VNIVERSITAT DE VALÈNCIA Facultat de Química

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REACCIONES DE CICLOADICIÓN FORMAL ENANTIOSELECTIVAS CON ISOCIANOACETATOS

Tesis Doctoral

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CERTIFICAN:

Que la presente Tesis Doctoral, titulada "**Reacciones de cicloadición formal enantioselectivas con isocianoacetatos**" ha sido realizada bajo su dirección en el Departamento de Química Orgánica de la Universitat de València por el graduado en química **D. Pablo Martínez Pardo** y autorizan su presentación para que sea calificada como Tesis Doctoral.

Agosto, 2020

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Índice

Lista de abreviaturas

En castellano:

acac	Acetilacetonato
AcOEt	Acetato de etilo
Ar	Aromático
bs	Singlete ancho
bd	Doblete ancho
Bn	Bencilo
Boc	*terc*-Butoxicarbonilo
BOX	Bisoxazolina
Bz	Benzoilo
c	Concentración
CAN	Nitrato amónico cérico
Cat	Catalizador
^{c}Pr	Ciclopropilo
d	Doblete
DCC	Diciclohexilcarbodiimida
DCM	Diclorometano
dd	Doble doblete
ddd	Doble doble doblete
DIAD	Diisopropil diazadicarboxilato
DMF	Dimetilformamida
DMAP	4-(dimetilamino)piridina
DMSO	Dimetilsulfóxido
DPPA	Difenilfosforil azida
dt	Doble triplete
ee	Exceso enantiomérico
equiv	Equivalentes
ESI	Ionización por electrospray
Et	Etilo

EtOH	Etanol
g	gramo
h	Hora
HCl	Ácido clorhídrico
Hal	Halógeno
HPLC	Cromatografía líquida de alta eficacia
HRMS	Espectrometría de masas de alta resolución
Hz	Hercio
^{i}Bu	Isobutilo
^{i}Pr	Isopropilo
^{i}PrOH	Isopropanol
J	Constante de acoplamiento
L	Litro
m	multiplete
M	Molar
Me	Metilo
MeOH	Metanol
mg	Miligramo
MHz	Megahercio
min	Minuto
mL	Mililitro
mmol	Milimol
mol	Mol
MTBE	Metil *terc*-butil éter
^{n}Bu	Butilo
NOE	Efecto Overhauser Nuclear
OC	Organocatalizador
Ph	Fenilo
PMB	Cloruro de *p*-metoxibenzoilo
PMP	*p*-Metoxifenilo

ppm	Partes por millón
Pr	Propilo
*p*TSA	Ácido *p*-toluensulfónico
q	Cuadruplete
SQ	Escuaramida
t.a.	Temperatura ambiente
TM	Tamiz molecular
Tol	Tolueno
rd	Relación diastereoisomérica
Rto	Rendimiento
RMN	Resonancia magnética nuclear
s	Singlete
t	Tiempo
t	Triplete
T	Temperatura
t_r	Tiempo de retención
TBAF	Fluoruro de tetrabutilamonio
^{t}Bu	*terc*-Butilo
THF	Tetrahidrofurano
TMS	Trimetilsililo
UV	Ultravioleta
vs	Versus
[α]	Rotación específica
Å	Armstrong
µL	Microlitro
δ	Desplazamiento químico
ºC	Grados centígrados

In english:

Ar	Aromatic
c	Concentration
bs	Broad singlet
bd	Broad doblet
d	Doblet
DCC	Dicyclohexilcarbodiimide
dd	Double doublet
ddd	Double double doublet
DEPT	Distertionless enhancement by polarization transfer
DMF	Dimethylformamide
DMAP	4-(Dimethylamino)pyridine
Ee	Enantiomeric excess
EtOAc	Ethyl acetate
equiv.	Equivalents
ESI	Electrospray ionization mass spectra
g	Grams
GC	Gas chromatography
Hz	Hertz
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
^{i}PrOH	Isopropanol
J	Chemical shift
m	Multiplet
M	Molar
min	Minutes
mL	Mililiter
mg	milligram
MHz	Megahertz
MTBE	Metil *tert*-butyl ether

NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
q	Quadruplet
s	Singlet
SQ	Squaramide
t	Time
t	Triplet
^{t}Bu	*tert*-Butyl
td	Triplet doublet
TLC	Thin layer chromatography
t_r	Retention time
µL	Microliter
[α]	Specific rotation

1. Introducción

La obtención de moléculas quirales con una estereoquímica definida es uno de los objetivos más fascinantes de la síntesis orgánica moderna. La orientación espacial de los átomos en las moléculas determina en gran medida la actividad de fármacos[1] y compuestos agroquímicos así como las propiedades de muchos materiales.[2] Esta necesidad de controlar la estereoquímica en las nuevas moléculas que se producen ha propiciado el desarrollo en las últimas décadas de nuevos métodos de síntesis enantioselectiva. Entre estos, cabe señalar la catálisis asimétrica caracterizada por el uso de catalizadores quirales que se utilizan en cantidades subestequiométricas respecto a las especies reaccionantes.[3] En este contexto, dos tipos de catálisis han resultado especialmente productivas: la catálisis mediante metales y la organocatálisis. La primera dominó el área de la catálisis asimétrica entre las décadas de los 80 y 90 del siglo XX y se basaba en la utilización de complejos de metales con ligandos orgánicos quirales.[4] Durante las dos últimas décadas, la investigación ha estado especialmente centrada en la organocatálisis que utiliza moléculas orgánicas como catalizadores, en general, en condiciones operacionales más sencillas que la catálisis metálica.[5]

Ambas metodologías han permitido obtener grandes logros en la síntesis de moléculas quirales. Sin embargo, todavía persisten limitaciones y oportunidades de mejora en términos de alcance, estereoselectividad (diastereo- y enantioselectividad), economía atómica, consumo de energía o producción de residuos. Una posibilidad para expandir el espectro de aplicación de la catálisis asimétrica consiste en el uso de sistemas multicatalíticos[6,7] en los que dos catalizadores, al menos uno de ellos quiral, actúan conjuntamente permitiendo nuevos modos de activación que dan lugar a reactividades no accesibles con un único catalizador. Según la naturaleza de los centros catalíticos podemos distinguir entre: a) sistemas multimetálicos (ambos centros catalíticos son metálicos); b) sistemas orgánicos (ambos centros catalíticos son grupos funcionales orgánicos y no participan metales); y c) sistemas mixtos (un centro catalítico es un metal y el otro un grupo funcional orgánico).

Por otra parte, los heterociclos nitrogenados de cinco miembros quirales se encuentran ampliamente extendidos en química orgánica. Sus estructuras forman parte de las moléculas de productos naturales y otros compuestos que muestran una amplia gama de actividades biológicas y farmacéuticas.[8,9] Como por ejemplo el insecticida etoxazol,[10] el metabolito marino westielamida,[11] el alcaloide citotóxico 4,5-dihidro-6'-desoxibromotopsentina,[12] el inhibidor del proteasoma lactacistina,[13] o el antagonista del receptor de vasopresina V1b nelivaptan,[14] entre muchos otros (**Figura 1**).

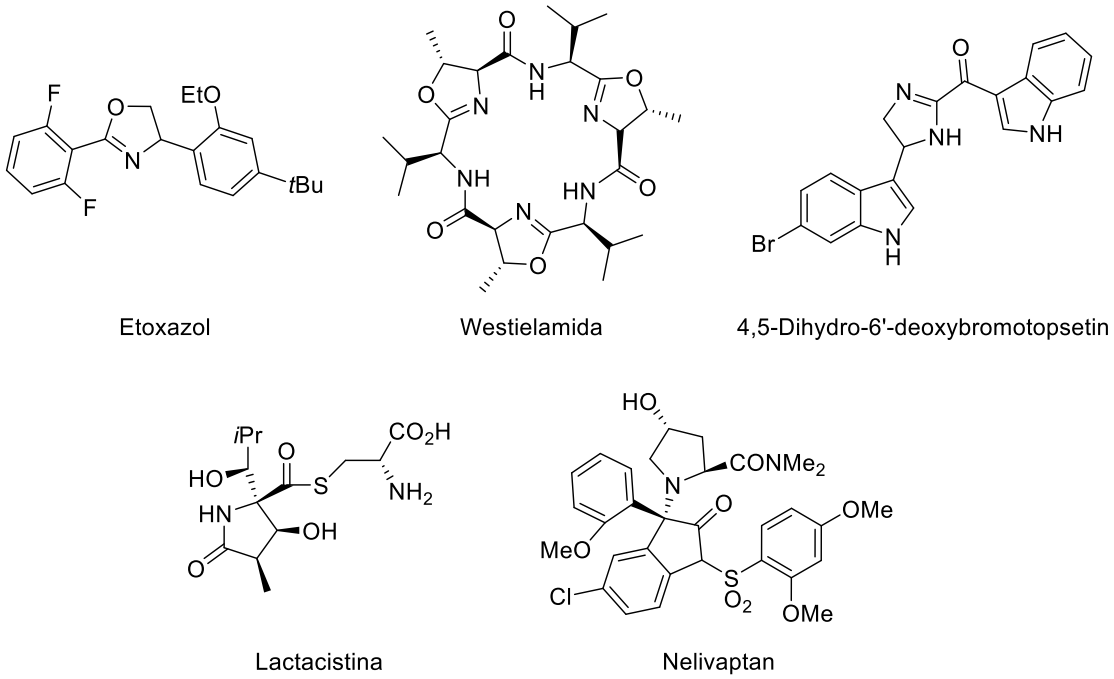


Figura 1. Ejemplos de productos naturales y compuestos activos que presentan un heterociclo nitrogenado quiral.

Estos heterociclos también son intermedios sintéticos de uso generalizado en síntesis orgánica y ligandos para complejos metálicos. De acuerdo con esto, el desarrollo de nuevos métodos sintéticos para su obtención de manera estereoselectiva es de gran interés en química orgánica y química médica.[15,16] Entre las muchas rutas sintéticas estereoselectivas disponibles para estos compuestos, la reacción de cicloadición 1,3-dipolar constituye uno de los enfoques más atractivos, dada la variedad de dipolos y dipolarófilos que pueden emplearse, permitiendo el acceso a una amplia gama de heterociclos con uno o más heteroátomos. Desde un punto de vista sintético, las reacciones de cicloadición 1,3-dipolar son útiles no solo para síntesis de compuestos heterocíclicos sino también para la formación de enlaces C–C, pudiéndose formar hasta cuatro centros estereogénicos y dos enlaces C–C simultáneamente. Se trata, además, de reacciones átomo-económicas en las que, normalmente, todos los átomos de las especies reaccionantes se incorporan al producto de reacción. Entre los dipolos utilizados en reacciones de cicloadición enantioselectivas destacan los iluros de azometino, y en menor medida los óxidos de nitrilo, diazoalcanos e iluros de carbonilo.[17]

A este respecto, algunos compuestos con un grupo isocianuro han ganado importancia como posibles 1,3-dipolos formales. Los isocianuros son sintones muy versátiles en síntesis orgánica debido a su estado de valencia y reactividad inusuales. La estructura electrónica del grupo isocianuro se puede representar mediante dos formas resonantes una de tipo carbénica y la otra de tipo zwitteriónica (**Figura 2**).

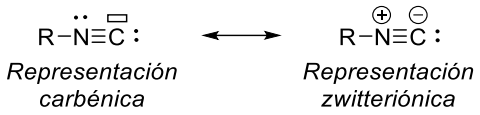
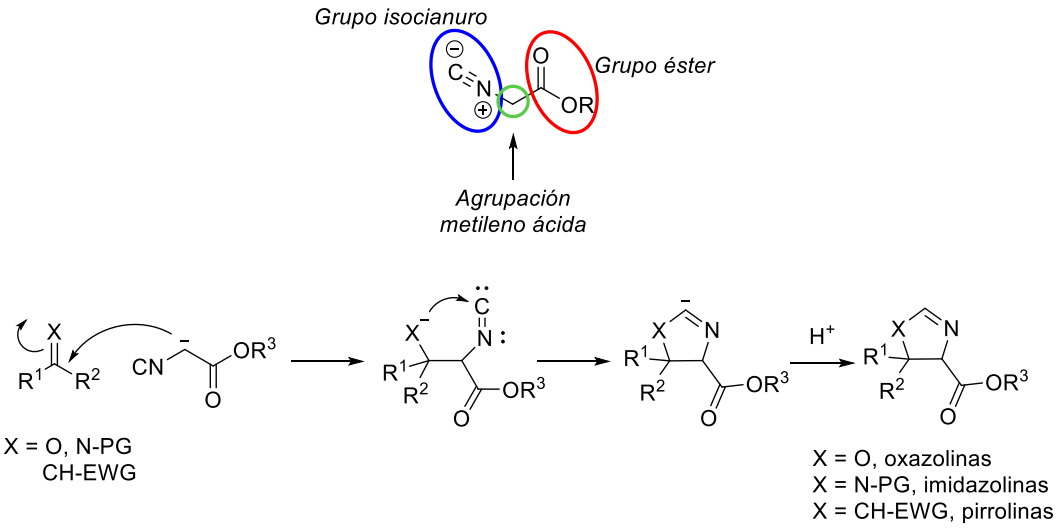


Figura 2. Formas resonantes de los isocianuros.

Esta estructura electrónica es responsable de una de las características más representativas de los isocianuros, consistente en su capacidad de reaccionar tanto con nucleófilos como con electrófilos en el carbono del isocianuro, una característica que se ha explotado a fondo en el desarrollo de reacciones de múltiples componentes. Otra característica importante de los isocianuros es su acidez en α, que puede incrementarse mediante la presencia de sustituyentes electronaceptores, tales como ésteres, nitrilos, ésteres fosfóricos o grupos sulfonilo. Entre estos, los derivados de isocianoacetato ocupan un lugar importante en la síntesis de *aza*-heterociclos. Así, la adición nucleofílica de un carbanión de un α-isocianoéster a un grupo insaturado electrofílico (carbonilo, imina, doble enlace electrofílico) conduce a un nuevo anión que tiende a ciclar mediante la adición del par de electrones aniónico al orbital vacío del isocianuro, dando lugar a un heterociclo de cinco miembros, en una reacción que puede considerarse formalmente como una cicloadición [3 + 2] (**Esquema 1**).[18]



Esquema 1. Características de los isocianoacetatos y cicloadición formal [3+2]

En esta tesis se plantea el desarrollo de diversas reacciones de cicloadición formal [3+2] enantioselectiva con derivados de isocianoacetato para la obtención de estructuras heterocíclicas quirales utilizando un sistema catalítico dual que combina la organocatálisis con derivados de alcaloides de la *cinchona* y sales metálicas como el óxido de plata.

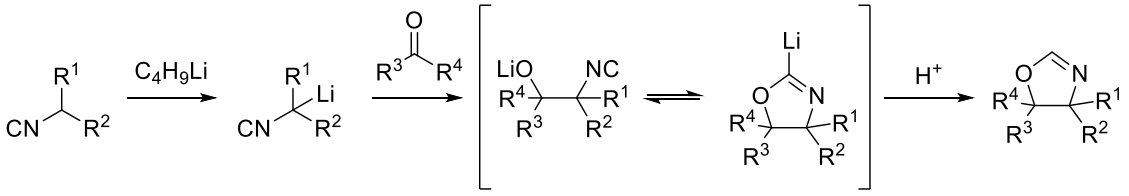
2. Antecedentes bibliográficos

En este capítulo se lleva a cabo una revisión de las reacciones que implican la adición de isocianoacetatos a diferentes electrófilos de forma enantioselectiva para la generación de nuevas moléculas quirales de interés en química orgánica, principalmente compuestos que contienen un heterociclo nitrogenado (*aza*-heterociclos).

2.1 Síntesis enantioselectiva de 2-oxazolinas a partir de compuestos carbonílicos

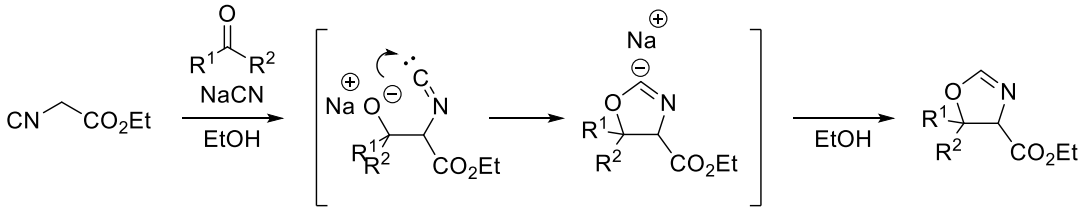
Las 2-oxazolinas son heterociclos de cinco miembros que presentan un átomo de oxígeno y uno de nitrógeno en las posiciones 1 y 3, además, en las 2-oxazolinas, encontramos un doble enlace entre el carbono en posición 2 del ciclo y el átomo de nitrógeno. Este tipo de estructura está muy extendida en productos naturales, fármacos y productos agroquímicos, pudiéndose encontrar también en ligandos para la catálisis asimétrica y en intermedios sintéticos para la obtención de 1,2-aminoalcoholes.

La primera síntesis de este tipo de compuestos empleando isocianoacetatos fue descrita por Schöllkopf en 1968. La reacción requiere condiciones fuertemente básicas para conseguir la desprotonación en posición α al grupo isocianuro, utilizando un reactivo organolítico como base (**Esquema 2**).[19]



Esquema 2. Formación de oxazolinas a partir de isocianuros de alquilo y cetonas utilizando un reactivo organolítico como base.

En 1970, el mismo autor describió la síntesis de 2-oxazolinas, pero esta vez utilizando un isocianoacetato, donde la presencia del grupo éster facilita la desprotonación en alfa, consiguiendo llevar a cabo la reacción en condiciones más suaves, en presencia de una cantidad catalítica de cianuro como base (**Esquema 3**). La reacción conduce a la oxazolina *trans* como producto mayoritario.[20]



Esquema 3. Primera síntesis de 2-oxazolinas empleando un isocianoacetato y un compuesto carbonílico.

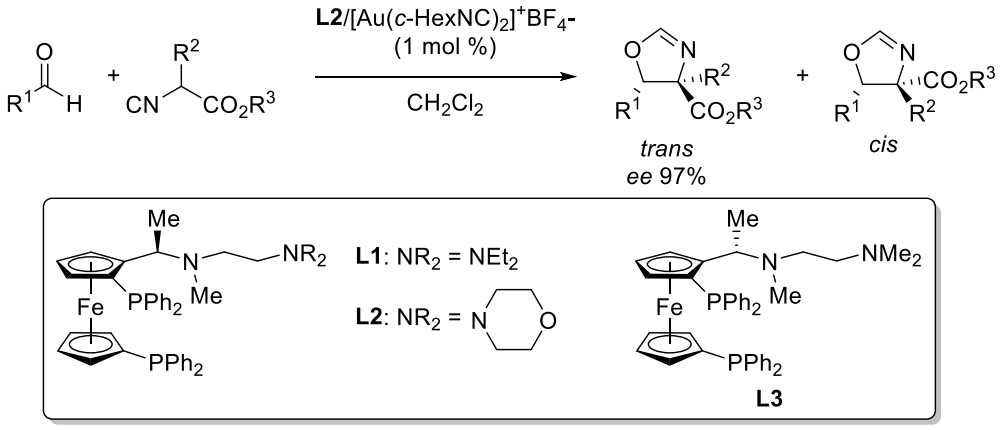
Esta reacción de cicloadición [3+2] formal transcurre en dos etapas, la primera de ellas consiste en la adición aldólica del enolato del isocianoacetato al compuesto carbonílico, y la segunda etapa consiste en la adición intramolecular del alcóxido generado sobre el orbital vacío del grupo isocianuro.

Desde esta primera síntesis, se han desarrollado numerosos protocolos para la realización de esta reacción de forma enantioselectiva, haciendo uso de diferentes condiciones de reacción y catalizadores; primero con aldehídos y más recientemente con cetonas.

2.1.1 Reacciones enantioselectivas de isocianoacetatos con aldehídos

2.1.1.1 *Reacciones catalizadas por oro y plata*

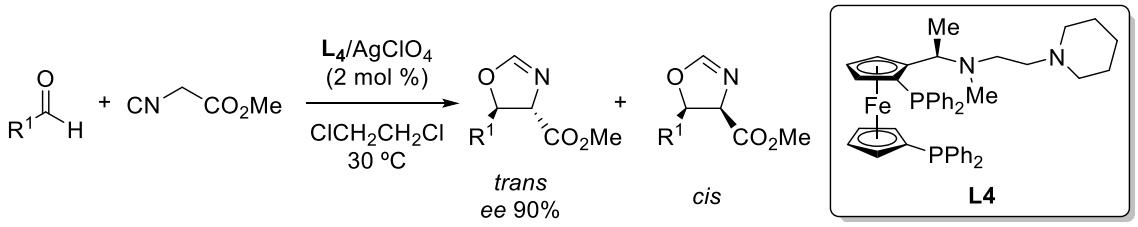
La primera síntesis enantioselectiva fue descrita por Ito y Hayashi en 1986, utilizando un complejo quiral de oro generado *in situ* a partir de tetrafluoroborato de bis(ciclohexilisocianuro)oro (I) y un ligando de tipo (*R*)-*N*-metil-*N*-[2-(dialquilamino)etil]-l-[(*S*)-l,2-bis(difenilfosfino)ferrocenil]etilamina (**Esquema 4**).[21]



Esquema 4. Primera síntesis enantioselectiva de 2-oxazolinas a partir de aldehídos e isocianoacetatos.

El complejo formado con el ligando **L2**, el cual tiene un grupo morfolina al final de la cadena alifática, proporcionó los mejores resultados, dando la oxazolina *trans* como producto mayoritario, con alto rendimiento y excesos enantioméricos de hasta el 97%.

Más tarde, en el año 1991, Hayashi estudió la reacción entre aldehídos e isocianoacetato de metilo utilizando un complejo de plata preparado a partir de perclorato de plata y el ligando **L4**, llevando a cabo una adición lenta del isocianoacetato a una disolución del aldehído en dicloroetano a 30 °C. Se obtuvieron las oxazolinas *trans* como producto mayoritario y con unos excesos enantioméricos de hasta el 90% (**Esquema 5**).[22]



Esquema 5. Formación de sistemas de 2-oxazolina catalizadas por plata.

2.1.1.2 *Reacciones catalizadas por platino y paladio*

La adición aldólica de isocianoacetato de metilo a aldehídos para la generación de 2-oxazolinas también ha sido estudiada empleando como catalizadores diversos complejos de platino y paladio con ligandos quirales tridentados PCP y NCN (**Figura 3**).

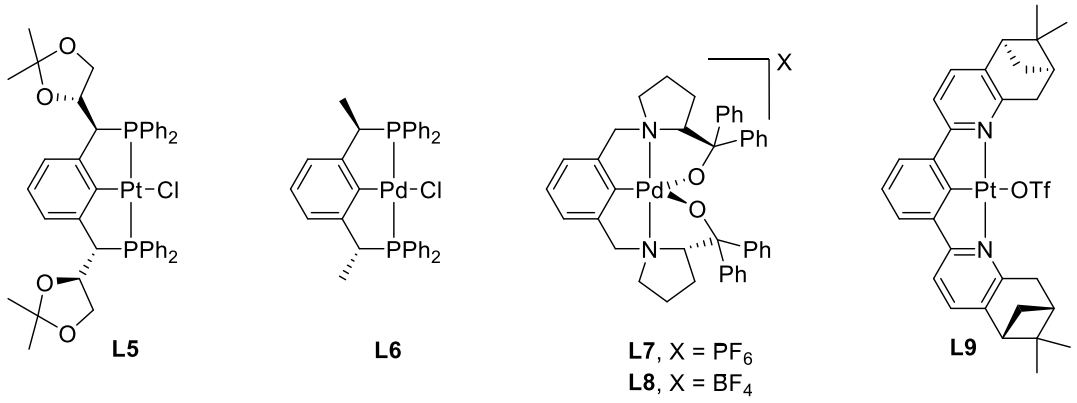


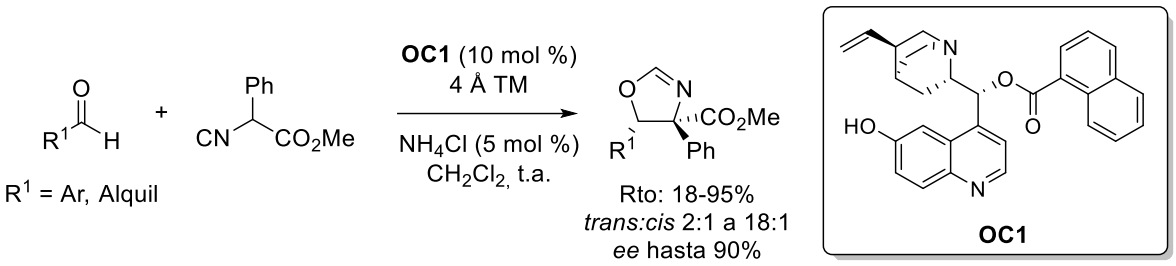
Figura 3. Complejos de platino y paladio ensayados en la reacción enantioselectiva de aldehídos e isocianoacetato de metilo.

Los intentos de llevar a cabo esta reacción de forma enantioselectiva con este tipo de complejos metálicos ha dado como resultado bajos excesos enantioméricos en todos los casos. El complejo terdentado de platino **L5** fue sintetizado y utilizado por Venanzi,[23] proporcionando diastereoselectividades *trans*:*cis* desde 56:44 hasta 93:7 y excesos enantioméricos de hasta el 64% para la oxazolina *trans* y del 32% para la *cis*. De forma similar, el complejo de paladio **L6**[23] proporcionó las oxazolinas *trans*:*cis* con relaciones diastereoisoméricas entre 45:55 y 91:9, pero con mayores excesos enantioméricos (hasta 77%) para el diastereoisómero minoritario *cis* que para el diastereoisómero mayoritario *trans* (hasta 31%).

Por su parte, los complejos de tipo NCN de paladio y platino **L7-L9** fueron capaces de promover la reacción, pero con bajas diastereoselectividades y bajos excesos enantioméricos en todos los casos.[24,25]

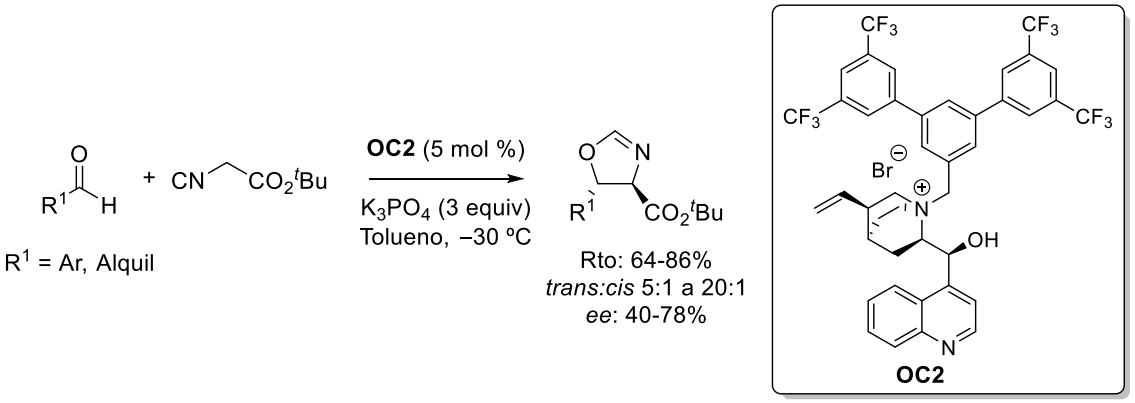
2.1.2 Reacciones organocatalíticas

El primer ejemplo enantioselectivo organocatalítico fue descrito por Guo en 2009 empleando un éster de cupreína como catalizador **OC1** en la reacción de adición de 2-fenil-2-isocianoacetato de metilo a diferentes aldehídos (**Esquema 6**). Como producto, se obtuvieron las oxazolinas con un centro estereogénico cuaternario en posición 4 con excelentes diastereoselectividades *trans:cis* (18:1) y elevados excesos enantioméricos (hasta 90%).[26]



Esquema 6. Cicloadición formal [3+2] entre aldehídos e isocianoacetatos catalizada por un éster de cupreína.

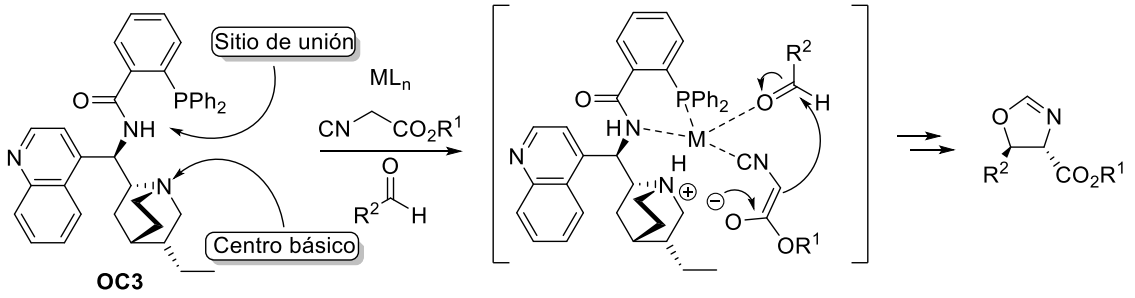
En 2016 se describió la síntesis de 2-oxazolinas utilizando un catalizador de transferencia de fase (*Phase-Transfer Catalysis, PTC*) derivado de cinchonina llevando a cabo la reacción a −30 °C en tolueno en presencia de tres equivalentes de K_3PO_4. Los productos de reacción se obtuvieron con buena diastereoselectividad y moderado exceso enantiomérico (**Esquema 7**).[27]



Esquema 7. Reacción organocatalítica promovida por un catalizador de transferencia de fase.

2.1.3 Catálisis cooperativa metal/orgánica

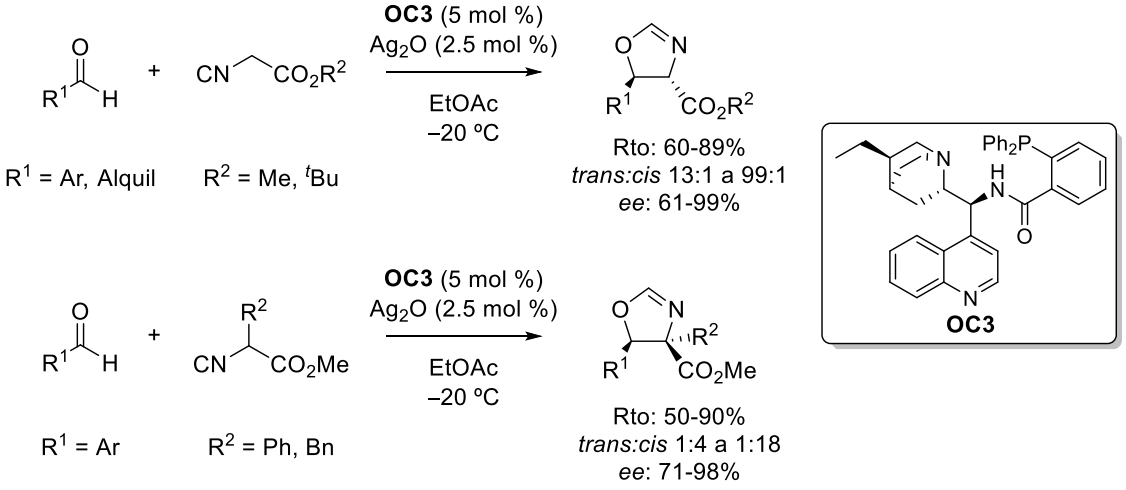
En el año 2011, Dixon describió un sistema catalítico cooperativo para la cicloadición formal [3+2] de isocianoacetatos y aldehídos. El sistema combina un pre-catalizador con una amidofosfina con el esqueleto quiral del alcaloide 9-amino(9-desoxi)epicinchonidina **OC3** y óxido de plata (**Esquema 8**).[28]



Esquema 8. Sistema catalítico diseñado por Dixon.

Los autores previeron que la diferencia de carácter duro/blando de las dos bases de Lewis existentes en el organocatalizador, debía permitir una unión selectiva del catión de plata con la fosfina, dejando la amina del anillo de quinuclidina libre, pudiendo así actuar

como base en la reacción de interés. Mediante este sistema catalítico se obtuvieron las oxazolinas *trans* con excelentes diastereo- y enantioselectividades. Pese a los buenos resultados obtenidos con aldehídos aromáticos, el uso de aldehídos alifáticos en la reacción proporcionó las oxazolinas con un pobre enantiocontrol (**Esquema 9**).



Esquema 9. Síntesis enantioselectiva de oxazolinas mediante catálisis dual.

El sistema catalítico admite el uso de isocianoacetatos con un sustituyente en posición α a los grupos isocianuro y éster, obteniéndose las oxazolinas *cis*, con un centro estereogénico cuaternario, de forma mayoritaria con excelentes resultados de diastereoselectividad y altos excesos enantioméricos.

Simultáneamente al trabajo descrito por Dixon, el grupo de Oh diseñó otro sistema catalítico cooperativo que combina CoI_2, un amino alcohol quiral **OC4** y una tiourea aquiral **OC5** (**Figura 4**).[29] La reacción se llevó a cabo empleando también DBU como base en THF. Se obtuvieron las oxazolinas *trans* con excelentes relaciones diastereoisoméricas (>20:1) y enantioselectividades (90-98% ee). Sin embargo, el uso de aldehídos heteroaromáticos, alifáticos voluminosos o benzaldehídos sustituidos en las posiciones *orto* y *meta* suponen una limitación al método catalítico ya que los productos de cicloadición se obtienen con menor exceso enantiomérico (20-50%).

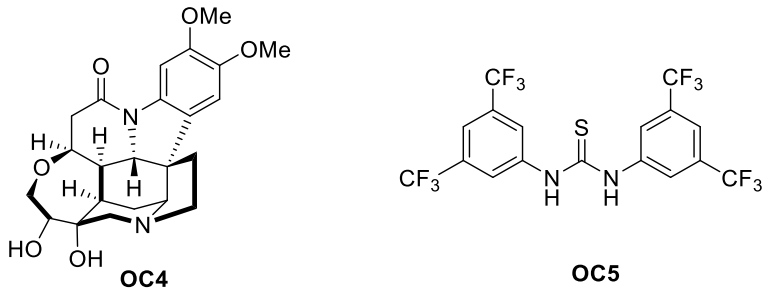


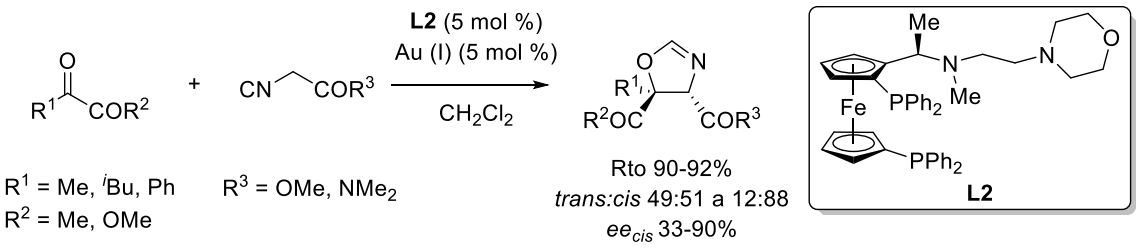
Figura 4. Aminoalcohol quiral y tiourea aquiral empleadas por Oh.

2.2 Reacciones enantioselectivas de isocianoacetatos con cetonas

2.2.1 *Reacciones enantioselectivas con compuestos 1,2-dicarbonílicos*

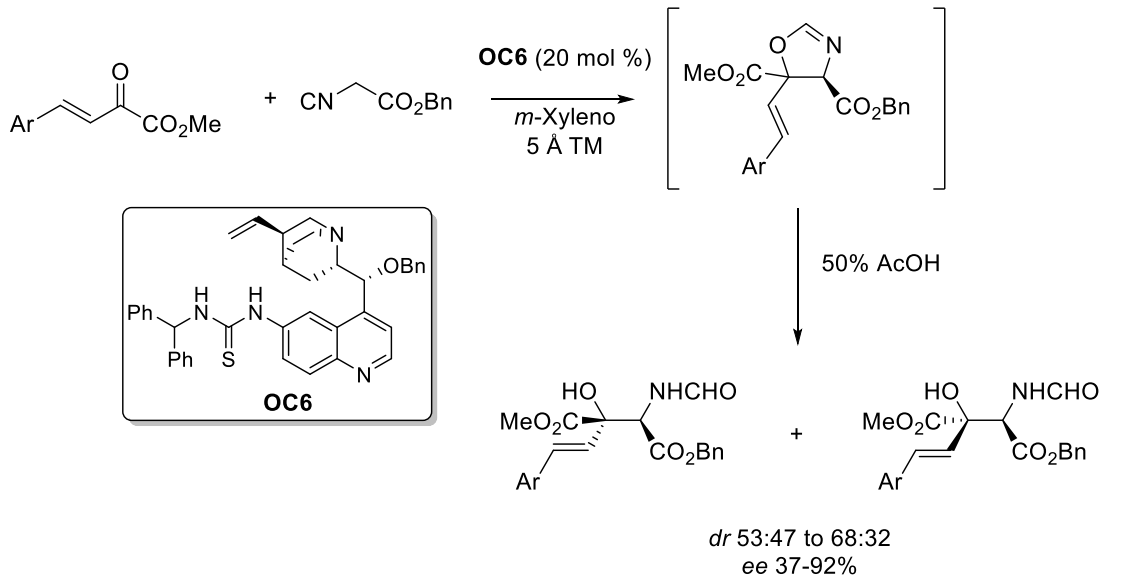
La primera cicloadición de un isocianoacetato con una cetona (α-cetoéster) de forma enantioselectiva fue descrita por Ito y Hayashi en 1989,[30] utilizando como

catalizador un complejo de oro similar al empleado por los mismos autores en la reacción con aldehídos (**Esquema 10**). La reacción es compatible con isocianoacetatos e isocianoacetamidas obteniendo mejores resultados con estas últimas. Se obtiene como producto mayoritario de reacción el isómero *cis* con diastereoselectividades y enantioselectividades moderadas



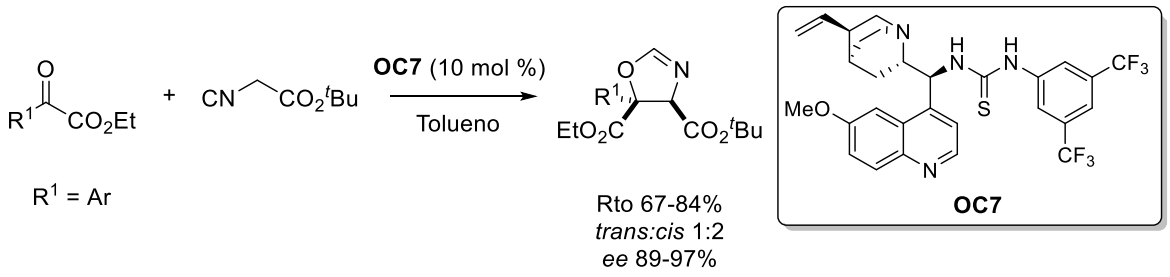
Esquema 10. Primera adición enantioselectiva de isocianoacetatos a cetonas.

Por otra parte, la primera adición enantioselectiva a α-cetoésteres β,γ-insaturados mediante organocatálisis fue llevada a cabo por el grupo de Lu en 2014 (**Esquema 11**).[31] Para ello se utilizó una tiourea bifuncional **OC6** derivada de un alcaloide de la cinchona. Las oxazolinas formadas no fueron aisladas y, después de hidrólisis ácida en el propio medio de reacción, permitieron obtener derivados de β-hidroxi-α-aminoácidos con diastereoselectividad baja y enantioselectividad moderada.



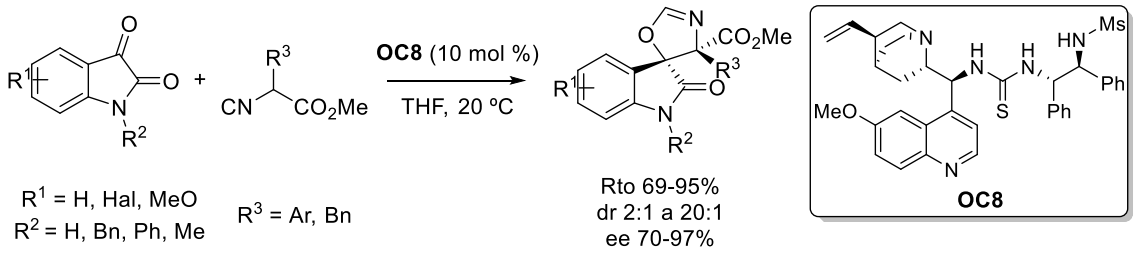
Esquema 11. Reacción aldólica enantioselectiva de isocianoacetato de bencilo con α-cetoésteres β,γ-insaturados.

En el año 2017, Wang describió otro ejemplo de adición enantioselectiva de isocianoacetatos a α-cetoésteres (**Esquema 12**).[32] El uso de un catalizador bifuncional de tipo tiourea **OC7** derivado de quinina y 3,5-bis(trifluorometil)anilina permitió la obtención de oxazolinas *cis* con buenos rendimientos y excesos enantioméricos, aunque con baja diastereoselectividad.



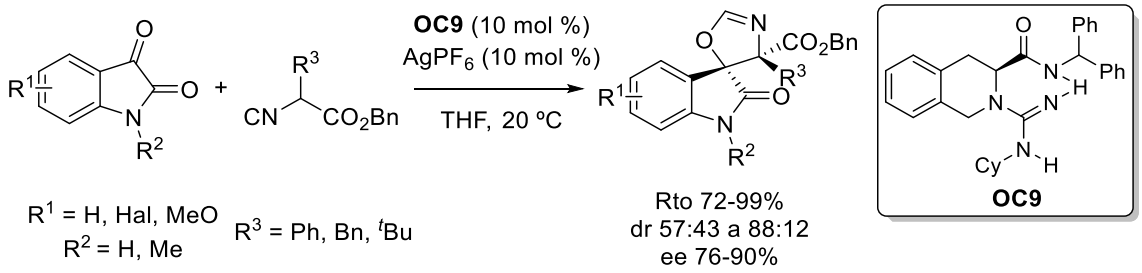
Esquema 12. Obtención de oxazolinas *cis* a partir de α-cetoésteres e isocianoacetato de *terc*-butilo descrita por Wang.

Zhao, describió en el año 2013, la formación de oxazolinas espirocíclicas a partir de isatinas e isocianoacetatos sustituidos en la posición α. Para ello empleó un organocatalizador quiral de tipo tiourea capaz de activar el sustrato mediante enlaces de hidrógeno (**Esquema 13**).[33] Los espirociclos se obtuvieron en general con buenos rendimientos, diastereoselectividad entre moderada y buena y buenos excesos enantioméricos, si bien, la reacción funciona mejor cuando las isatinas están sustituidas con grupos aceptores de electrones. El uso de otros isocianuros no sustituidos en posición alfa, proporcionó pobres diastereoselectividades y enantioselectividades.



Esquema 13. Reacción entre isatinas e isocianoacetatos catalizada por una tiourea quiral.

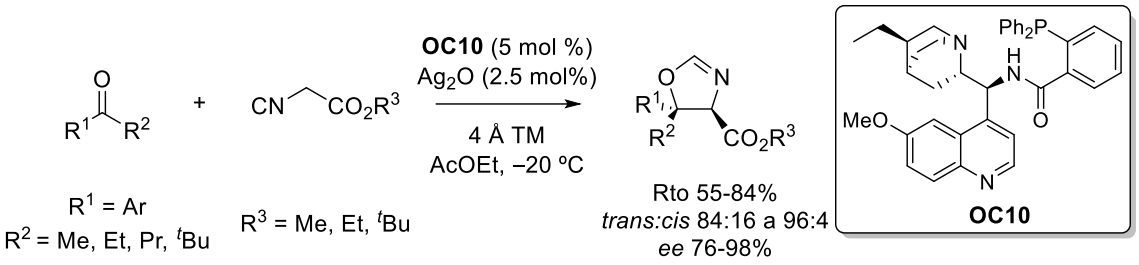
Posteriormente, en 2015, Feng publicó una síntesis similar de oxazolinas espirocíclicas a partir de isatinas, utilizando un sistema catalítico basado en una guanidina **OC9** y una sal de plata (I), lo que permitió la obtención de los espirociclos de oxazolina con rendimientos de hasta el 99%, de moderada a buena diastereoselectividad y excesos enantioméricos de hasta el 90% (**Esquema 14**).[34] Igual que ocurre en el sistema descrito anteriormente por Zhao, los isocianoacetatos sustituidos en posición alfa funcionan mejor que los no sustituidos.



Esquema 14. Síntesis de oxazolinas espirocíclicas catalizadas por un sistema catalítico de guanidina-Ag(I)

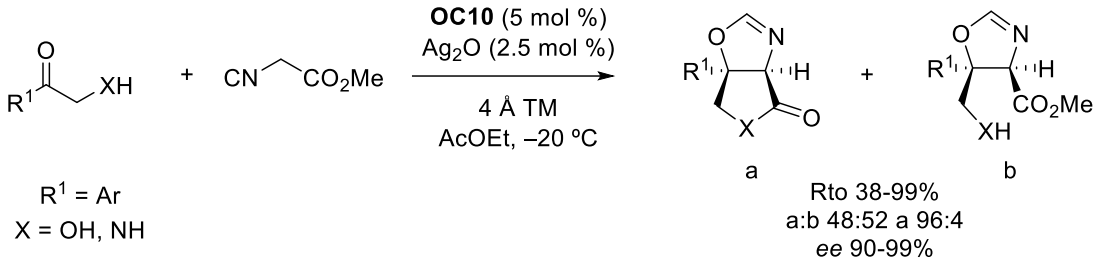
2.2.2 *Reacciones enantioselectivas con cetonas no activadas*

Tan solo existen dos ejemplos de adición de isocianoacetatos a cetonas no activadas, ambos descritos por el grupo Dixon en 2015 y 2018. El sistema catalítico es similar al utilizado anteriormente en su trabajo con aldehídos, pero con un ligando diferente, derivado esta vez de dihidroquinina (**Esquema 15**).[35] En el primer ejemplo, la reacción proporciona las oxazolinas *trans* como producto mayoritario de reacción, con un centro estereogénico cuaternario en posición alfa al oxígeno. Se obtienen las oxazolinas con buenos rendimientos, diastereoselectividades y altos excesos enantioméricos.



Esquema 15. Síntesis de oxazolinas con un centro estereogénico cuaternario a partir de cetonas descrita por Dixon.

En el segundo trabajo, se describe la adición de isocianoacetatos a α-hidroxy y α-amino cetonas para la obtención de productos bicíclicos con un sistema de oxazolina fusionado a un sistema de lactona o lactama en función del sustituyente en beta de la cetona (**Esquema 16**).[36]



Esquema 16. Anillos de oxazolina fusionado con lactamas o lactonas.

La reacción proporciona mezclas de los productos bicíclico (a) y monocíclico (b), siendo mayoritario en casi todos los casos el producto bicíclico. Los rendimientos son moderados y en todos los casos los productos se obtienen con alto exceso enantiomérico.

2.3 Síntesis enantioselectiva de 2-imidazolinas a partir de iminas

Las 2-imidazolinas son heterociclos de cinco miembros que contienen dos átomos de nitrógeno en las posiciones 1 y 3, además de un doble enlace entre las posiciones 2 y 3 del anillo. La síntesis de este tipo de productos de forma enantioselectiva es una investigación atractiva ya que su estructura está presente en productos naturales, auxiliares quirales o en ligandos quirales. Además, estos anillos son "*building blocks*" ideales para la preparación de moléculas biológicamente activas, como pueden ser los α,β-diaminoácidos y sus derivados.

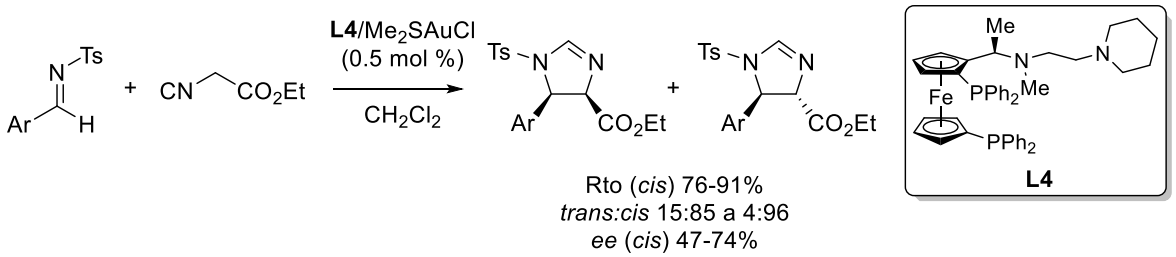
En los últimos años se han desarrollado diversos métodos catalíticos con el fin de obtener este tipo de productos, de entre ellos, la adición de isocianoacetatos a iminas se

ha demostrado como uno de los métodos más interesantes por su sencillez y economía atómica.

2.3.1 Reacciones enantioselectivas de α-isocianoésteres con aldiminas

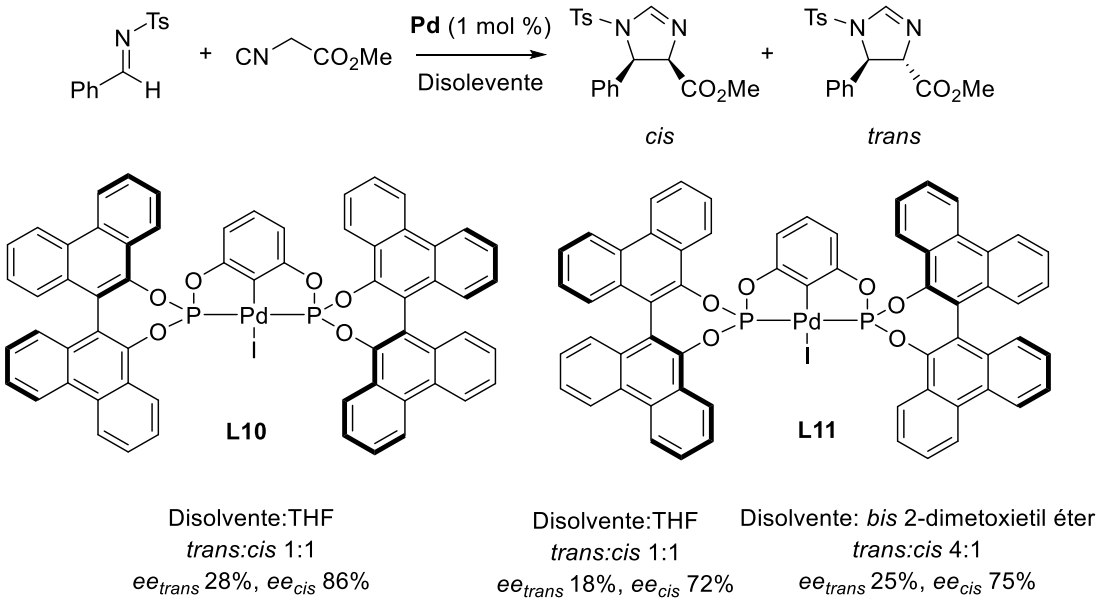
2.3.1.1 *Reacciones catalizadas por metales*

El primer ejemplo de adición de isocianoacetatos a aldiminas de forma enantioselectiva fue descrito por Lin en 1999, utilizando un complejo de oro generado *in situ* a partir del complejo Me_2SAuCl y el ligando quiral de ferrocenilfosfina **L4** (**Esquema 17**).[37] La reacción permite la obtención de 2-imidazolinas *cis* como producto mayoritario y proporciona buenos rendimientos de reacción, sin embargo, los excesos enantioméricos de los productos son entre bajos y moderados, aunque pueden incrementarse hasta un 99% tras una cristalización.



Esquema 17. Primera síntesis enantioselectivas de 2-imidazolinas a partir de isocianoacetatos y aldiminas descrita por Lin.

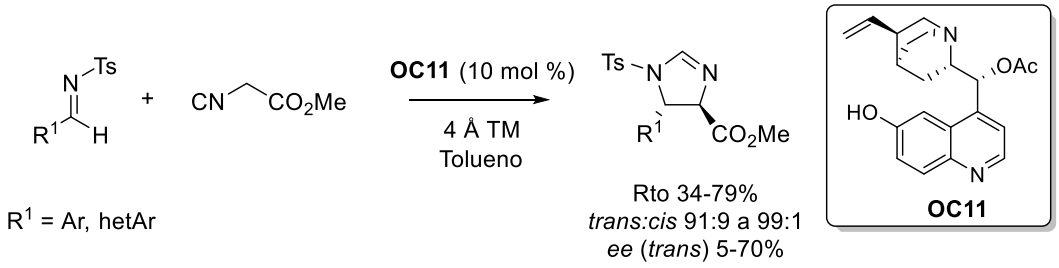
Más tarde, el grupo de Szabó describió el uso de complejos de paladio con ligandos quirales de tipo pinza **L10** y **L11** para la adición enantioselectiva de isocianoacetatos a *N*-tosil benzaldimina (**Esquema 18**).[38] Con el ligando **L10** en THF como disolvente de reacción se obtuvieron las 2-imidazolinas *cis* como producto mayoritario con excesos enantioméricos de hasta el 86%, pero con nula diastereoselectividad. El complejo con el ligando **L11** en THF proporcionó los productos de cicloadición con menor exceso enantiomérico (72%), sin embargo, cambiando este disolvente por *bis* 2-dimetoxietil éter, se obtuvieron los productos con mayor diastereoselectividad, favoreciendo el isómero *trans* (4:1) y con similares excesos enantioméricos (75%).



Esquema 18. Síntesis de 2-imidazolinas catalizada por complejos de paladio.

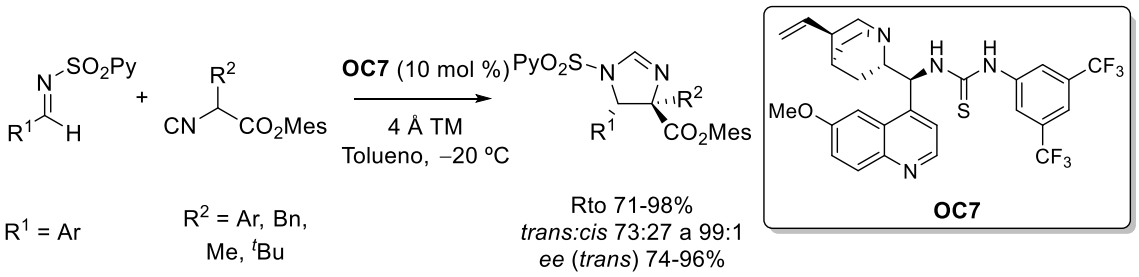
2.3.1.2 *Reacciones organocatalíticas*

En 2010, el grupo de Lu describió la primera adición organocatalítica enantioselectiva de isocianoacetatos a aldiminas con organocatálisis (**Esquema 19**).[39] Los autores utilizaron un éster de cupreidina para obtener los productos de reacción con rendimientos moderados, excelentes diastereoselectividades y moderados excesos enantioméricos. La adición de tamiz molecular aceleró la reacción permitiendo además obtener enantioselectividades significativamente mayores.



Esquema 19. Primera síntesis organocatalítica de 2-imidazolinas descrita por Lu.

Por su parte, Nakamura y Shibata describieron la primera adición enantioselectiva de isocianoacetatos alfa sustituidos a *N*-sulfonil iminas para la síntesis de 2-imidazolinas con un centro estereogénico cuaternario. Los autores emplearon un organocatalizador bifuncional de tipo tiourea derivado de quinina **OC7**, tamiz molecular, tolueno como disolvente y una temperatura de −20 °C, lo que permitió la obtención de las 2-imidazolinas con buen rendimiento, moderada a excelente diastereoselectividad y de buenos a excelentes excesos enantioméricos (**Esquema 20**).[40]

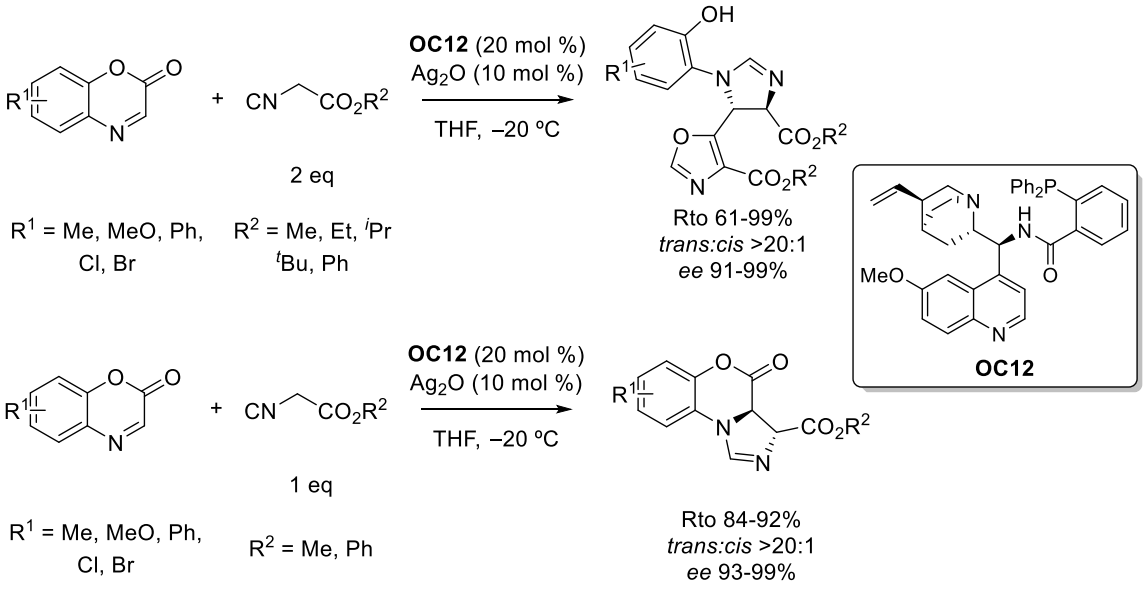


Esquema 20. Reacción organocatalítica para la síntesis de 2-imidazolinas con un centro cuaternario.

El grupo protector de la imina juega un papel crucial en la reacción, obteniéndose los mejores resultados cuando este es un grupo 2-piridinosulfonilo. Igualmente, el grupo éster del isocianuro resulta importante de forma que los mejores resultados se obtienen con ésteres de 2,4,6-trimetilfenilo (Mes). Además, la presencia de tamiz molecular proporciona un aumento de la relación diastereoisomérica sin mermar el exceso enantiomérico.

2.3.1.3 *Catálisis cooperativa metal/orgánica*

Zhao y colaboradores describieron en 2014 una interesante metodología para la síntesis de un sistema de 2-imidazolina y oxazol unidos por un enlace carbono-carbono empleando el sistema catalítico diseñado por Dixon. La reacción requiere el uso de dos equivalentes de isocianoacetato y tiene lugar de forma secuencial, una vez formado el anillo de 2-imidazolina, se adiciona sobre el grupo éster otra molécula de isocianoacetato para formar el oxazol. Los autores optimizaron también la reacción para la obtención del anillo de 2-imidazolina fusionado al sustrato de partida empleando un solo equivalente de isocianoacetato (**Esquema 21**).[41]



Esquema 21. Reacción de doble de cicloadición [3+2] diastereo y enantioselectiva.

En ambos casos, los productos se obtuvieron con excelentes resultados en cuanto a rendimiento, diastereoselectividad y enantioselectividad, sin embargo, cuando se ensayó

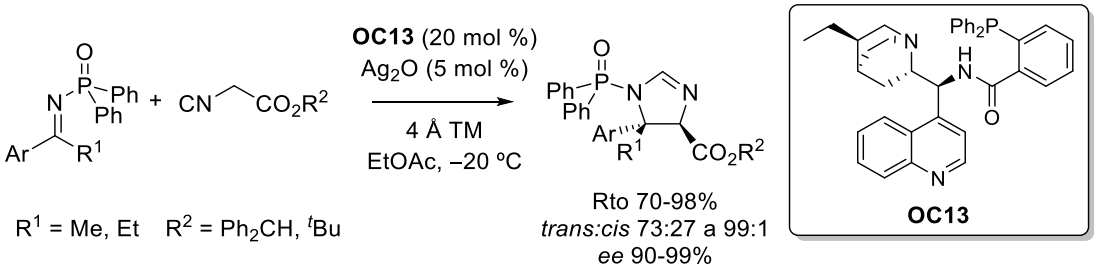
la reacción con un derivado de cetimina se obtuvo mayoritariamente el producto *cis* con buena diastereoselectividad, pero con un rendimiento bajo y pobre enantioselectividad.

2.3.2 Reacciones enantioselectivas de α-isocianoésteres con cetiminas

2.3.2.1 *Reacciones enantioselectivas con cetiminas acíclicas*

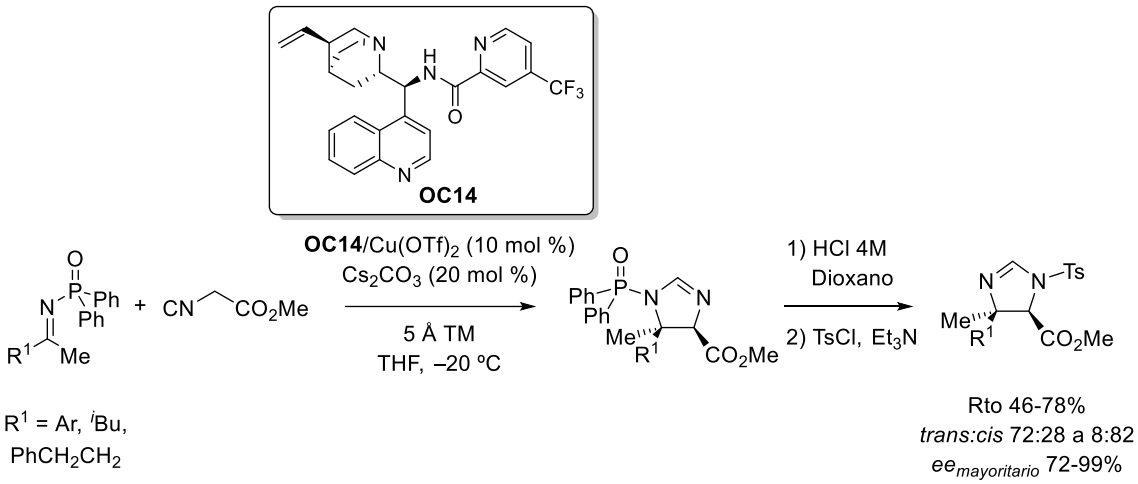
Las reacciones de adición a cetiminas suponen un reto sintético mayor que las adiciones a aldiminas ya que tienen un menor carácter electrofílico. La adición de isocianoacetatos a este tipo de sustratos conduce a anillos de 2-imidazolina con un centro estereogénico cuaternario en el carbono sobre el cual tiene lugar el ataque nucleofílico.

En 2014, Dixon describió la primera reacción de adición a este tipo de sustratos con isocianoacetatos empleando el sistema catalítico previamente desarrollado por su grupo de investigación (**Esquema 22**).[42] La reacción se llevó a cabo con *N*-difenilfosfinoil cetiminas derivadas de diferentes acetofenonas obteniendo los productos de cicloadición deseados con buenos rendimientos, de moderada a excelente diastereoselectividad y altos excesos enantioméricos.



Esquema 22. Síntesis enantioselectiva de 2-imidazolinas a partir de cetiminas e isocianoacetatos mediante catálisis cooperativa.

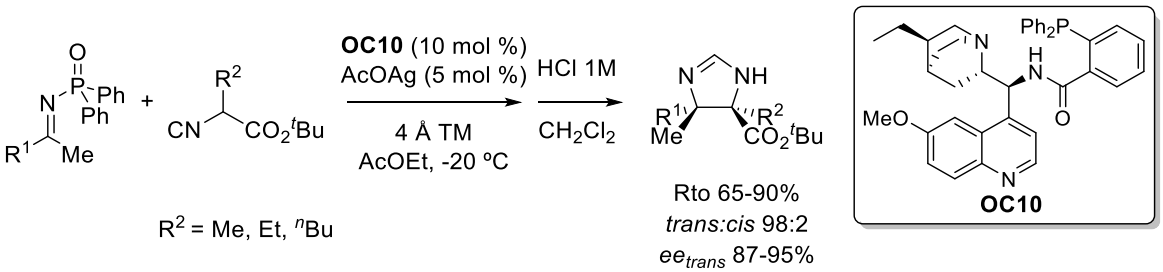
El mismo año, el grupo de Nakamura describió un nuevo sistema catalítico para la misma reacción, complementario al descrito por Dixon, formado por un organocatalizador derivado de *N*-picolinoil-9-amino-9-desoxi-*epi*-cinchonina (**OC14**) y triflato de cobre (II) (**Esquema 23**).[43] Se obtuvieron las 2-imidazolinas *cis* como producto mayoritario de reacción, pero debido a la baja estabilidad de los productos, estos fueron sometidos a transformaciones para obtener las tosil imidazolinas correspondientes en dos pasos. Se obtuvieron moderados rendimientos y diastereoselectividades y excesos enantioméricos de moderados a excelentes.



Esquema 23. Reacción de adición enantioselectiva de isocianoacetatos a *N*-difenilfosfinoil cetiminas mediante catálisis cooperativa.

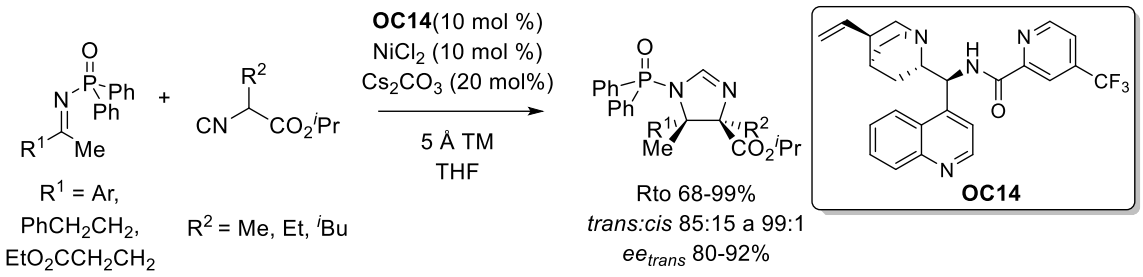
En 2016, tanto Dixon como Nakamura describieron la extensión de sus respectivos trabajos para la obtención de 2-imidazolinas con dos centros estereogénicos cuaternarios consecutivos empleando cetiminas e isocianoacetatos sustituidos en la posición alfa.

Dixon aplicó su sistema catalítico empleando el catalizador derivado de dihidroquinina **OC10** en combinación con acetato de plata (**Esquema 24**).[44] Antes de caracterizar los productos de reacción, estos se trataron con ácido clorhídrico 1 M para desproteger el grupo difenilfosfinoilo y obtener de esta forma los 1*H*-dihidroimidazoles. Se obtuvieron los productos *trans* con buenos resultados de rendimiento, excelente diastereoselectividad en todos los casos y alto exceso enantiomérico.



Esquema 24. Extensión del trabajo de Dixon para la síntesis de imidazoles con dos centros cuaternarios consecutivos.

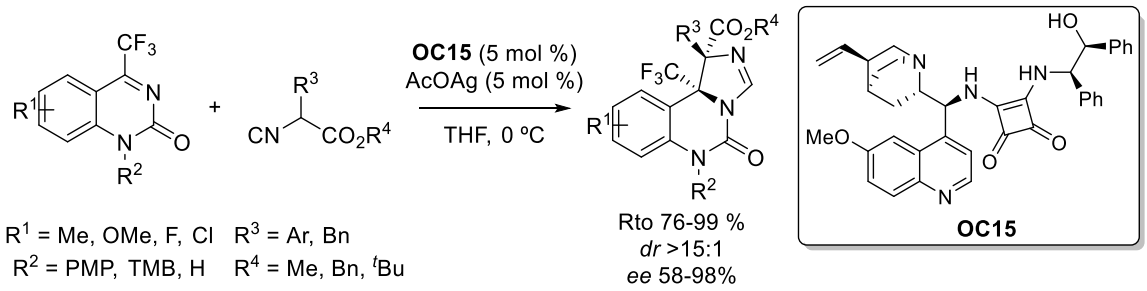
Por su parte, Nakamura utilizó un sistema catalítico relacionado con el anterior pero modificando la parte aromática del organocatalizador y empleando cloruro de níquel (II) en lugar de triflato de cobre (II) (**Esquema 25**).[45] Se obtuvieron las 2-imidazolinas con altos rendimientos, excelentes diastereoselectividades y altos excesos enantioméricos.



Esquema 25. Ampliación del trabajo de Nakamura llevada a cabo en 2016.

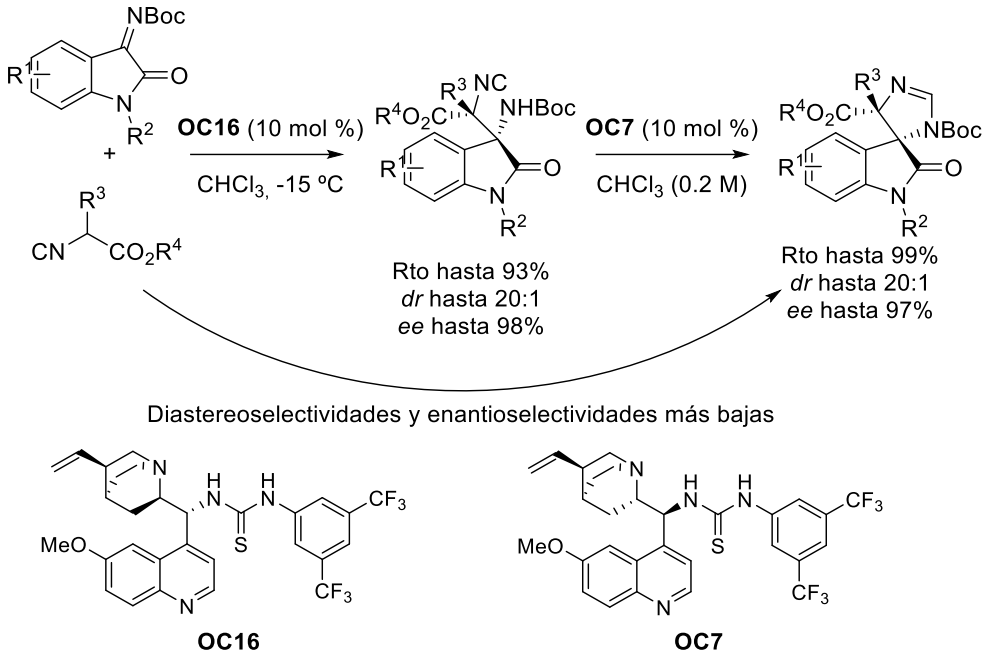
2.3.2.2 *Reacciones enantioselectivas con cetiminas cíclicas*

El primer ejemplo de este tipo de reacción fue descrito por el grupo de Shi en 2014. Se llevó a cabo una adición enantioselectiva de isocianoacetatos α-sustituidos a cetiminas cíclicas sustituidas con un grupo trifluorometilo empleando un sistema catalítico formado por un organocatalizador bifuncional de tipo escuaramida y acetato de plata. La reacción se llevó a cabo en THF y a 0 °C (**Esquema 26**). Se obtuvieron derivados de tetrahidroimidazo[1,5-c]quinozalina sustituidos con un grupo trifluorometilo con dos centros estereogénicos cuaternarios consecutivos. El sistema catalítico proporcionó los productos con buenos rendimientos, elevada diastereoselectividad y entre moderado y excelente exceso enantiomérico.[46]



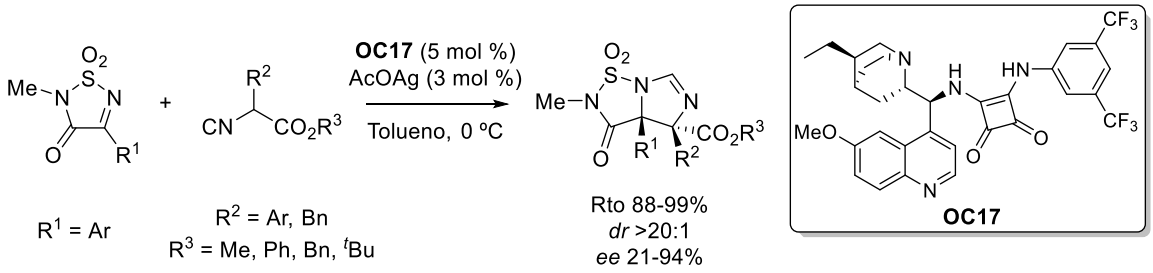
Esquema 26. Reacción de adición enantioselectiva de isocianoacetatos a 4-triflurometilquinazolinonas.

Los mismos autores describieron un año más tarde una reacción de tipo Mannich entre isocianoacetatos sustituidos en la posición alfa e iminas derivadas de la isatina para la formación espiroimidazolinas.[47] Para obtener buena estereoselectividad la reacción se llevó a cabo en dos etapas. En la primera de ellas se utilizó un organocatalizador de tipo tiourea derivado de quinidina y −15 °C de temperatura para evitar la ciclación, obteniéndose el producto de adición de tipo Mannich, posteriormente, este producto se agitó en presencia de otra tiourea derivada de quinina para obtener el producto espirocíclico (**Esquema 27**). La reacción se llevó a cabo de esta forma ya que el uso directo de la tiourea derivada de quinina proporcionaba los productos espirocíclicos con menor diastereoselectividad y enantioselectividad. Los productos espiránicos se obtuvieron con buenos rendimientos, excelentes diastereoselectividades y enantioselectividades.



Esquema 27. Síntesis enantioselectiva de oxindol-espiroimidazolinas en dos etapas descrita por Shi en 2015.

El ejemplo más reciente de estas reacciones cascada Mannich/ciclación intramolecular, ha sido descrito por los mismos autores en 2018.[48] Como sustrato de partida se emplearon sulfamidacetiminas sobre las cuales adicionaron isocianoacetatos sustituidos en la posición alfa para la generación de sistemas bicíclicos fusionados con dos centros estereogénicos cuaternarios consecutivos. Los autores desarrollaron un sistema catalítico compuesto por una escuaramida derivada de dihidroquinina **OC17** y acetato de plata (**Esquema 28**). Los productos se obtuvieron con excelentes rendimientos y diastereoselectividades y con excesos enantioméricos que van desde bajos hasta excelentes.

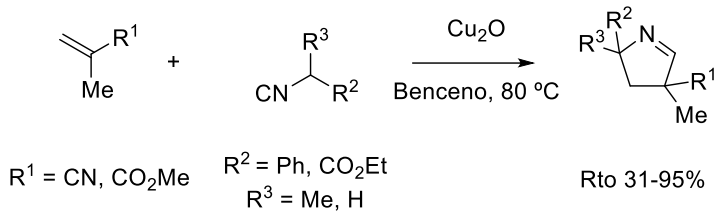


Esquema 28. Reacción de cicloadición [3+2] formal enantioselectiva entre isocianoacetatos y sulfamidocetiminas mediante catálisis cooperativa.

2.4 Síntesis de dihidropirroles mediante reacciones de adición de isocianoésteres a alquenos electrofílicos

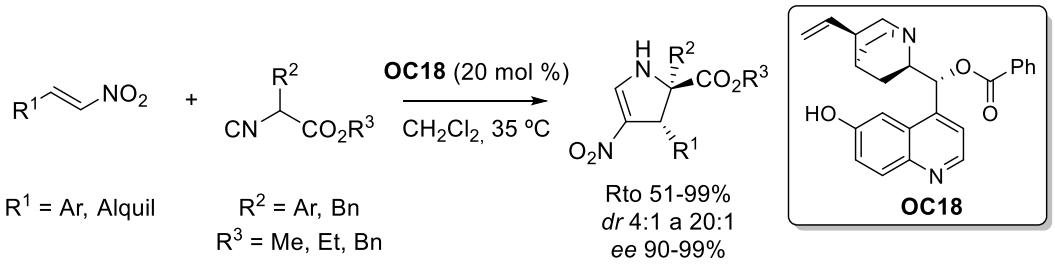
La reacción de cicloadición formal [3+2] entre aceptores de Michael e isocianoacetatos para la síntesis de dihidropirroles altamente funcionalizados ha sido ampliamente estudiada.

El primer ejemplo de este tipo de reacción fue descrito en 1971 por el grupo de Saegusa. La reacción implicó la formación de un complejo entre el cobre y dos moléculas de isocianuro que, posteriormente, se adicionó a una disolución del aceptor de Michael con el consiguiente ataque nucleofílico y la posterior la ciclación intramolecular para proporcionar el azaheterociclo (**Esquema 29**).[49]



Esquema 29. Primera reacción de tipo Michael con isocianuros descrita por el grupo de Saegusa en 1971.

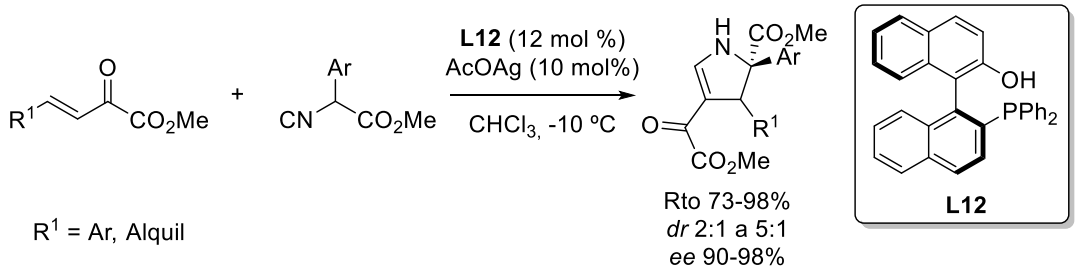
Para encontrar la primera adición enantioselectiva de isocianoacetatos a aceptores de Michael hubo que esperar hasta el año 2008, cuando el grupo de Gong desarrolló un método organocatalítico utilizanco un éster de cupreína derivado de quinidina como catalizador. Como aceptores de Michael se utilizaron nitroolefinas y como nucleófilos se emplearon isocianoacetatos con sustitución en posición alfa (**Esquema 30**).[50]



Esquema 30. Reacción de adición de isocianoacetatos sobre nitroolefinas descrita por Gong.

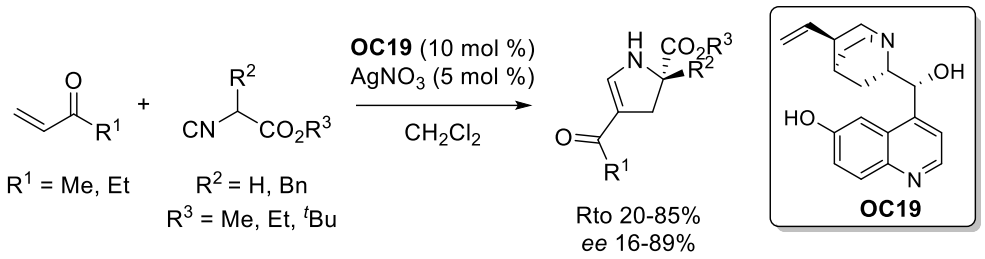
Sin embargo, la aplicación de este sistema catalítico a compuestos carbonílicos insaturados condujo a las pirrolidinas con rendimientos moderados y baja estereoselectividad.

El mismo grupo, desarrolló en 2011 un nuevo sistema catalítico capaz de llevar a cabo la reacción de adición a compuestos carbonílicos α,β-insaturados de forma satisfactoria. El sistema catalítico utilizado estaba consituido por una difenilfosfina derivada de un sistema de hidroxibinaftilo y acetato de plata. Se obtuvieron las pirrolidinas con buenos rendimientos, moderada diastereoselectividad y alto exceso enantiomérico (**Esquema 31**).[51]



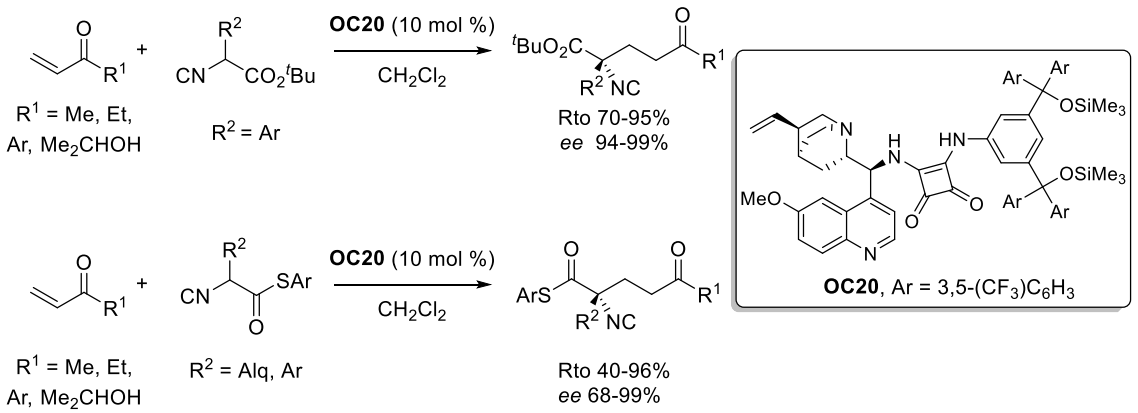
Esquema 31. Adición de isocianoacetatos a sistemas carbonílicos insaturados.

Casi simultáneamente a este trabajo de Gong, el grupo de Escolano describió la cicloadición a sistemas carbonílicos α,β-insaturados con isocianoacetatos. Desarrollaron un sistema catalítico multicomponente para la adición de isocianoacetatos a vinil cetonas compuesto por un organocatalizador bifuncional y nitrato de plata (**Esquema 32**).[52] De acuerdo con los autores, el ion plata coordina con el grupo isocianuro aumentando la acidez del hidrógeno en alfa, facilitando la desprotonación del grupo metileno por el nitrógeno del anillo de quinuclidina. El par iónico resultante experimenta adición 1,4 a la vinil cetona facilitado por la formación de un enlace de hidrógeno entre el organocatalizador y la enona. Una vez producido el ataque, se obtienen los sistemas de pirrolidina. Los productos de reacción se obtuvieron con rendimientos bajos y excesos enantioméricos moderados en la mayoría de los casos.



Esquema 32. Cicloadición asimétrica de α-isocianoésteres a vinil cetonas mediante un sistema multicatalítico de Ag/organocatalizador.

En 2017, el grupo de Palomo desarrolló un sistema catalítico sin cocatalizador metálico, formado únicamente por una escuaramida bifuncional, para la adición de isocianoacetatos e isocianotioésteres a sistemas de vinil cetona (**Esquema 33**).[53]

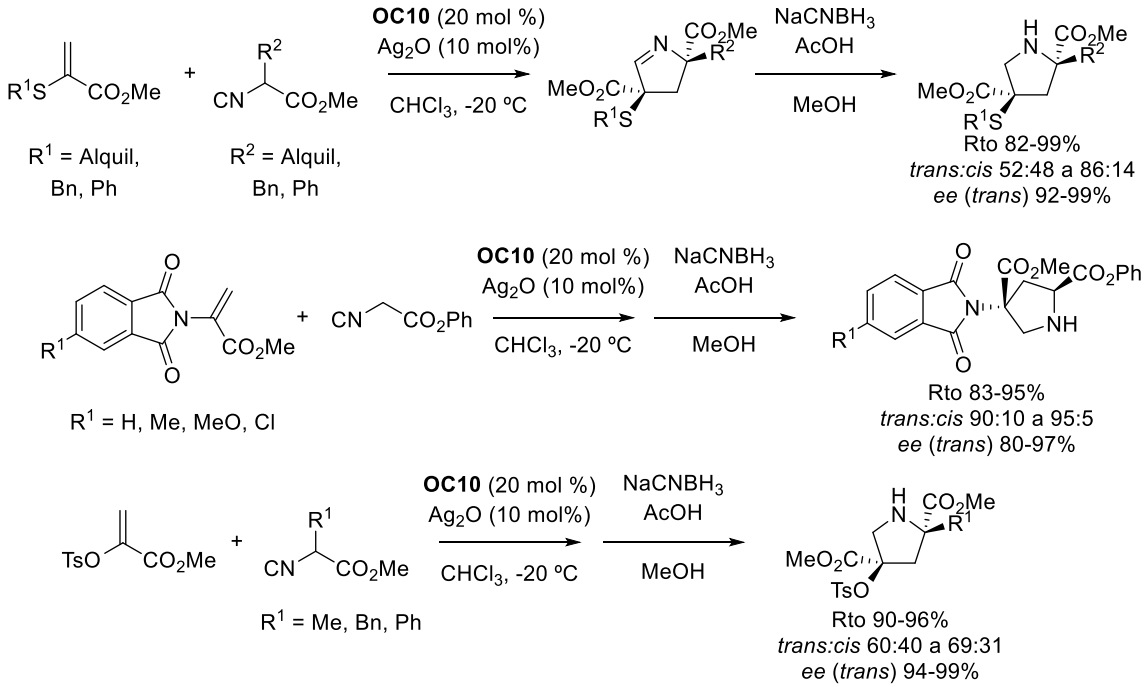


Esquema 33. Adición 1,4 de isocianoésteres organocatalítica a sistemas de vinil cetona.

Los productos de adición se obtuvieron con buenos rendimientos y excelentes excesos enantioméricos, no obstante, no pudieron emplearse sistemas de aril vinil cetona sustituidos en la posición *orto* del anillo aromático. Los compuestos obtenidos son interesantes ya que pueden someterse a un gran número de modificaciones sintéticas generando un amplio abanico de productos.

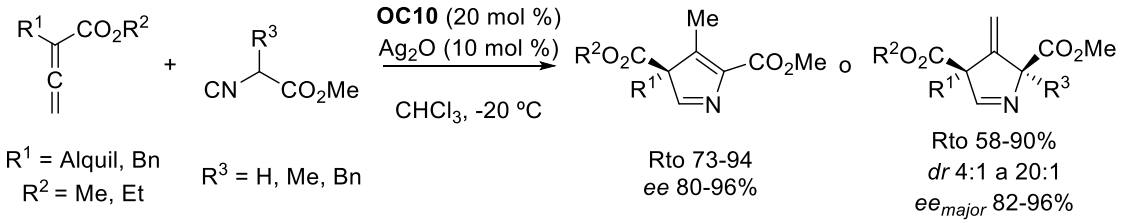
En 2017, el grupo de Shao y He describió la cicloadición formal [3+2] de isocianoacetatos con alquenos sustituidos captodativamente, tales como acrilatos sustituidos con un heteroátomo en la posición alfa, para dar pirrolidinas con un estereocentro cuaternario. Los mejores resultados se obtuvieron con el sistema catalítico

desarrollado por el grupo de Dixon.[44] Los productos se obtuvieron con excelentes resultados en cuanto a enantioselectividad, pero con moderada diastereoselectividad (**Esquema 34**).[54]



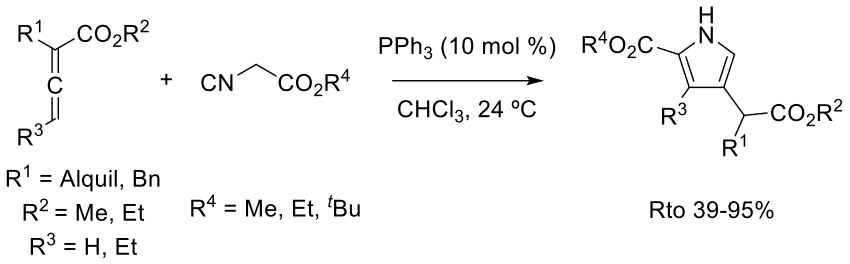
Esquema 34. Reacciones enantioselectivas descritas por Shao y He para la formación de pirrolidinas.

El mismo sistema catalítico puede emplearse para la reacción enantioselectiva entre alenoatos e isocianoacetatos. Esta reacción fue descrita por el grupo de Zhao en 2015 para la síntesis de diferentes tipos de pirroles con uno o dos centros estereogénicos cuaternarios, en función de si el isocianoacetato se encuentra sustituido o no en posición alfa (**Esquema 35**).[55] Los productos enantioenriquecidos se obtienen con buen rendimiento, buena diastereoselectividad (en el caso de los productos con dos centros cuaternarios) y altos excesos enantioméricos.



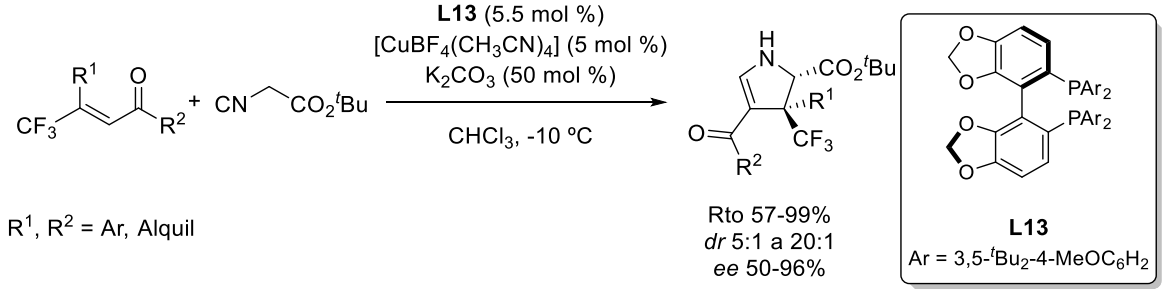
Esquema 35. Reacción enantioselectiva de adición de isocianoacetatos a alenos.

Además, utilizando estos sustratos de partida, es posible sintetizar pirroles con tres sustituyentes cambiando las condiciones catalíticas, empleando trifenilfosfina como catalizador (**Esquema 36**).



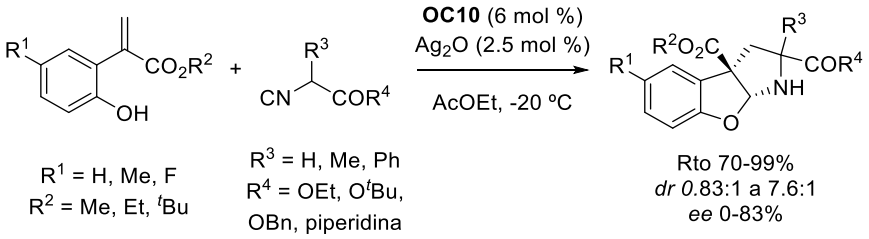
Esquema 36. Síntesis de 1*H*-pirroles a partir de alenos e isocianoacetatos.

El grupo de Zhang, ha descrito recientemente la síntesis asimétrica de dihidropirroles mediante la reacción entre enonas β,β-disustituidas en las que uno de los sustituyentes en la posición β es un grupo trifluorometilo, e isocianoacetato de *terc*-butilo (**Esquema 37**).[56] El sistema catalítico emplea un complejo generado *in situ* a partir de (*R*)-DTBM-SEGPHOS y cobre. Además, la reacción requiere de una cantidad subestequiométrica de base. Los productos de reacción se obtienen con buenos rendimientos, altas diastereoselectividades y de moderados a excelentes excesos enantioméricos. Sin embargo, las cetonas con grupos alquílicos en alfa al grupo carbonilo proporcionan bajos excesos enantioméricos. De forma similar, si el sustituyente en posición beta es modificado, la diastereoselectividad disminuye.



Esquema 37. Adición enantioselectiva de isocianoacetato de *terc*-butilo a β-trifluorometilenonas β,β-disustituidas.

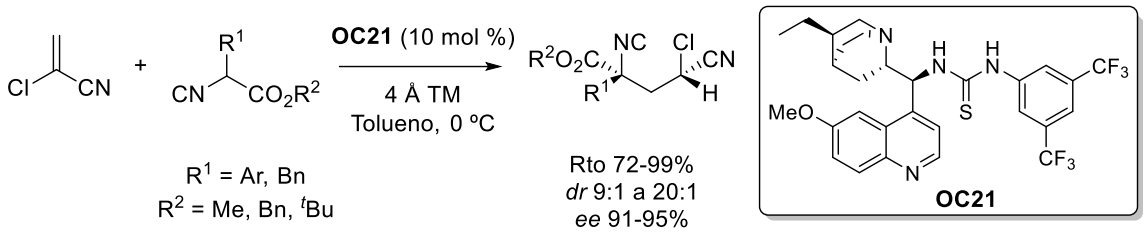
Xie, ha descrito la adición de isocianoacetatos a sistemas de 2-(2-hidroxifenil)acrilato de etilo. La reacción implica la adición inicial al doble enlace seguida de ciclacion del fenol sobre la imina resultante, generando un sistema tricíclico con dos centros estereogénicos consecutivos, uno de ellos cuaternario. La reacción es catalizada por el sistema catalítico desarrollado por Dixon (**Esquema 38**).[57]



Esquema 38. Sistema tricíclico quiral formado mediante la reacción de adición de isocianoacetatos a 2-hidroxiacrilatos.

Muy recientemente en 2019, Zhao ha publicado la adición enantioselectiva de isocianoacetatos α-sustituidos a 2-cloroacrilonitrilo. En este caso no se produce una

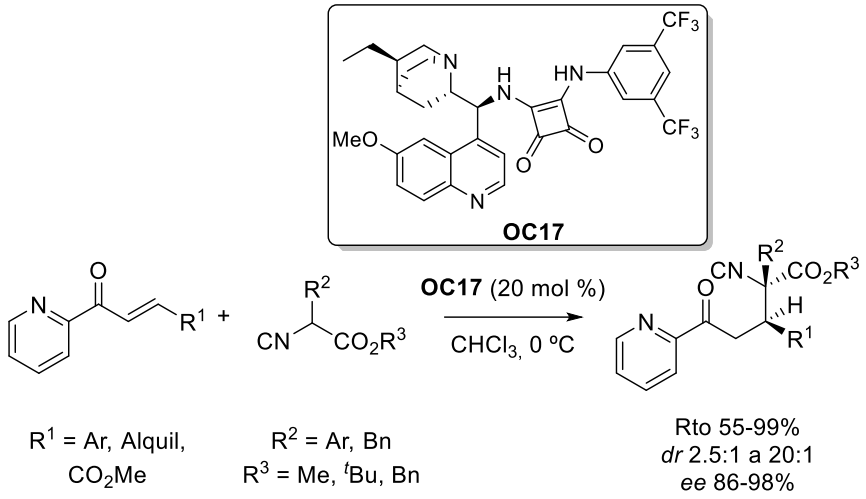
reacción de cicloadición, sino que la reacción proporciona un isocianoester α,α-disustituido con dos centros estereogénicos (**Esquema 39**).[58]



Esquema 39. Reacción entre 2-cloroacrilonitrilo e isocianoacetatos α-sustituidos.

La reacción se lleva a cabo con un organocatalizador bifuncional de tipo tiourea derivado de dihidroquinina en presencia de tamiz molecular y a 0 °C de temperatura obteniéndose altos rendimientos, y excelentes diastereoselectividades y enantioselectividades.

También en 2019, el grupo de Shi ha llevado a cabo la adición de α-isocianoésteres a 2-enoilpiridinas. Igual que ocurría en la reacción anterior descrita por Zhao (**Esquema 39**), esta adición no va seguida de una etapa de ciclación intramolecular. Para llevar a cabo la reacción se utiliza una escuaramida derivada de dihidroquinina y 3,5-bis(trifluorometil)anilina (**Esquema 40**).[59]



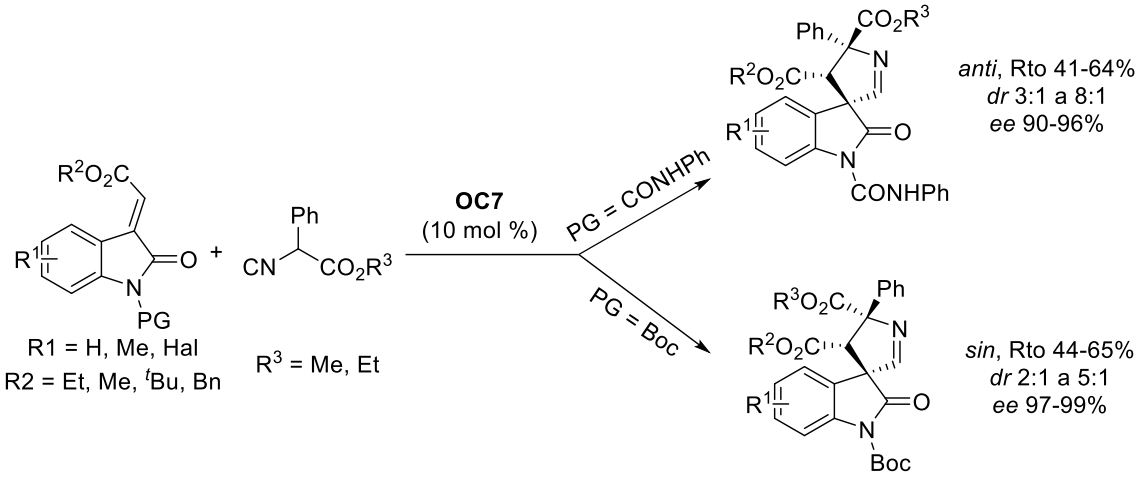
Esquema 40. Adición enantioselectiva de isocianoacetatos a 2-enoilpiridinas.

2.4.1 Síntesis enantioselectivas de compuestos espirocíclicos

En los últimos años, las estructuras de tipo espirocíclicas han cobrado importancia en la industria farmacéutica dado que tienen una conformación espacial fijada. Este tipo de estructuras pueden encontrarse en la naturaleza, en alcaloides y en moléculas bioactivas. Recientemente, las reacciones de cicloadición formal [3+2] con isocianoacetatos y metilenindolinonas han permitido acceder a este tipo de productos de forma sencilla y enantioselectiva.

El trabajo pionero para la obtención de este tipo de estructuras, fue llevado a cabo por el grupo de Xu y Wang en 2012 (**Esquema 41**).[60] Utilizando un catalizador bifuncional derivado de quinina. Los autores realizaron una síntesis diastereodivergente

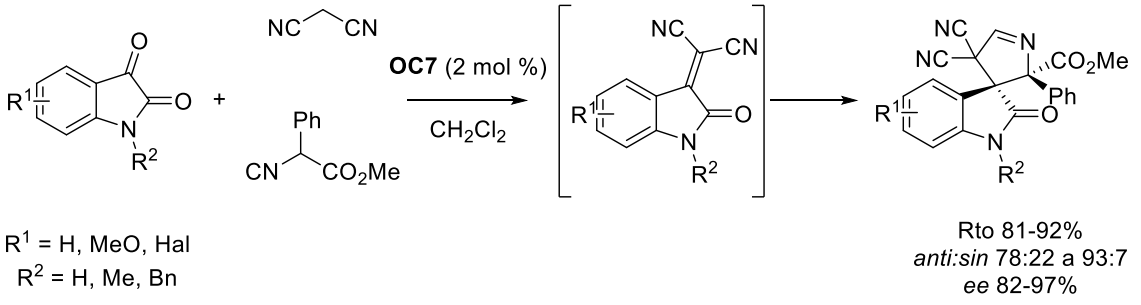
en la cual, en función del grupo protector del nitrógeno del oxindol, se obtienen los productos *sin* o *anti*.



Esquema 41. Síntesis de espiro-oxindoles.

