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Novel Stereoselective Intramolecular Processes for the Generation of New Molecular Entities

Tesis Doctoral

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Valencia, Julio 2019

Fdo. Santos Fustero Lardiés

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„Nimmt man von den einflußreichsten wissenschaftlichen Leistungen der größten Männer die Gedanken hinweg, die sie von anderen hatten, so bleibt für sie immer etwas übrig, was die anderen nicht hatten, in der Regel nur ein kleines Stückchen von einem neuen Gedanken, aber dies macht eben schon den großen Mann."

[If, from the most influential contributions of the greatest scientists, one takes away the thoughts that they in turn took from others, there is always something left that the others did not think about, generally a small part of a new idea, which is precisely what makes a man great.]

Justus Freiherr von Liebig (1803-1873), German chemist

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Resumen

La Química Orgánica, además de constituir una fuente inagotable de fascinación académica por su capacidad de generar un número virtualmente infinito de nuevas estructuras moleculares, ha proporcionado una poderosa herramienta, el cribado de librerías de moléculas orgánicas, en el ámbito de la química biológica/médica y el descubrimiento de fármacos que se ha convertido en el caballo de batalla en la identificación de nuevas dianas terapéuticas y sus correspondientes moduladores y potenciales fármacos, con un impacto directo sobre la salud humana. La principal problemática de estas librerías es el aspecto de la diversidad estructural, ya que la probabilidad de dar con un fármaco candidato es mayor cuanto mayor sea la variabilidad de los núcleos estructurales (en inglés, *scaffold*, literalmente "andamio"), puesto que a día de hoy la posibilidad real de diseñar de forma racional un fármaco es una quimera, más aún teniendo en cuenta que normalmente se desconoce la diana terapéutica. De hecho, éste es el motivo del fracaso del Cribado de Alto Rendimiento (*High-Throughput Screening*), una metodología muy popular en los años 90 en la industria farmacéutica basada en la química combinatoria. En aproximaciones posteriores como la Síntesis Orientada a la Diversidad (DOS, Schreiber) o la Síntesis Orientada a la Biología (BIOS, Waldmann), se trató de generar librerías con una mayor diversidad (y complejidad) molecular.

La presente tesis doctoral, dentro de los límites de tiempo y recursos que implican el trabajo de 4 años de un estudiante de doctorado, aborda esta problemática, si bien de un modo secundario ya que la prioridad es el estudio de las reacciones que se especificarán más abajo y de su alcance, cuyo hilo conductor es el carácter intramolecular de las mismas. Sin embargo, se espera que este trabajo al menos deje constancia del potencial de las reacciones intramoleculares en la generación de diversidad y complejidad estructural molecular en forma de nuevas entidades moleculares (NME). Como el lector se percatará rápidamente, las reacciones estudiadas pueden dividirse en dos grandes bloques temáticos: reacciones de cicloadición 1,3-dipolar intramolecular con sustratos fluorados (Capítulos 1 y 2) y reacciones tándem intramoleculares organocatalizadas

(Capítulo 3). En todos los casos, estas reacciones intramoleculares son capaces de generar productos de relativa complejidad, puesto que se trata siempre de policiclos con uno o varios estereocentros.

En atención a la estructura de los capítulos, cada uno se abre con una breve introducción que cubre los aspectos generales relativos al tipo de reacción o sustratos/productos estudiados así como los antecedentes bibliográficos más relevantes y directos del presente trabajo. Sigue la presentación y discusión de los resultados experimentales y finalmente se aporta la caracterización de todos los compuestos nuevos en la sección experimental. Adicionalmente, en los Capítulos 1 y 2, se añade una sección especial dedicada a la presentación y análisis de los estudios computacionales realizados para las correspondientes reacciones, que permiten estudiar desde un punto de vista teórico los resultados obtenidos experimentalmente.

Capítulo 1: Cicloadición 1,3-dipolar intramolecular de nitronas de α-trifluorometil estirenos

Las cicloadiciones 1,3-dipolares constituyen una herramienta sintética sin parangón en la preparación de heterociclos de 5 miembros que ha encontrado aplicación en diversas subdisciplinas de la Química Orgánica, como son la síntesis de productos naturales, la química biológica o la ciencia de los materiales. La reacción implica a un 1,3-dipolo (una molécula en la que 3 átomos comparten 4 electrones de tipo π) y un dipolarófilo, generalmente un alqueno o alquino. El mecanismo ampliamente aceptado es de tipo Hückel (4π+2π), concertado y asincrónico. El carácter concertado de la reacción se traduce en su estereoespecificidad, que supone la retención de configuración de los sustituyentes del dipolarófilo. Además, se pueden imaginar dos regioisómeros según la aproximación de dipolo y dipolarófilo y dos diastereoisómeros de cada uno de ellos según la disposición de los sustituyentes del dipolarófilo con respecto al dipolo (productos *exo* y *endo*, empleando la nomenclatura de las reacciones Diels-Alder).

Por su fácil preparación (frecuentemente por condensación de un compuesto carbonílico con una hidroxilamina) y su relativa estabilidad, las nitronas son los dipolos más ampliamente empleados. Su reacción con alquenos da lugar a isoxazolidinas que son interesantes intermedios de síntesis de 1,3-aminoalcoholes, a su vez precursores de β-aminoácidos y β-lactamas. Debido al factor entrópico, en la cicloadición intramolecular de nitronas se minimizan los problemas de regio- y diastereoselectividad que sí pueden estar presentes en las correspondientes reacciones intermoleculares. Sus energías de activación más bajas permiten trabajar a temperaturas menores o emplear dipolarófilos menos reactivos, como olefinas no activadas, al tiempo que la menor libertad conformacional resulta en un aumento de la estereoselectividad del proceso. Se trata de una reacción muy interesante para la preparación de isoxazolidinas con hasta tres estereocentros con una elevada selectividad. En el caso más frecuente de este tipo de reacciones, la nitrona y el alqueno están unidos por una cadena que termina en el carbono azometínico de la nitrona, y se pueden plantear dos regioisómeros: uno con los anillos fusionados y el otro con un puente. A su vez son posibles dos aproximaciones, *exo* y *endo*, aunque habitualmente se suele obtener un único o un número limitado de isómeros como consecuencia de las restricciones estéricas.

A modo de ilustración del potencial de las reacciones de cicloadición intramolecular de nitronas, se incluyen en la introducción de este capítulo una serie de ejemplos seleccionados desde las primeras reacciones en los años 60 hasta la actualidad. Muy frecuentemente, se trata de reacciones asimétricas, puesto que los precursores de nitronas empleados son quirales no racémicos, generalmente derivados de aminoácidos y azúcares. Además, en la literatura pueden encontrarse muchos ejemplos de reacciones intermoleculares de nitronas por catálisis enantioselectiva, tanto en la variante metálica como en la organocatalítica. Sin embargo, la versión intramolecular aún supone un desafío puesto que las condiciones en las que se ha de generar la nitrona *in situ* suelen ser incompatibles con los catalizadores asimétricos más habituales para estas transformaciones, lo cual resulta en productos racémicos y/o en el envenenamiento del catalizador. Una estrategia que permite sortear este problema

consiste en la funcionalización organocatalítica del precursor de la nitrona seguido de la reacción de cicloadición intramolecular en una segunda operación. La α-funcionalización de aldehídos con aceptores de Michael, el caso más frecuente con diferencia, emplea la catálisis enamínica con aminas secundarias quirales del tipo Jørgensen-Hayashi o MacMillan. Los precedentes bibliográficos más directos en este sentido se recogen de forma exhaustiva en la introducción de este primer capítulo.

Los Capítulos 1 y 2 se inscriben en el marco de la síntesis de compuestos organofluorados, cuyas posibilidades sobre todo en ciencias de la vida (química médica y agroquímica) han sido ampliamente explotadas en las últimas décadas. El efecto de la sustitución hidrógeno/flúor sobre las propiedades físico-químicas y biológicas de las moléculas orgánicas es un fenómeno bien estudiado que se atribuye principalmente a la elevada electronegatividad, pequeño tamaño y escasa polarizabilidad del átomo de flúor así como a la elevada energía del enlace C-F. Estas características confieren a los fármacos fluorados una mayor estabilidad metabólica y potencia. Además su mayor lipofilia se traduce en una mayor biodisponibilidad para la clase de dianas terapéuticas tratadas.

El interés por los compuestos orgánicos fluorados llevó al desarrollo de distintas metodologías basadas, por un lado, en los agentes de fluoración (y trifluorometilación) y, por otro lado, en el uso de sintones o *building blocks* fluorados. A este último caso se ha de asociar la presente tesis doctoral, y se trata del uso y transformación de sustratos de partida fluorados de bajo peso molecular y fácil disponibilidad, muy frecuentemente en condiciones de reacción concretas y muchas veces distintas de las que serían válidas para los correspondientes compuestos no fluorados. Entre todos los grupos fluorados, el grupo trifluorometilo (CF_3) reviste una particular importancia debido a su amplia incidencia en los principios activos y pesticidas fluorados. Además, el desarrollo de metodologías sintéticas que permiten la creación de estereocentros que soportan un grupo trifluorometilo es aún hoy un reto en síntesis orgánica. En este contexto, las reacciones de cicloadición 1,3-dipolar intramolecular con sustratos fluorados han sido escasamente exploradas (en la introducción se detallan todos los antecedentes directos), pese a que los productos accesibles a través de ellas son de

alto interés. Así, la correspondiente reacción con nitronas daría lugar a isoxazolidinas fluoradas, precursores de los correspondientes 1,3-amino alcoholes y β-aminoácidos fluorados.

- *Parte A: Papel del grupo trifluorometilo en la regioselectividad de las reacciones de cicloadición intramolecular de nitronas*

En esta primera parte, el objetivo es el estudio de la reactividad de α-trifluorometilestirenos como nuevos dipolarófilos en reacciones de cicloadición intramolecular de nitronas, con un especial énfasis en el papel que juega el grupo trifluorometilo en la distribución de regioisómeros de la reacción. Para ello se combinan un estudio experimental con cálculos computacionales complementarios.

El primer paso consiste en la preparación de los correspondientes sustratos de partida, lo cual requiere la instalación de un grupo α-trifluoropropenilo en un anillo aromático sustituido en posición *orto* con una cadena que soporta un aldehído en posición remota. La metodología empleada ya había sido desarrollada en nuestro grupo de investigación con anterioridad para sustratos similares. Con esto sustratos de partida (de baja estabilidad y que han de ser tratados rápidamente con la correspondiente *N*-alquilhidroxilamina en la siguiente etapa) se procede a la optimización de las condiciones de la reacción de cicloadición, siendo las más adecuadas en términos de rendimiento y distribución de regioisómeros el calentamiento en tolueno por radiación de microondas. El estudio del alcance de la reacción revela que el regioisómero fusionado es el producto que se forma preferentemente en la reacción. Es más, cuando los sustituyentes en el anillo aromático del precursor de la nitrona son grupos dadores, se obtiene de forma exclusiva. En general, los rendimientos globales, suma de los dos regioisómeros, son de moderados a buenos.

Llegado este punto, se estudia el papel del grupo trifluorometilo en la regioselectividad. En primer lugar se sintetizan dos derivados no fluorados y se someten a las mismas condiciones de cicloadición anteriores. El resultado es la

obtención exclusiva de los correspondientes regioisómeros puenteados. Por tanto, es evidente que el flúor es capaz de invertir la tendencia de la regioselectividad, de forma completa incluso con sustituyentes electrón-dadores. Un estudio computacional por DFT, llevado a cabo en nuestro grupo de investigación, confirma las tendencias observadas. En la distribución de regioisómeros operan distintos factores estereoelectrónicos que se oponen entre sí. Así, el grupo trifluorometilo favorece la formación del producto fusionado por factores estéricos, aunque electrónicamente lo contrario (la formación del regioisómero puenteado) esté más favorecido. Además, la presencia de grupos dadores en el anillo aromático favorece también desde el punto de vista electrónico la obtención del regioisómero fusionado.

Finalmente, una selección de isoxazolidinas fusionadas y puenteadas se abrieron en condiciones reductoras para dar lugar a los correspondientes 1,3-amino alcoholes fluorados.

- *Parte B: Síntesis organocatalítica enantioselectiva de derivados de tetralina fluorados mediante una secuencia reacción (hetero-)Michael/cicloadición intramolecular de nitronas*

El siguiente paso en el desarrollo de esta metodología es el estudio de una versión enantioselectiva de la misma que permita obtener derivados fluorados de tetralina (1,2,3,4-tetrahidronaftaleno) enantioméricamente puros. La estrategia más evidente y que requiere la menor modificación de los sustratos de la Parte A es el uso de una hidroxilamina quiral en el paso de cicloadición. Sin embargo, esta aproximación diastereoselectiva empleando hidroxilaminas con un estereocentro definido (comercialmente accesibles o preparadas en el laboratorio) da lugar a una baja relación diastereomérica en el caso de los sustratos diseñados en el apartado anterior. La siguiente estrategia que se intenta es la α-alquilación de los mismos sustratos mediante aminas secundarias quirales del tipo Jørgensen-Hayashi. El problema en este caso es encontrar un agente de alquilación adecuado, con la reactividad suficiente y que asegure altos niveles de diastereo- y enantioselectividad en los productos finales. Como esta estrategia no da frutos, se

opta por una tercera que exige en este caso la modificación de los sustratos de partida, pero que en sí misma representa una novedad en la literatura sobre estas secuencias sintéticas que combinan organocatálisis y cicloadiciones 1,3-dipolares.

De forma análoga a la Parte A, se preparan los cinamaldehídos fluorados necesarios para esta aproximación, en la que una reacción de Michael precede a la ciclación por cicloadición intramolecular de nitronas. La optimización de la reacción requiere un cribado previo de nucleófilos para la misma. La *orto*-sustitución con el grupo α-trifluoropropenilo, un grupo muy voluminoso estéricamente, bloquea el ataque de los nucleófilos a la posición β de los enales, por lo que encontrar el nucleófilo adecuado requiere un trabajo extenso. Afortunadamente se encuentra que el nitrometano, una molécula de tamaño relativamente pequeño, es un nucleófilo adecuado para esta transformación. Ajustando las condiciones de reacción para la primera etapa organocatalítica, en particular la identidad del catalizador y la temperatura, y aprovechando las condiciones de reacción desarrolladas en la Parte A para la cicloadición intramolecular, se optimiza la secuencia sintética que, a continuación, se aplica a todos los sustratos de partida preparados. De esta forma, se obtiene una primera familia de tetralinas fluoradas con rendimientos moderados (pero en dos etapas de reacción) y excelentes enantioselectividades en general. Además se ha de mencionar que, respecto a la Parte A, en este caso se obtiene un único regioisómero (el fusionado), aunque en forma de dos diastereoisómeros con relaciones diastereoisoméricas de bajas a moderadas siendo ambos diastereoisómeros separables por columna cromatográfica.

El segundo nucleófilo que se encuentra para esta transformación es una hidroxilamina que, en la primera etapa de la secuencia sintética, da lugar a una reacción tándem aza-Michael/formación de hemiacetal que es la razón del éxito de este nucleófilo. De nuevo, se ajustan las condiciones de reacción (catalizador, disolvente, temperatura) y se aplican a los mismos sustratos de partida anteriores, de forma que se obtiene una segunda familia de tetralinas fluoradas con rendimientos moderados, altas enantioselectividades y moderadas diastereoselectividades. Curiosamente, al observar la estructura de rayos X de un

cristal de un representante de cada familia de derivados, se observa que el diastereoisómero mayoritario tiene una configuración absoluta opuesta.

De nuevo, se lleva a cabo un estudio computacional complementario (DFT), aunque esta vez en colaboración con el profesor Pedro Merino de la Universidad de Zaragoza. Se calculan las energías para las distintas aproximaciones posibles entre nitrona y dipolarófilo para las dos familias de tetralinas fluoradas. La conclusión es que la inversión de la selectividad facial que da lugar al diastereoisómero opuesto en cada familia se debe a la interacción no covalente entre el *N*-hidroxilo y el protón azometínico de la nitrona en la segunda familia de tetralinas.

Finalmente, una selección de cicloaductos de cada familia se someten a condiciones de hidrogenación para obtener los correspondientes diamino alcoholes fluorados.

Capítulo 2: Síntesis asimétrica de derivados policíclicos de 3-fluoroalquilprolinas mediante cicloadición intramolecular de iluros de azometino

El segundo capítulo de la presente tesis doctoral se centra en el desarrollo de una nueva metodología basada en reacciones de cicloadición 1,3-dipolar intramolecular de nuevo con dipolarófilos fluorados, pero en este caso con iluros de azometino como dipolos. Se trata del segundo tipo de dipolo más empleado en síntesis orgánica y su uso se ha establecido como una estrategia sintética muy útil para la construcción de pirrolidinas, pirrolinas y pirroles. Si el dipolarófilo es un alqueno, se pueden formar pirrolidinas con un máximo de cuatro estereocentros. Las pirrolidinas, aisladas o fusionadas, son estructuras presentes en un gran número de compuestos biológicamente activos, particularmente en alcaloides. De entre todos los métodos de generación de iluros de azometino destaca la condensación de aldehídos con α-amino ácidos o ésteres. (En el primer caso, el iluro de azometino se forma por descarboxilación.) Esta estrategia se conoce de forma general como la ruta del iminio.

En cuanto a la cicloadición intramolecular de iluros de azometino, se pueden dar dos casos respecto a la forma en que dipolo y dipolarófilo se unen. O bien la cadena espaciadora está unida al carbono azometínico del iluro (en cuyo caso se pueden formar un regioisómero fusionado y otro puenteado, mucho menos frecuente) o lo está al nitrógeno del dipolo (con lo que los dos posibles regioisómeros son puenteados). Como consecuencia de la restricción conformacional impuesta por el carácter intramolecular de la reacción, se suelen obtener altos niveles de regio- y diastereoselectividad. Como en el Capítulo 1, en la introducción del presente capítulo se incluye sólo una selección de ejemplos representativos de esta metodología, ya que se trata de una herramienta ya muy establecida en el repertorio de la síntesis orgánica y la literatura es muy extensa.

La versión asimétrica de esta clase de reacciones suele ir asociada al uso de auxiliares o sustratos de partida quirales. Si bien la cicloadición 1,3-dipolar de iluros de azometino ha sido ampliamente desarrollada de forma catalítica enantioselectiva en su versión intermolecular, sólo se conocen tres ejemplos de este tipo en la literatura de la versión intramolecular. Observando detalladamente la estructura de los sustratos de partida empleados en las reacciones catalíticas mencionadas, se observa que los dipolarófilos implicados son olefinas activadas (acrilatos, enonas, nitroalquenos, etc.). Por su parte, aquellas reacciones que hacen uso de sustratos o auxiliares quirales requieren condiciones de reacción más vigorosas, pero admiten la participación de dipolarófilos menos reactivos, como es el caso de los trifluorometil alquenos que se emplean en este capítulo.

El empleo de morfolinonas derivadas de glicina y un 1,2-amino alcohol quiral permite acceder de forma efectiva a estructuras que contengan una pirrolidina con varios estereocentros. Generalmente mediante una segunda etapa de hidrogenación, el auxiliar quiral (o más bien “plantilla”, ya que solamente se recupera una parte del precursor del iluro de azometino) puede eliminarse del cicloaducto.

Además de las consideraciones del Capítulo 1 en cuanto a química de compuestos organofluorados, hay que destacar en el contexto del capítulo 2 la importancia de los aminoácidos fluorados en química médica. La presencia de

flúor es esencial en muchos fármacos basados en péptidos y en modificación de proteínas, puesto que modulan extraordinariamente su lipofilia, estabilidad metabólica y conformación. Se ha estudiado en profundidad como la sustitución hidrógeno-flúor afecta a la estructura secundaria y al plegamiento de proteínas o a las interacciones entre éstas.

Por su parte, los derivados fluorados de prolina se han empleado para estudiar la estrutura de péptidos y proteínas, su dinámica y las interacciones entre péptidos y receptores. De entre los 20 aminoácidos naturales, la prolina es un caso particular puesto que es el único aminoácido cíclico y aporta rigidez conformacional a los péptidos y proteínas que la contienen. La sustitución con flúor en el anillo de prolina permite modular esta rigidez y proporciona una alternativa técnica adicional (la resonancia magnética nuclear de flúor 19) para el estudio de péptidos y proteínas. Todo ello justifica el interés por disponer de metodologías sintéticas que permitan acceder a derivados fluorados de prolina.

Si en el Capítulo 1 los antecedentes de cicloadición intramolecular de nitronas en sustratos fluorados eran escasos, en el caso de los iluros de azometino sólo se conoce un caso de un dipolarófilo fluorado en este tipo de reacciones, y se trata de una síntesis racémica. La exploración de nuevos dipolarófilos fluorados en esta clase de reacciones, haciendo uso de precursores de iluros de azometino quirales, es justamente el objetivo de este capítulo.

El primer paso en este trabajo consiste en el diseño y síntesis de los sustratos de partida. El esqueleto de salicilaldehído se elige porque se conoce que los benzadehídos son buenos compuestos carbonílicos para la generación de los correspondientes iluros de azometino y al mismo tiempo el grupo hidroxilo permite unir de forma sencilla (mediante una reacción de sustitución nucleofílica) el dipolarófilo al aldehído. Como dipolarófilo en este capítulo se emplea el grupo 4,4,4-trifluoro-2-butenilo (unido al grupo hidroxilo del salicilaldehído). La metodología empleada permite acceder a análogos con distintos grupos fluorados y derivados de nitrógeno o azufre en lugar de saliciladehídos.

Una vez sintetizados los sustratos de partida, se optimiza la reacción probando, como precursores de iluros de azometino, morfolinonas derivadas de

distintos 1,2-amino alcoholes quirales. El derivado de (1*S*,2*R*)-*cis*-1-amino-2-indanol da el mayor exceso diastereomérico y un posterior ajuste de las condiciones de reacción permite obtener un buen rendimiento y una excelente diastereoselectividad. Habiendo establecido las condiciones de reacción óptimas se estudia el alcance de la reacción aplicándolas a todos los sustratos de partida sintetizados anteriormente. En general, los rendimientos son buenos y las diastereoselectividades excelentes, en particular en el caso de los derivados nitrogenados. Hay que destacar que se pueden obtener los correspondientes cicloaductos con distintos grupos fluorados (CF_2H, CH_2F, C_2F_5) además del grupo trifluorometilo. Además, se ha de destacar que cuanto mayor es el número de átomos de flúor en el sustituyente, mayor es la diastereoselectividad observada, lo cual apunta al papel del flúor en el control del curso de la reacción.

Adicionalmente, se sintetiza un derivado no fluorado (con un grupo metilo en lugar de trifluorometilo) y se somete a las condiciones de cicloadición optimizadas. El cicloaducto obtenido es una mezcla casi equimolar de tres diastereoisómeros con un rendimiento global más bajo que en los casos anteriores. Este resultado apunta en la misma dirección que la sustitución creciente con átomos de flúor.

Para comprender en mayor profundidad estos resultados experimentales y de nuevo en colaboración con el profesor Pedro Merino de la Universidad de Zaragoza, se lleva a cabo un estudio DFT de la reacción para el caso fluorado y no fluorado. Estos cálculos confirman casi perfectamente los resultados encontrados de forma experimental y el estudio de las interacciones no covalentes revela que principalmente la interacción entre un átomo de flúor y el carbonilo de la morfolinona es la responsable de la elevada diastereoselectividad en el caso fluorado.

Finalmente, una selección de cicloaductos se somete a dos derivatizaciones alternativas que dan lugar a prolinamidas y prolinoles respectivamente. En el primer caso, se trata de una secuencia de apertura de la morfolinona con *n*-butilamina seguida de desprotección oxidativa de la amina terciaria con CAN. En el

segundo caso, se reduce la morfolinona con $LiALH_4$ y se desprotege la amina, de nuevo con CAN.

Capítulo 3: Reacción tándem organocatalítica intramolecular de cicloaromatización/alquilación de Friedel-Crafts para la síntesis de derivados de indolizinonas y pirrolo-azepinonas

El pirrol es una de las estructuras heterocíclicas aromáticas fundamentales y un motivo recurrente en numerosos productos naturales y biológicamente activos. Cabe mencionar como ejemplo relevante la Atorvastatina (Lipitor), el medicamento de marca con más ventas en el mercado farmacéutico, que contiene un núcleo de pirrol en su estructura. Asimismo, los derivados fusionados de pirrol también son estructuras comunes en fármacos y productos naturales. Hay que destacar particularmente las indolizinas e indolizidinas, en las que un anillo de pirrol está fusionado con un segundo ciclo de seis miembros (aromático o alifático) de modo que el nitrógeno queda como cabeza de puente. Los alcaloides indolizidínicos representan alrededor del 30% de todos los alcaloides y derivan de la biosíntesis de la lisina.

Por los motivos anteriormente mencionados, estas estructuras tienen un gran interés como moléculas objetivo en síntesis orgánica. La mayoría de los métodos en los que se construye el núcleo bicíclico de indolizidina (y su homólogo de pirrolo-azepina) parten de pirroles adecuadamente funcionalizados en el nitrógeno con una cadena que, mediante una reacción de alquilación o acilación de Friedel-Crafts, da lugar al ciclo de seis miembros deseado. El objetivo de este capítulo es desarrollar una síntesis que no sólo permita construir el anillo de seis, sino a la vez el de cinco miembros de pirrol. Para ello, se plantea como la estrategia más eficiente un proceso tándem o dominó organocatalizado, una clase de reacciones que permiten construir a partir de sustratos de partida relativamente sencillos una gran complejidad molecular en un único paso de reacción mediante subetapas de reacción consecutivas y con una gran economía atómica. Con este fin y dadas la amplísima literatura sobre organocascadas así como la experiencia del

grupo de investigación, se escogen organocatalizadores como promotores de este proceso.

En la primera etapa de la secuencia tándem, la formación del anillo de pirrol, se ha de disponer de una γ-amidoenona para que pueda tener lugar la cicloaromatización (por pérdida de una molécula de agua). Este sustrato de partida es accesible por metátesis cruzada de olefinas, una poderosa metodología para la formación de enlaces carbono-carbono. En este momento, sólo existen dos precedentes bibliográficos de la síntesis de pirroles empleando este método, aunque nunca se ha empleado para la síntesis de indolizidinas y derivados. En la segunda etapa de la secuencia, la estrategia escogida es la ciclación por alquilación de Friedel-Crafts organocatalizada. Esta metodología ya ha sido explorada en la literatura, y se ha descrito el uso de distintos organocatalizadores, por catálisis covalente y no covalente, si bien es cierto que el pirrol como nucléofilo de esta reacción ha sido menos estudiado y plantea un reto mayor en cuanto al control de la estereoselectividad. Atendiendo al tipo de organocatalizadores más habituales para los dos tipos de transformaciones por separado, se puede prever que los ácidos de Brønsted puedan resultar la elección más adecuada.

De nuevo, como en los capítulos anteriores, el comienzo es el diseño y síntesis de los materiales de partida. Para ello se plantea una reacción de metátesis cruzada bidireccional para instalar los dos aceptores de Michael (enonas) necesarios para disponer de la γ-amidoenona y del agente de alquilación para la segunda etapa. La variabilidad estructural se introduce tanto en los restos de las enonas como en la cadena espaciadora que las separa y que contiene la amida que desencadena la organocascada.

Con los sustratos de partida ya disponibles, la optimización del proceso tándem comienza con un cribado inicial de condiciones de reacción para identificar el modo catalítico más adecuado. La catálisis no covalente por ácidos de Brønsted resulta ser la alternativa más eficiente y, llegado este punto, se realiza un primer cribado de "superácidos" BINOL-fosfóricos (es decir, las correspondientes *N*-triflil fosforamidas), cuya preparación y uso están bien establecidos en la literatura. Tras un extenso trabajo de optimización, se identifica el ácido sustituido

con grupos 2,4,6-triisopropilfenil (TRIP) como el mejor catalizador y posteriormente se ajustan las condiciones de reacción en cuanto a disolvente y temperatura. El estudio del alcance de la reacción revela que el sistema encontrado proporciona buenos rendimiento para el proceso tándem, aunque los excesos enatioméricos son moderados. Hasta el momento no se han encontrado sustratos de partida modificados u otros catalizadores que proporcionen mayor enantioselectividad.

Abstract

The present doctoral thesis is devoted to the study of novel stereoselective intramolecular reactions as synthetic tools for the generation of complex New Molecular Entities. Along its three chapters, the focus is put, in the first place, on intramolecular 1,3-dipolar cycloadditions with novel fluorinated substrates and, in the second place, on new organocatalysed tandem sequences.

In Chapter 1, the synthesis of three families of fluorinated polycyclic isoxazolidines is described by means of an intramolecular nitrone cycloaddition reaction of unprecedented *ortho*-substituted α-trifluoromethyl styrenes. The trifluoromethyl group plays an important role in the regioselectivity of the process and it is able to invert the regioisomeric outcome of the reaction compared to the non-fluorinated case. Additionally, combining an organocatalytic step for the convenient functionalisation of the nitrone precursors with a subsequent cycloaddition event, enantiopure derivatives are accessible. Complementary computational calculations allow for a deeper understanding of the regio- and diastereoisomeric reaction outcome.

In Chapter 2, an asymmetric synthesis of fluorinated polycyclic proline derivatives was developed by means of an intramolecular dipolar cycloaddition between a homochiral *in situ* generated azomethine ylide and a trifluoromethyl-substituted alkene, ensuring high levels of regio- and diastereoselectivity. Again, theoretical calculations correctly predict the drop of selectivity observed when a non-fluorinated alkene was used.

Finally, in Chapter 3, a novel tandem organocatalysed cycloaromatisation/intramolecular Friedel-Crafts alkylation sequence is reported, leading to the synthesis of a new family of annulated pyrrole derivatives in moderate to good yields. An asymmetric approach was developed using chiral, non-racemic Brønsted acid organocatalysts, obtaining moderate levels of enantioselectivity.

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

Index

Foreword

Organic synthesis can be seen as a Lego set in the hands of organic chemists, offering virtually infinite possibilities for the creation of novel structures and also novel properties. But besides being an endless source of academic fascination, it has provided important improvements in human life, for example *via* medical sciences: The screening of libraries of small organic molecules is the workhorse in chemical biology and drug discovery to simultaneously identify the therapeutic (protein) targets and modulators of these biological systems. Given that the bioactivity of the screened ligands is intrinsically related to their molecular structure, a matter of great concern is the scaffold diversity[1] present in the screened libraries, since it increases the hit probablity in the studied systems for most of which the biological target is unknown and rational ligand design is a pipe-dream. The term scaffold is itself problematic to define, but it is generally understood as the core molecular framework providing the rough molecular shape and a certain degree of flexibility/rigidity by which the peripheral substituents are exposed to the 3D-space (and to the target). For medicinal chemists, scaffold might rather be a synonym for pharmacophore.

After the disappointing results of High-Throughput Screening (HTS) of combinatorial chemistry libraries in the 90s, other strategies emerged to tackle the poor structural diversity provided by the latter approach. Schreiber and coworkers pioneered the Diversity-Oriented Synthesis (DOS) strategy, whereby chemical libraries are constructed by reagent-based or reaction-based branching pathways from simple building blocks.[2] The Waldmann group coined meanwhile the term Biology-Oriented Synthesis (BIOS), an alternative strategy aiming to explore

[1] A number of interesting papers have addressed the problematic of scaffold diversity generation. See for example: (a) Garcia-Castro, M.; Zimmermann, S.; Sankar, M. G.; Kumar, K. *Angew. Chem. Int. Ed.* **2016**, *55*, 7586. (b) Nicolaou, K. C.; Hale, C. R. H.; Nilewskia, C.; Ioannidou, H. A. *Chem. Soc. Rev.,* **2012**, *41*, 5185. (c) Galloway, W. R. J. D.; Díaz-Gavilán, M.; Isidro-Llobet, A.; Spring, D. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 1194.

[2] (a) Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46. (b) Schreiber, S. L. *Science* **2000**, *287*, 1964.

natural-product-like compound collections.[3] Besides skeletal diversity, a further concern in the design and synthesis of compound libraries is molecular complexity, *i.e.* stereochemical features and functionalisation. It has been suggested that more struturally complex molecules (which are in general more natural-product-like) are more likely to interact with biological macromolecules in a selective and specific manner.[4]

Regarding the theme of molecular diversity, the typical span of four years for a doctoral thesis in the field of development of new methodologies in organic synthesis is normally insufficient to generate a great amount of molecular diversity, since the focus is put elsewhere (on the study of the reaction itself, naturally) and the exploration of the reaction scope tends to be restricted to (trivial) substituent variation and assessment of functional group compatibility, while keeping unaltered the core molecular structure accessible by the developed methodology. These considerations are, of course, applicable to the present doctoral thesis as well. However, the ensemble of reactions presented here hints at the potential of intramolecular processes for the generation of diverse chemical entities.

Intramolecular reactions are complexity-generating reactions since the products are polycycles that can be regarded as complex molecular architectures on the basis of the number of cycles. As it will be discussed in the individual introductions of each chapter, intramolecular reactions offer a powerful way to construct compact polycyclic scaffolds generally in a very stereoselective manner. This fact has repeatedly been exemplified in numerous total syntheses of natural products. Intramolecularity will remain the leitmotiv along the chapters of the present doctoral thesis, which the reader will rapidly be able to classify in two clearly differentiated blocks. The first thematic block, comprising Chapters 1 and 2, is devoted to intramolecular 1,3-dipolar cycloaddition reactions. The challenge

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[3] (a) Wetzel, S.; Bon, R. S.; Kumar, K.; Waldmann, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 10800. (b) Bon, R. S.; Waldmann, H. *Acc. Chem. Res.* **2010**, *43*, 1103. (c) Noren-Muller, A.; Reis-Correa, I., Jr.; Prinz, H.; Rosenbaum, C.; Saxena, K.; Schwalbe, H. J.; Vestweber, D.; Cagna, G.; Schunk, S.; Schwarz, O.; Schiewe, H.; Waldmann, H. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 10606.

[4] (a) Hopkins, A. L.; Mason, J. S.; Overington, J. P. *Curr. Opin. Struct. Biol.* **2006**, *16*, 127. (b) Lipinski, C.; Hopkins, A. *Nature* **2004**, *432*, 855.

posed by the regio-, diastereo- and enantioselectivity issues in dipolar cycloadditions will be confronted applying the intramolecular version of these reactions. Moreover, the special features of fluorine in organic molecules will be exploited to access different unprecedented fluorinated scaffolds of potential interest in medicinal chemistry. The second thematic block is contained in Chapter 3, in which a novel organocascade process leading to a new family of annulated pyrroles will be presented. The use of cascade sequences for the concise and efficient generation of scaffold diversity and complexity is a known strategy.[5] The close ressemblance of the obtained collection of products with the indolizidine natural product family illustrates the potential of this methodology.

Thus, the general goals of the present research work can be summed up as follows:

- the study of novel intramolecular stereoselective reactions for the generation of New Molecular Entities (NME), as a general objective comprising all the chapters.

- the exploration of unprecedented fluorinated dipolarophiles in intramolecular 1,3-dipolar cycloadditions and the development of an asymmetric version thereof (Chapters 1 and 2). The focus will be put on simple (per)fluoroalkyl-substituted olefins as dipolarophile counterparts.

- the development of novel intramolecular cascade processes for the generation of poly-heterocyclic compounds from acyclic substrates (Chapter 3). Organocatalysis will be applied to render these reactions enantioselective.

With respect to the structure of the chapters, a brief Introduction, covering the most relevant general aspects related to the kind of reaction and substrates/products described, concludes with a bibliographic review of the direct

[5] See for example: Wang, Y.; Lu, H.; Xu, P.-F. *Acc. Chem. Res.* **2015**, *48*, 1832.

precedents to the reaction under study. Next, the Objectives are defined prior to the discussion of the experimental Results. In the Experimental Section, all new compounds are fully characterised. In Chapters 1 and 2, an additional rubric has been included in the Results and Discussion and Experimental Sections with the complementary computational calculations.

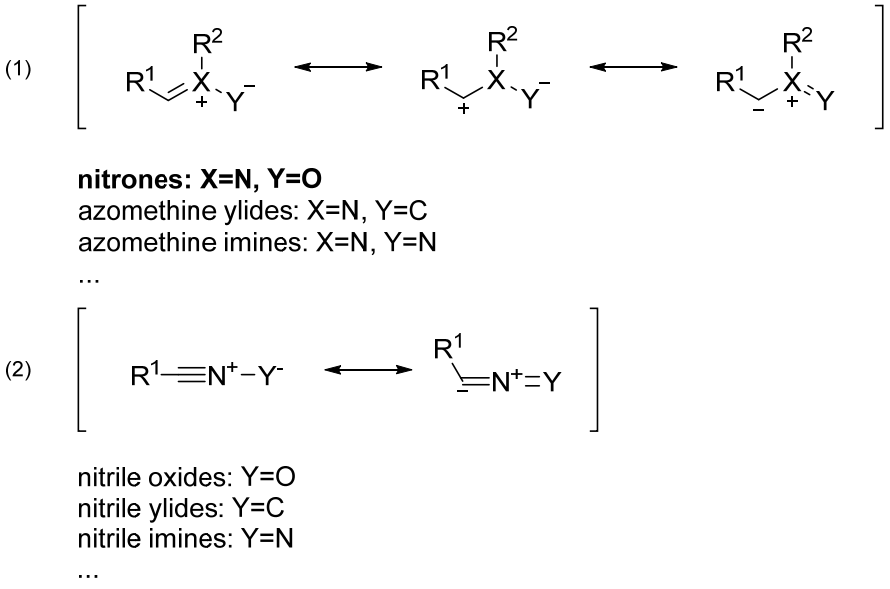
Chapter 1

Intramolecular Nitrone Cycloaddition of α-Trifluoromethyl Styrenes

1.1. Introduction

1.1.1. General remarks on 1,3-dipolar cycloaddition reactions

The 1,3-dipolar cycloaddition reaction, initially proposed by L. I. Smith,[6] constitutes an outstanding methodology for the synthesis of five-membered ring heterocycles.[7] It involves the combination of a 1,3-dipole with a multiple bond called dipolarophile. This methodology, which found widespread application in several fields such as natural product synthesis, material science or biological chemistry, started to be recognised as a powerful tool in organic chemistry after the seminal work by Huisgen in the early sixties.[8]



Scheme 1.1

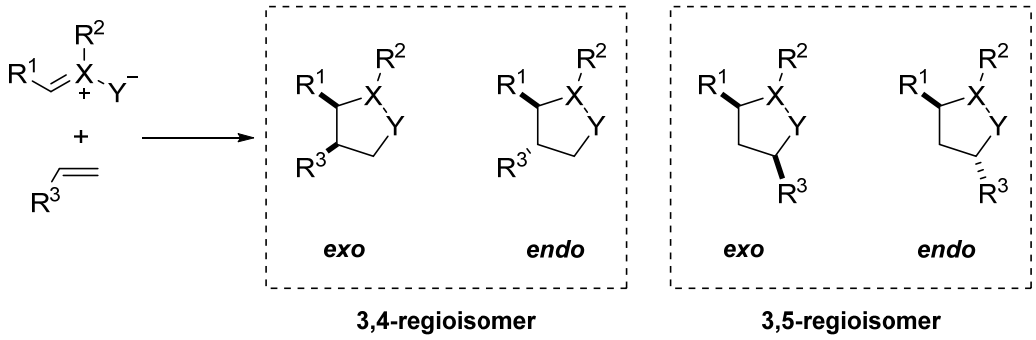
A 1,3-dipole is an organic molecule in which three atoms share 4π electrons. There is a great variety of dipoles, and they can be classified considering the nature of the heteroatoms present in them (nitrogen and oxygen being the most frequent

[6] Smith, L. I. *Chem. Rev.* **1938**, *23*, 193.
[7] For recent reviews, see: (a) Anderson, L. L. *Asian J. Org. Chem.* **2016**, *5*, 9. (b) Singh, S. S.; Chowdhury, S.; Koley, S. *Tetrahedron* **2016**, *72*, 1603. (c) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366. (d) Kanemasa, S. *Heterocycles* **2010**, *82*, 87. (e) Kissane, M.; Maguire, A. R. *Chem. Soc. Rev.* **2010**, *39*, 845. (f) Nájera, C.; Sansano, J. M. *Org. Biomol. Chem.* **2009**, *7*, 4567. (g) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235.
[8] (a) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 565. (b) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 633. (c) Huisgen, R. *Angew. Chem. Int. Ed.* **1968**, *7*, 321.

ones) and their geometry as allyl-type dipoles (bent geometry) and allenyl-type dipoles (linear geometry). Dipoles can be represented using the most contributing resonance structures which differ in the position of the charges. The resonance structures of allyl-type and allenyl-type dipoles are represented on Scheme 1.1 (equations 1 and 2, respectively). On their behalf, alkenes and alkynes are by far the most frequent dipolarophiles, although heteroatom-containing multiple bonds are also found to take part in 1,3-dipolar cycloadditions. The dipolarophile contributes with the remaining 2π electrons to the cycloaddition.

The generally accepted mechanism is a one-step, symmetry-allowed, Hückel-type (4π+2π), asynchronous, concerted process with a single transition state. The Frontier Molecular Orbital (FMO) theory allows determining which reaction pathway is responsible for the energetically lowest transition state, either $HOMO_{dipole}$-$LUMO_{dipolarophile}$ or $HOMO_{dipolarophile}$-$LUMO_{dipole}$. The dominant FMO interaction is thus responsible for the formation of the observed product. The most nucleophilic, electron-rich end of the dipole bears the largest coefficient of the HOMO, while the LUMO corresponds to the electrophilic end. The stereospecificity, *i.e.* the retention of configuration of the substituents of the dipolarophile, is probably the strongest proof of the concerted nature of the reaction. Thus, if the dipolarophile is a 1,2-disubstituted alkene, the *syn* attack of the dipole will keep the geometry of the double bond (*E* or *Z*) in the configuration of the final product. Regarding the dipole, its stereochemistry (*E* or *Z*) is not as decisive since bond rotation is generally possible.

Last but not least, the issue of regioselectivity is decisive for the product distribution. In theory, two regioisomeric cycloadducts are always conceivable in which the new bonds are formed from opposite dipole-dipolarophile orientations. In practice, one regiochemistry is commonly preferred, as in intramolecular reactions where steric constraints usually override the preference set by orbital interactions and limit the viable dipole-dipolarophile approaches. Moreover, if the dipolarophile is a substituted alkene, different diastereoisomers can be formed depending on the preferred *exo* or *endo* approach (in an analogous nomenclature to that employed in Diels-Alder reactions) (Scheme 1.2).



Scheme 1.2

1.1.2. Nitrone cycloadditions in organic synthesis

Among the great variety of 1,3-dipoles described, nitrones (formally imine *N*-oxides, Scheme 1.1, equation 1) are probably the most widely employed in dipolar cycloadditions.[9,10] This is due to their easy access from readily available starting materials, as well as to the high stability and biological significance of these intermediates.[11] Nitrones are mainly generated by hydroxylamine oxidation, oxime alkylation (often in intramolecular reactions), oxime/nitrone tautomerism or, most importantly, condensation of a carbonyl compound, frequently an aldehyde, with an *N*-substituted hydroxylamine (Scheme 1.3).

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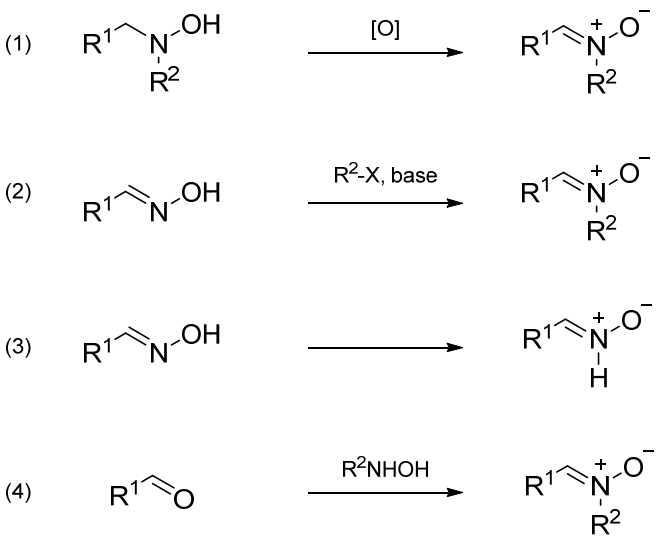
[9] (a) Bablee, M.; Basudeb, B. *Topics Het. Chem.* **2013**, *30*, 85. (b) Yang, J. *Synlett* **2012**, *23*, 2293. (c) Nguyen, T. B.; Martel, A.; Gaulon-Nourry, C.; Dhal, R.; Gilles, D. *Org. Prep. Proc. Int.* **2012**, *44*, 1. (d) Bokach, N. A.; Kuznetsov, M. L.; Kukuskin, V. Y. *Coord. Chem. Rev*. **2011**, *255*, 2496. (e) Nguyen, T. B.; Martel, A.; Gaulon-Nourry, C.; Dhal, R.; Gilles, D. *Org. Prep. Proc. Int.* **2010**, *42*, 287. (f) Bokach, N. A. *Rus. Chem. Rev.* **2010**, *79*, 89. (g) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Eur. J.* **2009**, *15*, 7808. (h) Rueck-Braun, K.; Freysoldt, T. H. E; Wierschem, F. *Chem. Soc. Rev.* **2005**, *34*, 507.

[10] (a) Martin, J. N.; Jones, R. C. F. In: *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry: Nitrones* in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products* (Eds.: Padwas, A.; Pearson, W. H.), Wiley, Chichester, UK, **2002**, *Vol. 59*, p. 1. (b) Wang, L. J.; Tang, Y. In: *Intermolecular 1,3-dipolar cycloadditions of alkenes, alkynes, and allenes* in *Comprehensive Organic Synthesis*, *2nd ed*. (Eds.: Knochel, P.; Molander, G. A.), Elsevier B.V., **2014**, *Vol. 4*, p. 1342.

[11] Merino, P. In: *Nitrones and Cyclic Analoges* in *Science of Synthesis* (Eds.: Bellus, D.; Padwa, A.), George Thieme, Stuttgart, **2004**; *Vol. 27*, p. 511. Update: Merino, P. In: *Science of Synthesis* (Ed.: Schaumann, E.), George Thieme, Stuttgart, **2011**; *Vol. 2010/4*, p. 325.



Scheme 1.3

Depending on the nature of the dipolarophile moiety, either isoxazoline or isoxazolidine skeletons are formed in their reaction with alkynes or alkenes, respectively (Scheme 1.4).[12] These heterocycles are present in a broad variety of alkaloids and natural products.[13] Examples of their preparation using this [3+2] cycloaddition reaction are widespread in the literature.[14] They can further be converted by reductive ring-opening into 1,3-amino alcohols,[15] which are precursors of β-amino acids and β-lactams. In addition, nitrone cycloadditions may be involved in the biosynthesis of some alkaloids without enzymatic catalysis.[16] Also, other heterocyclic systems can be accessed through different reactions,

[12] For recent reviews, see ref. 7.

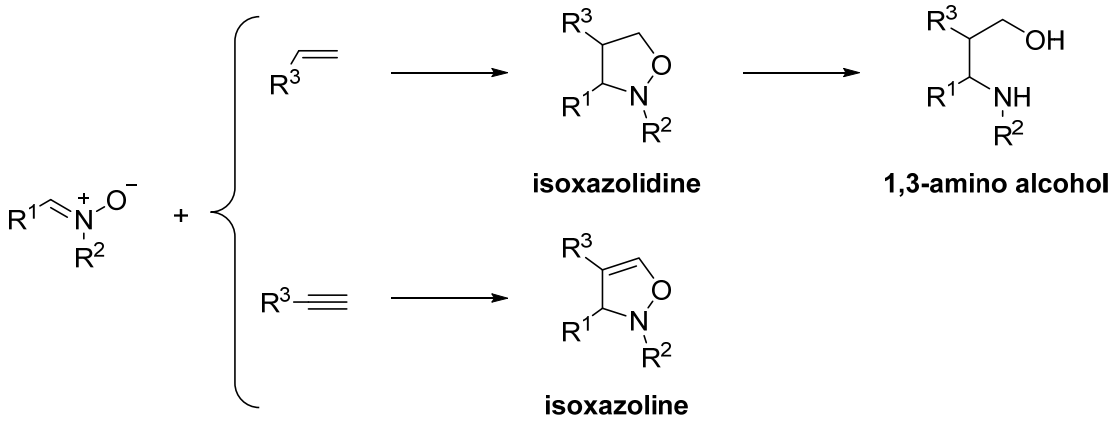
[13] For discussions on the biological activity of isoxazolines and isoxazolidines, see: (a) Kumar, K. A.; Govindaraju, M.; Renuka, N.; Kumar, G. V. *J. Chem. Pharm. Res.* **2015**, *7*, 250. (b) Casida, J. E. *Chem. Res. Toxicol.* **2015**, *28*, 560. (c) Kaur, K.; Kumar, V.; Sharma, A.; Gupta, G. K. *Eur. J. Med. Chem.* **2014**, *77*, 121. (d) Hosking, M. P.; Carroll, R. C. *Curr. Opin. Cardiovasc. Pulm. Renal Invest. Drugs* **2000**, *2*, 165.

[14] (a) Ref. 9g. (b)Ref. 7f. (c) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247. (d) Revuelta, J.; Cicchi, S.; Goti, A.; Brandi, A. *Synthesis* **2007**, 485. (e) Frederickson, M. *Tetrahedron* **1997**, *53*, 403.

[15] For the relevance of 1,3-amino alcohols in organic synthesis, see: Lait, S. M.; Rankic, D. A.; Keay, B. A. *Chem. Rev.* **2007**, *107*, 767.

[16] Baunach, M.; Hertweck, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 12550.

including Mannich-type,[17] and Kinugasa[18] reactions as well as less common transformations.[19]



Scheme 1.4

1.1.3. Intramolecular Nitrone Cycloaddition Reactions (INCR)

The regio- and stereochemical issues that arise in intermolecular cycloaddition reactions are minimised in the intramolecular variants of these processes. In a system where dipole and dipolarophile are linked, the entropic factor increases the reactivity and lowers the energy barrier, thus allowing for lower reaction temperatures and/or the use of less reactive reaction partners, especially less activated olefins as dipolarophile counterparts. At the same time, the limitation of the degree of spatial freedom in the transition state causes an increase of the stereoselectivity in all its facets: regioselectivity, diastereofacial selectivity and *exo/endo* selectivity. Therefore, Intramolecular Nitrone Cycloaddition Reactions (abbreviated INCR from now on) are unequalled when it

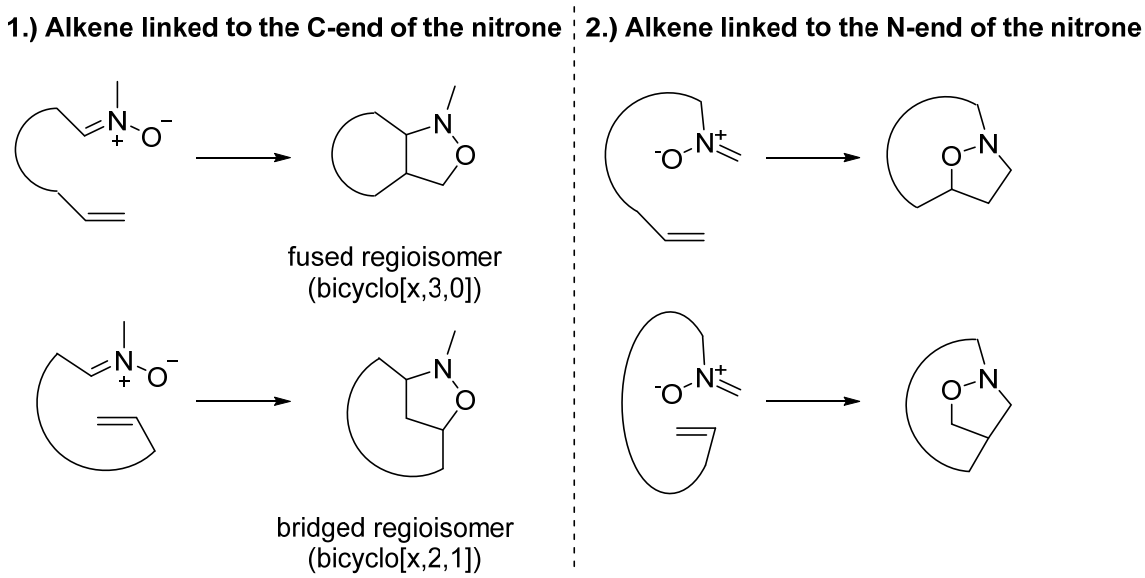
[17] (a) Merino, P.; Tejero, T. *Synlett* **2011**, 1965. (b) Merino, P. In: *Mannich-type reactions* in *Science of Synthesis. C-1 Building Blocks in Organic Synthesis* (Ed.: Leeuwen, P. W. N. M.), Georg Thieme, Stuttgart, **2014**, p. 311.

[18] (a) Khangarot, R. K.; Kaliappan, K. P. *Eur. J. Org. Chem.* **2013**, *2013*, 7664. (b) Marco-Contelles, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 2198. (c) Evans, D. A.; Kleinbeck, F.; Rueping, M. In: *Copper-Bis(oxazoline) Catalyzed Synthesis of β-Lactams. Enantioselective Reaction of Alkynes with Nitrones* in *Asymmetric Synthesis. The Essentials* (Eds.: Christmann, M.; Bräse, S.), Wiley-VCH, Weinheim, **2007**, p. 77. (d) Mandal, B.; Basu, B. *Top. Heterocycl. Chem.* **2013**, *30*, 85.

[19](a) Ref. 9b (b) Cardona, F.; Goti, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7832.

comes to building several stereocentres with high stereoselectivity in one reaction step.[20] Depending on the substitution pattern of the reactants, up to three new stereocentres may be formed.

INCR can be classified on the basis of how nitrone and dipolarophile (olefin) are put together. In the most usual kind of INCR, the alkene is linked to the iminic carbon of the nitrone. In this case, two regioisomers are possible: the fused isoxazolidine (systematically, a bicyclo[x,3,0]) or the bridged isoxazolidine (bicyclo[x,2,1]). Each one can be formed following an *exo* or *endo* cyclisation mode respectively. For sterical reasons, the most frequently observed products in the literature are the fused regioisomers with an *exo* selectivity (with respect to the linker between nitrone and alkene) and a *cis* configuration at the ring fusion. Other dipole/dipolarophile approaches would require an impossible twist of the alkenyl nitrone. It is also frequently the case that mixtures of isomers are obtained with a major product reflecting the most favourable regiochemistry and configuration. In a second type of INCR, the alkene is part of the *N*-substituent of the nitrone, and invariably bridged products are obtained (Scheme 1.5).



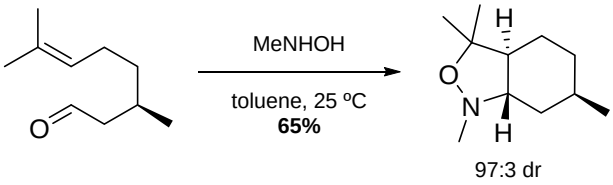
Scheme 1.5

The purpose of the present section is to offer a glimpse of the ubiquity and utility of INCR in organic synthesis and it is by no means intended to be comprehensive. INCR has become a routine methodology in the organic chemist's

[20] See ref. 14c

toolkit and it would be an impossible task, and certainly beyond the purpose of this introduction, to track down every work where it has found use. The choice of examples from the literature, ranging from the sixties to the present day, is hence purely subjective, just aiming to present some of the most frequent synthetic strategies associated with these reactions.

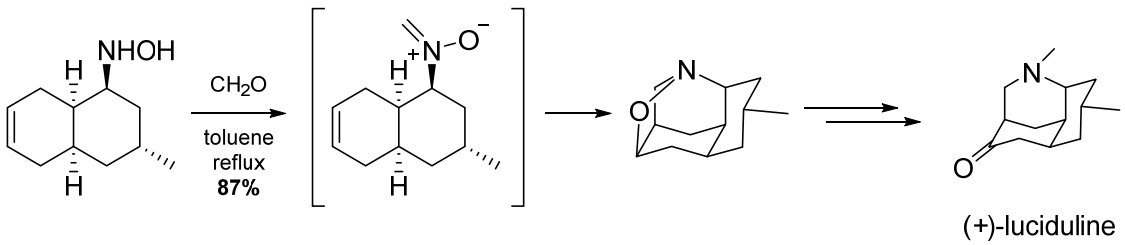
The investigation of INCR was pioneered by LeBel *et al.* with their description of the intramolecular cycloaddition of (*R*)-(+)-citronellal and *N*-methylhydroxylamine.[21] At a reaction temperature as low as 25 °C, the *in situ* formed nitrone underwent intramolecular cycloaddition with an unactivated, trisubstituted olefin with total regioselectivty and an impressive diastereoselectivity of 97:3 in favour of the fused regioisomer with *trans* configuration at the ring junction (Scheme 1.6).



Scheme 1.6

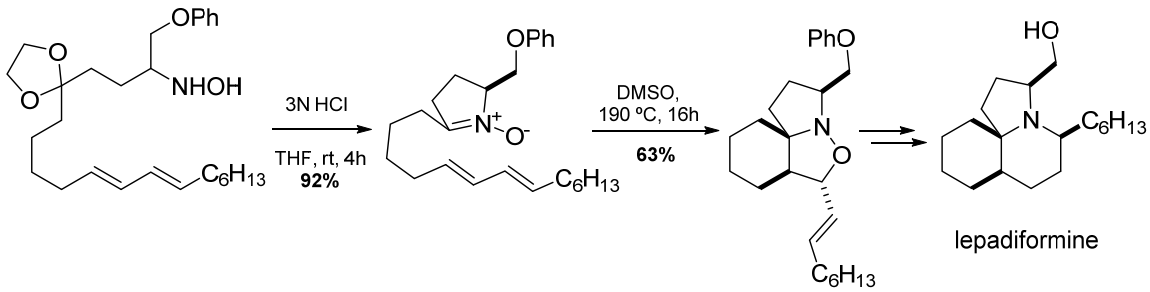
The evidence of the synthetic utility of INCR was first brought by Oppolzer's elegant total synthesis of the lycopodium alkaloid (+)-luciduline.[22] The starting enantiomerically pure hydroxylamine, derived from (*R*)-5-methyl-2-cyclohexenone, was reacted with paraformaldehyde in refluxing toluene affording a transient nitrone, which further evolved to the resulting isoxazolidine with the core structure of luciduline as a single regioisomer. This product was further transformed to the natural product by simple operations (Scheme 1.7).

[21] (a) LeBel, N. A.; Whang, J. J. *J. Am. Chem. Soc.* **1959**, *81*, 6334. (b) LeBel, N. A.; Lajiness, T. A. *Tetrahedron Lett.* **1966**, *19*, 2173. (c) LeBel, N. A.; Post, M. E.; Whang, J. J. *J. Am. Chem. Soc.* **1964**, *86*, 3759. (d) LeBel, N. A.; Banucci, E. G. *J. Org. Chem.* **1971**, *36*, 2440.
[22] Oppolzer, W.; Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 2755.



Scheme 1.7

The usefulness of INCR for the stereoselective construction of the polycyclic core of complex natural products has been exploited ever since. For instance, Weinreb *et al.* carried out the racemic total synthesis of tricyclic indolizidine alkaloid lepadiformine applying an INCR in the key step.[23] In one step of the synthesis, an intermediate hydroxylamine underwent acetal deprotection and subsequent intramolecular condensation to provide a cyclic ketonitrone. Thermolysis of this intermediate afforded a tricyclic isoxazolidine as a single diastereoisomer, which was further elaborated to the target compound (Scheme 1.8).



Scheme 1.8

In the field of carbohydrate chemistry, INCR have become an invaluable tool for the construction of polyhydroxylated carbocycles.[24] In an illustrative example, Shing and Yamada explored the stereo- and regiochemical outcome of the reaction of different hept-6-enoses depending on the position of a *trans*-acetonide group.[25]

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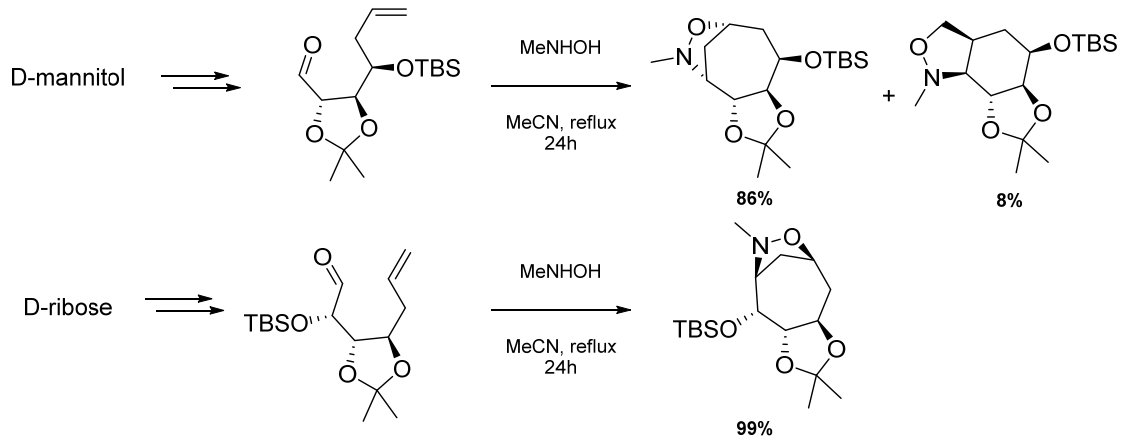
[23] Werner, K. M.; de los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 686.
[24] (a) Koumbis, A. E.; Gallos, J. K. *Curr. Org. Chem.* **2003**, *7*, 585. (b) von Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990. (c) Shing, T. K. M.; Elsley, D. A.; Gillhouley, J. G. *J. Chem. Soc. Chem. Commun.* **1989**, 1280.
[25] Shing, T. K. M.; Wong, W. F.; Ikeno, T.; Yamada, T. *Chem. Eur. J.* **2009**, *15*, 2693.

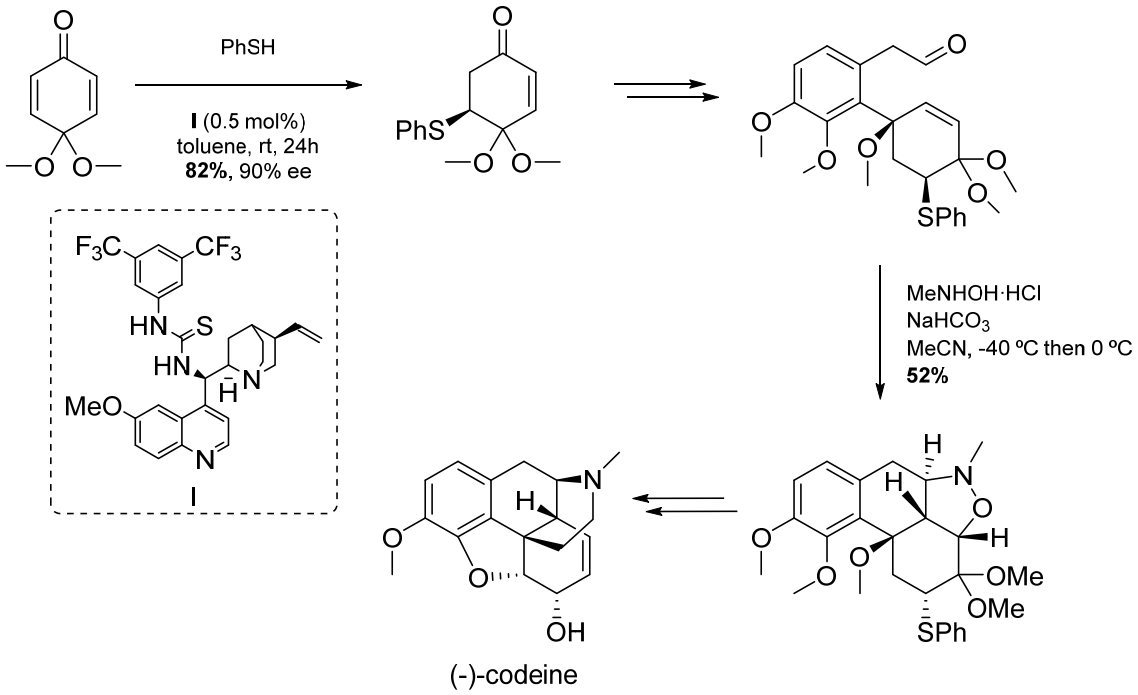
Moving the *trans*-O-isopropylidene ring along the carbon chain results in a change of the regioselectivity and *exo/endo* distribution, usually with high selectivities. A computational study showed that the torsional strain imposed by the trans-acetonide group dramatically affects the conformation of the transition state and the possible nitrone/alkene approaches (Scheme 1.9).



Scheme 1.9

Recently, Metz *et al.* reported a formal total synthesis of (-)-codeine.[26] The key feature of this work is the preparation of the enantiomerically pure starting material required for the construction of the phenanthrene core by INCR. To this end, the desymmetrisation of *p*-quinone dimethyl monoacetal by organocatalytic sulfa-Michael addition was described using a chiral quinidine derived urea. This intermediate was coupled with a synthon derived from isovanillin by 1,2-addition to the ketone carbonyl group affording the required enantiopure nitrone precursor. The INCR afforded the required *trans* configuration of the stereocentres of the isoxazolidine ring, and the α-carbon of the sulfenyl ketone epimerised *in situ* (Scheme 1.10).

[26] (a) Rautschek, J.; Jäger, A.; Metz, P. *Org. Lett.* **2018**, *20*, 832. (b) Erhard, T.; Ehrlich, G.; Metz, P. *Angew. Chem. Int. Ed.* **2011**, *50*, 3892.



Scheme 1.10

1.1.4. Asymmetric approaches in INCR: the case of organocatalysis

As it is clear from the previous section, discussing the asymmetric version of INCR separately might seem artificial, since a good deal of reported syntheses employing nitrone cycloadditions are at the same time asymmetric and intramolecular reactions. The asymmetric version of INCR has received significant attention in the literature.[27] Early examples relied on the use of chiral auxiliaries[28] and/or chiral starting materials, mainly based on chiral nitrones derived from amino acids[29] and sugars.[30] With the development of enantioselective catalysis, a

[27] (a) Padwa, A.; Bur, S. *Chem. Het. Comp.* **2016**, *52*, 616. (b) Ref 7c. (c) Ref 7f. (d) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun*. **2000**, 1449. (e) Merino, P.; Franco, S.; Merchán, F. L.; Tejero, T. *Synlett* **2000**, *4*, 442. (f) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.
[28] (a) *Chiral Auxiliaries in Cycloadditions* (Eds.: Ruck-Braun, K.; Kunz, H.), Wiley, New York, **1999**. (b) Ref. 14d. (c) Ishikawa, T.; Tajima, Y.; Fukui, M.; Saito, S. *Angew. Chem. Int. Ed.* **2003**, *35*, 1863. For overviews of the use of chiral auxiliaries in organic synthesis and cycloadditions see: (d) Gnas, Y.; Glorius, F. *Synthesis* **2006**, 1899. (e) Evans, D. A.; Helmchen, G.; Rueping, M. In: *Asymmetric Synthesis-the Essentials* (Eds.: Christmann, M., Brase, S.), Wiley-VCH, Weinheim, Germany, **2006**; p.3.
[29] (a) Merino, P.; Tejero, T.; Diez-Martinez, A.; Gultekin, Z. *Eur. J. Org. Chem.* **2011**, 6567. (b) Merino, P.; Greco, G.; Tejero, T.; Hurtado-Guerrero, R.; Matute, R.; Chiacchio, U.; Corsaro, A.; Pistara, V.; Romeo, R. *Tetrahedron* **2013**, *69*, 9381.

large number of reports have appeared in the literature that take advantage of both transition metal catalysis[31] and organocatalysis,[32] reaching a high degree of control in the diastereo- and enantioselectivity of the process.

Despite this exponential growth, recently highlighted by Maruoka,[33] the intramolecular version of those reactions is still a big challenge[34] and, as far as we know, no examples of enantioselective intramolecular [3+2] cycloadditions of nitrones have been described to date.[35] The main difficulty for achieving this transformation is to design the correct system in which the cycloaddition is favoured once the nitrone is generated *in situ*. As mentioned before (Section 1.1.2), generation of nitrones is usually made by either condensation or oxidation processes, which should be compatible with the presence of the catalyst whether it is a chiral Lewis acid or an organocatalyst. In the first case, in both condensation and oxidation methods, the starting reagents (amines and hydroxylamines) are nucleophiles that can sequester the metal catalyst avoiding the formation of the nitrone and/or blocking the action of the catalyst. In the second case, the required aldehyde (for condensation methods) or amine/hydroxylamine (for oxidation methods) can interfere with the catalyst removing it from the reaction medium.

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[30] For recent examples, see: (a) Tejero, T.; García-Viñuales, S.; Delso, I.; Merino, P. *Synthesis* **2016**, *48*, 3339. (b) Martella, D.; D'Adamio, G.; Parmeggiani, C.; Cardona, F.; Moreno-Clavijo, E.; Robina, I.; Goti, A. *Eur. J. Org. Chem.* **2016**, 1588. (c) Delso, I.; Tejero, T.; Goti, A.; Merino, P. *J. Org. Chem.* **2011**, *76*, 4139. For reviews, see: (d) Osborn, H. M. I.; Gemmell, N.; Harwood, L. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2419. (e) Fisera, L.; Altimari, U. A. R.; Ertl, P. In: *Stereoselectivity of 1,3-Dipolar Cycloaddition of Glycosyl Nitrones to Normal-Arylmaleimides* in *Cycloaddition Reactions in Carbohydrate Chemistry* (Ed.: Giuliano, R. M.), ACS, Washington, DC, **1992**, p. 158.

[31] For recent representative examples, see: (a) Hu, J. L.; Wang, L.; Xu, H.; Xie, Z.; Tang, Y. *Org. Lett.* **2015**, *17*, 2680. (b) Xie, L.; Yu, X.; Li, J.; Zhang, Z.; Qin, Z.; Fu, B. *Eur. J. Org. Chem.* **2017**, 657. (c) Selim, K. B.; Martel, A.; Laurent, M. Y.; Lhoste, J.; Py, S.; Dujardin, G. *J. Org. Chem.* **2014**, *79*, 3414. For a review: (d) Pellissier, H. *Tetrahedron* **2015**, *71*, 8855.

[32] For recent representative examples, see: (a) Prieto, L.; Juste-Navarro, V.; Uria, U.; Delso, I.; Reyes, E.; Tejero, T.; Carrillo, L.; Merino, P.; Vicario, J. L. *Chem. Eur. J.* **2017**, *23*, 2764. (b) Liu, Y.; Ao, J.; Paladhi, S.; Song, C. E.; Yan, H. *J. Am. Chem. Soc.* **2016**, *138*, 16486. (c) Duschmale, J.; Wiest, J.; Wiesner, M.; Wennemers, H. *Chem. Sci.* **2013**, *4*, 1312. For a review: (d) Vicario, J. L. *Synlett* **2016**, *27*, 1006.

[33] See ref. 7c.

[34] Menon, R. S.; Nair, V. In: *Comprehensive Organic Synthesis*, *2nd edition* (Eds.: Knochel, P.; Molander, G. A.), Elsevier B.V., **2014**; *Vol. 4*, p. 1281.

[35] The only similar process is the formal enantioselective [3+3] intramolecular cycloaddition of a nitrone with a dirhodium carbene: Xu, X.; Zavalij, P. J.; Doyle, M. P. *Chem. Commun.* **2013**, *49*, 10287.

Regarding the electronic nature of the reaction, normal demand reactions are $HOMO_{dipole}$-$LUMO_{dipolarophile}$ controlled while inverse demand reactions are $LUMO_{dipole}$-$HOMO_{dipolarophile}$ controlled. Catalysis by Lewis acids is due to coordination, which contributes to lowering the LUMO, so coordination must be done with dipolarophile in normal demand reactions and with dipole in inverse demand reactions, being other interactions non-productive. In the absence of chelating reagents (such as 1,3-dicarbonyl compounds) nitrone is preferred for coordination to Lewis acids; under these circumstances normal demand reactions are clearly disfavoured. Moreover, the spontaneous cyclisation that may take place once the nitrone is generated in the presence of the dipolarophile (background reactivity) poses additional inherent difficulties.

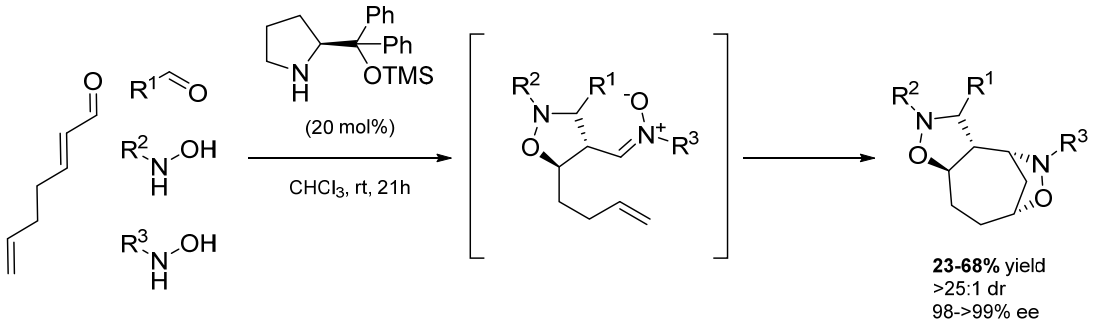
- **Merging organocatalysis with INCR**

In order to incorporate the chiral information for the asymmetric intramolecular cycloaddition of nitrones, a successfully employed strategy is the combination of this process with a previous organocatalytic event, thus circumventing the problems highlighted above. In this manner, the enantioselectivity induced in the organocatalytic step is transferred to the final products in the subsequent cyclisation step. In this context, the organocatalytic α-functionalisation of aldehydes is a well established methodology, using enamine catalysis with chiral secondary amines such as Jørgensen-Hayashi or MacMillan catalysts.[36]

Most examples that merge organocatalytic processes with intramolecular nitrone cycloaddition reactions (INCR) rely on this strategy, usually by means of an enantioselective conjugated addition reaction of aldehydes to nitroalkenes and other α,β-unsaturated systems. A bibliographic review follows covering the direct precedents for the present doctoral thesis.

[36] For representative reviews of enamine catalysis, see: (a) Kano, T.; Maruoka, K. *Chem. Sci.* **2013**, *4*, 907. (b) Pihko, P. M.; Majander, I.; Anniina, E. *Topics Curr. Chem.* **2010**, *291*, 29. (c) Kano, T.; Maruoka, K. *Chem. Commun.* **2008**, 5465. (d) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev*. **2007**, *107*, 5471.

Córdova *et al.* reported a one-pot multicomponent protocol for a highly selective synthesis of cycloheptane derivatives.[37] A chiral proline-derived amine catalyses first a three-component intermolecular cycloaddition between an α,β-unsaturated aldehyde and a nitrone previously formed by condensation of one of the hydroxylamines and the second aldehyde. The resulting aldehyde bearing two new stereocentres is then reacted with the second hydroxylamine affording a further nitrone which reacts intramolecularly with the remote dipolarophile linked to the initial enal by an aliphatic chain. The chirality introduced *via* the first organocatalysed nitrone cycloaddition controls the regiochemistry of the subsequent INCR (in favour of the fused regioisomer) and the absolute configuration of the second isoxazolidine ring (Scheme 1.11).

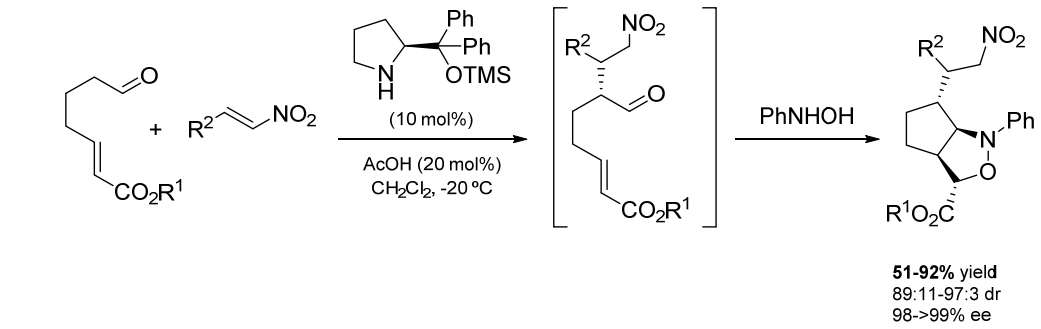


Scheme 1.11

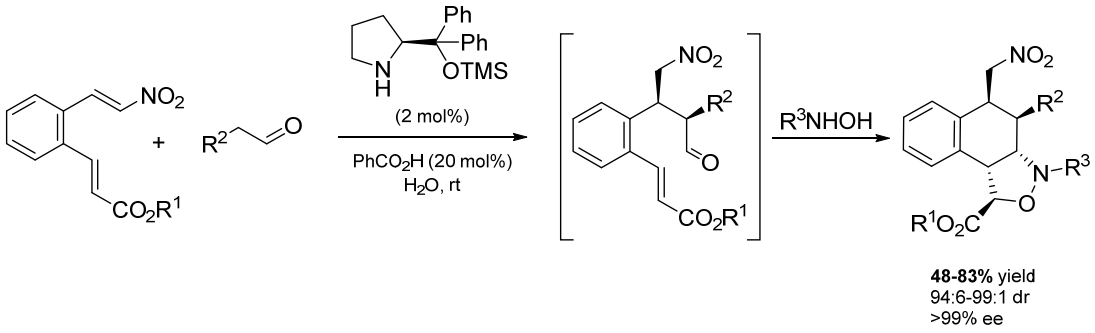
The group of Zhong has been particularly active in this field. They explored various combinations of the one-pot sequence organocatalytic α-alkylation of aldehydes/INCR rendering highly substituted enantiomerically pure bi- or tricyclic isoxazolidines.[38] The dipolarophile for the second step was linked through an aliphatic or aromatic spacer either to the aldehyde moiety or to the electrophile employed for the α-funtionalisation. Interestingly, enantiopure tetralins are accessible by this methodology, a significant scaffold for the present work as it will be seen later (Scheme 1.12).

[37] Vesely, J.; Rios, R.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem. Eur. J.* **2008**, *14*, 2693.
[38] (a) Tan, B.; Zhu, D.; Zhang, L.; Chua, P. J.; Zeng, X.; Zhong, G. *Chem. Eur. J.* **2010**, *16*, 3842. (b) Chua, P. J.; Tan, B.; Yang, L.; Zeng, X.; Zhu, D.; Zhong, G. *Chem. Commun,* **2010**, 611. (c) Zhu, D.; Lu, M.; Dai, L.; Zhong, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 6089.

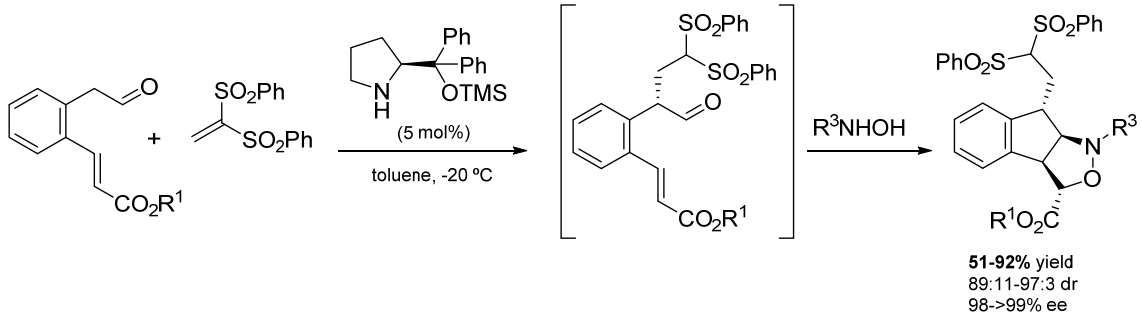
Ref. 38c



Ref. 38a



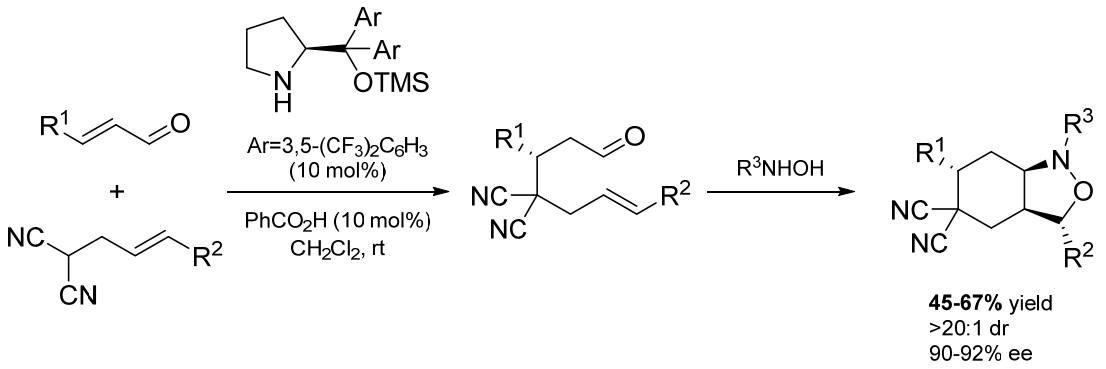
Ref. 38b



Scheme 1.12

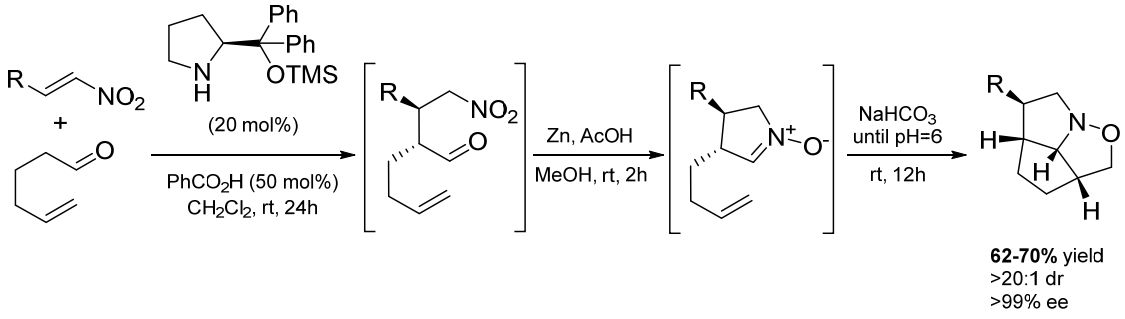
Prior to the present work, only one example of organocatalytic β-functionalisation of aldehydes had been reported in combination with an INCR, taking advantage of iminium catalysis.[39] In this case, the nucleophile (a monoalkylated malononitrile) is attached to the dipolarophile (Scheme 1.13).

[39] Worgull, D.; Dickmeiss, G.; Jensen, K. L.; Franke, P. T.; Holub, N.; Jørgensen, K. A. *Chem. Eur. J*. **2011**, *17*, 4076.



Scheme 1.13

Finally, Merino *et al.* described a one-pot organocatalytic synthesis of tricyclic isoxazolidines starting from acyclic starting materials.[40] In the first step of the synthesis, the α-alkylation of 6-hexenal with 2-nitrostyrenes afforded an enantioenriched aldehyde. In a second operation, this intermediate was subjected to reductive conditions to transform the nitro group into a hydroxylamine, which underwent cyclisation with the aldehyde moiety *in situ*. Finally, correction of the pH allowed the INCR to occurr (Scheme 1.14).



Scheme 1.14

[40] Sádaba, D.; Delso, I.; Tejero, T.; Merino, P. *Tetrahedron Lett.* **2011**, *52*, 5976.

1.1.5. Contextualisation of this work in the field of organofluorine chemistry

The use of organofluorinated compounds has become a valuable and well established tool in life sciences and various industries.[41] The effects of the H/F substitution on the physicochemical and biological properties of biactive compounds is a well understood phenomenon. The first application of this finding dates back to 1953, when it was observed that fluorination of the 9α position of cortisone significantly increased the glucocorticoid activity.[42] The reason lies in the unique properties of fluorine: its high electronegativity, relatively small size, low polarisability and high C-F bond energy.[43] These features make fluorinated drugs more resistant to metabolism and thus especially potent. Lipophilicity is also enhanced in comparison to the non-fluorinated parent molecules. All these results in an increased bioavailability and binding affinity to the corresponding target proteins. For these reasons, organofluorine chemistry has been intensively applied in medicinal chemistry[44] and crop protection.[45] Fluorine has also been used for the elucidation of reaction (or enzimatic) mechanisms as well as in diverse analytical techniques, such as ^{19}F-NMR spectroscopy or ^{18}F-PET, in protein studies on structure, interactions and dynamics.

Given the scarcity of naturally occurring fluorinated compounds, the synthesis of organofluorinated compounds has been and continues to be an active field in organic chemistry. The two main strategies for the incorporation of fluorine atoms into the target compounds are the direct fluorination with

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[41] (a) *Biomedical Frontiers of Fluorine Chemistry* (Eds.Ojima, I.; McCarthy, J. R.; Welch, J. T.), ACS. Symp. Series, 639, American Chemical Society: Washington, D. C., **1996**. (b) *Organofluorine Compounds: Chemistry and Applications* (Ed. Yamamoto, H.), Springer-Verlag, Berlin-Heidelberg, **2000**.

[42] Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1953**, *75*, 2273.

[43] O´Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.

[44] For recent reviews, see: (a) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (d) Hagmann, W. K. *J. Med. Chem.*, **2008**, *51*, 4359. (e) Kirk, K. L. *J. Fluor. Chem.* **2006**, *127*, 1013. (f) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem*, **2004**, *5*, 637.

[45] Jeschke, P. *ChemBioChem* **2004**, *5*, 570.

fluorinating agents and the use of fluorinated building blocks.[46] The latter alternative, to which the present work should be circumscribed, involves the chemical transformation of readily available, easy-to-handle fluorinated small molecules, which very often require special reaction conditions given the particular reactivity arising from fluorine substitution.

Among the fluorinated moieties known in organofluorine chemistry, the incidence of CF_3 groups into pharmaceuticals and agrochemicals is outstandingly high, which converts this moiety into the most widely used among fluorine-containing functional groups.[47] In this context, the generation of novel CF_3-containing scaffolds is always of high interest. Due to the importance of the incorporation of the trifluoromethyl group into organic molecules and considering the benefits of the introduction of fluorine atoms into biologically active compounds,[48] the development of new methodologies that allow for the introduction of this fluorinated one carbon unit has attracted growing attention.[49] It is worth mentioning that the development of new synthetic strategies for the enantioselective construction of chiral centres bearing a CF_3 group represents an

[46] (a) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (b) Shimizu, M.; Hiyama, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 214.

[47] (a) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422. (b) Zhu, W.; Wang, J.; Wang, S.; Gu, Z.; Aceña, J. L.; Izawa, K.; Liu, H.; Soloshonok, V. A. *J. Fluorine Chem.* **2014**, *167*, 37. (c) O'Hagan, D. *J. Fluorine Chem.* **2014**, *167*, 16. (d) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071. (e) Isambor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303. (g) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013.

[48] (a) Bassetto, M.; Salvatore, F.; Fabrizio, P. *Future Med. Chem.* **2015**, *7*, 527. (b) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315. (c) Prakash, G. K. S.; Fang, W. *Chim. Oggi* **2012**, *30*, 30. (d) Furuya, T. Kamlet, A. S. Ritter, T. *Nature* **2011**, *473*, 470. (e) Yamazaki, T.; Taguchi, T.; Ojima, I. *Fluor. Med. Chem. and Chem. Biol.* **2009**, 3. (f) Filler, R.; S., Rituparna *Future Med. Chem.* **2009**, *1*, 777. (g) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (h) Ref. 44c.

[49] For recent reviews on trifluoromethylation reactions, see: (a) Alonso, C.; Martínez de Marigorta, E.; Rubiales, G.; Palacios, F. *Chem. Rev*. **2015**, *115*, 1847. (b) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev*. **2015**, *115*, 826. (c) Ni, C.; Hu, M.; Hu, J. *Chem. Rev*. **2015**, *115*, 765. (d) Xu, X.-H.; Matsukazi, K.; Shibata, N. *Chem. Rev*. **2015**, *115*, 731. (e) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev*. **2015**, *115*, 683. (f) Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev*. **2015**, *115*, 650. (g) Gao, P.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M. *Chem. Eur. J.* **2015**, *21*, 7648. (h) Wang, S.-M.; Han, J.-B.; Zhang, C.-P.; Qin, H.-L.; Xiao, J.-C. *Tetrahedron* **2015**, *71*, 7949.

important challenge in organic synthesis. In fact, few examples have recently been reported in the literature, and all of them concern intermolecular processes.[50]

1.1.6. Fluorinated dipolarophiles in INCR

Despite the widespread use of 1,3-dipolar cycloadditions with nitrones as the dipole counterpart, the use of fluorinated starting materials lagged behind. Nitrones, azomethine ylides and azides are the most widely used dipoles in conjunction with fluorinated substrates.[51] In this context, the development of new methodologies that give access to fluorinated isoxazolidine derivatives[52] is highly attractive since hydrogenolysis of the N-O bond would generate 1,3-amino alcohols as precursors of the corresponding fluorinated β-amino acids.[53]

Furthermore, while several examples of intermolecular reactions (most of them involving fluorinated dipolarophiles) have been reported in the literature, the INCR concerning fluorine-containing substrates remained almost unexplored. A bibliographic review on these precedents follows.

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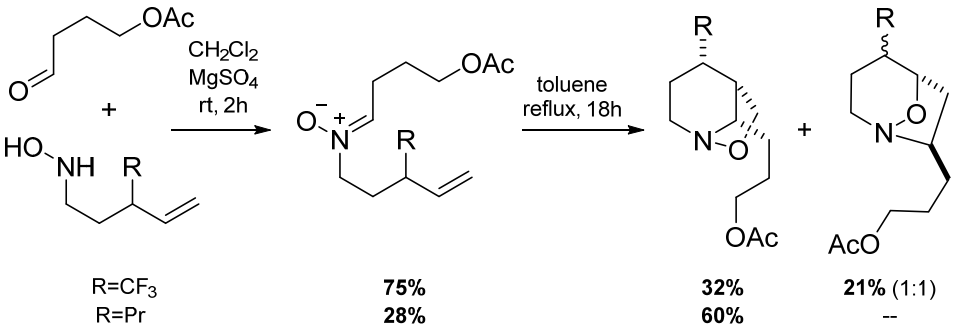
[50] (a) Hou, X.; Ma, H.; Zhang, Z.; Xie, L.; Qin, Z.; Fu, B. *Chem. Commun.* **2016**, *52*, 1470. (b) Chen, Q.; Wang, G.; Jiang, X.; Xu, Z.; Lin, L.; Wang, R. *Org. Lett.* **2014**, *16*, 1394. (c) Kawai, H.; Yuan, Z.; Kitayama, T.; Tokunaga, E.; Shibata, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 5575. (d) Kawai, H.; Okusu, S.; Tokunaga, E.; Sato, H.; Shiro, M.; Shibata, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 4959. (e) Gao, J.-R.; Wu, H.; Xiang, B.; Yu, W.-B.; Han, H.; Jia, Y.-X. *J. Am. Chem. Soc.* **2013**, *135*, 2983. (f) Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2012**, *134*, 10769.

[51] For selected recent references, see: (a) Ponce, A.; Alonso, I.; Adrio, I.; Carretero, J. C. *Chem. Eur. J.* **2016**, *22*, 4952. (b) Yamada, S.; Higashi, M.; Konno, T.; Ishihara, T. *Eur. J. Org. Chem.* **2016**, 4561.(c) Tomaszewska, J.; Kowalska, K.; Koroniak-Szejn, K. *J. Fluorine Chem.* **2016**, *191*, 1. (d) McAlpine, I.; Tran-Dube, M.; Wang, F.; Scales, S.; Matthews, J.; Collins, M. R.; Nair, S. K.; Nguyen, M.; Bian, J.; Martinez Alsina, L.; Sun, J.; Zhong, J.; Warmus, J. S.; O'Neill, B. T. *J. Org. Chem.* **2015**, *80*, 7266. (e) Li, Q.-H.; Wei, L.; Chen, X.; Wang, C.-J. *Chem. Commun.* **2013**, *49*, 6277. (f) Li, Q.-H.; Xue, Z.-Y.; Tao, H.-Y.; Wang, C.-J. *Tetrahedron Lett.* **2012**, *53*, 3650. (g) Yan, D.; Li, Q.; Wang, C.-J. *Chin. J. Chem.* **2012**, *30*, 2714. (h) Li, Q.-H.; Tong, M.-C.; Li J.; Tao, H.-Y.; Wang, C.-J. *Chem. Commun.* **2011**, *47*, 11110. (i) Xie, H.; Zhu, J.; Chen, Z.; Li, S.; Wu, Y. *J. Org. Chem.* **2010**, *75*, 7468.

[52] Kumar, V.; Kaur, K. *J. Fluorine Chem.* **2015**, *180*, 55.

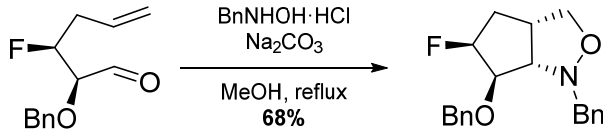
[53] For the relevance of fluorinated beta-amino acids, see: (a) March, T. L.; Johnston, M. R.; Duggan, P. J.; Gardiner, J. *Chem. & Biodiv.* **2012**, *9*, 2410. (b) Mikami, K.; Fustero, S.; Sánchez-Roselló, M.; Aceña, J. L.; Soloshonok, V. A.; Sorochinsky, A. *Synthesis* **2011**, 3045. (c) Qiu, X.-L.; Qing, F.-L. *Eur. J. Org. Chem.* **2011**, 3261. (d) Aceña, J. L.; Simón-Fuentes, A.; Fustero, S. *Curr. Org. Chem.* **2010**, *14*, 928. (e) Sorochinsky, A.; Soloshonok, V. A. *J. Fluorine Chem.* **2010**, *131(2),* 127. (f) Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711. (g) Fustero, S.; Sanz-Cervera, J. F.; Soloshonok, V. A. In: *Enantioselective Synthesis of* β*-Amino Acids*, *2nd edition* (Eds.; Juaristi, E. C.; Soloshonok, V. A.), Wiley-VCH Ltd, New York, **2005,** p. 319.

Holmes *et al.* explored the utility of INCR for the synthesis of polyhydroxylated alkaloids.[54] The nitrone bearing a trifluoromethyl group in an allylic position affords upon cycloaddition a mixture of the two possible regioisomers, one of them as a single diastereoisomer and the other one as an equimolar mixture of two. In contrast, the non-fluorinated nitrone bearing a propyl group reacts to a single product. It is thus a case of inversion of regioselectivity promoted by the presence of a CF_3 group (Scheme 1.15).



Scheme 1.15

Resnati *et al.* reported the synthesis of deoxy-fluoro aminocyclopentanols as potential inhibitors of glycoprotein processing enzymes applying an INCR in the synthetic sequence.[55] A cyclopentanoisoxazolidine was obtained as a single isomer (Scheme 1.16).



Scheme 1.16

The same group reported later the asymmetric synthesis of fluoromethyl substituted β-amino acid derivatives of related structures *via* INCR and reductive cleavage (Scheme 1.17).[56]

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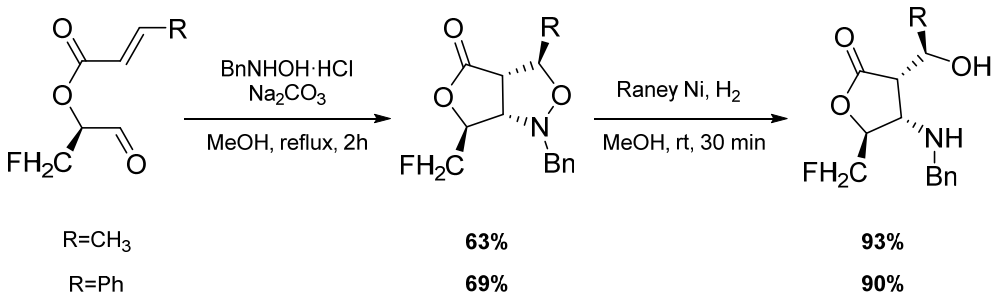
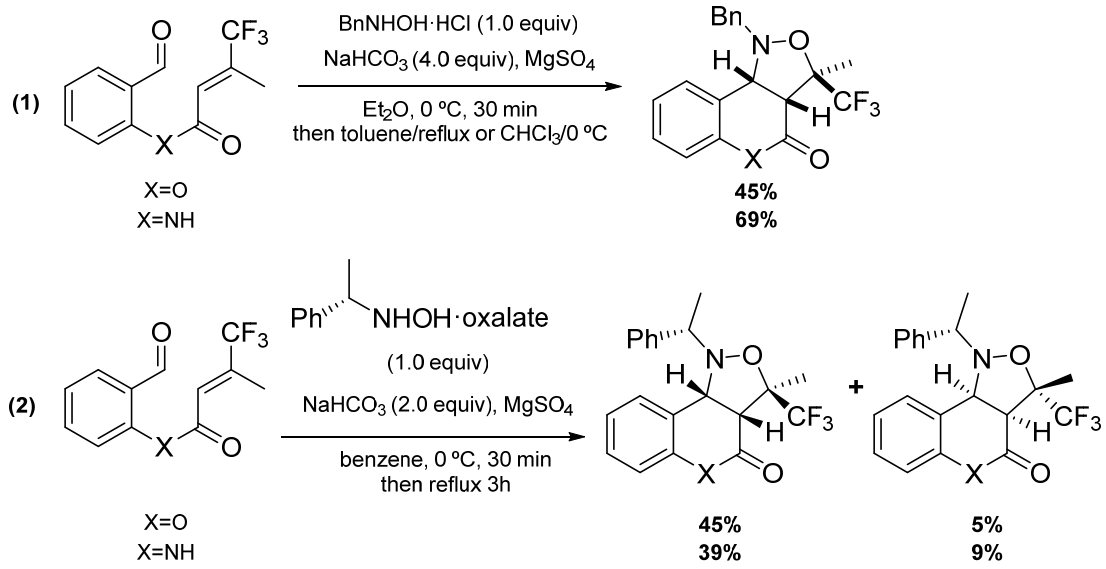
[54] Collins, I.; Nadin, A.; Holmes, A. B.; Long, M. E.; Man, J.; Baker, R. *J. Chem. Soc., Perkin Trans I* **1994**, 2205.
[55] Arnone, A.; Cavicchioli, M.; Donadelli, A.; Resnati, G. *Tetrahedron: Asymmetry* **1994**, *5*, 1019.
[56] Arnone, A.; Blasco, F.; Resnati, G. *Tetrahedron* **1997**, *53*, 17513.



Scheme 1.17

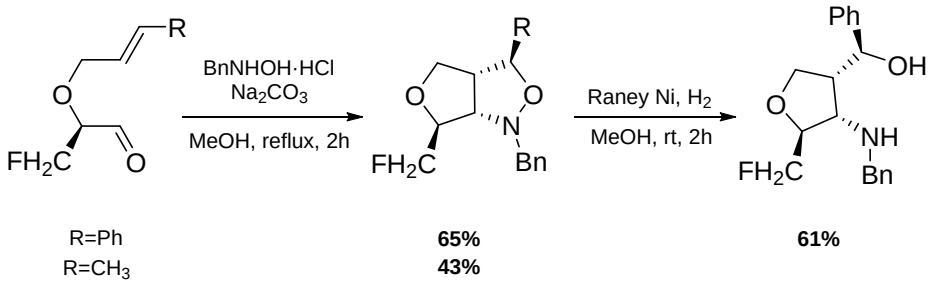
Bruché *et al.* described the synthesis of CF_3-containing isoxazolidino[4,3c] chroman-4-ones and quinolin-4-ones by INCR both in a racemic and a diastereoselective manner.[57] Reaction of the starting fluorinated benzaldehydes with *N*-benzylhydroxilamine afforded the *cis*-fused isoxazolidine as a single isomer (Scheme 1.18, equation 1), while the use of (*S*)-*N*-(1-phenylethyl)hydroxylamine resulted in a 4:1 to 9:1 mixture of the two diastereoisomers of the corresponding isoxazolidine (Scheme 1.18, equation 2).



Scheme 1.18

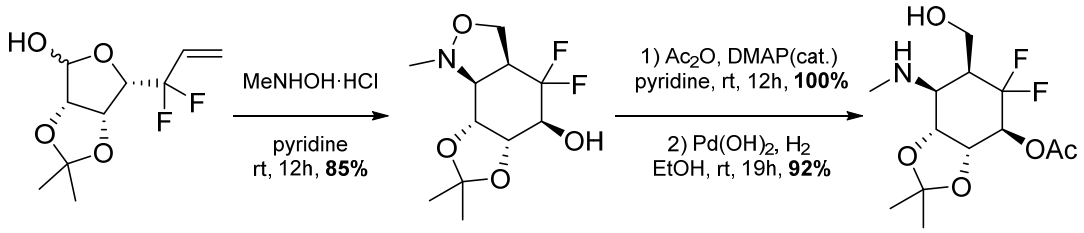
The same group reported a similar synthetic sequence of that by Resnati, rendering the tetrahydrofuran derivatives depicted in Scheme 1.19.[58]

[57] (a) Arnone, A.; Broggini, G.; Bruché, L.; Molteni, G.; Zecchi, G. *J. Chem. Res. (S)* **1998**, *10*, 188. (b) Arnone, A.; Bruché, L.; Garanti, L.; Zecchi, G. *J. Chem. Res. (S)* **1995**, *7*, 282.
[58] Bandiera, P.; Bravo, P.; Bruché, L.; Zanda, M.; Arnone, M. *Synth. Commun.* **1998**, *28*, 2665.



Scheme 1.19

Finally, carbohydrate derived, fluorinated substrates can also serve as chiral templates for an asymmetric INCR. The group of Singh reported the synthesis of a difluorinated carbasugar (a cyclic monosaccharide analogue in which the ring oxygen atom is substituted by a methylene group) as a potential carbohydrate mimic (glycosidase inhibitor).[59] A D-ribose derived fluorinated hemiacetal was subjected to cycloaddition conditions affording the corresponding fused isoxazolidine as a single isomer. After simple transformations, the target fluorinated carbasugar was obtained in 92% yield (Scheme 1.20).



Scheme 1.20

From the examples shown in this introduction, it is clear that the use of fluorinated substrates in INCR is underdeveloped in comparison with the non-fluorinated counterparts. In the present work, the use of trifluoromethyl styrenes as novel fluorinated dipolarophiles in INCR will be evaluated, as it is indicated in the objectives shown below.

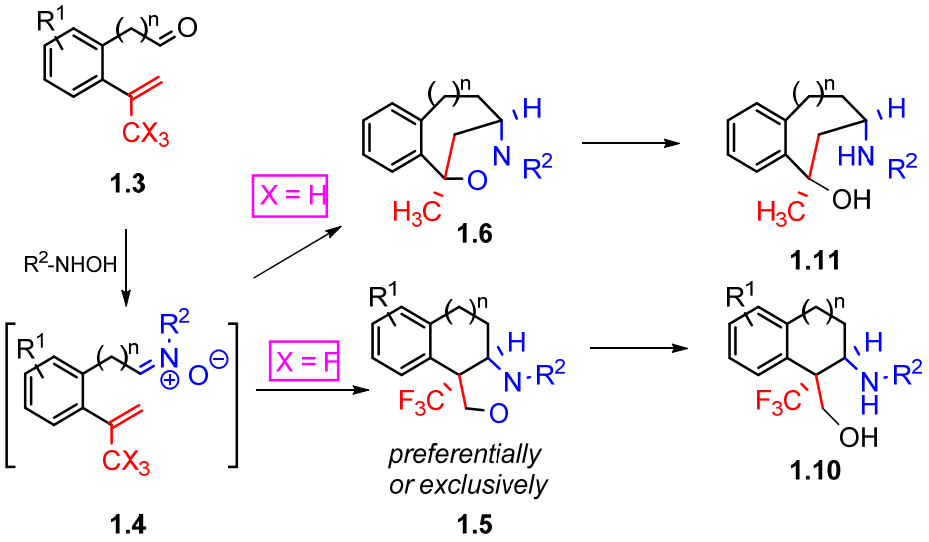
[59] Jiang, S.; Singh, G.; Batsanov, A. *Tetrahedron: Asymmetry* **2000**, *11*, 3873.

1.2. Objectives

1.2.1. Objectives in Part A: Intramolecular Nitrone Cycloaddition of α-Trifluoromethyl Styrenes. Role of the CF_3 Group in the Regioselectivity

The main goal of the first part of Chapter 1 is the exploration of the reactivity of 1,1,1-trifluoromethylstyrene derivatives **1.3** as novel fluorinated dipolarophiles in intramolecular nitrone cycloadditions.

The role of the trifluoromethyl group in the regioselectiviy of the reaction will be investigated both experimentally (by comparison with non-fluorinated analogues) and with the aid of a complementary computational study.

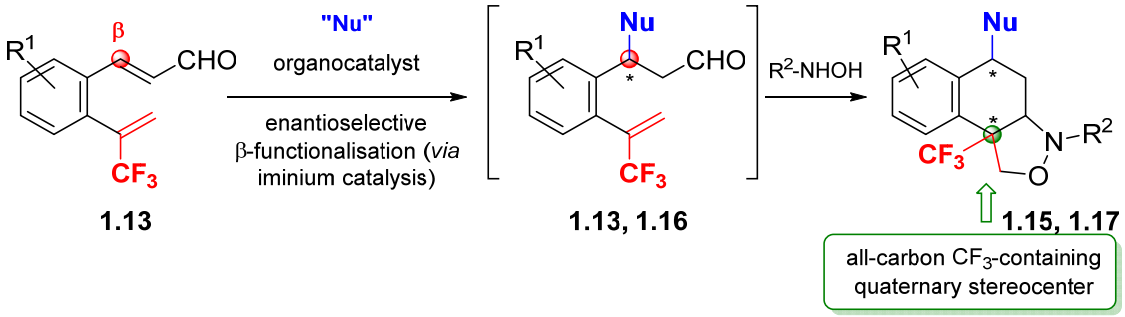


Scheme 1.21

To illustrate the synthetic utility of this methodology, the obtained isoxazolidines will be reductively opened to the corresponding 1,3-amino alcohols with an all-carbon stereocentre bearing a trifluoromethyl group.

1.2.2. Objectives in Part B: Organocatalytic Enantioselective Synthesis of Trifluoromethyl-Containing Tetralin Derivatives by Sequential (Hetero)Michael Reaction-Intramolecular Nitrone Cycloaddition

In the second part of this chapter, an asymmetric version of the previously established intramolecular nitrone cycloaddition will be developed. To this end, the enantioselective organocatalytic β-functionalisation of the starting aldehydes by iminium catalysis followed by intramolecular nitrone cycloaddition in the conditions optimised in Part A is envisaged.



Scheme 1.22

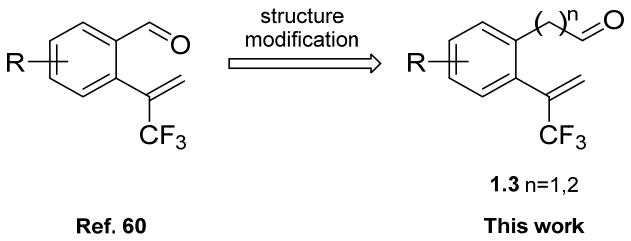
A screening of different nucleophiles will be undertaken in order to generate different families of fluorinated cycloadducts by the mentioned sequence. The stereochemical outcome of the cycloaddition step in the synthesis of each family of compounds will be studied experimentally, as well as on the basis of a comprehensive computational analysis.

Finally, as in Part A, the synthesised products will be further transformed into the corresponding fluorinated 1,3-amino alcohols.

1.3. Results and Discussion. Part A: Intramolecular Nitrone Cycloaddition of α-Trifluoromethyl Styrenes. Role of the CF_3 Group in the Regioselectivity

1.3.1. Design and synthesis of starting materials 1.3

Our interest for new fluorinated dipolarophiles in 1,3-dipolar cycloaddition reactions arose from the wish to comprehensively study the reactivity of a family of fluorine-containing substrates previously synthesised using a methodology developed in our group.[60] These compounds were benzaldehydes bearing a 3,3,3-trifluoropropenyl group in the *ortho* position which was incorporated by a slight modification of an earlier methodology (Scheme 1.23).[61]



Scheme 1.23

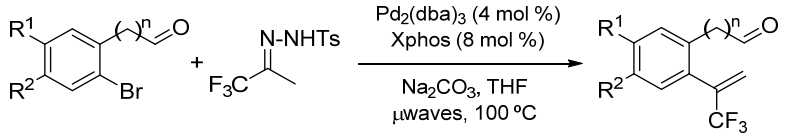
Among the alkene reactivity modes that were programmed for screening, we envisioned that this fluorinated moiety could render an interesting dipolarophile in 1,3-dipolar cycloaddition reactions. The aromatic linker is both necessary for the incorporation of the dipolarophile under study and synthetically useful as it allows structural variability from commercially available starting materials. However, from the onset, it was obvious that the linker distance would need to be lenghthened to permit the formation of products of significant ring-size (5- and 6-membered rings). We decided to keep the aldehyde group in our new substrate since it is a versatile functionality serving as a precursor for different dipoles (nitrones and azomethine ylides among others). Thus, for the sake of

[60] Sedgwick, D. M.; Barrio, P.; Simón, A.; Román, R.; Fustero. S. *J. Org. Chem.* **2016**, *81*, 8876.
[61] Jiménez-Aquino, A.; Vega, J. A.; Trabanco, A. A.; Valdés, C. *Adv. Synth. Catal.* **2014**, *356*, 1079.

simplicity, we decided to place one or two additional methylene groups between the aromatic ring and the aldehyde moiety (Scheme 1.23).

To this end, *o*-bromoacetaldehydes (n=1) and *o*-bromopropionaldehydes (n=2) **1.1** were subjected to the mentioned cross-coupling conditions, which involved the use of fluorinated hydrazone **1.2**, $Pd_2(dba)_3$ as the catalyst, Xphos as a ligand and Na_2CO_3 as a base, in THF under microwave irradiation. Under these conditions, moderate to good yields of the corresponding trifluoromethyl styrenes **1.3** were obtained, as depicted in Table 1.1.

Table 1.1 Synthesis of the starting trifluoromethyl-containig aldehydes **1.3**



1.1 **1.2** **1.3**

Entry	**1.1**	n	R^1	R^2	**1.3**	% yield[a]
1	**1.1a**	1	H	H	**1.3a**	63
2	**1.1b**	2	H	H	**1.3b**	77
3	**1.1c**	1	F	H	**1.3c**	44
4	**1.1d**	2	F	H	**1.3d**	81
5	**1.1e**	1	-O-CH_2-O-		**1.3e**	41
6	**1.1f**	2	-O-CH_2-O-		**1.3f**	72

[a] Isolated yield after flash column chromatography. Due to their instability, these aldehydes have to be used immediately after purification.

At this point, it should be mentioned that the greatest difficulty of this whole project was no doubt the preparation of starting materials. First of all, these fluorinated aldehydes are themselves quite unstable and they had to be purified quickly and used immediately in the cycloaddition step. (See the Experimental Section for further details.) If left for a prolonged time under air and/or at room

temperature, additional NMR signals appear on the spectra. It was assumed that they correspond to subproducts possibly originating from the oxidation or aldol condensation of the aliphatic chain of the aldehydes. Secondly, the cross-coupling reaction referred above is of a somehow capricious nature, since some batches failed to provide complete or any conversion at all under the exact same conditions. This is a big issue given that starting material and product are not separable by column chromatography. A strict procedure has to be followed to prevent this from happening, and it basically involves careful drying of all the solid reagents under vacuum and moderate heating from a heat gun until a loose grey powder is obtained. It was speculated that ethanol traces contained in the hydrazone interfere harmfully in the palladium catalysis. Even taking these precautions, some of the batches failed for reasons still unknown.

1.3.2. Optimisation of the INCR

With starting aldehydes **1.3** in hand, the next step of our study was the formation of the corresponding nitrones by condensation with hydroxyl amines. The optimisation of the reaction conditions was performed with compound **1.3b** as a model substrate and *N*-methylhydroxyl amine (Table 1.2). In all cases, intermediate nitrones **1.4** were not isolated, but cyclised spontaneously under the reaction conditions in the 1,3-dipolar mode hence rendering the corresponding isoxazolidines **1.5** and **1.6**. The stereochemistry of the regioisomers will be discussed in 1.3.3.

Table 1.2 Optimisation of the dipolar cycloaddition reaction

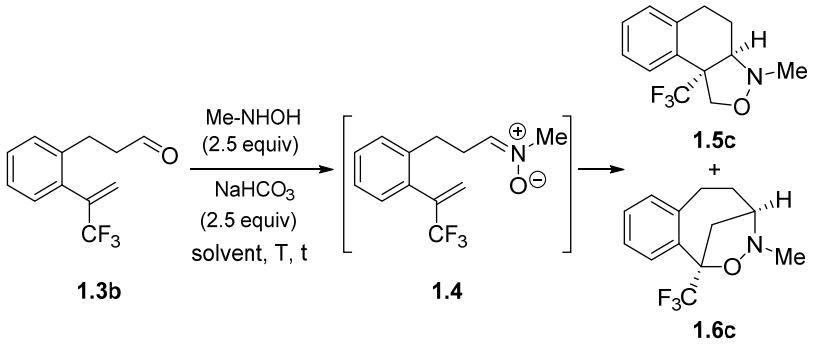


Table 1.2 *(continued)*

Entry	Reaction conditions	**1.5c** (% yield)[a]	**1.6c** (% yield)[a]
1	EtOH/H_2O (80/20), rt, 15h	-[b]	-[b]
2	EtOH/H_2O (80/20), reflux, 15h	14	28
3	EtOH/H_2O (80/20), μwaves, 100 °C, 3h	14	28
4	DCM, μwaves, 60 °C, 3h	13	13
5	toluene, μwaves, 120 °C, 30 min	55	29

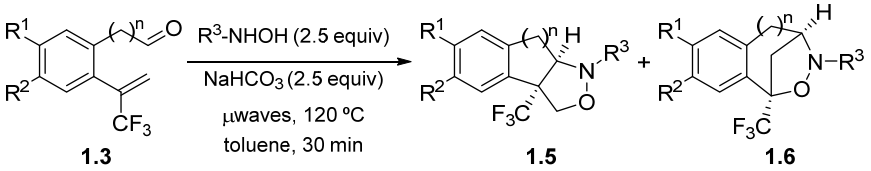
[a] Isolated yield after flash column chromatography.
[b] Complex mixture of products.

The formation of the nitrone and subsequent dipolar cycloaddition was initially tested with *N*-methylhydroxylamine hydrochloride in the presence of sodium bicarbonate in a mixture of ethanol and water as the solvent. Unfortunately, after 15h at room temperature, a complex mixture of products was observed (Table 1.2, entry 1). Nevertheless, when the reaction mixture was heated at reflux, a mixture of two regioisomeric cycloadducts **1.5c** and 1.**6c** was isolated albeit in low yield (Table 1.2, entry 2). (Both regioisomers were unambiguously identified by mono- and bidimensional NMR experiments. See the Experimental Section for details.) In order to reduce the reaction time, microwave irradiation was employed and, after 3h at 100 °C, comparable results to those obtained under conventional heating were obtained (Table 1.2, entry 3). Changing the solvent to dichloromethane did not improve the efficiency of the process (Table 1.2, entry 4); however, the use of toluene produced a dramatic change since, after 30 min at 120 °C, 55% of the linear adduct **1.5c** was obtained together with 29% of the bridged product **1.6c** (Table 1.2, entry 5). These last reaction conditions were chosen for the rest of the project, both in Parts A and B.

1.3.3. Study of the scope of the INCR

The optimised reaction conditions for the INCR were then applied to the rest of trifluoromethyl styrenes **1.3**. The results obtained are depicted in Table 1.3.

Table 1.3 Scope of the dipolar cycloaddition of substrates **1.3**



Entry	**1.3**	n	R^1	R^2	R^3	**1.5**, % yield[a]	**1.6**, % yield[a]
1	**1.3a**	1	H	H	Me	**1.5a**, 44	**1.6a**, 25
2	**1.3a**	1	H	H	Bn	**1.5b**, 35	traces
3	**1.3b**	2	H	H	Me	**1.5c**, 55	**1.6c**, 29
4	**1.3b**	2	H	H	Bn	**1.5d**, 46	**1.6d**, 23
5	**1.3c**	1	F	H	Me	**1.5e**, 33	**1.6e**, 3
6	**1.3c**	1	F	H	Bn	**1.5f**, 28	**1.6f**, 30
7	**1.3d**	2	F	H	Me	**1.5g**, 50	**1.6g**, 13
8	**1.3d**	2	F	H	Bn	**1.5h**, 39[b]	**1.6h**, 16[b]
9	**1.3e**	1	-O-CH_2-O-		Me	**1.5i**, 42	traces
10	**1.3e**	1	-O-CH_2-O-		Bn	**1.5j**, 97	traces
11	**1.3f**	2	-O-CH_2-O-		Me	**1.5k**, 88	traces
12	**1.3f**	2	-O-CH_2-O-		Bn	**1.5l**, 79	traces

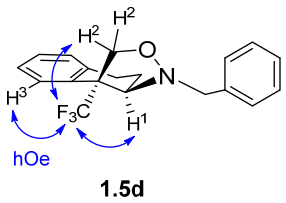
[a] Isolated yield after flash column chromatography.
[b] An inseparable mixture of isoxazolidines **1.5h** and **1.6h** was obtained.

In almost all cases, the dipolar cycloaddition leading to fused tricyclic derivatives **1.5** was preferred over the formation of bridged compounds **1.6**. On

the other hand, starting aldehydes **1.3** with two methylene groups (n=2) cyclised more efficiently, probably due to steric reasons.

Substrates non-substituted in the aromatic ring provided better yields with methyl hydroxylamine, rendering ca. 2:1 mixtures of regioisomers **1.5** and **1.6** (Table 1.3, entries 1,3). The reactions with *N*-benzylhydroxylamine gave lower yields of the corresponding cycloadducts, again favouring fused products **1.5** over bridged ones **1.6** (Table 1.3, entries 2,4). The presence of an electron-withdrawing group in the aromatic ring such as a fluorine atom led to lower yields and comparable regioselectivities, in general (Table 1.3, entries 5-8). In contrast, when electron-donating groups were placed in the aromatic ring, fused compounds **1.5** were obtained as unique products in generally good yields (Table 1.3, entries 9-12).

The relative stereochemistry of the fused derivatives **1.5** was determined by means of NMR experiments on compound **1.5d**. Heteronuclear correlation (HOESY) between the fluorine nuclei and proton H^1 at the fusion of the two aliphatic rings allowed us to assign the *cis* relative stereochemistry between them. Additional correlations with protons H^2 and H^3 were also observed (Figure 1.1). The same stereochemistry was assumed for all derivatives **1.5**. See the Experimental Section for further details.



1.5d

Figure 1.1

Regarding the structural elucidation, ^{19}F-NMR of bridged compounds **1.6c,d,g,h** showed broad signals. However, after performing an NMR study at different temperatures on compound **1.6g**, we found that it was formed as a single product. ^{19}F-NMR at high temperature (100 °C, DMSO-d6) afforded a singlet signal for the CF_3 group (Figure 1.2) whereas three signals corresponding to the three different fluorine atoms were observed at low temperature (-40 °C, $CDCl_3$). (Figures 1.3 and 1.4).

