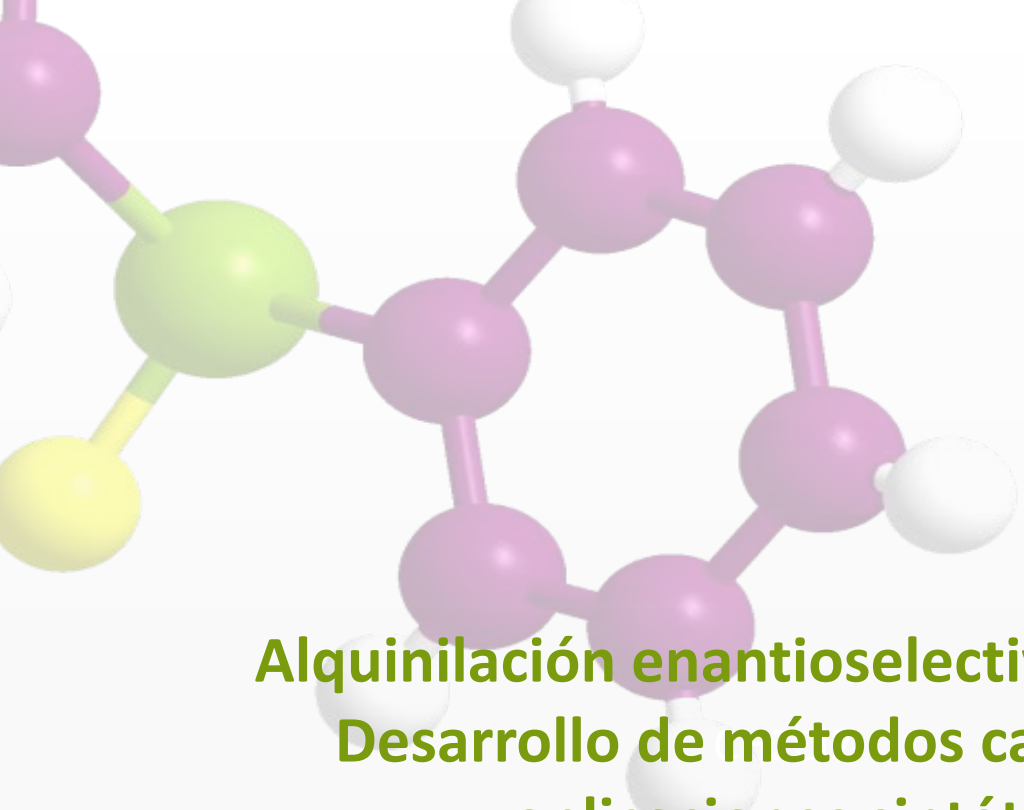

Alquinilación enantioselectiva de iminas: Desarrollo de métodos catalíticos y aplicaciones sintéticas

Tesis doctoral

Alicia Monleón Ventura

VNIVERSITAT DE VALÈNCIA

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FACULTAD DE QUÍMICA

Departamento de Química Orgánica

Programa de doctorado:

Química orgánica en la industria químico-farmacéutica

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Alicia Monleón Ventura

Directores

José R. Pedro y Gonzalo Blay

Valencia, 2013

Dr. D. José Ramón Pedro Llinares, Catedrático de Química Orgánica del Departamento de Química Orgánica de la Universitat de València, y

Dr. D. Gonzalo Blay Llinares, Catedrático de Química Orgánica del Departamento de Química Orgánica de la Universitat de València.

CERTIFICAN:

Que la presente Tesis Doctoral, titulada **"Alquinilación enantioselectiva de iminas: Desarrollo de métodos catalíticos y aplicaciones sintéticas"** ha sido realizada bajo su dirección en el Departamento de Química Orgánica de la Universitat de València por la licenciada en Química **Dña. Alicia Monleón Ventura** y autorizan su presentación para que sea calificada como Tesis Doctoral.

Valencia, septiembre 2013

Fdo. José Ramón Pedro Llinares

Fdo. Gonzalo Blay Llinares

AGRADECIMIENTOS

Es difícil agradecer en pocas líneas a todas las personas que de un modo u otro me han ayudado a lograr este objetivo. Sin duda, he de comenzar mostrando mi agradecimiento a los directores de esta tesis, el profesor José Ramón Pedro, por su gran confianza, dedicación y paciencia todos estos años, y el profesor Gonzalo Blay, por estar siempre dispuesto a ayudarme y enseñarme. También quiero dar las gracias a Isabel Fernández y M. Luz Cardona por sus consejos y entretenida compañía.

A la Generalitat Valenciana por la concesión de la beca predoctoral BFPI.

A todo el personal de Secretaría, a los técnicos del Departamento y del SCSIE. También a Luis Domingo por la realización de los cálculos teóricos y a M. Carmen Muñoz por la resolución de las estructuras de Rayos X.

I would like to express my gratitude to Professor Carsten Bolm and Dr. Eva Hevia for giving me the opportunity to work in their groups and for their kind attention.

Gracias a todos los compañeros de laboratorio porque de todos ellos he aprendido algo y han hecho que los largos días de trabajo fueran más agradables y llevaderos. Sobre todo, gracias a Carlos porque me supo transmitir su pasión por la investigación y porque hemos compartido experiencias inolvidables. A Santi y a Uxu, porque incluso en la distancia, siempre están presentes. A los compañeros de otros laboratorios, por tan buenos ratos juntos, por vuestra ayuda y consejos. Gracias a Rosa L. y Vio por vuestra amistad y por tantos ratos divertidos. A Rosa A., mi compañera de viaje y burocracias, pero sobre todo, mi amiga.

A todas las personas que, aunque no aparecen aquí con nombre y apellidos, han estado presentes de alguna forma durante el desarrollo de este trabajo, especialmente a mis amigos, que han sabido disculpar mis ausencias, por todo el ánimo y comprensión durante estos años.

A mi familia, mi pilar fundamental. Sobre todo a mis padres y mi hermana, por apoyarme en todas las decisiones que he tomado a lo largo de mi vida y por enseñarme a luchar por lo que quiero. Gracias por compartir mis alegrías y animarme en momentos de frustración.

A Pau, por estar incondicionalmente a mi lado. Por su amor, amistad y paciencia. Gracias por acompañarme en este viaje y sufrirlo y disfrutarlo tanto como yo. Juntos seguiremos alcanzando sueños.

A todos, gracias.

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ABREVIATURAS/ABBREVIATIONS

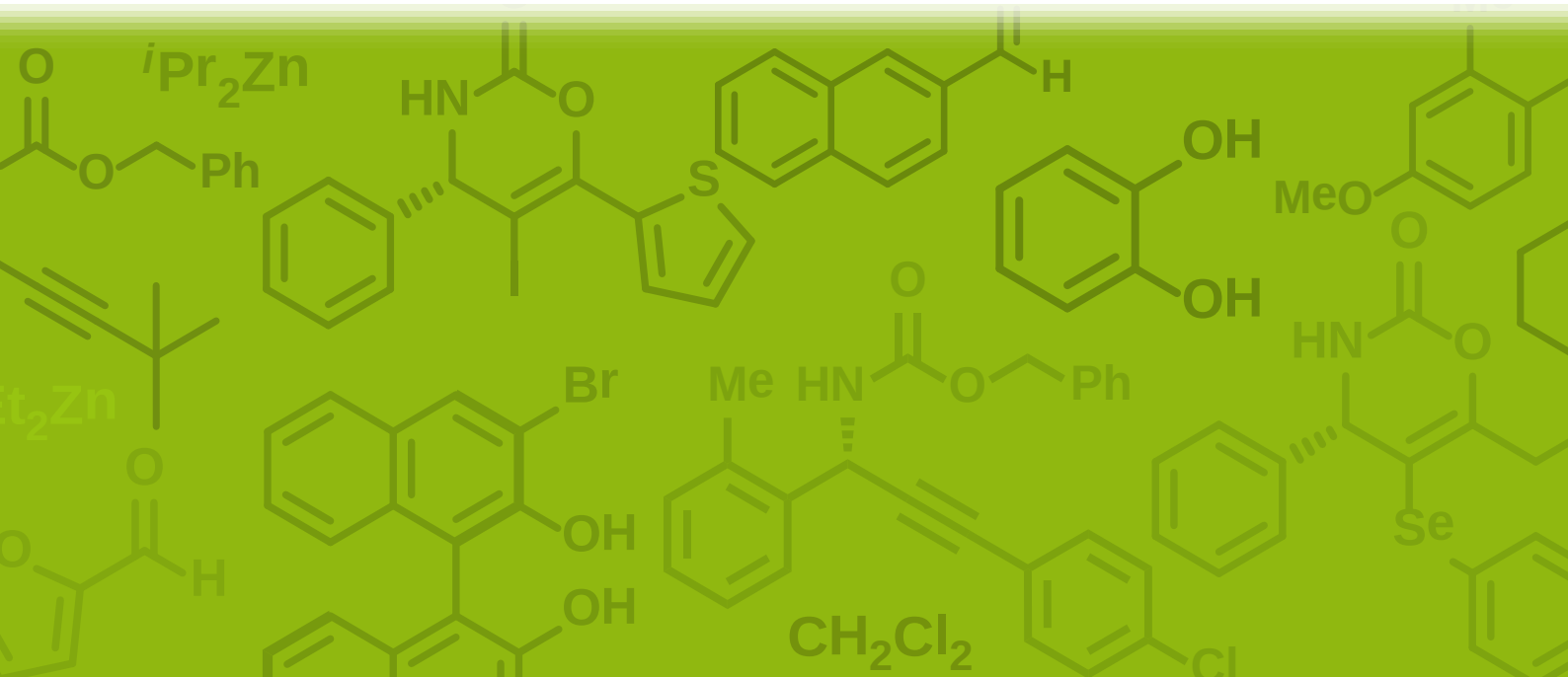
Å	angstrom
a	ancho
Ac	acetilo
AcO	acetato/acetate
Ar	arilo/aryl
aq.	aqueous
au	atomic units
BINAP	2,2'-bis(difenilfosfino)-1,1'-binaftil
BINOL	1,1’-binaftil-2,2’-diol/1,1’-binaphthyl-2,2’-diol
Bn	bencilo/benzyl
Boc	*terc*-butiloxicarbonilo/*tert*-butyloxycarbonyl
BOX	bisoxazolina
Bu	butilo/butyl
br	broad
Bz	benzoílo
c	concentración/concentration (g/100 mL)
CAN	nitrato de cerio y amonio
Cbz	benciloxicarbonilo/benzyloxycarbonyl
CCF	cromatografía de capa fina
coll	collidine
conc.	concentrado
d	doblete/doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEPT	distortionless enhancement by polarization transfer
DMSO	dimetilsulfóxido/dimethylsulfoxide
DMSO-d_6	dimetilsulfóxido deuterado/deuterated dimethylsulfoxide
E	electrophile
ee	exceso enantiomérico/enantiomeric excess
equiv	equivalente/equivalent

ESI	ionización por electroespray/Electrospray ionization
Et	etilo/ethyl
eV	electron volts
g	gramo/gram
GP	grupo protector
h	hora/hour
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
Hz	hertzio/hertz
IN	intermediate
J	constante de acoplamiento/coupling constant
L	ligando/ligand
m	multiplete/multiplet
M	molar
MC	molecular complex
MCPBA	ácido *meta*-cloroperbenzoico
Me	metilo/methyl
min	minuto/minute
mL	mililitro/milliliter
mmol	milimol/millimol
mp	punto de fusión/melting point
NaHMDS	Sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
p.	página/page
PMB	*para*-metoxibencilo
PG	protecting group
PMP	*para*-metoxifenilo
ppm	partes por millón/parts per million
Pr	propilo/propyl
py	piridina/pyridine

PyBIM	piridinabisimidazolina
PyBOX	bis(oxazolinil)piridina
q	cuadruplete/quartet
QUINAP	1-(2-difenilfosfino-1-naftil)isoquinolina
R	rendimiento
RMN	resonancia magnética nuclear
rt	room temperature
s	singulete/singlet
salen	*N*,*N*'-etilenebis(salicilimina)
sat.	saturated
t	tiempo/time
t	triplete/triplet
T	temperatura/temperature
ta	temperatura ambiente
TBAF	tetra-*n*-butyl ammonium fluoride
Tf	triflato (trifluorometanosulfonato)
THF	tetrahidrofurano/tetrahydrofuran
TLC	thin layer chromatography
TMS	trimetilsililo/trimethylsilyl
Tol	tolueno/toluene
Ts	tosilo (*p*-toluenosulfonilo)/tosyl (*p*-toluenesulfonyl)
TS	transition state
VIH	virus de la inmunodeficiencia humana
[α]	rotación específica/specific rotation
δ	desplazamiento químico/chemical shift
µ	micro

CAPÍTULO 1

Introducción y objetivos generales



1.1. INTRODUCCIÓN GENERAL

La búsqueda de nuevos métodos dirigidos a la obtención de sustancias enantioméricamente puras ha supuesto uno de los principales desafíos de la química orgánica durante las últimas décadas debido a la influencia que la estereoquímica absoluta de las moléculas ejerce sobre su actividad biológica, así como en las propiedades de los materiales. Esta importancia de la quiralidad se hace evidente en multitud de productos naturales, así como en los receptores moleculares de los sistemas biológicos. Por ello es necesario el desarrollo de procedimientos de síntesis de compuestos enantioméricamente puros con una configuración determinada, ya que de esta dependerán sus propiedades fisiológicas y farmacológicas.[1]

Tradicionalmente, los métodos de obtención de sustancias enantioméricamente puras se basaban en la utilización de fuentes naturales procedentes del "chiral-pool" y en la resolución de mezclas racémicas. Sin embargo, nuevos aspectos que se deben tener en cuenta en la síntesis orgánica moderna, tales como la eficiencia sintética, el consumo de quiralidad o la necesidad de mayor selectividad, han hecho emerger la catálisis asimétrica como una nueva metodología sintética con un potencial de crecimiento enorme. Su mayor ventaja radica en la obtención de productos enriquecidos enantioméricamente con una elevada pureza, un bajo consumo de quiralidad y una menor producción de residuos.[2]

La aplicación de la catálisis asimétrica en reacciones de formación de enlaces C-C es de gran importancia debido a que permite obtener centros estereogénicos con una configuración determinada en moléculas estructuralmente complejas. Así, se han utilizado en multitud de reacciones tales como Friedel Crafts, Diels-Alder, reacciones de alquilación, Henry, etc.[3-5] En concreto, la adición enantioselectiva de alquinos terminales a grupos carbonilo e imina permite la obtención de alcoholes y aminas propargílicas quirales respectivamente, cuya funcionalización es de gran valor en la síntesis de moléculas con elevada complejidad.[6]

Las aminas propargílicas han emergido en los últimos años como precursores versátiles en la síntesis de un amplio abanico de compuestos nitrogenados como

alilaminas, pirrolidinas, oxazoles y pirroles,[7] y se han utilizado como intermedios en la preparación de productos naturales, farmacéuticos, herbicidas y fungicidas.[8-10]

Asimismo, la propia estructura aminopropargílica se encuentra presente en un considerable número de compuestos con actividad biológica y farmacológica.[11] Así, por ejemplo, esta estructura está presente en compuestos con propiedades inhibidoras de la enzima monoamida oxidasa B (MAO-B),[12] antagonistas de un subtipo selectivo del receptor del *N*-metil-D-aspartato (NMDA)[13] (Figura 1a), inhibidoras de la agregación de plaquetas,[14] inhibidoras de la degradación del ácido γ-aminobutírico (GABA),[15] antibióticos,[16] inhibidoras de la acetil-CoA oxidasa (ACC)[17] (Figura 1b), inhibidores de la transcriptasa de VIH (Figura 1c)[18] o herbicidas entre otros.[19]

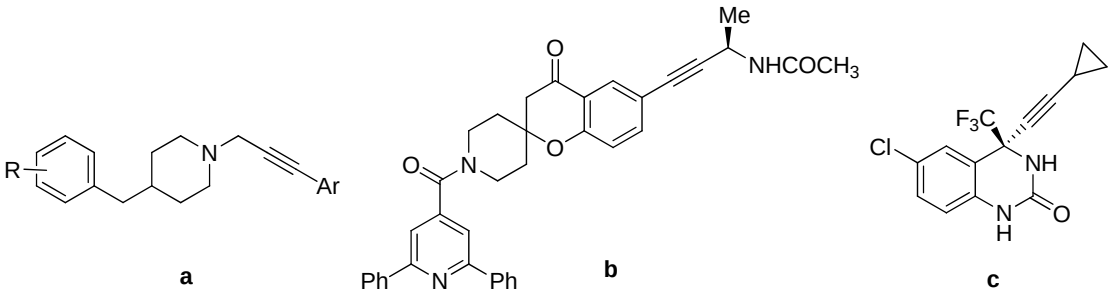
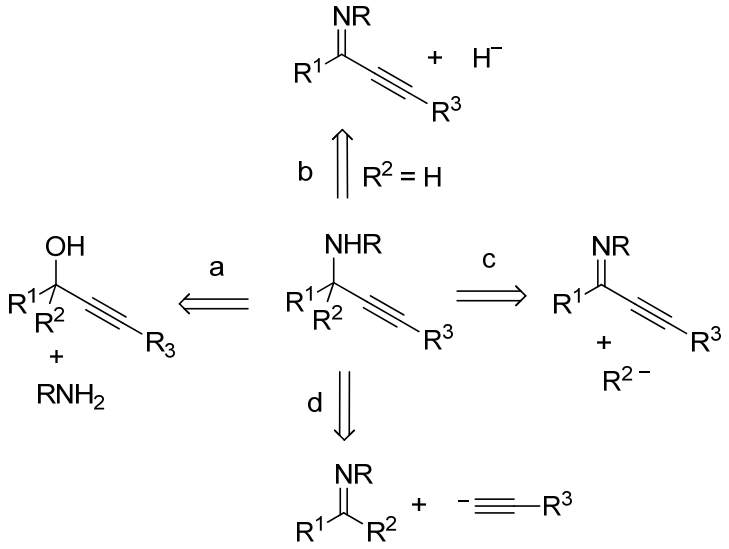


Figura 1.1. (a) Antagonista del receptor de *N*-metil-D-aspartato (NMDA). (b) Inhibidor de la acetil-CoA oxidasa (ACC). (c) Inhibidor no-nucleósido reverso de la transcriptasa de VIH, DPC-961.

En términos generales, son cuatro los métodos que permiten la síntesis de aminas propargílicas quirales (Esquema 1.1): la sustitución nucleofílica de alcoholes propargílicos quirales con reactivos nitrogenados nucleofílicos[20] (aproximación a), la reducción selectiva del doble enlace C=N en cetiminas α,β-insaturadas[21] (aproximación b), la adición 1,2- de reactivos carbonados nucleofílicos a iminas α,β-insaturadas[22] (aproximación c) y la adición de alquinos nucleofílicos a iminas[23] (aproximación d).

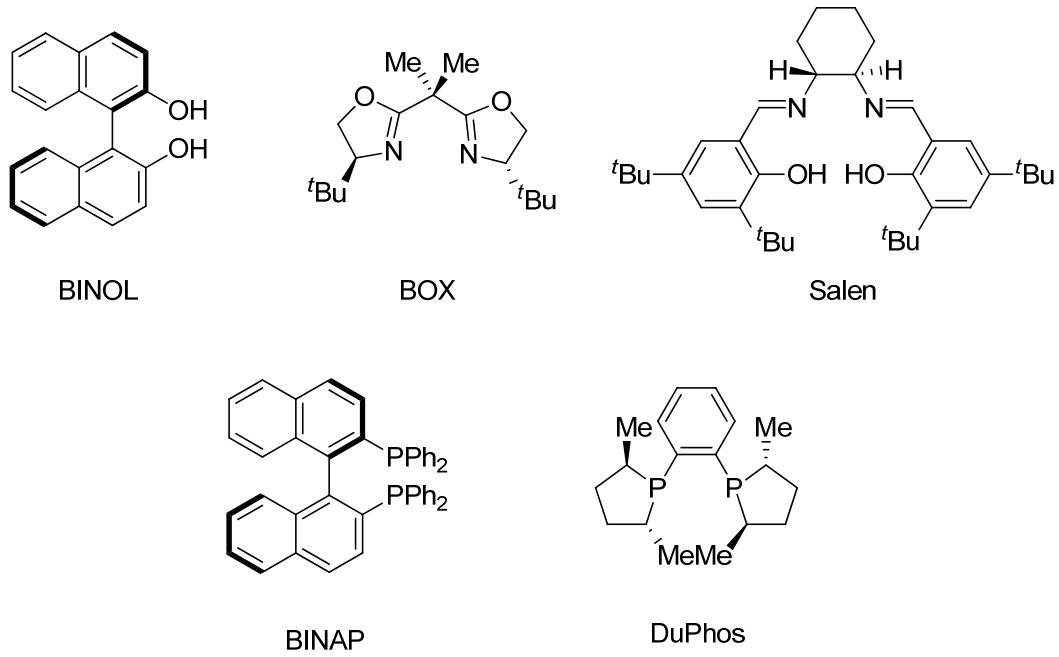


Esquema 1.1. Aproximaciones generales para la síntesis de propargilaminas.

En esta última aproximación, se aprovecha la acidez del protón acetilénico terminal para formar un reactivo alquinil-metálico que actúa como un carbono nucleófilo. La adición nucleofílica a los dobles enlaces C=N es uno de los métodos más practicados para la síntesis de derivados nitrogenados. Sin embargo, mientras que la adición de acetilenos a compuestos carbonílicos ha sido objeto de un gran número de publicaciones, la alquinilación asimétrica de iminas y sus derivados supone un desafío sintético debido a la menor electrofilia del átomo de carbono azometínico comparada con el átomo de carbono carbonílico de aldehídos y cetonas. No obstante, la reactividad del doble enlace C=N puede incrementarse mediante el uso de nitronas, la generación *in situ* de iones iminio o a través de la introducción de grupos electrón-atrayentes en el átomo de nitrógeno de la imina. La utilización de estas estrategias ha permitido la síntesis de aminas propargílicas mediante la reacción de alquinilación.

Aunque es posible la síntesis de aminas propargílicas quirales a través de procedimientos diastereoselectivos recurriendo a la introducción de sustituyentes quirales en el átomo de nitrógeno, especialmente, mediante la utilización de sulfiniliminas quirales, en los últimos años la síntesis de aminas propargílicas se ha centrado en procedimientos enantioselectivos, especialmente, en aquellos basados en metodologías catalíticas por las ventajas señaladas anteriormente y a ellos se les prestará atención en la presente tesis doctoral.

La utilización de complejos de metales de transición y ligandos quirales como catalizadores, junto con el empleo de organocatalizadores, constituye una de las estrategias más comúnmente extendidas para llevar a cabo con éxito las reacciones enantioselectivas. Durante las últimas décadas se han desarrollado multitud de ligandos eficientes, a algunos de los cuales se les ha catalogado como "ligandos privilegiados" por su capacidad de mediar enantioselectivamente reacciones de diversa naturaleza. A este grupo de ligandos pertenecen los denominados BINOL, BOX, Salen, BINAP o DuPhos, entre otros.[24]

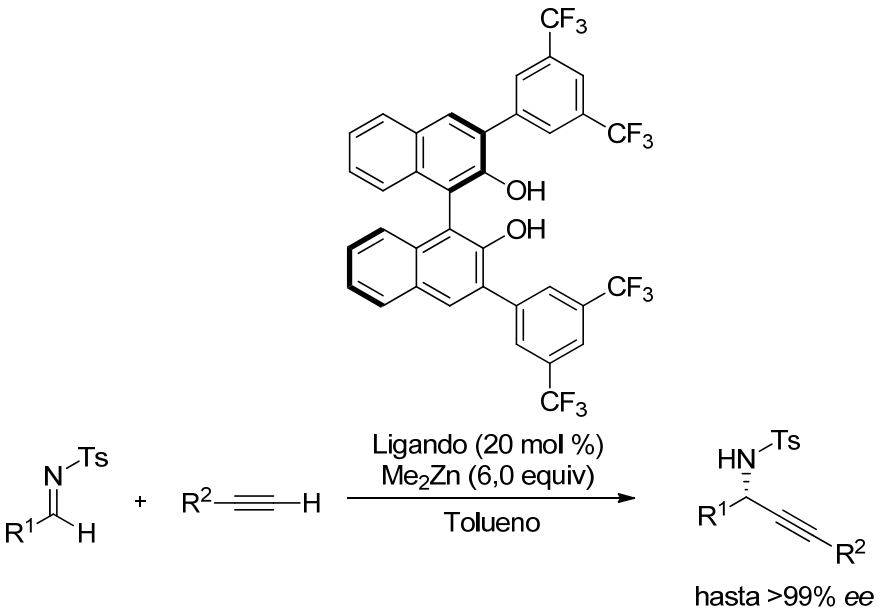


BINOL BOX Salen

BINAP DuPhos

Figura 1.2. Ligandos privilegiados.

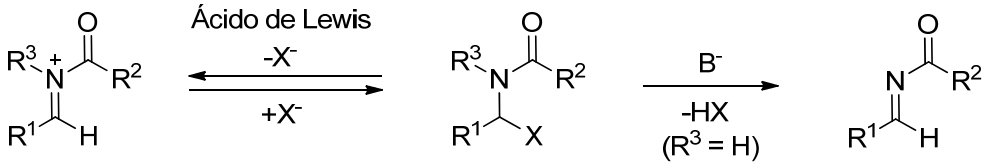
Los ligandos de tipo BINOL, en los que nuestro grupo de investigación tiene experiencia,[23] presentan un eje axial con simetría C_2 y han sido empleados en reacciones enantioselectivas de formación de enlace C-C junto con ácidos de Lewis como Ti, Zr, Al o Zn.[23,25-27] Concretamente, el complejo quiral formado por Zn(II)-BINOL ha demostrado ser una herramienta poderosa en la reacción de alquinilación enantioselectiva de *N*-tosiliminas (Esquema 1.2).[23] Por ello, se ha escogido este sistema catalítico para llevar a cabo las reacciones de adición de alquinos terminales a iminas en este trabajo.



Esquema 1.2. Alquinilación enantioselectiva de *N*-tosiliminas promovida por Me_2Zn y ligandos de tipo BINOL.

Uno de los inconvenientes derivados de la utilización de iminas es su posible enolización. Esta reacción adversa dificulta cualquier reacción de adición eficiente y, además, puede producir la isomerización del doble enlace C=N.

Una posible aproximación para superar este obstáculo es la formación *in situ* de *N*-aciliminas a partir de amidas con un buen grupo saliente en α que pueda ser fácilmente eliminado en las condiciones adecuadas, tanto básicas como en presencia de un ácido de Lewis (Esquema 1.3).[28]

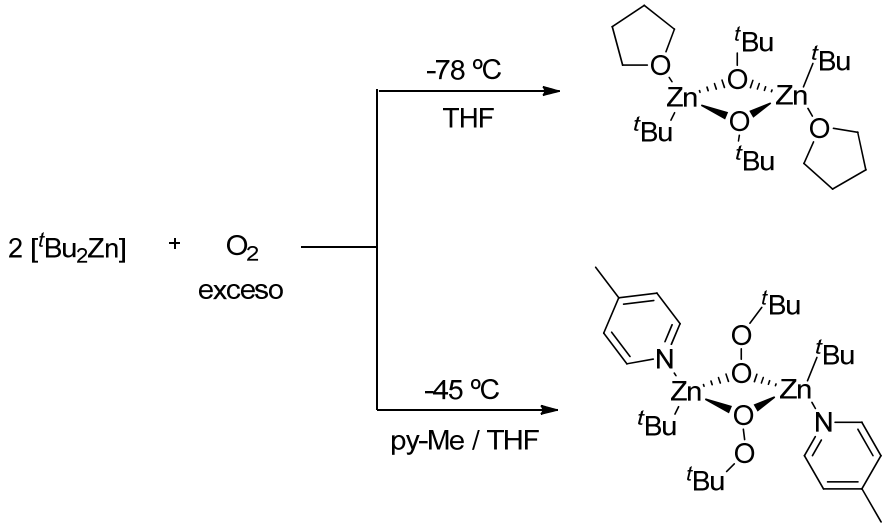


X = Cl, Br, benzotriazolil, $NHCOR^4$, OR^4, $OCOR^4$, SR^4, SO_2R^4

Esquema 1.3. Formación de iones *N*-aciliminio y *N*-aciliminas a partir de amidas con un buen grupo saliente en α.

Las α-amido sulfonas (X = SO_2R^4) son un ejemplo de este tipo de sustratos que ha sido utilizado en la reacción no enantioselectiva de adición de alquinos[29] y pueden utilizarse como precursores de iminas en presencia del sistema catalítico formado por dialquilzinc y BINOL.

Los reactivos de dialquilzinc reaccionan con oxígeno molecular dando lugar a especies oxigenadas. Debido al carácter radicalario de las especies intermedias de esta reacción, siempre se ha considerado un proceso de difícil control en el que se puede oxidar uno o los dos enlaces Zn-C para dar lugar tanto a los alcóxidos como a los alquilperóxidos de zinc. No obstante, algunos estudios recientes del grupo de Lewinski demuestran cómo es posible llevar a cabo la oxigenación controlada de los aductos de dialquilzinc con ligandos dadores (Esquema 1.4).[30]



Esquema 1.4. Oxidación controlada de $^{t}Bu_2Zn$.

Las especies obtenidas tras la oxidación controlada de los reactivos de dialquilzinc pueden ser utilizadas en reacciones de adición a α-amido sulfonas, generando así aminas oxigenadas en la posición α. Estas, especialmente si contienen la agrupación peróxido, son muy interesantes tanto desde el punto de vista estructural como de sus aplicaciones, ya que los peroxocompuestos presentan características antitumorales y antimaláricas (Figura 1.3) y se utilizan como antibacterianos.[31]

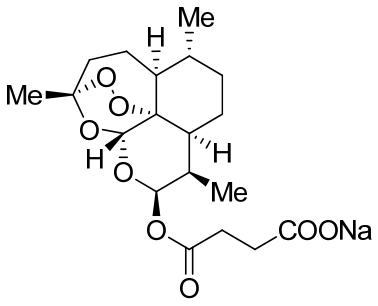
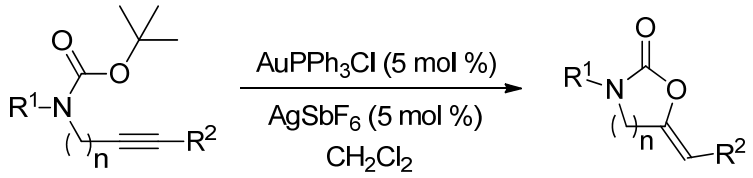


Figura 1.3. Artesunato de sodio.

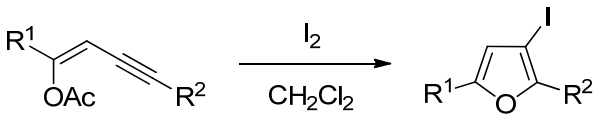
Por otra parte, las aminas propargílicas obtenidas en la reacción de alquinilación poseen una elevada funcionalización, lo que hace que estos sustratos sean susceptibles de experimentar diversas transformaciones, proporcionando una gran versatilidad sintética a este tipo de compuestos. Así, por ejemplo, la reducción del triple enlace o su ozonólisis permiten la obtención de derivados amínicos que amplían la aplicabilidad sintética de los productos de alquinilación.

Además, la activación electrofílica del triple enlace frente al ataque de un nucleófilo aumenta las posibilidades de transformación de las aminas propargílicas. El ataque intramolecular de un grupo nucleofílico próximo a la agrupación acetilénica es un método excelente que conduce a la síntesis de estructuras cíclicas. La utilización de metales de transición, especialmente Au, Ag y Pt, como activadores del triple enlace C-C ha demostrado ser una estrategia muy útil en la síntesis de diversos compuestos heterocíclicos como oxazoles, imidazoles o benzoxazinas (Esquema 1.5).[32]



Esquema 1.5. Ciclación electrofílica mediada por Au(I).

Asimismo, la ciclacición electrofílica mediada por halógenos o calcógenos a través de la formación de un ion halonio o calconio, resulta en la formación de halo- y calcoderivados heterocíclicos o carbocíclicos altamente funcionalizados y de gran versatilidad en posteriores procesos sintéticos (Esquema 1.6).[33]



Esquema 1.6. Ciclación electrofílica mediada por yodo.

La regioselectividad de estas ciclaciones electrofílicas no siempre se consigue con facilidad debido a la competencia entre los modos de ciclación *exo*- y *endo*-.

1.2. OBJETIVOS GENERALES

La adición nucleofílica a dobles enlaces C=N es uno de los métodos más utilizados para la síntesis de derivados nitrogenados. La utilización de alquinos terminales como nucleófilos constituye una herramienta sintética de gran interés, ya que la adición enantioselectiva de los mismos a iminas o precursores de iminas permite la síntesis de aminas propargílicas quirales con un enorme valor en la formación de una amplia variedad de productos naturales y farmacéuticos. Además, la elevada funcionalización de las aminas propargílicas hace posible la obtención de productos derivados de gran interés en química orgánica.

Por otra parte, el sistema catalítico formado por reactivos de dialquilzinc como ácidos de Lewis y derivados de 1,1'-binaftil-2,2'-diol (BINOL) como ligandos quirales ha demostrado inducir un elevado estereocontrol en numerosas transformaciones sintéticas.

Teniendo en cuenta estas consideraciones, en la presente tesis se han planteado los siguientes objetivos generales:

- Adición enantioselectiva de alquinos terminales a *N*-(difenilfosfinoil)iminas catalizada por complejos de tipo BINOL-Zn.
- Adición enantioselectiva de alquinos terminales a iminas generadas *in situ* a partir de α-amido sulfonas catalizada por complejos de tipo BINOL-Zn.
- Adición de especies de zinc alquiloxigenadas a α-amido sulfonas.
- Ciclación regioselectiva de aminas propargílicas *N*-Cbz-protegidas mediada por halógenos y calcógenos.

1.3. REFERENCIAS

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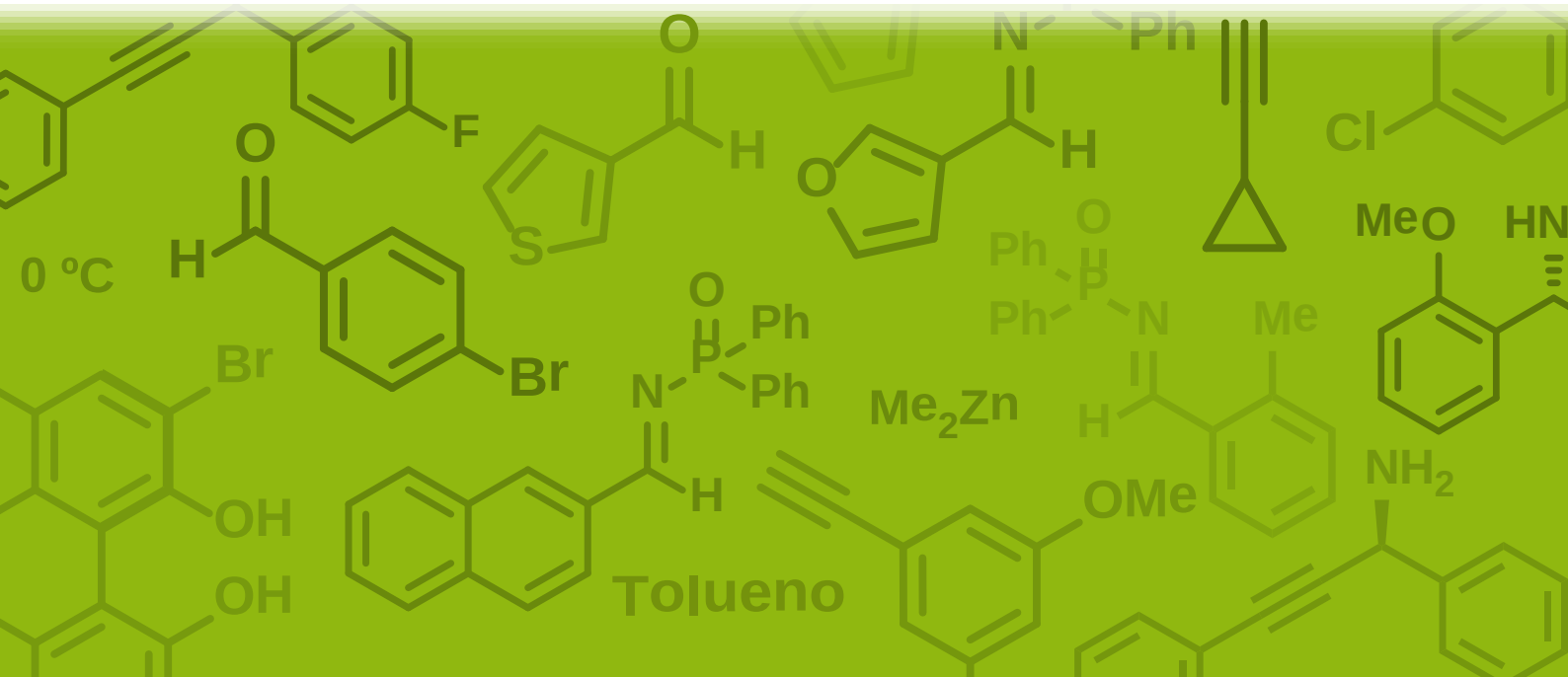
CAPÍTULO 2

Adición enantioselectiva de alquinos terminales a *N*-(difenilfosfinoil)iminas

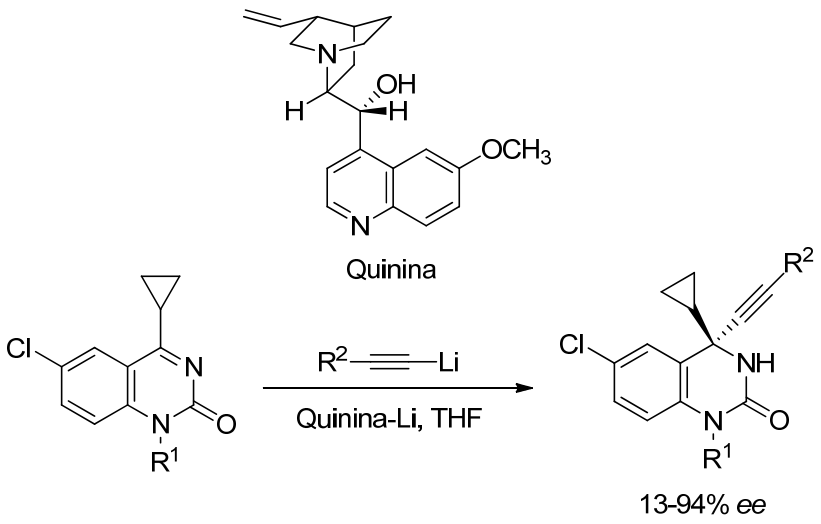


2.1. ANTECEDENTES

Uno de los métodos que mayor importancia ha adquirido en los últimos años para la obtención de aminas propargílicas quirales es la alquinilación enantioselectiva de iminas. Este procedimiento se ha desarrollado tanto en condiciones estequiométricas como catalíticas, aunque es esta última metodología la que resulta más atractiva y ha sido más explorada recientemente. A continuación se realiza una revisión bibliográfica sobre este tipo de reacción.

2.1.1. Procedimientos enantioselectivos estequiométricos

El primer ejemplo de alquinilación enantioselectiva no catalítica de iminas se describió en 1995. Huffman y colaboradores[1] llevaron a cabo por primera vez la adición enantioselectiva de acetiluro a *N*-acilcetiminas cíclicas utilizando el alcóxido de litio de la quinina como aditivo quiral estequiométrico (Esquema 2.1). Una optimización extensa mostró que la enantioselectividad dependía tanto de la concentración como de la temperatura de la reacción. La utilidad de esta reacción quedó demostrada en la síntesis de un inhibidor no-nucleósido de la transcriptasa inversa de VIH.

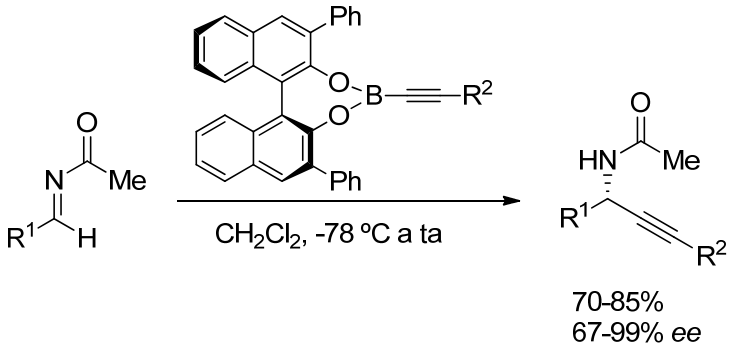


Esquema 2.1. Alquinilación enantioselectiva de *N*-acilcetiminas cíclicas.

Al igual que en el ejemplo anterior, muchos procesos diseñados para la síntesis de propargilaminas quirales utilizaban reactivos básicos fuertes incompatibles con sustratos sensibles, lo cual conducía a la necesidad de llevar a cabo la desprotonación

del alquino en un paso previo. Por otra parte, la elevada reactividad de los alquiniluros de litio, magnesio o aluminio resultantes no siempre permitía un buen estereocontrol de la reacción, repercutiendo de forma negativa en la enantioselectividad del proceso de alquinilación. Este problema se solucionó generando *in situ* los reactivos organometálicos acetilénicos a partir de un precursor metálico adecuado que permitiera la adición directa de los acetilenos a las iminas bajo condiciones compatibles con otros grupos electrofílicos. Para ello, se han utilizado con éxito alquil cupratos, boranos, estannanos o reactivos organozíncicos.

Chong y colaboradores[2] publicaron un ejemplo de adición de alquinilboronatos a *N*-aciliminas en presencia de cantidades estequiométricas de 2,2'-binaftoles 3,3'-disustituidos (Esquema 2.2). Los mejores resultados en términos de rendimiento y estereoselectividad se alcanzaron con los binaftoles 3,3'-difenil disustituidos, con diversos alquil y aril acetilenos, pero únicamente con iminas no enolizables. Esta reacción mostró su utilidad en la síntesis de (-)-*N*-acetilcolchinol.



Esquema 2.2. Alquinilación enantioselectiva de *N*-acetilaldiminas con alquinilboronatos.

2.1.2. Procedimientos enantioselectivos catalíticos

2.1.2.1. Adiciones enantioselectivas catalizadas por cobre

La primera reacción catalítica de alquinilación enantioselectiva de iminas la llevaron a cabo Wei y Li[3] en 2002, quienes emplearon sales de Cu(I) y ligandos de tipo *N,N* (Figura 2.1) en la adición de fenilacetileno a *N*-fenilbenzaldiminas en agua.

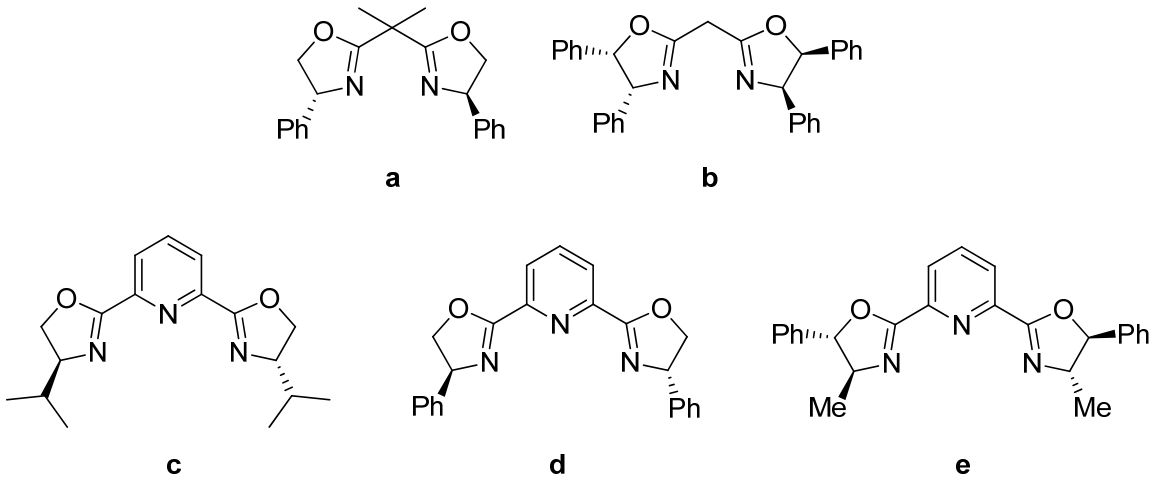
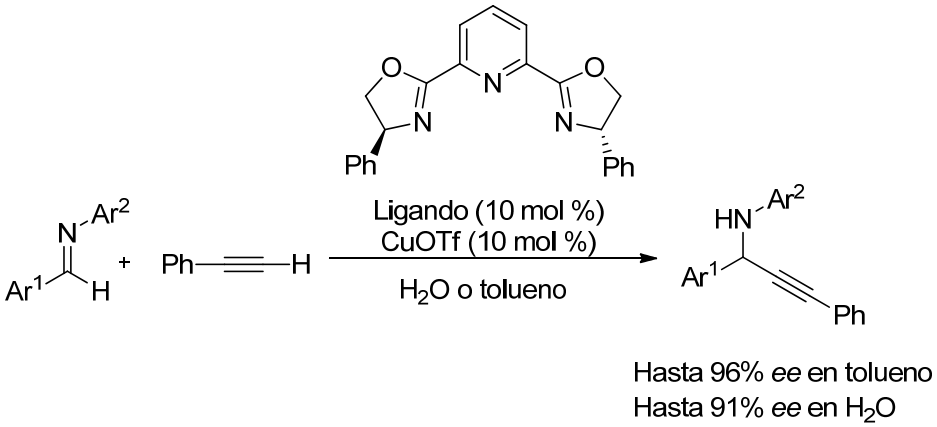


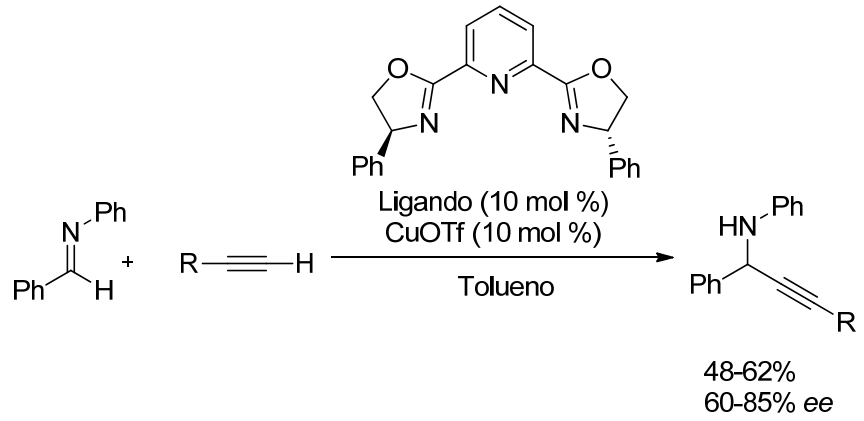
Figura 2.1. (a y b) Ligandos de tipo bisoxazolina (BOX). (c, d y e) Ligandos de tipo 2,6-bis(oxazolin-2'-il)piridina (PyBOX).

La combinación de ligandos de tipo PyBOX y triflato de cobre (I) dio los mejores resultados. Se examinó la reacción con un conjunto de iminas aromáticas y fenilacetileno en las condiciones optimizadas, obteniéndose las correspondientes propargilaminas con enantioselectividades elevadas y buenos rendimientos tanto en agua como en tolueno (Esquema 2.3).



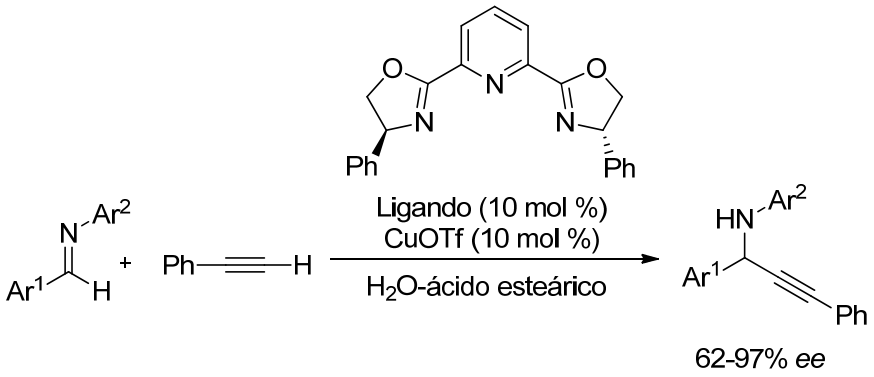
Esquema 2.3. Adición enantioselectiva de fenilacetileno a iminas aromáticas catalizada por CuOTf-PyBOX.

En un trabajo posterior, estos mismos autores utilizaron este sistema catalítico con alquinos alifáticos,[4] con los cuales se obtuvieron peores rendimientos y enantioselectividades que con fenilacetileno (Esquema 2.4). El estudio también mostró la gran influencia del disolvente sobre la enantioselectividad de la reacción.



Esquema 2.4. Adición enantioselectiva de alquinos alifáticos a *N*-fenilbenzaldimina catalizada por CuOTf-PyBOX.

Varios años más tarde, en 2007, Li y Chan[5] consiguieron disminuir el tiempo de reacción requerido para la reacción desarrollada por Wei y Li en agua mediante la adición de ácido esteárico como surfactante (Esquema 2.5). La reacción de adición de fenilacetileno a *N*-fenilbenzaldimina se completó en la mitad de tiempo proporcionando el compuesto deseado con un 86% rendimiento y 85% *ee*, que eran ligeramente superiores a los obtenidos sin surfactante (71%, 84% *ee*). Además, el catalizador podía reutilizarse tras la extracción de los productos de la fase acuosa con hexano. Aunque se observó una ligera pérdida de la actividad con los sucesivos ciclos, la enantioselectividad se mantuvo consistente.

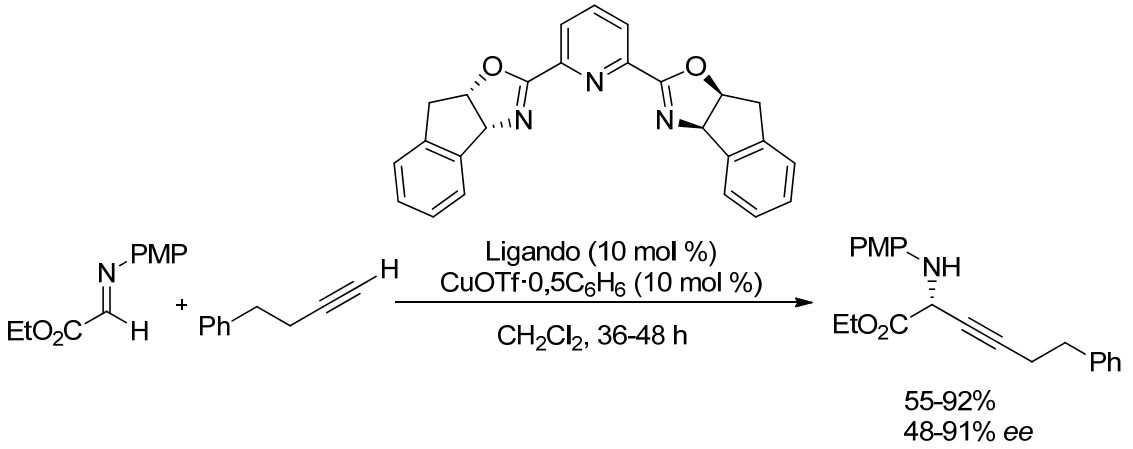


Esquema 2.5. Alquinilación enantioselectiva de *N*-ariliminas con Cu(I)-PyBOX y ácido esteárico en agua.

Chan y colaboradores emplearon un sistema catalítico similar para la alquinilación enantioselectiva de α-imino ésteres.[6,7] El desarrollo de esta reacción se

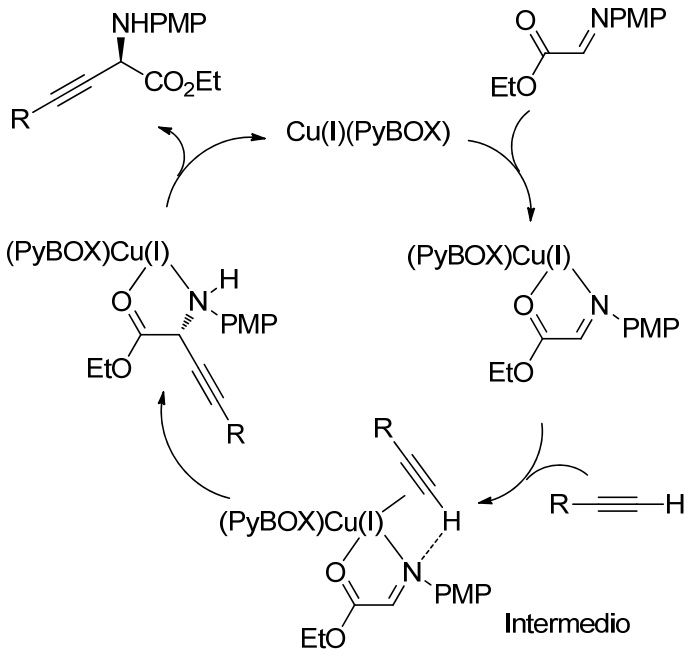
basó en un estudio previo realizado por estos mismos autores sobre la síntesis de aminas propargílicas racémicas.[8] En él, llevaron a cabo la adición de alquinos alifáticos terminales a α-imino ésteres en presencia de cantidades catalíticas de sales de Ag(I) para dar los correspondientes β,γ-alquinil α-amino ácidos.

En la versión enantioselectiva, los autores examinaron la reacción entre 4-fenil-1-butino y el imino éster etílico derivado del ácido glioxílico en presencia de Ag(I) (Esquema 2.6), sin encontrar resultados satisfactorios. Por este motivo, centraron sus esfuerzos en otros metales de transición. La utilización de iminas derivadas de la *para*-metoxianilina (PMP-NH_2), CuOTf·0,5C_6H_6 y un ligando quiral de tipo PyBOX derivado de 1-amino-2-indanol con gran congestión estérica proporcionaron el producto deseado con 90% de rendimiento y 85% *ee*.



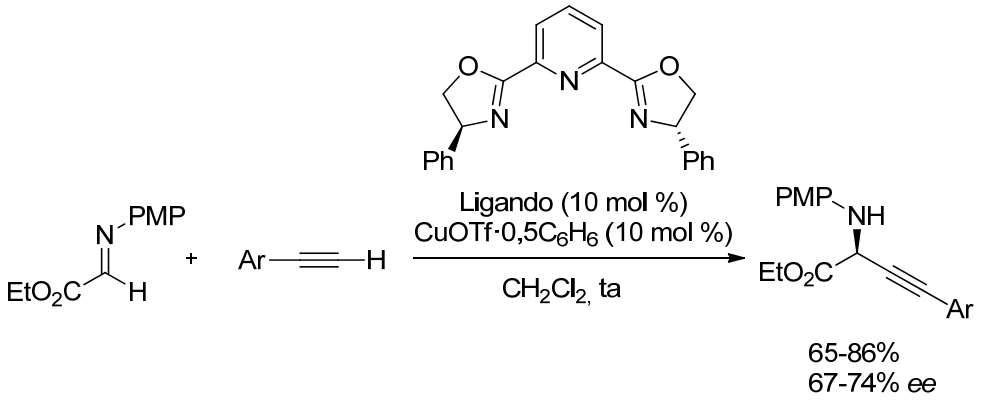
Esquema 2.6. Adición enantioselectiva de 4-fenil-1-butino a imino ésteres.

Los autores propusieron un mecanismo (Esquema 2.7) que implica la coordinación del sustrato y el alquino al centro metálico para producir el correspondiente intermedio, en el que el átomo de nitrógeno del imino éster actúa como base en la formación del alquiniluro de Cu(I) y el ion metálico se coordina al triple enlace. A continuación, se produce la transferencia intramolecular de protón y alquino para alcanzar el complejo final cuya descoordinación supone la liberación del producto y la regeneración del catalizador.



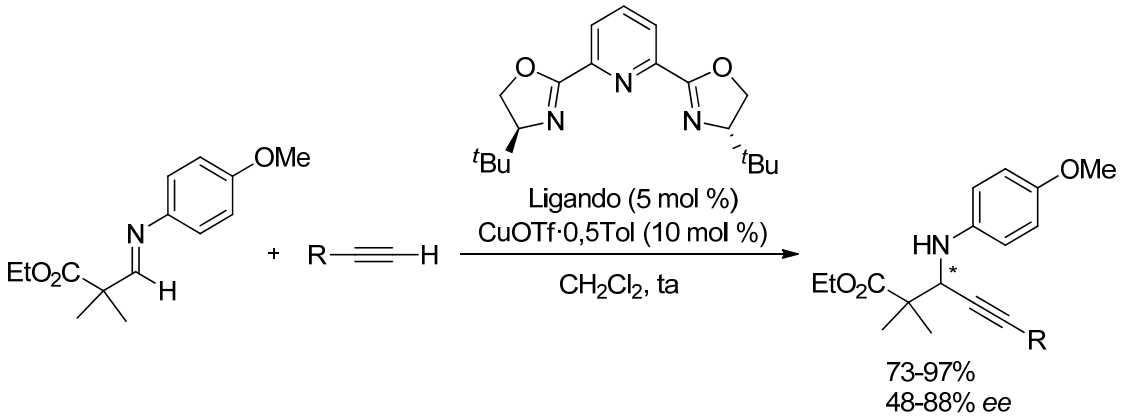
Esquema 2.7. Mecanismo propuesto para la alquinilación de α-imino ésteres.

Posteriormente, estos mismos autores, describieron la adición de fenilacetileno al mismo α-imino éster empleando condiciones similares a las anteriores en presencia de *para*-metoxianilina como aditivo.[9,10] Sin embargo, el producto se obtuvo con un rendimiento moderado (51%) y baja enantioselectividad (41% *ee*) tras 48 h de reacción, haciendo evidente la diferencia de reactividad entre alquinos alifáticos y aromáticos. Los resultados mejoraron cuando se llevó a cabo la reacción en ausencia de aditivo (64% rendimiento, 61% *ee*). El ligando difenil PyBOX resultó ser el más eficiente (Esquema 2.8). Por otra parte, se observó que un pequeño exceso de ligando disminuía la enantioselectividad, mientras que un exceso de cobre resultaba beneficioso. Además, el estudio mecanístico de la reacción indicaba la presencia moderada de efectos no lineales positivos.[11]



Esquema 2.8. Adición enantioselectiva de fenilacetileno a α-imino ésteres.

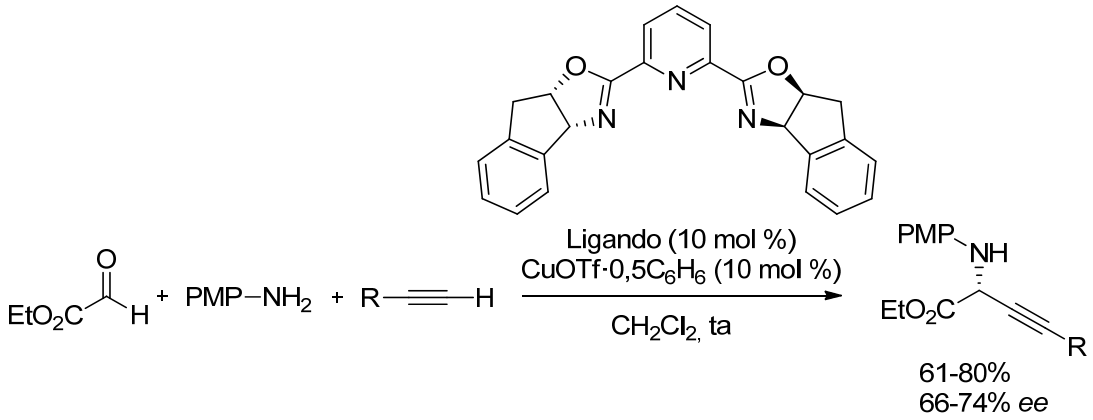
En 2009, estos mismos autores publicaron la primera adición catalítica enantioselectiva de alquinos a β-imino ésteres promovida por ligandos de tipo PyBOX y CuOTf·0,5Tol.[12] Tanto alquinos alifáticos como aromáticos reaccionaron dando el producto de alquinilación con rendimientos elevados y buena enantioselectividad (Esquema 2.9).



Esquema 2.9. Adición de alquinos a β-imino ésteres catalizada por Cu(I) y PyBOX.

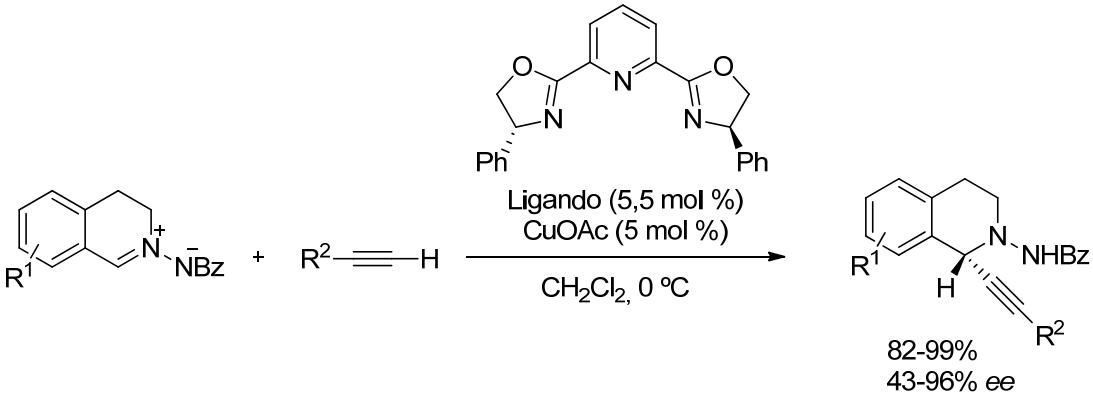
Debido a la baja estabilidad que presentan los α-imino ésteres, Chan y colaboradores pensaron en la posibilidad de generar estos sustratos *in situ* y de diseñar un sistema catalítico eficaz tanto con alquinos alifáticos como aromáticos. Así, desarrollaron la adición enantioselectiva de tres componentes utilizando un α-ceto éster, *p*-metoxianilina y un alquino terminal conducente a β,γ-alquinil α-amino ácidos mediante la utilización de un ligando de tipo PyBOX derivado de 1-amino-2-indanol, con gran congestión estérica, y CuOTf·0,5C_6H_6 (Esquema 2.10). La reacción transcurrió

con rendimientos buenos (61-80%) y enantioselectividades moderadas tanto con alquinos alifáticos como aromáticos (66-74% *ee*).[13]



Esquema 2.10. Adición enantioselectiva de tres componentes catalizada por un ligando de tipo PyBOX y CuOTf·0,5C_6H_6. Sintesis de β,γ-alquinil α-amino ácidos.

El grupo de Maruoka[14] ha utilizado el sistema catalítico formado por Cu(I)/PyBOX en la adición enantioselectiva de alquinos terminales a sales de iminio derivadas de dihidroisoquinoleína (Esquema 2.11). Independientemente de la naturaleza electrónica de los sustituyentes y de su posición en el anillo aromático de la sal de iminio, se obtuvieron rendimientos casi cuantitativos (93-99%) y elevados excesos enantioméricos (85-94% *ee*). En esta reacción se evaluaron diversos alquinos aromáticos y alifáticos con rendimientos (82-99%) y enantioselectividades elevados (89-96% *ee*), a excepción de la reacción con el 2-tolilacetileno y 1-heptino (43% y 75% *ee*, respectivamente).



Esquema 2.11. Adición enantioselectiva de alquinos a sales de iminio derivadas de la dihidroisoquinoleína.

Los autores también llevaron a cabo la alquinilación enantioselectiva de sales de iminio derivadas de la dihidroisoquinoleína sustituidas en el C1. Para ello, aplicaron las condiciones de reacción anteriores utilizando un ácido de Brønsted quiral como co-catalizador (Figura 2.2). Las tetrahidroisoquinoleínas quirales se obtuvieron con buenos rendimientos (85-99%) y enantioselectividades (79-95% *ee*).

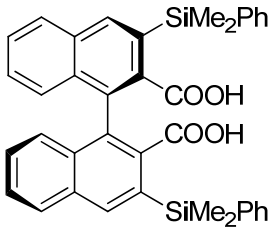
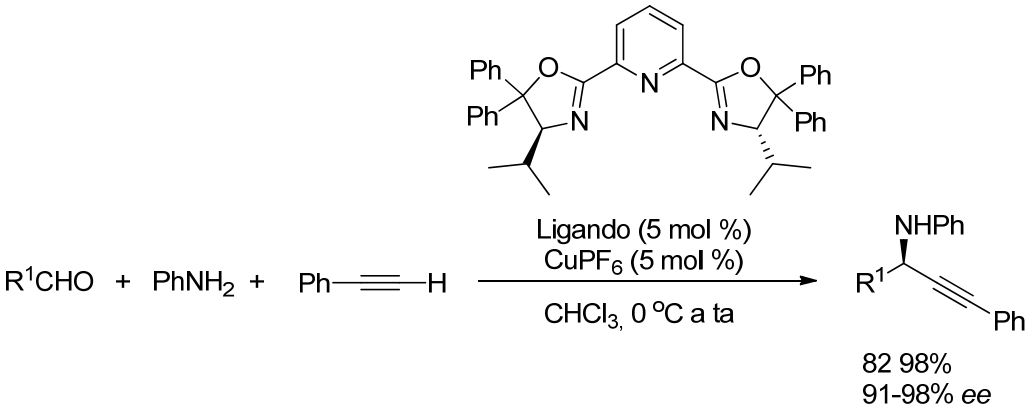


Figura 2.2. Ácido de Brønsted quiral.

Con el objetivo de mejorar los resultados de las reacciones de alquinilación catalítica enantioselectiva de iminas, diversos grupos han centrado sus investigaciones en la especie activa formada por complejos de Cu(I) y ligandos de tipo PyBOX modificados.

En 2006, Bisai y Singh[15] desarrollaron la adición enantioselectiva de tres componentes empleando una mezcla 1:1:1,5 de benzaldehído, anilina y fenilacetileno en presencia de Cu(I)-PyBOX (Esquema 2.12).



Esquema 2.12. Alquinilación enantioselectiva de tres componentes catalizada por Cu(I)-PyBOX.

Los mejores resultados se alcanzaron con 5 mol % de $CuPF_6$ y el ligando altamente sustituido mostrado en el Esquema 2.12 en $CHCl_3$, aunque se obtuvieron enantioselectividades similares utilizando otras sales como CuOTf o incluso $Cu(OTf)_2$.

La reacción con distintos aldehídos, aminas y alquinos demostró la amplia aplicabilidad de esta estrategia catalítica. Se observaron enantioselectividades superiores a 91% *ee* empleando aldehídos con sustituyentes de distinta naturaleza electrónica, anilina y fenilacetileno.

Otros autores también han preparado nuevos ligandos de tipo PyBOX a los que han incorporado estructuras de carbohidratos como fuente de quiralidad. El grupo de Boysen diseñó y sintetizó un ligando de este tipo a partir de D-glucosamina (Figura 2.3).[16]

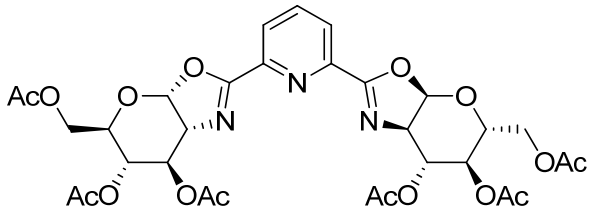
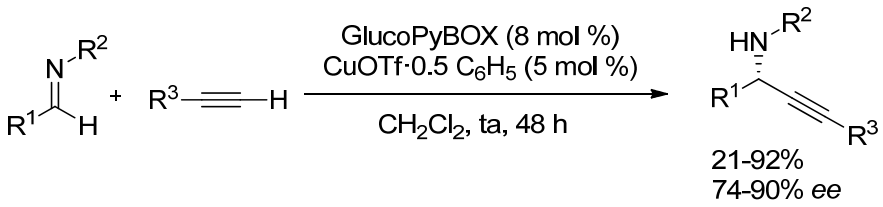


Figura 2.3. Ligando glucoPyBOX.

Los autores han descrito la utilización del complejo formado por el ligando glucoPyBOX y CuOTf·0,5C_6H_5 en la reacción entre benzaldehído y anilina con fenilacetileno en diclorometano con una excelente enantioselectividad (99% *ee*), pero con un rendimiento del 69% (Esquema 2.13). Cuando se ensayaron las condiciones optimizadas utilizando diferentes benzaldehídos sustituidos, anilina y fenilacetileno, la reacción tuvo lugar con buenos rendimientos y enantioselectividades entre 70-80% *ee*. No obstante, la adición de trimetilsililacetileno, aunque con buena enantioselectividad (90% *ee*), transcurrió con un rendimiento bajo (21%). A pesar de no ser un resultado excelente, era el mejor *ee* obtenido en las reacciones descritas hasta ese momento con el trimetilsililacetileno.



Esquema 2.13. Alquinilación enantioselectiva de iminas con el ligando glucoPyBOX.

En 2010, Boysen sintetizó un nuevo ligando quiral de tipo PyBOX en el que también habían incorporado estructuras de carbohidratos como fuente de quiralidad.[17] En concreto sintetizó la bisespiro(isoxazolina) que se muestra en la Figura 2.4. Sin embargo, su aplicación en la alquinilación de *N*-fenilbenzaldimina dio la amina propargílica con un rendimiento del 52% y una enantioselectividad del 17% *ee*.

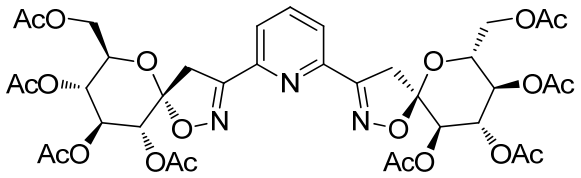
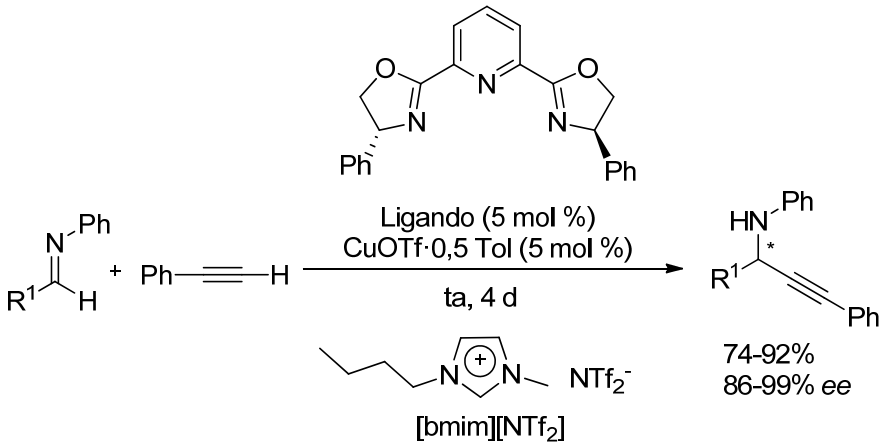


Figura 2.4. Ligando espiro bisespiro(isoxazolina) derivado de carbohidratos.

Debido al éxito alcanzado por los complejos de Cu(I) y ligandos de tipo PyBOX en la alquinilación de iminas, algunos autores centraron su atención en nuevas estrategias encaminadas al reciclaje y reutilización del catalizador.

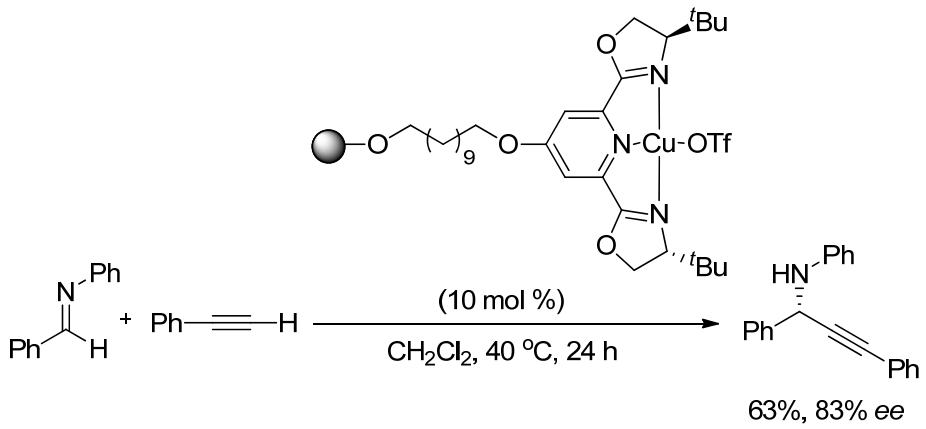
Afonso y colaboradores publicaron la primera aproximación basada en la inmovilización del catalizador en líquidos iónicos.[18] Se observó una fuerte dependencia entre la estructura del catión y la enantioselectividad, pero no se apreciaron cambios significativos en la enantioselectividad con respecto a la estructura del anión. Los mejores resultados para la reacción entre fenilacetileno y *N*-fenilbenzaldimina en presencia de Cu(I) y el ligando quiral PyBOX se obtuvieron con el líquido iónico 1-*n*-butil-3-metilimidazolio bis(trifluorometilsulfonil)imida ([bmim][NTf_2]) (74%, 94% *ee*) (Esquema 2.14), similares a los obtenidos por Li y colaboradores[3] en tolueno, pero mejores que los obtenidos en agua. Se ensayaron diversas iminas, alcanzándose en todos los casos buenos rendimientos (74-92%) y enantioselectividades (86-99%).



Esquema 2.14. Alquinilación enantioselectiva de iminas con Cu(I)-PyBOX inmovilizado en líquido iónico [bmim][NTf_2].

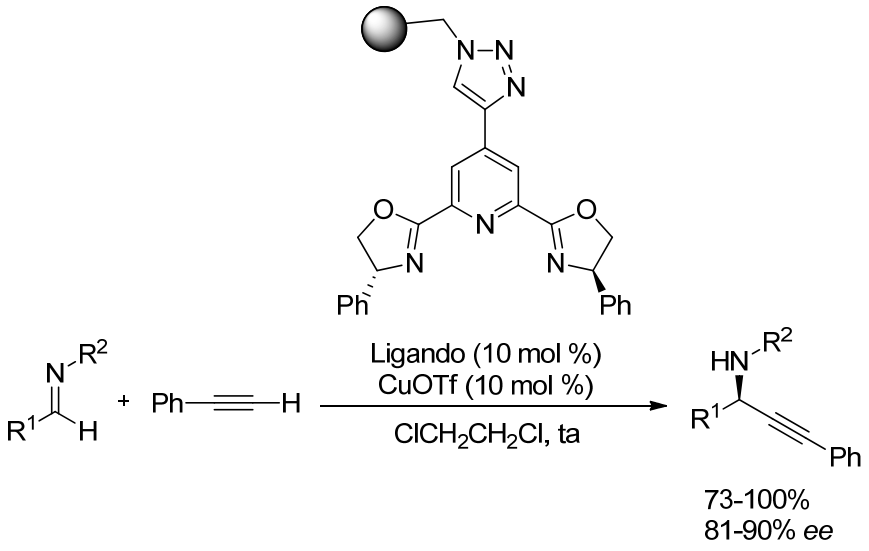
Los autores demostraron la eficiencia del catalizador tras ser reciclado durante 6 ciclos por extracción del producto con hexano.

En 2005, Portoy y colaboradores[19] prepararon un conjunto de ligandos de tipo PyBOX soportados sobre poliestireno. Tras incubarlos con CuOTf, llevaron a cabo la reacción de adición de fenilacetileno a *N*-fenilbenzaldimina (Esquema 2.15). Se observó una gran influencia del sustituyente de la oxazolina sobre la enantioselectividad, aumentando esta al aumentar el tamaño del sustituyente. Sorprendentemente, el ligando que dio los mejores resultados en disolución, fue el que dio los peores resultados cuando se utilizó soportado sobre poliestireno. El mejor resultado se obtuvo con el ligando con sustituyentes *terc*-butilo (63% rendimiento, 83% *ee*). Desafortunadamente, la utilización en ciclos posteriores de catalizador recuperado condujo a una disminución de la reactividad. La adición de ácido ascórbico permitió la completa recuperación del catalizador en sucesivos ciclos, pero a costa de una pérdida total de la enantioselectividad.



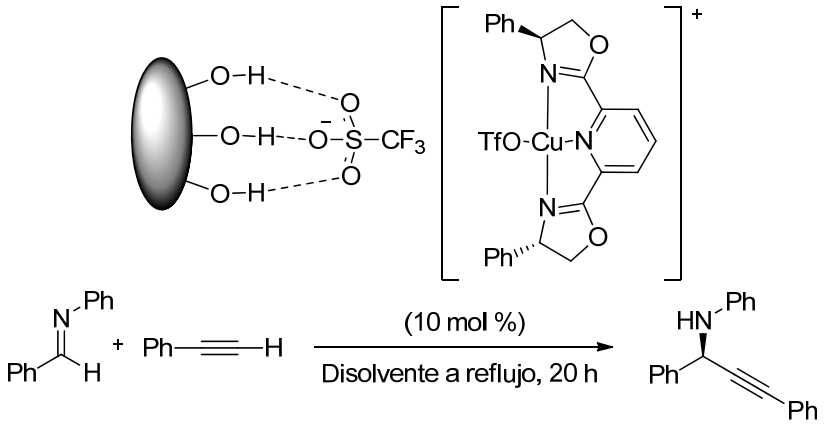
Esquema 2.15. Alquinilación enantioselectiva de iminas con Cu(I)-PyBOX soportado sobre poliestireno.

Moberg y Levacher diseñaron un nuevo ligando PyBOX unido a polímero de poliestireno mediante "click-chemistry".[20] Este se ensayó en la alquinilación de diversas iminas aromáticas (Esquema 2.16). Aunque la enantioselectividad fue menor a la lograda bajo condiciones homogéneas, superó los resultados observados con el catalizador soportado de Portnoy (Esquema 2.15) y sus posibilidades de reciclaje fueron superiores. La selectividad se reestableció recargando el polímero con triflato de cobre.



Esquema 2.16. Alquinilación enantioselectiva de iminas con el catalizador Cu(I)-PyBOX unido al polímero mediante "click-chemistry".

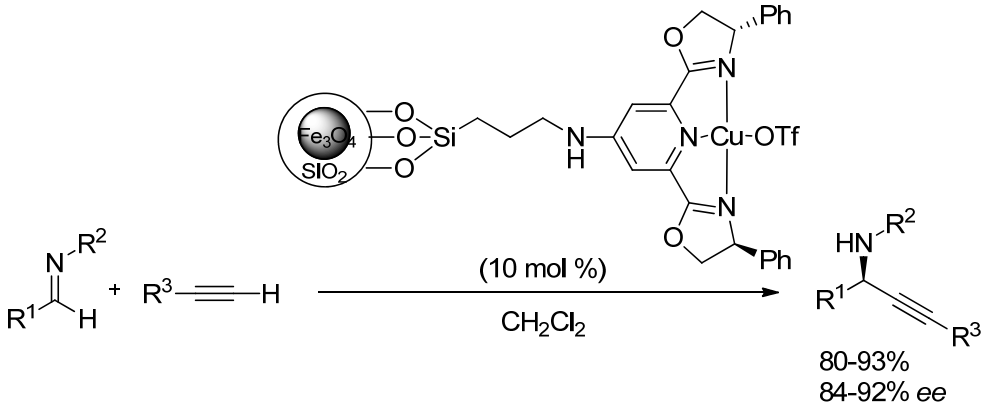
En 2007, O'Leary y colaboradores estudiaron el sistema formado por triflato de Cu(I) y Cu(II)-fenil PyBOX inmovilizado electrostáticamente en tolueno (Esquema 2.17).[21]



Esquema 2.17. Alquinilación enantioselectiva de iminas utilizando un catalizador inmovilizado electrostáticamente.

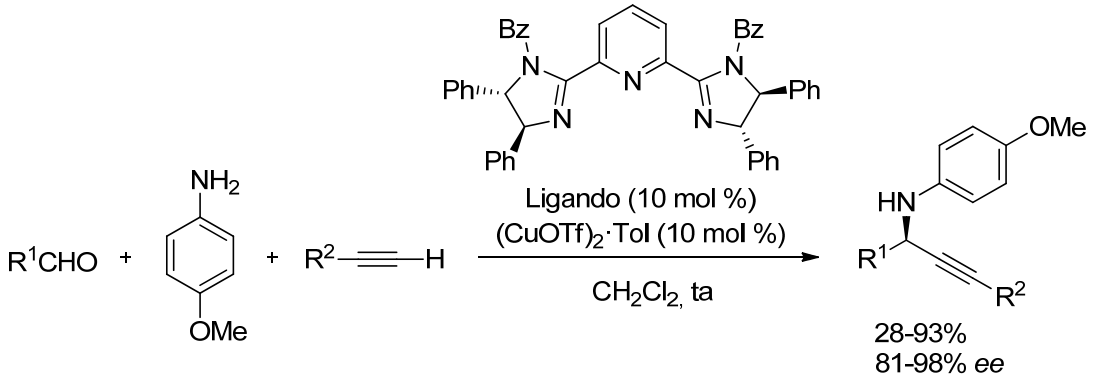
Los resultados fueron similares a los hallados en disolución homogénea. El Cu(II) proporcionó enantioselectividades superiores y mayor capacidad de reutilización, ya que aunque en los sucesivos ciclos los rendimientos disminuyeron, la enantioselectividad no varió.

En 2011, Li y colaboradores[22] diseñaron un catalizador de tipo Cu(I)-PyBOX soportado sobre nanopartículas de Fe_3O_4 que fue utilizado con éxito en la adición enantioselectiva de alquinos aromáticos a iminas aromáticas (Esquema 2.18). La principal ventaja de este catalizador es su fácil recuperación por decantación con ayuda de un imán externo.



Esquema 2.18. Alquinilación enantioselectiva de iminas utilizando un catalizador soportado sobre nanopartículas de Fe_3O_4.

En 2010, el grupo de Nakamura[23] llevó a cabo la reacción de tres componentes entre aldehídos, aminas y alquinos alifáticos catalizada por complejos de tipo PyBIM y $(CuOTf)_2$·tolueno para dar lugar a las aminas propargílicas con rendimientos y enantioselectividades elevadas independientemente de la naturaleza electrónica y estérica del sustituyente unido al grupo carbonilo del aldehído (89-98% *ee*) (Esquema 2.19). El valor más bajo de exceso enantiomérico se obtuvo cuando se empleó 3-metilbutanal y 4-fenil-1-butino (81% *ee*).



Esquema 2.19. Síntesis de tres componentes de aminas propargílicas quirales catalizada por PyBIM y $Cu(OTf)_2$·tolueno.

El grupo de Benaglia[24,25] introdujo un nuevo tipo de catalizadores quirales diferentes a los PyBOX para alquinilaciones enantioselectivas de iminas. Estos autores sintetizaron una serie de bis-iminas con simetría C_2 (Figura 2.5) y las examinaron en la adición de fenilacetileno a *N*-feniliminas derivadas del benzaldehído con triflato de cobre (I).

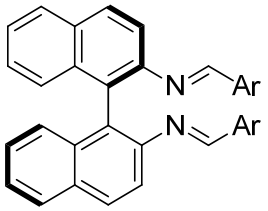
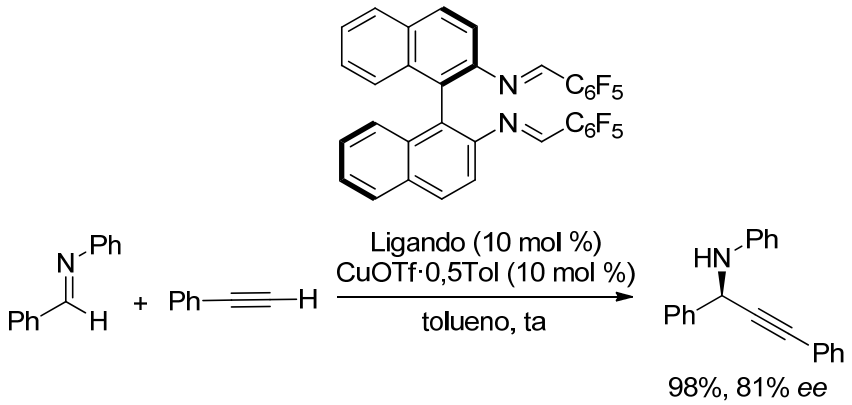


Figura 2.5. Bis-iminas con simetría C_2.

Los mejores resultados se consiguieron con la bis-imina en la que el sustituyente arilo es el grupo pentafluorofenilo, CuOTf y tolueno como disolvente (98% rendimiento, 81% *ee*) (Esquema 2.20). El sistema catalítico también funcionó con otras iminas con diferentes sustituyentes aromáticos unidos tanto al N como al C con

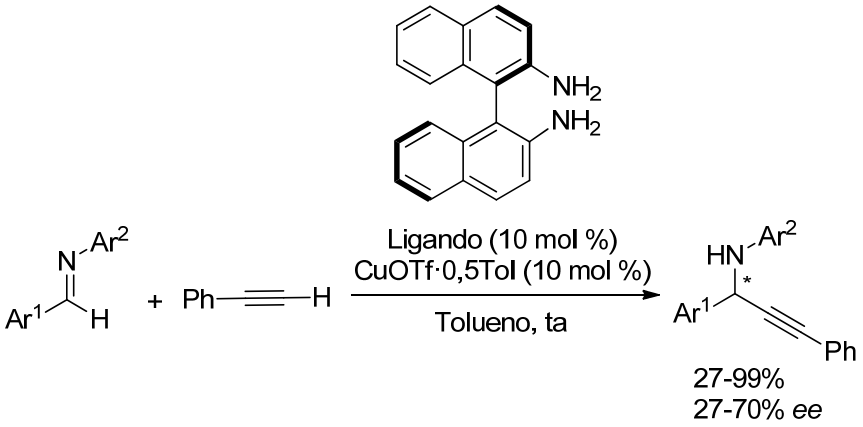
rendimientos entre buenos y excelentes y enantioselectividades hasta 80% *ee*. La aplicabilidad de la reacción pudo extenderse a alquinos alifáticos, pero no mostró enantioselectividades satisfactorias con propiolato de metilo y trimetilsililacetileno.



Esquema 2.20. Adición enantioselectiva de fenilacetileno a *N*-fenilbenzaldimina promovida por el complejo de bis-imina/Cu(I).

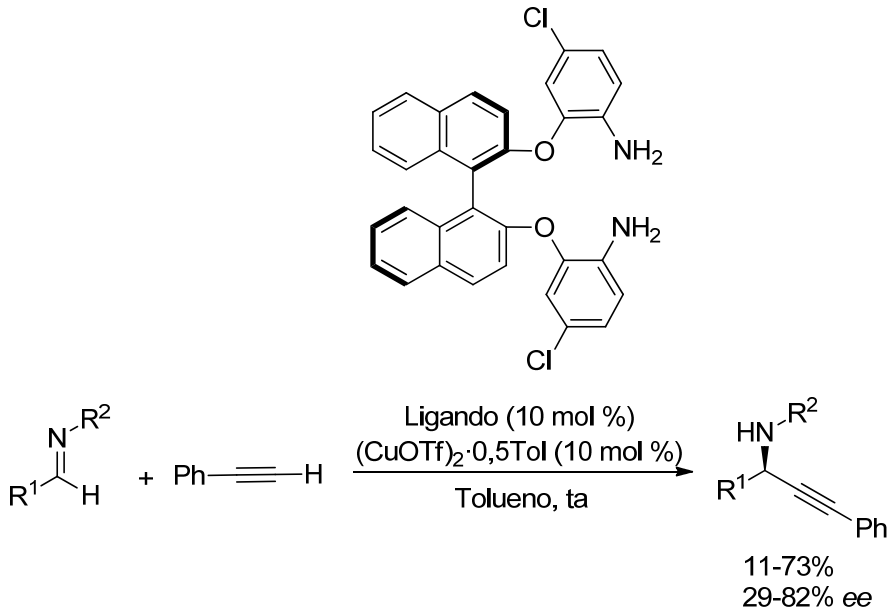
Estos autores aplicaron el mismo sistema catalítico a una versión de tres componentes de la reacción utilizando diferentes ligandos.[26] Únicamente la utilización como ligando de la bis-imina con el grupo 2-hidroxifenilo condujo a resultados satisfactorios y solo en el caso del 2-hidroxibenzaldehído. Sin embargo, el resto de aldehídos y aminas dieron resultados inferiores que la reacción de dos componentes.

También se ensayaron ligandos de tipo bis-aminas en la reacción con *N*-fenilbenzaldiminas.[27] Solamente el ligando binaftil diamina (BINAM) proporcionó los productos de alquinilación con buenos rendimientos y enantioselectividades moderadas (Esquema 2.21).



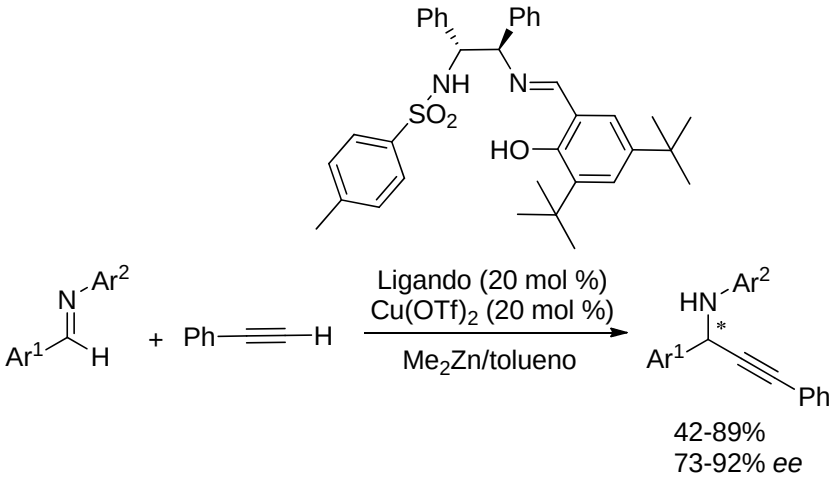
Esquema 2.21. Adición enantioselectiva de fenilacetileno a iminas sustituidas promovida con complejo de bis-amina/Cu(I).

El grupo de Ishara desarrolló un nuevo tipo de ligandos en los que incorporaron un grupo fenilamino a la estructura quiral de binaftilo.[28] Ensayaron su eficiencia en la alquinilación de *N*-fenilbenzaldimina en presencia de Cu(I). Se observó una fuerte dependencia de la enantioselectividad respecto a la sustitución en el anillo de anilina del ligando, presentándose el ligando mostrado en el Esquema 2.22 como el más eficiente (73% rendimiento, 82% *ee*). No obstante, cuando se realizó la reacción con iminas sustituidas se obtuvieron rendimientos bajos y enantioselectividades comprendidas entre 11 y 46% *ee*. Otros alquinos como *p*-bromofenilacetileno o trimetilsililacetileno mostraron una reactividad escasa o nula (16% y 0%, respectivamente).



