmetric three-component Povarov reaction, providing an efficient methodology to access structurally diverse *cis*-disubstituted tetrahydroquinolines (Scheme 1.10).[84] The employment of a silicon-substituted BINOL-derived phosphoric acid, resulted in the corresponding di-aryl substituted tetrahydroquinolines with high levels of diastereo- and enantioselectivity.

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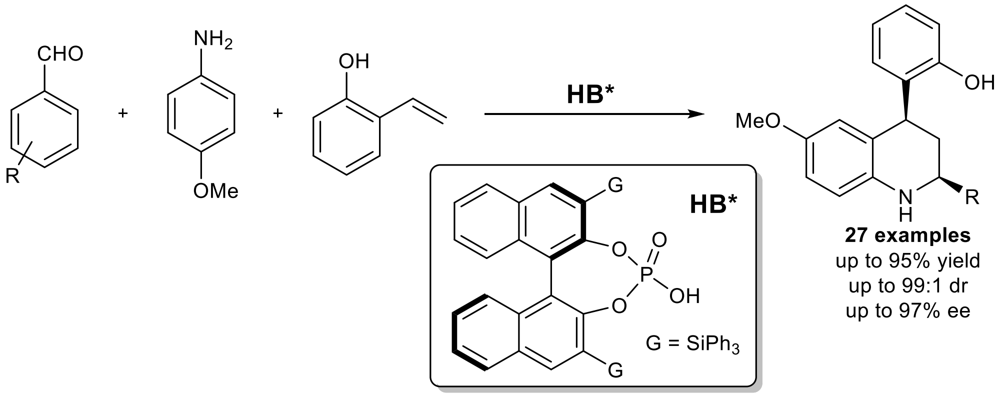
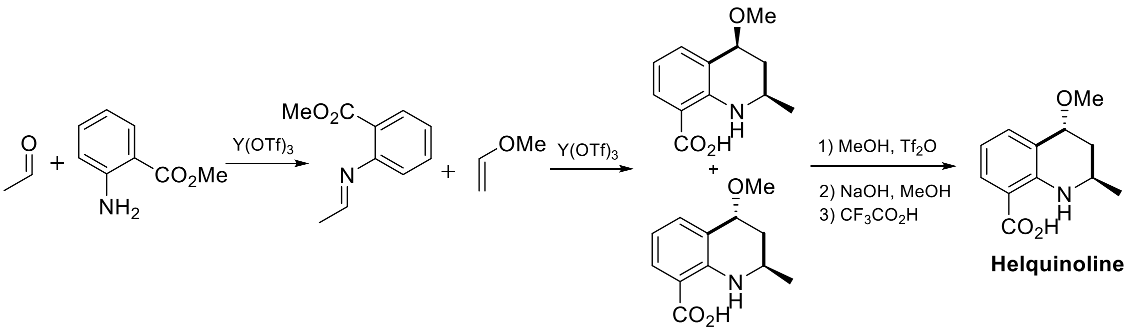
[83] H. Liu; G. Dagousset; G. Masson; P. Retailleau; J. Zhu, *J. Am. Chem. Soc.,* **2009,** *131*, 4598-4599.

[84] F. Shi; G.-J. Xing; Z.-L. Tao; S.-W. Luo; S.-J. Tu; L.-Z. Gong, *J. Org. Chem.,* **2012,** *77*, 6970-6979.



Scheme 1.10. Chiral phosphoric acid-catalysed enantioselective Povarov reaction by Gong.

On the other hand, chiral Lewis acid catalysts also configure a useful tool for the synthesis of tetrahydroquinolines. For instance, Stevenson and co-workers described in 2014 the synthesis of the antibiotic Helquinoline (Figure 1.2) by a Povarov reaction, starting from methyl vinyl ether, acetaldehyde and the corresponding *ortho*-substituted aniline (Scheme 1.11).[85]



Scheme 1.11. Synthesis of Helquinoline by Stevenson.

Despite a huge family of transition metal-containing catalytic systems have been designed over the last decades in the synthesis of tetrahydroquinolines, including In, Y, Sc, Fe, etc. –derived complexes,[86] our work will emphasise in those examples involving the use of gold species.

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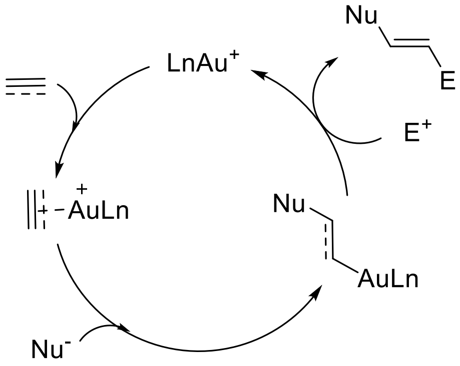
[85] P. J. Stevenson; P. He; B. Daly, *Tetrahedron,* **2014,** *70*, 7350-7357.

[86] I. Muthukrishnan; V. Sridharan; J. C. Menéndez, *Chem. Rev.,* **2019,** *119*, 5057-5191.

1.1.4. The golden age of chemistry.

Despite the widely generalised presence of gold along the history as a precious metal, it was not until the last couple of decades that the most desirable metal in the world became valuable for synthetic chemists. Since then, gold has become an innovative and powerful synthetic tool for the generation of C-C and C-heteroatom bonds, probably due to its unique ability to act as a π–soft Lewis acid promoting the addition of a wide variety of nucleophiles towards non-activated functionalities (alkynes, allenes, alkenes, etc.) under mild conditions.[87]



Scheme 1.12. Catalytic cycle for gold-catalysed nucleophilic additions.

Despite other Lewis acids as Ag(I) or Pt(II) can occasionally promote gold-catalysed transformations,[88] no other late transition metal shows the same ream of applications displayed by homogeneous Au(I) complexes. As soft centers, gold species show low oxophilicity,[89] making gold-catalysed reactions do not require rigorous inert conditions. It is worth noting that, in the presence of water or alcohols, gold species may interact with them enhancing their Brønsted acidity, rendering Lewis acid assisted- Brønsted acid catalysed processes.[90]

Nevertheless, whereas most gold-catalysed reactions proceed through gold soft Lewis acid properties, activating C-C multiple bonds, its competency towards the formation of σ-complexes with heteroatoms has been proved as well, especially when harder Au(III)

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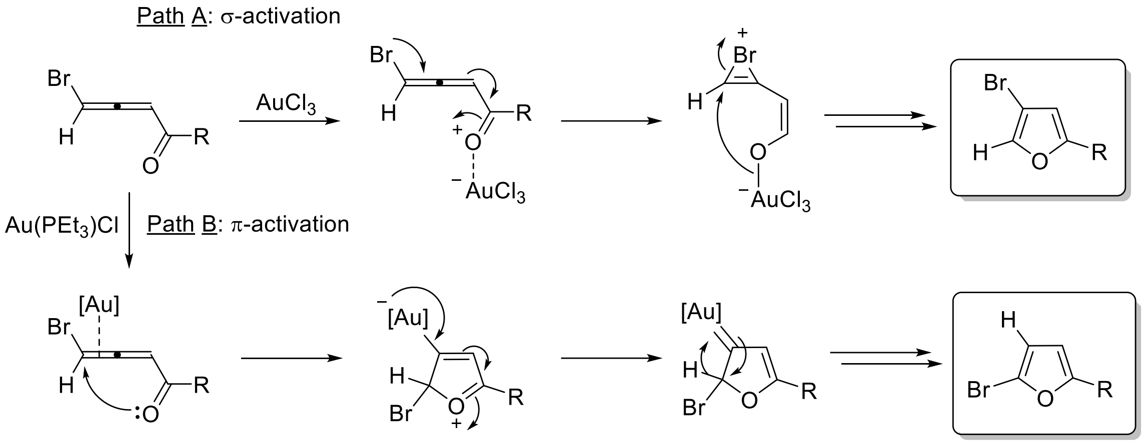
[87] (a) A. S. K. Hashmi, *Acc. Chem. Res.,* **2014,** *47*, 864-876; (b) C. Obradors; A. M. Echavarren, *Acc. Chem. Res.,* **2014,** *47*, 902-912; (c) C. Obradors; A. M. Echavarren, *Chem. Commun.,* **2014,** *50*, 16-28.

[88] M. P. Muñoz, *Chem. Soc. Rev.,* **2014,** *43*, 3164-3183.

[89] A. Furstner; P. W. Davies, *Angew. Chem. Int. Ed.,* **2007,** *46*, 3410-49.

[90] (a) O. Kanno; W. Kuriyama; Z. J. Wang; F. D. Toste, *Angew. Chem. Int. Ed.,* **2011,** *50*, 9919-9922; (b) H. Yamamoto; K. Futatsugi, *Angew. Chem. Int. Ed.,* **2005,** *44*, 1924-1942.

species are involved. This dual role exhibited by gold species as σ- and π-Lewis acids was exemplified in the regiodivergent cyclisation of halogenated allenones reported by Gevorgyan in 2005 (Scheme 1.13).[91] The authors were able to synthesise rather 1- or 2-bromo furanes by changing the gold species utilised as catalyst. While harder gold species like $AuCl_3$ led to 2-bromo furans through σ-activation (Path A), softer Gold complexes led to 1-bromo furans through π-activation (Path B).



Scheme 1.13. Regiodivergent synthesis of halogenated furans by Gevorgyan.

Catalysis with gold species have also been applied to quinoline and tetrahydroquinolines synthesis.

In 2009 Chan and co-workers developed an efficient gold catalysed route to dihydroquinolines based on an intramolecular allylic amination promoted by a dual $AuCl_3/AgSbF_6$ catalytic system under mild conditions (Scheme 1.14).[92] Although the nature of the actual catalytic species is not clear, the combination of $AuCl_3$ and $AgSbF_6$ was the only one able to efficiently catalyse the reaction. The synthetic applicability of the procedure was exemplified in the synthesis of the bioactive tetrahydroquinoline alkaloid "(±)-angustureine".

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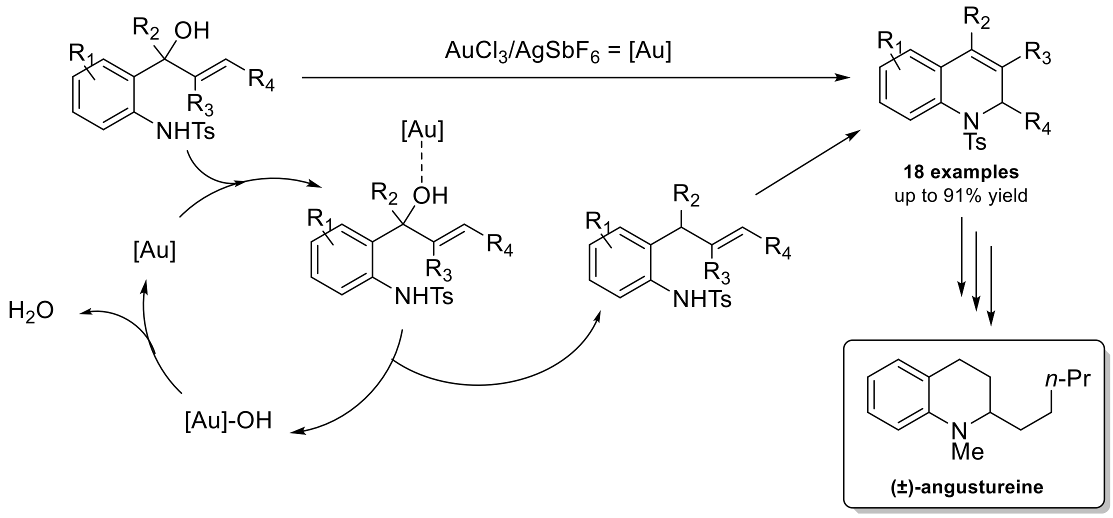
[91] A. W. Sromek; M. Rubina; V. Gevorgyan, *J. Am. Chem. Soc.,* **2005,** *127*, 10500-10501.

[92] P. Kothandaraman; S. J. Foo; P. W. H. Chan, *J. Org. Chem.,* **2009,** *74*, 5947-5952.



Scheme 1.14. Gold-catalysed angusturine alkaloid synthesis by Chan.

More recently, the group of Han developed a highly efficient chiral gold phosphate-catalysed tandem hydroamination-asymmetric transfer hydrogenation (Scheme 1.15).[93] In this case, the authors disclosed a new protocol to obtain optically active tetrahydroquinolines with highly reduced catalyst loadings.

The employment of a chiral gold phosphate generated *in situ* from IMesAuMe and a chiral phosphoric acid provided the corresponding tetrahydroquinolines in good yields and great enantioselectivities. Notably, in this reaction, the gold catalyst enables both the intramolecular hydroamination as a π-Lewis acid and the asymmetric reduction as a σ-Lewis acid, showcasing the dual role of gold as soft and hard Lewis acid.

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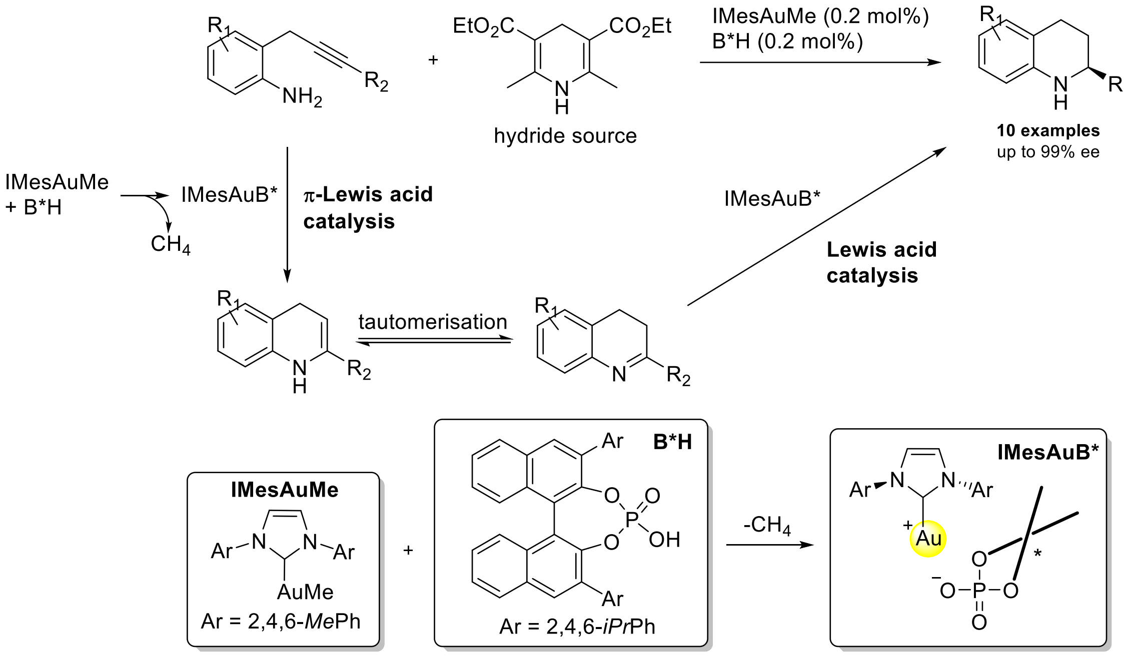
[93] Y.-L. Du; Y. Hu; Y.-F. Zhu; X.-F. Tu; Z.-Y. Han; L.-Z. Gong, *J. Org. Chem.,* **2015,** *80*, 4754-4759.



Scheme 1.15. Asymmetric gold-catalysed synthesis of chiral tetrahydroquinolines by Han.

Despite the great amount of Lewis acid-catalysed Povarov reactions found in the literature, only few of these examples are reported under gold catalysis.

1.1.4.1. Gold-catalysed Povarov reactions.

In 2014, Liu and co-workers described an oxa-Povarov reaction catalysed by gold species **A** (Scheme 1.16).[94] The carbene-based gold salt efficiently led to dihydrobenzopyrans with high levels of diastereoselectivity. The procedure tolerates a wide range of substituents in the alkene. The stereoselectivity of the reaction is determined by the chair-like transition state **TSII**, disposing the bulkier of substituents R_1/R_2 and the phenyl ring in equatorial positions, avoiding 1,3-diaxial interactions.

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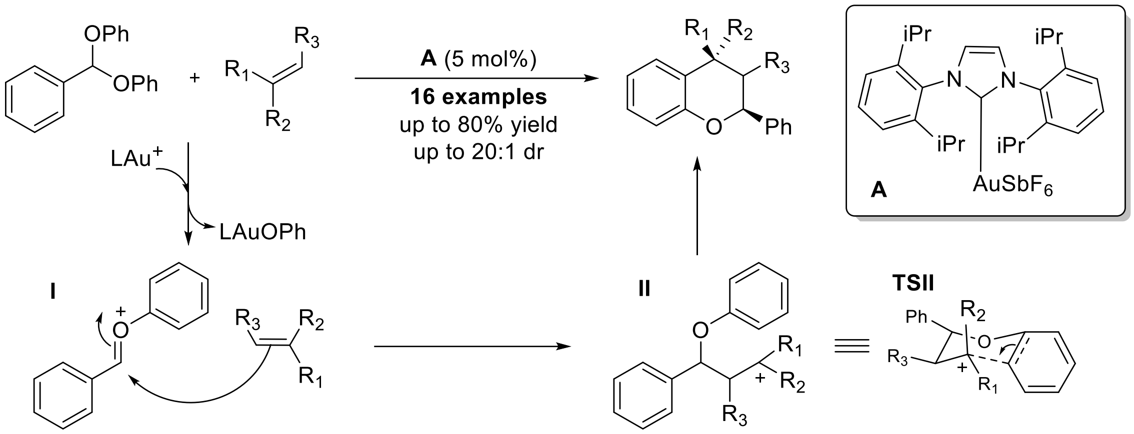
[94] V. V. Pagar, C.-C. Tseng, R.-S. Liu, *Chem. Eur. J.,* **2014,** *20*, 10519-10526.



Scheme 1.16. Gold-catalysed diastereoselective Povarov reaction.

The same year, professor Fañanás developed a new and straightforward asymmetric synthetic protocol for the diastereo- and enantioselective synthesis of tetrahydrofuran-fused tetrahydroquinolines, using a metal-organo catalytic system in which an alkynol, an aldehyde and an arylamine combine to afford the heterocyclic products (Scheme 1.17).[95] It is worth to remark that this strategy allows the straightforward preparation of tetrahydrofuran-fused tetrahydroquinolines incorporating functional groups suitable for further reactivity as part of the dienophile component, one of the main limitations of the conventional Povarov reactions. The gold-catalyst promotes a hydroalkoxylation after protonolysis, whereas the chiral BINOL-derived phosphoric acid promotes both the imine formation and the asymmetric Povarov reaction. This example of orthogonal-relay catalysis clearly demonstrates the potential of these one-pot reactions to generate enantiopure molecules with high structural complexity.

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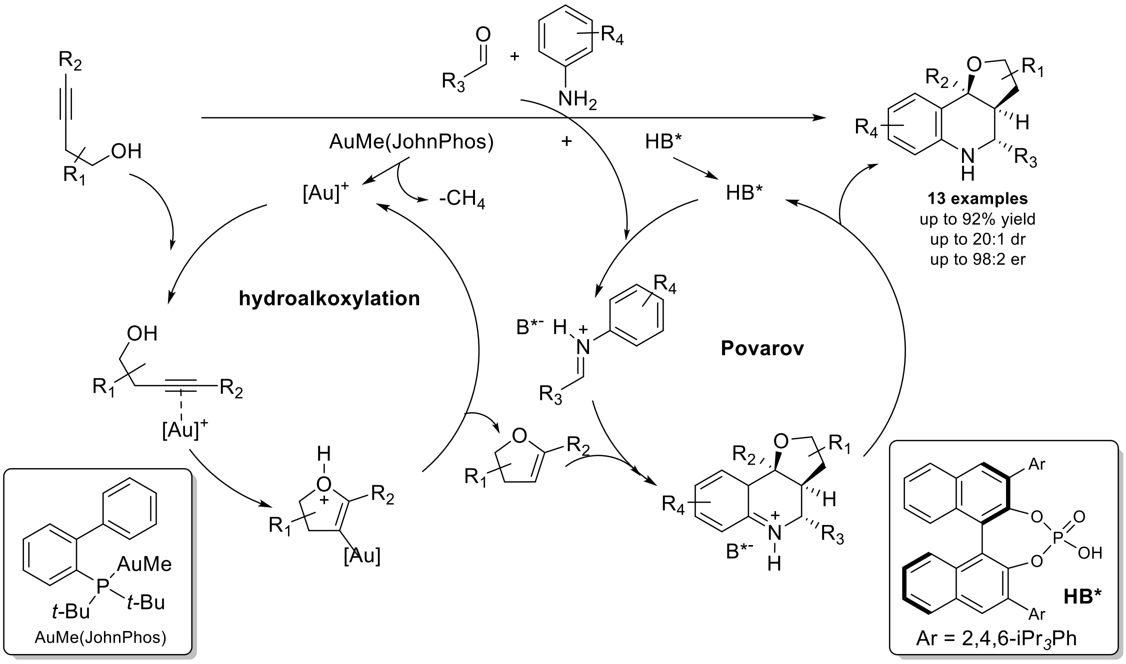
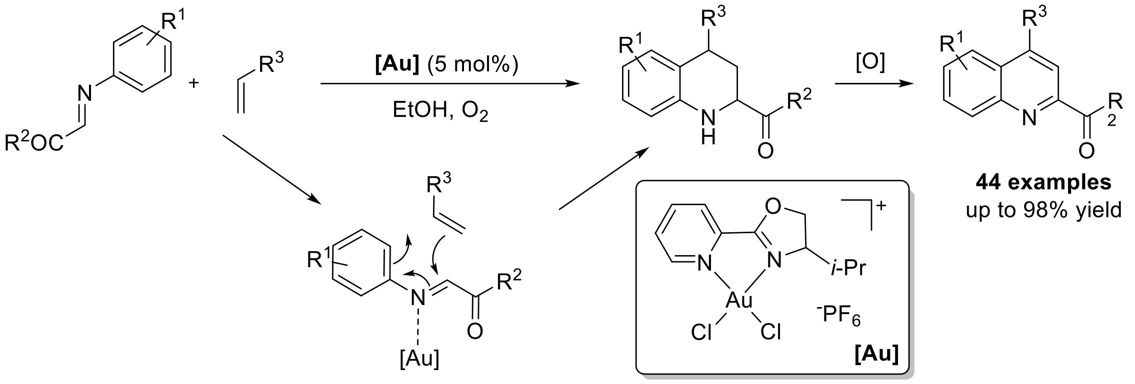
[95] J. Calleja; A. B. González-Pérez, A. R. de Lera, R. Alvarez, F. J. Fañanas, F. Rodriguez, *Chem. Sci.,* **2014,** *5*, 996-1007.



Scheme 1.17. Gold-catalysed terahydrofuran-fused tetrahydroquinolines synthesis by Fañanas.

A Au(III)-oxazoline complex catalyses a dehydrogenative Povarov reaction for the synthesis of substituted quinolines from glycine derivatives and alkenes (Scheme 1.18).[96] The reaction performs under mild reaction conditions in the presence of oxygen as the oxidant and features a broad substrate scope and excellent functional group tolerance.



Scheme 1.18. Gold-catalysed quinoline synthesis by Feng.

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[96] M. Ni; Y. Zhang; T. Gong; B. Feng, *Adv. Synth. Catal.,* **2017,** *359*, 824-831.

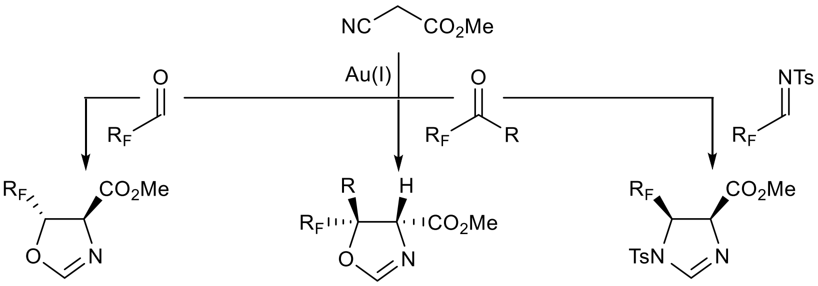
According to the author’s hypothesis, O_2 is indispensable for the synthesis of the final quinolines, not only in the imine formation stage, but also in the nucleophilic addition and aromatization steps.

In general terms, the specific and novel features displayed by gold species and its combination with either fluorinated building blocks or fluorinated reagents emerge as a powerful tool in to access interesting fluorinated compounds.[97]

1.1.4.2. Fluorine in gold chemistry.

As mentioned in the *“General Introduction”*, the employment of fluorinated building blocks has been an extensively used strategy over the years in the synthesis of new fluorine-containing molecules. Its combination with gold catalysis, known for promoting new unconventional modes of reactivity, opens new possibilities in the field of organofluorine chemistry. Despite the potential of fluorine and gold partnership, only a few reports concerning the use of fluorinated starting materials have been published to date.

The first example was reported by Hayashi and co-workers in the late 90’s (Scheme 1.19). The authors evaluated the aldol condensation of isocyanoacetic esters with fluorinated aldehydes,[98] ketones[99] and imines.[100]



Scheme 1.19. Au-catalysed aldol condensations by Hayashi.

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[97] J. Miro; C. del Pozo, *Chem Rev,* **2016,** *116*, 11924-11966.

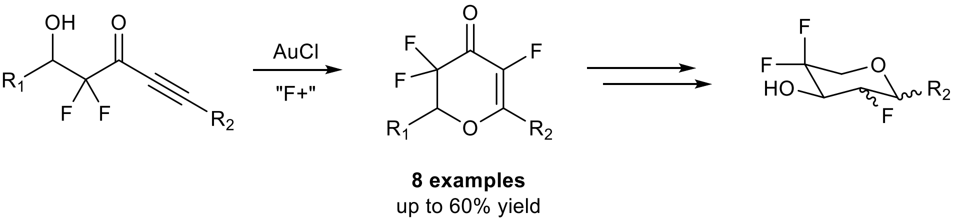
[98] V. A. Soloshonok; A. D. Kacharov; T. Hayashi, *Tetrahedron,* **1996,** *52*, 245-254.

[99] V. A. Soloshonok; A. D. Kacharov; D. V. Avilov; K. Ishikawa; N. Nagashima; T. Hayashi, *J. Org. Chem.,* **1997,** *62*, 3470-3479.

[100] T. Hayashi; E. Kishi; V. A. Soloshonok; Y. Uozumi, *Tetrahedron Lett.,* **1996,** *37*, 4969-4972.

In this particular case, gold species coordinates to the nitrile moiety, lowering the pk$_a$ of the hydrogens at the α-position, thus enabling the deprotonation in the presence of a weaker base and, in turn, the aldol condensation with the carbonyl derivative. The role of gold in these reactions became essential as it allowed the employment of milder reaction conditions, showcasing a higher functional group tolerance as compared to other conventional aldol reactions that require stronger bases.

In 2008, the group of professor Gouverneur reported one of the very first examples of a gold-mediated C-F bond formation (Scheme 1.20).[101] They disclosed a Au(I)-catalysed heterocyclisation of α,α-difluoroynones, giving rise to a new family of dihydropyranones.This methodology was further applied for the synthesis of fluorinated carbohydrate analogues.[102]



Scheme 1.20. Gouverneur's Au-catalysed fluorocyclisation.

A great example of the influence that fluorine substitution may have in gold-catalysed processees was reported by our group in 2013 (Scheme 1.21).[103]

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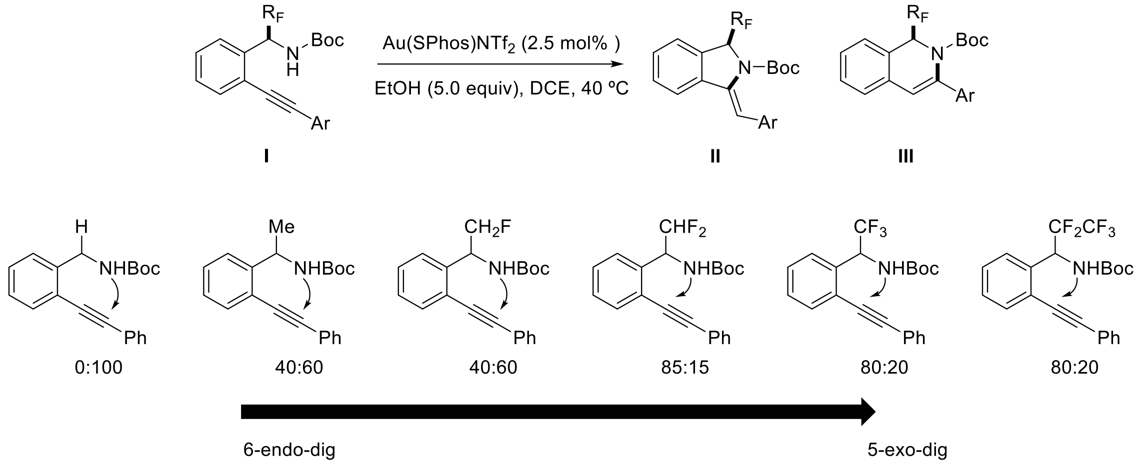
[101] M. Schuler; F. Silva; C. Bobbio; A. Tessier; V. Gouverneur, *Angew. Chem. Int. Ed.,* **2008,** *47*, 7927-7930.
[102] G. T. Giuffredi; B. Bernet; V. Gouverneur, *Eur. J. Org. Chem.,* **2011,** *2011*, 3825-3836.
[103] S. Fustero; I. Ibáñez; P. Barrio; M. A. Maestro; S. Catalán, *Org. Lett.,* **2013,** *15*, 832-835.



Scheme 1.21. Synthesis of luorinated isoindoline and isoquinolinoline derivatives by Fustero.

It was found that fluorine substitution plays a critical role in the regiochemical outcome of the intramolecular hydroamination of *ortho*-alkynyl benzyl carbamates. It is known that the electronics of the aryl substituent in the alkyne control the regioselectivity in these types of processes. Usually, electron-donating substituents in this position favour the 6-*endo*-dig cyclisation, whereas electron-withdrawing substituents lead to the 5-*exo*-trig pathway. However, in this case, likely a steric than an electronic effect was imparted by fluorine substitution, since the gradual addition of fluorine atoms to the α-position of the starting carbamates led to the 5-*exo*-dig products over the 6-*endo*-dig cyclisation. The sequential introduction of fluorine favors the formation of isoindoline derivatives **II** over isoquinolines **III**, unlike previously reported non-fluorinated reactions of this type.[104]

More recently, a gold-catalysed synthesis of fluorinated quinoline derivatives was developed in our research group (Scheme 1.22).[105] The reaction of several homopropargyl amino esters bearing aromatic substituents and a benzyl group as nitrogen substituents with gold(I) species [Au] gave rise to fluorinated quinolines in a tandem hydroarylation–isomerization process.

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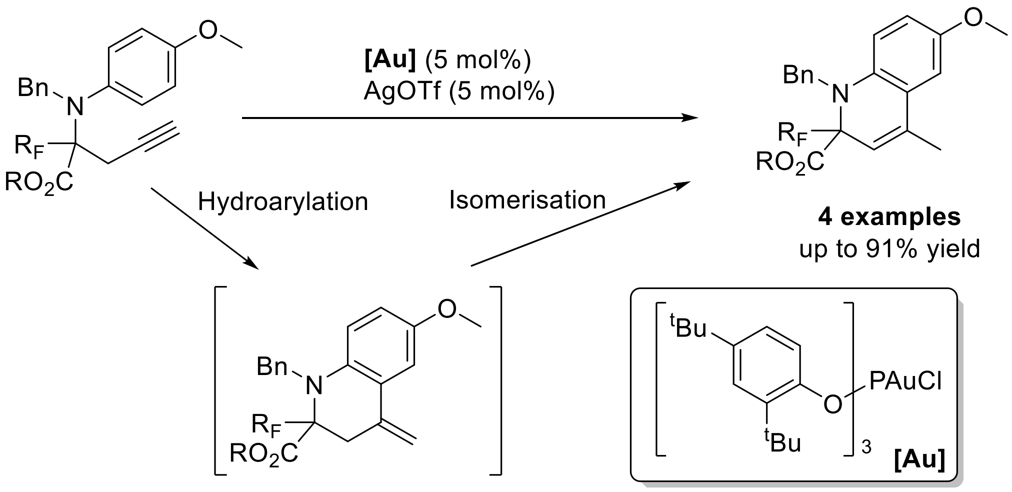
[104] T. Enomoto; A.-L. Girard; Y. Yasui; Y. Takemoto, *J. Org. Chem.,* **2009,** *74*, 9158-9164.

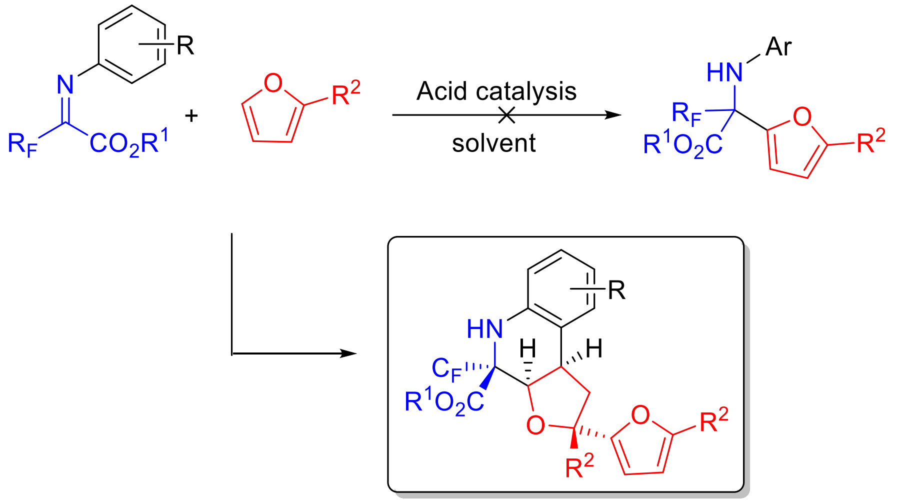
[105] M. Sánchez-Roselló; J. Miró; C. del Pozo; S. Fustero, *J. Fluorine Chem.,* **2015,** *171*, 60-66.



Scheme 1.22. Fluorinated quinoline derivatives synthesis by Fustero.

1.2. Objectives.

Despite the enormous amount of vinilogous Mannich reaction examples described over the last 20 years, the number of reactions involving the utilisation of fluorinated partners remains quite limited.[106] As illustrated in the "*General Introduction*", the incorporation of fluorine atoms to interesting organic scaffolds is a widely used strategy in order to improve its biological relevance. These two statements together reveal the great interest of applying the VMR to fluorinated substrates, in order to obtain biologically interesting molecules, increasing molecular complexity in an easy and efficient manner.[107]



Scheme 1.23. VMR over fluorinated imino esters approach.

As we indicated in the general objectives, the initial aim of this project was to evaluate the feasibility of an aza-Friedel Crafts reaction of several heterocycles (different from indoles) with fluorinated imino esters as fluorinated building blocks, in order to access the corresponding fluorinated α-amino acid derivatives. During this study, started with substituted furanes, we found a serendipitious reaction; instead of the Friedel-Crafts type addition, a Povarov type transformation took place, giving rise to the highly substituted tetrahidroquinoline derivatives showed in Scheme 1.23. We decided then to

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[106] (a) S. Preciado, E. Vicente-García, F. Labrés, F. J. Luque, R. Lavilla *Angew. Chem. Int. Ed.,* **2012,** *51*, 6874-6877; (b) J. H. Lin; G. Zong; R. B. Du; J. C. Xiao; S. Liu, *Chem. Commun.,* **2012,** *48*, 7738-7740; (c) C. Venkateswarlu; P. V. Balaji; K. De; B. Crousse; B. Figadère; J. Legros, *J. Fluorine Chem.,* **2013,** *152*, 94-98; (d) H. Yanai; H. Mimura; K. Kawada; T. Taguchi, *Tetrahedron,* **2007,** *63*, 2153-2160.

[107] G.-L. Xi; Z.-Q. Liu, *Eur. J. Med. Chem.,* **2014,** *86*, 759-768.

optimize the conditions to access those furoquinoline derivatives, and to determine the scope and limitations of the process.

1.3. Results and discussion.

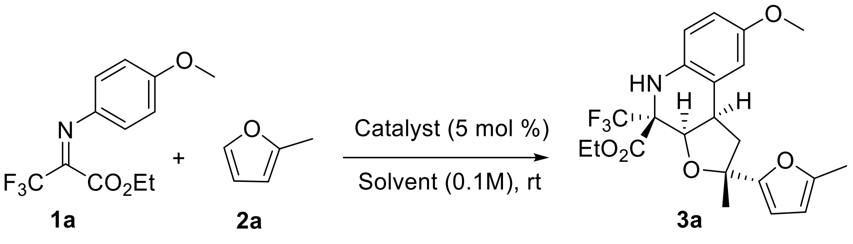
According to precedents in the literature involving the reaction with furans and highly electrophilic imines (Section I.3.1) and the elevated activation of the imine carbon of our iminoesters by two electron-withdrawing groups, namely a fluoroalkylic group and an ester group, we decided to explore the reactivity of furans against them in the presence of diverse acid catalysts.

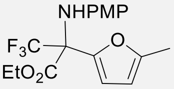
1.3.1. Optimisation.

The reaction of trifluoromethyl imino ester **1a** with 2-methyl furan **2a** was selected as model reaction in order to find the optimal conditions to carry out the desired protocol. Several catalysts were tested and the results obtained are shown in *Table 1.1*.

Firstly, several Brønsted acids were evaluated as catalysts in the reaction of one equivalent of **1a** and **2a**. In this context, the use of TFA rendered the aza-Friedel Craft product **4a** in excellent isolated yield (Table 1.1, entry 1), while triflic acid led to a different and more complex compound (later identified as **3a**) albeit in a low 20% yield (Table 1.1, entry 2). BINOL-derived phosphoric acids were examined next.[108] Unfortunately, when the model reaction was performed in the presence of either phosphoric acid **I** itself or the more acidic triflimide **II**, the starting imino ester **1a** remained unaltered (Table 1.1, entries 3, 4).

Table 1.1. Optimization of the reaction conditions for the synthesis of tricycle **3a**



Entry	Catalyst	Solvent	Conversion	Product (isolated yield)[a]
1	TFA	DCM	>95	

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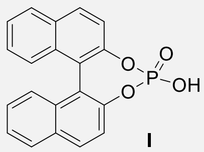
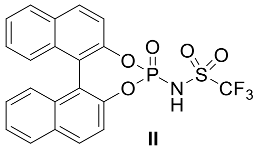
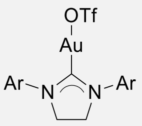
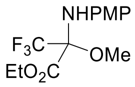
[108] T. Akiyama; Y. Honma; J. Itoh; K. Fuchibe, *Adv. Synth. Catal.,* **2008,** *350*, 399-402.

				4a (86%)
2	TfOH	DCM	>95	**3a** (20%)
3	 **I**	DCM	0	-
4	 **II**	DCM	0	-
5	$AuCl_3$	DCM	44	**3a** (37%)[b]
6	$AuCl_3$	DCM	>95	**3a** (81%)
7	PPh_3AuOTf	DCM	>95	**3a** (71%)
8	$[Au(P(4\text{-}CF_3C_6H_4)_3)]OTf$	DCM	>95	**3a** (75%)
9	 Ar = 2,6-(*i*-Pr)$_2$C$_6$H$_3$ SIPrAuOTf	DCM	>95	**3a** (86%)
10	$BF_3{\cdot}OEt_2$	DCM	>95	**3a** (67%)
11	$AuCl_3$	Toluene	<10	-
12	$AuCl_3$	THF	0	-
13	$AuCl_3$	MeCN	0	-
14	$AuCl_3$	MeOH		 **4d** (82%)

[a] Reactions were performed with **1a** (0.2 mmol) and 2 equiv of **2a** (0.4 mmol) in the presence of the corresponding catalyst (5 mol %) at rt for 12 h. [b] In this case, only 1 equiv of furan **2a** (0.2 mmol) was employed.

Considering the unpromising results obtained for the chiral Brønsted acid-catalysed examples, we decided to switch to Lewis acid catalysis.

In 2004 Li and coworkers described that gold salts are well suited catalysts for the addition of furanes to highly electrophilic imino esters (Scheme 1.24).[109] In this context, and due to the reactivity displayed by gold species in the activation of imines in their reaction with furanes, we decided to test Au(III) salts with the model substrates.

Scheme 1.24. VMR over fluorinated imino esters approach.

Imine **1a** and furan **2a** were stirred in the presence of a catalytic amount of $AuCl_3$. After 12h in dichloromethane at room temperature, together with some unreacted starting material, the formation of a new product was observed (44% conversion). After isolating this product by flash chromatography, the tricyclic tetrahydroquinoline **3a** was identified in 37% yield (Table 1.1, entry 5). The formation of **3a** would entail a Povarov-type process between the *N*-aromatic imine functionality in **1a** and one of the double bonds in the furan ring **2a**, followed by the addition of a second molecule of furan **2a** in a Friedel-Craft-type reaction.[94,110]

Noticing the incorporation of two molecules of furan to the final product, the reaction was then performed with two equivalents of **2a**, giving compound **3a** in 81% isolated yield with complete conversion (Table 1.1, entry 6). It is important to note that four stereocenters were created in only one reaction step and final tetrahydroquinoline products were obtained as mixtures of diastereoisomers, the major one being compound **3a** with the stereochemistry shown in the scheme in *Table 1.1* (see above).

Other gold(I) complexes were also tested. Hence, PPh_3AuOTf, in situ generated by combination of PPh_3AuCl and AgOTf, afforded tricycle **3a** in slightly lower yield (Table 1.1, entry 7). The use of electronically deficient phosphines such as $P(4\text{-}CF_3C_6H_4)_3$ in the

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[109] Y. Luo; C.-J. Li, *Chem. Commun.,* **2004**, 1930-1931.
[110] A. M. Jadhav; V. V. Pagar; R. S. Liu, *Angew. Chem. Int. Ed.,* **2012,** *51*, 11809-11813.

starting gold salt did not lead to better yields, giving rise to compound **3a** in 75% yield (Table 1.1, entry 8) whereas the NHC-derived gold(I) complex [1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene gold triflate, SIPrAuOTf] provided the best results, leading to **3a** in 86% yield (Table 1.1, entry 9).

Our tandem protocol was also suitable to be carried out with $BF_3.OEt_2$ as the Lewis acid although in a less efficient manner (Table 1.1, entry 10).[111]

Then, the solvent screening was performed subsequently. The reaction in toluene resulted in very poor conversion (<10%), whereas in the presence of more polar solvents such as THF or MeCN, the reactions did not proceed at all (Table 1.1, entries 11-13). Finally, when the reaction was carried out in MeOH, fluorinated hemiaminal **4d**, arising from the nucleophilic addition of the solvent to the starting imino ester **1a** was the only identified product (Table 1.1, entry 14).

At this point, the optimal reaction conditions were established when treating imino ester **1a** and 2 equivalents of furan **2a** with either $AuCl_3$ or SIPrAuOTf as the catalysts, in dichloromethane at room temperature. These conditions were applied to other fluorinated imino esters **1** and furans **2**. Thus, the evaluation of the scope of this tandem process produced the results displayed in *Table 2*.

1.3.2. Scope and limitations

In order to evaluate the scope and limitations of our protocol, we firstly prepared a small library of iminoesthers and furans. All starting materials were either commercially available or synthesised by already known and described methodologies.

On the one hand, iminoesters **1a-f** and **1j-m** were prepared by an aza-Wittig reaction involving the corresponding pyruvate and iminophosphorane, as described in *section I.2.1*. On the other hand, iminoesters **1g-i** needed an alkoxycarbonylation process to be prepared, from the corresponding fluorinated carboxylic acid and *p*-methoxy aniline. Aldimines **1n** and **1o** were synthesised by condensation of the hemiacetal and *p*-methoxy aniline (for detailed processes see *Experimental section*) (Figure 1.4).

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[111] Y. Gong; K. Kato; H. Kimoto, *Synlett,* **2000,** 1058-1060.

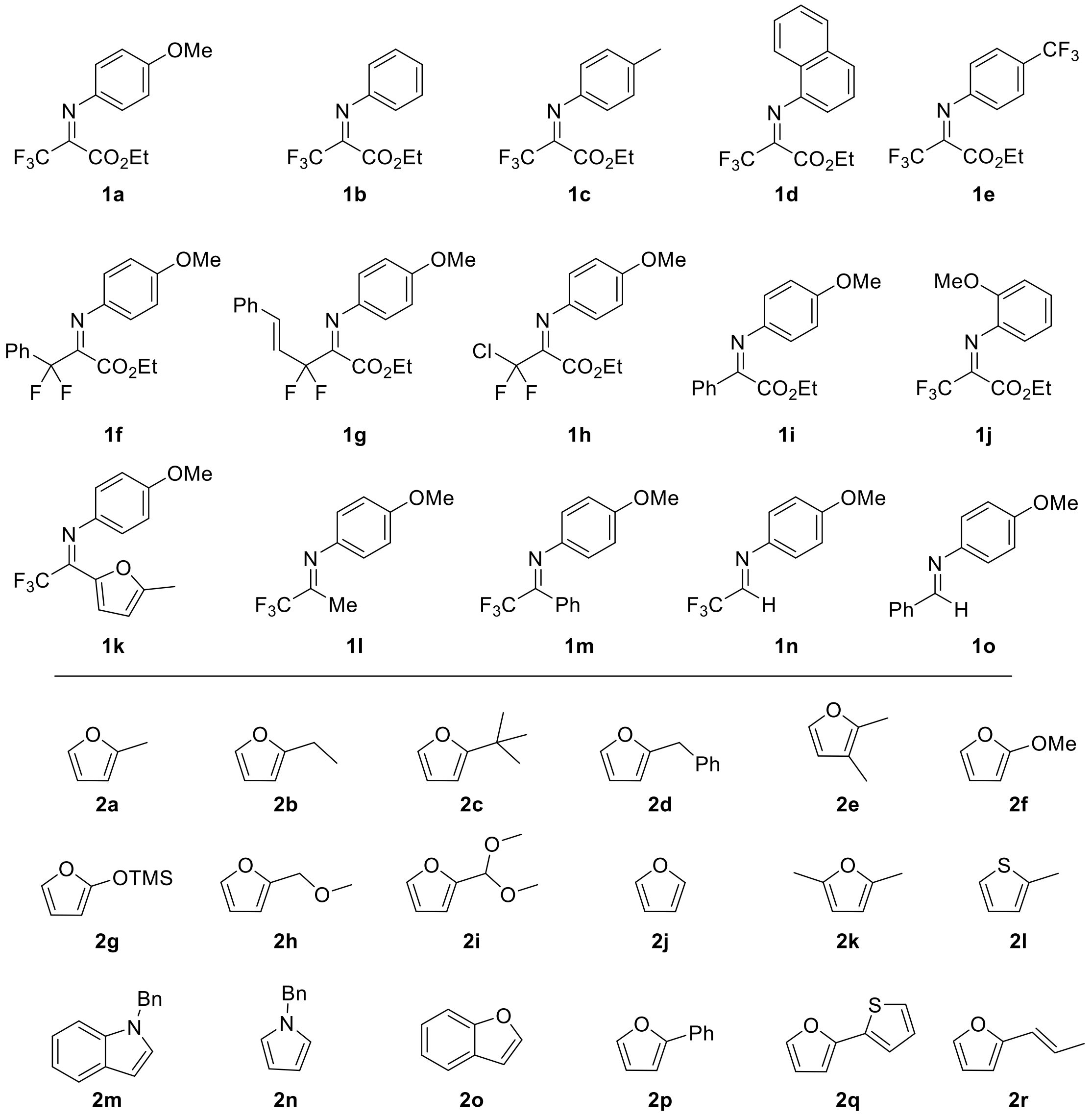
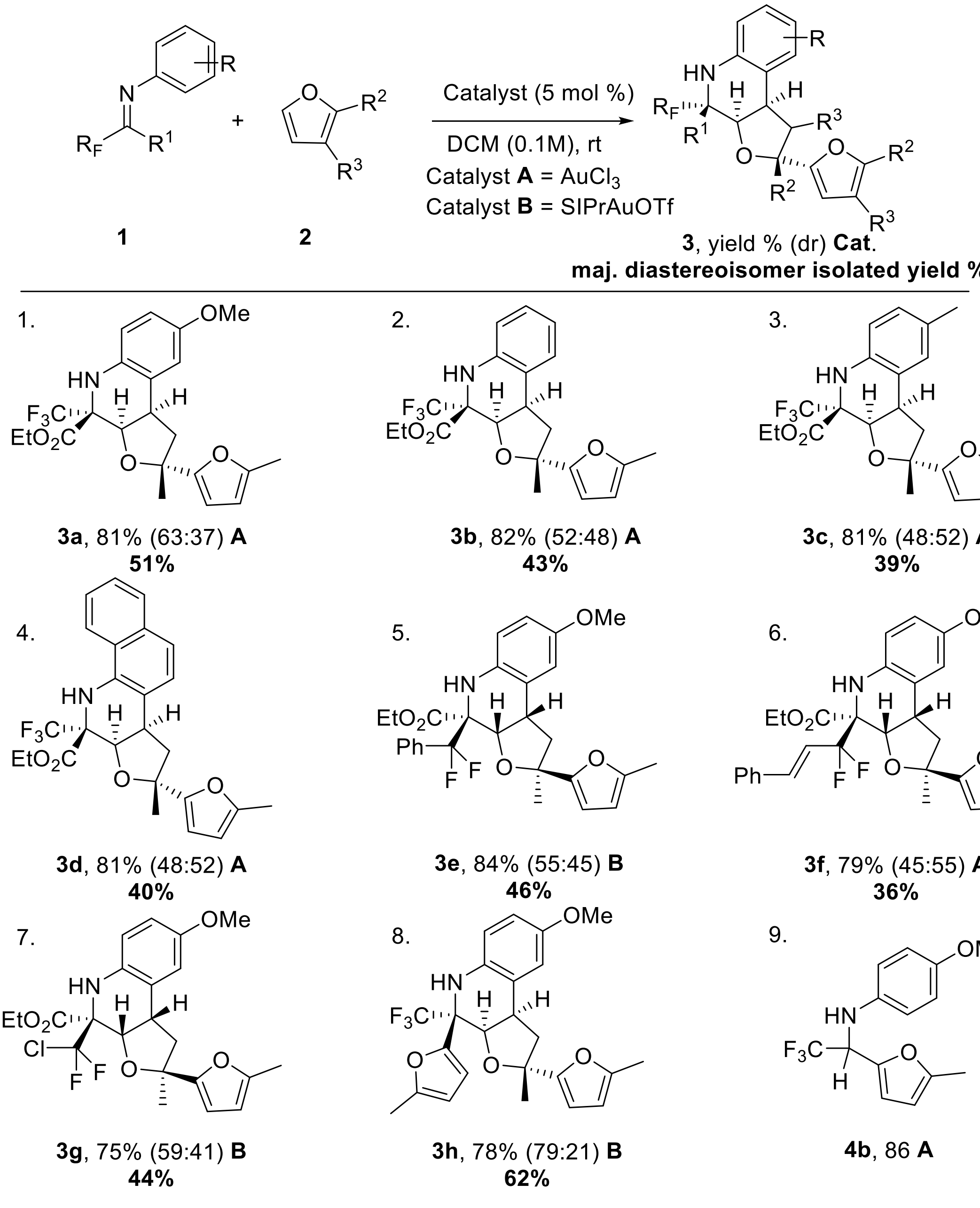


Figure 1.4. Library of imines and furans.

As indicated in *Table 1.1*, trifluoromethyl imino ester **1a** reacted with furan **2a** in the presence of $AuCl_3$ to render the corresponding tricyclic tetrahydroquinoline as a mixture of four diastereoisomers in 81% overall yield (Table 2, entry 1). Fortunately, the major diastereoisomer **3a**, which represented 63% of the products mixture, had a clearly different chromatographic behaviour and it could be isolated in 51% yield and fully characterized (see *Supporting Information*). The rest of diastereoisomers (37% of the products mixture) appeared together from the column and it was not possible to separate them. Analogous performance was observed for the rest of products **3**.

The next step of our study was directed at the evaluation of the influence of the substituents on the aromatic ring of the starting imino esters **1**. Substrates **1b** (with a phenyl ring), **1c** (with a *p*-tolyl) and **1d** (with a 1-naphthyl) attached to the nitrogen underwent the tandem protocol efficiently, affording final products in 82%, 81% and 81% overall yield, respectively (Table 1.2, entries 2-4).

Table 1.2. Scope of the reaction: imines.



3a, 81% (63:37) **A**
51%

3b, 82% (52:48) **A**
43%

3c, 81% (48:52) **A**
39%

3d, 81% (48:52) **A**
40%

3e, 84% (55:45) **B**
46%

3f, 79% (45:55) **A**
36%

3g, 75% (59:41) **B**
44%

3h, 78% (79:21) **B**
62%

4b, 86 **A**

Remarkably, substrate **1d** gave access to a fluorinated steroid-type skeleton, highly studied and used structures in biological and medicinal chemistry. On the other hand, imino ester **1e** bearing an electron-withdrawing group (CF_3) yielded a complex mixture of non-identified products. The reaction was also compatible with other fluorinated moieties such as $PhCF_2$, $Ph-CH=CH-CF_2$ or CF_2Cl. Tricycles **3e**, **3f** and **3g** were, therefore, obtained as the major diastereoisomers in good overall yields (Table 1.2, entries 5-7).

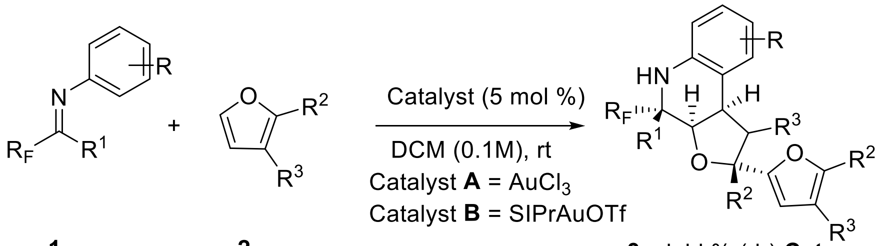
Non-fluorinated iminoester **1i** gave no reaction and the starting material was fully recovered while **1j**, with a methoxy group in the ortho position of the aromatic ring led to a complex mixture of products. Fluorinated ketimines **1l**, **m** and aldimine **1o** did not react under our protocol conditions. Finally, fluorinated aldimine **1n** was also tested in its reaction with furan **2a**. Trifluoromethyl amine **4b**, arising from the aza-Friedel Craft reaction, was isolated in 86% yield (Table 1.2, entry 9).

Trifluoromethyl ketimine **1k** was found to be a good partner in the tandem reaction with 2-methyl furan **2a**, giving rise to tetrahydroquinoline **3h** as the major product from a mixture of diastereoisomers with 78% overall yield (Table 1.2, entry 8).

The scope of the furan counterpart **2** was also explored. Accordingly, 2-ethyl furan **2b** took efficiently part in the tandem process with trifluoromethyl imino esters **1a-c**, leading to the corresponding tricyclic derivatives **3i-k** in good yields (Table 1.3, entries 1-3). The introduction of a methyl substituent at position 3 of the furan–ring **2e** (R^3) generated an additional stereocenter in the final product. An equimolecular mixture of diastereoisomers at the tetrahydrofuran ring in compound **3l** was observed in this case (Table 1.3, entry 4).

Surprisingly, the more activated furans **2f** and **2g**, bearing a methoxy and a trimethylsyliloxy group at position 2, did not react with imino ester **1a** under the reaction conditions. Our procedure was also limited by the employment of alkylated furans **2h** and **2i**, bearing oxygen atoms in the carbon chain and by the utilisation of vinyl substituted furan **2r**. At this point, we considered the possibility of an electrostatic interaction between the positively charged gold catalyst and the lone electron pairs from oxygen atoms, poisoning the catalyst and avoiding any conversion of the starting material.

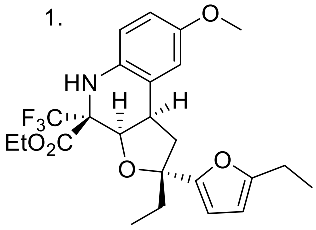
Table 1.3. Scope of the reaction: furans.



1 **2** **3**, yield % (dr) **Cat.**

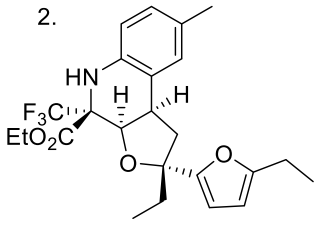
maj. diastereoisomer isolated yield

1.



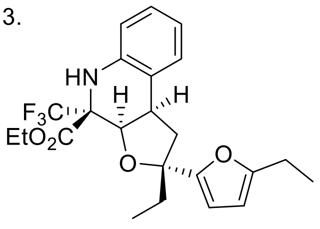
3i, 85% (45:55) **A**
38%

2.



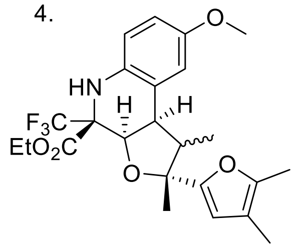
3j, 82% (46:54) **A**
38%

3.



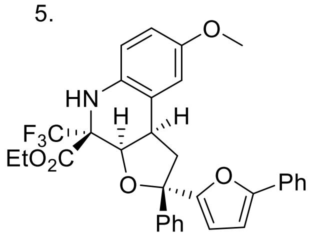
3k, 75% (42:58) **A**
32%

4.



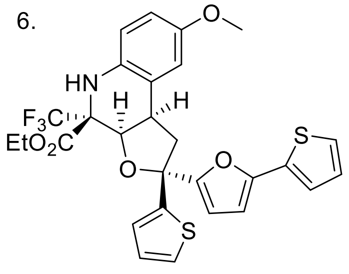
3l, 58% (45:55) **B**
37%

5.



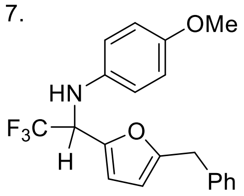
3m, 56% (71:29) **B**
40%

6.



3n, 51% (53:43) **B**
29%

7.



4c, 65 **A**

Other alkyl substituents at that position, such as the benzyl group in furan **2d**, gave the aza-Friedel Craft product **4c** in 65% yield (Table 1.3, entry 7), whereas *tert*-butyl group in **2c** led to a complex mixture of inseparable products. However, non-substituted furan **2j** and dimethyl furan **2k** were found to remain unreactive against imine **1a**.

Aryl and heteroaryl substituents in **2p** and **2q** were also suitable partners for the tandem protocol, although in those cases the conversion was not complete and some starting material was recovered (Table 1.3, entries 5, 6). In this manner, tetrahydroquinolines

3m and **3n** were successfully synthesised in a 40% and 27% isolated yield respectively as major diastereoisomers.

Different heterocycles were tested as nucleophilic partners for imine **1a**. Thiophene **2l**, benzyl protected indole **2m**, pyrrole **2n** or benzo-fused furane **2o** all remained unaltered under our reaction conditions with either the chlorinated gold salt catalyst and the carbene based one.

1.3.3. Stereochemistry.

The relative stereochemistry of the major diastereoisomer **3** was determined by means of NMR experiments on compound **3b**. Specifically, the combination of HOESY and NOESY studies led us to identify the arrangement of the protons and the trifluoromethyl group in the tricyclic structure. Initially, the relative disposition of the trifluoromethyl group and the tetrahydrofuran ring was elucidated by a HOESY experiment. The heteronuclear correlation between fluorine nuclei and protons **Ha** and **Hb** (Figure 1.5, left) allowed us to assign the relative cis stereochemistry at those positions. The cis relationship between those protons and the furan ring was determined by means of a NOESY experiment, which showed the correlation between proton **Ha** and protons **Hc** and **Hd** of the furan ring (Figure 1.5, right). The same stereochemical assignment was assumed for all tetrahydroquinolines **3**.

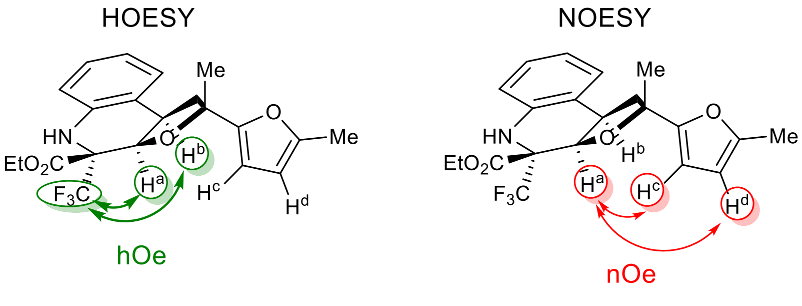


Figure 1.5. Stereochemical assignment on compound **3b**.