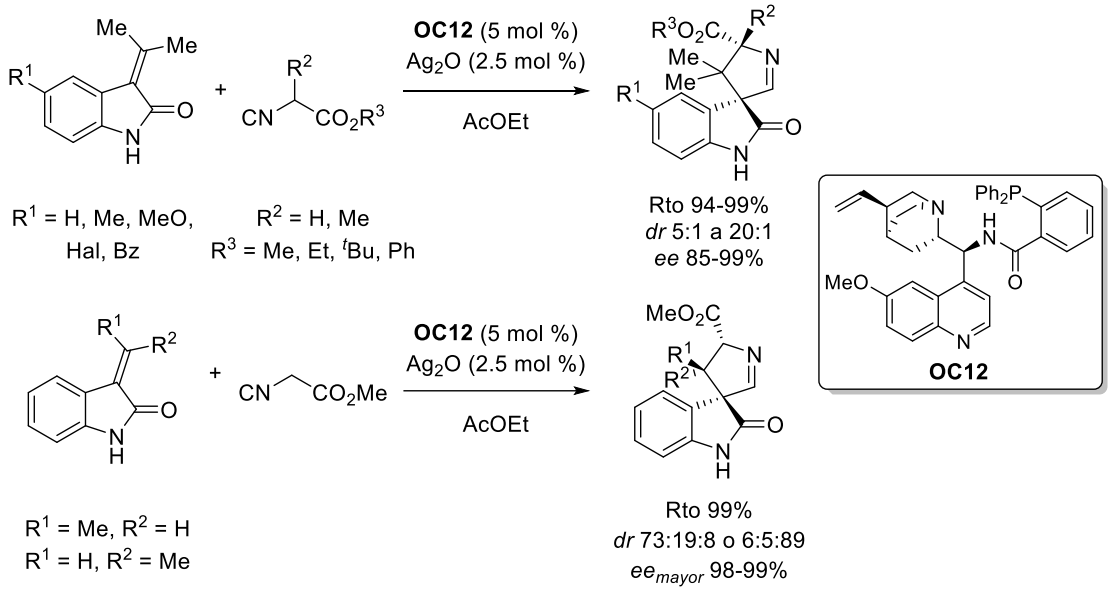
Los productos espirocíclicos se obtuvieron con moderado rendimiento y diastereoselectividad, pero excelente exceso enantiomérico.

Simultáneamente a este trabajo, el grupo de Yan describió una reacción multicomponente que emplea isatinas, malononitrilo y 2-fenil-2-isocianoacetato de metilo para dar compuestos espirocíclicos (**Esquema 42**).[61] La reacción se encuentra catalizada por un organocatalizador con estructura de tiourea y tiene lugar a través de la cicloadición del isocianoacetato y la dicianometilenindolinona generada *in situ* a partir de la isatina y el malononitrilo. Lamentablemente, la reacción con isocianoacetatos no sustituidos en alfa transcurrió con baja enantioselectividad.



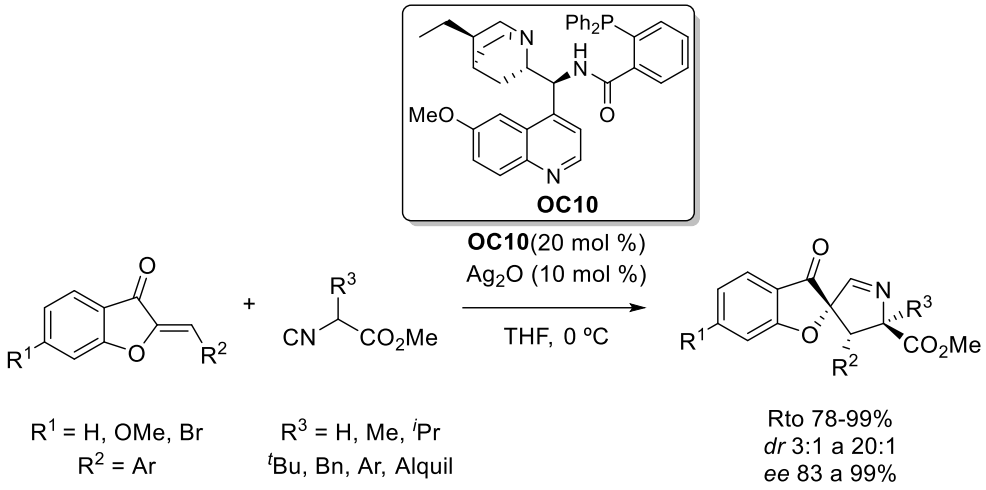
Esquema 42. Reacción multicomponente entre isatinas, malononitrilo e isocianoacetatos descrita por Yan.

Por su parte, Shao y Zhao emplearon el método catalítico de Dixon para llevar a cabo una reacción similar utilizando propilidenindolinonas como electrófilos. La reacción se llevó a cabo de forma enantioselectiva tanto con isocianoacetatos sustituidos en posición alfa como con isocianoacetatos no sustituidos (**Esquema 43**).[62] Los productos espirocíclicos se obtuvieron con excelentes rendimientos, altas diastereoselectividades y excelentes excesos enantioméricos.



Esquema 43. Obtención de espirociclos mediante catálisis cooperativa.

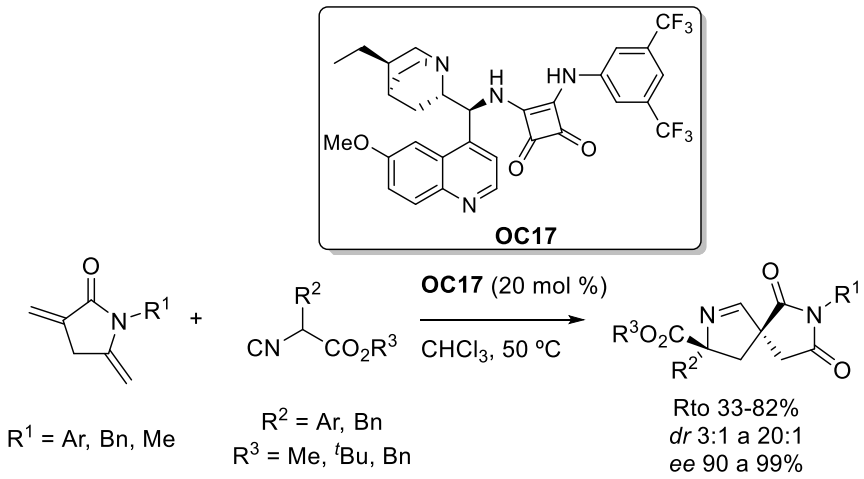
En 2018, He describió la adición enantioselectiva de isocianoacetatos a auronas para la síntesis de espirociclos con tres centros estereogénicos, pudiendo ser dos de ellos cuaternarios en función de si el isocianoacetato tiene sustitución en la posición alfa o no. La adición se llevó a cabo mediante la amidofosfina derivada de dihidroquinina y óxido de plata, sistema catalítico desarrollado por el grupo de Dixon (**Esquema 44**).[63]



Esquema 44. Formación de espirociclos a partir de sistemas de aurona e isocianoacetatos.

La reacción proporcionó los espirociclos en rendimientos cuantitativos, de buena a excelente diastereoselectividad y excelentes excesos enantioméricos.

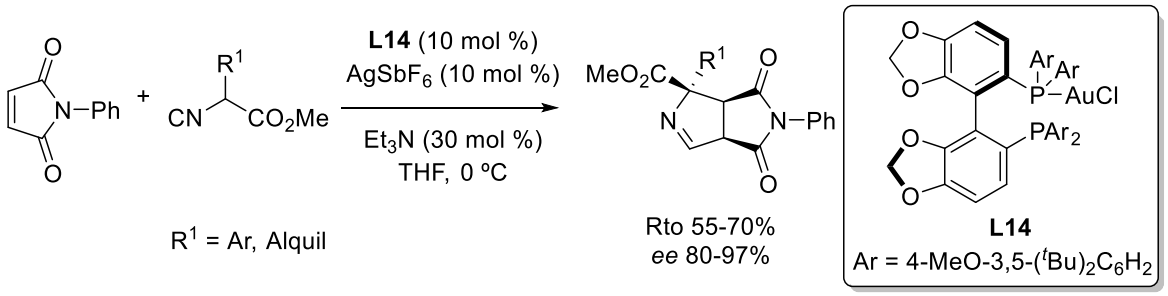
El último ejemplo descrito para la formación de espirociclos mediante el uso de isocianoacetatos α-sustituidos lo ha descrito el grupo de Zhao en 2020.[64] Como electrófilos se utilizan derivados de *N*-itaconamidas y se obtienen productos espirocíclicos con dos centros cuaternarios. Para catalizar la reacción se emplea la escuaramida bifuncional **OC17** derivada de dihidroquinina y 3,5-bis(trifluorometil)anilina. Los productos se obtienen con rendimientos moderados, elevada diastereoselectividad y excelente exceso enantiomérico (**Esquema 45**).



Esquema 45. Síntesis de espirociclos a partir de *N*-itaconamidas e isocianoacetatos sustituidos en posición alfa.

2.4.2 Reacciones de desimetrización de olefinas cíclicas

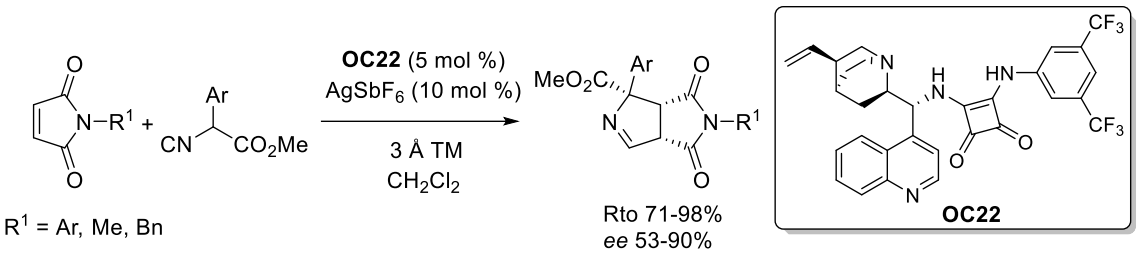
La primera desimetrización utilizando isocianoacetatos, fue descrita por el grupo de Carretero en 2012. Se llevó a cabo la adición de isocianoacetatos sustituidos en la posición alfa a *N*-fenilmaleimida para la obtención de compuestos bicíclicos con un centro estereogénico cuaternario (**Esquema 46**).[65] Para llevar a cabo la reacción de forma enantioselectiva utilizó un complejo de oro y plata y trietilamina como base. Cabe destacar que la sal de plata es necesaria para que la reacción tenga lugar, en ausencia de esta, no hay reacción. La sal de plata forma junto con el oro un complejo catiónico que es realmente la especie catalítica.



Esquema 46. Desimetrización de *N*-fenilmaleimida con isocianoacetatos catalizada por plata y oro.

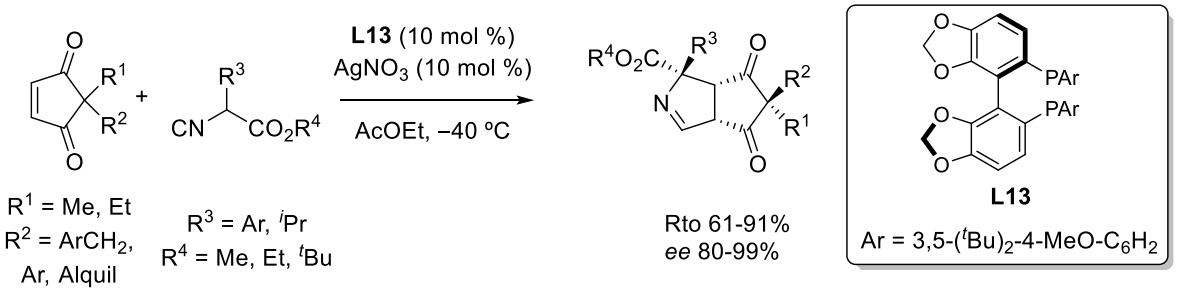
Como producto de reacción solo se observó un único diastereoisómero, obteniéndose los productos con alto exceso enantiomérico. Cuando se utiliza un isocianoacetato sin sustitución en posición alfa como el isocianoacetato de metilo, el exceso enantiomérico del producto disminuye hasta un 78%.

El mismo año, Zhao y Shi describieron un sistema catalítico diferente para llevar a cabo esta reacción de desimetrización, consitutido por una escuaramida y una sal de plata (**Esquema 47**).[66] Los productos bicíclicos de reacción se obtuvieron con buenos rendimientos y de moderada a alta enantioselectividad. Cuando se empleó un isocianoacetato sin sustitución en la posición alfa, el exceso enantiomérico disminuye dramáticamente hasta un 10%.



Esquema 47. Desimetrización descrita por Zhao y Shi mediante un sistema catalítico escuaramida/plata.

El precatalizador de Dixon también ha sido empleado por el grupo de Oh, para la cicloadición formal [3+2] a sistemas de ciclopentanodionas con isocianoacetatos sustituidos en la posición alfa (**Esquema 48**).[67] Como producto de reacción, se obtuvieron dos anillos de cinco miembros fusionados con cuatro centros estereogénicos, dos de ellos cuaternarios con buenos rendimientos y enantioselectividades altas. La enantioselectividad de los productos pudo incrementarse hasta un 99% tras una cristalización. Nuevamente, el uso de isocianoacetatos sin sustitución en posición alfa proporcionó los productos de reacción diastereoselectivamente, pero en forma racémica.

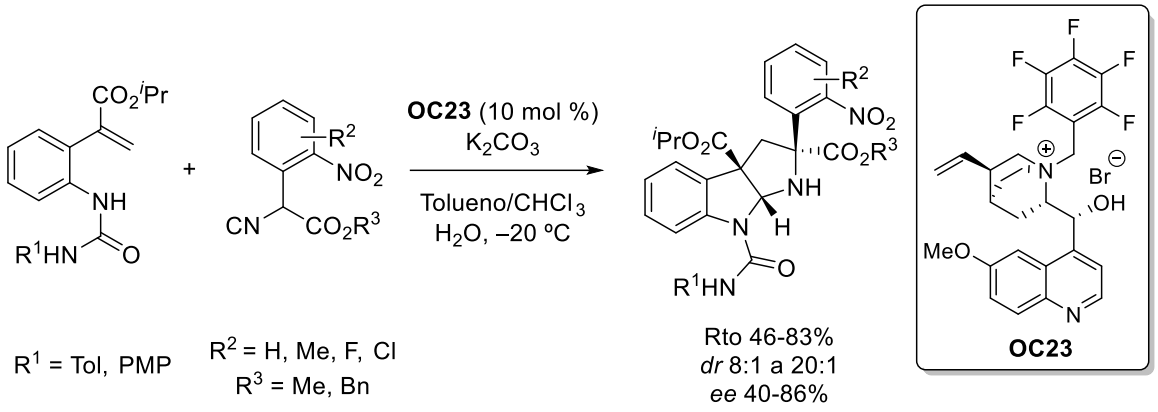


Esquema 48. Desimetrización ciclopentendionas con isocianoacetatos.

2.4.3 Síntesis enantioselectiva de pirroloindolinas mediante reacciones de tipo cascada

Los sistemas de pirroloindolinas son una estructura privilegiada en química orgánica, pudiéndose encontrar en estructuras activas biológicamente. Actualmente solo se encuentran dos versiones enantioselectivas para la obtención de este tipo de productos mediante el uso de isocianoacetatos.

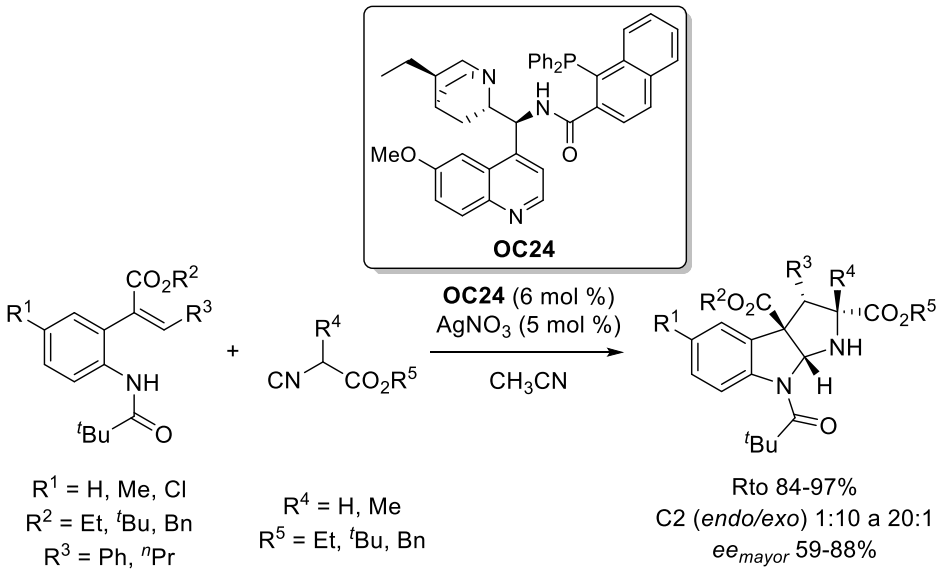
El primer ejemplo lo describió en 2014 el grupo de Smith, quien llevó a cabo la reacción entre un isocianoacetato α-sustituido y una urea derivada de 2-[2-(amino)fenil]-acrilato de isopropilo en condiciones de transferencia de fase (PTC). La adición inicial del isocianoacetato a la olefina generó un 2-imidazolina que recibió el ataque de la urea (**Esquema 49**).[68]



Esquema 49. Síntesis enantioselectiva de pirroloindolinas bajo condiciones de transferencia de fase.

Las pirroloindolinas se obtienen con buenos rendimientos, elevada diastereoselectividad y excesos enantioméricos que van desde bajos hasta altos. Además, la reacción es compatible con diferentes ésteres en el isocianoacetato.

El otro ejemplo de este tipo de reacciones fue descrito por Zhong. Emplea un sistema multicatalítico compuesto por un organocatalizador de tipo amidofosfina **OC24** y nitrato de plata (**Esquema 50**).[69] Los productos tricíclicos se obtienen con elevado rendimiento, alta diastereoselectividad y excesos enantioméricos que van desde moderados hasta altos.



Esquema 50. Reacción entre 2-[2-(amino)fenil]-acrilatos e isocianoacetatos mediante catálisis cooperativa.

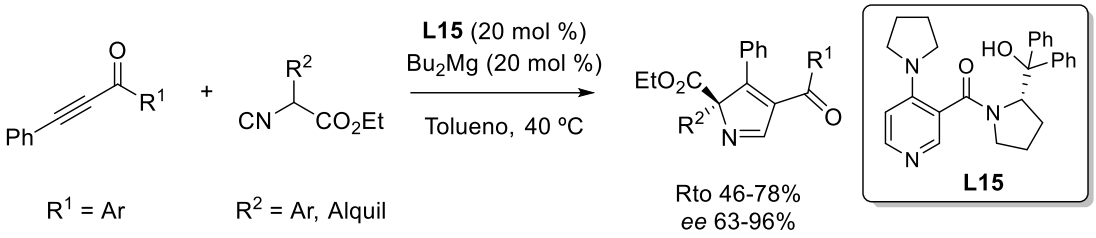
Lamentablemente, cuando se cambia el grupo protector de la amina, se obtienen los productos en forma racémica.

2.5 Adición enantioselectiva a alquinos

Mientras que la adición de isocianoacetatos a sistemas insaturados de tipo olefínico para la generación de una gran variedad de compuestos está ampliamente estudiada, la

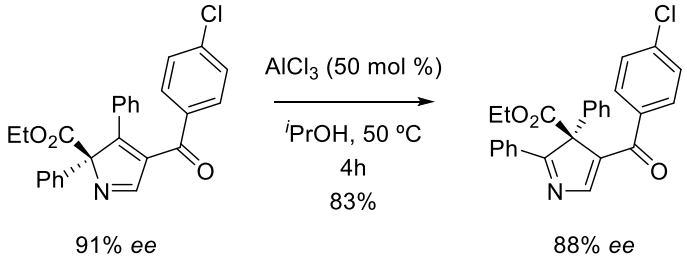
adición enantioselectiva a alquinos para la síntesis de 2*H*- y 3*H*-pirroles apenas ha sido explorada.

En el año 2019, el grupo de Yang y Wang ha descrito la adición de α-isocianoacetatos a sistemas de prop-2-in-1-onas mediante un sistema multicatalítico novedoso que engloba un derivado de prolinol y magnesio (II) (**Esquema 51**).[70]



Esquema 51. Adición de isocianoacetatos a alquinos para la generación de 2*H*-pirroles.

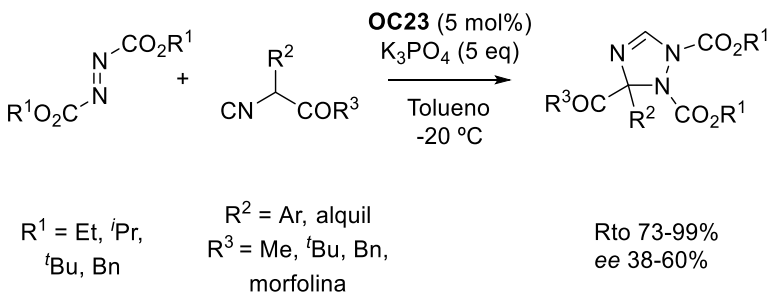
Los 2*H*-pirroles se obtienen con moderados rendimientos y excesos enantioméricos que van de moderados a excelentes. Los autores describen el reordenamiento de los sistemas quirales de 2*H*-pirrol para la obtención de sistemas de 3*H*-pirrol mediante el uso de $AlCl_3$ subestequiométrico sin apenas pérdida de la pureza enantiomérica y con buen rendimiento (**Esquema 52**).



Esquema 52. Reordenamiento de 2*H*-pirroles para la obtención de 3*H*-pirroles.

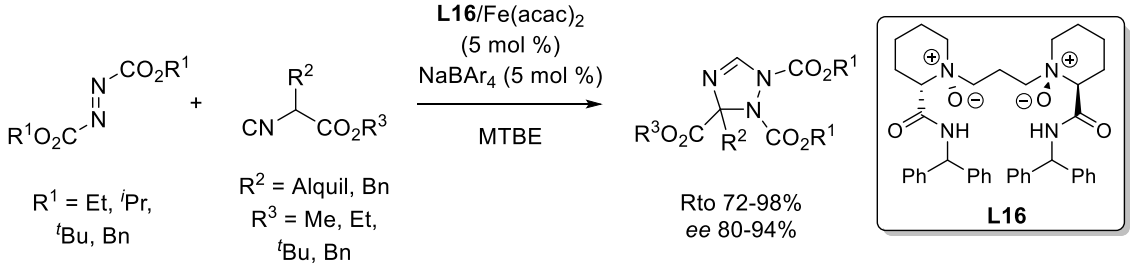
2.6 Síntesis enantioselectiva de 1,2,4-triazolinas

La primera versión enantioselectiva de la reacción entre azadicarboxilatos e isocianoacetatos fue descrita por Jørgensen en 2011. Como producto de reacción se obtienen 1,2,4-triazolinas enriquecidas enantioméricamente (**Esquema 53**).[71] La reacción se llevó a cabo en condiciones de PTC con el catalizador **OC23**, aunque lamentablemente los productos de reacción se obtuvieron con moderado exceso enantiomérico (por debajo del 60%).



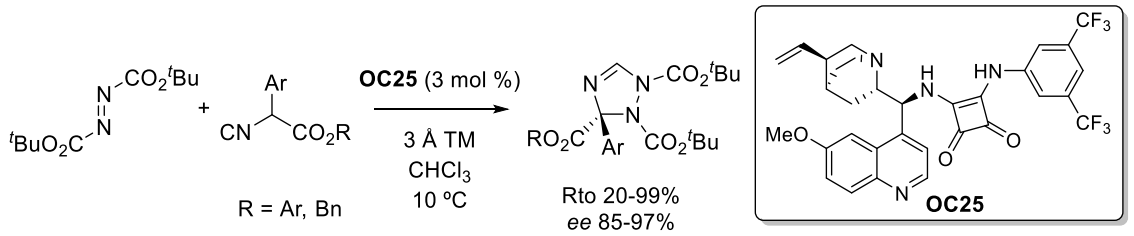
Esquema 53. Síntesis de 1,2,4-triazolinas mediante catálisis de transferencia de fase.

Más tarde, en 2013, Liu y Feng desarrollaron una nueva versión enantioselectiva de esta reacción utilizando un complejo de hierro generado a partir de acetilacetonato de hierro (II) y un ligando de *N*-óxidos de piperidina (**Esquema 54**).[72] El sistema catalítico permitió la obtención de las 1,2,4-triazolinas con buenos rendimientos y altos excesos enantioméricos. La introducción de una sal de boro en el medio de reacción favoreció enantioselectividades más altas.



Esquema 54. Síntesis enantioselectiva de 1,2,4-triazolinas catalizada por un complejo de Fe (II).

El mismo año, Zhao y Shi describieron la misma reacción catalizada mediante un organocatalizador bifuncional de tipo escuaramida (**Esquema 55**).[73] En este caso, el sistema catalítico no permitió variación en los ésteres del azodicarboxilato y los isocianoacetatos debían estar sustituidos en la posición alfa, cualquier variación en estos grupos disminuyó el exceso enantiomérico de los productos.

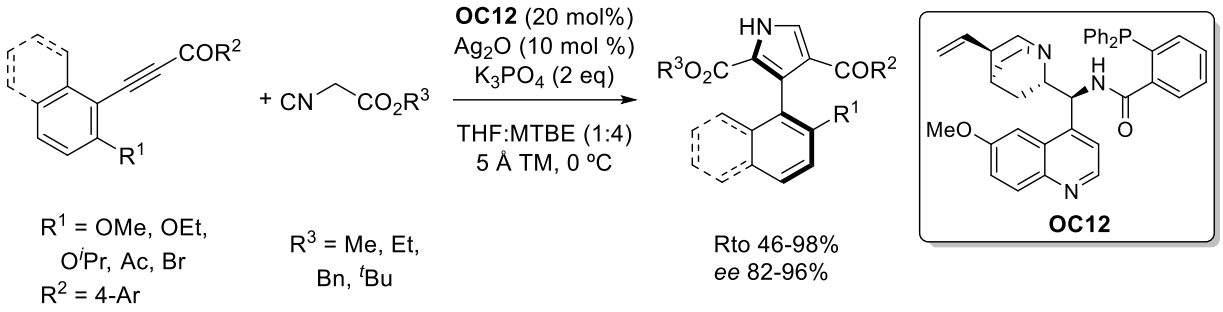


Esquema 55. Reacción organocatalítica para la síntesis de 1,2,4-triazolinas.

2.7 Resoluciones cinéticas y simetría C_2

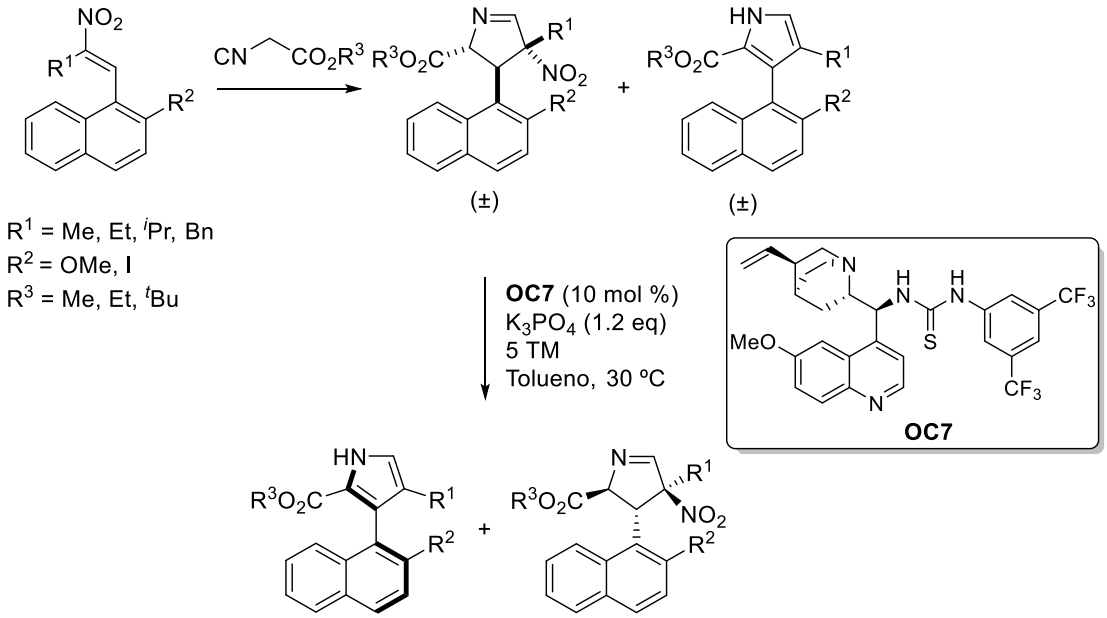
Recientemente, en 2019, el grupo de Zheng y Zhu, ha descrito por primera vez la síntesis de estructuras con simetría axial a partir de isocianoacetatos. En primer lugar, estos autores publicaron la formación de un sistema con quiralidad axial basado en la estructura de 3-arilpirrol y posteriormente llevaron a cabo una resolución racémica de 2,3-dihidropirroles sintetizados a partir de nitroolefinas e isocianoacetato de etilo para generar también sistemas de 3-arilpirroles con simetría axial.

El primero de los trabajos consiste en la adición de isocianoacetatos a 3-(2-metoxinaftalen-1-il)1-fenilprop-2-in-1-onas haciendo uso del sistema catalítico desarrollado por Dixon más la adición de fosfato potásico como base, se obtiene el arilpirrol quiral (**Esquema 56**).[74]



Esquema 56. Sistemas quirales de simetría C_2 construidos a partir de isocianoacetatos.

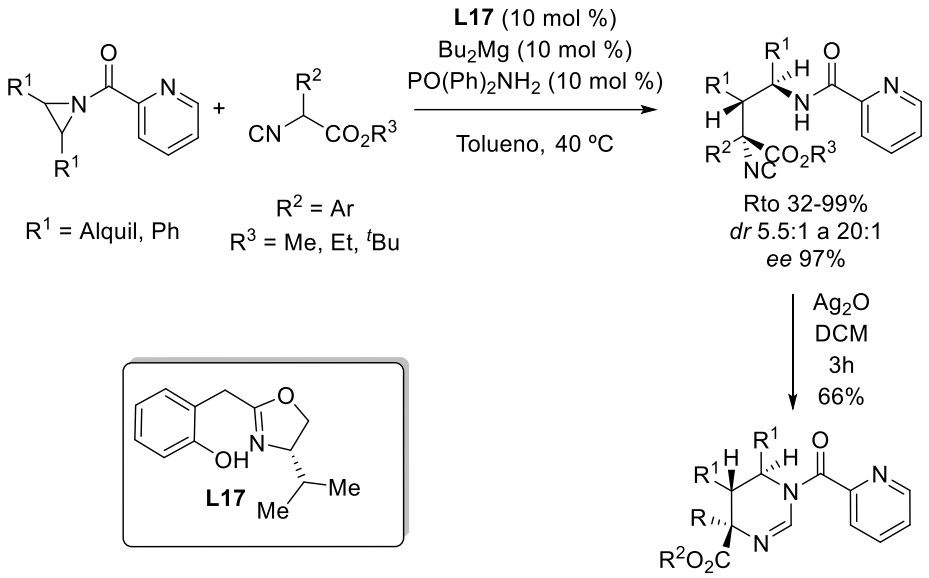
En el segundo trabajo publicado el mismo año, los autores describen la resolución racémica de sistemas de 3-aril-1*H*-pirroles para la obtención de 3-arilpirroles con quiralidad axial. La resolución cinética se llevó a cabo con un organocatalizador bifuncional de tipo tiourea y K_3PO_4 como base (**Esquema 57**).[75]



Esquema 57. Resolución racémica con pérdida de HNO_2 para la obtención de 3-arilpirroles con simetría axial.

2.8 Reacciones con aziridinas

Tan solo existe un ejemplo de adición enantioselectiva de isocianoacetatos a aziridinas, descrito por el grupo de Zhang y Wang en 2019. La reacción se lleva a cabo con un sistema multicatalítico similar al utilizado anteriormente por los autores, formado por una sal de magnesio y un ligando quiral derivado de una oxazolina. La reacción permite la adición del isocianoacetato con la consiguiente apertura del anillo de aziridina, posteriormente y con uso de óxido de plata, la amida resultante cicla sobre la agrupación isonitrilo (**Esquema 58**).[76]



Esquema 58. Apertura de aziridinas con isocianoacetatos alfa sustituidos.

Los productos de adición se obtienen con buenos resultados de enantioselectividad y diastereoselectividad. El rendimiento disminuye cuando los sustituyentes R^1 de la aziridina no constituyen un ciclo. Posteriormente, con óxido de plata se consigue la construcción de un anillo de pirimidina altamente funcionalizado.

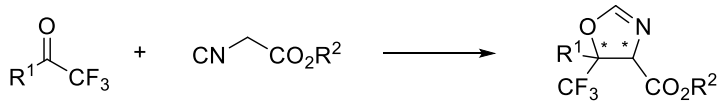
3. Objetivos

Los heterociclos nitrogenados de cinco miembros quirales tienen una gran importancia en química orgánica, tanto por su presencia en productos naturales y compuestos bioactivos como por sus aplicaciones en síntesis orgánica como precursores de diversos grupos funcionales. Como se ha mostrado en los antecedentes bibliográficos, los derivados de isocianoacetato proporcionan acceso a este tipo de sistemas cíclicos a través de reacciones en las que se comportan formalmente como 1,3-dipolos. Los antecedentes muestran que este tipo de reacciones con compuestos carbonílicos para dar oxazolinas han sido ampliamente estudiadas con aldehídos utilizando una gran variedad de catalizadores. Sin embargo, los ejemplos con cetonas son claramente escasos. Por otra parte, el espectro de dipolarófilos estudiados es también escaso, limitándose prácticamente a compuestos carbonílicos, iminas y alquenos conjugados. De acuerdo con esto, nos planteamos en este trabajo ampliar el espectro de reacciones de cicloadición enantioselectiva utilizando isocianoacetatos como 1,3-dipolos.

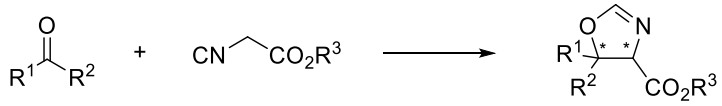
Para ello se ha utilizado un sistema multicatalítico que combina la organocatálisis con la catálisis ácida de Lewis.

Se plantearon los siguientes objetivos:

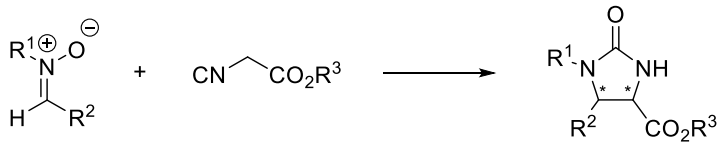
1. **Síntesis enantioselectiva de 5-trifluorometil-2-oxazolinas a partir de trifluorometilcetonas**



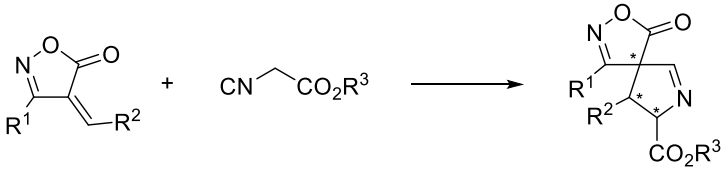
1. **Síntesis enantioselectiva de *cis*-2-oxazolinas mediante catálisis dual plata/organocatálisis**



2. **Síntesis catalítica enantioselectiva de 2-imidazolinonas**



3. **Adición catalítica enantioselectiva de isocianoacetatos a 4-alquilidenisoxazol-5-onas para la formación de compuestos espirocíclicos**



4. Resultados y discusión

4.1 2-Oxazolinas, significado y aproximación sintética a partir de isocianoacetatos.

El motivo estructural de 2-oxazolina está presente en un amplio número de compuestos orgánicos de interés entre los cuales encontramos productos naturales, fármacos y otros compuestos bioactivos. En la **Figura 5** se muestran algunos de estos compuestos que incluyen la agrupación 2-oxazolina en su estructura tales como el antihipertensivo rilmenidina,[77] el insecticida etoxazol,[10] el péptido cíclico westielamida,[11] o la fluvibactina,[78] un producto natural aislado de organismos marinos.

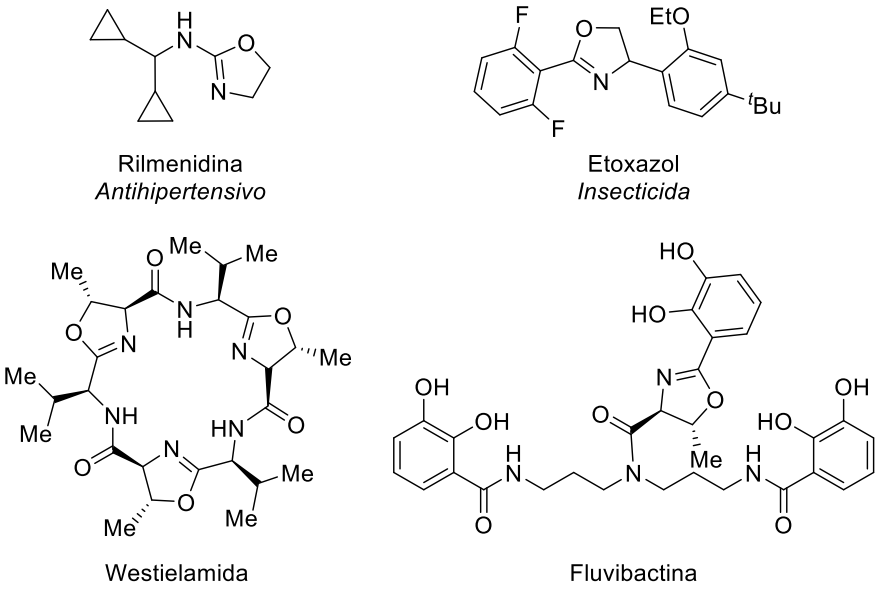


Figura 5. Compuestos con actividad biológica o de origen natural que contienen un motivo estructural de 2-oxazolina.

Además, las oxazolinas quirales presentan importantes aplicaciones en síntesis orgánica, pudiendo encontrar su estructura en ligandos privilegiados para catálisis asimétrica[79,80] y en building blocks para la obtención de 1,2-aminalcoholes quirales u otros compuestos de interés como el cloranfenicol (**Figura 6**).[81]

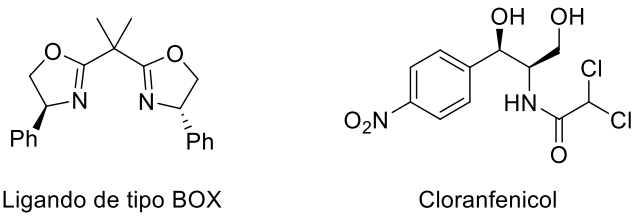
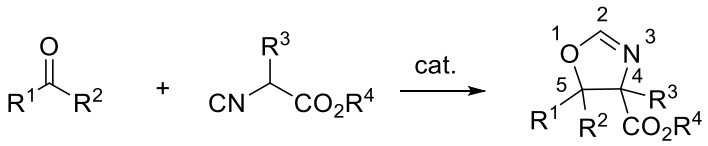


Figura 6. Ejemplo de un ligando para la catálisis asimétrica y un fármaco cuya estructura puede obtenerse a través de una 2-oxazolina quiral.

En los últimos años, la cicloadición formal [3+2] enantioselectiva entre compuestos carbonílicos e isocianoacetatos se ha convertido en un método de síntesis sencillo y elegante para la obtención de este tipo de compuestos. Mediante esta reacción se pueden obtener anillos de 2-oxazolina con dos centros estereogénicos de forma consecutiva. Como se ha visto en el capítulo de antecedentes bibliográficos, este tipo de reacción ha sido ampliamente estudiada utilizando aldehídos como electrófilos. Sin embargo, su

aplicación con cetonas supone un reto sintético debido a su menor electrofilia y apenas se encuentra explorada, limitándose a algunos ejemplos con compuestos 1,2-dicarbonílicos y acetofenonas. Por esta razón, nos planteamos en la primera parte de esta tesis el desarrollo de nuevos procedimientos catalíticos enantioselectivos para la cicloadición formal [3+2] enantioselectiva entre isocianoacetatos y cetonas (**Esquema 59**).



Esquema 59. Aproximación a la síntesis de 2-oxazolinas a partir de cetonas e isocianoacetatos.

Para llevar a cabo esta reacción de manera eficiente se planteó el uso de un sistema multicatalítico compuesto por una sal de plata que actua como ácido de Lewis y un organocatalizador bifuncional que combina una agrupación capaz de formar puentes de hidrógeno con el grupo carbonilo de la cetona (escuaramida, tiourea) y una amina terciaria capaz de actuar como base de Brønsted sobre una plataforma quiral (alcaloide de la *cinchona*), permitiendo la activación simultánea del electrófilo y del nucleófilo. De acuerdo con nuestra hipótesis, la agrupación escuaramida/tiourea activaría electrofílicamente la cetona mediante la formación de enlaces de hidrógeno al mismo tiempo que la coordinación del ion Ag^+ al grupo isocianuro facilitaría la desprotonación del isocianoacetato por parte de la amina del organocatalizador, incrementando la velocidad de reacción a través de esta doble activación del pronucleófilo (**Figura 7**). De esta forma, las especies reaccionantes quedarían posicionadas en el espacio para reaccionar siguiendo una orientación determinada por la estereoquímica de la plataforma quiral.

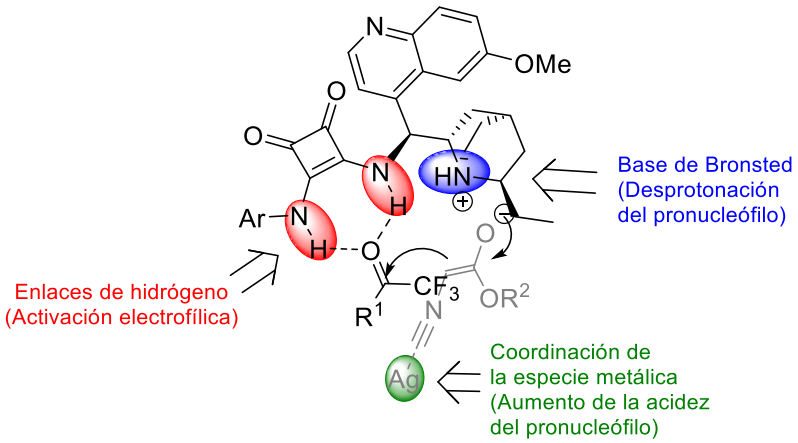


Figura 7. Hipótesis de activación catalítica.

4.2 Síntesis enantioselectiva de 5-trifluorometil-2-oxazolinas mediante catálisis dual plata/organocatálisis.

La introducción de átomos de flúor en moléculas orgánicas con potencial actividad biológica se ha convertido en los últimos años en una de las estrategias más empleadas por la industria química, farmacéutica y agroquímica para la obtención de nuevos compuestos activos que puedan ser introducidos en el mercado.[82] La introducción de átomos de fluor en una molécula orgánica produce cambios en sus propiedades físico-químicas que pueden alterar la afinidad entre el fármaco y el sitio activo, mejorar su biodisponibilidad o aumentar su estabilidad metabólica, resultando en una mejora de su acción.[83,84] Actualmente se estima que el 20% de los fármacos y el 30% de los productos agroquímicos contienen alguna función organofluorada. En la **Figura 8**, pueden observarse algunos ejemplos seleccionados de fármacos con alguna función organofluorada.

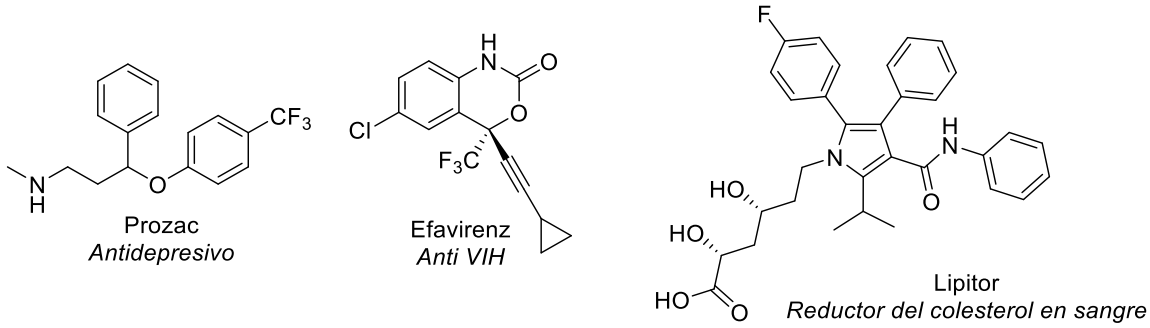
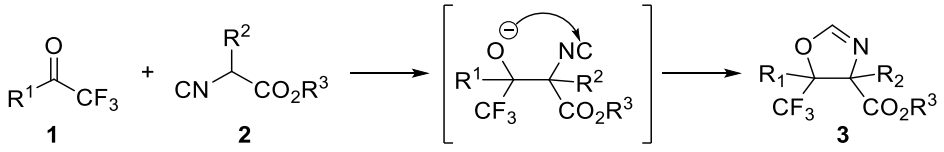


Figura 8. Ejemplos de fármacos con alguna función organofluorada en su estructura.

En este capítulo se describe la primera cicloadición formal [3+2] enantioselectiva de isocianoacetatos a trifluorometilcetonas para la generación de oxazolinas altamente funcionalizadas, con dos centros estereogénicos consecutivos, estando uno de ellos sustituido con un grupo trifluorometilo (**Esquema 60**).



Esquema 60. Síntesis de oxazolinas trifluorometiladas mediante cicloadición formal [3+2] entre trifluorometilcetonas y α-isocianoesteres

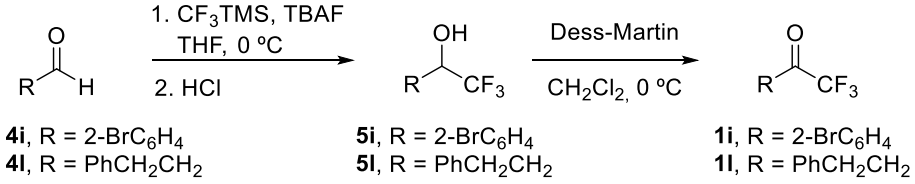
Una versión diastereoselectiva de esta reacción había sido descrita en 1994 por Hayashi,[85] sin embargo, no existían antecedentes en la bibliografía de dicha reacción de forma enantioselectiva.

A continuación, se describe la preparación de los materiales de partida y de los catalizadores utilizados en este estudio.

4.2.1 Síntesis de los materiales de partida

4.2.1.1 *Síntesis de las 2,2,2-trifluorometilcetonas*

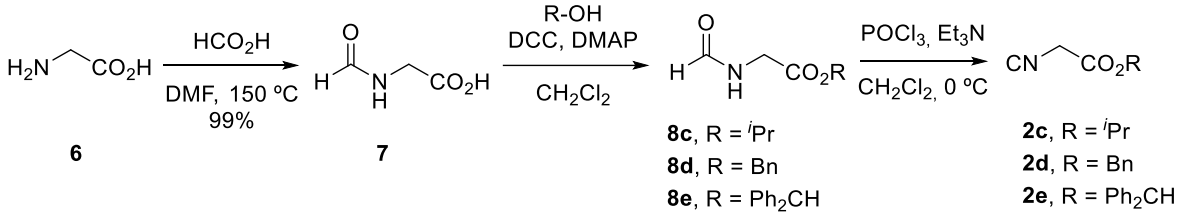
La mayoría de las trifluorometilcetonas utilizadas en este trabajo se obtuvieron de fuentes comerciales; no obstante, las trifluorometilcetonas **1i** y **1l** hubieron de sintetizarse en el laboratorio. La síntesis de estos productos se llevó a cabo en dos etapas de acuerdo con el procedimiento experimental descrito en la bibliografía.[86] En primer lugar, se adiciona el reactivo de Ruppert a los aldehídos correspondientes en THF a 0 °C, seguido de la hidrólisis en medio ácido del silil éter producido para dar el trifluorometil alcohol. A continuación, la oxidación de los alcoholes con el periodinano de Dess-Martin en diclorometano a 0 °C condujo a las trifluorometilcetonas correspondientes (**Esquema 61**).



Esquema 61. Síntesis de las trifluorometilcetonas.

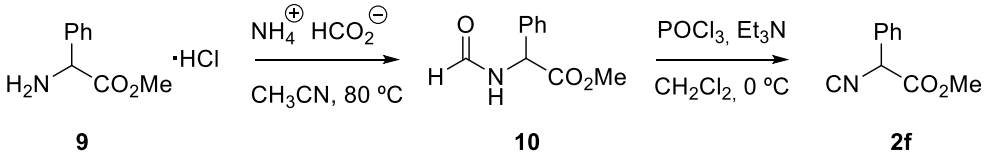
4.2.1.2 *Síntesis de los ésteres del ácido isocianoacético*

En este trabajo, se han utilizado principalmente isocianoacetato de metilo (**2a**) e isocianoacetato de *terc*-butilo (**2b**) obtenidos comercialmente. Además, se prepararon otros ésteres derivados del ácido isocianoacético tales como los isocianoacetatos de isopropilo (**2c**), bencilo (**2d**) y difenilmetilo (**2e**) a partir de *N*-formilglicina (**7**), obtenida cuantitativamente por tratamiento de glicina (**6**) con ácido fórmico en DMF a 150 °C. La *N*-formilglicina se esterificó con el alcohol correspondiente lo que seguido de deshidratación de la agrupación formamida con $POCl_3/Et_3N$ en diclorometano condujo a los correspondientes isocianoacetatos (**Esquema 62**).



Esquema 62. Procedimiento general para la síntesis de isocianoacetatos.

La síntesis de 2-fenil-2-isocianoacetato de metilo (**2f**) se sintetizó de forma similar a partir de una mezcla racémica del clorhidrato del éster metílico de fenilglicina (**Esquema 63**).



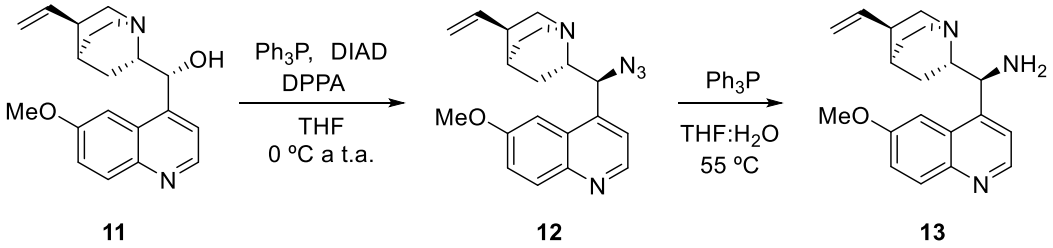
Esquema 63. Síntesis de 2-fenil-2-isocianoacetato de metilo.

4.2.1.3 *Síntesis de los organocatalizadores*

La mayoría de organocatalizadores utilizados en esta tesis poseen una agrupación escuaramida o tiourea sobre una estructura quiral derivada de alguno de los alcaloides de la *Cinchona*. Su síntesis se ha llevado a cabo siguiendo procedimientos descritos en la literatura.[87] A modo de ejemplo se describe las síntesis de la escuaramida **SQI** y de la tiourea **TI**, preparadas a partir de quinina, por ser los derivados de este alcaloide los que mejores resultados han proporcionado.

4.2.1.4 *Síntesis de 9-amino-9-desoxi-9-epiquinina*

Los organocatalizadores preparados presentan un átomo de nitrógeno en la posición 8 del alcaloide de la *cinchona*. La introducción de esta función oxigenada a partir del alcohol correspondiente se llevó a cabo mediante una reacción de Mitsonobu-Staudinger. En una primera etapa, el tratamiento de quinina (**11**) con trifenilfosfina, diisopropil diazacarboxilato (DIAD) y difenilfosforil azida (DPPA) conduce a la correspondiente azida **12**, con inversión en la configuración del carbono 8. El tratamiento reductor de esta azida con trifenilfosfina permite obtener la amina **13** (**Esquema 64**).

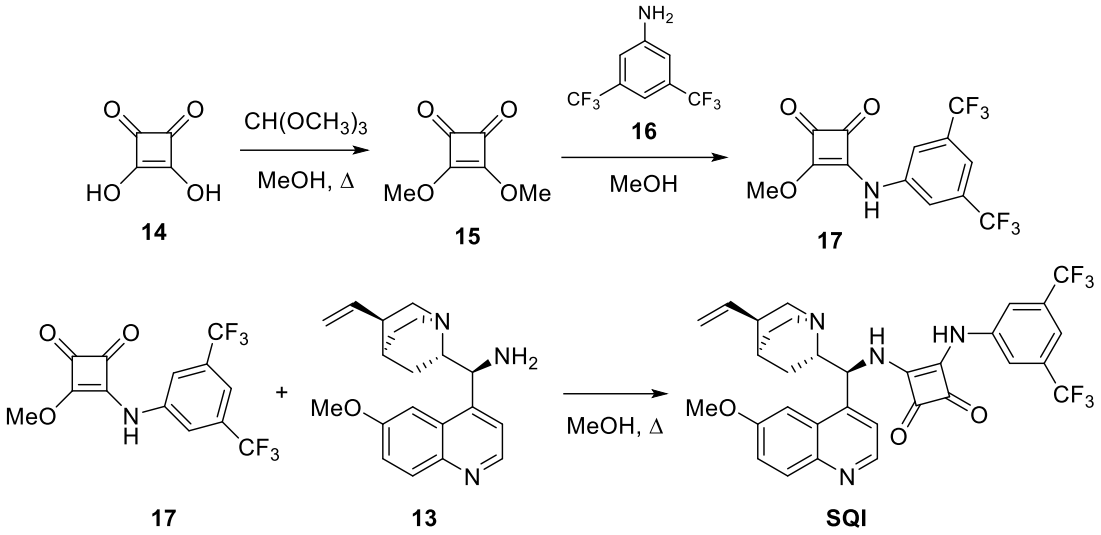


Esquema 64. Reacción de Mitsunobu-Staudinger sobre la quinina.

4.2.1.5 *Síntesis de la escuaramida SQI*

La escuaramida **SQI** se preparó por condensación de escuarato de metilo (**15**) con 3,5-bis(trifluorometil)anilina (**16**) y la amina **13** derivada de la quinina.

El escuarato de metilo (**15**) se preparó por tratamiento de ácido escuárico (**14**) con ortoformiato de metilo. La reacción de éste con 3,5-bis(trifluorometil)anilina (**16**) en metanol a temperatura ambiente condujo a la semiescuaramida **17.** En la preparación de otras escuaramidas que incorporan aminas menos nucleofílicas, la preparación de las semiescuaramidas correspondientes requirió la participación de triflato de cinc como ácido de Lewis en esta etapa. Finalmente, la adición de la amina **13** a la semiescuaramida **17** permitió obtener la escuaramida **SQI** (**Esquema 65**).



Esquema 65. Síntesis de las escuaramida **SQI** derivada de quinina.

Siguiendo un esquema análogo al anterior con alguna modificación se prepararon las escuaramidas que se muestran en la **Figura 9**.

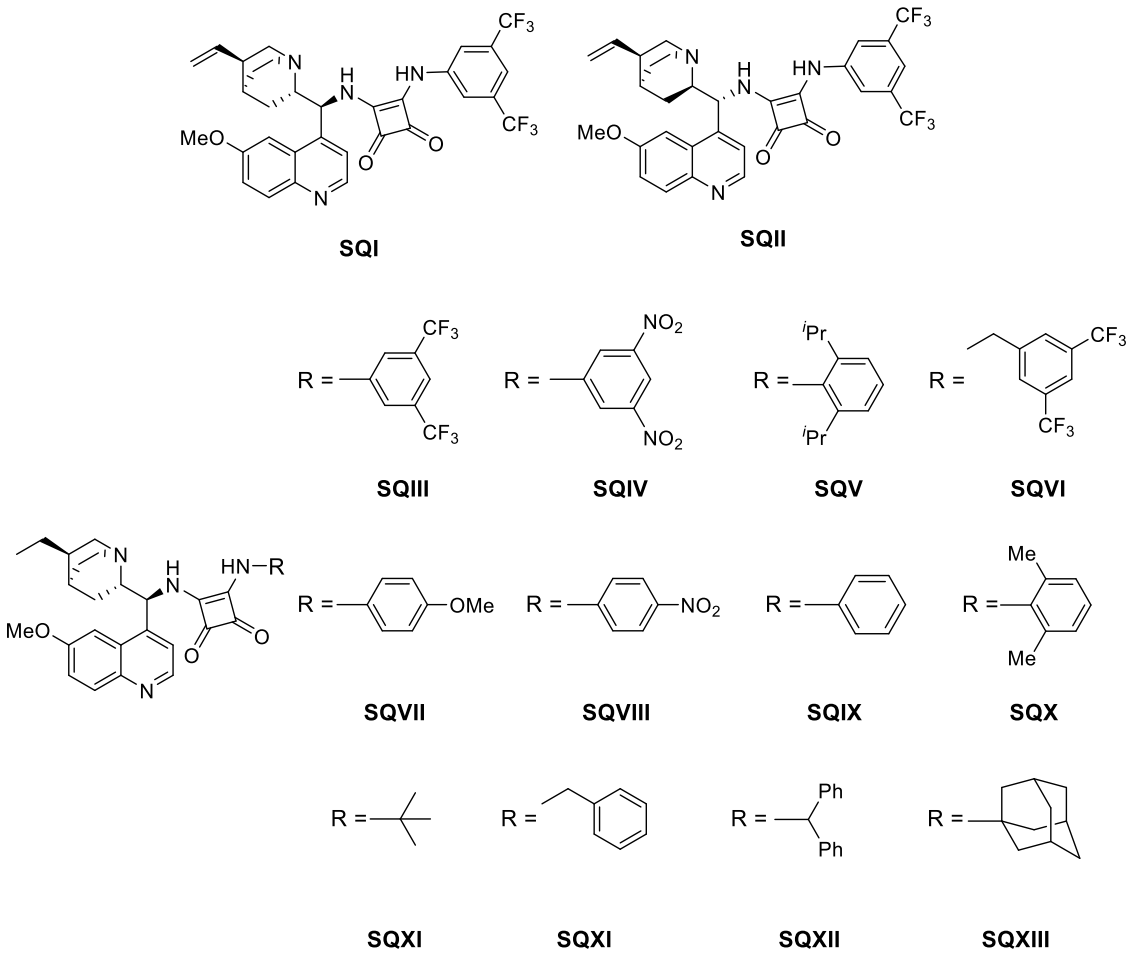
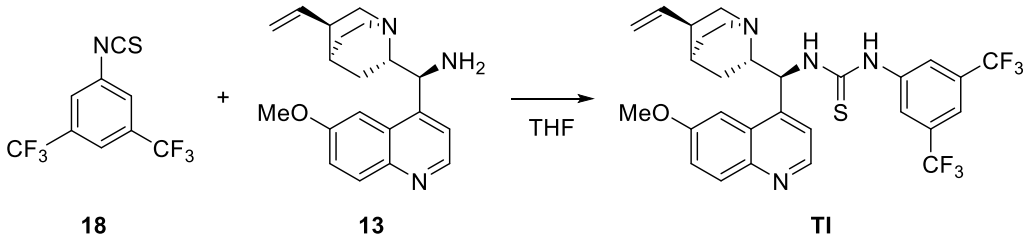


Figura 9. Escuaramidas más relevantes ensayadas en este trabajo.

4.2.1.6 *Síntesis de la tiourea TI*

Las tiourea **T1** se preparó en un paso mediante una reacción de adición de la amina **15** al 3,5-bis(trifluorometil)fenil-1-isotiocianato **18** (**Esquema 66**).



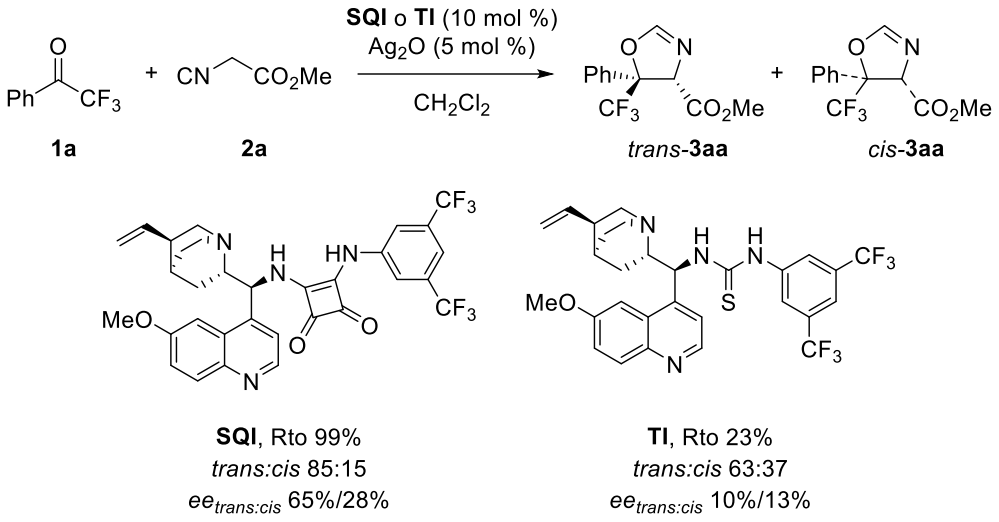
Esquema 66. Síntesis de la tiourea **T1**.

4.2.2 Síntesis enantioselectiva de oxazolinas fluoradas. Optimización de las condiciones de reacción

4.2.2.1 *Efecto de la estructura del organocatalizador*

La optimización de las condiciones de reacción se llevó a cabo utilizando como modelo la reacción entre isocianoacetato de metilo (**2a**) y 2,2,2-trifluorometilacetofenona (**1a**) para dar como producto la 2-oxazolina **3aa**. La reacción puede conducir a dos oxazolinas diastereoisoméricas *trans*-**3aa** y *cis*-**3aa**. La relación entre los dos diastereoisómeros se determinó en general por la integración relativa de las señales correspondientes al protón en la posición 4 del anillo de oxazolina, que suele aparecer a campo más bajo en el isómero *trans* que en el *cis*. En el caso de la oxazolina **3aa** esta señal aparece a δ 5.24 (d, J = 2.0 Hz) para el isómero *trans* y a δ 5.14 (dd, J = 2.1, 0.6 Hz) para el *cis*. Igualmente, la señal correspondiente al grupo metoxilo del éster aparece a campo más alto para el isómero *trans* (δ 3.27) que para el isómero *cis* (δ 3.92).

En una primera aproximación, se ensayó la reacción en presencia de la escuaramida **SQI** (10 mol %) o de la tiourea **TI** (10 mol %) y de óxido de plata (5 mol %), en diclorometano como disolvente a temperatura ambiente (**Esquema 67**).



Esquema 67. Primer ensayo de la reacción con una escuaramida y una tiourea.

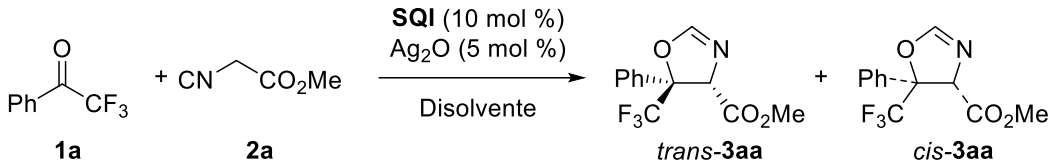
En idénticas condiciones, la escuaramida **SQI** se mostró mucho más activa que la tiourea **TI**, proporcionando el producto de reacción **3aa** con mayor rendimiento, diastereo- y enantioselectividad. La oxazolina *trans* se obtuvo como diastereoisómero mayoritario en ambos casos.

Cabe destacar que tanto la presencia de plata como del organocatalizador son necesarios para que se produzca la reacción, no observándose ningún avance después de 72 horas cuando la reacción se intentó únicamente con la participación de la escuaramida **SQI** o de óxido de plata por separado.

4.2.2.2 *Efecto del disolvente y de la temperatura*

Utilizando **SQI** (10 mol %) y óxido de plata (5 mol %) se ensayaron disolventes de distintas características, y diferentes temperaturas (**Tabla 1**).

Tabla 1. Ensayo de disolventes y temperaturas.[a]



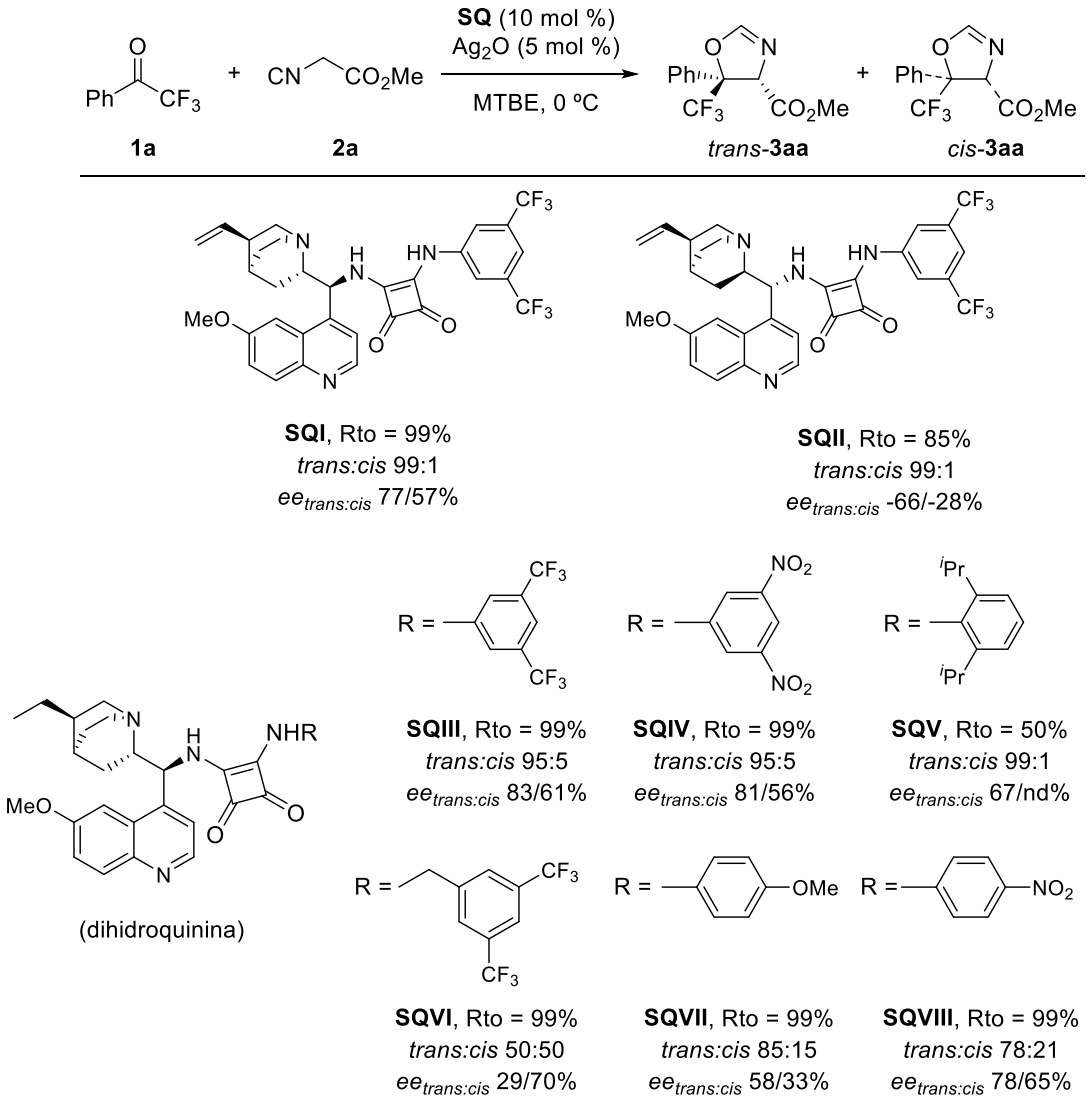
Entrada	Disolvente	T (°C)	t (h)	Rto (%)	*trans:cis*[b]	$ee_{trans/cis}$ (%)[c]
1	CH_2Cl_2	t.a.	6	99	85:15	65/28
2	AcOEt	t.a.	7	87	99:1	63/20
3	Tolueno	t.a.	0.5	72	99:1	58/nd
4	THF	t.a.	1	99	85:15	71/25
5	MTBE	t.a.	0.5	87	99:1	70/28
6	MTBE	0	0.5	99	99:1	77/57
7	MTBE	−20	0.5	89	99:1	77/29

[a] **1a** (0.25 mmol), **2a** (0.33 mmol), **SQI** (0.025 mmol), Ag_2O (0.0125 mmol), disolvente (2 mL). [b] Determinado por ^{1}H RMN. [c] Determinado mediante HPLC quiral.

El mejor disolvente para la reacción resultó ser el MTBE (**Tabla 1**, ***entrada 5***), ya que en conjunto ofrecía los mejores resultados, incluyendo buen rendimiento, diastereoselectividad completa y un exceso enantiomérico del 70%. Aunque en THF (***entrada 4***) se obtiene mejor rendimiento y un ee (71%) similar a MTBE, la diastereoselectividad disminuye sensiblemente por lo que se utilizó este último como disolvente de reacción. A continuación, se probó la reacción a 0 °C (***entrada 6***), produciéndose un incremento de exceso enantiomérico sin pérdida de diastereoselectividad. Sin embargo, un descenso mayor en la temperatura hasta −20 °C (***entrada 7***) no ofreció mayores ventajas.

4.2.2.3 *Efecto del catalizador*

En las mejores condiciones de reacción obtenidas (**Tabla 1**, ***entrada 6***), se ensayaron diferentes organocatalizadores de tipo escuaramida derivadas de alcaloides de la *cinchona* (**Esquema 68**).



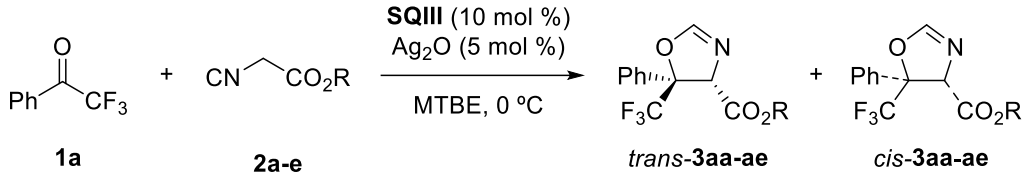
Esquema 68. Ampliación del estudio de la estructura del organocatalizador.

Como se observa, la escuaramida **SQII** derivada de quinidina, proporcionó el enantiómero contrario a la quinina, aunque con menor exceso enantiomérico que el obtenido con **SQI**. El organocatalizador **SQIII** derivado de dihidroquinina y 3,5-*bis*(trifluorometil)anilina, permitió elevar el exceso enantiomérico del producto hasta el 83%. A continuación, se ensayaron diferentes escuaramidas derivadas de dihidroquinina diferenciadas en la estructura de la amina no quiral. En general, todas las escuaramidas probadas proporcionaron la oxazolina **3aa** con buenos rendimientos en tiempos de reacción cortos. El diastereoisómero *trans* fue obtenido diastereoselectivamente en todos los casos excepto con la escuaramida **SQVI**. En definitiva, el mejor resultado en términos de enantioselectividad se obtuvo con la escuaramida **SQIII** que proporcionó la oxazolina **3aa** con rendimiento casi cuantitativo, relación diastereoisomérica *trans:cis* 95:5 y 83% de *ee* para el diastereoisómero mayoritario.

4.2.2.4 *Efecto del sustituyente en el grupo éster del isocianoacetato*

El efecto del grupo éster en el isocianoacetato sobre la estereoselectividad de la reacción se ensayó a continuación en las condiciones establecidas anteriormente (**Esquema 68**, **SQIII**). En estas condiciones se ensayó la reacción de la trifluorometilcetona **1a** con los isocianoacetatos de *terc*-butilo (**2b**), isopropilo (**2c**), bencilo (**2d**) y difenilmetilo (**2e**). Los resultados se recogen en la **Tabla 2**.

Tabla 2. Estudio de los diferentes isocianoacetatos ensayados.[a]



1a **2a-e**

Entrada	**2**	R	t (h)	**3**	Rto (%)[b]	*trans:cis*[c]	$ee_{trans/cis}$[d]
1	**2a**	Me	0.5	**3aa**	99	95:5	83/61
2	**2b**	^{t}Bu	24	**3ab**	99	68:32	90/75
3	**2c**	^{i}Pr	2	**3ac**	99	72:28	84/71
4	**2d**	Bn	2.5	**3ad**	99	85:15	73/nd
5	**2e**	Ph_2CH	23	**3ae**	99	64:36	17/53

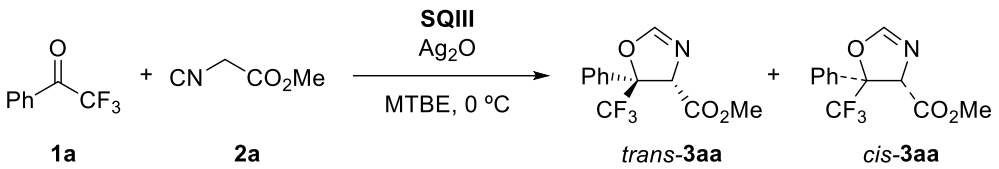
[a] **1a** (0.25 mmol), **2a** (0.33 mmol), **SQIII** (0.025 mmol), Ag_2O (0.0125 mmol), MTBE (2 mL). [b] Rendimiento del producto aislado. [c] Determinado por ^{1}H RMN. [d] Determinado mediante HPLC sobre fase estacionaria quiral.

Como se observa en la **Tabla 2**, la introducción de una agrupación éster más voluminosa produce una disminución de la diastereoselectividad. No obstante, resulta interesante señalar que con el éster *terc*-butílico se produce un aumento en el exceso enantiomérico del diastereoisómero mayoritario de hasta el 90% (***entrada 2***). Con los isocianoacetatos de isopropilo y de bencilo no se consigue mejorar la enantioselectividad de la reacción (***entradas 3 y 4***), mientras que con el ester de difenilmetilo, muy voluminoso, se observa una disminución acentuada tanto de la diastereo- como de la enantioselectividad (***entrada 5***).

4.2.2.5 *Efecto de la concentración y de la relación entre organocatalizador y sal de plata*

Por último, se estudió el efecto de la concentración y de la relación entre el organocatalizador **SQIII** y Ag_2O sobre el resultado de la reacción (**Tabla 3**).

Tabla 3. Reacción enantioselectiva entre 2,2,2-trifluoroacetofenona e isocianoacetato de metilo. Efecto de la concentración y de la relación entre **SQIII**/Ag_2O.[a]



1a **2a** *trans*-**3aa** *cis*-**3aa**

Entrada	[**1a**][b]	**III**:Ag_2O	*t* (h)	Rto (%)[c]	*trans:cis*[d]	$ee_{trans/cis}$(%)[e]
1	0.13	2:1	0.5	99	95:5	83/61
2	0.26	2:1	0.5	99	87:13	75/52
3	0.06	2:1	1	99	92:8	86/59
4	0.04	2:1	3	99	97:3	89/61
5	0.033	2:1	4	99	96:4	90/58
6[f]	0.033	1:2	3	90	99:1	82/–
7[g]	0.033	1:1	18	99	94:6	90/67

[a] **1a** (0.25 mmol), **2a** (0.33 mmol), **SQIII** (0.025 mmol), Ag_2O (0.0125 mmol), MTBE, 0 ºC. [b] Concentración molar. [c] Rendimiento del producto aislado. [d] Determinado mediante ^{1}H RMN. [e] Determinado mediante HPLC sobre fase estacionaria quiral. [f] Ag_2O (0.0125 mmol). [g] **SQIII** (0.063 mmol).

Como puede observarse en la tabla, la concentración tiene un efecto importante en la estereoselectividad. Conforme se aumenta la dilución se favorecen diastereoselectividades y excesos enantioméricos mayores sin afectar al rendimiento de la reacción (***entradas 1-5***), mientras que un aumento de la concentración conduce a las 2-oxazolinas con un descenso tanto en la enantioselectividad como en la diastereoselectividad (***entrada 2***). Los mejores resultados se obtienen a una concentración 0.033 M en 2,2,2-trifluoroacetofenona, alcanzando una diastereoselectividad 96:4, obteniendo como producto mayoritario el diastereoisómero *trans* con un exceso enantiomérico del 90% (***entrada 5***).

El último factor estudiado fue la relación molar entre organocatalizador y óxido de plata (***entradas 6-7***). Como se observa, el uso de dos equivalentes de Ag_2O por equivalente de escuaramida (***entrada 6***) conduce a una mejora de la diastereoselectividad, aunque lamentablemente con un descenso significativo de la enantioselectividad. Notablemente, el uso de una relación 1:1 escuaramida/Ag_2O proporciona resultados similares a la mezcla 2:1 utilizada inicialmente, siendo posible disminuir la carga catalítica hasta el 2.5 mol % sin un efecto notable en la estereoselectividad de la reacción, aunque con tiempos de reacción mayores (***entradas 6 y 7***).

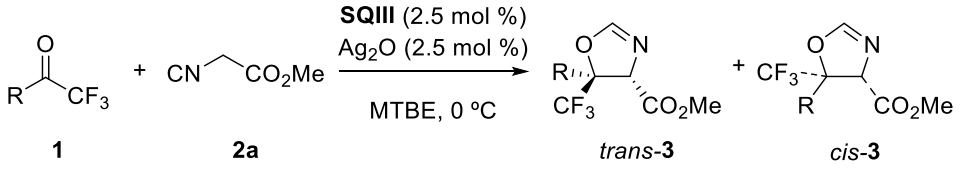
4.2.3 Alcance y limitaciones de la reacción

Como se ha mostrado en la sección **4.2.2.4** la adición de isocianoacetato de metilo proporciona las oxazolinas con buena diastereoselectividad, pero con enantioselectividad moderada, mientras que la reacción con isocianoacetato de *terc*-butilo, permite obtener mejores enantioselectividad a expensas de disminuir la diastereoselectividad. Por esta razón se decidió estudiar el alcance de ambas reacciones por separado.

4.2.3.1 *Adición de isocianoacetato de metilo a trifluorometilcetonas*

En las condiciones optimizadas (**Tabla 3**, ***entrada 7***) se llevó a cabo la reacción de isocianoacetato de metilo con diversas 2,2,2-trifluoroacetofenonas sustituidas en distintas posiciones del anillo aromático, con grupos de diferente naturaleza electrónica, grupos electrón dadores o sustituyentes halogenados. Los resultados se recogen en la **Tabla 4**.

Tabla 4. Reacción enantioselectiva de las 2,2,2-trifluorometilcetonas con isocianoacetato de metilo.[a]



Entrada	**1**	R	*t* (h)	**3**	Rto (%)[b]	*trans:cis*[c]	ee_{trans} (%)[d]
1	**1a**	Ph	4	**3aa**	99	96:4	90
2	**1b**	4-MeC_6H_4	5	**3ba**	99	94:6	87
3	**1c**	4-$MeOC_6H_4$	3.5	**3ca**	88	96:4	85
4	**1d**	4-ClC_6H_4	4	**3da**	99	80:20	84
5	**1e**	3-MeC_6H_4	5	**3ea**	99	94:6	90
6	**1f**	3-$MeOC_6H_4$	4	**3fa**	94	92:8	88
7	**1g**	3-BrC_6H_4	3.5	**3ga**	95	86:14	92
8	**1h**	2-$MeOC_6H_4$	16	**3ha**	99	99:1	85
9	**1i**	2-BrC_6H_4	14	**3ia**	93	85:15	70
10	**1j**	3,4-$Cl_2C_6H_3$	16	**3ja**	99	77:23	85
11	**1k**	2-tienil	5.5	**3ka**	99	92:8	90
12	**1l**	$PhCH_2CH_2$	15	**3la**	66	86:14	81
13	**1m**	CH_3	7	**3ma**	80	92:8	82
14[e]	**1a**	Ph	2	**3aa**	99	92:8	90

[a] **1a** (0.25 mmol), **2a** (0.33 mmol), **SQIII** (0.0063 mmol), Ag_2O (0.0063 mmol), MTBE (8 mL), 0 °C. [b] Rendimiento de los productos aislados. [c] Determinado mediante ^1H RMN. [d] Determinado mediante HPLC sobre fase estacionaria quiral. [e] Reacción escalada a 1.25 mmol de **1a**.

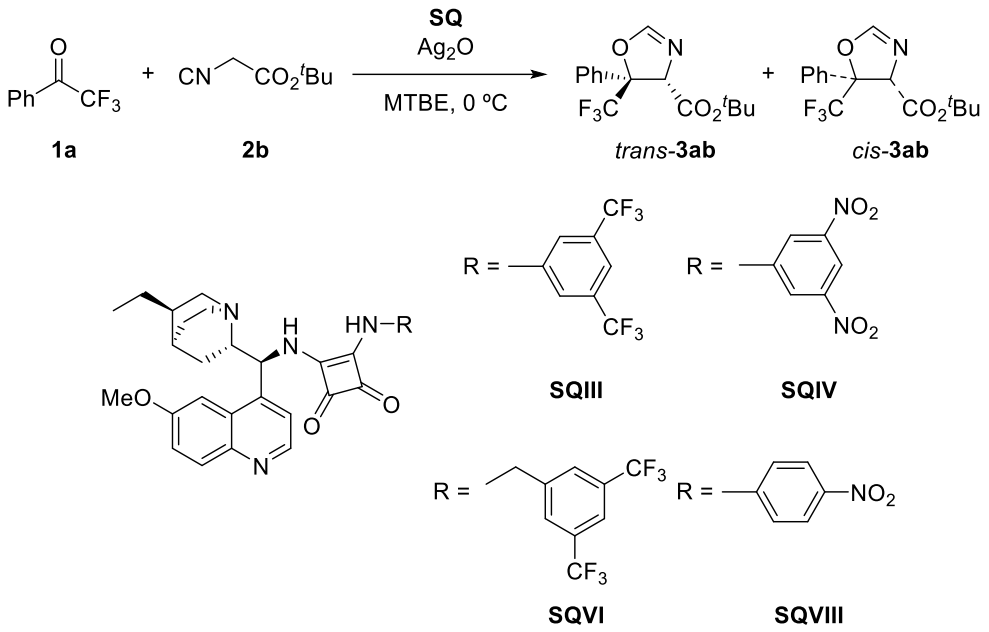
En general, se obtienen los productos de reacción con buenos rendimientos, altas diastereoselectividades y altos excesos enantioméricos. La presencia de sustituyentes en las posiciones *orto* o *para* del anillo aromático provocó una disminución de la enantioselectividad, mientras que las trifluoroacetofenonas *meta*-sustituidas dieron excesos enantioméricos similares o mayores que los obtenidos con la cetona **1a** (***entradas 5-7***). También se observó un efecto negativo de los grupos electrón aceptores en la diastereoselectividad (***entradas 4, 9 y 10***). El sustrato heterocíclico trifluoroacetiltiofeno (**1ka**) demostró ser un sustrato adecuado que reaccionó con buena diastereo y enantioselectividad con un *ee* del 90% (***entrada 11***). También se analizaron trifluorometilcetonas sustituidas con grupos alquilo **1l** y **1m**, que proporcionaron las oxazolinas **3la** y **3ma**, respectivamente, con diastereo y enantioselectividad moderada (***entradas 12 y 13***). Finalmente, la reacción se escaló a 1.25 mmoles del compuesto **1a**, obteniendo oxazolina **3aa** sin ninguna pérdida de eficiencia, lo que indica la robustez del método (***entrada 14***).

La configuración de los centros estereogénicos en el compuesto *trans*-**3ga** se determinó como (4*S*,5*S*) después de hidrólisis y análisis por rayos X del aminoalcohol resultante (ver apartado **4.2.4**). Para el resto de compuestos *trans*-**3aa-3ma** la estereoquímica absoluta se asignó suponiendo un mecanismo estereoquímico uniforme. La estereoquímica absoluta de las oxazolinas *cis*-**3aa-3ma** minoritarias no pudo ser determinada. Basado en resultados obtenidos en las reacciones con cetonas no fluoradas (ver apartado **4.3**) asumimos que presentan la configuración (4*S*,5*R*).

4.2.3.2 *Adición de isocianoacetato de terc-butilo a trifluorometilcetonas.*

Como se ha comentado en el apartado **4.2.2.4** la reacción con isocianoacetato de *terc*-butilo permitía la obtención de las 2-oxazolinas con mejor exceso enantiomérico. Antes de estudiar el alcance y limitaciones de la reacción, se decidió hacer una pequeña optimización adicional en la que se ensayaron distintas escuaramidas, la concentración de la reacción y la carga catalítica (**Tabla 5**).

Tabla 5. Reacción enantioselectiva entre 2,2,2-trifluroacetofenona e isocianoacetato de *terc*-butilo. Optimización adicional.[a]



Entrada	**SQ**	t (h)	Rto (%)[b]	*trans:cis*[c]	$ee_{trans/cis}$ (%)[d]
1	**SQIII**	0.5	99	68:32	90/75
2	**SQIV**	24	99	58:42	85/75
3	**SQVI**	20	99	56:44	57:43
4	**SQVIII**	24	99	65:35	93/83
5[e]	**SQVIII**	24	99	70:30	96/90
6[e,f]	**SQVIII**	48	99	70:30	96/89

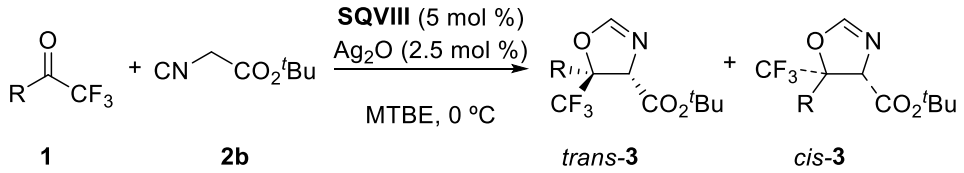
[a] **1a** (0.25 mmol), **2b** (0.33 mmol), **SQ** (0.026 mmol), Ag_2O (0.0125 mmol), MTBE (2 mL), 0 ºC. [b] Rendimiento del producto aislado. [c] Determinado por ^{1}H RMN. [d] Determinado mediante HPLC sobre fase estacionaria quiral.[e] MTBE (8 mL). [f] **SQVIII** (0.0063 mmol), Ag_2O (0.0063 mmol).

Los ensayos de la reacción de adición de isocianoacetato de *terc*-butilo a 2,2,2-trifluoroacetofenona con las escuaramidas **SQIV** y **SQVI** (***entradas 2 y 3***), condujeron a la oxazolina **3ab** con menor diastereo- y enantioselectividad que con **SQIII**. Con la

escuaramida **SQVIII**, se obtuvo aumento en el exceso enantiomérico hasta el 93% (***entrada 4***). Al llevar a cabo la reacción con este catalizador en condiciones de menor concentración se pudo mejorar tanto la diastereo- como la enantioselectividad obteniéndose **3ab** con una relación de diastereoisómeros 70:30 y un ee del 96% para el isómero mayoritario (***entrada 5***). Finalmente, la carga catalítica de **SQVIII** se puede reducir hasta el 2.5 mol % manteniendo los buenos resultados, aunque con un tiempo de reacción mayor (***entrada 6***), por lo que para el estudio del alcance y limitaciones de la reacción se decidió mantener las condiciones de la ***entrada 5***.

Después de este proceso de optimización adicional se estudió el alcance y limitaciones en la reacción con isocianoacetato de *terc*-butilo (**Tabla 6**).

Tabla 6. Reacción enantioselectiva de las trifluorometilcetonas con isocianoacetato de *terc*-butilo.[a]



Entrada	**1**	R	*t* (h)	**3**	Rto (%)[b]	*trans:cis*[c]	ee$_{trans/cis}$ (%)[d]
1	**1a**	Ph	4	**3ab**	99	70:30	96/90
2	**1b**	4-MeC_6H_4	5	**3bb**	87	66:34	93/96
3	**1c**	4-MeOC_6H_4	3.5	**3cb**	99	63:37	84/77
4	**1d**	4-ClC_6H_4	4	**3db**	99	53:47	96/90
5	**1e**	3-MeC_6H_4	5	**3eb**	94	76:24	97/87
6	**1f**	3-MeOC_6H_4	4	**3fb**	84	72:28	97/85
7	**1g**	3-BrC_6H_4	3.5	**3gb**	99	64:36	97/90
8	**1h**	2-MeOC_6H_4	16	**3hb**	80	94:6	94/70
9	**1i**	2-BrC_6H_4	14	**3ib**	99	99:1	91/nd
10	**1j**	3,4-$Cl_2C_6H_3$	16	**3jb**	99	53:47	94/85
11	**1k**	2-tienil	5.5	**3kb**	99	62:38	97/91
12	**1l**	PhCH_2CH_2	15	**3lb**	83	72:28	84/87

[a] **1a** (0.25 mmol), **2b** (0.33 mmol), **SQVIII** (0.0125 mmol), Ag_2O (0.0063 mmol), MTBE (8 mL), 0 °C. [b] Rendimiento de los productos aislados. [c] Determinado mediante ^{1}H RMN. [d] Determinado mediante HPLC sobre fase estacionaria quiral.

La reacción de las trifluorometilcetonas **1** con isocianoacetato de *terc*-butilo **2b** mostró un alcance similar a la reacción con el isocianoaetato de metilo **2a** obteniéndose diastereoselectividades moderadas y excelentes excesos enantioméricos en la mayoría de los casos. Las cetonas **1** con sustituyentes en la posición *orto* del anillo aromáticos condujeron esta vez a la mejor relación entre diastereoisómeros (***entradas 8 y 9***). El ensayo de la reacción con la 2,2,2-trifluoroacetofenona **1k** sustituida con un anillo heteroaromático de tiofeno proporcionó la oxazolina con moderada diastereoselectividad y alto exceso enantiomérico (***entrada 11***). Finalmente, se ensayó una trifluorometilcetona de cadena alifática obteniendo moderada diastereoselectividad y alto exceso enantiomérico (***entrada 12***).

El compuesto **3ib** pudo ser cristalizado y analizado por difracción de rayos X (**Figura 10**), el compuesto **3ib** se cristalizó de hexano:AcOEt. $C_{15}H_{15}BrF_3NO_3$;

Mr=394.19; monoclínico; grupo espacial = *P* 2_1; a=8.7236 (5), b=11.9043 (4); c=8.7256(4) Å, b= 118.539 (7); V=796.03 (8) $Å_3$; Z=2; ρ_{calcd}=1.645 Mg m^{-3}; μ=2.626 mm^{-1}; F (000) =396, lo que permitió asignar la estereoquímica absoluta de los compuestos **3ab-3lb** como (4*S*,5*S*), indicando un mecanismo estereoquímico similar al seguido por la reacción con isocianoacetato de metilo.

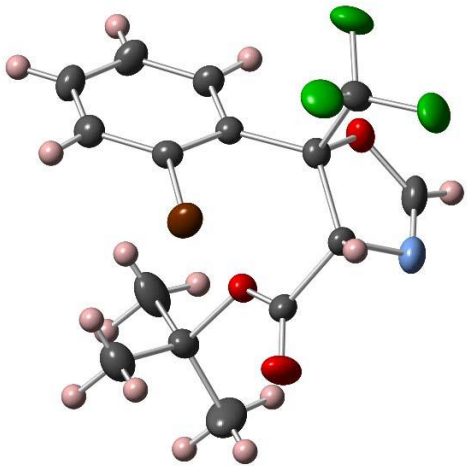


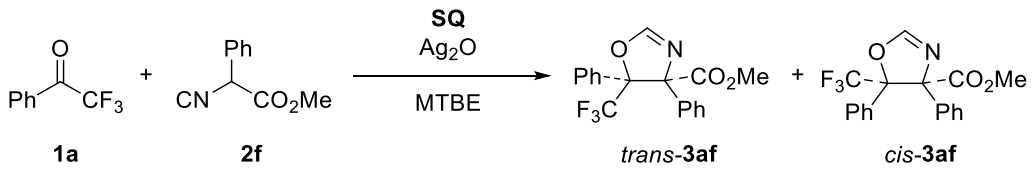
Figura 10. ORTEP para el compuesto **3ib**. Los elipsoides termales estan dibujados al nivel de 50% de probabilidad. Parámetro de Flack = 0.030(7). CCDC 1844052

4.2.3.3 *Adición de 2-fenil-2-isocianoacetato de metilo a trifluorometilcetonas.*

En la parte final de este trabajo nos planteamos el uso de un isocianoacetato sustituido en la posición alfa para la generación de oxazolinas con dos centros estereogénicos cuaternarios en posiciones consecutivas, uno de ellos sustituido con un grupo trifluorometilo, lo que constituye un reto sintético considerable.

La reacción entre la 1,1,1-trifluoroacetofenona (**1a**) y el 2-fenil-2-isocianoacetato de metilo (**2f**) se ensayó tanto en las condiciones optimizadas tanto para la reacción con isocianoacetato de metilo como para la reacción con isocianoacetato de *terc*-butilo (**Tabla 7**, ***entradas 1*** y ***2***), conduciendo en ambos casos a resultados similares. Además, contrariamente a lo sucedido en la adición de los isocianoacetatos de metilo y *terc*-butilo, la reacción con el isocianoéster **2f** condujo mayoritariamente a la oxazolina *cis*-**3af**.

Tabla 7. Reacción enantioselectiva entre 2,2,2-trifluroacetofenona y 2-fenil-2-isocianoacetato de metilo. Ajuste de condiciones.[a]



Entrada	**SQ**	T (°C)	t (h)	Rto (%)[b]	*trans:cis*[c]	$ee_{trans/cis}$ (%)[d]
1[e]	**SQIII**	0	24	99	25:75	38/83
2	**SQVIII**	0	10	99	24:76	0/85
3[f]	**SQVIII**	0	10	99	19:81	0/87
4[f]	**SQVIII**	–20	24	99	15:85	0/90

[a] **1a** (0.25 mmol), **2b** (0.33 mmol), **SQ** (0.0125 mmol), Ag_2O (0.0063 mmol), MTBE (8 mL), 0 °C, 24 h. [b] Rendimiento del producto aislado. [c] Determinado por ^{1}H RMN. [d] Determinado mediante HPLC sobre fase estacionaria quiral. [e] 0.0063 mmol de **SQIII**. [f] MTBE (2 mL).

La asignación de la estereoquímica relativa de las oxazolinas **3af** se llevó a cabo por comparación de los desplazamientos de la señal de los grupos metoxilo en el espectro de ^{1}H RMN, de acuerdo con lo observado previamente en las oxazolinas **3aa**. Así, la señal a 3.98 ppm se asignó a la oxazolina *cis*-**3af** mayoritaria, mientras que la señal a 3.13 ppm se asignó a la oxazolina *trans*-**3af** minoritaria (**Figura 11**).

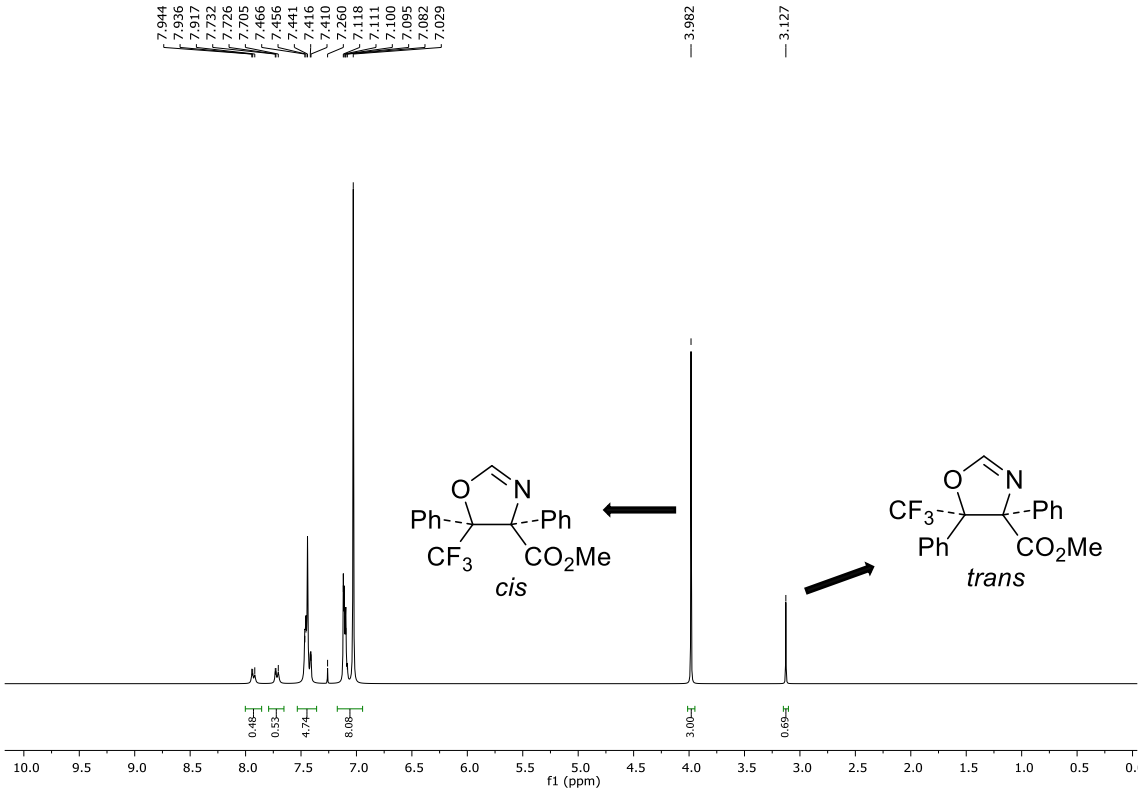


Figura 11. Espectro de RMN de la mezcla de diastereoisómeros del producto **3af**.

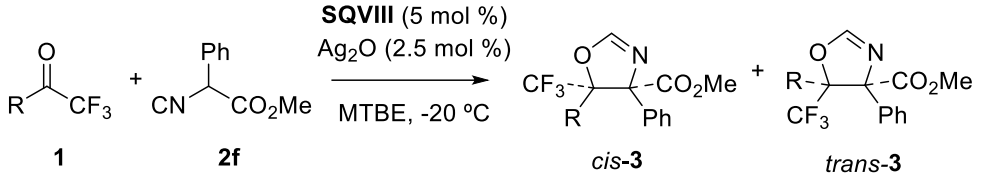
Con la escuaramida **SQVIII**, se reevaluó el efecto de la concentración (***entrada 3***). A una mayor concentración, mejoró tanto la diastereoselectividad (*trans:cis* 19:81), como

la enantioselectividad diastereoisómero mayoritario (87%), conservando el rendimiento cuantitativo de reacción.

Por último, dado que la reacción se completaba en pocas horas (~10 horas), se decidió bajar la temperatura de reacción a –20 °C (***entrada 4***) lo que condujo a la obtención de la oxazolina **3af**, con un rendimiento del 89%, alta diastereoselectividad (*trans:cis* = 15:85) y alto exceso enantiomérico para el diastereoisómero *cis* (90%).

Bajo estas condiciones se ensayó la reacción de cicloadición de 2-fenil-2-isocianoacetato de metilo a diversas trifluorometilcetonas para obtener las oxazolinas correspondientes con dos centros estereogénicos consecutivos (**Tabla 8**).

Tabla 8. Reacción enantioselectiva de las trifluorometilcetonas con 2-fenil-2-isocianoacetato de metilo.[a]



Entrada	**1**	R	t (d)	**3**	Rto (%)[b]	*trans:cis*[c]	$ee_{trans/cis}$ (%)[d]
1	**1a**	Ph	1	**3af**	89	15:85	90
2	**1c**	4-$MeOC_6H_4$	3	**3cf**	42	21:79	89
3	**1d**	4-ClC_6H_4	1	**3df**	95	10:90	89
4[f]	**1n**	4-BrC_6H_4	2	**3nf**	82	13:87	89
5	**1e**	3-MeC_6H_4	1	**3ef**	86	1:99	90
6	**1f**	3-$MeOC_6H_4$	3	**3ff**	86	15:85	89
7	**1g**	3-BrC_6H_4	7	**3gf**	81	2:98	88
8[e]	**1h**	2-$MeOC_6H_4$	5	**3hf**	–	–	–

[a] **1a** (0.25 mmol), **2b** (0.33 mmol), **SQVIII** (0.0125 mmol), Ag_2O (0.0063 mmol), MTBE (2 mL), –20 °C. [b] Rendimiento de los productos aislados. [c] Determinado mediante ^1H RMN. [d] Determinado mediante HPLC sobre fase estacionaria quiral. [e] No se observó avance de reacción transcurridos 5 días.