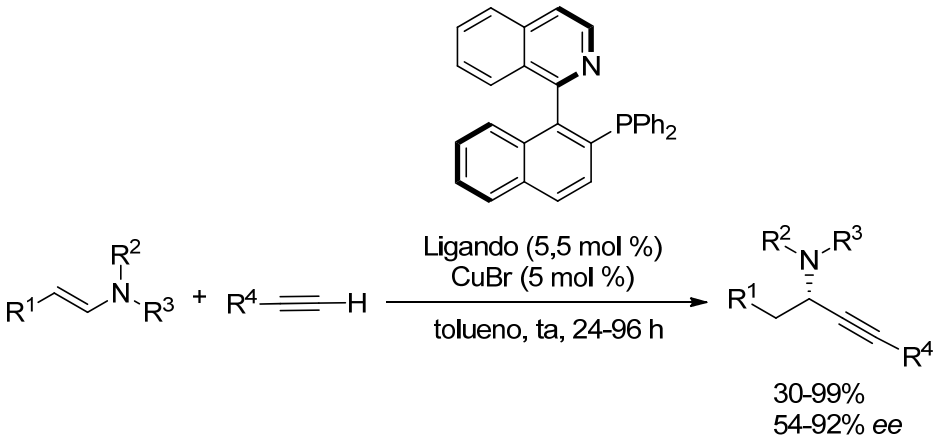
Esquema 2.22. Adición enantioselectiva de fenilacetileno a iminas promovida por el ligando binaftilo anilina/Cu(I).

En 2007, Chan y Li[29,30] diseñaron una nueva clase de ligandos quirales tridentados con estructura de *N*-tosilaminosalicilaldimina (Esquema 2.23). Estos ligandos fueron capaces de catalizar la reacción entre el reactivo de alquinilzinc formado a partir de fenilacetileno y Me_2Zn e iminas aromáticas en presencia de Cu(II). Sin embargo, la aplicabilidad de esta reacción está limitada a aldiminas aromáticas.



Esquema 2.23. Adición enantioselectiva de fenilacetileno a iminas sustituidas promovida por el ligando *N*-tosilaminosalicilaldimino y $Cu(OTf)_2$.

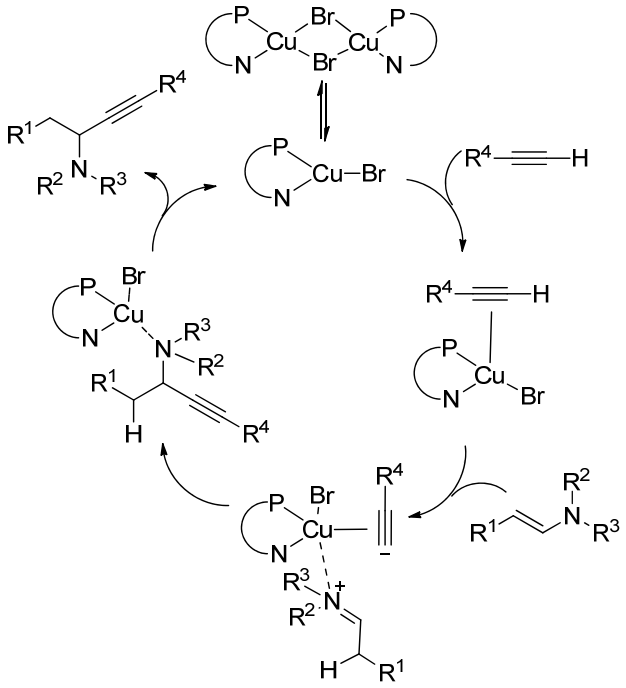
Simultáneamente al trabajo pionero desarrollado por Wei y Li,[3,4] el grupo de Knochel publicó la primera adición enantioselectiva de alquinos a enaminas catalizada por CuBr-QUINAP en tolueno a temperatura ambiente (Esquema 2.24).[31,32]



Esquema 2.24. Alquinilación enantioselectiva de enaminas catalizada por QUINAP/CuBr.

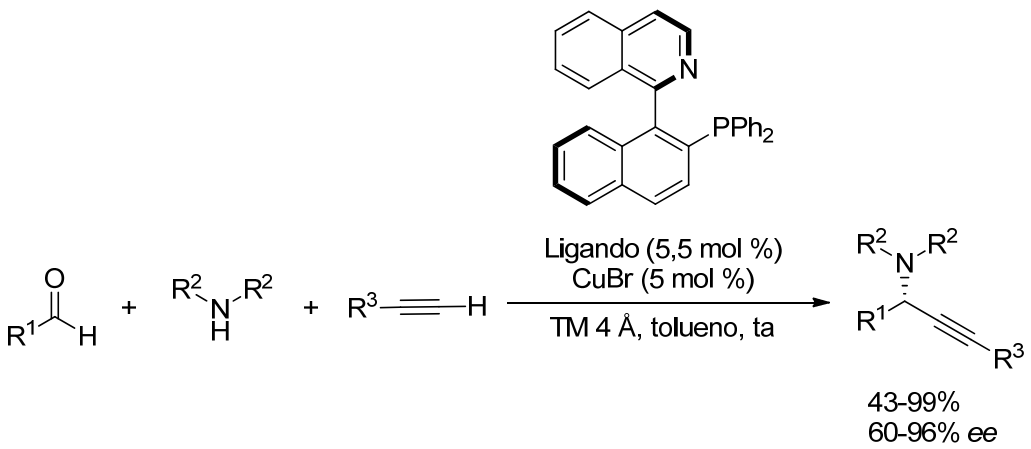
La enantioselectividad de la reacción aumentó con el tamaño de los grupos unidos al átomo de nitrógeno, dando mejores resultados con las *N*,*N*-dibencil- y *N*-alil-*N*-bencilenaminas que con las *N*,*N*-dialilenaminas. Alquinos aromáticos proporcionaron enantioselectividades superiores a 80% *ee*, mientras que con alquinos heteroaromáticos o alifáticos se observaron enantioselectividades comprendidas entre 54 y 72% *ee*. Los autores realizaron un estudio mecanístico que determinó que el protón acetilénico del alquino se transfiere a la posición β de la enamina. Teniendo en

cuenta este hecho, propusieron un mecanismo de reacción (Esquema 2.25) según el cual el complejo dimérico de cobre se disocia dando las especies de cobre monoméricas. A esta especie se coordinan sucesivamente el alquino y la enamina formándose un intermedio zwitteriónico que, tras la transferencia intramolecular del alquino al ion iminio, se disocia produciendo la amina propargílica libre y la regeneración del catalizador.



Esquema 2.25. Mecanismo propuesto para la síntesis enantioselectiva de propargilaminas a partir de enaminas con QUINAP/CuBr.

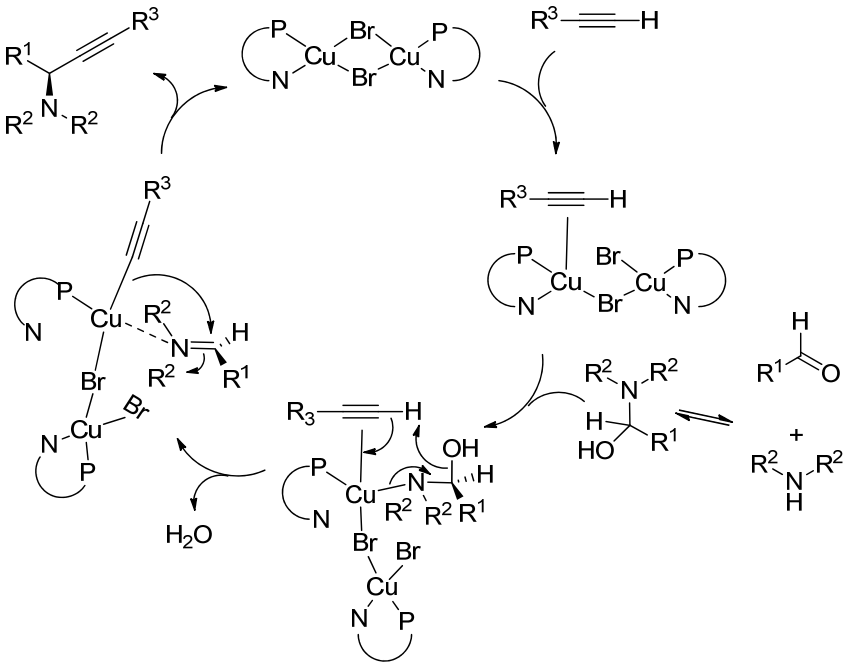
Con el objetivo de evitar la preparación de enaminas sensibles y extender la aplicabilidad de la reacción anterior a aldehídos no enolizabes, estos mismos autores publicaron en 2003 la síntesis enantioselectiva de tres componentes utilizando el mismo sistema catalítico y tamiz molecular de 4 Å (Esquema 2.26).[33]



Esquema 2.26. Síntesis enantioselectiva de tres componentes de propargilaminas.

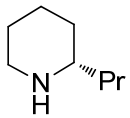
La alquinilación requirió tiempos de reacción largos (1-6 días), pero las propargilaminas se obtuvieron con rendimientos altos y enantioselectividades de moderadas a excelentes empleando tanto alquinos aromáticos como alifáticos. Asimismo, la reacción permitió modificaciones en la sustitución de la amina y el aldehído. Sin embargo, la presencia de sustituyentes en *orto* al grupo carbonilo del aldehído proporcionó los productos con resultados insatisfactorios.

Knochel y colaboradores propusieron un mecanismo (Esquema 2.27) en el que el complejo dimérico de cobre quiral, después de coordinarse con el alquino, se coordina con el aminal intermedio (formado por la reacción entre la amina y el aldehído). La desprotonación del alquino coordinado y la eliminación de H_2O da lugar al complejo de cobre coordinado con el acetiluro y con un ion iminio. La adición del acetiluro a la sal de iminio situado en la esfera de coordinación del complejo quiral de Cu(I) conduce a la propargilamina quiral y a la regeneración del catalizador.



Esquema 2.27. Propuesta mecanística para la síntesis de tres componentes de propargilaminas.

Los autores también estudiaron la adición de trimetilsililacetileno en la reacción de tres componentes obteniendo los productos sililados con rendimientos altos y enantioselectividades elevadas.[34-36] Las enantioselectividades observadas eran menores para las reacciones con aldehídos aromáticos que para las reacciones con aldehídos alifáticos, tanto ramificados como lineales. Como una muestra de la utilidad de esta reacción se llevó a cabo la síntesis de (*S*)-(+)-coniina, un alcaloide altamente tóxico (Figura 2.6).

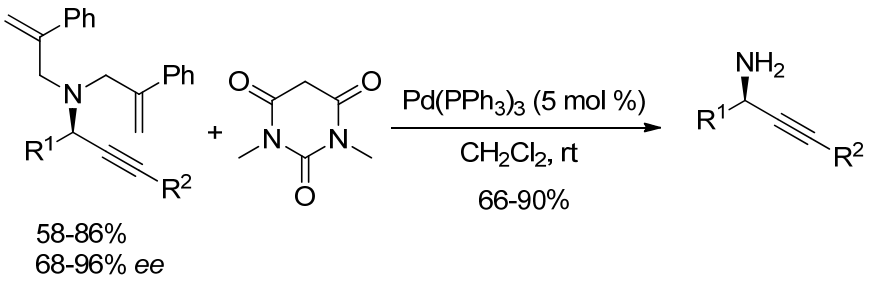


(90% *ee*)

Figura 2.6. (*S*)-(+)-Coniina.

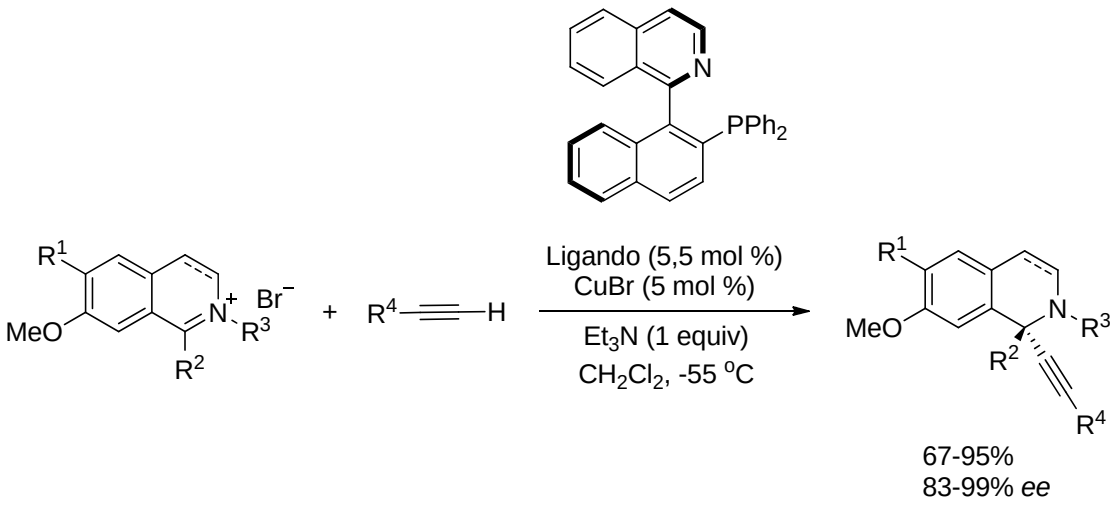
Uno de los mayores problemas que plantean los grupos unidos al átomo de nitrógeno es su dificultad de eliminación. Knochel y Gommermman[37] observaron que se obtenían mayores enantioselectividades con dibencilaminas (98%) que con dialilaminas (90% *ee*). Sin embargo, los protocolos de desprotección del grupo bencílico no fueron compatibles con el triple enlace de las aminas propargílicas. Por

ello, desarrollaron la reacción con bis(fenilalil)aminas. Estas proporcionaron el producto deseado con valores de exceso enantiomérico superiores que las dialilaminas. Además, se podían desproteger eficientemente utilizando una reacción de sustitución alílica catalizada por Pd(0) con ácido dimetilbarbitúrico (Esquema 2.28).



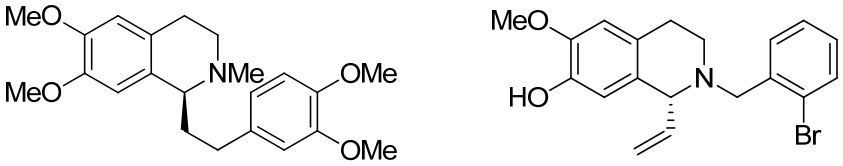
Esquema 2.28. Reacción de desprotección de *N,N*-bis(fenilalil)propargilaminas.

El sistema catalítico formado por CuBr-QUINAP también se ha aplicado a la adición de alquinos terminales a iones iminio derivados de la isoquinoleína. Schreiber y Taylor[38] realizaron esta reacción con varios alquinos obteniendo rendimientos altos y enantioselectividades de buenas a excelentes (Esquema 2.29). Por otra parte, los autores aplicaron esta metodología a reacciones en fase sólida uniendo los sustratos a unas macroesferas de resina de poliestireno, aunque las enantioselectividades alcanzadas fueron inferiores.



Esquema 2.29. Adición enantioselectiva de alquinos terminales a sales de alquilisoquinolinio catalizada por CuBr/QUINAP.

Este sistema catalítico se utilizó en a la síntesis de (*S*)-(-)-homolaudanosina, un producto natural con actividad neurológica, y en la preparación de una molécula inhibidora de crecimiento de levaduras (Figura 2.7).



96% *ee* 98% *ee*

a **b**

Figura 2.7. (a) (*S*)-Homolaudanosina. (b) Molécula inhibidora del crecimiento de levaduras.

A pesar del éxito obtenido con los sistemas de tipo CuBr-QUINAP, este ligando presenta ciertos inconvenientes debido tanto a su costosa síntesis y resolución de los enantiómeros, como a su elevado precio cuando se adquiere comercialmente. Por ello, Carreira y colaboradores desarrollaron en 2004 una serie de nuevos ligandos P,N (PINAP) preparados en cuatro pasos sencillos (Figura 2.8).[39] La presencia de un grupo quiral, (*R*)-feniletilo, unido covalentemente a la unidad de biarilo quiral facilitaba la separación de los diastereoisómeros por cristalización o cromatografía en sílica gel.

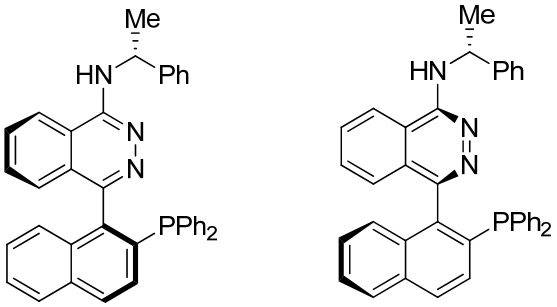
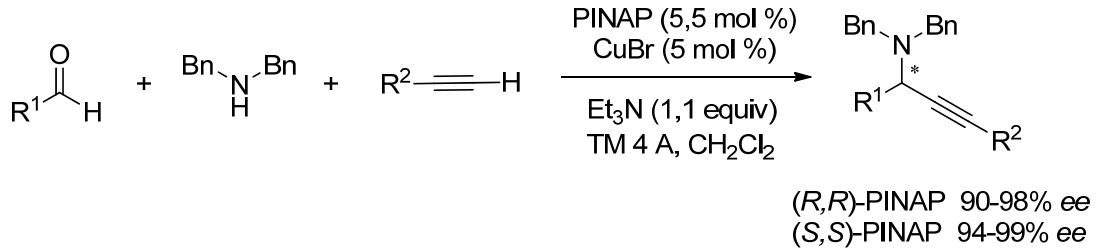


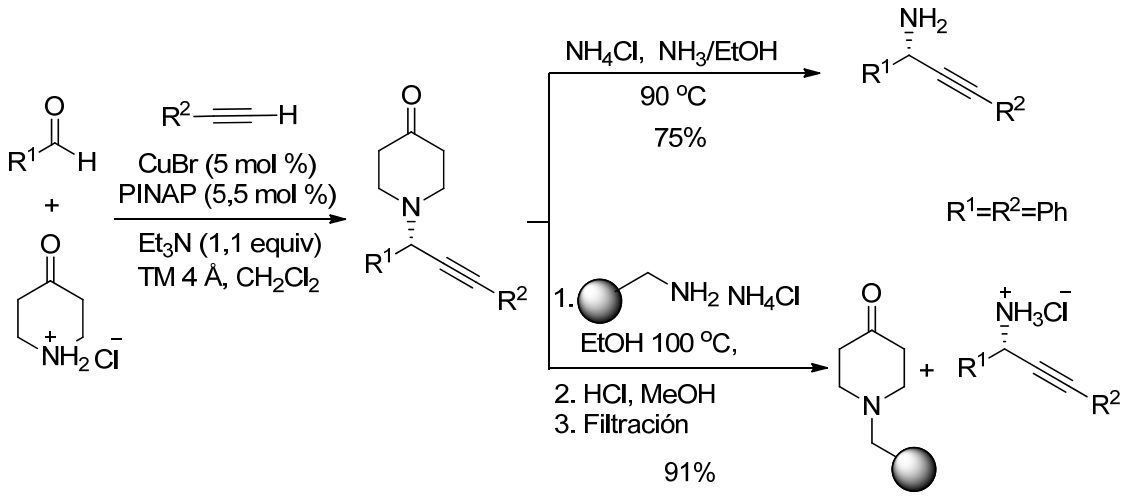
Figura 2.8. Diastereoisómeros del ligando PINAP.

Estos autores emplearon el nuevo ligando PINAP para la misma reacción de tres componentes previamente realizada por Knochel con CuBr-QUINAP. La enantioselectividad observada con el complejo Cu(I)-PINAP es superior a la lograda con el QUINAP (Esquema 2.30).



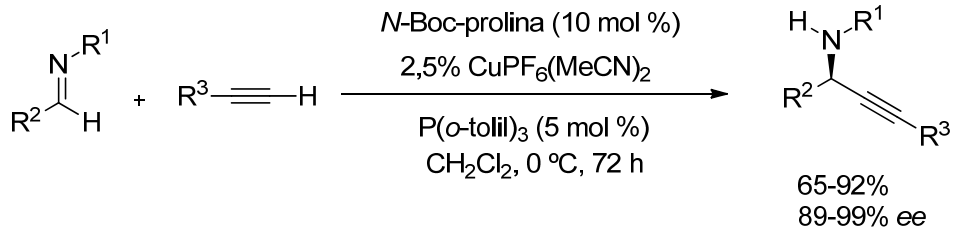
Esquema 2.30. Síntesis enantioselectiva de tres componentes de propargilaminas catalizada por Cu/PINAP.

Posteriormente, estos autores llevaron a cabo la misma reacción utilizando clorhidrato de 4-piperidona en lugar de dibencilamina (Esquema 2.31).[40] El benzaldehído no condujo a resultados satisfactorios. Sin embargo, aldehídos alifáticos lineales y ramificados, así como 2-furaldehído, participaron en la reacción con buenos rendimientos y enantioselectividades elevadas. Las piperidonas *N*-sustituidas resultantes se transformaron en aminas primarias con facilidad.



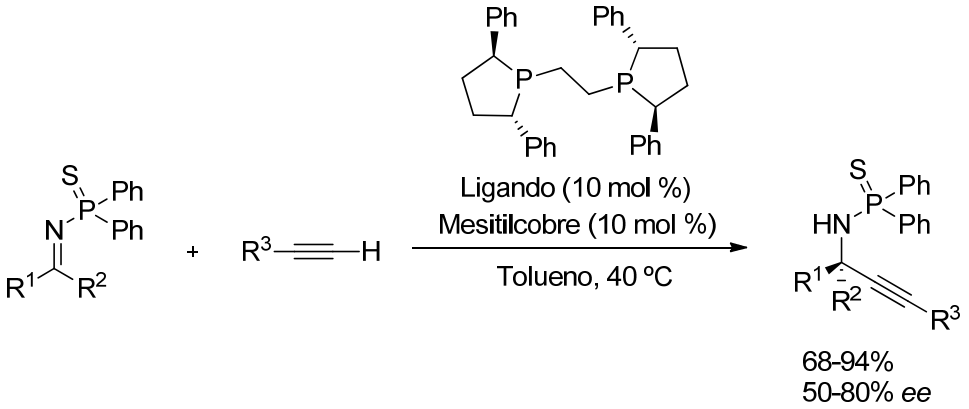
Esquema 2.31. Reacción de acoplamiento de tres componentes con 4-piperidona·HCl y desprotección de las aminas propargílicas resultantes.

En 2009, Ardnsten y colaboradores[41] examinaron la adición de alquinos a iminas utilizando como fuente de quiralidad diferentes derivados de amino ácidos capaces de formar enlaces de hidrógeno con el nitrógeno azometínico (Esquema 2.32), aumentando así la electrofilia del doble enlace C=N. La utilización conjunta de P(*o*-tolil)$_3$ con *N*-Boc-prolina condujo a los mejores resultados.



Esquema 2.32. Alquinilación enantioselectiva de iminas promovida por P(*o*-tolil)$_3$, *N*-Boc-prolina y $CuPF_6(MeCN)_2$.

Recientemente, el grupo de Shibasaki[42] ha desarrollado un procedimiento para la alquinilación asimétrica catalítica de cetoiminas no cíclicas basado en la activación simultánea del alquino y de la imina mediante condiciones de transferencia de protón (Esquema 2.33). El sistema catalítico utilizado está formado por un ligando quiral tipo bifosfina, (*S*,*S*)-Ph-BPE y mesitilcobre. Los productos de alquinilación se obtuvieron con buenos rendimientos y enantioselectividades moderadas.



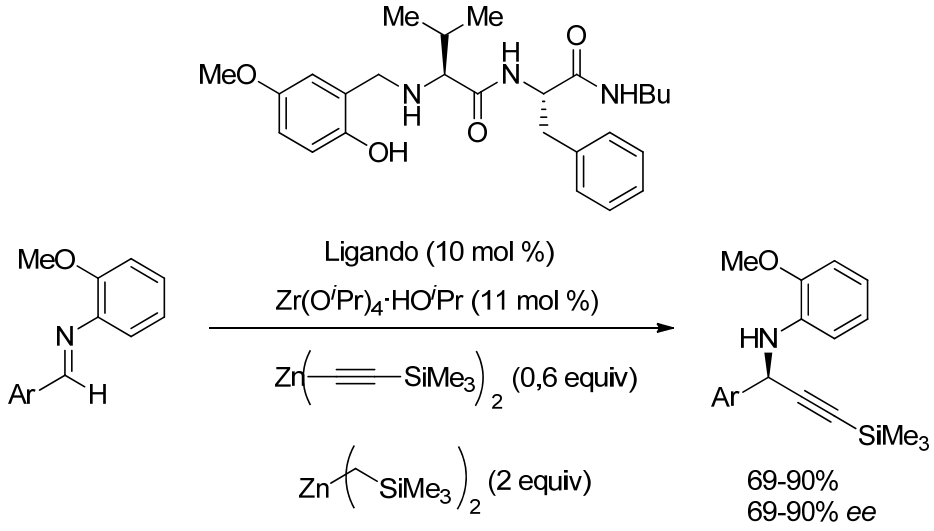
Esquema 2.33. Alquinilación enantioselectiva de cetiminas catalizada por (*S*,*S*)-Ph-BPE y mesitilcobre

2.1.2.2. Adiciones enantioselectivas catalizadas por otros metales

Los compuestos de dialquilzinc han sido ampliamente utilizados en reacción de alquinilación de iminas.[43] Sin embargo, no es tan común encontrar métodos de alquinilación de iminas empleando reactivos de dialquinilzinc o alquilalquinilzinc. A continuación se presentan los más destacados.

En 2003, el grupo de Hoveyda[44] describió la adición catalítica enantioselectiva de reactivos mixtos de alquinilzinc a *o*-anisidilbenzaldiminas promovida por el ligando

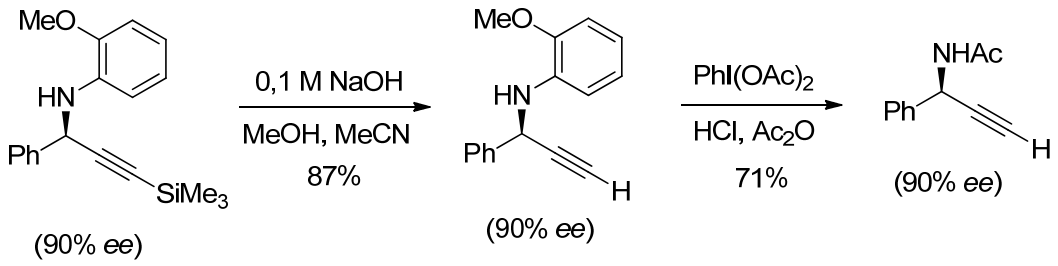
quiral de tipo aminoácido que se muestra en el Esquema 2.34 y en presencia de $Zr(O^iPr)_4 \cdot HO^iPr$.



Esquema 2.34. Adición enantioselectiva de reactivos de alquinilzinc a iminas catalizada por Zr(IV).

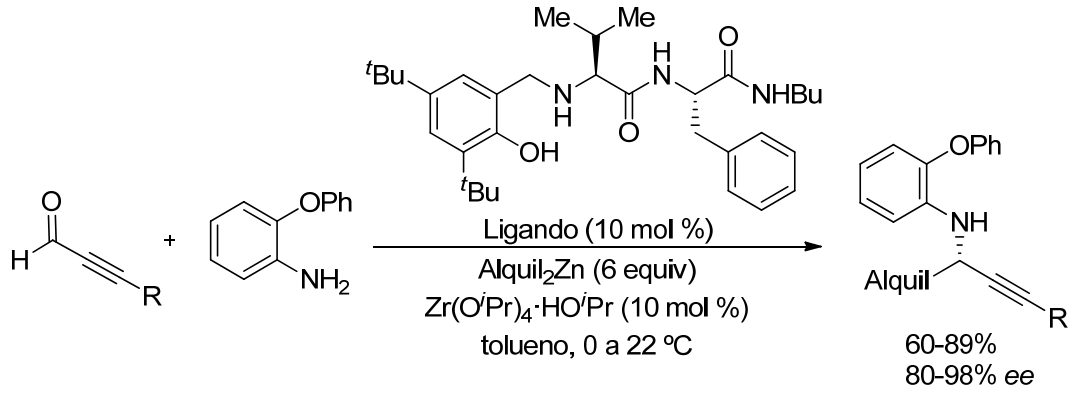
Este ligando se puede preparar fácilmente a partir de aminoácidos comerciales y 5-metoxisalicilaldehído. Se examinaron diferentes *o*-anisidilbenzaldiminas con sustituyentes de diversa naturaleza electrónica obteniéndose enantioselectividades entre 81 y 90% *ee* y rendimientos superiores a 69%. La presencia de sustituyentes en *orto* condujo a un descenso de la enantioselectividad (69% *ee*). El estudio se centró en reactivos del tipo trimetilsililacetileno que proporcionaron aminas propargílicas terminales tras la eliminación del grupo TMS. También se emplearon en esta reacción otros reactivos de alquinilzinc alifáticos y aromáticos. Se pudo disminuir la carga de catalizador hasta 2,5% de ligando y 10% de $Zr(O^iPr)_4 \cdot HO^iPr$, obteniéndose buenos resultados (90% rendimiento, 86% *ee*).

Las aminas propargílicas sintetizadas se pudieron desproteger oxidativamente para dar la correspondiente amina libre (Esquema 2.35).



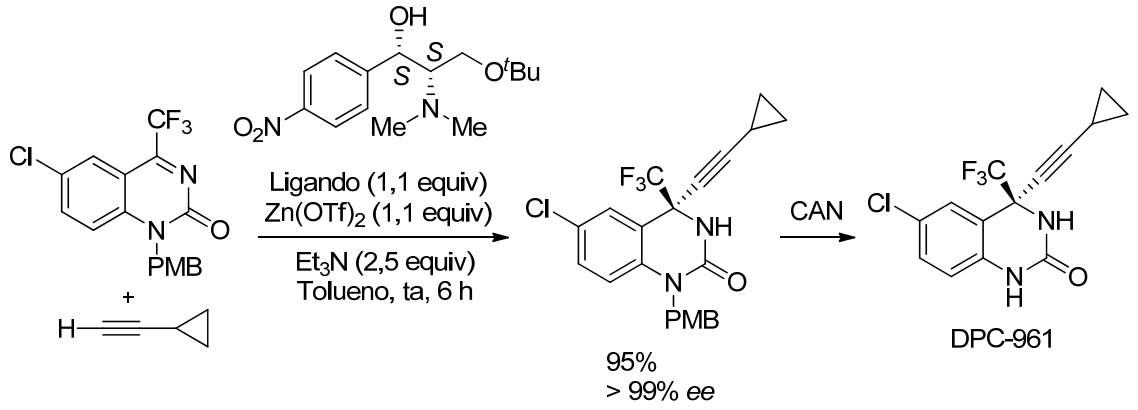
Esquema 2.35. Desprotección oxidativa del grupo *o*-anisidilo.

Estos mismos autores desarrollaron la síntesis de aminas propargílicas mediante la reacción de tres componentes entre aldehídos propargílicos, una amina primaria aromática y un reactivo de alquilzinc (Esquema 2.36).[45]



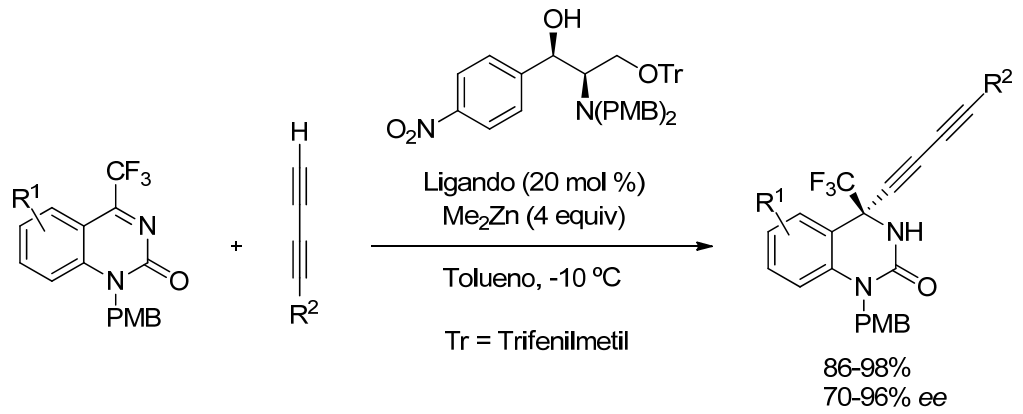
Esquema 2.36. Síntesis enantioselectiva de tres componentes de propargilaminas utilizando reactivos de dialquilzinc.

Posteriormente, Jiang y Si[46] describieron la aplicación del aminoalcohol indicado en el Esquema 2.37 como ligando estequiométrico quiral para la adición de alquinos a iminas cíclicas activadas por el grupo trifluorometilo, en presencia de triflato de zinc y trietilamina. Esta reacción supuso el paso clave en la síntesis del compuesto conocido como DPC-961, un análogo del fármaco contra el VIH, Efavirenz (Sustiva®, Bristo-Myers-Squibb) (Esquema 2.37). Además, se ensayaron otros acetilenos aromáticos, alílicos y sililsustituidos alcanzando resultados excelentes (rendimientos superiores al 63%, hasta 99,5% *ee*).



Esquema 2.37. Adición enantioselectiva de ciclopropilacetileno a trifluorometilimina cíclica.

Recientemente, el grupo de Ma[47] ha llevado a cabo la adición de diinos a *N*-acil trifluorometiliminas cíclicas utilizando un ligando quiral de tipo amino alcohol y Me_2Zn (Esquema 2.38). La reacción tolera sustituyentes electrón-dadores y electrón-aceptores en el anillo aromático de la imina, así como la adición de diinos aromáticos, alicíclicos y alifáticos con rendimientos y enantioselectividades elevados.



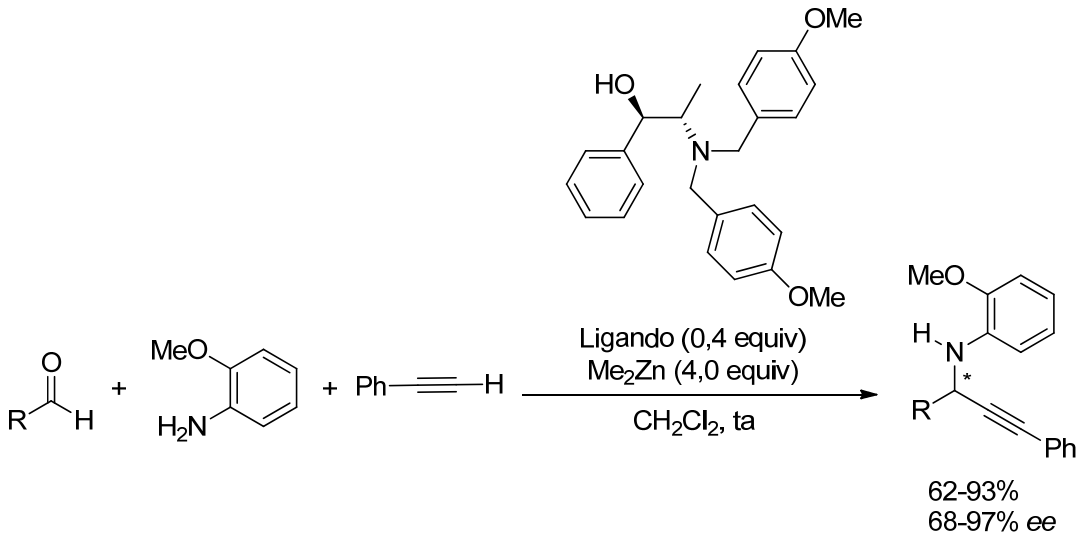
Esquema 2.38. Adición de diinos a *N*-aciliminas catalizada por un ligando de tipo amino alcohol y Me_2Zn.

Los autores también sintetizaron los enantiómeros opuestos de los productos de diinilación empleando el enantiómero del ligando amino alcohol mostrado en el Esquema 2.38. La eliminación del grupo *p*-metoxibencilo y la reducción parcial del triple enlace procede sin pérdida de la pureza óptica.

En 2006, el grupo de Bolm describió el primer ejemplo de adición de acetilenos terminales a *N*-ariliminas promovida por Me_2Zn, en ausencia de ligando.[48] Poco tiempo después, desarrollaron la síntesis de tres componentes de aminas propargílicas

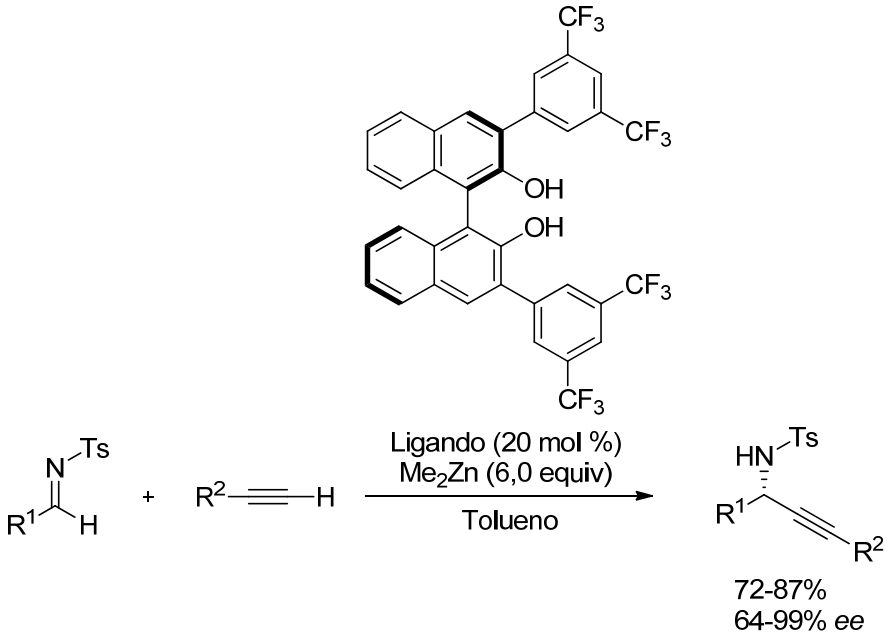
mediada por Me_2Zn utilizando varios aldehídos y *o*-metoxianilina.[49] La eficiencia de la reacción con fenilacetileno pudo mejorarse trabajando bajo condiciones concentradas empleando como único disolvente el tolueno de la disolución de Me_2Zn utilizada (2 M).

A continuación, desarrollaron la versión enantioselectiva aplicando esta metodología en presencia de un derivado de (1*R*,2*S*)-norepinefrina como inductor quiral (Esquema 2.39). Se utilizaron aldehídos aromáticos, heteroaromáticos y alifáticos α-sustituidos, *o*-metoxianilina y fenilacetileno obteniéndose rendimientos entre moderados y altos y enantioselectividades comprendidas entre 68 y 97% *ee*. Sin embargo, otros alquinos alifáticos y trimetilsililacetileno dieron lugar a enantioselectividades inferiores (13-53% *ee*).



Esquema 2.39. Síntesis enantioselectiva de tres componentes de aminas propargílicas utilizando un aminoalcohol y Me_2Zn.

Teniendo en cuenta que la presencia de grupos electrón-aceptores en el nitrógeno azometínico aumenta la electrofilia del enlace C=N, nuestro grupo de investigación ha descrito la primera alquinilación enantioselectiva de *N*-sulfoniliminas promovida por Me_2Zn en presencia de ligandos de tipo BINOL (Esquema 2.40).[50] En esta reacción, la reducción del volumen de disolvente al 50% supuso una mejora adicional de la enantioselectividad (de 96 a 98% *ee*), lo cual coincidía con las observaciones de Bolm.[48,49]

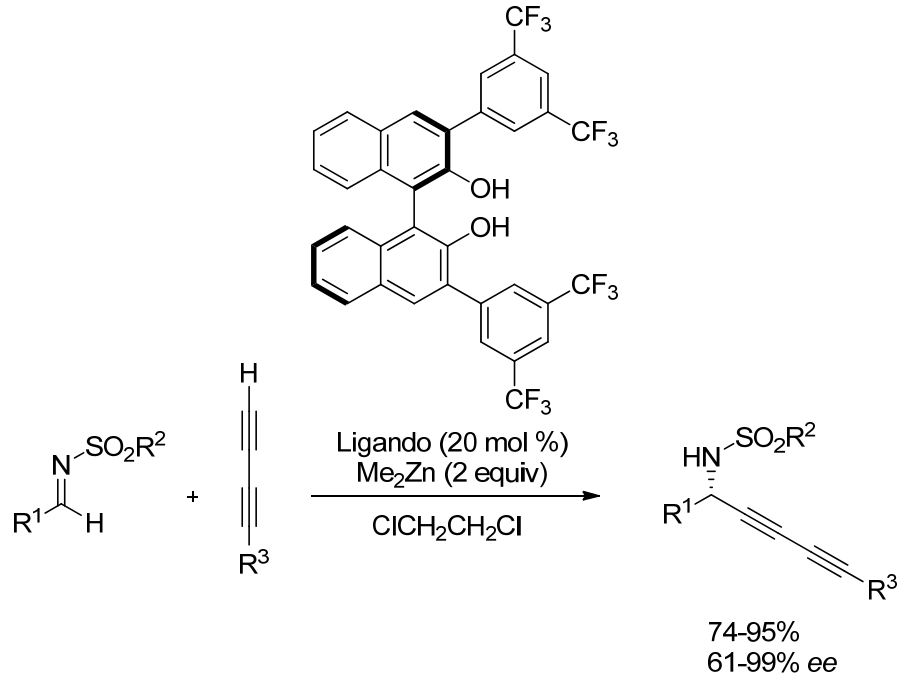


Esquema 2.40. Adición enantioselectiva de alquinos a *N*-tosiliminas promovida por Me_2Zn y ligandos tipo BINOL.

Se obtuvieron enantioselectividades elevadas (87->99% *ee*) con diferentes *N*-tosilbenzaldiminas independientemente de la naturaleza electrónica de los sustituyentes del anillo bencénico. *N*-tosiliminas derivadas de aldehídos heteroaromáticos dieron la correspondiente sulfonilamida propargílica con buenos rendimientos y valores de *ee* (64-91% *ee*). Sin embargo, iminas alifáticas mostraron enantioselectividades inferiores (18-38% *ee*). También se evaluó la reacción utilizando alquinos alifáticos como 4-fenil-1-butino y 1-hexino con los que se alcanzaron *ee* comprendidos entre 87-100% y 76-93%, respectivamente. La fácil eliminación del grupo tosilo en aminas propargílicas derivadas de alquinos alifáticos con SmI_2 hace este método útil en el área de química fina.

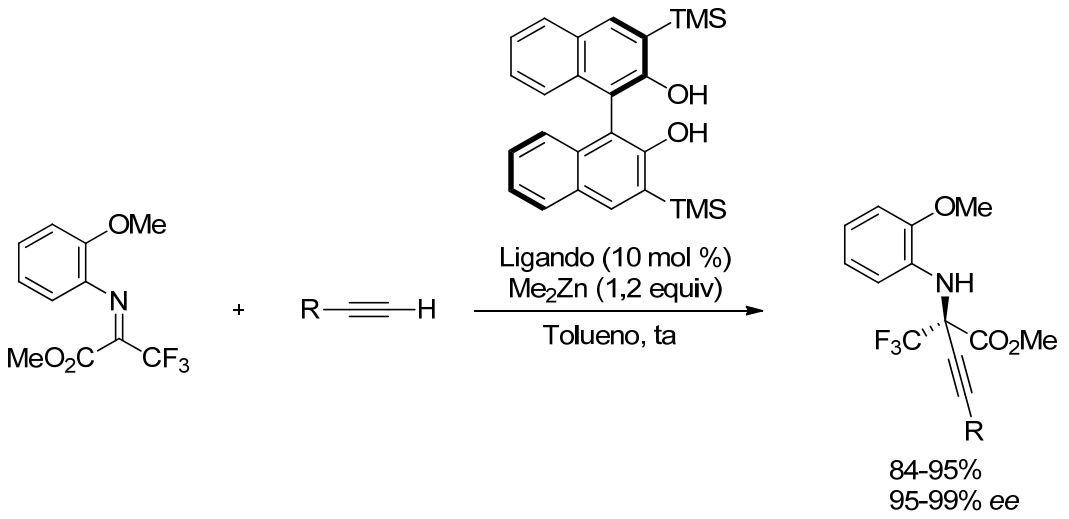
Recientemente, el grupo de Ma ha aplicado este mismo sistema catalítico en la adición de diinos a *N*-tosiliminas.[51] La adición de 4-fenil-1,3-butadiino a iminas aromáticas con grupos electrón-dadores y electrón-aceptores en las posiciones *orto*, *meta* y *para* del anillo transcurrió con rendimientos y enantioselectividades elevados. Sin embargo, la utilización de iminas alifáticas condujo a peores resultados. Este protocolo también pudo extenderse con éxito al uso de diversos diinos aromáticos y alifáticos.

La reducción total de los triples enlaces se llevó a cabo con Pd/C y la reducción parcial de uno de los tripes enlaces se realizó con $LiAlH_4$. Ambos procesos proceden sin pérdida de la enantiopureza. La desprotección del grupo amino se llevó a cabo sobre el producto de reducción total utilizando SmI_2.



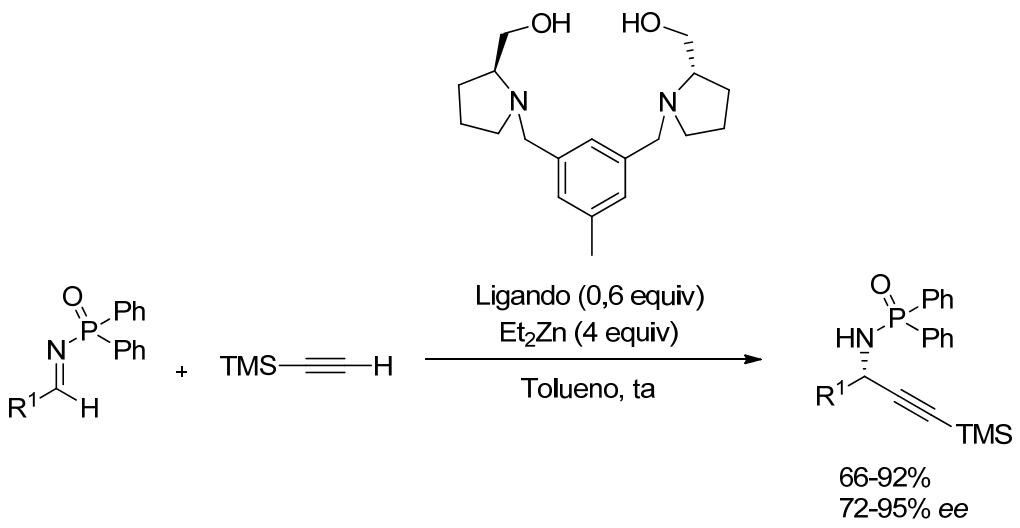
Esquema 2.41. Adición enantioselectiva de diinos a *N*-tosiliminas catalizada por BINOL-Zn.

El sistema catalítico formado por BINOL-Zn también fue utilizado por Zhang y colaboradores[52] en la alquinilación enantioselectiva de alquinos a α-trifluorometilcetoimino ésteres (Esquema 2.42). Se examinaron alquinos de diversa naturaleza, aril-, alquil- y sililsustituidos. En todos los casos proporcionaron los productos de adición con enantioselectividades excelentes.



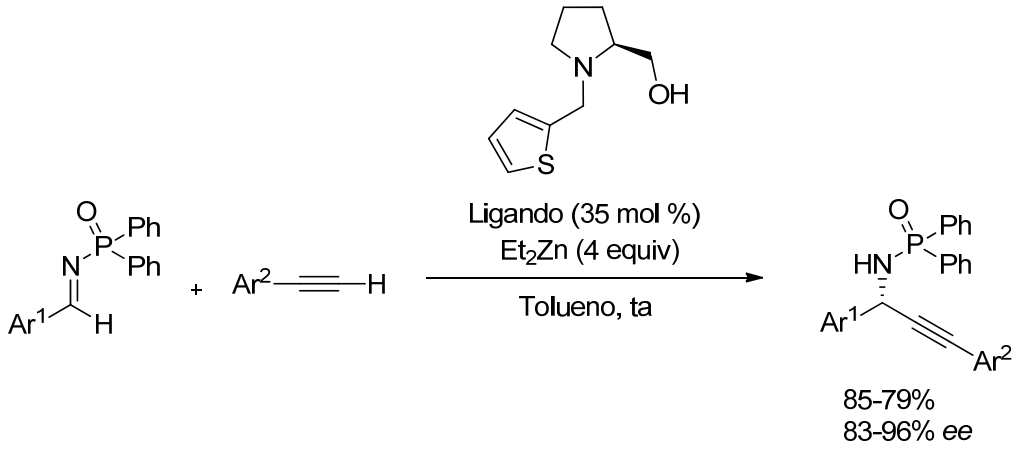
Esquema 2.42. Alquinilación enantioselectiva de α-trifluorometilcetoimino ésteres catalizada por BINOL-Zn.

En 2008, el grupo de Wang[53] publicó la alquinilación enantioselectiva de *N*-(difenilfosfinoil)benzaldiminas promovida por Et_2Zn y ligandos de tipo β-amino alcohol. Los resultados alcanzados con cantidades subestequiométricas de ligando no fueron satisfactorios (68% *ee*), por lo que fue necesario aumentar la carga de promotor quiral hasta 100 mol % con lo que consiguieron un 78% rendimiento y una enantioselectividad del 95% *ee*. Poco después, estos autores emplearon el mismo tipo de iminas en la reacción de adición de trimetilsililacetileno (Esquema 2.43).[54] Como precursores quirales, sintetizaron y ensayaron diferentes amino alcoholes con simetría C_2 y C_3. Examinaron aril, heteroaril y alquil iminas con buenos rendimientos y enantioselectividades entre moderadas y altas (72-95% *ee*). También examinaron varias *N*-(dietoxifosfinoil)iminas obteniendo buenos resultados. La ventaja de estas iminas es que en los productos formados resulta fácil la desprotección con HCl/MeOH y la desililación con Bu_4NF.



Esquema 2.43. Adición enantioselectiva de trimetilsililacetileno a *N*-(difenilfosfinoil)iminas promovida por Et_2Zn y ligandos de tipo β-amino alcohol.

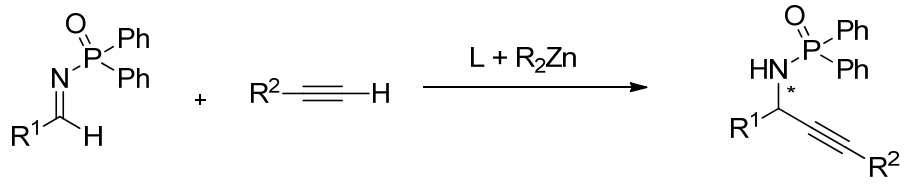
En 2010, este mismo grupo diseñó y sintetizó un conjunto de ligandos tridentados de tipo amino alcohol derivados de la prolina.[55] Estos ligandos fueron evaluados en la reacción de adición enantioselectiva de fenilacetileno, 2-tienil- y 3-tienilacetileno a *N*-(difenilfosfinoil)benzaldiminas aromáticas en presencia de dietilzinc, proporcionando los correspondientes productos de adición con buenos rendimientos y enantioselectividades elevadas (Esquema 2.44). Sin embargo, la obtención de aminas propargílicas alifáticas se consiguió con enantioselectividades moderadas y únicamente utilizando α-amido sulfonas como precursores de las *N*-(difenilfosfinoil)benzaldiminas.



Esquema 2.44. Adición enantioselectiva de alquinos a *N*-(difenilfosfinoil)iminas.

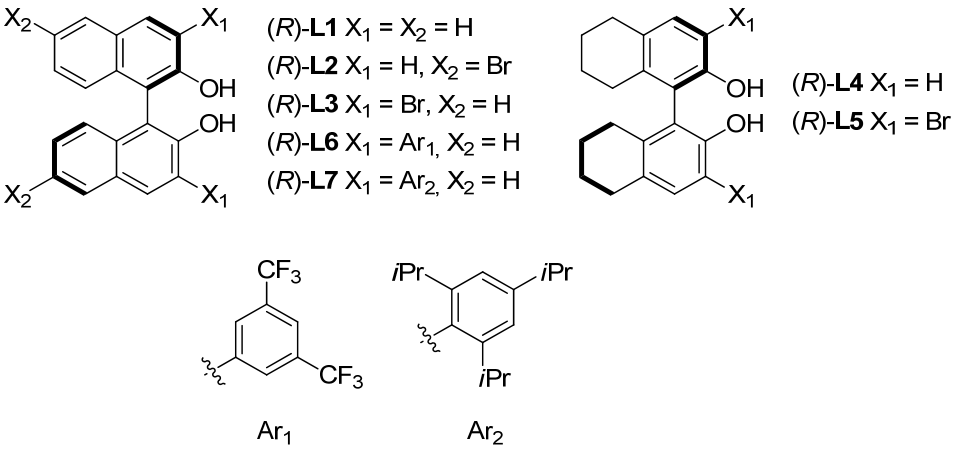
2.2. OBJETIVOS

La finalidad de este primer capítulo es el diseño de un sistema catalítico que permita llevar a cabo la síntesis enantioselectiva de aminas propargílicas quirales mediante la reacción de adición de alquinos terminales a *N*-(difenilfosfinoil)aldiminas con buenos rendimientos y excesos enantioméricos.



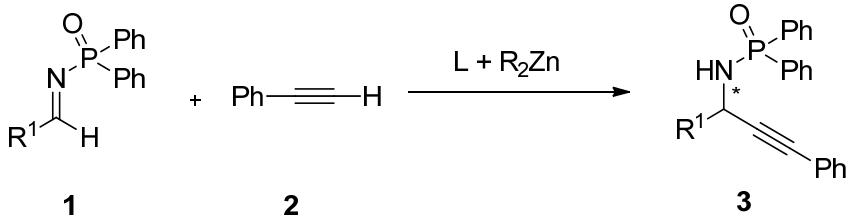
Para ello, se va a llevar a cabo el estudio de los siguientes aspectos:

1. Identificación de las condiciones óptimas de reacción: Influencia de la estructura de diversos ligandos de tipo (*R*)-BINOL (**L1**-**L7**) sobre el rendimiento y la enantioselectividad de la reacción de adición de fenilacetileno a *N*-(difenilfosfinoil)benzaldimina.



2. Identificación de las condiciones óptimas de reacción: Influencia de la temperatura, el disolvente y el reactivo de dialquilzinc utilizado.

3. Alcance y limitaciones de la reacción: Evaluación de diversas *N*-(difenilfosfinoil)aldiminas aromáticas y alifáticas con diferente naturaleza electrónica y estérica en la reacción de adición de fenilacetileno.



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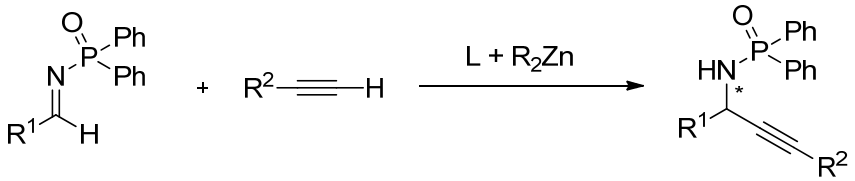
4. Alcance y limitaciones de la reacción: Evaluación de distintos alquinos aromáticos y alifáticos con diferente naturaleza electrónica y estérica en la reacción con *N*-(difenilfosfinoil)aldiminas.



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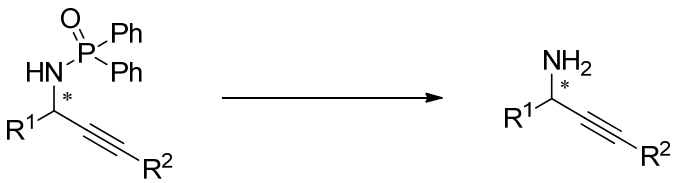
5. Desprotección del grupo amino en los productos de alquinilación para obtener las aminas propargílicas libres.



3 **4**

6. Determinación de la configuración absoluta del centro estereogénico presente en las aminas propargílicas quirales obtenidas.

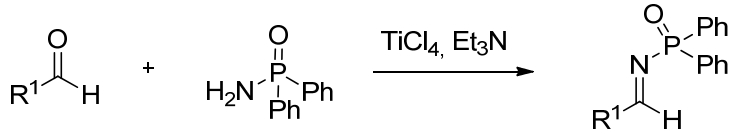
2.3. RESULTADOS Y DISCUSIÓN

2.3.1. Síntesis de *N*-(difenilfosfinoil)iminas

Las *N*-(difenilfosfinoil)iminas **1** se prepararon de acuerdo con el procedimiento experimental descrito en la bibliografía.[56] Este consistió en la reacción de *P*,*P*-difenilfosfinamida con el aldehído correspondiente en presencia de tetracloruro de titanio y trietilamina utilizando diclorometano como disolvente a 0 °C (Tabla 2.1).

La purificación de las iminas sintetizadas se realizó mediante cromatografía de columna sin que se observara descomposición por hidrólisis de las mismas. No obstante, todas las iminas se obtuvieron con rendimientos bajos o moderados.

Tabla 2.1. Síntesis de *N*-(difenilfosfinoil)iminas **1**.



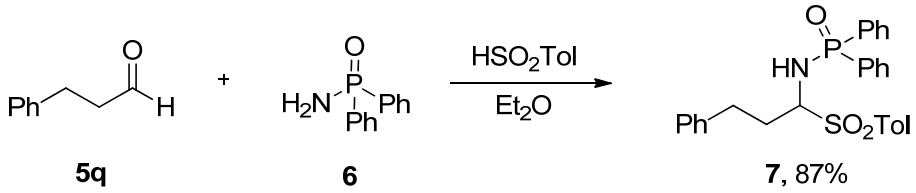
5 **6** **1**

Entrada	**5**[a]	**R[1]**	**1**	**R (%)**[b]
1	**5a**	Ph	**1a**	52
2	**5b**	4-MeC_6H_4	**1b**	64
3	**5c**	4-$MeOC_6H_4$	**1c**	61
4	**5d**	4-FC_6H_4	**1d**	38
5	**5e**	4-ClC_6H_4	**1e**	45
6	**5g**	3-MeC_6H_4	**1g**	63
7	**5h**	2-MeC_6H_4	**1h**	51
8	**5i**	2-$MeOC_6H_4$	**1i**	60
9	**5k**	2-naftil	**1k**	52
10	**5m**	2-furanil	**1m**	16
11	**5n**	2-tienil	**1n**	53
12	**5o**	3-furanil	**1o**	43

[a] La numeración de los aldehídos se corresponde con la indicada en el Anexo II. [b] Rendimiento de producto aislado por cromatografía de columna.

Todos los intentos de sintetizar la *N*-(difenilfosfinoil)imina derivada del dihidrocinamaldehído mediante el procedimiento anteriormente descrito o modificaciones de este fueron insatisfactorios. Por ello, esta imina se preparó *in situ* a partir de la α-amido sulfona correspondiente en las condiciones de la reacción de alquinilación.

La preparación de la α-amido sulfona se realizó mediante la reacción entre la *P,P*-difenilfosfinamida y dihidrocinamaldehído en presencia de ácido sulfínico utilizando dietiléter anhidro como disolvente a temperatura ambiente (Esquema 2.45). Tras 15 h de reacción, se obtuvo el producto deseado como precipitado blanco, que se purificó por filtración y lavado con dietiléter.



Esquema 2.45. Síntesis de *N*-{1-[(4-metilfenil)sulfonil]-3-fenilpropil}-*P*,*P*-difenilfosfinamida **7**.

2.3.2. Optimización de las condiciones de reacción

Para llevar a cabo el proceso de optimización de la reacción de alquinilación enantioselectiva de *N*-fosfoniliminas, se eligió la reacción de adición de fenilacetileno (**2a**) a *N*-(difenilfosfinoil)benzaldimina (**1a**). Inicialmente, se tomaron como referencia las condiciones optimizadas para la alquinilación enantioselectiva de *N*-tosiliminas publicada anteriormente por nuestro grupo.[50] Así, se añadió una disolución de Me_2Zn 2 M en tolueno sobre fenilacetileno. Tras 1 hora de agitación, se añadió una disolución de BINOL (**L1**) en tolueno y, transcurridos 15 min, se adicionó la imina (Procedimiento A, Figura 2.9). Sin embargo, después de sucesivos intentos de optimización, no encontramos resultados satisfactorios, por lo que decidimos modificar el procedimiento experimental. Dicha modificación se basó en variar el orden de adición de los reactivos implicados en la formación de la especie catalítica. El nuevo procedimiento consistió en disolver el fenilacetileno y BINOL (**L1**) en tolueno, añadir la disolución de Me_2Zn 2 M en tolueno y, tras formar la especie catalítica durante 1 hora, adicionar la imina (Procedimiento B, Figura 2.9).

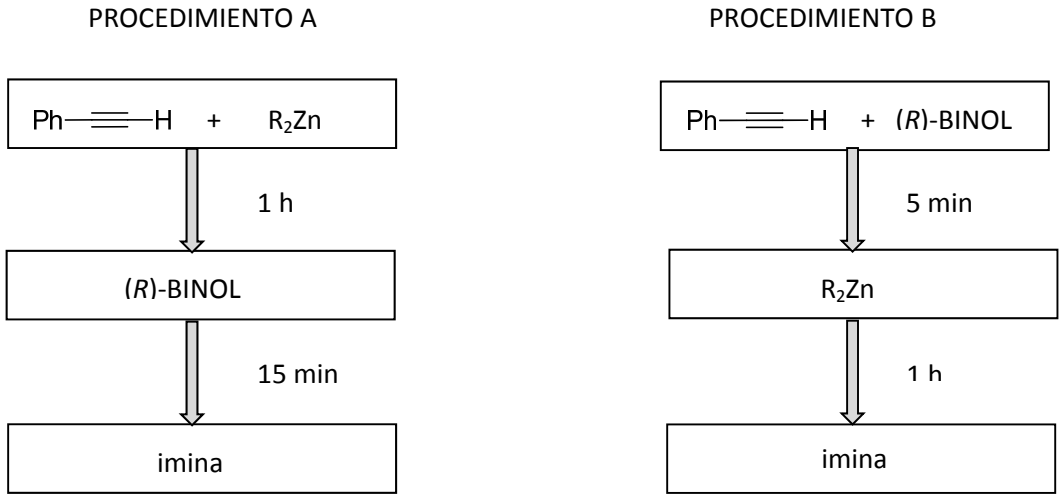


Figura 2.9. Procedimientos experimentales A y B.

Debido a que la aplicación de este nuevo procedimiento (Procedimiento B, Figura 2.9), condujo a resultados esperanzadores, comenzamos el proceso de optimización ensayando una serie de ligandos de tipo BINOL en presencia de 6 equivalentes de Me_2Zn (2 M en tolueno), utilizando tolueno como disolvente a 0 °C (Tabla 2.2). Los resultados revelaron que el tamaño de los sustituyentes en las posiciones 3,3' del BINOL utilizado como ligando tiene un efecto esencial sobre el rendimiento y la enantioselectividad de la reacción.

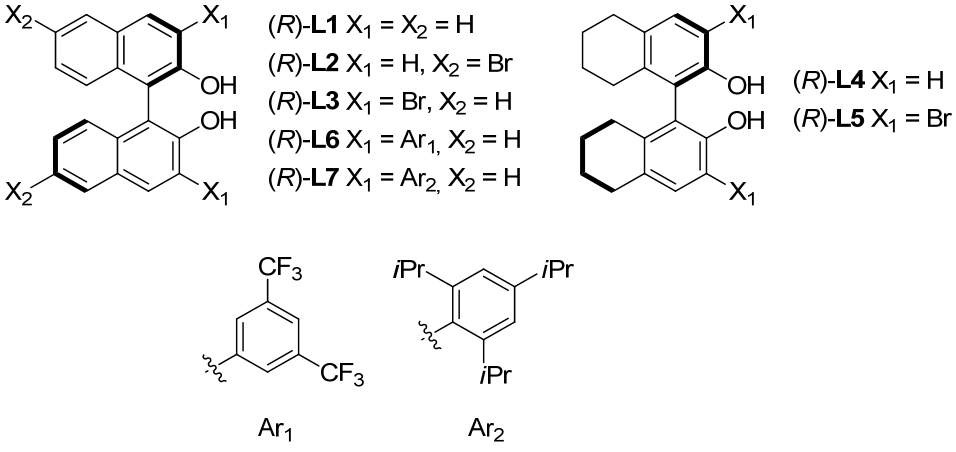
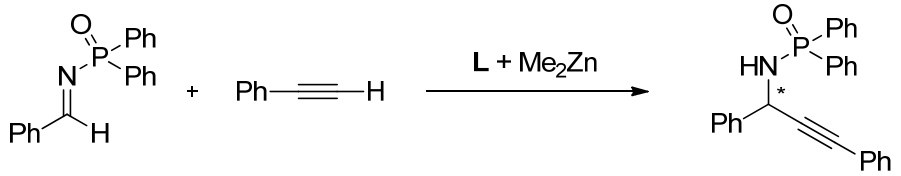


Figura 2.10. Ligandos de tipo BINOL.

El ligando **L1**, que soporta el sustituyente de menor tamaño (X_1 = H), proporcionó la enantioselectividad más baja y un rendimiento moderado (Tabla 2.2), mientras que el 3,3'-dibromobinol (**L3**) (X_1 = Br) dio el mejor resultado (84% *ee* y 81% de rendimiento). Sin embargo, un mayor incremento del impedimento estérico de los

sustituyentes en las posiciones 3,3' condujo a menores enantioselectividades. Así, con el ligando **L6** (X_1 = 3,5-di$CF_3C_6H_3$), se obtuvo una enantioselectividad del 36% *ee* y con el ligando **L7** (X_1 = 2,4,6-tri^{i}PrC_6H_2) del 22% *ee*.

Tabla 2.2. Adición enantioselectiva de fenilacetileno (**2a**) a *N*-(difenilfosfinoil)imina **1a** utilizando Me_2Zn. Screening de ligandos, temperaturas y disolventes.[a]



1a **2a** **3aa**

Entrada	L	Disolvente[b]	T (°C)	t (h)	R (%)[c]	*ee* (%)[d]
1	**L1**	Tolueno	0	20	68	3
2	**L2**	Tolueno	0	48	66	37
3	**L3**	Tolueno	0	30	81	84
4	**L4**	Tolueno	0	24	57	12
5	**L5**	Tolueno	0	30	75	72
6	**L6**	Tolueno	0	24	63	36
7	**L7**	Tolueno	0	35	68	22
8	**L3**	Tolueno	ta	20	84	24
9	**L3**	Tolueno	-20	48	63	65
10	**L3**	Hexano	0	20	70	5
11	**L3**	CH_2Cl_2	0	30	61	57
12	**L3**	THF	0	48	73	20
13[e]	**L3**	Tolueno	0	30	75	73
14[f]	**L3**	Tolueno	0	48	66	73

[a] **1a** (0,125 mmol), **2a** (0,900 mmol), Me_2Zn 2 M en tolueno (0,750 mmol), **L** (0,025 mmol). [b] 0,2 mL con **L** y 0,4 mL con la imina. [c] Rendimiento de producto aislado. [d] Determinado por HPLC usando fases estacionarias quirales. [e] Et_2Zn en lugar de Me_2Zn. [f] Me_2Zn (0,500 mmol).

Una vez identificado el ligando **L3** como el que proporcionaba los mejores resultados entre los BINOLES ensayados, la optimización de las condiciones de reacción continuó ensayando la reacción a distintas temperaturas, con varios

disolventes y reactivos de dialquilzinc (Tabla 2.2, Entradas 8-14). Tanto una disminución de la temperatura a -20 °C, como un incremento hasta temperatura ambiente (ta), tuvieron un efecto negativo sobre la enantioselectividad. Asimismo, la utilización de otros disolventes (hexano, diclorometano y tetrahidrofurano) resultó en un detrimento del rendimiento y la enantioselectividad. Finalmente, la utilización de Et_2Zn en lugar de Me_2Zn, también proporcionó peores valores de exceso enantiomérico. Por tanto, los mejores resultados en términos de rendimiento y enantioselectividad se obtuvieron cuando se llevó a cabo la reacción con el ligando **L3**, dimetilzinc y tolueno a 0 °C (Tabla 2.2, Entrada 3).

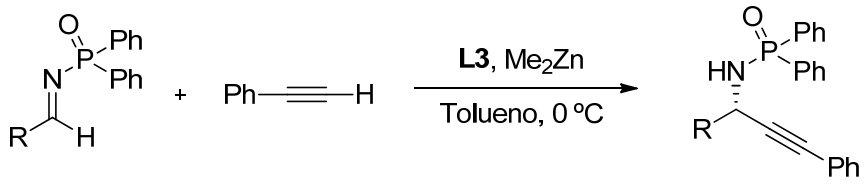
2.3.3. Alcance y limitaciones de la reacción

A continuación, se examinó la reacción de adición de fenilacetileno (**2a**) a varias *N*-(difenilfosfinoil)iminas **1** bajo las condiciones optimizadas (Tabla 2.3).

Las diferentes benzaldiminas ensayadas proporcionaron los productos de alquinilación con enantioselectividades entre buenas y muy buenas, independientemente de la naturaleza electrónica o estérica de los sustituyentes en el anillo aromático de la imina (Tabla 2.3, Entrada 1-8). Tanto los sustituyentes electrón-dadores (Me, MeO), como los electrón-aceptores (F, Cl), así como la sustitución en *orto*, *meta* y *para* fueron bien toleradas. Es destacable que las arilaldiminas con un sustituyente en la posición *orto* proporcionaron el producto de alquinilación con rendimiento moderado y buena enantioselectividad (Tabla 2.3, Entradas 7-8). Resulta particularmente interesante la reacción de fenilacetileno (**2a**) con *N*-(difenilfosfinoil)-2-metil benzaldimina (**1h**), la cual dio, con nuestro sistema catalítico, el producto **3ha** con un 71% de rendimiento y una enantioselectividad del 86% *ee*, frente a un 72% de rendimiento y 33% *ee* con el sistema catalítico descrito por Wang.[53]

La *N*-(difenilfosfinoil)imina **1k** voluminosa derivada de 2-naftilcarbaldehído proporcionó la correspondiente amida propargílica **3ka** con un buen valor de exceso enantiomérico (76%) (Tabla 2.3, Entrada 9).

Tabla 2.3. Adición enantioselectiva de fenilacetileno (**2a**) a *N*-(difenilfosfinoil)iminas **1**.[a]



1 **2a** **3**

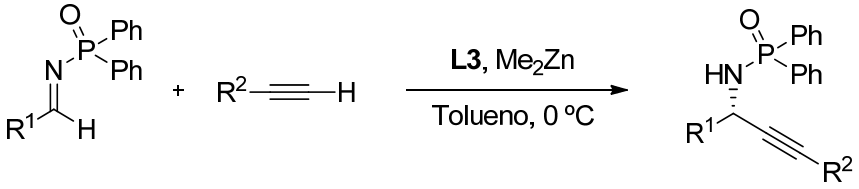
Entrada	1	R	t (h)	3	R (%)[b]	*ee* (%)[c]
1	**1a**	Ph	30	**3aa**	81	84
2	**1b**	4-MeC_6H_4	24	**3ba**	60	85
3	**1c**	4-$MeOC_6H_4$	30	**3ca**	54	96
4	**1d**	4-FC_6H_4	42	**3da**	67	76
5	**1e**	4-ClC_6H_4	24	**3ea**	61	65
6	**1g**	3-MeC_6H_4	48	**3ga**	59	68
7	**1h**	2-MeC_6H_4	30	**3ha**	71	86
8	**1i**	2-$MeOC_6H_4$	42	**3ia**	56	77
9	**1k**	2-naftil	48	**3ka**	62	76
10	**1m**	2-furanil	24	**3ma**	68	91
11	**1n**	2-tienil	30	**3na**	68	78
12	**1o**	3-furanil	30	**3oa**	46	83
13[d]	**1q**	$PhCH_2CH_2$	30	**3qa**	37	16

[a] **1** (0,125 mmol), **2a** (0,900 mmol), 2 M Me_2Zn en tolueno (0,750 mmol), **L3** (0,025 mmol). [b] Rendimiento tras la cromatografía de columna. [c] Determinado mediante HPLC usando fases estacionarias quirales. [d] Esta alquilimina fue preparada *in situ* a partir de la correspondiente α-amido sulfona.

También se evaluaron un conjunto de *N*-(difenilfosfinoil)arilaldiminas derivadas de aldehídos heteroaromáticos (Tabla 2.3, Entradas 10-12). Todas ellas dieron los productos de alquinilación con buenos excesos enantioméricos (78-91%). Sin embargo, la adición de fenilacetileno a la imina alquil sustituida generada *in situ* a partir de la α-amido sulfona correspondiente transcurrió con bajo rendimiento y enantioselectividad (Tabla 2.3, Entrada 13).

Por otra parte, se estudió la aplicabilidad de la reacción utilizando otros alquinos. Los resultados se muestran en la Tabla 2.4.

Tabla 2.4. Adición enantioselectiva de alquinos **2** a *N*-(difenilfosfinoil)iminas **1a** and **1h**.[a]



1 **2** **3**

Entrada	1	R^1	2	R^{2b}	t (h)	3	R (%)[c]	*ee* (%)[d]
1	**1a**	Ph	**2b**	4-$MeOC_6H_4$	20	**3ab**	69	85
2	**1a**	Ph	**2d**	4-FC_6H_4	30	**3ad**	69	91
3	**1a**	Ph	**2e**	4-ClC_6H_4	24	**3ae**	79	92
4	**1a**	Ph	**2g**	3,5-$(MeO)_2C_6H_3$	20	**3ag**	64	90
5	**1a**	Ph	**2j**	3-tienil	50	**3aj**	70	76
6	**1a**	Ph	**2l**	*n*-butil	72	**3al**	22	14
7	**1a**	Ph	**2p**	ciclopropil	48	**3ap**	38	72
8	**1h**	2-MeC_6H_4	**2b**	4-$MeOC_6H_4$	48	**3hb**	93	90
9	**1h**	2-MeC_6H_4	**2d**	4-FC_6H_4	24	**3hd**	77	93
10	**1h**	2-MeC_6H_4	**2e**	4-ClC_6H_4	48	**3he**	81	73
11	**1h**	2-MeC_6H_4	**2g**	3,5-$(MeO)_2C_6H_3$	48	**3hg**	67	85
12	**1h**	2-MeC_6H_4	**2j**	3-tienil	48	**3hj**	90	83

[a] **1** (0,125 mmol), **2** (0,900 mmol), 2 M Me_2Zn en tolueno (0,750 mmol), **L3** (0,025 mmol). [b] La numeración de los alquinos se corresponde con la indicada en el Anexo I. [c] Rendimiento tras purificación por cromatografía de columna. [d] Determinado por HPLC utilizando fases estacionarias quirales.

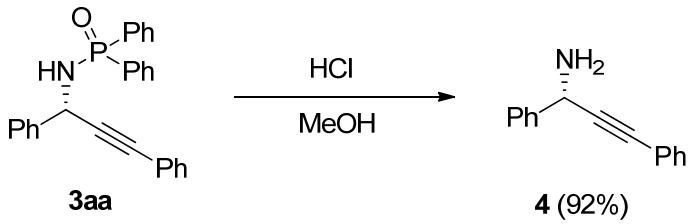
Las reacciones con 4-metoxifenilacetileno (**2b**), 4-fluorofenilacetileno (**2d**), 4-clorofenilacetileno (**2e**) y 3,5-dimetoxifenilacetileno (**2g**) con *N*-(difenilfosfinoil)benzaldimina (**1a**) condujeron a los correspondientes productos con buenas enantioselectividades (89-93%), por lo que podemos concluir que el sistema tolera bien sustituyentes de distinta naturaleza electrónica en el anillo aromático del alquino (Tabla 2.4, Entradas 1-4).

La reacción con alquinos heteroaromáticos como 3-tienilacetileno (**2j**) transcurrió con enantioselectividad moderada, 76% *ee* (Tabla 2.4, Entrada 5). La adición de alquinos alifáticos como el 1-hexino o el ciclopropilacetileno a *N*-(difenilfosfinoil)benzaldimina (**1a**) tuvo lugar con rendimientos bajos (Tabla 2.4, Entradas 6-7). No obstante, el producto de alquinilación **3ap** se obtuvo con enantioselectividad moderada.

Una de las principales ventajas que presenta el sistema catalítico que hemos identificado para la alquinilación enantioselectiva de iminas, frente a los descritos previamente es que es compatible con la utilización de sustratos cuyo anillo aromático se encuentra sustituido en la posición *orto*. Por ello, se examinó la reacción de adición de diversos alquinos aromáticos a la imina *orto* sustituida **1h**, obteniéndose los correspondientes productos de alquinilación con enantioselectividades entre moderadas y buenas (73-93%) (Tabla 2.4, Entradas 8-12).

2.3.4. Desprotección de la agrupación *N*-(difenilfosfinoil) amina

La desprotección del grupo amino en las *N*-(difenilfosfinoil)propargilaminas sintetizadas puede llevarse a cabo fácilmente mediante un tratamiento con ácido clorhídrico en metanol. Esta reacción proporcionó la amina libre **4** con un rendimiento de 92% (Esquema 2.46).

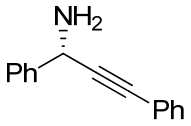


Esquema 2.46. Desprotección del grupo amino.

2.3.5. Determinación de la estereoquímica absoluta

El compuesto **4** obtenido por desprotección del grupo amino nos permitió establecer la estereoquímica absoluta del centro estereogénico formado en la reacción de alquinilación, por comparación de su poder rotatorio con el descrito para este mismo compuesto en la bibliografía[53] (Figura 2.11). La amina propargílica **4** presenta

una configuración (*S*). La estereoquímica del resto de las *N*-(difenilfosfinoil)aminas se asignó por analogía.



4

$[\alpha]_D^{20}$ = -21,7 (c = 0,9, $CHCl_3$, 84% *ee*)
Bib.[53] $[\alpha]_D^{20}$ = -27,0 (c = 0,6, $CHCl_3$, 99% *ee*)

Figura 2.11. Determinación de la estereoquímica absoluta de la amina propargílica **4**.

2.3.6. Propuesta mecanística para la alquinilación de *N*-(difenilfosfinoil)iminas

A continuación, se propone un posible ciclo catalítico para la reacción de alquinilación de *N*-(difenilfosfinoil)iminas con (*R*)-BINOL y Me_2Zn (Figura 2.12). Inicialmente se produce la desprotonación del ligando BINOL y del acetileno por parte del dimetilzinc para dar lugar a un complejo catalítico BINOL zincato-metilalquinilzinc **I**. Este complejo se coordinaría con la *N*-(difenilfosfinoil)imina para dar lugar al intermedio **II**. A continuación tendría lugar la transferencia del alquiniluro desde el metilalquinilzinc a la imina, que liberaría el producto de reacción y el BINOL-zincato **III**. Este se coordinaría con otra molécula de metilalquinilzinc, regenerando así el complejo catalítico y reiniciando el ciclo.

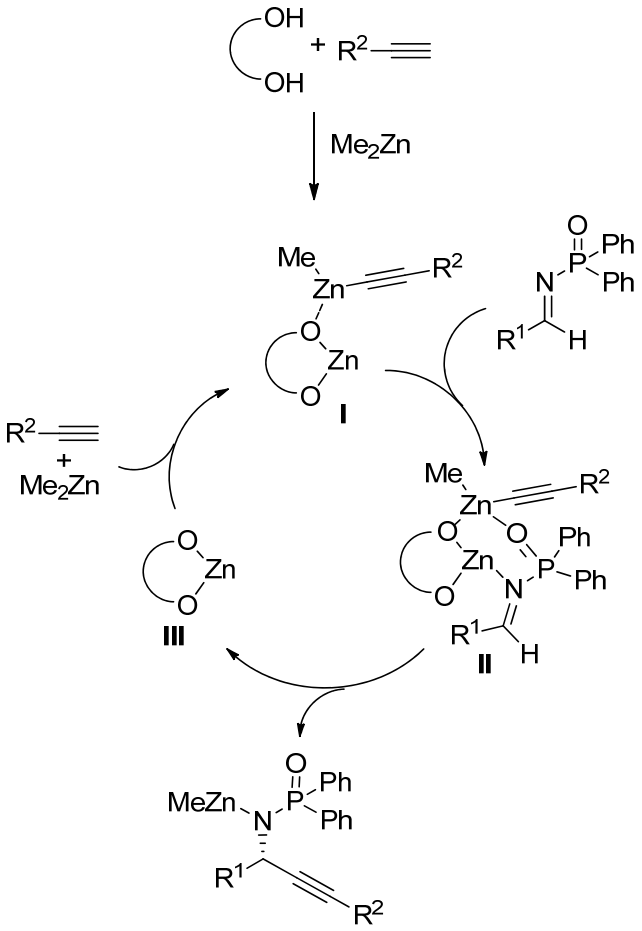


Figura 2.12. Ciclo catalítico simplificado para la alquinilación de *N*-(difenilfosfinoil)iminas en presencia de complejos de BINOL-Zn.

La molécula de alquinilmetilzinc coordinada a un oxígeno del BINOL en el intermedio **II**, se coordina también al átomo de oxígeno de la fosfinoil amida a través de un anillo de seis miembros. Esta coordinación asiste la transferencia del alquiniluro del zinc a la imina proporcionando la amida propargílica con la configuración (*S*).

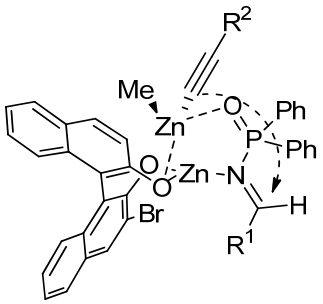


Figura 2.13. Modelo estereoquímico para la alquinilación de *N*-(difenilfosfinoil)iminas en presencia de complejos BINOL-Zn (uno de los sustituyentes en el C(3) del ligando ha sido omitido por claridad).

2.4. CONCLUSIONES

Se ha diseñado un método enantioselectivo de adición de alquinos terminales a *N*-(difenifosfinoil)iminas catalizada por un sistema formado por un ligando de tipo BINOL y Me_2Zn a 0 °C en tolueno.

El tamaño de los sustituyentes en las posiciones 3,3' del BINOL tiene una gran influencia sobre el rendimiento y la enantioselectividad de la reacción. El ligando (*R*)-(+)-3,3'-dibromo-1,1'-bi-naphtol (**L3**) proporcionó los mejores resultados.

Se han ensayado trece *N*-(difenifosfinoil)iminas aromáticas y heteroaromáticas con sustituyentes de diversa naturaleza electrónica y estérica en la reacción de alquinilación con fenilacetileno. Los correspondientes productos de alquinilación se han obtenido con rendimientos entre moderados y buenos y con enantioselectividades de moderadas a elevadas. La utilización de una *N*-(difenifosfinoil)imina alifática condujo a rendimiento y enantioselectividad bajos.

Se han utilizado cinco alquinos aromáticos de diversa naturaleza electrónica y estérica en la adición a las *N*-(difenifosfinoil)iminas derivadas del benzaldehído y del *o*-tolualdehído, proporcionando las correspondientes amidas propargílicas con buenos rendimientos y enantioselectividades elevadas. Se obtuvieron resultados moderados con la utilización de un alquino heteroaromático. Alquinos alifáticos condujeron a resultados variables.

Se ha llevado a cabo la desprotección de la agrupación *N*-(difenilfosfinoil) amina, lo cual ha permitido establecer la estereoquímica absoluta de los productos de alquinilación.

Se ha realizado una propuesta mecanística que explica la obtención de las amidas propargílicas con configuración (*S*).

2.5. SECCIÓN EXPERIMENTAL

2.5.1. Técnicas generales

2.5.1.1. Técnicas físicas y espectroscópicas

Punto de fusión

Los puntos de fusión de los productos sólidos se han determinado en tubos capilares en un aparato Büchi Punto de Fusión M-560 y en ningún caso han sido corregidos.

Poder rotatorio

La determinación de los valores de rotación óptica se han medido en un polarímetro Perkin-Elmer utilizando una lámpara de sodio (línea D, 589 nm) y una celda de 1 dm de longitud. Las concentraciones (*c*) se expresan en g/100 mL.

Resonancia Magnética Nuclear (RMN)

La mayoría de los espectros de RMN se han registrado en un espectrómetro Bruker Avance 300 DPX (300,13 MHz para RMN ^{1}H y 75,48 MHz para ^{13}C). En algunos casos, se ha utilizado un espectrómetro Bruker Avance 400.

Se ha empleado $CDCl_3$ como disolvente, tomando el residuo de disolvente no deuterado como referencia (7,26 ppm para ^{1}H y 77,00 ppm para ^{13}C). Los valores de desplazamiento químico están expresados en unidades δ (ppm) y las constantes de acoplamiento (*J*) en hertzios (Hz). La multiplicidad del carbono se ha determinado mediante experimentos DEPT. (Abreviaturas: doblete (d), multiplete (m), cuadruplete (q), singulete (s), triplete (t)).

Espectrometría de Masas

Los espectros de masas por ionización por electrospray (ESI) se registraron en un espectrómetro de masas Waters Q-TOF premier equipado con una fuente de electrospray con un voltaje capilar de 3,3 kV.

2.5.1.2. Técnicas cromatográficas

Cromatografía de capa fina (CCF)

Para llevar a cabo la cromatografía de capa fina se han utilizado placas cromatográficas de Sílica Gel Merck 60 F-254 (ref 5554 Merck) de 0,2 mm de grosor sobre soporte de aluminio. Una vez eluidas, se han observado a la luz UV y se han revelado químicamente con una disolución de 10 g de $Ce(SO_4)_2$, 25 g de ácido fosfomolíbdico y 80 mL de H_2SO_4 (conc.) en un litro de agua. Seguidamente, se han calentado hasta observar la coloración adecuada.

Cromatografía de columna flash

En la cromatografía de columna se ha utilizado Sílica Gel Merck 60, 0,040-0,063 mm de tamaño de partícula (ref 109385 Merck). La fase móvil se ha especificado en cada caso.

Cromatografía líquida de alta presión (HPLC)

Los análisis HPLC sobre fase estacionaria quiral se han desarrollado en un instrumento Agilent 1100 Series o en un instrumento Hitachi Elite Lachrom, ambos equipados con un detector L-4500 Hitachi UV diodo-array. Se han utilizado columnas CHIRALPAK AD-H (4,6 x 250 mm), CHIRALCEL OD-H (4,6 x 250 mm) y CHIRALPAK IC (4,6 x 250 mm), fabricadas por Daicel. Las muestras se han inyectado en un bucle de 20 µL y se han eluido con una mezcla de hexano: isopropanol en proporciones adecuadas con un flujo de 1 mL/minuto. Los tiempos de retención (t_r) están expresados en minutos.

2.5.1.3. Disolventes

Los disolventes utilizados para extracciones y eluciones en cromatografía de capa fina y columna son de grado técnico, convenientemente destilados. Para la cromatografía de HPLC, se han utilizado disolventes de calidad HPLC. Los disolventes utilizados en las reacciones se han secado y purificado siempre que ha sido necesario. El CH_2Cl_2 y el tolueno se han secado sobre CaH_2 y destilado en atmósfera de nitrógeno.

El THF y Et_2O se han destilado sobre Na/benzofenona bajo atmósfera de nitrógeno. El hexano se seca y se destila sobre CaH_2.

2.5.1.4. Reactivos

Todos los reactivos adquiridos comercialmente se han utilizado sin purificación previa.

2.5.1.5. Reacciones

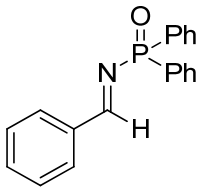
Las reacciones se llevaron a cabo bajo atmósfera de nitrógeno en matraces de fondo redondo secados en estufa durante toda la noche a 120 °C.

2.5.2. Procedimientos generales de síntesis y caracterización de nuevos productos

2.5.2.1. Síntesis y caracterización de N-(difenilfosfinoil)-iminas 1

Se añadió difenilfosfinamida (1,00 g, 4,6 mmol) y diclorometano (50 mL) en un matraz de fondo redondo de 250 mL y se enfrió a 0 °C bajo atmósfera de nitrógeno. A continuación, se añadió trietilamina (1,93 mL, 4,6 mmol), tetracloruro de titanio (0,30 mL, 2,8 mmol) y aldehído (4,6 mmol). Se dejó que la mezcla de reacción alcanzara temperatura ambiente y, tras 1,5 h de agitación, se filtró a gravedad para eliminar el óxido de titanio. El filtrado se recogió y el disolvente se eliminó a presión reducida en el rotavapor. El residuo se trató con dietil éter (40 mL) a reflujo y se filtró para eliminar el cloruro de trietilamonio. El filtrado de este proceso se recogió y el disolvente se eliminó a presión reducida en el rotavapor. El residuo sólido resultante se purificó mediante cromatografía de columna flash sobre sílica gel empleando como eluyente una mezcla de hexano:AcOEt, 4:6 para dar el producto **1**. Debido a que las *N*-(difenilfosfinoil)iminas **1** habían sido descritas con anterioridad,[56] solo se caracterizaron mediante ^{1}H RMN.

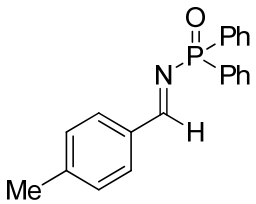
(*E*)-*N*-(difenilfosfinoil)benzaldimina (1a)



1a

Sólido blanco; ^{1}H RMN (300 MHz, $CDCl_3$) δ 9.33 (d, *J* = 32.0 Hz, 1H), 8.03-7.91 (m, 6H), 7.61-7.55 (m, 1H), 7.53-7.41 (m, 8H).

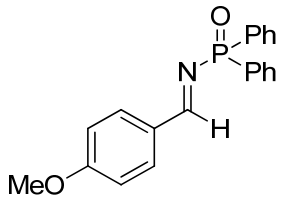
(*E*)-*N*-(difenilfosfinoil)-*p*-tolilaldimina (1b)



1b

Sólido amarillo pálido; ^{1}H RMN (300 MHz, $CDCl_3$) δ 9.28 (d, *J* = 32.2 Hz, 1H), 7.97-7.89 (m, 6H), 7.50-7.41 (m, 6H), 7.31 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 3H).

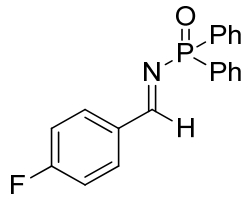
(*E*)-*N*-(difenilfosfinoil)-4-metoxifenilaldimina (1c)



1c

Sólido amarillo; ^{1}H RMN (300 MHz, $CDCl_3$) δ 9.22 (d, *J* = 32.1 Hz, 1H), 7.98-7.89 (m, 6H), 7.49-7.40 (m, 6H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H).

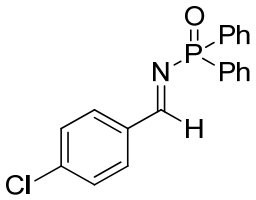
(*E*)-*N*-(difenilfosfinoil)-4-fluorofenilaldimina (1d)



1d

Sólido blanco; ^{1}H RMN (300 MHz, $CDCl_3$) δ 9.27 (d, *J* = 31.8 Hz, 1H), 8.06-7.99 (m, 2H), 7.97-7.89 (m, 4H), 7.54-7.42 (m, 6H), 7.19 (t, *J* = 8.6 Hz, 2H).