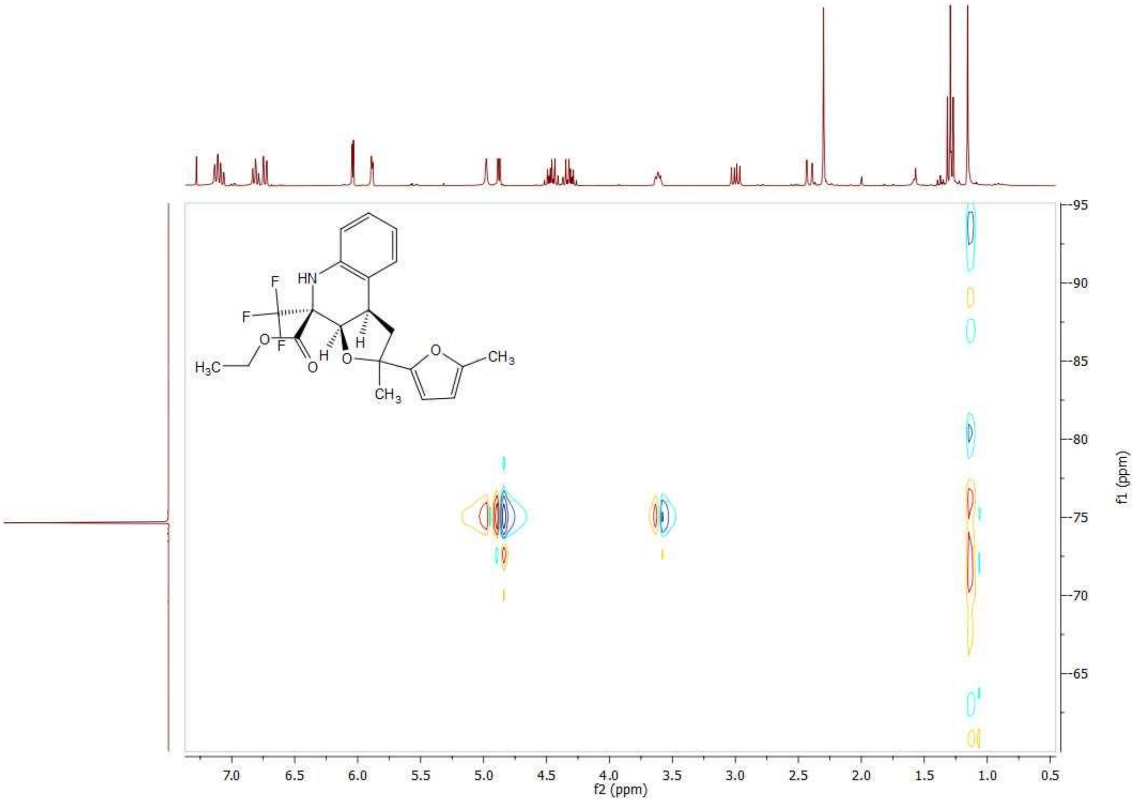


Figure 1.6. HOESY of compound **3b**.

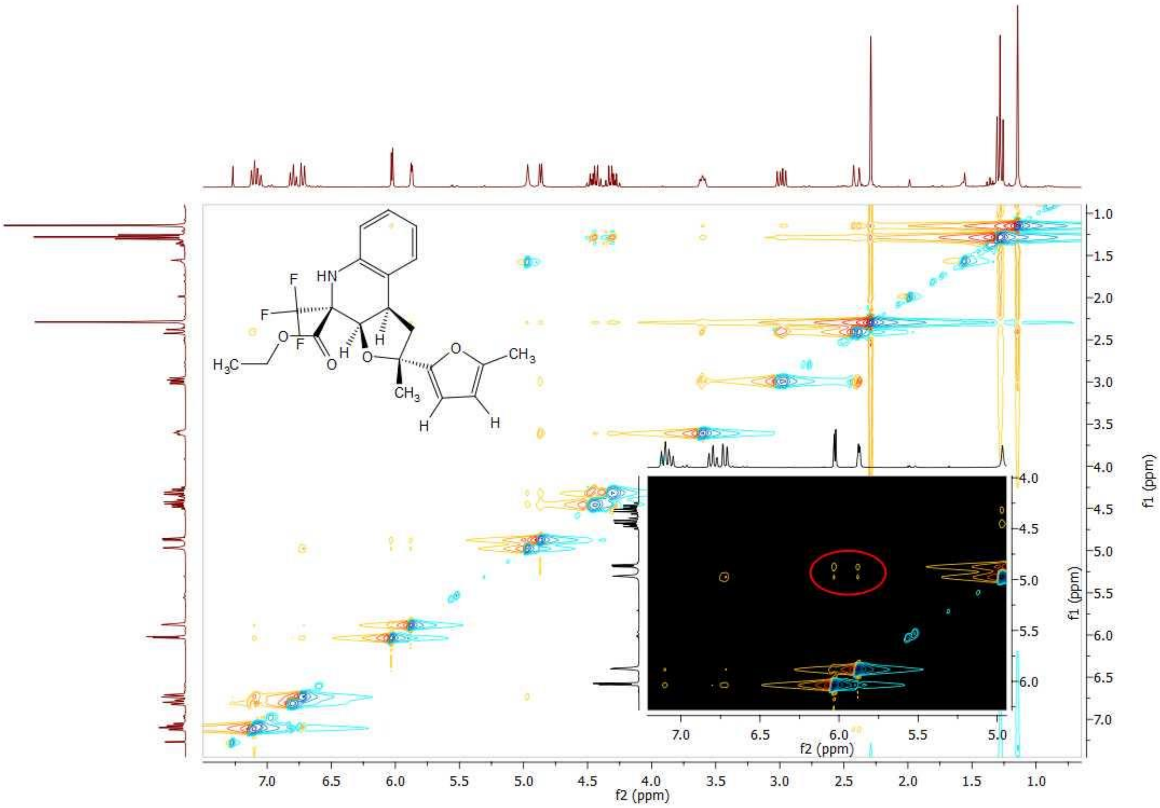


Figure 1.7. NOESY of compound **3b**.

1.3.4. Mechanistic proposal.

A plausible mechanistic rationale for the transformation presented herein is depicted in *Scheme 1.25*. In a first step, imino ester **1** would be activated by the gold salt (acting as σ-Lewis acid) for the vinilogous Mannich addition of the furan–ring through its position 5. This attack would generate oxonium salt intermediate **A**, which would evolve through the nucleophilic attack by the *ortho* position of the aromatic ring giving rise to tricyclic intermediate **B** (aza-Diels Alder product in a Povarov reaction).[112] Upon [1,3]-proton shift and coordination of the gold salt (acting as π-Lewis acid) with the enol ether moiety (intermediate **C**), the nucleophilic addition of a second molecule of furan **2** would take place in a formal Friedel-Craft type process, consequently releasing the final tetrahydroquinoline **3** and regenerating the gold catalytic species (Scheme 1.25). It is noteworthy to mention that this tandem protocol constitutes another example of the dual σ- and π-Lewis role imparted by gold salts.[113]

Considering this reaction pathway, it is possible to rationalize the results shown in *Table 1.2* and *1.3*. On the one hand, the introduction of electron–withdrawing substituents into the aromatic ring (imino ester **1e**; R = CF_3) would decrease the nucleophilicity of the *ortho* position, avoiding the formation of intermediate **B** and, therefore, the whole process. On the other hand, the formation of intermediate **D** is most likely to play an important role in the success of the tandem protocol: after the activation of the enol ether functionality in intermediate **C** by the gold salt, the addition of the second molecule of furan would render final products **3** in an irreversible way. With more activated furans such as **2g** (R = OMe), intermediate **B** would contain an acetal functionality instead of an enol ether. The activation of the acetal moiety would not take place in this case and the equilibrium would be shifted to the starting material which indeed remained unaltered. Alternatively, when steric hindrance at the 2-position of the furan increases, which is the case of 2-benzyl furan **2d**, complexation of the gold salt is disfavored, thus rendering the aza-Friedel-Craft products **4**. More difficult to explain is the behavior observed with fluorinated aldimine **1n**.

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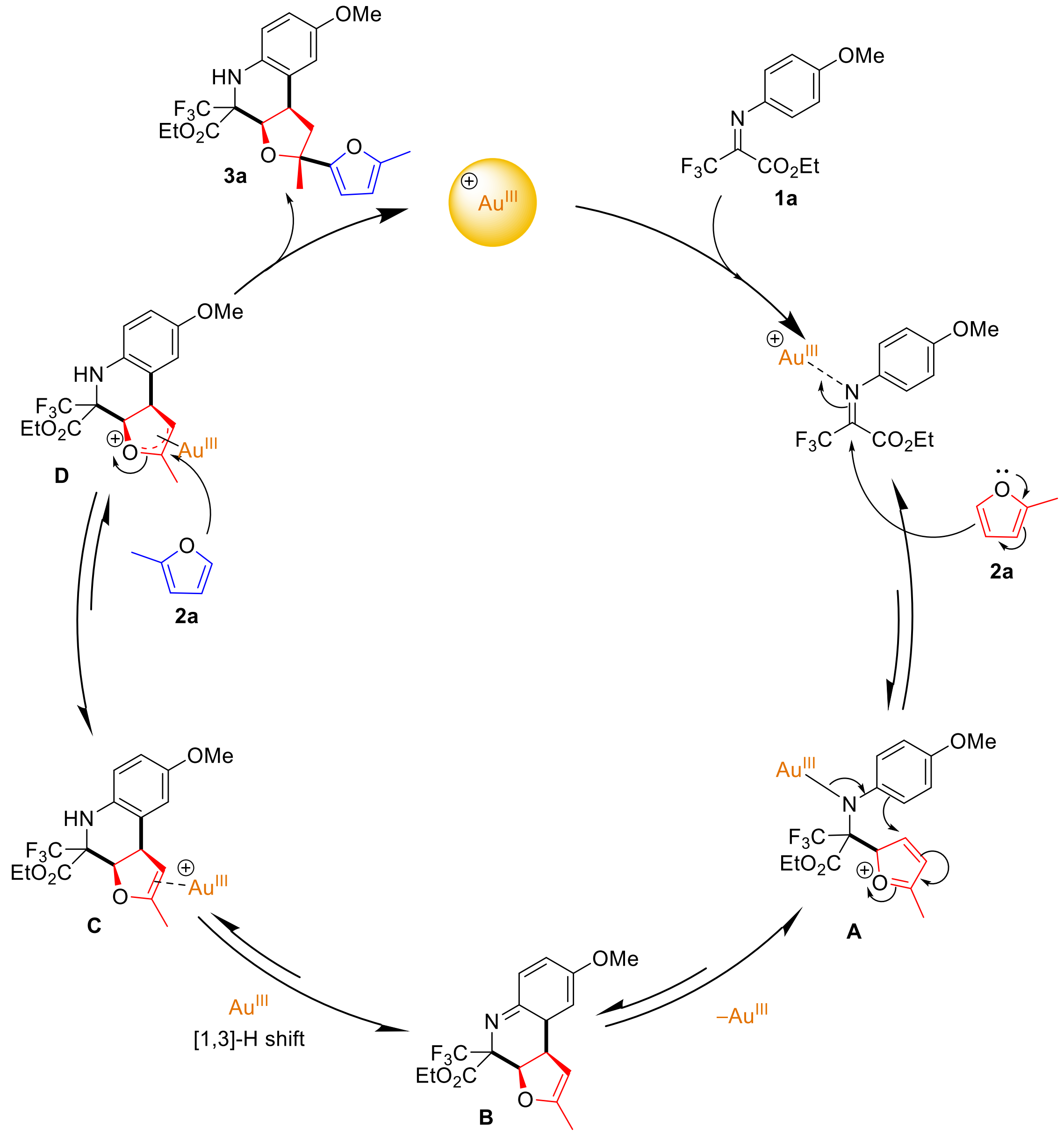
[112] J. Miró; M. Sánchez-Roselló; J. González; C. del Pozo; S. Fustero, *Chem. Eur. J.,* **2015,** *21*, 5459-5466.

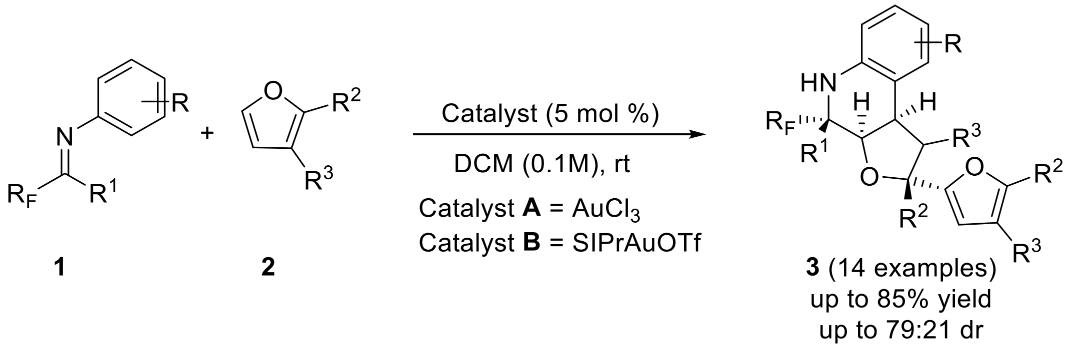
[113] S. Fustero; J. Miró; M. Sánchez-Roselló; C. del Pozo, *Chem. Eur. J.,* **2014,** *20*, 14126-14131.



Scheme 1.25. Mechanistic proposal for the synthesis of tricyclic tetrahydroquinolines **3**.

1.4. Conclusions.

In summary, the vinilogous addition of furans to fluorinated imines have been studied. Nevertheless, the Lewis acid catalysed reaction was found to yield tetrahydrofuran-fused tetrahydroquinolines in one reaction step, generating complex fluorinated scaffolds in a very simple manner.[114]



Scheme 1.26. Gold-catalysed tandem procedure.

In this chapter we have developed a new tandem protocol that involves a Povarov-type reaction followed by a formal Friedel–Crafts reaction, which rendered furoquinoline derivatives **3** in good yields and moderate levels of diastereoselectivity. Additionally, major diastereoisomers could be separated from the rest in most cases, allowing their isolation and characterization.

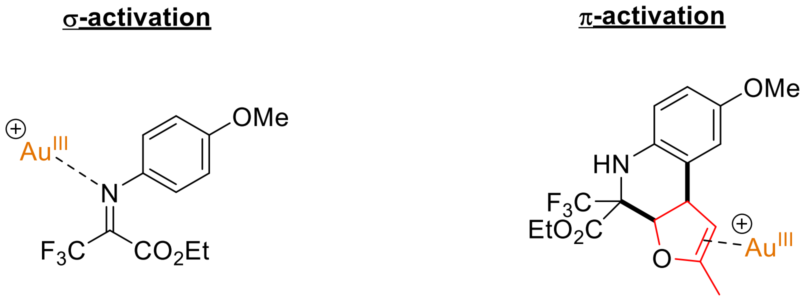


Figure 1.8. Gold dual σ- *vs* π-activation.

The process was efficiently catalysed by gold complexes, either $AuCl_3$ or SIPrAuOTf, promoting a tandem protocol that highlights the dual role imparted by gold species over

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[114] Á. Sanz-Vidal; J. Miró; M. Sánchez-Roselló; C. del Pozo; S. Fustero, *J. Org. Chem.*, **2016,** *81*, 6515-6524.

multiple C-C bonds, thus acting as σ- and π-Lewis acid in different stages of the same reaction pathway.

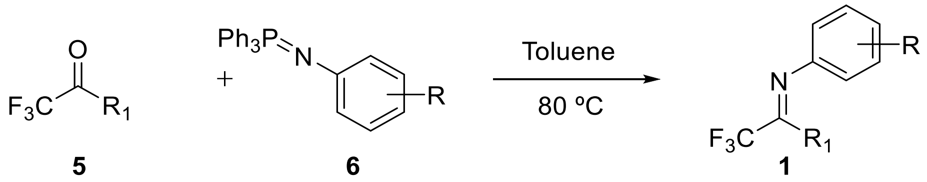
A wide variety of imino esters **1** were compatible with the process, allowing electron-donating, -neutral and –withdrawing substitution in the aromatic moiety as well as different moieties in the fluorinated alkyl chain. However, the scope regarding the starting furans **2** is more limited.

It is noteworthy that this is the first reported Povarov-type protocol involving furans as dienophiles.

1.5. Experimental section.

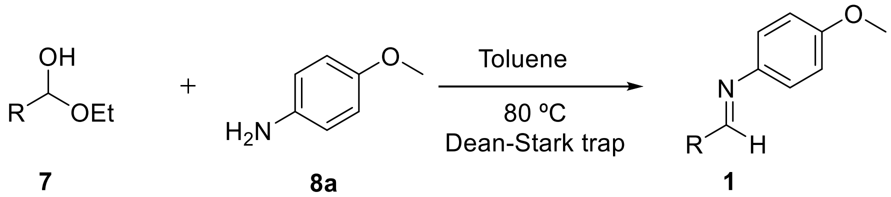
1.5.1. Preparation of the starting imines **1**.

Procedure A: Ketone condensation.



To a solution of the iminophosphorane[115] **6** (5 mmol) in dry toluene (20 mL), the corresponding ketone **5** (5 mmol) was added dropwise and the reaction mixture was stirred at 80ºC for 18 hours. Then the reaction mixture was cooled to room temperature and solvents were eliminated under reduced pressure. Et_2O (20 mL) was added and cooled to 0ºC. The white precipitate was filtered through a pad of Celite and washed with cold Et_2O (3 x 10 mL). The filtrate was concentrated under reduced pressure and purified by *flash* column chromatography.

Procedure B: Aldehyde condensation.



To a solution of the aldehyde **7** (5 mmol) and *p*-anisidine **8a** (5 mmol) in dry toluene (15 mL), *p*-toluene sulfonic acid (5 mg) was added and the reaction mixture was stirred at reflux under Ar atmosphere for 1.5 hours with a Dean-Stark trap. The mixture was washed with a saturated solution of $NaHCO_3$ (3 x 15 mL) and brine (20 mL). The organic phase was then dried over Na_2SO_4 and solvents eliminated under reduced pressure. The crude product was purified by *flash* column chromatography.

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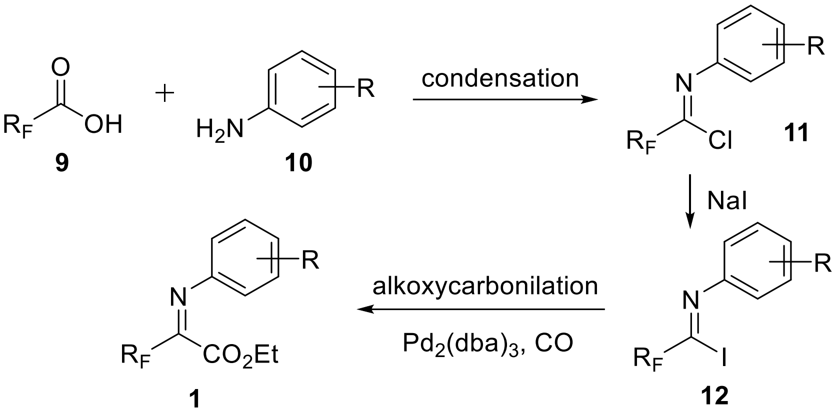
[115] S. Fustero; P. Bello; J. Miro; M. Sanchez-Rosello; M. A. Maestro; J. Gonzalez; C. d. Pozo, *Chem. Commun.,* **2013,** *49*, 1336-1338.

Procedure C: Alkoxycarbonilation.[25a]

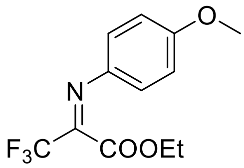


To a solution of triphenyl phosphine (33 mmol) and triethylamine (13.2 mmol) in CCl_4 (20 mL) the corresponding carboxylic acid **9** (11 mmol) was added and stirred for 5 minutes at room temperature. Then, the aryl amine **10** (13.2 mmol) dissolved in more CCl_4 (10 mL) was added and the reaction mixture refluxed overnight. After cooling to room temperature and evaporation of the solvents, triphenyl phosphine oxide precipitate was eliminated by filtration with hexane and the crude product purified by column chromatography.

NaI (11.6 mmol) was added to a solution of the corresponding imidoyl chloride **11** (7.1 mmol) in dry acetone (20 mL) and the mixture was stirred at room temperature protected from light for 48 hours. The reaction mixture was then quenched with a saturated aqueous solution of $Na_2S_2O_3$ and the aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (3 x 15 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation of solvents quantitatively gave the corresponding crude imidoyl iodides **12** as yellow oils; these were subsequently used in the next step of the synthesis with no further purification.

Under CO atmosphere (1 atm), a solution of the previously obtained imidoyl iodide **12** in a toluene/DMF mixture (10 mL/1 mL) and the corresponding alcohol (8.5 mmol) were both added to a two-necked flask containing K_2CO_3 (14.2 mmol) and palladium catalyst $Pd_2(dba)_3·CHCl_3$ (0.28 mmol). The reaction mixture was stirred at room temperature until the starting material was totally consumed, as confirmed by means of TLC. The crude reaction mixture was then filtered through a silica pad and washed with CH_2Cl_2.

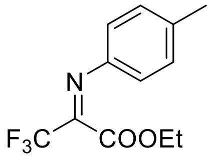
The solvents were eliminated under reduced pressure and the mixture was purified by means of *flash* column chromatography.



Ethyl-3,3,3-trifluoro-2-[(4-methoxyphenyl)imino]propanoate (1a). Following general procedure **A**, from 5 mmol of the corresponding iminophosphorane and 5 mmol of trifluoropyruvate, 4.6 mmol (92%) of the desired imine were obtained after purification by column chromatography Hex:EtOAc (10:1) as an orange oil.

Spectroscopic data for the titled compound are consistent with the literature.[114]

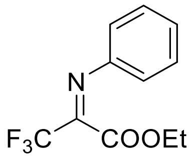
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.01 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).



Ethyl-3,3,3-trifluoro-2-(p-tolylimino)propanoate (1b). Following general procedure **A**, from 5 mmol of the corresponding iminophosphorane and 5 mmol of trifluoropyruvate, 4.55 mmol (91%) of the desired imine were obtained after purification by column chromatography Hex:EtOAc (10:1) as a pale yellow oil.

Spectroscopic data for the titled compound are consistent with the literature.[114]

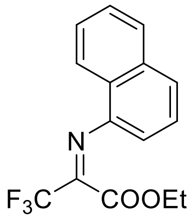
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.09 (d, *J* = 7.9 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.28 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H).



Ethyl-3,3,3-trifluoro-2-(phenylimino)propanoate (1c). Following general procedure **A**, from 5 mmol of the corresponding iminophosphorane and 5 mmol of trifluoropyruvate, 4.75 mmol (95%) of the desired imine were obtained after purification by column chromatography Hex:EtOAc (10:1) as a pale yellow oil.

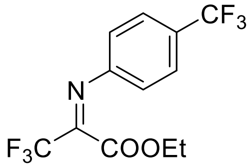
Spectroscopic data for the titled compound are consistent with the literature.[106]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24-7.31 (m, 1H), 7.10-7.20 (m, 1H), 7.02-7.09 (m, 1H), 6.83-6.89 (m, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 0.97 (t, *J* = 7.2 Hz, 3H).



Ethyl (E)-3,3,3-trifluoro-2-[(2-methoxyphenyl)imino]propanoate (1d). Following general procedure **A**, from 5 mmol of the corresponding iminophosphorane and 5 mmol of trifluoropyruvate, 4.35 mmol (87%) of the desired imine were obtained after purification by column chromatography Hex:EtOAc (10:1) as a brownish oil.

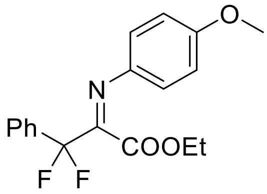
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.93 – 7.86 (m, 2H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.41 (dd, *J* = 8.3, 7.3 Hz, 1H), 6.87 (dd, *J* = 7.3, 0.9 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 0.93 (t, *J* = 7.1 Hz, 3H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -69.92 (s).^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.8 (s), 149.8 (q, *J* = 36.9 Hz), 143.6 (s), 134.1 (s), 128.2 (s), 127.8 (s), 127.4 (s), 127.0 (s), 126.6 (s), 125.4 (s), 123.6 (s), 118.6 (q, *J* = 277.5 Hz), 113.1 (s), 63.1 (s), 13.8 (s). HRMS (ES) calc. for (M+1) $C_{15}H_{12}F_3NO_2F_3$: 296.0893; found: 296.0899.



Ethyl-3,3,3-trifluoro-2-([4-(trifluoromethyl)phenyl]imino)propanoate (1e). Following general procedure **A**, from 5 mmol of the corresponding iminophosphorane and 5 mmol of trifluoropyruvate, 4.25 mmol (85%) of the desired imine were obtained after purification by column chromatography Hex:EtOAc (10:1) as a pale yellow oil.

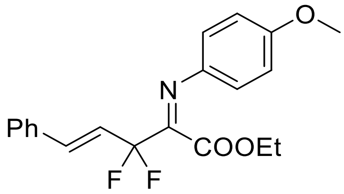
Spectroscopic data for the titled compound are consistent with the literature.[112]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.57 (d, *J* = 8.2 Hz, 2H), 6.94 (d, *J* = 8.1 Hz, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 1.00 (t, *J* = 7.1 Hz, 3H).



Ethyl (E)-3,3-difluoro-2-[(4-methoxyphenyl)imino]-3-phenylpropanoate (1f). Following general procedure **C**, from 11 mmol of the corresponding carboxylic acid and 13.2 mmol of *p*-anysidine, 8.91 mmol (81%) of the desired imine were obtained after purification by column chromatography Hex:EtOAc (10:1) as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68 – 7.65 (m, 2H), 7.50 – 7.46 (m, 3H), 6.91 (d, *J* = 9.1 Hz, 2H), 6.83 (d, *J* = 9.1 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -97.57 (s).^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.7 (s), 158.9 (s), 140.9 (s), 135.2 (s), 131.0 (s), 130.9 (s), 129.4 (s), 128.8 (s), 126.4 (t, *J* = 6.0 Hz), 122.0 (s), 117.3 (t, *J* = 246.4 Hz), 114.5 (s), 62.5 (s), 55.8 (s), 14.2 (s). HRMS (ES) calc. for (M+1) $C_{18}H_{17}F_2NO_3$: 334.1249; found: 334.1242.



Ethyl (2E,4E)-3,3-difluoro-2-[(4-methoxyphenyl)imino]-5-phenylpent-4-enoate (1g). Following general procedure **C**, from 11 mmol of the corresponding carboxylic acid and 13.2 mmol of *p*-anysidine, 8.69 mmol (79%) of the desired imine were obtained after purification by column chromatography Hex:EtOAc (10:1) as an orange oil.

Spectroscopic data for the titled compound are consistent with the literature.[116]

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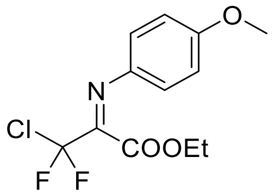
[116] S. Fustero; V. Rodrigo; M. Sanchez-Rosello; F. Mojarrad; A. Vicedo; T. Moscardo; C. del Pozo, *J. Fluorine Chem.,* **2008,** *129*, 943-950.

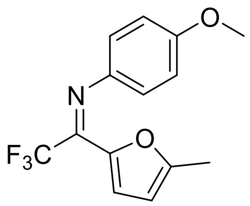
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53 – 7.50 (m, 2H), 7.45 – 7.35 (m, 2H), 7.15 (dt, *J* = 4.5, 2.5 Hz, 1H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.56 (dt, *J* = 16.2, 11.5 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H).



Ethyl (E)-3-chloro-3,3-difluoro-2-[(4-methoxyphenyl)imino]propanoate (1h). Following general procedure **C**, from 11 mmol of the corresponding carboxylic acid and 13.2 mmol of *p*-anysidine, 9.79 mmol (89%) of the desired imine were obtained after purification by column chromatography Hex:EtOAc (10:1) as a brownish oil.

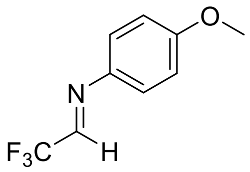
Spectroscopic data for the titled compound are consistent with the literature.[106]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.02 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H).



(E)-2,2,2-trifluoro-N-(4-methoxyphenyl)-1-(5-methylfuran-2-yl)ethan-1-imine (1i). Following general procedure **A**, from 5 mmol of the corresponding iminophosphorane and 5 mmol of the corresponding ketone, 4.45 mmol (89%) of the desired imine were obtained after purification by distillation under reduced pressure as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.90 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 9.0 Hz, 2H), 6.31 (d, *J* = 3.5 Hz, 1H), 5.99 (dd, *J* = 3.6, 0.9 Hz, 1H), 3.82 (s, 3H), 2.21 (s, 3H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -69.20 (d, J = 0.5 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.5 (s), 156.4 (s), 144.8 (s), 144.4 (s), 142.9 (s), 142.5 (s), 120.7 (s), 120.7 (s), 120.1 (q, J = 278.13), 119.9 (s), 114.8 (s), 108.9 (s), 55.9 (s), 14.0 (s). HRMS (ES) calc. for (M+1) $C_{14}H_{12}F_3NO_2$: 284.0893; found: 284.0898.



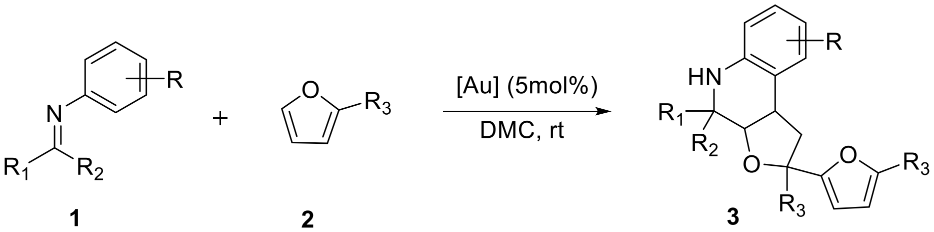
2,2,2-trifluoro-N-(4-methoxyphenyl)ethan-1-imine (1j). Following general procedure **B**, from 5 mmol of the corresponding iminophosphorane and 5 mmol of the corresponding aldehyde, 3.75 mmol (75%) of the desired imine were obtained after purification by distillation under reduced pressure as pale yellow oil.

Spectroscopic data for the titled compound are consistent with the literature.[117]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.85 (q, *J* = 3.7 Hz, 1H), 7.31 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 3.86 (s, 3H).

1.5.2. General procedure for the gold catalysis.

To a small vial fitted with a screw cap and a magnet, 0.1 mmol of the corresponding imine **1** was added with 1 mL of dry DCM and the vial purged with nitrogen. Then 0.2 mmol of the corresponding furan **2** was added and 5 mol% of either hydrogen gold tetrachloride or carbene gold (I) catalyst loaded and the reaction mixture was stirred overnight at room temperature. Once reaction time was completed, the mixture was filtered through a silica pad and the product purified by *flash* column chromatography.



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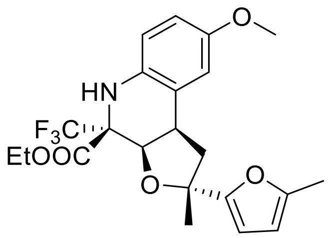
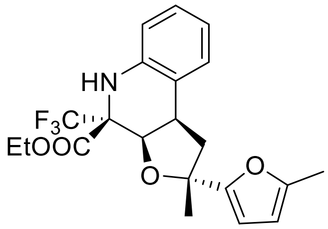
[117] (a) H. Mimura; K. Kawada; T. Yamashita; T. Sakamoto; Y. Kikugawa, *J. Fluorine Chem.,* **2010,** *131*, 477-486; (b) A. Abouabdellah; J.-P. Bégué; D. Bonnet-Delpon; T. T. Thanh Nga, *J. Org. Chem.,* **1997,** *62*, 8826-8833.



Ethyl (2*R,3a*R**,4*S**,9b*R**)-8-methoxy-2-methyl-2-(5-methylfuran-2-yl)-4-(trifluoromethyl)-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-4-carboxylate (3a).** Following the general procedure, from 28 mg of imine **1a**, 18 µL of 2-methyl furan and 1.5 mg of gold (III) tetrachloride, 35.5 mg (81%) of the desired product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.1), as a mixture of diastereoisomers 63:37 (major diastereoisomer : other diastereoisomers). **3a** was obtained (22 mg, 51%) as a yellowish oil, while the rest of diastereoisomers eluted together from the column.

Major diastereoisomer:

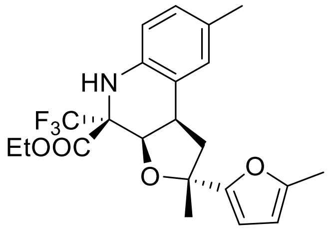
^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.69 – 6.68 (m, 3H), 6.01 (d, *J* = 3.1 Hz, 1H), 5.87 – 5.85 (m, 1H), 4.83 (d, *J* = 4.8 Hz, 1H), 4.43 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.29 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.76 (s, 3H), 3.58 – 3.54 (m, 1H), 2.97 (dd, *J* = 12.9, 7.5 Hz, 1H), 2.36 (dd, J = 12.9, 1.2 Hz, 1H), 2.28 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.16 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ: -74.96 (s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.3 (s), 157.3 (s), 153.2 (s), 151.6 (s), 133.8 (s), 124.1 (q, *J* = 293.5 Hz), 123.1 (s), 116.8 (s), 113.8 (s), 113.4 (s), 105.8 (s), 105.1 (s), 79.5 (s), 74.7 (s), 64.4 (q, *J* = 26.8 Hz), 63.2 (s), 55.8 (s), 45.4 (s), 39.2 (s), 26.9 (s), 13.9 (s), 13.7 (s). HRMS (ES) calc. for (M+1) $C_{22}H_{24}F_3NO_5$: 440.1679; found: 440.1694.



Ethyl (2*R,3a*R**,4*S**,9b*R**)-2-methyl-2-(5-methylfuran-2-yl)-4-(trifluoromethyl)-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-4-carboxylate (3b).** Following the general procedure, from 25 mg of imine **1b**, 18 µL of 2-methyl furan and 1.5 mg of gold (III) tetrachloride, 33.5 mg (82%) of the desired product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.1), as a mixture of diastereoisomers 52:48 (major diastereoisomer : other diastereoisomers). **3b** was obtained (17 mg, 43%) as a yellowish oil, while the rest of diastereoisomers eluted together from the column.

Major diastereoisomer:

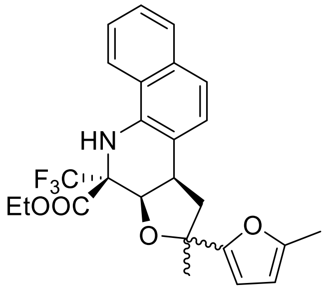
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.12 – 7.04 (m, 2H), 6.79 (td, *J* = 7.5, 1.2 Hz, 1H), 6.71 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.02 (d, *J* = 3.0 Hz, 1H), 5.87 (dd, *J* = 3.0, 1.0 Hz, 1H), 4.96 (s, 1H), 4.86 (dd, *J* = 4.8, 1 Hz, 1H), 4.44 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.30 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.61 – 3.57 (m, 1H), 2.98 (dd, *J* = 12.9, 7.4 Hz, 1H), 2.39 (dd, *J* = 12.9, 1.1 Hz, 1H), 2.28 (d, *J* = 1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.13 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ: -75.12 (s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.2 (s), 157.4 (s), 151.6 (s), 139.9 (s), 128.6 (s), 127.4 (s), 124.1 (q, *J* = 295.4 Hz), 121.6 (s), 119.3. (s), 115.4 (s), 105.8 (s), 105.0 (s), 79.6 (s), 74.7 (s), 64.1 (q, *J* = 26.5 Hz) 63.2 (s), 45.4 (s), 38.9 (s), 26.9 (s), 13.9 (s), 13.7 (s). HRMS (ES) calc. for (M+1) $C_{21}H_{22}F_3NO_4$: 410.1574; found: 410.1585.



Ethyl (2*R,3a*R**,4*S**,9b*R**)-2,8-dimethyl-2-(5-methylfuran-2-yl)-4-(trifluoromethyl)-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-4-carboxylate (3c).** Following the general procedure, from 26 mg of imine **1c**, 18 µL of 2-methyl furan and 1.5 mg of gold (III) tetrachloride, 34.3 mg (81%) of the desired product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.1), as a mixture of diastereoisomers 48:52 (major diastereoisomer : other diastereoisomers). **3c** was obtained (16 mg, 39%) as a yellowish oil, while the rest of diastereoisomers eluted together from the column.

Major diastereoisomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.90 – 6.86 (m, 2H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.02 (d, *J* = 3.1 Hz, 1H), 5.87 (dq, *J* = 3.0, 1.0 Hz, 1H), 4.85 (sa, 1H), 4.83 (s, 1H), 4.44 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.29 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.58 – 3.54 (m, 1H), 2.96 (dd, *J* = 12.9, 7.4 Hz, 1H), 2.38 (dd, *J* = 12.9, 1.3 Hz, 1H), 2.28 (d, *J* = 0.9 Hz, 3H), 2.25 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.15 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ: -75.03 (s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.3 (s), 157.5 (s), 151.5 (s), 137.4 (s), 128.9 (s), 128.4 (s), 128.1 (s), 124.2 (q, J = 290.1 Hz), 121.6 (s), 115.5 (s), 105.8 (s), 105.0 (s), 79.6 (s), 74.8 (s), 64.3 (q, J = 26.7 Hz), 63.1 (s), 45.4 (s), 38.9 (s), 26.9 (s), 20.8 (s), 13.9 (s), 13.7 (s). HRMS (ES) calc. for (M+1) $C_{22}H_{24}F_3NO_4$: 424.1730; found: 424.1746.

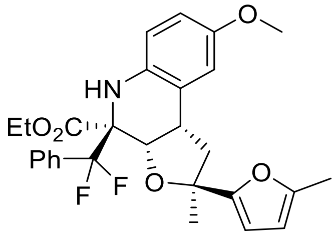


Ethyl (3a*R,11*S**,11a*R**)-2-methyl-2-(5-methylfuran-2-yl)-11-(trifluoromethyl)-2,3,3a,10,11,11a-hexahydrobenzo[h]furo[2,3-c]quinoline-11-carboxylate (3d)**. Following the general procedure, from 29.5 mg of imine **1d**, 18 µL of 2-methyl furan and 3 mg of SIPrAuOTf, 37.4 mg (85%) of the desired product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.1), as a mixture of diastereoisomers 48:52 (2 major diastereoisomers : other diastereoisomers). **3d** was obtained (18 mg, 40%) as a brownish oil together with other unseparable diastereoisomer in 3:1 ratio, while the rest of diastereoisomers eluted together from the column.

Major diastereoisomers mixture (3:1):

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.95 (dd, *J* = 8.2, 1.1 Hz, 0.3H), 7.80 – 7.77 (m, 1H), 7.72 – 7.69 (m, 0.3H), 7.55 – 7.41 (m, 2.6H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.25 (d, *J* = 10.3 Hz, 1.3H), 7.13 (d, *J* = 8.5 Hz, 0.3H), 6.02 (d, *J* = 3.0 Hz, 1H), 5.87 (dq, *J* = 3.0, 1.0 Hz, 1H), 5.56 (s, 1H), 5.48 (d, *J* = 3.0 Hz, 0.3H), 5.44 (s, 0.3H), 5.24 (dq, *J* = 3.0, 1.0 Hz, 0.3H), 4.96 (d, *J* = 4.8 Hz, 1.3H), 4.55 – 4.31 (m, 2.6H), 3.77 – 3.73 (m, 1.3H), 3.05 (dd, *J* = 13.0, 7.5 Hz, 1H), 2.87 (dd, *J* = 13.0, 0.6 Hz, 0.3H), 2.58 (dd, *J* = 13.0, 7.5 Hz, 0.3H), 2.49 (dd, *J* = 13.0, 0.6 Hz, 1H), 2.29 (d, *J* = 0.9 Hz, 3H), 1.64 (d, *J* = 0.9 Hz, 1H), 1.55 (s, 1H), 1.40 (t, *J* = 7.1 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.05 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ: -

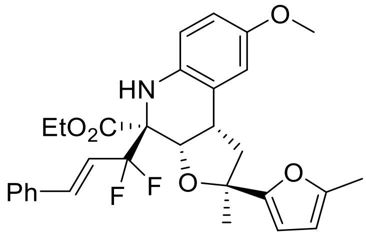
74.91 (s), -75.05 (s).^{13}C NMR (126 MHz, CDCl$_3$) δ: 166.3 (s), 166.3 (s), 157.3 (s), 155.6 (s), 151.4 (s), 150.1 (s), 134.6 (s), 134.3 (s), 133.0 (s), 132.9 (s), 128.3 (s), 128.1 (s), 126.3 (s), 126.2 (s), 125.7 (s), 125.5 (s), 125.3 (s), 125.1 (s),123.9 (q, *J* = 288.2 Hz), 123.8 (s), 120.6 (s), 120.4 (s), 119.7 (s), 119.2 (s), 116.2 (s), 116.0 (s), 105.7 (s), 105.4 (s), 104.9 (s), 104.7 (s), 79.8 (s), 79.6 (s), 74.4 (s), 64.1 (q, *J* = 27.1 Hz), 63.3 (s), 46.1 (s), 44.8 (s), 39.8 (s), 39.3 (s), 31.6 (s), 27.1 (s), 26.8 (s), 22.7 (s), 14.1 (s), 14.0 (s), 13.8 (s), 13.6 (s), 12.7 (s). HRMS (ES) calc. for (M+MeOH) $C_{25}H_{24}F_3NO_4$: 492.1992; found: 492.1999.



Ethyl (2*S,3a*S**,4*R**,9b*S**)-4-[difluoro(phenyl)methyl]-8-methoxy-2-methyl-2-(5-methylfuran-2-yl)-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-4-carboxylate (3e).** Following the general procedure, from 33 mg of imine **1f**, 18 µL of 2-methyl furan and 3 mg of SIPrAuOTf, 41.7 mg (84%) of the desired product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.1), as a mixture of diastereoisomers 55:45 (major diastereoisomer : other diastereoisomers). **3e** was obtained (23 mg, 46%) as a yellowish oil, while the rest of diastereoisomers eluted together from the column.

Major diastereoisomer:

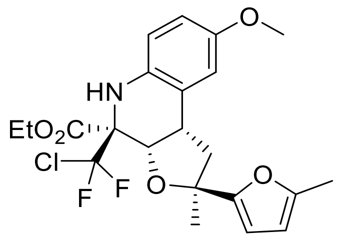
^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.45 – 7.35 (m, 5H), 6.72 – 6.69 (m, 2H), 6.64 (d, *J* = 9.4 Hz, 1H), 6.04 (d, *J* = 3.0 Hz, 1H), 5.89 – 5.88 (m, 1H), 5.11 (d, *J* = 4.8 Hz, 1H), 4.50 (bs, 1H), 4.33 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.12 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.79 (s, 3H), 3.74 – 3.72 (m, 1H), 3.01 (dd, *J* = 12.9, 7.6 Hz, 1H), 2.39 (dd, *J* = 12.9, 0.8 Hz, 1H), 2.30 (d, *J* = 0.7 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.17 (s, 3H).^{19}F NMR (282 MHz, CDCl$_3$) δ: -103.19 (d, *J* = 37.2 Hz).^{13}C NMR (126 MHz, CDCl$_3$) δ: 167.0 (s), 156.8 (s), 151.6 (s), 150.2 (s), 133.5 (s), 132.5 (t, *J* = 26.0 Hz), 129.2 (s), 126.8 (s), 125.4 (t, *J* = 6.3 Hz), 123.0 (s), 119.9 (t, *J* = 233.4 Hz), 115.2 (s), 112.8 (s), 111.9 (s), 104.6 (s), 103.6 (s), 77.9 (s), 74.1 (s), 65.4 (t, *J* = 26.8 Hz), 61.3 (s), 54.7 (s), 44.5 (s), 38.7 (s), 26.0 (s), 12.8 (s), 12.6 (s). HRMS (ES) calc. for (M+1) $C_{28}H_{29}F_2NO_5$: 498.2087; found: 498.2096.



Ethyl (2*S,3a*S**,4*R**,9b*S**)-4-[(E)-1,1-difluoro-3-phenylallyl]-8-methoxy-2-methyl-2-(5-methylfuran-2-yl)-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-4-carboxylate (3f).** Following the general procedure, from 36 mg of imine **1g**, 18 µL of 2-methyl furan and 1.5 mg of gold (III) tetrachloride, 41.3 mg (79%) of the desired product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.1), as a mixture of diastereoisomers 45:55 (major diastereoisomer : other diastereoisomers). **3f** was obtained (23 mg, 36%) as a yellowish oil, while the rest of diastereoisomers eluted together from the column.

Major diastereoisomer:

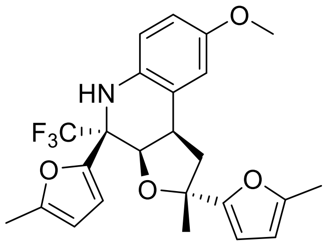
^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.24 – 7.21 (m, 3H), 7.15 (dd, *J* = 6.9, 2.7 Hz, 2H), 6.83 (dd, *J* = 16.1, 2.2 Hz, 1H), 6.63 (d, *J* = 1.5 Hz, 2H), 6.55 (s, 1H), 6.11 (dt, *J* = 16.1, 12.1 Hz, 1H), 5.93 (d, *J* = 3.0 Hz, 1H), 5.78 – 5.77 (m, 1H), 4.79 (d, *J* = 4.8 Hz, 1H), 4.74 (s, 1H), 4.33 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.19 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.67 (s, 3H), 3.45 (dd, *J* = 6.3, 5.6 Hz, 1H), 2.85 (dd, *J* = 12.9, 7.6 Hz, 1H), 2.24 (dd, *J* = 12.9, 1.1 Hz, 1H), 2.19 (d, *J* = 0.8 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.08 (s, 3H).^{19}F NMR (282 MHz, CDCl$_3$) δ: -103.00 (ddd, *J* = 246.1, 11.6, 2.3 Hz, 1F), -105.88 (dd, J = 242.1, 12.4 Hz, 1F).^{13}C NMR (126 MHz, CDCl$_3$) δ: 168.3 (s), 157.7 (s), 152.8 (s), 151.3 (s), 135.1 (t, *J* = 9.5 Hz), 134.9 (s), 134.8 (s), 129.1 (s), 128.7 (s), 127.3 (s), 123.6 (s), 120.3 (t, *J* = 254.4 Hz), 120.0 (t, *J* = 24.4 Hz), 116.6 (s), 113.7 (s), 113.4 (s), 105.6 (s), 104.6 (s), 78.9 (s), 75.2 (s), 66.4 (t, *J* = 26.2 Hz), 62.4 (s), 55.8 (s), 45.5 (s), 39.3 (s), 27.0 (s), 13.9 (s), 13.6 (s). HRMS (ES) calc. for (M+1) $C_{30}H_{31}F_2NO_5$: 524.2243; found: 524.2246.



Ethyl (2*S,3a*S**,4*R**,9b*S**)-4-(chlorodifluoromethyl)-8-methoxy-2-methyl-2-(5-methylfuran-2-yl)-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-4-carboxylate (3g).** Following the general procedure, from 29 mg of imine **1h**, 18 µL of 2-methyl furan and 3 mg of SIPrAuOTf, 34.1 mg (75%) of the desired product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.2), as a mixture of diastereoisomers 59:41 (major diastereoisomer : other diastereoisomers). **3g** was obtained (20 mg, 44%) as a brownish oil, while the rest of diastereoisomers eluted together from the column.

Major diastereoisomer:

^{1}H NMR (300 MHz, CDCl$_3$) δ: 6.71 – 6.69 (m, 3H), 6.03 (d, *J* = 3.0 Hz, 1H), 5.88 (dd, *J* = 3.0, 1.0 Hz, 1H), 4.92 (d, *J* = 3.8 Hz, 2H), 4.45 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.31 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.78 (s, 3H), 3.64 – 3.57 (m, 1H), 2.99 (dd, *J* = 12.9, 7.5 Hz, 1H), 2.39 (dd, *J* = 12.9, 0.9 Hz, 1H), 2.30 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.18 (s, 3H).^{19}F NMR (282 MHz, CDCl$_3$) δ: -58.98 (d, *J* = 158.8 Hz, 1F), -60.78 (dd, *J* = 158.8, 2.1 Hz, 1F).^{13}C NMR (126 MHz, CDCl$_3$) δ: 166.5 (s), 157.3 (s), 152.9 (s), 151.4 (s), 133.7 (s), 129.3 (dd, *J* = 311.1, 305.5 Hz), 122.9 (s), 116.4 (s), 113.7 (s), 113.2 (s), 105.7 (s), 104.9 (s), 79.3 (s), 74.7 (s), 68.5 (t, *J* = 22.6 Hz), 63.0 (s), 55.7 (s), 45.3 (s), 39.2 (s), 26.8 (s), 13.8 (s), 13.6 (s). HRMS (ES) calc. for (M+1) $C_{22}H_{24}ClF_2NO_5$: 456.1384; found: 456.1390.

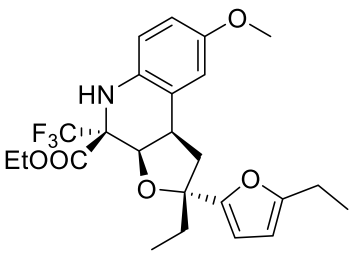


(2*R,3a*R**,4*S**,9b*R**)-8-methoxy-2-methyl-2,4-bis(5-methylfuran-2-yl)-4-(trifluoromethyl)-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline (3h).** Following the general procedure, from 28 mg of imine **1k**, 21 µL of 2-ethyl furan and 1.5 mg of

SIPrAuOTf, 34.9 mg (78%) of the desired product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.2), as a mixture of diastereoisomers 79:21 (major diastereoisomer : other diastereoisomers). **3h** was obtained (28 mg, 62%) as a yellowish oil, while the rest of diastereoisomers eluted together from the column.

Major diastereoisomer:

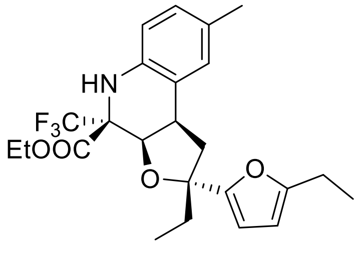
^{1}H NMR (500 MHz, CDCl$_3$) δ: 6.67 (d, *J* = 8.7 Hz, 1H), 6.59 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.47 (d, *J* = 2.4 Hz, 1H), 6.10 (d, *J* = 3.2 Hz, 1H), 6.05 (d, *J* = 3.0 Hz, 1H), 5.83 (dd, *J* = 3.0, 1.0 Hz, 1H), 5.78 (dd, *J* = 3.2, 1.0 Hz, 1H), 4.90 (d, *J* = 5.8 Hz, 1H), 4.20 (bs, 1H), 3.66 (s, 3H), 3.32 – 3.28 (m, 1H), 2.85 (dd, *J* = 12.8, 8.2 Hz, 1H), 2.23 (d, *J* = 0.8 Hz, 3H), 2.15 (d, J = 0.7 Hz, 3H), 2.07 (dd, J = 12.8, 3.3 Hz, 1H), 1.29 (s, 3H).^{19}F NMR (282 MHz, CDCl$_3$) δ: -74.13 (s).^{13}C NMR (126 MHz, CDCl$_3$) δ: 156.2 (s), 152.8 (s), 151.9 (s), 150.4 (s), 147.0 (s), 133.1 (s), 125.3 (s), 123.5 (q, *J* = 286.4 Hz), 116.7 (s), 112.7 (s), 111.9 (s), 109.9 (s), 105.5 (s), 104.9 (s), 104.1 (s), 80.0 (s), 60.6 (q, *J* = 27.7 Hz), 54.5 (s), 43.6 (s), 39.2 (s), 29.9 (s), 25.8 (s), 12.7 (s), 12.6 (s). HRMS (ES) calc. for (M+1) $C_{24}H_{24}F_3NO_4$: 448.1730; found: 448.1740.



Ethyl (2*R,3a*R**,4*S**,9b*R**)-2-ethyl-2-(5-ethylfuran-2-yl)-8-methoxy-4-(trifluoromethyl)-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-4-carboxylate (3i).** Following the general procedure, from 28 mg of imine **1a**, 21 µL of 2-ethyl furan and 1.5 mg of gold (III) tetrachloride, 39.7 mg (85%) of the desired product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.2), as a mixture of diastereoisomers 45:55 (major diastereoisomer : other diastereoisomers). **3i** was obtained (18 mg, 38%) as a yellowish oil, while the rest of diastereoisomers eluted together from the column.

Major diastereoisomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.67 – 6.62 (m, 3H), 6.06 (d, *J* = 3.1 Hz, 1H), 5.89 (dt, *J* = 3.1, 1.0 Hz, 1H), 4.74 (sa, 1H), 4.73 (s, 1H), 4.42 (ddd, *J* = 12.6, 8.1, 4.5 Hz, 1H), 4.38 – 4.30 (m, 1H), 3.75 (s, 3H), 3.55 – 3.51 (m, 1H), 2.90 (dd, *J* = 13.0, 8.0 Hz, 1H), 2.62 (q, *J* = 7.6 Hz, 2H), 2.35 (dd, *J* = 13.0, 1.7 Hz, 1H), 1.48 (q, *J* = 7.4 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.6 Hz, 3H), 0.52 (t, *J* = 7.4 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ: -74.92 (s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.3 (s), 157.3 (s), 155.8 (s), 153.3 (s), 133.7 (s),124.2 (q, *J* = 290.1 Hz), 123.6 (s), 116.8 (s), 113.8 (s), 113.4 (s), 105.7 (s), 104.1 (s), 83.5 (s), 74.2 (s),64.5 (q, *J* = 26.7 Hz), 63.2 (s), 55.8 (s), 44.0 (s), 38.9 (s), 32.8 (s), 21.6 (s), 14.0 (s), 12.3 (s), 8.7 (s). HRMS (ES) calc. for (M+1) $C_{24}H_{28}F_3NO_5$: 468.1992; found: 468.2017.

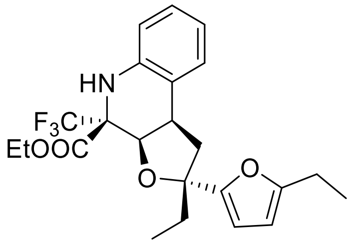


Ethyl (2*R,3a*R**,4*S**,9b*R**)-2-ethyl-2-(5-ethylfuran-2-yl)-8-methyl-4-(trifluoromethyl)-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-4-carboxylate (3j).** Following the general procedure, from 26 mg of imine **1c**, 21 µL of 2-ethyl furan and 1.5 mg of gold (III) tetrachloride, 37.0 mg (82%) of the desired product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.2), as a mixture of diastereoisomers 46:54 (major diastereoisomer : other diastereoisomers). **3j** was obtained (17 mg, 38%) as a yellowish oil, while the rest of diastereoisomers eluted together from the column.

Major diastereoisomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.80 – 6.77 (m, 2H), 6.53 (d, *J* = 8.7 Hz, 1H), 5.98 (d, *J* = 3.1 Hz, 1H), 5.81 (dt, *J* = 3.1, 1.0 Hz, 1H), 4.73 (sa, 1H), 4.67 (d, *J* = 5.2 Hz, 1H), 4.36 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.26 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.47 – 3.43 (m, 1H), 2.81 (dd, *J* = 13.0, 8.0 Hz, 1H), 2.54 (qd, *J* = 7.5, 0.9 Hz, 1H), 2.28 (dd, *J* = 13.0, 1.7 Hz, 1H), 2.17 (s, 3H), 1.40 (q, *J* = 7.4 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.6 Hz, 3H), 0.44 (t, *J* = 7.4 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ: -74.99 (s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.3 (s), 157.3 (s), 155.9 (s), 137.3 (s), 128.9 (s), 128.5 (s), 128.0 (s), 124.2 (q, J = 290.3 Hz), 122.2 (s), 115.5

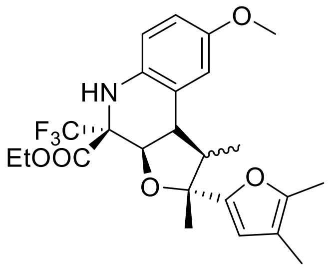
(s), 105.6 (s), 104.1 (s), 83.5 (s), 74.2 (s), 64.4 (q, J = 26.86 Hz), 63.2 (s), 44.0 (s), 38.5 (s), 32.8 (s), 21.6 (s), 20.8 (s), 14.0 (s), 12.3 (s), 8.7 (s). HRMS (ES) calc. for (M+1) $C_{24}H_{28}F_3NO_4$: 452.2043; found: 452.2067.



Ethyl (2*R,3a*R**,4*S**,9b*R**)-2-ethyl-2-(5-ethylfuran-2-yl)-4-(trifluoromethyl)-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-4-carboxylate (3k).** Following the general procedure, from 25 mg of imine **1b**, 21 µL of 2-ethyl furan and 1.5 mg of gold (III) tetrachloride, 32.7 mg (75%) of the desired product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.2), as a mixture of diastereoisomers 42:58 (major diastereoisomer : other diastereoisomers). **3k** was obtained (14 mg, 32%) as a yellowish oil, while the rest of diastereoisomers eluted together from the column.

Major diastereoisomer:

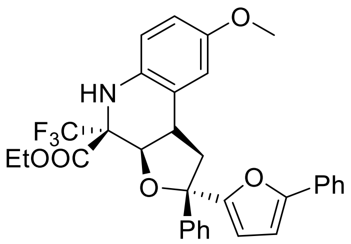
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.08 – 7.03 (m, 2H), 6.78 (td, *J* = 7.5, 1.1 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.06 (d, *J* = 3.1 Hz, 1H), 5.89 (dt, *J* = 3.1, 0.9 Hz, 1H), 4.92 (s, 1H), 4.76 (d, *J* = 4.9 Hz, 1H), 4.44 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.34 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.58 – 3.54 (m, 1H), 2.90 (dd, *J* = 13.0, 7.9 Hz, 1H), 2.62 (qd, *J* = 7.5, 0.6 Hz, 2H), 2.38 (dd, *J* = 13.0, 1.5 Hz, 1H), 1.46 (q, *J* = 7.3 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.5 Hz, 3H), 0.50 (t, *J* = 7.5 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ: -75.11 (s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.3 (s), 157.3 (s), 155.9 (s), 139.7 (s), 128.6 (s), 127.3 (s), 124.1 (q, J = 290.0 Hz), 121.1 (s), 119.3 (s), 115.3 (s), 105.7 (s), 104.1 (s), 83.5 (s), 74.1 (s), 64.2 (q, *J* = 27.68 Hz), 63.2 (s), 43.8 (s), 38.5 (s), 32.8 (s), 21.6 (s), 14.0 (s), 12.3 (s), 8.7 (s). HRMS (ES) calc. for (M+1) $C_{23}H_{26}F_3NO_4$: 438.1887; found: 438.1906.



Ethyl (2*R,3a*R**,4*S**,9b*S**)-2-(4,5-dimethylfuran-2-yl)-8-methoxy-1,2-dimethyl-4-(trifluoromethyl)-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-4-carboxylate (3l).** Following the general procedure, from 28 mg of imine **1a**, 21 µL of 2, 3-dimethyl furan and 3 mg of SIPrAuOTf, 38.3 mg (82%) of the desired product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.1), as a mixture of diastereoisomers 46:54 (2 major diastereoisomers : other diastereoisomers). **3l** was obtained (17 mg, 37%) as a brownish oil together with other unseparable diastereoisomer in 3:1 ratio, while the rest of diastereoisomers eluted together from the column

Major diastereoisomers mixture (3:1):

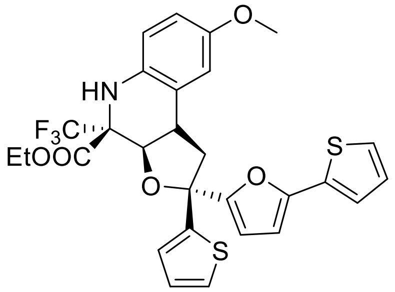
^{1}H NMR (300 MHz, CDCl$_3$) δ: 6.73 – 6.56 (m, 2.6H), 6.53 (d, *J* = 2.5 Hz, 1H), 6.49 (d, *J* = 2.6 Hz, 0.3H), 5.94 (sa, 0.3H), 5.93 (sa, 1H), 5.21 (d, *J* = 8.4 Hz, 0.3H), 5.16 (d, *J* = 6.2 Hz, 1H), 4.12 – 3.92 (m, 2.6H), 3.68 (s, 3H), 3.67 (s, 1H), 3.49 – 3.40 (m, 1.3H), 3.11 – 2.95 (m, 1.3H), 2.12 (s, 3H), 2.02 (s, 1H), 1.83 (s, 3H), 1.76 (s, 1H), 1.20 – 0.90 (m, 13.3H). ^{19}F NMR (282 MHz, CDCl$_3$) δ: -70.73 (s, 1F), -71.99 (s, 3F). ^{13}C NMR (126 MHz, CDCl$_3$) δ: 168.2 (s), 168.0 (s), 155.3 (s), 154.2 (s), 153.8 (s), 153.3 (s), 146.8 (s), 146.4 (s), 136.5 (s), 135.8 (s), 125.6 (q, J = 245.3 Hz), 122.3 (s), 121.2 (q, J = 268.9 Hz), 118.6 (s), 118.4 (s), 115.5 (s), 114.4 (s), 113.6 (s), 113.6 (s), 112.9 (s), 109.1 (s), 108.7 (s), 83.4 (s), 83.2 (s), 70.2 (q, J = 26.3 Hz), 68.7 (q, J = 27.0 Hz), 62.8 (s), 62.7 (s), 55.7 (s), 55.7 (s), 50.2 (s), 47.9 (s), 44.9 (s), 43.4 (s), 31.7 (s), 31.1 (s), 21.2 (s), 19.1 (s), 14.3 (s), 13.9 (s), 13.9 (s), 13.7 (s), 12.4 (s), 11.6 (s), 11.4 (s), 10.0 (s), 10.0 (s). HRMS (ES) calc. for (M+1) $C_{24}H_{28}F_3NO_5$: 468.1992; found: 468.1991.