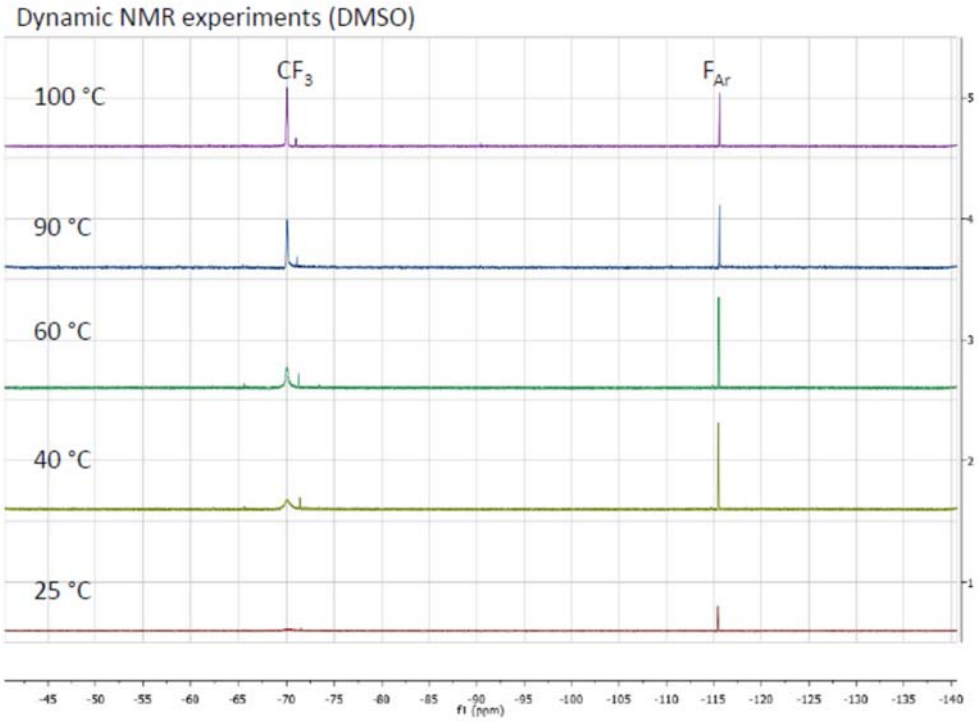


Figure 1.2

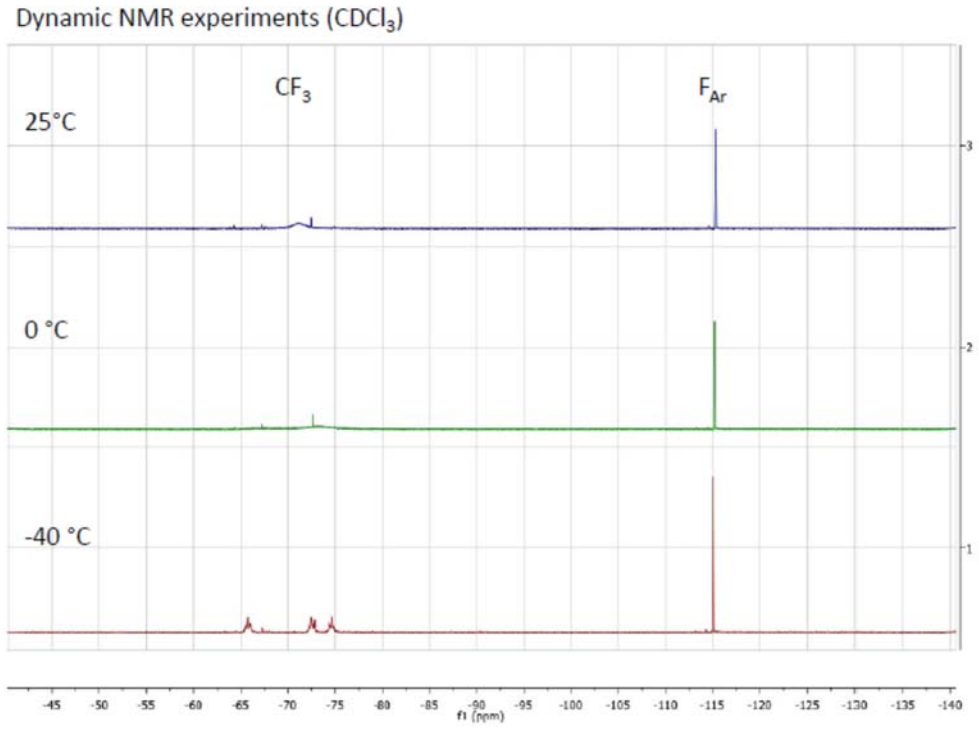


Figure 1.3

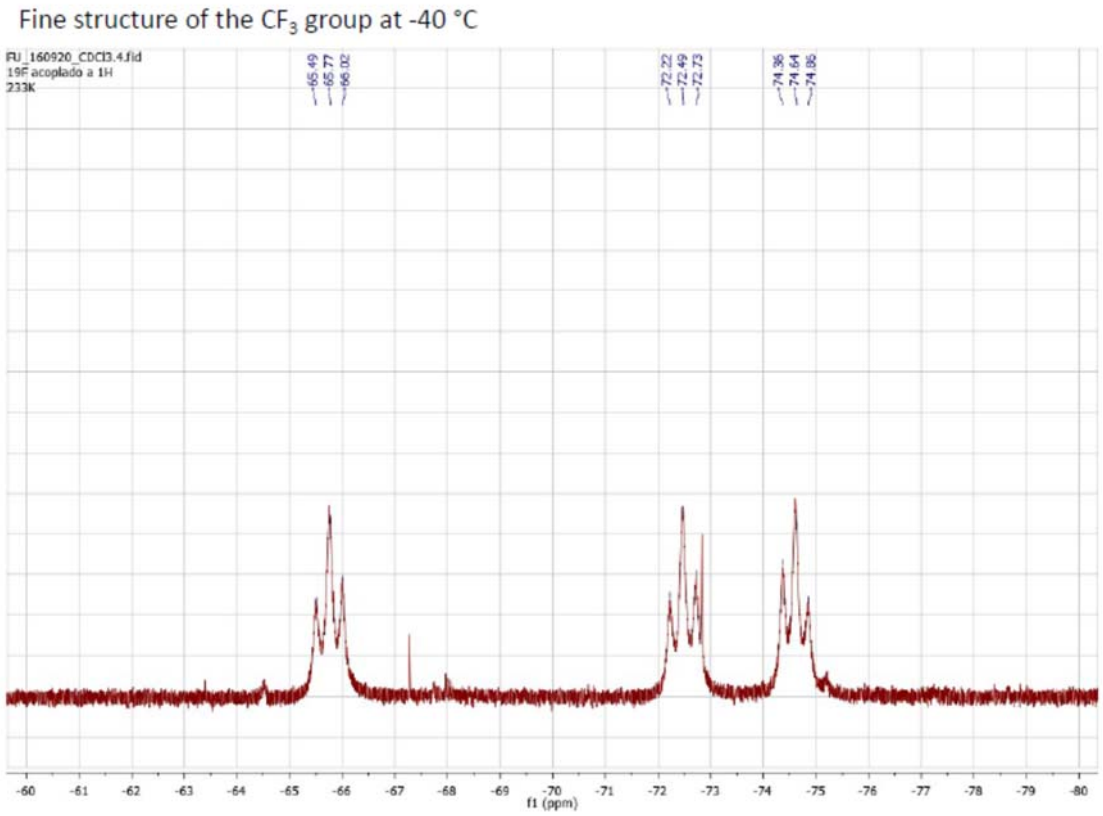
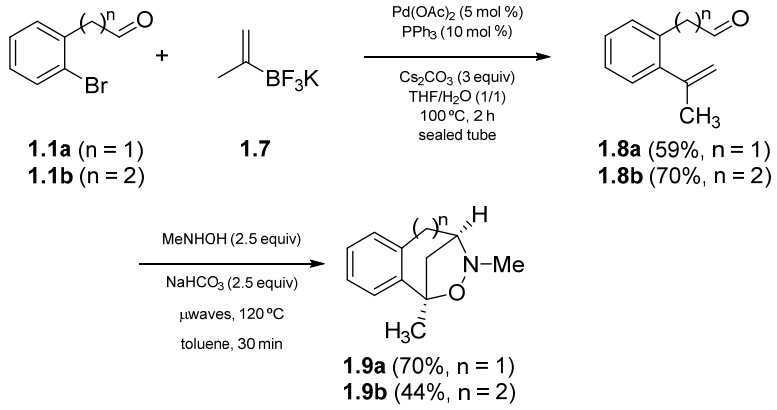


Figure 1.4

1.3.4. Role of the CF_3 Group in the Regioselectivity. Experimental study

In order to evaluate the influence of the fluorinated moiety in the cycloaddition process, styrenes containing a methyl instead of the trifluoromethyl group were synthesised. Accordingly, substrates **1.8** were assembled by Suzuki coupling of the starting bromo-aldehydes **1.1** and trifluoroalkylborate **1.7**.[62] After heating both components in the presence of $Pd(OAc)_2$ in a sealed tube in a THF/H_2O mixture, *ortho*-substituted styrenes **1.8** were obtained in good yields (Scheme 1.24). When these substrates were subjected to the optimised INCR conditions, bridged products **1.9** were observed in moderate to good yields together with trace amounts of the corresponding fused products. Therefore, an inversion of the regioselectivity occurred when compared to the cyclisation of fluorinated derivatives **1.3**.

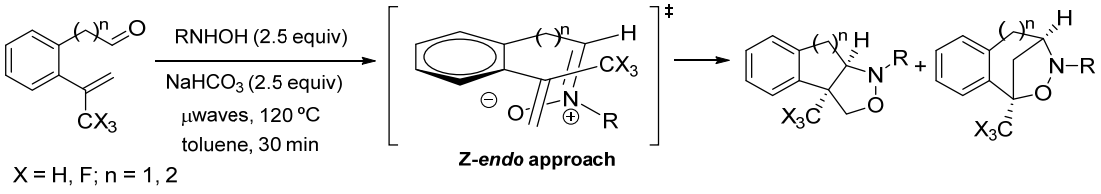
[62] Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107.



Scheme 1.24

1.3.5. Role of the CF_3 Group in the Regioselectivity. Computational study

To gain insight into the mechanistic details of this transformation, we carried out a preliminary theoretical study by using DFT method at the B3LYP/6-31G* (d, p) level. (Computational calculations were carried out by Professor Amparo Asensio from the University of Valencia.) The stationary points were characterised by frequency computations in order to verify their nature. Transition structures (TS) were found to have only one imaginary frequency.



Scheme 1.25

In order to simplify the results, among 32 possible TS only 8 that correspond to the *Z*-nitrone with an *endo* approach were included as they were the lowest in energy (Scheme 1.25). The TS A-D, related to the methyl derivatives (X = H), indicated that the formation of the bridged cycloadducts is slightly more favourable when n = 2 as TS D is 1.10 Kcal/mol more stable than TS C. Nevertheless, the energy difference is minimum when n=1 being TS B only 0.07

Kcal/mol more stable than TS A (Figure 1.5) (for details, see the Experimental Section). In fact, experimental results showed that bridged products **1.9** were isolated (see Scheme 1.24) while only traces of the regioisomeric fused products were detected by NMR. This is probably due to the instability of the linear derivatives that decompose under the reaction conditions. The situation is different with fluorinated substrates; *i.e.* in this case both TS E and TS G, which lead to fused cycloadducts **1.5** with n = 1 and n = 2, are 3.63 Kcal/mol and 2.71 Kcal/mol more stable, respectively than TS F and TS H (Figure 1.5). These theoretical findings showed the same trend as the experimental results (see Table 1.3 and Scheme 1.24).

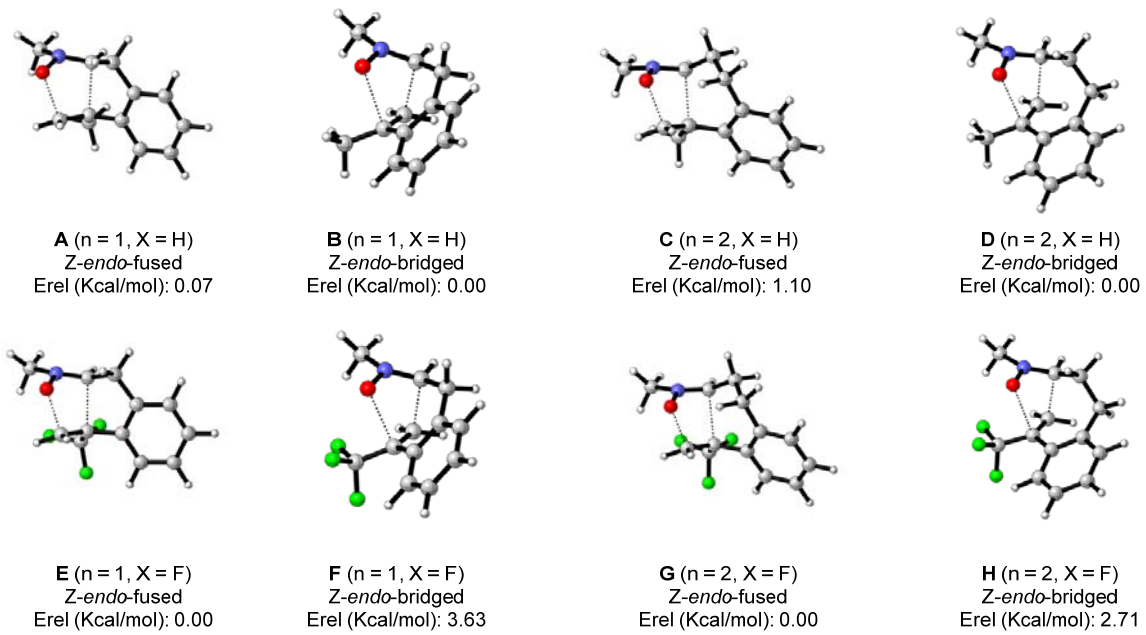


Figure 1.5

Table 1.4 B3LYP/6-31G* total (E, in au) and relative[a] (ΔE, in kcal/mol) gas phase energies of transition states involved in the cycloaddition reaction of nitrones and distances for the two forming bonds in the TSs

System	n	***X=H***	E	ΔE	d(C-C) Å	d(C-O) Å
TSA	1		-595.922374	0.07	2.167	2.084
TSB	1		-595.92249	0.00	2.065	2.458
TSC	2		-635.198214	1.10	2.276	2.028
TSD	2		-635.199971	0.00	2.073	2.444
System	n	***X=H***	E	ΔE	d(C-C) Å	d(C-O) Å
TSE	1		-893.675523	0.00	2.226	1.986
TSF	1		-893.669742	3.63	2.060	2.418
TSG	2		-932.951685	0.00	2.361	1.923
TSH	2		-932.947371	2.71	2.045	2.452

[a] Relative to the most stable TS in any series.

With this data in hand, it became apparent that both steric and electronic effects play an important role in the cycloaddition process. Steric reasons are always invoked to explain the preferred formation of fused over bridged cycloadducts in intramolecular 1,3-dipolar cycloadditions with nitrones. However, in our case the regioselectivity of the process is also clearly influenced by the electronic nature of the substituents in the aromatic ring and the presence of the trifluoromethyl moiety.

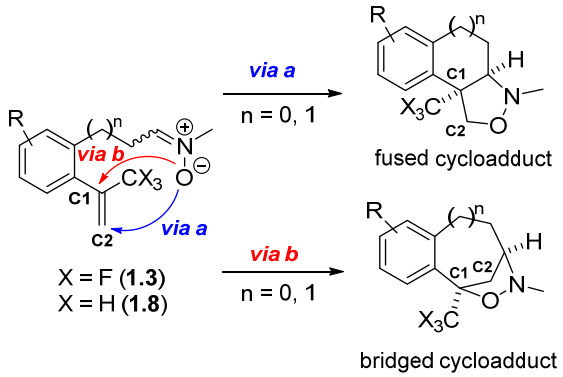
Regarding the trifluoromethyl group, its electron-withdrawing effect makes the benzylic carbon C1 more electrophilic for the *O*-nitrone attack. However, substrates **1.3** rendered as major products fused cycloadducts **1.5** in contrast to substrates **1.8** containing a methyl group, which rendered exclusively bridged adducts **1.9** arising from the C1-attack (Scheme 1.26). This indicates that steric requirements of the CF_3 moiety are more important than electronic effects since the preferential nitrone approach leads to the C2-O bond (Scheme 1.26, *via a*). On the other hand, from Table 1.4 it can be seen that for the bridged transition

structures (B, D, F and H), forming C–C bond lengths (2.065, 2.073, 2.060 and 2.045 Å, respectively) are shorter than C–O distances. However, the opposite trend is found for fused transition structures (A, C, E and G), with forming C-O bond lengths (2.084, 2.028, 1.986 and 1.923 Å, respectively) being shorter than C–C distances. Such a reversed situation is in agreement with 1,3-dipolar cycloadditions with electron-deficient dipolarophiles.[63]

Taking into account that C-O distances are shorter in the TSs leading to fused cycloadducts, it can be assumed that the reaction proceeds as a Michael-type addition with the nitrone oxygen acting as a nucleophile. Moreover, the bridged TSs, representing a typical asynchronous process, can be considered as early transition states as indicated by the relative long distance of the forming C-O bonds.[64] Since both CF_3- and CH_3- containing substrates follow the same trend in terms of bond forming lengths, this indicates that the C2-position is not playing an important role in the regioselectivity. Therefore, it seems that steric effects of the trifluoromethyl group are more important than electronic effects.

Regarding the electronic nature of substituents in the aromatic ring, electron-withdrawing groups would enhance the electrophilicity of the benzylic carbon C1, thereby increasing the preference for the oxygen attack on this carbon (Scheme 1.26, *via b*), while electron-donating substituents would induce the opposite effect (Scheme 1.26, *via a*). When both effects operate in the same direction, *i. e.,* substrates bearing a trifluoromethyl group and electron-donating substituents in the aromatic ring, an excellent control of the regioselectivity could be achieved, rendering exclusively the fused adducts **1.5i-l** (See Table 1.3, entries 9-12).

[63] Merino, P.; Revuelta, J.; Tejero, T.; Chiacchio, U.; Rescifina, A.; Romeo, G. *Tetrahedron* **2003**, *59*, 3581.
[64] Aurell, M. J.; Domingo, L. R.; Pérez, P.; Contreras, R. *Tetrahedron* **2004**, *60*, 11503.



Scheme 1.26

1.3.6. Synthesis of fluorinated 1,3-amino alcohols 1.10 and 1.11

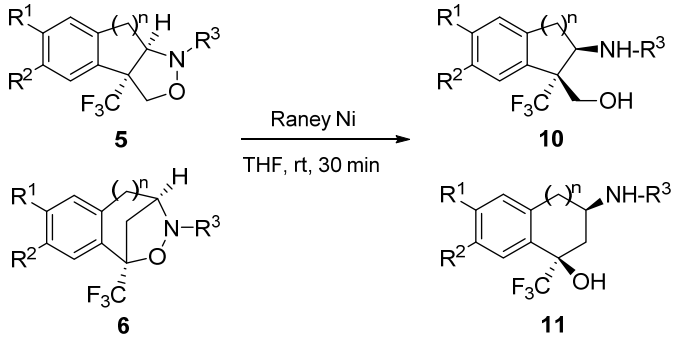
Finally, in terms of the synthetic value of the reaction studied, the obtained tricyclic isoxazolidines **1.5/1.6** can easily be cleaved to the corresponding 1,3-amino alcohols, which represent an interesting moiety for both organic synthesis and medicinal chemistry applications. Among the reductive conditions tested for the ring opening of the isoxazolidine ring of compounds **1.5** and **1.6** (Zn, Pd/C, $Pd(OH)_2$, $LiAlH_4$, Raney Ni), best results were obtained with Raney Ni ® in THF at room temperature (Table 1.5).

Unsubstituted compounds **1.5a-d** and **1.6a,c,d** afforded moderate to very good yields of the corresponding 1,3-amino alcohols (Table 1.5, entries 1-7). It is important to note that substrates containing the benzyl *N*-protecting group (**1.5b**, **1.5d** and **1.6d**) can be selectively cleaved at the isoxazolidine ring without affecting the benzylic nitrogen (Table 1.5, entries 3, 6 and 7) provided that the reaction is performed in 30 minutes. Longer reaction times led to variable mixtures of isoxazolidine ring-opening products with or without debenzylation of the amine functionality.

Substrates containing the fluorine substituent in the aromatic ring **1.5e** and **1.5g** gave also very good yields of the final products (Table 1.5, entries 8, 9) without detecting reductive cleavage of the C-F bond. Finally, compounds bearing the dioxolane moiety **1.5i** and **1.5k** were efficiently cleaved to the corresponding bicyclic 1,3-amino alcohols (Table 1.5, entries 10,11). It is worth mentioning that

all 1,3-amino alcohols obtained hold an interesting structural feature, namely a quaternary stereocentre bearing a trifluoromethyl group.

Table 1.5. Synthesis of fluorinated bicyclic 1,3-amino alcohols **1.10** and **1.11**



5 **6** **10** **11**

Entry	**1.5/1.6**	n	R^1	R^2	R^3	**1.10/1.11**, % yield[a]
1	**1.5a**	1	H	H	Me	**1.10a**, 50
2	**1.6a**	1	H	H	Me	**1.11a**, 83
3	**1.5b**	1	H	H	Bn	**1.10b**, 75
4	**1.5c**	2	H	H	Me	**1.10c**, 89
5	**1.6c**	2	H	H	Me	**1.11c**, 57
6	**1.5d**	2	H	H	Bn	**1.10d**, 93
7	**1.6d**	2	H	H	Bn	**1.11d**, 33
8	**1.5e**	1	F	H	Me	**1.10e**, 70
9	**1.5g**	2	F	H	Me	**1.10g,** 99
10	**1.5i**	1	-O-CH_2-O-		Me	**1.10i**, 57
11	**1.5k**	2	-O-CH_2-O-		Me	**1.10k**, 99

[a] Isolated yield after flash column chromatography.

1.4. Results and Discussion. Part B: Organocatalytic Enantioselective Synthesis of Trifluoromethyl-Containing Tetralin Derivatives by Sequential (Hetero)Michael Reaction-Intramolecular Nitrone Cycloaddition

1.4.1. Towards an enantioselective version of the INCR with fluorinated substrates

The next step in our study was directed towards the development of an enantioselective version of the INCR with our substrates. To make this synthetic methodology more attractive, a further goal was to control regioselectivity so as to obtain a sole regioisomer. As depicted in the Introduction, the steric bias in nitrone cycloadditions can be introduced *via* the *N*-substituent of the nitrone or the carbon end, *i.e.* the starting aldehyde precursor when the nitrone is formed by condensation with a hydroxylamine. The first case would be the most practical one, since the structure of the substrates would be maintained in this case and just a different, chiral non-racemic hydroxylamine should be chosen for condensation (Schemes 1.27 and 1.28). In the second case, the fluorinated aldehyde has to be functionalised to introduce chirality into its backbone prior to the INCR (Schemes 1.29 and 1.30).

In any case, the final products of the planned sequence would be a novel family of fluorinated tetralins bearing an all-carbon CF_3-containing quaternary stereocentre. The tetralin or 1,2,3,4-tetrahydronaphthalene core is present in a great variety of natural products and drugs,[65] therefore being classified as a privileged structural motif for the construction of drug-like

[65] For some representative examples of the preparation of biologically relevant tetralins, see: (a) Roesner, S.; Casatejada, J. M.; Elford, T. G.; Sonawane, R. P.; Aggarwal, V. K. *Org. Lett.* **2011**, *13*, 5740. (b) Efange, S. M. N.; Khare, A. B.; von Hohemberg, K.; Mach, R. H.; Parsons S. M.; Tu, Z. *J. Med. Chem*. **2010**, *53*, 2825. (c) Tu, Z.; Efange, S. M. N.; Xu, J.; Li, S.; Jones, L. A.; Parsons, S. M.; Mach, R. H. *J. Med. Chem.* **2009**, *52*, 1358. (d) Zhang, A.; Neumeyer, J. L.; Baldessarini, R. J. *Chem. Rev.* **2007**, *107*, 274. (e) Kraus, G. A.; Geon, I. *Org. Lett.* **2006**, *8*, 5315. (f) Garrido, M.; Urones, J. G. *Tetrahedron Lett.* **2003**, *44*, 5419. (g) Nair, V.; Rajan, R.; Rath, N. P. *Org. Lett*. **2002**, *4*, 1575. (h) Lautens, M.; Rovis, T. *Tetrahedron* **1999**, 55, 8967. (i) Bucholtz, E. C.; Brown, R. L.; Tropsha, A.; Booth, R. G.; Wyrick, S. D. *J. Med. Chem.* **1999**, *42*, 3041. (j) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75.

molecules.[66] Moreover, the incorporation of fluorinated moieties in the carbon skeleton of chiral tetralins has been scarcely explored to date.[67]

- ***Approaches based on chiral non-racemic hydroxylamines***

Our first attempts were of course directed towards the easier case. Among the chiral templates employed in asymmetric intramolecular nitrone cycloaddition, the hydroxylamine derived from (*R*)-phenylethylamine is a commonly employed one, since upon reductive cleavage to the final 1,3-aminoalcohol by hydrogenolysis also the *N*-substituent is removed.

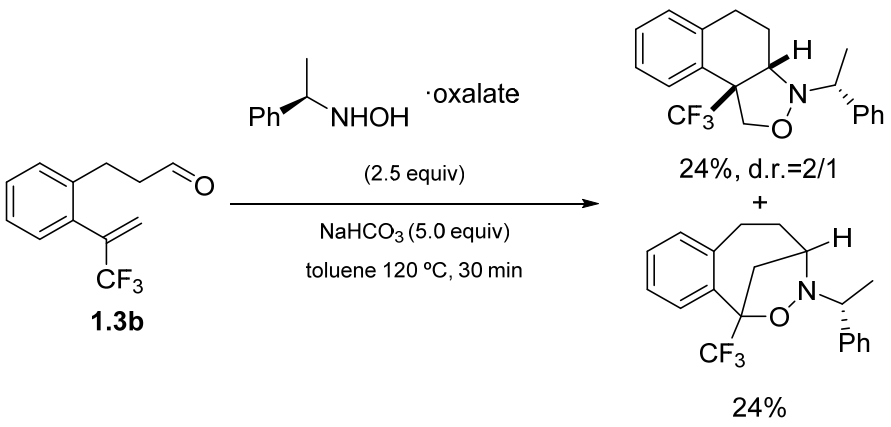
When aldehyde **1.3b** was treated with (*R*)-phenylethylhydroxylamine[68] under the optimised conditions used previously for the racemic approach, a non separable equimolar mixture of both regioisomers was obtained (Scheme 1.27). From the ^{19}F-NMR spectrum, two diastereoisomers of the fused regioisomer could be identified in a 2:1 ratio. The bridged regioisomer shows a broad ^{19}F-NMR due to coalescence as in the case of the racemic bridged products and it is difficult to say, without further NMR experiments recorded at other temperatures, whether it is a sole diastereoisomer or two.

---

[66] a) The term "privileged structure" was introduced in 1988 as a molecular scaffold that is highly represented in biologically active compounds (capable of binding to multiple receptors with high affinity): (a) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (c) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235.

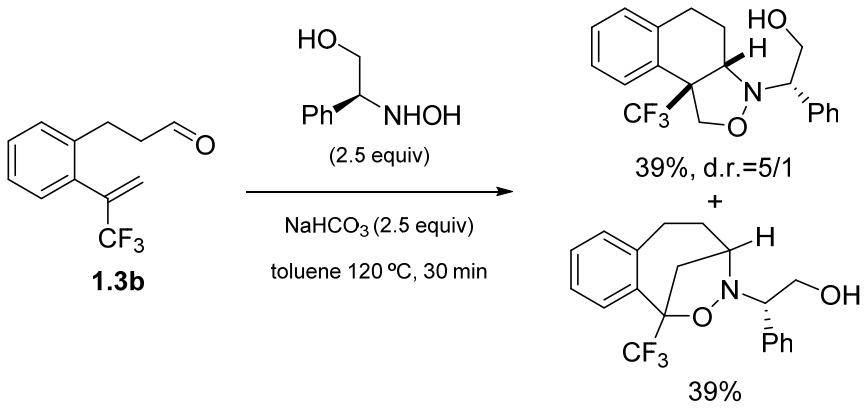
[67] To the best of our knowledge, only one example of chiral tetralins bearing fluorine in their carbon skeleton has been reported: (a) Lázaro, R.; Román, R.; Sedgwick, D. M.; Haufe, G.; Barrio, P.; Fustero, S. *Org. Lett.* **2016**, *18*, 948. For examples of other fluorine-containing tetralins, see: (b) Zhang, Z.; Martinez, H.; Dolbier, W. R. *J. Org. Chem.* **2017**, *82*, 2589. (c) Barker, M.; Clackers, M.; Copley, R.; Demaine, D. A.; Humphreys, D.; Inglis, G. G. A.; Johnston, M. J.; Jones, H. T.; Haase, M. V.; House, D.; Loiseau, R.; Nisbet, L.; Pacquet, F.; Skone, P. A.; Shanahan, S. E.; Tape, D.; Vinader, V. M.; Washington, M.; Uings, I.; Upton, R.; McLay, I. M.; Macdonald, S. J. F. *J. Med. Chem.* **2006**, *49*, 4216.

[68] (a) Wovkulich, P. M.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 3956. (b) Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron* **1985**, *41*, 3455.



Scheme1.27

The hydroxylamine derived from (*R*)-phenylglycinol was prepared according to a literature procedure[69] and applied analogously in the hope to observe some directing effect from the additional free OH group. In fact, the diastereoselectivity of the fused regioisomer was improved (to a ratio of 5:1), but both regioisomers were still obtained in equimolar amounts (Scheme 1.28). The regio- and diastereoselectivity could neither be improved by the addition of a Lewis acid such as $MgBr_2$ or $Zn(OTf)_2$ which in theory could render a metal-chelated nitrone.[70]



Scheme 1.28

[69] Breuning, M; Häuser, T.; Tanzer, E.-M. *Org. Lett.* **2009**, *11*, 4032.
[70] Zhao, Q.; Han, F.; D. L. *J. Org. Chem.* **2002**, *67,* 3317.

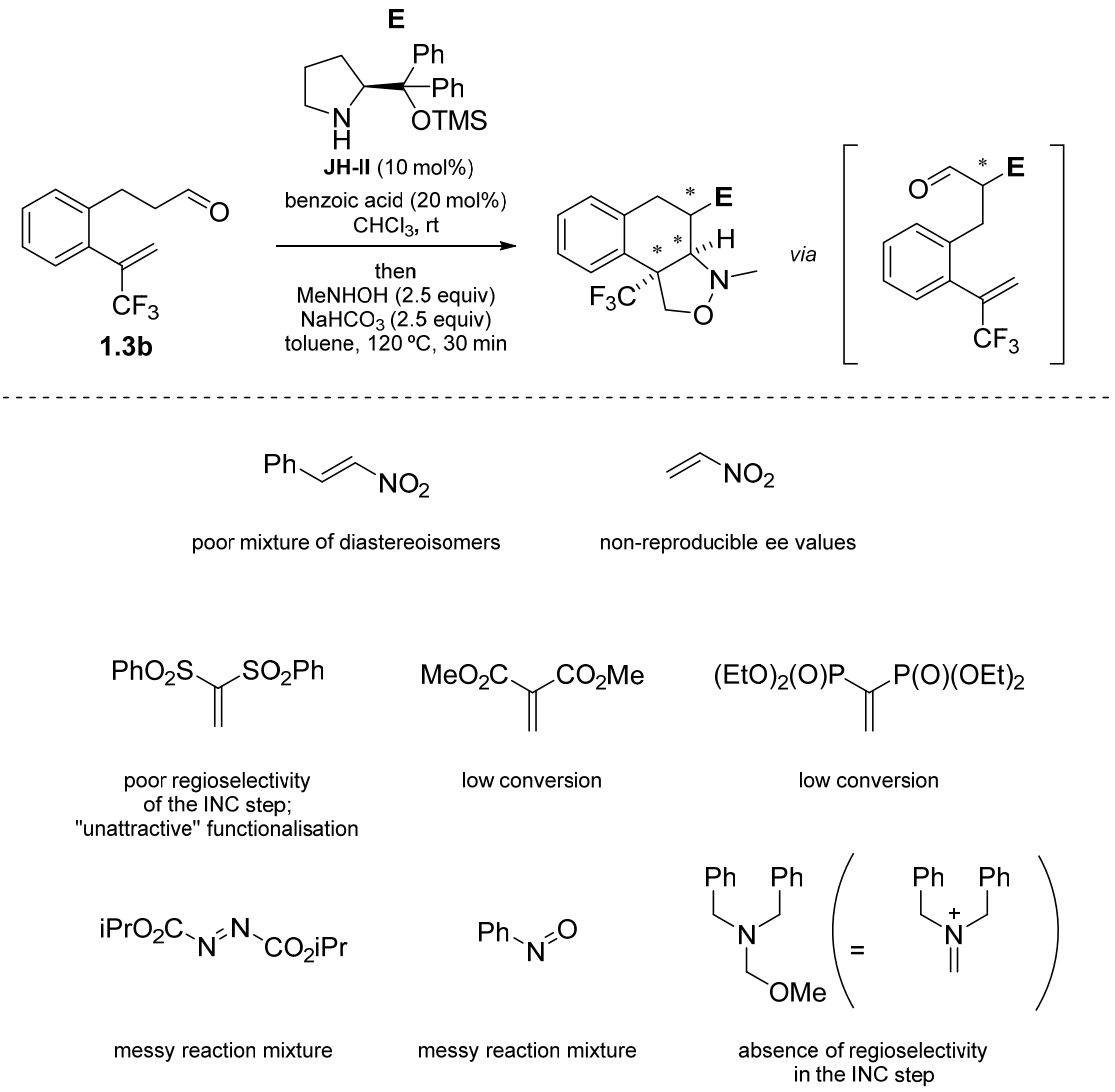
Given the distribution of products obtained so far, the approach based on the use of chiral non-racemic hydroxylamines was discarded. It was then clear that chirality had to be introduced in the carbon backbone of the nitrone. Taking into account that in practice just the two carbon atoms of the aldehyde aliphatic chain are amenable for functionalisation, there are two possibilities left in this sense: the α- and β-funtionalisation of the aldehyde.

- ***Approaches based on α-functionalisation of aliphatic aldehydes***

Different methodologies for the α-functionalisation of aldehyde **1.3b** based on enamine catalysis were assayed in order to obtain an enantiomerically enriched nitrone precursor. The substrates for this sequence would still be the same ones as in Part A. Unfortunately, these attempts were unfruitful for various reasons, and these results are summed up next.

Employing Jørgensen-Hayashi diphenyl prolinol silyl ether **JH-II**[71] as the catalyst, an acid cocatalyst (benzoic acid) and the corresponding electrophile, aldehyde **1.3b** was functionalised in the α-position and after work-up without further purification of the intermediate aldehyde, it was cyclised to the final isoxazolidine in the standard reaction conditions. Several electrophiles were tried (Scheme 1.29).

[71] (a) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212 (b) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T.C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296.



Scheme 1.29

When 2-nitrostyrene was used, the corresponding aldehyde was obtained with poor diastereoselectivity (dr 2:1) as determined by ^{19}F-NMR and the subsequent step afforded an even more complicated mixture of diastereoisomers of no synthetic use. From this point on, it was decided to only try electrophiles which do not give rise to more than one stereocentre in the intermediate aldehyde. Nitroethylene was thus chosen as electrophile,[72] but the reaction was not reproducible in terms of the ee values obtained. Other Michael acceptors were tried. A vinyl disulfone[73] afforded the fused regioisomer as a single

[72] Chi, Y.; Guo, L.; Kopf, N. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2008**, *130*, 5608.
[73] Zhu, Q. Lu, Y. *Org. Lett.* **2008**, *10*, 4803.

diastereoisomer in 92% ee and 53% yield, but unfortunately the bridged regioisomer was also obtained in 14% yield. Moreover, from the point of view of synthetic utility, the functionality introduced by this acceptor is not extremely attractive. The reactions with the corresponding diester and diphosphonate were sluggish. The α-oxygenation with nitrosobenzene,[74] the α-amination with diisopropyl aza-dicarboxylate[75] and the α-aminomethylation with *N,N*-dibenzyl-*N*-(methoxy)methylamine[76] were assayed as well, but the reaction was either messy in the organocatalytic step or in the subsequent cycloaddition. Variation of the standard reaction conditions (solvent, catalyst, cocatalyst) did not provide any better results in our hands.

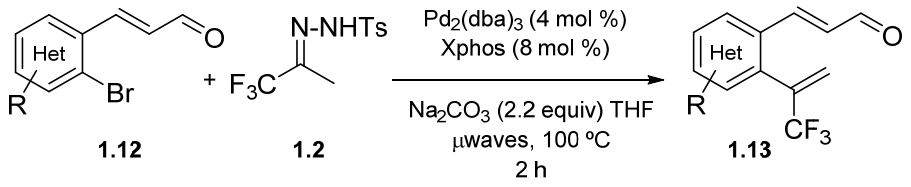
- ***Approaches based on β-functionalisation of cinnamaldehydes***

  Preparation of starting materials

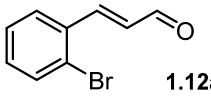
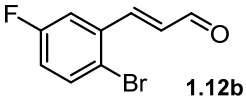
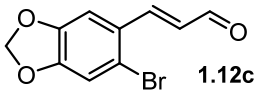
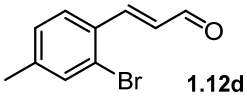
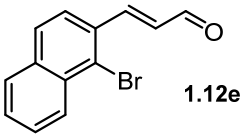
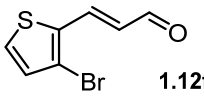
Regarding the second possibility for aldehyde derivatisation mentioned above, the β-funtionalisation requires a slight change in the structure of the starting material: The necessary aldehyde is the *ortho*-substituted cinnamaldehyde **1.13**. Following an analogous methodology, the preparation of the starting *ortho*-substituted cinnamaldehydes **1.13a-d** and related compounds **1.13e,f** was performed by means of the already discussed palladium-catalysed cross-coupling reaction of 1,1,1-trifluoroacetone tosylhydrazone **1.2** with several *ortho*-bromo cinnamaldehydes or derivatives **1.12**. Under optimised reaction conditions, good to excellent yields of conveniently functionalised (trifluoromethyl)styrenes **1.13** were obtained, as depicted in Table 1.6.

[74] Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808.
[75] List, B. *J. Am. Chem. Soc.* **2002**, *124,* 5656.
[76] (a) Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128,* 6804. (b) Ibrahem, I.; Zhao, G.-L.; Córdova, A. *Chem. Eur. J.* **2007**, *13*, 683.

Table 1.6 Synthesis of the starting CF_3-containing α,β-unsaturated aldehydes **1.13**



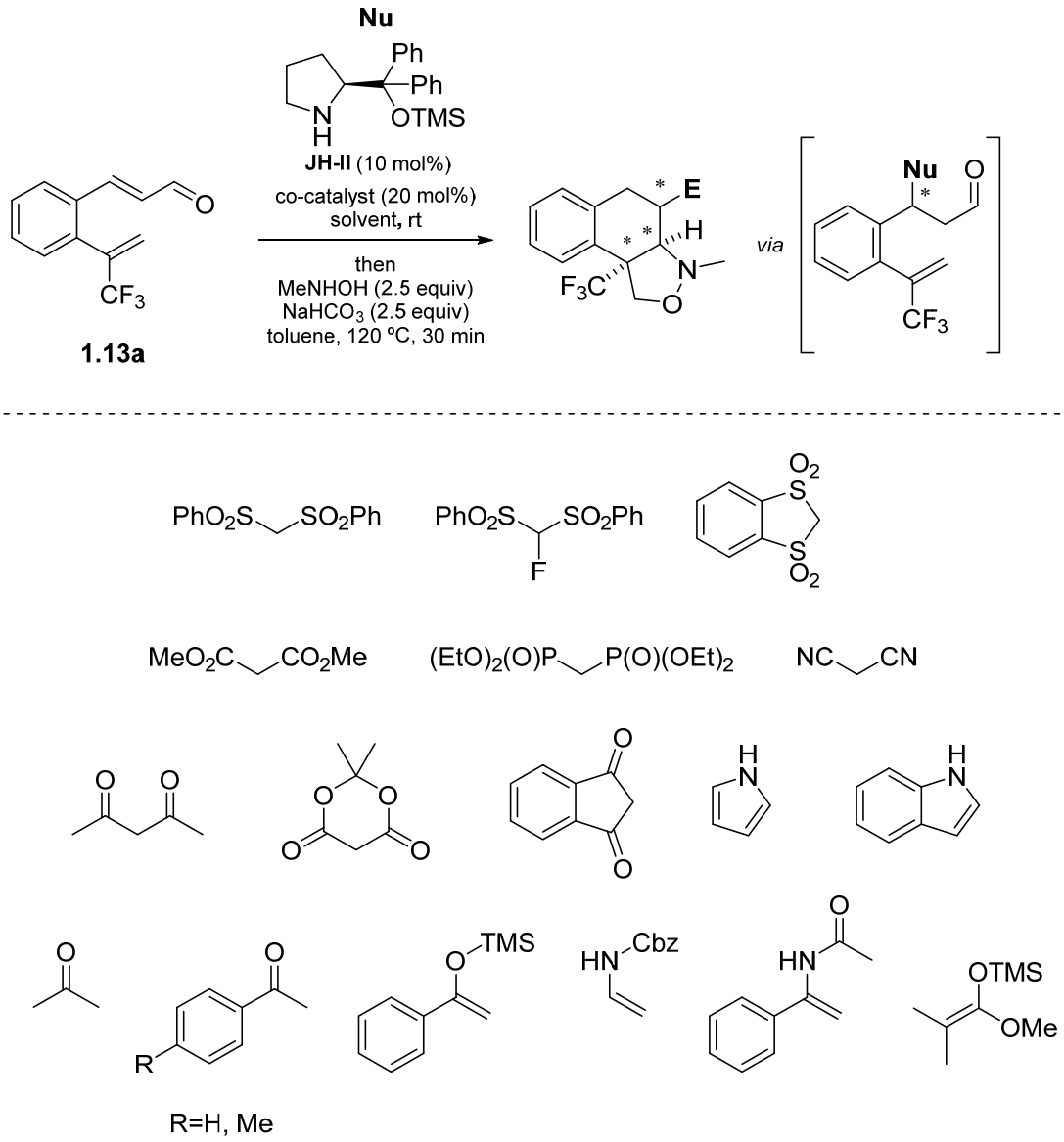
1.12 **1.2** **1.13**

Entry	1.12	1.13	% yield[a]
1	 **1.12a**	**1.13a**	89
2	 **1.12b**	**1.13b**	88
3	 **1.12c**	**1.13c**	81
4	 **1.12d**	**1.13d**	99
5	 **1.12e**	**1.13e**	82
6	 **1.12f**	**1.13f**	90

[a] Isolated yield after flash column chromatography.

Preliminar screening of nucleophiles

With the starting materials in hand, the organocatalytic β-functionalisation of the aldehyde moiety was examined next. Iminium catalysis is well known to enable the enantioselective functionalisation at the β-position of enals by means of a Michael-type nucleophilic addition. In this manner, we would generate suitable precursors of the nitrone functionality, bearing a stereodefined centre at the β-position, able to undergo the INCR in a diastereoselective fashion. A variety of carbon-centred nucleophiles were tested using **1.13a** as the model substrate and diphenylprolinol **JH-II** as the iminium catalyst (Scheme 1.30).



Scheme1.30

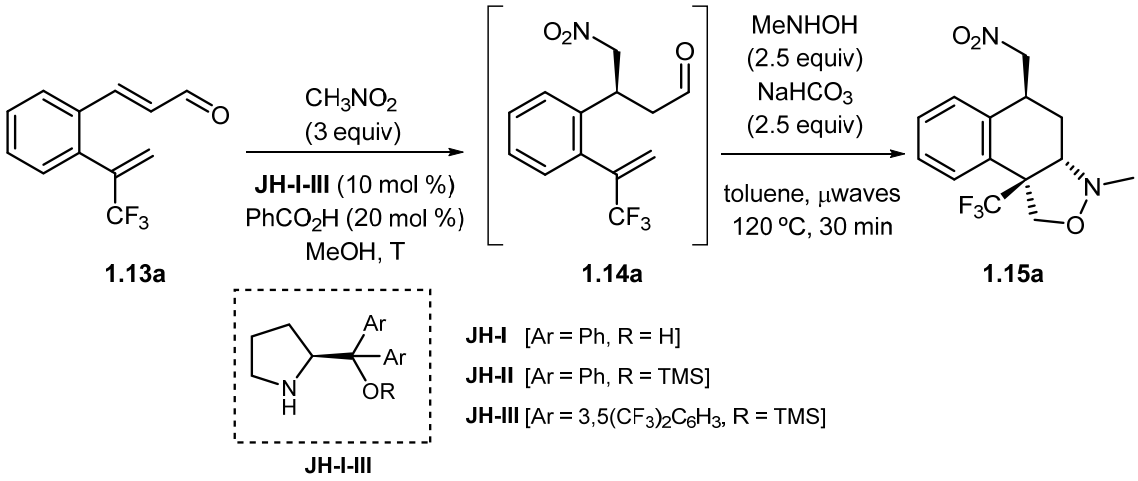
However, even screening different solvents (DCM, THF, EtOH, toluene, DMF, MeCN) and additives (triethylamine, benzoic acid, K_2CO_3, NaOAc, NaH, *t*-BuOK), no significant conversion was observed. We speculated that the sluggishness of the reaction was due to the effect of the *ortho*-substitution. It should be reminded how sterically demanding a trifluoromethyl group is, and it would easily impede the attack of the nucleophile on the close β-position. In fact, we were surprised by the scarcity of *ortho*-substituted examples in the reaction scope of similar works.

Nitromethane as a nucleophile: Reaction optimisation and scope

Luckily, we found that nitromethane was a suitable nucleophile for the desired transformation and in the reaction conditions reported by Hayashi *et al.* the reaction was brought to completion.[77] The enantioselective synthesis of chiral pharmaceuticals such as *Baclofen* or *Pregabalin* in the cited work illustrates how useful nitromethane is as an aminomethylation reagent. Bearing this precedent in mind, a rough screening of reaction conditions was carried out on fluorinated cinnamaldehyde **1.13a** as a model substrate (Table 1.7). Following these conditions previously described for the organocatalytic conjugate addition of nitroalkanes to enals, a first attempt was made with nitromethane, employing diphenylprolinol (**JH-I)** as the catalyst in methanol at room temperature. The complete consumption of the starting aldehyde **1.13a** was observed after 7 days, when solvents were removed under reduced pressure. After standard aqueous work-up, the crude mixture (containing **1.14a**) was re-dissolved in toluene and subjected to the INCR in the presence of *N*-methylhydroxyl amine hydrochloride and sodium bicarbonate. Heating the reaction mixture under microwave irradiation at 120 °C for 30 min gave rise to a 4:1 mixture of diastereomeric tetrahydronaphthalene isoxazolidines in 29% overall yield. Both diastereoisomers were separated by column chromatography and the major one **1.15a** was obtained in 82% ee (Table 1.7, entry 1). When diphenylprolinol silyl ether (**JH-II**) was employed as the chiral catalyst, the disappearance of the starting material was observed after 16 hours at room temperature. Upon condensation with *N*-methylhydroxyl amine, the INCR took place efficiently affording again a 4:1 mixture of diastereoisomers in 46% yield and complete enantioselection in favour of compound **1.15a** (Table 1.7, entry 2). Trying to improve the diastereoselectivity of the process, lower temperatures in the organocatalytic Michael addition step were tested. However, neither at 0 °C nor at 10 °C the reaction progressed after 16h (Table 1.7, entries 3, 4). Finally, bis(trifluoromethyl) substituted catalyst **JH-III** was also tested, resulting in product **1.15a** in 39% yield and 86% ee (Table 1.7, entry 5).

[77] Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307.

Table 1.7 Optimisation of the sequence nitro-Michael addition/INCR



Entry	Catalyst	T [°C]	Time	% yield[a,b]	% ee[c]
1	**JH-I**	25	7d	29	82
2	**JH-II**	25	16h	46	>99
3	**JH-II**	0	16h	-[d]	-
4	**JH-II**	10	16h	-[d]	-
5	**JH-III**	25	10d	39	86

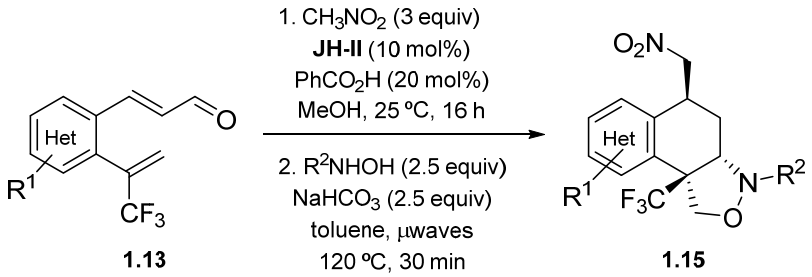
[a] Isolated yield after flash column chromatography (from **1.13a**, without purifying intermediate **1.14a**).
[b] The INCR gave a 4:1 mixture of diastereoisomers, as determined by ^{19}F-NMR of the crude reaction mixture.
[c] Enantiomeric excess of the major diastereoisomer determined by HPLC on a chiral stationary phase; see the Experimental Section for details.
[d] No conversion in the organocatalytic step.

Notably, under the optimised reaction conditions, the reaction did not work with 2-nitropropane and when nitroethane was used instead, a complex non-separable mixture of diastereoisomers was obtained. Apparently, the organocatalytic step was not diastereoselective.

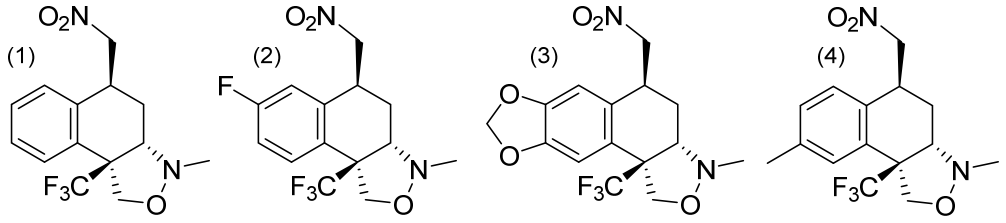
Having identified the optimal conditions for the sequential Michael addition/condensation/INCR (Table 1.7, entry 2), this synthetic method was examined regarding its generality with the rest of trifluoromethylstyrenes **1.13**. The results obtained are shown in Table 1.8.

Starting cinnamaldehydes **1.13a-d**, with electronically different substitution patterns on the aromatic ring, afforded the corresponding enantiomerically enriched isoxazolidines **1.15a-d** in good yields, moderate diastereoselectivities and excellent enantioselectivities (Table 1.8, entries 1-4).

Table 1.8 Scope of the sequence nitro-Michael addition/INCR



1.13 **1.15**

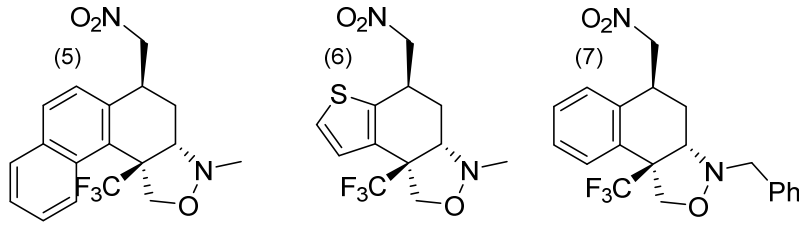


1.15a (46%, 4:1)[a,b] major: 99% ee[c] minor: 96% ee

1.15b (62%, 4.6:1)[a,b] major: 96% ee[c] minor: 96% ee

1.15c (44%, 5:1)[a,b] major: 96% ee[c] minor: 96% ee

1.15d (53%, 2.5:1)[a,b] major: 96% ee[c]



1.15e (58%, 6.6:1)[a,b] major: 96% ee[c] minor: 96% ee

1.15f (30%, 1.1:1)[a,b,d] major: 96% ee[c] minor: 96% ee

1.15g (39%, 3.3:1)[a,b] major: 96% ee[c]

[a] Isolated yield after flash column chromatography.
[b] Diastereisomeric ratio determined by ^{19}F-NMR analysis of the crude reaction mixture.
[c] Enantiomeric excess of the major diastereoisomer determined by HPLC methods. The ee value of the minor diastereoisomer is given when purification and chiral resolution were possible.
[d] The bridged regioisomer was also formed in 14% yield; see the Experimental Section.

Additionally, other aromatic linkers between the α,β-unsaturated aldehyde and the fluorinated dipolarophile were compatible with the reaction system,

including a naphthyl and a thienyl groups (Table 1.8, entries 5,6). It should be mentioned that, in the case of the thienyl derivative (Table 1.8, entry 6), the bridged regioisomer was formed in the INCR together with the fused one **1.15f**. Structural variability could also be introduced by changing the *N*-alkylhydroxylamine employed in the cyclisation step. Thus, the process was also performed with *N*-benzylhydroxylamine to yield isoxazolidine **1.15g** with moderate diastereoselectivity and excellent enantioselectivity in the major diastereoisomer (Table 1.8, entry 7). In this manner, a family of enantiomerically enriched tetraline derivatives bearing a CF_3-containing quaternary stereocentre were efficiently synthesised.

The absolute configuration of the products was inferred from X-ray analysis of an appropriate crystal of compound **1.15c**,[78] which displays a *cis* relative relationship of the trifluoromethyl and the nitromethyl groups (Figure 1.6). The same stereochemistry was assumed for all compounds **1.15.**

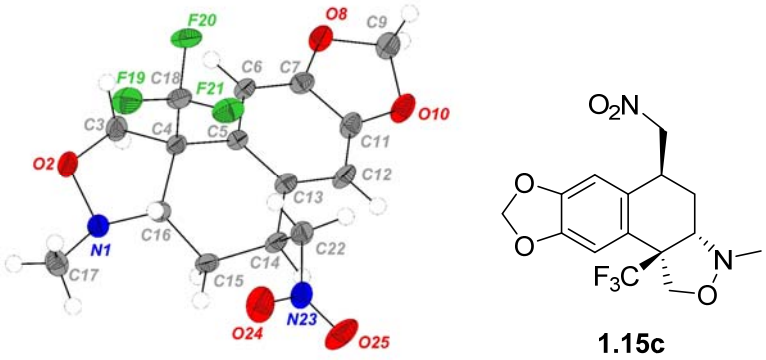


Figure 1.6

N-Hydroxybenzylcarbamate as a nucleophile: Reaction optimisation and scope

A second type of organocatalytic conjugate addition we attempted for the enantioselective β-functionalisation of enals **1.13** was the aza-Michael reaction,[79]

[78] See the Experimental Section.

[79] For recent reviews on the organocatalytic aza-Michael reaction, see: (a) Sánchez-Roselló, M.; Simón-Fuentes, A.; Aceña, J. L.; del Pozo, C. *Chem. Soc. Rev.* **2014**, *43*, 7430. (b) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058. (c) Reyes, E.; Fernández,

because of our ongoing interest in this field. A preliminary screening of nitrogen nucleophiles was carried out employing **1.13a** as a model substrate. Several heterocyclic amine derivatives such as pyrrole, indole, phtalimide or isatin were tested unsuccessfully as no conjugate addition was observed. Apparently, the retro-aza-Michael reaction is faster for these systems and the steric requirements for the addition to an *ortho*-substituted cinnamaldehyde could not be disregarded. Another commonly used nucleophile for enantioselective aza-Michael reactions is *O*-TBS-protected *N*-Cbz-hydroxylamine.[80] Unfortunately, in our reaction no conversion was detected again. Nevertheless, when the hydroxyl group was unprotected, *i.e*. when using *N*-Cbz-hydroxylamine,[81] the aza-Michael reaction took place in the presence of diphenylprolinol silyl ether (**JH-II**) and yielded hemiacetal derivative **1.16a** (Table 1.9). Its formation in a tandem fashion seems to be the driving force of the process. This reaction was driven to full conversion in chloroform at room temperature. Then, the reaction mixture was evaporated to dryness and the crude mixture was re-dissolved in toluene for the cyclisation step. The subsequent domino condensation with *N*-methylhydroxyl amine /INCR took place under microwave irradiation at 120 °C for 30 min, rendering a 3:1 mixture of diastereoisomers in 42% yield overall yield. The enantiomeric excess of the major diastereoisomer was found to be 22% (Table 1.9, entry 1). It is worth mentioning that aqueous work-up or isolation of the intermediate hemiacetal **1.16a** did not improve the yield or the enantioselectivity of the process.

Once a compatible nitrogen nucleophile for the reaction with **1.13a** had been identified, an optimisation of the reaction conditions was performed. In order to improve the selectivity of the sequential protocol, lower temperatures in the organocatalytic conjugate addition step were tested. We found that temperature has a dramatic effect on enantioselectivity. While the reaction at -20 °C did not proceed at all (Table 1.9, entry 2), at 5 °C, after the INCR, final tetrahydronaphthalene product **1.17a** was obtained with 96% ee and 51% global

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M.; Uría, U.; Vicario, J. L.; Badía, D.; Carrillo L. *Curr. Org. Chem.* **2012**, *16*, 521. (d) Wang, J.; Li, P.; Choi, P. Y.; Chan, A. S. C.; Kwong, F. Y. *ChemCatChem*. **2012**, *4*, 917.

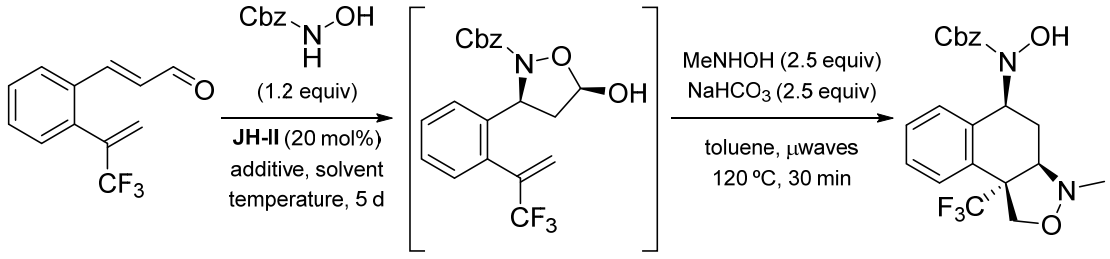
[80] Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328.

[81] (a) Zhao, G.-L.; Lin, S.; Korotvička, A.; Deiana, L.; Kullberg, M.; Córdova, A. *Adv. Synth. Catal.* **2010**, *352*, 2291. (b) Ibrahem, I.; Rios, R.; Vesely, J.; Zhao, G.-L.; Córdova, A. C*hem. Commun.* **2007**, 849.

yield (Table 1.9, entry 3). On the other hand, organocatalytic reactions with diarylprolinol derivatives as the catalysts usually require an acidic co-catalyst such as benzoic acid. However, in our case, the incorporation of this additive entailed lower enantioselectivity in the formation of compound **1.17a** (Table 1.9, entry 4). Fluorinated Jørgensen-Hayashi catalyst **JH-III** was not effective in the aza-Michael reaction in $CHCl_3$ at 25 °C (Table 1.9, entry 5). Finally, changing the solvent to toluene gave slightly lower yield and enantioselectivity (Table 1.9, entry 6).

Again in this sequence the INCR was completely regioselective, although the fused regioisomer **1.17a** was obtained with moderate diastereoselection (dr 3:1).

Table 1.9 Optimisation of the sequence aza-Michael addition/INCR



1.13a **1.16a** **1.17a**

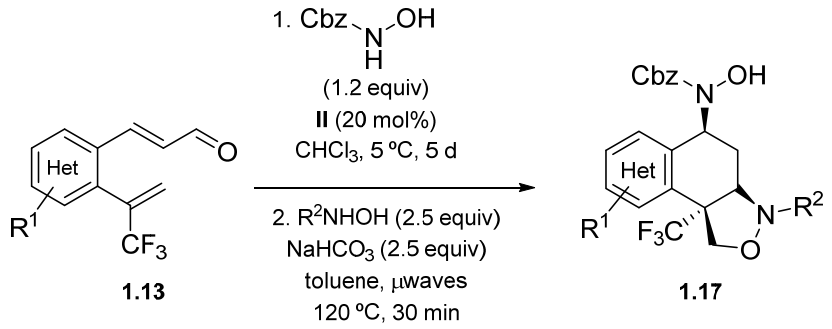
Entry	Cat.	Solv.	Additive	T [°C]	% yield[a,b]	% ee[c]
1	**JH-II**	$CHCl_3$	-	25	42	22
2[c]	**JH-II**	$CHCl_3$	-	-20	-[d]	-
3	**JH-II**	$CHCl_3$	-	5	51	96
4	**JH-II**	$CHCl_3$	$PhCO_2H$	5	49	80
5[c]	**JH-III**	$CHCl_3$	-	25	-[d]	-
6	**JH-II**	toluene	-	5	50	94

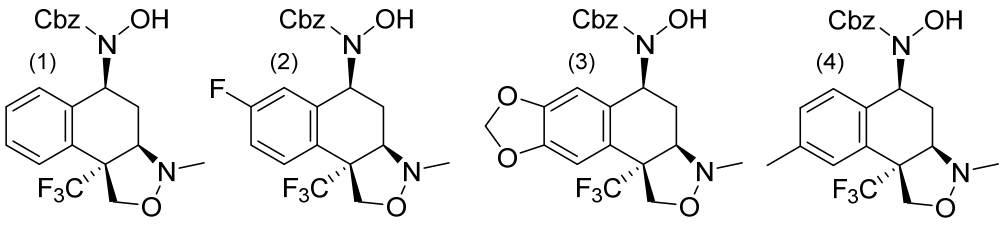
[a] Isolated yield after flash column chromatography (from **1.13a**, without purifying intermediate **1.16a**).
[b] The INCR gave a 3:1 mixture of diastereoisomers, as determined by ^{19}F-NMR of the crude reaction mixture.
[c] Enantiomeric excess of the major diastereoisomer determined by HPLC on a chiral stationary phase; see the Experimental Section for details.
[d] No conversion in the organocatalytic step.

With the optimised reaction conditions in hand (Table 1.9, entry 3), the scope of the sequential process was evaluated on trifluoromethylstyrenes **1.13**. The results are summarised in Table 1.10.

Electron-withdrawing, electron-donating and electron neutral substituents on the aromatic backbone of the starting cinnamaldehydes **1.13a-d** were compatible with this process. The corresponding trifluoromethylated products **1.17a-d** were obtained in good yields but moderate diastereoselectivities; whereas enantioselectivities ranged from good to excellent (Table 1.10, entries 1-4).

Table 1.10 Scope of the sequence aza-Michael addition/INCR



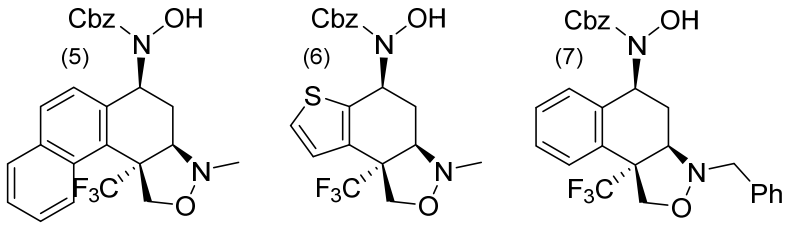


1.17a (51%, 3:1)[a,b]
major: 96% ee[c]
minor: 90% ee

1.17b (70%, 5.2:1)[a,b]
major: 92% ee[c]
minor: 99% ee

1.17c (60%,2.4:1)[a,b]
major: 90% ee[c]
minor: 84% ee

1.17d (62%,3.7:1)[a,b]
major: 72% ee[c]



1.17e (17%,>20:1)[a,b]
major: 86% ee[c]

1.17f (14%,>20:1)[a,b]
major: 54% ee[c]

1.17g (45%,4:1)[a,b]
major: 86% ee[c]
minor: 84% ee

[a] Isolated yield after flash column chromatography.
[b] Diastereoisomeric ratio determined by ^{19}F-NMR of the crude mixture.
[c] Enantiomeric excess of the major diastereoisomer. The ee value of the minor diastereoisomer is given when purification and chiral resolution were possible.

The change in the nature of the aromatic linker between the trifluoromethyl alkene and the enal, *i.e.* when this is a naphthyl or a thienyl moiety, resulted in a

drop in chemical yield and enantioselectivity. However, isoxazolidines **1.17e** and **1.17f** were isolated practically as single diastereoisomers (Table 1.10, entries 5, 6). Finally, the use of *N*-benzylhydroxylamine afforded the corresponding product **1.17g** with comparable diastereoselectivity and slightly lower enantioselectivity (Table 1.10, entry 7)

The absolute configuration of this family of tetralin-derived isoxazolidines **1.17** was determined by X-ray diffraction of a suitable crystal of the major diastereoisomer of compound **1.17b**. (Figure 1.7).[82] Surprisingly, the trifluoromethyl and the hydroxycarbamate groups lay *trans* to each other in this case, suggesting that different stereoelectronic factors in the transition state play a role in the preference of the *in situ* formed nitrone for the opposed face of the dipolarophile when compared to the nitromethane derivatives.

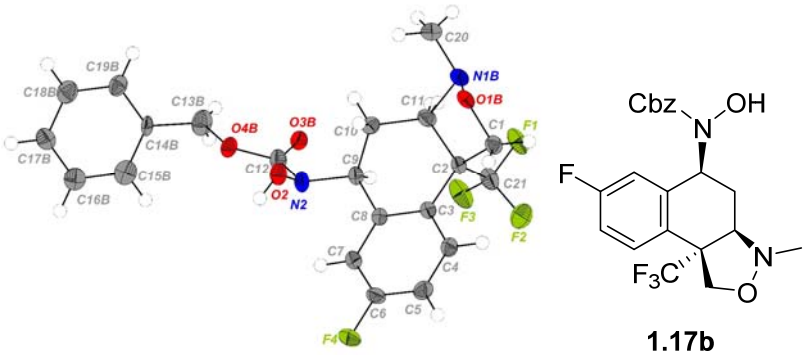


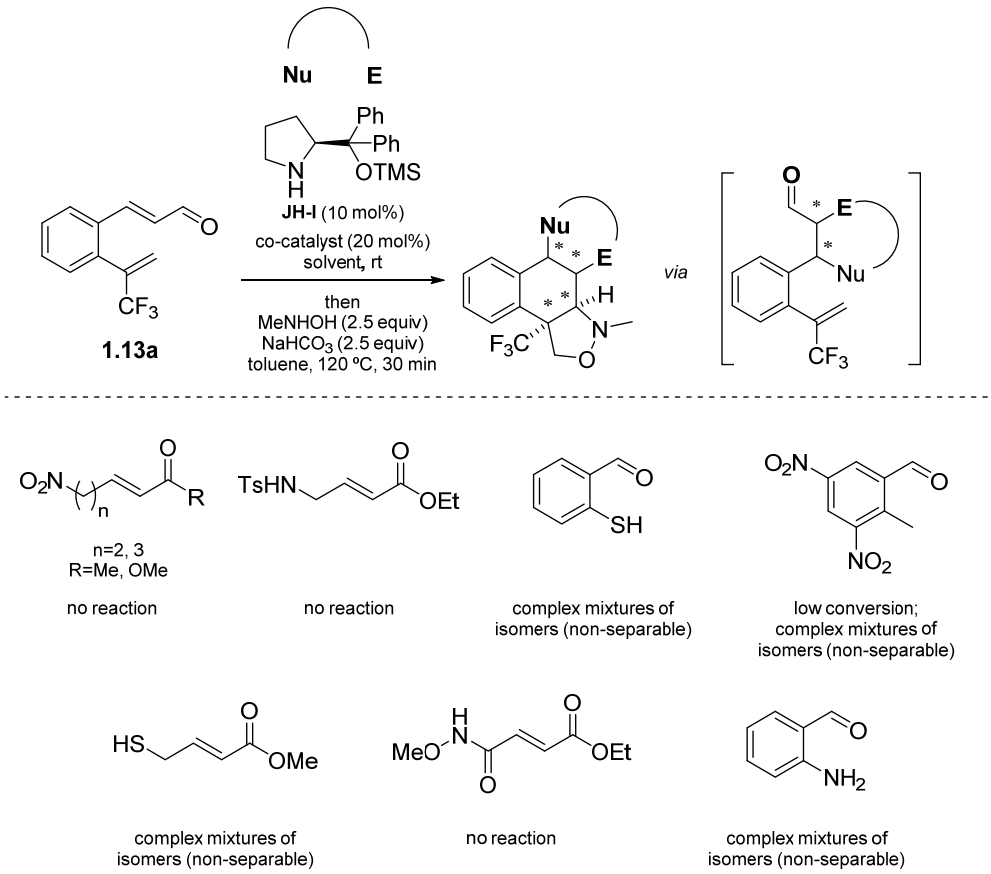
Figure 1.7

- ***Approaches based on tandem α,β-functionalisation of cinnamaldehydes***

Finally, we reasoned that if the hemiacetal formation could drive the previously exposed reaction to completion overcoming the energetic requirements of the nucleophilic attack, other analogous tandem processes could be thought of as well. (Aza/thia)-Michael/Michael,[83] Henry/Michael,[84]

[82] For details, see the Experimental Section.
[83] (a) Yokosaka, T.; Hamajima, A.; Nemoto, T.; Hamada, Y. *Tetrahedron Lett.* **2012**, *53*, 1245. (b) Li, H.; Zu, L.; Xie, H.; Wang, J.; Wang, W. *Chem. Commun.* **2008**, 5636. (c) Li, H.; Zu, L.; Xie, H.; Wang, J.; Jiang, W.; Wang, W: *Org. Lett.* **2007**, *9*, 1833.
[84] (a) Hong, B.-C.; Liao, W.-K.; Dange, N. S.; Liao, J.-H. *Org. Lett.* **2013**, *15*, 468. (b) Yang, V.-W.; Hong, B.-C.; Kao, H.-K.; Tu,T.-H.; Shen, J.-Y.; Chen, C.-L.; Lee, G.-H.; Chou, P.-T. *Org. Lett.*

Michael/aldol/dehydration[85] and (aza/thia)-Michael/aldol/dehydration[86] sequences followed by the standard INCR were tested. In all cases, the reaction (tested on the model substrate under the corresponding optimised conditions from the literature) was either unproductive, low-yielding, unselective or/and rendering a non-separable mixture of diastereo- and regioisomers (Scheme 1.31).



Scheme 1.31

1.4.2. Computational study: An explanation for the stereochemical outcome of the reaction

To shed light on this interesting finding, computational calculations were carried out in collaboration with Professor Pedro Merino from the University of

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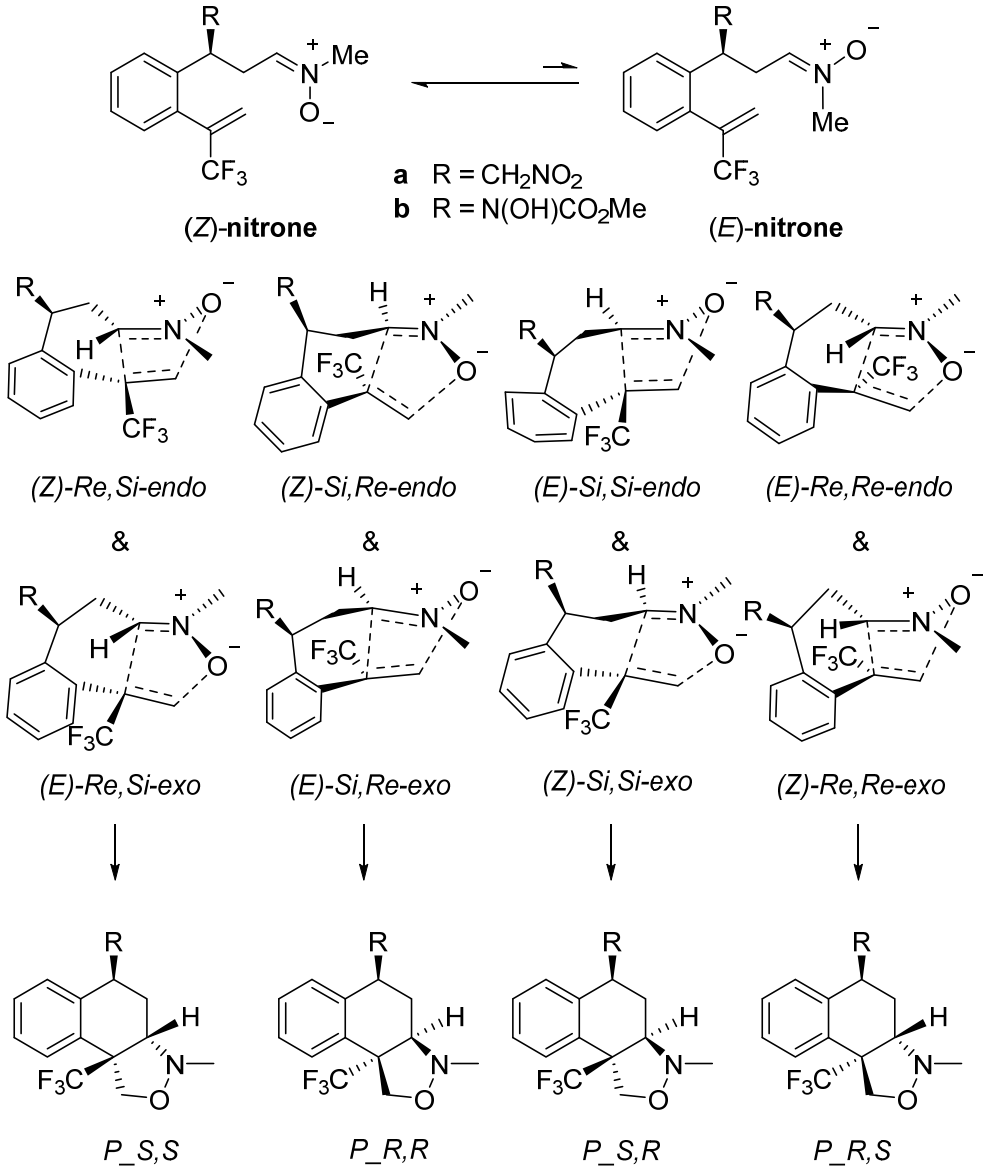
2015, *17*, 5816. (c) Zhao,G.-L.; Ibrahem, I.; Dziedzic, P.; Sun, J.; Bonneau, C.; Córdova, A. *Chem. Eur. J.* **2008**, *14*, 10007.

[85] Li, X.; Wang, S.; Li, T.; Li, J.; Li, H.; Wang, W. *Org. Lett.* **2013**, *15*, 5634.

[86] (a) Sundén, H.; Rios, R.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Adv. Synth. Catal.* **2007**, *349*, 827. (b) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354.

Zaragoza. The cycloaddition reaction was studied at B3LYP-D3BJ/Def2SVP level of theory to calculate geometries and then single point calculations at B3LYP-D3BJ/Def2TZVP/PCM=toluene level of theory were performed (for details see the Experimental Section). *E*/*Z* isomerisation of nitrones has been considered since the difference was in the range of 20-30 kcal/mol,[87] compatible with the reaction conditions. Four approaches can be defined for each nitrone, thus a total of eight approaches leading to four different compounds have been studied (Scheme 1.32).



Scheme 1.32

[87] Roca-Lopez, D.; Tejero, T.; Merino, P. *J. Org. Chem.* **2014**, *79*, 8358.

Diastereotopic faces correspond to nitrone (first) and alkene (second). The corresponding orientation of diastereotopic faces defines the *endo*/*exo* approach in each case. Moreover, even though the formation of 3,4-regioisomers was not observed experimentally, it was also computed. In the case of 3,4-regioisomers only four approaches are possible due to steric constraints imposed by the intramolecularity of the reaction.

R = CH_2NO_2 (**a** series) and R = $N(OH)CO_2Me$ (**b** series) were compared as substituents. A total of 24 transition structures were located. (*Z*)-*Endo* approaches were the most stable ones in all cases. The remaining approaches showed considerable higher energies due to steric constraints imposed by the intramolecularity of the process.

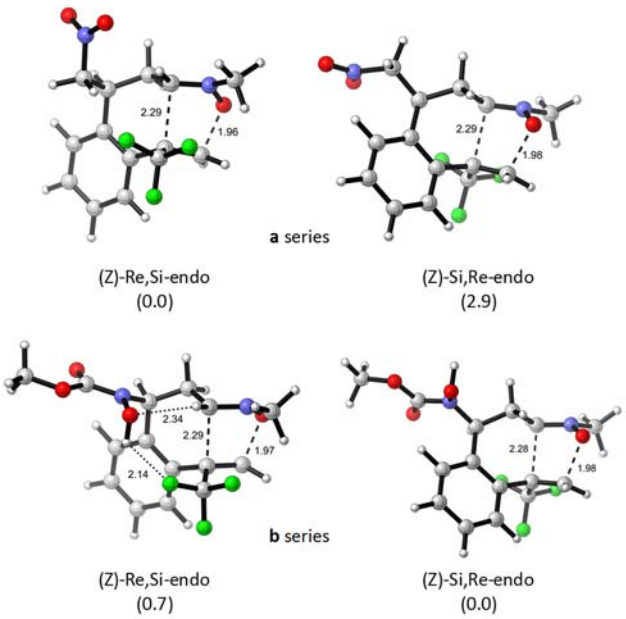


Figure 1.8

For R = CH_2NO_2 (**a** series) the most stable transition structure (by 2.9 Kcal/mol) corresponds to the (*Z*)-*Re*,*Si*-*endo* approach leading to the *S*,*S* adduct. The lowest energy barrier corresponding to those approaches was 12.3 kcal/mol for the **a** series. On the contrary, for R = N(OH)CO2Me (**b** series) the most stable transition structure (although only by 0.7 kcal/mol) corresponds to the (*Z*)-*Si*,*Re*-*endo* (energy barrier of 18.9 kcal/mol) approach leading to *R*,*R* adducts, in good agreement with the experimental results. In Figure 1.8, the transition structures

corresponding to the most stable (*Z*)-*endo* approaches for the **a** and **b** series are depicted. (Relative energies are given in kcal/mol).

Although the energy difference is only 0.7 kcal/mol being in the range of DFT error,[88] there is a clear trend from the **a** to **b** series towards inverting the diastereotopicity. Since the geometries of the transition structures are relativity similar for the different R substituents considered, there is no clear difference between steric requirements. However, some interactions are present in the (*Z*)-*Re*,*Si*-*endo* approach for the **b** series that cannot be found in the other models. The interaction between the N(OH) group and a fluorine atom is weak and might reinforce this transition structure minimizing the difference with (*Z*)-*Si*,*Re*-*endo*. On the other hand, the interaction between the N(OH) group and the azomethine proton of the nitrone affects the electronic system of the dipole. Since the reaction is a normal-demand process in which the nitrone moiety acts as a nucleophile, any interaction affecting such nucleophilicity will contribute to lowering the stability. Consequently, the (*Z*)-*Si*,*Re*-*endo* approach in which such interaction is not present becomes the most stable TS.

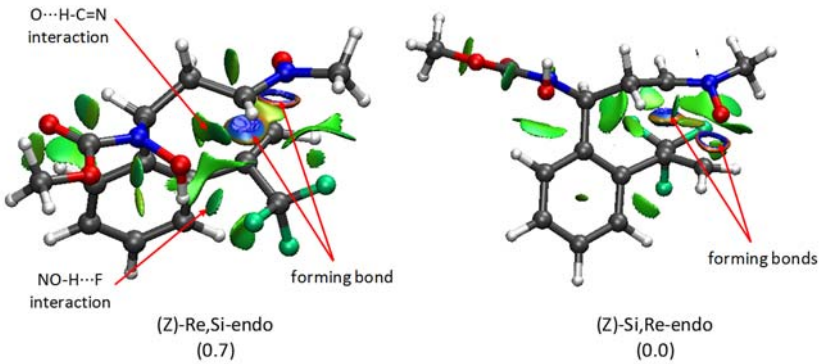


Figure 1.9

These non-covalent interactions (NCI) can be visualised through a topological NCI analysis,[89] in which interactions are visualised as isosurfaces. Figure 1.9 illustrates the presence of interactions in the less favoured (*Z*)-*Re*,*Si*-

[88] (a) Cohen, A. J.; Mori-Sánchez, P.; Yang, W. *Chem. Rev.* **2012**, *112*, 289. (b) Kim, M.-C.; Sim, E.; Burke, K. *Phys. Rev. Lett.* **2013**, *111*, 73003.
[89] (a) Johnson, E. R.; Keinan, S.; Mori-Sanchez, P.; Contreras-Garcia, J.; Cohen, A. J.; Yang, W. *J. Am. Chem. Soc.* **2010**, *132*, 6498. (b) Lane, J. R.; Contreras-Garcia, J.; Piquemal, J.-P.; Miller, B. J.; Kjaergaard, H. G. *J. Chem. Theory Comput.* **2013**, *9*, 3263.

endo approach which are not present in the preferred (*Z*)-*Si*,*Re-endo* approach (green for weak attractive interactions, blue for strong attractive interactions and red for repulsive interactions).

A (*Z*)-*Si*,*Re-endo* approach in which an H-bond interaction is present between the N(OH) group and the nitrone oxygen (Figure 1.10) was also calculated, being 2.8 kcal/mol less stable than the most stable conformation of the (*Z*)-*Si*,*Re-endo* approach (shown in Figure 1.10). Confirmation of these interactions came from the NCI analysis (Figure 1.10, right) (Relative energy is given in kcal/mol and referred to (*Z*)-*Si*,*Re-endo* corresponding to the **b** series shown in Figure 1). Alternative routes considering intermediate hydroxyamino anions were also considered but higher barriers were found in all cases (see the Experimental Section).

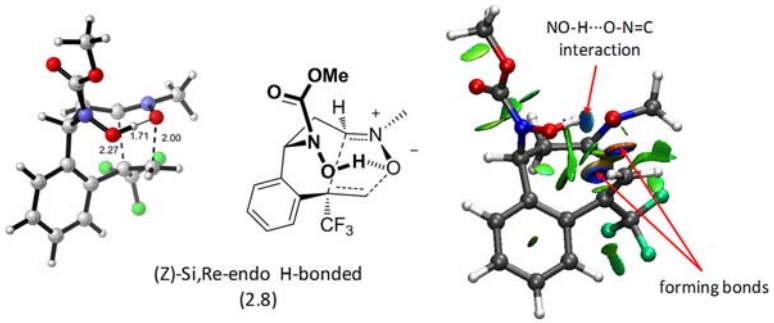
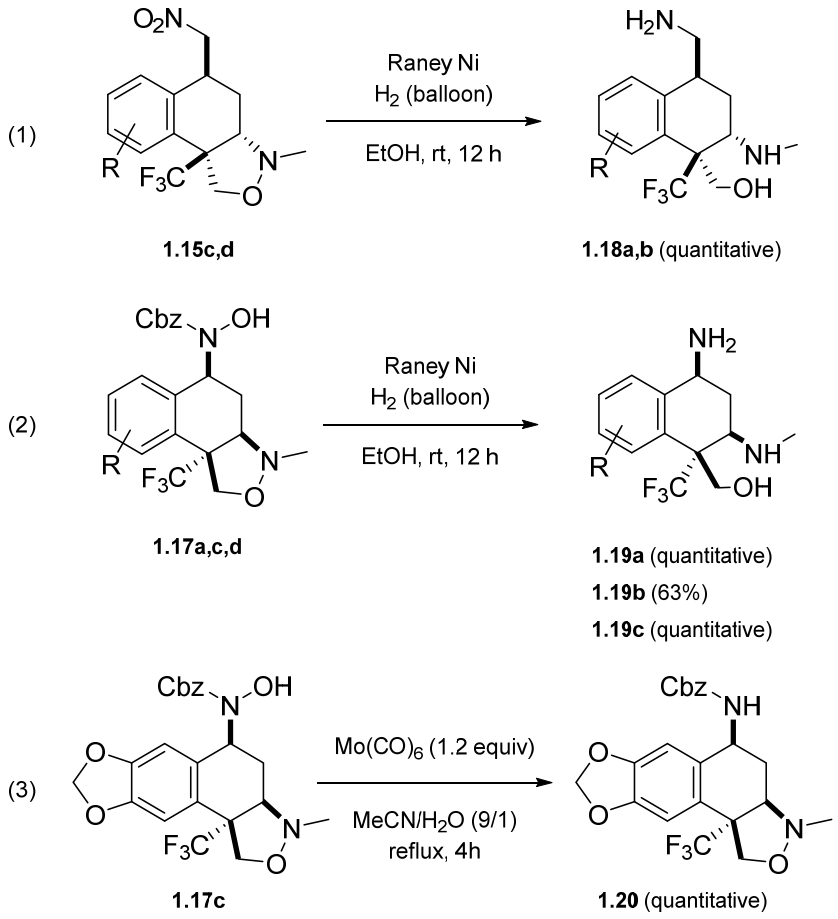


Figure 1.10

In order to verify that the diastereofacial inversion was due to the exclusive presence of the hydroxyamino group, calculations were carried out with R = $NHCO_2Me$ (see the Experimental Section). In this case, the same diastereoisomeric preference by a (*Z*)-*Re*,*Si*-*endo* approach, which was found for R = CH_2NO_2, was observed, confirming that the additional OH group is responsible for the above-mentioned interactions, explaining the diastereofacial inversion. For comparative purposes, calculations replacing the trifluoromethyl group by a methyl group were also carried out (see the Experimental Section).

1.4.3. Further derivatisation of the cycloadducts

The nitromethane-derived isoxazolidines **1.15c** and **1.15d** could then be easily transformed into the corresponding 1,3-amino alcohols by cleavage of the O-N bond with Raney Ni under hydrogen atmosphere in ethanol. This reaction proceeded with concomitant reduction of the nitro group to afford trifluoromethylated diamino alcohols **1.18a** and **1.18b** in quantitative yield (Scheme 3, equation 1). The same hydrogenation conditions were applied to compounds **1.17**, rendering diaminoalcohols **1.19** bearing an amino group directly attached to the tetralin skeleton (Scheme 3, equation 2). Moreover, the selective cleavage of the *N*(Cbz)-OH bond in product **1.17c** was achieved with $Mo(CO)_6$, leaving the *N*(Me)-*O* bond of the isoxazolidine untouched (Scheme 3, equation 3).



Scheme 1.33

1.5. Conclusions

1.5.1. Conclusions of Part A: Intramolecular Nitrone Cycloaddition of α-Trifluoromethyl Styrenes. Role of the CF_3 Group in the Regioselectivity

The synthesis of a new family of racemic fluorinated polycyclic isoxazolidines was performed by means of an INCR of *ortho*-substituted α-trifluoromethyl styrenes. Despite the widespread applications of INCR, the use of fluorinated substrates in this type of processes remained almost unprecedented. Additionally, the 1-trifluoromethyl-vinyl unit was used for the first time as dipolarophile in INCR. Interestingly, the trifluoromethyl group plays an important role in the regioselectivity of the process: While α-methyl styrenes gave rise preferentially to the bridged cycloadducts, an inversion of the regioselectivity occurred with α-trifluoromethyl styrenes, affording fused products preferentially or exclusively. It seems that this inversion is due mainly to steric effects of the trifluoromethyl group.

1.5.2. Conclusions of Part B: Organocatalytic Enantioselective Synthesis of Trifluoromethyl-Containing Tetralin Derivatives by Sequential (Hetero)Michael Reaction-Intramolecular Nitrone Cycloaddition

An enantioselective synthesis of two new families of tetrahydronaphthalene derivatives containing a trifluoromethyl-bearing, all-carbon quaternary stereocentre has been developed. The applied synthetic approach to these interesting chiral building blocks begins with an organocatalytic conjugate addition reaction on conveniently functionalised cinnamaldehydes and related aromatic compounds bearing a 1-trifluoromethyl alkene group at the *ortho* position. Once introduced the chirality at the β-position of the aldehyde, the *in situ* condensation with an hydroxylamine followed by INCR gives rise to the desired tetralin derivatives fused with an isoxazolidine moiety, with three stereogenic centres in good yields and excellent enantioselectivities.

It was observed that the diastereofacial selectivity in the cycloaddition step was reversed when nitromethane or *N*-Cbz-hydroxylamine were employed as the nucleophiles in the initial organocatalytic step. Theoretical calculations determined that this inversion is due to unfavourable interactions lowering the stability of the (*Z*)-*Re*,*Si*-endo approach in the second case (*N*-Cbz-hydroxylamine as nucleophile), being the (*Z*)-*Si*,*Re*-endo approach the most stable one.

1.6. Experimental Section

1.6.1. General Methods

Reactions were carried out under a nitrogen atmosphere unless otherwise indicated. Solvents were purified prior to use: THF and toluene 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. Visualisation 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). ^{1}H 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. Microwave reactions were carried out in a 2–5 or 15 mL vial with a Biotage Initiator TM 2.0 microwave synthesizer. The solutions were stirred before the irradiation was started, and the absorbance of the solvent was set as "normal". The reaction time was initiated as soon the system reached the input temperature, although it took approximately 2 min to reach it. A QTOF mass analyzer system has been used for the HRMS measurements. Enantiomeric excess was determined by means of HPLC using chiral columns and mixtures of hexane and isopropanol as mobile phase.

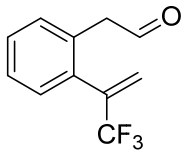
1.6.2. Part A: Experimental procedures and characterisation of new compounds

- **Synthesis of isoxazolidines 1.5 and 1.6**

a) Synthesis of fluorinated aldehydes **1.3**. General procedure

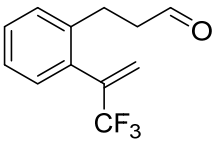
A 10 mL microwave glass vial was charged with $Pd_2(dba)_3$ (4 mol %, 0.06 mmol), Xphos (10 mol %, 0.15 mmol), Na_2CO_3 (2.2 equiv, 3.3 mmol) and *N*-tosylhydrazone **1.2** (1.5 equiv, 2.25 mmol), which was previously prepared from

1,1,1−trifluoroacetone (1 equiv, 22 mmol) and *N*-tosylhydrazine (1 equiv, 22 mmol) by heating at 70 °C in EtOH (0.5 M) for 5 h and then filtering the precipitate solid at room temperature as a crystalline white solid. The solid reagents were dried together under reduced pressure before being used. The corresponding 2-(2-bromophenyl)acetaldehyde or 3-(2-bromophenyl)propionaldehyde **1.1** (1.5 mmol) dissolved in THF (0.3 M) was added. The vial was sealed and the mixture was heated by microwave irradiation at 100 °C for 2 h. The reaction mixture was cooled to room temperature, opened, filtered through Celite and concentrated under reduced pressure. The residue obtained was purified by flash chromatography [*n*-hexane-EtOAc (20:1)]. The product obtained was used immediately in the next step.[90]



1.3a

2-[2-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl]acetaldehyde (1.3a): Starting from 2-(2-bromophenyl)acetaldehyde **1.1a**[91] and following the general procedure indicated above, **1.3a** was obtained as a yellow oil in 63% yield (202 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (t, *J* = 1.8 Hz, 1H), 7.51–7.19 (m, 4H), 6.14 (q, *J* = 1.5 Hz, 1H), 5.49 (q, *J* = 1.3 Hz, 1H), 3.74 (d, *J* = 1.8 Hz, 2H). ^{19}F NMR (282.4 MHz, $CDCl_3$) δ -67.91 (s).



1.3b

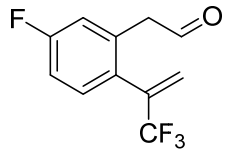
3-(2-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl)propanal (1.3b): Starting from 3-(2-bromophenyl)propanal **1.1b**[92] and following the general procedure indicated above, **1.3b** was obtained as a yellow oil in 77% yield (264 mg). ^{1}H NMR (300 MHz,

[90] Due to their instability, HRMS could not be obtained for these derivatives. ^{13}C spectra of freshly purified samples did not account for the right number of signals in the aromatic region, suggesting decomposition in the deuterated solvents in which the samples were dissolved.

[91] Besandre, R.; Jaimes, M.; May, J. A. *Org. Lett.* **2013**, *15*, 1666.

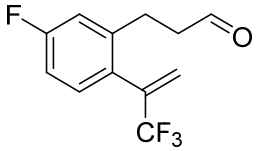
[92] Cooke Jr., M. P.; Widener, R. K. *J. Org. Chem.* **1987**, *52*, 1381.

$CDCl_3$) δ 9.70 (t, *J* = 1.3 Hz, 1H), 7.48–7.00 (m, 4H), 6.05 (d, *J* = 1.4 Hz, 1H), 5.44 (d, *J* = 1.4 Hz, 1H), 2.87 (dd, *J* = 8.6, 6.8 Hz, 2H), 2.70–2.56 (m, 2H). ^{19}F NMR (282.4 MHz, $CDCl_3$) δ -67.46 (s).



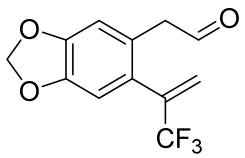
1.1c

2-(5-Fluoro-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)acetaldehyde (1.3c): Starting from 2-(2-bromo-5-fluorophenyl)acetaldehyde **1.1c**[93] and following the general procedure indicated above, **1.3c** was obtained as a yellow oil in 44% yield (153 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (t, *J* = 1.6 Hz, 1H), 7.56–7.31 (m, 1H), 7.11 – 6.88 (m, 2H), 6.15 (q, *J* = 1.4 Hz, 1H), 5.49 (d, *J* = 1.4 Hz, 1H), 3.73 (d, *J* = 1.6 Hz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$,) δ -68.10 (s, 3F), -112.32 (ddd, *J* = 9.1, 8.2, 5.7 Hz, 1F).



1.1d

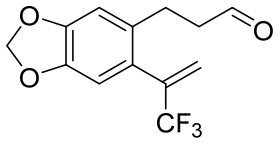
3-(5-Fluoro-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)propanal (1.3d): Starting from 3-(2-bromo-5-fluorophenyl)propanal **1.1d**[94] and following the general procedure indicated above, **1.3d** was obtained as a yellow oil in 81% yield (299 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (t, *J* = 1.1 Hz, 1H), 7.22–7.14 (m, 1H), 7.02–6.88 (m, 2H), 6.16 (q, *J* = 1.4 Hz, 1H), 5.53 (q, *J* = 1.3 Hz, 1H), 2.94 (t, *J* = 7.5 Hz, 2H), 2.80–2.69 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.71 (s, 3F), -112.69 (ddd, *J* = 9.7, 8.2, 5.9 Hz, 1F).



1.3e

[93] Baker, S. J.; Zhang, Y.-Z.; Akama, T.; Lau, A.; Zhou, H.; Hernandez, V.; Mao, W.; Alley, M. R. K.; Sanders, V.; Plattner, J. J. *J. Med. Chem.* **2006**, *49*, 4447.
[94] Pawliczek, M.; Milde, B.; Jones, P. G.; Werz, D. B. *Chem. Eur. J.* **2015**, *21*, 12303.

2-(6-(3,3,3-Trifluoroprop-1-en-2-yl)benzo[*d*][1,3]dioxol-5-yl)acetaldehyde (1.3e): Starting from 2-(6-bromobenzo[*d*][1,3]dioxol-5-yl)acetaldehyde **1.1e**[95] and following the general procedure indicated above, **1.3e** was obtained as a yellow oil in 41% yield (159 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (t, *J* = 1.7 Hz, 1H), 6.75 (s, 1H), 6.70 (s, 1H), 6.11 (q, *J* = 1.4 Hz, 1H), 6.00 (s, 2H), 5.46 (q, *J* = 1.4 Hz, 1H), 3.63 (d, *J* = 1.7 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -68.07 (s).



1.3f

3-(6-(3,3,3-Trifluoroprop-1-en-2-yl)benzo[*d*][1,3]dioxol-5-yl)propanal (1.3f): Starting from 3-(6-bromobenzo[*d*][1,3]dioxol-5-yl)propanal **1.1f**[96] and following the general procedure indicated above, **1.3f** was obtained as a yellow oil in 72% yield (294 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H), 6.71 (s, 1H), 6.67 (s, 1H), 6.12 (q, *J* = 1.4 Hz, 1H), 5.96 (s, 2H), 5.50 (q, *J* = 1.2 Hz, 1H), 2.86 (t, *J* = 7.4 Hz, 2H), 2.71–2.63 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.67 (s).

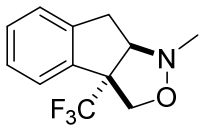
b) INCR of fluorinated aldehydes **1.3**. General procedure

To a solution of the corresponding starting fluorinated aldehyde **1.3** (0.5 mmol) in toluene (0.2 M) in a 10 mL microwave glass vial were added *N*-alkylhydroxylamine hydrochloride (2.6 equiv) and sodium bicarbonate (2.6 equiv, 109 mg). The vial was sealed and the mixture was heated by microwave irradiation at 120 °C for 30 min. The reaction mixture was cooled to room temperature, opened and concentrated under reduced pressure. The residue obtained was subjected to flash chromatography to purify and/or separate the formed regioisomeric isoxazolidines **1.5** and **1.6**.

Starting from **1.3a** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, a mixture of **1.5a** (44%, 54 mg, yellow oil) and **1.6a** (25%, 30 mg, yellow solid, mp=73-75 °C) was obtained which

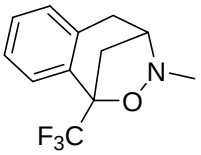
[95] Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Org. Lett.* **2006**, *8*, 2143.
[96] Rochette, E. M.; Lewis, W.; Dossetter, A. G.; Stockman, R. A. *Chem. Commun.* **2013**, *49*, 9395.

were separated by flash chromatography [*n*-hexane-EtOAc (4:1)].



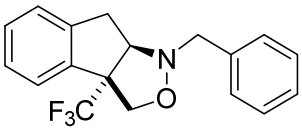
1.5a

1-Methyl-3a-(trifluoromethyl)-3,3a,8,8a-tetrahydro-1*H*-indeno[2,1-*c*]isoxazole (1.5a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.12 (m, 4H), 4.45 (d, *J* = 8.9 Hz, 1H), 3.81 (dq, *J* = 8.9, 1.6 Hz, 1H), 3.41 (d, *J* = 6.6 Hz, 1H), 3.17 (dd, *J* = 17.0, 6.6 Hz 1H), 2.80 (d, *J* = 17.0 Hz, 1H), 2.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 138.5, 129.5, 127.9, 127.2 (CF_3, q, *J* = 279.9 Hz), 125.6, 125.2, 74.4, 73.3, 71.2 (C-CF_3, q, *J* = 26.2 Hz), 43.4, 35.2. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ -72.63 (s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{12}H_{13}F_3NO$ 244.0944; Found 244.0934.



1.6a

3-Methyl-1-(trifluoromethyl)-1,3,4,5-tetrahydro-1,4-methanobenzo[*e*][1,2]oxazepine (1.6a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.09 (m, 4H), 3.70 (br s, 1H), 3.35–3.12 (m, 2H), 2.95 (dd, *J* = 11.3, 5.3 Hz, 1H), 2.81 (s, 3H), 2.36 (d, *J* = 11.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 134.1, 129.8, 129.0, 125.8, 124.9 (CF_3,q, *J* = 281.1 Hz), 123.3, 83.5 (C-CF_3, q, *J* = 26.7 Hz), 62.7, 46.9, 37.9, 35.2. ^{19}F-RMN (282.4 MHz, $CDCl_3$) δ -71.70 (s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{12}H_{13}F_3NO$ 244.0944; Found 244.0943.

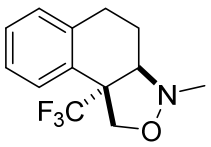


1.5b

1-Benzyl-3a-(trifluoromethyl)-3,3a,8,8a-tetrahydro-1*H*-indeno[2,1-*c*]isoxazole (1.5b): Starting from **1.3a** and *N*-benzylhydroxylamine hydrochloride and following the general procedure indicated above, **1.5b** (35%, 56 mg, yellow solid, mp= 88-90 °C) was obtained and purified by flash chromatography [*n*-hexane-Et_2O (25:1)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53–7.01 (m, 9H), 4.47 (d, *J* = 9.0 Hz, 1H), 4.05 (d, *J* = 13.6 Hz, 1H), 3.99 (d, *J* = 13.6 Hz, 1H), 3.81 (dq, *J* = 9.0, 1.6 Hz,

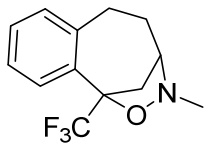
1H), 3.69 (d, *J* = 7.0 Hz, 1H), 3.12 (dd, *J* = 17.1, 7.0 Hz, 1H), 2.77 (d, *J* = 17.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 138.3, 136.8, 129.5, 129.1 (2xCH), 128.6 (2xCH), 127.8, 127.7, 127.3 (CF_3,q, *J* = 279.7 Hz), 125.5, 125.1, 73.1, 72.4, 70.9 (C-CF_3, q, *J* = 26.1 Hz), 61.0, 35.9. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ -72.38 (s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{18}H_{17}F_3NO$ 320.1257; Found 320.1255.

Starting from **1.3b** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, a mixture of **1.5c** (55%, 71 mg, yellow oil) and **1.6c** (29%, 37 mg, yellow solid, mp=65-67 °C) was obtained which were separated by flash chromatography [*n*-hexane-EtOAc (4:1)]. See COSY spectra of both compounds below.



1.5c

3-Methyl-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazole (1.5c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 6.96 (m, 4H), 4.63 (d, *J* = 9.2 Hz, 1H), 3.97 (dq, *J* = 9.2, 1.8 Hz, 1H), 3.17 (dd, *J* = 7.1, 7.1 Hz, 1H), 2.81 (s, 3H), 2.77-2.73 (m, 2H), 2.32 – 2.12 (m, 1H), 1.66 – 1.50 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 132.1, 129.1, 128.4, 128.1, 127.5 (CF_3, q, *J* = 282.2 Hz), 126.9, 73.4, 68.2, 58.9 (C-CF_3, q, *J* = 24.2 Hz), 43.6, 26.5, 25.2**.** ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ -72.34 (s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{13}H_{15}F_3NO$ 258.1100; Found 258.1105.



1.6c

3-Methyl-1-(trifluoromethyl)-3,4,5,6-tetrahydro-1*H*-1,4-methanobenzo[*f*][1,2]oxazocine (1.6c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.04 (m, 4H), 3.85–3.59 (m, 2H), 3.09 (ddd, *J* = 12.6, 7.0, 1.6 Hz, 1H), 2.89 (s, 3H), 2.87–2.77 (m, 1H), 2.63 (dt, *J* = 14.8, 3.8 Hz, 0H), 2.23-2.13 (m, 2H), 1.63 (tdd, *J* = 13.6, 3.4, 1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 137.7, 132.5, 128.5, 126.3, 125.6 (CF_3, q, *J* = 283.8 Hz), 125.0, 89.0, 66.0, 47.0, 43.2, 34.1, 32.4. ^{19}F NMR ($CDCl_3$, 282.4

MHz) δ -70.83 (s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{13}H_{15}F_3NO$ 258.1100; Found 258.1099.

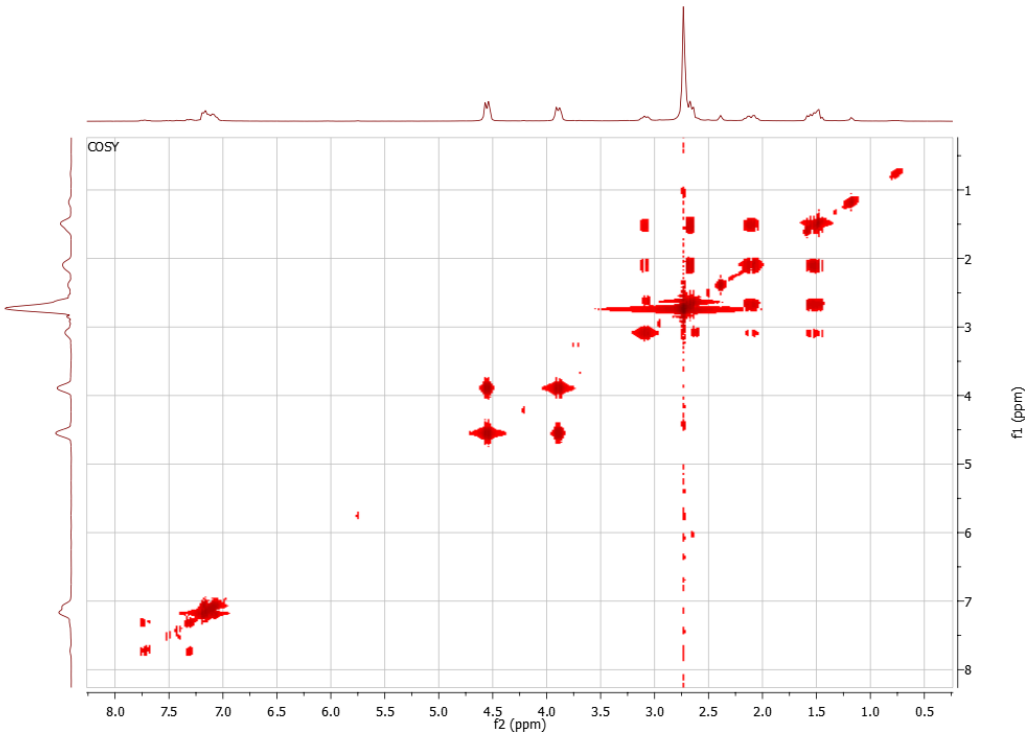


Figure S1.1 COSY spectrum of compound **1.5c**.

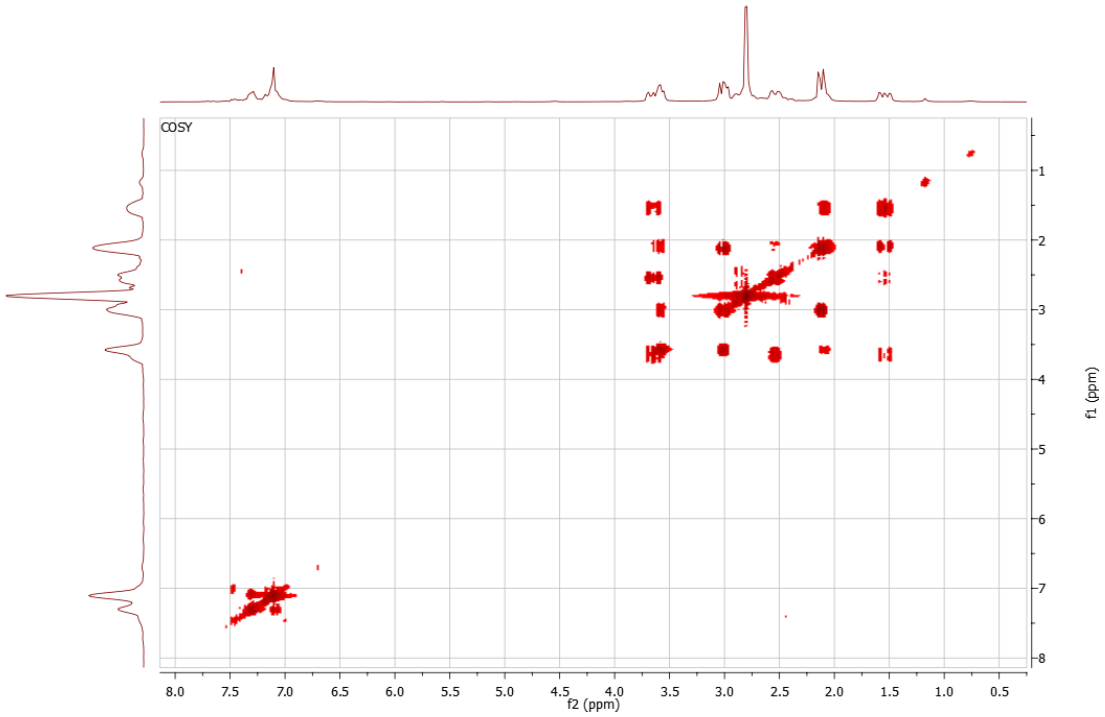
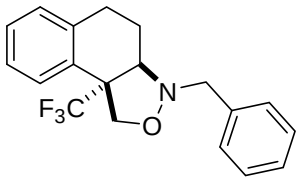


Figure S1.2 COSY spectrum of compound **6c**.

Starting from **1.3b** and *N*-benzylhydroxylamine hydrochloride and following the general procedure indicated above, a mixture of **1.5d** (46%, 77 mg, white solid, mp= 95-97 °C) and **1.6d** (23%, 38 mg, white solid, mp=110-112 °C) was obtained which were separated by flash chromatography [*n*-hexane-Et_2O (30:1)].



1.5d

3-Benzyl-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazole (1.5d): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33-7.06 (m, 9 H), 4.56 (d, *J*= 9.3 Hz, 1H), 4.06 (d, *J*=13.7 Hz, 1H), 3.97 (d, *J*=13.7 Hz, 1H), 3.92 (dq, *J*=9.3, 1.8 Hz, 1H), 3.37 (dd, *J*=8.6, 6.3 Hz, 1 H), 2.73-2.58 (m, 2H), 2.04-1.95 (m, 1H), 1.59-1.49 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 137.1, 132.1, 129.1, 129.0 (2xCH), 128.5 (2xCH), 128.3, 128.1, 127.6, 127.6 (CF_3, q, *J* = 282.3 Hz), 126.9, 73.2, 73.2, 66.3, 61.0, 58.7 (C-CF_3, q, *J* = 24.0 Hz), 26.8, 26.0. ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ -72.35 (s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{19}H_{19}F_3NO$ 334.1413; Found 334.1409.

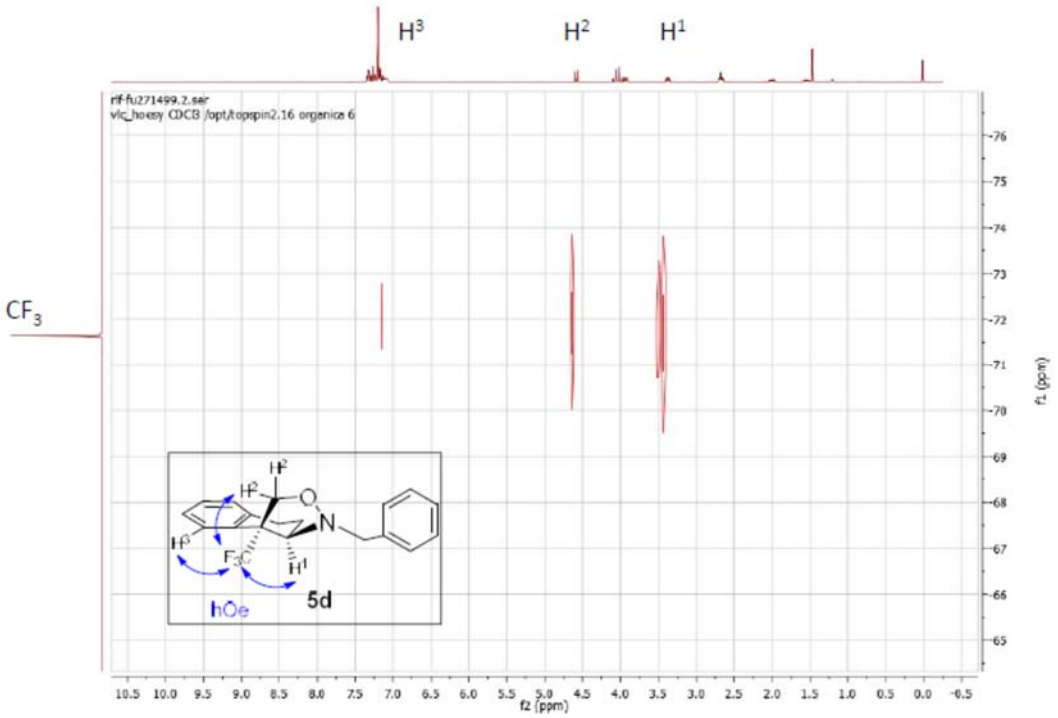
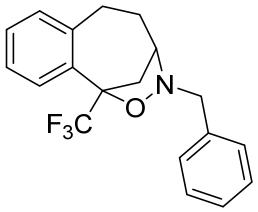
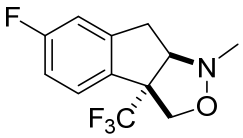


Figure S1.3 HOESY spectrum of compound **1.5d**.



1.6d

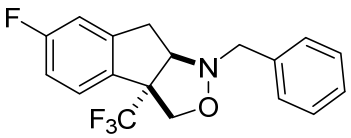
3-Benzyl-1-(trifluoromethyl)-3,4,5,6-tetrahydro-1*H*-1,4-methanobenzo[*f*][1,2]oxazocine (1.6d): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–6.95 (m, 9H), 4.33 (d, *J* = 13.0 Hz, 1H), 3.87 (d, *J* = 13.0 Hz, 1H), 3.81–3.63 (m, 2H), 3.05 (ddd, *J* = 12.6, 7.0, 1.5 Hz, 1H), 2.53 (dt, *J* = 14.8, 3.8 Hz, 1H), 2.16 (d, *J* = 12.6 Hz, 1H), 2.02–1.86 (m, 1H), 1.62–1.39 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 141.6, 138.0, 137.8, 132.5, 129.3, 128.8, 128.5, 127.8, 125.8 (CF_3, q, *J*= 283.8 Hz), 125.0, 89.3 (C-CF_3, q, *J* = 25.6 Hz), 63.3, 62.8, 43.4, 34.3, 32.6. ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ -70.70 (s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{19}H_{19}F_3NO$ 334.1413; Found 334.1421.



1.5e

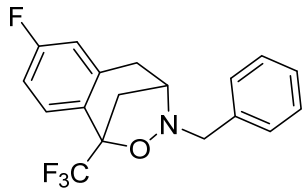
6-Fluoro-1-methyl-3a-(trifluoromethyl)-3,3a,8,8a-tetrahydro-1*H*-indeno[2,1-*c*]isoxazole (1.5e): Starting from **1.3c** and *N* methylhydroxylamine hydrochloride and following the general procedure indicated above, **1.5e** (33%, 43 mg, yellow solid, mp = 49-51 °C) was obtained and purified by flash chromatography [*n*-hexane-EtOAc (50:1)]. Only trace amounts of the bridged regioisomer could be detected when the reaction was upscaled. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 1H), 7.03–6.91 (m, 2H), 4.51 (d, *J* = 8.9 Hz, 1H), 3.85 (dq, *J* = 8.9, 1.6 Hz, 1H), 3.51 (d, *J* = 6.5 Hz, 1H), 3.23 (dd, *J* = 17.1, 6.5 Hz, 1H), 2.86 (d, *J* = 17.1 Hz, 1H), 2.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 162.4, 130.1, 127.0 (CF_3, q, *J* = 279.6 Hz), 126.5 (d, *J* = 9.3 Hz), 115.3 (d, *J* = 23.0 Hz), 112.6 (d, *J* = 22.5 Hz), 74.9, 73.2, 70.5 (C-CF_3, q, *J* = 26.2 Hz), 43.3, 35.2. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -72.89 (s, 3F), -113.45 (ddd, *J* = 8.8, 8.8, 5.1 Hz, 1F). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{12}H_{12}F_4NO$ 262.0850; Found 262.0854.

Starting from **1.3c** and *N*-benzylhydroxylamine hydrochloride and following the general procedure indicated above, a mixture of **1.5f** (28%, 47 mg, yellow oil) and **1.6f** (30%, 51 mg, yellow oil) was obtained which were separated by flash chromatography [*n*-hexane-EtOAc (50:1)]. Only **1.5f** could be completely separated, whilst **1.6f** was invariably obtained in a mixture of both regioisomers and the ^{1}H NMR signals below were inferred from the spectrum of the mixture by comparison with the spectrum of pure **1.5f**.



1.5f

1-Benzyl-6-fluoro-3a-(trifluoromethyl)-3,3a,8,8a-tetrahydro-1*H*-indeno[2,1-*c*]isoxazole (1.5f): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.20 (m, 6H), 7.06–6.88 (m, 2H), 4.54 (d, *J* = 9.0 Hz, 1H), 4.11 (s, 2H), 3.87 (dq, *J* = 9.0, 1.5 Hz, 1H), 3.81 (dd, *J* = 7.0, 1.1 Hz, 1H), 3.19 (dd, *J* = 17.4, 7.0 Hz, 1H), 2.83 (d, *J* = 17.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 162.4, 145.6 (d, *J* = 8.7 Hz), 136.6, 128.6, 127.8, 127.1 (CF_3, q, *J* = 279.9 Hz), 126.4 (d, *J* = 9.5 Hz), 115.2 (d, *J* = 23.1 Hz), 112.4 (d, *J* = 22.5 Hz), 73.1, 72.8, 70.2 (C-CF_3,q, *J* = 26.4 Hz), 60.9, 36.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ -72.62 (s, 3F), -113.47 (ddd, *J* = 8.8, 8.8, 5.1 Hz, 1F). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{18}H_{16}F_4NO$ 338.1163; Found 338.1162.

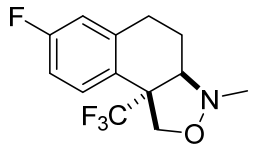


1.6f

3-Benzyl-7-fluoro-1-(trifluoromethyl)-1,3,4,5-tetrahydro-1,4-methanobenzo[*e*][1,2]oxazepine (1.6f): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 6H), 6.91 – 6.77 (m, 2H), 4.24 (d, *J* = 12.7 Hz, 1H), 3.89 (d, *J* = 12.7 Hz, 1H), 3.84 (s, 1H), 3.24 – 3.05 (m, 2H), 3.03 – 2.90 (m, 1H), 2.34 (d, *J* = 11.4 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -71.68 (br s, 3F), -113.46 (ddd, *J* = 8.8, 8.8, 5.6 Hz, 1F).

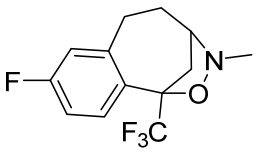
Starting from **1.3d** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, a mixture of **1.5g** (50%, 69 mg, yellow oil) and **1.6g** (13%, 18 mg, yellow oil) was obtained which were separated

by flash chromatography [*n*-hexane-EtOAc (50:1)].



1.5g

7-Fluoro-3-methyl-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazole (1.5g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 – 7.08 (m, 1H), 7.00–6.86 (m, 2H), 4.61 (d, *J* = 9.1 Hz, 1H), 3.92 (dq, *J* = 9.1, 1.7 Hz, 1H), 3.16 (t, *J* = 6.7 Hz, 1H), 2.80 (s, 3H), 2.74 (m, 4.8 Hz, 2H), 2.25–2.09 (m, 1H), 1.69–1.52 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 160.5, 141.7, 141.6, 130.8 (d, *J* = 8.2 Hz), 127.4 (CF_3, q, *J* = 282.3 Hz), 115.1 (d, *J* = 21.0 Hz), 114.1 (d, *J* = 21.5 Hz), 73.5, 68.0, 58.5 (C-CF_3, q, *J* = 23.6 Hz), 43.6, 26.6, 24.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ -72.47 (s, 3F), -114.58 (ddd, *J* = 8.7, 8.7., 5.5 Hz, 1F). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{13}H_{14}F_4NO$ 276.1006; Found 276.1013.

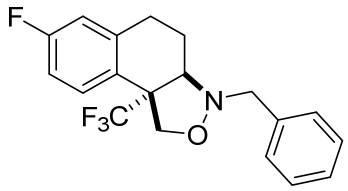


1.6g

8-Fluoro-3-methyl-1-(trifluoromethyl)-3,4,5,6-tetrahydro-1*H*-1,4-methanobenzo[*f*][1,2]oxazocine (1.6g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, 1H), 6.90 (dd, *J* = 9.7, 3.1 Hz, 1H), 6.87 – 6.77 (m, 1H), 3.85 – 3.56 (m, 2H), 3.08 (ddd, *J* = 12.6, 7.0, 1.6 Hz, 1H), 2.87 (s, 3H), 2.57 (dt, *J* = 15.0, 3.7 Hz, 1H), 2.25-2.07 (m, 2H), 1.62 (tdd, *J* = 13.7, 3.3, 1.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 160.2, 144.3, 126.6, 125.3 (CF_3, q, *J* = 283.6 Hz), 119.0 (d, *J* = 21.1 Hz), 112.2 (d, *J* = 20.6 Hz), 88.5 (C-CF_3, q, *J* = 28.4 Hz), 65.6, 46.7, 42.9, 33.6, 32.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ -71.17 (br s, 3F), -115.31 (ddd, *J* = 8.7, 8.7, 5.7 Hz, 1F). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{13}H_{14}F_4NO$ 276.1006; Found 276.0999.

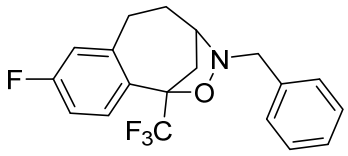
Starting from **1.3d** and *N*-benzylhydroxylamine hydrochloride and following the general procedure indicated above, a mixture of **1.5h** (39%, 69 mg) and **1.6h** (16%, 28 mg) was obtained as a colourless oil, which was purified but could not be separated by flash chromatography [n-hexane-EtOAc (50:1)]. The ^{1}H

and ^{19}F-NMR data were extracted from the spectra of the mixture.



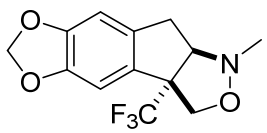
1.5h

3-Benzyl-7-fluoro-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazole (1.5h): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-6-70 (m, 8H), 4.54 (d, *J* = 9.2 Hz, 1H), 4.04 (d, *J* = 13.9 Hz, 1H), 3.96 (d, *J* = 13.9 Hz, 1H), 3.84 (dq, *J* = 9.2, 1.8 Hz, 1H), 3.34 (dd, *J* = 8.4, 6.1 Hz, 1H), 2.71–2.57 (m, 2H), 2.02-1.89 (m, 1H), 1.62–1.41 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -72.47 (s, 3F), -114.52 (ddd, J = 8.7, 8.7, 5.4 Hz, 1F).



1.6h

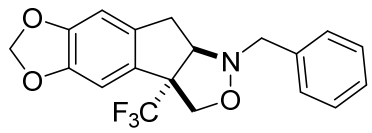
3-Benzyl-8-fluoro-1-(trifluoromethyl)-3,4,5,6-tetrahydro-1*H*-1,4-methanobenzo[*f*][1,2]oxazocine (1.6h): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-6-70 (m, 8H), 4.31 (d, *J* = 13.0 Hz, 1H), 3.86 (d, *J* = 13.0 Hz, 1H), 3.80–3.62 (m, 2H), 3.05 (ddd, *J* = 12.6, 7.0, 1.5 Hz, 1H), 2.47 (dt, *J* = 14.8, 3.7 Hz, 1H), 2.12 (dd, J = 12.6, 0.9 Hz, 1H), 2.02-1.89 (m, 1H), 1.62 – 1.41 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -70.92 (br s, 3F), -115.28 (ddd, *J* = 9.4, 8.0, 5.5 Hz, 1F).