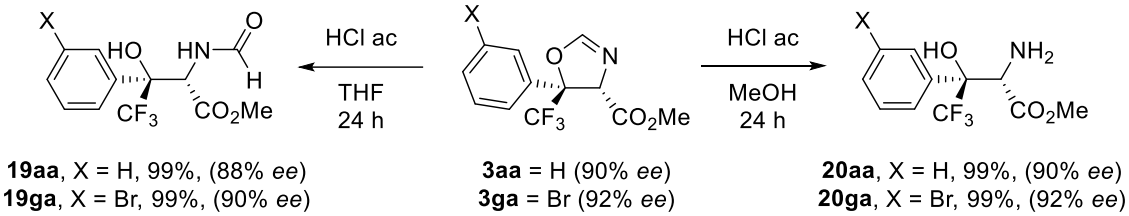
El sistema catalítico funciona satisfactoriamente con 2,2,2-trifluoroacetofenonas sustituidas en las posiciones *para* y *meta* del anillo aromático con grupos electrón dadores o ligeramente electrón aceptores, proporcionando el producto de reacción con buena diastereoselectividad y excesos enantioméricos cercanos al 90% en todos los casos ensayados (**Tabla 8**, ***entradas 1-7***). Sin embargo, la reacción no funciona con trifluoroacetofenonas sustituidas en la posición *orto*, así, por ejemplo, con la 2-metoxi-1,1,1-trifluoroacetofenona (**1h**) tras cinco días de reacción no se observó avance alguno de la reacción (***entrada 8***).

Lamentablemente, no pudimos obtener un monocristal de ninguna de las 2-oxazolinas con dos centros cuaternarios preparadas ni derivatizarlas a ningún producto de estereoquímica conocida, por lo que no ha sido posible asignar su configuración.

4.2.4 Transformaciones sintéticas

Las oxazolinas preparadas en este trabajo son precursores sintéticos de aminoalcoholes con una agrupación trifluorometilo, entre otros.

En primer lugar, se llevó a cabo la hidrólisis de las oxazolinas **3aa** y **3ga** con ácido clorhídrico cuyo resultado depende del disolvente en el que se realiza la reacción (**Esquema 69**).



19aa, X = H, 99%, (88% *ee*)
19ga, X = Br, 99%, (90% *ee*)

3aa = H (90% *ee*)
3ga = Br (92% *ee*)

20aa, X = H, 99%, (90% *ee*)
20ga, X = Br, 99%, (92% *ee*)

Esquema 69. Hidrólisis de las oxazolinas **3aa** y **3ga**.

La hidrólisis en un disolvente aprótico como el THF conduce a las hidroxiamidas **19aa** y **19ga**, tras la ruptura del anillo de 2-oxazolina, sin erosión en el exceso enantiomérico y con rendimiento cuantitativo. Por otra parte, la hidrólisis en metanol produce los 1,2-aminoalcoholes quirales **20aa** y **20ga**, con un centro cuaternario que contiene un grupo trifluorometilo. Este tipo de compuestos son interesantes ya que pueden utilizarse para la obtención de aminoácidos no proteinogénicos. La obtención de estos aminoalcoholes también se produce sin disminución del exceso enantiomérico.

Interesantemente, el aminoalcohol **20ga** pudo ser cristalizado y analizado por rayos X (**Figura 12**), datos cristalográficos para el compuesto **20ga**, cristalizado de hexano:AcOEt; $C_{11}H_{11}BrF_3NO_3$; Mr = 342.12; ortorómbico; grupo espacial = P_{212121}; a = 5.7871 (2), b = 13.5493 (6); c = 16.8357 (6) Å, V = 1320.11 (9) Å3; Z = 4; ρ_{calcd} = 1.721 Mg m^{-3}; μ = 3.153 mm^{-1}; F (000)=680, lo que permitió a su vez asignar la configuración de las oxazolinas obtenidas a partir de isocianoacetato de metilo **3aa-3ma**.

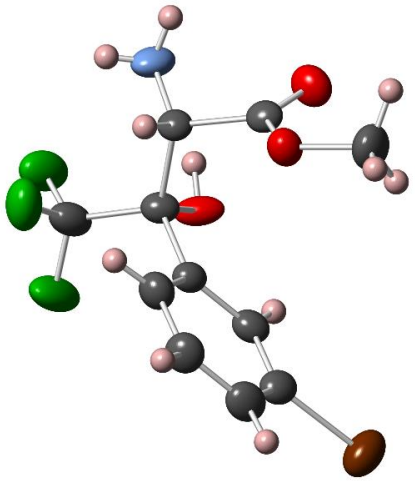
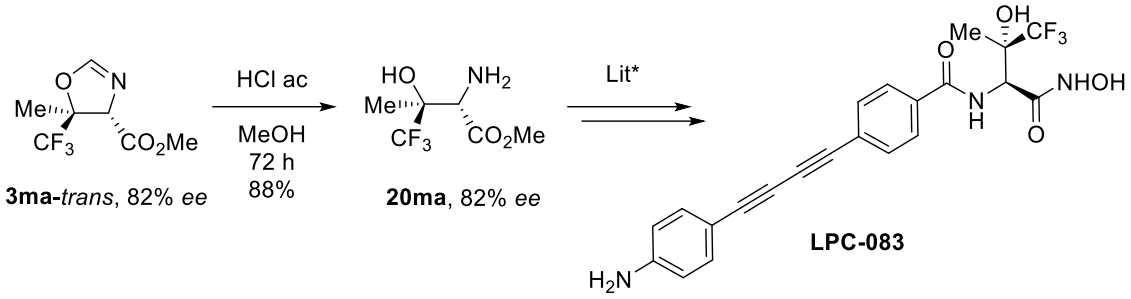


Figura 12. ORTEP para el compuesto **20ga**. Los elipsoides termales estan dibujados al nivel de 50% de probabilidad. Parámetro de Flack = 0.005(8). CCDC 1844051

Además, la hidrólisis de la oxazolina **3ma**, preparada con un 82% de *ee* a partir de isocianoacetato de metilo y 1,1,1-trifluoroacetona, con HCl en metanol durante 72 horas

permitió obtener el aminoalcohol **20ma**, el cual es un conocido precursor en la síntesis del compuesto antibacteriano **LPC-083**, el cual inhibe el LpxC, un enzima esencial en la ruta biosintética del lípido A en bacterias gram-negativas (**Esquema 70**).[88]



Esquema 70. Síntesis enantioselectiva formal de **LPC-083**.

En resumen, hemos desarrollado la primera cicloadición formal enantioselectiva [3 + 2] catalítica entre trifluorometilcetonas e isocianoacetatos. Utilizando un enfoque multicatalítico que combina un organocatalizador bifuncional escuaramida/base de Brønsted y Ag^+ como ácido de Lewis, se han podido obtener oxazolinas quirales con un centro estereogénico cuaternario sustituido con un grupo trifluorometilo y otro centro estereogénico contiguo terciario o cuaternario con diastereo- y enantioselectividad de buena a excelente. La reacción es aplicable a un amplio rango de aril y heteroaril trifluorometil cetonas y permite el acceso a hidroxiamino ésteres trifluorometilados quirales.

4.3 Síntesis enantioselectiva de *cis*-2-oxazolinas mediante catálisis dual plata/organocatálisis

Como se ha indicado en los antecedentes bibliográficos, la reacción entre isocianoacetatos y compuestos carbonílicos conduce a oxazolinas sustituidas, las cuales permiten un fácil acceso a la obtención de β-hidroxi-α-amino ácidos, que pueden presentar actividad biológica o ser utilizados en la síntesis de otros compuestos de interés farmacológico.

Debido a la importancia de las oxazolinas como "*building blocks*" y de la quiralidad en la actividad biológica y farmacológica, el desarrollo de procedimientos de catálisis asimétrica para llevar a cabo estas reacciones resulta de gran interés. A pesar de esto, los mayores avances en esta área se han descrito en reacciones de adición de isocianoacetatos a aldehídos mientras que las adiciones enantioselectivas a cetonas proquirales, que conducirían a la formación de centros estereogénicos cuaternarios, son escasas. Esto se debe principalmente a dos factores:

a) La menor reactividad de las cetonas debido a su menor carácter electrofílico y mayor impedimento estérico.

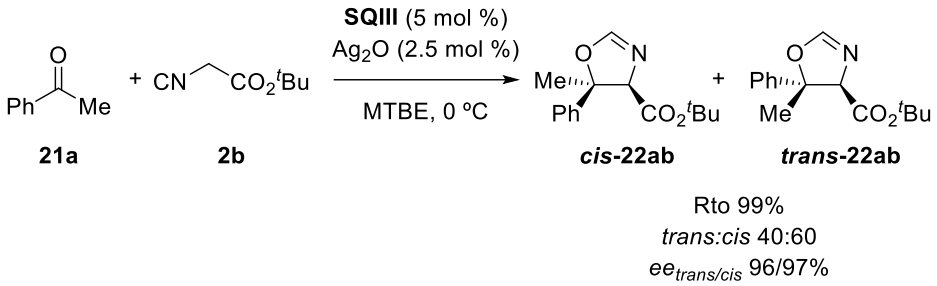
b) La mayor dificultad de diferenciación de las caras enantiotópicas.[35]

Como consecuencia de estas dificultades, cuando iniciamos nuestra investigación sólo se encontraban descritos en la bibliografía unos pocos ejemplos de reacción de isocianoacetatos con compuestos 1,2-dicarbonílicos, más reactivos, tales como isatinas[33] o α-ceto ésteres.[32] Por otra parte, Dixon había publicado el único ejemplo disponible de reacción con cetonas no activadas, consistente en la adición de isocianoacetatos a aril-alquil cetonas para dar *trans*-4-carboxil-2-oxazolinas con buena diastereo y enantioselectividad.[35]

En el capítulo anterior hemos descrito el desarrollo de una reacción enantioselectiva de adición de isocianoacetatos a triflouorometil cetonas utilizando un sistema multicatalítico. A continuación, describimos la aplicación de este sistema catalítico en la adición a cetonas no activadas que, a diferencia del sistema de Dixon, conduce a la obtención de *cis*-4-carboxil-2-oxazolinas.

4.3.1 Optimización de las condiciones de reacción

Para llevar a cabo la optimización de las condiciones de reacción se utilizó la reacción entre isocianoacetato de *terc*-butilo (**2a**) y acetofenona (**21a**). Inicialmente se emplearon las condiciones optimizadas para la reacción con trifluorometil cetonas descrita en el capítulo anterior. Se utilizó el organocatalizador bifuncional **SQIII** (5 mol %), óxido de plata (2.5 mol %), a una concentración 0.033 M de acetofenona en MTBE como disolvente, y a una temperatura de 0 °C (**Esquema 71**).

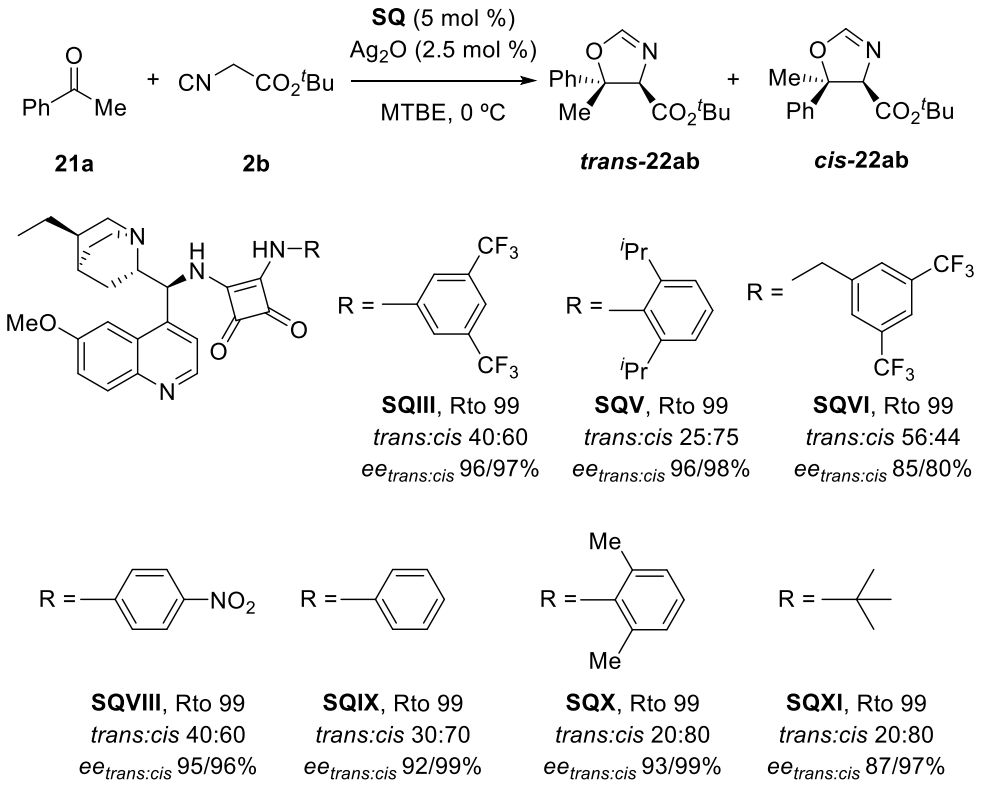


Esquema 71. Reacción de adición de isocianoacetato de *terc*-butilo a acetofenona.

En estas condiciones, la reacción se completó en 24 horas con un rendimiento cuantitativo y se obtuvo una mezcla de dos oxazolinas diastereoisoméricas en relación *trans:cis* de 40 a 60, estando ligeramente favorecida la formación de la oxazolina *cis*. Además, ambos diastereoisómeros se obtuvieron con excelente exceso enantiomérico (*trans* = 96%, *cis* = 97%). Cabe remarcar que, contrariamente al método descrito por Dixon que favorecía la formación de la oxazolina *trans*, nuestro procedimiento conducía mayoritariamente a la oxazlina *cis*. La proporción entre ambos diastereoisómeros se determinó por la integración relativa de las señales correspondientes a los grupos *terc*-butilo y metilo que aparecen a 1.56 ppm y a 1.66 ppm en el isómero *trans* y 0.97 ppm y 1.80 ppm en el isómero *cis*, respectivamente.

4.3.1.1 *Estudio de la estructura del organocatalizador*

Con el fin de incrementar la diastereoselectividad hacia el diastereoisómero *cis* se ensayaron diversos organocatalizadores de tipo escuaramida, conservando el disolvente, la temperatura y las proporciones de los reactivos. En las escuaramidas ensayadas se mantuvo la amina derivada de dihidroquinina como estructura quiral, la cual había proporcionado los mejores resultados en la adición a trifluoacetofenonas, y se modificó la amina aquiral de la estructura de la escuaramida (**Esquema 72**).



Esquema 72. Escuaramidas derivadas de dihidroquinina ensayadas en este trabajo.

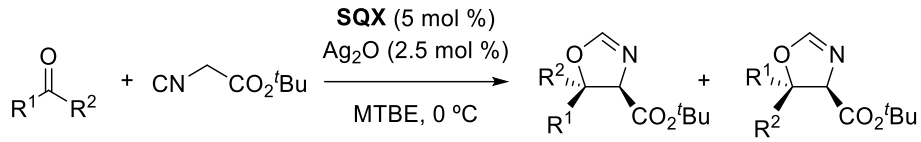
Se ensayaron diferentes escuaramidas derivadas de anilinas sustitutidas. En primer lugar, se ensayaron las escuaramidas **SQIII** y **SQVIII** que habían proporcionado buenos resultados en la adición de isocianoacetatos a 2,2,2-trifluoroacetofenonas. Ambas proporcionaron resultados muy similares, con rendimientos cuantitativos y elevada enantioselectividad, aunque con pobre diastereoselectividad. Por otra parte, la escuaramida **SQIX** derivada de anilina permitió obtener el compuesto **22ab** con mejor diastereoselectividad (*trans:cis* = 30:70), pero con un exceso enantiomérico del 99% para el diastereoisómero mayoritario *cis*. La introducción de sustituyentes en las posiciones 2 y 6 del anillo de anilina permitió incrementar la diastereoselectividad. Así, la escuaramida **SQV**, con dos grupos isopropilo en estas posiciones, permitió obtener la oxazolina con una relación diastereomérica *trans:cis* 25:75 y 98% de exceso enantiomérico, mientras que con la escuaramida **SQX**, derivada de 2,6-dimetilanilina se obtuvo la mejor diastereoselectividad *trans:cis* (20:80) con excelente enantioselectividad, 93% y 99% *ee*, respectivamente, para ambos diastereoisómeros. Por último, considerando el hecho de que la introducción de impedimento estérico en las proximidades del átomo de nitrógeno mejoraba la distereoselectividad, se sintetizó la escuaramida **SQXI,** derivada de *terc*-butilamina que proporcionó resultados similares a la escuaramida **SQX,** con buena diastereoselectividad (*trans:cis* = 20:80), pero con un exceso enantiomérico ligeramente menor.

4.3.2 Alcance y limitaciones de la reacción

En las condiciones optimizadas establecidas en el apartado anterior con la combinación **SQX**/Ag_2O se estudió el alcance y las limitaciones de la reacción, ensayando un gran número de derivados de acetofenona y otras cetonas con diferentes

isocianoacetatos. En la **Tabla 9** se presentan los resultados de la reacción entre acetofenonas e isocianoacetato de *terc*-butilo.

Tabla 9. Reacción enantioselectiva entre cetonas e isocianoacetatos.



Entrada	**21**	R^1	R^2	T (h)	**22**	Rto (%)	*cis:trans*	$ee_{cis/trans}$
1	**21a**	Ph	Me	26	**22ab**	99	80:20	99/93
2	**21b**	4-MeC_6H_4	Me	20	**22bb**	79	77:23	99/90
3	**21c**	4-$MeOC_6H_4$	Me	72	**22cb**	70	78:22	98/99
4	**21d**	4-BrC_6H_4	Me	48	**22db**	99	75:25	98/93
5	**21e**	4-$NO_2C_6H_4$	Me	20	**22eb**	95	56:44	96/95
6	**21f**	3-MeC_6H_4	Me	13	**22fb**	88	62:38	99/97
7	**21g**	3-$MeOC_6H_4$	Me	14	**22gb**	60	70:30	98/93
8	**21h**	3-ClC_6H_4	Me	14	**22hb**	75	74:26	99/91
9	**21i**	3-$NO_2C_6H_4$	Me	13	**22ib**	97	63:37	95/90
10	**21j**	2-MeC_6H_4	Me	24	**22jb**	91	91:9	99/89
11	**21k**	2-$MeOC_6H_4$	Me	16	**22kb**	99	95:5	99/-
12	**21l**	2-ClC_6H_4	Me	12	**22lb**	99	92:8	98/92
13	**21m**	2-$NO_2C_6H_4$	Me	12	**22mb**	99	73:27	9530
14	**21n**	2-Tiofeno	Me	20	**22nb**	81	45:55	92/98
15	**21o**	Ph	^{i}Pr	12	**22ob**	63	98:2	97
16	**21p**	Ph	$PhCH_2$	48	**22pb**	99	61:39	97/95
17	**21q**	Me	Me	20	**22qb**	85	–	96
18	**21r**	-$(CH_2)_5$-	Me	20	**22rb**	96	–	95
19	**21s**	^{i}Pr-CH_2	Me	48	**22sb**	71	70:30	98/56
20	**21t**	^{c}Pr	Me	48	**22tb**	81	56:44	97/87
21[e]	**21a**	Ph	Me	72	**22aa**	82	80:20	96/84
22[f]	**21a**	Ph	Me	48	**22ac**	76	70:30	97/90
23[g]	**21a**	Ph	Me	48	**22ad**	78	80:20	96/82

[a] 1 (0.25 mmol), 2 (0.32 mmol) Ag_2O (0.0063 mmol), **SQX** (0.0125 mmol), MTBE (8 mL), 0 °C. [b] Rendimiento de los productos aislados. [c] Determinado mediante ^{1}H RMN. [d] Determinado mediante HPLC con fase estacionaria quiral. [e] Reacción llevada a cabo con isocianoacetato de metilo (**2a**). [f] Reacción llevada a cabo con isocianoacetato de isopropilo **2c**. [g] Reacción llevada a cabo con isocianoacetato de bencilo **2e**.

La reacción de isocianoacetato de *terc*-butilo con diversas acetofenonas sustituidas con grupos electrón aceptores o electrón dadores en diferentes posiciones del anillo aromático proporcionó las *cis*-oxazolinas correspondientes **22ab**-**22mb** con buenos rendimientos y diastereoselectividad entre buena y alta (*cis:trans* de 62:38 a 95:5) (**Tabla 9**, ***entradas 1-13***) que fue más moderada en el caso de nitroacetofenonas (***entradas 5, 9*** y ***13***). La diastereoselectividad fue especialmente altas con acetofenonas *orto*-sustituidas (***entradas 10-13***). En todos los casos, ambos diastereoisómeros se obtuvieron con excelentes excesos enantioméricos, superiores al 95% para el principal diastereómero *cis*. En general, la reacción con acetofenonas sustituidas tuvo lugar con una

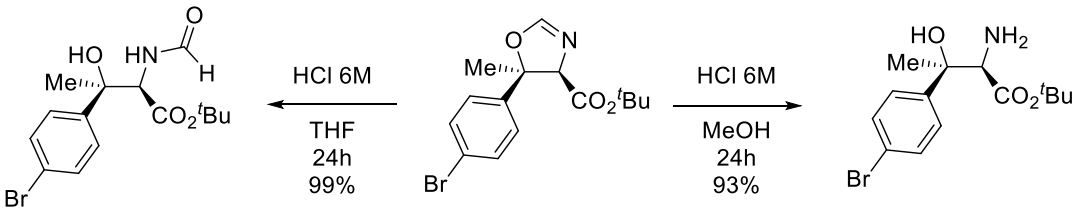
diastereoselectividad ligeramente inferior, pero con excesos enantioméricos superiores a los obtenidos con el catalizador de Dixon para sustratos similares.[35]

La reacción también funcionó con un sustrato heterocíclico como el 2-acetiltiofeno (**21n**) para dar la oxazolina **22nb,** aunque con baja diastereoselectividad, favoreciendo ligeramente el isómero *trans*, pero aún con excelentes excesos enantioméricos para ambos diastereómeros (***entrada 14***). La fenilisopropil cetona **21o** proporcionó la *cis* oxazolina **22ob** prácticamente como un único diastereisómero con un 97% *ee* (***entrada 15***), mientras que la desoxibenzoína (**21p**) produjo una mezcla diastereomérica 61:39 de oxazolinas **22pb** con excelente enantioselectividad para ambos isómeros (***entrada 16***). Finalmente, se estudió la reacción con varias cetonas alifáticas, que son sustratos desafiantes para esta reacción. Sorprendentemente, la propanona (**21q**), que en las condiciones de Dixon proporciona la oxazolina correspondiente casi en forma racémica, condujo en nuestro caso a la oxazolina **22qb** con excelente rendimiento y exceso enantiomérico (***entrada 17***). De manera similar, la ciclohexanona (**21r**) dio la oxazolina espirocíclica **22rb** con un rendimiento del 96% y un 95% de *ee* (***entrada 18***). Las cetonas asimétricas como la 4-metil-2-pentanona (**21s**) y el acetilciclopropano (**21t**) condujeron, respectivamente, a las oxazolinas **22sb** y **22tb** con diastereoselectividad moderada pero excelente enantioselectividad para los principales diastereómeros (***entradas 19*** y ***20***), demostrando el amplio alcance de la reacción con respecto a las cetonas no activadas.

Finalmente, se llevó a cabo la reacción con los isocianoacetatos de metilo, isopropilo y bencilo, obteniendo en todos los casos rendimientos cuantitativos, moderada diastereoselectividad, algo menor para el isocianoacetato de isopropilo, y excelentes excesos enantioméricos en la oxazolina mayoritaria *cis* (***entradas 21, 22*** y ***23***).

4.3.3 Transformaciones sintéticas y determinación de la configuración absoluta

Como se ha descrito en el capítulo anterior, las oxazolinas son precursores sintéticos de aminoalcoholes. Así, el tratamiento de la oxazolina *cis*-**22db** con ácido clorhídrico 6 M en MeOH durante 24 horas proporcionó el aminoalcohol **24** con un rendimiento del 93%, aunque lamentablemente con una pérdida notable de exceso enantiomérico (**Esquema 73**). De manera similar, la hidrólisis parcial del compuesto *cis*-**22db** por tratamiento con ácido clorhídrico acuoso en THF dio un rendimiento cuantitativo de la hidroxiformamida **23** sin ninguna pérdida de *ee*.



23, 98% *ee* — *cis*-**23db**, 98% *ee* — **24**, 81% *ee*

Esquema 73. Hidrólisis de la oxazolina *cis*-**23db**.

Para determinar la configuración absoluta, se cristalizó la formamida **23** obtenida de la hidrólisis del producto *cis*-**22db** y se sometió a análisis por difracción de rayos X. De esta forma se pudo asignar la configuración 4*R*,5*R* para la oxazolina mayoritaria *cis*-**22db** (**Figura 13**).

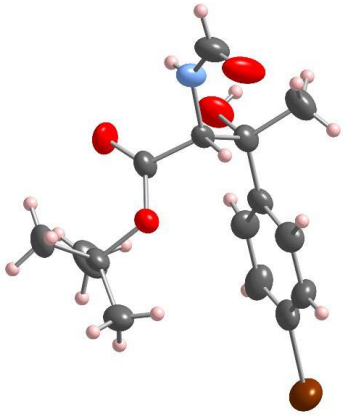


Figura 13. Espectro de rayos X del compuesto *cis*-**23**.

La estereoquímica absoluta de las oxazolinas *cis*-**22** restantes se asignó de la misma forma, suponiendo una ruta estereoquímica uniforme para todas ellas. Por otro lado, la estereoquímica absoluta de los diastereoisómeros minoritarios *trans* se asignó como 4*R*,5*S* comparando los datos con los descritos por Dixon para estos compuestos.[35]

En resumen, en este capítulo hemos desarrollado un nuevo procedimiento catalítico enantioselectivo para la reacción entre cetonas no activadas e isocianoacetatos para dar oxazolinas quirales que contienen un centro estereogénico cuaternario. Nuestra estrategia se basa en un enfoque multicatalítico que combina un organocatalizador con una base de Brønsted bifuncional y Ag^+ como ácido de Lewis. La reacción proporciona *cis*-oxazolinas con buena diastereoselectividad y excelente enantioselectividad. De esta manera, nuestro método puede considerarse complementario al desarrollado por Dixon que conduce a *trans*-oxazolinas. Además, la reacción en nuestras condiciones muestra un alcance mayor y puede aplicarse tanto a aril-alquil como a alquil-alquil cetonas.

4.4 Síntesis catalítica enantioselectiva de 2-imidazolinonas

Las 2-imidazolinonas son compuestos que presentan una agrupación de tipo urea formando parte de un anillo de cinco miembros. Esta estructura se encuentra frecuentemente en productos naturales y en compuestos con actividad biológica o farmacológica como por ejemplo la espironaamidina aislada de la esponja marina *Leucetta microraphis*,[89] un inhibidor de la proteasa del VIH.[90] Además, las 2-imidazolinonas quirales se utilizan como auxiliares quirales,[91] ligandos quirales[92] o intermedios en síntesis orgánica (**Figura 14**).[93]

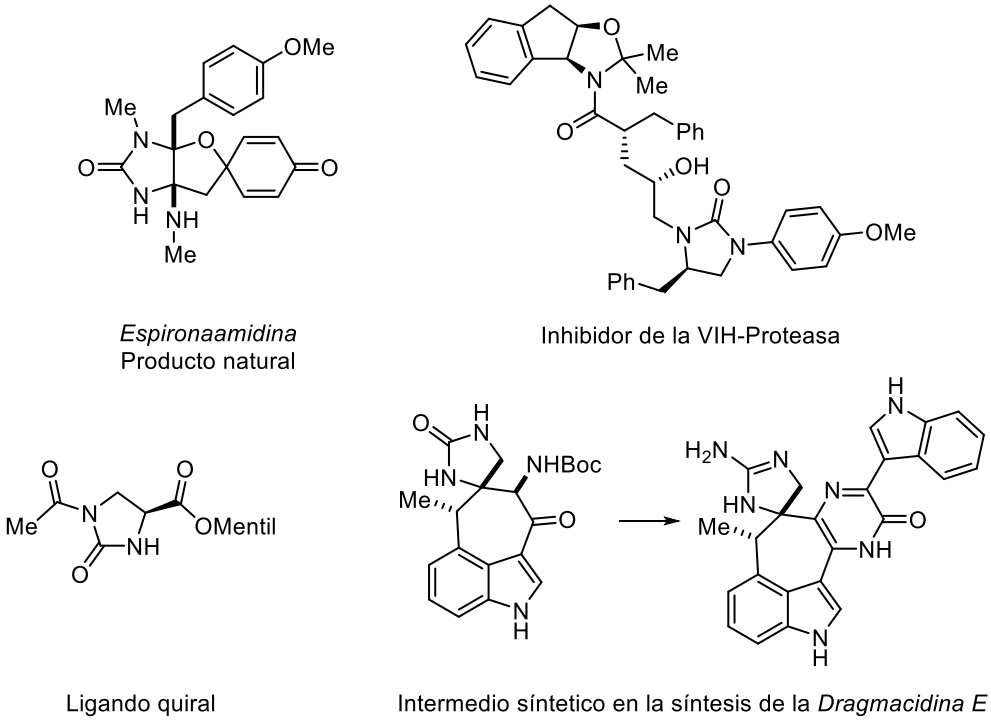
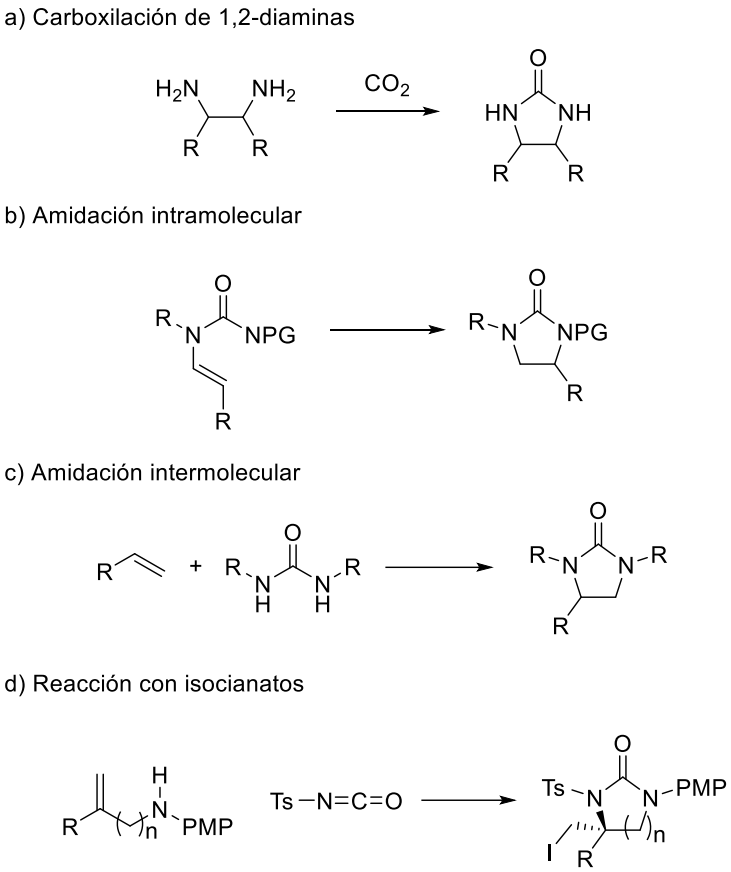


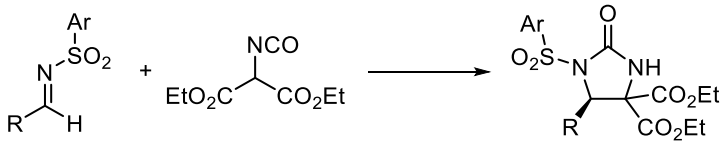
Figura 14. Ejemplos de compuestos orgánicos relevantes que contienen la estructura de 2-imidazolinona en su estructura.

Dada su prevalencia e importancia en química orgánica, se han desarrollado numerosas metodologías para la obtención de este tipo de productos, como por ejemplo la carboxilación de 1,2-diaminas,[94] reacciones de amidación intramolecular[95] o intermolecular,[96] o las reacciones entre aminas e isocianatos (**Esquema 74**).[97]



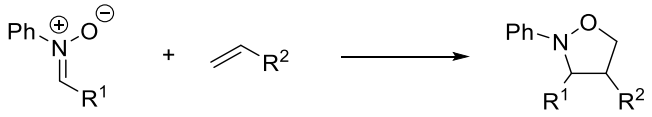
Esquema 74. Diferentes estrategias utilizadas para la síntesis de 2-imidazolinonas.

Sin embargo, apenas existen procedimientos que permitan la construcción enantioselectiva del anillo de 2-oxazolinona con formación concomitante de un enlace C–C. En este sentido, cabe señalar la reacción de cicloadición formal entre *N*-sulfoniliminas e isocianatos derivados del ácido malónico descrita por Takemoto que conduce a las correspondientes oxazolinonas con un único centro estereogénico (**Esquema 75**).[98]



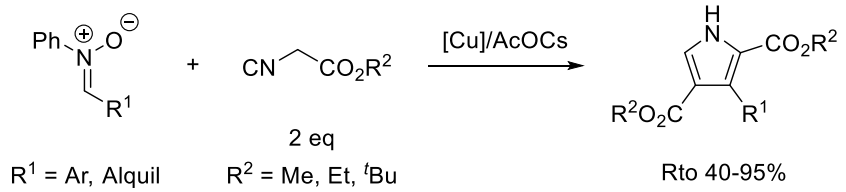
Esquema 75. Síntesis enantioselectiva de 2-imidazolinonas mediante tosiliminas e isocianatos descrita por Takemoto.

Por otra parte, las nitronas son compuestos 1,3-dipolares ampliamente utilizados en reacciones de cicloadición conducentes a diferentes tipos de heterociclos nitrogenados. Las reacciones de cicloadición más estudiadas empleando nitronas son aquellas que conducen a la obtención de isoxazoles por reacción con alquenos (**Esquema 76**).



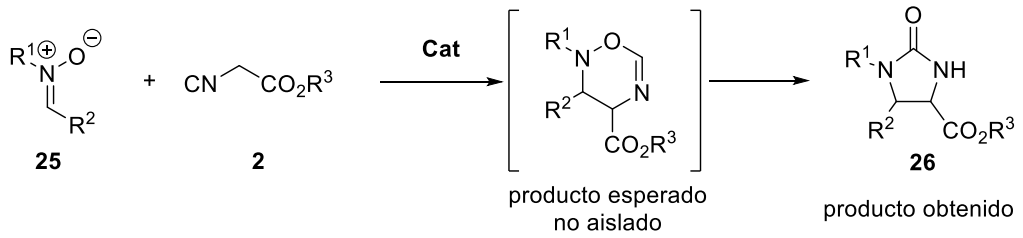
Esquema 76. Síntesis de isoxazoles a partir de una nitrona y una olefina.

En los capítulos anteriores se ha descrito la aplicación de isocianoacetatos como 1,3-dipolos formales y su aplicación en la síntesis de oxazolinas quirales a través de reacciones de cicloadición [3+2] formal con cetonas. Continuando con la investigación y con el fin de extender la diversidad estructural de compuestos quirales que pueden prepararse enantioselectivamente utilizando la química de isocianoacetatos mediante nuestro sistema multicatalítico, nos planteamos el estudido de su reacción con nitronas. En la bibliografía, el grupo de Xu describió en 2018 la reacción de nitronas con dos equivalentes de isocianoacetatos para dar sistemas de 1*H*-pirrol trisustituido mediante una reacción de cicloadición [3+1+1] catalizada por cobre (**Esquema 77**).[99]



Esquema 77. Reacción de adición de dos equivalentes de isocianoacetatos a nitronas catalizada por cobre.

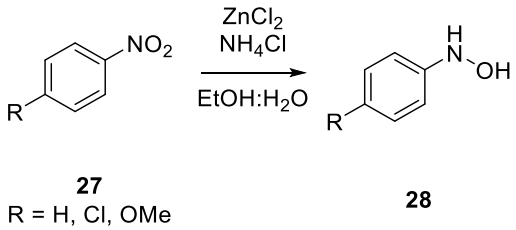
Como objetivo en este capítulo, nos planteamos el estudio de reacción de cicloadición [3+3] entre nitronas **25** e isocianoacetatos **2** para dar 3,4-dihidro-2*H*-1,2,5-oxadiazinas, la cual no se encuentra descrita en la bibliografía. Este estudió condujo, sin embargo, a la obtención de 2-oxazolinonas quirales **26** en lugar del producto esperado de cicloadición [3+3] (**Esquema 78**).



Esquema 78. Formación catalítica de 2-imidazolinonas a partir de nitronas e isocianoacetatos.

4.4.1 Síntesis de las nitronas de partida

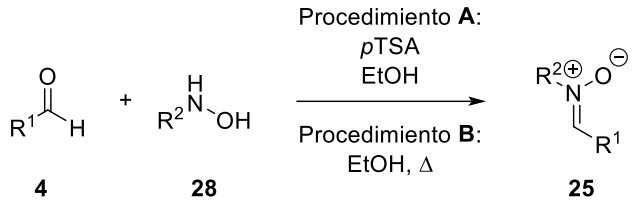
Todas las nitronas utilizadas fueron sintetizadas en el laboratorio. La síntesis se llevó a cabo en dos etapas, en primer lugar, se sintetizó la *N*-fenilhidroxilamina (**28**) mediante una reducción parcial de nitrobenceno (**27**) con cinc (**Esquema 79**).



Esquema 79. Síntesis de *N*-fenilhidroxilamina.

Posteriormente la *N*-fenilhidroxilamina (**28**) resultante se adicionó a diferentes aldehídos (**4**) empleando dos procedimientos distintos, uno para la síntesis de nitronas

derivadas de benzaldehídos (procedimiento **A**) y otro para aquellas derivadas de cicloalquilcarbaldehídos (Procedimiento **B**, **Esquema 80**).[99]



25a, R_1 = Ph, R_2 = Ph, Rto 65%
25b, R_1 = 4-MeC_6H_4, R_2 = Ph, Rto 40%
25c, R_1 = 4-$OMeC_6H_4$, R_2 = Ph, Rto 69%
25d, R_1 = 4-BrC_6H_4, R_2 = Ph, Rto 98%
25e, R_1 = 4-$NO_2C_6H_4$, R_2 = Ph, Rto 67%
25f, R_1 = 3-$OMeC_6H_4$, R_2 = Ph, Rto 90%
25g, R_1 = 3-BrC_6H_4, R_2 = Ph, Rto 79%
25h, R_1 = 3-$NO_2C_6H_4$, R_2 = Ph, Rto 83%
25i, R_1 = 2-$OMeC_6H_4$, R_2 = Ph, Rto 94%
25j, R_1 = 2-BrC_6H_4, R_2 = Ph, Rto 91%
25k, R_1 = 2-$NO_2C_6H_4$, R_2 = Ph, Rto 79%
25l, R_1 = Naftilo, R_2 = Ph, Rto 41%
25m, R_1 = Py, R_2 = Ph, Rto 85%
25n, R_1 = Ciclohexil, R_2 = Ph, Rto 35%*
25o, R_1 = Ciclopropano, R_2 = Ph, Rto 35%*
25p, R_1 = Ph, R_2 = 4-ClC_6H_4, Rto 79%
25q, R_1 = Ph, R_2 = 4-$OMeC_6H_4$, Rto 39%

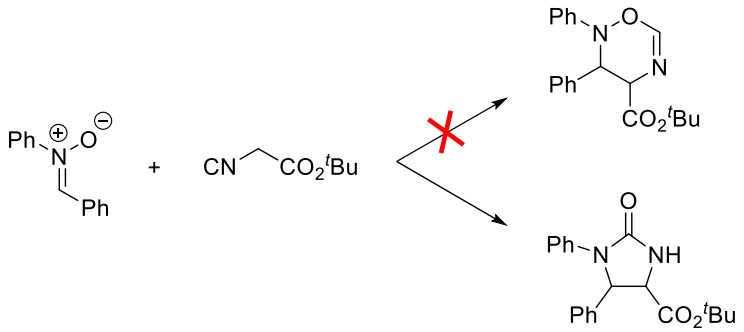
*Sintetizadas con el procedimiento **B**

Esquema 80. Síntesis de nitronas utilizadas en este trabajo.

Los procedimientos **A** y **B** son muy similares, en el primero, la reacción se lleva a cabo a temperatura ambiente y se añade una cantidad catalítica de ácido para facilitar la eliminación de agua. El segundo procedimiento consiste en la agitación del aldehído y la *N*-fenilhidroxilamina a reflujo de etanol. Este último procedimiento se utiliza con los cicloalquilcarbaldehídos.

4.4.2 Optimización de las condiciones de reacción

Para iniciar la investigación se eligió la reacción de adición de isocianoacetato de *terc*-butilo (**2b**) a óxido de *N*-1-difeniletanimina utilizando el sistema catalítico formado por escuaramidas bifuncionales y óxido de plata. El análisis de los productos resultantes en la reacción mediante RMN reveló la formación de la imidazolinona **26ab** en lugar del producto de cicloadición [3+3] esperado (**Esquema 81**).

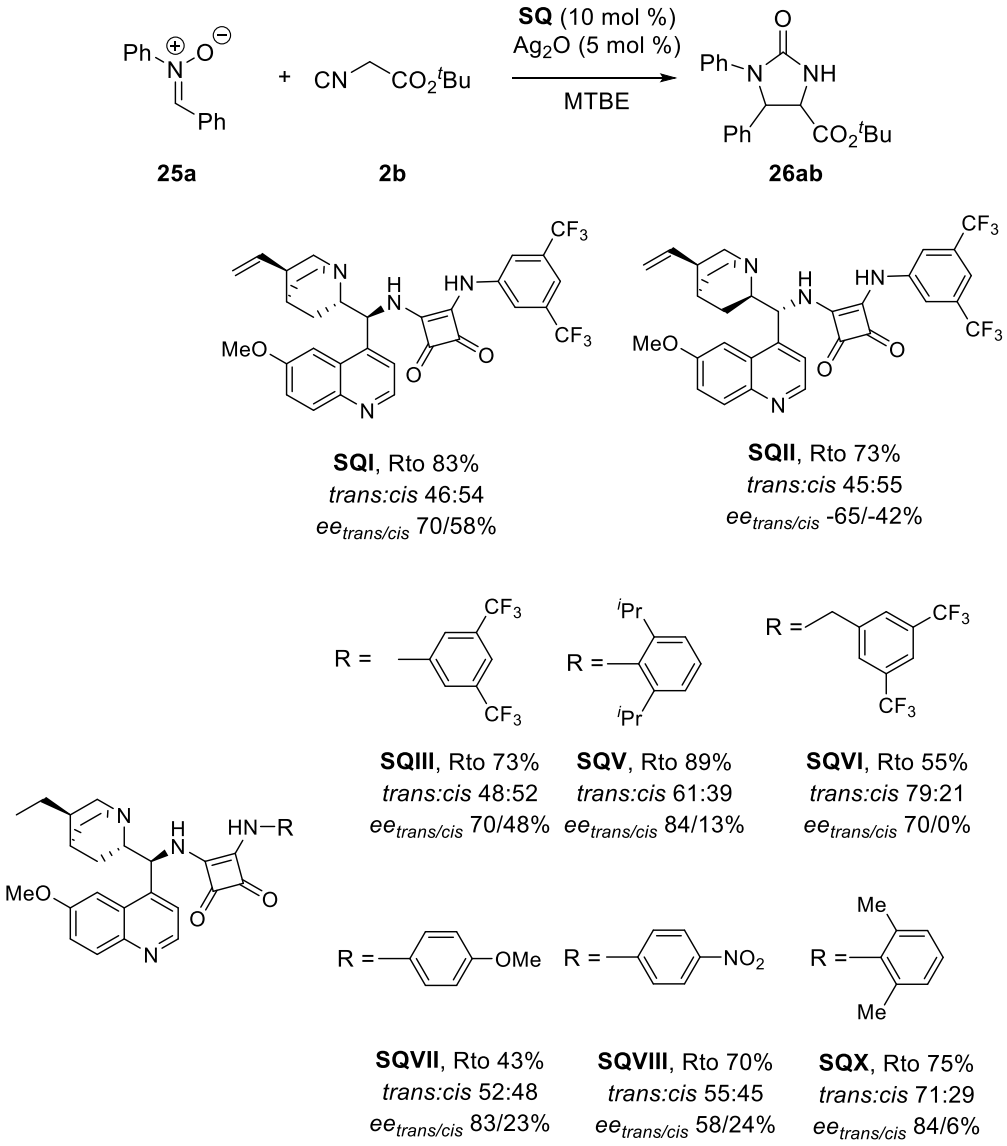


Esquema 81. Reacción entre nitronas e isocianoacetatos. Cicloadición [3+3] *vs* cicloadición [3+2]

4.4.2.1 *Efecto del catalizador*

Se ensayaron diferentes escuaramidas (y una tiourea) bifuncionales combinadas con óxido de plata en MTBE como disolvente a temperatura ambiente (**Esquema 82**).

Únicamente las escuaramidas fueron capaces de catalizar la reacción mientras que con la tiourea **TI** no se observó avance de la misma. Utilizando la escuaramida **SQI**, derivada de quinina, se obtuvo la 2-imidazolinona **26ab** con buen rendimiento, pobre control diastereoisomérico y moderado exceso enantiomérico. La escuaramida derivada de quinidina **SQII** condujo al enantiómero opuesto con similar diastereoselectividad, pero menor rendimiento y exceso enantiomérico que **SQI**. A continuación, se ensayó la escuaramida derivada de dihidroquinina **SQIII** obteniendo resultados muy similares a los obtenidos con **SQI** derivada de quinina. Se ensayaron un gran número de escuaramidas derivadas de hidroquinina que se diferencian en la parte no quiral de la escuaramida. Los mejores resultados en términos de diastereo- y enantioselectividad se obtuvieron con las escuaramidas **SQV** y **SQX** derivadas de dihidroquinina y de anilinas 2,6-disubstituidas.



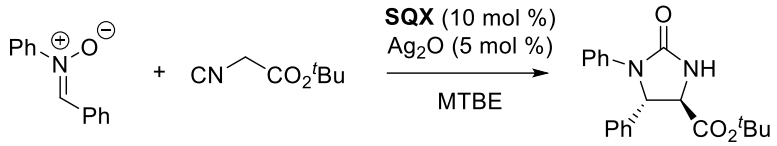
Esquema 82. Organocatalizadores ensayados en este proyecto.

4.4.2.2 *Efecto del disolvente*

Decidimos continuar la optimización de las condiciones de reacción con el catalizador **SQX** ya que éste presentaba el mejor balance de resultados en rendimiento, diastereoselectividad y exceso enantiomérico.

Utilizando este catalizador se ensayaron disolventes de diferentes características (**Tabla 10**).

Tabla 10. Reacción entre isocianoacetato de *terc*-butilo y óxido de *N*-1-difeniletanimina. Efecto del disolvente.[a]



25a **2b** **26ab**

Entrada	Disolvente	Rto (%)[b]	*trans:cis*[c]	ee_{trans} (%)[d]
1	MTBE	74	71:29	84
2	Éter etílico	70	69:31	79
3	Diisopropiléter	68	60:40	68
4	THF	51	69:31	76
5	Dioxano	70	71:29	90
6	Tolueno	71	70:30	87
7	Benceno	65	71:29	89
8	*p*-Xileno	69	68:32	85
9	*o*-Xileno	60	68:32	86
10	AcOEt	60	65:35	79
11	CH_2Cl_2	39	41:59	59
12	$CHCl_3$	30	47:53	51

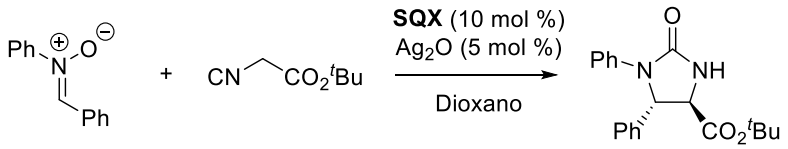
[a] **26a** (0.13 mmol), **2b** (0.165 mmol), **SQX** (0.013 mmol), Ag_2O (0.0063 mmol), MTBE (1 mL). [b] Rendimiento del producto aislado. [c]Determinado por ^1H RMN. [d] Determinado mediante HPLC quiral.

Como puede observarse en la **tabla 10**, con disolventes de tipo éter (**Tabla 10**, ***entradas 1-5***) se obtienen moderados rendimientos, moderada diastereoselectividad y alto exceso enantiomérico con MTBE (84%, ***entrada 1***) y dioxano (90%, ***entrada 5***). Los disolventes aromáticos ofrecieron también muy buenos resultados (***entradas 6-9***), obteniéndose los mejores resultados en benceno (89%). Los disolventes halogenados (***entradas 11 y 12***) no resultaron adecuados para esta reacción, proporcionando el compuesto **26ab** con bajo rendimiento, nula diastereoselectividad y baja enantioselectividad. Empleando un disolvente polar como el acetato de etilo (***entrada 10***), se obtiene el producto de reacción con menor exceso enantiomérico y peor diastereoselectividad. Los mejores resultados entre todos los disolventes ensayados se obtuvieron en 1,4-dioxano (***entrada 5***).

4.4.2.3 *Efecto de la concentración*

Como hemos visto en los capítulos anteriores, la concentración de las especies reaccionantes suele tener un efecto determinante en la estereoselectividad de las reacciones catalizadas por el sistema escuaramida/Ag_2O. Por este motivo se estudió la reacción a diferentes diluciones utilizando la escuaramida **SQX** y dioxano como disolvente (**Tabla 11**).

Tabla 11. Reacción entre isocianoacetato de *terc*-butilo y óxido de *N*-1-difeniletanimina. Efecto de la concentración.[a]



25a **2b** **26ab**

Entrada	[**26a**] M	Rto (%)[b]	*trans:cis*[c]	ee_{trans} (%)[d]
1	0.13	70	71:29	90
2	0.063	46	73:27	99
3	0.042	28	75:25	94

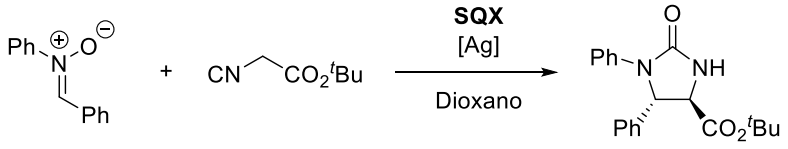
[a] **26a** (0.13 mmol), **2b** (0.165 mmol), **SQX** (0.013 mmol), Ag_2O (0.0063 mmol), dioxano. [b] Rendimiento del producto aislado. [c] Determinado por ^{1}H RMN. [d] Determinado mediante HPLC quiral.

Disminuyendo la concentración de nitrona de 0.13 M (condiciones iniciales) a 0.063 M el exceso enantiomérico aumentó hasta el 99%, pero se produjo un descenso pronunciado en el rendimiento (**Tabla 11**, ***entrada 2***). Una dilución mayor hasta 0.042 M en nitrona redujo aún más el rendimiento, hasta el 28% sin mejorar la estereoselectividad de la reacción (***entrada 3***).

4.4.2.4 *Efecto de la carga catalítica y de la especie de plata*

A continuación, se ensayó el efecto de la carga catalítica y de la relación entre **SQX** y la sal de plata. También se ensayaron diferentes sales de plata con el fin de encontrar condiciones que permitieran mejorar el rendimiento manteniendo una estereoselectividad elevada (**Tabla 12**).

Tabla 12. Efecto de la carga catalítica.[a]



25a **2b** **26ab**

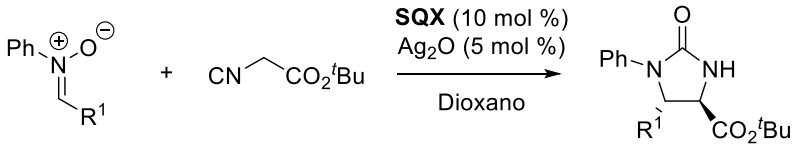
Entrada	**SQX** (mol %)	Ag_2O (mol %)	*t* (d)	Rto (%)[b]	*trans:cis*[c]	ee_{trans} (%)[d]
1	10	Ag_2O (5)	2	46	73:27	99
2	10	Ag_2O (10)	4	36	74:26	91
3	20	Ag_2O (10)	4	46	65:35	91
4	5	Ag_2O (10)	2	62	67:37	86
5	10	Ag_2SO_4 (5)	2	47	66:34	86
6	10	CF_3CO_2Ag (5)	2	n.r.	–	–
7	10	$AgNO_3$(5)	2	n.r.	–	–

[a] **26a** (0.13 mmol), **2b** (0.165 mmol), **SQX** (0.013 mmol), Ag_2O (0.0063 mmol), dioxano (2 mL). [b]Rendimiento del producto aislado. [c]Determinado por ^{1}H RMN. [d]Determinado mediante HPLC quiral.

Lamentablemente, ninguno de los ensayos realizados variando la carga catalítica y la relación entre la escuaramida y la sal de plata permitieron mejorar el resultado (***entradas 1-4***).

Se estudiaron diferentes fuentes de plata. Únicamente el sulfato de plata fue capaz de promover la reacción para dar el compuesto esperado, aunque con menor estereoselectividad que la obtenida con óxido de plata (***entrada 5*** *vs* ***entrada 1***). Por otra parte, la reacción no funciónó en presencia de nitrato de plata o de trifluoroacetato de plata (***entradas 6 y 7***). Ante la imposibilidad de aumentar el rendimiento de la reacción en las condiciones diluidas (0.063 M en nitrona) se decidió iniciar el estudio del alcance de la reacción en las condiciones descritas en la ***entrada 1*** de la **Tabla 11** (0.13 M en nitrona). Sin embargo, cuando en estas condiciones se llevó a cabo la reacción de adición de isocianoacetato de *terc*-butilo a dos nitronas sustituidas en la posición *para*, los productos de reacción se obtuvieron de nuevo con un bajo rendimiento (**Tabla 13**, ***entradas 2 y 3***).

Tabla 13. Adición de isocianoacetato de *terc*-butilo a nitronas *p*-sustituidas catalizada por **SQX**-Ag_2O.[a]



25a **2b** *trans*-**26**

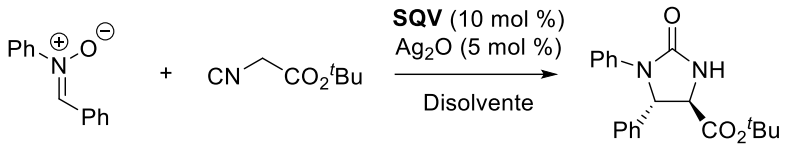
Entrada	**R^1**	**Rto**	**27**	***trans:cis***	***ee*$_{trans}$**
1	Ph	70	**27ab**	71:29	90
2	4-$MeOC_6H_4$	42	**27cb**	63:37	90
3	4-BrC_6H_4	51	**27db**	62:38	80

[a] **26a** (0.25 mmol), **2b** (0.33 mmol), **SQX** (0.025 mmol), Ag_2O (0.0125 mmol), dioxano (1 mL). [b]Rendimiento del producto aislado. [c]Determinado por ^{1}H RMN. [d]Determinado mediante HPLC quiral.

4.4.2.5 *Investigación de la reacción con la escuaramida SQV*

En vista de los resultados obtenidos con la escuaramida **SQX**, decidimos investigar de nuevo la actividad de la escuaramida **SQV**, que durante los ensayos de catalizadores había proporcionado el mayor rendimiento con estereoselectividad ligeramente inferior a la proporcionada por la escuaramida **SQX** (ver **Esquema 82**). Los resultados obtenidos con la escuaramida **SQV** se resumen en la **Tabla 14**.

Tabla 14. Reacción entre isocianoacetato de *terc*-butilo y óxido de *N*-1-difeniletanimina. Optimización con **SQV**.[a]



25a **2b** **26ab**

Entrada	Disolvente	[**26a**] M	T (°C)	*t* (d)	Rto (%)[b]	*trans:cis*[c]	ee_{trans} (%)[d]
1	dioxano	0.063	t.a.	3	60	50:50	78
2	MTBE	0.063	t.a.	2	84	68:32	88
3	MTBE	0.063	0	4	78	67:37	88
4	MTBE	0.063	35	1	60	66:33	88
5	MTBE	0.042	t.a.	4	78	71:29	90

[a] **25a** (0.13 mmol), **2b** (0.165 mmol), **SQV** (0.013 mmol), Ag_2O (0.0063 mmol), disolvente. [b] Rendimiento del producto aislado. [c] Determinado por ^{1}H RMN. [d] Determinado mediante HPLC quiral.

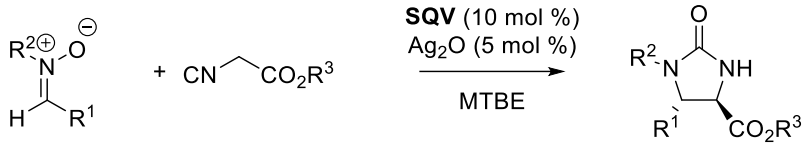
Inicialmente, la escuaramida **SQV** se probó en dioxano como disolvente en condiciones idénticas a las utilizadas previamente con **SQX** (ver **Tabla 14**, ***entrada 2***) proporcionando el compuesto **27ab** como una mezcla 1:1 de diastereisómeros con un 78% *ee* (**Tabla 14**, ***entrada 1***). Dado que el dioxano parecía no ser un buen disolvente para este catalizador, la reacción se repitió en MTBE produciendo la 2-imidazolinona esperada **26ab** con diastereoselectividad moderada (*dr* = 68:32) y alta enantioselectividad (88% *ee*), sin perjudicar el rendimiento (***entrada 2***). Los intentos de mejorar la estereoselectividad cambiando la temperatura de reacción no tuvieron éxito (***entradas 3 y 4***). Finalmente, se pudo obtener un pequeño aumento de diastereo y enantioselectividad mediante la dilución adicional de la mezcla de reacción (***entrada 5***).

Por tanto, las condiciones óptimas de reacción quedaron establecidas con el uso de un sistema cocatalítico formado por la escuaramida **SQV** (10 mol %) y óxido de plata (5 mol %), en MTBE como disolvente, a una concentración en nitrona de 0.042 M y a temperatura ambiente.

4.4.3 Estudio del alcance y limitaciones de la reacción

Con las condiciones de reacción optimizadas, se estudió el alcance de la reacción con una variedad de nitronas e isocianoacetatos. Los resultados se recogen en la **Tabla 15**.

Tabla 15. Alcance y limitaciones de la reacción.[a]



25 **2** *trans*-**26**

Entr.	**25**	R^1	R^2	**2**	**26**	Rto (%)[b]	*trans:cis*[c]	*ee* (%)[d]
1	**25a**	Ph	Ph	**2b**	**26ab**	78	76:24	90
2	**25b**	4-MeC_6H_4	Ph	**2b**	**26bb**	83	78:22	90
3	**25c**	4-$MeOC_6H_4$	Ph	**2b**	**26cb**	48	69:31	89
4	**25d**	4-BrC_6H_4	Ph	**2b**	**26db**	65	71:29	86
5	**25e**	4-$NO_2C_6H_4$	Ph	**2b**	**26eb**	60	62:38	87
6	**25f**	3-$MeOC_6H_4$	Ph	**2b**	**26fb**	63	71:29	89
7	**25g**	3-BrC_6H_4	Ph	**2b**	**26gb**	74	71:29	89
8	**25h**	3-$NO_2C_6H_4$	Ph	**2b**	**26hb**	92	72:28	83
9	**25i**	2-$MeOC_6H_4$	Ph	**2b**	**26ib**	84	72:28	94
10	**25j**	2-BrC_6H_4	Ph	**2b**	**26jb**	83	75:25	87
11	**25k**	2-$NO_2C_6H_4$	Ph	**2b**	**26kb**	91	64:36	67
12	**25l**	1-Naftilo	Ph	**2b**	**26lb**	75	72:28	94
13	**25m**	2-Piridinilo	Ph	**2b**	**26mb**	99	88:12	95
14[e]	**25m**	2-Piridinilo	Ph	**2b**	**26mb**	98	86:14	-92
15	**25n**	Ciclohexilo	Ph	**2b**	**26nb**	67	92:8	91
16	**25o**	^{c}Pr	Ph	**2b**	**26ob**	96	80:20	99
17	**25p**	Ph	4-ClC_6H_4	**2b**	**26pb**	83	60:40	84
18	**25q**	Ph	4-$MeOC_6H_4$	**2b**	**26qb**	24	74:26	91
19[f]	**25a**	Ph	Ph	**2a**	**26aa**	41	75:25	84
20[g]	**25a**	Ph	Ph	**2d**	**26ad**	60	76:24	82
21[h]	**25a**	Ph	Ph	**2b**	**26ab**	79	75:25	88

[a] **25** (0.25 mmol), **2** (0.33 mmol), **SQV** (0.013 mmol), Ag_2O (0.0063 mmol), MTBE (6 mL). [b] Rendimiento del producto aislado. [c] Determinado por ^{1}H RMN. [d] Para el diastereómero mayoritario *trans*. Determinado mediante HPLC quiral. [e] Reacción llevada a cabo con **SQV'**. [f] Reacción llevada a cabo con isocianoacetato de metilo **2a**. [g] Reacción llevada a cabo con isocianoacetato de bencilo **2d**. [h] Reacción llevada a cabo con 1 mmol de nitrona **25a**.

En general, las condiciones de reacción pudieron aplicarse en la adición de isocianacetato de *terc*-butilo (**2b**) con una amplia variedad de *N*-fenilnitronas derivadas de benzaldehídos sustituidos con grupos de diferente naturaleza electrónica en las distintas posiciones del anillo aromático. Las 2-imidazolinonas quirales **26ab**-**26kb** (***entradas 1***-***11***) se obtuvieron con diastereoselectividad entre moderada y buena (62:38 a 78:22) y altos excesos enantioméricos para el diastereoisómero mayoritario *trans* (67-94%). La presencia de grupos electrón dadores (***entradas 2, 3, 5*** y ***9***) favoreció mayores enantioselectividades que la de grupos electrón aceptores (***entradas 4, 5, 7, 8, 10*** y ***11***) independientemente de la posición de estos grupos en el anillo aromático. La reacción también funcionó con la *N*-fenil nitrona derivada de un aldehído voluminoso como el 1-naftilcarbaldehído que suministró la urea **26lb** con buen rendimiento, buen *dr* y excelente *ee* (***entrada 12***). La nitrona derivada de 2-formilpiridina reaccionó con el isocianacetato de *terc*-butilo para dar el compuesto **26mb** con rendimiento cuantitativo, con buena

diastereoselectividad (*dr* = 88:12) y excelente enantioselectividad (95% *ee*). Este resultado contrasta con los obtenidos con nitronas derivadas de nitrobenzaldehídos (***entradas 5, 8*** y ***11***) y es bastante sorprendente, ya que tanto la piridina como el grupo nitrofenilo son anillos pobres en electrones. Además, su enantiómero *ent*-**26mb** también pudo obtenerse con muy buenos resultados usando la escuaramida **SQV'** (**Figura 15**), derivada de dihidroquinidina, en lugar de **SQV** (***entrada14***).

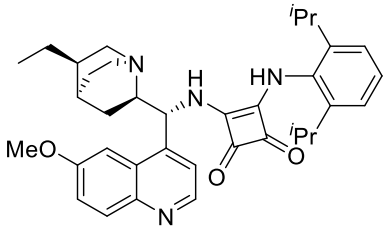


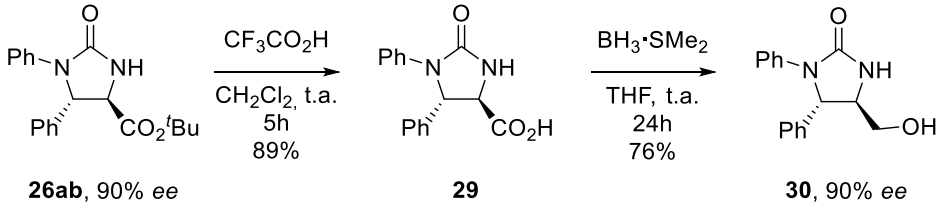
Figura 15. Catalizador **SQV'**, derivado de dihidroquinidina.

Las nitronas derivadas de cicloalquilcarbaldehídos también fueron sustratos adecuados para la reacción. Los compuestos **26nb** y **26ob**, que presentan un sustituyente ciclohexilo o ciclopropilo, respectivamente, se obtuvieron con excelentes excesos enantioméricos (***entradas 15*** y ***16***). También se probó el efecto del sustituyente sobre el átomo de nitrógeno de la nitrona. La *N*-(4-clorofenil) nitrona **25p** reaccionó con isocianoacetato de *terc*-butilo para dar el compuesto **25pb** con buen rendimiento, pero diastereo- y enantioselectividad moderada (***entrada 17***). Por otro lado, la *N*-(4-metoxifenil) nitrona proporcionó el compuesto **26qb** con buena enantioselectividad (91% *ee*) pero con muy bajo rendimiento (24%), desafortunadamente (***entrada 18***). Finalmente, probamos la reacción con isocianoacetato de metilo (**2a**) y de bencilo (**2d**). Ambos condujeron a las respectivas oxazolinonas con diastereoselectividad similar a la obtenida con el isocianoacetato de *terc*-butilo, aunque con excesos enantioméricos ligeramente inferiores (***entradas 19 y 20***).

Finalmente se comprobó que la reacción puede llevarse a cabo a una escala mayor de 1 mmol sin afectar al rendimiento, diastereoselectividad ni exceso enantiomérico (***entrada 21***).

4.4.4 Modificaciones sintéticas y determinación de la configuración absoluta

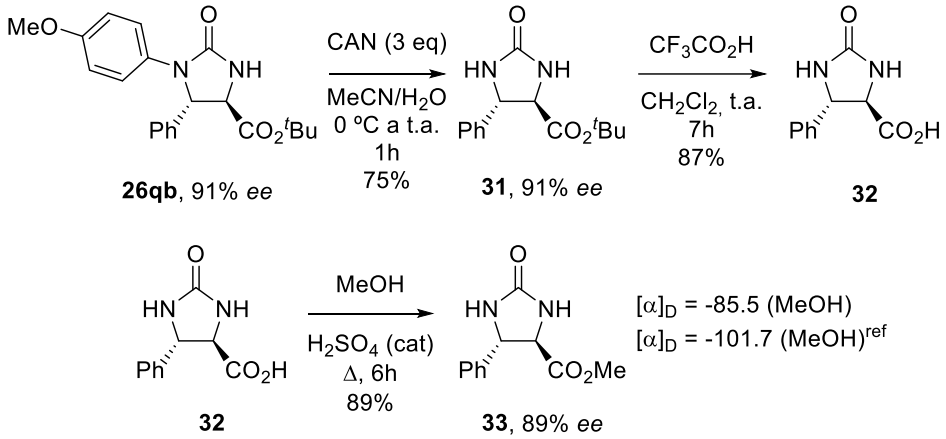
Como se ha indicado en la introducción, las 3-alcoxicarbonilimidazolinonas obtenidas pueden ser precursoras de derivados de α-aminoácidos y α-aminoalcoholes. A continuación, se muestran algunas modificaciones sintéticas llevadas a cabo sobre la 2-imidazolinona **26ab** (**Esquema 83**).



Esquema 83. Síntesis del ácido **29** y del alcohol **30** a partir del compuesto **26ab**.

En primer lugar, se sintetizó el ácido carboxílico **29** hidrolizando el ester *terc*-butílico de la 2-imidazolinona **26ab** con ácido trifluoroacético. A continuación, este ácido fue reducido con el complejo de borano dimetilsulfuro para la obtención del alcohol **30** sin pérdida de exceso enantiomérico.

Por otra parte, la determinación de la configuración absoluta de los productos de reacción se llevó a cabo mediante correlación química entre la imidazolinona **26qb** y el compuesto **33** de configuración conocida (**Esquema 84**).



Esquema 84. Determinación de la estereoquímica absoluta de **27qb** por correlación química.

Se utilizó la nitrona **26qb** sustituida con un grupo *para*-metoxifenilo unido al nitrógeno. El tratamiento de esta nitrona con nitrato amónico cérico (CAN) condujo a la 2-imidazolinona **31** sin sustitución en los átomos de nitrógeno. Este compuesto se transformó al ácido carboxílico **32** mediante hidrólisis del éster *terc*-butílico con ácido trifluoroacético y, por último, se llevó a cabo una esterificación de Fisher con metanol y ácido sulfúrico para obtener la 2-imidazolinona sustituida con un éster metílico **33**. Durante la secuencia sintética se mantuvo el exceso enantiomérico. El compuesto **33** preparado de esta forma mostró características espectroscópicas idénticas y signo de rotación óptica coincidentes con los descritos en la bibliografía para el compuesto (4*R*,5*S*)-**35**,[100] permitiendo asignar la estereoquímica absoluta del compuesto **26qb**. La estereoquímica absoluta de las imidazolinonas **26** restantes se asignó suponiendo un mecanismo estereoquímico uniforme.

4.4.5 Propuesta mecanística para la formación de las 2-imidazolinonas

Como se ha indicado anteriormente, el objetivo inicial perseguía la obtención del producto de cicloadición [3+3] entre las nitronas y los isocianoacetatos. A continuación, planteamos un posible mecanismo de reacción que explica la formación de las imidazolinonas (**Figura 16**).

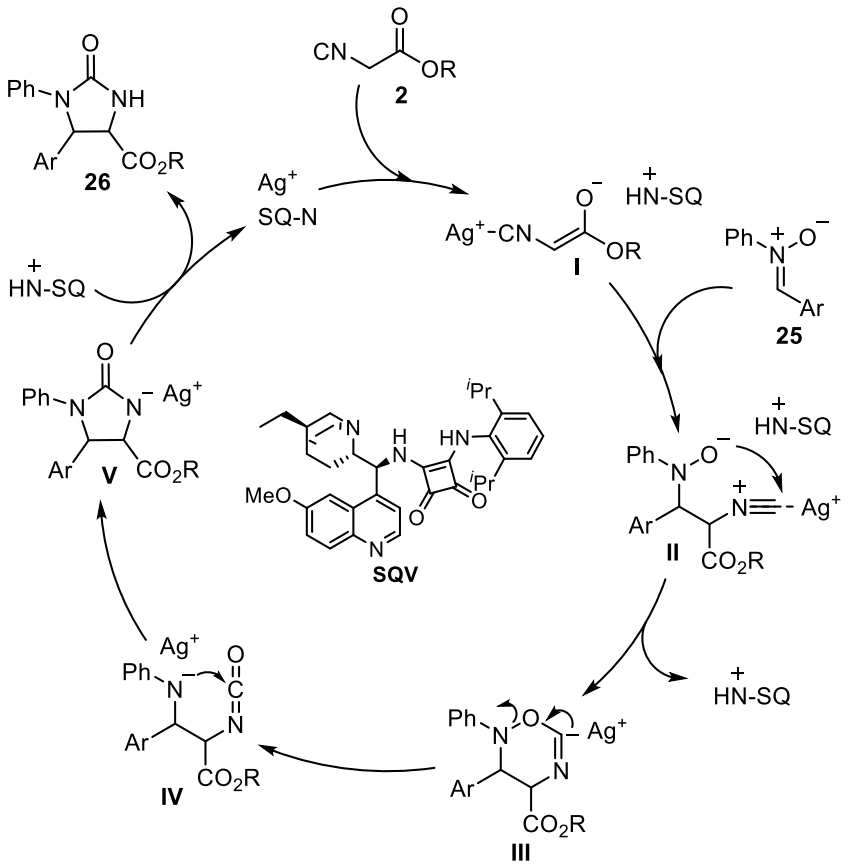


Figura 16. Propuesta mecanística para la formación de 2-imidazolinonas.

El primer paso de reacción implicaría la desprotonación del isocianoacetato por parte de la amina en el anillo de quinuclidina del organocatalizador, asistida por el ion Ag^+, para dar el enolato **I.** La adición del enolato al doble enlace C–N de la nitrona conduciría al intermedio **II** que tras un proceso de ciclación intramolecular entre el *N*-óxido y el grupo isocianuro permitiría formar el producto de cicloadición [3+3] esperado inicialmente **III**. Este intermedio no debe ser estable y sufre un reagrupamiento para dar el amiduro-isocianato **IV**. La adición intramolecular del amiduro al grupo isocianato conduciría a una sal de la 2-imidazolonona **V**, la cual por protonación con el ácido conjugado del organocatalizador daría el producto de reacción **27** y regeneraría el catalizador.

En conclusión, en este capítulo hemos desarrollado un nuevo procedimiento para la síntesis catalítica, diastereo y enantioselectiva de ureas cíclicas (2-imidazolinonas) por reacción de ésteres de isocianoacetato y nitronas. La reacción se encuentra catalizada por un sistema que combina un organocatalizador bifuncional escuaramida/base de Brønsted y Ag^+ como ácido de Lewis. El método proporciona *trans*-2-imidazolinonas quirales con buena diastereoselectividad y elevada enantioselectividad en la mayoría de los ejemplos ensayados, siendo de aplicación tanto a nitronas derivadas de aldehídos aromáticos y heteroaromáticos como a nitronas derivadas de cicloalquilcarbaldehídos. Se ha propuesto una explicación mecanística para la reacción que implica la cicloadición [3 + 3] inicial de la nitrona y el éster de isocianoacetato, seguida de reagrupamiento a un amiduro-isocianato y ciclación a la 2-imidazolinona.

4.5 Adición catalítica enantioselectiva de isocianoacetatos a 4-alquilidenisoxazol-5-onas para la formación de compuestos espirocíclicos

Los compuestos espirocíclicos se caracterizan por presentar estructuras en las que dos anillos comparten un único átomo de carbono (el carbono espiránico). Esta característica estructural se encuentra en numerosos productos de origen natural tales como la horsfilina, extraída de la planta *Horsfielda superba*,[101] la β-vetivona,[102] aislada del aceite de vetiver o el (–)-gleenol,[103] presente en el alga *Taonia atomaria*. Además, algunos productos espirocíclicos tienen aplicación como ligandos en catálisis asimétrica, como el spinol.[104] Por otra parte, la estructura espirocíclica presenta una gran importancia en el diseño de fármacos debido a la restricción conformacional que el carbono espiro impone.[105] Esta fijación de la estructura permite la disminución de la penalización entrópica que implica la unión de un fármaco a un centro activo, ya que para que la unión sea efectiva, el fármaco necesita una conformación determinada. De esta manera es posible mejorar en algunos casos la actividad. Entre los ejemplos de fármacos comerciales que presentan estructura espirocíclica podemos señalar el antitusivo Fenispirida (**Figura 17**).[106]

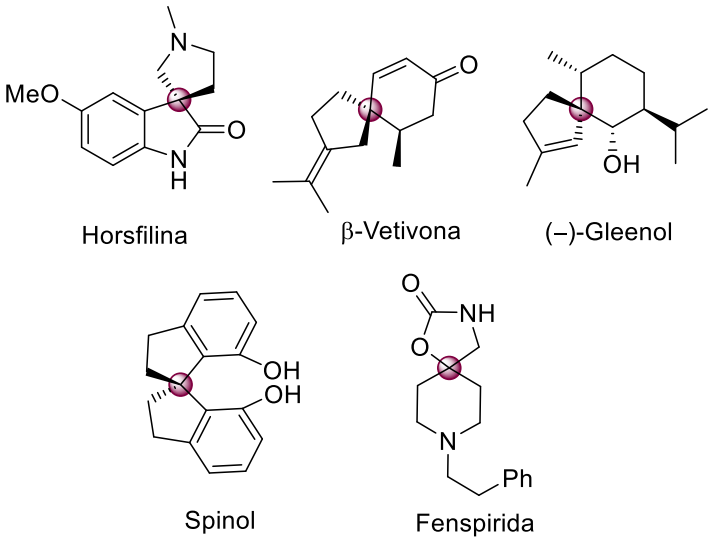


Figura 17. Ejemplos de productos relevantes en química orgánica que contienen alguna estructura de tipo espiro.

Por estos motivos, la síntesis de compuestos espirocíclicos, en particular de manera enantioselectiva, ha recibido un interés creciente en los últimos años.[107] En este sentido, a la ya de por sí difícil tarea de construir centros estereogénicos cuaternarios enantioselectivamente, hay que sumar la tensión de anillo asociada al carbono espiránico y su sensibilidad a la presencia de grupos funcionales en el anillo, de ahí que resulte difícil sintetizar espirociclos altamente funcionalizados. Además, hay que considerar también la diastereoselectividad porque la formación de sistemas espiránicos va acompañada a menudo de la formación de estereocentros adicionales.

En la **Figura 18**, se muestran algunas de las estrategias más utilizadas para la síntesis de compuestos espirocíclicos. Entre ellas podemos mencionar la doble alquilación inter/intramolecular de carbonos (a), reacciones de adición intramolecular catalizadas por metales (b), cierre de anillos en sistemas cíclicos con carbonos que

presentan dos sustituyentes (c), reacciones de cicloadición (d), cierre de anillos sobre el carbono espiránico mediante reacciones radicalarias (e), o reacciones de reordenamiento (f).[107]

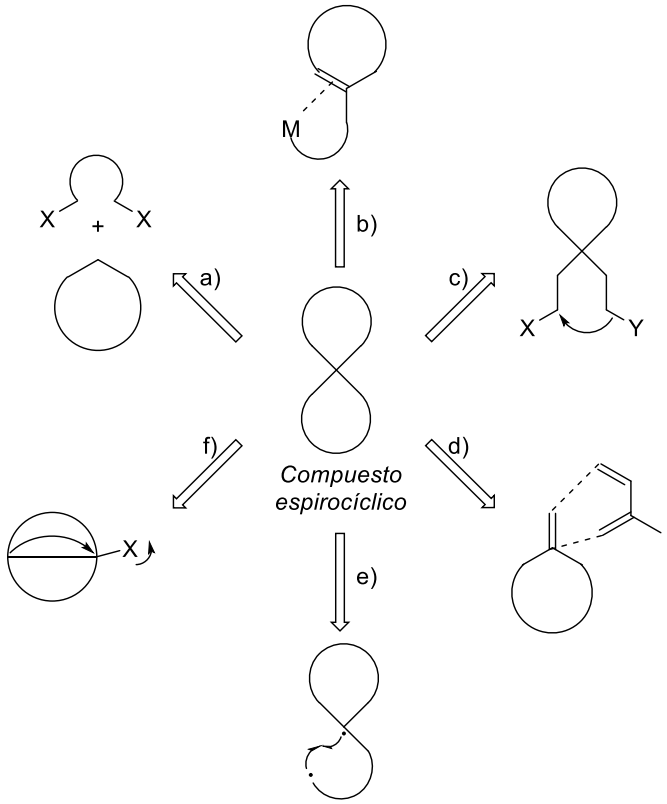
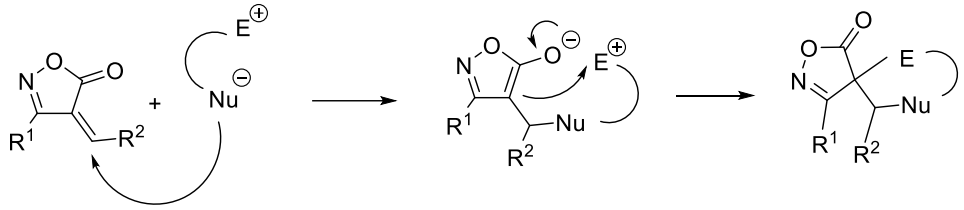


Figura 18. Diferentes estrategias para la síntesis de espirociclos. a) Métodos de alquilación, b) métodos de adición con metales, c) métodos de cierre de anillos, d) estrategias de cicloadición, e) métodos radicalarios, f) estrategias de reordenamiento.

Entre estos métodos, las reacciones de cicloadición sobre grupos funcionales insaturados exocíclicos son muy atractivas debido a su simplicidad y a la variedad de compuestos que pueden utilizarse como reactantes en este tipo de reacciones.

De esta forma, los isocianoacetatos se han utilizado como 1,3-dipolos formales en algunas reacciones de cicloadición que conducen a espirociclos que continenen un anillo de isoxazolina o pirrolina. Así, los grupos de Wang, Yan, Shi y He han utilizado esta estrategia en la preparación de spirooxindoles,[33,47,54,60,61] mientras que los grupos de Shao/He y Zhao han descrito la síntesis de espirociclos mediante la reacción de isocianoacetatos con aurona y *N*-itaconimidas, respectivamente.[63,108]

Por otra parte, las 4-alquilidenisoxazol-5-onas son aceptores de Michael muy interesantes dado que su estructura está altamente funcionalizada y sobre ella se pueden llevar a cabo numerosas modificaciones sintéticas. Los nucleófilos se adicionan a estas estructuras de forma exclusiva sobre la posición 1,4, en una reacción que está favorecida porque implica la aromatización del anillo de isoxazolona (**Esquema 85**).[109] En el caso de compuestos que tienen carácter dipolar, la adición nucleofílica puede ir seguida de una reacción de adición intramolecular del enolato resultante para dar una reacción de cicloadición.

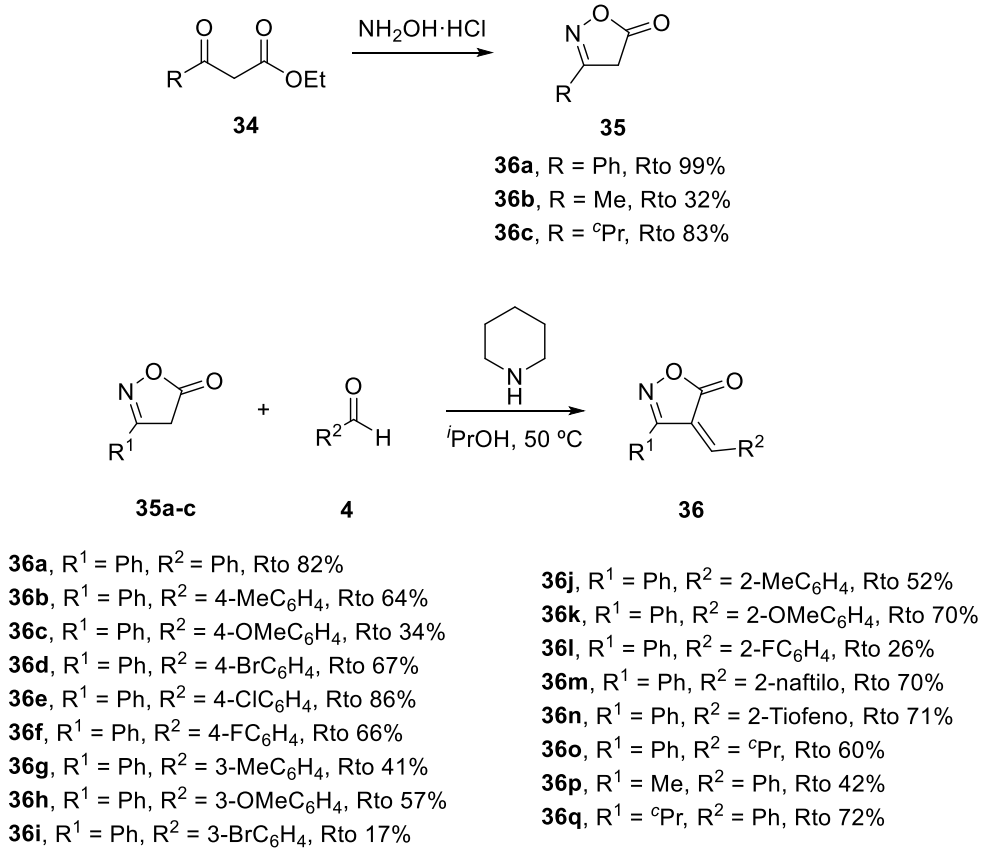


Esquema 85. Reacciones de cicloadición formal sobre una 4-alquilidenisoxazol-5-ona.

En este capítulo describimos la reacción enantioselectiva entre isocianoacetatos y 4-alquilidenisoxazol-5-onas para dar compuestos espirocíclicos que combinan un anillo de isoxazolona con otro de pirrolina, dos heterociclos nitrogenados de cinco miembros de gran importancia en química médica.

4.5.1 Síntesis de 4-alquilidenisoxazol-5-onas

Las 4-alquilidenisoxazol-5-onas utilizadas como sustratos en la reacción se sintetizaron a través de una secuencia sintética de dos etapas siguiendo el procedimiento descrito en la bibliografía.[110,111] En primer lugar, se prepararon las isoxazol-5-onas sustituidas en posición 3 mediante la condensación del β-cetoéster correspondiente con hidroxilamina para dar una oxima que cicla en el medio de reacción. En la mayoría de los casos se requiere la adición de ácido clorhídrico para completar este paso. A continuación, la isoxazol-5-ona se hace reaccionar con el aldehído deseado para la obtención de las 4-alquilidenisoxazol-5-onas mediante una condensación de Knoevenagel (**Esquema 86**).



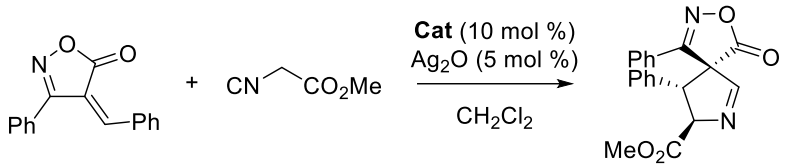
Esquema 86. Síntesis de las 4-alquilidenisoxazol-5-onas ensayadas en este trabajo.

4.5.2 Optimización de las condiciones de reacción

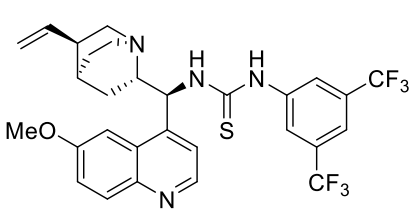
4.5.2.1 Experimentos preliminares y de control

Como punto de partida para este estudio, se eligió la reacción que tiene lugar entre la benciliden-3-fenilisoxazol-5-ona (**36a**) e isocianoacetato de metilo (**2a**) para proporcionar el diazaespirociclo correspondiente **37aa**. Inicialmente ensayamos la reacción empleando un sistema catalítico cooperativo formado por óxido de plata y un organocatalizador de tipo escuaramida o tiourea en diclorometano (**Tabla 16**).

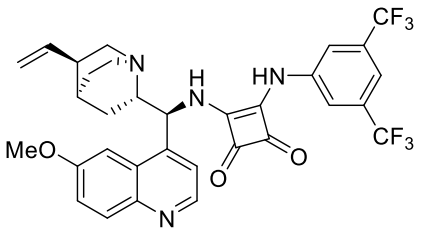
Tabla 16. Adición de isocianoacetato de metilo a benciliden-3-fenilisoxazol-5-ona. Ensayos preliminares y de control.[a]



36a **2a** **37aa**



TI



SQI

Entrada	**Cat**	Ag_2O	Rto (%)[b]	*trans:cis*[c]	$ee_{trans/cis}$[d]
1	**SQ1**	(5 mol %)	54	89:11	39/44
2	**T1**	(5 mol %)	44	91:9	38/60
3	–	(5 mol %)	70	95:5	–
4	**SQ1**	–	12	95:5	85/nd
5	**T1**	–	18	81:19	57/76
6[e]	**SQ1**	–	trazas	nd	89/nd
7[f]	**SQ1**	(5 mol %)	55	75:25	80/98

[a] **36a** (0.1 mmol), **2a** (0.13 mmol), **Cat** (0.01 mmol), CH_2Cl_2 (1 mL). [b] Rendimiento del producto aislado. [c] Determinado por RMN. [d] Determinado por HPLC quiral. [e,f] Reacción llevada a cabo en 5 mL de CH_2Cl_2.

Como puede observarse de los datos recogidos en las ***entradas 1*** y ***2*** (**Tabla 16**), tanto la tiourea **TI** como la escuaramida **SQI** proporcionan resultados muy similares en cuanto a rendimiento, diastereoselectividad y exceso enantiomérico en las condiciones inicialmente probadas.

En este punto, decidimos llevar a cabo una serie de reacciones de control para conocer los elementos determinantes en la reacción. Así, se llevó a cabo la reacción con óxido de plata en ausencia de organocatalizador (***entrada 3***), observándose después de 12 horas que la reacción había finalizado con un rendimiento del 70% y de forma diastereoselectiva para dar el producto esperado en forma racémica. Con el fin de evitar

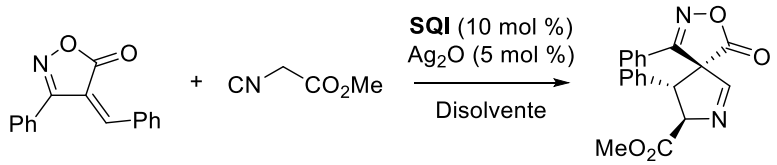
esta reacción de fondo no enantioselectiva, se llevó a cabo la reacción sin óxido de plata, tanto con la escuaramida **SQI** como con la tiourea **TI** (***entradas 4 y 5***). Después de 48 horas, en ambos casos se había consumido totalmente el compuesto de partida **36a** obteniéndose el compuesto **37aa** con un incremento de diastereo- y enantioselectividad respecto a la reacción en presencia de plata, alcanzándose una relación entre diastereómeros del 95:5 y 85% *ee* en el caso de la escuaramida, aunque con rendimientos muy bajos. Con la tiourea **TI** se obtuvo una enantioselectividad mucho menor. De las mezclas de estas reacciones se aisló un subproducto cuya estructura no se pudo determinar, dicho producto, parecía proceder exclusivamente de la alquilidenisoxazolona (posible polimerización). De hecho, en un experimento de control, se observó que el compuesto **36a** se descomponía totalmente después de permanecer 24 horas en disolución de diclorometano a la concentración utilizada, lo cual podría explicar los bajos rendimientos obtenidos en ausencia de plata, durante períodos más largos de reacción.

A la vista de este último resultado, llevamos a cabo la reacción a una dilución mayor con el objetivo de evitar la descomposición del producto de partida (***entrada 6***). Si bien, en este experimento se obtuvieron sólo trazas del producto deseado, pudimos determinar que la alquilidenisoxazolona **36a** se descomponía más lentamente en estas condiciones de concentración, permitiendo además mejorar el exceso enantiomérico hasta el 89%. Por último, con el fin de acelerar de nuevo la reacción decidimos reintroducir el uso del óxido de plata (***entrada 7***). El rendimiento aumentó hasta un 55%, mientras que el compuesto **37aa** se obtuvo con una relación *trans:cis* de 75:25, y un exceso enantiomérico del 80% para el diastereoisómero mayoritario y del 98% para el minoritario.

4.5.2.2 *Efecto del disolvente y la temperatura*

Con estas condiciones de reacción, ensayamos el efecto de diferentes disolventes y temperaturas (**Tabla 17**).

Tabla 17. Adición de isocianoacetato de metilo a benciliden-3-fenilisoxazol-5-ona. Estudio del disolvente y la temperatura.[a]



36a **2a** **37aa**

Entrada	Disolvente	T (ºC)	Rto(%)[b]	*trans:cis*[c]	$ee_{trans/cis}$[d]
1	CH_2Cl_2	t.a.	55	75:25	80/98
2	$CHCl_3$	t.a.	47	83:17	56/93
3	$ClCH_2CH_2Cl$	t.a.	43	95:5	71/91
4	Dioxano	t.a.	31	75:25	80/96
5	THF	t.a.	61	95:5	60/nd
6	MTBE	t.a.	15	79:21	64/86
7	Tolueno	t.a.	12	91:9	11/54
8	CH_2Cl_2	0 °C	36	86:14	38/88

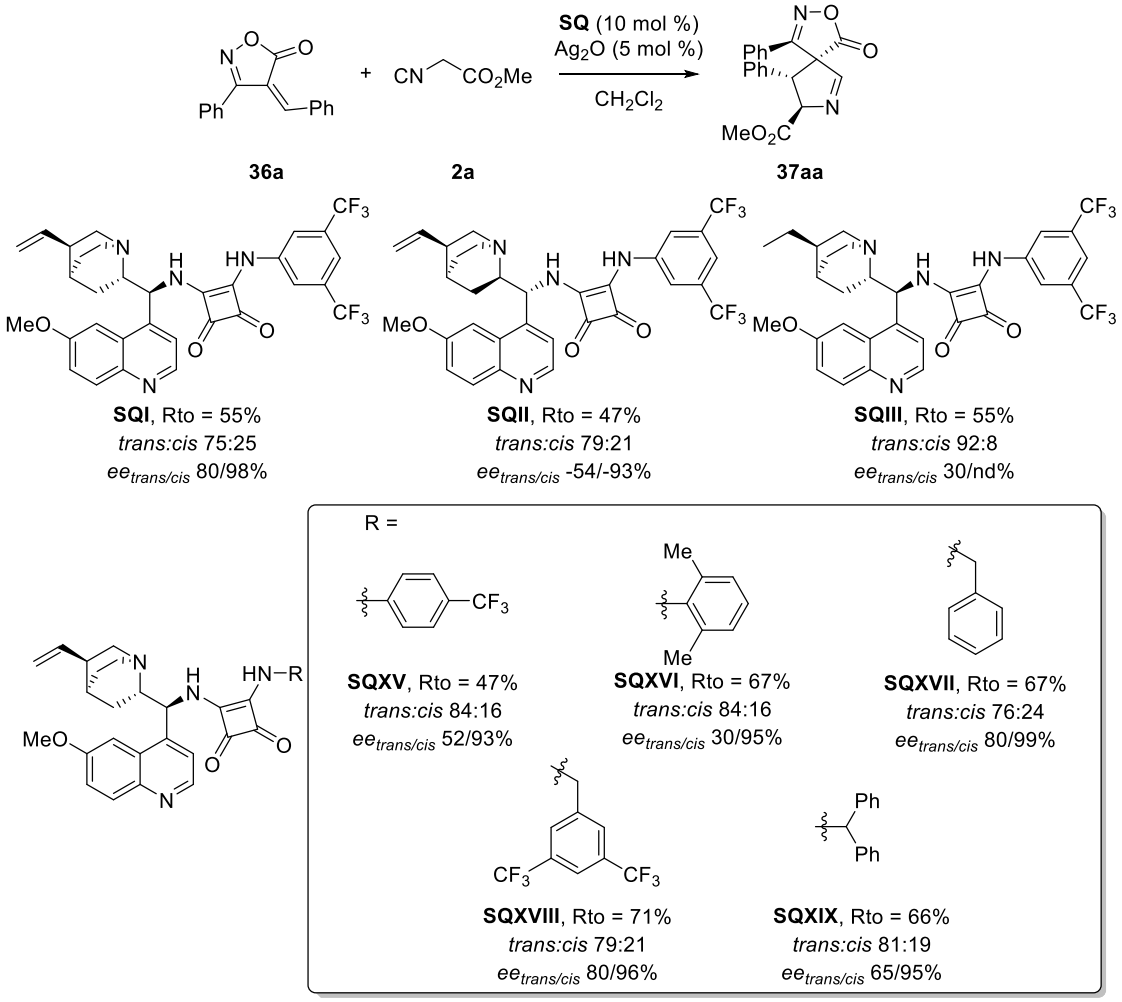
[a] **36a** (0.1 mmol), **2a** (0.13 mmol), **SQI** (0.01 mmol), Ag_2O (0.005 mmol), disolvente (1 mL). [b] Rendimiento del producto aislado. [c] Determinado por ^{1}H RMN. [d] Determinado por HPLC quiral.

Otros disolventes clorados, como cloroformo y dicloroetano (***entradas 2 y 3***), disminuyeron tanto el rendimiento como la diastereo y la enantioselectividad de la reacción. Se ensayaron también disolventes de tipo éter que habían proporcionado buenos resultados en otras reacciones estudiadas. De ellos, el dioxano proporcionó estereoselectividad similar a la obtenida en diclorometano, pero con un rendimiento inferior, mientras que en THF el exceso enantiomérico obtenido fue bastante inferior (***entradas 4 y 5***). MTBE o Tolueno no fueron disolventes adecuados debido a la baja solubilidad del compuesto **36a** en los mismos (***entradas 6 y 7***). En ninguno de los casos fue posible mejorar los resultados obtenidos en diclorometano. En este disolvente se ensayó la reacción a 0 °C. Si bien la diastereoselectividad aumentó hasta una relación 86:14, obteniendo como diastereoisómero mayoritario el producto *trans*, el exceso enantiomérico disminuyó dramáticamente hasta un 38% para este isómero (***entrada 8***).

Por tanto, la optimización se continuó a temperatura ambiente y haciendo uso de diclorometano como disolvente.

4.5.2.3 *Efecto del organocatalizador*

A continuación, se estudió el efecto de la estructura del organocatalizador. Se utilizaron diferentes escuaramidas disponibles en el laboratorio (**Esquema 87)**.



Esquema 87. Escuaramidas ensayadas en este capítulo.

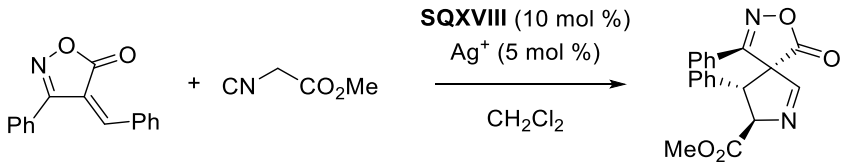
La escuaramida derivada de dihidroquinina y 3,5-bis(trifluorometil)anilina (**SQIII**) permitió mejorar la diastereoselectivida, pero con un descenso pronunciado en el exceso enantiomérico. El organocatalizador derivado de quinidina (**SQII**) proporcionó el enantiómero opuesto, incrementando el rendimiento de la reacción hasta un 72%, mejorando la diastereoselectividad a una relación *trans:cis* de 95:5, pero con un exceso enantiomérico moderado (58%), menor que el obtenido con el derivado de quinina (80%). A continuación, ensayamos distintas escuaramidas derivadas de quinina modificando la parte no quiral del catalizador. Entre todas las escuaramidas ensayadas, únicamente las escuaramidas derivadas de bencilamina (**SQXVII** y **SQXVIII**), proporcionaron resultados similares a los obtenidos con **SQI**, con una mejora en la diastereoselectividad para **SQXVIII**.

Por tanto, el proceso de optimización se continuó haciendo uso del organocatalizador **SQXVIII**, derivado de quinina y 3,5-bis(trifluorometil)bencilamina, ya que es el que proporcionó mejor balance en cuanto a rendimiento, diastereoselectividad y enantioselectividad.

4.5.2.4 *Efecto del compuesto de plata*

Con el fin de determinar el efecto de la especie metálica en la reacción se ensayaron otras sales de plata (**Tabla 18**).

Tabla 18. Adición de isocianoacetato de metilo a benciliden-3-fenilisoxazol-5-ona. Efecto de la sal metálica.[a]



36a **2a** **37aa**

Entrada	Fuente de Ag^+	Rto (%)[b]	*trans:cis*[c]	$ee_{trans/cis}$[d]
1	Ag_2O	71	79:21	80/96
2	$AgNO_3$	77	78:22	64/94
3	AgOAc	75	75:25	80/96
4	Ag_2CO_3	66	74:26	80/95
5	$AgSbF_6$	17	80:20	64/93
6	AgCl	26	80:20	64/93
7	CuO	Trazas	–	–
8	Et_3N	Trazas	–	–

[a] **37a** (0.1 mmol), **2a** (0.13 mmol), **SQXVIII** (0.01 mmol), Ag_2O (0.005 mmol), CH_2Cl_2 (7.5 mL). [b] Rendimiento del producto aislado. [c] Determinado por ^1H RMN. [d] Determinado por HPLC quiral.