Ethyl (2*S,3a*R**,4*S**,9b*R**)-8-methoxy-2-phenyl-2-(5-phenylfuran-2-yl)-4-(trifluoromethyl)-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-4-carboxylate (3m).** Following the general procedure, from 28 mg of imine **1a**, 24 µL of 2-phenyl furan[i] and 3 mg of **B**, 28.4 mg (56%) of the desired product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.2), as a mixture of diastereoisomers 71:22:7. **3m** was obtained (20.2 mg, 40%) as a colorless oil together with other unseparable diastereoisomer in 1:0.8 ratio, while the rest of diastereoisomers eluted together from the column.

Major diastereoisomers mixture (1:0.8):

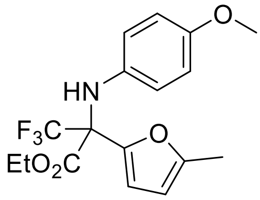
^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.69 – 7.66 (m, 1.8H), 7.52 – 7.50 (m, 1.8H), 7.43 – 7.38 (m, 3.6H), 7.35 – 7.30 (m, 1.6H), 7.27 – 7.16 (m, 5.6H), 7.11 – 7.06 (m, 2.6H), 6.74 – 6.64 (m, 3.6H), 6.59 – 6.47 (m, 3.6H), 6.25 (d, *J* = 3.3 Hz, 1H), 6.09 (d, *J* = 3.3 Hz, 0.8H), 5.71 (d, *J* = 3.4 Hz, 1H), 5.09 (d, *J* = 5.3 Hz, 0.8H), 4.92 (d, *J* = 4.8 Hz, 1H), 4.82 (br s, 0.8H), 4.80 (br s, 1H), 4.56 – 4.33 (m, 3.6H), 3.75 – 3.69 (m, 1.8H), 3.64 (s, 3H), 3.63 (s, 2.6H), 3.52 (dd, *J* = 12.9, 7.4 Hz, 0.8H), 3.45 (dd, *J* = 13.0, 0.9 Hz, 1H), 3.07 (dd, *J* = 13.0, 7.5 Hz, 1H), 2.86 (dd, *J* = 12.9, 2.1 Hz, 0.8H), 1.49 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 2.6H). ^{19}F NMR (282 MHz, CDCl$_3$) δ: -74.68 (s), -74.98 (s). ^{13}C NMR (126 MHz, CDCl$_3$) δ: 166.4 (s), 166.2 (s), 157.1 (s), 155.8 (s), 154.0 (s), 153.4 (s), 153.3 (s), 153.1 (s), 144.9 (s), 143.2 (s), 133.9 (s), 133.8 (s), 130.9 (s), 130.8 (s), 128.9 (s), 128.8 (s), 128.5 (s), 128.4 (s), 127.6 (s), 127.6 (s), 127.5 (s), 127.1 (s), 127.0 (s), 126.3 (q, *J* = 226.8 Hz), 125.6 (s), 125.3 (s), 124.2 (q, J = 239.4 Hz), 124.2 (s), 123.8 (s), 123.7 (s), 122.4 (s), 122.1 (s), 116.9 (s), 116.6 (s), 113.9 (s), 113.7 (s), 113.6 (s), 109.7 (s), 109.7 (s), 105.6 (s), 105.4 (s), 83.5 (s), 83.5 (s), 75.4 (s), 75.1 (s), 64.6 (q, *J* = 27.4 Hz), 64.4 (q, *J* = 25.9 Hz), 63.5 (s), 63.4 (s), 56.0 (s), 55.7 (s), 47.6 (s), 47.0 (s), 39.9 (s), 39.1 (s), 31.7 (s), 29.9 (s), 22.8 (s), 14.3 (s), 14.2 (s), 14.0 (s). HRMS (ES) calc. for (M+1) $C_{32}H_{28}F_3NO_5$: 564.1920; found: 564.1901.



Ethyl (2*R,3a*R**,4*S**,9b*R**)-8-methoxy-2-(thiophen-2-yl)-2-[5-(thiophen-2-yl)furan-2-yl]-4-(trifluoromethyl)-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-4-carboxylate (3n).** Following the general procedure, from 28 mg of imine **1a**, 24 µL of 2-(2-thienyl) furan and 3 mg of **B**, 26.4 mg (51%) of the desired product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.2), as a mixture of diastereoisomers 57:18:11:14. **3n** was obtained (15 mg, 29%) as a yellowish oil, while the rest of diastereoisomers eluted together from the column

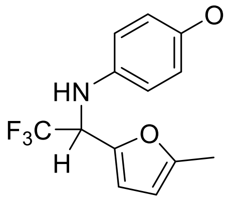
Major diastereoisomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.25 – 7.23 (m, 1H), 7.13 (dd, *J* = 4.9, 1.3 Hz, 1H), 6.97 – 6.90 (m, 4H), 6.60 (br s, 1H), 6.56 (d, *J* = 1.6 Hz, 2H), 6.05 (d, *J* = 3.4 Hz, 1H), 5.86 (d, *J* = 3.4 Hz, 1H), 5.04 (d, *J* = 5.1 Hz, 1H), 4.75 (br s, 1H), 4.46 (qd, *J* = 7.1, 0.9 Hz, 1H), 3.71 (t, *J* = 5.8 Hz, 1H), 3.58 (s, 3H), 3.35 (dd, *J* = 12.9, 1.2 Hz, 1H), 3.09 (dd, *J* = 12.9, 7.1 Hz, 1H), 1.41 (t, *J* = 7.1 Hz, 3H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -74.89 (s).^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.1 (s), 154.4 (s), 153.3 (s), 149.2 (s), 148.6 (s), 133.8 (s), 133.7 (s), 127.5 (s), 127.0 (s), 124.7 (s), 124.3 (s), 124.1 (q, *J* = 290.5 Hz), 123.9 (s), 122.6 (s), 121.6 (s), 116.7 (s), 113.9 (s), 113.4 (s), 108.8 (s), 105.7 (s), 82.1 (s), 75.7 (s), 64.4 (q, *J* = 26.9 Hz), 63.5 (s), 55.7 (s), 48.1 (s), 39.7 (s), 14.2 (s). HRMS (ES) calc. for (M+1) $C_{28}H_{24}F_3NO_5S_2$: 576.1121; found: 576.1096.



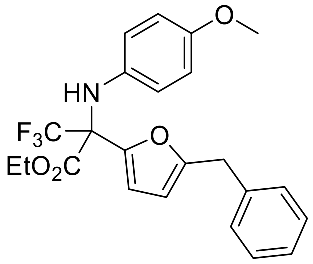
Ethyl 3,3,3-trifluoro-2-[(4-methoxyphenyl)amino]-2-(5-methylfuran-2-yl)propanoate (4a). Following the general procedure, from 28 mg of imine **1a**, 18 µL of 2-methyl furan and 2 µL of trifuoroacetic acid, 31.1 mg (86%) of the monoaddition product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.2) as a yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.60 – 6.55 (m, 2H), 6.52 – 6.47 (m, 2H), 6.37 (dd, *J* = 3.0, 0.9 Hz, 1H), 5.87 (dq, *J* = 3.1, 0.9 Hz, 1H), 4.77 (br s, 1H), 4.30 – 4.19 (m, 2H), 3.63 (s, 3H), 2.13 (d, J = 0.7 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -71.88 (s).^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.9 (s), 154.9 (s), 153.6 (s), 143.4 (s), 137.1 (s), 124.0 (q, *J* = 288.4 Hz), 121.3 (s), 121.3 (s), 114.3 (s), 113.2 (s), 113.2 (s), 107.0 (s), 68.8 (q, *J* = 28.5 Hz), 64.0 (s), 55.8 (s), 14.2 (s), 13.8 (s). HRMS (ES) calc. for (M+1) $C_{17}H_{18}F_3NO_4$: 358.1261; found: 358.1270.



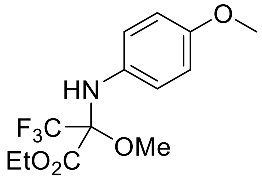
4-methoxy-N-[2,2,2-trifluoro-1-(5-methylfuran-2-yl)ethyl]aniline (4b). Following the general procedure, from 20 mg of imine **1n**, 18 µL of 2-methyl furan and 1.5 mg of gold (III) tetrachloride, 24.5 mg (86%) of the monoaddition product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.2) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.74 – 6.68 (m, 2H), 6.64 – 6.58 (m, 2H), 6.21 (d, *J* = 3.2 Hz, 1H), 5.88 – 5.86 (m, 1H), 4.77 (q, *J* = 7.0 Hz, 1H), 3.67 (s, 3H), 2.21 (s, 3H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -74.99 (d, *J* = 7.0 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.0 (s), 153.5 (s), 145.6 (s), 139.8 (s), 124.8 (q, *J* = 282.6 Hz), 116.4 (s), 116.4 (s), 115.2 (s), 110.7 (s), 107.0 (s), 56.7 (q, *J* = 32.1 Hz), 56.0 (s), 13.9 (s). HRMS (ES) calc. for (M+1) $C_{14}H_{14}F_3NO_2$: 286.1049; found: 286.1054.



Ethyl 2-(5-benzylfuran-2-yl)-3,3,3-trifluoro-2-[(4-methoxyphenyl)amino]propanoate (4c). Following the general procedure, from 28 mg of imine **1a**, 29 µL of 2-benzyl furan and 1.5 mg of SIPrAuOTf, 26.4 mg (65%) of the monoaddition product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.2) as a brownwish oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.25 – 7.18 (m, 3H), 7.04 – 7.01 (m, 2H), 6.63 – 6.55 (m, 4H), 6.49 (dd, *J* = 3.2, 1.2 Hz, 1H), 5.98 (dt, *J* = 3.3, 0.8 Hz, 1H), 4.90 (bs, 1H), 4.34 – 4.22 (m, 2H), 3.85 (s, 2H), 3.71 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).^{19}F NMR (282 MHz, CDCl$_3$) δ: -71.99 (s).^{13}C NMR (126 MHz, CDCl$_3$) δ: 166.5 (s), 155.5 (s), 154.6 (s), 143.6 (s), 137.7 (s), 136.6 (s), 128.4 (s), 126.4 (s), 123.6 (q, *J* = 288.0 Hz), 121.1 (s), 113.9 (s), 113.0 (s), 107.3 (s), 68.5 (q, *J* = 28.7 Hz), 63.7 (s), 55.4 (s), 34.2 (s), 13.7 (s). HRMS (ES) calc. for (M+1) $C_{23}H_{22}F_3NO_4$: 434.1574; found: 434.1580.



Ethyl 3,3,3-trifluoro-2-methoxy-2-[(4-methoxyphenyl)amino]propanoate (4d). Following the general procedure, from 28 mg of imine **1a**, 18 µL of 2-methyl furan and 1.5 mg of gold (III) tetrachloride, 25 mg (82%) of the methanol addition product were obtained, after purification by column chromatography using as eluent a mixture of Hex:DCM:EtOAc (9:0.5:0.2).

Spectroscopic data for the titled compound are consistent with the literature.[29]

^{1}H NMR (300 MHz, CDCl$_3$) δ: 6.91 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 9.1 Hz, 2H), 5.02 (bs, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 3.40 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).

» Chapter 2 «

Asymmetric Vinylogous Mannich-Type Addition of α,α-Dicyanoalkenes to α-Fluoroalkyl Sulfinyl Imines

2.1. Introduction.

As pointed out before, the study of the vinilogous Mannich reaction constitute the main pillar of this thesis, oriented by the employment of different nucleophiles over fluorine containing imines, in order to bring some light to this field of chemistry, with the elucidation of efficient ways to achieve new molecular entities as a benchmark.

Although "*Chapter 1"* produced highly interesting fluorinated scafolds from relatively simple substrates, the employment of furans in this reaction revealed to behave through a tandem procedure, involving several transformations after the VMR, which drives away the main topic of this research. Hence, the chemical insights of *Chapter 2* will be driven by the finding of new nucleophiles that react with imines through VMR, allowing us to enlighten this very useful reaction.

To this point, α,α-dicyanoolefins took the greater part of our interest. As explained above (section I.3.4.), this type of alkenes were introduced as electron-donors by Jørgensen and Deng in 2005, and although they are well known for their enhanced electrophilic character, they have also shown a really applicable behaviour as pro-nucleophiles.

2.1.1. α,α-Dicyanoolefins: versatile vinilogous pro-nucleophiles.

The development of novel C–C bond construction methods is very important to synthetic organic chemistry. Over the past century, great advances have been made by employing nucleophilic carbanions from the deprotonation of an acidic C–H adjacent to one or more functional groups.[118] Nevertheless, the discovery of new synthons and synthetic strategies is still essential for the development of new synthetic protocols.

In 1935, R. C. FusoN[119] formulated the principle of vinylogy to explain the anomalous reactivity of some unsaturated compounds: ''*In a molecule containing a system of conjugated double linkages, the influence of a functional group may sometimes be propagated along the chain and make itself apparent at a remote point in the molecule*''. This concept allows the extension of the electrophilic or nucleophilic character of a

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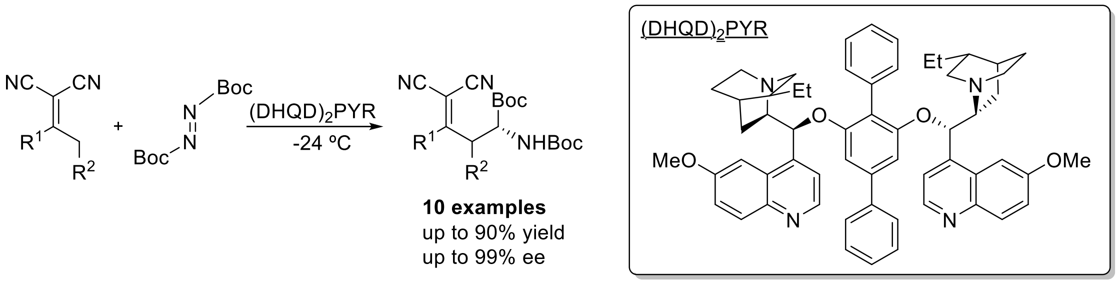
[118] F. A. Carey; R. J. Sundberg, Advanced Organic Chemistry. 4th ed.; Kluwer: New York, **2000**; p 57.

[119] R. C. FusoN, *Chem. Rev.,* **1935,** *16*, 1-27.

functional group through the system of a C-C double bond. Since then, the vinylogous principle has been applied to many reactions.

α,α-Dicyanoalkenes are considered as ready available materials, as they can be prepared by condensation of the corresponding ketone and malonitrile. This fact also reveals the dicyanoolefin motif as a masked ketone. They have been prepared and used since the late 19th century,[120] but they were not rediscovered as vinilogous donors until 2005, with the novel publications of Jørgensen and Deng.[121]

Both authors published independently. Jørgensen and co-workers reported an enantioselective organocatalytic allylic amination, using the commercially available Cinchona alkaloid derivative $(DHQD)_2PYR$ as catalyst, obtaining great yields and enantioselectivities (Scheme 2.1), while Deng published simultaneously an asymmetric direct vinilogous Michel addition under similar conditions (Scheme 2.2).



Scheme 2.1. Jørgensen's organocatalysed allylic amination.

Since then, α,α-dicyanoalkenes have been successfully employed as pro-nucleophiles in a great number of reactions, denoting their versatility and applicability in this field.

2.1.1.1. Asymmetric Michael addition to nitroalkenes.

Professor Deng's group published the first direct asymmetric vinilogous Michael addition of α,α-dicyanoalkenes to nitroalkenes, employing $(DHQD)_2PYR$, a modified cinchona alkaloid as the organocatalyst.[122] The vinylogous products were generally obtained in high regio-, diastereo- and enantioselectivities for a range of nitroalkenes

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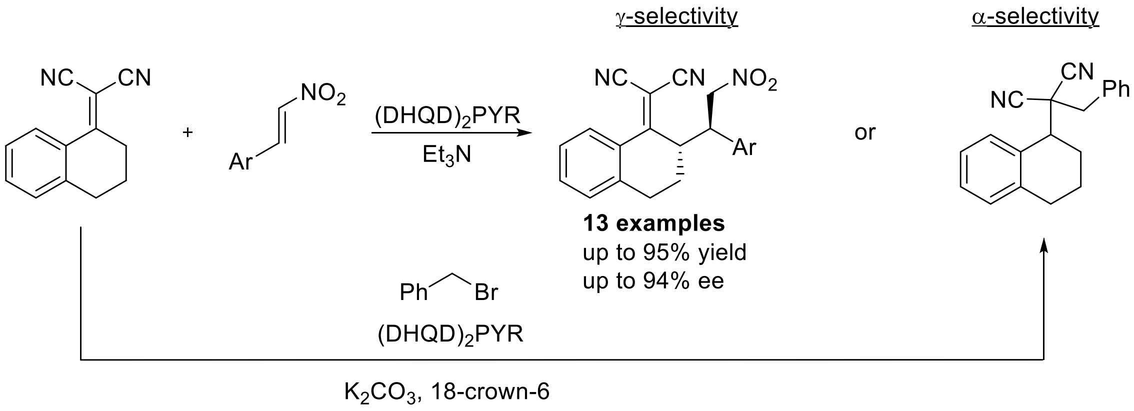
[120] R. Wolffenstein, *Berichte der deutschen chemischen Gesellschaft,* **1895,** *28*, 2265-2269.

[121] (a) T. B. Poulsen; C. Alemparte; K. A. Jorgensen, *J. Am. Chem. Soc.,* **2005,** *127*, 11614-11615; (b) D. Xue; Y. C. Chen; Q. W. Wang; L. F. Cun; J. Zhu; J. G. Deng, *Org. Lett.,* **2005,** *7*, 5293-5296.

[122] S. K. Tian; Y. Chen; J. Hang; L. Tang; P. McDaid; L. Deng, *Acc Chem Res,* **2004,** *37*, 621-31.

bearing aryl or heteroaryl groups and α,α-dicyanoalkenes derived from the corresponding ketones (Scheme 2.2).



Scheme 2.2. Deng's organocatalysed Michael addition over nitro styrenes.

Moreover, the authors were able to selectively direct the α- *vs* γ-selectivity of the reaction by slightly changing the reaction conditions. Employing aryl halides led to a complete regioselectivity for the α-position, while styrene nitro-derivatives only produced the desired γ-Michael adducts.

2.1.1.2. Asymmetric Michael addition to α,β-unsaturated aldehydes and ketones.

In 2008, Loh and co-workers described a water compatible enantioselective Michael addition of α,α-dicyanoalkenes to α,β-unsaturated aldehydes in brine, by employing a disubstituted prolinol with long alkyl chains. High enantioselectivities were obtained for the corresponding vinylogous adducts.[123] Same year, the authors designed a chiral azabicyclic catalyst able to promote those asymmetric vinylogous Michael additions in a very efficient manner.[124]

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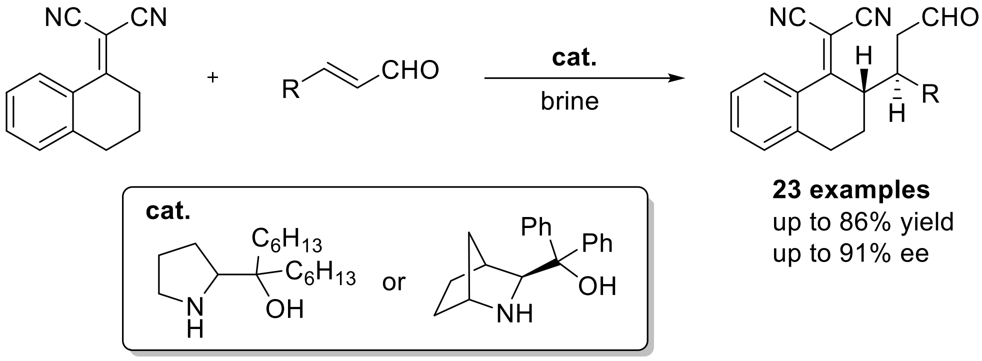
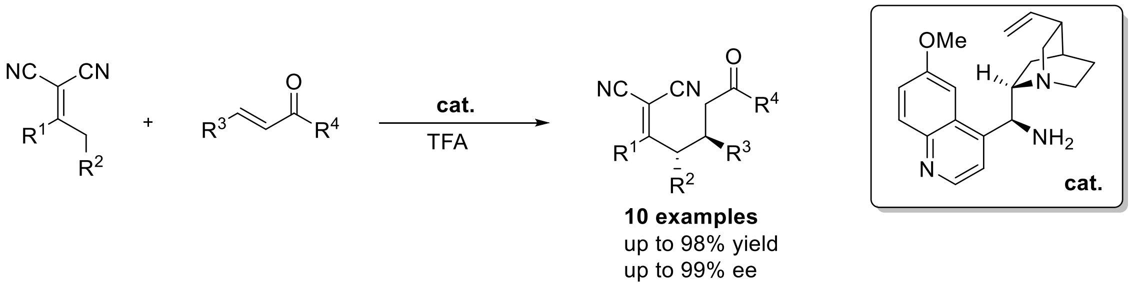
[123] J. Lu; F. Liu; T.-P. Loh, *Adv. Synth. Catal.,* **2008,** *350*, 1781-1784.

[124] J. Lu; F. Liu; W.-J. Zhou; T.-P. Loh, *Tetrahedron Lett.,* **2008,** *49*, 5389-5392.



Scheme 2.3. Asymmetric Michael addition to aldehydes by Loh.

Inspired on the amine-catalysed chemistry, Deng and co-workers developed a procedure catalysed by the primary amine 9-amino-9-deoxyepiquinine[125] in combination with trifluoroacetic acid. In this case, the authors were able to react α,α-dicyanoalkenes with different α,β-unsaturated ketones, obtaining the expectable Michael addition adducts with excellent results. Furthermore, the enantioselectivity of the reaction could be switched by changing the organocatalyst, also with great enantioselectivities.[126]



Scheme 2.4. Organocatalysed Michael addition to ketones by Deng.

Interestingly, under the same conditions as above, the reaction of a particular acyclic α,α-dicyanoalkene with the corresponding unsaturated ketone gave not only the vinylogous Michael product, but also the corresponding 2-cyclohexen-1-one derivative with higher optical purity (Scheme 2.5). Apparently an unexpected domino Michael–Michael reactions occurred, followed by a further retro-Michael reaction to generate the enone product.

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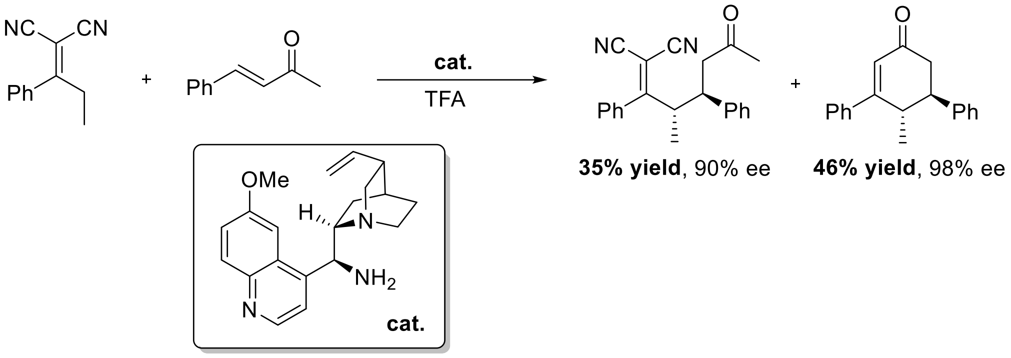
[125] G. Bartoli; P. Melchiorre, *Synlett,* **2008**, 1759-1772.

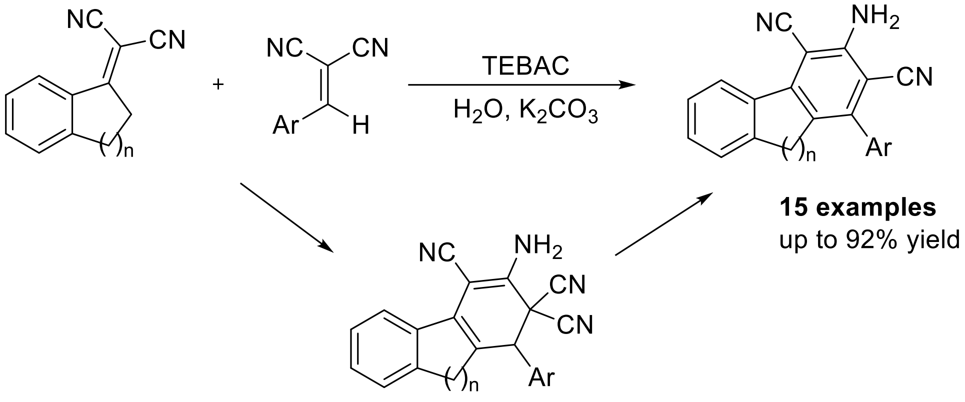
[126] J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L, Yue, Y.-C. Chen, Y. Wu, J. Zhu, J.-G. Deng, *Angew. Chem. Int. Ed.* **2007**, *46*, 389-392.



Scheme 2.5. Tandem Michael-Michael addition of α,α-dicyanoalkenes to conjugated ketones by Deng.

2.1.1.3. Michael addition to α,α-dicianoalkenes.

Wang and co-workers reported a domino procedure for the synthesis of 2,6-dicyanoanilines catalysed by TEBAC (triethylbenzylammonium chloride)[127] In the presence of K_2CO_3, α,α-dicyanoalkenes derived from ketones could react with dicyanoalkenes derived from aldehydes to afford polysubstituted benzenes. By eliminating the potassium carbonate from the ecuation, the authors were able to isolate a non-aromatic intermediate that proved the mechanism undergoing by a base-mediated aromatisation as the key step.



Scheme 2.6. Michael addition to α,α-dicyanoalkenes by Wang.

2.1.1.4. Asymmetric vinilogous Mannich reactions with α,α-dicyanoalkenes.

As mentioned in the *"General Introduction"* (section I.3), asymmetric Mannich reaction is among the most powerful tools for the preparation of optically pure amine-containing

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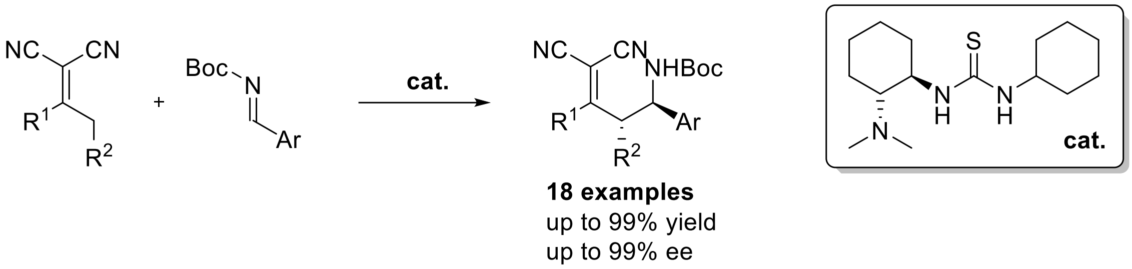
[127] X.-S. Wang; M.-M. Zhang; Q. Li; C.-S. Yao; S.-J. Tu, *Tetrahedron,* **2007,** *63*, 5265-5273.

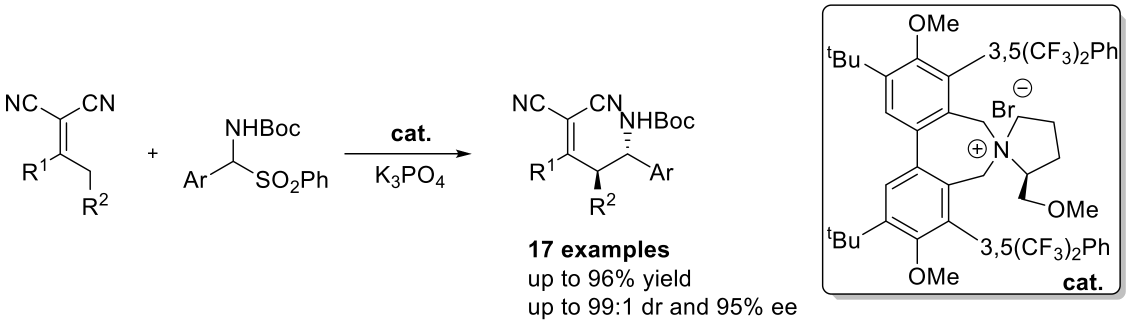
compounds, and its vinilogous variant, although less studied, also configures a great tool in the development of new and powerful methodologies.

Deng and co-workers developed the first direct asymmetric vinylogous Mannich reaction of N-Boc aldimines and α,α-dicyanoalkenes via the synergistic activation of a chiral bifunctional thiourea–tertiary amine organocatalyst.[59] Excellent stereoselectivities were achieved for a broad spectrum of substrates.



Scheme 2.7. Vinilogous Mannich reaction with α,α-dicyanoalkenes by Deng.

A similar methodology was developed by Jørgensen and co-workers but, in this particular case, they made use of a phase transfer catalyst to promote the transformation.[58] The authors employed a rigid pyrrolidinium salt[128] to catalyse the reaction between α-aminosulfones (as imine precursors) and α,α-dicyanoalkenes under phase transfer catalysis conditions,[58] obtaining great yields and excellent levels of diastereo- and enantioselectivity.



Scheme2.8. Phase transfer catalysed VMR with α,α-dicyanoalkenes by Jørgensen.

On the other hand, as the electrophilic acceptor of the vinilogous Mannich reaction, a great deal of well-known electrophiles have been used over the years. For the purpose

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[128] B. Lygo; B. Allbutt; S. R. James, *Tetrahedron Lett.,* **2003,** *44*, 5629-5632.

of this thesis, and already being studied the iminoester family of imines in "*Chapter 1"*, further investigations will be done throughout this chapter on aldimines.

2.1.2. Aldimines, versatile electrophiles.

As pointed out in the "*General Introduction"* (Section I.2.2) aldimines have a reduced electrophilicity compared to its iminoester analogous, used as electrophiles in "*Chapter 1"*, however, they have been proved to be versatile building blocks in the design of amine-containing drugs and other biologically interesting molecules.[37]

Over the years, they have been used in a wide range of different reactions.

2.1.2.1. Transition Metal catalysed asymmetric reactions with aldimines.

The Hoveyda group disclosed an efficient Zr-catalysed addition of dialkylzinc to a variety of aromatic aldimines in the presence of a dipeptide Schiff base ligand, which gave products mostly in high yields and enantioselectivities (Scheme 2.9, a).[129] Interestingly, there were evidence to support an important role of the reduced form of the Schiff base. The authors proposed the amine derivative from the iminic ligand, produced in situ by the reduction of the original Schiff base by β-hydride transfer from the ethyl group, as the active asymmetric induction species. Reactions of imines in the presence of the independently synthesized amine Schiff base also gave the products in excellent enantioselectivity.

Hayashi and Ishigedani were the first group to report a rhodium-catalysed asymmetric arylation of imines for the preparation of optically active diarylmethylamines. They discovered that the complexes of Rh with chiral monodentate phosphine ligands (**L2**) catalysed the addition of arylstannanes to N-sulfonimines with high yields and enantioselectivity (Scheme 2.9, b).[130]

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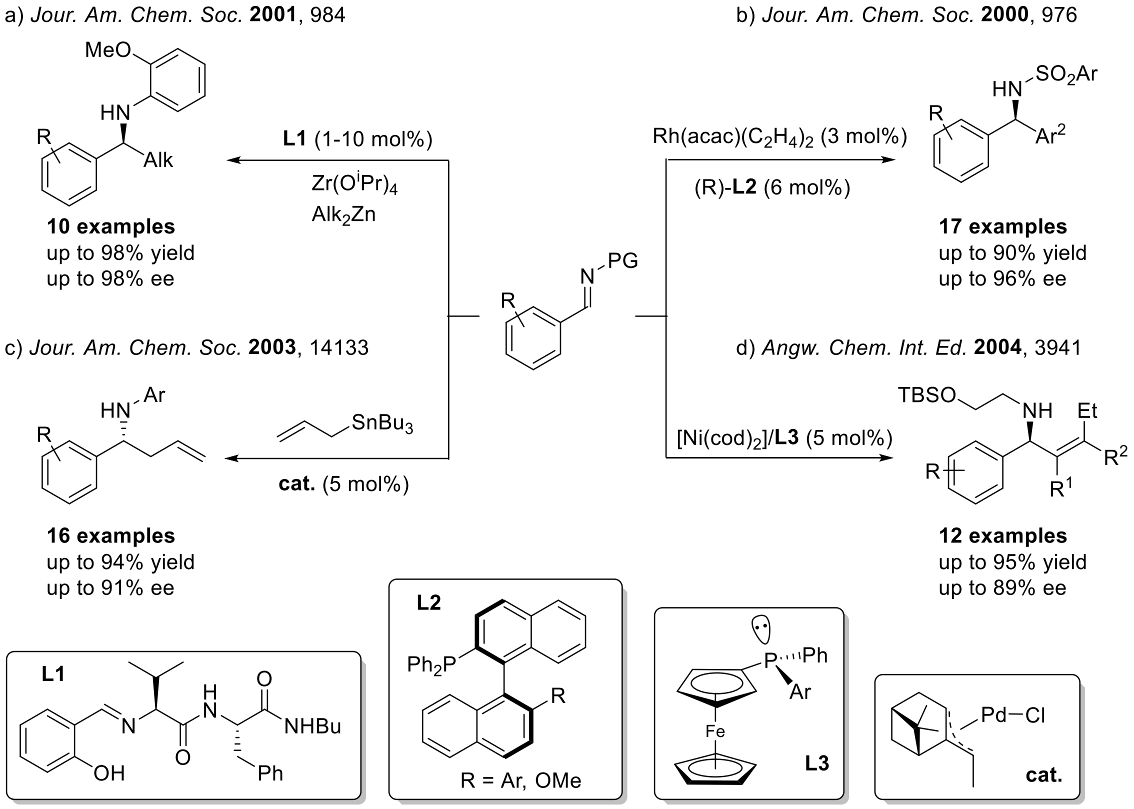
[129] J. R. Porter; J. F. Traverse; A. H. Hoveyda; M. L. Snapper, *J. Am. Chem. Soc.,* **2001,** *123*, 984-985.

[130] T. Hayashi; M. Ishigedani, *J. Am. Chem. Soc.,* **2000,** *122*, 976-977.



Scheme 2.9. Representative TM-catalysed asymmetric transformations on aldimines.

Also extensive studies on catalytic asymmetric allylation of imines have been carried out by Yamamoto group. Based on the finding that imines underwent allylation in the presence of palladium catalysts to furnish corresponding homoallylamines in high yields, they have developed several paladium catalysed asymmetric allylation of imines. In the presence of an optically active π-allylpalladium complex with pinene-based chiral ligand, the first catalytic asymmetric allylation of imines with allyltributylstannane was reported (Scheme 2.9, c).[131] Reactions of a wide variety of imines in the presence of allyltributylstannane and the palladium catalyst resulted in the formation of the corresponding homoallylamines in moderate to good yields, with low to good enantioselectivity.[132]

Jamison developed a catalytic enantioselective alkenylation of imines, in which alkynes, imines and triethylborane reacted in the presence of Ni(cod)$_2$ and a phosphane-derived

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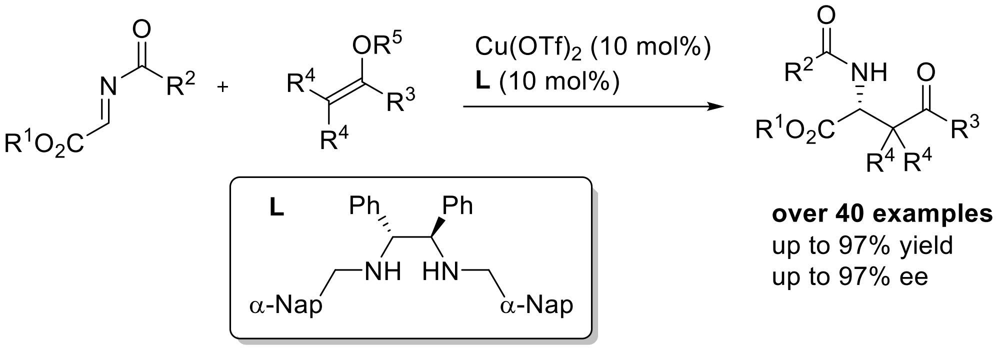
[131] H. Nakamura; K. Nakamura; Y. Yamamoto, *J. Am. Chem. Soc.,* **1998,** *120*, 4242-4243.
[132] R. A. Fernandes; A. Stimac; Y. Yamamoto, *J. Am. Chem. Soc.,* **2003,** *125*, 14133-14139.

ligand to give highly substituted allylic amines as the coupling product in good yields and enantioselectivities (Scheme 2.9, d).[133]

Transition Metal- catalysed Mannich-type reactions have been also widely studied by Kovayashi's group. The authors were able to react different aldimines with poli-substituted enoleters in the presence of a copper-based diamine catalyst to afford the corresponding Mannich-type adducts in great yields and enantioselectivities.[134]



Scheme 2.9. TM-catalysed asymmetric Mannich reaction with aldimines by Kobayashi.

2.1.2.2. Organocatalysed asymmetric reactions with aldimines.

In 2005, Terada and co-workers developed an organocatalytic asymmetric addition of an α-diazoester to an electron deficient aldimine by exploiting the bifunctional nature of a phosphoric acid catalyst, bearing bulky 9-anthryl substituents at 3 and 3' positions. An assisted deprotonation of the adduct resulting from the Brønsted acid catalyzed reaction of N-acyl imine with the diazoester was proposed (Scheme 2.10).[135] Under this condition, aziridination, which can easily occur in the absence of a suitable base, was efficiently prevented. This eventually allowed the efficient isolation of synthetically useful enantionriched, protected α-diazo-β-amino acid derivatives in the presence of the catalyst.

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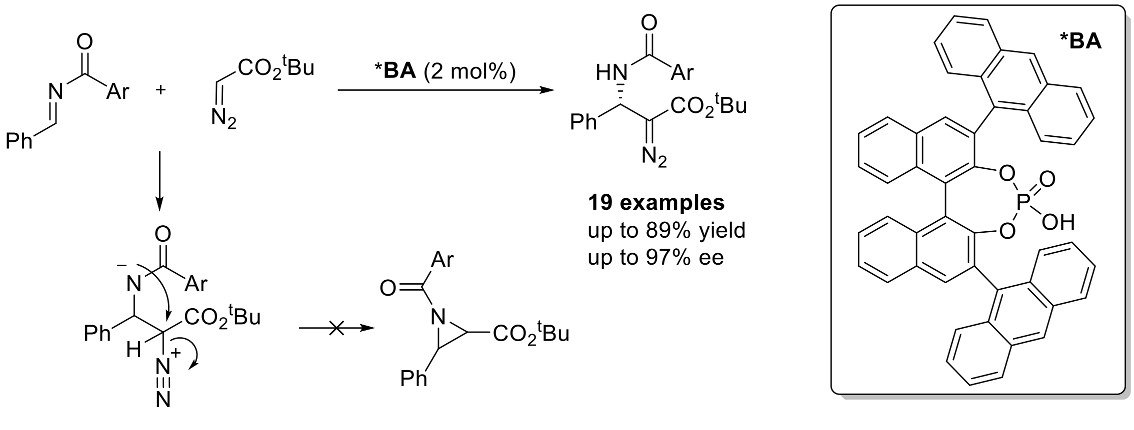
[133] S. J. Patel; T. F. Jamison, *Angew. Chem. Int. Ed.,* **2004,** *43*, 3941-3944.

[134] (a) S. Kobayashi; R. Matsubara; Y. Nakamura; H. Kitagawa; M. Sugiura, *J. Am. Chem. Soc.,* **2003,** *125*, 2507-2515; (b) S. Kobayashi; R. Matsubara; H. Kitagawa, *Org. Lett.,* **2002,** *4*, 143-145; (c) Y. Nakamura; R. Matsubara; H. Kiyohara; S. Kobayashi, *Org. Lett.,* **2003,** *5*, 2481-2484.

[135] D. Uraguchi; K. Sorimachi; M. Terada, *J. Am. Chem. Soc.,* **2005,** *127*, 9360-9361.



Scheme 2.10. First enantioselective organocatalytic addition of diazoesters to aldimines by Terada.

In 2007, Prof. Akiyama and co-workers obtained β-amino esters with high enantioselectivity and diastereoselectivity from aromatic aldimines and ketene silyl acetals (Scheme 2.11, a).[136] The hydroxyphenyl group of aldimine played a key role for the success of this asymmetric transformation. The reaction apparently proceeds by a dicordination pathway through a nine-membered cyclic transition state involving the aldimine and the bifunctional chiral phosphoric acid bearing both Brønsted acidic and basic groups. In a similar manner, Gong et al. employed simple ketones as nucleophiles in the presence of chiral phosphoric acids to afford β-amino carbonyl compounds in good yields, diastereoselectivities and enantioselectivities (Scheme 2.11, b).[137] Cyclic ketones, acetone, as well as acetophenone derivatives were used in this reaction.

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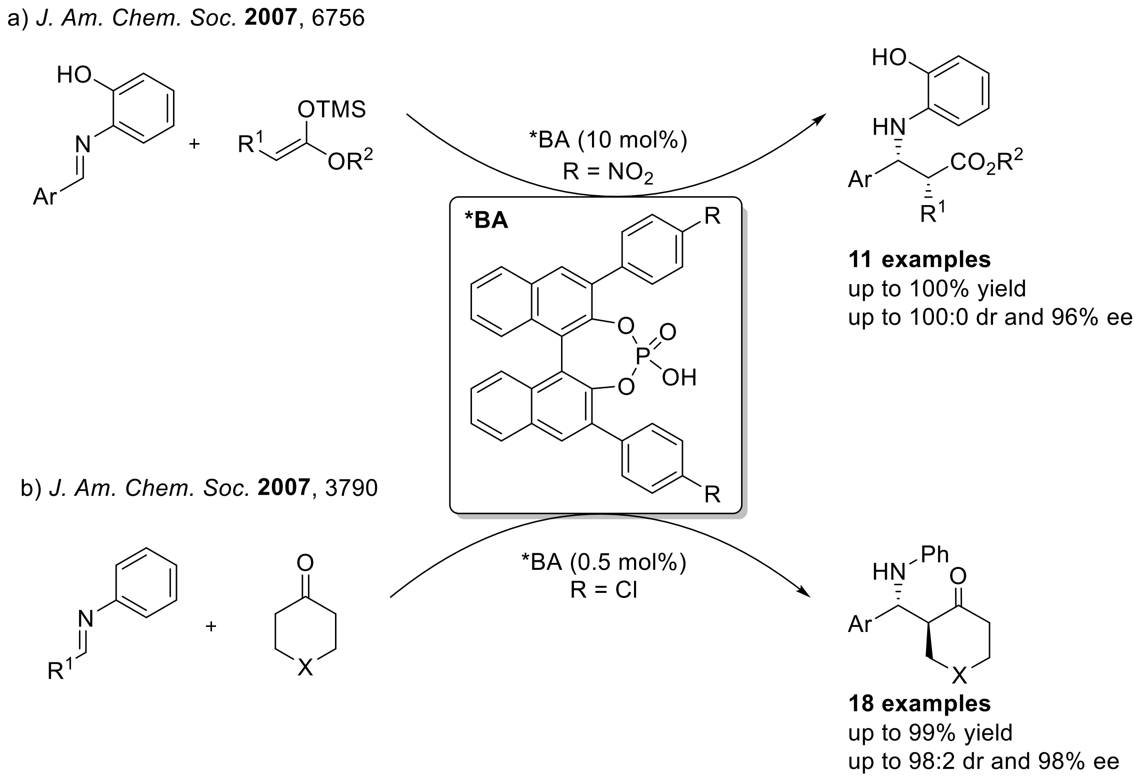
[136] M. Yamanaka; J. Itoh; K. Fuchibe; T. Akiyama, *J. Am. Chem. Soc.,* **2007,** *129*, 6756-6764.

[137] Q.-X. Guo; H. Liu; C. Guo; S.-W. Luo; Y. Gu; L.-Z. Gong, *J. Am. Chem. Soc.,* **2007,** *129*, 3790-3791.



Scheme 2.11. Organocatalytic Mannich reactions with aldimines by Akiyama (a) and Gong (b).

The first asymmetric Brønsted acid-catalyzed diastereo- and enantioselective aza-Henry reaction of aldimines with nitroalkanes was developed by Rueping and Antonchick, providing valuable β-nitro-α-amino acids.[138] The reaction employed several 3,3’-disubstituted chiral BINOL-derived phosphoric acid organocatalysts to induce simultaneous activation of nitroalkanes and imines allowing desired amino acid esters to be isolated in good yields, excellent enantioselectivities and with a wide substrate scope (Scheme 2.12). It should be noted here that the sterically demanding triphenyl-silyl-substituted Brønsted acid afforded not only the best diastereoselectivity but also exhibited enhanced reactivity compared to all other catalysts tested.

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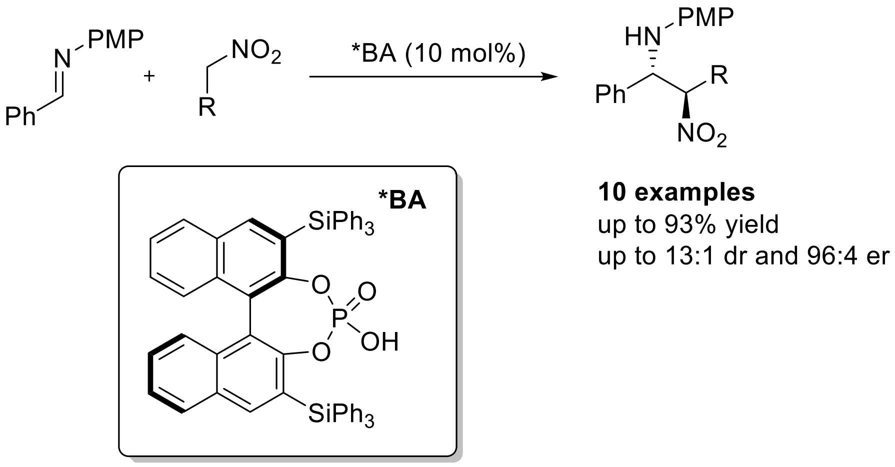
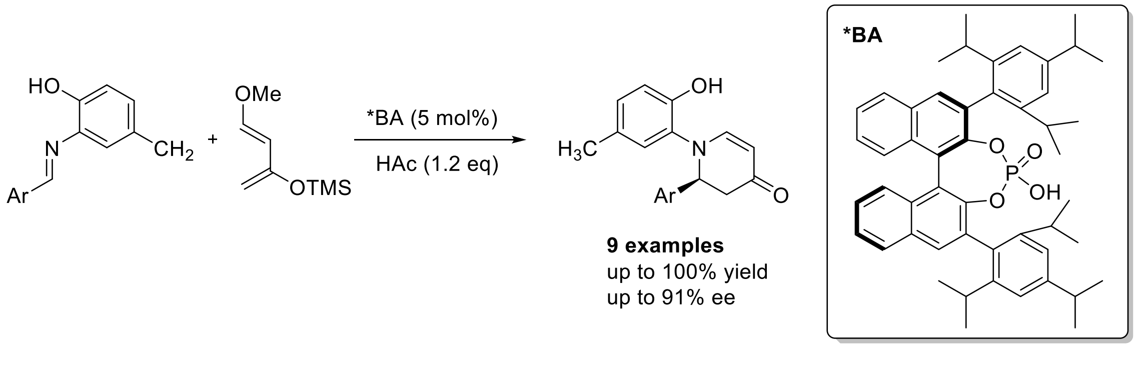
[138] T. P. Yoon; E. N. Jacobsen, *Angew. Chem. Int. Ed.,* **2005,** *44*, 466-468.



10 examples
up to 93% yield
up to 13:1 dr and 96:4 er

Scheme 2.12. Organocatalysed asymmetric direct aza-Henry reaction of aldimines by Rueping.

Also Diels-Alder reactions have been performed over this type of imines. The aza-Diels-Alder reaction is an important tool to prepare nitrogen-containing heterocycles present in numerous natural products and drugs. In 2006, Akiyama and co-workers catalysed an asymmetric aza-Diels-Alder reaction of aldimines derived from 2-amino-4-methylphenol with electron rich Danishefsky's diene by BINOL-derived Brønsted acid in the presence of acetic acid to afford piperidinones in good yields and enantioselectivities (Scheme 2.13).[139] Acetic acid was used as an additive to improve both reactivity and selectivity. The catalyst-imine interaction as appears to control the stereochemical outcome of the Diels-Alder reaction. The imine with a free hydroxyl group was proved ideal for binding to the phosphoryl oxygen of the phosphoric acid moiety through hydrogen bonding.



9 examples
up to 100% yield
up to 91% ee

Scheme 2.13. Organocatalysed enantioselective aza-Diels-Alder with aldimines by Akiyama.

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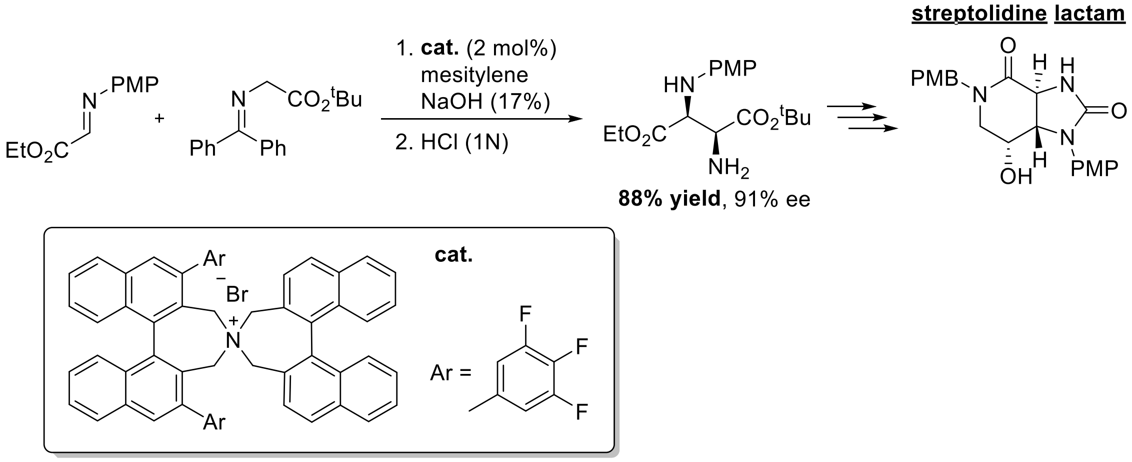
[139] T. Akiyama; Y. Tamura; J. Itoh; H. Morita; K. Fuchibe, *Synlett,* **2006,** 141-143.

2.1.2.3. Phase Transfer catalysis with aldimines.

Taking advantage of the axial chirality of those widely employed BINOL-derived organocatalysts and TM complexes, Maruoka and co-workers developed a procedure in 2004 to approach an asymmetric direct Mannich reaction over different aldimines under phase transfer conditions.[140] The authors developed an *N*-spiro *C2*-symmetric chiral quaternary ammonium bromide capable of yielding the corresponding Mannich-type adduct in great yield and enantioselectivity, which led, after several steps, to the total synthesis of the biologicaly interesting streptolidine lactam.



Scheme 2.14. Phase transfer catalysed direct asymmetric Mannich addition by Maruoka.

More recently, a novel enantioselective Mannich reaction of γ-malonate-substituted α,β-unsaturated esters with N-protected arylaldimines was developed by Zhao and co-workers by using asymmetric phase-transfer catalysis (APTC).[141] With an amino acid-derived bifunctional thiourea-phosphonium salt as a catalyst, a series of enantio-enriched Mannich products were synthesised under very mild and simple reaction conditions with high yields and enantioselectivities.

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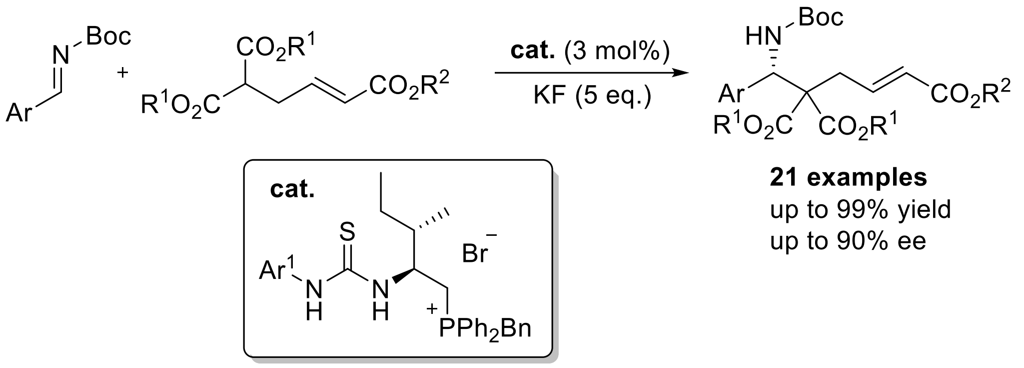
[140] T. Ooi; M. Kameda; J.-i. Fujii; K. Maruoka, *Org. Lett.,* **2004,** *6*, 2397-2399.

[141] J. Zhang; G. Zhao, *Tetrahedron,* **2019,** *75*, 1697-1705.

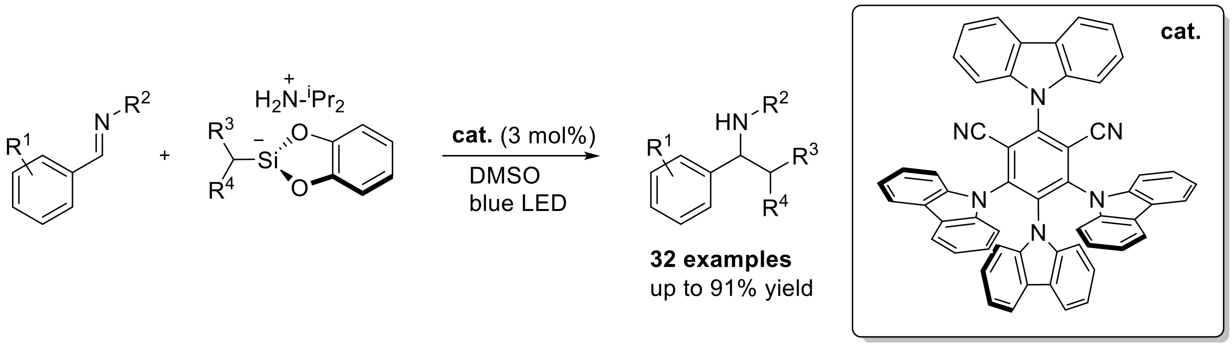


Scheme 2.15. Phase transfer catalysed direct asymmetric Mannich addition by Zhao.

2.1.2.4. Photocatalysis with aldimines.

In recent years, among the new methodologies developed involving the utilisation of aldimines as starting materials, we could emphasise on those photocatalysis to perform different transformations.

In 2017, Molander and co-workers developed an operationally simple, mild, redox-neutral method for the photoredox alkylation of imines. Utilizing an inexpensive organic photoredox catalyst, alkyl radicals are readily generated from the single-electron oxidation of ammonium alkyl bis(catecholato)silicates and are subsequently engaged in a C−C bond-forming reaction with imines. The process is highly selective, metal-free, and does not require a large excess of the alkylating reagent or the use of acidic additives.[142]



Scheme 2.16. Photocatalysis-mediated alkylation of aldimines by Molander.

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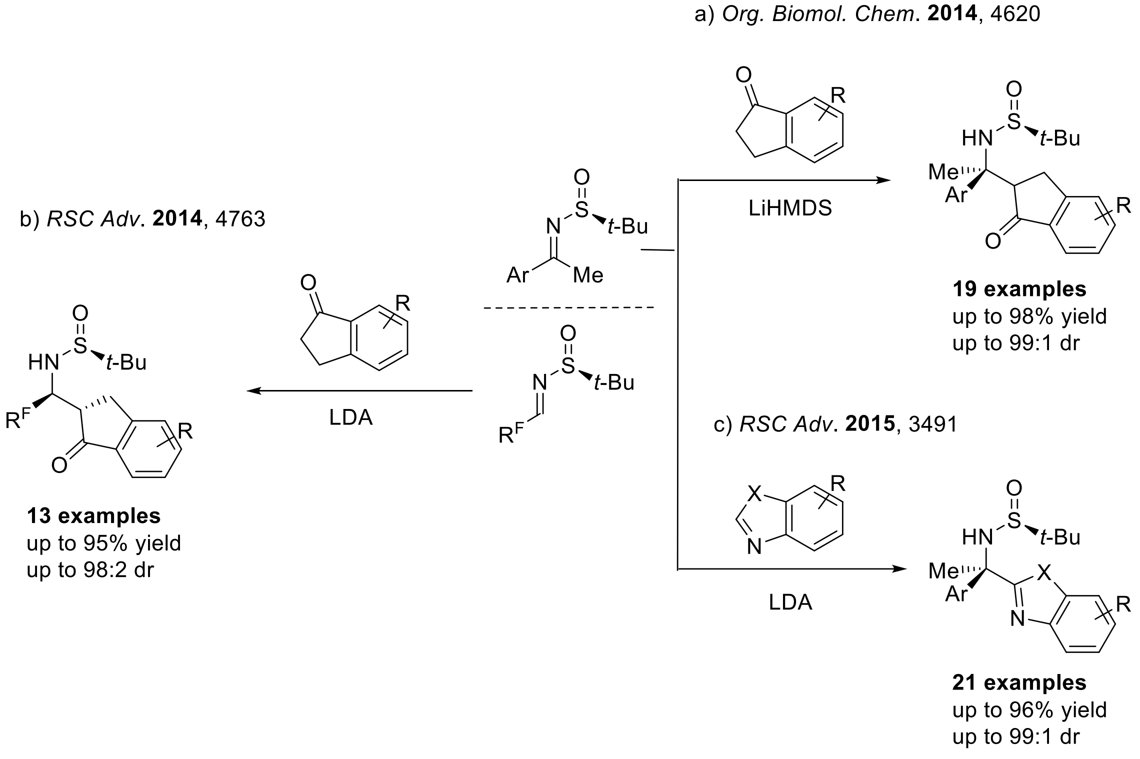
[142] N. R. Patel; C. B. Kelly; A. P. Siegenfeld; G. A. Molander, *ACS Catal.,* **2017,** *7*, 1766-1770.

2.1.2.5. Chiral auxiliary assisted reactions with aldimines.

Although the use of chiral auxiliaries involves de addition of two extra steps (addition and removal of the auxiliary) to a synthetic procedure and decreases the atom-economy of the protocol, they have been widely used in organic synthesis due to the great results they provide in terms of efficiency and stereocontrol.

In particular, the chemistry of *(S)*- and *(R)*-*N*-tert-butylsulfinyl imines has been extensively studied in recent years in the context of synthesising nitrogen-containing interesting molecules.

In 2014, Jianlin Han and co-workers reported that, unlike other ketones, 1-indanone and acetophenone derived enolates undergo Mannich-type addition reactions with *N*-tert-butanesulfinyl ketimines with excellent yields and diastereoselectivities (Scheme 2.15, a).[143]



Scheme 2.17. Chiral *N*-tert-butanesulfinyl group-mediated nucleophilic additions by Han.

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[143] L. Wu; C. Xie; H. Mei; V. A. Soloshonok; J. Han; Y. Pan, *Org. Biomol. Chem.,* **2014,** *12*, 4620-4627.

The resulting compounds represented a new type of biologically relevant β-aminoketone derivative bearing a quaternary stereogenic carbon, which could be further converted into the corresponding β-amino ketones and β-amino alcohols, possessing three consecutive stereogenic centres. Later on, the authors extended the procedure to the fluorinated version by reacting 1-indanones and (*S,S*)-*N*-tert-butanesulfinyl-(3,3,3)-trifluoroacetaldimine in the presence of catalytic amounts of LDA (Scheme 2.15, b). The reaction occurred with virtually complete stereochemical selectivity, offering reliable and generalized access to biologically relevant β-trifluoromethyl-β-amino indanone derivatives.[144] Moreover, the protocol also tolerated the employment of different heterocyclic nucleophiles, giving rise to a previously unknown type of biologically relevant benzothiazol derivatives (Scheme 2.15, c).[145]

Along the last decades, fluorinated *N*-tert-butanesulfinyl imines have been extensively employed in so many types of reactions, giving access to an outstanding amount of amine-containing interesting structures (Figure 2.1).[146] Among them, we could highlight the great work formulated by Han and co-workers, able to achieve β-aminoketones or β-aminoacids in an easy, efficient and stereoselective manner.[147]

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[144] C. Xie; H. Mei; L. Wu; V. A. Soloshonok; J. Han; Y. Pan, *RSC Adv.,* **2014,** *4*, 4763-4768.

[145] Y. Dai; C. Xie; L. Wu; H. Mei; V. A. Soloshonok; J. Han; Y. Pan, *RSC Adv.,* **2015,** *5*, 3491-3497.

[146] (a) D. M. Sedgwick; P. Barrio; A. Simón; R. Román; S. Fustero, *J. Org. Chem.,* **2016,** *81*, 8876-8887; (b) L. Wu; C. Xie; H. Mei; V. A. Soloshonok; J. Han; Y. Pan, *J. Org. Chem.,* **2014,** *79*, 7677-7681; (c) H. Mei; Y. Xiong; C. Xie; V. A. Soloshonok; J. Han; Y. Pan, *Org. Bimol. Chem.,* **2014,** *12*, 2108-2113.

[147] (a) P. Qian; Y. Dai; H. Mei; V. A. Soloshonok; J. Han; Y. Pan, *RSC Adv.,* **2015,** *5*, 26811-26814; (b) Y. Dai; C. Xie; H. Mei; J. Han; V. A. Soloshonok; Y. Pan, *Tetrahedron,* **2015,** *71*, 9550-9556.