1.5i

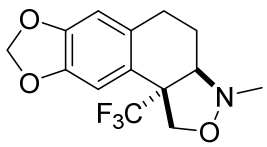
1-Methyl-3a-(trifluoromethyl)-3,3a,9,9a-tetrahydro-1*H*-[1,3]dioxolo[4',5':5,6]indeno[2,1-*c*]isoxazole (1.5i): Starting from **1.3e** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **1.5i** (42%, 60 mg, yellow solid, mp= 59-61 °C) was obtained and purified by flash chromatography [*n*-hexane-EtOAc (50:1)]. The corresponding bridged regioisomer could not be found in the reaction mixture**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.67 (s, 1H), 5.96 (s, 2H), 4.46 (d, *J* = 8.9 Hz, 1H), 3.84 (dq, *J* =

8.9, 1.6 Hz, 1H), 3.46 (d, *J* = 6.6 Hz, 1H), 3.14 (dd, *J* = 17.0, 6.6 Hz, 1H), 2.79 (s, 3H), 2.75 (d, *J* = 17.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 147.9, 136.1, 130.8, 127.2 (CF_3, q, *J* = 280.1 Hz), 105.6, 105.1, 101.7, 75.0, 73.1, 70.7 (C-CF_3, q, *J* = 26.2 Hz), 43.4, 35.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ -72.89 (s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{13}H_{13}F_3NO_3$ 288.0842; Found 288.0848.



1.5j

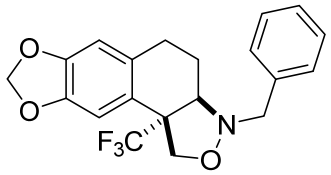
1-Benzyl-3a-(trifluoromethyl)-3,3a,9,9a-tetrahydro-1*H*-[1,3]dioxolo[4',5':5,6]indeno[2,1-*c*]isoxazole (1.5j): Starting from **1.3e** and *N*-benzylhydroxylamine hydrochloride and following the general procedure indicated above, **1.5j** (97%, 176 mg, yellow oil) was obtained and purified by flash chromatography [*n*-hexane-EtOAc (20:1)]. The corresponding bridged regioisomer could not be found in the reaction mixture. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.10 (m, 5H), 6.61 (s, 1H), 6.54 (s, 1H), 5.85 (s, 2H), 4.39 (d, *J* = 8.9 Hz, 1H), 3.99 (s, 2H), 3.76 (dq, *J* = 8.9, 1.4 Hz, 1H), 3.66 (d, *J* = 6.9 Hz, 1H), 2.99 (dd, *J* = 16.9, 7.0 Hz, 1H), 2.62 (d, *J* = 16.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 148.2, 137.0, 136.6, 130.4, 129.4, 127.6 (CF_3, q, *J* = 285.4 Hz), 128.8, 128.0, 105.7, 105.3, 102.0, 73.2, 70.8 (C-CF_3, q, *J* = 26.2 Hz), 61.2, 36.0, 22.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ -72.60 (s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{19}H_{17}F_3NO_3$ 364.1155; Found 364.1161.



1.5k

3-Methyl-10b-(trifluoromethyl)-1,3,3a,4,5,10b-hexahydro-[1,3]dioxolo[4',5':6,7]naphtho[2,1-*c*]isoxazole (1.5k): Starting from **1.3f** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **1.5k** (88%, 133 mg, white solid, mp= 76-78 °C) was obtained and purified by flash chromatography [*n*-hexane-EtOAc (10:1)]. Only trace amounts of the bridged regioisomer could be detected when the reaction was up scaled. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (s, 1H), 6.63 – 6.58 (m, 1H), 5.94 (d, *J* = 1.4 Hz, 1H),

5.93 (d, *J* = 1.4 Hz, 1H), 4.56 (d, *J* = 9.1 Hz, 1H), 3.91 (dq, *J* = 9.1 Hz, *J* = 1.8 Hz, 1H), 3.11 (t, *J* = 6.8 Hz, 1H), 2.79 (s, 3H), 2.70 – 2.59 (m, 2H), 2.20 – 2.06 (m, 1H), 1.67 – 1.50 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 146.9, 133. 5, 128.9, 127.7 (CF_3, q, J= 282.5 Hz), 124.8, 109.2, 109.1, 108.7, 101.5, 73.8, 68.3, 59.6 (C-CF_3, q, J= 23.1 Hz), 43.9, 26.8, 25.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ -72.47(s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{14}H_{15}F_3NO_3$ 302.0999; Found 302.1007.



1.5l

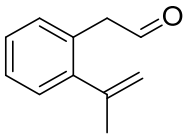
3-Benzyl-10b-(trifluoromethyl)-1,3,3a,4,5,10b-hexahydro-[1,3]dioxolo[4',5':6,7]naphtho[2,1-*c*]isoxazole (1.5l): Starting from **1.3f** and *N*-benzylhydroxylamine hydrochloride and following the general procedure indicated above, **1.5l** (79%, 149 mg, yellow oil) was obtained and purified by flash chromatography [*n*-hexane-EtOAc (10:1)]. Only trace amounts of the bridged regioisomer could be detected when the reaction was up scaled. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.06 (m, 5H), 6.65 (s, 1H), 6.63 – 6.55 (m, 1H), 5.94 (d, *J* = 1.4 Hz, 1H), 5.93 (d, *J* = 1.4 Hz, 1H), 4.57 (d, *J* = 9.2 Hz, 1H), 4.12 (d, *J* = 13.8 Hz, 1H), 4.03 (d, *J* = 13.8 Hz, 1H), 3.93 (dq, *J* = 9.2 Hz, *J* = 1.7 Hz, 1H), 3.38 (dd, *J* = 8.4, 6.2 Hz, 1H), 2.73 – 2.54 (m, 2H), 2.11 – 1.91 (m, 1H), 1.67 – 1.47 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 146.6, 137.0, 133.6, 129.0, 128.5, 127.6, 127.5 (CF_3, q, *J* = 282.5 Hz), 124.5, 109.0, 108.4, 101.3, 73.3, 66.2, 61.0, 58.7 (C-CF_3, q, *J* = 23.1 Hz), 26.8, 26.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ -72.47 (s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{20}H_{19}F_3NO_3$ 378.1312; Found 378.1328.

- **Synthesis of non-fluorinated aldehydes 1.8. General procedure**

These substrates were prepared adapting a known methodology from the literature.[97] A solution of 2-(2-bromophenyl)acetaldehyde **1.1a** or 3-(2-bromophenyl)propionaldehyde **1.1b** (1.5 mmol), palladium(II) acetate (5 mol%, 0.075 mmol), triphenylphosphine (10 mol%, 0.15 mmol), cesium carbonate (3.0

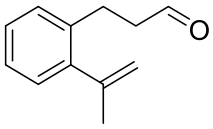
[97] See ref. 62.

equiv, 4.5 mmol) and potassium isopropenyl trifluoroborate **1.7** (1.25 equiv, 1.88 mmol) in THF/water 10:1 (0.3 M) was heated in a sealed 10 mL microwave glass vial at 100 ºC by microwave irradiation for 2 h. The reaction mixture was cooled to room temperature, opened, filtered through Celite and concentrated under reduced pressure. The residue obtained was purified by flash chromatography [*n*-hexane-EtOAc (20:1)]. Due to its instability, the product obtained was used immediately in the next step.



1.8a

2-[2-(Prop-1-en-2-yl)phenyl]acetaldehyde (1.8a): Starting from 2-(2-bromophenyl)acetaldehyde **1.1a** and following the general procedure indicated above, **1.8a** was obtained as a yellow oil in 59% yield (142 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (t, *J* = 2.1 Hz, 1H), 7.31–7.15 (m, 4H), 5.23 (dq, *J* = 1.9, 1.5 Hz, 1H), 4.82 (dq, *J* = 1.9, 0.9 Hz, 1H), 3.74 (d, *J* = 2.1 Hz, 2H), 2.02 (dd, *J* = 1.5, 0.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 144.9, 144.8, 130.7, 129.0, 128.6, 127.6, 127.5, 116.3, 48.3, 25.2.



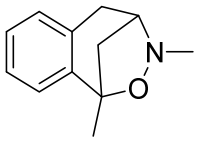
1.8b

3-[2-(Prop-1-en-2-yl)phenyl]propanal (1.8b): Starting from 3-(2-bromophenyl)propanal **1.1b** and following the general procedure indicated above, **1.8b** was obtained as a yellow oil in 70% yield (183 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (t, *J* = 1.4 Hz, 1H), 7.25 – 6.99 (m, 4H), 5.22-5.19 (m, 1H), 4.86-4.83 (m, 1H), 3.02-2.94 (m, 2H), 2.77-2.69 (m, 2H), 2.06 – 2.04 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 145.5, 143.9, 136.9, 129.7, 128.5, 127.3, 126.4, 115.4, 45.7, 25.6, 25.3.

- **INCR of non-fluorinated aldehydes 1.8. General procedure**

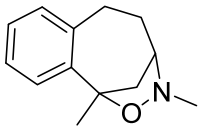
To a solution of the corresponding starting aldehyde **1.8** (0.5 mmol) in toluene (0.2 M) in a 10 mL microwave glass vial were added *N*-alkylhydroxylamine

hydrochloride (2.6 equiv) and sodium bicarbonate (2.6 equiv, 109 mg). The vial was sealed and the mixture was heated by microwave irradiation at 120 °C for 30 min. The reaction mixture was cooled to room temperature, opened and concentrated under reduced pressure. The residue obtained was subjected to flash chromatography to purify the formed isoxazolidines **1.9**.



1.9a

1,3-Dimethyl-1,3,4,5-tetrahydro-1,4-methanobenzo[*e*][1,2]oxazepine (1.9a): Starting from **1.8a** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **1.9a** (70%, 66 mg, colorless oil) was obtained and purified by flash chromatography [*n*-hexane-EtOAc (20:1)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.06 (m, 4H), 3.54 (br s, 1H), 3.20 (d, *J* = 17.1 Hz, 1H), 3.08 (dd, *J* = 17.1, 3.4 Hz, 1H), 2.77 (s, 3H), 2.44 (dd, *J* = 11.2, 5.5 Hz, 1H), 2.23 (d, *J* = 11.2 Hz, 1H), 1.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 133.9, 129.5, 128.1, 125.9, 122.8, 80.1, 63.6, 47.7, 40.3, 38.6, 20.8. HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{12}H_{16}NO$ 190.1226; Found 190.1225.

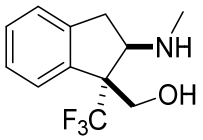


1.9b

1,3-Dimethyl-3,4,5,6-tetrahydro-1*H*-1,4-methanobenzo[*f*] [1,2]oxazocine (1.9b): Starting from **1.8b** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **1.9b** (44%, 45 mg, white solid, mp= 94-96 °C) was obtained and purified by flash chromatography [*n*-hexane-EtOAc (20:1)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.07 (m, 4H), 3.70 (td, *J* = 14.2, 3.6 Hz, 1H), 3.59 (t, *J* = 6.3 Hz, 1H), 2.91 (s, 3H), 2.75 (ddd, *J* = 12.4, 6.8, 1.5 Hz, 1H), 2.59 (dt, *J* = 14.7, 3.8 Hz, 1H), 2.25–2.01 (m, 2H), 1.93 (s, 3H), 1.60 (tdd, *J* = 13.6, 3.5, 1.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 141.1, 131.5, 127.1, 125.8, 123.8, 85.9, 66.3, 47.5, 47.4, 33.9, 32.6, 29.1. HRMS (ESI/Q-TOF) m/z: [M + H - O]+ Calcd for $C_{13}H_{18}N$ 188.1434; Found 188.1436.

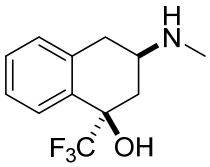
- **Reductive opening of the isoxazolidines. General procedure**

To a solution of the corresponding isoxazolidine **1.5** or **1.6** (0.2 mmol) in THF (0.1 M) was added Raney ® Nickel (0.5 mL as a slurry in water) and the resulting mixture was stirred at room temperature for 20 minutes. The reaction mixture was then filtered through Celite, dried (Na_2SO_4) and concentrated under reduced pressure to afford the corresponding 1,3-aminoalcohols **1.10** or **1.11** respectively without further purification.



1.10a

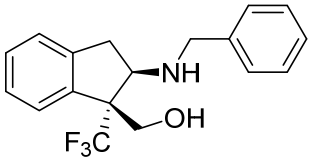
2-Methylamino-1-trifluoromethyl-2,3-dihydro-1*H*-inden-1-yl)methanol (1.10a): Starting from **1.5a** and following the general procedure indicated above, **1.10a** was obtained as a white solid (mp= 81-83 °C) in 50% yield (25 mg). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23-7.15 (m, 4H), 4.11 (d, *J*= 12.2 Hz, 1H), 3.84 (dq, *J* = 12.2, 1.2 Hz, 1H), 3.79 (t, *J* = 8.0Hz, 1H), 3.30 (dd, *J* = 15.8, 8.0 Hz, 1 H), 3.12 (br s, 2H), 2.80 (dd, *J* = 15.8, 8.0 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.4, 138.3, 129.0, 127.8 (CF_3, q, *J* = 282.7 Hz), 127.6, 125.0, 124.5, 64.3, 64.1, 60.1 (C-CF_3, q, *J* = 23.3 Hz), 38.5, 35.4. ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ -70.81 (s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{12}H_{15}F_3NO$ 246.1100; Found 244.1098.



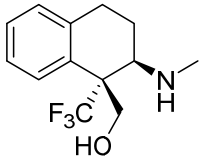
1.11a

3-Methylamino-1-trifluoromethyl-1,2,3,4-tetrahydronaphthalen-1-ol (1.11a): Starting from **1.6a** and following the general procedure indicated above, **1.11a** was obtained as a yellow solid (mp= 118-120 °C) in 83% yield (41 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79–7.73 (m, 1H), 7.30–7.26 (m, 2H), 7.15–7.09 (m, 1H), 3.33-3.30 (m, 1H), 3.16 (dd, *J*= 17.2, 4.6 Hz, 1H, 1H), 3.05 (br s, 2H), 2.87–2.78 (m, 1H), 2.47 (s, 3H), 2.42 – 2.35 (m, 1H), 2.17 (dd, *J* = 14.2, 2.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.3, 132.5, 128.4, 127.8, 126.8, 126.1, 124.8 (CF_3, q, *J* = 284.7 Hz),

72.5 (C-CF_3, q, *J* = 28.5 Hz), 51.7, 35.3, 33.1, 32.8. ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ -78.19 (s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{12}H_{15}F_3NO$ 246.1100; Found 246.1099.

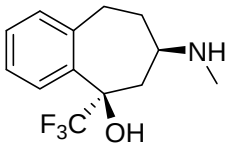


2-Benzylamino-1-trifluoromethyl-2,3-dihydro-1*H*-inden-1-yl)methanol (1.10b): Starting from **1.5b** and following the general procedure indicated above, **1.10b** was obtained as a white solid (mp= 88-90 °C) in 75% yield (48 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.12 (m, 9H), 4.13 (d, *J*= 12.6 Hz, 1H), 3.95-3.77 (m, 4H), 3.26 (dd, *J*= 15.8, 8.2 Hz, 1H), 3.09 (br s, 2H), 2.84 (dd, *J*= 15.8, 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 139.0, 138.1, 129.1, 128.9 (2xCH), 128.2 (2xCH), 127.8 (CF_3, q, *J* = 282.8 Hz), 127.7, 127.6, 124.9, 124.5, 64.2, 61.6, 60.1 (C-CF_3, q, *J* = 23.2 Hz), 53.0, 39.0. ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ -71.00 (s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{18}H_{19}F_3NO$ 322.1413; Found 322.1419.



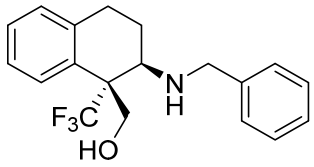
1.10c

2-Methylamino-1-trifluoromethyl-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (1.10c): Starting from **1.5c** and following the general procedure indicated above, **1.10c** was obtained as a white solid (mp= 72-74 °C) in 89% yield (46 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.37 (m, 1H), 7.20-7.13 (m, 2H), 7.10-7.06 (m, 1H), 4.23-4.14 (m, 2H), 3.27 (dd, *J*= 5.9, 3.4 Hz, 1H), 3.11 (br s, 2H), 2.83-2.78 (m, 2H), 2.46 (s, 3H), 2.23-2.05 (m, 1H), 2.02-1.91 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 133.0, 130.0, 129.5, 128.0, 127.3 (CF_3, q, *J* = 285.4 Hz), 126.6, 64.9, 58.9, 51.1 (C-CF_3, q, *J* = 21.1 Hz), 34.4, 25.0, 22.0. ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ -69.08 (s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{13}H_{17}F_3NO$ 260.1257; Found 260.1255.



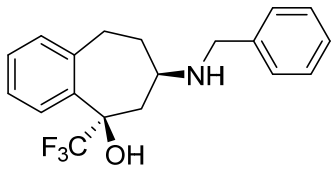
1.11c

7-Methylamino-5-trifluoromethyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ol (1.11c): Starting from **1.6c** and following the general procedure indicated above, **1.11c** was obtained as a yellow solid (mp= 91-93 °C) in 57% yield (30 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.39 (m, 1H), 7.22 – 7.10 (m, 3H), 4.62 (br s, 2H), 3.80 (t, *J* = 13.7 Hz, 1H), 3.32-3.26 (m, 1H), 2.74 – 2.48 (m, 5H), 2.16 – 2.00 (m, 1H), 1.98-1.87 (m, 1H), 1.82 (d, *J* = 14.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 139.9, 131.4, 128.0, 126.4 (CF_3, q, *J* = 286.3 Hz), 126.1, 125.5, 80.0 (C-CF_3, q, *J* = 27.3 Hz), 58.4, 33.9, 33.8, 30.4, 29.9. ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ -79.52 (s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{13}H_{17}F_3NO$ 260.1257; Found 260.1248.



1.10d

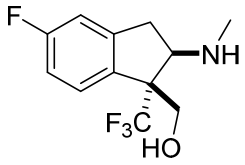
2-Benzylamino-1-trifluoromethyl-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (1.10d): Starting from **1.5d** and following the general procedure indicated above, **1.10d** was obtained as a colorless oil in 93% yield (62 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.08 (m, 9H), 4.25 (s, 2H), 3.97 (d, *J* = 12.4 Hz, 1H), 3.84 (d, *J* = 12.4 Hz, 1H), 3.55 (dd, *J* = 5.5, 3.4 Hz, 1H), 3.09 (br s, 2H), 2.96 – 2.87 (m, 2H), 2.25-1.94 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 137.5, 129.9, 129.6, 129.5, 128.9 (2xCH), 128.5 (2xCH), 128.1, 127.8, 127.3 (q, *J* = 285.5 Hz), 126.6, 64.8, 56.3, 52.2, 51.2 (C-CF_3, q, *J* = 21.2 Hz), 25.0, 22.5. ^{19}F-RMN ($CDCl_3$, 282.4 MHz) δ -67.38 (s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{19}H_{21}F_3NO$ 336.1570; Found 336.1562.



1.11d

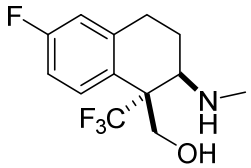
7-Benzylamino-5-trifluoromethyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-

ol (1.11d): Starting from **1.6d** and following the general procedure indicated above, **1.11d** was obtained as a colorless oil in 33% yield (22 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 6.94 (m, 9H), 4.08 (d, *J* = 12.7 Hz, 1H), 3.90-3.70 (m, 2H), 3.52-3.44 (m, 1H), 2.69-2.57 (m, 2H), 2.17 – 1.78 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.7, 139.7, 138.5, 131.4, 129.0 (2xCH), 128.5 (2xCH), 128.1, 127.8, 126.4 (CF_3, q, *J* = 286.0 Hz), 126.2, 125.8, 80.0, 55.6, 51.4, 34.1, 30.5, 29.9. ^{19}F NMR ($CDCl_3$, 282.4 MHz) δ -79.01 (s). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{19}H_{21}F_3NO$ 336.1570; Found 336.1566.



1.10e

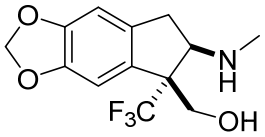
5-Fluoro-2-methylamino-1-trifluoromethyl-2,3-dihydro-1*H*-inden-1-yl)methanol (1.10e): Starting from **1.5e** and following the general procedure indicated above, **1.10e** was obtained as a white solid (mp= 54-56 °C) in 70% yield (37 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.21 (m, 1H), 7.00–6.89 (m, 2H), 4.18 (d, *J* = 12.1 Hz, 1H), 3.92–3.81 (m, 2H), 3.35 (dd, *J* = 15.9, 7.9 Hz, 1H), 2.99 (br s, 2H), 2.87 (dd, *J* = 16.1, 7.6 Hz, 1H), 2.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 161.9, 143.8 (d, *J* = 8.5 Hz), 127.7 (CF_3, q, *J* = 282.5 Hz), 125.9 (d, *J* = 9.0 Hz), 114.9 (d, *J* = 22.8 Hz), 112.0 (d, *J* = 22.3 Hz), 64.3, 64.2, 59.6 (C-CF_3,q, *J* = 23.5 Hz), 38.6, 35.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ -71.75 (s, 3F), -113.77 (ddd, *J* = 8.8, 8.8, 5.1 Hz, 1F). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{12}H_{14}F_4NO$ 264.1006; Found 264.0999.



1.10g

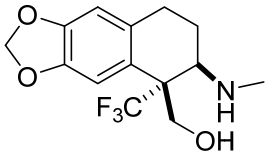
6-Fluoro-2-methylamino-1-trifluoromethyl-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (1.10g): Starting from **1.5g** and following the general procedure indicated above, **1.10g** was obtained as a white solid (mp= 83-85 °C) in quantitative yield (55 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.37 (m, 1H), 7.01 – 6.90 (m, 1H), 6.86 (dd, *J* = 9.3, 2.8 Hz, 1H), 4.23 (m, 2H), 3.33 (dd, *J* = 5.5, 3.5 Hz, 1H), 3.19 (br s, 2H), 3.00–2.74 (m, 2H), 2.53 (s, 3H), 2.26–1.94 (m, 2H). ^{13}C NMR

(75 MHz, $CDCl_3$) δ 163.8, 160.6, 140.3, 131.6 (d, *J* = 8.3 Hz), 127.1 (CF_3, q, *J* = 285.4 Hz), 115.7 (d, *J* = 20.8 Hz), 114.0 (d, *J* = 21.4 Hz), 64.8, 58.9, 50.8 (C-CF_3, q, *J* = 21.4 Hz), 34.5, 25.0, 21.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ -69.54 (s, 3F), -115.03 (ddd, *J* = 8.7, 8.7, 5.7 Hz, 1F). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{13}H_{16}F_4NO$ 278.1163; Found 278.1165.



1.10i

6-Methylamino-5-trifluoromethyl-6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]dioxol-5-yl)methanol (1.10i): Starting from **1.5i** and following the general procedure indicated above, **1.10i** was obtained as a white solid (mp= 97-99 °C) in 57% yield (33 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.66 (s, 1H), 5.95 (d, *J* = 1.4 Hz, 1H), 5.94 (d, *J* = 1.4 Hz, 1H), 4.14 (d, *J* = 12.0 Hz, 1H), 3.92 – 3.74 (m, 2H), 3.26 (dd, *J* = 15.5, 8.1 Hz, 1H), 3.05 (br s, 2H), 2.77 (dd, *J* = 15.6, 7.4 Hz, 1H), 2.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 147.6, 134.7, 130.5, 127.8 (CF_3, q, *J* = 282.9 Hz), 105.2, 104.8, 101.5, 64.3, 64.1, 59.9 (C-CF_3,q, *J* = 23.3 Hz), 38.4, 35.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ -71.76 (s, 3F). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{13}H_{15}F_3NO_3$ 290.0999; Found 290.0998.



1.10k

6-Methylamino-5-trifluoromethyl-5,6,7,8-tetrahydronaphtho[2,3-*d*][1,3]dioxol-5-yl)methanol (1.10k): Starting from **1.5k** and following the general procedure indicated above, **1.10k** was obtained as a white solid (mp= 139-141 °C) in quantitative yield (61 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.59 (s, 1H), 5.93 (d, *J* = 1.4 Hz, 1H), 5.92 (d, *J* = 1.4 Hz, 1H), 4.18 (m, 2H), 3.29 (dd, *J* = 5.2, 3.4 Hz, 1H), 2.89–2.68 (m, 2H), 2.51 (s, 3H), 2.04 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 146. 7, 131.6, 127.2 (CF_3, q, *J* = 285.6 Hz), 122.5, 109.0, 108.8, 101.3, 64.9, 58.7, 51.0 (C-CF_3, q, *J* = 21.2 Hz), 34.4, 24.9, 21.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ -72.27 (s, 3F). HRMS (ESI/Q-TOF) m/z: [M + H]+ Calcd for $C_{14}H_{17}F_3NO_3$ 304.1155; Found 304.1160.

1.6.3. Part A: Computational calculations

- **Theoretical calculations**

The quantum chemical calculations described in this work were carried out with Gaussian09 package,[98] using the density functional theory.

- **Nitrones**

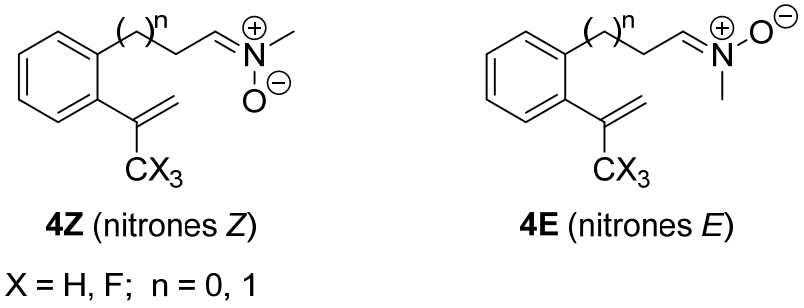


Figure S1.4

Table S1.1 B3LYP/6-31G(d) total (E, in au) and relative[a] (ΔE, in kcal/mol) gas phase energies of the stationary points (**X=H**).

nitrone	E	ΔE[a]
4Z (n=1)	-595,95131	0.0
4E (n=1)	-595,942625	5.5
4Z (n=2)	-635,235192	0.0
4E (n=2)	-635,229363	3.7

[a] relative to the most stable nitrone

[98] *Gaussian 09*, Revision B.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A. Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. J.; Burant, C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. J.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski J.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2010**.

Table S1.2 B3LYP/6-31G(d) total (E, in au) and relative[a] (ΔE, in kcal/mol) gas phase energies of the stationary points (**X=F**)

nitrone	E	ΔE[a]
4Z (n=1)	-893,696163	0.0
4E (n=1)	-893,683978	7.65
4Z (n=2)	-932,97981	0.0
4E (n=2)	-932,970686	5.73

[a] relative to the most stable nitrone.

- **Regioisomeric ratios**

Table S1.3 B3LYP/6-31G* total (E, in au) and relative[a] (ΔE, in kcal/mol) gas phase energies of transition states involved in the cycloaddition reaction of nitrones and regioisomeric ratios.

System	n	***X=H***	E	ΔE[a]	Ratio[b]
TSA	1		-595.922374	0.07	**A/B** (48.2/51.8)
TSB	1		-595.92249	0.00	
TSC	2		-635.198214	1.10	**C/D** (24.9/75.1)
TSD	2		-635.199971	0.00	
System	n	***X=F***	E	ΔE[a]	Ratio[b]
TSE	1		-893.675523	0.00	**E/F** (97.4/2.6)
TSF	1		-893.669742	3.63	
TSG	2		-932.951685	0.00	**G/H** (93.7/6.3)
TSH	2		-932.947371	2.71	

[a] Relative to the most stable TS in any series. [b] Regioisomeric ratio calculated theoretically.

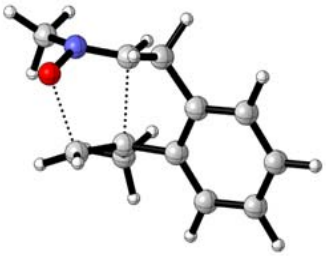
We studied the regioselectivities for the reaction shown in Scheme 1.25. For each transition state both, E and Z configurations of the nitrones were evaluated and the most stable conformations were chosen. Relative energies (shown in Table S1.2 and Table S1.3) indicate that energy differences among E and Z isomers of nitrone are quite significant. In all cases, the Z-isomer is the preferred one, which is in agreement with previous calculations published for these systems.[99]

When the structures X=H are considered, there is not a clear preference between fused and bridged transition structures, thus predicting that a mixture of fused and bridged adducts will be obtained. This situation is particularly manifested for TSs when X=H and n=1 (**A**, **B**) for which the difference is below 1.0 kcal/mol.

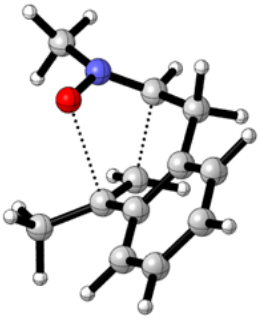
The optimized geometries of 8 transition states corresponding to the Z nitrones and *endo* approximation are illustrated in Scheme 4 and Table S1. As expected for 1,3-dipolar cycloadditions all transition structures are asynchronous. TSs for the fused products are more asynchronous than the corresponding TSs for the bridged counterparts for the endo approaches and in spite of the significant asynchronicity the values are within the range of a concerted process.

[99] Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473.

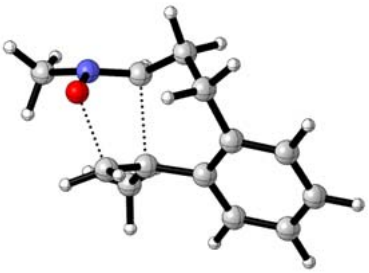
- **Transition structures A-H (corresponding to the Z-nitrones with an endo approach in all cases)**



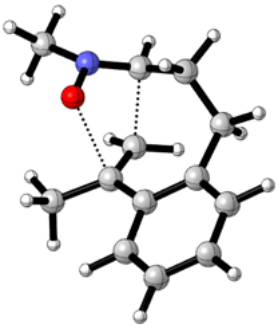
A (n = 1, X = H)
Z-endo-fused
Erel (Kcal/mol): 0.07



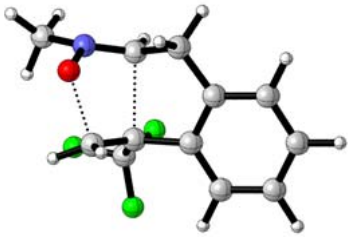
B (n = 1, X = H)
Z-endo-bridged
Erel (Kcal/mol): 0.00



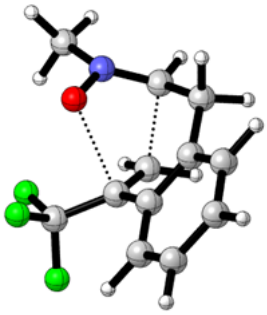
C (n = 2, X = H)
Z-endo-fused
Erel (Kcal/mol): 1.10



D (n = 2, X = H)
Z-endo-bridged
Erel (Kcal/mol): 0.00

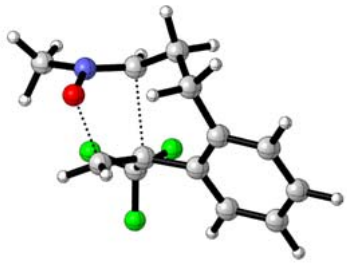


E (n = 1, X = F)
Z-endo-fused
Erel (Kcal/mol): 0.00

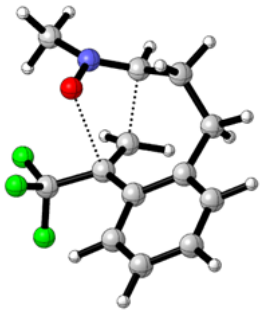


F (n = 1, X = F)
Z-endo-bridged
Erel (Kcal/mol): 3.63

Figure S1.5



G (n = 2, X = F)
Z-endo-fused
Erel (Kcal/mol): 0.00



H (n = 2, X = F)
Z-endo-bridged
Erel (Kcal/mol): 2.71

Figure S1.5 (continued)

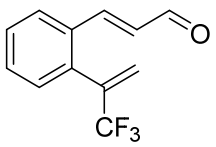
1.6.4. Part B: Experimental procedures and characterisation of new compounds

- **General procedure for the synthesis of fluorinated cinnamaldehydes 1.13**

A 10 mL microwave glass vial was charged with $Pd_2(dba)_3$ (4 mol %, 0.06 mmol), Xphos (8 mol %, 0.12 mmol), Na_2CO_3 (2.2 equiv, 3.3 mmol) and *N*-tosylhydrazone **1.2** (1.5 equiv, 2.25 mmol), which was previously prepared from 1,1,1–trifluoroacetone (1 equiv, 22 mmol) and *N*-tosylhydrazine (1 equiv, 22 mmol) by heating at 70 °C in EtOH (0.5 M) for 5 h and then filtering the precipitate solid at room temperature as a crystalline white solid. The solid reagents were dried together under reduced pressure before being used. 2-bromocinnamaldehyde **1.12** (1.0 equiv, 1.5 mmol), prepared from the corresponding 2-bromobenzaldehyde by a literature procedure,[100] was dissolved in THF (0.3 M) and then added to the vial, which was subsequently sealed and heated by microwave irradiation at 100 °C for 2 h. The reaction mixture was cooled to room temperature, opened, filtered through Celite and concentrated under reduced pressure. The residue obtained was purified by flash

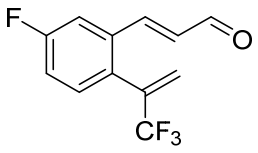
[100] Challa, C.; Vellekkatt, J.; Ravindran, J.; Lankalapalli, R.S. *Org. Biomol. Chem.* **2014**, *12*, 8588.

chromatography [*n*-hexane-EtOAc (20:1)]. The product **1.13** obtained was used immediately in the next step.[101]



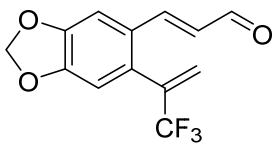
1.13a

(*E*)-3-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)acrylaldehyde (1.13a): Starting from **1.12a** and following the general procedure indicated above, **1.13a** was obtained as a yellow oil in 89% yield (302 mg). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.69 (d, *J* = 7.7 Hz, 1H), 7.77-7.72 (m, 1H), 7.61 (d, *J* = 15.9 Hz, 1H), 7.52 – 7.34 (m, 3H), 6.70 (dd, *J* = 15.9, 7.7 Hz, 1H), 6.27 (q, *J* = 1.4 Hz, 1H), 5.57 (q, *J* = 1.3 Hz, 1H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -67.35 (s, 3F).



1.13b

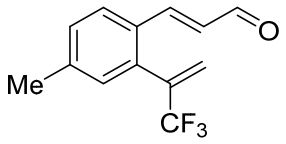
(*E*)-3-(5-fluoro-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)acrylaldehyde (1.13b): Starting from **1.12b** and following the general procedure indicated above, **1.13b** was obtained as a yellow oil in 88% yield (322 mg). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.70 (d, *J* = 7.6 Hz, 1H), 7.53 (dd, *J* = 15.9, 1.6 Hz, 1H), 7.44 – 7.33 (m, 2H), 7.17 (ddd, *J* = 8.6, 7.9, 2.6 Hz, 1H), 6.66 (dd, *J* = 15.9, 7.6 Hz, 1H), 6.29 (q, *J* = 1.4 Hz, 1H), 5.57 (q, *J* = 1.4 Hz, 1H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -67.56 (s, 3F), -111.23 (m, 1F).



1.13c

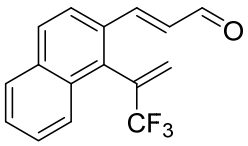
[101] Due to their instability, HRMS could not be obtained for these derivatives. ^{13}C spectra of freshly purified samples did not account for the right number of signals in the aromatic region, suggesting decomposition in the deuterated solvents in which the samples were disolved.

(***E***)**-3-(6-(3,3,3-trifluoroprop-1-en-2-yl)benzo[*d*][1,3]dioxol-5-yl)acrylaldehyde (1.13c):** Starting from **1.12c** and following the general procedure indicated above, **1.13c** was obtained as a yellow oil in 81% yield (328 mg). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.63 (d, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 15.8 Hz, 1H), 7.16 (s, 1H), 6.82 (s, 1H), 6.55 (dd, *J* = 15.8, 7.7 Hz, 1H), 6.26 (q, *J* = 1.4 Hz, 1H), 6.08 (s, 2H), 5.55 (q, *J* = 1.4 Hz, 1H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -67.49 (s, 3F).



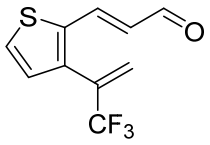
1.13d

(*E*)-3-(4-methyl-2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)acrylaldehyde (1.13d): Starting from **1.12d** and following the general procedure indicated above, **1.13d** was obtained as a yellow oil in 99% yield (357 mg). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.66 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 15.9 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.17 (s, 1H), 6.67 (dd, *J* = 15.9, 7.7 Hz, 1H), 6.25 (q, *J* = 1.4 Hz, 1H), 5.54 (q, *J* = 1.3 Hz, 1H), 2.41 (s, 3H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -67.30 (s, 3F).



1.13e

(*E*)-3-(1-(3,3,3-trifluoroprop-1-en-2-yl)naphthalen-2-yl)acrylaldehyde (1.13e): Starting from **1.12e** and following the general procedure indicated above, **1.13e** was obtained as a yellow oil in 82% yield (340 mg). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.74 (d, *J* = 7.6 Hz, 1H), 7.98 – 7.85 (m, 3H), 7.82-7.75 (m, 2H), 7.65 – 7.53 (m, 2H), 6.81 (dd, *J* = 15.9, 7.6 Hz, 1H), 6.59 (q, *J* = 1.3 Hz, 1H), 5.76 (q, *J* = 1.2 Hz, 1H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -66.54 (s, 3F).



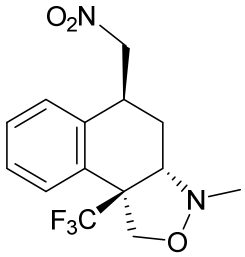
1.13f

(E)-3-(3-(3,3,3-trifluoroprop-1-en-2-yl)thiophen-2-yl)acrylaldehyde (1.13f): Starting from **1.12f** and following the general procedure indicated above, **1.13f** was obtained as a yellow oil in 90% yield (313 mg). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.64 (d, *J* = 7.6 Hz, 1H), 7.55 (dd, *J* = 15.7, 0.8 Hz, 1H), 7.48 (dd, *J* = 5.2, 0.8 Hz, 1H), 7.14 (dq, *J* = 5.2, 1.0 Hz, 1H), 6.58 (dd, *J* = 15.7, 7.6 Hz, 1H), 6.26 (q, *J* = 1.4 Hz, 1H), 5.62 (q, *J* = 1.4 Hz, 1H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -67.07 (s, 3F).

- **General procedure for the synthesis of nitromethane-derived isoxazolidines 1.15**

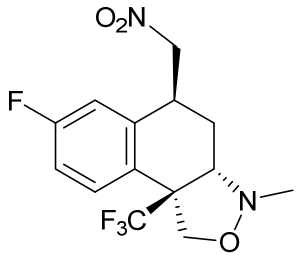
To a solution of the corresponding fluorinated cinnamaldehyde **1.13** (1.0 equiv, 0.5 mmol), Jørgensen-Hayashi catalyst **JH-II** (10 mol%, 0.05 mmol) and benzoic acid (20 mol%, 0.10 mmol) in methanol (0.05 M), nitromethane (3.0 equiv, 1.5 mmol) was added. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then quenched by addition of 20 mL of water and extracted with DCM (15 mL x 3). The organic layer was washed with brine (15 mL x 2), dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The crude aldehyde **1.14** was then used without further purification. To a solution of the corresponding intermediate fluorinated aldehyde in toluene (0.1 M) in a 10 mL microwave glass vial, *N*-alkylhydroxylamine hydrochloride (2.5 equiv, 1.25 mmol) and sodium bicarbonate (2.5 equiv, 1.25 mmol) were added. The vial was sealed and the mixture was heated by microwave irradiation at 120 °C for 30 min. The reaction mixture was cooled to room temperature, opened and concentrated under reduced pressure. The residue obtained was subjected to flash chromatography [*n*-hexane-EtOAc (20:1)] to purify and/or separate the formed diastereomeric isoxazolidines **1.15**. When complete separation of the minor

diastereoisomer was not possible, the ^{1}H and ^{19}F-NMR data were extracted from the spectra of the mixture.



1.15a

(3a*S*,5*S*,9b*S*)-3-methyl-5-(nitromethyl)-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazole (1.15a): Starting from **1.13a** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **1.15a** (46% overall yield) was obtained as a mixture of its diastereoisomers (d.r.=4.0/1.0) which were separated by flash chromatography [*n*-hexane-EtOAc (20:1)]. Major diasteroisomer (58 mg, colorless oil): $[\alpha]_D^{25}$ = +69.6° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 – 7.23 (m, 4H), 4.75 (dd, *J*=12.3, 5.6 Hz, 1H), 4.69 – 4.57 (m, 2H), 3.91 (d, *J* = 10.8 Hz, 1H), 3.84-3.75 (m, 1H), 3.40-3.25 (m, 1H), 2.83 (s, 1H), 2.19 (ddd, *J* = 14.0, 5.6, 5.6 Hz, 1H), 1.93 (ddd, *J* = 13.9, 8.6, 4.9 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 135.6, 131.9, 129.8, 129.0, 128.6, 128.0, 127.1 (<u>C</u>F_3, q, *J* = 282.4 Hz), 79.0, 73.7, 64.6 (d, *J* = 2.6 Hz), 58.8 (<u>C</u>-CF_3, q, *J* = 22.5 Hz), 43.7, 35.4, 27.9. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -70.69 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{16}F_3N_2O_3$ 317.1108; found 317.1115. HPLC (Phenomenex Amylose 1, 90:10 hexane/ iPrOH, 1 mL/min) t_R(major) = 7.60 min, t_R(minor) = 12.32 min. Minor diasteroisomer (14 mg, colorless oil): ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 – 7.16 (m, 4H), 4.89 (dd, *J* = 12.3, 10.0 Hz, 1H), 4.70 – 4.59 (m, 2H), 3.90 (dq, *J* = 9.1, 1.7 Hz, 1H), 3.81-3.73 (m, 1H), 3.20 (t, *J* = 4.9, 1H), 2.80 (s, 3H), 2.26 (dt, *J* = 14.8, 4.9 Hz, 1H), 1.92 (dt, *J* = 14.8, 4.9 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 135.0, 132.4, 129.8, 128.9, 128.4, 127.7, 127.1 (<u>C</u>F_3, q, *J* = 282.2 Hz), 80.7, 74.1, 67.4, 58.3 (<u>C</u>-CF_3, q, *J* = 24.0 Hz), 43.2, 35.4, 25.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -71.58 (s). HPLC (Phenomenex Amylose 1, 90:10 hexane/ iPrOH, 1 mL/min) t_R(major) = 6.92 min, t_R(minor) = 7.33 min.



1.15b

(3a*S*,5*S*,9b*S*)-7-fluoro-3-methyl-5-(nitromethyl)-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazole (1.15b): Starting from **1.13b** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **1.15b** (63% overall yield) was obtained as a mixture of its diastereoisomers (d.r.=4.6/1.0) which were separated by flash chromatography [*n*-hexane-EtOAc (20:1)]. Major diasteroisomer (86 mg, colorless oil): $[\alpha]_D^{25}$ = +58.2° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 – 7.23 (m, 1H), 7.13 – 7.02 (m, 1H), 7.02 – 6.95 (m, 1H), 4.75 (dd, *J* = 12.5, 5.7 Hz, 1H), 4.66-4.56 (m, 2H), 3.86 (dq, *J* = 9.2, 1.5 Hz, 1H), 3.83 – 3.72 (m, 1H), 3.36-3.22 (m, 1H), 2.82 (s, 3H), 2.17 (dt, *J* = 14.3, 6.1 Hz, 1H), 2.03 – 1.87 (m, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 164.1, 160.8, 138.1, 132.8 (dq, *J* =8.5, 2.4 Hz), 127.0 (<u>C</u>F_3, q, *J* = 283.5 Hz), 116.0 (d, *J* = 21.4 Hz), 114.7 (d, *J* = 21.9 Hz), 78.6, 73.8, 64.7, 58.4 (<u>C</u>-CF_3, q, *J* = 23.9 Hz), 43.6, 35.1, 27.6. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -70.82 (s, 3F), -112.34 (m, 1F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{15}F_4N_2O_3$ 335.1013; found 335.1027. HPLC (Chiralcel ODH, 90:10 hexane/ iPrOH, 1 mL/min) t_R(major) = 11.71 min, t_R(minor) = 13.71 min. Minor diasteroisomer (19 mg, colorless oil): ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.32 – 7.23 (m, 1H), 7.09-7.03 (m, 1H), 6.92 (m, 1H), 4.88 (dd, *J* = 12.5, 9.8 Hz, 1H), 4.70 – 4.57 (m, 2H), 3.86 (dq, *J* = 9.0, 1.8 Hz, 1H), 3.79-3.69 (m, 1H), 3.20 (t, *J* = 4.9 Hz, 1H), 2.79 (s, 3H), 2.25 (dt, *J* = 14.9, 5.2 Hz, 1H), 1.91 (dt, *J* = 14.9, 4.9 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 164.1, 160.8, 137.6, 131.8, 127.0 (<u>C</u>F_3, q, *J* = 282.6 Hz), 115.9 (d, *J* = 21.4 Hz), 114.4 (d, *J* = 21.7 Hz), 80.3, 74.1, 67.3, 58.0 (<u>C</u>-CF_3, q, *J* = 24.2 Hz), 43.2, 35.4, 24.9. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -71.80 (s, 3F), -112.35 (ddd, *J* = 8.6, 8.6, 5.5 Hz, 1F). HPLC (Chiralcel ODH, 90:10 hexane/ iPrOH, 1 mL/min) t_R(major) = 10.91 min, t_R(minor) = 9.88 min.

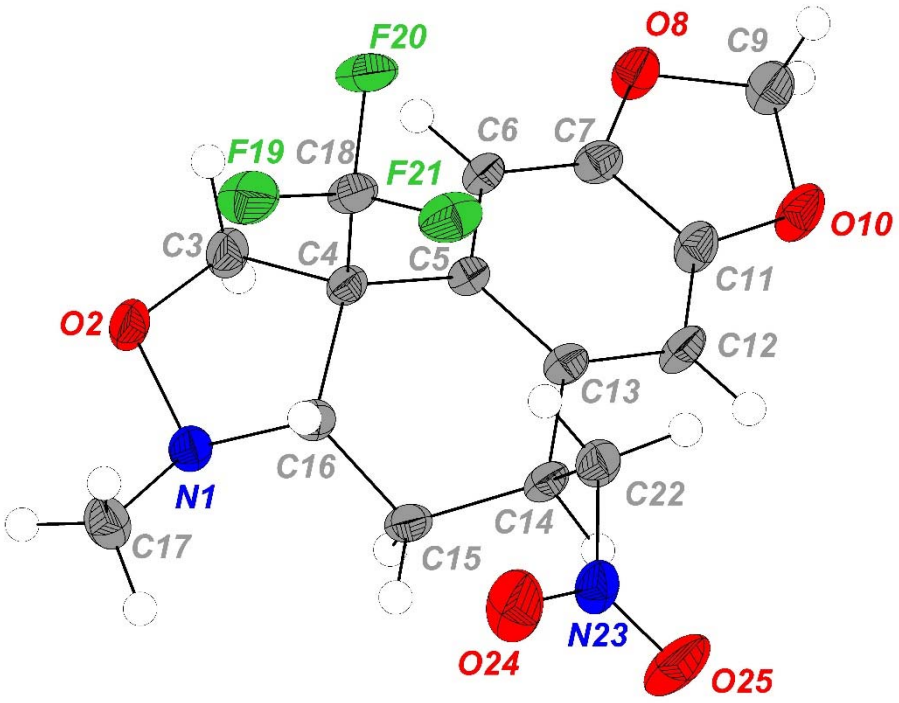
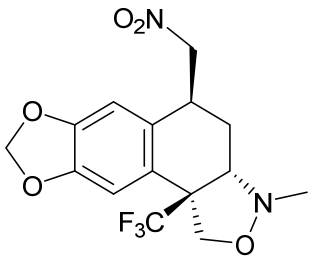


Figure S1.6 X-Ray structure (Ortep diagram) for compound **1.15c**[102]

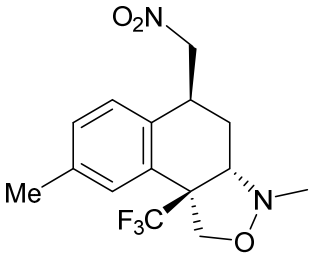


1.15c

(3a*S*,5*S*,10b*S*)-3-methyl-5-(nitromethyl)-10b-(trifluoromethyl)-1,3,3a,4,5,10b-hexahydro-[1,3]dioxolo[4',5':6,7]naphtho[2,1-*c*]isoxazole (1.15c): Starting from **1.13c** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **1.15c** (44% overall yield) was obtained as a mixture of its diastereoisomers (d.r.=5.0/1.0) which were separated by flash chromatography [*n*-hexane-EtOAc (20:1)]. Major diasteroisomer (66 mg,

[102] CCDC 1564490 contains the supplementary crystallographic data of compound **1.15c**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk].

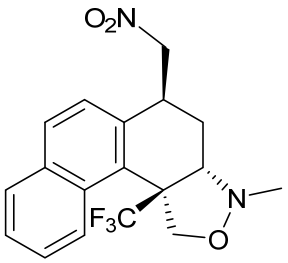
white solid, mp= 129-131 °C): $[\alpha]_D^{25}$ = +67.0° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, Chloroform-*d*) δ 6.71 (s, 1H), 6.68 (q, *J* = 1.5 Hz, 1H), 6.00 (d, *J* = 1.3 Hz, 1H), 5.98 (d, *J* = 1.3 Hz, 1H), 4.77 – 4.46 (m, 3H), 3.87 (d, *J* = 9.5 Hz, 1H), 3.73-3.63 (m, 1H), 2.82 (s, 3H), 2.15 (dt, *J* = 14.3, 5.2 Hz, 1H), 1.88 (ddd, *J* = 14.3, 9.2, 5.2 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 148.2, 148.1, 129.6, 127.1 (<u>C</u>F_3, q, *J* = 282.7 Hz), 124.7, 109.3, 108.0, 101.9, 78.9, 73.6, 64.3, 59.0 (<u>C</u>-CF_3, q, *J* = 23.5 Hz), 43.9, 36.0, 28.4. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -70.99 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{16}F_3N_2O_5$ 361.1006; found 361.1010. HPLC (Chiralcel ODH, 90:10 hexane/ iPrOH, 1 mL/min) t_R(major) = 23.08 min, t_R(minor) = 25.89 min. Minor diasteroisomer (13 mg, colorless oil): ^1H NMR (300 MHz, Chloroform-*d*) δ 6.73 (q, *J* = 1.6 Hz, 1H), 6.65 (s, 1H), 5.99 (s, 1H), 4.91 (dd, *J* = 12.3, 10.1 Hz, 1H), 4.60 – 4.50 (m, 2H), 3.82 (dq, *J* = 9.0, 1.7 Hz, 1H), 3.72 – 3.60 (m, 1H), 3.14 (t, *J* = 4.4 Hz, 1H), 2.78 (s, 3H), 2.29 – 2.15 (m, 1H), 1.95 (dt, *J* = 14.9, 4.0 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 148.2, 148.0, 128.6, 127.1 (<u>C</u>F_3, q, *J* = 282.5 Hz), 125.4, 109.1, 107.7, 101.8, 81.0, 74.2, 67.3, 58.3 (<u>C</u>-CF_3, q, *J* = 24.4 Hz), 43.1, 35.8, 24.3. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -71.45 (s, 3F). HPLC (Chiralcel ODH, 90:10 hexane/ iPrOH, 1 mL/min) t_R(major) = 19.64 min, t_R(minor) = 14.75 min.



1.15d

(3a*S*,5*S*,9b*S*)-3,8-dimethyl-5-(nitromethyl)-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazole (1.15d): Starting from **1.13d** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **1.15d** (53% overall yield) was obtained as a mixture of its diastereoisomers (d.r.=2.5/1.0) which were separated by flash chromatography [*n*-hexane-EtOAc (20:1)]. Major diasteroisomer (63 mg, white solid, mp= 89-91 °C): $[\alpha]_D^{25}$ = +67.3° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, Chloroform-*d*) δ 7.15 (s, 1H), 7.14 (s, 1H), 7.07 (s, 1H), 4.81 – 4.51 (m, 3H), 3.90 (d, *J* = 9.2 Hz, 1H), 3.79-3.70 (m, 1H), 3.35-3.23 (m, 1H), 2.82 (s, 3H), 2.35 (s, 3H), 2.21-2.12 (m, 1H), 2.02 – 1.83 (m,

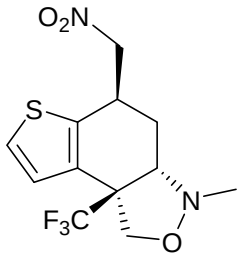
1H). ^{13}C NMR (500 MHz, Chloroform-*d*) δ 138.5, 132.5, 131.6, 130.3, 129.8, 127.9, 127.2 (C-CF_3, q, *J* = 282.4 Hz), 79.1, 73.6, 64.7, 43.8, 35.1, 29.9, 21.4. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -70.65 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{18}F_3N_2O_3$ 331.1264; found 331.1256. HPLC (Phenomenex Amylose 1, 90:10 hexane/ iPrOH, 1 mL/min) t_R(major) = 5.76 min, t_R(minor) = 12.83 min. Minor diastereoisomer (25 mg, colorless oil): ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.19 – 7.12 (m, 1H), 7.10 – 7.05 (m, 2H), 4.86 (dd, *J* = 12.2, 9.9 Hz, 1H), 4.68 – 4.58 (m, 2H), 3.89 (dq, *J* = 9.1, 1.6 Hz, 1H), 3.76-3.67 (m, 1H), 3.18 (dd, *J* = 4.9, 4.9Hz, 1H), 2.79 (s, 3H), 2.35 (s, 3H), 2.24 (dt, *J* = 15.0, 4.9 Hz, 1H), 1.89 (dt, *J* = 15.0, 4.9 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 138.3, 132.2, 132.1, 130.3, 129.8, 127.5, 127.2 (C-CF_3, q, *J* = 282.3 Hz), 80.8, 74.1, 67.4, 58.1 (C-CF_3, q, *J* = 23.9 Hz), 43.2, 35.1, 25.1, 21.3. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -71.51 (s, 3F).



1.15e

(3a*S*,5*S*,11c*S*)-3-methyl-5-(nitromethyl)-11c-(trifluoromethyl)-1,3,3a,4,5,11c-hexahydrophenanthro[3,4-*c*]isoxazole (1.15e): Starting from **1.13e** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **1.15e** (58% overall yield) was obtained as a mixture of its diastereoisomers (d.r.=6.6/1.0) which were separated by flash chromatography [*n*-hexane-EtOAc (20:1)]. Major diasteroisomer (92 mg, colorless oil): $[\alpha]_D^{25}$ = +44.0° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.91 – 7.83 (m, 1H), 7.82 – 7.72 (m, 1H), 7.59 – 7.46 (m, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 5.31 – 5.10 (m, 1H), 4.90 – 4.65 (m, 2H), 4.52 – 4.31 (m, 1H), 4.02-3.93 (m, 1H), 3.59 – 3.36 (m, 1H), 2.85 (s, 3H), 2.33 (ddd, *J* = 14.2, 5.3, 5.3 Hz, 1H), 1.99 (ddd, *J* = 14.4, 9.5, 5.5 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 135.9, 134.5, 132.5, 130.9, 129.7, 129.6, 128.2, 127.8 (CF_3, q, *J* = 284.8 Hz), 126.9, 126.5, 126.1, 125.9, 78.9, 73.5, 66.8, 60.2 (C-CF_3, q, *J* = 24.7 Hz), 43.5, 37.9, 27.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -67.98 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{18}F_3N_2O_3$ 367.1264; found

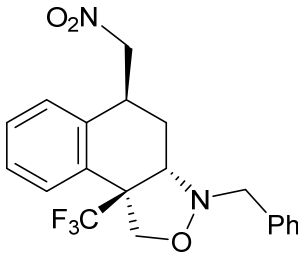
367.1253. HPLC (Chiralcel ODH, 90:10 hexane/ iPrOH, 1 mL/min) t_R(major) = 23.76 min, t_R(minor) = 22.23 min. Minor diasteroisomer (14 mg, colorless oil): ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.91 – 7.80 (m, 2H), 7.70 – 7.57 (m, 1H), 7.57 – 7.45 (m, 2H), 7.31 (d, *J* = 8.5 Hz, 1H), 5.05 (d, *J* = 9.0 Hz, 1H), 4.95 (dd, *J* = 12.2, 10.6 Hz, 1H), 4.57 (ddd, *J* = 12.2, 4.4, 1.0 Hz, 1H), 4.28 (dq, *J* = 8.9, 1.9 Hz, 1H), 4.04 – 3.89 (m, 1H), 3.30 – 3.25 (m, 1H), 2.82 (s, 3H), 2.50 (dt, *J* = 15.5, 5.6 Hz, 1H), 2.08 (dt, *J* = 15.8, 3.4 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 134.3, 133.7, 132.1, 130.9, 129.4, 128.4, 127.7 (CF_3, q, *J* = 284.8 Hz), 126.5, 126.2, 126.1, 126.0, 81.1, 74.0, 69.8, 58.9 (C-CF_3, q, *J* = 24.7 Hz), 42.7, 37.1, 22.8. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -68.21 (s, 3F). HPLC (Chiralcel ODH, 90:10 hexane/ iPrOH, 1 mL/min) t_R(major) = 10.59 min, t_R(minor) = 15.39 min.



1.15f

(3a*S*,5*R*,8b*S*)-3-methyl-5-(nitromethyl)-8b-(trifluoromethyl)-1,3,3a,4,5,8b-hexahydrothieno[3',2':3,4]benzo[1,2-*c*]isoxazole (1.15f): Starting from **1.13f** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, a mixture of **1.15f** (30% overall yield, d.r.=1.1/1.0) and the corresponding bridged regioisomer (14% overall yield) was obtained. The major fused diastereoisomer was separated by flash chromatography [*n*-hexane-EtOAc (20:1)], while the ^{1}H and ^{19}F-NMR data for the minor diastereoisomer and the bridged regioisomer were extracted from the spectrum of the mixture. Major diastereoisomer (25 mg, colorless oil): $[\alpha]_D^{25}$ = -121.6° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.31 (d, *J* = 5.3 Hz, 1H), 6.96 (dq, *J* = 5.3, 1.8 Hz, 1H), 4.93 (dd, *J* = 12.6, 9.5 Hz, 1H), 4.63 (dd, *J* = 12.6, 5.7 Hz, 1H), 4.49 (d, *J* = 9.0 Hz, 1H), 3.96 (ddt, *J* = 9.5, 5.7, 2.1 Hz, 1H), 3.65 (dq, *J* = 9.0, 1.7 Hz, 1H), 3.12 (dd, *J* = 4.1, 3.0, 1H), 2.77 (s, 3H), 2.33 – 2.21 (m, 1H), 2.21 – 2.12 (m, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 143.5, 136.1, 126.8 (CF_3, q, *J* = 281.6 Hz), 126.7, 125.8, 80.5, 73.4, 67.3, 57.2 (C-CF_3, q, *J* = 25.2 Hz), 43.0, 32.4, 24.9. ^{19}F NMR (282 MHz, Chloroform-*d*)

δ -72.35 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{13}F_3N_2O_3S$ 323.0672; found 323.0662. HPLC (Chiralcel ODH, 90:10 hexane/ iPrOH, 1 mL/min) t_R(major) = 7.19 min, t_R(minor) = 10.13 min. Minor diastereoisomer (23 mg; mixture): ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.29 – 7.26 (m, 1H), 7.03 – 6.97 (m, 1H), 5.26 (dd, *J* = 13.4, 6.7 Hz, 1H), 4.54 – 4.42 (m, 2H), 3.90 – 3.72 (m, 1H), 3.64 (dq, *J* = 8.9, 1.6 Hz, 1H), 3.11 (dd, *J* = 3.2, 3.2 Hz, 1H), 2.76 (s, 3H), 2.25 – 2.13 (m, 1H), 2.05 – 1.95 (m, 1H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -71.94 (s, 3F). HPLC (Chiralcel ODH, 90:10 hexane/ iPrOH, 1 mL/min) t_R(major) = 12.09 min, t_R(minor) = 9.63 min. Bridged regioisomer (23 mg; mixture): ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.08 (d, *J* = 5.4 Hz, 1H), 7.03 – 6.97 (m, 1H), 4.97 – 4.77 (m, 2H), 4.08 (ddd, *J* = 13.0, 6.9, 2.5 Hz, 1H), 3.90 – 3.72 (m, 1H), 3.05 (ddd, *J* = 12.6, 7.3, 1.1 Hz, 1H), 2.80 (q, *J* = 0.6 Hz, 3H), 2.37 (dddd, *J* = 14.6, 5.9, 2.4, 1.1 Hz, 1H), 2.30 (d, *J* = 12.6 Hz, 1H), 1.93 (ddd, *J* = 14.6, 7.3, 2.4 Hz, 1H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -73.80 (s, 3F).



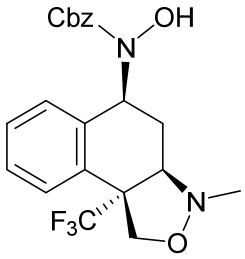
1.15g

(3a*S*,5*S*,9b*S*)-3-benzyl-5-(nitromethyl)-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazole (1.15g): Starting from **1.13a** and *N*-benzylhydroxylamine hydrochloride and following the general procedure indicated above, **1.15g** (39% overall yield) was obtained as a mixture of its diastereoisomers (d.r.=3.3/1.0). Flash chromatography [*n*-hexane-EtOAc (20:1)] allowed for the complete separation of the major diastereoisomer. Major diastereoisomer (59 mg, colorless oil): $[\alpha]_D^{25}$ = +26.9° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.45 – 7.21 (m, 9H), 4.74 – 4.61 (m, 2H), 4.54 (dd, *J* = 12.2, 9.7 Hz, 1H), 4.20 (d, *J* = 13.2 Hz, 1H), 4.08 (d, *J* = 13.2 Hz, 1H), 3.93 (dq, *J* = 9.5, 1.7 Hz, 1H), 3.79-3.71(m, 1H), 3.59 (dd, *J* = 8.7, 6.2 Hz, 1H), 1.98-1.82 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 136.3, 135.9, 131.6, 129.8, 129.2, 129.0, 128.7, 128.3, 128.0, 127.2 (<u>C</u>F_3, d, *J* = 283.7 Hz), 78.7, 73.3, 62.3, 61.1, 58.7 (<u>C</u>-CF_3, q, *J* = 23.7 Hz),

36.0, 28.8. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -70.58 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{20}F_3N_2O_3$ 393.1421; found 393.1428. HPLC (Phenomenex Amylose 1, 90:10 hexane/ iPrOH, 1 mL/min) t_R(major) = 7.27 min, t_R(minor) = 8.99 min. Minor diastereoisomer (from the mixture): ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.45 – 7.27 (m, 9H), 4.95 (dd, *J* = 12.4, 9.7 Hz, 1H), 4.72 (dd, *J* = 12.4, 5.2 Hz, 1H), 4.64 (d, *J* = 9.3 Hz, 1H), 4.26 (d, *J* = 13.7 Hz, 1H), 4.00 – 3.84 (m, 2H), 3.83 – 3.70 (m, 1H), 3.50 (t, *J* = 5.3 Hz, 1H), 2.21 (dt, *J* = 14.7, 5.2 Hz, 1H), 1.96 (dt, *J* = 14.7, 5.5 Hz, 1H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -71.53 (s, 3F).

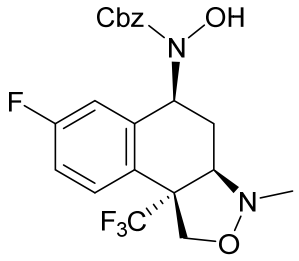
- **General procedure for the synthesis of aza-derived isoxazolidines 1.17**

To a solution of the corresponding fluorinated cinnamaldehyde **1.13** (1.0 equiv, 0.5 mmol), Jørgensen-Hayashi catalyst **JH-II** (20 mol%, 0.1 mmol) in chloroform (0.05 M), *N*-(benzyloxycarbonyl)hydroxylamine (1.2 equiv, 0.6 mmol) was added at 0-5 °C. The resulting mixture was stirred at this temperature for 3-5 d until disappearance of the starting material (TLC analysis). The reaction mixture was then concentrated to dryness under reduced pressure. The crude hemiaminal **1.16** was then used without further purification. To a solution of the corresponding intermediate fluorinated hemiaminal in toluene (0.1 M) in a 10 mL microwave glass vial, *N*-alkylhydroxylamine hydrochloride (2.5 equiv, 1.25 mmol) and sodium bicarbonate (2.5 equiv, 1.25 mmol) were added. The vial was sealed and the mixture was heated by microwave irradiation at 120 °C for 30 min. The reaction mixture was cooled to room temperature, opened and concentrated under reduced pressure. The residue obtained was subjected to flash chromatography [*n*-hexane-EtOAc (10:1 to 4:1)] to purify and/or separate the formed diastereomeric isoxazolidines **1.17**. When complete separation of the minor diastereoisomer was not possible, the ^{1}H and ^{19}F-NMR data were extracted from the spectra of the mixture.



1.17a

Benzyl hydroxy((3a*R*,5*S*,9b*R*)-3-methyl-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazol-5-yl)carbamate (1.17a): Starting from **1.13a** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **1.17a** (51% overall yield) was obtained as a mixture of its diastereoisomers (d.r.=3.0/1.0) which were separated by flash chromatography [*n*-hexane-EtOAc (10:1 to 4:1)]. Major diasteroisomer (81 mg, colorless oil): $[\alpha]_D^{25}$ = -103.3° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.24 (br s, 1H), 7.60 – 7.24 (m, 9H), 5.65-5.57 (m, 1H), 5.28 (d, *J* = 12.3 Hz, 1H), 5.22 (d, *J* = 12.3 Hz, 1H), 4.63 (d, *J* = 9.3 Hz, 1H), 3.92 (dq, *J* = 9.3, 1.6 Hz, 1H), 3.21 (t, *J* = 3.9 Hz, 1H), 2.72 (s, 3H), 2.37 (dt, *J* = 15.6, 4.7 Hz, 1H), 2.27 – 2.17 (m, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 156.2 (C=O), 136.4, 132.9, 132.6, 129.8, 129.3, 129.1, 128.7, 128.6, 128.6, 128.4, 127.0 (CF_3, q, *J* = 282.4 Hz), 74.5, 67.9, 65.6, 57.5 (C-CF_3, q, *J* = 24.5 Hz), 53.6, 42.3, 27.4. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -71.41 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{22}F_3N_2O_4$ 423.1526; found 423.1534. HPLC (Chiralcel IC, 85:15 hexane/ iPrOH, 1 mL/min) t_R(major) = 8.39 min, t_R(minor) = 16.64 min. Minor diasteroisomer (27 mg, colorless oil): ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.52 – 7.25 (m, 9H), 6.19 (br s, 1H), 5.40 (dd, *J* = 12.2, 5.2 Hz, 1H), 5.34 (d, *J* = 12.1 Hz, 1H), 5.21 (d, *J* = 12.1 Hz, 1H), 4.53 (d, *J* = 8.8 Hz, 1H), 3.80 (dq, *J* = 8.8, 1.5 Hz, 1H), 3.17 (t, *J* = 3.2 Hz, 1H), 2.69 (s, 3H), 2.58 (ddd, *J* = 14.3, 12.2, 3.2 Hz, 1H), 2.00 (ddd, *J* = 14.3, 5.2, 3.2 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 157.8 (C=O), 135.8, 134.5, 133.5, 129.5, 128.8, 128.6, 128.4, 128.4, 128.3, 126.9 (CF_3, q, *J* = 274.4 Hz), 125.9, 74.8, 68.6, 67.3, 57.8 (C-CF_3, q, *J* = 24.1 Hz), 53.9, 42.8, 24.1. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -69.87 (s, 3F). HPLC (Chiralcel IC, 90:10 hexane/ iPrOH, 1 mL/min) t_R(major) = 9.87 min, t_R(minor) = 6.68 min.



1.17b

Benzyl ((3a*R*,5*S*,9b*R*)-7-fluoro-3-methyl-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazol-5-yl)(hydroxy)carbamate (1.17b): Starting from **1.13b** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **1.17b** (70% overall yield) was obtained as a mixture of its diastereoisomers (d.r.=5.2/1.0) which were separated by flash chromatography [*n*-hexane-EtOAc (10:1 to 4:1)]. Major diasteroisomer (129 mg, white solid, mp= 101-103 °C): $[\alpha]_D^{25}$ = -90.5° (c 1.0; $CHCl_3$). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.45 – 7.22 (m, 6H), 7.11 – 7.00 (m, 2H), 5.60-5.50 (m, 1H), 5.27 (d, *J* = 12.2 Hz, 1H), 5.23 (d, *J* = 12.2 Hz, 1H), 4.61 (d, *J* = 9.2 Hz, 1H), 3.88 (d, *J* = 9.2 Hz, 1H), 3.23-3.18 (m, 1H), 2.72 (s, 3H), 2.33 (dt, *J* = 15.3, 4.9 Hz, 1H), 2.27 – 2.14 (m, 1H). ^{13}C NMR (75 MHz, Acetonitrile-d_3) δ 164.2, 160.9, 159.0, 156.3 (C=O), 136.2, 130.5, 128.7 (2xCH, Ph), 128.5, 128.4 (2xCH, Ph), 126.8 (CF_3, q, *J* = 272.2 Hz), 116.8 (d, *J* = 21.8 Hz), 116.0 (d, *J* = 22.2 Hz), 74.4, 68.1, 67.9, 65.5, 57.3 (C-CF_3, q, *J* = 24.8 Hz), 42.3, 27.3. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -71.63 (s, 3F), -112.55 (s, 1F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{21}F_4N_2O_4$ 441.1432; found 441.1439. HPLC (Chiralcel IC, 85:15 hexane/ iPrOH, 1 mL/min) t_R(major) = 15.85 min, t_R(minor) = 9.03 min. Minor diasteroisomer (25 mg, colorless oil): ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.46 – 7.30 (m, 6H), 7.13-7.08 (m, 1H), 7.06-6.99 (m, 1H), 6.75 (br s, 1H), 5.43 – 5.29 (m, 1H), 5.21 (d, *J* = 12.1 Hz, 1H), 4.52 (d, *J* = 8.8 Hz, 1H), 3.76 (dq, *J* = 8.8, 1.5 Hz, 1H), 3.16 (t, *J* = 3.1 Hz, 1H), 2.67 (s, 3H), 2.56 (ddd, *J* = 15.2, 12.4, 3.2 Hz, 1H), 1.98 (dt, *J* = 14.2, 4.3, 4.3 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 164.4, 161.1, 158.1, 137.6 (d, *J* = 7.2 Hz), 135.6, 128.8 (2xCH, Ph), 128.8, 128.4 (2xCH, Ph), 126.8 (CF_3, q, *J* = 282.2 Hz), 115.7 (d, *J* = 21.6 Hz), 113.0 (d, *J* = 22.6 Hz), 74.8, 68.8, 67.2, 57.5 (C-CF_3, q, *J* = 24.5 Hz), 53.9, 42.7, 23.9. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -70.14 (s, 3F), -113.44 (m, 1F). HPLC (Chiralcel IC, 85:15 hexane/ iPrOH, 1 mL/min) t_R(major) = 5.80 min, t_R(minor) = 4.97 min.

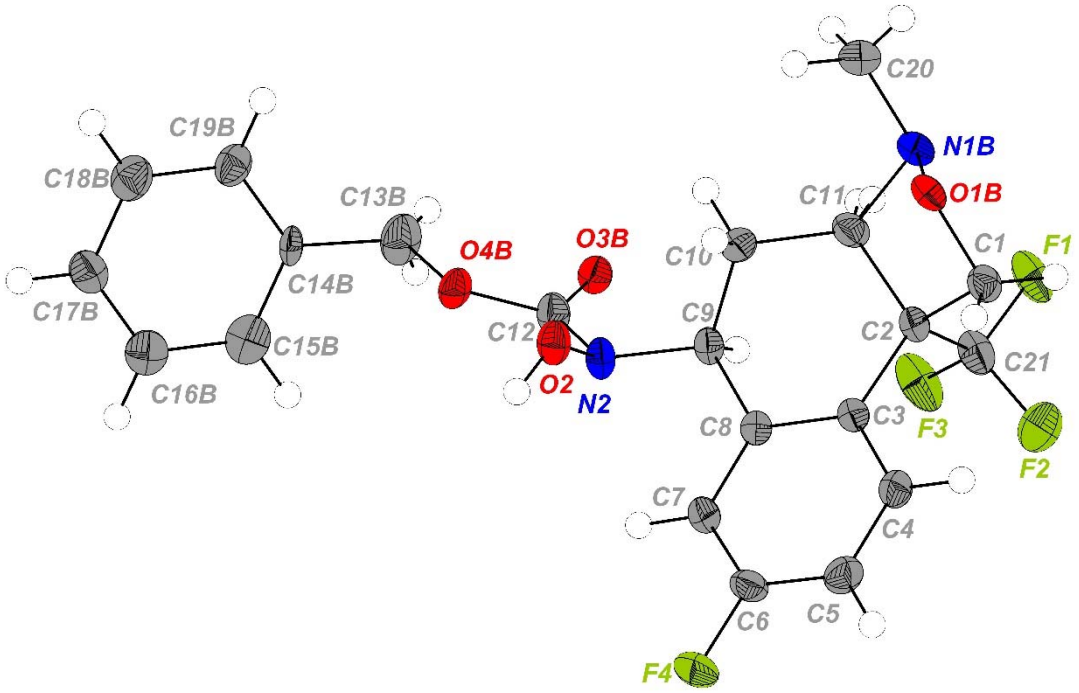
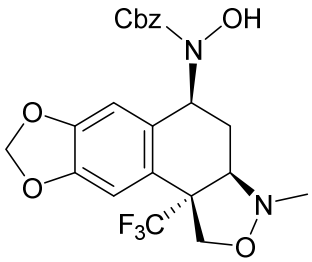


Figure S1.7 X-Ray structure (Ortep diagram) of compound **1.17b**[103]

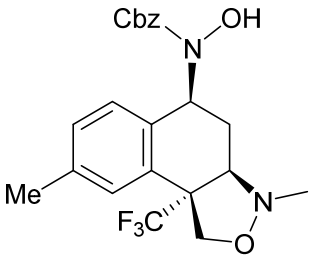


1.17c

Benzyl hydroxy((3a*R*,5*S*,10b*R*)-3-methyl-10b-(trifluoromethyl)-1,3,3a,4,5,10b-hexahydro-[1,3]dioxolo[4',5':6,7]naphtho[2,1-*c*]isoxazol-5-yl)carbamate (1.17c): Starting from **1.13c** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **1.17c** (60% overall yield) was obtained as a mixture of its diastereoisomers (d.r.=2.4/1.0) which were separated by flash chromatography [*n*-hexane-EtOAc (10:1 to 4:1)]. Major diasteroisomer (99 mg, thick oil): $[\alpha]_D^{25}$ = -92.1° (c 1.0; $CHCl_3$). ^1H NMR (300

[103] CCDC 1564495 contains the supplementary crystallographic data of compound **1.17b**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk].

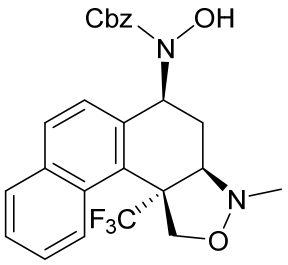
MHz, Chloroform-*d*) δ 9.38 (br s, 1H), 7.46 – 7.27 (m, 5H), 6.75-6.73(m, 2H), 5.99 (d, *J* = 1.4 Hz, 1H), 5.96 (d, *J* = 1.4 Hz, 1H), 5.55-5.47 (m, 1H), 5.31 – 5.18 (m, 2H), 4.56 (d, *J* = 9.3 Hz, 1H), 3.87 (dq, *J* = 9.3, 1.7 Hz, 1H), 3.18 – 3.12 (m, 1H), 2.70 (s, 3H), 2.34 (dt, *J* = 15.5, 4.8 Hz, 1H), 2.18 (d, *J* = 15.5 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 158.9 (C=O), 148.9, 148.3, 136.4, 128.7, 128.5, 128.4, 127.0 (CF_3, q, *J* = 282.6 Hz), 126.7, 125.9, 109.2, 107.84, 101.8, 74.6, 67.9, 65.4, 57.6 (C-CF_3, q, *J* = 24.6 Hz), 53.6, 42.2, 27.4. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -71.44 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{22}F_3N_2O_6$ 467.1424; found 467.1439. HPLC (Chiralcel IC, 85:15 hexane/ iPrOH, 1 mL/min) t_R(major) = 20.60 min, t_R(minor) = 23.61 min. Minor diasteroisomer (41 mg, mixture): ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42 – 7.28 (m, 5H), 6.82 (d, *J* = 0.9 Hz, 1H), 6.81-6.78 (m, 1H), 5.95 (d, *J* = 1.4 Hz, 1H), 5.93 (d, *J* = 1.4 Hz, 1H), 5.33 (d, *J* = 12.2 Hz, 1H), 5.27 (dd, *J* = 12.1, 5.0 Hz, 1H), 5.19 (d, *J* = 12.2 Hz, 1H), 4.76 (br s, 1H), 4.47 (d, *J* = 8.7 Hz, 1H), 3.76 (dq, *J* = 8.8, 1.6 Hz, 1H), 3.12 (t, *J* = 3.3 Hz, 1H), 2.67 (s, 3H), 2.52 (ddd, *J* = 14.9, 12.2, 3.3 Hz, 1H), 1.94 (ddd, *J* = 14.1, 4.4, 4.4 Hz, 1H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -70.09 (s, 3F). HPLC (Chiralcel IC, 85:15 hexane/ iPrOH, 1 mL/min) t_R(major) = 11.23 min, t_R(minor) = 7.76 min.



1.17d

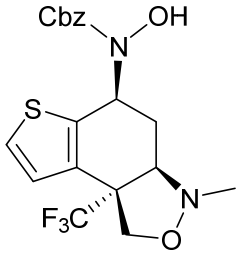
Benzyl ((3a*R*,5*S*,9b*R*)-3,8-dimethyl-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazol-5-yl)(hydroxy)carbamate (1.17d): Starting from **1.13d** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **1.17d** (62% overall yield) was obtained as a mixture of its diastereoisomers (d.r.=3.7/1.0). Only the major diastereoisomer could be purified by flash chromatography [*n*-hexane-EtOAc (10:1 to 4:1)]. Major diasteroisomer (135 mg, colorless oil): $[\alpha]_D^{25}$ = -94.8° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.47 – 7.29 (m, 5H), 7.23 – 7.07 (m, 3H), 5.57 (br s, 1H), 5.27 (d, *J* = 12.3 Hz, 1H), 5.22 (d, *J* = 12.4 Hz, 1H), 4.61 (d, *J* = 9.3 Hz, 1H), 3.92 (dq, *J* =

9.3, 1.5 Hz, 1H), 3.19 (dd, *J* = 3.9, 3.9 Hz, 1H), 2.71 (s, 3H), 2.41 – 2.28 (m, 4H), 2.26 – 2.12 (m, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 159.0, 156.2, 139.1, 136.4, 130.0, 129.0, 128.7, 128.6 (2xCH, Ph), 128.4, 128.3 (2xCH, Ph), 127.00 (C-CF_3, q, *J* = 282.2 Hz), 74.5, 67.8, 65.6, 57.4 (C-CF_3, q, *J* = 24.3 Hz), 53.3, 42.2, 27.5, 21.5. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -71.31 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{24}F_3N_2O_4$ 437.1683; found 437.1676. HPLC (Chiralcel IC, 85:15 hexane/ iPrOH, 1 mL/min) t_R(major) = 22.39 min, t_R(minor) = 19.15 min.



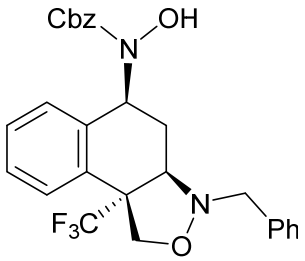
1.17e

Benzyl hydroxy((3a*R*,5*S*,11c*R*)-3-methyl-11c-(trifluoromethyl)-1,3,3a,4,5,11c-hexahydrophenanthro[3,4-*c*]isoxazol-5-yl)carbamate (1.17e): Starting from **1.13e** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **1.17e** was obtained as a single diastereoisomer (17% overall yield, 40 mg, d.r.>20.0/1.0, colorless oil) after flash chromatography [*n*-hexane-EtOAc (10:1 to 4:1)]. $[\alpha]_D^{25}$ = -92.2° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.15 (br s, 1H), 7.99 – 7.78 (m, 3H), 7.65 – 7.30 (m, 9H), 5.78 (br s, 1H), 5.30-5.21 (m, 2H), 5.09 (d, *J* = 9.3 Hz, 1H), 4.47 – 4.26 (m, 1H), 3.29 (dd, *J* = 4.0, 4.0 Hz, 1H), 2.73 (s, 3H), 2.70 – 2.53 (m, 1H), 2.37 – 2.21 (m, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 159.0, 156.1(C=O), 136.3, 135.5, 134.9, 131.6, 130.9, 129.6, 128.8, 128.7 (2xCH, Ph), 128.5, 128.4 (2xCH, Ph), 127.6 (CF_3, q, *J* = 285.0 Hz), 126.3, 126.0, 125.9, 74.3, 68.0, 67.9, 54.9 (C-CF_3), 42.0, 26.6, 18.1. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -66.32 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{24}F_3N_2O_4$ 473.1683; found 473.1665. HPLC (Chiralcel IC, 85:15 hexane/ iPrOH, 1 mL/min) t_R(major) = 8.97 min, t_R(minor) = 14.15 min.



1.17f

Benzyl hydroxy((3a*R*,5*S*,8b*R*)-3-methyl-8b-(trifluoromethyl)-1,3,3a,4,5,8b-hexahydrothieno[3',2':3,4]benzo[1,2-*c*]isoxazol-5-yl)carbamate (1.17f): Starting from **1.13f** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **1.17f** was obtained as a single diastereoisomer (14% overall yield, 30 mg, d.r.>20.0/1.0, colorless oil) after flash chromatography [*n*-hexane-EtOAc (10:1 to 4:1)]. $[\alpha]_D^{25}$ = -20.0° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.37 (br s, 1H), 7.47 – 7.29 (m, 6H), 6.98 – 6.91 (m, 1H), 5.77-5.75 (m, 1H), 5.27 (d, *J* = 12.3 Hz, 1H), 5.22 (d, *J* = 12.3 Hz, 1H), 4.52 (d, *J* = 9.4 Hz, 1H), 3.74 (dq, *J* = 9.4, 1.6 Hz, 1H), 3.12 (dd, *J* = 4.5, 2.5 Hz, 1H), 2.71 (s, 3H), 2.39 (dt, *J* = 16.0, 4.5 Hz, 1H), 2.28 (dd, *J* = 16.0, 2.5 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 155.9 (C=O), 136.3, 134.4, 132.9, 128.7 (2xCH, Ph), 128.5 (2xCH, Ph), 128.4, 127.4, 126.7 (CF_3, q, *J* = 281.7 Hz), 125.7, 73.8, 67.9, 65.1, 56.8 (C-CF_3, q, *J* = 25.9 Hz), 50.0, 42.2, 29.1. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -72.85 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{20}F_3N_2O_4S$ 429.1090; found 429.1079. HPLC (Chiralcel IC, 85:15 hexane/ iPrOH, 1 mL/min) t_R(major) = 18.04 min, t_R(minor) = 27.13 min.



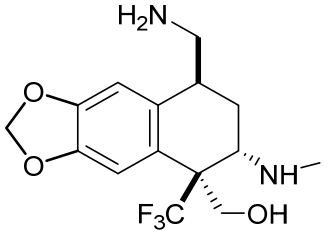
1.17g

Benzyl ((3a*R*,5*S*,9b*R*)-3-benzyl-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazol-5-yl)(hydroxy)carbamate (1.17g): Starting from **1.13a** and *N*-benzylhydroxylamine hydrochloride and following the general procedure indicated above, **1.17g** (112 mg, 45% overall yield) was obtained as a non separable mixture of its diastereoisomers (d.r.=4.0/1.0). Major

diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.22 (m, 14H), 5.59-5.66 (m, 1H), 5.32 (d, *J* = 12.3 Hz, 1H), 5.22 (d, *J* = 12.3 Hz, 1H), 4.61 (d, *J* = 9.4 Hz, 1H), 4.17 (d, *J* = 13.3 Hz, 1H), 3.47 (t, *J* = 4.0 Hz, 1H), 3.91-3.83 (m, 2H), 2.36 (m, 1H), 2.23 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -71.31 (3F, s). HPLC (Chiralcel IC, 85:15 hexane/ iPrOH, 1 mL/min) t_R(major) = 7.91 min, t_R(minor) = 10.97 min. Minor diastereoisomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ -69.65 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{27}H_{25}F_3N_2O_4$ 499.1839; found 499.1856. HPLC (Chiralcel IC, 85:15 hexane/ iPrOH, 1 mL/min) t_R(major) = 5.35 min, t_R(minor) = 6.31 min.

- **General procedure for the synthesis of fluorinated diaminoalcohols 1.18 and 1.19**

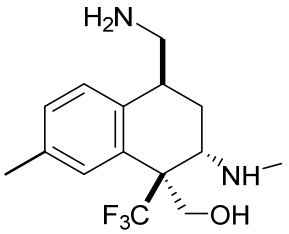
To a solution of the corresponding isoxazolidine **1.15** or **1.17** (0.2 mmol) in dry ethanol (0.05 M), Raney Nickel ® (0.5 mL as a slurry in water) was added and the resulting mixture was stirred at room temperature under a hydrogen atmosphere (balloon) for 16 h. The reaction mixture was then filtered through Celite, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the corresponding diaminoalcohol without further purification.



1.18a

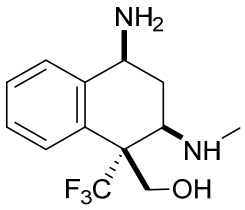
((5*S*,6*S*,8*S*)-8-(aminomethyl)-6-(methylamino)-5-(trifluoromethyl)-5,6,7,8-tetrahydronaphtho[2,3-*d*][1,3]dioxol-5-yl)methanol (1.18a): Starting from **1.15c** and following the general procedure indicated above, **1.18a** was obtained in quantitative yield (66 mg, pale yellow oil). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.92 (s, 1H), 6.74 (s, 1H), 5.92 (s, 2H), 4.19-4.09 (s, 2H), 3.30 (dd, *J* = 6.2, 3.8 Hz, 1H), 3.10 – 2.92 (m, 2H), 2.88 – 2.73 (m, 1H), 2.50 (s, 3H), 2.17-1.97 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 147.8, 146.8, 133.1, 127.2 (<u>C</u>F_3,q, *J* = 285.5 Hz), 123.5, 109.2, 107.9, 101.4, 65.3, 57.6, 51.1 (<u>C</u>-CF_3, q, *J* = 21.3 Hz), 47.5, 37.7, 34.5, 26.1. ^{19}F

NMR (282 MHz, Chloroform-*d*) δ -68.65 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{20}F_3N_2O_4S$ 333.1421; found 333.1423.



1.18b

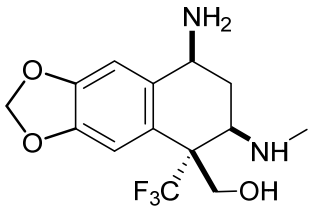
((1*S*,2*S*,4*S*)-4-(aminomethyl)-7-methyl-2-(methylamino)-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (1.18b): Starting from **1.15d** and following the general procedure indicated above, **1.18b** was obtained in quantitative yield (60 mg, colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 4.21 (s, 2H), 3.38-3.32 (m, 1H), 3.10 – 2.63 (m, 3H), 2.51 (s, 3H), 2.34 (s, 4H), 2.21 – 1.97 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 136.5, 136.0, 130.4, 130.2, 129.3, 128.5, 127.3 (CF_3, q, *J* = 283.2 Hz), 65.4, 57.6, 51.1 (C-CF_3, q, *J* = 21.0 Hz), 47.5, 37.4, 34.5, 26.2, 21.4. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -68.25 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{22}F_3N_2O$ 303.1679; found 303.1674.



1.19a

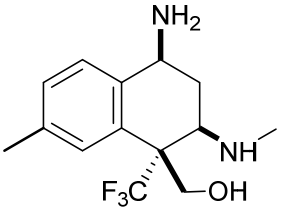
((1*R*,2*R*,4*S*)-4-amino-2-(methylamino)-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (1.19a): Starting from **1.17a** and following the general procedure indicated above, **1.19a** was obtained in quantitative yield (55 mg, colorless oil). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.59-7.53 (m, 1H), 7.43 – 7.29 (m, 3H), 4.37 (d, *J* = 11.8 Hz, 1H), 4.33 (dd, *J* = 4.9, 3.8 Hz, 1H), 4.24 (d, *J* = 11.8 Hz, 1H), 3.31 (dd, *J* = 4.9, 3.7 Hz, 1H), 3.22 (br s, 4H), 2.51 (s, 3H), 2.31 – 2.19 (m, 1H), 2.05 – 1.94 (m, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 141.5, 129.9, 129.4, 128.6, 128.5, 127.9, 127.0 (CF_3, q, *J* = 285.8 Hz), 64.5, 59.7, 51.2 (C-CF_3, q, *J* = 21.0 Hz), 48.1, 35.1, 30.4. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -

69.80 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{18}F_3N_2O$ 275.1371; found 275.1374.



1.19b

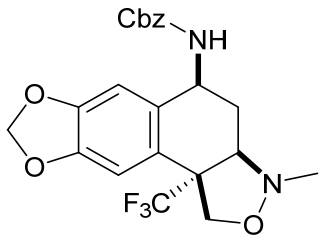
((5*R*,6*R*,8*S*)-8-amino-6-(methylamino)-5-(trifluoromethyl)-5,6,7,8-tetrahydronaphtho[2,3-*d*][1,3]dioxol-5-yl)methanol (1.19b): Starting from **1.17c** and following the general procedure indicated above, **1.19b** was obtained in 63% yield (40 mg, pale yellow solid, mp= 64-66 °C). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.00 (q, *J* = 1.4 Hz, 1H), 6.80, 5.97 (d, *J* = 1.4 Hz, 1H), 5.95 (d, *J* = 1.4 Hz, 1H), 4.28 (d, *J* = 11.7 Hz, 1H), 4.24 (dd, *J* = 5.1, 3.3 Hz, 2H), 4.17 (d, *J* = 11.7 Hz, 1H), 3.25 (t, *J* = 4.1 Hz, 1H), 2.49 (s, 3H), 2.18 (ddd, 14.4, 5.1, 4.1 Hz 1H), 1.96 (ddd, *J* = 14.4, 4.1, 3.3 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 148.0, 147.5, 135.6, 126.9 (CF_3, q, *J* = 285.9 Hz), 122.5, 109.5, 108.1, 101.5, 64.6, 59.7, 51.2 (C-CF_3, q, *J* = 20.7 Hz), 48.2, 35.1, 30.2. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -70.09 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{18}F_3N_2O_3$ 319.1270; found 319.1261.



1.19c

((1*R*,2*R*,4*S*)-4-amino-7-methyl-2-(methylamino)-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (1.19c): Starting from **1.17d** and following the general procedure indicated above, **1.19c** was obtained in quantitative yield (58 mg, colorless oil). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.35 (s, 1H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 4.37 (d, *J* = 11.7 Hz, 1H), 4.28 (dd, *J* = 4.1, 4.1 Hz, 1H), 4.22 (d, *J* = 11.7 Hz, 1H), 3.50 (br s, 4H), 3.29 (dd, *J* = 4.3, 3.9 Hz, 949 (s, 3H), 2.36 (s, 3H), 2.21 (dt, *J* = 8.0, 4.3 Hz, 1H), 1.97 (dt, *J* = 8.0, 3.9 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 138.4, 137.3, 130.1, 129.6, 129.0, 128.4,

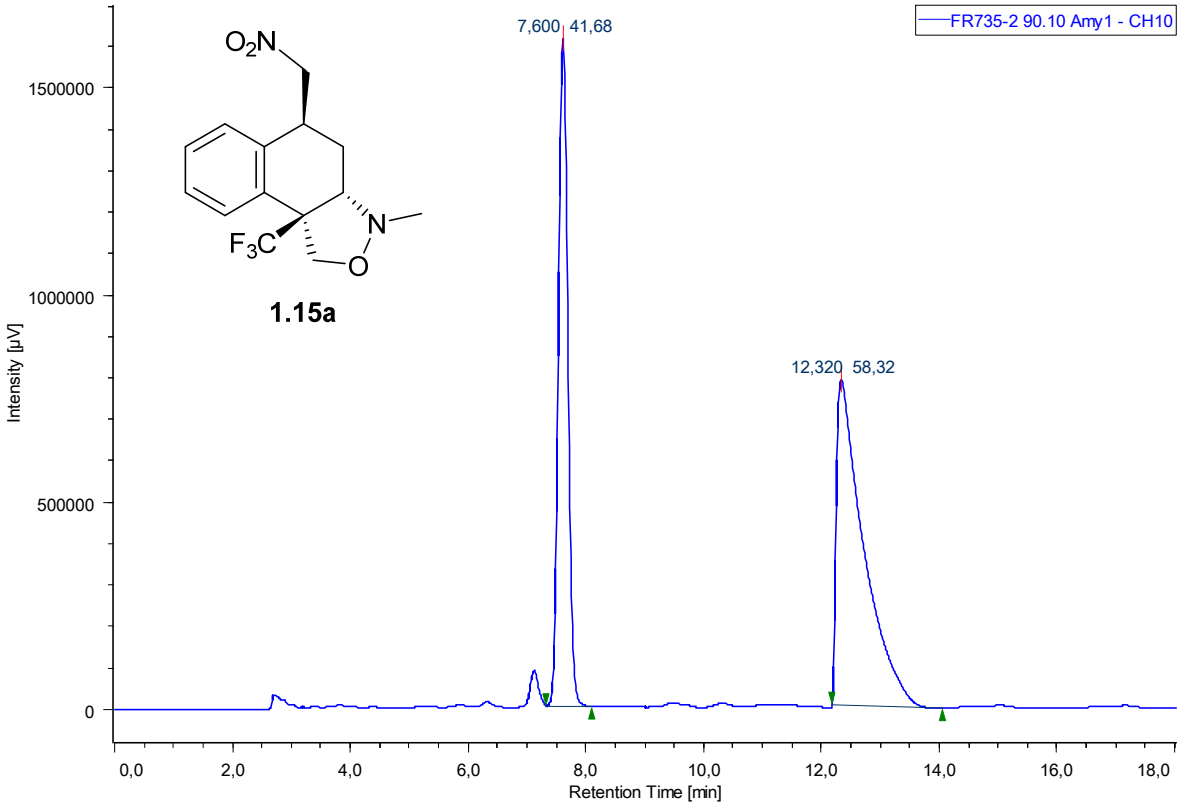
127.0 (<u>C</u>F_3, q, *J* = 285.7 Hz), 64.4, 59.7, 51.1 (<u>C</u>-CF_3, q, *J* = 20.8 Hz), 34.9, 30.2, 21.4. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -69.69 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{20}F_3N_2O$ 289.1528; found 289.1519.



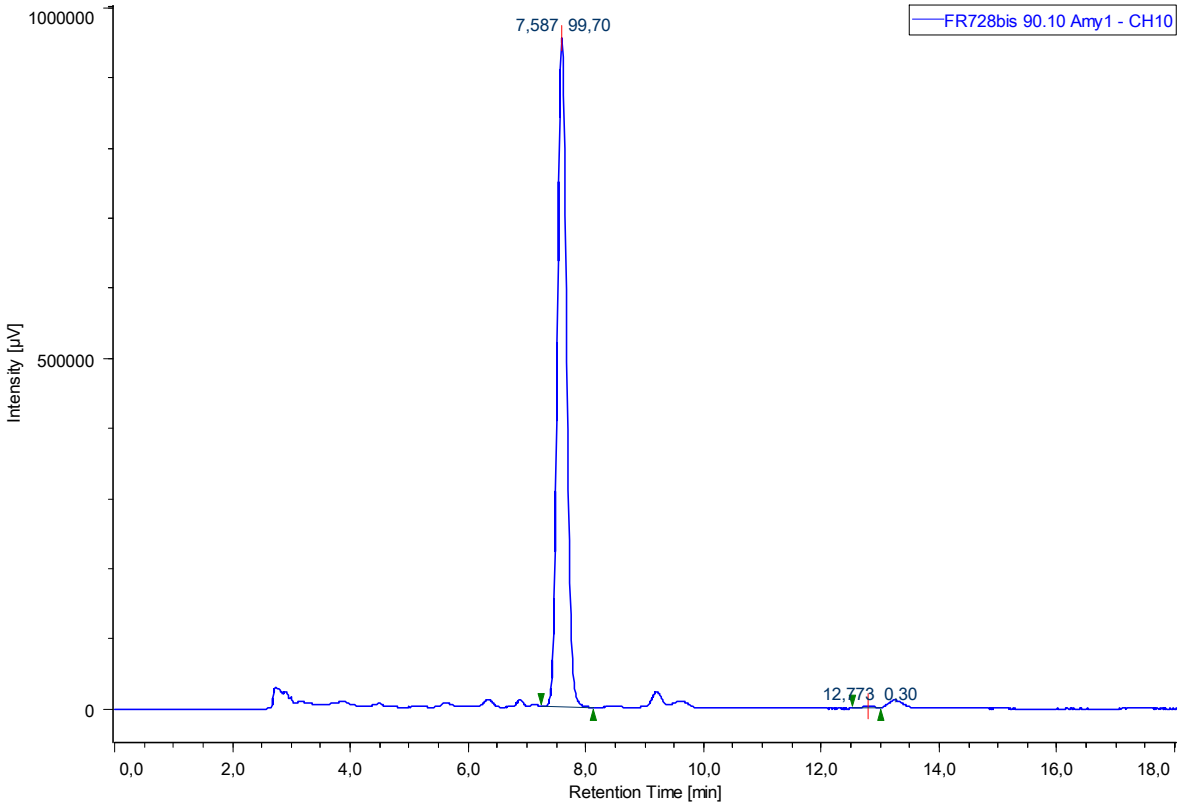
1.20

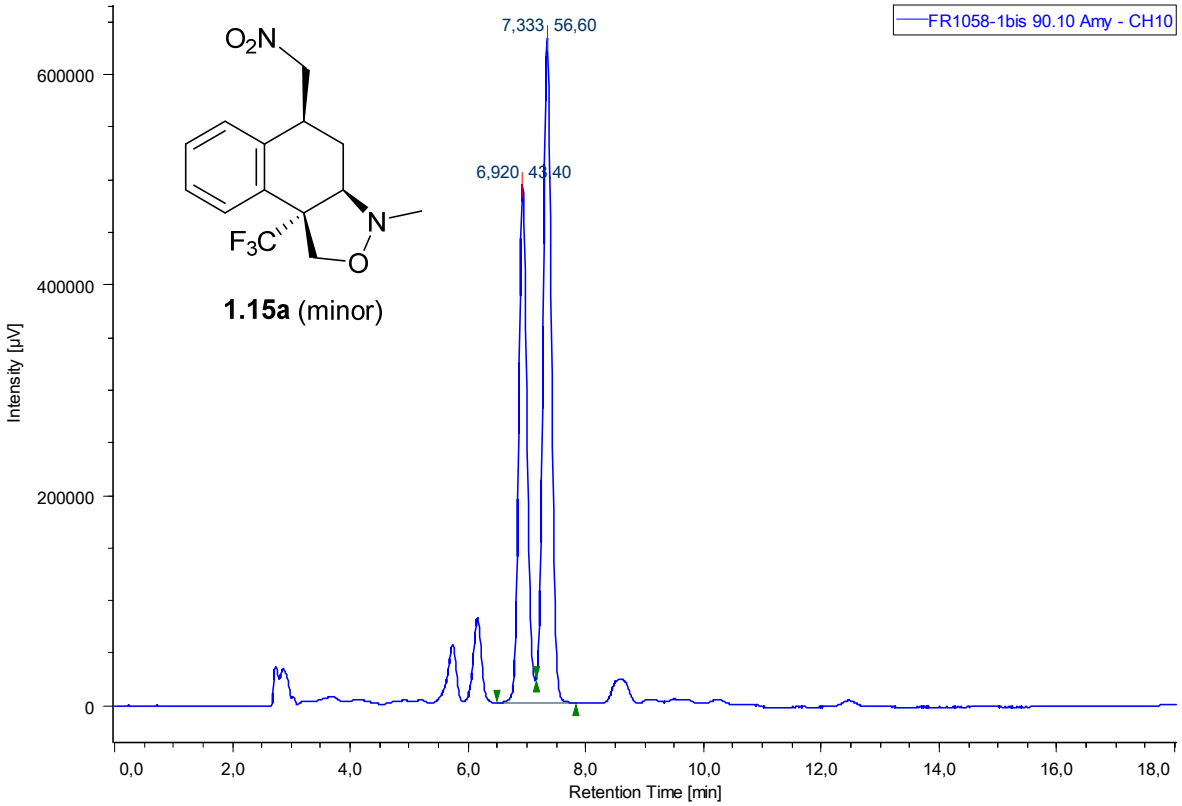
Benzyl ((3a*R*,5*S*,10b*R*)-3-methyl-10b-(trifluoromethyl)-1,3,3a,4,5,10b-hexahydro-[1,3]dioxolo[4',5':6,7]naphtho[2,1-*c*]isoxazol-5-yl)carbamate (1.20): To a solution of isoxazolidine **1.17c** (1.0 equiv, 0.1 mmol, 47 mg) in acetonitrile/water (9/1, 0.03 M), $Mo(CO)_6$ (1.2 equiv, 0.12 mmol) was added and the resulting mixture was refluxed for 3 h. The crude reaction mixture was then filtered through a short column of silica gel (washed by EtOAc) and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography [*n*-hexane-EtOAc (10:1)] to furnish **1.20** in quantitative yield (45 mg, colorless oil). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.41 – 7.29 (m, 5H), 6.95 (s, 1H), 6.70 (q, *J* = 1.3 Hz, 1H), 5.97 – 5.95 (m, 2H), 5.12-5.10 (m, 2H), 5.01 – 4.91 (m, 1H), 4.67 (br s, 1H), 4.53 (d, *J* = 8.9 Hz, 1H), 3.84 (dq, *J* = 8.9, 1.5 Hz, 1H), 3.18 (dd, *J* = 4.0, 4.0 Hz, 1H), 2.74 (s, 3H), 2.31 (dt, *J* = 15.0, 4.5 Hz, 1H), 2.01 (dt, *J* = 15.0, 4.0 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 156.0 (<u>C</u>=O), 148.3, 148.0, 136.6, 132.0, 128.7, 128.7, 128.4, 128.3, 128.2, 127.1 (<u>C</u>F_3, q, *J* = 282.3 Hz), 124.2, 108.7, 108.2, 101.6, 74.4, 67.3, 66.9, 58.1 (<u>C</u>-CF_3, q, *J* = 23.6 Hz), 47.0, 42.8, 28.6. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -71.33 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{22}F_3N_2O_5$ 451.1475; found 451.1454.