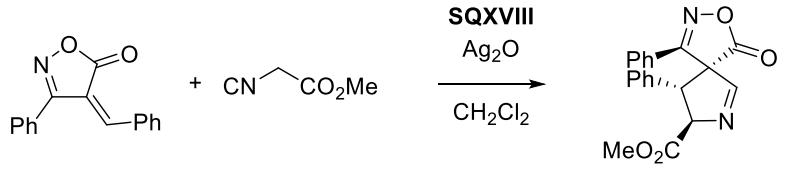
Como puede observarse de los datos recogidos en la **Tabla 18**, ninguna de las sales de plata ensayadas permitió superar los resultados obtenidos con óxido de plata. El nitrato de plata (***entrada 2***), mantuvo la diastereoselectividad, pero generó una perdida notable del exceso enantiomérico del diastereoisómero mayoritario. El acetato y el carbonato de plata (***entradas 3*** y ***4***) condujeron a resultados muy similares a los obtenidos con el óxido de plata. Por otra parte, el hexafluoroantimoniato y el cloruro de plata, cuyos aniones son poco básicos, condujeron al producto de reacción con bajo rendimiento (***entradas 5*** y ***6***).

También se ensayó la reacción con óxido de cobre (II), pero no se obtuvo el producto esperado (***entrada 7***), no observándose reacción al igual que ocurrió en presencia de una base orgánica como la trietilamina (***entrada 8***)

4.5.2.5 *Efecto de la carga catalítica y relación molar del sistema catalítico*

A continuación, estudiamos la carga catalítica y relación molar de ambos componentes del sistema catalítico (**Tabla 19**).

Tabla 19. Estudio entre la relación molar entre escuaramida y Ag_2O.[a]



36a **2a** **37aa**

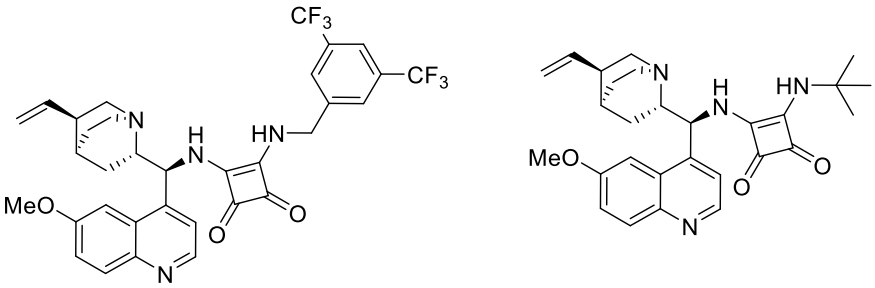
Entrada	**SQ** (mol %)	Ag_2O (mol %)	Rto (%)[b]	*trans:cis*[c]	$ee_{trans/cis}$[d]
1	10	5	71	79:21	80/96
2	10	2.5	52	78:22	80/99
3	10	10	65	82:18	78/92
4	5	5	73	79:21	72/95
5	5	2.5	67	73:27	70/92

[a] **37a** (0.1 mmol), **2a** (0.13 mmol), **SQXVIII** (0.01 mmol), Ag_2O (0.005 mmol), CH_2Cl_2 (1 mL). [b] Rendimiento del producto aislado. [c] Determinado por ^{1}H RMN. [d] Determinado por HPLC quiral.

Aunque en otras de las reacciones estudiadas la relación entre el organocatalizador y la sal de plata jugaba un papel importante, en este caso su efecto sobre la diastereo- y enantioselectividad de la reacción fue menor y el mejor resultado, considerando conjuntamente rendimiento y estereoselectividad se consiguió utilizando un 10 mol % de escuaramida y un 5 mol % de óxido de plata (**Tabla 19**, ***entrada 1***).

4.5.2.6 Ensayo con un catalizador adicional

A la vista de que no fue posible alcanzar niveles elevados de estereoselectividad con la escuaramida **SQXVIII** modificando las condiciones de reacción, decidimos explorar la eficacia de la escuaramida **SQXX** sustituida con un grupo *terc*-butilo en la parte aquiral de la escuaramida (**Figura 19**).



SQXVIII, **37aa**, Rto = 73%
trans:cis 78:22
$ee_{trans/cis}$ 80/96%

SQXX, **37aa**, Rto = 76%
trans:cis 69:31
$ee_{trans/cis}$ 90/99%

Figura 19. Comparación entre la escuaramida **SQXVIII** y **SQXX** en la reacción de cicloadición objetivo de estudio.

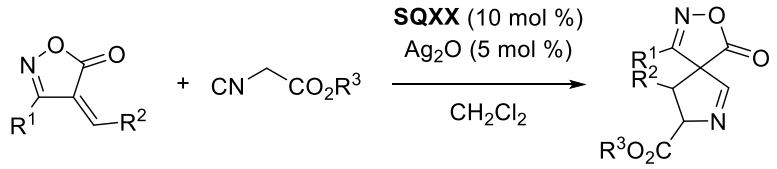
Como puede observarse, con este último organocatalizador en las mismas condiciones optimizadas, se incrementó ligeramente el rendimiento y se aumentó la velocidad de reacción pasando a completarse en 12 horas. Aunque lamentablemente la diastereoselectividad disminuyó, con una relación *trans:cis* de 69:31, la enantioselectividad aumentó sensiblemente hasta un 90% *ee* para el diastereoisómero mayoritario y hasta 99% para el minoritario.

Primando la enantioselectividad sobre la diastereoselectividad decidimos estudiar el alcance y las limitaciones de la reacción en estas últimas condiciones

4.5.3 Alcance y limitaciones

Una vez establecidas las condiciones de reacción, estudiamos el alcance y limitaciones de la reacción con diferentes isocianoacetatos y 4-alquilidenisoxazol-5-onas diferentemente sustituidas (**Tabla 20**).

Tabla 20. Reacción entre isocianoacetatos **2** y 4-alquiliden-isoxazol-5-onas **1** catalizada por **SQXX** y óxido de plata. Alcance y limitaciones.[a]



36 **2** **37**

Entrada	**36**	R^1	R^2	**2**	**37**	Rto (%)[b]	*trans:cis*[c]	$ee_{trans:cis}$ (%)[d]
1	**36a**	Ph	Ph	**2a**	**37aa**	76	69:31	90/99
2	**36b**	Ph	4-MeC_6H_4	**2a**	**37ba**	87	68:32	85/99
3	**36c**	Ph	4-$MeOC_6H_4$	**2a**	**37ca**	49	91:9	85/nd
4	**36d**	Ph	4-BrC_6H_4	**2a**	**37da**	52	94:6	47/nd
5	**36e**	Ph	4-ClC_6H_4	**2a**	**37ea**	74	72:28	81:98
6	**36f**	Ph	4-FC_6H_4	**2a**	**37fa**	74	72:28	84/98
7	**36g**	Ph	3-MeC_6H_4	**2a**	**37ga**	77	70:30	85/98
8	**36h**	Ph	3-$MeOC_6H_4$	**2a**	**37ha**	76	66:34	80/98
9	**36i**	Ph	3-BrC_6H_4	**2a**	**37ia**	76	67:33	78/99
10	**36j**	Ph	2-MeC_6H_4	**2a**	**37ja**	85	70:30	85/98
11	**36k**	Ph	2-$MeOC_6H_4$	**2a**	**37ka**	95	52:48	87/98
12	**36l**	Ph	2-FC_6H_4	**2a**	**37la**	87	57:43	90/6
13	**36m**	Ph	Naftilo	**2a**	**37ma**	56	66:34	84/96
14	**36n**	Ph	Tiofeno	**2a**	**37na**	76	73:27	84/91
15	**36o**	Ph	^{c}Pr	**2a**	**37oa**	50	69:31	87/56
16	**36p**	Me	Ph	**2a**	**37pa**	77	58:42	95/42
17	**36q**	^{c}Pr	Ph	**2a**	**37qa**	62	65:35	86/91
18	**36r**	Ph	Ph	**2d**	**37ad**	73	76:24	90/99

[a] **36** (0.25 mmol), **2** (0.33 mmol), **SQXX** (0.025 mmol), Ag_2O (0.0125 mmol), CH_2Cl_2 (20 mL). [b] Rendimiento del producto aislado. [c] Determinado por ^{1}H RMN. [d] Determinado por HPLC quiral.

En primer lugar, se estudió la reacción entre isocianoacetato de metilo y 4-ariliden-3-fenilisoxazolinonas que presentaban en el doble enlace exocíclico anillos aromáticos sustituidos con grupos de diferente carácter electrónico. En general, los productos

espirocíclicos se obtuvieron con rendimientos entre moderados y excelentes, diastereoselectividades moderadas y altos excesos enantioméricos para ambos diastereómeros, dependiendo en parte de la posición y la naturaleza electrónica del sustituyente sobre el anillo. Se toleraron grupos de carácter electrón dador o electrón aceptor en la posición *para* del grupo fenilo (***entradas 2-6***). Sin embargo, en el caso de grupos *p*-halofenilo, el tamaño y electronegatividad del halógeno fueron determinantes, aumentando la enantioselectividad de la reacción con la electronegatividad (Br<Cl<F). Cuando el anillo aromático se encuentra *meta* sustituido, la reacción proporcionó los productos correspondientes con buenos rendimientos, moderada diastereoselectividad y alto exceso enantiomérico independientemente del carácter electrónico del sustituyente (***entradas 7-9***). La reacción con arilidenisoxazolinonas **36** que presentaban un anillo sutituido en la posición *orto* (***entradas 10-12***), condujo a los espirociclos correspondientes con elevados rendimientos, aunque con relaciones diastereoisoméricas más bajas, pero manteniendo los excesos enantioméricos altos por encima del 85%. Además, el derivado de isoxazolona puede presentar un grupo naftilo voluminoso (***entrada 13***), obteniéndose el espirociclo **37ma** con resultados similares a los obtenidos con derivados de fenilo.

Finalmente, los compuestos **36n** y **36o** que presentan un grupo heterocíclico 2-tienilo o un anillo de ciclopropilo también reaccionaron con isocianatoacetato de metilo para dar los productos esperados con moderado rendimiento y moderada diastereoselectividad, pero alto exceso enantiomérico (***entradas 14*** y ***15***). El sustituyente en la posición 3 de la 4-bencilidenisoxazol-5-ona también puede ser un grupo metilo. Así, el compuesto **36p** reaccionó con isocianoacetato de metilo proporcionando el producto correspondiente con buen rendimiento, baja diastereoselectividad y excelente enantioselectividad para ambos diastereómeros (***entrada 16***). Por otro lado, el compuesto **36q** con un grupo ciclopropilo en esta posición produjo **37qa** con buenos resultados (***entrada 17***). Por último, se llevó a cabo la reacción empleando isocianoacetato de bencilo (***entrada 18***). El producto de cicloadición [3+2] se obtuvo con buen rendimiento, moderada diastereoselectividad y alto exceso enantiomérico.

Cabe destacar, que en todos los casos la reacción de cicloadición entre las isoxazol-5-onas **36** y los isocianoacetatos **2** condujo únicamente a dos de los cuatro posibles diastereoisómeros.

4.5.4 Modificaciones sintéticas y determinación de la configuración absoluta

Para determinar la estereoquímica relativa y absoluta de ambos diastereoisómeros se llevó a cabo una combinación de estudios de RMN y modificaciones sintéticas. En primer lugar, se realizaron experimentos de tipo NOE (*Nuclear Overhauser Effect*) sobre la molécula **37ha**. Los experimentos se realizaron sobre el diastereoisómero mayoritario (**Figura 20**).

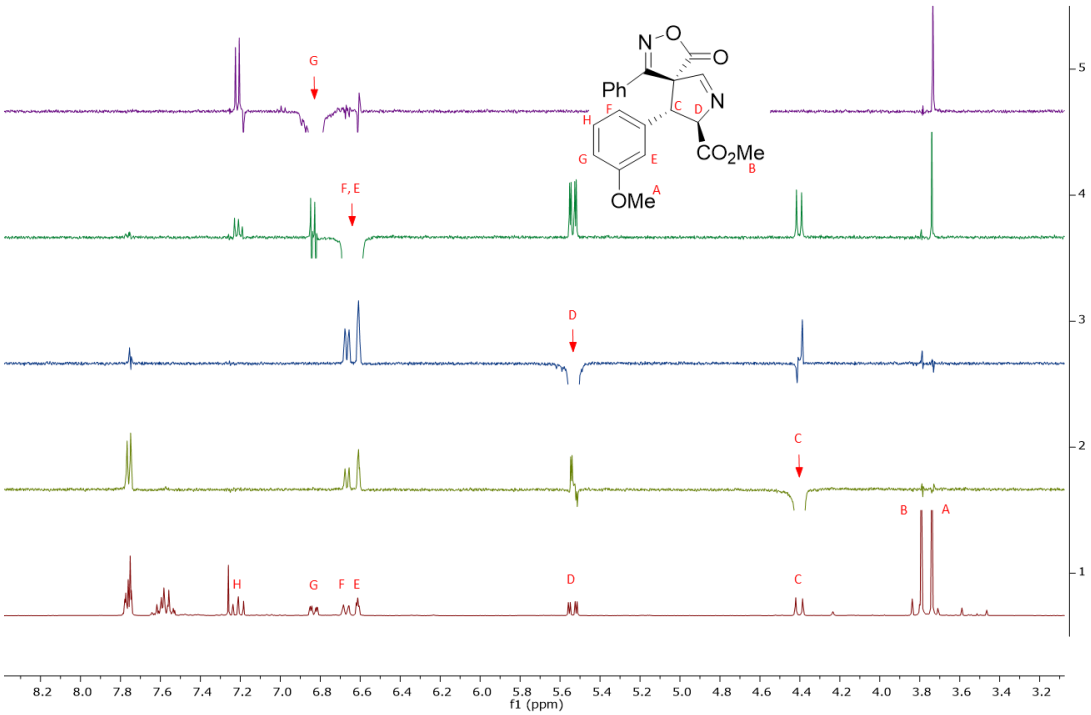
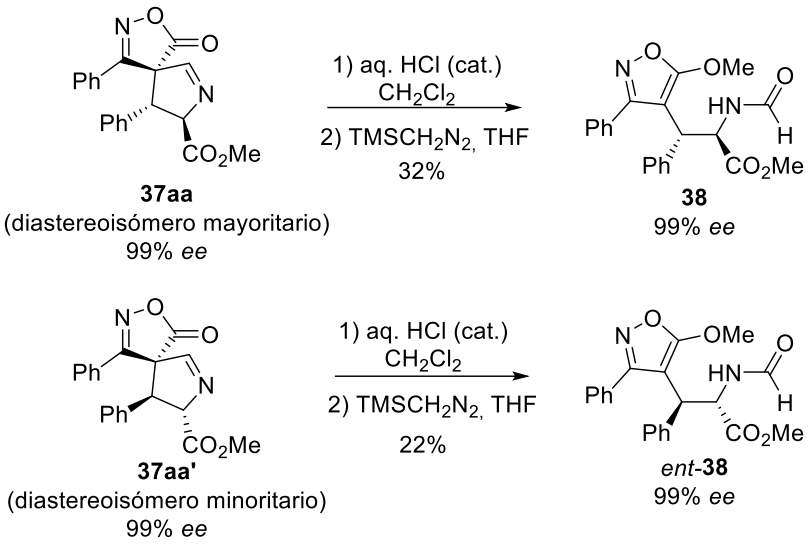


Figura 20. Experimentos de tipo NOE llevados a cabo sobre la molécula **37ha**.

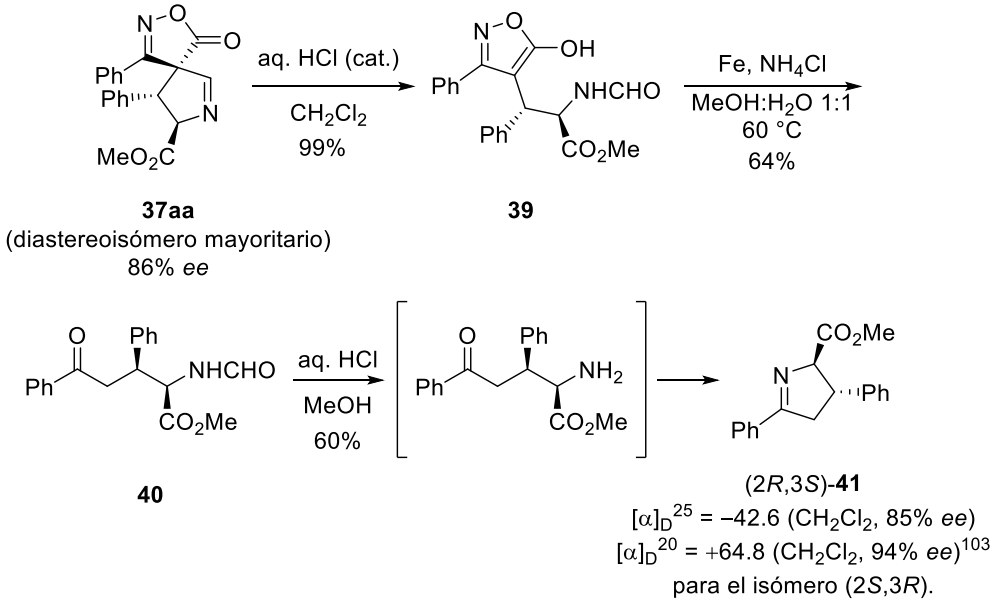
Cuando se irradió sobre el protón D, se observó NOE positivo sobre los protones aromáticos F y E, indicando la disposición *cis* entre el hidrógeno D y el anillo aromático sustituido con el grupo metoxilo. Esto se confirmó al irradiar sobre los protones F y E que produjo efecto NOE positivo sobre el hidrógeno D. Cuando se irradió sobre el hidrógeno C del anillo pirrolínico, se observó NOE positivo con los hidrógenos en *orto* del anillo aromático de la isoxazol-5-ona, lo que nos permitió asignar la disposición *trans* entre el grupo éster y el anillo de *p*-metoxifenilo. Por último, una irradiación sobre el protón G del anillo de *p*-metoxifenilo no produjo NOE positivo sobre el grupo fenilo unido al anillo de isoxazol-5-ona. Para el resto de productos **37** resultantes en las reacciones de cicloadición con las diferentes arilidensisoxazolinonas asumimos una estereoquímica relativa similar.

Por otra parte, cuando los dos diastereómeros del compuesto **37aa** (**37aa'**) se separaron en forma enantioméricamente pura mediante HPLC en fase quiral y se sometieron por separado a hidrólisis en condiciones ácidas seguidas de *O*-metilación, proporcionaron las formamidas enantioméricas **38** y *ent*-**38**, respectivamente, sin perdida de exceso enantiomérico (**Esquema 88**). Este resultado indicaba que ambos diastereómeros **37aa** y **37aa'** tenían la misma configuración en el carbono espiránico y configuraciones opuesta en los otros dos centros estereogénicos de sus moléculas.



Esquema 88. Hidrólisis de los enantiómeros **37aa** y **37aa'**.

Una vez establecida la relación estereoquímica entre los dos diastereoisómeros obtenidos en la reacción llevamos a cabo una serie de modificaciones químicas sobre el producto **37aa** para determinar su configuración absoluta mediante correlación química con un compuesto de estereoquímica absoluta conocida (**Esquema 89**).

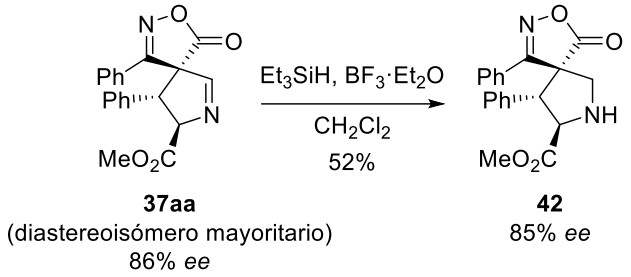


Esquema 89. Determinación de la configuración absoluta del compuesto **37aa**.

En primer lugar, se llevó a cabo la hidrólisis del producto **37aa** en medio ácido para la obtención de la formamida **39** de forma cuantitativa. Esta formamida se transformó en la formamidocetona **40** a través de una modificación del anillo de isoxazolona utilizando hierro como agente reductor. Una posterior hidrólisis de la amida con HCl acuoso en metanol generó una aminocetona, que cicla *in situ* sobre la cetona para generar la pirrolina **43** sin pérdida en el exceso enantiomérico. El compuesto **41** obtenido de esta forma mostró características espectroscópicas idénticas y signo de rotación optica opuesto al compuesto de estereoquímica conocida (2*S*,3*R*)-**41**.[112] De esta forma, asignamos la configuración (5*S*,8*R*,9*R*) al diastereoisómero mayoritario **37aa** y (5*S*,8*S*,9*S*) al

diasteroisómero minoritario **37aa'**. Para el resto de compuestos **37** se asume una configuración absoluta idéntica.

Por otra parte, también llevamos a cabo una transformación adicional sobre el compuesto **37aa**. El grupo imina de la pirrolina se redujo con trietilsilano y trifluoruro de boro como ácido de Lewis para dar la pirrolidina espirocíclica **42** sin pérdida del exceso enantiomérico (**Esquema 90**).



Esquema 90. Síntesis de la pirrolina espirocíclica **42**.

En conclusión, se ha desarrollado una síntesis diastereo- y enantioselectiva de nuevos compuestos espirocíclicos altamente funcionalizados con un carbono espiránico cuaternario y dos estereocentros terciarios, todos ellos consecutivos. Los nuevos espirociclos presentan anillos de pirrolina e isoxazol-5-ona, que son estructuras privilegiadas en química medicinal. La síntesis involucró una reacción de cicloadición formal [3 + 2] entre 4-arilideneisoxazol-5-onas y ésteres de isocianoacetato usando un sistema catalítico cooperativo que combina un organocatalizador bifuncional escuaramida/base de Brønsted derivado de un alcaloide de la *Cinchona* y óxido de plata como ácido de Lewis. La reacción presenta una amplia aplicabilidad y transcurre con buenos rendimientos, buena diastereoselectividad (solo dos de cuatro posibles diastereómeros) y alto exceso enantiomérico.

5. Experimental section

General procedures

All catalytic reactions were carried out in a round bottom flask protected from light. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm.

Solvents and reagents

Analytical quality solvents were used for general purposes. The following solvents were dried and purified when needed: CH_2Cl_2, toluene were freshly distilled from CaH_2 under nitrogen. THF and diethyl ether were freshly distilled from Na/benzophenone under nitrogen. Most reagents were commercially available and used as purchased without further purification.

Melting points

Melting points were measured in capillary tubes in a "Büchi M-560" instrument and are uncorrected.

Nuclear magnetic resonance (NMR)

NMR spectra were run in a Bruker Avance 300 DPX spectrometer (300MHz for ^{1}H, 75MHz for ^{13}C and 282 MHz for ^{19}F NMR). In some cases, a Bruker Avance 400 spectrometer or a Bruker Avance 500 spectrometer were used, especially for NOE and NOESY experiments. Samples were dissolved in deuterated solvents as stated, using the residual nondeuterated solvent as internal standard (δ 7.26 ppm for ^{1}H NMR and δ 77.00 ppm for ^{13}C NMR in the case of $CDCl_3$, δ 2.50 ppm for ^{1}H NMR and δ 39.52 ppm for ^{13}C NMR in the case of DMSO-d_6, δ 4.87 ppm for ^{1}H NMR and δ 49.00 ppm for ^{13}C NMR in the case of MeOD-d_4. For ^{19}F NMR experiments, $CFCl_3$ was used as internal standard. Chemical shifts (δ values) are given in ppm. Coupling constants (J) are given in Hz. The carbon multiplicity was determined by DEPT experiments.

Polarimetry

Specific optical rotations were measured in a Perkin-Elmer polarimeter using a sodium light lamp (D line, 589 nm) and 1 dm cell. Concentrations (c) are given in g/100 mL.

Mass spectrometry

Electrospray ionization mass spectra (ESI) were recorded on a Waters Q-TOF premier mass spectrometer equipped with an electrospray source with a capillary voltage of 3.3 kV.

HPLC analyses

Chiral HPLC analyses were performed with a Hitachi Elite Lachrom instrument equipped with a Hitachi L-4500 diode-array detector using chiral stationary phase columns from Daicel or Phenomenex. Variable mixtures of hexane and isopropanol were used as eluents. Retention times (t_r) are expressed in minutes.

Gas chromatography analyses

Chiral gas chromatography analyses were performed in a Termoquest Trace GC 2000 Series instrument equipped with a Supelco Beta-DEX 225 column (30 m × 0.25 mm × 0.25 μm). N_2 was used as carrier at 1 mL/minute. Injector and detector temperature was set at 220 °C.

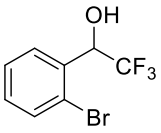
5.1 Enantioselective synthesis of 5-trifluoromethyl-2-oxazolines under dual silver/organocatalysis

All the trifluoromethyl ketones were commercially available except **1i** and **1l** which were synthesized in two steps, according to the literature.[113]

5.1.1 Synthesis of the trifluoromethyl alcohols 5i and 5l

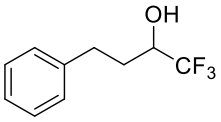
A solution of TBAF in THF (0.66 mL, 0.66 mmol) were added to a solution with the aldehyde (6.6 mmol) and $TMSCF_3$ (1.3 mL, 8.7 mmol) in pentane at 0 °C under N_2 atmosphere. The reaction was followed by TLC. The solvent was evaporated and THF (5 mL) and HCl 4M (5 mL) were added to the mixture and was stirred for 24 hours. The mixture was diluted in EtOAc and washed with brine, dried over $MgSO_4$ and purified by chromatography column (hexane:EtOAc).

1-(2-Bromophenyl)-2,2,2-trifluoroethan-1-ol (5i)



Colorless liquid. 1.69 g (99%). **NMR ^{1}H** (300 MHz, $CDCl_3$) δ 8.27 (2H, d, *J* = 8.7 Hz, Ar), 7.70 (2H, d, *J* = 8.7, Ar), 5.18 (1H, m, CH), 2.92 (1H, d, *J* = 4.5 Hz, OH).[114]

1,1,1-Trifluoro-4-phenylbutan-2-ol (5l)

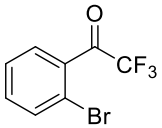


Colorless liquid. 0.498 g (37%). **NMR ^{1}H** (300 MHz, $CDCl_3$) δ 7.29-7.16 (5H, m, Ar), 3.84 (1H, bs, CH), 2.93-2.65 (2H, m, CH_2), 2.25 (1H, bd, *J* = 4.5 Hz, OH), 1.98-1.87 (2H, m, CH_2).[115]

5.1.2 Synthesis of the trifluoromethylketones 1i and 1l

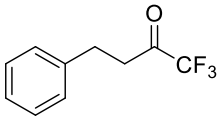
Dess-Martin periodinane (1.3 equiv.) were added in one portion to a solution of trifluoroalcohol in dichloromethane (0.5 M) at room temperature under N_2 atmosphere. The reaction mixture was stirred 24 hours. The product was purified by chromatography column (hexane:EtOAc).

1-(2-Bromophenyl)-2,2,2-trifluoroethan-1-one (**1i**)



Pale yellow liquid. 1.17 g (70%). **NMR ^{1}H** (300 MHz, $CDCl_3$) δ 7.72 (2H, m, Ar), 7.75 (2H, m, Ar). **NMR ^{19}F** (282 MHz, $CDCl_3$) δ -73.55 (s, CF_3). Data consistent with the literature.[114]

1,1,1-Trifluoro-4-phenylbutan-2-one (**1l**)

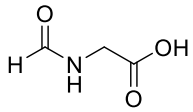


Colorless liquid. 0.336 g (68%). **NMR ^{1}H** (300 MHz, $CDCl_3$) δ 7.31-7.16 (5H, m, Ar), 3.06-2.93 (4H, m, CH_2CH_2). **NMR ^{19}F** (282 MHz, $CDCl_3$) δ -79.74 (s, CF_3). Data consistent with the literature.[115]

5.1.3 Synthesis of the isocyanoacetates 2

All the isocyanoacetates were synthesized according to the literature.[116]

5.1.3.1 Synthesis of *N*-formylglycine (7)

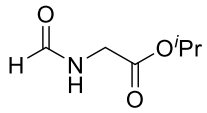


A mixture of glycine (**6**, 9.0 g, 120 mmol) and formic acid (7.68 mL, 204 mmol) in DMF (60 mL) were stirred at 150 °C for 1 hour. The solvent was removed with a vacuum distillation and the residue was crystallized of toluene. The crystals were dried in vacuum to afford 13 g of *N*-formylglycine **9** (99%). **NMR ^{1}H** (300 MHz, DMSO) δ 8.25 (1H, bs, NH), 8.06 (1H, d, *J* = 1.5 Hz, CHO), 3.77 (2H, d, *J* = 5.7 Hz, CH_2).

5.1.3.2 Synthesis of the *N*-formylglycinates 8c-e

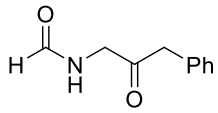
To a suspension of *N*-formylglycine (**7**, 2.5 g, 24.2 mmol) and the corresponding alcohol (22 mmol) in dry dichloromethane (76 mL) were added DCC (4.53 g, 22 mmol) and DMAP (268 mg, 2.2 mmol). The reaction was stirred at room temperature and followed by TLC. The reaction mixture was filtered and the solvents removed under vacuum. The residue was purified by chromatography column (hexane:EtOAc).

Isopropyl formylglycinate (**8c**)



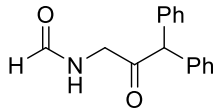
White solid. 2.02 g (63%). **NMR ^{1}H** (300 MHz, $CDCl_3$) δ 8.22 (1H, t, *J* = 0.6 Hz, CHO), 6.37 (1H, bs, NH), 5.06 (1H, sp, *J* = 6.3 Hz, CH), 4.02 (2H, dd, *J* = 5.04, 0.6 Hz, CH_2), 1.26 (3H, s, CH_3), 1.24 (3H, s, CH_3).

Benzyl formylglycinate (**8d**)



White solid. 2.02 g (63%). **NMR ^{1}H** (300 MHz, $CDCl_3$) δ 8.23 (1H, t, *J* = 0.6 Hz, CHO), 7.40-7.33 (5H, m, Ar), 6.30 (1H, bs, NH), 5.19 (2H, s, CH_2), 4.12 (2H, dd, *J* = 5.1, 0.6 Hz, CH_2).

Benzhydryl formylglycinate (**8d**)

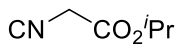


White solid. 3.17 g (73%). **NMR ^{1}H** (300 MHz, $CDCl_3$) δ 8.19 (1H, t, *J* = 0.6Hz, CHO), 7.36-7.30 (10H, m, Ar), 6.93 (1H, s, CH), 6.30 (1H, bs, NH), 4.18 (2H, dd, *J* = 5.4, 0.9 Hz, CH_2).

5.1.3.3 Synthesis of the isocyanoacetates 2c-e

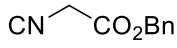
To a solution of the *N*-formylglycinate **8** and trietylamine in dichloromethane at 0 °C, $POCl_3$ were added dropwise over a period of 20 minutes. The reaction mixture was stirred until the consumption of the *N*-formylglycynate (30-90 minutes). A solution of $NaHCO_3$ (sat) were added and the layers were separated. The aqueous layer was extracted with dichloromethane two times. The organic layers were dried over K_2CO_3 and purified by chromatography column (hexane:EtOAc).

Isopropyl 2-isocyanoacetate (**2c**)



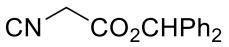
Yellow liquid. 1.51 g (85%). **NMR ^{1}H** (300 MHz, $CDCl_3$) δ 5.09 (1H, sp, *J* = 6.3 Hz, CH), 4.17 (2H, s, CH_2), 1.29 (3H, s, CH_3), 1.27 (3H, s, CH_3).

Benzyl 2-isocyanoacetate (**2d**)



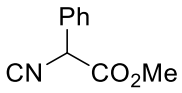
White solid. 2.08 g (80%). **NMR ^{1}H** (300 MHz, $CDCl_3$) δ 7.41-7.35 (5H, m, Ar), 5.25 (2H, s, CH_2), 4.25 (2H, s, CH_2).

Benzhydryl 2-isocyanoacetate (**2e**)



White solid. 2.40 g (81%). **NMR ^{1}H** (300 MHz, $CDCl_3$) δ 7.40-7.32 (10H, m, Ar), 6.98 (1H, s, CH), 4.31 (2H, s, CH_2).

5.1.3.4 Synthesis of methyl 2-isocyano-2-phenylacetate (**2f**)



A solution of methyl (±)-2-phenylglycinate chlorhydrate (**9**, 4.0 g, 18.34 mmol) and ammonium formate (1.56 g, 24.79 mmol) in acetonitrile (17 mL) were stirred over 12 hours at 80 °C. The solvent was removed in vacuum and the residue was solved in EtOAc (150 mL) and washed with water (40 mL). The aqueous layer was extracted with EtOAc (20 mL) and the organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered and the solvent was removed under vacuum. The product was used in the next step without further purification. The formamide was solved in dichloromethane (56 mL) and put in an ice bath under N_2 atmosphere. Triethylamine were added and later $POCl_3$ was added dropwise. The reaction mixture was stirred for 90 minutes and Na_2CO_3 (sat, 37 mL) was added. The layers were separated and the organic layer was washed with water (37 mL) and brine (37 mL), dried over Na_2SO_4 and purified by chromatography column (hexane:EtOAc) to afford 2.44 g (75%) of **2f**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.50-7.43 (5H, m, Ar), 5.37 (1H, s, CH), 3.78 (3H, s, CH_3).

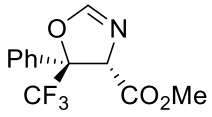
5.1.4 General procedure for the enantioslective synthesis of 5-trifluoromehtyl-2-oxazolines

General procedure for the enantioselective formal [3+2] cycloaddition reaction with methyl isocyanoacetate

SQIII (3.9 mg, 0.0063 mmol) and silver oxide (1.5 mg, 0.0063 mmol) were introduced in a 25 mL round-bottom flask followed by MTBE (8 mL) and trifluoroacetophenone **1** (0.25 mmol). The flask was closed with a stopper and introduced in an ice bath. After 5 min, methyl isocyanoacetate (**2a**, 30 μL, 0.33 mmol) was added and the mixture was stirred at 0 °C until consumption of the trifluoroacetophenone **1** (TLC). After this time, the reaction mixture was filtered through a short pad of silica gel and concentrated under reduced pressure. A small aliquot was analyzed by ^{1}H NMR to determine the diastereomer ratio and by HPLC to determine the enantiomeric excess of products 3. The remaining crude was chromatographed on silica gel eluting with hexane:EtOAc mixtures (9:1 to 8:2) to obtain the oxazolines **3**.

The racemic products were obtained by a similar procedure using *N*-[3,5-bis(trifluoromethyl)phenyl]-*N′*-(3-(dimethylamino)propyl)-squaramide as a substitute for **SQIII**.

Methyl 5-Phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3aa**).

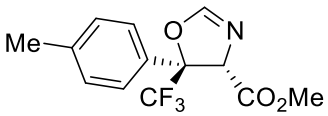


Colorless oil (83.4 mg, 99% from 55.0 mg of **1a**). HPLC (Chiracel IC, hexane:^{i}PrOH 95:5, 0.7 mL/min): *trans*-(**4S,5S**)-**3aa** (major diastereomer, 90% *ee*): major enantiomer, t_r = 12.4 min, minor enantiomer, t_r = 18.3 min; *cis*-**3aa** (minor diastereomer): major enantiomer, t_r = 22.6 min, minor enantiomer t_r = 28.6 min; *trans:cis* = 96:4.

trans-(**4S,5S**)-**3aa** (major diastereomer): $[\alpha]_D^{25}$ +143.0 (*c* 0.30, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$), δ 7.44−7.43 (2H, m, Ar), 7.39−7.37 (3H, m, Ar), 7.24 (1H, d, *J* = 1.8 Hz, N=CHO), 5.24 (1H, d, *J* = 1.8 Hz, CH), 3.27 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.1 (C), 155.7 (CH), 130.7 (C), 129.6 (CH), 128.4 (CH), 125.9 (CH, q, J_{CF} = 1.6 Hz), 123.8 (C, q, J_{CF} = 283 Hz), 87.6 (C, q, J_{CF} = 30 Hz), 74.2 (CH), 52.2 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −80.1 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{12}H_{11}F_3NO_3^+$: 274.0686, found: 274.0689.

cis-**3aa** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.70−7.35 (5H, Ar), 7.16 (1H, d, *J* = 2.4 Hz, N=CHO), 5.14 (1H, dd, J = 2.1, 0.6 Hz, CH), 3.91 (3H, s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −76.0 (s, CF_3).

Methyl 5-(p-Tolyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3ba**).

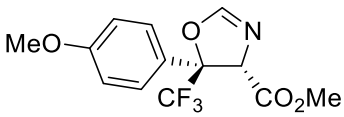


Colorless oil (68.9 mg, 99% from 47.0 mg of **1b**). HPLC (Chiralpak AS-H, hexane:^{i}PrOH 95:5, 1 mL/min): trans-(**4S,5S**)-**3ba** (major diastereomer, 87% *ee*): major enantiomer, t_r = 6.0 min, minor enantiomer, t_r = 8.6 min; cis-**3ba** (minor diastereomer): major enantiomer, t_r = 15.7 min, minor enantiomer, t_r = 17.0 min; *trans:cis* = 94:6.

trans-(**4S,5S**)-**3ba** (major diastereomer): $[\alpha]_D^{25}$+127.8 (*c* 0.58, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 8.1 Hz, Ar), 7.23 (1H, d, *J* = 1.8 Hz, N=CHO), 7.17 (2H, d, *J* = 8.1 Hz, Ar), 5.22 (1H, d, *J* = 2.1 Hz, CH), 3.30 (3H, s, CH_3), 2.34 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.1 (C), 155.7 (CH), 139.6 (C), 129.0 (CH), 127.6 (C), 125.7 (CH, q, J_{CF} = 1.6 Hz), 123.8 (C, q, J_{CF} = 283 Hz), 87.5 (C, q, J_{CF} = 30 Hz), 74.0 (CH), 52.1 (CH_3), 21.0 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −80.2 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{13}H_{12}F_3NO_3^+$: 288.0842, found: 288.0849.

cis-**3ba** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.12 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.83 (3H, s, CH_3), 2.38 (3H, s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −76.1 (s, CF_3).

Methyl 5-(4-Methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3ca**).



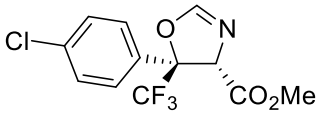
Colorless oil (65.9 mg, 88% from 51.0 mg of **1c**). HPLC (Chiralpak IC, hexane:^{i}PrOH 95:5, 1 mL/min): trans-(**4S,5S**)-**3ca** (major diastereomer, 85% *ee*): major enantiomer, t_r = 13.2 min, minor enantiomer, t_r = 29.0 min; cis-**3ca** (minor diastereomer): major enantiomer, t_r = 27.9 min, minor enantiomer, t_r = 34.7 min; *trans:cis* = 96:4.

trans-(**4S,5S**)-**3ca** (major diastereomer): $[\alpha]_D^{25}$ +122.5 (*c* 0.25, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 (2H, d, *J* = 8.6 Hz, Ar), 7.23 (1H, dd, *J* = 2.1, 0.6 Hz, N=CHO), 6.88 (2H, d, *J* = 9.0 Hz, Ar), 5.20 (1H, d, *J* = 2.1 Hz, CH), 3.80 (s, CH_3), 3.33 (s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.2 (C), 160.3 (C), 155.7 (CH), 127.3 (CH, q, J_{CF} = 1.9 Hz), 123.8 (C, q, J_{CF} = 283 Hz), 122.4 (C), 113.8 (CH), 87.5 (C, q, J_{CF} = 30 Hz), 74.0 (CH), 55.2 (CH_3), 52.3 (CH_3); **^{19}F NMR** (282 MHz,

$CDCl_3$) δ −80.4 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{13}H_{13}F_3NO_4^+$: 304.0791, found: 304.0795.

cis-**3ca** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, CDCl3) δ 7.13 (1H, d, *J* = 2.4 Hz, CH), 5.11 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.89 (3H, s, CH_3), 3.82 (3H, s, CH_3); **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ −76.7 (s, CF_3).

Methyl 5-(4-Chlorophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3da**).

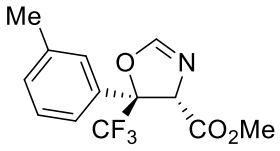


Colorless oil (75.7 mg, 99% from 54.1 mg of **1d**). HPLC (Chiralpak IC, hexane:iPrOH 90:10, 1 mL/min): *trans*-(**4S,5S**)-**3da** (major diastereomer, 84 % *ee*): major enantiomer, t_r = 5.9 min, minor enantiomer, t_r = 8.1 min; *cis*-**3da** (minor diastereomer, 64% *ee*): major enantiomer, t_r = 12.7 min, minor enantiomer, t_r = 13.1 min; *trans:cis* = 80:20.

trans-(**4S,5S**)-**3da** (major diastereomer): $[\alpha]_D^{25}$ +120.8 (*c* 0.20, $CHCl_3$, 84% *ee*); **^{1}H NMR** (300 MHz, CDCl3), δ 7.37−7.35 (4H, m, Ar), 7.23 (1H, d, *J* = 2.1 Hz, N=CHO), 5.23 (1H, d, *J* = 2.1 Hz, CH), 3.33 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.9 (C), 155.6 (CH), 135.9 (C), 129.3 (C), 128.7 (CH), 127.4 (CH, q, J_{CF} = 1.6 Hz), 123.6 (C, q, J_{CF} = 283 Hz), 87.2 (C, q, J_{CF} = 30.8 Hz), 74.0 (CH), 52.4 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −80.2 (s, CF3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{12}H_{10}ClF_3NO_3^+$: 308.0296, found: 308.0299.

cis-**3da** (minor diastereomer): $[\alpha]_D^{25}$ +63.5 (*c* 0.14, CHCl3, 64% *ee*); **^{1}H NMR** (300 MHz, CDCl3) δ 7.66 (2H, d, *J* = 8.5 Hz, Ar), 7.45 (2H, d, *J* = 8.5 Hz, Ar), 7.16 (1H, d, *J* = 2.1 Hz, CH), 5.08 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.92 (3H, s, CH3); **^{13}C{^{1}H} NMR** (75 MHz, CDCl3) δ 167.3 (C), 154.5 (CH), 136.2 (C), 133.5 (C), 129.2 (CH), 127.9 (CH), 122.6 (C, q, J_{CF} = 283 Hz), 87.7 (C, q, J_{CF} = 31 Hz), 76.5 (CH), 53.3 (CH3); **^{19}F{^{1}H} NMR** (282 MHz, CDCl3) δ −76.0 (s, CF3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{12}H_{10}ClF_3NO_3^+$: 308.0296, found: 308.0299.

Methyl 5-(m-Tolyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3ea**).

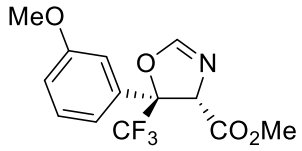


Colorless oil (68.8 mg, 99% from 47.0 mg of **1e**). HPLC (Chiralpak IC, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-(***4S,5S***)-**3ea** (major diastereomer, 90% *ee*): major enantiomer, t_r = 8.3 min, minor enantiomer, t_r = 12.0 min; *cis*-**3ea** (minor diastereomer): major enantiomer, t_r = 13.8 min, minor enantiomer, t_r = 18.2 min; *trans:cis* = 94:6.

trans-(***4S,5S***)-**3ea** (major diastereomer): $[\alpha]_D^{25}$ +132.4 (*c* 0.50, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.24−7.15 (5H, m, Ar, N=CHO), 5.22 (1H, d, *J* = 1.8 Hz, CH), 3.30 (3H, s, CH_3), 2.36 (3H, d, *J* = 0.6 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.1 (C), 155.7 (CH), 138.2 (C), 130.6 (C), 130.3 (CH), 128.3 (CH), 126.4 (CH, q, J_{CF} = 1.8 Hz), 123.8 (C, q, J_{CF} = 283 Hz), 122.9 (CH, q, J_{CF} = 1.9 Hz), 87.6 (C, q, J_{CF} = 30 Hz), 74.1 (CH), 52.2 (CH_3), 21.4 (CH3); **^{19}F NMR** (282 MHz, CDCl3) δ −80.1 (s, CF3); HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{13}H_{13}F_3NO_3^+$: 288.0842, found: 288.0845.

cis-**3ea** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.13 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.83 (3H, s, CH_3), 2.41 (3H, s, CH3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −75.8 (s, CF_3).

Methyl 5-(3-Methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3fa**).

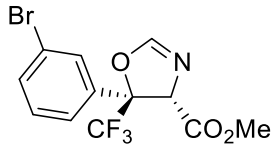


Colorless oil (71.3 mg, 94% from 51.0 mg of **1f**). HPLC (Chiralpak AS-H, hexane:iPrOH 95:5, 1 mL/min): *trans*-(***4S,5S***)-**3fa** (major diastereomer, 88% *ee*): major enantiomer, t_r = 7.3 min, minor enantiomer, t_r = 10.0 min; *cis*-**3fa** (minor diastereomer): major enantiomer, t_r = 21.8 min, minor enantiomer, t_r = 19.9 min; trans:cis = 92:8.

trans-(***4S,5S***)-**3fa** (major diastereomer): $[\alpha]_D^{25}$ −26.7 (*c* 0.56, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 (1H, t, *J* = 8.4 Hz, Ar), 7.22 (1H, d, *J* = 2.1 Hz, N=CHO), 7.01−6.98 (2H, m, Ar), 6.92−6.90 (1H, m, Ar), 5.22 (1H, d, *J* = 1.8 Hz, CH), 3.80 (3H, s, CH_3), 3.33 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.1 (C), 159.5 (C), 155.7 (CH), 132.1 (C), 129.5 (CH), 123.7 (C, q, J_{CF} = 283 Hz), 118.1 (CH, q, J_{CF} = 2.2 Hz), 114.9 (CH), 111.9 (CH, q, J_{CF} = 1.7 Hz), 87.5 (C, q, J_{CF} = 30 Hz), 74.1 (CH), 55.3 (CH_3), 52.3 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −80.2 (s, CF_3); HRMS (ESI) m/z: [M + H]+ calculated for $C_{13}H_{13}F_3NO_4^+$: 304.0791, found: 304.0794.

cis-**3fa** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.14 (1H, d, *J* = 2.1 Hz, N=CHO), 5.13 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.91 (3H, s, CH_3), 3.84 (3H, s, CH_3); **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ −75.9 (s, CF_3).

Methyl 5-(3-Bromophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3ga**).



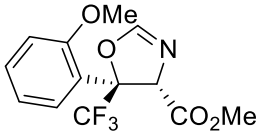
Colorless oil (83.0 mg, 95% from 63.3 mg of **1g**). HPLC (Chiralpak IC, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-(***4S,5S***)-**3ga** (major diastereomer, 92% *ee*): major enantiomer, t_r = 7.3 min, minor enantiomer, t_r = 9.8 min; *cis*-**3ga** (minor diastereomer): major enantiomer, t_r = 14.5 min, minor enantiomer, t_r = 18.3 min; *trans:cis* = 86:14.

trans-(***4S,5S***)-**3ga** (major diastereomer): $[\alpha]_D^{25}$ +107.7 (*c* 0.66, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 (1H, s, Ar), 7.53 (1H, ddd, *J* = 8.0, 1.9, 1.1 Hz, Ar), 7.38 (1H, bd, *J* = 8.0 Hz, Ar), 7.25 (1H, t, *J* = 8.0 Hz, Ar), 7.23 (1H, d, *J* = 1.8 Hz, N=CHO), 5.23 (1H, d, J = 2.1 Hz, CH), 3.36 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.8 (C), 155.5 (CH), 132.9 (C), 132.8 (CH), 129.9 (CH), 129.1 (CH, q, J_{CF} = 1.7 Hz), 125.4 (C, q, J_{CF} = 283 Hz), 124.6 (CH, q, J_{CF} = 1.7 Hz), 122.6 (C), 86.9 (C, q, J_{CF} = 30 Hz), 74.1 (CH), 52.4 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −80.1 (s, CF_3); HRMS (ESI) m/z: [M + H]$^+$ calculated for $C_{12}H_{10}BrF_3NO_3^+$: 351.9791, found: 351.9791.

cis-**3ga** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.15 (1H, d, *J* = 2.1 Hz, N=CHO),

5.08 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.90 (3H, s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −75.8 (s, CF_3).

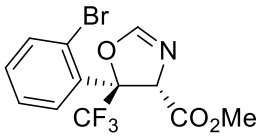
Methyl 5-(2-Methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3ha**).



White solid (86.3 mg, 99% from 58.1 mg of **1h**). HPLC (Chiralpak IC, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-(***4S,5S***)-**3ha** (major diastereomer, 85% *ee*): major enantiomer, t_r = 11.6 min, minor enantiomer, t_r = 15.9 min; *cis*-**3ha** (minor diastereomer): major enantiomer, t_r = 17.2 min, minor enantiomer, t_r = 26.9 min; *trans:cis* = 99:1.

trans-(***4S,5S***)-**3ha** (major diastereomer): mp 129−130 °C; $[\alpha]_D^{25}$ +228.1 (*c* 0.41, $CHCl_3$, for the diastereomer mixture, *trans:cis* = 99:1); **^{1}H NMR** (300 MHz, CDCl3) δ 7.61 (1H, dd, *J* = 7.8, 1.8 Hz, Ar), 7.38 (1H, td, *J* = 7.5, 1.8 Hz, Ar), 7.13 (1H, d, *J* = 2.1 Hz, N=CHO), 7.05 (1H, td, *J* = 7.8, 1.2 Hz, Ar), 6.86 (1H, dd, *J* = 8.1, 0.9 Hz, Ar), 5.28 (1H, d, *J* = 2.1 Hz, CH), 3.75 (3H, s, CH_3), 3.54 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.7 (C), 155.3 (C), 155.2 (CH), 130.9 (CH), 128.8 (CH), 123.8 (C, q, J_{CF} = 283 Hz), 120.9 (CH), 119.8 (C), 110.3 (CH), 86.9 (C, q, J_{CF} = 30.8 Hz), 72.8 (CH), 54.7 (CH3), 52.1 (CH3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −81.9 (s, CF_3); HRMS (ESI) m/z: [M+H]+ calculated for $C_{13}H_{13}F_3NO_4^+$: 304.0791, found: 304.0791.

Methyl 5-(2-Bromophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3ia**).

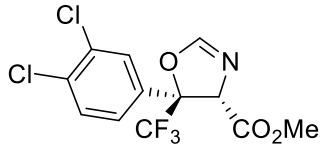


Colorless oil (81.7 mg, 93% from 63.3 mg of **1i**). HPLC (Chiralpak IC, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-(***4S,5S***)-**3ia** (major diastereomer, 70% *ee*): major enantiomer, t_r = 8.9 min, minor enantiomer, t_r = 12.6 min; *cis*-**3ia** (minor diastereomer): major enantiomer, t_r = 17.8 min, minor enantiomer, t_r = 24.3 min; trans:cis = 85:15.

trans-(***4S,5S***)-**3ia** (major diastereomer): $[\alpha]_D^{25}$ +150.9 (*c* 0.43, $CHCl_3$, for the diastereomer mixture, *trans:cis* = 85:15); **^{1}H NMR** (500 MHz, CDCl3, 50 °C) δ 7.90 (1H, unresolved d, Ar), 7.73 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.52 (1H, td, *J* = 8.0, 1.0 Hz, Ar), 7.37 (1H, td, *J* = 8.0, 1.5 Hz, Ar), 7.27 (1H, d, *J* = 2.0 Hz, N=CHO), 5.62 (1H, s, CH), 3.72 (3H, s, CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$, 50 °C) δ 167.4 (C), 155.0 (CH), 136.3 (C), 134.6 (br CH), 130.8 (CH), 130.4 (CH), 127.6 (CH), 123.7 (C, q, J_{CF} = 283 Hz), 120.8 (C), 88.8 (C, q, J_{CF} = 29.0 Hz), 72.9 (CH), 52.6 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −79.4 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{12}H_{10}BrF_3NO_3^+$: 351.9791, found: 351.9798.

cis-**3ia** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.93 (br d, *J* = 8.1 Hz, Ar), 7.83 (1H, dd, *J* = 8.1, 1.3 Hz, Ar), 7.52 (1H, td, *J* = 8.0, 1.0 Hz, Ar), 7.39 (1H, td, *J* = 8.0, 1.5 Hz, Ar), 7.26 (1H, d, *J* = 2.0 Hz, N=CHO), 5.62 (1H, s, CH), 3.98 (3H, s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −72.2 (s, CF_3).

Methyl 5-(3,4-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3ja**).

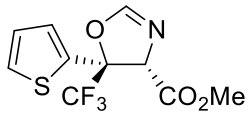


Yellow oil (90.1 mg, 99% from 64.1 mg of **1j**). HPLC (Chiralpak IC, hexane:iPrOH 95:5, 1 mL/min): *trans*-(***4S,5S***)-**3ja** (major diastereomer, 85% *ee*): major enantiomer, t_r = 6.4 min, minor enantiomer, t_r = 8.7 min; *cis*-**3ja** (minor diastereomer): major enantiomer, t_r = 16.4 min, minor enantiomer, t_r = 19.6 min; trans:cis = 77:23.

trans-(***4S,5S***)-**3ja** (major diastereomer): $[\alpha]_D^{25}$ +105.0 (*c* 0.92, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.56 (1H, d, *J* = 2.3 Hz, Ar), 7.46 (1H, d, *J* = 8.7 Hz, Ar), 7.27 (1H, ddd, *J* = 8.4, 2.1, 0.9 Hz, Ar), 7.22 (1H, d, *J* = 1.8 Hz, N=CHO), 5.22 (1H, d, *J* = 1.8 Hz, CH), 3.40 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.7 (C), 155.4 (CH), 134.3 (C), 133.1 (C), 131.0 (C), 130.5 (CH), 128.2 (CH, q, J_{CF} = 1.8 Hz), 125.4 (CH, q, J_{CF} = 1.7 Hz), 125.2 (C, q, J_{CF} = 283 Hz), 86.6 (C, q, J_{CF} = 29 Hz), 74.0 (CH), 52.5 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −80.2 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{12}H_9Cl_2F_3NO_3^+$: 341.9906, found: 341.9909.

cis-**3ja** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, CDCl3) δ 7.14 (1H, d, *J* = 2.1 Hz, N=CHO), 5.05 (1H, dd, *J* = 2.1, 0.9 Hz, CH), 3.91 (3H, s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −76.0 (s, CF_3).

Methyl 5-(Thiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3ka**).

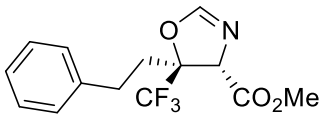


Yellow oil (80.1 mg, 99% from 52.3 mg of **1k**). HPLC (Chiralpak IC, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-(***4S,5S***)-**3ka** (major diastereomer, 90% *ee*): major enantiomer, t_r = 10.0 min, minor enantiomer, t_r = 13.8; *cis*-**3ka** (minor diastereomer): major enantiomer, t_r = 17.6 min, minor enantiomer, t_r = 22.1 min; trans:cis = 92:8.

trans-(***4S,5S***)-**3ka** (major diastereomer): $[\alpha]_D^{25}$ +48.0 (*c* 0.79, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 (1H, dd, *J* = 5.1, 1.5 Hz, Ar), 7.19 (1H, dd, *J* = 2.1, 0.6 Hz, N=CHO), 7.10−7.08 (1H, m, Ar), 7.03 (1H, dd, *J* = 5.1, 3.9 Hz, Ar), 5.22 (1H, d, *J* = 2.1 Hz, CH), 3.41 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.7 (C), 155.1 (CH), 132.7 (C), 127.5 (CH), 126.9 (CH), 126.8 (CH, q, J_{CF} = 2.1 Hz), 123.2 (C, q, J_{CF} = 283 Hz), 86.3 (C, q, J_{CF} = 32 Hz), 74.6 (CH), 52.4 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −81.5 (s, CF_3); HRMS (ESI) m/z: [M+H]+ calculated for $C_{10}H_9F_3NO_3S^+$: 280.0250, found: 280.0253.

cis-**3k** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.12 (1H, d, *J* = 2.1 Hz, N=CHO), 5.19 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.89 (3H, s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −76.4 (s, CF_3).

Methyl 5-Phenethyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3la**).

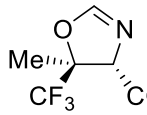


Yellow oil (50.1 mg, 66% from 51.0 mg of **1l**). HPLC (Chiralpak IC, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-(***4S,5S***)-**3la** (major diastereomer, 81% *ee*): major enantiomer, t_r = 7.9 min, minor enantiomer, t_r = 19.6 min; *cis*-**3la** (minor diastereomer): major enantiomer, t_r = 39.5 min, minor enantiomer, t_r = 28.4 min; *trans:cis* = 86:14.

trans-(***4S,5S***)-**3la** (major diastereomer): $[\alpha]_D^{25}$ +17.5 (*c* 0.81, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30−7.26 (4H, m, Ar), 7.13−7.10 (1H, m, Ar), 7.03 (1H, d, *J* = 2.4 Hz, N=CHO), 4.98 (1H, d, *J* = 2.4 Hz, CH), 3.81 (3H, s, CH*3*), 2.78−2.55 (2H, m, CH*2*), 2.33−2.06 (2H, m, CH*2*); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.1 (C), 155.2 (CH), 139.9 (C), 128.6 (CH), 128.1 (CH), 126.4 (CH), 124.2 (C, q, J_{CF} = 283 Hz), 85.7 (C, q, J_{CF} = 30.1 Hz), 71.3 (CH), 52.8 (CH_3), 31.4 (CH_2), 28.6 (CH_2); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −80.7 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{14}H_{15}F_3NO_3^+$: 302.0999, found: 302.1004.

cis-**3la** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.82 (1H, d, *J* = 2.1 Hz, CH), 3.81 (3H, s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −76.3 (s, CF_3).

Methyl 5-Methyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3ma**).



Volatile colorless oil (42.2 mg, 80% from 28.1 mg of **1m**). HPLC (Chiralpak IC, hexane:^{i}PrOH 90:10, 1 mL/min): *trans*-(***4S,5S***)-**3ma** (major diastereomer 82% *ee*): major enantiomer, t_r = 6.9 min, minor enantiomer, t_r = 8.5 min; *cis*-**3ma** (minor diastereomer): major enantiomer, t_r = 12.7 min, minor enantiomer, t_r = 14.0 min; trans:cis = 92:8.

trans-(***4S,5S***)-**3ma** (major diastereomer): $[\alpha]_D^{25}$ +75.3 (*c* 0.33, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, CDCl3) δ 6.97 (1H, d, *J* = 1.5 Hz, N=CHO), 4.88 (1H, d, *J* = 2.5 Hz, CH), 3.79 (3H, s, CH_3), 1.49 (3H, m, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.0 (C), 155.5 (CH), 124.0 (C, q, J_{CF} = 283 Hz), 83.9 (C, q, J_{CF} = 32 Hz), 71.3 (CH), 52.7 (CH_3), 15.3 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −83.3 (s, CF_3); HRMS (ESI) m/z: $[M+ H]^+$ calculated for $C_7H_9F_3NO_3^+$: 212.0529, found: 212.0536.

cis-**3ma** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, CDCl3) δ 4.62 (1H, dd, *J* = 2.2, 0.6 Hz, CH), 3.79 (3H, s, CH_3), 1.74 (3H, s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −77.7 (s, CF_3).

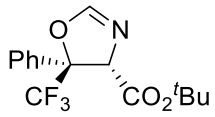
General procedure for the enantioselective formal [3+2] cycloaddition reaction with tert-butyl isocyanoacetate

SQVIII (6.8 mg, 0.0125 mmol) and silver oxide (1.5 mg, 0.0063 mmol) were introduced in a 25 mL round-bottom flask followed by MTBE (8 mL) and trifluoroacetophenone **1** (0.25 mmol). The flask was closed with a stopper and introduced in an ice bath. After 5 min, *terc*-butyl isocyanoacetate (**2b**, 48 μL, 0.33 mmol) was added and the mixture was stirred at 0 °C until consumption of the trifluoroacetophenone **1** (TLC). After this time, the reaction mixture was filtered through a short pad of silica gel and concentrated under reduced pressure. A small aliquot was analyzed by ^{1}H NMR to determine the

diastereomer ratio and by HPLC to determine the enantiomeric excess of products 3. The remaining crude was chromatographed on silica gel eluting with hexane:EtOAc mixtures (9:1 to 8:2) to obtain the oxazolines **3**.

The racemic products were obtained by a similar procedure using *N*-[3,5-bis(trifluoromethyl)phenyl]-*N*′-(3-(dimethylamino)propyl)-squaramide as a substitute for **SQVIII**.

***tert*-Butyl 5-Phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate** (**3ab**)

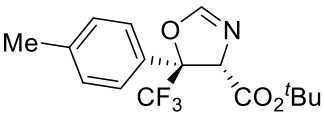


Colorless oil (102.2 mg, 99% from 57.3 mg of **1a**). HPLC (Chiralpak IC, hexane:^{i}PrOH 90:10, 0.7 mL/min): *trans*-(***4S,5S***)-**3ab** (major diastereomer, 96% *ee*): major enantiomer, t_r = 7.2 min, minor enantiomer, t_r = 8.5 min; *cis*-**3ab** (minor diastereomer, 90% *ee*): major enantiomer, t_r = 11.1 min, minor enantiomer, t_r = 15.2 min; *trans:cis* = 70:30.

trans-(***4S,5S***)-**3ab** (major diastereomer): $[\alpha]_D^{25}$ +178.1 (*c* 1.15, $CHCl_3$, 96% *ee*); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.50−7.46 (2H, m, Ar), 7.39−7.37 (3H, m, Ar), 7.20 (1H, d, *J* = 1.8 Hz, N=CHO), 5.08 (1H, d, *J* = 1.8 Hz, CH), 1.03 (9H, s, CH_3); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 165.3 (C), 155.3 (CH), 131.0 (C), 129.4 (CH), 128.4 (CH), 126.4 (CH, q, J_{CF} = 2.0 Hz), 123.9 (C, q, J_{CF} = 284 Hz), 87.6 (C, q, J_{CF} = 30 Hz), 82.7 (C), 74.6 (CH), 27.1 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −80.3 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{15}H_{17}F_3NO_3^+$: 316.1155, found: 316.1154.

cis-**3ab** (minor diastereomer): $[\alpha]_D^{25}$ +77.2 (*c* 0.23, $CHCl_3$, 90% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.72−7.69 (2H, m, Ar), 7.46−7.44 (3H, m, Ar), 7.12 (1H, d, *J* = 2.4 Hz, N=CHO), 5.02 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 1.58 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.7 (C), 154.0 (CH), 135.6 (C), 129.7 (CH), 128.7 (CH), 128.6 (C, q, J_{CF} = 283 Hz), 126.4 (CH), 123.0 (C, q, J_{CF} = 283 Hz), 87.9 (C, q, J_{CF} = 30.7 Hz), 83.6 (C), 77.4 (CH), 27.7 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −75.0 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{15}H_{17}F_3NO_3^+$: 316.1155, found: 316.1154.

***tert*-Butyl 5-(*p*-Tolyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate** (**3bb**).

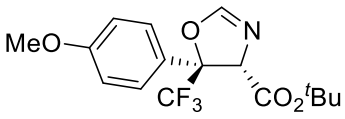


White solid (71.7 mg, 87% from 47.0 mg of **1b**). HPLC (Chiralpak IC, hexane:iPrOH 95:5, 1 mL/min): *trans*-(***4S,5S***)-**3bb** (major diastereomer, 93% *ee*): major enantiomer, t_r = 6.9 min, minor enantiomer, t_r = 9.4 min; *cis*-**3bb** (minor diastereomer, 96% *ee*): major enantiomer, t_r = 12.2 min, minor enantiomer, t_r = 18.3 min; *trans:cis* = 66:34.

trans-(***4S,5S***)-**3bb** (major diastereomer): mp: 63−65 °C; $[\alpha]_D^{25}$ +153.3 (*c* 0.96, $CHCl_3$, 93% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 (2H, d, *J* = 8.1, Ar), 7.19 (1H, d, *J* = 2.1 Hz, N=CHO), 7.18 (2H, d, *J* = 8.1 Hz, Ar), 5.05 (1H, d, *J* = 2.1 Hz, CH), 2.33 (3H, d, *J* = 0.9 Hz, CH_3), 1.05 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.4 (C), 155.3 (CH), 139.4 (C), 129.0 (CH), 128.0 (C), 126.3 (CH, q, J_{CF} = 1.7 Hz), 123.9 (C, q, J_{CF} = 283 Hz), 87.6 (C, q, J_{CF} = 30 Hz), 82.6 (C), 74.5 (CH), 27.1 (CH_3), 21.0 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −80.4 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{19}F_3NO_3^+$: 330.1312, found: 330.1316.

cis-**3bb** (minor diastereomer): colorless oil; $[\alpha]_D^{25}$ +84.8 (*c* 1.09, $CHCl_3$, 96% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.57 (2H, d, *J* = 8.1 Hz, Ar), 7.26 (2H, d, *J* = 8.1 Hz, Ar), 7.10 (1H, d, *J* = 2.1 Hz, N=CHO), 5.00 (1H, dd, *J* = 2.4, 0.9 Hz, CH), 2.38 (3H, s, CH_3), 1.57 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.8 (C), 154.0 (CH), 139.7 (C), 132.6 (C), 129.4 (CH), 126.3 (CH), 123.0 (C, q, J_{CF} = 283 Hz), 87.9 (C, q, J_{CF} = 30.1 Hz), 83.5 (C), 27.7 (CH_3), 21.1 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −75.1 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{19}F_3NO_3^+$: 330.1312, found: 330.1316.

***tert*-Butyl 5-(4-Methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate** (**3cb**).

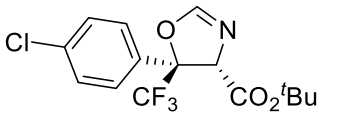


Colorless oil (84.0 mg, 99% from 51.2 mg of **1c**). HPLC (Chiralpak IC, hexane:^{i}PrOH 90:10, 0.7 mL/min): *trans*-(***4S,5S***)-**3cb** (major diastereomer, 84% *ee*): major enantiomer, t_r = 8.7 min, minor enantiomer, t_r = 14.2 min; *cis*-**3cb** (minor diastereomer, 77% *ee*): major enantiomer, t_r = 16.8 min, minor enantiomer, t_r = 20.9 min; *trans:cis* = 63:37.

trans-(***4S,5S***)-**3cb** (major diastereomer): $[\alpha]_D^{25}$ +127.3 (*c* 0.82, $CHCl_3$, 84% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 (2H, d, *J* = 9.0, Ar), 7.18 (1H, d, *J* = 1.8 Hz, N=CHO), 6.89 (2H, d, *J* = 9.0 Hz, Ar), 5.04 (1H, d, *J* = 1.8 Hz, CH), 3.79 (3H, s, CH_3), 1.08 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.5 (C), 160.4 (C), 155.3 (CH), 127.9 (CH, q, J_{CF} = 1.8 Hz), 123.9 (C, q, J_{CF} = 284 Hz), 122.9 (C), 113.8 (CH), 87.5 (C, q, J_{CF} = 29 Hz), 82.7 (C), 74.5 (CH), 55.3 (CH_3), 27.3 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −80.5 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1251.

cis-**3cb** (minor diastereomer): $[\alpha]_D^{25}$ +47.1 (*c* 0.75, $CHCl_3$, 77% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 9.0 Hz, Ar), 7.10 (1H, d, *J* = 2.4 Hz, N=CHO), 6.96 (2H, d, *J* = 9.0 Hz, Ar), 5.00 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.83 (3H, s, CH_3), 1.57 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.8 (C), 160.5 (C), 154.0 (CH), 127.8 (CH), 127.4 (C), 123.0 (C, q, J_{CF} = 283 Hz), 114.1 (CH), 87.8 (C, q, J_{CF} = 30 Hz), 83.5 (C), 77.4 (CH), 55.3 (CH_3), 27.7 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −75.4 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1251.

***tert*-Butyl 5-(4-Chlorophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate** (**3db**).



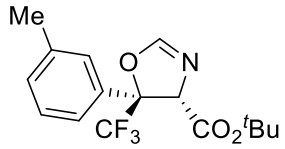
Colorless oil (103.4 mg, 99% from 62.0 mg of **1d**). HPLC (Chiralpak IC, hexano:^{i}PrOH 95:5, 1 mL/min): *trans*-(***4S,5S***)-**3db** (major diastereomer, 96% *ee*): major enantiomer, t_r = 7.6 min, minor enantiomer, t_r = 9.0 min; *cis*-**3db** (minor diastereomer, 90% *ee*): major enantiomer, t_r = 16.7 min, minor enantiomer, t_r = 18.5 min; *trans:cis* = 53:47.

trans-(***4S,5S***)-**3db** (major diastereomer): $[\alpha]_D^{25}$ +81.7 (*c* 0.30, CHCl3, 96% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* = 9.0 Hz, Ar), 7.37 (2H, d, *J* = 9.0 Hz, Ar), 7.19 (1H, d, *J* = 2.0 Hz, N=CHO), 5.07 (1H, d, *J* = 2.0 Hz, CH), 1.08 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.2 (C), 155.2 (CH), 135.8 (C), 129.5 (C), 128.7 (CH), 128.0 (CH, q, J_{CF} = 1.9 Hz), 123.7 (C, q, J_{CF} = 283 Hz), 87.5 (C, q, J_{CF} = 30 Hz), 83.1 (C), 74.6 (CH),

27.3 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −80.4 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{15}H_{16}ClF_3NO_3^+$: 350.0765, found: 350.0757.

cis-**3db** (minor diastereomer): $[\alpha]_D^{25}$ +48.6 (*c* 0.46, CHCl3, 90% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.64 (2H, d, J = 9.0 Hz, Ar), 7.42 (2H, d, J = 9.0 Hz, Ar), 7.10 (1H, d, J = 2.1 Hz, N=CHO), 4.96 (1H, dd, J = 2.1, 0.6 Hz, CH), 1.57 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.4 (C), 153.9 (CH), 136.0 (C), 133.9 (C), 129.0 (CH), 127.9 (CH), 122.8 (C, q, J_{CF} = 283 Hz), 87.5 (C, q, J_{CF} = 31 Hz), 83.9 (C), 77.4 (CH), 27.7 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −75.2 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{15}H_{16}ClF_3NO_3^+$: 350.0765, found: 350.0757.

***tert*-Butyl 5-(*m*-Tolyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate** (**3eb**).

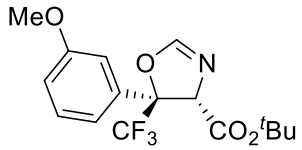


Colorless oil (77.1 mg, 94% from 47.2 mg of **1e**). HPLC (Chiralpak IC, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-(***4S,5S***)-**3eb** (major diastereomer, 97% *ee*): major enantiomer, t_r = 5.6 min, minor enantiomer, t_r = 6.7 min; *cis*-**3eb** (minor diastereomer, 87% *ee*): major enantiomer: t_r = 10.0 min, minor enantiomer: t_r = 14.4 min; *trans:cis* = 76:24.

trans-(***4S,5S***)-**3eb** (major diastereomer): $[\alpha]_D^{25}$ +166.8 (*c* 0.55, CHCl3, 97% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27−7.25 (3H, m, Ar), 7.21−7.18 (2H, m, Ar, N=CHO), 5.06 (1H, d, *J* = 2.1 Hz, CH), 2.35 (3H, s, CH_3), 1.04 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.3 (C), 155.3 (CH), 138.0 (C), 130.9 (C), 130.1 (CH), 128.3 (CH), 126.9 (CH, q, J_{CF} = 2.0 Hz), 123.9 (C, q, J_{CF} = 283 Hz), 123.5 (CH, q, J_{CF} = 1.9 Hz), 87.6 (C, q, J_{CF} = 30 Hz), 82.5 (C), 74.6 (CH), 27.1 (CH_3), 21.4 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −80.3 (s, CF_3); HRMS (ESI) m/z: $[M+ H]^+$ calculated for $C_{16}H_{19}F_3NO_3^+$: 330.1312, found: 330.1308.

cis-**3eb** (minor diastereomer): $[\alpha]_D^{25}$ +52.9 (*c* 0.98, CHCl3, 87% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51 (1H, s, Ar), 7.49 (1H, d, *J* = 9.0 Hz, Ar), 7.33 (1H, td, *J* = 7.5, 0.6 Hz, Ar), 7.25 (1H, br d, *J* = 7.6 Hz, Ar), 7.11 (1H, d, *J* = 2.1 Hz, N=CHO), 5.01 (1H, dd, J = 2.4, 0.9 Hz, CH), 2.40 (3H, s, CH_3), 1.58 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.7 (C), 154.0 (CH), 138.5 (C), 135.5 (C), 130.4 (CH), 128.6 (CH), 126.9 (CH), 123.4 (CH), 123.0 (C, q, J_{CF} = 283 Hz), 87.9 (C, q, J_{CF} = 30 Hz), 83.5 (CH), 77.4 (CH), 27.7 (CH_3), 21.5 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −75.0 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{19}F_3NO_3^+$: 330.1312, found: 330.1308.

***tert*-Butyl 5-(3-Methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate** (**3fb**).



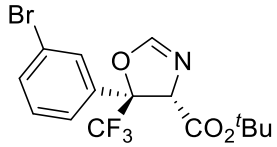
Colorless oil (72.7 mg, 84% from 51.1 mg of **1f**). HPLC (Chiralpak IC, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-(***4S,5S***)-**3fb** (major diastereomer, 97% *ee*): major enantiomer, t_r = 6.8 min, minor enantiomer, t_r = 16.0 min, *cis*-**3fb** (minor diastereomer, 85% *ee*): major enantiomer, t_r = 13.2 min, minor enantiomer, t_r = 20.9 min; *trans:cis* = 72:28.

trans-(***4S,5S***)-**3fb** (major diastereomer): $[\alpha]_D^{25}$ +164.7 (*c* 0.49, $CHCl_3$, 97% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 (1H, td, *J* = 8.0, 0.6 Hz, Ar), 7.19 (1H, dd, *J* = 1.9, 0.5 Hz,

N=CHO), 7.06 (1H, m, Ar), 7.00 (1H, m, Ar), 6.91 (1H, ddd, *J* = 8.2, 2.5, 0.9 Hz, Ar), 5.06 (1H, d, *J* = 1.9 Hz, CH), 3.80 (3H, s, CH_3), 1.07 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.3 (C), 159.5 (C), 155.3 (CH), 132.3 (C), 129.5 (CH), 123.8 (C, q, J_{CF} = 283 Hz), 118.6 (CH, q, J_{CF} = 2.0 Hz), 114.8 (CH), 112.5 (CH, q, J_{CF} = 1.8 Hz), 87.5 (C, q, J_{CF} = 30 Hz), 82.7 (C), 74.6 (CH), 55.3 (CH_3), 27.2 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −80.4 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1260.

cis-**3fb** (minor diastereomer): $[\alpha]_D^{25}$ +56.9 (*c* 0.77, $CHCl_3$, 85% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 (1H, t, *J* = 7.8, Ar), 7.30−7.24 (2H, m, Ar), 7.11 (1H, d, *J* = 2.1 Hz, N=CHO), 6.96 (1H, ddd, *J* = 8.1, 2.6, 1.2 Hz, Ar), 5.02 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.84 (3H, s, CH_3), 1.57 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.7 (C), 159.7 (C), 154.0 (CH), 132.2 (C), 129.8 (CH), 122.9 (C, q, J_{CF} = 283 Hz), 118.5 (CH), 115.1 (CH), 112.2 (CH), 87.9 (C, q, J_{CF} = 30 Hz), 83.6 (C), 77.4 (CH), 55.4 (CH_3), 27.7 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −74.9 (s, CF_3); HRMS (ESI) m/z: $[M+ H]^+$ calculated for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1260.

***tert*-Butyl 5-(3-Bromophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate** (**3gb**).

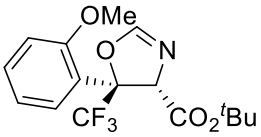


Colorless oil (95.7 mg, 99%, from 63.5 mg of **1g**). HPLC (Chiralpak IC, hexane:^{i}PrOH 95:5, 0.5 mL/min): *trans*-(***4S,5S***)-**3gb** (major diastereomer, 90% *ee*): major enantiomer, t_r = 10.8 min, minor enantiomer, t_r = 12.7 min, *cis*-**3gb** (minor diastereomer, 97% *ee*): major enantiomer, t_r = 24.3 min, minor enantiomer, t_r = 35.5 min; *trans:cis* = 64:36.

trans-(***4S,5S***)-**3gb** (major diastereomer): $[\alpha]_D^{25}$ +143.5 (*c* 0.52, $CHCl_3$, 97% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.63 (1H, bs, Ar), 7.52 (1H, ddd, *J* = 7.9, 1.9, 1.0 Hz, Ar), 7.42 (1H, m, Ar), 7.26 (1H, td, *J* = 8.1, 0.6 Hz, Ar), 7.19 (1H, dd, *J* = 2.1, 0.6, N=CHO), 5.06 (1H, d, *J* = 2.0 Hz, CH), 1.10 (9H, s, CH_3); **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ 165.1 (C), 155.1 (CH), 133.2 (C), 132.6 (CH), 130.0 (CH), 129.5 (CH, q, J_{CF} = 1.8 Hz), 125.1 (CH, q, J_{CF} = 2.0 Hz), 123.6 (C, q, J_{CF} = 283 Hz), 122.6 (C), 86.9 (C, q, J_{CF} = 30 Hz), 83.1 (C), 74.6 (CH), 27.2 (CH_3); **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ −80.3 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{15}H_{16}BrF_3NO_3^+$: 394.0260, found: 394.0251.

cis-**3gb** (minor diastereomer): $[\alpha]_D^{25}$ +42.7 (*c* 1.39, $CHCl_3$, 90% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.89 (1H, bs, Ar), 7.64 (1H, br d, *J* = 8.0 Hz, Ar), 7.58 (1H, ddd, *J* = 8.0, 1.9, 1.0 Hz, Ar), 7.33 (1H, t, *J* = 7.9 Hz, Ar), 7.11 (1H, d, *J* = 2.3 Hz, N=CHO), 4.96 (1H, dd, *J* = 2.3, 0.9 Hz, CH), 1.58 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.2 (C), 153.9 (CH), 137.6 (C), 132.9 (CH), 130.3 (CH), 129.7 (CH), 125.1 (CH), 122.8 (C), 122.7 (C, q, J_{CF} = 283 Hz), 87.2 (C, q, J_{CF} = 30.1 Hz), 83.9 (C), 77.3 (CH), 27.7 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −75.1 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{15}H_{16}BrF_3NO_3^+$: 394.0260, found: 394.0251.

***tert*-Butyl 5-(2-Methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate** (**3hb**).

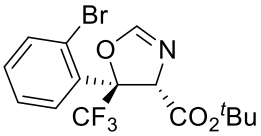


White solid (69.0 mg, 80% from 51.0 mg of **1h**). HPLC (Chiralpak IC, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-(***4S,5S***)-**3hb** (major diastereomer, 94% *ee*): major enantiomer, t_r = 7.0 min, minor enantiomer, t_r = 23.0 min; *cis*-**3hb** (minor diastereomer, 70% *ee*): major enantiomer, t_r = 19.9 min, minor enantiomer, t_r = 30.2 min; *trans:cis* = 94:6.

trans-(***4S,5S***)-**3hb** (major diastereomer): mp: 76−79 °C; $[\alpha]_D^{25}$ +252.5 (*c* 0.78, $CHCl_3$, 94% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.57 (1H, dd, *J* = 7.8, 1.8 Hz, Ar), 7.37 (1H, ddd, *J* = 8.4, 7.5, 1.8 Hz, Ar), 7.09 (1H, d, *J* = 2.0 Hz, N=CHO), 7.02 (1H, td, *J* = 7.5, 1.0 Hz, Ar), 6.85 (1H, dd, *J* = 8.4, 1.2 Hz, Ar), 5.12 (1H, d, *J* = 2.0 Hz, CH), 3.76 (3H, s, CH_3), 1.12 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.6 (C), 155.7 (C), 154.9 (CH), 130.6 (CH), 128.6 (CH), 123.9 (C, q, J_{CF} = 283 Hz), 120.6 (CH), 120.5 (C), 110.4 (CH), 87.0 (C, q, J_{CF} = 30 Hz), 81.5 (C), 74.2 (CH), 54.7 (CH_3), 27.3 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −81.7 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1259.

cis-**3hb** (minor diastereomer): $[\alpha]_D^{25}$ +70.7 (*c* 0.17, $CHCl_3$, 70% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.56 (1H, td, *J* = 7.8, 1.5 Hz, Ar), 7.40 (1H, ddd, *J* = 8.2, 7.4, 1.7 Hz, Ar), 7.09 (1H, dd, *J* = 2.1, 0.6 Hz, N=CHO), 7.00 (1H, td, *J* = 7.5, 1.2 Hz, Ar), 6.98 (1H, dd, *J* = 7.2, 2.4 Hz, Ar), 5.23 (1H, dd, *J* = 2.1, 0.9 Hz, CH), 3.89 (3H, s, CH_3), 1.54 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.2 (C), 156.6 (C), 153.6 (CH), 131.3 (CH), 128.2 (CH), 123.3 (C, q, J_{CF} = 283 Hz), 123.0 (C), 120.6 (CH), 111.9 (CH), 87.6 (C, q, J_{CF} = 32 Hz), 82.4 (C), 75.5 (CH), 55.2 (CH_3), 27.8 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −72.4 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1259.

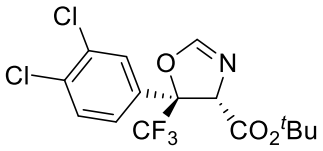
***tert*-Butyl 5-(2-Bromophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate** (**3ib**).



White solid (122.8 mg, 99% from 79.0 mg of 1i). HPLC (Chiralpak IC, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-(***4S,5S***)-**3ib** (major diastereomer, 91% *ee*): major enantiomer, t_r = 5.8 min, minor enantiomer, t_r = 9.3 min; *trans:cis* > 99:1.

trans-(***4S,5S***)-**3ib** (major diastereomer): mp: 96−99 °C; $[\alpha]_D^{25}$ +190.2 (*c* 0.54, $CHCl_3$, 91% *ee*); (two possible rotamers are observed) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74 (1H, unresolved d, *J* = 7.4 Hz, Ar), 7.60 (1H, dd, *J* = 7.8, 1.2 Hz, Ar), 7.38 (1H, ddd, *J* = 7.9, 7.3, 1.3 Hz, Ar), 7.24 (1H, ddd, *J* = 8.0, 7.4, 1.7 Hz, Ar), 7.13 (1H, d, *J* = 1.8 Hz, N=CHO), 5.35 (1H, bs, CH), 1.22 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.3 (C), 154.8 (CH), 136.1 (C), 134.5 (CH), 130.6 (CH), 130.3 (CH), 127.4 (CH), 123.7 (C, q, J_{CF} = 286 Hz), 120.8 (C), 88.5 (C, q, J_{CF} = 30 Hz), 82.6 (CH), 74.0 (CH), 27.2 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −79.0 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{15}H_{16}BrF_3NO_3^+$: 394.0260, found: 394.0251.

***tert*-Butyl 5-(3,4-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate** (**3jb**).

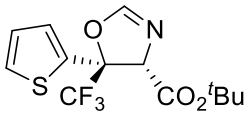


Colorless oil (95.1 mg, 99% from 61.0 mg of **1j**). HPLC (Chiralpak IC, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-(***4S,5S***)-**3jb** (major diastereomer, 94% *ee*): major enantiomer, t_r = 6.7 min, minor enantiomer, t_r = 7.5 min; *cis*-**3jb** (minor diastereomer, 85% *ee*): major enantiomer, t_r = 14.9 min, minor enantiomer, t_r = 17.2 min; *trans:cis* = 53:47.

trans-(***4S,5S***)-**3jb** (major diastereomer): $[\alpha]_D^{25}$ +131.8 (*c* 0.48, $CHCl_3$, 94% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.57 (1H, d, *J* = 1.8 Hz, Ar), 7.47 (1H, d, *J* = 8.4 Hz, Ar), 7.33 (1H, ddd, *J* = 8.4, 2.2, 0.8 Hz, Ar), 7.19 (1H, d, *J* = 2.1 Hz, N=CHO), 5.06 (1H, d, *J* = 2.1 Hz, CH), 1.13 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.0 (C), 155.0 (CH), 134.2 (C), 132.9 (C), 131.1 (C), 130.5 (CH), 128.7 (CH, q, J_{CF} = 1.9 Hz), 125.8 (CH, q, J_{CF} = 1.7 Hz), 123.5 (C, q, J_{CF} = 283 Hz), 86.5 (C, q, J_{CF} = 30 Hz), 83.4 (C), 74.6 (CH), 27.3 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −80.4 (s, CF_3); HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{15}H_{15}Cl_2F_3NO_3^+$: 384.0376, found: 384.0371.

cis-**3jb** (minor diastereomer): $[\alpha]_D^{25}$ +68.2 (*c* 0.45, $CHCl_3$, 85% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.84 (1H, bs, Ar), 7.60−7.50 (2H, m, Ar), 7.11 (1H, d, *J* = 2.4 Hz, N=CHO), 4.94 (1H, dd, *J* = 2.4, 0.9 Hz, CH), 1.58 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) 165.1 (C), 153.8 (CH), 135.4 (C), 134.4 (C), 133.3 (C), 130.9 (CH), 128.7 (CH), 125.8 (CH), 122.6 (C, q, J_{CF} = 283 Hz), 86.9 (C, q, J_{CF} = 30.8 Hz), 84.1 (CH), 77.4 (CH), 27.7 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −75.2 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{15}H_{15}Cl_2F_3NO_3^+$: 384.0376, found: 384.0371.

***tert*-Butyl 5-(Thiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate** (**3kb**).



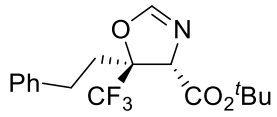
Yellow oil (87.1 mg, 99% from 48.9 mg of **1k**). HPLC (Lux Cellulose-4, hexane:^{i}PrOH 98:2, 1 mL/min): *trans*-(***4S,5S***)-**3kb** (major diastereomer, 97% *ee*): major enantiomer, t_r = 7.7 min, minor enantiomer, t_r = 9.3 min, *cis*-**3kb** (minor diastereomer, 91% *ee*): major enantiomer, t_r = 15.3 min, minor enantiomer, t_r = 17.7 min; *trans:cis* = 62:38.

trans-(***4S,5S***)-**3kb** (major diastereomer): $[\alpha]_D^{25}$ +127.4 (*c* 0.49, $CHCl_3$, 97% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 (1H, dd, *J* = 5.1, 1.2 Hz, Ar), 7.16−7.11 (2H, m, Ar, N=CHO), 7.02 (1H, dd, *J* = 5.1, 3.6 Hz, Ar), 5.06 (1H, d, *J* = 2.1 Hz, CH), 1.14 (9H, s, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.0 (C), 154.6 (CH), 132.8 (C), 127.5 (CH), 127.3 (CH, q, J_{CF} = 2.0 Hz, Ar), 126.5 (CH), 123.3 (C, q, J_{CF} = 283 Hz), 86.3 (C, q, J_{CF} = 32 Hz), 82.9 (C), 75.0 (CH), 27.3 (CH_3). **^{19}F NMR** (282 MHz, $CDCl_3$) δ −81.8 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{13}H_{15}F_3NO_3S^+$: 322.0719, found:322.0713.

cis-**3kb** (minor diastereomer): $[\alpha]_D^{25}$ +164.7 (*c* 0.49, $CHCl_3$, 91% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 (1H, dd, *J* = 5.1, 1.3 Hz, Ar), 7.39−7.38 (1H, m, Ar), 7.09 (1H, d, *J* = 2.4 Hz, N=CHO), 7.08 (1H, t, *J* = 3.7 Hz, Ar), 5.08 (1H, dd, *J* = 2.4, 0.9 Hz, CH), 1.55 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.0 (C), 153.9 (CH), 137.7 (C), 127.4 (CH), 127.3 (CH), 127.2 (CH), 122.5 (C, q, J_{CF} = 283 Hz), 86.4 (C, q, J_{CF} = 32 Hz), 83.7

(C), 78.2 (CH), 27.7 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −75.5 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{13}H_{15}F_3NO_3S^+$: 322.0719, found: 322.0713.

***tert*-Butyl 5-Phenethyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate** (**3lb**).



Yellow oil (71.2 mg, 83% from 50.0 mg of **1l**). HPLC (Chiralpak AY-H, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-(***4S,5S***)-**3lb** (major diastereomer, 84% *ee*): minor enantiomer, t_r = 5.2 min, major enantiomer, t_r = 7.0 min; *cis*-**3lb** (minor diastereomer, 87% *ee*): minor enantiomer, t_r = 8.7 min, major enantiomer, t_r = 12.6 min; *trans:cis* = 72:28.

trans-(***4S,5S***)-**3lb** (major diastereomer): $[\alpha]_D^{25}$ +51.2 (*c* 0.86, $CHCl_3$, 84% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30−7.26 (2H, m, Ar), 7.22−7.19 (1H, m, Ar), 7.17−7.13 (2H, m, Ar), 7.00 (1H, d, *J* = 2.2 Hz, N=CHO), 4.88 (1H, d, *J* = 2.3 Hz, CH), 2.75 (2H, t, *J* = 8.9 Hz, CH_2), 2.38−2.27 (1H, m, CH), 2.22−2.11 (1H, m, CH), 1.47 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.5 (C), 154.8 (CH), 140.1 (C), 128.5 (CH), 128.0 (CH), 126.4 (CH), 124.3 (C, q, J_{CF} = 282 Hz), 85.7 (C, q, J_{CF} = 30 Hz), 83.4 (C), 72.1 (CH), 31.3 (CH2), 28.6 (CH2), 27.9 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −79.9 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{17}H_{21}F_3NO_3^+$: 344.1468, found: 344.1472.

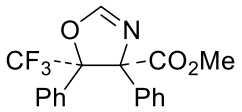
cis-**3lb** (minor diastereomer): $[\alpha]_D^{25}$ +52.1 (*c* 0.59, $CHCl_3$, 87% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35−7.29 (2H, m, Ar), 7.26−7.17 (3H, m, Ar), 7.01 (1H, d, *J* = 2.2 Hz, N=CHO), 4.71 (1H, d, *J* = 1.7 Hz, CH), 2.81−2.66 (2H, m, CH_2), 2.46−2.36 (1H, m, CH), 2.30−2.17 (1H, m, CH), 1.50 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.7 (C), 154.7 (CH), 139.7 (C), 128.7 (CH), 128.2 (CH), 126.6 (CH), 123.7 (C, q, J_{CF} = 284.3 Hz), 86.9 (C, q, J_{CF} = 29 Hz), 83.2 (CH), 73.2 (C), 35.7 (CH2), 28.4 (CH2), 27.7 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −74.6 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{17}H_{21}F_3NO_3^+$: 344.1468, found: 344.1472.

General Procedure for the Enantioselective Formal [3 + 2] Cycloaddition Reaction with Methyl 2-Isocyano-2-phenylacetate.

SQVIII (6.8 mg, 0.0125 mmol) and silver oxide (1.5 mg, 0.0063 mmol) were introduced in a round-bottom flask followed by MTBE (2 mL) and trifluoroacetophenone **1** (0.25 mmol). The flask was closed with a stopper and introduced in a bath at −20 °C. After 5 min, methyl 2-isocyano-2-phenylacetate (**2f**, 40 μL, 0.33 mmol) was added and the mixture was stirred at −20 °C until consumption of the trifluoroacetophenone **1** (TLC). After this time, the reaction mixture was filtered through a short pad of silica gel and concentered under reduced pressure. This compounds were quickly hydrolyzed during slow column chromatography, so separation of both diastereomers by this procedure was not possible.

The racemic product was obtained using a similar procedure using the catalyst *N*-[3,5-bis(trifluoromethyl)phenyl]-*N*′-(3-(dimethylamino)propyl)-squaramide and silver oxide as substituent for **SQVIII**.

Methyl 4,5-Diphenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3af**).



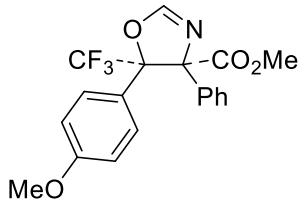
Yellow oil (76.9 mg, 89% from 43.0 mg of **1a**). HPLC (Chiralpak IC, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-**3af** (minor diastereomer): major enantiomer, t_r = 8.4 min, minor enantiomer, t_r = 6.7 min; *cis*-

3af (major diastereomer, 90% *ee*): major enantiomer, t_r = 18.3 min, minor enantiomer, t_r = 12.3 min; *trans:cis* = 15:85.

cis-**3af** (major diastereomer): $[\alpha]_D^{25}$ −5.3 (*c* 1.0, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46−7.41 (3H, m, Ar), 7.43 (1H, s, N=CHO), 7.15−7.08 (2H, s, Ar), 7.03 (5H, s, Ar), 3.98 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.6 (C), 153.2 (CH), 134.4 (C), 130.6 (C), 128.7 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 127.51 (CH), 127.46 (CH), 123.7 (C, q, J_{CF} = 283 Hz), 92.6 (C, q, J_{CF} = 29 Hz), 86.1 (C), 53.4 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −72.9 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{18}H_{15}F_3NO_3^+$: 350.0999, found: 350.0995.

trans-**3af** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92 (2H, dd, J = 8.1, 3.0 Hz, Ar), 7.72 (2H, dd, J = 8.0, 3.0 Hz, Ar), 7.50−7.35 (7H, m, Ar, N=CHO), 3.14 (3H, s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −72.3 (s, CF_3).

Methyl 5-(4-Methoxyphenyl)-4-phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3cf**).

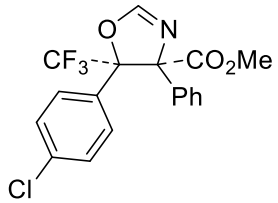


Yellow oil (40.3 mg, 42% from 51.0 mg of **1c**). HPLC (Chiralpak IC, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-**3cf** (minor diastereomer): major enantiomer, t_r = 8.6 min, minor enantiomer, t_r = 12.1 min; *cis*-**3cf** (major diastereomer, 89% *ee*): major enantiomer, t_r = 25.6 min, minor enantiomer t_r = 18.5 min; *trans:cis* = 21:79.

cis-**3cf** (major diastereomer): $[\alpha]_D^{25}$ −12.3 (c 1.7, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 (1H, s, N=CHO), 7.34 (2H, d, *J* = 8.4 Hz, Ar), 7.05−7.03 (5H, s, Ar), 6.62 (2H, d, *J* = 9.0 Hz, Ar), 3.97 (3H, s, CH_3), 3.68 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.7 (C), 159.6 (C), 153.2 (CH), 134.6 (C), 129.7 (C), 129.0 (CH), 128.3 (C), 127.8 (CH), 127.5 (CH), 123.7 (C, q, J_{CF} = 283 Hz), 112.9 (CH), 92.6 (C, q, J_{CF} = 28.5 Hz), 86.1 (C), 55.0 (CH3), 53.3 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −73.28 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{19}H_{17}F_3NO_4^+$: 380.1104, found: 380.1106.

trans-**3cf** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.93−7.90 (2H, m, Ar), 7.62 (2H, d, *J* = 8.7 Hz, Ar), 7.44 (1H, s, N=CHO), 6.96 (2H, d, *J* = 9.0 Hz, Ar), 3.84 (3H, s, CH_3), 3.19 (3H, s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −72.6 (s, CF_3).

Methyl 5-(4-Chlorophenyl)-4-phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3df**).

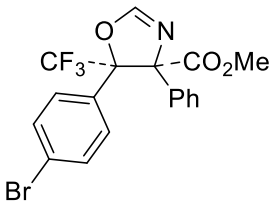


Yellow oil (95.9 mg, 95% from 53.0 mg of **1d**). HPLC (Chiralpak IC, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-**3df** (minor diastereomer): major enantiomer, t_r = 8.0 min, minor enantiomer, t_r = 6.0 min; *cis*-**3df** (major diastereomer, 89% *ee*): major enantiomer, t_r = 15.7 min, minor enantiomer, t_r = 12.0 min; *trans:cis* = 10:90.

cis-**3df** (major diastereomer): $[\alpha]_D^{25}$ −8.0 (*c* 0.93, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 (1H, s, N=CHO), 7.39 (2H, d, *J* = 8.7 Hz, Ar), 7.13−6.96 (7H, m, Ar), 3.98 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.5 (C), 153.1 (CH), 134.9 (C), 134.0 (C), 129.5 (C), 129.1 (CH), 128.6 (CH), 128.0 (CH), 127.8 (CH), 127.3 (CH), 123.5 (C, q, J_{CF} = 283 Hz), 92.2 (C, q, J_{CF} = 29 Hz), 86.1 (C), 53.5 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −73.2 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{18}H_{14}ClF_3NO_3^+$: 384.0609, found: 384.0609.

trans-**3df** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.00 (2H, d, *J* = 8.1 Hz, Ar), 7.52 (2H, d, *J* = 9.0 Hz, Ar), 3.2 (3H, s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −71.5 (s, CF_3).

Methyl 5-(4-Bromophenyl)-4-phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3nf**).

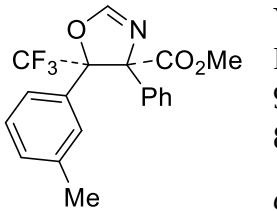


Yellow oil (87.5 mg, 82% from 63.1 mg of **1n**). HPLC (Chiralpak IC, hexane:^{i}PrOH 90:10, 1 mL/min): *trans*-**3nf** (minor diastereomer): both enantiomers 3.6 min; *cis*-**3nf** (major diastereomer, 89% *ee*): major enantiomer, t_r = 10.5 min, minor enantiomer, t_r = 8.6 min; *trans:cis* = 13:87.

cis-**3nf** (major diastereomer): $[\alpha]_D^{25}$ −12.0 (*c* 0.82, $CHCl_3$, 89% *ee*, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 (1H, s, N=CHO), 7.26 (2H, d, *J* = 8.5 Hz, Ar), 7.17 (2H, d, *J* = 9.0 Hz, Ar), 7.04−6.90 (5H, m, Ar), 3.91 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.5 (C), 153.1 (CH), 134.0 (C), 130.8 (CH), 129.7 (CH), 129.4 (CH), 128.7 (CH), 128.1 (CH), 127.3 (CH), 123.4 (C, q, J_{CF} = 283 Hz), 123.3 (C), 92.3 (C, q, J_{CF} = 29 Hz), 86.1 (C), 53.5 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −73.1 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{18}H_{14}BrF_3NO_3^+$: 428.0104, found: 428.0107.

trans-**3nf** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81−7.78 (2H, m, Ar), 7.37 (1H, s, N=CHO), 3.14 (3H, s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −72.4 (s, CF_3).

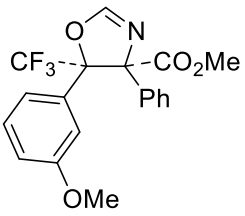
Methyl 4-Phenyl-5-(m-tolyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3ef**).



Yellow oil (78.5 mg, 86% from 47.0 mg of **1e**). HPLC (Chiralpak IC, hexane:^{i}PrOH 90:0, 1 mL/min): *cis*-**3ef** (major diastereomer, 90% *ee*): major enantiomer, t_r = 11.4 min, minor enantiomer, t_r = 8.5 min; *trans:cis* = 1:99.

cis-**3ef** (major diastereomer): $[\alpha]_D^{25}$ −6.5 (*c* 0.69, $CHCl_3$, 90% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 (1H, s, N=CHO), 7.26−7.22 (2H, unresolved m, Ar), 7.04 (5H, s, Ar), 6.98 (1H, t, *J* = 7.7 Hz, Ar), 6.91 (1H, br d, *J* = 7.5 Hz, Ar), 3.97 (3H, s, CH_3), 2.17 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.7 (C), 153.3 (CH), 137.1 (C), 134.4 (C), 130.5 (C), 129.4 (CH), 128.3 (CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 124.6 (C), 123.7 (C, q, J_{CF} = 283 Hz), 92.6 (C, q, J_{CF} = 29 Hz), 86.1 (C), 53.3 (CH_3), 21.2 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −72.8 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{19}H_{17}F_3NO_3^+$: 364.1155, found: 364.1157.