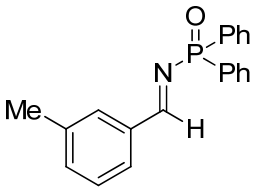
(*E*)-*N*-(difenilfosfinoil)-*4*-clorofenilaldimina (1e)



1e

Sólido blanco; ^{1}H RMN (300 MHz, $CDCl_3$) δ 9.28 (d, *J* = 31.7 Hz, 1H), 7.96-7.89 (m, 6H), 7.54-7.42 (m, 8H).

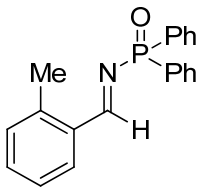
(*E*)-*N*-(difenilfosfinoil)-*m*-tolilaldimina (1g)



1g

Sólido blanco; ^{1}H RMN (300 MHz, $CDCl_3$) δ 9.29 (d, *J* = 32.2 Hz, 1H), 7.98-7.91 (m, 4H), 7.83 (s a, 1H), 7.79 (td, *J* = 4.5, 1.4 Hz, 1H), 7.53-7.41 (m, 6H), 7.39 (d a, *J* = 5.1 Hz, 2H), 2.43 (s, 3H).

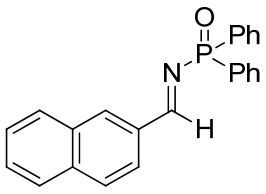
(*E*)-*N*-(difenilfosfinoil)-*o*-tolilaldimina (1h)



1h

Sólido blanco; ^{1}H RMN (300 MHz, $CDCl_3$) δ 9.62 (d, *J* = 32.6 Hz, 1H), 8.15 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.99-7.92 (m, 4H), 7.52-7.40 (m, 7H), 7.32 (t a, *J* = 7.4 Hz, 1H), 7.24 (d a, *J* = 7.3 Hz, 1H), 2.67 (s, 3H).

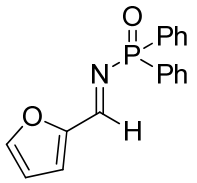
(*E*)-*N*-(difenilfosfinoil)-naftalen-2-il-aldimina (1k)



1k

Sólido blanco; ^{1}H RMN (300 MHz, $CDCl_3$) δ 9.47 (d, *J* = 31.9 Hz, 1H), 8.33 (s a, 1H), 8.22 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.02-7.88 (m, 7H), 7.63-7.54 (m, 2H), 7.51-7.43 (m, 6H).

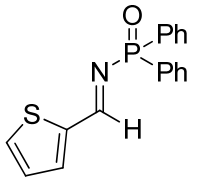
(*E*)-*N*-(difenilfosfinoil)-furan-2-il-aldimina (1m)



1m

Sólido marrón; ^{1}H RMN (300 MHz, $CDCl_3$) δ 9.47 (dd, *J* = 32.8, 0.6 Hz, 1H), 7.95-7.88 (m, 4H), 7.71-7.70 (m, 1H), 7.52-7.40 (m, 6H), 7.19 (d, *J* = 3.5 Hz, 1H), 6.60 (dd, *J* = 3.6, 1.7 Hz, 1H).

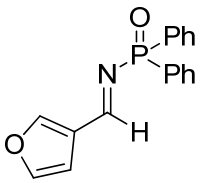
(*E*)-*N*-(difenilfosfinoil)-tien-2-il-aldimina (1n)



1n

Sólido marrón; ^{1}H RMN (300 MHz, $CDCl_3$) δ 9.33 (dd, *J* = 30.9, 0.7 Hz, 1H), 7.95-7.88 (m, 4H), 7.67 (d, *J* = 4.1 Hz, 2H), 7.53-7.41 (m, 6H), 7.19-7.16 (m, 1H).

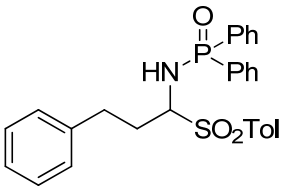
(*E*)-*N*-(difenilfosfinoil)-furan-3-il-aldimina (1o)



1o

Sólido marrón; ^{1}H RMN (300 MHz, $CDCl_3$) δ 9.24 (dt, *J* = 31.8, 0.6 Hz, 1H), 8.00-7.99 (m, 1H), 7.94-7.86 (m, 4H), 7.52-7.41 (m, 7H), 6.97 (dt, *J* = 1.9, 0.6 Hz, 1H).

2.5.2.2. Síntesis y caracterización del precursor de N-(difenilfosfinoil)-2-feniletil aldimina (7)[57]



7

Sobre una suspensión de *P,P*-difenilfosfinamida (1,00 g, 4,6 mmol) y ácido sulfínico (1,08 g, 6,9 mmol) en dietil éter anhidro (40 mL) se añadió dihidrocinamaldehído (6,9 mmol, 6,9 mmol) a temperatura ambiente. La mezcla se agitó durante 15 h, durante las cuales se fue formando un precipitando blanco. Cuando la reacción se completó, la mezcla de reacción se filtró y el sólido blanco se lavó con dietil éter anhidro (15 mL) y se secó a vacío para obtener el producto **7**.

^{1}H RMN (300 MHz, DMSO-d_6) δ 7.82-7.76 (m, 2H), 7.56-7.43 (m, 10H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.21-7.18 (m, 3H), 7.00 (d, *J* = 6.9 Hz, 2H), 6.45 (t, *J* = 11.6 Hz, 1H), 4.39 (tdd, *J* =

21.2, 21.2, 2.1 Hz, 1H), 2.69-2.64 (m, 1H), 2.53-2.46 (m, 1H), 2.35 (s, 3H), 2.31-2.24 (m, 1H), 1.96-1.89 (m, 1H).

^{13}C RMN (75.5 MHz, DMSO-d_6) 145.3 (C), 141.4 (C), 136.0 (C), 134.3 (CH), 133.4 (CH), 132.6 (d, *J* = 2.4 Hz, C), 132.4 (d, *J* = 2.4 Hz, C), 132.3 (CH), 132.1 (CH), 132.0 (CH), 130.5 (CH), 129.4 (CH), 129.3 (CH), 129.2 (CH), 129.0 (CH), 128.9 (CH), 127.0 (CH), 72.9 (CH), 31.9 (CH_2), 31.7 (CH_2), 22.0 (CH_3).

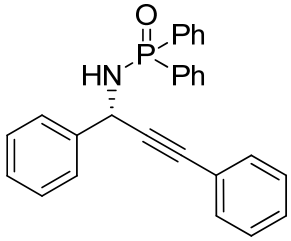
2.5.2.3. Síntesis y caracterización de P,P-difenilfosfinamidas propargílicas 3

Procedimiento general para la alquinilación enantioselectiva de N-(difenilfosfinoil)iminas 1

Se añadió gota a gota una disolución de Me_2Zn en tolueno (0,375 mL, 0,750 mmol) sobre una disolución de ligando **L3** (11,2 mg, 0,025 mmol) y alquino **2** (0,900 mmol) en tolueno (0,2 mL) a temperatura ambiente bajo atmósfera de nitrógeno. Tras agitar durante 1 h, la mezcla de reacción se enfrió a 0 °C. Tras 15 min, una disolución de imina **1** (0,125 mmol) en tolueno (0,4 mL) se añadió vía jeringuilla. La disolución se agitó hasta que la reacción se completó (CCF). La mezcla de reacción se hidrolizó con HCl 1 M (15 mL), se extrajo con CH_2Cl_2 (3×15 mL), se secó sobre $MgSO_4$ y se concentró a vacío. El producto se purificó mediante cromatografía flash en columna de sílica gel empleando como eluyente una mezcla de hexano:AcOEt para dar **3**.

La alquinilación de *N*-(difenilfosfinoil)iminas racémica se llevó a cabo siguiendo el mismo procedimiento en presencia de ligando racémico (±)-**L1**.

(*S*)-*N*-(1,3-difenilprop-2-inil)-*P*,*P*-difenilfosfinamida (3aa)



3aa

El exceso enantiomérico (84%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 13.9 min, enantiómero minoritario t_r = 12.5 min.

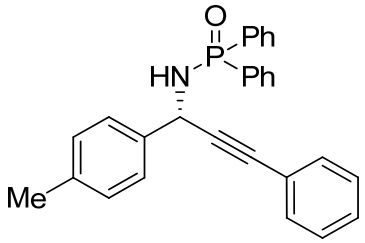
Mp 173-175 °C; $[\alpha]_D^{20}$ -63.1 (*c* 0.90, $CHCl_3$, 84% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.13-8.06 (m, 2H), 7.90-7.83 (m, 2H), 7.71-7.69 (m, 2H), 7.54-7.46 (m, 4H), 7.44-7.37 (m, 5H), 7.35-7.30 (m, 5H), 5.40 (t, *J* = 9.6 Hz, 1H), 3.55 (t, *J* = 9.3 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 140.4 (d, J_{C-P} = 4.5 Hz, C), 133.4 (CH), 132.8 (d, J_{C-P} = 9.8 Hz, CH), 132.1 (d, J_{C-P} = 6.8 Hz, CH), 131.7 (CH), 131.5 (CH), 129.0 (CH), 128.7 (d, J_{C-P} = 6 Hz, CH), 128.4 (d, J_{C-P} = 12 Hz, CH), 128.0 (CH), 127.4 (CH), 122.8 (C), 89.0 (d, J_{C-P} = 6 Hz, C), 85.6 (C), 47.2 (CH).

HRMS (ESI) *m/z*: 430.1336 $[M+Na]^+$, $C_{27}H_{22}NNaOP$ requiere 430.1337.

***(S)-N*-(3-fenil-1-*p*-tolilprop-2-inil)-*P*,*P*-difenilfosfinamida (3ba)**



3ba

El exceso enantiomérico (85%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 16.7 min, enantiómero minoritario t_r = 15.0 min.

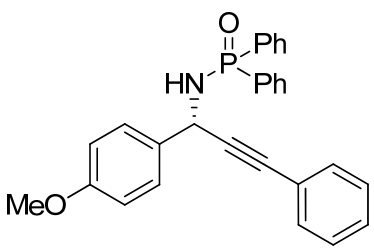
Mp 183-185 °C; $[\alpha]_D^{20}$ -60.4 (*c* 0.79, $CHCl_3$, 85% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.12-8.01 (m, 2H), 7.91-7.89 (m, 2H), 7.58-7.53 (m, 2H), 7.52-7.42 (m, 4H), 7.42-7.34 (m, 4H), 7.32-7.26 (m, 3H), 7.15 (d, *J* = 7.9 Hz, 2H), 5.34 (d, *J* = 9.31 Hz, 1H), 3.64 (s a, 1H), 2.32 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 137.7 (C), 137.4 (d, J_{C-P} = 4.6 Hz, C), 132.9 (d, J_{C-P} = 47.0 Hz, C), 132.8 (CH), 132.7 (CH), 132.1 (CH), 132.00 (CH), 131.96 (CH), 131.8 (CH) (d, J_{C-P} = 9.9 Hz, C), 131.6 (CH), 131.2 (d, *J* = 49.0 Hz, C), 129.3 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 127.2 (CH), 122.7 (C), 89.0 (d, *J* = 6.5 Hz, C), 85.4 (C), 46.9 (CH), 21.1 (CH_3).

HRMS (ESI) *m/z*: 444.1483 $[M+Na]^+$, $C_{28}H_{24}NNaOP$ requiere 444.1493.

***(S)-N*-(1-(4-metoxifenil)-3-fenilprop-2-inil)-*P*,*P*-difenilfosfinamida (3ca)**



3ca

El exceso enantiomérico (96%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-

^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 19.9 min, enantiómero minoritario t_r = 15.7 min.

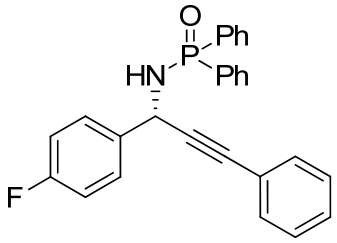
Mp 187-189 °C; $[\alpha]_D^{20}$ -62.6 (*c* 1.06, $CHCl_3$, 96% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.12-8.02 (m, 2H), 7.89-7.79 (m, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 7.52-7.42 (m, 4H), 7.41-7.34 (m, 4H), 7.33-7.26 (m, 3H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.34 (t, *J* = 9.7 Hz, 1H), 3.78 (s, 3H), 3.54 (t, *J* = 9.1 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 159.2 (C), 133.4 (C), 132.8 (CH), 132.7 (CH), 132.5 (d, J_{C-P} = 4.3 Hz, C), 132.0 (d, *J* = 2.9 Hz, CH), 131.9 (d, *J* = 2.8 Hz, CH), 131.8 (d, J_{C-P} = 9.8 Hz, CH), 131.6 (CH), 128.6 (CH), 128.39 (CH), 128.37 (CH), 128.34 (CH), 128.2 (CH), 122.7 (C), 113.9 (CH), 89.0 (d, J_{C-P} = 6.2 Hz, C), 85.3 (C), 55.3 (CH_3), 46.6 (CH).

HRMS (ESI) *m/z*: 438.1621 $[M+H]^+$, $C_{28}H_{25}NO_2P$ requiere 438.1617.

(*S*)-*N*-(1-(4-fluorofenil)-3-fenilprop-2-inil)-*P*,*P*-difenilfosfinamida (3da)



3da

El exceso enantiomérico (76%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 14.5 min, enantiómero minoritario t_r = 11.3 min.

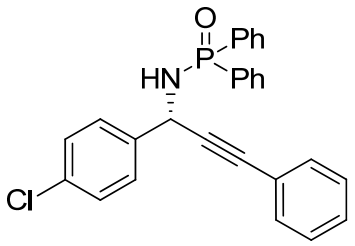
Mp 174-175 °C; $[\alpha]_D^{20}$ -55.5 (*c* 1.04, $CHCl_3$, 76% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.12-8.02 (m, 2H), 7.88-7.79 (m, 2H), 7.71-7.63 (m, 2H), 7.55-7.28 (m, 11H), 7.02 (t, *J* = 8.7 Hz, 2H), 5.37 (t, *J* = 8.6 Hz, 1H), 3.73 (t a, *J* = 8.1 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 162.3 (d, J_{C-F} = 246.5 Hz, C), 136.1 (dd, J_{C-P} = J_{C-F} = 3.6 Hz, C), 133.1 (C), 132.8 (CH), 132.7 (CH), 132.1 (d, J_{C-P} = 2.8 Hz, CH), 132.0 (d, J_{C-P} = 2.7 Hz, CH), 131.8 (CH), 131.7 (CH), 131.6 (CH), 131.4 (C), 130.7 (C), 129.2 (CH), 129.1 (CH), 128.6 (d, *J* = 3.3 Hz, CH), 128.5 (CH), 128.4 (d, *J* = 3.2 Hz, CH), 128.3 (CH), 122.4 (C), 115.36 (d, J_{C-F} = 21.6 Hz, C), 88.5 (d, J_{C-P} = 6.7 Hz, C), 85.7 (C), 46.5 (CH).

HRMS (ESI) *m/z*: 426.1420 $[M+H]^+$, $C_{27}H_{21}FNOP$ requiere 426.1418.

(*S*)-*N*-(1-(4-clorofenil)-3-fenilprop-2-inil)-*P*,*P*-difenilfosfinamida (3ea)



3ea

El exceso enantiomérico (65%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 17.5 min, enantiómero minoritario t_r = 12.7 min.

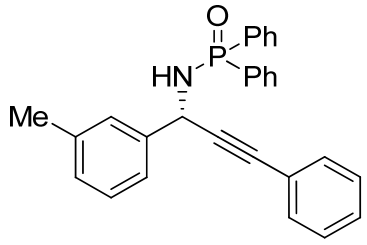
Mp 193-195 °C. $[\alpha]_D^{20}$ -46.4 (*c* 0.60, $CHCl_3$, 65% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.12-8.02 (m, 2H), 7.88-7.79 (m, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.59-7.44 (m, 4H), 7.44-7.36 (m, 4H), 7.36-7.28 (m, 5H), 5.36 (d, *J* = 9.3 Hz, 1H), 3.93-3.55 (s a, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 138.8 (d, $J_{C\text{-}P}$ = 4.0 Hz, C), 133.8 (C), 132.8 (CH), 132.7 (CH), 122.4 (C), 132.2 (d, *J* = 2.7 Hz, CH), 132.1 (d, *J* = 2.7 Hz, CH), 131.8 (CH), 131.7 (CH), 131.6 (CH), 128.8 (CH), 128.7 (CH), 128.7 (CH), 128.6 (d, $J_{C\text{-}P}$ = 3.1 Hz, CH), 128.5 (d, *J* = 2.7 Hz, CH), 128.3 (CH), 88.2 (d, $J_{C\text{-}P}$ = 6.7 Hz, C), 85.9 (C), 46.6 (CH).

HRMS (ESI) *m/z*: 464.0945 $[M+Na]^+$, $C_{27}H_{21}ClNNaOP$ requiere 464.0947.

(*S*)-*N*-(3-fenil-1-*m*-tolilprop-2-inil)-*P*,*P*-difenilfosfinamida (3ga)



3ga

El exceso enantiomérico (68%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 14.5 min, enantiómero minoritario t_r = 13.7 min.

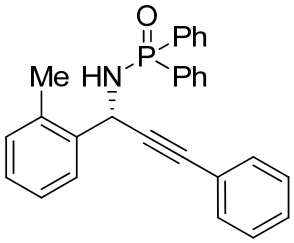
Mp 129-131 °C; $[\alpha]_D^{20}$ -42.1 (*c* 1.45, $CHCl_3$, 68% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.09-8.02 (m, 2H), 7.87-7.80 (m, 2H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 5.34 (t, *J* = 9.3 Hz, 1H), 3.59 (t, *J* = 8.2 Hz, 1H), 2.34 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 140.3 (d, $J_{C\text{-}P}$ = 4.7 Hz, C), 138.3 (C), 132.7 (d, $J_{C\text{-}P}$ = 9.9 Hz, CH), 131.8 (d, $J_{C\text{-}P}$ = 9.9 Hz, CH), 131.6 (CH), 128.7 (CH), 128.6 (CH), 128.54 (CH), 128.51 (CH), 128.4 (CH), 128.3 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 124.3 (CH), 122.7 (C), 89.0 (d, $J_{C\text{-}P}$ = 6.0 Hz, C), 85.4 (C), 47.1 (CH), 21.4 (CH_3).

HRMS (ESI) *m/z*: 444.1495 $[M+Na]^+$, $C_{28}H_{24}NNaOP$ requiere 444.1493.

***(R)*-*N*-(3-fenil-1-*o*-tolilprop-2-inil)-*P*,*P*-difenilfosfinamida (3ha)**



3ha

El exceso enantiomérico (86%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 15.4 min, enantiómero minoritario t_r = 18.1 min.

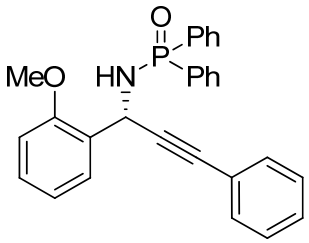
Mp 184-186 °C; $[\alpha]_D^{20}$ -57 (*c* 0.99, $CHCl_3$, 86% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.10-7.99 (m, 2H), 7.84-7.74 (m, 2H), 7.70-7.64 (m, 1H), 7.55-7.12 (m, 14H), 5.52 (t, *J* = 8.8 Hz, 1H), 3.52 (t a, *J* = 7.0 Hz, 1H), 2.41 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) [1] δ 138.7 (d, J_{C-P} = 5.6 Hz, C), 135.6 (C), 132.5 (d, J_{C-P} = 9.9 Hz, CH), 131.9 (d, J_{C-P} = 4.6 Hz, CH), 131.9 (CH), 131.8 (CH), 131.6 (CH), 130.9 (CH), 128.5 (d, J_{C-P} = 2.5 Hz, CH), 128.3 (d, J_{C-P} = 2.4 Hz, CH), 128.2 (CH), 128.1 (CH), 127.0 (CH), 126.4 (CH), 122.7 (C), 89.1 (d, J_{C-P} = 4.6 Hz, C), 85.0 (C), 44.4 (CH), 19.1 (CH_3).

HRMS (ESI) *m/z*: 422.1683 $[M+H]^+$, $C_{28}H_{25}NOP$ requiere 422.1668.

***(R)*-*N*-(1-(2-metoxifenil)-3-fenilprop-2-inil)-*P*,*P*-difenilfosfinamida (3ia).**



El exceso enantiomérico (77%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 20.9 min, enantiómero minoritario t_r = 26.5 min.

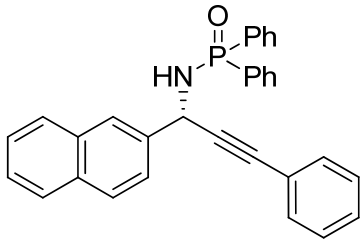
Mp 178-180 °C; $[\alpha]_D^{20}$ -68.3 (*c* 0.65, $CHCl_3$, 77% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.99-7.91 (m, 2H), 7.85-7.78 (m, 2H), 7.48-7.23 (m, 13H), 6.92 (td, *J* = 7.5, 1.1 Hz, 1H), 6.86 (dd, *J* = 8.3, 0.9 Hz, 1H), 5.47 (t a, *J* = 9.4 Hz, 1H), 4.03 (t a, *J* = 8.8 Hz, 1H), 3.78 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 156.6 (C), 133.4 (C), 132.3 (d, J_{C-P} = 9.8 Hz, CH), 132.2 (d, J_{C-P} = 9.9 Hz, CH), 131.8 (d, J_{C-P} = 2.7 Hz, CH), 131.7 (d, *J* = 2.9 Hz, CH), 131.6 (CH), 129.3 (CH), 129.1 (d, J_{C-P} = 5.0 Hz, C), 128.5 (CH), 128.3 (d, J_{C-P} = 3.1 Hz, CH), 128.2 (d, J_{C-P} = 4.4 Hz, CH), 128.0 (CH), 123.0 (C), 120.8 (CH), 111.3 (CH), 89.4 (d, J_{C-P} = 6.1 Hz, C), 83.8 (C), 55.5 (CH_3), 43.7 (CH).

HRMS (ESI) *m/z*: 438.1624 $[M+H]^+$, $C_{28}H_{25}NO_2P$ requiere 438.1617.

***(S)-N*-(1-(naftalen-2-il)-3-fenilprop-2-inil)-*P,P*-difenilfosfinamida (3ka)**



3ka

El exceso enantiomérico (76%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 15.6 min, enantiómero minoritario t_r = 14.6 min.

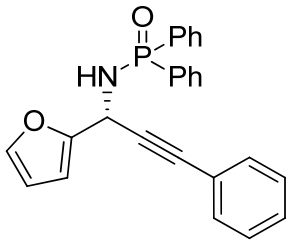
Mp 190-192 °C; $[\alpha]_D^{20}$ -33.9 (*c* 1.33, $CHCl_3$, 76% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.12-8.05 (m, 2H), 8.04 (s a, 1H), 7.88-7.79 (m, 6H), 7.51-7.30 (m, 13H), 5.54 (t a, *J* = 9.5 Hz, 1H), 3.72 (t a, *J* = 8.8 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 137.6 (d, J_{C-P} = 4.5 Hz, C), 133.1 (C), 133.0 (C), 132.8 (d, J_{C-P} = 9.9 Hz, CH), 132.1 (d, J_{C-P} = 2.8 Hz, CH), 132.0 (d, J_{C-P} = 2.7 Hz, CH), 131.9 (CH), 131.8 (CH), 131.7 (CH), 128.7 (CH), 128.6 (d, J_{C-P} = 4.1 Hz, CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 126.2 (CH), 125.9 (CH), 125.5 (CH), 122.7 (C), 88.8 (d, J_{C-P} = 6.0 Hz, C), 85.8 (C), 47.3 (CH).

HRMS (ESI) *m/z*: 480.1489 $[M+Na]^+$, $C_{31}H_{24}NNaOP$ requiere 480.1493.

***(R)-N*-(1-(furan-2-il)-3-fenilprop-2-inil)-*P,P*-difenilfosfinamida (3ma)**



3ma

El exceso enantiomérico (91%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 13.6 min, enantiómero minoritario t_r = 11.8 min.

Mp 133-136 °C; $[\alpha]_D^{20}$ -44.7 (*c* 1.03, $CHCl_3$, 91% *ee*).

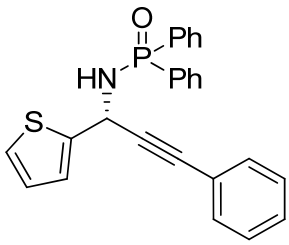
^{1}H RMN (300 MHz, $CDCl_3$) δ 8.01-7.85 (m, 4H), 7.50-7.36 (m, 9H), 7.30-7.26 (m, 3H), 6.37 (dt, *J* = 3.2, 0.8 Hz, 1H), 6.29 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.38 (t a, *J* = 9.2 Hz, 1H), 3.69 (t a, *J* = 8.4 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 152.1 (d, J_{C-P} = 5.8 Hz, C), 142.7 (CH), 132.7 (C), 132.5 (CH), 132.3 (CH), 132.2 (CH), 132.1 (d, J_{C-P} = 6.5 Hz, CH), 131.8 (CH), 131.0 (C), 128.6 (d,

J_{C-P} = 3.0 Hz, CH), 128.5 (CH), 128.4 (d, J_{C-P} = 2.9 Hz, CH), 128.2 (CH), 122.3 (C), 110.4 (CH), 107.5 (CH), 86.5 (d, J_{C-P} = 5.6 Hz, C), 84.4 (C), 41.4 (CH).

HRMS (ESI) *m/z*: 398.1307 $[M + H]^+$, $C_{25}H_{21}NO_2P$ requiere 398.1304.

***(R)-N*-(3-fenil-1-(tien-2-il)prop-2-inil)-*P,P*-difenilfosfinamida (3na)**



3na

El exceso enantiomérico (78%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 14.3 min, enantiómero minoritario t_r = 13.1 min.

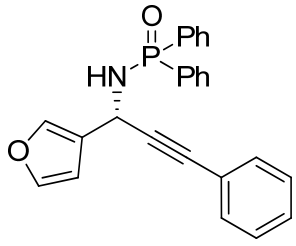
Mp 131-133 °C; $[\alpha]_D^{20}$ -58.4 (*c* 0.91, $CHCl_3$, 78% *ee*)

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.07-8.00 (m, 2H), 7.93-7.85 (m, 2H), 7.52-7.38 (m, 8H), 7.30-7.23 (m, 5H), 6.93 (dd, *J* = 5.0, 3.7 Hz, 1H), 5.55 (t a, *J* = 9.5 Hz, 1H), 3.78 (dd, *J* = 9.9, 8.1 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 144.8 (d, J_{C-P} = 6.1 Hz, C), 132.8 (C), 132.5 (d, J_{C-P} = 10.0 Hz, CH), 132.1 (d, J_{C-P} = 2.3 Hz, CH), 131.9 (d, J_{C-P} = 10.0 Hz, CH), 131.7 (CH), 131.0 (d, J_{C-P} = 16.2 Hz, C), 128.6 (d, J_{C-P} = 1.1 Hz, CH), 128.5 (CH), 128.4 (d, J_{C-P} = 0.8 Hz, CH), 128.2 (CH), 126.9 (CH), 125.9 (CH), 125.5 (CH), 122.3 (C), 88.3 (d, J_{C-P} = 5.4 Hz, C), 84.7 (C), 43.1 (CH).

HRMS (ESI) *m/z*: 414.1074 $[M+H]^+$, $C_{25}H_{21}NOPS$ requiere 414.1076.

***(R)-N*-(1-(furan-3-il)-3-fenilprop-2-inil)-*P,P*-difenilfosfinamida (3oa)**



3oa

El exceso enantiomérico (83%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 11.5 min, enantiómero minoritario t_r = 10.1 min.

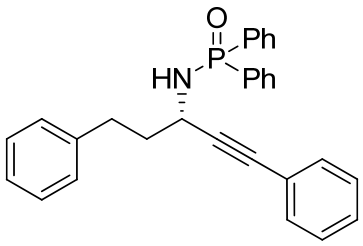
Oil; $[\alpha]_D^{20}$ -49.0 (*c* 1.21, $CHCl_3$, 83% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.10-8.04 (m, 2H), 7.92-7.85 (m, 2H), 7.58-7.32 (m, 13H), 6.70 (d, *J* = 0.9 Hz, 1H), 5.26 (t a, *J* = 9.6 Hz, 1H), 3.51 (t a, *J* = 9.3 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 143.6 (C), 140.4 (CH), 132.8 (d, J_{C-P} = 9.8 Hz, CH), 132.1 (C), 131.8 (CH), 131.7 (CH), 128.7 (d, J_{C-P} = 4.5 Hz, CH), 128.5 (d, J_{C-P} = 3.8 Hz, CH), 128.3 (CH), 126.5 (CH), 122.5 (C), 110.1 (CH), 88.3 (C), 83.6 (C), 39.8 (CH).

HRMS (ESI) *m/z*: 398.1305 $[M+H]^+$, $C_{25}H_{21}NO_2P$ requiere 398.1304.

***(S)-N*-(1,5-difenilpent-1-in-3-il)-*P,P*-difenilfosfinamida (3qa)**



3qa

El exceso enantiomérico (16%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 13.3 min, enantiómero minoritario t_r = 10.0 min.

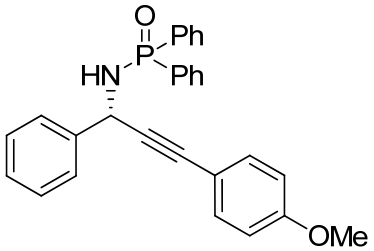
Mp 127-129 °C; $[\alpha]_D^{20}$ -9.7 (*c* 1.20, $CHCl_3$, 16% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.01-7.93 (m, 2H), 7.87-7.80 (m, 2H), 7.50-7.36 (m, 8H), 7.32-7.27 (m, 3H), 7.25-7.11 (m, 5H), 4.21-4.09 (m, 1H), 3.27 (dd, *J* = 10.2, 8.1 Hz, 1H), 2.94-2.75 (m, 2H), 2.27-2.07 (m, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 141.0 (C), 133.5 (C), 132.6 (d, J_{C-P} = 9.9 Hz), 132.0 (d, J_{C-P} = 2.7 Hz, CH), 131.7 (d, J_{C-P} = 9.9 Hz, CH), 131.7 (CH), 130.8 (C), 128.6 (CH), 128.5 (CH), 128.42 (CH), 128.39 (CH), 128.3 (CH), 128.4 (CH), 125.9 (CH), 122.8 (C), 89.7 (d, J_{C-P} = 7.4 Hz, C), 84.2 (C), 43.8 (CH), 40.3 (d, J_{C-P} = 3.7 Hz, CH_2), 32.0 (CH_2).

HRMS (ESI) *m/z*: 458.1651 $[M+Na]^+$, $C_{29}H_{26}NOPNa$ requiere 458.1650.

***(S)-N*-(3-(4-metoxifenil)-1-fenilprop-2-inil)-*P,P*-difenilfosfinamida (3ab)**



3ab

El exceso enantiomérico (85%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 20.7 min, enantiómero minoritario t_r = 16.9 min.

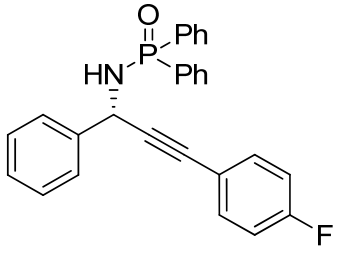
Mp 173-175 °C; $[\alpha]_D^{20}$ -67.9 (*c* 1.02, $CHCl_3$, 85% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.10-8.03 (m, 2H), 7.87-7.80 (m, 2H), 7.68-7.65 (m, 2H), 7.37-7.27 (m, 11H), 6.82 (d, *J* = 8.9 Hz, 2H), 5.36 (t, *J*= 9.6 Hz, 1H), 3.79 (s, 3H), 3.57 (t, *J* = 9.0 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 159.7 (C), 140.5 (d, J_{C-P} = 4.5 Hz, C), 133.1 (CH), 132.8 (d, J_{C-P} = 9.8 Hz, CH), 132.0 (CH), 131.97 (CH), 131.93 (CH), 131.89 (CH), 131.8 (CH), 128.6 (CH), 128.5 (d, J_{C-P} = 12.6 Hz, CH), 127.9 (CH), 126.5 (CH), 126.3 (CH), 114.8 (C), 113.8 (CH), 87.4 (d, J_{C-P} = 6.1 Hz, C), 85.5 (C), 55.3 (CH_3), 47.2 (CH).

HRMS (ESI) *m/z*: 460.1448 $[M+Na]^+$, $C_{28}H_{24}NNaO_2P$ requiere 460.1442.

***(S)-N*-(3-(4-fluorofenil)-1-fenilprop-2-inil)-*P,P*-difenilfosfinamida (3ad)**



3ad

El exceso enantiomérico (91%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 16.6 min, enantiómero minoritario t_r = 14.7 min.

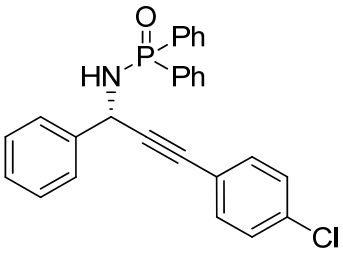
Oil; $[\alpha]_D^{20}$ -47.3 (*c* 1.42, $CHCl_3$, 91% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.08-8.01 (m, 2H), 7.87-7.80 (m, 2H), 7.65-7.62 (m, 2H), 7.51-7.28 (m, 11H), 6.97 (t, *J* = 8.8 Hz, 2H), 5.30 (t, *J* = 9.0 Hz, 1H), 3.55 (t, *J* = 7.8 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 162.5 (d, J_{C-F} = 249.6 Hz, C), 140.2 (d, J_{C-P} = 4.9 Hz, C), 133.5 (d, J_{C-P} = 8.3 Hz, CH), 132.7 (d, J_{C-P} = 9.7 Hz, CH), 132.0 (d, J_{C-P} = 2.2 Hz, CH), 131.9 (d, J_{C-P} = 9.9 Hz, CH), 128.7 (CH), 128.5 (d, J_{C-P} = 12.7 Hz, CH), 128.0 (CH), 127.2 (CH), 118.7 (d, J_{C-F} = 3.6 Hz, C), 115.5 (d, J_{C-F} = 22.0 Hz, CH), 88.5 (d, J_{C-P} = 4.5 Hz, CH), 84.5 (C), 47.1 (CH).

HRMS (ESI) *m/z*: 448.1247 $[M+Na]^+$, $C_{27}H_{21}FNNaOP$ requiere 448.1242.

***(S)-N*-(3-(4-clorofenil)-1-fenilprop-2-inil)-*P,P*-difenilfosfinamida (3ae)**



3ae

El exceso enantiomérico (92%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 18.5 min, enantiómero minoritario t_r = 16.7 min.

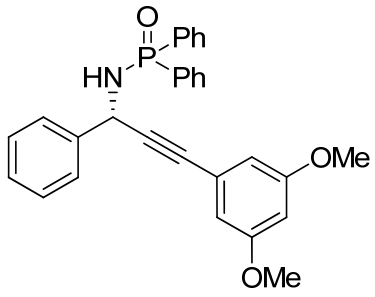
Mp 165-167; $[\alpha]_D^{20}$ -72.5 (*c* 0.32, $CHCl_3$, 92% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.07-8.00 (m, 2H), 7.86-7.78 (m, 2H), 7.64-7.62 (m, 2H), 7.51-7.24 (m, 13H), 5.30 (t, *J* = 9.1 Hz, 1H), 3.53 (t, *J* = 7.9 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 140.1 (d, J_{C-P} = 5.2 Hz, C), 134.4 (C), 132.9 (CH), 132.7 (d, J_{C-P} = 9.8 Hz, CH), 132.0 (d, J_{C-P}= 2.3 Hz, 2 CH), 131.8 (d, J_{C-P}= 9.8 Hz, CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 127.2 (CH), 121.0 (C), 89.8 (d, J_{C-P} = 6.0 Hz, C), 84.5 (C), 47.1 (CH).

HRMS (ESI) *m/z*: 464.0943 $[M+Na]^+$, $C_{27}H_{21}ClNNaOP$ requiere 464.0947.

_(S)-N_-(3-(3,5-dimetoxifenil)-1-fenilprop-2-inil)-_P,P_-difenilfosfinamida (3ag)



3ag

El exceso enantiomérico (90%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 20.7 min, enantiómero minoritario t_r = 16.9 min.

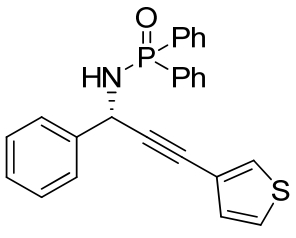
Mp 169-171 °C; $[\alpha]_D^{20}$ -63.4 (*c* 0.69, $CHCl_3$, 90% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.09-8.02 (m, 2H), 7.86-7.79 (m, 2H), 7.67-7.64 (m, 2H), 7.51-7.27 (m, 10H), 6.54 (d, *J* = 2.3 Hz, 2H), 6.43 (t, *J*= 2.3 Hz, 1H), 5.37 (t, *J* = 9.3 Hz, 1H), 3.76 (s, 6H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 160.4 (C), 140.3 (d, J_{C-P} = 4.6 Hz, C), 132.8 (d, J_{C-P} = 9.9 Hz, CH), 132.1 (CH), 132.02 (CH), 131.99 (CH), 131.8 (d, J_{C-P} = 9.8 Hz, CH), 128.5 (d, J_{C-P} = 12.6 Hz, CH), 128.0 (CH), 127.3 (CH), 123.9 (C), 109.5 (CH), 101.7 (CH), 88.4 (d, J_{C-P} = 5.9 Hz, C), 85.5 (C), 55.4 (CH_3), 47.1 (CH).

HRMS (ESI) *m/z*: 490.1557 $[M+Na]^+$, $C_{29}H_{26}NO_3PNa$ requiere 490.1548.

_(S)-N_-(1-fenil-3-(tien-3-il)prop-2-inil)-_P,P_-difenilfosfinamida (3aj)



3aj

El exceso enantiomérico (76%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 18.5 min, enantiómero minoritario t_r = 17.0 min.

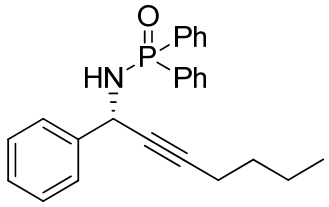
Mp 163-165 °C; $[\alpha]_D^{20}$ -51.3 (*c* 0.85, $CHCl_3$, 76% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.10-8.03 (m, 2H), 7.88-7.81 (m, 2H), 7.67-7.63 (m, 2H), 7.53-7.24 (m, 11H), 7.07 (dd, *J* = 5.1, 1.2 Hz, 1H), 5.37 (t, *J* = 9.9 Hz, 1H), 3.61 (t a, *J* = 9.3 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 140.2 (d, J_{C-P} = 5.2 Hz, C), 132.7 (d, J_{C-P} = 9.8 Hz, CH), 132.05 (d, J_{C-P} = 2.3 Hz, CH), 132.02 (d, J_{C-P}= 2.3 Hz, CH), 131.8 (d, J_{C-P}= 9.8 Hz, CH), 129.8 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.0 (CH), 127.3 (CH), 125.2 (CH), 121.6 (C), 88.3 (d, J_{C-P}= 6.0 Hz, C), 80.7 (C), 47.1 (CH).

HRMS (ESI) *m/z*: 414.1075 $[M+H]^+$, $C_{25}H_{21}NOPS$ requiere 414.1076.

***(S)-N*-(1-fenilhept-2-in-1-il)-*P,P*-difenilfosfinamida (3al)**



3al

El exceso enantiomérico (14%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 11.1 min, enantiómero minoritario t_r = 10.4 min.

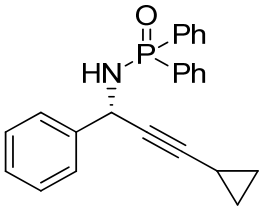
Mp 114-116 °C; $[\alpha]_D^{20}$ -5.2 (*c* 0.70, $CHCl_3$, 14% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.05-7.98 (m, 2H), 7.84-7.78 (m, 2H), 7.60-7.57 (m, 2H), 7.52-7.26 (m, 9H), 5.12 (t, *J* = 9.8 Hz, 1H), 3.38 (t, *J* = 9.0 Hz, 1H), 2.20 (td, *J* = 6.9, 2.1 Hz, 2H), 1.53-1.33 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 141.0 (d, J_{C-P} = 4.6 Hz, C), 132.7 (d, J_{C-P} = 9.8 Hz, CH), 132.0 (CH), 131.93 (CH), 131.89 (CH), 131.8 (CH), 128.5 (CH), 128.3 (CH), 127.7 (CH), 127.2 (CH), 86.3 (C), 79.7 (d, J_{C-P} = 6.2 Hz, C), 46.8 (CH), 30.7 (CH_2), 22.0 (CH_2), 18.4 (CH_2), 13.6 (CH_3).

HRMS (ESI) *m/z*: 410.1646 $[M+Na]^+$, $C_{25}H_{26}NNaOP$ requiere 410.1650.

***(S)-N*-(3-ciclopropil-1-fenilprop-2-inil)-*P,P*-difenilfosfinamida (3ap)**



3ap

El exceso enantiomérico (72%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 21.4 min, enantiómero minoritario t_r = 20.3 min.

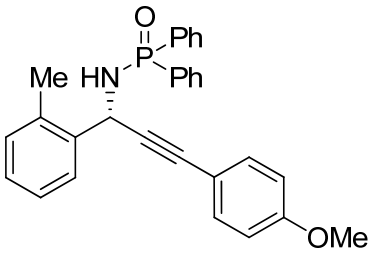
Mp 148-150 °C; $[\alpha]_D^{20}$ -19.5 (*c* 2.15, $CHCl_3$, 72% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.98-7.91 (m, 2H), 7.86-7.80 (m, 1H), 7.77-7.71 (m, 2H), 7.51-7.17 (m, 10H), 5.03 (t, *J* = 8.2 Hz, 1H), 3.38 (s a, 1H), 1.22-1.13 (m, 1H), 0.71-0.61 (m, 2H), 0.60-0.51 (m, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 140.9 (d, J_{C-P} = 4.8 Hz, C), 133.1 (d, J_{C-P} = 37.2 Hz, C), 132.7 (d, J_{C-P} = 8.9 Hz, CH), 131.9 (d, J_{C-P} = 2.9 Hz, CH), 131.8 (CH), 131.7 (CH), 131.4 (d, J_{C-P}= 39.1 Hz, C), 128.4 (CH), 128.5 (d, J_{C-P}= 12.8 Hz, CH), 128.3 (CH), 127.7 (CH), 127.2 (CH), 89.2 (C), 74.8 (d, J_{C-P} = 6.1 Hz, C), 46.8 (CH), 8.1 (CH_2), -0.47 (CH).

HRMS (ESI) *m/z*: 394.1328 $[M+Na]^+$, $C_{24}H_{22}NNaOP$ requiere 394.1337.

***(R)-N*-(3-(4-metoxifenil)-1-*o*-tolilprop-2-inil)-*P,P*-difenilfosfinamida (3hb)**



3hb

El exceso enantiomérico (90%) se determinó mediante HPLC quiral (Chiralpak IC), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 9.1 min, enantiómero minoritario t_r = 11.9 min.

Mp 167-169 °C; $[\alpha]_D^{20}$ -55.5 (*c* 1.94, $CHCl_3$, 90% *ee*).

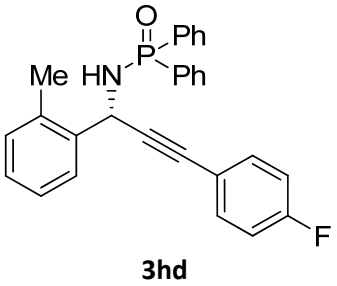
^{1}H RMN (300 MHz, $CDCl_3$) δ 8.07-8.00 (m, 2H), 7.81-7.75 (m, 2H), 7.68-7.65 (m, 1H), 7.51-7.42 (m, 4H), 7.37-7.32 (m, 2H), 7.26-7.11 (m, 5H), 6.78 (d, *J* = 8.9 Hz, 1H), 5.51 (t a, *J*= 9.0 Hz, 1H), 3.78 (s, 3H), 3.54 (t, *J* = 8.0 Hz, 1H), 2.40 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 159.5 (C), 138.9 (d, J_{C-P} = 5.6 Hz, C), 135.5 (C), 133.0 (CH), 132.5 (d, J_{C-P} = 9.8 Hz, CH), 131.9 (CH), 131.8 (d, J_{C-P} = 7.0 Hz, CH), 130.8 (CH), 128.4 (d,

J_{C-P} = 2.5 Hz, CH), 128.2 (d, J_{C-P} = 2.4 Hz, CH), 127.0 (CH), 126.3 (CH), 114.8 (C), 113.7 (CH), 87.7 (d, J_{C-P} = 4.6 Hz, C), 84.8 (C), 55.2 (CH_3), 44.4 (CH), 19.1 (CH_3).

HRMS (ESI) *m/z*: 474.1598 $[M+Na]^+$, $C_{29}H_{26}NO_2PNa$ requiere 474.1599.

***(R)*-*N*-(3-(4-fluorofenil)-1-*o*-tolilprop-2-inil)-*P,P*-difenilfosfinamida (3hd)**



3hd

El exceso enantiomérico (93%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 21.4 min, enantiómero minoritario t_r = 23.0 min.

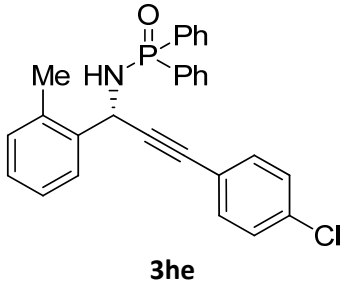
Mp 196-198 °C; $[\alpha]_D^{20}$ -57.5 (*c* 1.595, $CHCl_3$, 93% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.08-8.00 (m, 2H), 7.83-7.76 (m, 2H), 7.69-7.66 (m, 1H), 7.53-7.43 (m, 4H), 7.40-7.34 (m, 2H), 7.29-7.22 (m, 4H), 7.20-14 (m, 1H), 6.96 (t, *J* = 8.8 Hz, 2H), 5.53 (t, *J* = 8.9 Hz, 1H), 3.53 (t, *J* = 8.1 Hz, 1H), 2.41 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 162.4 (d, J_{C-F} = 249.4 Hz, C), 138.6 (d, J_{C-P} = 6.0 Hz, C), 135.5 (C), 133.5 (d, J_{C-P} = 8.3 Hz, CH), 133.0 (d, J_{C-P} = 11.2 Hz, CH), 132.5 (d, J_{C-P} = 9.9 Hz, CH), 132.0 (CH), 131.94 (CH), 131.91 (CH), 131.8 (d, J_{C-P} = 10.0 Hz, CH), 131.3 (d, J_{C-P} = 11.6 Hz, CH), 130.9 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 127.0 (CH), 126.4 (CH), 118.7 (d, J_{C-F} = 3.6 Hz, C), 115.3 (d, J_{C-F} = 22.0 Hz, CH), 88.8 (d, J_{C-P} = 5.5 Hz, C), 84.0 (C), 44.3 (CH), 19.1 (CH_3).

HRMS (ESI) *m/z*: 462.1401 $[M+Na]^+$, $C_{28}H_{23}FNOPNa$ requiere 462.1399.

***(R)*-*N*-(3-(4-clorofenil)-1-*o*-tolilprop-2-inil)-*P,P*-difenilfosfinamida (3he)**



3he

El exceso enantiomérico (73%) se determinó mediante HPLC quiral (Chiralpak IC), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 10.7 min, enantiómero minoritario t_r = 17.8 min.

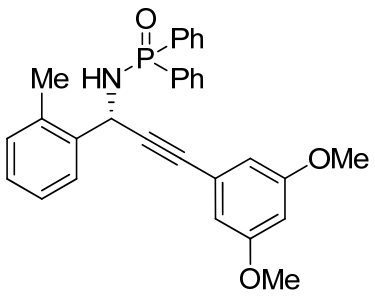
Mp 203-205 °C; $[\alpha]_D^{20}$ -49.7 (c 0.5, $CHCl_3$, 73% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.06-7.98 (m, 2H), 7.81-7.44 (m, 2H), 7.64 (m, 1H), 7.54-7.33 (m, 6H), 7.26-7.13 (m, 7H), 5.52 (t, *J* = 8.7 Hz, 1H), 3.48 (t a, *J* = 8.0 Hz, 1H), 2.40 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 138.4 (d, J_{C-P} = 5.9 Hz, C), 135.6 (C), 134.2 (C), 132.8 (CH), 132.5 (d, J_{C-P} = 9.8 Hz, CH), 132.03 (d, J_{C-P} = 2.3 Hz, CH), 132.00 (d, J_{C-P} = 2.3 Hz, CH), 131.8 (d, J_{C-P} = 9.8 Hz, CH), 130.9 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.0 (CH), 126.5 (CH), 121.1 (C), 90.0 (d, J_{C-P} = 4.4 Hz, C), 84.0 (C), 44.3 (CH), 19.1 (CH_3).

HRMS (ESI) *m/z*: 478.1102 $[M+Na]^+$, $C_{28}H_{23}ClNNaOP$ requiere 478.1104.

***(R)*-*N*-(3-(3,5-dimetoxifenil)-1-*o*-tolilprop-2-inil)-*P,P*-difenilfosfinamida (3hg)**



3hg

El exceso enantiomérico (85%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 24.2 min, enantiómero minoritario t_r = 27.7 min.

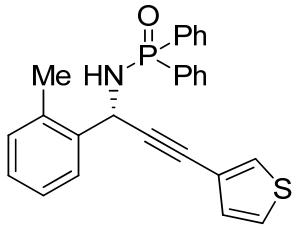
Mp 165-167 °C; $[\alpha]_D^{20}$ -50.1 (*c* 1.67, $CHCl_3$, 85% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.99-7.91 (m, 2H), 7.72-7.65 (m, 2H), 7.59-7.56 (m, 1H), 7.43-7.33 (m, 4H), 7.29-7.23 (m, 2H), 7.17-7.10 (m, 2H), 7.07-7.03 (s, 1H), 6.36 (d, *J* = 2.3 Hz, 2H), 6.32 (t, *J* = 2.3 Hz, 1H), 5.44 (t, *J* = 9.1 Hz, 1H) 3.65 (s, 6H), 3.46 (t, *J* = 8.3 Hz, 1H), 2.32 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 160.3 (C), 138.6 (d, J_{C-P} = 5.5 Hz, C), 135.5 (CH), 133.0 (d, J_{C-P} = 24.3 Hz, C), 132.5 (d, J_{C-P} = 9.9 Hz, CH), 131.91 (CH), 131.88 (CH), 131.84 (CH), 131.7 (CH), 131.3 (d, J_{C-P} = 24.5 Hz, C), 130.8 (CH), 128.4 (d, J_{C-P} = 2.6 Hz, CH), 128.3 (d, J_{C-P} = 2.4 Hz, CH), 128.1 (CH), 127.0 (CH), 126.4 (CH), 124.0 (C), 109.3 (CH), 101.7 (CH), 88.7 (d, J_{C-P} = 4.7 Hz, C), 84.8 (C), 55.3 (CH_3), 44.3 (CH), 19.1 (CH_3).

HRMS (ESI) *m/z*: 504.1705 $[M+Na]^+$, $C_{30}H_{28}NO_3PNa$ requiere 504.1704.

***(R)-N*-(3-(tien-3-il)-1-*o*-tolilprop-2-inil)-*P,P*-difenilfosfinamida (3hj)**



3hj

El exceso enantiomérico (83%) se determinó mediante HPLC quiral (Chiralpak AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 22.05 min, enantiómero minoritario t_r = 23.60 min.

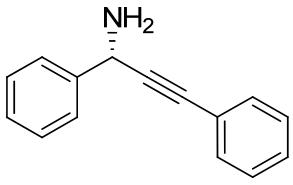
Mp 181-183 °C; $[\alpha]_D^{20}$ -53.8 (*c* 1.13, $CHCl_3$, 83% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.05-7.98 (m, 2H), 7.81-7.74 (m, 2H), 7.65 (dd, *J* = 6.3, 2.7 Hz, 2H), 7.54-7.12 (m, 10H), 6.96 (dd, *J* = 5.1, 1.2 Hz, 1H), 5.50 (t, *J* = 9.0 Hz, 1H), 3.54 (t a, *J*= 7.8 Hz, 1H), 2.34 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 138.6 (d, J_{C-P}= 5.5 Hz, C), 135.5 (C) 132.5 (d, J_{C-P}= 9.8 Hz, CH), 131.9 (d, J_{C-P}= 2.7 Hz, 2CH), 131.8 (d, J_{C-P}= 9.8 Hz, CH), 130.8 (CH), 129.8 (CH), 128.8 (CH), 128.5 (CH), 128.30 (CH), 127.29 (CH), 127.0 (CH), 126.4 (CH), 125.0 (CH), 121.7 (C), 88.6 (d, J_{C-P}= 4.5 Hz, C), 80.2 (C), 44.4 (CH), 19.1 (CH_3).

HRMS (ESI) *m/z*: 428.1240 $[M+H]^+$, $C_{26}H_{23}NOPS$ requiere 428.1238.

2.5.2.4. Síntesis y caracterización de (S)-1,3-difenilprop-2-in-1-amina (4)



4

Ácido clorhídrico concentrado (1 mL) se añadió a una disolución del compuesto **3aa** (55 mg, 0,12 mmol, 84% *ee*) en MeOH (15 mL). Tras 2 h, la mezcla de reacción se concentró a vacío, el residuo se disolvió en HCl 1 M (6 mL) y el precipitado se eliminó por filtración. El filtrado se basificó con NaOH 2 M (10 mL) y se extrajo con CH_2Cl_2 (3×20 mL). La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró a vacío. Cromatografía flash de columna en sílica gel eluyendo con hexane:EtOAc (1:9) dio el compuesto **4.**

$[\alpha]_D^{20}$ -21.7 (*c* 0.90, $CHCl_3$, 84% *ee*), bibliografía[53] $[\alpha]_D^{20}$ -27 (*c* 0.6, $CHCl_3$, 99% *ee*) para el enantiómero (*S*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.2 Hz, 2H), 7.48–7.45 (m, 2H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.33–7.30 (m, 4H), 5.03 (s, 2H), 2.31 (t, *J* = 7.5 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 142.2 (C), 128.7 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 127.7 (CH), 126.8 (CH), 123.0 (C), 91.3 (C), 84.2 (C), 48.1 (CH).

HRMS (ESI) *m/z*: 208.1129 $[M+H]^+$, $C_{15}H_{13}N$ requiere 208.1121.

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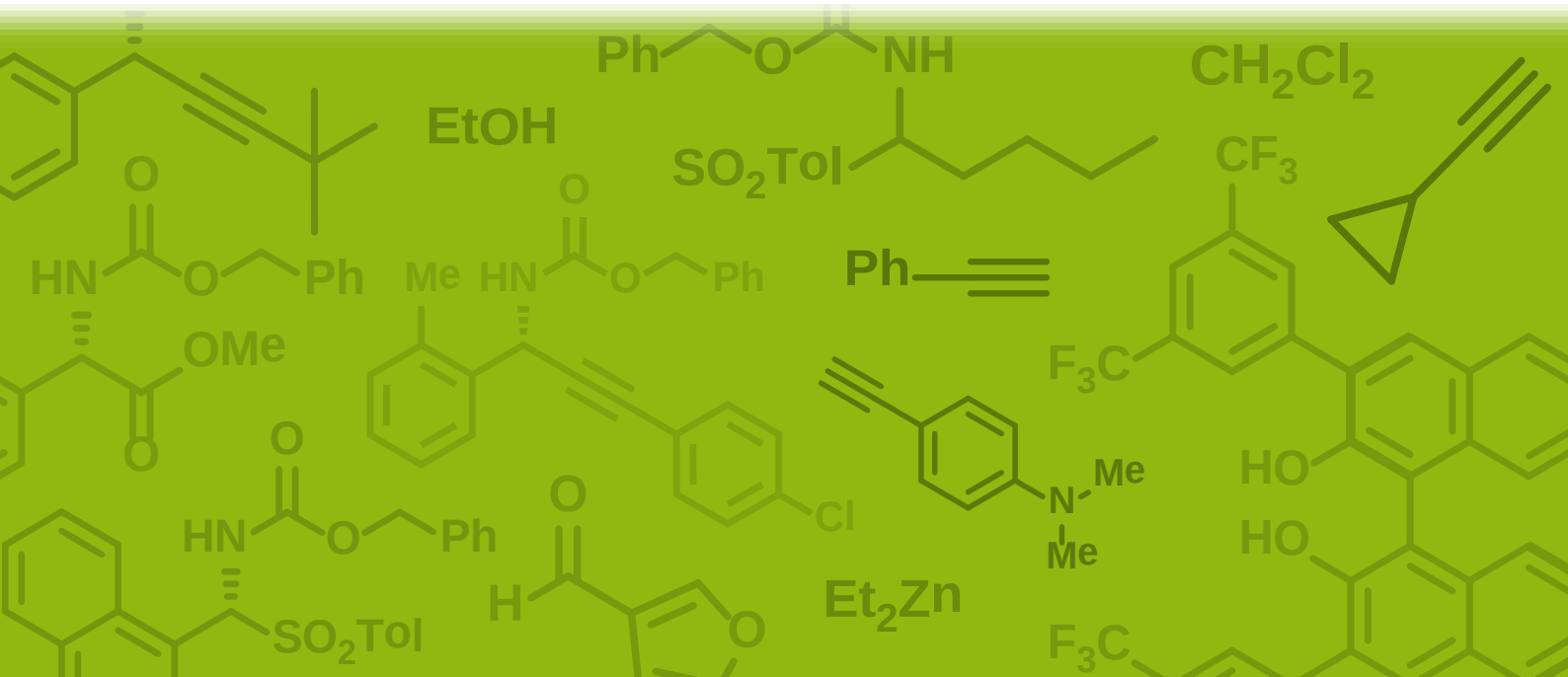
CAPÍTULO 3

Adición enantioselectiva de alquinos terminales a α-amido sulfonas



3.1. ANTECEDENTES

La adición nucleofílica al doble enlace C=N de las iminas es uno de los métodos más practicados en química orgánica para la síntesis de compuestos nitrogenados. Sin embargo, la baja electrofilia del carbono azometínico comparada con la del grupo carbonilo, convierte estas adiciones en un desafío sintético.

3.1.1. α-Amido sulfonas como precursores de iminas

Con el objetivo de superar este obstáculo, se han desarrollado dos estrategias para llevar a cabo una adición nucleofílica eficiente. La primera consiste en la utilización de sistemas nucleófilos con elevada reactividad y baja basicidad, como reactivos organocéricos, alquilcupratos, boranos, estannanos o reactivos de dialquilzinc. La segunda pretende aumentar la electrofilia del carbono azometínico. Esto puede conseguirse mediante la coordinación de un ácido de Lewis al par de electrones del nitrógeno o mediante la unión de un grupo electrón-aceptor sobre el nitrógeno (Figura 3.1), tal y como sucede en las nitronas (**a**), iones iminio (**b**), *N*-sulfiniliminas (**c**), *N*-sulfoniliminas (**d**), *N*-fosfinoiliminas (**e**) o *N*-aciliminas (**f**).

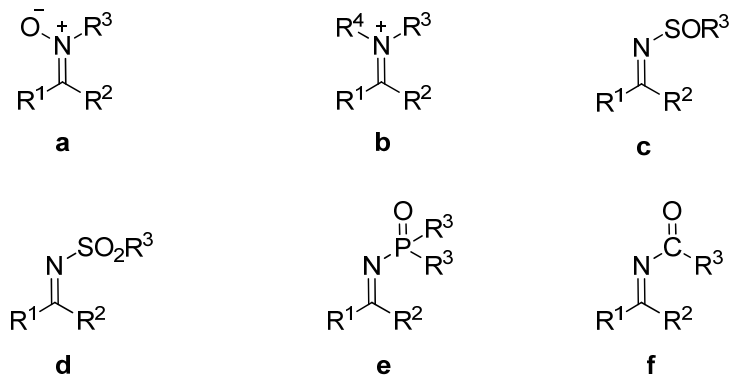
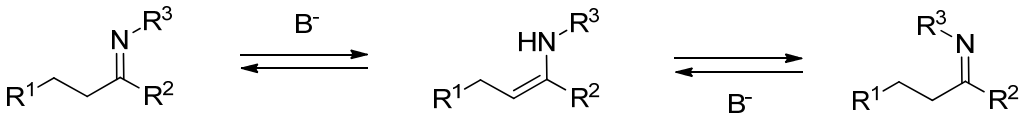


Figura 3.1. Iminas e imino derivados.

Las nitronas o *N*-óxidos de iminas y los iones iminio son más reactivos que las iminas, pero su estabilidad depende de la naturaleza de los sustituyentes que forman parte de su estructura. La principal ventaja de las *N*-sulfiniliminas es su posibilidad de inducir estereocontrol sobre las reacciones de adición aunque implican el empleo de cantidades estequiométricas de material quiral. Las *N*-sulfoniliminas y en concreto las *N*-tosiliminas derivadas de aldehídos aromáticos son sustratos estables, mientras que

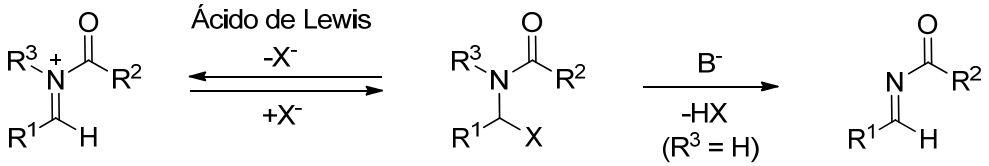
aquellas derivadas de aldehídos alifáticos deben utilizarse inmediatamente tras su preparación. Este problema también lo presentan las *N*-fosfinoiliminas, así como *N*-aciliminas.

Todas las iminas e iones iminio anteriores han demostrado su utilidad en reacciones de adición. Sin embargo, cuando se trabaja con sustratos alifáticos ocurren con frecuencia procesos adversos como su enolización. Esta reacción compite con la reacción de adición nucleofílica al carbono azometínico y, además, puede producir la isomerización del doble enlace C=N (Esquema 3.1). La utilización de los mencionados nucleófilos menos básicos disminuye la susceptibilidad a la α-enolización, pero no siempre se consigue eliminar este proceso.



Esquema 3.1. α-Enolización de iminas e isomerización del enlace C=N.

Para soslayar este problema, así como los derivados de la síntesis, purificación y almacenamiento de las iminas, se puede llevar a cabo la formación *in situ* de estas a partir de amidas o grupos funcionales relacionados que tengan un buen grupo saliente en α que pueda ser fácilmente eliminado en las condiciones adecuadas, tanto básicas como ácidas (Esquema 3.2).[1] De este modo, se pueden obtener iminas empleando una base con una fuerza apropiada para asegurar la irreversibilidad del proceso. Por otra parte, cuando se utiliza un ácido de Lewis se produce de forma reversible la formación del ion iminio cuya posición del equilibrio depende del ácido de Lewis y de la naturaleza del grupo acilo sobre el átomo de nitrógeno. La estabilidad del catión es mayor cuando el grupo protector es de tipo acilo. En particular, un carbamato estabiliza mejor al catión que una amida, debido, probablemente, a la mayor disponibilidad del par solitario del nitrógeno del carbamato.

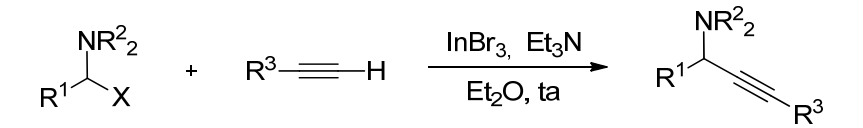


X = Cl, Br, benzotriazolil, NHCOR, OR^4, $OCOR^4$, SR^4, SO_2R^4

Esquema 3.2. Formación de iones *N*-aciliminio y *N*-aciliminas a partir de amidas y compuestos relacionados con un buen grupo saliente en α.

Se han utilizado diferentes amidas de este tipo en diversas reacciones.[1, 2] Las α-haloamidas[3] (X = Cl, Br) se han empleado ocasionalmente como sustratos electrofílicos debido a su escasa estabilidad. Los α-amidoalquil benzotriazoles[4] (X = benzotriazolilo) han participado en numerosos procesos de alquilación. Las bisamidas[5] (X = NHCOR) han sido ampliamente utilizadas en reacciones de cicloadición.

Las amidas α-oxigenadas (X = OR^4, $OCOR^4$) son los precursores más explotados por su estabilidad y su fácil preparación. El grupo de Konakahara[6] ha utilizado estos sustratos en la reacción de adición de alquinos terminales para obtener las correspondientes aminas propargílicas (Esquema 3.3). Inicialmente, estos autores estudiaron la alquinilación de aldehídos en presencia de tribromuro de indio y trietilamina. Las condiciones optimizadas para esta reacción se aplicaron a la alquinilación de aminas protegidas que presentaban un grupo metoxilo en α. También se evaluó la reacción cuando el sustrato presentaba un grupo feniltio en α a la amina. La adición de fenilacetileno condujo a rendimientos mayores que cuando se emplearon alquinos alifáticos. El trimetilsililacetileno proporcionó las correspondientes aminas propargílicas con rendimientos entre moderados y buenos. La reacción también se llevó a cabo con la amina *N*-silil protegida derivada del formaldehído con rendimientos moderados.

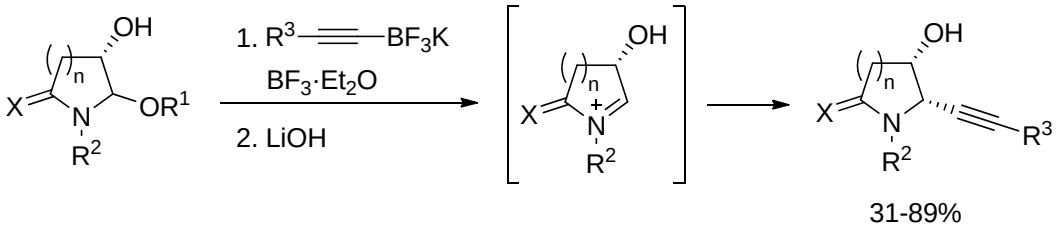


X = MeO, PhS

X = MeO (40-99%)
X = PhS (24-56%)

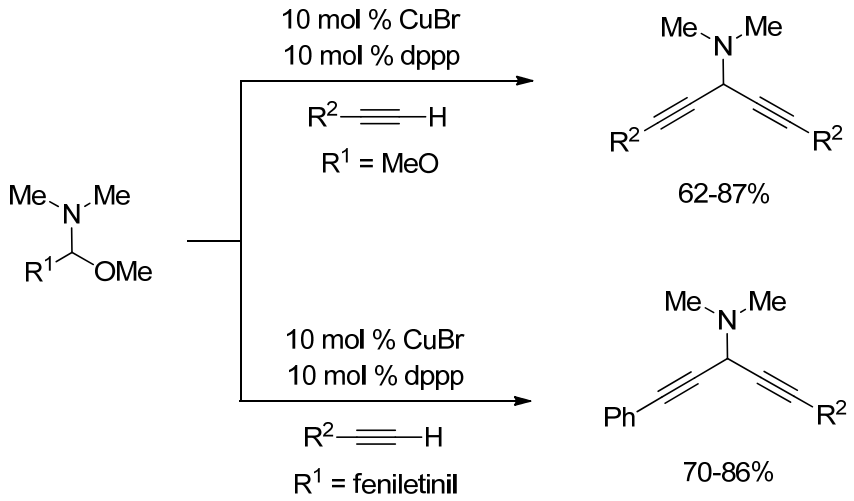
Esquema 3.3. Alquinilación de aminas protegidas con un buen grupo saliente en α.

En 2009, Pyne y colaboradores[7] llevaron a cabo la alquinilación diastereoselectiva de β-hidroxi aminas y amidas cíclicas α-oxigenadas (Esquema 3.4). Los correspondientes productos de alquinilación se transformaron después en furo[3,2-*b*]pirroles y furo[3,2-*b*]piridinas vía una reacción de cicloisomerización.



Esquema 3.4. Alquinilación diastereoselectiva de β-hidroxi aminas y amidas cíclicas α-oxigenadas.

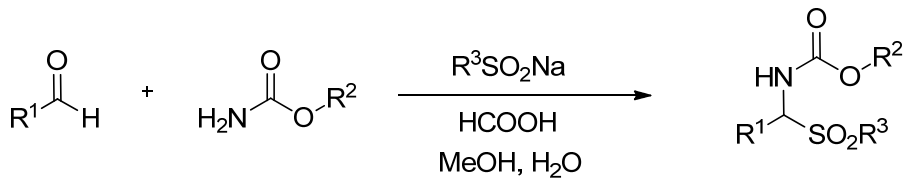
El grupo de Zhang[8] ha descrito un método para la doble alquinilación de los dialquil acetales de la *N,N*-dimetilformamida en presencia de CuBr y 1,2-bis(difenilfosfino)propano (dppp) para dar lugar a 3-amino-1,4-diinos (Esquema 3.5). La utilización de tamiz molecular de 3 Å mejoró el rendimiento de la reacción, probablemente debido a que este absorbe el MeOH producido en la formación de la sal de iminio intermedia. Los 1,4-diinos resultantes pueden emplearse como dadores de Michael en la adición a triples enlaces deficientes en electrones en presencia de $NaHCO_3$.



Esquema 3.5. Alquinilación de dialquil acetales de *N,N*-dimetilformamida.

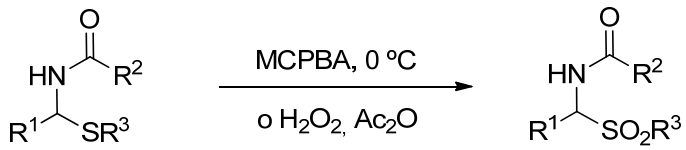
Por último, la utilización de α-amido sulfonas (X = SO_2R) como precursores de iminas ha sido ampliamente estudiada, ya que la habilidad del grupo RSO_2 para actuar como buen grupo saliente es bien conocida.[9] Además, estos sustratos son sólidos altamente estables, que no necesitan ser utilizados inmediatamente después de su preparación y purificación.

Se han desarrollado varios métodos para la preparación de α-amido sulfonas. En 1964, Engberts y Strating[10] describieron uno de los procedimientos más empleados desde entonces que consiste en el acoplamiento de tres componentes, aldehído, carbamato y sulfinato de sodio en medio ácido (Esquema 3.6). Este procedimiento también se ha aplicado utilizando otros nucleófilos nitrogenados, como amidas, ureas, tioureas, tiocarbamatos, tionocarbamatos o ditiocarbamatos. Sin embargo, cuando se utiliza difenilfosfinamida como nucleófilo nitrogenado, se debe utilizar ácido sulfínico en lugar de sulfinato de sodio y dietiléter como disolvente.



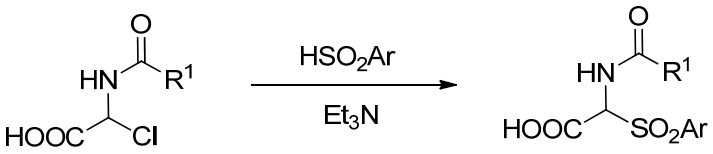
Esquema 3.6. Síntesis de α-amido sulfonas mediante reacción de acoplamiento entre aldehído, carbamato y sulfinato de sodio.

Un método alternativo de síntesis de α-amido sulfonas es la oxidación de los correspondientes sulfuros empleando MCPBA o peróxido de hidrógeno (Esquema 3.7).[11]



Esquema 3.7. Síntesis de α-amido sulfonas por oxidación de α-amido sulfuros.

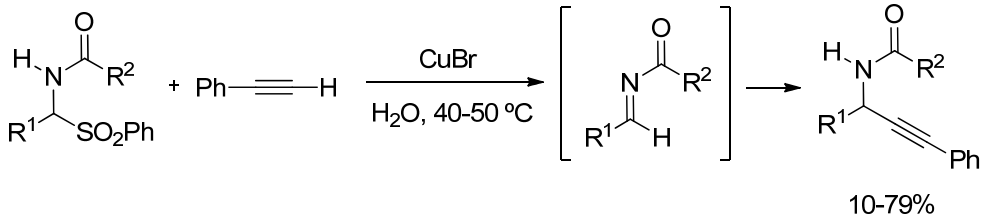
En 1978, Matthies[12] describió un procedimiento de síntesis de este tipo de sustratos consistente en la sustitución del anión cloruro de las *N*-acil-α-cloroglicinas con iones sulfinato (Esquema 3.8).



Esquema 3.8. Síntesis de α-amido sulfonas a partir de *N*-acil-α-cloroglicinas.

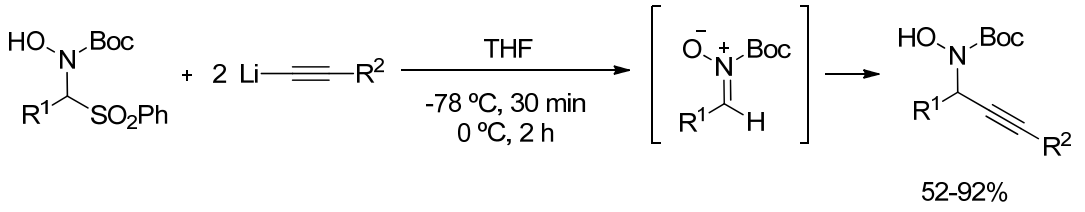
Debido a las ventajas que ofrece la síntesis de las α-amido sulfonas y a su enorme estabilidad, se ha descrito su utilización en numerosas reacciones de adición como Friedel-Crafts,[13] reacciones de Mannich, aza-Henry, reacciones de Strecker, alquilación o hidrofosfonilación, entre otras.[2]

No obstante, son escasos los ejemplos de alquinilación descritos en la bibliografía. En 2002, Li y Zhang publicaron la adición no enantioselectiva de fenilacetileno a α-amido sulfonas en presencia de CuBr en agua (Esquema 3.9).[14]



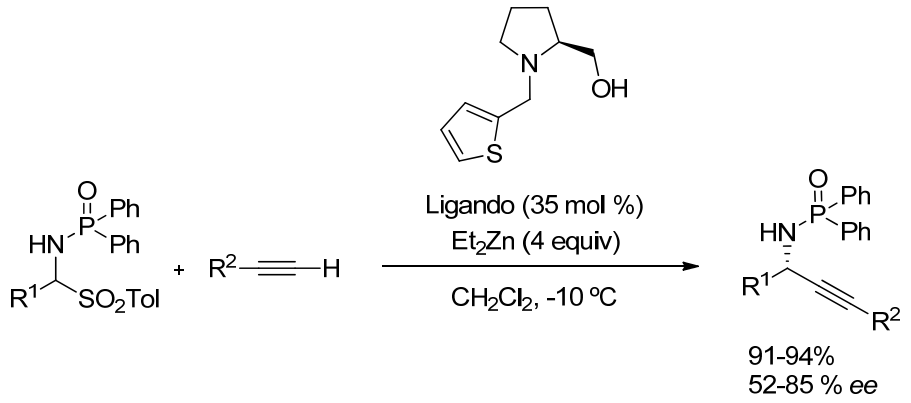
Esquema 3.9. Adición de fenilacetileno a iminas generadas *in situ* a partir de α-amido sulfonas.

Posteriormente, Denis y colaboradores[15] emplearon *N*-Boc-*N*-hidroxiaminas con un grupo sulfona en α como precursores de nitronas en la reacción de adición no enantioselectiva de alquiniluros de litio (Esquema 3.10). El tratamiento en medio ácido de las *N*-hidroxiaminas propargílicas obtenidas produjo la eliminación del grupo protector Boc, conduciendo a *N*-hidroxiaminas propargílicas. Por otra parte, la reducción del grupo N-O, que se llevó a cabo con SmI_2, condujo a *N*-Boc aminas propargílicas.



Esquema 3.10. Alquinilación de *N*-Boc nitronas generadas *in situ* a partir de las correspondientes sulfonas.

En 2010, el grupo de Wang[16] realizó la alquinilación enantioselectiva de *N*-(difenilfosfinoil)iminas aromáticas catalizada por un ligando tridentado y Et_2Zn (Esquema 2.44, p. 51). Sin embargo, la alquinilación de las iminas derivadas de aldehídos alifáticos se llevó a cabo generando estas *in situ* a partir de α-amido sulfonas (Esquema 3.11). Las correspondientes *N*-difenilfosfinoil aminas propargílicas se obtuvieron con rendimientos elevados y excesos enantioméricos moderados.



Esquema 3.11. Adición enantioselectiva de alquinos a α-*N*-(difenilfosfinoil)amido sulfonas.

3.1.2. Utilización de ciclopropilacetileno en reacciones de alquinilación de iminas

Durante los últimos años, la presencia del grupo ciclopropilo en los compuestos orgánicos ha suscitado una enorme atención debido a que presenta propiedades excepcionales de tipo estérico, electrónico y conformacional como consecuencia de su estructura tensionada. Asimismo, existe un creciente interés por este anillo de ciclopropano desde el punto de vista de la química médica y biológica, ya que se encuentra en una gran variedad de compuestos naturales como terpenos, antibióticos, feromonas o ácidos grasos (Figura 3.2). En muchos procesos, este elemento estructural

es una entidad estable presente en distintos metabolitos secundarios, mientras que en otros se trata simplemente de un intermedio en las rutas metabólicas.[17]

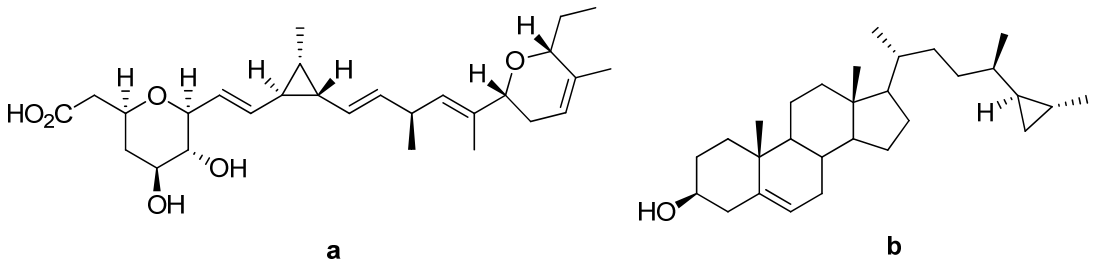


Figura 3.2. (a) Ambruticino, antibiótico antifúngico presente en el medio de fermentación de *Polyangium cellulosum* var. *fulvum* y (b) petrosterol, metabolito detectado en la esponja marina *Petrosia ficiformis*.

La presencia del grupo ciclopropilo en la naturaleza ha conducido a la búsqueda de nuevos compuestos biológicamente activos que incorporaran este anillo. Así, se han desarrollado compuestos con actividad antitumoral,[18] antiinflamatoria[19] o antimalárica,[20] entre otras. Uno de los fármacos que contiene la agrupación ciclopropilo es Prasugrel (Efient, Daiichi Sankyo Co.). Se trata de un inhibidor selectivo de la agregación plaquetaria a través de la unión irreversible de su metabolito activo a los receptores adenosin-difosfato de las plaquetas. Este ha demostrado ser más seguro, rápido y efectivo que sus análogos ticlopidina y clopidogrel (Figura 3.3).[21,22]

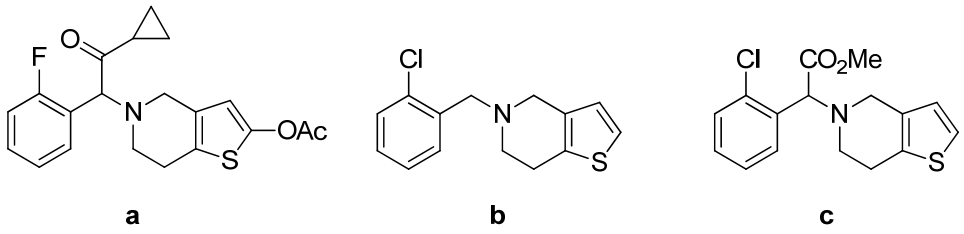


Figura 3.3. Estructuras de (a) prasugrel, (b) ticlopidina y (c) clopidogrel.

Otros fármacos que también contienen la agrupación ciclopropilacetileno en su estructura son Efavirenz[23] (Sustiva®, Bristo-Myers-Squibb) y Neviparina[24] (Viramune®, Boehringer Ingelheim). Se trata de inhibidores no nucleósidos de la transcriptasa inversa indicados en el tratamiento antiviral del virus de la inmunodeficiencia humana (VIH) (Figura 3.4).

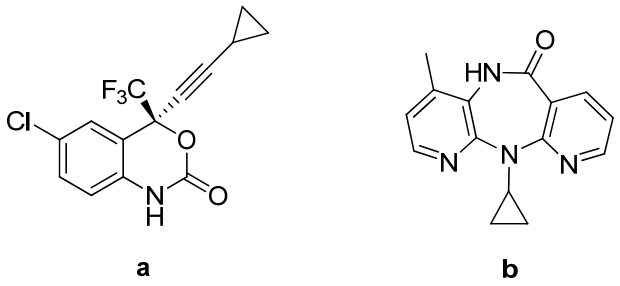
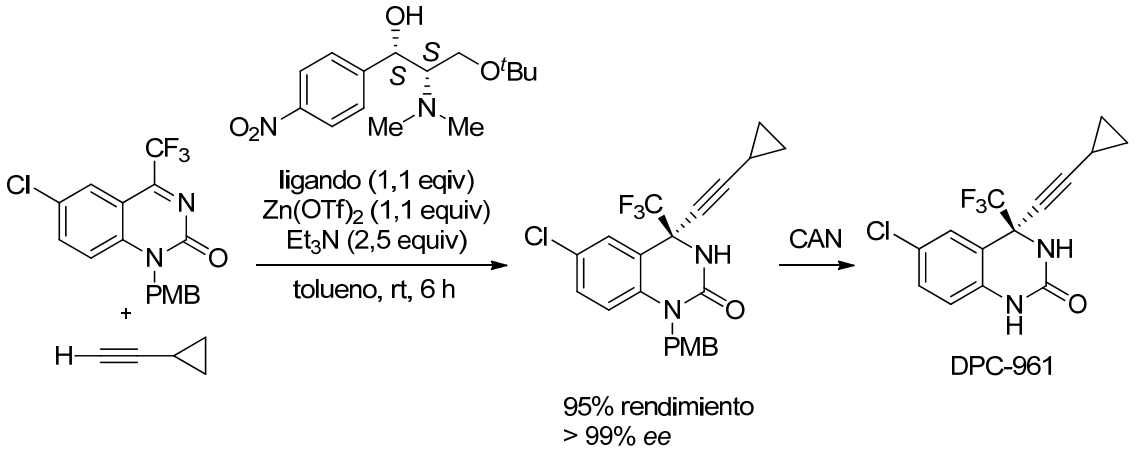


Figura 3.4. Estructuras de (a) Efavirenz y (b) Neviparina.

En 2004, Jiang y Si[25] describieron la reacción de adición enantioselectiva de ciclopropilacetileno a *N*-acilcetiminas cíclicas utilizando un ligando quiral derivado del cloranfenicol y triflato de zinc en presencia de 2,5 equivalentes de trietilamina. Este procedimiento les permitió la síntesis de DPC-961, un inhibidor no nucleósido de la transcriptasa inversa del VIH de segunda generación, análogo al Efavirenz (Esquema 3.12).

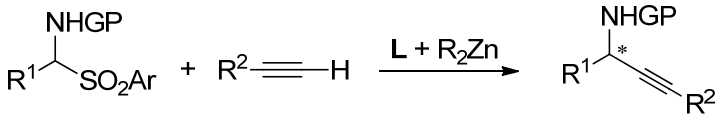


Esquema 3.12. Síntesis de DPC-961 mediante adición enantioselectiva de ciclopropilacetileno a *N*-acilcetiminas cíclicas.

3.2. OBJETIVOS

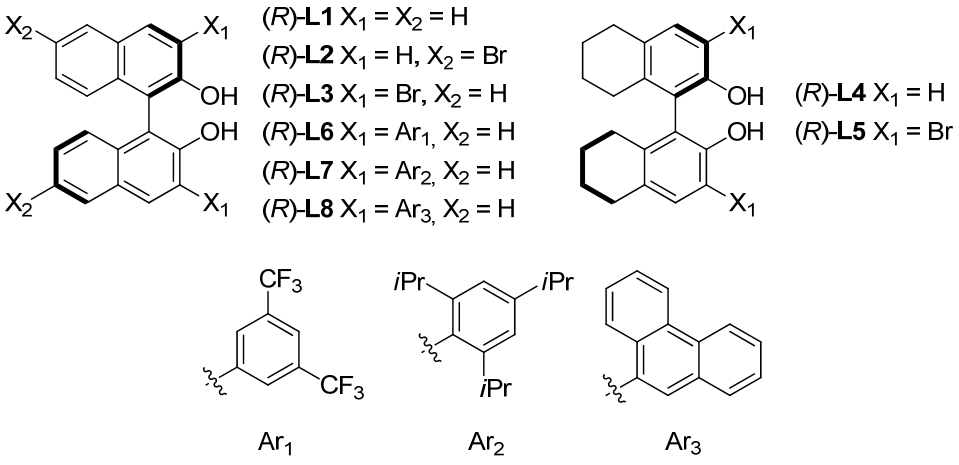
Las α-amido sulfonas han demostrado presentar enormes ventajas en diversas reacciones de adición nucleofílica enantioselectiva. Sin embargo, la reacción de alquinilación con este tipo de sustratos se encuentra poco explotada. Por ello, el objetivo de este capítulo se basa en el desarrollo de un método catalítico y enantioselectivo de adición de alquinos a α-amido sulfonas que transcurra con buenos rendimientos y excesos enantioméricos.

En concreto se llevará a cabo un estudio detallado de la reacción de adición de alquinos terminales a aciliminas, generadas *in situ* a partir de α-amido sulfonas, utilizando un sistema catalítico formado por ligandos de tipo (*R*)-BINOL y reactivos de dialquilzinc.



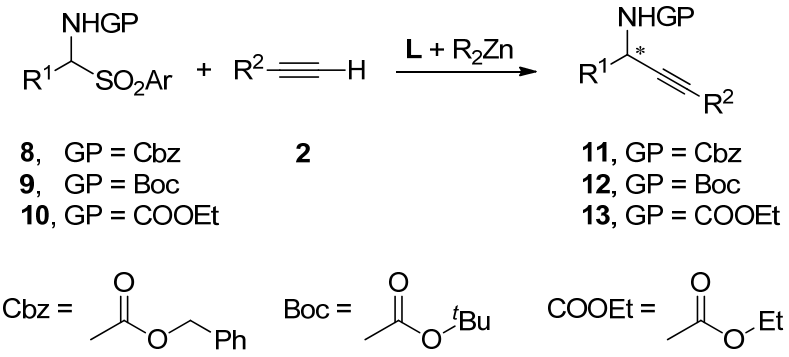
En este estudio se considerarán los siguientes aspectos:

1. Identificación de las condiciones óptimas de reacción: Influencia de la estructura de diversos ligandos de tipo (*R*)-BINOL (**L1**-**L8**), de la temperatura y del disolvente sobre el rendimiento y la enantioselectividad de la reacción de adición de fenilacetileno a *N*-benciloxicarbonilamino-*p*-toluenosulfona derivada del benzaldehído.

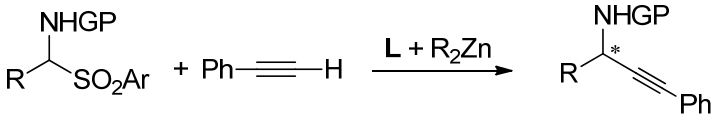


2. Identificación de las condiciones óptimas de reacción: Influencia de la naturaleza del reactivo de dialquilzinc utilizado (Me_2Zn y Et_2Zn).

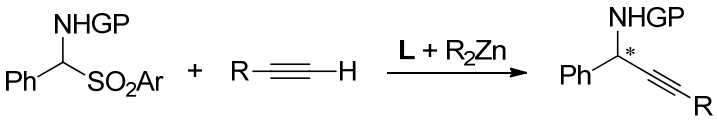
3. Identificación de las condiciones óptimas de reacción: Influencia de diferentes grupos protectores, fácilmente eliminables y compatibles con los grupos funcionales presentes en los productos de alquinilación, sobre el rendimiento y la enantioselectividad de la reacción.



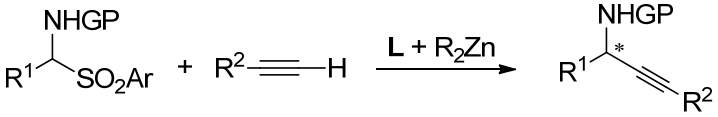
4. Alcance y limitaciones de la reacción: Evaluación de diversas α-amido sulfonas aromáticas y alifáticas con diferente naturaleza electrónica y estérica en la reacción de alquinilación con fenilacetileno.



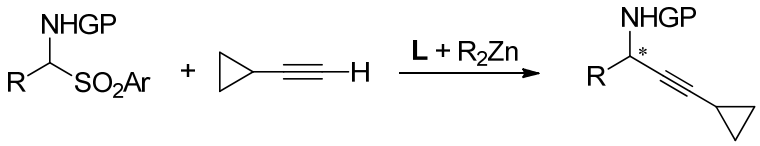
5. Alcance y limitaciones de la reacción: Evaluación de diversos alquinos con diferente naturaleza electrónica y estérica en la reacción con la α-amido sulfona derivada del benzaldehído.



6. Alcance y limitaciones de la reacción: Evaluación de diversas α-amido sulfonas aromáticas con diferente naturaleza electrónica y estérica en la reacción con alquinos aromáticos con elevada densidad electrónica.



7. Alcance y limitaciones de la reacción: Evaluación de diversas α-amido sulfonas con diferente naturaleza electrónica y estérica en la reacción de adición de ciclopropilacetileno.



8. Utilidad sintética: Evaluación de distintas transformaciones basadas en la reactividad del triple enlace y el grupo protector de los productos de alquinilación enantioselectiva.

3.3. RESULTADOS Y DISCUSIÓN

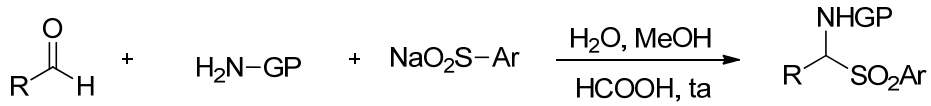
3.3.1. Síntesis de α-amido sulfonas

Para llevar a cabo la reacción de adición de alquinos terminales a iminas, se utilizaron diversas α-amido sulfonas como precursores *in situ* de aciliminas. Las α-amido sulfonas se prepararon siguiendo el procedimiento descrito por Engberts y Strating en 1964.[10] Este método consiste en la reacción de acoplamiento de tres componentes entre un aldehído, un carbamato y sulfinato de sodio en condiciones ácidas.