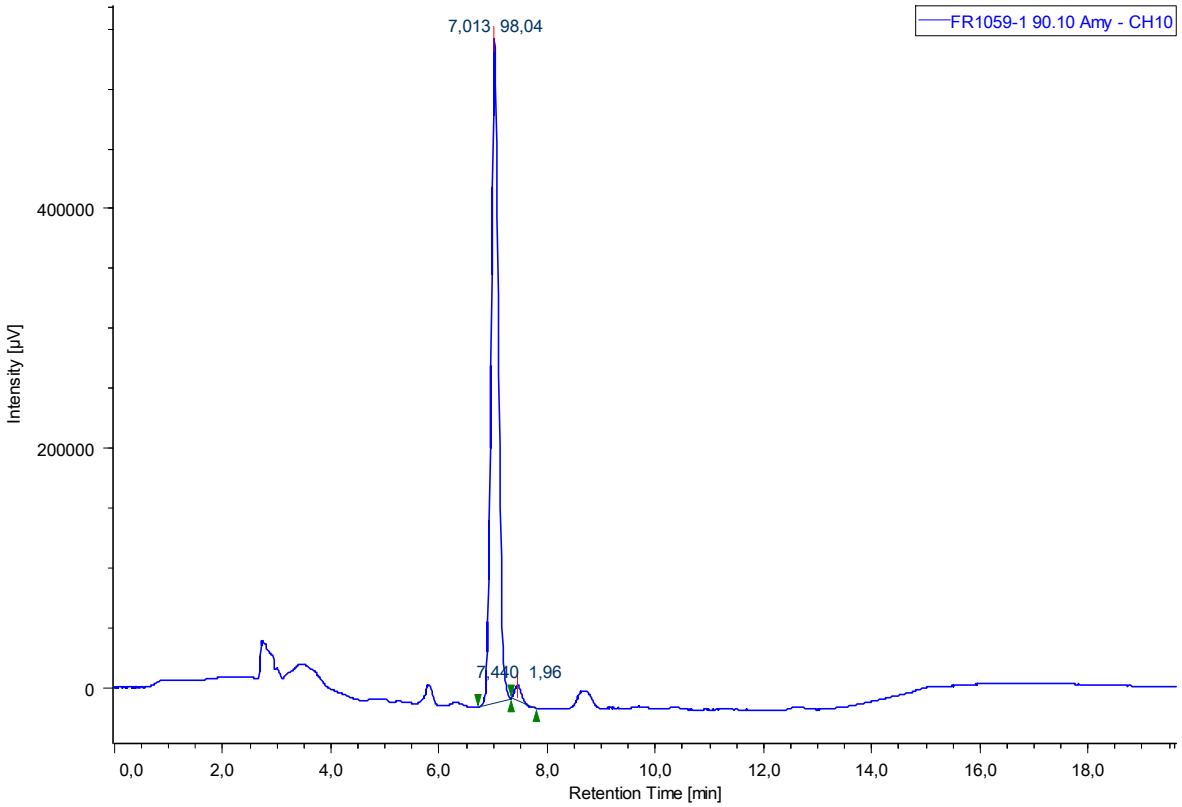
- **HPLC Traces of enantioenriched compounds 1.15 and 1.17**



1.15a




FR1058-1bis 90.10 Amy - CH10
7,333 56,60
6,920 43,40
O2N
F3C
N
O
1.15a (minor)
Intensity [µV]
600000
400000
200000
0
0,0
2,0
4,0
6,0
8,0
10,0
12,0
14,0
16,0
18,0
Retention Time [min]


FR1059-1 90.10 Amy - CH10
7,013 98,04
7,440 1,96
Intensity [µV]
400000
200000
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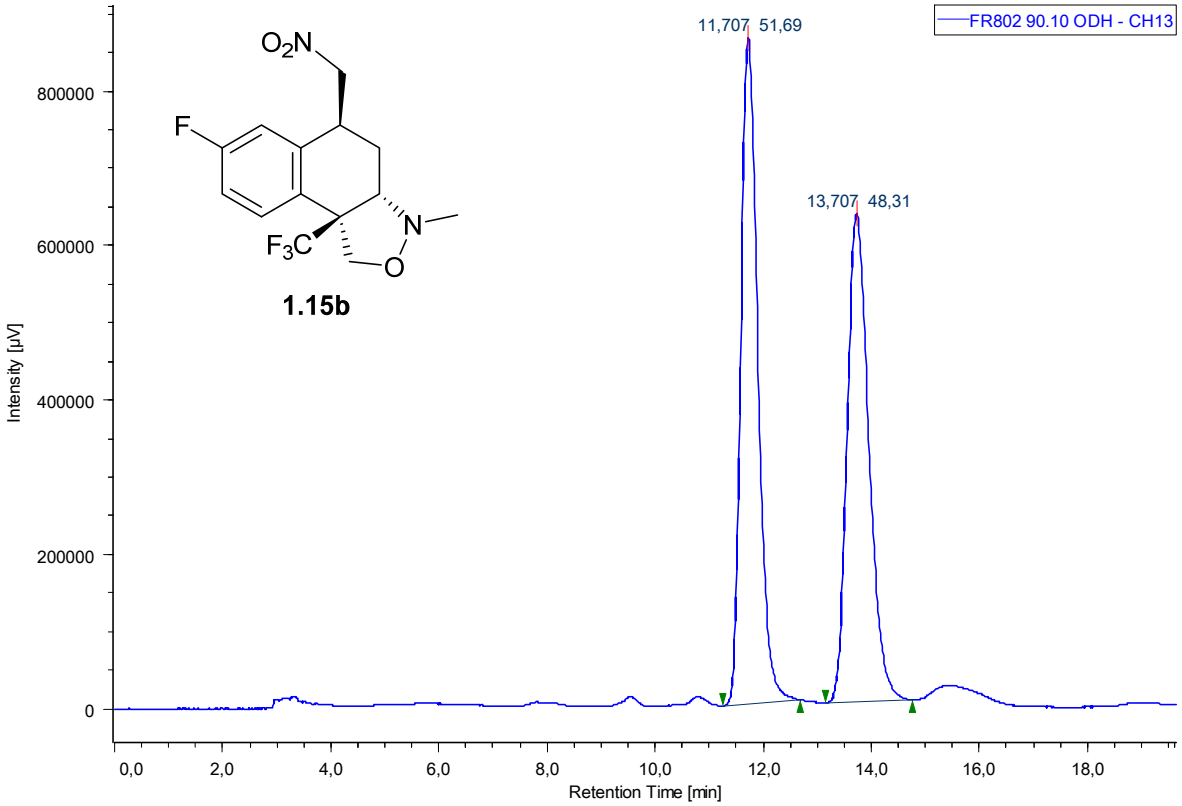
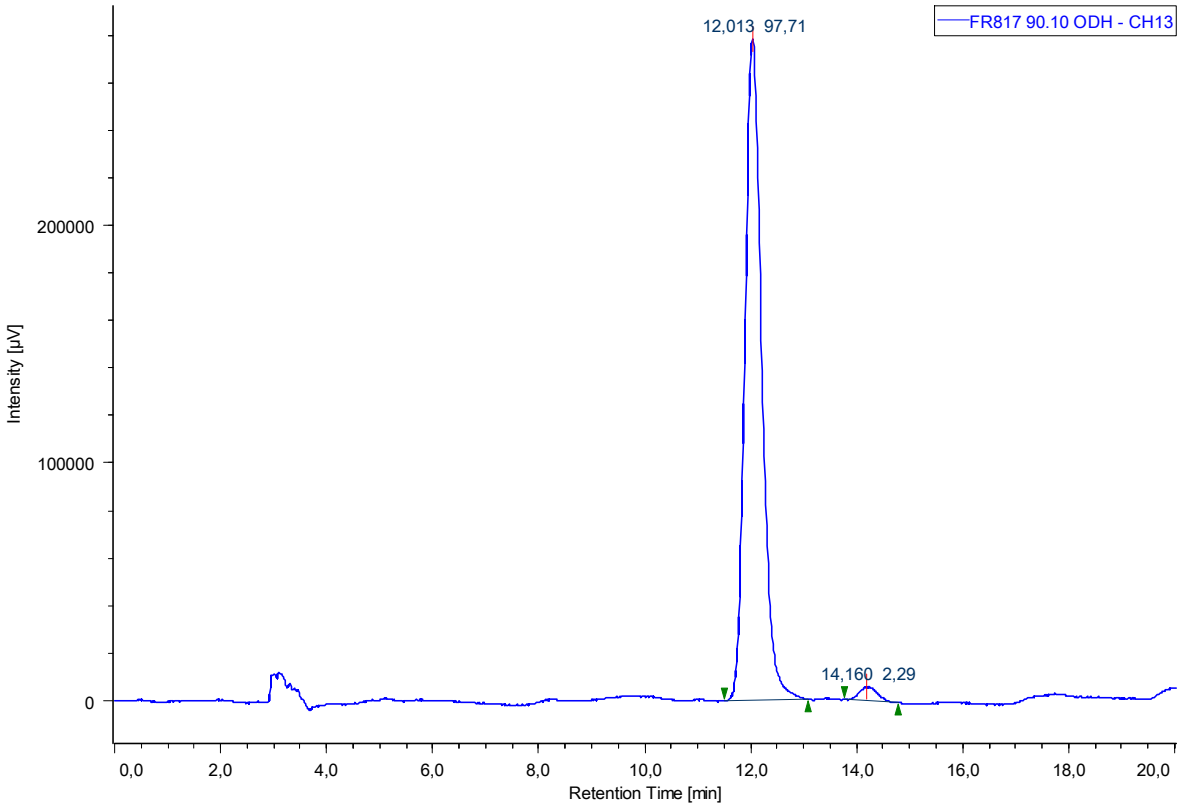
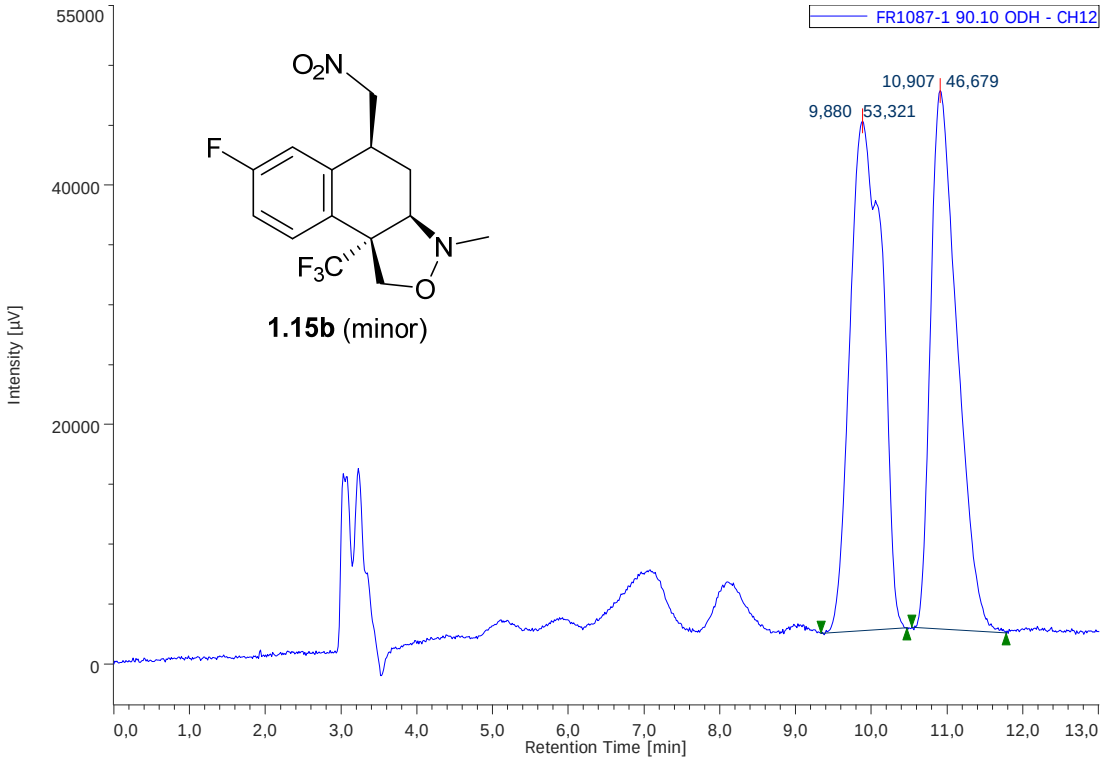
4,0
6,0
8,0
10,0
12,0
14,0
16,0
18,0
Retention Time [min]

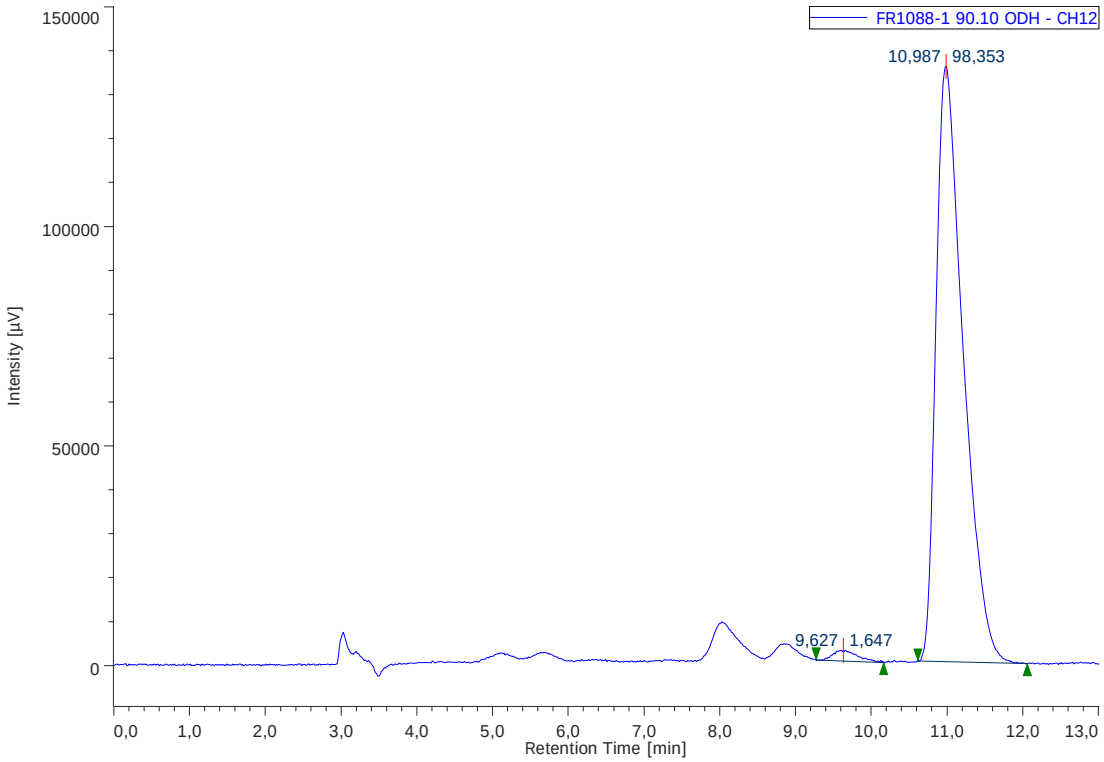

FR802 90.10 ODH - CH13
11,707 51,69
13,707 48,31
Intensity [µV]
800000
600000
400000
200000
0
0,0
2,0
4,0
6,0
8,0
10,0
12,0
14,0
16,0
18,0
Retention Time [min]

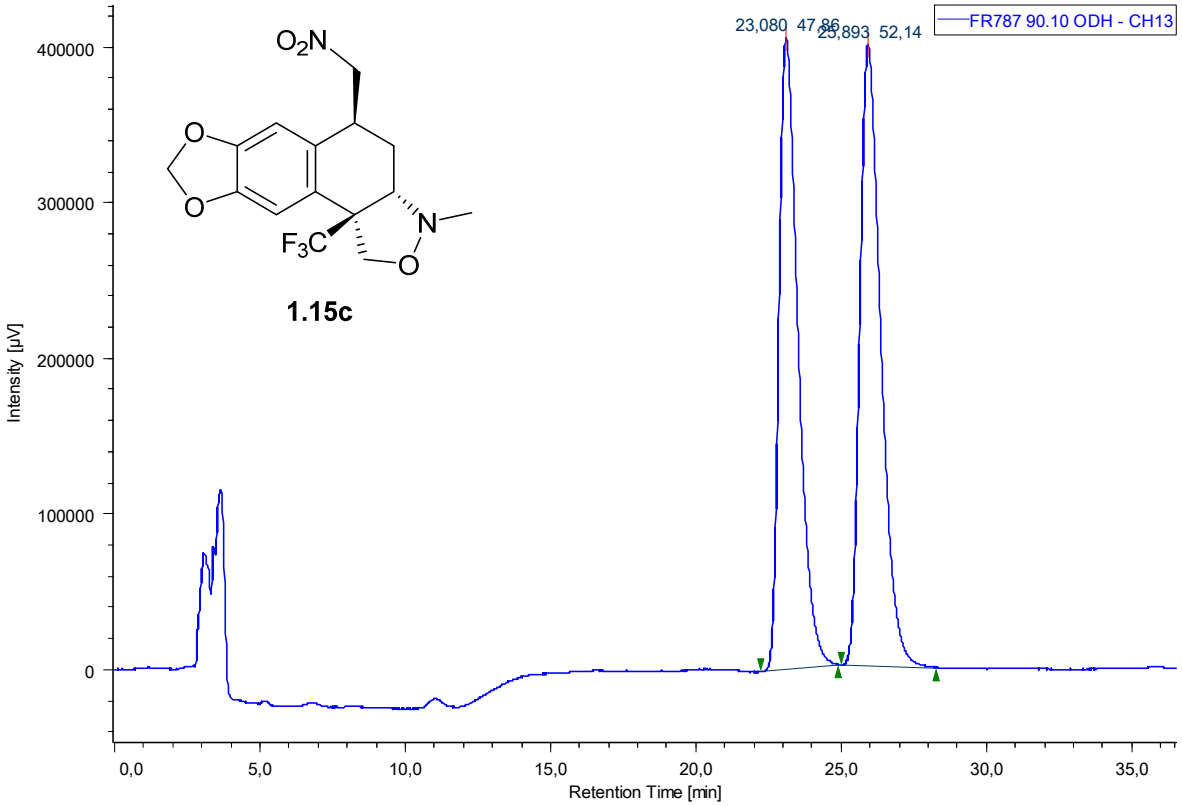
1.15b

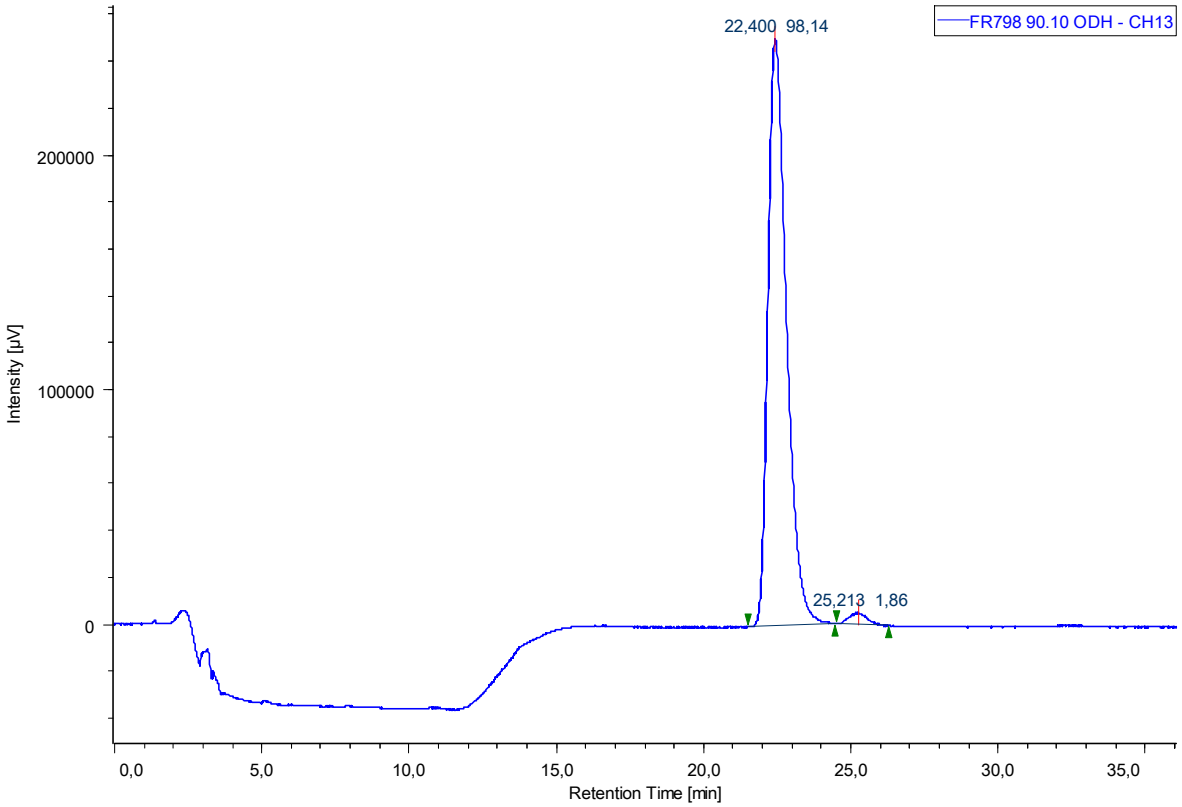

FR817 90.10 ODH - CH13
12,013 97,71
14,160 2,29
Intensity [µV]
200000
100000
0
0,0
2,0
4,0
6,0
8,0
10,0
12,0
14,0
16,0
18,0
20,0
Retention Time [min]

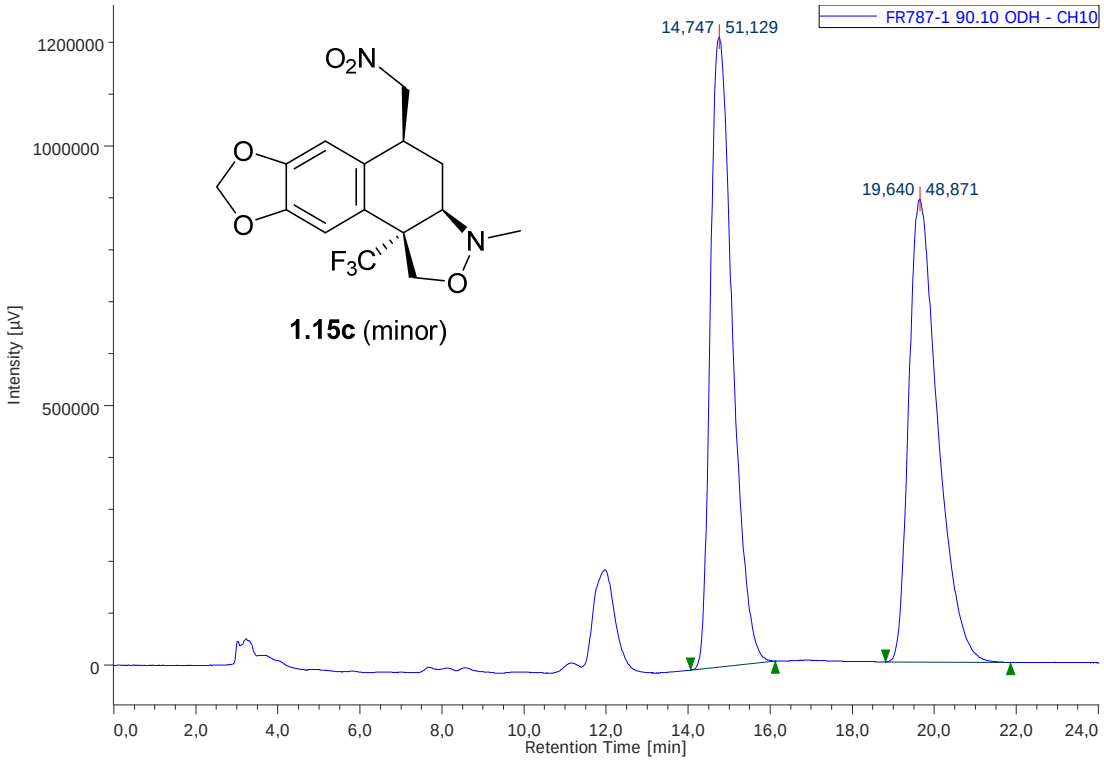

FR1087-1 90.10 ODH - CH12
10,907 46,679
9,880 53,321
Intensity [µV]
Retention Time [min]

1.15b (minor)


FR1088-1 90.10 ODH - CH12
10,987 98,353
9,627 1,647
Intensity [µV]
Retention Time [min]

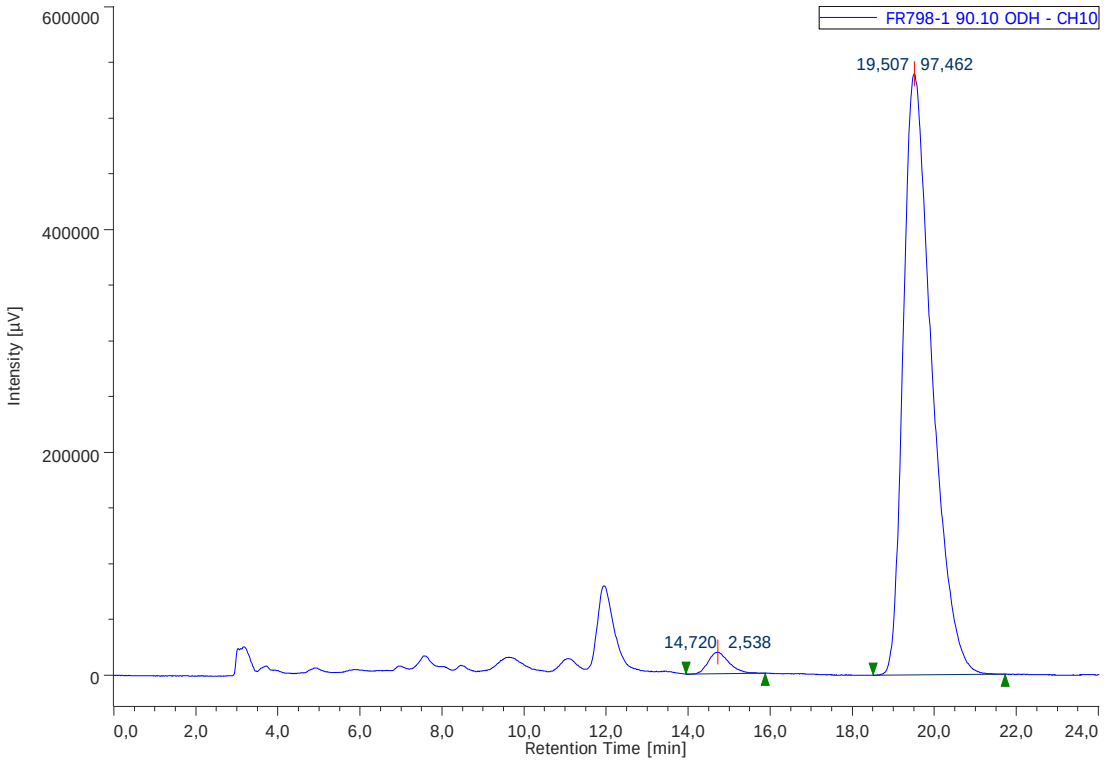

FR787 90.10 ODH - CH13
23,080 47,86
25,893 52,14
1.15c
Intensity [µV]
Retention Time [min]

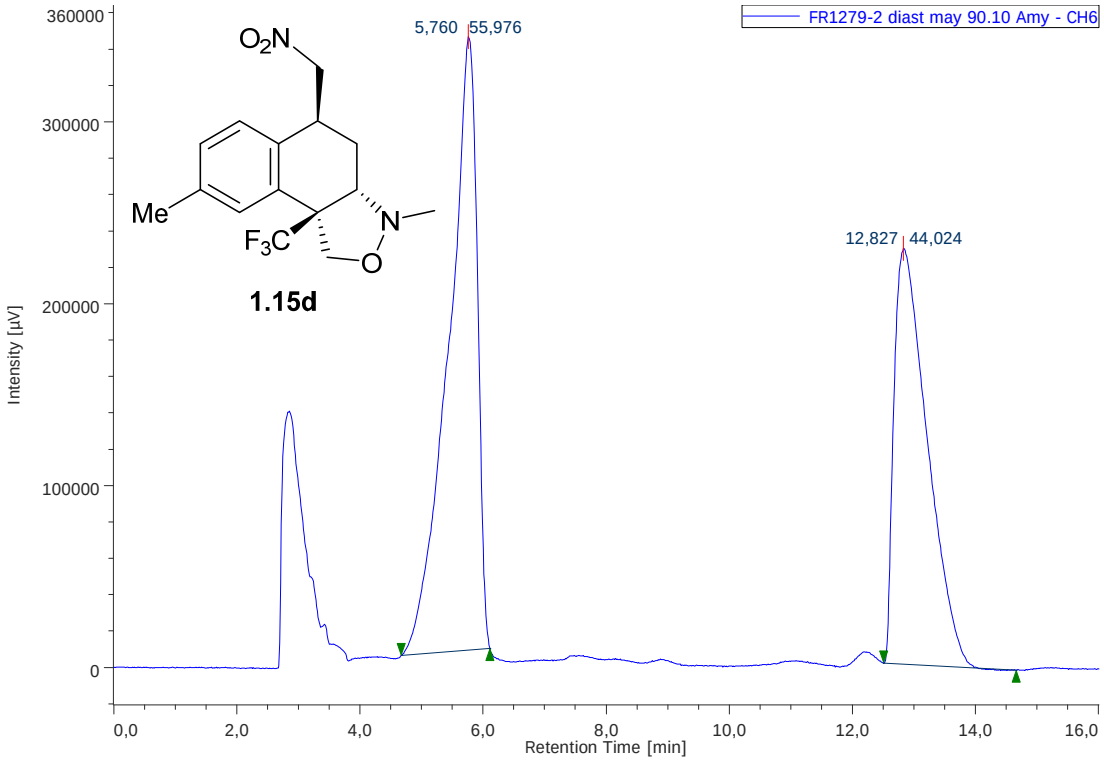

FR798 90.10 ODH - CH13
22,400 98,14
25,213 1,86
Intensity [µV]
Retention Time [min]

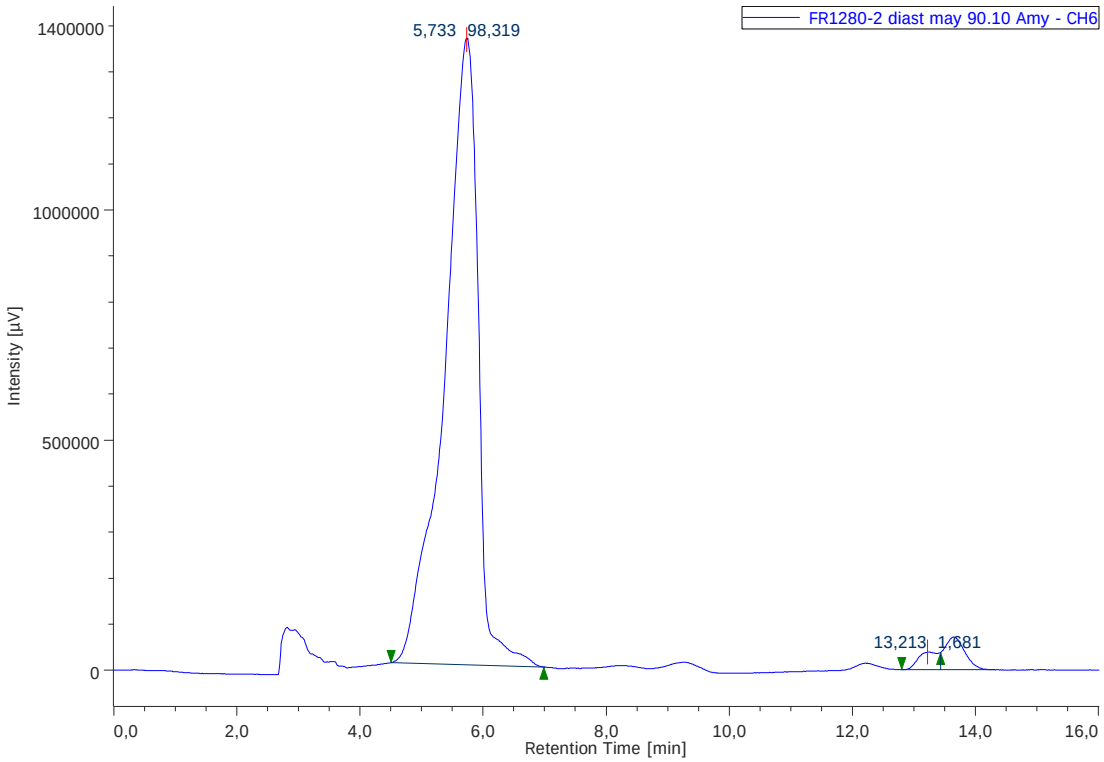

FR787-1 90.10 ODH - CH10
14,747 51,129
19,640 48,871
1200000
1000000
500000
0
Intensity [µV]
0,0 2,0 4,0 6,0 8,0 10,0 12,0 14,0 16,0 18,0 20,0 22,0 24,0
Retention Time [min]

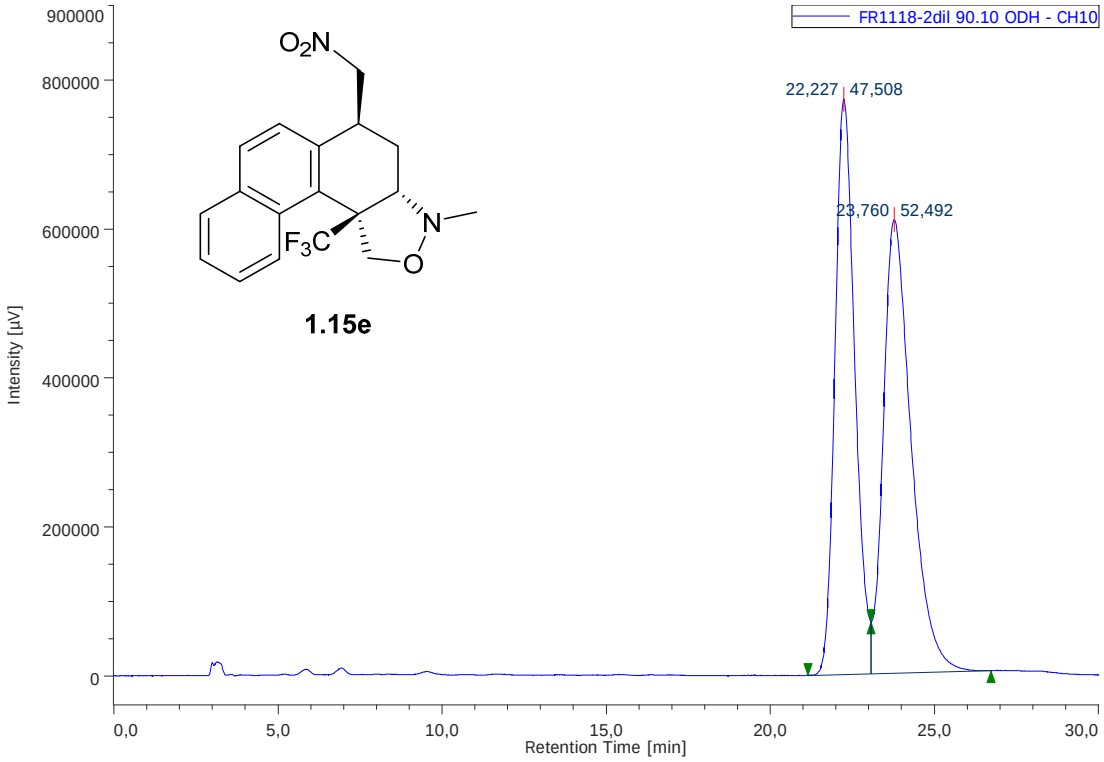
O2N
O
O
F3C
N
O

1.15c (minor)


FR798-1 90.10 ODH - CH10
19,507 97,462
14,720 2,538
600000
400000
200000
0
Intensity [µV]
0,0 2,0 4,0 6,0 8,0 10,0 12,0 14,0 16,0 18,0 20,0 22,0 24,0
Retention Time [min]

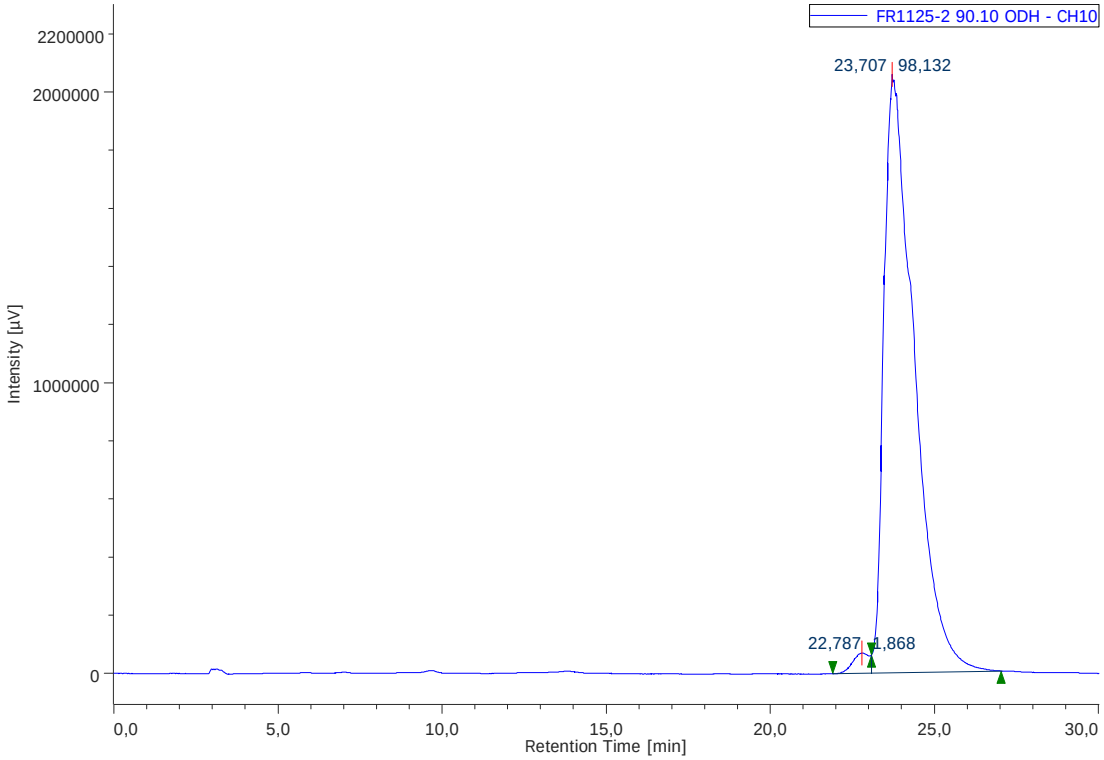

FR1279-2 diast may 90.10 Amy - CH6
5,760 55,976
12,827 44,024
O_2N
Me
F_3C
N
O
1.15d
Intensity [µV]
Retention Time [min]

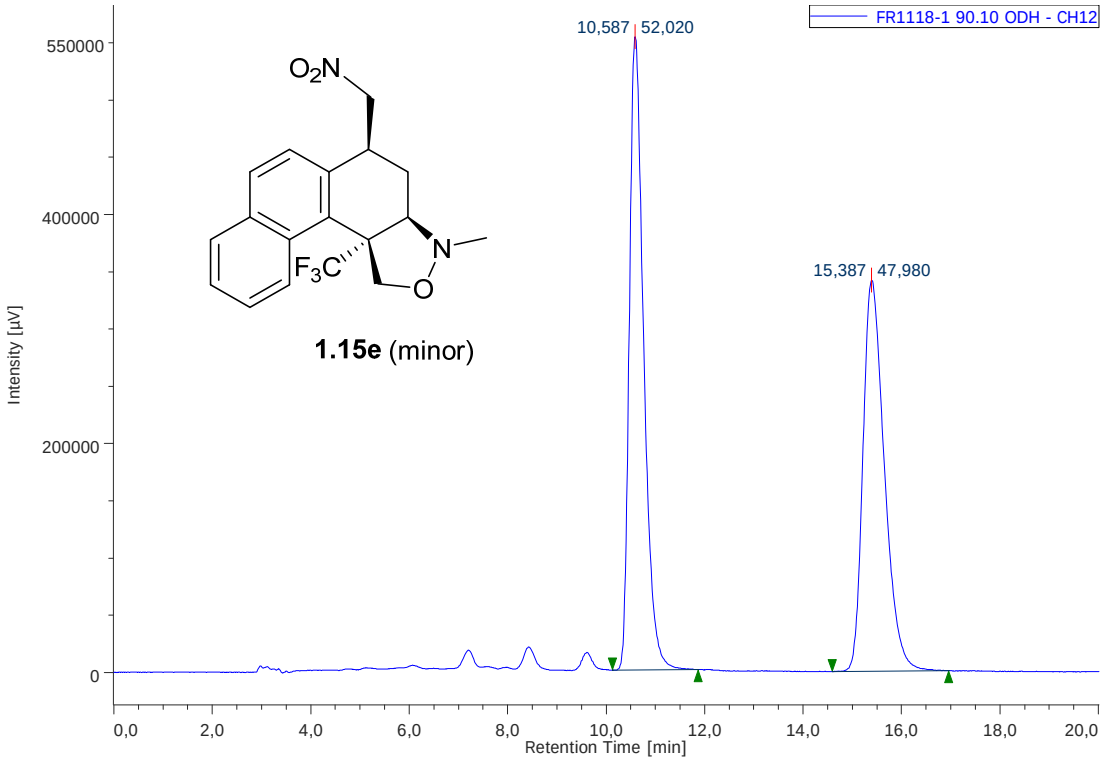

FR1280-2 diast may 90.10 Amy - CH6
5,733 98,319
13,213 1,681
Intensity [µV]
Retention Time [min]

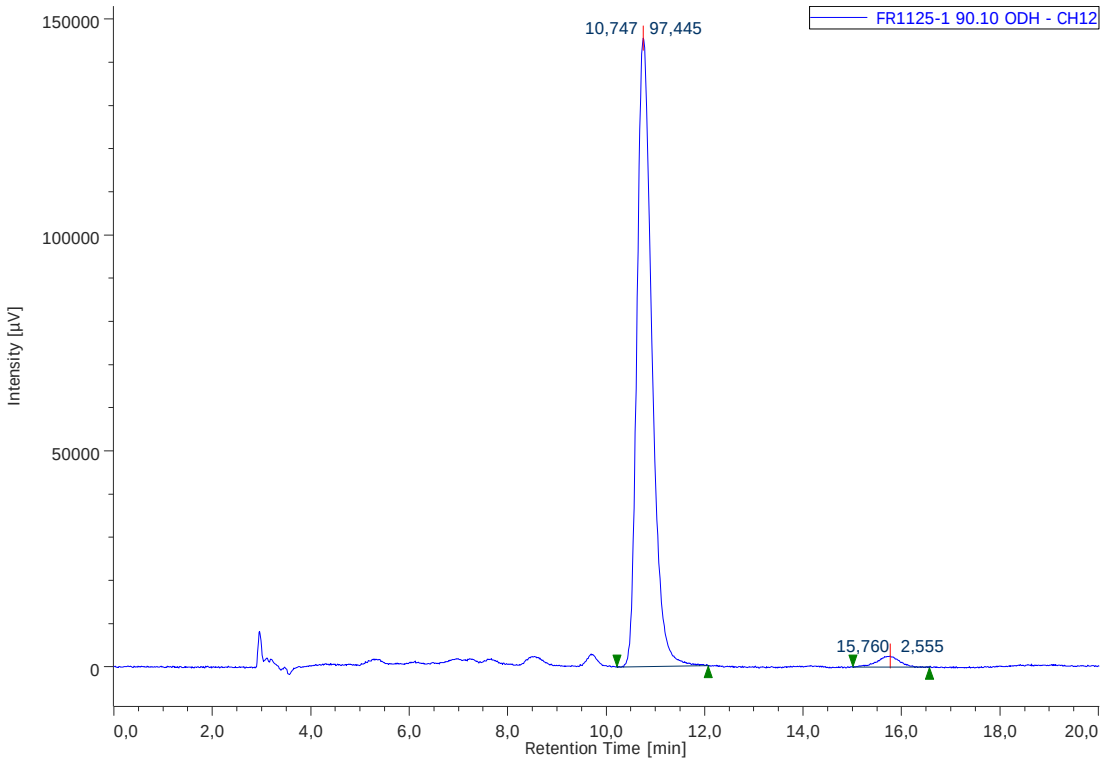

FR1118-2dil 90.10 ODH - CH10
22,227 47,508
23,760 52,492
900000
800000
600000
400000
200000
0
Intensity [µV]
0,0
5,0
10,0
15,0
20,0
25,0
30,0
Retention Time [min]

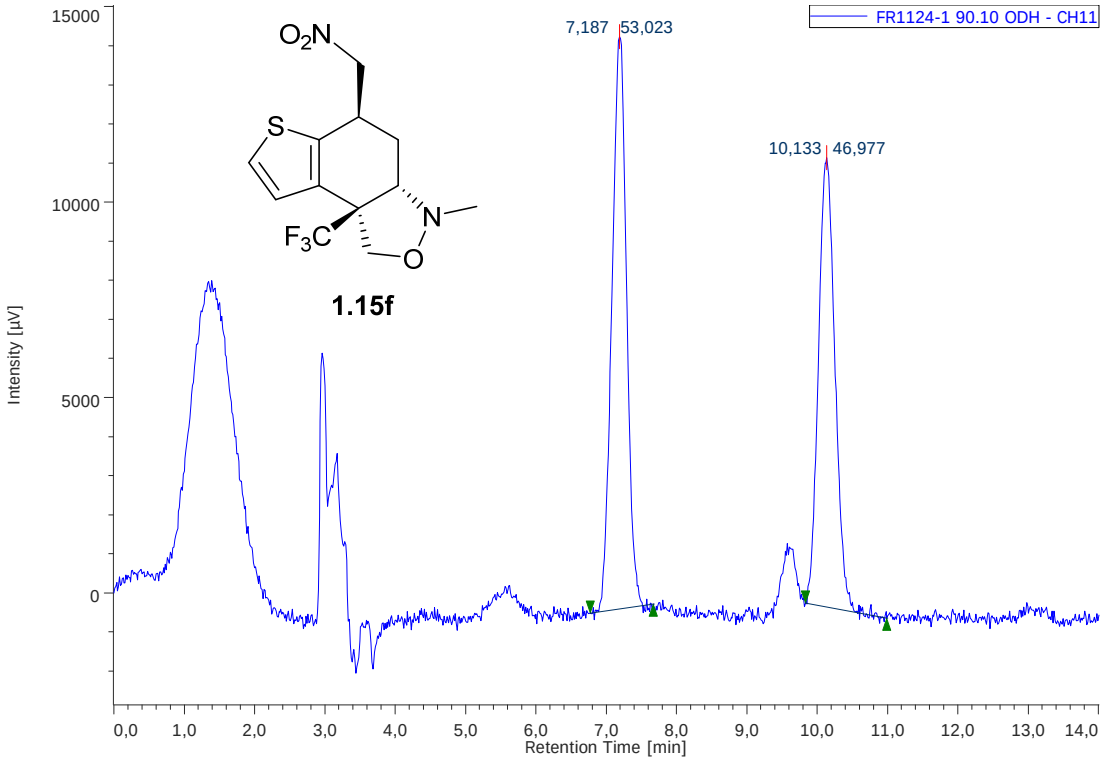
O2N
F3C
N
O

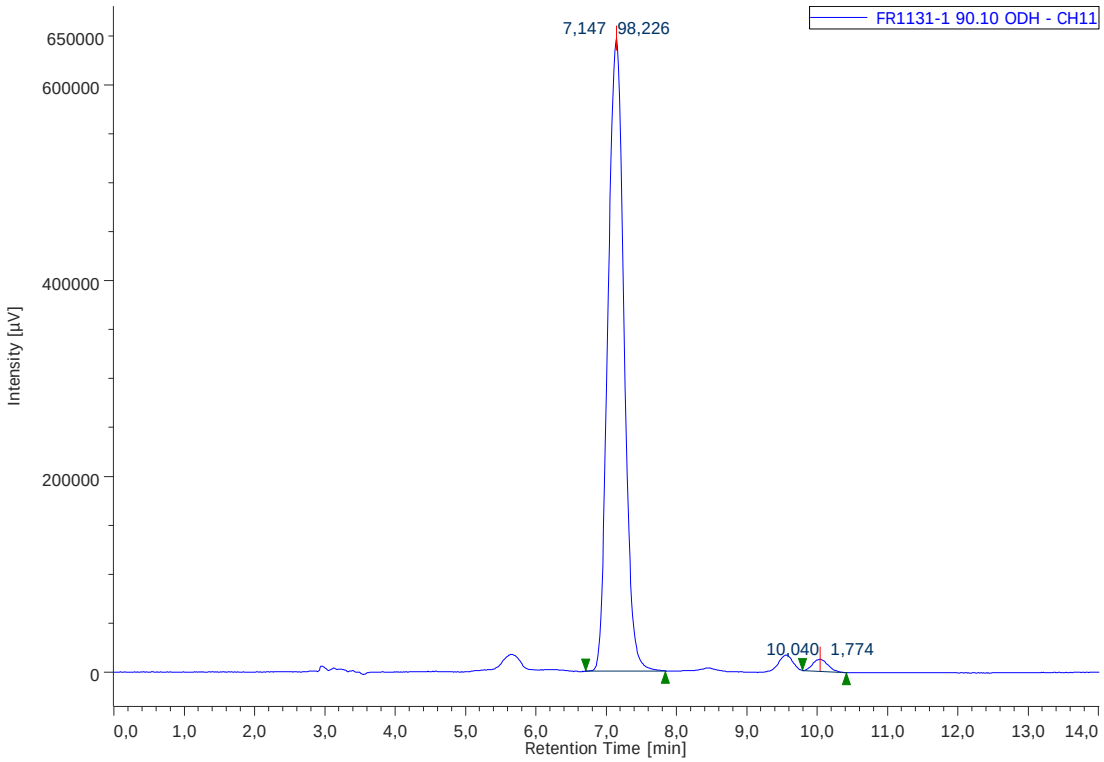
1.15e

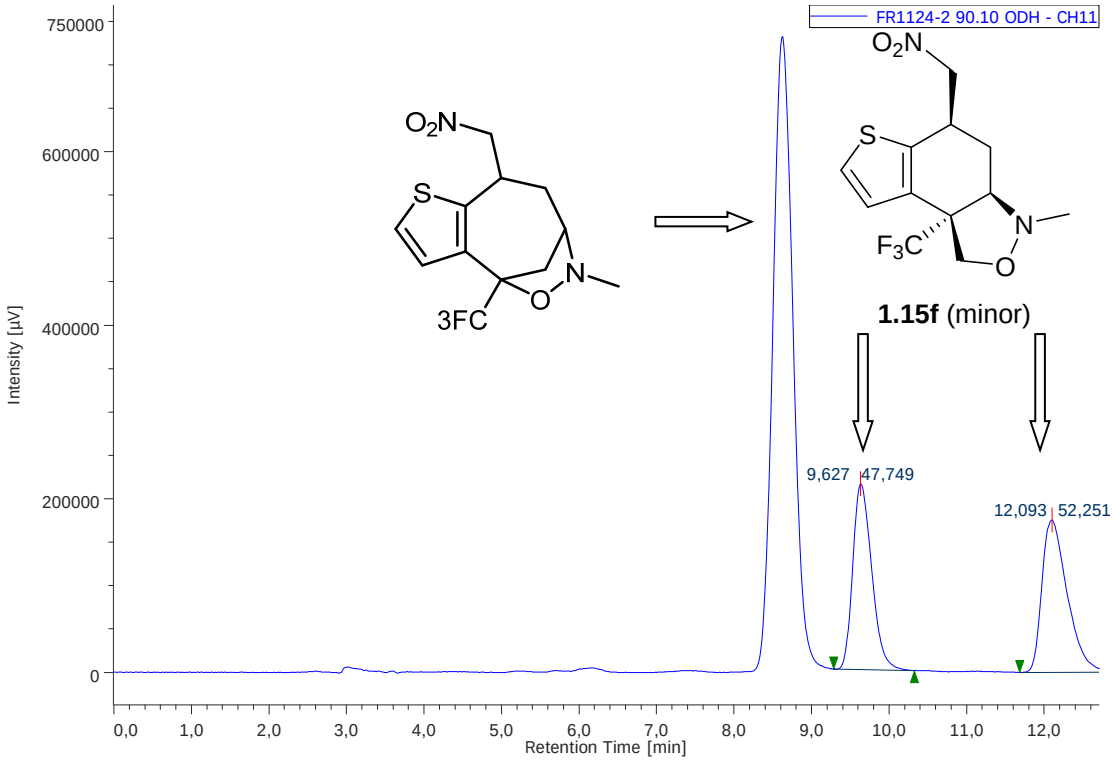

FR1125-2 90.10 ODH - CH10
23,707 98,132
22,787 1,868
2200000
2000000
1000000
0
Intensity [µV]
0,0
5,0
10,0
15,0
20,0
25,0
30,0
Retention Time [min]

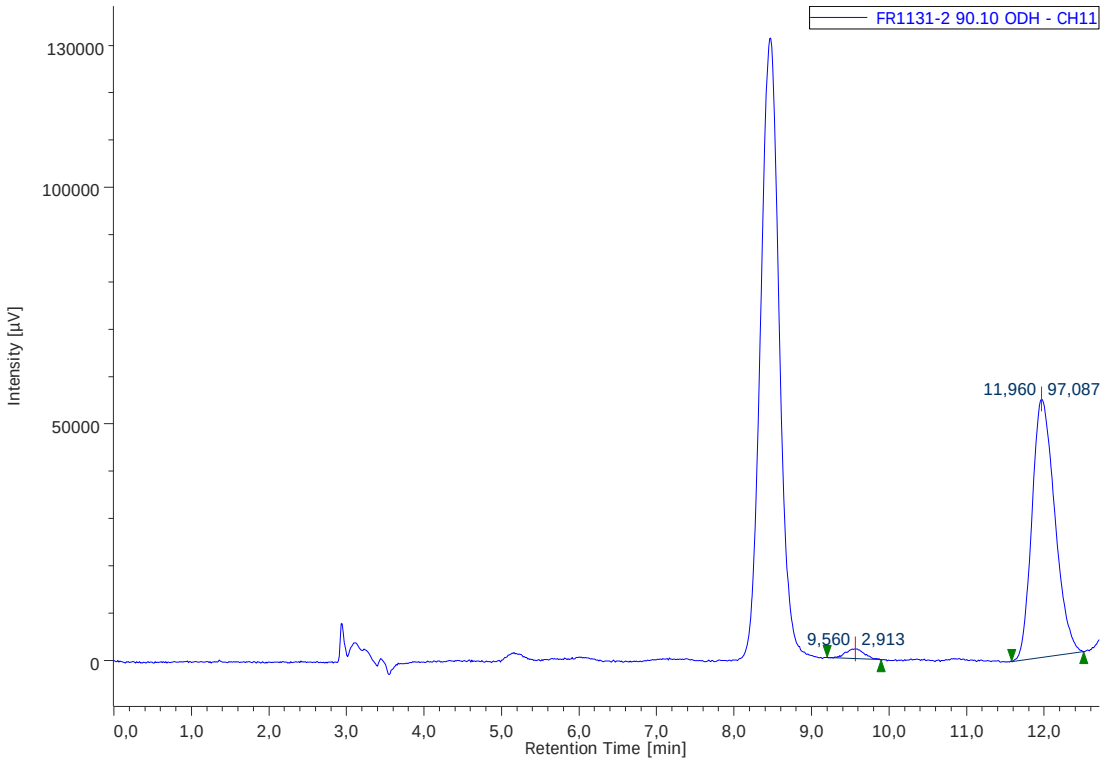

FR1118-1 90.10 ODH - CH12
10,587 52,020
15,387 47,980
O_2N
F_3C
N
O
1.15e (minor)
Intensity [µV]
550000
400000
200000
0
0,0 2,0 4,0 6,0 8,0 10,0 12,0 14,0 16,0 18,0 20,0
Retention Time [min]

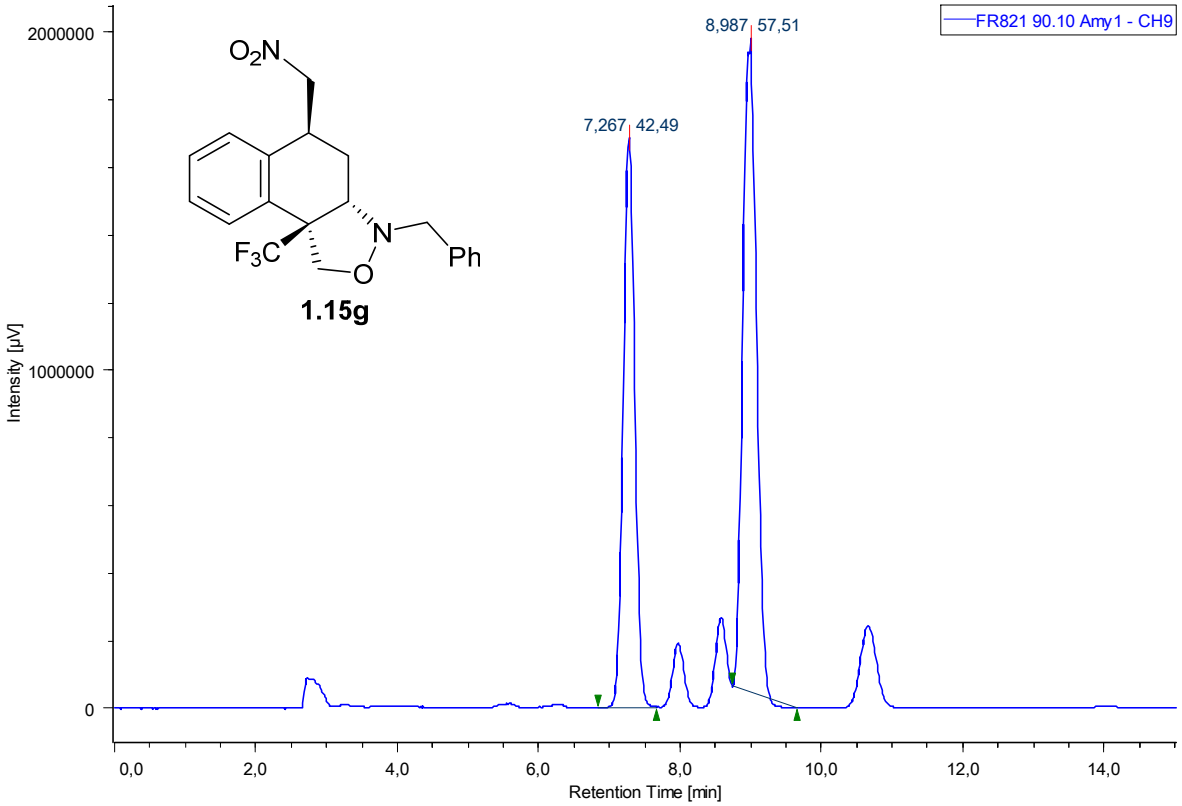

FR1125-1 90.10 ODH - CH12
10,747 97,445
15,760 2,555
Intensity [µV]
150000
100000
50000
0
0,0 2,0 4,0 6,0 8,0 10,0 12,0 14,0 16,0 18,0 20,0
Retention Time [min]

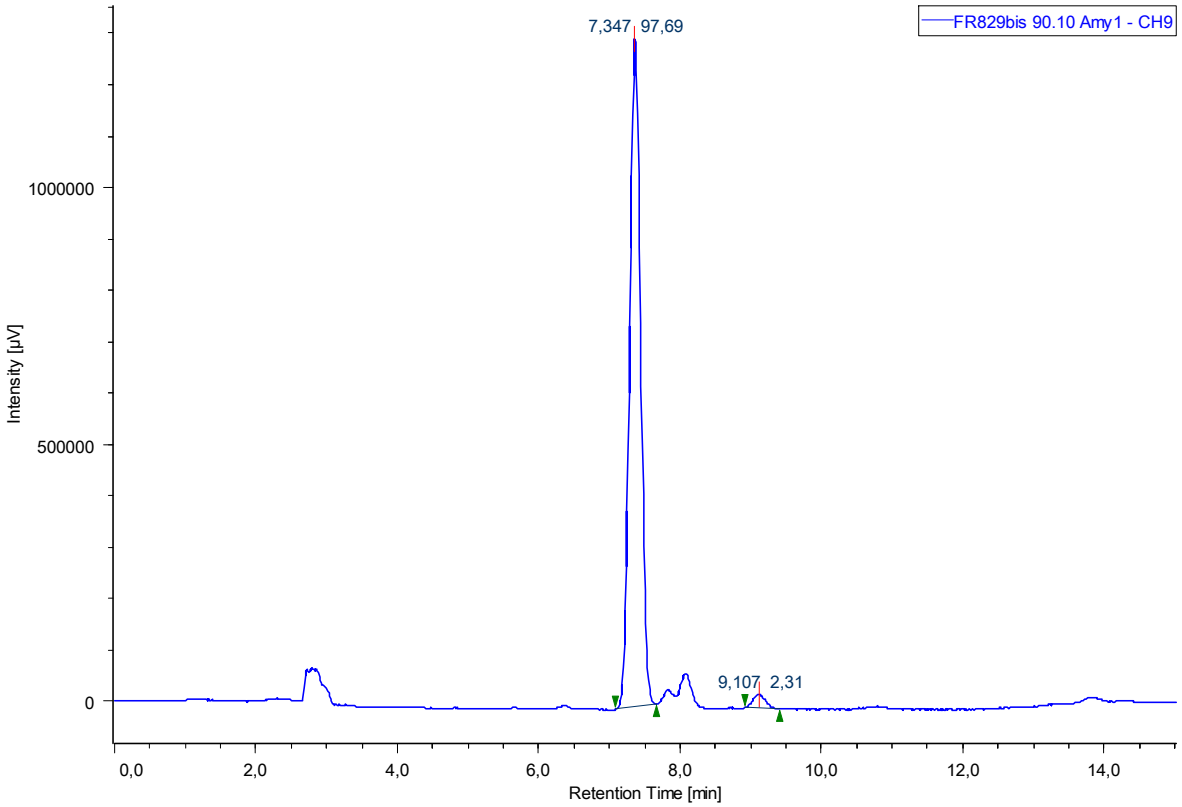

FR1124-1 90.10 ODH - CH11
7,187 53,023
10,133 46,977
1.15f
Intensity [µV]
Retention Time [min]


FR1131-1 90.10 ODH - CH11
7,147 98,226
10,040 1,774
Intensity [µV]
Retention Time [min]


FR1124-2 90.10 ODH - CH11
Intensity [µV]
750000
600000
400000
200000
0
O2N
S
N
O
3FC
F3C
1.15f (minor)
9,627
47,749
12,093
52,251
0,0
1,0
2,0
3,0
4,0
5,0
6,0
7,0
8,0
9,0
10,0
11,0
12,0
Retention Time [min]


FR1131-2 90.10 ODH - CH11
Intensity [µV]
130000
100000
50000
0
11,960
97,087
9,560
2,913
0,0
1,0
2,0
3,0
4,0
5,0
6,0
7,0
8,0
9,0
10,0
11,0
12,0
Retention Time [min]


FR821 90.10 Amy1 - CH9
8,987 57,51
7,267 42,49
O_2N
F_3C
N
O
Ph
1.15g
Intensity [µV]
2000000
1000000
0
0,0
2,0
4,0
6,0
8,0
10,0
12,0
14,0
Retention Time [min]


FR829bis 90.10 Amy1 - CH9
7,347 97,69
9,107 2,31
Intensity [µV]
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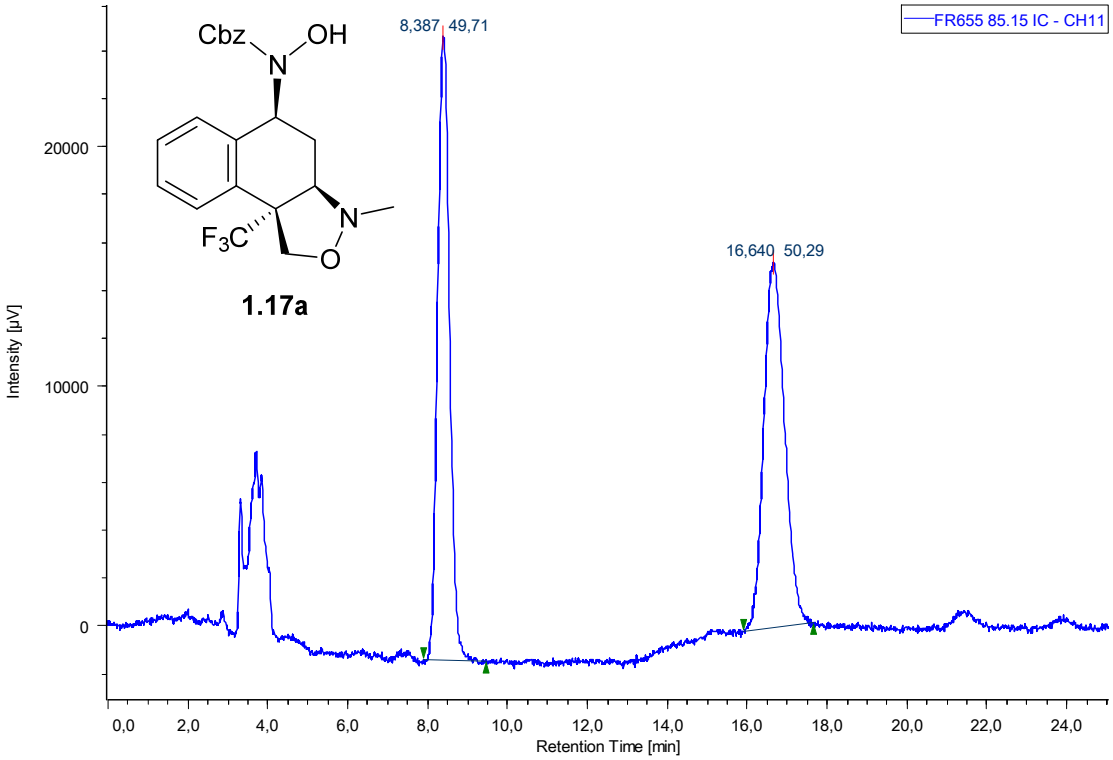
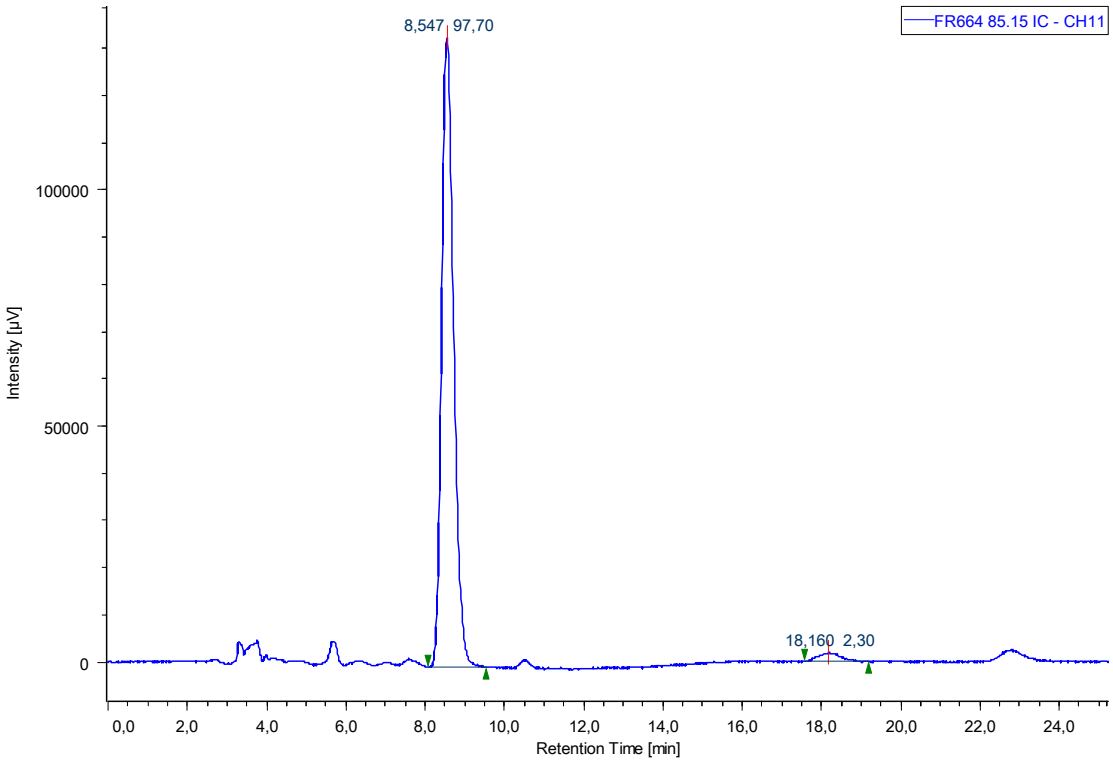
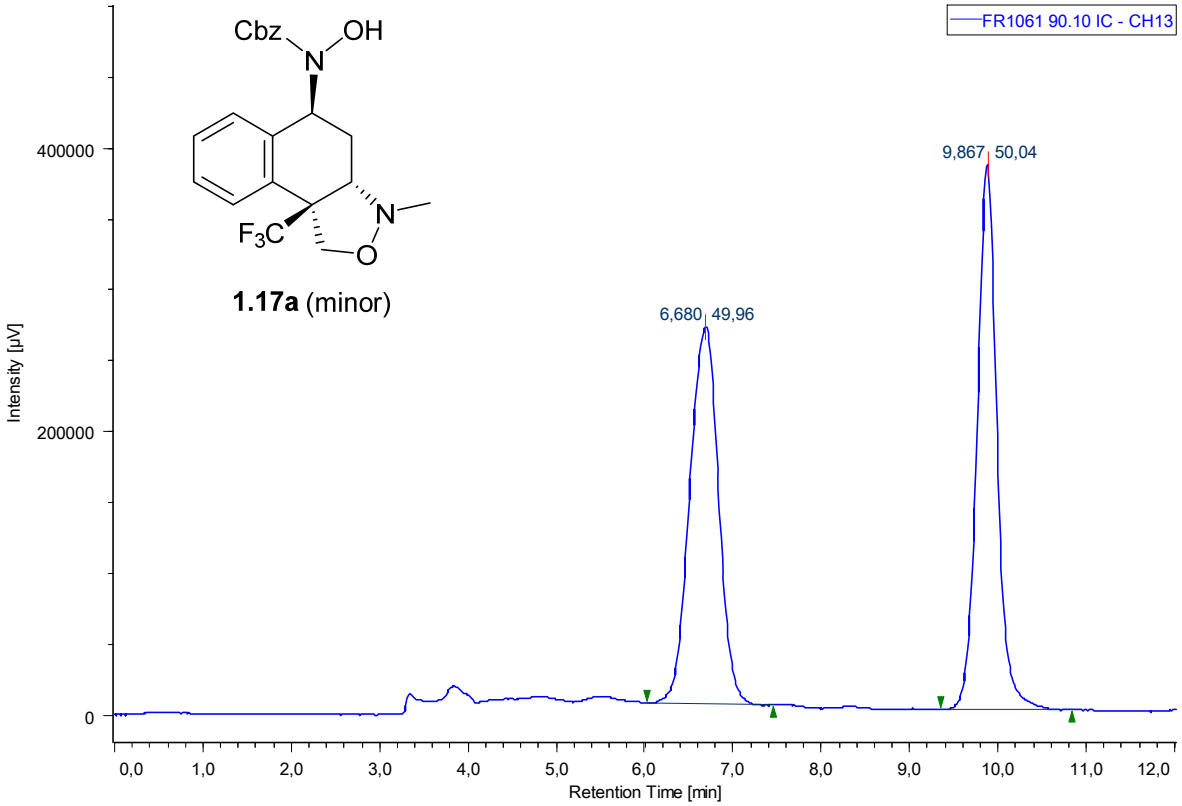
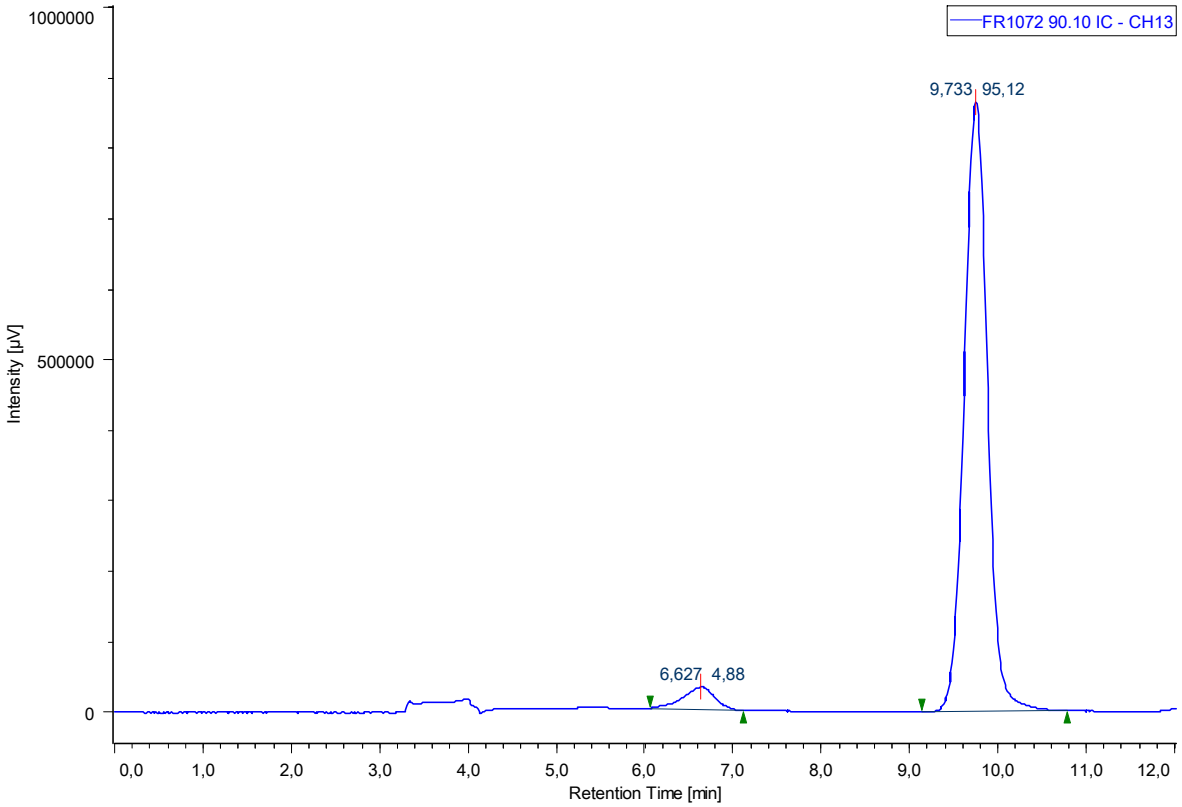
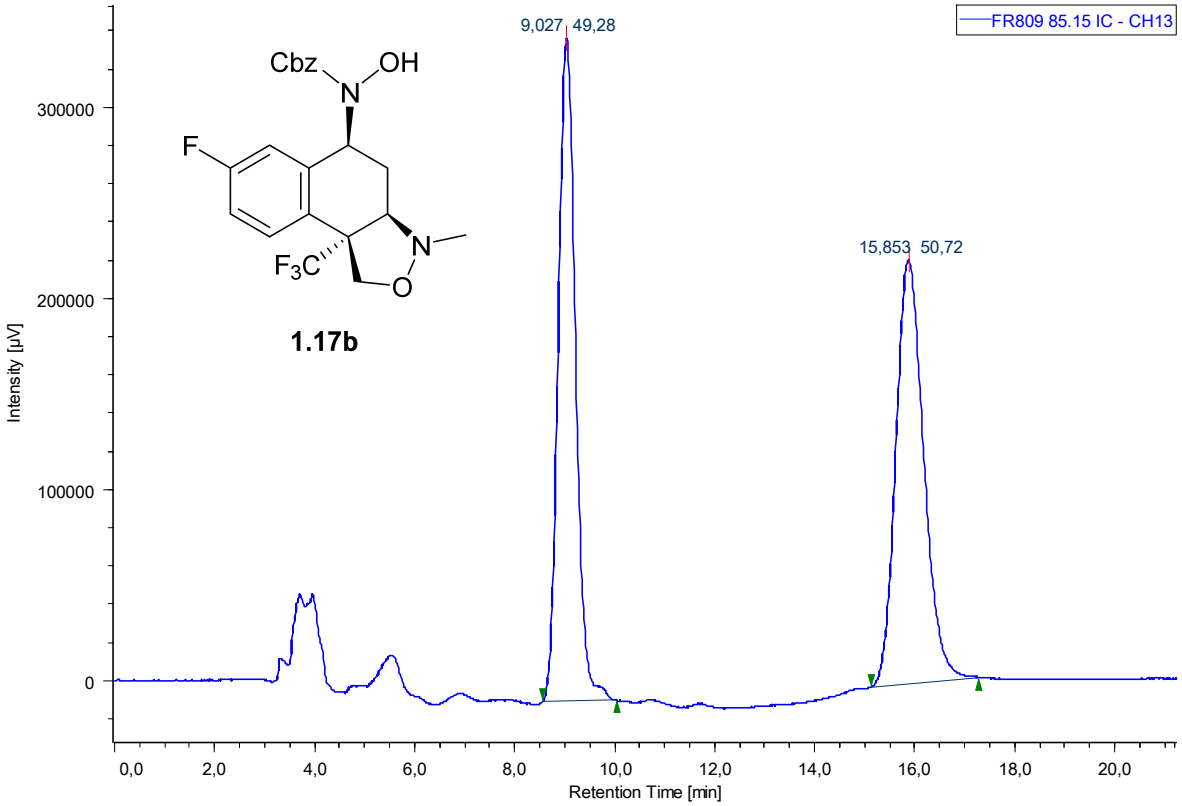
500000
0
0,0
2,0
4,0
6,0
8,0
10,0
12,0
14,0
Retention Time [min]

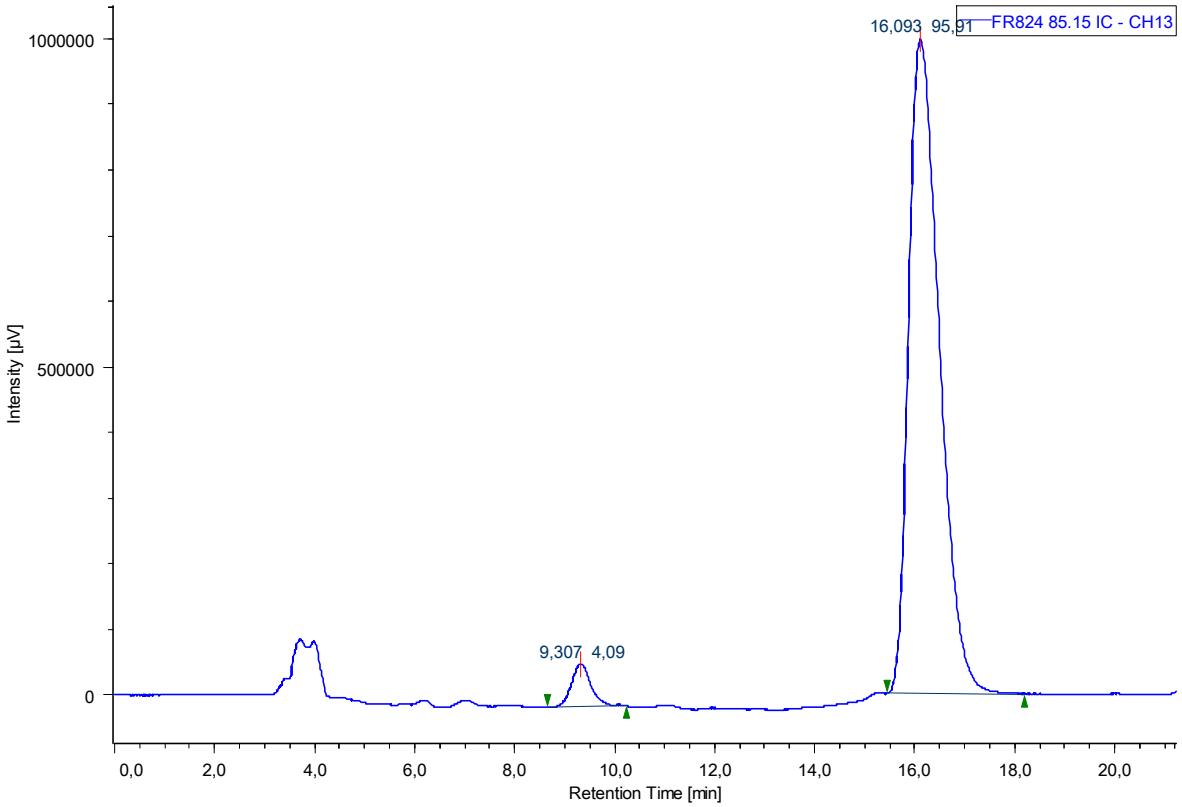

Cbz
N
OH
N
F3C
O
1.17a
8,387 49,71
16,640 50,29
FR655 85.15 IC - CH11
Intensity [µV]
20000
10000
0
0,0 2,0 4,0 6,0 8,0 10,0 12,0 14,0 16,0 18,0 20,0 22,0 24,0
Retention Time [min]

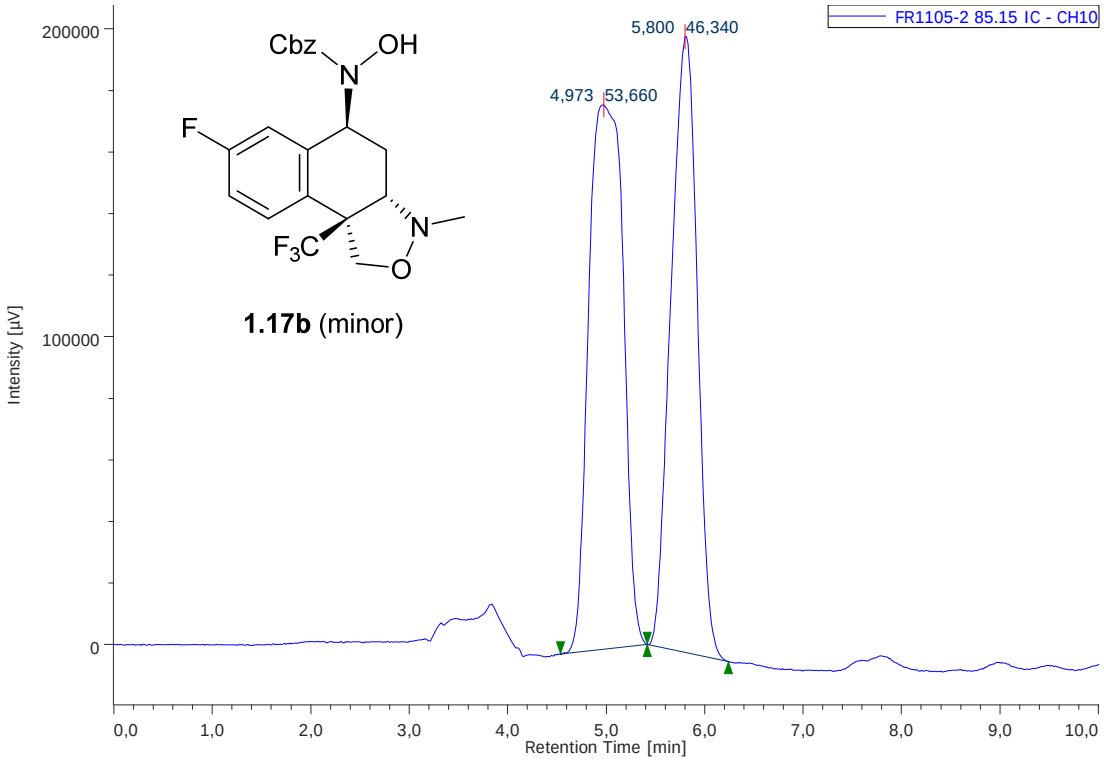

8,547 97,70
18,160 2,30
FR664 85.15 IC - CH11
Intensity [µV]
100000
50000
0
0,0 2,0 4,0 6,0 8,0 10,0 12,0 14,0 16,0 18,0 20,0 22,0 24,0
Retention Time [min]


Cbz
N
OH
F3C
N
O
1.17a (minor)
FR1061 90.10 IC - CH13
9,867 50,04
6,680 49,96
Intensity [µV]
400000
200000
0
0,0 1,0 2,0 3,0 4,0 5,0 6,0 7,0 8,0 9,0 10,0 11,0 12,0
Retention Time [min]


FR1072 90.10 IC - CH13
9,733 95,12
6,627 4,88
Intensity [µV]
1000000
500000
0
0,0 1,0 2,0 3,0 4,0 5,0 6,0 7,0 8,0 9,0 10,0 11,0 12,0
Retention Time [min]


FR809 85.15 IC - CH13
9,027 49,28
15,853 50,72
Cbz
N
OH
F
F3C
N
O
1.17b
Intensity [µV]
300000
200000
100000
0
0,0
2,0
4,0
6,0
8,0
10,0
12,0
14,0
16,0
18,0
20,0
Retention Time [min]


FR824 85.15 IC - CH13
16,093 95,91
9,307 4,09
Intensity [µV]
1000000
500000
0
0,0
2,0
4,0
6,0
8,0
10,0
12,0
14,0
16,0
18,0
20,0
Retention Time [min]


FR1105-2 85.15 IC - CH10
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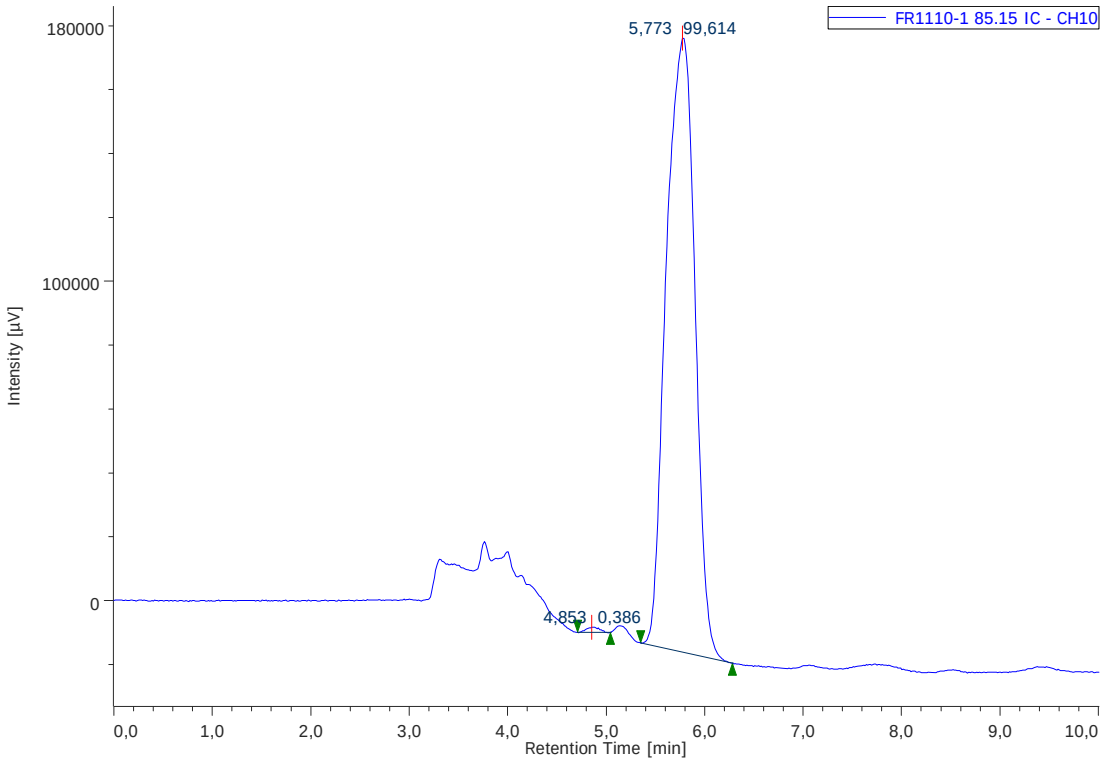
4,973 53,660
Cbz
N
OH
F
N
F3C
O
1.17b (minor)
200000
100000
0
Intensity [µV]
0,0 1,0 2,0 3,0 4,0 5,0 6,0 7,0 8,0 9,0 10,0
Retention Time [min]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5,773 99,614
4,853 0,386
180000
100000
0
Intensity [µV]
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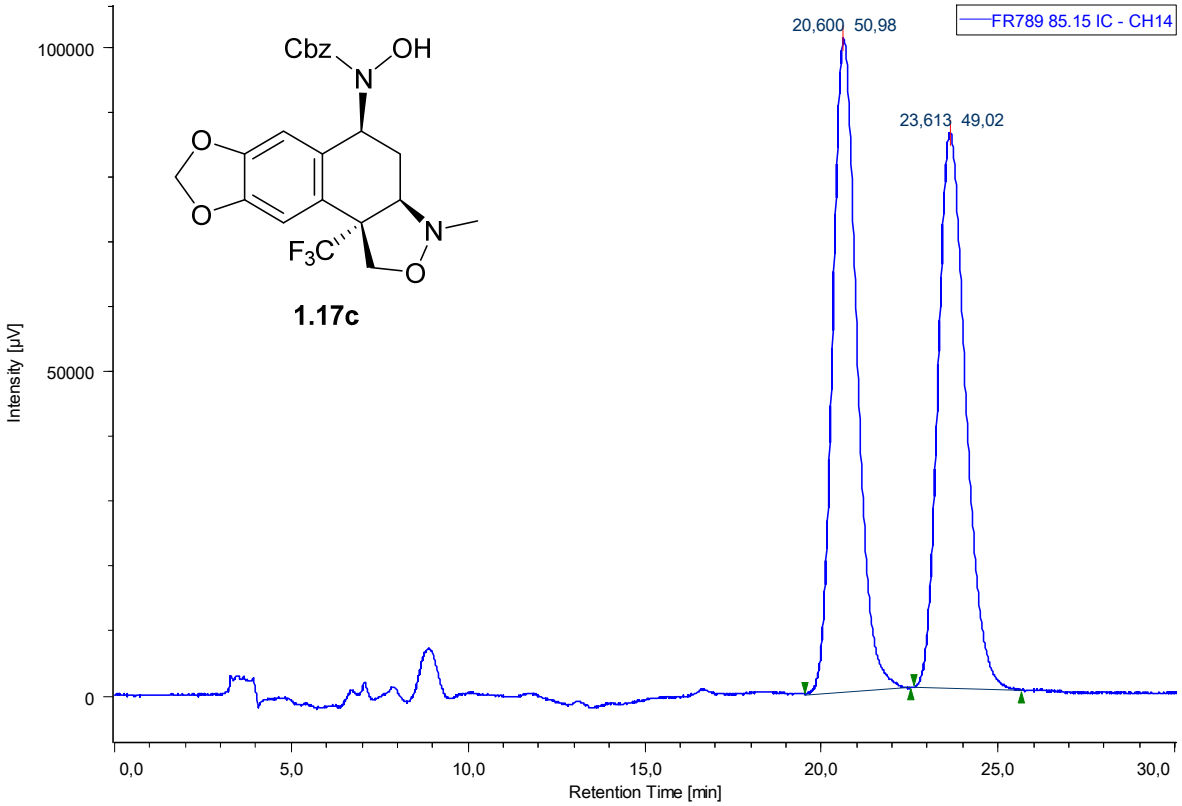
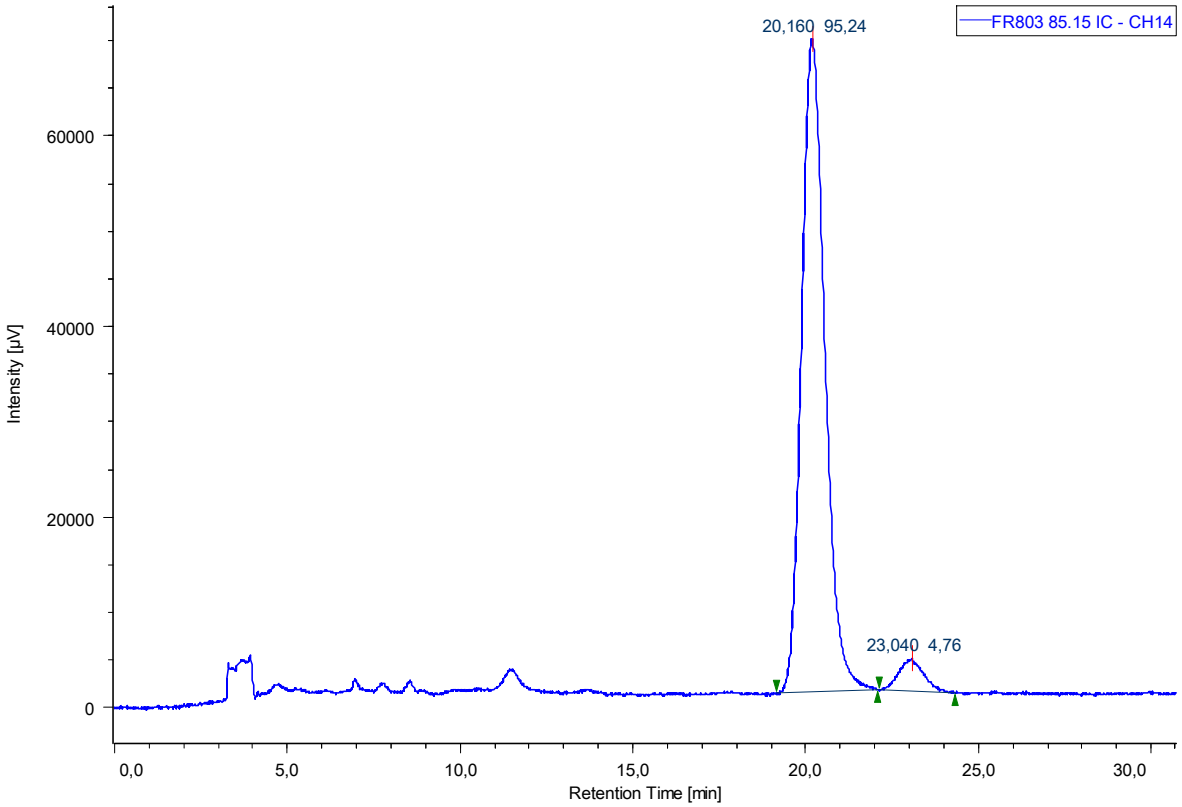
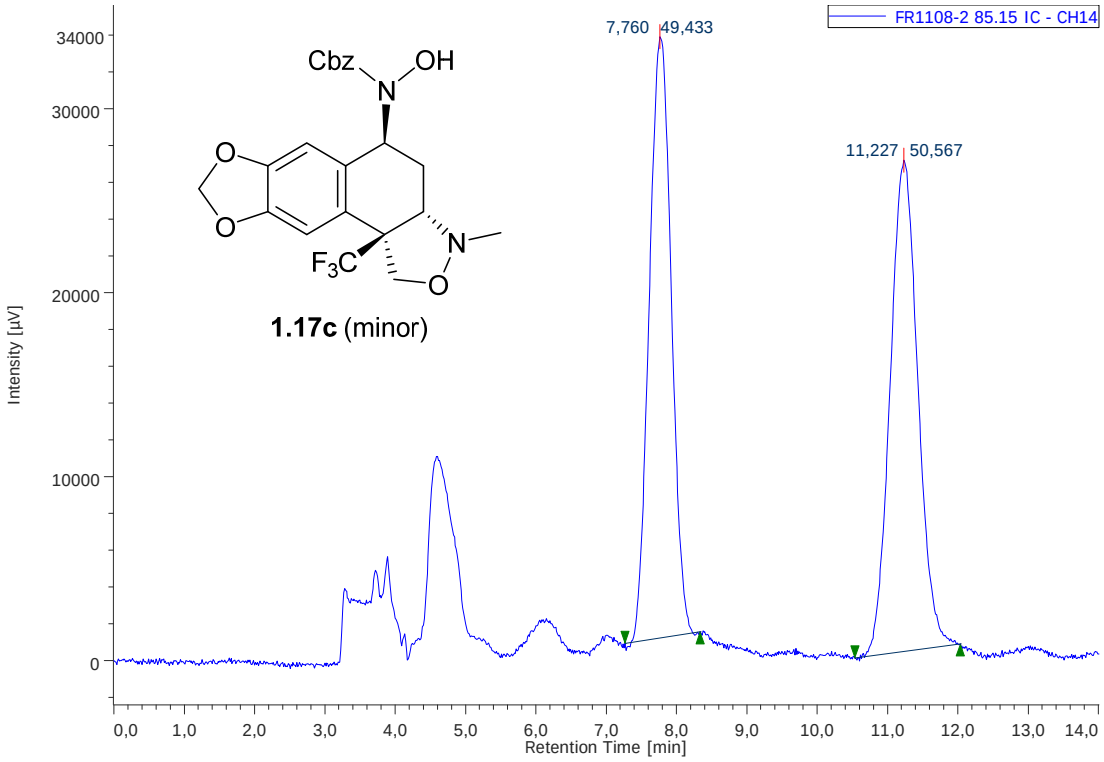
Retention Time [min]


Cbz
OH
N
O
O
N
F3C
O
1.17c
FR789 85.15 IC - CH14
20,600 50,98
23,613 49,02
Intensity [µV]
100000
50000
0
0,0
5,0
10,0
15,0
20,0
25,0
30,0
Retention Time [min]


FR803 85.15 IC - CH14
20,160 95,24
23,040 4,76
Intensity [µV]
60000
40000
20000
0
0,0
5,0
10,0
15,0
20,0
25,0
30,0
Retention Time [min]


FR1108-2 85.15 IC - CH14
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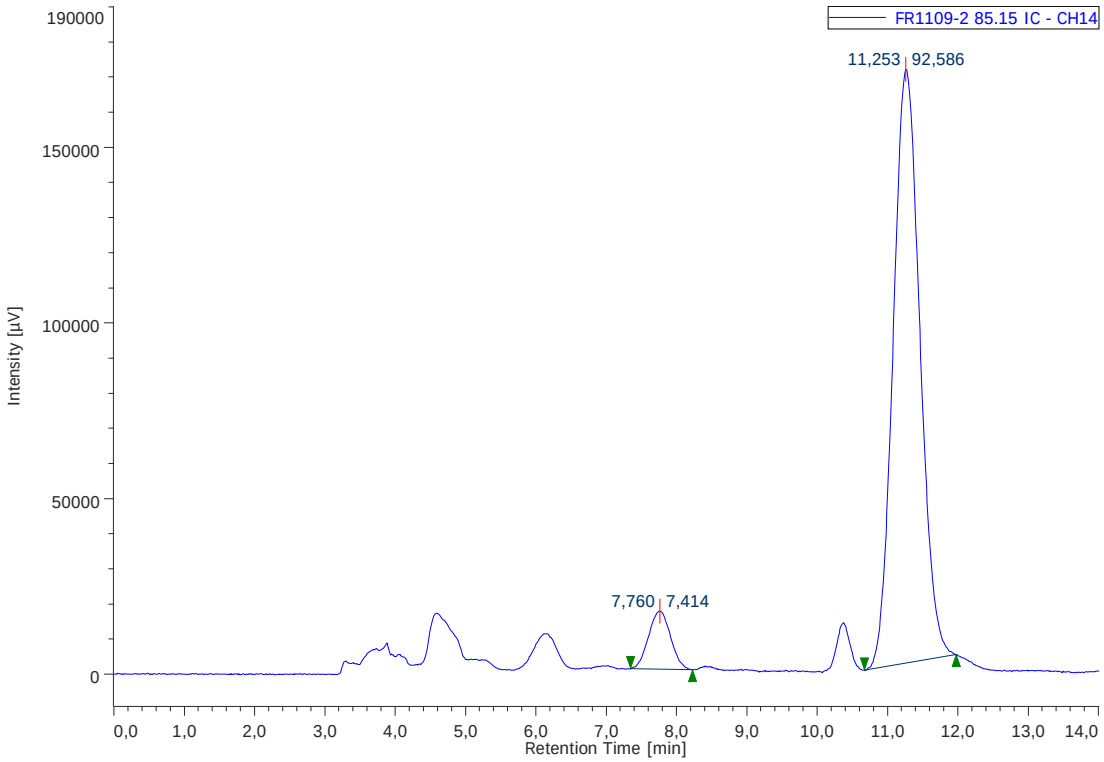
11,227 50,567
Cbz
OH
N
O
O
N
F3C
O
1.17c (minor)
Intensity [µV]
Retention Time [min]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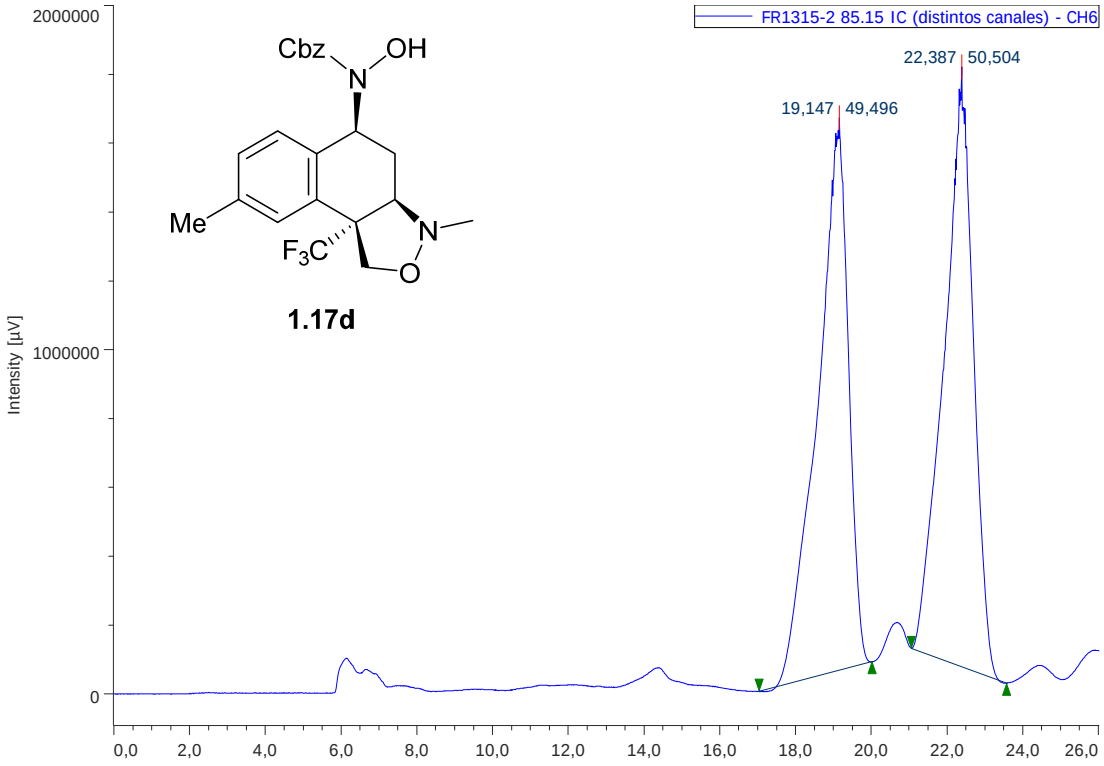
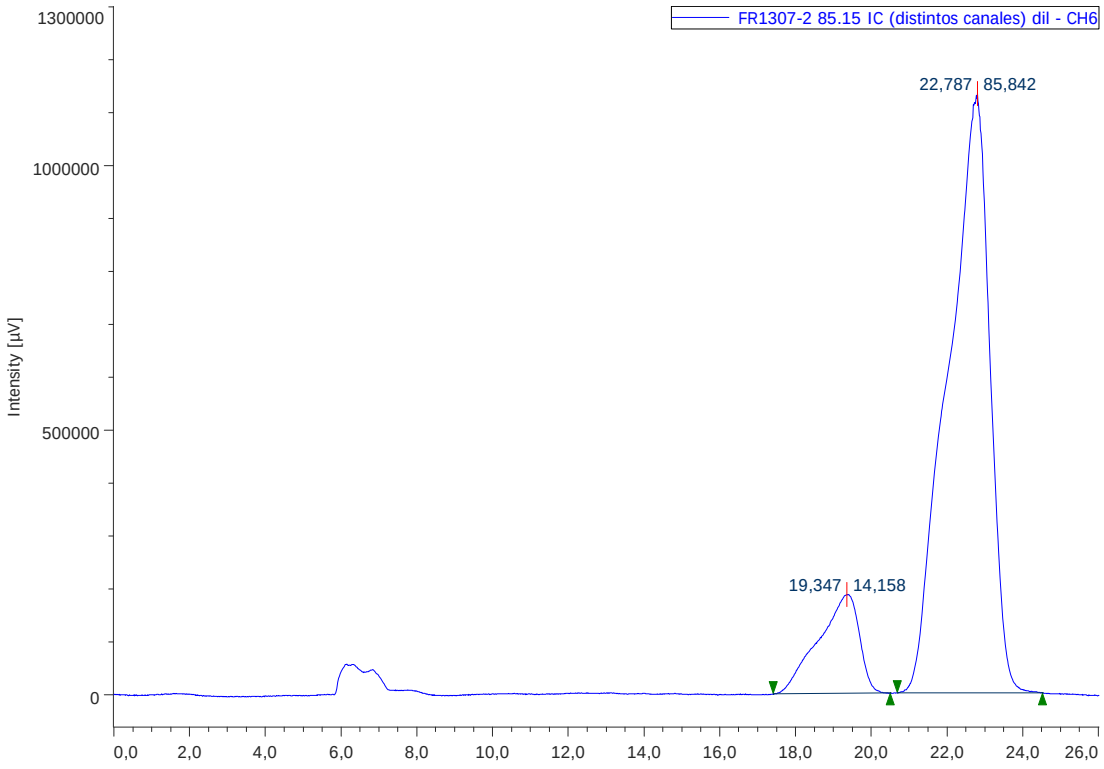
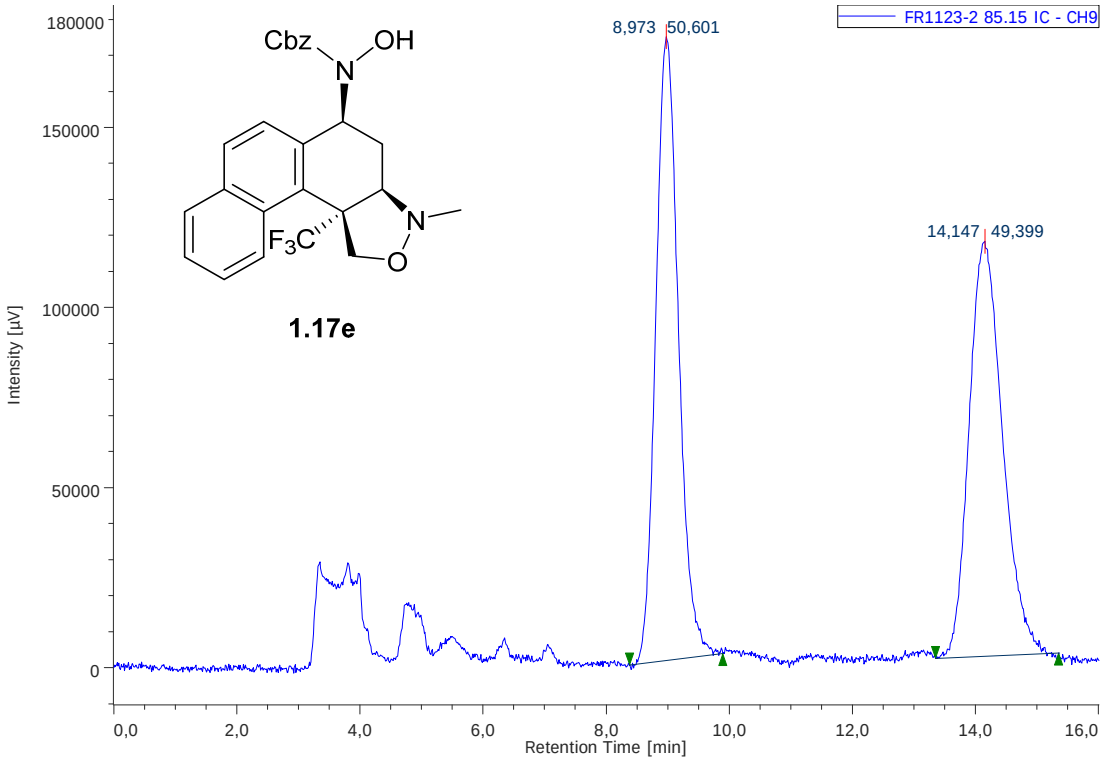
7,760 7,414
Intensity [µV]
Retention Time [min]


FR1315-2 85.15 IC (distintos canales) - CH6
Intensity [µV]
2000000
1000000
0
Cbz
OH
N
Me
F3C
N
O
1.17d
19,147
49,496
22,387
50,504
0,0
2,0
4,0
6,0
8,0
10,0
12,0
14,0
16,0
18,0
20,0
22,0
24,0
26,0


FR1307-2 85.15 IC (distintos canales) dil - CH6
Intensity [µV]
1300000
1000000
500000
0
22,787
85,842
19,347
14,158
0,0
2,0
4,0
6,0
8,0
10,0
12,0
14,0
16,0
18,0
20,0
22,0
24,0
26,0


FR1123-2 85.15 IC - CH9
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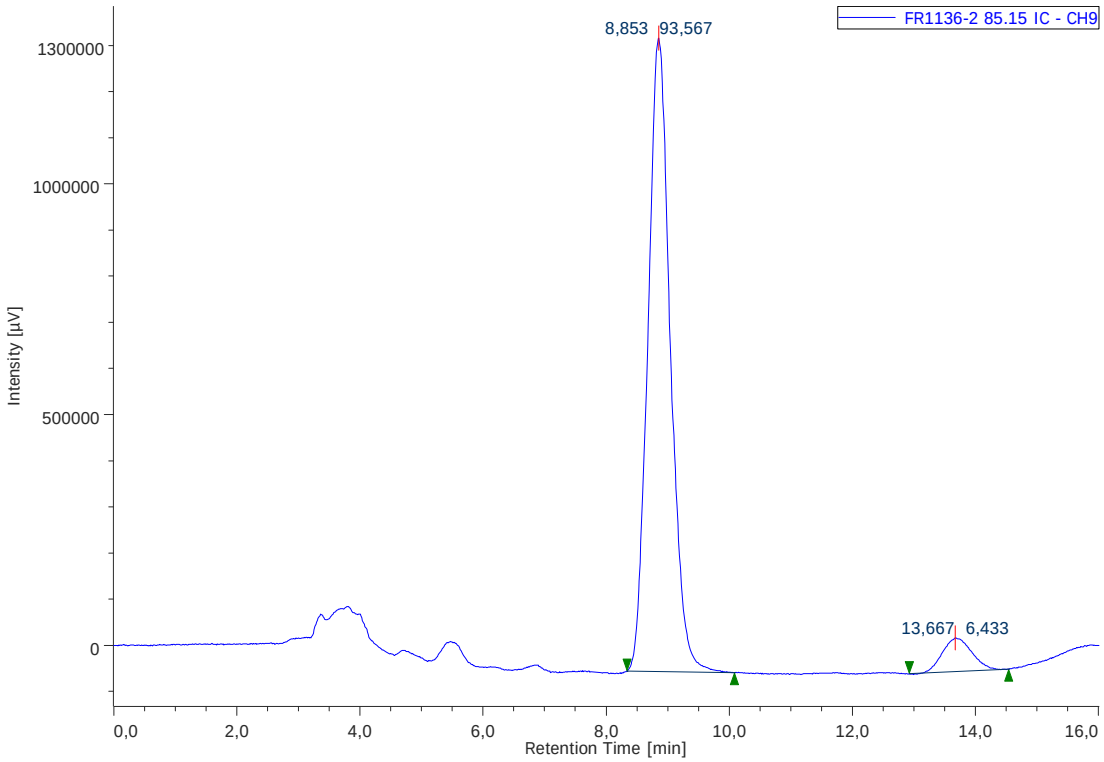
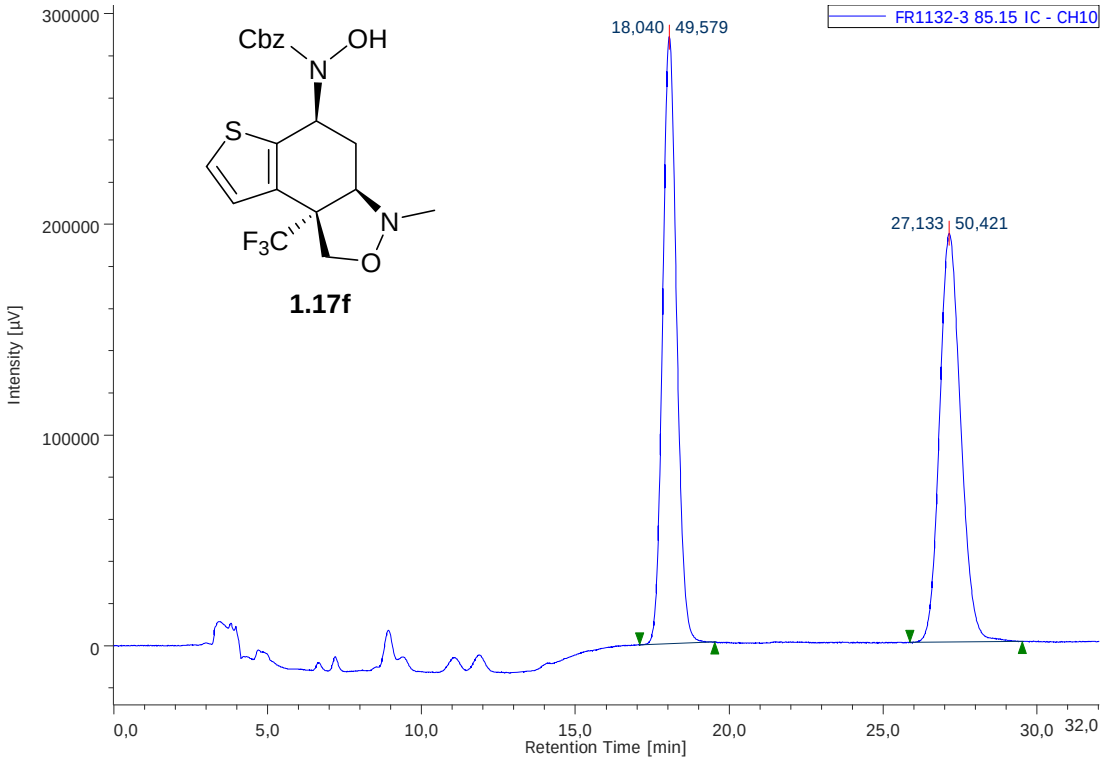
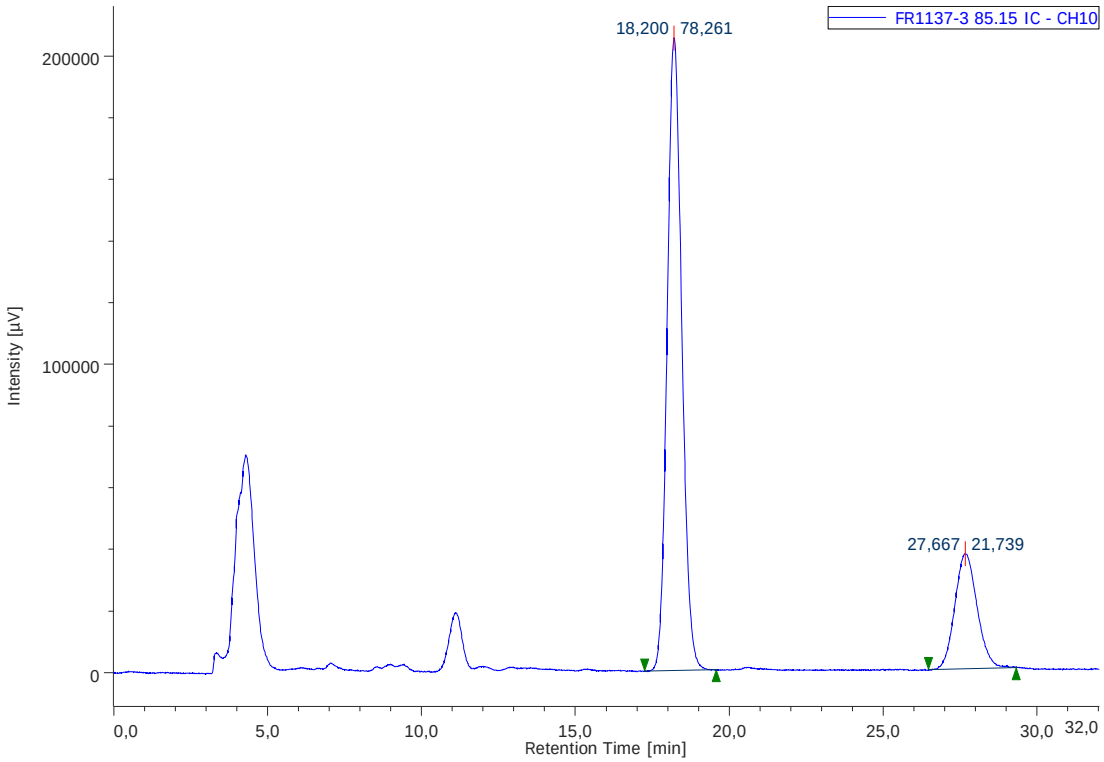
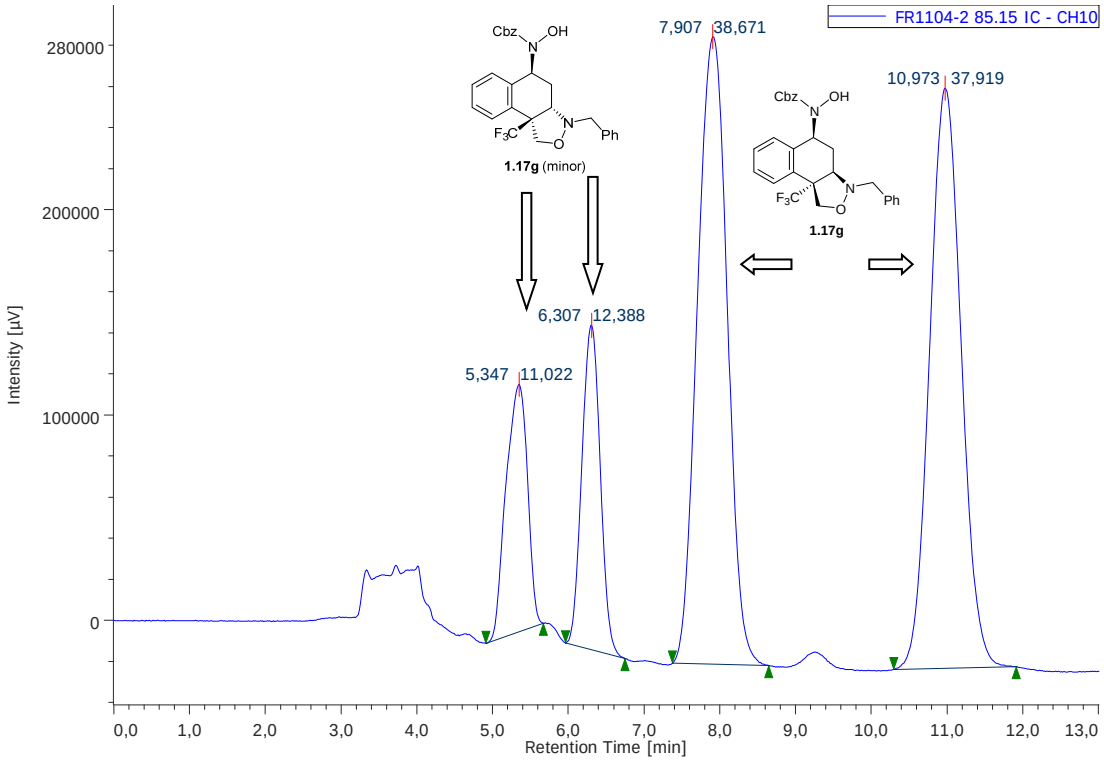
14,147 49,399
Cbz
OH
N
N
O
F3C
1.17e
Intensity [µV]
Retention Time [min]


FR1136-2 85.15 IC - CH9
8,853 93,567
13,667 6,433
Intensity [µV]
Retention Time [min]


Cbz
OH
N
S
N
O
F3C
1.17f
FR1132-3 85.15 IC - CH10
18,040
49,579
27,133
50,421
Intensity [µV]
300000
200000
100000
0
0,0
5,0
10,0
15,0
20,0
25,0
30,0
32,0
Retention Time [min]


FR1137-3 85.15 IC - CH10
18,200
78,261
27,667
21,739
Intensity [µV]
200000
100000
0
0,0
5,0
10,0
15,0
20,0
25,0
30,0
32,0
Retention Time [min]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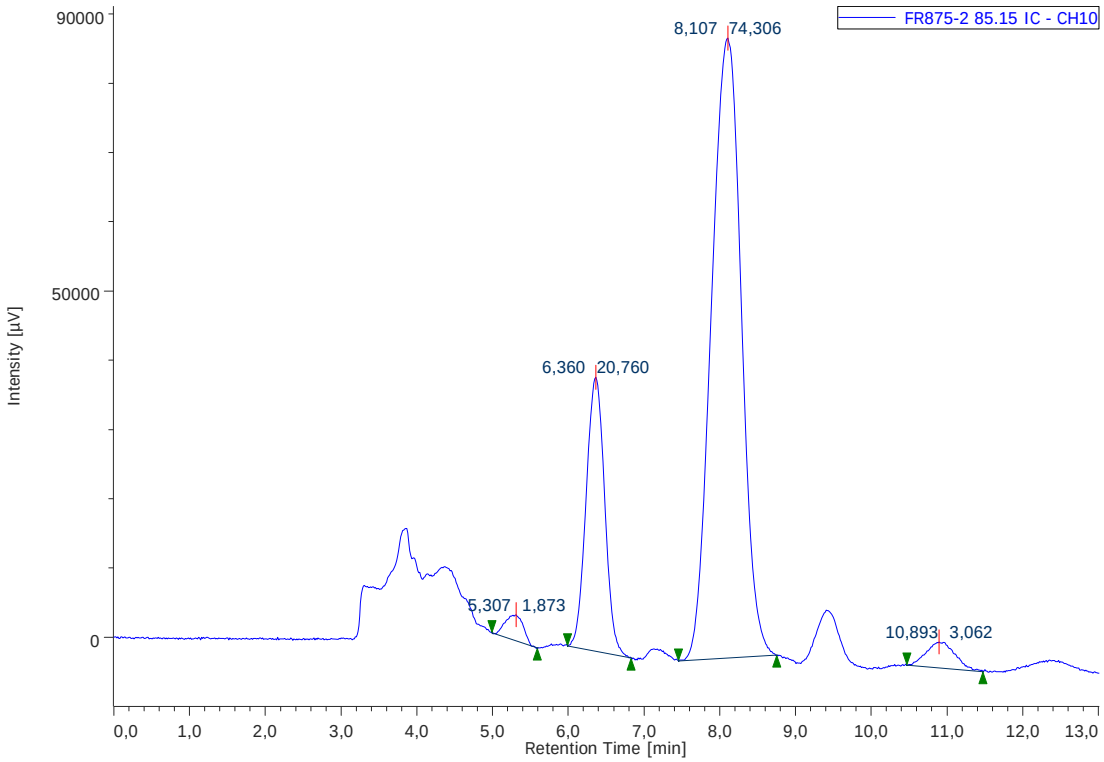
Cbz
OH
N
F3C
O
N
Ph
1.17g (minor)
1.17g
7,907 38,671
10,973 37,919
6,307 12,388
5,347 11,022
280000
200000
100000
0
Intensity [µV]
0,0 1,0 2,0 3,0 4,0 5,0 6,0 7,0 8,0 9,0 10,0 11,0 12,0 13,0
Retention Time [min]


FR875-2 85.15 IC - CH10
8,107 74,306
6,360 20,760
5,307 1,873
10,893 3,062
90000
50000
0
Intensity [µV]
0,0 1,0 2,0 3,0 4,0 5,0 6,0 7,0 8,0 9,0 10,0 11,0 12,0 13,0
Retention Time [min]

1.6.5. Part B: Computational calculations

Computational Details

All of the calculations were performed using the Gaussian09 program.[104] Computations were done using B3LYP functional[105] in conjuction with Grimme's dispersion correction.[106] Standard basis sets def2SVP and def2TZVP were employed.[107] Geometry full optimizations were made at B3LYP-D3BJ/def2SVP level and then single point calculations at B3LYP-D3BJ/def2TZVP level were carried out in order to obtain more accurate values of the energies. Solvent effects (toluene) were considered using the PCM model.[108] The nature of stationary points was defined on the basis of calculations of normal vibrational frequencies (force constant Hessian matrix). The optimizations were carried out using the Berny analytical gradient optimization method.[109] Minimum energy pathways for the reactions studied were found by gradient descent of transition states in the forward and backward direction of the transition vector (IRC analysis),[110] using using the Hratchian-Schlegel algorithm.[111] NCI (non-covalent interactions) were computed using the methodology previously described.[112] Data were obtained with the NCIPLOT program.[113] A density cutoff of ρ=0.2 a.u. was applied and the pictures were created for an isosurface value of s=0.5 and colored in the [-

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[104] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A. Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. J.; Burant, C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. J.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski J.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2009**.

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[107] (a) Weigend, F. *Phys. Chem. Chem. Phys.* **2006**, *8*, 227. (b) Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.*, **2005**, *7*, 3297.

[108] (a) Tomasi J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027. (b) Cossi, M.; Scalmani, G.; Rega N.; Barone, V. *J. Chem. Phys.* **2002**, *117*, 43.

[109] (a) Schlegel, H. B. *J. Comput. Chem.* **1982**, *3*, 214. (b) Schlegel, H. B. In *Modern Electronic Structure Theory*; Yarkony, D. R., Ed.; World Scientific Publishing: Singapore, **1994**.

[110] (a) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363. (b) Fukui, K. *J. Phys. Chem.* **1970**, *74*, 4161.

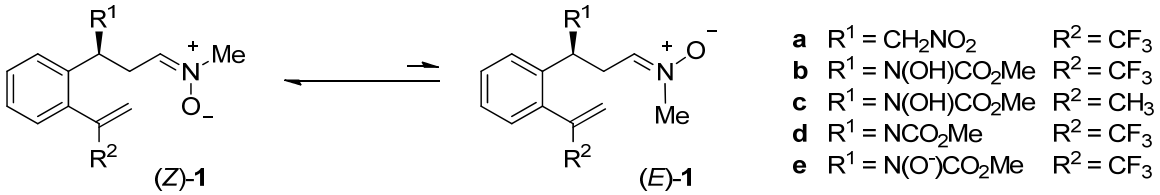
[111] Hratchian, H. P.; Schlegel, H. B. *J. Phys. Chem. A* **2002**, *106*, 165.

[112] (a) Johnson, E. R.; Keinan, S.; Mori-Sanchez, P.; Contreras-Garcia, J.; Cohen, A. J.; Yang, W. *J. Am. Chem. Soc.* **2010**, *132*, 6498. (b) Lane, J. R.; Contreras-Garcia, J.; Piquemal, J.-P.; Miller, B. J.; Kjaergaard, H. G. *J. Chem. Theory Comput.* **2013**, *9*, 3263.

[113] Contreras-Garcia, J.; Johnson, E. R.; Keinan, S.; Chaudret, R.; Piquemal, J.-P.; Beratan, D. N.; Yang, W. *J. Chem. Theory Comput.* **2011**, *7*, 625.

0.02,0.02] a.u. sign(λ_2)ρ range using VMD software.[114] NCI calculations have also shown their utility in studying ionic interactions.[115] Structural representations were generated using CYLView.[116]

Nomenclature. Stationary points are named indicating configuration of starting nitrone (E/Z), approach (n for *endo*, x for *exo*), diastereofaces (*Re/Si,* first for nitrone, second for alkene). TS for transition structure; P for product. Approaches for 3,4 regioisomers are indicated by adding 34. Five series **a-e** have been considered for the reaction illustrated below: First letter in the name indicates the series



Scheme S1.1

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[115] Contreras-García, J.; Calatayud, M.; Piquemal, J.-P.; Recio, J. M. *Comput. Theor. Chemi.* **2012**, *998*, 193.
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$R^1 = CH_2NO_2$ $R^2 = CF_3$ (a series)

Table S1.1 Absolute (hartrees) and relative (kcal/mol) energies (B3LYP-D3BJ/Def2TZVP/PCM=toluene//B3LYP-D3BJ/Def2SVP) corresponding to **a** series

	E(0)	G	im. freq.	ΔE(0)	ΔG
a(Z)-nitrone	-1177.323776	-1177.369917		0.0	0.0
a(E)-nitrone	-1177.309968	-1177.359504		8.7	6.5
aTS01_ZnReSi	**-1177.303891**	**-1177.350278**	**-343.8**	**12.5**	**12.3**
aTS02_ZnSiRe	-1177.299222	-1177.345669	-352.3	15.4	15.2
aTS03_EnSiSi	-1177.292327	-1177.338943	-315.4	19.7	19.4
aTS04_EnReRe	-1177.291717	-1177.337970	-351.2	20.1	20.0
aTS05_ZxReRe	-1177.259917	-1177.306733	-395.9	40.1	39.6
aTS06_ZxSiSi	-1177.263769	-1177.311471	-434.7	37.7	36.7
aTS07_ExSiRe	-1177.287097	-1177.332694	-244.1	23.0	23.4
aTS08_ExReSi	-1177.297562	-1177.344909	-285.3	16.4	15.7
aTS09_34ZnReRe	-1177.287261	-1177.333024	-301.7	22.9	23.2
aTS10_34ZnSiSi	-1177.292828	-1177.339138	-433.0	19.4	19.3
aTS11_34ExReRe	-1177.270798	-1177.317611	-501.9	33.2	32.8
aTS12_34ExSiSi	-1177.268617	-1177.315300	-505.9	34.6	34.3
aP_RR	-1177.349223	-1177.395268		-16.0	-15.9
aP_RS	-1177.335261	-1177.382803		-7.2	-8.1
aP_SR	-1177.340394	-1177.388986		-10.4	-12.0
aP_SS	-1177.351123	-1177.399463		-17.2	-18.5

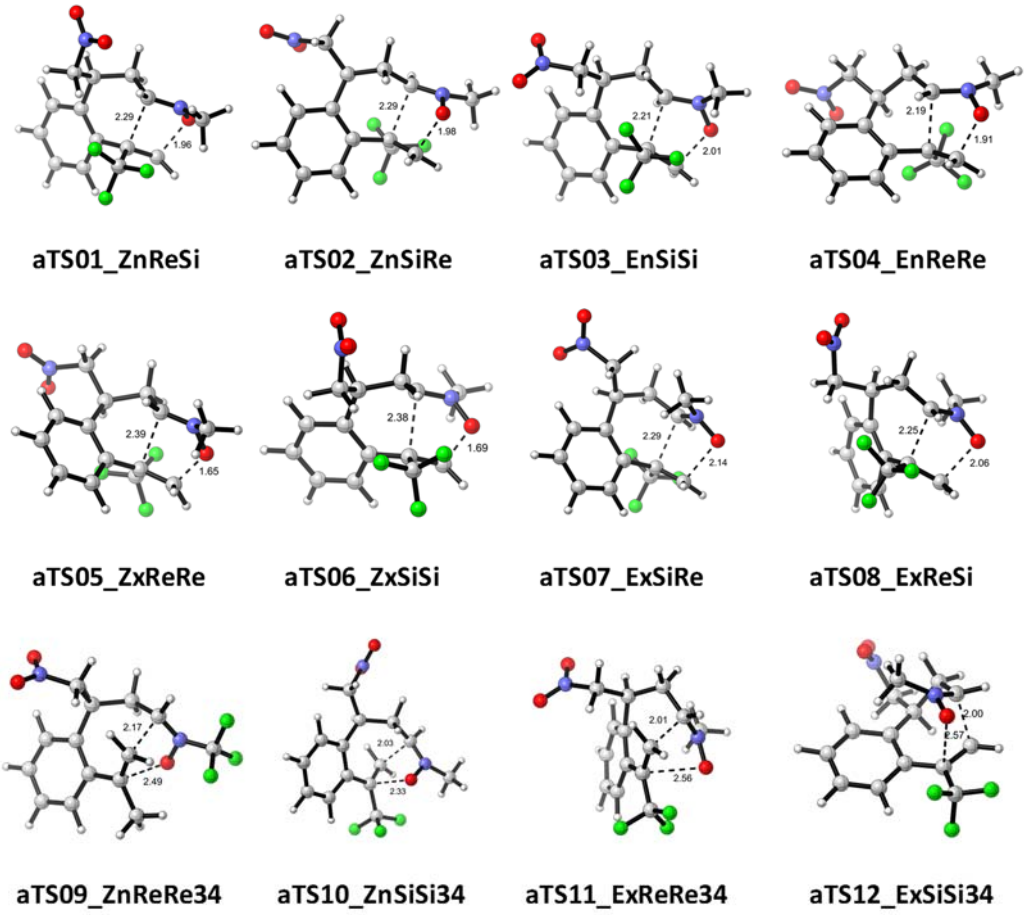


Figure S1.8 Transition structures (B3LYP-D3BJ/Def2SVP) corresponding to **a** series

R^1 = N(OH)CO_2Me R^2 =CF_3 (b series)

Table S1.2 Absolute (hartrees) and relative (kcal/mol) energies (B3LYP-D3BJ/Def2TZVP/PCM=toluene//B3LYP-D3BJ/Def2SVP) corresponding to **b** series

	E(0)	G	im. freq.	ΔE(0)	ΔG
b(Z)-nitrone	-1291.931782	-1291.984597		0.0	0.0
b(E)-nitrone	-1291.924493	-1291.977444		4.6	4.5
bTS01_ZnReSi	-1291.905026	-1291.954444	-337.3	16.8	18.9
bTS02_ZnSiRe	**-1291.905911**	**-1291.955483**	**-354.5**	**16.2**	**18.3**
bTS02_ZnSiRe_H1	-1291.902120	-1291.950976	-367.4	18.6	21.1
bTS03_EnSiSi	-1291.893679	-1291.941277	-318.3	23.9	27.2
bTS04_EnReRe	-1291.896981	-1291.946084	-301.5	21.8	24.2
bTS05_ZxReRe	-1291.870748	-1291.920557	-420.0	38.3	40.2
bTS06_ZxSiSi	-1291.863226	-1291.912298	-402.4	43.0	45.4
bTS07_ExSiRe	-1291.893943	-1291.942463	-287.9	23.7	26.4
bTS08_ExReSi	-1291.898982	-1291.947749	-310.4	20.6	23.1
bTS09_34ZnReRe	-1291.890983	-1291.941214	-316.7	25.6	27.2
bTS10_34ZnSiSi	-1291.894480	-1291.943365	-409.9	23.4	25.9
bTS11_34ExReRe	-1291.875258	-1291.924527	-484.7	35.5	37.7
bTS12_34ExSiSi	-1291.875873	-1291.925026	-505.3	35.1	37.4
bP_RR	-1291.954917	-1292.003366		-14.5	-11.8
bP_RS	-1291.940918	-1291.990579		-5.7	-3.8
bP_SR	-1291.937747	-1291.986885		-3.7	-1.4

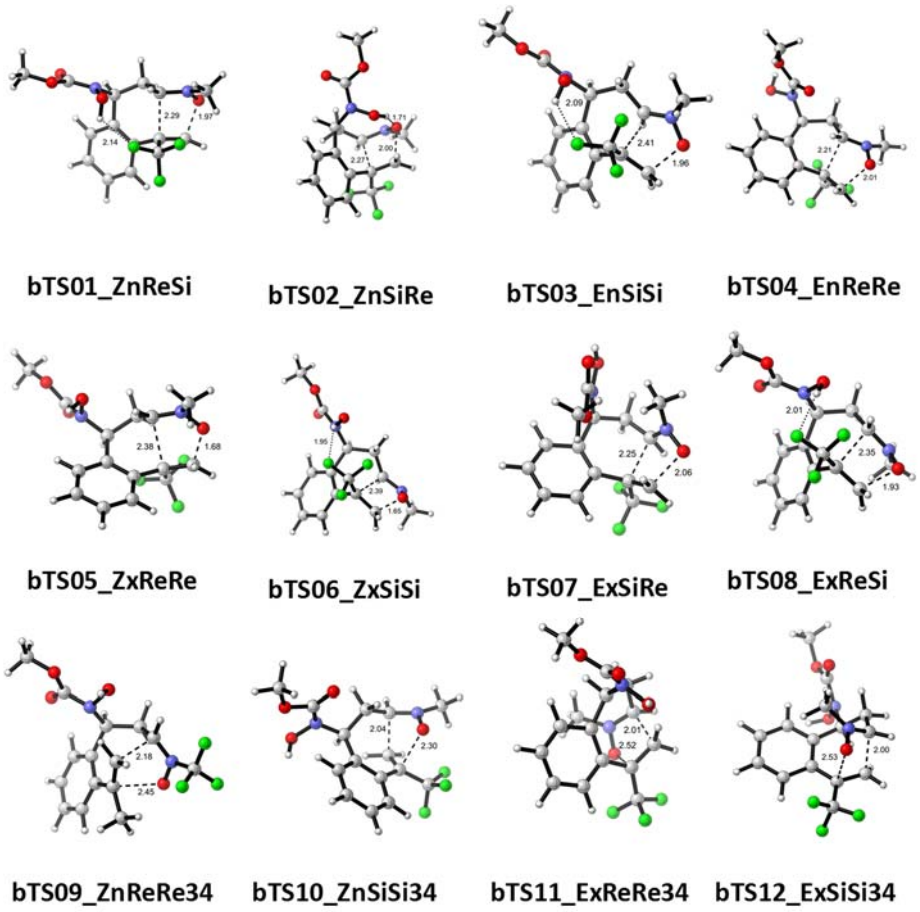


Figure S1.9 Transition structures (B3LYP-D3BJ/Def2SVP) corresponding to **b** series

R^1 = N(OH)CO_2Me R^2 =CH_3 (c series)

Table S3. Absolute (hartrees) and relative (kcal/mol) energies (B3LYP-D3BJ/Def2TZVP/PCM=toluene//B3LYP-D3BJ/Def2SVP) corresponding to **c** series

	E(0)	G	im. freq	ΔE(0)	ΔG
c(Z)-nitrone	-994.043588	-994.094071		8.4	6.5
c(E)-nitrone	-994.056974	-994.104393		0.0	0.0
cTS01_ZnReSi	**-994.012235**	**-994.058012**	**-406.5**	**28.1**	**29.1**
cTS02_ZnSiRe	-993.969827	-994.015290	-402.8	54.7	55.9
cTS03_EnSiSi	-994.008522	-994.054461	-381.0	30.4	31.3
cTS04_EnReRe	-994.005188	-994.050822	-371.7	32.5	33.6
cTS05_ZxReRe	-993.939881	-993.984945	-483.4	73.5	75.0
cTS06_ZxSiSi	-993.944551	-993.989901	-485.5	70.5	71.8
cTS07_ExSiRe	-993.961246	-994.009436	-358.8	60.1	59.6
cTS08_ExReSi	-993.974932	-994.020741	-382.3	51.5	52.5
cTS09_34ZnReRe	-994.006038	-994.051514	-379.3	32.0	33.2
cTS10_34ZnSiSi	-994.006449	-994.051743	-387.9	31.7	33.0
cTS11_34ExReRe	-993.987618	-994.033689	-477.8	43.5	44.4
cTS12_34ExSiSi	-993.988277	-994.033851	-510.7	43.1	44.3
cP_RR	-994.065059	-994.110922		-5.1	-4.1
cP_RS	-994.038017	-994.081579		11.9	14.3
cP_SR	-994.049926	-994.097055		4.4	4.6
cP_SS	-994.063304	-994.109079		-4.0	-2.9

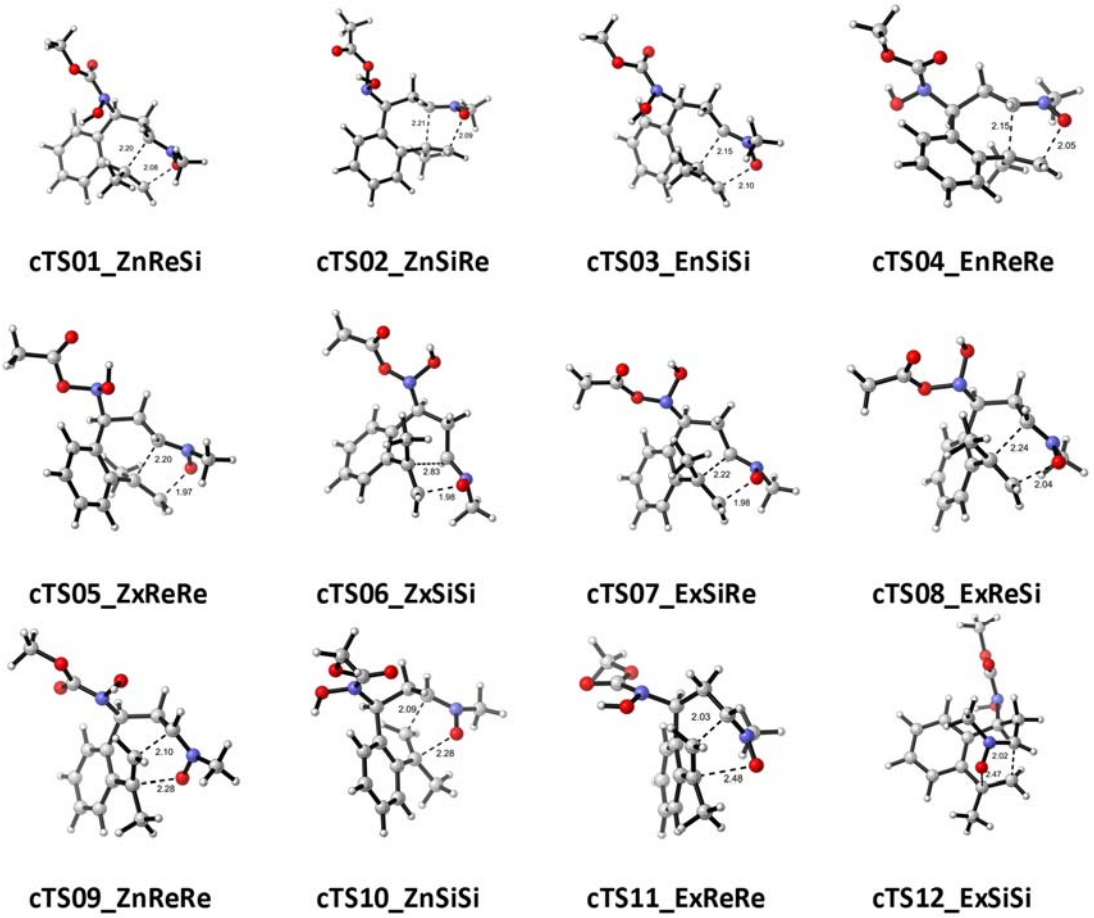


Figure S1.10 Transition structures (B3LYP-D3BJ/Def2SVP) corresponding to **c** series

R = $NHCO_2Me$ (d series). Model Verification

In order to verify that the diastereofacial inversion was due to the exclusive presence of the hydroxyamino group, calculations were carried out with R = NHCOOMe (**d** series). In this case, the same diastereomeric preference by a (*Z*)-*Re,Si-endo* approach that was found for R = CH_2NO_2 was observed confirming that it is the additional OH group the responsible of the above-mentioned interactions responsible of the diastereofacial inversion.In addition, the preferred (*Z*)-*Re,Si-endo* approach showed a NH··F interaction between the NH and CF_3 groups.