Methyl 5-(3-Methoxyphenyl)-4-phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3ff**).

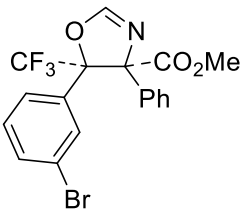


Yellow oil (75.4 mg, 86% from 51.0 mg of **1f**). HPLC (Chiralpak IC, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-**3ff** (minor diastereomer): major enantiomer, t_r = 7.5 min, minor enantiomer, t_r = 10.1 min, *cis*-**3ff** (major diastereomer, 89% *ee*): major enantiomer, t_r = 19.6 min, minor enantiomer, t_r = 12.5 min; *trans:cis* = 15:85.

cis-**3ff** (major diastereomer): $[\alpha]_D^{25}$ +5.40 (*c* 0.72, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 (1H, s, N=CHO), 7.10−6.90 (8H, m, Ar), 6.65 (1H, ddd, *J* = 7.4, 2.6, 1.7 Hz, Ar), 3.98 (3H, s, CH3), 3.65 (3H, s, CH3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.6 (C), 158.7 (C), 153.2 (CH), 134.4 (C), 131.9 (C), 128.7 (CH), 128.4 (CH), 127.8 (CH), 127.4 (CH), 123.6 (C, q, J_{CF} = 287 Hz), 120.0 (CH), 114.6 (CH), 113.4 (C), 92.4 (C, q, J_{CF} = 28 Hz), 86.1 (C), 55.1 (CH_3), 53.4 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −72.9 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{19}H_{17}F_3NO_4^+$: 380.1104, found: 380.1107.

trans-**3ff** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, CDCl3) δ 7.93−7.90 (1H, m, Ar), 7.45 (1H, s, N=CHO), 3.85 (3H, s, CH3), 3.18 (3H, s, CH3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −72.3 (s, CF_3).

Methyl 5-(3-Bromophenyl)-4-phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3gf**).

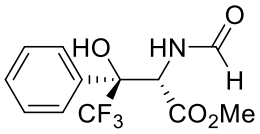


Yellow oil (86.8 mg, 81% from 63.0 mg of **1g**). HPLC (Chiralpak IC, hexane:^{i}PrOH 90:10, 1 mL/min): *trans*-**3gf** (minor diastereomer): major enantiomer, t_r = 7.0 min, minor enantiomer, t_r = 5.7 min; *cis*-**3gf** (major diastereomer, 88% *ee*): minor enantiomer, t_r = 10.1 min, major enantiomer, t_r = 14.3 min; *trans:cis* = 2:98.

cis-**3gf** (major diastereomer): $[\alpha]_D^{25}$ −15.4 (*c* 0.92, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.51 (1H, s, Ar), 7.36 (1H, s, N=CHO), 7.32 (1H, br d, *J* = 8.0 Hz, Ar), 7.17 (1H, d, *J* = 9.0 Hz), 7.03−6.92 (5H, m, Ar), 6.88 (1H, t, *J* = 8.1 Hz, Ar), 3.91 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.4 (C), 153.1 (CH), 133.8 (C), 132.8 (C), 131.9 (CH), 130.6 (br, CH), 129.0 (CH), 128.7 (CH), 128.0 (CH), 127.3 (CH), 126.4 (CH), 123.4 (C, q, J_{CF} = 283 Hz), 121.7 (C), 92.0 (C, q, J_{CF} = 29 Hz), 86.2 (C), 53.5 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −72.8 (s, CF3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{18}H_{14}BrF_3NO_3^+$: 428.0104, found: 428.0107.

trans-**3gf** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.12 (1H, s, Ar), 7.93 (1H, d, *J* = 9.2 Hz, Ar), 7.80−7.70 (2H, m, Ar), 3.15 (3H, s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −71.5 (s, CF_3).

Methyl (2*S*,3*S*)-4,4,4-Trifluoro-2-formamido-3-hydroxy-3-phenylbutanoate (**19aa**).

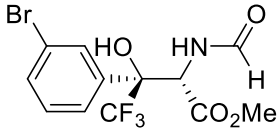


Aqueous HCl (6 M, six drops) was added to a solution of compound **3aa** (54.0 mg, 0.20 mmol) in THF (1 mL). The reaction mixture was stirred at r.t. for 24 h. Saturated aqueous $NaHCO_3$ (1 mL) and water (10 mL) were added, and the mixture extracted with EtOAc (3 × 20 mL), washed with brine (20 mL), and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded compound **19aa** as a colorless oil (58.0 mg, 95%). HPLC (Chiracel OD-H, hexane:^{i}PrOH 90:10, 1 mL/min): *trans*-**19aa** (major diastereomer, 88% *ee*); major enantiomer, t_r = 14.0 min, minor enantiomer, t_r = 11.0 min; *cis*-**19aa** (minor diastereomer), major enantiomer, t_r = 8.5 min, minor enantiomer, t_r = 7.9 min; *trans:cis* = 96:4.

trans-**19aa** (major diastereomer): $[\alpha]_D^{25}$ −23.6 (*c* 0.68, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.24 (1H, dd, *J* = 1.2, 0.7 Hz, CHO), 7.59−7.57 (2H, m, Ar), 7.42−7.40 (3H, m, Ar), 6.79 (1H, d, *J* = 9.0 Hz, NH), 5.57 (1H, dd, *J* = 9.0, 0.6 Hz, CH), 4.68 (1H, bs, OH), 3.47 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.0 (C), 160.7 (CH), 134.4 (C), 129.6 (CH), 128.6 (CH), 126.1 (CH), 123.9 (C, q, J_{CF} = 283 MHz), 78.20 (C, q, J_{CF} = 30 Hz), 53.5 (CH), 52.9 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −75.8 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{12}H_{13}F_3NO_4^+$: 292.0791, found: 292.0798.

cis-**19aa** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.85 (d, *J* = 10.5 Hz, CH), 3.54 (3H, s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −76.4 (s, CF_3).

Methyl (2*S*,3*S*)-3-(3-Bromophenyl)-4,4,4-trifluoro-2-formamido-3-hydroxybutanoate (**19ga**).

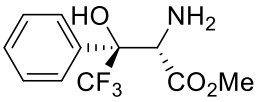


Following a procedure similar to that used for the synthesis of compound **19aa**, from compound **3ga** (42.3 mg, 0.12 mmol) was obtained formamide **19ga** as a colorless oil (42.6 mg, 95%). HPLC (Chiralpak AY-H, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-**19ga** (major diastereomer, 91% *ee*): major enantiomer, t_r = 21.9 min, minor enantiomer, t_r = 29.6 min; *cis*-**19ga** (minor diastereomer): major enantiomer, t_r = 10.9 min, minor enantiomer, t_r = 8.7 min; trans:cis = 83:17.

trans-**19ga** (major diastereomer): $[\alpha]_D^{25}$ +5.41 (*c* 0.72, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.25 (1H, dd, *J* = 1.0, 0.7 Hz, CHO), 7.77 (1H, bs, Ar), 7.57−7.50 (2H, m, Ar), 7.29 (1H, t, *J* = 8.0 Hz, Ar), 6.75 (1H, d, *J* = 8.8 Hz, NH), 5.52 (1H, d, *J* = 9.0 Hz, CH), 4.85 (1H, bs, OH), 3.55 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.7 (C), 160.8 (CH), 136.8 (C), 132.7 (CH), 130.0 (CH), 129.5 (CH), 124.9 (CH), 123.7 (C, q, J_{CF} = 285 MHz), 122.9 (C), 77.8 (C, q, J_{CF} = 29 MHz), 53.6 (CH), 53.1 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −75.2 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{12}H_{12}BrF_3NO_4^+$: 369.9896, found: 369.9883.

cis-**19ga** (minor diastereomer): **^{1}H NMR** (300 MHz, $CDCl_3$) representative signals taken from the NMR spectra of the diastereomer mixture, δ 7.93 (1H, s, CHO), 7.82 (1H, t, *J* = 1.7 Hz, Ar), 6.16 (1H, d, *J* = 9.0 Hz, NH), 5.42 (1H, d, *J* = 9.0 Hz, CH), 3.87 (3H, s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −71.5 (s, CF_3).

Methyl (2*S*,3*S*)-2-amino-4,4,4-trifluoro-3-hydroxy-3-phenylbutanoate (**20aa**).

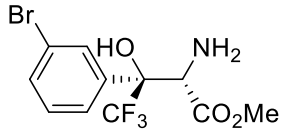


Aqueous HCl (6 M, six drops) was added to a solution of compound **3aa** (28.6 mg, 0.11 mmol) in MeOH (1 mL). The reaction mixture was stirred at rt for 24 h. Saturated aqueous $NaHCO_3$ (1 mL) and water (10 mL) were added, and the mixture extracted with EtOAc (3 × 20 mL), washed with brine (20 mL), and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded compound **20aa** as a colorless oil (27.6 mg, 95%). HPLC (Chiralpak AY-H, hexane:^{i}PrOH 95:5, 1 mL/min): *trans*-**20aa** (major diastereomer, 90% *ee*): major enantiomer, t_r = 15.8 min, minor enantiomer, t_r = 17.3 min; *cis*-**20aa** (minor diastereomer): major enantiomer, t_r = 11.8 min; minor enantiomer, t_r = 9.6 min; *trans:cis* 92:8.

trans-**20aa** (major diastereomer): $[\alpha]_D^{25}$ +47.9 (*c* 1.23, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61−7.54 (2H, m, Ar), 7.38−7.35 (3H, m, Ar), 4.33 (1H, s, CH), 3.29 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.3 (C), 135.1 (C), 128.8 (CH), 128.0 (CH), 126.3 (CH, q, J_{CF} = 2.0 Hz), 125.2 (C, q, J_{CF} = 283 Hz), 76.4 (C, q, J_{CF} = 27 Hz), 57.3 (CH), 52.0 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −75.9 (s, CF_3); HRMS (ESI) m/z: $[M+ H]^+$ calculated for $C_{11}H_{13}F_3NO_3^+$: 264.0842, found: 264.0851.

cis-**20aa** (minor diastereomer): **^{1}H NMR** (300 MHz, CDCl3) representative signals taken from the NMR spectra of the diastereomer mixture, δ 7.65−7.60 (2H, m, Ar), 7.45−7.31 (3H, m, Ar), 4.07 (1H, s, CH), 3.83 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 56.5(CH), 52.9 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −75.0 (s, CF_3).

Methyl (2*S*,3*S*)-2-Amino-3-(3-bromophenyl)-4,4,4-trifluoro-3-hydroxybutanoate (**20ga**).

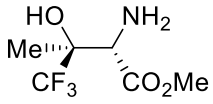


Following a procedure similar to that used for the synthesis of compound **20aa**, from compound **3ga** (22.7 mg, 0.064 mmol), was obtained **20ga** (21.0 mg, 95%). HPLC (Chiralpak AD-H, hexane:^{i}PrOH 98:2, 0.7 mL/min): *trans*-**20ga**: (major diastereomer, 92% *ee*): major enantiomer, t_r = 36.5 min, minor enantiomer, t_r = 34.9 min. *cis*-**20ga** (minor diastereomer): major enantiomer, t_r = 32.8 min, minor enantiomer, t_r = 28.9 min; *trans:cis* 93:7.

trans-**20ga**: (major diastereomer): $[\alpha]_D^{25}$ +49.1 (*c* 0.68, $CHCl_3$, for the diastereomer mixture); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77 (1H, t, *J* = 1.9 Hz, Ar), 7.55−7.48 (2H, m, Ar), 7.24 (1H, t, *J* = 7.9 Hz, Ar), 4.32 (1H, s, CH), 3.35 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.8 (C), 137.3 (C), 132.0 (CH), 129.7 (CH, q, J_{CF} = 1.6 Hz), 129.5 (CH), 125.1 (CH, q, J_{CF} = 1.6 Hz), 124.9 (C, q, J_{CF} = 289 MHz), 75.9 (C, q, J_{CF} = 27 Hz), 57.1 (CH), 52.2 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −75.6 (s, CF_3); HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{11}H_{12}BrF_3NO_3^+$: 341.9947, found: 341.9948.

cis-**20ga** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.82 (1H, bs, Ar), 7.56−7.44 (2H, m, Ar), 7.31 (1H, t, *J* = 8.0 Hz, Ar), 4.00 (1H, s, CH), 3.84 (3H, s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −76.6 (s, CF_3).

Methyl (2*S*,3*S*)-2-Amino-4,4,4-trifluoro-3-hydroxy-3-methylbutanoate (**20ma**).



Following a procedure similar to that used for the synthesis of compound **20aa**, from compound **3ma** (56.2 mg, 0.16 mmol) after 72h was obtained **20ma** (60.2 mg, 88%). GLC (Supelco β-dex-225, Tcolumn = 60 °C (1 min) to 150 °C at 7 °C/min, and to 220 °C at 16 °C/min, *trans*-**20ma** (major diastereomer, 82%): major enantiomer, t_r = 12.3 min, minor enantiomer, t_r = 13.2 min; *cis*-**20ma** (minor diastereomer): enantiomer 1, t_r = 17.7 min, enantiomer 2, t_r = 17.8 min; *trans:cis* = 97:3;

trans-**20ma** (major diastereomer): $[\alpha]_D^{25}$ −38.2 (*c* 0.98, $CHCl_3$, 82% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.79 (4H, s, CH, CH3 overlapped), 1.32 (3H, s, CH_3); **^{1}H NMR** (300 MHz, DMSO-d_6, for **21ma**·HCl) δ 8.82 (3H, bs, NH_3), 7.47 (1H, bs, OH), 4.10 (1H, s, CH-N), 3.75 (3H, s, CH_3), 1.39 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.2 (C), 125.8 (C, q, J_{CF} = 285 MHz), 72.6 (C, q, J_{CF} = 31 Hz), 55.7 (br, CH), 52.5 (CH_3), 18.1 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −80.6 (s, CF_3); HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_6H_{11}F_3NO_3^+$: 202.0686, found: 202.0684. Data consistent with the literature.[88]

cis-**20ma** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.83 (3H, s, CH_3), 1.44 (3H, s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −78.6 (s, CF_3).

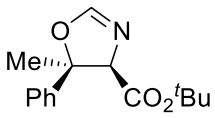
5.2 Enantioselective synthesis of *cis*-2-oxazolines under dual catalysis Silver/Organocatalysis

General Procedure for the Enantioselective Formal [3 + 2] Cycloaddition Reaction.

Squaramide **SQX** (6.6 mg, 0.0125 mmol) and silver oxide (1.5 mg, 0.0063 mmol) were introduced in 25 mL round bottom flask followed by MTBE (8 mL) and ketone **22** (0.25 mmol). The flask was closed with a stopper and introduced in an ice bath. After 5 min, *tert*-butyl isocyanoacetate **2b** (48 µL, 0.33 mmol) was added and the mixture was stirred at 0 °C until consumption of the ketone **21** (TLC). After this time, the reaction mixture was filtered through a short pad of silica gel and concentrated under reduced pressure. A small aliquot was analyzed by **^{1}H NMR** to determine the diastereomer ratio and by HPLC to determine the enantiomeric excess of products **22**. The remaining crude was chromatographed on silica gel eluting with hexane:EtOAc mixtures (9:1 to 8:2) to obtain the separated diastereomers *cis*-**22** and *trans*-**22**.

The racemic products were obtained by a similar procedure using *N*-[3,5-bis(trifluoromethyl)phenyl]-*N*'-(3-dimethylaminopropyl)squaramide as a substitutive for **SQX**.

***tert*-Butyl 5-methyl-5-phenyl-4,5-dihydrooxazole-4-carboxylate** (**22ab**)

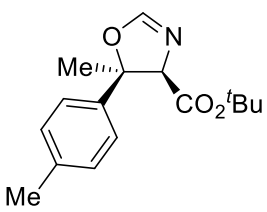


Obtained 61.8 mg (95%). The enantiomeric excess (minor isomer: 91%, major isomer: 99%) was determined by HPLC (Lux Cellulose 4), hexane:^{i}PrOH 95:5, 1 mL/min, *trans*-(**4*R*,5*S***)-**22ab** (minor diastereomer): minor enantiomer, t_r = 15.5 min, major enantiomer, t_r = 22.1 min; *cis*-(**4*R*,5*R***)-**22ab** (major diastereomer): minor enantiomer, t_r = 20.4 min, major enantiomer, t_r = 30.5 min.

cis-(**4*R*,5*R***)-**22ab** (major diastereomer). Colorless oil; $[\alpha]_D^{25}$ –174.3 (*c* 0.65, $CHCl_3$, 99% *ee*); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.32-7.27 (5H, m, Ar), 7.15 (1H, d, *J* = 2.1 Hz, N=CHO), 4.49 (1H, d, *J* = 2.1 Hz, CH), 1.80 (3H, s, CH_3), 0.97 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.5 (C), 156.0 (CH), 139.6 (C), 128.0 (CH), 127.9 (CH), 125.8 (CH), 88.3 (C), 81.4 (C), 78.7 (CH), 28.6 (CH_3), 27.1 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{15}H_{20}NO_3^+$: 262.1438, found 262.1434.

trans-(**4*R*,5*S***)-**22a** (minor diastereomer). Colorless oil: $[\alpha]_D^{25}$ –98.4 (*c* 0.72, $CHCl_3$, 93% *ee*), –72.6 (*c* 1.0, $CHCl_3$, 88% *ee*);[117] **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.48-7.46 (2H, m, Ar), 7.41-7.32 (2H, m, Ar), 7.30-7.27 (1H, m, Ar), 7.08 (1H, d, *J* = 2.1 Hz, N=CHO), 4.70 (1H, d, *J* = 2.1 Hz, CH), 1.66 (3H, s, CH_3), 1.56 (9H, s, CH_3); **^{13}C NMR** (75 MHz, CDCl3) δ 168.5 (C), 155.3 (CH), 145.3 (C), 128.6 (CH), 127.7 (CH), 124.0 (CH), 87.8 (C), 82.5 (C), 77.9 (CH), 28.0 (CH_3), 24.7 (CH_3).

***tert*-Butyl 5-methyl-5-(*p*-tolyl)-4,5-dihydrooxazole-4-carboxylate** (**22bb**)

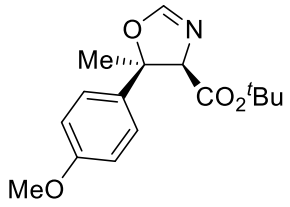


Obtained 54.6 mg (79%) The enantiomeric excess (minor isomer: 90%, *major* isomer 99%) was determined by HPLC (Chiracel IC), hexane:^{i}PrOH 90:10, 1 mL/min, *trans*-(**4*R*,5*S***)-**22bb** (minor diastereomer): minor enantiomer, t_r = 20.5 min, major enantiomer, t_r = 26.0 min. *cis*-(**4*R*,5*R***)-**22bb (major diastereomer)**: minor enantiomer, t_r = 24.7 min, major enantiomer, t_r = 28.2 min.

cis-(**4*R*,5*R***)-**22bb** (major diastereomer). white solid, m.p. 57-59 °C; $[\alpha]_D^{25}$ –100.8 (*c* 1.86, CHCl3, 99% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.21 (2H, d, *J* = 8.4 Hz, Ar), 7.15 (1H, d, *J* = 1.8 Hz, N=CHO), 7.11 (2H, d, *J* = 8.1 Hz, Ar), 4.47 (1H, d, *J* = 1.8 Hz, CH), 2.3 (3H, s, CH_3), 1.78 (3H, s, CH_3), 0.98 (9H, s, CH_3); **^{13}C NMR** (75 MHz, CDCl3) δ 167.6 (C), 156.1 (CH), 137.6 (C), 136.6 (C), 128.6 (CH), 125.8 (CH), 88.3 (C), 81.4 (C), 78.7 (CH), 28.5 (CH3), 27.1 (CH_3), 20.9 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{16}H_{22}NO_3^+$: 276.1594, found 276.1593.

trans-(**4*R*,5*S***)-**22bb** (minor diastereomer). Colorless oil; $[\alpha]_D^{25}$ –194.5 (*c* 0.37, $CHCl_3$, 90% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 (2H, d, *J* = 8.1 Hz, Ar), 7.18 (2H, d, *J* = 8.1 Hz, Ar), 7.07 (1H, d, *J* = 2.1 Hz, N=CHO), 4.68 (1H, d, *J* = 2.1 Hz, CH), 2.35 (3H, s, CH_3), 1.64 (3H, s, CH_3), 1.55 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.6 (C), 155.4 (CH), 142.4 (C), 137.5 (C), 129.3 (CH), 124.0 (CH), 87.8 (C), 82.4 (C), 77.9 (CH), 28.0 (CH_3), 24.6 (CH_3), 21.0 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{16}H_{22}NO_3^+$: 276.1594, found 276.1593.

***tert*-Butyl 5-(4-methoxyphenyl)-5-methyl-4,5-dihydrooxazole-4-carboxylate (22cb)**

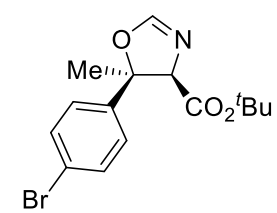


Obtained 51.1 mg (70%). The enantiomeric excess (minor isomer: 90%, major isomer: 98%) was determined by HPLC using a chiral column (Lux Cellulose 4), hexane:^{i}PrOH 90:10, 1 mL/min, *trans*-(**4*R*,5*S***)-**22cb** (minor diastereomer): minor enantiomer, t_r = 18.3 min, major enantiomer, t_r = 21.8 min. *cis*-(**4*R*,5*R***)-**22cb** (major diastereomer): minor enantiomer, t_r = 19.9 min, major enantiomer, t_r = 22.8 min.

cis-(**4*R*,5*R***)-2**2cb** (major diastereomer). White solid, m.p. 68-69 °C; $[\alpha]_D^{25}$ –146.9 (*c* 1.3, $CHCl_3$, 98% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 9 Hz, Ar), 7.18 (1H, d, *J* = 1.8 Hz, N=CHO), 6.88 (2H, d, *J* = 9 Hz, Ar), 4.50 (1H, d, *J* = 1.8 Hz, CH), 3.80 (3H, s, CH_3), 1.82 (3H, s, CH_3), 1.04 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.6 (C), 159.3 (C), 156.0 (CH), 131.7 (C), 127.2 (CH), 113.4 (CH), 88.1 (C), 81.4 (C), 78.6 (CH), 55.3 (CH_3), 28.6 (CH_3), 27.3 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{16}H_{22}NO_4^+$: 292.1543, found 292.1547.

*trans-(***4*R*,5*S***)-**22cb** (minor diastereomer). Colorless oil; $[\alpha]_D^{25}$ -159.9 (*c* 0.47, $CHCl_3$, 99% *ee*), $[\alpha]_D^{25}$ -61.9 (*c* 0.8, $CHCl_3$, 88% *ee*);[117] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* = 9.0 Hz, Ar), 7.06 (1H, d, *J* = 1.8 Hz, N=CHO), 6.90 (2H, d, *J* = 9.0 Hz, Ar), 4.68 (1H, d, *J* = 2.1 Hz, CH), 3.81 (3H, s, CH_3), 1.64 (3H, s, CH_3), 1.55 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.6 (C), 159.0 (C), 155.6 (CH), 137.4 (C), 125.4 (CH), 113.9 (CH), 87.7 (C), 82.4 (C), 80.0 (CH), 55.3 (CH_3), 28.0 (CH_3), 24.6 (CH_3).

***tert*-Butyl 5-(4-bromophenyl)-5-methyl-4,5-dihydrooxazole-4-carboxylate** (**22db**)

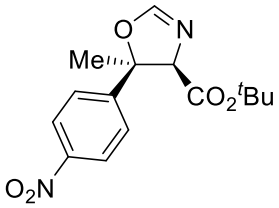


Obtained 89.7 mg (99%). The enantiomeric excess (major isomer: 98%, minor isomer: 93%) was determined by HPLC using a chiral column (Lux Cellulose 4), hexane:^{i}PrOH 90:10, 1mL/min, *cis*-(**4*R*,5*R***)-**22db** (major diastereomer): minor enantiomer, t_r = 10.8 min, major enantiomer, t_r = 11.5 min; *trans*-(**4*R*,5*S***)-**22db** (minor diastereomer): major enantiomer, t_r = 13.4 min, minor enantiomer, t_r = 16.9 min.

cis-(**4*R*,5*R***)-**22db** (major diastereomer). White solid, m.p. 73-74 °C; $[\alpha]_D^{25}$ –98.9 (*c* 1.5, $CHCl_3$, 98% *ee*); **^{1}H NMR** (300 MHz, C_6D_6) δ 7.24 (2H, d, *J* = 9 Hz, Ar), 6.99 (2H, d, *J* = 9 Hz, Ar), 6.65 (1H, d, *J* = 1.8 Hz, N=CHO), 4.41 (1H, d, *J* = 1.8 Hz, CH), 1.26 (3H, s, CH_3), 0.93 (9H, s, CH_3); **^{13}C NMR** (75 MHz, C_6D_6) δ 167.4 (C), 155.5 (CH), 139.8 (C), 131.3 (CH), 128.2 (CH), 122.0 (C), 87.8 (C), 81.0 (C), 79.5 (CH), 28.5 (CH_3), 27.3 (CH_3). HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{15}H_{19}BrNO_3^+$: 340.0543, found 340.0542.

trans-(**4*R*,5*S***)-**22db** (minor diastereomer). Colorless oil; $[\alpha]_D^{25}$ –93.8 (*c* 0.89, $CHCl_3$, 93% *ee*), $[\alpha]_D^{25}$ –102.0 (*c* 1.0, $CHCl_3$, 90% *ee*);[117] **^{1}H NMR** (300 MHz, C_6D_6) δ 7.22 (2H, d, *J* = 9.0 Hz, Ar), 7.09 (2H, d, *J* = 9.0 Hz, Ar), 6.51 (1H, d, *J* = 2.1 Hz, N=CHO), 4.65 (1H, d, *J* = 2.1 Hz, CH), 1.50 (3H, s, CH_3), 1.30 (9H, s, CH_3); **^{13}C NMR** (75 MHz, C_6D_6) δ 168.3 (C), 154.7 (CH), 145.2 (C), 132.0(CH), 126.3 (CH), 122.0 (C), 87.2 (C), 81.8 (C), 78.8 (CH), 27.9 (CH3), 24.7 (CH_3).

***tert*-Butyl 5-methyl-5-(4-nitrophenyl)-4,5-dihydrooxazole-4-carboxylate** (**22eb**)

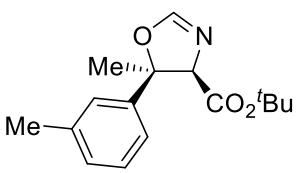


Obtained 76.4 mg (95%). The enantiomeric excess (minor isomer: 95%, *major* isomer 96%) was determined by HPLC (Chiracel IC), hexane:^{i}PrOH 90:10, 1 mL/min, *cis*-(**4*R*,5*R***)-**22eb** (major diastereomer): major enantiomer, t_r = 23.4 min, minor enantiomer, t_r = 26.9 min. *trans*-(**4*R*,5*S***)-**22eb** (minor diastereomer): major enantiomer, t_r = 58.6 min, minor enantiomer, t_r = 83.3 min.

cis-(**4*R*,5*R***)-**22eb** (major diastereomer). White solid, m.p. 102-103 °C; $[\alpha]_D^{25}$ –257.1 (*c* 0.5, $CHCl_3$, 96% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 9.0 Hz, Ar), 7.54 (2H, d, *J* = 9.0 Hz, Ar), 7.18 (1H, d, *J* = 1.8 Hz, N=CHO), 4.57 (1H, d, *J* = 1.8 Hz, CH), 1.82 (3H, s, CH_3), 1.00 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.0 (C), 155.8 (CH), 147.4 (C), 146.9 (C), 127.0 (CH), 123.2 (CH), 87.2 (C), 82.2 (C), 78.9 (CH), 28.7 (CH_3), 27.3 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{15}H_{19}N_2O_5^+$: 307.1288, found 307.1285.

trans-(**4*R*,5*S***)-**22eb** (minor diastereomer). Colorless oil; $[\alpha]_D^{25}$ –60.3 (*c* 1.3, $CHCl_3$, 95% *ee*), $[\alpha]_D^{25}$ –86.5 (*c* 1.0, $CHCl_3$, 90% *ee*);[117] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.23 (2H, d, *J* = 9.0 Hz, Ar), 7.67 (2H, d, *J* = 9.0 Hz, Ar), 7.09 (1H, d, *J* = 2.1 Hz, N=CHO), 4.65 (1H, d, *J* = 2.1 Hz, CH), 1.67 (3H, s, CH_3), 1.57 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8 (C), 155.0 (CH), 152.1 (C), 147.4 (C), 125.3 (CH), 124.0 (CH), 87.2 (C), 83.2 (C), 77.7 (CH), 28.0 (CH3), 24.7 (CH_3).

***tert*-Butyl 5-methyl-5-(*m*-tolyl)-4,5-dihydrooxazole-4-carboxylate** (**22fb**)

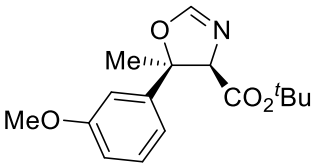


Obtained 60.8 mg (88%). The enantiomeric excess (minor isomer: 97%, *major* isomer 99%) was determined by HPLC (Lux Cellulose 4), hexane:^{i}PrOH 90:10, 1 mL/min, *trans*-(**4*R*,5*S***)-**22fb** (minor diastereomer): minor enantiomer, t_r = 8.9 min, major enantiomer, t_r = 12.4 min. *cis*-(**4*R*,5*R***)-**22fb** (major diastereomer): minor enantiomer, t_r = 10.5 min, minor enantiomer, t_r = 14.2 min.

cis-(**4*R*,5*R***)-**22fb** (major diastereomer). White solid, m.p. 75-76 °C; $[\alpha]_D^{25}$ –155.9 (*c* 1.0, $CHCl_3$, 99% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.26-7.14 (4H, m, Ar), 7.08-7.06 (1H, m, Ar), 4.48 (1H, d, *J* = 2.1 Hz, N=CHO), 2.33 (3H, s, CH_3), 1.79 (3H, s, CH_3), 0.99 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.5 (C), 156.1 (CH), 139.5 (C), 137.5 (C), 128.5 (CH), 128.0 (CH), 126.5 (CH), 122.8 (CH), 88.3 (C), 81.3 (C), 78.7 (CH), 28.6 (CH3), 27.1 (CH_3), 21.4 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{16}H_{22}NO_3^+$: 276.1594, found 276.1594.

trans-(**4*R*,5*S***)-**22fb** (minor diastereomer). Colorless oil; $[\alpha]_D^{25}$ –92.5 (*c* 1.0, $CHCl_3$, 97% *ee*); 1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.26 (3H, m, Ar), 7.13-7.10 (1H, m, Ar), 7.07 (1H, d, *J* = 1.8 Hz, N=CHO), 4.69 (1H, d, *J* = 1.8 Hz, CH), 2.38 (3H, s, CH_3), 1.65 (3H, s, CH_3), 1.56 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.6 (C), 155.3 (CH), 145.3 (C), 138.3 (C), 128.5 (CH), 128.4 (CH), 124.7 (CH), 121.0 (CH), 87.8 (C), 82.4 (C), 77.9 (CH), 28.0 (CH_3), 24.7 (CH_3), 21.2 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{16}H_{22}NO_3^+$: 276.1594, found 276.1597.

***tert*-Butyl 5-(3-methoxyphenyl)-5-methyl-4,5-dihydrooxazole-4-carboxylate** (**22gb**)

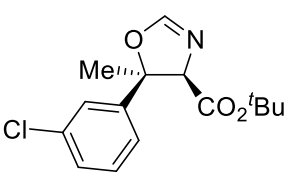


Obtained 43.3 mg (60%). The enantiomeric excess (minor isomer: 93%, *major* isomer 98%) was determined by HPLC (Lux Cellulose 4), hexane:^{i}PrOH 90:10, 1 mL/min, *trans*-(**4*R*,5*S***)-**22gb** (minor diastereomer): minor enantiomer, t_r = 13.2 min, major enantiomer, t_r = 19.1 min. *cis*-(**4*R*,5*R***)-**22gb** (major diastereomer): minor enantiomer, t_r = 15.4 min, major enantiomer, t_r = 20.2 min.

cis-(**4*R*,5*R***)-**22gb** (major diastereomer). Colorless oil; $[\alpha]_D^{25}$ –149.1 (*c* 1.0, $CHCl_3$, 99% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.23 (1H, t, *J* = 8.1 Hz, Ar), 7.16 (1H, d, *J* = 1.8 Hz, CH), 6.91 (1H, d, *J* = 7.8 Hz, Ar), 6.88 (1H, m, Ar), 6.81 (1H, dd, *J* = 8.4, 2.1 Hz, Ar), 4.50 (1H, d, *J* = 1.8 Hz, N=CHO), 3.80 (3H, s, CH_3), 1.79 (3H, s, CH_3), 1.02 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.5 (C), 159.3 (C), 156.1 (CH), 142.2 (C), 129.1 (CH), 118.2 (CH), 113.4 (CH), 111.8 (CH), 88.3 (C), 81.5 (C), 78.7 (CH), 55.3 (CH_3), 28.7 (CH_3), 27.2 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{16}H_{22}NO_4^+$: 292.1543, found 292.1547.

trans-(**4*R*,5*S***)-**22gb** (minor diastereomer). Colorless oil; $[\alpha]_D^{25}$ –88.3 (*c* 0.63, $CHCl_3$, 91% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 (1H, t, *J* = 8.1 Hz, Ar), 7.08-7.01 (3H, m, Ar), 6.83 (1H, dd, *J* = 7.8, 2.1 Hz, Ar), 4.70 (1H, d, *J* = 1.8 Hz, N=CHO), 3.82 (3H, s, CH_3), 1.65 (3H, s, CH_3), 1.56 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.5 (C), 159.8 (C), 155.3 (CH), 147.0 (C), 129.8 (CH), 116.3 (CH), 112.9 (CH), 110.1 (CH), 87.7 (C), 82.5 (C), 77.8 (CH), 55.3 (CH_3), 28.1 (CH_3), 24.8 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{16}H_{22}NO_4^+$: 292.1543, found 292.1546.

***tert*-Butyl 5-(3-chlorophenyl)-5-methyl-4,5-dihydrooxazole-4-carboxylate** (**22hb**)

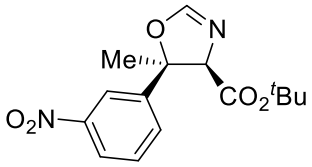


Obtained 55.8 mg (75%). The enantiomeric excess (minor isomer: 91%, *major* isomer 99%) was determined by HPLC (Chiracel IC), hexane:^{i}PrOH 95:5, 1 mL/min, *cis*-(**4*R*,5*R***)-**22hb** (major diastereomer): major enantiomer, t_r = 27.2 min, minor enantiomer, t_r = 29.2 min. *trans*-(**4*R*,5*S***)-**22hb** (minor diastereomer): major enantiomer, t_r = 34.7 min, minor enantiomer, t_r = 39.7 min.

cis-(**4*R*,5*R***)-**22hb** (major diastereomer). White solid, m.p. 74-75 °C; $[\alpha]_D^{25}$ –160.5 (*c* 1.0, $CHCl_3$, 99% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 (1H, bs, Ar), 7.27-7.23 (3H, m, Ar), 7.16 (1H, d, *J* = 1.8 Hz, N=CHO), 4.51 (1H, d, *J* = 2.1 Hz, CH), 1.79 (3H, s, CH_3), 1.05 (9H, s, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.2 (C), 155.9 (CH), 141.7 (C), 134.1 (C), 129.4 (CH), 128.0 (CH), 126.3 (CH), 124.0 (CH), 87.7 (C), 81.8 (C), 78.7 (CH), 28.6 (CH_3), 27.2 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{15}H_{19}ClNO_3^+$: 296.1048, found 296.1046.

trans-(**4*R*,5*S***)-**22hb** (minor diastereomer). Colorless oil; $[\alpha]_D^{25}$ –82.7 (*c* 0.80, $CHCl_3$, 91% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 (1H, bs, Ar), 7.32-7.20 (3H, m, Ar), 7.01 (1H, d, *J* = 1.8 Hz, N=CHO), 4.60 (1H, d, *J* = 2.1 Hz, CH), 1.58 (3H, s, CH_3), 1.51 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.2 (C), 155.2 (CH), 147.3 (C), 134.6 (C), 130.0 (CH), 127.9 (CH), 124.6 (CH), 122.3 (CH), 87.2 (C), 82.8 (C), 77.8 (CH), 28.0 (CH_3), 24.7 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{15}H_{19}ClNO_3^+$: 296.1048, found 296.1043.

***tert*-Butyl 5-methyl-5-(3-nitrophenyl)-4,5-dihydrooxazole-4-carboxylate (22ib)**

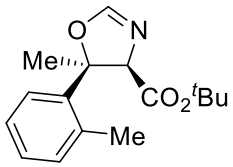


Obtained 74.6 mg (97%). The enantiomeric excess (minor isomer: 90%, *major* isomer 95%) was determined by HPLC (Lux Cellulose 4), hexane:^{i}PrOH 90:10, 1 mL/min, *cis*-(**4*R*,5*R***)-**22ib** (major diastereomer): major enantiomer, t_r = 17.3 min, minor enantiomer, t_r = 19.4 min. *trans*-(**4*R*,5*S***)-**22ib** (minor diastereomer): minor enantiomer, t_r = 29.8 min, major enantiomer, t_r = 36.0 min.

cis-(**4*R*,5*R***)-**22ib** (major diastereomer). Yellow oil; $[\alpha]_D^{25}$ –127.0 (*c* 0.65, $CHCl_3$, 95% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.25 (1H, t, *J* = 1.8 Hz, Ar), 8.16 (1H, d, *J* = 9 Hz, Ar), 7.69 (1H, d, *J* = 8.1 Hz, Ar), 7.54 (1H, t, *J* = 8.1 Hz, Ar), 7.19 (1H, d, *J* =1.8 Hz, N=CHO), 4.58 (1H, d, *J* = 1.8 Hz, CH), 1.87 (3H, s, CH_3), 1.00 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.1 (C), 155.8 (CH), 148.0 (C), 142.0 (C), 132.0 (CH), 129.3 (CH), 122.9 (CH), 121.1 (CH), 87.5 (C), 82.2 (C), 78.8 (CH), 28.7 (CH_3), 27.3 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{15}H_{19}N_2O_5^+$: 307.1288, found 307.1286.

trans-(**4*R*,5*S***)-**22ib** (minor diastereomer). Yellow oil; $[\alpha]_D^{25}$ –37.9 (*c* 0.51, $CHCl_3$, 90% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.41 (1H, t, *J* = 1.8 Hz, Ar), 8.19 (1H, dd, *J* = 8.4, 1.2 Hz, Ar), 7.84 (1H, d, *J* = 7.8 Hz, Ar), 7.59 (1H, t, *J* = 7.8 Hz, Ar), 7.10 (1H, d, *J* = 2.1 Hz, N=CHO), 4.68 (1H, d, *J* = 2.1 Hz, CH), 1.69 (3H, s, CH_3), 1.60 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8 (C), 155.05 (CH), 148.5 (C), 147.3 (C), 130.3 (CH), 129.9 (CH), 122.8 (CH), 119.7 (CH), 87.0 (C), 83.3 (C), 77.8 (CH), 28.0 (CH_3), 24.8 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{15}H_{19}N_2O_5^+$: 307.1288, found 307.1286.

***tert*-butyl 5-methyl-5-(*o*-tolyl)-4,5-dihydrooxazole-4-carboxylate** (**22jb**)

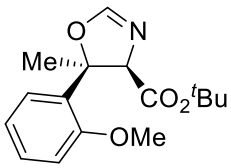


Obtained 63.2 mg (91%). The enantiomeric excess (*major* isomer: 99%, minor isomer: 89%) was determined by HPLC (Lux Cellulose 4), hexane:^{i}PrOH 90:10, 1 mL/min, *cis*-(**4*R*,5*R***)-**22jb** (major diastereomer): minor enantiomer, t_r = 7.6 min, major enantiomer, t_r = 10.2 min. *trans*-(**4*R*,5*S***)-**22jb** (minor diastereomer): minor enantiomer, t_r = 9.3 min, major enantiomer, t_r = 11.8 min. Both diastereomers could not be separated by column chromatography.

cis-(**4*R*,5*R***)-**22jb** (major diastereomer). White solid, m.p. 53-56 °C; $[\alpha]_D^{25}$ –285.9 (*c* 1.0, $CHCl_3$, for the diastereomer mixture, *cis:trans* 91:9); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 (1H, m, Ar), 7.18-7.07 (4H, m, Ar, N=CHO), 4.61 (1H, d, *J* = 2.1 Hz, CH), 2.41 (3H, s, CH_3), 1.71 (3H, s, CH_3), 0.97 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.4 (C), 155.9 (CH), 138.5 (C), 134.0 (C), 131.9 (CH), 127.8 (CH), 126.3 (CH), 125.7 (CH), 90.1 (C), 81.4 (C), 77.5 (CH), 27.8 (CH_3), 27.0 (CH_3), 22.4 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{16}H_{22}NO_3^+$: 276.1594, found 276.1593.

trans-(**4*R*,5*S***)-**22jb** (minor diastereomer): **^{1}H NMR** (300 MHz, $CDCl_3$), representative signals taken from the NMR spectrum of the diastereomer mixture, δ 7.50-7.00 (5H, Ar, N=CHO), 4.76 (1H, d, *J* = 1.8 Hz, CH), 2.49 (3H, s, CH_3), 2.02 (3H, s, CH_3), 1.52 (9H, s, CH_3).

***tert*-Butyl 5-(2-methoxyphenyl)-5-methyl-4,5-dihydrooxazole-4-carboxylate** (**22kb**)

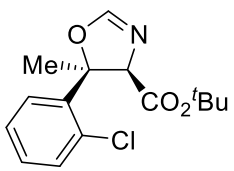


Obtained 73.2 mg (99%). The enantiomeric excess (*major* isomer: 99%, minor isomer: 95%) was determined by HPLC (Lux Cellulose 4), hexane:^{i}PrOH 90:10, 1 mL/min, *cis*-(**4*R*,5*R***)-**22kb** (major diastereomer): minor enantiomer, t_r = 8.2 min, major enantiomer, t_r = 10.7 min. *trans*-(**4*R*,5*S***)-**22kb** (minor diastereomer): minor enantiomer, t_r = 12.5 min, major enantiomer, t_r = 21.2 min. Both diastereomers could not be separated by column chromatography.

cis-(**4*R*,5*R***)-**22kb** (major diastereomer). Colorless oil; $[\alpha]_D^{25}$ –315.0 (*c* 0.85, $CHCl_3$, for the diastereomer mixture, *trans:cis* 95:5); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 (1H, dd, *J* = 7.8, 1.8 Hz, Ar), 7.24 (1H, m, Ar), 7.05 (1H, d, *J* = 1.8 Hz, N=CHO), 6.92 (1H, td, *J* = 7.5, 1.2 Hz, Ar), 6.80 (1H, dd, *J* = 8.1, 1.2 Hz, Ar), 4.58 (1H, d, *J* = 1.8 Hz, CH), 3.77 (3H, s, CH_3), 1.61 (3H, s, CH_3), 0.98 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.6 (C), 155.5 (CH), 154.7 (C), 129.6 (C), 128.6 (CH), 126.0 (CH), 120.4 (CH), 110.3 (CH), 88.4 (C), 80.4 (C), 77.9 (CH), 54.8 (CH_3), 27.1 (CH_3), 27.0 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{16}H_{22}NO_4^+$: 292.1543, found 292.1545.

trans-(**4*R*,5*S***)-**22kb** (minor diastereomer): **^{1}H NMR** (300 MHz, $CDCl_3$), representative signals taken from the NMR spectrum of the diastereomer mixture, δ 7.7-7.20 (5H, m, Ar, N=CHO), 4.68 (1H, d, *J* = 1.8 Hz, CH), 3.85 (3H, s, CH_3), 1.52 (9H, s, CH_3), 1.47 (3H, s, CH_3).

***tert*-Butyl 5-(2-chlorophenyl)-5-methyl-4,5-dihydrooxazole-4-carboxylate** (**22lb**)



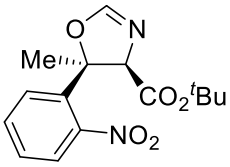
Obtained 74.2 mg (99%). The enantiomeric excess (minor isomer: 92%, *major* isomer 97%) was determined by HPLC (Lux Cellulose 4), hexane:^{i}PrOH 90:10, 1 mL/min, *cis*-(**4*R*,5*R***)-**22lb** (major diastereomer): minor enantiomer, t_r = 7.7 min, major enantiomer, t_r = 9.9 min. *trans*-(**4*R*,5*S***)-**22lb** (minor diastereomer): minor enantiomer, t_r = 9.1 min, major enantiomer, t_r = 13.8 min. Both diastereomers could not be separated by column chromatography.

cis-(**4*R*,5*R***)-**22lb** (major diastereomer). Colorless oil; $[\alpha]_D^{25}$ –275.9 (*c* 1.1, $CHCl_3$, for the diastereomer mixture, *trans:cis* 92:8); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.69 (1H, dd, *J* = 7.5, 1.5 Hz, Ar), 7.42-7.20 (3H, m, Ar), 7.12 (1H, s, N=CHO), 4.79 (1H, s, CH), 1.78

(3H, s, CH_3), 1.11 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.4 (C), 155.4 (CH), 139.2 (C), 130.4 (CH), 130.2 (C), 129.0 (CH), 127.5 (CH), 127.0 (CH), 89.4 (C), 81.4 (C), 77.1 (CH), 27.2 (CH_3), 26.3 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{15}H_{19}ClNO_3^+$: 296.1048, found 296.1046.

trans-(**4*R*,5*S***)-**22lb** (minor diastereomer): **^{1}H NMR** (300 MHz, $CDCl_3$), representative signals taken from the NMR spectrum of the diastereomer mixture, δ 7.7-7.20 (5H, m, Ar, N=CHO), 4.92 (1H, s, CH), 1.87 (3H, s, CH_3), 1.53 (9H, s, CH_3).

***tert*-Butyl 5-methyl-5-(2-nitrophenyl)-4,5-dihydrooxazole-4-carboxylate** (**22mb**)

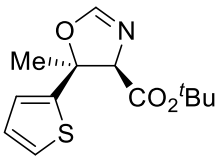


Obtained 76.9 mg (99%). The enantiomeric excess (*major* isomer: 95%, minor isomer: 30%) was determined by HPLC (Chiracel IC), hexane:^{i}PrOH 90:10, 1 mL/min, *cis*-(**4*R*,5*R***)-**22mb** (major diastereomer): major enantiomer, t_r = 31.5 min, minor enantiomer, t_r = 35.4 min. *trans*-(**4*R*,5*S***)-**22mb** (minor diastereomer): major enantiomer, t_r = 50.5 min, minor enantiomer, t_r = 102.4 min. Both diastereomers could not be separated by column chromatography.

cis-(**4*R*,5*R***)-**22mb** (major diastereomer). Yellow oil; $[\alpha]_D^{25}$ –77.2 (*c* 0.87, $CHCl_3$, for the diastereomer mixture, *trans:cis* 71:29); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.87 (1H, dd, *J* = 8.1, 1.5 Hz, Ar), 7.81 (1H, dd, *J* = 8.1, 1.5 Hz, Ar), 7.59 (1H, m, Ar), 7.43 (1H, m, Ar), 7.06 (1H, d, *J* = 1.8 Hz, N=CHO), 4.84 (1H, d, *J* = 2.1 Hz, CH), 1.64 (3H, s, CH_3), 1.10 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.4 (C), 154.7 (CH), 147.1 (C), 135.8 (C), 133.0 (CH), 128.7 (CH), 128.6 (CH), 125.0 (CH), 88.7 (C), 81.6 (C), 78.6 (CH), 27.7 (CH_3), 27.2 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{15}H_{19}N_2O_5^+$: 307.1288, found 307.1284.

trans-(**4*R*,5*S***)-**22mb** (minor diastereomer): **^{1}H NMR** (300 MHz, $CDCl_3$), signals taken from the NMR spectrum of the diastereomer mixture, δ 7.68 (1H, dd, *J* = 7.8, 1.2 Hz, Ar), 7.57-7.39 (3H, m, Ar), 6.89 (1H, d, *J* = 2.1 Hz, N=CHO), 4.87 (1H, d, *J* = 2.1 Hz, CH), 1.76 (3H, s, CH_3), 1.53 (9H, s, CH_3); **^{13}C NMR** (75 MHz, CDCl3), signals taken from the NMR spectrum of the diastereomer mixture, δ 167.8 (C), 154.7 (CH), 148.5 (C), 136.5 (C), 131.5 (CH), 128.9 (CH), 127.5 (CH), 123.9 (CH), 86.9 (C), 82.3 (C), 78.1 (CH), 27.9 (CH_3), 24.0 (CH_3).

***tert*-Butyl 5-methyl-5-(thiophen-2-yl)-4,5-dihydrooxazole-4-carboxylate (22nb)**



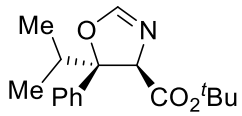
Obtained 54.4 mg (81%). The enantiomeric excess (minor isomer: 92%, *major* isomer 98%) was determined by HPLC (Lux Celullose 4) hexane:^{i}PrOH 90:10, 1 mL/min, *trans*-(**4*R*,5*S***)-**22nb** (minor diastereomer): minor enantiomer, t_r = 11.9 min, major enantiomer, t_r = 17.5 min, *cis*-(**4*R*,5*R***)-**22nb** (major diastereomer): minor enantiomer, t_r = 16.0 min, major enantiomer, t_r = 22.4 min.

trans-(**4*R*,5*S***)-**22nb** (major diastereomer). Colourless oil; $[\alpha]_D^{25}$ –143.6 (*c* 1.22, $CHCl_3$, 98% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.26 (1H, dd, *J* =5.0, 1.5 Hz, Ar), 7.07 (1H, dd, *J* = 3.6, 1.2 Hz, Ar), 7.02 (1H, d, *J* = 1.8 Hz, N=CHO), 6.98 (1H, dd, *J* = 5.0, 3.6 Hz, Ar), 4.78 (1H, d, *J* = 1.8 Hz, CH), 1.74 (3H, s, CH_3), 1.52 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.9 (C), 155.1 (CH), 148.3 (C), 127.0 (CH), 125.0 (CH), 123.4 (CH), 85.9

(C), 82.6 (C), 78.3 (CH), 28.0 (CH_3), 24.1 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{13}H_{18}NO_3S^+$: 268.1002, found 268.1003.

cis-(**4*R*,5*R***)-**22nb** (minor diastereomer). Colourless oil; $[\alpha]_D^{25}$ –93.8 (*c* 1.00, $CHCl_3$, 92% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.22 (1H, dd, *J* = 3.9, 2.4 Hz, Ar), 7.11 (1H, d, *J* = 1.8 Hz, N=CHO), 6.97-6.95 (2H, m, Ar), 4.53 (1H, d, *J* = 1.8 Hz, CH), 1.91 (3H, s, CH_3), 1.12 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.2 (C), 155.6 (CH), 142.9 (C), 126.9 (CH), 125.5 (CH), 124.9 (CH), 86.4 (C), 81.7 (C), 78.8 (CH), 29.3 (CH_3), 27.3 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{13}H_{18}NO_3S^+$: 268.1002, found 268.1003.

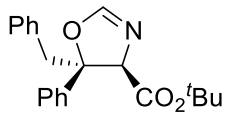
***tert*-Butyl 5-isopropyl-5-phenyl-4,5-dihydrooxazole-4-carboxylate** (**22ob**)



Obtained 45.9 mg (63%). The enantiomeric excess (*major* isomer: 97%) was determined by HPLC (Chiracel AD-H), hexane:^{i}PrOH 90:10, 1 mL/min, *cis*-(**4*R*,5*R***)-**22ob** (major diastereomer): minor enantiomer, t_r = 5.6 min, major enantiomer, t_r = 6.0 min. *trans*- (**4*R*,5*S***)-**22ob** (minor diastereomer): minor enantiomer, t_r = 7.1 min, major enantiomer, t_r = 4.8 min.

cis-(**4*R*,5*R***)-**22ob** (major diastereomer). Colourless oil; $[\alpha]_D^{25}$ –218.2 (*c* 0.45, $CHCl_3$, 97% *ee*, for the diastereomer mixture, *trans:cis* 98:2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.24-7.16 (5H, m, Ar), 7.08 (1H, d, *J* = 1.5 Hz, N=CHO), 4.58 (1H, d, *J* = 1.5 Hz, CH), 2.23 (1H, sept, *J* = 6.9 Hz, CH), 0.94 (9H, s, CH_3), 0.91 (3H, d, *J* = 6.9 Hz, CH_3), 0.66 (3H, d, *J* = 6.9 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.1 (C), 156.3 (CH), 139.0 (C), 127.9 (CH), 127.3 (CH), 126.0 (CH), 93.5 (C), 81.4 (C), 76.5 (CH), 38.1 (CH), 27.2 (CH3), 17.2 (CH_3), 16.2 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{17}H_{24}NO_3^+$: 290.1751, found 290.11754.

***tert*-Butyl 5-benzyl-5-phenyl-4,5-dihydrooxazole-4-carboxylate** (**22pb**)



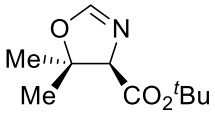
Obtained 84.7 mg (99%). The enantiomeric excess (*major* isomer: 97%, minor isomer 95%) was determined by HPLC (Chiracel IC), hexane:^{i}PrOH 90:10, 1 mL/min, *trans*-(**4*R*,5*S***)-**22pb** (minor diastereomer): minor enantiomer, t_r = 14.3 min, major enantiomer, t_r = 28.4 min, *cis*-(**4*R*,5*R***)-**22pb** (major diastereomer): minor enantiomer, t_r = 22.9 min, major enantiomer, t_r = 23.7 min. Both diastereomers could not be separated by column chromatography.

cis-(**4*R*,5*R***)-**22pb** (major diastereomer). Colorless oil; $[\alpha]_D^{25}$ –133.7 (*c* 0.86, $CHCl_3$, for the diastereomer mixture, *trans:cis* 61:39); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42-7.12 (10H, m, Ar), 6.83 (1H, d, *J* = 1.8 Hz, N=CHO), 4.75 (1H, d, *J* = 1.8 Hz, CH), 3.40 (2H, d, *J* = 2.4 Hz, CH_2), 1.08 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.5 (C), 155.8 (CH), 138.5 (C), 134.5 (C), 130.5 (CH), 127.92 (CH), 127.90 (CH), 127.4 (CH), 126.9 (CH), 126.1 (CH), 90.6 (C), 81.5 (C), 77.4 (CH), 46.9 (CH_2), 28.0 (CH_3), 27.2 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{21}H_{24}NO_3^+$: 338.1751, found 338.1749.

trans-(**4*R*,5*S***)-**22pb** (minor diastereomer): **^{1}H NMR** (300 MHz, $CDCl_3$), signals taken from the NMR spectrum of the diastereomer mixture, δ 7.42-7.12 (10H, m, Ar), 6.81 (1H, d, *J* = 1.8 Hz, N=CHO), 4.95 (1H, d, *J* = 1.8 Hz, CH), 3.34 (1H, d, *J* = 13.2 Hz, CH), 3.23 (1H, d, *J* = 13.2 Hz, CH), 1.70 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$), signals taken from the NMR spectrum of the diastereomer mixture, δ 168.5 (C), 155.2 (CH), 142.9 (C),

134.8 (C), 130.4 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 126.5 (CH), 124.8 (CH), 89.8 (C), 82.8 (C), 78.8 (CH), 43.4 (CH_2), 28.1 (CH_3), 27.2 (CH_3).

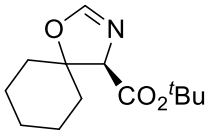
***tert*-Butyl (*R*)-5,5-dimethyl-4,5-dihydrooxazole-4-carboxylate (22qb)**



Obtained 48.0 mg (85%). The enantiomeric excess (96%) was determined by HPLC (Chiracel OD-H), hexane:^{i}PrOH 90:10, 1 mL/min, minor enantiomer, t_r = 4.7 min, major enantiomer, t_r = 5.9 min.

22qb. Colorless oil; $[\alpha]_D^{25}$ –91.9 (*c* 0.65, CHCl3, 96% *ee*); **^{1}H NMR** (300 MHz, CDCl3) δ 6.87 (1H, d, *J* = 1.8 Hz, CH), 4.23 (1H, d, *J* = 1.8 Hz, N=CHO), 1.50 (3H, s, CH_3), 1.47 (9H, s, CH_3), 1.34 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.7 (C), 155.8 (CH), 85.1 (C), 82.0 (C), 76.2 (CH), 28.7 (CH_3), 27.9 (CH_3), 22.5 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{10}H_{18}NO_3^+$: 200.1281, found 200.1283.

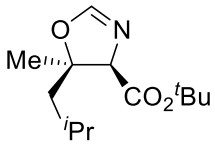
***tert*-Butyl (*R*)-1-oxa-3-azaspiro[4.5]dec-2-ene-4-carboxylate (22rb)**



Obtained 59.0 mg (96%). The enantiomeric excess (95%) was determined by HPLC using a chiral column (Chiracel IC), hexane:^{i}PrOH 90:10, 1mL/min, minor enantiomer, t_r = 20.4 min, major enantiomer, t_r = 21.4 min.

22rb. Colorless oil; $[\alpha]_D^{25}$ –72.6 (*c* 0.46, $CHCl_3$, 95% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.91 (1H, d, *J* = 1.8 Hz, N=CHO), 4.13 (1H, d, *J* = 1.8 Hz, CH), 1.84-1.74 (2H, m), 1.68-1.52 (7H, m), 1.47 (9H, s, CH_3), 1.34-1.24 (1H, m); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.7 (C), 155.9 (CH), 86.8 (C), 81.9 (C), 76.3 (CH), 37.6 (CH_2), 31.2 (CH_2), 27.9 (CH_3), 24.8 (CH_2), 22.4 (CH_2); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{13}H_{22}NO_3^+$: 240.1594, found 240.1593.

***tert*-Butyl 5-isobutyl-5-methyl-4,5-dihydrooxazole-4-carboxylate (22sb)**



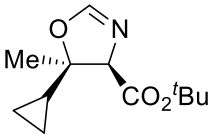
Obtained 35.3 mg (71%). The enantiomeric excess (*major* isomer: 97%, minor isomer: 56%) was determined by HPLC (Chiracel IC), hexane:^{i}PrOH 90:10, 1 mL/min, ***cis*-(4*R*,5*R*)-22sb** (major diastereomer): major enantiomer, t_r = 12.2 min, minor enantiomer, t_r = 14.6 min, ***trans*-(4*R*,5*S*)-22sb** (minor diastereomer): major enantiomer, t_r = 21.7 min, minor enantiomer, t_r = 24.1 min.

***cis*-(4*R*,5*R*)-22sb** (major diastereomer). Colourless oil; $[\alpha]_D^{25}$ –45.4 (*c* 1.09, $CHCl_3$, 97% *ee*); **^{1}H NMR** (300 MHz, CDCl3) δ 6.89 (1H, d, *J* = 1.8 Hz, N=CHO), 4.22 (1H, d, *J* = 1.8 Hz, CH), 1.87 (1H, sept, *J* = 6.6 Hz, CH), 1.53-1.50 (2H, m), 1.47 (9H, s, CH_3), 1.45 (3H, s, CH_3), 0.94 (3H, d, *J* = 6.6 Hz, CH_3), 0.93 (3H, d, *J* = 6.6 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.7 (C), 156.1 (CH), 87.6 (C), 82.0 (C), 78.0 (CH), 43.2 (CH), 28.0 (CH3), 25.6 (CH2), 24.8 (CH3), 24.3 (CH_3), 23.0 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{13}H_{24}NO_3^+$: 242.1751, found 242.1755.

***trans*-(4*R*,5*S*)-22sb** (minor diastereomer). Colourless oil; $[\alpha]_D^{25}$ –67.7 (*c* 0.18, $CHCl_3$, 56% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.89 (1H, d, *J* = 1.8 Hz, N=CHO), 4.29 (1H, d, *J* = 1.8 Hz, CH), 1.85 (1H, sept, *J* = 6.6 Hz, CH), 1.73 (1H, dd, *J* = 14.4, 5.1 Hz, CH), 1.63 (1H, m, CH), 1.49 (9H, s, CH_3), 1.33 (3H, s, CH_3), 0.98 (3H, d, *J* = 6.6 Hz, CH_3),

0.97 (3H, d, *J* = 6.6 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.9 (C), 155.9 (CH), 88.8 (C), 82.0 (C), 75.9 (CH), 49.9 (CH), 28.0 (CH_3), 24.3 (CH_2), 24.2 (CH_3), 23.7 (CH_3), 20.7 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{13}H_{24}NO_3^+$: 242.1751, found 242.1747.

***tert*-Butyl -5-cyclopropyl-5-methyl-4,5-dihydrooxazole-4-carboxylate (22tb)**

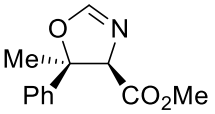


Obtained 37.3 mg (81%). The enantiomeric excess (*major* isomer: 97%, minor isomer 87%) was determined by HPLC (Lux Celullose 4), hexane:^{i}PrOH 90:10, 1 mL/min, *trans*-(**4*R*,5*S*)-22tb** (minor diastereomer): minor enantiomer, t_r = 9.2 min, major enantiomer, t_r = 12.5 min, *cis*-(**4*R*,5*R*)-22tb** (major diastereomer): minor enantiomer, t_r = 11.3 min, major enantiomer, t_r = 13.2 min.

cis-(**4*R*,5*R*)-22tb** (major diastereomer). Colourless oil; $[\alpha]_D^{25}$ –35.2 (*c* 0.62, $CHCl_3$, 97% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.84 (1H, d, *J* = 1.8 Hz, N=CHO), 4.32 (1H, d, *J* = 1.8 Hz, CH), 1.47 (9H, s, CH_3), 1.46 (3H, s, CH_3), 1.10-1.05 (1H, m, CH), 0.45-0.38 (4H, m, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.5 (C), 155.5 (CH), 86.0 (C), 81.7 (C), 76.9 (CH), 28.0 (CH3), 26.7 (CH_3), 15.5 (CH), 1.8 (CH_2), 1.3 (CH_2); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{12}H_{20}NO_3^+$: 226.1438, found 226.1437.

trans-(**4*R*,5*S*)-22tb** (minor diastereomer). Colourless oil; $[\alpha]_D^{25}$ –88.8 (*c* 0.75, $CHCl_3$, 87% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.83 (1H, d, *J* = 1.8 Hz, N=CHO), 4.35 (1H, d, *J* = 1.8 Hz, CH), 1.49 (9H, s, CH_3), 1.34 (3H, s, CH_3), 1.22-1.17 (1H, m, CH), 0.55-0.42 (4H, m, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.8 (C), 155.6 (CH), 86.6 (C), 82.0 (C), 75.1 (CH), 28.0 (CH_3), 21.0 (CH), 21.0 (CH_3), 1.4 (CH_2), 0.73 (CH_2); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{12}H_{20}NO_3^+$: 226.1438, found 226.1438.

Methyl 5-methyl-5-phenyl-4,5-dihydrooxazole-4-carboxylate (22aa)

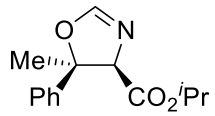


Obtained 45.2 mg (82%). The enantiomeric excess (minor isomer: 84%, major isomer: 96%) was determined by HPLC (Chiralpak AS-H) hexane:^{i}PrOH 95:5, 1mL/min, *trans*-(**4*R*,5*S*)-22aa** (minor diastereomer): minor enantiomer, t_r = 12.8 min, major enantiomer, t_r = 14.2 min; *cis*-(**4*R*,5*R*)-22aa** (major diastereomer): minor enantiomer, t_r = 10.8 min, major enantiomer, t_r = 28.6 min. Both diastereomers could not be separated by column chromatography.

cis-(**4*R*,5*R*)-22aa** (major diastereomer). Colorless oil; $[\alpha]_D^{25}$ –166.0 (*c* 0.50, $CHCl_3$, 96% *ee*, for the diastereomer mixture, *trans:cis* 80:20); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.48-7.26 (5H, m, Ar), 7.20 (1H, d, *J* = 1.8 Hz, N=CHO), 4.64 (1H, d, *J* = 1.8 Hz, CH), 3.15 (3H, s, CH_3), 1.86 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.0 (C), 156.6 (CH), 139.2 (C), 127.9 (CH), 125.2 (CH), 88.4 (C), 78.6 (CH), 51.6 (CH_3), 28.2 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{12}H_{14}NO_3^+$: 220.0968, found 220.0970.

trans-(**4*R*,5*S*)-22aa** (minor diastereomer). Colorless oil; **^{1}H NMR** (CDCl3, 300 MHz), signals taken from the NMR spectrum of the diastereomer mixture, δ 7.48-7.26 (5H, m, Ar), 7.11 (1H, d, *J* = 1.8 Hz, N=CHO), 4.83 (1H, d, *J* = 1.8 Hz, CH), 3.85 (3H, s, CH_3), 1.61 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$), signals taken from the NMR spectrum of the diastereomer mixture, δ 170.0 (C), 155.8 (CH), 144.8 (C), 128.7 (CH), 127.8 (CH), 124.0 (CH), 87.9 (C), 77.6 (CH), 52.4 (CH_3), 24.5 (CH_3).

Isopropyl 5-methyl-5-phenyl-4,5-dihydrooxazole-4-carboxylate (**22ac**)

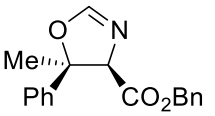


Obtained 48.4 mg (78%). The enantiomeric excess (minor isomer: 90%, major isomer: 97%) was determined by HPLC (Lux Cellulose 4) hexane:^{i}PrOH 90:10, 1mL/min, *trans*-(**4*R*,5*S***)-**22ac** (minor diastereomer): minor enantiomer, t_r = 11.7 min, major enantiomer, t_r = 15.5 min; *cis*-(**4*R*,5*R***)-**22ac** (major diastereomer): minor enantiomer, t_r = 14.0 min, major enantiomer, t_r = 17.9 min.

cis-(**4*R*,5*R***)-**22ac** (major diastereomer). Colorless oil; $[\alpha]_D^{25}$ –173.9 (*c* 0.57, $CHCl_3$, 97% *ee*); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.35-7.26 (5, m, Ar), 7.20 (1H, d, *J* = 1.8 Hz, N=CHO), 4.59 (1H, d, *J* = 1.8 Hz, CH), 4.47 (1H, sept, *J* = 6.3 Hz, CH), 1.84 (3H, s, CH_3), 0.86 (3H, d, *J* = 6.3 Hz, CH_3), 0.77 (3H, d, *J* = 6.3 Hz, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.2 (C), 156.4 (CH), 139.3 (C), 128.0 (CH), 127.9 (CH), 125.6 (CH), 88.4 (C), 78.3 (CH), 68.8 (CH), 28.5 (CH_3), 21.2 (CH_3), 21.0 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{14}H_{18}NO_3^+$: 248.1281, found 248.1282.

trans-(**4*R*,5*S***)-**22ac** (minor diastereomer). Colorless oil; $[\alpha]_D^{25}$ –79.5 (*c* 0.73, $CHCl_3$, 90% *ee*); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.49-7.29 (5H, m, Ar), 7.10 (1H, d, *J* = 1.8 Hz, N=CHO), 5.20 (1H, sept, *J* = 6.3 Hz, CH), 4.76 (1H, d, *J* = 2.1 Hz, CH), 1.63 (3H, s, CH_3), 1.35 (3H, d, *J* = 6.3 Hz, CH_3), 1.33 (3H, d, *J* = 6.3 Hz, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.0 (C), 155.6 (CH), 145.0 (C), 128.7 (CH), 127.8 (CH), 124.0 (CH), 87.8 (C), 77.5 (CH), 69.3 (CH), 24.5 (CH_3), 21.9 (CH_3), 21.8 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{14}H_{18}NO_3^+$: 248.1281, found 248.1282.

Benzyl 5-methyl-5-phenyl-4,5-dihydrooxazole-4-carboxylate (**22ad**)

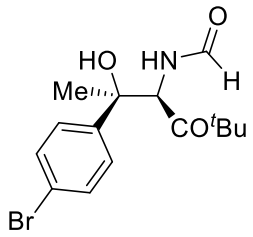


Obtained 56.1 mg (76%). The enantiomeric excess (minor isomer: 82%, major isomer: 96%) was determined by HPLC (Lux Cellulose 4) hexane:^{i}PrOH 90:10, 1mL/min, *trans*-(**4*R*,5*S***)-**22ad** (minor diastereomer): minor enantiomer, t_r = 21.9 min, major enantiomer, t_r = 33.2 min; *cis*-(**4*R*,5*R***)-**22ad** (major diastereomer): minor enantiomer, t_r = 25.2 min, major enantiomer, t_r = 34.6 min.

cis-(**4*R*,5*R***)-**22ad** (major diastereomer). Colorless oil; $[\alpha]_D^{25}$ –118.0 (*c* 0.72, $CHCl_3$, 96% *ee*); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.29-7.26 (8H, m, Ar), 7.20 (1H, d, *J* = 1.8 Hz, N=CHO), 7.08-7.04 (2H, m, Ar), 4.67 (1H, d, *J* = 1.8 Hz, CH), 4.65 (1H, d, *J* = 12.0 Hz, CH), 4.36 (1H, d, *J* = 12.0 Hz, CH), 1.83 (3H, s, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.6 (C), 156.6 (CH), 139.1 (C), 134.8 (C), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.04 (CH), 128.01 (CH), 125.3 (CH), 88.4 (C), 78.4 (CH), 66.8 (CH_2), 28.3 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{18}H_{18}NO_3^+$: 296.1281 found 296.1283.

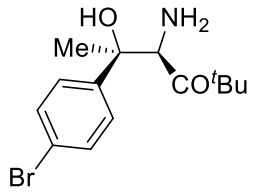
trans-(**4*R*,5*S***)-**22ad** (minor diastereomer). Colorless oil; $[\alpha]_D^{25}$ –91.4 (*c* 0.56, $CHCl_3$, 82% *ee*); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.45-7.29 (10H, m, Ar), 7.11 (1H, d, *J* = 2.1 Hz, N=CHO), 5.30 (2H, s, CH_2), 4.84 (1H, d, *J* = 2.1 Hz, CH), 1.51 (3H, s, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.4 (C), 155.9 (CH), 144.8 (C), 135.1 (C), 128.8 (CH), 128.7 (CH), 128.64 (CH), 128.62 (CH), 127.8 (CH), 124.0 (CH), 88.0 (C), 77.6 (CH), 67.3 (CH_2), 24.4 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{18}H_{18}NO_3^+$: 296.1281 found 296.1283.

***tert*-butyl 3-(4-bromophenyl)-2-formamido-3-hydroxybutanoate** (**23**)



6 M Aqueous HCl (6 drops) was added to a solution of compound **22db** (33.0 mg, 0.096 mmol) in THF (1 mL). The reaction mixture was stirred at r.t. for 24 h. Work up as described in the previous procedure (**19aa**) afforded 34.6 mg (99%) of compound **23**. The enantiomeric excess (98%) was determined by HPLC (Chiracel IC), hexane:^{i}PrOH 90:10, 1 mL/min, major enantiomer, t_r = 5.0 min, minor enantiomer, t_r = 9.0 min. White solid; m.p. 130-131 °C; $[\alpha]_D^{25}$ +22.8 (*c* 0.37, $CHCl_3$, 98% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.33 (1H, s, CHO), 7.49 (2H, d, *J* = 8.7 Hz, Ar), 7.33 (2H, d, *J* = 8.7 Hz, Ar), 6.53 (1H, d, *J* = 9.3 Hz, OH), 4.96 (1H, dd, *J* = 9.0, 0.6 Hz, CHN), 3.41 (1H, bs, NH), 1.49 (3H, s, CH_3), 1.14 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.2 (C), 161.0 (C), 142.9 (C), 131.2 (CH), 127.0 (CH), 121.5 (CH), 83.4 (C), 76.0 (C), 57.7 (CH3), 27.4 (CH_3); HRMS (ESI) *m/z* $[M+Na]^+$ calculated for $C_{15}H_{20}BrNNaO_4^+$: 380.0468, found 380.0461.

***tert*-Butyl (2*R*,3*R*)-2-amino-3-(4-bromophenyl)-3-hydroxybutanoate** (**24**)



6 M Aqueous HCl (6 drops) was added to a solution of compound **22db** (25.0 mg, 0.073 mmol) in MeOH (1 mL). The reaction mixture was stirred at rt for 24 h. Work up as described in the previous procedure (**20aa**) afforded 22.3 mg (93%) of compound **24**. The enantiomeric excess (81%) was determined by HPLC (Lux Cellulose 4), hexane:^{i}PrOH 90:10, 1 mL/min, minor enantiomer, t_r = 11.8 min, major enantiomer, t_r = 10.0 min. Colorless oil; $[\alpha]_D^{25}$ –23.9 (*c* 1.1, $CHCl_3$, 81% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* = 8.7 Hz, Ar), 7.28 (2H, d, *J* = 8.7 Hz, Ar), 3.55 (1H, s, CHN), 2.62 (3H, bs, NH_2, OH), 1.59 (3H, s, CH_3), 1.25 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.0 (C), 143.8 (C), 130.9 (CH), 127.4 (CH), 121.1 (C), 82.3 (C), 62.6 (CH), 27.7 (CH_3), 26.4 (CH_3); HRMS (ESI) *m/z* $[M+Na]^+$ calculated for $C_{14}H_{20}BrNNaO_3^+$: 352.0518, found 352.0516.

5.3 Enantioselective catalytic synthesis of 2-imidazoline

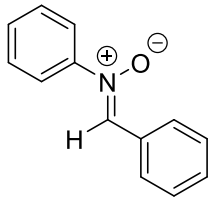
5.3.1 Synthesis of nitrones 25

All the nitrones used in this work were synthetized with two different procedures:

General procedure A: The corresponding benzaldehyde (1 mmol) was added to a solution of *N*-phenylhydroxylamine (1 mmol) in ethanol (1 mL), followed of two drops of concentrated HCl. The mixture was stirred at room temperature until it was completed (TLC). The nitrone was isolated by filtration under reduced pressure and washed with cold ethanol. In the cases where the nitrone does not precipitate, the solvent was removed under reduced pressure and the crude product purified by column chromatography eluting with hexane:EtOAc mixtures.

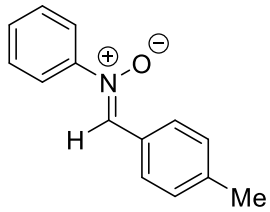
General procedure B: A mixture of *N*-phenylhydroxylamine (1 mmol) and the corresponding benzaldehyde (1 mmol) in ethanol (4 mL) was heated at reflux temperature for 2 hours until the reaction was completed (TLC). The solvent was removed under reduced pressure and the crude product was crystallized from hexane:EtOAc mixtures.

_N_-1-Diphenylmethanimine oxide (25a)



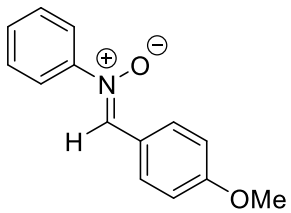
Procedure A. From *N*-phenylhydroxylamine (300 mg, 2.75 mmol) and benzaldehyde (278 µL, 2.75 mmol), 352 mg (65%) of compound **25a** were obtained after column chromatography. Pale yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.42-8.38 (2H, m, Ar), 7.93 (1H, s, CH), 7.80-7.77 (2H, m, Ar), 7.51-7.46 (6H, m, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.1 (C), 134.7 (CH), 131.0 (CH), 130.6 (C), 129.9 (CH), 129.2 (CH), 129.1 (CH), 128.6 (CH), 121.8 (CH). Data consistent with the literature.[99]

_N_-Phenyl-1-(p-tolyl)methanimine oxide (25b)



Procedure A. From *N*-phenylhydroxylamine (700 mg, 6.41 mmol) and 4-methylbenzaldehyde (756 µL, 6.41 mmol), 908 mg (67%) of compound **25b** were obtained after column chromatography. Pale yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.30 (2H, d, *J* = 8.4 Hz, Ar), 7.89 (1H, s, CH), 7.81-7.72 (2H, m, Ar), 7.52-7.41 (3H, m, Ar), 7.29 (2H, *J* = 8.4 Hz, Ar), 2.41 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.0 (C), 141.6 (C), 134.8 (CH), 129.8 (CH), 129.4 (CH), 129.13 (CH), 129.09 (CH), 128.0 (C), 121.7 (CH), 21.8 (CH_3). Data consistent with the literature.[99]

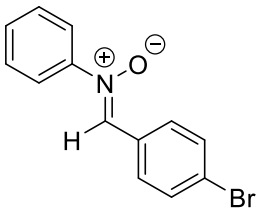
1-(4-Methoxyphenyl)-_N_-phenylmethanimine oxide (25c)



Procedure A. From *N*-phenylhydroxylamine (500 mg, 4.58 mmol) and 4-methoxybenzaldehyde (557 µL, 4.58 mmol), 414 mg (40%) of compound **25c** were obtained. Yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.40 (2H, d, *J* = 8.8 Hz, Ar), 7.85 (1H, s, CH), 7.76 (2H, dd, *J* = 8.0, 1.8 Hz, Ar), 7.52-7.41 (3H, m, Ar), 6.98 (2H, d, *J* = 8.8 Hz, Ar), 3.87 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.5 (C), 148.9 (C), 134.1 (CH), 131.1 (CH), 129.6 (CH),

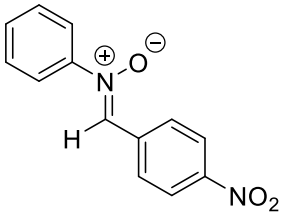
129.1 (CH), 123.7 (C), 121.6 (CH), 114.0 (CH), 55.4 (CH). Data consistent with the literature.[99]

1-(4-bromophenyl)-*N*-phenylmethanimine oxide (25d)



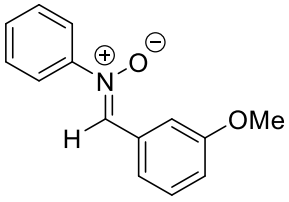
Procedure A. From *N*-phenylhydroxylamine (500 mg, 4.58 mmol) and 4-bromobenzaldehyde (847 mg, 4.58 mmol), 873 mg (69%) of compound **25d** were obtained after filtration. White solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.28 (2H, d, *J* = 8.6 Hz, Ar), 7.89 (1H, s, CH), 7.80-7.72 (2H, m, Ar), 7.60 (2H, d, *J* = 8.6 Hz, Ar), 7.52-7.46 (3H, m, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.9 (C), 133.5 (CH), 131.9 (CH), 130.3 (CH), 130.1 (CH), 129.5 (C), 129.2 (CH), 124.8 (C), 121.7 (CH). Data consistent with the literature.[99]

1-(4-Nitrophenyl)-*N*-phenylmethanimine oxide (25e)



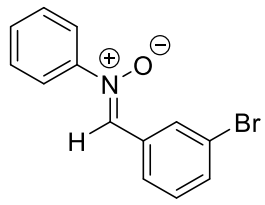
Procedure A. From *N*-phenylhydroxylamine (500 mg, 4.58 mmol) and 4-nitrobenzaldehyde (692 mg, 4.58 mmol), 1.101 g (98%) of compound **25e** were obtained after filtration. Yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.55 (2H, d, *J* = 9Hz, Ar), 8.32 (2H, d, *J* = 9.0 Hz, Ar), 8.07 (1H, s, CH), 7.80-7.77 (2H, m, Ar), 7.54-7.51 (3H, m, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.9 (C), 148.0 (C), 136.2 (CH), 132.3 (C), 130.7 (CH), 129.4 (CH), 129.2 (CH), 123.9 (CH), 121.7 (CH). Data consistent with the literature.[99]

1-(3-Methoxyphenyl)-*N*-phenylmethanimine oxide (25f)



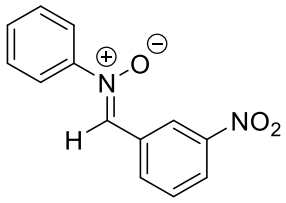
Procedure A. From *N*-phenylhydroxylamine (500 mg, 4.58 mmol) and 3-methoxybenzaldehyde (558 µL, 4.58 mmol), 934 mg (90%) of compound **25f** were obtained after column chromatography. Orange oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.37 (1H, dd, *J* = 2.5, 1.5 Hz, Ar), 7.91 (1H, s, CH), 7.80-7.73 (2H, m, Ar), 7.65 (1H, d, *J* = 8.0 Hz, Ar), 7.51-7.43 (3H, m, Ar), 7.36 (1H, t, *J* = 8.0 Hz, Ar), 7.03 (1H, ddd, *J* = 8.0, 2.5, 1.5 Hz, Ar), 3.87 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.5 (C), 149.0 (C), 134.6 (CH), 131.8 (C), 129.9 (CH), 129.4 (CH), 129.1 (CH), 122.2 (CH), 121.7 (CH), 117.9 (CH), 112.5 (CH), 55.3 (CH_3). Data consistent with the literature.[99]

1-(3-Bromophenyl)-*N*-phenylmethanimine oxide (25g)



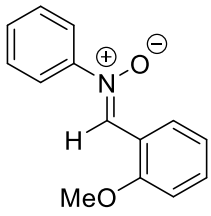
Procedure A. From *N*-phenylhydroxylamine (500 mg, 4.58 mmol) and 3-bromobenzaldehyde (534 µL, 4.58 mmol), 984 mg (79%) of compound **25g** were obtained after filtration. Yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.68 (1H, t, *J* = 1.7 Hz, Ar), 8.23 (1H, d, *J* = 7.9 Hz, Ar), 7.89 (1H, s, CH), 7.77-7.73 (2H, m, Ar), 7.58 (1H, ddd, *J* = 8.0, 2.0, 1.0 Hz, Ar), 7.52-7.45 (3H, m, Ar), 7.34 (1H, t, *J* = 8.0 Hz, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.9 (C), 133.7 (CH), 133.1 (CH), 132.4 (C), 131.3 (CH), 130.2 (CH), 130.1 (CH), 129.2 (CH), 127.4 (CH), 122.8 (C), 121.7 (CH). Data consistent with the literature.[99]

1-(3-Nitrophenyl)-*N*-phenylmethanimine oxide (25h)



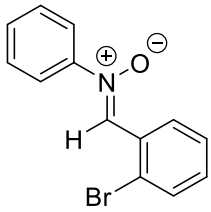
Procedure A. From *N*-phenylhydroxylamine (500 mg, 4.58 mmol) and 3-nitrobenzaldehyde (692 mg, 4.58 mmol), 916 (83%) of compound **25h** were obtained after filtration. Yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.21- 9.17 (1H, t, *J* = 1.8 Hz, Ar), 8.82 (1H, d, *J* = 8.0 Hz, Ar), 8.29 (1H, ddd, *J* = 8.0, 1.8, 1.0 Hz, Ar), 8.07 (1H, s, CH), 7.83-7.75 (2H, m, Ar), 7.67 (1H, t, *J* = 8.0, Ar), 7.56-7.50 (3H, m, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.7 (C), 148.3 (C), 133.8 (CH), 132.1 (C), 132.1 (CH), 130.6 (CH), 129.7 (CH), 129.4 (CH), 124.9 (CH), 123.4 (CH), 121.7 (CH). Data consistent with the literature.[99]

1-(2-Methoxyphenyl)-*N*-phenylmethanimine oxide (25i)



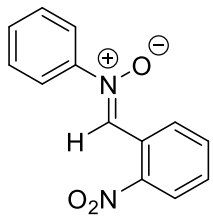
Procedure A. From *N*-phenylhydroxylamine (124 mg, 1.14 mmol) and 2- methoxybenzaldehyde (155.2 mg, 1.14 mmol), 243 mg (94%) of compound **25i** were obtained after column chromatography. Yellow pale solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.48 (1H, dd, *J* = 8.1, 1.8 Hz, Ar), 8.40 (1H, s, CH), 7.80-7.77 (2H, m, Ar), 7.50-7.39 (4H, m, Ar), 7.08 (1H, t, *J* = 7.8 Hz, Ar), 6.92 (1H, dd, *J* = 8.4, 1.2 Hz, Ar), 3.84 (CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.4 (C), 149.5 (C), 132.1 (CH), 129.6 (CH), 129.3 (C), 129.0 (CH), 128.7 (CH), 121.8 (CH), 120.8 (CH), 119.8 (CH), 109.8 (CH), 55.5 (CH_3). Data consistent with the literature.[99]

1-(2-Bromophenyl)-*N*-phenylmethanimine oxide (25j)



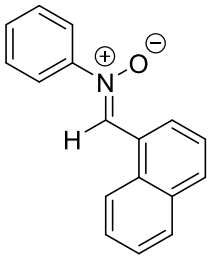
Procedure A. From *N*-phenylhydroxylamine (500 mg, 4.58 mmol) and 2-methoxybenzaldehyde (535 µL, 4.58 mmol), 1.15 g (91%) of compound **25j** were obtained. Yellow pale solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.51 (1H, dd, *J* = 8.1, 1.8 Hz, Ar), 8.42 (1H, s, CH), 7.81-7.77 (2H, m, Ar), 7.66 (1H, dd, *J* = 8.1, 1.2 Hz, Ar), 7.53-7.43 (4H, m, Ar), 7.29 (1H, td, *J* = 7.5, 1.8 Hz, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.4 (C), 133.1 (CH), 132.9 (CH), 131.8 (CH), 130.2 (CH), 129.7 (C), 129.5 (CH), 129.2 (CH), 127.8 (CH), 124.1 (C), 121.8 (CH). Data consistent with the literature.[99]

1-(2-nitrophenyl)-*N*-phenylmethanimine oxide (25k)



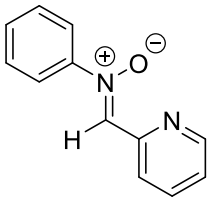
Procedure A. From *N*-phenylhydroxylamine (500 mg, 4.58 mmol) and 3-nitrobenzaldehyde (692 mg, 4.58 mmol), 873 mg (79%) of compound **25k** were obtained after filtration. Yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.38 (1H, dd, *J* = 8.1, 1.5 Hz, Ar), 8.59 (1H, s, CH), 8.09 (1H, dd, *J* = 8.1, 1.2 Hz, Ar), 7.81-7.74 (3H, m, Ar), 7.57 (1H, dt, *J* = 8.4, 1.5 Hz, Ar), 7.53-7.49 (3H, m, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.2 (C), 147.5 (C), 133.6 (CH), 130.6 (CH), 130.5 (CH), 129.5 (CH), 129.3 (CH), 128.5 (CH), 125.0 (CH), 124.5 (C), 121.8 (CH). Data consistent with the literature.[99]

1-(Naphthalen-1-yl)-*N*-phenylmethanimine oxide (25l)



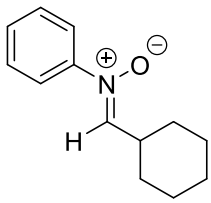
Procedure A. From *N*-phenylhydroxylamine (360 mg, 3.30 mmol) and 1-naphthtaldehyde (450 µL, 3.30 mmol, 334 mg (41%) of compound **25l** were obtained after column chromatography. Yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.78 (1H, dd, *J* = 7.6, 1.2 Hz, Ar), 8.71 (1H, s, CH), 8.09 (1H, d, *J* = 7.4 Hz, Ar), 7.97 (1H, d, *J* = 8.3 Hz, Ar), 7.93 (1H, dd, *J* = 7.8, 1.7 Hz, Ar), 7.88-7.82 (2H, m, Ar), 7.64 (1H, t, *J* = 7.8 Hz, Ar), 7.60-7.48 (5H, m, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.9 (C), 133.5 (C), 131.6 (CH), 130.9 (C), 130.5 (CH), 130.0 (CH), 129.4 (CH), 129.3 (CH), 127.03 (CH), 127.02 (CH), 126.0 (CH), 125.8 (CH), 125.7 (C), 122.0 (CH), 121.7 (CH). Data consistent with the literature.[99]

***N*-Phenyl-1-(pyridin-2-yl)methanimine oxide (25m)**



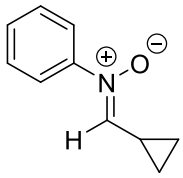
Procedure A. From *N*-phenylhydroxylamine (500 mg, 4.58 mmol) and picolinaldehyde (436 µL, 4.58 mmol), 770 mg (85%) of compound **25m** were obtained after column chromatography. Yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.35 (1H, d, *J* = 8.1 Hz, Ar), 8.69 (1H, ddd, *J* = 4.8, 1.8, 0.9 Hz, Ar), 8.31 (1H, s, CH), 7.92-7.79 (3H, m, Ar), 7.54-7.46 (3H, m, Ar), 7.34 (1H, ddd, *J* = 7.6, 4.8, 1.2 Hz, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.61 (CH), 149.60 (C), 148.7 (C), 137.1 (CH), 135.3 (CH), 130.4 (CH), 129.2 (CH), 124.6 (CH), 124.0 (CH), 121.6 (CH). Data consistent with the literature.[99]

1-Cyclohexyl-*N*-phenylmethanimine oxide (25n)



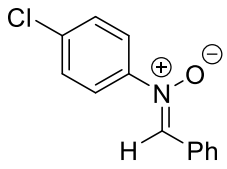
Procedure B. From *N*- phenylhydroxylamine (300 mg, 2.74 mmol) and cyclohexanecarbaldehyde (330 µL, 2.74 mmol), 192 mg (35%) of compound **25n** were obtained after recrystallization from hexane:EtOAc. White solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.66-7.62 (2H, m, Ar), 7.43-7.39 (3H, m, Ar), 7.03 (1H, d, *J* = 7.5 Hz, CH), 3.18 (1H, m, CH), 2.03-1.98 (2H, m), 1.79-1.67 (3H, m), 1.52-1.34 (2H, m), 1.30-7.21 (3H, m); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.9 (C), 143.5 (CH), 129.7 (CH), 129.0 (CH), 121.7 (CH), 35.6 (CH), 28.8 (CH_2), 25.9 (CH_2), 25.2 (CH_2). Data consistent with the literature.[99]

1-Cyclopropyl-*N*-phenylmethanimine oxide (25o)



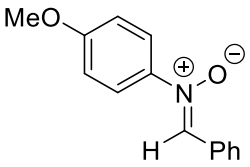
Procedure B. From *N*- phenylhydroxylamine (467 mg, 4.28 mmol) and cyclohexanecarbaldehyde (320 µL, 4.28 mmol), 351 mg (35%) of compound **25o** were obtained after recrystallization from hexane:EtOAc. White solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.66-7.60 (2H, m, Ar), 7.44-7.36 (3H, m, Ar), 6.66 (1H, d, *J* = 8.6 Hz, CH), 2.62 (1H, qt, *J* = 8.5, 4.9 Hz, CH), 1.23-1.14 (2H, m), 0.86-0.78 (2H, m); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.4 (C), 142.9 (CH), 129.6 (CH), 129.0 (CH), 121.4 (CH), 10.5 (CH), 7.75 (CH_2). Data consistent with the literature.[99]

_N_-(4-Chlorophenyl)-1-phenylmethanimine oxide (25p)



Procedure A. From *N*-(4-chlorophenyl)hydroxylamine (300 mg, 2.09 mmol) and benzaldehyde (211 µL, 2.09 mmol), 386 mg (79%) of compound **25p** were obtained after filtration. White solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.40-8.36 (2H, m, Ar), 7.91 (1H, s, CH), 7.75 (2H, d, *J* = 8.9 Hz, Ar), 7.52-7.42 (4H, m, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.4 (C), 135.8 (C), 134.8 (CH), 131.3 (CH), 130.4 (C), 129.3 (CH), 129.2 (CH), 128.7 (CH), 123.0 (CH). Data consistent with the literature.[99]

_N_-(4-Methoxyphenyl)-1-phenylmethanimine oxide (25q)



Procedure A. From *N*-(4-methoxyphenyl)hydroxylamine (1.0 g, 7.2 mmol) and benzaldehyde (732 µL, 7.2 mmol), 634 mg (39%) of compound **25q** were obtained after column chromatography. Grey solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.40-8.36 (2H, m, Ar), 7.87 (1H, s, CH), 7.73 (2H, d, *J* = 9.1 Hz, Ar), 7.50-7.44 (3H, m, Ar), 6.96 (2H, d, *J* = 9.1 Hz, Ar), 3.86 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.6 (C), 142.5 (C), 133.7 (CH), 130.8 (C), 130.7 (CH), 128.9 (CH), 128.6 (CH), 123.0 (CH), 114.0 (CH), 55.6 (CH_3). Data consistent with the literature.[99]

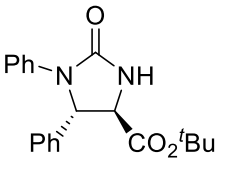
5.3.2 Enantioselective synthesis of 2-imidazolinones 26

General procedure for the [3+2] cycloaddition reaction

Squaramide **SQV** (14.6 mg, 0.025 mmol) and silver oxide (3.0 mg, 0.013 mmol) were introduced in a 25 mL round bottom flask followed by MTBE (6 mL) and nitrone **25** (0.25 mmol). *tert*-Butyl isocyanoacetate **2b** (48 µL, 0.33 mmol) was added, the flask was closed with a stopper and the mixture was stirred at room temperature until consumption of the nitrone **25** (TLC). After this time, the reaction mixture was filtered through a short pad of silica gel and concentrated under reduced pressure. A small aliquot was analyzed by **^{1}H NMR** to determinate the diastereomer ratio. The remaining crude was chromatographed on silica gel eluting with toluene:diethyl ether mixtures (9:1 to 5:5) to obtain the separated diastereomers *trans*-**26** and *cis*-**26**.

Near racemic compounds were obtained by a similar procedure using an equimolar mixture of **SQI** and **SQII** derived from quinidine in place of **SQV**.

***tert*-Butyl 2-oxo-1,5-diphenylimidazolidine-4-carboxylate (26ab)**



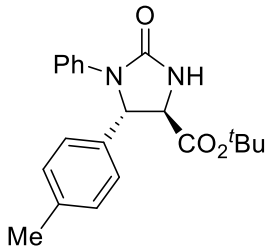
Obtained 66.2 mg (78%) from 49.5 mg (0.25 mmol) of **25a**. The enantiomeric excess (minor isomer: 3%, major isomer 90%) was determined by HPLC (Amylose 1), hexane:^{i}PrOH 80:20, 1 mL/ min, *cis*-**26ab** (minor diastereomer): minor enantiomer, t_r = 9.0 min, major enantiomer, t_r = 16.9 min, *trans*-(**4*R*,5*S***)-**26ab** (major diastereomer): minor enantiomer t_r = 14.8 min, major enantiomer, t_r = 23.2 min.

trans-(**4*R*,5*S***)-**26ab** (major diastereomer). White solid, m.p. 184-188 °C; $[\alpha]_D^{25}$ – 54.5 (*c* 0.95, $CHCl_3$, 90% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 (2H, dd, *J* = 8.7, 1.0 Hz, Ar), 7.40-7.27 (5H, m, Ar), 7.25-7.18 (2H, m, Ar), 6.99 (1H, t, *J* = 7.4 Hz, Ar), 5.85 (1H, bs, NH), 5.43 (1H, d, *J* = 4.1 Hz, CH), 3.97 (1H, d, *J* = 4.1 Hz, CH), 1.53 (9H, s, CH_3); **^{13}C**

NMR (75 MHz, $CDCl_3$) δ 169.6 (C), 158.4 (C), 139.7 (C), 138.3 (C), 129.1 (CH), 128.7 (CH), 128.3 (CH), 126.1 (CH), 123.4 (CH), 120.1 (CH), 83.3 (C), 63.0 (CH), 60.3 (CH), 28.0 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{20}H_{23}N_2O_3^+$:339.1703, found 339.1703.

cis-**26ab** (minor diastereomer). White solid, m.p. 198-203 °C; $[\alpha]_D^{25}$ +3.8 (*c* 0.63, $CHCl_3$, 3% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 (2H, dd, *J* = 8.8, 1.1 Hz, Ar), 7.35-7.23 (5H, m, Ar), 7.22-7.15 (2H, m, Ar) 6.96 (1H, t, *J* = 7.4 Hz, Ar), 5.50 (1H, d, *J* = 9.6 Hz, CH), 5.34 (1H, bs, NH), 4.70 (1H, dd, *J* = 9.6, 0.9 Hz, CH), 1.05 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.5 (C), 158.6 (C), 138.2 (C), 135.9 (C), 128.7 (CH), 128.61 (CH), 128.59 (CH), 128.0 (CH), 123.5 (CH), 120.5 (CH), 82.6 (C), 62.6 (CH), 57.5 (CH), 27.3 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{20}H_{23}N_2O_3^+$: 339.1703, found 339.1703.

***tert*-Butyl 2-oxo-1-phenyl-5-(*p*-tolyl)imidazolidine-4-carboxylate (26bb)**

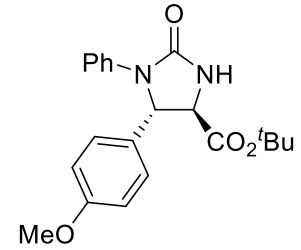


Obtained 73.7 mg (83%) from 53.0 mg (0.25 mmol) of **25b**. The enantiomeric excess (minor isomer: 7%, major isomer 90%) was determined by HPLC (Amylose 1), hexane:^{i}PrOH 80:20, 1 mL/min, *cis*-**26bb** (minor diastereomer): minor enantiomer, t_r = 6.9 min, major enantiomer, t_r = 10.6 min, *trans*-(**4*R*,5*S***)-**26bb** (major diastereomer): minor enantiomer t_r = 12.4 min, major enantiomer, t_r = 21.9 min.

trans-(**4*R*,5*S***)-**26bb** (major diastereomer). White solid, m.p. 176-181 °C; $[\alpha]_D^{25}$ – 46.2 *(c* 0.71, $CHCl_3$, 90% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 (2H, dd, *J* = 8.8, 1.1 Hz, Ar), 7.30-7.18 (4H, m, Ar), 7.14 (2H, d, *J* = 7.9 Hz, Ar), 6.99 (1H, t, *J* = 7.4 Hz, Ar), 5.39 (1H, d, *J* = 4.1 Hz, CH), 3.94 (1H, d, *J* = 4.1 Hz, CH), 2.31 (3H, s, CH_3), 1.52 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.7 (C), 158.3 (C), 138.3 (C), 138.2 (C), 129.8 (CH), 128.7 (CH), 126.1 (CH), 123.5 (CH), 120.2 (CH), 83.3 (C), 62.9 (CH), 60.4 (CH), 28.0 (CH_3), 21.1 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{21}H_{25}N_2O_3^+$: 353.1860, found 353.1855.

cis-**26bb** (minor diastereomer). White solid, m.p. 197-201 °C; $[\alpha]_D^{25}$ +4.3 (*c* 0.74, CHCl3, 7% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 (2H, dd, *J* = 8.8, 1.1 Hz, Ar), 7.22-7.16 (4H, m, Ar), 7.07 (2H, d, *J* = 7.9 Hz, Ar), 6.96 (1H, t, *J* = 7.4 Hz, Ar), 5.46 (1H, d, *J* = 9.6 Hz, CH), 5.35 (1H, bs, NH), 4.68 (1H, d, *J* = 9.6 Hz, CH), 2.27 (3H, s, CH_3), 1.06 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.6 (C), 158.6 (C), 138.4 (C), 138.3 (C), 132.8 (C), 129.2 (CH), 128.6 (CH), 127.9 (CH), 123.4 (CH), 120.5 (CH), 82.5 (C), 62.4 (CH), 57.6 (CH), 27.3 (CH_3), 21.05 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{21}H_{25}N_2O_3^+$: 353.1860, found 353.1855.