Las α-amido sulfonas obtenidas son sólidos blancos o marrones estables que precipitan de la mezcla de reacción y se purifican fácilmente por filtración y lavado con agua y dietiléter.

Todas ellas se prepararon con rendimientos entre moderados y buenos (31-80%) y se caracterizaron por resonancia magnética nuclear (^{1}H RMN, ^{13}C RMN).

Tabla 3.1. Síntesis de α-amido sulfonas mediante una reacción de tres componentes.

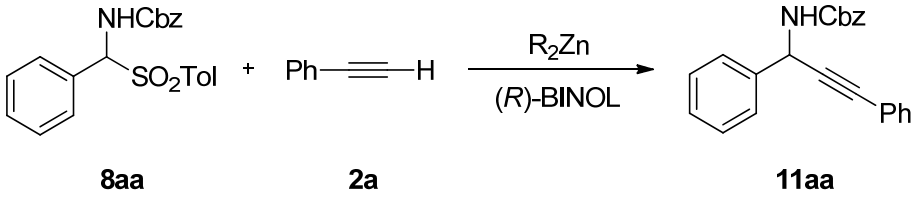


5 **14**, GP = Cbz; **15**, GP = Boc; **16**, GP = COOEt **17** **8**, GP = Cbz; **9**, GP = Boc; **10**, GP = COOEt

	5	**R**	**GP**		**Ar**		**α-Amido sulfona**	**R (%)**
1	**5a**	Ph	**14**	Cbz	**17a**	Tol	**8aa**	80
2	**5b**	4-MeC_6H_4	**14**	Cbz	**17a**	Tol	**8ba**	78
3	**5c**	4-$MeOC_6H_4$	**14**	Cbz	**17a**	Tol	**8ca**	73
4	**5d**	4-FC_6H_4	**14**	Cbz	**17a**	Tol	**8da**	71
5	**5e**	4-ClC_6H_4	**14**	Cbz	**17a**	Tol	**8ea**	63
6	**5f**	4-BrC_6H_4	**14**	Cbz	**17a**	Tol	**8fa**	60
7	**5g**	3-MeC_6H_4	**14**	Cbz	**17a**	Tol	**8ga**	72
8	**5h**	2-MeC_6H_4	**14**	Cbz	**17a**	Tol	**8ha**	56
9	**5j**	2-ClC_6H_4	**14**	Cbz	**17a**	Tol	**8ja**	66
10	**5k**	2-naftil	**14**	Cbz	**17a**	Tol	**8ka**	36
11	**5l**	1-naftil	**14**	Cbz	**17a**	Tol	**8la**	47
12	**5m**	2-furanil	**14**	Cbz	**17a**	Tol	**8ma**	35
13	**5n**	2-tienil	**14**	Cbz	**17a**	Tol	**8na**	31
14	**5o**	3-furanil	**14**	Cbz	**17a**	Tol	**8oa**	41
15	**5p**	3-tienil	**14**	Cbz	**17a**	Tol	**8pa**	76
16	**5q**	$C_6H_5CH_2CH_2$	**14**	Cbz	**17a**	Tol	**8qa**	66
17	**5r**	*n*-butil	**14**	Cbz	**17a**	Tol	**8ra**	62
18	**5s**	ciclohexil	**14**	Cbz	**17a**	Tol	**8sa**	85
19	**5a**	Ph	**15**	Boc	**17a**	Tol	**9aa**	73
20	**5a**	Ph	**16**	COOEt	**17a**	Tol	**10aa**	70
21	**5a**	Ph	**14**	Cbz	**17b**	Ph	**8ab**	78
22	**5a**	Ph	**14**	Cbz	**17c**	4-ClC_6H_4	**8ac**	75
23	**5b**	4-MeC_6H_4	**14**	Cbz	**17b**	Ph	**8bb**	69
24	**5b**	4-MeC_6H_4	**14**	Cbz	**17c**	4-ClC_6H_4	**8bc**	70

3.3.2. Optimización de las condiciones de reacción

Para abordar el proceso de optimización de la reacción de alquinilación de α-amido sulfonas, se escogió la reacción entre la *N*-benciloxicarbonilamino-*p*-toluenosulfona derivada del benzaldehído **8aa** y fenilacetileno (**2a**) y se evaluó tanto el rendimiento como la enantioselectividad en función del ligando, la temperatura, el disolvente, el dialquilzinc utilizado, el grupo protector y la sustitución del grupo sulfona.



Esquema 3.13. Reacción de adición de fenilacetileno (**2a**) a *N*-benciloxicarbonilamino-*p*-toluenosulfona **8aa** catalizada por (*R*)-BINOL y dialquilzinc.

Influencia de la estructura del ligando, la temperatura y el disolvente

Inicialmente, siguiendo el mismo patrón de trabajo que para la reacción de alquinilación de *N*-(difenilfosfinoil)iminas, se estudió la reacción utilizando condiciones similares a las descritas por nuestro grupo de investigación[26] para la alquinilación enantioselectiva de *N*-sulfonilaldiminas. En este trabajo se generó el acetiluro de zinc a partir de fenilacetileno y Me_2Zn. Transcurrida 1 h, se adicionó (*R*)-BINOL disuelto en tolueno y finalmente, se añadió la *N*-sulfonilimina disuelta en tolueno (Procedimiento A, Figura 2.9, p. 57).

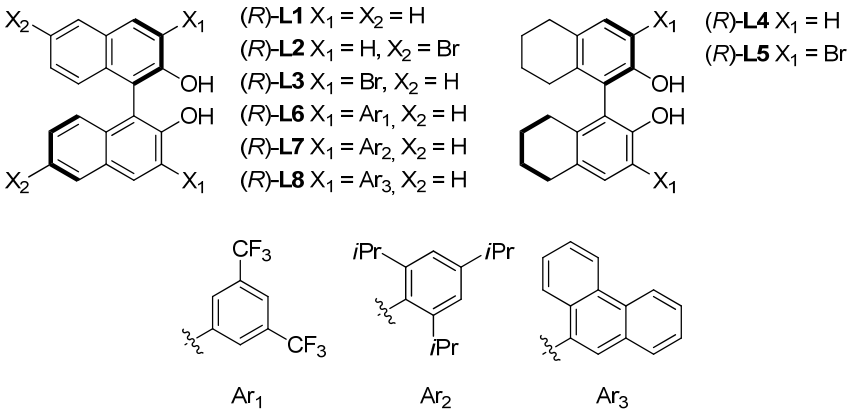


Figura 3.5. Ligandos de tipo BINOL.

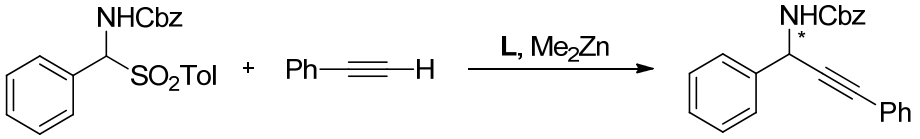
En primer lugar, se analizó la influencia de la estructura del ligando (20 mol %) utilizando distintos derivados de (*R*)-BINOL con grupos electrón-aceptores en las posiciones 3,3' y 6,6', así como con anillos tetrahidrogenados (Figura 3.5).

La reacción se llevó a cabo con 6 equivalentes de Me_2Zn 2 M en tolueno. Asimismo, se ensayaron disolventes de diversa naturaleza. Los resultados se recogen en la Tabla 3.2.

Los resultados sugieren que la presencia de grupos voluminosos en las posiciones 3,3' del ligando favorece la enantioselectividad de la reacción (Tabla 3.2, Entradas 3, 5-7). Este resultado está de acuerdo con lo observado por nuestro grupo de investigación en un trabajo anterior,[26] así como por Wu y Chong,[27] quienes describieron que la sustitución en las posiciones 3,3' de un BINOL-alquinil boronato era esencial para obtener enantioselectividades elevadas. No obstante, un impedimento estérico excesivo impide que la adición transcurra selectivamente (Tabla 3.2, Entrada 8). El ligando **L6** proporcionó una enantioselectividad superior al resto de ligandos. Utilizando tolueno como disolvente y llevando a cabo la reacción a temperatura ambiente, se obtuvo el producto de reacción **11aa** con un 81% *ee* aunque con un rendimiento bajo (35%) (Tabla 3.2, Entrada 6).

Se logró aumentar el rendimiento hasta el 50% manteniendo la enantioselectividad llevando a cabo la reacción a 0 °C, mientras que se redujo drásticamente a -25 °C (Tabla 2, Entradas 9 y 10, respectivamente).

Tabla 3.2. Adición enantioselectiva de fenilacetileno (**2a**) a *N*-benciloxicarbonilamino-*p*-toluenosulfona **8aa** utilizando Me_2Zn. Screening de ligandos, temperaturas y disolventes siguiendo el Procedimiento A.[a]



8aa **2a** **11aa**

Entrada	L	Disolvente[b]	T (°C)	t (h)	R (%)[c]	*ee* (%)[d]
1	**L1**	Tolueno	ta	3	35	11
2	**L2**	Tolueno	ta	4	64	13
3	**L3**	Tolueno	ta	2	64	33
4	**L4**	Tolueno	ta	2	26	18
5	**L5**	Tolueno	ta	2	32	43
6	**L6**	Tolueno	ta	2	35	81
7	**L7**	Tolueno	ta	21	24	51
8	**L8**	Tolueno	ta	3	18	5
9	**L6**	Tolueno	0	2	50	83
10	**L6**	Tolueno	-25	24	7	-
11	**L6**	Hexano	0	5	20	81
12	**L6**	CH_2Cl_2	0	5	52	84
13	**L6**	$ClCH_2CH_2Cl$	0	5	45	83
14	**L6**	$CHCl_3$	0	7	24	80
15	**L6**	THF	0	17	16	5

[a] **8aa** (0,125 mmol), **2a** (0,900 mmol), Me_2Zn 2 M en tolueno (0,375 mL, 0,750 mmol), **L** (0,025 mmol). [b] 0,2 mL de disolvente excepto cuando se utiliza hexano (0,4 mL). [c] Rendimiento de producto aislado. [d] Determinado por HPLC usando fases estacionarias quirales.

En cuanto a la utilización de diferentes disolventes, el hexano no aportó ninguna mejora en los resultados (Tabla 3.2, Entrada 11). Por su parte, la utilización de disolventes clorados condujo a buenos *ee* y rendimientos moderados (Tabla 3.2, Entradas 12-14), mientras que un disolvente coordinante como el THF proporcionó el producto de alquinilación deseado **11aa** con bajo rendimiento y enantioselectividad

(Tabla 3.2, Entrada 15). Así pues, el mejor resultado se obtuvo utilizando CH_2Cl_2 como disolvente (52% de rendimiento, 83% *ee*) (Tabla 3.2, Entrada 12).

Influencia de la naturaleza del reactivo de dialquilzinc

Teniendo en cuenta que no considerábamos satisfactorio el rendimiento de la reacción, decidimos, tomando como referencia un trabajo publicado por Wang para la reacción de alquinilación de fosfinoiliminas,[28] utilizar Et_2Zn en lugar de Me_2Zn (Tabla 3.3, Entrada 1).

Sin embargo, los resultados de la reacción fueron esencialmente idénticos, por lo que decidimos determinar la estructura de un producto secundario que observábamos por cromatografía de capa fina. El análisis por resonancia magnética nuclear de este concluyó que no se trataba de un único producto. La mezcla se consiguió separar con una posterior cromatografía de columna tras la que se obtuvieron los dos productos secundarios, a los que denominamos **18** y **19**, cuyas estructuras se elucidaron mediante RMN y espectrometría de masas.

A partir de la comparación del RMN del producto de alquinilación **11aa** con los espectros de RMN de los dos productos secundarios obtenidos, se extrajeron las siguientes conclusiones:

- Ambos productos secundarios conservaban el grupo protector Cbz, ya que los espectros mostraban una señal a aproximadamente 5,2 ppm que corresponde al metileno del grupo bencilo.
- En ambos productos se había incorporado un nucleófilo distinto al alquino y no estaba presente el grupo sulfona.

Además, en cuanto al producto **18**:

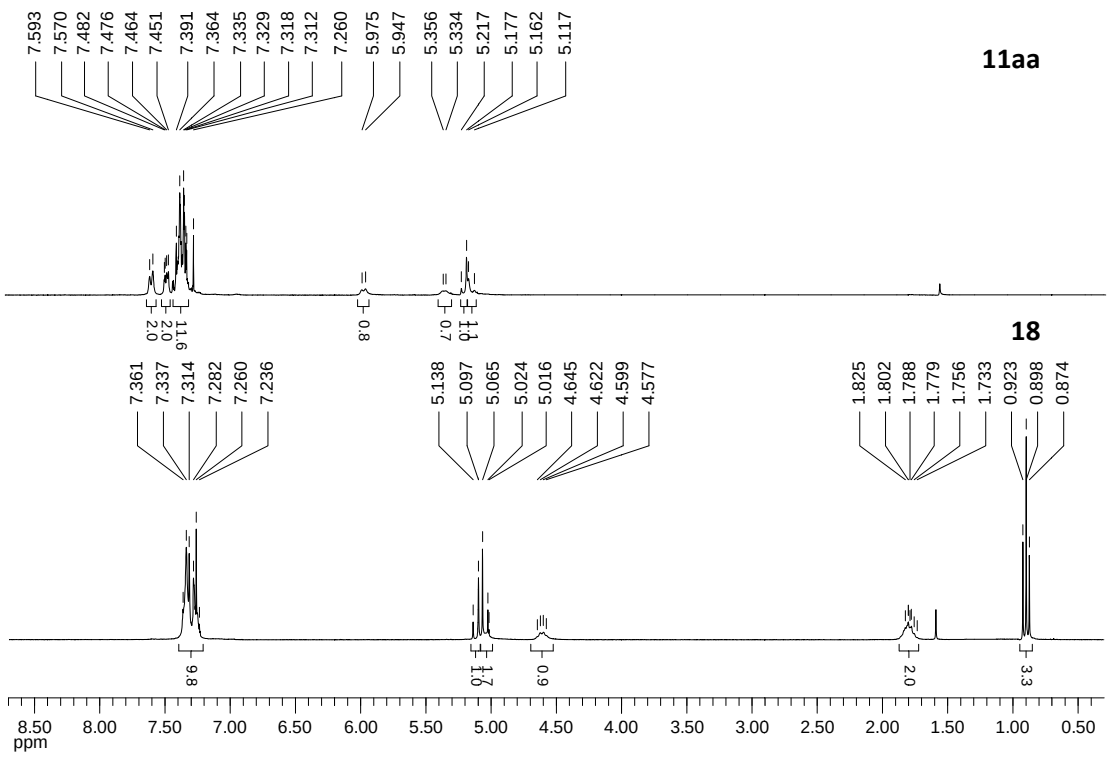


Figura 3.6. Espectros de RMN ^{1}H de los productos **11aa** y **18**.

- La señal a 1,8 ppm, perteneciente a un CH_2 del nucleófilo adicionado, acoplaba con el protón unido al C estereogénico.
- La señal a 0,9 ppm, perteneciente a un CH_3, acoplaba con el metileno anterior.
- Tanto las integraciones (3H y 2H) como los desplazamientos (0,9 y 1,8 ppm) de los protones correspondientes al nucleófilo, así como los argumentos anteriores, nos permitieron concluir que el producto **18** es el derivado de la adición del grupo etilo a la α-amido sulfona. El análisis por espectrometría de masas confirmó esta hipótesis.

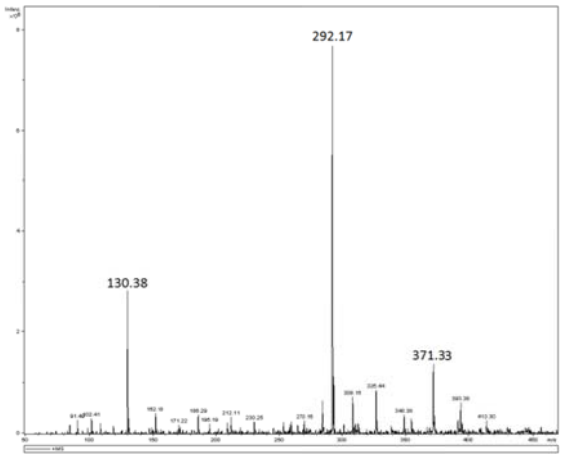


Figura 3.7. Espectro de masas del producto **18**. $[M+Na]^{+}$ = 292.2.

En cuanto al producto **19**:

- La señal a 6,5 ppm corresponde al protón del C estereogénico y se encuentra desplazada a campo bajo respecto a la señal equivalente en el producto de alquinilación **11aa** (5,9 ppm).
- La señal a 4,1 ppm perteneciente a un CH_2 del nucleófilo adicionado, no acoplaba con el protón del C estereogénico.
- La señal a 1,21 ppm, perteneciente a un CH_3, acoplaba con el metileno anterior.
- Las intensidades de las señales correspondientes a los protones del nucleófilo y sus desplazamientos indican que se trata de un grupo etilo unido a heteroátomo.
- La espectrometría de masas fue determinante para la elucidación de la estructura del compuesto **19**. El ion molecular ($[M+Na]^+$ 324,1), 32 uma superior al del producto **18** ($[M+Na]^+$ 292,2), nos indica que el compuesto **19** es el producto de adición de peróxido de etilo a la α-amido sulfona **8aa**.

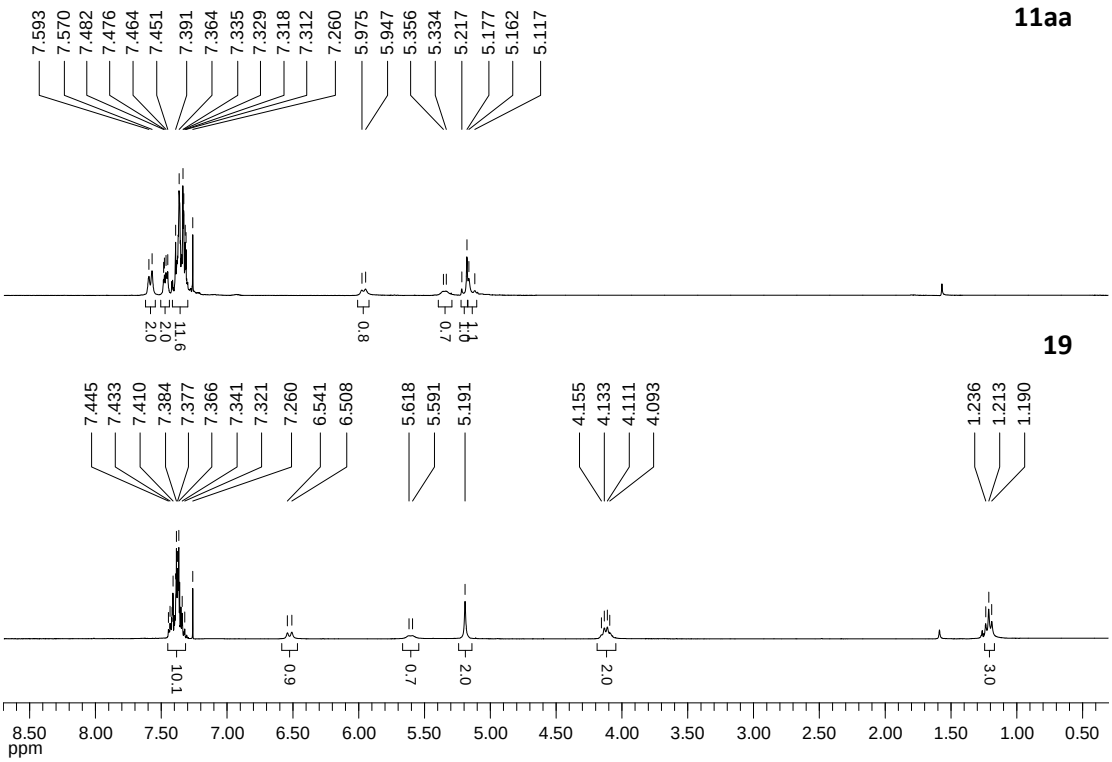


Figura 3.8. Espectros de RMN ^1H de los productos **11aa** y **19**.

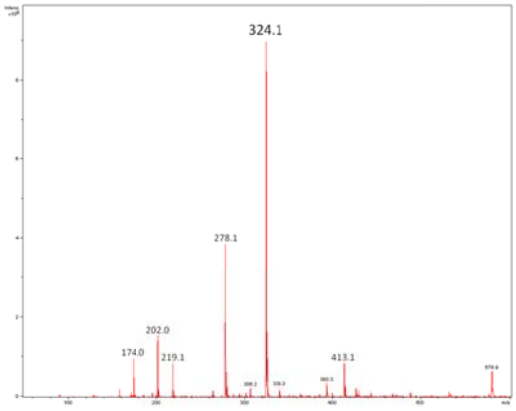
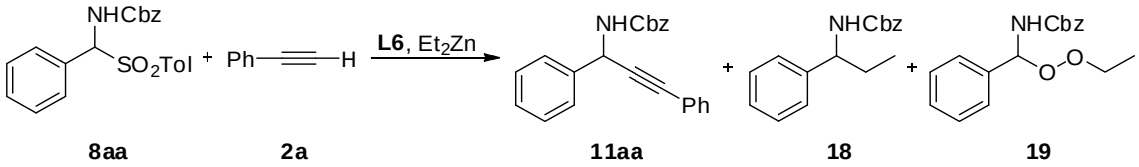


Figura 3.9. Espectro de masas del producto **19**. $[M+Na]^+$ = 324,1.

Por tanto, el producto **18** resulta de la adición del grupo etilo del Et_2Zn a la α-amido sulfona de partida,[29] mientras que el producto **19** debe formarse por adición del radical peróxido generado a partir del Et_2Zn y oxígeno dirradical.[30,31]



8aa **2a** **11aa** **18** **19**

Esquema 3.14. Formación de los productos secundarios **18** y **19** en la reacción de alquinilación de α-amido sulfonas.

Con el objetivo de eliminar la formación de este último, se extremaron las condiciones de purga y se redujeron posibles entradas de O_2 en el montaje de reacción. Por otra parte, decidimos modificar el procedimiento experimental, ya que la presencia del producto de alquilación parecía indicar una formación incompleta de la especie activa (el acetiluro metálico). Dicha modificación se basó en variar el orden de adición de los reactivos implicados en la formación de la especie catalítica. El nuevo procedimiento consistía en disolver fenilacetileno y BINOL en 0,4 mL de CH_2Cl_2, añadir el dietilzinc (1 M en hexano) y, tras la formación de la especie catalítica, adicionar la α-amido sulfona (Figura 3.10, Procedimiento B). De este modo, el producto deseado se obtuvo con rendimiento (60%) y enantioselectividad (84% *ee*) superiores a los conseguidos siguiendo el Procedimiento A (Tabla 3.3, Entrada 2), ya que disminuyó la formación de los productos secundarios.

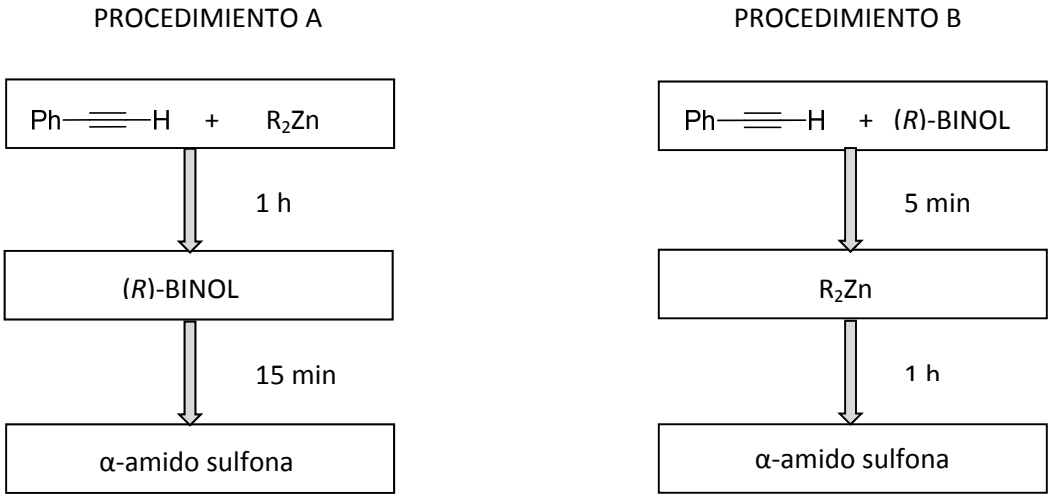
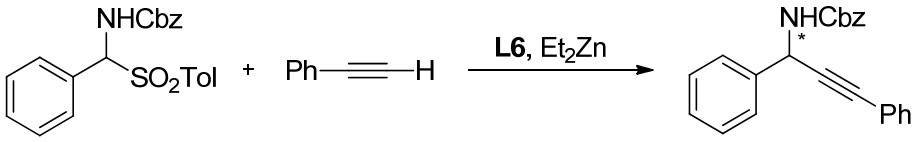


Figura 3.10. Procedimientos experimentales A y B.

Debido a que todavía se observaba la aparición de una pequeña cantidad de producto de alquilación, se incrementó el tiempo de formación de la especie catalítica de 1 a 1,5 horas. De este modo se logró reducir la formación del producto no deseado y se aumentó el rendimiento hasta 69%, conservándose la enantioselectividad (Tabla 3.3, Entrada 3). Sin embargo, un incremento del tiempo de formación del complejo activo a 2 h condujo a un descenso tanto del rendimiento como del *ee* (Tabla 3.3, Entrada 4).

Por tanto, los mejores resultados se alcanzaron cuando se utilizó Et_2Zn siguiendo el Procedimiento B con 1,5 h de tiempo de formación de la especie catalítica.

Tabla 3.3. Adición enantioselectiva de fenilacetileno (**2a**) a *N*-benciloxicarbonilamino-*p*-toluenosulfona **8aa** utilizando Et_2Zn.[a]



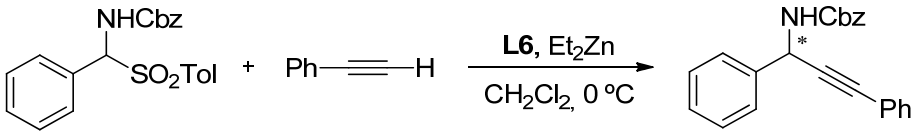
8aa **2a** **11aa**

	Proc.	R_2Zn (M)	Disolvente	T (°C)	t_f (h)[b]	t (h)	R (%)[c]	*ee* (%)[d]
1	A	Et_2Zn (1 M)	CH_2Cl_2	0	0,25	4	54	85
2	B	Et_2Zn (1 M)	CH_2Cl_2	0	1	4	60	84
3	B	Et_2Zn (1 M)	CH_2Cl_2	0	1,5	4	69	85
4	B	Et_2Zn (1 M)	CH_2Cl_2	0	2	4	53	82

[a] **8aa** (0,125 mmol), **2a** (0,900 mmol), Et_2Zn 1 M en hexano (0,750 mL, 0,750 mmol), **L6** (0,025 mmol). [b] Tiempos de formación de la especie catalítica. [c] Rendimiento de producto aislado. [d] Determinado por HPLC usando fases estacionarias quirales.

Siguiendo con el proceso de optimización, a continuación analizamos cómo afectaba la concentración de la mezcla de reacción a la enantioselectividad, ya que en sistemas similares se había observado una dependencia de la selectividad con la dilución.[26, 32] No obstante, en nuestro caso no observamos dicha dependencia (Tabla 3.4, Entradas 1-7). Finalmente, se redujo la cantidad de dietilzinc hasta 3 y 2,5 equivalentes (Tabla 3.4, Entradas 8 y 9). Se obtuvo una mayor enantioselectividad cuando la reacción se llevó a cabo con Et_2Zn 1 M en hexano (0,375 mmol, 3 equivalentes respecto a α-amido sulfona **8aa**), utilizando el ligando **L6** en CH_2Cl_2 a 0 °C (Tabla 3.4, Entrada 8).

Tabla 3.4. Adición enantioselectiva de fenilacetileno (**2a**) a *N*-benciloxicarbonilamino-*p*-toluenosulfona **8aa** utilizando Et_2Zn en CH_2Cl_2. Screening a distintas concentraciones y volumen de disolvente.[a]



8aa **2a** **11aa**

Entrada	Et_2Zn (M)[b]	Disolvente (mL)	t (h)	R (%)[c]	*ee* (%)[d]
1	Et_2Zn (1 M)	CH_2Cl_2 (0,2)	17	63	80
2	Et_2Zn (1 M)	CH_2Cl_2 (0,4)	4	69	85
3	Et_2Zn (1 M)	CH_2Cl_2 (0,8)	3	54	84
4	Et_2Zn (1,1 M)	CH_2Cl_2 (0,2)	3,5	60	69
5	Et_2Zn (1,1 M)	CH_2Cl_2 (0,37)	4	64	81
6	Et_2Zn (1,5 M)	CH_2Cl_2 (0,27)	3	52	78
7	Et_2Zn (1,5 M)	CH_2Cl_2 (0,65)	3	53	81
8	Et_2Zn (1 M)[e]	CH_2Cl_2 (0,4)	3	70	87
9	Et_2Zn (1 M)[f]	CH_2Cl_2 (0,4)	3	51	76

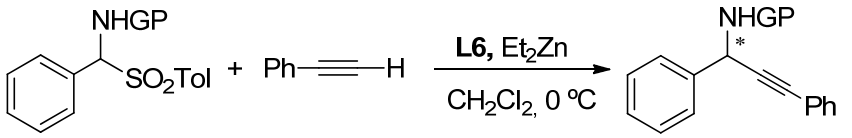
[a] Todas las reacciones se realizaron siguiendo el Procedimiento B. **8aa** (0,125 mmol), **2a** (0,900 mmol), **L6** (0,025 mmol). [b] Et_2Zn en hexano (0,750 mmol). [c] Rendimiento del producto aislado. [d] Determinado por HPLC usando fases estacionarias quirales. [e] Et_2Zn (0,375 mmol). [f] Et_2Zn (0,275 mmol).

Influencia del grupo protector

Finalizado el proceso de optimización para la reacción de adición de fenilacetileno (**2a**) a *N*-benciloxicarbonilamino-*p*-toluenosulfona derivada del benzaldehído **8aa**, se examinó la influencia del grupo protector (Tabla 3.5). Para ello, se ensayaron además del grupo benciloxicarbonilo (Cbz), *t*-butiloxicarbonilo (Boc) y etiloxicarbonilo (COOEt). En base a los antecedentes bibliográficos en los que se lleva a cabo la eliminación de estos grupos protectores, el benciloxicarbonilo generalmente se elimina por hidrogenolisis, el *t*-butiloxicarbonilo se puede eliminar en medio ácido y, por último, el etiloxicarbonilo se elimina en medio básico.[33] Debe tenerse en cuenta que el triple enlace de la amina propargílica puede sufrir reducción en la etapa de

hidrogenolisis, por lo que podría ser necesaria la búsqueda de métodos selectivos de desprotección del benciloxicarbonilo.

Tabla 3.5. Adición enantioselectiva de fenilacetileno (**2a**) a α-amido sulfonas **8aa**, **9aa** y **10aa**.[a]



8aa, GP = Cbz
9aa, GP = Boc
10aa, GP = COOEt

2a

11aa, GP = Cbz
12aa, GP = Boc
13aa, GP = COOEt

	α-Amido sulfona	**Grupo Protector**	**t (h)**	**Producto**	**R (%)[b]**	***ee* (%)[c]**
1	**8aa**	Cbz	3	**11aa**	70	87
2	**9aa**	Boc	3	**12aa**	59	84
3	**10aa**	COOEt	4	**13aa**	-[d]	-

[a] **α-amido sulfona** (0,125 mmol), **2a** (0,900 mmol), **L6** (0,025 mmol), Et_2Zn (0,375 mmol). [b] Rendimiento del producto aislado. [c] Determinado por HPLC usando fases estacionarias quirales. [d] Mezcla compleja, rendimiento no determinado.

Con ninguno de los dos nuevos grupos estudiados se obtuvieron mejores resultados respecto al grupo protector inicialmente utilizado, Cbz.

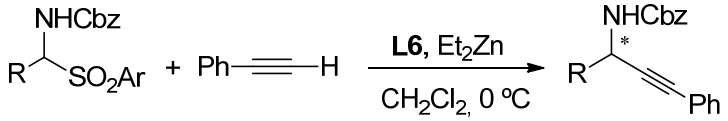
Influencia de la sustitución del grupo sulfona

Se acepta generalmente que la eliminación asistida por base de ácido bencenosulfínico a partir de las α-amido sulfonas **8** conduce a la formación de *N*-aciliminas que reaccionan con reactivos nucleofílicos para dar los correspondientes productos de adición. El proceso global puede considerarse como una reacción tándem de eliminación-adición que puede llevarse a cabo usando un reactivo nucleofílico que sea suficientemente básico para promover la etapa de eliminación, y que a continuación tuviera lugar la reacción de adición enantioselectiva.

No obstante, también se podría considerar que la reacción tuviera lugar a través de la sustitución directa del grupo sulfona por el reactivo nucleofílico, dando lugar a una resolución cinética dinámica.

Con el objeto de diferenciar entre ambas posibilidades, se evaluó la influencia sobre el rendimiento y la enantioselectividad de la sustitución en el grupo arilo de la α-amido sulfona. Se ensayaron tres tipos de sustratos distintos derivados del benzaldehído y del *p*-toluenaldehído: *N*-benciloxicarbonilamino-*p*-toluenosulfona, *N*-benciloxicarbonilaminofenilsulfona y *N*-benciloxicarbonilamino-*p*-clorofenilsulfona (Tabla 3.6).

Tabla 3.6. Adición enantioselectiva de fenilacetileno (**2a**) a α-amido sulfonas **8**.[a]

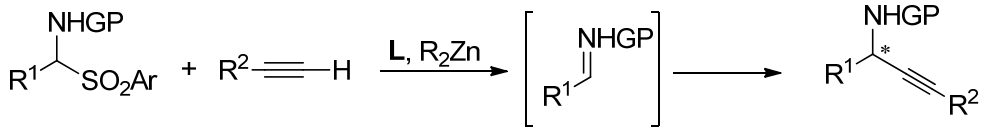


8 **2a** **11**

	α-Amido sulfona	R	Ar	t (h)	11	R (%)[b]	*ee* (%)[c]
1	**8aa**	Ph	Tol	3	**11aa**	70	87
2	**8ab**	Ph	Ph	3	**11aa**	68	88
3	**8ac**	Ph	*p*-ClC_6H_4	3	**11aa**	67	88
4	**8ba**	*p*-MeC_6H_4	Tol	3	**11ba**	49	87
5	**8bb**	*p*-MeC_6H_4	Ph	3	**11ba**	50	87
6	**8bc**	*p*-MeC_6H_4	*p*-ClC_6H_4	3	**11ba**	52	87

[a] **8** (0,125 mmol), **2a** (0,900 mmol), **L6** (0,025 mmol), Et_2Zn (0,375 mmol). [b] Rendimiento del producto aislado. [c] Determinado por HPLC usando fases estacionarias quirales.

Como puede observarse tanto la enantioselectividad como el rendimiento de la reacción son independientes de la sustitución del grupo arilo en la α-amido sulfona, lo cual está de acuerdo con un proceso tándem de eliminación-adición.



8, GP = Cbz
9, GP = Boc
10, GP = COOEt

2

11, GP = Cbz
12, GP = Boc
13, GP = COOEt

Esquema 3.15. Alquinilación enantioselectiva de iminas generadas *in situ* a partir de α-amido sulfonas.

3.3.3. Alcance y limitaciones de la reacción

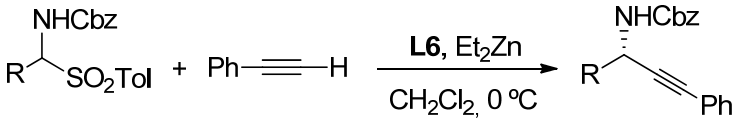
En el estudio del alcance de la reacción, se aplicaron las condiciones optimizadas para la reacción entre fenilacetileno (**2a**) y *N*-benciloxicarbonilamino-*p*-toluenosulfona **8aa** a distintas combinaciones α-amido sulfona y alquino terminal.

Evaluación de distintas α-amido sulfonas

En primer lugar se evaluó la reacción entre distintas α-amido sulfonas (**8aa-8sa**) y fenilacetileno (**2a**). Los resultados se encuentran en la Tabla 3.7.

α-Amido sulfonas con grupos electrón-dadores y electrón-aceptores dieron lugar a los correspondientes productos de alquinilación con buenos rendimientos y enantioselectividades en torno a 90% *ee* (Tabla 3.7, Entradas 2-6), a excepción del flúor y el grupo metoxilo, con los que el exceso enantiomérico disminuyó hasta 83% (Tabla 3.7, Entradas 3-4). Esto puede atribuirse al fuerte carácter electrónico del sustituyente, ya sea electrón-aceptor (F) o electrón-dador (MeO). La presencia de grupos en la posición *orto* del anillo aromático condujo a elevados excesos enantioméricos independientemente de la naturaleza electrónica del sustituyente (Tabla 3.7, Entradas 8-9). La reacción con el sustrato derivado de 2-naftaldehído transcurrió con rendimiento bajo, pero enantioselectividad elevada, mientras que con el sustrato derivado del 1-naftaldehído el producto deseado se obtuvo prácticamente racémico (Tabla 3.7, Entradas 10-11). La aplicabilidad de la reacción puede extenderse a α-amido sulfonas heteroaromáticas, con las cuales se obtuvieron enantioselectividades comprendidas entre 74-88% *ee* (Tabla 3.7, Entradas 12-15). Finalmente, se ensayó la reacción con tres α-amido sulfonas alifáticas. Con todas ellas se obtuvieron los correspondientes productos de alquinilación con rendimientos y enantioselectividades moderados (Tabla 3.7, Entrada 16-18).

Tabla 3.7. Adición enantioselectiva de fenilacetileno (**2a**) a α-amido sulfonas **8**.[a]



8 **2a** **11**

Entrada	8	R	t (h)	11	R (%)[b]	*ee* (%)[c]
1	**8aa**	Ph	3	**11aa**	70	87
2	**8ba**	4-MeC_6H_4	3	**11ba**	61	87
3	**8ca**	4-$MeOC_6H_4$	5	**11ca**	60	83[d]
4	**8da**	4-FC_6H_4	3	**11da**	42	83
5	**8ea**	4-ClC_6H_4	3	**11ea**	73	90
6	**8fa**	4-BrC_6H_4	3	**11fa**	61	90
7	**8ga**	3-MeC_6H_4	2	**11ga**	61	86
8	**8ha**	2-MeC_6H_4	2	**11ha**	62	90
9	**8ja**	2-ClC_6H_4	3	**11ja**	63	90
10	**8ka**	2-naftil	3	**11ka**	33	87
11	**8la**	1-naftil	2	**11la**	33	3
12	**8ma**	2-furanil	3	**11ma**	63	88
13	**8na**	2-tienil	2	**11na**	58	79
14	**8oa**	3-furanil	3	**11oa**	41	78
15	**8pa**	3-tienil	2	**11pa**	66	74
16	**8qa**	$C_6H_5CH_2CH_2$	2	**11qa**	52	60
17	**8ra**	*n*-butil	3	**11ra**	59	46
18	**8sa**	ciclohexil	3	**11sa**	72	55

[a] **8** (0,125 mmol), **2a** (0,900 mmol), **L6** (0,025 mmol), Et_2Zn (0,375 mmol). [b] Rendimiento del producto aislado. [c] Determinado por HPLC usando fases estacionarias quirales. [d] El valor de exceso enantiomérico se determinó tras obtener el producto de derivatización según el Esquema 3.16.

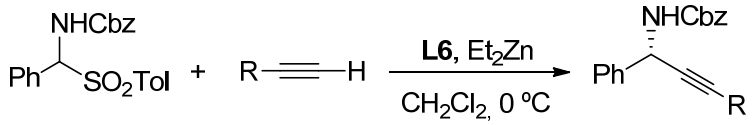
Evaluación de distintos alquinos terminales

La aplicabilidad de esta reacción se ensayó también con distintos alquinos proporcionando buenos rendimientos y elevados excesos enantioméricos. Los resultados se muestran en la Tabla 3.8.

Se examinaron diferentes alquinos con sustituyentes electrón-dadores y electrón-aceptores en el anillo aromático en la posición *para* (Tabla 3.8, Entrada 1-4). Todos ellos dieron los productos de alquinilación deseados con buenos rendimientos y enantioselectividades elevadas (85-91% *ee*). Sin embargo, los rendimientos fueron inferiores en el caso del alquino *p*-fluorofenil acetileno (**2d**) (Tabla 3.8, Entrada 3). Los sustratos con anillos aromáticos sustituidos en *orto* y *meta* dieron lugar a enantioselectividades variables y rendimientos inferiores (Tabla 3.8, Entradas 5-7). Se ensayaron alquinos con anillos heteroaromáticos con los cuales se obtuvieron buenos rendimientos y valores de *ee* elevados (Tabla 3.8, Entradas 8-9).

La aplicabilidad de la reacción puede extenderse al uso de los alquinos alifáticos **2k** y **2m** (Tabla 3.8, Entradas 10-11). Ambos proporcionaron los correspondientes productos de alquinilación con rendimientos moderados y enantioselectividades elevadas (82 y 88% *ee*, respectivamente). Finalmente se evaluaron tres alquinos alicíclicos de seis, cinco y tres miembros (Tabla 3.8, Entradas 12-14). La reacción transcurrió con rendimientos moderados y enantioselectividades elevadas en las que se observa un mayor valor de exceso enantiomérico a medida que disminuye el tamaño del anillo.

Tabla 3.8. Adición enantioselectiva de varios alquinos **2** a *N*-benciloxicarbonilamino-*p*-toluenosulfona **8aa**.[a]



8aa **2** **11a**

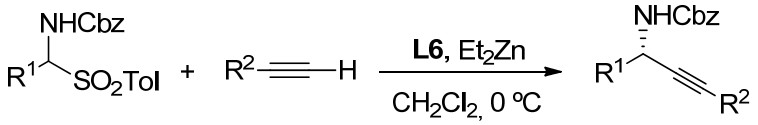
	2	**R**	**t (h)**	**11**	**R (%)[b]**	***ee* (%)[c]**
1	**2b**	4-$MeOC_6H_4$	4	**11ab**	84	86
2	**2c**	4-(*N*,*N*-diMe)C_6H_4	4	**11ae**	70	85
3	**2d**	4-FC_6H_4	4	**11ac**	43	88
4	**2e**	4-ClC_6H_4	4	**11ad**	76	91
5	**2f**	2-$MeOC_6H_4$	4	**11af**	74	66
6	**2g**	3,5-di$MeOC_6H_3$	3	**11ag**	41	90
7	**2h**	2-Me-4-$MeOC_6H_3$	4	**11ah**	55	80
8	**2i**	2-tienil	4	**11ai**	81	90
9	**2j**	3-tienil	4	**11aj**	66	90
10	**2k**	$C_6H_5CH_2CH_2$	3	**11ak**	53	82
11	**2m**	*terc*-butil	3	**11am**	46	88
12	**2n**	ciclohexil	3	**11an**	59	78
13	**2o**	ciclopentil	3	**11ao**	66	83
14	**2p**	ciclopropil	3	**11ap**	72	86

[a] **8aa** (0,125 mmol), **2** (0,900 mmol), **L6** (0,025 mmol), Et_2Zn (0,375 mmol). [b] Rendimiento del producto aislado. [c] Determinado por HPLC usando fases estacionarias quirales.

Evaluación de distintas α-amido sulfonas y alquinos terminales

Para profundizar en el estudio del alcance y limitaciones de la reacción, se escogieron los cuatro alquinos que proporcionaron las aminas propargílicas *N*-Cbz protegidas con mejores resultados globales (Tabla 3.8, Entradas 1, 3, 8-9) y se estudió su adición a cinco α-amido sulfonas diferentemente sustituidas.

Tabla 3.9. Adición enantioselectiva de varios alquinos aromáticos a diferentes α-amido sulfonas aromáticas.[a]



8 **2** **11**

	8a	R^1	2	R^2	t (h)	Producto	R (%)[b]	*ee* (%)[c]
1	**8aa**	Ph	**2b**	4-$MeOC_6H_4$	4	**11ab**	84	86
2	**8ba**	4-MeC_6H_4	**2b**	4-$MeOC_6H_4$	4	**11bb**	72	88
3	**8ea**	4-ClC_6H_4	**2b**	4-$MeOC_6H_4$	4	**11eb**	72	92
4	**8ha**	2-MeC_6H_4	**2b**	4-$MeOC_6H_4$	4	**11hb**	89	91
5	**8na**	2-tienil	**2b**	4-$MeOC_6H_4$	4	**11nb**	74	86
6	**8aa**	Ph	**2e**	4-ClC_6H_4	4	**11ae**	76	91
7	**8ba**	4-MeC_6H_4	**2e**	4-ClC_6H_4	4	**11be**	84	92
8	**8ea**	4-ClC_6H_4	**2e**	4-ClC_6H_4	4	**11ee**	62	91
9	**8ha**	2-MeC_6H_4	**2e**	4-ClC_6H_4	4	**11he**	60	95
10	**8na**	2-tienil	**2e**	4-ClC_6H_4	4	**11ne**	75	87
11	**8aa**	Ph	**2i**	2-tienil	4	**11ai**	81	90
12	**8ba**	4-MeC_6H_4	**2i**	2-tienil	4	**11bi**	83	90
13	**8ea**	4-ClC_6H_4	**2i**	2-tienil	4	**11ei**	72	94
14	**8ha**	2-MeC_6H_4	**2i**	2-tienil	4	**11hi**	74	92
15	**8na**	2-tienil	**2i**	2-tienil	4	**11ni**	94	88
16	**8aa**	Ph	**2j**	3-tienil	4	**11aj**	66	90
17	**8ba**	4-MeC_6H_4	**2j**	3-tienil	4	**11bj**	57	89
18	**8ea**	4-ClC_6H_4	**2j**	3-tienil	4	**11ej**	80	91
19	**8ha**	2-MeC_6H_4	**2j**	3-tienil	4	**11hj**	56	94
20	**8na**	2-tienil	**2j**	3-tienil	4	**11nj**	56	89

[a] **8a** (0,125 mmol), **2** (0,900 mmol), **L6** (0,025 mmol), Et_2Zn (0,375 mmol). [b] Rendimiento del producto aislado. [c] Determinado por HPLC usando fases estacionarias quirales.

Las veinte reacciones de alquinilación ensayadas proporcionaron las correspondientes propargilamidas con excelentes enantioselectividades y buenos rendimientos.

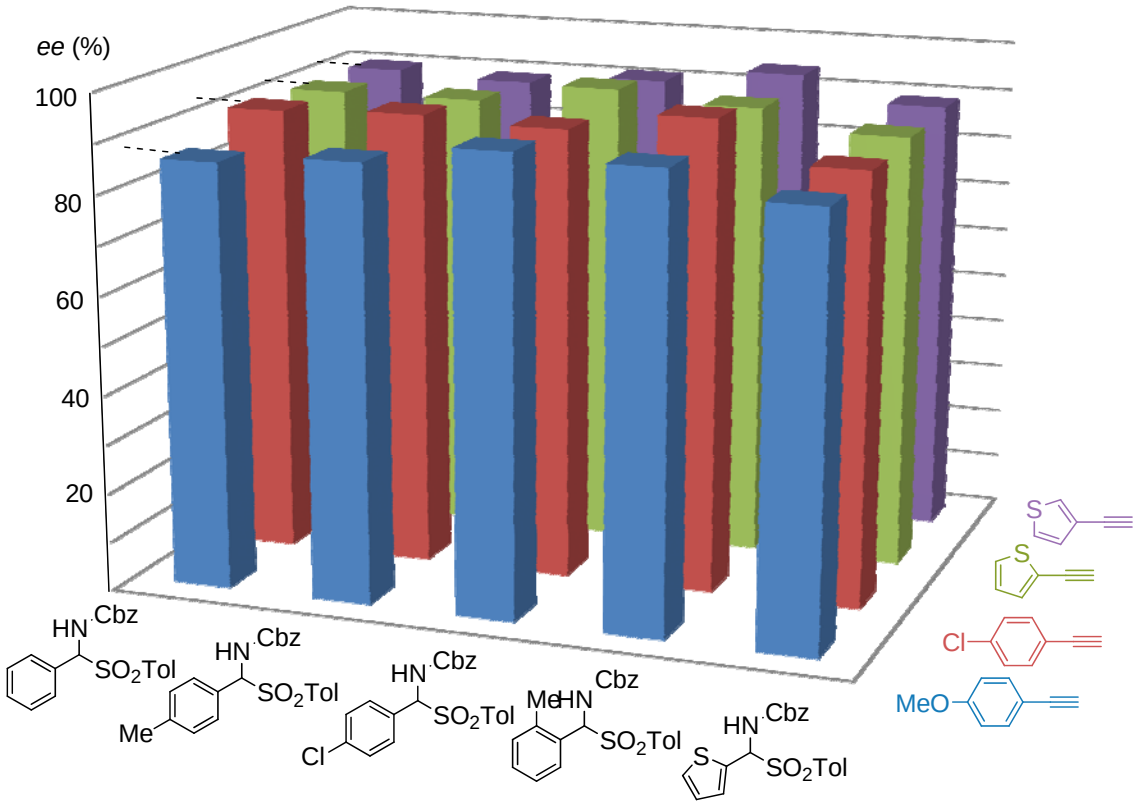
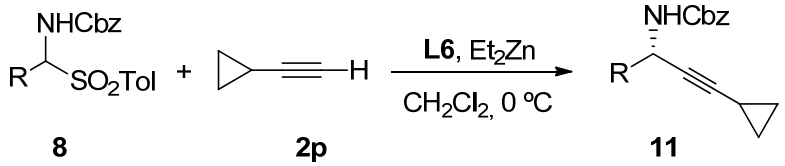


Figura 3.11. Exceso enantiomérico (%) de la reacción de alquinilación entre cuatro alquinos y cinco α-amido sulfonas.

La reacción de adición de ciclopropilacetileno (**2p**) a *N*-benciloxicarbonilamino-*p*-toluenosulfona derivada del benzaldehído **8aa** (Tabla 3.8, Entrada 14) condujo a la formación del correspondiente producto de alquinilación con un rendimiento del 72% y 86% *ee*. Este resultado y el enorme interés que ha despertado la presencia del anillo de ciclopropilo en los compuestos orgánicos en el campo de la química médica, nos condujo a examinar la reacción entre este alquino **2p** y diversas α-amido sulfonas.

Tabla 3.10. Adición enantioselectiva de ciclopropilacetileno (**2p**) a diferentes α-amido sulfonas **8**.[a]



8 **2p** **11**

	8	**R**	**t (h)**	**11**	**R (%)**[b]	***ee* (%)**[c]
1	**8aa**	Ph	2	**11ap**	72	86
2	**8ba**	4-MeC_6H_4	3	**11bp**	58	93
3	**8da**	4-FC_6H_4	3	**11dp**	69	89
4	**8ea**	4-ClC_6H_4	3	**11ep**	45	95
5	**8fa**	4-BrC_6H_4	4	**11fp**	50	93
6	**8ga**	3-MeC_6H_4	3	**11gp**	52	89
7	**8ha**	2-MeC_6H_4	3	**11hp**	53	96
8	**8ja**	2-ClC_6H_4	4	**11jp**	30	92
9	**8ka**	2-naftil	3	**11kp**	46	91
10	**8ma**	2-furanil	3	**11mp**	68	84
11	**8na**	2-tienil	3	**11np**	64	84
12	**8oa**	3-furanil	3	**11op**	52	64
13	**8qa**	$C_6H_4CH_2CH_2$	4	**11qp**	59	42
14	**8ra**	*n*-butil	3	**11rp**	50	43
15	**8sa**	ciclohexil	3	**11sp**	63	65

[a] **8aa** (0,125 mmol), **2** (0,900 mmol), **L6** (0,025 mmol), Et_2Zn (0,375 mmol). [b] Rendimiento del producto aislado. [c] Determinado por HPLC usando fases estacionarias quirales.

La reacción transcurrió con rendimientos moderados y enantioselectividades elevadas cuando se utilizaron α-amido sulfonas con grupos tanto electrón-dadores como electrón-atractores en la posición *para* de su anillo aromático (Tabla 3.10, Entradas 2-5). También se alcanzó un valor de *ee* elevado cuando se llevó a cabo la reacción con un grupo metilo en la posición *meta* (Tabla 3.10, Entrada 6).

Del mismo modo que para la adición de alquinos aromáticos, la adición de ciclopropilacetileno a α-amido sulfonas sustituidas en *orto* dio lugar a los correspondientes productos de adición con enantioselectividades excelentes, independientemente de la naturaleza electrónica del sustituyente (Tabla 3.10, Entradas 7-8). No obstante, la reacción tuvo lugar con rendimientos moderados.

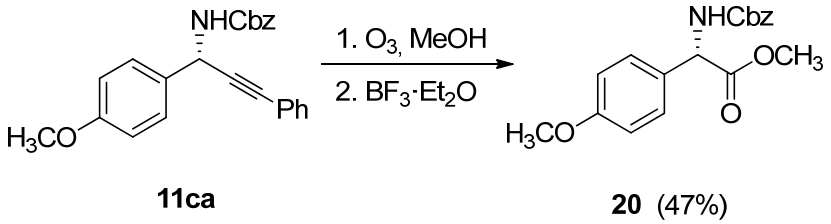
La reacción con la α-amido sulfona derivada del 2-naftaldehído **8ka** (Tabla 3.10, Entrada 9), así como las derivadas de 2-furanocarbaldehído **8ma** y 2-tiofenocarbaldehído **8na** (Tabla 3.10, Entradas 10-11) proporcionaron las correspondientes aminas propargílicas *N*-Cbz protegidas con rendimientos moderados y enantioselectividades elevadas. Por el contrario, la reacción con la α-amido sulfona derivada del 3-furanocarbaldehído **8oa** transcurrió con *ee* moderado (Tabla 3.10, Entrada 12).

Por último, la alquinilación de α-amido sulfonas alifáticas tuvo lugar con rendimientos y enantioselectividades moderadas (Tabla 3.10, Entradas 13-15).

3.3.4. Modificaciones sintéticas

Los productos obtenidos contienen dos grupos, *N*-benciloxicarbonilamino y triple enlace, con posibilidad de sufrir transformaciones que amplíen las aplicaciones sintéticas de los mismos.

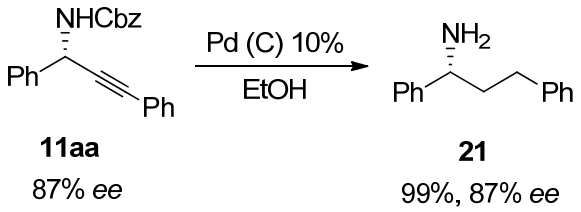
En primer lugar, llevamos a cabo la ozonolisis del triple enlace de las aminas propargílicas protegidas y la esterificación del ácido obtenido (Esquema 3.16). Esto permite la obtención de un α-aminoácido no proteinogénico, el cual se obtuvo con rendimiento del 47% (para los dos pasos).



11ca **20** (47%)

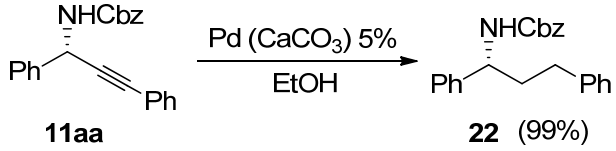
Esquema 3.16. Síntesis de α-aminoácidos por ozonolisis de aminas propargílicas.

A continuación, abordamos la reducción del triple enlace. Para ello llevamos a cabo la hidrogenación catalítica con Pd sobre C activo al 10% en etanol, obteniéndose así la correspondiente amina alifática (Esquema 3.17). Esta reacción transcurrió con rendimiento cuantitativo manteniendo la integridad estereoquímica del centro estereogénico.



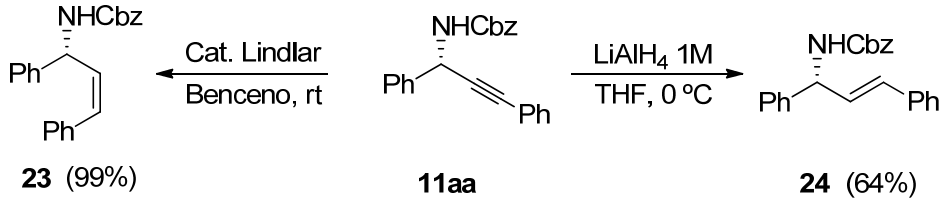
Esquema 3.17. Reducción del triple enlace y desprotección de la amina.

La reducción selectiva del triple enlace para dar lugar a la correspondiente amina alifática protegida se consiguió con la utilización de un catalizador menos activo, Pd sobre $CaCO_3$ al 5%, en etanol (Esquema 3.18).



Esquema 3.18. Reducción selectiva del triple enlace.

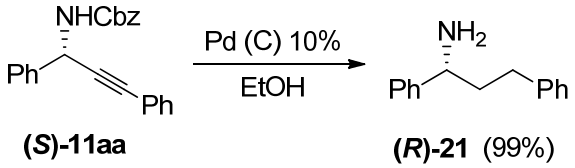
La utilización de un catalizador de Pd sobre $CaCO_3$ al 5% envenenado con Pb (catalizador de Lindlar) condujo a la formación de la correspondiente amina alílica protegida con isomería *cis* (99% de rendimiento), mientras que el isómero *trans* se pudo obtener por reducción de la amina propargílica protegida con $LiAlH_4$ 1 M en THF (64 % de rendimiento).



Esquema 3.19. Síntesis de aminas alílicas protegidas *cis* (**23**) y *trans* (**24**).

3.3.5. Determinación de la configuración absoluta

La obtención de la amina **21** (Esquema 3.17) permitió determinar la configuración absoluta de la amina propargílica **11aa** por comparación del valor de su poder rotatorio con el descrito en la bibligrafía.[26] La amina **21** obtenida por nosotros presenta una configuración (*R*), por lo que la configuración de la amina propargílica protegida **11aa** es (*S*). Para el resto de productos **11** se asignó la configuración absoluta asumiendo un mecanismo estereogénico uniforme.



(*S*)-11aa **(*R*)-21** (99%)

$[\alpha]_D^{25}$ = +18,1 (c 1,3, $CHCl_3$, 87% *ee*)
Bib.[26] $[\alpha]_D^{25}$ = +9,1 (c 0,5, $CHCl_3$, 97% *ee*)

Esquema 3.20. Determinación de la configuración absoluta de la amina propargílica protegida **11aa**.

3.3.6. Propuesta mecanística para la alquinilación de iminas generadas *in situ* a partir de α-amido sulfonas

La Figura 3.12 muestra un ciclo catalítico plausible para la reacción de alquinilación de α-amido sulfonas con (*R*)-BINOL y Et_2Zn. En primer lugar, la desprotonación del ligando BINOL y del acetileno por parte del dietilzinc daría lugar a un complejo catalítico BINOL zincato-etilalquinilzinc **I**. Por otra parte, la reacción entre la α-amido sulfona y otro equivalente de dietilzinc proporcionaría la imina *N*-Cbz protegida, que se coordinaría con el catalizador **I** para dar lugar al intermedio **II**. La transferencia del alquiniluro desde el etilalquinilzinc a la imina liberaría el producto de reacción y el BINOL-zincato **III**. Este, tras la coordinación con otra molécula de etilalquinilzinc regeneraría el complejo catalítico, reiniciando el ciclo.

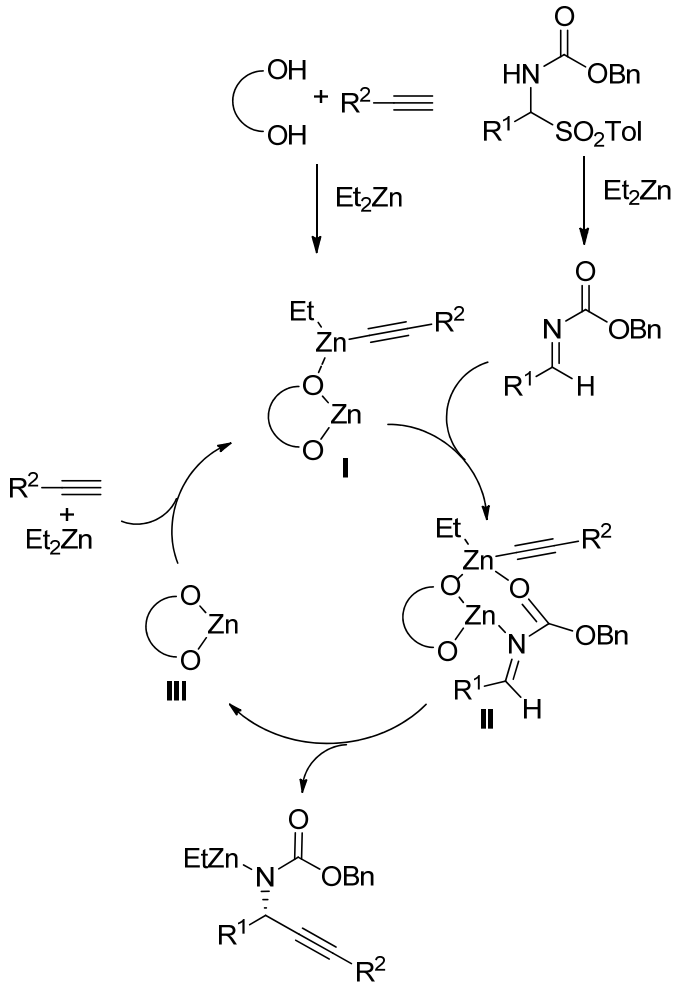


Figura 3.12. Ciclo catalítico simplificado para la alquinilación de α-amido sulfonas en presencia de complejos de BINOL-Zn.

La transferencia del alquiniluro desde la molécula de alquiniletilzinc coordinada a un oxígeno del BINOL en el intermedio **II** estaría asistida mediante la coordinación del átomo de oxígeno carbonílico del carbamato a través de un anillo de seis miembros, proporcionando la amina propargílica *N*-Cbz protegida con la configuración (*S*).

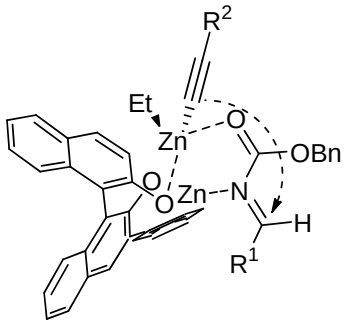


Figura 3.13. Modelo estereoquímico para la alquinilación de iminas *N*-Cbz protegidas generadas *in situ* a partir de α-amido sulfonas en presencia de complejos BINOL-Zn (uno de los sustituyentes en el C(3) del ligando ha sido omitido por claridad).

3.4. CONCLUSIONES

Se ha diseñado un método enantioselectivo de adición de alquinos terminales a *N*-aciliminas generadas *in situ* a partir de α-amido sulfonas catalizada por un sistema formado por un ligando de tipo BINOL y Et_2Zn a 0 °C en CH_2Cl_2.

Es necesaria la presencia de sustituyentes en las posiciones 3,3' del ligando de tipo BINOL para conseguir enantioselectividades elevadas. El ligando (*R*)-(+)-3,3'-bis(3,5-bis(trifluorometil)-fenil)-1,1'-bi-2-naftol (**L6**) proporcionó los mejores resultados.

Se ha utilizado el grupo benciloxicarbonilo (Cbz) como protector, debido a que dio lugar a un mayor rendimiento y enantioselectividad que los grupos *terc*-butiloxicarbonilo y etiloxicarbonilo.

Los sustituyentes sobre el anillo aromático del grupo sulfona no afectan a la enantioselectividad y rendimiento del proceso, lo cual confirma que la reacción transcurre a través de una reacción tándem de eliminación-adición.

Se han utilizado un conjunto de quince α-amido sulfonas aromáticas y heteroaromáticas de distinta naturaleza electrónica y estérica en la reacción de alquinilación con fenilacetileno, proporcionando las correspondientes aminas propargílicas protegidas con buenos rendimientos y enantioselectividades de buenas a elevadas. La presencia de sustituyentes en *orto* condujo a elevadas enantioselectividades independientemente de la naturaleza electrónica del sustituyente. Se han ensayado tres α-amido sulfonas alifáticas con rendimientos y enantioselectividades moderados.

Se han ensayado nueve alquinos aromáticos con grupos electrón-dadores y electrón-aceptores en el anillo aromático en la reacción con la benciloxicarbonilaminofenilmetil *p*-toluenosulfona con rendimientos y enantioselectividades elevados. La presencia de sustituyentes en la posición *orto* del anillo aromático del alquino disminuye de forma variable la enantioselectividad. Se han evaluado cinco alquinos alifáticos proporcionando los productos de alquinilación con buenas enantioselectividades.

Se han ensayado cinco α-amido sulfonas aromáticas con diferente naturaleza electrónica y estérica con cuatro alquinos aromáticos, proporcionando las correspondientes aminas propargílicas protegidas con rendimientos y enantioselectividades elevados.

Se han llevado a cabo diversas transformaciones sintéticas que han permitido demostrar la utilidad sintética de los productos de alquinilación formados. Con estas transformaciones se han obtenido α-aminoácidos no proteinogénicos, se ha podido determinar la configuración absoluta de los productos de alquinilación y se han sintetizado las correspondientes aminas alifáticas y alílicas protegidas.

3.5. SECCIÓN EXPERIMENTAL

3.5.1. Técnicas generales

Ver apartado 2.5.1.

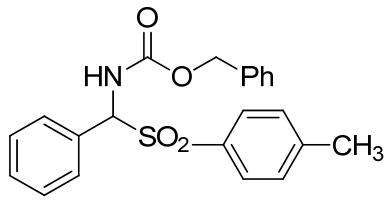
Resonancia Magnética Nuclear (RMN): Se ha utilizado DMSO-d_6 como disolvente para el análisis y caracterización de las α-amido sulfonas de partida, utilizando el residuo de disolvente no deuterado como referencia (2,50 ppm para ^{1}H y 39,51 ppm para ^{13}C).

3.5.2. Procedimientos generales de síntesis y caracterización de nuevos productos

3.5.2.1. Síntesis y caracterización de α-amido sulfonas 8

En un matraz de fondo redondo de 250 mL se disuelven 18 mmol del carbamato adecuado y 36 mmol de sulfinato de sodio en una mezcla de MeOH:H_2O (1:2) (18:36 mL). Se añade 36 mmol de aldehído, 1,37 mL de ácido fórmico y se agita a temperatura ambiente durante 72 horas. La mezcla de reacción se filtra a vacío en un embudo Büchner y se lava con agua y éter para dar lugar a la α-amido sulfona pura.

Benciloxicarbonilaminofenilmetil *p*-toluenosulfona (8aa)

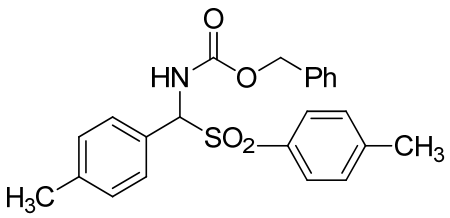


8aa

RMN ^{1}H (300 MHz, DMSO-d_6) δ 9.13 (d, *J* = 10.8 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.61 (dd, *J* = 7.3, 2.0 Hz, 2H), 7.42-7.32 (m, 8H), 7.22 (dd, *J* = 7.8, 2.1 Hz, 2H), 6.04 (d, *J* = 10.8 Hz, 1H), 4.93 (d, *J* = 12.6 Hz, 1H), 4.86 (d, *J* = 12.6 Hz, 1H), 2.40 (s, 3H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.2 (C), 144.6 (C), 136.4 (C), 133.8 (C), 130.4 (C), 129.6 (CH), 129.5 (CH), 129.3 (CH), 129.1 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.6 (CH), 74.9 (CH), 66.0 (CH_2), 21.2 (CH_3).

Benciloxicarbonilamino-*p*-tolilmetil *p*-toluenosulfona (8ba)

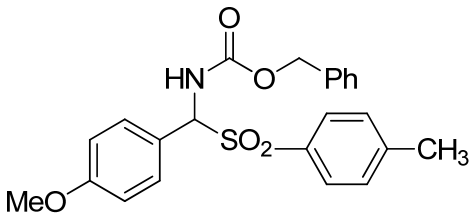


8ba

RMN ^{1}H (300 MHz, DMSO-d_6) δ 9.07 (d, *J* = 10.7 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.38-7.33 (m, 5H), 7.22-7-18 (m, 4H), 5.98 (d, *J* = 10.7 Hz, 1H), 4.92 (d, *J* = 12.6 Hz, 1H), 4.85 (d, *J* = 12.6 Hz, 1H), 2.40 (s, 3H), 2.31 (s, 3H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.3 (C), 144.5 (C), 138.9 (C), 136.4 (C), 133.9 (C), 129.5 (CH), 129.1 (CH), 128.7 (CH), 128.3 (CH), 127.9 (CH), 127.6 (CH), 127.4 (C), 74.7 (CH), 66.0 (CH), 21.2 (CH_3), 20.8 (CH_3).

Benciloxicarbonilamino-*p*-metoxifenilmetil *p*-toluenosulfona (8ca)

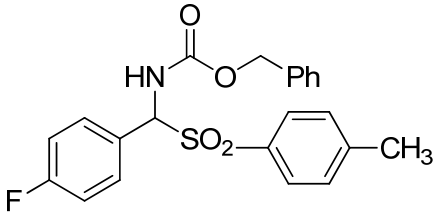


8ca

RMN ^{1}H (300 MHz, DMSO-d_6) δ 9.05 (d, *J* = 10.7 Hz, H), 7.68 (d, *J* = 8.23 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.38-7.33 (m, 5H), 7.23-7.20 (m, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.98 (d, *J* = 10.7 Hz, 1H), 4.92 (d, *J* = 12.6 Hz, 1H), 4.85 (d, *J* = 12.6 Hz, 1H), 3.77 (s, 3H), 2.40 (s, 3H).

RMN 13C (75.5 MHz, DMSO-d_6) δ 160.0 (C), 155.2 (C), 144.4 (C), 136.4 (C), 133.9 (C), 131.0 (CH), 129.5 (CH), 129.1 (CH), 128.3 (CH), 127.9 (C), 127.6 (CH), 122.2 (C), 113.6 (CH), 74.5 (CH), 66.0 (CH2), 55.2 (CH_3), 21.2 (CH_3).

Benciloxicarbonilamino-*p*-fluorofenilmetil *p*-toluenosulfona (8da)



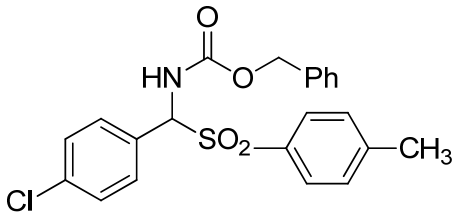
8da

RMN ^{1}H (300 MHz, DMSO-d_6) δ 9.20 (d, *J* = 10.2 Hz, 1H), 7.74-7.72 (m, 4H), 7.38-7.22 (m, 9H), 6.17 (d, *J* = 10.3 Hz, 1H), 4.96 (d, *J* = 12.6 Hz, 1H), 4.88 (d, *J* = 12.5, 1H), 2.38 (s, 3H).

RMN 13C (75.5 MHz, DMSO-d_6) δ 162.8 (d, *J* =

246.4 Hz, C), 155.3 (C), 144.7 (C), 136.4 (C), 133.7 (C), 132.0 (d, *J* = 8.5 Hz, CH), 129.6 (CH), 129.2 (CH), 128.4 (CH), 128.0 (CH), 127.7 (CH), 126.8 (d, *J* = 2.8 Hz, C), 115.1 (d, *J* = 21.6 Hz, CH), 74.1 (CH), 66.1 (CH_2), 21.2 (CH_3).

Benciloxicarbonilamino-*p*-clorofenilmetil *p*-toluenosulfona (8ea)

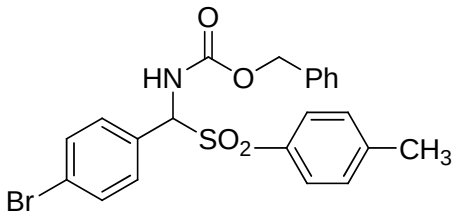


8ea

RMN ^{1}H (300 MHz, DMSO-d_6) δ 9.18 (d, *J* = 10.4 Hz, 1H), 7.73-7.67 (m, 4H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.40-7.33 (m, 5H), 7.21 (d, *J* = 5.7 Hz, 2H), 6.15 (d, *J* = 10.3 Hz, 1H), 4.93 (d, *J* = 12.5 Hz, 1H), 4.86 (d, *J* = 12.5 Hz, 1H), 2.40 (s, 3H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.2 (C=O), 144.8 (C), 136.3 (C), 134.4 (C), 133.6 (C), 131.5 (CH), 129.6 (CH), 129.2 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 127.7 (CH), 74.1 (CH), 66.1 (CH_2), 21.2 (CH_3).

Benciloxicarbonilamino-*p*-bromofenilmetil *p*-toluenosulfona (8fa)

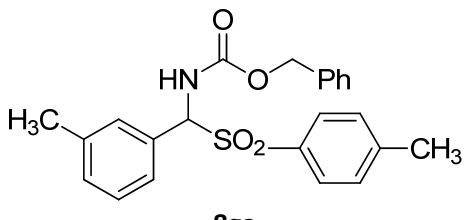


8fa

RMN ^{1}H (300 MHz, DMSO-d_6) δ 9.13 (d, *J* = 10.7 Hz, 1H), 7.84 (d, *J* = 1.5 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 3.0 Hz, 3H), 7.40-7.33 (m, 5H), 7.21 (dd, *J* = 7.6, 2.1 Hz, 2H), 6.10 (d, *J* = 10.5 Hz, 1H), 4.92 (d, *J* = 12.6 Hz, 1H), 4.85 (d, *J* = 12.6 Hz, 1H), 2.40 (s, 3H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.2 (C=O), 144.8 (C), 136.3 (C), 133.5 (C), 132.3 (CH), 131.7 (CH), 131.1 (CH), 129.6 (CH), 129.1 (CH), 128.3 (CH), 127.6 (CH), 123.1 (C), 74.2 (CH), 66.1 (CH_2), 21.2 (CH_3).

Benciloxicarbonilamino-*m*-tolilmetil *p*-toluenosulfona (8ga)



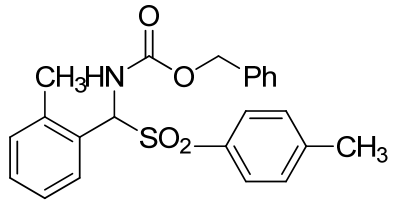
8ga

RMN ^{1}H (300 MHz, DMSO-d_6) δ 9.09 (d, *J* = 10.7 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.42-7.20 (m, 11H), 5.97 (d, *J* = 10.7 Hz, 1H), 4.91 (d, *J* = 12.6 Hz, 1H), 4.84 (d, *J* = 12.6 Hz, 1H),

2.40 (s, 3H), 2.30 (s, 3H).

RMN 13C (75.5 MHz, DMSO-d_6) δ 155.3 (C=O), 144.6 (C), 137.4 (C), 136.4 (C), 133.9 (C), 130.3 (C), 130.2 (CH), 130.0 (CH), 129.6 (CH), 129.2 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 126.8 (CH), 74.9 (CH), 66.0 (CH_2), 21.2 (CH_3), 21.0 (CH_3).

Benciloxicarbonilamino-*o*-tolilmetil *p*-toluenosulfona (8ha)

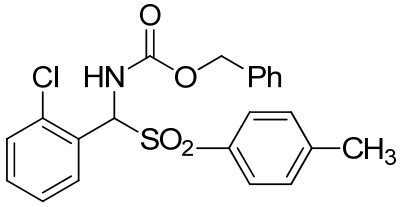


8ha

RMN ^{1}H (300 MHz, DMSO-d_6) δ 9.15 (d, *J* = 10.5 Hz, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.41-7.20 (m, 10H), 6.20 (d, *J* = 10.5 Hz, 1H), 4.93 (d, *J* = 12.6 Hz, 1H), 4.83 (d, 12.6 Hz, 1H), 2.41 (s, 3H), 2.35 (s, 3H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.6 (C), 145.0 (C), 137.5 (C), 136.4 (C), 134.0 (C), 130.3 (CH), 129.8 (CH), 129.54 (C), 129.50 (CH), 129.3 (CH), 129.0 (CH), 128.5 (CH), 128.1 (CH), 127.8 (CH), 126.2 (CH), 70.8 (CH), 66.2 (CH_2), 21.3 (CH_3), 19.3 (CH_3).

Benciloxicarbonilamino-*o*-clorofenilmetil *p*-toluenosulfona (8ja)

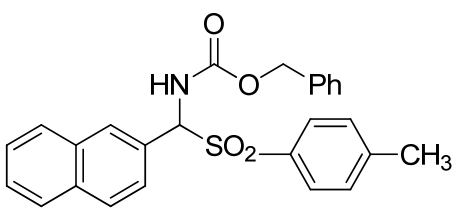


8ja

RMN ^{1}H (300 MHz, DMSO-d_6) δ 9.28 (d, *J* = 10.5 Hz, 1H), 7.95-7.92 (m, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.51-7.44 (m, 3H), 7.41-7.34 (m, 5H), 7.24 (dd, *J* = 7.6, 1.9 Hz, 2H), 6.55 (d, *J* = 10.6 Hz, 1H), 4.97 (d, *J* = 12.5 Hz, 1H), 4.89 (d, *J* = 12.5 Hz, 1H), 2.40 (s, 3H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.3 (C), 145.0 (C), 136.2 (C), 134.0 (C), 133.7 (C), 131.3 (CH), 130.9 (CH), 129.8 (CH), 129.3 (CH), 128.9 (C), 128.9 (CH), 128.3 (CH), 128.0 (CH), 127.8 (CH), 127.4 (CH), 70.8 (CH), 66.3 (CH_2), 21.2 (CH_3).

Benciloxicarbonilamino-(naft-2-il)-metil *p*-toluenosulfona (8ka)



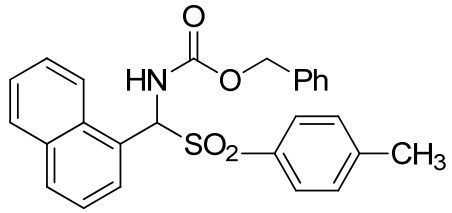
8ka

RMN ^{1}H (300 MHz, DMSO-d_6) δ 9.27 (d, *J* = 10.7 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 2H), 7.91 (d, *J* = 6.7 Hz, 1H), 7.75-7.73 (m, 3H), 7.59-7.56 (m, 2H), 7.39-7.33 (m, 6H), 7.22 (d, *J* = 6.5 Hz, 2H), 6.23

(d, *J* = 10.7 Hz, 1H), 4.94 (d, *J* = 12.6 Hz, 1H), 4.87 (d, *J* = 12.6 Hz, 1H), 2.40 (s, 3H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.3 (C), 144.7 (C), 136.4 (C), 135.9 (C), 134.6 (CH), 133.8 (C), 133.1 (C), 132.3 (C), 129.6 (CH), 129.5 (CH), 129.2 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 127.0 (C), 126.7 (CH), 126.6 (CH), 122.3 (CH), 75.1 (CH), 66.1 (CH_2), 21.2 (CH_3).

Benciloxicarbonilamino-(naft-1-il)-metil *p*-toluenosulfona (8la)

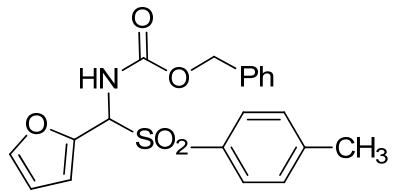


8la

RMN ^{1}H (400 MHz, DMSO-d_6) δ 9.40 (d, *J* = 10.5 Hz, 1H), 8.24 (d, *J* = 8.6 Hz, 1H), 8.09-7.98 (m, 3H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.67-7.55 (m, 3H), 7.40-7.32 (m, 5H), 7.22-7.20 (m, 2H), 6.93 (d, *J* = 10.5 Hz, 1H), 4.95 (d, *J* = 12.6 Hz, 1H), 4.86 (d, *J* = 12.6 Hz, 1H), 2.39 (s, 3H).

RMN ^{13}C (100 MHz, DMSO-d_6) δ 155.5 (C), 144.8 (C), 136.3 (C), 134.0 (C), 133.0 (C), 131.4 (C), 130.1 (CH), 129.7 (CH), 129.1 (CH), 128.7 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 127.1 (C), 127.1 (CH), 126.0 (CH), 125.2 (CH), 123.2 (CH), 69.8 (CH), 66.2 (CH_2), 21.2 (CH_3).

Benciloxicarbonilamino-(furan-2-il)-metil *p*-toluenosulfona (8ma)

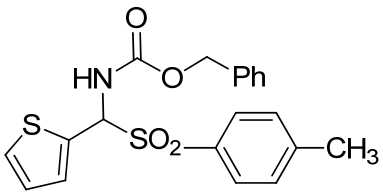


8ma

RMN ^{1}H (300 MHz, DMSO-d_6) δ 9.14 (d, *J* = 10.3 Hz, 1H), 7.72 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.39-7.32 (m, 5H), 7.26 (dd, *J* = 7.7, 1.8 Hz, 2H), 6.73 (d, *J* = 3.3 Hz, 1H), 6.51 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.05 (d, *J* = 10.3 Hz, 1H), 6.05 (d, *J* = 10.3 Hz, 1H), 4.98 (d, *J* = 12.5 Hz, 1H), 4.92 (d, *J* = 12.6 Hz, 1H), 2.40 (s, 3H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.2 (C), 144.9 (C), 144.4 (CH), 144.3 (C), 136.3 (C), 133.4 (C), 129.6 (CH), 129.0 (CH), 128.3 (CH), 127.9 (CH), 127.7 (CH), 112.1 (CH), 111.2 (CH), 70.0 (CH), 66.2 (CH_2), 21.2 (CH_3).

Benciloxicarbonilamino-(tien-2-il)-metil *p*-toluenosulfona (8na)

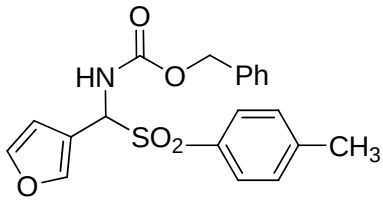


8na

RMN ^{1}H (300 MHz, DMSO-d_6) δ 9.21 (d, *J* = 10.4 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.64 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.39-7.34 (m, 6H), 7.24-7.21 (m, 2H), 7.08 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.25 (d, *J* = 10.5 Hz, 1H), 4.94 (d, *J* = 12.6 Hz, 1H), 4.87 (d, *J* = 12.6 Hz, 1H), 2.40 (s, 3H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.1 (C), 144.8 (C), 136.3 (C), 133.3 (C), 131.3 (C), 129.9 (CH), 129.6 (CH), 129.2 (CH), 128.5 (CH), 128.3 (CH), 127.9 (CH), 127.6 (CH), 127.0 (CH), 71.0 (CH), 66.1 (CH_2), 21.2 (CH_3).

Benciloxicarbonilamino-(furan-3-il)-metil *p*-toluenosulfona (8oa)

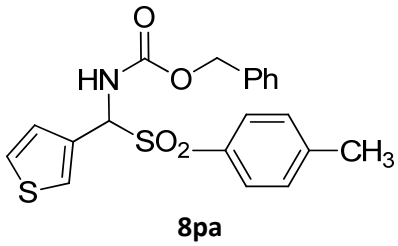


8oa

RMN ^{1}H (300 MHz, DMSO-d_6) δ 8.93 (d, *J* = 10.3 Hz, 1H), 7.84 (s, 1H), 7.67-7.64 (m, 3H), 7.39-7.33 (m, 5H), 7.25 (dd, *J* = 7.5, 1.5 Hz, 2H), 6.72 (s, 1H), 6.02 (d, J = 10.3 Hz, 1H), 4.95 (d, *J* = 12.5 Hz, 1H), 4.88 (d, *J* = 12.6 Hz, 1H), 2.4 (s, 3H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.1 (C), 144.6 (C), 143.5 (CH), 143.4 (CH), 136.4 (C), 133.4 (C), 129.5 (CH), 129.2 (CH), 128.4 (CH), 128.0 (CH), 127.8 (CH), 115.7 (C), 110.7 (CH), 68.5 (CH), 66.1 (CH_2), 21.2 (CH_3).

Benciloxicarbonilamino-(tien-3-il)-metil *p*-toluenosulfona (8pa)

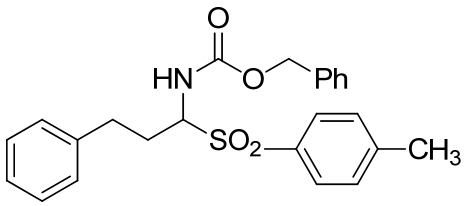


8pa

RMN ^{1}H (300 MHz, DMSO-d_6) δ 9.03 (d, *J* = 10.5 Hz, 1H), 7.76 (d, *J* = 2.4 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.55 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.38-7.34 (m, 6H), 7.24 (dd, *J* = 7.2, 2.0 Hz, 2H), 6.16 (d, *J* = 10.5 Hz, 1H), 4.94 (d, *J* = 12.6 Hz, 1H), 4.88 (d, *J* = 12.6 Hz, 1H), 2.39 (s, 3H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.1 (C), 144.6 (C), 136.4 (C), 133.6 (C), 130.8 (C), 129.5 (CH), 129.1 (CH), 128.3 (CH), 128.3 (CH), 127.9 (CH), 127.7 (CH), 127.3 (CH), 126.2 (CH), 71.4 (CH), 66.1 (CH_2), 21.2 (CH_3).

Benciloxicarbonilamino-2-feniletilmetil *p*-toluenosulfona (8qa)

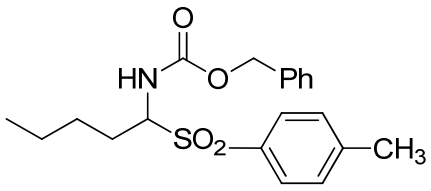


8qa

RMN ^{1}H (300 MHz, DMSO-d_6) δ 8.42 (d, *J* = 9.6 Hz, 1H), 7.66-7.57 (m, 2H), 7.41-7.33 (m, 5H), 7.29-7.19 (m, 5H), 7.14-7.12 (m, 2H), 4.94 (d, *J* = 12.6 Hz, 1H), 4.88 (d, *J* = 12.6 Hz, 1H), 4.75-4.67 (m, 1H), 2.68-2.79 (m, 1H), 2.59-2.52 (m, 1H), 2.37 (s, 3H), 2.30-2.16 (m, 1H), 2.02-1.89 (m, 1H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.3 (C), 144.4 (C), 140.1 (C), 136.5 (C), 133.5 (C), 129.5 (CH), 128.9 (CH), 128.32 (CH), 128.25 (CH), 127.8 (CH), 127.5 (CH), 126.1 (CH), 71.3 (CH), 61.7 (CH_2), 30.6 (CH_2), 27.9 (CH_2), 21.0 (CH_3).

Benciloxicarbonilamino-*n*-butilmetil *p*-toluenosulfona (8ra)

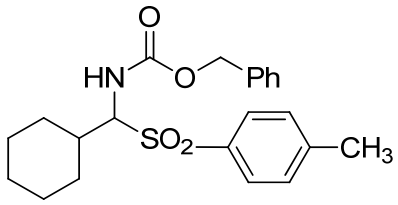


8ra

RMN ^{1}H (300 MHz, DMSO-d_6) δ 8.38 (d, *J* = 9.6 Hz, 1H), 7.64-7.53 (m, 2H), 7.41-7.30 (m, 5H), 7.14-7.12 (m, 2H), 4.93 (d, *J* = 12.0 Hz, 1H), 4.87 (d, *J* = 12.2 Hz, 1H), 4.73-4.66 (m, 1H), 2.36 (s, 3H), 1.80-1.71 (m, 2H), 1.52-1.43 (m, 2H), 1.40-1.38 (m, 2H), 0.92 (t, *J* = 7.5 Hz, 3H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.1 (C), 140.1 (C), 136.5 (C), 133.5 (C), 129.5 (CH), 128.9 (CH), 128.32 (CH), 128.25 (CH), 127.8 (CH), 71.1 (CH), 61.4 (CH_2), 27.1 (CH_2), 24.9 (CH_2), 22.3 (CH_2), 21.1 (CH_3), 14.0 (CH_3).

Benciloxicarbonilamino-ciclohexilmetil *p*-toluenosulfona (8sa)

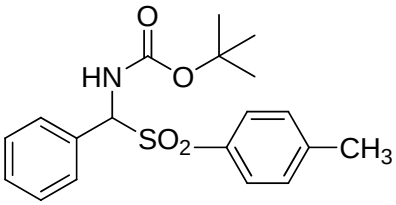


8sa

RMN ^{1}H (300 MHz, DMSO-d_6) δ 8.40 (d, *J* = 9.6 Hz, 1H), 7.64-7.57 (m, 2H), 7.26-7.18 (m, 5H), 7.15-7.12 (m, 2H), 4.92 (d, *J* = 12.3 Hz, 1H), 4.84 (d, *J* = 12.4 Hz, 1H), 4.53 (dd, *J* = 8.1, 6.0 Hz, 1H), 2.36 (s, 3H), 1.90-1.79 (m, 4H), 1.73-1.66 (m, 2H), 1.39-1.13 (m, 5H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.0 (C), 140.0 (C), 136.4 (C), 133.2 (C), 129.5 (CH), 128.9 (CH), 128.3 (CH), 127.8 (CH), 127.5 (CH), 69.8 (CH), 61.3 (CH_2), 27.4 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 21.0 (CH_3).

terc-Butiloxicarbonilaminofenilmetil _p_-toluenosulfona (9aa)

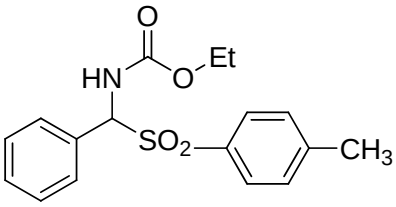


9aa

RMN ^{1}H (300 MHz, DMSO-d_6) δ 8.69 (d, *J* = 10.8 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.64 (dd, *J* = 7.4, 1.9 Hz, 2H), 7.43-7.39 (m, 5H), 5.96 (d, *J* = 10.7 Hz, 1H), 2.38 (s, 3H), 1.18 (s, 9H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 154.1 (C=O), 144.4 (C), 134.0 (C), 130.4 (C), 129.9 (CH), 129.5 (CH), 129.25 (CH), 129.22 (CH), 128.1 (CH), 79.3 (C), 74.4 (CH), 27.8 (CH_3), 21.1 (CH_3).

Etiloxicarbonilaminofenilmetil _p_-toluenosulfona (10aa)

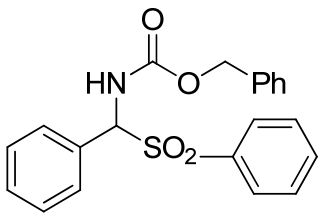


10aa

RMN ^{1}H (300 MHz, DMSO-d_6) δ 8.95 (d, *J* = 10.8 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.62-7.60 (m, 2H), 7.41-7.38 (m, 5H), 6.02 (d, *J* = 10.8 Hz, 1H), 3.89-7.80 (m, 2H), 2.38 (s, 3H), 1.01 (t, *J* = 7.1 Hz, 9H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.3 (C), 144.6 (C), 133.8 (C), 130.5 (C), 129.7 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 128.1 (CH), 75.0 (CH), 60.7 (CH_2), 21.2 (CH_3), 14.4 (CH_3).