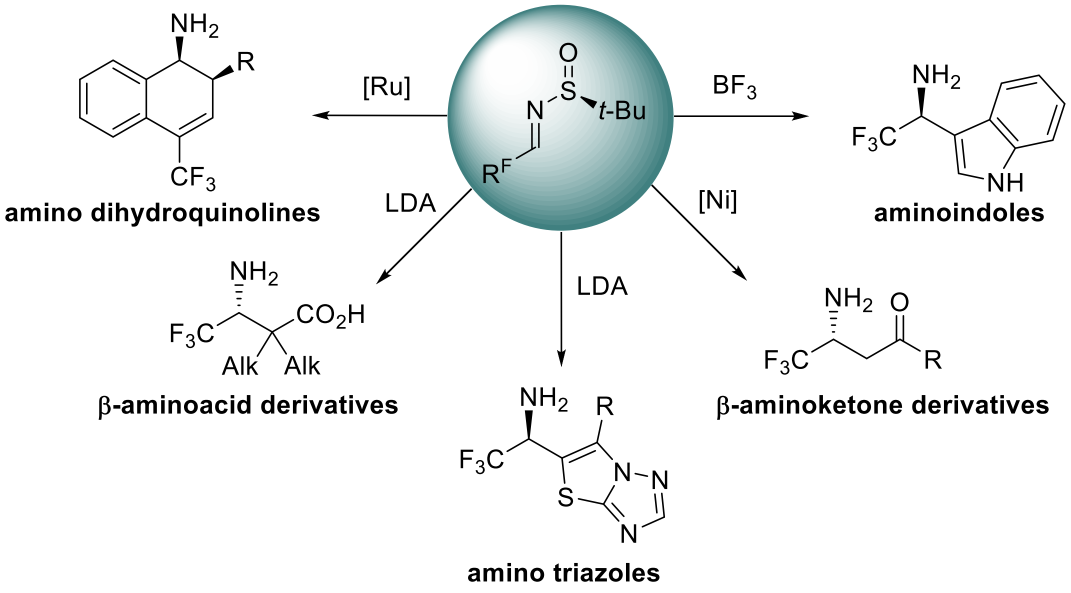

Figure 2.1. Synthetic versatility of *N*-tert-butanesulfinyl aldimines.

2.1.3. Chiral amines.

Chiral amines, as the big family of nitrogen-containing compounds they are, form a great and fascinating group of organic small molecules for many reasons. For instance, this type of molecules are widely spread among biological entities, fine chemicals and marketed drugs. Lopinavir, designed by Abbott and marketed as “Kaletra” in 2000, has been demonstrated to possess, in combination with other drugs, high anti-retroviral properties against HIV virus and it has up to three chiral amines in its structure. Some other drugs, as Rivastigmine (used in the treatment of Alzheimer’s patients), Dilevalol (an adrenergic antagonist) or the well known Morphine also have chiral amines within their chemical skeleton.[148]

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[148] E. E. Ferrandi; D. Monti, *World J. Microbiol. Biotechnol.,* **2017,** *34*:13.

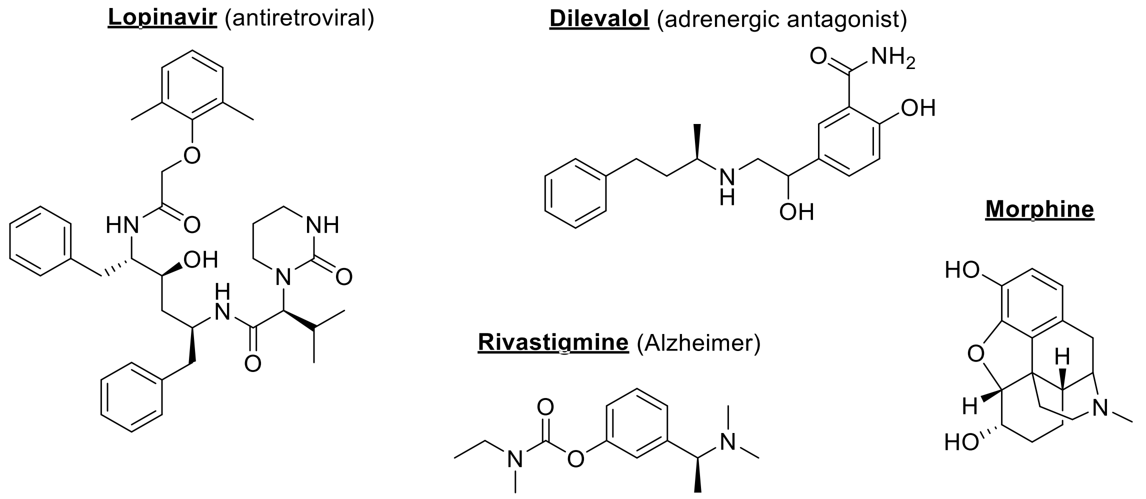

Figure 2.2. Chiral amine-containing marketed drugs.

Over recent decades, organic compounds possessing both nitrogen and fluorine atoms and especially fluorinated amines and amino acids have received noticeable attention from the bioorganic and medicinal chemistry practitioners due to profound change of their overall reactivity and functional properties, such as acidity and basicity.[149] Introduction of fluorine affects nearly all physical, adsorption and distribution properties of amines and amino acids. On the biological level, these changes can lead to significant alteration of the original biological activity or even to completely new mode ''substrate-receptor'' interactions relative to the hydrocarbon analogues.[150]

2.1.3.1. Fluorinated chiral amines.

Because of the profound stereoelectronic modifications brought about by incorporation of fluorine into organic molecules, the reactivity of fluoro-organic compounds is intriguing, exciting and often unpredictable.[151] Additional interest, fascination and scientific challenge stem from the introduction of the stereochemical factor.[152] Finally, on considering the well known importance of fluorinated fine chemicals and materials in many fields of science, such as engineering and medicine, and therefore of life,[153] one can safely state that the chemistry of chiral fluoro-organic compounds holds strong

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[149] 148(a) V. A. Soloshonok; V. P. Kukhar, *Tetrahedron,* **1997,** *53*, 8307-8314, (b) V. A. Soloshonok; D. V. Avilov; V. P. Kukhar; L. Van Meervelt; N. Mischenko, *Tetrahedron Lett.,* **1997,** *38*, 4903-4904.

[150] (a) J.-P. Bégué; D. Bonnet-Delpon, *J. Fluorine Chem.,* **2006,** *127*, 992-1012; (h) W. K. Hagmann, *J. Med. Chem.,* **2008,** *51*, 4359-4369; (b) N. C. Yoder; K. Kumar, *Chem. Soc. Rev.,* **2002,** *31*, 335-341.

[151] M. Schlosser, *Angew. Chem. Int. Ed.,* **1998,** *37*, 1496-1513.

[152] G. Resnati, *Tetrahedron,* **1993,** *49*, 9385-9445.

[153] J. T. Welch; S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*. Wiley: New York, **1991**.

promises for the future and is therefore worth of intensive scientific investigation. In this scenario, fluorinated chiral amino compounds can play a major role.

In the past decades, fluorine-containing amino derivatives have become important building blocks for the design and synthesis of fluorinated biologically active compounds,[1] especially those bearing fluoroalkyl moieties in the α-position.[154] This strategy was successfully applied in the design and synthesis of Odanacatib,[155] a drug used in the treatment of osteoporosis and bone metastasis.

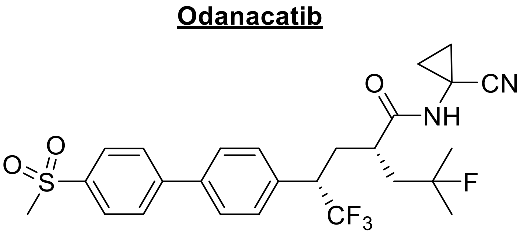

Figure 2.3. Structure of Odanacatib.

As commented above (Section 2.2.5), among the strategies employed to synthesize chiral α-fluoroalkylamines, the asymmetric addition of nucleophiles to fluorinated aldimines is the one most widely used. In this context, the chemistry of (*S*)- and (*R*)-N-tert-butylsulfinyl-3,3,3-trifluoroacetaldimines has been extensively studied in recent years. Several nucleophilic additions to these imines gave rise to different classes of compounds containing the 2,2,2-trifluoroethylamino pharmocophoric moiety.[30] In general, those addition reactions take place with high levels of diastereoselectivity affording, after the removal of the chiral auxiliary, the desired chiral fluorinated amines in a straightforward way.

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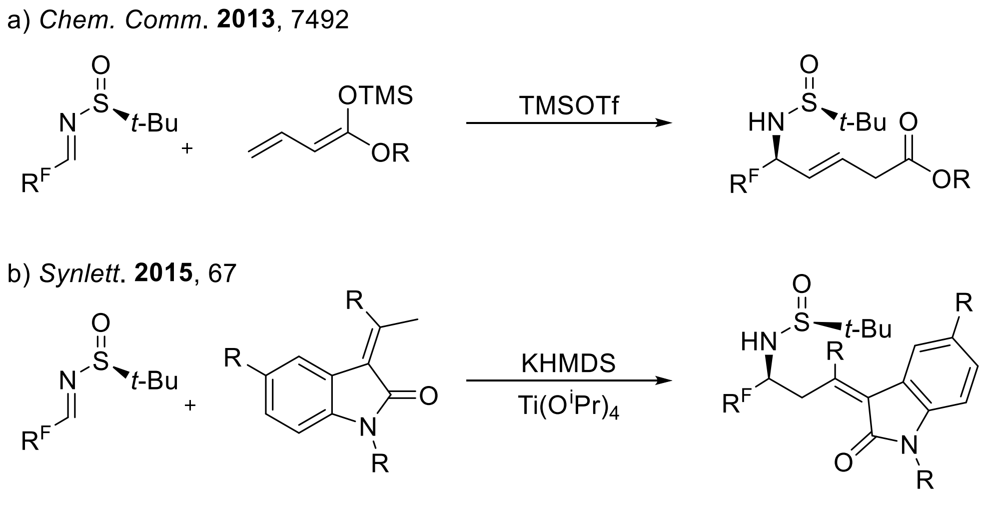
[154] A. Jose Luis; S.-F. Antonio; F. Santos, *Curr. Org. Chem.,* **2010,** *14*, 928-949.

[155] J. Y. Gauthier; N. Chauret; W. Cromlish; S. Desmarais; L. T. Duong; J.-P. Falgueyret; D. B. Kimmel; S. Lamontagne; S. Léger; T. LeRiche; C. S. Li; F. Massé; D. J. McKay; D. A. Nicoll-Griffith; R. M. Oballa; J. T. Palmer; M. D. Percival; D. Riendeau; J. Robichaud; G. A. Rodan; S. B. Rodan; C. Seto; M. Thérien; V.-L. Truong; M. C. Venuti; G. Wesolowski; R. N. Young; R. Zamboni; W. C. Black, *Bioor. Med. Chem. Let.,* **2008,** *18*, 923-928.


a) *Chem. Comm.* **2013**, 7492

b) *Synlett.* **2015**, 67

Scheme 2.18. Previous AVMRs with fluorinated aldimines.

Most examples of this strategy rely on Mannich type additions (Section I.3), while only two of them involve the AVMR: the first consists of a TMSOTf-catalyzed reaction with silyl dienolates[156] (Scheme 2.16, a) and the second one entails the reaction with 3-alkenyl-2-oxoindoles (Scheme 2.16, b).[157]

Among the great variety of substrates employed in various vinylogous processes, α,α-dicyanoalkenes, the vinylogous surrogates of malononitrile, are appealing skeletons for several reasons (Section 2.1): they are easy to prepare, more reactive in those type of processes than the corresponding carbonyl counterparts, and the conjugated malononitrile moiety is suitable for further transformations such as cyclization, reduction or elimination reactions. The combination of dicyanoalkenes chemistry and fluorinated imines in an AVMR has been unprecedented to date. Therefore, the vinylogous addition of α,α-dicyanoalkenes to chiral fluoroalkyl sulfinamides will be studied in this Chapter.

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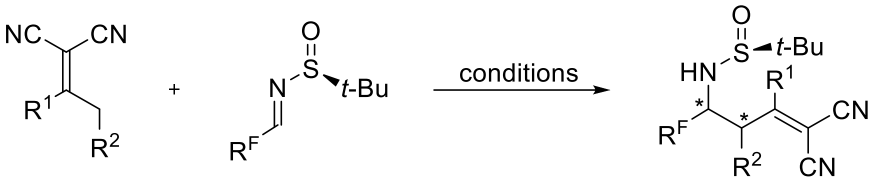
[156] Y. Liu; J. Liu; Y. Huang; F.-L. Qing, *Chem. Commun.,* **2013,** *49*, 7492-7494.
[157] Y. Liu; Y. Yang; Y. Huang; X.-H. Xu; F.-L. Qing, *Synlett,* **2015,** *26*, 67-72.

2.2. Objectives.

The main goal of this chapter will be, as in "*Chapter 1"*, the deep study of the vinylogous Mannich reaction, disclosing how far it could go and also its limitations and peculiarities.

As explained in the introduction, the utilisation of fluorinated imines in a VMR possesses a great interest due to the formation of new fluorinated amino-containing entities, and its study remains quite limited in the literature. On the other hand, the employment of α,α-dicyanoalkenes in VMRs has been proved to be a powerful tool in the formation of new C-C bonds.



Scheme 2.18. Asymmetric vinylogous Mannich reaction (AVMR) of α,α-dicyanoalkenes and fluorinated imines.

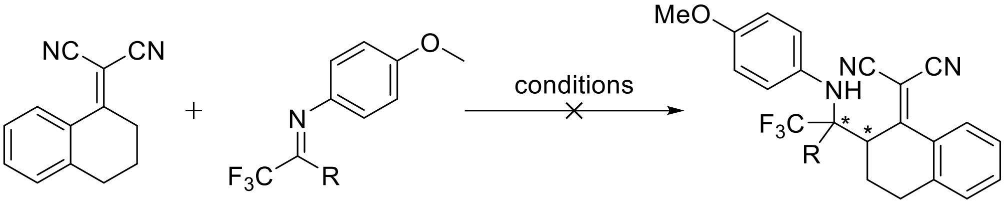
Herein, "*Chapter 2*" will include the use of α,α-dicyanoolefins as pronucleophiles in an asymmetric vinylogous Mannich reactions over fluorinated imines. Concentrate efforts will be done in the employment of *N*-tert-butylsulfinyl aldimines as acceptors, with the aim in mind of providing with a new strategy to achieve chiral fluorinated amines as products.

If a successful methodology is found, it is worth to notice that two stereogenic centres will be generated in a single reaction step.

2.3. Results and discussion.

Given the small amount of precedents found for the reaction of dicyanoalkenes and fluorinated imines to give chiral amines, we decided to investigate the possibility of developing a synthetic methodology in order to give an easy access to this type of transformations.

Based on precedents found in the literature for VMR and the great results obtained for this reaction in "*Chapter 1*",[114] we firs tried to react iminoesther **1a** (model substrate in *Chapter 1*) with dicyanoalkene **5a** under different conditions. We observed that no conversion was achieved at all under neither transition metal catalysis nor strong acid or base conditions.



13a **1a** (R = CO_2Et) **1n** (R = H)

Scheme 2.19. α,α-Dicyanoalkene reactivity towards imines **1a** and **1n**.

Finding no reactivity between these reaction partners, we decided to switch from iminoesters to fluorinated aldimines due to its well known and particular reactivity.[30] The use of aldimine **1n** provided similar results, remained unreacted in all conditions tested (Scheme 2.18).

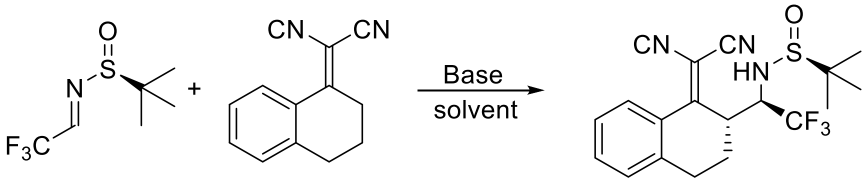
However, despite the electrophilicity reduction of the iminic carbon compared to the iminoesther analogues, the use of fluorinated sulfinyl aldimines provided the solution of the problem.

2.3.1. Optimisation.

With this idea in hand, aldimine **14a** was treated with dicyanoalkene **13a** in the presence of several bases, in order to find suitable conditions to obtain the vinilogous addition product **15a**.

Initially, the reaction was performed in DCM at room temperature employing a bunch of different bases. Organic bases such as Et_3N or DABCO gave complex mixtures of non-identified products (Table 2.1, entries 1,2), while our VMA partners remained unreactive under inorganic or weak base conditions (Table 2.1, entries 3-5). Other bases like TBAF or NaOAc also produced no conversion of the starting material (Table 2.1, entries 6,7).

Table 2.1. Protocol optimisation: bases.



14a **13a** **15a**

Entry	Base (1.1eq)	Solvent (0.3M)	Time	T ºC	Yield (%)	dr
1	Et_3N	DCM	ovn	rt	CM[a]	
2	DABCO	DCM	ovn	rt	CM[a]	
3	Na_2CO_3	DCM	ovn	rt	-	
4	Pyridine	DCM	ovn	rt	-	
5	DBU	DCM	ovn	rt	-	
6	TBAF	DCM	ovn	rt	-	
7	NaOAc	DCM	ovn	rt	-	
8	NaH	DCM	ovn	rt	68	3:1
9	KHMDS	DCM	ovn	rt	35	>99:1
10	^tBuOK	DCM	ovn	rt	95	>99:1
11	Et-P2	DCM	ovn	rt	CM[a]	
12	Verkade	DCM	ovn	rt	CM[a]	
13	^tBu-P2	DCM	ovn	rt	CM[a]	
14	LDA	THF	6h	0ºC	-	

[a] Complex mixture of undefined products.

The firs positive result was obtained for the reaction with NaH, since the addition product **15a** was formed as a 3 to 1 mixture of diastereoisomers in a 68% yield (Table 2.1, entry 8). The employment of KHMDS entailed a great improvement of the diastereoselectivity along with a severe drop of the yield (Table 2.1, entry 9). Phosphazene-derived bases such as Et-P2, *t*-Bu-P2 or Verkade's base, led to a good conversion of the starting material into a complex mixture of non-identified products (Table 2.1, entries 11-13), while LDA gave no conversion of the imine at all (Table 2.1, entry 14). Best results were obtained with *t*-BuOK, affording the vinilogous adduct **15a** in an excellent 95% yield and complete diastereoselectivity (Table 2.1, entry 10).

Table 2.2. Protocol optimisation: solvents effect study.

Entry	Base (1.1eq)	Solvent (0.3M)	Time	T ºC	Yield (%)	dr
1	^{t}BuOK	DCM	ovn	rt	95 (82)[a]	>99:1
2	^{t}BuOK	DCE	ovn	rt	92 (82)[a]	>99:1
3	^{t}BuOK	THF	ovn	rt	-	
4	^{t}BuOK	Tol	ovn	rt	68	10:1
5	^{t}BuOK	Acetone	ovn	rt	52	2:1
6	^{t}BuOK	MeCN	ovn	rt	61	2:1
7	^{t}BuOK	Cloroformo	ovn	rt	CM[b]	
8	^{t}BuOK	Et_2O	ovn	rt	64	>99:1
9	^{t}BuOK	DCM:MeCN	ovn	rt	90	1:2
10	^{t}BuOK	DCM:Acetone	ovn	rt	62	1.5:1
11	^{t}BuOK	DCM:Tol	ovn	rt	65	10:1
12	^{t}BuOK	DCM:H_2O	ovn	rt	31	>99:1

[a] Isolated yield in brackets.

[b] Complex mixture of undefined products.

Once determined the optimal base for our vinilogous Mannich protocol, several solvents were explored for the model reaction between **13a** and **14a** with potassium *tert*-butoxide. Best results were found for reaction in either DCM or DCE, leading to the addition product **15a** with complete conversion and high isolated yields (Table 2.2, entries 1,2). Other solvents like toluene, acetone or acetonitrile led to a good conversion of the starting material, but product was obtained as a mixture of diastereoisomers in different ratios (Table 2.2, entries 4-6), while chloroform produced a complex mixture of inseparable products (Table 2.2, entry 7). Remarkably, THF led to no conversion of the starting material at all (Table 2.2, entry 3). Moreover, different solvent mixtures were tested, giving good diastereoselectivity only in the case of a 1:1 mixture of DCM:H_2O, at the expense of the yield (Table 2.2, entry 12).

Table 2.3. Protocol optimisation: concentration study.

Entry	Base (1.1eq)	Solvent (0.3M)	Time	T ºC	Yield (%)	dr
1	tBuOK	0.03M	ovn	rt	95 (82)[a]	>99:1
2	tBuOK	0.06M	ovn	rt	75	>99:1
3	tBuOK	0.1M	ovn	rt	77	>99:1
4	tBuOK	0.3M	ovn	rt	55	>99:1

[a] Isolated yield in brackets.

Concentration was also studied and any increase of it resulted in a drop of the yield, regardless of the complete diastereoselectivity obtained in all cases (Table 2.3, entries 1-4).

After all the optimisation studies, the best reaction conditions for our methodology were those depicted in Table 2.1, entry 10. From then on, all reactions were carried out with ^{t}BuOK in DCM (0.03M) at room temperature. It is worth to notice that all reactions were performed under an air-open atmosphere and no variation was observed when inert atmosphere was employed.

2.3.2. Scope and limitations.

Next step was to study the scope and limitations of our methodology. For that aim, several fluorinated sulfinylimines **14** (Figure 2.4) were prepared according to already described literature procedures. A small library of dicyanoalkenes **13** (Figure 2.4) was also prepared according to literature procedures.

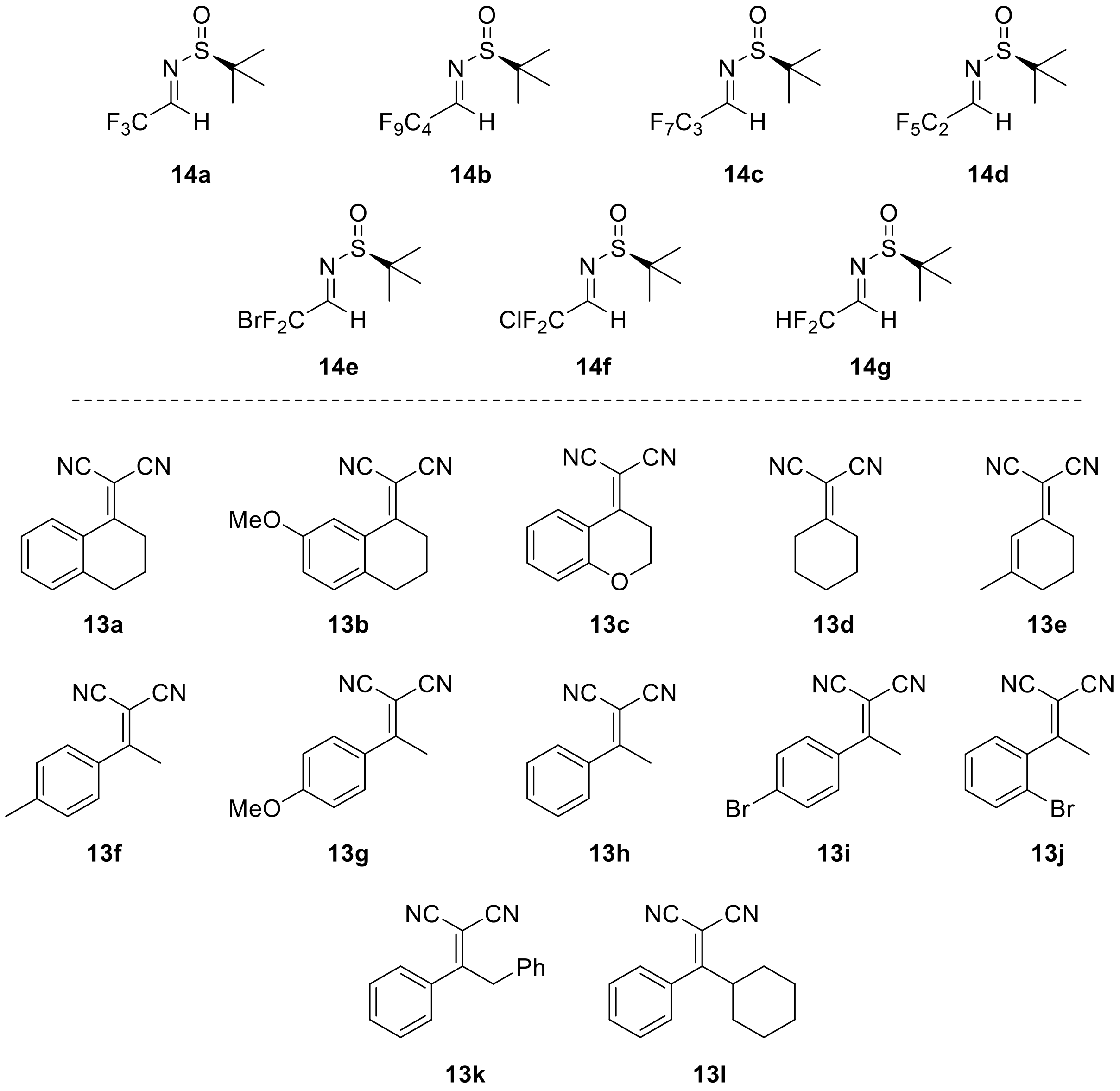
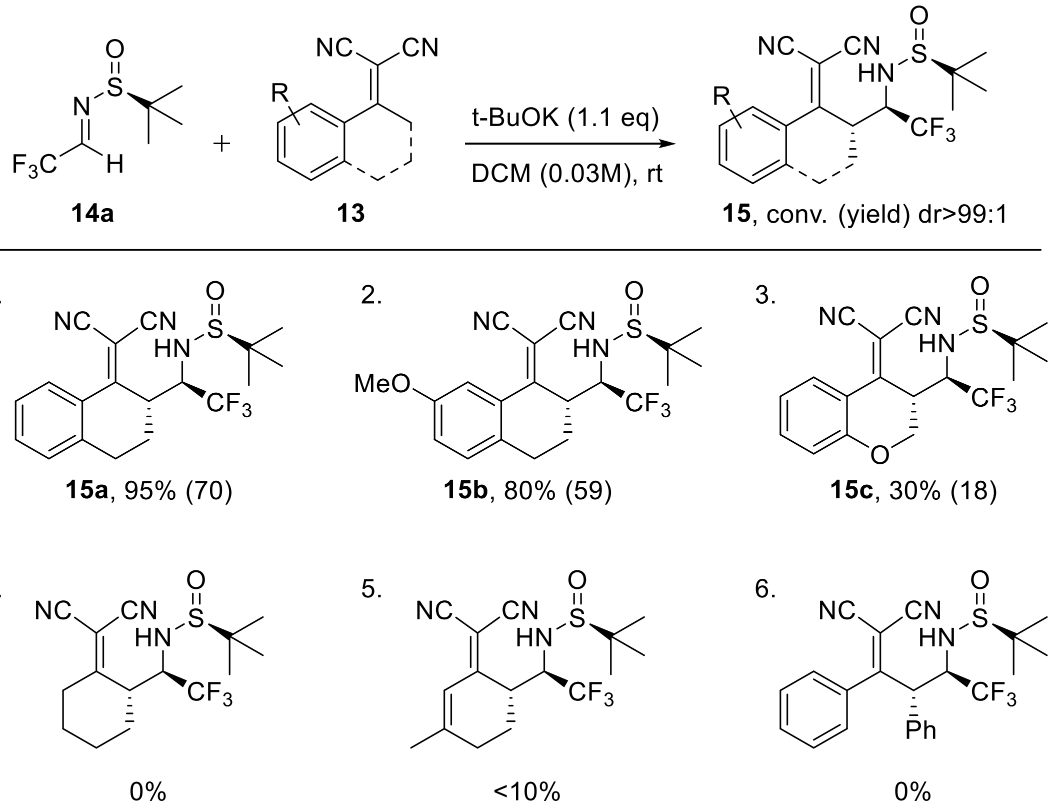


Figure 2.4. Sulfinylimines and dicyanoalkenes library.

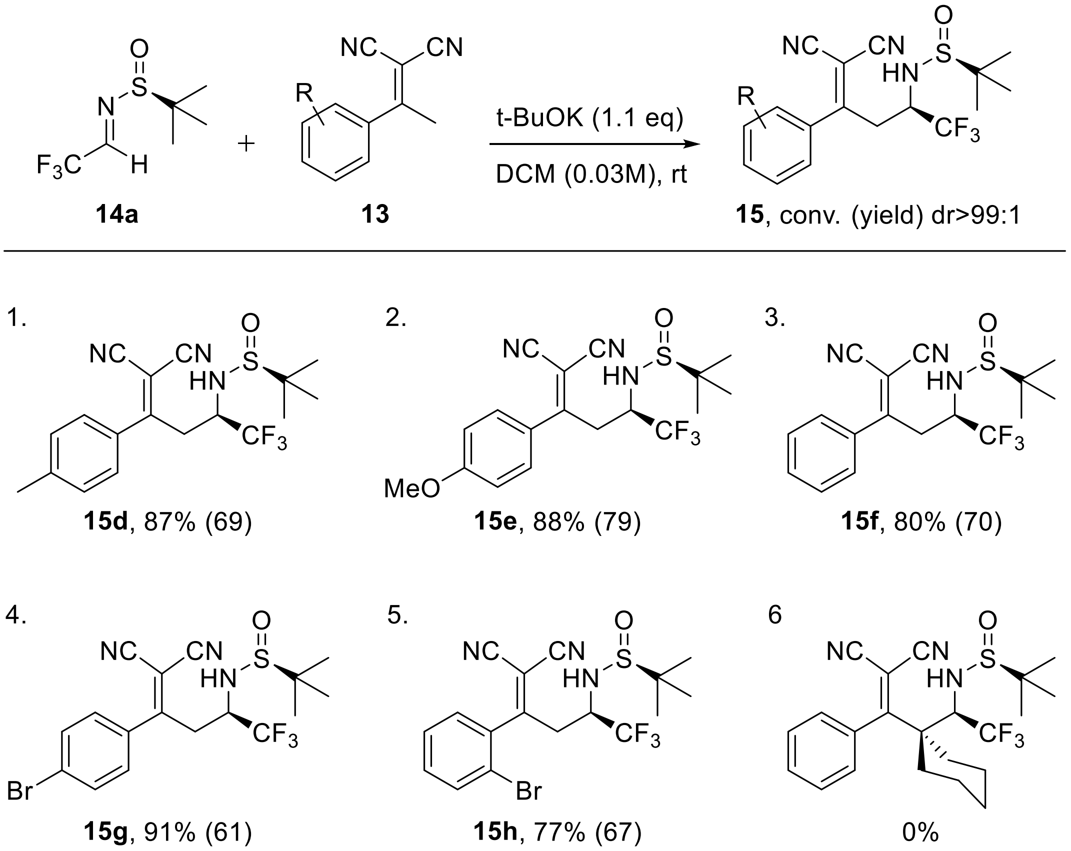
Bicyclic dicyanoalkenes **13a** and **13b** reacted efficiently with sulfinylimine **14a**, affording the addition products **15a** and **15b** in good yields and complete diastereoselectivity, with the simultaneous generation of two stereocenters (Table 2.4, entries 1,2). Nevertheless, reaction with chromanone-derived dicyanoalkene **13c** produced the desired fluoroalkyl amine **15c** as a single diastereoisomer, although in lower yield (Table 2.4, entry 3). Non-aromatic dicyanoalkene **13d** gave a mixture of undesirable products, while the conjugated one **13e** scarcely achieved a 10% of the addition product (Table 2.4, entries 4-5). Also non-rigid dicyanoalkene **13k** was tested, giving no isolable outcome at all (Table 2.4, entry 6). Those results led us to think that both reduction of electronic density and structure rigidity of the cyanoalkene were traduced into an important or total reduction of the reactivity for our reaction protocol.

Table 2.4. Scope of the reaction: bicyclic dicyanoalkene **13**.



We then switched from secondary to primary conjugated pro-nucleophiles. Monocyclic dicyanoalkenes **13f-j** showed a great reactivity against sulfinylimine **14a**, leading to the corresponding α-fluorinated sulfinylamines **15d-h** in good yields as single diastereoisomers (Table 2.5, entries 1-5). Our reaction conditions provided a solid procedure to react sp^3 aromatic dicyanoalkenes, bearing either electron-donating or electron-withdrawing moieties at the aromatic ring, with fluorinated aldimines. It is worth to notice that no negative effect was observed with substrate **13j**, containing a bromine substituent at the *ortho* position of the aromatic ring (Table 2.5, entry 5), meaning that our methodology also tolerates steric hindrance with good results and no significant loss of yield or diastereoselectivity.

Table 2.5. Scope of the reaction: monocyclic dicyanoalkenes **13**.



In order to expand the limits of our investigations, tertiary dicyanoalkene **13l** was tested. Unluckily the reaction did not take place, probably because of the impossibility for the constricted anion to reach the electrophilic imine carbon.

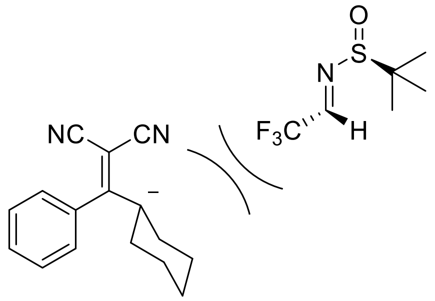
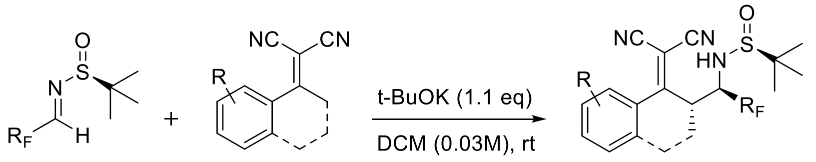


Figure 2.5. Impeded tertiary anionic nucleophile.

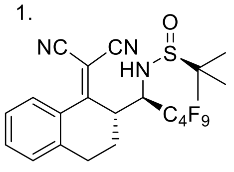
On the other hand, several fluorinated and perfluorinated sulfinylimines were tested under our reaction conditions. Bicyclic dicyanoalkene **13a** and monocyclic olefin **13g** were reacted with imines **14b-g**, and the process took place efficiently in all cases, rendering fluorinated amines **15i-t** in moderate to good yields and complete diastereoselectivity (Table 2.6, entries 1-12).

Table 2.6. Scope of the reaction: imines.



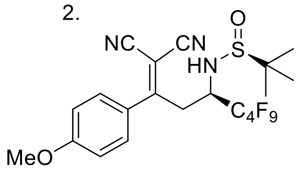
14 **13** **15**, conv. (yield) dr>99:1

1.



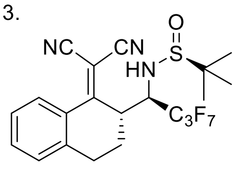
15i, 95% (65)

2.



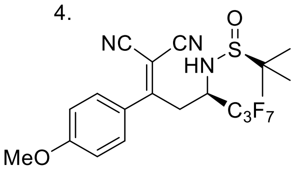
15j, 95% (75)

3.



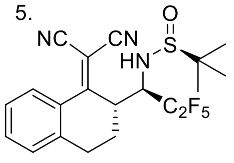
15k, 55% (39)

4.



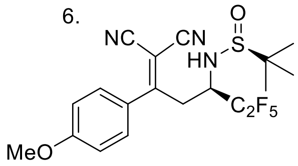
15l, 92% (79)

5.



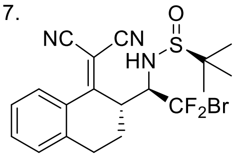
15m, 59% (43)

6.



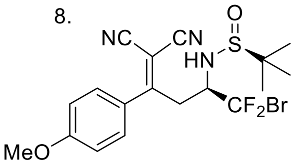
15n, 90% (81)

7.



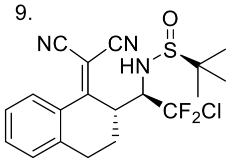
15o, 65% (55)

8.



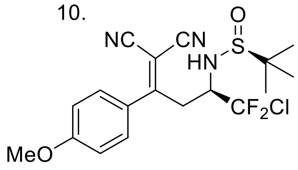
15p, 89% (82)

9.



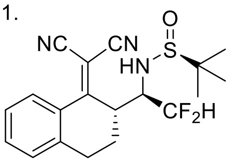
15q, 71% (55)

10.



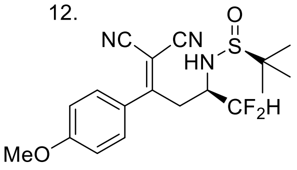
15r, 91% (81)

11.



15s, 39% (27)

12.



15t, 74% (57)

2.3.3. Stereochemistry.

In order to elucidate the absolute configuration of products **15**, *ent*-**15a** (this compound was obtained by using the R enantiomer of the starting imine **14a** in the reaction) and **15e** were crystallised and subjected to X-ray diffraction analysis. Those experiments displayed a *cis* relative configuration between the fluorinated group and the *tert*-butyl sulfoxide group (Figure 2.7). The same stereochemical outcome was assumed for all compounds **15**.

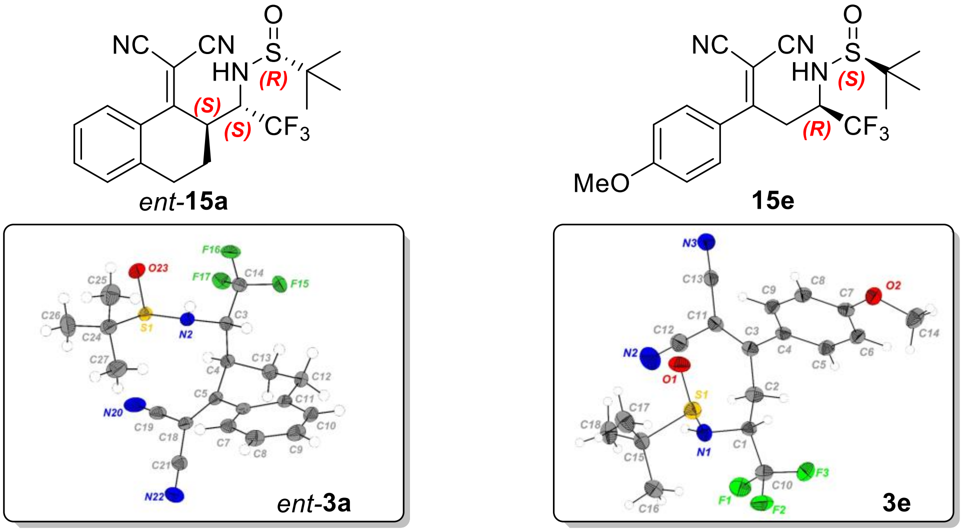
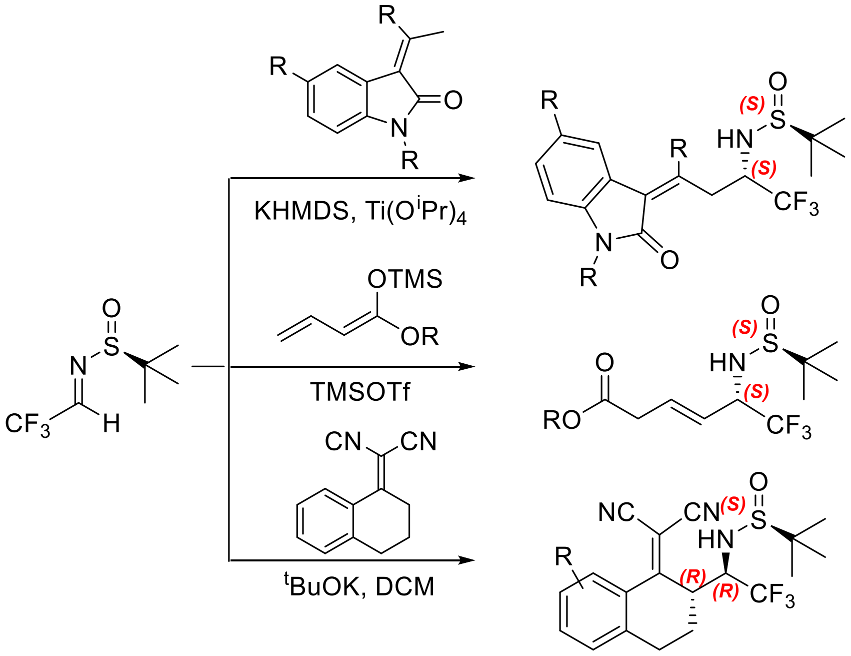


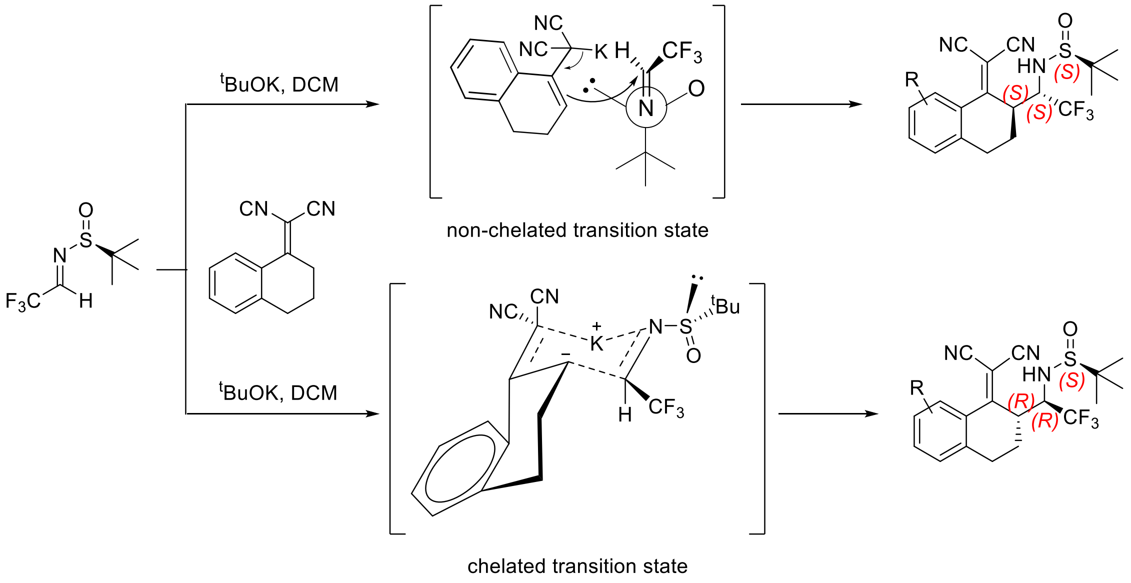
Figure 2.7. X-Ray diffraction studies.

With these results in hand, we realised that the outcome of our procedure showed an inversion in the stereoselectivity of the final products in comparison to the previously described AVMRs with fluorinated sulfinylimines depicted above (Scheme 2.18).[42,43] In those reactions, a *trans* configuration between the fluorinated moiety and the *tert*-butyl group was observed in contrast to the *cis*- results obtained under our reaction conditions (Scheme 2.20). This fact suggested a different mechanistic pathway operating in our protocol.



Scheme 2.20. Comparison with existing examples.

In the last years, a non-chelated transition state model has been depicted in most of the cases to rationalise the addition of nucleophiles to fluorinated sulfinylimines, which explains the *trans* selectivity observed in the reaction of silyl dienolates and 3-alkenyl-2-oxoindoles with fluorinated sulfinylimines through the less hindered approach of the nucleophile in a Newman's representation. However, a different mechanistic pathway and transition states should be proposed in order to explain the opposite configuration in the outcome of our procedure.



Scheme 2.21. Diastereoselectivity inversion rationalization.

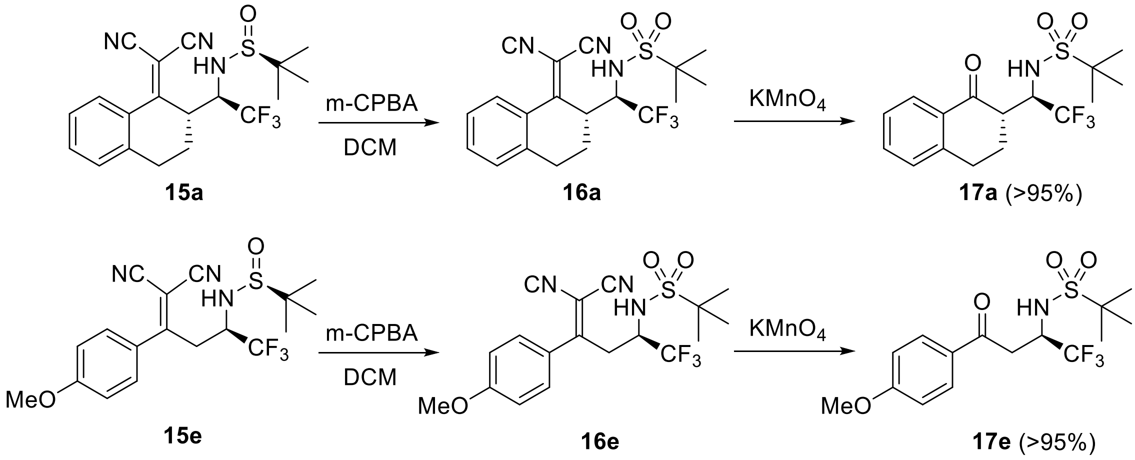
At this point, we proposed a chelated chair-like transition state. On one hand, the bulky substituents like trifluoromethyl group or *tert*-butyl sulfinyl group are placed in equatorial positions, minimising the sterical hindrance between them and the carbocycle of the cyanoalkene. On the other hand, the potassium counterion from the base plays the most important role in the enolate, fixing the chair-like conformation of the transition state and promoting the nucleophilic attack of the dicyanoalkene to the *Re* face of the imine electrophile, leading to our fluoroalkyl amines with reverse selectivity.

This proposal is experimentally supported through the results obtained during the optimisation of the reaction conditions. As presented in *Table 2.2*, the use of more polar solvents such as acetone or acetonitrile, which would avoid the formation of the chelate, resulted in a severe drop of the selectivity (Table 2.2, entries 5,6).

2.3.4. Derivatisations

In order to broaden the relevance and applicability of our methodology and due to the high susceptibility of the malonitrile motif for multiple transformations, we decided to derivatise addition products **15**.

As it is widely known, the dicyanomethylene group could be considered as a masked ketone and taking that fact in hand, we firstly attempted the double bond cleavage to obtain the corresponding fluorinated β-amino ketones. Initially, we tried to perform these transformations under described conditions,[58] using $KMnO_4$ as the oxidant but unluckily, the application of this methodology led to a mixture of ketones containing both the sulfinyl and the sulfonyl moieties. In order to avoid the formation of this mixture of products, a previous oxidation of the sulfoxide group was carried out before the double bond cleavage, reacting products **15a,e** with *m*-CPBA. In this manner, *tert*-butylsulfonyl-protected aminoketones **17a** and **17e** were obtained in quantitative yield (Scheme 2.22).

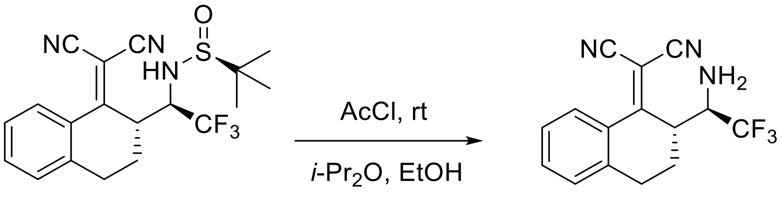


Scheme 2.22. Oxidation of products **15a** and **15e**.

Next step was the removal of the sulfoxide auxiliary, giving access to α-fluoroalkyl chiral free amines. Different procedures were tested in order to achieve the amine deprotection, but no described conditions for this transformation were found efficient for our products. Strong acid conditions like HCl/Dioxane, HCl/MeOH or TfOH/Anisole resulted in a low conversion to the free amine and high levels of decomposition were found. Finally, treatment of compound **15a** with acetyl chloride in a 6:1 mixture of i-Pr_2O

and EtOH allowed the ready elimination of the *tert*-butylsulfinyl protecting moiety to give the corresponding trifluoromethyl free amine **18a** in good yield and no loss of stereochemical purity at all.

Table 2.7. Amine deprotection.



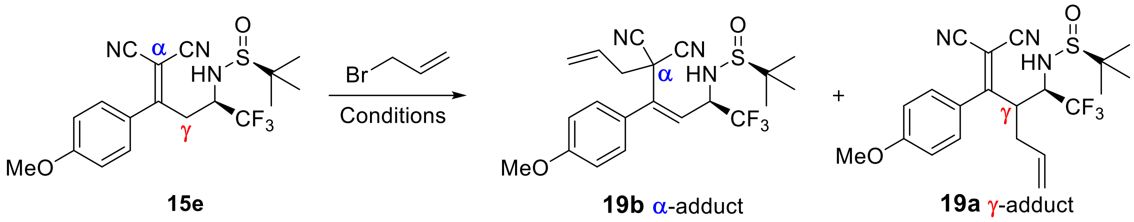
15a **18a** (66%)

entry	Acidic system	conditions	12a (%)
1	HCl/Dioxane	MeOH, rt	0
2	HCl/MeOH	MeOH, rt	0
3	TfOH/Anisole	DCM, rt	0
4	AcCl/EtOH	*i*-Pr_2O : EtOH (6:1)	66

According to a widely published literature, activated alkylidenes display a dual reactivity profile, giving a straightforward access to both α- and γ-functionalisation. However, in the particular case of the dicyanoalkylidenes only their reactivity through the γ-position has been evaluated to the best of our knowledge, usually by reactions with α,β-unsaturated compounds, carbonyls and imines. The lack of examples regarding the dual functionalisation of this type of structures made us consider the possibility of studying a way to allow the α-attack to the dicyanoalkenes motif.

For that aim, we designed an experiment involving our fluoroalkyl amine **15e** and allyl bromide in order to evaluate the conditions for the alkylation reaction, looking for a selective α *vs* γ -alkylation of our products.

Table 2.8. α *vs* γ -alkylation of product **15e**.



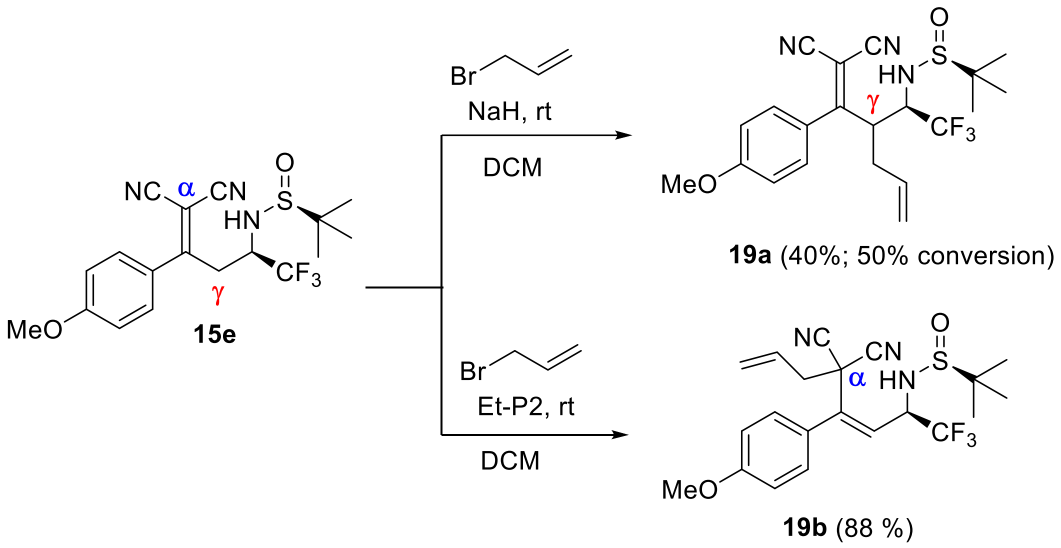
Entry	Base	Solvent	Tª	Conv. (%)ª	α:γ ratio
1	^{t}BuOK	DCM	rt	50	1:1
2	^{t}BuOK	DCM	0	50	1:1
3	^{t}BuOK	DCM	60	75	1:1
4	DABCO	DCM	rt	0	-
5	KHMDS	DCM	rt	50	1:0
6	NaHMDS	DCM	rt	50	1:0
7	LiHMDS	DCM	rt	50	1:0
8	P2-Et	DCM	rt	100 (88%)	1:0
9	NaH	DCM	rt	50 (40%)	0:1
10	NaH	DCM	50	75	1:3
11	NaH	THF	80	100	3:1
12	NaH	THF:DMF	rt	50	1:1
13	NaH	DCE	rt	25	0:1
14	NaH	Acetone	rt	75	1:0
15	NaH	MeCN	rt	100	4:1
16	NaH	$HCCl_3$	rt	100	10:1
17	LiH	DCM	rt	0	-
18	KH	DCM	rt	25	1:0
19	KH	THF	rt	50	1:0

[a] Isolated yield in brackets.

We firstly reacted product **15e** and allyl bromide in the presence of ^{t}BuOK at room temperture, obtaining a 50% conversion of a 1:1 mixture of α and γ-products (Table 2.8, entry 1). Higher and lower temperatures were tested under the same conditions but no increase of selectivity was observed, despite the conversion rise at 60 degrees (Table 2.8, entries 2,3). Weaker bases like DABCO produced no conversion at all, while stronger ones like LiH, NaH and KHMDS led to a 50% conversion with complete α-selectivity (Table 2.8, entries 4-7). Organic phosphazene-derived base Et-P2 entailed full conversion of the starting material to the α-product regioselectively in an 88% isolated yield (Table 2.8, entry 8).

With these results in hand, we switched to optimise the γ-alkylation. A first attempt with NaH at rt produced a 50% conversion to the desired γ-product with complete selectivity and 40% isolated yield (Table 2.8, entry 9), so we tried to rise the temperature in order to increase the yield of the reaction. However, higher temperatures resulted in better yields at the expense of a reversion in the regioselectivity, turning to a 3 to 1 α-selectivity at 80 degrees (Table 2.8, entries 10,11). Different solvent systems were explored but no selectivity for the γ-attack was found but for the case of DCE, even with lower yield than its chlorinated partner DCM (Table 2.8, entries 12-16). Also LiH and KH were unluckily tested, leading to the α-product (Table 2.8, entries 17-19).

Summarising, we have found suitable conditions to perform the regioselective alkylation of products **15**. Namely, the reaction with NaH in DCM at room temperature rendered exclusively the γ-allyl product **19a** as a single diastereoisomer in a 50% conversion and a 40% isolated yield. On the other hand, the reaction with phosphazene-derived base Et-P2 in DCM at the same temperature afforded the α-adduct **19b** in a 88% isolated yield as the single reaction product.



Scheme 2.23. Regiodivergent allylation of fluoroalkyl product **15e**.

As an extended conclusion, we could suggest that strong bases, high temperatures and polar solvents are acting in benefit of the yield and the α-attack as a visible trend depicted from optimisation table 2.8.

Due to the steric hindrance of the trifluoromethyl group, the α-allylation is preferred when using either bulky or stronger bases, more polar solvents that increases the solvation of the alkyl anion and higher temperatures that promotes quicker reactions.

The hydrogenation of the alkene moiety of the dicyanoalkene was evaluated next. Usually, according the literature, this type of hydrogenations are performed using Hantzsch ester as the hydrogen source.[158] However, when dicyanoalkene **15a** was subjected to these reaction conditions, only partial reduction of the double bond was observed, providing an inseparable mixture with the Hantzsch ester oxidation by-product. Moreover, treatment of dicyanoalkene **15a** with $NaBH_4$ led to a complex mixture of products, whereas it was completely unreactive under 1 atm of H_2 in the presence of Pd/C or $Pd(OH)_2$.

Stuck at this point, we decided to increase the H_2 pressure using a packed-bed hydrogenation flow reactor (H-Cube^{TM}). First attempt carried out on compound **15a**, using $Pd(OH)_2$ as catalyst was unsuccessful, probably due to the inactivation of the

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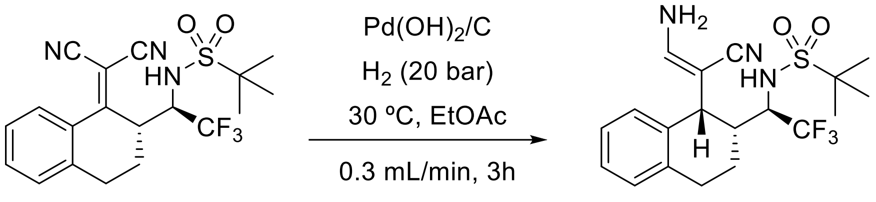
[158] J.-W. Xie; L. Yue; D. Xue; X.-L. Ma; Y.-C. Chen; Y. Wu; J. Zhu; J.-G. Deng, *Chem. Commun.,* **2006**, 1563-1565.

catalyst by the sulfoxide moiety. To avoid this obstacle, compound **15a** was pre-oxidised to BUS-protected one **16a**, as described above. Now, the employment of aminosulfonyl compound **16a** as starting substrate gave different results.

Table 2.9. Flow hidrogenation optimisation of product **16a**.



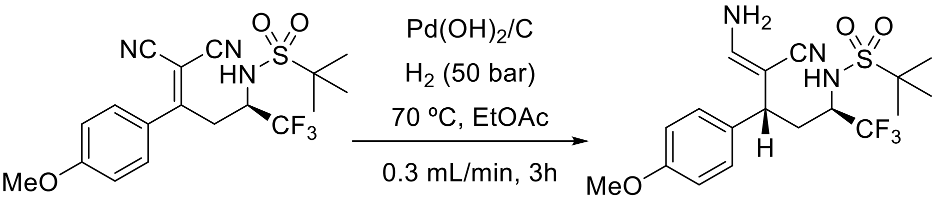
16a **H-Cube^{TM}** **20a** (62%, 9:1 dr)

entry	Cat.	Tª (ºC)	Pres. (bar)	Flow (mL/min)	Conc. (M)	Conv. (%)	d.r.
1	Pd(OH)$_2$	30	10	0.5	0.005	49	90:10
2	Pd(OH)$_2$	30	20	0.3	0.005	82 (62)[a]	90:10
3	Pd(OH)$_2$	30	25	0.3	0.005	35	90:10
4	Pd(OH)$_2$	30	40	0.3	0.005	10	90:10

[a] Isolate yield in brackets

After some optimisation of the flow reaction conditions, we found that flushing **16a** through a pad of Pd(OH)$_2$/C 20% *wt*. under high pressure of H$_2$ (20 bar) led to the clean formation of compound **20a** as a 9 to 1 mixture of diastereoisomers in 62% isolated yield. In addition, compound **16e** evolved in a similar way, although it was necessary heating the reaction mixture to 70 degrees to reach complete conversion of the starting material. Under these conditions, a 2 to 1 separable mixture of diastereoisomers of **20e** was obtained in 58% isolated yield.

Table 2.10. Flow hidrogenation optimisation of product **16e**.

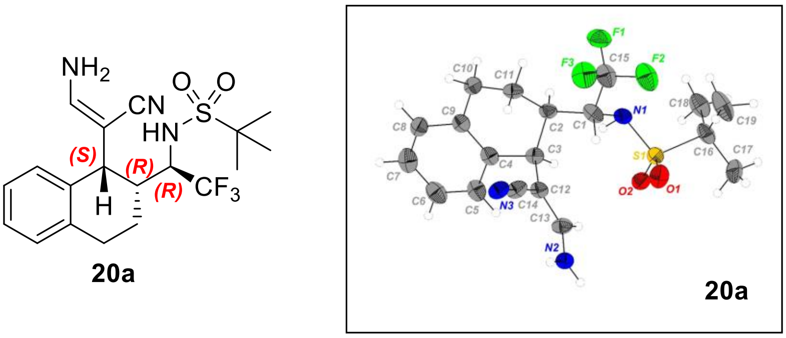


16e **H-Cube^{TM}** **20e** (58%, 2:1)

Entry	Cat.	Tª	(bar)	(mL/min)	(M)	Conv.	d.r.
1	Pd(OH)2	30	20	0.3	0.005	35	2:1
2	Pd(OH)2	30	50	0.3	0.005	39	2:1
3	Pd(OH)2	50	20	0.3	0.005	65	2:1
4	Pd(OH)2	70	20	0.3	0.005	100 (58)	2:1

[a] Isolated yield in brackets

The structure and absolute configuration of the major diastereoisomer was determined by X-Ray diffraction experiments (Figure 2.8), and it revealed a selective reduction of the double bond together with the partial reduction of one of the nitrile functionalities and tautomerisation of the final product, leading to products **20a** and **20e**.

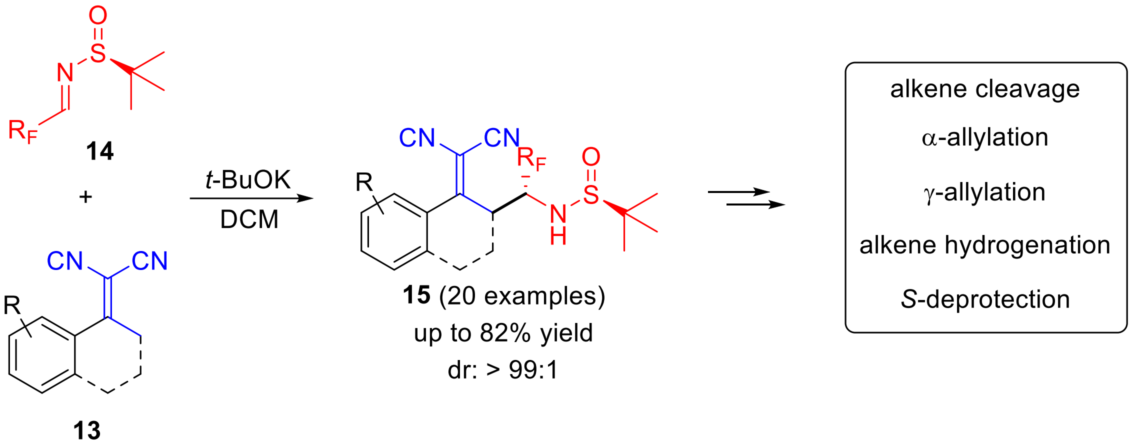


20a **20a**

Figure 2.8. X-Ray diffraction studies of compound **20a**.