***tert*-Butyl 5-(4-methoxyphenyl)-2-oxo-1-phenylimidazolidine-4-carboxylate (26cb)**

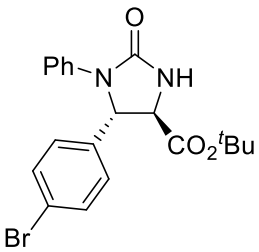


Obtained 44.4 mg (48%) from 57.0 mg (0.25 mmol) of **25b**. The enantiomeric excess (minor isomer: 16%, major isomer 89%) was determined by HPLC (Lux Cellulose 4), hexane:^{i}PrOH 80:20, 1 mL/min, *cis*-**26cb** (minor diastereomer): minor enantiomer, t_r = 53.5 min, major enantiomer, t_r = 35.6 min, *trans*-(**4*R*,5*S***)-**26cb** (major diastereomer): minor enantiomer, t_r = 23.7 min, major enantiomer, t_r = 36.4 min.

trans-(**4*R*,5*S***)-**26cb** (major diastereomer). White solid, m.p. 173-178 °C; $[\alpha]_D^{25}$ –40.6 (*c* 0.97, $CHCl_3$, 89% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 (2H, dd, *J* = 8.7, 1.1 Hz, Ar), 7.29 (2H, d, *J* = 8.7 Hz, Ar), 7.25-7.18 (2H, m, Ar), 6.99 (1H, t, *J* = 7.4 Hz, Ar), 6.86 (2H, d, *J* = 8.8 Hz, Ar), 5.62 (1H, bs, NH), 5.37 (1H, d, *J* = 4.3 Hz, CH), 3.95 (1H, d, *J* = 4.3 Hz, CH), 3.76 (3H, s, CH_3), 1.51 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.7 (C), 159.5 (C), 158.3 (C), 138.3 (C), 131.6 (C), 128.6 (CH), 127.4 (CH), 123.5 (CH), 120.4 (CH), 114.4 (CH), 83.2 (C), 62.7 (CH), 60.5 (CH), 55.2 (CH_3), 28.0 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{21}H_{25}N_2O_4^+$: 369.1809, found 369.1808.

cis-**26cb** (minor diastereomer). White solid, m.p. 194-197 °C; $[\alpha]_D^{25}$ +5.8 (*c* 0.44, $CHCl_3$, 16% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 (2H, dd, *J* = 8.7, 1.1 Hz, Ar), 7.24 (2H, d, *J* = 9.4 Hz, Ar), 7.22-7.14 (2H, m, Ar), 6.97 (1H, t, *J* = 7.4 Hz, Ar), 6.80 (2H, d, *J* = 8.8 Hz, Ar), 5.45 (1H, d, *J* = 9.5 Hz, CH), 5.19 (1H, bs, NH), 4.67 (1H, d, *J* = 9.5 Hz, CH), 3.74 (3H, s, CH_3), 1.10 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.6 (C), 159.8 (C), 158.5 (C), 138.2 (C), 129.2 (CH), 128.6 (CH), 127.9 (C), 123.5 (CH), 120.5 (CH), 114.0 (CH), 82.5 (C), 62.2 (CH), 57.7 (CH), 55.3 (CH_3), 27.5 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{21}H_{25}N_2O_4^+$: 369.1809, found 369.1808.

***tert*-Butyl 5-(4-bromophenyl)-2-oxo-1-phenylimidazolidine-4-carboxylate (26db)**

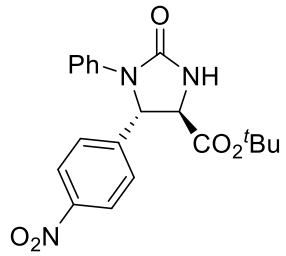


Obtained 68.5 mg (65%) from 69.3 mg (0.25 mmol) of **25d**. The enantiomeric excess (minor isomer: 6%, major isomer 86%) was determined by HPLC (Amylose 1), hexane:^{i}PrOH 80:20, 1 mL/min-1, *cis*-**26db** (minor diastereomer): minor enantiomer, t_r = 7.4 min, major enantiomer, t_r = 9.6 min, *trans*-(**4*R*,5*S***)-**26db** (major diastereomer): minor enantiomer, t_r = 13.7 min, major enantiomer, t_r = 19.3 min.

trans-(**4*R*,5*S***)-**26db** (major diastereomer). White solid, m.p. 163-164 °C; $[\alpha]_D^{25}$ –37.4 (*c* 0.86, $CHCl_3$, 86% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.47 (2H, d, *J* = 8.5 Hz, Ar), 7.39 (2H, dd, *J* = 8.8, 1.1 Hz, Ar), 7.29-7.15 (4H, m, Ar), 7.01 (1H, t, *J* = 7.4 Hz, Ar), 5.97 (1H, bs, NH), 5.39 (1H, d, *J* = 4.3 Hz, CH), 3.93 (1H, d, *J* = 4.3 Hz, CH), 1.52 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ169.3 (C), 158.3 (C), 138.7 (C), 138.0 (C), 132.3 (CH), 128.8 (CH), 127.9 (CH), 123.7 (CH), 122.3 (C), 120.2 (CH), 83.5 (C), 62.4 (CH), 60.1 (CH), 28.0 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{20}H_{21}BrN_2O_3^+$: 417.0808, found 417.0801.

cis-**26db** (minor diastereomer). White solid, m.p. 199-202 °C; $[\alpha]_D^{25}$ +5.5 (*c* 0.63, $CHCl_3$, 6% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 (2H, d, *J* = 8.5 Hz, Ar), 7.35 (2H, dd, *J* = 8.6, 1.0 Hz, Ar), 7.23-7.18 (4H, m, Ar), 6.99 (1H, t, *J* = 7.3 Hz, Ar), 5.47 (1H, d, *J* = 9.6 Hz, CH), 5.32 (1H, bs, NH), 4.69 (1H, d, *J* = 9.6 Hz, CH), 1.10 (9H, s, CH_3); **^{13}C NMR** (75 MHz, CDCl3) δ 167.4 (C), 158.4 (C), 137.9 (C), 134.9 (C), 131.8 (CH), 129.7 (CH), 128.8 (CH), 123.9 (CH), 122.7 (C), 120.6 (CH), 82.9 (C), 62.0 (CH), 57.3 (CH), 27.4 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{20}H_{21}BrN_2O_3^+$: 417.0808, found 417.0801.

***tert*-Butyl 5-(4-nitrophenyl)-2-oxo-1-phenylimidazolidine-4-carboxylate (26eb)**

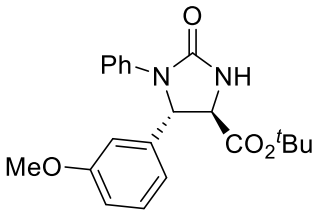


Obtained 58.2 mg (60%) from 60.8 mg (0.25 mmol) of **25e**. The enantiomeric excess (minor isomer: 10%, major isomer 87%) was determined by HPLC (lux Cellulose 3), hexane:^{i}PrOH 95:5, 1.5 mL/min, *cis*-**26eb** (minor diastereomer): minor enantiomer, t_r = 20.5 min, major enantiomer, t_r = 15.4 min, *trans*-(**4*R*,5*S***)-**26eb** (major diastereomer): minor enantiomer, t_r = 26.8 min, major enantiomer, t_r = 28.5 min.

trans-(**4*R*,5*S***)-**26eb** (major diastereomer). brown oil; $[\alpha]_D^{25}$ –26.6 (*c* 0.81, $CHCl_3$, % *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.21 (2H, d, *J* = 8.8 Hz, Ar), 7.57 (2H, d, *J* = 8.7 Hz, Ar), 7.38 (2H, dd, *J* = 8.7, 1.1 Hz, Ar), 7.24-7.12 (2H, m, Ar), 7.02 (1H, t, *J* = 7.4 Hz, Ar), 5.96 (1H, bs, NH), 5.57 (1H, d, *J* = 4.4 Hz, CH), 3.95 (1H, d, *J* = 4.4 Hz, CH), 1.54 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.9 (C), 158.0 (C), 147.9 (C), 146.7 (C), 137.6 (C), 129.0 (CH), 127.3 (CH), 124.4 (CH), 124.1 (CH), 120.2 (CH), 84.0 (C), 62.2 (CH), 59.7 (CH), 28.0 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{20}H_{22}N_3O_5^+$: 384.1554, found 384.1549.

cis-**26eb** (minor diastereomer). White solid, m.p. 199-207 °C; $[\alpha]_D^{25}$ +2.1 (*c* 0.54, $CHCl_3$, 10% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.16 (2H, d, *J* = 8.8 Hz, Ar), 7.54 (2H, d, *J* = 8.8 Hz, Ar), 7.33 (2H, dd, *J* = 8.6, 0.9 Hz, Ar), 7.21 (2H, t, *J* = 8.0 Hz, Ar), 7.01 (1H, t, *J* = 7.3 Hz, Ar), 5.63 (1H, d, *J* =9.6 Hz, CH), 5.41 (1H, bs, NH), 4.76 (1H, d, *J* = 9.6 Hz, CH), 1.08 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.0 (C), 158.2 (C), 148.1 (C), 143.2 (C), 137.5 (C), 129.2 (CH), 128.9 (CH), 124.3 (CH), 123.8 (CH), 120.6 (CH), 83.3 (C), 61.8 (CH), 57.1 (CH), 27.5 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{20}H_{22}N_3O_5^+$: 384.1554, found 384.1549.

***tert*-Butyl 5-(3-methoxyphenyl)-2-oxo-1-phenylimidazolidine-4-carboxylate (26fb)**



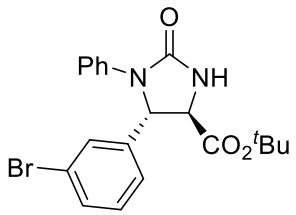
Obtained 58.6 mg (63%) from 57.0 mg (0.25 mmol) of **25f**. The enantiomeric excess (minor isomer: 6%, major isomer 89%) was determined by HPLC (Chiracel OD-H), hexane:^{i}PrOH 90:10, 1 mL/min, *cis*-**26fb** (minor diastereomer): minor enantiomer, t_r = 23.1 min, major enantiomer, t_r = 27.2 min, *trans*-(**4*R*,5*S***)-**26fb** (major diastereomer): minor enantiomer, t_r = 13.2 min, major enantiomer, t_r = 14.9 min.

trans-(**4*R*,5*S***)-**26fb** (major diastereomer). White solid, m.p. 162-166 °C; $[\alpha]_D^{25}$ –45.7 (*c* 0.95, $CHCl_3$, 89% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 (2H, dd, *J* = 8.7, 1.0 Hz, Ar), 7.27-7.20 (3H, m, Ar), 7.01-6.95 (2H, m, Ar), 6.90 (1H, t, *J* = 1.5 Hz, Ar), 6.81 (1H, ddd, *J* = 8.2, 2.5, 0.8 Hz, Ar), 5.69 (1H, bs, NH), 5.39 (1H, d, *J* = 4.1 Hz, CH), 3.96 (1H, d, *J* = 4.1 Hz, CH), 3.76 (3H, s, CH_3), 1.52 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.6 (C), 160.2 (C), 158.3 (C), 141.4 (C), 138.3 (C), 130.2 (CH), 128.7 (CH), 123.5 (CH), 120.1 (CH), 118.3 (CH), 113.7 (CH), 111.6 (CH), 83.3 (C), 62.9 (CH), 60.2 (CH), 55.2 (CH_3), 28.0 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{21}H_{25}N_2O_4^+$: 369.1809, found 369.1807.

cis-**26fb** (minor diastereomer). White solid, m.p. 172-175 °C; $[\alpha]_D^{25}$ –1.1 (*c* 0.61, $CHCl_3$, 6% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 (2H, dd, *J* = 8.7, 1.1 Hz, Ar), 7.23-7.16 (3H,

m, Ar), 6.98 (1H, t, *J* = 7.4 Hz, Ar), 6.92 (1H, d, *J* = 7.7 Hz, Ar), 6.85-6.84 (1H, m, Ar), 6.78 (1H, ddd, *J* = 8.2, 2.5, 0.8 Hz, Ar), 5.47 (1H, d, *J* = 9.7 Hz, CH), 5.31 (1H, bs, NH), 4.68 (1H, d, *J* = 9.7 Hz, CH), 3.73 (3H, s, CH_3), 1.08 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.6 (C), 159.7 (C), 158.6 (C), 138.2 (C), 137.3 (CH), 129.6 (CH), 128.6 (CH), 123.6 (CH), 120.6 (CH), 120.4 (C), 114.3 (CH), 113.5 (CH), 82.5 (C), 62.6 (CH), 57.5 (CH), 55.2 (CH_3), 27.4 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{21}H_{25}N_2O_4^+$: 369.1809, found 369.1807.

***tert*-Butyl 5-(3-bromophenyl)-2-oxo-1-phenylimidazolidine-4-carboxylate (26gb)**

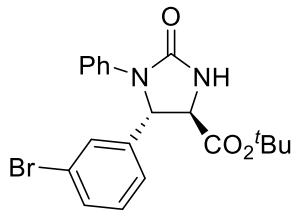


Obtained 77.7 mg (74%) from 69.3 mg (0.25 mmol) of **25g**. The enantiomeric excess (minor isomer: 9%, major isomer 89%) was determined by HPLC (Amylose 1), hexane:^{i}PrOH 90:10, 1 mL/min-1, *cis*-**26gb** (minor diastereomer): minor enantiomer, t_r = 18.3 min, major enantiomer, t_r = 29.0 min, *trans*-(**4*R*,5*S***)-**26gb** (major diastereomer): minor enantiomer, t_r = 20.9 min, major enantiomer, t_r = 26.9 min.

trans-(**4*R*,5*S***)-**26gb** (major diastereomer). White solid, m.p. 163-166 °C; $[\alpha]_D^{25}$ –42.5 (*c* 0.84, $CHCl_3$, 89% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.55 (1H, t, *J* = 1.7 Hz, Ar), 7.44-7.38 (3H, m, Ar), 7.31 (1H, d, *J* = 7.8 Hz, Ar), 7.24-7.15 (3H, m, Ar), 7.01 (1H, t, *J* = 7.4 Hz, Ar), 5.99 (1H, bs, NH), 5.38 (1H, d, *J* = 4.2 Hz, CH), 3.95 (1H, dd, *J* = 4.3, 0.7 Hz, CH), 1.52 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.3 (C), 158.3 (C), 142.0 (C), 138.0 (C), 131.6 (CH), 130.7 (CH), 129.4 (CH), 128.8 (CH), 124.7 (CH), 123.7 (CH), 123.1 (C), 120.2 (CH), 83.6 (C), 62.4 (CH), 60.1 (CH), 28.0 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{20}H_{22}BrN_2O_3^+$: 417.0808, found 417.0801.

cis-**26gb** (minor diastereomer). White solid, m.p. 204-208 °C; $[\alpha]_D^{25}$ +6.9 (*c* 0.77, $CHCl_3$, 9% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 (1H, bs, Ar), 7.43-7.33 (3H, m, Ar), 7.28-7.13 (4H, m, Ar), 7.00 (1H, t, *J* = 7.3 Hz, Ar), 5.45 (1H, d, *J* = 9.6 Hz, CH), 5.30 (1H, bs, NH), 4.70 (1H, d, *J* = 9.6 Hz, CH), 1.12 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.2 (C), 158.3 (C), 138.3 (C), 137.9 (C), 131.9 (CH), 131.3 (CH), 130.4 (CH), 128.8 (CH), 126.3 (CH), 123.4 (CH), 122.3 (C), 120.5 (CH), 83.0 (C), 61.9 (CH), 57.4 (CH), 27.4 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{20}H_{22}BrN_2O_3^+$: 417.0808, found 417.0801.

***tert*-Butyl 5-(3-nitrophenyl)-2-oxo-1-phenylimidazolidine-4-carboxylate (26hb)**



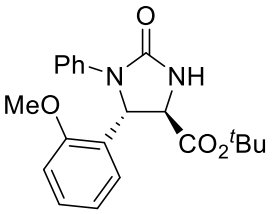
Obtained 88.6 mg (92%) from 60.8 mg (0.25 mmol) of **25h**. The enantiomeric excess (minor isomer: 27%, major isomer 83%) was determined by HPLC (Chiracel IC), hexane:^{i}PrOH 80:20, 1 mL/min, *cis*-**26hb** (minor diastereomer): minor enantiomer, t_r = 39.7 min, major enantiomer, t_r = 27.5 min, *trans*-(**4*R*,5*S***)-**26hb** (major diastereomer): minor enantiomer, t_r = 54.5 min, major enantiomer, t_r = 57.8 min.

trans-(**4*R*,5*S***)-**26hb** (major diastereomer). White solid, m.p. 144-146 °C; $[\alpha]_D^{25}$ –41.6 (*c* 0.84, $CHCl_3$, 83% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.28 (1H, t, *J* = 1.9 Hz, Ar), 8.16 (1H, ddd, *J* = 8.2, 2.2, 1.0 Hz, Ar), 7.72 (1H, d, *J* = 7.8 Hz, Ar), 7.53 (1H, t, *J* = 7.9 Hz, Ar), 7.39 (2H, dd, *J* = 8.7, 1.1 Hz, Ar), 7.29-7.20 (2H, m, Ar), 7.03 (1H, t, *J* = 7.4 Hz,

Ar), 5.70 (1H, bs, NH), 5.57 (1H, d, *J* = 4.6 Hz, CH), 3.98 (1H, d, *J* = 4.6 Hz, CH), 1.54 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.9 (C), 157.9 (C), 148.7 (C), 141.8 (C), 137.5 (C), 132.2 (CH), 130.4 (CH), 129.0 (CH), 124.2 (CH), 123.6 (CH), 121.7 (CH), 120.5 (CH), 84.1 (C), 62.3 (CH), 59.8 (CH), 28.0 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{20}H_{22}N_3O_5^+$: 384.1554, found 384.1549.

cis-**26hb** (minor diastereomer). White solid, m.p. 187-194 °C; $[\alpha]_D^{25}$ +0.6 (*c* 0.38, $CHCl_3$, 27% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.22 (1H, t, *J* = 2.0 Hz, Ar), 8.14 (1H, ddd, *J* = 8.2, 2.3, 1.0 Hz, Ar), 7.70 (1H, d, *J* = 7.8 Hz, Ar), 7.49 (1H, t, *J* = 8.0 Hz, Ar), 7.41-7.31 (2H, m, Ar), 7.22 (2H, t, *J* = 8.0 Hz, Ar), 7.01 (1H, t, *J* = 7.4 Hz, Ar), 5.64 (1H, d, *J* = 9.5 Hz, CH), 5.42 (1H, bs, NH), 4.78 (1H, d, *J* = 9.5 Hz, CH), 1.07 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.9 (C), 158.2 (C), 148.2 (C), 138.2 (C), 137.5 (C), 133.6 (CH), 130.0 (CH), 129.0 (CH), 124.2 (CH), 123.8 (CH), 123.5 (CH), 120.6 (CH), 83.2 (C), 61.7 (CH), 57.3 (CH), 27.5 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{20}H_{22}N_3O_5^+$: 384.1554, found 384.1549.

***tert*-Butyl 5-(2-methoxyphenyl)-2-oxo-1-phenylimidazolidine-4-carboxylate (26ib)**

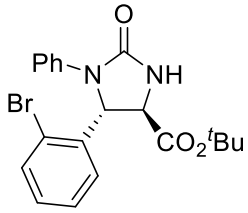


Obtained 77.3 mg (84%) from 57.0 mg (0.25 mmol) of **25i**. The enantiomeric excess (minor isomer: 73%, major isomer 94%) was determined by HPLC (Amylose 1), hexane:^{i}PrOH 90:10, 1 mL/min, *cis*-**26ib** (minor diastereomer): minor enantiomer, t_r = 21.7 min, major enantiomer, t_r = 48.0 min, *trans*-(**4*R*,5*S***)-**26ib** (major diastereomer): minor enantiomer, t_r = 32.5 min, major enantiomer, t_r = 34.9 min.

trans-(**4*R*,5*S***)-**26ib** (major diastereomer). Pale yellow oil; $[\alpha]_D^{25}$ –70.7 (*c* 0.68, $CHCl_3$, 94% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.49 (2H, dd, *J* = 8.8, 1.1 Hz, Ar), 7.35-7.16 (4H, m, Ar), 6.99 (1H, t, *J* = 7.4 Hz, Ar), 6.95-6.86 (2H, m, Ar), 5.82 (1H, d, *J* = 3.0 Hz, CH), 5.68 (1H, bs, NH), 3.93 (1H, d, *J* = 3.0 Hz, CH), 3.92 (3H, s, CH_3), 1.53 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.9 (C), 158.7 (C), 156.4 (C), 138.6 (C), 129.3 (CH), 129.0 (C), 128.6 (CH), 128.2 (CH), 126.8 (CH), 123.0 (CH), 120.8 (CH), 119.3 (CH), 110.65 (CH), 82.5 (C), 59.5 (CH), 57.6 (CH), 55.4 (CH3), 27.9 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{21}H_{25}N_2O_4^+$: 369.1809, found 369.1807.

cis-**26ib** (minor diastereomer). White solid, m.p. 55-59 °C; $[\alpha]_D^{25}$ –17.6 (*c* 0.26, $CHCl_3$, 73% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 (2H, dd, *J* = 8.7, 1.0 Hz, Ar), 7.19 (3H, t, *J* = 8.1 Hz, Ar), 7.14 (1H, dd, *J* = 7.7, 1.6 Hz, Ar), 6.96 (1H, t, *J* = 7.4 Hz, Ar), 6.86 (1H, d, *J* = 8.2 Hz, Ar), 6.78 (1H, t, *J* = 7.5 Hz, Ar), 6.10 (1H, d, *J* = 9.7 Hz, CH), 5.23 (1H, bs, NH), 4.65 (1H, d, *J* = 9.7 Hz, CH), 3.93 (3H, s, CH_3), 1.02 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.4 (C), 159.2 (C), 157.4 (C), 138.4 (C), 129.4 (CH), 128.5 (CH), 128.0 (CH), 123.8 (C), 123.3 (CH), 120.9 (CH), 120.2 (CH), 109.9 (CH), 82.0 (C), 56.3 (CH), 55.4 (CH_3), 54.9 (CH), 27.3 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{21}H_{25}N_2O_4^+$: 369.1809, found 369.1807.

***tert*-Butyl 5-(2-bromophenyl)-2-oxo-1-phenylimidazolidine-4-carboxylate (26jb)**

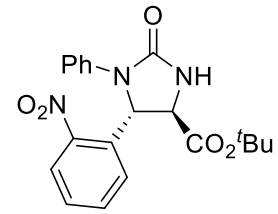


Obtained 86.8 mg (83%) from 69.3 mg (0.25 mmol) of **25j**. The enantiomeric excess (minor isomer: 86%, major isomer 87%) was determined by HPLC (Amylose 1), hexane:^{i}PrOH 80:20, 1 mL/min, *cis*-**26jb** (minor diastereomer): minor enantiomer, t_r = 10.3 min, major enantiomer, t_r = 16.6 min, *trans*-(**4*R*,5*S***)-**26jb** (major diastereomer): minor enantiomer, t_r = 12.9 min, major enantiomer, t_r = 16.9 min.

trans-(**4*R*,5*S***)-**26jb** (major diastereomer). Brown oil; $[\alpha]_D^{25}$ –93.2 (*c* 0.77, $CHCl_3$, 87% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.60 (1H, dd, *J* = 7.9, 1.2 Hz, Ar), 7.44 (2H, dd, *J* = 8.7, 1.0 Hz, Ar), 7.34 (1H, dd, *J* = 7.8, 1.8 Hz, Ar), 7.29-7.20 (3H, m, Ar), 7.16 (1H, dt, *J* = 7.9, 1.9 Hz, Ar), 6.99 (1H, t, *J* = 7.4 Hz, Ar), 5.95 (1H, bs, NH), 5.87 (1H, d, *J* = 2.3 Hz, CH), 3.92 (1H, bs, CH), 1.52 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.2 (C), 158.7 (C), 138.1 (C), 137.7 (C), 133.5 (CH), 129.9 (CH), 128.8 (CH), 128.2 (CH), 127.6 (CH), 123.4 (CH), 122.32 (C), 119.4 (CH), 83.3 (C), 61.8 (CH), 59.4 (CH), 27.9 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{20}H_{22}BrN_2O_3^+$: 417.0808, found 417.0801.

cis-**26jb** (minor diastereomer). Brown oil; $[\alpha]_D^{25}$ –11.2 (*c* 0.56, $CHCl_3$, 86% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.54 (1H, dd, *J* = 7.7, 1.5 Hz, Ar), 7.34 (2H, dd, *J* = 8.7, 1.1 Hz, Ar), 7.29 (1H, dd, *J* = 7.6, 1.9 Hz, Ar), 7.24-7.18 (2H, m, Ar), 7.15 (1H, dd, *J* = 7.6, 1.5 Hz, Ar), 7.10 (1H, dt, *J* = 7.7, 1.9 Hz, Ar), 6.99 (1H, t, *J* = 7.3 Hz, Ar), 6.10 (1H, d, *J* = 10.0 Hz, CH), 5.32 (1H, bs, NH), 4.74 (1H, d, *J* = 10.0 Hz, CH), 1.06 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.9 (C), 158.7 (C), 137.8 (C), 135.1 (C), 132.6 (CH), 130.0 (CH), 129.1 (CH), 128.7 (CH), 128.1 (CH), 124.7 (C), 123.8 (CH), 120.4 (CH), 82.8 (C), 60.6 (CH), 55.8 (CH), 27.4 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{20}H_{22}BrN_2O_3^+$: 417.0808, found 417.0801.

***tert*-Butyl 5-(2-nitrophenyl)-2-oxo-1-phenylimidazolidine-4-carboxylate (26kb)**

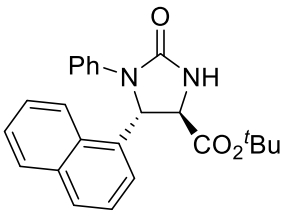


Obtained 87.3 mg (91%) from 60.8 mg (0.25 mmol) of **25k**. The enantiomeric excess (minor isomer: 70%, major isomer 67%) was determined by HPLC (Chiracel IC), hexane:^{i}PrOH 80:20, 1 mL/min-1, *cis*-**26kb** (minor diastereomer): minor enantiomer, t_r = 61.8 min, major enantiomer, t_r = 66.0 min, *trans*-(**4*R*,5*S***)-**26kb** (major diastereomer): minor enantiomer, t_r = 18.0 min, major enantiomer, t_r = 20.8 min. Both diastereomers could not be separated by column chromatography.

trans-(**4*R*,5*S***)-**26kb** (major diastereomer). Yellow oil; $[\alpha]_D^{25}$ –49.2 (*c* 0.57, $CHCl_3$, for the diastereomer mixture, *trans:cis* 64:36); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.07 (1H, dd, *J* = 8.1, 1.0 Hz, Ar), 7.65-7.40 (4H, m, Ar), 7.28-7.22 (2H, m, Ar), 7.19-7.13 (1H, m, Ar), 7.02 (1H, t, *J* = 7.4 Hz, Ar), 6.20 (1H, d, *J* = 2.4 Hz, CH), 5.55 (1H, bs, NH), 3.94 (1H, d, *J* = 3.94, CH), 1.53 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.0 (C), 158.4 (C), 147.8 (C), 137.9 (C), 134.2 (CH), 134.1 (C), 129.4 (CH), 129.0 (CH), 128.9 (CH), 128.2 (CH), 127.8 (CH), 125.6 (CH), 123.8 (CH), 119.5 (CH), 83.6 (C), 59.6 (CH), 58.4 (CH), 27.9 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{20}H_{22}N_3O_5^+$: 384.1554, found 384.1549.

cis-**26kb** (minor diastereomer). **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum, of the diastereomer mixture, δ 8.13 (1H, dd, *J* = 7.9, 1.3 Hz, Ar), 7.65-7.40 (3H, m, Ar), 7.33 (2H, dd, *J* = 8.7, 1.1 Hz, Ar), 7.23-7.22 (1H, m, Ar), 7.19-7.13 (1H, m, Ar), 7.05 (1H, m, Ar), 6.57 (1H, d, *J* = 10.0 Hz, CH), 5.46 (1H, bs, NH), 4.88 (1H, d, *J* = 10.0 Hz, Ar), 1.01 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.3 (C), 158.9 (CH), 149.0 (C), 137.6 (C), 134.4 (CH), 131.8 (C), 129.6 (CH), 129.4 (CH), 125.3 (CH), 125.2 (CH), 124.5 (CH), 120.9 (CH), 82.9 (C), 57.2 (CH), 56.1 (CH), 27.3 (CH_3).

***tert*-Butyl 5-(naphthalen-1-yl)-2-oxo-1-phenylimidazolidine-4-carboxylate (26lb)**

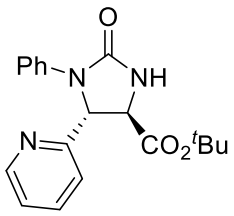


Obtained 73.4 mg (75%) from 62.1 mg (0.25 mmol) of **25l**. The enantiomeric excess (minor isomer: 68%, major isomer 94%) was determined by HPLC (Chiracel IC), hexane:^{i}PrOH 80:20, 1 mL/min, *cis*-**26lb** (minor diastereomer): minor enantiomer, t_r = 33.0 min, major enantiomer, t_r = 46.1 min, *trans*-(**4*R*,5*S***)-**26lb** (major diastereomer): minor enantiomer, t_r = 19.6 min, major enantiomer, t_r = 22.8 min.

trans-(**4*R*,5*S***)-**26lb** (major diastereomer). Grey oil; $[\alpha]_D^{25}$ –96.0 (*c* 0.81, $CHCl_3$, 94% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.44 (1H, d, *J* = 8.3 Hz, Ar), 7.95 (1H, d, *J* = 7.7 Hz, Ar), 7.83 (1H, d, *J* = 8.0 Hz, Ar), 7.65 (1H, dt, *J* = 6.9, 1.5 Hz, Ar), 7.58 (1H, t, *J* = 6.9 Hz, Ar), 7.50 (2H, d, *J* = 8.1 Hz, Ar), 7.46 (1, d, *J* = 7.4 Hz, Ar), 7.43-7.36 (1H, m, Ar), 7.19 (2H, t, *J* = 8.0 Hz, Ar), 6.97 (1H, t, *J* = 7.4 Hz, Ar), 6.24 (1H, bs, CH), 5.73 (1H, bs, NH), 3.97 (1H, bs, CH), 1.60 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.0 (C), 158.6 (C), 138.6 (C), 134.3 (CH), 133.4 (CH), 129.9 (C), 129.3 (CH), 128.9 (C), 128.7 (CH), 126.7 (CH), 125.9 (CH), 125.5 (CH), 123.0 (C), 122.5 (CH), 118.8 (CH), 83.7 (C), 59.52 (CH), 59.50 (CH), 28.0 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{24}H_{25}N_2O_3^+$: 389.1860, found 389.1841.

cis-**26lb** (minor diastereomer). Colorless oil; $[\alpha]_D^{25}$ –2.4 (*c* 0.60, $CHCl_3$, 68% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.17 (1H, d, *J* = 8.4 Hz, Ar), 7.89 (1H, d, *J* = 8.1 Hz, Ar), 7.75 (1H, d, *J* = 8.1 Hz, Ar), 7.68-7.60 (1H, m, Ar), 7.58-7.51 (1H, m, Ar), 7.45 (1H, dd, *J* = 7.3, 0.9 Hz, Ar), 7.36-7.29 (3H, m, Ar), 7.18-7.08 (2H, m, Ar), 6.93 (1H, t, *J* = 7.4 Hz, Ar), 6.47 (1H, d, *J* = 9.9 Hz, CH), 5.36 (1H, bs, NH), 4.86 (1H, d, *J* = 9.9 Hz, CH), 0.60 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.0 (C), 159.1 (C), 138.4 (C), 133.6 (C), 131.7 (C), 131.0 (C), 129.1 (CH), 128.9 (CH), 128.6 (CH), 126.7 (CH), 125.8 (CH), 125.7 (CH), 125.4 (CH), 123.4 (CH), 122.6 (CH), 120.1 (CH), 82.2 (C), 57.4 (CH), 56.9 (CH), 26.8 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for C24H25N2O3+: 389.1860, found 389.1841.

***tert*-Butyl 2-oxo-1-phenyl-5-(pyridin-2-yl)imidazolidine-4-carboxylate (26mb)**



Obtained 84.2 mg (99%) from 49.8 mg (0.25 mmol) of **25m**. The enantiomeric excess (minor isomer: 7%, major isomer 95%) was determined by HPLC (Amylose 1), hexane:^{i}PrOH 80:20, 1 mL/min, *cis*-**26mb** (minor diastereomer): minor enantiomer, t_r = 28.8 min, major enantiomer, t_r = 25.0 min, *trans*-(**4*R*,5*S***)-**26mb** (major

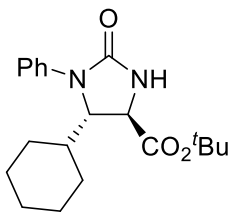
diastereomer): minor enantiomer, t_r = 16.4 min, major enantiomer, t_r = 30.4 min. Both diastereomers could not be separated by column chromatography.

trans-(**4*R*,5*S***)-**26mb** (major diastereomer). Yellow oil; $[\alpha]_D^{25}$ –50.1 (*c* 0.96, $CHCl_3$, for the diastereomer mixture, *trans:cis* 88:12); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.65 (1H, ddd, *J* = 4.8, 1.7, 0.9 Hz, Ar), 7.63 (1H, td, *J* = 7.7, 1.8 Hz, Ar), 7.50 (2H, dd, *J* = 8.7, 1.0 Hz, Ar), 7.32-7.18 (4H, m, Ar), 7.01 (1H, t, *J* = 7.4 Hz, Ar), 6.17 (1H, bs, NH), 5.60 (1H, d, *J* = 3.5 Hz, CH), 4.19 (1H, dd, *J* = 3.5, 0.7 Hz, CH), 1.52 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.4 (C), 158.44 (C), 158.37 (C), 150.0 (CH), 138.3 (C), 137.0 (CH), 128.7 (CH), 123.3 (CH), 123.1 (CH), 120.9 (CH), 119.7 (CH), 83.1 (C), 64.1 (CH), 58.7 (CH), 27.8 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{19}H_{22}N_3O_3^+$: 340.1656, found 340.1657.

cis-**26mb** (minor diastereomer). **^{1}H NMR** (300 MHz, $CDCl_3$), signals taken from the NMR spectrum, of the diastereomer mixture, δ 8.60 (1H, dd, *J* = 4.8, 0.9 Hz, Ar), 7.56 (1H, dd, *J* = 6.2, 1.5 Hz, Ar), 7.44 (2H, d, *J* = 7.9 Hz, Ar), 7.38-7.18 (4H, m, Ar), 6.98 (1H, t, *J* 7.4 Hz, Ar), 6.07 (1H, bs, NH), 5.75 (1H, dd, *J* = 9.9, 3.3 Hz, CH), 4.82 (1H, ddd, *J* = 9.9, 1.6, 0.8 Hz, CH), 1.1 (9H, d, *J* = 1.8 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.7 (C), 158.8 (C), 156.3 (C), 149.1 (CH), 138.1 (C), 136.9 (CH), 128.5 (CH), 125.5 (CH), 122.3 (CH), 120.1 (CH), 82.4 (C), 63.8 (CH), 56.6 (CH), 27.3 (CH_3).

ent-**26mb** Obtained 83.1 mg (98%) from 49.8 mg (0.25 mmol) of **25m**, using **SQV'** as organocatalyst. The enantiomeric excess (minor isomer: 22%, major isomer 92%) was determined by HPLC (Amylose 1), hexane:^{i}PrOH 80:20, 1 mL/min-1, *cis*-**26mb** (minor diastereomer): minor enantiomer, t_r = 23.9 min, major enantiomer, t_r = 26.3 min, *trans*-(**4*R*,5*S***)-**26mb** (major diastereomer): minor enantiomer, t_r = 29.7 min, major enantiomer, t_r = 15.7 min. $[\alpha]_D^{25}$ +45.1 (*c* 0.97, $CHCl_3$, for the diastereomer mixture, *trans:cis* 86:14);

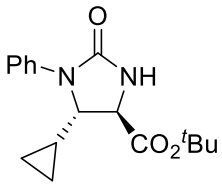
***tert*-Butyl 5-cyclohexyl-2-oxo-1-phenylimidazolidine-4-carboxylate (26nb)**



Obtained 58.3 mg (67%) from 51.0 mg (0.25 mmol) of **25n**. The enantiomeric excess (minor isomer: nd, major isomer 91%) was determined by HPLC (Amylose 1), hexane:^{i}PrOH 90:10, 1 mL/min-1, *trans*-(**4*R*,5*S***)-**26nb** (major diastereomer): minor enantiomer, t_r = 13.5 min, major enantiomer, t_r = 15.9 min.

trans-(**4*R*,5*S***)-**26nb** (major diastereomer). White solid, m.p. 180-187 °C; $[\alpha]_D^{25}$ –34.9 (*c* 0.95, $CHCl_3$, 91% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 (2H, dd, *J* = 8.7, 1.2 Hz, Ar), 7.38-7.30 (2H, m, Ar), 7.10 (1H, t, *J* = 7.3 Hz, Ar), 5.59 (1H, bs, NH), 4.39 (1H, t, *J* = 3.3 Hz, CH), 3.92 (1H, d, *J* = 3.1 Hz, CH), 1.80-1.57 (6H, m), 1.47 (9H, s, CH_3), 1.26-0.90 (5H, m); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.0 (C), 158.4 (C), 137.8 (C), 128.9 (CH), 124.1 (CH), 122.0 (CH), 82.7 (C), 63.8 (CH), 53.1 (CH), 38.7 (CH), 28.4 (CH_2), 27.9 (CH_3), 26.3 (CH_2), 26.0 (CH_2), 25.5 (CH_2), 25.4 (CH_2); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{20}H_{29}N_2O_3^+$: 345.2173, found 345.2161.

***tert*-Butyl 5-cyclopropyl-2-oxo-1-phenylimidazolidine-4-carboxylate (26ob)**

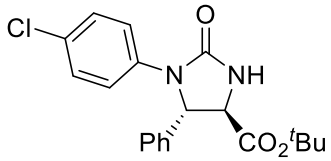


Obtained 72.9 mg (96%) from 40.4 mg (0.25 mmol) of **25o**. The enantiomeric excess (minor isomer: 68%, major isomer 99%) was determined by HPLC (Amylose 1), hexane:^{i}PrOH 80:20, 1 mL/min, *cis*-**26ob** (minor diastereomer): minor enantiomer, t_r = 9.8 min, major enantiomer, t_r = 20.7 min, *trans*-(**4*R*,5*S***)-**26ob** (major diastereomer): minor enantiomer, t_r = 11.4 min, major enantiomer, t_r = 18.3 min.

trans-(**4*R*,5*S***)-**26ob** (major diastereomer). White solid, m.p. 142-145 °C; $[\alpha]_D^{25}$ –64.5 (*c* 0.79, $CHCl_3$, 99% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 (2H, dd, *J* = 8.6, 1.4 Hz, Ar), 7.36-7.29 (2H, m, Ar), 7.14 (1H, t, *J* = 7.0 Hz, Ar), 5.8 (1H, bs, NH), 3.99 (1H, d, *J* = 3.5 Hz, CH), 3.75 (1H, dd, *J* = 8.7, 3.5 Hz, CH), 1.46 (9H, s, CH_3), 1.21-1.05 (1H, m, CH), 0.56-0.40 (2H, m, CH_2), 0.35-0.17 (2H, m, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.3 (C), 158.5 (C), 138.1 (C), 128.8 (CH), 125.0 (CH), 124.0 (CH), 82.7 (C), 64.9 (CH), 58.3(CH), 27.8 (CH_3), 15.6 (CH), 5.47 (CH_2), 0.7 (CH_2); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{17}H_{23}N_2O_3^+$: 303.1703, found 303.1693.

cis-**26ob** (minor diastereomer). White solid, m.p. 177-180 °C; $[\alpha]_D^{25}$ +17.9 (*c* 0.81, $CHCl_3$, 68% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40-7.30 (4H, m, Ar), 7.19 (1H, ddd, *J* = 8.6, 5.7, 2.5 Hz, Ar), 5.15 (1H, bs, NH), 4.41 (1H, d, *J* = 8.6 Hz, CH), 3.75-3.67 (1H, m, CH), 1.52 (9H, s, CH_3), 1.03- 0.89 (1H, m, CH), 0.52-0.31 (2H, m, CH_2), 0.23 (1H, td, *J* = 9.7, 5.0 Hz, CH), –0.01 (1H, td, *J* = 9.8, 4.8 Hz, CH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.7 (C), 159.3 (C), 138.0 (C), 128.9 (CH), 125.7 (CH), 125.6 (CH), 82.6 (C), 65.0 (CH), 57.6 (CH), 28.0 (CH_3), 10.8 (CH), 4.8 (CH_2), 2.5 (CH_2); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{17}H_{23}N_2O_3^+$: 303.1703, found 303.1693.

***tert*-Butyl 1-(4-chlorophenyl)-2-oxo-5-phenylimidazolidine-4-carboxylate (26pb)**



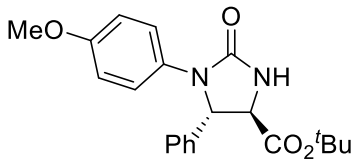
Obtained 77.5 mg (83%) from 58.2 mg (0.25 mmol) of **25p**. The enantiomeric excess (minor isomer: 6%, major isomer 84%) was determined by HPLC (Amylose 1), hexane:^{i}PrOH 80:20, 1 mL/min, *cis*-**26pb** (minor diastereomer): minor enantiomer, t_r = 9.4 min, major enantiomer, t_r = 18.8 min, *trans*-(**4*R*,5*S***)-**26pb** (major diastereomer): minor enantiomer, t_r = 20.2 min, major enantiomer, t_r = 31.0 min.

trans-(**4*R*,5*S***)-**26pb** (major diastereomer). White solid, m.p. 186-189 °C; $[\alpha]_D^{25}$ –46.1 (*c* 0.90, $CHCl_3$, 84% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* = 9.1 Hz, Ar), 7.36-7.27 (5H, m, Ar), 7.16 (2H, d, *J* = 9.1 Hz, Ar), 5.95 (1H, bs, NH), 5.38 (1H, d, *J* = 4.3 Hz, CH), 3.98 (1H, d, *J* = 4.3 Hz, CH), 1.52 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.4 (C), 158.2 (C), 139.2 (C), 136.9 (C), 129.2 (CH), 128.7 (CH), 128.54 (CH), 128.49 (C), 126.1 (CH), 121.2 (CH), 83.4 (C), 62.9 (CH), 60.2 (CH), 28.0 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{20}H_{22}ClN_2O_3^+$: 373.1313, found 373.1296.

cis-**26pb** (minor diastereomer). White solid, m.p. 202-206 °C; $[\alpha]_D^{25}$ –8.4 (*c* 0.66, $CHCl_3$, 6% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 (2H, d, *J* = 9.1 Hz, Ar), 7.31-7.27 (5H, m, Ar), 7.14 (2H, d, *J* = 9.1 Hz, Ar), 5.46 (1H, d, *J* = 9.7 Hz, CH), 5.20 (1H, bs, NH), 4.69 (1H, d, *J* = 9.6 Hz, CH), 1.05 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) 167.3 (C), 158.2

(C), 136.8 (C), 135.4 (C), 128.9 (C), 128.7 (CH), 128.7 (CH), 128.0 (CH), 121.5 (CH), 82.8 (C), 62.5 (CH), 57.3 (CH), 27.3 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{20}H_{22}ClN_2O_3^+$: 373.1313, found 373.1296.

***tert*-Butyl 1-(4-methoxyphenyl)-2-oxo-5-phenylimidazolidine-4-carboxylate (26qb)**

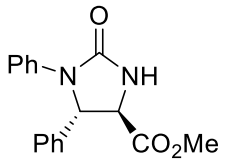


Obtained 22.3 mg (24%) from 57.0 mg (0.25 mmol) of **25q**. The enantiomeric excess (minor isomer: 2%, major isomer 91%) was determined by HPLC (Amylose 1), hexane:^{i}PrOH 80:20, 1 mL/min, *cis*-**26qb** (minor diastereomer): minor enantiomer, t_r = 14.8 min, major enantiomer, t_r = 31.0 min, *trans*-(**4*R*,5*S***)-**266qb** (major diastereomer): minor enantiomer, t_r = 33.3 min, major enantiomer, t_r = 58.0 min.

trans-(**4*R*,5*S***)-**26qb** (major diastereomer). White solid, m.p. 177-179 °C; $[\alpha]_D^{25}$ –24.1 (*c* 0.87, $CHCl_3$, 91% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39-7.31 (4H, m, Ar), 7.27 (2H, d, *J* = 9.1 Hz, Ar), 6.76 (2H, d, *J* = 9.1 Hz, Ar), 5.32 (1H, d, *J* = 4.5 Hz, CH), 5.27 (1H, bs, NH), 3.98 (1H, d, *J* = 4.5 Hz, CH), 3.71 (3H, s, CH_3), 1.52 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.6 (C), 158.6 (C), 156.2 (C), 139.7 (C), 131.1 (C), 129.1 (CH), 128.4 (CH), 126.4 (CH), 122.9 (CH), 114.1 (CH), 83.3 (C), 63.9 (CH), 60.3 (CH), 55.3 (CH_3), 28.0 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{21}H_{25}N_2O_4^+$: 369.1809, found 369.1806.

cis-**26qb** (minor diastereomer). White solid, m.p. 171-179 °C; $[\alpha]_D^{25}$ –2.0 (*c* 0.37, $CHCl_3$, 2% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33-7.25 (5H, m, Ar), 7.23 (2H, d, *J* = 9.1 Hz, Ar), 6.74 (2H, d, *J* = 9.1 Hz, Ar), 5.42 (1H, d, *J* = 9.7 Hz, CH), 5.05 (1H, bs, NH), 4.69 (1H, d, *J* = 9.7 Hz, CH), 3.70 (3H, s, CH_3), 1.04 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.7 (C), 159.0 (C), 156.2 (C), 136.0 (C), 131.0 (C), 128.6 (CH), 128.5 (CH), 128.1 (CH), 123.3 (CH), 114.0 (CH), 82.4 (C), 63.3 (CH), 57.6 (CH), 55.3 (CH_3), 27.3 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{21}H_{25}N_2O_4^+$: 369.1809, found 369.1806.

Methyl 2-oxo-1,5-diphenylimidazolidine-4-carboxylate (26aa)

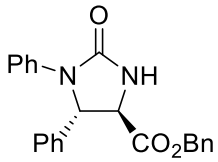


Obtained 30.8 mg (41%) from 49.5 mg (0.25 mmol) of **25a** and 30 µL (0.33 mmol) of methyl isocyanoacetate (**2a**). The enantiomeric excess (minor isomer: 9%, major isomer 84%) was determined by HPLC (Amylose 1), hexane:^{i}PrOH 80:20, 1 mL/min, *cis*-**26aa** (minor diastereomer): minor enantiomer, t_r = 19.3 min, major enantiomer, t_r = 12.1 min, *trans*-(**4*R*,5*S***)-**26aa** (major diastereomer): minor enantiomer, t_r = 33.2 min, major enantiomer, t_r = 23.6 min.

trans-(**4*R*,5*S***)-**26aa** (major diastereomer). White solid, m.p. 84-91 °C; $[\alpha]_D^{25}$ –39.3 (*c* 1.0, $CHCl_3$, 84% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 (2H, dd, *J* = 8.8, 1.1 Hz, Ar), 7.40-7.27 (5H, m, Ar), 7.25-7.19 (2H, m, Ar), 6.99 (1H, t, *J* = 6.8 Hz, Ar), 5.63 (1H, bs, NH), 5.47 (1H, d, *J* = 3.5 Hz, CH), 4.07 (1H, d, *J* = 3.5 Hz, CH), 3.85 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.2 (C), 158.3 (C), 139.3 (C), 138.1 (C), 129.2 (CH), 128.7 (CH), 128.5 (CH), 126.0 (CH), 123.6 (CH), 120.0 (CH), 63.0 (CH), 59.7 (CH), 53.1 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{17}H_{17}N_2O_3^+$: 297.1234, found 297.1222.

cis-**26aa** (minor diastereomer). White solid, m.p. 178-180 °C; $[\alpha]_D^{25}$ +5.0 (*c* 0.34, $CHCl_3$, 9% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 (2H, dd, *J* = 8.7, 1.1 Hz, Ar), 7.30-7.26 (5H, m, Ar), 7.24-7.17 (2H, m, Ar), 6.99 (1H, t, *J* = 7.4 Hz, Ar), 5.58 (1H, d, *J* = 9.5 Hz, CH), 5.31 (1H, bs, NH), 4.77 (1H, d, *J* = 4.77 Hz, CH), 3.25 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.3 (C), 158.8 (C), 137.9 (C), 135.2 (C), 128.8 (CH), 128.7 (CH), 128.6 (CH), 123.8 (CH), 120.6 (CH), 62.6 (CH), 57.6 (CH), 52.0 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{17}H_{17}N_2O_3^+$: 297.1234, found 297.1231.

Benzyl 2-oxo-1,5-diphenylimidazolidine-4-carboxylate (26ad)

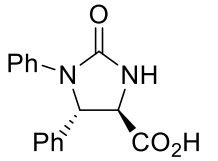


Obtained 60.0 mg (60%) from 49.5 mg (0.25 mmol) of **25a** and 57.9 mg (0.33 mmol) of benzyl isocyanoacetate (**2d**). The enantiomeric excess (minor isomer: 23%, major isomer 82%) was determined by HPLC (Amylose 1), hexane:^{i}PrOH 80:20, 1 mL/min, *cis*-**26ad** (minor diastereomer): minor enantiomer, t_r = 26.9 min, major enantiomer, t_r = 14.8 min, *trans*-(**4*R*,5*S***)-**26ad** (major diastereomer): minor enantiomer, t_r = 29.0 min, major enantiomer, t_r = 35.2 min.

trans-(**4*R*,5*S***)-**26ad** (major diastereomer). White solid, m.p. 145-152 °C; $[\alpha]_D^{25}$ –69.6 (*c* 0.80, $CHCl_3$, 82% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 (2H, d, *J* = 8.8, 1.1 Hz, Ar), 7.37 (5H, s, Ar), 7.35-7.28 (5H, m, Ar), 7.24-7.18 (2H, m, Ar), 7.00 (1H, t, *J* = 7.4 Hz, Ar), 5.80 (1H, bs, NH), 5.45 (1H, d, *J* = 3.8 Hz, CH), 5.30 (1H, d, *J* = 12.1 Hz, CH), 5.23 (1H, d, *J* = 12.1 Hz, CH), 4.11 (1H, d, *J* = 3.8 Hz, CH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.5 (C), 158.3 (C), 139.2 (C), 138.1 (C), 134.8 (C), 129.2 (CH), 128.7 (CH), 128.5 (CH), 128.5 (CH), 128.4 (CH), 126.1 (CH), 123.6 (CH), 120.1 (CH), 67.8 (CH_2), 63.0 (CH), 59.9 (CH); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{23}H_{21}N_2O_3^+$: 373.1547, found 373.1528.

cis-**26ad** (minor diastereomer). White solid, m.p. 195-200 °C; $[\alpha]_D^{25}$ +1.9 (*c* 0.61, CHCl3, 23% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 (2H, dd, *J* = 8.7, 1.0 Hz, Ar), 7.35-7.26 (8H, m, Ar), 7.25-7.19 (2H, m, Ar), 7.09 (2H, dd, *J* = 6.6, 3.0 Hz, Ar), 7.00 (1H, t, *J* = 7.4 Hz, Ar), 5.59 (1H, d, *J* = 9.5 Hz, CH), 5.54 (1H, bs, NH), 4.83 (1H, d, *J* = 12.0 Hz, CH), 4.81 (1H, d, *J* = 9.5 Hz, CH), 4.41 (1H, d, *J* = 12.0 Hz, CH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.8 (C), 158.8 (C), 137.9 (C), 135.1 (C), 134.4 (C), 128.8 (CH), 128.6 (CH), 128.54 (CH), 128.49 (CH), 127.5 (CH), 123.8 (CH), 120.7 (CH), 67.4 (CH_2), 62.6 (CH), 57.6 (CH); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{23}H_{21}N_2O_3^+$: 373.1547, found 373.1550.

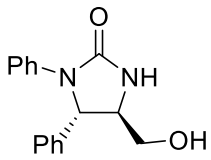
(*4R,5S*)-2-Oxo-1,5-diphenylimidazolidine-4-carboxylic acid (29)



Trifluoroacetic acid (0.3 mL) was added to a solution of compound **26ab** (20 mg, 0.059 mmol, 90% *ee*) in dichloromethane (0.7 mL). The mixture was stirred at room temperature for 5 h and the volatiles were removed under reduced pressure to give 14.1 mg (89%) of acid **29**. White solid, m.p. 166 °C (dec.); $[\alpha]_D^{25}$ –44.5 (*c* 1.0, MeOH, 90% *ee*); **^{1}H NMR** (300 MHz, MeOD) δ 10.16 (1H, s, COOH), 7.38-7.26 (7H, m, Ar), 7.19 (2H, t, *J* = 7.0 Hz, Ar), 6.99 (1H, t, *J* = 7.2 Hz, Ar), 5.53 (1H, bs, CH), 4.14 (1H, bs, CH); **^{13}C NMR** (125 MHz, MeOD) 173.7 (C), 160.8 (C), 139.1 (C), 137.3 (C), 129.2 (CH), 128.8

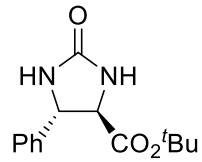
(CH), 128.6 (CH), 126.2 (CH), 124.4 (CH), 121.1 (CH), 63.5 (CH), 60.4 (CH); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{16}H_{15}N_2O_3^+$: 283.1077, found 283.1076.

(4*R*,5*S*)-4-(Hydroxymethyl)-1,5-diphenylimidazolidin-2-one (30)



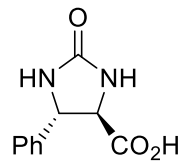
A 2M solution of $BH_3 \cdot SMe_2$ in THF (75 µL, 0.149 mmol) was added to a solution of acid **29** in dry THF (1 mL) under N_2 atmosphere. The mixture was stirred at room temperature for 24h. The reaction was quenched with MeOH (3 mL) and the volatiles were removed under reduced pressure, this operation was repeated three additional times. Column chromatography eluting with EtOAc gave 12.1 mg (76%) of compound **30**. The enantiomeric excess was determined by HPLC (Amylose 1) hexane:^{i}PrOH,80:20, 1ml/min, minor enantiomer, t_r = 20,4 min, major enantiomer, t_r = 16,5 min. White solid; m.p. = 178-181 °C; $[\alpha]_D^{25}$ – 16.9 (*c* 0.66, MeOH, 90% *ee*); **^{1}H RMN** (300 MHz, DMSO) δ 7.45 (2H, d, *J* = 8.0 Hz, Ar), 7.37-7.12 (7H, m, Ar), 6.89 (1H, t, *J* = 7.3 Hz, Ar), 5.19 (1H, d, *J* = 3.8 Hz, CH), 3.99 (2H, bs), 3.50 (2H, d, *J* = 5.2 Hz, CH), 3.36-3.23 (1H, m, CH); **^{13}C NMR** (75 MHz, DMSO) δ 158.2 (C), 141.4 (C), 139.6 (C), 128.9 (CH), 128.4 (CH), 127.6 (CH), 126.0 (CH), 121.9 (CH), 118.9 (CH), 63.1 (CH_2), 61.0 (CH), 59.8 (CH); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{16}H_{17}N_2O_2^+$: 269.1285, found 269.1287.

***tert*-butyl (4*R*,5*S*)-2-oxo-5-phenylimidazolidine-4-carboxylate (31)**



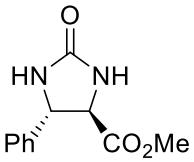
A solution of CAN (101.3 mg, 0.185 mmol) in water (0.5 mL) was added to a solution of compound *trans*-**26qb** (22.7 mg, 0.062 mmol, 91% ee) in MeCN (1.5 mL) at 0 °C. The reaction was warmed to room temperature and stirred until consumption of starting material (TLC). Then, the mixture was diluted with EtOAc (10 mL) and washed with aqueous saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. After removing the solvent under reduced pressure, column chromatography eluting with hexane:EtOAc (4:6 to 3:7) yielded 12.2 mg (75%) of compound **31**. The enantiomeric excess (88%) was determined by HPLC (Amylose 1), hexane:^{i}PrOH 80:20, 1 mL/min, minor enantiomer, t_r = 8.0 min, major enantiomer, t_r = 12.8 min. White solid; m.p. 175-178 °C; $[\alpha]_D^{25}$ –39.6 (*c* 0.81, $CHCl_3$, 88% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44-7.29 (5H, m, Ar), 5.54 (2H, bs, 2 × NH), 4.93 (1H, d, *J* = 5.1 Hz, CH), 3.99 (1H, d, *J* = 5.1 Hz, CH), 1.50 (9H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.7 (C), 162.0 (C), 141.2 (C), 128.9 (CH), 128.4 (CH), 126.1 (CH), 83.0 (C), 62.9 (CH), 59.1 (CH), 28.0 (CH_3); HRMS (ESI) *m*/*z* $[M+H]^+$ calculated for $C_{14}H_{19}N_2O_3^+$: 263.1390, found 263.1378.

(4*R*,5*S*)-2-Oxo-5-phenylimidazolidine-4-carboxylic acid (32)



Trifluoroacetic acid (0.3 mL) was added to a solution of compound **31** (11 mg, 0.042 mmol, 89% ee) in DCM (0.6 mL). The mixture was stirred at room temperature for 7 h and the volatiles were removed under reduced pressure to give 7.5 mg (87%) of acid **32**. **^{1}H NMR** (300 MHz, MeOD) δ 7.42-7.29 (5H, m, Ar), 4.88 (1H, d, *J* = 4.6 Hz, CH), 4.11 (1H, d, *J* = 4.6 Hz, CH); **^{13}C NMR** (75 MHz, MeOD) δ 173.3 (C), 165.0 (C), 143.1 (C), 129.9 CH), 129.4 (CH), 126.7 (CH), 63.8 (CH), 60.5 (CH).

Methyl (4*R*,5*S*)-2-oxo-5-phenylimidazolidine-4-carboxylate (33)



A solution of the crude product **32** (7.5 mg, 0.036 mmol) and a drop of concentrated sulfuric acid in MeOH (2 mL) was heated at reflux temperature for 6 hours. The mixture was concentrated under reduced pressure, diluted in EtOAc (30 mL), washed with aqueous saturated $NaHCO_3$ (5 mL), brine (5 mL) and dried over $MgSO_4$. After filtering and removing the solvent under reduced pressure 7.1 mg (89%) of methyl ester **33** were obtained. The enantiomeric excess (89%) was determined by HPLC (Amylose 1), hexane:^{i}PrOH 80:20, 1 mL/min^{-1}, minor enantiomer, t_r = 8.7 min, major enantiomer, t_r = 15.4 min. White solid; m.p. 199-206 °C (dec.); $[\alpha]_D^{25}$ –85.5 (*c* 0.46, MeOH, 89% *ee*), $[\alpha]_D^{25}$ –101.7 (*c* 1.0, MeOH);[100] **^{1}H NMR** (300 MHz, MeOD) δ 7.42-7.29 (5H, m, Ar), 4.88 (1H, d, *J* = 4.6 Hz, CH), 4.11 (1H, d, *J* = 4.6 Hz, CH), 3.82 (3H, s, CH_3) **^{13}C NMR** (75 MHz, MeOD) δ 173.3 (C), 165.0 (C), 143.1 (C), 129.9 (CH), 129.4 (CH), 127.0 (CH), 63.8 (CH), 60.5 (CH), 53.1 (CH_3); HRMS (ESI) *m/z* $[M+H]^+$ calculated for $C_{14}H_{19}N_2O_3^+$: 263.1390, found 263.1378. Data consistent with the literature.[100]

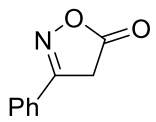
5.4 Enantioselective catalytic synthesis of diazaspirocycles from 4-alkylideneisoxazol-5-ones and isocyanoacetate esters

5.4.1 Synthesis of isoxazol-5-ones 35

All the 4-alquilideneisoxazol-5-ones used in this work were synthetized in the laboratory in an experimental procedure of two steps.[109,110]

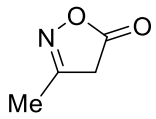
Synthesis and characterization data for isoxazol-5-ones 35

3-Phenylisoxazol-5(4*H*)-one (35a)



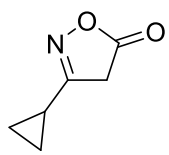
A procedure described in the literature was followed. To a round-bottom flask containing hydroxylamine hydrochloride (4.0 g, 57.8 mmol, 1.0 equiv.) and K_2CO_3 (4.0 g, 28.9 mmol, 0.5 equiv.) was added a 1:1 EtOH:H_2O mixture (55 mL). The mixture was stirred for 5 min and ethyl benzoylacetate was added (**34a**, 10 mL, 57.8 mmol, 1.0 equiv.) After 20 h an abundant amount of precipitate was observed, which was filtered and washed with cold water to yield product **35a** (9.3 g, 99%), which was used without further purification. Pale pink solid; **^{1}H NMR** (300MHz, $CDCl_3$) δ 7.65–7.61 (3H, m, Ar), 7.58–7.44 (2H, m, Ar), 3.81 (2H, s, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.7 (C), 163.0 (C), 132.2 (CH), 129.2 (CH), 127.6 (C), 126.6 (CH), 34.0 (CH_2). Data consistent with the literature.[111]

3-Methylisoxazol-5(4*H*)-one (35b)



A literature procedure was followed. To a suspension of hydroxylamine hydrochloride (4.3 g, 62.4 mmol, 1.5 equiv.) in EtOH (80 mL) was added anhydrous sodium acetate (5.1 g, 62.4 mmol, 1.5 equiv.) and the mixture was stirred for 5 min. Ethyl acetoacetate (**34b**, 5.3 mL, 41.6 mmol, 1.0 equiv.) was added and the reaction was heated to reflux. After 1 h the complete consumption of the ethyl acetoacetate was observed (TLC), as well as the presence of the desired product and the oxime-type intermediate. 0.2 mL HCl 37% were added at room temperature and the reaction is brought again to reflux until complete consumption of the oxime intermediate (TLC, *ca*. 4 h). The reaction was filtered by gravity to remove the formed NaCl and the filtrate was concentrated under reduced pressure. The reaction crude was suspended in AcOEt, and a white precipitate appeared, which was filtered by gravity. The filtrate is concentrated under reduced pressure and purified through flash column chromatography (eluent gradient: Hexane:EtOAc 8:2, 7:3 and 5:5) to obtain 1.3 g of **35b** (32%). Brown oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.39 (2H, q, J = 0.9 Hz, CH_2), 2.15 (3H, d, J = 0.9 Hz, CH3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.2 (C), 163.4 (C), 37.0 (CH_3), 14.8 (CH_2). Data consistent with the literature.[110]

3-Cyclopropylisoxazol-5(4H)-one (35c)



A literature procedure was followed.[118] A mixture of hydroxylamine hydrochloride (1.1 g, 15.7 mmol) and methyl 3-cyclopropyl-3-oxopropanoate (**35c**, 1.7 mL, 14.1 mmol) was stirred for 5 min. Et_3N (2.2 mL, 15.7 mmol) was then added dropwise and the reaction was refluxed for 1.5 h. The reaction was allowed to cool to room temperature and concentrated under reduced pressure. Purification by flash column chromatography afforded 1.46 g (83%) of **36c**. Oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.25 (2H, t, J = 0.5 Hz,

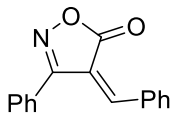
CH_2), 1.85–1.78 (1H, m, CH), 1.09–1.06 (2H, m, CH_2), 0.91-0.86 (2H, m, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.0 (C), 168.9 (C), 34.2 (CH), 10.1 (CH_2), 7.39 (CH_2).

5.4.2 Synthesis of 4-alkylidenisoxazol-5-ones 36

General procedure[110]

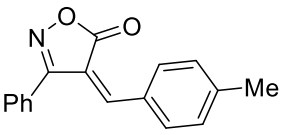
To a 0.5 M solution of isoxazole-5-one **35** in ^{i}PrOH was added the aldehyde **4** (1.2 equiv.). Piperidine was then added (5 µL/mmol **35**) and the reaction was stirred at 50 °C. The reaction was monitored by TLC until complete consumption of the starting material. The mixture was allowed to stand at room temperature. In some cases, precipitation of the product was immediately observed, while in other cases it was necessary to keep the reaction overnight in the freezer until the product crashed out of the solution. The solid was filtered and washed with cold pentane.

(*Z*)-4-Benzylidene-3-phenylisoxazol-5(4*H*)-one (36a)



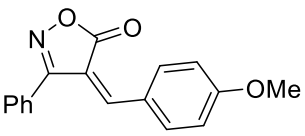
From **35a** (2.16 g, 13.4 mmol) and benzaldehyde (1.64 mL, 16.1 mmol), 2.75 g (82%) of compound **36a** were obtained. Pale yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.32 (2H, d, J = 8.8 Hz, Ar), 7.68–7.45 (9H, m, Ar + CH=C); **^{13}C NMR** (75MHz, $CDCl_3$) δ 168.2 (C), 164.2 (C), 152.9 (CH), 134.3 (CH), 134.1 (CH), 132.5 (C), 131.2 (CH), 129.5 (CH), 129.1 (CH), 128.9 (CH), 127.5 (C), 119.0 (C). Data consistent with the literature.[109]

(*Z*)-4-(4-Methylbenzylidene)-3-phenylisoxazol-5(4*H*)-one (36b)



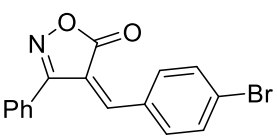
From **35a** (0.31 g, 1.9 mmol) and *p*-tolualdehyde (0.27 mL, 2.3 mmol), 0.32 g of compound **36b** were obtained. Yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.25 (2H, d, J = 8.3 Hz, Ar), 7.63–7.52 (6H, m, Ar + CH=C), 7.32 (2H, d, J = 8.4 Hz, Ar), 2.45 (s, 3H, CH3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.5 (C), 164.3 (C), 152.9 (CH), 146.1 (C), 134.5 (CH), 131.1 (CH), 130.2 (CH), 130.0 (C), 129.4 (CH), 128.9 (CH), 127.66 (C), 117.63 (C), 22.22 (CH_3). Data consistent with the literature.[119]

(*Z*)-4-(4-Methoxybenzylidene)-3-phenylisoxazol-5(4*H*)-one (36c)



From **35a** (1.00 g, 6.2 mmol) and *p*-anisaldehyde (0.9 mL, 7.45 mmol), 0.59 g (34%) of compound **36c** were obtained. Intense yellow solid; **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.55 (2H, d, J = 8.8 Hz, Ar), 7.75 (1H, CH=C), 7.73–7.66 (2H, m, Ar), 7.65–7.57 (3H, m, Ar), 3.96 (3H, s, CH3); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 169.7 (C), 165.8 (C), 165.2 (C), 153.2 (CH), 138.1 (CH), 131.5 (CH), 130.0 (CH), 129.7 (CH), 128.9 (C), 127.0 (C), 115.9 (C), 115.3 (CH), 56.2 (CH_3). Data consistent with the literature.[120]

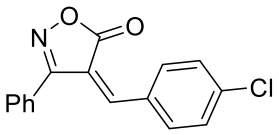
(*Z*)-4-(4-Bromobenzylidene)-3-phenylisoxazol-5(4*H*)-one (36d)



From **35a** (0.40 g, 2.5 mmol) and 4-bromobenzaldehyde (551 mg, 2.98 mmol), 0.55 g (67%) of compound **36d** were obtained. Yellow solid; **^{1}H NMR** (300MHz, $CDCl_3$) δ 8.20 (2H, d, J = 8.6 Hz, Ar), 7.65 (2H, d, J = 8.7 Hz, Ar), 7.61–5.55 (5H, m, Ar), 7.53 (1H, CH=C); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.1 (C), 164.0 (C), 151.2 (CH), 135.3

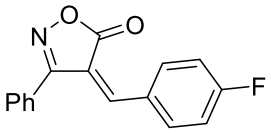
(CH), 132.6 (CH), 131.3 (CH), 131.3 (C), 129.7 (C), 129.5 (CH), 128.9 (CH), 127.3 (C), 119.5 (C). Data consistent with the literature.[121]

(*Z*)-4-(4-Chlorobenzylidene)-3-phenylisoxazol-5(4*H*)-one (36e)



From **35a** (0.68 g, 0.4 mmol) and 4-chlorobenzaldehyde (0.67 g, 0.48 mmol), 2.54 g (86%) of compound **36e** were obtained. Yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.29 (2H, d, J = 8.8 Hz, Ar), 7.64–7.56 (5H, m, Ar), 7.55 (1H, CH=C), 7.48 (2H, d, J = 8.7 Hz, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.0 (C), 163.9 (C), 150.9 (CH), 140.7 (C), 135.2 (CH), 131.1 (CH), 130.7 (C), 129.4 (CH), 129.3 (CH), 128.7 (CH), 127.1 (C), 119.2 (C). Data consistent with the literature.[120]

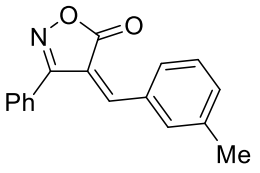
(*Z*)-4-(4-Fluorobenzylidene)-3-phenylisoxazol-5(4*H*)-one (36f)



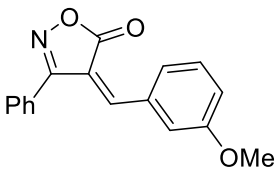
From **35a** (0.40 g, 2.48 mmol) and 4-fluorobenzaldehyde (0.31 mL, 2.98 mmol), 0.44 g (66%) of compound **36f** were obtained. Yellow solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (2H, dd, J = 8.7, 5.4 Hz, Ar), 7.65–7.54 (6H, m, Ar + CH=C), 7.19 (2H, dd, J = 8.8, 8.4Hz, Ar); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.3 (C), 166.2 (d, C, $J_{C\text{-}F}$ = 259.8 Hz), 164.1 (C), 151.3 (CH), 137.1 (d, CH, $J_{C\text{-}F}$ = 9.5 Hz), 131.2 (CH), 129.5 (CH), 129.1 (C), 128.9 (CH), 127.4 (C), 118.4 (d, C, $J_{C\text{-}F}$ = 2.4 Hz), 116.6 (d, CH, $J_{C\text{-}F}$ = 21.9 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −100.93 (tt, J = 8.2, 5.4 Hz). Data consistent with the literature.[122]

(*Z*)-4-(3-Methylbenzylidene)-3-phenylisoxazol-5(4*H*)-one (36g)

From **35a** (0.40 g, 2.48 mmol) and *m*-tolualdehyde (0.35 mL, 2.98 mmol), 0.27 g (41%) of **36g** were obtained. Pale yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.30 (1H, td, J = 4.7, 1.9 Hz, Ar), 8.08 (1H, s, CH=C), 7.65–7.51 (6H, m, Ar), 7.41 (2H, d, J = 4.5 Hz, Ar), 2.42 (3H, s, CH_3); **^{13}C NMR** (75 MHz. $CDCl_3$) δ 168.2 (C), 164.2 (C), 153.2 (CH), 138.9 (C), 135.3 (CH), 134.8 (CH), 132.5 (C), 131.3 (CH), 131.1 (CH), 129.4 (CH), 128.9 (CH), 128.4 (CH), 127.6 (C), 118.6 (C), 21.4 (CH_3). Data consistent with the literature.[123]

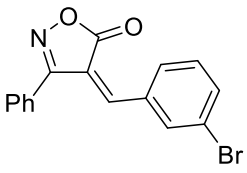


(*Z*)-4-(3-Methoxybenzylidene)-3-phenylisoxazol-5(4*H*)-one (36h)



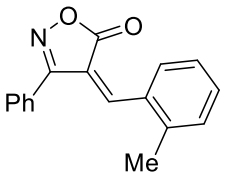
From **35a** (0.40 g, 2.48 mmol) and *m*-anisaldehyde (0.36 mL, 2.98 mmol), 0.39 g (57%) of **36h** were obtained. Yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.31 (1H, t, J = 2.0 Hz, Ar), 7.67–7.50 (7H, m, Ar + CH=C), 7.39 (1H, t, J = 8.0 Hz, Ar), 7.16 (1H, ddd, J = 8.4, 2.4, 0.6 Hz, Ar), 3.90 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.3 (C), 164.2 (C), 159.9 (C), 153.0 (CH), 133.8 (C), 131.2 (CH), 129.9 (CH), 129.4 (CH), 128.9 (CH), 127.7 (CH), 127.5 (C), 121.9 (CH), 118.9 (C), 116.8 (CH), 55.7 (CH_3). Data consistent with the literature.[124]

(*Z*)-4-(3-bromobenzylidene)-3-phenylisoxazol-5(4*H*)-one (36i)



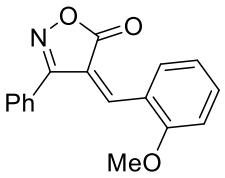
From **35a** (1.0 g, 6.21 mmol) and 3-bromobenzaldehyde (0.88 mL, 7.45 mmol), 0.36 g (17%) of **36i** were obtained. Yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.37 (1H, t, J = 1.8 Hz, Ar), 8.34 (1H, d, J = 7.9 Hz, Ar), 7.70 (1H, ddd, J = 8.0, 1.9, 1.0 Hz, Ar), 7.52 (1H, s, CH=C), 7.39 (1H, t, J = 7.9 Hz, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8 (C), 163.9 (C), 150.7 (C), 136.8 (CH), 136.3 (CH), 134.1 (C), 132.1 (CH), 131.3 (CH), 130.6 (CH), 129.5 (CH), 128.8 (CH), 127.1 (C), 123.0 (C), 120.4 (C).

(*Z*)-4-(2-Methylbenzylidene)-3-phenylisoxazol-5(4*H*)-one (36j)



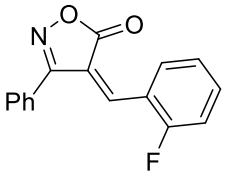
From **35a** (0.40 g, 2.48 mmol) and 2-methylbenzaldehyde (0.34 mL, 2.98 mmol), 0.34 g (52%) of **36j** were obtained. Pale yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.55 (1H, d, J = 7.7 Hz, Ar), 8.00 (1H, s, CH=C), 7.68–7.52 (5H, m, Ar), 7.45 (1H, td, J = 7.4, 1.4 Hz, Ar), 7.34 (1H, t, J = 7.3 Hz, Ar), 7.27 (1H, d, J = 6.9 Hz, Ar), 2.35 (s, 3H, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.0 (C), 163.8 (C), 150.5 (CH),140.6 (C),133.9 (CH), 132.1 (CH), 131.2 (CH), 130.9 (CH), 130.7 (C), 129.4 (CH), 128.7 (CH), 127.5 (C), 126.4 (CH), 118.8 (C), 20.3 (CH_3).

(*Z*)-4-(2-Methoxybenzylidene)-3-phenylisoxazol-5(4*H*)-one (36k)



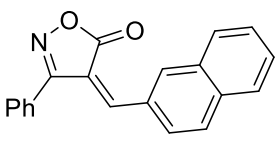
From **35a** (0.40 g, 2.48 mmol) and *o*-anisaldehyde (405 mg, 2.98 mmol), 0.48 g (70%) of **36k** were obtained. Yellow solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.86 (1H, dd, J = 8.0, 1.7 Hz, Ar), 8.25 (1H, s, CH=C), 7.66–7.60 (2H, m, Ar), 7.59–7.52 (4H, m, Ar), 7.08 (1H, dddd, J = 7.9, 7.4, 1.1, 0.5 Hz, Ar), 6.93 (1H, dd, J = 8.5, 1.0 Hz, Ar), 3.84 (3H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.6 (C), 164.3 (C), 160.1 (C), 147.4 (CH), 136.6 (CH), 133.5 (CH), 131.0 (CH), 129.3 (CH), 128.8 (CH), 127.8 (C), 121.4 (C), 120.8 (CH), 117.3 (C), 110.8 (CH), 56.0 (CH_3). Data consistent with the literature.[124]

(*Z*)-4-(2-fluorobenzylidene)-3-phenylisoxazol-5(4*H*)-one (36l)



From **35a** (0.50 g, 3.10 mmol) and 2-fluorobenzaldehyde (0.4 mL, 3.72 mmol), 0.22 g (26%) if **36l** were obtained. Yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.95 (1H, td, J = 7.9, 1.7 Hz, Ar), 7.66–7.53 (6H, m, Ar), 7.33 (1H, dt, J = 7.8, 0.9, Ar), 7.15 (1H, ddd, J = 10.4, 8.4, 1.1 Hz, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.9 (C), 163.9 (C), 162.6 (d, C, $J_{C\text{-}F}$ = 257.3 Hz), 143.3 (d, CH, $J_{C\text{-}F}$ = 7.8 Hz), 136.5 (d, CH, $J_{C\text{-}F}$ = 9.4 Hz), 133.4 (CH), 131.3 (CH), 129.5 (CH), 128.8 (CH), 127.2 (C), 124.8 (d, CH, $J_{C\text{-}F}$ = 3.7 Hz), 120.7 (C), 120.3 (d, C, $J_{C\text{-}F}$ = 37.7 Hz), 115.8 (d, CH, $J_{C\text{-}F}$ = 22.0 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -110.59 (s).

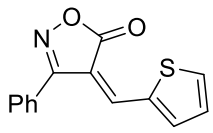
(*Z*)-4-(Naphthalen-2-ylmethylene)-3-phenylisoxazol-5(4*H*)-one (36m)



From **35a** (0.40 g, 2.48 mmol) and 2-naphthaldehyde (465 mg, 2.98 mmol), 0.52 g (70%) of **36m** were obtained. Yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.81 (1H, s, Ar), 8.46 (1H, dd, J = 8.7, 1.8 Hz, Ar), 7.96 (1H, d, J = 8.2 Hz, Ar), 7.92 (1H, d, J = 8.7 Hz, Ar), 7.88 (1H, d, J = 8.0 Hz, Ar), 7.76 (1H, s, CH=C), 7.68–7.51 (7H, m, Ar); **^{13}C**

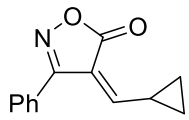
NMR (75 MHz, $CDCl_3$) δ 168.4 (C), 164.3 (C), 152.8 (CH), 137.2 (CH), 135.9 (C), 132.9 (C), 131.2 (CH), 130.3 (C), 130.1 (CH), 129.8 (CH), 129.5 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 128.0 (CH), 127.6 (C), 127.2 (CH), 118.7 (C).

(*Z*)-3-Phenyl-4-(thiophen-2-ylmethylene)isoxazol-5(4*H*)-one (36n)



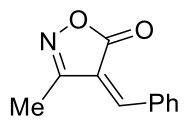
From **35a** (0.60 g, 3.72 mmol) and thiophene-2-carbaldehyde (0.41 mL, 4.47 mmol), 0.68 g (71%) of **36n** were obtained. Yellow solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (1H, d, J = 3.8 Hz, Ar), 7.97 (1H, dt, J = 5.0, 0.8 Hz, Ar), 7.78 (1H, s, CH=C), 7.64–7.53 (5H, m, Ar), 7.27 (1H, dd, J = 5.2, 4.0 Hz, Ar); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.1 (C), 163.5 (C), 142.2 (CH), 141.6 (CH), 140.3 (CH), 136.8 (C), 131.1 (CH), 129.5 (CH), 129.0 (CH), 128.6 (CH), 127.7 (C), 113.59 (C). Data consistent with the literature.[125]

(*Z*)-4-(Cyclopropylmethylene)-3-phenylisoxazol-5(4*H*)-one (36o)



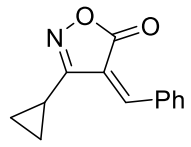
From **35a** (0.40 g, 2.48 mmol) and cyclopropane-carbaldehyde (0.22 mL, 2.98 mmol), 0.32 g (60%) of **36o** were obtained. Pale pink solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55-7.46 (5H, m, Ar), 6.50 (1H, d, J = 11.5 Hz, CH=C), 3.31 (1H, dddd, J = 12.2, 11.5, 7.8, 4.4 Hz, CH), 1.49–1.42 (m, 2H, CH_2), 1.03–0.98 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.1 (C), 166.2 (CH), 161.2 (C), 131.0 (CH), 129.3 (CH), 128.3 (CH), 127.5 (C), 118.8 (C), 14.9 (CH), 13.7 (CH_2). Data consistent with the literature.[126]

(*Z*)-4-Benzylidene-3-methylisoxazol-5(4*H*)-one (36p)



Combined product of precipitation and flash column chromatography of the mother liquor (eluent gradient: Hexane:AcOEt 9.1, 8:2 and 6:4). From **35b** (1.31 g, 13.2 mmol) and benzaldehyde (1.61 mL, 15.8 mmol), 1.04 (42%) of **36p** were obtained. Pale yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.35 (2H, d, J = 7.1 Hz, Ar), 7.63–7.47 (3H, m, Ar), 7.43 (1H, s, CH=C), 2.30 (s, 3H, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.0 (C), 161.2 (C), 150.0 (CH), 134.1 (CH), 133.9 (CH), 132.4 (C), 129.2 (CH), 119.8 (C), 11.8 (CH_3). Data consistent with the literature.[120]

(*Z*)-4-Benzylidene-3-cyclopropylisoxazol-5(4*H*)-one (36q)



From **35c** (0.44 g, 3.52 mmol) and benzaldehyde (0.43 mL, 4.2 mmol), 0.38 g (72%) of **36q** were obtained. Yellow solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.37 (2H, d, J = 6.9 Hz, Ar), 7.70 (1H, s, CH=C), 7.63–7.46 (3H, m, Ar), 1.84–1.74 (1H, m, CH), 1.13–1.04 (m, 4H, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.4 (C), 165.3 (C), 149.9 (CH), 134.0 (CH), 133.9 (CH), 132.5 (C), 129.1 (CH), 120.0 (C), 6.6 (CH), 6.2 (CH_2).

5.4.2 Synthesis and characterization data for diazaspirocycles 37

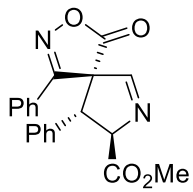
General procedure for the [3+2] cycloaddition reaction

The 4-alkylideneisoxazol-5-one (0.25 mmol), the organocatalyst **SQXX** (11.9 mg, 0.025 mmol) and silver oxide (2.9 mg, 0.0125 mmol) were dissolved in DCM (19.2 mL) and methyl isocyanoacetate (**2a**, 30 µL; 0.33 mmol; 1.3 equiv.) was added. The reaction was stirred until complete consumption of the 4-alkylideneisoxazol-5-one (TLC, *ca.* 12 h).

The product was purified via flash column chromatography, using hexane:AcOEt mixtures. The products **37** were obtained as a diastereomeric mixture.

The racemic products were obtained using Ag_2O as catalyst.

Methyl 1-oxo-4,9-diphenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37aa)

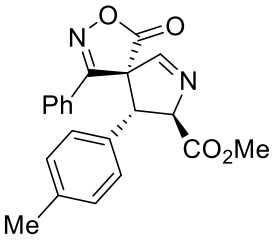


39.9 mg (76%) of **37aa** were obtained from **36a** (62.3 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 89%, minor diastereomer: 98%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL/min, *trans*-(**5S**,**8R**,**9R**)-**37aa** (major diastereomer): major enantiomer: t_r = 18.6 min, minor enantiomer: t_r = 23.5 min, *cis*-**37aa minor diastereomer**: major enantiomer: t_r = 28.6 min, minor enantiomer: t_r = 32.4 min.

trans-(**5S**,**8R**,**9R**)-**37aa** (major diastereomer). Orange oil; $[\alpha]_D^{25}$ -27.4 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 65:35); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81–7.72 (3H, m, Ar + CH=N), 7.66–7.51 (3H, m, Ar), 7.34–7.23 (3H, m, Ar), 7.12–7.04 (2H, m, Ar), 5.57 (1H, dd, *J* = 10.3, 3.0 Hz, CH), 4.43 (1H, d, *J* = 10.3 Hz, CH), 3.37 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4 (C), 170.5 (C), 163.5 (C), 160.3 (CH), 132.7 (CH), 131.1 (C), 129.9 (CH), 129.2 (CH), 129.1 (CH), 128.2 (CH), 127.3 (CH), 126.3 (C), 76.2 (CH), 71.7 (C), 55.7 (CH), 53.1 (CH_3);

cis-**37** (minor diastereomer). **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.76 (1H, d, *J* = 2.9 Hz, CH=N), 7.48–7.38 (2H, m, Ar), 7.21–7.13 (2H, m, Ar), 7.04–6.97 (3H, m, Ar), 6.77–6.68 (3H, m, Ar), 5.20 (1H, dd, *J* = 10.0, 3.1 Hz, CH), 4.53 (1H, d, *J* = 10.0 Hz, CH), 3.79 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.3 (C), 169.5 (C), 163.0 (C), 159.4 (CH), 131.9 (CH), 131.5 (C), 129.2 (CH), 128.8 (CH), 128.5 (CH), 128.5 (CH), 127.4 (CH), 126.8 (C), 77.0 (CH), 71.5 (C), 56.4 (CH), 53.2 (CH_3).

Methyl 1-oxo-4-phenyl-9-(*p*-tolyl)-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37ba)

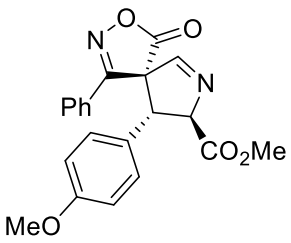


78.6 mg (87%) of **37ba** were obtained from **36b** (65.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 85%, minor diastereomer: 99%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL/min, *trans*-(**5S**,**8R**,**9R**)-**37ba** (major diastereomer): major enantiomer: t_r = 20.8 min, minor enantiomer: t_r = 22.4 min, *cis*-**37ba** (minor diastereomer): major enantiomer: t_r = 30.4 min, minor enantiomer: t_r = 34.1 min.

trans-(**5S**,**8R**,**9R**)-**37ba** (major diastereomer). Orange oil; $[\alpha]_D^{25}$ +2.4 (*c* 1.1, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 68:32); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79–7.72 (3H, m, Ar + C=N), 7.65–7.50 (3H, m, Ar), 7.10 (2H, d, *J* = 8.0 Hz, Ar), 6.98 (2H, d, *J* = 8.1 Hz, Ar), 5.54 (1H, dd, *J* = 10.3, 3.0 Hz, CH), 4.40 (1H, d, *J* = 10.3 Hz, CH), 3.77 (3H, s, CH_3), 2.29 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.5 (C), 170.6 (C), 163.5 (C), 160.4 (CH), 139.0 (C), 132.7 (CH), 129.9 (CH), 129.9 (CH), 128.1 (CH), 127.9 (C), 127.3 (CH), 126.4 (C), 76.3 (CH), 71.8 (C), 55.6 (CH), 53.1 (CH_3), 21.2 (CH_3);

cis-**37ba** (minor diastereomer): **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.77 (1H, d, J = 3.0 Hz, CH=N), 7.49–7.40 (3H, m, Ar), 7.30 (2H, d, J = 8.0 Hz, Ar), 6.88 (2H, d, J = 7.9 Hz, Ar), 6.81 (2H, d, J = 8.0 Hz, Ar), 5.16 (1H, dd, J = 10.1, 3.1 Hz, CH), 4.48 (1H, d, J = 10.1 Hz, CH), 3.78 (3H, s, CH_3), 2.24 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.3 (C), 169.5 (C), 163.0 (C), 159.5 (CH), 138.4 (C), 131.8 (CH), 129.4 (CH), 129.1 (CH), 128.6 (C), 128.3 (C), 127.4 (CH), 126.9 (CH), 77.4 (CH), 71.5 (C), 56.5 (CH), 53.1 (CH_3), 21.1 (CH_3).

Methyl 9-(4-methoxyphenyl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37ca)

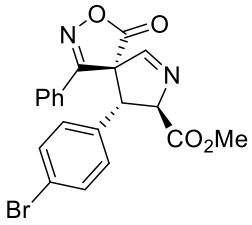


46.2 mg (49%) of **37ca** were obtained from **36c** (69.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 85%, minor diastereomer: n.d.) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL/min, *trans*-(**5S**,**8R**,**9R**)-**37ca** (major diastereomer): major enantiomer: t_r = 26.3 min, minor enantiomer: t_r = 28.4 min.

trans-(**5S**,**8R**,**9R**)-**37ca** (major diastereomer). Orange oil; $[\alpha]_D^{25}$ -56.6 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 91:9); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80–7.72 (3H, m, Ar + CH=N), 7.65–7.51 (3H, m, Ar), 7.02 (2H, d, J = 8.7 Hz, Ar), 6.82 (2H, d, J = 8.8 Hz, Ar), 5.50 (1H, dd, J = 10.4, 2.9 Hz, CH), 4.39 (1H, d, J = 10.3 Hz, CH), 3.78 (3H, s, CH_3), 3.77 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.5 (C), 170.6 (C), 163.5 (C), 160.4 (CH), 160.1 (C), 132.7 (CH), 129.9 (CH), 129.5 (CH), 127.3 (CH), 126.4 (C), 122.6 (C), 114.6 (CH), 76.4 (CH), 71.8 (C), 55.6 (CH), 55.3 (CH_3), 53.1 (CH_3);

cis-**37ca minor** (minor diastereomer). **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.50–7.41 (2H, m, Ar), 7.34–7.28 (3H, m, Ar), 7.08 (2H, d, J = 7.2 Hz, Ar), 6.63 (2H, d, J = 7.2 Hz, Ar), 5.13 (1H, dd, J = 10.1, 3.1 Hz, CH), 4.47 (1H, d, J = 10.1 Hz, CH), 3.79 (3H, s, CH_3), 3.72 (3H, s, CH_3).

Methyl 9-(4-bromophenyl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37da)

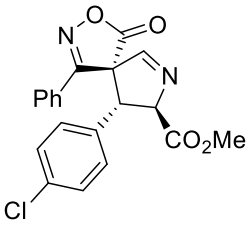


56.0 mg (52%) of **37da** were obtained from **36d** (82.0 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 47%, minor diastereomer: n.d) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, *trans*-(**5S**,**8R**,**9R**)-**37da** (major diastereomer): major enantiomer: t_r = 16.1 min, minor enantiomer: t_r = 19.2 min.

trans-(**5S**,**8R**,**9R**)-**37da** (major diastereomer). Orange oil; $[\alpha]_D^{25}$ -18.8 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 94:6); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77–7.72 (3H, m, Ar + CH=N), 7.65–7.53 (3H, m, Ar), 7.43 (2H d, J = 8.5 Hz, Ar), 6.97 (2H, d, J = 8.3 Hz, Ar) 5.50 (1H, dd, J = 10.3, 3.0 Hz, CH), 4.36 (1H, d, J = 10.3 Hz, CH), 3.79 (3H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.3 (C), 170.3 (C), 163.3 (C), 160.2 (CH), 132.9 (CH), 132.5 (CH), 130.1 (CH), 130.0 (C), 130.0 (CH), 127.3 (CH), 126.2 (C), 123.5 (C), 76.4 (CH), 71.6 (C), 55.2 (CH), 53.2 (CH_3).

cis-**37da** (minor diastereomer). **^{1}H NMR** (400 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 5.15 (1H, dd, J = 10.0, 3.1 Hz, CH), 4.44 (1H, d, J = 10.0 Hz, CH), 3.80 (3H, s, CH_3).

Methyl 9-(4-chlorophenyl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37ea)

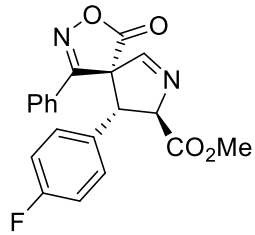


70.6 mg (74%) of **37ea** were obtained from **36e** (70.9 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 81%, minor diastereomer: 98%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL/min, *trans*-(**5S**,**8R**,**9R**)-**37ea** (major diastereomer): major enantiomer: t_r = 14.8 min, minor enantiomer: t_r = 17.1 min, *cis*-**37ea** (minor diastereomer): major enantiomer: t_r = 25.5 min, minor enantiomer: t_r = 27.7 min.

trans-(**5S**,**8R**,**9R**)-**37ea** (major diastereomer) Orange oil; $[\alpha]_D^{25}$ +2.1 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 72:28); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78–7.71 (3H, m, Ar + CH=N), 7.62–7.52 (3H, m, Ar), 7.28 (2H, d, J = 8.6 Hz, Ar), 7.03 (2H, d, J = 8.5 Hz, Ar), 5.50 (1H, dd, J = 10.2, 3.0 Hz, CH), 4.38 (1H, d, J = 10.3 Hz, CH), 3.79 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.3 (C), 170.3 (C), 163.3 (C), 160.2 (CH), 135.3 (C), 132.9 (CH), 130.0 (CH), 129.7 (CH), 129.6 (C), 129.5 (CH), 127.3 (CH), 126.2 (C), 76.4 (CH), 71.6 (C), 55.1 (CH), 53.2 (CH_3).

cis-**37ea** (minor diastereomer). **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.73 (2H, d, J = 8.0 Hz, Ar), 6.66 (2H, d, J = 8.3 Hz, Ar), 5.15 (1H, dd, J = 10.3, 3.1 Hz, CH), 4.46 (1H, d, J = 10.0 Hz, CH), 3.80 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.1 (C), 169.3 (C), 162.7 (C), 159.4 (CH), 134.6 (C), 132.1 (CH), 130.1 (C), 129.4 (CH), 129.0 (CH), 128.9 (CH), 128.4 (C), 126.8 (CH), 77.4 (CH), 71.3 (C), 55.9 (CH), 53.3 (CH_3).

Methyl 9-(4-fluorophenyl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37fa)

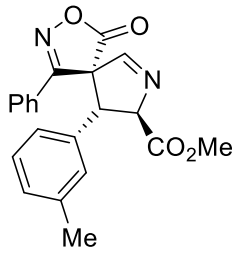


68.1 mg (74%) of **37fa** were obtained from **36f** (66.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 84%, minor diastereomer: 98%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL/min, *trans*-(**5S**,**8R**,**9R**)-**37fa** (major diastereomer): major enantiomer: t_r = 16.2 min, minor enantiomer: t_r = 18.9 min, *cis*-**37fa** (minor diastereomer): major enantiomer: t_r = 28.4 min, minor enantiomer: t_r = 31.2 min.

trans-(**5S**,**8R**,**9R**)-**37fa** (major diastereomer). Orange oil; $[\alpha]_D^{25}$ -25.4 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 72:28); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77 (1H, d, J = 3.0 Hz, CH=N), 7.76–7.70 (2H, m, Ar), 7.65–7.50 (3H, m, Ar), 7.11–7.03 (2H, m, Ar), 6.98 (Hz, t, J = 8.6, 2H, Ar), 5.50 (1H, dd, J = 10.3, 3.0 Hz, CH), 4.39 (1H, d, J = 10.4 Hz, CH), 3.78 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4 (C), 170.3 (C), 163.4 (C), 163.0 (C, d, $J_{C\text{-}F}$ = 247.5 Hz), 160.3 (CH), 132.8 (CH), 130.1 (CH, d, $J_{C\text{-}F}$ = 8.3 Hz), 130.0 (CH), 128.5 (C), 127.3 (CH), 126.2 (C), 116.3 (CH, d, $J_{C\text{-}F}$ = 21.7 Hz), 76.5 (CH), 71.7 (C), 55.1 (CH), 53.2 (CH_3); **RMN ^{19}F** (282 MHz, $CDCl_3$) δ −112.19 (tt, J = 8.4, 5.2 Hz),

cis-**37fa** (minor diastereomer). **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.50–7.42 (2H, m, Ar), 7.35–7.27 (3H, m, Ar), 6.78 (2H, t, J = 8.6 Hz, Ar), 6.73–6.66 (2H, m, Ar), 5.15 (1H, dd, J = 10.0, 3.1 Hz, CH), 4.47 (1H, d, J = 10.0 Hz, CH), 3.79 (3H, s, CH_3), **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.1 (C), 169.4 (C), 162.8 (C), 162.5 (C, d, $J_{C\text{-}F}$ = 246.8 Hz), 159.5 (CH), 132.1 (CH), 129.3 (CH), 129.3 (CH, d, $J_{C\text{-}F}$ = 8.3 Hz), 127.3 (C), 126.8 (C), 126.8 (CH), 115.8 (CH, d, $J_{C\text{-}F}$ = 21.7 Hz), 77.4 (CH), 71.3 (C), 55.9 (CH), 53.2 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −112.78 (tt, J = 8.2, 5.2 Hz).

Methyl 1-oxo-4-phenyl-9-(*m*-tolyl)-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37ga)

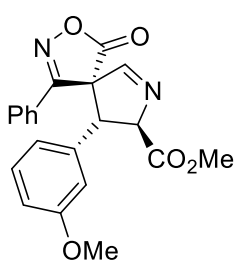


70.2 mg (77%) of **37ga** were obtained from **36g** (65.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 85%, minor diastereomer: 98%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL/min, *trans*-(**5S**,**8R**,**9R**)-**37ga** (major diastereomer): major enantiomer: t_r = 16.7 min, minor enantiomer: t_r = 20.5 min, *cis*-**37ga minor diastereomer**: major enantiomer: t_r = 29.0 min, minor enantiomer: t_r = 32.4 min.

trans-(**5S**,**8R**,**9R**)-**37ga** (major diastereomer). Orange oil; $[\alpha]_D^{25}$ -21.9 (*c* 1.2, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 70:30); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80–7.73 (3H, m, Ar + CH=N), 7.66–7.52 (3H, m, Ar), 7.22–7.07 (2H, m, Ar), 6.92–6.85 (2H, m, Ar), 5.55 (1H, dd, J = 10.3, 3.0 Hz, CH), 4.40 (1H, d, J = 10.3 Hz, CH), 3.78 (3H, s, CH_3), 2.29 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4 (C), 170.5 (C), 163.5 (C), 160.3 (CH), 138.9 (C), 132.7 (CH), 130.9 (C), 129.9 (CH), 129.1 (CH), 128.9 (CH), 128.2 (CH), 127.3 (CH), 126.4 (C), 125.3 (CH), 76.3 (CH), 71.8 (C), 55.7 (CH), 53.1 (CH_3), 21.5 (CH_3);

cis-**37ga** (minor diastereomer). **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.50–7.40 (2H, m, Ar), 7.34–7.27 (3H, m, Ar), 7.06–7.01 (2H, m, Ar), 7.00–6.96 (2H, m, Ar), 5.18 1H, (dd, J = 10.0, 3.1 Hz, CH), 4.48 (1H, d, J = 10.0 Hz, CH), 3.79 (3H, s, CH_3), 2.09 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.3 (C), 169.5 (C), 163.0 (C), 159.4 (CH), 138.5 (C), 131.8 (CH), 131.2 (C), 129.9 (CH), 129.3 (CH), 129.1 (CH), 128.7 (CH), 128.7 (C), 126.9 (CH), 124.8 (CH), 77.1 (CH), 71.5 (C), 56.6 (CH), 53.2 (CH_3), 21.3 (CH_3).