Benciloxicarbonilaminofenilmetil fenilsulfona (8ab)

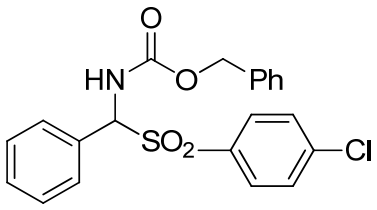


8ab

RMN ^{1}H (300 MHz, DMSO-d_6) δ 9.15 (d, *J* = 10.7 Hz, 1H), 7.83 (d, *J* = 7.2 Hz, 2H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.64-7.56 (m, 4H), 7.41-7.31 (m, 6H), 7.20 (dd, *J* = 7.6, 1.7 Hz, 2H), 6.09 (d, *J* = 10.7 Hz, 1H), 4.90 (d, *J* = 12.5 Hz, 1H), 4.84 (d, *J* = 12.7 Hz, 1H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.2 (C), 136.7 (C), 136.3 (C), 134.1 (CH), 130.2 (C), 129.6 (CH), 129.4 (CH), 129.1 (CH), 129.0 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 74.9 (CH), 66.1 (CH_2).

Benciloxicarbonilaminofenilmetil *p*-clorofenilsulfona (8ac)

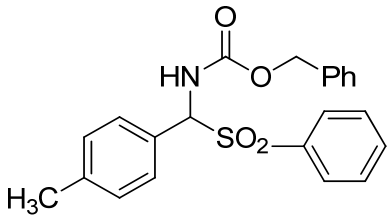


8ac

RMN ^{1}H (300 MHz, DMSO-d_6) δ 9.18 (d, *J* = 10.7 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 2H), 7.68-7.63 (m, 4H), 7.44-7.32 (m, 6H), 7.21 (dd, *J* = 7.7, 1.9 Hz, 2H), 6.16 (d, *J* = 10.7 Hz, 1H), 4.95 (d, *J* = 12.6 Hz, 1H), 4.86 (d, *J* = 12.6 Hz, 1H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.2 (C), 139.3 (C), 136.3 (C), 135.6 (C), 131.1 (CH), 129.9 (C), 129.7 (CH), 129.5 (CH), 129.2 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 127.7 (CH), 74.9 (CH), 66.1 (CH_2).

Benciloxicarbonilamino-*p*-tolilmetil fenilsulfona (8bb)

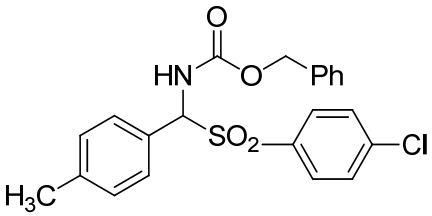


8bb

RMN ^{1}H (300 MHz, DMSO-d_6) δ 9.11 (d, *J* = 10.7 Hz, 1H), 7.83 (d, *J* = 7.3 Hz, 2H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.37-7.31 (m, 3H), 7.21-7.18 (m, 4H), 6.04 (d, *J* = 10.7 Hz, 1H), 4.88 (d, *J* = 12.6 Hz, 1H), 4.83 (d, *J* = 12.6 Hz, 1H), 2.32 (s, 3H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.2 (C), 139.0 (C), 136.8 (C), 136.3 (C), 134.1 (CH), 129.6 (CH), 129.1 (CH), 129.0 (CH), 128.7 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 127.2 (C), 74.7 (CH), 66.0 (CH_2), 20.8 (CH_3).

Benciloxicarbonilamino-*p*-tolilmetil *p*-clorofenilsulfona (8bc)



8**bc**

RMN ^{1}H (300 MHz, DMSO-d_6) δ 9.16 (d, *J* = 10.6 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.38-7.31 (m, 3H), 7.23-7.21 (m, 4H), 6.12 (d, *J* = 10.6 Hz, 1H), 4.95 (d, *J* = 12.6 Hz, 1H), 4.86 (d, *J* = 12.6 Hz, 1H), 2.32 (s, 3H).

RMN ^{13}C (75.5 MHz, DMSO-d_6) δ 155.2 (C), 139.3 (C), 139.1 (C), 136.3 (C), 135.8 (C), 131.1 (CH), 129.6 (CH), 129.2 (CH), 128.8 (CH), 128.4 (CH), 128.0 (CH), 127.7 (CH), 126.9 (C), 74.8 (CH), 66.1 (CH_2), 20.8 (CH_3).

3.5.2.2. Síntesis y caracterización de las N-benciloxicarbonil aminas propargílicas 11 y de sus derivados

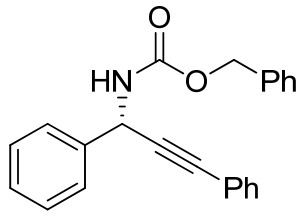
Procedimiento general para la alquinilación enantioselectiva de las α-amido sulfonas 8 (Procedimiento B)

Una disolución de Et_2Zn 1 M en hexano (0,375 mL, 0,375 mmol) se añadió gota a gota sobre una disolución de ligando **L6** (17,7 mg, 0,025 mmol) y alquino **2** (0,900 mmol) en CH_2Cl_2 (0,4 mL). Se agitó 1,5 h a temperatura ambiente. Se enfrió la reacción a 0 °C durante 15 min y se añadió una disolución de α-amido sulfona **8** (0,125 mmol) en CH_2Cl_2 (1,0 mL) mediante jeringuilla. La disolución se agitó hasta que la reacción se completó (CCF). La reacción se paró con 1,0 mL de agua. La fase acuosa se extrajo con CH_2Cl_2 (3x15 mL). La fase orgánica se lavó con salmuera (25 mL) y se secó sobre $MgSO_4$. La evaporación del disolvente a vacío condujo al crudo del producto, el cual se purificó por columna de cromatografía flash con una mezcla de eluyentes hexano:AcOEt (97,5:2,5 mL) para dar el compuesto **11**.

Procedimiento general para la síntesis de los productos racémicos.

Una disolución Me_2Zn en tolueno (0,09 mL, 0,188 mmol) se añadió gota a gota sobre una disolución de alquino **2** (0,188 mmol) en tolueno (1,2 mL). Tras agitar durante 30 min a temperature ambiente, la mezcla de reacción se calentó a 70 °C y se añadió la α-amido sulfona **8** (0,125 mmol). La disolución se agitó hasta que la reacción se completó (CCF). La reacción se paró con 1,0 mL de agua. La fase acuosa se extrajo con CH_2Cl_2 (3x15 mL). La fase orgánica se lavó con salmuera (25 mL) y se secó sobre $MgSO_4$. La evaporación del disolvente a vacío condujo al crudo del producto, el cual se purificó por columna de cromatografía flash empleando como eluyente una mezcla de hexano:AcOEt (97,5:2,5 mL) para dar el compuesto racémico **11**.

(*S*)-*N*-benciloxicarbonil-1,3-difenilprop-2-in-1-amina (11aa)



11aa

El exceso enantiomérico (87%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 19.6 min, enantiómero minoritario t_r = 10.6 min.

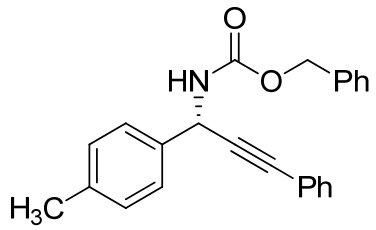
Mp 99-101 °C; $[\alpha]_D^{20}$ –17.4 (*c* 0.83, $CHCl_3$, 87% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.2 Hz, 2H), 7.47-7.44 (m, 2H), 7.40-7.24 (m, 11H), 5.95 (d, *J* = 8.7 Hz, 1H), 5.36 (d, *J* = 6.8 Hz, 1H), 5.18 (d, *J* = 12.0 Hz, 1H), 5.12 (d, *J* = 12.7 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.4 (C), 139.0 (C), 136.2 (C), 131.8 (CH), 128.7 (CH), 128.54 (CH), 128.52 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.0 (CH), 122.4 (C), 87.0 (C), 85.1 (C), 67.2 (CH_2), 47.4 (CH).

HRMS (ESI) *m/z*: 364.1314 $[M+Na]^+$, $C_{23}H_{19}NO_2Na$ requiere 364.1313.

(*S*)-*N*-benciloxicarbonil-3-fenil-1-*p*-tolilprop-2-in-1-amina (11ba)



11ba

El exceso enantiomérico (88%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 16.7 min, enantiómero minoritario t_r = 17.8 min.

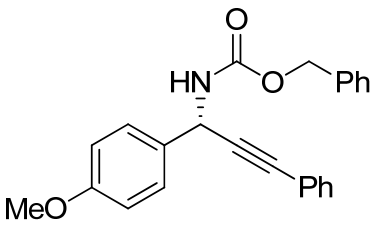
Mp 123-124 °C; $[\alpha]_D^{20}$ –16.50 (*c* 1.06, $CHCl_3$, 88% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.45-7.43 (m, 4H), 7.36-7.29 (m, 8H), 7.17 (d, *J* = 7.9 Hz, 2H), 5.89 (d, *J* = 8.2 Hz, 1H), 5.30 (d, *J* = 7.3 Hz, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.11 (d, *J* = 11.1 Hz, 1H), 2.34 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 138.0 (C), 136.2 (C), 136.1 (C), 131.7 (CH), 129.4 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 126.9 (CH), 122.5 (C), 87.2 (C), 84.9 (C), 67.1 (CH_2), 47.2 (CH), 21.1 (CH_3).

HRMS (ESI) *m/z*: 378.1465 $[M+Na]^+$, $C_{24}H_{21}NO_2Na$ requiere 378.1470.

(*S*)-*N*-benciloxicarbonil-3-fenil-1-(*p*-metoxifenil)-prop-2-in-1-amina (11ca)



11ca

El exceso enantiomérico (83%) se determinó mediante la ozonolisis del producto **20** con HPLC quiral (Chiralpak IC), hexano-^{i}PrOH 97:3, 1 mL/min, enantiómero mayoritario t_r = 76.6 min, enantiómero minoritario t_r = 100.5 min.

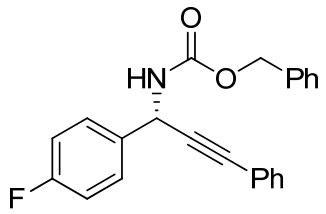
Mp 56-58 °C; $[\alpha]_D^{20}$ –11.6 (*c* 0.61, $CHCl_3$, 83% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.50-7.43 (m, 4H), 7.36-7.29 (m, 8H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.88 (d, *J* = 8.5 Hz, 1H), 5.32 (d, *J* = 8.1 Hz, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.11 (d, *J* = 10.8 Hz, 1H), 3.79 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 159.4 (C), 155.3 (C), 136.2 (C), 131.7 (CH), 128.5 (CH), 128.3 (CH), 128.17 (CH), 122.4 (C), 114.0 (CH), 87.2 (C), 84.9 (C), 67.1 (CH_2), 55.3 (CH_3), 47.0 (CH).

HRMS (ESI) *m/z*: 394.1416 $[M+Na]^+$, $C_{24}H_{21}NO_3Na$ requiere 394.1419.

(*S*)-*N*-benciloxicarbonil-3-fenil-1-(*p*-fluorofenil)-prop-2-in-1-amina (11da)



11da

El exceso enantiomérico (83%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 15.5 min, enantiómero minoritario t_r = 13.8 min.

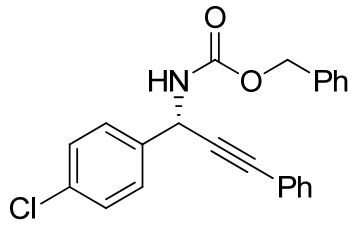
Mp 114-116 °C; $[\alpha]_D^{20}$ –6.1 (*c* 0.81, $CHCl_3$, 83% *ee*).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.55-7.52 (m, 2H), 7.45-7.43 (m, 2H), 7.35-7.30 (m, 8H), 7.04 (d, *J* = 8.7 Hz, 2H), 5.91 (d, *J* = 7.6 Hz, 1H), 5.34 (d, *J* = 6.1 Hz, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H).

^{13}C RMN (100 MHz, $CDCl_3$) δ 162.6 (d, *J* = 246.8 Hz, C), 155.4 (C), 136.1 (C), 135.0 (C), 131.8 (CH), 128.8 (CH), 128.7 (d, *J* = 4.3 Hz, CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 122.2 (C), 115.6 (d, *J* = 21.8 Hz, CH), 86.7 (C), 85.4 (C), 67.3 (CH_2), 46.9 (CH).

HRMS (ESI) *m/z*: 382.1224 $[M+Na]^+$, $C_{23}H_{18}FNO_2Na$ requiere 382.1219.

(*S*)-*N*-benciloxicarbonil-1-(*p*-clorofenil)-3-fenilprop-2-in-1-amina (11ea)



11ea

El exceso enantiomérico (90%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 15.8 min, enantiómero minoritario t_r = 14.8 min.

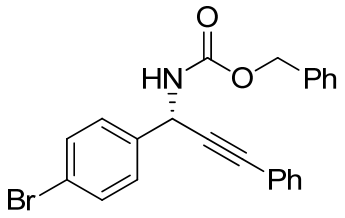
Mp 140-142 °C; $[\alpha]_D^{20}$ –11.8 (c 1.23, $CHCl_3$, 90% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.3 Hz, 2H), 7.45-7.42 (m, 2H), 7.36-7.29 (m, 10H), 5.90 (d, *J* = 8.1 Hz, 1H), 5.36 (d, *J* = 8.4 Hz, 1H), 5.17 (d, *J* = 12.1 Hz, 1H), 5.11 (d, *J* = 12.7 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.4 (C), 137.7 (C), 136.0 (C), 134.0 (C), 131.7 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.33 (CH), 128.26 (CH), 128.2 (CH), 122.1 (C), 86.3 (C), 85.5 (C), 67.3 (CH_2), 46.9 (CH).

HRMS (ESI) *m/z*: 398.0921 $[M+Na]^+$, $C_{23}H_{18}ClNO_2Na$ requiere 398.0924.

(*S*)-*N*-benciloxicarbonil-1-(*p*-bromofenil)-3-fenilprop-2-in-1-amina (11fa)



11fa

El exceso enantiomérico (91%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 18.0 min, enantiómero minoritario t_r = 17.0 min.

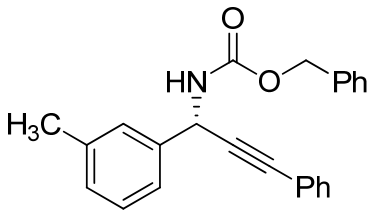
Mp 153-155 °C; $[\alpha]_D^{20}$ –5.6 (*c* 0.76, $CHCl_3$, 91% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.50-7.41 (m, 6H), 7.34-7.30 (m, 8H), 5.89 (d, *J* = 8.4 Hz, 1H), 5.35 (d, *J* = 8.4 Hz, 1H), 5.17 (d, *J* = 12.1 Hz, 1H), 5.11 (d, *J* = 12.0 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 138.2 (C), 136.0 (C), 131.8 (CH), 131.7 (CH), 128.73 (CH), 128.71 (CH), 128.6 (CH), 128.33 (CH), 128.28 (CH), 128.2 (CH), 122.2 (C), 122.1 (C), 86.2 (C), 85.5 (C), 67.3 (CH_2), 47.0 (CH).

HRMS (ESI) *m/z*: 442.0423 $[M+Na]^+$, $C_{23}H_{18}BrNO_2Na$ requiere 442.0419.

(*S*)-*N*-benciloxicarbonil-3-fenil-1-*m*-tolilprop-2-in-1-amina (11ga)



11ga

El exceso enantiomérico (86%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 15.6 min, enantiómero minoritario t_r = 9.9 min.

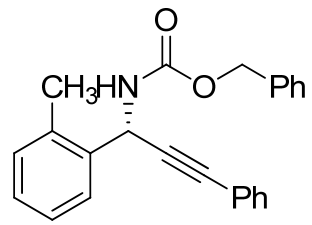
Mp 118-120 °C; $[\alpha]_D^{20}$ –16.1 (*c* 1.12, $CHCl_3$, 86% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.38-7.28 (m, 10H), 7.25 (d, *J* = 6.3 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 5.91 (d, *J* = 8.4 Hz, 1H), 5.34 (d, *J* = 7.1 Hz, 1H), 5.18 (d, *J* = 12.0 Hz, 1H), 5.12 (d, *J* = 12.6 Hz, 1H), 2.36 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.4 (C), 138.9 (C), 138.5 (C), 136.2 (C), 131.8 (CH), 128.9 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 124.0 (CH), 122.5 (C), 87.1 (C), 84.9 (C), 67.2 (CH_2), 47.4 (CH), 21.4 (CH_3).

HRMS (ESI) *m/z*: 378.1471 $[M+Na]^+$, $C_{24}H_{21}NO_2Na$ requiere 378.1470.

(*S*)-*N*-benciloxicarbonil-3-fenil-1-*o*-tolilprop-2-in-1-amina (11ha)



11ha

El exceso enantiomérico (90%) se determinó mediante HPLC (Chiralcel OD-H), hexano-^{i}PrOH 80:20, 1 mL/min, enantiómero mayoritario t_r = 17.5 min, enantiómero minoritario t_r = 7.4 min.

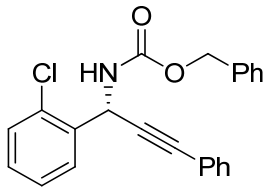
Mp 126-128 °C; $[\alpha]_D^{20}$ -26.3 (*c* 0.75, $CHCl_3$, 90% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.66-7.63 (m, 1H), 7.45-7.42 (m, 2H), 7.34-7.29 (m, 8H), 7.25-7.17 (m, 3H), 6.02 (d, *J* = 8.4 Hz, 1H), 5.29 (d, *J* = 7.2 Hz, 1H), 5.16 (d, *J* = 11.8 Hz, 1H), 5.12 (d, *J* = 12.6 Hz, 1H), 2.45 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.1 (C), 136.8 (C), 136.2 (C), 136.0 (C), 131.7 (CH), 130.9 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.22 (CH), 128.16 (CH), 128.1 (CH), 127.0 (CH), 126.4 (CH), 122.5 (C), 87.2 (C), 84.7 (C), 67.1 (CH_2), 45.2 (CH), 19.1 (CH_3).

HRMS (ESI) *m/z*: 378.1469 $[M+Na]^+$, $C_{24}H_{21}NO_2Na$ requiere 378.1470.

(*S*)-*N*-benciloxicarbonil-1-(*p*-clorofenil)-3-fenil-2-in-1-amina (11ja)



11ja

El exceso enantiomérico (90%) se determinó mediante HPLC (Chiralcel AD-H), hexano-^{i}PrOH 80:20, 1 mL/min, enantiómero mayoritario t_r = 14.7 min, enantiómero minoritario t_r = 18.5 min.

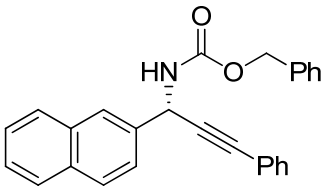
Mp 139-141 °C; $[\alpha]_D^{20}$ –20.1 (*c* 0.81, $CHCl_3$, 90% *ee*).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 1H), 7.43-7.38 (m, 3H), 7.35-7.27 (m, 10H), 6.15 (d, *J* = 8.1 Hz, 1H), 5.51 (s, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 5.11 (d, *J* = 7.4 Hz, 1H).

^{13}C RMN (100 MHz, $CDCl_3$) δ 155.0 (C), 136.3 (C), 136.1 (C), 133.3 (C), 131.8 (CH), 130.2 (CH), 129.6 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 128.23 (CH), 128.15 (CH), 128.1 (C), 127.2 (CH), 122.3 (CH), 86.2 (C), 84.9 (C), 67.2 (CH_2), 45.9 (CH).

HRMS (ESI) *m/z*: 398.0921 [M+Na], $C_{23}H_{18}ClNO_2Na$ requiere 398.0924.

(*S*)-*N*-benciloxicarbonil-3-fenil-1-(naft-2-il)-prop-2-in-1-amina (11ka)



11ka

El exceso enantiomérico (88%) se determinó mediante HPLC (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 19.7 min, enantiómero minoritario t_r = 21.3 min.

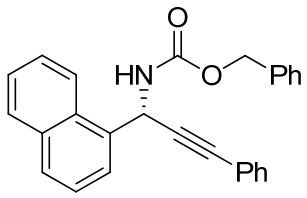
Mp 140-143 °C; $[\alpha]_D^{20}$ –1.6 (*c* 1.06, $CHCl_3$, 88% *ee*)

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.87-7.82 (m, 3H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.50-7.47 (m, 4H), 7.35-7.31 (m, 8H), 6.11 (d, *J* = 8.5 Hz, 1H), 5.46 (d, *J* = 7.6 Hz, 1H), 5.19 (d, *J* = 12.0 Hz, 1H), 5.14 (d, *J* = 13.6 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.4 (C), 136.3 (C), 136.1 (C), 133.1 (C), 133.0 (C), 131.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 126.4 (CH), 126.3 (CH), 125.8 (CH), 124.8 (CH), 122.4 (C), 86.9 (C), 85.4 (C), 67.2 (CH_2), 47.6 (CH).

HRMS (ESI) *m/z*: 414.1474 $[M+Na]^+$, $C_{27}H_{21}NO_2Na$ requiere 414.1470.

(*S*)-*N*-benciloxicarbonil-3-fenil-1-(naft-2-il)-prop-2-in-1-amina (11la)



11la

El exceso enantiomérico (2%) se determinó mediante HPLC (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 15.6 min, enantiómero minoritario t_r = 18.9 min.

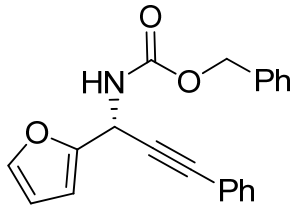
Mp 133-135 °C; $[\alpha]_D^{20}$ –0.3 (*c* 0.36, $CHCl_3$, 2% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.8 Hz, 1H), 7.92-7.84 (m, 3H), 7.53-7.44 (m, 4H), 7.36-7.29 (m, 9H), 6.60 (d, *J* = 9.1 Hz, 1H), 5.37 (d, *J* = 6.0 Hz, 1H), 5.17 (s, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.2 (C), 136.2 (C), 134.1 (C), 131.8 (CH), 130.4 (C), 129.4 (CH), 128.9 (CH), 128.6 (C), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.0 (CH), 126.8 (CH), 126.0 (CH), 125.4 (CH), 125.2 (CH), 123.4 (CH), 122.5 (C), 87.3 (C), 85.5 (C), 67.2 (CH_2), 45.3 (CH).

HRMS **(ESI)** *m/z*: 414.1473 $[M+Na]^+$, $C_{27}H_{21}NO_2Na$ requiere 414.1470.

(*S*)-*N*-benciloxicarbonil-3-fenil-1-(furan-2-il)-prop-2-in-1-amina (11ma)



11ma

El exceso enantiomérico (88%) se determinó mediante HPLC (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 16.6 min, enantiómero minoritario t_r = 15.1 min.

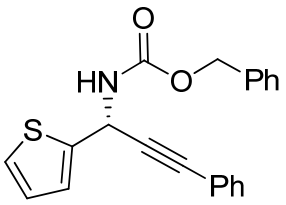
Mp 67-69 °C; $[\alpha]_D^{20}$ –8.0 (*c* 0.64, $CHCl_3$, 88% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.45-7.42 (m, 2H), 7.40-7.39 (m, 1H), 7.36-7.29 (m, 8H), 6.43 (d, *J* = 3.0 Hz, 1H), 6.34 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.99 (d, *J* = 8.5 Hz, 1H), 5.39 (d, *J* = 7.2 Hz, 1H), 5.18 (d, *J* = 11.9 Hz, 1H), 5.13 (d, *J* = 13.3 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.2 (C), 151.0 (C), 142.9 (CH), 136.1 (C), 131.8 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 122.1 (C), 110.4 (CH), 107.6 (CH), 84.7 (C), 84.0 (C), 67.3 (CH_2), 41.7 (CH).

HRMS (ESI) *m/z*: 354.1112 $[M+Na]^+$, $C_{21}H_{17}NO_3Na$ requiere 354.1106.

(*S*)-*N*-benciloxicarbonil-3-fenil-1-(tien-2-il)-prop-2-in-1-amina (11na)



11na

El exceso enantiomérico (78%) se determinó mediante HPLC (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 22.0 min, enantiómero minoritario t_r = 14.1 min.

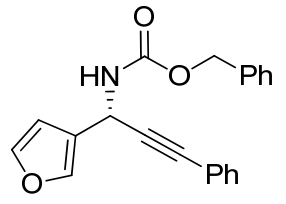
Mp 97-99 °C; $[\alpha]_D^{20}$ -10.8 (*c* 0.85, $CHCl_3$, 78% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.36-7.30 (m, 8H), 7.26 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.22 (d, *J* = 2.9 Hz, 1H), 7.0 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.14 (d, *J* = 8.5 Hz, 1H), 5.44 (d, *J* = 7.6 Hz, 1H), 5.19 (d, *J* = 11.9 Hz, 1H), 5.13 (d, *J* = 14.3 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.1 (C), 142.9 (C), 136.0 (C), 131.8 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 128.23 (CH), 128.15 (CH), 126.8 (CH), 125.8 (CH), 125.7 (CH), 122.1 (C), 86.4 (C), 84.4 (C), 67.3 (CH_2), 43.3 (CH).

HRMS (ESI) *m/z*: 370.0872 $[M+Na]^+$, $C_{21}H_{17}NO_2SNa$ requiere 370.0878.

(*S*)-*N*-benciloxicarbonil-3-fenil-1-(furan-3-il)-prop-2-in-1-amina (11oa)



11oa

El exceso enantiomérico (76%) se determinó mediante HPLC (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 14.0 min, enantiómero minoritario t_r = 12.2 min.

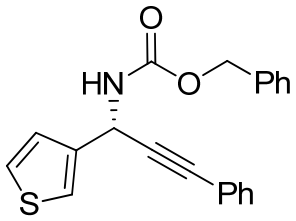
Mp 103-105 °C; $[\alpha]_D^{20}$ –18.5 (*c* 0.38, $CHCl_3$, 76% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.45-7.41 (m, 2H), 7.38 (t, *J* = 1.7 Hz, 1H), 7.35-7.29 (m, 8H), 6.47 (s, 1H), 5.83 (d, *J* = 8.9 Hz, 1H), 5.24 (d, *J* = 7.1 Hz, 1H), 5.15 (s, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 143.7 (CH), 140.4 (CH) 136.1 (C), 131.8 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 124.7 (C), 122.2 (C), 109.4 (CH), 86.4 (C), 83.5 (C), 67.2 (CH_2), 40.0 (CH).

HRMS (ESI) *m/z*: 354.1117 $[M+Na]^+$, $C_{21}H_{17}NO_3Na$ requiere 354.1106.

(*S*)-*N*-benciloxicarbonil-3-fenil-1-(tien-3-il)-prop-2-in-1-amina (11pa)



11pa

El exceso enantiomérico (74%) se determinó mediante HPLC (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 15.4 min, enantiómero minoritario t_r = 13.9 min.

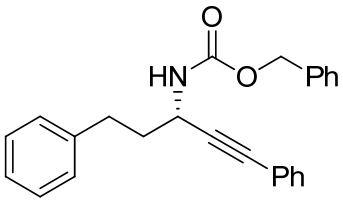
Mp 105-107 °C; $[\alpha]_D^{20}$ –4.0 (*c* 0.41, $CHCl_3$, 74% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.46-7.43 (m, 3H), 7.35-7.29 (m, 9H), 7.18 (d, *J* = 4.8 Hz, 1H), 5.97 (d, *J* = 8.8 Hz, 1H), 5.34 (d, *J* = 7.3 Hz, 1H), 5.18 (d, *J* = 11.9 Hz, 1H), 5.13 (d, *J* = 14.1 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 140.0 (C), 136.1 (C), 131.8 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 126.7 (CH), 126.5 (CH), 122.8 (CH), 122.3 (C), 86.8 (C), 84.2 (C), 67.2 (CH_2), 43.4 (CH).

HRMS (ESI) *m/z*: 370.0882 $[M+Na]^+$, $C_{21}H_{17}NO_2SNa$ requiere 370.0878.

(*S*)-*N*-benciloxicarbonil-3-fenil-1-(2-feniletil)-prop-2-in-1-amina (11qa)



11qa

El exceso enantiomérico (60%) se determinó mediante HPLC (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 20.7 min, enantiómero minoritario t_r = 17.9 min.

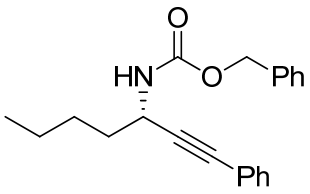
Mp 106-108 °C; $[\alpha]_D^{20}$ –10.2 (*c* 0.58, $CHCl_3$, 60% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.42-7.38 (m, 2H), 7.34-7.25 (m, 10H), 7.22-7.18 (m, 3H), 5.12 (s, 2H), 5.01 (d, *J* = 7.7 Hz, 1H), 4.73 (q, *J* = 6.9 Hz, 1H), 2.82 (t, *J* = 7.8 Hz, 2H), 2.02-2.00 (m, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 140.9 (C), 136.2 (C), 131.7 (CH), 128.54 (CH), 128.48 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 126.1 (CH), 122.5 (C), 88.0 (C), 83.8 (C), 67.0 (CH_2), 43.8 (CH), 37.9 (CH_2), 29.7 (CH_2).

HRMS (ESI) *m/z*: 392.1628 $[M+Na]^+$, $C_{25}H_{23}NO_2Na$ requiere 392.1626.

(*S*)-*N*-benciloxicarbonil-1-fenilhept-1-in-3-amina (11ra)



11ra

El exceso enantiomérico (46%) se determinó mediante HPLC (Chiralcel AD-H), hexano-^{i}PrOH 95:50, 1 mL/min, enantiómero mayoritario t_r = 11.7 min, enantiómero minoritario t_r = 11.1 min.

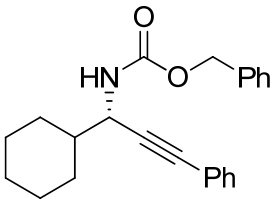
Mp 55-57 °C; $[\alpha]_D^{20}$ -26.9 (*c* 0.78, $CHCl_3$, 46% *ee*).

RMN ^{1}H (300 MHz, $CDCl_3$) δ 7.42-7.29 (m, 10H), 5.14 (s, 2H), 5.03 (d a, *J* = 7.3 Hz, 1H), 4.73 (q, *J* = 6.9 Hz, 1H), 1.81-1.72 (m, 2H), 1.52-1.45 (m, 2H), 1.43-1.34 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H).

RMN ^{13}C (75.5 MHz, $CDCl_3$) δ 155.4 (C), 136.4 (C), 131.7 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 122.7 (C), 88.5 (C), 83.2 (C), 66.9 (CH_2), 44.1 (CH), 36.1 (CH_2), 27.8 (CH_2), 22.2 (CH_2), 14.0 (CH_3).

HRMS (ESI) *m/z*: 344.1618 $[M+Na]^+$, $C_{21}H_{23}NO_2Na$ requiere 344.1626.

(*S*)-*N*-benciloxicarbonil-1-ciclohexil-3-fenilprop-2-in-1-amina (11sa)



11sa

El exceso enantiomérico (55%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 7.16 min, enantiómero minoritario t_r = 6.4 min.

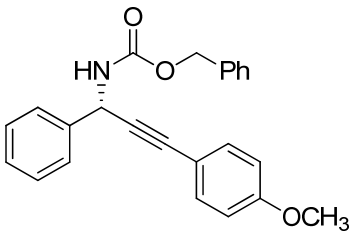
Mp 107-109 °C; $[\alpha]_D^{20}$ -33.0 (*c* 1.35, $CHCl_3$, 55% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.41-7.27 (m, 10H), 5.16-5.07 (m, 2H), 5.04 (d, *J* = 8.7 Hz, 1H), 4.59 (dd, *J* = 8.3, 6.2 Hz, 1H), 1.85-1.76 (m, 4H), 1.69-1.65 (m, 2H), 1.34-1.09 (m, 5H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.6 (C), 136.3 (C), 131.7 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 122.7 (C), 87.4 (C), 84.0 (C), 67.0 (CH_2), 49.2 (CH), 29.2 (CH_2), 28.4 (CH_2), 26.2 (CH_2), 25.9 (CH_2), 25.8 (CH_2).

HRMS (ESI) *m/z*: 370.1768 $[M+Na]^+$, $C_{23}H_{25}NO_2Na$ requiere 370.1783.

(*S*)-*N*-benciloxicarbonil-1-fenil-3-(*p*-metoxifenil)-prop-2-in-1-amina (11ab)



11ab

El exceso enantiomérico (88%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 17.3 min, enantiómero minoritario t_r = 18.5 min.

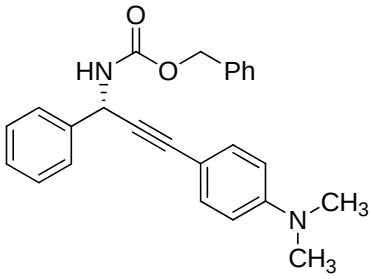
Mp 86-88 °C; $[\alpha]_D^{20}$ –18.7 (*c* 1.59, $CHCl_3$, 88% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.2 Hz, 2H), 7.40-7.28 (m, 10H), 6.83 (d, *J* = 8.9 Hz, 2H), 5.93 (d, *J* = 8.2 Hz, 1H), 5.38 (d, *J* = 6.7 Hz, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.12 (d, *J* = 12.6 Hz, 1H), 3.79 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 159.8 (C), 155.4 (C), 139.3 (C), 136.2 (C), 133.2 (CH), 128.7 (CH), 128.5 (CH), 128.15 (CH), 128.09 (CH), 127.0 (CH), 114.5 (C), 113.9 (CH), 85.6 (C), 85.0 (C), 67.1 (CH_2), 55.2 (CH_3), 47.5 (CH).

HRMS (ESI) *m/z*: 394.1423 $[M+Na]^+$, $C_{24}H_{21}NO_3Na$ requiere 394.1419.

(*S*)-*N*-benciloxicarbonil-1-fenil-3-(4-(*N,N*-dimetilamino)fenil)-prop-2-in-1-amina (11ac)



11ac

El exceso enantiomérico (85%) se determinó mediante HPLC (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 19.9 min, enantiómero minoritario t_r = 11.4 min.

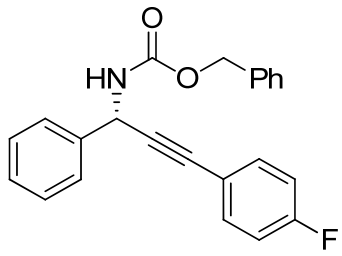
Mp 97-99 °C; $[\alpha]_D^{20}$ -21.6 (*c* 0.97, $CHCl_3$, 85% *ee*).

RMN ^{1}H (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.0 Hz, 2H), 7.38-7.27 (m, 10H), 6.60 (d, *J* = 8.9 Hz, 2H), 5.92 (d, *J* = 8.3 Hz, 1H), 5.33 (d, *J* = 7.4 Hz, 1H), 5.17 (d, *J* = 11.9 Hz, 1H), 5.11 (d, *J* = 12.9 Hz, 1H), 2.95 (s, 6H).

RMN ^{13}C (75.5 MHz, $CDCl_3$) δ 155.4 (C), 150.3 (C), 139.7 (C), 136.3 (C), 132.8 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 127.0 (CH), 111.7 (CH), 109.1 (C), 86.1 (C), 84.6 (C), 67.1 (CH_2), 47.6 (CH), 40.2 (CH_3).

HRMS (ESI) *m/z*: 407.1734 $[M+Na]^+$, $C_{25}H_{24}N_2O_2Na$ requiere 407.1735.

(*S*)-*N*-benciloxicarbonil-1-fenil-3-(*p*-fluorofenil)-prop-2-in-1-amina (11ad)



11ad

El exceso enantiomérico (88%) se determinó mediante HPLC (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 17.2 min, enantiómero minoritario t_r = 11.4 min.

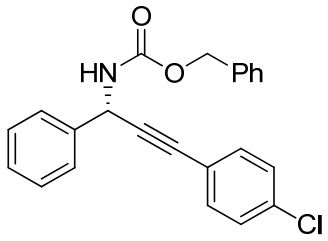
Mp 105-107 °C; $[\alpha]_D^{20}$ -22.0 (*c* 1.33, $CHCl_3$, 88% *ee*).

RMN ^{1}H (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 6.7 Hz, 2H), 7.42-7.31 (m, 10H), 6.99 (t, *J* = 8.8 Hz, 2H), 5.92 (d, *J* = 8.0 Hz, 1H), 5.30 (d, *J* = 9.3 Hz, 1H), 5.17 (d, *J* = 11.9 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H).

RMN ^{13}C (75.5 MHz, $CDCl_3$) δ 162.7 (d, *J* = 249 Hz, C), 155.4 (C), 138.9 (C), 136.1 (C), 133.7 (d, *J* = 8 Hz, CH), 128.8 (CH), 128.5 (CH), 128.3 (CH), 128.23 (CH), 128.18 (CH), 126.9 (CH), 118.5 (d, *J* = 3 Hz, C), 115.6 (d, *J* = 22 Hz, CH), 86.7 (C), 84.0 (C), 67.2 (CH_2), 47.4 (CH).

HRMS (ESI) *m/z*: 382.1216 $[M+Na]^+$, $C_{23}H_{18}FNO_2Na$ requiere 382.1219.

(*S*)-*N*-benciloxicarbonil-3-(4-clorofenil)-1-fenilprop-2-in-1-amina (11ae)



11ae

El exceso enantiomérico (91%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 15.9 min, enantiómero minoritario t_r = 12.6 min.

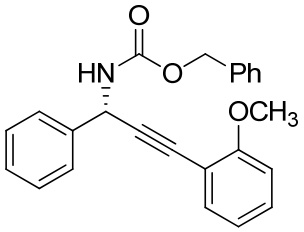
Mp 117-119 °C; $[\alpha]_D^{20}$ −19.0 (*c* 1.00, $CHCl_3$, 91% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.0 Hz, 2H), 7.42-7.28 (m, 12H), 5.95 (d a, *J* = 8.4 Hz, 1H), 5.36 (d a, *J* = 7.7 Hz, 1H), 5.19 (d, *J* = 11.9 Hz, 1H), 5.14 (d, *J* = 12.8 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 138.7 (C), 136.1 (C), 134.6 (C), 133.0 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 126.9 (CH), 120.9 (C), 88.0 (C), 84.0 (C), 67.2 (CH_2), 47.4 (CH).

HRMS (ESI) *m/z*: 398.0932 $[M+Na]^+$, $C_{23}H_{18}ClNO_2Na$ requiere 398.0924;

(*S*)-*N*-benciloxicarbonil-1-fenil-3-(*o*-metoxifenil)-prop-2-in-1-amina (11af)



11af

El exceso enantiomérico (66%) se determinó mediante HPLC (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 30.1 min, enantiómero minoritario t_r = 16.8 min.

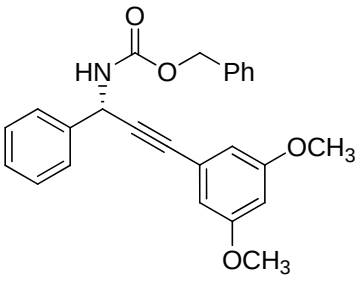
Mp 124-127 °C; $[\alpha]_D^{20}$ -14.6 (*c* 1.48, $CHCl_3$, 66% *ee*).

RMN ^{1}H (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.0 Hz, 2H), 7.41-7.26 (m, 10H), 6.89 (td, *J* = 7.4, 1.0 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 5.99 (d, *J* = 8.7 Hz, 1H), 5.38 (d, *J* = 6.9 Hz, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.11 (d, *J* = 12.7 Hz, 1H), 3.86 (s, 3H).

RMN ^{13}C (75.5 MHz, $CDCl_3$) δ 160.3 (C), 155.4 (C), 139.3 (C), 136.2 (C), 133.6 (CH), 130.0 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.1 (CH), 120.4 (CH), 111.6 (C), 110.6 (CH), 90.9 (C), 81.6 (C), 67.1 (CH_2), 55.7 (CH_3), 47.7 (CH).

HRMS (ESI) *m/z*: 394.1423 $[M+Na]^+$, $C_{24}H_{21}NO_3Na$ requiere 394.1419.

(*S*)-*N*-benciloxicarbonil-1-fenil-3-(3,5-dimetoxifenil)-prop-2-in-1-amina (11ag)



11ag

El exceso enantiomérico (90%) se determinó mediante HPLC (Chiralcel AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 26.6 min, enantiómero minoritario t_r = 18.1 min.

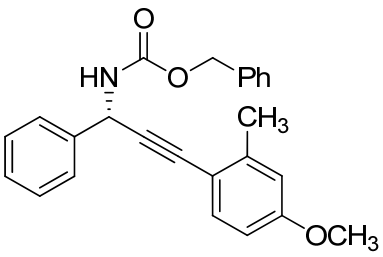
Mp 118-120 °C; $[\alpha]_D^{20}$ -25.4(*c* 0.20, $CHCl_3$, 90% *ee*).

RMN ^{1}H (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.2 Hz, 2H), 7.39-7.31 (m, 8H), 6.60 (d, *J* = 2.2 Hz, 2H), 6.44 (t, *J* = 2.3 Hz, 1H), 5.93 (d, *J* = 8.6 Hz, 1H), 5.36 (d, *J* = 7.8 Hz, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.11 (d, *J* = 13.0 Hz, 1H), 3.76 (s, 6H).

RMN ^{13}C (75.5 MHz, $CDCl_3$) δ 160.5 (C), 155.4 (C), 138.9 (C), 136.1 (C), 128.7 (CH), 128.5 (CH), 128.21 (CH), 128.15 (CH), 127.0 (CH), 123.6 (C), 109.5 (CH), 102.0 (CH), 86.5 (C), 85.0 (C), 67.2 (CH_2), 55.4 (CH_3), 47.4 (CH).

HRMS (ESI) *m/z*: 424.1529 $[M+Na]^+$, $C_{25}H_{23}NO_4Na$ requiere 424.1525.

(*S*)-*N*-benciloxicarbonil-1-fenil-3-(2-metil-4-metoxifenil)-prop-2-in-1-amina (11ah)



11ah

El exceso enantiomérico (80%) se determinó mediante HPLC (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 24.1 min, enantiómero minoritario t_r = 11.7 min.

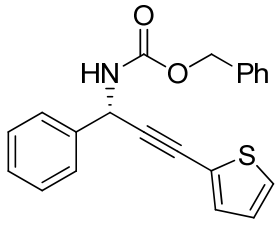
Mp 98-100 °C; $[\alpha]_D^{20}$ -22.1 (*c* 0.90, $CHCl_3$, 80% *ee*).

RMN ^{1}H (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.1 Hz, 2H), 7.39-7.30 (m, 9H), 6.72 (d, *J* = 2.4 Hz, 1H), 6.66 (dd, *J* = 8.5, 2.6 Hz, 1H), 5.95 (d, *J* = 8.2 Hz, 1H), 5.32 (d, *J* = 6.3 Hz, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.11 (d, *J* = 12.6 Hz, 1H), 3.78 (s, 3H), 2.38 (s, 3H).

RMN ^{13}C (75.5 MHz, $CDCl_3$) δ 159.7 (C), 155.4 (C), 142.2 (C), 139.4 (C), 136.2 (C), 133.4 (CH), 128.7 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.0 (CH), 115.0 (CH), 114.5 (C), 111.2 (CH), 89.3 (C), 84.1 (C), 67.1 (CH_2), 55.2 (CH_3), 47.7 (CH), 21.0 (CH_3).

HRMS (ESI) *m/z*: 408.1576 $[M+Na]^+$, $C_{25}H_{23}NO_3Na$ requiere 408.1576.

(*S*)-*N*-benciloxicarbonil-1-fenil-3-(tien-2-il)-prop-2-in-1-amina (11ai)



11ai

El exceso enantiomérico (90%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 24.0 min, enantiómero minoritario t_r = 11.9 min.

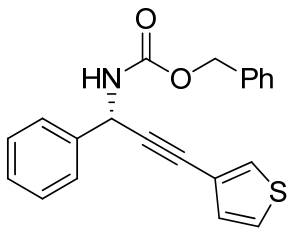
Mp 121-123 °C; $[\alpha]_D^{20}$ –21.0 (*c* 1.12, $CHCl_3$, 90% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.1 Hz, 2H), 7.40-7.29 (m, 8H), 7.25 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.22 (d, *J* = 3.6 Hz, 1H), 6.96 (dd, *J* = 5.1, 3.7 Hz, 1H), 5.95 (d, *J* = 8.5 Hz, 1H), 5.33 (d, *J* = 7.4 Hz, 1H), 5.17 (d, *J* = 11.9 Hz, 1H), 5.12 (d, *J* = 12.8 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 138.7 (C), 136.1 (C), 132.4 (CH), 128.8 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.4 (CH), 126.9 (CH), 122.3 (C), 90.8 (C), 78.4 (C), 67.2 (CH_2), 47.6 (CH).

HRMS (ESI) *m/z*: 370.0873 $[M+Na]^+$, $C_{21}H_{17}NO_2SNa$ requiere 370.0878.

(*S*)-*N*-benciloxicarbonil-1-fenil-3-(tien-3-il)-prop-2-in-1-amina (11aj)



11aj

El exceso enantiomérico (90%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario tr = 23.9, enantiómero minoritario tr = 13.3.

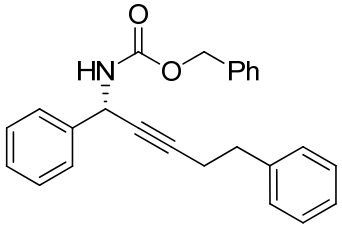
Mp 115-117 °C; $[\alpha]_D^{20}$ –17.3 (*c* 1.12, $CHCl_3$, 90% *ee*).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.1 Hz, 2H), 7.45 (d, *J* = 2.1 Hz, 1H), 7.40-7.30 (m, 8H), 7.25 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.11 (dd, *J* = 5.0, 1.0 Hz, 1H), 5.92 (d, *J* = 8.5 Hz, 1H), 5.31 (d, *J* = 7.5 Hz, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.11 (d, *J* = 12.7 Hz, 1H).

^{13}C RMN (100 MHz, $CDCl_3$) δ 155.4 (C), 138.9 (C), 136.1 (C), 129.9 (CH), 129.2 (CH), 128.7 (CH), 128.5 (CH), 128.20 (CH), 128.16 (CH), 126.9 (CH), 125.3 (CH), 121.4 (C), 86.6 (C), 80.3 (C), 67.2 (CH_2), 47.5 (CH).

HRMS (ESI): 370.0873 $[M+Na]^+$, $C_{21}H_{17}NO_2SNa$ requiere 370.0878.

(*S*)-*N*-benciloxicarbonil-1,5-difenilpent-2-in-1-amina (11ak)



11ak

El exceso enantiomérico (82%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexane-^{i}PrOH 90:10, 1 mL/min, major enantiomer t_r = 19.4 min, minor enantiomer t_r = 17.9 min.

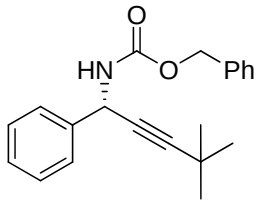
Mp 85-87 °C; $[\alpha]_D^{20}$ –10.2 (*c* 0.56, $CHCl_3$, 82% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.41-7.27 (m, 12H), 7.22 (d, *J* = 7.9 Hz, 3H), 5.67 (d, *J* = 7.5 Hz, 1H), 5.17-5.10 (m, 3H), 2.84 (t, *J* = 7.4 Hz, 2H), 2.55 (td, *J* = 7.4, 2.0 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.4 (C), 140.5 (C), 139.4 (C), 136.3 (C), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 126.9 (CH), 126.3 (CH), 85.0 (C), 78.8 (C), 67.1 (CH_2), 47.1 (CH), 34.8 (CH_2), 20.9 (CH_2).

HRMS (ESI) *m/z*: 392.1634 $[M+Na]^+$, $C_{25}H_{23}NO_2Na$ requiere 392.1626.

(*S*)-*N*-benciloxicarbonil-4,4-dimetil-1-fenilpent-2-in-1-amina (11am)



11am

El exceso enantiomérico (88%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexane-^{i}PrOH 90:10, 1 mL/min, major enantiomer t_r = 8.3 min, minor enantiomer t_r = 5.2 min.

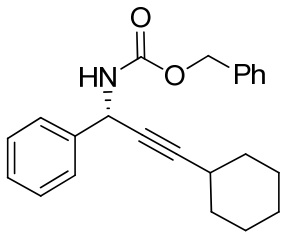
Mp 57-58 °C; $[\alpha]_D^{20}$ –23.8 (*c* 1.00, $CHCl_3$, 88% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.52 (d a, *J* = 7.0 Hz, 2H), 7.37-7.30 (m, 8H), 5.72 (d a, *J* = 8.3 Hz, 1H), 5.24 (d a, *J* = 7.8 Hz, 1H), 5.18 (d, *J* = 12.1 Hz, 1H), 5.11 (d, *J* = 12.3 Hz, 1H), 1.26 (s, 9H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.4 (C), 139.9 (C), 136.3 (C), 128.50 (CH), 128.48 (CH), 128. 1 (CH), 127.9 (CH), 126.9 (CH), 94.1 (C), 76.3 (C), 67.0 (CH_2), 46.9 (CH), 30.9 (CH_3), 27.4 (C).

HRMS (ESI) *m/z*: 344.1621 $[M+Na]^+$, $C_{21}H_{23}NO_2Na$ requiere 344.1626.

(*S*)-*N*-benciloxicarbonil-3-ciclohexil-1-fenil-prop-2-in-1-amina (11an)



11an

El exceso enantiomérico (78%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 11.5 min, enantiómero minoritario t_r = 7.2 min.

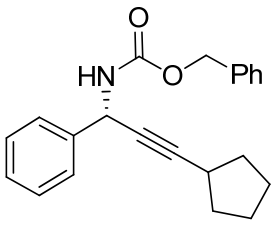
Mp 87-89 °C; $[\alpha]_D^{20}$ –7.4 (c 1.01, $CHCl_3$, 78% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.16 (d, *J* = 7.2 Hz, 2H), 7.38-7.29 (m, 8H), 5.71 (d, *J* = 8.1 Hz, 1H), 5.22-5.15 (m, 2H), 5.10 (d, *J* = 14.0 Hz, 1H), 2.47-2.39 (m, 1H), 1.83-1.26 (m, 10H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.4 (C), 139.8 (C), 136.3 (C), 128.54 (CH), 128.50 (CH), 128.2 (CH), 127.9 (CH), 126.9 (CH), 90.0 (C), 77.8 (C), 67.0 (CH_2), 47.1 (CH), 32.5 (CH_2), 29.0 (CH), 25.8 (CH_2), 24.8 (CH_2).

HRMS (ESI) *m/z*: 348.1966 $[M+H]^+$, $C_{23}H_{26}NO_2$ requiere 348.1964.

(*S*)-*N*-benciloxicarbonil-3-ciclopentil-1-fenil-prop-2-in-1-amina (11ao)



11ao

El exceso enantiomérico (83%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 11.5 min, enantiómero minoritario t_r = 7.1 min.

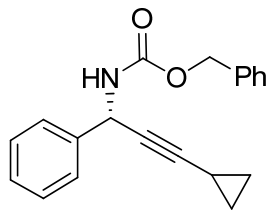
Mp 81-84 °C; $[\alpha]_D^{20}$ –10.2 (c 1.00, $CHCl_3$, 83% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.2 Hz, 2H), 7.38-7.30 (m, 8H), 5.71 (d, *J* = 7.8 Hz, 1H), 5.23 (d, *J* = 7.1 Hz, 1H), 5.17 (d, *J* = 12.1 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H), 2.72-2.62 (m, 1H), 1.98-1.87 (m, 2H), 1.75-1.55 (m, 6H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 139.8 (C), 136.3 (C), 128.53 (CH), 128.48 (CH), 128.1 (CH), 127.9 (CH), 126.9 (CH), 80.1 (C), 77.4 (C), 67.0 (CH_2), 47.1 (CH), 33.7 (CH_2), 30.1 (CH), 24.9 (CH_2).

HRMS (ESI) *m/z*: 334.1808 $[M+H]^+$, $C_{22}H_{24}NO_2$ requiere 334.1807.

(*S*)-*N*-benciloxicarbonil-3-ciclopropil-1-fenil-prop-2-in-1-amina (11ap)



11ap

El exceso enantiomérico (86%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 13.4 min, enantiómero minoritario t_r = 9.5 min.

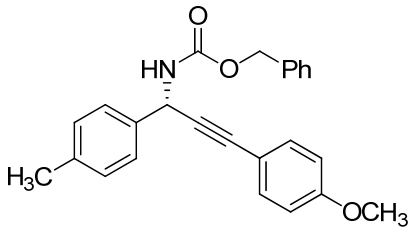
Mp 102-104 °C; $[\alpha]_D^{20}$ –3.1 (c 1.01, $CHCl_3$, 86% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.1 Hz, 2H), 7.38-7.29 (m, 8H), 5.66 (d, *J* = 7.9 Hz, 1H), 5.22 (d, *J* = 6.5 Hz, 1H), 5.16 (d, *J* = 12.1 Hz, 1H), 5.10 (d, *J* = 12.4 Hz, 1H), 1.34 (m, 1H), 0.82-0.76 (m, 2H), 0.74-0.68 (m, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 139.6 (C), 136.2 (C), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 126.9 (CH), 88.8 (C), 73.1 (C), 67.0 (CH_2), 47.1 (CH), 8.2 (CH_2), -0.5 (CH).

HRMS (ESI) *m/z*: 306.1489 $[M+H]^+$, $C_{20}H_{20}NO_2$ requiere 306.1489.

(*S*)-*N*-benciloxicarbonil-3-(*p*-metoxifenil)-1-(*p*-tolil)-prop-2-in-1-amina (11bb)



11bb

El exceso enantiomérico (89%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 11.9 min, enantiómero minoritario t_r = 10.6 min.

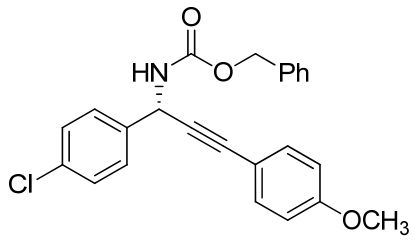
Mp 102-103 °C; $[\alpha]_D^{20}$ –18.4 (*c* 1.36, $CHCl_3$, 89% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.9 Hz, 2H), 7.39-7.31 (m, 7H), 7.17 (d, *J* = 7.9 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 5.88 (d, *J* = 8.3 Hz, 1H), 5.33 (d, *J* = 6.4 Hz, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.11 (d, *J* = 12.5 Hz, 1H), 3.79 (s, 3H), 3.34 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 159.7 (C), 155.3 (C), 137.9 (C), 136.4 (C), 136.2 (C), 133.2 (CH), 129.3 (CH), 128.5 (CH), 128.1 (CH), 126.9 (CH), 114.6 (C), 113.9 (CH), 85.8 (C), 84.8 (C), 67.1 (CH_2), 55.2 (CH_3), 47.2 (CH), 21.1 (CH_3).

HRMS (ESI) *m/z*: 408.1576 $[M+Na]^+$, $C_{25}H_{23}NO_3Na$ requiere 408.1576.

(*S*)-*N*-benciloxicarbonil-1-(*p*-clorofenil)-3-(*p*-metoxifenil)-prop-2-in-1-amina (11eb)



11eb

El exceso enantiomérico (92%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 13.6 min, enantiómero minoritario t_r = 12.4 min.

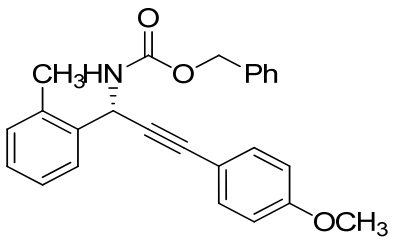
Mp 110-112 °C; $[\alpha]_D^{20}$ –15.4 (*c* 1.59, $CHCl_3$, 92% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.2 Hz, 2H), 7.38-7.30 (m, 9H), 6.82 (d, *J* = 8.9 Hz, 2H), 5.88 (d, *J* = 7.9 Hz, 1H), 5.38 (d, *J* = 6.9 Hz, 1H), 5.16 (d, *J* = 12.1 Hz, 1H), 5.11 (d, *J* = 12.3 Hz, 1H), 3.79 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 159.9 (C), 155.4 (C), 137.9 (C), 136.1 (C), 133.9 (C), 133.2 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 114.1 (C), 113.9 (CH), 85.4 (C), 84.9 (C), 67.2 (CH_2), 55.3 (CH_3), 46.9 (CH).

HRMS (ESI) *m/z*: 428.1031 $[M+Na]^+$, $C_{24}H_{20}ClNO_3Na$ requiere 428.1029.

(*S*)-*N*-benciloxicarbonil-3-(*p*-metoxifenil)-1-(*o*-tolil)-prop-2-in-1-amina (11hb)



11hb

El exceso enantiomérico (91%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 14.8 min, enantiómero minoritario t_r = 18.0 min.

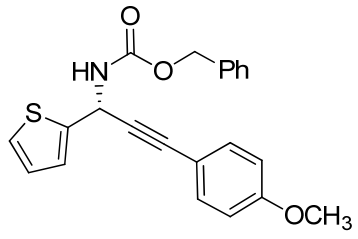
Mp 115-116 °C; $[\alpha]_D^{20}$ –20.1 (*c* 1.06, $CHCl_3$, 91% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.65-7.62 (m, 1H), 7.38-7.31 (m, 7H), 7.23-7.17 (m, 3H), 6.81 (d, *J* = 8.9 Hz, 2H), 5.99 (d, *J* = 8.3 Hz, 1H), 5.28 (d, *J* = 4.9 Hz, 1H), 5.14 (s, 2H), 3.79 (s, 3H), 3.44 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 159.7 (C), 155.1 (C), 137.0 (C), 136.2 (C), 135.9 (C), 133.2 (CH), 130.9 (CH), 128.5 (CH), 128.2 (CH), 128.12 (CH), 128.08 (CH),126.9 (CH), 126.3 (CH), 114.6 (C), 113.9 (CH), 85.8 (C), 84.6 (C), 67.1 (CH_2), 55.2 (CH_3), 45.3 (CH), 19.1 (CH_3).

HRMS (ESI) *m/z*: 408.1572 $[M+Na]^+$, $C_{25}H_{23}NO_3Na$ requiere 408.1576.

(*S*)-*N*-benciloxicarbonil-3-(*p*-metoxifenil)-1-(tien-2-il)-prop-2-in-1-amina (11nb)



11nb

El exceso enantiomérico (86%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 85:15, 1 mL/min, enantiómero mayoritario t_r = 19.1 min, enantiómero minoritario t_r = 14.1 min.

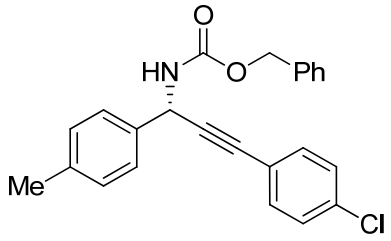
Mp 113-114 °C; $[\alpha]_D^{20}$ –16.8 (*c* 1.45, $CHCl_3$, 86% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.41-7.30 (m, 7H), 7.25 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.21 (d, *J* = 2.8 Hz, 1H), 6.96 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.13 (d, *J* = 8.4 Hz, 1H), 5.44 (d, *J* = 7.6 Hz, 1H), 5.18 (d, *J* = 11.7 Hz, 1H), 5.13 (d, *J* = 12.3 Hz, 1H), 3.80 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 159.9 (C), 155.1 (C), 143.2 (C), 136.1 (C), 133.3 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 126.8 (CH), 125.7 (CH), 125.5 (CH), 114.1 (C), 113.9 (CH), 85.1 (C), 84.4 (C), 67.2 (CH_2), 55.3 (CH_3), 43.4 (CH).

HRMS (ESI) *m/z*: 400.0990 $[M+Na]^+$, $C_{22}H_{19}NO_3SNa$ requiere 400.0983.

(*S*)-*N*-benciloxicarbonil-3-(4-clorofenil)-1-(*p*-tolil)-prop-2-in-1-amina (11be)



11be

El exceso enantiomérico (92%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 19.2 min, enantiómero minoritario t_r = 22.0 min.

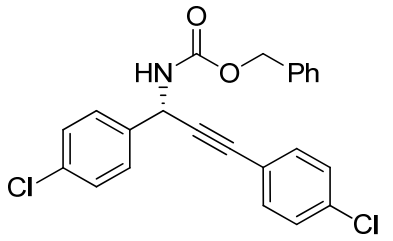
Mp 113-116 °C; $[\alpha]_D^{20}$ –15.4 (*c* 1.00, $CHCl_3$, 92% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.9 Hz, 2H), 7.35-7.29 (m, 7H), 7.26-7.22 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 5.86 (d a, *J* = 8.1 Hz, 1H), 5.31 (d a, *J* = 7.5 Hz, 1H), 5.15 (d, *J* = 11.9 Hz, 1H), 5.09 (d, *J* = 12.7 Hz, 1H), 2.32 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 138.1 (C), 136.1 (C), 135.8 (C), 134.5 (C), 133.0 (CH), 129.4 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 126.9 (CH), 121.0 (C), 88.2 (C), 83.7 (C), 67.2 (CH_2), 47.2 (CH), 21.1 (CH_3).

HRMS (ESI) *m/z*: 412.1082 $[M+Na]^+$, $C_{24}H_{20}ClNO_2Na$ requiere 412.1080.

(*S*)-*N*-benciloxicarbonil-1,3-di-(4-clorofenil)-prop-2-in-1-amina (11ee)



11ee

El exceso enantiomérico (91%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 16.6 min, enantiómero minoritario t_r = 15.5 min.

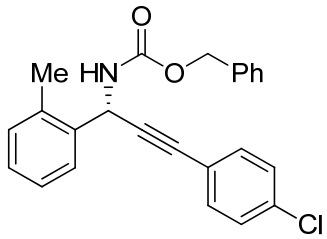
Mp 115-117 °C; $[\alpha]_D^{20}$ –12.3 (*c* 1.00, $CHCl_3$, 91% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.3 Hz, 2H), 7.39-7.28 (m, 11H), 5.90 (d a, *J* = 8.4 Hz, 1H), 5.33 (d a, *J* = 8.0 Hz, 1H), 5.18 (d, *J* = 12.0 Hz, 1H), 5.13 (d, *J* = 12.4 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.7 (C), 137.4 (C), 136.0 (C), 134.8 (C), 134.2 (C), 133.0 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 120.6 (C), 87.3 (C), 84.4 (C), 67.4 (CH_2), 46.8 (CH).

HRMS (ESI) *m/z*: 432.0535 $[M+Na]^+$, $C_{23}H_{17}ClNO_2Na$ requiere 432.0534.

(*S*)-*N*-benciloxicarbonil-3-(4-clorofenil)-1-(*o*-tolil)-prop-2-in-1-amina (11he)



11he

El exceso enantiomérico (95%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 13.2 min, enantiómero minoritario t_r = 16.6 min.

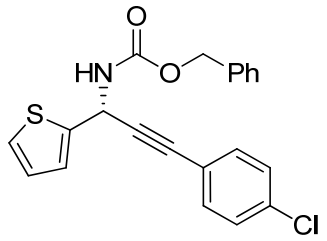
Mp 108-112 °C; $[\alpha]_D^{20}$ –12.2 (*c* 1.00, $CHCl_3$, 95% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.64-7.61 (m, 1H), 7.38-7.33 (m, 7H), 7.29-7.20 (m, 5H), 6.01 (d a, *J* = 8.3 Hz, 1H), 5.26 (d, *J* = 7.9 Hz, 1H), 5.15 (s, 2H), 2.44 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.1 (C), 136.5 (C), 136.1 (C), 136.0 (C), 134.5 (C), 133.0 (CH), 131.0 128.8 (CH), 128.6 (CH), 128.52 (CH), 128.45 (CH), 128.2 (CH), 128.1 (CH), 126.9 (CH), 126.4 (CH), 121.0 (C), 88.3 (C), 83.6 (C), 67.2 (CH_2), 45.2 (CH), 19.1 (CH_3);

HRMS (ESI) *m/z*: 412.1082 $[M+Na]^+$, $C_{24}H_{20}ClNO_2Na$ requiere 412.1080.

(*S*)-*N*-benciloxicarbonil-3-(4-clorofenil)-1-(tien-2-il)-prop-2-in-1-amina (11ne)



11ne

El exceso enantiomérico (87%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 23.6 min, enantiómero minoritario t_r = 20.9 min.

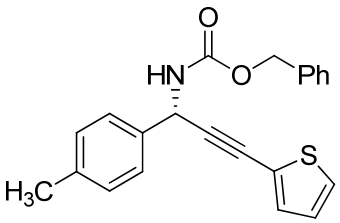
Mp 108-109 °C; $[\alpha]_D^{20}$ –18.1 (*c* 1.00, $CHCl_3$, 87% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.41-7.27 (m, 10H), 7.21 (d, *J* = 3.1 Hz, 1H), 6.98 (dd, *J* = 3.6, 5.1 Hz, 1H), 6.15 (d a, *J* = 8.3 Hz, 1H), 5.42 (d a, *J* = 7.3 Hz, 1H), 5.20 (d, *J* = 11.9 Hz, 1H), 5.15 (d, *J* = 13.0 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.1 (C), 142.5 (C), 136.0 (C), 134.9 (C), 133.0 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 126.9 (CH), 125.9 (CH), 125.8 (CH), 120.6 (C), 87.4 (C), 83.3 (C), 67.3 (CH_2), 43.3 (CH).

HRMS (ESI) *m/z*: 398.0932 $[M+Na]^+$, $C_{23}H_{18}ClNO_2Na$ requiere 398.0924.

(*S*)-*N*-benciloxicarbonil-3-(tien-2-il)-1-(*p*-tolil)-prop-2-in-1-amina (11bi)



11bi

El exceso enantiomérico (91%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 14.3 min, enantiómero minoritario t_r = 11.2 min.

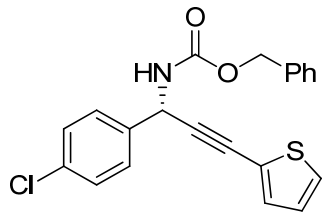
Mp 133-136 °C; $[\alpha]_D^{20}$ –22.1 (c 1.62, $CHCl_3$, 91% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.9 Hz, 2H), 7.36-7.30 (m, 5H), 7.24 (dd, *J* = 5.2, 1.1 Hz, 1H), 7.22 (d, *J* = 3.6 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.96 (dd, *J* = 5.1, 3.7 Hz, 1H), 5.91 (d, *J* = 8.1 Hz, 1H), 5.33 (d, *J* = 6.8 Hz, 1H), 5.17 (d, *J* = 11.9 Hz, 1H), 5.11 (d, *J* = 11.7 Hz, 1H), 2.35 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 138.1 (C), 136.2 (C), 135.8 (C), 132.4 (CH), 129.4 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.3 (CH), 126.89 (CH), 126.86 (CH), 122.4 (C), 91.0 (C), 78.2 (C), 67.2 (CH_2), 47.4 (CH), 21.1 (CH_3).

HRMS (ESI) *m/z*: 384.1034 $[M+Na]^+$, $C_{22}H_{19}NO_2SNa$ requiere 384.1034.

(*S*)-*N*-benciloxicarbonil-1-(*p*-clorofenil)-3-(tien-2-il)-prop-2-in-1-amina (11ei)



11ei

El exceso enantiomérico (92%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 17.6 min, enantiómero minoritario t_r = 13.1 min.

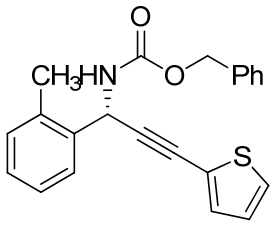
Mp 133-135 °C; $[\alpha]_D^{20}$ –20.2 (c 1.45, $CHCl_3$, 92% *ee*);

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.3 Hz, 2H), 7.35-7.31 (m, 7H), 7.26 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.22 (dd, *J* = 3.6, 1.0 Hz, 1H), 6.96 (dd, *J* = 5.2, 3.7 Hz, 1H), 5.91 (d, *J* = 8.0 Hz, 1H), 5.34 (d, *J* = 6.8 Hz, 1H), 5.16 (d, *J* = 12.1 Hz, 1H), 5.11 (d, *J* = 12.3 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.4 (C), 137.3 (C), 136.0 (C), 134.1 (C), 132.6 (CH), 128.9 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 127.0 (CH), 122.0 (C), 90.2 (C), 78.9 (C), 67.3 (CH_2), 47.1 (CH).

HRMS (ESI) *m/z*: 404.0497 $[M+Na]^+$, $C_{21}H_{16}ClNO_2SNa$ requiere 404.0488.

(*S*)-*N*-benciloxicarbonil-3-(tien-2-il)-1-(*o*-tolil)-prop-2-in-1-amina (11hi)



11hi

El exceso enantiomérico (95%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario tr = 11.9, enantiómero minoritario tr = 17.1.

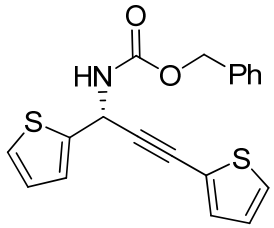
Mp 111-113 °C; $[\alpha]_D^{20}$ –21.4 (*c* 0.95, $CHCl_3$, 95% *ee*).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.60-7.57 (m, 1H),), 7.34-7.28 (m, 5H), 7.22-7.16 (m, 5H), 6.94 (dd, *J* = 5.2, 3.7 Hz, 1H), 6.02 (d, *J* = 8.5 Hz, 1H), 5.24 (d, *J* = 7.3 Hz, 1H), 5.13 (s, 2H), 2.42 (s, 3H).

^{13}C RMN (100 MHz, $CDCl_3$) δ 155.1 (C), 136.5 (C), 136.2 (C), 136.0 (C), 132.3 (CH), 131.0 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.2 (CH), 127.0 (CH), 126.9 (CH), 126.4 (CH), 122.4 (C), 91.1 (C), 78.0 (C), 67.2 (CH_2), 45.4 (CH), 19.1 (CH_3).

HRMS (ESI) *m/z*: 384.1032 $[M+Na]^+$, $C_{22}H_{19}NO_2SNa$ requiere 384.1034.

(*S*)-*N*-benciloxicarbonil-1,3-(ditien-2-il)-prop-2-in-1-amina (11ni)



11ni

El exceso enantiomérico (88%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 22.4 min, enantiómero minoritario t_r = 13.3 min.

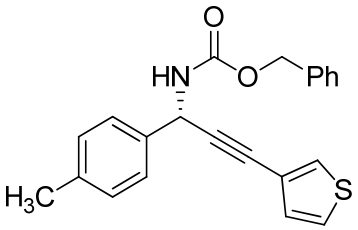
Mp 81-82 °C; $[\alpha]_D^{20}$ –21.5 (c 1.47, $CHCl_3$, 88% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.37-7.30 (m, 5H), 7.27-7.23 (m, 3H), 7.19 (d, *J* = 3.4 Hz, 1H), 6.98-6.94 (m, 2H), 6.15 (d, *J* = 8.7 Hz, 1H), 5.43 (d, *J* = 7.9 Hz, 1H), 5.18 (d, *J* = 11.9 Hz, 1H), 5.13 (d, *J* = 12.6 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.1 (C), 142.4 (C), 136.0 (C), 132.7 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 127.0 (CH), 126.9 (CH), 125.9 (CH), 125.7 (CH), 121.9 (C), 90.2 (C), 77.9 (C), 67.3 (CH_2), 43.5 (CH**).**

HRMS (ESI) *m/z*: 376.0445 $[M+Na]^+$, $C_{19}H_{15}NO_2S_2Na$ requiere 376.0442.

(*S*)-*N*-benciloxicarbonil-3-(tien-3-il)-1-(*p*-tolil)-prop-2-in-1-amina (11bj)



11bj

El exceso enantiomérico (89%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario tr = 20.6, enantiómero minoritario tr = 23.9.

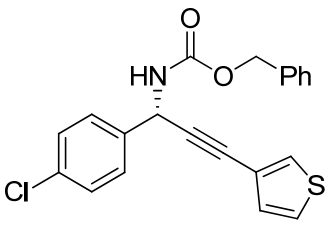
Mp 120-122 °C; $[\alpha]_D^{20}$ –14.9 (*c* 1.07, $CHCl_3$, 89% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.44-7.41 (m, 3H), 7.35-7.29 (m, 5H), 7.24 (dd, *J* = 4.8, 3.2 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.10 (dd, *J* = 5.0, 1.0 Hz, 1H), 5.89 (d, *J* = 8.3 Hz, 1H), 5.28 (d, *J* = 6.2 Hz, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 5.10 (d, *J* = 7.1 Hz, 1H), 2.34 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 138.0 (C), 136.2 (C), 136.1 (C), 129.9 (CH), 129.4 (CH), 129.1 (CH), 128.5 (CH), 128.2 (CH), 126.9 (CH), 125.3 (CH), 121.5 (C), 86.8 (C), 80.1 (C), 67.1 (CH_2), 47.2 (CH), 21.1 (CH_3).

HRMS (ESI) *m/z*: 384.1031 $[M+Na]^+$, $C_{22}H_{19}NO_2SNa$ requiere 384.1034.

(*S*)-*N*-benciloxicarbonil-1-(*p*-clorofenil)-3-(tien-3-il)-prop-2-in-1-amina (11ej)



11ej

El exceso enantiomérico (92%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 21.2 min, enantiómero minoritario t_r = 15.5 min.

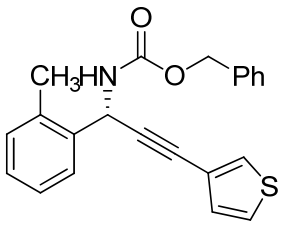
Mp 130-132 °C; $[\alpha]_D^{20}$ –13.3 (*c* 1.05, $CHCl_3$, 92% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.48-7.45 (m, 3H), 7.33-7.31 (m, 7H), 7.25 (dd, *J* = 5.2, 3.2 Hz, 1H), 7.10 (dd, *J* = 5.0, 1.1 Hz, 1H), 5.87 (d, *J* = 7.7 Hz, 1H), 5.31 (d, *J* = 7.3 Hz, 1H), 5.16 (d, *J* = 12.1 Hz, 1H), 5.11 (d, *J* = 11.7 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.4 (C), 137.6 (C), 136.0 (C), 134.1 (C), 129.8 (CH), 129.4 (CH), 128.9 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 125.5 (CH), 121.1 (C), 86.0 (C), 80.7 (C), 67.3 (CH_2), 46.9 (CH).

HRMS (ESI) *m/z*: 404.0492 $[M+Na]^+$, $C_{21}H_{16}ClNO_2SNa$ requiere 404.0492.

(*S*)-*N*-benciloxicarbonil-3-(tien-3-il)-1-(*o*-tolil)-prop-2-in-1-amina (11hj)



11hj

El exceso enantiomérico (94%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 15.3 min, enantiómero minoritario t_r = 22.1 min.

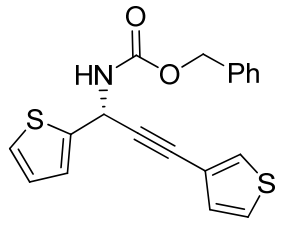
Mp 119-121 °C; $[\alpha]_D^{20}$ –17.2 (*c* 1.28, $CHCl_3$, 94% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.63-7.60 (m, 1H), 7.43 (d, *J* = 2.5 Hz, 1H), 7.33-7.31 (m, 5H), 7.25-7.16 (m, 4H), 7.09 (d, *J* = 5.0 Hz, 1H), 5.99 (d, *J* = 8.1 Hz, 1H), 5.24 (d, *J* = 6.8 Hz, 1H), 5.13 (s, 2H), 2.43 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.1 (C), 136.8 (C), 136.2 (C), 135.9 (C), 130.9 (CH), 129.9 (CH), 129.1 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 126.9 (CH), 126.4 (CH), 125.3 (CH), 121.5 (C), 86.9 (C), 79.9 (C), 67.1 (CH_2), 45.2 (CH), 19.1 (CH_3).

HRMS (ESI) *m/z*: 384.1026 $[M+Na]^+$, $C_{22}H_{19}NO_2SNa$ requiere 384.1034.

(*S*)-*N*-benciloxicarbonil-1-(tien-2-il)-3-(tien-3-il)-prop-2-in-1-amina (11nj)



11nj

El exceso enantiomérico (89%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 26.8 min, enantiómero minoritario t_r = 16.0 min.

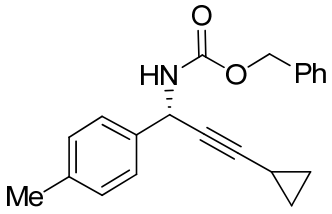
Mp 96-97 °C; $[\alpha]_D^{20}$ –15.6 (c 0.98, $CHCl_3$, 89% *ee*).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 2.1 Hz, 1H), 7.37-7.33 (m, 5H), 7.27-7.24 (m, 2H), 7.20 (d, *J* = 1.6 Hz, 1H), 7.12 (dd, *J* = 5.0, 0.8 Hz, 1H), 6.96 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.12 (d, *J* = 8.1 Hz, 1H), 5.42 (d, *J* = 6.2 Hz, 1H), 5.18 (d, *J* = 11.9 Hz, 1H), 5.13 (d, *J* = 12.6 Hz, 1H).

^{13}C RMN (100 MHz, $CDCl_3$) δ 155.1 (C), 142.8 (C), 136.1 (C), 129.8 (CH), 129.5 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 126.8 (CH), 125.8 (CH), 125.7 (CH), 125.4 (CH), 121.1 (C), 86.1 (C), 79.7 (C), 67.3 (CH_2), 43.3 (CH).

HRMS (ESI) *m/z*: 376.0441 $[M+Na]^+$, $C_{19}H_{15}NO_2S_2Na$ requiere 376.0442.

(*S*)-*N*-benciloxicarbonil-3-ciclopropil-1-(*p*-tolil)-prop-2-in-1-amina (11bp)



11bp

El exceso enantiomérico (93%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 11.9 min, enantiómero minoritario t_r = 12.6 min.

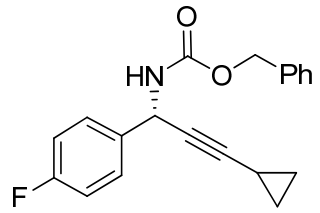
Mp 104-107 °C; $[\alpha]_D^{20}$ -9.4 (c 1.00, $CHCl_3$, 93% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.37-7.29 (m, 7H), 7.15 (d, *J* = 8.0 Hz, 2H), 5.19-5.13 (m, 2H), 5.09 (d, *J* = 12.4 Hz, 1H), 2.34 (s, 3H), 1.33-1.24 (m, 1H), 0.81-0.75 (m, 2H), 0.73-0.67 (m, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 137.7 (C), 136.8 (C), 136.3 (C), 129.2 (CH), 128.5 (CH), 128.1 (CH), 126.8 (CH), 88.6 (C), 73.3 (C), 67.0 (CH_2), 46.8 (CH), 21.1 (CH_3), 8.2 (CH_2), -0.5 (CH).

HRMS (ESI) *m/z*: 320.1643 $[M+H]^+$, $C_{21}H_{22}NO_2$ requiere 320.1645.

(*S*)-*N*-benciloxicarbonil-3-ciclopropil-1-(*p*-fluorofenil)-prop-2-in-1-amina (11dp)



11dp

El exceso enantiomérico (89%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 12.8 min, enantiómero minoritario t_r = 11.5 min.

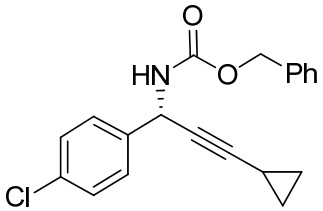
Mp 116-117 °C; $[\alpha]_D^{20}$ -16.6 (c 1.02, $CHCl_3$, 89% *ee*).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.47-7.42 (m, 2H), 7.35-7.31 (m, 5H), 7.02 (t, *J* = 8.7 Hz, 2H), 5.63 (d, *J* = 7.7 Hz, 1H), 5.22 (d, *J* = 5.4 Hz, 1H), 5.15 (d, *J* = 12.1 Hz, 1H), 5.09 (d, *J* = 12.1 Hz, 1H), 1.33-1.24 (m, 1H), 0.83-0.74 (m, 2H), 0.73-0.67 (m, 2H).

^{13}C RMN (100 MHz, $CDCl_3$) δ 162.4 (d, *J* = 246.5 Hz, C), 155.3 (C), 136.2 (C), 135.6 (d, *J* = 3.2 Hz, C), 128.7 (d, *J* = 8.3 Hz, CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 115.4 (d, *J* = 21.6 Hz, CH), 89.1 (C), 72.9 (C), 67.1 (CH_2), 46.5 (CH), 8.2 (CH_2), -0.6 (CH).

HRMS (ESI) *m/z*: 324.1389 $[M+H]^+$, $C_{20}H_{19}NO_2F$ requiere 324.1394.

(*S*)-*N*-benciloxicarbonil-3-ciclopropil-1-(*p*-clorofenil)-prop-2-in-1-amina (11ep)



11ep

El exceso enantiomérico (95%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 12.5 min, enantiómero minoritario t_r = 12.0 min.

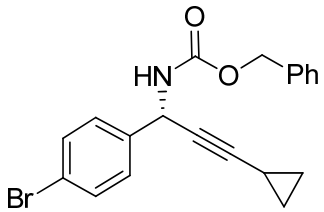
Mp 116-117 °C; $[\alpha]_D^{20}$ -6.3 (c 1.05, $CHCl_3$, 95% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.42-7.29 (m, 9H), 5.61 (d, *J* = 7.9 Hz, 1H), 5.20 (d, *J* = 6.5 Hz, 1H), 5.15 (d, *J* = 12.1 Hz, 1H), 5.09 (d, *J* = 12.8 Hz, 1H), 1.33-1.23 (m, 1H), 0.32-0.74 (m, 2H), 0.72-0.67 (m, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 138.3 (C), 136.1 (C), 133.7 (C), 128.7 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 89.3 (C), 72.3 (C), 67.2 (CH_2), 46.5 (CH), 8.2 (CH_2), -0.6 (CH).

HRMS (ESI) *m/z*: 340.1097 $[M+H]^+$, $C_{20}H_{19}NO_2Cl$ requiere 340.1099.

(*S*)-*N*-benciloxicarbonil-3-ciclopropil-1-(*p*-bromofenil)-prop-2-in-1-amina (11fp)



11fp

El exceso enantiomérico (93%) se determinó mediante HPLC quiral (Chiralcel IC-H), hexano-^{i}PrOH 98:2, 1 mL/min, enantiómero mayoritario t_r = 22.2 min, enantiómero minoritario t_r = 23.8 min.

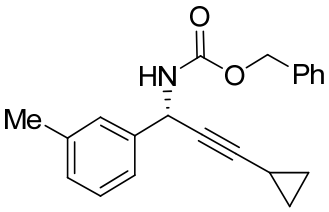
Mp 131-133 °C; $[\alpha]_D^{20}$ –3.6 (c 1.06, $CHCl_3$, 93% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.5 Hz, 2H), 7.39-7.30 (m, 7H), 5.59 (d, *J* = 8.3 Hz, 1H) 5.20-5.13 (m, 2H), 5.08 (d, *J* = 12.1 Hz, 1H), 1.32-1.23 (m, 1H), 0.82-0.74 (m, 2H), 0.72-0.66 (m, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.2 (C), 138.8 (C), 136.1 (C), 131.6 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 121.9 (C), 89.3 (C), 72.5 (C), 67.2 (CH_2), 46.6 (CH), 8.2 (CH_2), -0.6 (CH).

HRMS (ESI) *m/z*: 384.0591/386.0571 $[M+H]^+$ 100.0/97.5, $C_{20}H_{19}NO_2Br$ requiere 384.0594/386.0574.

(*S*)-*N*-benciloxicarbonil-3-ciclopropil-1-(*m*-tolil)-prop-2-in-1-amina (11gp)



11gp

El exceso enantiomérico (89%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 11.1 min, enantiómero minoritario t_r = 9.3 min.

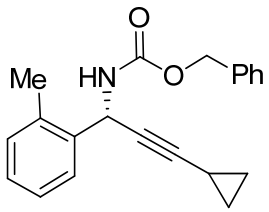
Mp 81-83 °C; $[\alpha]_D^{20}$ –10.6 (c 1.01, $CHCl_3$, 89% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.36-7.31 (m, 5H), 7.26-7.21 (m, 3H), 7.11 (d, *J* = 7.0 Hz, 1H), 5.62 (d, *J* = 7.8 Hz, 1H), 5.21-5.14 (m, 2H), 5.10 (d, *J* = 12.4 Hz, 1H), 2.35 (s, 3H), 1.34-1.24 (m, 1H), 0.82-0.75 (2H), 0.74-0.68 (2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 139.6 (C), 138.3 (C), 136.3 (C), 128.7 (CH), 128.5 (CH), 128.1 (CH), 127.7 (CH), 123.9 (CH), 88.6 (C), 73.2 (C), 67.0 (CH_2), 47.0 (CH), 21.4 (CH_3), 8.2 (CH_2), -0.5 (CH).

HRMS (ESI) *m/z*: 320.1642 $[M+H]^+$, $C_{21}H_{22}NO_2$ requiere 320.1645.

(*S*)-*N*-benciloxicarbonil-3-ciclopropil-1-(*o*-tolil)-prop-2-in-1-amina (11hp)



11hp

El exceso enantiomérico (96%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 11.2 min, enantiómero minoritario t_r = 13.2 min.

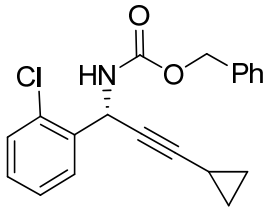
Mp 120-122 °C; $[\alpha]_D^{20}$ –24.4 (c 0.98, $CHCl_3$, 96% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.54-7.51 (m, 1H), 7.37-7.30 (m, 5H), 7.20 (dd, *J* = 3.5, 5.6 Hz, 2H), 7.18-7.13 (m, 1H), 5.73 (d, *J* = 8.2 Hz, 1H), 5.16-5.07 (m, 3H), 2.38 (s, 3H), 1.31-1.22 (m, 1H), 0.80-0.73 (m, 2H), 0.72-0.65 (m, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.0 (C), 137.4 (C), 136.3 (C), 135.8 (C), 129.5 (CH), 128.5 (CH), 128.12 (CH), 128.06 (CH), 126.7 (CH), 126.2 (CH), 88.3 (C), 73.3 (C), 67.0 (CH_2), 44.8 (CH), 19.0 (CH_3), 8.2 (CH_2), -0.5 (CH).

HRMS (ESI) *m/z*: 320.1643 $[M+H]^+$, $C_{21}H_{22}NO_2$ requiere 320.1645.

(*S*)-*N*-benciloxicarbonil-3-ciclopropil-1-(*o*-clorofenil)-prop-2-in-1-amina (11jp)



11jp

El exceso enantiomérico (92%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 13.1 min, enantiómero minoritario t_r = 16.4 min.

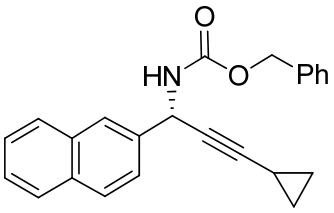
Mp 110-113 °C; $[\alpha]_D^{20}$ -20.0 (c 0.92, $CHCl_3$, 92% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.57-7.54 (m, 1H), 7.38-7.29 (m, 6H), 7.27-7.21 (m, 2H), 5.86 (d, *J* = 7.7 Hz, 1H), 5.33 (d, *J* = 5.9 Hz, 1H), 5.14 (d, *J* = 12.1 Hz, 1H), 5.08 (d, *J* = 12.4 Hz, 1H), 1.30-1.21 (m, 1H), 0.80-0.73 (m, 2H), 0.72-0.65 (m, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 154.9 (C), 136.8 (C), 136.2 (C), 133.1 (C), 130.1 (CH), 129.3 (CH), 128.8 (CH), 128.5 (CH), 128.1 (CH), 127.1 (CH), 88.7 (C), 72.2 (C), 67.0 (CH_2), 45.4 (CH), 8.2 (CH_2), -0.5 (CH).

HRMS (ESI) *m/z*: 340.1085 $[M+H]^+$, $C_{20}H_{19}NO_2Cl$ requiere 340.1099.

(*S*)-*N*-benciloxicarbonil-3-ciclopropil-1-(naftalen-2-il)-prop-2-in-1-amina (11kp)



11kp

El exceso enantiomérico (91%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 16.6 min, enantiómero minoritario t_r = 17.5 min.

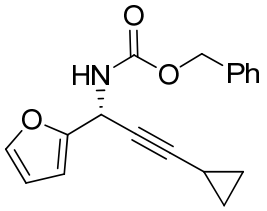
Mp 106-108 °C; $[\alpha]_D^{20}$ +1.6 (c 0.87, $CHCl_3$, 91% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.93 (s a, 1H), 7.84-7.81 (m, 3H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.50-7.47 (m, 2H), 7.39-7.30 (m, 5H), 5.82 (d, *J* = 8.5 Hz, 1H), 5.31 (d, *J* = 6.8 Hz, 1H), 5.18 (d, *J* = 12.1 Hz, 1H), 5.11 (d, *J* = 12.5 Hz, 1H), 1.37-1.30 (m, 1H), 0.84-0.79 (m, 2H), 0.78-0.71 (m, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 137.0 (C), 136.2 (C), 133.1 (C), 133.0 (C), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 126.3 (CH), 126.2 (CH), 125.6 (CH), 124.9 (CH), 89.1 (C), 73.1 (C), 67.1 (CH_2), 47.3 (CH), 8.3 (CH_2), -0.5 (CH).

HRMS (ESI) *m/z*: 356.1645 $[M+H]^+$, $C_{24}H_{22}NO_2$ requiere 356.1645.

(*S*)-*N*-benciloxicarbonil-3-ciclopropil-1-(furan-2-il)-prop-2-in-1-amina (11mp)



11mp

El exceso enantiomérico (84%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 14.4 min, enantiómero minoritario t_r = 12.7 min.

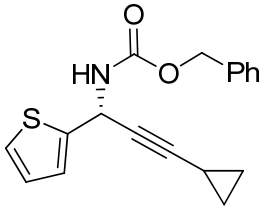
Aceite marrón; $[\alpha]_D^{20}$ +5.9 (c 1.12, $CHCl_3$, 84% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.37-7.33 (m, 6H), 6.32-6.31 (m, 2H), 5.69 (d, *J* = 8.6 Hz, 1H), 5.24 (d, *J* = 5.4 Hz, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 5.10 (d, *J* = 12.5 Hz, 1H), 1.31- 1.22 (m, 1H), 0.81-0.75 (m, 2H), 0.73-0.67 (m, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.1 (C), 151.6 (C), 142.6 (CH), 136.1 (C), 128.5 (CH), 128.2 (CH), 110.3 (CH), 107.2 (CH), 87.8 (C), 70.9 (C), 67.1 (CH_2), 41.3 (CH), 8.2 (CH_2), -0.6 (CH).