2.4. Conclusions

In summary, the vinilogous addition of dicyanoalkenes **13** to fluoroalkyl sulfinyl imines **14** have been studied. By means of this transformation, the asymmetric synthesis of a new family of chiral α-fluoroalkylamines **15** have been stablished, important scaffolds in medicinal chemistry (Scheme 2.24).



Scheme 2.24. Vinylogous Mannich addition of dicyanoalkenes **13** to fluorinated sulfinyl imines **14**.

The process takes place in moderate to good yields and complete selectivity, generating fluorinated amines **15** with reverse stereochemistry when compared to reactions of the same kind of imines **14** and different vinylogous donors. Consequently, we suggest a chelated transition state to explain the stereochemical outcome of our vinylogous reaction.[159]

Additionally, the synthetic applicability of the addition products has been exemplified with several transformations showing the particular reactivity of the dicyanoalkene moiety of these α-fluorinated amines.

Is important to mention that this transformation is unprecedented with fluorinated imines and, at the same time, the use of dicyanoalkenes in AVMR has been scarcely reported.

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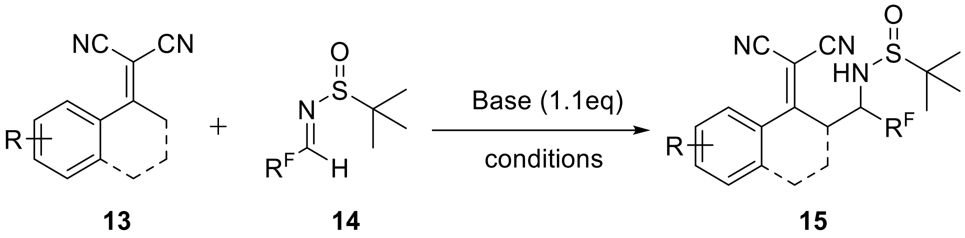
[159] Á. Sanz-Vidal; J. Torres; V. A. Soloshonok; Y. Zhu; J. Han; S. Fustero; C. del Pozo, *Adv. Synth. Catal.*, **2018**, *360*, 366-373.

2.5. Experimental section.

2.5.1. General methods

Reactions were carried out under a nitrogen atmosphere unless otherwise indicated. Solvents were purified prior to use: THF and PhMe were distilled from sodium, and CH_2Cl_2 was distilled from calcium hydride. The reactions were monitored with the aid of TLC on 0.25 mm precoated silica gel plates. Visualization was carried out with UV light and potassium permanganate stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040−0.063 mm). ^1H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents. Coupling constants (J) are given in hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. The designation br indicates that the signal is broad. The abbreviations DCM and THF indicate dichloromethane and tetrahydrofuran, respectively. A QTOF mass analyzer system has been used for the HRMS measurements. Sulfinyl imines **14**[160] and dicyano olefins **13**[123,161] were prepared following known methodologies.

2.5.2. General procedure for the Vinylogous Mannich reaction.



In a vial fitted with a screw cap and a magnet, the corresponding dicyanoalkene **13** (0.1 mmol), DCM (2 mL) and potassium tertbuthoxyde (0.1 mmol) were loaded. After stirring at room temperature for 5 minutes, the corresponding sulfinylimine **14** (0.09 mmol) was added and the pipette washed with DCM (1 mL). After stirring for 16 hours, the solvents

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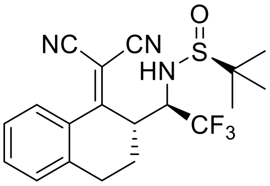
[160] (a) C. Xie; L. Zhang; H. Mei; J. Han; V. A. Soloshonok; Y. Pan, *ChemistrySelect,* **2016,** *1*, 4435-4439; (b) C. Xie; H. Mei; L. Wu; J. Han; V. A. Soloshonok; Y. Pan, *J. Fluorine Chem.,* **2014,** *165*, 67-75.

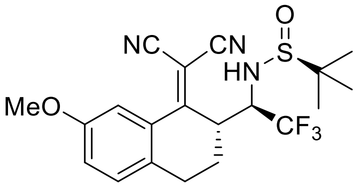
[161] D. Xue; Y.-C. Chen; X. Cui; Q.-W. Wang; J. Zhu; J.-G. Deng, *J. Org. Chem.,* **2005,** *70*, 3584-3591.

were removed and the crude product purified by means of flash column chromatography.



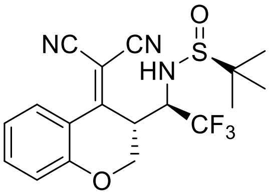
(S)-N-((R)-1-((R)-1-(dicyanomethylene)-1,2,3,4-tetrahydronaphthalen-2-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (15a). From 2-(3,4-dihydronaphthalen-1(2H)-ylidene)malononitrile **13a** (19.4 mg) and (S, E)-2-methyl-N-(2,2,2-trifluoroethylidene)propane-2-sulfinamide **14a** (18.1 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15a** was purely obtained as a pale yellow solid (24.9 mg, 0.063 mmol, 70%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.54 (td, *J* = 7.5, 1.3 Hz, 1H), 7.40 (td, *J* = 8.0, 1.3 Hz, 1H), 7.29 (dd, *J* = 7.7, 0.7 Hz, 1H), 3.76 – 3.65 (m, 2H), 3.48 (d, *J* = 8.4 Hz, 1H), 3.16 – 2.94 (m, 2H), 2.46 – 2.37 (m, 1H), 2.34 – 2.20 (m, 1H), 1.16 (s, 9H). ^{19}F NMR (282 MHz, $CDCl_3$) δ: -73.02 (d, *J* = 6.4 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.8 (s), 139.6 (s), 134.6 (s), 130.7 (s), 129.7 (s), 128.9 (s), 127.7 (s), 124.9 (q, *J* = 282.5 Hz), 114.1 (s), 113.3 (s), 84.1 (s), 60.1 (q, *J* = 30.0 Hz), 57.8 (s), 43.5 (s), 25.2 (s), 22.7 (s). HRMS (ES): calculated for (M + 1) C19H20F3N3OS: 396.1352, found 396.1356. $[\alpha]_D^{25}$ = +215.9 (*c* = 1.0 in $HCCl_3$). M.P. = 98ºC



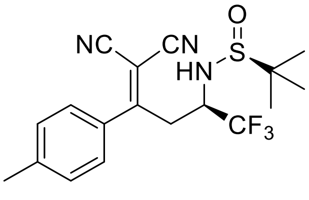
(S)-N-((R)-1-((R)-1-(dicyanomethylene)-7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (15b). From 2-(7-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene)malononitrile **13b** (22.43 mg) and (S, E)-2-methyl-N-(2,2,2-trifluoroethylidene)propane-2-sulfinamide **14a** (18.1 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15b** was purely obtained as a yelowish solid (22.6 mg, 0.053 mmol, 59%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.66 (d, *J* = 2.6 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.11 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.87 (s, 3H), 3.87 – 3.62 (m, 2H), 3.48 (d, *J* = 8.7 Hz, 1H), 3.09 – 2.86 (m, 2H), 2.45 – 2.37 (m, 1H), 2.30 – 2.18 (m, 1H), 1.17 (s, 9H).^{19}F NMR (282 MHz, CDCl$_3$) δ: -73.02 (d, *J* = 6.7 Hz).^{13}C NMR (126 MHz, CDCl$_3$) δ: 171.8 (s), 158.3 (s), 131.4 (s), 130.4 (s), 124.7 (q, *J* = 282.5 Hz), 122.8 (s), 113.9 (s), 113.3 (s), 113.2 (s), 83.8 (s), 60.0 (q, *J* = 29.9 Hz), 57.6 (s), 56.0 (s), 43.3 (s), 25.4 (s), 24.2 (s), 22.5 (s). HRMS (ES): calculated for (M + 1) C20H22F3N3O2S: 426.1458, found 426.1461. $[\alpha]_D^{25}$ = +189.8 (*c* = 1.0 in HCCl$_3$). M.P. = 102ºC



(S)-N-((R)-1-((R)-4-(dicyanomethylene)chroman-3-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (15c). From 2-(chroman-4-ylidene)malononitrile **13c** (19.6 mg) and (S, E)-2-methyl-N-(2,2,2-trifluoroethylidene)propane-2-sulfinamide **14a** (18.1 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15c** was purely obtained as an orange solid(6.4 mg, 0.016 mmol, 18%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

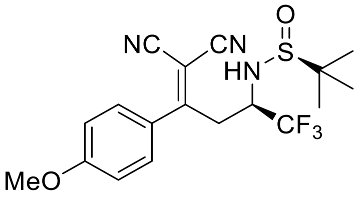
^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.34 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.54 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H), 7.13 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.00 (dd, *J* = 8.4, 1.2 Hz, 1H), 4.75 (dd, *J* = 13.1, 0.9 Hz, 1H), 4.35 (d, *J* = 13.1 Hz, 1H), 3.96 – 3.82 (m, 1H), 3.73 (d, *J* = 9.9 Hz, 1H), 3.41 (dt, *J* = 10.6, 2.0 Hz, 1H), 1.20 (s, 9H).^{19}F NMR (282 MHz, CDCl$_3$) δ: -72.67 (d, *J* = 6.7 Hz).^{13}C NMR (75 MHz, CDCl$_3$) δ: 162.7 (s), 155.7 (s), 137.3 (s), 129.9 (s), 124.5 (q, *J* = 282.7 Hz), 122.6 (s), 117.9 (s), 115.3 (s), 114.2 (s), 112.8 (s), 81.9 (s), 65.7 (s), 58.4 (q, *J* = 30.6 Hz), 57.7 (s), 40.9 (s), 22.5 (s). HRMS (ES): calculated for (M + 1) C18H18F3N2O3S: 398.1145, found 398.1146. $[\alpha]_D^{25}$ = +336.5 (*c* = 1.0 in HCCl$_3$). M.P. = 68ºC



(S)-N-((R)-5,5-dicyano-1,1,1-trifluoro-4-(p-tolyl)pent-4-en-2-yl)-2-methylpropane-2-sulfinamide (15d). From 2-(1-(p-tolyl)ethylidene)malononitrile

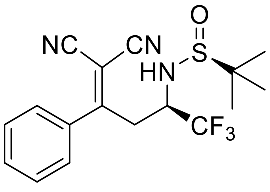
13f (18.2 mg) and (S, E)-2-methyl-N-(2,2,2-trifluoroethylidene)propane-2-sulfinamide **14a** (18.1 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15d** was purely obtained as an orange oil (23.8 mg, 0.062 mmol, 69%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.57 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 3.65 – 3.55 (m, 2H), 3.46 – 3.32 (m, 2H), 2.43 (s, 3H), 1.21 (s, 9H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -76.66 (d, *J* = 6.7 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.6 (s), 144.4 (s), 130.8 (s), 130.6 (s), 128.7 (s), 124.7 (q, *J* = 281.7 Hz), 113.6 (s), 112.7 (s), 88.2 (s), 58.9 (q, *J* = 30.9 Hz), 57.6 (s), 38.4 (s), 22.8 (s), 22.0 (s). HRMS (ES): calculated for (M + 1) C18H20F3NO3S: 384.1352, found 384.1354. $[\alpha]_D^{25}$ = +72.9 (*c* = 1.0 in $HCCl_3$).



(S)-N-((R)-5,5-dicyano-1,1,1-trifluoro-4-(4-methoxyphenyl)pent-4-en-2-yl)-2-methylpropane-2-sulfinamide (15e). From 2-(1-(4-methoxyphenyl)ethylidene)malononitrile **13g** (19.8 mg) and (S, E)-2-methyl-N-(2,2,2-trifluoroethylidene)propane-2-sulfinamide **14a** (18.1 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15e** was purely obtained as an orange oil (28.4 mg, 0.071 mmol, 79%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

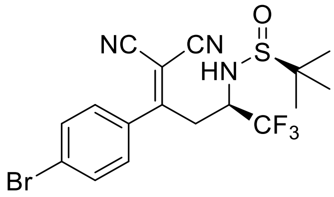
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.66 (d, *J* = 9.0 Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H), 3.67 – 3.55 (m, 2H), 3.46 – 3.31 (m, 2H), 1.20 (s, 9H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -76.71 (d, *J* = 6.6 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.5 (s), 163.6 (s), 130.6 (s), 125.1 (s), 124.7 (q, *J* = 281.7 Hz), 115.2 (s), 113.7 (s), 112.8 (s), 86.4 (s), 59.1 (q, *J* = 30.9 Hz), 57.3 (s), 55.7 (s), 37.7 (s), 22.5 (s). HRMS (ES): calculated for (M + 1) C18H20F3N3O2S: 400.1301, found 400.1303. $[\alpha]_D^{25}$ = +132.0 (*c* = 1.0 in $HCCl_3$).



(S)-N-((R)-5,5-dicyano-1,1,1-trifluoro-4-phenylpent-4-en-2-yl)-2-methylpropane-2-sulfinamide (15f). From 2-(1-phenylethylidene)malononitrile **13h**

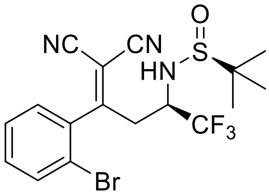
(16.8 mg) and (S, E)-2-methyl-N-(2,2,2-trifluoroethylidene)propane-2-sulfinamide **14a** (18.1 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15f** was purely obtained as a yellowish oil (23.3 mg, 0.063 mmol, 70%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.66 – 7.52 (m, 5H), 3.75 (d, *J* = 9.6 Hz, 1H), 3.66 – 3.52 (m, 1H), 3.40 (dd, *J* = 6.7, 3.9 Hz, 2H), 1.19 (s, 9H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -76.58 (d, *J* = 6.8 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.7 (s), 133.6 (s), 133.2 (s), 130.1 (s), 128.6 (s), 124.6 (q, *J* = 281.8 Hz), 113.4 (s), 112.4 (s), 89.2 (s), 58.8 (q, *J* = 31.0 Hz), 57.6 (s), 38.6 (s), 22.8 (s). HRMS (ES): calculated for (M + 1) $C_{17}H_{18}F_3N_3OS$: 370.1195, found 370.1191. $[\alpha]_D^{25}$ = +65.2 (*c* = 1.0 in $HCCl_3$).



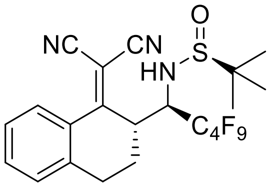
(S)-N-((R)-4-(4-bromophenyl)-5,5-dicyano-1,1,1-trifluoropent-4-en-2-yl)-2-methylpropane-2-sulfinamide (15g). From 2-(1-(4-bromophenyl)ethylidene)malononitrile **13i** (24.7 mg) and (S, E)-2-methyl-N-(2,2,2-trifluoroethylidene)propane-2-sulfinamide **14a** (18.1 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15g** was purely obtained as an orange oil (24.6 mg, 0.055 mmol, 61%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72 – 7.67 (m, 2H), 7.56 – 7.52 (m, 2H), 3.76 (d, *J* = 9.8 Hz, 1H), 3.64 – 3.47 (m, 1H), 3.36 (d, *J* = 7.3 Hz, 2H), 1.20 (s, 9H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -76.68 (d, *J* = 6.8 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.8 (s), 137.0 (s), 135.8 (s), 133.7 (s), 131.7 (s), 127.9 (q, *J* = 284.5 Hz), 116.7 (s), 115.7 (s), 93.2 (s), 62.4 (q, *J* = 31.2 Hz), 61.2 (s), 42.0 (s), 26.3 (s). HRMS (ES): calculated for (M + 1) C17H17F3N3OSBr: 448.0301, found 448.0298. $[\alpha]_D^{25}$ = +92.2 (*c* = 1.0 in $HCCl_3$).



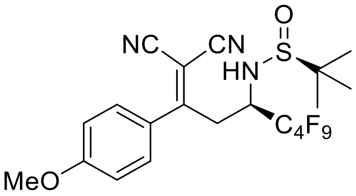
(S)-N-((R)-4-(2-bromophenyl)-5,5-dicyano-1,1,1-trifluoropent-4-en-2-yl)-2-methylpropane-2-sulfinamide (15h). From 2-(1-(2-bromophenyl)ethylidene)malononitrile **13j** (24.7 mg) and (S, E)-2-methyl-N-(2,2,2-trifluoroethylidene)propane-2-sulfinamide **14a** (18.1 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15h** was purely obtained as a yellowish oil (27.0 mg, 0.060 mmol, 67%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.83 (d, *J* = 5.6 Hz, 1H), 7.72 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.44 – 7.39 (m, 1H), 3.86 – 3.79 (m, 1H), 3.72 – 3.60 (m, 1H), 3.51 (dd, *J* = 13.9, 2.2 Hz, 2H), 3.27 (t, *J* = 12.7 Hz, 1H), 1.27 (s, 9H).^{19}F NMR (282 MHz, CDCl$_3$) δ: -77.14 (d, *J* = 3.7 Hz).^{13}C NMR (75 MHz, CDCl$_3$) δ: 171.2 (s), 135.1 (s), 134.4 (s), 133.1 (s), 131.1 (s), 129.1 (s), 124.5 (q, *J* = 281.4 Hz), 120.2 (s), 113.0 (s), 111.0 (s), 58.5 (q, *J* = 31.2 Hz), 57.8 (s), 37.8 (s), 22.8 (s). HRMS (ES): calculated for (M + 1) C17H17F3N3OSBr: 448.0301, found 448.0297. $[\alpha]_D^{25}$ = +20.5 (*c* = 1.0 in HCCl$_3$).



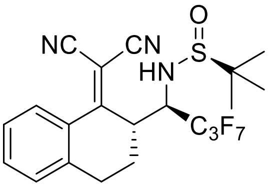
(S)-N-((R)-1-((R)-1-(dicyanomethylene)-1,2,3,4-tetrahydronaphthalen-2-yl)-5,5,5,5,5,5,5,5,5-nonafluoro-5l12-penta-2,4-diyn-1-yl)-2-methylpropane-2-sulfinamide (15i). From 2-(3,4-dihydronaphthalen-1(2H)-ylidene)malononitrile **13a** (19.4 mg) and (S, E)-2-methyl-N-(2,2,3,3,4,4,5,5,5-nonafluoropentylidene)propane-2-sulfinamide **14b** (31.6 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15i** was purely obtained as a dark brown oil (31.9 mg, 0.058 mmol, 65%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.20 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.53 (td, *J* = 7.6, 1.3 Hz, 1H), 7.41 (td, *J* = 8.0, 1.2 Hz, 1H), 7.29 (dd, *J* = 7.7, 0.7 Hz, 1H), 4.08 – 3.97 (m, 1H), 3.88 – 3.83 (m, 1H), 3.58 (d, *J* = 9.7 Hz, 1H), 3.11 – 3.02 (m, 1H), 2.94 (ddd, *J* = 18.0, 6.2, 4.3 Hz, 1H), 2.41 – 2.24 (m, 2H), 1.18 (s, 9H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -81.25 (ddt, *J* = 11.4, 8.5, 2.9 Hz), -108.32 – -129.48 (m).^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.8 (s), 139.5 (s), 134.1 (s), 130.8 (s), 129.1 (s), 128.8 (s), 127.3 (s), 118.8 – 106.7 (m), 114.0 (s), 113.1 (s), 84.1 (s), 60.3 (t, *J* = 25.2 Hz), 57.8 (s), 44.1 (s), 25.5 (s), 24.7 (s), 22.6 (s). HRMS (ES): calculated for (M + 1) C22H20F9N3OS: 546.1256, found 546.1257. $[\alpha]_D^{25}$ = -150.6 (*c* = 1.0 in $HCCl_3$).



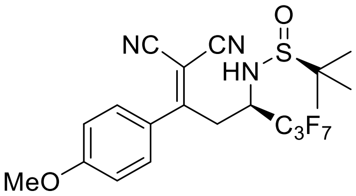
(S)-N-((R)-1,1-dicyano-5,5,6,6,7,7,8,8,8-nonafluoro-2-(4-methoxyphenyl)oct-1-en-4-yl)-2-methylpropane-2-sulfinamide (15j). From 2-(1-(4-methoxyphenyl)ethylidene)malononitrile **13g** (19.8 mg) and (S, E)-2-methyl-N-(2,2,3,3,4,4,5,5,5-nonafluoropentylidene)propane-2-sulfinamide **14b** (31.6 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15j** was purely obtained as a pale yellow oil (37.1 mg, 0.068 mmol, 75%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, *J* = 9.0 Hz, 2H), 7.07 (d, *J* = 9.0 Hz, 2H), 3.87 – 3.76 (m, 1H), 3.56 – 3.43 (m, 3H), 1.22 (s, 9H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -81.29 – -81.38 (m), -115.21 – -128.23 (m).^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.9 (s), 163.5 (s), 130.6 (s), 124.9 (s), 121.2 – 105.6 (m), 115.2 (s), 113.6 (s), 112.9 (s), 85.9 (s), 58.2 (dd, *J* = 26.5, 23.3 Hz), 57.4 (s), 55.7 (s), 37.7 (s), 22.5 (s). HRMS (ES): calculated for (M + 1) C21H20F9N3O2S: 550.1205, found 550.1207. $[\alpha]_D^{25}$ = -54.0 (*c* = 1.0 in $HCCl_3$).



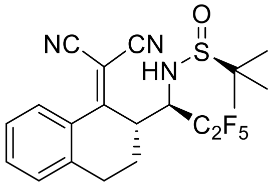
(S)-N-((R)-1-((R)-1-(dicyanomethylene)-1,2,3,4-tetrahydronaphthalen-2-yl)-4,4,4,4,4,4,4-heptafluoro-4l8-but-2-yn-1-yl)-2-methylpropane-2-sulfinamide (15k). From 2-(3,4-dihydronaphthalen-1(2H)-ylidene)malononitrile **13a** (19.4 mg) and (E)-N-(2,2,3,3,4,4,4-heptafluorobutylidene)-2-methylpropane-2-sulfinamide **14c** (27.1 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15K** was purely obtained as a dark brown oil (17.4 mg, 0.035 mmol, 39%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.19 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.53 (td, *J* = 7.5, 1.3 Hz, 1H), 7.40 (td, *J* = 8.0, 1.2 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 4.06 – 3.98 (m, 1H), 3.87 – 3.83 (m, 1H), 3.59 (d, *J* = 9.7 Hz, 1H), 3.09 – 2.90 (m, 2H), 2.40 – 2.24 (m, 2H), 1.18 (s, 9H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -81.28 (dd, *J* = 14.0, 7.8 Hz), -108.51 – -109.72 (m), -116.99 – -118.14 (m), -121.20 – -122.33 (m), -126.06 – -127.97 (m).^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.8 (s), 139.5 (s), 134.1 (s), 130.8 (s), 129.1 (s), 128.7 (s), 127.3 (s), 121.3 – 106.3 (m), 114.0 (s), 113.1 (s), 84.0 (s), 60.0 (t, *J* = 25.2 Hz), 57.8 (s), 44.0 (s), 25.4 (s), 24.7 (s), 22.5 (s). HRMS (ES): calculated for (M + 1) C21H20F7N3OS: 496.1288, found 496.1275. $[\alpha]_D^{25}$ = -173.0 (*c* = 1.0 in $HCCl_3$).



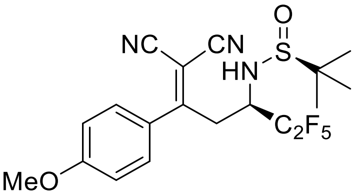
(S)-N-((R)-1,1-dicyano-5,5,6,6,7,7,7-heptafluoro-2-(4-methoxyphenyl)hept-1-en-4-yl)-2-methylpropane-2-sulfinamide (15l). From 2-(1-(4-methoxyphenyl)ethylidene)malononitrile **13g** (19.8 mg) and (E)-N-(2,2,3,3,4,4,4-heptafluorobutylidene)-2-methylpropane-2-sulfinamide **14c** (27.1 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15l** was purely obtained as a dark orange oil (35.5 mg, 0.071 mmol, 79%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 9.0 Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 3.88 (s, 3H), 3.83 – 3.77 (m, 1H), 3.74 (d, *J* = 10.2 Hz, 1H), 3.52 (ddd, *J* = 22.6, 14.9, 6.4 Hz, 1H), 1.21 (s, 9H).^{19}F NMR (282 MHz, CDCl3) δ: -81.39 (dd, *J* = 12.4, 8.5 Hz), -113.96 – -117.29 (m), -121.57 (dddd, *J* = 31.7, 24.6, 16.4, 8.2 Hz), -123.11 (ddd, *J* = 290.6, 14.5, 7.8 Hz), -126.08 (dd, *J* = 290.4, 14.3 Hz).^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.7 (s), 163.4 (s), 130.5 (s), 124.8 (s), 121.1 – 106.6 (m), 115.1 (s), 113.4 (s), 112.8 (s), 85.8 (s), 57.9 (dd, *J* = 26.5, 23.3 Hz), 57.3 (s), 55.5 (s), 37.5 (s), 22.4 (s). HRMS (ES): calculated for (M + 1) C20H20F7N3O2S: 500.1237, found 500.1234. $[\alpha]_D^{25}$ = -64.3 (*c* = 1.0 in $HCCl_3$).



(S)-N-((R)-1-((R)-1-(dicyanomethylene)-1,2,3,4-tetrahydronaphthalen-2-yl)-2,2,3,3,3-pentafluoropropyl)-2-methylpropane-2-sulfinamide (15m). From 2-(3,4-dihydronaphthalen-1(2H)-ylidene)malononitrile **13a** (19.4 mg) and (E)-2-methyl-N-(2,2,3,3,3-pentafluoropropylidene)propane-2-sulfinamide **14d** (22.6 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15m** was purely obtained as a brownish oil (17.4 mg, 0.04 mmol, 43%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

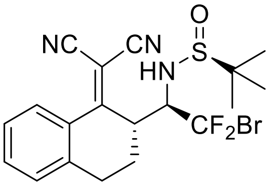
^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.17 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.54 (td, *J* = 7.5, 1.3 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.29 (dd, *J* = 7.7, 0.8 Hz, 1H), 3.73 – 3.65 (m, 2H), 3.50 (d, *J* = 8.4 Hz, 1H), 3.15 – 2.93 (m, 2H), 2.45 – 2.38 (m, 1H), 2.31 – 2.20 (m, 1H), 1.15 (s, 9H). ^{19}F NMR (282 MHz, CDCl$_3$) δ: -72.98 (d, *J* = 6.3 Hz), -79.87 – -82.29 (m). ^{13}C NMR (126 MHz, CDCl$_3$) δ: 171.5 (s), 139.3 (s), 134.1 (s), 130.3 (s), 129.3 (s), 127.3 (s), 124.5 (q, *J* = 282.6 Hz), 113.7 (s), 112.9 (s), 83.7 (s), 59.8 (q, *J* = 30.0 Hz), 57.4 (s), 43.14 (s), 24.8 (s), 22.3 (s). HRMS (ES): calculated for (M + 1) C20H20F5N3OS: 446.1249, found 446.1245. $[\alpha]_D^{25}$ = -240.7 (*c* = 1.0 in HCCl$_3$).



(S)-N-((R)-6,6-dicyano-1,1,1,2,2-pentafluoro-5-(4-methoxyphenyl)hex-5-en-3-yl)-2-methylpropane-2-sulfinamide (15n). From 2-(1-(4-methoxyphenyl)ethylidene)malononitrile **13g** (19.8 mg) and (E)-2-methyl-N-(2,2,3,3,3-pentafluoropropylidene)propane-2-sulfinamide **14d** (22.6 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15n** was purely obtained as a brownish oil (32.8 mg, 0.07 mmol, 81%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

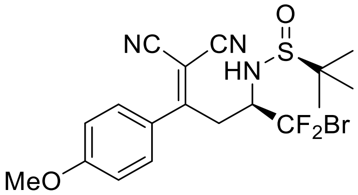
^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.67 (d, *J* = 9.0 Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H), 3.75 – 3.67 (m, 2H), 3.49 (ddd, *J* = 22.5, 14.8, 6.2 Hz, 2H), 1.20 (s, 9H). ^{19}F NMR (282 MHz,

$CDCl_3$) δ: -80.73 (s), -117.71 (d, *J* = 275.6 Hz), -125.96 (d, *J* = 275.6 Hz).^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.7 (s), 163.5 (s), 130.7 (s), 124.9 (s), 122.7 – 110.4 (m), 115.2 (s), 113.6 (s), 112.9 (s), 85.9 (s), 57.6 (dd, *J* = 27.0, 23.1 Hz), 57.4 (s), 55.7 (s), 37.5 (s), 22.5 (s). HRMS (ES): calculated for (M + 1) C19H20F5N3O2S: 450.1269, found 450.1277. $[\alpha]_D^{25}$ = -48.6 (*c* = 1.0 in $HCCl_3$).



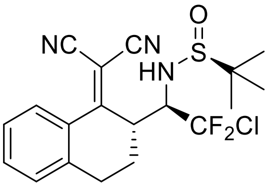
(S)-N-((R)-2-bromo-1-((R)-1-(dicyanomethylene)-1,2,3,4-tetrahydronaphthalen-2-yl)-2,2-difluoroethyl)-2-methylpropane-2-sulfinamide (15o). From 2-(3,4-dihydronaphthalen-1(2H)-ylidene)malononitrile **13a** (19.4 mg) and (E)-N-(2-bromo-2,2-difluoroethylidene)-2-methylpropane-2-sulfinamide **14e** (26.2 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15o** was purely obtained as a dark orange oil (22.8 mg, 0.05 mmol, 55%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.17 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.54 (td, *J* = 7.5, 1.3 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.29 (dd, *J* = 7.7, 0.8 Hz, 1H), 3.73 – 3.66 (m, 2H), 3.49 (d, *J* = 8.3 Hz, 1H), 3.16 – 2.93 (m, 2H), 2.44 – 2.38 (m, 1H), 2.31 – 2.24 (m, 1H), 1.16 (s, 9H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -46.88 (d, *J* = 163.6 Hz), -52.16 (d, *J* = 163.6 Hz).^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.4 (s), 139.2 (s), 134.2 (s), 130.3 (s), 129.3 (s), 128.5 (s), 127.3 (s), 125.6 (t, *J* = 282.6 Hz), 113.7 (s), 112.9 (s), 83.7 (s), 59.9 (t, *J* = 62.6 Hz), 57.4 (s), 43.1 (s), 24.79 (s), 22.7 (s), 22.3 (s). HRMS (ES): calculated for (M + 1) C19H20BrF2N3OS: 456.0479, found 456.0471. $[\alpha]_D^{25}$ = -190.8 (*c* = 1.0 in $HCCl_3$).



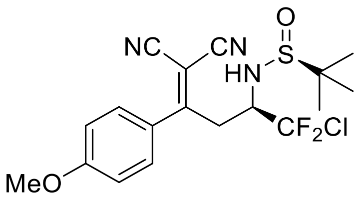
(S)-N-((R)-1-bromo-5,5-dicyano-1,1-difluoro-4-(4-methoxyphenyl)pent-4-en-2-yl)-2-methylpropane-2-sulfinamide (15p). From 2-(1-(4-methoxyphenyl)ethylidene)malononitrile **13g** (19.8 mg) and (E)-N-(2-bromo-2,2-difluoroethylidene)-2-methylpropane-2-sulfinamide **14e** (26.2 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15p** was purely obtained as a brownish oil (34.1 mg, 0.07 mmol, 82%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.65 (d, *J* = 9.0 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 3.84 (s, 3H), 3.75 (d, *J* = 9.3 Hz, 1H), 3.58 – 3.48 (m, 2H), 3.30 (dd, *J* = 14.4, 9.2 Hz, 1H), 1.21 (s, 9H).^{19}F NMR (282 MHz, CDCl$_3$) δ: -54.23 (dd, *J* = 161.6, 8.0 Hz), -56.12 (dd, *J* = 161.6, 7.2 Hz).^{13}C NMR (126 MHz, CDCl$_3$) δ: 170.4 (s), 163.5 (s), 130.6 (s), 125.2 (s), 123.4 (t, *J* = 310.7 Hz), 115.1 (s), 113.8 (s), 112.8 (s), 86.2 (s), 64.7 (dd, *J* = 25.6, 23.7 Hz), 57.4 (s), 55.6 (s), 39.0 (s), 22.5 (s). HRMS (ES): calculated for (M + 1) C18H20BrF2N3O2S: 460.0500, found 460.0510. $[\alpha]_D^{25}$ = -159.0 (*c* = 1.0 in HCCl$_3$).



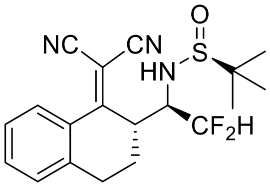
(S)-N-((R)-2-chloro-1-((R)-1-(dicyanomethylene)-1,2,3,4-tetrahydronaphthalen-2-yl)-2,2-difluoroethyl)-2-methylpropane-2-sulfinamide (15q). From 2-(3,4-dihydronaphthalen-1(2H)-ylidene)malononitrile **13a** (19.4 mg) and (E)-N-(2-chloro-2,2-difluoroethylidene)-2-methylpropane-2-sulfinamide **14f** (19.6 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15q** was purely obtained as a brownish solid (20.6 mg, 0.05 mmol, 55%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

^{1}H NMR (500 MHz, CDCl$_3$) δ: 8.19 (d, *J* = 8.0 Hz, 1H), 7.52 (td, *J* = 7.6, 1.3 Hz, 1H), 7.38 (td, *J* = 7.8, 0.6 Hz, 1H), 7.28 (d, *J* = 7.1 Hz, 1H), 3.73 – 3.67 (m, 2H), 3.61 (d, *J* = 8.2 Hz, 1H), 3.08 (ddd, *J* = 17.4, 11.2, 5.8 Hz, 1H), 2.98 (ddd, *J* = 18.4, 6.9, 2.2 Hz, 1H), 2.45 – 2.40 (m, 1H), 2.26 – 2.19 (m, 1H), 1.17 (s, 9H).^{19}F NMR (282 MHz, CDCl$_3$) δ: -53.07 (dd, *J* = 166.6, 2.6 Hz), -58.49 (dd, *J* = 164.7, 2.3 Hz).^{13}C NMR (126 MHz, CDCl$_3$) δ: 171.7 (s), 139.4 (s), 134.2 (s), 130.6 (s), 129.5 (t, *J* = 297.2 Hz), 129.4 (s), 128.6 (s), 127.2 (s), 114.0 (s), 113.0 (s), 83.6 (s), 63.7 (dd, *J* = 29.5, 23.3 Hz), 57.6 (s), 44.6 (s), 44.6 (s), 24.8 (dd, *J* = 26.8, 3.9 Hz), 22.5 (s). HRMS (ES): calculated for (M + 1) C19H20ClF2N3OS: 411.0984, found 411.0979. $[\alpha]_D^{25}$ = -183.9 (*c* = 1.0 in HCCl$_3$). M.P. = 71ºC



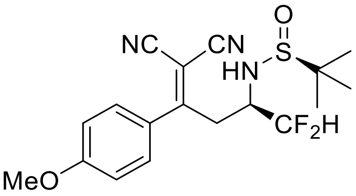
(S)-N-((R)-1-chloro-5,5-dicyano-1,1-difluoro-4-(4-methoxyphenyl)pent-4-en-2-yl)-2-methylpropane-2-sulfinamide (15r). From 2-(1-(4-methoxyphenyl)ethylidene)malononitrile **13g** (19.8 mg) and (E)-N-(2-chloro-2,2-difluoroethylidene)-2-methylpropane-2-sulfinamide **14f** (19.6 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15r** was purely obtained as a brownish oil (30.4 mg, 0.073 mmol, 81%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.66 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 3.75 (d, *J* = 9.5 Hz, 1H), 3.66 – 3.59 (m, 1H), 3.49 (dd, *J* = 14.5, 4.0 Hz, 1H), 3.32 (dd, *J* = 14.5, 9.3 Hz, 1H), 1.21 (s, 9H).^{19}F NMR (282 MHz, CDCl$_3$) δ: -60.63 (dd, *J* = 164.0, 7.3 Hz), -62.29 (dd, *J* = 164.0, 7.0 Hz).^{13}C NMR (126 MHz, CDCl$_3$) δ: 170.5 (s), 163.5 (s), 130.6 (s), 128.8 (t, J = 296.9 Hz), 125.1 (s), 115.1 (s), 113.8 (s), 112.8 (s), 86.2 (s), 63.6 (dd, J = 27.5, 26.4 Hz), 57.3 (s), 55.6 (s), 38.5 (s), 38.5 (s), 22.5 (s). HRMS (ES): calculated for (M + 1) C18H20ClF2N3O2S: 416.1006, found 416.1003. $[\alpha]_D^{25}$ = -157.8 (*c* = 1.0 in HCCl$_3$).



(S)-N-((R)-1-((R)-1-(dicyanomethylene)-1,2,3,4-tetrahydronaphthalen-2-yl)-2,2-difluoroethyl)-2-methylpropane-2-sulfinamide (15s). From 2-(3,4-dihydronaphthalen-1(2H)-ylidene)malononitrile **13a** (19.4 mg) and (E)-N-(2,2-difluoroethylidene)-2-methylpropane-2-sulfinamide **14g** (16.5 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15s** was purely obtained as a brownish oil (9.05 mg, 0.02 mmol, 27%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

^{1}H NMR (500 MHz, CDCl$_3$) δ: 8.17 (d, *J* = 8.8 Hz, 1H), 7.51 (td, *J* = 7.6, 1.2 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 5.89 (t, *J* = 55.3 Hz, 1H), 3.63 (dt, *J* = 8.8, 4.3 Hz, 1H), 3.54 – 3.47 (m, 2H), 3.03 – 2.92 (m, 2H), 2.29 – 2.24 (m, 2H), 1.16 (s, 9H).^{19}F NMR (282 MHz, CDCl$_3$) δ: -125.49 (ddd, *J* = 286.3, 55.0, 13.6 Hz), -128.08 (ddd, *J* = 286.1, 54.9, 11.9 Hz).^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.9 (s), 139.3 (s), 133.9 (s), 130.0 (s), 129.2 (s), 129.0 (s), 127.4 (s), 114.8 (t, *J* = 246.7 Hz), 114.0 (s), 113.2 (s), 83.9 (s), 59.8 (t, *J* = 21.5 Hz), 57.3 (s), 43.1 (s), 25.3 (s), 24.6 (s), 22.5 (s). HRMS (ES): calculated for (M + 1) C19H21F2N3OS: 378.1446, found 378.1456. $[\alpha]_D^{25}$ = -238.5 (*c* = 1.0 in $HCCl_3$).

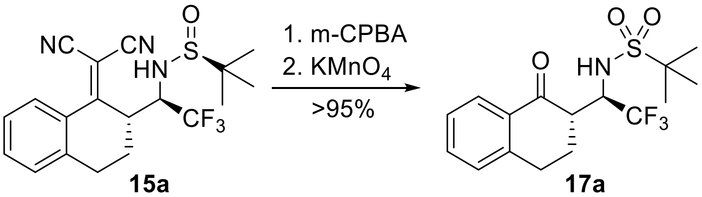


(S)-N-((R)-5,5-dicyano-1,1-difluoro-4-(4-methoxyphenyl)pent-4-en-2-yl)-2-methylpropane-2-sulfinamide (15t). From 2-(1-(4-methoxyphenyl)ethylidene)malononitrile **13g** (19.8 mg) and (E)-N-(2,2-difluoroethylidene)-2-methylpropane-2-sulfinamide **14g** (16.5 mg) in the presence of potassium tertbuthoxyde (11.2 mg), the titled compound **15t** was purely obtained as a brownish oil (19.5 mg, 0.05 mmol, 57%) after purification by column chromatography with an eluent mixture of Hex:EtOAc (10:1).

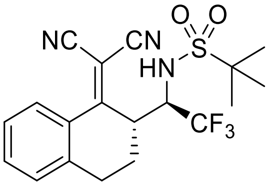
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.66 (d, *J* = 8.9 Hz, 2H), 7.04 (d, *J* = 8.9 Hz, 2H), 5.71 (td, *J* = 55.6, 2.6 Hz, 1H), 3.87 (s, 3H), 3.67 (d, *J* = 9.5 Hz, 1H), 3.48 – 3.40 (m, 1H), 3.37 (td, *J* = 14.5, 6.6 Hz, 2H), 1.20 (s, 9H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -123.40 (ddd, *J* = 284.1, 55.2, 7.8 Hz), -129.93 (ddd, *J* = 284.4, 56.0, 16.6 Hz).^{13}C NMR (126 MHz, $CDCl_3$) δ: 172.2 (s), 163.3 (s), 130.5 (s), 125.4 (s), 115.1 (t, *J* = 247.1 Hz), 115.0 (s), 113.6 (s), 113.0 (s), 85.5 (s), 58.3 (t, *J* = 23.2 Hz), 56.9 (s), 55.6 (s), 36.9 (s), 22.5 (s). HRMS (ES): calculated for (M + 1) C18H21F2N3O2S: 382.1395, found 382.1397. $[\alpha]_D^{25}$ = -68.5 (*c* = 1.0 in $HCCl_3$).

2.5.3. AVM Addition products derivatisation.

2.5.3.1. Oxidation of 15a.



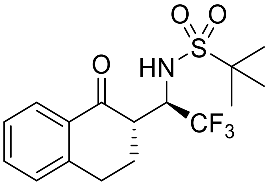
To a 100 mL round bottom flask fitted with a magnetic stirring bar, aminoalkene **15a** (600 mg, 1eq) was dissolved in DCM (30 mL). m-CPBA (750 mg, 2 eq) was then added and the mixture stirred for 10 min at room temperature. The mixture was quenched with $NaHCO_3$, extracted with DCM, dried over Na_2SO_4 and solvents removed under vacuum to give product **16a** quantitatively as a yellowish oil without further purification.



N-((R)-1-((R)-1-(dicyanomethylene)-1,2,3,4-tetrahydronaphthalen-2-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfonamide (16a).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.09 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.53 (td, *J* = 7.5, 1.3 Hz, 1H), 7.37 (td, *J* = 8.0, 1.2 Hz, 1H), 7.28 (d, *J* = 7.0 Hz, 1H), 4.64 (d, *J* = 10.4 Hz, 1H), 4.16 - 4.04 (m, 1H), 3.71 (dt, *J* = 10.2, 4.2 Hz, 1H), 3.14 – 2.91 (m, 2H), 2.40 – 2.19 (m, 2H), 1.34 (s, 9H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -71.10 (d, *J* = 6.4 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.1 (s), 139.7 (s), 134.5 (s), 130.7 (s), 129.7 (s), 129.0 (s), 127.4 (s), 124.8 (q, *J* = 283.4 Hz), 114.0 (s), 113.5 (s), 84.2 (s), 61.5 (s), 56.8 (q, *J* = 30.4 Hz), 44.4 (s), 25.4 (s), 24.5 (s). HRMS (ES): calculated for (M + 1) C19H20F3N3O2S: 412.1301, found 412.1295. $[\alpha]_D^{25}$ = -162.0 (*c* = 1.0 in $HCCl_3$).

The crude product **16a** was then dissolved in 30 mL of a mixture of Acetone:H_2O (5:1) and $MgSO_4$ (360 mg, 1.5 eq) and $KMnO_4$ (600, 2 eq) were subsequently added. After stirring for 30 min the solvents were removed under vacuum and the crude product subjected to flash column chromatography with an eluent mixture of Hex:EtOAc (10:1 → 4:1) to give product **17a** quantitatively as a yellow oil.

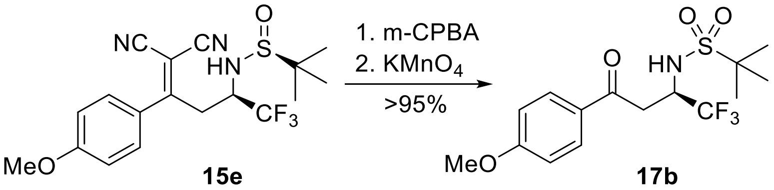


2-methyl-N-((R)-2,2,2-trifluoro-1-((S)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)ethyl)propane-2-sulfonamide (17a).

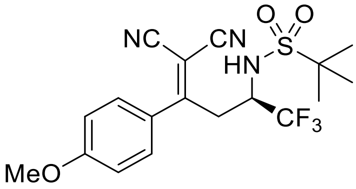
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.49 (td, *J* = 7.5, 1.5 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 1H), 5.40 (d, *J* = 10.7 Hz, 1H), 4.61 (dqd, *J* = 10.4, 8.5, 1.8 Hz, 1H), 3.19 – 3.03 (m, 3H), 2.35 – 2.27 (m, 2H), 1.43 (s, 9H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -70.56 (d, *J* = 8.5 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ: 196.5 (s), 143.8 (s), 134.5

(s), 132.6 (s), 129.2 (s), 128.1 (s), 127.3 (s), 125.0 (q, *J* = 282.7 Hz), 61.2 (s), 57.1 (q, *J* = 30.9 Hz), 49.8 (s), 29.8 (s), 27.0 (s), 24.5 (s). HRMS (ES): calculated for (M + 1) C16H20F3NO3S: 364.1189, found 364.1186. $[\alpha]_D^{25}$ = -27.9 (*c* = 1.0 in $HCCl_3$).

2.5.3.2. Oxidation of 15e.



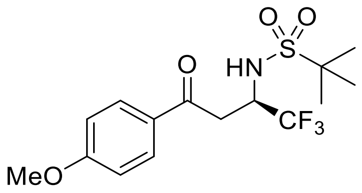
To a 100 mL round bottom flask fitted with a magnetic stirring bar, aminoalkene **15e** (600 mg, 1eq) was dissolved in DCM (30 mL). m-CPBA (750 mg, 2 eq) was then added and the mixture stirred for 10 min at room temperature. The mixture was quenched with $NaHCO_3$, extracted with DCM, dried over Na_2SO_4 and solvents removed under vacuum to give product **16b** quantitatively as a yellowish oil without further purification.



(R)-N-(5,5-dicyano-1,1,1-trifluoro-4-(4-methoxyphenyl)pent-4-en-2-yl)-2-methylpropane-2-sulfonamide (16b).

^1H NMR (300 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 9.0 Hz, 2H), 7.04 (d, *J* = 9.0 Hz, 2H), 4.87 (d, *J* = 10.6 Hz, 1H), 4.01 – 3.91 (m, 1H), 3.88 (s, 3H), 3.45 (qd, *J* = 14.7, 6.9 Hz, 2H), 1.36 (s, 9H). ^{19}F NMR (282 MHz, $CDCl_3$) δ: -74.89 (d, *J* = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.3 (s), 164.0 (s), 131.1 (s), 125.2 (s), 124.6 (q, *J* = 282.3 Hz), 115.3 (s), 113.6 (s), 113.3 (s), 85.6 (s), 61.4 (s), 56.0 (s), 55.5 (q, *J* = 31.1 Hz), 38.6 (s), 24.4 (s). HRMS (ES): calculated for (M + 1) C18H20F3N3O3S: 416.1250, found 416.1231. $[\alpha]_D^{25}$ = -137.4 (*c* = 1.0 in $HCCl_3$).

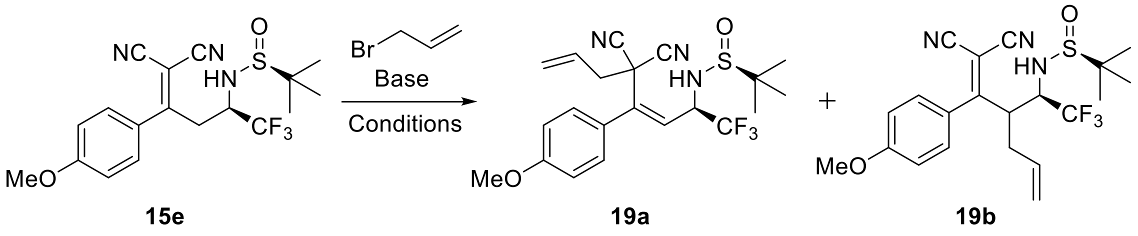
The crude product **16b** was then dissolved in 30 mL of a mixture of Acetone:H_2O (5:1) and $MgSO_4$ (360 mg, 1.5 eq) and $KMnO_4$ (600, 2 eq) were subsequently added. After stirring for 30 min the solvents were removed under vacuum and the crude product subjected to flash column chromatography with an eluent mixture of Hex:EtOAc (10:1 → 4:1) to give product **17b** quantitatively as a yellow-orenge oil.



(R)-2-methyl-N-(1,1,1-trifluoro-4-(4-methoxyphenyl)-4-oxobutan-2-yl)propane-2-sulfonamide (17b).

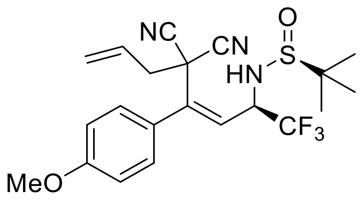
^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.92 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 5.54 (d, J = 10.3 Hz, 1H), 4.67– 4.52 (m, 1H), 3.88 (s, 3H), 3.43 (ddd, J = 23.4, 17.4, 5.0 Hz, 2H), 1.42 (s, 9H).^{19}F NMR (282 MHz, CDCl$_3$) δ: -74.13 (d, J = 7.8 Hz).^{13}C NMR (75 MHz, CDCl$_3$) δ: 194.6 (s), 164.4 (s), 130.8 (s), 129.2 (s), 125.2 (d, J = 281.8 Hz), 114.2 (s), 60.8 (s), 55.7 (s), 53.4 (q, J = 31.9 Hz), 37.5 (s), 24.2 (s). HRMS (ES): calculated for (M + 1) C15H20F3NO4S: 368.1138, found 368.1142. $[\alpha]_D^{25}$ = -54.7 (c = 1.0 in HCCl$_3$).

2.5.3.3. Alkylation.



Method A

To a stirred solution of aminoalkene **15e** (40 mg, 0.1 mmol, 1 eq) in dry DCM (3 mL), P2-Et Phosphazene (75 mg, 2.2 eq) was added and the reaction stirred for 5 min. Then, allyl bromide (12 µL, 1.2 eq) was added dropwise and the reaction stirred at room temperature for 16h. Reaction was quenched with NH_4Cl, extracted with DCM and dried over Na_2SO_3. After purification by column with an eluent mixture of Hex:EtOAc (4:1) product **19a** was obtained (38.7 mg, 88%) as a yellowish oil.

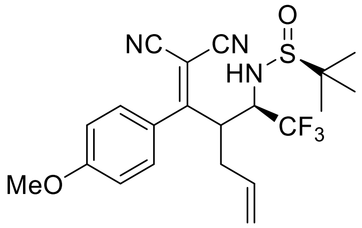


(S)-N-((R,Z)-5,5-dicyano-1,1,1-trifluoro-4-(4-methoxyphenyl)octa-3,7-dien-2-yl)-2-methylpropane-2-sulfinamide (19a).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.31 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.27 (d, *J* = 9.9 Hz, 1H), 5.88 (ddt, *J* = 17.2, 10.2, 7.2 Hz, 1H), 5.46 – 5.36 (m, 2H), 4.15 – 4.03 (m, 1H), 3.86 (s, 3H), 3.58 (d, *J* = 9.2 Hz, 1H), 2.72 (dd, *J* = 7.2, 3.2 Hz, 2H), 1.20 (s, 9H).^{19}F NMR (282 MHz, CDCl$_3$) δ: -75.63 (d, *J* = 7.0 Hz).^{13}C NMR (75 MHz, CDCl$_3$) δ: 160.5 (s), 138.5 (s), 131.0 (s), 127.7 (s), 126.3 (s), 123.6 (q, *J* = 281.1 Hz), 123.6 (s), 122.4 (s), 114.5 (s), 113.0 (d, *J* = 6.0 Hz), 57.8 (q, *J* = 32.0 Hz), 57.0 (s), 55.0 (s), 44.3 (s), 41.1 (s), 22.0 (s). HRMS (ES): calculated for (M + 1) C21H24F3N3O2S: 440.1541, found 440.1543. $[\alpha]_D^{25}$ = -129.4 (*c* = 1.0 in HCCl$_3$).

Method B

To a stirred solution of aminoalkene **15e** (40 mg, 0.1 mmol, 1 eq) in dry DCM (3 mL), NaH (5.3 mg, 2.2 eq) was added and the reaction stirred for 5 min. Then, allyl bromide (12 µL, 1.2 eq) was added dropwise and the reaction stirred at room temperature for 16h. Reaction was quenched with NH$_4$Cl, extracted with DCM and dried over Na$_2$SO$_3$. After purification by column with an eluent mixture of Hex:EtOAc (4:1) product **19b** was obtained (17.6 mg, 40%) as a light yellow oil.

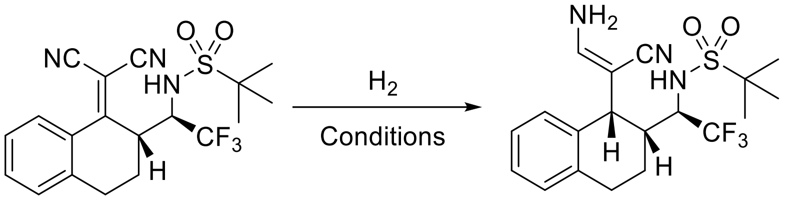


(S)-N-((2R)-3-(2,2-dicyano-1-(4-methoxyphenyl)vinyl)-1,1,1-trifluorohex-5-en-2-yl)-2-methylpropane-2-sulfinamide (19b).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.24 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 5.74 (ddt, *J* = 17.4, 9.8, 6.5 Hz, 1H), 5.12 (dq, *J* = 5.6, 1.4 Hz, 1H), 5.08 (t, *J* = 1.5 Hz, 1H), 3.77 (s, 3H), 3.55 – 3.42 (m, 2H), 3.15 (dd, *J* = 14.1, 10.0 Hz, 1H), 3.00 (dd, *J* = 13.7, 2.3 Hz, 1H), 2.92 – 2.82 (m, 1H), 1.16 (s, 9H).^{19}F NMR (282 MHz, CDCl$_3$) δ: -77.16 (d, *J* = 6.8 Hz).^{13}C NMR (75 MHz, CDCl$_3$) δ: 160.8 (s), 151.3 (s), 133.3 (s), 130.0 (s), 128.2 (s), 125.1 (d, *J* = 281.6

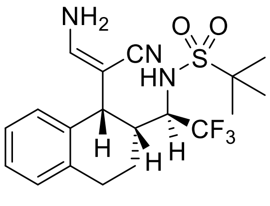
Hz), 119.7 (s), 118.8 (s), 114.9 (s), 57.7 (q, *J* = 30.2 Hz), 57.3 (s), 55.7 (s), 39.0 (s), 35.8 (s), 22.8 (s). HRMS (ES): calculated for (M + 1) C21H24F3N3O2S: 440.1541, found 440.1549. $[\alpha]_D^{25}$ = -98.3 (*c* = 1.0 in HCCl$_3$).

2.5.3.4. Selective reduction.



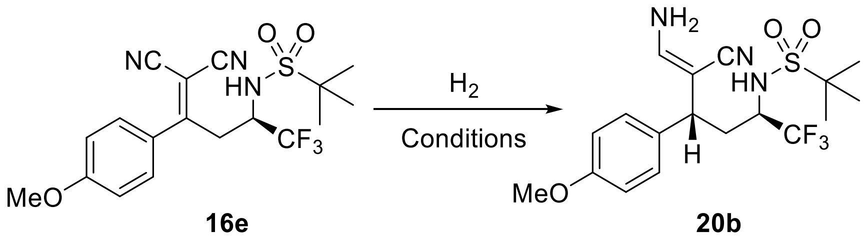
16a **20a**

A 0.005 M solution of aminoalkene **16a** (40 mg, 0.1 mmol) in EtOAc (20 mL) was flushed through a packed-bed of Pd(OH)$_2$/C 20% wt. at 0.3 mL/min flow and 30ºC under 20 bar H$_2$ atmosphere. After purification by column chromatography with an eluent mixture of Hex:EtOAC (10:1 → 2:1), product **20a** (25.8 mg, 0.062 mmol, 62%) was purely obtained as a white solid.

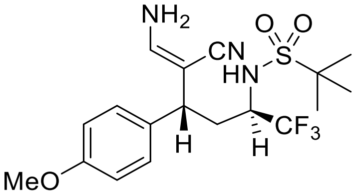


N-((R)-1-((1R,2R)-1-((Z)-2-amino-1-cyanovinyl)-1,2,3,4-tetrahydronaphthalen-2-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfonamide (20a).

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.19 – 7.08 (m, 3H), 7.08 – 6.97 (m, 2H), 4.68 (d, *J* = 10.5 Hz, 2H), 4.35 – 4.29 (m, 2H), 3.71 (d, *J* = 3.6 Hz, 1H), 3.09 (dd, *J* = 17.3, 6.2 Hz, 1H), 2.95 – 2.88 (m, 1H), 2.50 – 2.41 (m, 1H), 2.38 – 2.34 (m, 1H), 1.94 (dd, *J* = 13.6, 6.9 Hz, 1H), 1.47 (s, 9H). ^{19}F NMR (282 MHz, CDCl$_3$) δ: -70.60 (d, *J* = 7.8 Hz). ^{13}C NMR (126 MHz, CDCl$_3$) δ: 136.7 (s), 135.2 (s), 129.5 (s), 129.3 (s), 129.2 (q, *J* = 247.0 Hz), 127.2 (s), 126.2 (s), 118.8 (s), 81.7 (s), 61.1 (s), 58.0 (q, *J* = 29.4 Hz), 40.9 (s), 40.2 (s), 28.6 (s), 24.3 (s), 21.8 (s). HRMS (ES): calculated for (M + 18) C19H24F3N3O2S: 433.1880, found 433.1873. $[\alpha]_D^{25}$ = -47.3 (*c* = 1.0 in HCCl$_3$). M.P. = 81ºC



A 0.005 M solution of aminoalkene **16e** (40 mg, 0.1 mmol) in EtOAc (20 mL) was flushed through a packed-bed of $Pd(OH)_2/C$ 20% wt. at 0.3 mL/min flow and 70ºC under 20 bar H_2 atmosphere. After purification by column chromatography with an eluent mixture of Hex:EtOAC (10:1 → 2:1), product **20b** (24.3 mg, 0.058 mmol, 58%) was purely obtained as a white solid.



N-((2R,4R,Z)-6-amino-5-cyano-1,1,1-trifluoro-4-(4-methoxyphenyl)hex-5-en-2-yl)-2-methylpropane-2-sulfonamide (20b).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.22 (d, *J* = 8.7 Hz, 2H), 7.01 (t, *J* = 10.6 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.54 (d, *J* = 10.5 Hz, 2H), 4.12 – 4.04 (m, 1H), 3.84 (d, *J* = 9.5 Hz, 1H), 3.79 (s, 3H), 3.58 (dd, *J* = 11.9, 3.1 Hz, 1H), 2.53 (ddd, *J* = 14.4, 11.9, 2.5 Hz, 1H), 1.82 (ddd, *J* = 14.3, 10.8, 3.2 Hz, 1H), 1.44 (s, 9H).^{19}F NMR (282 MHz, $CDCl_3$) δ: -75.18 (d, *J* = 7.2 Hz).^{13}C NMR (126 MHz, $CDCl_3$) δ: 158.6 (s), 148.4 (s), 134.8 (s), 127.9 (s), 124.9 (q, *J* = 281.9 Hz), 117.9 (s), 114.2 (s), 81.9 (s), 60.9 (s), 55.3 (s), 53.9 (q, *J* = 30.7 Hz), 40.6 (s), 36.0 (s), 24.2 (s). HRMS (ES): calculated for (M + 1) C18H24F3N3O3S: 420.1490, found 420.1495. $[\alpha]_D^{25}$ = -68.3 (*c* = 1.0 in $HCCl_3$). M.P. = 76ºC

» Chapter 3 «

Unexpected metal-free synthesis of trifluoroarenes via tandem coupling of dicyanoalkenes and conjugated fluorinated sulfinylimines

3.1. Introduction.

At this point of our research journey, we decided to go deeper in our thorough understanding of the vinylogous Mannich reaction over fluorinated structures. Hence, new fluorine-containing building blocks should be designed to expand the limits of our knowledge on this reaction.

As already reviewed in *Chapter 1*, highly electrophilic iminoesters were subjected to VMR, promoting a Povarov-type reaction and yielding biologically interesting furan-fused tetrahydroquinolines in an easy and stereoselective manner. On the other hand, *Chapter 2* was based on the employment of fluorinated chiral aldimines, undergoing the AVMR and producing a large amount of novel interesting fluorine-containing structures.

In order to broaden the limits of this reaction, we started to think about plausible ways to enhance its versatility. While in previous chapters, the reaction of the nucleophile was always directed to the iminic carbon, undergoing a 1,2-nucleophilic addition over different iminoesters and aldimines, in this chapter we will try to apply the vinylogy concept not only to the nucleophile, but also to the electrophilic counterpart of the reaction.