Methyl 9-(3-methoxyphenyl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37ha)



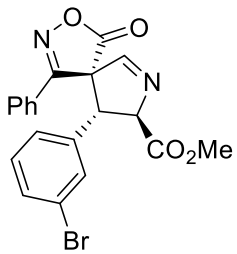
71.9 mg (76%) of **37ha** were obtained from **36h** (69.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 80%, minor diastereomer: 98%) was measured by HPLC (Lux® Amylose-1), hexane:^{i}PrOH 80:20, 1.0 mL/min, *trans*-(**5S**,**8R**,**9R**)-**37ha** (major diastereomer): major enantiomer: t_r = 18.2 min, minor enantiomer: t_r = 34.5 min, *cis*-**37ha** (minor diastereomer): major enantiomer: t_r = 22.6 min, minor enantiomer: t_r = 26.4 min.

trans-(**5S**,**8R**,**9R**)-**37ha** (major diastereomer). Orange oil; $[\alpha]_D^{25}$ -11.7 (*c* 1.1, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 67:33); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80–7.73

(2H, m, Ar), 7.76 (1H, d, *J* = 3.0 Hz, CH=N), 7.66–7.52 (3H, m, Ar), 7.21 (1H, t, *J* = 8.0 Hz, Ar), 6.83 (1H, ddd, *J* = 8.3, 2.5, 0.9 Hz, Ar), 6.67 (1H, dt, *J* = 7.8, 0.9 Hz, Ar), 6.61 (1H, t, *J* = 2.2 Hz, Ar), 5.54 (1H, dd, *J* = 10.3, 3.0 Hz, CH), 4.40 (1H, d, *J* = 10.3 Hz, CH), 3.78 (3H, s, CH_3), 3.74 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 172.4 (C), 170.5 (C), 163.6 (C), 160.3 (CH), 159.9 (CH), 132.7 (CH), 132.6 (C), 129.9 (CH), 129.4 (C), 127.3 (CH), 126.4 (C), 120.3 (CH), 114.3 (CH), 114.1 (CH), 76.3 (CH), 71.7 (C), 55.6 (CH), 55.3 (CH_3), 53.1 (CH_3);

cis-**37ha** (minor diastereomer): **^{1}H NMR** (400 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, *δ* 7.50–7.33 (3H, m, Ar), 7.33–7.26 (2H, m, Ar), 7.07–7.03 (1H, m, Ar), 7.00 (1H, t, *J* = 8.0 Hz, Ar), 6.78 (1H, dd, *J* = 7.4, 1.7 Hz, Ar), 6.70 (1H, dd, *J* = 8.3, 2.5 Hz, Ar), 5.17 (1H, dd, *J* = 9.9, 3.1 Hz, CH), 4.50 (1H, d, *J* = 10.0 Hz, CH), 3.79 (3H, s, CH_3), 3.58 (3H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* 176.3 (C), 169.5 (C), 162.9 (C), 159.7 (CH), 159.4 (CH), 132.9 (C), 131.8 (CH), 130.3 (CH), 129.2 (CH), 128.6 (C), 128.0 (C), 126.8 (CH), 119.8 (CH), 112.9 (CH), 77.1 (CH), 71.5 (C), 56.4 (CH), 55.2 (CH_3), 53.2 (CH_3).

Methyl 9-(3-bromophenyl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37ia)

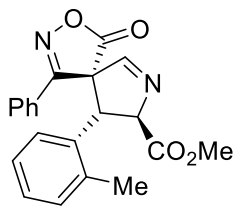


81.5 mg (76%) of **37ia** were obtained from **36i** (82.0 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 78%, minor diastereomer: 99%) was measured by HPLC (Lux® i-Amylose-1), hexane:^{i}PrOH 85:15, 1.0 mL/min, *trans*-(**5S**,**8R**,**9R**)-**37ia** (major diastereomer): major enantiomer: t_r = 15.1 min, minor enantiomer: t_r = 18.4 min, *cis*-**37ia** (minor diastereomer): major enantiomer: t_r = 40.5 min, minor enantiomer: t_r = 48.2 min.

trans-(**5S**,**8R**,**9R**)-**37ia** (major diastereomer). Orange oil; $[\alpha]_D^{25}$ -11.3 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 67:33); **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 7.79–7.71 (3H, m, Ar + CH=N), 7.67–7.52 (3H, m, Ar), 7.45 (1H, ddd, *J* = 8.0, 1.8, 1.0 Hz, Ar), 7.21 (1H, t, *J* = 1.6 Hz, Ar), 7.19 (1H, t, *J* = 7.9 Hz, Ar), 7.05 (1H d, *J* = 7.8 Hz, Ar), 5.51 (1H, dd, *J* = 10.2, 3.0, CH), 4.37 (1H, d, *J* =10.2 Hz, CH), 3.79 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 172.2 (C), 170.2 (C), 163.3 (CH), 160.1 (CH), 133.5 (C), 132.9 (CH), 132.4 (CH), 131.4 (CH), 130.7 (CH), 130.0 (CH), 127.3 (CH), 126.7 (CH), 126.1 (C), 123.2 (C), 76.4 (CH), 71.6 (C), 54.9 (CH), 53.3 (CH_3).

cis-**37ia** (minor diastereomer). **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, *δ* 7.76 (1H, d, *J* = 3.1 Hz, CH=N), 7.52–7.46 (2H, m, Ar), 7.38–7.28 (3H, m, Ar), 7.00 (1H, d, *J* = 7.8 Hz, Ar), 6.78–6.70 (2H, m, Ar), 5.14 (1H, dd, *J* = 9.9, 3.1 Hz, CH), 4.45 (1H, d, *J* = 9.9 Hz, CH), 3.80 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 175.9 (C), 169.2 (C), 162.7 (CH), 159.2 (CH), 133.8 (C), 132.2 (CH), 131.8 (CH), 130.5 (CH), 130.4 (CH), 129.5 (CH), 128.4 (C), 126.9 (CH), 126.8 (CH), 122.9 (C), 77.2 (CH), 71.3 (C), 55.9 (CH), 53.3 (CH_3).

Methyl 1-oxo-4-phenyl-9-(*o*-tolyl)-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37ja)

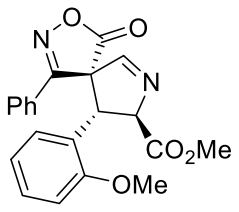


76.6 mg (85%) of **37ja** were obtained from **36j** (65.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 85%, minor diastereomer: 98%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL/min, *trans*-(**5S**,**8R**,**9R**)-**37ja** (major diastereomer): major enantiomer: t_r = 14.5 min, minor enantiomer: t_r = 21.2 min, **37ja** (minor diastereomer): major enantiomer: t_r = 31.0 min, minor enantiomer: t_r = 40.3 min.

trans-(**5S**,**8R**,**9R**)-**37ja** (major diastereomer). Orange oil; $[\alpha]_D^{25}$ +7.1 (*c* 0.9, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 70:30); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81–7.76 (2H, m, Ar), 7.70 (1H, d, *J* = 3.0 Hz, CH=N), 7.57–7.48 (3H, m, Ar), 7.23–7.17 (2H, m, Ar), 7.10–7.04 (2H, m, Ar), 5.47 (1H, dd, *J* = 9.7, 3.0 Hz, CH), 4.86 (1H, d, *J* = 9.8 Hz, CH), 3.76 (3H, s, CH_3), 1.81 (3H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.6 (C), 170.5 (C), 163.3 (C), 160.2 (CH), 137.9 (C), 132.7 (CH), 131.0 (CH), 129.8 (CH), 129.6 (C), 128.8 (CH), 128.4 (CH), 127.0 (CH), 126.8 (C), 126.7 (CH), 79.7 (CH), 71.3 (C), 53.1 (CH), 50.9 (CH_3), 19.7 (CH_3).

cis-**37ja** (minor diastereomer). **^{1}H NMR** (400 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.71 (1H, d, *J* = 3.0 Hz, CH=N), 5.36 (1H, dd, *J* = 8.6, 3.0 Hz, CH), 4.79 (1H, d, *J* = 8.7 Hz, CH), 3.79 (3H, s, CH_3), 2.27 (3H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.4 (C), 169.6 (C), 163.3 (C), 158.9 (CH), 137.7 (C), 131.8 (CH), 131.2 (CH), 130.0 (C), 129.1 (CH), 129.1 (C), 128.2 (CH), 127.5 (CH), 126.8 (CH), 125.4 (CH), 80.0 (CH), 70.1 (C), 53.2 (CH), 52.7 (CH_3), 20.0 (CH_3).

Methyl 9-(2-methoxyphenyl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37ka)



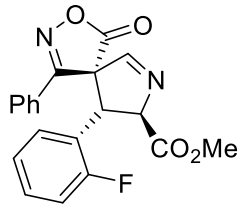
90.1 mg (95%) of **37ka** were obtained from **36k** (69.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 87%, minor diastereomer: 98%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL/min, *trans*-(**5S**,**8R**,**9R**)-**37ka** (major diastereomer): major enantiomer: t_r = 26.8 min, minor enantiomer: t_r = 35.6 min, *cis*-**37ka** (minor diastereomer): major enantiomer: t_r = 50.1 min, minor enantiomer: t_r = 55.1 min.

trans-(**5S**,**8R**,**9R**)-**37ka** (major diastereomer). Orange oil; $[\alpha]_D^{25}$ +20.2 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 52:48); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81 (2H, dd, *J* = 8.0, 1.7 Hz, Ar), 7.68 (1H, d, *J* = 3.2 Hz, CH=N), 7.42 (1H, d, *J* = 7.9 Hz, Ar), 7.25 (1H, d, *J* = 8.4 Hz, Ar), 7.15 (1H, t, *J* = 7.8 Hz, Ar), 6.96 (1H, td, *J* = 7.6, 0.9 Hz, Ar), 6.90–6.83 (2H, m, Ar), 5.36 (1H, dd, *J* = 9.8, 3.1 Hz, CH), 4.90 (1H, d, *J* = 10.3 Hz, CH), 3.78 (3H, s, CH_3), 3.34 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.0 (C), 169.8 (C), 164.1 (C), 159.8 (CH), 157.0 (C), 132.1 (CH), 129.4 (CH), 129.2 (CH), 128.2 (CH), 127.5 (C), 126.2 (CH), 121.2 (C), 120.8 (CH), 110.3 (CH), 76.6 (CH), 70.9 (C), 54.4 (CH), 53.1 (CH_3), 50.0 (CH_3).

cis-**37ka** (minor diastereomer). **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.66 (1H, d, *J* = 3.0 Hz, CH=N),

7.56–7.51 (2H, m, Ar), 7.31 (2H, t, *J* = 7.5 Hz, Ar), 7.08 (1H, d, *J* = 7.8 Hz, Ar), 6.76 (1H, d, *J* = 7.8 Hz, Ar), 6.74 (1H, d, *J* = 8.4 Hz, Ar), 6.62 (1H, d, *J* = 7.7 Hz, Ar), 6.48 (1H, td, *J* = 7.5, 0.2 Hz, Ar), 5.64 (1H, dd, *J* = 10.2, 3.0 Hz, CH), 4.50 (1H, d, *J* = 9.8 Hz, CHAr), 3.79 (3H, s, CH_3), 3.76 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 172.3 (C), 170.8 (C), 163.1 (C), 160.8 (CH), 157.4 (C), 131.2 (CH), 130.0 (CH), 128.9 (CH), 128.6 (C), 126.8 (CH), 126.6 (CH), 120.2 (CH), 120.0 (C), 109.7 (CH), 76.1 (CH), 70.6 (C), 54.4 (CH), 53.0 (CH_3), 49.0 (CH_3).

Methyl 9-(2-fluorophenyl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37la)

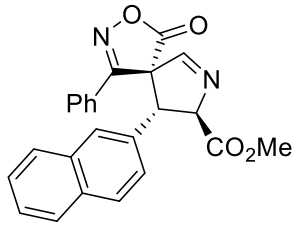


79.6 mg (87%) of **37la** were obtained from **36l** (66.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 90%, minor diastereomer: 96%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL/min, *trans*-(**5S**,**8R**,**9R**)-**37la** (major diastereomer): major enantiomer: t_r = 16.2 min, minor enantiomer: t_r = 21.9 min, *cis*-**37la** (minor diastereomer): major enantiomer: t_r = 41.4 min, minor enantiomer: t_r = 49.4 min.

trans-(**5S**,**8R**,**9R**)-**37la** (major diastereomer). Orange oil; $[\alpha]_D^{25}$ +9.5 (*c* 1.1, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 57:43); **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 7.79–7.71 (3H, m, Ar + CH=N), 7.63–7.50 (3H, m, Ar), 7.45 (1H, td, *J* = 7.6, 1.6 Hz, Ar), 7.35–7.27 (1H, m, Ar), 7.23–7.13 (1H, m, Ar), 7.03–6.93 (1H, m, Ar), 5.61 (1H, dd, *J* = 10.2, 3.0 Hz, CH), 4.75 (1H, d, *J* = 10.2 Hz, CH), 3.79 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 172.3 (C), 170.2 (C), 163.8 (C), 161.4 (C, d, $J_{C\text{-}F}$ = 247.6 Hz), 160.3 (CH), 132.5 (CH), 130.8 (CH, d, $J_{C\text{-}F}$ = 8.4 Hz), 129.7 (CH), 129.1 (CH, d, $J_{C\text{-}F}$ = 3.0 Hz), 127.2 (CH), 126.7 (C), 124.8 (CH, d, $J_{C\text{-}F}$ = 3.8 Hz), 118.7 (C, d, $J_{C\text{-}F}$ = 14.4 Hz), 115.8 (CH, d, $J_{C\text{-}F}$ = 22.1 Hz), 76.4 (CH), 71.1 (C), 53.2 (CH_3), 48.0 (CH);

cis-**37la** (minor diastereomer). **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, *δ* 7.72 (1H, d, *J* = 3.2 Hz, CH=N), 7.37 (1H, td, *J* = 7.5, 1.2 Hz, Ar), 7.25–7.09 (3H, m, Ar), 7.03–6.93 (3H, m, Ar), 6.68 (1H, td, *J* = 7.6, 1.1, Ar), 6.62 (1H, td, *J* = 7.1, 1.6, Ar), 5.37 (1H, dd, *J* = 9.6, 3.1 Hz, CH), 4.61 (1H, d, *J* = 9.7 Hz, CH), 3.81 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 175.7 (C), 169.3 (C), 162.4 (C), 161.0 (C, d, $J_{C\text{-}F}$ = 245.7 Hz), 159.5 (CH), 131.7 (CH), 130.1 (CH, d, $J_{C\text{-}F}$ = 8.7 Hz), 129.1 (CH), 128.4 (C), 127.7 (CH, d, $J_{C\text{-}F}$ = 3.6 Hz), 126.4 (CH), 124.0 (CH, d, $J_{C\text{-}F}$ = 3.5 Hz), 119.8 (C, d, $J_{C\text{-}F}$ = 15.5 Hz), 115.6 (CH, d, $J_{C\text{-}F}$ = 21.8 Hz), 76.9 (CH), 70.4 (C), 53.3 (CH_3), 49.1 (CH).

Methyl 9-(naphthalen-2-yl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37ma)



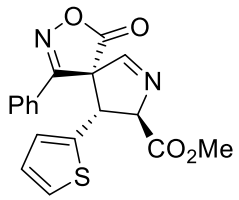
56.0 mg (56%) of **37ma** were obtained from **36m** (74.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 84%, minor diastereomer: 96%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL/min, *trans*-(**5S**,**8R**,**9R**)-**37ma** (major diastereomer): major enantiomer: t_r = 21.7 min, minor enantiomer: t_r = 27.2 min, *cis*-**37ma** (minor diastereomer):

major enantiomer: t_r = 39.7 min, minor enantiomer: t_r = 44.1 min.

trans-(**5S**,**8R**,**9R**)-**37ma** (major diastereomer). Orange oil; $[\alpha]_D^{25}$ +22.9 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 66:34); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.85–7.74 (6H, m, Ar + CH=N), 7.70–7.56 (4H, m, Ar), 7.49 (2H, dd, *J* = 6.2, 3.3 Hz, Ar), 7.15 (1H, dd, *J* = 8.6, 1.8 Hz, Ar), 5.71 (1H, dd, *J* = 10.3, 3.0 Hz, CH), 4.61 (1H, d, *J* = 10.3 Hz, CH), 3.78 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4 (C), 170.5 (C), 163.5 (C), 160.4 (CH), 133.4 (C), 133.3 (C), 132.8 (CH), 130.0 (CH), 129.1 (CH), 128.5 (C), 128.2 (CH), 127.9 (CH), 127.8 (CH), 127.4 (CH), 126.9 (CH), 126.8 (CH), 126.4 (C), 125.5 (CH), 76.5 (CH), 71.8 (C), 56.0 (CH), 53.2 (CH_3);

cis-**37ma** (minor diastereomer). **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.85– 7.74 (6H, m, Ar + CH=N), 7.70–7.56 (2H, m, Ar), 7.48–7.36 (2H, m, Ar), 7.22–7.17 (1H, m, Ar), 6.95 (1H, d, *J* = 8.1 Hz, Ar), 5.34 (1H, dd, *J* = 10.0, 3.1 Hz, CH), 4.68 (1H, d, *J* = 10.0 Hz, CH), 3.79 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.3 (C), 169.5 (C), 162.9 (C), 159.4 (CH), 133.0 (C), 132.8 (C), 131.8 (CH), 129.2 (CH), 128.9 (CH), 128.6 (C), 127.9 (CH), 127.6 (CH), 126.8 (CH), 126.7 (CH), 126.4 (C), 125.4 (CH), 77.4 (CH), 71.5 (C), 57.0 (CH), 53.2 (CH_3).

Methyl 1-oxo-4-phenyl-9-(thiophen-2-yl)-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37na)

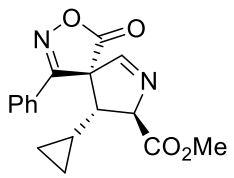


67.5 mg (76%) of **37na** were obtained from **36n** (63.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 84%, minor diastereomer: 91%) was measured by HPLC (Lux® i-Amylose-1), hexane:^{i}PrOH 85:15, 1.0 mL/min, *trans*-(**5S**,**8R**,**9R**)-**37na** (major diastereomer): major enantiomer: t_r = 22.0 min, minor enantiomer: t_r = 17.2 min, *cis*-**37na** (minor diastereomer): major enantiomer: t_r = 30.4 min, minor enantiomer: t_r = 18.0 min.

trans-(**5S**,**8R**,**9R**)-**37na** (major diastereomer). Orange oil; $[\alpha]_D^{25}$ -82.7 (*c* 1.1, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 73:27); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 (1H, d, *J* = 3.0 Hz, CH=N), 7.73 (2H, dd, *J* = 8.2, 1.5 Hz, Ar), 7.65–7.51 (3H, m, Ar), 7.23 (1H, dd, *J* = 8.2, 1.5 Hz, Ar), 7.00–6.93 (2H, m, Ar), 5.46 (1H, dd, *J* = 10.2, 3.0 Hz, CH), 4.64 (1H, d, *J* = 10.2 Hz, CH), 3.81 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.0 (C), 170.1 (C), 163.4 (C), 160.6 (CH), 133.0 (C), 132.8 (CH), 129.9 (CH), 127.3 (CH), 127.0 (CH), 126.7 (CH), 126.4 (CH), 126.2 (C), 77.9 (CH), 71.6 (C), 53.3 (CH), 51.1 (CH_3).

cis-**37na** (minor diastereomer). **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.76 (1H, d, *J* = 3.1 Hz, CH=N), 7.50–7.42 (1H, m, Ar), 7.35–7.27 (2H, m, Ar), 7.16–7.11 (2H, m, Ar), 7.07 (1H, dd, *J* = 5.1, 1.1 Hz, Ar), 6.73 (1H, dd, *J* = 5.2, 3.6 Hz, Ar), 6.45 (1H, d, *J* = 3.6 Hz, Ar), 5.11 (1H, dd, *J* = 9.8, 3.1 Hz, CH), 4.71 (1H, dd, *J* = 9.8, 0.9 Hz, CH), 3.82 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.7 (C), 169.0 (C), 162.5 (C), 159.7 (CH), 133.8 (C), 131.9 (CH), 129.2 (CH), 128.4 (C), 127.7 (CH), 127.2 (CH), 126.7 (CH), 125.8 (CH), 79.6 (CH), 71.5 (C), 53.3 (CH), 51.7 (CH_3).

Methyl 9-cyclopropyl-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37oa)

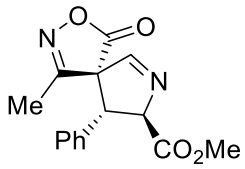


39.0 mg (50%) of **37oa** were obtained from **36o** (53.3 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 87%, minor diastereomer: 56%) was measured by HPLC (Lux® Amylose-1), hexane:^{i}PrOH 85:15, 1.0 mL/min, *trans*-(**5S**,**8R**,**9R**)-**37oa** (major diastereomer): major enantiomer: t_r = 12.6 min, minor enantiomer: t_r = 15.4 min, *cis*-**37oa** (minor diastereomer): major enantiomer: t_r = 19.5 min, minor enantiomer: t_r = 14.2 min.

trans-(**5S**,**8R**,**9R**)-**37oa** (major diastereomer). Orange oil; $[\alpha]_D^{25}$ -42.7 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 69:31); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.67–7.61 (3H, m, Ar + CH=N), 7.58–7.40 (3H, m, Ar), 5.01 (1H, dd, *J* = 9.3, 3.0 Hz, CH), 3.85 (3H, s, CH_3) 2.41 (1H, dd, *J* = 10.4, 9.2 Hz, CH), 1.10 (1H, dddd, *J* = 12.8, 9.2, 8.0, 4.8 Hz, CH), 0.53 (2H, qq, *J* = 9.2, 4.6 Hz, CH_2), 0.17–0.05 (2H, m, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.4 (C), 171.1 (C), 164.3 (C), 160.8 (CH), 132.6 (CH), 129.7 (CH), 127.2 (CH), 126.3 (C), 78.9 (CH), 70.2 (C), 56.5 (CH), 53.1 (CH_3), 8.3 (CH), 4.0 (CH_2), 2.9 (CH_2);

cis-**37oa** (minor diastereomer). **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 4.75 (1H, dd, *J* = 8.8, 3.1 Hz, CH), 2.53 (1H, dd, *J* = 10.2, 8.7 Hz, CH), 0.46–0.26 (2H, m, CH_2), 0.20–0.00 (m, 2H, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.4 (C), 170.0 (C), 163.0 (C), 160.0 (CH), 132.2 (CH), 129.3 (CH), 126.7 (CH), 80.6 (CH), 69.9 (C), 58.3 (CH), 53.1 (CH), 9.4 (CH), 5.5 (CH_2), 3.5 (CH_2).

Methyl 4-methyl-1-oxo-9-phenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37pa)

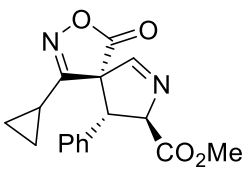


55.0 mg (77%) of **37pa** were obtained from **36p** (46.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 95%, minor diastereomer: 94%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL/min, *trans*-(**5S**,**8R**,**9R**)-**37pa** (major diastereomer): major enantiomer: t_r = 19.2 min, minor enantiomer: t_r = 34.1 min, *cis*-**37pa minor diastereomer**: major enantiomer: t_r = 25.4 min, minor enantiomer: t_r = 38.1 min.

trans-(**5S**,**8R**,**9R**)-**37pa** (major diastereomer). Orange oil; $[\alpha]_D^{25}$ -151.9 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 58:42); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 (1H, d, *J* = 3.0 Hz, CH=N), 7.34–7.29 (3H, m, Ar), 7.22–7.16 (2H, m, Ar), 5.49 (1H, dd, *J* = 9.8, 3.0 Hz, CH), 4.18 (1H, d, *J* = 9.8 Hz, CH), 3.80 (3H, s, CH_3), 2.28 (3H, s, CH_3);

cis-**37pa** (minor diastereomer). **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.39 (1H, d, *J* = 3.0 Hz, CH=N), 7.38–7.34 (3H, m, Ar), 7.16–7.11 (2H, m, Ar), 5.34 (1H, dd, *J* = 9.8, 3.0 Hz, CH), 4.53 (1H, d, *J* = 9.8 Hz, CH), 3.85 (3H, s, CH_3), 1.61 (3H, s, CH_3).

Methyl 4-cyclopropyl-1-oxo-9-phenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37qa)

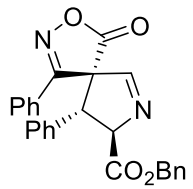


48.4 mg (62%) of **37qa** were obtained from **36q** (53.3 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 87%, minor diastereomer: 56%) was measured by HPLC (Lux® Amylose-1), hexane:^{i}PrOH 85:15, 1.0 mL/min, *trans*-(**5S**,**8R**,**9R**)-**38qa** (major diastereomer): major enantiomer: t_r = 24.0 min, minor enantiomer: t_r = 14.0 min, *cis*-**37qa** (minor diastereomer): major enantiomer: t_r = 20.2 min, minor enantiomer: t_r = 14.7 min.

trans-(**5S**,**8R**,**9R**)-**37qa** (major diastereomer). Orange oil; $[\alpha]_D^{25}$ -105.2 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 65:35); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 (1H, d, *J* = 3.0 Hz, CH=N), 7.39–7.30 (5H, m, Ar), 5.48 (1H, dd, *J* = 9.9, 3.0 Hz, CHN), 4.36 (1H, d, *J* = 9.9 Hz, CH), 3.79 (3H, s, CH_3), 1.61 (1H, tt, *J* = 7.9, 5.2 Hz, CH), 1.35–1.19 (3H, m), 0.91–0.79 (1H, m); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.5 (C), 170.6 (C), 169.3 (C), 159.6 (CH), 132.7 (C), 129.2 (CH), 128.5 (CH), 127.3 (CH), 77.2 (CH), 73.1 (C), 54.4 (CH), 53.2 (CH_3), 10.5 (CH_2), 9.0 (CH_2), 7.8 (CH).

cis-**37qa** (minor diastereomer). **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.44 (1H, d, *J* = 3.0 Hz, CH=N), 7.25–7.23 (3H, m, Ar), 7.18–7.12 (2H, m, Ar), 5.41 (1H, dd, *J* = 9.0, 3.0 Hz, CH), 4.53 (1H, d, *J* = 9.9 Hz, CH), 3.85 (3H, s, CH_3), 1.30–1.19 (1H, m, CH), 1.00-0.91 (m, 2H, CH_2), 0.58 (1H, dddd, *J* = 9.3, 8.1, 7.0, 4.6 Hz, CH), 0.27 (1H, ddt, *J* = 9.7, 6.7, 4.8 Hz, CH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.1 (C), 169.7 (C), 167.7 (C), 159.4 (CH), 131.4 (C), 129.4 (CH), 129.1 (CH), 128.6 (CH), 76.8 (CH), 72.6 (C), 55.2 (CH), 53.3 (CH_3), 10.0 (CH_2), 9.0 (CH_2), 8.6 (CH).

Benzyl 1-oxo-4,9-diphenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (37ad)



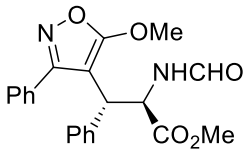
77.6 mg (73%) of **37ad** were obtained from **36a** (62.3 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 90%, minor diastereomer: 99%) was measured by HPLC (Lux® Amylose-1), hexane:^{i}PrOH 80:10, 1.0 mL/min, *trans*-(**5S**,**8R**,**9R**)-**37ad** (major diastereomer): major enantiomer: t_r = 31.5 min, minor enantiomer: t_r = 20.4 min, *cis*-**37ad** (minor diastereomer): major enantiomer: t_r = 28.5 min, minor enantiomer: t_r = 18.7 min.

trans-(**5S**,**8R**,**9R**)-**37ad** (major diastereomer). Orange oil; $[\alpha]_D^{25}$ -45.4 (*c* 0.9, $CHCl_3$, for the diastereomeric mixture, *trans:cis* 76:24); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79–7.72 (3H, m, Ar + CH=N), 7.63–7.55 (1H, m, Ar), 7.53–7.46 (2H, m, Ar), 7.34–7.28 (6H, m, Ar), 7.22–7.14 (2H, m, Ar), 7.12–7.05 (2H, m, Ar), 5.62 (1H, dd, *J* = 10.4, 3.0 Hz, CH), 5.20 (2H, s, CH_2), 4.41 (1H, d, *J* = 10.3 Hz, CH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4 (C), 169.9 (C), 163.5 (C), 160.4 (CH), 135.0 (C), 132.7 (CH), 131.0 (C), 129.9 (CH), 129.3 (CH), 129.1 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 128.0 (CH), 127.3 (CH), 126.3 (C), 76.5 (CH), 71.7 (C), 67.7 (CH_2), 56.1 (CH).

cis-**37ad** (minor diastereomer). **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.76 (1H d, *J* = 2.9 Hz, CH=N),

6.70–6.67 (2H, m, Ar), 5.24 (1H, dd, J = 9.9, 3.0 Hz, CH), 5.22 (2H, s, CH_2), 4.54 (1H, d, J = 10.1 Hz, CH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.2 (C), 169.0 (C), 162.9 (C), 159.5 (CH), 134.5 (C), 131.8 (CH), 131.4 (C), 129.2 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.5 (C), 128.2 (CH), 127.5 (CH), 126.8 (CH), 77.1 (CH), 71.4 (C), 67.7 (CH_2), 56.7 (CH).

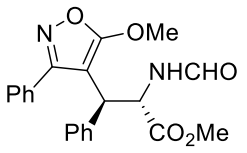
Methyl (2*R*,3*R*)-2-formamido-3-(5-methoxy-3-phenylisoxazol-4-yl)-3-phenylpropanoate (38)



Compound **37aa** (8.4 mg, 0.024 mmol, 99% *ee*, obtained after chiral HPLC- CHIRALPAK® IC) was dissolved in dichloromethane (0.3 mL). Water (1 drop) and 2M HCl in Et_2O (1 drop) was added. After 4 hours, the volatiles were removed and the residue dried under vacuum in the presence of P_2O_5. The crude product (8.7 mg) was dissolved in dry THF (0.4 mL) under nitrogen atmosphere, 2.0 M (trimethylsilyl)diazomethane in Et_2O (38 µL, 0.076 mmol) was added and the reaction mixture was stirred overnight at room temperature. Purification by flash chromatography (Hexane:AcOEt 4:6) furnished 2.9 mg (32%) of compound **4**. Enantiomeric excess (99%) was determined by HPLC (CHIRALPAK® AD-H), hexane:^{i}PrOH 80:20, 1.0 mL/min, major enantiomer: t_r = 9.1 min, minor enantiomer: t_r = 15.7 min.

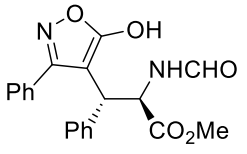
Colorless oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.03 (1H, s, CHO), 7.48–7.37 (4H, m, Ar), 7.37–7.23 (6H, m, Ar), 6.35 (1H, d, J = 9.3 Hz, CH), 5.42 (1H, td, J = 9.0, 0.8 Hz, CH), 4.26 (3H, s, CH_3), 3.37 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.2 (C), 169.8 (C), 166.3 (C), 160.6 (CH), 138.4 (C), 130.1 (CH), 129.0 (C), 128.9 (CH), 128.9 (CH), 128.5 (CH), 128.1 (CH), 127.8 (CH), 90.1 (C), 58.9 (CH_3), 54.0 (CH), 52.3 (CH_3), 42.4 (CH); **HRMS** (ESI) *m/z*: 403.1271 $[M+Na]^+$, $C_{21}H_{20}N_2NaO_5^+$ requires 403.1264.

Methyl (2*S*,3*S*)-2-formamido-3-(5-methoxy-3-phenylisoxazol-4-yl)-3-phenylpropanoate (*ent*-38)



The previous procedure was performed with **37aa'** (8.0 mg, 0.022 mmol, 99% *ee*, obtained after chiral HPLC- CHIRALPAK® IC), which afforded 1.8 mg (22%) of *ent*-**4**. Enantiomeric excess (99%) was determined by HPLC (CHIRALPAK® AD-H), hexane:^{i}PrOH 80:20, 1.0 mL/min, major enantiomer: t_r = 15.7 min, minor enantiomer: t_r = 9.1 min. Spectroscopical data coincided with those observed for the previous compound **39**.

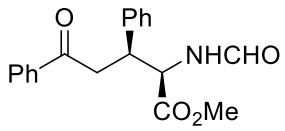
Methyl (2*R*,3*R*)-2-formamido-3-(5-hydroxy-3-phenylisoxazol-4-yl)-3-phenylpropanoate (39)



Diastereomer **37aa** (63.0 mg, 0.18 mmol, 86% *ee*, obtained by semi-preparative HPLC) was dissolved in dichloromethane (1 mL), H_2O (15 µL) and 2.0 M HCl solution in Et_2O (6 µL, 12 µmol) was added. The mixture was stirred for 4 h and concentrated under reduced pressure to yield 68.9 mg (99%) of **39**. White foam; $[\alpha]_D^{25}$ –72.7 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 11.0 (1H, bs, OH), 8.41 (1H, d, J = 9.4 Hz, CHO), 7.61–7.27 (10H, m, Ar), 5.36 (1H, dd, J = 9.3, 5.3 Hz, CH), 4.63 (1H, d, J = 5.3 Hz, CH), 3.55 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.2 (CH), 170.5 (C), 163.9

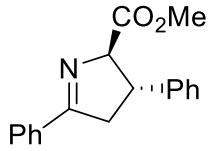
(C), 162.0 (C), 138.3 (C), 131.7 (CH), 129.4 (CH), 128.9 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 126.0 (C), 96.0 (C), 55.2 (CH), 52.5 (CH_3), 40.8 (CH); **HRMS** (ESI) *m/z*: 389.1117 $[M+Na]^+$, $C_{20}H_{18}N_2NaO_5^+$ requires 389.1108.

Methyl (2*R*,3*S*)-2-formamido-5-oxo-3,5-diphenylpentanoate (40)



Compund **39** (29.2 mg, 0.08 mmol, 86% *ee*), iron powder (44.5 mg, 0.80 mmol, 10.0 equiv.) and ammonium chloride (42.6 mg, 0.80 mmol) in MeOH:H_2O 1:1 (0.4 mL) was stirred at 60 °C. After 2 h, the reaction was filtered over celite and concentrated under reduced pressure. Purification by flash chromatography furnished 16.6 mg of product **40** (64%). Colorless oil; $[\alpha]_D^{25}$ –38.4 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.17 (1H, dd, *J* = 1.5, 0.8 Hz, CHO), 7.96–7.88 (2H, m, Ar), 7.59–7.51 (1H, m, Ar), 7.50–7.40 (2H, m, Ar), 7.34–7.27 (3H, m, Ar), 7.25–7.19 (2H, m, Ar), 6.40 (1H, d, *J* = 9.0 Hz, NH), 5.01 (1H, ddd, *J* = 9.1, 8.3, 0.9 Hz, CH), 3.88 (1H, dt, *J* = 8.3, 6.6, CH), 3.55 (2H, dd, *J* = 6.6, 2.6 Hz, CH_2), 3.50 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.2 (CH), 171.2 (C), 160.9 (C), 139.5 (C), 136.7 (C), 133.5 (CH), 128.9 (CH), 128.8 (CH), 128.2 (CH), 128.2 (CH), 127.8 (CH), 55.6 (CH), 52.3 (CH_3), 43.6 (CH), 41.7 (CH_2); **HRMS** (ESI) *m/z*: 326.1385 $[M+H]^+$, $C_{19}H_{20}N_2O_4^+$ requires 326.1387.

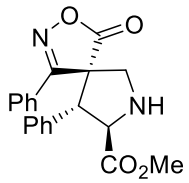
Methyl (2*R*,3*S*)-3,5-diphenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (41)



To a solution of compound **40** (16.6 mg, 0.051 mmol) in MeOH (0.6 mL) was added 0.1 M HCl (aq.) (153 µL, 0.153 mmol). The reaction was stirred for 3 h and quenched with $NaHCO_3$ (aq.) 0.1 M (1.53 mL, 0.153 mmol). The methanol was removed under reduced pressure and the aqueous mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The mixture was chromatographed (Hexane:AcOEt 7:3) and 8.5 mg (60%) of **41** were obtained. The spectroscopical data are in accordance with the literature description. Enantiomeric excess (85%) was determined by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 80:20, 1.0 mL/min, major enantiomer: t_r = 12.8 min, minor enantiomer: t_r = 15.7 min.

Yellow oil; $[\alpha]_D^{25}$ –41.8 (*c* 0.7, $CHCl_3$), $[\alpha]_D^{25}$ –42.6 (*c* 0.7, CH_2Cl_2), reported in the literature[13] for the opposite enantiomer +64.8 (*c* 0.42, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96–7.88 (2H, m, Ar), 7.53–7.40 (3H, m, Ar), 7.37–7.29 (2H, m, Ar), 7.28–7.20 (3H, m, Ar), 4.97 (1H, dt, *J* = 6.0, 1.9 Hz, CH), 3.90 (1H, dt, *J* = 9.7, 6.3 Hz, 1H, CH), 3.79 (s, 3H, CH_3), 3.67 (1H, ddd, *J* = 17.3, 9.7, 2.1 Hz, CH_2), 3.18 (1H, ddd, *J* = 17.4, 6.5, 1.7 Hz, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.2 (C), 172.8 (C), 143.3 (C), 133.7 (C), 131.4 (CH), 129.1 (CH), 128.7 (CH), 128.3 (CH), 127.1 (CH), 127.1 (CH), 82.7 (CH), 52.6 (CH_3), 46.4 (CH), 44.9 (CH_2); **HRMS** (ESI) *m/z*: 302.1160 $[M+Na]^+$, $C_{18}H_{17}NNaO_2^+$ requires 302.1151. Data consistent with the literature.[112]

Methyl (5*S*,8*R*,9*R*)-1-oxo-4,9-diphenyl-2-oxa-3,7-diazaspiro[4.4]non-3-ene-8-carboxylate (42)



A modification of a literature procedure was employed. To a solution of the major diastereomer **37aa** (10.0 mg, 0.029 mmol, *ee* 86% obtained by semi-preparative HPLC) and Et_3SiH (14 µL, 0.086 mmol) in dichloromethane (0.9 mL) was added $BF_3{\cdot}Et_2O$ (12 µL, 0.096 mmol). The reaction was stirred for 3 h and quenched with saturated $NaHCO_3$ (5 mL). Dichloromethane (10 mL) was added and the organic phase was washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (Hexane:AcOEt 7:3) afforded 5.3 mg (52%) of compund **42**. Enantiomeric excess (85%) was measured by HPLC (Lux® i-Amylose-1), hexane:^{i}PrOH 80:20, 1.0 mL/min, major enantiomer: t_r = 17.9 min, minor enantiomer: t_r = 21.1 min.

White foam; $[\alpha]_D^{25}$ –43.1 (*c* 0.4, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.00–7.93 (2H, m, Ar), 7.63–7.53 (3H, m, Ar), 7.29–7.23 (3H, m, Ar), 7.11–7.04 (2H, m, Ar), 4.71 (1H, d, *J* = 9.9 Hz, CH), 4.26 (1H, d, *J* = 9.8 Hz, CH), 3.97 (1H, d, *J* = 12.1 Hz, CH), 3.69 (1H, d, *J* = 12.0 Hz, 1H, CH), 3.68 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 179.0 (C), 172.7 (C), 165.3 (C), 132.4 (C), 132.2 (CH), 129.7 (CH), 129.0 (CH), 128.8 (CH), 128.3 (CH), 127.2 (C), 127.0 (C), 63.0 (CH), 62.2 (C), 57.8 (CH), 54.8 (CH_2), 52.8 (CH_3); **HRMS** (ESI) *m/z*: 373.1163 $[M+Na]^+$, $C_{20}H_{18}N_2NaO_4^+$ requires 373.1159.

6. Conclusiones

1. Se han desarrollado nuevas reacciones de adición enantioselectivas haciendo uso de isocianoacetatos y diferentes electrófilos. Se han sintetizado diferentes heterociclos nitrogenados mediante un sistema multicatalítico que consiste en un organocatalizador bifuncional de tipo escuaramida y Ag^+ como ácido de Lewis.

2. Se ha llevado a cabo la adición enantioselectiva de isocianoacetatos a 2,2,2-trifluorometilcetonas de forma enantioselectiva para la formación de oxazolinas con un centro cuaternario sustituido con un grupo trifluorometilo. Se ha optimizado la reacción con isocianoacetato de metilo, de *terc*-butilo y 2-fenil-2-isocianoacetato. Se han estudiado un amplio número 2,2,2-trifluorometilcetonas alcanzando excelentes rendimientos, diastereoselectividades y excesos enantioméricos. Haciendo uso de 2-fenil-2-isocianoacetato de metilo se obtienen las oxazolinas con dos centros cuaternarios consecutivos y excelentes diastereoselectividades y enantioselectividades.

   Se ha asignado la configuración absoluta de las oxazolinas como 4*S*,5*S* mediante análisis de rayos X para los isocianoacetatos de metilo y *terc*-butilo. Desafortunadamente la configuración absoluta de las oxazolinas obtenidas con 2-fenil-2-isocianoacetato no ha podido ser determinada.

3. Se ha descrito la síntesis de *cis*-oxazolinas a partir de cetonas con moderada diastereoselectividad y excelente exceso enantiomérico. El sistema catalítico diseñado permite la obtención de oxazolinas a partir de acetofenonas sustituidas con grupos de diferente naturaleza electrónica en el anillo aromático y cetonas con excelente enantioselectividad en todos los casos (95-99%).

   La configuración absoluta de los productos se ha asignado mediante análisis de rayos X, asignando la configuración absoluta como 4*R*,5*R*.

4. Se ha descrito la síntesis de 2-imidazolinonas quirales mediante una reacción de cicloadición entre nitronas e isocianoacetatos. Se obtiene un producto de cicloadición formal [3+2] en lugar del esperado [3+3]. Los productos se obtienen con buenos rendimientos, moderada diastereoselectividad y altos excesos enantioméricos. La reacción es compatible con una gran variedad de nitronas llegando a alcanzar enantioselectividades del 99%.

   Se ha determinado la configuración absoluta de las 2-imidazolinonas mediante correlación química como 4*R*,5*S*.

5. Por primera vez se han sintetizado diazaespirociclos altamente funcionalizados mediante la reacción entre 4-alquiliden-5-isoxazolonas e isocianoacetatos. Se han evitado los problemas de polimerización y reacción de fondo obteniendo los productos con moderada diastereoselectividad y alta enantioselectividad. Los espirociclos tienen tres centros estereogénicos consecutivos siendo uno de ellos

cuaternario y espiránico. La reacción se puede llevar a cabo con numerosas 4-alquiliden-5-isoxazolonas.

La configuración absoluta se ha determinado mediante una combinación de experimentos de RMN y correlación química. La configuración absoluta se ha asignado para el mayor de los diastereoisómeros obtenidos en la reacción siendo 5*S*,8*R*,9*R*.

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Publicaciones

Martinez-Pardo, P.; Blay, G.; Muñoz, M. C.; Pedro, J. R.; Sanz-Marco, A.; Vila, C. Enantioselective synthesis of chiral oxazolines from unactivated ketones and isocyanoacetate esters by synergistic silver/organocatalysis. *Chem. Commun.* **2018.** *54*, 2862–2865. https://doi.org/10.1039/C8CC00856F.

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Enantioselective synthesis of chiral oxazolines from unactivated ketones and isocyanoacetate esters by synergistic silver/organocatalysis†

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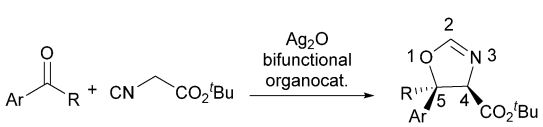
A multicatalytic approach that combines a bifunctional Brønsted base–squaramide organocatalyst and Ag^+ as Lewis acid has been applied in the reaction of unactivated ketones with *tert*-butyl isocyanoacetate to give chiral oxazolines bearing a quaternary stereocenter. The formal [3+2] cycloaddition provided high yields of the corresponding *cis*-oxazolines with good diastereoselectivity and excellent enantioselectivity, being applied to aryl–alkyl and alkyl–alkyl ketones.

Oxazolines are five-membered heterocycles bearing an O atom and a N atom in 1,3-positions, and a double bond that can be located in one of three different positions. The most common 2-oxazolines have a great relevance in natural product, pharmaceutical and agricultural chemistry,[1] and they have found wide application as privileged chiral ligands in asymmetric catalysis.[2] In particular, the chiral 2-oxazoline-4-carboxyl framework is present in a large number of natural products with antibacterial, antiviral or antitumor activities.[3] These compounds are also intermediates in the synthesis of β-hydroxy-α-amino acids *via* hydrolysis or reduction of the oxazoline ring.[4] Accordingly, the development of procedures for the efficient enantioselective synthesis of such compounds is of great interest to synthetic and medicinal chemists. In 1970 Schöllkopf described a straightforward procedure for the synthesis of 2-oxazoline-4-carboxylate esters *via* a formal [3+2] cycloaddition reaction between ethyl isocyanoacetate and carbonyl compounds catalyzed by sodium cyanide.[5] Since then, different experimental conditions have been implemented[6] to achieve this reaction even in an enantioselective fashion. Thus, the catalytic asymmetric version has been widely studied with aldehydes under metal,[7] organo,[8] or mixed metal-organo catalysis.[9] In contrast, the asymmetric reaction of isocyanoacetates with ketones, which provides oxazolines having a quaternary stereocenter, has been scarcely studied. Two examples involving 1,2-dicarbonyl compounds have been reported. Zhao and Shi achieved the addition of 2-phenylisocyanoacetates to isatins using an amine-thiourea organocatalyst obtaining spirooxindole oxazolines with good diastereo- and enantioselectivity,[10] while Chen and Huang have also used a thiourea organocatalyst to carry out the reaction between isocyanoacetates and α-keto esters with good enantioselectivity and moderate diastereoselectivity.[11] Furthermore, Dixon has reported the, so far, only example of this kind of reaction with unactivated aryl–alkyl ketones giving rise to *trans*-4-carboxyl-2-oxazolines with good diastereo- and enantioselectivity.[12] Despite these advances, limitations regarding stereoselectivity and the substrate scope still remain strong. Therefore, the development of new procedures for this formal [3+2] cycloaddition that allow modifying the diastereoselectivity and/or expanding the application to other unactivated ketones is highly desirable.

In this communication we report a new catalytic procedure for the reaction of *tert*-butyl isocyanoacetate with unactivated ketones which provides *cis*-4-carboxyl-2-oxazolines in a complementary mode to the reaction described by Dixon (Scheme 1).

Our strategy is based on a multicatalytic approach that combines a bifunctional Brønsted base–squaramide organocatalyst and Ag^+ as Lewis acid (Fig. 1). In this catalytic system, the squaramide moiety would provide electrophilic activation of the ketone through hydrogen bonding at the same time as the coordination of Ag^+ to the isocyano group would facilitate the deprotonation of the isocyanoacetate by the Brønsted base



Scheme 1 Formal [3+2] cycloaddition of ketones and isocyanoacetate ester.

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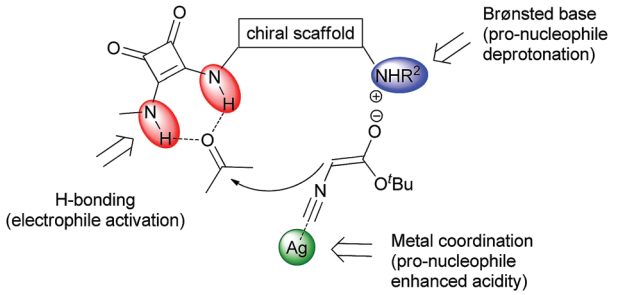


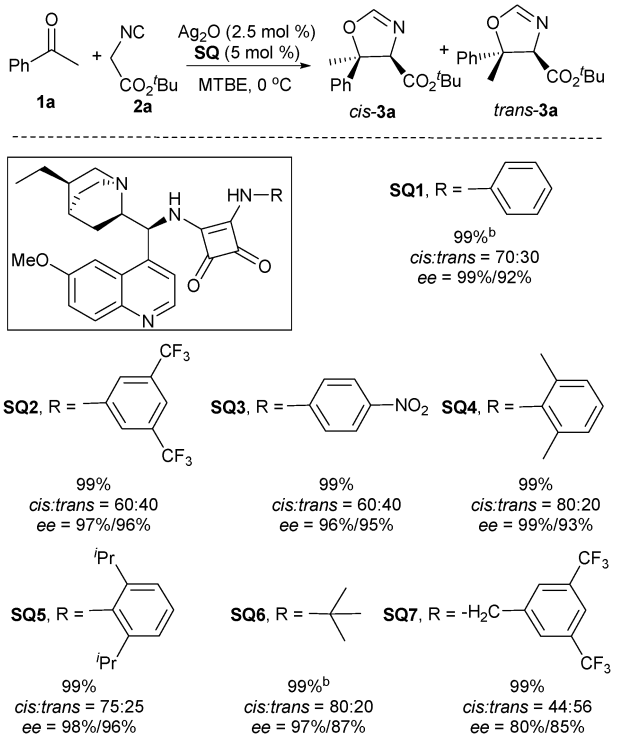
Fig. 1 Multicatalytic approach.

organocatalyst, enhancing the reaction rate *via* this double activation of the pronucleophile.[13]

The reaction of acetophenone (**1a**) with *tert*-butyl isocyanoacetate (**2**) in methyl *tert*-butyl ether (MTBE) was selected as a model system to assess the performance of several Ag_2O/dihydroquinine–squaramide catalytic systems, which were employed in a 1 : 2 ratio of metal oxide and organocatalysts (Table 1).‡

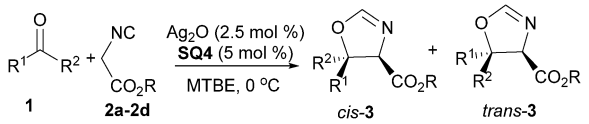
All the organocatalysts (5 mol%) tested in combination with silver oxide (2.5 mol%) provided oxazoline **3a** in quantitative yield after 24 hours of reaction. In all the cases, except with **SQ7** derived from a benzylic amine, the *cis* oxazoline was obtained as the major diastereomer. This result contrasts with that reported by Dixon, who obtained the *trans* isomer as the major product with his catalyst. Most of the squaramides tested gave the expected oxazolines with excellent enantiomeric excesses.

Table 1 Organocatalyst screening[a]



[a] **1a** (0.25 mmol), **2** (0.32 mmol) Ag_2O (0.0063 mmol), **SQ** (0.0125 mmol), MTBE (8 mL), 0 °C. [b] Reaction carried out at r.t.

Table 2 Substrate scope of the formal [3+2] cycloaddition[a]



2a R = ^{t}Bu **2c** R = ^{i}Pr
2b R = Me **2d** R = Bn

Entry	1	2	R^1	R^2	t (h)	3	Yield[b] (%)	*cis* : *trans*[c]	ee[d] (%)
1	**1a**	**2a**	Ph	Me	26	**3a**	99	80 : 20	99/93
2	**1b**	**2a**	4-MeC_6H_4	Me	20	**3b**	79	77 : 23	99/90
3	**1c**	**2a**	4-$MeOC_6H_4$	Me	72	**3c**	70	78 : 22	98/99
4	**1d**	**2a**	4-BrC_6H_4	Me	48	**3d**	99	75 : 25	98/93
5	**1e**	**2a**	4-$NO_2C_6H_4$	Me	20	**3e**	95	56 : 44	96/95
6	**1f**	**2a**	3-MeC_6H_4	Me	13	**3f**	88	62 : 38	99/97
7	**1g**	**2a**	3-$MeOC_6H_4$	Me	14	**3g**	60	70 : 30	98/93
8	**1h**	**2a**	3-ClC_6H_4	Me	14	**3h**	75	74 : 26	99/91
9	**1i**	**2a**	3-$NO_2C_6H_4$	Me	13	**3i**	97	63 : 37	95/90
10	**1j**	**2a**	2-MeC_6H_4	Me	24	**3j**	91	91 : 9	99/89
11	**1k**	**2a**	2-$MeOC_6H_4$	Me	16	**3k**	99	95 : 5	99/—
12	**1l**	**2a**	2-ClC_6H_4	Me	12	**3l**	99	92 : 8	98/92
13	**1m**	**2a**	2-$NO_2C_6H_4$	Me	12	**3m**	99	73 : 30	95/30
14	**1n**	**2a**	2-Thienyl	Me	20	**3n**	81	45 : 55	92/98
15	**1o**	**2a**	Ph	^{i}Pr	12	**3o**	63	98 : 2	97/—
16	**1p**	**2a**	Ph	$PhCH_2$	48	**3p**	99	61 : 39	97/95
17	**1q**	**2a**	Me	Me	20	**3q**	85	—	96
18	**1r**	**2a**	$-(CH_2)_5-$		20	**3r**	96	—	95
19	**1s**	**2a**	^{i}Pr-CH_2	Me	48	**3s**	71	70 : 30	98/56
20	**1t**	**2a**	Cyclopropyl	Me	48	**3t**	81	56 : 44	97/87
21	**1a**	**2b**	Ph	Me	72	**3u**	82	80 : 20	96/84
22	**1a**	**2c**	Ph	Me	48	**3v**	76	70 : 30	97/90
23	**1a**	**2d**	Ph	Me	48	**3w**	78	80 : 20	96/82

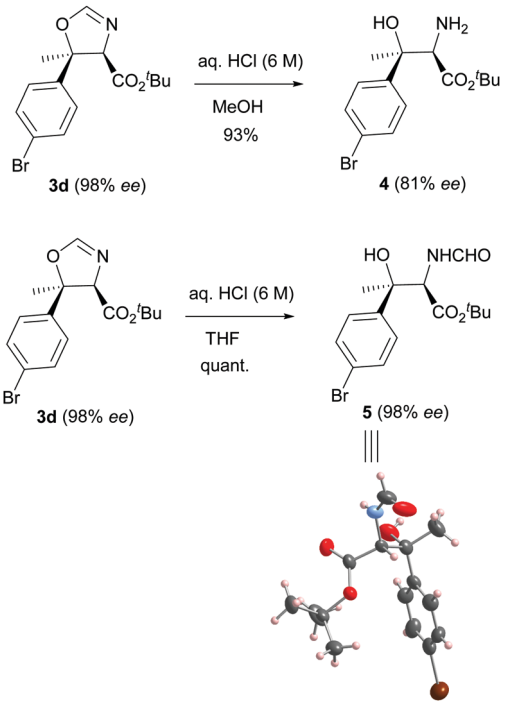
[a] **1** (0.25 mmol), **2** (0.32 mmol) Ag_2O (0.0063 mmol), **SQ4** (0.0125 mmol), MTBE (8 mL), 0 °C. [b] Yield of isolated products. [c] Determined by ^{1}H NMR. [d] Determined by HPLC over chiral chromatography phases.

Squaramides **SQ4** and **SQ6**, derived from 1,6-dimethylaniline and *tert*-butyl amine, respectively, also provided the best diastereoselectivity, keeping high enantiomeric excesses.

Using **SQ4**/Ag_2O as the best combination, we proceeded to study the scope of the reaction of *tert*-butyl isocyanoacetate with different ketones (Table 2).§ Several acetophenone derivatives substituted with either electron-withdrawing or electron-donating groups at different positions of the aromatic ring afforded the *cis*-configured oxazolines **3a–3m** with good yields and fair to good (62 : 38 to 95 : 5) diastereoselectivities (Table 2, entries 1–13) except for nitroacetophenones (Table 2, entries 5, 9 and 13). Diastereoselectivities were especially high with *ortho*-substituted acetophenones (Table 2, entries 10–13).

In all the cases, both diastereomers were obtained with excellent enantiomeric excesses, higher than 95% for the major *cis*-diastereomer. In general, the reaction with substituted acetophenones took place with slightly lower diastereoselectivity but higher enantiomeric excesses than those obtained with Dixon's catalyst for similar substrates.

The reaction also proceeded with heterocyclic 2-acetylthiophene (**1n**) to give the corresponding oxazoline **3n** with low diastereoselectivity, slightly favoring the *trans* isomer, but still with excellent enantiomeric excesses for both diastereomers (Table 2, entry 14). Isopropyl ketone **1o** afforded the *cis* oxazoline



Scheme 2 Hydrolysis of compound *cis*-**3d**. ORTEP plot for the X-ray structure of compound **5**. Flack parameter = 0.019(10), Hooft parameter = 0.037(10).

3o as almost only one diastereomer with 97% ee (Table 2, entry 15), while deoxybenzoin (**1p**) yielded a 61 : 39 diastereomer mixture of oxazolines **3p** with excellent enantioselectivity for both isomers (Table 2, entry 16). Finally, we studied the reaction with several aliphatic ketones, which are challenging substrates for this reaction. Remarkably, acetone (**1q**), which provided the corresponding oxazoline almost in the racemic form under Dixon's conditions, gave oxazoline **3q** in excellent yield and enantiomeric excess (Table 2, entry 17). Similarly, cyclohexanone (**1r**) gave spirocyclic oxazoline **3r** in 96% yield and 95% ee (Table 2, entry 18). Unsymmetrical ketones such as 4-methyl-2-pentanone (**1s**) and acetylcyclopropane (**1t**) lead to the corresponding oxazolines **3s** and **3t** with moderate diastereoselectivity but excellent enantioselectivity for the major diastereomers (Table 2, entries 19 and 20), demonstrating the broad scope of the reaction with respect to unactivated ketones.

Other isocyanoacetate esters were tested (Table 2, entries 21–23). Methyl- (**2b**), isopropyl- (**2c**) and benzyl- (**2d**) isocyanoacetates reacted with acetophenone (**1a**) to give the expected oxazolines **3u–3w** with good yields, diastereoselectivities and excellent enantioselectivities for the major diastereomer. Methyl- and benzyl-isocyanoacetates gave similar diastereomeric ratios to those of the *tert*-butyl ester, while isopropyl isocyanoacetate gave lower diastereoselectivity.

Oxazolines are synthetic precursors of amino alcohols. Thus, treatment of oxazoline **3d** with aqueous hydrochloric acid in MeOH for 24 hours provided amino alcohol **4** in 93% yield, although with a noticeable loss of enantiomeric excess (Scheme 2). Similarly, partial hydrolysis of compound **3d** upon treatment with aqueous hydrochloric acid in THF gave a quantitative yield of hydroxyformamide **5** without any noticeable loss of ee, which could be crystallized and subjected to X-ray analysis.¶ In this way, the absolute stereochemistry of compound **5** could be determined, and hence compound *cis*-**3d** was assigned the 4*R*,5*R* configuration. The stereochemistry of the remaining oxazolines *cis*-**3a–3r** was assigned on the assumption of a uniform stereochemical pathway. On the other hand, the absolute stereochemistry of the minor *trans*-diastereomers **3a–3r** was assigned as 4*R*,5*S* by comparing with the data reported by Dixon for these compounds in his pioneering work.[12]

In summary, we have developed a new catalytic enantioselective procedure for the reaction between unactivated ketones and isocyanoacetates to give chiral oxazolines bearing a quaternary stereocenter. Our strategy is based on a multicatalytic approach that combines a bifunctional Brønsted base–squaramide organocatalyst and Ag^+ as a Lewis acid. The reaction provides the corresponding *cis*-oxazolines with good diastereoselectivity and excellent enantioselectivity. In this way, our method may be considered complementary to that of Dixon since we obtain *cis*- instead of *trans*-oxazolines. Furthermore, our reaction shows a broader substrate scope and can be applied not only to aryl–alkyl but also to alkyl–alkyl ketones. Further research addressed to develop new applications of this reaction is underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ In the absence of either Ag_2O or squaramide, no progress of the reaction between **1a** and **2a** was observed after 48 h at 0 °C. These control experiments indicate that catalysis requires the synergistic action of both metal and the organocatalyst.

§ Squaramide **SQ4** (6.6 mg, 0.0125 mmol) and silver oxide (1.5 mg, 0.0063 mmol) were introduced in a 25 mL round bottom flask followed by MTBE (8 mL) and ketone **1** (0.25 mmol). The flask was closed with a stopper and placed in an ice bath. After 5 min, *tert*-butyl isocyanoacetate **2** (48 μL, 0.330 mmol) was added and the mixture was stirred at 0 °C until consumption of the ketone **1** (TLC). After this, the reaction mixture was filtered through a short pad of silica gel and concentrated under reduced pressure. A small aliquot was analyzed by ^{1}H NMR to determine the diastereomer ratio and by HPLC to determine the enantiomeric excess of products **3**. The remaining crude was chromatographed on silica gel eluting with hexane:EtOAc mixtures (9 : 1 to 8 : 2) to obtain the separated diastereomers *cis*-**3** and *trans*-**3**.

¶ CCDC 1818227 contains the supplementary crystallographic data for compound **5**.

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Enantioselective Synthesis of 5-Trifluoromethyl-2-oxazolines under Dual Silver/Organocatalysis

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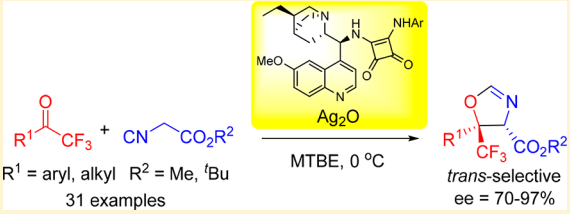
Supporting Information

ABSTRACT: The first enantioselective formal [3 + 2] cycloaddition between α-isocyanoesters and trifluoromethylketones to give 5-trifluoromethyl-2-oxazolines bearing two contiguous stereogenic centers, one of them being a quaternary stereocenter substituted with a CF_3 group, has been developed. The reaction is based upon a multicatalytic approach that combines a bifunctional Brønsted base-squaramide organocatalyst and Ag^+ as Lewis acid. The reaction could be achieved with a range of aryl and heteroaryl trifluoromethyl ketones, and the resulting oxazolines were obtained with good to excellent diastereo- and enantioselectivity.



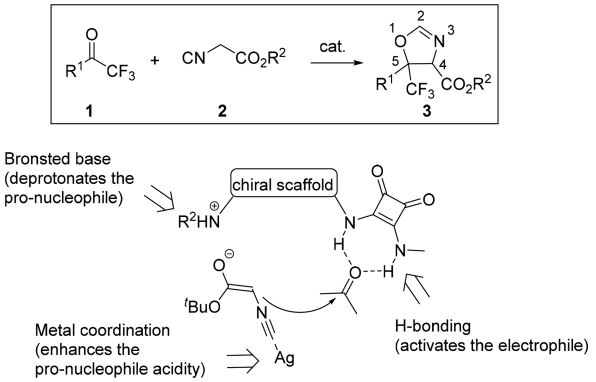
INTRODUCTION

The 2-oxazoline moiety is present in a large number of natural products, drugs, and bioactive compounds.[1] Chiral oxazolines have also found important applications in organic synthesis as ligands in asymmetric catalysis,[2] as well as synthetic intermediates for 1,2-aminoalcohols and other relevant compounds.[3] In recent years, the enantioselective formal [3 + 2] cycloaddition of α-isocyanoesters with carbonyl compounds has emerged as an elegant and powerful strategy for the construction of chiral substituted 2-oxazolines bearing two adjacent stereocenters and considerable success on this reaction has been obtained with aldehydes[4] and, to a lesser extent, with ketones.[5]

On the other hand, the introduction of trifluoromethyl substituents[6] into organic molecules has attracted great attention in the field of medicinal chemistry because of the significant impact of the trifluoromethyl group on the metabolic stability and bioavailability of drugs.[7] For these reasons, different strategies have been devised for the synthesis of trifluoromethylated heterocycles, involving either the trifluoromethylation of nonfluorinated heterocycles[8] or cycloaddition/cyclization reactions from trifluoromethylated building blocks.[9] In this context, the 5-trifluoromethyl-2-oxazoline moiety is especially appealing, as it is a synthetic precursor for fluorinated nonproteinogenic amino acids and trifluoromethyl amino alcohols, which have important applications in medicinal chemistry[10] and biochemical studies,[11] and as conformational modifiers in physiologically active proteins and enzymes.[12]

Herein, we report the enantioselective formal [3 + 2] cycloaddition between α-isocyanoesters and trifluoromethylketones to give 5-trifluoromethyl-2-oxazolines bearing two contiguous stereogenic centers, one of them being a quaternary stereocenter substituted with a CF_3 group (Scheme 1). Although such a reaction has been diastereoselectively performed, a catalytic asymmetric version has not been developed so far, to the best of our knowledge.[13]

Scheme 1. Formal [3 + 2] Cycloaddition between Trifluoromethylketones and α-Isocyanoesters and Plausible Mode of Action of the Catalyst



RESULTS AND DISCUSSION

Recently, on the basis of a cooperative strategy previously reported by Escolano et al. for the asymmetric cycloaddition of isocyanoacetates with vinyl ketones,[14] our group developed a highly catalytic enantioselective cycloaddition reaction between ketones and α-isocyanoesters using a multicatalytic approach that combined a bifunctional Brønsted base-

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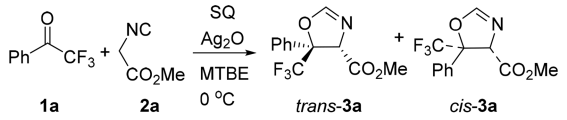
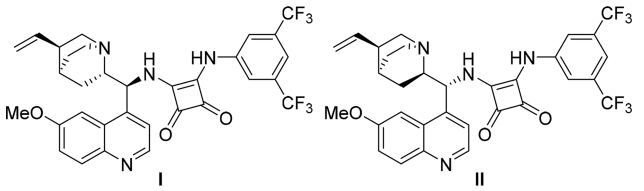
squaramide organocatalyst and Ag^+ as Lewis acid (Scheme 1).[5d]

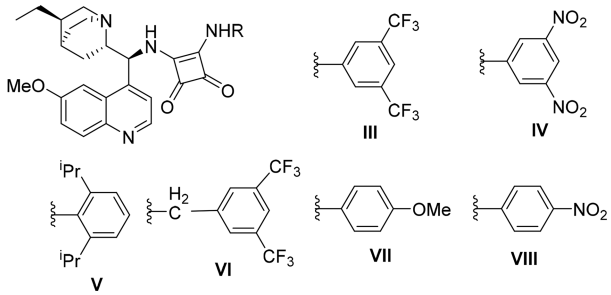
Following this approach,[14] we tested the reaction of trifluoroacetophenone (**1a**) and methyl isocyanoacetate (**2a**) in the presence of several bifunctional squaramides (**SQ**, 10 mol %) and Ag_2O (5 mol %) in methyl *tert*-butyl ether (MTBE) at 0 °C (Table 1, see also Tables S1–S3 in the Supporting Information). The reaction did not proceed in the absence of Ag_2O (Table 1, entry 1). On the other hand, all of the squaramides tested in combination with silver oxide provided oxazoline **3a** in good yields and in a short reaction time. The *trans* diastereomer was obtained diastereoselectively in all of the cases except with squaramide **VI** (Table 1, entry 7). The best result in terms of enantioselectivity was obtained with squaramide **III**, derived from dihydroquinine and 3,5-bis(trifluoromethyl)aniline, that provided oxazoline **3a** in almost quantitative yield with 95:5 dr and 83% ee for the major diastereomer (Table 1, entry 4).

Table 1. Bifunctional Squaramide Screening[a]



1a 2a *trans*-3a *cis*-3a





entry	SQ	*t* (h)	yield[b] (%)	*trans:cis*[c]	$ee_{trans/cis}$[d] (%)
1[e]	**I**	72			
2	**I**	0.5	>95	99:1	77/57
3	**II**	0.5	85	99:1	−66/−28[f]
4	**III**	0.5	>95	95:5	83/61
5	**IV**	17	>95	95:5	81/56
6	**V**	0.5	50	100:--	67/--
7	**VI**	5	>95	50:50	29/70
8	**VII**	0.5	>95	85:15	58/33
9	**VIII**	0.5	>95	79:21	78/65

[a]**1a** (0.25 mmol), **2a** (0.33 mmol), **SQ** (0.026 mmol), Ag_2O (0.0125 mmol), MTBE (2 mL), 0 °C. [b]Yield of isolated product. [c]Determined by ^1H NMR. [d]Determined by HPLC over chiral chromatography phases. [e]Reaction carried out in the absence of silver salt. No advance was observed after the indicated time. [f]The opposite enantiomer was obtained.

A strong concentration effect was also found, with the diastereo- and enantioselectivity of the reaction increasing with the dilution of the reaction mixture (Table 2, entries 1–3). The use of a 1:2 squaramide/Ag_2O ratio increased the diastereoselectivity but unfortunately lowered the enantioselectivity (Table 2, entry 4). Notably, the use of a 1:1 squaramide/Ag_2O mixture provided similar results to the initially tested 2:1 mixture, with it being possible to reduce the catalyst load to 2.5 mol % without a noticeable effect on the stereoselectivity (Table 2, entries 3 and 5).

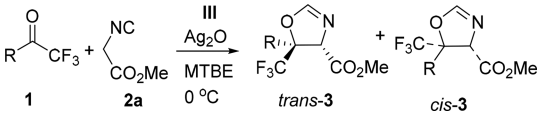
Table 2. Effect of Concentration and Squaramide/Ag_2O Ratio[a]

entry	[**1a**][b]	**III**:Ag_2O	*t* (h)	yield[c] (%)	*trans:cis*[d]	ee_{trans}[e] (%)
1	0.13	2:1	0.5	>95	95:5	83
2	0.26	2:1	0.5	>95	87:13	75
3	0.033	2:1	4	>95	96:4	90
4[f]	0.033	1:2	3	90	99:1	82
5[g]	0.033	1:1	18	>95	94:6	90

[a]**1a** (0.25 mmol), **2a** (0.33 mmol), **III** (0.026 mmol), Ag_2O (0.0125 mmol), MTBE, 0 °C. [b]Molar concentration. [c]Yield of isolated product. [d]Determined by ^1H NMR. [e]Determined by HPLC over chiral chromatography phases. [f]**III** (0.0065 mmol). [g]**III** (0.0033 mmol).

Under the optimized conditions, the scope of the reaction of methyl isocyanoacetate (**2a**) and several substituted trifluoroacetophenones **1** was studied (Table 3).[15] In general, the presence of substituents at the *ortho* or *para* positions of the aromatic ring brought about some decrease of enantioselectivity, while the *meta*-substituted trifluoroacetophenones gave similar or higher enantiomeric excesses than ketone **1a** (Table 3, entries 5–7). A negative effect of electron-withdrawing groups on the diastereoselectivity was also observed (Table 3, entries 4, 9, and 10). The heterocyclic trifluoroacetylthiophene

Table 3. Enantioselective Reaction of Trifluoromethylketones and Methyl Isocyanoacetate. Substrate Scope[a]



1 2a *trans*-3 *cis*-3

entry	**1**	R	*t* (h)	**3**	yield[b] (%)	*trans:cis*[c]	ee_{trans}[d] (%)
1	**1a**	Ph	4	**3a**	>95	96:4	90
2	**1b**	4-MeC_6H_4	5	**3b**	>95	94:6	87
3	**1c**	4-$MeOC_6H_4$	3.5	**3c**	88	96:4	85
4	**1d**	4-ClC_6H_4	4	**3d**	>95	80:20	84
5	**1e**	3-MeC_6H_4	5	**3e**	>95	94:6	90
6	**1f**	3-$MeOC_6H_4$	4	**3f**	94	92:8	88
7	**1g**	3-BrC_6H_4	3.5	**3g**	95	86:14	92
8	**1h**	2-$MeOC_6H_4$	16	**3h**	>95	99:1	85
9	**1i**	2-BrC_6H_4	14	**3i**	93	85:15	70
10	**1j**	3,4-$Cl_2C_6H_3$	16	**3j**	>95	77:23	85
11	**1k**	2-thienyl	5.5	**3k**	>95	92:8	90
12	**1l**	$PhCH_2CH_2$	15	**3l**	66	86:14	81
13	**1m**	CH_3	7	**3m**	80	92:8	82
14[e]	**1a**	Ph	2	**3a**	>95	92:8	90

[a]**1a** (0.25 mmol), **2a** (0.33 mmol), **III** (0.0063 mmol), Ag_2O (0.0063 mmol), MTBE (8 mL), 0 °C. [b]Yield of isolated product. [c]Determined by ^1H NMR. [d]Determined by HPLC over chiral chromatography phases. [e]Reaction scaled up to 1.25 mmol of **1a**.

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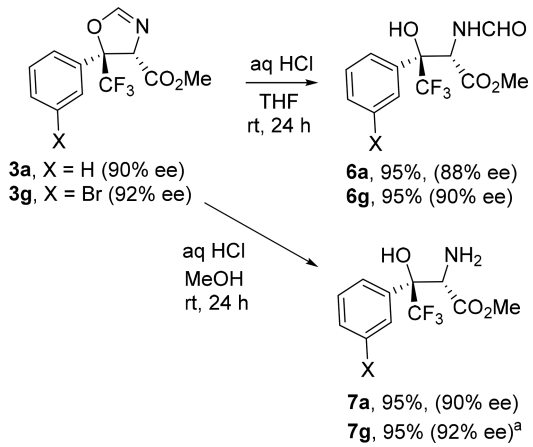
(**1k**) proved to be a suitable substrate that reacted with good diastereo- and enantioselectivity (Table 2, entry 11). Alkyl-substituted trifluoromethylketones **1l** and **1m** were also tested, which provided oxazolines **3l** and **3m**, respectively, with moderate diastereo- and enantioselectivity (Table 2, entries 12 and 13). Finally, the reaction was scaled up to 1.25 mmol of compound **1a**, obtaining oxazoline **3a** without any noticeable loss of efficiency, indicating the robustness of the method (Table 3, entry 14).

The configuration of the stereogenic centers in compound *trans*-**3g** was determined as (4*S*,5*S*) after hydrolysis and X-ray analysis of the resulting amino alcohol **7g** (Scheme 2).[16] For the remaining compounds **3**, the stereochemistry was assigned under the assumption of a uniform mechanistic pathway.[17]

Scheme 2. Hydrolysis of Oxazolines 3a and 3g



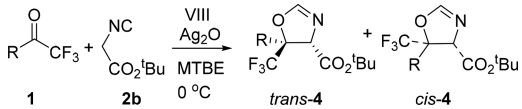
[a]Structure determined by X-ray analysis (see ref 16).

Next, we tested the performance of other isocyano esters having different alkoxy groups (see Table S4 in the Supporting Information). *tert*-Butyl isocyanoacetate seemed to promote the highest enantioselectivity using squaramide **VIII** instead of **III**. The reaction of trifluoromethylketones **1** with *tert*-butyl isocyanoacetate (**2b**) showed a similar substrate scope as the reaction with the methyl ester. In general, the reaction took place with moderate to good diastereoselectivity and high to excellent enantioselectivity for the major diastereomer (Table 4). X-ray analysis of compound **4i**[16] allowed us to assign the absolute sterochemistry of compounds **4** as (4*S*,5*S*), indicating a similar stereochemical pathway as the reaction with methyl isocyanoacetate.[17]

Finally, the reaction of several trifluoromethylketones **1** with methyl 2-isocyano-2-phenylacetate (**2c**) to give oxazolines **5** bearing two contiguous quaternary stereocenters was achieved in the presence of squaramide **VIII** and Ag_2O (Table 5).[18] In this case, the reaction worked better under higher concentration and with a 2:1 ratio of squaramide/Ag_2O and yielded the *cis* diastereomer as the major one.[17] Fair to good diastereomeric ratios and high enantiomeric excesses were obtained for trifluoroacetophenone derivatives having electron-donating or slightly electron-withdrawing groups. However, the reaction did not proceed with *ortho*-substituted trifluoroacetophenones.

Tosylmethylisocyanide (TOSMIC) was also tested in the reaction with trifluoromethylketone **1a**, although, unfortunately, no reaction was observed under any of the optimized conditions.

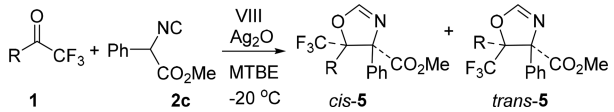
Table 4. Enantioselective Reaction of Trifluoromethylketones and *tert*-Butyl Isocyanoacetate. Substrate Scope[a]



entry	1	R	t (d)	4	yield[b] (%)	trans:cis[c]	ee$_{trans/cis}$[d] (%)
1	**1a**	Ph	1	**4a**	>95	70:30	96/90
2	**1b**	4-MeC_6H_4	7	**4b**	87	66:34	93/96
3	**1c**	4-MeOC_6H_4	7	**4c**	>95	63:37	84/77
4	**1d**	4-ClC_6H_4	1	**4d**	>95	53:47	96/90
5	**1e**	3-MeC_6H_4	6	**4e**	94	76:24	97/87
6	**1f**	3-MeOC_6H_4	4	**4f**	84	72:28	97/85
7	**1g**	3-BrC_6H_4	1	**4g**	>95	64:36	97/90
8	**1h**	2-MeOC_6H_4	12	**4h**	80	94:6	94/70
9	**1i**	2-BrC_6H_4	3	**4i**[e]	>95	99:1	91/nd
10	**1j**	3,4-$Cl_2C_6H_3$	1	**4j**	>95	53:47	94/85
11	**1k**	2-thienyl	1	**4k**	>95	62:38	97/91
12	**1l**	CH_2CH_2Ph	1	**4l**	83	72:28	84/87

[a]**1** (0.25 mmol), **2b** (0.33 mmol), **VIII** (0.0063 mmol), Ag_2O (0.0063 mmol), MTBE (8 mL), 0 °C. [b]Yield of isolated product. [c]Determined by ^1H NMR. [d]Determined by HPLC over chiral chromatography phases. [e]Structure determined by X-ray analysis (see ref 16).

Table 5. Enantioselective Reaction of Trifluoromethylketones and Methyl 2-Isocyano-2-phenylacetate. Substrate Scope[a]



entry	1	R	t (d)	5	yield[b] (%)	trans:cis[c]	ee$_{cis}$[d] (%)
1	**1a**	Ph	1	**5a**	89	15:85	90
2	**1c**	4-MeOC_6H_4	3	**5c**	42	21:79	89
3	**1d**	4-ClC_6H_4	1	**5d**	>95	10:90	89
4	**1n**	4-BrC_6H_5	2	**5n**	82	13:87	89
5	**1e**	3-MeC_6H_4	1	**5e**	86	1:99	90
6	**1f**	3-MeOC_6H_4	3	**5f**	86	15:85	89
7	**1g**	3-BrC_6H_4	7	**5g**	81	2:98	88
8	**1h**	2-MeOC_6H_4	5	**5h**	*e*		

[a]**1** (0.25 mmol), **2c** (0.33 mmol), **VIII** (0.0125 mmol), Ag_2O (0.0063 mmol), MTBE (2 mL), −20 °C. [b]Yield of isolated product. [c]Determined by ^1H NMR. [d]Determined by HPLC over chiral chromatography phases. [e]No advance observed after 5 days.

The prepared oxazolines are synthetic precursors for trifluoromethylated amino alcohols. Thus, treatment of oxazolines **3a** or **3g** with aqueous HCl in THF gave almost quantitative yields of hydroxyformamides **6a** or **6g**, respectively, with a minor decrease of ee. On the other hand, treatment of **3a** or **3g** with aqueous hydrochloric acid in MeOH yielded amino alcohols **7a** and **7g** in high yields, without erosion of enantiomeric excesses (Scheme 2).

Furthermore, oxazoline **3m**, prepared in 82% ee from methyl isocyanoacetate and 1,1,1-trifluoroacetone (Table 1, entry 13), upon treatment with aqueous HCl in methanol for 72 h, could be transformed into amino alcohol **7m** (82% ee), a known

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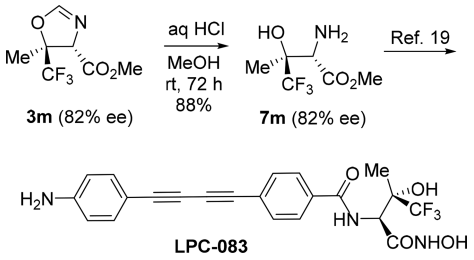
intermediate in the synthesis of LPC-083, which is an inhibitor of LpxC, an essential enzyme of the lipid A biosynthetic pathway in Gram-negative bacteria and a validated antibiotic target (Scheme 3).[19]

Scheme 3. Formal Enantioselective Synthesis of LPC-083



CONCLUSIONS

In summary, we have developed the first catalytic enantioselective formal [3 + 2] cycloaddition of trifluoromethylketones and isocyanoacetates. Using a multicatalytic approach that combines a bifunctional Brønsted base-squaramide organocatalyst and Ag^+ as Lewis acid, we were able to obtain chiral oxazolines bearing a quaternary stereocenter substituted with a trifluoromethyl group and a contiguous tertiary or quaternary stereocenter. The reaction was broad in scope and provided a straightforward access to chiral trifluoromethylated hydroxy amino esters.

EXPERIMENTAL SECTION

General Experimental Methods. Formal [3 + 2] cycloaddition reactions were carried out in round-bottom flasks closed with a stopper. Starting materials, including trifluoromethylketones and methyl and *t*-butyl isocyanoacetate, were obtained from commercial sources. Methyl *tert*-butyl ether (MTBE) was stored over 4 Å MS until it was used. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck Silica Gel 60, 0.040−0.063 mm. Melting points were determined in capillary tubes. Unless otherwise stated, NMR spectra were run at 300 MHz for ^{1}H and at 75 MHz for ^{13}C NMR using residual nondeuterated solvent ($CHCl_3$) as an internal standard (δ 7.26 and 77.0 ppm, respectively) and at 282 MHz for ^{19}F NMR using $CFCl_3$ as an internal standard. Chemical shifts are given in ppm. The carbon type was determined by DEPT experiments. High resolution mass spectra (ESI) were recorded on a Q-TOF spectrometer equipped with an electrospray source with a capillary voltage of 3.3 kV (ESI). Specific optical rotations were measured using sodium light (D line 589 nm). Chiral HPLC analyses were performed in a chromatograph equipped with a UV diode-array detector using chiral stationary phase columns from Daicel or Phenomenex. Chiral GLC analyses were carried out in a chromatograph equipped with a flame ionization detector using nitrogen (1 mL/min) as carrier gas, $T_{injector}$ = 220 °C, $T_{detector}$ = 220 °C.

General Procedure for the Enantioselective Formal [3 + 2] Cycloaddition Reaction with Methyl Isocyanoacetate. Squaramide **III** (3.9 mg, 0.0063 mmol) and silver oxide (1.5 mg, 0.0063 mmol) were introduced in a 25 mL round-bottom flask followed by MTBE (8 mL) and trifluoroacetophenone **1** (0.25 mmol). The flask was closed with a stopper and introduced in an ice bath. After 5 min, methyl isocyanoacetate (**2a**, 30 μL, 0.33 mmol) was added and the mixture was stirred at 0 °C until consumption of the trifluoroacetophenone **1** (TLC). After this time, the reaction mixture was filtered through a short pad of silica gel and concentrated under reduced pressure. A small aliquot was analyzed by ^{1}H NMR to determine the diastereomer ratio and by HPLC to determine the enantiomeric excess of products **3**. The remaining crude was chromatographed on silica gel eluting with hexane:EtOAc mixtures (9:1 to 8:2) to obtain the oxazolines **3**.[20]

The racemic products were obtained by a similar procedure using *N*-[3,5-bis(trifluoromethyl)phenyl]-*N*′-(3-(dimethylamino)propyl)-squaramide as a substitute for squaramide **III**.

*Methyl 5-Phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3a**).* Colorless oil (83.4 mg, >95% from 55.0 mg of **1a**). HPLC (Chiracel IC, hexane:*i*PrOH 95:5, 0.7 mL/min): ***trans*-(4*S*,5*S*)-3a** (major diastereomer, 90% ee): major enantiomer, t_r = 12.4 min, minor enantiomer 18.3 min; ***cis*-3a** (minor diastereomer): major enantiomer, t_r = 22.6 min, minor enantiomer t_r = 28.6 min; dr *trans:cis* = 96:4. ***trans*-(4*S*,5*S*)-3a** (major diastereomer): $[\alpha]_D^{25}$ +143.0 (*c* 0.30, $CHCl_3$, for the diastereomer mixture); ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.44−7.43 (2H, m, Ar), 7.39−7.37 (3H, m, Ar), 7.24 (1H, d, *J* = 1.8 Hz, N=CHO), 5.24 (1H, d, *J* = 1.8 Hz, CH), 3.27 (3H, s, CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.1 (C), 155.7 (CH), 130.7 (C), 129.6 (CH), 128.4 (CH), 125.9 (CH, q, J_{C-F} = 1.6 Hz), 123.8 (C, q, J_{C-F} = 283 Hz), 87.6 (C, q, J_{C-F} = 30 Hz), 74.2 (CH), 52.2 (CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −80.1 (s, CF_3); HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{12}H_{11}F_3NO_3^+$: 274.0686, found: 274.0689. ***cis*-3a** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.35 (5H, Ar), 7.16 (1H, d, *J* = 2.4 Hz, N=CHO), 5.14 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.91 (3H, s, CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −76.0 (s, CF_3).

*Methyl 5-(p-Tolyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3b**).* Colorless oil (68.9 mg, >95% from 47.0 mg of **1b**). HPLC (Chiralpak AS-H, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3b** (major diastereomer, 87% ee): major enantiomer, t_r = 6.0 min, minor enantiomer, t_r = 8.6 min; ***cis*-3b** (minor diastereomer): major enantiomer, t_r = 15.7 min, minor enantiomer, t_r = 17.0 min; dr *trans:cis* = 94:6. ***trans*-(4*S*,5*S*)-3b** (major diastereomer): $[\alpha]_D^{25}$ +127.8 (*c* 0.58, $CHCl_3$, for the diastereomer mixture); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 8.1 Hz, Ar), 7.23 (1H, d, *J* = 1.8 Hz, N=CHO), 7.17 (2H, d, *J* = 8.1 Hz, Ar), 5.22 (1H, d, *J* = 2.1 Hz, CH), 3.30 (3H, s, CH_3), 2.34 (3H, s, CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.1 (C), 155.7 (CH), 139.6 (C), 129.0 (CH), 127.6 (C), 125.7 (CH, q, J_{C-F} = 1.6 Hz), 123.8 (C, q, J_{C-F} = 283 Hz), 87.5 (C, q, J_{C-F} = 30 Hz), 74.0 (CH), 52.1 (CH_3), 21.0 (CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −80.2 (s, CF_3); HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{13}H_{12}F_3NO_3^+$: 288.0842, found: 288.0849. ***cis*-3b** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.83 (3H, s, CH_3), 2.38 (3H, s, CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −76.1 (s, CF_3).

*Methyl 5-(4-Methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3c**).* Colorless oil (65.9 mg, 88% from 51.0 mg of **1c**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3c** (major diastereomer, 85% ee): major enantiomer, t_r = 13.2 min, minor enantiomer, t_r = 29.0 min; ***cis*-3c** (minor diastereomer): major enantiomer, t_r = 27.9 min, minor enantiomer, t_r = 34.7 min; dr *trans:cis* = 96:4. ***trans*-(4*S*,5*S*)-3c** (major diastereomer): $[\alpha]_D^{25}$ +122.5 (*c* 0.25, $CHCl_3$, for the diastereomer mixture); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (2H, d, *J* = 8.6 Hz, Ar), 7.23 (1H, dd, *J* = 2.1, 0.6 Hz, N=CHO), 6.88 (2H, d, *J* = 9.0 Hz, Ar), 5.20 (1H, d, *J* = 2.1 Hz, CH), 3.80 (s, CH_3), 3.33 (s, CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.2 (C), 160.3 (C), 155.7 (CH), 127.3 (CH, q, J_{C-F} = 1.9 Hz), 123.8 (C, q, J_{C-F} = 283 Hz), 122.4 (C), 113.8 (CH), 87.5 (C, q, J_{C-F} = 30 Hz), 74.0 (CH), 55.2 (CH_3), 52.3 (CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −80.4 (s, CF_3); HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{13}H_{13}F_3NO_4^+$: 304.0791, found: 304.0795. ***cis*-3c** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (1H, d, *J* = 2.4 Hz, CH), 5.11 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.89 (3H, s, CH_3), 3.82 (3H, s, CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −76.7 (s, CF_3).

*Methyl 5-(4-Chlorophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3d**).* Colorless oil (75.7 mg, >95% from 54.1 mg of **1d**). HPLC (Chiralpak IC, hexane:*i*PrOH 90:10, 1 mL/min):

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***trans*-(4*S*,5*S*)-3d** (major diastereomer, 84% ee): major enantiomer, t_r = 5.9 min, minor enantiomer, t_r = 8.1 min; ***cis*-3d** (minor diastereomer, 64% ee): major enantiomer, t_r = 12.7 min, minor enantiomer, t_r = 13.1 min; dr *trans:cis* = 80:20. ***trans*-(4*S*,5*S*)-3d** (major diastereomer): $[\alpha]_D^{25}$ +120.8 (*c* 0.20, $CHCl_3$, 84% ee); ^1H NMR (300 MHz, $CDCl_3$), δ 7.37−7.35 (4H, m, Ar), 7.23 (1H, d, *J* = 2.1 Hz, N═CHO), 5.23 (1H, d, *J* = 2.1 Hz, CH), 3.33 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.9 (C), 155.6 (CH), 135.9 (C), 129.3 (C), 128.7 (CH), 127.4 (CH, q, J_{C-F} = 1.6 Hz), 123.6 (C, q, J_{C-F} = 283 Hz), 87.2 (C, q, J_{C-F} = 30.8 Hz), 74.0 (CH), 52.4 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −80.2 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{10}ClF_3NO_3^+$: 308.0296, found: 308.0299. ***cis*-3d** (minor diastereomer): $[\alpha]_D^{25}$ +63.5 (*c* 0.14, $CHCl_3$, 64% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (2H, d, *J* = 8.5 Hz, Ar), 7.45 (2H, d, *J* = 8.5 Hz, Ar), 7.16 (1H, d, *J* = 2.1 Hz, CH), 5.08 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.92 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.3 (C), 154.5 (CH), 136.2 (C), 133.5 (C), 129.2 (CH), 127.9 (CH), 122.6 (C, q, J_{C-F} = 283 Hz), 87.7 (C, q, J_{C-F} = 31 Hz), 76.5 (CH), 53.3 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −76.0 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{10}ClF_3NO_3^+$: 308.0296, found: 308.0299.

*Methyl 5-(m-Tolyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3e**).* Colorless oil (68.8 mg, >95% from 47.0 mg of **1e**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3e** (major diastereomer, 90% ee): major enantiomer, t_r = 8.3 min, minor enantiomer, t_r = 12.0 min; ***cis*-3e** (minor diastereomer): major enantiomer, t_r = 13.8 min, minor enantiomer, t_r = 18.2 min; dr *trans:cis* = 94:6. ***trans*-(4*S*,5*S*)-3e** (major diastereomer): $[\alpha]_D^{25}$ +132.4 (*c* 0.50, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.24−7.15 (5H, m, Ar, N═CHO), 5.22 (1H, d, *J* = 1.8 Hz, CH), 3.30 (3H, s, CH_3), 2.36 (3H, d, *J* = 0.6 Hz, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.1 (C), 155.7 (CH), 138.2 (C), 130.6 (C), 130.3 (CH), 128.3 (CH), 126.4 (CH, q, J_{C-F} = 1.8 Hz), 123.8 (C, q, J_{C-F} = 283 Hz), 122.9 (CH, q, J_{C-F} = 1.9 Hz), 87.6 (C, q, J_{C-F} = 30 Hz), 74.1 (CH), 52.2 (CH_3), 21.4 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −80.1 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{13}F_3NO_3^+$: 288.0842, found: 288.0845. ***cis*-3e** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^1H NMR (300 MHz, $CDCl_3$) δ 5.13 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.83 (3H, s, CH_3), 2.41 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.8 (s, CF_3).

*Methyl 5-(3-Methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3f**).* Colorless oil (71.3 mg, 94% from 51.0 mg of **1f**). HPLC (Chiralpak AS-H, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3f** (major diastereomer, 88% ee): major enantiomer, t_r = 7.3 min, minor enantiomer, t_r = 10.0 min; ***cis*-3f** (minor diastereomer): major enantiomer, t_r = 21.8 min, minor enantiomer, t_r = 19.9 min; dr *trans:cis* = 92:8. ***trans*-(4*S*,5*S*)-3f** (major diastereomer): $[\alpha]_D^{25}$ −26.7 (*c* 0.56, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (1H, t, *J* = 8.4 Hz, Ar), 7.22 (1H, d, *J* = 2.1 Hz, N═CHO), 7.01−6.98 (2H, m, Ar), 6.92−6.90 (1H, m, Ar), 5.22 (1H, d, *J* = 1.8 Hz, CH), 3.80 (3H, s, CH_3), 3.33 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.1 (C), 159.5 (C), 155.7 (CH), 132.1 (C), 129.5 (CH), 123.7 (C, q, J_{C-F} = 283 Hz), 118.1 (CH, q, J_{C-F} = 2.2 Hz), 114.9 (CH), 111.9 (CH, q, J_{C-F} = 1.7 Hz), 87.5 (C, q, J_{C-F} = 30 Hz), 74.1 (CH), 55.3 (CH_3), 52.3 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −80.2 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{13}F_3NO_4^+$: 304.0791, found: 304.0794. ***cis*-3f** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (1H, d, *J* = 2.1 Hz, N═CHO), 5.13 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.91 (3H, s, CH_3), 3.84 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.9 (s, CF_3).

*Methyl 5-(3-Bromophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3g**).* Colorless oil (83.0 mg, 95% from 63.3 mg of **1g**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3g** (major diastereomer, 92% ee): major enantiomer, t_r = 7.3 min, minor enantiomer, t_r = 9.8 min; ***cis*-3g** (minor diastereomer): major enantiomer, t_r = 14.5 min, minor enantiomer, t_r = 18.3 min; dr *trans:cis* = 86:14. ***trans*-(4*S*,5*S*)-3g** (major diastereomer): $[\alpha]_D^{25}$ +107.7 (*c* 0.66, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (1H, s, Ar), 7.53 (1H, ddd, *J* = 8.0, 1.9, 1.1 Hz, Ar), 7.38 (1H, brd, *J* = 8.0 Hz, Ar), 7.25 (1H, t, *J* = 8.0 Hz, Ar), 7.23 (1H, d, *J* = 1.8 Hz, N═CHO), 5.23 (1H, d, *J* = 2.1 Hz, CH), 3.36 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.8 (C), 155.5 (CH), 132.9 (C), 132.8 (CH), 129.9 (CH), 129.1 (CH, q, J_{C-F} = 1.7 Hz), 125.4 (C, q, J_{C-F} = 283 Hz), 124.6 (CH, q, J_{C-F} = 1.7 Hz), 122.6 (C), 86.9 (C, q, J_{C-F} = 30 Hz), 74.1 (CH), 52.4 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −80.1 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{10}BrF_3NO_3^+$: 351.9791, found: 351.9791. ***cis*-3g** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (1H, d, *J* = 2.1 Hz, N═CHO), 5.08 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.90 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.8 (s, CF_3).

*Methyl 5-(2-Methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3h**).* White solid (86.3 mg, >95% from 58.1 mg of **1h**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3h** (major diastereomer, 85% ee): major enantiomer, t_r = 11.6 min, minor enantiomer, t_r = 15.9 min; ***cis*-3h** (minor diastereomer): major enantiomer, t_r = 17.2 min, minor enantiomer, t_r = 26.9 min; dr *trans:cis* = 99:1. ***trans*-(4*S*,5*S*)-3h** (major diastereomer): mp 129−130 °C; $[\alpha]_D^{25}$ +228.1 (*c* 0.41, $CHCl_3$, for the diastereomer mixture, dr = 98:2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (1H, dd, *J* = 7.8, 1.8 Hz, Ar), 7.38 (1H, td, *J* = 7.5, 1.8 Hz, Ar), 7.13 (1H, d, *J* = 2.1 Hz, N═CHO), 7.05 (1H, td, *J* = 7.8, 1.2 Hz, Ar), 6.86 (1H, dd, *J* = 8.1, 0.9 Hz, Ar), 5.28 (1H, d, *J* = 2.1 Hz, CH), 3.75 (3H, s, CH_3), 3.54 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.7 (C), 155.3 (C), 155.2 (CH), 130.9 (CH), 128.8 (CH), 123.8 (C, q, J_{C-F} = 283 Hz), 120.9 (CH), 119.8 (C), 110.3 (CH), 86.9 (C, q, J_{C-F} = 30.8 Hz), 72.8 (CH), 54.7 (CH_3), 52.1 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −81.9 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{13}F_3NO_4^+$: 304.0791, found: 304.0791.

*Methyl 5-(2-Bromophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3i**).* Colorless oil (81.7 mg, 93% from 63.3 mg of **1i**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3i** (major diastereomer, 70% ee): major enantiomer, t_r = 8.9 min, minor enantiomer, t_r = 12.6 min; ***cis*-3i** (minor diastereomer): major enantiomer, t_r = 17.8 min, minor enantiomer, t_r = 24.3 min; dr *trans:cis* = 85:15. ***trans*-(4*S*,5*S*)-3i** (major diastereomer): $[\alpha]_D^{25}$ +150.9 (*c* 0.43, $CHCl_3$, for the diastereomer mixture, dr = 85:15); ^1H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.90 (1H, unresolved d, Ar), 7.73 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.52 (1H, td, *J* = 8.0, 1.0 Hz, Ar), 7.37 (1H, td, *J* = 8.0, 1.5 Hz, Ar), 7.27 (1H, d, *J* = 2.0 Hz, N═CHO), 5.62 (1H, s, CH), 3.72 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 50 °C) δ 167.4 (C), 155.0 (CH), 136.3 (C), 134.6 (br CH), 130.8 (CH), 130.4 (CH), 127.6 (CH), 123.7 (C, q, J_{C-F} = 283 Hz), 120.8 (C), 88.8 (C, q, J_{C-F} = 29 Hz), 72.9 (CH), 52.6 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −79.4 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{10}BrF_3NO_3^+$: 351.9791, found: 351.9798. ***cis*-3i** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (br d, *J* = 8.1 Hz, Ar), 7.83 (1H, dd, *J* = 8.1, 1.3 Hz, Ar), 7.52 (1H, td, *J* = 8.0, 1.0 Hz, Ar), 7.39 (1H, td, *J* = 8.0, 1.5 Hz, Ar), 7.26 (1H, d, *J* = 2.0 Hz, N═CHO), 5.62 (1H, s, CH), 3.98 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −72.2 (s, CF_3).

*Methyl 5-(3,4-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3j**).* Yellow oil (90.1 mg, >95% from 64.1 mg of **1j**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3j** (major diastereomer, 85% ee): major enantiomer, t_r = 6.4 min, minor enantiomer, t_r = 8.7 min; ***cis*-3j** (minor diastereomer): major enantiomer, t_r = 16.4 min, minor enantiomer, t_r = 19.6 min; dr *trans:cis* = 77:23. ***trans*-(4*S*,5*S*)-3j** (major diastereomer): $[\alpha]_D^{25}$ +105.0 (*c* 0.92, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (1H, d, *J* = 2.3 Hz, Ar), 7.46 (1H, d, *J* = 8.7 Hz, Ar), 7.27 (1H, ddd, *J* = 8.4, 2.1, 0.9 Hz, Ar), 7.22 (1H, d, *J* = 1.8 Hz, N═CHO), 5.22 (1H, d, *J* = 1.8 Hz, CH), 3.40 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz) δ 166.7 (C), 155.4 (CH), 134.3 (C), 133.1 (C), 131.0 (C), 130.5 (CH), 128.2 (CH, q, J_{C-F} = 1.8 Hz), 125.4 (CH, q, J_{C-F} = 1.7 Hz), 125.2

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(C, q, J_{C-F} = 283 Hz), 86.6 (C, q, J_{C-F} = 29 Hz), 74.0 (CH), 52.5 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −80.2 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_9Cl_2F_3NO_3^+$: 341.9906, found: 341.9909. ***cis*-3j** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (1H, d, *J* = 2.1 Hz, N=CHO), 5.05 (1H, dd, *J* = 2.1, 0.9 Hz, CH), 3.91 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −76.0 (s, CF_3).