HRMS (ESI) *m/z*: 296.1284 $[M+H]^+$, $C_{18}H_{18}NO_3$ requiere 296.1281.

(*S*)- *N*-benciloxicarbonil-3-ciclopropil-1-(tien-2-il)-prop-2-in-1-amina (11np)



11np

El exceso enantiomérico (84%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 14.9 min, enantiómero minoritario t_r = 12.4 min.

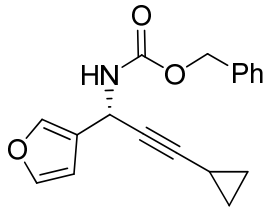
Mp 91-94 °C; $[\alpha]_D^{20}$ –4.8 (c 1.04, $CHCl_3$, 84% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.37-7.33 (m, 5H), 7.23 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.12 (dd, *J* = 2.7 Hz, 1H), 6.94 (dd, *J* = 5.1, 3.5 Hz, 1H), 5.86 (d, *J* = 8.5 Hz, 1H), 5.29 (d, *J* = 8.1 Hz, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.11 (d, *J* = 12.7 Hz, 1H), 1.34- 1.24 (m, 1H), 0.83-0.77 (m, 2H), 0.76-0.70 (m, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.1 (C), 143.7 (C), 136.1 (C), 128.5 (CH), 128.2 (CH), 128.1 (CH), 126.7(CH), 125.5 (CH), 125.3 (CH), 88.3 (C), 72.7 (C), 67.1 (CH_2), 42.9 (CH), 8.19 (CH_2), 8.17 (CH_2), -0.6 (CH).

HRMS (ESI) *m/z*: 312.1054 $[M+H]^+$, $C_{18}H_{18}NO_2S$ requiere 312.1053.

(*S*)-*N*-benciloxicarbonil-3-ciclopropil-1-(furan-3-il)-prop-2-in-1-amina (11op)



11op

El exceso enantiomérico (64%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 13.6 min, enantiómero minoritario t_r = 11.8 min.

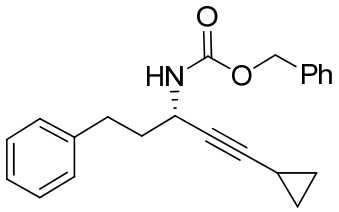
Aceite naranja; $[\alpha]_D^{20}$ –11.0 (c 1.00, $CHCl_3$, 64% *ee*);

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.29-7.26 (m, 6H), 6.33 (s, 1H), 5.47 (d, *J* = 7.7 Hz, 1H), 5.10-5.01 (m, 3H), 1.24-1.14 (m, 1H), 0.74-0.68 (m, 2H), 0.63-0.58 (m, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 143.5 (CH), 140.2 (CH), 136.2 (C), 128.5 (CH), 128.2 (CH), 128.1 (CH), 125.3 (C), 109.3 (CH), 87.2 (C), 72.6 (C), 67.1 (CH_2), 39.5 (CH), 8.2 (CH_2), -0.7 (CH).

HRMS (ESI) *m/z*: 296.1285 $[M+H]^+$, $C_{18}H_{18}NO_3$ requiere 296.1281.

(*S*)-*N*-benciloxicarbonil-1-ciclopropil-5-fenil-pent-1-in-3-amina (11qp)



11qp

El exceso enantiomérico (42%) se determinó mediante HPLC quiral (Chiralcel AD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 11.7 min, enantiómero minoritario t_r = 13.1 min.

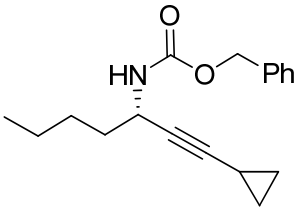
Aceite amarillo; $[\alpha]_D^{20}$ -6.6 (c 0.99, $CHCl_3$, 42% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.37-7.26 (m, 7H), 7.21-7.16 (m, 3H), 5.10 (s, 2H), 4.89 (d, *J* = 7.7 Hz, 1H), 4.46 (q, *J* = 7.7 Hz, 1H), 2.76-2.70 (m, 2H), 2.04-1.87 (m, 2H), 1.29-1.19 (m, 1H), 0.80-0.74 (m, 2H), 0.69-0.63 (2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 141.1 (C), 136.3 (C), 128.5 (CH), 128.4 (CH), 128.1 (CH), 126.0 (CH), 87.4 (C), 74.0 (C), 66.8 (CH_2), 43.5 (CH), 38.1 (CH_2), 31.9 (CH_2), 8.20 (CH_2), 8.19 (CH_2), -0.7 (CH).

HRMS (ESI) *m/z*: 334.1797 $[M+H]^+$, $C_{22}H_{24}NO_2$ requiere 334.1802.

(*S*)-*N*-benciloxicarbonil-1-ciclopropil-hept-1-in-3-amina (11rp)



11rp

El exceso enantiomérico (43%) se determinó mediante HPLC quiral (Chiralcel IC), hexano-^{i}PrOH 95:5, 1 mL/min, enantiómero mayoritario t_r = 9.6 min, enantiómero minoritario t_r = 9.2 min.

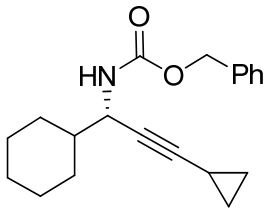
Aceite blanco; $[\alpha]_D^{20}$ –15.6 (c 1.00, $CHCl_3$, 43% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.36-7.31 (m, 5H), 5.10 (s, 2H), 5.84 (d, *J* = 5.7 Hz, 1H), 4.40 (q, *J* = 10.5 Hz, 1H), 1.66-1.55 (m, 2H), 1.40-1.25 (m, 4H), 1.22-1.16 (m, 1H), 0.90 (t, *J* = 13.9 Hz, 3H), 0.77-0.71 (m, 2H), 0.66-0.60 (m, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.3 (C), 136.4 (C), 128.5 (CH), 128.1 (CH), 86.7 (C), 74.6 (C), 66.8 (CH_2), 43.7 (CH), 36.3 (CH_2), 27.7 (CH_2), 22.2 (CH_2), 14.0 (CH_3), 8.14 (CH_2), 8.13 (CH_2), -0.7 (CH).

HRMS (ESI) *m/z*: 286.1802 $[M+H]^+$, $C_{18}H_{24}NO_2$ requiere 286.1802.

(*S*)-*N*-benciloxicarbonil-1-ciclohexil-3-ciclopropil-prop-2-in-1-amina (11sp)



11sp

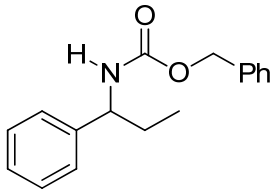
El exceso enantiomérico (65%) se determinó mediante HPLC quiral (Chiralcel IC), hexano-^{i}PrOH 98:2, 1 mL/min, enantiómero mayoritario t_r = 17.7 min, enantiómero minoritario t_r = 19.2 min.

Mp 101-104 °C; $[\alpha]_D^{20}$ -23.6 (c 0.90, $CHCl_3$, 65% *ee*); ^{1}H RMN (300 MHz, $CDCl_3$) δ 7.37-7.34 (m, 5H), 5.12 (d, *J* = 12.1 Hz, 1H), 5.07 (d, *J* = 12.1 Hz, 1H), 4.86 (d, *J* = 7.4 Hz, 1H), 4.29 (d, *J* = 7.0 Hz, 1H), 1.76-1.63 (m, 5H), 1.25-1.03 (m, 7H), 0.77-0.69 (m, 2H), 0.66-0.60 (m, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.5 (C), 136.4 (C), 128.5 (CH), 128.1 (CH), 87.5 (C), 73.2 (C), 66.8 (CH_2), 48.8 (CH), 42.9 (CH), 29.2 (CH_2), 28.3 (CH_2), 26.2 (CH_2), 25.9 (CH), 25.8 (CH), 8.2 (CH_2), -0.6 (CH).

HRMS (ESI) *m/z*: 312.1959 $[M+H]^+$, $C_{20}H_{26}NO_2$ requiere 312.1958.

_N_-benciloxicarbonil-1-fenilpropanamina (18)



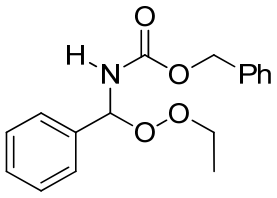
18

RMN ^{1}H (300 MHz, $CDCl_3$) δ 7.32-7.22 (m, 10H), 5.10 (d, *J* = 12.3 Hz, 1H), 5.03 (d, *J* = 12.2 Hz, 2H), 4.59 (q, *J* = 6.8 Hz, 1H), 1.84-1.74 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H).

RMN ^{13}C (75.5 MHz, $CDCl_3$) δ 155.7 (C), 142.4 (C), 136.5 (C), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.3 (CH), 126.4 (CH), 66.7 (CH_2), 56.9 (CH), 29.7 (CH_2), 10.6 (CH_3).

HRMS (ESI) *m/z*: 292.1399 $[M+Na]^+$, $C_{17}H_{19}NO_2Na$ requiere 292.1313.

_N_-benciloxicarboniletilperoxibencilamina (19)



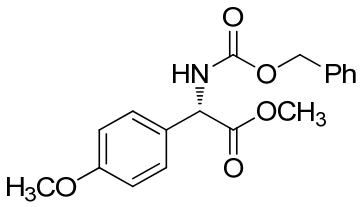
19

RMN ^{1}H (300 MHz, $CDCl_3$) δ 7.42-7.30 (m, 10H), 6.51 (d, *J* = 10.0 Hz, 1H), 5.57 (d, *J* = 8.2 Hz, 1H), 5.17 (s, 2H), 4.10 (q, *J* = 6.2 Hz, 2H), 1.19 (t, *J* = 6.9 Hz, 3H).

RMN ^{13}C (75.5 MHz, $CDCl_3$) δ 155.5 (C), 136.1 (C), 136.5 (C), 129.1 (CH), 128.7 (CH), 128.5 (CH), 128.23 (CH), 128.15 (CH), 126.3 (CH), 85.3 (CH), 70.4 (CH_2), 67.2 (CH_2), 30.3 (CH), 13.3 (CH_3).

HRMS (ESI) *m/z*: 324.1254. $[M+Na]^+$, $C_{17}H_{19}NO_4Na$ requiere 324.1212.

(*S*)-2-benciloxicarbonilamino-2-(*p*-metoxifenil)-acetato de metilo (20)



20

Oxígeno enriquecido en ozono se burbujeó a través de una disolución de producto **11ca** (18.6 mg, 0,050 mmol) en MeOH (15 mL) a -40 °C durante 1 h. El exceso de ozono se eliminó mediante burbujeo de nitrógeno durante 5 min. Se dejó que la disolución

resultante alcanzara temperatura ambiente, se añadió $BF_3{\cdot}Et_2O$ (0,19 mL) y la mezcla se calentó a temperatura de reflujo durante 3,5 h. Tras enfriar a ta, se añadió $NaHCO_3$ acuoso saturado (10 mL), el disolvente orgánico se eliminó a vacío y la disolución acuosa resultante se extrajo con diclorometano (3×15 mL), se lavó con salmuera (10 mL) y se secó sobre $MgSO_4$. La eliminación del disolvente bajo presión reducida seguida de una columna cromatográfica flash eluyendo con hexano-AcOEt (8:2) dio el producto **20** (47%).

El exceso enantiomérico (83%) se determinó mediante HPLC quiral (Chiralpak IC), hexano-^{i}PrOH 97:3, 1 mL/min, enantiómero mayoritario t_r = 76.6 min, enantiómero minoritario t_r = 100.5 min.

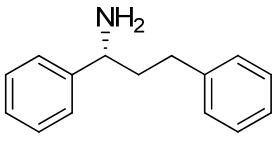
Mp 66-68 °C; $[\alpha]_D^{20}$ + 45.1 (*c* 0.7, $CHCl_3$, 83% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.35-7.28 (m, 7H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.75 (d, *J* = 7.1 Hz, 1H), 5.29 (d, *J* = 6.6 Hz, 1H), 5.10 (d, *J* = 12.4 Hz, 1H), 5.04 (d, *J* = 12.4 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 171.5 (C), 159.8 (C), 155.3 (C), 136.1 (C), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.20 (C), 128.16 (CH), 114.3 (CH), 67.1 (CH_2), 57.3 (CH), 55.3 (CH_3), 52.8 (CH_3).

HRMS (ESI) *m/z*: 352.1583 $(M+Na)^+$, $C_{18}H_{19}NO_5Na$ requiere 352.1161.

(*R*)-1,3-difenilpropan-1-amina (21)



21

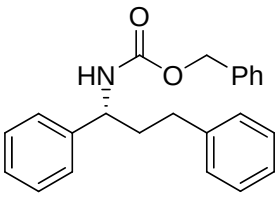
Una disolución del compuesto **11aa** (33.5 mg, 0.098 mmol) en EtOH absoluto (9.0 mL) se agita bajo atmósfera de hidrógeno (globo) en presencia de Pd/C (10%) (12.7 mg) durante 30 min. Tras este tiempo, la mezcla se filtró a través de sílica gel, eluyendo con EtOAc, y se eliminó el disolvente bajo presión reducida para dar el compuesto **21** (99%).

RMN ^{1}H (300 MHz, $CDCl_3$) δ 7.32-7.22 (m, 7H), 7.17-7.10 (m, 3H), 3.85 (t, *J* = 6.9 Hz, 1H), 2.63-2.45 (m, 2H), 2.00-1.93 (m, 2H), 1.79 (s, 2H).

RMN ^{13}C (75.5 MHz, $CDCl_3$) δ 141.8 (C), 128.6 (CH), 128.3 (CH), 127.2 (CH), 126.5 (CH), 125.8 (CH), 55.8 (CH), 40.8 (CH_2), 32.7 (CH_2).

HRMS (ESI) *m/z*: 212.1441 $[M+H]^+$, $C_{15}H_{18}N$ requiere 212.1439.

(*R*)-*N*-benciloxicarbonil-1,3-difenilpropan-1-amine (22)



22

Una disolución del compuesto **11aa** (27.5 mg, 0.081 mmol) en EtOH absoluto (7.5 mL) se agita bajo atmósfera de hidrógeno (globo) en presencia de $Pd/CaCO_3$ (5%) (10.5 mg) durante 1 h. Tras este tiempo, la mezcla se filtró a través de sílica gel, eluyendo con EtOAc, y se eliminó el disolvente bajo presión reducida para dar el compuesto **22** (99%).

El exceso enantiomérico (87%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 22.9 min, enantiómero minoritario t_r = 27.0 min.

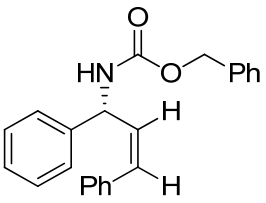
Mp 65-67 °C; $[\alpha]_D^{20}$ + 18.1 (*c* 1.29, $CHCl_3$, 87% *ee*).

^1H RMN (300 MHz, $CDCl_3$) δ 7.33-7.24 (m, 12H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 7.7 Hz, 2H), 5.110 (s, 1H), 5.113 (d, *J* = 12.3 Hz, 1H), 5.04 (d, *J* = 12.2 Hz, 1H), 4.73 (q, *J* = 7.2 Hz, 1H), 2.70-2.52 (m, 2H), 2.17-2.02 (m, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.6 (C), 142.2 (C), 141.2 (C), 136.4 (C), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.5 (CH), 126.4 (CH), 126.0 (CH), 66.8 (CH_2), 55.2 (CH_2), 38.3 (CH), 32.5 (CH_2).

HRMS (ESI) *m/z*: 368.2292 $[M+Na]^+$, $C_{23}H_{23}NO_2Na$ requiere 368.1626.

***(R,Z)*-*N*-benciloxicarbonil-1,3-difenil-2-propen-1-amina (23)**



23

Una disolución de **11aa** (0,056 mmol) en benceno (0,56 mL) se agitó en presencia del catalizador de Lindlar (3,6 mg) bajo una atmósfera de hidrógeno durante 1,5 h. Tras este tiempo, la mezcla se filtró a través de Celite®, eluyendo con EtOAc, y

se eliminó el disolvente bajo presión reducida para dar el compuesto **23** (99%).

El exceso enantiomérico (87%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 95:5, 1 mL/min, enantiómero mayoritario t_r = 22.9 min, enantiómero minoritario t_r = 26.0 min.

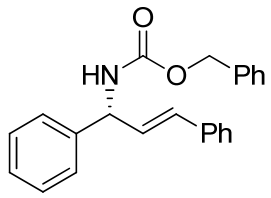
Mp 67-69 °C; $[\alpha]_D^{20}$ + 13.8 (*c* 1.04, $CHCl_3$, 87% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.34-7.23 (m, 13H), 7.16 (d, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 10.3 Hz, 1H), 5.78-5.75 (m, 2H), 5.17 (s, 1H), 5.09 (s, 2H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.4 (C), 141.5 (C), 136.1 (C), 131.4 (C), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 126.6 (CH), 120.3 (CH), 66.8 (CH_2), 42.5 (CH).

HRMS (ESI) *m/z*: 366.1920 $[M+Na]^+$, $C_{23}H_{21}NO_2Na$ requiere 366,1470.

***(R,E)-N*-benciloxicarbonil-1,3-difenilprop-2-en-1-amine (24)**



24

Una disolución de $LiAlH_4$ 1 M en THF (0,050 mmol, 50 µL) se añade gota a gota a una disolución de **11aa** (0,050 mmol) en THF (0,4 mL) a 0 °C bajo nitrógeno. Se deja que la reacción alcance temperature ambiente. Tras 3 horas, se añade 1 mL de agua. La fase acuosa se extrae con diclorometano (3x15 mL), se lava con salmuera (10 mL) y se seca sobre $MgSO_4$. La eliminación del disolvente bajo presión reducida seguida de una columna cromatográfica flash eluyendo con hexano-AcOEt (9:1) dio el producto **24** (64%).

El exceso enantiomérico (87%) se determinó mediante HPLC quiral (Chiralcel OD-H), hexano-^{i}PrOH 90:10, 1 mL/min, enantiómero mayoritario t_r = 28.4 min, enantiómero minoritario t_r = 19.3 min.

Mp 110-111 °C; $[\alpha]_D^{20}$ + 29.4 (*c* 0.68, $CHCl_3$, 87% *ee*).

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.33-7.22 (m, 15H), 6.54 (d, *J* = 16.6 Hz, 1H), 6.31 (dd, *J* = 15.9, 6.0 Hz, 1H), 5.52 (s, 1H), 5.18 (s, 1H), 5.14 (d, *J* = 12.2 Hz, 1H), 5.10 (q, *J* = 12.2 Hz, 1H).

^{13}C RMN (75.5 MHz, $CDCl_3$) δ 155.5 (C), 144.8 (C), 136.34 (C), 136.30 (C), 131.2 (C), 129.0 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 127.81 (CH), 127.76 (CH), 127.0 (CH), 126.5 (CH), 67.0 (CH_2), 56.8 (CH).

HRMS (ESI) *m/z*: 366.1920 $[M+Na]^+$, $C_{23}H_{21}NO_2Na$ requiere 366,1470.

3.6. REFERENCIAS

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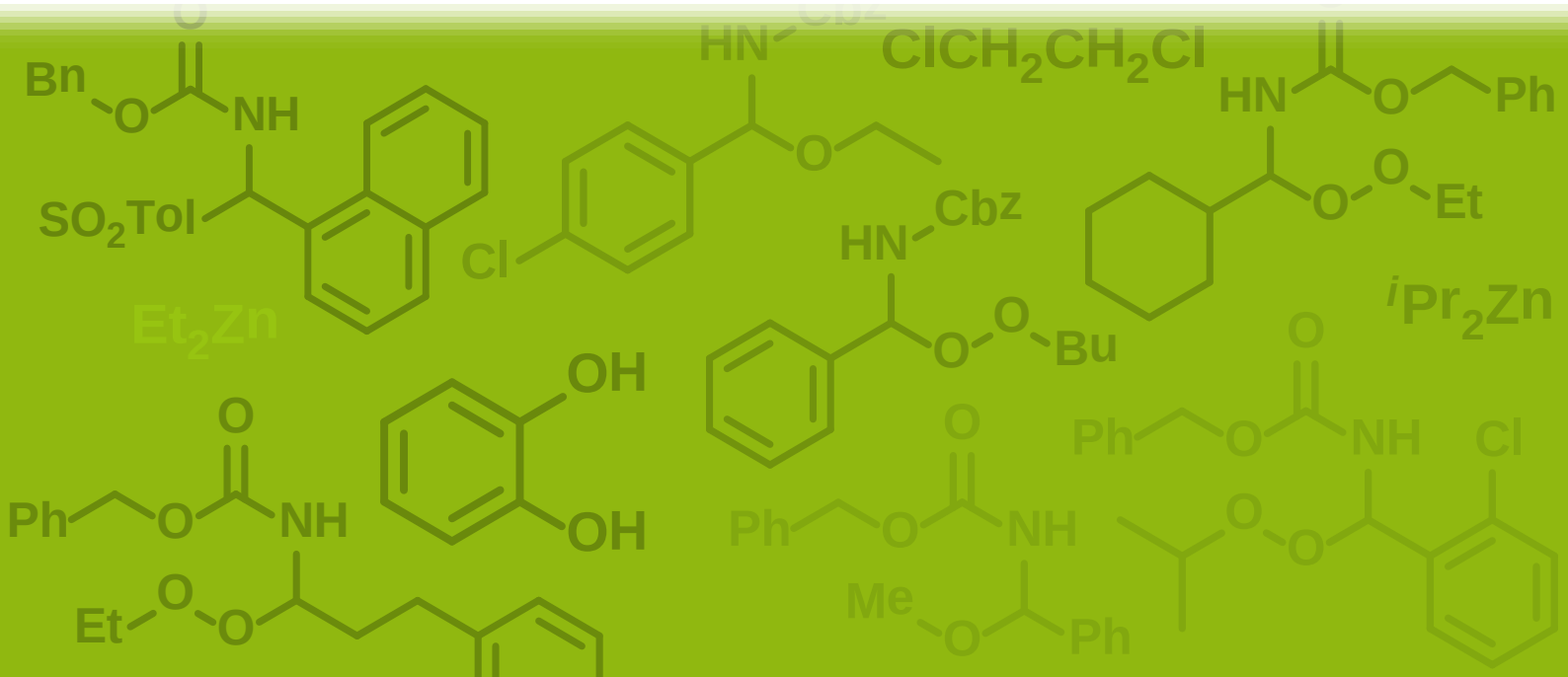
CHAPTER 4

Addition of zinc alkyloxygenated species to α-amido sulfones



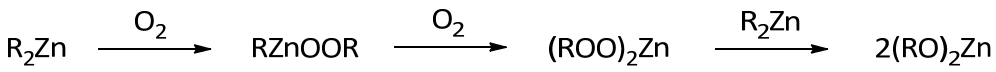
4.1. ANTECEDENTS

The enantioselective addition of alkynes to α-amido sulfones described in Chapter 3 is carried out in the presence of diakylzinc reagents. During our studies, we observed the formation of a product derived from the addition of an oxygenated dialkylzinc species to the α-amido sulfone. This prompted us to study the controlled oxidation of dialkylzinc reagents and their subsequent addition to α-amido sulfones.

4.1.1. Oxidation of dialkylzinc reagents

It has been over 160 years since Frankland's pioneering studies led to the discovery of dialkylzinc reagents when he was investigating the reaction between metallic zinc and ethyl iodide in the search for ethyl radical.[1,2] He rapidly noted the high reactivity of those novel species toward molecular oxygen and in 1849 postulated that controlled oxidation of Et_2Zn affords the alkoxide $Zn(OEt)_2$. In 1864 Lissenko[3] and Butlerov[4] independently reported the formation of partly oxygenated species, RZnOR. Some years later, in 1890, Demuth and Meyer[5] argued for the formation of alkylperoxide, EtZnOOEt, from the insertion of an oxygen molecule into the Zn-C bond. However, all these interpretations have been subjected to debate and, since then, interest in the reaction of dialkylzinc with O_2 have persisted over the years.

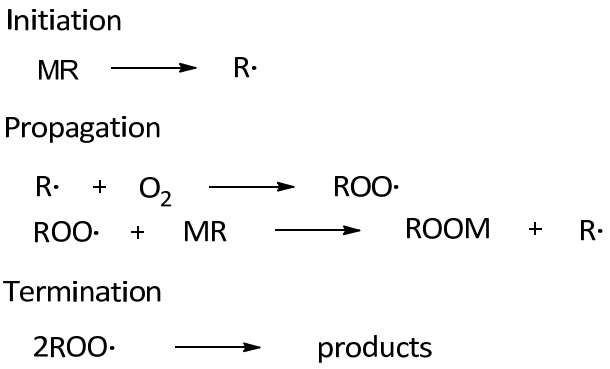
For example, in 1960 Abraham[6] questioned the formation of partially oxygenated species as he reported that both Zn-C bonds in R_2Zn molecules are easily oxidized in some minutes after the start of the reaction. Thus, he suggested the formation of $Zn(OOR)_2$, ROZnOOR, $Zn(OR)_2$, which was later supported by Davies (Scheme 4.1).[7]



Scheme 4.1. Possible species formed in the reaction between dialkylzinc and molecular oxygen.

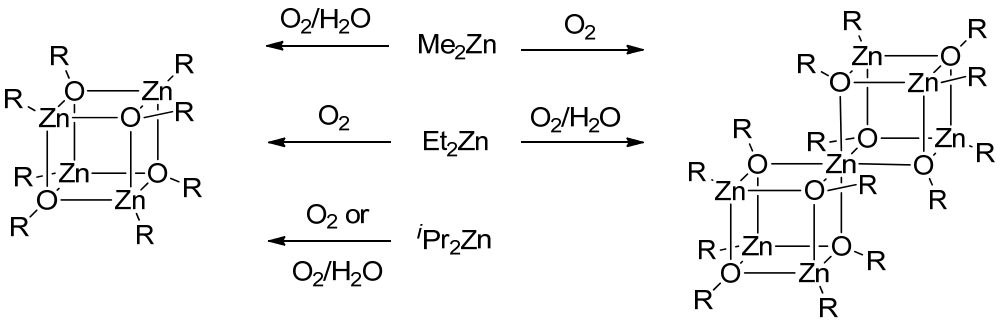
On the other hand, there has also been extensive controversy regarding the mechanism followed by this oxidation. Despite some authors' attempts to demonstrate that the reaction occurred via a polar pathway,[6,8] a radical-chain

mechanism is generally admitted nowadays (Scheme 4.2). Indeed, this radical-chain character, which would be initiated by an adventitious alkyl radical followed by a cascade of fast reactions, has been considered to be responsible for the difficulty to control the oxidation of only one Zn-C bond. This radical-chain mechanism is supported by a recent EPR spectroscopy study using spin-trapping techniques which gave evidence for the formation of alkyl, alkoxyl and alkylperoxyl radicals.[9,10]



Scheme 4.2. Plausible chain-radical mechanism of dialkylzinc oxidation reaction with O_2.

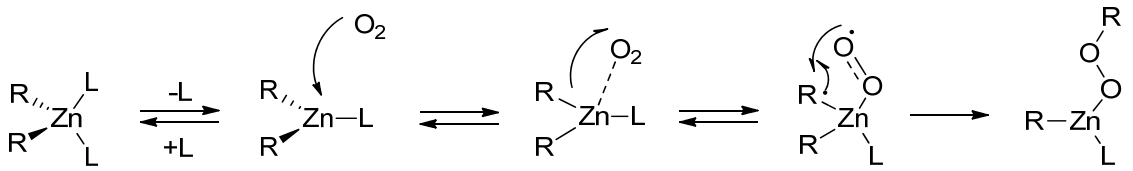
Although some authors have accomplished the controlled oxygenation of simple dialkylzinc compounds[11] (Scheme 4.3), most studies have focused on the oxygenation of these organometallic species in the presence of donor ligands, which have demonstrated to have significant influence on the oxygenation process by decreasing the reactivity of the R_2Zn-L adduct as well as enhancing the stability of the resulting oxygenated products. In fact, recent studies by Lewinski on dialkylzinc compounds have proved that R_2Zn adducts with donor ligands have a marked tendency to undergo oxidation of only one alkyl group with subsequent formation of RZnOOR or RZnOR species.



Scheme 4.3. Controlled oxidation of dialkylzinc reagents.

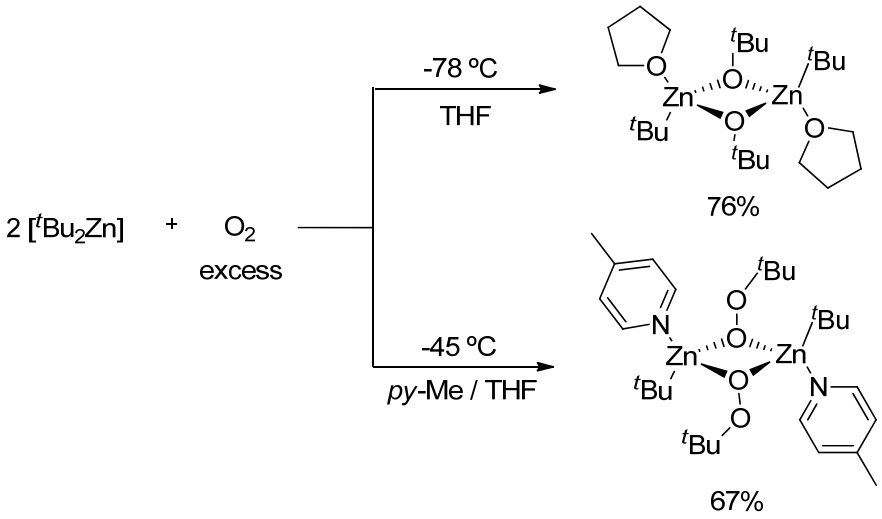
In 2003, Lewinski's group[12] exposed a solution of the aggregate $[EtZn(azol)]_n$ where azol-H is 1-aziridineethanol, to an excess of dry O_2 to afford a white crystalline precipitate of $[EtOOZn(azol)]_2[EtZn(azol)]_2$. In spite of the generally assumed high reactivity of zinc alkyls toward oxygen, this compound did not undergo further oxygenation in the presence of O_2 at -78 °C.

In a later work, the same research group advanced a plausible hypothesis concerning the mechanism of oxygen activation by organometallic compounds which would involve the attack of O_2 on the metal center, followed by electron transfer from the Zn-C bond to O_2 to afford a solvent caged radical pair which at low temperature would rearrange to an alkylperoxide species (Scheme 4.4).[13]



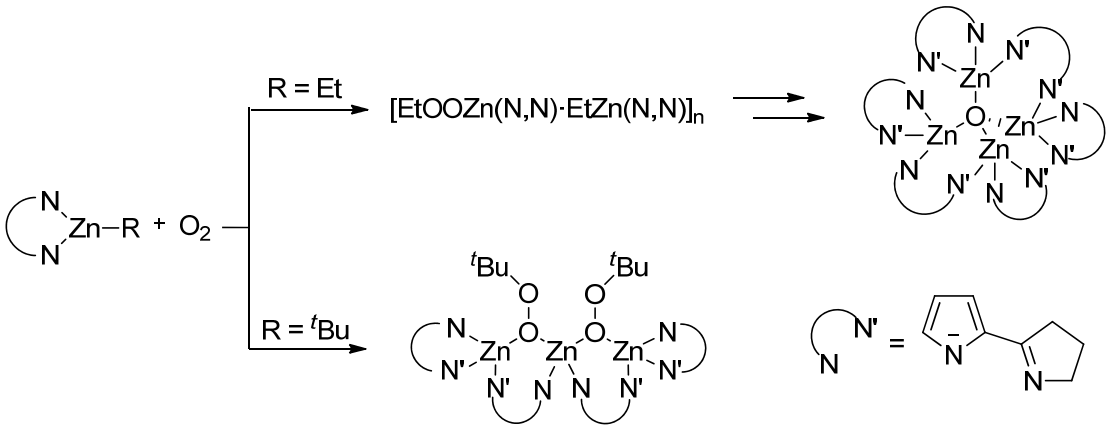
Scheme 4.4. Proposed mechanism for the activation of organometallic compounds by O_2.

In the same publication, these authors conducted a study to determine the effect of the strength of donor ligands on the oxygenation reactions. $^tBu_2Zn$ was treated with O_2 in the presence of two different donor ligands, tetrahydrofuran (THF) and 4-methylpyridine (*py*-Me) (Scheme 4.5). The former led to the selective oxygenation of one Zn-C and the formation of the alkoxide compound $[\{Zn^tBu(\mu\text{-}O^tBu)(THF)\}_2]$. The stronger *N*-donor ligand (*py*-Me) decreased the reactivity of the adduct, higher temperatures were required, and enhanced the stability of the oxygenated products giving the *tert*-butyl peroxide species that results from the insertion of O_2 into on Zn-C bond.



Scheme 4.5. Oxidation of zinc complexes by variation of donor ligand.

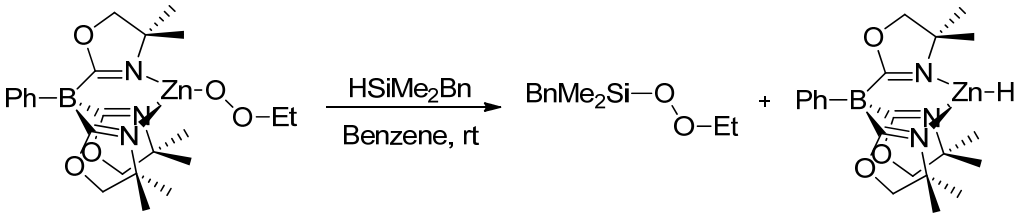
In a more recent investigation, Lewinski's group[14] has reported the unprecedented switch on the reaction outcome produced by changing the character of the zinc-bonded alkyl group (Scheme 4.6). Thus, the use of Et_2Zn led to a tetranuclear zinc oxo-encapsulated cluster, whereas the analogous reaction with $^tBu_2Zn$ generated the corresponding zinc alkylperoxide.



Scheme 4.6. Preparation of zinc oxo-encapsulated cluster versus zinc alkylperoxide complex by modifying the alkyl group attached to Zn.

Recently, Sadow's group[15] has described the synthesis and features of a series of monomeric alkyperoxides of the type To^MZnOOR (To^M = tris(4,4-dimethyl-2-oxazolinyl)phenylborate) which are available from the reaction between To^MZnR and O_2 in quantitative yields. These compounds are reactive as oxidants, so they react with phosphines to afford $OPPh_3$ and the corresponding alkoxide complex and can also

react with organosilanes giving a peroxy-group transfer from zinc to silicon (Scheme 4.7).



Scheme 4.7. Reaction of To^{M}ZnOOR with organosilanes.

Although preparation of alkylperoxyl clusters from Et_2Zn and $^{t}Bu_2Zn$ is well documented, the synthesis of methylperoxide species from Me_2Zn remains almost unattended. In 2008, Lewinski's group[16] reported the selective oxygenation of Me_2Zn with ^{t}Bu-DAB, where DAB is 1,4-diazabutadiene, to provide a novel zinc oxo(methylperoxide) cubane (Figure 4.1).

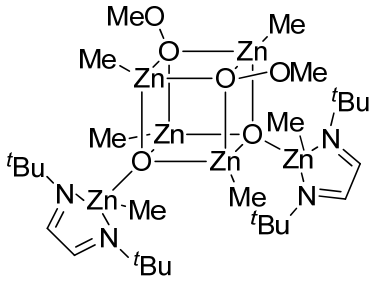
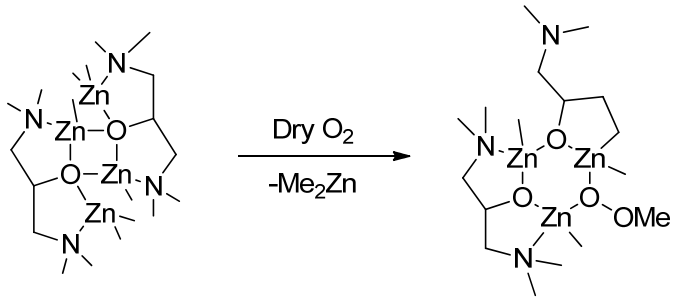


Figure 4.1. Oxo(methylperoxide) cubane.

In a later work, Molloy and co-workers[17] disclosed the reaction of Me_2Zn with 1,3-bis(dimethylamino)propan-2-ol (Hbdmap) in 2:1 ratio to afford $[MeZn(bdmap)\cdot ZnMe_2]_2$ which, after exposure to O_2 gave the isolable peroxide $[MeZn(bdmap)]_2MeZnOOMe$ (Scheme 4.8). This complex decomposes slowly to provide $[MeZn(bdmap)]_2MeZnOH$, probably arising from the homolysis of the O-O bond, $(MeZn)_5(bdmap)_3O$ and $(MeZn)_4(bdmap)_4ZnO$. The formation of these species could be associated to a radical mechanism.



Scheme 4.8. Synthesis of peroxide $[MeZn(bdmap)]_2MeZnOOMe$.

On the other hand, homolytic RZnO-OR bond cleavage has been shown to be responsible for the formation of oxo and metal carboxylate species (Figure 4.2), which could find future applications in the fields of catalysis or hydrogen storing.[18-20]

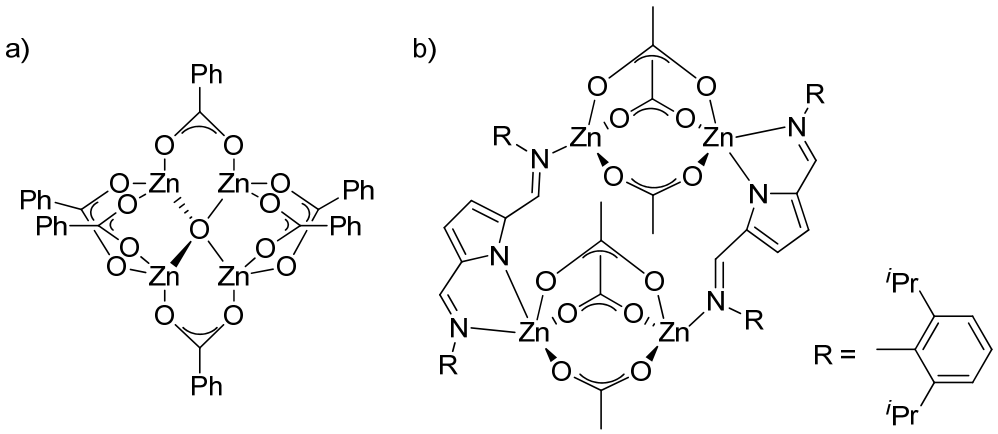


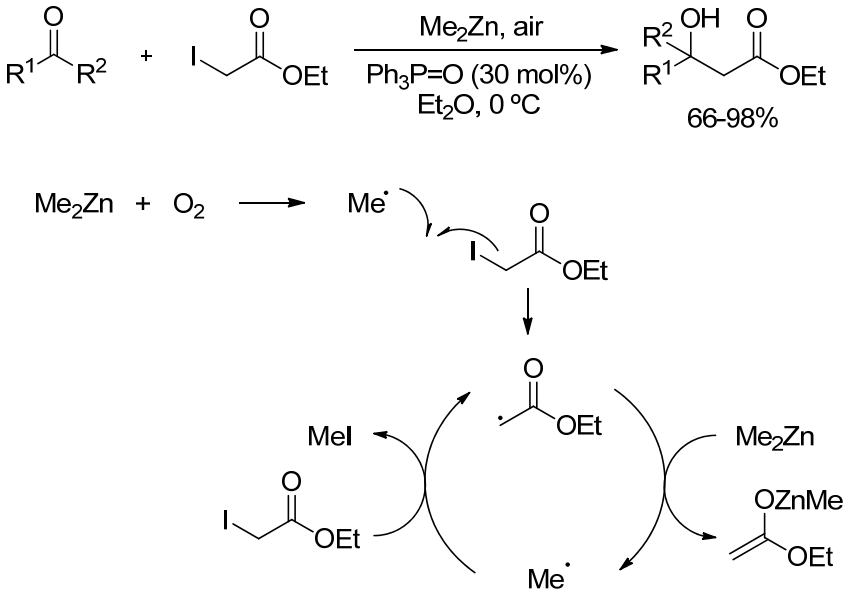
Figure 4.2. a) Zinc oxocarboxilate cluster. b) Zinc acetate complex.

4.1.2. Application of dialkylzinc oxygenation reactions in organic synthesis

In addition, dialkylzinc oxygenation reactions can be useful tools in organic synthesis. However, this application remains almost unexplored. In recent years most of the interest has been focused in radical additions initiated by the R_2Zn/O_2 system. Among the few examples, the dimethylzinc-air promoted Reformatsky reaction has been described independently by Cozzi and Feringa.[21-25]

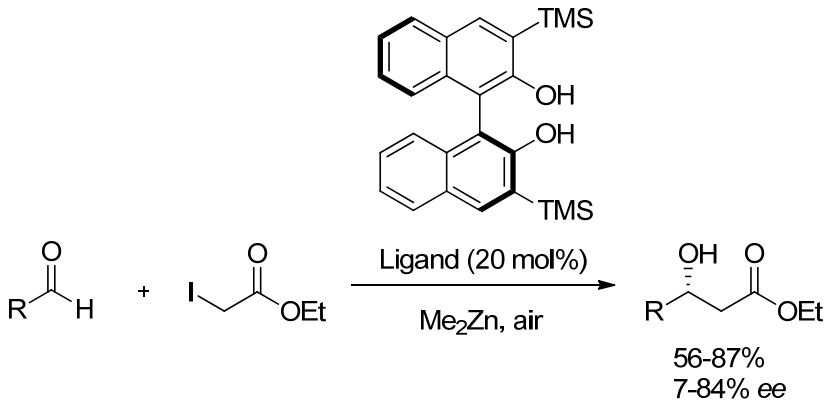
Cozzi's group[22] has performed the Reformatsky reaction between ethyl iodoacetate and aldehydes and ketones employing Me_2Zn as a source of methyl radicals and Zn, as depicted in Scheme 4.9. The authors have reported the addition of

$Ph_3P{=}O$ to shorten reaction times as well as to permit the use of rather unreactive ketones, obtaining the final addition products in good to excellent yields. An enantioselective variant of this reaction was evaluated with chiral amino alcohols as ligands with promising results.



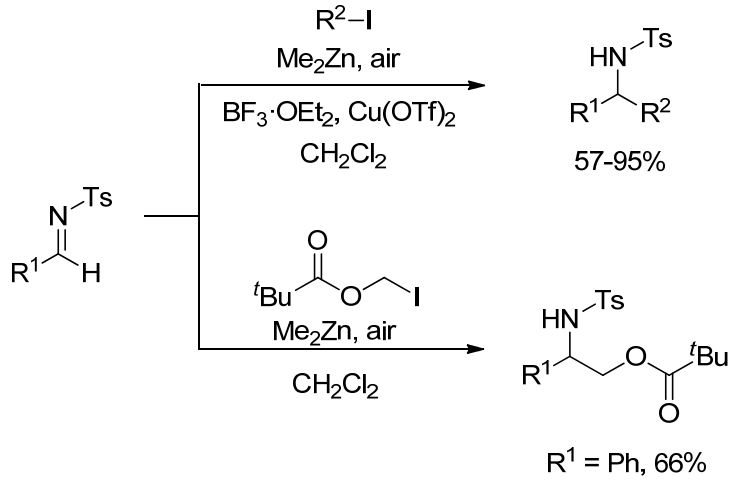
Scheme 4.9. Reformatsky reaction mediated by Me_2Zn-air and proposed catalytic cycle.

Concurrently, Feringa and co-workers[23] developed the enantioselective Reformatsky reaction with aldehydes and ethyl iodoacetate mediated by Me_2Zn and promoted by air, which was found to be crucial to initiate the radical mechanism (Scheme 4.10). A BINOL-type ligand was chosen to carry out the reaction. The use of aromatic and heteroaromatic aldehydes led to moderate to high enantioselectivities (42-84% *ee*), whereas aliphatic substrates provided lower stereocontrol (7-50% *ee*). Besides, the same methodology was applied to the reaction with ketones yielding the corresponding products in similar results.[24,25]



Scheme 4.10. Enantioselective Reformatsky reaction of aldehydes catalyzed by BINOL-type ligand mediated by Me_2Zn-air.

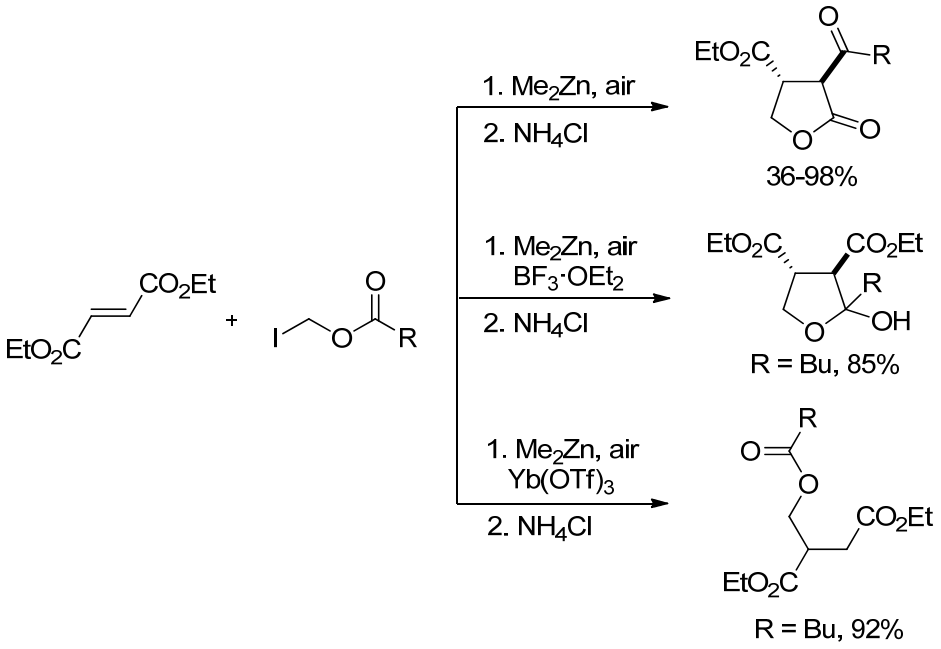
The Me_2Zn-air-promoted homolytic cleavage of carbon-iodine bond has also been reported by Tomioka's and Bertrand's groups.[26-30] The former research group[26] has disclosed the addition of alkyl radicals from alkyl, chloroalkyl and acetoxyalkyl iodides to *N*-tosylimines in good to high yields (57-95%). The reaction required stoichiometric amount of boron trifluoride-diethyl etherate and a catalytic amount of copper(II) triflate to accelerate the process. Later, they performed the reaction between iodomethyl pivalate and *N*-tosylbenzaldimine in the presence of Me_2Zn and air with a 66% yield. Surprisingly, the use of Et_2Zn furnished the ethyl addition adduct instead of the expected product (Scheme 4.11).[27]



Scheme 4.11. Radical addition to *N*-tosylimines promoted by Me_2Zn-air.

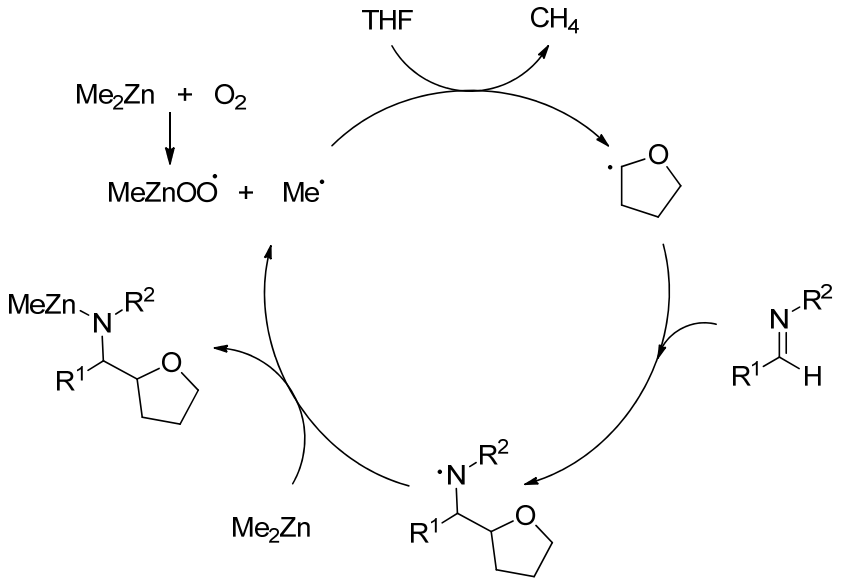
Bertrand[29] and co-workers have described a stereoselective radical-anionic tandem reaction promoted by Me_2Zn-air employing iodomethyl esters as radical

precursors and ethyl fumarate as radical acceptor to afford γ-lactones in moderate to high yields (36-98%). The chemoselectivity of the process was modified by addition of Lewis acids (Scheme 4.12). In a recent work,[30] the same research group found evidence of the formation of the phtalamidomethyl radical upon reaction with dialkylzinc and air by spin-trapping experiments. These radicals were added to diethyl fumarate providing functionalized pyrrolidine derivatives.



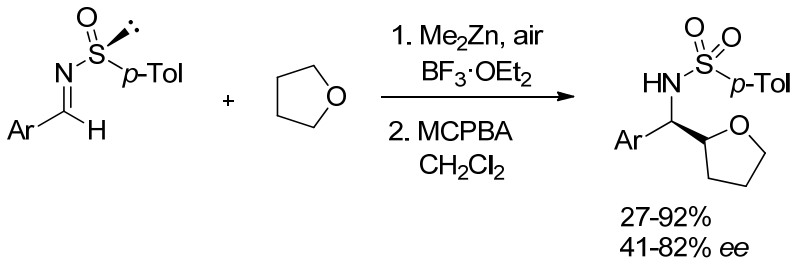
Scheme 4.12. Radical-anionic tandem reaction promoted by Me_2Zn-air employing iodomethyl esters and ethyl fumarate.

On the other hand, Tomioka[31] and co-workers have reported the use of dimethylzinc in conjunction with air as an efficient radical initiator to generate carbon-centered radicals from C-H bonds which were added to electrophilic substrates to afford the corresponding adducts. For example, imines have been found to be suitable electrophilic substrates for the production of these adducts in the reaction with cyclic ethers[32-34] or cycloalkanes.[35] The plausible mechanism for this process with THF begins with the generation of methyl radical by the action of oxygen on dimethylzinc (Scheme 4.13). Then, the resulting methyl radical abstracts an α-hydrogen from THF to produce a tetrahydrofuran-2-yl radical which adds to the imine to give an aminyl radical. Its subsequent reaction with dimethylzinc generates a methyl radical (as the reaction chain carrier) and a zinc amide, which upon workup affords the final adduct.[33]



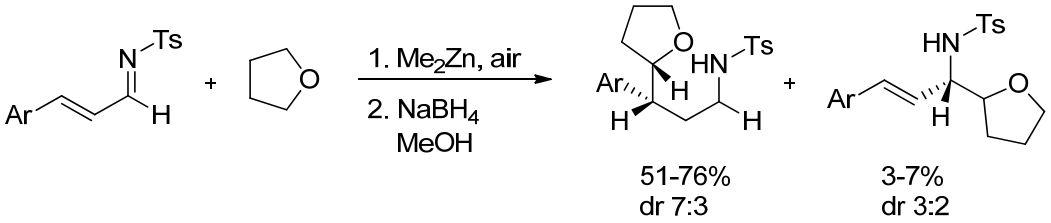
Scheme 4.13. Proposed mechanism for the radical addition of THF to imine.

This methodology has also been applied in the stereoselective addition of α-alkoxyalkyl radicals to *N*-sulfinylimines promoted by Me_2Zn-air, followed by the oxidation of the resulting products with dry MCPBA to afford sulfonamides enantiomerically enriched (Scheme 4.14). Lewis acid activation of the *N*-sulfinylimine substrates facilitated the radical addition and further investigations showed that substitution of the *p*-tolyl group at the stereogenic centre led to higher levels of stereocontrol.[36,37]



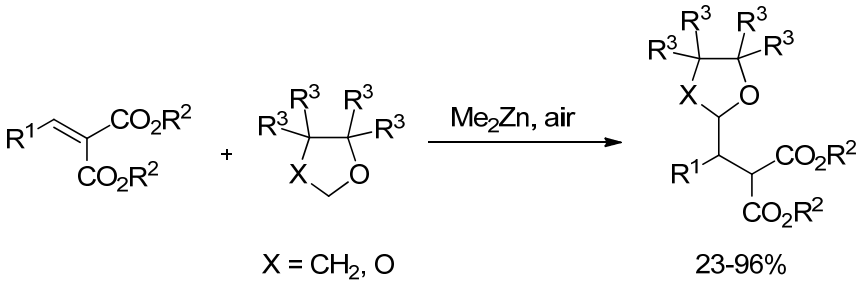
Scheme 4.14. Diastereoselective radical addition of cyclic ethers to *N*-sulfinilimines and subsequent oxidation to afford *N*-sulfonamides.

Additionally, the authors have extended this approach to the utilization of *N*-tosyl α,β-unsaturated imines with THF (Scheme 4.15). The reaction preferentially proceeds in a 1,4-addition manner to give 2-(3-aminoalkyl)tetrahydrofurans in good yields. The use of dimethylzinc rather than diethylzinc or triethylborane was essential for the efficiency of the addition.[38]



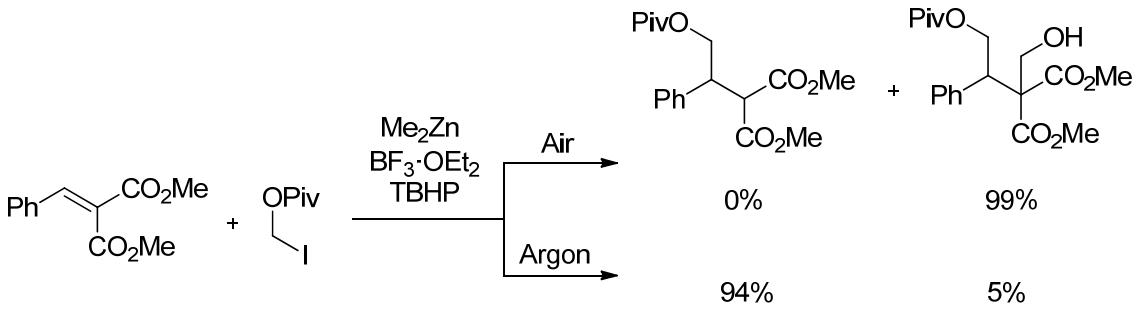
Scheme 4.15. Radical addition of THF to *N*-tosyl α,β-unsaturated imines.

Although α,β-unsaturated imines demonstrated to be good Michael acceptors, the precursor of ether radical was limited to THF. On the contrary, alkylidenemalonates have been found to be useful Michael acceptors toward the radical addition of diverse cyclic ethers (Scheme 4.16).[39-41]



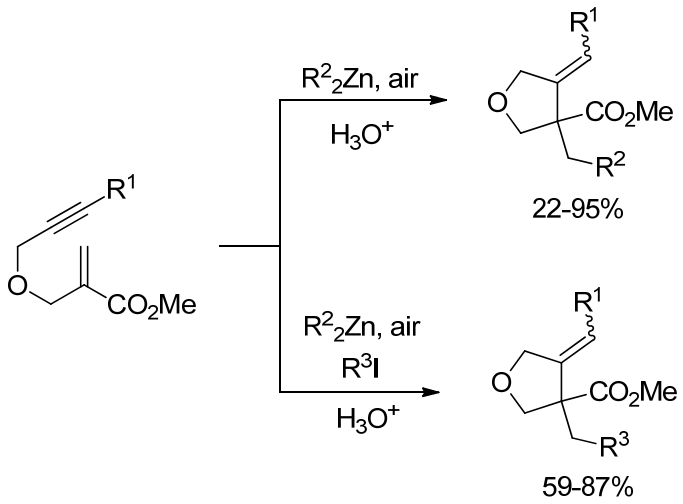
Scheme 4.16. Radical addition of THF to alkylidenemalonates.

More recently, these substrates were employed in the reaction with iodomethyl pivalate in the presence of Me_2Zn, air and *tert*-butylhydroperoxide (TBHP) (Scheme 4.17).[42] When the reaction was performed under air, α,β-dual oxymethylation products were obtained. However, β-pivaloyloxymethylation products were obtained under argon. This radical conjugate addition was applicable to the preparation of the bioactive lignin hinokinin.



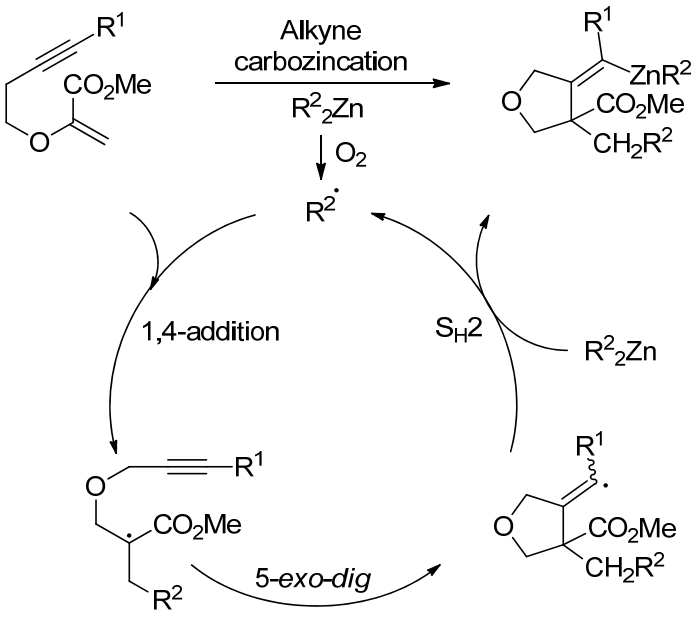
Scheme 4.17. Radical addition of iodomethyl pivalate to alkylidenemalonates.

Finally, some authors have employed R_2Zn/O_2 system as radical initiator in the carbozincation of alkynes. Taking into consideration previous studies by Knochel[43] and Cohen,[44] Chemla and co-workers[45,46] have disclosed a domino 1,4-addition/alkyne carbozincation sequence based on a radical zinc-atom transfer. They have developed two multicomponent approaches to polysubstituted alkylidene tetrahydrofurans from β-(propargyloxy)enoates (Scheme 4.18). The first one consists of the direct addition of dialkylzinc compounds, whereas the second one involves the dimethylzinc-promoted addition of alkyl iodides. The procedure tolerates well a wide variety of substituted alkynes.



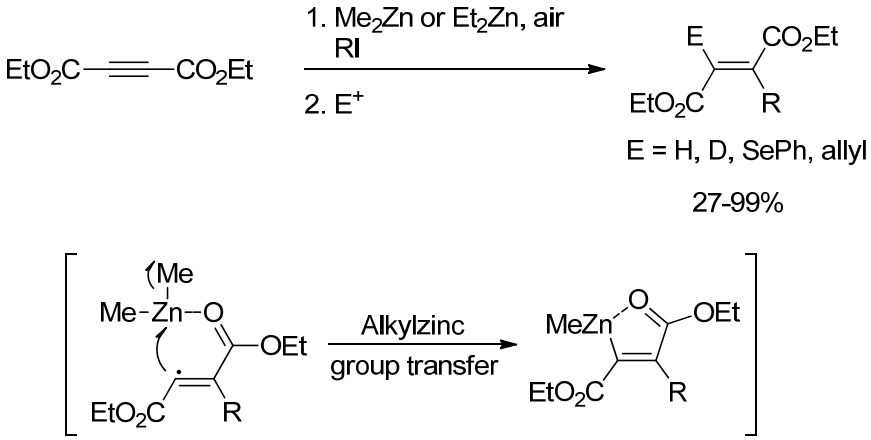
Scheme 4.18. Me_2Zn-air promoted synthesis of tetrahydrofurans through 5-*exo*-*dig* cyclization reaction.

A plausible mechanism for the carbozincation reaction starts with the oxidation of the dialkylzinc by traces of oxygen. This process produces a radical that undergoes 1,4-addition into the α,β-unsaturated ester to afford an inoxy radical, which experiences a 5-*exo*-*dig* cyclization reaction to give a vinyl radical that reacts with R_2Zn via homolytic substitution. A nucleophilic alkenyl zinc species suitable for further reactions with electrophiles is formed (Scheme 4.19).



Scheme 4.19. Me_2Zn-air promoted synthesis of tetrahydrofurans through 5-*exo*-*dig* cyclization reaction.

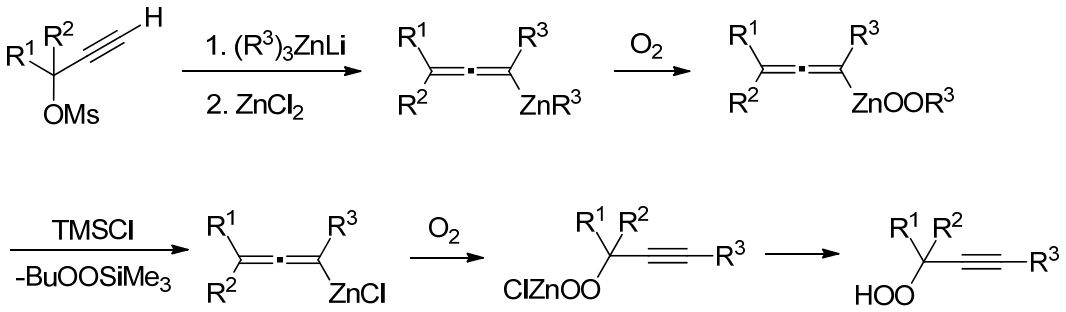
Bertrand's group[47] has accomplished the dialkylzinc/air-promoted synthesis of α-alkylidene-γ-lactams through a similar strategy. Moreover, they have employed the same system to trigger the stereoselective *anti*-carbozincation of diethyl acetylenedicarboxylate to give diethylfumarate derivatives in good yields (Scheme 4.20). The stereochemical outcome of the process is explained by means of the coordination of Zn(II) with the oxygen atom of the ester group and the subsequent reaction of an electrophile, which occurs in position *cis* relative to the carboxylate.[48]



Scheme 4.20. *Anti*-carbozincation of diethyl acetylenedicarboxylate through alkylzinc group radical transfer.

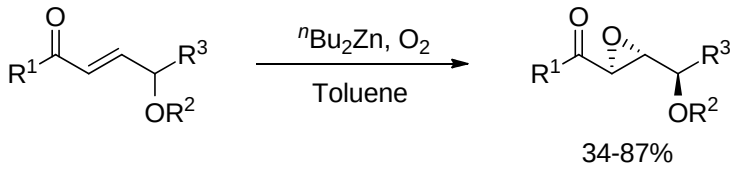
With respect to the oxygenated species originated by the oxidation of dialkylzinc with oxygen, their main synthetic applications have been limited to the preparation of hydroperoxides or alcohols, and their use as epoxidizing reagents for enones.

For example, Harada and Kutsuda[49] have generated propargylic hydroperoxides from the reaction between propargylic derivatives and lithium triorganozincates (Scheme 4.21). The reaction proceeds via allenyl zinc species which react regioselectively at the γ position with molecular oxygen. The use of $ZnCl_2$ is crucial to obtain the hydroperoxide instead of the propargyl alcohol. Moreover, addition of chlorotrimethylsilane is necessary to trap the resulting zinc hydroperoxide with the concomitant formation of trimethylsilylperoxide and allenic chlorozinc.



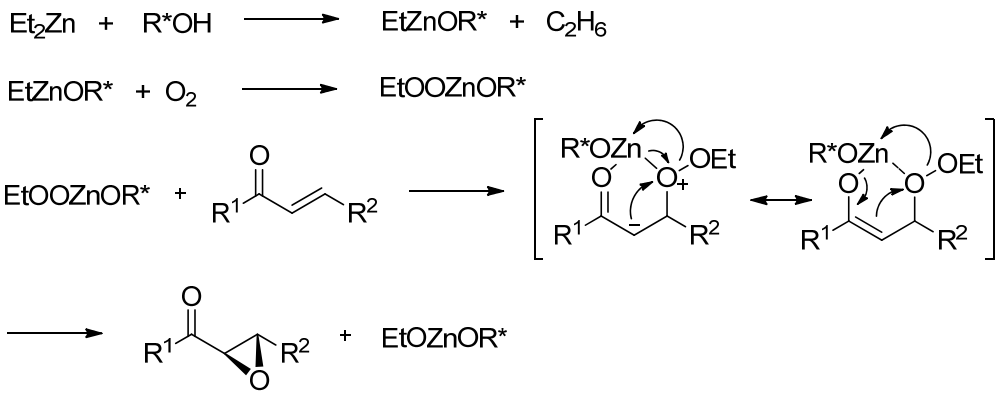
Scheme 4.21. Synthesis of hydroperoxides from propargylic derivatives and lithium triorganozincates in the presence of molecular oxygen.

The use of oxygenated dialkylzinc species as epoxidizing reagents has aroused widespread attention among scientists. In 1989, Yamamoto[50] reported the oxidation of Et_2Zn and the addition of the resulting alkylperoxozinc to α,β-unsaturated ketones to form alkylperoxozinc species, which finally gave the epoxidation products (Scheme 4.22). The process occurred through an *erythro*-selective attack (>99%) of the nucleophilic reagent when ^{i}Pr was used as substituent. Besides, the procedure is chemoselective and is not applicable to the epoxidation of α,β-unsaturated esters.



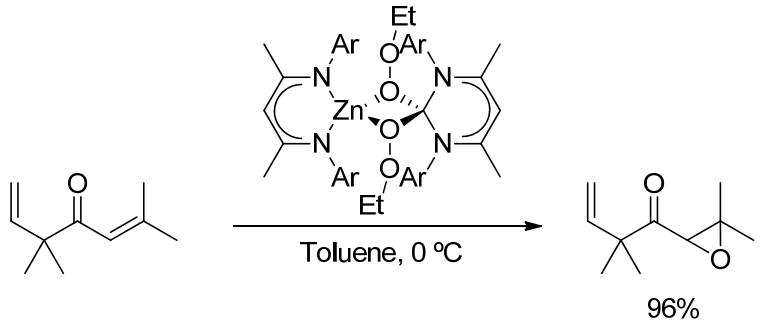
Scheme 4.22. Epoxidation of α,β-unsaturated ketones mediated by $^{n}Bu_2Zn$ and molecular oxygen.

Later, Enders' group[51] reported the enantioselective epoxidation of α,β-unsaturated ketones with Et_2Zn and O_2 in the presence of (*R*,*R*)-*N*-methylpseudoephedrine to obtain chiral (*R*,*S*)-α,β-epoxyketones in excellent yields (94-99%), diastereoselectivities (>99% de) and high enantiomeric excesses (82-92%). According to their observations, the authors postulated a mechanism which starts with the formation of ethylzinc alkoxide from diethylzinc and the chiral alcohol. Then, O_2 inserts into the Zn-C bond furnishing the chiral alkoxy(ethylperoxy)zinc. The zinc atom coordinates to the oxygen of the carbonyl group in the ketone and concomitant attack of the ethylperoxy anion in β-position occurs. The subsequent cyclization gives the α,β-epoxyketone (Scheme 4.23).



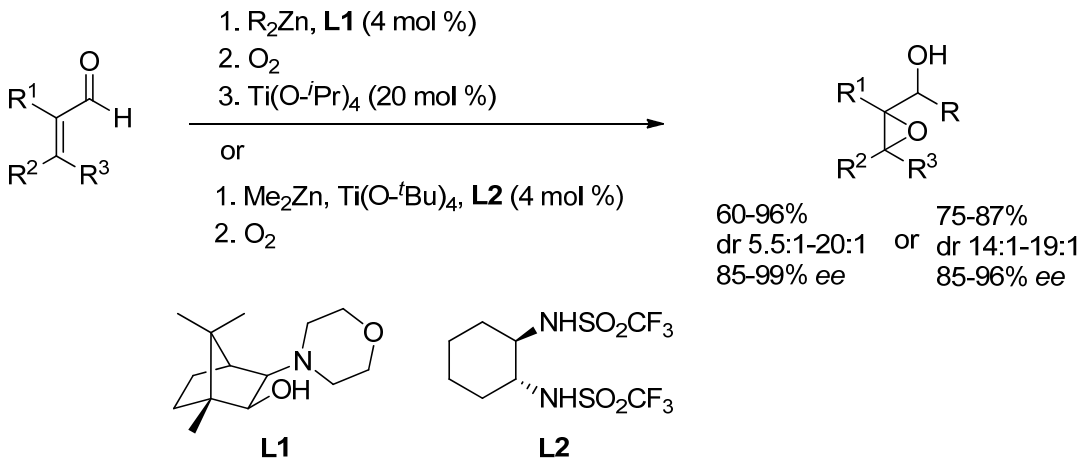
Scheme 4.23. Plausible mechanism for the enantioselective epoxidation of α,β-unsaturated ketones with Et_2Zn and O_2 in the presence of a chiral ligand.

Lewinski and co-workers[52] have designed a zinc alkylperoxide complex from Et_2Zn, 2-[(2,6-diisopropylphenyl)amino]-4-[2,6-diisopropylphenyl)imino]-pent-2-ene (BDI-H) and molecular oxygen which demonstrated to be efficient in the regio- and chemoselective epoxidation of α,β-unsaturated ketones bearing an unconjugated alkene (Scheme 4.24).



Scheme 4.24. Chemoselective epoxidation of α,β-unsaturated ketones by an zinc alkylperoxide complex.

Walsh and co-workers have demonstrated that acyclic epoxy alcohols containing up to three stereogenic centres can be synthetized from α,β-unsaturated ketones using dialkylzinc and a chiral ligand in the presence of $Ti(O^iPr)_4$ or $Ti(O^tBu)_4$ and molecular oxygen (Scheme 4.25). A similar methodology can be applied starting from aldehydes and ethyl vinyl zinc species. Both approaches yield the corresponding products with high enantio- and diastereoselectivities for a wide range of substituents.[53-55]



Scheme 4.25. Diastereoselective epoxidation of α,β-unsaturated ketones using dialkylzinc and a chiral ligand.

Despite the variety of processes described in literature where R_2Zn species and imines participate in radical addition reactions, to the best of our knowledge, the addition of alkylperoxide species generated by the reaction of oxygen and dialkylzinc reagents with imines has not been described so far. The resulting products, particularly

those derived from the addition of alkylperoxide, would be of special interest since a wide variety of natural products contain a peroxide group and present antibacterial, antimalarial or antitumor activities.[56] For example, artemisinin has demonstrated to possess high effects as antimalarial drug.[57,58]

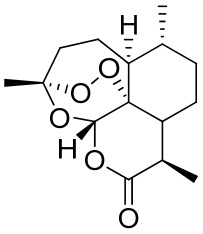
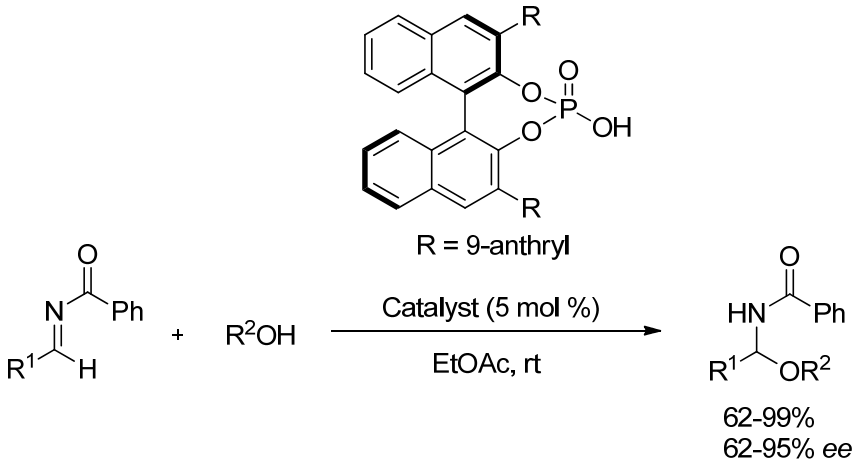


Figure 4.3. Artimisinin.

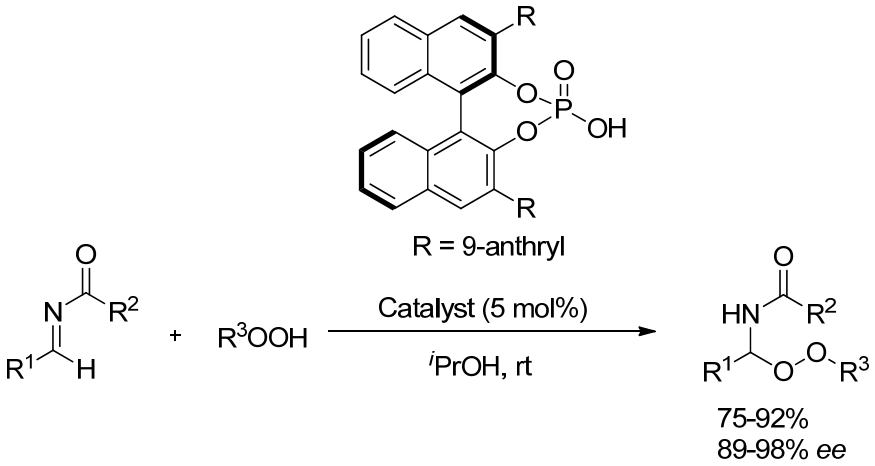
The alkoxidation and peroxidation of imines by means of non-radical approaches has been perfomed by Antilla and co-workers.[59] In 2008, they reported the enantioselective addition of alcohols to *N*-acylimines catalyzed by chiral phosphoric acids. The utilization of differently substituted *N*-acylbenzaldimines led to the resulting products in high yields with excellent enantiomeric excesses (76-99%, 81-95% *ee*). On the contrary, an imine derived from an aliphatic aldehyde provided lower results (62%, 65% *ee*).



Scheme 4.26. Enantioselective addition of alcohols to *N*-acylimines.

In a more recent work (2010),[60] the same authors extended this strategy for enantioselective peroxidation of *N*-acylimines catalyzed by the same chiral phosphoric acid (Scheme 4.27). The utilization of aromatic imines and tertiary peroxides yielded

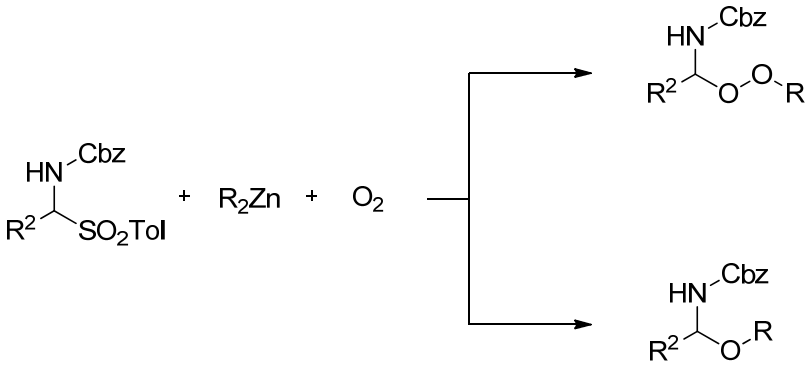
the corresponding α-amino peroxides with good yields (75-92%) and excellent enantioselectivities (89-98% *ee*).



Scheme 4.27. Enantioselective peroxidation of *N*-acylimines.

4.2. OBJECTIVES

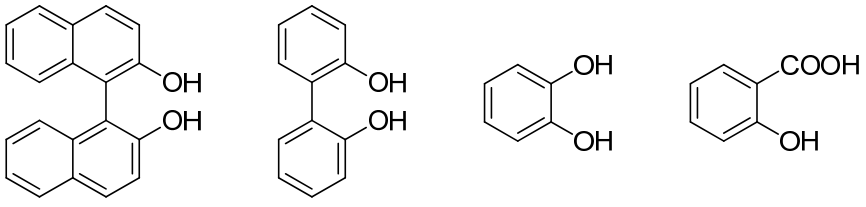
The main objective of this chapter is to perform the addition of zinc alkylperoxide species resulting from the controlled oxygenation of dialkylzinc reagents to α-amido sulfones. This process would directly provide α–amido alkylperoxides in a three component protocol. In addition, we intend to modify the oxygenation conditions to obtain zinc alkoxide species whose addition to α-amido sulfones would afford α-amido alkoxides.



In order to develop this work, we will study the following aspects:

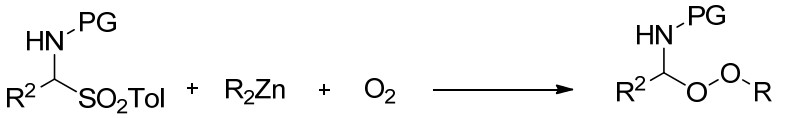
<u>Addition of zinc alkylperoxide species to α-amido sulfones</u>

1. Identification of optimal conditions of the reaction: Influence of the structure of diverse *O,O'*-donor ligands and solvents on the yield of the reaction.



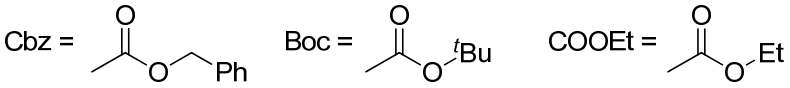
(±)-L1 **L9** **L10** **L11**

2. Influence of different protecting groups on the yield of the reaction.

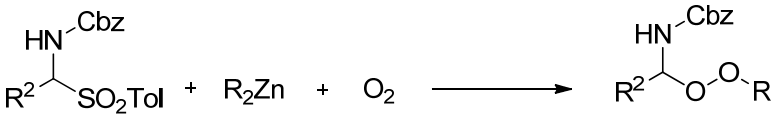


8, PG = Cbz
9, PG = Boc
10, PG = COOEt

19, PG = Cbz
25, PG = Boc
26, PG = COOEt



3. Scope and limitations of the reaction: evaluation of aromatic and aliphatic α-amido sulfones with different electronic and steric nature in the reaction with Et_2Zn, $^{n}Bu_2Zn$, $^{i}Pr_2Zn$ and Me_2Zn and O_2.



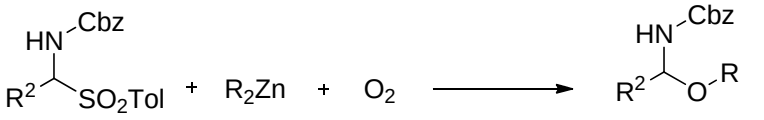
8

19, R = Et
27, R = ^{n}Bu
28, R = ^{i}Pr
29, R = Me

<u>Addition of zinc alkoxide species to α-amido sulfones</u>

1. Identification of optimal conditions of the reaction: Influence of the structure of diverse *O,O'*-donor ligands, solvents and temperatures on the yield.

2. Scope and limitations of the reaction: evaluation of aromatic and aliphatic α-amido sulfones with different electronic and steric nature with Et_2Zn, $^{n}Bu_2Zn$, Me_2Zn and O_2.



8

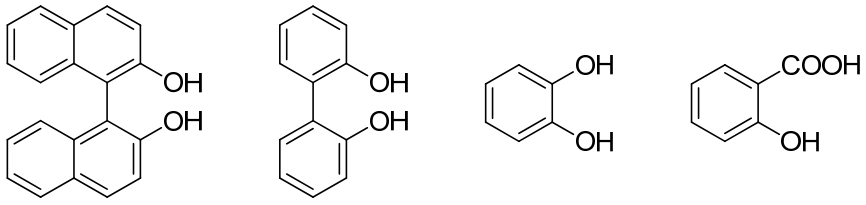
30, R = Et
31, R = ^{n}Bu
32, R = Me

4.3. RESULTS AND DISCUSSION

4.3.1. Addition of zinc alkylperoxides to α-amido sulfones

4.3.1.1. Optimization of reaction conditions

The formation of α–amido alkylperoxides was initially discovered during our studies about enantioselective alkynylation of α-amido sulfones using diethylzinc (Chapter 3, p. 117). For this reason, we first investigated the addition of diethylzinc in the presence of dry oxygen to α-amido sulfone **8aa** with a catalytic amount (20 mol %) of several *O*,*O'*-donor ligands in dichloromethane at 0 °C.



(±)-L1 **L9** **L10** **L11**

Figure 4.4. *O*,*O'*-donor ligands.

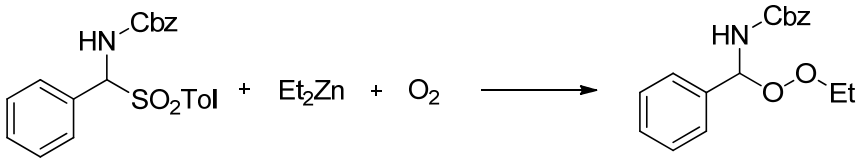
1,1'-Bi-2-naphtol ((±)-**L1**), 2,2'-biphenol (**L9**), cathecol (**L10**) and salicylic acid (**L11**) were evaluated providing exclusively α–amido alkylperoxides in all cases. (±)-**L1**, **L9** and **L10** led to good yields (73-82%) (Table 4.1, Entries 1-3). However, salicylic acid (**L11**) was found to be the most effective ligand (Table 4.1, Entry 4). On the other hand, changing solvent to toluene did not have any effect on the yield (Table 4.1, Entry 5).

Surprisingly, when the reaction was performed in the absence of ligand, the desired product was obtained in quantitative yield (Table 4.1, Entry 6). This permitted us to isolate pure products by a simple extraction of the reaction mixture with water.

Finally, an increase in temperature led to α–amido alkylperoxide in 74% (Table 4.1, Entry 7).

So, we concluded that the best results were afforded when the ethylperoxidation reaction of α-amido sulfones was carried out with diethylzinc/dry oxygen in dichloromethane at 0 °C and in the absence of ligand.

Table 4.1. Three component addition of Et_2Zn/O_2 to α-amido sulfone **8aa**. Screening of ligands and solvent.[a]



8aa **19a**

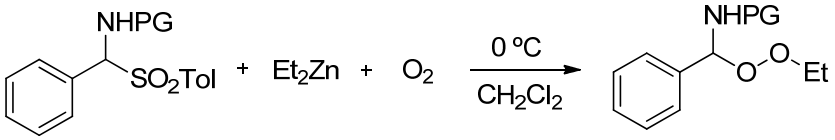
Entry	L	Solvent	T (°C)	t (h)	Yield (%)[b]
1	(±)-**L1**	CH_2Cl_2	0	20	73
2	**L9**	CH_2Cl_2	0	20	80
3	**L10**	CH_2Cl_2	0	20	82
4	**L11**	CH_2Cl_2	0	20	97
5	**L11**	Toluene	0	20	93
6	**/**	CH_2Cl_2	0	20	97
7	**/**	CH_2Cl_2	rt	20	74

[a] **8aa** (0.125 mmol), **L** (0.025 mmol), 1 M Et_2Zn in hexanes (0.375 mmol), solvent (1.6 mL). [b] Yield of isolated product.

Then, the influence of the protecting group was examined. The screening showed that Cbz and Boc protected α-amido sulfones performed better than ethyloxycarbonyl protected ones (Table 4.2).

Due to the slightly better result provided by the Cbz protecting group and the availability of a wide variety of *N*-Cbz-protected α-amido sulfones which had been previously synthesized, these substrates were selected to study the scope of the process.

Table 4.2. Screening of reaction conditions for the ethylperoxidation of α-amido sulfones.[a]



8, PG = Cbz
9, PG = Boc
10, PG = COOEt

19, PG = Cbz
25, PG = Boc
26, PG = COOEt

Entry	α-amido sulfone	PG	t (h)	Product	Yield (%)[b]
1	**8aa**	Cbz	20	**19a**	97
2	**9aa**	Boc	20	**25a**	93
3	**10aa**	COOEt	20	**26a**	72

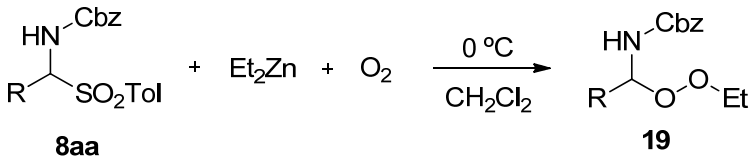
[a] α-Amido sulfones (0.125 mmol), 1 M Et_2Zn in hexanes (0.375 mmol), CH_2Cl_2 (1.6 mL). [b] Yield of isolated product.

4.3.1.2. Scope and limitations of the reaction

Under the optimized conditions, the reaction with Et_2Zn/O_2 was found to be general for a number of *N*-Cbz-protected α-amido sulfones **8** derived from aromatic, heteroaromatic and aliphatic aldehydes (Table 4.3).

Both electron-withdrawing and electron-donating groups in the aromatic ring of the α-amido sulfones were well tolerated and led to excellent results (Table 4.3, Entries 1-8). Likewise, α-amido sulfones derived from 1-naphthaldehyde and 2-thiophenecarbaldehyde provided the desired products in very high yields (95 and 98%) (Table 4.3, Entries 9-10). Finally, the reaction was also successfully performed with aliphatic substrates which gave the corresponding α–amido alkylperoxide with yields between 94 and 99% (Table 4.3, Entries 11-13).

Table 4.3. Three component addition of Et_2Zn/O_2 to α-amido sulfones **8**.[a]



8aa **19**

Entry	8	R	t (h)	19	Yield (%)[b]
1	**8aa**	Ph	20	**19a**	97
2	**8ba**	4-MeC_6H_4	20	**19b**	93
3	**8ca**	4-$MeOC_6H_4$	20	**19c**	91
4	**8ea**	4-ClC_6H_4	20	**19e**	93
5	**8fa**	4-BrC_6H_4	20	**19f**	95
6	**8ga**	3-MeC_6H_4	20	**19g**	92
7	**8ha**	2-MeC_6H_4	20	**19h**	97
8	**8ja**	2-ClC_6H_4	20	**19j**	94
9	**8la**	1-naphthyl	20	**19l**	95
10	**8na**	2-thienyl	20	**19n**	98
11	**8qa**	$C_6H_5CH_2CH_2$	20	**19q**	99
12	**8ra**	*n*-butyl	20	**19r**	94
13	**8sa**	cyclohexyl	20	**19s**	94

[a] **8aa** (0.125 mmol), 1 M Et_2Zn in hexanes (0.375 mmol), CH_2Cl_2 (1.6 mL). [b] Yield of isolated product.

The structure of these α-amido alkylperoxides was established by spectroscopy methods and confirmed by X-ray diffraction analysis of product **19f**, which showed the peroxide group (Figure 4.5).

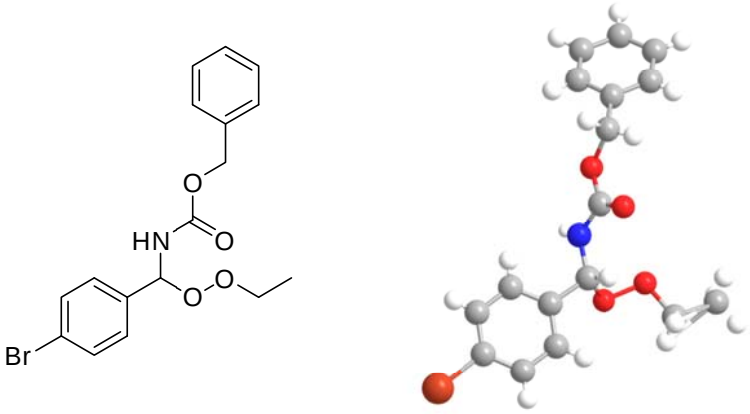
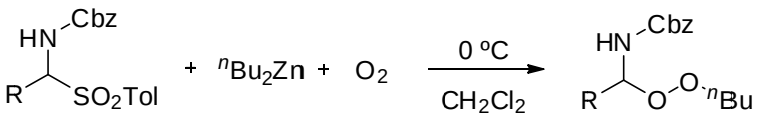


Figure 4.5. X-ray structure of **19f**.

The reaction also performed well with the larger dialkylzinc $^{n}Bu_2Zn$. This reagent is also compatible with electron-withdrawing and electron-donating groups in different positions in the aromatic ring of the α-amido sulfone (Table 4.4, Entries 1-3). Heteroaromatic α–amido sulfone **8na** yielded the corresponding peroxide derivative quantitatively (98%) (Table 4.4, Entry 4). Finally, aliphatic α-amido sulfones derived from dihydrocinnamaldehyde and cyclohexylcarbaldehyde were also subjected to the addition of $^{n}Bu_2Zn$ and oxygen and the corresponding α-amido butylperoxides were isolated in 90 and 91% yield, respectively (Table 4.4, Entries 5-6).

Table 4.4. Three component addition of $^{n}Bu_2Zn/O_2$ to α-amido sulfones **8**.[a]



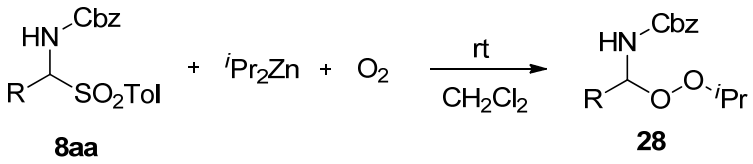
8aa **27**

Entry	8	R	t (h)	27	Yield (%)[b]
1	**8aa**	Ph	20	**27a**	93
2	**8ba**	4-MeC_6H_4	20	**27b**	91
3	**8ja**	2-ClC_6H_4	20	**27j**	98
4	**8na**	2-thienyl	20	**27n**	98
5	**8qa**	$C_6H_5CH_2CH_2$	20	**27q**	90
6	**8sa**	cyclohexyl	20	**27s**	91

[a] **8aa** (0.125 mmol), 1 M $^{n}Bu_2Zn$ in heptane (0.375 mmol), CH_2Cl_2 (1.6 mL). [b] Yield of isolated product.

We also extended our studies to the utilization of the secondary dialkylzinc $^{i}Pr_2Zn$ (Table 4.5).

Table 4.5. Three component addition of $^{i}Pr_2Zn/O_2$ to α-amido sulfones **8**.[a]



8aa **28**

Entry	8	R	t (h)	28	Yield (%)[b]
1[c]	**8aa**	Ph	20	**28a**	92
2	**8aa**	Ph	20	**28a**	95
3	**8ba**	4-MeC_6H_4	20	**28b**	94
4	**8ja**	2-ClC_6H_4	20	**28j**	98
5	**8na**	2-thienyl	20	**28n**	91
6	**8qa**	$C_6H_5CH_2CH_2$	20	**28q**	95
7	**8ra**	*n*-butyl	20	**28r**	96

[a] **8aa** (0.125 mmol), 1 M $^{i}Pr_2Zn$ in toluene (0.375 mmol), CH_2Cl_2 (1.6 mL). [b] Yield of isolated product. [c] The reaction was performed at 0 °C.

This reaction could be carried out at room temperature instead of 0 °C. As shown in Table 4.5, all desired products were obtained in excellent yields above 90%, regardless of the electronic and steric nature of the substituents in the α-amido sulfone.

Finally, α-amido sulfone **8aa** was subjected to the reaction with Me_2Zn and oxygen. Due to the high reactivity of this dialkylzinc toward oxygen, we decided to slightly modify the experimental procedure. The reactions with Et_2Zn, $^{n}Bu_2Zn$ and $^{i}Pr_2Zn$ were all entirely performed under oxygen atmosphere. However, in the case of Me_2Zn, the addition of the reagent to the reaction mixture was realized under a nitrogen atmosphere and, then, nitrogen was replaced by oxygen.