Table S1.4 Absolute (hartrees) and relative (kcal/mol) energies (B3LYP-D3BJ/Def2TZVP/PCM=toluene//B3LYP-D3BJ/Def2SVP) corresponding to **d** series

	E(0)	G	im. freq.	ΔE(0)	ΔG
d(Z)-nitrone	-1216.746538	-1216.796742		0.0	0.0
d(E)-nitrone	-1216.738490	-1216.788588		5.1	5.1
dTS01_ZnReSi	**-1216.718960**	**-1216.766874**	**-314.2**	**17.3**	**18.7**
dTS02_ZnSiRe	-1216.717313	-1216.765410	-314.6	18.3	19.7
dTS03_EnSiSi	-1216.709979	-1216.758083	-274.5	22.9	24.3
dTS04_EnReRe	-1216.706933	-1216.754518	-248.3	24.9	26.5
dTS05_ZxReRe	-1216.679069	-1216.728243	-452.7	42.3	43.0
dTS06_ZxSiSi	-1216.681051	-1216.729384	-469.3	41.1	42.3
dTS07_ExSiRe	-1216.698644	-1216.745738	-232.7	30.1	32.0
dTS08_ExReSi	-1216.699509	-1216.748813	-263.0	29.5	30.1
dP_RR	-1216.766566	-1216.813602		-12.6	-10.6
dP_RS	-1216.767028	-1216.814579		-12.9	-11.2
dP_SR	-1216.750772	-1216.798398		-2.7	-1.0
dP_SS	-1216.745837	-1216.793109		0.4	2.3

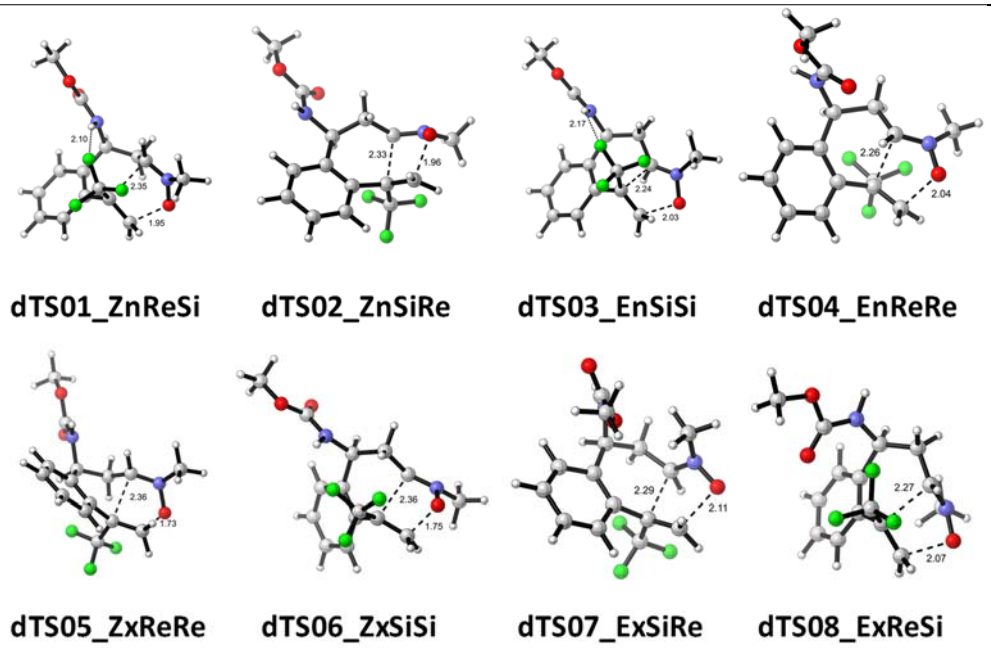
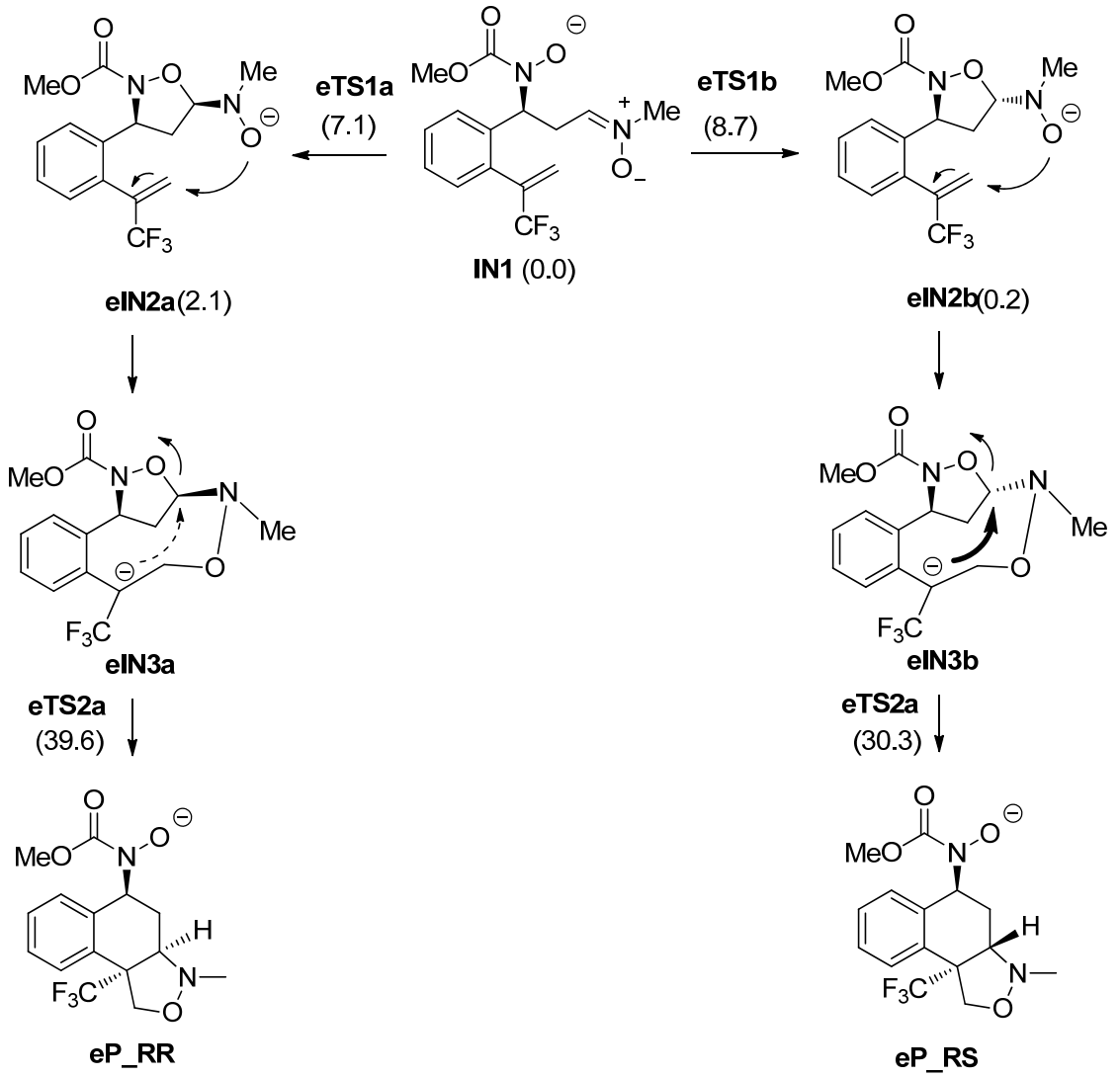


Figure S1.11 Transition structures (B3LYP-D3BJ/Def2SVP) corresponding to **d** series

R = N(O$^-$)CO$_2$Me (e series). Alternative route

In the case of **b** series, the presence of the N(OH) moiety promotes the formation of stable cyclic hydroxylamines as reported in the literature (Scheme S1.2).[117] The reaction is carried out in the presence of sodium bicarbonate so, it should be plausible that a Michael addition of the corresponding hydroxyamino anion take place over the electron-poor double bond. Under these conditions, a further attack of the resulting anion would furnish the final product.



Scheme S1.2 Alternative route.

Preliminary calculations at B3LYP-D3BJ/Def2SVP level showed high barriers (39.6 and 30.3 kcal/mol for the two diastereomeric channels) for the rate-limiting step of the process, *i.e.* the final cyclization to give the final adduct. We also calculated the possibility of direct 1,3-dipolar cycloaddition of the anionic

[117] Merchan, F.L.; Merino, P.; Tejero, T. *Glycoconjugate J.* **1997**, *14*, 497.

intermediate **IN1** to give the corresponding adducts. In that case, the preferred approach was (*Z)-Re,Si-endo* also with a higher barrier (27.9 kcal/mol) than that found for the neutral form (15.3 kcal/mol). Consequently, given a difference of ca. 15 kcal/mol with the previously found approaches based on 1,3-dipolar cycloadditions, the anionic form in both open-chain 1,3-dipolar cycloaddition and hydroxylamino Michael addition were definitively ruled out.

Table S1.5 Absolute (hartrees) and relative (kcal/mol) energies (B3LYP-D3BJ/Def2SVP) corresponding to **e** series

	E(0)	G	im. freq	ΔE(0)	ΔG
e(Z)IN1	-1290.262458	-1290.316460		0.0	0.0
e(E)IN1	-1290.248916	-1290.303244		8.6	8.3
eIN2a	-1290.263214	-1290.313134		-1.3	2.1
eIN2b	-1290.265542	-1290.316217		-2.9	0.2
eIN3a	-1290.264437	-1290.314068		-2.6	1.5
eIN3b	-1290.235373	-1290.285034		15.7	19.7
eIN4a	-1290.298853	-1290.348305		-24.1	-20.0
eIN4b	-1290.295454	-1290.344678		-22.0	-17.7
eTS1a	-1290.253493	-1290.305184	-122.8	5.1	7.1
eTS1b	-1290.252157	-1290.302557	-174.8	5.6	8.7
eTS2a	-1290.205539	-1290.253387	-286.9	34.0	39.6
eTS2b	-1290.218810	-1290.268153	-385.7	26.1	30.3

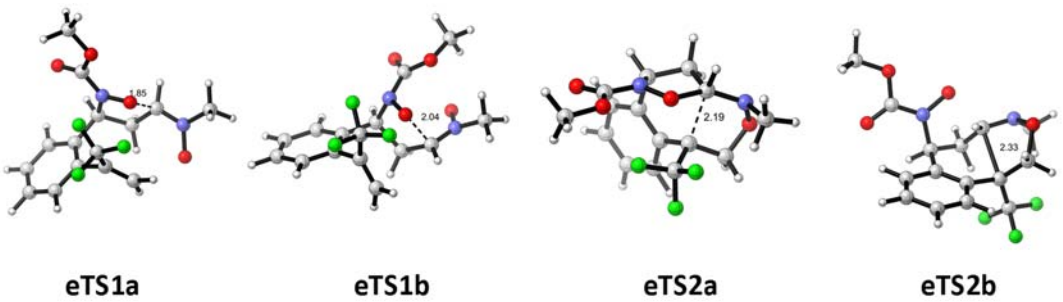


Figure S1.12 Transition structures (B3LYP-D3BJ/Def2SVP) corresponding to **e** series

Chapter 2

Asymmetric Synthesis of Polycyclic 3-Fluoroalkylproline Derivatives by Intramolecular Azomethine Ylide Cycloaddition

2.1. Introduction

2.1.1. Particularities of Azomethine Ylide Cycloadditions

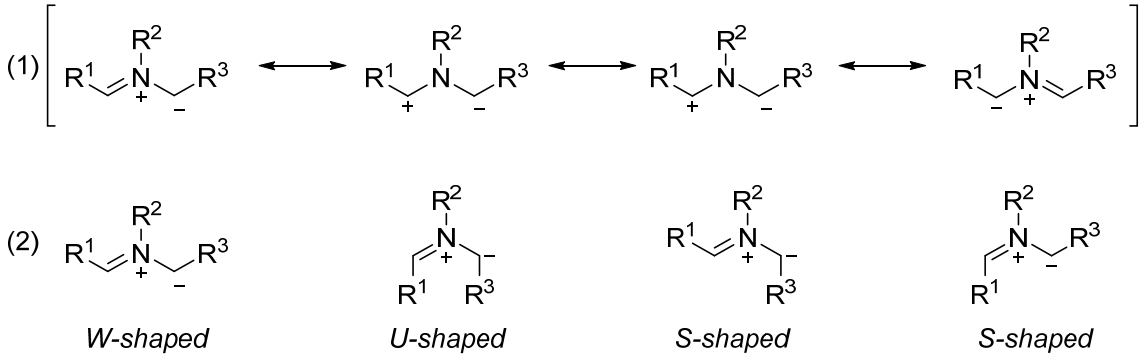
Azomethine ylides (AMY), together with nitrones, are probably the most widely used types of dipoles. By virtue of their utility for the construction of pyrrolidines, dihydropyrroles and pyrroles, the 1,3-dipolar cycloaddition of azomethine ylides and alkenes/alkynes has become a reliable and well studied synthetic tool in organic chemistry. If the dipolarophile is an alkene, pyrrolidines are obtained and a maximum of four stereocentres are formed in the course of the cycloaddition. Isolated and fused pyrrolidines are common scaffolds found in many biologically active alkaloids; therefore, these cycloadditions, particularly in their intramolecular version, are used ubiquitously as a synthetic tool for the synthesis of natural products and biologically active compounds.[118]

The general aspects of 1,3-dipolar cycloadditions discussed in Chapter 1 (Section 1.1.1.) are naturally applicable to azomethine ylides and so are the particularities of intramolecular cycloadditions (Section 1.1.3.). In the present section, the focus will be put on the distinctive features of azomethine ylide cycloadditions. Early reviews on the matter, especially the one by Coldham and Hufton, have been a valuable basis for the preparation of this introduction.[119]

Azomethine ylides are *N*-centred allyl-type dipoles with 4π electrons spread over a 3-atom C-N-C unit. Four resonance forms are possible (Scheme 2.1, equation 1), being the most contributing (and frequent representation) the ones in which the nitrogen atom bears a positive charge and the negative charge is placed on one of the carbon atoms (normally due to an electron-withdrawing substituent on this same atom). Recalling nitrones, existing as configurational *E* and *Z* isomers of the C-N double bond, also azomethine ylides can present four different shapes,

[118] For some representative reviews, see: (a) Fang, X.; Wang, C.-J. *Org. Biomol. Chem.* **2018**, *16*, 2591. (b) Arrastia, I.; Arrieta, A.; Cossio, F. P. *Eur. J. Org. Chem.* **2018**, 5889. (c) Pandey, G.; Day, D.; Tiwary, S. K. *Tetrahedron Lett.* **2017**, *58*, 699. (d) Nayaran, R.; Potowski, M.; Jia, Z.-J.; Antonchick, A. P.; Waldmann, H. *Acc. Chem. Res.* **2014**, *47*, 1296.
[119] (a) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (b) Nájera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105. (c) Ref. 27f. (d) Ref. 14c.

depending on the relative position of the carbon substituents (Scheme 2.1, equation 2).

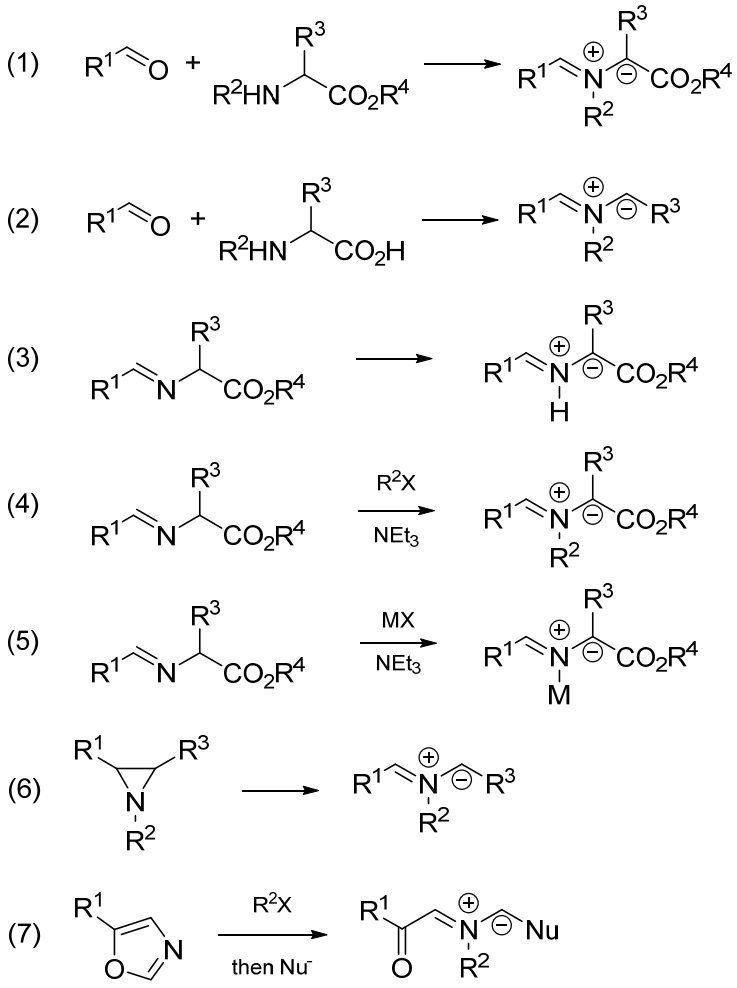


Scheme 2.1

Regarding the FMO theory, azomethine ylides can be regarded as electron-rich dipoles and the dominant interaction should generally be $HOMO_{dipole}$-$LUMO_{dipolarophile}$, especially when dipolarophiles are electron-poor alkenes. However, in intramolecular reactions, the preferred FMO interaction is not necessarily obvious since the entropy factor makes also unactivated alkenes suitable for this transformation and steric constraints may invert the predicted reactivity.

Regioselectivity of AMY cycloadditions is a result of electronic (FMO) and steric effects, being the latter the dominant factor in intramolecular reactions and responsible for high levels of selectivity. In addition, especially in the azomethine ylide/alkene cycloaddition generating up to four new chiral centres, many (up to 16) stereoisomers are conceivable. Azomethine ylides can isomerise in the course of the reaction and give rise to mixtures of products. The reaction outcome depends on the extent to which each ylide geometry imposes itself over the others. W- and U-shaped azomethine ylides result in 2,5-*cis*-disubstituted pyrrolidines, while S-shaped ylides render the corresponding *trans*-products. As the reaction is stereospecific, the configuration of the dipolarophile is maintained in the final product, *cis*-olefins resulting in 3,4-*cis*-pyrrolidines and *trans*-olefins resulting in 3,4-*trans*-pyrrolidines. On top of these factors, there is the *exo/endo* isomery whereby a different product is formed depending on the position of the substituents of the alkene in its approach to the azomethine ylide. The general preference is for the obtention of the *endo* isomer.

Several methods exist for AMY generation (Scheme 2.2) and they have in common that the dipole has to be generated *in situ* for the subsequent cycloaddition.



Scheme 2.2

By far, the most popular strategy employs an aldehyde precursor which upon condensation with a secondary amine renders an iminium ion that is deprotonated (in the case of secondary α-amino esters,[120] Scheme 2.2, equation 1) or decarboxylates (in the case of α-amino acids,[121] Scheme 2.2, equation 2). This

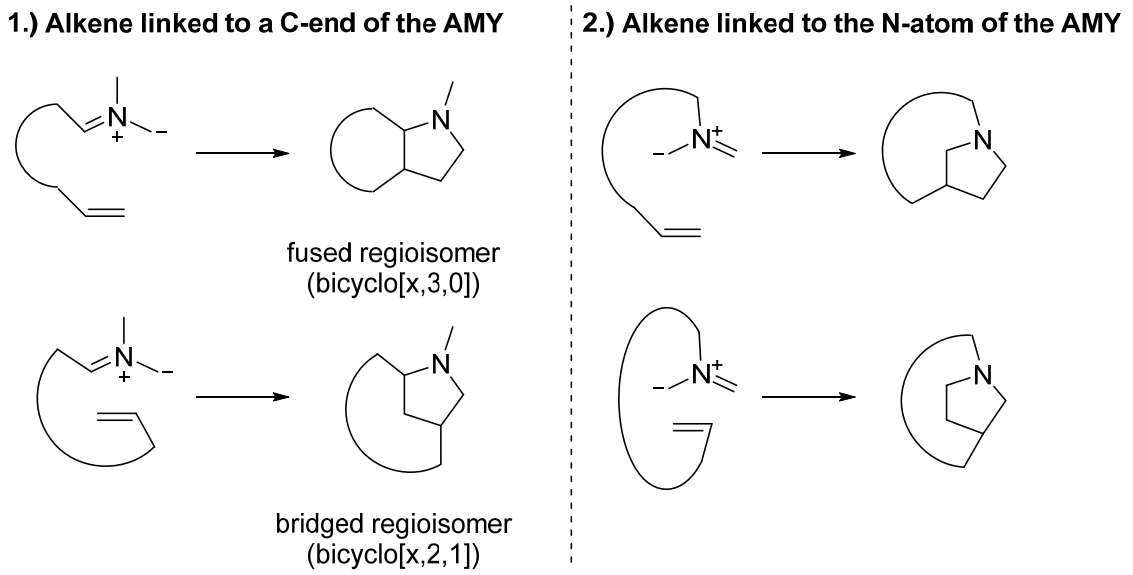
[120] (a) Harwood, L. M.; Vickers R. J. In: *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: Padwa, A.; Pearson, W. H.), Wiley, New York, **2003**, p. 169. (b) Tsuge, O.; Kanemasa, S. In: *Advances in Heterocyclic Chemistry* (Ed.: Katritzky, A.), Academic Press, London, **1989**, Vol. 45, p. 231. (c) Lown, J. W. In: *1,3-Dipolar Cycloaddition Chemistry*, (Ed.Padwa, A.), Wiley, New York, **1984**, Vol. 1, p. 653.

[121] See for example the work by Grigg *et al.*: (a) Ardill, H.; Grigg, R.; Sridharan, V.; Surendrakumar, S. *Tetrahedron* **1988**, *44*, 4953. (b) Grigg, R.; Thianpatanagul, S. *J. Chem.*

method of preparation is commonly referred to as the *iminium route*. Other possible methods include prototropy (Scheme 2.2, equation 3),[122] alkylation (Scheme 2.2, equation 4)[123] or metalation (Scheme 2.2, equation 5)[124] of imines, thermal/light-induced ring-opening of aziridines (Scheme 2.2, equation 6)[125] and the use of other heterocyclic compounds such as 4-oxazolines (Scheme 2.2, equation 7)[126] can be found in the literature. Depending on the synthetic strategy applied, stabilised or unstabilised ylides are obtained; this distinction serves as a further criterion for classification in the literature.

2.1.2. Intramolecular Azomethine Ylide Cycloadditions

As for intramolecular cycloadditions, two possibilities exist for the way in which the azomethine ylide is linked to the dipolarophile (Scheme 2.3).



Scheme 2.3

Soc., Chem. Commun. **1984**, 180. (c) Grigg, R.; Aly, M. F.; Sridharan, V.; Thianpatanagul, S. *J. Chem. Soc., Chem. Commun.* **1984**, 182.

[122] Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89.

[123] For an early example, see: Deyrup, C. L.; Deyrup, J. A.; Hamilton, M. *Tetrahedron Lett.***1977**, 3437.

[124] Kanemasa, S.; Tsuge, O. In: *Advances in Cycloaddition* (Ed.: Curran, D. P.), JAI Press, Greenwich, CN, **1993**, Vol. 3, p. 99.

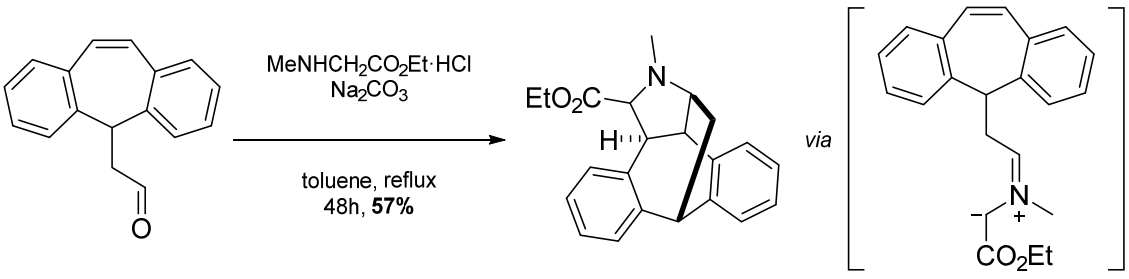
[125] For an early example, see: Heine, H. W.; Peavy, R. *Tetrahedron Lett.* **1965**, 3123.

[126] For an early example, see: Vedejs, E.; Dax, S. L. *Tetrahedron Lett.* **1989**, *30*, 2627.

If the linker chain is connected to one carbon atom of the dipole, fused bicylic products are obtained (although a bridged product is possible if the tether is sufficiently long), while bridged products arise from a substrate in which the linker chain ends in the nitrogen of the ylide. In the former case, the obtained pyrrolidines frequently show a *cis*-configuration at the ring junction. In general, high levels of regio- and stereoselectivity are attained as a result of the limited degree of spatial freedom.

Again, as in the case of INCR (Section 1.1.3.), the literature on intramolecular azomethine ylide cycloaddition is so vast that only a selection of examples can be presented here. The chosen references should give an idea of the synthetic utility of this methodology. For the sake of clarity and conciseness, only examples employing the iminium route will be included in this introduction.

The first reported example of the use of the iminium route (by Confalone *et al.*) involved the condensation of an aldehyde precursor linked to the dipolarophile with *N*-methyl glycine ethyl ester (sarcosine ethyl ester) (Scheme 2.4).[127] In the presence of the dipolarophile as in intramolecular reactions, the dipole is not isolated, but reacts *in situ*. The ester group is the most frequent anion-stabilising group present in stabilised ylides.

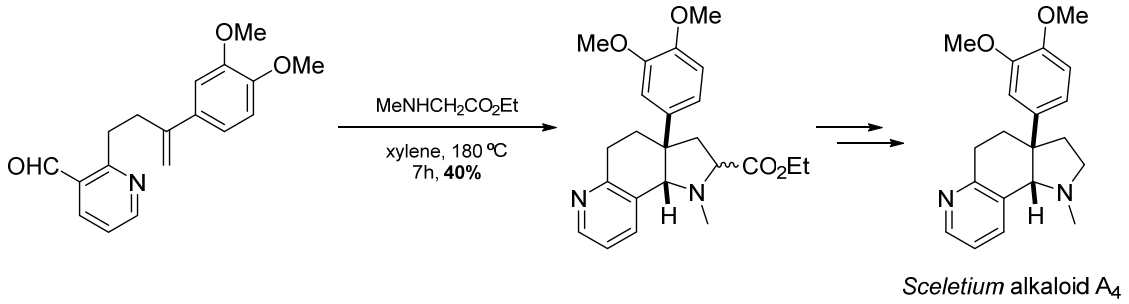


Scheme 2.4

The same authors recognised the potential of this methodology for the stereoselective synthesis of polycyclic natural products, which they soon illustrated in the racemic total synthesis of *Sceletium* alkaloid A_4 (Scheme 2.5).[128] Intramolecular cycloaddition of a conveniently functionalised benzaldehyde leads to a tricyclic product bearing a quaternary stereocentre. Hydrolysis and

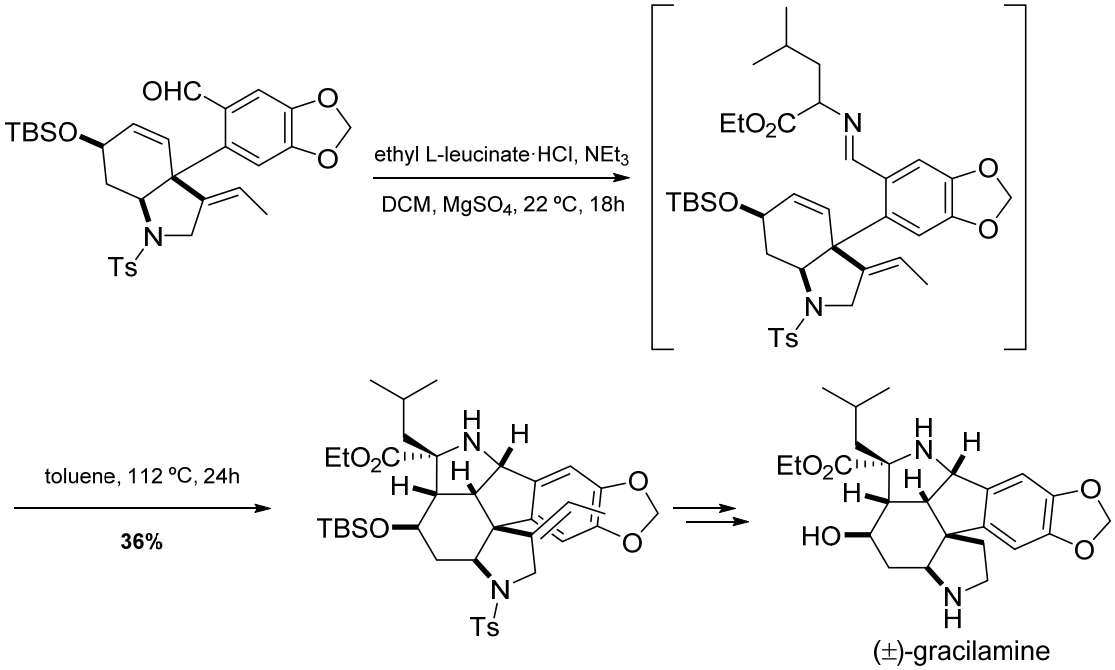
[127] Confalone, P. N.; Huie, E. M. *J. Org. Chem.* **1983**, *48*, 2994.
[128] Confalone, P. N.; Huie, E. M. *J. Am. Chem. Soc.* **1984**, *106*, 7175.

decarboxylation of the ester moiety of this cycloadduct renders the natural product.



Scheme 2.5

Since the seminal work by Confalone, the strategy based on AMY generation and subsequent intramolecular cycloaddition has become a valuable tool for the synthesis of complex natural products. Just to give a recent example, Banwell *et al.* reported the racemic total synthesis of pentacyclic alkaloid gracilamine (Scheme 2.6).[129]



Scheme 2.6

An intramolecular AMY cycloaddition on an elaborated substrate was the key step in the synthesis of the natural product as it is responsible for the

[129] Gao, N.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2017**, *19*, 162.

construction of the pentacyclic ABCDE framework and it mimics the biosynthesis of this compound. The corresponding imine of ethyl *L*-leucinate was prepared and isolated. Under refluxing toluene, this imine underwent a prototropic shift rendering the azomethine ylide which then cyclised *in situ* to the necessary cycloadduct in 36% yield. A secondary reaction with the other olefin present in the substrate rendered a second cycloadduct in 32% yield as a subproduct (structure not shown).

2.1.3. Asymmetric approaches in Intramolecular Azomethine Ylide cycloadditions

As already mentioned in Chapter 1, trying to separate the discussion of intramolecular AMY cycloadditions and of asymmetric approaches is extremely difficult (and probably useless in the context of the present investigation), since both strategies are frequently combined for the synthesis of enantiopure polycyclic compounds. Regarding the asymmetric version of these reactions,[130] the more traditional use of chiral non-racemic substrates on the side of the dipole or dipolarophile[131] is still a reliable and useful method in many cases. In fact, in view of the scarcity of catalytic asymmetric examples of the intramolecular version of this kind of reactions, it is *the* method of reference. To the best of our knowledge, only three examples (listed next) are reported of a catalytic enantioselective intramolecular AMY cycloaddition.

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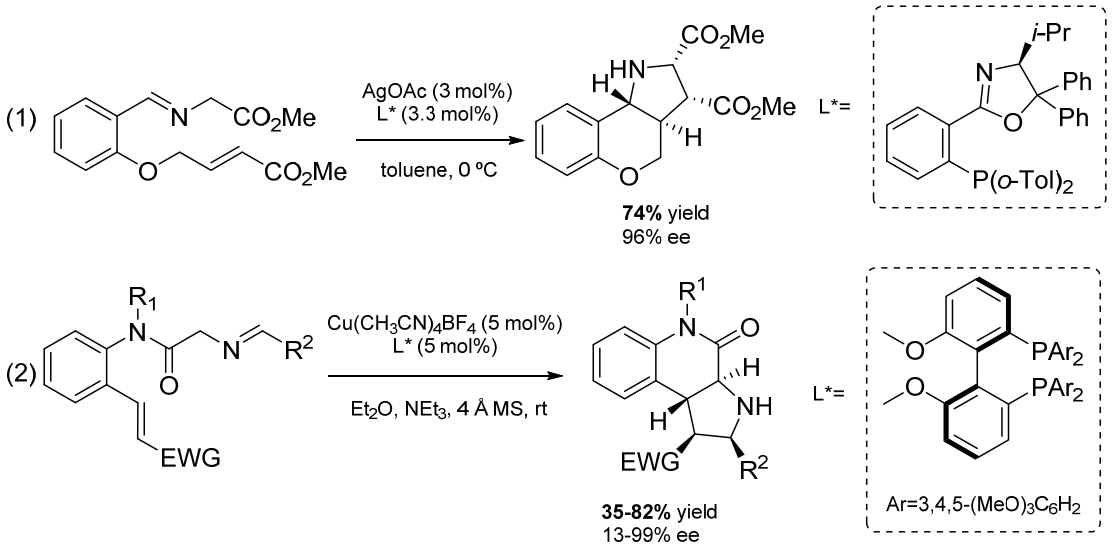
[130] For recent reviews on asymmetric (catalytic) AMY cycloadditions, see: (a) Bdiri, B.; Zhao, B.-J.; Zhou, Z.-M. *Tetrahedron: Asymmetry* **2017**, *28*, 876. (b) Döndas, H. A.; de Gracia Retamosa, M.; Sansano, J. M. *Synthesis* **2017**, *49*, 2819. (c) Ref 2c. (d) Han, M.-Y.; Jia, J.-Y.; Wang, W. *Tetrahedron Lett.* **2014**, *55*, 784. (e) Nájera, C.; Sansano, J. M. *J. Organomet. Chem.* **2014**, *771*, 78. (f) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2014**, *50*, 12434. (g) Xing, Y.; Wang, N.-X. *Coord. Chem. Rev.* **2012**, *256*, 938. (h) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6784.

[131] Selected earlier reviews cover the use of enantiopure substrates and chiral auxiliaries in (intramolecular) AMY cycloadditions: (a) Ref 2g. (b) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484. (c) Bonin, M.; Chauveau, A.; Micouin, L. *Synlett* **2006**, *15*, 2349. (d) Ref. 119.

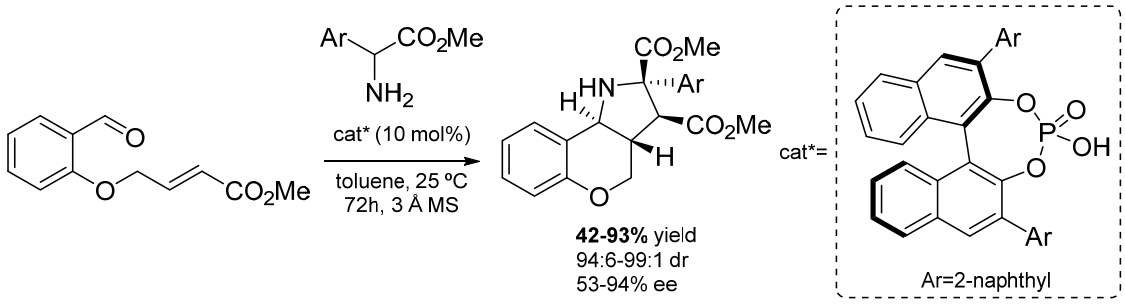
Pfaltz *et al.* reported the enantioselective intramolecular cycloaddition of the imine derived from glycine methyl ester and a salicylaldehyde derivative (bearing an activated dipolarophile in a remote position) catalysed by a Ag(I)/Phox complex (Scheme 2.7, equation 1).[132] It should be noted that the observed regioselectivity is the opposite to the natural polarity of the reactants, illustrating that the steric requirements (and the participation of a Lewis acid) can alter the expected regiochemistry. Applying a similar strategy, Waldmann and collaborators accessed pyrrolidino-piperidines by a highly enantioselective intramolecular AMY cycloaddition of glycine *N*-aryl amides catalysed by a Cu(I)/MeOBiphep complex (Scheme 2.7, equation 2).[133]



Scheme 2.7

Gong *et al.* described the only example of an organocatalytic enantioselective intramolecular AMY cycloaddition (Scheme 2.8).[134] They employed a chiral BINOL-derived phosphoric acid as the catalyst for the imine formation and the subsequent intramolecular cycloaddition.

[132] Stohler, R.; Wahl, F.; Pfaltz, A. *Synthesis* **2005**, 1431.
[133] Vidadala, S. R.; Golz, C.; Strohmann, C.; Daniliuc, C.-G.; Waldmann, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 651.
[134] Li, N.; Song, J.; Tu, X.-F.; Bin, L.; Chen, X.-H.; Gong, L.-Z. *Org. Biomol. Chem.* **2010**, *8*, 2016.



Scheme 2.8

The fact that only few examples of catalytic asymmetric intramolecular AMY cycloadditions have been reported and that all of them imply the participation of a highly activated dipolarophile (acrylates) suggests that this is a challenging transformation and that unactivated starting materials[135] are not suitable for it, at least with the catalytic modes described to date. In this context, the use of enantiopure substrates and chiral auxiliaries is justified and, given the number of reported syntheses that still make use of them, it is the method of choice.

A very common and simple strategy to generate optically active azomethine ylides is the use of homochiral substituted morpholin-2-ones (systematic name: 2,3,5,6-tetrahydro-4H-oxazinone). The groups of Harwood[136] and Williams[137] were the first to report the use of morpholinone-templated azomethine ylides in stereoselective cycloadditions.[138,139] Harwood was also the first to describe their use in an intramolecular fashion (Scheme 2.9)[140] and demonstrated that, in

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[135] For a recent review of azomethine ylide cycloaddition with non-electrophilic dipolarophiles, see: J. Otero-Fraga, M. Montesinos-Magraner, A. Mendoza, *Synthesis* **2017**, *49*, 802.

[136] Anslow, A. S.; Harwood, L. M.; Phillips, H.; Watkin, D. *Tetrahedron: Asymmetry* **1991**, *2*, 169.

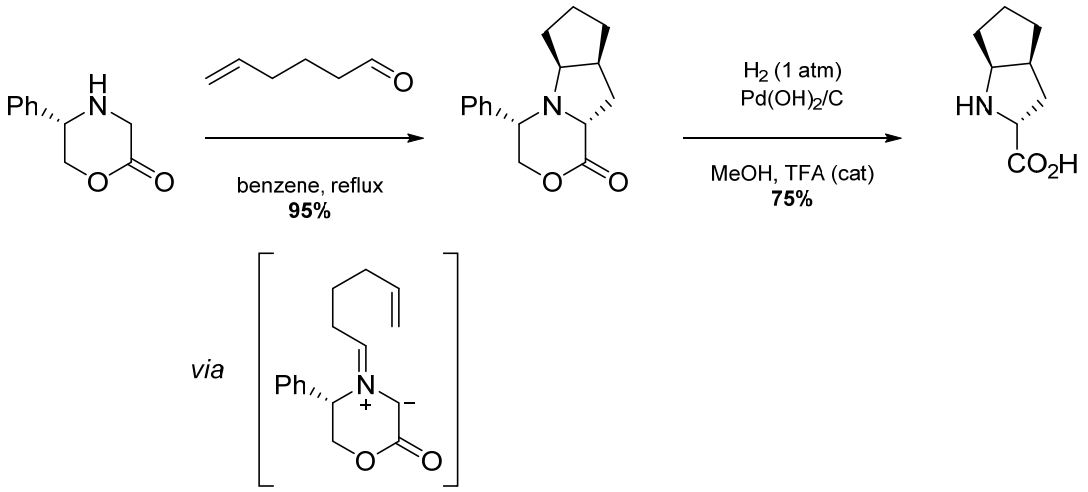
[137] Williams, R. M.; Zhai, W.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1992**, *57*, 6527.

[138] The usefulness of chiral morpholinones is best exemplified by the work of Williams *et al.* in the asymmetric total synthesis of spirotryprostatins A and B: (a) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135. (b) Sebahar, P. R.; Osada, H.; Usui, T.; Williams, R. M. *Tetrahedron* **2002**, *58*, 6311. (c) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666. The same strategy has been applied to the synthesis of the AD-spyrocyclic system of nakadomarin A: (d) Ahrendt, K. A.; Williams, R. M. *Org. Lett.* **2004**, *6*, 4539.

[139] Schreiber *et al.* synthesised a library of more than 3000 spirooxindoles applying this strategy: Lo, M. M. C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077.

[140] (a) Drew, M. G. B.; Harwood, L. M.; Price, D. W.; Choi, M.-S.; Park, G. *Tetrahedron Lett.* **2000**, *41*, 5077. (b) Harwood, L. M.; Lilley, I. A. *Tetrahedron Lett.* **1993**, *34*, 537. (c) Harwood, L. M.; Kitchen, L. C. *Tetrahedron Lett.* **1993**, *34*, 6603.

comparison to its intermolecular counterpart, the efficiency of the intramolecular process eliminates the necessity of placing electron withdrawing groups on the dipolarophile. The cycloadduct from the reaction between 5-hexenal and (*S*)-5-phenylmorpholin-2-one was obtained as a single diastereoisomer *via* an S-shaped ylide, as confirmed by computational studies. Removal of the chiral template by hydrogenation renders a bicylic proline derivative.

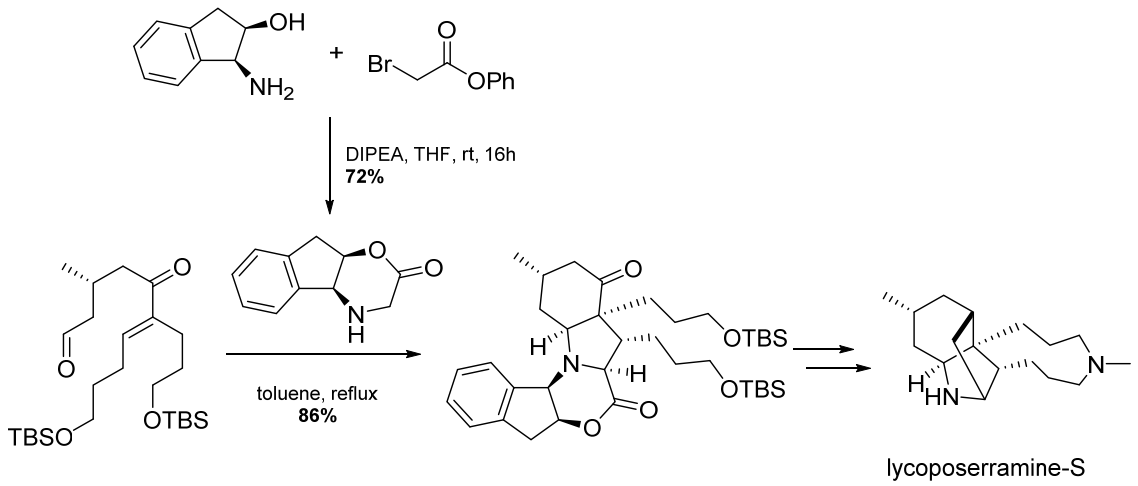


Scheme 2.9

Formally, these amino esters are chiral glycine equivalents which circumvent the unavoidable problem that the original chiral information present in the α-carbon of α-amino acid is necessarily lost in the moment of dipole generation. These azomethine ylide precursors can be regarded as chiral templates rather than chiral auxiliaries, since normally only the glycine half of the molecule is maintained in the final product while the rest is usually removed by hydrogenation to yield enantiomerically pure annelated proline derivatives. The very commonly used (5*S*,6*R*)-5,6-diphenylmorpholin-2-one (and its enantiomer) can be accessed from its corrresponding commercially available Boc carbamate via TFA treatment. Other derivatives can be easily obtained by the method of Dellaria,[141] *i.e.* reacting phenyl bromoacetate with the corresponding homochiral amino alcohol (as depicted in Scheme 2.10).

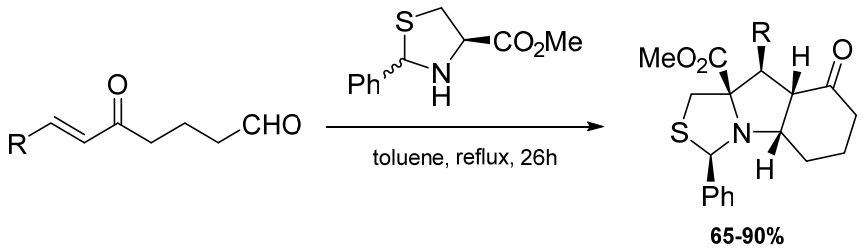
[141] Dellaria, J. F.; Santarsiero, B. D. *J. Org. Chem.* **1989**, *54*, 3916.

The group of Fukuyama applied the morpholinone strategy to the asymmetric total synthesis of alkaloid (-)-lycoposerramine-S (Scheme 2.10).[142] They found that the morpholinone derived from (1*R*, 2*S*)-*cis*-1-amino-2-indanol was the best AMY precursor in terms of yield and selectivity.



Scheme 2.10

Other AMY precursors can be found as well in the literature that condensate with an aldehyde moiety and render the corresponding iminium intermediate. Kanemasa *et al.* employed a chiral thiazolidine derivative as the AMY precursor in the intramolecular cycloaddition on an enone dipolarophile (Scheme 2.11).[143]

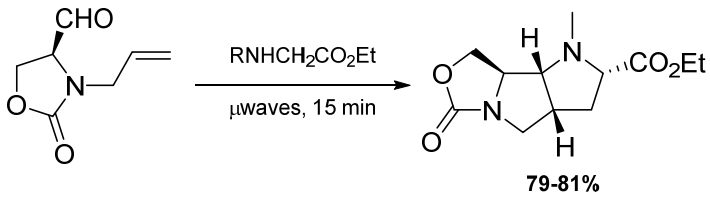


Scheme 2.11

An alternative strategy to introduce chirality in intramolecular AMY cycloadditions consists in placing defined stereocentres on the precursor bearing the dipolarophile instead of the AMY precursor. For example, Cheng *et al.*

[142] Shimada, N.; Abe, Y.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 11824.
[143] Kanemasa, S.; Doi, K.; Wada, E. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2866.

developed a protocol for microwave-induced intramolecular cycloaddition employing different dipoles generated from a chiral non-racemic aldehyde precursor (Scheme 2.12).[144] In particular, AMY cycloaddition provided the corresponding funtionalised *N*-heterocycles with total diastereoselectivity and good yields.



Scheme 2.12

2.1.4. Contextualisation of this work in the field of Organofluorine Chemistry

In addition to the general aspects already commented in Section 1.1.6., some particular considerations should be made in the present chapter. Fluorinated amino acids are at the core of the development of peptide-based drugs and protein modification since they are able to modify the chemical properties of biopolymers such as lipophilicity, metabolic stability and conformation.[145] These features allow them to enhance the so-called "druggability" of pharmaceutical candidates. In particular, it was found that fluorine substitution dramatically changes the secondary structure propensity of aliphatic amino acids and, accordingly, the folding properties of modified peptides and proteins, influencing their proteolytic stability at the same time. Moreover, fluorine is capable of influencing other more complex biochemical processes, such as protein-protein interactions or ribosomal translation.

Proline itself is a unique case in that it is the only of the 20 proteinogenic amino acids featuring a cyclic structure. This results in a restricted conformation of

[144] Cheng, Q.; Zhang, W.; Tagami, Y.; Oritani, T. *J. Chem. Soc. Perkin Trans. I* **2001**, 452.
[145] (a) Berger, A. A.; Völler, J.-S.; Budisa, N.; Koksch, B. *Acc. Chem. Res.* **2017**, *50*, 2093. (b) Salwiczek, M.; Nyakatura, E. K.; Gerling, U. I. M.; Ye, S.; Koksch, B. *Chem. Soc. Rev.* **2012**, *41*, 2135.

proline-containing peptides and proteins (the so-called *proline ring pucker*). Moreover, the absence of the NH makes proline residues invisible to routine protein NMR experiments (*e.g.* ^{1}H-^{15}N HSQC) for polypeptide structure analyses. Isotope labelling with fluorine atoms on the proline backbone helps restoring NMR visibility. At the same time, the introduction of fluorine into prolines can be used to modulate the molecular rigidity of the corresponding analogs by hyperconjugation interactions and facilitate the interconversion between *cis*- and *trans*-conformers by inductive effect (the very same effect renders the NH group of fluorine-substituted prolines less basic and the COOH group more acidic). Particularly, fluorinated proline derivatives have been used as a practical tool to study peptide/protein structure and dynamics, and interactions between peptides and receptors, since proteins bearing the valuable fluorine label provide a sensitive reporter for ^{19}F-NMR studies.[146] Furthermore, the incorporation of fluorinated prolines in proteins and small molecules results in improved potency compared to the unsubstituted proline analogues.[147]

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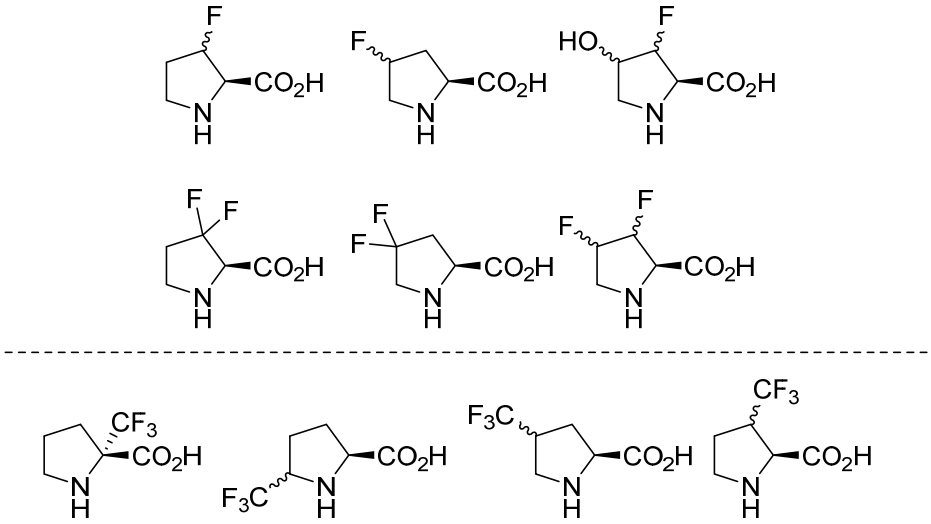
[146] For recent examples, see: (a) Hofman, G.-J.; Ottoy, E.; Light, M. E.; Kieffer, B.; Martins, J. C.; Kuprov, I.; Sinnaeve, D.; Linclau, B. *J. Org. Chem.* **2019**, *84*, 3100. (b) Verhoork, S. J. N.; Killoran, P. M.; Coxon, C. R. *Biochem*. **2018**, *57*, 6132. (c) Testa, A.; Lucas, X.; Castro, G. V.; Chan, K.-H.; Wright, J. E.; Runcie, A. C.; Gadd, M. S.; Harrison, W. T. A.; Ko, E.-J.; Fletcher, D.; Ciulli, A. *J. Am. Chem. Soc.* **2018**, *140*, 9299. (d) Somovilla, V. J.; Bermejo, I. A.; Albuquerque, I. S.; Martínez-Sáez, N.; Castro-López, J.; García-Martín, F.; Compañón, I.; Hinou, H.; Nishimura, S.-I.; Jiménez-Barbero, J.; Asensio, J. L.; Avenoza, A.; Busto, J. H.; Hurtado-Guerrero, R.; Peregrina, J. M.; Bernardes, G. J. L.; Corzana, F. *J. Am. Chem. Soc.* **2017**, *139*, 18255. (e) Reener, C.; Alefelder, S.; Bae, J. H.; Budisa, N.; Huber, R.; Moroder, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 923.

[147] For recent representative examples, see: (a) Sumii, Y.; Hibino, H.; Saidalimu, I.; Kawahara, H.; Shibata, N. *Chem. Commun.* **2018**, *54*, 9749. (b) Chen, H.; Volgraf, M.; Do, S.; Kolesnikov, A.; Shore, D. G.; Verma, V. A.; Villemure, E.; Wang, L.; Chen, Y.; Hy, B.; Lu, A.-J.; Wu, G.; Xu, X.; Yuen, P.-W.; Zhang, Y.; Erickson, S. D.; Dahl, M.; Brotherton-Pleiss, C.; Tay, S.; Ly, J. Q.; Murray, L. J.; Chen, J.; Amm, D.; Lange, W.; Hackos, D. H.; Reese, R. M.; Shields, S. D.; Lyssikatos, J. P.; Safina, B. S.; Estrada, A. A. *J. Med. Chem.* **2018**, *61*, 3641. (c) Jurica, A. A.; Wu, X.; Williams, K. N.; Hernandez, A. S.; Nirschl, D. S.; Rampulla, R. A.; Mathur, A.; Zhou, M.; Cao, G.; Xie, C.; Jacob, B.; Cai, H.; Wang, T.; Murphy, B. J.; Liu, H.; Xu, C.; Kunselman, L. K.; Hicks, M. B.; Sun, Q.; Schnur, D. M.; Sitkoff, D. F.; Dierks, E. A.; Apedo, A.; Moore, D. B.; Foster, K. A.; Cvijic, M. E.; Panemangalore, R.; Flynn, N. A.; Maxwell, B. D.; Hong, Y.; Tian, Y.; Wilkes, J. J.; Zinkler, B. A.; Whaley, J. M.; Barrish, J. C.; Robl, J. A.; Ewing, W. R.; Ellsworth, B. A. *J. Med. Chem.* **2017**, *60*, 1417. (d) Tamborini, L.; Pinto, A.; Ettari, R.; Gotti, C.; Fasoli, F.; Conti, P.; De Micheli, C. *ChemMedChem.* **2015**, *10*, 1071. (e) Ji, X.; Xia, C.; Wang, J.; Su, M.; Zhang, L.; Dong, T.; Li, Z.; Wan, X.; Li, J.; Li, J.; Zhao, L.; Gao, Z.; Jiang, H.; Liu, H. *Eur. J. Med. Chem.* **2014**, 242. (f) Ji, X.; Su, M.; Wang, J.; Deng, G.; Deng, S.; Li, Z.; Tang, C.; Li, J.; Li, J.; Zhao, L.; Jiang, H.; Liu, H. *Eur. J. Med. Chem.* **2014**, 111. (g) Torbeev, V. Y.; Hilvert, D. *PNAS*

Given the utility of fluoroprolines as structural probes to assess the conformational biases of protein structure, the synthesis of novel variants of these compounds in an enantiomerically pure form is still of great interest.[148] In particular, it is important to expand the toolbox of available proline analogues (Scheme 2.13) with different, well-separated ^{19}F-NMR chemical shifts for site-specific multiresidue-labeling strategies of proteins, as for the study of relatively simple proline-rich proteins (collagen, transcriptional activators, etc.).



Scheme 2.13

The fluorine label incorporated on prolines has traditionally consisted in the H/F substitution of the 3 and 4 positions of the proline ring. Vicinal and *gem*-disubstitution can also be found in the literature.[149] Interestingly, the CF_3 group in the 4 position was identified as a convenient tag as well, since it does not greatly influence the conformational behaviour of proline as it is placed at the most remote position with respect to the peptide bond.[150] The synthesis of 3-trifluoromethylproline has only recently been reported (in 10 steps).[151] According to this work, other polyfluoroalkyl rests are also accessible at the same position.

2013, *110*, 20051. (h) Wang, J.; Feng, Y.; Ji, X.; Deng, G.; Leng, Y.; Liu, H. *Bioorg. Med. Chem.* **2013**, *21*, 7418.

[148] For a recent example, see: Doebelin, C.; He, Y.; Kamenecka, T. M. *Tetrahedron Lett.* **2016**, *57*, 5658 and references therein.

[149] For examples, see ref. 146.

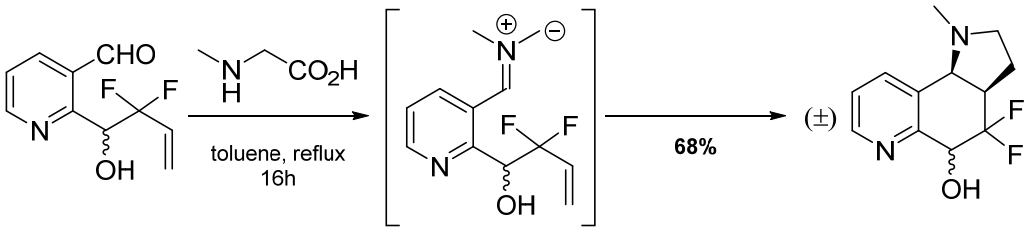
[150] (a) Kubyshkin, V.; Pridma, S.; Budisa, N. *New J. Chem.* **2018**, *42*, 13461. (b) Kubyshkin, V.; Afonin, S.; Kara, S.; Budisa, N.; Mykhailiuk, P. K.; Ulrich, A. S. *Org. Biomol. Chem.* **2015**, *13*, 3171.

[151] Tolmachova, N. A.; Kondratov, I. S.; Dolovanyuk, V. G.; Pridma, S. O.; Chernykh, A. V.; Daniliuc, C. G.; Haufe, G. *Chem. Commun.* **2018**, *54*, 9683.

2.1.5. Fluorinated dipolarophiles in Intramolecular Azomethine Ylide Cycloadditions

The kind of dipolarophiles used in AMY cycloadditions is mostly restricted to activated olefins (acrylates, enones, nitroalkenes, vinylsulfones, etc.). In much the same way, known fluorinated dipolarophiles include fluorinated acrylates, crotonates, nitroalkenes and imines.[152] These are highly polarised (and thus reactive) double bonds which easily undergo 1,3-dipolar cycloadditions with azomethine ylides under relatively mild reaction conditions. "Simple" trifluoromethylalkenes, however, require much harsher conditions, as we have concluded from our previous work with nitrones (Chapter 1).

Despite the high efficiency reached in AMY cycloadditions, to the best of our knowledge, only one example of the intramolecular variant using fluorinated dipolarophiles has been described to date, in a racemic manner (Scheme 2.14).[153]

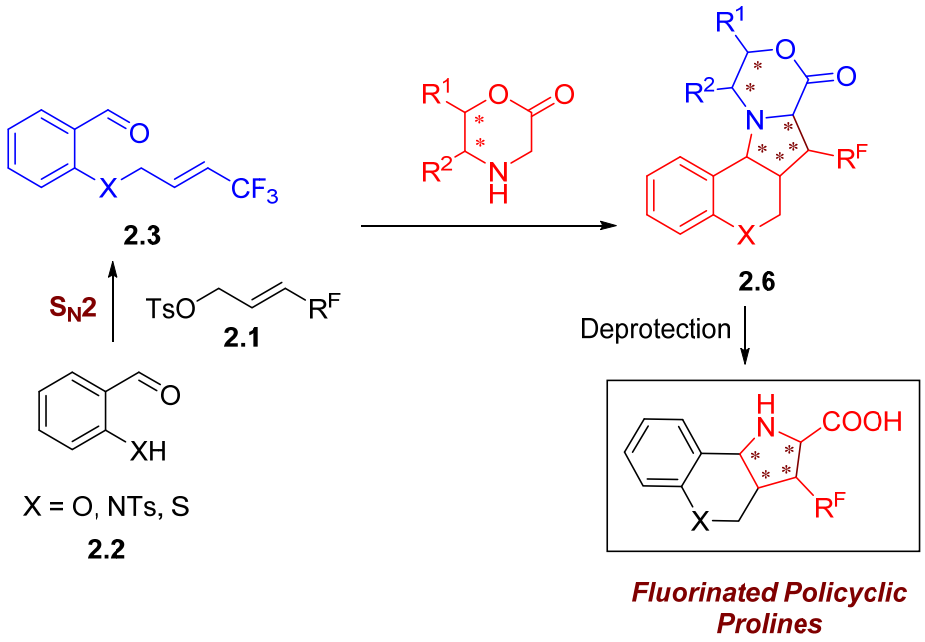


Scheme 2.14

[152] Adrio and Carretero have conveniently devoted a section of their review to this kind of dipolarophiles. See ref. 130f.
[153] Cheng, B.; Zhai, H. *Synlett* **2009**, *12*, 1955.

2.2. Objectives

The main goal in Chapter 2 will be the exploration of novel fluorinated dipolarophiles in intramolecular azomethine ylide cycloadditions. In particular, the focus will be put on simple unactivated fluoroalkyl olefins. We envisioned that the combination of an interesting fluorinated synthon, (*E*)-4,4,4-trifluoro-2-butenyl tosylate **2.1**, scarcely used so far in the literature, and salicylaldehydes (or their nitrogen or sulfur counterparts) **2.3** would render adequate substrates for this transformation.



Scheme 2.15

In order to obtain enantiomerically pure products, chiral non-racemic morpholin-2-ones will be used as azomethine ylide precursors. These chiral templates are then easily removed and render the corresponding pyrrolidines. In this work, enantiomerically pure polycyclic 3-fluoroalkylprolines derivatives with up to four stereocentres will be synthesised, given their interest as interesting scaffolds in medicinal chemistry or in protein studies.

The role of the trifluoromethyl group in the regio- and stereoselectiviy of the reaction will be investigated both experimentally (by comparison with synthesised non fluorinated analogues) and with the aid of a complementary computational study.

2.3. Results and Discussion

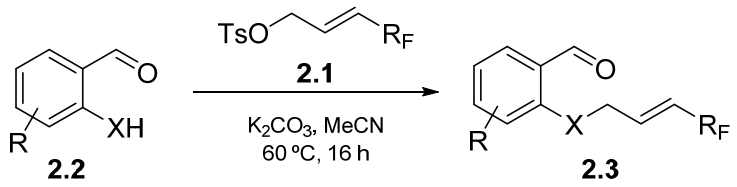
2.3.1. Design and synthesis of starting materials 2.3

At the onset of our study, we searched for adequate starting materials for the intramolecular dipolar cycloaddition. Paquin and collaborators have systematically studied the introduction of the (*E*)-4,4,4-trifluoro-2-butenyloxy chain *via* S_N2 reaction of a nucleophile (phenols particularly) and (*E*)-4,4,4-trifluoro-2-butenyl tosylate **2.1a**.[154] With this methodology in mind, we planned to tether this fluorinated dipolarophile to the required aldehyde moiety.[155] Starting from a series of substituted salicylaldehydes and their tosyl-protected nitrogen analogs **2.2**, fluorinated benzaldehydes 2.**3** were obtained in good yields after reaction with tosylates **2.1** (Table 2.1). Fluorinated rests other than CF_3 were introduced as well with substrates **2.1b** (CF_2H), **2.1c** (CH_2F) and **2.1d** (C_2F_5) (entries 8, 9, 10, 15, 16).

[154] (a) Forcellini, E.; Hemelaere, R.; Desroches, J.; Paquin, J.-F. *J. Fluorine Chem.* **2015**, *180*, 216. (b) Hemelaere, R.; Desroches, J.; Paquin, J.-F. *Org. Lett.* **2015**, *17*, 1770.

[155] During the preparation of the manuscript of the present doctoral thesis, Schreiber *et al.* reported the use of the referred dipolarophile in the INCR of very similar substrates for the synthesis of DNA-encoded libraries of small molecules: Gerry, C. J.; Yang, Z.; Stasi, M.; Schreiber, S. L. *Org. Lett.* **2019**, *21*, 1325.

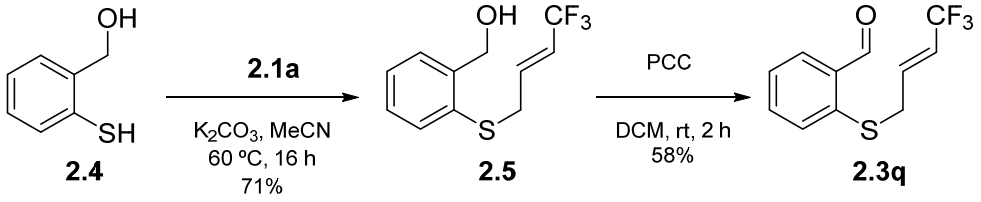
Table 2.1 Synthesis of starting fluorinated benzaldehydes **2.3a-m**



Entry	**2.1**	**2.2**	R	R_F	X	**2.3**	% yield[a]
1	**2.1a**	**2.2a**	H	CF_3	O	**2.3a**	85
2	**2.1a**	**2.2b**	5-Me	CF_3	O	**2.3b**	78
3	**2.1a**	**2.2c**	5-OMe	CF_3	O	**2.3c**	93
4	**2.1a**	**2.2d**	5-Cl	CF_3	O	**2.3d**	69
5	**2.1a**	**2.2e**	3-OMe	CF_3	O	**2.3e**	86
6	**2.1a**	**2.2f**	4-OMe	CF_3	O	**2.3f**	82
7	**2.1a**	**2.2g**	4-Br	CF_3	O	**2.3g**	55
8	**2.1b**	**2.2a**	H	CF_2H	O	**2.3h**	63
9	**2.1c**	**2.2a**	H	CH_2F	O	**2.3i**	71
10	**2.1d**	**2.2a**	H	C_2F_5	O	**2.3j**	83
11	**2.1a**	**2.2h**	H	CF_3	NTs	**2.3k**	83
12	**2.1a**	**2.2i**	5-Me	CF_3	NTs	**2.3l**	75
13	**2.1a**	**2.2j**	5-OMe	CF_3	NTs	**2.3m**	88
14	**2.1a**	**2.2k**	5-Cl	CF_3	NTs	**2.3n**	83
15	**2.1b**	**2.2h**	H	CF_2H	NTs	**2.3o**	55
16	**2.1d**	**2.2h**	H	C_2F_5	NTs	**2.3p**	71

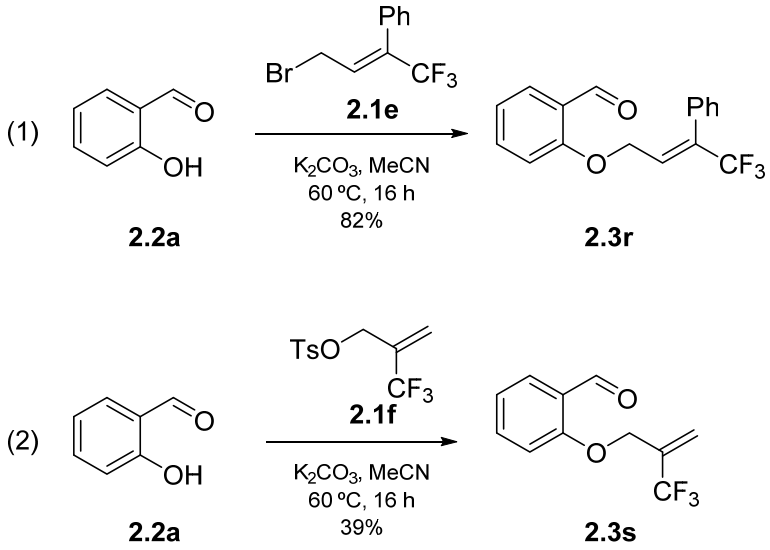
[a] Isolated yield after flash column chromatography.

In the case of the sulfur derivative **2.3q**, the fluorinated moiety had to be incorporated prior to the oxidation of the benzylic alcohol to the benzaldehyde (Scheme 2.16), since the direct alkylation of thiosalicylaldehyde afforded a complex mixture of products.



Scheme 2.16

Two additional substrates (**2.3r** and **2.3s**) with a structurally different fluorinated dipolarophile were prepared under the standard conditions (Scheme 2.17). For the synthesis of substrates **2.1a-f**, see the Experimental Section.

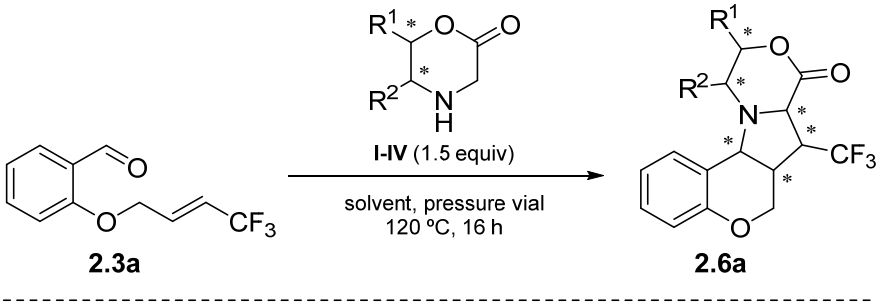


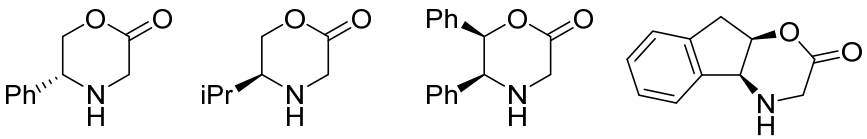
Scheme 2.17

2.3.2. Optimisation of the Intramolecular Azomethine Ylide Cycloaddition Reaction

With the required starting materials in hand, the asymmetric intramolecular azomethine ylide cycloaddition reaction was optimised for the given system using fluorinated benzaldehyde **2.3a** as the model substrate (Table 2.2).

Table 2.2 Optimisation of the Intramolecular Azomethine Ylide Cycloaddition[a]





Entry	AMY precursor	Solvent	% conversion[b]	*dr*[b]
1	**I**	toluene	46	60:40
2	**II**	toluene	56	60:40
3	**III**	toluene	100	86:14
4	**IV**	toluene	100	92:8[c]
5	**IV**	toluene	84	87:13[d]
6	**IV**	xylene	100	79:21
7	**IV**	DMF	100	86:14
8	**IV**	dioxane	100	89:11
9	**IV**	EtOH	96	75:25

AMY = azomethine ylide; Conv.=conversion

[a] Reactions were carried out with **2.3a** (1 equiv) and AMY precursor **I-IV** (1.5 equiv) in the corresponding solvent (0.1M) at 120 °C for 16 h.

[b] Conversions and diastereoisomeric ratios were determined by ^{19}F-NMR of the crude reaction mixture.

[c] Compound **2.6a** was isolated in 73% yield after flash column chromatography.

[d] The reaction was run at 80 °C for 3 days.

The nature of the azomethine ylide precursor was first screened (Table 2.2, entries 1-4). Among the amino esters **I-IV** assayed, morpholinone **IV**[156] derived from (1*S*,2*R*)-*cis*-1-amino-2-indanol provided the best results in terms of conversion and diastereoselectivity (entry 4), rendering compound **2.6a** as a 92:8 mixture of two diastereoisomers with simultaneous generation of four stereocentres. Seemingly, the polycyclic structure of the morpholinone increases the rigidity and rotational barrier of the intermediate azomethine ylide, thus enhancing the facial selectivity arising from the chiral template. Deviation of the standard conditions (toluene, 120 °C, 16 h) in terms of solvent, temperature or reaction time only resulted in lower yields or selectivities (entries 5-9).

The absolute configuration of the hexacyclic cycloaddition product **2.6a** was established by X-ray diffraction analysis of an appropriate crystal and confirmed by the spatial interactions observed on the HOESY spectrum (Figure 2.1).

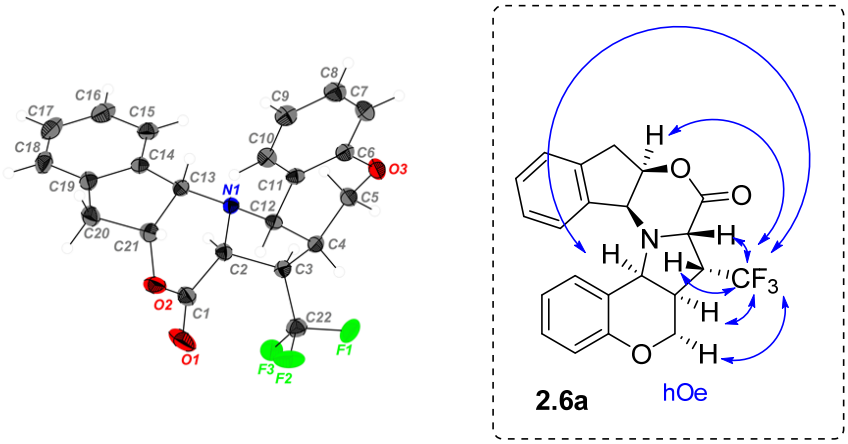


Figure 2.1

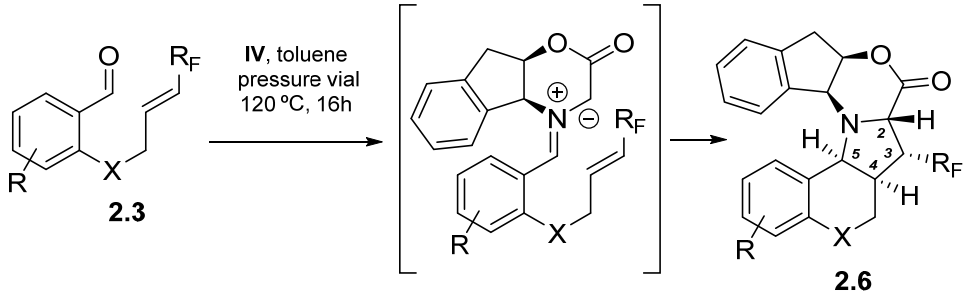
It should be noted that the reaction, in addition to the observed diastereoselectivity, is completely regioselective, since only the fused regioisomer was obtained. The 2,5-*trans* configuration of the proline ring suggests a preference for an attack in which the CF_3 group adopts an endo orientation to an intermediate S-shaped ylide; the 3,4-*trans* configuration comes from the initial configuration of the dipolarophile. The 4,5-*cis* configuration at the ring junction is the preferred substituent disposition in the major diastereoisomer. The same stereochemistry was assumed for all cycloadducts **2.6**.

[156] This AMY precursor has already been encountered in the Introduction (Section 2.1.3., Scheme 2.10).

2.3.3. Study of the scope of the Intramolecular Azomethine Ylide Cycloaddition Reaction

Having established the optimised reaction conditions for this transformation, we examined the scope of the reaction on the already synthesised family of starting materials **2.3** (Table 2.3). Good yields and diastereoisomeric ratios were obtained in general. Structural variability was introduced *via* substitution on the aromatic ring and changing the nature of the linker between the dipolarophile and the aldehyde moiety (X=O, NTs, S). Only when an electron-donating substituent was placed in position 4, a slight drop in diastereoselectivity was observed (Table 2.3, entry 6). Prolines bearing a CH_2F, CF_2H or C_2F_5 group could also be accessed applying the same conditions (Table 2.3, entries 6, 7, 8, 13). Moreover, a clear trend can be observed: the greater the fluorine atom substitution, the better the diastereoselectivity. It has to be remarked that in the case of the nitrogen containing analogs the selectivity was excellent since only one diastereoisomer was obtained in each case (Table 2.3, entries 11-16).

Table 2.3 Scope of the Intramolecular Azomethine Ylide Cycloaddition[a]



Entry	**2.3**	R	R_F	X	**2.6**	% yield[b]	*dr*[c]
1	**2.3a**	H	CF_3	O	**2.6a**	73	92:8
2	**2.3b**	5-Me	CF_3	O	**2.6b**	88	92:8
3	**2.3c**	5-OMe	CF_3	O	**2.6c**	75	92:8
4	**2.3d**	5-Cl	CF_3	O	**2.6d**	71	93:7
5	**2.3e**	3-OMe	CF_3	O	**2.6e**	67	91:9

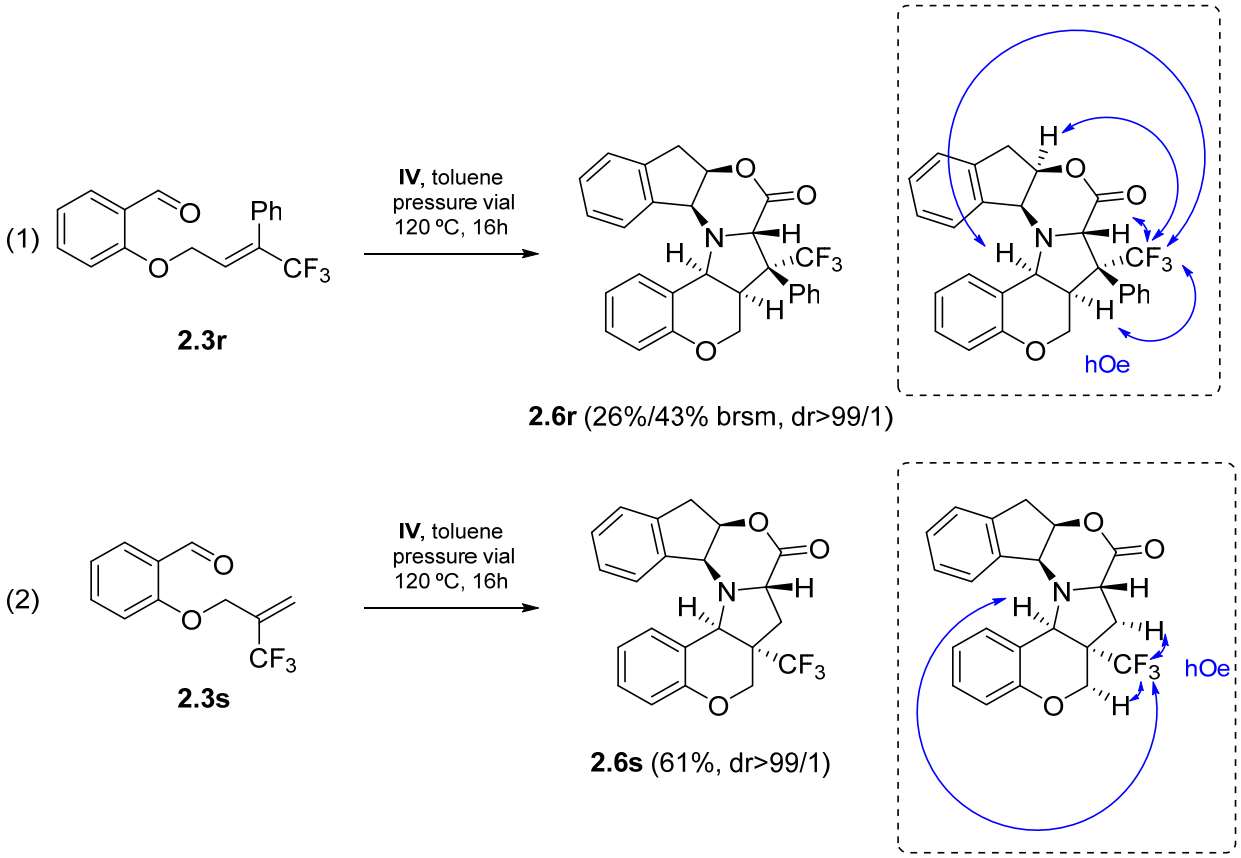
Table 2.3 *(continued)*

Entry	**2.3**	R	R_F	X	**2.6**	% yield[b]	*dr*[c]
6	**2.3f**	4-OMe	CF_3	O	**2.6f**	77	80:20
7	**2.3g**	4-Br	CF_3	O	**2.6g**	60	92:8
8	**2.3h**	H	CF_2H	O	**2.6h**	68	88:12
9	**2.3i**	H	CH_2F	O	**2.6i**	72	62:38
10	**2.3j**	H	C_2F_5	O	**2.6j**	65	91:9
11	**2.3k**	H	CF_3	NTs	**2.6k**	70	98:2
12	**2.3l**	5-Me	CF_3	NTs	**2.6l**	67	97:3
13	**2.3m**	5-OMe	CF_3	NTs	**2.6m**	76	98:2
14	**2.3n**	5-Cl	CF_3	NTs	**2.6n**	51	98:2
15	**2.3o**	H	CF_2H	NTs	**2.6o**	77	>99:1
16	**2.3p**	H	C_2F_5	NTs	**2.6p**	77	98:2
17	**2.3q**	H	CF_3	S	**2.6q**	79	95:5

[a]Reactions were carried out under optimised conditions described in Table 2.
[b] Yield after flash column chromatography.
[c] Diastereoisomeric ratios were determined by ^{19}F-NMR of the crude reaction mixture.

Fluorinated salicylaldehyde derivatives **2.3r** and **2.3s** were cyclised as well under the optimised reaction conditions affording in both cases cycloadducts with a structural feature already encountered in Chapter 1: a trifluoromethyl-bearing, all-carbon quaternary stereocentre (Scheme 2.18). In addition, the stereoselectivity in these two last examples was excellent since only one

diastereoisomer could be observed. However, the reaction of benzaldehyde **2.3r**[157] is much more sluggish, probably due to the steric hindrance posed by the higher substitution of the dipolarophile (Scheme 2.18, equation 1). The absolute stereochemistry of **2.6r** and **2.6s** was assigned in analogy to **2.6a** and on the basis of the spacial interactions observed on the HOESY-spectrum (see the Experimental Section).



Scheme 2.18

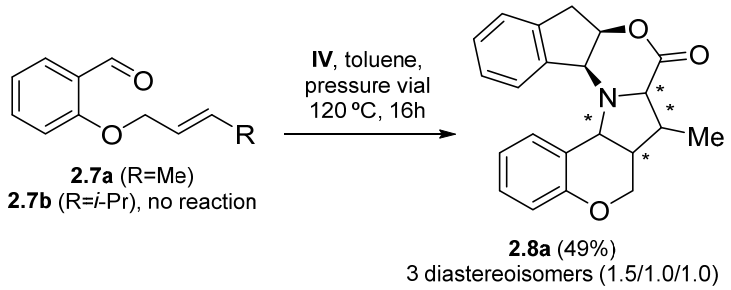
2.3.4. Role of the CF_3 Group in the Stereoselectivity: Experimental study

In order to evaluate the influence of the fluorinated moiety in the cycloaddition process, non-fluorinated benzaldehyde **2.7a**,[158] in which the CF_3

[157] This compound was recently described in the literature for the enantioselective synthesis of chromanones: Wang, B.; Huang, L.; Hou, Y.; Lan, S.; Cheng, J. *Org. Lett.* **2018**, *20*, 6012.

[158] This compound was prepared according to a literature procedure: Schmidt, B.; Riemer, M.; Schilde, U. *Eur. J. Org. Chem.* **2015**, 7602.

group has formally been replaced by a methyl group, was subjected to the standard reaction conditions (Scheme 2.19). The reaction outcome was a nearly equimolar, inseparable mixture of three compounds which were assigned to three diastereoisomers of **2.8a**. This result suggests that the trifluoromethyl group plays an important role in the stereoselectivity of the cycloaddition in favour of a sole diastereoisomer. To further assess the role of the CF_3 in the cycloaddition process, the CF_3 group was also replaced by an isopropyl group, which is known to be of a similar size.[159] However in this case, no cycloadduct formation was observed, and 68% of **2.7b** was recovered.



Scheme 2.19

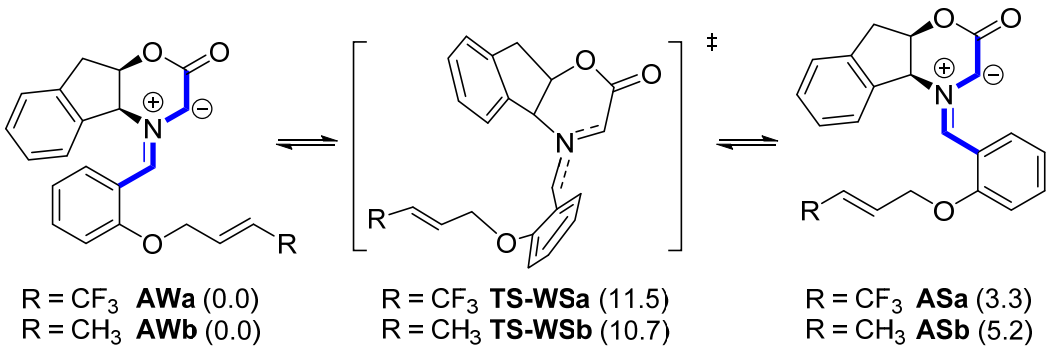
Finally, it should be highlighted how an increasing fluorine substitution on the terminal alkyl group attached to the dipolarophile (in the series **2.7a**-**2.3i**-**2.3h**-**2.3a**) results in an increasing diastereoselectivity of the cycloaddition.

2.3.5. Role of the CF_3 Group in the Stereoselectivity: Computational study

To shed light on this interesting finding, computational calculations were carried out in collaboration with Professor Pedro Merino from the University of Zaragoza. We studied the intramolecular cycloaddition of the azomethine ylides derived from the condensation between aldehydes **2.3a** and **2.7**, and **IV**. We employed the b3lyp functional with Grimme's dispersion correction and Ahlrichs' basis sets def2svp and def2tzvp. Solvent effects were included in energy calculations (for details see the Experimental Section). Condensation of **2.3a** and

[159] (a) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (b) Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1320.

2.7 with **IV** can lead to two different ylides, named as **AWa,b** and **ASa,b**, that can be in equilibrium through the corresponding transition structure **TS-WSa,b** (Scheme 2.20).



Scheme 2.20 (Relative energies are given in kcal/mol in brackets.)

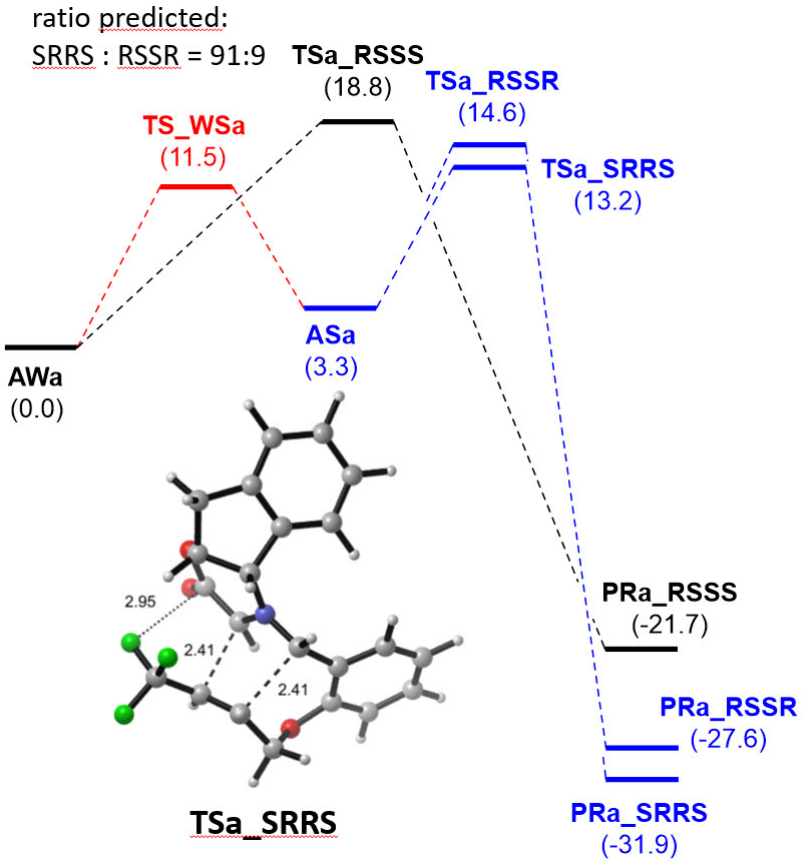


Figure 2.2 Energy profiles corresponding to the reaction with azomethine ylides derived from **2.3a** and **IV**. Relative energy values have been calculated at b3lyp-d3bj/def2tzvp (toluene, 400 K) and are given in kcal/mol.

In the case of R = CF_3, **AW** was found to be 3.3 kcal/mol more stable (5.2 for R=CH_3) than **AS** with an energy barrier of 11.5 kcal/mol (10.7 for R=CH_3). We calculated, for each ylide, the four possible approaches by considering the reaction between *Re,Re* and *Si,Si* diastereofaces of both alkene and ylide moieties. A total of eight transition structures were located for both R=CF_3 and R=CH_3 leading to the eight possible diastereomers that can be obtained (see the Experimental Section for complete data). The corresponding energy profiles for the more stable paths for R=CF_3 and R=CH_3 are given in Figures 2.2 and 2.3, respectively (for full energy profiles see the Experimental Section).

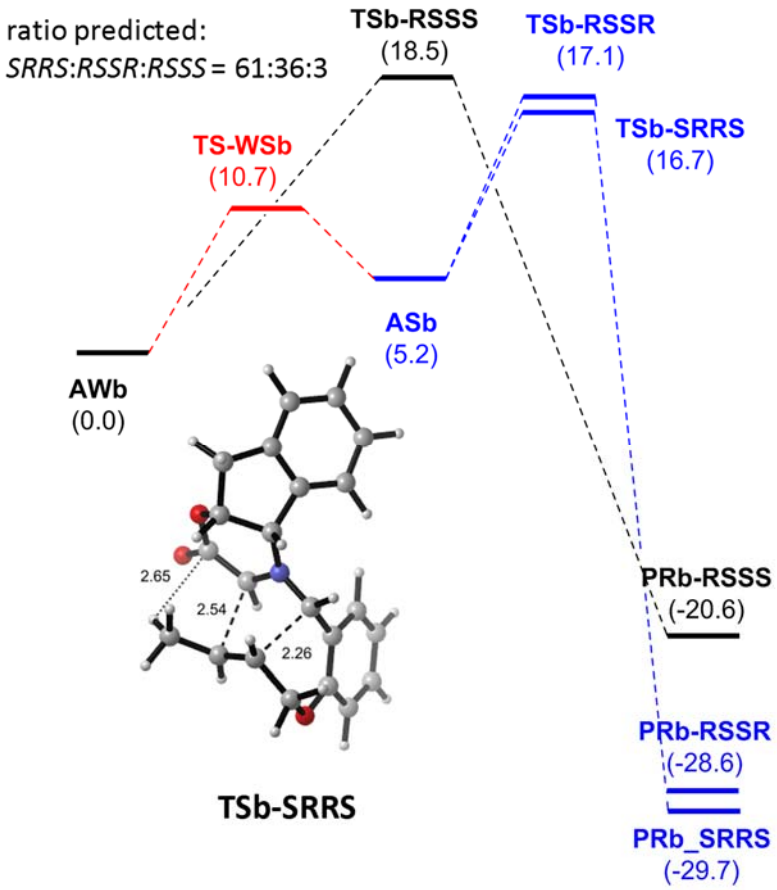


Figure 2.3 Energy profiles corresponding to the reaction with azomethine ylides derived from **2.7** and **IV**. Relative energy values have been calculated at b3lyp-d3bj/def2tzvp (toluene, 400 K) and are given in kcal/mol.

In both cases the isomerisation barrier of ylides W and S is lower than the corresponding barrier for the intramolecular cycloaddition so, in agreement with Curtin-Hammet's principle[160] it can be expected an equilibrium between both ylides. According to the energy profiles showed in Figures 2.2 and 2.3, the preferred adduct is that having a *S,R,R,S* configuration, coming from the *S*-ylide through the reaction between *Re,Re* and *Si,Si* faces of alkene and ylide, respectively, with the R group in an *endo* orientation (**TS-SRRS**). For R=CF_3 a ratio (*S,R,R,S*):(*R,S,S,R*) of 91:9 is predicted. On the other hand, a lower selectivity is foreseen for R=CH_3, and three adducts are expected to be obtained (*S,R,R,S*):(*R,S,S,R*):(*R,S,S,S*) = 61:36:6. These results are in perfect agreement with the experimental observations.

For the two competitive transition structures corresponding to R=CF_3 a subtle difference is found in the F···C=O interaction (longer distance for the less stable **TSa-RSSR**) and geometry (**TSa-RSSR** more asynchronous due to steric interactions). These slight differences are the origin of relative predominance of **TSa-SRRS**. For R=CH_3, **TSb-RSSR** is more synchronous and a slightly stronger H···C=O interaction is observed. These effects combined with steric reasons makes that energies of both TSs are rather similar leading to mixtures of the corresponding products (for details see the Experimental Section).

When the two more stable TSs (**TS-SRRS**) from CF_3 and CH_3 are compared, that from CF_3 is much more synchronous. In all cases, interactions of F (or H) are found with the electron-deficient carbonyl carbon. However, the distances cannot be used as a criterion for determining the magnitude of the interaction since the atoms are different. Because of that we carried out a topological analysis of non-covalent interactions (NCI)[161] that showed a stronger F··C=O interaction in **TSa-SRRS** with respect to the H···C=O interaction in **TSb-SRRS** (Figure 2.4). Accordingly, the green surfaces corresponding to F···C=O interactions are greater than those corresponding surface for H···C=O interactions. Overall, more attractive

[160] Seeman, J. I. *Chem. Rev.* **1989**, *83*, 83.
[161] Ref. 84.

London stabilizing forces are observed for CF_3-derivatives in agreement with a slightly higher stability for those structures.[162]

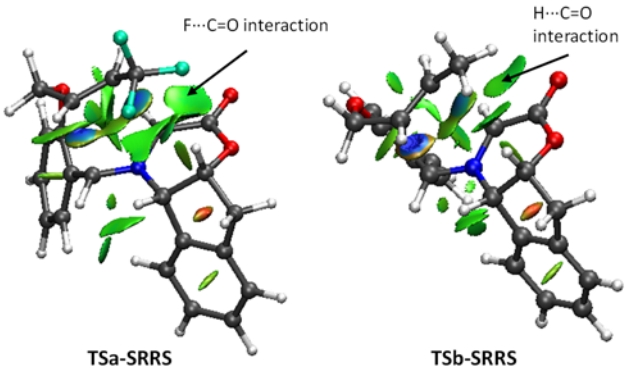


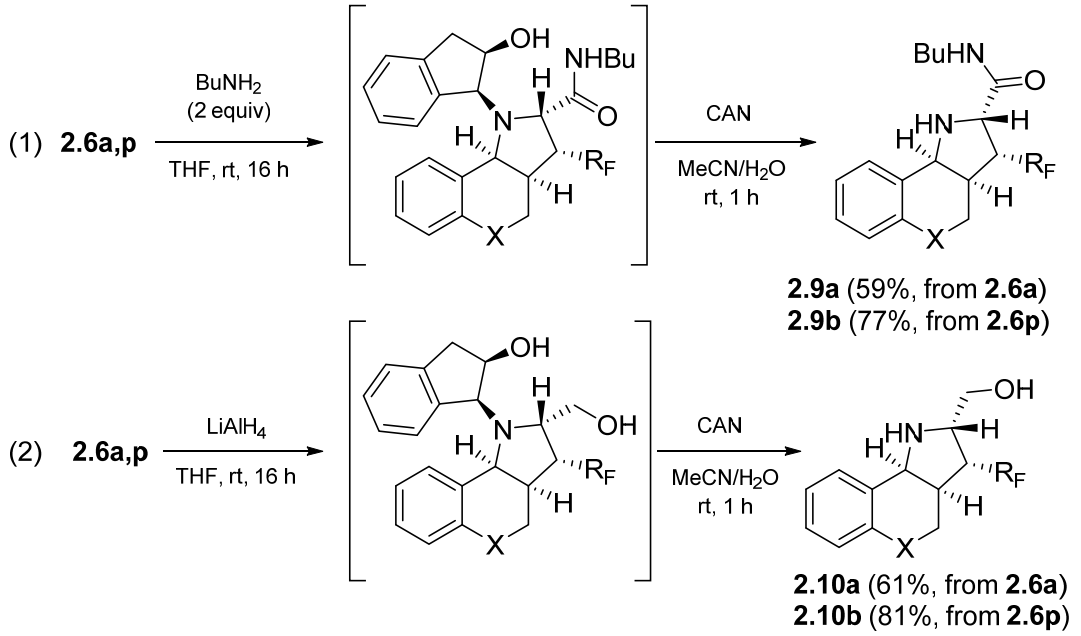
Figure 2.4 NCI analysis for **TSa-SRRS** and **TSb-SRRS**. NCI analyses are qualitative and provide information of the magnitude on non-covalent interactions (green: weak attractive; blue: strong attractive; red: repulsive;). Blue-green interactions are observed in the area in which bonds are being formed as expected for a transition state.

2.3.6. Further Derivatisation of the Cycloaddition products

Finally, the chiral template was removed to obtain fluorinated prolinamides **2.9** and prolinols **2.10** (Scheme 2.21). For the preparation of products **2.9**, the intermediate cycloaddition products **2.6** were treated with excess of *n*-butylamine followed by oxidative deprotection of the tertiary amine with ceric ammonium nitrate (CAN) (Scheme 2.21, equation 1). Alternatively, prolinols **2.10** were obtained by means of the sequence lithium aluminum hydride reduction of the lactone moiety/CAN deprotection of the amine over cycloaddition products **2.6** (Scheme 2.21, equation 2). Representative examples of each set of compounds **2.9a,b** and **2.10a,b** respectively were synthesised in good overall yields. It is

[162] For the importance of London interactions in organic reactivity see: Wagner, J. P.; Schreiner, P. R. *Angew. Chem. Int. Ed.* **2015**, *54*, 12274.

noteworthy that the oxidative deprotection agent was chosen over hydrogenolysis to avoid the unselective cleavage of the other benzylic position.[163]



Scheme 2.21 Derivatisation of compounds **2.6a,p** to polycyclic fluorinated prolinamides **2.9a,b** and prolinols **2.10a,b**

[163] Lubin, H.; Pytkowicz, J.; Chaume, G.; Sizun-Thomé, G.; Brigaud, T. *J. Org. Chem*. **2015**, *80*, 2700.

2.4. Conclusions

In conclusion, we have developed an asymmetric synthesis of fluorinated polycyclic proline derivatives by means of an intramolecular dipolar cycloaddition between a homochiral *in situ* generated azomethine ylide and a CF_3-substituted alkene unprecedented in this kind of reactions. Remarkably, the presence of the fluorinated rest on the dipolarophile combined with a suitable chiral inductor on the dipole ensures high levels of regio- and diastereoselectivity. Theoretical calculations correctly predict the drop of selectivity observed when a non-fluorinated alkene was used in comparison with the efficiency achieved with trifluoromethyl alkenes as dipolarophiles. Finally, simple operations allow the transformation of the cycloadducts into enantiomerically pure fluorine-containing prolinamides and prolinols.

2.5. Experimental Section

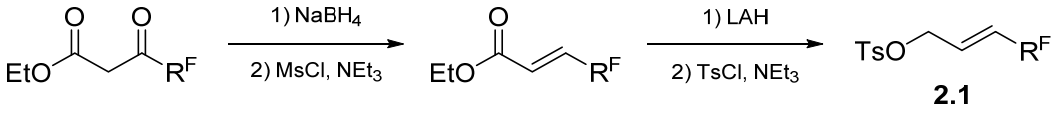
2.5.1. General methods

Reactions were carried out under a nitrogen atmosphere unless otherwise indicated. Solvents were purified prior to use: THF and toluene 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. Visualisation 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). ^{1}H, ^{19}F 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.

2.5.2. Experimental procedures and characterisation of new compounds

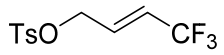
- **General procedure for the synthesis of tosylates 2.1**

Tosylates **2.1** were synthesised following a literature procedure[164] from the corresponding crotonates, which were obtained in turn from the corresponding fluorinated oxoesters according to a reported procedure.[165]



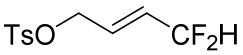
Scheme S2.1

[164] See ref. 154a.
[165] M. Berger, S. Veit, H. P. Niedermann, T. Kappesser, A., Stutz, A. Patent WO2015177179, **2015**.



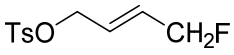
2.1a

(*E*)-4,4,4-Trifluorobut-2-en-1-yl 4-methylbenzenesulfonate (2.1a): Starting from commercially available ethyl (*E*)-trifluorocrotonate and following the procedure referred above, **2.1a** was obtained as a colorless oil in 55% yield (over 2 steps). The spectroscopic data matched those from the literature. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85–7.77 (m, 2H), 7.41–7.33 (m, 2H), 6.36-6.25 (m, 1H), 5.96–5.81 (m, 1H), 4.67-4.62 (m, 2H), 2.46 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.86–-64.93 (m, 3F). Spectroscopic data are in agreement with those reported in the literature.[164]



2.1b

(*E*)-4,4-Difluorobut-2-en-1-yl 4-methylbenzenesulfonate (2.1b): Starting from ethyl (*E*)-difluorocrotonate and following the procedure referred above, **2.1b** was obtained as a colorless oil in 3% yield (over 2 steps). The low yield was attributed to the high volatility of the intermediate fluorinated alcohol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84–7.72 (m, 2H), 7.43–7.32 (m, 2H), 6.39–5.66 (m,C<u>*H*</u>=C<u>*H*</u>-CF_2<u>*H*</u>, 3H), 4.71–4.50 (m, 2H), 2.46 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.98–-113.33 (m, 2F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 132.9, 130.5 (t, *J* = 11.5 Hz), 130.2, 128.1, 126.7 (t, *J* = 24.3 Hz), 113.5 (t, *J* = 235.6 Hz, <u>*C*</u>F_2H), 67.8, 21.8. HRMS (ESI/Q-TOF) m/z: $[M+NH_4]^+$ Calcd for $C_{11}H_{16}F_2NO_3S$ 280.0813; found 280.0817.



2.1c

(*E*)-4-Fluorobut-2-en-1-yl 4-methylbenzenesulfonate (2.1c): This compound was prepared according to a different route from a reported procedure.[166] Spectroscopic data are in agreement with those from the literature. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.84–7.75 (m, 2H), 7.39–7.31 (m, 2H), 6.03–5.69 (m, 2H), 4.93-4.72 (m, 2H), 4.60-4.54 (m, 2H), 2.45 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.16–-217.58 (m, 1F).

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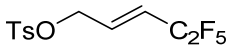
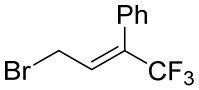
[166] Dollé, F.; Emond, P.; Mavel, S.; Demphel, S.; Hinnen, F.; Mincheva, Z.; Saba, W.; Valette, H.; Chalon, S.; Halldin, C.; Helfenbein, J.; Legaillard, J.; Madelmont, J.-C.; Deloye, J.-B.; Bottlaender, M.; Guilloteau. D. *Bioorg. Med. Chem.* **2006**, *14*, 1115.



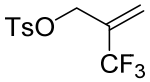
2.1d

(*E*)-4,4,5,5,5-Pentafluoropent-2-en-1-yl 4-methylbenzenesulfonate (2.1d): Starting from ethyl (*E*)-4,4,5,5,5-pentafluoropent-2-enoate and following the procedure referred above, **2.1d** was obtained as a colorless oil in 53% yield (over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84–7.77 (m, 2H), 7.39-7.36 (m, 2H), 6.40-6.30 (m, 1H), 5.93-5.79 (m, 1H), 4.70–4.65 (m, 2H), 2.46 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -85.13 (t, *J* = 2.0 Hz, 3F), -116.20 (q, *J* = 2.0 Hz, 2F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 134.3 (t, *J* = 8.9 Hz), 132.6, 131.4-101.9 (m, C_2F_5), 130.2 (2xCH), 128.1 (2xCH), 119.5 (t, *J* = 23.7 Hz), 67.11, 21.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{16}F_3N_2O_5$; found. HRMS (ESI/Q-TOF) m/z: $[M+NH_4]^+$ Calcd for $C_{12}H_{15}F_5NO_3S$ 348.0687; found 348.0688.



2.1e

(E)-(4-Bromo-1,1,1-trifluorobut-2-en-2-yl)benzene (2.1e): This compound was prepared according to a different route according to a reported procedure.[167] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.49–7.40 (m, 3H), 7.35–7.28 (m, 2H), 6.64 (tq, *J* = 8.3, 1.6 Hz, 1H), 3.81 (dq, *J* = 8.3, 1.6 Hz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -66.47 (s, 3F).



2.1f

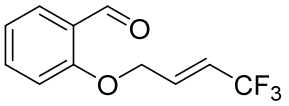
2-(Trifluoromethyl)allyl 4-methylbenzenesulfonate (2.1f): This compound was prepared according to a different route according to a reported procedure.[168] Spectroscopic data are in agreement with those reported in the literature.^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.83-7.78 (m, 2H), 7.41–7.32 (m, 2H), 5.92 (br s, 1H),

[167] See ref. 157.
[168] De Matteis, V.; van Delft, F. L.; Jakobi, H.; Lindell, S.; Tiebes, J.; Rutjes, F. P. J. T. *J. Org. Chem.* **2006**, *71*, 7527.

5.76 (q, *J* = 1.4 Hz, 1H), 4.64 (br s, 2H), 2.46 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.48 (s, 3F).

- **General procedure for the synthesis of starting fluorinated benzaldehydes 2.3a-p**

This procedure was adapted from the literature procedure.[164] A solution of the corresponding commercially available salicylaldehyde **2.2a-g** or *N*-(2-formylaryl)-4-methylbenzenesulfonamide **2.2h-k**[169] (0.78 mmol, 1.1 equiv) and K_2CO_3 (98 mg, 0.71 mmol, 1.0 equiv) in dry acetonitrile (2 mL) in a pressure vial was heated in an oil bath at 60 °C for 10 min. A solution of the corresponding tosylate **2.1** (200 mg, 0.71 mmol, 1.0 equiv) in dry acetonitrile (2 mL) was added and the resulting mixture was heated at the same temperature for 16 h. Water (4 mL) was added to quench the reaction and the aqueous phase was extracted with ethyl acetate (3x 10 mL). The combined organic phases were washed with brine (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel [*n*-hexane-EtOAc (10:1)] to afford fluorinated benzaldehydes **2.3a-p**.

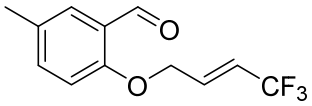


2.3a

(*E*)-2-[(4,4,4-Trifluorobut-2-en-1-yl)oxy]benzaldehyde (2.3a): Starting from salicylaldehyde **2.2a** and tosylate **2.1a** and following the procedure described above, **2.3a** was obtained as a white solid (mp=51-53 °C) in 85% yield (139 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.53 (d, *J* = 0.7 Hz, 1H), 7.88 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.57 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H), 7.15–7.06 (m, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.66-6.56 (m, 1H), 6.19–6.02 (m, 1H), 4.84–4.73 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.46--64.51 (m, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2, 160.0, 136.1, 134.2 (q, *J* = 6.5 Hz), 129.4, 125.3, 121.8, 120.5, 120.2 (q, 34.4 Hz), 118.2 (q, *J* = 275. Hz, CF_3),

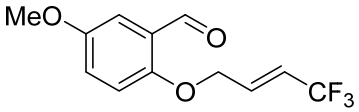
[169] Giustiniano, M.; Pelliccia, S.; Sangaletti, L.; Meneghetti, F.; Amato, J.; Novellino, E.; Tron, G. C. *Tetrahedron Lett.* **2017**, *58*, 4264.

116.4, 112.6, 66.2. HRMS (ESI/Q-TOF) m/z: $[M+Me]^+$ Calcd for $C_{12}H_{12}F_3O_2$ 245.0784; found 245.0786. (Methanol was used for sample preparation).



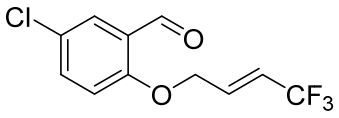
2.3b

(*E*)-5-Methyl-2-[(4,4,4-trifluorobut-2-en-1-yl)oxy]benzaldehyde (2.3b): Starting from 5-methylsalicylaldehyde **2.2b** and tosylate **2.1a** and following the procedure described above, **2.3b** was obtained as a white solid (mp=50-52 °C) in 78% yield (136 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.50 (s, 1H), 7.67 (d, *J* = 2.2 Hz, 1H), 7.36 (ddd, *J* = 8.5, 2.2, 0.6 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 6.67–6.53 (m, 1H), 6.20–6.00 (m, 1H), 4.81–4.69 (m, 2H), 2.33 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.44--64.497 (m, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4, 158.2, 136.7, 134.4 (d, *J* = 6.4 Hz), 131.4), 129.3, 125.0, 121.7 (d, *J* = 273.5 Hz).120.1 (d, *J* = 34.6 Hz), 112.7, 66.4, 20.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{12}F_3O_2$ 245.0784; found 245.0786.



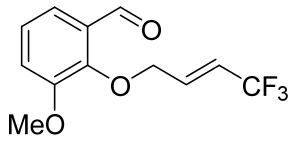
2.3c

(*E*)-5-Methoxy-2-[(4,4,4-trifluorobut-2-en-1-yl)oxy]benzaldehyde (2.3c): Starting from 5-methoxysalicylaldehyde **2.2c** and tosylate **2.1a** and following the procedure described above, **2.3c** was obtained as a white solid (mp=55-57 °C) in 69% yield (127 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.50 (s, 1H), 7.36 (d, *J* = 3.3 Hz, 1H), 7.13 (dd, *J* = 9.0, 3.3 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 1H), 6.64-6.54 (m, 1H), 6.14–6.00 (m, 1H), 4.78–4.70 (m, 2H), 3.82 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.45--64.50 (m, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.1, 155.0, 154.6, 134.6 (q, *J* = 6.3 Hz), 127.6 (q, *J* = 275.3 Hz, CF_3), 125.8, 123.6, 120.2 (q, *J* = 34.5 Hz), 114.8, 111.2, 67.1, 56.1. HRMS (ESI/Q-TOF) m/z: $[M+Me]^+$ Calcd for $C_{13}H_{14}F_3O_3$ 275.0878; found 275.0888. (Methanol was used for sample preparation).



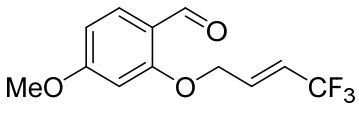
2.3d

(*E*)-5-Chloro-2-[(4,4,4-trifluorobut-2-en-1-yl)oxy]benzaldehyde (2.3d): Starting from 5-chlorosalicylaldehyde **2.2d** and tosylate **2.1a** and following the procedure described above, **2.3d** was obtained as a white solid (mp=33-35 °C) in 93% yield (174 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.76 (d, *J* = 2.7 Hz, 1H), 7.44 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.84 (d, *J* = 8.9 Hz, 1H), 6.57-6.47 (m, 1H), 6.10–5.91 (m, 1H), 4.75–4.66 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.53--64.58 (m, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.8, 158.5, 135.6, 133.7 (q, *J* = 6.4 Hz), 128.9, 127.6, 126.3 (q, *J* = 274.1 Hz, CF_3), 126.2, 120.5 (q, *J* = 34.7 Hz), 66.6. HRMS (ESI/Q-TOF) m/z: $[M+Me]^+$ Calcd for $C_{12}H_{11}ClF_3O_2$ 279.0394; found 279.0393. (Methanol was used for sample preparation.



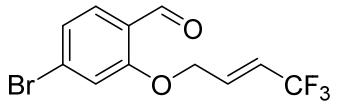
2.3e

(*E*)-3-Methoxy-2-((4,4,4-trifluorobut-2-en-1-yl)oxy)benzaldehyde (2.3e): Starting from 3-methoxysalicylaldehyde **2.2e** and tosylate **2.1a** and following the procedure described above, **2.3e** was obtained as a white solid in 86% yield (160 mg). The product could not be separated from the excess of 3-methoxysalicylaldehyde and was used as a mixture in the subsequent step. The given yield has already been corrected considering the purity of the product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.4 (s, 1H), 7.44 (dd, *J* = 6.5, 2.9 Hz, 1H), 7.19–7.17 (m, 2H), 6.60-6.54 (m, 1H), 6.16–6.06 (m, 1H), 4.76 (m, 2H), 3.90 (s, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -64.41--64.42 (m, 3F).



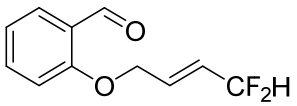
2.3f

(*E*)-4-methoxy-2-((4,4,4-trifluorobut-2-en-1-yl)oxy)benzaldehyde (2.3f): Starting from salicylaldehyde **2.2f** and tosylate **2.1a** and following the procedure described above, **2.3f** was obtained as a light yellow solid (mp=59-61 °C) in 82% yield (152 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.35 (s, 1H), 7.85 (d, *J* = 8.7 Hz, 1H), 6.66–6.52 (m, 2H), 6.40 (d, *J* = 2.2 Hz, 1H), 6.18-6.04 (m, 1H), 4.78-4.72 (m, 2H), 3.88 (s, 3H).^{19}F NMR (282 MHz, $CDCl_3$) δ -64.47--64.52 (m, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.8, 166.2, 161.7, 134.0 (q, *J* = 6.4 Hz), 131.5, 122.8 (q, *J* = 269.4 Hz, CF_3), 120.2 (q, *J* = 34.5 Hz), 106.5, 99.3, 66.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{12}F_3O_3$ 261.0733; found 261.0735.



2.3g

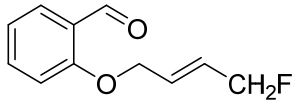
(*E*)-4-bromo-2-((4,4,4-trifluorobut-2-en-1-yl)oxy)benzaldehyde (2.3g): Starting from salicylaldehyde **2.2g** and tosylate **2.1a** and following the procedure described above, **2.3g** was obtained as a white solid (mp=89-91 °C) in 55% yield (121 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.45 (d, *J* = 0.7 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.28-7.24 (m, 1H), 7.13 (d, *J* = 1.6 Hz, 1H), 6.66–6.53 (m, 1H), 6.17-6.03 (m, 1H), 4.83–4.73 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.54--64.58 (m, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.2, 160.1, 133.5 (q, *J* = 6.4 Hz), 130.7, 130.5, 125.4, 124.1, 123.4 (q, *J* = 275.4 Hz, CF_3), 120.6 (q, *J* = 34.7 Hz), 116.3, 66.6. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_9BrF_3O_2$ 308.9733; found 308.9732.



2.3h

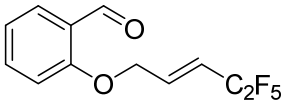
(*E*)-2-[(4,4-Difluorobut-2-en-1-yl)oxy]benzaldehyde (2.3h): Starting from salicylaldehyde **2.2a** and tosylate **2.1b** and following the procedure described above, **2.3h** was obtained as a colorless oil in 69% yield (104 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.54 (d, *J* = 0.7 Hz, 1H), 7.87 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.56 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H), 7.13–7.04 (m, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.41–5.90 (m, C*H*=C*H*-CF_2*H*, 3H), 4.78-4.73 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.11–-112.51

(m, 2F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4, 160.4, 136.1, 132.8 (t, *J* = 11.4 Hz), 129.1, 125.3, 125.3 (t, *J* = 24.2 Hz), 121.6, 114.1 (t, *J* = 235.2 Hz, <u>*C*</u>F_2H), 112.7, 66.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_{11}F_2O_2$ 213.0722; found 213.0722.



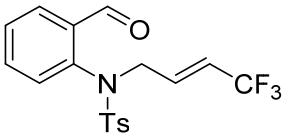
2.3i

(*E*)-2-((4-Fluorobut-2-en-1-yl)oxy)benzaldehyde (2.3i): Starting from salicylaldehyde **2.2a** and tosylate **2.1c** and following the procedure described above, **2.3i** was obtained as a colorless oil in 71% yield (98 mg). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 10.53 (d, *J* = 0.8 Hz, 1H), 7.85 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.54 (ddd, *J* = 8.4, 7.3, 1.9 Hz, 1H), 7.10–7.00 (m, 1H), 7.00–6.93 (m, 1H), 6.41–5.89 (m, 2H), 5.08–4.80 (m, 2H), 4.73-4.67 (dt, *J* = 4.9, 2.4 Hz, 2H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -215.01--215.61 (m, 1F). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 189.7, 160.8, 136.0, 128.8, 128.3 (d, *J* = 6.2 Hz), 128.1 (d, *J* = 11.2 Hz), 125.3, 121.2, 112.8, 82.4 (d, *J* = 164.9 Hz, <u>*C*</u>H_2F), 68.0. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_{12}FO_2$ 195.0816; found 195.0820.