*Methyl 5-(Thiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3k**).* Yellow oil (80.1 mg, >95% from 52.3 mg of **3k**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3k** (major diastereomer, 90% ee): major enantiomer, t_r = 10.0 min, minor enantiomer, t_r = 13.8; ***cis*-3k** (minor diastereomer): major enantiomer, t_r = 17.6 min, minor enantiomer, t_r = 22.1 min; dr *trans:cis* = 92:8. ***trans*-(4*S*,5*S*)-3k** (major diastereomer): $[\alpha]_D^{25}$ +48.0 (*c* 0.79, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (1H, dd, *J* = 5.1, 1.5 Hz, Ar), 7.19 (1H, dd, *J* = 2.1, 0.6 Hz, N=CHO), 7.10−7.08 (1H, m, Ar), 7.03 (1H, dd, *J* = 5.1, 3.9 Hz, Ar), 5.22 (1H, d, *J* = 2.1 Hz, CH), 3.41 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.7 (C), 155.1 (CH), 132.7 (C), 127.5 (CH), 126.9 (CH), 126.8 (CH, q, J_{C-F} = 2.1 Hz), 123.2 (C, q, J_{C-F} = 283 Hz), 86.3 (C, q, J_{C-F} = 32 Hz), 74.6 (CH), 52.4 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −81.5 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_9F_3NO_3S^+$: 280.0250, found: 280.0253. ***cis*-3k** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^1H NMR (300 MHz, $CDCl_3$) δ 7.12 (1H, d, *J* = 2.1 Hz, N=CHO), 5.19 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.89 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −76.4 (s, CF_3).

*Methyl 5-Phenethyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3l**).* Yellow oil (50.1 mg, 66% from 51.0 mg of **1l**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3l** (major diastereomer, 81% ee): major enantiomer, t_r = 7.9 min, minor enantiomer, t_r = 19.6 min; ***cis*-3l** (minor diastereomer): major enantiomer, t_r = 39.5 min, minor enantiomer, t_r = 28.4 min; dr *trans:cis* = 86:14. ***trans*-(4*S*,5*S*)-3l** (major diastereomer): $[\alpha]_D^{25}$ +17.5 (*c* 0.81, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.26 (4H, m, Ar), 7.13−7.10 (1H, m, Ar), 7.03 (1H, d, *J* = 2.4 Hz, N=CHO), 4.98 (1H, d, *J* = 2.4 Hz, CH), 3.81 (3H, s, CH_3), 2.78−2.55 (2H, m, CH_2), 2.33−2.06 (2H, m, CH_2); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.1 (C), 155.2 (CH), 139.9 (C), 128.6 (CH), 128.1 (CH), 126.4 (CH), 124.2 (C, q, J_{C-F} = 283 Hz), 85.7 (C, q, J_{C-F} = 30.1 Hz), 71.3 (CH), 52.8 (CH_3), 31.4 (CH_2), 28.6 (CH_2); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −80.7 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{15}F_3NO_3^+$: 302.0999, found: 302.1004. ***cis*-3l** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (1H, d, *J* = 2.1 Hz, CH), 3.81 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −76.3 (s, CF_3).

*Methyl 5-Methyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3m**).* Volatile colorless oil (42.2 mg, 80% from 28.1 mg of **1m**). HPLC (Chiralpak IC, hexane:*i*PrOH 90:10, 1 mL/min): ***trans*-(4*S*,5*S*)-3m** (major diastereomer 82%): major enantiomer, t_r = 6.9 min, minor enantiomer, t_r = 8.5 min; ***cis*-3m** (minor diastereomer): major enantiomer, t_r = 12.7 min, minor enantiomer, t_r = 14.0 min; dr *trans:cis* = 92:8. ***trans*-(4*S*,5*S*)-3m** (major diastereomer): $[\alpha]_D^{25}$ +75.3 (*c* 0.33, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (1H, d, *J* = 1.5 Hz, N=CHO), 4.88 (1H, d, *J* = 2.5 Hz, CH), 3.79 (3H, s, CH_3), 1.49 (3H, m, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.0 (C), 155.5 (CH), 124.0 (C, q, J_{C-F} = 283 Hz), 83.9 (C, q, J_{C-F} = 32 Hz), 71.3 (CH), 52.7 (CH_3), 15.3 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −83.3 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_7H_9F_3NO_3^+$: 212.0529, found: 212.0536. ***cis*-3m** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^1H NMR (300 MHz, $CDCl_3$) δ 4.62 (1H, dd, *J* = 2.2, 0.6 Hz, CH), 3.79 (3H, s, CH_3), 1.74 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −77.7 (s, CF_3).

General Procedure for the Enantioselective Formal [3 + 2] Cycloaddition Reaction with *tert*-Butyl Isocyanoacetate. Squaramide **VIII** (6.8 mg, 0.0125 mmol) and silver oxide (1.5 mg, 0.0063 mmol) were introduced in a round-bottom flask followed by MTBE (8 mL) and trifluoroacetophenone **1** (0.25 mmol). The flask was closed with a stopper and introduced in an ice bath. After 5 min, *tert*-butyl isocyanoacetate (**2b**, 48 μL, 0.33 mmol) was added and the mixture was stirred at 0 °C until consumption of the trifluoroacetophenone **1** (TLC). After this time, the reaction mixture was filtered through a short pad of silica gel and concenterd under reduced pressure. A small aliquot was analyzed by ^1H NMR to determine the diastereomer ratio and by HPLC to determine the enantiomeric excess of products **4**. The remaining crude was chromatographed on silica gel eluting with hexane:EtOAc mixtures (9:1 to 8:2) to obtain compounds **4**.[20]

The racemic product was obtained using a similar procedure using the catalyst 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-((3-(dimethylamino)propyl)amino)cyclobut-3-ene-1,2-dione and silver oxide.

*tert-Butyl 5-Phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4a**).* Colorless oil (102.2 mg, >95% from 57.3 mg of **1a**). HPLC (Chiralpak IC, hexane:*i*PrOH 90:10, 0.7 mL/min): ***trans*-(4*S*,5*S*)-4a** (major diastereomer, 96% ee): major enantiomer, t_r = 7.2 min, minor enantiomer, t_r = 8.5 min; ***cis*-4a** (minor diastereomer, 90% ee): major enantiomer, t_r = 11.1 min, minor enantiomer, t_r = 15.2 min; dr *trans:cis* = 70:30. ***trans*-(4*S*,5*S*)-4a** (major diastereomer): $[\alpha]_D^{25}$ +178.1 (*c* 1.15, $CHCl_3$, 96% ee); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.46 (2H, m, Ar), 7.39−7.37 (3H, m, Ar), 7.20 (1H, d, *J* = 1.8 Hz, N=CHO), 5.08 (1H, d, *J* = 1.8 Hz, CH), 1.03 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 165.3 (C), 155.3 (CH), 131.0 (C), 129.4 (CH), 128.4 (CH), 126.4 (CH, q, J_{C-F} = 2.0 Hz), 123.9 (C, q, J_{C-F} = 284 Hz), 87.6 (C, q, J_{C-F} = 30 Hz), 82.7 (C), 74.6 (CH), 27.1 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −80.3 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{17}F_3NO_3^+$: 316.1155, found: 316.1154. ***cis*-4a** (minor diastereomer): $[\alpha]_D^{25}$ +77.2 (*c* 0.23, $CHCl_3$, 90% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.72−7.69 (2H, m, Ar), 7.46−7.44 (3H, m, Ar), 7.12 (1H, d, *J* = 2.4 Hz, N=CHO), 5.02 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 1.58 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 154.0 (CH), 135.6 (C), 129.7 (CH), 128.7 (CH), 128.6 (C, q, J_{C-F} = 283 Hz), 126.4 (CH), 123.0 (C, q, J_{C-F} = 283 Hz), 87.9 (C, q, J_{C-F} = 30.7 Hz), 83.6 (C), 77.4 (CH), 27.7 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.0 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{17}F_3NO_3^+$: 316.1155, found: 316.1154.

*tert-Butyl 5-(p-Tolyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4b**).* White solid (71.7 mg, 87% from 47.0 mg of **1b**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-4b** (major diastereomer, 93% ee): major enantiomer, t_r = 6.9 min, minor enantiomer, t_r = 9.4 min; ***cis*-4b** (minor diastereomer, 96% ee): major enantiomer, t_r = 12.2 min, minor enantiomer, t_r = 18.3 min; dr *trans:cis* = 66:34. ***trans*-(4*S*,5*S*)-4b** (major diastereomer): mp: 63−65 °C; $[\alpha]_D^{25}$ +153.3 (*c* 0.96, $CHCl_3$, 93% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (2H, d, *J* = 8.1, Ar), 7.19 (1H, d, *J* = 2.1 Hz, N=CHO), 7.18 (2H, d, *J* = 8.1 Hz, Ar), 5.05 (1H, d, *J* = 2.1 Hz, CH), 2.33 (3H, d, *J* = 0.9 Hz, CH_3), 1.05 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.4 (C), 155.3 (CH), 139.4 (C), 129.0 (CH), 128.0 (C), 126.3 (CH, q, J_{C-F} = 1.7 Hz), 123.9 (C, q, J_{C-F} = 283 Hz), 87.6 (C, q, J_{C-F} = 30 Hz), 82.6 (C), 74.5 (CH), 27.1 (CH_3), 21.0 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −80.4 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{19}F_3NO_3^+$: 330.1312, found: 330.1316. ***cis*-4b** (minor diastereomer): colorless oil; $[\alpha]_D^{25}$ +84.8 (*c* 1.09, $CHCl_3$, 96% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (2H, d, *J* = 8.1 Hz, Ar), 7.26 (2H, d, *J* = 8.1 Hz, Ar), 7.10 (1H, d, *J* = 2.1 Hz, N=CHO), 5.00 (1H, dd, *J* = 2.4, 0.9 Hz, CH), 2.38 (3H, s, CH_3), 1.57 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.8 (C), 154.0 (CH), 139.7 (C), 132.6 (C), 129.4 (CH), 126.3 (CH), 123.0 (C, q, J_{C-F} = 283 Hz), 87.9 (C, q, J_{C-F} = 30.1 Hz), 83.5 (C), 27.7 (CH_3), 21.1 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.1 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{19}F_3NO_3^+$: 330.1312, found: 330.1316.

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*tert-Butyl (4S,5S)-5-(4-Methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4c**).* Colorless oil (84.0 mg, >95% from 51.2 mg of **1c**). HPLC (Chiralpak IC, hexane:*i*PrOH 90:10, 0.7 mL/min): ***trans*-(4*S*, 5*S*)-4c** (major diastereomer, 84%): major enantiomer, t_r = 8.7 min, minor enantiomer, t_r = 14.2 min; ***cis*-4c** (minor diastereomer, 77% ee): major enantiomer, t_r = 16.8 min, minor enantiomer, t_r = 20.9 min; dr *trans:cis* = 63:37. ***trans*-(4*S*, 5*S*)-4c** (major diastereomer): $[\alpha]_D^{25}$ +127.3 (*c* 0.82, $CHCl_3$, 84% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (2H, d, *J* = 9.0, Ar), 7.18 (1H, d, *J* = 1.8 Hz, N═CHO), 6.89 (2H, d, *J* = 9.0 Hz, Ar), 5.04 (1H, d, *J* = 1.8 Hz, CH), 3.79 (3H, s, CH_3), 1.08 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.5 (C), 160.4 (C), 155.3 (CH), 127.9 (CH, q, J_{C-F} = 1.8 Hz), 123.9 (C, q, J_{C-F} = 284 Hz), 122.9 (C), 113.8 (CH), 87.5 (C, q, J_{C-F} = 29 Hz), 82.7 (C), 74.5 (CH), 55.3 (CH_3), 27.3 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −80.5 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1251. ***cis*-4c** (minor diastereomer): $[\alpha]_D^{25}$ +47.1 (*c* 0.75, $CHCl_3$, 77% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 9.0 Hz, Ar), 7.10 (1H, d, *J* = 2.4 Hz, N═CHO), 6.96 (2H, d, *J* = 9.0 Hz, Ar), 5.00 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.83 (3H, s, CH_3), 1.57 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.8 (C), 160.5 (C), 154.0 (CH), 127.8 (CH), 127.4 (C), 123.0 (C, q, J_{C-F} = 283 Hz), 114.1 (CH), 87.8 (C, q, J_{C-F} = 30 Hz), 83.5 (C), 77.4 (CH), 55.3 (CH_3), 27.7 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.4 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1251.

*tert-Butyl 5-(4-Chlorophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4d**).* Colorless oil (103.4 mg, >95% from 62.0 mg of **1d**). HPLC (Chiralpak IC, hexano:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-4d** (major diastereomer, 96% ee): major enantiomer, t_r = 7.6 min, minor enantiomer, t_r = 9.0 min; ***cis*-4d** (minor diastereomer, 90% ee): major enantiomer, t_r = 16.7 min, minor enantiomer, t_r = 18.5 min; dr *trans:cis* = 53:47. ***trans*-(4*S*,5*S*)-4d** (major diastereomer): $[\alpha]_D^{25}$ +81.7 (*c* 0.30, $CHCl_3$, 96% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* = 9.0 Hz, Ar), 7.37 (2H, d, *J* = 9.0 Hz, Ar), 7.19 (1H, d, *J* = 2.0 Hz, N═CHO), 5.07 (1H, d, *J* = 2.0 Hz, CH), 1.08 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.2 (C), 155.2 (CH), 135.8 (C), 129.5 (C), 128.7 (CH), 128.0 (CH, q, J_{C-F} = 1.9 Hz), 123.7 (C, q, J_{C-F} = 283 Hz), 87.5 (C, q, J_{C-F} = 30 Hz), 83.1 (C), 74.6 (CH), 27.3 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −80.4 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{16}ClF_3NO_3^+$: 350.0765, found: 350.0757. ***cis*-4d** (minor diastereomer): $[\alpha]_D^{25}$ +48.6 (*c* 0.46, $CHCl_3$, 90% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 9.0 Hz, Ar), 7.42 (2H, d, *J* = 9.0 Hz, Ar), 7.10 (1H, d, *J* = 2.1 Hz, N═CHO), 4.96 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 1.57 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.4 (C), 153.9 (CH), 136.0 (C), 133.9 (C), 129.0 (CH), 127.9 (CH), 122.8 (C, q, J_{C-F} = 283 Hz), 87.5 (C, q, J_{C-F} = 31 Hz), 83.9 (C), 77.4 (CH), 27.7 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.2 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{16}ClF_3NO_3^+$: 350.0765, found: 350.0757.

*tert-Butyl 5-(m-Tolyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4e**).* Colorless oil (77.1 mg, 94% from 47.2 mg of **1e**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-4e** (major diastereomer, 97% ee): major enantiomer, t_r = 5.6 min, minor enantiomer, t_r = 6.7 min; ***cis*-4e** (minor diastereomer, 87% ee): major enantiomer: t_r = 10.0 min, minor enantiomer: t_r = 14.4 min; dr *trans:cis* = 76:24. ***trans*-(4*S*,5*S*)-4e** (major diastereomer): $[\alpha]_D^{25}$ +166.8 (*c* 0.55, $CHCl_3$, 97% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.27−7.25 (3H, m, Ar), 7.21−7.18 (2H, m, Ar, NCHO), 5.06 (1H, d, *J* = 2.1 Hz, CH), 2.35 (3H, s, CH_3), 1.04 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.3 (C), 155.3 (CH), 138.0 (C), 130.9 (C), 130.1 (CH), 128.3 (CH), 126.9 (CH, q, J_{C-F} = 2.0 Hz), 123.9 (C, q, J_{C-F} = 283 Hz), 123.5 (CH, q, J_{C-F} = 1.9 Hz), 87.6 (C, q, J_{C-F} = 30 Hz), 82.5 (C), 74.6 (CH), 27.1 (CH_3), 21.4 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −80.3 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{19}F_3NO_3^+$: 330.1312, found: 330.1308. ***cis*-4e** (minor diastereomer): $[\alpha]_D^{25}$ +52.9 (*c* 0.98, $CHCl_3$, 87% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (1H, s, Ar), 7.49 (1H, d, *J* = 9.0 Hz, Ar), 7.33 (1H, td, *J* = 7.5, 0.6 Hz, Ar), 7.25 (1H, br d, *J* = 7.6 Hz, Ar), 7.11 (1H, d, *J* = 2.1 Hz, N═CHO), 5.01 (1H, dd, *J* = 2.4, 0.9 Hz, CH), 2.40 (3H, s, CH_3), 1.58 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 154.0 (CH), 138.5 (C), 135.5 (C), 130.4 (CH), 128.6 (CH), 126.9 (CH), 123.4 (CH), 123.0 (C, q, J_{C-F} = 283 Hz), 87.9 (C, q, J_{C-F} = 30 Hz), 83.5 (CH), 77.4 (CH), 27.7 (CH_3), 21.5 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.0 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{19}F_3NO_3^+$: 330.1312, found: 330.1308.

*tert-Butyl 5-(3-Methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4f**).* Colorless oil (72.7 mg, 84% from 51.1 mg of **1f**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-4f** (major diastereomer, 97% ee): major enantiomer, t_r = 6.8 min, minor enantiomer, t_r = 16.0 min, ***cis*-4f** (minor diastereomer, 85% ee): major enantiomer, t_r = 13.2 min, minor enantiomer, t_r = 20.9 min; dr *trans:cis* = 72:28. ***trans*-(4*S*,5*S*)-4f** (major diastereomer): $[\alpha]_D^{25}$ +164.7 (*c* 0.49, $CHCl_3$, 97% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (1H, td, *J* = 8.0, 0.6 Hz, Ar), 7.19 (1H, dd, *J* = 1.9, 0.5 Hz, N═CHO), 7.06 (1H, m, Ar), 7.00 (1H, m, Ar), 6.91 (1H, ddd, *J* = 8.2, 2.5, 0.9 Hz, Ar), 5.06 (1H, d, *J* = 1.9 Hz, CH), 3.80 (3H, s, CH_3), 1.07 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.3 (C), 159.5 (C), 155.3 (CH), 132.3 (C), 129.5 (CH), 123.8 (C, q, J_{C-F} = 283 Hz), 118.6 (CH, q, J_{C-F} = 2.0 Hz), 114.8 (CH), 112.5 (CH, q, J_{C-F} = 1.8 Hz), 87.5 (C, q, J_{C-F} = 30 Hz), 82.7 (C), 74.6 (CH), 55.3 (CH_3), 27.2 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −80.4 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1260. ***cis*-4f** (minor diastereomer): $[\alpha]_D^{25}$ +56.9 (*c* 0.77, $CHCl_3$, 85% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (1H, t, *J* = 7.8, Ar), 7.30−7.24 (2H, m, Ar), 7.11 (1H, d, *J* = 2.1 Hz, N═CHO), 6.96 (1H, ddd, *J* = 8.1, 2.6, 1.2 Hz, Ar), 5.02 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.84 (3H, s, CH_3), 1.57 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 159.7 (C), 154.0 (CH), 132.2 (C), 129.8 (CH), 122.9 (C, q, J_{C-F} = 283 Hz), 118.5 (CH), 115.1 (CH), 112.2 (CH), 87.9 (C, q, J_{C-F} = 30 Hz), 83.6 (C), 77.4 (CH), 55.4 (CH_3), 27.7 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −74.9 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1260.

*tert-Butyl 5-(3-Bromophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4g**).* Colorless oil (95.7 mg, >95%, from 63.5 mg of **1g**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 0.5 mL/min): ***trans*-(4*S*,5*S*)-4g** (major diastereomer, 90% ee): major enantiomer, t_r = 10.8 min, minor enantiomer, t_r = 12.7 min, ***cis*-4g** (minor diastereomer, 97% ee): major enantiomer, t_r = 24.3 min, minor enantiomer, t_r = 35.5 min; dr *trans:cis* = 64:36. ***trans*-(4*S*,5*S*)-4g** (major diastereomer): $[\alpha]_D^{25}$ +143.5 (*c* 0.52, $CHCl_3$, 97% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (1H, bs, Ar), 7.52 (1H, ddd, *J* = 7.9, 1.9, 1.0 Hz, Ar), 7.42 (1H, m, Ar), 7.26 (1H, td, *J* = 8.1, 0.6 Hz, Ar), 7.19 (1H, dd, *J* = 2.1, 0.6, N═CHO), 5.06 (1H, d, *J* = 2.0 Hz, CH), 1.10 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.1 (C), 155.1 (CH), 133.2 (C), 132.6 (CH), 130.0 (CH), 129.5 (CH, q, J_{C-F} = 1.8 Hz), 125.1 (CH, q, J_{C-F} = 2.0 Hz), 123.6 (C, q, J_{C-F} = 283 Hz), 122.6 (C), 86.9 (C, q, J_{C-F} = 30 Hz), 83.1 (C), 74.6 (CH), 27.2 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −80.3 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{16}BrF_3NO_3^+$: 394.0260, found: 394.0251. ***cis*-4g** (minor diastereomer): $[\alpha]_D^{25}$ +42.7 (*c* 1.39, $CHCl_3$, 90% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (1H, bs, Ar), 7.64 (1H, br d, *J* = 8.0 Hz, Ar), 7.58 (1H, ddd, *J* = 8.0, 1.9, 1.0 Hz, Ar), 7.33 (1H, t, *J* = 7.9 Hz, Ar), 7.11 (1H, d, *J* = 2.3 Hz, N═CHO), 4.96 (1H, dd, *J* = 2.3, 0.9 Hz, CH), 1.58 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.2 (C), 153.9 (CH), 137.6 (C), 132.9 (CH), 130.3 (CH), 129.7 (CH), 125.1 (CH), 122.8 (C), 122.7 (C, q, J_{C-F} = 283 Hz), 87.2 (C, q, J_{C-F} = 30.1 Hz), 83.9 (C), 77.3 (CH), 27.7 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.1 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{16}BrF_3NO_3^+$: 394.0260, found: 394.0251.

*tert-Butyl 5-(2-Methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4h**).* White solid (69.0 mg, 80% from 51.0 mg of **1h**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-4h** (major diastereomer, 94% ee): major enantiomer, t_r = 7.0 min, minor enantiomer, t_r = 23.0 min; ***cis*-4h** (minor diastereomer, 70% ee): major enantiomer, t_r = 19.9 min,

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minor enantiomer, t_r = 30.2 min; dr *trans:cis* = 94:6. ***trans*-(4*S*,5*S*)-4h** (major diastereomer): Mp: 76−79 °C; $[\alpha]_D^{25}$ +252.5 (*c* 0.78, $CHCl_3$, 94% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (1H, dd, *J* = 7.8, 1.8 Hz, Ar), 7.37 (1H, ddd, *J* = 8.4, 7.5, 1.8 Hz, Ar), 7.09 (1H, d, *J* = 2.0 Hz, N═CHO), 7.02 (1H, td, *J* = 7.5, 1.0 Hz, Ar), 6.85 (1H, dd, *J* = 8.4, 1.2 Hz, Ar), 5.12 (1H, d, *J* = 2.0 Hz, CH), 3.76 (3H, s, CH_3), 1.12 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.6 (C), 155.7 (C), 154.9 (CH), 130.6 (CH), 128.6 (CH), 123.9 (C, q, J_{C-F} = 283 Hz), 120.6 (CH), 120.5 (C), 110.4 (CH), 87.0 (C, q, J_{C-F} = 30 Hz), 81.5 (C), 74.2 (CH), 54.7 (CH_3), 27.3 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −81.7 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1259. ***cis*-4h** (minor diastereomer): $[\alpha]_D^{25}$ +70.7 (*c* 0.17, $CHCl_3$, 70% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (1H, td, *J* = 7.8, 1.5 Hz, Ar), 7.40 (1H, ddd, *J* = 8.2, 7.4, 1.7 Hz, Ar), 7.09 (1H, dd, *J* = 2.1, 0.6 Hz, N═CHO), 7.00 (1H, td, *J* = 7.5, 1.2 Hz, Ar), 6.98 (1H, dd, *J* = 7.2, 2.4 Hz, Ar), 5.23 (1H, dd, *J* = 2.1, 0.9 Hz, CH), 3.89 (3H, s, CH_3), 1.54 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.2 (C), 156.6 (C), 153.6 (CH), 131.3 (CH), 128.2 (CH), 123.3 (C, q, J_{C-F} = 283), 123.0 (C), 120.6 (CH), 111.9 (CH), 87.6 (C, q, J_{C-F} = 32 Hz), 82.4 (C), 75.5 (CH), 55.2 (CH_3), 27.8 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −72.4 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1259.

*tert-Butyl 5-(2-Bromophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4i**).* White solid (122.8 mg, >95% from 79.0 mg of **1i**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-4i** (major diastereomer, 91% ee): major enantiomer, t_r = 5.8 min, minor enantiomer, t_r = 9.3 min; dr *trans:cis* >99:1. ***trans*-(4*S*,5*S*)-4i** (major diastereomer): Mp: 96−99 °C; $[\alpha]_D^{25}$ +190.2 (*c* 0.54, $CHCl_3$, 91% ee); (two possible rotamers are observed) ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (1H, unresolved d, *J* = 7.4 Hz, Ar), 7.60 (1H, dd, *J* = 7.8, 1.2 Hz, Ar), 7.38 (1H, ddd, *J* = 7.9, 7.3, 1.3 Hz, Ar), 7.24 (1H, ddd, *J* = 8.0, 7.4, 1.7 Hz, Ar), 7.13 (1H, d, *J* = 1.8 Hz, N═CHO), 5.35 (1H, bs, CH), 1.22 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.3 (C), 154.8 (CH), 136.1 (C), 134.5 (CH), 130.6 (CH), 130.3 (CH), 127.4 (CH), 123.7 (C, q, *J* = 286 Hz), 120.8 (C), 88.5 (C, q, J_{C-F} = 30 Hz), 82.6 (CH), 74.0 (CH), 27.2 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −79.0 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{16}BrF_3NO_3^+$: 394.0260, found: 394.0251. For the X-ray structure of **4i**, see Figure S1 in the Supporting Information.

*tert-Butyl 5-(3,4-Dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4j**).* Colorless oil (95.1 mg, >95% from 61.0 mg of **1j**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-4j** (major diastereomer, 94% ee): major enantiomer, t_r = 6.7 min, minor enantiomer, t_r = 7.5 min; ***cis*-4j** (minor diastereomer, 85% ee): major enantiomer, t_r = 14.9 min, minor enantiomer, t_r = 17.2 min; dr *trans:cis* = 53:47. ***trans*-(4*S*,5*S*)-4j** (major diastereomer): $[\alpha]_D^{25}$ +131.8 (*c* 0.48, $CHCl_3$, 94% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (1H, d, *J* = 1.8 Hz, Ar), 7.47 (1H, d, *J* = 8.4 Hz, Ar), 7.33 (1H, ddd, *J* = 8.4, 2.2, 0.8 Hz, Ar), 7.19 (1H, d, *J* = 2.1 Hz, N═CHO), 5.06 (1H, d, *J* = 2.1 Hz, CH), 1.13 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.0 (C), 155.0 (CH), 134.2 (C), 132.9 (C), 131.1 (C), 130.5 (CH), 128.7 (CH, q, J_{C-F} = 1.9 Hz), 125.8 (CH, q, J_{C-F} = 1.7 Hz), 123.5 (C, q, J_{C-F} = 283 Hz), 86.5 (C, q, J_{C-F} = 30 Hz), 83.4 (C), 74.6 (CH), 27.3 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −80.4 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{15}Cl_2F_3NO_3^+$: 384.0376, found: 384.0371. ***cis*-4j** (minor diastereomer): $[\alpha]_D^{25}$ +68.2 (*c* 0.45, $CHCl_3$, 85% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (1H, brs, Ar), 7.60−7.50 (2H, m, Ar), 7.11 (1H, d, *J* = 2.4 Hz, N═CHO), 4.94 (1H, dd, *J* = 2.4, 0.9 Hz, CH), 1.58 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) 165.1 (C), 153.8 (CH), 135.4 (C), 134.4 (C), 133.3 (C), 130.9 (CH), 128.7 (CH), 125.8 (CH), 122.6 (C, q, J_{C-F} = 283 Hz), 86.9 (C, q, J_{C-F} = 30.8 Hz), 84.1 (CH), 77.4 (CH), 27.7 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.2 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{15}Cl_2F_3NO_3^+$: 384.0376, found: 384.0371.

*tert-Butyl 5-(Thiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4k**).* Yellow oil (87.1 mg, >95% from 48.9 mg of **1k**). HPLC (Lux Cellulose-4, hexane:*i*PrOH 98:2, 1 mL/min): ***trans*-(4*S*,5*S*)-4k** (major diastereomer, 97% ee): major enantiomer, t_r = 7.7 min, minor enantiomer, t_r = 9.3 min, ***cis*-4k** (minor diastereomer, 91% ee): major enantiomer, t_r = 15.3 min, minor enantiomer, t_r = 17.7 min; dr *trans:cis* = 62:38. ***trans*-(4*S*,5*S*)-4k** (major diastereomer): $[\alpha]_D^{25}$ +127.4 (*c* 0.49, $CHCl_3$, 97% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (1H, dd, *J* = 5.1, 1.2 Hz, Ar), 7.16−7.11 (2H, m, Ar, N═CHO), 7.02 (1H, dd, *J* = 5.1, 3.6 Hz, Ar), 5.06 (1H, d, *J* = 2.1 Hz, CH), 1.14 (9H, s, CH_3). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.0 (C), 154.6 (CH), 132.8 (C), 127.5 (CH), 127.3 (CH, q, J_{C-F} = 2.0 Hz, Ar), 126.5 (CH), 123.3 (C, q, J_{C-F} = 283 Hz), 86.3 (C, q, J_{C-F} = 32 Hz), 82.9 (C), 75.0 (CH), 27.3 (CH_3). $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −81.8 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{15}F_3NO_3S^+$: 322.0719, found:322.0713. ***cis*-4k** (minor diastereomer): $[\alpha]_D^{25}$ +164.7 (*c* 0.49, $CHCl_3$, 91% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (1H, dd, *J* = 5.1, 1.3 Hz, Ar), 7.39−7.38 (1H, m, Ar), 7.09 (1H, d, *J* = 2.4 Hz, N═CHO), 7.08 (1H, t, *J* = 3.7 Hz, Ar), 5.08 (1H, dd, *J* = 2.4, 0.9 Hz, CH), 1.55 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.0 (C), 153.9 (CH), 137.7 (C), 127.4 (CH), 127.3 (CH), 127.2 (CH), 122.5 (C, q, J_{C-F} = 283 Hz), 86.4 (C, q, J_{C-F} = 32 Hz), 83.7 (C), 78.2 (CH), 27.7 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.5 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{15}F_3NO_3S^+$: 322.0719, found: 322.0713.

*tert-Butyl 5-Phenethyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4l**).* Yellow oil (71.2 mg, 83% from 50.0 mg of **1l**). HPLC (Chiralpak AY-H, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-4l** (major diastereomer, 84% ee): minor enantiomer, t_r = 5.2 min, major enantiomer, t_r = 7.0 min; ***cis*-4l** (minor diastereomer, 87% ee): minor enantiomer, t_r = 8.7 min, major enantiomer, t_r = 12.6 min; dr *trans:cis* = 72:28. ***trans*-(4*S*,5*S*)-4l** (major diastereomer): $[\alpha]_D^{25}$ +51.2 (*c* 0.86, $CHCl_3$, 84% ee); ^1H NMR (300 MHz, $CDCl_3$) δ ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.26 (2H, m, Ar), 7.22−7.19 (1H, m, Ar), 7.17−7.13 (2H, m, Ar), 7.00 (1H, d, *J* = 2.2 Hz, N═CHO), 4.88 (1H, d, *J* = 2.3 Hz, CH), 2.75 (2H, t, *J* = 8.9 Hz, CH_2), 2.38−2.27 (1H, m, CH), 2.22−2.11 (1H, m, CH), 1.47 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.5 (C), 154.8 (CH), 140.1 (C), 128.5 (CH), 128.0 (CH), 126.4 (CH), 124.3 (C, q, J_{C-F} = 282 Hz), 85.7 (C, q, J_{C-F} = 30 Hz), 83.4 (C), 72.1 (CH), 31.3 (CH_2), 28.6 (CH_2), 27.9 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −79.9 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{21}F_3NO_3^+$: 344.1468, found: 344.1472. ***cis*-4l** (minor diastereomer): $[\alpha]_D^{25}$ +52.1 (*c* 0.59, $CHCl_3$, 87% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.29 (2H, m, Ar), 7.26−7.17 (3H, m, Ar), 7.01 (1H, d, *J* = 2.2 Hz, N═CHO), 4.71 (1H, d, *J* = 1.7 Hz, CH), 2.81−2.66 (2H, m, CH_2), 2.46−2.36 (1H, m, CH), 2.30−2.17 (1H, m, CH), 1.50 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 154.7 (CH), 139.7 (C), 128.7 (CH), 128.2 (CH), 126.6 (CH), 123.7 (C, q, J_{C-F} = 284.3 Hz), 86.9 (C, q, J_{C-F} = 29 Hz), 83.2 (CH), 73.2 (C), 35.7 (CH_2), 28.4 (CH_2), 27.7 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −74.6 (s, CF_3); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{21}F_3NO_3^+$: 344.1468, found: 344.1472.

General Procedure for the Enantioselective Formal [3 + 2] Cycloaddition Reaction with Methyl 2-Isocyano-2-phenylacetate. Squaramide **VIII** (6.8 mg, 0.0125 mmol) and silver oxide (1.5 mg, 0.0063 mmol) were introduced in a round-bottom flask followed by MTBE (2 mL) and trifluoroacetophenone **1** (0.25 mmol). The flask was closed with a stopper and introduced in a bath at −20 °C. After 5 min, methyl 2-isocyano-2-phenylacetate (**2c**, 40 μL, 0.33 mmol) was added and the mixture was stirred at −20 °C until consumption of the trifluoroacetophenone **1** (TLC). After this time, the reaction mixture was filtered through a short pad of silica gel and concenterd under reduced pressure. Compounds **5** were quickly hydrolyzed during slow column chromatography, so separation of both diastereomers by this procedure was not possible.

The racemic product was obtained using a similar procedure using the catalyst 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-((3-(dimethylamino)propyl)amino)cyclobut-3-ene-1,2-dione and silver oxide.

*Methyl 4,5-Diphenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**5a**).* Yellow oil (76.9 mg, 89% from 43.0 mg of **1a**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-5a**

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(minor diastereomer): major enantiomer, t_r = 8.4 min, minor enantiomer, t_r = 6.7 min; ***cis*-5a** (major diastereomer, 90% ee): major enantiomer, t_r = 18.3 min, minor enantiomer, t_r = 12.3 min; dr *trans:cis* = 15:85. ***cis*-5a** (major diastereomer): $[\alpha]_D^{25}$ −5.3 (*c* 1.0, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46−7.41 (3H, m, Ar), 7.43 (1H, s, N═CHO), 7.15−7.08 (2H, s, Ar), 7.03 (5H, s, Ar), 3.98 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.6 (C), 153.2 (CH), 134.4 (C), 130.6 (C), 128.7 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 127.51 (CH), 127.46 (CH), 123.7 (C, q, J_{C-F} = 283 Hz), 92.6 (C, q, J_{C-F} = 29 Hz), 86.1 (C), 53.4 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −72.9 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{15}F_3NO_3^+$: 350.0999, found: 350.0995. ***trans*-5a** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (2H, dd, *J* = 8.1, 3.0 Hz, Ar), 7.72 (2H, dd, *J* = 8.0, 3.0 Hz, Ar), 7.50−7.35 (7H, m, Ar, N═CHO), 3.14 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −72.3 (s, CF_3).

*Methyl 5-(4-Methoxyphenyl)-4-phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**5c**).* Yellow oil (40.3 mg, 42% from 51.0 mg of **1c**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-5c** (minor diastereomer): major enantiomer, t_r = 8.6 min, minor enantiomer, t_r = 12.1 min; ***cis*-5c** (major diastereomer, 89% ee): major enantiomer, t_r = 25.6 min, minor enantiomer t_r = 18.5 min; dr *trans:cis* = 21:79. ***cis*-5c** (major diastereomer): $[\alpha]_D^{25}$ −12.3 (*c* 1.7, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (1H, s, N═CHO), 7.34 (2H, d, *J* = 8.4 Hz, Ar), 7.05−7.03 (5H, s, Ar), 6.62 (2H, d, *J* = 9.0 Hz, Ar), 3.97 (3H, s, CH_3), 3.68 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.7 (C), 159.6 (C), 153.2 (CH), 134.6 (C), 129.7 (C), 129.0 (CH), 128.3 (C), 127.8 (CH), 127.5 (CH), 123.7 (C, q, J_{C-F} = 283 Hz), 112.9 (CH), 92.6 (C, q, J_{C-F} = 28.5 Hz), 86.1 (C), 55.0 (CH_3), 53.3 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −73.28 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{17}F_3NO_4^+$: 380.1104, found: 380.1106. ***trans*-5c** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93−7.90 (2H, m, Ar), 7.62 (2H, d, *J* = 8.7 Hz, Ar), 7.44 (1H, s, N═CHO), 6.96 (2H, d, *J* = 9.0 Hz, Ar), 3.84 (3H, s, CH_3), 3.19 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −72.6 (s, CF_3).

*Methyl 5-(4-Chlorophenyl)-4-phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**5d**).* Yellow oil (95.9 mg, >95% from 53.0 mg of **1d**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-5d** (minor diastereomer): major enantiomer, t_r = 8.0 min, minor enantiomer, t_r = 6.0 min; ***cis*-5d** (major diastereomer, 89% ee): major enantiomer, t_r = 15.7 min, minor enantiomer, t_r = 12.0 min; dr *trans:cis* = 10:90. ***cis*-5d** (major diastereomer): $[\alpha]_D^{25}$ −8.0 (*c* 0.93, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (1H, s, N═CHO), 7.39 (2H, d, *J* = 8.7 Hz, Ar), 7.13−6.96 (7H, m, Ar), 3.98 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.5 (C), 153.1 (CH), 134.9 (C), 134.0 (C), 129.5 (C), 129.1 (CH), 128.6 (CH), 128.0 (CH), 127.8 (CH), 127.3 (CH), 123.5 (C, q, J_{C-F} = 283 Hz), 92.2 (C, q, J_{C-F} = 29 Hz), 86.1 (C), 53.5 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −73.2 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{14}ClF_3NO_3^+$: 384.0609, found: 384.0609. ***trans*-5d** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (2H, d, *J* = 8.1 Hz, Ar), 7.52 (2H, d, *J* = 9.0 Hz, Ar), 3.2 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −71.5 (s, CF_3).

*Methyl 5-(4-Bromophenyl)-4-phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**5n**).* Yellow oil (87.5 mg, 82% from 63.1 mg of **5n**). HPLC (Chiralpak IC, hexane:*i*PrOH 90:10, 1 mL/min): ***trans*-5n** (minor diastereomer): both enantiomers 3.6 min; ***cis*-5n** (major diastereomer, 89% ee): major enantiomer, t_r = 10.5 min, minor enantiomer, t_r = 8.6 min; dr *trans:cis* = 13:87. ***cis*-5n** (major diastereomer): $[\alpha]_D^{25}$ −12.0 (*c* 0.82, $CHCl_3$, 89% ee, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (1H, s, N═CHO), 7.26 (2H, d, *J* = 8.5 Hz, Ar), 7.17 (2H, d, *J* = 9.0 Hz, Ar), 7.04−6.90 (5H, m, Ar), 3.91 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.5 (C), 153.1 (CH), 134.0 (C), 130.8 (CH), 129.7 (CH), 129.4 (CH), 128.7 (CH), 128.1 (CH), 127.3 (CH), 123.4 (C, q, J_{C-F} = 283 Hz), 123.3 (C), 92.3 (C, q, J_{C-F} = 29 Hz), 86.1 (C), 53.5 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −73.1 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{14}BrF_3NO_3^+$: 428.0104, found: 428.0107. ***trans*-5n** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81−7.78 (2H, m, Ar), 7.37 (1H, s, N═CHO), 3.14 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −72.4 (s, CF_3).

*Methyl 4-Phenyl-5-(m-tolyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**5e**).* Yellow oil (78.5 mg, 86% from 47.0 mg of **1e**). HPLC (Chiralpak IC, hexane:*i*PrOH 90:0, 1 mL/min): ***cis*-5e** (major diastereomer, 90% ee): major enantiomer, t_r = 11.4 min, minor enantiomer, t_r = 8.5 min; dr *trans:cis* = 1:99. ***cis*-5e** (major diastereomer): $[\alpha]_D^{25}$ −6.5 (*c* 0.69, $CHCl_3$, 90% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (1H, s, N═CHO), 7.26−7.22 (2H, unresolved m, Ar), 7.04 (5H, s, Ar), 6.98 (1H, t, *J* = 7.7 Hz, Ar), 6.91 (1H, br d, *J* = 7.5 Hz, Ar), 3.97 (3H, s, CH_3), 2.17 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.7 (C), 153.3 (CH), 137.1 (C), 134.4 (C), 130.5 (C), 129.4 (CH), 128.3 (CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 124.6 (C), 123.7 (C, q, J_{C-F} = 283 Hz), 92.6 (C, q, J_{C-F} = 29 Hz), 86.1 (C), 53.3 (CH_3), 21.2 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −72.8 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{17}F_3NO_3^+$: 364.1155, found: 364.1157.

*Methyl 5-(3-Methoxyphenyl)-4-phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**5f**).* Yellow oil (75.4 mg, 86% from 51.0 mg of **1f**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-5f** (minor diastereomer): major enantiomer, t_r = 7.5 min, minor enantiomer, t_r = 10.1 min, ***cis*-5f** (major diastereomer, 89%): major enantiomer, t_r = 19.6 min, minor enantiomer, t_r = 12.5 min; dr *trans:cis* = 15:85. ***cis*-5f** (major diastereomer): $[\alpha]_D^{25}$ +5.40 (*c* 0.72, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (1H, s, N═CHO), 7.10−6.90 (8H, m, Ar), 6.65 (1H, ddd, *J* = 7.4, 2.6, 1.7 Hz, Ar), 3.98 (3H, s, CH_3), 3.65 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.6 (C), 158.7 (C), 153.2 (CH), 134.4 (C), 131.9 (C), 128.7 (CH), 128.4 (CH), 127.8 (CH), 127.4 (CH), 123.6 (C, q, J_{C-F} = 287 Hz), 120.0 (CH), 114.6 (CH), 113.4 (C), 92.4 (C, q, J_{C-F} = 28 Hz), 86.1 (C), 55.1 (CH_3), 53.4 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −72.9 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{17}F_3NO_4^+$: 380.1104, found: 380.1107. ***trans*-5f** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93−7.90 (1H, m, Ar), 7.45 (1H, s, N═CHO), 3.85 (3H, s, CH_3), 3.18 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −72.3 (s, CF_3).

*Methyl 5-(3-Bromophenyl)-4-phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**5g**).* Yellow oil (86.8 mg, 81% from 63.0 mg of **1g**). HPLC (Chiralpak IC, hexane:*i*PrOH 90:10, 1 mL/min): ***trans*-5g** (minor diastereomer): major enantiomer, t_r = 7.0 min, minor enantiomer, t_r = 5.7 min; ***cis*-5g** (major diastereomer, 88% ee): minor enantiomer, t_r = 10.1 min, major enantiomer, t_r = 14.3 min; dr *trans:cis* = 2:98. ***cis*-5g** (major diastereomer): $[\alpha]_D^{25}$ −15.4 (*c* 0.92, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) 7.51 (1H, s, Ar), 7.36 (1H, s, N═CHO), 7.32 (1H, br d, *J* = 8.0 Hz, Ar), 7.17 (1H, d, *J* = 9.0 Hz), 7.03−6.92 (5H, m, Ar), 6.88 (1H, t, *J* = 8.1 Hz, Ar), 3.91 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.4 (C), 153.1 (CH), 133.8 (C), 132.8 (C), 131.9 (CH), 130.6 (br, CH), 129.0 (CH), 128.7 (CH), 128.0 (CH), 127.3 (CH), 126.4 (CH), 123.4 (C, q, J_{C-F} = 283 Hz), 121.7 (C), 92.0 (C, q, J_{C-F} = 29 Hz), 86.2 (C), 53.5 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −72.8 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{14}BrF_3NO_3^+$: 428.0104, found: 428.0107. ***trans*-5g** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (1H, s, Ar), 7.93 (1H, d, *J* = 9.2 Hz, Ar), 7.80−7.70 (2H, m, Ar), 3.15 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −71.5 (s, CF_3).

*Methyl (2S,3S)-4,4,4-Trifluoro-2-formamido-3-hydroxy-3-phenylbutanoate (**6a**).* Aqueous HCl (6 M, six drops) was added to a solution of compound **3a** (54.0 mg, 0.20 mmol) in THF (1 mL). The reaction mixture was stirred at rt for 24 h. Saturated aqueous

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$NaHCO_3$ (1 mL) and water (10 mL) were added, and the mixture extracted with EtOAc (3 × 20 mL), washed with brine (20 mL), and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded compound **6a** as a colorless oil (58.0 mg, 95%). HPLC (Chiracel OD-H, hexane:*i*PrOH 90:10, 1 mL/min): ***trans*-6a** (major diastereomer, 88% ee); major enantiomer, t_r = 14.0 min, minor enantiomer, t_r = 11.0 min; ***cis*-6a** (minor diastereomer), major enantiomer, t_r = 8.5 min, minor enantiomer, tr = 7.9 min; dr *trans:cis* = 96:4. ***trans*-6a** (major diastereomer): $[\alpha]_D^{25}$ −23.6 (*c* 0.68, $CHCl_3$, for the diastereomer mixture); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (1H, dd, *J* = 1.2, 0.7 Hz, CHO), 7.59−7.57 (2H, m, Ar), 7.42−7.40 (3H, m, Ar), 6.79 (1H, d, *J* = 9.0 Hz, NH), 5.57 (1H, dd, *J* = 9.0, 0.6 Hz, CH), 4.68 (1H, bs, OH), 3.47 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.0 (C), 160.7 (CH), 134.4 (C), 129.6 (CH), 128.6 (CH), 126.1 (CH), 123.9 (C, q, J_{C-F} = 283 MHz), 78.20 (C, q, J_{C-F} = 30 Hz), 53.5 (CH), 52.9 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.8 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{13}F_3NO_4^+$: 292.0791, found: 292.0798. ***cis*-6a** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.85 (d, *J* = 10.5 Hz, CH), 3.54 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −76.4 (s, CF_3).

*Methyl (2S,3S)-3-(3-Bromophenyl)-4,4,4-trifluoro-2-formamido-3-hydroxybutanoate (**6g**).* Following a procedure similar to that used for the synthesis of compound **6a**, from compound **3g** (42.3 mg, 0.12 mmol) was obtained formamide **6g** as a colorless oil (42.6 mg, 95%). HPLC (Chiralpak AY-H, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-6g** (major diastereomer, 91% ee): major enantiomer, t_r = 21.9 min, minor enantiomer, t_r = 29.6 min; ***cis*-6g** (minor diastereomer): major enantiomer, t_r = 10.9 min, minor enantiomer, t_r = 8.7 min; dr *trans:cis* = 83:17. ***trans*-6g** (major diastereomer): $[\alpha]_D^{25}$ +5.41 (*c* 0.72, $CHCl_3$, for the diastereomer mixture); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (1H, dd, *J* = 1.0, 0.7 Hz, CHO), 7.77 (1H, bs, Ar), 7.57−7.50 (2H, m, Ar), 7.29 (1H, t, *J* = 8.0 Hz, Ar), 6.75 (1H, d, *J* = 8.8 Hz, NH), 5.52 (1H, d, *J* = 9.0 Hz, CH), 4.85 (1H, bs, OH), 3.55 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.7 (C), 160.8 (CH), 136.8 (C), 132.7 (CH), 130.0 (CH), 129.5 (CH), 124.9 (CH), 123.7 (C, q, J_{C-F} = 285 MHz), 122.9 (C), 77.8 (C, q, J_{C-F} = 29 MHz), 53.6 (CH), 53.1 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.2 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{12}BrF_3NO_4^+$: 369.9896, found: 369.9883. ***cis*-6g** (minor diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$) representative signals taken from the NMR spectra of the diastereomer mixture, δ 7.93 (1H, s, CHO), 7.82 (1H, t, *J* = 1.7 Hz, Ar), 6.16 (1H, d, *J* = 9.0 Hz, NH), 5.42 (1H, d, *J* = 9.0 Hz, CH), 3.87 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −71.5 (s, CF_3).

*Methyl (2S,3S)-2-Amino-4,4,4-trifluoro-3-hydroxy-3-phenylbutanoate (**7a**).* Aqueous HCl (6 M, six drops) was added to a solution of compound **3a** (28.6 mg, 0.11 mmol) in MeOH (1 mL). The reaction mixture was stirred at rt for 24 h. Saturated aqueous $NaHCO_3$ (1 mL) and water (10 mL) were added, and the mixture extracted with EtOAc (3 × 20 mL), washed with brine (20 mL), and dried over $MgSO_4$. Removal of the solvent under reduced pressure aforded compound **7a** as a colorless oil (27.6 mg, 95%). HPLC (Chiralpak AY-H, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-7a** (major diastereomer, 90% ee): major enantiomer, t_r = 15.8 min, minor enantiomer, t_r = 17.3 min; ***cis*-7a** (minor diastereomer): major enantiomer, t_r = 11.8 min; minor enantiomer, t_r = 9.6 min; dr *trans:cis* 92:8. ***trans*-7a** (major diastereomer): $[\alpha]_D^{25}$ +47.9 (*c* 1.23, $CHCl_3$, for the diastereomer mixture); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61−7.54 (2H, m, Ar), 7.38−7.35 (3H, m, Ar), 4.33 (1H, s, CH), 3.29 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.3 (C), 135.1 (C), 128.8 (CH), 128.0 (CH), 126.3 (CH, q, J_{C-F} = 2.0 Hz), 125.2 (C, q, J_{C-F} = 283 Hz), 76.4 (C, q, J_{C-F} = 27 Hz), 57.3 (CH), 52.0 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.9 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{13}F_3NO_3^+$: 264.0842, found: 264.0851. ***cis*-7a** (minor diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$) representative signals taken from the NMR spectra of the diastereomer mixture, δ 7.65−7.60 (2H, m, Ar), 7.45−7.31 (3H, m, Ar), 4.07 (1H, s, CH), 3.83 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 56.5(CH), 52.9 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.0 (s, CF_3).

*Methyl 2-Amino-3-(3-bromophenyl)-4,4,4-trifluoro-3-hydroxybutanoate (**7g**).* Following a procedure similar to that used for the synthesis of compound **7a**, from compound **3g** (22.7 mg, 0.064 mmol), was obtained **7g** (21.0 mg, 95%). HPLC (Chiralpak AD-H, hexane:*i*PrOH 98:2, 0.7 mL/min): ***trans*-7g**: (major diastereomer, 92% ee): major enantiomer, t_r = 36.5 min, minor enantiomer, t_r = 34.9 min. ***cis*-7g** (minor diastereomer): major enantiomer, t_r = 32.8 min, minor enantiomer, t_r = 28.9 min; dr *trans:cis* 93:7. ***trans*-7g**: (major diastereomer): $[\alpha]_D^{25}$ +49.1 (*c* 0.68, $CHCl_3$, for the diastereomer mixture); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (1H, t, *J* = 1.9 Hz, Ar), 7.55−7.48 (2H, m, Ar), 7.24 (1H, t, *J* = 7.9 Hz, Ar), 4.32 (1H, s, CH), 3.35 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.8 (C), 137.3 (C), 132.0 (CH), 129.7 (CH, q, J_{C-F} = 1.6 Hz), 129.5 (CH), 125.1 (CH, q, J_{C-F} = 1.6 Hz), 124.9 (C, q, J_{C-F} = 289 MHz), 75.9 (C, q, J_{C-F} = 27 Hz), 57.1 (CH), 52.2 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.6 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{12}BrF_3NO_3^+$: 341.9947, found: 341.9948. For the X-ray structure of ***trans*-7g**, see Figure S2 in the Supporting Information. ***cis*-7g** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (1H, br s, Ar), 7.56−7.44 (2H, m, Ar), 7.31 (1H, t, *J* = 8.0 Hz, Ar), 4.00 (1H, s, CH), 3.84 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −76.6 (s, CF_3).

*Methyl 2-Amino-4,4,4-trifluoro-3-hydroxy-3-methylbutanoate (**7m**).* Following a procedure similar to that used for the synthesis of compound **7a**, from compound **3m** (56.2 mg, 0.16 mmol) after 72 h was obtained **7m** (60.2 mg, 88%). GLC (Supelco β-dex-225, T_{column} = 60 °C (1 min) to 150 °C at 7 °C/min, and to 220 °C at 16 °C/min, ***trans*-7m** (major diastereomer, 82%): major enantiomer, t_r = 12.3 min, minor enantiomer, t_r = 13.2 min; ***cis*-7m** (minor diastereomer): enantiomer 1, t_r = 17.7 min, enantiomer 2, t_r = 17.8 min; dr *trans:cis* = 97:3; ***trans*-7m** (major diastereomer): $[\alpha]_D^{25}$ −38.2 (*c* 0.98, $CHCl_3$, 82% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (4H, s, CH, CH_3 overlapped), 1.32 (3H, s, CH_3); ^{1}H NMR (300 MHz, DMSO-d_6, for **7m**·HCl) δ 8.82 (3H, br s, NH_3), 7.47 (1H, br s, OH), 4.10 (1H, s, CH-N), 3.75 (3H, s, CH_3), 1.39 (3H, s, CH_3);[19] $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.2 (C), 125.8 (C, q, J_{C-F} = 285 MHz), 72.6 (C, q, J_{C-F} = 31 Hz), 55.7 (br, CH), 52.5 (CH_3), 18.1 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −80.6 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_6H_{11}F_3NO_3^+$: 202.0686, found: 202.0684. ***cis*-7m** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (3H, s, CH_3), 1.44 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −78.6 (s, CF_3).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02808.

Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra, HPLC chromatograms, and X-ray crystallographic data of **4i** and **7g** (PDF)

X-ray crystallographic data of **4i** (CIF)

X-ray crystallographic data of **7g** (CIF)

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Notes

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(15) Caution has to be taken during the purification of the reaction products to avoid alteration of the ee values due to the self-disproportionation of enantiomers phenomenon. See: (a) Soloshonok, V. A. Remarkable amplification of the self-disproportionation of enantiomers on achiral-phase chromatography columns. *Angew. Chem., Int. Ed.* **2006**, *45*, 766. (b) Soloshonok, V. A.; Roussel, C.; Kitagawa, O.; Sorochinsky, A. E. Self-disproportionation of enantiomers via achiral chromatography: a warning and an extra dimension in optical purifications. *Chem. Soc. Rev.* **2012**, *41*, 4180.

(16) The structure and absolute stereochemistry of compounds **7g** and **4i** were determined by X-ray analysis, CCDC 1844051−1844052, respectively; see the Supporting Information.

(17) The absolute stereochemistry of the minor *cis*-**3** and *cis*-**4** oxazolines could not be determined. On the basis of our previous results with ketones (see ref 5d), we assume they may have the (*4S,5R*) configuration.

(18) The absolute stereochemistry of compound **5** could not be determined.

(19) Lee, C.-J.; Liang, X.; Wu, Q.; Najeeb, J.; Zhao, J.; Gopalaswamy, R.; Titecat, M.; Sebbane, F.; Lemaitre, N.; Toone, E. J.; Zhou, P. Drug design from the cryptic inhibitor envelope. *Nat. Commun.* **2016**, *7*, 10638.

(20) Compounds **3** and **4** showed some tendency to hydrolyze during column chromatography, which in some cases made their purification by this technique difficult. In a reduced number of cases, the reaction products contained trace amounts of residual isocyanoacetates or their byproducts. See the NMR spectra in the Supporting Information for the possible presence of small amounts of contaminants.

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Catalytic Diastereo- and Enantioselective Synthesis of 2-Imidazolinones

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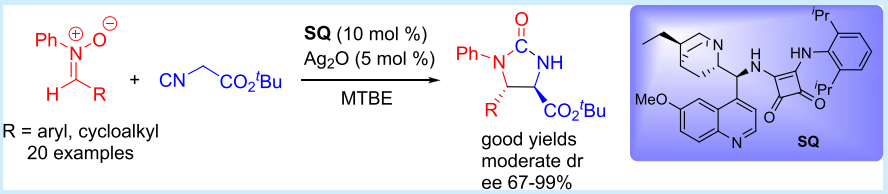
Supporting Information

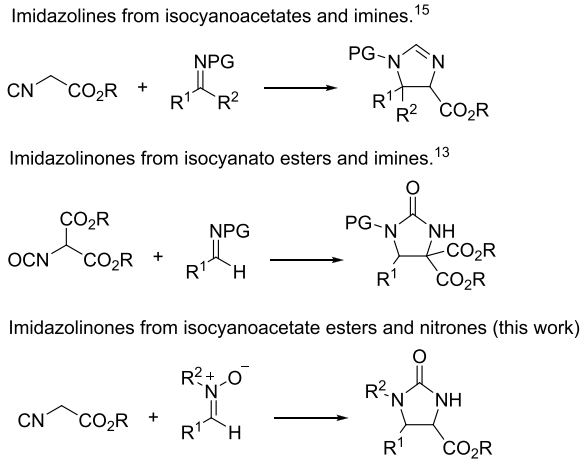


ABSTRACT: Chiral cyclic ureas (2-imidazolinones) were prepared by the reaction of nitrones and isocyanoacetate esters using a multicatalytic system that combines a bifunctional Brønsted base−squaramide organocatalyst and Ag^+ as a Lewis acid. The reaction could be achieved with a range of nitrones derived from aryl- and cycloalkylaldehydes with moderate diastereo- and good enantioselectivity. A plausible mechanism involving an initial formal [3 + 3] cycloaddition of the nitrone and isocyanoacetate ester, followed by rearrangement to an aminoisocyanate and cyclization to the imidazolinone, is proposed.

Cyclic ureas, in particular 2-imidazolinones, are structural units often found in natural products,[1] as well as biologically and pharmacologically interesting molecules, including HIV protease inhibitors,[2] 5-HT3 receptor and PX27 receptor antagonists,[3] NK1 antagonists,[4] and ACE inhibitor hypertensive drugs.[5] Chiral imidazolidin-2-ones have also been widely utilized as chiral auxiliaries,[6] chiral ligands,[7] and intermediates in organic synthesis.[8] For these reasons, many methodologies have been developed to generate these molecules. Examples include the carboxylation of 1,2-diamines,[9] intramolecular amidation reactions,[10] intermolecular diamidation reactions,[11] or reactions involving isocyanates.[12] However, only few procedures allow the enantioselective formation of the 2-imidazolinone ring and a C−C bond simultaneously.[13]

In recent years, isocyanoacetate esters have emerged as formal 1,3-dipoles that can react with different electrophilic unsaturated functional groups to give five-membered, nitrogen-containing heterocycles.[14] Thus, chiral imidazolines have been prepared by several authors from isocyano acetates and imines under different conditions (Scheme 1).[15] Within this area, our group has contributed with the development of a highly enantioselective synthesis of 2-oxazolines from ketones and isocyanoacetate esters using a multicatalytic system that combines a bifunctional squaramide−Brønsted base and silver as a Lewis acid.[16] Wishing to extend the structural diversity of compounds that can be prepared enantioselectively with this chemistry, we became interested in studying other nitrogen-containing electrophiles. Herein we report the reaction of isocyanoacetates with nitrones, which are typical 1,3-dipoles used in cycloaddition reactions. The reaction provided chiral 2-imidazolinones instead of the expected [3 + 3] cycloaddition products.[17]

Scheme 1. Synthesis of Imidazolines and Imidazolinones from Imine Derivatives



The reaction of nitrone **1a** and *tert*-butyl isocyanoacetate (**2a**) was chosen to optimize the reaction conditions (Table 1). Following our methodology previously developed for the reaction with ketones, we tested different chiral squaramide organocatalysts in the presence of silver oxide in *tert*-butyl methyl ether as the solvent (Table 1). **SQ3** and **SQ4**, which are derivatives of dihydro 9-deoxy-9-*epi*-9-aminoquinine and 2,6-disubstituted anilines, provided the highest enantioselec-

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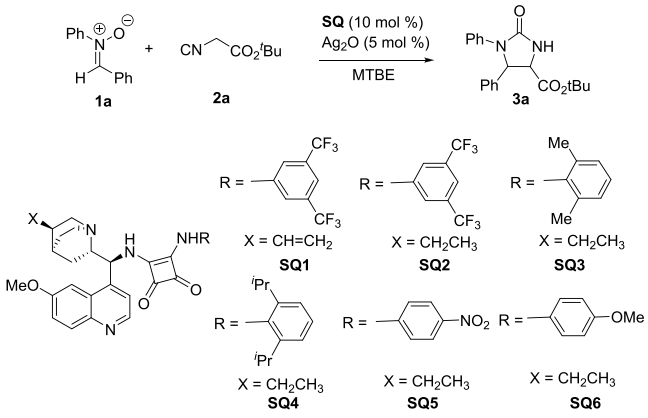
Table 1. Screening of Organocatalysts[a]



entry	SQ	t (d)	yield (%)[b]	trans/cis[c]	ee_{trans} (%)[d]
1	**SQ1**	1	83	46:54	70
2	**SQ2**	1	73	48:52	70
3	**SQ3**	1	75	71:29	84
4	**SQ4**	2	89	61:39	84
5	**SQ5**	2	70	55:45	58
6	**SQ6**	7	43	52:48	83

[a]Conditions: **1a** (0.13 mmol), **2a** (0,17 mmol), **SQ** (0.013 mmol), Ag_2O (0.0063 mmol), TBME (1 mL), room temperature. [b]Isolated yield after column chromatography. [c]Determined by ^1H NMR. [d]Determined by HPLC over chiral stationary phases.

tivity for the major *trans* diastereomer (Table 1, entries 3 and 4).

Further optimization was carried out first with organocatalyst **SQ3** (Table 2). From the different solvents tested

Table 2. Effect of Solvents and Concentration[a]

entry	SQ	solvent	[**1a**][b]	t (d)	yield (%)[c]	trans/cis[d]	ee_{trans} (%)[e]
1	**SQ3**	MTBE	0.13	1	75	71:29	84/−6
2	**SQ4**	MTBE	0.13	1	83	61:39	84/−13
3	**SQ3**	dioxane	0.13	2	70	71:29	90/30
4	**SQ3**	toluene	0.13	2	71	70:30	87/3
5	**SQ3**	Et_2O	0.13	2	70	69:31	79/6
6	**SQ3**	EtOAc	0.13	2	60	65:35	79/6
7	**SQ3**	DCM	0.13	2	39	41:59	59:12
8	**SQ3**	dioxane	0.063	2	46	73:27	99/3
9	**SQ4**	dioxane	0.063	3	60	50:50	78/21
10	**SQ4**	MTBE	0.063	2	84	68:32	88/−9
11[f]	**SQ4**	MTBE	0.063	4	78	67:37	88/−3
12[g]	**SQ4**	MTBE	0.063	1	60	66:33	88/−2
13	**SQ4**	MTBE	0.042	4	78	71:29	90/−3

[a]Conditions: **1a** (0.13 mmol), **2a** (0.17 mmol), **SQ** (0.013 mmol), Ag_2O (0.0063 mmol), solvent, room temperature. [b]Molar concentration of **1a**. [c]Isolated yield after column chromatography. [d]Determined by ^1H NMR. [e]Determined by HPLC over chiral stationary phases. [f]Reaction carried out at 0 °C. [g]Reaction carried out at 35 °C

(Table 2, entries 3−7), dioxane allowed the best diastereo- (*trans:cis* 71:29) and enantioselectivity (90%) to be obtained. By performing the reaction under more dilute conditions, the ee could be raised up to 99%, however with a huge detriment to yield (Table 2, entry 8). Other attempts to increase the yield and/or stereoselectivity with **SQ3** in dioxane were unsuccessful (see Supporting Information). Therefore, we turned our attention back to squaramide **SQ4**. This organocatalyst was tested in dioxane as the solvent under identical conditions as those previously used for **SQ3** providing compound **3aa** as a 1:1 mixture of diastereomers in 78% ee (Table 2, entry 9). Since dioxane seemed not to be a good solvent for this catalyst, the reaction was repeated in MTBE under dilute conditions yielding the expected urea **3aa** with fair diastereoselectivity (dr = 68:32) and high enantioselectivity (88% ee), without detriment in the yield (Table 1, entry 10). Attempts to improve the stereoselectivity by changing the reaction temperature were unsuccessful (Table 1, entries 11 and 12). Finally, a small increase of diastereo- and enantioselectivity could be obtained by further dilution of the reaction mixture (Table 1, entry 13).

Given the similar results obtained either with **SQ3** in dioxane (Table 2, entry 3) or with **SQ4** in MTBE (Table 2, entry 13), both reaction condition manifolds were tested with two nitrones **3b** and **3c** derived from *p*-substituted aldehydes (Scheme 2). The **SQ3**/dioxane system provided the expected ureas **3ba** and **3ca** with similar or lower stereoselectivities to those obtained with **SQ4**/MTBE, and in significant lower yields. Accordingly, the study of the reaction scope was continued under the optimized conditions for **SQ4** in MTBE. In general, the reaction conditions could be applied to the addition of *tert*-butyl isocyanoacetate (**2a**) with a large range of *N*-phenylnitrones derived from substituted benzaldehydes bearing substituents of different electronic nature in different positions of the aromatic ring. The chiral 2-imidazolinones **3aa**−**3ka** were obtained with fair to good diastereoselectivity (62:38 to 78:22) and high enantiomeric excesses (67−94%). The presence of electron-donating groups (Me, MeO) (**3ba**, **3ea**, **3fa**, **3ia**) favored higher enantioselectivities than electron-withdrawing groups (Br, NO_2) (**3ca**, **3da**, **3ga**, **3ha**, **3ja**, **3ka**) regardless of the position of these groups on the aromatic ring. The reaction also worked with the *N*-phenyl nitrone derived of the bulky 2-naphthylcarbaldehyde delivering urea **3la** with good yield, good dr, and excellent ee. 2-Pyridine-derived nitrone **1m** reacted with *tert*-butyl isocyanoacetate to give compound **3ma** in quantitative yield, with good diastereoselectivity (dr = 88:12) and excellent enantioselectivity (95% ee). This result contrasts with those obtained with nitrones derived from nitrobenzaldehydes, and it is quite surprising since both the pyridine and the nitrophenyl are electron-poor rings. Furthermore, the enantiomer of **3ma** could be also obtained with a very good result by using squaramide **SQ7**, derived from dihydroquinidine, in place of **SQ4**. Cycloalkylcarbaldehyde-derived nitrones were also suitable substrates for the reaction.[18] Compounds **3na** and **3oa**, bearing a cyclohexyl or cyclopropyl substituent, respectively, were obtained with very high enantiomeric excesses. The effect of the substituent on the N atom of the nitrone was also tested. *N*-(4-Chlorophenyl) imine reacted with *tert*-butyl isocyanoacetate to give compound **3pa** with good yield but moderate diastereo- and enantioselectivity. On the other hand, the *N*-(4-methoxyphenyl) nitrone provided compound **3qa** with good enantioselectivity (91% ee) but in very low yield (24%), unfortunately. Finally, we tested the reaction with benzyl (**2b**) and methyl (**2c**) isocyanoacetates, yet neither performed better than *tert*-butyl isocyanoacetate. The reaction could be carried out at 1 mmol scale without noticeable effect on the results (Scheme 2, footnote c).

Scheme 3 outlines some synthetic modifications of compounds **3**. Deprotection of the *tert*-butyl ester can be

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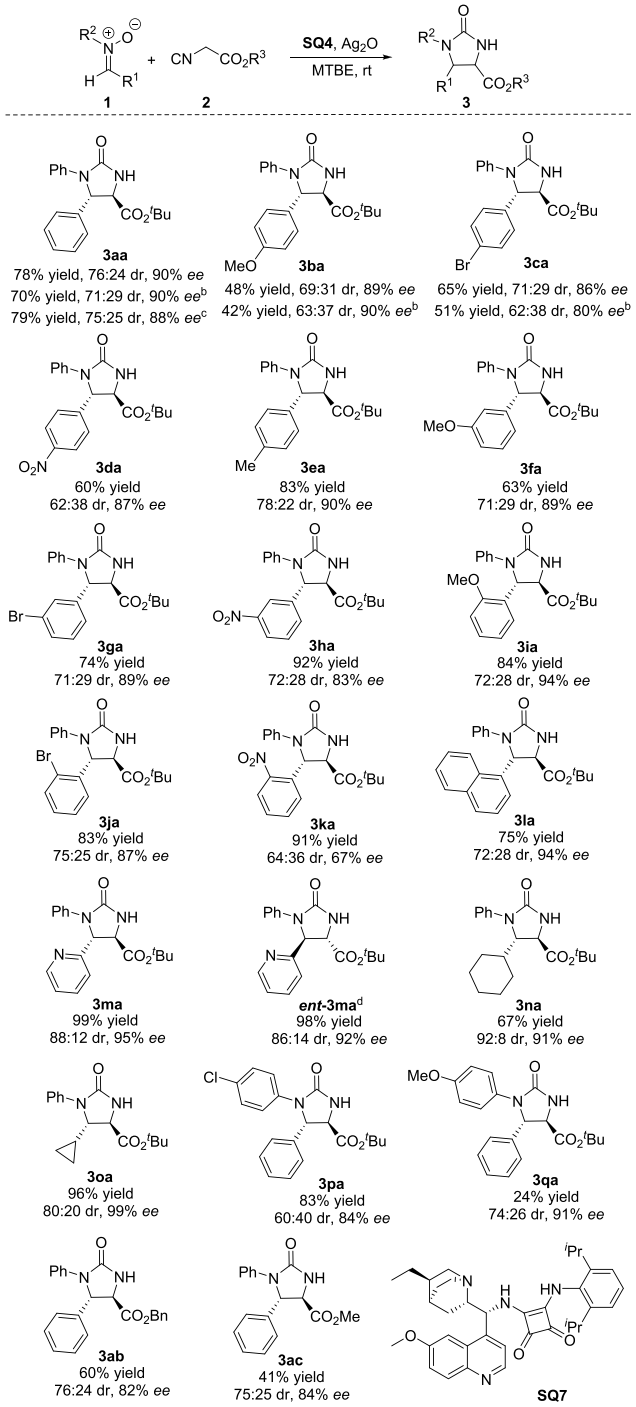
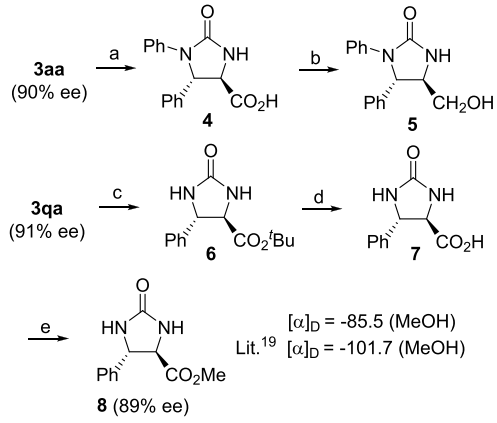
Scheme 2. Scope of the Reaction of Nitrones 1 and Isocyanoacetates 2[a]



[a]Reaction conditions: **1** (0.25 mmol), **2** (0.33 mmol), **SQ4** (0.025 mmol), Ag_2O (0.013 mmol), MTBE (6 mL), rt. [b]Reaction conditions: **1** (0.13 mmol), **2** (0.17 mmol), **SQ3** (0.013 mmol), Ag_2O (0.0063 mmol), dioxane (1 mL), rt. [c]Reaction carried out with 1 mmol of **1a**. [d]Reaction carried out with squaramide **SQ7**. Yields after column chromatography, dr determined by ^1H NMR, *ee* determined by HPLC.

achieved with trifluoroacetic acid to give acid **4** which can be converted into alcohol **5** after reduction with borane. On the other hand, the absolute stereochemistry of compounds **3** was determined by chemical correlation with a compound of

Scheme 3. Synthetic Modifications and Determination of the Absolute Stereochemistry of Compounds 3[a]

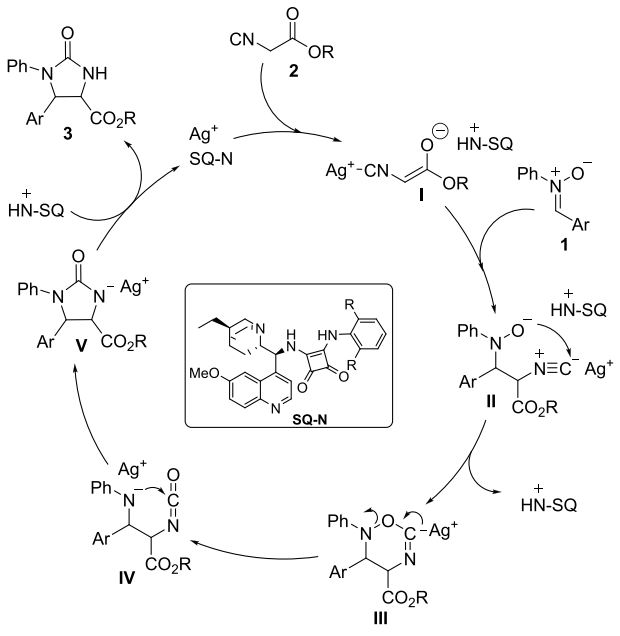


[a]Reaction conditions: (a) CF_3CO_2H/CH_2Cl_2, rt, 5h, 89%; (b) $BH_3\cdot SMe_2$, THF, rt, 24 h, 76%; (c) CAN (3.0 equiv), $MeCN/H_2O$, 0 °C to rt, 1 h, 75%; (d) CF_3CO_2H/CH_2Cl_2, rt, 7 h, 87%; (e) H_2SO_4 (cat.), MeOH, reflux, 6 h, 89%.

known stereochemistry (Scheme 3). Thus, the N atom in compound **3qa** was deprotected with CAN to give compound **6**, which after hydrolysis of the *tert*-butyl ester with trifluoroacetic acid yielded acid **7**. Finally, Fisher esterification gave the ester **8**, which showed identical spectroscopic features and optical rotation sign as those described in the literature for (4*R*,5*S*)-**8**,[19] allowing assignment of the stereochemistry of compound **3qa**. The absolute stereochemistry of the remaining compounds **3** was assigned upon the assumption of a uniform mechanistic pathway.

Scheme 4 shows a plausible mechanism for the formation of cyclic ureas **3**. Thus, deprotonation of the isocyanoacetate **2** by the basic bifunctional squaramide assisted by silver would give the corresponding enolate **I** that would undergo nucleophilic addition to the C−N double bond of nitrone **1** to give

Scheme 4. Proposed Catalytic Cycle for the Synthesis of 2-Imidazolinones



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intermediate **II**, followed by intramolecular alkoxide addition to the isocyanide giving the formal [3 + 3] cycloaddition product **III**. This would rearrange to the amino isocyanate **IV**, which after amide addition would give the deprotonated imidazolinone **V**. Finally, protonation by the catalyst conjugate acid provides product **3** and releases the catalyst.

In summary, we have developed an unprecedented catalytic diastereo- and enantioselective synthesis of cyclic ureas (2-imidazolinones) by reaction of isocyanoacetate esters and nitrones. The reaction is catalyzed by a bifunctional Brønsted base−squaramide organocatalyst and Ag^+ as a Lewis acid and provides the chiral *trans*-2-imidazolinones with good diastereoselectivity and high enantioselectivity in most of the examples tested, applicable to nitrones derived from aromatic and heteroaromatic aldehydes as well as nitrones derived from cycloalkylcarbaldehydes. The reaction most probably involves the initial formal [3 + 3] cycloaddition of the nitrone and isocyanoacetate ester, followed by rearrangement to an amino isocyanate and cyclization to the imidazolinone.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01244.

Experimental procedures, characterization data, NMR spectra, and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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Advanced Synthesis & Catalysis

Enantioselective Synthesis of Functionalized Diazaspirocycles from 4-Benzylideneisoxazol-5(4*H*)-one Derivatives and Isocyanoacetate Esters

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Abstract: Enantioenriched spirocyclic compounds bearing three contiguous stereocenters and high functionalization were obtained through a formal [3 + 2] cycloaddition reaction catalyzed by a cooperative system. The spiro compounds were synthesized from 4-arylideneisoxazol-5-ones and isocyanoacetate esters using a bifunctional squaramide/Brønsted base organocatalyst derived from a Cinchona alkaloid and silver oxide as Lewis acid. This method afforded two out of the four possible diastereomers with good yields and high enantiomeric excess for both diastereomers.

Keywords: Asymmetric catalysis; Enantioselectivity; Heterocycles; Cycloaddition; Spiro compounds

Organic spirocycles are unique compounds that feature two rings connected through just one shared carbon (the spiroatom). This structural feature is often present in natural products isolated from different sources, from plants to marine organisms.[1] Examples of spirocompounds of natural origin include horsfiline, a natural product isolated from *Horsfielda superba*,[1d] β-vetivone, extracted from vetiver oil,[1e] or (−)-gleenol isolated from the brown alga *Taonia atomaria* (Figure 1).[1f] Spirocyclic compounds have also found some interesting applications as privileged ligands for asymmetric catalysis such as spinol,[2] or in the production of circularly polarized photoluminescence.[3] Furthermore, the spirocyclic motif is becoming a prevalent template in drug discovery,[4] since this structural feature conveys both increased three-dimensionality for potential improved activity, and novelty for patenting purposes. An example of spirocyclic drugs is the marketed fenspiride,[5] used for the treatment of some respiratory diseases (Figure 1).

For these reasons, the synthesis of spirocyclic compounds has received a growing interest in the last decade.[6] In this context, the catalytic enantioselective construction of a chiral spiro quaternary carbon results especially challenging. The synthesis of quaternary stereocenters, in general, is hampered by the huge steric hindrance and low steric dissimilarity of the two carbon substituents on the prochiral center. Furthermore, the generation of a spiro quaternary stereocenter often requires overcoming ring strain to install useful functionalities, and the diastereoselectivity needs to be controlled because the construction of spiro systems is

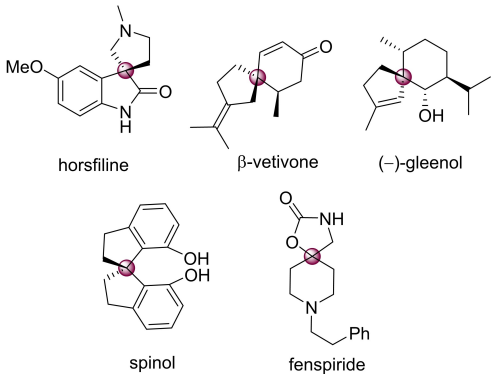


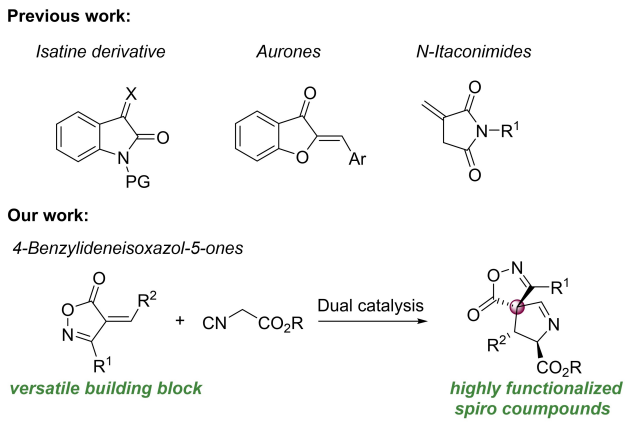
Figure 1. Selected examples of natural products and drugs with spirocyclic structure.

often accompanied by the formation of additional stereocenters.

Among the different methodologies designed to achieve this goal,[7] cycloaddition reactions with cyclic compounds bearing an exocyclic double bond result especially appealing because of its simplicity and the vast variety of reaction partners that can participate in this kind of reactions. Five-membered nitrogen-containing heterocycles are privileged structures in medicinal chemistry. Among these, the spiropyrroline,[8] as well as the spiroisoxazol-5-one[9] scaffolds are featured in a great number of natural products, biologically active compounds and pharmaceuticals.

Isocyanoacetate esters are versatile scaffolds in organic synthesis and can participate as formal 1,3-dipoles in cycloaddition reactions leading to five-membered nitrogen-containing heterocycles.[10] In the last years, this approach has been used in the enantioselective synthesis of several spirocyclic compounds (Scheme 1). Thus, the groups of Zhong, Wang, Yan, Shi and He have reported the addition of isocyanoacetate esters to different isatin derivatives for the preparation of spirooxindoles.[11] Also recently, the groups of Shao/He and Zhao have reported the synthesis of spirocycles by the reaction of isocyanoacetate esters with aurones or *N*-itaconimides, respectively.[12]

On the other hand, 4-arylideneisoxazol-5-ones, featuring an isoxazole-5-one ring with an exocyclic double bond, are structures present in natural products and other biologically active compounds, and have raised increased interest as electrophiles in Michael-type reactions, including organocatalyzed reactions. Moreover, the isoxazole-5-one ring is a versatile building block being used as synthetic equivalent of alkynes or ketones among others.[13] Following our research on enantioselective cycloaddition reactions with isocyanoacetate esters,[14] we report here the synthesis of chiral hybrid diazaspirocyclic compounds[15] combining a pyrroline and an isoxazol-5-one ring, via the formal [3+2] cycloaddition reaction of 4-benzylideneisoxazol-5-ones and isocyanoacetate esters (Scheme 1).



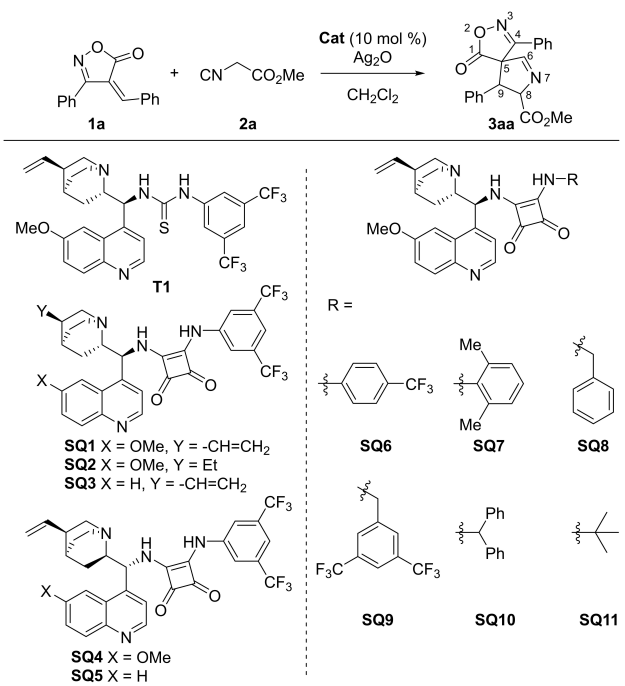
Scheme 1. Synthesis of spiro compounds employing iso-cyanoacetates as pronucleophiles.

In the onset of our research, the reaction between methyl isocyanoacetate (**2a**) and benzylidene-3-phenylisoxazol-5-one (**1a**) in dichloromethane was chosen to optimize the reaction conditions (Table 1). We started by checking bifunctional thiourea **T1** and squaramide **SQ1** catalysts in the presence of silver oxide following conditions previously established in our group,[14] which performed in a similar way providing the expected product **3aa** with good diastereoselectivity but low enantioselectivity (Table 1, entries 1 and 2). We also observed that silver oxide alone was able to catalyze the diastereoselective reaction in a non-enantioselective manner (Table 1, entry 3). To avoid this undesired background reaction, we performed the reaction with **T1** or **SQ1** in the absence of silver oxide (Table 1, entries 4 and 5). However, although in both cases the enantiomeric excess of the reaction product was improved under these conditions, the reaction required longer times and product **3aa** was obtained in low yield despite total consumption of the starting material. Also we observed that **SQ1** provided better enantioselectivity than **T1**.

Further investigation revealed that **1a** decomposed in great extent by standing in solution at the reaction concentration, bringing about the low yields observed. We also found out that decomposition rate of **1a** decreased in more diluted solution, unfortunately, the reaction of **1a** with the isocyano ester **2a** also slowed down and led to a small yield of **3aa**, although with high *ee* (Table 1, entry 6). At this point, addition of silver oxide to the diluted reaction accelerated the reaction and allowed to obtain the spirocyclic compound in 55%, with fair diastereoselectivity (75:25), and high enantiomeric excess for both diastereomers, 80% *ee* for the major diastereomer and 98% *ee* for the minor one (Table 1, entry 7). However, performing the reaction under these conditions with thiourea **T1** notably decreased the enantioselectivity (Table 1, entry 8).

Other solvents and temperatures were tested, but none of these changes improved the results (see SI). Next, we carried out a screening of squaramide catalysts (Table 1, entries 9–17, see also SI). Catalyst **SQ2** derived from dihydroquinine improved the diastereoselectivity, but the enantiomeric excess suffered a dramatic decrease (Table 1, entry 9). Squaramide **SQ3**, derived from cinchonidine, performed with similar diastereoselectivity as **SQ1** but with silightly lower enantioselectivity (Table 1, entry 10). Squaramides **SQ3** and **SQ4**, derived from quinidine and cinchonine, respectively, delivered the opposite enantiomer but with lower enantioselectivity (Table 1,

Table 1. Reaction of methyl isocyanoacetate (**2a**) and benzylidene-3-phenylisoxazol-5-one (**1a**). Conditions and catalyst screening.[a]



Entry	cat	Ag_2O	yield (%)	dr[b]	ee (%)[c]
1[d]	**T1**	5 mol%	54	91:9	38/60
2[d]	**SQ1**	5 mol%	44	89:11	39/44
3[d]	–	5 mol%	70	95:5	–
4[d]	**T1**	–	18	81:19	57/76
5[d]	**SQ1**	–	12	95:5	85/n.d.
6	**SQ1**	–	traces	n.d	89/n.d.
7	**SQ1**	5 mol%	55	75:25	80/98
8	**T1**	5 mol%	72	95:5	58/n.d.
9	**SQ2**	5 mol%	55	92:8	30/n.d.
10	**SQ3**	5 mol%	48	74:26	75/98
11	**SQ4**	5 mol%	47	79:21	−54/−93
12	**SQ5**	5 mol%	51	74:26	−71–94
13	**SQ6**	5 mol%	47	84:16	52/93
14	**SQ7**	5 mol%	67	84:16	30/95
15	**SQ8**	5 mol%	67	76:24	80/99
16	**SQ9**	5 mol%	71	79:21	80/96
17	**SQ10**	5 mol%	66	81:19	65/95
18[e]	**SQ9**	5 mol%	75	74:26	84/96
19	**SQ11**	5 mol%	76	65:35	89/99

[a] Conditions: **1a** (0.1 mmol), **2a** (0.13 mmol), **cat** (0.01 mmol), Ag_2O, CH_2Cl_2 (5 mL). [b] Determined by ^1H NMR. [c] Determined by HPLC over chiral stationary phases. [d] Reaction carried out in 1 mL of CH_2Cl_2. [e] Reaction carried out in 7.5 mL of CH_2Cl_2.

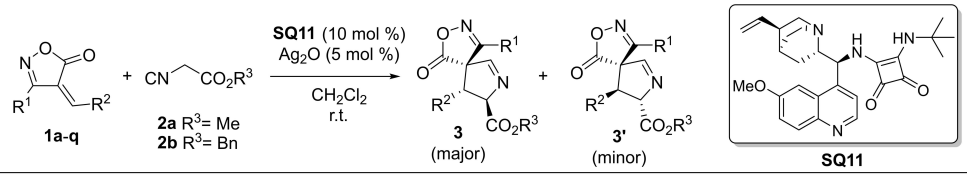
entries 11 and 12). Therefore, we decided to test other squaramides derived from quinine bearing an aniline or benzylamine derivative at the second amide moiety (Table 1, entries 13–17). Squaramides **SQ8**, **SQ9** lead to similar results as **SQ1**, with slightly better diastereoselectivity for **SQ9** (Table 1, entries 7, 15 and 16). At this point, further dilution of the reaction mixture allowed to improve the enantiomeric excess of **3aa** (Table 1, entry 18), despite some decrease of diastereoselectivity. Eventually, squaramide **SQ11** derived from *tert*-butylamine offered the best yield (76%), a slightly decreased diastereoselecivity (65:35), but the highest enantiomeric excess for both diastereomers (89% and 99%, respectively), under diluted conditions (Table 1, entry 19). Further attempts to improve the results by modifying the silver source, catalyst loading or **SQ**/Ag molar ratios were not successful (see SI).

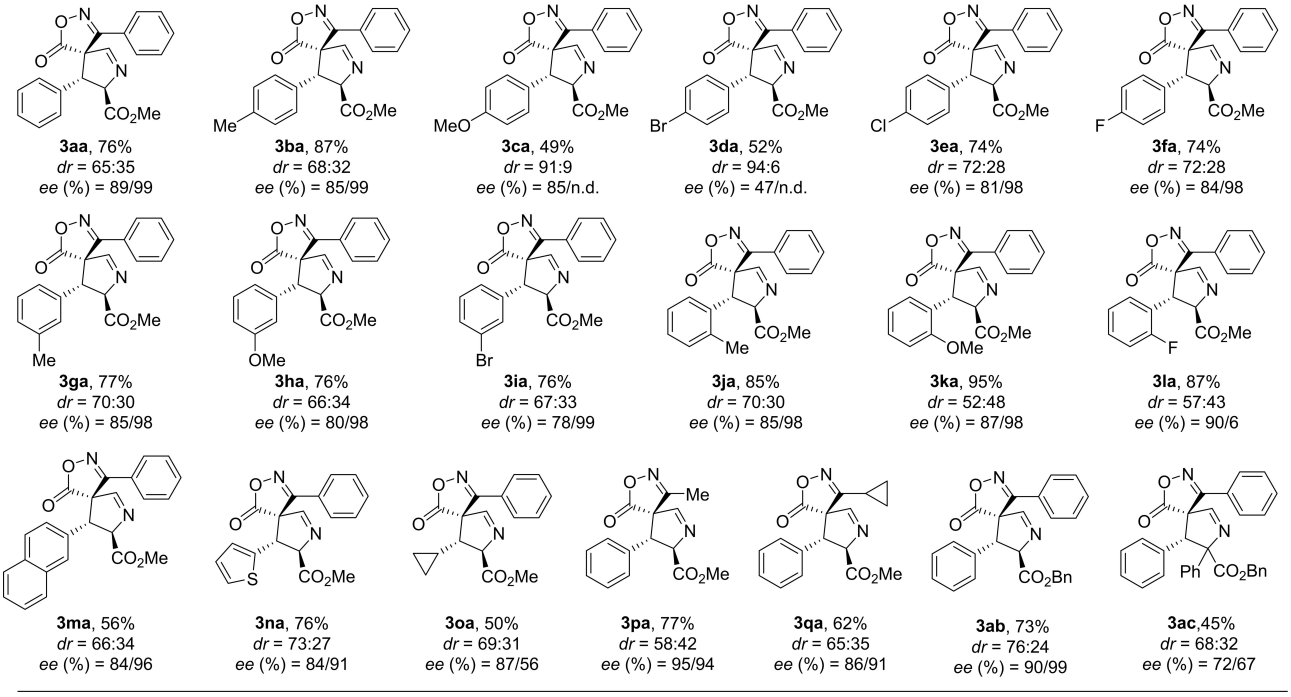
Under the reaction conditions recorded in Table 1, entry 19, we studied the scope of the reaction (Table 2). Methyl isocyanoacetate (**2a**) was reacted with a number of 4-benzylidene-3-phenylisoxazol-5-one derivatives **1a–l** (R^1 = Ph, R^2 = aryl) bearing differently substituted aromatic rings attached to the exocyclic double bond. In general, the spirocyclic products were obtained in moderate to excellent yields, moderate diastereoselectivities and high enantiomeric excesses in both diastereomers, somehow depending on the position and electronic nature of the substituent. Groups of either electron-donating or electron-withdrawing character at the para position of the phenyl group were tolerated. However, in the case of *p*-halophenyl groups the size and electronegativity of the halide was determinant, the enantioselectivity of the reaction increasing through the series Br < Cl < F (products **3da**, **3ea**, **3fa**).

Electron-donating or electron-withdrawing groups at the *meta* (**1g–i**) or *ortho* (**1j–l**) positions were also compatible with the reaction. From these, compounds **1** having an *ortho*-substituted phenyl ring gave better yields although lower diastereomeric ratios, keeping the high enantiomeric excess in all the cases (products **3ja**, **3ka** and **3la**). Furthermore, the isoxazolone derivative can have a bulky naphthyl group (**1m**) providing spirocycle **3ma** with similar results to those obtained with phenyl derivatives.

Finally, compounds **1n** and **1o** bearing a heterocyclic 2-thienyl or a cyclopropyl group also reacted with methyl isocyanoacetate to give the expected products with good enantioselectivity. The substituent at the 3 position of the 4-benzilideneisoxazol-5-one can also be a methyl group, thus compound **1p** (R^1 = Ph, R^2 = Me) reacted with methyl isocyanoacetate providing **3pa** in good yield, fair diastereoselectivity and excellent enantioselectivity for both diastereomers. On the other hand, compound **1q** bearing a cyclopropyl group at this position yielded **3qa** with good results. Finally, benzyl isocyanoacetate (**2b**) could be used instead of methyl isocyanoacetate to give **3ab** upon reaction with **1a** with good results in terms of both diastereo- and enantioselectivity. The reaction can also be performed with α-substituted isocyanides such as methyl 2-isocyano-2-phenylacetate, although in this

Table 2. Reaction of arylidene-3-phenylisoxazol-5-ones **1** and isocyanoacetate esters **2**. Reaction scope.[a]

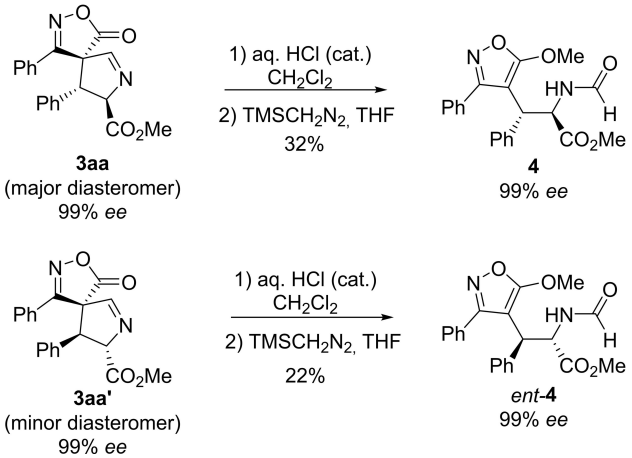




[a] Conditions: **1** (0.25 mmol), **2** (0.33 mmol), **SQ11** (0.025 mmol), Ag_2O (0.0125 mmol), CH_2Cl_2 (19 mL); dr determined by ^1H NMR; *ee* determined by HPLC over chiral stationary phases.

case the reaction product **3 ac** was obtained with low yield (45%) and moderate diastereoselectivity and enantiomeric excess. Compound **3 ac** was not stable and decomposed on standing in the NMR tube for a few days.

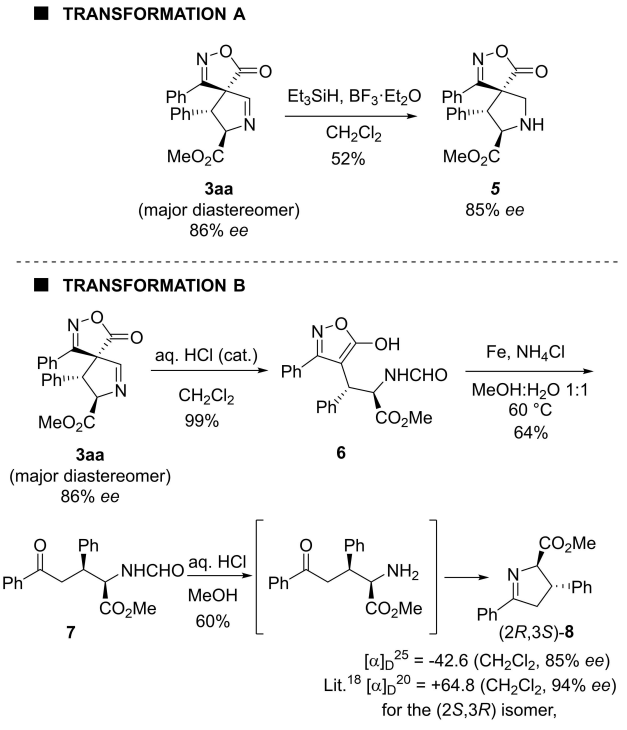
It should be remarked that the cycloaddition reaction between the arylidene-3-phenylisoxazol-5-ones **1** and the isocyanoacetate esters **2** only gives two out of the four possible diastereomers. The relative stereochemistry of the two diastereomers produced in the reactions was determined by a combination of NMR experiments and synthetic transformations. Multiple ^1H–^1H nuclear Overhauser effect (NOE) spectroscopy experiments carried on **3 ha** showed a *trans* disposition between the methyl ester group and the *m*-methoxyphenyl substituent, as well as a *trans* disposition between the phenyl group bonded to the isoxazol-5-one moiety and the *m*-methoxymethyl group, in the major diastereomer (see SI, Figure S1). A similar relative stereochemistry was assumed for the major diastereomer in all the cycloaddition reactions studied. Furthermore, when both diastereomers of compound **3 aa** (**3 aa'**) were separated[16] and subjected to hydrolysis and *O*-methylation, they afforded enantiomer products **4** and *ent*-**4**, respectively, without loss of enantiomeric excess (Scheme 2 and also SI). This fact, indicated that both diastereomers **3 aa** and **3 aa'**



Scheme 2. Hydrolysis and *O*-methylation of product **3 aa**.

had identical configuration at the spiro carbon and opposite configurations at the two other stereogenic centers.

Scheme 3 outlines some synthetic transformations of compound **3 aa**. Transformation A shows the selective reduction of the imine group in the pyrrolinic moiety to give the pyrrolidine spirocycle **5** with moderate yield (52%) and preservation of the enantiomeric excess, using triethylsilane and trifluoroborane as a Lewis acid catalyst. Transformation B exploits the transformation potential of the isoxazol-5-one structure and was used to determine the absolute stereochemistry of compound **3 aa** by chemical correlation with a compound of known stereochemistry **8**. Acidic hydrolysis of the major diastereomer **3 aa** gave quantitatively formamide **6**, which was transformed into the amidoketone **7** by reductive cleavage of the isoxazol-5-one ring with iron.[17] Further acidic hydrolysis of the formamide and concomitant cyclization of the intermediate aminoketone afforded pyrroline **8** without loss of enantiomeric excess and in 54% yield over the three steps. Compound **8** obtained in this way was assigned the (2*R*,3*S*) configuration as it showed identical spectroscopical features and opposite optical rotation sign compared with the known compound (2*S*,3*R*)-**8**.[18] Accordingly, the absolute stereochemistry for compound **3 aa** (major diastereomer) should be (5*S*,8*R*,9*R*) and for compound **3 aa'** (minor diastereomer) it should be (5*S*,8*S*,9*S*). For the remaining compounds **3**, the stereochemistry of both diastereomers was assigned upon the assumption of a uniform stereochemical pathway.[19]



Scheme 3. Synthetic modifications and determination of the absolute stereochemical configuration of **3 aa**.

In conclusion, we have developed an efficient, diastereo- and enantioselective synthesis of novel, highly functionalized spirocyclic compounds bearing a spiro quaternary and two tertiary stereocenters. The new spirocycles feature pyrroline and isoxazol-5-one rings, which are privileged structures in medicinal chemistry. The synthesis involved a formal [3 + 2] cycloaddition reaction between 4-arylideneisoxazol-5-ones and isocyanoacetate esters using a cooperative catalytic system that englobes a bifunctional squaramide/Brønsted base organocatalyst derived from a *Cinchona* alkaloid and silver oxide as Lewis acid. The transformation featured broad scope and simple operation, and delivered the resulting products in good yields, good diastereoselectivity (only two out of four possible diastereomers) and high enantiomeric excess. The potential applicability of the method has been shown by several transformations.

Experimental Section

Experimental procedure for the enantioselective reaction. Methyl isocyanoacetate (**2 a**, 30 µL, 0.33 mmol) was added to a solution of 4-arylideneisoxazol-5-one (**1**, 0.25 mmol), organocatalyst **SQ11** (11.9 mg, 0.025 mmol) and silver oxide (2.9 mg, 0.0125 mmol) in dichloromethane (19 mL) protected from light. The reaction was stirred until complete consumption of compound **1** (TLC, *ca.* 12 h). The product **3** was obtained as a two diastereomer mixture after purification by flash chromatography eluting with hexane:EtOAc mixtures.

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