Under this modification of the optimized conditions for the reaction with Et_2Zn, Me_2Zn provided a mixture of two products which could not be totally separated by flash chromatography. The ^{1}H NMR of this mixture revealed that one of them was the

desired α-amido methylperoxide **29a**. The other (**32a**) showed a similar ^{1}H NMR spectrum where, apparently, CH, NH and CH_3 protons were shifted at higher field (Figure 4.6).

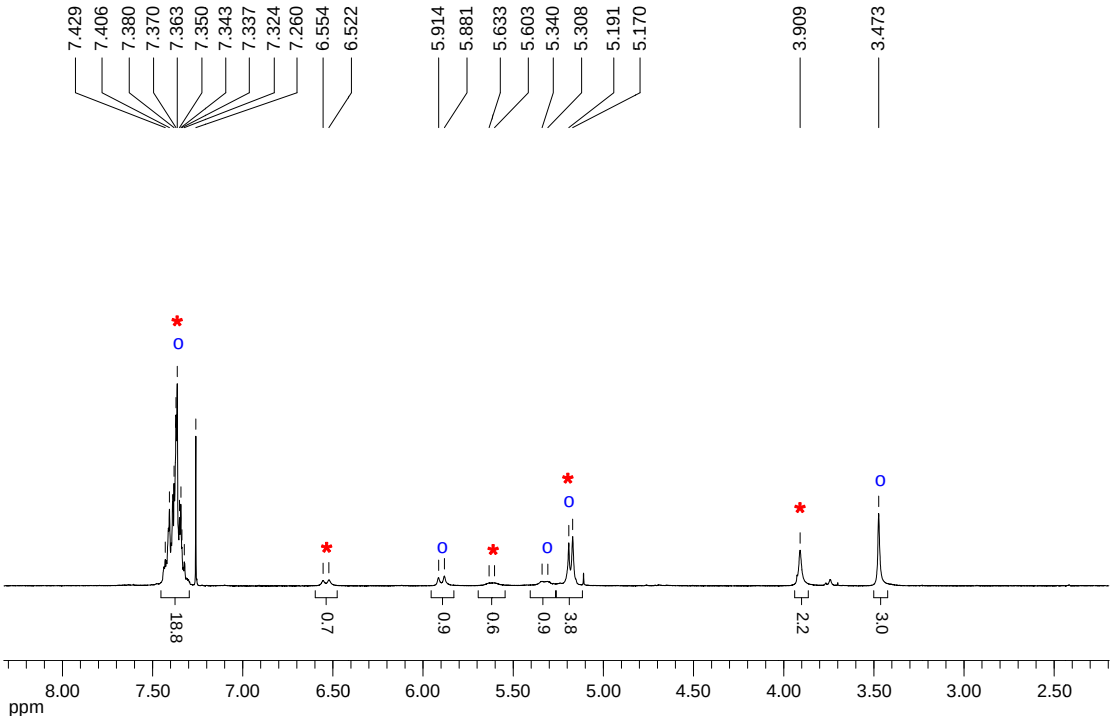


Figure 4.6. ^{1}H NMR spectrum of the products obtained in the reaction between α-amido sulfone **8aa**, Me_2Zn and O_2. * Signals corresponding to **29a**. ° Signals corresponding to **32a**.

The molecular weight of **32a** was determined by mass spectrometry, which indicated a $[M+H]^+$ = 272.17, 16 units less than α-amido methylperoxide **29a**, as illustrated in Figure 4.7.

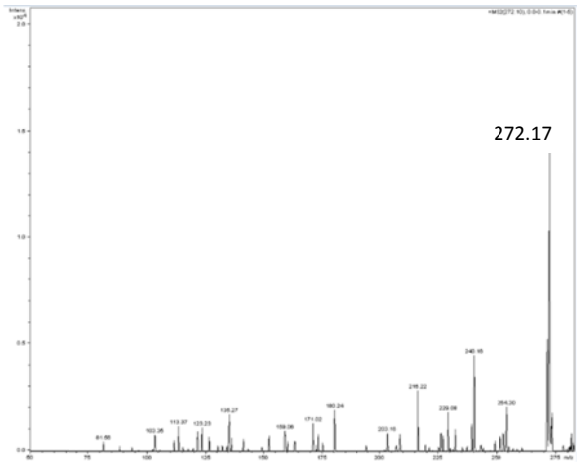
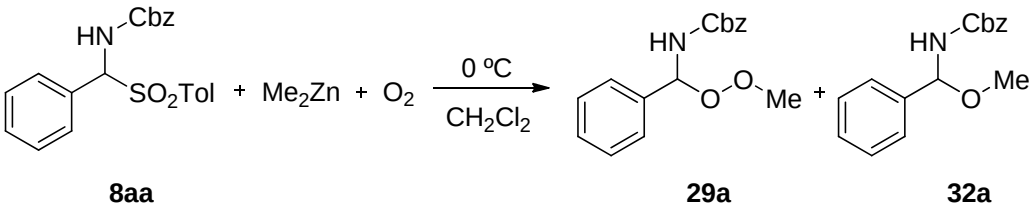


Figure 4.7. Mass spectrum of **32a**. $[M+H]^+$ = 272.17.

This finding was crucial to elucidate the structure of product **32a**, which must correspond to the addition of methoxide to α-amido sulfone **8aa** (Scheme 4.28)



8aa **29a** **32a**

Scheme 4.28. Addition of oxygenated dimethyl zinc species to α-amido sulfone **8aa**.

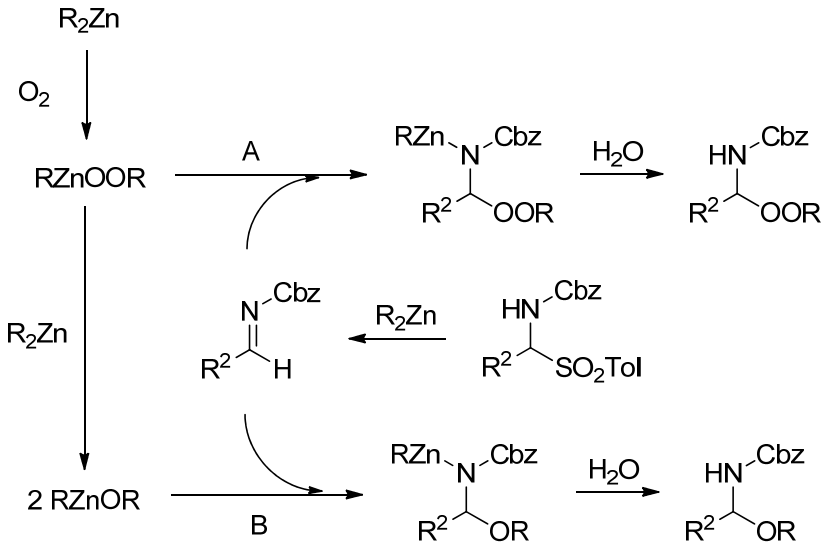
Several reactions were performed in order to achieve exclusively α-amido methylperoxide **29a**. However, all attempts failed and a mixture of compounds **29a** and **32a** was always obtained. These results prompted us to study the controlled oxygenation of dialkylzinc reagents to afford α-amido alkoxides.

4.3.1.3. Proposed mechanism for the addition of dialkylzinc oxygenated species to α-amido sulfones in the absence of a ligand

A plausible mechanism for the addition of dialkylzinc oxygenated species to α-amido sulfones is depicted in Scheme 4.29. Initially, R_2Zn would react with O_2 to give the alkylperoxide species RZnOOR. Besides these alkylperoxide species, RZnOOR may react with another equivalent of R_2Zn to form the alkoxide species RZnOR.

On the other hand, reaction between α-amido sulfone and another equivalent of dialkylzinc would afford the *N*-Cbz-protected propargylic imine. Subsequent addition of RZnOOR to this protected imine would provide the α-amido alkylperoxide after hydrolysis (Route A), whilst the addition of RZnOR to the *N*-Cbz protected imine would afford the α-amido alkoxide (Route B).

This proposed mechanism would explain the formation of both products, **29a** and **32a**, when dimethylzinc is employed (Scheme 4.28).



Scheme 4.29. Plausible mechanism for the addition of dialkylzinc oxygenated species to α-amido sulfone **8aa**.

4.3.2. Addition of zinc alkoxides to α-amido sulfones

4.3.2.1. Optimization of reaction conditions

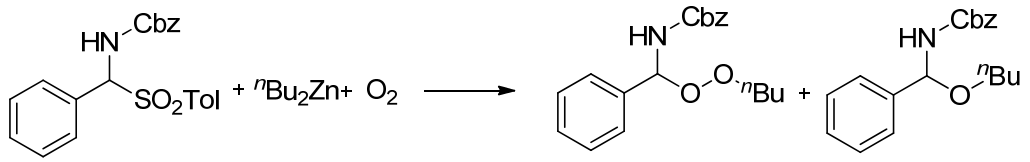
To carry out the addition of zinc alkoxide species to α-amido sulfones, we decided to investigate the reaction with dibutylzinc/O_2. The optimization process consisted of changing the reaction conditions progressively starting from the conditions for the formation of α-amido alkylperoxide **27a** (Table 4.4, Entry 1).

Gratifyingly, a simple increase in temperature from 0 °C to rt led to the appearance of the desired product **31a** (Table 4.6, Entry 2). A greater increase in temperature to 40 °C improved the results considerably. The tendency indicated that formation of α-amido alkoxide **31a** required higher temperatures. For this reason, a solvent with a higher boiling point than dichloromethane was evaluated. The reaction seemed to follow the same tendency in toluene (Table 4.6, Entries 4-5). However, when it was performed at 80 °C, compound **27a** was not obtained; instead, a mixture of unidentified products was observed (Tabla 4.6, Entry 6). The utilization of a chlorinated solvent, 1,2-dichloroethane, led to promising results (Table 4.6, Entries 7-8), but eventually only the addition of an *O,O'*-donor ligand allowed us to further increase the proportion of the alkoxide product.

Several *O,O'*-donor ligands (Figure 4.4) were examined in the reaction with 1,2-dichloroethane at 40 °C (Table 4.6, Entries 9-12). All of them provided a higher proportion of the desired product (**31a**) compared to the reaction in the absence of ligand (Table 4.6, Entry 7). Cathecol (**L10**) led to products in a 0.3 : 1 ratio at 40 °C and could finally lead to the exclusive formation of **31a** at 60 °C in a 61% yield.

Thus, we established that α-amido butoxide **31a** could be isolated as the only reaction product (61% yield) in the reaction between α-amido sulfone **8aa**, $^{n}Bu_2Zn$ and molecular oxygen in 1,2-dichloroethane at 60 °C in the presence of catechol.

Table 4.6. Three component addition of $^{n}Bu_2Zn/O_2$ to α-amido sulfone **8aa** to give α-amido butoxide **31a**. Screening of temperature, solvent and ligands.[a]



8aa **27a** **31a**

Entry	Solvent	L	T (° C)	t (h)	27 : 31[b] (% yield)[c]
1	CH_2Cl_2	/	0	20	1.0 : 0 (93)
2	CH_2Cl_2	/	rt	20	1.2 : 1
3	CH_2Cl_2	/	40	20	0.6 : 1
4	Toluene	/	40	20	0.8 : 1
5	Toluene	/	60	20	0.4 : 1
6	Toluene	/	80	20	-[d]
7	$ClCH_2CH_2Cl$	/	40	20	0.6 : 1
8	$ClCH_2CH_2Cl$	/	60	20	0.4 : 1
9	$ClCH_2CH_2Cl$	(±)-**L1**	40	20	0.5 : 1
10	$ClCH_2CH_2Cl$	**L9**	40	20	0.5 : 1
11	$ClCH_2CH_2Cl$	**L10**	40	20	0.3 : 1
12	$ClCH_2CH_2Cl$	**L11**	40	20	0.4 : 1
13	$ClCH_2CH_2Cl$	**L10**	60	20	0.0 : 1 (61)

[a] **8aa** (0.125 mmol), **L** (0.025 mmol), 1 M $^{n}Bu_2Zn$ in heptane (0.375 mmol), solvent (1.6 mL). [b] Proportion of products determined by ^{1}H NMR. [c] Yield of isolated product. [d] Mixture of unidentified products.

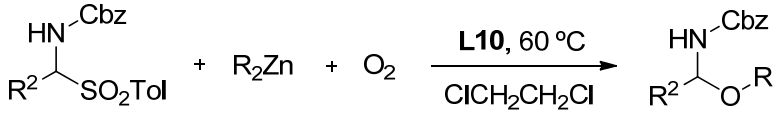
4.3.2.2. Scope and limitations of the reaction

With the optimized conditions in hand, a variety of α-amido sulfones was subjected to the butoxylation reaction conditions (Table 4.7, Entries 1-5).

The utilization of substrates derived from benzaldehyde afforded the desired products in good yields (59-67%) regardless the substituent in the aromatic ring (Me or Cl) and its *para* or *ortho* position (Table 4.7, Entries 2-4). α-Amido sulfone **8qa** derived from dihydrocinnamaldehyde yielded the corresponding α-amido butoxide in similar results (61%) (Table 4.7, Entry 5).

Furthermore, the reaction was also performed in the presence of Et_2Zn (Table 4.7, Entries 6-8). The desired product could be isolated in moderate yield (53%) for aromatic α-amido sulfone bearing an electron-withdrawing substituent in *para* (Table 4.7, Entry 7). A lower yield was afforded with the α-amido sulfone derived from *o*-tolyl aldehyde (41%) (Table 4.7, Entry 8).

Table 4.7. Three component addition of R_2Zn/O_2 to α-amido sulfones **8** to give α-amido alkoxides **30** and **31**.[a]



8

30 R = Et
31 R = ^{n}Bu

Entry	8	R^2	R_2Zn	t (h)	Product	Yield (%)[b]
1	**8aa**	Ph	$^n Bu_2Zn$	20	**31a**	61
2	**8ba**	4-MeC_6H_4	$^n Bu_2Zn$	20	**31b**	67
3	**8ja**	4-ClC_6H_4	$^n Bu_2Zn$	20	**31j**	63
4	**8na**	2-MeC_6H_4	$^n Bu_2Zn$	20	**31n**	59
5	**8qa**	$C_6H_5CH_2CH_2$	$^n Bu_2Zn$	20	**31q**	61
6	**8aa**	Ph	Et_2Zn	20	**30a**	60
7	**8ja**	4-ClC_6H_4	Et_2Zn	20	**30j**	53
8	**8na**	2-MeC_6H_4	Et_2Zn	20	**30n**	41

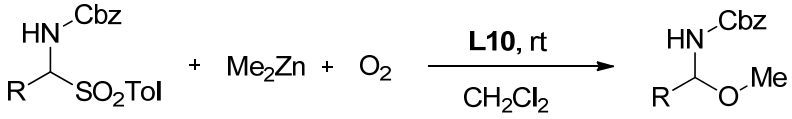
[a] **8** (0.125 mmol), 1 M $^n Bu_2Zn$ in heptane or 1 M Et_2Zn in hexanes (0.375 mmol), $ClCH_2CH_2Cl$ (1.6 mL). [b] Yield of isolated product.

All attempts to obtain α-amido alkoxides from $^{i}Pr_2Zn$ resulted in the formation of the peroxide derivative.

Finally, the controlled oxygenation of Me_2Zn and the methoxylation reaction of α-amido sulfones were performed. This oxygenated species was easily afforded at room temperature, so the reaction was carried out in dichloromethane instead of 1,2-dichloroethane (Table 4.8).

α-Amido sulfone derived from benzaldehyde led to the reaction product in a 60% yield (Table 4.8, Entry 1). Electron-donating (Me) and electron-withdrawing (Cl) groups in the aromatic ring of the α-amido sulfone provided α-amido methoxides in good yields in both *para* and *ortho* positions (Table 4.8, Entries 2-4). Besides, the procedure tolerated well the utilization of an α-amido sulfone derived from an aliphatic aldehyde (Table 4.8, Entry 5).

Table 4.8. Three component addition of Me_2Zn/O_2 to α-amido sulfones **8** to give α-amido methoxide **32**.[a]



8 **32**

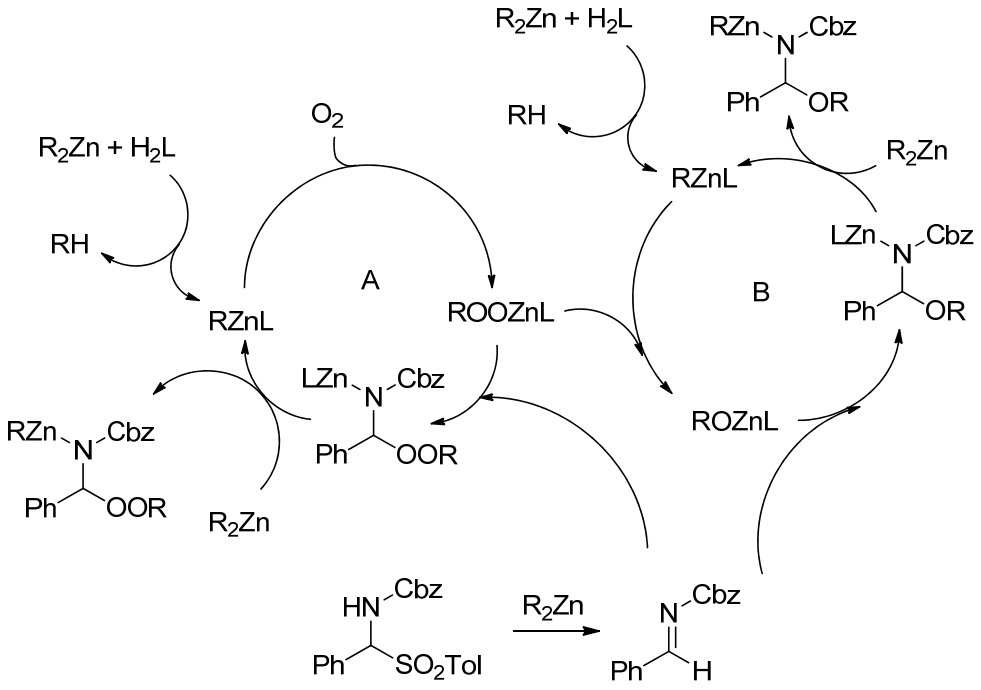
Entry	8	R	t (h)	Product	Yield (%)[b]
1	**8aa**	Ph	20	**32a**	60
2	**8ja**	4-ClC_6H_4	20	**32j**	71
3	**8na**	2-MeC_6H_4	20	**32n**	68
4	**8oa**	2-ClC_6H_4	20	**32o**	72
5	**8ra**	cyclohexyl	20	**32r**	60

[a] **8** (0.125 mmol), 2 M Me_2Zn in toluene (0.375 mmol), CH_2Cl_2 (1.6 mL). [b] Yield of isolated product.

4.3.2.3. Proposed mechanism for the addition of dialkylzinc oxygenated species to α-amido sulfones in the presence of a ligand

A plausible catalytic cycle is outlined in Scheme 4.30 for the peroxidation or alkoxylation of α-amido sulfones in the presence of a *O,O'*-donor ligand. Initially, the RZnL complex, formed by the reaction between R_2Zn and the ligand, would be oxidized by O_2 to a zinc alkylperoxide ROOZnL. This species could follow two different routes, A or B. In route A, the addition of this alkylperoxide species to the imine generated from the α-amido sulfones in the basic medium would give an α-amido alkylperoxide complex which after L-R exchange with another molecule of dialkylzinc would give the final product and regenerate the active species.

On the other hand, ROOZnL could react with a molecule of RZnL to afford the alkoxide ROZnL (Route B). The addition of this alkoxide to the imine would give an α-amido alkoxide complex which after L-R exchange with another molecule of dialkylzinc would give the final product and regenerate the active species.



Scheme 4.30. Catalytic cycle for the peroxidation (Route A) or alkoxylation (Route B) of α-amido sulfones in the presence of a ligand.

The formation of α-amido alkoxide products (Route B) is favoured by the increase of temperature, as observed in the reaction of α-amido sulfone **11aa** with $^{n}Bu_2Zn$ under different reaction conditions (Table 4.6). On the other hand, the alkyl group in the dialkylzinc reagent plays an important role in the outcome of the reaction. Thus, primary dialkylzinc reagents (Me_2Zn, Et_2Zn and $^{n}Bu_2Zn$) form alkoxide species in the presence of a *O,O'*-donor ligand at appropriate temperatures, whereas $^{i}Pr_2Zn$ only provides alkylperoxide species.

4.4. CONCLUSIONS

We have designed a methodology for the addition to α-amido sulfones of zinc alkyloxygenated species resulting from the controlled oxygenation of dialkylzinc reagents of different chain length in the presence of molecular oxygen.

The reaction was evaluated in the presence of several *O*,*O'*-donor ligands. However, in the addition of alkylperoxide species the best results were obtained in the absence of ligand, using dichloromethane at 0 °C.

Benzyloxycarbonyl group in the starting α-amido sulfones provided better yields than *tert*-butyloxycarbonyl and ethyloxycarbonyl protecting groups.

The reaction of Et_2Zn and oxygen was performed with ten aromatic α-amido sulfones of different electronic and steric nature, providing the corresponding α-amido alkylperoxides in excellent yields. The utilization of three aliphatic α-amido sulfones has also led to excellent results. The structure of these products was confirmed by X-ray analysis.

The utilization of $^{n}Bu_2Zn$ and oxygen with five aromatic and one aliphatic α-amido sulfones gave the ethylperoxidation products in excellent yields regardless the electronic and steric characteristics of the substituents.

The reaction of $^{i}Pr_2Zn$ and oxygen with different α-amido sulfones was carried out at room temperature. The corresponding α-amido alkylperoxides were obtained in excellent yields with both aromatic and aliphatic substrates.

The reaction with Me_2Zn and oxygen under these conditions led to mixtures of α-amido methylperoxide and α-amido methoxide. All attempts to exclusively obtain the peroxide derivative were unsuccessful.

We have also carried out the addition to α-amido sulfones of zinc alkoxides species resulting from the controlled oxygenation of dialkylzinc reagents of different chain length in the presence of molecular oxygen.

This process requires higher temperatures and the presence of an *O*,*O*'-donor ligand to afford α-amido alkoxides as the unique reaction products.

The utilization of $^{n}Bu_2Zn$ with several aromatic α-amido sulfones with electron-donating and electron-withdrawing groups in *ortho* and *para* position led to good yields. A similar result was obtained with an aliphatic α-amido sulfone. Et_2Zn provided the corresponding α-amido ethoxides in moderate yields.

The reaction of Me_2Zn and oxygen with different α-amido sulfones proceeded with good yields regardless the electronic and steric nature of the substituents.

All attempts to obtain the isopropoxide derivative were unfruitful and only the formation of the peroxide derivative was observed.

4.5. EXPERIMENTAL SECTION

4.5.1. General techniques

See Section 2.5.1.

Three component reactions were carried out under oxygen atmosphere in round bottom flasks oven-dried overnight at 120 °C.

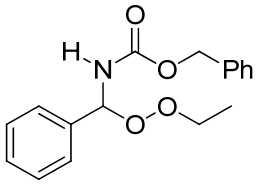
Diethylzinc 1 M solution in hexanes, dimethylzinc 2 M solution in toluene and diisopropylzinc 1 M in toluene were purchased from Aldrich. Dibutylzinc 1 M solution in heptanes was purchased from Fluka. They were used without further purification.

4.5.2. General synthetic procedures and characterization of new products

4.5.2.1. Alkylperoxidation of α-amido sulfones 8 with Et_2Zn

A 1 M solution of Et_2Zn in hexanes (0.375 mL, 0.375 mmol) was stirred in CH_2Cl_2 (0.6 mL) at room temperature under oxygen atmosphere. After 1 h, the reaction mixture was stirred at 0 °C for 15 min. Then, a solution of α-amido sulfone **8** (0.125 mmol) in CH_2Cl_2 (1.0 mL) was added. After 20 h, the reaction mixture was quenched with water (1 mL), extracted with CH_2Cl_2 (3x15 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give compound **19**.

***N*-(ethylperoxy(phenyl)methyl)-benzylcarbamate (19a)**



19a

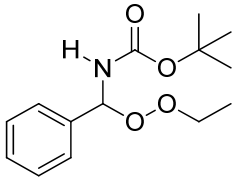
White solid; mp 55-57 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.32 (m, 10H), 6.53 (d, *J* = 10.0 Hz, 1H), 5.60 (d, *J* = 8.2 Hz, 1H), 5.19 (s, 2H), 4.16-4.08 (m, 2H), 1.21 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.5 (C), 136.09 (C), 136.05 (C), 129.1 (CH), 128.7 (CH), 128.5 (CH), 128.24 (CH), 128.16 (CH), 126.3 (CH), 85.3 (CH), 70.4 (CH_2), 67.2 (CH_2), 13.3 (CH_3).

HRMS (ESI) *m/z*: 324.1254 $[M+Na]^+$, $C_{17}H_{19}NO_4Na$ requires 324.1212.

_N_-(ethylperoxy(phenyl)methyl)-_tert_-butylcarbamate (25a)



25a

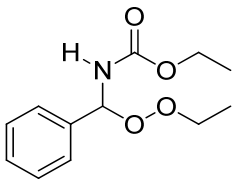
White solid; mp 57-59 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.34 (m, 5H), 6.45 (d, *J* = 9.8 Hz, 1H), 5.38 (d, *J* = 9.2 Hz, 1H), 4.17-4.09 (m, 2H), 1.49 (s, 9H), 1.23 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.8 (C), 136.5 (C), 128.9 (CH), 128.6 (CH), 126.4 (CH), 84.9 (CH), 80.3 (C), 70.3 (CH_2), 28.3 (CH_3), 13.3 (CH_3).

HRMS (ESI) *m/z*: 290.1370 $[M+Na]^+$, $C_{14}H_{21}NO_4Na$ requires 290.1368.

_N_-(ethylperoxy(phenyl)methyl)-ethylcarbamate (26a)



26a

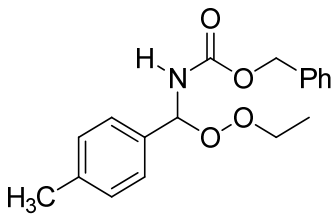
White solid; mp 48-51 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.33 (m, 5H), 6.49 (d, *J* = 9.9 Hz, 1H), 5.50 (d, *J* = 6.1 Hz, 1H), 4.24-4.10 (m, 4H), 1.31-1.21 (m, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.7 (C), 136.2 (C), 129.0 (CH), 128.6 (CH), 126.3 (CH), 85.3 (CH), 70.4 (CH_2), 61.4 (CH_2), 14.5 (CH_3), 13.3 (CH_3).

HRMS (ESI) *m/z*: 262.1056 $[M+Na]^+$, $C_{12}H_{17}NO_4Na$ requires 262.1055.

_N_-(ethylperoxy(4-tolyl)methyl)-benzylcarbamate (19b)



19b

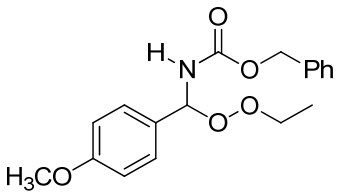
White solid; mp 71-72 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.29 (m, 7H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.49 (d, *J* = 9.9 Hz, 1H), 5.62 (d, *J* = 9.1 Hz, 1H), 5.19 (s, 2H), 4.15-4.08 (m, 2H), 2.35 (s, 3H), 1.21 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.5 (C), 139.0 (C), 136.1 (C), 133.1 (C), 129.3 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 126.2 (CH), 85.3 (CH), 70.4 (CH_2), 67.1 (CH_2), 21.2 (CH_3), 13.3 (CH_3).

HRMS (ESI) *m/z*: 338.1372 $[M+Na]^+$, $C_{18}H_{21}NO_4Na$ requires 338.1368.

_N_-(ethylperoxy(4-methoxyphenyl)methyl)-benzylcarbamate (19c)



19c

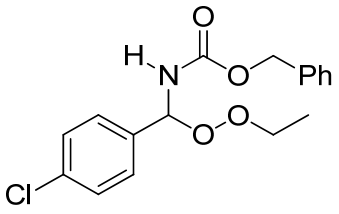
Pale brown solid; mp 150-152 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.32 (m, 7H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.48 (d, *J* = 9.9 Hz, 1H), 5.66 (d, *J* = 9.4 Hz, 1H), 5.18 (s, 2H), 4.14-4.08 (m, 2H), 3.80 (s, 3H), 1.21 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.1 (C), 155.6 (C), 136.1 (C), 136.0 (C), 128.5 (CH), 128.1 (CH), 127.7 (CH), 127.0 (CH), 114.0 (CH), 85.1 (CH), 70.4 (CH_2), 67.1 (CH_2), 55.3 (CH_3), 13.3 (CH_3).

HRMS (ESI) *m/z*: 354.1372 $[M+Na]^+$, $C_{18}H_{21}NO_5Na$ requires 354.1317.

_N_-((4-chlorophenyl)(ethylperoxy)methyl)-benzylcarbamate (19e)



19e

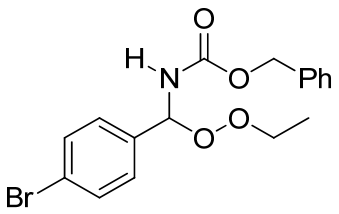
White needles; decomp.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 –7.34 (m, 9H), 6.49 (d, *J* = 9.8 Hz, 1H), 5.62 (d, *J* = 8.1 Hz, 1H), 5.19 (s, 2H), 4.14-4.07 (m, 2H), 1.20 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.5 (C), 135.9 (C), 134.9 (C), 134.7 (C), 128.8 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 84.8 (CH), 70.5 (CH_2), 67.3 (CH_2), 13.2 (CH_3).

HRMS (ESI) *m/z*: 358.0824 $[M+Na]^+$, $C_{17}H_{18}ClNO_4Na$ requires 358.0822.

_N_-((4-bromophenyl)(ethylperoxy)methyl)-benzylcarbamate (19f)



19f

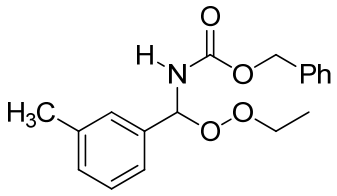
White solid; mp 68-69 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.6 Hz, 2H), 7.36-7.28 (m, 7H), 6.47 (d, *J* = 9.9 Hz, 1H), 5.68 (d, *J* = 10.2 Hz, 1H), 5.18 (s, 2H), 4.13-4.07 (m, 2H), 1.20 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.5 (C), 135.9 (C), 135.2 (C), 131.7 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 123.1 (C), 84.8 (CH), 70.5 (CH_2), 67.3 (CH_2), 13.2 (CH_3).

HRMS (ESI) *m/z*: 402.0322 $[M+Na]^+$, $C_{17}H_{18}BrNO_4Na$ requires 402.0317.

_N_-(ethylperoxy(3-tolyl)methyl)-benzylcarbamate (19g)



19g

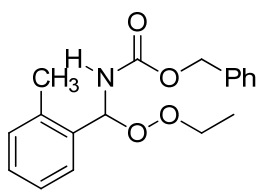
Colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.19 (m, 8H), 7.18 (t, *J* = 6.8 Hz, 1H), 6.49 (d, *J* = 10.0 Hz, 1H), 5.65 (d, *J* = 8.6 Hz, 1H), 5.19 (s, 2H), 4.17-4.10 (m, 2H), 2.37 (s, 3H), 1.22 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.5 (C), 138.4 (C), 136.0 (C), 135.9 (C), 129.8 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.0 (CH), 123.4 (CH), 85.3 (CH), 70.4 (CH_2), 67.1 (CH_2), 21.4 (CH_3), 13.3 (CH_3).

HRMS (ESI) *m/z*: 338.1366 $[M+Na]^+$, $C_{18}H_{21}NO_4Na$ requires 338.1368.

_N_-(ethylperoxy(2-tolyl)methyl)-benzylcarbamate (19h)



19h

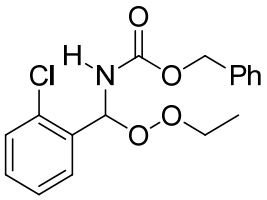
Brown solid; mp 71-72 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.18 (m, 9H), 6.67 (d, *J* = 9.9 Hz, 1H), 5.57 (d, *J* = 8.6 Hz, 1H), 5.18 (s, 2H), 4.14-4.12 (m, 2H), 2.42 (s, 3H), 1.20 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.4 (C), 136.1 (C), 134.2 (C), 130.8 (CH), 129.0 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 126.1 (CH), 125.2 (CH), 82.9 (CH), 70.3 (CH_2), 67.1 (CH_2), 19.0 (CH_3), 13.3 (CH_3).

HRMS (ESI) *m/z*: 338.1364 $[M+Na]^+$, $C_{18}H_{21}NO_4Na$ requires 338.1368.

_N_-(ethylperoxy(2-chlorophenyl)methyl)-benzylcarbamate (19j)



19j

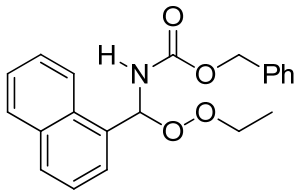
Pale yellow solid; mp 41-43 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.46 (m, 1H), 7.41-7.29 (m, 8H), 6.77 (d, *J* = 9.8 Hz, 1H), 5.69 (d, *J* = 8.7 Hz, 1H), 5.18 (s, 2H), 4.17-4.15 (m, 2H), 1.22 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.1 (C), 136.0 (C), 133.8 (C), 133.1 (C), 130.3 (CH), 130.1 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.7 (CH), 127.0 (CH), 83.1 (CH), 70.5 (CH_2), 67.2 (CH_2), 13.2 (CH_3).

HRMS (ESI) *m/z*: 358.0828 $[M+Na]^+$, $C_{17}H_{18}ClNO_4Na$ requires 358.0822.

_N_-(ethylperoxy(1-naphthyl)methyl)-benzylcarbamate (19l)



19l

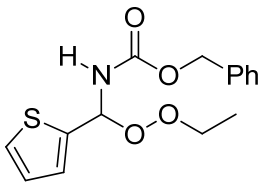
Pale brown solid; mp 111-113 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.2 Hz, 1H), 7.90-7.85 (m, 2H), 7.65-7.36 (m, 9H), 7.17 (d, *J* = 9.9 Hz, 1H), 5.79 (d, *J* = 9.7 Hz, 1H), 5.22 (s, 2H), 4.21-4.19 (m, 2H), 1.24 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.4 (C), 136.0 (C), 133.8 (C), 131.8 (C), 130.3 (C), 129.8 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 126.8 (CH), 126.0 (CH), 125.0 (CH), 123.9 (CH), 123.3 (CH), 83.4 (CH), 70.5 (CH_2), 67.2 (CH_2), 13.3 (CH_3).

HRMS (ESI) *m/z*: 374.1372 $[M+Na]^+$, $C_{21}H_{21}NO_4Na$ requires 374.1368.

_N_-(ethylperoxy(2-thienyl)methyl)-benzylcarbamate (19n)



19n

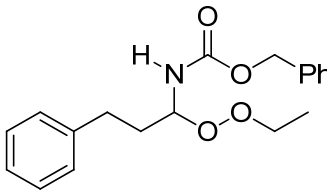
Orange needles; mp 57-59 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.35 (m, 5H), 7.32 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.11 (dt, *J* = 3.6, 1.1 Hz, 1H), 7.00 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.73 (d, *J* = 9.9 Hz, 1H), 5.76 (d, *J* = 9.0 Hz, 1H), 5.19 (s, 2H), 4.16-4.09 (m, 2H), 1.22 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.2 (C), 138.6 (C), 135.9 (C), 128.5 (CH), 128.3 (CH), 128.2 (CH), 126.9 (CH), 126.4 (CH), 126.0 (CH), 82.5 (CH), 70.7 (CH_2), 67.3 (CH_2), 13.2 (CH_3).

HRMS (ESI) *m/z*: 330.0779 $[M+Na]^+$, $C_{15}H_{17}NO_4SNa$ requires 330.0776.

_N_-(ethylperoxy(3-phenyl)propyl)-benzylcarbamate (19q)



19q

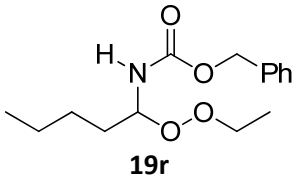
Colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.17 (m, 10H), 5.54-5.47 (m, 1H), 5.34 (d, *J* = 9.5 Hz, 1H), 5.15 (s, 2H), 4.09-4.02 (m, 2H), 2.73 (t, *J* = 7.7 Hz, 2H), 2.10-1.98 (m, 1H), 1.94-1.82 (m, 1H), 1.19 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.6 (C), 140.6 (C), 136.2 (C), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 126.1 (CH), 84.3 (CH), 70.2 (CH_2), 66.9 (CH_2), 34.1 (CH_2), 31.2 (CH_2), 13.2 (CH_3).

HRMS (ESI) *m/z*: 352.1528 $[M+Na]^+$, $C_{19}H_{23}NO_4Na$ requires 352.1525.

_N_-(ethylperoxypentyl)-benzylcarbamate (19r)



19r

Colorless oil.

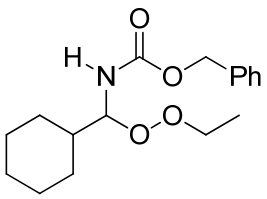
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.32 (m, 5H), 5.51-5.43 (m, 1H), 5.26 (d, *J* = 9.9 Hz, 1H), 5.13 (s, 2H), 4.07-4.00 (m,

2H), 1.72-1.64 (m, 1H), 1.59-1.47 (m, 1H), 1.39-1.30 (m, 4H), 1.17 (t, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.7 (C), 136.2 (C), 128.5 (CH), 128.12 (CH), 128.08 (CH), 84.8 (CH), 70.1 (CH_2), 66.8 (CH_2), 32.1 (CH_2), 27.0 (CH_2), 22.3 (CH_2), 13.8 (CH_3), 13.2 (CH_3).

HRMS (ESI) *m/z*: 304.1520 $[M+Na]^+$, $C_{15}H_{23}NO_4Na$ requires 304.1525.

_N_-(ethylperoxy(cyclohexyl)methyl)-benzylcarbamate (19s)



19s

White solid; mp 44-45 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.33 (m, 5H), 5.30-5.17 (m, 2H), 5.13 (s, 2H), 4.07-4.00 (m, 2H), 1.84-1.61 (m, 6H), 1.20-1.02 (m, 8H).

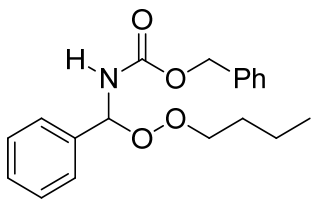
^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.0 (C), 136.3 (C), 128.5 (CH), 128.14 (CH), 128.09 (CH), 88.2 (CH), 69.9 (CH_2), 66.8 (CH_2), 40.3 (CH), 28.4 (CH_2), 28.0 (CH_2), 26.1 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 13.3 (CH_3).

HRMS (ESI) *m/z*: 330.1692 $[M+Na]^+$, $C_{17}H_{25}NO_4Na$ requires 330.1681.

4.5.2.2. Alkylperoxidation of α-amido sulfones 8 with ^{n}Bu$_2$Zn

A 1 M solution of ^{n}Bu_2Zn in heptane (0.375 mL, 0.375 mmol) was stirred in CH_2Cl_2 (0.6 mL) at room temperature under oxygen atmosphere. After 1 h, the reaction mixture was stirred at 0 °C for 15 min. Then, a solution of α-amido sulfone **8** (0.125 mmol) in CH_2Cl_2 (1.0 mL) was added. After 20 h, the reaction mixture was quenched with water (1 mL), extracted with CH_2Cl_2 (3x15 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give compound **27**.

_N_-(*n*-butylperoxy(phenyl)methyl)-benzylcarbamate (27a)



27a

White oil.

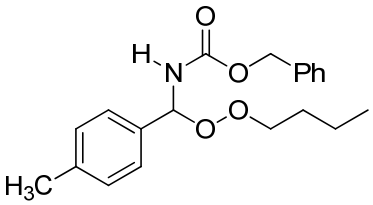
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.32 (m, 10H), 6.53 (d, *J* = 9.9 Hz, 1H), 5.64 (d, *J* = 8.7 Hz, 1H), 5.19 (s, 2H), 4.07 (t,

J = 6.1 Hz, 2H), 1.63-1-54 (m, 2H), 1.42-1.29 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.5 (C), 136.1 (C), 136.1 (C), 129.0 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 126.3 (CH), 85.3 (CH), 74.8 (CH_2), 67.1 (CH_2), 29.8 (CH_2), 19.2 (CH_2), 13.8 (CH_3).

HRMS (ESI) *m/z*: 352.1521 $[M+Na]^+$, $C_{19}H_{23}NO_4Na$ requires 352.1525.

_N_-(_n_-butylperoxy(4-tolyl)methyl)-benzylcarbamate (27b)



27b

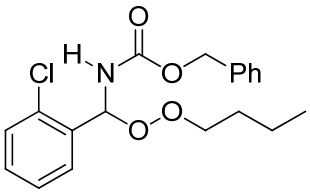
White solid; mp 36-38 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, 7H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.49 (d, *J* = 9.9 Hz, 1H), 5.61 (d, *J* = 9.0 Hz, 1H), 5.18 (s, 2H), 4.06 (t, *J* = 6.3 Hz, 2H), 2.35 (s, 3H), 1.60-1-53 (m, 2H), 1.42-1.31 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.5 (C), 139.0 (C), 136.1 (C), 133.1 (C), 129.3 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 126.3 (CH), 85.2 (CH), 74.7 (CH_2), 67.1 (CH_2), 29.8 (CH_2), 21.2 (CH_3), 19.2 (CH_2), 13.9 (CH_3).

HRMS (ESI) *m/z*: 366.1684 $[M+Na]^+$, $C_{20}H_{25}NO_4Na$ requires 366.1681.

_N_-(_n_-butylperoxy(2-chlorophenyl)methyl)-benzylcarbamate (27j)



27j

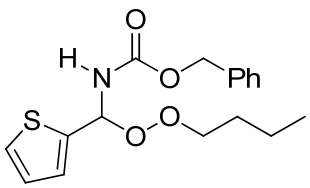
White solid; mp 39-40 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.45 (m, 1H), 7.41-7.28 (m, 8H), 6.77 (d, *J* = 6.8 Hz, 1H), 5.66 (d, *J* = 8.8 Hz, 1H), 5.18 (s, 2H), 4.10 (t, *J* = 5.5 Hz, 2H), 1.63-1-53 (m, 2H), 1.41-1.29 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.1 (C), 136.0 (C), 133.8 (C), 133.1 (C), 130.3 (CH), 130.1 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.7 (CH), 127.0 (CH), 83.0 (CH), 74.8 (CH_2), 67.2 (CH_2), 29.7 (CH_2), 19.1 (CH_2), 13.8 (CH_3).

HRMS (ESI) *m/z*: 386.1134 $[M+Na]^+$, $C_{19}H_{22}ClNO_4Na$ requires 386.1135.

_N_-(_n_-butylperoxy(2-thienyl)-benzylcarbamate (27n)



27n

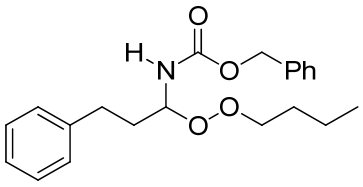
Orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.31 (m, 6H), 7.11 (dt, *J* = 3.6, 1.1 Hz, 1H), 7.00 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.73 (d, *J* = 9.9 Hz, 1H), 5.76 (d, *J* = 9.3 Hz, 1H), 5.19 (s, 2H), 4.08 (t, *J* = 6.4 Hz, 2H), 1.63-1-54 (m, 2H), 1.42-1.30 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.2 (C), 138.7 (C), 135.9 (C), 128.5 (CH), 128.3 (CH), 128.2 (CH), 126.9 (CH), 126.4 (CH), 126.0 (CH), 82.4 (CH), 75.0 (CH_2), 67.2 (CH_2), 29.8 (CH_2), 19.1 (CH_2), 13.8 (CH_3).

HRMS (ESI) *m/z*: 358.1062 $[M+Na]^+$, $C_{17}H_{21}NO_4SNa$ requires 358.1089.

_N_-(_n_-butylperoxy(3-phenyl)propyl)-benzylcarbamate (27q)



27q

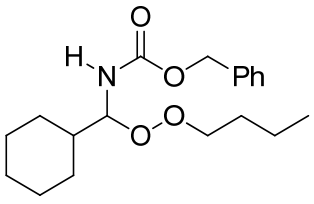
White solid; mp 41-43 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.16 (m, 10H), 5.54-5.46 (m, 1H), 5.33 (d, *J* = 9.6 Hz, 1H), 5.14 (s, 2H), 3.99 (t, *J* = 6.4 Hz, 2H), 2.72 (t, *J* = 7.7 Hz, 2H), 2.09-1.91 (m, 1H), 1.93-1.81 (m, 1H), 1.60-1-51 (m, 2H), 1.41-1.29 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.6 (C), 140.6 (C), 136.1 (C), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.11 (CH), 128.06 (CH), 126.1 (CH), 84.3 (CH), 74.6 (CH_2), 66.9 (CH_2), 34.1 (CH_2), 31.2 (CH_2), 29.8 (CH_2), 19.2 (CH_2), 13.8 (CH_3).

HRMS (ESI) *m/z*: 380.1824 $[M+Na]^+$, $C_{21}H_{27}NO_4Na$ requires 380.1838.

_N_-(_n_-butylperoxy(cyclohexyl)methyl)-benzylcarbamate (27s)



27s

White solid; mp 36-38 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.31 (m, 5H), 5.30-5.20 (m, 2H), 5.13 (s, 2H), 3.98 (t, *J* = 6.5 Hz, 2H), 1.84-1.71 (m, 6H), 1.57-1.50 (m, 3H), 1.41-1.31 (m, 2H),

1.20-1.02 (m, 4H), 0.90 (t, *J* = 7.3 Hz, 3H).

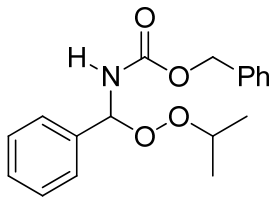
^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.0 (C), 136.3 (C), 128.5 (CH), 128.10 (CH), 128.07 (CH), 88.1 (CH), 74.3 (CH_2), 66.8 (CH_2), 40.3 (CH), 29.8 (CH_2), 28.4 (CH_2), 28.0 (CH_2), 26.1 (CH_2), 25.6 (CH_2), 25.5 (CH_2), 19.2 (CH_2), 13.9 (CH_3).

HRMS (ESI) *m/z*: 358.1980 $[M+Na]^+$, $C_{19}H_{29}NO_4Na$ requires 358.1994.

4.5.2.3. Alkylperoxidation of α-amido sulfones 8 with $^{i}Pr_2Zn$

A 1 M solution of $^{i}Pr_2Zn$ (0.375 mL, 0.375 mmol) was stirred in CH_2Cl_2 (0.6 mL) at room temperature under oxygen atmosphere. After 1 h, a solution of α-amido sulfone **8** (0.125 mmol) in CH_2Cl_2 (1.0 mL) was added and the reaction mixture was stirred at rt. After 20 h, the reaction mixture was quenched with water (1 mL), extracted with CH_2Cl_2 (3 x 15 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give compound **28**.

_N_-(isopropylperoxy(phenyl)methyl)-benzylcarbamate (28a)



28a

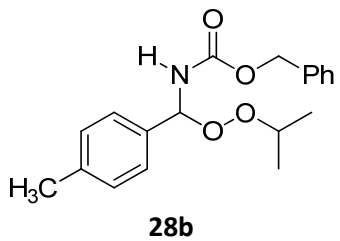
White solid; mp 67-68 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.32 (m, 10H), 6.51 (d, *J* = 10.0 Hz, 1H), 5.64 (d, *J* = 8.7 Hz, 1H), 5.19 (s, 2H), 4.40-4.32 (m, 1H), 1.21-1-18 (m, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.6 (C), 136.2 (C), 136.1 (C), 129.0 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 126.4 (CH), 85.4 (CH), 76.2 (CH), 67.1 (CH_2), 20.4 (CH_3), 20.3 (CH_3).

HRMS (ESI) *m/z*: 338.1362 $[M+Na]^+$, $C_{18}H_{21}NO_4Na$ requires 338.1368.

_N_-(isopropylperoxy(4-tolyl)methyl)-benzylcarbamate (28b)



28b

White solid; mp 59-61 °C.

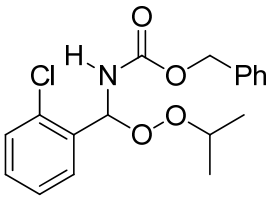
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, 7H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.47 (d, *J* = 9.9 Hz, 1H), 5.58 (d, *J* = 8.1

Hz, 1H), 5.18 (s, 2H), 4.38-4.30 (m, 1H), 2.35 (s, 3H), 1.20-1.18 (m, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.6 (C), 138.9 (C), 136.2 (C), 133.2 (C), 129.3 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 126.3 (CH), 85.4 (CH), 76.2 (CH), 67.0 (CH_2), 21.2 (CH_3), 20.40 (CH_3), 20.37 (CH_3).

HRMS (ESI) *m/z*: 352.1528 $[M+Na]^+$, $C_{19}H_{23}NO_4Na$ requires 352.1525.

_N_-(isopropylperoxy(2-chlorophenyl)methyl)-benzylcarbamate (28j)



28j

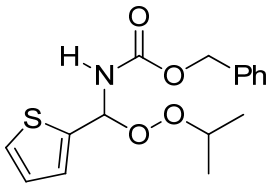
White solid; mp 76-77 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.46 (m, 1H), 7.41-7.28 (m, 8H), 6.75 (d, *J* = 9.8 Hz, 1H), 5.67 (d, *J* = 8.9 Hz, 1H), 5.18 (s, 2H), 4.44-4.37 (m, 1H), 1.194-1.186 (br m, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.1 (C), 136.0 (C), 134.0 (C), 133.1 (C), 130.2 (CH), 130.1 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 127.0 (CH), 83.2 (CH), 76.3 (CH), 67.2 (CH_2), 20.4 (CH_3), 20.3 (CH_3).

HRMS (ESI) *m/z*: 372.0980 $[M+Na]^+$, $C_{18}H_{20}ClNO_4Na$ requires 372.0979.

_N_-(isopropylperoxy(2-thienyl)methyl)-benzylcarbamate (28n)



28n

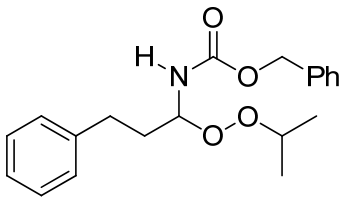
Yellow solid; mp 125-127 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.35 (m, 5H), 7.31 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.11 (dt, *J* = 3.6, 1.1 Hz, 1H), 7.00 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.71 (d, *J* = 10.1 Hz, 1H), 5.73 (d, *J* = 9.6 Hz, 1H), 5.19 (s, 2H), 4.41-4.29 (m, 1H), 1.22-1.18 (m, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.3 (C), 138.7 (C), 135.9 (C), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 126.8 (CH), 126.0 (CH), 82.5 (CH), 76.5 (CH), 66.9 (CH_2), 20.3 (CH_3).

HRMS (ESI) *m/z*: 344.1656 $[M+Na]^+$, $C_{16}H_{19}NO_4SNa$ requires 344.1681.

_N_-(isopropylperoxy(3-phenyl)propyl)-benzylcarbamate (28q)



28q

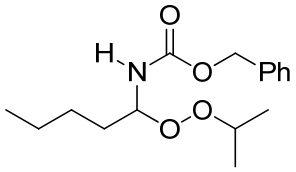
Pale yellow solid; mp 34-36 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.27 (m, 7H), 7.23-7.17 (m, 3H), 5.53-5.46 (m, 1H), 5.32 (d, *J* = 9.7 Hz, 1H), 5.15 (s, 2H), 4.32-4.20 (m, 1H), 2.73 (t, *J* = 7.7 Hz, 2H), 2.11-1.99 (m, 1H), 1.95-1.83 (m, 1H), 1.18-1.15 (m, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.6 (C), 140.7 (C), 136.2 (C), 128.5 (CH), 128.3 (CH), 128.1 (CH), 126.1 (CH), 84.4 (CH), 75.8 (CH), 66.8 (CH_2), 34.1 (CH_2), 31.2 (CH_2), 20.4 (CH_3), 20.3 (CH_3).

HRMS (ESI) *m/z*: 366.1638 $[M+Na]^+$, $C_{20}H_{25}NO_4Na$ requires 366.1681.

_N_-(isopropylperoxypentyl)-benzylcarbamate (28r)



28r

White solid; mp 34-36 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 5.49-5.41 (m, 1H), 5.23 (d, *J* = 9.4 Hz, 1H), 5.13 (s, 2H), 4.31-4.19 (m, 1H), 1.73-1.64 (m, 1H), 1.59-1.48 (m, 1H), 1.39-1.30 (m, 4H), 1.15 (d, *J* = 6.0 Hz, 6H), 0.89 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.7 (C), 136.3 (C), 128.5 (CH), 128.1 (CH), 84.9 (CH), 75.7 (CH), 66.8 (CH_2), 32.1 (CH_2), 27.0 (CH_2), 22.3 (CH_2), 20.4 (CH_3), 20.3 (CH_3), 13.8 (CH_3).

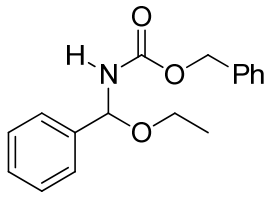
HRMS (ESI) *m/z*: 318.1624 $[M+Na]^+$, $C_{16}H_{25}NO_4Na$ requires 318.1681.

4.5.2.4. Alkoxylation of α-amido sulfones 8 with Et_2Zn

A 1 M solution of $^nBu_2Zn$ in heptane (0.375 mL, 0.375 mmol) was added dropwise to a solution of catechol (2.8 mg, 0.025 mmol) and $ClCH_2CH_2Cl$ (0.6 mL) at room temperature under oxygen atmosphere. After stirring for 1 h, a solution of α-amido sulfone **8** (0.125 mmol) in $ClCH_2CH_2Cl$ (1.0 mL) was added and the reaction mixture was stirred at 60 °C. After 20 h, the reaction mixture was quenched with water (1 mL), extracted with CH_2Cl_2 (3x15 mL), dried over $MgSO_4$ and concentrated under

reduced pressure. Purification by flash chromatography on silica gel afforded compound **30**.

***N*-benzyl (ethoxy(phenyl)methyl)carbamate (30a)**



30a

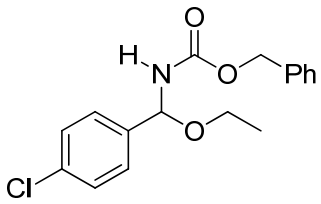
White solid; mp 63-65 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.32 (m, 10H), 6.00 (d, *J* = 9.7 Hz, 1H), 5.35 (d, *J* = 8.9 Hz, 1H), 5.16 (s, 2H), 3.83-3.73 (m, 1H), 3.67-3.57 (m, 1H), 1.27 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.9 (C), 139.4 (C), 136.1 (C), 128.6 (CH), 128.54 (CH), 128.47 (CH), 128.2 (CH), 128.1 (CH), 125.9 (CH), 82.4 (CH), 67.0 (CH_2), 63.7 (CH_2), 15.1 (CH_3).

HRMS (ESI) *m/z*: 308.1265 $[M+Na]^+$, $C_{17}H_{19}NO_3Na$ requires 308.1263.

***N*-benzyl ((4-chlorophenyl)(ethoxy)methyl)carbamate (30e)**



30e

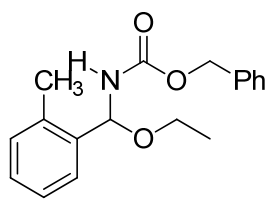
White solid; mp 96-99 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.31 (m, 9H), 5.98 (d, *J* = 9.8 Hz, 1H), 5.29 (d, *J* = 8.8 Hz, 1H), 5.16 (s, 2H), 3.83-3.73 (m, 1H), 3.66-3.56 (m, 1H), 1.26 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.9 (C), 138.0 (C), 136.0 (C), 134.3 (C), 128.7 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.4 (CH), 81.8 (CH), 67.2 (CH_2), 63.8 (CH_2), 15.0 (CH_3).

HRMS (ESI) *m/z*: 342.0871 $[M+Na]^+$, $C_{17}H_{18}ClNO_3Na$ requires 342.0873.

***N*-benzyl (ethoxy(*o*-tolyl)methyl)carbamate (30h)**



30h

White solid; mp 55-57 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53–7.51 (m, 1H), 7.35-7.31 (m, 5H), 7.24-7.15 (m, 3H), 6.09 (d, *J* = 9.7 Hz, 1H), 5.29 (d, *J* = 10.0 Hz, 1H), 5.18 (d, *J* = 12.0 Hz, 1H), 5.12 (d, *J* = 12.2 Hz,

1H), 3.82-3.72 (m, 1H), 3.64-3.54 (m, 1H), 2.33 (s, 3H), 1.27 (t, *J* = 7.0 Hz, 3H).

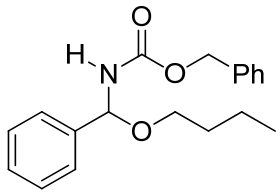
^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.7 (C), 137.4 (C), 136.1 (C), 135.5 (C), 130.7 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 126.2 (CH), 124.9 (CH), 80.2 (CH), 67.0 (CH_2), 63.5 (CH_2), 18.9 (CH_3), 15.1 (CH_3).

HRMS (ESI) *m/z*: 322.1416 $[M+Na]^+$, $C_{18}H_{21}NO_3Na$ requires 322.1419.

4.5.2.5. Alkoxylation of α-amido sulfones 8 with ^{n}Bu$_2$Zn

A 1 M solution of ^{n}Bu_2Zn in heptane (0.375 mL, 0.375 mmol) was added dropwise to a solution of catechol (2.8 mg, 0.025 mmol) and $ClCH_2CH_2Cl$ (0.6 mL) at room temperature under oxygen atmosphere. After stirring for 1 h, a solution of α-amido sulfone **8** (0.125 mmol) in $ClCH_2CH_2Cl$ (1.0 mL) was added and the reaction mixture was stirred at 60 °C. After 20 h, the reaction mixture was quenched with water (1 mL), extracted with CH_2Cl_2 (3x15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **31**.

_N_-(_n_-butoxy(phenyl)methyl)-benzylcarbamate (31a)



31a

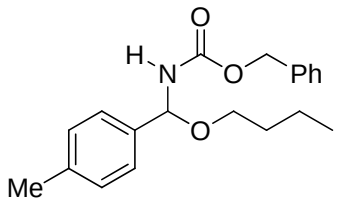
White solid; mp 49-51 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.31 (m, 10H), 5.99 (d, *J* = 9.7 Hz, 1H), 5.34 (d, *J* = 10.2 Hz, 1H), 5.16 (s, 2H), 3.76-3.68 (m, 1H), 3.59-3.52 (m, 1H), 1.68-1.58 (m, 2H), 1.48-1.35 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.9 (C), 139.5 (C), 136.1 (C), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 125.9 (CH), 82.6 (CH), 68.0 (CH_2), 67.0 (CH_2), 31.7 (CH_2), 19.4 (CH_2), 13.9 (CH_3).

HRMS (ESI) *m/z*: 324.1582 $[M+Na]^+$, $C_{19}H_{23}NO_3Na$ requires 336.1576.

***N*-(butoxy(*p*-tolyl)methyl)-benzylcarbamate (31b)**



31b

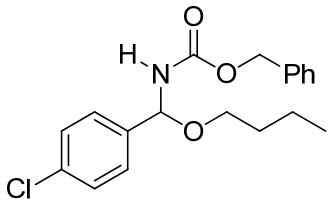
White solid; mp 93-96 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.30 (m, 7H), 7.16 (d, *J* = 7.9 Hz, 2H), 5.94 (d, *J* = 9.6 Hz, 1H), 5.31 (d, *J* = 9.3 Hz, 1H), 5.15 (s, 2H), 3.73-3.66 (m, 1H), 3.57-3.49 (m, 1H), 2.34 (s, 3H), 1.66-1.54 (m, 2H), 1.46-1.34 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.9 (C), 138.2 (C), 136.6 (C), 136.2 (C), 129.2 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 125.8 (CH), 82.5 (CH), 68.0 (CH_2), 67.0 (CH_2), 31.6 (CH_2), 21.1 (CH_3), 19.4 (CH_2), 13.9 (CH_3).

HRMS (ESI) *m/z*: 350.1730 $[M+Na]^+$, $C_{20}H_{25}NO_3Na$ requires 350.1732.

***N*-(*n*-butoxy(4-chlorophenyl)methyl)-benzylcarbamate (31e)**



31e

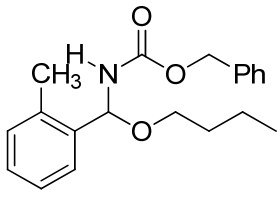
White solid; mp 78-79 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.30 (m, 9H), 5.97 (d, *J* = 9.8 Hz, 1H), 5.31 (d, *J* = 8.9 Hz, 1H), 5.16 (s, 2H), 3.75-3.68 (m, 1H), 3.58-3.51 (m, 1H), 1.66-1.57 (m, 2H), 1.46-1.34 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.9 (C), 138.1 (C), 136.0 (C), 134.2 (C), 128.63 (CH), 128.56 (CH), 128.3 (CH), 128.1 (CH), 127.4 (CH), 81.9 (CH), 68.1 (CH_2), 67.1 (CH_2), 31.6 (CH_2), 19.3 (CH_2), 13.9 (CH_3).

HRMS (ESI) *m/z*: 370.1172 $[M+Na]^+$, $C_{19}H_{18}ClNO_3Na$ requires 370.1186.

***N*-(*n*-butoxy(2-tolyl)methyl)-benzylcarbamate (31h)**



31h

White solid; mp 47-49 °C.

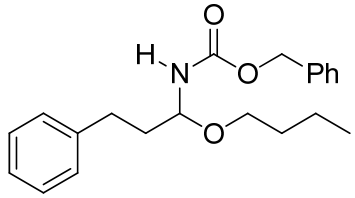
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.51 (m, 1H), 7.35-7.31 (m, 5H), 7.24-7.15 (m, 3H), 6.07 (d, *J* = 9.7 Hz, 1H), 5.28 (d, *J* = 9.9 Hz, 1H), 5.16 (s, 2H), 3.74-3.66 (m, 1H), 3.57-3.49 (m,

1H), 2.33 (s, 3H), 1.67-1.58 (m, 2H), 1.47-1.35 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.7 (C), 137.5 (C), 136.2 (C), 135.5 (C), 130.6 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 126.1 (CH), 125.0 (CH), 80.4 (CH), 67.9 (CH_2), 66.9 (CH_2), 31.7 (CH_2), 19.4 (CH_2), 18.9 (CH_3), 13.9 (CH_3).

HRMS (ESI) *m/z*: 370.1752 $[M+Na]^+$, $C_{20}H_{25}NO_3Na$ requires 350.1732.

_N_-(_n_-butoxy(3-phenyl)propyl)-benzylcarbamate (31q)



31q

White solid; mp 42-44 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.25 (m, 7H), 7.21-7.16 (m, 3H), 5.12 (s, 2H), 4.99-4.95 (m, 2H), 3.65-3.58 (m, 1H), 3.47-3.39 (m, 1H), 2.75-2.67 (m, 2H), 2.04-1.81 (m, 2H), 1.58-1.50 (m, 2H), 1.43-1.31 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).

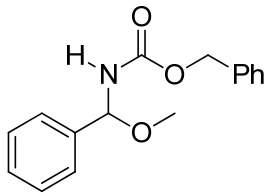
^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.9 (C), 141.2 (C), 136.2 (C), 128.6 (CH), 128.43 (CH), 128.36 (CH), 128.2 (CH), 128.1 (CH), 126.0 (CH), 81.7 (CH), 67.9 (CH_2), 66.8 (CH_2), 37.5 (CH_2), 31.8 (CH_2), 31.3 (CH_2), 19.4 (CH_2), 13.9 (CH_3).

HRMS (ESI) *m/z*: 364.1864 $[M+Na]^+$, $C_{21}H_{27}NO_3Na$ requires 364.1889.

4.5.2.6. Alkoxylation of α-amido sulfones 8 with Me_2Zn

A 2 M solution of Me_2Zn in toluene (0.188 mL, 0.375 mmol) was added dropwise to a solution of catechol (2.8 mg, 0.025 mmol) and CH_2Cl_2 (0.6 mL) at room temperature under nitrogen atmosphere. Then, nitrogen was replaced by oxygen atmosphere. After stirring for 1 h, a solution of α-amido sulfone **8** (0.125 mmol) in CH_2Cl_2 (1.0 mL) was added and the reaction mixture was stirred at rt. After 20 h, the reaction mixture was quenched with water (1 mL), extracted with CH_2Cl_2 (3 x 15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **32**.

***N*-(methoxy(phenyl)methyl)-benzylcarbamate (32a)**



32a

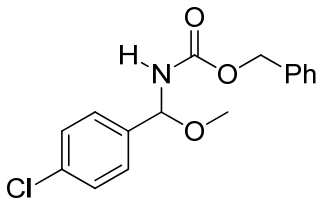
White solid; mp 50-52 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.32 (m, 10H), 5.90 (d, *J* = 9.8 Hz, 1H), 5.35 (d, *J* = 9.0 Hz, 1H), 5.17 (s, 2H), 3.47 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.9 (C), 139.0 (C), 136.1 (C), 128.61 (CH), 128.58 (CH), 128.55 (CH), 128.3 (CH), 128.1 (CH), 125.8 (CH), 84.0 (CH), 67.1 (CH_2), 55.7 (CH_3).

HRMS (ESI) *m/z*: 294.1106 $[M+Na]^+$, $C_{16}H_{17}NO_3Na$ requires 294.1106.

***N*-((4-chlorophenyl)(methoxy)methyl)-benzylcarbamate (32e)**



32e

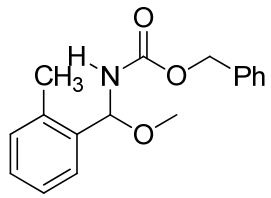
White solid; mp 85-87 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.30 (m, 9H), 5.88 (d, *J* = 9.9 Hz, 1H), 5.33 (d, *J* = 9.1 Hz, 1H), 5.17 (s, 2H), 3.46 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.9 (C), 137.6 (C), 136.0 (C), 134.4 (C), 128.7 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.3 (CH), 83.3 (CH), 67.2 (CH_2), 55.8 (CH_3).

HRMS (ESI) *m/z*: 328.0719 $[M+Na]^+$, $C_{16}H_{16}ClNO_3Na$ requires 328.0716.

***N*-(methoxy(*o*-tolyl)methyl)-benzylcarbamate (32h)**



32h

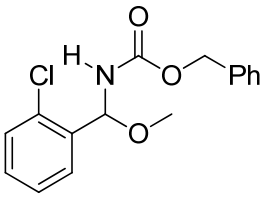
White solid; mp 55-56 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.48 (m, 1H), 7.38-7.34 (m, 5H), 7.24-7.15 (m, 3H), 6.00 (d, *J* = 9.6 Hz, 1H), 5.31 (d, *J* = 9.6 Hz, 1H), 5.16 (s, 2H), 3.46 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.8 (C), 137.0 (C), 136.1 (C), 135.5 (C), 130.7 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 126.2 (CH), 124.8 (CH), 81.7 (CH), 67.0 (CH_2), 55.6 (CH_3), 18.8 (CH_3).

HRMS (ESI) *m/z*: 308.1268 $[M+Na]^+$, $C_{17}H_{19}NO_3Na$ requires 308.1263.

_N_-((2-chlorophenyl)(methoxy)methyl)-benzylcarbamate (32j)



32j

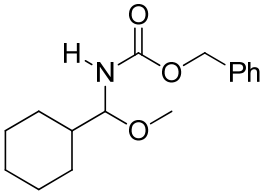
White solid; mp 73-77 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.56 (m, 1H), 7.39-7.26 (m, 8H), 6.13 (d, *J* = 9.6 Hz, 1H), 5.38 (d, *J* = 8.2 Hz, 1H), 5.17 (s, 2H), 3.48 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.7 (C), 136.4 (C), 136.1 (C), 132.7 (C), 129.9 (CH), 129.7 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.0 (CH), 81.7 (CH), 67.1 (CH_2), 55.8 (CH_3).

HRMS (ESI) *m/z*: 328.0716 $[M+Na]^+$, $C_{16}H_{16}ClNO_3Na$ requires 328.0716.

_N_-(cyclohexyl(methoxy)methyl)-benzylcarbamate (32s)



32s

White solid; mp 60-62 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.34 (m, 5H), 5.13 (s, 2H), 5.01 (d, *J* = 10.0 Hz, 1H), 4.64 (dd, *J* = 10.2, 6.2 Hz, 1H), 3.34 (s, 3H), 1.82-1.67 (m, 5H), 1.53-1.43 (m, 1H), 1.26-0.95 (m, 5H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.4 (C), 136.3 (C), 128.5 (CH), 128.2 (CH), 128.0 (CH), 87.2 (CH), 66.8 (CH_2), 55.8 (CH_3), 42.8 (CH), 28.2 (CH_2), 27.7 (CH_2), 26.3 (CH_2), 25.74 (CH_2), 25.67 (CH_2).

HRMS (ESI) *m/z*: 300.1576 $[M+Na]^+$, $C_{16}H_{23}NO_3Na$ requires 300.1576.

4.6. REFERENCES

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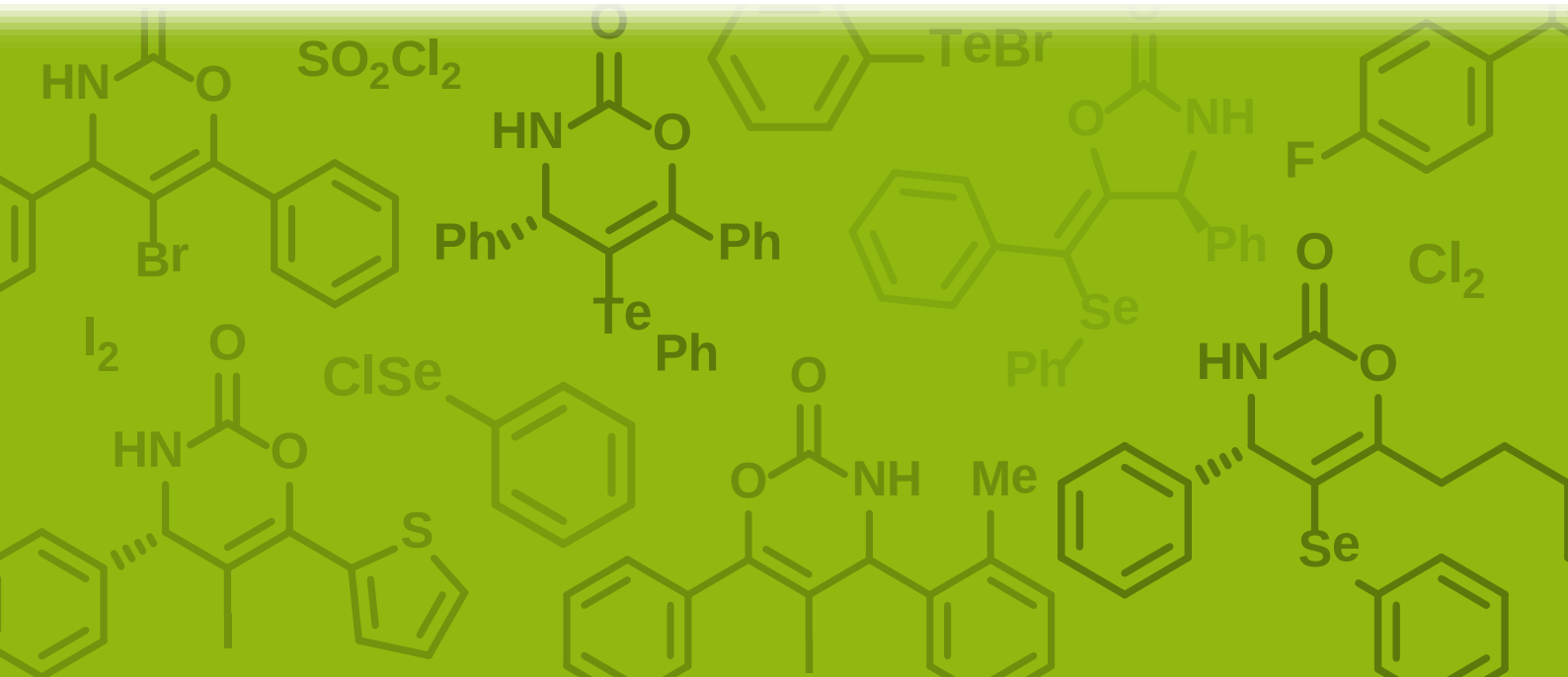
CHAPTER 5

Halogen- and chalcogen-mediated cyclization of *N*-Cbz protected propargylic amines



5.1. ANTECEDENTS

5.1.1. Activation of alkynes toward nucleophilic attack

The activation of a strong bond is the key step in most catalytic chemical transformations. This activation, and therefore splitting of the strong bond, is achieved by the perturbation of the pair bonding electrons in a way so as to form a chemically active species.

Activation of carbon-carbon triple bonds toward nucleophilic attack has typically been performed by the formation of a cationic metal complex in transition metal catalyzed reactions. However, alkyne activation by electrophiles in halogen or organochalcogen reagent mediated processes has gained strength during the last years. This latter reaction proceeds through the formation of a halonium or chalconium ion and allows the synthesis of halo- and chalcoderivatives, which are versatile precursors in many synthetic transformations.

When the nucleophile involved in these processes and the triple bond are in proper relative positions, the reaction occurs through an intramolecular mechanism which leads to heterocycle and carbocycle derivatives.

These rings can be formed via *endo* or *exo* cyclization modes, depending on the chain length, the substitution pattern of the chain and the electrophile employed. In 1976, Sir Jack E. Baldwin[1] formulated a qualitative set of guidelines for the rational design of such cyclization step. Baldwin described his rules in terms of three features of the reaction:

a) The ring size being formed (indicated through a numerical index).
b) The nature of the breaking bond (*exo*, the breaking bond is external to the newly formed ring, and *endo*, the breaking bond is within newly formed ring).
c) The hybridized state of the carbon atom undergoing the ring closing reaction (*digonal* for sp carbon; *trigonal* for sp^2 carbon and *tetrahedral* for sp^3 carbon).

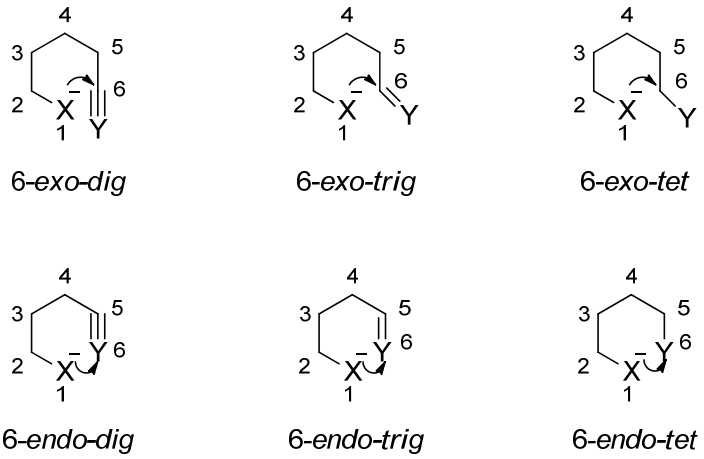


Figure 5.1. Baldwin's rules in six-membered ring formation.

With regard to the internal nucleophile, a wide range of nucleophilic groups such as alcohols, ethers, thioethers, selenoethers, amines, oximes, azides, aldehydes and ketones, carboxylic acids and derivatives, 1,3-dicarbonyl compounds and aromatic rings has been investigated.

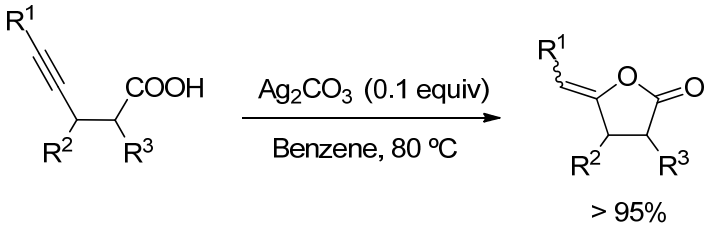
5.1.1.1. Activation of alkynes by transition metals

The utilization of transition metals as alkyne activators has been widely developed during the last 30 years. Among other metals, gold and silver have been successfully applied in the synthesis of heterocycles and carbocycles through the intramolecular addition of nucleophiles to triple bonds.

Some of the most relevant and recent examples of these reactions using oxygen, nitrogen, chalcogen or carbon nucleophiles are exposed below.

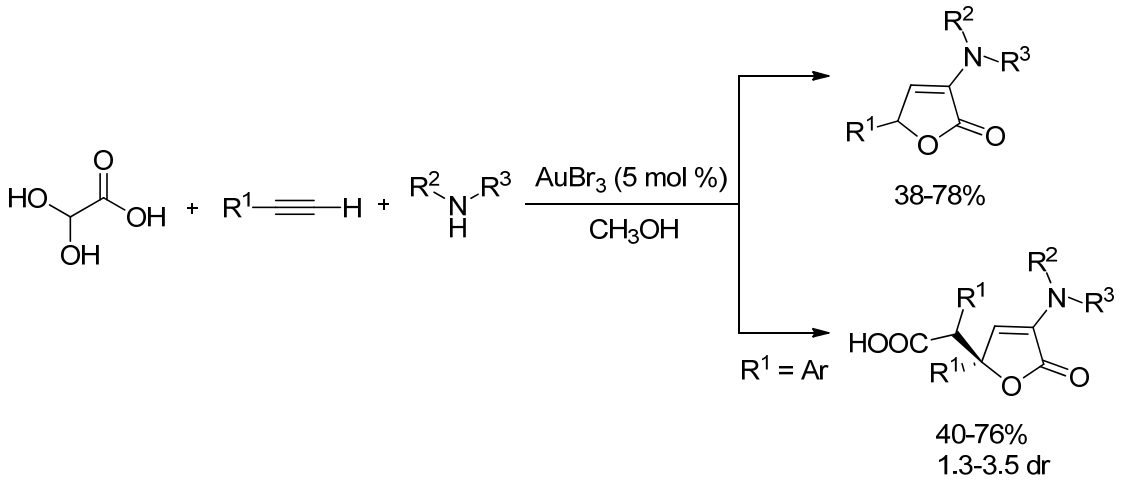
Metal-catalyzed cyclizations using oxygen nucleophile

As early as 1958, Pascual's group[2] originally carried out the cyclization of acetylenic acids catalyzed by silver nitrate to afford furanones in a 5-*exo*-*dig* cyclization mode. Later on, Pale and co-workers[3] studied this reaction in more detail. They observed that the counterion was crucial for the regioselectivity of the reaction and obtained the best results with silver carbonate (Scheme 5.1). It is worth noting that the reaction proceeds via a 6-*endo*-*dig* cyclization mechanism in the presence of zinc bromide.[4]



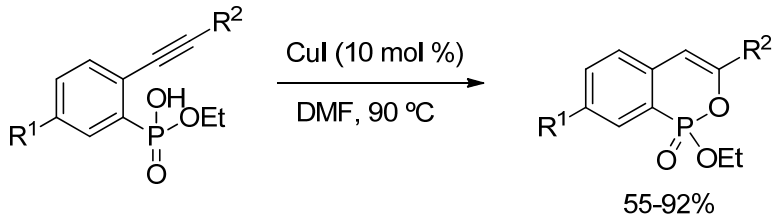
Scheme 5.1. 5-*exo*-*dig* cyclization of acetylenic acids.

More recently, Ji and co-workers[5] have developed a gold-catalyzed tandem three component process for the synthesis of butenolides, which involves the nucleophilic attack of a carboxylate group to a gold-activated triple bond, as shown in Scheme 5.2. The use of aliphatic alkynes afforded the cyclization products in good yields, whereas the use of aromatic alkynes required a trapping iminium ion to obtain the products in higher yields.



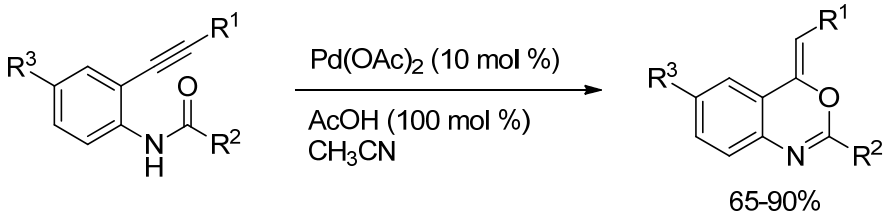
Scheme 5.2. Synthesis of butenolides by a tandem three component reaction.

It has also been demonstrated that phosphoric acids behave as their carboxylic analogues toward activated alkynes.[6] Ding and Peng[7] reported a cyclization of *o*-ethylylphenylphosphoric acid monoethyl esters catalyzed by copper iodide to afford phosphaisocoumarins (Scheme 5.3). Their analogues, isocoumarin[8] and iminoisocoumarin[9] derivatives, have also been prepared following similar approaches through a 6-*endo*-*dig* cyclization of *o*-alkynylbenzoic acid alkyl esters or *o*-(1-alkynyl)benzamides, respectively.



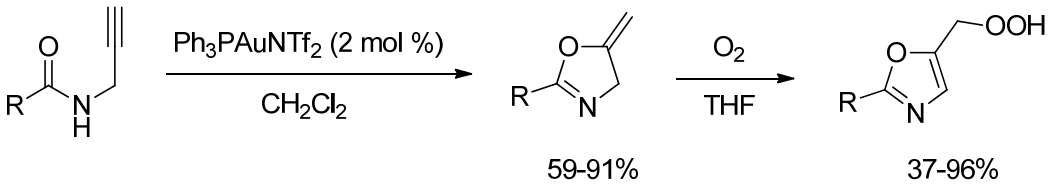
Scheme 5.3. Synthesis of phosphaisocoumarins by 6-*endo*-*dig* cyclization of *o*-ethylylphenylphosphoric acid monoethyl esters.

The 6-*exo*-*O*-cyclization of *N*-acyl-*o*-alkynylanilines has been reported by Saito[10] and co-workers using $Pd(OAc)_2$ as catalyst to give *N*-alkylidene-4*H*-3,1-benzoxazines (Scheme 5.4). This reaction occured in a regio- and stereoselective manner. A variety of alkyl and aryl substituents were examined obtaining the cyclization products in moderate to high yields. The addition of 100 mol % AcOH accelerates the formation of the final product and the regeneration of the $Pd(OAc)_2$.



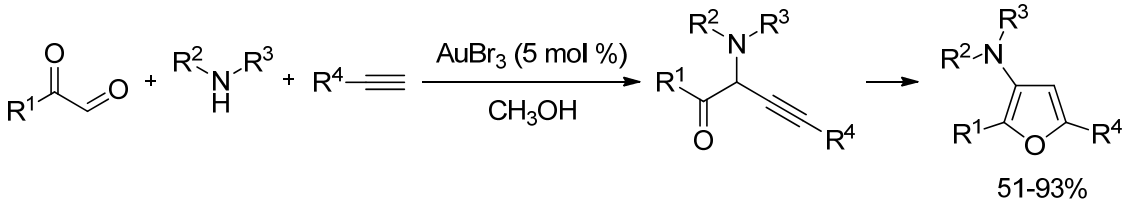
Scheme 5.4. 6-*endo*-*dig* cyclization of *N*-acyl-*o*-alkynylanilines catalyzed by Pd(II).

O-Cyclization of propargylic amides has also demonstrated to be a useful method for the synthesis of oxazole derivatives.[11-15] In an initial work, Hashmi's group[12] proved the efficiency of gold (III) for this process. The reaction was monitored by ^{1}H NMR spectroscopy showing the formation of the intermediate 5-methylene-4,5-dihydrooxazole, which results from a 5-*exo*-cyclization reaction. Although a great variety of functional groups was well tolerated, only terminal alkynes underwent this transformation in the presence of $AuCl_3$. In a later research,[13] they discovered that higher yields were obtained using $Ph_3PAuNTf_2$ (Scheme 5.5) and internal alkynes reacted to give the corresponding alkylideneoxazolines when the reaction was carried out using (IPr)AuCl and AgOTs. The reaction product, in the presence of air, delivered in the hydroperoxide oxazole derivatives.



Scheme 5.5. Synthesis of hydroperoxide oxazole derivatives by 5-*exo*-*dig* cyclization of propargylic amides and further oxidation.

The utilization of ketones and aldehydes as nucleophiles permits the synthesis of heterocycles such as isochromenes[16] or furans[17-20]. Very recently, Liu and coworkers[21] have developed a gold-catalyzed three-component coupling reaction of phenylglyoxal, secondary amines and terminal alkynes that undergoes a 5-*endo*-*dig* cyclization process to afford furan derivatives. Alkynes bearing an electron-withdrawing group were more suitable substrates than those with an electron-donating group. *Meta*- and *para*-substituted phenylglyoxal derivatives could be employed to give the cyclization products in moderate to good yields (Scheme 5.6).

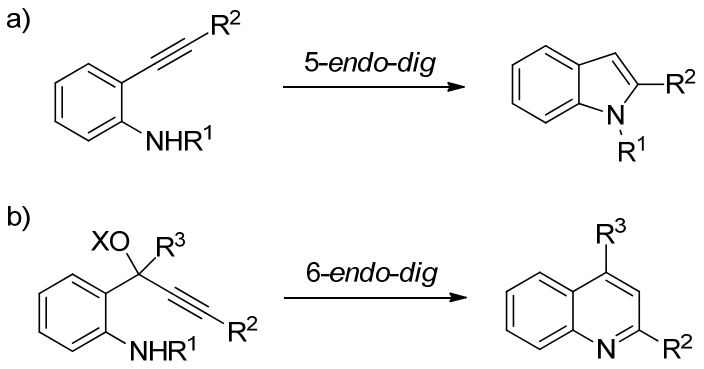


Scheme 5.6. Three-component reaction of phenylglyoxal, secondary amines and terminal alkynes, followed by 5-*endo*-*dig* cyclization to obtain furan derivatives.

Metal-catalyzed cyclizations using nitrogen nucleophile

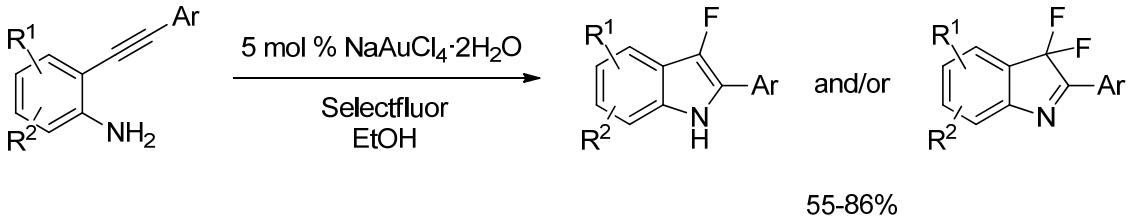
Transition metal catalyzed intramolecular cyclization processes have been successfully employed in the preparation of nitrogen containing heterocycles.

The synthesis of indole and quinoline derivatives employing 5-*endo*-*dig* cyclization reactions of *o*-alkynylanilines and 6-*endo*-*dig* cyclization reactions of *o*-(prop-2-yn-1-yl)anilines, respectively, has been extensively reported (Scheme 5.7).[22,23]



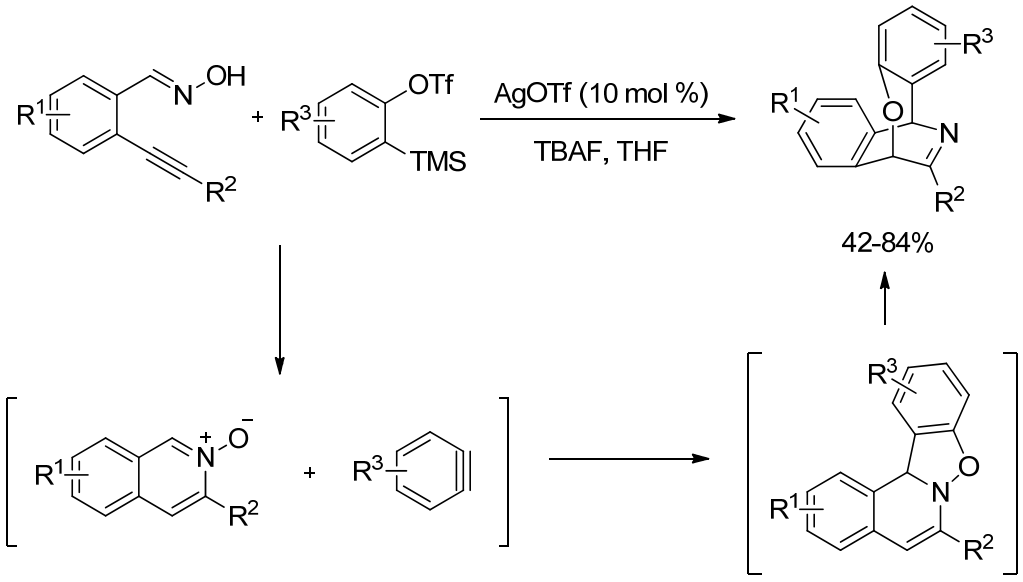
Scheme 5.7. a) Synthesis of indoles by 5-*endo-dig* cyclization. b) Synthesis of quinolines by 6-*endo-dig* cyclization reaction.

As an example, Arcadi[24] has recently reported a 5-*endo-dig* cyclization reaction of unprotected *o*-alkynylanilines and the electrophilic fluorination of the resulting intermediates for the synthesis of mono- and difluorinated indoles (Scheme 5.8). A one-pot procedure was carried out, using $NaAuCl_4 \cdot H_2O$ as catalyst and Selectfluor as fluorinating agent.



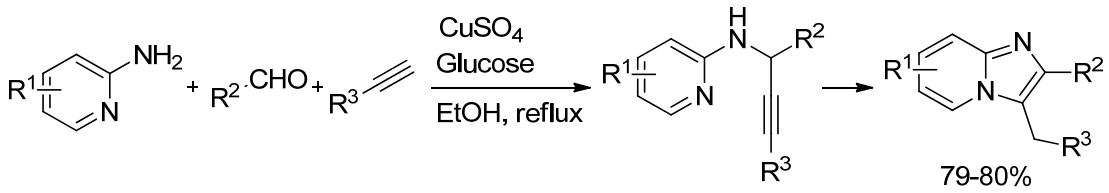
Scheme 5.8. Synthesis of mono- and difluorinated indoles.

2-alkynylbenzaldoximes,[25,26] *N*'-(2-alkynylbenzylidene)hydrazides[27, 28] and 2-(1-alkynyl)phenyl aldimines[29] can also undergo a 6-*endo-dig* cyclization process to afford isoquinoline or dihydroisoquinoline derivatives. Wu and co-workers[25] have achieved the silver triflate catalyzed cyclization of 2-alkynylbenzaldoxime, followed by the reaction with aryne to afford 2-oxo-6-aza-bicyclo[3.2.2]nona-6,8-diene derivatives in moderate to good yields (50-84%) (Scheme 5.9). The reaction proceeded through a 6-*endo-dig* cyclization to furnish isoquinoline *N*-oxide, a subsequent [3+2] cycloaddition with the *in situ* formed aryne and a rearrangement to obtain the final products.