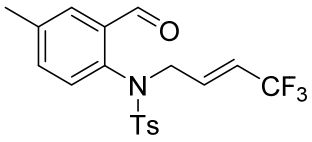
2.3j

(*E*)-2-[(4,4,5,5,5-Pentafluoropent-2-en-1-yl]oxy)benzaldehyde (2.3j): Starting from salicylaldehyde **2.2a** and tosylate **2.1d** and following the procedure described above, **2.3j** was obtained as a colorless oil in 63% yield (125 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.53 (d, *J* = 0.7 Hz, 1H), 7.88 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.57 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H), 7.16–7.07 (m, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.72–6.59 (m, 1H), 6.15-6.02 (m, 1H), 4.88–4.76 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -85.11 (t, *J* = 1.8 Hz, 3F), -115.83--115.91 (m, 2F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3, 160.1, 136.5 (t, *J* = 9.2 Hz), 136.2, 129.5, 125.4, 122.0, 121.3-116.3 (m, C_2F_5), 118.6 (t, *J* = 23.8 Hz), 112.7, 66.7. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{10}F_5O_2$ 281.0595; found 281.0594.



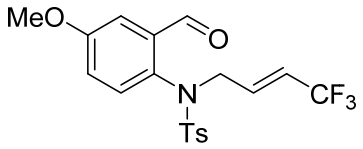
2.3k

(*E*)-*N*-(2-Formylphenyl)-4-methyl-*N*-(4,4,4-trifluorobut-2-en-1-yl)benzenesulfonamide (2.3k): Starting from *N*-(2-formylphenyl)-4-methylbenzenesulfonamide **2.2h** and tosylate **2.1a** and following the procedure described above, **2.3k** was obtained as a white solid (mp=99-101 °C) in 83% yield (225 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.29 (d, *J* = 0.5 Hz, 1H), 8.06–7.95 (m, 1H), 7.55–7.44 (m, 4H), 7.32-7.28 (m, 2H), 6.84–6.73 (m, 1H), 6.40–6.26 (m, 1H), 5.76–5.59 (m, 1H), 4.61-3.97 (m, 2H, CH_2), 2.45 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.73--64.77 (m, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.5, 144.9, 141.0, 135.8, 134.6, 134.4, 134.1 (d, *J* = 6.4 Hz), 131.6 (q, *J* = 272.5 Hz, CF_3), 130.1, 129.5 (q, *J* = 11.6 Hz), 128.6, 128.2, 123.1 (q, *J* = 34.5 Hz), 52.3, 21.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{17}F_3NO_3S$ 384.0876; found 384.0876.



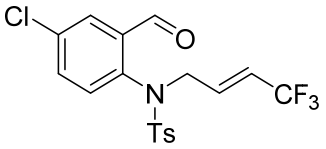
2.3l

(*E*)-*N*-(2-Formyl-4-methylphenyl)-4-methyl-*N*-(4,4,4-trifluorobut-2-en-1-yl) benzenesulfonamide (2.3l): Starting from *N*-(2-formyl-4-methylphenyl)-4-methylbenzenesulfonamide **2.2i** and tosylate **2.1a** and following the procedure described above, **2.3l** was obtained as a white solid (mp=70-72 °C) in 83% yield (233 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.24 (s, 1H), 7.79 (d, *J* = 2.1 Hz, 1H), 7.53–7.43 (m, 2H), 7.35–7.27 (m, 3H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.38-6.26 (m, 1H), 5.76–5.60 (m, 1H), 4.60-3.95 (m, 2H, CH_2), 2.45 (s, 3H), 2.42 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.69--64.73 (m, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8, 144.8, 139.8, 138.4, 135.4, 134.5, 134.2 (q, *J* = 6.4 Hz), 130.1, 129.9, 128.6 (q, *J* = 275.6 Hz, CF_3), 128.4, 128.2, 123.0 (q, *J* = 34.4 Hz), 52.4, 21.9, 21.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{19}F_3NO_3S$ 398.1032; found 398.1040.



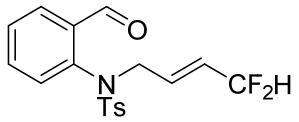
2.3m

(*E*)-*N*-(2-Formyl-4-methoxyphenyl)-4-methyl-*N*-(4,4,4-trifluorobut-2-en-1-yl) benzenesulfonamide (2.3m): Starting from *N*-(2-formyl-4-methoxyphenyl)-4-methylbenzenesulfonamide **2.2j** and tosylate **2.1a** and following the procedure described above, **2.3m** was obtained as a white solid (mp=81-83 °C) in 88% yield (258 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.24 (s, 1H), 7.52–7.42 (m, 3H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.01 (dd, *J* = 8.8, 3.1 Hz, 1H), 6.65 (d, *J* = 8.8 Hz, 1H), 6.37-6.27 (m, 1H), 5.76–5.61 (m, 1H), 4.58-4.44 (m, 1H, CH_2), 4.21–3.97 (m, 1H, CH_2), 3.87 (s, 3H), 2.45 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.68--64.72 (m, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4, 159.8, 144.7, 136.7, 134.3, 134.0 (q, *J* = 6.4 Hz), 133.6, 130.0, 129.6, 128.1, 122.9 (q, *J* = 34.5 Hz), 122.1 (q, *J* = 269.9 Hz, CF_3), 121.8, 111.6, 55.9, 52.3, 21.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{19}F_3NO_4S$ 414.0981; found 414.0982.



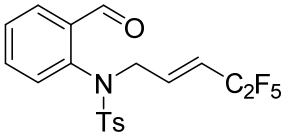
2.3n

(*E*)-*N*-(4-Chloro-2-formylphenyl)-4-methyl-*N*-(4,4,4-trifluorobut-2-en-1-yl) benzenesulfonamide (2.3n): Starting from *N*-(4-chloro-2-formylphenyl)-4-methylbenzenesulfonamide **2.2k** and tosylate **2.1a** and following the procedure described above, **2.3n** was obtained as a white solid (mp=98-100 °C in 75% yield (222 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.23 (s, 1H), 7.96 (d, *J* = 2.5 Hz, 1H), 7.49-7.44 (m, 3H), 7.30-7.33 (m, 2H), 6.70 (d, *J* = 8.5 Hz, 1H), 6.43–6.18 (m, 1H), 5.86–5.60 (m, 1H), 4.34 (m, 2H, CH_2), 2.46 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.73--64.77 (m, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.0, 145.1, 139.2, 136.9, 135.8, 134.3, 133.9, 133.6 (q, *J* = 6.5 Hz), 130.1, 129.7, 129.3, 128.2 (q, *J* = 270.8 Hz, CF_3), 128.1, 123.3 (q, *J* = 34.4 Hz), 52.1, 21.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{16}F_3ClNO_3S$ 418.0486; found 418.0487.



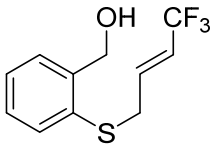
2.3o

(*E*)-N-(4,4-difluorobut-2-en-1-yl)-N-(2-formylphenyl)-4-methylbenzenesulfonamide (2.3o): Starting from salicylaldehyde **2.2h** and tosylate **2.1b** and following the procedure described above, **2.3o** was obtained as a white solid (mp=114-116 °C) in 55% yield (143 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.33 (d, *J* = 0.5 Hz, 1H), 8.07–7.95 (m, 1H), 7.56–7.43 (m, 4H), 7.32-7.27 (m, 2H), 6.82–6.72 (m, 1H), 6.22–5.73 (m, 2H, C*H*=CH-CF_2*H*), 5.73–5.51 (m, 1H), 4.70-3.85 (m, 2H, CH_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.20--112.46 (m, 2F). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 189.7, 144.7, 141.1, 135.8, 134.4, 134.3, 132.5 (t, *J* = 11.4 Hz), 130.0 (2xCH), 129.2, 128.1 (2xCH), 128.0 (t, *J* = 24.4 Hz), 113.6 (t, *J* = 235.2 Hz, CF_2H), 52.7, 21.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{18}F_2NO_3S$ 366.0970; found 366.0969.



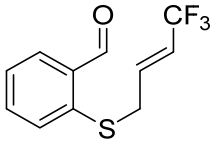
2.3p

(*E*)-*N*-(2-Formylphenyl)-4-methyl-N-(4,4,5,5,5-pentafluoropent-2-en-1-yl) benzenesulfonamide (2.3p): Starting from *N*-(2-formylphenyl)-4-methylbenzenesulfonamide **2.2h** and tosylate **2.1d** and following the procedure described above, **2.3p** was obtained as a white solid (mp=69-71 °C) in 83% yield (255 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.05–7.96 (m, 1H), 7.54–7.45 (m, 4H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.83–6.72 (m, 1H), 6.45–6.28 (m, 1H), 5.69-5.57 (m, 1H), 4.65-4.05 (m, 2H, CH_2), 2.45 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -85.29 (t, *J* = 1.7 Hz, 3F), -116.16–-116.37 (m, 2F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4, 144.8, 140.7, 136.1 (t, *J* = 9.8 Hz), 135.7, 134.4, 134.3, 130.0, 129.5, 129.3, 128.5, 128.1, 125.3-117.9 (m, C_2F_5), 121.7 (t, *J* = 23.8 Hz), 52.5, 21.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{17}F_5NO_3S$ 434.0844; found 434.0846.



2.5

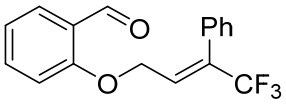
(*E*)-[2-(4,4,4-Trifluorobut-2-en-1-yl)thio]phenyl)methanol (2.5): This synthesis was adapted from the literature procedure.[170] Starting from (2-mercaptophenyl)methanol[171] **2.4** and tosylate **2.1a** and following the procedure described above, **2.5** was obtained as a yellow oil in 71% yield (125 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.44 (m, 1H), 7.43–7.38 (m, 1H), 7.35–7.30 (m, 2H), 6.48-6.36 (m, 1H), 5.65–5.43 (m, 1H), 4.83 (d, *J* = 6.3 Hz, 2H), 3.65–3.46 (m, 2H), 2.02 (t, *J* = 6.3 Hz, 1H, O*H*). ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.18–-64.27 (m, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 135.1 (q, *J* = 6.6 Hz), 132.8, 132.5, 129.9 (q, *J* = 286.5 Hz, CF_3), 128.9, 128.6, 128.3, 120.9 (q, *J* = 33.9 Hz), 63.9, 35.8.



2.3q

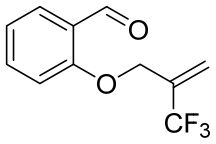
Synthesis of (*E*)-2-((4,4,4-trifluorobut-2-en-1-yl)thio)benzaldehyde (2.3q): The intermediate alcohol **2.5** was redissolved in 5 mL DCM and PCC (162 mg, 0.75 mmol, 1.5 equiv) was added in one portion. The resulting mixture was stirred for 2 h at room temperature and then it was filtered through a short pad of silica gel affording **2.3q** as a light yellow solid (mp=31-33 °C) in 58% yield (71 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.38 (s, 1H), 7.93–7.85 (m, 1H), 7.55 (td, *J* = 7.6, 1.6 Hz, 1H), 7.42-7.36 (m, 2H), 6.53–6.36 (m, 1H), 5.76-5.67 (m, 1H), 3.74–3.57 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.32 (s, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 139.1, 134.9, 134.5 (q, *J* = 6.5 Hz), 134.2, 132.6, 129.8, 126.8, 122.5 (q, *J* = 269.6 Hz, CF_3), 121.8 (q, *J* = 34.0 Hz), 34.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_{10}F_3OS$ 247.0399; found 247.0400.

[170] Piel, I.; Steinmetz, M.; Hirano, K.; Fröhlich, R.; Grimme, S.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 4983.
[171] Li, M.; Petersen, J. L.; Hoover, J. M. *Org. Lett* **2017**, *19*, 638.



2.3r

(*E*)-2-((4,4,4-Trifluoro-3-phenylbut-2-en-1-yl)oxy)benzaldehyde (2.3r): Starting from salicylaldehyde **2.2a** and bromide **2.1e** and following the procedure described above, **2.3r** was obtained as a light yellow oil in 82% yield (178 mg). Spectroscopic data are in agreement with those reported in the literature.[167] ^{1}H NMR (300 MHz, Chloroform-*d*) δ 10.45 (d, *J* = 0.8 Hz, 1H), 7.84 (dd, *J* = 7.7, 1.9, 1H), 7.52–7.41 (m, 4H), 7.34–7.27 (m, 2H), 7.08–7.00 (m, 1H), 6.78–6.64 (m, 2H), 4.64 (dq, *J* = 6.2, 2.1 Hz, 2H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -66.36 (s, 3F).

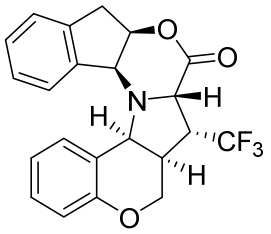


2.3s

2-((2-(Trifluoromethyl)allyl)oxy)benzaldehyde (2.3s): Starting from salicylaldehyde **2.2a** and tosylate **2.1f** and following the procedure described above, **2.3s** was obtained as a light yellow oil in 39% yield (64 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.52 (d, *J* = 0.7 Hz, 1H), 7.87 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.57 (ddd, *J* = 8.4, 7.4, 1.9 Hz, 1H), 7.17 – 7.06 (m, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.00 (q, *J* = 1.3 Hz, 1H), 5.86 (q, *J* = 1.4 Hz, 1H), 4.79 (s, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.42 (s, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4, 160.1, 136.1, 132.1 (q, *J* = 282.4 Hz, CF_3), 129.1, 128.0, 125.4, 121.9, 121.3 (q, *J* = 5.4 Hz), 112.6, 65.1 (q, *J* = 1.4 Hz). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_{10}F_3O_2$ 231.0627; found 231.0628.

- **General procedure for the asymmetric intramolecular dipolar cycloaddition of substrates 2.3 and azomethine ylide precursor IV**

A solution of the corresponding fluorinated benzaldehyde **2.3** (0.10 mmol, 1.0 equiv) and morpholinone **IV**[172] (28 mg, 0.15 mmol, 1.5 equiv) in toluene (3 mL) was heated at 120 °C for 16 h in a pressure vial. The solvent was removed under reduced pressure and the crude was purified by flash chromatography on silica gel [*n*-hexane-EtOAc (10:1 to 4:1)] to afford **2.6**. The diastereomeric ratio (d.r.) was determined by ^{19}F-NMR of the crude mixture. Major diastereoisomers were characterised as follows.



2.6a

(9a*R*,14b*S*)-17-(Trifluoromethyl)-7,7a,9a,14b-tetrahydro-10*H*,16*H*-7,16-methanobenzo[*b*]indeno[1',2':5,6][1,4]oxazino[4,3-*e*][1,5]oxazocin-8(6*H*)-one (2.6a): Starting from **2.3a**, **2.6a** was obtained as a white solid (mp=75-77 °C) in 73% yield (29 mg). $[\alpha]_D^{25}$ = -62.7° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.27 (m, 2H), 7.25–7.15 (m, 3H), 7.00 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.96–6.83 (m, 2H), 5.55–5.42 (m, 1H), 4.54 (d, *J* = 4.9 Hz, 1H), 4.49 (d, *J* = 7.2 Hz, 1H), 4.28 (dd, *J* = 11.4, 5.6 Hz, 1H), 4.20 (dd, *J* = 11.4, 3.6 Hz, 1H), 4.09 (d, *J* = 8.9 Hz, 1H), 3.43–3.17 (m, 3H), 3.05-2.98 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.64 (d, *J* = 10.1 Hz, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 155.7, 139.3, 139.3, 130.1, 129.6, 129.3, 127.6, 126.2 (q, *J* = 278.7 Hz, CF_3), 126.0, 125.2, 121.7, 121.2, 117.6, 81.2, 66.0, 58.2, 57.8, 56.4, 48.0 (q, *J* = 29.0 Hz), 38.9, 37.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{19}F_3NO_3$ 402.1312; found 402.1310.

[172] This compound was prepared according to ref. 142.

HOESY

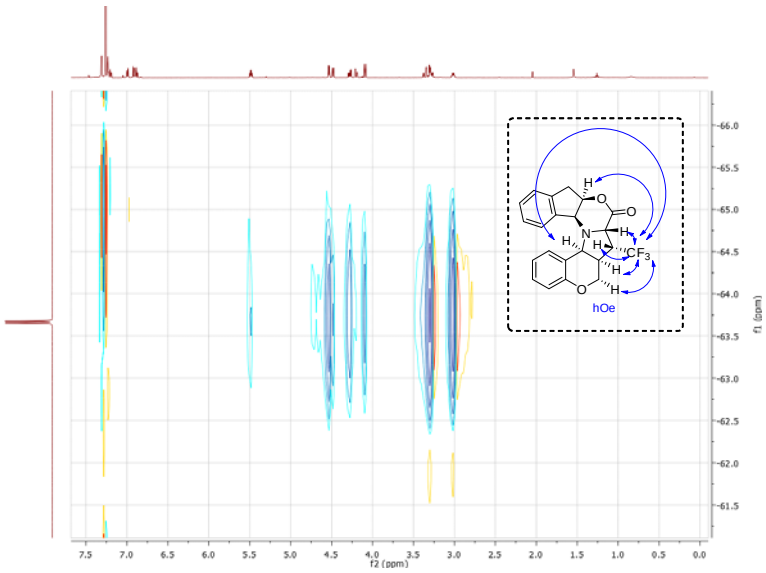


Figure S2.1 HOESY spectrum of compound **2.6a**.

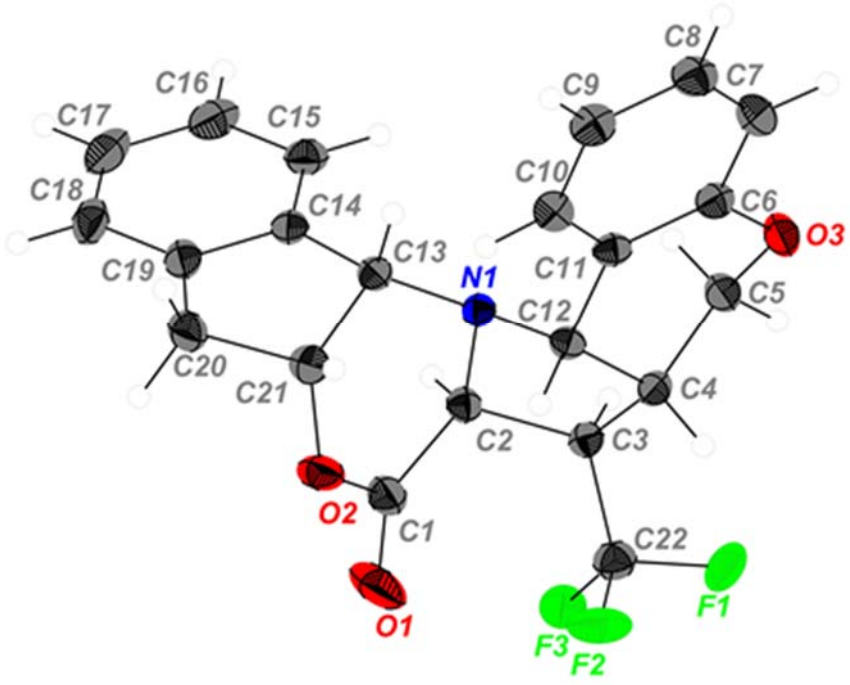
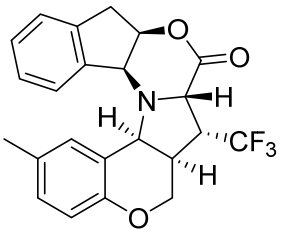


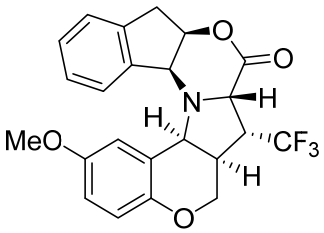
Figure S2.2 X-Ray structure of **2.6a**[173] (Ortep diagram).

[173] CCDC 1899383 contains the supplementary crystallographic data of compound **2.6a**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk].



2.6b

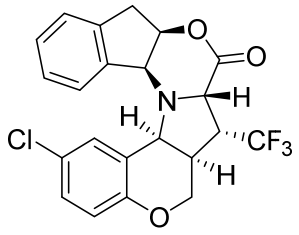
(9a*R*,14b*S*)-2-Methyl-17-(trifluoromethyl)-7,7a,9a,14b-tetrahydro-10*H*,16*H*-7,16-methanobenzo[*b*]indeno[1',2':5,6][1,4]oxazino[4,3-*e*][1,5]oxazocin-8(6*H*)-one (2.6b): Starting from **2.3b**, **2.6b** was obtained as a white solid (mp=38-40 °C) in 88% yield (37 mg). $[\alpha]_D^{25}$ = -47.4° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.28 (m, 2H), 7.28–7.20 (m, 2H), 7.01 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.78 (d, *J* = 2.1 Hz, 1H), 5.50 (ddd, *J* = 5.3, 4.9, 4.2 Hz, 1H), 4.56 (d, *J* = 4.9 Hz, 1H), 4.44 (d, *J* = 7.3 Hz, 1H), 4.25 (dd, *J* = 11.4, 5.6 Hz, 1H), 4.14 (dd, *J* = 11.4, 3.6 Hz, 1H), 4.09 (d, *J* = 8.8 Hz, 1H), 3.44 – 3.16 (m, 3H), 3.03-2.95 (m, 1H), 2.21 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.55 (d, *J* = 10.1 Hz, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 153.5, 139.3, 139.3, 131.0, 130.3, 130.1, 129.3, 127.6, 126.2 (q, *J* = 278.6 Hz, CF_3), 126.0, 125.2, 121.0, 117.3, 81.2, 66.1, 58.3, 57.9, 56.5, 47.9 (q, *J* = 28.9 Hz), 38.9, 37.3 (q, *J* = 1.9 Hz), 20.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{21}F_3NO_3$ 416.1468; found 416.1471.



2.6c

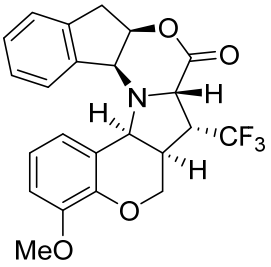
(9a*R*,14b*S*)-2-Methoxy-17-(trifluoromethyl)-7,7a,9a,14b-tetrahydro-10*H*,16*H*-7,16-methanobenzo[*b*]indeno[1',2':5,6][1,4]oxazino[4,3-*e*][1,5]oxazocin-8(6*H*)-one (2.6c): Starting from **2.3c**, **2.6c** was obtained as a white solid (mp=45-47 °C) in 75% yield (32 mg). $[\alpha]_D^{25}$ = -46.0° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.18 (m, 4H), 6.84 (d, *J* = 8.9 Hz, 1H), 6.76 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.45 (d, *J* = 3.0 Hz, 1H), 5.43 (dt, *J* = 10.0, 5.0 Hz, 1H), 4.59–4.42 (m, 2H), 4.26 (dd, *J* = 11.5, 4.7 Hz, 1H), 4.12 (dd, *J* = 11.5, 3.3 Hz, 1H), 4.07 (d, *J* = 8.8 Hz, 1H), 3.64 (s, 3H), 3.50–3.20 (m, 3H), 3.05-2.98 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$)

δ -63.62 (d, *J* = 10.2 Hz, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 154.2, 149.8, 139.4, 139.4, 129.4, 127.5, 126.2 (q, *J* = 278.9 Hz, CF_3), 126.0, 125.3, 122.4, 118.1, 114.9, 114.7, 81.2, 66.3, 58.2, 58.1, 56.7, 55.7, 48.2 (q, *J* = 28.8 Hz), 38.7, 37.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{21}F_3NO_4$ 432.1417; found 432.1413.



2.6d

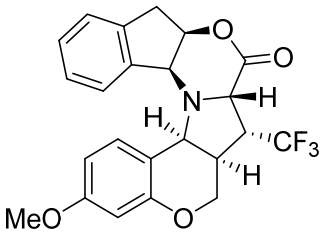
(9a*R*,14b*S*)-2-Chloro-17-(trifluoromethyl)-7,7a,9a,14b-tetrahydro-10*H*,16*H*-7,16-methanobenzo[*b*]indeno[1',2':5,6][1,4]oxazino[4,3-*e*][1,5]oxazocin-8(6*H*)-one (2.6d): Starting from **2.3d**, **2.6d** was obtained as a white solid (mp=46-48 °C) in 71% yield (31 mg). $[\alpha]_D^{25}$ = -31.0° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.30 (m, 2H), 7.29–7.21 (m, 2H), 7.15 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.92 (d, *J* = 2.5 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 5.44 (dt, *J* = 9.8, 4.9 Hz, 1H), 4.50–4.43 (m, 2H), 4.29 (dd, *J* = 11.5, 5.1 Hz, 1H), 4.18 (dd, *J* = 11.5, 3.4 Hz, 1H), 4.08 (d, *J* = 8.9 Hz, 1H), 3.46–3.22 (m, 3H), 3.07–2.98 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.61 (d, *J* = 10.1 Hz, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 154.3, 139.4, 139.0, 129.7, 129.6, 129.4, 127.6, 126.5, 126.1, 126.1 (q, *J* = 278.7 Hz, CF_3), 125.2, 123.0, 119.0, 81.2, 66.1, 58.1, 57.7, 56.6, 56.6, 48.0 (q, *J* = 28.9 Hz), 38.8, 37.0 (q, *J* = 1.9 Hz). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{18}ClF_3NO_3$ 436.0922; found 436.0924.



2.6e

(9a*R*,14b*S*)-4-Methoxy-17-(trifluoromethyl)-7,7a,9a,14b-tetrahydro-10*H*,16*H*-7,16-methanobenzo[*b*]indeno[1',2':5,6][1,4]oxazino[4,3-

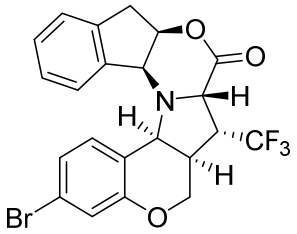
***e*][1,5]oxazocin-8(6*H*)-one (2.6e):** Starting from **2.3e**, **2.6e** was obtained as a yellow solid (mp=42-44 °C) in 67% yield (29 mg). $[\alpha]_D^{25}$ = -61.4° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.30 (m, 2H), 7.25–7.20 (m, 2H), 6.88–6.77 (m, 2H), 6.60 (dd, *J* = 6.6, 2.5 Hz, 1H), 5.50–5.42 (m, 1H), 4.53 (d, *J* = 4.9 Hz, 1H), 4.50 (d, *J* = 7.3 Hz, 1H), 4.38 (dd, *J* = 11.4, 5.5 Hz, 1H), 4.25 (dd, *J* = 11.4, 3.5 Hz, 1H), 4.08 (d, *J* = 8.8 Hz, 1H), 3.89 (s, 3H), 3.41–3.22 (m, 3H), 3.06–2.97 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.65 (d, *J* = 10.1 Hz, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 148.7, 145.1, 139.3, 139.3, 129.3, 127.6, 126.1 (q, *J* = 278.6 Hz, CF_3), 125.9, 125.2, 122.0, 121.5, 121.3, 111.1, 81.2, 66.4, 58.2, 57.7, 56.4, 56.1, 47.9 (q, *J* = 28.9 Hz), 38.8, 37.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{21}F_3NO_4$ 432.1417; found 432.1424.



2.6f

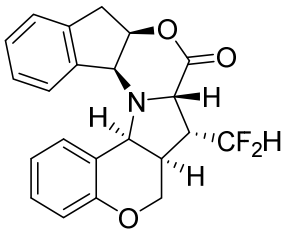
(6a*R*,7*R*,7a*S*,9a*R*,14b*S*,15a*S*)-3-methoxy-7-(trifluoromethyl)-6a,7,7a,9a,14b,15a-hexahydro-6*H*,8*H*,10*H*-chromeno[3',4':4,5]pyrrolo[1,2-d]indeno[2,1-b][1,4]oxazin-8-one (2.6f): Starting from **2.3f**, **2.6f** was obtained as a light yellow solid (mp=108-110 °C) in 77% yield (33 mg). $[\alpha]_D^{25}$ = -68.9° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, Chloroform-*d*) δ 7.36–7.24 (m, 2H), 7.27–7.19 (m, 2H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.53–6.41 (m, 2H), 5.48 (td, *J* = 5.3, 4.1 Hz, 1H), 4.52 (d, *J* = 4.9 Hz, 1H), 4.41 (d, *J* = 7.0 Hz, 1H), 4.25 (dd, *J* = 11.3, 6.1 Hz, 1H), 4.18 (dd, *J* = 11.3, 3.9 Hz, 1H), 4.09 (d, *J* = 8.9 Hz, 1H), 3.76 (s, 3H), 3.43–3.11 (m, 3H), 2.96 (qd, *J* = 6.3, 3.8 Hz, 1H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -63.70 (d, *J* = 10.2 Hz, 3F). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 165.7, 160.7, 156.6, 139.3, 130.8, 130.3, 129.3, 127.6, 126.2 (d, *J* = 278.6 Hz, CF_3), 126.0, 125.1, 113.0, 108.9, 101.9, 81.2, 66.1, 58.0, 57.5, 56.3, 55.5, 48.0 (q, *J* = 29.0 Hz), 38.9, 37.0 (q, *J* = 2.2 Hz). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{21}F_3NO_4$ 432.1417; found 432.1418. The minor diastereoisomer was isolated in a mixed fraction with the major one. The ^1H NMR signals given next were inferred from the spectrum of the mixture. ^1H NMR (300 MHz, $CDCl_3$) δ 7.73–7.66 (m, 1H), 7.44–7.32 (m, 3H), 7.30–7.22 (m, 1H), 6.57–6.48 (m, 2H), 5.12 (ddd, *J* = 5.7, 4.2, 1.7 Hz, 1H), 4.98 (d, *J* = 5.7 Hz, 1H), 4.56 (d, *J* = 5.2

Hz, 1H), 4.19–4.09 (m, 1H), 3.96 (dd, *J* = 11.0 Hz, 11.0 Hz, 1H), 3.79 (s, 3H), 3.65 (d, *J* = 6.2 Hz, 1H), 3.26–3.09 (m, 2H), 2.91–2.73 (m, 1H), 2.67 (dtd, *J* = 11.3, 5.1, 2.1 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -69.78 (d, *J* = 9.4 Hz, 3F).



2.6g

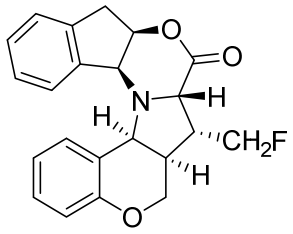
(6a*R*,7*R*,7a*S*,9a*R*,14b*S*,15a*S*)-3-bromo-7-(trifluoromethyl)-6a,7,7a,9a,14b,15a-hexahydro-6*H*,8*H*,10*H*-chromeno[3',4':4,5]pyrrolo[1,2-d]indeno[2,1-b][1,4]oxazin-8-one (2.6g): Starting from **2.3g**, **2.6g** was obtained as a white solid (mp=88-90 °C) in 60% yield (29 mg). $[\alpha]_D^{25}$ = -57.7° (c 1.0; $CHCl_3$). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36–7.28 (m, 2H), 7.27–7.18 (m, 2H), 7.10 (d, *J* = 2.0 Hz, 1H), 7.01 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.83 (d, *J* = 8.2, 1H), 5.45 (dt, *J* = 5.6, 4.5 Hz, 1H), 4.47 (d, *J* = 4.5 Hz, 1H), 4.44 (d, *J* = 7.2 Hz, 1H), 4.27 (dd, *J* = 11.5, 5.6 Hz, 1H), 4.19 (dd, *J* = 11.5, 3.6 Hz, 1H), 4.08 (d, *J* = 8.9 Hz, 1H), 3.49–3.17 (m, 3H), 3.01 (tdd, *J* = 6.8, 5.6, 3.6 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.67 (d, *J* = 10.0 Hz, 3F). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.4, 156.3, 139.3, 139.1, 131.2, 129.5, 127.7, 126.1, 126.1 (d, *J* = 278.7 Hz, CF_3), 125.1, 125.0, 122.7, 120.8, 120.3, 81.2, 66.1, 58.2, 57.5, 56.5, 48.1 (q, *J* = 29.0 Hz), 38.8, 36.9 (d, *J* = 2.3 Hz), 36.9. HRMS (ESI/Q-TOF) m/z: $[M+Me]^+$ Calcd for $C_{22}H_{18}BrF_3NO_3$ 480.0417; found 480.0409.



2.6h

(9a*R*,14b*S*)-17-(Difluoromethyl)-7,7a,9a,14b-tetrahydro-10*H*,16*H*-7,16-methanobenzo[*b*]indeno[1',2':5,6][1,4]oxazino[4,3-*e*][1,5]oxazocin-8(6*H*)-one (2.6h): Starting from **2.3h**, **2.6h** was obtained as a white solid (mp=69-71 °C) in 68% yield (26 mg). $[\alpha]_D^{25}$ = -94.3° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.17 (m, 5H), 7.12 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.97 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.92

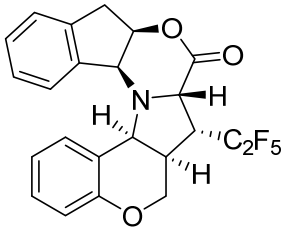
(td, *J* = 7.4, 1.2 Hz, 1H), 6.44 (td, *J* = 56.1, 3.0 Hz, 1H), 5.64 (td, *J* = 4.7, 2.2 Hz, 1H), 4.75 (d, *J* = 4.7 Hz, 1H), 4.29–4.12 (m, 3H), 4.07 (d, *J* = 9.5 Hz, 1H), 3.38–3.20 (m, 2H), 2.97-2.89 (m, 1H), 2.79-2.62 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -118.65 (ddd, *J* = 285.9, 56.1, 6.3 Hz), -125.12 (ddd, *J* = 285.9, 56.1, 29.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 155.6, 139.0, 138.9, 130.9, 129.8, 129.1, 127.7, 126.0, 124.7, 120.9, 120.5, 117.7, 115.64 (dd, *J* = 241.3, 238.7 Hz, CF_2H), 80.8, 66.4, 58.0, 57.6, 55.5 (dd, *J* = 6.8, 2.1 Hz), 45.4 (dd, *J* = 22.1, 22.1 Hz,), 39.2, 34.8 (dd, *J* = 3.9, 2.4 Hz). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{20}F_2NO_3$ 384.1406; found 384.1404.



2.6i

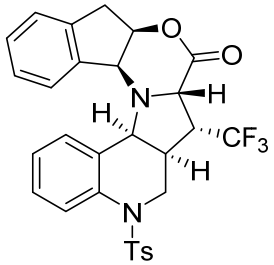
(6a*R*,7*R*,7a*S*,9a*R*,14b*S*,15a*S*)-7-(Fluoromethyl)-6a,7,7a,9a,14b,15a-hexahydro-6*H*,8*H*,10*H*-chromeno[3',4':4,5]pyrrolo[1,2-*d*]indeno[2,1-*b*][1,4]oxazin-8-one (2.6i): Starting from **2.3i**, **2.6i** was obtained in 72% overall yield as a 62:38 mixture of two diastereoisomers which were separated by flash column chromatography. Major diastereoisomer: light yellow oil (127 mg, 49% yield). $[\alpha]_D^{25}$ = -85.0° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.31–7.19 (m, 5H), 7.15 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.99–6.87 (m, 2H), 5.63 (td, *J* = 4.5, 1.7 Hz, 1H), 4.85 (d, *J* = 4.3 Hz, 1H), 4.76 (d, *J* = 4.5 Hz, 1H), 4.69 (d, *J* = 4.6 Hz, 1H), 4.32–4.13 (m, 3H), 4.02 (d, *J* = 9.3 Hz, 1H), 3.41–3.05 (m, 2H), 2.75–2.44 (m, 2H).^{19}F NMR (282 MHz, Chloroform-*d*) δ -221.22 (td, *J* = 46.9, 31.0 Hz). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 168.8, 155.3, 139.1, 139.0, 131.0, 129.6, 128.9, 127.5, 126.0, 124.7, 120.7, 117.6, 83.5 (d, *J* = 166.8 Hz, CH_2F), 80.7, 66.1, 58.5, 57.4 (d, *J* = 1.4 Hz), 55.7 (d, *J* = 5.8 Hz), 42.5 (d, *J* = 19.9 Hz), 39.3, 39.0 (d, *J* = 1.9 Hz). Minor diastereoisomer: light yellow oil (60 mg, 23% yield). $[\alpha]_D^{25}$ = +111.8° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.82–7.68 (m, 1H), 7.43–7.24 (m, 5H), 7.00 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.92 (td, *J* = 7.4, 1.3 Hz, 1H), 5.13 (ddd, *J* = 5.4, 4.4, 1.1 Hz, 1H), 5.00 (d, *J* = 5.1 Hz, 1H), 4.83–4.65 (m, 1H), 4.68–4.49 (m, 1H), 4.50 (d, *J* = 5.6 Hz, 1H), 4.14 (dd, *J* = 10.7, 5.1 Hz, 1H), 3.95 (t, *J* = 11.1 Hz, 1H), 3.49 (d, *J* = 7.7 Hz, 1H), 3.23–3.02 (m, 2H), 2.58-2.49 (m, 1H), 2.32–2.11 (m, 1H). ^{19}F NMR (282

MHz, Chloroform-*d*) δ -226.68 (td, *J* = 47.2, 30.7 Hz). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 169.5, 155.6, 141.8, 137.5, 130.8, 129.8, 129.0, 127.6, 126.9, 125.5, 120.6, 117.9, 84.2 (d, *J* = 169.7 Hz, CH_2F), 66.1, 59.7, 56.2, 55.7 (d, *J* = 5.4 Hz), 43.1 (d, *J* = 19.0 Hz), 38.3, 36.9 (d, *J* = 2.2 Hz). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{21}FNO_3$ 366.1500; found 366.1508.



2.6j

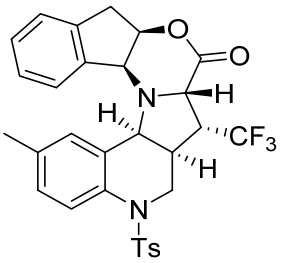
(9a*R*,14b*S*)-17-(Perfluoroethyl)-7,7a,9a,14b-tetrahydro-10*H*,16*H*-7,16-methanobenzo[*b*]indeno[1',2':5,6][1,4]oxazino[4,3-*e*][1,5]oxazocin-8(6*H*)-one (2.6j): Starting from **2.3j**, **2.6j** was obtained as a white solid (mp=40-42 °C) in 75% yield (34 mg). $[\alpha]_D^{25}$ = -22.5° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.14 (m, 5H), 7.08–6.83 (m, 3H), 5.50 (ddd, *J* = 5.3, 5.3, 5.3 Hz, 1H), 4.50 (d, *J* = 5.2 Hz, 1H), 4.46 (d, *J* = 7.4 Hz, 1H), 4.28–4.12 (m, 2H), 4.08 (d, *J* = 8.1 Hz, 1H), 3.41–3.31 (m, 2H), 3.30-3.13 (m, 1H), 3.11–2.97 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -82.32 (s, 3F), -109.46 (dd, *J* = 272.1, 9.1 Hz, 1F), -116.14 (dd, *J* = 272.1, 26.2 Hz, 1F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 156.1, 139.4, 139.4, 130.2, 129.6, 129.4, 127.7, 125.9, 125.3, 121.8, 121.2, 120.9-111.5 (m, C_2F_5), 117.6, 81.2, 66.5, 58.5, 57.8 (d, *J* = 3.0 Hz), 57.3, 46.5 (dd, *J* = 22.9, 21.9 Hz, <u>*C*</u>H-C_2F_5), 39.0, 36.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{19}F_5NO_3$ 452.1280; found 452.1277.



2.6k

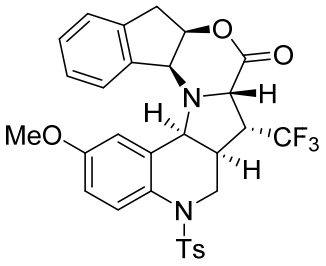
(9a*R*,14b*S*)-5-Tosyl-17-(trifluoromethyl)-5,7,7a,9a,14b,16-hexahydro-10*H*-7,16-methanobenzo[*f*]indeno[1',2':5,6][1,4]oxazino[4,3-*a*][1,5]diazocin-

8(6*H*)-one (2.6k): Starting from **2.3k**, **2.6k** was obtained as a white solid (mp=81-83 °C) in 70% yield (39 mg). $[\alpha]_D^{25}$ = -11.3° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.78–7.68 (m, 2H), 7.56 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.37–7.13 (m, 9H), 5.48 (td, *J* = 4.9, 1.7 Hz, 1H), 4.41 (d, *J* = 5.0 Hz, 1H), 4.06 (d, *J* = 7.7 Hz, 1H), 3.99 (d, *J* = 9.0 Hz, 1H), 3.89–3.72 (m, 2H), 3.36–3.13 (m, 3H), 3.02-2.93 (m, 1H), 2.46 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.45 (d, *J* = 9.5 Hz, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 144.3, 139.1, 139.0, 138.5, 137.9, 130.2, 129.7, 129.3, 129.3 (q, *J* = 275.0 Hz, CF_3), 129.0, 127.9, 127.2, 125.9, 125.6, 125.0, 124.0, 80.6, 59.5, 59.2, 56.3, 49.6, 48.9 (q, *J* = 29.1 Hz), 40.1, 39.4, 21.7. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{26}F_3N_2O_4S$ 555.1560; found 555.1563.



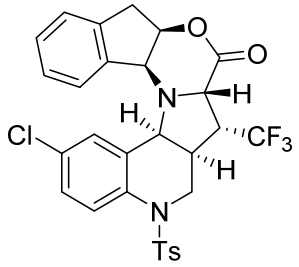
2.6l

(9a*R*,14b*S*)-2-Methyl-5-tosyl-17-(trifluoromethyl)-5,7,7a,9a,14b,16-hexahydro-10*H*-7,16-methanobenzo[*f*]indeno[1',2':5,6][1,4]oxazino[4,3-*a*][1,5]diazocin-8(6*H*)-one (2.6l): Starting from **2.3l**, **2.6l** was obtained as a white solid (mp=74-76 °C) in 67% yield (38 mg). $[\alpha]_D^{25}$ = +17.1° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.69–7.62 (m, 2H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.22–7.14 (m, 4H), 7.04 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.93 (s, 1H), 5.39 (td, *J* = 4.9, 1.8 Hz, 1H), 4.36 (d, *J* = 5.0 Hz, 1H), 3.97 (d, *J* = 7.7 Hz, 1H), 3.83 (d, *J* = 9.0 Hz, 1H), 3.77 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.65 (dd, *J* = 14.0, 5.4 Hz, 1H), 3.32–3.05 (m, 3H), 2.95–2.79 (m, 1H), 2.39 (s, 3H), 2.23 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.46 (d, *J* = 9.5 Hz, 3F). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 165.5, 144.1, 139.0, 138.6, 138.0, 136.4, 135.6, 130.1, 129.7, 129.6, 129.6, 129.3, 127.9, 127.2, 125.9, 125.7 (q, *J* = 278.1 Hz, CF_3), 125.0, 124.1, 80.6, 59.5, 59.4, 56.3, 49.6, 49.1 (q, *J* = 29.3 Hz), 40.1, 39.4, 21.7, 21.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{30}H_{28}F_3N_2O_4S$ 569.1716; found 569.1700.



2.6m

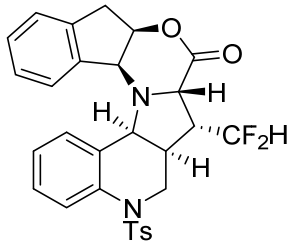
(9a*R*,14b*S*)-2-Methoxy-5-tosyl-17-(trifluoromethyl)-5,7,7a,9a,14b,16-hexahydro-10*H*-7,16-methanobenzo[*f*]indeno[1',2':5,6][1,4]oxazino[4,3-*a*][1,5]diazocin-8(6*H*)-one (2.6m): Starting from **2.3m**, **2.6m** was obtained as a white solid (mp=63-65 °C) in 76% yield (44 mg). $[\alpha]_D^{25}$ = +37.1° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.29–7.19 (m, 4H), 6.83 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.76 (d, *J* = 2.9 Hz, 1H), 5.33 (td, *J* = 5.0, 2.1 Hz, 1H), 4.41 (d, *J* = 4.9 Hz, 1H), 4.11–3.98 (m, 2H), 3.73 (s, 3H), 3.69 (d, *J* = 9.2 Hz, 1H), 3.52 (dd, *J* = 14.3, 6.7 Hz, 1H), 3.28 (dd, *J* = 17.1, 2.0 Hz, 1H), 3.23–3.03 (m, 2H), 3.02–2.88 (m, 1H), 2.46 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.53 (d, *J* = 9.3 Hz, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 157.8, 144.2, 139.1, 138.5, 137.9, 132.3, 131.1, 130.2, 129.5, 128.0, 127.4, 126.5, 126.1, 125.6 (q, *J* = 278.0 Hz, CF_3), 125.0, 114.3, 113.4, 80.8, 60.0, 59.4, 56.5, 55.7, 49.9 (q, *J* = 29.4 Hz), 49.3, 39.7, 39.3, 21.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{30}H_{28}F_3N_2O_5S$ 585.1666; found 585.1642.



2.6n

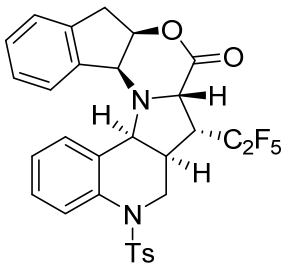
(9a*R*,14b*S*)-2-Chloro-5-tosyl-17-(trifluoromethyl)-5,7,7a,9a,14b,16-hexahydro-10*H*-7,16-methanobenzo[*f*]indeno[1',2':5,6][1,4]oxazino[4,3-*a*][1,5]diazocin-8(6*H*)-one (2.6n): Starting from **2.3n**, **2.6n** was obtained as a white solid (mp=95-97 °C) in 51% yield (30 mg). $[\alpha]_D^{25}$ = +48.0° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.79–7.66 (m, 2H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.32 – 7.20 (m, 5H), 7.17 (d, *J* = 2.4 Hz, 1H), 5.40 (td, *J* = 4.9, 2.1 Hz, 1H),

4.39 (d, *J* = 4.9 Hz, 1H), 4.04 (d, *J* = 7.6 Hz, 1H), 3.92 (dd, *J* = 14.2, 6.1 Hz, 1H), 3.83 (d, *J* = 9.2 Hz, 1H), 3.64 (dd, *J* = 14.2, 6.0 Hz, 1H), 3.33-3.07 (m, 3H), 3.04-2.94 (m, 1H), 2.47 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.47 (d, *J* = 9.3 Hz, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 144.6, 139.0, 138.2, 137.5, 137.3, 132.0, 131.4, 130.3, 129.5, 129.0, 128.7, 128.0, 127.2, 126.1, 125.8, 125.5 (q, *J* = 278.1 Hz, CF_3), 124.9, 80.7, 59.6, 59.1, 56.4, 49.3 (q, *J* = 29.3 Hz), 49.2, 40.0, 39.3, 21.7. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{25}ClF_3N_2O_4S$ 589.1170; found 589.1144.



2.6o

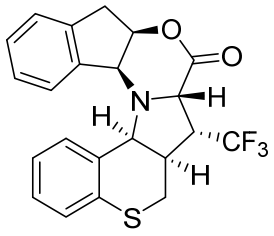
(6a*S*,7*R*,7a*S*,9a*R*,14b*S*,15a*S*)-7-(difluoromethyl)-5-tosyl-5,6,6a,7,7a,9a,14b,15a-octahydro-8*H*,10*H*-indeno[1'',2'':5',6'][1,4]oxazino[4',3':1,5]pyrrolo[3,2-c]quinolin-8-one (2.6o): Starting from **2.3o**, **2.6o** was obtained as a white solid (mp=82-84 °C) in 77% yield (41 mg). $[\alpha]_D^{25}$ = -30.3° (c 1.0; $CHCl_3$). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75–7.61 (m, 3H), 7.38–7.26 (m, 3H), 7.28–7.13 (m, 6H), 6.37 (ddd, *J* = 56.8, 54.7, 4.8 Hz, 1H, $CF_2\underline{H}$), 5.48 (td, *J* = 4.6, 1.8 Hz, 1H), 4.50 (d, *J* = 5.0 Hz, 1H), 3.96 (d, *J* = 7.9 Hz, 1H), 3.92–3.83 (m, 2H), 3.74 (dd, *J* = 13.9, 6.2 Hz, 1H), 3.32–3.10 (m, 2H), 2.94–2.60 (m, 2H), 2.43 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.19 (ddd, *J* = 289.5, 54.7, 7.5 Hz, 1F), -122.63 (ddd, *J* = 289.5, 56.8, 21.4 Hz, 1F). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.9, 144.1, 138.9, 138.8, 138.6, 137.7, 130.1 (2xCH), 129.5, 129.3, 129.1, 128.9, 127.9, 127.2 (2xCH), 125.8, 125.3, 124.9, 124.2, 116.2 (t, *J* = 240.7, CF_2H), 80.3, 59.4, 58.9, 56.2 (dd, *J* = 5.8, 3.9 Hz), 49.5 (d, *J* = 2.1 Hz), 47.6 (t, *J* = 22.7 Hz), 39.4, 38.4 (d, *J* = 5.3 Hz), 21.7. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{27}F_2N_2O_4S$ 537.1654; found 537.1655.



2.6p

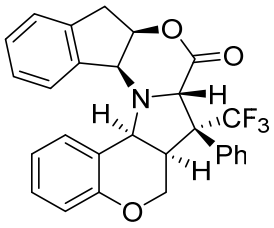
(9a*R*,14b*S*)-17-(Perfluoroethyl)-5-tosyl-5,7,7a,9a,14b,16-hexahydro-10*H*-7,16-methanobenzo[*f*]indeno[1',2':5,6][1,4]oxazino[4,3-*a*][1,5]diazocin-

8(6*H*)-one (2.6p): Starting from **2.3p**, **2.6p** was obtained as a white solid (mp=37-39 °C) in 77% yield (47 mg). $[\alpha]_D^{25}$ = +11.9° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.70–7.60 (m, 2H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.31–7.25 (m, 2H), 7.25–7.14 (m, 4H), 7.13–7.01 (m, 2H), 5.40 (td, *J* = 5.1, 3.3 Hz, 1H), 4.23 (d, *J* = 5.4 Hz, 1H), 3.97 (d, *J* = 7.1 Hz, 1H), 3.93 (d, *J* = 9.0 Hz, 1H), 3.69 (d, *J* = 5.4 Hz, 1H), 3.41–3.11 (m, 3H), 3.06-2.97 (m, 1H), 2.40 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -82.60 (s, 3F), -112.65 (dd, *J* = 272.7, 13.1 Hz, 1F), -114.33 (dd, *J* = 272.7, 20.9 Hz, 1F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 144.0, 139.4, 138.9, 138.7, 138.1, 130.0, 129.5, 129.4, 129.2, 129.0, 127.9, 126.9, 125.6, 125.6, 125.1, 123.8, 118.2 (qt, *J* = 287.1, 36.6 Hz, $\underline{C}F_2$), 113.9 (ddq, *J* = 261.4, 254.3, 37.5 Hz, $\underline{C}F_3$), 80.5, 60.1, 58.4, 57.0, 49.9, 46.0, 39.9, 39.3, 21.6. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{30}H_{26}F_5N_2O_4S$ 605.1528; found 605.1510.



2.6q

(9a*R*,14b*S*)-17-(Trifluoromethyl)-7,7a,9a,14b-tetrahydro-10*H*,16*H*-7,16-methanobenzo[*b*]indeno[1',2':5,6][1,4]oxazino[4,3-*e*][1,5]thiazocin-8(6*H*)-one (2.6q): Starting from **2.3q**, **2.6q** was obtained as a yellow thick oil in 79% yield (33 mg). $[\alpha]_D^{25}$ = -15.8° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.34–7.13 (m, 7H), 5.61 (td, *J* = 5.1, 2.0 Hz, 1H), 4.41-4.37 (m, 2H), 4.12 (d, *J* = 7.1 Hz, 1H), 3.55–3.34 (m, 2H), 3.30 (dd, *J* = 17.2, 2.0 Hz, 1H), 3.21 (dd, *J* = 17.2, 5.0 Hz, 1H), 3.03 (dd, *J* = 13.6, 4.6 Hz, 1H), 2.77 (dd, *J* = 13.6, 3.9 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.33 (d, *J* = 9.0 Hz, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 139.2, 138.8, 137.4, 134.7, 130.4, 130.4, 129.2, 128.1, 127.8, 126.2, 125.9, 125.9 (q, *J* = 277.9 Hz, CF_3). 125.0, 80.6, 62.5, 59.1, 56.5 (q, *J* = 1.8 Hz), 48.0 (q, *J* = 29.0 Hz), 41.0, 39.4, 33.7. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{19}F_3NO_2S$ 418.1083; found 418.1078.



2.6r

(9a*R*,14b*S*)-17-Phenyl-17-(trifluoromethyl)-7,7a,9a,14b-tetrahydro-10*H*,16*H*-7,16-methanobenzo[*b*]indeno[1',2':5,6][1,4]oxazino[4,3-*e*][1,5]oxazocin-8(6*H*)-one (2.6r): Starting from **2.3r, 2.6r** was obtained as a white solid (mp=265-267 °C) in 26% yield (12 mg) (43% brsm). $[\alpha]_D^{25}$ = +110.0° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 6.8 Hz, 2H), 7.48–7.35 (m, 3H), 7.33–7.11 (m, 5H), 7.03–6.97 (m, 1H), 6.97–6.86 (m, 2H), 5.63 (t, *J* = 3.7 Hz, 1H), 4.89–4.85 (m, 2H), 4.67 (d, *J* = 2.4 Hz, 1H), 4.03 (dd, *J* = 11.4, 4.7, 0.8 Hz, 1H), 3.84 (t, *J* = 11.4 Hz, 1H), 3.41 (dt, *J* = 11.4, 4.4 Hz, 1H), 3.33 (d, *J* = 16.8 Hz, 1H), 3.18 (dd, *J* = 16.8, 3.7 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.59 (s, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 154.4, 139.2, 138.7, 132.8 (q, *J* = 1.5 Hz), 131.2, 130.1, 129.6, 128.9, 128.9, 128.8, 127.5, 126.7 (q, *J* = 286.1 Hz, CF_3), 126.1, 124.2, 120.7, 120.0, 117.2, 81.4, 64.1, 62.7 (q, *J* = 24.5 Hz), 58.2, 57.7 (q, *J* = 2.6 Hz), 57.6, 40.4, 38.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{23}F_3NO_3$ 478.1625; found 478.1621.

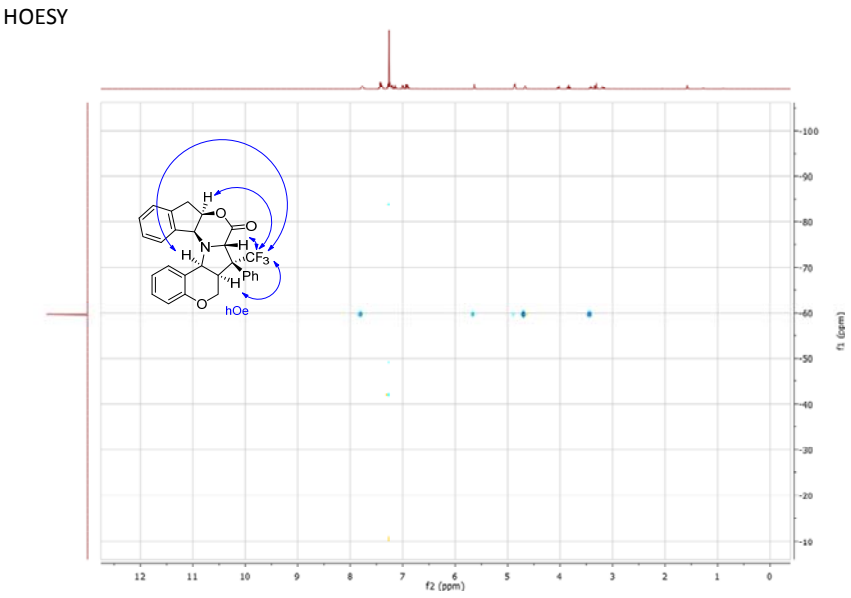
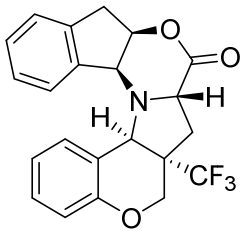


Figure S2.3 HOESY spectrum of compound **2.6r**.



2.6s

(9a*R*,14b*S*)-6a-(Trifluoromethyl)-6a,7,7a,9a,14b,15a-hexahydro-6*H*,8*H*,10*H*-chromeno[3',4':4,5]pyrrolo[1,2-*d*]indeno[2,1-*b*][1,4]oxazin-8-one (2.6s): Starting from **2.3s**, **2.6s** was obtained as a white solid (mp=185-187 °C) in 61% yield (24 mg). $[\alpha]_D^{25}$ = -105.1° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.14 (m, 6H), 7.06–6.93 (m, 2H), 5.81–5.65 (m, 1H), 4.80 (d, *J* = 4.8 Hz, 1H), 4.40 (dq, *J* = 11.7, 0.9 Hz, 1H), 4.27 (dq, *J* = 11.7, 1.8 Hz, 1H), 4.13 (s, 1H), 3.84 (dd, *J* = 9.8, 2.5 Hz, 1H), 3.40–3.21 (m, 2H), 2.79 (dd, *J* = 14.6, 2.5 Hz, 1H), 1.98 (dd, *J* = 14.6, 9.8 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -72.72 (d, *J* = 1.5 Hz, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 154.3, 139.1, 138.6, 131.0, 130.4, 129.1, 127.8, 126.6 (q, *J* = 272.3 Hz, CF_3), 126.0, 124.4, 120.9, 118.0, 117.7, 80.7, 65.3 (q, *J* = 1.5 Hz), 57.7, 57.6, 53.8, 46.5 (q, *J* = 26.0 Hz), 39.6, 31.2 (q, *J* = 2.0 Hz). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{19}F_3NO_3$ 402.1312; found 402.1308.

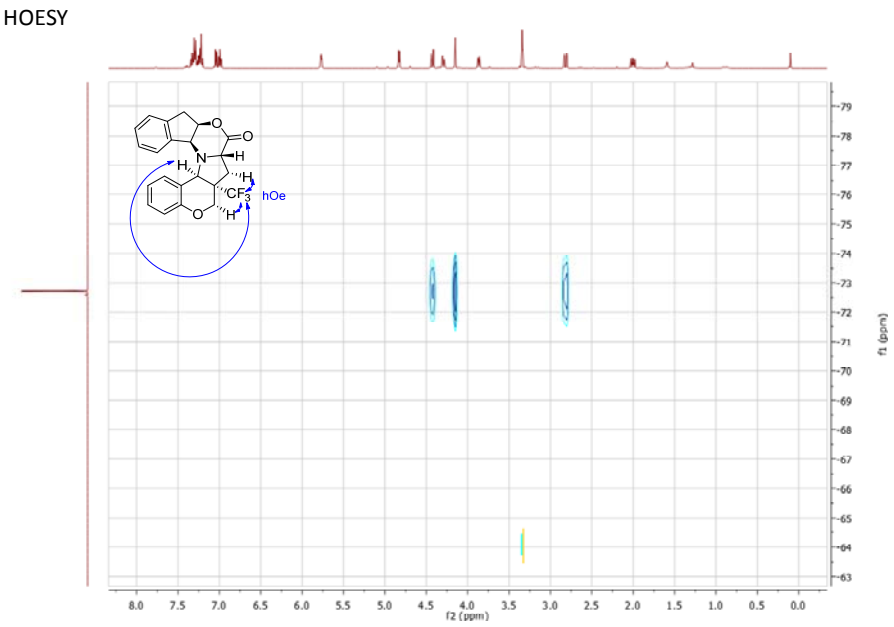
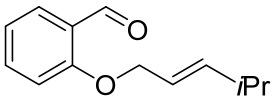


Figure S2.4 HOESY spectrum of compound **2.6s**.

- **Synthesis of (*E*)-2-((4-methylpent-2-en-1-yl)oxy)benzaldehyde (2.7b):**



2.7b

A solution of salicylaldehyde **2.2a** (0.14 mL, 1.35 mmol, 1.1 equiv) and K_2CO_3 (187 mg, 1.35 mmol, 1.0 equiv) in dry acetonitrile (3 mL) in a pressure vial was heated in an oil bath at 60 °C for 10 min. A solution of the (*E*)-1-bromo-4-methylpent-2-ene (prepared according to a literature procedure)[174] (200 mg, 1.23 mmol, 1.0 equiv) in dry acetonitrile (3 mL) was added and the resulting mixture was heated at the same temperature for 16 h. Water (4 mL) was added to quench the reaction and the aqueous phase was extracted with ethyl acetate (3x 10 mL). The combined organic phases were washed with brine (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel [*n*-hexane-EtOAc (30:1)] to afford non-fluorinated benzaldehyde **2.7b** as a colorless oil in 28% yield (70 mg). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 10.53 (d, *J* = 0.8 Hz, 1H), 7.84 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.52 (ddd, *J* = 8.4, 7.3, 1.8 Hz, 1H), 7.10–6.89 (m, 2H), 5.85 (ddt, *J* = 15.6, 6.4, 1.2 Hz, 1H), 5.66 (dtd, *J* = 15.6, 5.8, 1.2 Hz, 1H), 4.60 (dt, *J* = 5.8, 1.2 Hz, 2H), 2.49–2.27 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.1, 161.4, 143.0, 135.9, 128.5, 125.3, 121.2, 120.8, 113.2, 69.6, 31.0, 22.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}O_2$ 205.1223; found 205.1221.

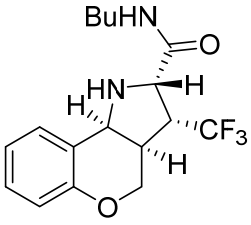
- **Further derivatisation and removal of the chiral auxiliary**

*Synthesis of amides **2.9***

To a solution of **2.6** (0.10 mmol, 1.0 equiv) in THF (1 mL), n-butylamine (0.02 mL, 0.20 mmol, 2.0 equiv) was added and the resulting mixture was stirred at room temperature for 16 h. A saturated NH_4Cl solution (2 mL) was added, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3x5 mL). The combined organic phases were washed with brine (20 mL) and dried over anhydrous sodium sulfate and the solvent was removed under

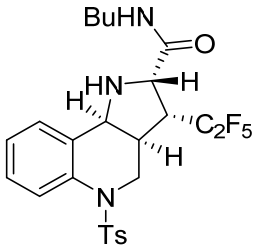
[174] Vyas, D. J.; Oestreich, M. *Chem. Commun.* **2010**, *46*, 568.

vacuum. The crude amide was redissolved in 1 mL of a water/acetonitrile mixture (1/1) and to the resulting solution ammonium cerium (IV) nitrate (110 mg, 0.20 mmol, 2.0 equiv) was added. After 1 h at room temperature, the reaction was quenched with saturated sodium bicarbonate (2 mL), extracted with ethyl acetate (3x 5 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel [*n*-hexane-EtOAc (1:1) to pure EtOAc] to afford compounds **2.9**.



2.9a

***N*-Butyl-11-(trifluoromethyl)-3,4,5,6-tetrahydro-2*H*-3,6-methanobenzo[*b*][1,5]oxazocine-4-carboxamide (2.9a):** Starting from **2.6a**, **2.9a** was obtained as a white solid (mp=103-105 °C) in 59% yield (20 mg). $[\alpha]_D^{25}$ = +23.1° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.17 (td, *J* = 8.2, 1.5 Hz, 1H), 6.98 (td, *J* = 7.6, 1.1 Hz, 1H), 6.96 (br s, 1H), 6.86 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.61 (d, *J* = 7.3 Hz, 1H), 4.14 (dd, *J* = 11.5, 3.2 Hz, 1H), 4.02 (dd, *J* = 11.5, 5.2 Hz, 1H), 3.83 (d, *J* = 8.5 Hz, 1H), 3.41–3.11 (m, 3H), 2.97–2.83 (m, 1H), 1.95 (br s, 1H), 1.60–1.42 (m, 2H), 1.43–1.26 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -65.82 (d, *J* = 9.9 Hz, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 155.0, 129.1, 128.9, 126.76 (q, *J* = 279.9 Hz, CF_3), 124.1, 122.4, 117.5, 66.0, 60.0, 54.1, 47.5 (q, *J* = 27.0 Hz), 39.2, 39.1 (q, *J* = 1.9 Hz), 31.4, 20.2, 13.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{22}F_3N_2O_2$ 343.1628; found 343.1620.

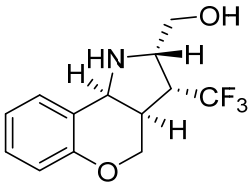


2.9b

***N*-Butyl-11-(perfluoroethyl)-1-tosyl-1,2,3,4,5,6-hexahydro-3,6-methanobenzo[*b*][1,5] diazocine-4-carboxamide (2.9b):** Starting from **2.6p**, **2.9b** was obtained as a white solid (mp=42-44 °C) in 77% yield (42 mg). $[\alpha]_D^{25}$ =-74.0° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.73–7.65 (m, 1H), 7.51–7.42 (m, 2H), 7.34–7.26 (m, 2H), 7.25–7.16 (m, 3H), 6.51 (t, *J* = 5.5 Hz, 1H), 4.25 (d, *J* = 7.7 Hz, 1H), 4.17 (dd, *J* = 14.0, 5.4 Hz, 1H), 3.89 (d, *J* = 7.1 Hz, 1H), 3.32–3.12 (m, 3H), 3.01–2.77 (m, 1H), 2.73–2.56 (m, 1H), 2.39 (s, 3H), 1.98 (br s, 1H), 1.57–1.39 (m, 2H), 1.41–1.18 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -82.47 (s, 3F), -112.04 (dd, *J* = 273.5, 8.2 Hz, 1F), -120.11 (dd, *J* = 273.5, 25.7 Hz, 1F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 144.4, 136.9, 136.3, 131.4, 130.0, 129.1, 128.2, 127.0, 126.4, 124.8, 123.3-111.9 (m, C_2F_5), 60.6, 55.6, 47.9 (t, *J* = 20.3 Hz), 47.8, 39.3, 37.4, 31.3, 21.7, 20.2, 13.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{29}F_5N_3O_3S$ 546.1795; found 546.1821

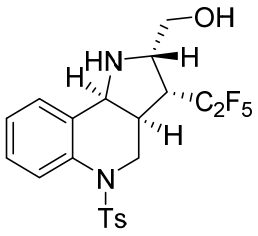
*Synthesis of amino alcohols **2.10***

To a solution of **2.6** (0.10 mmol, 1.0 equiv) in THF (1 mL), lithium aluminum hydride (8 mg, 0.20 mmol, 2.0 equiv) was carefully added and the resulting mixture was stirred at room temperature for 16 h. A saturated NH_4Cl solution (2 mL) was added dropwise, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3x5 mL). The combined organic phases were washed with brine (20 mL) and dried over anhydrous sodium sulfate and the solvent was removed under vacuum. The crude amino alcohol was redissolved in 1 mL of a water/acetonitrile mixture (1/1) and to the resulting solution ammonium cerium (IV) nitrate (110 mg, 0.20 mmol, 2.0 equiv) was added. After 1 h at room temperature, the reaction was quenched with saturated sodium bicarbonate (2 mL), extracted with ethyl acetate (3x 5 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel [*n*-hexane-EtOAc (1:1) to pure EtOAc] to afford compounds **2.10**.



2.10a

[11-(Trifluoromethyl)-3,4,5,6-tetrahydro-2*H*-3,6-methanobenzo[*b*][1,5]oxazocin-4-yl] methanol (2.10a): Starting from **2.6a**, **2.10a** was obtained as a white solid (mp=53-55 °C) in 61% yield (17 mg). $[\alpha]_D^{25}$ =+88.1° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.23–7.14 (m, 1H), 6.99 (td, *J* = 7.6, 1.2 Hz, 1H), 6.89 (dd, *J* = 8.2, 1.2 Hz, 1H), 4.43 (d, *J* = 7.3 Hz, 1H), 4.19–4.10 (m, 1H), 3.95 (dd, *J* = 11.4, 5.1 Hz, 1H), 3.74–3.45 (m, 3H), 2.94–2.76 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.24 (d, *J* = 9.8 Hz, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 129.5, 129.0, 127.0 (q, *J* = 278.9 Hz, CF_3), 124.1, 122.4, 117.5, 66.4, 60.31 (q, *J* = 3.1 Hz), 59.0, 53.5, 47.08 (q, *J* = 26.9 Hz), 39.71 (q, *J* = 1.7 Hz). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{15}F_3NO_2$ 274.1049; found 274.1044.



2.10b

[11-(Perfluoroethyl)-1-tosyl-1,2,3,4,5,6-hexahydro-3,6-methanobenzo[*b*][1,5]diazocin-4-yl]methanol (2.10b): Starting from **2.6p**, **2.10b** was obtained as a white solid (mp=46-48 °C) in 81% yield (39 mg). $[\alpha]_D^{25}$ =+8.2° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.46–7.39 (m, 2H), 7.34 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.29–7.20 (m, 1H), 7.19–7.09 (m, 3H), 4.15 (dd, *J* = 14.1, 5.6 Hz, 1H), 3.76 (d, *J* = 8.5 Hz, 1H), 3.51 (ddd, *J* = 11.5, 7.2, 4.3 Hz, 2H), 3.28 (ddd, *J* = 11.5, 7.0, 2.1 Hz, 1H), 2.99 (dd, *J* = 14.1, 10.1 Hz, 1H), 2.64–2.37 (m, 2H), 2.34 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -83.79 (s, 3F), -114.57 (dd, *J* = 274.7, 19.2 Hz, 1F), -116.50 (dd, *J* = 274.5, 16.3 Hz, 1F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 137.1, 136.9, 130.3, 130.0, 129.2, 128.4, 127.1, 126.5, 125.4, 119.7-

110.4 (m, C_2F_5), 60.1, 58.7–58.2 (m), 53.9, 48.7, 48.5, 38.1, 21.7. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{22}F_5N_2O_3S$ 477.1243; found 477.1260.

2.5.3. Computational Calculations

- **Computational details**

All of the calculations were performed using the Gaussian09 program.[175] Computations were done using B3LYP functional[176] in conjuction with Grimme's dispersion correction.[177] Standard basis sets def2SVP and def2TZVP were employed.[178] Geometry full optimisations were made at B3LYP-D3BJ/def2SVP level and then single point calculations at B3LYP-D3BJ/def2TZVP level were carried out in order to obtain more accurate values of the energies. Solvent effects (toluene) were considered using the PCM model.[179] The nature of stationary points was defined on the basis of calculations of normal vibrational frequencies (force constant Hessian matrix). The optimisations were carried out using the Berny analytical gradient optimisation method.[180] Minimum energy pathways for the reactions studied were found by gradient descent of transition states in the forward and backward direction of the transition vector (IRC analysis),[181] using using the Hratchian-Schlegel algorithm.[182] Analytical second derivatives of the energy were calculated to classify the nature of every stationary point, to determine the harmonic vibrational frequencies, and to provide zero-point vibrational energy corrections. The thermal and entropic contributions to the free energies were also obtained from the vibrational frequency calculations, using the unscaled frequencies. NCI (non-covalent interactions) were computed using the methodology previously described.[183] Data were obtained with the NCIPLOT program.[184] A density cutoff of ρ=0.1 a.u. was applied and the pictures were

[175] See ref. 104.
[176] See ref. 105.
[177] See ref. 106.
[178] See ref. 107.
[179] See ref. 108.
[180] See ref. 109.
[181] See ref. 110.
[182] See ref. 111.
[183] See ref. 112.
[184] See ref. 113.

created for an isosurface value of s=0.4 and colored in the [-0.02,0.02] a.u. sign(λ_2)ρ range using VMD software.[185] Structural representations were generated using CYLView.[186]

[185] See ref. 114.
[186] See ref. 116.

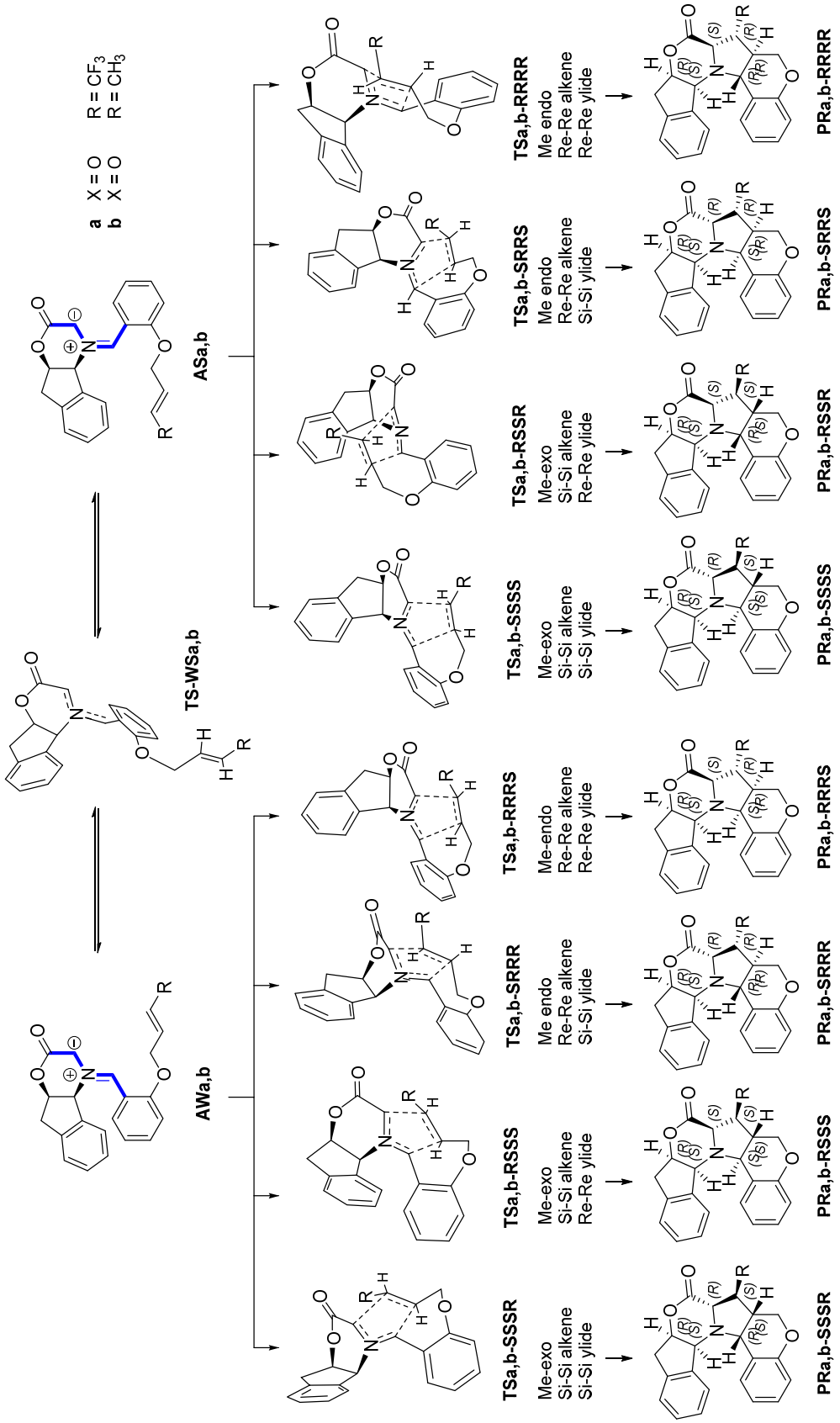


Figure S2.5 Approaches considered for the intramolecular cycloaddition of azomethine ylides

- **Energy values**

Table S2.1 Calculated (B3LYP-D3BJ/def2TZVP/PCM=toluene//B3LYP-D3BJ/def2SVP) absolute (hartrees) and relative (kcal/mol) energies for the intramolecular cycloaddition of the azomethine ylide derived from **2.3a** and **IV**

	E_0	ΔE_0[a]	G	ΔG[a]	im. freq	%[b]
AWa	-1429.383117	0.0	-1429.439121	0.0		
ASa	-1429.378491	2.9	-1429.433866	3.3		
TS-WSa	-1429.365027	11.4	-1429.420814	11.5	-44.4	
TSa-RRRR	-1429.350423	20.5	-1429.401690	23.5	-356.3	0.0
TSa-RSSR	-1429.364022	12.0	-1429.415886	14.6	-243.2	9.0
TSa-SRRS	-1429.365290	11.2	-1429.418069	13.2	-277.7	91.0
TSa-SSSS	-1429.353454	18.6	-1429.405921	20.8	-355.1	0.0
TSa-RRRS	-1429.295365	55.1	-1429.347784	57.3	-180.6	0.0
TSa-RSSS	-1429.357805	15.9	-1429.409191	18.8	-375.5	0.0
TSa-SRRR	-1429.315701	42.3	-1429.370171	43.3	-256.5	0.0
TSa-SSSR	-1429.314283	43.2	-1429.368104	44.6	-142.8	0.0
PRa-RRRR	-1429.431657	-30.5	-1429.483230	-27.7		
PRa-RRRS	-1429.447725	-40.5	-1429.498639	-37.3		
PRa-RSSR	-1429.432097	-30.7	-1429.483179	-27.6		
PRa-RSSS	-1429.422902	-25.0	-1429.473628	-21.7		
PRa-SRRR	-1429.426440	-27.2	-1429.478486	-24.7		
PRa-SRRS	-1429.437830	-34.3	-1429.489983	-31.9		
PRa-SSSR	-1429.441904	-36.9	-1429.495100	-35.1		
PRa-SSSS	-1429.437424	-34.1	-1429.490844	-32.5		

[a] referred to **AWa**.
[b] % abundance according to Boltzmann distribution

Table S2.2 Calculated (B3LYP-D3BJ/def2TZVP/PCM=toluene//B3LYP-D3BJ/def2SVP) absolute (hartrees) and relative (kcal/mol) energies for the intramolecular cycloaddition of the azomethine ylide derived from **2.7a** and **IV**

	E_0	ΔE_0[a]	G	ΔG[a]	im. freq	%[b]
AWb	-1131.498183	0.0	-1131.552321	0.0		
ASb	-1131.492855	3.3	-1131.544041	5.2		
TS-WSb	-1131.479465	11.7	-1131.535213	10.7	-40.2	
TSb-RRRR	-1131.458744	24.7	-1131.507087	28.4	-415.3	0.0
TSb-RSSR	-1131.476805	13.4	-1131.525129	17.1	-336.0	35.9
TSb-SRRS	-1131.476433	13.6	-1131.525630	16.7	-334.0	61.0
TSb-SSSS	-1131.463061	22.0	-1131.512105	25.2	-413.1	0.0
TSb-RRRS	-1131.417883	50.4	-1131.465298	54.6	-330.5	0.0
TSb-RSSS	-1131.474769	14.7	-1131.522827	18.5	-369.2	3.1
TSb-SRRR	-1131.428292	43.9	-1131.479921	45.4	-371.6	0.0
TSb-SSSR	-1131.423960	46.6	-1131.474964	48.5	-241.6	0.0
PRb-RRRR	-1131.543232	-28.3	-1131.591394	-24.5		
PRb-RRRS	-1131.557753	-37.4	-1131.605362	-33.3		
PRb-RSSR	-1131.549325	-32.1	-1131.597904	-28.6		
PRb-RSSS	-1131.537287	-24.5	-1131.585195	-20.6		
PRb-SRRR	-1131.540951	-26.8	-1131.589845	-23.5		
PRb-SRRS	-1131.552472	-34.1	-1131.600238	-30.1		
PRb-SSSR	-1131.555497	-36.0	-1131.604795	-32.9		
PRb-SSSS	-1131.550506	-32.8	-1131.599607	-29.7		

[a] referred to **AWa**.
[b] % abundance according to Boltzmann distribution.

- **Energy profiles**

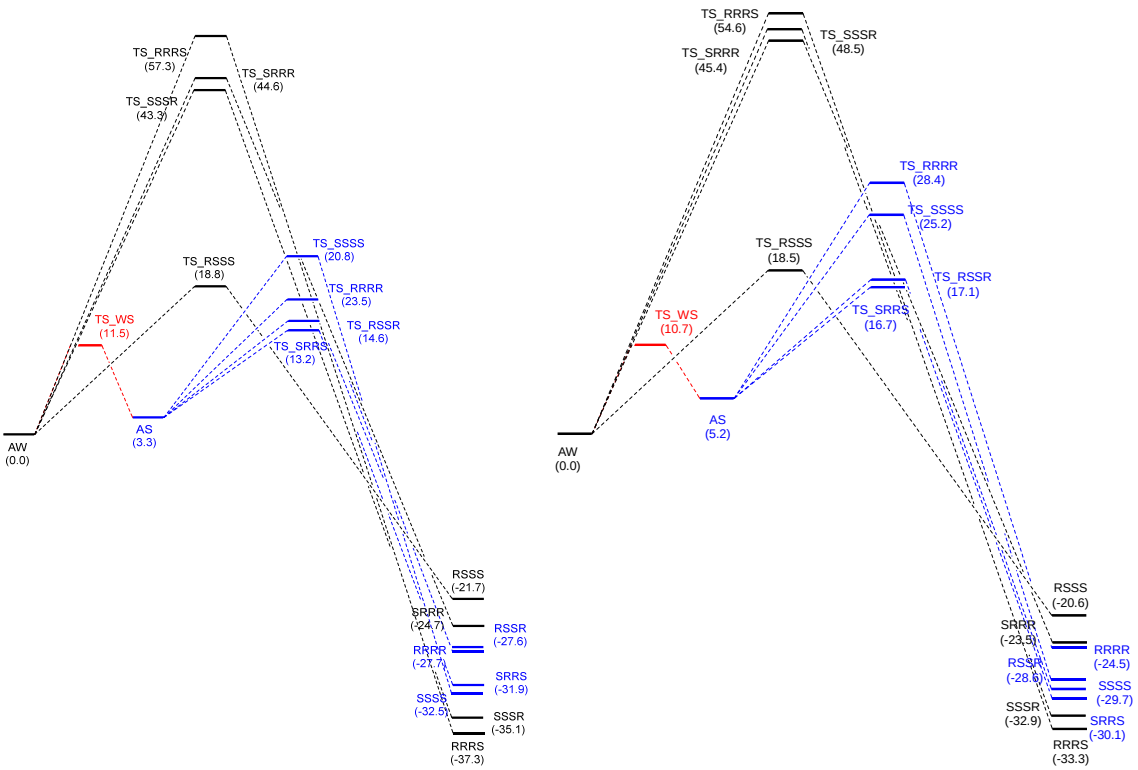


Figure S2.6 Energy profile for the intramolecular cycloaddition of the azomethine ylide derived from **2.3a** and **IV** (left) and the azomethine ylide derived from **2.7a** and **IV** (right)

- **Transition state structures**

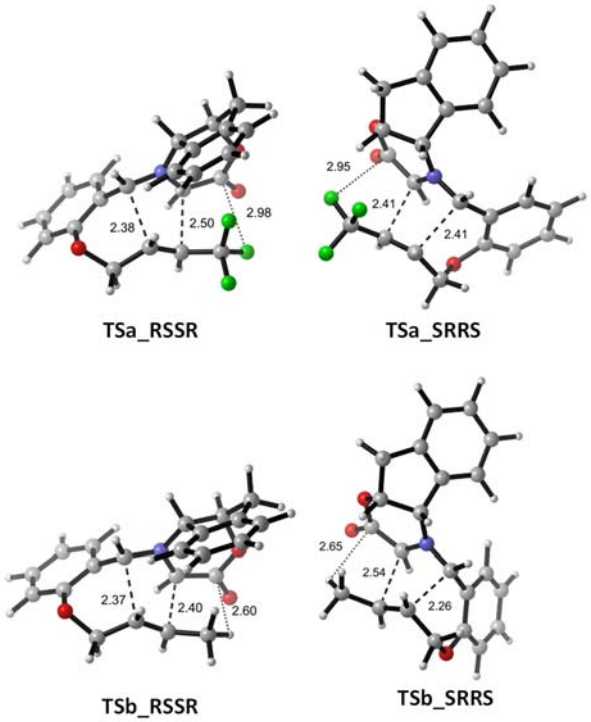


Figure S2.7 Optimised (b3lyp-3dbj/def2svp) for the intramolecular cycloaddition of the azomethine ylide derived from **2.3a** and **IV** (top) and the azomethine ylide derived from **2.7a** and **IV** (bottom)

- **NCI analyses**

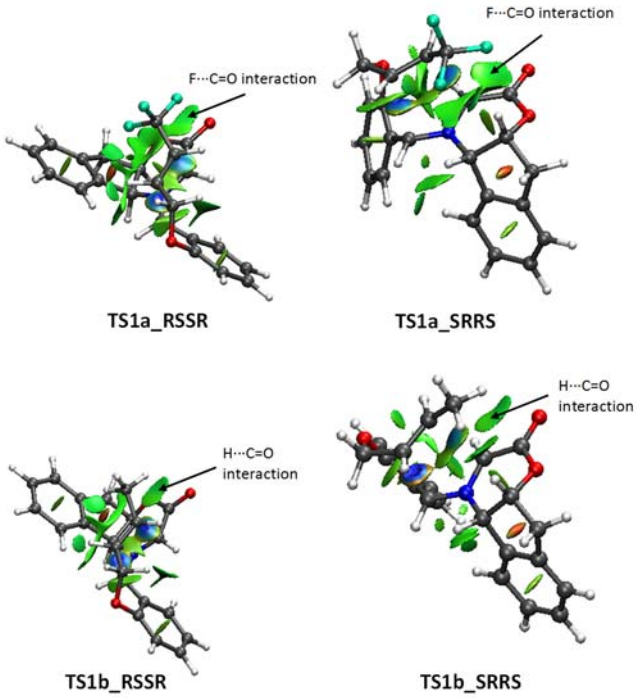


Figure S2.8 NCI analyses corresponding to the transition structures corresponding to the intramolecular cycloaddition of the azomethine ylide derived from **2.3a** and **IV** (top) and the azomethine ylide derived from **2.7a** and **IV** (bottom)

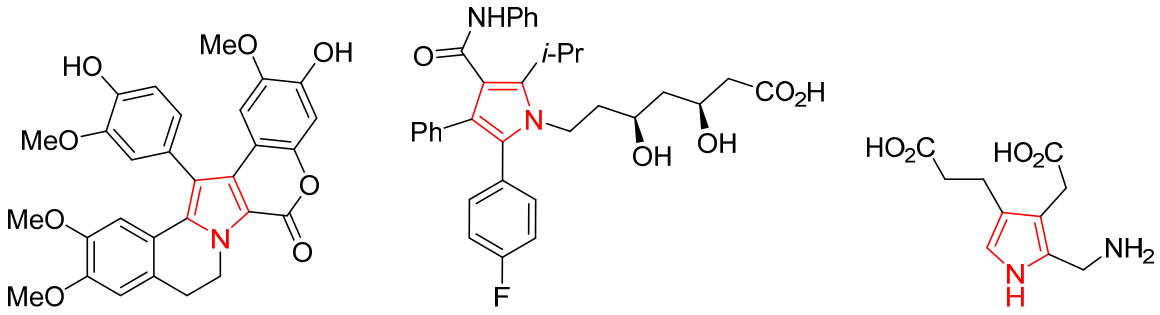
Chapter 3

Tandem Organocatalytic Intramolecular Cycloaromatisation/ Friedel-Crafts Alkylation Sequence for the Synthesis of Indolizinones and Pyrrolo-azepinone Derivatives

3.1. Introduction

3.1.1. Interest of Indolizidine and Pyrrolo-azepine derivatives

Pyrrole is the fundamental 5-membered ring, aromatic *N*-heterocycle and a prevalent structural motif in natural and synthetic biologically active compounds,[187] such as natural products, drugs and agrochemicals as well as in catalysts and advanced materials.[188]



lamellarin D | Atorvastatin (Lipitor) | porphobilinogen

Figure 3.1

Just to mention a few examples (Figure 3.1), the respiratory pigment haem found in red blood cells and the photosynthetic pigment chlorophyll present in green plants are both biosynthesised from pyrrole-derived porphobilinogen.[189] Lamellarins are a family of natural products isolated from marine invertebrates that exhibit antitumor and anti-HIV activities.[190] The active pharmaceutical ingredient Atorvastatin (Lipitor), the top-selling branded drug, is itself a pyrrole

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[187] For general reviews, see: (a) Mal, D.; Shome, B.; Dinda, B. K. In: *Pyrrole and its Derivatives in Heterocycles in Natural Product Synthesis* (Eds.: Majumdar, K. C.; Chattopadhyay, S. K.), Wiley-VCH, Weinheim, **2011**, ch. 6. (b) Bergman, J.; Janosik, T. In: *Five-Membered Heterocycles: Pyrrole and Related Systems in Modern Heterocyclic Chemistry* (Eds.: Álvarez-Builla, J.; Vaquero, J. J.; Barluenga, J.), Wiley-VCH, Weinheim, **2011**, ch. 4. (c) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.* **2006** *23*, 517. (d) Gupton, J. T. In: *Heterocyclic Antitumor Antibiotics* (Ed.: Lee, M.), Springer-Verlag, Berlin, **2006**, p. 53.

[188] For a concise introduction into the importance of pyrroles, see the reviews by Menéndez *et al.* on multicomponent pyrrole synthesis: (a) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2014**, *43*, 4633. (b) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402. For their recent work on Diversity-Oriented Synthesis of novel pyrrole-containing scaffolds, see: (c) Leonardi, M.; Estévez, V.; Villacampa, M.; Menéndez, J. C. *Adv. Synth. Catal.* **2019**, *361*, 2054.

[189] Roth, B. D. *Prog. Med. Chem.***2002**, *40*, 1.

[190] Fukuda, T.; Ishibashi, F.; Iwao, M. *Heterocycles* **2011**, *83*, 491.

derivative.[191] Polypyrroles are conducting polymers that have found application in batteries[192] and solar cells.[193]

Particularly, annulated pyrroles and pyrrolidines are highly represented moieties in clinically useful pharmaceuticals and natural products.[194] Indolizines are hetereoaromatic compounds containing two fused rings (5- and 6-membered) with a bridgeheaded nitrogen.[195] Being an isomeric form of indole, it has been speculated that the bioactivity of indolizine derivatives comes precisely from this structural analogy. Aromatic indolizine is not found in nature, but its reduced derivatives globally known as indolizidines define an important class of natural products.[196] To illustrate the variety of indolizidinic compounds, a selection of some representative examples is depicted in Figure 3.2. These secondary metabolites derived from lysine can be isolated from diverse sources, like fungi, bacteria, higherplants, invertebrates and vertebrates, and they are present in 25-30% of naturally occurring alkaloids.[197] Indolizidine-based alkaloids (commonly abbreviated as IBAs) display a wide range of biological activities.[198] Anticancer, antileukemia, anticholinergic, antiviral, antifungal and antimicrobial properties are

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[191] Joule, J. A.; Mills, K. In: *Heterocyclic Chemistry*, *5th edition*, Wiley, UK, **2010**, chapter 16.
[192] Nishide, H.; Oyaizu, K. *Science* **2008**, *319*, 737.
[193] Hagfeldt, A.; Boschloo, G.; Sun, L.; Kloo, L.; Pettersson, H. *Chem. Rev.* **2010**, *110*, 6595.
[194] Gossauer, A. *Prog. Chem. Org. Nat. Prod.* **2003**, *86*, 1.
[195] For reviews on the indolizine core, see: (a) Janosik, T.; Bergman J. In: *Progress in Heterocyclic Chemistry* (Eds.: Gribble, G. W.; Joule, J. A.), Pergamon, Amsterdam, **2003**, Vol. 15, p. 140. (b) Le Quesne, P. W.; Dong, Y.; Blythe, T. A. *Alkaloids Chem. Biol. Perspect.* **1999**, *13*, 237. (c) Gribble, G. W. In: *Comprehensive Heterocyclic Chemistry II* (Eds.: Katritzky, A. R.; Rees, C. W.; Scriven, E. S. V.), Pergamon, New York, **1996**, p. 207. (d) Bull, L. B.; Culvenor, C. C. J.; Dick, A. T. *The Pyrrolizidine Alkaloids*, North-Holland Publishing Co., Amsterdam, **1968**.
[196] (a) Kim, I. S.; Jung, Y. H. *Heterocycles* **2011**, *83*, 2489. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. (c) Daly J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat Prod.* **2005**, *68*, 1556. (d) Liddell, J. R. *Nat. Prod. Rep.* **1998**, *15*, 363.
[197] (a) Dewick, P. M. *Medicinal Natural Products, A Biosynthetic Approach*, *3rd edition*, Wiley, Chichester, **2009**. (b) Takahata, H.; Momose, T. In: *The Alkaloids, Chemistry and Pharmacology* (Ed.: Cordell, G.), Academic Press, San Diego, **1993**, p. 189.
[198] (a) Bunsupa, S.; Yamazaki, M.; Saito, K. *Mini Rev. Med. Chem.* **2017**, *17*, 1002. (b) Kim, E.; Lee, Y.; Lee, S.; Park, S. B. *Acc. Chem. Res.* **2015**, *48*, 538. (c) Chen, C.-Y.; Zhu, G.-Y.; Wang, J.-R.; Jiang, Z.-H. *RSC Adv.* **2016**, *6*, 79958. (d) Yap, V. A.; Loong, B.-J.; Ting, K.-N.; Loh, S. H.; Yong, K. T.; Low, Y. Y.; Kam, T. S.; Lim, K. H. *Phytochemistry* **2015**, *109*, 96. (e) Dhiman, M.; Parab, R. R.; Manju, S. L.; Desai, D. C.; Mahajan, G. B. *Nat. Prod. Commun.* **2012**, *7*, 1171. (f) Clarke, M. O.; Byun, D.; Chen, X.; Doerffler, E.; Leavitt, S. A.; Sheng, X. C.; Yang, C. Y.; Kim, C. U. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1095. (g) Singh, G. S.; E. E. Mmatli, *Eur. J. Med. Chem.* **2011**, *46*, 5237. (h) Samoylenko, V.; Ashfaq, M. K.; Jacob, M. R.; Tekwani, B. L.; Khan, S. I.; Manly, S. P.; Joshi, V. C.; Walker, L. A.; Muhammad, I. *J. Nat. Prod.* **2009**, *72*, 92.

among the biological activities for which indolizine derivatives can account.[199] Particularly, certain indolizidine derivatives have been shown to be effective, non-competitive blockers for nicotinic receptor channels,[200] and thus promising candidates against diseases such as Alzheimer, schizophrenia, epilepsy, and Parkinson.[201] Also of interest is the glycosidase inhibitory activity (with anti-HIV potential) of certain polyhydroxylated indolizidine alkaloids belonging to the family of aza-sugars or carbohydrate mimics, such as swainsonine (Figure 3.2).

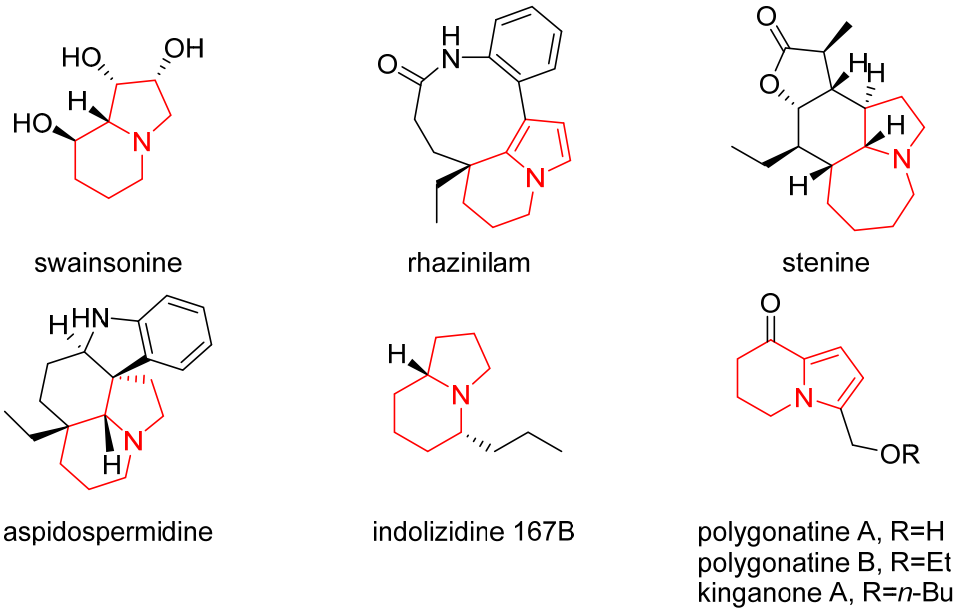

Figure 3.2

For the reasons given above, these interesting frameworks have drawn interest in synthetic organic chemistry. Cyclisation of *N*-tethered substrates is by far the most common strategy for the preparation of annulated pyrroles.[202] In

[199] For selected examples, see: (a) Baudoin, O.; Guénard, D.; Guéritte, F. *Mini-Rev. Org. Chem.* **2004**, 1, 333. (b) Sayah, B.; Pelloux-Léon, Vallée, N. Y. *J. Org. Chem.* **2000**, *65*, 2824. (c) Schröder, F.; Sinnwell, V.; Baumann, H.; Kaib, M.; Francke, W. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 77. (d) Katritzky, A. R.; Fali, C. N.; Li, J. *J. Org. Chem.* **1997**, *62*, 4148. (e) Weidner, M. F.; Sigurdsson, S. T.; Hopkins, P. B. *Biochemistry* **1990**, *29*, 9225. (f) Anderson, W. K.; Corey, P. F. *J. Med. Chem.* **1977**, *20*, 812. (g) Abraham, D. J.; Rosenstein, R. D.; Lyon, R. L.; Fong, H. H. S. *Tetrahedron Lett.* **1972**, *13*, 909.

[200] Daly, J. W.; Nishizawa, Y.; Padgett, W. L.; Tokuyama, T.; Smith, A. L.; Holmes, A. B.; Kibayashi, C.; Aronstam, R. S. *Neurochem. Res.* **1991**, *16*, 1213.

[201] (a) *Alkaloids: Chemical and Biological Perspectives: Amphibian Alkaloids: Chemistry, Pharmacology, and Biology* (Eds.: Daly, J. W.; Spande, T. F.), Wiley-Interscience, New York, **1986**. (b) Mensah-Dwumah, M.; Daly, J. W. *Toxicon* **1978**, *16*, 189.

[202] A recent review covers the literature on cyclisation reactions of pyrroles: Olivier, W. J.; Smith, J. A.; Bissember, A. C. *Org. Biomol. Chem.* **2018**, *16*, 1216.

particular, intramolecular Friedel-Crafts alkylation and acylation of pyrrole derivatives give access to indolizines and the corresponding pyrrolo-azepines (see the structure of stenine in Figure 3.2), which are as well widely extended frameworks in natural products.[203] Syntheses based on asymmetric catalysis (metal and organocatalysis) can also be found in the literature.[204]

3.1.2. General remarks on Organocatalysed Domino Reactions

Domino processes are the combination of a set of organic reactions allowing the formation of multiple bonds in a single operation (in contrast to classical multistep and one-pot syntheses), transforming simple starting materials into complex molecular frameworks.[205] (Nowadays, the terms *domino, cascade* and

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[203] (a) Nakayama, Y.; Maeda, Y.; Kotatsu, M.; Sekiya, R.; Ichiki, M.; Sato, T.; Chida, N. *Chem. Eur. J.* **2016**, *22*, 3300. (b) Fujioka, H.; Nakahara, K.; Kotoku, N.; Ohba, Y.; Nagatomi, Y.; Wang, T.-L.; Sawama, Y.; Murai, K.; Hirano, K.; Oki, T.; Wakamatsu, S.; Kita, Y. *Chem. Eur. J.* **2012**, *18*, 13861. (c) Chen, J.; Chen, J.-C.; Xie, Y.; Zhang, H.-B. *Angew. Chem. Int. Ed.* **2012**, *51*, 1024. (d) Pilli, R. A.; Ferreira de Oliveira, M. d. C. *Nat. Prod. Rep.* **2010**, *27*, 1908. (e) Alibés, R.; Figueredo, M. *Eur. J. Org. Chem.* **2009**, 2421. (f) Morimoto, Y.; Iwahashi, M.; Kinoshita, T.; Nishida, K. *Chem. Eur. J.* **2001**, 7, 4107. (g) Pilli, R. A.; Rosso, G. B.; Ferreira de Oliveira, M. d. C. *Nat. Prod. Rep.* **2000**, *17*, 117. (h) Kam, T.-S.; Tee, Y.-M.; Subramaniam, G. *Nat. Prod. Lett.* **1998**, *12*, 307. (i) Morimoto, Y.; Iwahashi, M.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Angew. Chem. Int. Ed.* **1996**, *35*, 904. (j) Uyeo, S.; Irie, H.; Haroda, H. *Chem. Pharm. Bull.* **1967**, *15*, 768. (k) Linde, H. H. A. *Helv. Chim. Acta.* **1965**, *48*, 1822.

[204] For selected examples, see: (a) Magné, V.; Lorton, C.; Marinetti, A.; Guinchard, X.; Voituriez, A. *Org. Lett.* **2017**, *19*, 4794. (b) Shemet, A.; Carreira, E. M. *Org. Lett.* **2017**, 19, 5529. (c) Zhao, K.; Xu, S.-B.; Pan, C.-Q.; Sui, X.-W.; Gu, Z.-H. *Org. Lett.* **2016**, *18*, 3782. (d) Conrad, J. C.; Kong, J.; Laforteza, B. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11640. (e) For organocatalytic approaches see references in Section 3.1.4.

[205] For general reviews on domino reactions, see: (a) Bonne, D.; Constantieux, T.; Coquerel, Y.; Rodriguez, J. *Chem. Eur. J.* **2013**, *19*, 2218. (b) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442. (c) Pellissier, H. *Tetrahedron* **2013**, *69*, 7171. (d) *Domino Reactions: Concepts for Efficient Organic Synthesis* (Ed.: Tietze, L. F.), John Wiley & Sons: NewYork, **2013**. (e) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.*, **2012**, *45*, 1278. (f) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237. (g) Ruiz, M.; López-Alvarado, P.; Giorgi, G.; Menéndez, J. C. *Chem. Soc. Rev.* **2011**, *40*, 3445. (h) Zhou, J. *Chem. Asian J.* **2010**, *5*, 422. (i) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (j) Poulin, J.; Grisé-Bard, C. M.; Barriault, L. *Chem. Soc. Rev.* **2009**, *38*, 3092. (k) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993. (l) Barluenga, J.; Rodríguez, F.; Fañanás, F. J. *Chem. Asian J.* **2009**, *4*, 1036. (m) Alba, A. N.; Companyo, X.; Viciano, M.; Rios, R. *Curr. Org. Chem.* **2009**, *13*, 1432. (n) Vilotijevic, I.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 5250. (o) Shindoh, N.; Takemoto, Y.; Takasu, K. *Chem. Eur. J.* **2009**, *15*, 12168. (p) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (q) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570. (r) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134. (s) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619.

tandem are often employed equally.)[206] This kind of reactions represent several advantages. On the one hand, the attained atom- and step-economy is the ideal situation from the point of view of green chemistry, whose requirements are increasingly important in the chemical science: Domino processes reduce the use of solvents and purification steps, thus minimising waste, operation time and overall costs. On the other hand, molecular complexity and structural diversity (great concerns in the field of medicinal chemistry and drug discovery, always in search of novel biactive scaffolds) are generated in an easy manner.

In particular, asymmetric organocatalysis has provided a valuable tool in the hands of organic chemists to promote novel cascade reactions in an efficient and selective manner and frequently following biomimetic pathways. (Organocatalysts can be regarded as "small" enzyme mimics.) Organocascades have been found to be an efficient mean for the synthesis of chiral cyclic molecules with several stereogenic centres. The chemical community recognised long ago the potential of organocatalytic domino reactions; many classifications of the ever increasing literature are available, basing on the number of bonds formed, on the underlying mechanism (*i.e.* on the structure of organocatalyst and substrate involved) or on the difference between single-organocatalysed and organomulticatalysed processes (the latter with the intervention of more than one organocatalyst). The discussion of all these aspects is beyond the limits and purpose of the present introduction. To this end, recent literature on the matter has been selected.[207]

As it will be outlined later in the Objectives, the synthetic goal of this chapter is the preparation of indolizidines and pyrrolo-azepines by a tandem

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[206] Quoting Tietze, "a domino reaction is a process involving two or more consecutive reactions in which subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step". Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131.

[207] For some recent general reviews on organocatalytic domino reactions, see: (a) Chanda, T.; Zhao, J. C. G. *Adv. Synth. Catal.* **2018**, *360*, 2. (b) Evans, C. S.; Davis, L. O. *Molecules* **2018**, *23*, 33. (c) Chauhan, P; Mahajan, S.; Enders, D. *Acc. Chem. Res.* **2017**, *50*, 2809. (d) Nayak, S.; Panda, P.; Bhakta, S.; Mishra, S. K.; Mohapatra, S. *RSC Adv.* **2016**, *6*, 96154. (e) Wang, Y.; Lu, H.; Xu, P.-F. *Acc. Chem. Res.* **2015**, *48*, 1832. (f) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253. (g) Vetica, F.; de Figueiredo, R. M.; Orsinib, M.; Tofania, D.; Gasperi, T. *Synthesis* **2015**, *47*, 2139. (h) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2013**, *114*, 2390. (i) Marson, C. M. *Chem. Soc. Rev.* **2012**, *41*, 7712. (j) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037.

sequence comprising a pyrrole formation step (*via* cycloaromatisation from aminoenones synthesised by olefin cross-metathesis) and an intramolecular Friedel-Crafts alkylation reaction. Indolizine derivatives have scarcely been prepared by domino organocatalytic processes.[208] To the best of our knowledge, this work represents the first example of an intramolecular organocascade leading to the indolizine core in which the pyrrole ring is formed *in situ*.[209] Organocatalytic intramolecular Friedel-Crafts alkylation of pyrroles has been engaged in domino processes, but less frequently than indoles as it will be discussed at a later point. The following sections will be devoted to an analysis and literature review of the precedents for the individual steps comprised in the proposed tandem process.

3.1.3. Olefin Cross-Metathesis for the Synthesis of Pyrroles

The classical Paal-Knorr reaction,[210,211] involving a primary amine and a 1,4-dicarbonyl compound, remains the cornerstone of pyrrole synthesis from acyclic substrates. Given the importance of pyrrole derivatives in pharmaceutical and agricultural development, efficient new methodologies for the construction of the pyrrole core are still needed, offering alternative starting materials (and thus products) and gentle conditions.

Olefin metathesis, broadly recognised as one of the most powerful methodologies for the generation of C-C double bonds,[212] has experienced a rapid

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[208] For some examples, see: (a) You, Y.; Cui, B.-D.; Zhou, M.-Q.; Zuo, J.; Zhao, J.-Q.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2015**, *80*, 5951. (b) Zhou, Y.; Yang, Q.; Shen, J.; Chen, X.; Peng, Y.; Gong, Y. *J. Org. Chem.* **2015**, *80*, 1446. (c) Scorzelli, F.; Di Mola, A.; Croce, G.; Palombi, L.; Massa, A. *Tetrahedron Lett.* **2015**, *56*, 2787. (d) Tiso, S.; Palombi, L.; Vignes, C.; Di Mola, A.; Massa, A. *RSC Adv.* **2013**, *3*, 19380. (e) Antonchick, A. P.; López-Tosco, S.; Parga, J.; Sievers, S.; Schürmann, M.; Preut, H.; Höing, S.; Schöler, H. R.; Sterneckert, J.; Rauh, D.; Waldmann, H. *Chem. Biol.* **2013**, *20*, 500. (f) Jiang, X.; Tan, B.; Barbas III, C. F. *Angew. Chem. Int. Ed.* **2013**, *52*, 9261.

[209] Recently, Chan *et al.* reported a sequential one-pot dehydrative Nazarov-type electrocyclisation/alkyne hydroamination process for the enantioselective synthesis of 1,8-dihydroindeno[2,1-*b*]pyrroles. The first part of the transformation is catalysed by a chiral BINOL-derived phosphoramide, while in the second step the pyrrole ring is formed by gold (I) catalysis: Jin, J.; Zhao, Y.; Sze, E. M. L.; Kothandaraman, P.; Chan, P. W. H. *Adv. Synth. Catal.* **2018**, *360*, 4744.

[210] Paal, C. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2756.

[211] Knorr, L. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2863.

[212] Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243.

development in the last decade, driven by the appearance of more stable and selective catalysts capable of performing different metathetic transformations with an outstanding functional group compatibility.[213] Particularly, the emergence of the commercially available and operationally robust second-generation Hoveyda-Grubbs complex[214] (and its derivatives such as Zhan-1B)[215] for the intermolecular olefin cross-metathesis has uncovered a whole world of synthetic possibilities[216] as exemplified by its extensive use in the synthesis of complex molecules and natural products.[217]

Olefin metathesis has also found wide application in the synthesis of (hetero)aromatics.[218] Especially, its intramolecular variant (thermed ring-closing metathesis and often abbreviated as RCM) has been combined with an aromatisation event *via* oxidation or elimination of a leaving group for the synthesis of carbo- and heterocycles. But even more interestingly, cross-metathesis of two relatively simple, conveniently functionalised alkene partners followed by cyclisation allows for a more convergent synthesis. To the best of our knowledge, only two examples are found in the literature concerning this reaction in pyrrole synthesis.

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[213] For recent reviews that exemplify the relevance of metathesis reactions, see: (a) Higman, C. S.; Lummiss, J. A. M.; Fogg, D. E. *Angew. Chem. Int. Ed.* **2016**, *55*, 3552. (b) Jacques, R.; Pal, R.; Parker, N. A.; Sear, C. E.; Smith, P. W.; Ribaucourt, D.; Hodgson, D. M. *Org. Biomol. Chem.* **2016**, *14*, 5875. (c) Fustero, S.; Simón-Fuentes, A.; Barrio, P.; Haufe, G. *Chem. Rev.* **2015**, *115*, 871. (d) Hoveyda, A. H. *J. Org. Chem.* **2014**, *79*, 4763. (e) Kress, S.; Blechert, S. *Chem. Soc. Rev.* **2012**, *41*, 4389. (f) Dragutan, I.;Dragutan, V.; Demonceau, A. *RSC Adv.* **2012**, *2*, 719. (g) Cusak, A. *Chem. Eur. J.* **2012**, *18*, 5800. (h) Kotha, S.; Dipak, M. K. *Tetrahedron* **2012**, *68*, 397. (i) Prunet, J. *Eur. J. Org. Chem.* **2011**, 3634.(j) Nolan, S. P.; Clavier, H. *Chem. Soc. Rev.* **2010**, *39*, 3305.

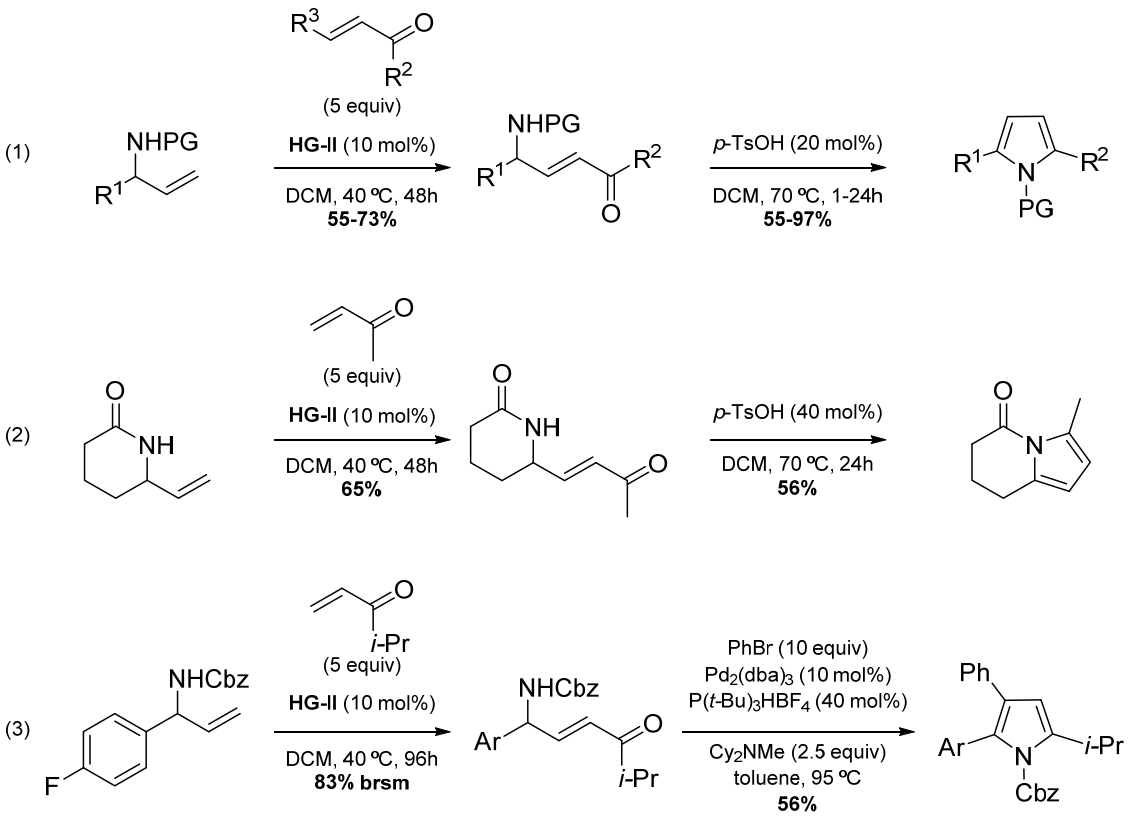
[214] Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

[215] Zhan, Z.-Y. J. US Patent **2007**, 20070043180.

[216] Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900.

[217] For reviews on CM reactions including synthetic applications, see: (a) Herbert, M. B.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2015**, *54*, 5018. (b) Lafaye, K.; Bosset, C.; Nicolas, L.; Guérinot, A.; Cossy, J. *Beilstein J. Org. Chem.* **2015**, *11*, 2223. (c) Donohoe, T. H.; Bower, J. F.; Chan, L. K. M. *Org. Biomol. Chem.* **2012**, *10*, 1322. (d) Miao, X.; Dixneuf, P. H.; Fischmeister, C.; Bruneau, C. *Green Chem.* **2011**, *13*, 2258. (e) Fischmeister, C.; Bruneau, C. *Beilstein J. Org. Chem.* **2011**, *7*, 156. (f) Aljarilla, A.; López, J. C.; Plumet, J. *Eur. J. Org. Chem.* **2010**, 6213.

[218] For reviews on the use of olefin metathesis in the synthesis of aromatic compounds, see: (a) Donohoe, T. J.; Bower, J. F.; Chan, L. K. M. *Org. Biomol. Chem,* **2012**, *10*, 1322. (b) van Otterlo, W. A. L.; de Koning, C. B. *Chem. Rev.* **2009**, *109*, 3743. (c) Donohoe, T. J.; Fishlock, L. P.; Procopiou, P. A. *Chem. Eur. J.* **2008**, *14*, 5716. (d) Donohoe, T. J.; Orr, A. J.; Bingham, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 2664.



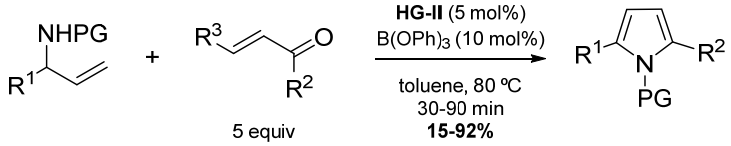
Scheme 3.1

Donohoe *et al.*[219] and Grela *et al.*[220] independently reported the combination of a cross-metathesis reaction with an acid-catalysed cycloaromatisation. In the first step of this sequence, a *trans*-γ-aminoenone is generated which upon addition of an acid co-catalyst undergoes *trans*/*cis* isomerisation and subsequent dehydration to the final pyrrole. In the work by Donohoe, *trans*-γ-aminoenones were obtained in moderate to good yields. In a second step, treatment with a catalytic amount of toluenesulfonic acid afforded the final 2,5-disubstituted pyrroles in almost quantitative yield in the majority of cases (Scheme 3.1, equation 1). A one-pot protocol was also shown to be feasible, albeit less efficient. This methodology was extended to the synthesis of a bicyclic pyrrole derivative (dihydroindolizinone) starting from a cyclic allylic amide (Scheme 3.1, equation 2).[221] Finally, a second family of 2,3,5-trisubstituted pyrroles was prepared, for

[219] Donohoe, T. J.; Race, N. J.; Bower, J. F.; Callens, C. K. A. *Org. Lett.* **2010**, *12*, 4094.
[220] Shafi, S.; Kędziorek, M.; Grela, K. *Synlett* **2011**, 124.
[221] The dihydroindolizinone is present in natural products such as rhazinicine: Gerasimenko, I.; Sheludko, Y.; Stöckigt, J. *J. Nat. Prod.* **2001**, *64*, 114.

which the Brønsted acid catalysis was replaced by a Heck arylation step which caused the *trans/cis* isomerisation with concomitant cycloaromatisation. The utility of this variation of the methodology was illustrated by the synthesis of an intermediate in the synthesis of Atorvastatin (Lipitor), the world's largest selling pharmaceutical (Scheme 3.1, equation 3 and Figure 3.1).

In Grela's version, $B(OPh)_3$ is added as a co-catalyst to the cross-metathesis reaction in such a way that the intermediate *trans*-γ-aminoenone is not isolated, but isomerises and cyclises *in situ* to the final pyrrole. In addition, the choice of the Lewis acid makes the reaction much faster than in Donohoe's protocol (Scheme 3.2).



Scheme 3.2

3.1.4. Organocatalytic Enantioselective Friedel-Crafts Alkylation of Pyrroles

The C-C bond formation lies at the core of synthetic organic chemistry. The Friedel-Crafts alkylation (FCA) is one of the oldest methodologies for this transformation,[222] but it is still a prevailing, powerful tool and it is included early on in every organic chemistry course syllabus.[223] The FCA remains at the same time one of the most straightforward approaches to the functionalisation of aromatic compounds and the introduction of benzylic carbon stereocentres.

Originally, the FCA required stoichiometric amounts of a Lewis acid. Later on, also inorganic Brønsted acids were reported to catalyse this transformation.

[222] (a) Friedel, C.; Crafts, J. M. *C. R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1392. (b) Friedel, C.; Crafts, J. M. *C. R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1450. (c) Friedel, C.; Crafts, J. M. *Bull. Soc. Chim. Fr.* **1877**, *27*, 530.

[223] (a) Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. In: *Comprehensive Organic Synthesis* (Eds.: Trost, B. M.; Fleming, I.), Pergamon Press, Oxford, **1991,** vol. 3, p. 293. (b) Roberts, R. M.; Khalaf, A. A. *Friedel–Crafts Alkylation Chemistry*, Marcel Dekker, New York, **1984**. (c) *Friedel–Crafts Chemistry* (Ed.: Olah, G. A.), Wiley, New York, **1973**. (d) *Friedel–Crafts and Related Reactions* (Ed.: Olah, G. A.), Wiley-Interscience, New York, **1963–65**; vols. 1–4.

The first examples of catalytic and asymmetric FCA reactions, en route to environmentally and economically more benign processes and allowing the syntheses of enantioenriched compounds, did not appear until the middle of the 1980s[224] after which the field was hugely developed.[225] Initially, these asymmetric approaches implied the use of chiral metal complexes. Since the early 2000s, the emergence of asymmetric organocatalysis,[226] *i.e.* the process involving the use of low molecular-weight, metal-free organic molecules as chiral catalysts, offered an economical, less toxic and environmentally friendly alternative, expanding at the same time the range of substrates used and of transformations involved in this methodology.[227] In addition, organocatalysts are generally bench-stable, easy-to-handle compounds readily available from Nature's chiral pool.

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[224] (a) Erker, G.; van der Zeijden, A. A. H. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 512. (b) Bigi, F.; Casiraghi, G.; Casnati, G.; Sartori, G.; Fava, G. G.; Belicchi, M. F. *J. Org. Chem.* **1985**, *50*, 5018.

[225] (a) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190. (b) Marquez-Lopez, E.; Diez-Martinez, A.; Merino, P.; Herrera, R. P. *Curr. Org. Chem.* **2009**, *13*, 1585. (c) *Catalytic Asymmetric Friedel–Crafts Alkylations* (Eds.: Bandini, M.; Umani-Ronchi, A.), Wiley-VCH, **2009**. (d) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903. (e) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 550 and references cited therein. (f) Wang, Y.; Ding, K.; Dai, L. *Chemtracts* **2001**, *14*, 610.