For this aim, fluorine-containing α,β-unsaturated imines should be designed in order to target the 1,4-nucleophilic addition of nucleophiles to imines. Theoretically, this approach should also give us the opportunity to promote a subsequent intramolecular reaction of the newly formed nucleophilic amine with an electrophile present in the starting nucleophile (Scheme 3.1, b).

In 2008, Chen and co-workers developed a domino Michael-Michael protocol involving the use of α,α-dicyanoalkenes as vinylogous pro-nucleophiles and conjugated ketones as acceptor.[162] In this procedure, the outcome of the first Michael reaction underwent an intramolecular second Michael reaction (Scheme 3.1, a), demonstrating that the introduction of conjugation to the electrophile broadened the limits of a simple Michael reaction and generated substantial molecular complexity by an easy procedure.

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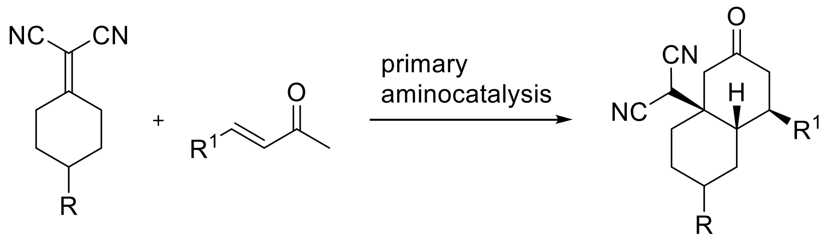
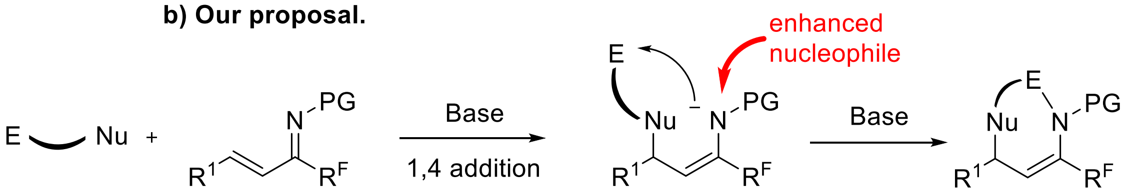
[162] T.-R. Kang; J.-W. Xie; W. Du; X. Feng; Y.-C. Chen, *Org. Biomol. Chem.*, **2008,** *6*, 2673-2675.

a) Chen's domino Michael-Michael reaction.



b) Our proposal.



Scheme 3.1. Asymmetric domino reaction by Chen vs our imine version proposal.

Chen's publication inspired our original idea for *Chapter 3* line of investigations, providing with prove of concept enough to start thinking about the design of fluorine-containing conjugated ketimines capable of undergo a first 1,4-vinylogous type addition with dicyanoalkenes, followed by the subsequent intramolecular attack of the nucleophilic enhanced amine moiety to the dicyanoalkene, acting now as a Michael acceptor. This approach should generate important molecular complexity in a single reaction step.

A revision of the synthetic utility of conjugated imines is summarised below.

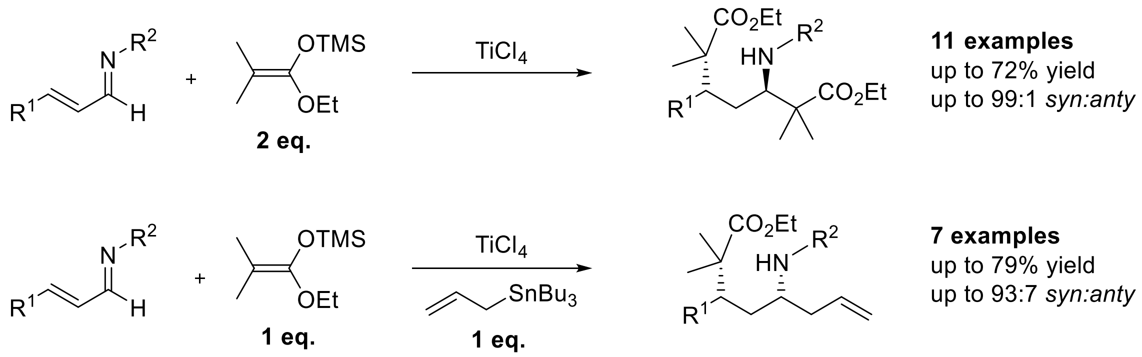
3.1.1. Conjugated imines.

The widespread existence of nitrogen-containing compounds such as amino acids, alkaloids, and functional materials coupled with their use as useful synthons have stimulated a growing interest in the development of synthetic methodologies to access them. Among those protocols, nucleophilic addition reactions to the iminic carbon of α,β-unsaturated imines utilized as crucial step constitute one of the most straight-forward approaches. However, since there are two electrophilic carbons in α,β-unsaturated imines, difficulties are always encountered regarding the regioselectivity. On the other hand, the iminic functionality do not always have enough electrophilicity as compared with their parent carbonyl counterparts or iminoesters employed in *Chapter 1*.

Along the years, some procedures have been designed to achieve selective 1,2- and 1,4-additions to conjugated imines, using different types of nucleophiles and always revealing the great challenge of directing the reaction to only one of the electrophilic carbons. The use of both potentially electrophilic centres for C-C bond forming reactions in a stereocontrolled fashion has been also a difficult task.[163]

3.1.1.1. Ketene silyl acetals and allylstannanes as nucleophiles.

The first example of a double nucleophilic addition to α,β-unsaturated aldimines induced by a Lewis acid was reported in 1999 by Shimizu and co-workers.[164] In the presence of $TiCl_4$, ketene silyl acetals underwent 1,4- and subsequently 1,2-addition to α,β-unsaturated aldimines to give the corresponding doubly alkylated products in good yields and diastereoselectivities (Scheme 3.2). Moreover, the reaction of a mixture of a ketene silyl acetal and an allyltributylstannane with a particular α,β-unsaturated aldimine gave regio- and chemoselectively 1,4- and 1,2-doubly alkylated product, in which the ketene silyl acetal underwent a 1,4-addition, while the allyltributylstannane did a 1,2-addition.



Scheme 3.2. Double nucleophilic addition to conjugated aldimines by Shimizu.

Using the same methodology, the authors were able to synthesise different pyrrole derivatives. This approach enables a six-step synthesis of imidazole glycerol phosphate dehydratase inhibitors (IGPDIs) of herbicidal activity.[165]

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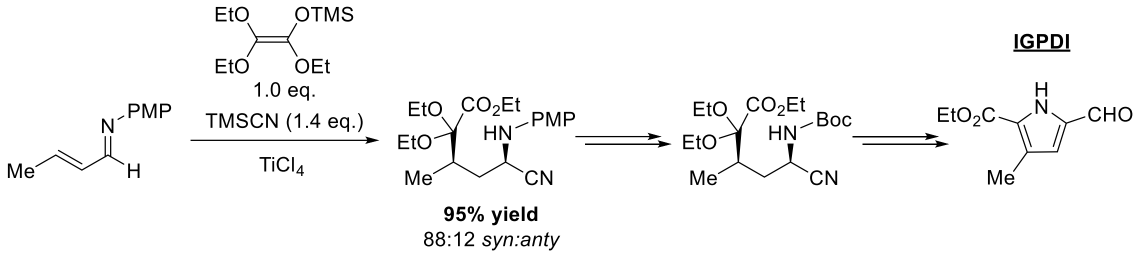
[163] (a) A. V. Kel'in; A. W. Sromek; V. Gevorgyan, *J. Am. Chem. Soc.,* **2001,** *123*, 2074-2075; (b) J. R. Porter; W. G. Wirschun; K. W. Kuntz; M. L. Snapper; A. H. Hoveyda, *J. Am. Chem. Soc.,* **2000,** *122*, 2657-2658; (c) D. Berger; W. Imhof, *Tetrahedron,* **2000,** *56*, 2015-2023.

[164] M. Shimizu; A. Morita; T. Kaga, *Tetrahedron Lett.,* **1999,** *40*, 8401-8405.

[165] M. Shimizu; A. Takahashi; S. Kawai, *Org. Lett.,* **2006,** *8*, 3585-3587.



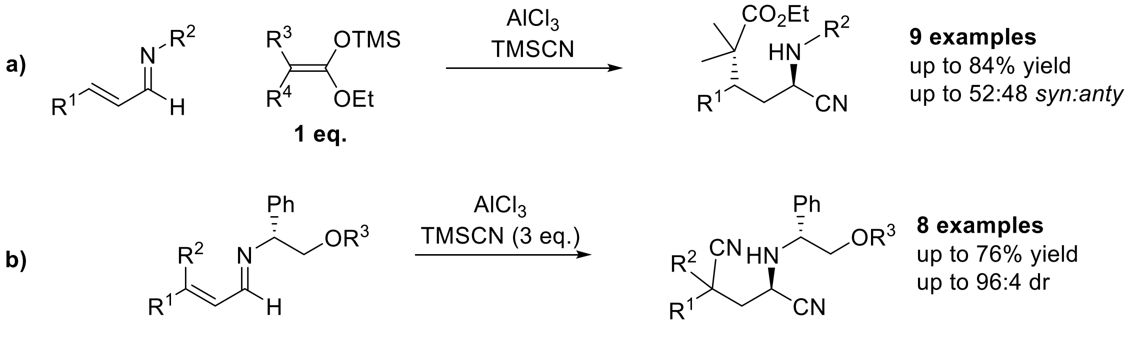
Scheme 3.3. Pyrrole synthesis by Shimizu.

The treatment of the ketene silyl acetal and trimethylsilyl cyanide with the corresponding conjugated imine in the presence of $AlCl_3$, gave the doubly alkylated product in a great 95% yield. After switching of the PMP group into a Boc analogue, a cyclization was carried out to achieve the desired pyrrole (Scheme 3.3).

3.1.1.2. TMSCN as nucleophile.

The Strecker reaction is one of the most efficient methods for the synthesis of α-amino acids.[166] A variety of asymmetric Strecker reactions has been reported to date. The double nucleophilic addition of ketene silyl acetals and trimethylsilyl cyanide to α,β-unsaturated aldimines also proceeds, providing with α-amino acid precursors in milder conditions.[167]

In the procedure described by Shimizu, a first 1,4-addition reaction of ketene silyl acetal to the generated metalloenamine would occur, followed by the 1,2-attack of TMSCN to afford the corresponding 1,4- and 1,2-adduct (Scheme 3.4, a).



Scheme 3.4. Double nucleophilic additions to conjugated aldimines by Shimizu.

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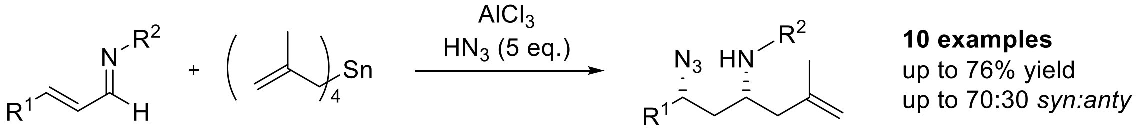
[166] (a) O. Iwao; I. Shin-ichi; N. Kimiyo; N. Yoichiro, *Chem. Lett.,* **1975,** *4*, 331-334; (b) A. Strecker, *Justus Lieb. Ann. Chem.,* **1850,** *75*, 27-45.
[167] S. Makoto; K. Makiko; H. Iwao, *Chem. Lett.,* **2003,** *32*, 606-607.

TMSCN is also an excellent nucleophile for both the 1,4- and 1,2-additions to α,β-unsaturated aldimines to give 2-aminopentanedinitriles.[168] Conjugated imines possessing chiral auxiliaries derived from (*R*)-phenylglycinol underwent diastereoselective addition in good yields (Scheme 3.4, b).

3.1.1.3. HN_3 as nucleophile.

Recent interests in 1,3-diamine derivatives for use as catalysts in the asymmetric synthesis and medicinal chemistry involving HIV protease inhibitors have prompted exploration of simple approaches to them. As proposed by professor Shimizu, in the presence of $AlCl_3$, a mixture of hydrogen azide and tetramethallyltin underwent a double nucleophilic addition with α,β-unsaturated aldimines to give 1,3-amino azides in good yields.[169] A posterior reduction to 1,3-diamines was readily carried out using $LiAlH_4$ as a reducing agent (Scheme 3.5).



Scheme 3.5. 1,3-Diamines synthesis by Shimizu.

Also fluorine-containing conjugated imines have been subjected to nucleophilic additions.

3.1.1.4. Fluorinated α,β-unsaturated imines.

Chiral allylic amines are ubiquitous in natural products and pharmaceuticals, as pointed out in *Chapter 2*. On the other hand, owing to the unique properties of fluorine, the incorporation of a fluoroalkyl group into organic compounds may significantly change their physical, chemical, and biological properties.[1] However, only a few methods are available for the asymmetric synthesis of a-fluoroalkyl allylic amines.[170]

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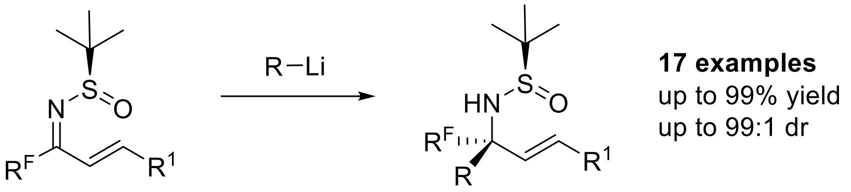
[168] S. Makoto; K. Makiko; H. Iwao, *Chem. Lett.,* **2005,** *34*, 1456-1457.

[169] S. Makoto; Y. Chiaki; O. Toshiki, *Chem. Lett.,* **2004,** *33*, 606-607.

[170] (a) Z.-J. Liu; J.-T. Liu, *Chem. Commun.,* **2008**, 5233-5235; (b) J. Liu; J. Hu, *Chem. Eur. J.,* **2010,** *16*, 11443-11454; (c) M. Kawatsura; S. Terasaki; M. Minakawa; T. Hirakawa; K. Ikeda; T. Itoh, *Org. Lett.,* **2014,** *16*, 2442-2445.

In 2015, Liu and co-workers disclosed a high regio- and diastereoselective 1,2-addition of organolithium nucleophiles to chiral fluoroalkyl conjugated sulfinyl ketimines.[171] The protocol easily proceeded with great yields and diastereoselectivities, providing a general and efficient method for the asymmetric synthesis of structurally diverse fluoroalkyl allylic amines.



Scheme 3.6. Nucleophilic addition to fluorine-containing conjugated imines by Liu.

To the best of our knowledge, only 1,2-additions have been reported over fluorine-containing conjugated sulfinyl imines to date, revealing the great challenge of enabling 1-4-addition reactions to this type of imines.[171,172]

For the nucleophilic side of our proposal, given the great results obtained in **Chapter** *2* and the applicability found by Chen's group for α,α-dicyanoalkenes over vinilogous 1,4-Michael reactions, we thought these entities should serve our aim of targeting a 1,4-addition to conjugated imines and further intramolecular reactivity.

3.1.2. α,α-Dicyanoalkenes.

The peculiar structural features of these compounds render them appealing for several reasons: i) they are easily obtained by Knoevenagel-type condensation of malononitrile to the corresponding carbonyl compounds; ii) they are generally more reactive as vinylogous donors than the corresponding carbonyl precursors, allowing the execution of chemical reactions which would otherwise not be viable for carbonyls; iii) the mild base catalysis needed for their activation allows for direct catalytic execution; and iv) after homologation with a suitable acceptor, the unsaturated malononitrile moiety

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[171] P. Liu; Z.-J. Liu; F. Wu, *Adv. Synth. Catal.,* **2015,** *357*, 818-822.

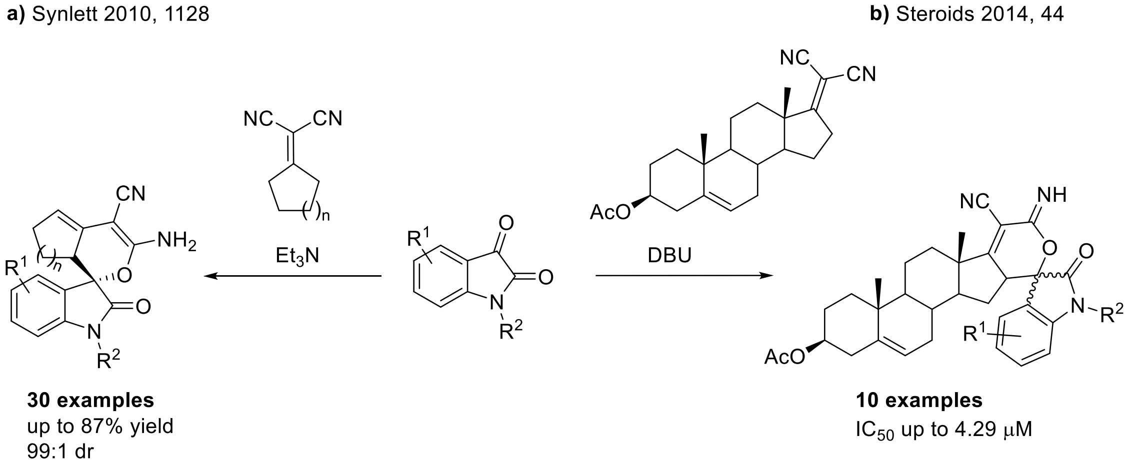
[172] (a) Y.-Y. Peng, P. Liu, Z.-J. Liu, J.-T. Liu, H.-F. Mao, Y.-L. Yao, *Tetrahedron* **2018**, *74*, 3074-3080; (b) P. Li, M. Jiang, J.-T. Liu, *Chin. J. Chem.* **2014**, *32*, 1003-1006; (d) X.-M. Yuang, J. Xu, Z.-J. Liu, X.-J. Yang, L.-M. Wang, Y. Zhang, X.-Y. Yang, X.-P. He, J.-T. Liu, *J. Fluorine Chem.*, **2012**, *144*, 102-107; (e) F. Zhang, F.-J. Liu, J.-T. Liu, *Org. Biomol. Chem.*, **2011**, *9*, 3625-3628; (f) Z.-J. Liu, J.-T. Liu, *Chem. Commun.,* **2008**, 5233-5235.

restored in the target may be prone to further broad manipulation including cyclization, tandem processes or even elimination.

As already explained in *Chapter 2* (Section 2.1.1-2.1.3), different methodologies to perform vinylogous Michael additions with α,α-dicyanealkenes have been described since the novel contributions of Deng and Jørgensen in 2005. Despite vinylogous malononitriles have been extensively used as vinylogous donors in Michael additions, their reactivity in aldol additions has been only scantily investigated.

3.1.2.1. α,α-Dicyanoalkenes in vinylogous aldol-type additions.

In 2010, Perumal and co-workers for the first time reported the one-pot synthesis of functionalized spirooxindoles via base-promoted vinylogous aldol addition of cycloalkylidene malononitriles with various isatin derivatives (Scheme 3.7, a).[173] The racemic products were isolated in good to high yields as single diastereoisomers.



Scheme 3.7. Vinylogous Aldol reactions of α,α-dicyanealkenes by Perumal (a) and Liu (b)

A conceptually similar chemistry was adopted by Shan, Liu and co-workers for the synthesis of novel steroidal pyran oxindole hybrids (Scheme 3.7, b),[174] with the aim of obtaining potent and selective cytotoxic agents that could merge, in a single molecular architecture, the structural features of the oxindole, steroid, and pyran moieties.

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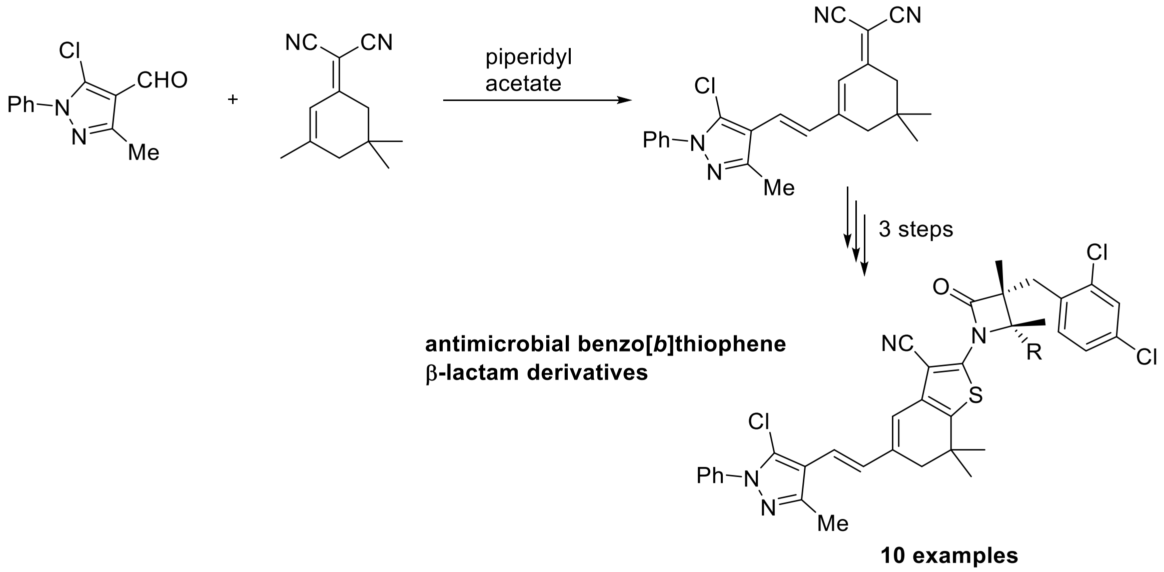
[173] (a) T. H. Babu; K. Karthik; P. T. Perumal, *Synlett,* **2010,** *2010*, 1128-1132; (b) T. Hari Babu; A. Abragam Joseph; D. Muralidharan; P. T. Perumal, *Tetrahedron Lett.,* **2010,** *51*, 994-996.

[174] B. Yu; P. P. Qi; X. J. Shi; L. H. Shan; D. Q. Yu; H. M. Liu, *Steroids,* **2014,** *88*, 44-52.

Thus, the DBU-promoted aldol addition of the corresponding malononitrile to various isatins produced steroidal oxindoles as single diastereoisomers. In contrast to the previous case, the aldol addition was followed by spiroannulation without any further isomerization reaction. Unfortunately, neither the yields, nor the configurations of the two newly created stereocenters, were reported.

Finally, the vinylogous aldol condensation of an isophorone derivative with pyrazoles (Scheme 3.8) was reported in 2012 as the starting reaction in a multi-step sequence directed toward the synthesis and antimicrobial evaluation of benzo[b]thiophene-β-lactam congeners.[175] After the main vinylogous aldol reaction, the dicyanoolefin moiety within the product served then to construct the fused thiophene heterocycle and the β-lactam moiety of the advanced intermediate showed in the scheme.



Scheme 3.8. Vinylogous Aldol reaction in benzothiophene β-lactam derivatives synthesis by Desai and Dodiya.

3.1.2.2. α,α-Dicyanoalkenes in vinylogous Mannich-type reactions.

The virtues of α,α-dicyanoolefins as smart pro-nucleophiles were also exploited in the domain of the Mannich reaction, even if only a few valuable examples have indeed been

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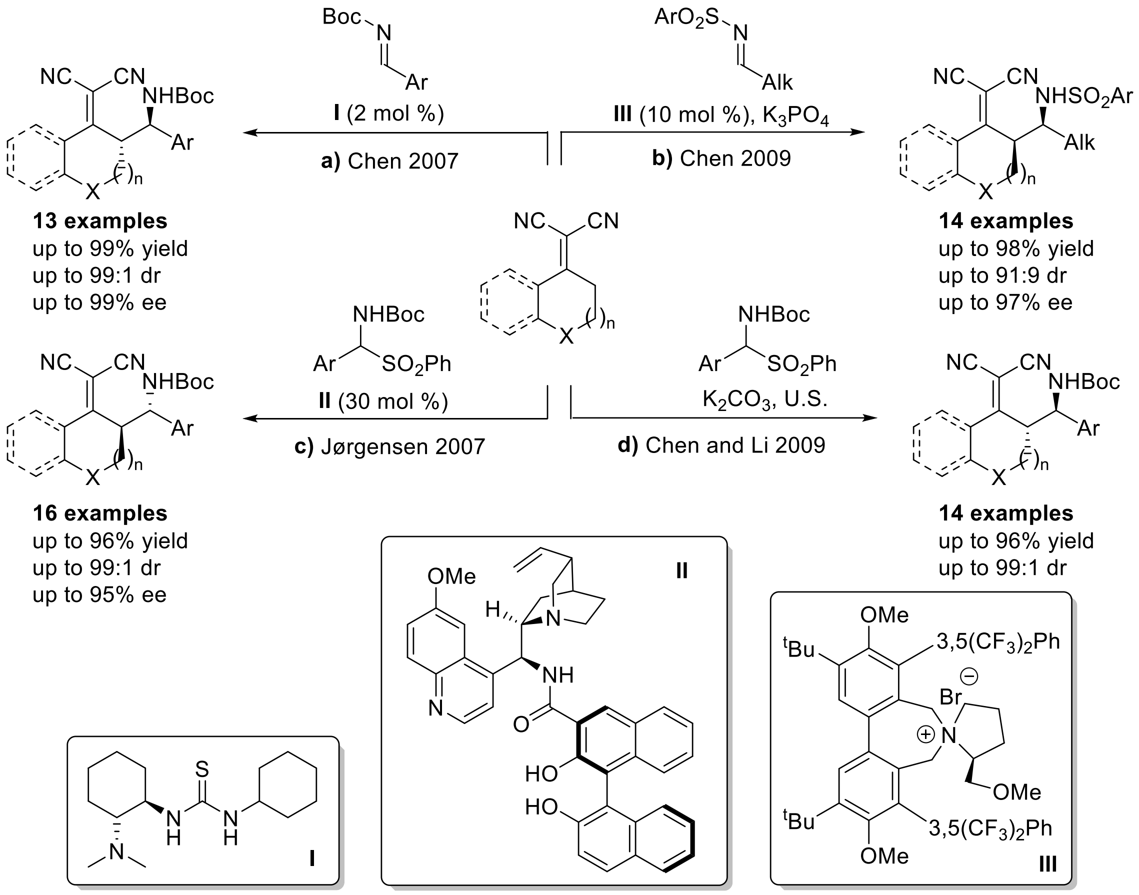
[175] A. R. Trivedi; J. M. Desai; B. H. Dholariya; D. K. Dodiya; V. H. Shah, *Med. Chem. Res.,* **2012,** *21*, 1471-1479.

reported so far. Interesting research in this field mainly focused on direct, asymmetric executions using chiral organocatalysts.

As explained in *Chapter 2* (Section 2.1.4), Chen and collaborators in 2007 reported the direct asymmetric vinylogous Mannich reaction of cycloalkylidene malononitriles to N-Boc aldimines via a tertiary amine-thiourea organocatalyst (Scheme 3.9, a).[59] A couple of years later, they succeeded in applying this chemistry to alkylimine substrates,[61] which reacted with dicyanoolefins under similar conditions employing a different organocatalyst (Scheme 3.9, b).

On the other hand, Jørgensen and Niess studied the asymmetric Mannich reaction of dicyanoalkylidenes with α-amido sulfones as suitable *N*-Boc-protected arylimine precursors (Scheme 3.9, c).[58] A rigid chiral pyrrolidium salt was used as the chiral phase-transfer organocatalyst in the presence of potassium phosphate, generally giving anti-configured aminated compounds in good yields and stereoselectivity.



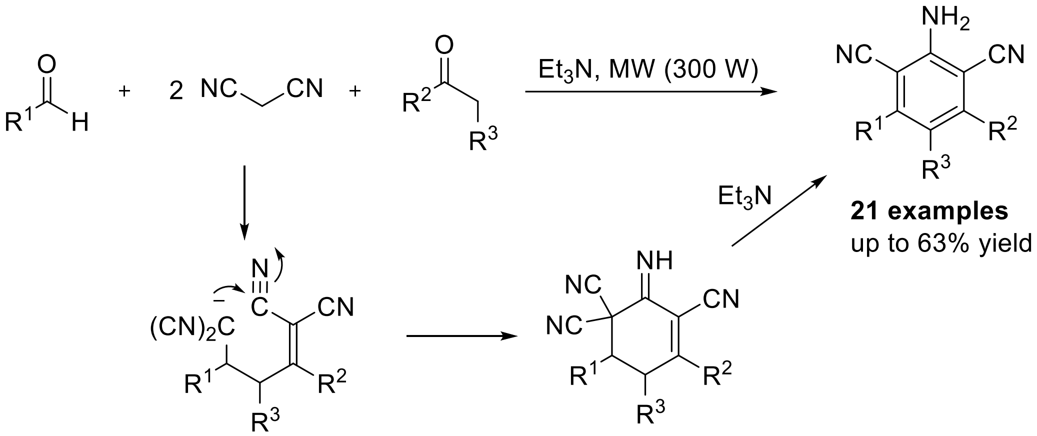
Sheme 3.9. Vinylogous Mannich reactions with α,α-dicyanoalkenes review.

A quite similar vinylogous Mannich reaction of cycloalkylidene malononitriles with α-amido sulfones was conducted by Chen and Li using potassium carbonate in solvent-free conditions under ultrasound irradiation (Scheme 3.9, d).[176] The corresponding products were recovered in high yields and complete anti-selectivity in racemic form.

On a further reactivity profile, α,α-dicyanoalkenes have been found to be great substrates to undergo, after the corresponding addition reaction (depicted above), different reactions through the malononitrile moiety, such as eliminations, tandem processes or even cyclisation and cycloaromatisation processess.[177]

3.1.2.3. α,α-Dicyanoalkenes in cycloaromatisation processes.

In 2005, Wang and co-workers developed a facile parallel synthesis of polysubstituted 2,6-dicyano-anilines via the microwave-promoted three-component reaction of aldehydes, ketones, and propanedinitrile in solution and also on polymer supported fashion.[178] By this one pot procedure, the authors were able to produce a large number of novel fluorescent 2,6-dicyano-anilines in moderate to good yields (Scheme 3.10).



Scheme 3.10. Base-mediated tandem vinylogous addition-cycloaromatisation by Wang.

A couple years later, the authors published an efficient method for the synthesis of the one-donor poly-acceptors systems containing 2,6-dicyano-amine moiety by condensation of 1-arylethylidenemalono-dinitriles with arylidenemalonodinitriles in

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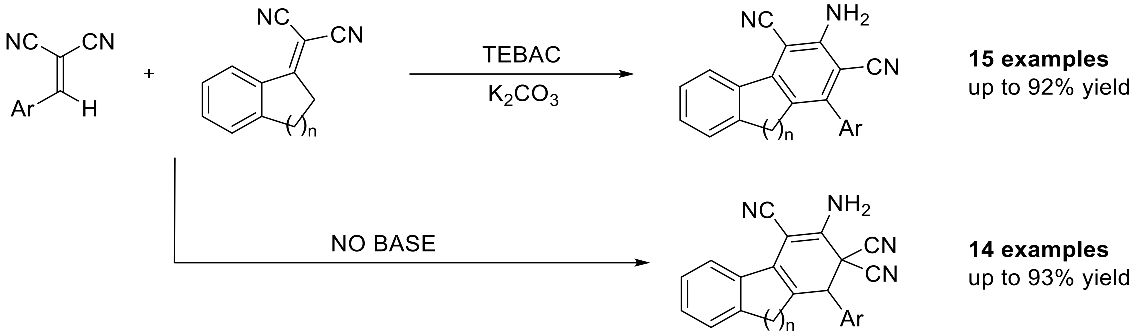
[176] W.-Y. Chen; X.-S. Li, *Catal. Commun.,* **2009,** *10*, 549-551.

[177] (a) H.-L. Cui; Y.-C. Chen, *Chem. Commun.,* **2009**, 4479-4486; (b) L. Battistini; C. Curti; G. Rassu; A. Sartori; F. Zanardi, *Synthesis,* **2017,** *49*, 2297-2336.

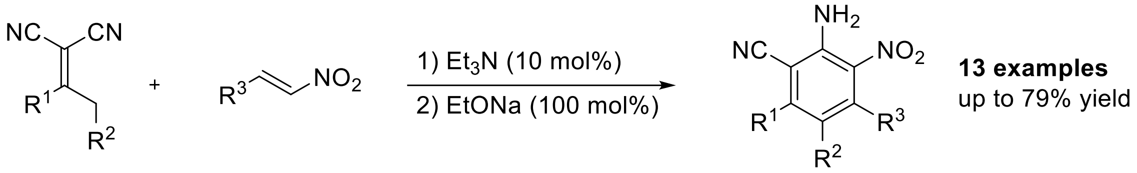
[178] S.-L. Cui; X.-F. Lin; Y.-G. Wang, *J. Org. Chem.,* **2005,** *70*, 2866-2869.

aqueous media catalysed by TEBAC in the presence of K_2CO_3.[127] In this case, for the sake of a better understanding of the mechanism occurring in these type of transformations, the authors were able to isolate, in the absence of the base, the addition-cyclisation product preceding the final anilines through a bas-mediated aromatisation process.



Scheme 3.11. Procedure expansion by Wang and mechanistic evidence of a last base-mediated aromatisation process.

Contemporarily, Deng and co-workers applied their organocatalised Michael addition to nitroalkenes (see Chapter 2, section 2.1.1) and further derivatise the obtained products. In this case, the utilisation of both cyclic and acyclic dicyanoolefins and nitroalkenes in the presence of a base led to the obtaining of the corresponding *ortho*-nitroanilines in good yields.[179]



Scheme 3.12. Base-mediated synthesis of poly-substituted *ortho*-nitroanilines by Deng.

Yan and co-workers also developed in 2008 the one-step synthesis of polysubstituted aniline derivatives by multi-component cyclization of α-bromoacetate, malononitrile and aromatic aldehydes.[180] The process required the presence of pyridine to achieve the target aromatic products. Deeper mechanistic investigations conducted by the authors showed that the pyridine took a role play in the development of the reaction, not only as a proton abstractor but also as part of the actual reaction mechanism.

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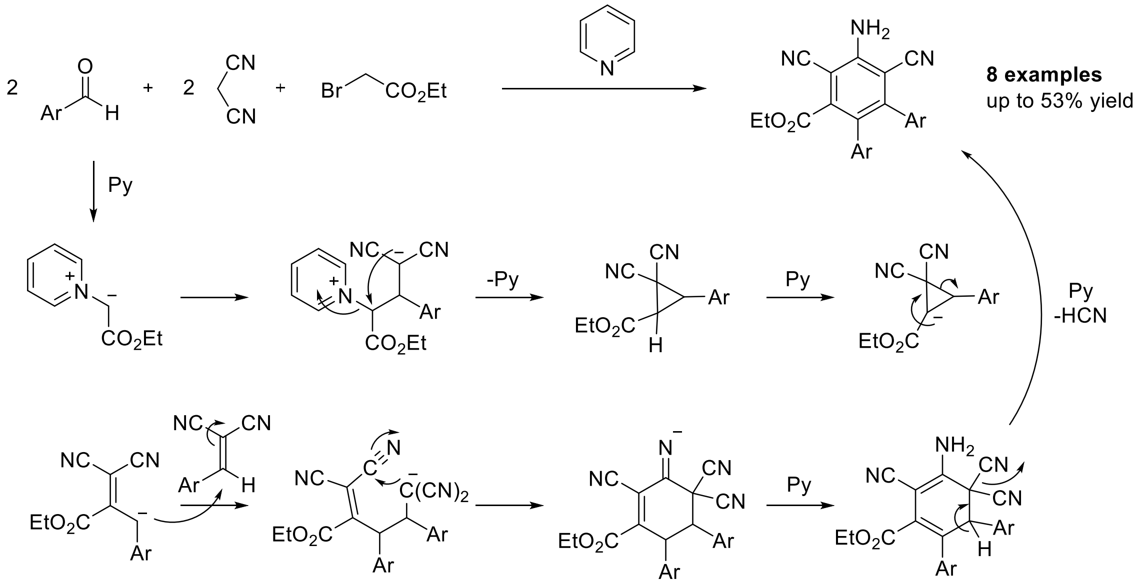
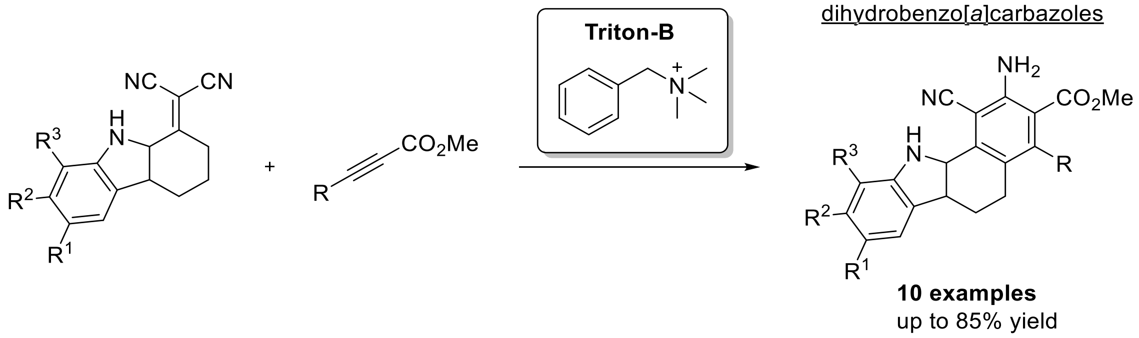
[179] D. Xue; J. Li; Z.-T. Zhang; J.-G. Deng, *J. Org. Chem.,* **2007,** *72*, 5443-5445.

[180] C. G. Yan; X. K. Song; Q. F. Wang; J. Sun; U. Siemeling; C. Bruhn, *Chem. Commun.,* **2008**, 1440-1442.



Scheme 3.13. Base-mediated multicomponent synthesis of anilines and mechanism by Yan.

In order to demonstrate the importance and applicability of this powerful tool which is the cycloaromatisation process of α,α-dicyanoalkene derivatives, Yamuna et al. applied this type of reactivity to tetrahydrocarbazole dinitrile derivatives, reacting them with acetylenic esters in the presence of a base, which did undergo a tandem addition-cycloaromatisation process to give highly biologically active benzo-fused dihydrocarbazoles.[181] After screening several base sources, it was found that a benzo trimethyl ammonium hydroxide (Triton-B) was able to promote this process achieving the target molecules in good to great yields.



Scheme 3.14. Dihydrobenzo[*a*]carbazole derivatives synthesis by Yamuna.

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[181] E. Yamuna; M. Zeller; K. J. R. Prasad, *Tetrahedron Lett.*, **2011,** *52*, 1649-1652.

At this point, it is worth to mention that although different acceptors have been used for this tandem addition-cycloaromatisation processes over the years, the employment of conjugated imines on this matter, which could eventually lead to heteroaromatic products (see *Objectives*, section 2), remains unstudied to the best of our knowledge.

3.1.3. Trifluomethyl arenes and heteroarenes.

Although fluorine is the most abundant halogen in the earth's crust, it is contained in very few molecules with biological origins.[182] However, it is very popular during lead optimization in drug discovery,[183] and approximately 20-25% of all drugs contain at least one fluorine atom.[62,184] In fact, five of the new drugs that were FDA (Food and Drug Administration) approved in 2012 contain a trifluoromethyl group. Enzalutamide (Figure 3.1) for the treatment of metastatic castration-resistant prostate cancer, teriflunomide (Figure 3.1) for the treatment of multiple sclerosis, lomitapide (Figure 3.1) for the treatment of homozygous familial hypercholesterolemia, ponatinib (Figure 3.1) for the treatment of chronic myeloid leukemia, and Philadelphia chromosome positive acute lymphoblastic leukemia and finally regorafenib (Figure 3.1) for the treatment of previously treated patients with metastatic colorectal cancer.

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[182] C. D. Murphy; C. Schaffrath; D. O'Hagan, *Chemosphere,* **2003,** *52*, 455-461.

[183] (a) K. Müller; H.-J. Böhm, *Chem. & Biol.,* **2009,** *16*, 1130-1131; (b) A. Vulpetti; C. Dalvit, *Drug Dicov. Today,* **2012,** *17*, 890-897.

[184] A. Mullard, *Nat. Rev. Drug Discov.,* **2013,** *12*, 87-90.

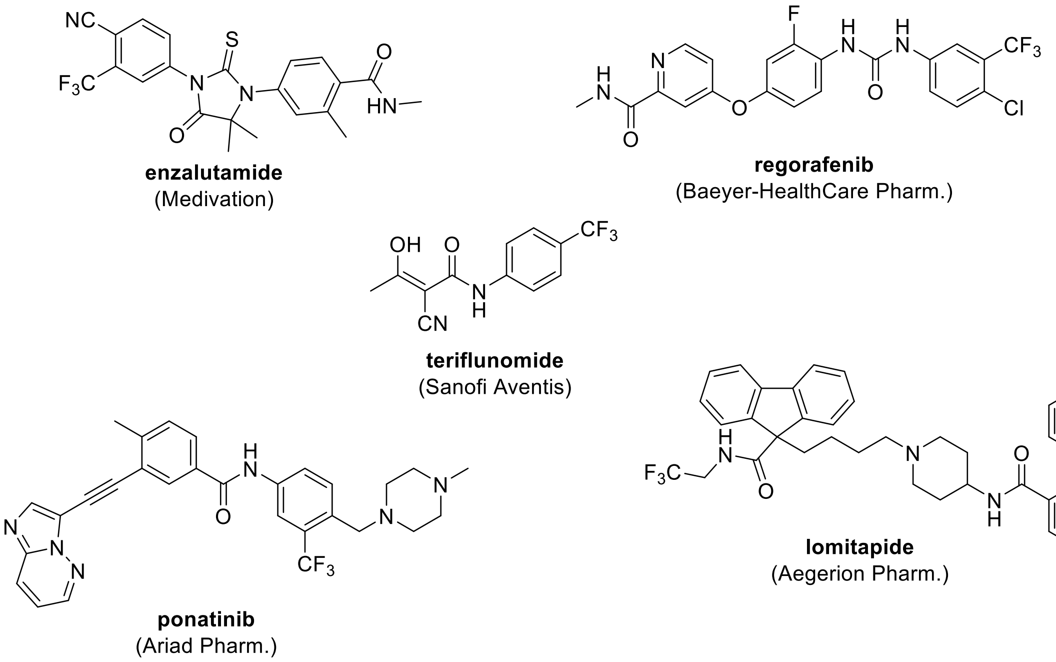

Figure 3.1. Drugs containing a trifluoromethyl group approved by FDA only in 2012.

Taking into account that many biologically active compounds contain the trifluoromethyl group, the introduction of this moiety is a hot topic, and the development of highly efficient methodologies for trifluoromethylation is of significant importance for many fields of science and technology.

Historically the trifluoromethyl group has been difficult to install, in part because the reactive intermediates that are generated during trifluoromethylation reactions are unstable under the conditions necessary for the reactions to proceed.[185]

More specifically, arenes and heteroarenes bearing trifluoromethyl groups have become important structural motifs found in compounds used in medicinal, agricultural, and material sciences. A large number of existing pharmaceutical candidates contain trifluoromethyl group introduced into an aromatic cycle because these moieties can favourably affect the physical and biological properties of the compound.[186]

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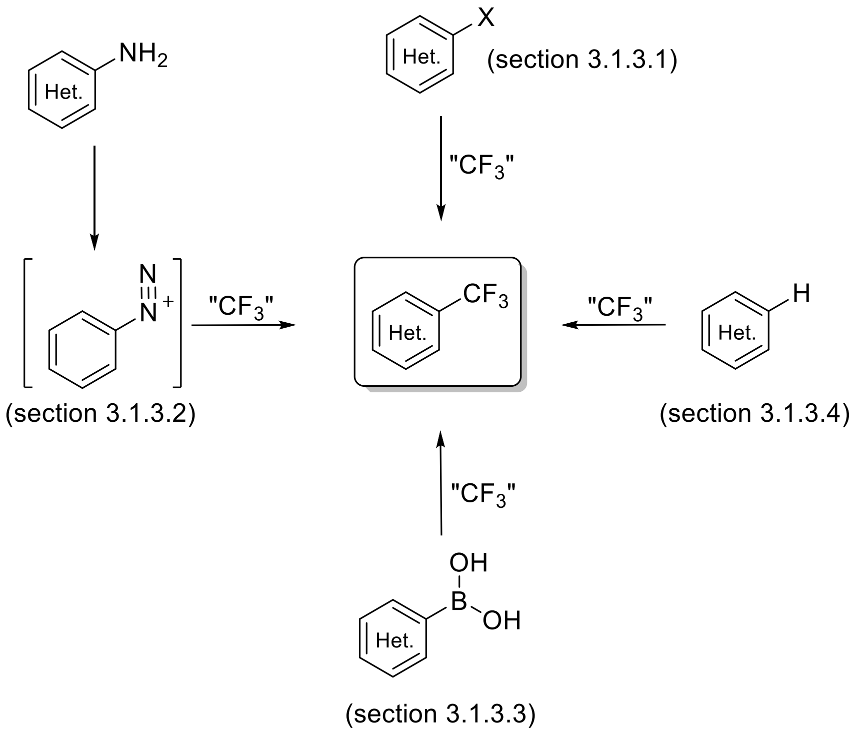
[185] A. Studer, *Angew. Chem. Int. Ed.,* **2012,** *51*, 8950-8958.

[186] (a) K. Uneyama, *Organofluorine Chemistry*. Blackwell: Oxford, U.K., **2006**; (b) S. Daniels; S. F. M. Tohid; W. Velanguparackel; A. D. Westwell, *Expert Opinion on Drug Discovery,* **2010,** *5*, 291-304.



Scheme 3.15. Trifluoromethylation of arenes and heteroarenes.

Since the late 19th century, when Swarts developed a good method for the preparation of trifluoromethyl aromatic compounds from benzotrichloride with antimony trifluoride as fluorination reagent (Scheme 3.16, left),[187] different strategies have been developed to incorporate the trifluoromethyl moiety in aromatic rings, as indicated in Scheme 3.15.

3.1.3.1. Trifluoromethylation of haloaryl and heteroaryl derivatives.

Since the original pioneering works of Kobayashi and Kumadaki[188] and those of McLoughlin and Thrower,[189] both in 1969, preparation of aromatic trifluoromethylated derivatives has been widely achieved by cross-coupling of aryl halides with trifluoromethyl copper complexes (Scheme 3.16, right). Over the years, this methodology has demonstrated to be a powerful and versatile tool, utilising a diversity of copper and CF_3 sources.

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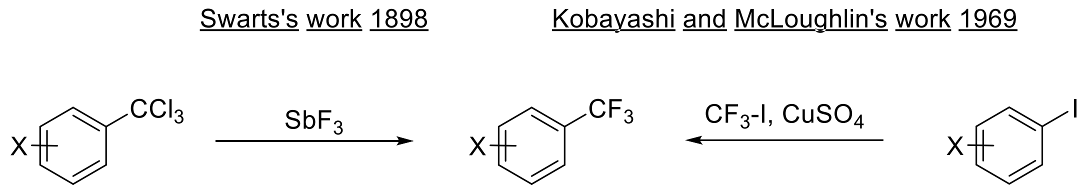
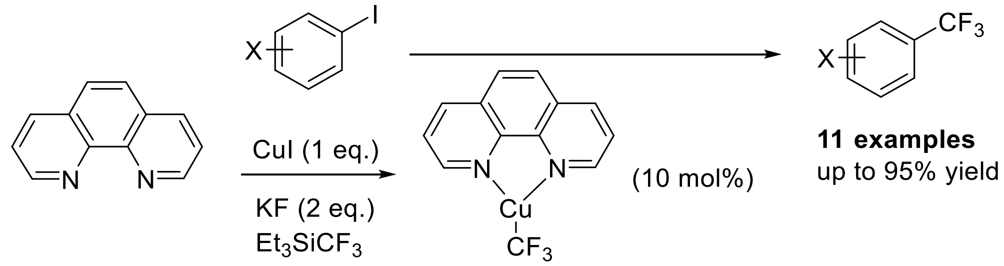
[187] F. Swarts, *Bull. Acad. R. Belg.* , **1898,** *35*, 375.
[188] Y. Kobayashi; I. Kumadaki, *Tetrahedron Lett.,* **1969,** *10*, 4095-4096.
[189] V. C. R. McLoughlin; J. Thrower, *Tetrahedron,* **1969,** *25*, 5921-5940.



Scheme 3.16. Novel work in trifluoromethylation processes by Swarts (left) and Kobayashi and McLoughlin(right).

Starting from simple species such as $CuSO_4$ and CF_3I or HF, different copper and fluorine sources have been successfully used as coupling partners. Perichon performed an electrochemical cross-coupling of bromotrifluoromethane with aromatic halides obtaining reasonable yields,[190] while Yagupolskii et al. prepared trifluoromethyl copper species conveniently via the combination of the solid complex [$Zn(CF_3)Br\cdot 2DMF$] with CuBr.[191] Similarly, reagents such as Bu_3SnCF_3 were effective in trifluoromethylation reactions of aryl iodides also via the intermediacy of [$CuCF_3$] species.[192]

The first copper-catalyzed trifluoromethylation process of aryl iodides was disclosed by Amii et al. in 2009.[193] The authors demonstrated the effectiveness of Cu-mediated reactions could be improved by the addition of chelating ligands as phenantroline, and using KF as fluorine source, trifluoromethyl aryl rings were obtained in a catalytic fashion (Scheme 3.17).



Scheme3.17. Catalytic trifluoromethylation by Amii.

Another efficient copper-catalyzed trifluoromethylation of aromatic iodides was achieved few years later by Novák using $TMSCF_3$ as a readily available CF_3 source and

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[190] J. M. S. Paratian, S.; Périchon, J., *J. Chem. Soc., Perkin Trans. I,* **1992,** *1*, 53-56.

[191] M. M. Kremlev; A. I. Mushta; W. Tyrra; Y. L. Yagupolskii; D. Naumann; M. Schäfer, *Dalton Trans.,* **2015,** *44*, 19693-19699.

[192] I. A. Sanhueza; M. C. Nielsen; M. Ottiger; F. Schoenebeck, *Helv. Chim. Acta,* **2012,** *95*, 2231-2236.

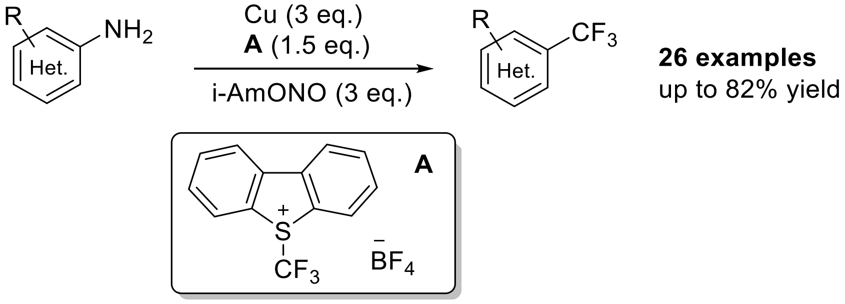
[193] M. Oishi; H. Kondo; H. Amii, *Chem. Commun.,* **2009**, 1909-1911.

trialkyl borates as Lewis acid for the temporary trapping of the CF_3 anion generated by KF from the trifluoromethylating agent.[194]

Most of the Cu-mediated coupling procedures are also capable of performing trifluoromethylation of heteroarenes.

3.1.3.2. Trifluoromethylation of *N*-functionalised aryl and heteroaryl derivatives.

The aromatic amino group could be also converted into a trifluoromethyl group by means of diazonium salts based on Sandmeyer reactions[195] of these substrates. In 2013, Fu et al. described the first example of the trifluoromethylation reaction of aromatic and heteroaromatic amines by a copper-promoted Sandmeyer strategy (Scheme 3.17).[196]



Scheme 3.18. Trifluoromethylation of arenes and heteroarenes by Fu.

The authors developed a copper-promoted trifluoromethylation process that operates under mild conditions, using Umemoto's reagent as trifluoromethyl source and isoamyl nitrite, producing the trifluoromethylated aromatic products in good to great yields.

3.1.3.3. Trifluoromethylation of aryl and heteroaryl boronic derivatives.

Also oxidative trifluoromethylation protocols have been developed for aryl boronic acids or borates. Among other copper catalysed procedures, a mild and general method for the cross-coupling of aryl boronic acids with CF_3I via visible-light photocatalysis (to generate CF_3 radical) and Cu catalysis (to generate reactive Cu-aryl species) was

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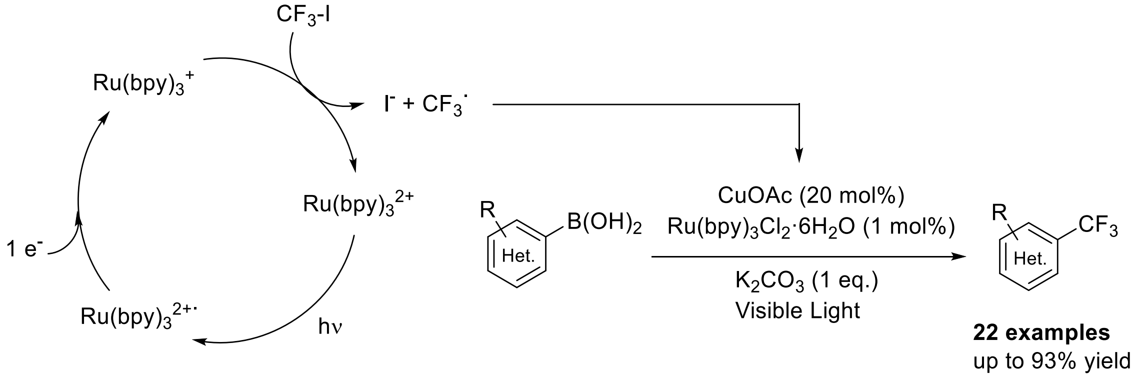
[194] Z. Gonda; S. Kovács; C. Wéber; T. Gáti; A. Mészáros; A. Kotschy; Z. Novák, *Org. Lett.,* **2014,** *16*, 4268-4271.

[195] C. Galli, *Chem. Rev.,* **1988,** *88*, 765-792.

[196] J.-J. Dai; C. Fang; B. Xiao; J. Yi; J. Xu; Z.-J. Liu; X. Lu; L. Liu; Y. Fu, *J. Am. Chem. Soc.,* **2013,** *135*, 8436-8439.

reported by Sanford and co-workers for the preparation of trifluoromethylated aryl and heteroaryl compounds (Scheme 3.18).[197]



Scheme 3.19. Photocatalysed trifluoromethylation of arenes and heteroarenes by Sandford.

3.1.3.4. Direct trifluoromethylation of aryl and heteroaryl derivatives.

Despite the significant progress made in the trifluoromethylation of functionalized aromatic derivatives, the most effective route for the preparation of CF_3-substituted arenes would be the direct trifluoromethylation of C-H bonds in aromatic substrates. Nevertheless, mixtures of regioisomers of trifluoromethylated derivatives are obtained when departing from substituted aromatic substrates. A number of pioneering methods for the direct radical trifluoromethylation of arene C-H moieties included CF_3I,[198] $(CF_3)_2Te$,[199] and $CF_3Br/Na_2S_2O_4$.[200]

Among all the methodologies described in the last decades, we could highlight the one proposed by Akiyama et al. in 1988,[201] who reported the results of a one-step photochemical trifluoromethylation of some aromatic compounds by irradiation with a high-pressure mercury lamp under bubbling CF_3Br to obtain the desired products in good yields (Scheme 3.19). The mechanistic study of the reaction indicated that it may

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[197] Y. Ye; M. S. Sanford, *J. Am. Chem. Soc.,* **2012,** *134*, 9034-9037.

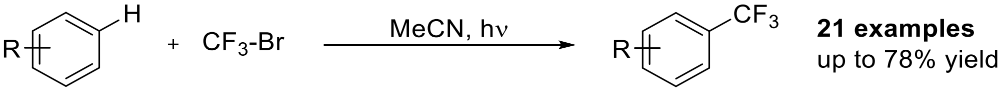
[198] A. B. Cowell; C. Tamborski, *J. Fluorine Chem.,* **1981,** *17*, 345-356.

[199] D. Naumann; J. Kischkewitz, *J. Fluorine Chem.,* **1990,** *47*, 283-299.

[200] M. Tordeux; B. Langlois; C. Wakselman, *J. Chem. Soc., Perkin Trans. 1,* **1990**, 2293-2299.

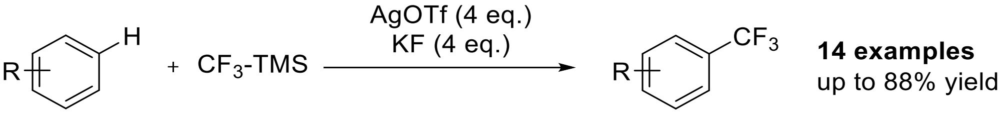
[201] T. Akiyama; K. Kato; M. Kajitani; Y. Sakaguchi; J. Nakamura; H. Hayashi; A. Sugimori, *Bull. Chem. Soc. Jap.,* **1988,** *61*, 3531-3537.

proceed via the electron transfer from the excited singlet state of substrate to CF_3Br and then the formation of a CF_3 radical.



Scheme 3.20. Photochemical trifluoromethylation of arenes by Akiyama.

More recently, Sanford and co-workers proposed the trifluoromethylation of unfunctionalized arenes via silver complexes obtained by the combination of AgOTf and KF, obtaining great results for a variety of aromatic compounds.[202] Even the formation of o-trifluoromethylmethoxy derivatives as major products were obtained when the corresponding substrates were treated under the optimised conditions (Scheme 3.21).



Scheme 3.21. Silver-mediated trifluoromethylation of arenes by Sanford.

To summarise, we will say that the great amount and variety of procedures described over the years to introduce a trifluoromethyl moiety into aryl and heteroaryl substrates, shows the great importance of this type of methodologies. Hence, the utilisation of trifluoromethylated imines in any reaction capable of leading to such trifluoromethylated aromatic products in an easy manner will take high interest in this chapter.

All these approaches take advantage of pre-existing aromatic precursors, in general with the involvement of a metal catalyst. However, strategies based on the novo construction of trifluoroarenes by using readily available fluorinated building blocks are sometimes a potent alternative approach to direct methods, especially in polyfunctional fluoroorganic molecules. In this context, the Diels-Alder reaction of fluorinated dienes/dienophiles followed by subsequent aromatization of the cycloadduct formed is a potent method to access trifluoroarenes (Scheme 3.22).[203]

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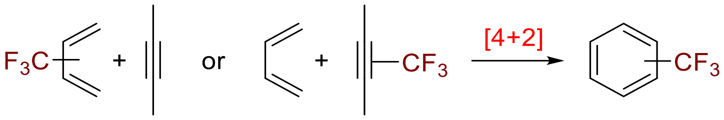
[202] Y. Ye; S. H. Lee; M. S. Sanford, *Org. Lett.,* **2011,** *13*, 5464-5467.

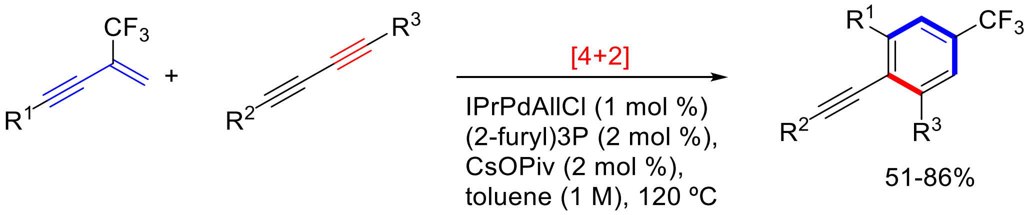
[203] For a recent review, see: I. S. Kondratov; N. A. Tolmachova; G. Haufe, *Eur. J. Org. Chem.,* **2018,** 3618-3647.



Scheme 3.22. Diels Alder stratety to acces trifluroarenes.

However, this versatile method is limited by substrate scope, harsh conditions, and regio- and chemoselectivity problems.

Two additional strategies that generate the aromatic ring through a benzannulation reaction have been described. The first one involved the reaction of conjugated fluorinated enynes and diynes under palladium catalysis, avoiding the final aromatization step necessary in the Diels Alder approach (Scheme 3.23).[204]



Scheme 3.23. Trifluoroarenes from fluorinated enynes.

The second one employs trisubstituted-CF$_3$ alkenes as starting materials. Either in a Michael-initiated [4+2] aromatization with 2-benzylidenemalononitriles or conjugated aldehydes, or in a Rauhut–Currier-initiated [3+3] benzannulation with 2-nitroallylic acetates or conjugated aldehydes, highly functionalized trifluoromethyl arenes can be accessed (Scheme 3.24).[205] The main drawback of both protocols is the limitation of the scope in the starting materials.