[226](a) *Stereoselective Organocatalysis: Bond Formation Methodologies and Activation Modes* (Eds.: Ríos Torres, R.), Wiley, **2013**. (b) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638. (c) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (d) *Enantioselective Organocatalysis* (Eds.: Dalko, P. I.), Wiley-VCH, Weinheim, Germany, **2007**. (e) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8. (f) Special issue on Organocatalysis: *Chem. Rev.* **2007**, *107*, issue 12. (g) List, B.; Yang, J. W. *Science* **2006**, *313*, 1584. (h) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (i) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (j) List, B. *Tetrahedron* **2002**, *58*, 5573. (k) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138. (l) Special issue on Organocatalysis: *Acc. Chem. Res.* **2004**, *37*, issue 8. (m) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, Germany, **2004.** (n) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726.

[227] For reviews on asymmetric Friedel-Crafts alkylation, see: (a) Chauhan, P.; Chimni, S. S. *RSC Adv.* **2012**, *2*, 6117. (b) Zeng, M.; You, S.-L. *Synlett* **2010**, 1289. (c) Terrasson, V.; de Figueiredo, R. M.; Campagne, J. M. *Eur. J. Org. Chem.* **2010**, 2635. (d) Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org. Chem.***2010**, *6*, 6. (e) *Catalytic Asymmetric Friedel–Crafts Alkylations* (Eds.: Bandini, M.; Umani-Ronchi, A.), Wiley-VCH, Weinheim, **2009**. (f) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190. (g) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608. (h) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199. (i) Sheng, Y.-F.; Zhang, A. J.; Zheng, X.-J.; You, S.-L. *Chin. J. Org. Chem.* **2008**, *28*, 605. (j) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903. (k) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 550. (l) Wang, Y.; Ding, K.-L. *Chin. J. Org. Chem.* **2001**, *21*, 763.

Asymmetric organocatalytic reactions, and this is also applicable to asymmetric FCA, can be classified according to the activation mode of the organocatalysts into covalent and non-covalent organocatalysis. The former strategy, in the context of asymmetric FCA, is practically a synonym for enamine/iminium catalysis[228] and it involves the condensation of the substrate and the catalyst (a chiral non-racemic primary or secondary amine) into a key reaction intermediate that is responsible for the stereoselection in the nucleophilic attack of the arene and thus for the enantioselectivity observed in the final product. In the latter case, the most important kind of non-covalent interactions involved in asymmetric FCA reactions is the hydrogen-bond[229] and the organocatalysts involved are mainly chiral phosphoric acids and thioureas. The work of the present chapter should be included in this second category.

Regarding the nature of the substrates involved (Figure 3.3), the most frequent (hetero)arenes involved as nucleophiles in asymmetric organocatalytic FCA are electron-rich aromatic compounds such as phenols/naphthols, anilines, indoles and pyrroles/dihydroindoles. The electrophilic counterparts are also utterly diverse and the activation mode of the catalyst is dependent on their structure. Just to mention the most commonly found electrophiles, enals and enones are employed in conjunction with covalent organocatalysis, while chalcones, nitroolefins, β,γ-unsaturated α-ketoesters or α,α-dicyanoolefins are activated with hidrogen-bond donors. This list of electrophiles corresponds to conjugate Michael acceptors which are by far the most popular substrates for asymmetric FCA, although other electrophiles do exist as for example 1,2-acceptors (imines and highly activated carbonyl compounds) or azodicarboxylates.

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[228] For reviews, see: (a) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun*. **2011**, *47*, 632. (b) List, B. *Angew. Chem. Int. Ed*. **2010**, *49,* 1730. (c) Melchiorre, P. *Angew. Chem. Int. Ed*. **2009**, *48*, 1360. (d) Melchiore, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138. (e) Yu, X.; Wnag, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (f) List, B. *Chem. Commun*. **2006**, 819.

[229] For selected reviews on hydrogen bond catalysis, see: (a) Chauhan, P.; Chimni, S. S. *RSC Adv.* **2012**, *2*, 737. (b) Connon, S. J. *Chem. Commun.* **2008**, 2499. (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (d) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520. (e) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418. (f) For selected reviews on the synthesis and use of chiral phosphoric acids, see ref. 257.

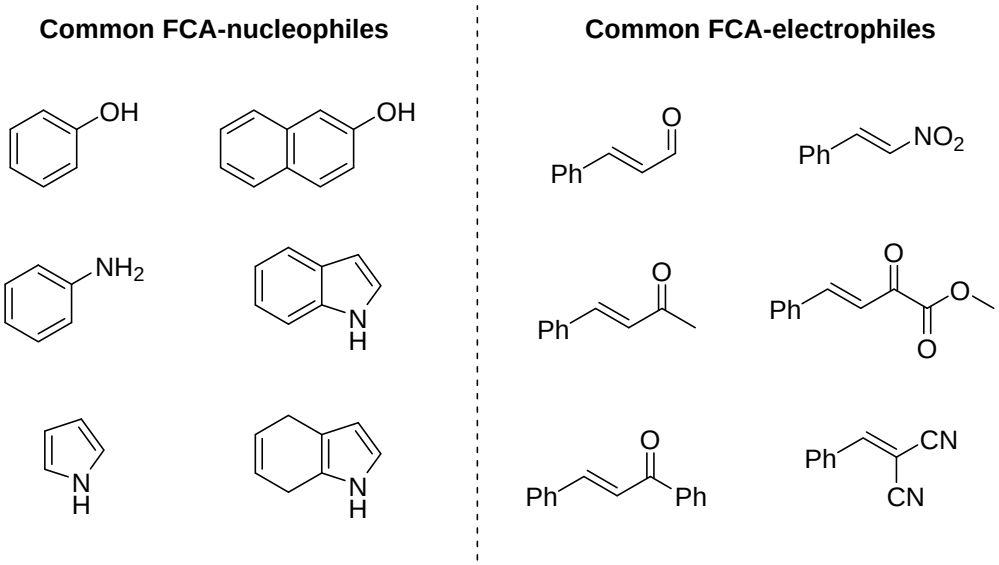


Figure 3.3

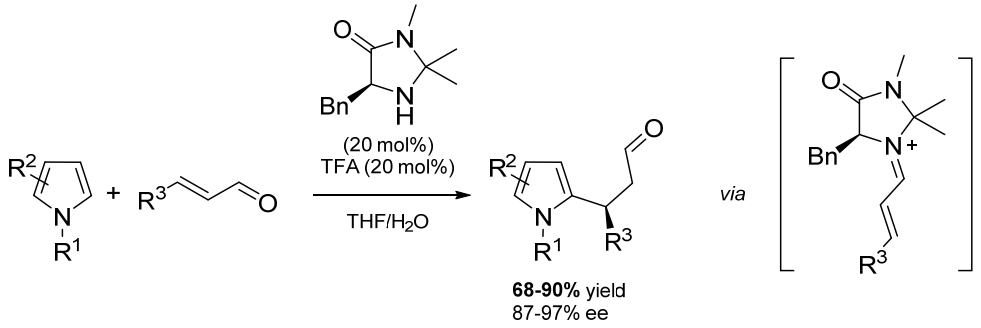
In comparison to indoles, for which a myriad of asymmetric procedures involving the FCA have been developed,[230] pyrroles have been relatively less used as nucleophilic counterparts in this reaction, even though substituted pyrroles, potentially accessible by this methodology, are interesting products because of their abundant natural occurrence and their different biological activities.[231] The reasons for the lack of reports on the use of pyrroles in (organocatalytic) FCA reactions might be found in the intrinsic high nucleophilicity of this heterocyclic ring, which in the reaction of unsubstituted pyrroles with Michael acceptors may cause selectivity issues (2-mono- *vs.* 2,5-di-alkylated product). The enantiofacial discrimination in asymmetric reactions of pyrrole is also more difficult in comparison to its benzannulated derivative indole. In addition, pyrroles, especially unsubstituted ones, are generally more sensitive towards heat, air and water than indoles and they are prone to polymerise.

In the following section, the main literature precedents regarding the asymmetric organocatalytic FCA will be reviewed, more exhaustively in the case of those involving intramolecular reactions to which the present work should be assigned.

[230] Zeng, M.; You, S.-L. *Synlett* **2010**, 1280.
[231] See references in Section 3.1.1.

❖ *Relevant organocatalytic intermolecular FCA reactions*

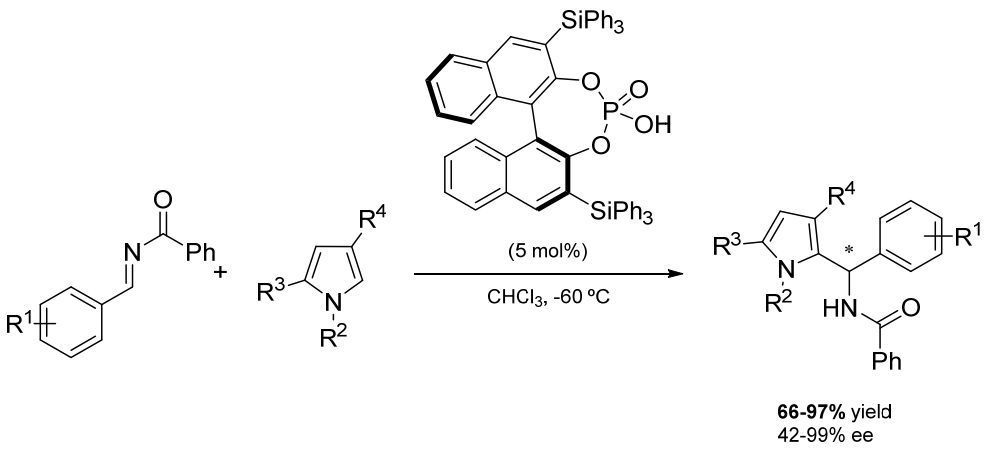
With their report on the enantioselective organocatalytic Michael-type FCA of pyrrols with enals (Scheme 3.3), MacMillan and coworkers were pioneers in the organocatalytic FCA chemistry.[232] The high optical purity of the products and high yields are explained by the formation of an iminium ion intermediate from the starting enal and the imidazolidinone catalyst. This contributes both to the LUMO-lowering activation of the enal (rendering it more reactive) and to the suppression of the competing 1,2-addition due to steric constraints imposed by the catalyst framework. Later on, other groups improved the protocols for this reaction.[233]



Scheme 3.3

Antilla *et al.* reported the first chiral Brønsted acid-catalysed FCA reaction of pyrroles (Scheme 3.4).[234] They employed imines as nucleophiles and the organocatalyst was a chiral BINOL-derived phosphoric acid, a chiral molecular architecture first reported by Terada[235] and Akiyama[236] to induce stereoselectivity in Mannich-type reactions. You *et al.* described a similar methodology employing nitroalkenes as electrophiles.[237]

[232] Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.
[233] (a) Kim, S.-G. *Bull. Korean Chem. Soc.* **2009**, *30*, 2519. (b) Akagawa, K.; Yamashita, T.; Sakamoto, S.; Kudo, K. *Tetrahedron Lett.* **2009**, *50*, 5602. (c) Breistein, P.; Karlsson, S.; Hedenström, E. *Tetrahedron: Asymmetry* **2006**, *17*, 107. (d) Zhang, Y.; Zhao, L.; Lee, S. S.; Ying, J. Y. *Adv. Synth. Catal.* **2006**, *348*, 2027.
[234] Li, G.; Rowland, G. B.; Rowland, E. B.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 4065.
[235] Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.
[236] Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566.
[237] Sheng, Y.-F.; Gu, Q.; Zhang, A.-J.; You, S.-L. *J. Org. Chem.* **2009**, *74*, 6899.

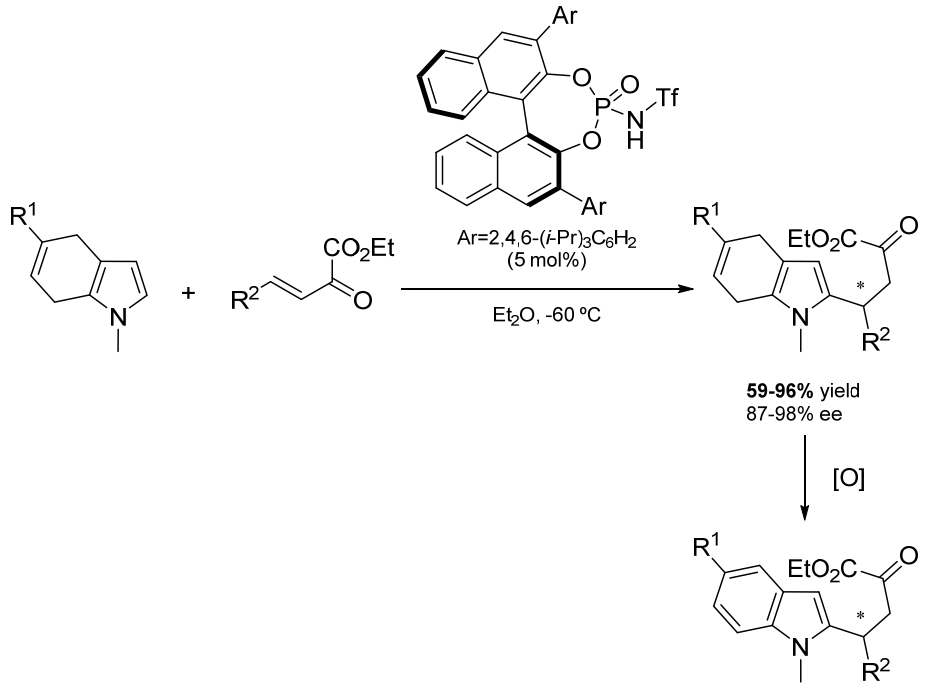


Scheme 3.4

The use of 4,7-dihydroindoles is an interesting strategy for the synthesis of 2-alkylated indoles: The FCA provides access to 2-alkylated-4,7-dihydroindoles in virtue of the natural reactivity of the pyrrole ring. (Indole reacts preferentially *via* C-3 in the aromatic electrophilic substitution reaction.) Oxidation of the resulting product (for instance, with *p*-benzoquinone) aromatises the six-member ring and renders 2-substituted indoles. You *et al.* reported the organocatalytic FCA of 4,7-dihydroindoles with various electrophiles followed by oxidation to the corresponding 2-alkylated indoles.[238] By way of illustration, their report on the use of β,γ-unsaturated α-ketoesters[239] is depicted on Scheme 3.5. Interestingly, it was found that chiral *N*-triflylphosphoramides were more efficient catalysts than the corresponding phosphoric acids for this particular transformation.

[238] (a) Sheng, Y.-F.; Li, G.-Q.; Kang, Q.; Zhang, A.-J.; You, S.-L. *Chem. Eur. J.* **2009**, *15*, 3351. (b) Kang, Q.; Zheng, X.-J.; You, S.-L. *Chem. Eur. J.* **2008**, *14*, 3539. (c) Zeng, M.; Kang, Q.; He, Q.-L.; You, S.-L. *Adv. Synth. Catal.* **2008**, *350*, 2169. Wang *et al.* used chiral 1,2-diamines derived from α-amino acids as catalysts in this same strategy: (d) Hong, L.; Sun, W.; Liu, C.; Wang, L.; Wong, K.; Wang, R. *Chem. Eur. J.* **2009**, *15*, 11105. The same group combined 4,7-dihydroindoles with enals and diaryl prolinol silyl ethers as catalysts in an analogous strategy: (e) Hong, L.; Liu, C.; Sun, W.; Wang, L.; Wong, K.; Wang, R. *Org. Lett.* **2009**, *11*, 2177. Akiyama's group reported a related similar work on the matter combining 4,7-dihydroindoles with different enones and chiral phosphoric acids as catalysts: (f) Sakamoto, T.; Itoh, J.; Mori, K.; Akiyama, T. *Org. Biomol. Chem.* **2010**, *8*, 5448.

[239] See ref. 238c.



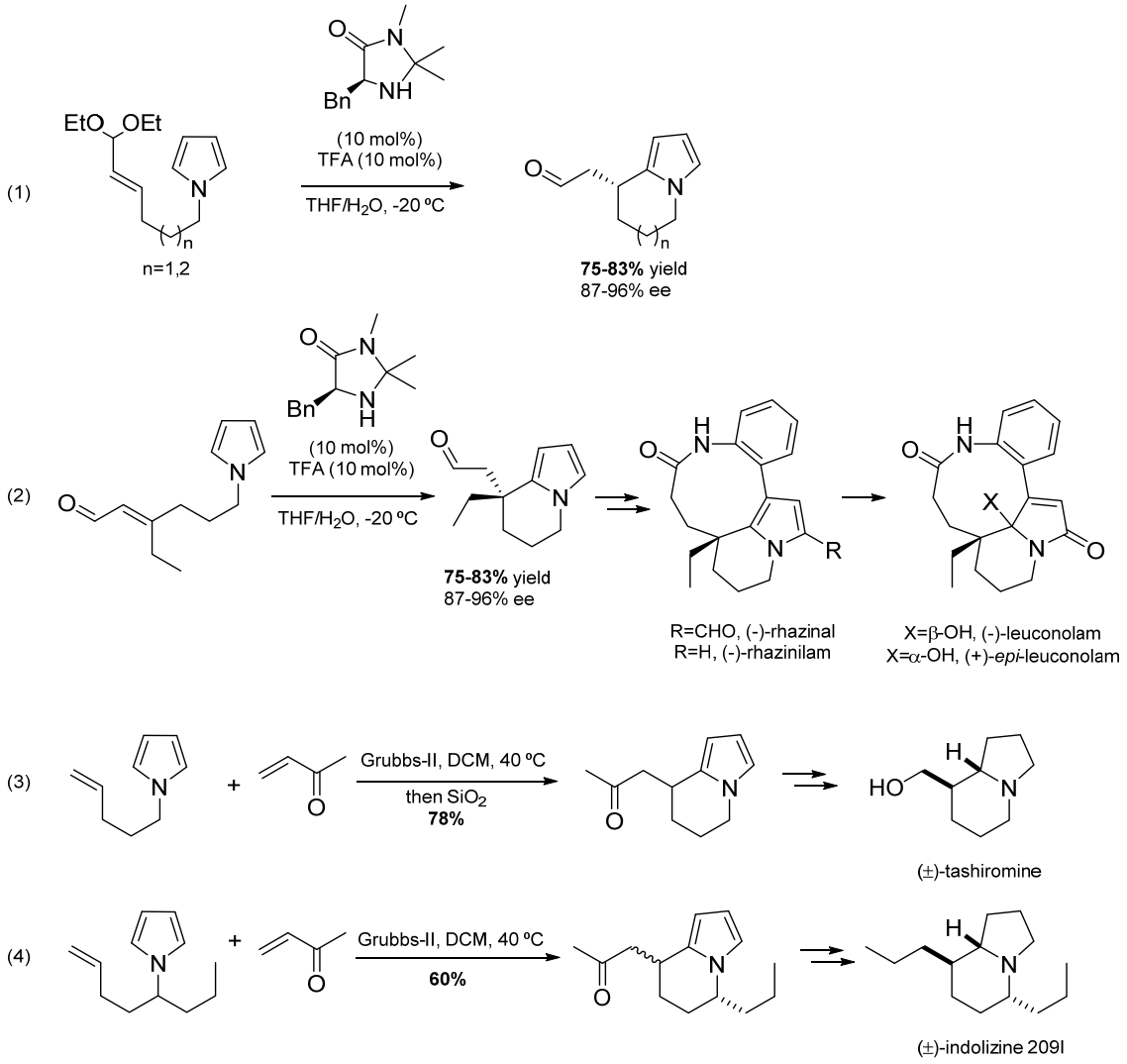
Scheme 3.5

As mentioned above, examples of organocatalytic FCA of pyrroles are much more limited than those of indoles. Nonetheless, the literature on the matter has built up in the last decade.[240]

❖ *Relevant organocatalytic intramolecular FCA reactions*

Smith and coworkers reported the intramolecular imidazolidinone catalysed enantioselective FCA reaction of an *N*-tethered pyrrol acetal which formed the corresponding enal and cyclised *in situ* (Scheme 3.6, equation 1)).[241] Six- and seven-membered ring products were obtained in good yields and enantioselectivities.

[240] For selected reports on organocatalytic intermolecular FCA reactions of pyrrole, see: (a) Nakamura, S.; Matsuda, N.; Ohara, M. *Chem. Eur. J.* **2016**, *22*, 9478. (b) Wu, K.; Zhuo, M.-H.; Sha, D.; Fan, Y.-S.; An, D.; Jiang, Y.-J.; Zhang, S. *Chem. Commun.* **2015**, *15*, 8054. (c) Brioche, J.; Courant, T.; Alcaraz, L.; Stocks, M.; Furber, M.; Zhu, J. P.; Masson, G. *Adv. Synth. Catal.* **2014**, *356*, 1719. (d) Wang, S.-G.; You, S.-L. *Angew. Chem. Int. Ed.* **2014**, *53*, 2194. (e) Hack, D.; Enders, D. *Synthesis* **2013**, *45*, 2904. (f) Riente, P.; Yadav, J.; Pericàs, M. A. *Org. Lett.*, **2012**, *14*, 3668. (g) Feng, J.; Yan, W.; Wang, D.; Li, P.; Sun, Q.; Wang, R. *Chem. Commun.* **2012**, *48*, 8003. (h) Curti, C.; Battistini, L.; Ranieri, B.; Pelosi, G.; Rassu, G.; Casiraghi, G.; Zanardi, F. *J. Org. Chem.* **2011**, *76*, 2248. (i) Ishihara, K.; Hatano, M.; Sugiura, Y.; Akakura, M. *Synlett* **2011**, 1247. (j) Kashikura, W.; Itoh, J.; Mori, K.; Akiyama, T. *Chem. Asian J.* **2010**, *5*, 470. (k) Nakamura, S.; Sakurai, Y.; Nakashima, H.; Shibata, N.; Toru, T. *Synlett* **2009**, 1639.
[241] Banwell, M. G.; Beck, D. A. S.; Smith, J. A. *Org. Biomol. Chem.* **2004**, *2*, 157.

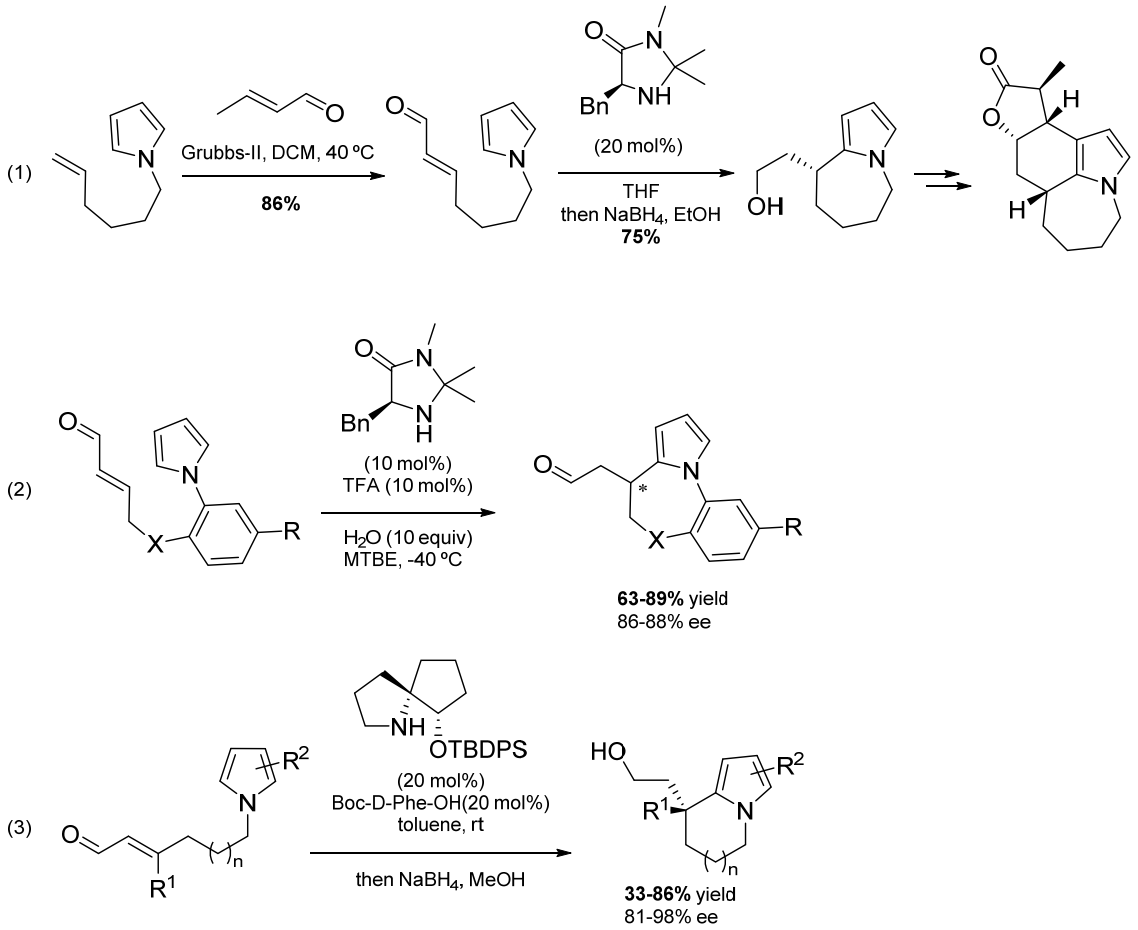


Scheme 3.6

This strategy was then applied to the total synthesis of a series of indolizidine derived natural products (Scheme 3.6, equation 2).[242] Recently, the same group reported the racemic total synthesis of the indolizidine alkaloids tashiromine and indolizine 209I.[243] In this case, a cross-metathesis reaction between pyrroles with an *N*-tethered olefin and methyl vinyl ketone provided access to the substrate for the intramolecular FCA reaction. In the case of the tashiromine synthesis, the enone reacted upon purification by column chromatography on silica gel (Scheme 3.6, equation 3), while in the case of indolizine 209I the enone could not even be observed as it cyclised *in situ* in a tandem process (Scheme 3.6, equation 4). As it is evident, this process is not an

[242] Banwell, M. G.; Beck, D. A. S.; Willis, A. C. *ARKIVOC* **2006**, *iii*, 163.
[243] Olivier, W. J.; Gardiner, M. G.; Bissember, A. C.; Smith, J. A. *Tetrahedron* **2018**, *74*, 5436.

organocatalysed process, but it was judged convenient to include it in this section due to its close resemblance to the report by You *et al.* (vide infra) and to the present work.



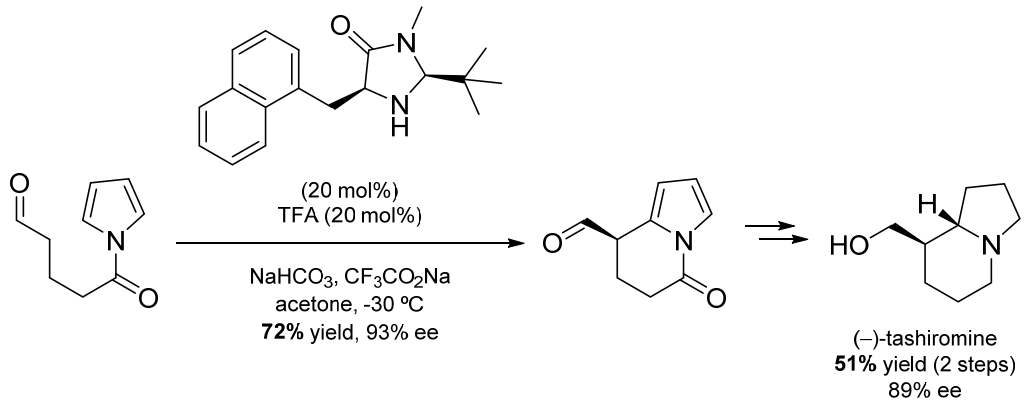
Scheme 3.7

Secondary amine-catalysed intramolecular Michael-type FCA of pyrroles has been reported by other groups as well. Bates *et al.* applied the methodology reported above for the construction of the pyrrolo-azepine ring system in the tetracyclic core of stemona alkaloids (Scheme 3.7, equation 1)[244] as in the structure of stenine (Figure 3.2). Xiao *et al.* extended their asymmetric organocatalysed approach to tetrahydrocarbazoles to the synthesis of pyrrole-fused heterocycles, obtained in good yields and enantioselectivities after an intramolecular FCA catalysed by MacMillan's imidazolidinone (Scheme 3.7, equation 2).[245] Recently,

[244] Bates, R.W.; Sridhar, S. *J. Org. Chem.* **2011**, *76*, 5026.
[245] Zhu, X.-Y.; An, X.-L.; Li, C.-F.; Zhang, F.-G.; Hua, Q.-L.; Chen, L.-R.; Xiao, W.-J. *ChemCatChem* **2011**, *3*, 679.

Tu, Tian *et al.* revisited the indolizine and pyrrolo-azepine synthesis by intramolecular organocatalytic FCA of pyrroles applying their spiropyrrolidine derived organocatalyst (Scheme 3.7, equation 3).[246]

A new covalent activation mode in the field of FCA introduced by MacMillan was the SOMO catalysis (single occupied molecular orbital). The gist of this methodology is the oxidation of the enamine intermediate (formed by condensation of an aliphatic aldehyde with the imidazolidinone catalyst) to a three-π-electron radical cation, which can react as an electrophile. The utility of this methodology was demonstrated in the enantioselective total synthesis of the alkaloid (-)-tashiromine (Scheme 3.8).[247] This natural product had already been synthesised by Smith *et al.* by a lengthy synthesis with the aid of an asymmetric Cu/BOX complex-catalysed intramolecular FCA in the key step.[248]

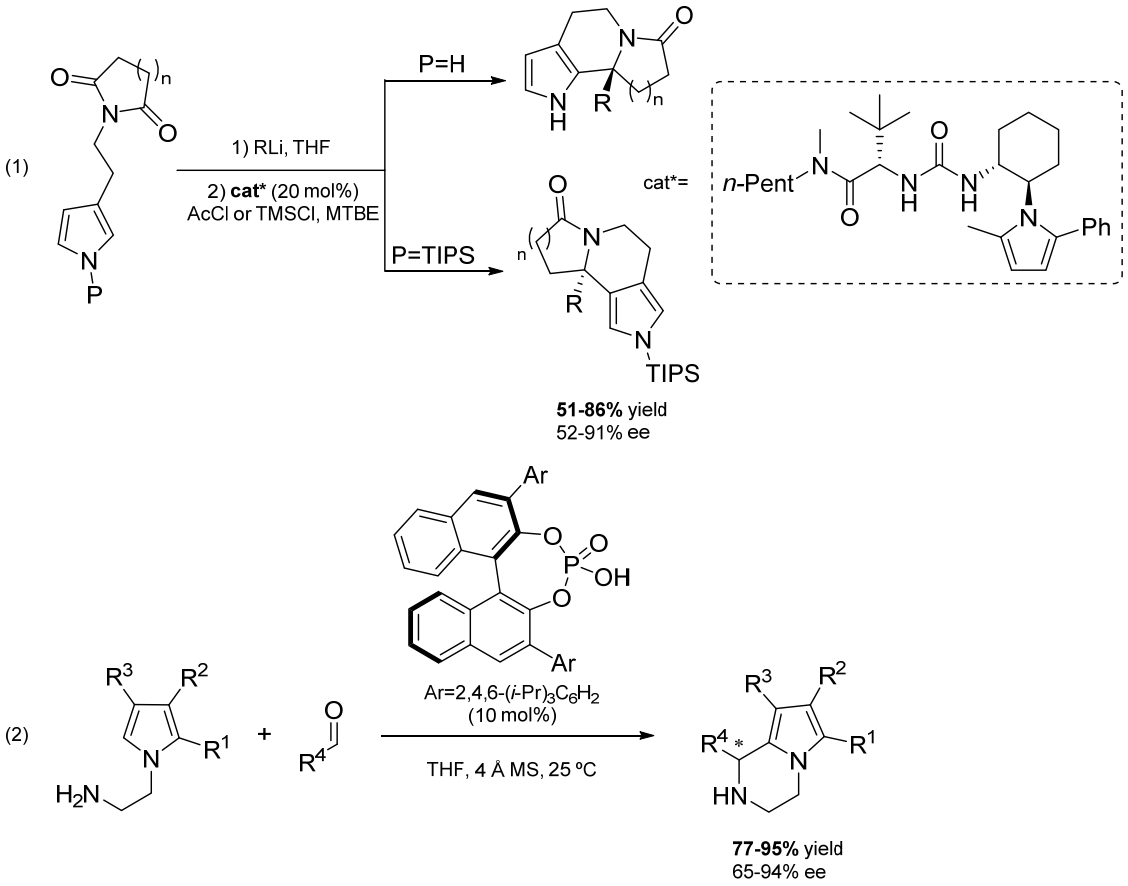


Scheme 3.8

Imines can also serve as electrophiles in the intramolecular aza-FCA, known in this case with the name reaction of Pictet-Spengler.[249] Jacobsen *et al.* reported a particular pyrrole cyclisation where an hydroxylactam forms the corresponding imine *in situ* which then undergoes intramolecular aza-FCA catalysed by a chiral thiourea. Interestingly, when the pyrrole was unprotected in the nitrogen, the cyclisation took place at the C-2 position as expected. However, when protected with the bulky triisopropylsilyl group, a change in regioselectivity was observed

[246] Zhang, Y.-H.; Yuan, Y.-H.; Zhang, S.-Y.; Tu, Y.-Q.; Tian, J.-M. *Tetrahedron Lett.* **2018**, *59*, 4015.
[247] Conrad, J. C.; Kong, J.; Laforteza, B. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11640.
[248] See ref. 241.
[249] Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030.

and position C-4 was rendered more reactive. Both regioisomers could be obtained in good yields and enantioselectivities (Scheme 3.9, equation 1).[250]

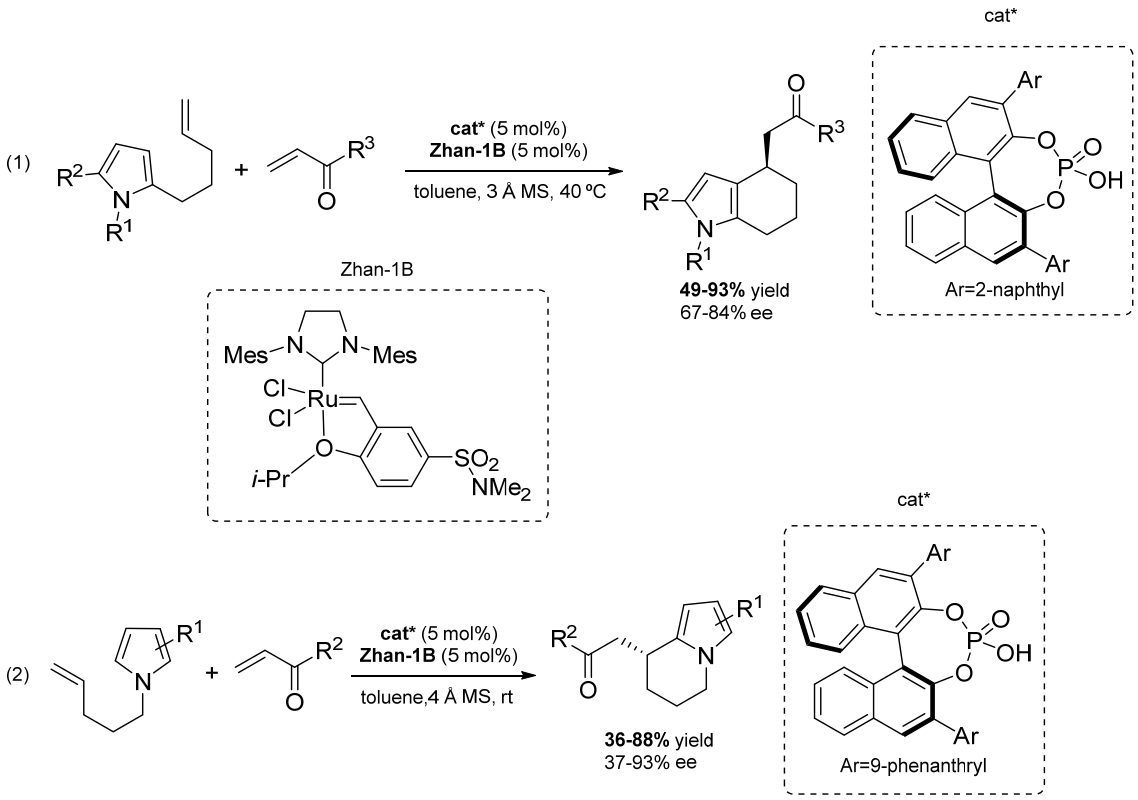


Scheme 3.9

Another example by Antilla *et al.* described the enantioselective synthesis of 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazines from *N*-aminoethyl pyrroles and aldehydes comprising a tandem imine formation/intramolecular Pictet-Spengler reaction sequence catalysed by a chiral BINOL phosphoric acid (Scheme 3.9, equation 2).[251] Similar transformations have been reported later, also in an organocatalytic manner.[252]

[250] Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577.
[251] He, Y.; Lin, M.; Li, Z.; Liang, X.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 4490.
[252] (a) Chen, H.-X.; Zhang, Y.; Zhang, Y.; He, X.; Zhang, Z.-W.; Liang, H.; He, W.; Jiang, X.; Chena, X.; Qiu, L. *RSC Adv,* **2018**, *8*, 37035. (b) Wang, Y.; Cui, L.; Wang, Y.; Zhou, Z. *Tetrahedron: Asymmetry* **2016**, *27*, 85. (c) Shen, X.; Wang, Y.; Wu, T.; Mao, Z.; Lin, X. *Chem. Eur. J.* **2015**, *21*, 9039. (d) Shen, X.; Wang, Y.; Wu, T.; Mao, Z.; Lin, X. *Chem. Eur. J.* **2015**, *21*, 9039. (e) Fan, Y.-S.; Jiang, Y.-J.; An, D.; Sha, D.; Antilla, J. C.; Zhang, S. *Org. Lett.* **2014**, *16*, 6112. (f) Du, H.; Rodríguez, J.; Bugaut, X.; Constantieux, T. *Adv. Synth. Catal.* **2014**, 356, 851.

Finally, the group of You developed a tandem one-pot protocol comprising a cross-metathesis/Michael-type FCA of pyrroles for the enantioselective synthesis of 4,5,6,7-tetrahydroindoles[253] and tetrahydroindolizines,[254] starting from *N*- or C-2-tethered pyrroles respectively (Scheme 3.10). The catalyst system consists of a ruthenium carbene complex and a chiral BINOL phosphoric acid. In both works, the authors demonstrate the convenience of the one-pot sequential reaction compared to the stepwise synthesis, as the former is superior both in terms of yield and enantioselectivity.

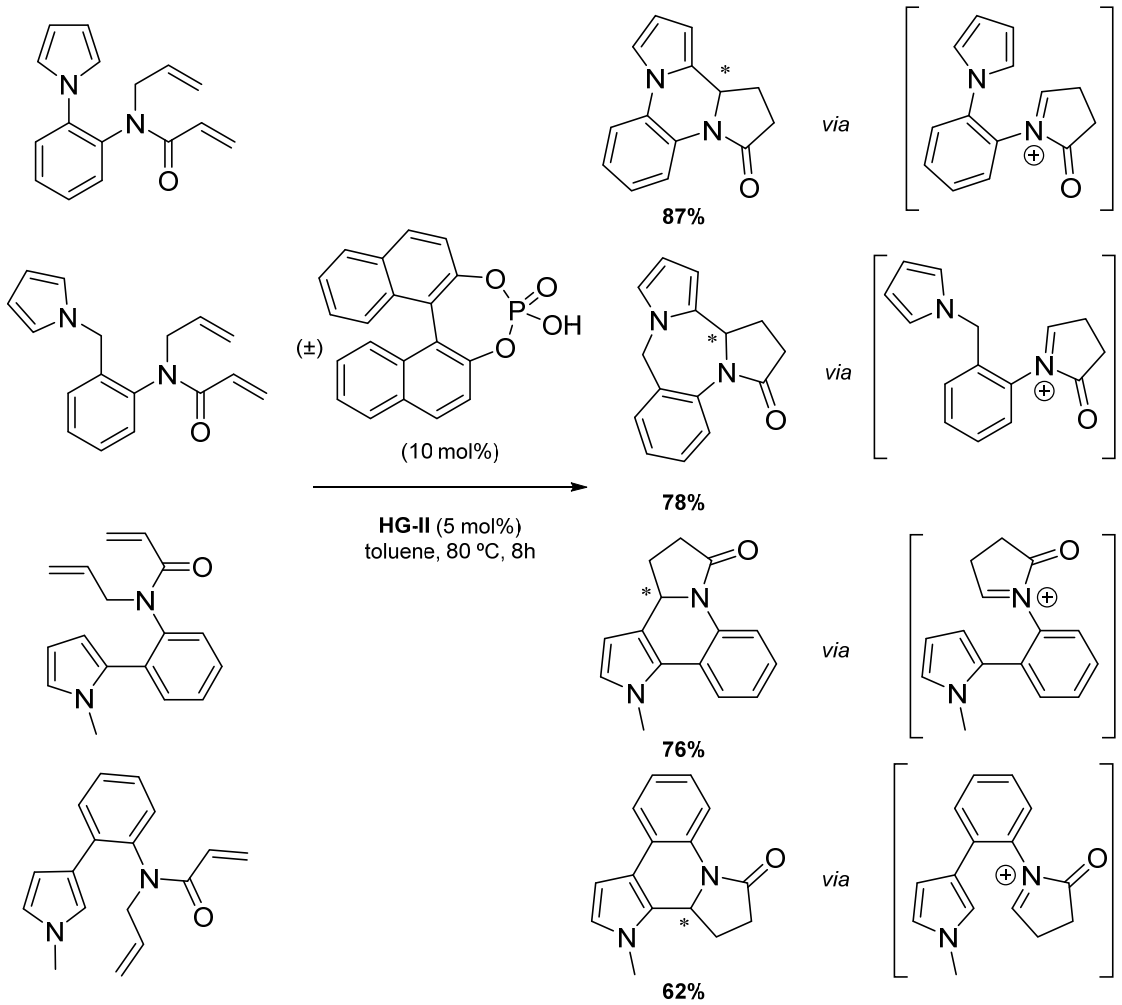


Scheme 3.10

A similar strategy by Patil *et al.* involved a RCM/isomerisation/Pictet-Spengler cascade catalysed again by a combination of a ruthenium metathesis catalyst and a BINOL phosphoric acid (Scheme 3.11).[255] A variety of 2-aminophenyl-substituted pyrroles could be accessed in racemic form using the racemic acid. An enantioselective approach using the corresponding chiral 3,3'-

[253] Zhang, J.-W.; Liu, X.-W.; Gu, Q.; Shi X.-X.; You, S.-L. *Org. Chem. Front.* **2015**, *2*, 476.
[254] Zhou, Y.; Liu, X.-W.; Gu, Q.; You, S.-L. *Synlett* **2016**, *27*, 586.
[255] Inamdar, S. M.; Chakrabarty, I.; Patil,N. T. *RSC Adv,* **2016**, *6*, 34428.

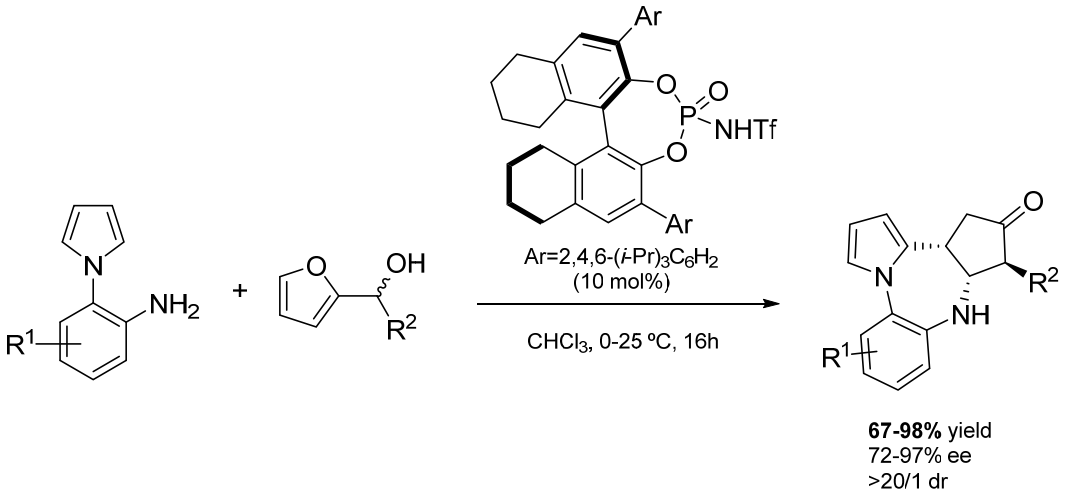
disubstituted acids was also attempted, but only low to moderate yields and poor enantioselectivities were obtained, evidencing that pyrroles are challenging substrates for this kind of asymmetric transformations.



Scheme 3.11

Recently, Jiang and collaborators reported an enantioselective organocascade comprising an aza-Piancatelli rearrangement followed by an intramolecular FCA (Scheme 3.12).[256] Cyclopentanone-containing pyrrolobenzodiazepines were obtained in high yields and enantioselectivities.

[256] Wei, Z.; Zhang, J.; Yang, H.; Jiang, G. *Org. Lett.* **2019**, *21*, 2790.

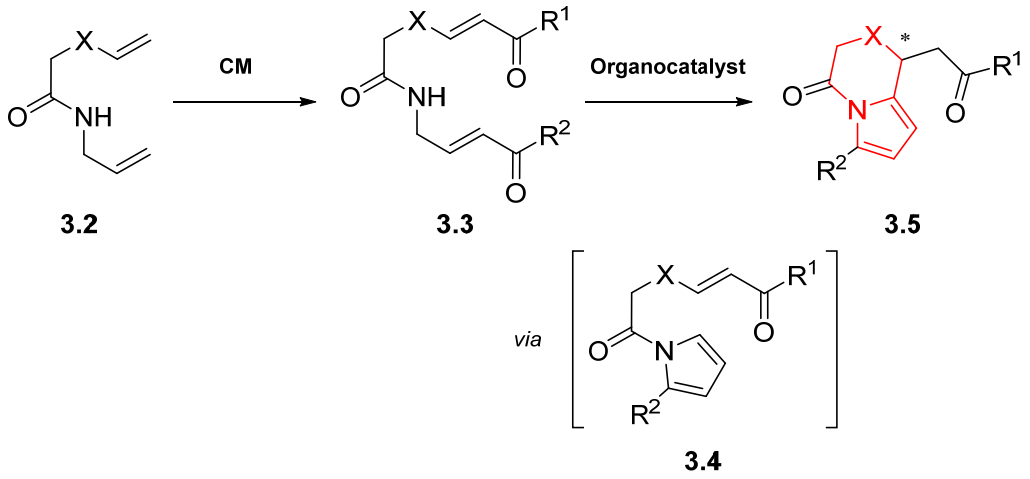

Ar
O
O
P
NHTf
O
Ar
Ar=2,4,6-(i-Pr)3C6H2
(10 mol%)
CHCl3, 0-25 ºC, 16h
N
NH2
R1
+
O
OH
R2
O
N
NH
R2
R1
67-98% yield
72-97% ee
>20/1 dr

Scheme 3.12

3.2. Objectives

The general goal in Chapter 3 is the development of a novel organocascade reaction for the synthesis of indolizidine and pyrrolo-azepine derivatives.

The tandem sequence will comprise a double cyclisation process from acyclic starting materials. The first step in the sequence will consist in a pyrrole formation reaction by cycloaromatisation of a γ-amidoenone moiety. In the subsequent reaction, the obtained pyrrole will react in an intramolecular Friedel-Crafts alkylation with a second Michael acceptor present in the starting material (Scheme 3.13).



Scheme 3.13

With this aim, the necessary starting materials will be prepared by bidirectional olefin cross-metathesis from the corresponding amides with an olefin at both the C- and N-ends.

An enantioselective organocatalytic version of this reaction will be developed. In view of the literature precedents for this kind of processes, chiral BINOL-derived Brønsted acids will be screened in search of an efficient catalyst.

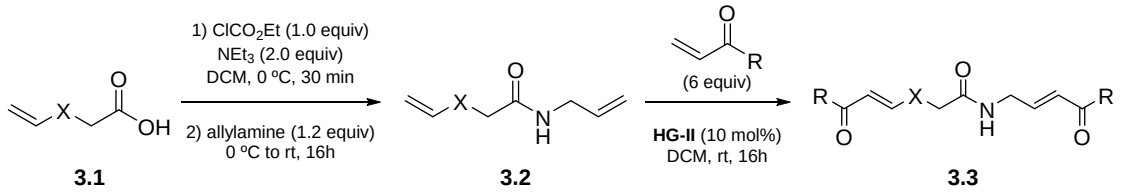
The ability of the proposed organocascade to give access to annulated pyrroles of different ring-sizes (indolizidine vs. pyrrolo-azepines) will be assessed.

3.3. Results and Discussion

3.3.1. Design and synthesis of starting materials 3.3

Our study began with the synthesis of the starting amides **3** (Table 3.1). It was accomplished in two steps. First, amides **3.2** were prepared from the corresponding free acid (commercially available or described in the literature) *via* the mixed anhydride. In the case of **3.2d** and **3.2f**, a more reactive acid derivative was necessary and thus the acid chloride was used instead.

Table 3.1. Synthesis of starting amides **3.3**

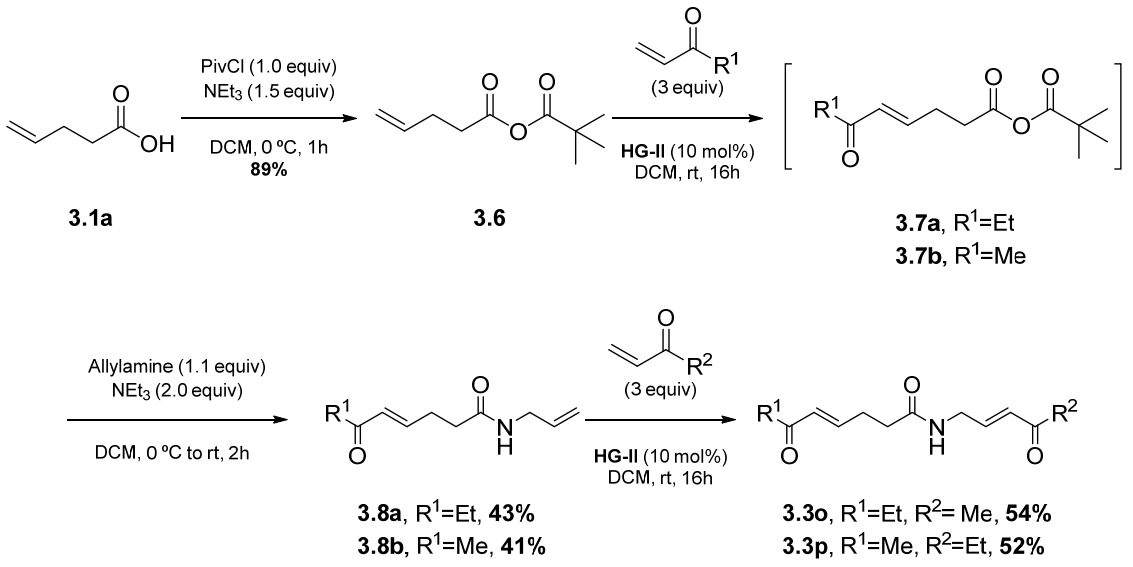


Entry	X	**3.2**	% yield[a]	R	**3.3**	% yield[a]
1	CH_2	**3.2a**	98	Me	**3.3a**	60
2	CH_2	**3.2a**		Et	**3.3b**	56
3	CH_2	**3.2a**		*n*-Pr	**3.3c**	36
4	CH_2	**3.2a**		*n*-Pent	**3.3d**	18
5	CH_2	**3.2a**		Ph	**3.3e**	12[c]
6	$(CH_2)_2$	**3.2b**	94	Me	**3.3f**	72
7	$(CH_2)_2$	**3.2b**		Et	**3.3g**	74
8	$(CH_2)_2$	**3.2b**		*n*-Pr	**3.3h**	51
9	$(CH_2)_2$	**3.2b**		*n*-Pent	**3.3i**	26
10	CH_2O	**3.2c**	36	Me	**3.3j**	39 (+31)[d]
11	CH_2S	**3.2d**	63[b]	Me	**3.3k**	12 (+19)[d]
12	$CH_2N(Boc)$	**3.2e**	89	Me	**3.3l**	40 (+41)[d]
13	$CH_2N(Ts)$	**3.2f**	89[b]	Me	**3.3m**	39
14	$CH_2C(CO_2Et)_2$	**3.2g**	34	Me	**3.3n**	59

[a]Isolated yield after flash column chromatography.
[b]A different procedure was used for amide synthesis. See the Experimental Section for details.
[c]The reaction was run at reflux.
[d]Recovered yields of mono cross-metathesis products are given in parentheses.

Bidirectional olefin cross-metathesis with the corresponding vinyl ketone and Hoveyda-Grubbs 2nd generation catalyst (**HG-II**) converted **3.2** into **3.3**. All reactions were run at room temperature, except in the case of **3.3e** in which the less reactive phenyl vinyl ketone required higher temperature (40 °C) and even so the reaction was low-yielding and messy (Table 3.1, entry 5). Compounds **3.3j**, **3.3k** and **3.3l** were obtained along with equimolar amounts of the corresponding mono-cross-metathesis products (as a non-separable mixture of the two possible isomers) (Table 3.1,entries 10-12).

In order to expand the generality of the present methodology, "unsymmetrical" amides **3.3o** and **3.3p** were prepared, in which the substituents of each ketone end are different. A stepwise synthesis was needed to sequentially introduce each enone into the structure of the final product (Scheme 3.14). Mixed anhydride **3.6** was prepared and then subjected to cross-metathesis conditions with the vinyl ketone required at the carbon end of the amide. It has to be underlined that the metathesis catalyst is perfectly compatible with the relatively reactive mixed anhydride. The obtained intermediates **3.7a** and **3.7b** were not isolated, but directly treated with allylamine to afford **3.8a** and 3.**8b** which were then purified by flash chromatography. Finally, a second cross-metathesis reaction with the second vinyl ketone provided access to **3.3o** or **3.3p**.

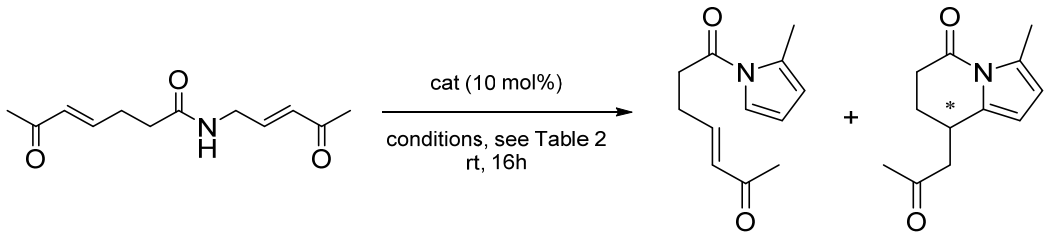


Scheme 3.14

3.3.2. Optimisation of the Tandem Reaction

With starting amides **3.3** in hand, their chemical behaviour was studied, choosing **3.3a** as a model substrate (Table 3.2).

Table 3.2. Preliminar screening of reaction conditions



3.3a **3.4a** **3.5a**

Entry	Catalyst	Solvent	% conversion[a]	Product(s)
1[b]	NaH	THF	decomposition	
2[b]	P_2Et	THF	decomposition	
3[b]	*t*-BuOK	THF	decomposition	
4[b]	DABCO	DCM	0	-
5	HQN-NH_2	DCM	0	-
6[b]	$BF_3{\cdot}OEt_2$	DCM	>95	**3.5a**
7[b]	TFA	DCM	>95	**3.5a**
8	$(PhO)_2P(O)OH$	DCM	>95	**3.4a/3.5a** (8/1)[c]
9	$(PhO)_2P(O)NHTf$	DCM	>95	**3.4a/3.5a** (1/1)[c]
10[d]	$(PhO)_2P(O)NHTf$	toluene	>95	**3.5a** (84%)[e]

[a]Conversion was determined from ^{1}H-NMR of the crude mixture.
[b]100 mol% of the corresponding catalyst was used.
[c]Product ratio was determined from ^{1}H-NMR of the crude mixture.
[d]The reaction was run at 60 °C.
[e]Isolated yield after flash column chromatography.

A preliminar screening of reaction conditions revealed that strong Brønsted bases decomposed the starting material (entries 1-3). DABCO and 9-amino-(9-deoxy)*epi*-hydroquinine (HQN-NH_2) did not promote any reactivity (entries 4 and 5). To our delight, Brønsted and Lewis acids catalysed the formation of dihydroindolizinone **3.5a** *via* pyrrole **3.4a** (entries 6 and 7). The sequence can be understood as a cycloaromatisation/intramolecular Friedel-Crafts alkylation process. With a view to develope an organocatalytic process, diphenyl phosphate and the corresponding *N*-triflyl phosphoramide were tested. The first catalyst enabled the pyrrole formation, but was insufficiently acid to efficiently activate the intermediate enone for the intramolecular Friedel-Crafts alkylation (entry 8). Longer reaction times or higher temperatures did not provide better product ratios. Generally, pyrroles are regarded electron-rich heterocycles, but in **3a** the free electron pair of the pyrrole nitrogen belongs at the same time to an amide moiety, which explains the relatively low reactivity in position 2 of the pyrrole ring. In contrast, the more acidic phosphoramide catalyses the whole process and it can drive it to completion (entries 9 and 10).

Looking at the structure of the final product (containing a stereocentre formed in the intramolecular FCA step) and taking into account that the catalyst is achiral, it was clear that it was obtained as a racemate. In the hope of developing an enantioselective process, a variety of (*R*)-BINOL derived *N*-triflyl phosphoramide[257,258] were screened (Table 3.3). Among all the tested catalysts, the one substituted with 2,4,6-triisopropylphenyl groups was identified as the best for this transformation in terms of enantioselectivity.

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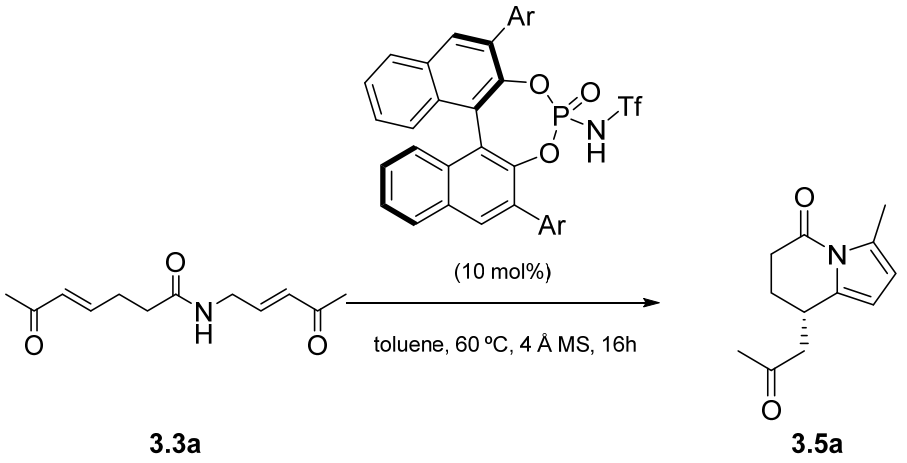
[257] For selected reviews on the synthesis and use of chiral phosphoric acids, see: (a) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047. (b) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539. (c) Rueping, M.; Nachtsheim, B. J.; Koenigs, R. M.; Ieawsuwan, W. *Chem. Eur. J.* **2010**, *16*, 13116. (d) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2010**, *8*, 5262. (e) Su, Y.; Shi, F. *Chin. J. Org. Chem.* **2010**, *30*, 486. (f) Terada, M. *Synthesis* **2010**, 1929. (g) Gao, Y.-J.; Yang, L.-H.; Song, S.-J.; Ma, J.-J.; Tang, R.-X.; Bian, R.-H.; Liu, H.-Y.; Wu, Q.-H.; Wang, C. *Chin. J. Org. Chem.* **2008**, *28*, 8. (h) Terada, M. *Chem. Commun.* **2008**, 4097. (i) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.

[258] For recent computational studies of this kind of catalysts, see: (a) Maji, R.; Mallojjala, S. C.; Wheeler, S. E. *Chem. Soc. Rev.* **2018**, *47*, 1142. (b) Reid, J. P.; Goodman, J. M. *Chem. Eur. J.* **2017**, *23*, 14248.

Table 3.3. Catalyst screening



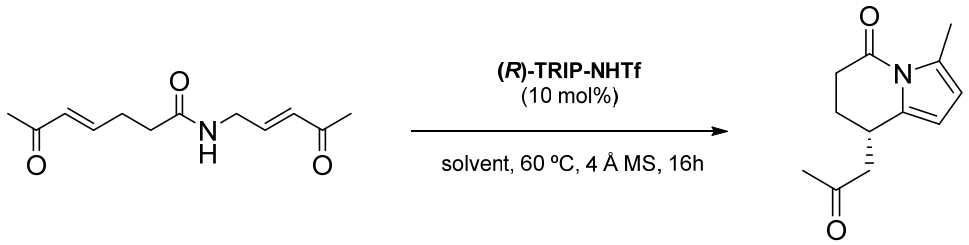
3.3a **3.5a**

Entry	Ar	% conversion	er
1	1-naphthyl	>95	58:42
2	2-naphthyl	>95	56:44
3	9-anthryl	>95	58:42
4	9-phenanthryl	>95	61:39
5	[H8]- 9-phenanthryl	>95	61:39
6	2,4,6-triisopropyl-phenyl	>95	73:27
7	2,4,6-tricyclohexyl-phenyl	>95	70:30
8	mesityl	>95	61:39
9	4-biphenyl	>95	52:48
10	3,5-bis-trifluoromethyl-phenyl	>95	57:43
11	2,4-bis-trifluoromethyl-phenyl	>95	59:41
12	4-trifluoromethyl-phenyl	>95	51:49
13	perfluorophenyl	>95	61:39

Hoping to further improve the ee values, a solvent screening was carried out (Table 3.4). It is remarkable how apparently subtle changes in the solvent result in dramatic effects on the enantioselectivity, as in the pair toluene/benzene (entries 1 and 3). Carbon tetrachloride provides the best result in terms of enantioselectivity, if only moderate (entry 14). The reaction temperature was adjusted to 40 °C, resulting in a reaction time of 5 days to ensure complete conversion to the final product of the tandem sequence (**3.5a**). Lower temperatures invariably resulted in mixtures of **3.4a** and **3.5a**, no matter how long

the reaction was run (entry 15). Thus, it was necessary to sacrifice some enantioselectivity in favour of conversion in reasonable reaction times.

Table 3.4. Solvent screening



3.3a **3.5a**

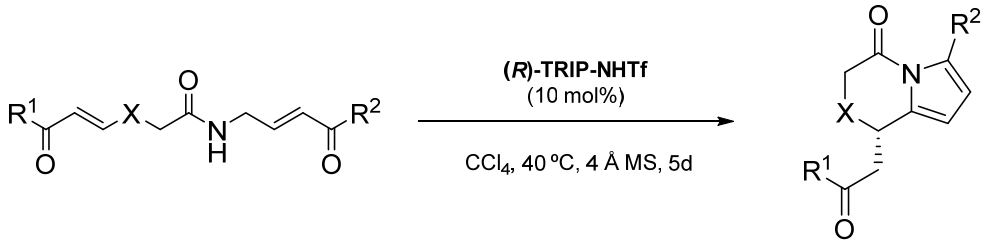
Entry	Solvent	% conversion	er
1	toluene	>95	73:27
2[a]	toluene	>95	69:31
3	benzene	>95	52:48
4	*p*-xylene	>95	69:31
5	*o*-xylene	>95	72:28
6	chlorobenzene	>95	52:48
7	trifluoromethylbenzene	>95	64:36
8	*n*-hexane	>95	73:27
9	cyclohexane	>95	79:21
10	DCM	>95	70:30
11	DCE	>95	58:42
12	$CHCl_3$	>95	75:25
13	CCl_4	>95	78:22
14[b]	CCl_4	>95 (76%)[c]	80:20
15[d]	CCl_4	>95[e]	82:18
16	CCl_4/cyclohexane	>95	79:21
17	MTBE	>95	55:45

[a]No molecular sieves were used.
[b]The reaction was run at 40 °C for 5 days.
[c]Isolated yield after flash column chromatography.
[d]The reaction was run at room temperature.
[e]A mixture of **3.4a** and **3.5a** was obtained in a ratio of 1:4 (**3.4a**:**3.5a**).

3.3.3. Study of the Scope of the Tandem Reaction

Finally, the best reaction conditions were applied to all amides **3** in order to study the reaction scope (Table 3.5).

Table 3.5. Scope of the enantioselective tandem cycloaromatisation/intramolecular Friedel-Crafts alkylation reaction



3.3 **3.5**

Entry	**3.3**	X	R^1	R^2	**3.5**	% yield[a]	er
1	**3.3a**	CH_2	Me	Me	**3.5a**	76	80:20
2	**3.3b**	CH_2	Et	Et	**3.5b**	70	81.5:18.5
3	**3.3c**	CH_2	*n*-Pr	*n*-Pr	**3.5c**	80	83:17
4	**3.3d**	CH_2	*n*-Pent	*n*-Pent	**3.5d**	63	85:15
5	**3.3e**	CH_2	Ph	Ph	**3.5e**	44	86:14
6	**3.3f**	$(CH_2)_2$	Me	Me	**3.5f**	70	73.5:26.5
7	**3.3g**	$(CH_2)_2$	Et	Et	**3.5g**	71	68:32
8	**3.3h**	$(CH_2)_2$	*n*-Pr	*n*-Pr	**3.5h**	63	69:31
9	**3.3i**	$(CH_2)_2$	*n*-Pent	*n*-Pent	**3.5i**	79	65:35
10	**3.3j**	CH_2O	Me	Me	**3.5j**	70	65:35
11	**3.3k**	CH_2S	Me	Me	**3.5k**	47	73:27
12	**3.3l**	CH_2N(Boc)	Me	Me	**3.5l**	59	76:24
13	**3.3m**	CH_2N(Ts)	Me	Me	**3.5m**	75	84:16
14	**3.3n**	$CH_2C(CO_2Et)_2$	Me	Me	**3.5n**	62	65:35
15	**3.3o**	CH_2	Et	Me	**3.5o**	70	84:16
16	**3.3p**	CH_2	Me	Et	**3.5p**	62	76:24

[a]Isolated yield after flash column chromatography.
[b]A different procedure was used for amide synthesis. See the Experimental Section for details.
[c]The reaction was run at reflux.
[d]Recovered yields of mono cross-metathesis products are given in parentheses.

A variety of indolizine and azepine derivatives were obtained with moderate enantioselectivies and moderate to good yields for this tandem sequence. Structural variability was introduced *via* the ketone substituents (R^1 and R^2) and the linker chain (X). When the appropriate heteroatom-bearing linker were used, oxazepine, thiazepine and diazepine ring systems were obtained (entries 10-13).

The absolute configuration of a recrystallysed sample of **3.5a** was determined to be (*S*) by Vibrational Circular Dichroism (VCD). (See Experimental Section for further details.)

3.3.4. Exploration of the substrate structure

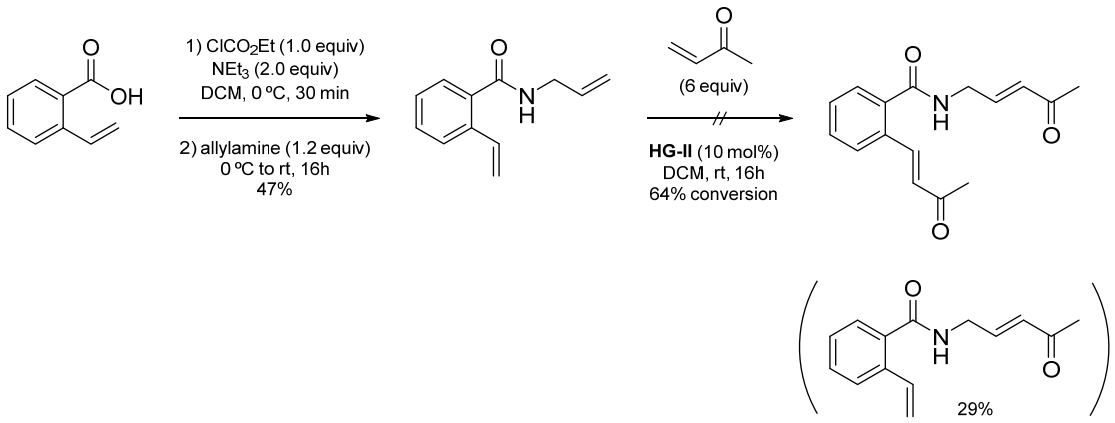
Having established the reaction conditions for the previously described tandem process, we planned to explore the potential (and the limitations) of this protocol regarding the structure of the starting material. In fact, efforts in this sense were already undertaken early since it was recognised that the optimised organocascade did only provide moderate enantioselectivities. The ultimate goal was, of course, to find a modified system rendering higher levels of enantioselectivity. Unfortunately, no such alternative was found that worked more efficiently. For this reason, and to prevent the reader losing the thread in a pointless discussion, only a selection of failed attempts will be presented.

This section will be divided into two parts: The first one will cover the failed syntheses of selected new substrates. In the second one, the focus will be put on a series of starting materials that were successfully prepared but were unable to undergo the tandem reaction.

❖ *Substrates whose synthesis failed*

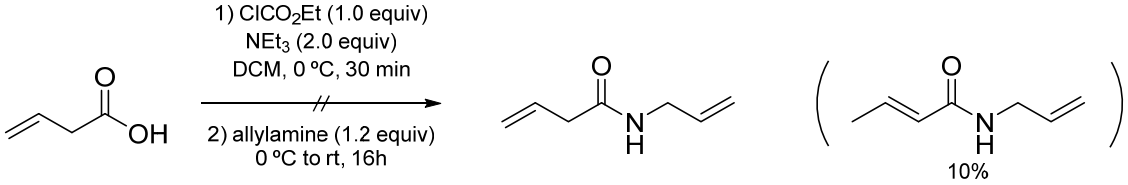
One of the first thoughts when trying to expand the substrate scope of the tandem transformation under study was to introduce an aromatic linker into the carbon end of the amide. To this end, 2-vinyl benzoic acid was converted into the

corresponding *N*-allyl amide by the standard protocol involving the mixed anhydride formation. However, the bidirectional cross-metathesis reaction under the standard conditions did not afford the wished product. In fact, the starting material was partly recovered (64% conversion) and only 29% of one of the mono-cross metathesis products could be identified from the reaction mixture (Scheme 3.15). The fact that the double cross-metathesis does not take place is not totally surprising, not only due to the obvious steric hindrance of the second alkene as reaction partner (*ortho*-substitution!), but because there is a literature precedent reporting the troublesome cross-metathesis of *N*-allyl benzamide with methyl vinyl ketone.[259]



Scheme 3.15

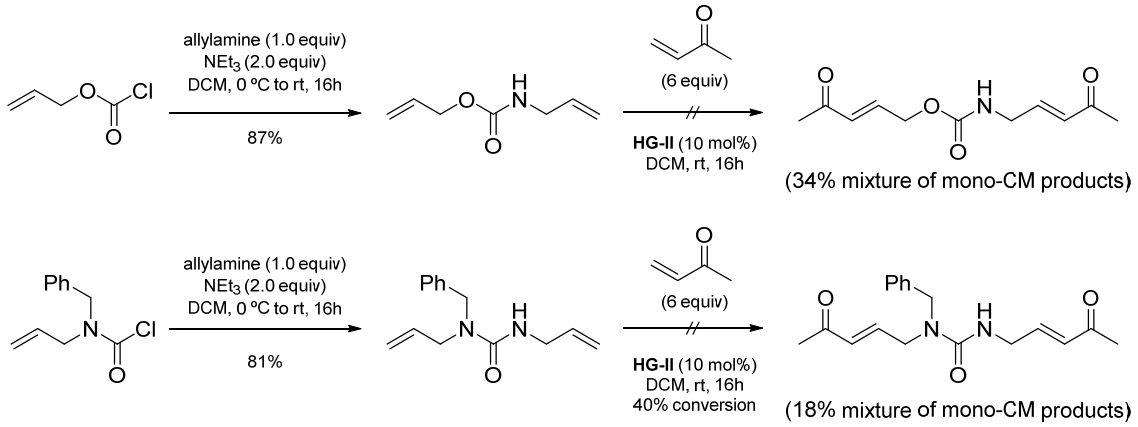
Another imaginable modification of the model substrate involves shortening the aliphatic linker chain starting from 3-butenoic acid. Under the standard conditions of the amide coupling, a complex reaction mixture was obtained from which only the isomerised product could be identified and isolated in 10% yield (Scheme 3.16).



Scheme 3.16

[259] Vieille-Petit, L.; Clavier, H.; Linden, A.; Blumentritt, S.; Nolan, S. P.; Dorta, R. *Organometallics* **2010**, *29*, 775.

Finally, it was tried to change the kind of nitrogen involved in the tandem process from amide to carbamate or urea (Scheme 3.17). The corresponding substrates were successfully prepared starting from allyl chloroformate and a carbamoyl chloride described in the literature.[260] However, the bidirectional cross-metathesis was unable to provide access to the necessary substrates. In the first case, the reaction was messy and only a mixture of the two mono-cross-metathesis products was isolated from the crude. In the second case, the reaction was sluggish: 60% starting material was recovered along with 18% of the mono-cross metathesis products.

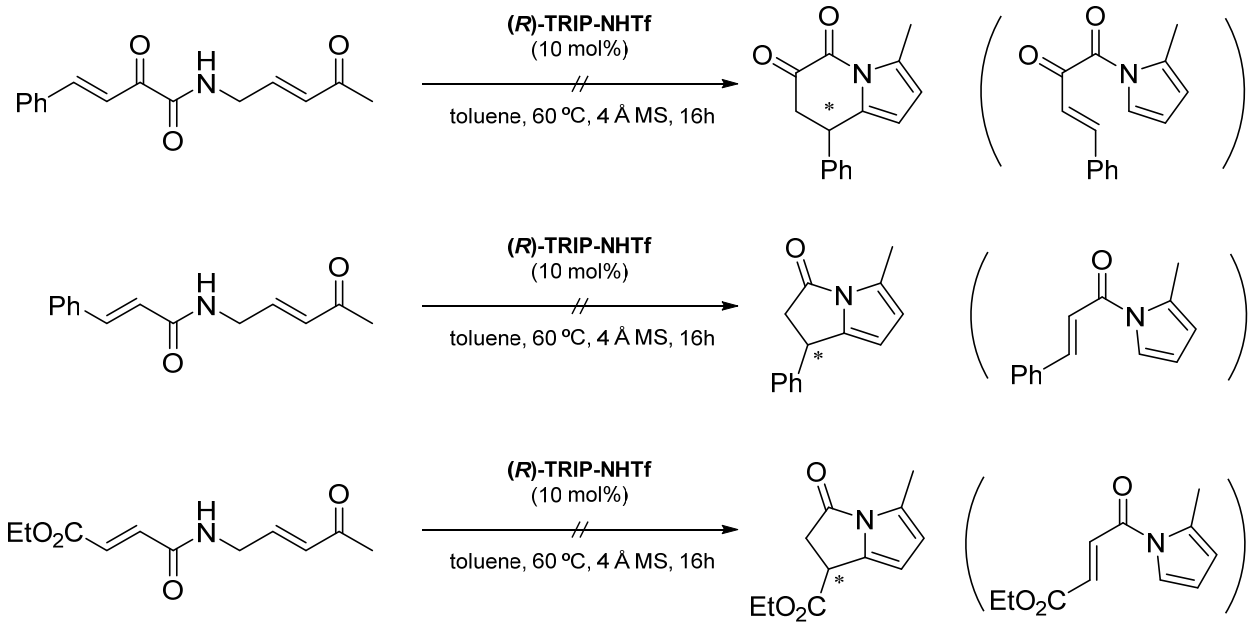


Scheme 3.17

❖ *Substrates unable to undergo the tandem process*

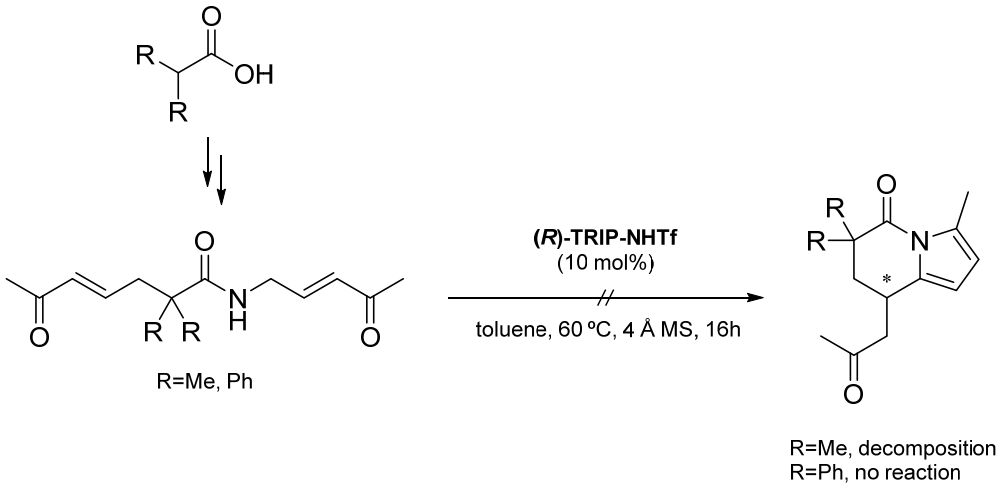
Other amides with a different linker structure were successfully synthesised by a sequence comprising amide coupling of the corresponding free acid with allylamine and cross-metathesis with methyl vinyl ketone. Unfortunately, under the standard conditions only the cycloaromatisation product could be detected (Scheme 3.18). The reason for the failure of the FCA step in these reactions can be rationalised considering the kind of ring closure that takes place. In the first case, the oxo-amide would require a 6-*endo*-trig cyclisation mode and in the last two cases a 5-*endo*-trig. According to Baldwin's rules,[261] these ring closure modes are disfavoured.

[260] Wu, T.; Cheng, J.; Chen, P.; Liu, G. *Chem. Commun.* **2013**, *49*, 8707.
[261] Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, *0*, 734.



Scheme 3.18

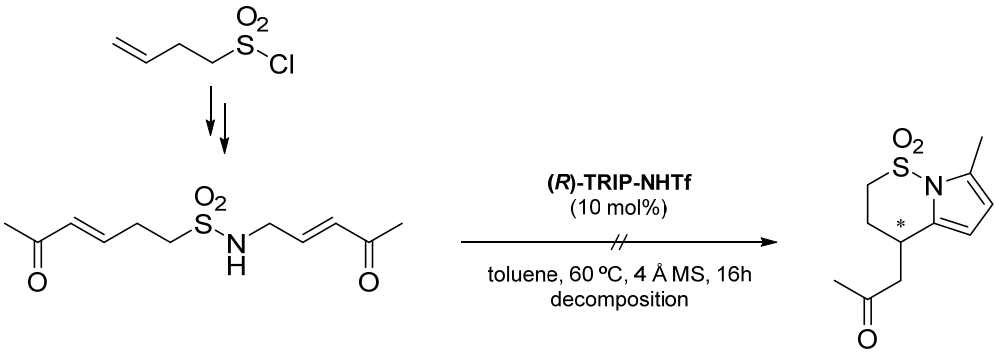
Amides featuring a *gem*-disubstitution in the α-position of the amide (synthesised by allylation of the corresponding disubstituted acetic acid, amide coupling with allylamine and bidirectional cross-metathesis with methyl vinyl ketone) were expected to render better results of enantioselectivity due to a less flexible conformation in the transition state. Nevertheless, the amide with phenyl groups was inert to the catalyst while the *gem*-dimethyl derivative decomposed under the same reaction conditions (Scheme 3.19).



Scheme 3.19

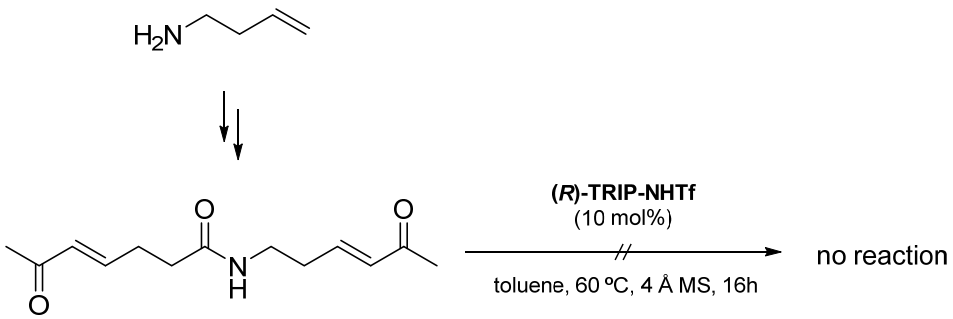
Finally, the carboxamide moiety was replaced by a sulfonamide group hoping to modulate the nucleophilicity of the substrate and, thus, the selectivity of

the process. To this end, 3-butene-1-sulfonyl chloride[262] was treated with allylamine and the product subjected to bidirectional cross-metathesis. Unfortunately, the obtained substrate decomposed under the standard reaction conditions (Scheme 3.20).



Scheme 3.20

As already discussed, the first step in the tandem sequence is the cycloaromatisation to render the intermediate pyrrole. As a proof of concept, we synthesised an homologue of the model substrate employing homo-allylamine (3-butenylamine) in the amide synthesis. The new substrate can not form the pyrrole ring, since the ring size would be bigger than 5. In theory, a dihydropyridine ring could be thought of.[263] In fact, the substrate is inert to the standard reaction conditions as expected (Scheme 3.21).



Scheme 3.21

[262] Parkhurst, R. R.; Balog, S.; Weder, C.; Simon, Y. C. *RSC Adv.* **2014**, *4*, 53967.
[263] Donohoe, T. J.; Bower, J. F.; Baker, D. B.; Basutto, J. A.; Chana, L. K. M.; Gallagher, P. *Chem. Commun.* **2011**, *47*, 10611.

3.4. Conclusions

In summary, we have developed a novel tandem organocatalysed cycloaromatisation/intramolecular Friedel-Crafts alkylation sequence leading to the synthesis of a new family of indolizinones and pyrrolo-azepinones in moderate to good yields. The starting amidodienones are accessible by bidirectional or sequential olefin cross-metathesis. An asymmetric approach was developed using an (*R*)-BINOL derived *N*-triflyl phosphoramide as Brønsted acid catalyst for the whole process, obtaining moderate levels of enantioselectivity. Further work in this sense and in the search for greener reaction conditions is currently being carried out in our laboratory.

3.5. Experimental Section

3.5.1. General methods

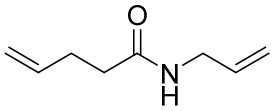
Reactions were carried out under a nitrogen atmosphere unless otherwise indicated. Solvents were purified prior to use: THF and toluene were distilled from sodium, and CH_2Cl_2 was distilled from calcium hydride. The reactions were monitored with the aid of TLC on 0.25 mm precoated silica gel plates. Visualisation 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). ^{1}H 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. Enantiomeric excess was determined by means of HPLC using chiral columns and mixtures of hexane and isopropanol as mobile phase.

3.5.2. Experimental procedures and characterisation of new compounds

- **General procedure for the synthesis of starting amides 3.2**

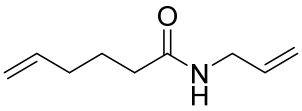
To a solution of the corresponding carboxylic acid (5 mmol) in DCM (20 mL, 0.25 M) at 0 °C, TEA (1.39 mL, 10 mmol, 2.0 equiv) and ethyl chloroformate (0.48 mL, 5 mmol, 1.0 equiv) were sequentially added. After 30 min at the same temperature, allylamine (0.45 mL, 6 mmol, 1.2 equiv) was added dropwise and the resulting mixture was stirred at room temperature for 16h. 20 mL of a saturated NH_4Cl solution were added, the organic phase was separated and the aqueous phase was extracted with DCM (2x20 mL). The combined organic phases were washed with brine (20 mL) and dried over anhydrous sodium sulfate and the

solvent was removed under vacuum. The crude amide **3.2** was used in the next step without further purification.



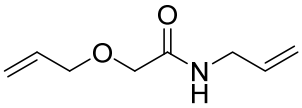
3.2a

***N*-Allylpent-4-enamide (3.2a):** Starting from commercially available 4-pentenoic acid and following the procedure described above, **3.2a** was obtained as a colorless oil in 98% yield (682 mg). The spectroscopic data matched those from the literature.[264]



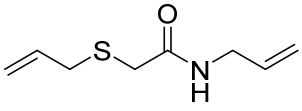
3.2b

***N*-Allylhex-5-enamide (3.2b):** Starting from commercially available 5-hexenoic acid and following the procedure described above, **3.2b** was obtained as a colorless oil in 94% yield (720 mg). The spectroscopic data matched those from the literature.[264]



3.2c

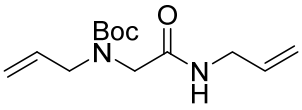
***N*-Allyl-2-(allyloxy)acetamide (3.2c):** Starting from 2-(allyloxy)acetic acid[265] and following the procedure described above, **3.2c** was obtained as a light yellow oil in 36% yield (279 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (br s, 1H), 5.96-5.79 (m, 2H), 5.38 – 5.05 (m, 4H), 4.06 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.97 (s, 2H), 3.94 (tt, *J* = 5.9, 1.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 134.1, 133.6, 118.4, 116.6, 72.5, 69.5, 41.3.



3.2d

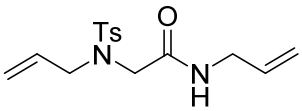
[264] Hassan, H. M. A.; Brown, F. K. *Chem. Commun.* **2010**, *46*, 3013.
[265] Rehbein, J.; Leick, S.; Hiersemann, M. *J. Org. Chem.* **2009**, *74*, 1531.

***N*-Allyl-2-(allylthio)acetamide (3.2d):** 2-(Allylthio)acetic acid[266] (500 mg, 3.78 mmol) was dissolved in DCM (15 mL) and cooled down to 0 °C in an ice bath. To this solution, oxalyl chloride (0.64 mL, 7.56 mmol, 2.0 equiv) and 2 drops of anhydrous DMF were added. The resulting solution was allowed to reach room temperature for 3h. Volatiles were then removed under vacuum and the residue was redissolved in DCM (15 mL) and cooled down to 0 °C. Allylamine (0.34 mL, 4.54 mmol, 1.2 equiv) and TEA (1.05 mL, 7.56 mmol, 2.0 equiv) were added dropwise and the resulting solution was allowed to reach room temperature for 16h. 20 mL of a saturated NH_4Cl solution were added, the organic phase was separated and the aqueous phase was extracted with DCM (2x20 mL). The combined organic phases were washed with brine (20 mL) and dried over anhydrous sodium sulfate and the solvent was removed under vacuum. **3.2d** was obtained as an orange oil in 63% yield (410 mg) and used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (br s, 1H), 5.97–5.63 (m, 2H), 5.33 – 5.06 (m, 4H), 3.92 (tt, *J* = 5.8, 1.5 Hz, 2H), 3.21 (s, 2H), 3.18–3.12 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 134.0, 132.7, 119.0, 116.8, 42.2, 35.8, 34.7.



3.2e

***tert*-Butyl allyl(2-(allylamino)-2-oxoethyl)carbamate (3.2e):** Starting from *N*-allyl-*N*-(*tert*-butoxycarbonyl)glycine[267] and following the procedure described above, **3.2e** was obtained as a yellow oil in 89% yield (1.13 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92–5.68 (m, 2H), 5.21-5.12 (m, 4H), 3.98–3.75 (m, 6H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 165.5, 134.1, 132.8, 118.0, 116.5, 81.2, 51.0, 45.9, 41.7, 28.4 (3xCH_3).

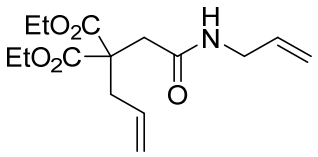


3.2f

***N*-Allyl-2-((*N*-allyl-4-methylphenyl)sulfonamido)acetamide (3.2f):** *N*-Allyl-*N*-tosylglycinoyl chloride[77] (535mg, 1.86 mmol) dissolved in DCM (5 mL) was added

[266] Olier, C.; Azzi, N.; Gil, G.; Gastaldi, S.; Bertrand, M. P. *J. Org. Chem.*, **2008**, *73*, 8469.
[267] Robinson, J. W.; Schlaad, H. *Chem. Commun.* **2012**, *48*, 7835.

to a solution of allylamine (0.17 mL, 2.23 mmol, 1.2 equiv) and TEA (0.52 mL, 3.72 mmol, 2.0 equiv) in DCM (10 mL) at 0 °C. The resulting solution was allowed to reach room temperature for 16h. 20 mL of a saturated NH_4Cl solution were added, the organic phase was separated and the aqueous phase was extracted with DCM (2x20 mL). The combined organic phases were washed with brine (20 mL) and dried over anhydrous sodium sulfate and the solvent was removed under vacuum. **3.2f** was obtained as a thick yellow oil in 89% yield (512 mg) and used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74–7.65 (m, 2H), 7.44–7.30 (m, 2H), 6.67 (br s, 1H), 5.83 (ddt, *J* = 17.2, 10.3, 5.5 Hz, 1H), 5.71–5.53 (m, 1H), 5.29 5.12 (m, 4H), 3.92 (tt, *J* = 5.5, 1.6 Hz, 2H), 3.80 (d, *J* = 6.9 Hz, 2H), 3.66 (s, 2H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 144.6, 134.8, 133.7, 131.2, 130.2 (2xCH), 127.6 (2xCH), 121.5, 116.8, 53.4, 51.1, 41.9, 21.7.



3.2g

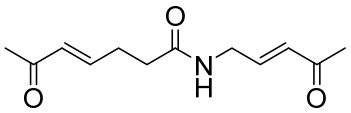
Diethyl 2-allyl-2-(2-(allylamino)-2-oxoethyl)malonate (3.2g): Starting from 3,3-bis(ethoxycarbonyl)hex-5-enoic acid[268] and following the procedure described above, **3.2g** was obtained as a colorless oil in 34% yield (505 mg) after flash column chromatography on silica gel [*n*-hexane-EtOAc (4:1)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93–5.53 (m, 3H), 5.24–5.06 (m, 4H), 4.21 (q, *J* = 7.1 Hz, 4H), 3.85 (tt, *J* = 5.7, 1.5 Hz, 2H), 2.83–2.76 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 (2xCO), 169.1, 134.2, 132.7, 119.7, 116.6, 61.9 (2xCH_2), 55.8, 42.0, 39.5, 38.0, 14.2 (2xCH_3).

- **General procedure for the synthesis of "symmetrical" diketo amides 3.3 by bidirectional olefin cross-metathesis**

To a solution of amide **3.2** (0.50 mmol) in DCM (5 mL, 0.10 M) under a nitrogen atmosphere, alkyl vinyl ketone (6 equiv) and Hoveyda-Grubbs 2nd generation catalyst (16 mg, 0.05 mmol, 5 mol%) were added. After stirring for 2h

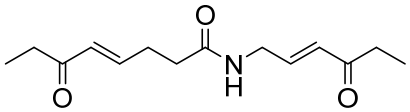
[268] Goh, K. K. K.; Kim, S.; Zard, S. Z. *Org. Lett.* **2013**, *15*, 4818.

at room temperature, a second equal addition of the catalyst followed and the reaction mixture was further stirred at room temperature for 16h. Volatiles were then removed under vacuum and the residue was purified by flash chromatography on silica gel [*n*-hexane-EtOAc (1:1) to pure EtOAc].



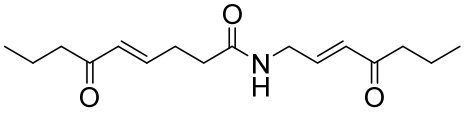
3.3a

(*E*)-6-Oxo-*N*-((*E*)-4-oxopent-2-en-1-yl)hept-4-enamide (3.3a): Starting from amide **3.2a** and methyl vinyl ketone, **3.3a** was obtained as a dark brown thick oil in 60% yield (67 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89–6.61 (m, 2H), 6.29 (br s, 1H), 6.18–6.02 (m, 2H), 4.05 (t, *J* = 4.4 Hz, 2H), 2.62-2.52 (m, 2H), 2.40 (t, *J* = 7.2 Hz, 2H), 2.24 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 198.3, 171.5, 146.3, 143.1, 131.8, 130.9, 40.4, 34.3, 27.9, 27.2, 27.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{17}NO_3$ 224.1281; found 224.1291.



3.3b

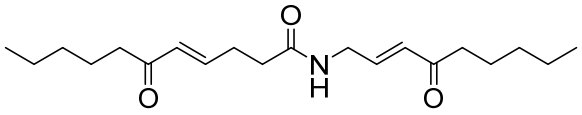
(*E*)-6-Oxo-*N*-((*E*)-4-oxohex-2-en-1-yl)oct-4-enamide (3.3b): Starting from amide **3.2a** and ethyl vinyl ketone, **3.3b** was obtained as a dark brown thick oil in 56% yield (70 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89–6.67 (m, 2H), 6.20–6.08 (m, 2H), 5.67 (br s, 1H), 4.07 (td, *J* = 5.8, 1.7 Hz, 2H), 2.65–2.50 (m, 6H), 2.44–2.33 (m, 2H), 1.15–1.01 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 200.6, 171.4, 144.5, 141.2, 130.8, 130.1, 40.5, 34.7, 33.7, 33.7, 28.0, 8.2, 8.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{21}NO_3$ 252.1594; found 252.1606.



3.3c

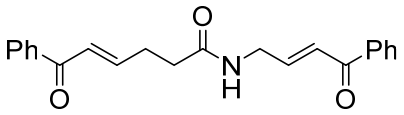
(*E*)-6-Oxo-*N*-((*E*)-4-oxohept-2-en-1-yl)non-4-enamide (3.3c): Starting from amide **3.2a** and propyl vinyl ketone, **3.3c** was obtained as a dark brown thick oil in 36% yield (50 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93–6.64 (m, 2H), 6.14 (dq, *J* =

15.9, 1.6 Hz, 2H), 5.78 (br s, 1H), 4.06 (td, *J* = 5.7, 1.6 Hz, 2H), 2.67–2.45 (m, 6H), 2.39 (t, *J* = 7.3 Hz, 2H), 1.75–1.52 (m, 6H), 0.92 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 200.2, 171.4, 144.7, 141.4, 131.1, 130.4, 42.4 (2xCH_2), 40.5, 34.7, 28.0, 17.7, 17.6, 13.9 (2xCH_3). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{25}NO_3$ 280.1907; found 280.1903.



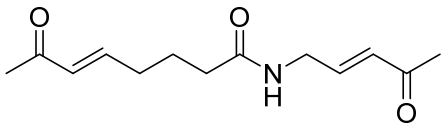
3.3d

(*E*)-6-Oxo-*N*-((*E*)-4-oxonon-2-en-1-yl)undec-4-enamide (3.3d): Starting from amide **3.2a** and pentyl vinyl ketone, **3.3d** was obtained as a dark brown thick oil in 18% yield (30 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89–6.66 (m, 2H), 6.13–6.10 (m, 2H), 5.62 (br s, 1H), 4.07 (td, *J* = 5.7, 1.7 Hz, 1H), 2.64–2.46 (m, 6H), 2.43–2.31 (m, 2H), 1.39–1.19 (m, 12H), 0.92–0.82 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 200.3, 171.4, 144.5, 141.2, 131.1, 130.4, 40.6, 40.5, 40.5, 36.5, 34.7, 31.6, 31.6, 29.2, 28.0, 24.0, 23.8, 22.6, 14.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{33}NO_3$ 336.2533; found 336.2542.



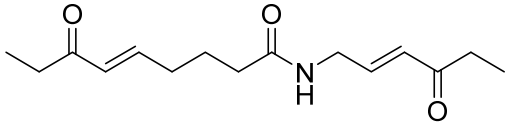
3.3e

(*E*)-6-Oxo-*N*-((*E*)-4-oxo-4-phenylbut-2-en-1-yl)-6-phenylhex-4-enamide (3.3e): In a variation of the general procedure, the reaction was run at reflux and phenyl vinyl ketone was used. Starting from amide **3.2a**, **3.3e** was obtained as a dark brown thick oil in 12% yield (21 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.84 (m, 4H), 7.61–7.51 (m, 2H), 7.51–7.40 (m, 4H), 7.12–6.82 (m, 4H), 5.78 (br s, 1H), 4.18 (dd, *J* = 5.8, 3.6 Hz, 2H), 2.77–2.63 (m, 2H), 2.48 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 190.5, 171.4, 147.1, 143.7, 137.8, 137.5, 133.2, 133.0, 128.8 (2xCH), 128.7 (2xCH), 128.7 (2xCH), 128.7 (2xCH), 127.0, 126.5, 40.9, 34.9, 28.5. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{21}NO_3$ 348.1594; found 348.1600.



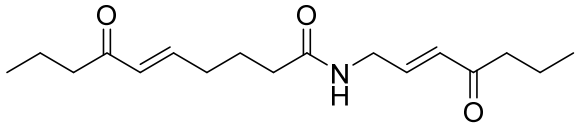
3.3f

(*E*)-7-Oxo-*N*-((*E*)-4-oxopent-2-en-1-yl)oct-5-enamide (3.3f): Starting from amide **3.2b** and methyl vinyl ketone, **3.3f** was obtained as a dark brown thick oil in 72% yield (85 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87–6.57 (m, 2H), 6.15-6.06 (m, 2H), 5.71 (br s, 1H), 4.07 (td, *J* = 5.9, 1.7 Hz, 2H), 2.35-2.19 (m, 10H), 1.86 (p, *J* = 7.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 198.1, 172.3, 147.0, 142.8, 132.1, 131.1, 40.4, 35.6, 31.9, 27.3, 27.1, 23.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{19}NO_3$ 238.1438; found 238.1447.



3.3g

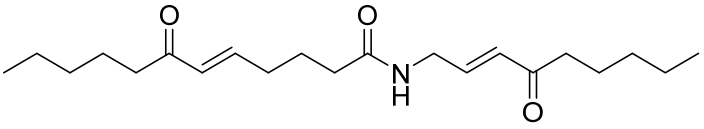
(*E*)-7-Oxo-*N*-((*E*)-4-oxohex-2-en-1-yl)non-5-enamide (3.3g): Starting from amide **3.2b** and ethyl vinyl ketone, **3.3g** was obtained as a dark brown thick oil in 74% yield (98 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87–6.67 (m, 2H), 6.18-6.09 (m, 2H), 5.67 (br s, 1H), 4.06 (td, *J* = 5.8, 1.7 Hz, 1H), 2.61-2.52 (m, 4H), 2.32–2.18 (m, 4H), 1.90-1.81 (m, 2H), 1.09 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 200.6, 172.3, 145.6, 141.4, 130.8, 130.1, 40.4, 35.6, 33.7, 33.5, 31.9, 23.9, 8.2, 8.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{23}NO_3$ 266.1751; found 266.1751.



3.3h

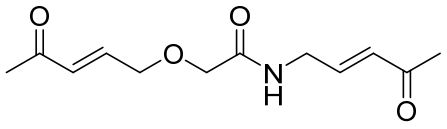
(*E*)-7-Oxo-*N*-((*E*)-4-oxohept-2-en-1-yl)dec-5-enamide (3.3h): Starting from amide **3.2b** and propyl vinyl ketone, **3.3h** was obtained as a dark brown thick oil in 51% yield (75 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87–6.65 (m, 2H), 6.18-6.09 (m, 2H), 5.61 (br s, 1H), 4.06 (td, *J* = 5.8, 1.7 Hz, 2H), 2.55-2.49 (m. 4H), 2.34–2.18 (m, 4H), 1.91-1.81 (m, 2H), 1.70-1.57 (m, 6H), 0.96-0.90 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 200.2, 172.3, 145.7, 141.5, 131.2, 130.4, 42.4, 42.3, 40.4, 35.6, 31.9,

23.9, 17.8, 17.6, 14.0, 13.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{27}NO_3$ 294.2064; found 294.2067.



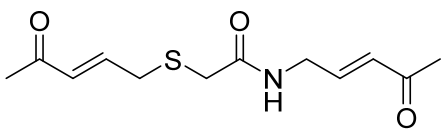
3.3i

(*E*)-7-Oxo-*N*-((*E*)-4-oxonon-2-en-1-yl)dodec-5-enamide (3.3i): Starting from amide **3.2b** and pentyl vinyl ketone, **3.3i** was obtained as a dark brown thick oil in 26% yield (45 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87–6.67 (m, 2H), 6.18-6.09 (m, 2H), 5.59 (br s, 1H), 4.11–4.01 (m, 2H), 2.56-2.50 (m, 4H), 2.33–2.16 (m, 4H), 1.95–1.78 (m, 2H), 1.68–1.60 (m, 2H), 1.40–1.18 (m, 10H), 0.91-0.87 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 200.3, 172.3, 145.6, 141.5, 131.1, 130.3, 40.5, 40.4 (2xCH_2), 35.7, 31.9, 31.6, 31.6, 24.1, 23.9, 23.9, 22.6, 22.6, 14.1, 14.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{35}NO_3$ 350.2690; found 350.2682.



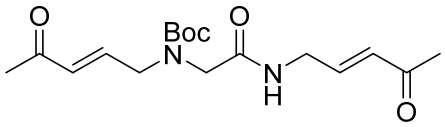
3.3j

***N*-((*E*)-4-Oxopent-2-en-1-yl)-2-(((*E*)-4-oxopent-2-en-1-yl)oxy)acetamide (3.3j):** Starting from amide **3.2c** and methyl vinyl ketone, **3.3j** was obtained as a dark brown thick oil in 39% yield (47 mg). A mixture of mono cross-metathesis products was recovered as well in 31% combined yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80-6.70 (m, 3H), 6.30 (dt, *J* = 16.1, 1.9 Hz, 1H), 6.15 (dt, *J* = 16.0, 1.8 Hz, 1H), 4.27 (dd, *J* = 4.6, 1.9 Hz, 2H), 4.17–4.11 (m, 2H), 4.06 (s, 2H), 2.30 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 197.9, 169.1, 142.3, 141.0, 131.2, 131.1, 70.2, 70.2, 39.7, 27.5, 27.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{17}NO_4$ 240.1230; found 240.1242.



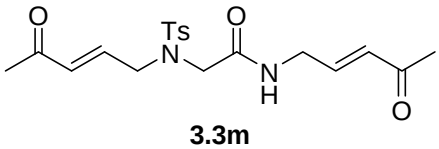
3.3k

***N*-((*E*)-4-Oxopent-2-en-1-yl)-2-(((*E*)-4-oxopent-2-en-1-yl)thio)acetamide (3.3k):** In a variation of the general procedure, the reaction was run at reflux. Starting from amide **3.2d** and methyl vinyl ketone, **3.3k** was obtained as a dark brown thick oil in 12% yield (47 mg). A mixture of mono cross-metathesis products was recovered as well in 19% combined yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (br s, 1H), 6.72-6.58 (m, 2H), 6.19–6.03 (m, 2H), 4.04 (s, 2H), 3.27 (d, *J* = 6.8 Hz, 2H), 3.15 (s, 2H), 2.23-2.20 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 197.8, 168.6, 142.4, 140.2, 132.9, 131.2, 40.6, 34.8, 33.9, 27.9, 27.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{17}NO_3S$ 256.1002; found 256.1005.



3.3l

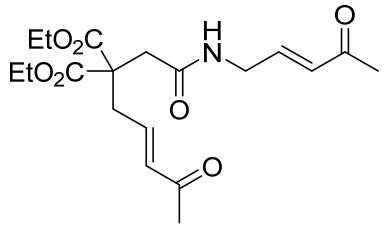
***tert*-Butyl (2-oxo-2-(((*E*)-4-oxopent-2-en-1-yl)amino)ethyl)((*E*)-4-oxopent-2-en-1-yl)carbamate (3.3l):** Starting from amide **3.2e** and methyl vinyl ketone, **3.3l** was obtained as a dark brown thick oil in 40% yield (68 mg). A mixture of mono cross-metathesis products was recovered as well in 41% combined yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76–6.62 (m, 2H), 6.15-6.05 (m, 2H), 4.12–4.03 (m, 4H), 3.85 (s, 2H), 2.26 (s, 3H), 2.25 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1 (2xC=O), 169.6, 142.5, 141.5, 131.7, 131.0, 82.1, 51.5, 50.0, 40.3, 28.5 (3xCH_3), 27.6, 27.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{26}N_2O_5$ 339.1914; found 339.1921.



3.3m

2-((4-Methyl-*N*-((*E*)-4-oxopent-2-en-1-yl)phenyl)sulfonamido)-*N*-((*E*)-4-oxopent-2-en-1-yl)acetamide (3.3m): Starting from amide **3.2f** and methyl vinyl ketone, **3.3m** was obtained as a dark brown thick oil in 39% yield (77 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 6.89 (br s, 1H), 6.71 (dt, *J* = 16.0, 5.0 Hz, 1H), 6.50 (dt, *J* = 15.9, 6.3 Hz, 1H), 6.18 (d, *J* = 16.0 Hz, 1H), 6.08 (d, *J* = 15.9 Hz, 1H), 4.13–4.04 (m, 2H), 4.00 (dd, *J* = 6.3, 1.1 Hz, 2H), 2.45 (s,

3H), 2.27 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 197.2, 168.2, 145.0, 142.0, 138.7, 134.6, 133.8, 131.7, 130.4 (2xCH), 127.6 (2xCH), 51.7, 51.2, 40.5, 27.7, 27.5, 21.7. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{24}N_2O_5S$ 393.1479, found 393.1478.



3.3n

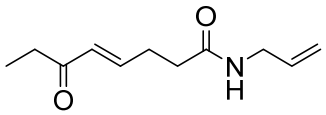
Diethyl 2-(2-oxo-2-(((*E*)-4-oxopent-2-en-1-yl)amino)ethyl)-2-((*E*)-4-oxopent-2-en-1-yl)malonate (3.3n): Starting from amide **3.2g** and methyl vinyl ketone, **3.3n** was obtained as a dark brown thick oil in 59% yield (113 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80–6.61 (m, 2H), 6.22 (br s, 1H), 6.11 (d, *J* = 15.9 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 4H), 4.02 (t, *J* = 4.4 Hz, 2H), 2.95 (d, *J* = 7.6 Hz, 2H), 2.86 (s, 2H), 2.24 (s, 3H), 2.22 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 198.2, 170.1, 169.2, 142.8, 141.9, 134.7, 131.1, 62.3 (2xCH_2), 62.0, 55.7, 40.4, 39.6, 36.8, 27.4, 27.4, 14.2 (2xCH_3). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{27}NO_7$ 382.1860, found 382.1863.

- **General procedure for the synthesis of "unsymmetrical" diketo amides 3.3o,p by sequential olefin cross-metathesis**

To a solution of 4-pentenoic acid (0.5 mL, 4.90 mmol) and TEA (1.02 mL, 7.35 mmol, 1.5 equiv) in DCM (7mL) at 0 °C, pivaloyl chloride (0.60 mL, 4.90 mmol, 1.0 equiv) was added dropwise. After stirring at the same temperature for 1h, the solvent was removed under vacuum and the residue was redissolved in a mixture of hexane/EtOAc (5/1) and filtered over Celite. After evaporation of the solvent, 801 mg of the crude mixed anhydride **3.6** were obtained (89% yield).

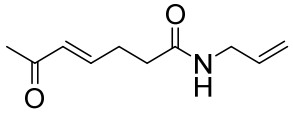
300 mg (1.63 mmol) of the mixed anhydride were dissolved in DCM (8 mL). The corresponding alkyl vinyl ketone (3 equiv) was added followed by Hoveyda-

Grubbs 2nd generation catalyst (51 mg, 0.08 mmol, 5 mol%). The mixture was stirred for 2h at room temperature after which additional 5 mol% of the catalyst were added. After stirring for 16h, volatiles were removed under vacuum. The residue, containing the intermediate functionalised mixed anhydride **3.7**, was redissolved in DCM (8 mL) and cooled down to 0 °C. TEA (0.45 mL, 3.26 mmol, 2 equiv) and allylamine (0.13 mL, 1.79 mmol, 1.1 equiv) were added and the resulting mixture was stirred for 1h at 0 °C and then for a further 1h at room temperature. At this time, 8 mL of a saturated NH_4Cl solution was added, the organic phase was separated and the aqueous phase was extracted with DCM (2x10 mL). The combined organic phases were dried over anhydrous sodium sulfate and the solvent was removed under vacuum. The crude was purified by flash chromatography on silica gel [*n*-hexane-EtOAc (1:1)] to afford the intermediate amide **3.8**.



3.8a

(*E*)-*N*-Allyl-6-oxooct-4-enamide (3.8a): Following the procedure described above and using ethyl vinyl ketone in the cross-metathesis step, **3.8a** was obtained as a brown oil in 43% yield over 2 steps from the mixed anhydride (137mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (dt, *J* = 15.9, 6.8 Hz, 1H), 6.13 (dt, *J* = 15.9, 1.5 Hz, 1H), 5.83 (ddt, *J* = 17.1, 10.2, 5.7 Hz, 1H), 5.52 (br s, 1H), 5.22–5.11 (m, 2H), 3.89 (tt, *J* = 5.7, 1.5 Hz, 2H), 2.61–2.52 (m, 4H), 2.35 (t, *J* = 7.4 Hz, 2H), 1.08 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 171.2, 144.8, 134.2, 130.8, 116.8, 42.2, 34.8, 33.6, 28.1, 8.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_{18}NO_2$ 196.1332, found 196.1332.

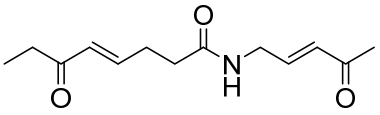


3.8b

(*E*)-*N*-Allyl-6-oxohept-4-enamide (3.8b): Following the procedure described above and using methyl vinyl ketone in the cross-metathesis step, **3.8b** was

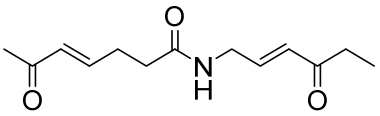
obtained as a brown oil in 41% yield over 2 steps from the mixed anhydride (121 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (dt, *J* = 16.0, 6.7 Hz, 1H), 6.10 (dt, *J* = 16.0, 1.5 Hz, 1H), 5.83 (ddt, *J* = 17.1, 10.2, 5.7 Hz, 1H), 5.51 (br s, 1H), 5.22-5.12 (m, 2H), 3.90 (tt, *J* = 5.7, 1.5 Hz, 2H), 2.67 – 2.52 (m, 2H), 2.36 (t, *J* = 7.3 Hz, 2H), 2.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 171.1, 146.2, 134.2, 131.9, 116.8, 42.2, 34.7, 28.1, 27.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{10}H_{16}NO_2$ 182.1176, found 182.1174.

To a solution of amide **3.8** (0.50 mmol) in DCM (5 mL, 0.10 M) under a nitrogen atmosphere, the corresponding alkyl vinyl ketone (3 equiv) and Hoveyda-Grubbs 2nd generation catalyst (16 mg, 0.05 mmol, 5 mol%) were added. After stirring for 2h at room temperature, a second equal addition of the catalyst followed and the reaction mixture was further stirred at room temperature for 16h. Volatiles were then removed under vacuum and the residue was purified by flash chromatography on silica gel [*n*-hexane-EtOAc (1:1) to pure EtOAc].



3.3o

(*E*)-6-Oxo-*N*-((*E*)-4-oxopent-2-en-1-yl)oct-4-enamide (3.3o): Starting from amide **3.8a** and methyl vinyl ketone, **3.3o** was obtained as a dark brown thick oil in 54% yield (64 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (dt, *J* = 15.9, 6.7 Hz, 1H), 6.71 (dt, *J* = 16.1, 5.2 Hz, 1H), 6.18-6.09 (m, 2H), 5.66 (br s, 1H), 4.08 (td, *J* = 6.0, 1.8 Hz, 2H), 2.66–2.51 (m, 4H), 2.40 (t, *J* = 7.5 Hz, 2H), 2.26 (s, 3H), 1.09 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9, 201.0, 171.4, 144.4, 142.6, 131.1, 130.9, 40.5, 34.7, 33.7, 28.0, 27.3, 8.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{19}NO_3$ 238.1438; found 238.1443.



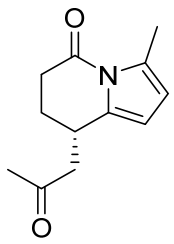
3.3p

(*E*)-6-Oxo-*N*-((*E*)-4-oxohex-2-en-1-yl)hept-4-enamide (3.3p): Starting from amide **3.8b** and ethyl vinyl ketone, **3.3p** was obtained as a dark brown thick oil in

52% yield (62 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93–5.88 (m, 1H), 5.80 (dd, *J* = 3.3, 1.4 Hz, 1H), 3.41-3.32 (m, 1H), 3.02–2.84 (m, 3H), 2.80–2.55 (m, 3H), 2.21 (s, 3H), 2.13 (ddd, *J* = 13.5, 9.1, 4.6 Hz, 1H), 1.75–1.58 (m, 1H), 1.20 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 198.6, 171.3, 145.9, 141.2, 132.0, 130.1, 40.5, 34.5, 33.7, 27.9, 27.3, 8.1.HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{19}NO_3$ 238.1438; found 238.1443.

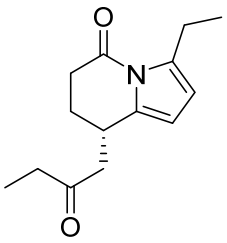
- **General procedure for the tandem organocatalytic cycloaromatisation/intramolecular Friedel-Crafts process**

To a solution of amide **3.3** (0.09 mmol) in CCl_4 (3 mL, 0.03 M) in a pressure vial, 4 Å MS (300 mg) and ***(R)*-TRIP-NHTf** (8 mg, 0.009 mmol, 10 mol%) were added. (When the starting amide **3.3** did not show enough solubility in CCl_4, it was sonicated in the solvent until complete dissolution prior to the addition of the catalyst.) The vial was sealed and the resulting mixture was stirred at 40 °C in an oil bath for 5 days. Volatiles were then removed under vacuum and the residue was purified by flash chromatography on silica gel.



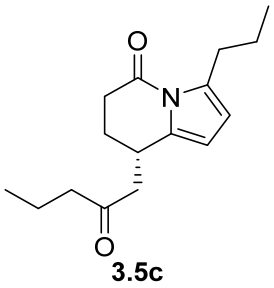
3.5a

(*S*)-3-Methyl-8-(2-oxopropyl)-7,8-dihydroindolizin-5(6*H*)-one (3.5a): Starting **3.3a**, **3.5a** was obtained as a light yellow solid (mp= 42-44 °C) in 76% yield (14 mg) after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = -20.0° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (s, 1H), 5.73 (d, *J* = 2.5 Hz, 1H), 3.50-3.43 (m, 1H), 3.02–2.80 (m, 3H), 2.70 (dd, *J* = 17.1, 7.8 Hz, 1H), 2.38 (s, 3H), 2.19 (s, 3H), 1.98-1.86 (m, 1H), 1.46–1.34 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7, 175.1, 135.4, 132.7, 110.6, 107.7, 47.7, 36.7, 31.6, 30.9, 30.6, 20.4, 16.0. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{15}NO_2$ 206.1176; found 206.1170.



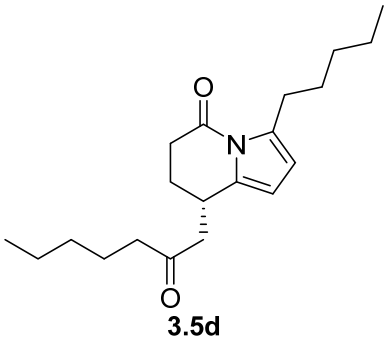
3.5b

(*S*)-3-Ethyl-8-(2-oxobutyl)-7,8-dihydroindolizin-5(6*H*)-one (3.5b): Starting **3.3b**, **3.5b** was obtained as a light yellow solid (mp= 64-66 °C) in 70% yield (15 mg) after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = -10.3° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (dt, *J* = 3.2, 1.2 Hz, 1H), 5.79 (dd, *J* = 3.2, 1.6 Hz, 1H), 3.44-3.35 (m, 1H), 3.01–2.83 (m, 3H), 2.81–2.55 (m, 3H), 2.55–2.40 (m, 2H), 2.12 (dq, *J* = 12.9, 4.8 Hz, 1H), 1.75–1.61 (m, 1H), 1.20 (t, *J* = 7.4 Hz, 3H), 1.10 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.5, 169.9, 138.0, 135.9, 109.5, 107.0, 46.3, 36.8, 34.2, 30.1, 27.7, 23.0, 13.1, 7.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{19}NO_2$ 234.1489; found 234.1480.



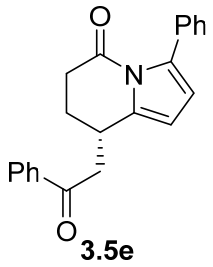
3.5c

(*S*)-8-(2-Oxopentyl)-3-propyl-7,8-dihydroindolizin-5(6H)-one (3.5c): Starting **3.3c**, **3.5c** was obtained as a yellow oil in 80% yield (19 mg) after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = -8.7° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (dt, *J* = 3.3, 1.1 Hz, 1H), 5.77 (dd, *J* = 3.3, 1.6 Hz, 1H), 3.47–3.29 (m, 1H), 2.98–2.53 (m, 6H), 2.47–2.38 (m, 2H), 2.15-2.06 (m, 1H), 1.78–1.52 (m, 5H), 0.99-0.91 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 169.9, 136.2, 135.9, 110.5, 106.9, 46.7, 45.5, 34.2, 31.6, 30.1, 27.7, 22.0, 17.4, 14.1, 13.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{23}NO_2$ 262.1802; found 262.1797.



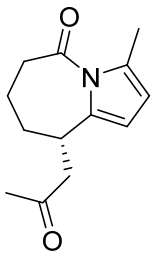
3.5d

(*S*)-8-(2-Oxoheptyl)-3-pentyl-7,8-dihydroindolizin-5(6*H*)-one (3.5d): Starting **3.3d**, **3.5d** was obtained as a colorless oil in 63% yield (18 mg) after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = -4.3° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (dt, *J* = 3.2, 1.0 Hz, 1H), 5.77 (dd, *J* = 3.2, 1.6 Hz, 1H), 3.50–3.30 (m, 1H), 3.04–2.53 (m, 5H), 2.52–2.37 (m, 2H), 2.22–2.01 (m, 1H), 1.77–1.46 (m, 5H), 1.46–1.16 (m, 9H), 1.00–0.78 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209., 169.9, 136.5, 135.9), 110.4, 106.9, 46.7, 43.7, 34.2, 31.8, 31.5, 30.1, 29.5, 28.5, 27.7, 23.6, 22.7, 22.6, 14.2, 14.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{31}NO_2$ 318.2428; found 318.2428.



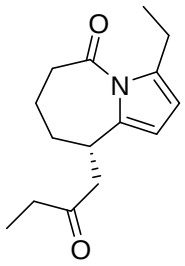
3.5e

(*S*)-8-(2-Oxo-2-phenylethyl)-3-phenyl-7,8-dihydroindolizin-5(6*H*)-one (3.5e): Starting **3.3e**, **3.5e** was obtained as an orange oil in 44% yield (13 mg) after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = -82.0° (c 1.0; $CHCl_3$).^1H NMR (300 MHz, $CDCl_3$) δ 8.07–7.98 (m, 2H), 7.66–7.58 (m, 1H), 7.58–7.46 (m, 2H), 7.39-7.29 (m, 5H), 6.17 (d, *J* = 3.4 Hz, 1H), 6.02 (dd, *J* = 3.4, 1.5 Hz, 1H), 3.77–3.64 (m, 1H), 3.56 (dd, *J* = 17.2, 5.2 Hz, 1H), 3.25 (dd, *J* = 17.2, 7.9 Hz, 1H), 2.90–2.71 (m, 2H), 2.31-2.22 (m, 1H), 1.98–1.79 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 168.9, 138.0, 136.9, 134.7, 134.2, 133.7, 129.1 (2xCH), 129.0 (2xCH), 128.3 (2xCH), 127.7 (2xCH), 127.3, 114.9, 108.1, 42.7, 34.1, 30.7, 28.0. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{19}NO_2$ 330.1489; found 330.1492.



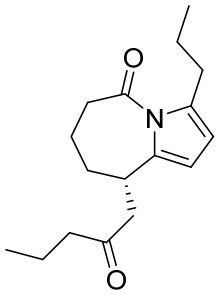
3.5f

(*S*)-3-Methyl-9-(2-oxopropyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-a]azepin-5-one (3.5f): Starting **3.3f**, **3.5f** was obtained as a colorless oil in 70% yield (14 mg) after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = +5.8° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.86–5.82 (m, 1H), 5.74 (dd, *J* = 3.3, 1.2 Hz, 1H), 3.45 (td, *J* = 11.5, 5.6 Hz, 1H), 2.96 (dd, *J* = 17.1, 6.0 Hz, 1H), 2.91–2.81 (m, 2H), 2.70 (dd, *J* = 17.1, 7.8 Hz, 1H), 2.40 (s, 3H), 2.20 (s, 3H), 2.01–1.85 (m, 2H), 1.77–1.62 (m, 1H), 1.47–1.33 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 175.1, 135.4, 132.7, 110.6, 107.7, 47.7, 36.8, 31.6, 30.9, 30.6, 20.4, 16.0. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}NO_2$ 220.1332; found 220.1330.



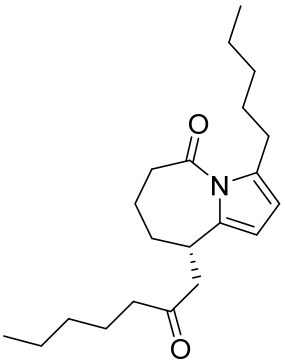
3.5g

(*S*)-3-Ethyl-9-(2-oxobutyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-a]azepin-5-one (3.5g): Starting **3.3g**, **3.5g** was obtained as a yellow oil in 71% yield (16 mg) after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = +4.6° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (dt, *J* = 3.2, 1.1 Hz, 1H), 5.76 (dd, *J* = 3.2, 1.2 Hz, 1H), 3.58–3.40 (m, 1H), 3.05–2.62 (m, 6H), 2.60–2.37 (m, 2H), 1.98–1.84 (m, 2H), 1.76–1.60 (m, 1H), 1.45–1.30 (m, 1H), 1.17 (t, *J* = 7.4 Hz, 3H), 1.07 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.5, 175.3, 139.2, 135.7, 108.6, 107.6, 46.5, 36.9, 36.7, 31.7, 30.9, 22.6, 20.4, 13.2, 7.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{21}NO_2$ 248.1645; found 248.1648.



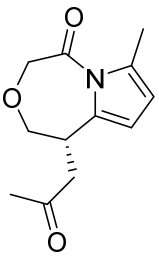
3.5h

(*S*)-9-(2-Oxopentyl)-3-propyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-a]azepin-5-one (3.5h): Starting **3.3h**, **3.5h** was obtained as a yellow oil in 63% yield (16 mg) after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = +5.0° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (d, *J* = 3.3 Hz, 1H), 5.75 (dd, *J* = 3.3, 1.1 Hz, 1H), 3.55–3.39 (m, 1H), 3.00–2.61 (m, 6H), 2.43 (td, *J* = 7.2, 2.2 Hz, 2H), 2.01–1.82 (m, 2H), 1.74–1.51 (m, 4H), 1.46–1.20 (m, 2H), 1.04–0.86 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 175.3, 137.4, 135.6, 109.6, 107.5, 46.9, 45.4, 36.9, 31.7, 31.2, 30.8, 22.3, 20.5, 17.4, 14.1, 13.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{25}NO_2$ 276.1958; found 276.1960.



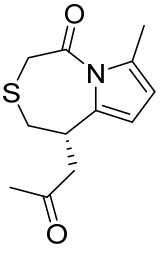
3.5i

(*S*)-9-(2-Oxoheptyl)-3-pentyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-a]azepin-5-one (3.5i): Starting **3.3i**, **3.5i** was obtained as a yellow oil in 79% yield (24 mg) after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = +3.9° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (d, *J* = 3.3 Hz, 1H), 5.75 (dd, *J* = 3.3, 1.1 Hz, 1H), 3.54–3.40 (m, 1H), 2.98–2.61 (m, 6H), 2.43 (td, *J* = 7.3, 2.4 Hz, 2H), 2.01–1.80 (m, 2H), 1.76–1.46 (m, 5H), 1.46–1.17 (m, 9H), 0.91-0.86 (m, 6H). ^{13}C NMR (75 MHz, CD_3CN) δ 209.2, 175.3, 137.6, 135.6, 109.4, 107.5, 46.8, 43.5, 36.9, 31.8, 31.7, 31.5, 30.8, 29.1, 28.8, 23.6, 22.7, 22.6, 20.5, 14.2, 14.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{33}NO_2$ 332.2584; found 332.2585.



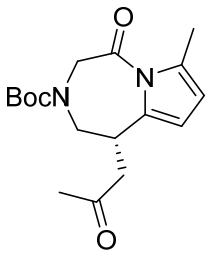
3.5j

(*S*)-7-Methyl-1-(2-oxopropyl)-1,2-dihydropyrrolo[1,2-d][1,4]oxazepin-5(4*H*)-one (3.5j): Starting **3.3j**, **3.5j** was obtained as a yellow (mp= 105-107 °C) in 70% yield (14 mg) after flash chromatography [*n*-hexane-EtOAc (3:2)]. $[\alpha]_D^{25}$ = +10.7° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.94–5.88 (m, 1H), 5.80 (dd, *J* = 3.2, 1.1 Hz, 1H), 4.54 (d, *J* = 17.9 Hz, 1H), 4.41 (d, *J* = 17.9 Hz, 1H), 4.00 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.86-3.75 (m, 1H), 3.41 (dd, *J* = 11.3, 10.0 Hz, 1H), 2.99 (dd, *J* = 17.7, 6.1 Hz, 1H), 2.64 (dd, *J* = 17.7, 7.3 Hz, 1H), 2.39 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 174.5, 132.9, 132.5, 111.3, 108.3, 72.4, 69.6, 43.3, 32.0, 30.4, 15.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{15}NO_3$ 222.1125; found 222.1127.



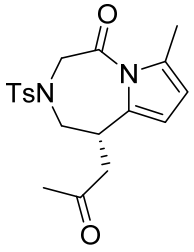
3.5k

(*S*)-7-Methyl-1-(2-oxopropyl)-1,2-dihydropyrrolo[1,2-d][1,4]thiazepin-5(4*H*)-one (3.5k): Starting **3.3k**, **3.5k** was obtained as a white solid (mp= 78-80 °C) in 47% yield (10 mg) after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = +19.0° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (dq, *J* = 3.3, 1.1 Hz, 1H), 5.86 (dd, *J* = 3.3, 0.9 Hz, 1H), 3.95 (d, *J* = 17.3 Hz, 1H), 3.71-3.61 (m, 1H), 3.47 (d, *J* = 17.3, 1H), 3.18 (dd, *J* = 11.4, 4.3 Hz, 1H), 3.08 (dd, *J* = 17.6, 5.9 Hz, 1H), 2.85 (dd, *J* = 17.6, 7.6 Hz, 1H), 2.46–2.31 (m, 4H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 172.3, 133.8, 133.7, 111.2, 109.4, 47.4, 34.7, 34.1, 32.6, 30.6, 16.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{15}NO_2S$ 238.0896; found 238.0901.



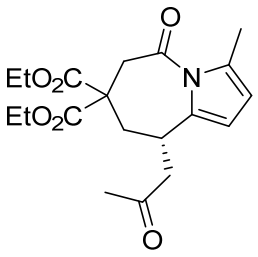
3.5l

(*S*)-*tert*-Butyl 7-methyl-5-oxo-1-(2-oxopropyl)-1,2,4,5-tetrahydro-3*H*-pyrrolo[1,2-d] [1,4]diazepine-3-carboxylate (3.5l): Starting **3.3l**, **3.5l** was obtained as a light yellow oil in 59% yield (17 mg) after flash chromatography [*n*-hexane-EtOAc (3:2)]. $[\alpha]_D^{25}$ = +11.6° (c 1.0; $CHCl_3$). Due to the presence of two major rotamers, two sets of signals are observable. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81-5.78 (m, 1H), 5.72-5.70 (m, 1H), 4.67 (d, *J* = 18.2 Hz, 0.3H), 4.47 (d, *J* = 18.3 Hz, 0.7H), 3.94-3.81 (m, 1H), 3.68–3.15 (m, 3H), 3.00 (d, *J* = 5.6 Hz, 0.3H), 2.96– 2.92 (m, 0.7H), 2.78–2.59 (m, 1H), 2.32 (s, 2.1H), 2.30 (s, 0.9H), 2.16 (s, 3H), 1.25 (s, 6.3H), 1.23 (s, 2.7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 173.1, 155.2, 132.6, 132.5, 111.2, 108.9, 81.2, 51.7, 49.8, 44.5, 32.3, 30.6, 28.2, 15.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{24}N_2O_4$ 321.1809; found 321.1813.



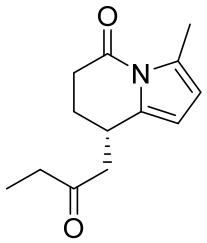
3.5m

(*S*)-7-Methyl-1-(2-oxopropyl)-3-tosyl-1,2,3,4-tetrahydro-5*H*-pyrrolo[1,2-d][1,4]diazepin-5-one (3.5m): Starting **3.3m**, **3.5m** was obtained as a yellow oil in 75% yield (25 mg) after flash chromatography [*n*-hexane-EtOAc (3:2)]. $[\alpha]_D^{25}$ = +6.7° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.41 (m, 2H), 7.19-7.13 (m, 1H), 5.75–5.69 (m, 2H), 4.65 (d, *J* = 18.9 Hz, 1H), 4.04 (d, *J* = 18.9 Hz, 1H), 3.63–3.31 (m, 3H), 3.07–2.97 (m, 1H), 2.80–2.70 (m, 1H), 2.37 (s, 3H), 2.21 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 170.8, 143.7, 136.1, 133.0, 132.0, 129.9 (2xCH), 126.6 (2xCH), 111.2, 109.1, 51.5, 50.7, 44.4, 31.9, 30.5, 21.6, 15.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{22}N_2O_4S$ 375.1373; found 375.1376.



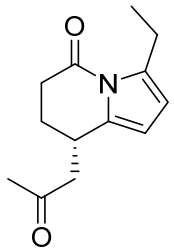
3.5n

Diethyl (*S*)-3-methyl-5-oxo-9-(2-oxopropyl)-5,6,8,9-tetrahydro-7*H*-pyrrolo[1,2-a]azepine-7,7-dicarboxylate (3.5n): Starting **3.3n**, **3.5n** was obtained as a yellow oil in 62% yield (20 mg) after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = -16.4° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (dq, *J* = 3.2, 1.0 Hz, 1H), 5.73 (dd, *J* = 3.2, 1.1 Hz, 1H), 4.34–4.13 (m, 2H), 4.11-3.95 (m, 2H), 3.51-3.35 (m, 3H), 3.01 (dd, *J* = 17.5, 5.5 Hz, 1H), 2.76 (dd, *J* = 17.5, 8.2 Hz, 1H), 2.39-2.30 (m, 4H), 2.26-2.17 (m, 4H), 1.28-1.14 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 170.4, 170.4, 170.4, 134.2, 132.8, 111.0, 108.2, 62.6, 62.3, 54.1, 47.1, 42.0, 38.0, 30.6, 29.9, 15.7, 14.1, 14.0. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{25}NO_6$ 364.1755; found 364.1759.



3.5o

(*S*)-3-Methyl-8-(2-oxobutyl)-7,8-dihydroindolizin-5(6*H*)-one (3.5o): Starting **3.3o**, **3.5o** was obtained as a whit solid (mp= 44-46 °C) in 70% yield (14 mg) after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = -9.2° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (dq, *J* = 3.2, 1.2 Hz, 1H), 5.76 (dd, *J* = 3.2, 1.5 Hz, 1H), 3.51–3.34 (m, 1H), 2.93 (dd, *J* = 17.2, 5.4 Hz, 1H), 2.82–2.54 (m, 3H), 2.54–2.40 (m, 5H), 2.13 (dq, *J* = 13.0, 4.8 Hz, 1H), 1.74-1.61 (m, 1H), 1.10 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.7, 170.2, 135.8, 131.3, 111.6, 106.9, 46.3, 36.8, 34.0, 30.1, 27.8, 16.2, 7.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}NO_2$ 220.1332; found 220.1338.



3.5p

(*S*)-3-Ethyl-8-(2-oxopropyl)-7,8-dihydroindolizin-5(6*H*)-one (3.5p): Starting **3.3p**, **3.5p** was obtained as a light brown solid (mp=55-57 °C) in 62% yield (12 mg) after flash chromatography [*n*-hexane-EtOAc (9:1)]. $[\alpha]_D^{25}$ = -13.0° (c 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (dq, *J* = 3.2, 1.2 Hz, 1H), 5.76 (dd, *J* = 3.2, 1.5 Hz, 1H), 3.51–3.34 (m, 1H), 2.93 (dd, *J* = 17.2, 5.4 Hz, 1H), 2.82–2.54 (m, 3H), 2.54–2.40 (m, 5H), 2.13 (dq, *J* = 13.0, 4.8 Hz, 1H), 1.74-1.61 (m, 1H), 1.10 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.7, 170.2, 135.8, 131.3, 111.6, 106.9, 46.3, 36.8, 34.0, 30.1, 27.8, 16.2, 7.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}NO_2$ 220.1332; found 220.1337.

- **VCD spectrum of 3.5a**

Compound **3.5a** was obtained with an er = 80:20. In order to perform the Vibrational Circular Dichroim experiment, this sample was recrystallised, and it was enriched until er = 92:8. Figure S1 shows the experimental VCD spectrum of this enriched sample of **3.5a** with the predicted spectra for the (*R*)-enantiomer (blue curve) and the (*S*)-enantiomer (red curve). To obtain the VCD baseline, the racemate was measured under the same conditions. Comparison of the prediction of both enantiomers with the enriched sample led us to determine that the newly created stereocentre has an (*S*)-configuration.

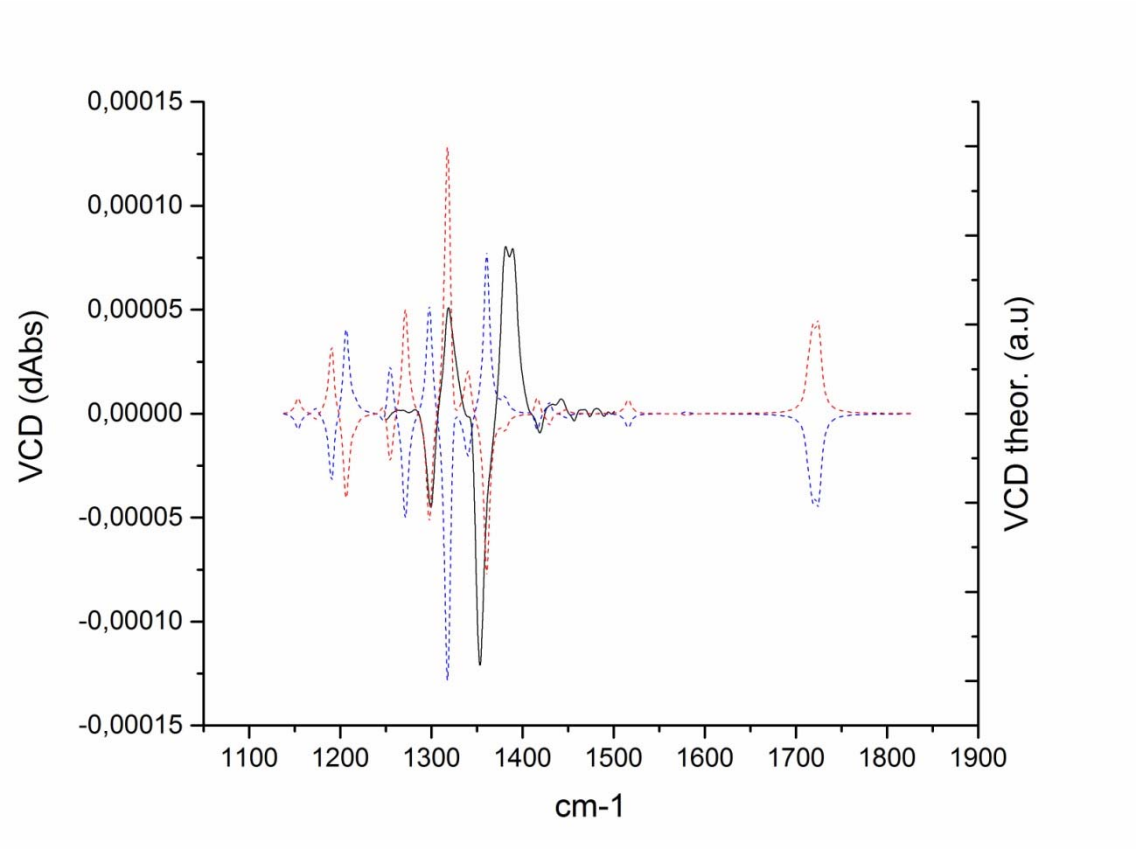
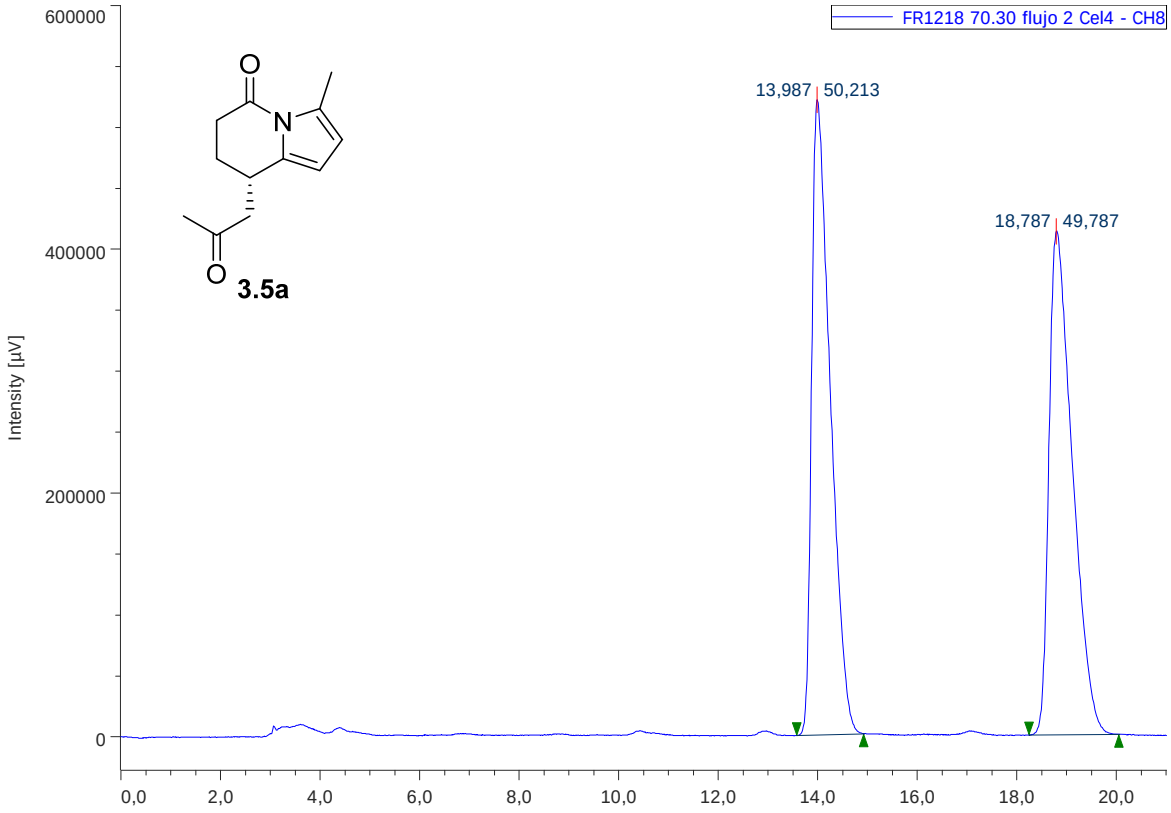
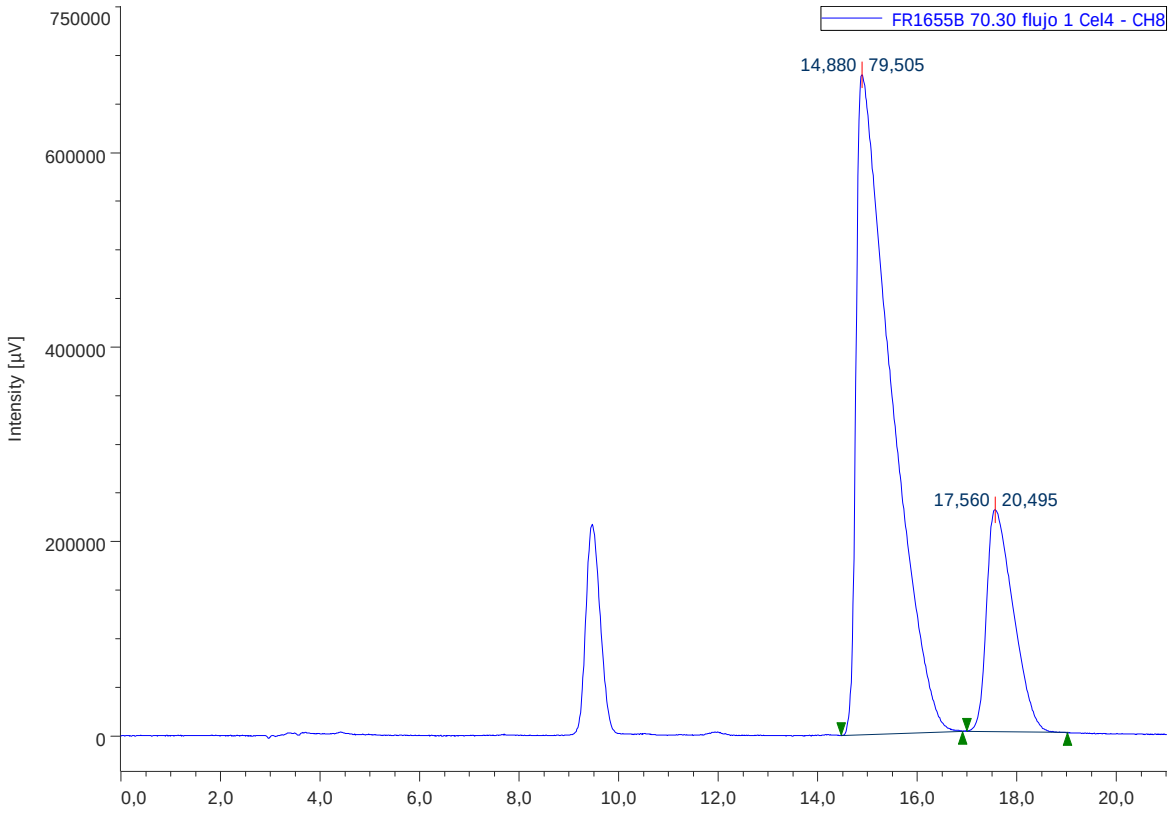
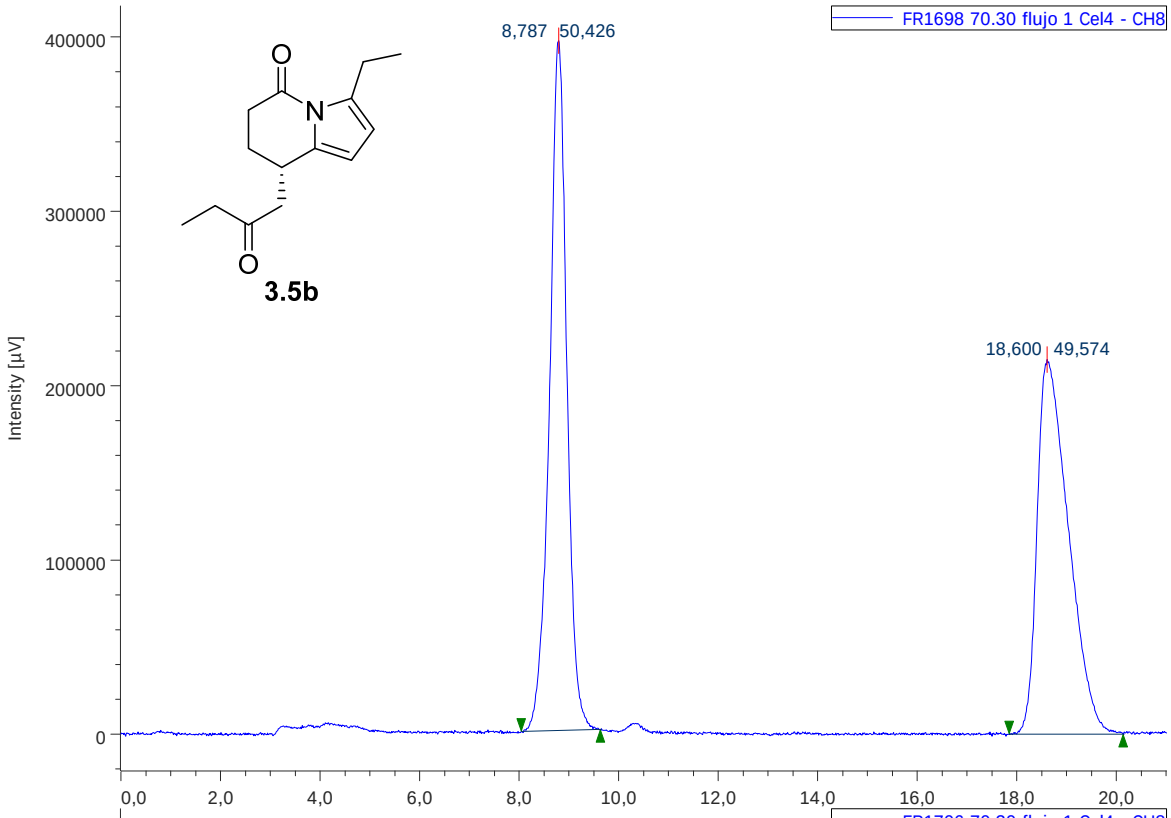


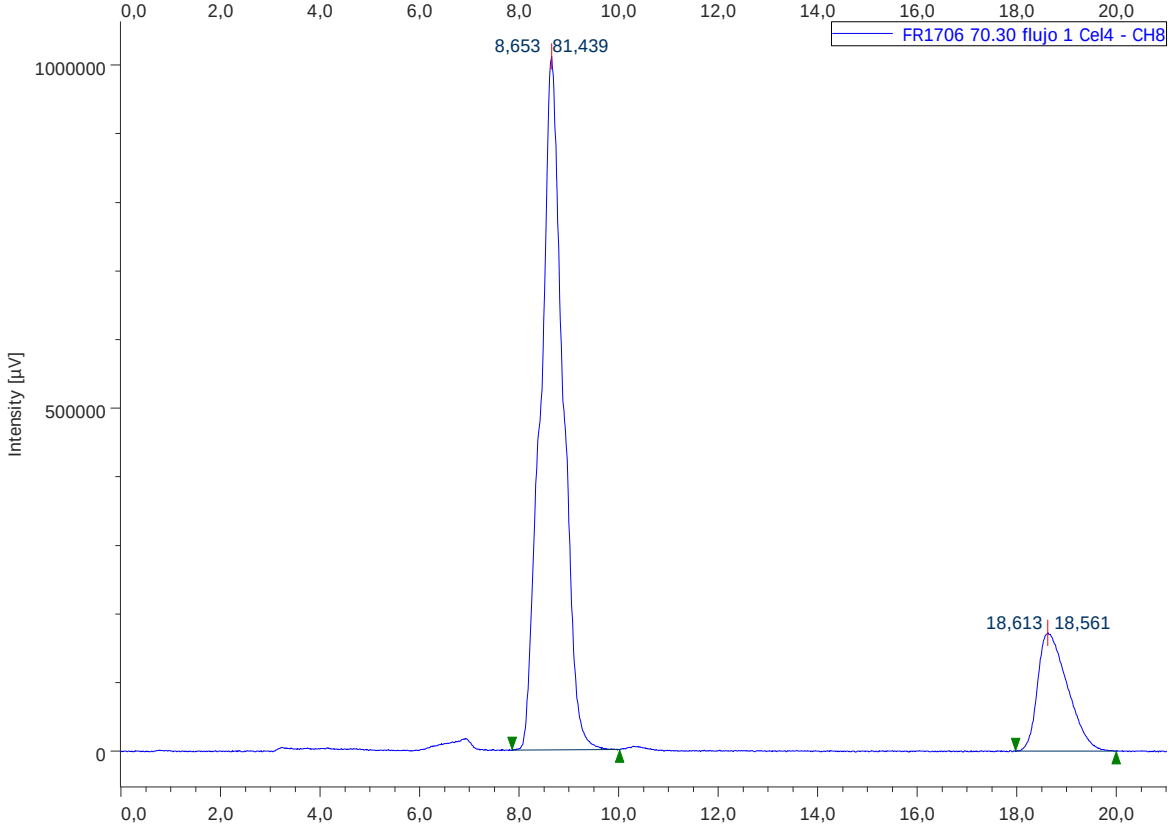
Figure S3.1

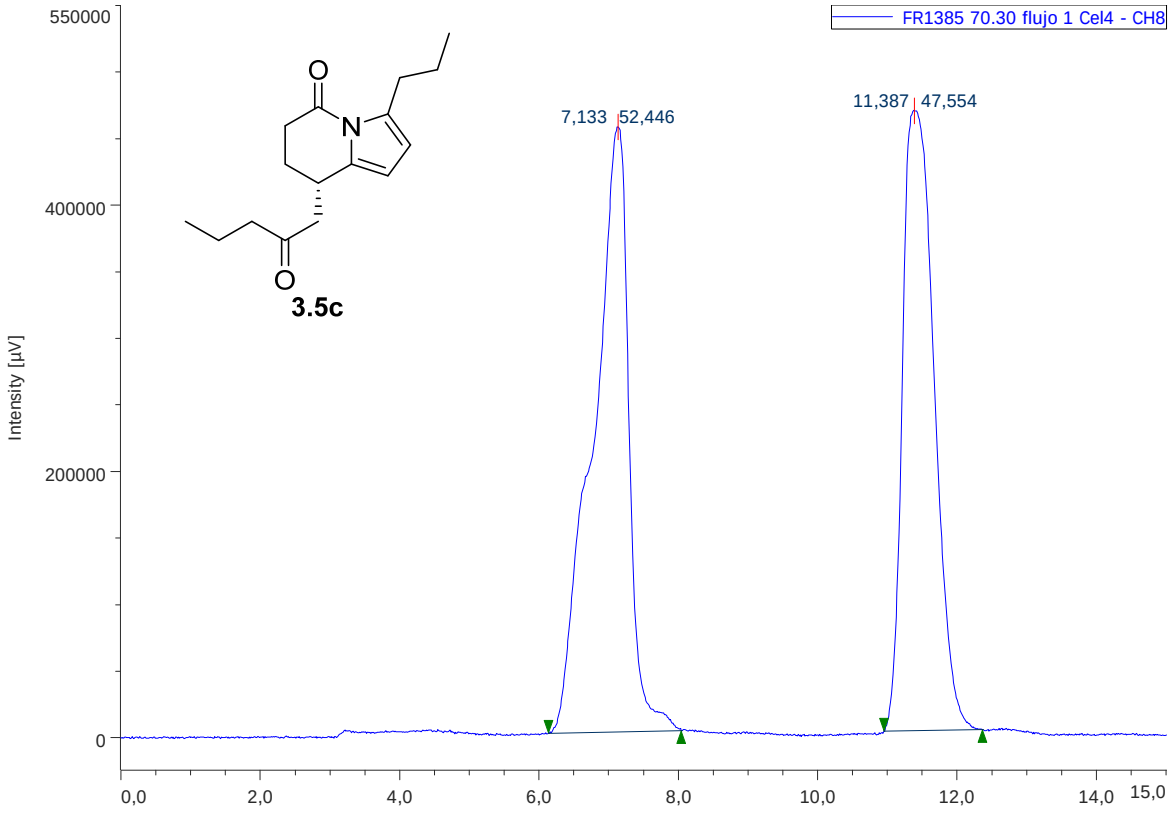
- **HPLC Traces of enantioenriched compounds 3.5**

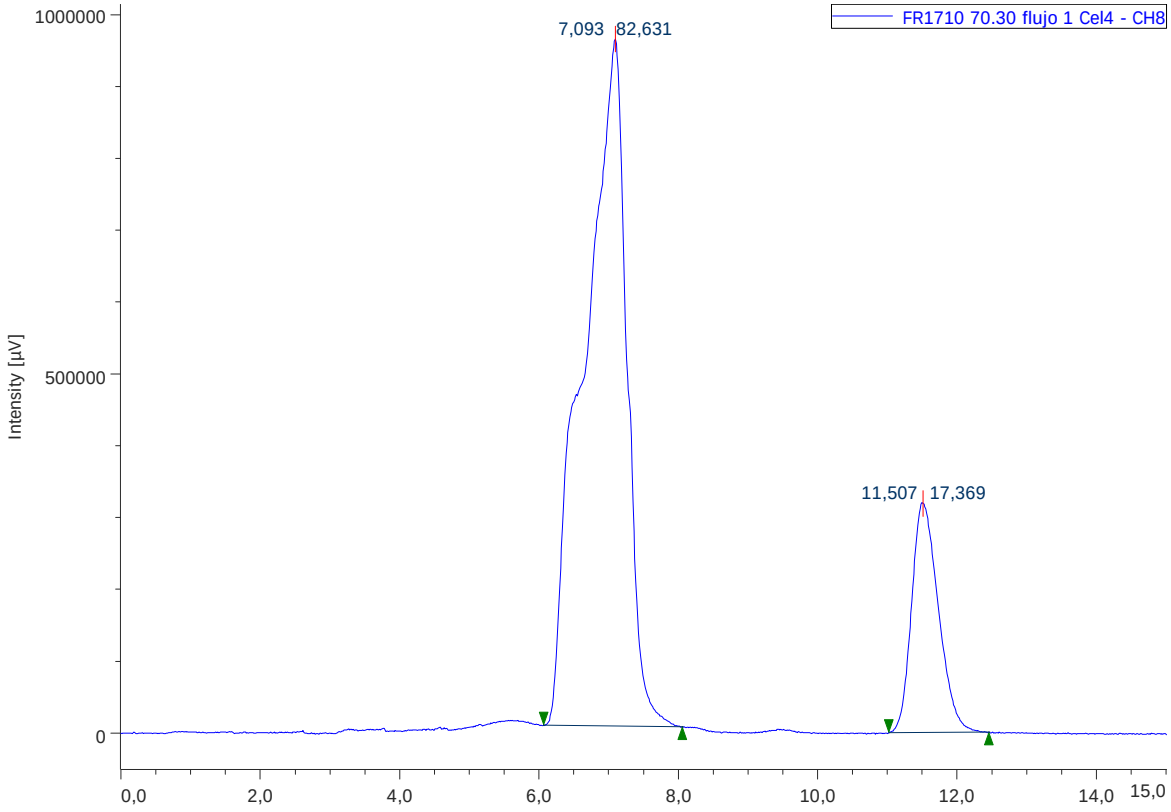





FR1698 70.30 flujo 1 Cel4 - CH8
8,787 50,426
18,600 49,574
3.5b
Intensity [µV]
400000
300000
200000
100000
0
0,0
2,0
4,0
6,0
8,0
10,0
12,0
14,0
16,0
18,0
20,0


FR1706 70.30 flujo 1 Cel4 - CH8
8,653 81,439
18,613 18,561
Intensity [µV]
1000000
500000
0
0,0
2,0
4,0
6,0
8,0
10,0
12,0
14,0
16,0
18,0
20,0


FR1385 70.30 flujo 1 Cel4 - CH8
7,133 52,446
11,387 47,554
Intensity [µV]
550000
400000
200000
0
0,0
2,0
4,0
6,0
8,0
10,0
12,0
14,0
15,0
O
N
O
3.5c


FR1710 70.30 flujo 1 Cel4 - CH8
7,093 82,631
11,507 17,369
Intensity [µV]
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500000
0
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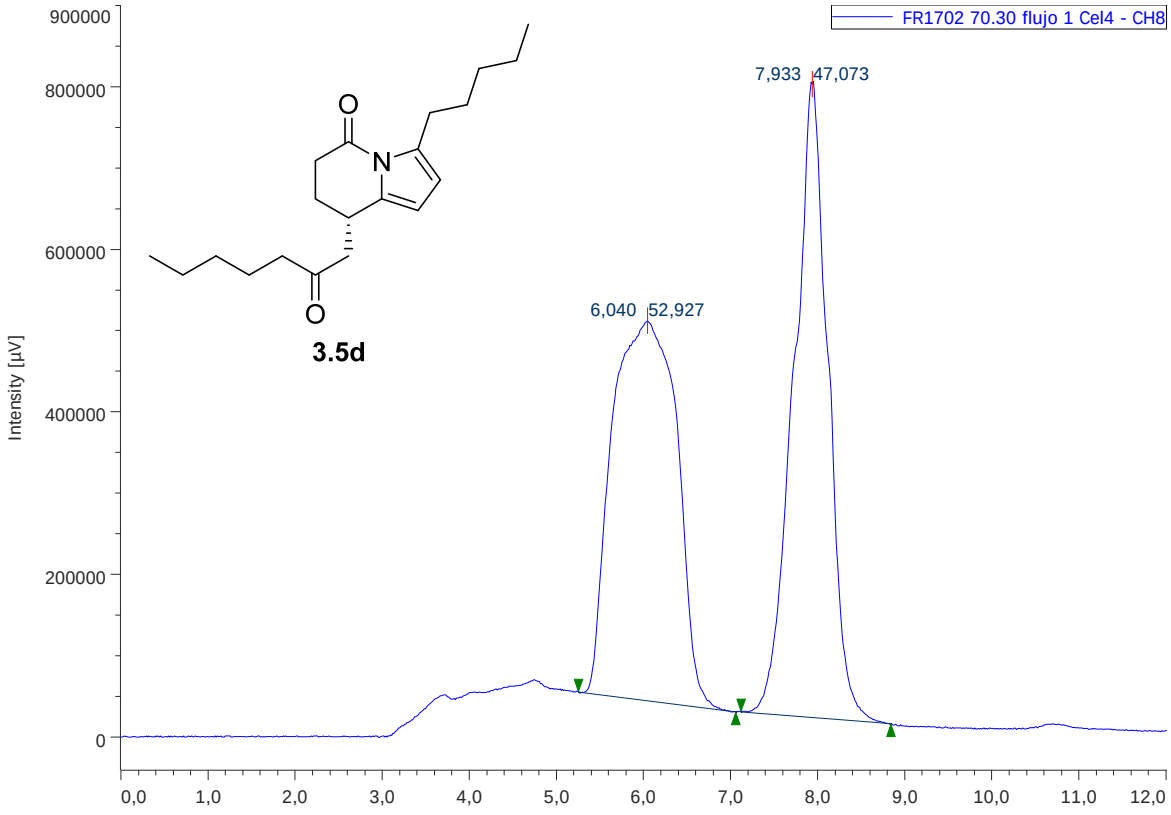
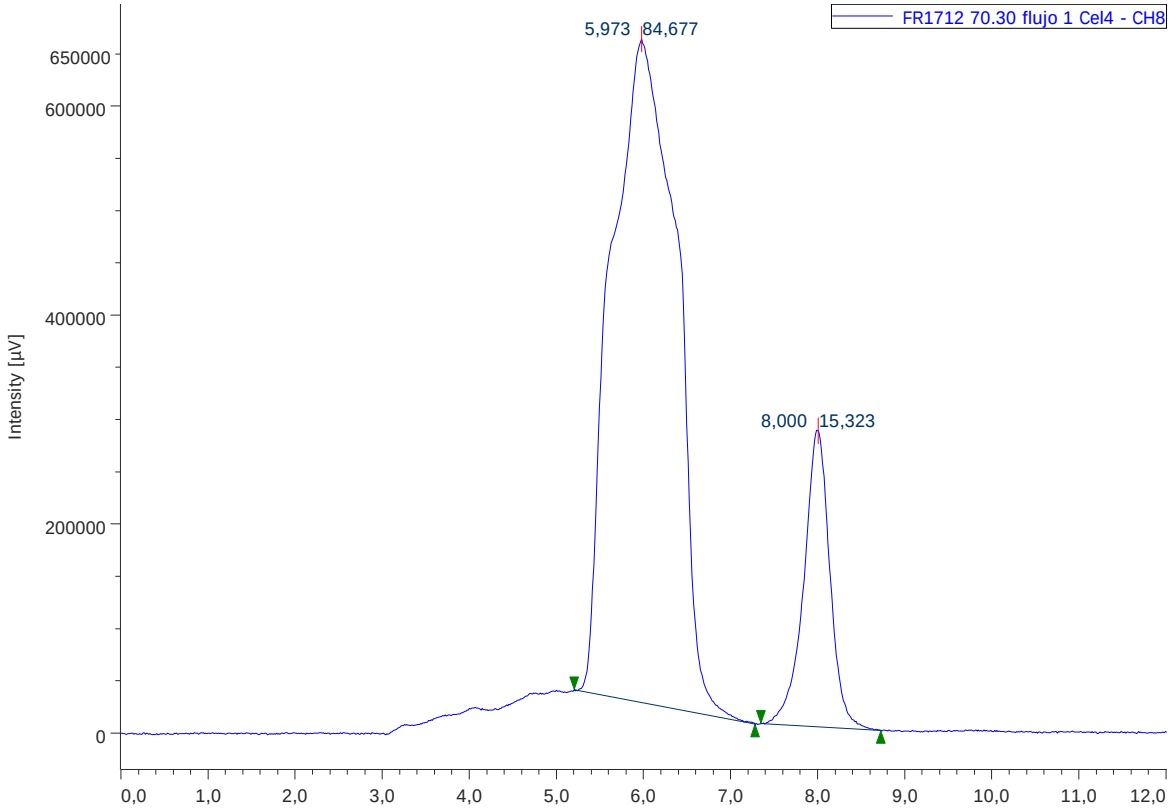
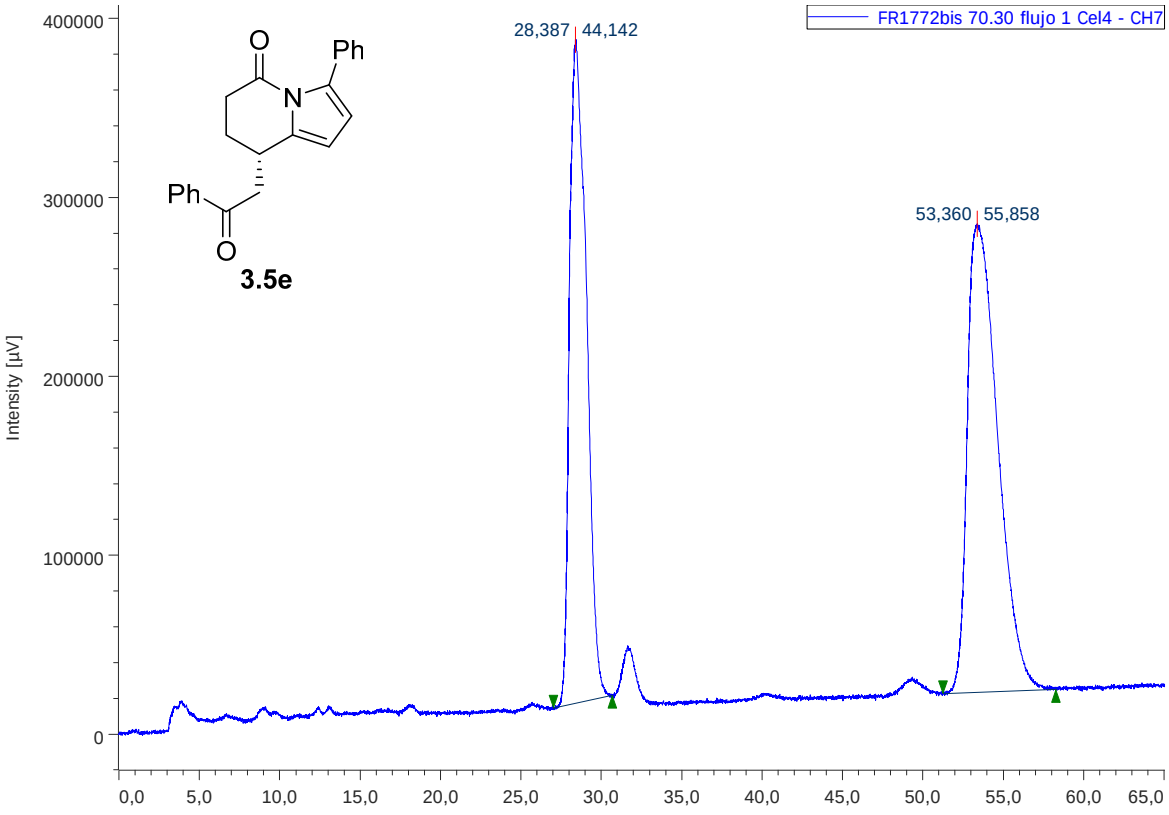
4,0
6,0
8,0
10,0
12,0
14,0
15,0


FR1702 70.30 flujo 1 Cel4 - CH8
7,933 47,073
6,040 52,927
3.5d
Intensity [µV]
900000
800000
600000
400000
200000
0
0,0 1,0 2,0 3,0 4,0 5,0 6,0 7,0 8,0 9,0 10,0 11,0 12,0


FR1712 70.30 flujo 1 Cel4 - CH8
5,973 84,677
8,000 15,323
Intensity [µV]
650000
600000
400000
200000
0
0,0 1,0 2,0 3,0 4,0 5,0 6,0 7,0 8,0 9,0 10,0 11,0 12,0


FR1772bis 70.30 flujo 1 Cel4 - CH7
28,387
44,142
53,360
55,858
Intensity [µV]
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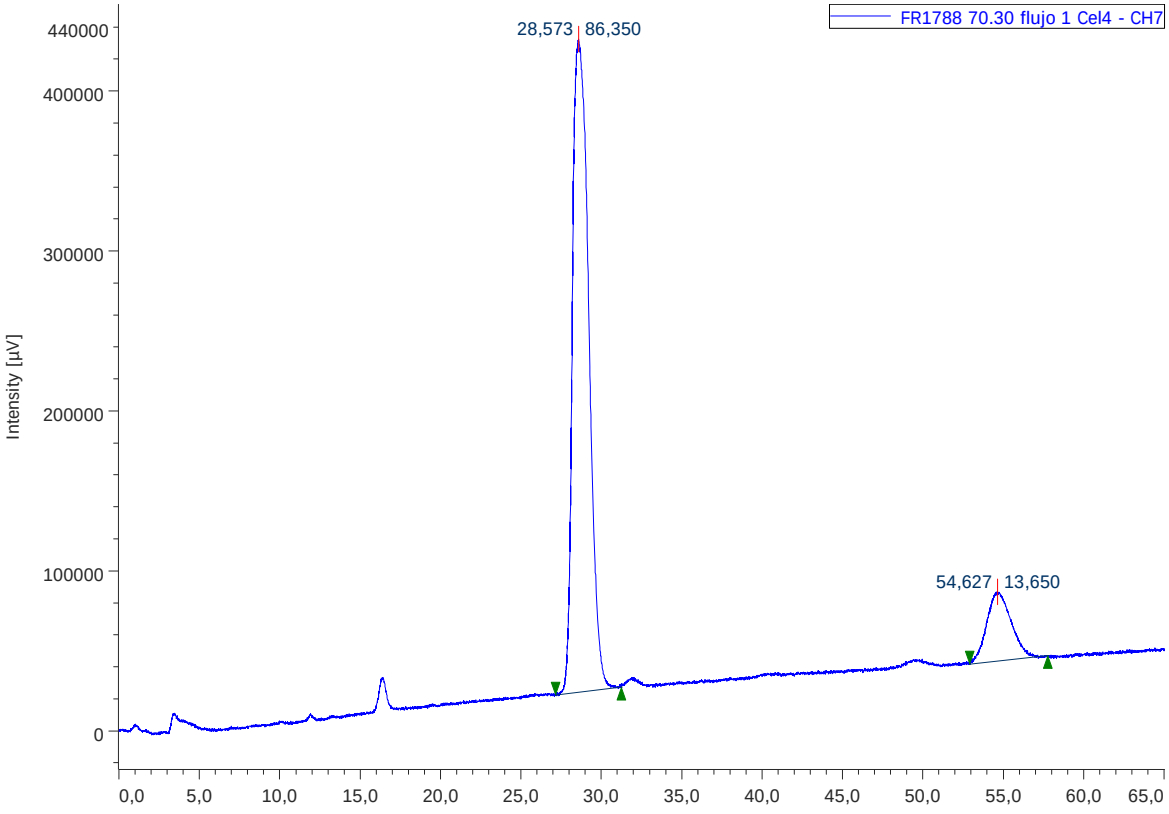
300000
200000
100000
0
0,0
5,0
10,0
15,0
20,0
25,0
30,0
35,0
40,0
45,0
50,0
55,0
60,0
65,0
O
Ph
N
Ph
O
3.5e


FR1788 70.30 flujo 1 Cel4 - CH7
28,573
86,350
54,627
13,650
Intensity [µV]
440000
400000
300000
200000
100000
0
0,0
5,0
10,0
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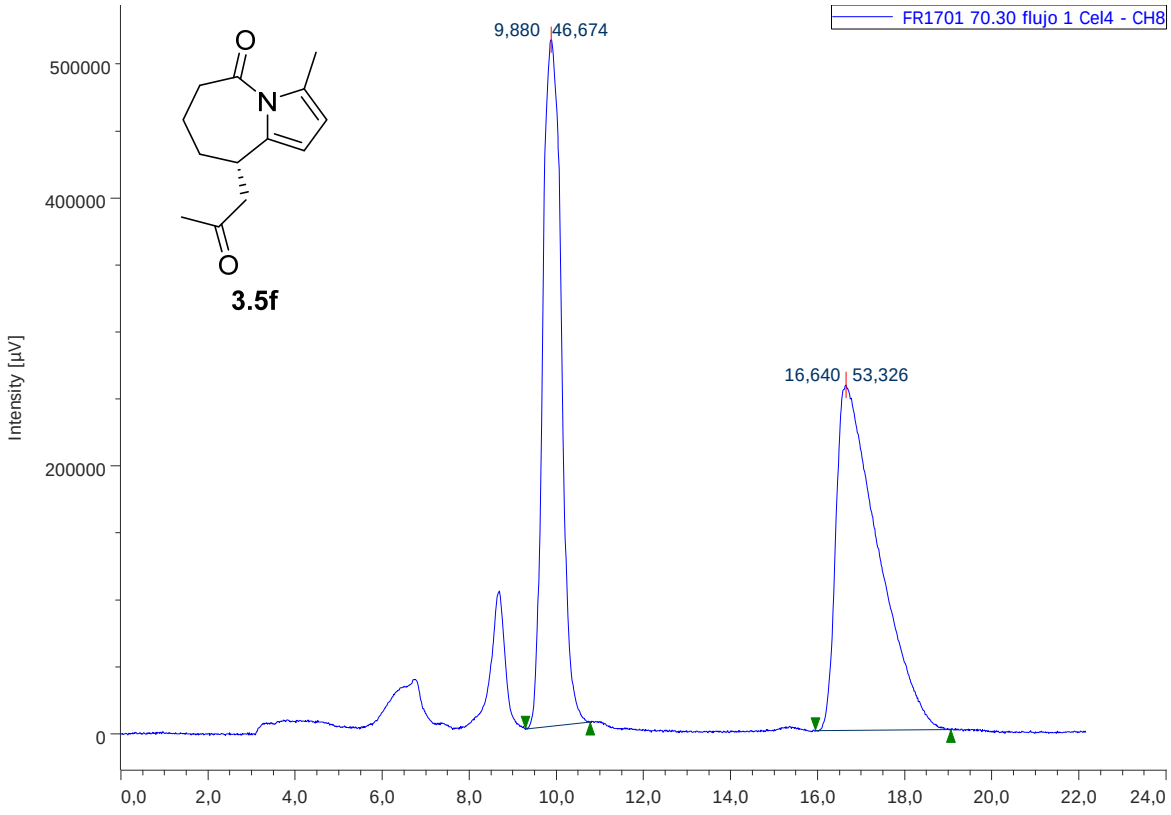
60,0
65,0


FR1701 70.30 flujo 1 Cel4 - CH8
9,880 46,674
16,640 53,326
3.5f
Intensity [µV]
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400000
200000
0
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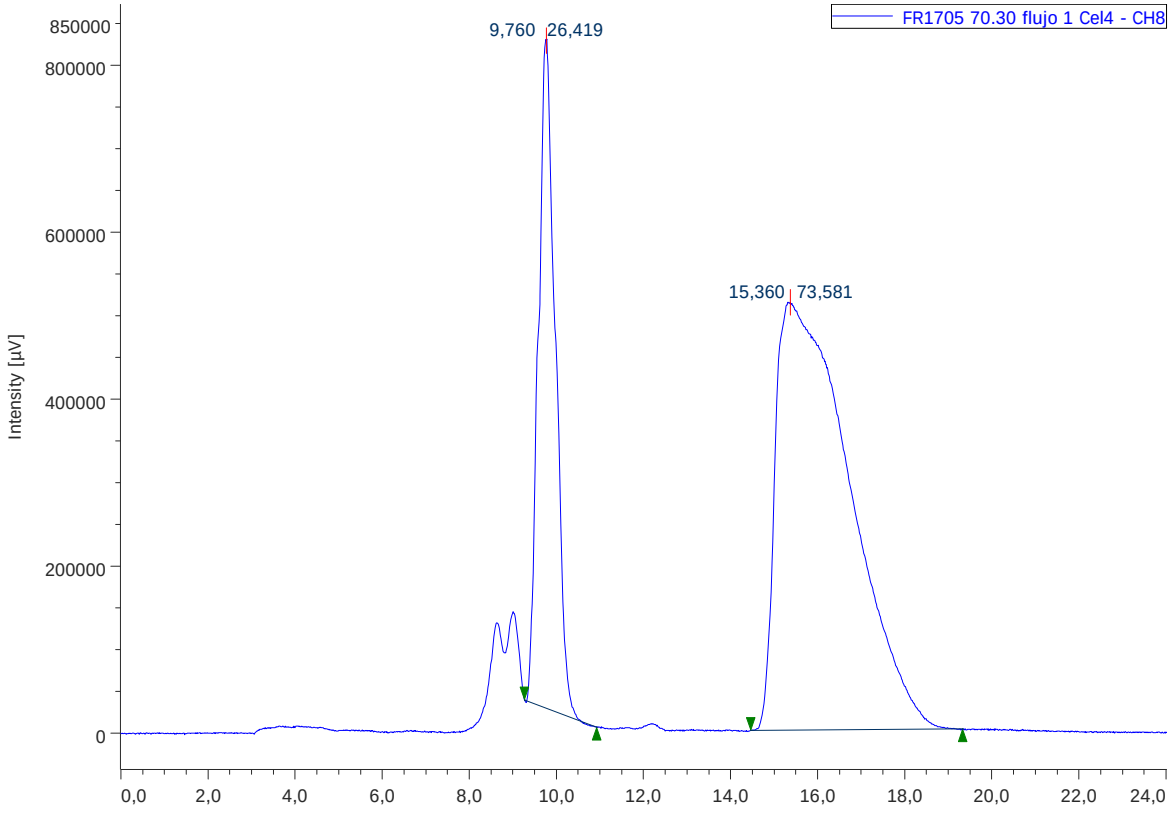
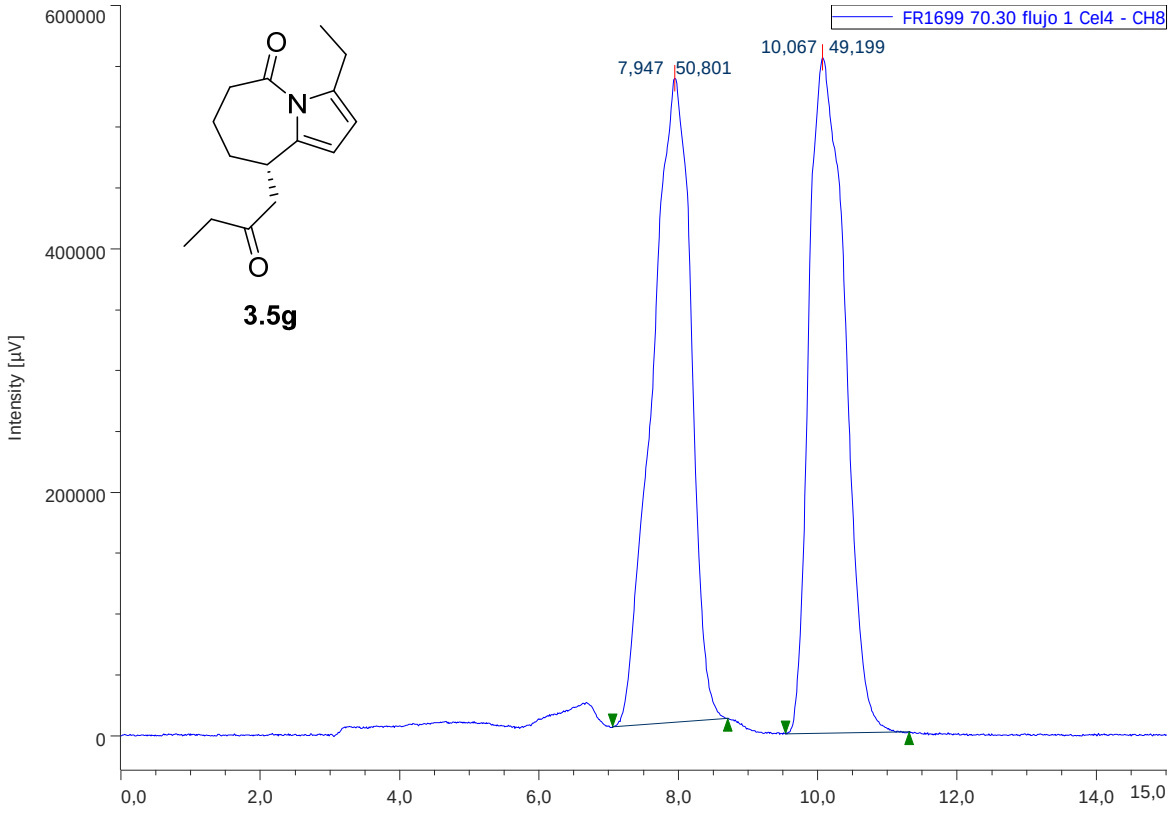

FR1705 70.30 flujo 1 Cel4 - CH8
9,760 26,419
15,360 73,581
Intensity [µV]
850000
800000
600000
400000
200000
0
0,0 2,0 4,0 6,0 8,0 10,0 12,0 14,0 16,0 18,0 20,0 22,0 24,0


FR1699 70.30 flujo 1 Cel4 - CH8
7,947 50,801
10,067 49,199
Intensity [µV]
600000
400000
200000
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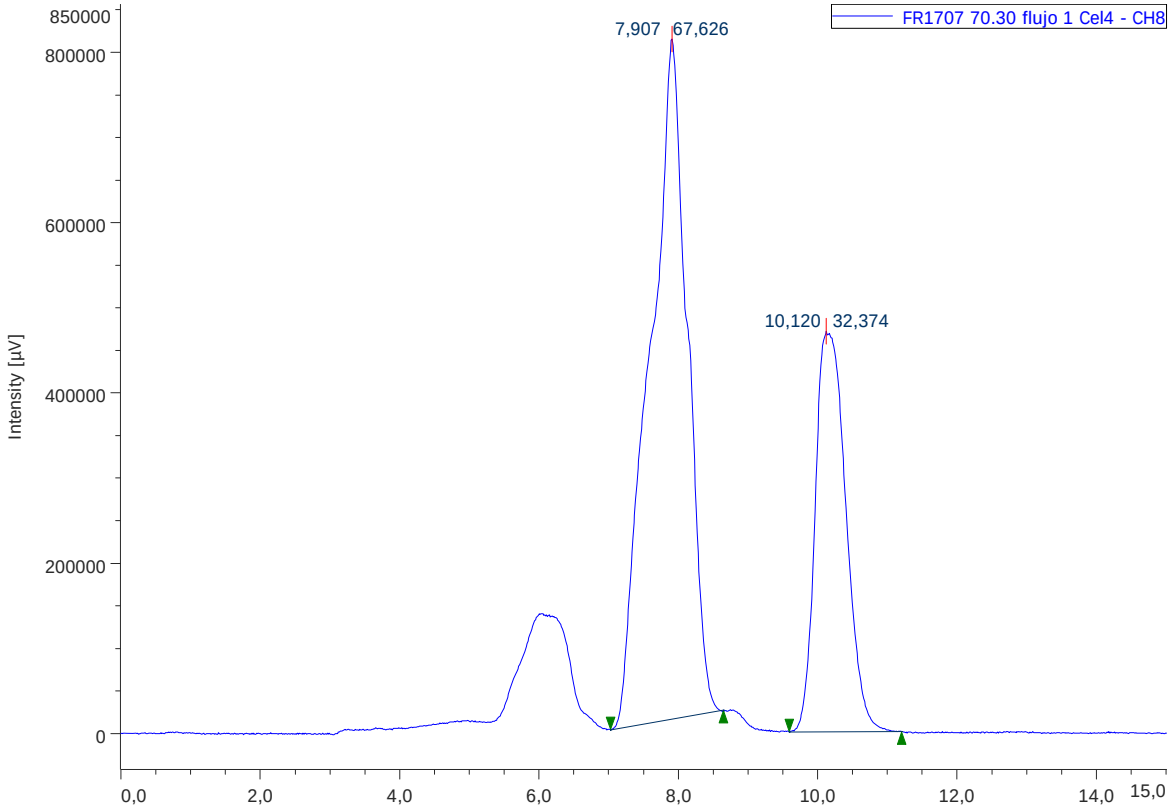
2,0
4,0
6,0
8,0
10,0
12,0
14,0
15,0

3.5g


FR1707 70.30 flujo 1 Cel4 - CH8
7,907 67,626
10,120 32,374
Intensity [µV]
850000
800000
600000
400000
200000
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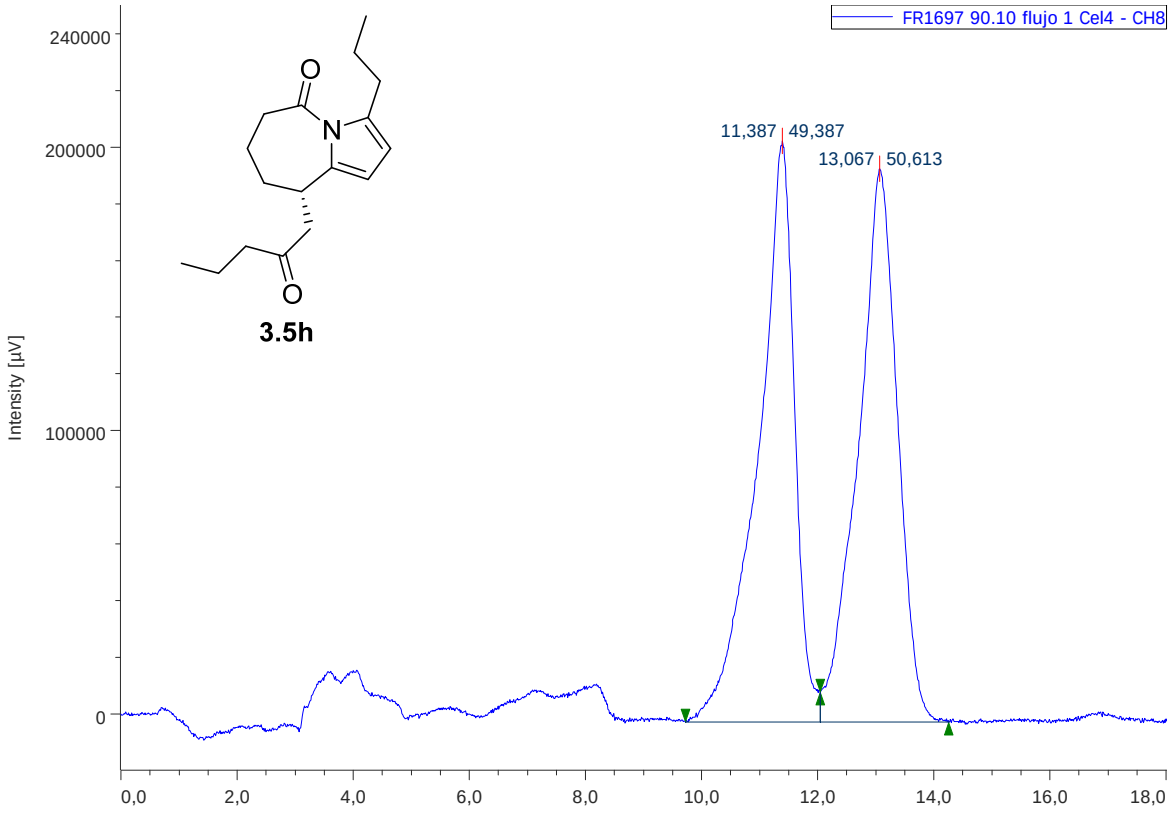
2,0
4,0
6,0
8,0
10,0
12,0
14,0
15,0


FR1697 90.10 flujo 1 Cel4 - CH8
Intensity [µV]
240000
200000
100000
0
11,387 49,387
13,067 50,613
0,0
2,0
4,0
6,0
8,0
10,0
12,0
14,0
16,0
18,0

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N
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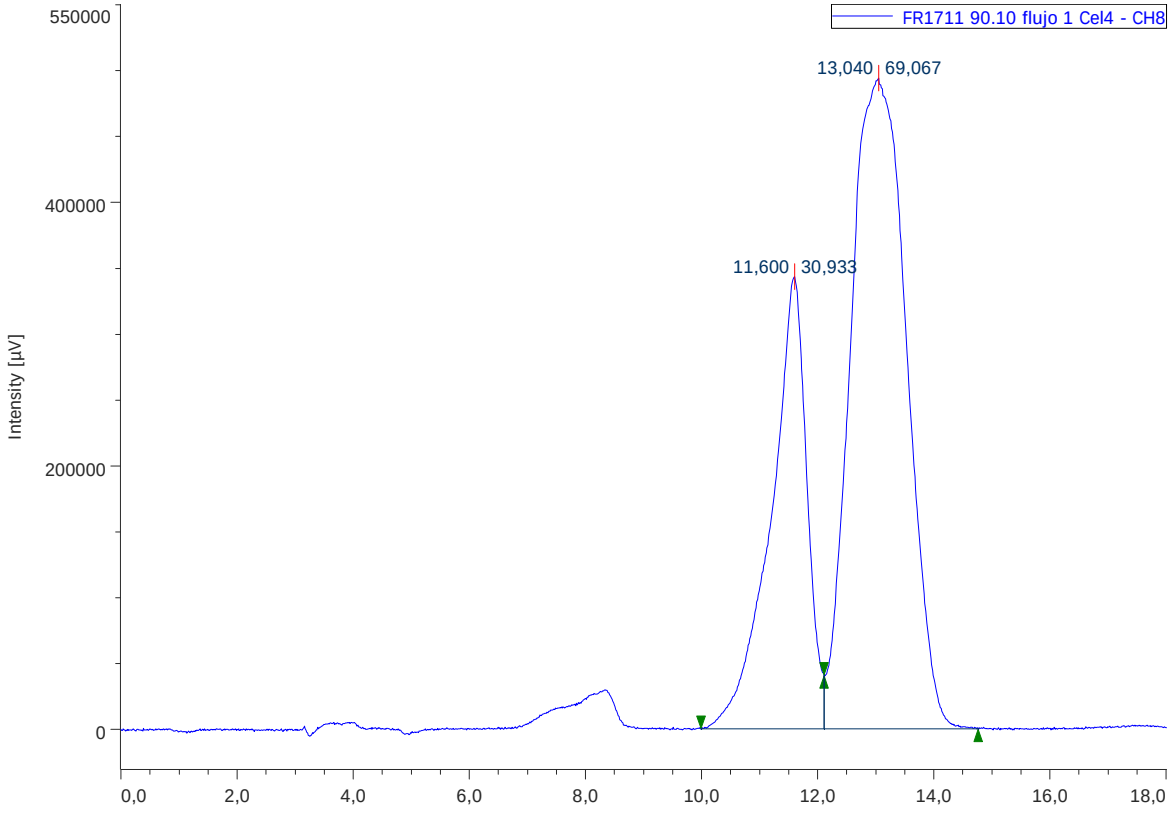
3.5h


FR1711 90.10 flujo 1 Cel4 - CH8
Intensity [µV]
550000
400000
200000
0
13,040 69,067
11,600 30,933
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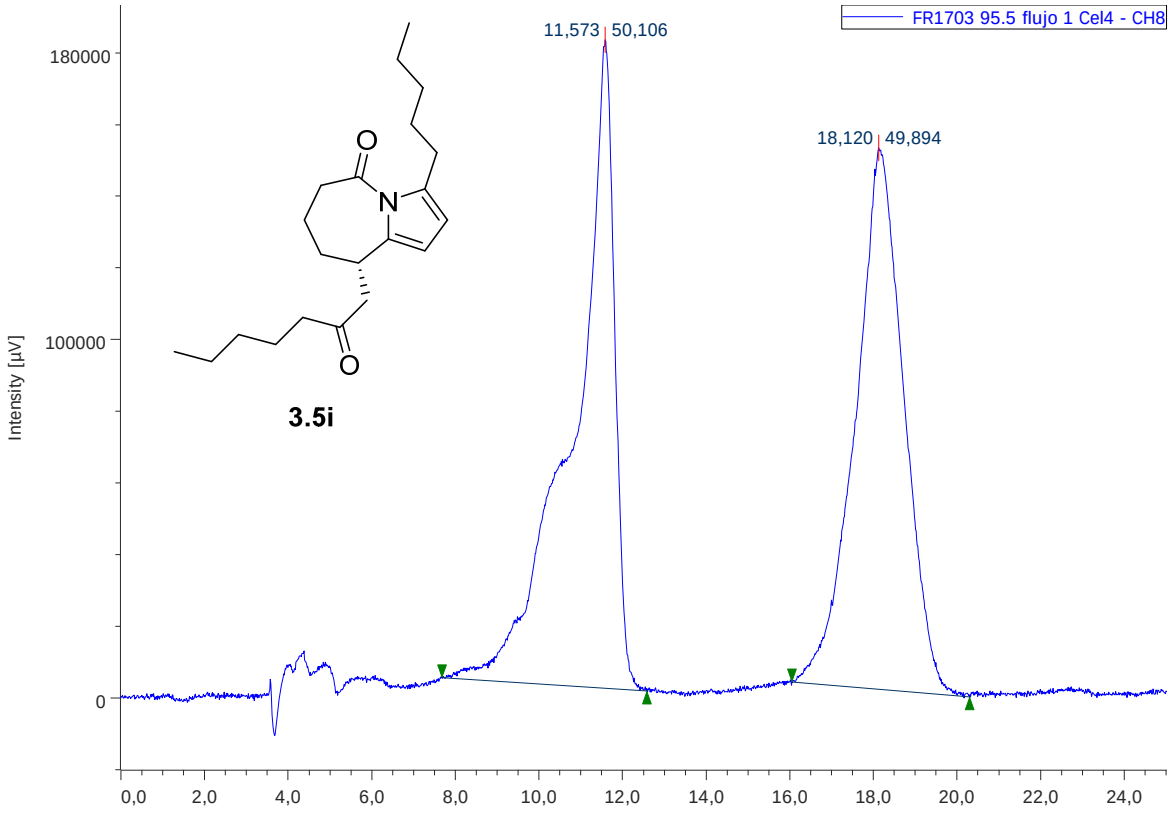
2,0
4,0
6,0
8,0
10,0
12,0
14,0
16,0
18,0


FR1703 95.5 flujo 1 Cel4 - CH8
11,573 50,106
18,120 49,894
180000
100000
0
Intensity [µV]
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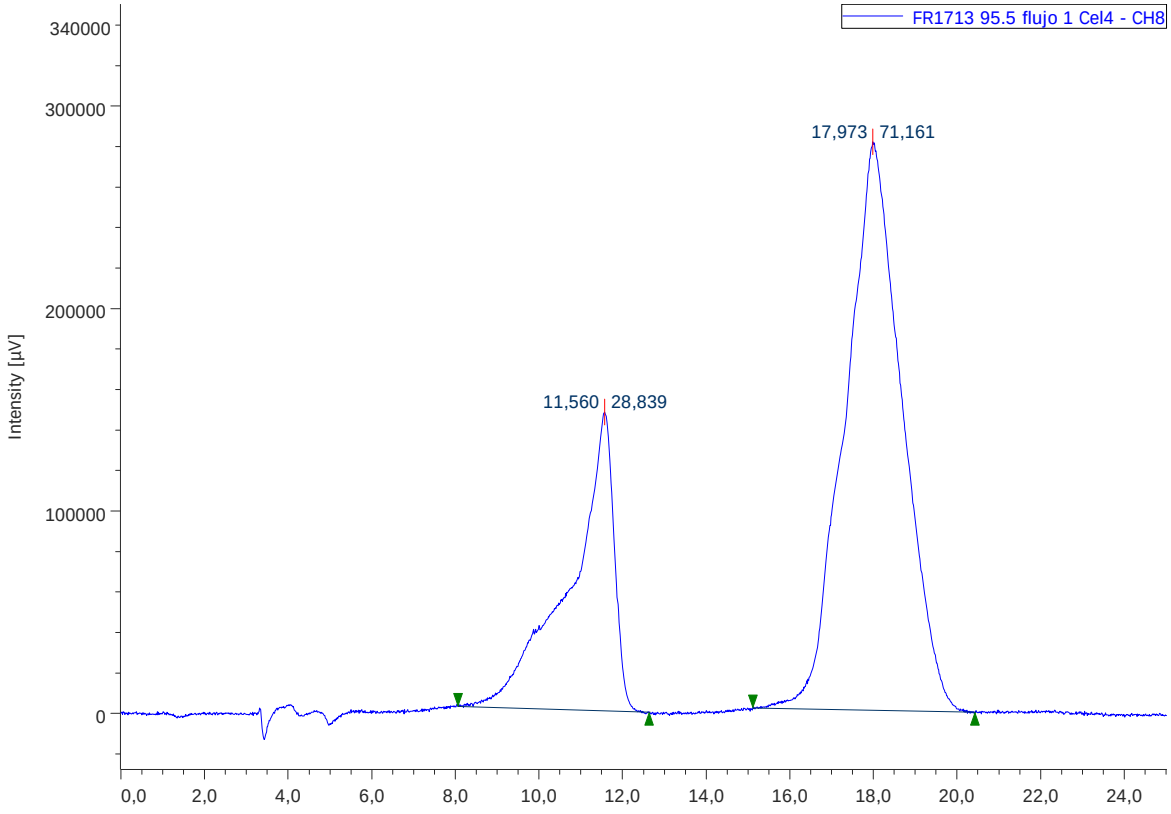
3.5i


FR1713 95.5 flujo 1 Cel4 - CH8
17,973 71,161
11,560 28,839
340000
300000
200000
100000
0
Intensity [µV]
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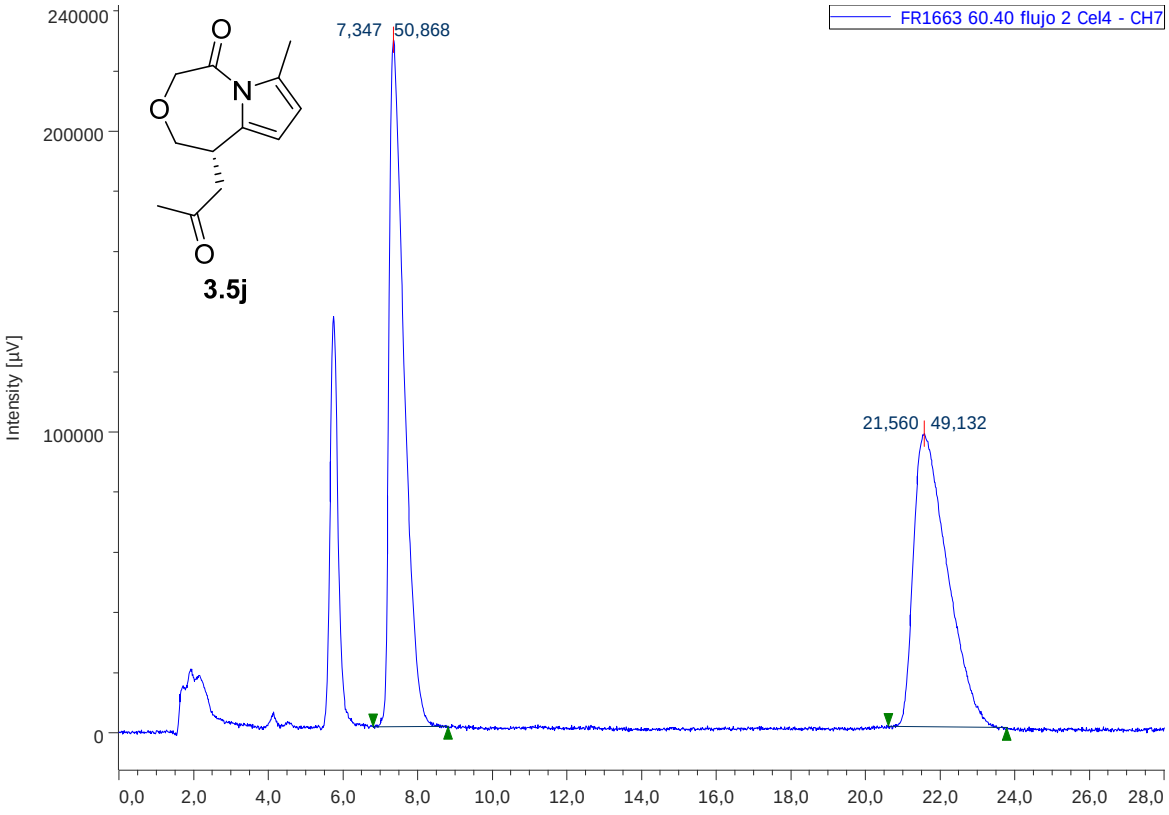
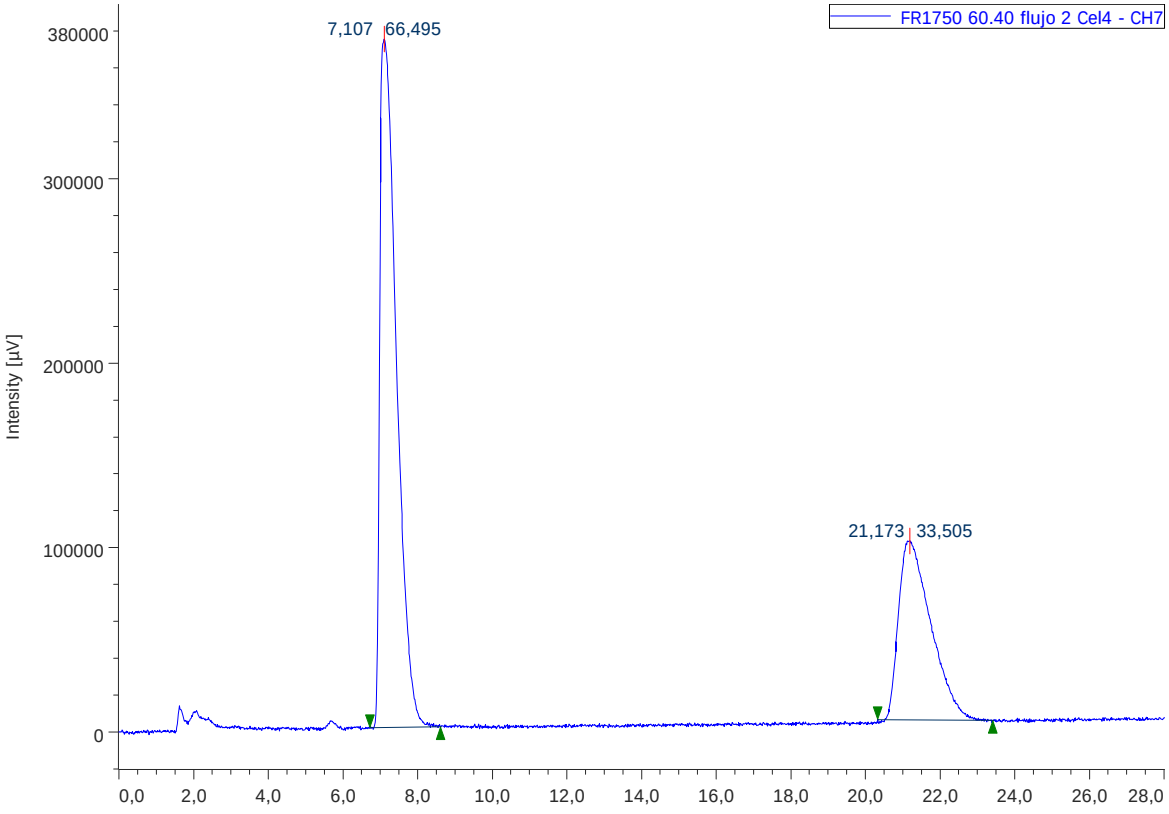
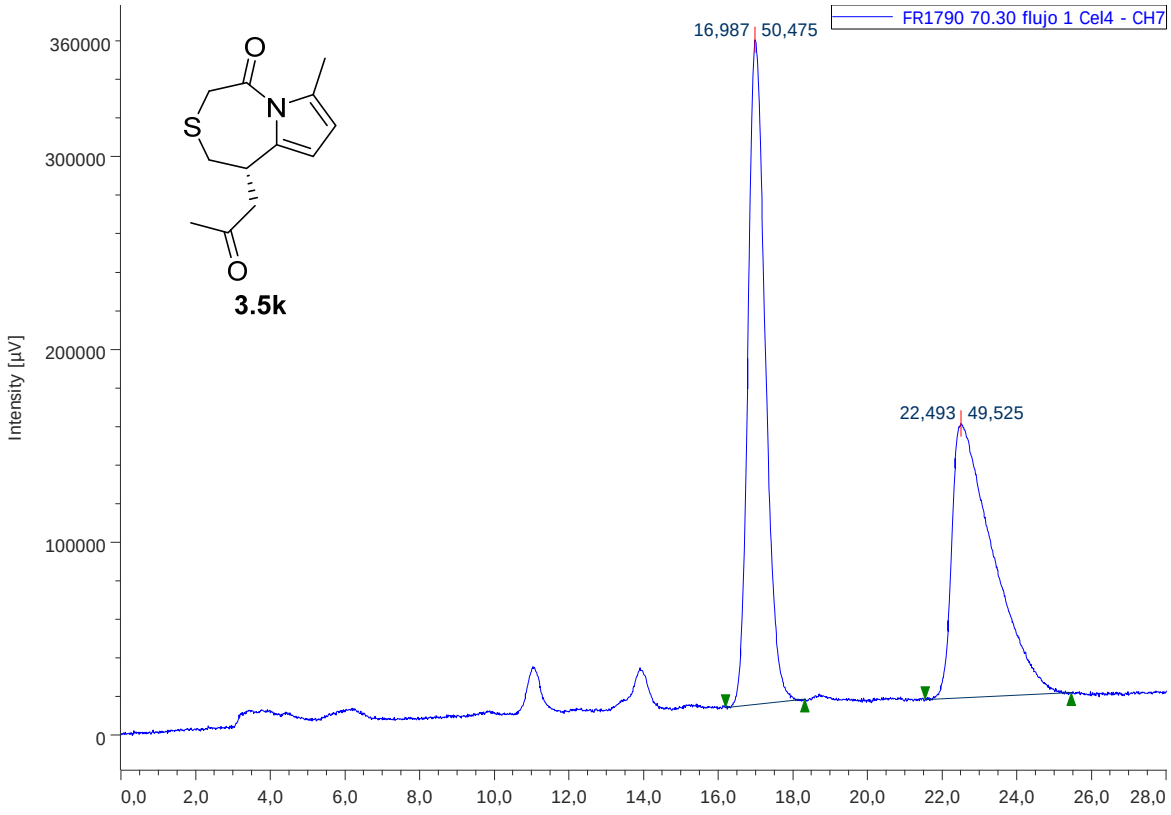

FR1663 60.40 flujo 2 Cel4 - CH7
7,347 50,868
21,560 49,132
3.5j
Intensity [µV]
240000
200000
100000
0
0,0 2,0 4,0 6,0 8,0 10,0 12,0 14,0 16,0 18,0 20,0 22,0 24,0 26,0 28,0


FR1750 60.40 flujo 2 Cel4 - CH7
7,107 66,495
21,173 33,505
Intensity [µV]
380000
300000
200000
100000
0
0,0 2,0 4,0 6,0 8,0 10,0 12,0 14,0 16,0 18,0 20,0 22,0 24,0 26,0 28,0


FR1790 70.30 flujo 1 Cel4 - CH7
16,987 50,475
22,493 49,525
Intensity [µV]
360000
300000
200000
100000
0
0,0 2,0 4,0 6,0 8,0 10,0 12,0 14,0 16,0 18,0 20,0 22,0 24,0 26,0 28,0

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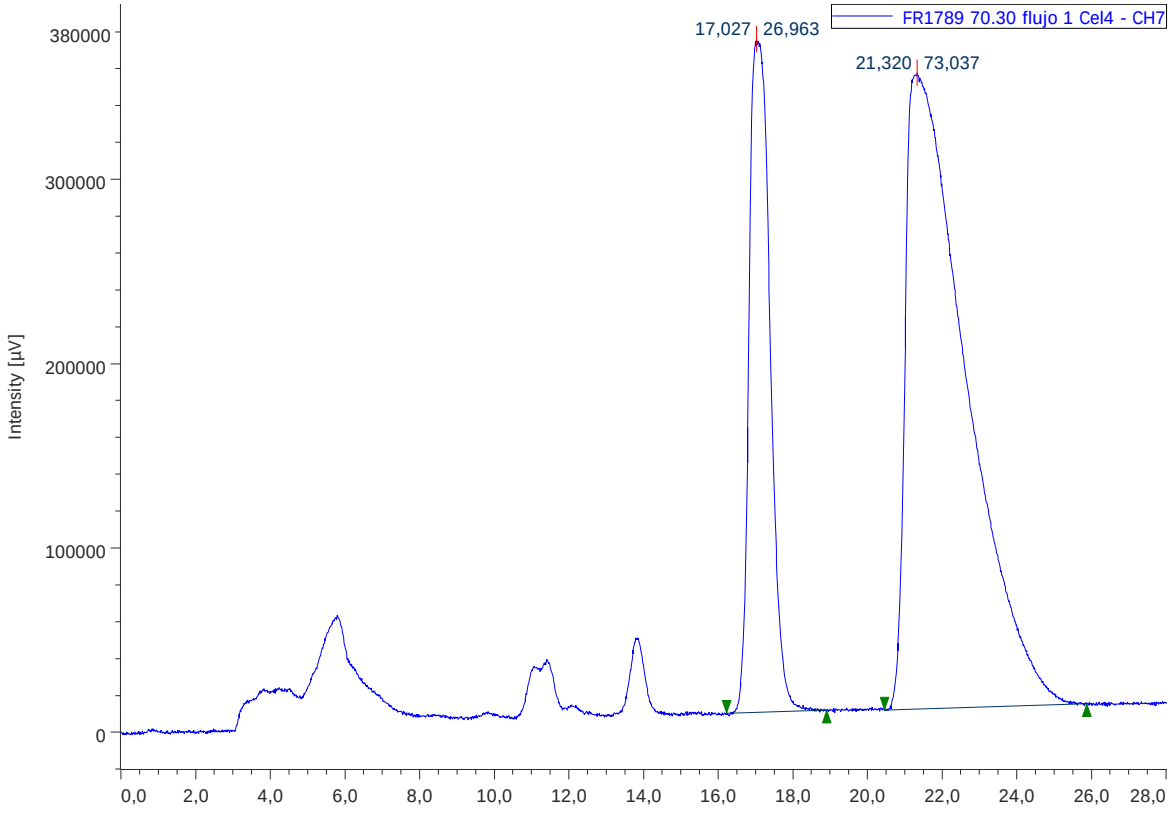
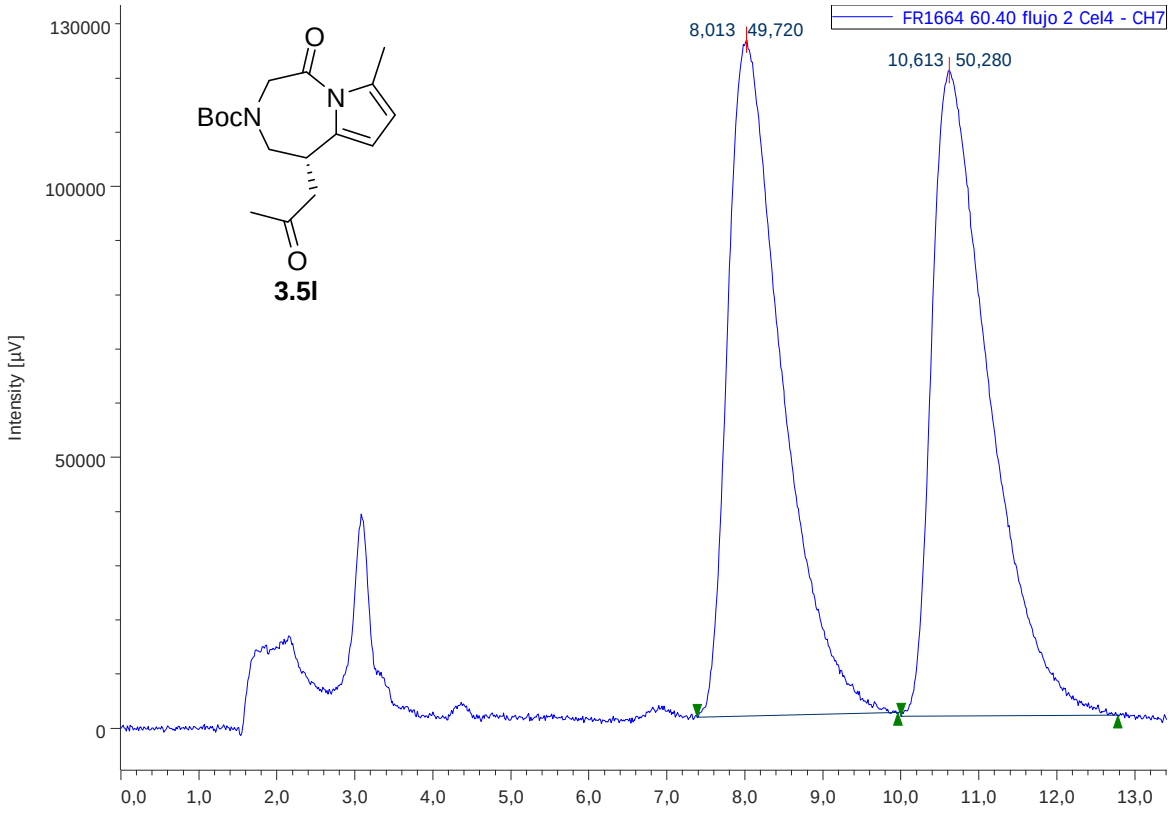

FR1789 70.30 flujo 1 Cel4 - CH7
17,027 26,963
21,320 73,037
Intensity [µV]
380000
300000
200000
100000
0
0,0 2,0 4,0 6,0 8,0 10,0 12,0 14,0 16,0 18,0 20,0 22,0 24,0 26,0 28,0


FR1664 60.40 flujo 2 Cel4 - CH7
8,013 49,720
10,613 50,280
Intensity [µV]
130000
100000
50000
0
0,0 1,0 2,0 3,0 4,0 5,0 6,0 7,0 8,0 9,0 10,0 11,0 12,0 13,0

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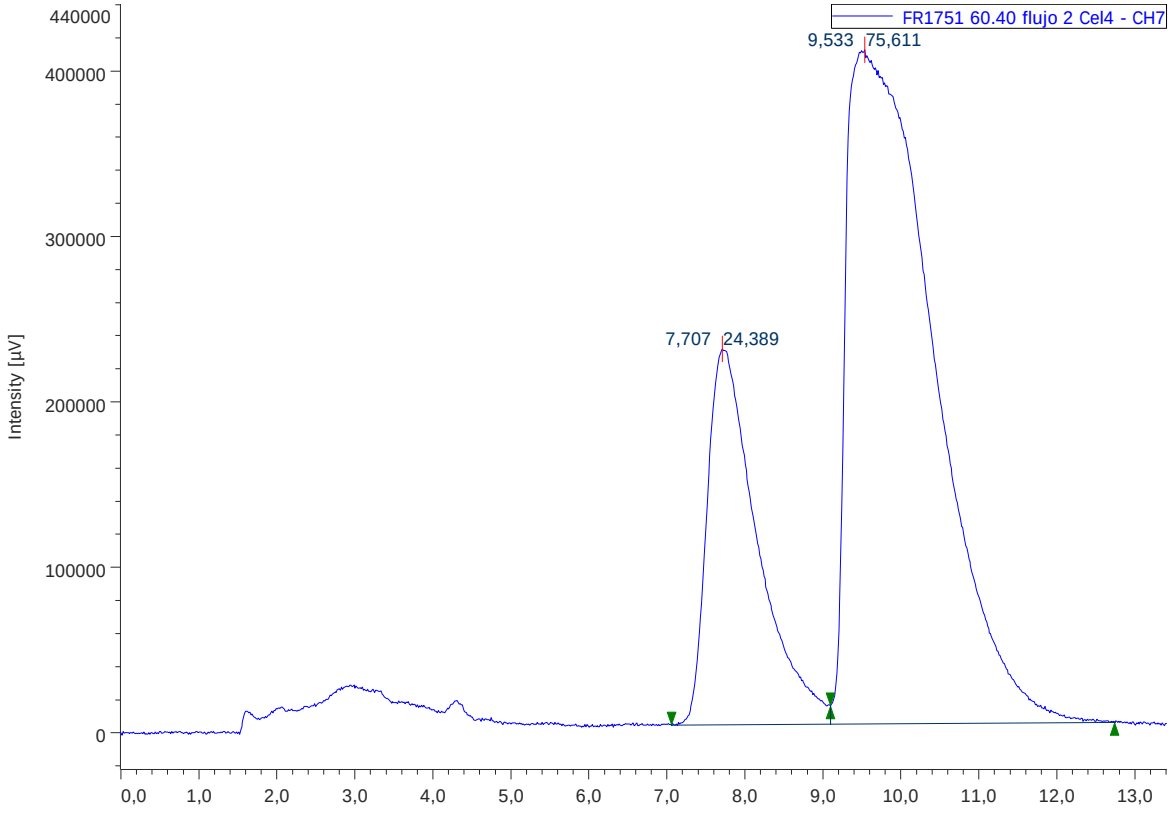
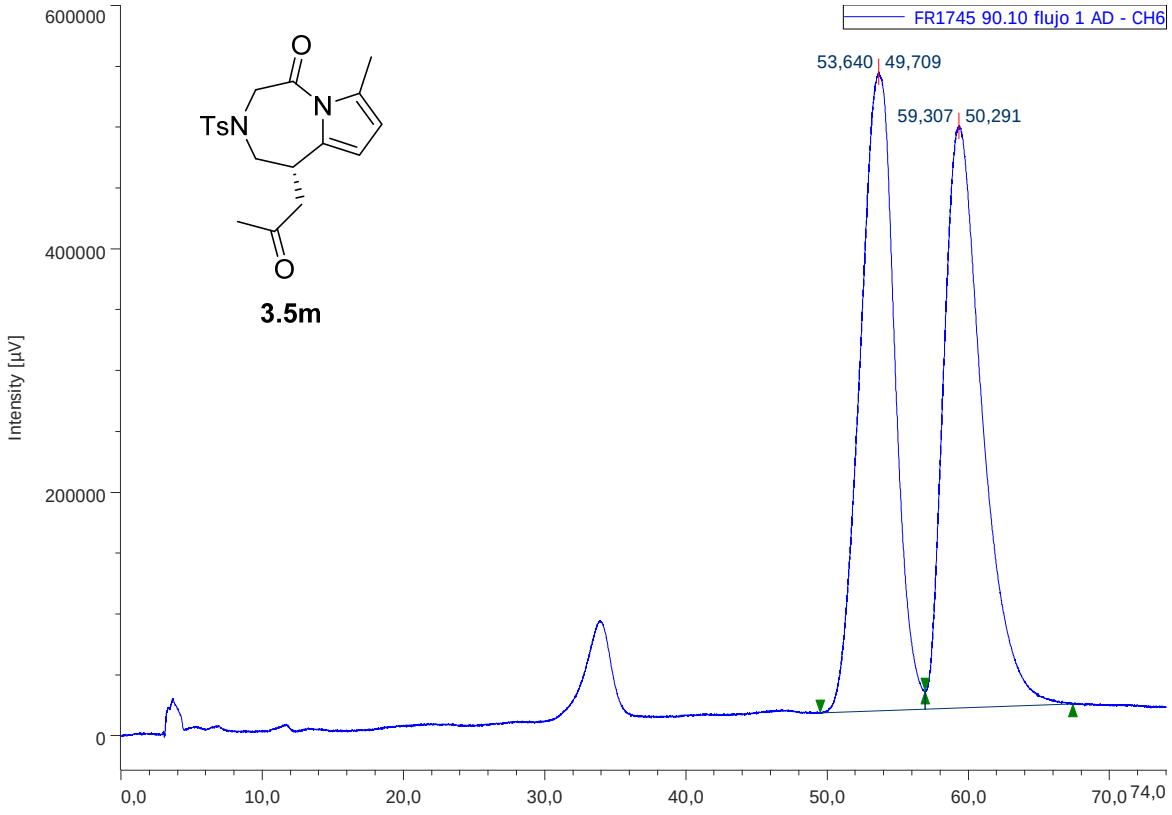
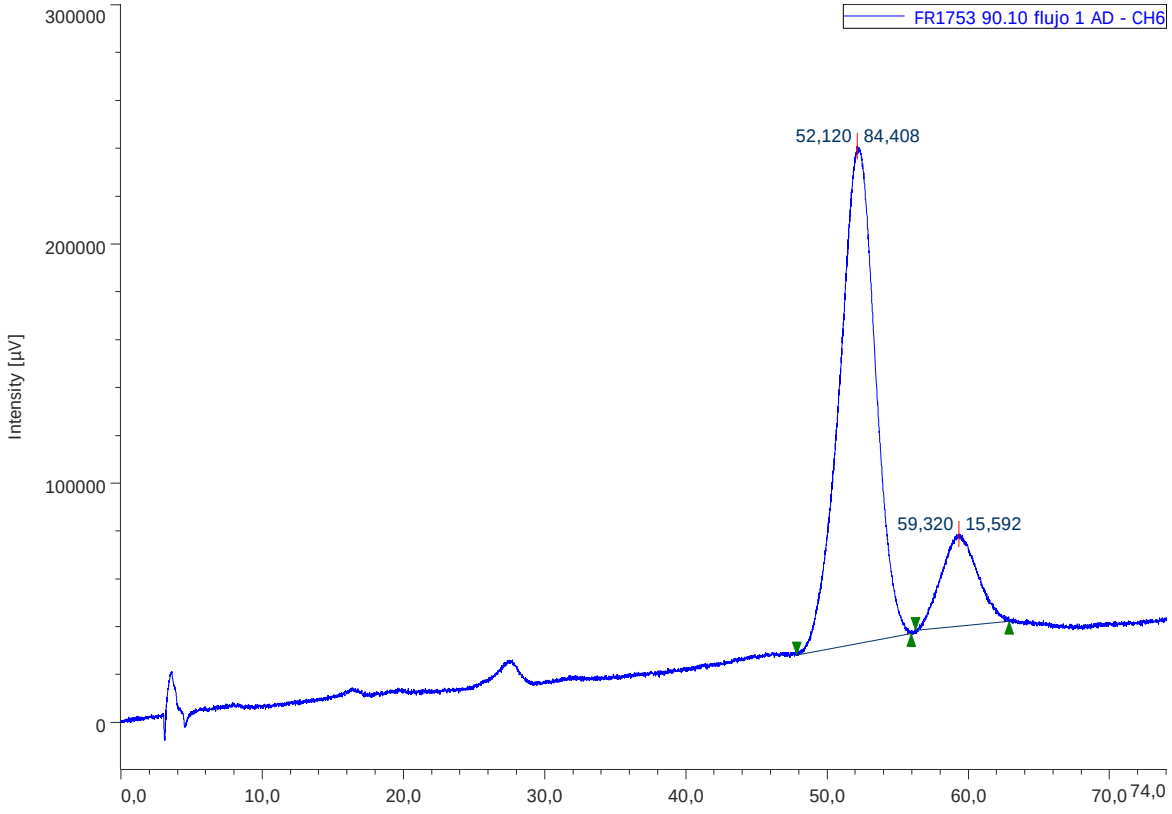
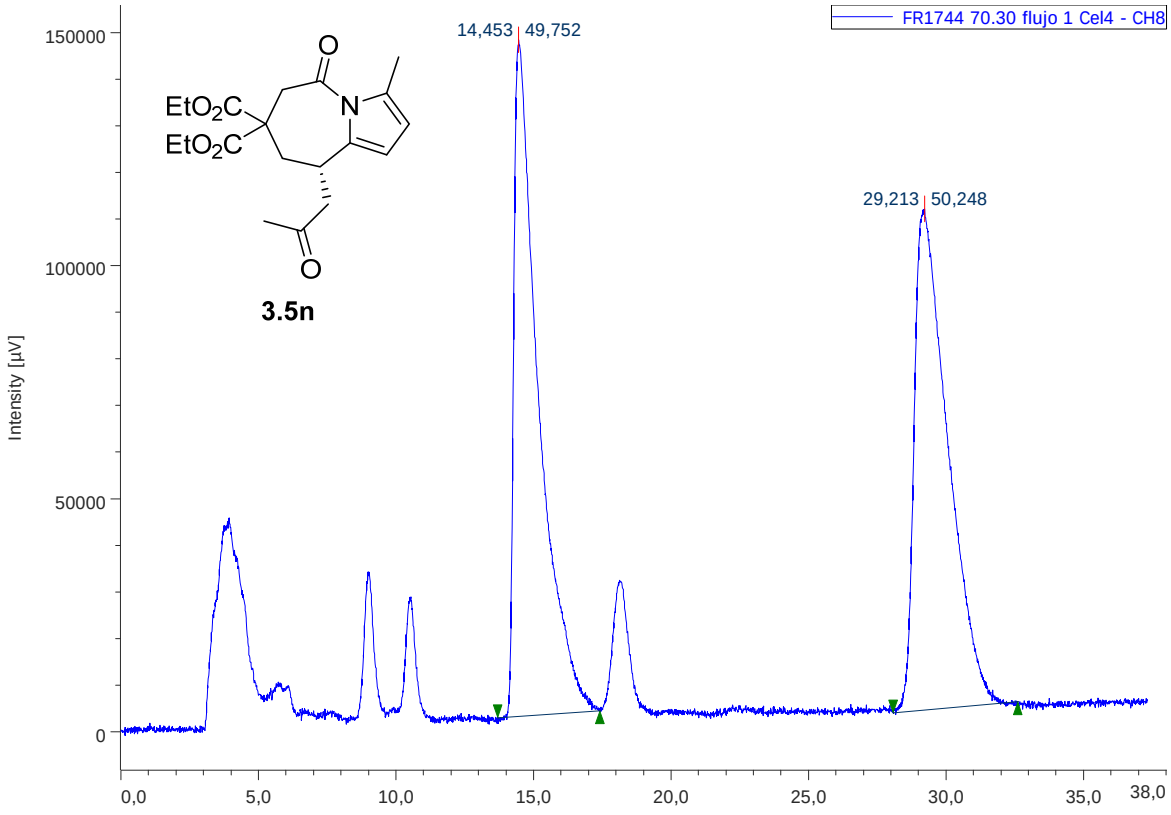
BocN
O

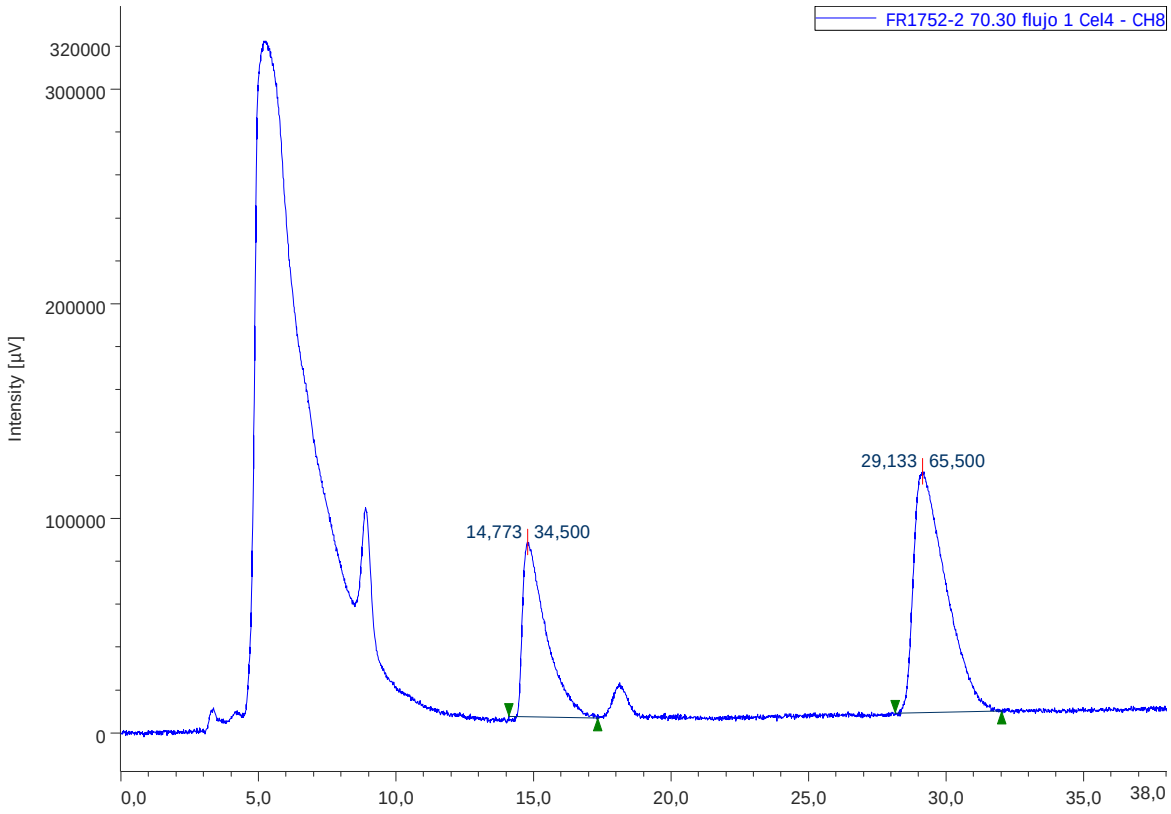
3.5l

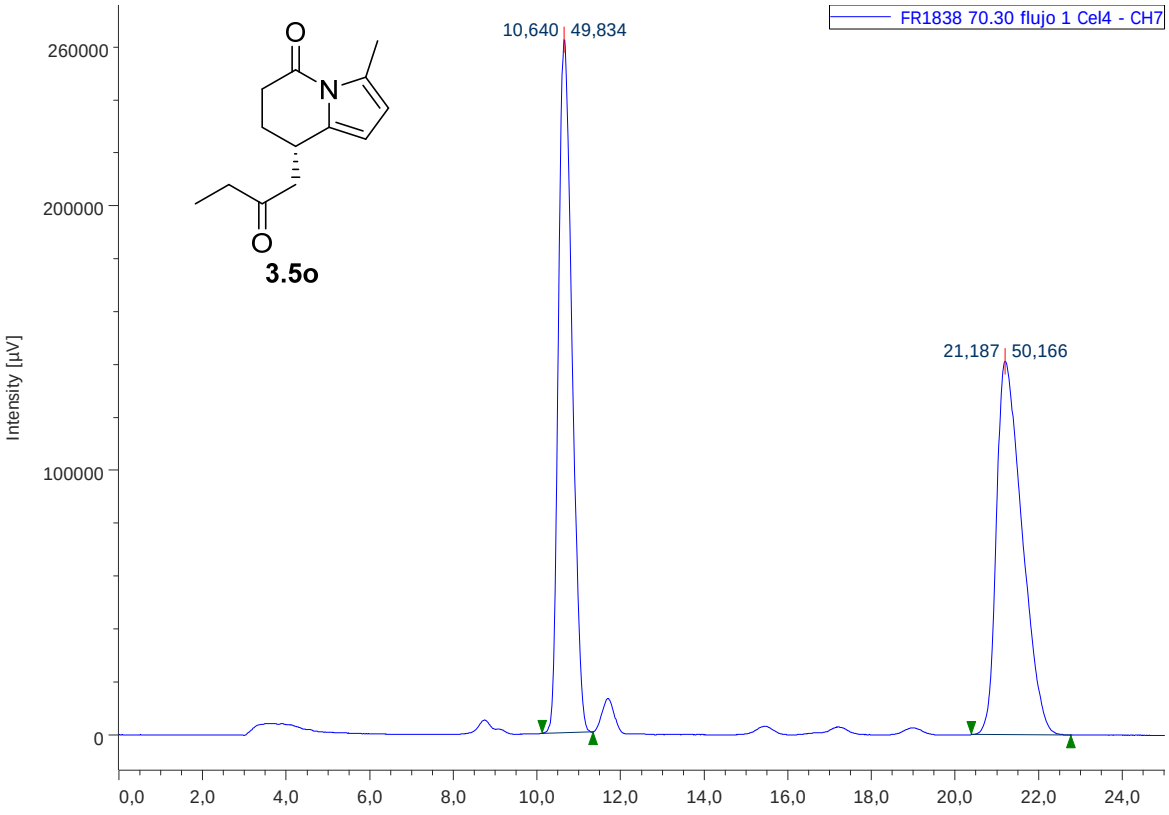

FR1751 60.40 flujo 2 Cel4 - CH7
9,533 75,611
7,707 24,389
Intensity [µV]
440000
400000
300000
200000
100000
0
0,0 1,0 2,0 3,0 4,0 5,0 6,0 7,0 8,0 9,0 10,0 11,0 12,0 13,0

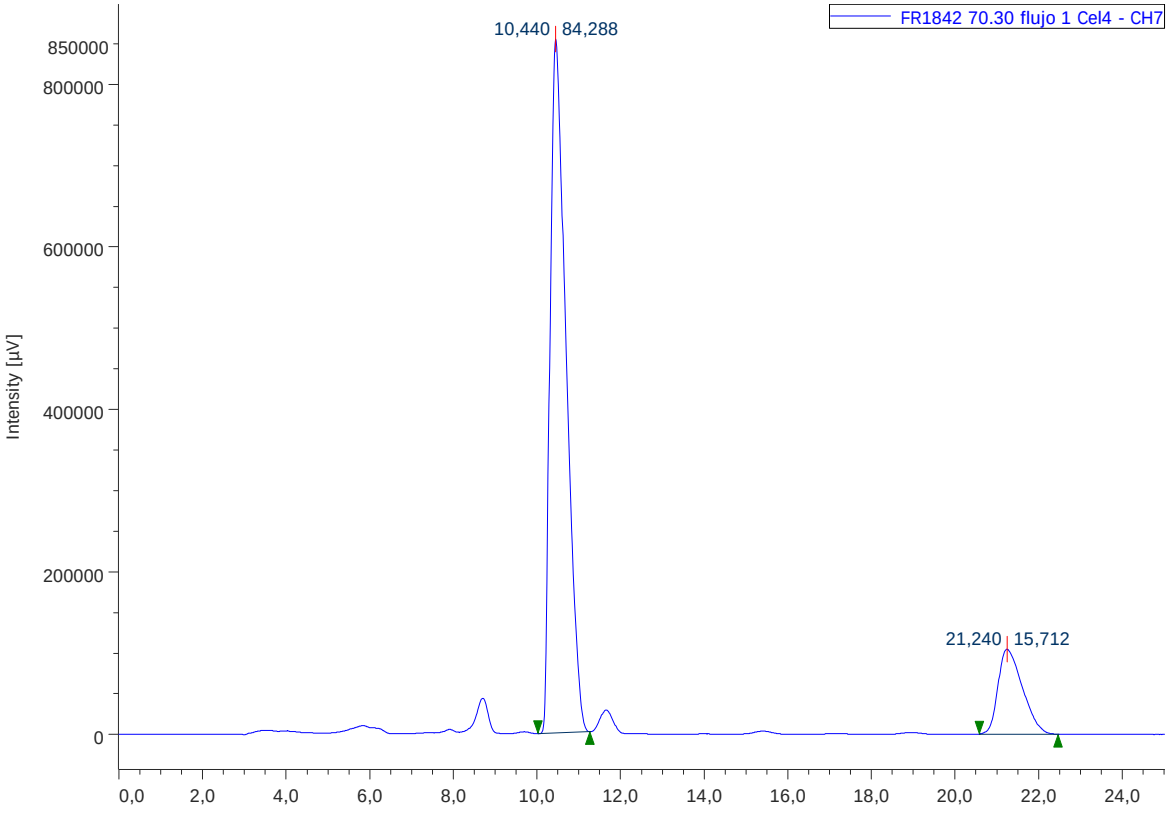

FR1745 90.10 flujo 1 AD - CH6
53,640
49,709
59,307
50,291
TsN
N
O
O
3.5m
Intensity [µV]
600000
400000
200000
0
0,0
10,0
20,0
30,0
40,0
50,0
60,0
70,0
74,0

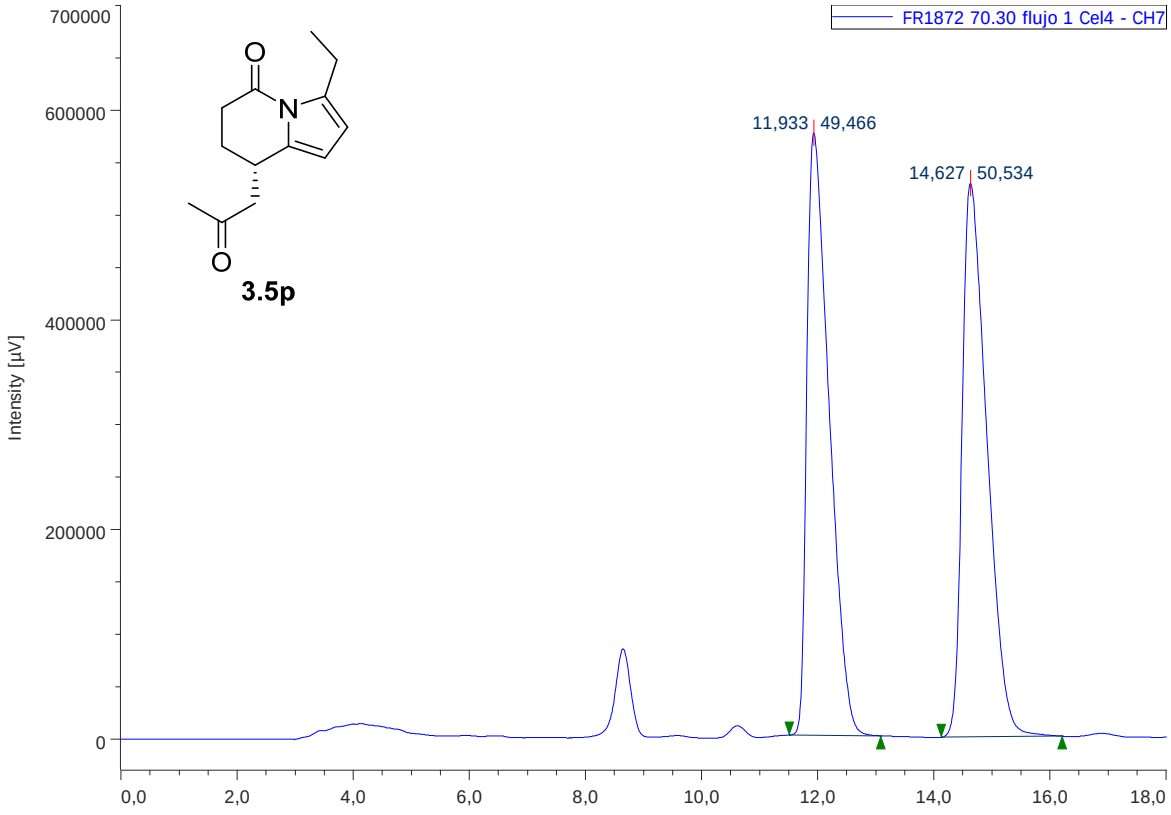

FR1753 90.10 flujo 1 AD - CH6
52,120
84,408
59,320
15,592
Intensity [µV]
300000
200000
100000
0
0,0
10,0
20,0
30,0
40,0
50,0
60,0
70,0
74,0

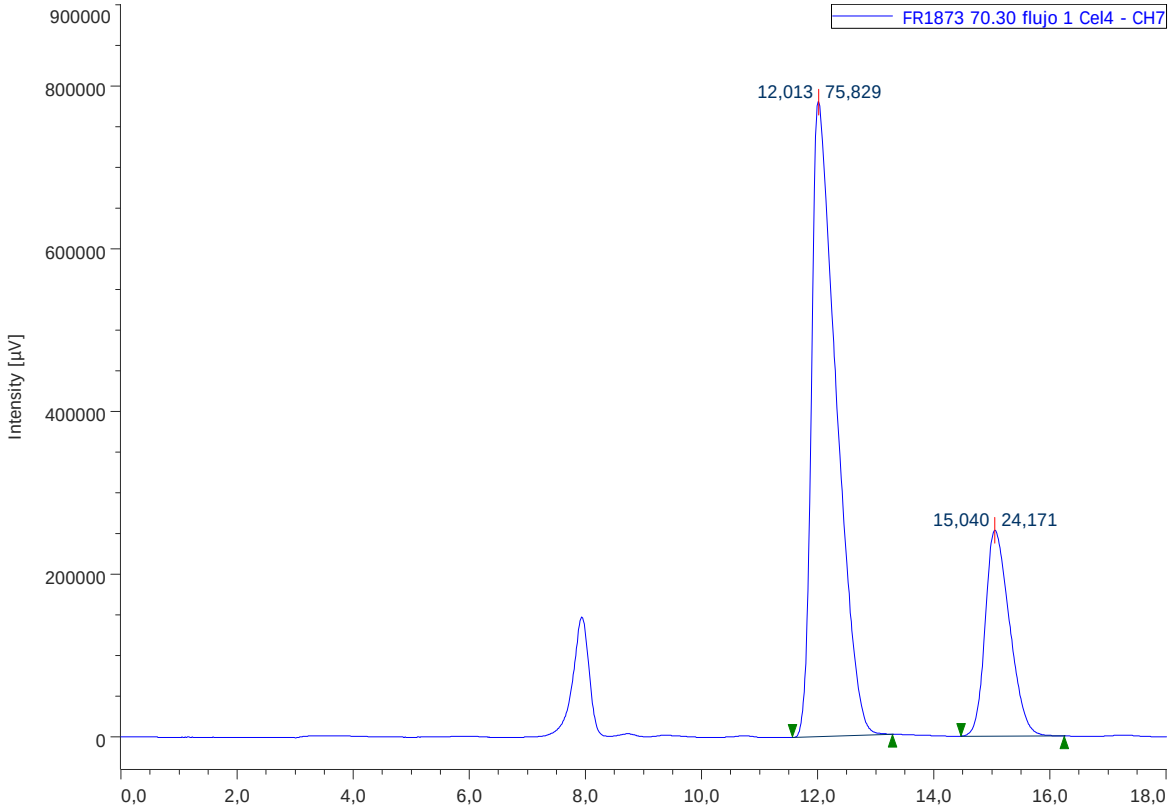

FR1744 70.30 flujo 1 Cel4 - CH8
14,453 49,752
29,213 50,248
EtO2C
EtO2C
O
N
O
3.5n
Intensity [µV]
150000
100000
50000
0
0,0
5,0
10,0
15,0
20,0
25,0
30,0
35,0
38,0


FR1752-2 70.30 flujo 1 Cel4 - CH8
29,133 65,500
14,773 34,500
Intensity [µV]
320000
300000
200000
100000
0
0,0
5,0
10,0
15,0
20,0
25,0
30,0
35,0
38,0


FR1838 70.30 flujo 1 Cel4 - CH7
10,640 49,834
21,187 50,166
Intensity [µV]
260000
200000
100000
0
0,0 2,0 4,0 6,0 8,0 10,0 12,0 14,0 16,0 18,0 20,0 22,0 24,0
O
N
O
3.5o


FR1842 70.30 flujo 1 Cel4 - CH7
10,440 84,288
21,240 15,712
Intensity [µV]
850000
800000
600000
400000
200000
0
0,0 2,0 4,0 6,0 8,0 10,0 12,0 14,0 16,0 18,0 20,0 22,0 24,0


FR1872 70.30 flujo 1 Cel4 - CH7
Intensity [µV]
700000
600000
400000
200000
0
11,933 49,466
14,627 50,534
0,0
2,0
4,0
6,0
8,0
10,0
12,0
14,0
16,0
18,0
O
N
O
3.5p


FR1873 70.30 flujo 1 Cel4 - CH7
Intensity [µV]
900000
800000
600000
400000
200000
0
12,013 75,829
15,040 24,171
0,0
2,0
4,0
6,0
8,0
10,0
12,0
14,0
16,0
18,0