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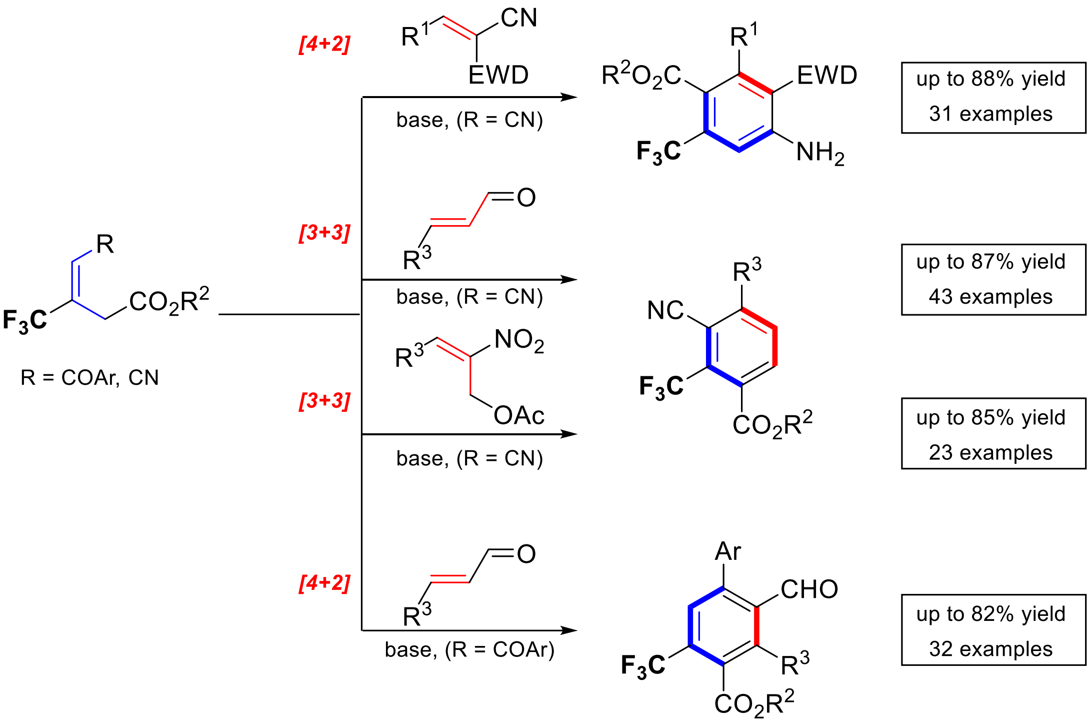
[204] O. V. Zatolochnaya; V. Gevorgyan, *Org. Lett.*, **2013,** *15*, 2562-2565.

[205] (a) F. Peng; Q. Zhao; W. Huang; S.-J. Liu; Y.-J. Zhong; Q. Mao; N. Zhang; G. He; B. Han, *Green Chem.*, **2019,** *21*, 6179-6186; (b) Y.-L. Ji; X.-H. He; G. Li; Y.-Y. Ai; H.-P. Li; C. Peng; B. Han, *Org. Chem. Front.*, **2020,** *7*, 563-570.

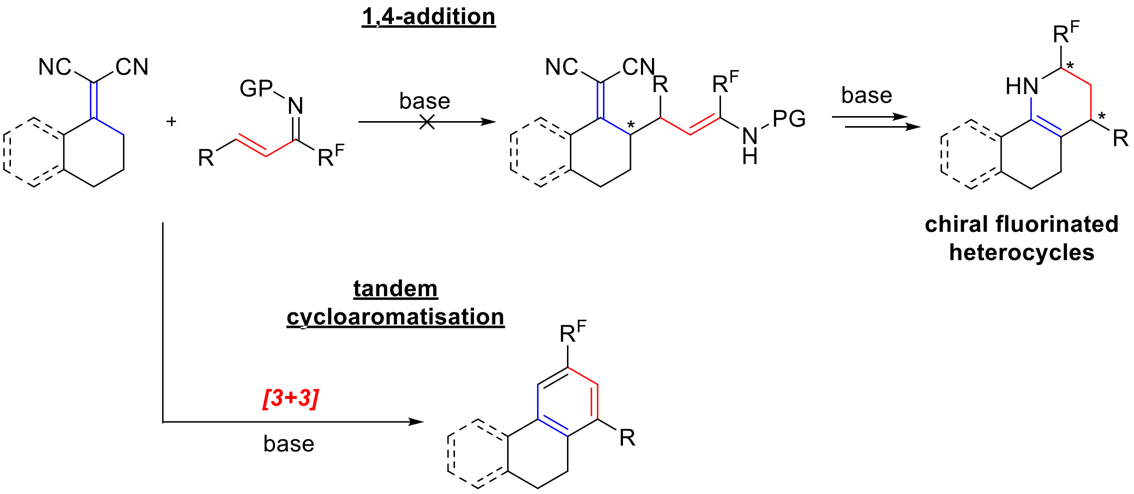


Scheme 3.24. Trifluoroarenes from trisubstituted CF_3-alkenes.

3.2. Objectives.

As explained in the Introduction section, the aim of this chapter will focus on the development and study of the vinylogous Mannich reaction of α,α-dicyanoalkenes over fluorine-containing conjugated imines (Scheme 3.25), focusing on the regioselectivity of the reaction and looking for the 1,4-addition over the so well-studied 1,2-addition. It is worth to notice that 1,4-additions on fluorinated imines remains unstudied in the literature to the best of our knowledge.

Assuming a fruitful 1,4-addition, the aza-enolate thus formed would undergo a subsequent 1,4-addition over the dicyanoalkene moiety, acting now as an electrophile. This tandem protocol would render the corresponding fluorinated nitrogen heterocycles with the generation of two stereocenters.



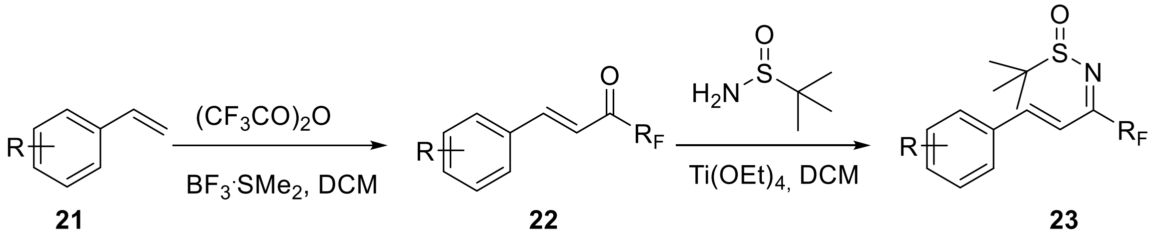
Scheme 3.25. *Chapter 3* objectives.

However, during this study a serendipitious reaction ocurred; instead of the expected heterocycle formation, a [3+3] cycloaromatization process took place, rendering in a tandem fashion polycyclic trifluoroarenes. Given the great biological and medicinal importance that such structures possess, we decide to evaluate the scope and limitations of this unusual transformation.

3.3. Results and discussion.

Due to the lack in the literature of reactions involving conjugated fluoroalkyl imines and dicyanoalkenes, the next step in our vinilogous Mannich reaction study and understanding was to explore the reactivity of these addition partners. It is worth to mention that, to the best of our knowledge, all examples found in the literature for fluoroalkyl conjugated sulfinyl imines showed a 1,2-reactivity, delivering the nucleophilic attack to de iminic carbon.[171,172]

We decided to initiate our study using those sulfinyl imines as starting materials. For that aim, fluoroalkyl conjugated sulfinyl imines **23** were synthesised according to the literature procedure,[170] reacting the corresponding styrene derivative **21** with trifluoroacetic anhydride to render fluorinated ketones **22**, that were treated in turn with Ellman's reagent to form the desired conjugated fluoroalkyl imines **23** (Scheme 3.26) (see experimental section for further details).

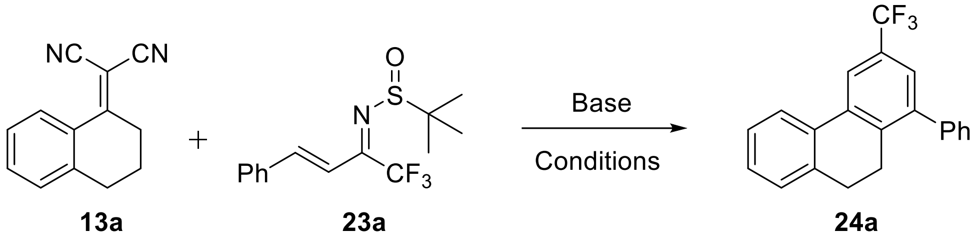


Scheme 3.26. Synthesis of starting imines **23**.

3.3.1. Optimisation.

With starting conjugated imines in hand, we evaluated the feasibility of the proposed 1,4-addition using dicyanoalkene **13a** and imine **23a** as model substrates. The optimization study is depicted in Table 3.1. Initially several bases were used in order to promote the addition. We tried conditions described in *Chapter 2* for the vinilogous Mannich protocol, reacting dicyanoalkene **13a** with imine **23a** in the presence of potassium *tert*-butoxide at room temperature in DCM, but those conditions led to a complex mixture of non-separable products (Table 3.1, entry 1).

Table 3.1. Process optimisation.



Entry	Base	Solvent	Yield of 24a[1]
Base screening			
1	^{t}BuOK	DCM	decomp.
2	NaH	THF	45
3	^{t}Bu-P2	DCM	>95
4	KHMDS	DCM	0
5	Na_2CO_3	DCM	0
6	DBU	DCM	>95
7	Et_3N	DCM	0
8	DABCO	DCM	0
9	TBAF	DCM	0
Solvent screening			
10	DBU	DCM	>95
11	DBU	DCE	>95
12	DBU	THF	>95
13	DBU	Acetone	>95
14	DBU	Tol	>95
15	DBU	MeCN	>95

[1] Final yields of product 24a were determined by ^{1}H-NMR.

Sodium hydride was also tested in THF at room temperature. Under those conditions, a new compound was isolated from the reaction mixture, that do not correspond to the 1,4-addition product. Surprisingly, the bicyclic structure from the dicyanoalkene and the fluorine moiety were contained in the product, but NMR experiments showed that final product arose from different reactivity than a simple α or γ-addition of dicyanoalkene **13a** to the conjugated imine **23a**. NMR spectra revealed those elements described above and a high level of aromaticity. Further spectroscopic experiments and a final X-Ray diffraction analysis revealed the product to be **24a**, a dihydrophenanthrene bearing a trifluoromethyl moiety and an extra phenyl ring in *metha* position to the fluorinated group. **24a** was obtained in 45% yield using NaH as base (Table 3.1, entry 2).

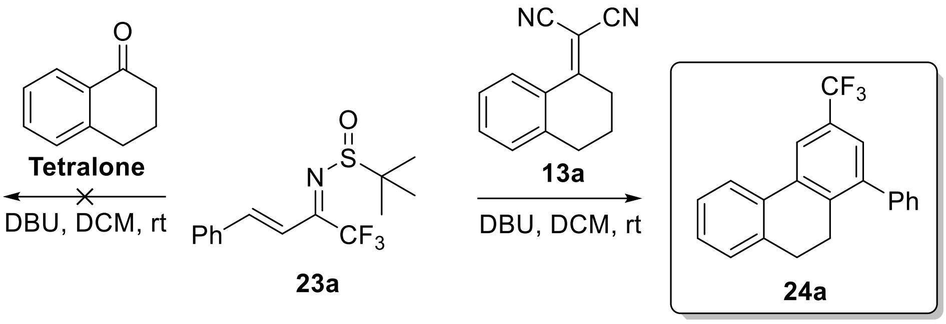
The use of other strong bases was explored next; using phosphacene-derived base ^{t}Bu-P_2 led to complete conversion of the starting material to product **24a** (Table 3.1, entry 3). With KHMDS our starting imine **23a** remained unreactive (Table 3.1, entry 4). Inorganic bases produced no conversion of the starting material (Table 3.1, entry 5). Weaker bases like Et_3N or DABCO showed no reactivity toward the desired dihydrophenanthrene **24a** (Table 3.1, entries 6,7). To our delight, the use of the organic bicyclic base DBU rendered **24a** with complete conversion and 88% isolated yield (Table 3.1, entry 8). Employing TBAF as a base, no conversion of the starting materials was observed (Table 3.1, entry 9).

Different solvents were also tested subsequently and our protocol revealed to work efficiently in chlorinated solvents like DCM or DCE (Table 3.1, entries 10,11) and both in polar and non-polar solvents (Table 3.1, entries 12-15).

At this point, the optimal reaction conditions were established when dicyanoalkene **13a** reacted with conjugated fluoroalkyl imine **23a** in DCM at room temperature in the presence of DBU. It is worth to notice that all reactions were carried out in an air-open atmosphere.

The reaction outcome of this tandem process revealed the very first dual α- and γ-attack from cyanoalkenes to conjugated sulfinylimines as explained bellow (see *Mechanistic proposal* for more details), followed by a cycloaromatisation to achieve the final fluorinated dihydrophenanthrene unit.

Considering that dicyanoalkenes could be considered as masked ketones, and in order to provide a solid proof-of-concept for this new tandem protocol, we reacted conjugated imine **23a** with tetralone in the presence of DBU (Scheme 3.27). The experiment showed that tetralone remained completely unreactive, while dicyanoalkene **13a** led to dihydrophenanthrene **24a** under identical conditions.



Scheme 3.27. Tandem reaction with dicyanoalkene **13a** *vs* non-reacting ketone.

3.3.2. Scope and limitations.

Once the reaction conditions were optimised, we boarded the study of the scope and limitations of our methodology.

For that aim, we synthesised a small library of conjugated fluoroalkyl imines according to already described procedures.[169,170,206] All the imines were prepared by condensation of the corresponding ketone and *tert*-butylsulfynilamine, except imines **12g** and **12i**, prepared according procedures described in *Chapter 2* (see *Experimental Section*). The conjugated ketone precursors were synthesised by the addition of the corresponding styrene to different anhydrides unless otherwise specified (for further details see *Experimental section*).[207] Dicyanoalkenes were prepared as specified in *Chapter 2*.

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[206] (a) L. G. Borrego; R. Recio; M. Alcarranza; N. Khiar; I. Fernández, *Adv. Synth. Catal.,* **2018,** *360*, 1273-1279; (b) D. Enders; K. Gottfried; G. Raabe, *Adv. Synth. Catal.,* **2010,** *352*, 3147-3152.

[207] V. G. Nenajdenko, I. D. Gridnev, E. S. Balenkova, *Tetrahedron* **1994**, *50*, 11023-11038.

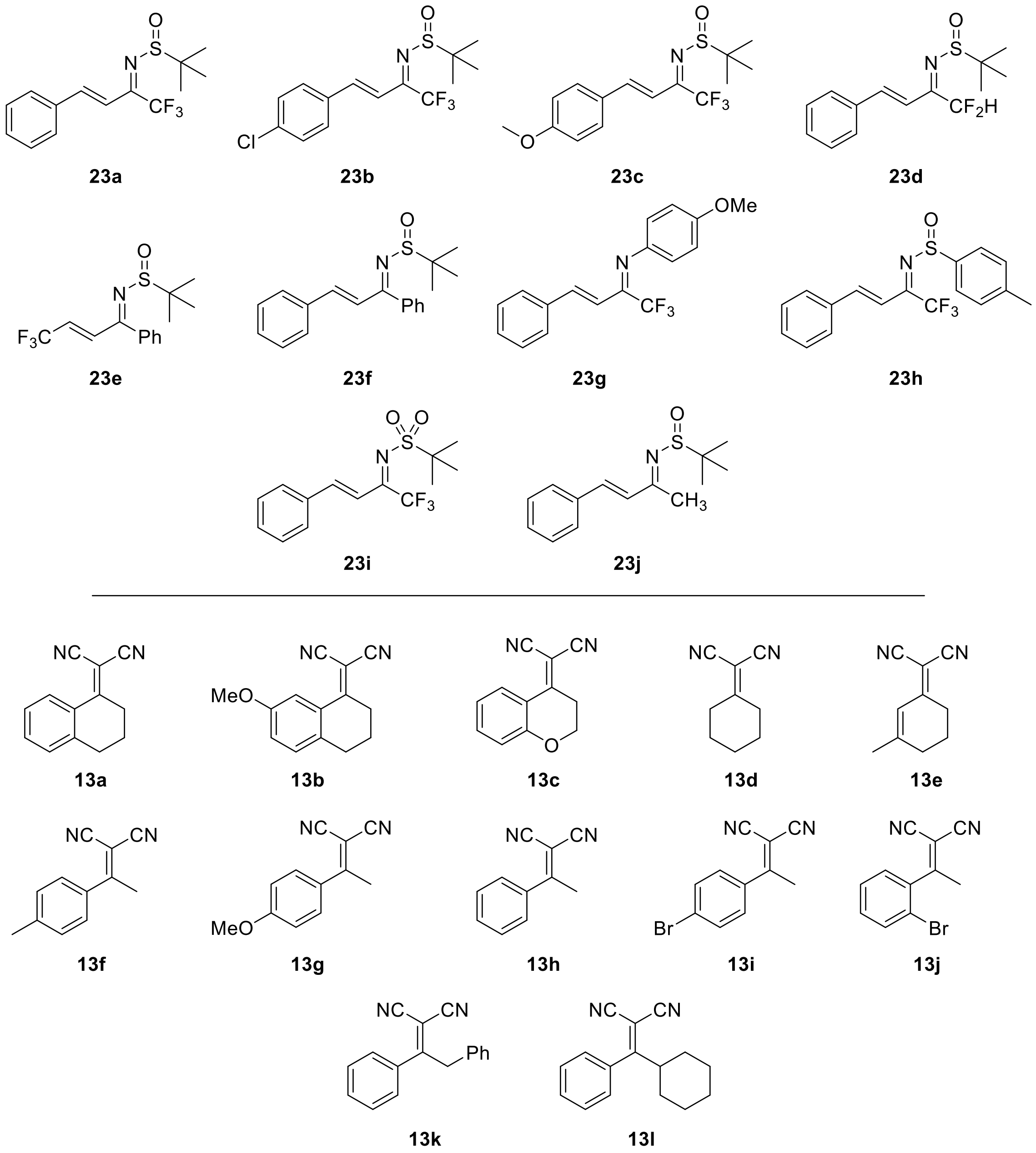


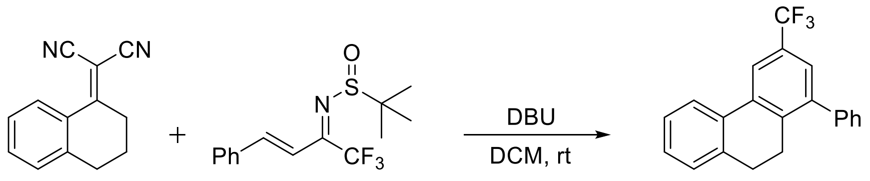
Figure 3.2. Starting materials library.

The results obtained in the extension of the optimised protocol to the rest of fluorinated imines **23** with dicyanoalquene **14a** are summarized in Table 3.2.

As depicted in Table 3.1, we firstly reacted imine **23a** with dicyanoalkene **13a** in the presence of DBU and it rendered fluorinated dihydrophenanthrene **24a** in 88% isolated yield (Table 3.2, entry 1). Imines **23b** and **23c**, bearing an electron-withdrawing and electron-donating groups in the phenyl ring also led to the corresponding dihydrophenanthrenes **24b** and **24c** in 85% and 66% isolated yields respectively (Table 3.2, entries 2,3), proving our protocol to tolerate this type of substitution. The use of different fluorinated moieties was also explored using imine **23d**, with a CF_2H group and in this case a separable mixture of the desired product **24d** and the product losing a fluorine atom **24e** was obtained in a 78% overall yield (61% and 17% respectively) (Table 3.2, entries 4,5).

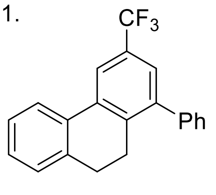
We switched the trifluoromethyl and the phenyl group positions in imine **23e**, notably reducing its electrophilicity and the reaction with dicyanoalkene **13a** resulted in a noticeable drop in the yield, leading to the desired product **24f** in a modest 40% isolated yield (Table 3.2, entry 6). In addition, the non-fluorinated imine **23f**, bearing phenyl rings in its 2nd and 4th positions, was tolerated under our reaction conditions, achieving dihydrophenanthrene **24g** in 41% yield (Table 3.2, entry 7).

Table 3.2. Reaction scope: imine substitution.



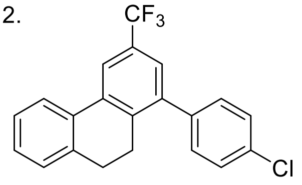
13a **23** **24**, yield%

1.



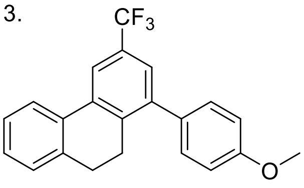
24a, 88%

2.



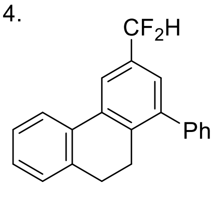
24b, 85%

3.



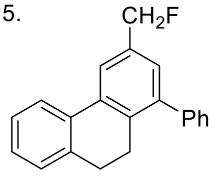
24c, 66%

4.



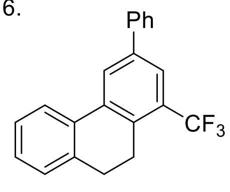
24d, 61%

5.



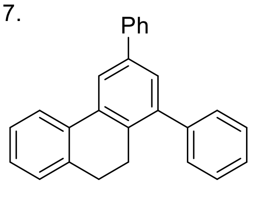
24e, 17%

6.



24f, 40%

7.



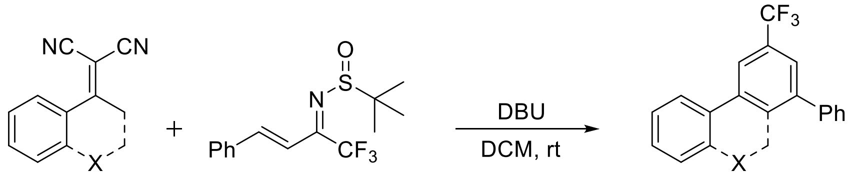
24g, 41%

In order to avoid the use of Ellman's chiral auxiliary, several imines with different protecting groups were synthesised and tested. The *para*-methoxyphenyl protected imine **23g** remained unreactive under our reaction conditions, while the para-tolyl one

23h led to a complex mixture of products. This fact revealed the crucial role of the tert-butylsulfynil group in our process development and outcome. Moreover, imine **23a** was oxidised to the BUS-protected imine **23i** and its behaviour was tested in the presence of **13a** and DBU, leading again to a complex mixture of products, denoting the irreplaceability of the tert-butylsulfynil group in order to render the tandem process.

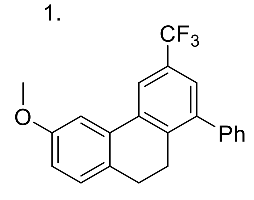
With these results in hand, we could summarise that in first place, the use of *tert*-butylsulfynil protecting group is necessary in order to observe the tandem protocol, achieving dihydrophenanthrenes **24**. In second place, our novel methodology tolerates both electron-donating and electron-withdrawing groups in the phenyl ring of the conjugated imine. Finally, electrophilicity reduction of the imine, changing the trifluoromethyl group, entails a severe reduction in the yield of the process.

Table 3.3. Reaction scope: cyanoalkenes.



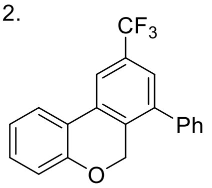
13 **23a** **24**, yield%

1.



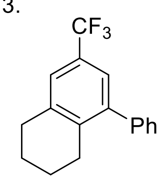
24h, 92%

2.



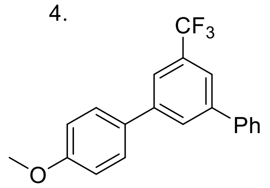
24i, 90%

3.



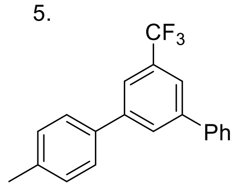
24j, 40%

4.



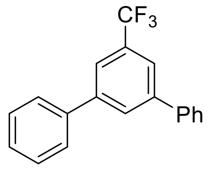
24k, 61%

5.



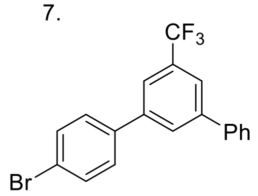
24l, 81%

6.



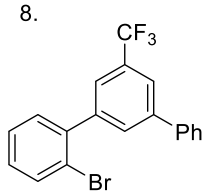
24m, 78%

7.



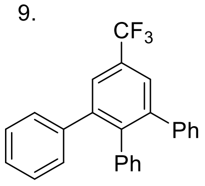
24n, 49%

8.



24o, 71%

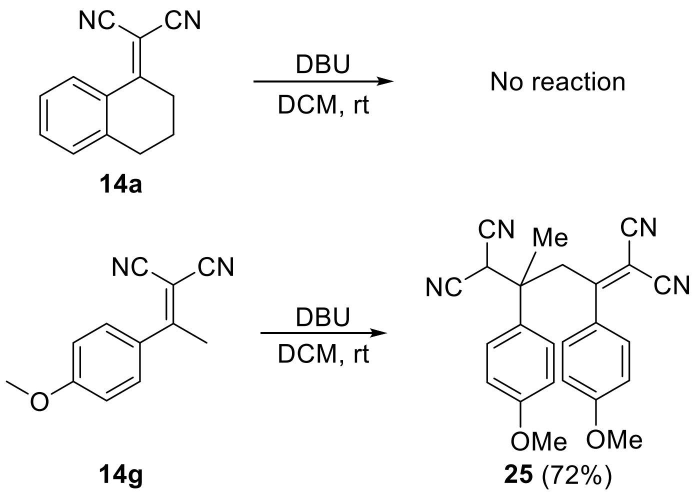
9.



24p, 0%

Subsequently, different dicyanoalkenes were tested under optimised conditions, and bicyclic olefins **13b** and **13c** proved to be great reaction partners with imine **23a**, achieving products **24h** and **24i** in 92% and 90% isolated yield respectively (Table 3.3, entries 1-2). When non-benzo-fused cyanoalkene **13d** was tried, the reaction evolved to the corresponding dihydrophenanthrene **24j** in a modest 40% yield, decreasing the efficiency of the tandem protocol (Table 3.3, entry 3).

We also tested unsubstituted dicyanoalkenes at the gamma position. Initially, the reaction of cyanoalkene **13g** with imine **23a**, provided a poor 20% isolated yield of **24k**. In order to investigate the reason for that severe drop in the yield, we ran some tests to check the stability of our reagents under optimised conditions. A parallel reaction of cyanoalkenes **13a** and **13g** with DBU in DCM at room temperature was performed and it revealed that while **13a** remained unaltered for 16 hours, **13g** was involved in a dimerization process, leading to dimer **25a** in good yield.



Scheme 3.28. Dimerization product of dicyanoalkene **13g**.

At this point, trying to avoid this competitivity issue, we tried the slow addition of **13g** over a mixture of the imine and DBU, giving rise to **24k** in a 61% isolated yield. Once this reactivity problem was solved, those conditions were applied to the rest of dicyanoalkenes unsubstituted at the gamma position.

Our methodology demonstrated to tolerate this type of nucleophile additions, as proved with dicyanoalkenes **13f-j**. Moreover, our protocol could be applied for the addition of CH_3 nucleophiles bearing both, electron-withdrawing and electron-donating moieties in the aromatic ring, producing tandem products **24k-n** in good to great yields (Table 3.3, entries 4-7). It is worth to notice that cyanoalkene **13j**, with a bromine in the *ortho*-position, also evolved to dihydrophenanthrene **24o**, proving our methodology as a robust protocol for the addition of sterically hindered nucleophiles (Table 3.3, entry 8).

Unfortunately, when this tandem protocol was applied to dicyanoalkene **14k**, a complex mixture of non-isolable products was observed, preventing us to achieve triphenyl-substituted fluorinated compound **24p** (Table 3.3, entry 9).

3.3.3. Mechanistic proposal.

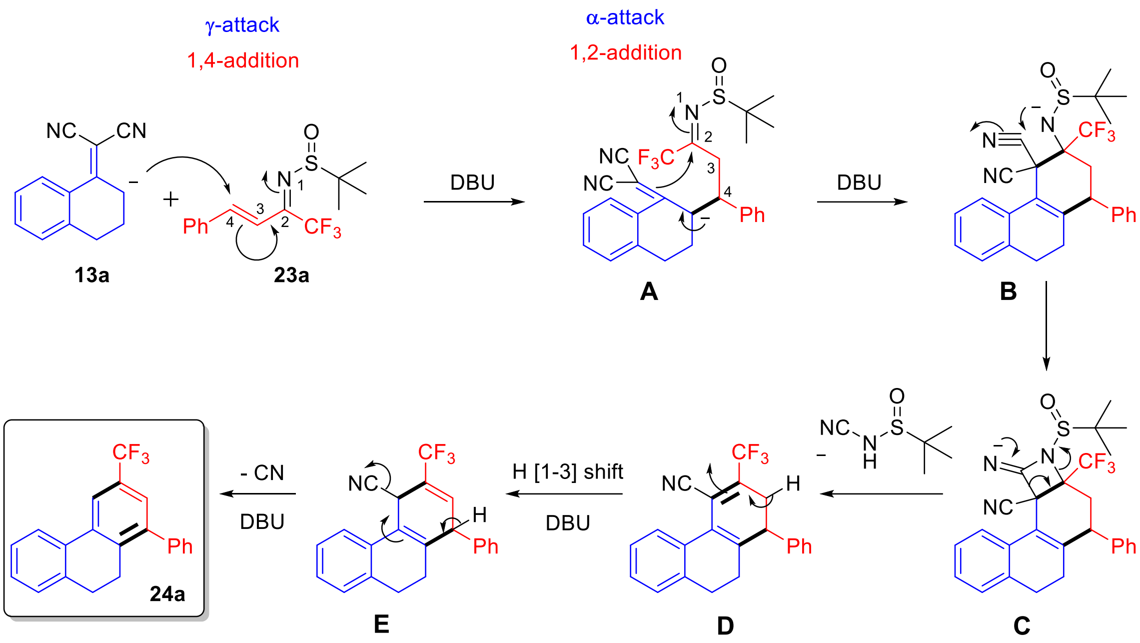
As mentioned above, the structure of the final products was elucidated from X-Ray diffraction analysis of properly crystallised products **24h** and **24i** and it was extended to the rest of dihydrophenanthrenes **24**.

At this point, we will try to provide a plausible mechanistic approach on behalf of a reasonable explanation for our unexpected protocol outcome (Scheme 3.29).

As a starting point, we suggest a γ-attack from the anionic cyanoalkene to the 4th position of the conjugated imine, providing with iminic intermediate **A**. This starting addition implies the very first 1,4-addition of a nucleophile to fluoroalkyl imines reported to date. To the best of our knowledge, all previously described methodologies in this field exhibit 1,2-addition selectivity.

Subsequently, a second equivalent of DBU base promotes the attack from the α-position of the dicyanoalkene, from its malonic carbon, to the iminic functionality of intermediate **A**, creating the 6-membered ring intermediate **B**.

So far, we are reporting a dual reactivity for both of our starting materials. On the one hand, we describe consecutive α- and γ- nucleophilic attacks from the dicyanoalkene, being the first time this dual reactivity is observed for this type of substrates. On the other hand, as mentioned above, the first 1,4-addition of a nucleophile to conjugated fluoroalkyl imines is depicted, also followed by a 1,2-addition to give a straight forward protocol for a new cyclisation methodology.



Scheme 3.29. Mechanistic approach.

At this point, deprotonated amine in **B**, attacks one of the nitrile groups of the dicyanoalkene, forming the four-membered heterocyclic intermediate **C**. This sterically hindered intermediate could evolve, with the loss of a cyanosulfynilamine, to highly unsaturated intermediate **D**, by means of a ring-opening of the constricted four-membered ring.

A double bond isomerisation with a [1-3] hydrogen shift takes place to achieve intermediate **E**, followed by a base-promoted aromatisation with the loss of HCN, giving rise to products **24** in a single reaction step.

3.3.4. Derivatisations.

As described in the *Introduction* of this chapter, the phenanthrene structure has grown a great importance over the years in both biochemical and medicinal chemistry. The Phenanthrene skeleton is present in diverse types of organic molecules with biologic interest.[208] Moreover, the incorporation of fluorine to this type of molecules has been scarcely studied.

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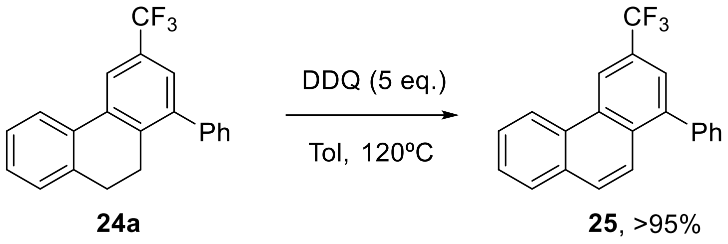
[208] (a) M. Leven, T. C. Knaab, J. Held, S. Duffy, S. Meister, C. Fischli, D. Meitzner, U. Lehmann, B. Lungerich, K. Kuna, P. Stahlke, M. J. Delves, M. Buchholz, E. A. Winzeler, V. M. Avery, B. Mordmüller, S. Wittlin, T. Kurz, *J. Med. Chem.*, **2017**, *60*, 6036-6044; (b) R. Friedman, A. Caflisch, *ChemMedChem.*, **2009**, *4*, 1317-1326; (c) J. A. McCubrey, M. H. LaHair, R. A. Franlin, *Mol. Pharmacol.*, **2006**, *70*, 437-439.

Given the lack of antecedents in the synthesis of fluorinated phenanthrenes, and in order to broaden the relevance and applicability of our methodology, we tried to oxidise dihydrophenanthrene **24a**.

Product **24a** was treated with five equivalents of DDQ in toluene and it was reacted overnight at 120 ºC. After reaction time, phenanthrene **25** was quantitatively isolated with an inseparable 5% impurity of the starting dihydrophenanthrene (Scheme 3.30).

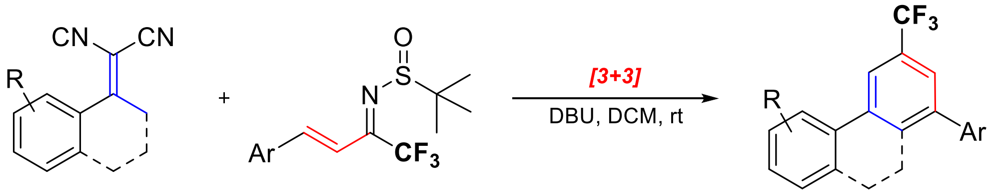
Herein we are reporting the synthesis of very new fluorinated phenanthrenes and dihydrophenanthrenes, both with high biological and medicinal relevance, in a tandem and straight forward manner.



Scheme 3.30. Oxidation of dihydrophenanthrenes **24** to phenanthrenes **25**.

3.4. Conclusions.

In summary, the reaction of dicyanoalkenes **13** and fluorinated conjugated imines **23** was evaluated. Imines containing the tert-butyl sulfinyl group reacted with dicyanoalkenes in the presence of DBU as base in a tandem protocol, rendering polycyclic trifluoroarenes **24** in good yields (Scheme 3.31).



14 **23** **24** (up to 92% yield)

- tandem process
- mild conditions
- readily available starting materials
- wide scope
- metal free
- air tolerant

Scheme 3.31. Synthesis of polycyclic trifluoroarenes **24**.

This methodology fulfils some of the important principles of the green chemistry: is a tandem process, which takes place under mild conditions, from readily available starting materials. Additionally, is a metal free and air tolerant process.

It is worth mentioning that this unprecedented protocol posseses several interesting features:

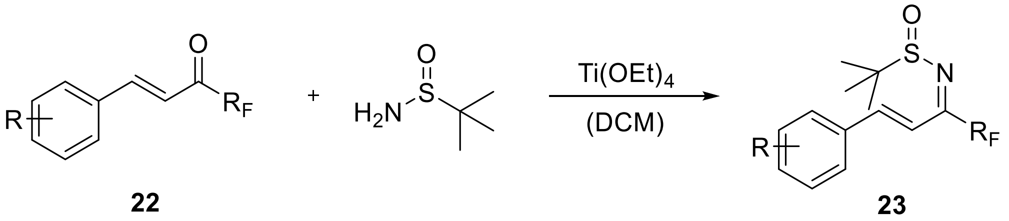
- Despite several cycloaromatizations with dicyanoalkenes have been previously described, no one took place with the elimination of the two cyano groups. Additionally, the gamma- and alfa addition of the dicyanoalkene takes place in the same synthetic operation, which is also unprecedented.
- Regarding the iminic counterpart, all the examples described before of nucleophilic addition to conjugated fluorinated sulfinyl imines gave rise to the 1,2-addition product. This is the first example of the use of those imines where the reaction is initiated by 1,4-addition.
- Finally, the tert-butyl sulfinyl group played a crucial role in the process, since all variations performed in this position was traduced in the fail of the process.

3.5. Experimental section.

3.5.1. General remarks.

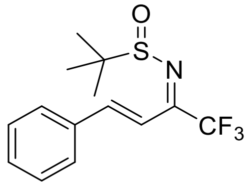
Reactions were carried out under a nitrogen atmosphere unless otherwise indicated. Solvents were purified prior to use: THF and PhMe were distilled from sodium, and CH_2Cl_2 was distilled from calcium hydride. The reactions were monitored with by means of TLC on 0.25 mm precoated silica gel plates. Visualization was carried out with UV light and potassium permanganate stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040–0.063 mm). ^1H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents. Coupling constants (J) are given in hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. The designation br indicates that the signal is broad. The abbreviations DCM and THF indicate dichloromethane and tetrahydrofuran, respectively. A QTOF mass analyzer system has been used for the HRMS measurements. Dicyanoolefins **13** were prepared following known methodologies (see experimental section of chapter 2).

3.5.2. General procedure for the preparation of conjugated imines **23**.

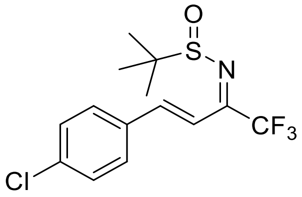


To a stirred solution of the corresponding conjugated ketone (5 mmol) and $Ti(OEt)_4$ (20 mmol), Ellman’s reagent (5 mmol) was added, and the neat reaction mixture was stirred at rt for 24h under N_2 atmosphere. The reaction mixture was diluted with 10 mL of DCM and quenched with 20 mL of a saturated NH_4Cl solution. The formed titanium salts were filtered over a Celite pad and the mixture extracted with more DCM, dried over sodium sulfate and evaporated under vacuum. The crude products were purified by means of flash column chromatography.

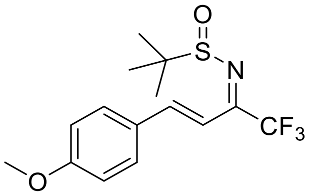
Reactions with solid ketones needed an addition of dry DCM (2 mL) for a proper homogenization of the reaction mixture.



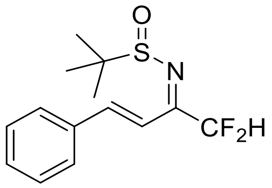
2-Methyl-*N*-[(2E,3E)-1,1,1-trifluoro-4-phenylbut-3-en-2-ylidene]propane-2-sulfinamide (23a). Starting from 1,1,1-trifluoro-4-phenylbut-3-en-2-one, the corresponding imine **23a** was obtained in good yield as an orange oil, after purification by column chromatography with Hex:EtOAc (4:1) as eluent. The spectroscopic data for the title compound were in accordance with the literature.[170]



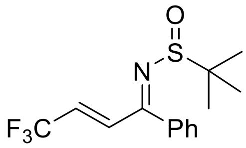
***N*-[(2E,3E)-4-(4-Chlorophenyl)-1,1,1-trifluorobut-3-en-2-ylidene]-2-methylpropane-2-sulfinamide (23b).** Starting from 4-(4-chlorophenyl)-1,1,1-trifluorobut-3-en-2-one, the corresponding imine **23b** was obtained in good yield as a yellow solid, after purification by column chromatography with Hex:EtOAc (4:1) as eluent. The spectroscopic data for the title compound were in accordance with the literature.[170]



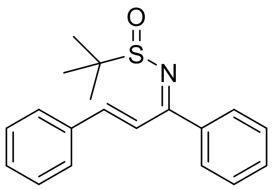
2-Methyl-*N*-[(2E,3E)-4-(4-methoxyphenyl)-1,1,1-trifluorobut-3-en-2-ylidene]propane-2-sulfinamide (23c). Starting from 1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-en-2-one, the corresponding imine **23c** was obtained in good yield as an orange solid, after purification by column chromatography with Hex:EtOAc (4:1) as eluent. The spectroscopic data for the title compound were in accordance with the literature.[170]



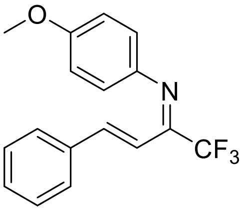
N-[(2E,3E)-1,1-Difluoro-4-phenylbut-3-en-2-ylidene]-2-methylpropane-2-sulfinamide (23d). Starting from 1,1-difluoro-4-phenylbut-3-en-2-one, the corresponding imine **23d** was obtained in good yield as an orange oil, after purification by column chromatography with Hex:EtOAc (4:1) as eluent. The spectroscopic data for the title compound were in accordance with the literature.[170]



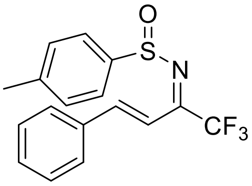
2-Methyl-N-[(1Z,2E)-4,4,4-trifluoro-1-phenylbut-2-en-1-ylidene]propane-2-sulfinamide (23e). Starting from 4,4,4-trifluoro-1-phenylbut-2-en-1-one, the corresponding imine **23e** was obtained in good yield as an yellowish oil, after purification by column chromatography with Hex:EtOAc (4:1) as eluent. The spectroscopic data for the title compound were in accordance with the literature.[170]



N-[(1Z,2E)-1,3-Diphenylallylidene]-2-methylpropane-2-sulfinamide (23f). Starting from chalcone, the corresponding imine **23f** was obtained in good yield as a yellow solid, after purification by column chromatography with Hex:EtOAc (4:1) as eluent. The spectroscopic data for the title compound were in accordance with the literature.[205a]

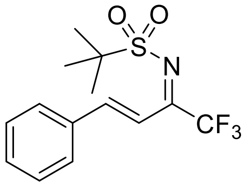


(2E,3E)-1,1,1-Trifluoro-N-(4-methoxyphenyl)-4-phenylbut-3-en-2-imine (23g). Imine **23g** was prepared by using the general procedure **A** described in *Chapter 1* (page 69). Condensation of the fluorinated ketone and the corresponding iminophosphorane, gave an easy acces to the title compound **23g**. The spectroscopic data for the title compound were in accordance with the literature.[205b]

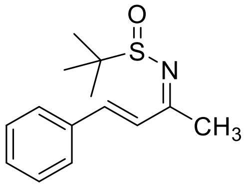


4-Methyl-*N*-[(2E,3E)-1,1,1-trifluoro-4-phenylbut-3-en-2-ylidene]benzenesulfinamide (23h). Starting from 1,1,1-trifluoro-4-phenylbut-3-en-2-one and p-tolyl sulfynilamide, the corresponding imine **23h** was obtained in good yield as a yellow solid, after purification by column chromatography with Hex:EtOAc (4:1) as eluent.

M. p. = 72-74 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.08 (dd, *J* = 16.9, 1.4 Hz, 1H), 7.74 – 7.69 (m, 2H), 7.59 (dd, *J* = 6.7, 2.9 Hz, 2H), 7.45 – 7.34 (m, 6H), 2.43 (s, 3H). ^{19}F NMR (282 MHz, CDCl$_3$) δ: -66.3. ^{13}C NMR (75 MHz, CDCl$_3$) δ 157.00 (q, *J* = 33.4 Hz), 144.74 (q, *J* = 2.6 Hz), 142.18, 141.31, 134.73, 131.29, 130.15, 129.19, 128.66, 125.49, 118.98 (q, *J* = 282.2 Hz), 114.98, 21.53.



2-Methyl-*N*-[(2E,3E)-1,1,1-trifluoro-4-phenylbut-3-en-2-ylidene]propane-2-sulfonamide (23i). Starting from imine **23a** and following the *m*-CPBA-mediated oxidation procedure described in *Chapter 2* (*oxidation of **15a**, page 142*), the corresponding imine **23i** was obtained in good yield as an orange oil, after purification by column chromatography with Hex:EtOAc (4:1) as eluent. The spectroscopic data for the title compound were in accordance with the literature.[170]

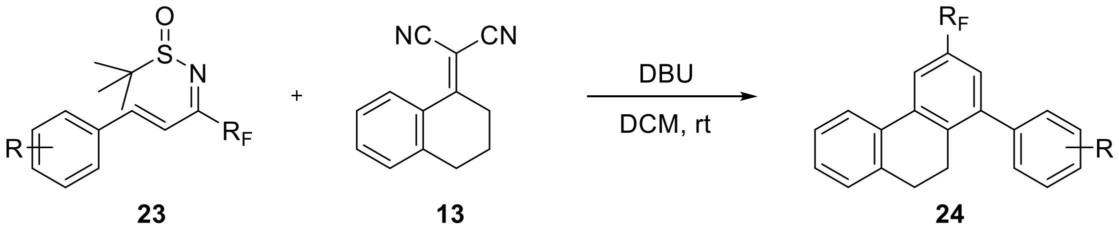


2-Methyl-N-((2Z,3E)-4-phenylbut-3-en-2-ylidene)propane-2-sulfinamide (23j). Starting from 4-phenylbut-3-en-2-one, the corresponding imine **23j** was obtained in good yield as an orange oil, after purification by column chromatography with Hex:EtOAc (4:1) as eluent.

The spectroscopic data for the title compound were in accordance with the literature.[205a]

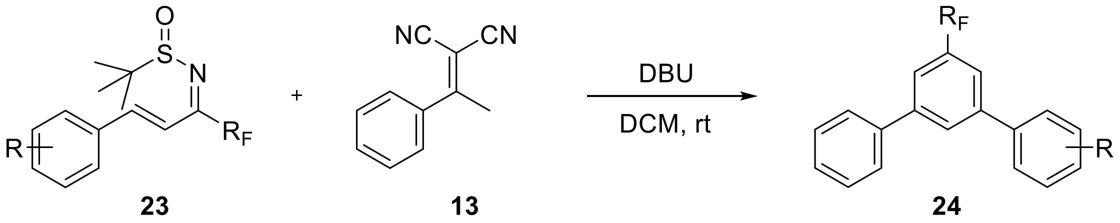
3.5.3. Preparation of dihydrophenanthrenes 24.

General procedure A for the vinylogous Mannich reaction with cyclic dicyanoalkenes

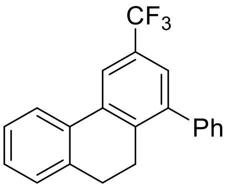


In a 50 mL round bottom flask fitted with a magnetic stirring bar, the corresponding dicyanoalkene **13** (0.6 mmol), DCM (6 mL) and DBU (0.6 mmol) were loaded. After stirring the reaction mixture for 5 min at room temperature, a solution of the corresponding sulfinylimine **23** (0.3 mmol) in DCM (3 mL) was added. After stirring for 16 h at rt, the solvents were removed and the crude product purified by means of flash column chromatography.

General procedure B for the vinylogous Mannich reaction with acyclic dicyanoalkenes



In a 50 mL round bottom flask fitted with a magnetic stirring bar, the corresponding sulfinylimine **23** (0.3 mmol), DCM (6 mL) and DBU (0.6 mmol) were loaded. After stirring the reaction mixture for 5 min at room temperature, a solution of the corresponding dicyanoalkene **13** (0.6 mmol) in DCM (3 mL) was slowly added with a syringe pump over 3 h (1 mL/h). After stirring for 3 additional hours at rt, the solvents were removed and the crude product purified by means of flash column chromatography.

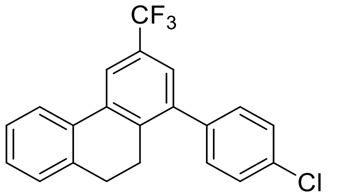


1-Phenyl-3-(trifluoromethyl)-9,10-dihydrophenanthrene (24a):

Starting from 2-(3,4-dihydronaphthalen-1(2H)-ylidene)malononitrile **13a** (116.5 mg), 2-methyl-N-((2Z,3E)-1,1,1-trifluoro-4-phenylbut-3-en-2-ylidene)propane-2-sulfinamide **23a** (91.0 mg) and DBU (90 µL), following the general procedure **A** mentioned above, the titled compound **24a** was obtained as a white solid (85.6 mg, 0.264 mmol, 88%) after purification by column chromatography with Hex:EtOAc (10:1) as eluent.

M.p. = 89-91 ºC. ^{1}H NMR (300 MHz, Chloroform-*d*) δ: 7.92 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.41 – 7.16 (m, 8H), 2.79 – 2.75 (m, 2H), 2.71 – 2.66 (m, 2H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ: -62.38 (s). ^{13}C NMR (75 MHz, Chloroform-*d*) δ: 141.8, 140.2, 138.8, 137.4, 136.0, 133.8, 129.2, 128.8 (q, *J* = 32.1 Hz), 128.4, 128.3, 128.0, 127.6, 127.2, 125.5

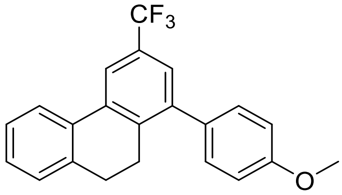
(q, *J* = 3.6 Hz), 124.4 (q, *J* = 270 Hz), 124.3, 119.9 (q, *J* = 3.7 Hz), 28.6, 26.5. HRMS (ES): calculated for $(M - H_2 + H^+)$ $C_{21}H_{14}F_3$: 323.1048; found 323.1058.



1-(4-Chlorophenyl)-3-(trifluoromethyl)-9,10-dihydrophenanthrene (24b):

Starting from 2-(3,4-dihydronaphthalen-1(2H)-ylidene)malononitrile **13a** (116.5 mg), N-((2Z,3E)-4-(4-chlorophenyl)-1,1,1-trifluorobut-3-en-2-ylidene)-2-methylpropane-2-sulfinamide **23b** (101.3 mg) and DBU (90 µL), following the general procedure **A** mentioned above, the titled compound **24b** was obtained as a yellowish oil (91.5 mg, 0.255 mmol, 85%) after purification by column chromatography with Hex:EtOAc (10:1) as eluent.

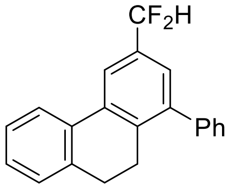
^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.91 (s, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.35 – 7.33 (m, 3H), 7.27 (td, *J* = 7.5, 1.0 Hz, 1H), 7.22 – 7.15 (m, 3H), 2.73 – 2.70 (m, 2H), 2.68 – 2.65 (m, 2H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ: -62.38 (s). ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 140.6, 138.8, 138.6, 137.3, 136.2, 133.8, 133.6, 130.6, 129.0 (q, *J* = 32.7 Hz), 128.6, 128.4, 128.0, 127.3, 125.3 (q, *J* = 3.7 Hz), 124.3, 124.3 (q, *J* = 273.4 Hz), 120.2 (q, *J* = 3.7 Hz), 28.6, 26.5. HRMS (ES): calculated for $(M - H_2 + H^+)$ $C_{21}H_{13}ClF_3$: 357.0652; found 357.0655.



1-(4-Methoxyphenyl)-3-(trifluoromethyl)-9,10-dihydrophenanthrene (24c):

Starting from 2-(3,4-dihydronaphthalen-1(2H)-ylidene)malononitrile **13a** (116.5 mg), 2-methyl-N-((2Z,3E)-1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-en-2-ylidene)propane-2-sulfinamide **23c** (100.0 mg) and DBU (90 µL), following the general procedure **A** mentioned above, the titled compound **24c** was obtained as a white solid (70.2 mg, 0.198 mmol, 66%) after purification by column chromatography with Hex:EtOAc (10:1) as eluent.

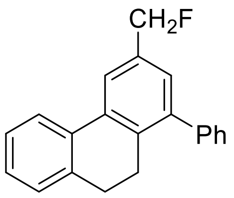
M.p. = 89-91 ºC. ^{1}H NMR (300 MHz, Chloroform-*d*) δ: 7.89 (s, 1H), 7.73 (d, *J* = 7.4 Hz, 1H), 7.40 (s, 1H), 7.28 (ddd, *J* = 13.4, 6.7, 1.6 Hz, 1H), 7.22 – 7.18 (m, 3H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 2.80 – 2.75 (m, 2H), 2.70 – 2.65 (m, 2H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ: -62.37 (s). ^{13}C NMR (75 MHz, Chloroform-*d*) δ: 159.1, 141.5, 138.9, 137.4, 136.0, 133.9, 132.5, 130.4, 128.8 (q, *J* = 32.2 Hz), 128.2, 127.9, 127.2, 125.5 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 272.2 Hz), 124.3, 119.6 (q, *J* = 3.7 Hz), 113.8, 55.4, 28.7, 26.5. HRMS (ES): calculated for (M –H$_2$ + H$^+$) $C_{22}H_{16}F_3O$: 353.1153; found 353.1162.



3-(Difluoromethyl)-1-phenyl-9,10-dihydrophenanthrene (24d):

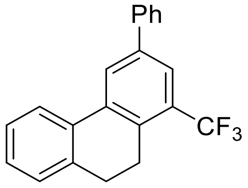
Starting from 2-(3,4-dihydronaphthalen-1(2H)-ylidene)malononitrile **13a** (116.5 mg), N-((2Z,3E)-1,1-difluoro-4-phenylbut-3-en-2-ylidene)-2-methylpropane-2-sulfinamide **23d** (85.6 mg) and DBU (90 µL), following the general procedure **A** mentioned above, the titled compound **24d** was obtained as a yellowish oil (56.1 mg, 0.183 mmol, 61%) after purification by column chromatography with Hex:EtOAc (10:1) as eluent.

^{1}H NMR (300 MHz, Chloroform-*d*) δ: 7.82 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.41 – 7.15 (m, 9H), 6.65 (t, *J* = 56.6 Hz, 1H), 2.78 – 2.73 (m, 2H), 2.70 – 2.65 (m, 2H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ: -110.15 (dt, *J* = 56.7, 1.2 Hz). ^{13}C NMR (75 MHz, Chloroform-*d*) δ: 141.7, 140.6, 137.7, 137.4, 135.8, 134.1, 132.6 (t, *J* = 22.4 Hz), 129.3, 128.3, 128.0, 127.9, 127.4, 127.2, 126.0 (t, *J* = 6.0 Hz), 124.3, 120.3 (t, *J* = 6.0 Hz), 114.9 (t, *J* = 238.8 Hz), 28.8, 26.5. HRMS (ES): calculated for (M – H$_2$+ H$^+$) $C_{21}H_{15}F_2$: 305.1142; found 305.1152.



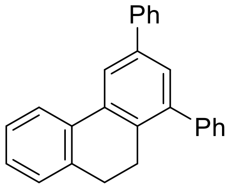
3-(Fluoromethyl)-1-phenyl-9,10-dihydrophenanthrene (24e): Starting from 2-(3,4-dihydronaphthalen-1(2H)-ylidene)malononitrile **13a** (116.5 mg), N-((2Z,3E)-1,1-difluoro-4-phenylbut-3-en-2-ylidene)-2-methylpropane-2-sulfinamide **23d** (85.6 mg) and DBU (90 µL), following the general procedure **A** mentioned above, the titled compound **24e** was obtained as a yellowish oil (14.7 mg, 0.051 mmol, 17%) after purification by column chromatography with Hex:EtOAc (10:1) as eluent.

^{1}H NMR (300 MHz, Chloroform-*d*) δ: 8.21 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.42 – 7.19 (m, 10H), 5.61 (d, *J* = 47.1 Hz, 2H), 2.69 – 2.65 (m, 2H), 2.61 – 2.57 (m, 2H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ: -213.14 (td, *J* = 47.0, 1.1 Hz). ^{13}C NMR (75 MHz, Chloroform-*d*) δ: 145.5, 139.6, 139.6 (d, *J* = 2.9 Hz), 139.2, 138.9 (d, *J* = 17.6 Hz), 138.2 (d, *J* = 2.5 Hz), 130.0 (d, *J* = 279.8 Hz), 129.4, 129.0, 128.6, 128.2, 128.2, 127.7, 127.3, 127.0, 117.6, 105.8, 29.1, 27.2. HRMS (ES): calculated for $(M – H_2 + H^+)$ $C_{21}H_{16}F$: 287.1236; found 287,1237.



3-Phenyl-1-(trifluoromethyl)-9,10-dihydrophenanthrene (24f): Starting from 2-(3,4-dihydronaphthalen-1(2H)-ylidene)malononitrile **13a** (116.5 mg), 2-Methyl-*N*-[(1Z,2E)-4,4,4-trifluoro-1-phenylbut-2-en-1-ylidene]propane-2-sulfinamide **23e** (91 mg) and DBU (90 µL), following the general procedure **A** mentioned above, the titled compound **24f** was obtained as a yellowish oil (77.8 mg, 0.24mmol, 40%) after purification by column chromatography with Hex:EtOAc (10:1) as eluent.

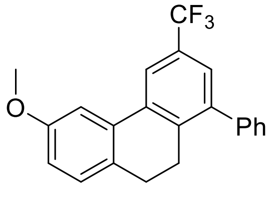
^{1}H NMR (300 MHz, Chloroform-*d*) δ: 8.14 (d, *J* = 1.3 Hz, 1H), 7.85 – 777 (m, 2H), 7.71 – 7.61 (m, 2H), 7.56 – 7.45 (m, 2H), 7.46 – 7.27 (m, 4H), 3.24 – 3.03 (m, 2H), 2.97 – 2.87 (m, 2H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ: -60.10. ^{13}C NMR (75 MHz, Chloroform-*d*) δ: 140.2, 139.9, 137.5, 137.0, 135.2 (q, J = 1.69 Hz), 133.7, 129.1, 1287, 128.4, 128.1, 128.0, 127.4, 127.2, 126.3, 124.7 (q, J = 275.0 Hz), 124.4, 123.6 (q, *J* = 5.7 Hz), 28.4, 24.9 (q, *J* = 2.3 Hz). HRMS (ES): calculated for $(M - H_2 + H^+)$ $C_{21}H_{14}F_3$: 323.1048; found 323.1056.



1,3-Diphenyl-9,10-dihydrophenanthrene (24g):

Starting from 2-(3,4-dihydronaphthalen-1(2H)-ylidene)malononitrile **13a** (116.5 mg), N-((1Z,2E)-1,3-diphenylallylidene)-2-methylpropane-2-sulfinamide **23f** (93.4 mg) and DBU (90 µL), following the general procedure **A** mentioned above, the titled compound **24g** was obtained as a yellowish oil (56.1 mg, 0.183 mmol, 61%) after purification by column chromatography with Hex:EtOAc (10:1) as eluent.

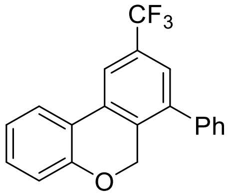
^{1}H NMR (300 MHz, Chloroform-*d*) δ: 7.92 (d, *J* = 1.8 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.61 – 7.58 (m, 2H), 7.41 – 7.14 (m, 12H), 2.79 – 2.74 (m, 2H), 2.71 – 2.66 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ: 141.6, 141.4, 141.2, 139.4, 137.6, 135.6, 134.9, 134.2, 129.4, 128.8, 128.2, 128.0, 127.9, 127.6, 127.3, 127.2, 127.1, 127.0, 124.2, 122.1, 29.2, 26.3. HRMS (ES): calculated for $(M - H_2 + H^+)$ $C_{21}H_{19}$: 331.1487; found 331.1489.



6-Methoxy-1-phenyl-3-(trifluoromethyl)-9,10-dihydrophenanthrene (24h):

Starting from 2-(7-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene)malononitrile **13b** (134.6 mg), 2-methyl-N-((2Z,3E)-1,1,1-trifluoro-4-phenylbut-3-en-2-ylidene)propane-2-sulfinamide **23a** (91.0 mg) and DBU (90 µL), following the general procedure **A** mentioned above, the titled compound **24h** was obtained as a yellowish solid (97.8 mg, 0.276 mmol, 92%) after purification by column chromatography with Hex:EtOAc (10:1) as eluent.

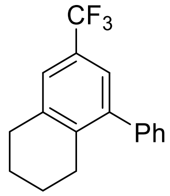
M.p. = 80-82 ºC. ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.97 (br s, 1H), 7.51 (br s, 1H), 7.49 – 7.46 (m, 2H), 7.44 – 7.40 (m, 1H), 7.37 – 7.35 (m, 3H), 7.18 (d, *J* = 8.2 Hz, 1H), 6.87 (dd, *J* = 8.2, 2.6 Hz, 1H), 3.91 (s, 3H), 2.85 – 2.82 (m, 2H), 2.72 – 2.69 (m, 2H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ: -62.36 (s). ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 158.9, 141.9, 140.2, 136.0, 134.7, 129.7, 129.2, 128.8, 128.8 (q, *J* = 32.7 Hz), 128.4, 127.6, 125.6 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 273.4 Hz), 119.9 (q, *J* = 3.7 Hz), 113.69, 110.01, 55.55, 27.75, 26.84. HRMS (ES): calculated for (M – H_2 + H^+) $C_{22}H_{16}F_3O$: 353.1153; found 353.1152.



7-Phenyl-9-(trifluoromethyl)-6H-benzo[c]chromene (24i):

Starting from 2-(chroman-4-ylidene)malononitrile **13c** (117.7 mg), 2-methyl-N-((2Z,3E)-1,1,1-trifluoro-4-phenylbut-3-en-2-ylidene)propane-2-sulfinamide **23a** (91.0 mg) and DBU (90 µL), following the general procedure **A** mentioned above, the titled compound **24i** was obtained as a colourless solid (88.1 mg, 0.27 mmol, 90%) after purification by column chromatography with Hex:EtOAc (10:1) as eluent.

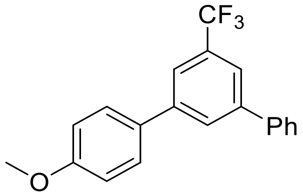
M.p. = 73-75 ºC. ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.86 (s, 1H), 7.74 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.45 (br s, 1H), 7.45 – 7.42 (m, 3H), 7.25 – 7.21 (m, 3H), 7.05 (td, *J* = 7.7, 1.0 Hz, 1H), 6.94 – 6.92 (m, 1H), 5.02 (s, 2H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ: -62.62 (s). ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 154.9, 140.1, 138.3, 132.7, 131.7, 130.4, 130.4 (q, *J* = 32.4 Hz), 128.9, 128.7, 128.2, 125.6 (q, *J* = 3.7 Hz), 124.1 (q, J = 273.4 Hz), 123.8, 122.6, 122.3, 118.1 (q, *J* = 3.8 Hz), 117.4, 66.1. (M + H^+) $C_{20}H_{14}F_3O$: 327.0997; found 327.0995.



5-Phenyl-7-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene (24j). Starting from 2-cyclohexylidenemalononitrile **13d** (87.7 mg), 2-methyl-N-((2Z,3E)-1,1,1-trifluoro-4-phenylbut-3-en-2-ylidene)propane-2-sulfinamide **23a** (91.0 mg) and DBU (90 µL), following the general procedure **A** mentioned above, the titled compound **24j** was obtained as a yellowish solid (33.2 mg, 0.120 mmol, 40%) after purification by column chromatography with Hex:EtOAc (10:1) as eluent.

* Tetrahydronaphtalene **13j** was isolated with an unseparable impurity of the loss of a fluorine atom.

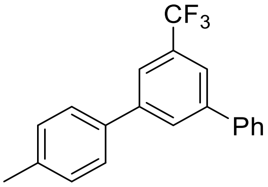
M.p. = 48-50 ºC.^{1}H NMR (300 MHz, Chloroform-*d*) δ: 7.42 – 7.33 (m, 4H), 7.20 – 7.16 (m, 3H), 3.03 – 2.99 (m, 2H), 2.59 – 2.53 (m, 2H), 1.87 – 1.78 (m, 2H), 1.70 – 1.62 (m, 2H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ: -61.76 (s). ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 146.5, 143.9, 140.6, 139.2, 130.3 (q, *J* = 32.2 Hz), 128.6, 128.5, 128.2, 125.0 (q, *J* = 4.7 Hz), 124.7 (q, *J* = 5.7 Hz), 122.7 (q, *J* = 277.2 Hz), 29.0, 28.6, 22.2, 21.9. HRMS (ES): calculated for (M$^+$) $C_{17}H_{16}F_3$: 277.1204; found 277.1192.



4-Methoxy-5'-(trifluoromethyl)-1,1':3',1''-terphenyl (24k):

Starting from 2-(1-(4-methoxyphenyl)ethylidene)malononitrile **13g** (118.9 mg), 2-methyl-N-((2Z,3E)-1,1,1-trifluoro-4-phenylbut-3-en-2-ylidene)propane-2-sulfinamide **23a** (91.0 mg) and DBU (90 µL), following the general procedure **B** mentioned above, the titled compound **24k** was obtained as a white solid (60.1 mg, 0.183 mmol, 61%) after purification by column chromatography with Hex:EtOAc (10:1) as eluent.

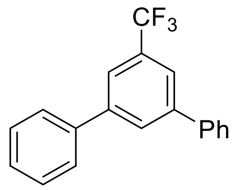
M.p. = 84-86 ºC. ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.92 (s, 1H), 7.77 (br s, 2H), 7.65 (d, *J* = 7.1 Hz, H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H). ^{19}F NMR (471 MHz, Chloroform-*d*) δ: -62.48. ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 159.8, 142.6, 142.2, 139.9, 132.2131.6 (q, *J* = 32.0 Hz), 129.0, 128.8, 128.4, 128.1, 127.3, 124.3 (q, *J* = 273.4 Hz), 122.3 (q, *J* = 3.7 Hz), 122.1 (q, *J* = 3.8 Hz), 114.5, 55.4. HRMS (ES): calculated for (M + H$^+$) $C_{20}H_{16}F_3O$: 329.1153; found 329.1156.



4-Methyl-5'-(trifluoromethyl)-1,1':3',1''-terphenyl (23l):

Starting from 2-(1-(p-tolyl)ethylidene)malononitrile **13f** (109.3 mg), 2-methyl-N-((2Z,3E)-1,1,1-trifluoro-4-phenylbut-3-en-2-ylidene)propane-2-sulfinamide **23a** (91.0 mg) and DBU (90 µL), following the general procedure **B** mentioned above, the titled compound **24l** was obtained as a white solid (75.9 mg, 0.243 mmol, 81%) after purification by column chromatography with Hex:EtOAc (10:1) as eluent.

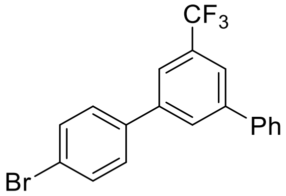
M.p. = 83-85 ºC. ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.96 (s, 0H), 7.80 (d, *J* = 5.1 Hz, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 0H), 7.31 (d, *J* = 8.0 Hz, 1H), 2.44 (s, 1H). ^{19}F NMR (471 MHz, Chloroform-*d*) δ: -62.46. ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 142.6, 142.6, 139.9, 138.1, 136.9, 131.7 (q, *J* = 32.0 Hz), 129.8, 129.1, 129.0, 128.1, 127.3, 127.1, 124.3 (q, *J* = 272.6 Hz), 122.5 (dq, *J* = 7.6, 3.8 Hz), 21.2. HRMS (ES): calculated for (M + H$^+$) $C_{20}H_{16}F_3$: 313.1204; found 313.1210.



5'-(Trifluoromethyl)-1,1':3',1''-terphenyl (24m):

Starting from 2-(1-phenylethylidene)malononitrile **13h** (100.9 mg), 2-methyl-N-((2Z,3E)-1,1,1-trifluoro-4-phenylbut-3-en-2-ylidene)propane-2-sulfinamide **23a** (91.0 mg) and DBU (90 µL), following the general procedure **B** mentioned above, the titled compound **24m** was obtained as a colorless solid (69.8 mg, 0.234 mmol, 78%) after purification by column chromatography with Hex:EtOAc (10:1) as eluent.

M.p. = 80-82 ºC. ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.98 (s, 1H), 7.83 (s, 1H), 7.68 – 7.66 (m, 2H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 1H). ^{19}F NMR (471 MHz, Chloroform-*d*) δ: -62.46 (s). ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 142.7, 139.8, 131.7 (q, *J* = 32.1 Hz), 129.3, 129.1, 128.2, 127.3, 124.2 (q, *J* = 272.7 Hz), 122.8 (q, *J* = 3.7 Hz). HRMS (ES): calculated for $(M + H^{+})$ $C_{19}H_{14}F_{3}$: 299.1048; found 299.2052.

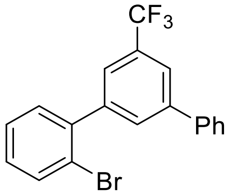


4-Bromo-5'-(trifluoromethyl)-1,1':3',1''-terphenyl (24n):

Starting from 2-(1-(4-bromophenyl)ethylidene)malononitrile **13i** (148.3 mg), 2-methyl-N-((2Z,3E)-1,1,1-trifluoro-4-phenylbut-3-en-2-ylidene)propane-2-sulfinamide **23a** (91.0 mg) and DBU (90 µL), following the general procedure **B** mentioned above, the titled compound **24n** was obtained as a colourless solid (55.5 mg, 0.147 mmol, 49%) after purification by column chromatography with Hex:EtOAc (10:1) as eluent.

M.p. = 78-80 ºC. ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.92 (s, 1H), 7.83 (s, 1H), 7.77 (s, 1H), 7.65 – 7.62 (m, 4H), 7.53 – 7.49 (m, 4H), 7.43 (t, *J* = 7.3 Hz, 1H). ^{19}F NMR (471 MHz, Chloroform-*d*) δ: -62.51 (s). ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 142.9, 141.4, 139.6, 138.7, 132.2, 131.9 (q, *J* = 32.2 Hz), 129.1, 129.0, 128.9, 128.3, 127.3, 124.1 (q, *J* = 273.4

Hz), 123.1 (q, *J* = 3.7 Hz), 122.6, 122.5 (q, *J* = 3.7 Hz). HRMS (ES): calculated for (M + H+) $C_{19}H_{13}BrF_3$: 377.0153; found 377.0152.



2-Bromo-5'-(trifluoromethyl)-1,1':3',1''-terphenyl (24o):

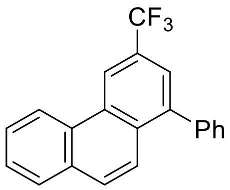
Starting from 2-(1-(2-bromophenyl)ethylidene)malononitrile **13j** (148.3 mg), 2-methyl-N-((2Z,3E)-1,1,1-trifluoro-4-phenylbut-3-en-2-ylidene)propane-2-sulfinamide **23a** (91.0 mg) and DBU (90 µL), following the general procedure **B** mentioned above, the titled compound **24o** was obtained as a colorless oil (80.3 mg, 0.213 mmol, 78%) after purification by column chromatography with Hex:EtOAc (10:1) as eluent.

^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.85 (d, *J* = 9.2 Hz, 2H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.66 – 7.64 (m, 3H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.43 – 7.38 (m, 3H), 7.29 – 7.25 (m, 1H). ^{19}F NMR (471 MHz, Chloroform-*d*) δ: -62.44 (s). ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 142.2, 141.8, 141.0, 139.5, 133.4, 131.6, 131.1 (q, *J* = 33.8 Hz), 131.2, 129.5, 129.0, 128.2, 127.7, 127.3, 125.0 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.6 Hz), 123.1 (q, *J* = 3.8 Hz), 122.5. HRMS (ES): calculated for (M + H+) $C_{19}H_{13}BrF_3$: 377.0153; found 377.0158.

3.5.4. Derivatisations.

Aromatization of dihydrophenanthrenes 24.

To a stirred solution of the corresponding dihydrophenanthrene **24** (0.2 mmol) in dry toluene (3 mL), DDQ (0.6) was added and the reaction mixture heated at 120 ºC for 16 h under N_2 athmosphere. Solvents were removed under reduced pressure and the crude product purified by means of flash column chromatography.



1-Phenyl-3-(trifluoromethyl)phenanthrene (25):

Starting from 1-phenyl-3-(trifluoromethyl)-9,10-dihydrophenanthrene **24a** (64.9 mg), product **25** (63.8 mg, 0.198 mmol, 99%) was quantitatively obtained after purification by column chromatography with Hex:EtOAc (10:1) as eluent.

M.p. = 98-100 ºC.^{1}H NMR (300 MHz, Chloroform-*d*) δ: 8.21 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.42 – 7.19 (m, 10H), 5.61 (d, *J* = 47.1 Hz, 2H), 2.69 – 2.65 (m, 2H), 2.61 – 2.57 (m, 2H). 19F NMR (282 MHz, Chloroform-*d*) δ: -213.14 (td, *J* = 47.0, 1.1 Hz). ^{19}F NMR (282 MHz, Chloroform-d) δ: -61.77 (s). ^{13}C NMR (75 MHz, Chloroform-*d*) δ: 142.0, 139.9, 131.9, 130.3, 130.2, 130.1, 129.2, 129.1, 128.7, 128.5, 127.9, 127.5, 127.5 (q, *J* = 7.5 Hz), 127.4, 124.6 (q, *J* = 273.3 Hz), 124.0, 123.6 (q, *J* = 3.2 Hz), 123.0, 119.5 (q, *J* = 4.3 Hz). HRMS (ES): calculated for (M + H$^+$) $C_{21}H_{14}F_3$: 323.1048; found 323.1052.

X-Ray structure of 24h.

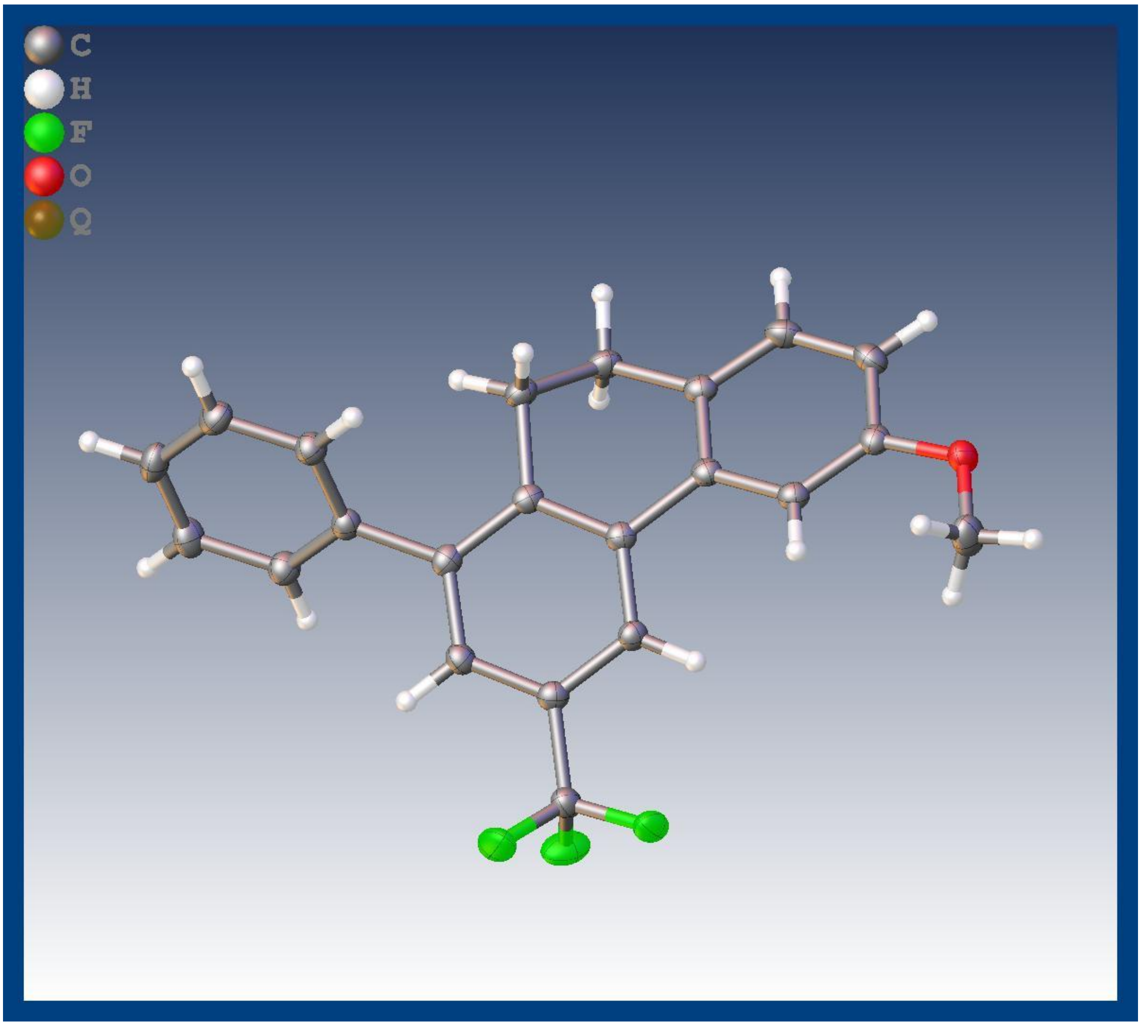


Figure 3.4. X-Ray diffraction structure of dihydrophenanthrene **24h**.

X-Ray structure of 24i.

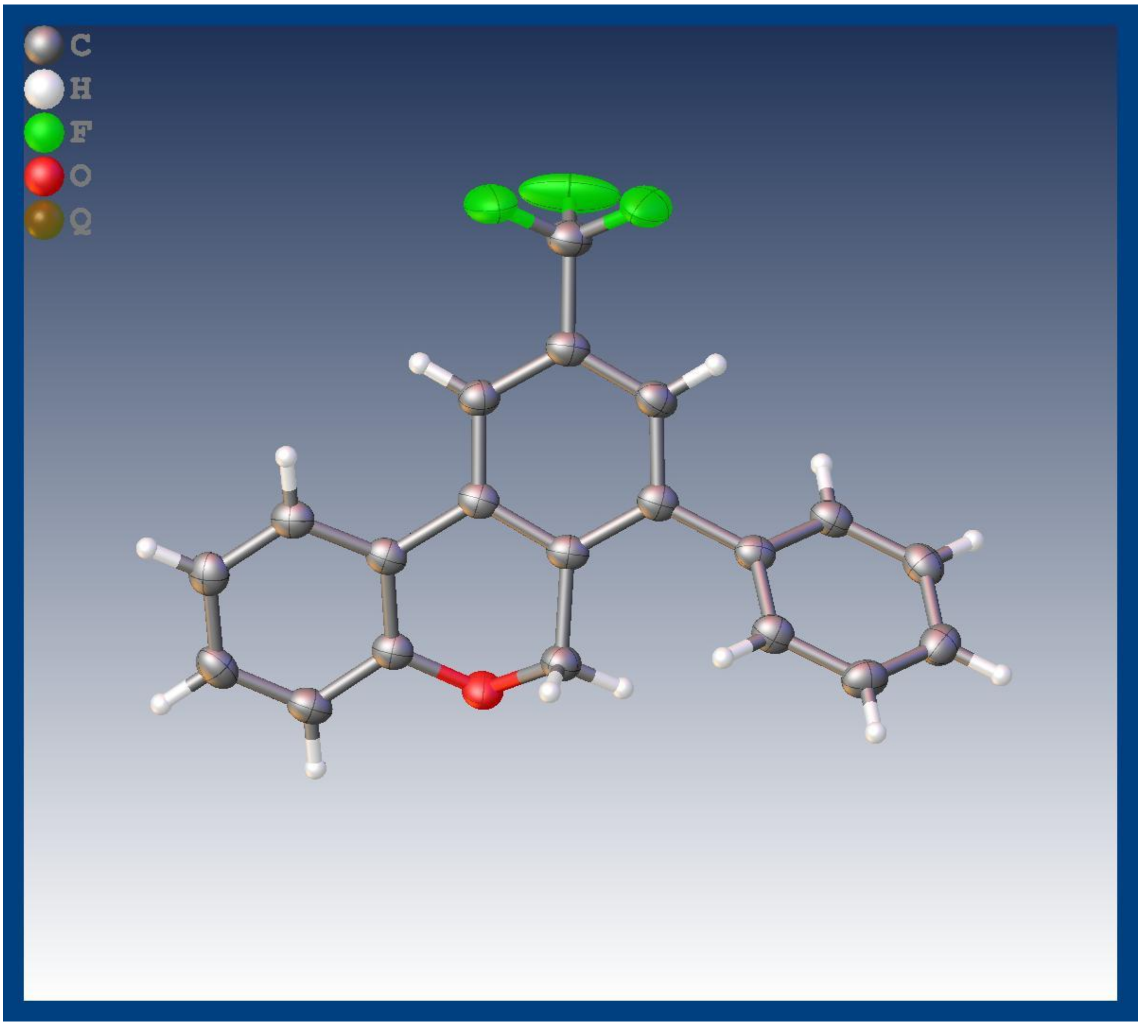


Figure 3.5. X-Ray diffraction structure of dihydrophenanthrene **24i**.

Bibliography

1(a) J. Wang; M. Sánchez-Roselló; J. L. Aceña; C. del Pozo; A. E. Sorochinsky; S. Fustero; V. A. Soloshonok; H. Liu, *Chem. Rev.,* **2014,** *114*, 2432-2506; (b) Y. Zhou; J. Wang; Z. Gu; S. Wang; W. Zhu; J. L. Aceña; V. A. Soloshonok; K. Izawa; H. Liu, *Chem. Rev.,* **2016,** *116*, 422-518; (c) S. Purser; P. R. Moore; S. Swallow; V. Gouverneur, *Chem. Soc. Rev.,* **2008,** *37*, 320-30; (d) H. Mei; J. Han; S. Fustero; M. Medio-Simon; D. M. Sedgwick; C. Santi; R. Ruzziconi; V. A. Soloshonok, *Chem. Eur. J.,* **2019,** *25*; (e) J.-P. Bégué; D. Bonnet-Delpon, *J. Fluorine Chem.,* **2006,** *127*, 992-1012; (f) C. Isanbor; D. O'Hagan, *J. Fluorine Chem.,* **2006,** *127*, 303-319; (g) K. L. Kirk, *J. Fluorine Chem.,* **2006,** *127*, 1013-1029; (h) W. K. Hagmann, *J. Med. Chem.,* **2008,** *51*, 4359-4369.
2B. S. Molloy, K., US 4018895, **1997**.
3M. Patel; S. S. Ko; R. J. McHugh; J. A. Markwalder; A. S. Srivastava; B. C. Cordova; R. M. Klabe; S. Erickson-Viitanen; G. L. Trainor; S. P. Seitz, *Bioor. Med. Chem. Let.,* **1999,** *9*, 2805-2810.
4K. Müller; C. Faeh; F. Diederich, *Science,* **2007,** *317*, 1881-1886.
5(a) R. E. Banks; B. E. Smart; J. C. Tatlow, *Organofluorine Chemistry, Principles and Commercial Applications*. **1994**; (b) D. O'Hagan, *Chem. Soc. Rev.,* **2008,** *37*, 308-319.
6(a) Q. A. Huchet; B. Kuhn; B. Wagner; N. A. Kratochwil; H. Fischer; M. Kansy; D. Zimmerli; E. M. Carreira; K. Müller, *J. Med. Chem.,* **2015,** *58*, 9041-9060; (b) E. P. Gillis; K. J. Eastman; M. D. Hill; D. J. Donnelly; N. A. Meanwell, *J. Med. Chem.,* **2015,** *58*, 8315-8359.
7B. Linclau; Z. Wang; G. Compain; V. Paumelle; C. Q. Fontenelle; N. Wells; A. Weymouth-Wilson, *Angew. Chem. Int. Ed.,* **2016,** *55*, 674-678.
8(a) B. Jeffries; Z. Wang; H. R. Felstead; J.-Y. Le Questel; J. S. Scott; E. Chiarparin; J. Graton; B. Linclau, *J. Med. Chem.,* **2020,** *63*, 1002-1031; (b) J. St-Gelais; M. Bouchard; V. Denavit; D. Giguère, *J. Org. Chem.,* **2019,** *84*, 8509-8522.
9(a) D.-Z. Liu; J.-K. Liu, *Natural Products and Bioprospecting,* **2013,** *3*, 161-206; (b) D. B. Harper; D. O'Hagan, *Natural Product Reports,* **1994,** *11*, 123-133; (c) N. Jaivel; C. Uvarani; R. Rajesh; D. Velmurugan; P. Marimuthu, *J. Nat. Prod.,* **2015,** *78*, 343-343.
10(a) J.-A. Ma; S. Li, *Org. Chem. Front.,* **2014,** *1*, 712-715; (b) V. Bizet; T. Besset; J. A. Ma; D. Cahard, *Curr. Top. Med. Chem.,* **2014,** *14*, 901-40; (c) X. Yang; T. Wu; R. J. Phipps; F. D. Toste, *Chem. Rev.,* **2015,** *115*, 826-70; (d) P. A. Champagne; J. Desroches; J. D. Hamel; M. Vandamme; J. F. Paquin, *Chem. Rev.,* **2015,** *115*, 9073-174.
11(a) W. J. Middleton; E. M. Bingham, *J. Org. Chem.,* **1980,** *45*, 2883-2887; (b) W. J. Middleton, *J. Org. Chem.,* **1975,** *40*, 574-578.
12(a) Y. R. Mirzaei; B. Twamley; J. n. M. Shreeve, *J. Org. Chem.,* **2002,** *67*, 9340-9345; (b) G. S. Lal; G. P. Pez; R. J. Pesaresi; F. M. Prozonic, *Chem. Commun.,* **1999**, 215-216.
13F. Sladojevich; S. I. Arlow; P. Tang; T. Ritter, *J. Am. Chem. Soc.,* **2013,** *135*, 2470-2473.
14M. K. Nielsen; C. R. Ugaz; W. Li; A. G. Doyle, *J. Am. Chem. Soc.,* **2015,** *137*, 9571-9574.
15(a) I. Ruppert; K. Schlich; W. Volbach, *Tetrahedron Lett.,* **1984,** *25*, 2195-2198; (b) R. Krishnamurti; D. R. Bellew; G. K. S. Prakash, *J. Org. Chem.,* **1991,** *56*, 984-989; (c) G. K. S. Prakash; A. K. Yudin, *Chem. Rev.,* **1997,** *97*, 757-786.
16P. Kirsch, *Modern Fluoroorganic Chemistry*. Wiley-VCH: **2004**.
17R. E. Banks, *J. Fluorine Chem.,* **1998,** *87*, 1-17.
18P. Eisenberger; S. Gischig; A. Togni, *Chem. Eur. J.,* **2006,** *12*, 2579-2586.
19(a) B. Lantaño; A. Postigo, *Organic & Biomolecular Chemistry,* **2017,** *15*, 9954-9973; (b) M. P. Sibi; Y. Landais, *Angew. Chem. Int. Ed.,* **2013,** *52*, 3570-3572.
20(a) M. A. Ischay; M. E. Anzovino; J. Du; T. P. Yoon, *J. Am. Chem. Soc.,* **2008,** *130*, 12886-12887; (b) D. A. Nicewicz; D. W. C. MacMillan, *Science,* **2008,** *322*, 77.
21(a) T. Chatterjee; N. Iqbal; Y. You; E. J. Cho, *Acc Chem Res,* **2016,** *49*, 2284-2294; (b) A. Arora; J. D. Weaver, *Accounts of Chemical Research,* **2016,** *49*, 2273-2283.

22(a) S. Fustero; J. F. Sanz-Cervera; J. L. Aceña; M. Sánchez-Roselló, *Synlett,* **2009,** *2009*, 525-549; (b) W. Dmowski, *J. Fluorine Chem.,* **2012,** *142*, 6-13; (c) W. Dmowski, *J. Fluorine Chem.,* **2011,** *132*, 504-511; (d) M. C. Pacheco; S. Purser; V. Gouverneur, *Chem. Rev.,* **2008,** *108*, 1943-81; (e) M. F. Kuehnel; D. Lentz; T. Braun, *Angew. Chem. Int. Ed.,* **2013,** *52*, 3328-48.
23(a) S. Fustero; J.-F. Sanz-Cervera; C. del Pozo; Aceña; J.-L., Nitrogen-Containing Organofluorine Compounds Through Metathesis Reactions, In Current Fluoroorganic Chemistry: New Synthetic Directions, Technologies, Materials, and Biological Applications. In *ACS Symposium Series* Soloshonok, V.; Mikami, K.; Yamazaki, T.; Welch, J. T.; Honek, J., Eds., Eds. American Chemical Society: Washington DC: **2007**; pp 54–68; (b) S. Fustero; J.-F. Sanz-Cervera; C. del Pozo; Aceña; J.-L., Nitrogen-Containing Organofluorine Compounds Through Metathesis Reactions, In Current Fluoroorganic Chemistry: New Synthetic Directions, Technologies, Materials, and Biological Applications. In *ACS Symposium Series*, Soloshonok, V.; Mikami, K.; Yamazaki, T.; Welch, J. T.; Honek, J., Eds., Eds. American Chemical Society: Washington DC: **2007**; pp 54–68.
24(a) J. P. Begue; D. Bonnet-Delpon; B. Crousse; J. Legros, *Chem Soc Rev,* **2005,** *34*, 562-72; (b) A. Roy; F. Gosselin; P. D. O'Shea; C.-y. Chen, *J. Org. Chem.,* **2006,** *71*, 4320-4323; (c) V. L. Truong; M. S. Menard; I. Dion, *Org. Lett.,* **2007,** *9*, 683-5; (d) C. Lauzon; A. B. Charette, *Org. Lett.,* **2006,** *8*, 2743-2745.
25(a) H. Amii; Y. Kishikawa; K. Kageyama; K. Uneyama, *J. Org. Chem.,* **2000,** *65*, 3404-3408; (b) H. Watanabe; Y. Hashizume; K. Uneyama, *Tetrahedron Lett.,* **1992,** *33*, 4333-4336.
26A. Asensio; P. Bravo; M. Crucianelli; A. Farina; S. Fustero; Juan G. Soler; Stefano V. Meille; W. Panzeri; F. Viani; A. Volonterio; M. Zanda, *Eur. J. Org. Chem.,* **2001,** *2001*, 1449-1458.
27S. N. Osipov; A. S. Golubev; N. Sewald; T. Michel; A. F. Kolomiets; A. V. Fokin; K. Burger, *J. Org. Chem.,* **1996,** *61*, 7521-7528.
28(a) M. Abid; L. Teixeira; B. Török, *Org. Lett.,* **2008,** *10*, 933-935; (b) G. Chaume; M.-C. Van Severen; S. Marinkovic; T. Brigaud, *Org. Lett.,* **2006,** *8*, 6123-6126.
29H. Abe; H. Amii; K. Uneyama, *Org. Lett.,* **2001,** *3*, 313-315.
30(a) H. Mei; C. Xie; J. Han; V. A. Soloshonok, *Eur. J. Org. Chem.,* **2016,** *2016*, 5917-5932; (b) P. Bravo; M. Guidetti; F. Viani; M. Zanda; A. L. Markovsky; A. E. Sorochinsky; I. V. Soloshonok; V. A. Soloshonok, *Tetrahedron,* **1998,** *54*, 12789-12806.
31S. Fustero; A. Navarro; B. Pina; J. G. Soler; A. Bartolomé; A. Asensio; A. Simón; P. Bravo; G. Fronza; A. Volonterio; M. Zanda, *Org. Lett.,* **2001,** *3*, 2621-2624.
32(a) J. A. Ellman; T. D. Owens; T. P. Tang, *Accounts of Chemical Research,* **2002,** *35*, 984-95; (b) M. T. Robak; M. A. Herbage; J. A. Ellman, *Chem. Rev.,* **2010,** *110*, 3600-3740.
33(a) J. Liu; J. Hu, *Future Medicinal Chemistry,* **2009,** *1*, 875-888; (b) A. E. Sorochinsky; V. A. Soloshonok, *J. Fluorine Chem.,* **2010,** *131*, 127-139; (c) L. Wu; C. Xie; J. Zhou; H. Mei; V. A. Soloshonok; J. Han; Y. Pan, *J. Fluorine Chem.,* **2015,** *170*, 57-65; (d) S. Fioravanti, *Tetrahedron,* **2016,** *72*, 4449-4489.
34(a) M.-W. Chen; Q. Yang; Z. Deng; Y. Zhou; Q. Ding; Y. Peng, *J. Org. Chem.,* **2018,** *83*, 8688-8694; (b) M. Urban; M. Franc; M. Hofmanová; I. Císařová; J. Veselý, *Organic & Biomolecular Chemistry,* **2017,** *15*, 9071-9076; (c) M.-W. Chen; B. Wu; Z.-P. Chen; L. Shi; Y.-G. Zhou, *Org. Lett.,* **2016,** *18*, 4650-4653; (d) M.-W. Chen; X. Mao; Y. Ji; J. Yuan; Z. Deng; Y. Peng, *Tetrahedron Lett.,* **2019,** *60*, 151280.
35S. Fustero; B. Pina; E. Salavert; A. Navarro; M. C. Ramírez de Arellano; A. S. Fuentes, *J. Org. Chem.,* **2002,** *67*, 4667-4679.
36(a) S. F. Martin, *Accounts of Chemical Research,* **2002,** *35*, 895-904; (b) S. K. Bur; S. F. Martin, *Tetrahedron,* **2001,** *57*, 3221-3242.
37M. S. Roselló; C. del Pozo; S. Fustero, *Synthesis,* **2016,** *48*, 2553-2571.
38G. Casiraghi; F. Zanardi; L. Battistini; G. Rassu, *Synlett,* **2009,** *2009*, 1525-1542.
39E. L. Carswell; M. L. Snapper; A. H. Hoveyda, *Angew. Chem. Int. Ed.,* **2006,** *45*, 7230-3.
40H. Mandai; K. Mandai; M. L. Snapper; A. H. Hoveyda, *J. Am. Chem. Soc.,* **2008,** *130*, 17961-17969.

41L. C. Wieland; E. M. Vieira; M. L. Snapper; A. H. Hoveyda, *J. Am. Chem. Soc.,* **2009,** *131*, 570-576.
42D. L. Silverio; P. Fu; E. L. Carswell; M. L. Snapper; A. H. Hoveyda, *Tetrahedron Lett.,* **2015,** *56*, 3489-3493.
43(a) H.-P. Deng; Y. Wei; M. Shi, *Adv. Synth. Catal.,* **2009,** *351*, 2897-2902; (b) Z.-L. Yuan; J.-J. Jiang; M. Shi, *Tetrahedron,* **2009,** *65*, 6001-6007.
44Q.-Y. Zhao; Z.-L. Yuan; M. Shi, *Adv. Synth. Catal.,* **2011,** *353*, 637-643.
45T. Akiyama; J. Itoh; K. Yokota; K. Fuchibe, *Angew. Chem. Int. Ed.,* **2004,** *43*, 1566-8.
46J. Yu; Z. Miao; R. Chen, *Organic & Biomolecular Chemistry,* **2011,** *9*, 1756-1762.
47S.-T. Ruan; J.-M. Luo; Y. Du; P.-Q. Huang, *Org. Lett.,* **2011,** *13*, 4938-4941.
48(a) M. Sickert; C. Schneider, *Angew. Chem. Int. Ed.,* **2008,** *47*, 3631-4; (b) M. Sickert; F. Abels; M. Lang; J. Sieler; C. Birkemeyer; C. Schneider, *Chem. Eur. J.,* **2010,** *16*, 2806-2818.
49F. Abels; C. Schneider, *Synthesis,* **2011,** *2011*, 4050-4058.
50Q. Wang; M. van Gemmeren; B. List, *Angew. Chem. Int. Ed.,* **2014,** *53*, 13592-5.
51A. Salvador González; R. Gómez Arrayás; M. Rodríguez Rivero; J. C. Carretero, *Org. Lett.,* **2008,** *10*, 4335-4337.
52Q. Zhang; Y. Hui; X. Zhou; L. Lin; X. Liu; X. Feng, *Adv. Synth. Catal.,* **2010,** *352*, 976-980.
53C.-L. Gu; L. Liu; D. Wang; Y.-J. Chen, *J. Org. Chem.,* **2009,** *74*, 5754-5757.
54(a) P. Nuclear; D. Sommit; N. Boonyuen; K. Pudhom, *Chemical & pharmaceutical bulletin,* **2010,** *58*, 1221-3; (b) Y.-F. Liu; S.-Y. Cai; X.-M. Hao; F. Cao; H.-J. Zhu, *Chemistry of Natural Compounds,* **2018,** *54*, 402-404.
55A. Yamaguchi; S. Matsunaga; M. Shibasaki, *Org. Lett.,* **2008,** *10*, 2319-2322.
56Y.-L. Guo; J.-F. Bai; L. Peng; L.-L. Wang; L.-N. Jia; X.-Y. Luo; F. Tian; X.-Y. Xu; L.-X. Wang, *J. Org. Chem.,* **2012,** *77*, 8338-8343.
57Y. Guo; Y. Zhang; L. Qi; F. Tian; L. Wang, *RSC Advances,* **2014,** *4*, 27286-27289.
58B. Niess; K. A. Jørgensen, *Chemical Communications,* **2007**, 1620-1622.
59T.-Y. Liu; H.-L. Cui; J. Long; B.-J. Li; Y. Wu; L.-S. Ding; Y.-C. Chen, *J. Am. Chem. Soc.,* **2007,** *129*, 1878-1879.
60Q.-A. Chen; W. Zeng; D.-W. Wang; Y.-G. Zhou, *Synlett,* **2009,** *2009*, 2236-2241.
61X.-F. Xiong; Z.-J. Jia; W. Du; K. Jiang; T.-Y. Liu; Y.-C. Chen, *Chem. Commun.,* **2009**, 6994-6996.
62D. O'Hagan, *J. Fluorine Chem.,* **2010,** *131*, 1071-1081.
63R. Husmann; E. Sugiono; S. Mersmann; G. Raabe; M. Rueping; C. Bolm, *Org. Lett.,* **2011,** *13*, 1044-1047.
64J. P. Michael, *Natural Products Reports,* **2008,** *25*, 166-187.
65J. Achan; A. O. Talisuna; A. Erhart; A. Yeka; J. K. Tibenderana; F. N. Baliraine; P. J. Rosenthal; U. D'Alessandro, *Malaria journal,* **2011,** *10*, 144.
66M. E. Wall; M. C. Wani; C. E. Cook; K. H. Palmer; A. T. McPhail; G. A. Sim, *J. Am. Chem. Soc.,* **1966,** *88*, 3888-3890.
67N. B. Perry; J. W. Blunt; M. H. G. Munro; T. Higa; R. Sakai, *J. Org. Chem.,* **1988,** *53*, 4127-4128.
68G. M. Staub; J. B. Gloer; D. T. Wicklow; P. F. Dowd, *J. Am. Chem. Soc.,* **1992,** *114*, 1015-1017.
69(a) O. Afzal; S. Kumar; M. R. Haider; M. R. Ali; R. Kumar; M. Jaggi; S. Bawa, *European journal of medicinal chemistry,* **2015,** *97*, 871-910; (b) S. Singh; G. Kaur; V. Mangla; M. K. Gupta, *Journal of enzyme inhibition and medicinal chemistry,* **2015,** *30*, 492-504.
70(a) V. Sridharan; P. A. Suryavanshi; J. C. Menéndez, *Chem. Rev.,* **2011,** *111*, 7157-7259; (b) B. Nammalwar; R. A. Bunce, *Molecules,* **2014**, 204-232; (c) K.-i. Fujita; K. Yamamoto; R. Yamaguchi, *Org. Lett.,* **2002,** *4*, 2691-2694.
71R. A. Bunce; D. M. Herron; L. B. Johnson; S. V. Kotturi, *J. Org. Chem.,* **2001,** *66*, 2822-2827.
72S. Mitsunaga; T. Ohbayashi; S. Sugiyama; T. Saitou; M. Tadokoro; T. Satoh, *Tetrahedron: Asymmetry,* **2009,** *20*, 1697-1708.
73N. Gigant; I. Gillaizeau, *Org. Lett.,* **2012,** *14*, 4622-4625.

74(a) S. CRAMP, Mary; H. DYKE, Joan; T. PALLIN, David; R. ZAHLER, PARTIALLY SATURATED TRICYCLIC COMPOUNDS AND METHODS OF MAKING AND USING SAME, WO/2012/154676, 15/11/2012, **2012**; (b) T. HUGHES, E., METHODS OF TREATING LIVER DISEASES, WO/2014/071368, 08/05/2014, **2014**.
75J. L. Rogers; J. J. Ernat; H. Yung; R. S. Mohan, *Catal. Commun. ,* **2009**, 625.
76K. C. Nicolaou; D. J. Edmonds; P. G. Bulger, *Angew. Chem. Int. Ed.,* **2006,** *45*, 7134-7186.
77R. A. Bunce; T. Nago; N. Sonobe; L. M. Slaughter, *J. Het. Chem.,* **2008,** *45*, 551-557.
78R. A. Bunce; E. J. Lee, *J. Het. Chem.,* **2010,** *47*, 1176-1182.
79R. A. Bunce; D. M. Herron; M. L. Ackerman, *J. Org. Chem.,* **2000,** *65*, 2847-2850.
80L. S. Povarov, *Russian Chemical Reviews,* **1967,** *36*, 656-670.
81V. V. Kouznetsov, *Tetrahedron,* **2009,** *65*, 2721-2750.
82D. Bello; R. Ramón; R. Lavilla, *Current Organic Chemistry,* **2010,** *14*, 332-356.
83H. Liu; G. Dagousset; G. Masson; P. Retailleau; J. Zhu, *J. Am. Chem. Soc.,* **2009,** *131*, 4598-4599.
84F. Shi; G.-J. Xing; Z.-L. Tao; S.-W. Luo; S.-J. Tu; L.-Z. Gong, *J. Org. Chem.,* **2012,** *77*, 6970-6979.
85P. J. Stevenson; P. He; B. Daly, *Tetrahedron,* **2014,** *70*, 7350-7357.
86I. Muthukrishnan; V. Sridharan; J. C. Menéndez, *Chem. Rev.,* **2019,** *119*, 5057-5191.
87(a) A. S. K. Hashmi, *Accounts of Chemical Research,* **2014,** *47*, 864-876; (b) C. Obradors; A. M. Echavarren, *Accounts of Chemical Research,* **2014,** *47*, 902-912; (c) C. Obradors; A. M. Echavarren, *Chem. Commun.,* **2014,** *50*, 16-28.
88M. P. Muñoz, *Chem. Soc. Rev.,* **2014,** *43*, 3164-3183.
89A. Furstner; P. W. Davies, *Angew. Chem. Int. Ed.,* **2007,** *46*, 3410-49.
90(a) O. Kanno; W. Kuriyama; Z. J. Wang; F. D. Toste, *Angew. Chem. Int. Ed.,* **2011,** *50*, 9919-22; (b) H. Yamamoto; K. Futatsugi, *Angew. Chem. Int. Ed.,* **2005,** *44*, 1924-42.
91A. W. Sromek; M. Rubina; V. Gevorgyan, *J. Am. Chem. Soc.,* **2005,** *127*, 10500-1.
92P. Kothandaraman; S. J. Foo; P. W. H. Chan, *J. Org. Chem.,* **2009,** *74*, 5947-5952.
93Y.-L. Du; Y. Hu; Y.-F. Zhu; X.-F. Tu; Z.-Y. Han; L.-Z. Gong, *J. Org. Chem.,* **2015,** *80*, 4754-4759.
94V. V. Pagar, *Chem. Eur. J.,* **2014,** *20*, 10519-10526.
95J. Calleja; J. Calleja, *Chemical science (Cambridge),* **2014,** *5*, 996-1007.
96M. Ni; Y. Zhang; T. Gong; B. Feng, *Adv. Synth. Catal.,* **2017,** *359*, 824-831.
97J. Miro; C. Del Pozo, *Chem Rev,* **2016,** *116*, 11924-11966.
98V. A. Soloshonok; A. D. Kacharov; T. Hayashi, *Tetrahedron,* **1996,** *52*, 245-254.
99V. A. Soloshonok; A. D. Kacharov; D. V. Avilov; K. Ishikawa; N. Nagashima; T. Hayashi, *J. Org. Chem.,* **1997,** *62*, 3470-3479.
100T. Hayashi; E. Kishi; V. A. Soloshonok; Y. Uozumi, *Tetrahedron Lett.,* **1996,** *37*, 4969-4972.
101M. Schuler; F. Silva; C. Bobbio; A. Tessier; V. Gouverneur, *Angew. Chem. Int. Ed.,* **2008,** *47*, 7927-30.
102G. T. Giuffredi; B. Bernet; V. Gouverneur, *Eur. J. Org. Chem.,* **2011,** *2011*, 3825-3836.
103S. Fustero; I. Ibáñez; P. Barrio; M. A. Maestro; S. Catalán, *Org. Lett.,* **2013,** *15*, 832-835.
104T. Enomoto; A.-L. Girard; Y. Yasui; Y. Takemoto, *J. Org. Chem.,* **2009,** *74*, 9158-9164.
105M. Sánchez-Roselló; J. Miró; C. del Pozo; S. Fustero, *J. Fluorine Chem.,* **2015,** *171*, 60-66.
106(a) S. Preciado, *Angew. Chem. Int. Ed.,* **2012,** *51*, 6874-6877; (b) J. H. Lin; G. Zong; R. B. Du; J. C. Xiao; S. Liu, *Chemical communications (Cambridge, England),* **2012,** *48*, 7738-40; (c) C. Venkateswarlu; P. V. Balaji; K. De; B. Crousse; B. Figadère; J. Legros, *J. Fluorine Chem.,* **2013,** *152*, 94-98; (d) H. Yanai; H. Mimura; K. Kawada; T. Taguchi, *Tetrahedron,* **2007,** *63*, 2153-2160.
107G.-L. Xi; Z.-Q. Liu, *European journal of medicinal chemistry,* **2014,** *86*, 759-768.
108T. Akiyama; Y. Honma; J. Itoh; K. Fuchibe, *Adv. Synth. Catal.,* **2008,** *350*, 399-402.
109Y. Luo; C.-J. Li, *Chem. Commun.,* **2004**, 1930-1931.
110A. M. Jadhav; V. V. Pagar; R. S. Liu, *Angew. Chem. Int. Ed.,* **2012,** *51*, 11809-13.
111Y. Gong; K. Kato; H. Kimoto, *Synlett,* **2000,** *2000*, 1058-1060.
112J. Miró; M. Sánchez-Roselló; J. González; C. del Pozo; S. Fustero, *Chem. Eur. J.,* **2015,** *21*, 5459-5466.

113S. Fustero; J. Miró; M. Sánchez-Roselló; C. del Pozo, *Chem. Eur. J.,* **2014,** *20*, 14126-14131.
114Á. Sanz-Vidal; J. Miró; M. Sánchez-Roselló; C. del Pozo; S. Fustero, *J. Org. Chem.,* **2016,** *81*, 6515-6524.
115S. Fustero; P. Bello; J. Miro; M. Sanchez-Rosello; M. A. Maestro; J. Gonzalez; C. d. Pozo, *Chem. Commun.,* **2013,** *49*, 1336-1338.
116S. Fustero; V. Rodrigo; M. Sanchez-Rosello; F. Mojarrad; A. Vicedo; T. Moscardo; C. del Pozo, *J. Fluorine Chem.,* **2008,** *129*, 943-950.
117(a) H. Mimura; K. Kawada; T. Yamashita; T. Sakamoto; Y. Kikugawa, *J. Fluorine Chem.,* **2010,** *131*, 477-486; (b) A. Abouabdellah; J.-P. Bégué; D. Bonnet-Delpon; T. T. Thanh Nga, *J. Org. Chem.,* **1997,** *62*, 8826-8833.
118F. A. Carey; R. J. Sundberg, Advanced Organic Chemistry. 4th ed.; Kluwer: New York, **2000**; p 57.
119R. C. FusoN, *Chem. Rev.,* **1935,** *16*, 1-27.
120R. Wolffenstein, *Berichte der deutschen chemischen Gesellschaft,* **1895,** *28*, 2265-2269.
121(a) T. B. Poulsen; C. Alemparte; K. A. Jorgensen, *J. Am. Chem. Soc.,* **2005,** *127*, 11614-5; (b) D. Xue; Y. C. Chen; Q. W. Wang; L. F. Cun; J. Zhu; J. G. Deng, *Org. Lett.,* **2005,** *7*, 5293-5296.
122S. K. Tian; Y. Chen; J. Hang; L. Tang; P. McDaid; L. Deng, *Acc Chem Res,* **2004,** *37*, 621-31.
123J. Lu; F. Liu; T.-P. Loh, *Adv. Synth. Catal.,* **2008,** *350*, 1781-1784.
124J. Lu; F. Liu; W.-J. Zhou; T.-P. Loh, *Tetrahedron Lett.,* **2008,** *49*, 5389-5392.
125G. Bartoli; P. Melchiorre, *Synlett,* **2008,** *2008*, 1759-1772.
126X.-S. Wang; M.-M. Zhang; Q. Li; C.-S. Yao; S.-J. Tu, *Tetrahedron,* **2007,** *63*, 5265-5273.
127B. Lygo; B. Allbutt; S. R. James, *Tetrahedron Lett.,* **2003,** *44*, 5629-5632.
128J. R. Porter; J. F. Traverse; A. H. Hoveyda; M. L. Snapper, *J. Am. Chem. Soc.,* **2001,** *123*, 984-985.
129T. Hayashi; M. Ishigedani, *J. Am. Chem. Soc.,* **2000,** *122*, 976-977.
130H. Nakamura; K. Nakamura; Y. Yamamoto, *J. Am. Chem. Soc.,* **1998,** *120*, 4242-4243.
131R. A. Fernandes; A. Stimac; Y. Yamamoto, *J. Am. Chem. Soc.,* **2003,** *125*, 14133-14139.
132S. J. Patel; T. F. Jamison, *Angew. Chem. Int. Ed.,* **2004,** *43*, 3941-3944.
133(a) S. Kobayashi; R. Matsubara; Y. Nakamura; H. Kitagawa; M. Sugiura, *J. Am. Chem. Soc.,* **2003,** *125*, 2507-2515; (b) S. Kobayashi; R. Matsubara; H. Kitagawa, *Org. Lett.,* **2002,** *4*, 143-145; (c) Y. Nakamura; R. Matsubara; H. Kiyohara; S. Kobayashi, *Org. Lett.,* **2003,** *5*, 2481-2484.
134D. Uraguchi; K. Sorimachi; M. Terada, *J. Am. Chem. Soc.,* **2005,** *127*, 9360-9361.
135M. Yamanaka; J. Itoh; K. Fuchibe; T. Akiyama, *J. Am. Chem. Soc.,* **2007,** *129*, 6756-6764.
136Q.-X. Guo; H. Liu; C. Guo; S.-W. Luo; Y. Gu; L.-Z. Gong, *J. Am. Chem. Soc.,* **2007,** *129*, 3790-3791.
137T. P. Yoon; E. N. Jacobsen, *Angew. Chem. Int. Ed.,* **2005,** *44*, 466-468.
138T. Akiyama; Y. Tamura; J. Itoh; H. Morita; K. Fuchibe, *Synlett,* **2006,** *2006*, 0141-0143.
139T. Ooi; M. Kameda; J.-i. Fujii; K. Maruoka, *Org. Lett.,* **2004,** *6*, 2397-2399.
140J. Zhang; G. Zhao, *Tetrahedron,* **2019,** *75*, 1697-1705.
141N. R. Patel; C. B. Kelly; A. P. Siegenfeld; G. A. Molander, *ACS Catal.,* **2017,** *7*, 1766-1770.
142L. Wu; C. Xie; H. Mei; V. A. Soloshonok; J. Han; Y. Pan, *Organic & Biomolecular Chemistry,* **2014,** *12*, 4620-4627.
143C. Xie; H. Mei; L. Wu; V. A. Soloshonok; J. Han; Y. Pan, *RSC Advances,* **2014,** *4*, 4763-4768.
144Y. Dai; C. Xie; L. Wu; H. Mei; V. A. Soloshonok; J. Han; Y. Pan, *RSC Advances,* **2015,** *5*, 3491-3497.
145(a) D. M. Sedgwick; P. Barrio; A. Simón; R. Román; S. Fustero, *J. Org. Chem.,* **2016,** *81*, 8876-8887; (b) L. Wu; C. Xie; H. Mei; V. A. Soloshonok; J. Han; Y. Pan, *J. Org. Chem.,* **2014,** *79*, 7677-7681; (c) H. Mei; Y. Xiong; C. Xie; V. A. Soloshonok; J. Han; Y. Pan, *Organic & Biomolecular Chemistry,* **2014,** *12*, 2108-2113.
146(a) P. Qian; Y. Dai; H. Mei; V. A. Soloshonok; J. Han; Y. Pan, *RSC Advances,* **2015,** *5*, 26811-26814; (b) Y. Dai; C. Xie; H. Mei; J. Han; V. A. Soloshonok; Y. Pan, *Tetrahedron,* **2015,** *71*, 9550-9556.

147E. E. Ferrandi; D. Monti, *World Journal of Microbiology and Biotechnology,* **2017,** *34*, 13.

148(a) V. A. Soloshonok; V. P. Kukhar, *Tetrahedron,* **1997,** *53*, 8307-8314; (b) V. A. Soloshonok; D. V. Avilov; V. P. Kukhar; L. Van Meervelt; N. Mischenko, *Tetrahedron Lett.,* **1997,** *38*, 4903-4904.

149N. C. Yoder; K. Kumar, *Chem. Soc. Rev.,* **2002,** *31*, 335-341.

150M. Schlosser, *Angew. Chem. Int. Ed.,* **1998,** *37*, 1496-1513.

151G. Resnati, *Tetrahedron,* **1993,** *49*, 9385-9445.

152J. T. Welch; S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*. Wiley: New York, **1991**.

153A. Jose Luis; S.-F. Antonio; F. Santos, *Current Organic Chemistry,* **2010,** *14*, 928-949.

154J. Y. Gauthier; N. Chauret; W. Cromlish; S. Desmarais; L. T. Duong; J.-P. Falgueyret; D. B. Kimmel; S. Lamontagne; S. Léger; T. LeRiche; C. S. Li; F. Massé; D. J. McKay; D. A. Nicoll-Griffith; R. M. Oballa; J. T. Palmer; M. D. Percival; D. Riendeau; J. Robichaud; G. A. Rodan; S. B. Rodan; C. Seto; M. Thérien; V.-L. Truong; M. C. Venuti; G. Wesolowski; R. N. Young; R. Zamboni; W. C. Black, *Bioor. Med. Chem. Let.,* **2008,** *18*, 923-928.

155Y. Liu; J. Liu; Y. Huang; F.-L. Qing, *Chem. Commun.,* **2013,** *49*, 7492-7494.

156Y. Liu; Y. Yang; Y. Huang; X.-H. Xu; F.-L. Qing, *Synlett,* **2015,** *26*, 67-72.

157J.-W. Xie; L. Yue; D. Xue; X.-L. Ma; Y.-C. Chen; Y. Wu; J. Zhu; J.-G. Deng, *Chem. Commun.,* **2006**, 1563-1565.

158Á. Sanz-Vidal; J. Torres; V. A. Soloshonok; Y. Zhu; J. Han; S. Fustero; C. del Pozo, *Adv. Synth. Catal.,* **2018,** *360*, 366-373.

159(a) C. Xie; L. Zhang; H. Mei; J. Han; V. A. Soloshonok; Y. Pan, *ChemistrySelect,* **2016,** *1*, 4435-4439; (b) C. Xie; H. Mei; L. Wu; J. Han; V. A. Soloshonok; Y. Pan, *J. Fluorine Chem.,* **2014,** *165*, 67-75.

160D. Xue; Y.-C. Chen; X. Cui; Q.-W. Wang; J. Zhu; J.-G. Deng, *J. Org. Chem.,* **2005,** *70*, 3584-3591.

161T.-R. Kang; J.-W. Xie; W. Du; X. Feng; Y.-C. Chen, *Organic & Biomolecular Chemistry,* **2008,** *6*, 2673-2675.

162(a) A. V. Kel'in; A. W. Sromek; V. Gevorgyan, *J. Am. Chem. Soc.,* **2001,** *123*, 2074-2075; (b) J. R. Porter; W. G. Wirschun; K. W. Kuntz; M. L. Snapper; A. H. Hoveyda, *J. Am. Chem. Soc.,* **2000,** *122*, 2657-2658; (c) D. Berger; W. Imhof, *Tetrahedron,* **2000,** *56*, 2015-2023.

163M. Shimizu; A. Morita; T. Kaga, *Tetrahedron Lett.,* **1999,** *40*, 8401-8405.

164M. Shimizu; A. Takahashi; S. Kawai, *Org. Lett.,* **2006,** *8*, 3585-3587.

165(a) O. Iwao; I. Shin-ichi; N. Kimiyo; N. Yoichiro, *Chemistry Letters,* **1975,** *4*, 331-334; (b) A. Strecker, *Justus Liebigs Annalen der Chemie,* **1850,** *75*, 27-45.

166S. Makoto; K. Makiko; H. Iwao, *Chemistry Letters,* **2003,** *32*, 606-607.

167S. Makoto; K. Makiko; H. Iwao, *Chemistry Letters,* **2005,** *34*, 1456-1457.

168S. Makoto; Y. Chiaki; O. Toshiki, *Chemistry Letters* **2004,** *33*, 606-607.

169(a) Z.-J. Liu; J.-T. Liu, *Chem. Commun.,* **2008**, 5233-5235; (b) J. Liu; J. Hu, *Chem. Eur. J.,* **2010,** *16*, 11443-11454; (c) M. Kawatsura; S. Terasaki; M. Minakawa; T. Hirakawa; K. Ikeda; T. Itoh, *Org. Lett.,* **2014,** *16*, 2442-2445.

170P. Liu; Z.-J. Liu; F. Wu, *Adv. Synth. Catal.,* **2015,** *357*, 818-822.

171(a) T. H. Babu; K. Karthik; P. T. Perumal, *Synlett,* **2010,** *2010*, 1128-1132; (b) T. Hari Babu; A. Abragam Joseph; D. Muralidharan; P. T. Perumal, *Tetrahedron Lett.,* **2010,** *51*, 994-996.

172B. Yu; P. P. Qi; X. J. Shi; L. H. Shan; D. Q. Yu; H. M. Liu, *Steroids,* **2014,** *88*, 44-52.

173A. R. Trivedi; J. M. Desai; B. H. Dholariya; D. K. Dodiya; V. H. Shah, *Med. Chem. Research,* **2012,** *21*, 1471-1479.

174W.-Y. Chen; X.-S. Li, *Catal. Commun.,* **2009,** *10*, 549-551.

175(a) H.-L. Cui; Y.-C. Chen, *Chem. Commun.,* **2009**, 4479-4486; (b) L. Battistini; C. Curti; G. Rassu; A. Sartori; F. Zanardi, *Synthesis,* **2017,** *49*, 2297-2336.

176S.-L. Cui; X.-F. Lin; Y.-G. Wang, *J. Org. Chem.,* **2005,** *70*, 2866-2869.

177D. Xue; J. Li; Z.-T. Zhang; J.-G. Deng, *J. Org. Chem.,* **2007,** *72*, 5443-5445.

178C. G. Yan; X. K. Song; Q. F. Wang; J. Sun; U. Siemeling; C. Bruhn, *Chem. Commun.,* **2008**, 1440-1442.

179E. Yamuna; M. Zeller; K. J. R. Prasad, *Tetrahedron Lett.,* **2011,** *52*, 1649-1652.

180C. D. Murphy; C. Schaffrath; D. O'Hagan, *Chemosphere,* **2003,** *52*, 455-61.

181(a) K. Müller; H.-J. Böhm, *Chemistry & Biology,* **2009,** *16*, 1130-1131; (b) A. Vulpetti; C. Dalvit, *Drug discovery today,* **2012,** *17*, 890-7.

182A. Mullard, *Nature Reviews Drug Discovery,* **2013,** *12*, 87-90.

183A. Studer, *Angew. Chem. Int. Ed.,* **2012,** *51*, 8950-8958.

184(a) K. Uneyama, *Organofluorine Chemistry*. Blackwell: Oxford, U.K., **2006**; (b) S. Daniels; S. F. M. Tohid; W. Velanguparackel; A. D. Westwell, *Expert Opinion on Drug Discovery,* **2010,** *5*, 291-304.

185F. Swarts, *Bull. Acad. R. Belg. ,* **1898,** *35*, 375.

186Y. Kobayashi; I. Kumadaki, *Tetrahedron Lett.,* **1969,** *10*, 4095-4096.

187V. C. R. McLoughlin; J. Thrower, *Tetrahedron,* **1969,** *25*, 5921-5940.

188J. M. S. Paratian, S.; Périchon, J., *J. Chem. Soc., Perkin Trans.,* **1992,** *1*, 53-56.

189M. M. Kremlev; A. I. Mushta; W. Tyrra; Y. L. Yagupolskii; D. Naumann; M. Schäfer, *Dalton Transactions,* **2015,** *44*, 19693-19699.

190I. A. Sanhueza; M. C. Nielsen; M. Ottiger; F. Schoenebeck, *Helvetica Chimica Acta,* **2012,** *95*, 2231-2236.

191M. Oishi; H. Kondo; H. Amii, *Chem. Commun.,* **2009**, 1909-1911.

192Z. Gonda; S. Kovács; C. Wéber; T. Gáti; A. Mészáros; A. Kotschy; Z. Novák, *Org. Lett.,* **2014,** *16*, 4268-4271.

193C. Galli, *Chem. Rev.,* **1988,** *88*, 765-792.

194J.-J. Dai; C. Fang; B. Xiao; J. Yi; J. Xu; Z.-J. Liu; X. Lu; L. Liu; Y. Fu, *J. Am. Chem. Soc.,* **2013,** *135*, 8436-8439.

195Y. Ye; M. S. Sanford, *J. Am. Chem. Soc.,* **2012,** *134*, 9034-9037.

196A. B. Cowell; C. Tamborski, *J. Fluorine Chem.,* **1981,** *17*, 345-356.

197D. Naumann; J. Kischkewitz, *J. Fluorine Chem.,* **1990,** *47*, 283-299.

198M. Tordeux; B. Langlois; C. Wakselman, *Journal of the Chemical Society, Perkin Transactions 1,* **1990**, 2293-2299.

199T. Akiyama; K. Kato; M. Kajitani; Y. Sakaguchi; J. Nakamura; H. Hayashi; A. Sugimori, *Bulletin of the Chemical Society of Japan,* **1988,** *61*, 3531-3537.

200Y. Ye; S. H. Lee; M. S. Sanford, *Org. Lett.,* **2011,** *13*, 5464-5467.

201I. S. Kondratov; N. A. Tolmachova; G. Haufe, *Eur. J. Org. Chem.,* **2018,** *2018*, 3618-3647.

202O. V. Zatolochnaya; V. Gevorgyan, *Org. Lett.,* **2013,** *15*, 2562-2565.

203(a) F. Peng; Q. Zhao; W. Huang; S.-J. Liu; Y.-J. Zhong; Q. Mao; N. Zhang; G. He; B. Han, *Green Chemistry,* **2019,** *21*, 6179-6186; (b) Y.-L. Ji; X.-H. He; G. Li; Y.-Y. Ai; H.-P. Li; C. Peng; B. Han, *Org. Chem. Front.,* **2020,** *7*, 563-570.

204(a) L. G. Borrego; R. Recio; M. Alcarranza; N. Khiar; I. Fernández, *Adv. Synth. Catal.,* **2018,** *360*, 1273-1279; (b) D. Enders; K. Gottfried; G. Raabe, *Adv. Synth. Catal.,* **2010,** *352*, 3147-3152.