Scheme 5.9. Synthesis of 2-oxo-6-aza-bicyclo[3.2.2]nona-6,8-diene derivatives via a 6-*endo-dig* cyclization of 2-alkynylbenzaldoximes.

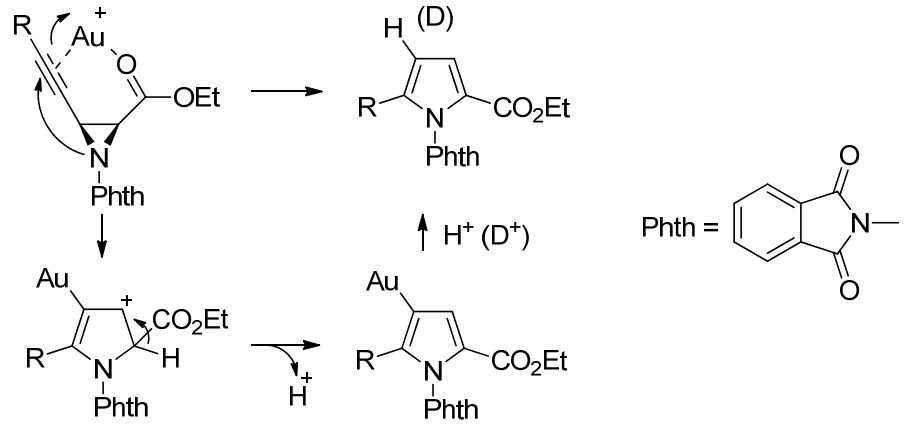
Pyridine derivatives can also behave as nucleophiles toward metal activated alkynes.[30] Guchhait and co-workers[31] have described a three-component reaction of 2-aminopyridine, aldehyde and alkyne followed by a 5-*exo-dig* *N*-cyclization and prototropic shift to afford *N*-fused imidazoles (Scheme 5.10). The reaction was catalyzed by a mixed Cu(I)-Cu(II) system *in situ* generated from partial reduction of $CuSO_4$ with glucose in ethanol and the products were isolated with good yields (66-82%). Other poorly reactive heterocyclic amidines were explored giving the corresponding cyclization products in moderate yields (45-78%).



Scheme 5.10. Synthesis of *N*-fused imidazoles by three-component reaction of 2-aminopyridine, aldehyde and alkyne, 5-*exo-dig* cyclization and prototropic shift.

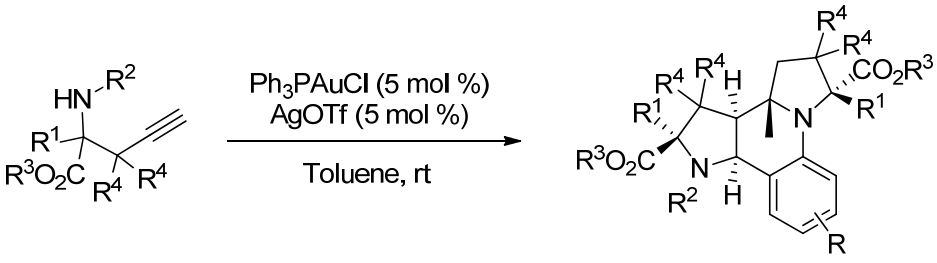
Eycken's group[32] has also developed a methodology to synthesize imizadole derivatives from propynylaminopyrazinones via a regioselective gold-catalyzed 5-*exo-dig* *N*-cyclization reaction.

Other 5-membered heterocycles have been successfully synthesized using metal-catalyzed cyclization strategies with alkynes and nitrogen containing nucleophiles.[33-35] Liu's group[36] has carried out a regioselective cyclization of alkynylaziridines to afford *N*-phthyl pyrroles using (PPh_3)AuCl and AgOTf as catalyst (Scheme 5.11). The authors propose a mechanism which involves coordination of gold to the triple bond, nucleophilic attack of the aziridine nitrogen followed by ring-opening to give a cationic intermediate which, after deprotonation and deauration affords *N*-phthyl pyrrole.



Scheme 5.11. Mechanism for the synthesis of *N*-phth pyrroles from *N*-phth alkynylaziridines.

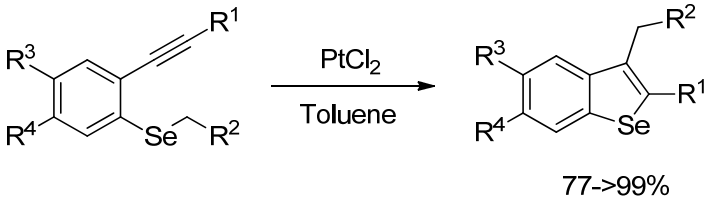
Very recently, Fustero's group has reported the synthesis of a tetracyclic framework as a single diastereoisomer from propargylic amino esters.[37] The process began with the activation of the alkyne by the gold catalyst followed by the attack of the amine to give a 5-*endo-dig* cyclization product which underwent a stereoselective tandem hydroamination-formal aza-Diels-Alder reaction providing the tetracycles with five stereocenters (Scheme 5.12)



Scheme 5.12. Synthesis of a tetracyclic framework as a single diastereoisomer from propargylic amino esters.

Metal-catalyzed cyclizations using chalcogen nucleophiles

Chalcogenophene heterocycles and their derivatives present interesting properties in the fields of organic synthesis, biochemistry[38] or material chemistry.[39] For this reason, not only the use of organochalcogen derivatives as electrophiles, but also their application as nucleophiles in the cyclization of alkynes has attracted the attention of a few authors.[40] One of the representative examples was carried out by Nakamura and co-workers.[41] They performed the platinum-catalyzed 5-*endo-dig* cyclization of alkyl *o*-alkynylphenyl selenides to furnish 2,3-disubstituted benzo[*b*]selenophenes in high to excellet yields (Scheme 5.13).

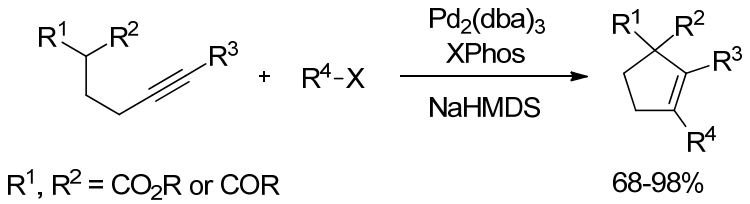


Scheme 5.13.Synthesis of 2,3-disubstituted benzo[*b*]selenophenes through 5-*endo-dig* cyclization of alkyl *o*-alkynylphenyl selenides .

Metal-catalyzed cyclizations using carbon nucleophiles

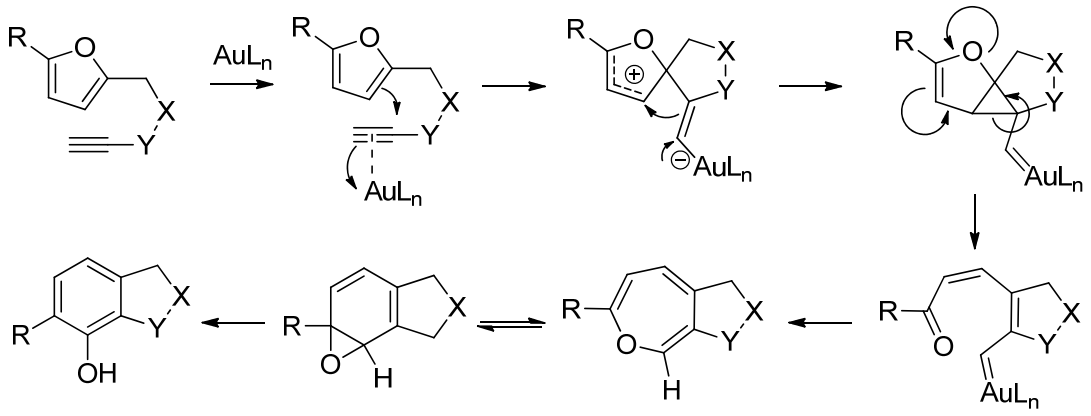
Transition-metal activation of alkynes toward carbon nucleophiles has been applied to the preparation of a variety of carbo- and heterocycles. In general, carbon nucleophiles can be divided into three categories: dicarbonylic compounds, arene and olefins. Some of the most recent representative publications are outlined below.

Some authors have taken advantage of the acidity of dicarbonylic compounds to develop cyclization strategies.[42,43] Yorimitsu and co-workers[44] have performed 5-*endo-dig* cyclization of homopropargyl-substituted dicarbonyl compounds, followed by C-C bond forming reductive elimination to provide 1,2-disubstituted cyclopentenes (Scheme 5.14). The reaction was catalyzed by palladium with bulky biaryl phosphine ligands in the presence of a base. Substituents of diverse nature were well tolerated providing the cyclization products in high yields.



Scheme 5.14. Palladium-XPhos-catalyzed cyclization of homopropargyl-substituted dicarbonyl compounds.

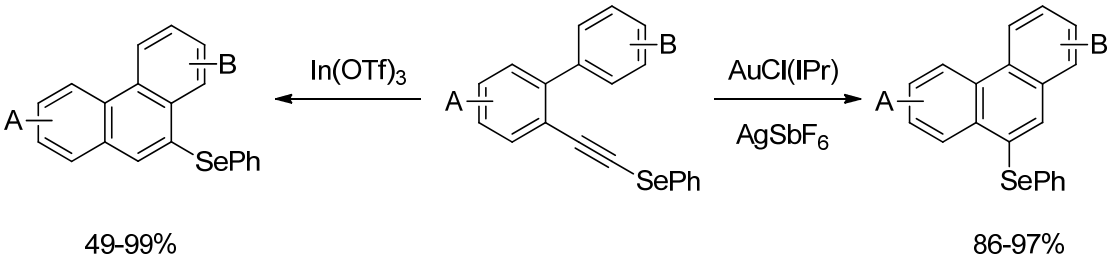
Furanyne systems have been employed in cyclization reactions for the formation of compounds such as phenols, fluorenes, phenanthrenes or benzofuranes.[45] Mechanistically, one of the most studied transformations is the synthesis of phenol derivatives catalyzed by gold (Scheme 5.15). Initially, gold coordinates the triple bond and the carbon at the α-position of the furan ring closes by a 5-*exo*-*dig* cyclization. The new cationic species evolves leading to a cyclopropyl carbenoid, which opens up to a vinyl carbenoid. Nucleophilic attack of the carbonyl oxygen atom and elimination of gold then gives an oxepine intermediate in tautomeric equilibrium with the arene oxide. Opening of the oxirane ring and aromatization leads to the phenol derivative.



Scheme 5.15. Mechanism for the 5-*exo*-*dig* cyclization of furanyne systems.

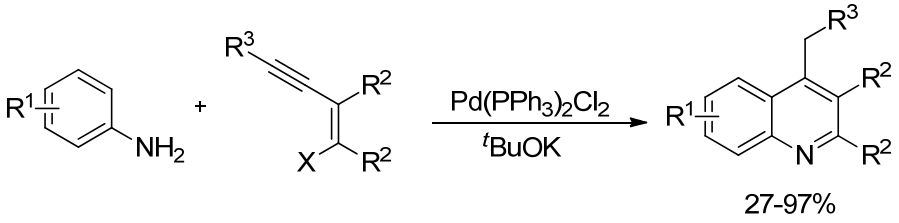
Aromatic carbocycles have been prepared using cyclization strategies. Rhee and Lim[46] have carried out a metal-catalyzed cyclization of *o*-phenylarylakynes to afford selectively 9- or 10-selenyl phenanthrenes depending on the catalyst (Scheme 5.16). $In(OTf)_3$ catalyst led to the 6-*endo*-*dig* cyclization product in which the selenium group is retained in the same carbon atom, whilst, the utilization of $AuCl(IPr)/AgSbF_6$ catalyst

system involved a vinylidene-gold formation that led to the isomeric product. In both cases, the reactions proceeded selectively and with high yields.



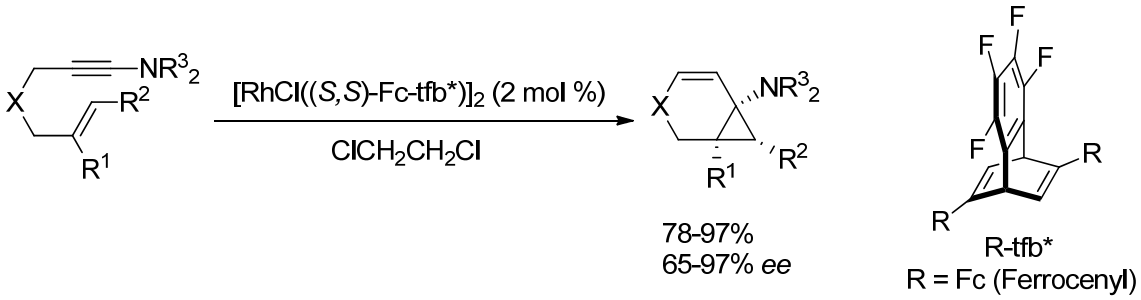
Scheme 5.16. Selective synthesis of 9- and 10-selenyl phenanthrenes.

Not only carbocycles, but also heterocycles have been furnished by carbon-nucleophilic attack to metal transition activated alkynes.[47,48] Xi and co-workers[49] have recently developed an efficient strategy for the preparation of quinolines by a palladium-catalyzed tandem *N*-vinylation and the 6-*exo*-*dig* cyclization of anilines and haloenynes (Scheme 5.17). Gagosz's group[50] have also accomplished the synthesis of tetrahydroquinolines and dihydroquinolines using a 6-*exo*-*dig* cyclization reaction of *N*-aminophenyl propargyl malonates.



Scheme 5.17. Synthesis of quinolines by 6-*exo*-*dig* cyclization of anilines and haloenynes.

On the other hand, enyne systems have demonstrated to be appropriate substrates to undergo cyclization reactions.[51] There are numerous examples in the literature describing this transformation. One of the most recent examples was reported by Hayashi.[52] He described the asymmetric preparation of 3-aza- and 3-oxabicyclo[4.1.0]heptane derivatives from heteroatom bridged 1,6-ene-ynamides (Scheme 5.18). The reaction was catalyzed by a rhodium/chiral diene complex through 6-*endo*-*dig* pathway affording the reaction product with high enantioselectivities. The 1,6-ene-ynamides substituted with 2-oxazolidinone and 2-azetidinone at the alkyne moiety were found to display high reactivity toward the catalyst.



Scheme 5.18. 6-*endo-dig* cyclization of 1,6-ene-ynamides.

5.1.1.2. Activation of alkynes by electrophiles

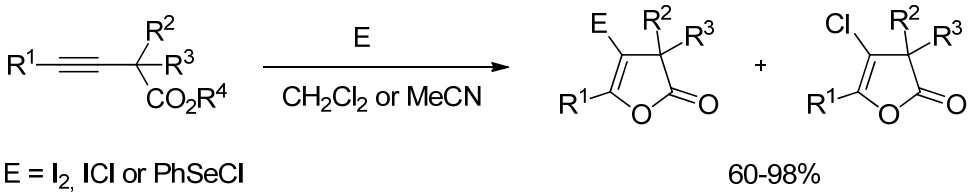
Activation of alkynes by an electrophilic source toward a nucleophilic intramolecular attack has demonstrated to be an efficient method for the synthesis of highly functionalized carbo- and heterocycles. Different electrophilic sources have been employed to carry out these reactions. Molecular halogens (X_2), halogenation agents such as *N*-halosuccinimides, trichloroisocyanuric acid, $I(coll)_2PF_6/BF_3{\cdot}OEt_2$ or IPy_2BF_4/HBF_4, ICl and organochalcogen reagents are some of the most widely used.[53]

Due to the enormous amount of publications regarding these reactions, only the latest approaches where molecular halogens (X_2) and organochalcogen reagents (RYYR or RYX) are used as electrophilic sources will be considered below.

Electrophilic-catalyzed cyclizations using oxygen nucleophiles

The behaviour of COOH or COO^- groups as internal nucleophile toward electrophilically activated alkynes is well known since the early report on the synthesis of halolactones by such a cyclization approach in 1981.[54] Subsequently, several authors have deepened into the usefulness of these nucleophiles to prepare heterocycles through electrophilic cyclization.

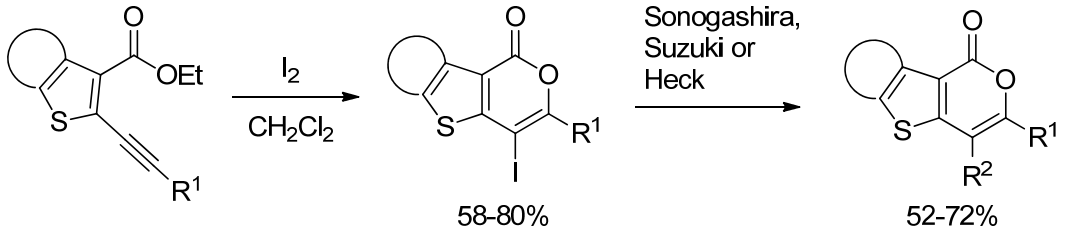
Larock's group[55] subjected a series of acetylenic acids and esters to electrophilic cyclization conditions to give 2(*3H*)-furanones in good to excellent yields (Scheme 5.19). They found that the electrophiles I_2, ICl and PhSeCl were suitable for this reaction. In most cases, the use of I_2 gave only 4-iodo-2(*3H*)-furanones, whereas for some substrates the utilization of ICl afforded mixtures of 4-iodo- and 4-chloro-2(*3H*)-furanones.



Scheme 5.19. Electrophilic 5-*endo-dig* cyclization of acetylenic acids.

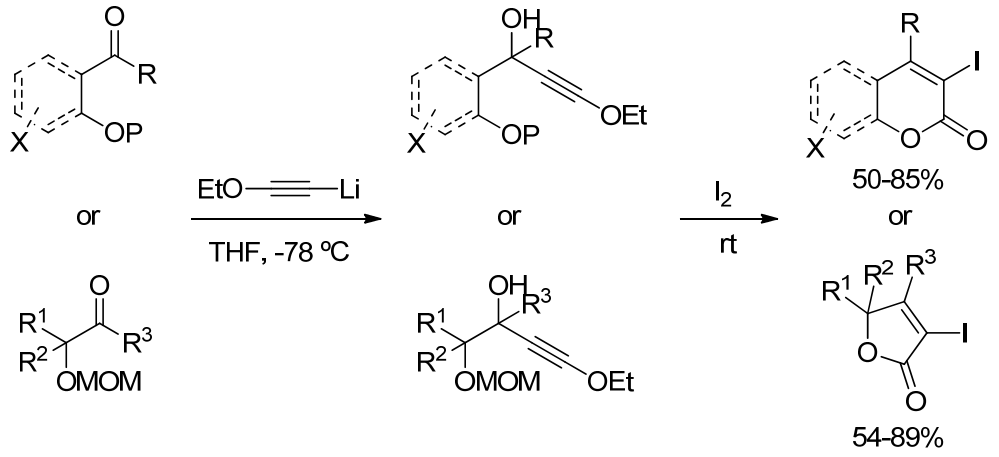
Some authors have employed this type of cyclization reaction with esters having an internal alkyne in the synthesis of isocoumarins and pyranone derivatives.

In 2012, Pal's group[56] designed a library of novel 7-iodo-4*H*-thieno[3,2-c]pyran-4-one derivatives by the regioselective 6-*endo-dig* iodocyclization of previously synthesized 2-alkynyl thiophene ester derivatives (Scheme 5.20). Molecular iodine was used as electrophile. The products were obtained in good to high yields (58-80%) and were subjected to further C-C bond forming reactions such as Sonogashira, Heck or Suzuki coupling reactions. In addition, some of the thienopyranone derivatives showed promising selective growth inhibition of cancer cells.



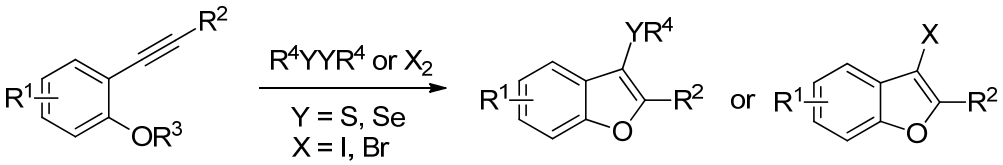
Scheme 5.20. Synthesis of pyranone derivatives by 6-*endo-dig* iodocyclization.

Very recently, Reddy and co-workers[57] have used OMe and OMOM (methoxymethyl ether) groups as efficient nucleophiles for the intramolecular cyclization of alkynols. On one hand, they carried out the 6-*endo-dig* iodocyclization of 3-ethoxy-1-(2-alkoxyphenyl)-2-yl-ols to afford various 4-substituted 3-iodocoumarins. They also developed the 5-*endo-dig* iodocyclization of 1-alkoxy-4-ethoxy-3-yn-1,2-diols to give 4,5-disubstituted 3-iodobutenolides (Scheme 5.21). The reactions were performed under very mild conditions using I_2. A great diversity of substituents was well tolerated obtaining the cyclization products in good to high yields (54-89%).



Scheme 5.21. Iodocyclization of alkynols to provide 3-iodocoumarins and 3-iodobutenolides.

Various authors have employed *o*-alkynylanisoles for the synthesis of benzo[*b*]furans through electrophilic cyclization.[58] In 2009, Zeni's group[59] described the synthesis of 2-halogen and chalcogen benzo[b]furans from 2-chalcogen-alkynylanisoles using I_2, ICl, Br_2 or PhSeBr. More recently, Zhong[60] and co-workers synthesized 3-chalcogen benzo[b]furans via the iodine-mediated cyclization of 2-alkynylanisoles with disulfides or diselenides in the presence of I_2 (Scheme 5.22).

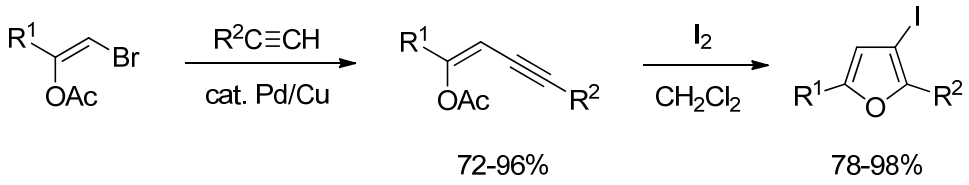


Scheme 5.22. 5-*endo*-*dig* cyclization of *o*-alkynylanisoles to provide benzo[b]furans.

The substrates employed for the synthesis of furans by electrophilic cyclization of alkynes having an internal nucleophile are diverse. Alcohols, carbonyl compounds and oxiranes have demonstrated to be efficient nucleophiles in this type of reaction.[61-63]

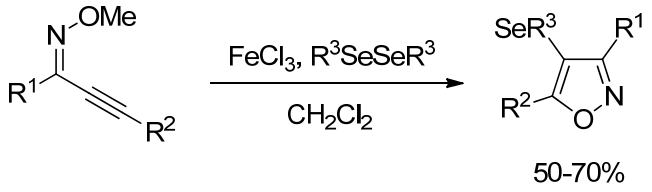
In 2011, Jiang and co-workers[62] reported the preparation of 2,5-disubstituted 3-iodofurans through the Sonogashira coupling of (*Z*)-β-bromoenol acetates with terminal alkynes, followed by intramolecular iodocyclization (Scheme 5.23). The reaction occurred through a 5-*endo*-*dig* cyclization pathway. The substituents attached to the triple bond had a great impact on the success of the reaction. The obtained 3-

iodofurans were subjected to Sonogashira reaction conditions, providing the desired coupling products in excellent yields.



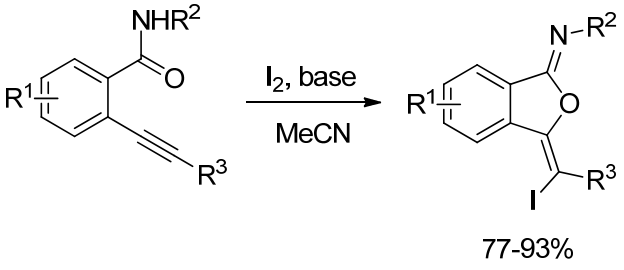
Scheme 5.23. Synthesis of furan derivatives by Sonogashira and iodocyclization reactions.

Isoxazoles can also be synthesized by electrophilic cyclization methodologies using alkynone *O*-methyloximes as substrates.[64] Zeni's group[65] has recently carried out the synthesis of 4-organoselenylisoxazoles via a 5-*endo*-*dig* cyclization reaction mediated by RSeSeR/$FeCl_3$ with good yields (50-70%) (Scheme 5.24).



Scheme 5.24. Synthesis of isoxazoles via a 5-*endo*-*dig* selenocyclization.

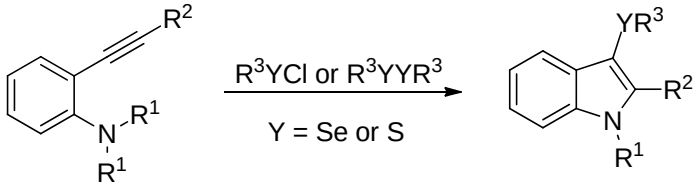
The oxygen atom of an amide group can act as an internal nucleophile toward an activated alkyne in order to furnish cyclic imidates.[66-68] Larock[68] has developed the *O*-cyclization reaction of 2-(1-alkynyl)benzamides using I_2 (Scheme 5.25). The procedure was also extended to other electrophilic sources such as ICl, NBS, PhSeCl and *p*-$NO_2C_6H_4SCl$. The reaction proceeded through a 5-*exo*-*dig* cyclization mode. However, the reaction was not totally regioselective and the 6-*endo*-*dig* cyclization products were also obtained. The utility of the products was demonstrated in further coupling reactions.



Scheme 5.25. Iodocyclization of 2-(1-alkynyl)benzamides.

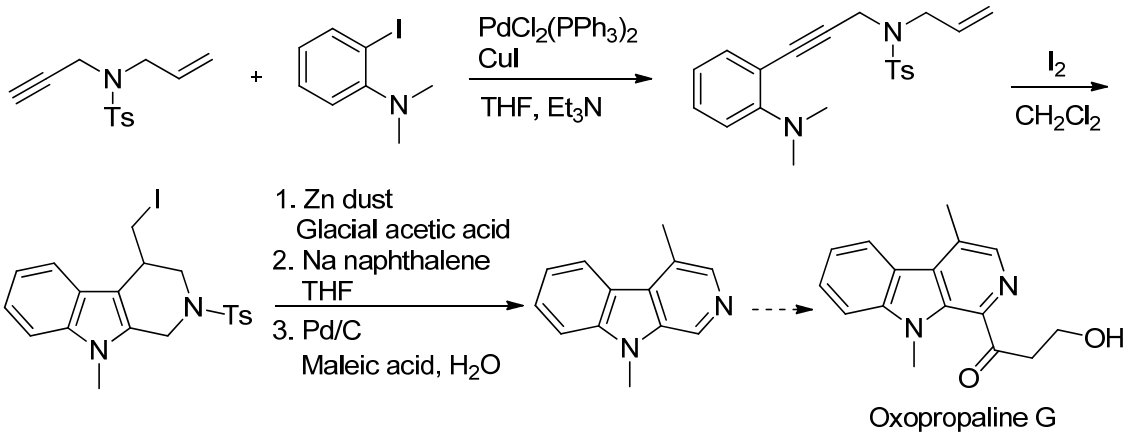
Electrophilic-catalyzed cyclizations using nitrogen nucleophiles

The enormous potential of the indole scaffold in the synthesis of biologically active species has encouraged many scientists to develop new strategies for its preparation.[69] Electrophilic cyclization of *o*-alkynylanilines via a 5-*endo-dig* pathway has proven to be an efficient approach in the synthesis of this heterocycle.[70] In the last years, several authors have carried out this cyclization reaction in the preparation of 3-chalcogenoindoles using organochalcogen reagents (Scheme 5.26).[71]



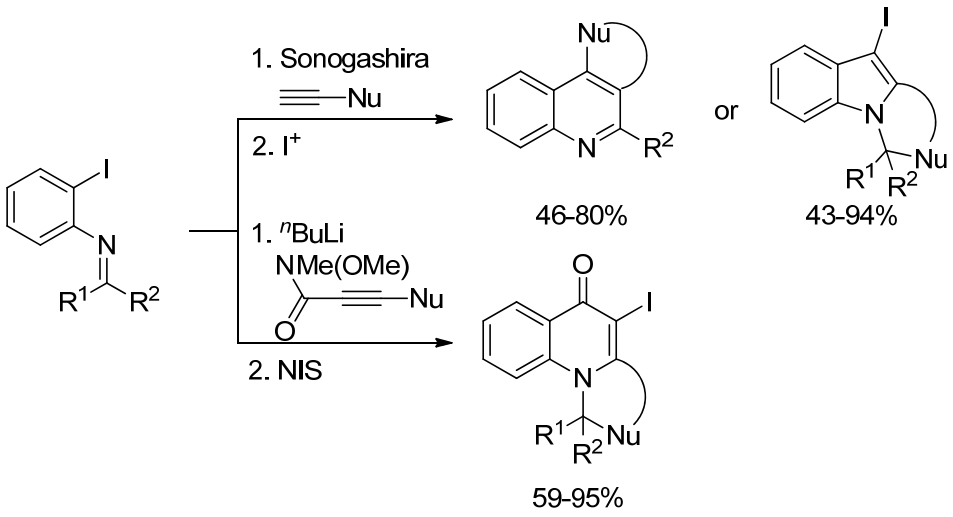
Scheme 5.26. Synthesis of indoles by electrophilic 5-*endo-dig* cyclization of *o*-alkynylanilines.

The utility of the electrophilic cyclization of *o*-alkynylanilines has been demonstrated in a formal synthesis of oxopropaline G. Wang's group[72] has accomplished the synthesis of this natural product in several steps (Scheme 5.27). Firstly, a Sonogashira coupling reaction gave access to the appropriate *o*-alkynylaniline substrate. Afterwards, it was subjected to a 5-*endo-dig* iodocyclization reaction, followed by a 6-*exo-trig* iodocyclization. Further deprotection of the *N*-tosyl group and oxidation provided the oxopropaline G precursor.



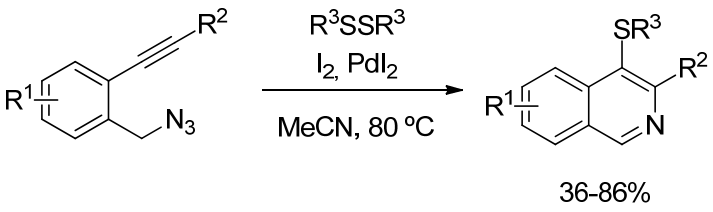
Scheme 5.27. Synthesis of oxopropaline G.

Very recently, Flynn and co-workers[73] have disclosed the synthesis of ring-fused indoles or quinolines from *N*-(2-iodophenyl)imines through the attachment of an alkyne, followed by cascade cyclization reactions (Scheme 5.28). The use of NIS as iodonium source led to ring-fused 3-iodoindoles, whereas the use of I_2 gave furano- and pyrano-fused quinolines. Only when diphenylimines were employed, both electrophilic sources provided the same ring-fused 3-iodoindole products. The authors extended this methodology to the synthesis of quinolones by performing acyl substitution of Weinreb amide and cyclization with NIS.



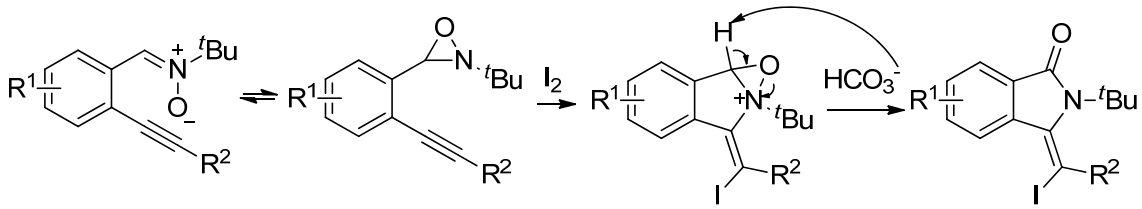
Scheme 5.28. Synthesis of indoles, quinolines and quinolones by iodocyclization approaches.

The preparation of isoquinolines through 6-*endo*-*dig* cyclization reactions has been fulfilled by various authors. In 2011, Wu's group performed different cyclization approaches for the synthesis of isoquinoline derivatives.[74,75] Concurrently, Li and co-workers[76] reported the PdI_2/I_2-catalyzed 6-*endo*-*dig* cyclization of 2-alkynylbenzyl azides with disulfides to afford 4-sulfenylisoquinolines (Scheme 5.29). A variety of 2-alkynylbenzyl azides were reacted with numerous disulfides with moderate to high yields (46-86%). However, disulfides with electron-deficient aryl groups were inert.



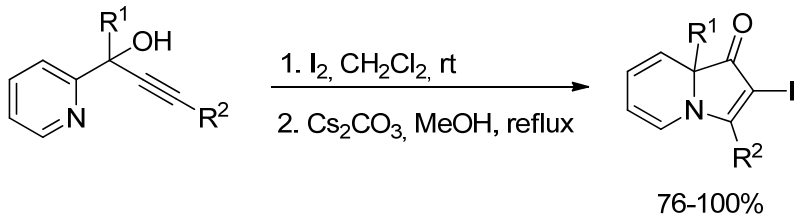
Scheme 5.29. Synthesis of 4-sulfenylisoquinolines via a PdI_2/I_2-catalyzed 6-*endo*-*dig* cyclization of 2-alkynylbenzyl azides with disulfides.

Isoindolinones and isoquinolinones can be formed from *o*-(1-alkynyl)benzamides through an electrophilic cyclization process. However, the regioselectivity of this reaction is not always high. Li and co-workers[77] have carried out a 5-*exo*-*dig* iodocyclization of nitrone-alkynes to afford 1-isoindolones regioselectively. They proposed a process with formal 1,2-oxygen transfer from the nitrogen to the carbon in the nitrone group which involved the activation of the triple bond by electrophilic iodonium, followed by nucleophilic addition of the oxaziridine nitrogen to give a vinyl iodide species that undergoes scission of the strained oxaziridine ring in order to furnish the final product (Scheme 5.30).



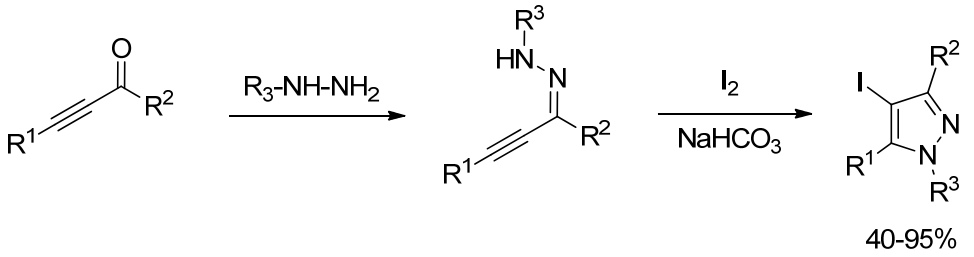
Scheme 5.30. Mechanism for the synthesis of 1-isoindolones.

Pyridine derivatives are other kind of compounds frequently employed in electrophilic cyclization of alkynes. For example, Kim's group[78] has described a 5-*endo*-*dig* iodocyclization of pyridinyl propargylic alcohols and subsequent 1,2-C-shift to provide 2-iodoindolizinones in excellent yields (Scheme 5.31). The potential of this functionalized heterocycles as precursors for increasing molecular complexity has been evaluated via palladium-catalyzed reactions.



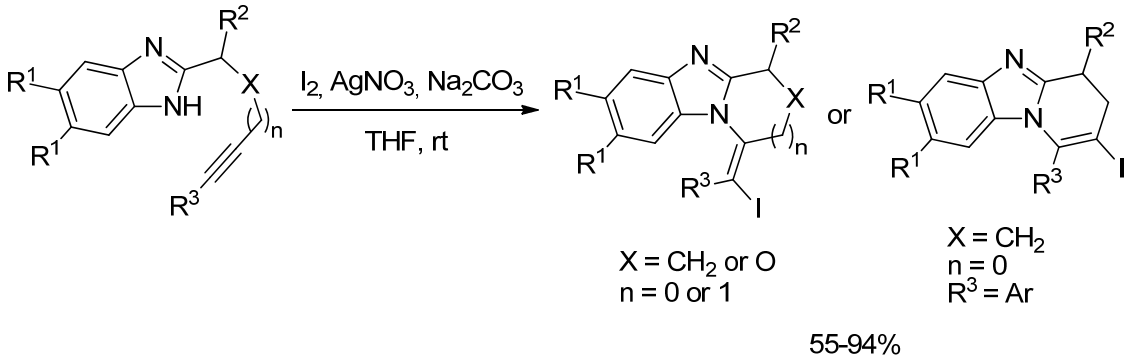
Scheme 5.31. Synthesis of 2-iodoindolizinones by 5-*endo-dig* iodocyclization and 1,2-shift.

Propargylic hydrazones can undergo electrophilic cyclization to afford pyrazoles as reported by Zora and co-workers (Scheme 5.32).[79] They have performed the condensation of hydrazines with propargyl aldehydes and a 5-*endo-dig* iodocyclization reaction of the resulting propargylic hydrazones providing 4-iodopyrazoles in good to excellent yields (40-95%). The presence of $NaHCO_3$ was required to obtain the reaction product in high yields.



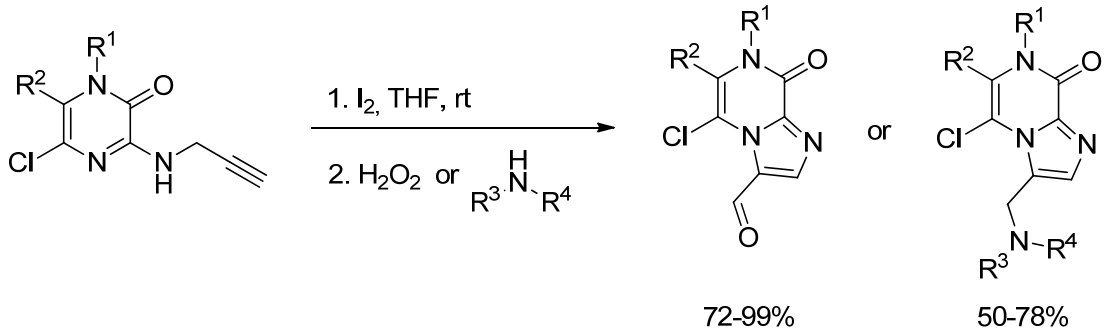
Scheme 5.32. Synthesis of pyrazoles via a 5-*endo-dig* iodocyclization reaction of propargylic hidrazones.

The construction of highly functionalized imidazole derivatives has also been accomplished using electrophilic cyclization strategies. Liu and co-workers[80] have developed the iodocyclization of benzo[*d*]imidazoles to provide pyrrole and piperidine[1,2-*α*]benzimidazoles, as well as oxa-fused benzimidazoles in good to excellent yields (55-94%) (Scheme 5.33). The reaction occurred via an *exo-dig* pathway. The authors hypothesize that the addition of silver nitrate assists the reaction by the removal of iodine ion in the solution and prevents it from attacking the activated triple bond and forming bis-iodine products.



Scheme 5.33. Iodocyclization of benzo[*d*]imidazoles.

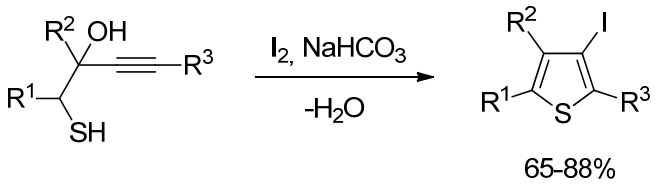
Very recently, Eycken's group[81] has reported a protocol for the formation of imidazo[1,2-*α*]pyrazinone core. This approach is based on a 5-*exo*-*dig* iodocyclization of propynylaminopyrazinones and subsequent oxidation or amination (Scheme 5.34). Further functionalization of the cyclization products could be afforded under Suzuki coupling conditions.



Scheme 5.34. Iodocyclization of propynylaminopyrazinones and further oxidation or amination.

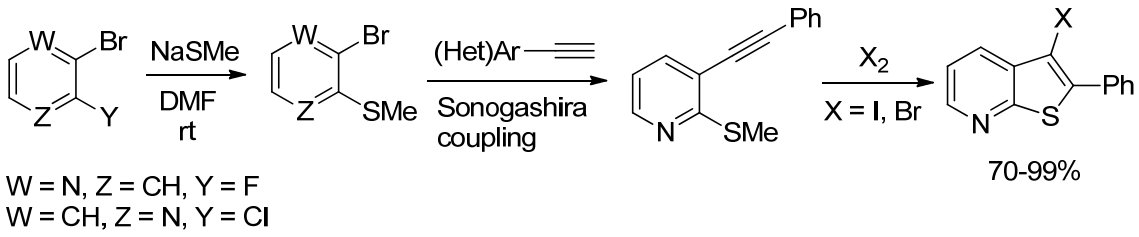
Electrophilic-catalyzed cyclization using chalcogen nucleophiles

The synthesis of thiophenes and benzo[*b*]thiophenes by electrophilic cyclization has been fulfilled by Larock and co-workers.[82,83] On one hand, thiophenes have been furnished by a 5-*endo*-*dig* iodocyclization of 1-mercapto-3-yn-2-ols and dehydrative aromatization (Scheme 5.35).[82] The corresponding 3-iodothiophenes were afforded in good yields (65-88%) in the presence of I_2 and $NaHCO_3$. On the other hand, the synthesis of benzo[*b*]thiophene derivatives has been performed by 5-*endo*-*dig* cyclization of *o*-alkynyl thioanisole derivatives.[83]



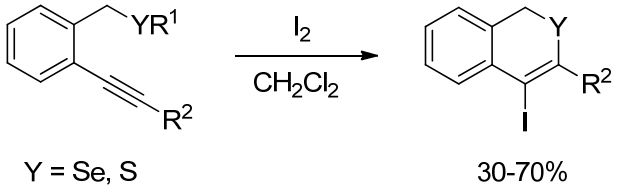
Scheme 5.35. Synthesis of thiophenes by a 5-*endo-dig* iodocyclization.

Very recently, Queiroz's group[84] has disclosed an approach for a three-step synthesis of 3-halo-2-(hetero)arylthieno[2,3-b]pyridines and 3-halo-2-(hetero)arylthieno[3,2-b]pyridines. The process started by an initial nucleophilic aromatic substitution with NaSMe on 3-bromo-2-chloropyridine or 2-bromo-3-fluoropyridine, followed by a subsequent Sonogashira coupling reaction. Final 5-*endo-dig* cyclization with Br_2 or I_2 furnished the corresponding 3-halo-2-(hetero)arylthieno[2,3-b]pyridines and 3-halo-2-(hetero)arylthieno[3,2-b]pyridines (Scheme 5.36).



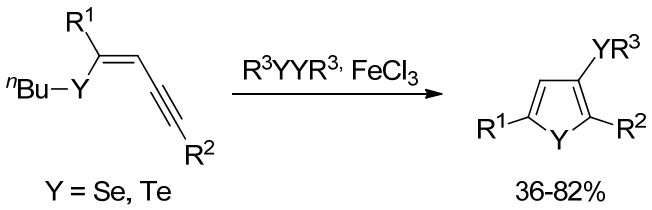
Scheme 5.36. Synthesis of 3-alkynyl-2-(methylthio)pyridines and subsequent halocyclization.

2-Alkynylbenzyl chalcogenide derivatives can also undergo electrophilic cyclization to provide isochalcogenochromenes. Zeni and co-workers[85] have presented the synthesis of the former 2-alkynylbenzyl selenide and sulfide derivatives by Sonogashira cross-coupling reactions and their subsequent iodocyclization with I_2 as iodonium source (Scheme 5.37). The process occurred in a regioselective manner through a 6-*endo-dig* cyclization giving 4-iodo-3-substituted 1*H*-isoselenochromenes or -isothiochromenes, as the only reaction products.



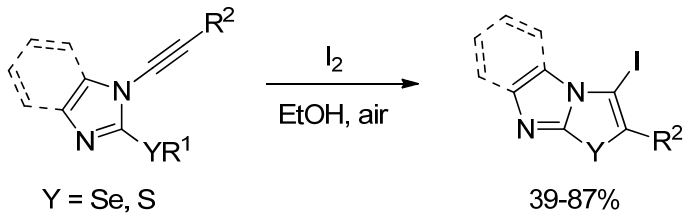
Scheme 5.37. 6-*Endo-dig* cyclization of 2-alkynylbenzyl selenide and sulfide derivatives.

In 2012, the same research group developed two different strategies for the synthesis of selenophenes[86] and tetrahydroselenophenes.[87] The former were prepared by a 5-*endo*-*dig* cyclization of (*Z*)-enynes, employing diorganoyl dichalcogenide derivatives as electrophilic sources in the presence of $FeCl_3$ (Scheme 5.38). The methodology was extended to the formation of tellurophenes with moderate yields. The antidepressant-like activity of the resulting 3-organochalcogen chalcogenophenes was evaluated and offered promising results. Tetrahydroselenophene derivatives were obtained from 1-butylseleno-4-alkynes through 5-*exo*-*dig* cyclization reactions using iodine with good to high yields for a wide range of substituents.



Scheme 5.38. Synthesis of chalcogenophenes by a 5-*endo*-*dig* cyclization of (*Z*)-enynes.

More recently, the same authors described the selective synthesis of 3-iodoimidazochalcogenazoles from *N*-alkynyl-2-(organochalcogen)imidazoles via a 5-*endo*-*dig* pathway in the presence of iodine (Scheme 5.39).[88] The main advantage of this approach is the high regioselectivitity with regards to a possible competition as nucleophiles between the selenium or sulfur and other oxygen atoms present in the R^1 group of the substrate, since only the chalcogen heterocycles were pursued.



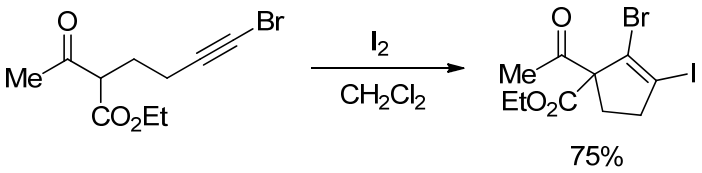
Scheme 5.39. Synthesis of 3-iodoimidazochalcogenazoles via a 5-*endo*-*dig* cyclization reaction.

Electrophilic-catalyzed cyclizations using carbon nucleophiles

Halo- and chalcocyclizations involving an initial C-C bond formation are less developed than those cyclizations of heteroatom nucleophiles with tethered alkynes. As for metal-transition alkyne activation, malonates and related active methyne

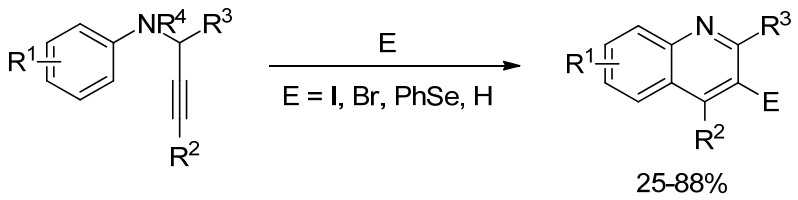
compounds, arenes, and olefins can behave as nucleophiles and the earliest and most representative examples will be summarized herein.

Despite the numerous publications reporting the use of dicarbonylic compounds as carbonucleophiles, its application in molecular halogen or organochalcogen-mediated cyclizations with internal alkynes is not broadly described. Barluenga's group[89] has carried out a 5-*endo*-*dig* cyclization of δ-alkynyl-β-ketoesters to provide iodocyclopentenes in good yields using molecular iodine as electrophile (Scheme 5.40). The synthetic utility of the resulting products was demonstrated in further palladium-catalyzed cross-coupling reactions.



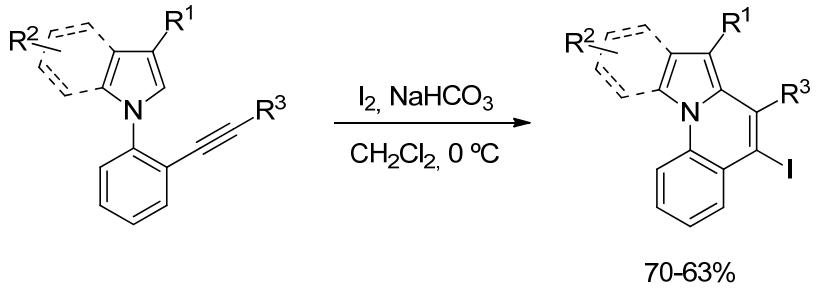
Scheme 5.40. Synthesis of iodocyclopentenes through a 5-*endo*-*dig* cyclization of δ-alkynyl-β-ketoesters.

A wide variety of heterocycles can be furnished by electrophilic cyclization of alkynes containing neighboring arenes. Some authors have employed this approach in the synthesis of quinolines starting from propargylic anilines. Larock and co-workers[90] have reported the synthesis of 3-halogen-, selenium- and sulfur-containing quinolines by a 6-*endo*-*dig* cyclization of *N*-(2-alkynyl)anilines using ICl, I_2, Br_2, PhSeBr and ArSCl as electrophilic sources (Scheme 5.41). A wide range of functional groups were well tolerated, obtaining the desired products in moderate to good yields. Iodoquinolines were converted to functionally-substituted quinolines through palladium-coupling reactions.



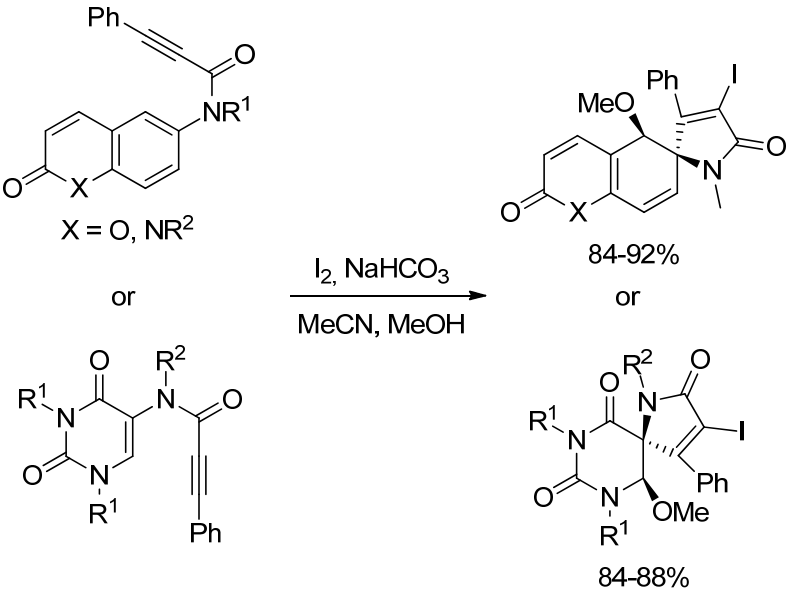
Scheme 5.41. 6-*endo*-*dig* cyclization of *N*-(2-alkynyl)anilines to obtain functionalized quinolines.

Later, Verma's group[91] carried out the preparation of 5-iodopyrrolo[1,2-*α*]quinolines and indolo[1,2-*α*]quinolines via regioselective 6-*endo-dig* cyclization reactions mediated by iodine in the presence of $NaHCO_3$. This transformation allowed the accommodation of various functional groups in the quinoline nucleus with moderate to excellent yields.



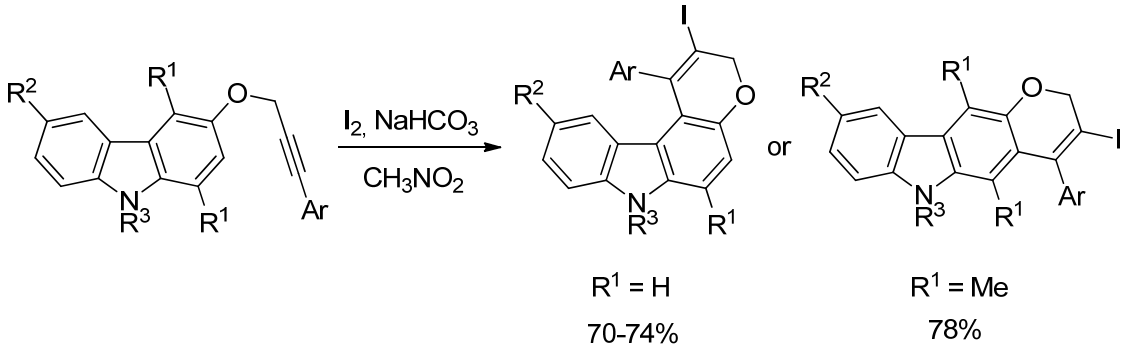
Scheme 5.42. 6-*endo-dig* cyclization of indolo[1,2-*α*]quinolines.

More complex cyclic structures have also been achieved by electrophilic cyclizations. For example, the formation of heterocycle-tethered spiro compounds has been fulfilled by the iodine-mediated ipso-cyclization reaction of *N*-alkyl-*N*-aryl phenylpropiolamides via a 5-*endo-dig* mode (Scheme 5.43).[92] This approach allowed the synthesis of azaspiro compounds tethered with coumarin, quinolone and pyrimidine heterocyclic motifs in excellent yields (84-92%).



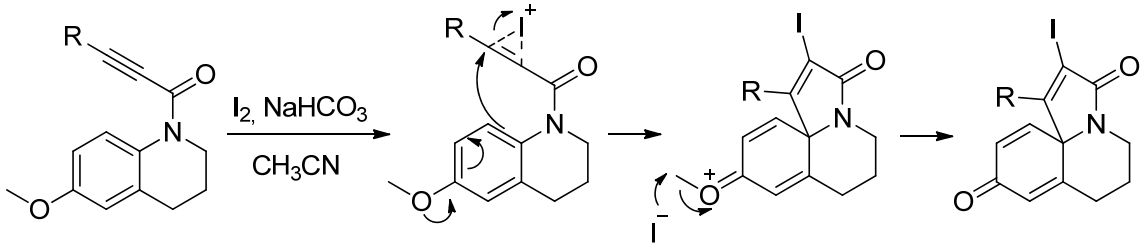
Scheme 5.43. Synthesis of azaspiro compounds by 5-*endo-dig* cyclization reactions.

In 2012, Nagarajan and co-workers[93] described the synthesis of pyranocarbazole derivatives from *O*-propargylated carbazoles by an iodocyclization reaction (Scheme 5.44). Although the reaction proceeded through a 6-*endo*-*dig* pathway, the utilization of 9-ethyl-1,4-dimethyl-3-(3-(4-*p*-tolyl-prop-2-ynyloxy)-9*H*-carbazole exclusively led to the competing 5-*exo*-*dig* cyclization product, giving access to furocarbazole derivatives.



Scheme 5.44. Synthesis of pyranocarbazole derivatives by 6-*endo*-*dig* cyclizations.

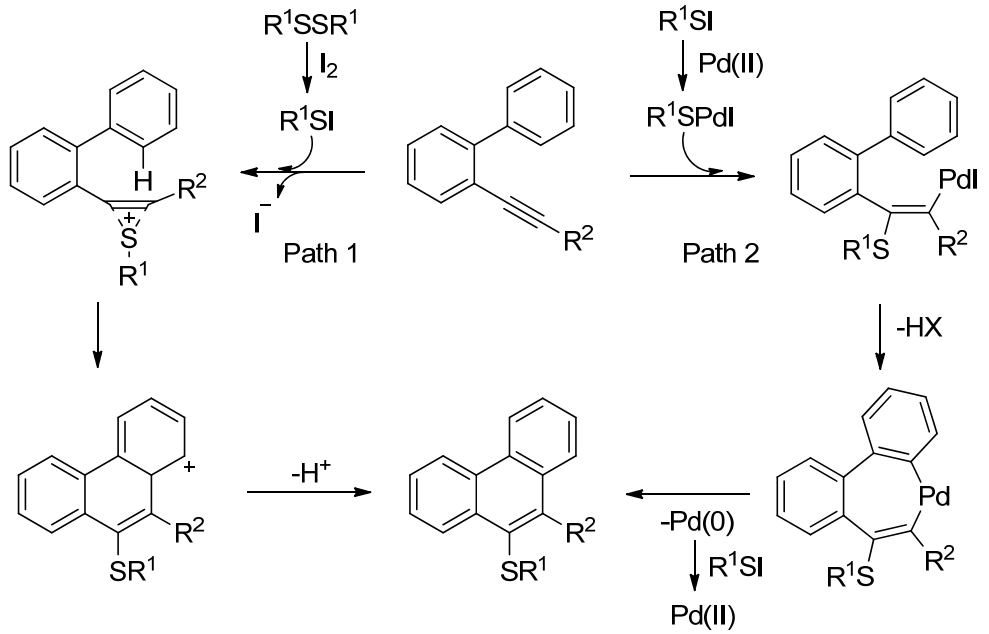
More recently, Kesharwani's group[94] has accomplished the synthesis of pyrrolo-[2,1-*j*]quinolone derivatives from *N*-(alkynoyl)-6-methoxytetrahydroquinoline in good yields. The reaction occurred via a 5-*endo*-*dig* mechanism as depicted in Scheme 5.45. Iodine was successfully employed as electrophilic source, whereas NIS poorly yielded the desired products. The cyclization with Br_2 and NBS failed for unknown reasons.



Scheme 5.45. Mechanism for the 5-*endo*-*dig* iodocyclization of *N*-(alkynoyl)-6-methoxytetrahydroquinoline.

Not only heterocyclic compounds have been synthesized by electrophilic cyclization reactions using arenes as nucleophiles, but also carbocycles have been successfully formed using this type of nucleophile, as reported by Zhang and co-workers.[95] They have described the palladium-catalyzed iodine-mediated 6-*endo*-*dig*

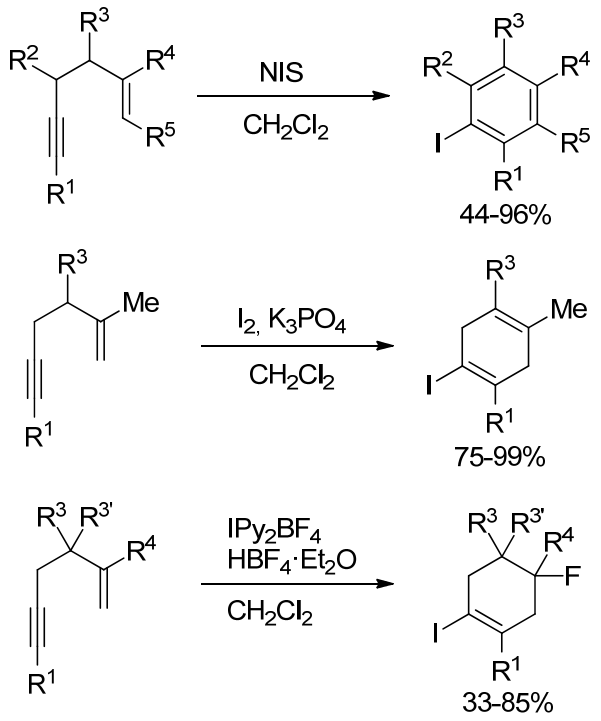
cyclization of 2-(1-alkynyl)biphenyls using disulfides as electrophiles. Iodine could promote the formation of 9-sulfenyl phenanthrenes without $PdCl_2$. However, only when both species were employed high yields were afforded. The authors enclosed a plausible mechanism explaining this evidence (Scheme 5.46).



Scheme 5.46. Two plausible pathways for the 6-*endo-dig* cyclization of 2-(1-alkynyl)biphenyls.

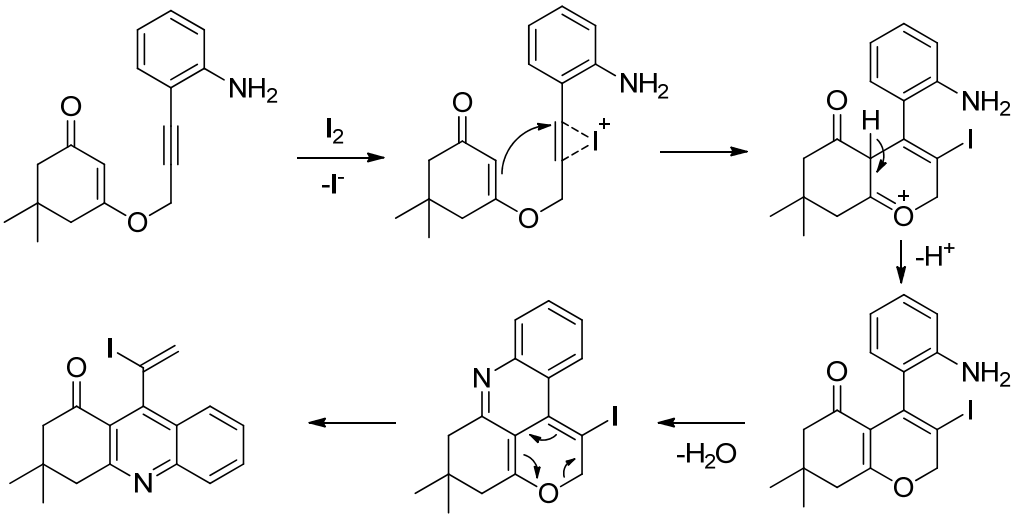
The utilization of olefins as internal carbon nucleophiles in halogen- and chalcogen-mediated cyclization reactions is also a powerful tool in the synthesis of functionalized carbocycles. Nevertheless, this approach is not broadly developed.

In 2010, Kirsch's group[96] performed the iodocyclization of 1,5-enynes to provide six-membered cyclic products such as benzenes, 1,4-cyclohexadienes and 4-fluorocyclohexenes using NIS, I_2 and IPy_2BF_4, respectively (Scheme 5.47). The procedure tolerates diverse functional groups. However, the introduction of a tethered carboxylic acid in the enyne structure leads to the iodolactonization product.



Scheme 5.47. Iodocyclization of 1,5-enynes using different iodonium sources.

Perumal's group[97] has achieved the synthesis of 9-(1-iodovinyl) acridin-1(2*H*)-one by a cascade transformation of 2-aminophenyl propynyl oxyenone. The reaction involves a 6-*endo*-*dig* iodocyclization and intramolecular condensation followed by 3,3-sigmatropic rearrangement to give the final products in good yields (50-68%) (Scheme 5.48). Iodine is employed as iodonium source. Br_2, NBS or $PhI(OAc)_2$ resulted ineffective.



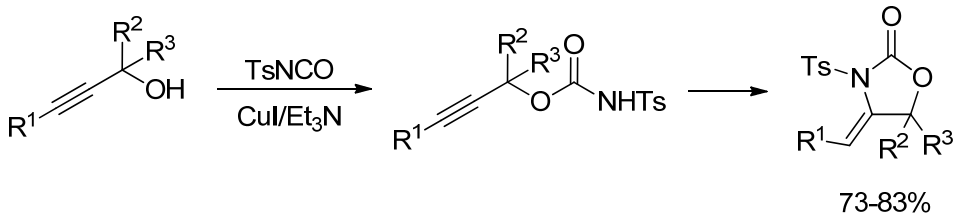
Scheme 5.48. Mechanism for the synthesis of 9-(1-iodovinyl) acridin-1(2*H*)-one from 2-aminophenyl propynyl oxyenone.

5.1.2. Synthesis of cyclic carbamates by electrophilic cyclization of alkynes

Carbamates represent an important class of compounds with interesting properties and have found wide utility in several areas, such as pharmaceuticals or agrochemicals.[98] Cyclic carbamates, although less known, have been used as chiral auxiliaries[99] and besides present interesting biological activity.[100] There are a variety of methods for the synthesis of this kind of compounds from different starting materials, such as alkenyl amides and carbamates, amino alcohol derivatives or aziridines.[101-105] However the development of practical and efficient approaches for the preparation of these cyclic carbamates, especially those densely functionalized, is still of great interest.

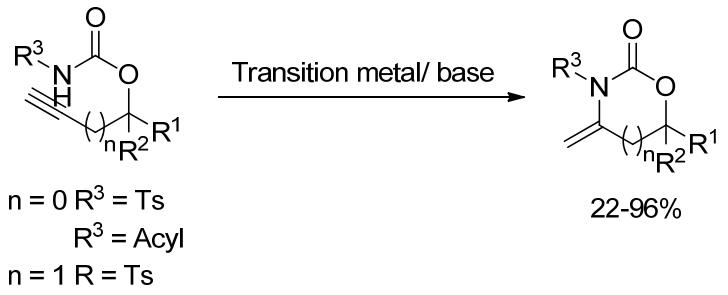
Carbamates containing an alkynyl group in an appropriate position may also undergo an electrophilic cyclization leading to cyclic carbamates. This strategy leads to 5-membered cyclic carbamates, known as oxazolidinones, or 6-membered cyclic carbamates, known as oxazinones depending on the regioselectivity of the reaction. In spite of the apparent easiness and advantages of this approach, it has been rarely pursued.

In 1991, Murai's group[106] described the 5-*exo*-*dig* regioselective synthesis of 4-alkylideneoxazolidinones having an *N*-tosyl group in good yields starting from propargylic alcohol and *p*-toluenesulfonyl isocyanate in the presence of CuI and Et_3N (Scheme 5.49). In the absence of CuI as catalyst, only simple addition reaction to give an acyclic carbamate was observed. 3-substituted propargyl alcohol derivatives (R^1 = Me) required higher temperatures to afford the cyclic carbamates.



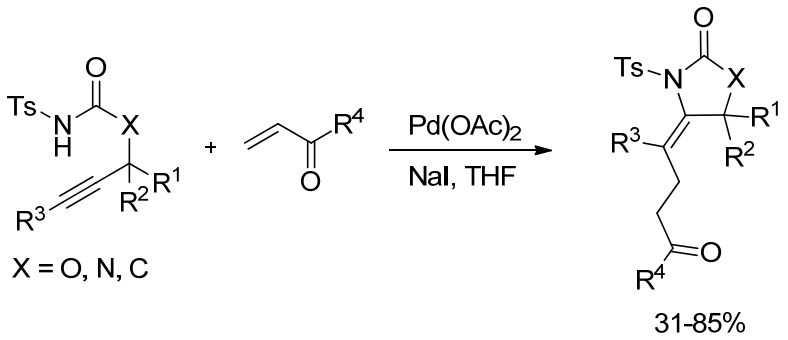
Scheme 5.49. Synthesis of 4-alkylideneoxazolidinones by 5-*exo*-*dig* cyclization.

Tamaru and co-workers[107,108] have reported the 5-*exo*-*dig* cyclization of 2-propynyl tosylcarbamates catalyzed by CuCl/Et_3N or AgNCO/Et_3N to furnish 4-methylene-2-oxazolidinones in good yields (Scheme 5.49). When they performed the cyclization of the *N*-acyl derivatives, AgNCO and ^{t}BuOK were most effective as catalysts. On the other hand, *N*-tosyl derivatives of 3-butynyl carbamates underwent a 6-*exo*-*dig* cyclization to give 4-methylenetetrahydro-1,3-oxazin-2-ones using AgNCO/Et_3N or AgNCO/^{t}BuOK as catalyst.



Scheme 5.50. Synthesis of cyclic carbamates by *exo-dig* cyclization approaches.

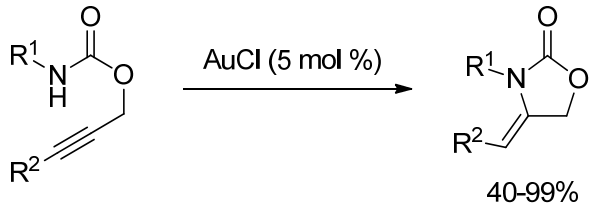
In 2000, Lu and Lei[109] developed the regioselective synthesis of oxazolidinones from *N*-tosyl carbamates and α,β-unsaturated carbonyl compounds catalyzed by $Pd(OAc)_2$ (Scheme 5.51). The reaction occured through a tandem intramolecular 5-*exo*-cyclization to afford an (*E*)-vinylpalladium intermediate (aminopalladation), followed by olefin insertion and protonolysis of the carbon-palladium bond. The procedure was extensive for the preparation of imidazolidinones and lactams.



Scheme 5.51. Regioselective synthesis of oxazolidinones, imidazolidinones and lactams.

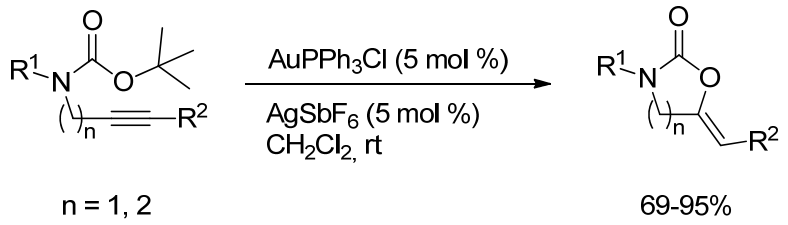
In 2006, Schmalz[110] accomplished the 5-*exo*-*dig* cyclization of *O*-propargyl carbamates to give differently substituted oxazolidinones in moderate to high yields

(Scheme 5.52). Alkyne was activated by Au(I) and the reaction proved to be effective in the presence of a base such as Et_3N or ^tBuOK.



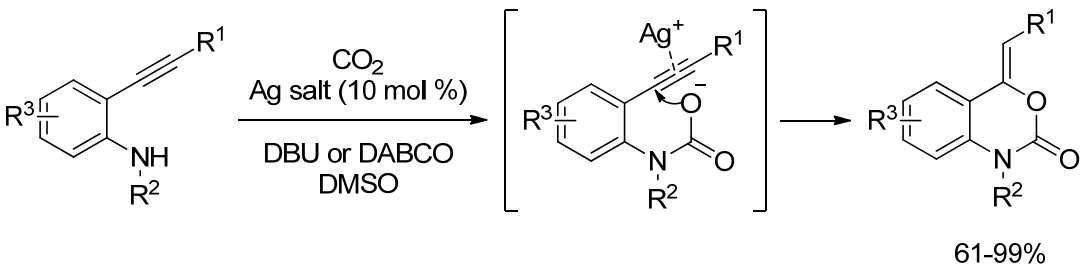
Scheme 5.52. Synthesis of oxazolidinones by 5-*exo*-*dig* cyclization of *O*-propargyl carbamates.

Concurrently, Carretero[111] accomplished the synthesis of alkylidene 2-oxazolidinones and 1,3-oxazin-2-ones by the Au(I)-catalyzed cyclization reaction of the *N*-Boc derivative of propargylamines and 3-butyn-1-amines, respectively. The reaction proceeded in a regioselective manner through a 5-*exo*-*dig* and 6-*exo*-*dig* pathway. This procedure provided the corresponding cyclic carbamates with good to high yields regardless the substitution at nitrogen and the alkyne moiety.



Scheme 5.53. Synthesis of oxazolidinone and oxazinone derivatives by 5-*exo*-*dig* and 6-*exo*-*dig* cyclizations, respectively.

Cyclic carbamates can also be synthesized by the incorporation of CO_2 to amines followed by a cyclization process as reported by Yamada and co-workers (Scheme 5.54).[112] They have recently prepared benzoxazine-2-one derivatives by the reaction of *o*-alkynylanilines with CO_2 catalyzed by silver salts in good to excellent yields. The cyclization occurred through a 6-*exo*-*dig* pathway and only *Z exo*-olefins were obtained.

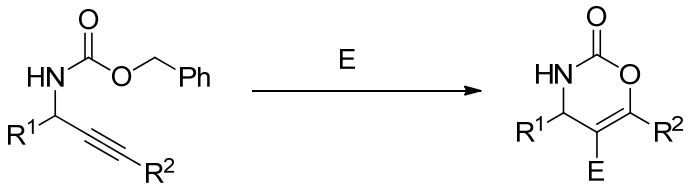


Scheme 5.54. Synthesis of benzoxazine-2-one derivatives by incorporation of CO_2 to *o*-alkynylanilines and 6-*exo*-*dig* cyclization reaction.

5.2. OBJECTIVES

On the basis of the early reported results on halo- and chalcoderivatives of heterocycles by electrophilic cyclization of alkynes conveniently functionalized, *N*-Cbz-protected propargylic amines must be suitable substrates for the synthesis of cyclic carbamates such as 1,3-oxazin-2-ones or oxazolidin-2-ones through an *O*-cyclization process.

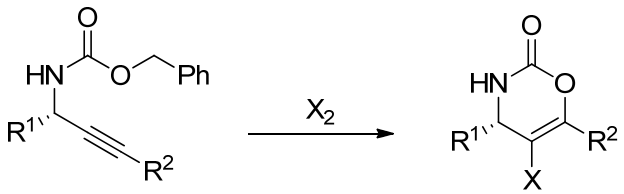
For this reason, the main objective of this chapter is to develop a convenient approach for the regioselective synthesis of highly functionalized 1,3-oxazin-2-ones by electrophilic cyclization of *N*-Cbz-protected propargylic amines.



The following aspects will be considered in this study:

Regioselective halogen-mediated cyclization of *N*-Cbz-protected propargylic amines. Synthesis of 5-halo-1,3-oxazin-2-ones.

1. Identification of the optimal reaction conditions: Influence of the solvent, base and temperature on the yield of the reaction.
2. Identification of the optimal reaction conditions: Influence of different protecting groups on the yield of the reaction.
3. Scope and limitations of the reaction: evaluation of *N*-Cbz-protected propargylic amines derived from aromatic and aliphatic aldehydes and alkynes in the cyclization with iodine, bromine and chlorine.



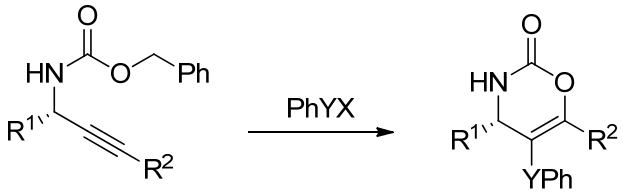
11

33, X = I
34, X = Br
35, X = Cl

4. Structure elucidation of the halocyclization products by means of X-ray diffraction analysis and ^{13}C NMR spectroscopic studies.
5. Computational study of the regioselective halocyclization of *N*-protected propargylic amines.

Regioselective chalcogen-mediated cyclization of *N*-Cbz-protected propargylic amines. Synthesis of 5-phenylchalco-1,3-oxazin-2-ones.

6. Identification of the optimal reaction conditions.
7. Scope and limitations of the reaction: evaluation of *N*-Cbz-protected propargylic amines derived from aromatic and aliphatic aldehydes and alkynes in the cyclization.



11

36, Y = Se
37, Y = S
38, Y = Te

8. Structure elucidation of the cyclization products by means of X-ray diffraction analysis and ^{13}C NMR spectroscopic studies.
9. Computational study of the regioselective cyclization of *N*-protected propargylic amines with phenylselenyl chloride.

5.3. RESULTS AND DISCUSSION

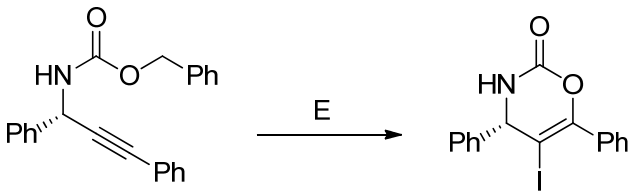
5.3.1. Regioselective halogen-mediated cyclization of *N*-Cbz-protected propargylic amines. Synthesis of 5-halo-1,3-oxazin-2-ones

5.3.1.1. Optimization of reaction conditions

The starting chiral *N*-Cbz-protected propargylic amines were readily available by the enantioselective alkynylation of imines generated *in situ* from α-amido sulfones as previously described in Chapter 3.

In order to determine the general conditions for the halocyclization reaction of *N*-Cbz propargylic amines **11**, *N*-Cbz-1,3-diphenylprop-2-yn-1-amine **11aa** was subjected to iodocyclization conditions in the presence of iodine as electrophilic source and $NaHCO_3$ in dichloromethane at rt, such as is described for the iodocyclization of several functionalized alkynes.[82,91]

Table 5.1. Screening of reaction conditions for the iodocyclization of *N*-Cbz-protected propargylic amines **11aa**.[a]



11aa **33aa**

Entry	E (Equiv)	Solvent	Base	T (°C)	t (h)	Yield (%)[b]
1	I_2 (2)	CH_2Cl_2	$NaHCO_3$	rt	12	67
2	I_2 (2)	CH_2Cl_2	NaOH	rt	24	/
3	I_2 (2)	CH_2Cl_2	$NaHCO_3$	0	16	75
4	I_2 (2)	CH_2Cl_2	-	0	15	74
5	I_2 (2)	CH_3CN	-	0	18	82
6	I_2 (1.5)	CH_3CN	-	0	20	71
7	NIS (2)	CH_3CN	-	0	10	n.d.[c]

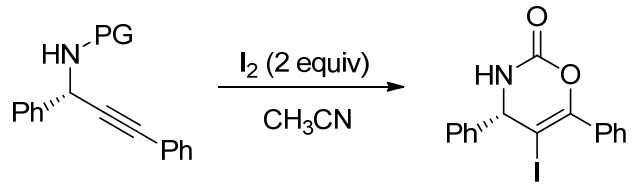
[a] **11aa** (0.1 mmol) in 2.5 mL of solvent. [b] Yield of isolated product. [c] Not determined.

In these conditions we obtained the corresponding iodinated 1,3-oxazin-2-one (**33aa**) as the only isolated product (67% yield) (Table 5.1, Entry 1). The use of NaOH failed to afford the cyclization product and the starting material was recovered. We then continued the optimization process with $NaHCO_3$ at 0 °C, obtaining the desired product with a better yield (75%). Interestingly, we found that the presence of a base was not required to afford the cyclization product in our reaction as it reached completion in 74% yield. With regard to the solvent, the utilization of acetonitrile instead of dichloromethane led to a higher yield (82%). We also studied the influence of the amount of the electrophilic source. It was observed that reducing the equivalents of iodine from 2 to 1.5 decreased the yield significantly. It is worth noting that *N*-iodosuccinimide as an iodonium source resulted inefficient in this reaction.

Thus, this brief optimization process revealed that the best result for the iodocyclization of *N*-Cbz-1,3-diphenylprop-2-yn-1-amine (**11aa**) was obtained with iodine (2 equiv) in acetonitrile at 0 °C and absence of $NaHCO_3$ (82% yield).

Finally, the influence of the protecting group was examined. *N*-Boc- and *N*-ethyloxycarbonyl-protected propargylic amines were submitted to the optimized conditions. However, not only did they require higher temperatures, but also longer reaction times, providing the cyclization products in moderate yields.

Table 5.2. Screening of protecting groups for the iodocyclization of *N*-protected-1,3-diphenylprop-2-yn-1-amines.[a]



11aa, PG = Cbz
12aa, PG = Boc
13aa, PG = COOEt

33aa

Entry	Amine	PG	T (°C)	t (h)	Yield (%)[b]
1	**11aa**	Cbz	0	18	82
2	**12aa**	Boc	rt	96	56
3	**13aa**	COOEt	rt	96	49

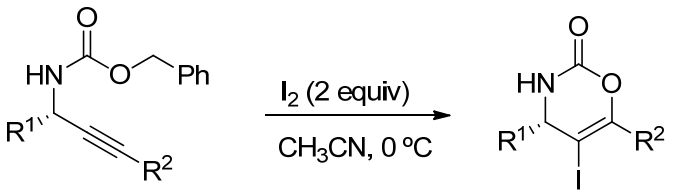
[a] 0.1 mmol of starting material in 2.5 mL of acetonitrile. [b] Yield of isolated product.

5.3.1.2. Scope and limitations of the reaction

Iodocyclization reaction of *N*-Cbz-protected propargylic amines

The optimized conditions were applied to the iodocyclization of several *N*-Cbz-protected propargylic amines **11** derived from the addition of phenylacetylene to imines of substituted benzaldehydes giving the corresponding 5-iodo-1,3-oxazin-2-ones **33** in good to excellent results (Table 5.3, Entries 1–4).

Table 5.3. Electrophilic cyclization of *N*-Cbz-protected propargylic amines **11** to 5-iodo-1,3-oxazin-2-ones **33**.[a]



11 **33**

Entry	11	R^1	R^2	t (h)	Product	Yield (%)[b]
1	**11aa**	Ph	Ph	18	**33aa**	82
2	**11ba**	4-MeC_6H_4	Ph	24	**33ba**	94
3	**11ea**	4-ClC_6H_4	Ph	30	**33ea**	76
4	**11ha**	2-MeC_6H_4	Ph	24	**33ha**	94
5	**11qa**	$C_6H_5CH_2CH_2$	Ph	20	**33qa**	70
6	**11ra**	*n*-butyl	Ph	4	**33ra**	45
7	**11sa**	cyclohexyl	Ph	4	**33sa**	94
8	**11ab**	Ph	4-$MeOC_6H_4$	2	**33ab**	91
9	**11ad**	Ph	4-FC_6H_4	18	**33ad**	98
10	**11af**	Ph	2-$MeOC_6H_4$	1	**33af**	93
11	**11ag**	Ph	3,5-$(MeO)_2C_6H_3$	52	**33ag**	97
12	**11ai**	Ph	2-thienyl	1	**33ai**	98
13	**11ak**	Ph	$C_6H_5CH_2CH_2$	30	**33ak**	97
14	**11am**	Ph	*tert*-butyl	24	**33am**	65

[a] **11** (0.1 mmol), iodine (0.2 mmol) in 2.5 mL of acetonitrile. [b] Yield of isolated product.

Both electron-donating (Me) and electron-withdrawing (Cl) substituents in *ortho* and *para* positions were well tolerated, with yields ranging from 76 to 94% (Table 5.3, Entries 2-4). On the other hand, the iodocyclization of *N*-Cbz-protected propargylic amines **11** derived from alkyl-substituted imines gave the corresponding products in variable yields (Table 5.3, entries 5-7). Whereas the cyclohexyl-substituted starting material **11sa** afforded the iodocyclization product **33sa** with excellent yield (Table 5.3, Entry 7), 2-phenylethyl-substituted **11qa** and the *n*-butyl-substituted **11ra** gave moderate yields (70 and 45%, respectively) (Table 5.3, Entries 5-6).

Then we examined the reactivity of various Cbz-protected propargylic amines **11** bearing different aromatic, heteroaromatic and aliphatic groups attached to the alkyne moiety, affording the corresponding products **33** in excellent yields in most cases (Table 5.3, Entries 8-14). The reaction is not sensitive to electronic and steric effects of the substituents in the aromatic ring tethered to the alkyne, as observed in Entries 8-11. In addition, heteroaromatic substituent 2-thienyl gave excellent yields (Table 5.3, Entry 12). The *N*-Cbz-protected propargylic amine derived from the aliphatic alkyne 4-phenyl-1-butyne furnished the corresponding 5-iodo-1,3-oxazin-2-one **33ak** in excellent yield (97%) (Table 5.3, Entry 13), whereas the propargylic amine bearing a *tert*-butyl group attached to the alkyne gave the desired product **33am** in a moderate yield (65%) (Table 5.3, Entry 14).

In order to establish the structure of the cyclization reaction products, **33af** and **33ai** were submitted to an X-ray diffraction analysis (Figure 5.2). They allowed us to establish the structure of 1,3-oxazin-2-one (6-membered ring) instead of 1,3-oxazolidinone (5-membered ring) and to confirm the absolute configuration of the stereogenic center of both products.

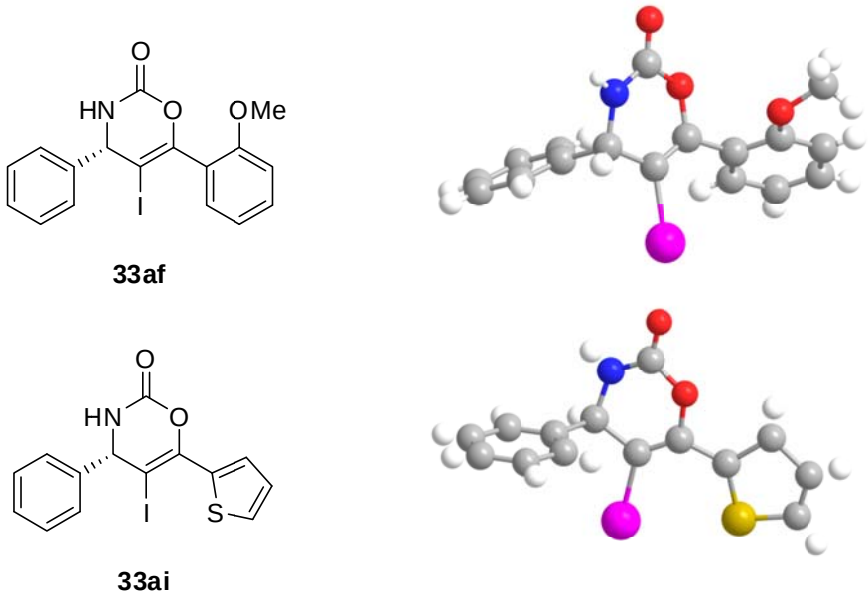
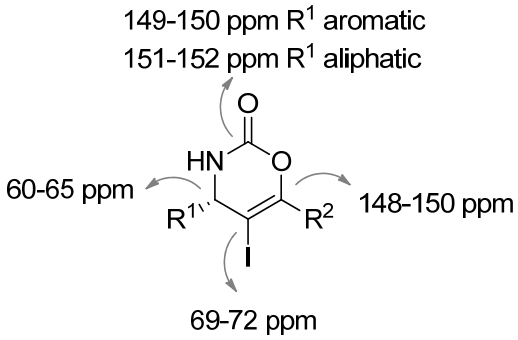


Figure 5.2. a) X-ray structure of **33af**. b) X-ray structure of **33ai**.

Moreover, to ensure that all the iodocyclization reactions proceeded via a 6-*endo-dig* cyclization pathway, we carried out a comparative NMR spectroscopy analysis of the characteristic signals of the obtained 5-iodo-1,3-oxazin-2-ones **33**. In particular, we compared the ^{13}C NMR signals of the four carbon atoms in the 6-membered-ring containing the cyclic carbamate (Table 5.4).

So, the carbonyl group resonates at δ 149-150 ppm (when R^1 is aromatic) and δ 151-152 ppm (when R^1 is aliphatic); the quaternary olefinic =C-O gives a signal at δ 148-150 ppm; the quaternary olefinic I-C= appears at high field at δ 69-72 ppm and the CH appears at δ 60-65 ppm. This concordance in the signals was an evidence of the formation of 6-membered ring 5-iodo-1,3-oxazin-2-ones by a 6-*endo-dig* cyclization mechanism in all cases.

Table 5.4. ^{13}C NMR signals of the four carbon atoms in the 6-membered-ring containing the cyclic carbamate.



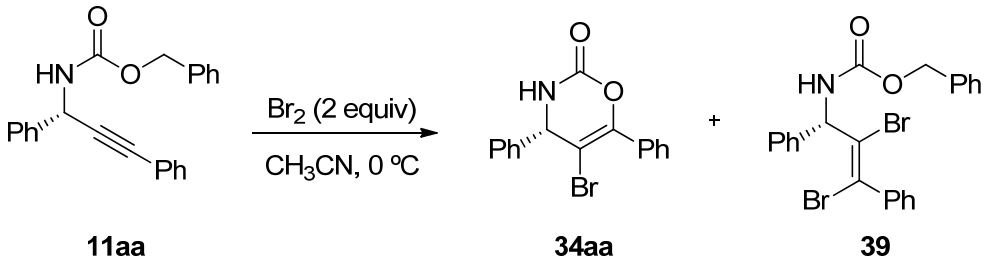
				δ (ppm)			
Entry	**33**	**R^1**	**R^2**	**C=O**	**=C-O**	**I-C=**	**CH**
1	**33aa**	Ph	Ph	149.56	149.02	71.33	65.05
2	**33ba**	4-MeC_6H_4	Ph	149.43	148.89	71.72	64.85
3	**33ea**	4-ClC_6H_4	Ph	149.60	149.20	70.70	64.50
4	**33ha**	2-MeC_6H_4	Ph	149.34	149.16	71.10	61.59
5	**33qa**	$C_6H_5CH_2CH_2$	Ph	151.52	150.05	70.31	65.14
6	**33ra**	*n*-butyl	Ph	151.72	149.76	71.75	60.78
7	**33sa**	cyclohexyl	Ph	150.92	149.75	70.81	59.91
8	**33ab**	Ph	4-$MeOC_6H_4$	149.61	148.79	70.35	65.12
9	**33ad**	Ph	4-FC_6H_4	149.29	148.13	71.58	65.08
10	**33af**	Ph	2-$MeOC_6H_4$	149.61	148.08	74.40	64.54
11	**33ag**	Ph	3,5-$(MeO)_2C_6H_3$	149.30	148.83	71.34	65.13
12	**33ai**	Ph	2-thienyl	149.03	143.85	69.63	65.67
13	**33ak**	Ph	$C_6H_5CH_2CH_2$	149.16	150.16	71.75	64.00
14	**33am**	Ph	*tert*-butyl	149.66	155.33	-[a]	66.00

[a] Not observed.

Bromocyclization reaction of *N*-Cbz-protected propargylic amines

Once we had studied the scope of the cyclization of *N*-Cbz-protected propargylic amines **11** with iodine as electrophilic source, we broadened our investigation to the use of bromine.

When we applied the optimized conditions for the iodocyclization to the reaction between *N*-Cbz-1,3-diphenylprop-2-yn-1-amine (**11aa**) and bromine in acetonitrile at 0 °C, a shorter reaction time was required, but besides to 3,4-dihydro-5-bromo-1,3-oxazin-2-one **34aa** corresponding to the cyclization process, a second product **39** was observed, probably resulting from a simple addition of bromine to the triple bond (Scheme 5.55). However, to our delight, in the presence of only 1.2 equivalents of bromine (instead of 2 equiv) and using a more diluted reaction mixture (1/5) this secondary addition reaction was completely avoided and the bromocyclization product **34aa** was obtained with good yield (93%) (Table 5.5, Entry 1).



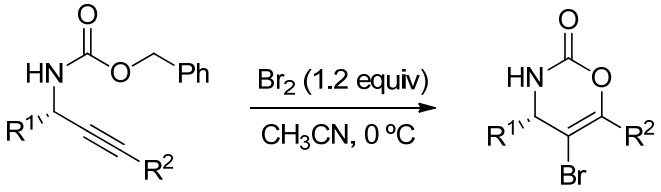
11aa **34aa** **39**

Scheme 5.55. Reaction between *N*-Cbz-1,3-diphenylprop-2-yn-1-amine (**11aa**) and Br_2 under the optimized conditions for the iodocyclization reaction.

The reaction scope was then explored under the new optimized conditions for the bromocyclization. The reaction has proved to be a general route to a variety of 3,4-dihydro-5-bromo-1,3-oxazin-2-ones **34** (Table 5.5, Entries 2-8). Both electron-donating (Me) and electron-withdrawing (Cl) substituents in *ortho* and *para* positions of the aromatic ring of the benzaldehyde delivered the cyclization products in high yields (79-82%) (Table 5.5, Entries 2-4). Cyclohexyl-substituted propargylic amine **11sa** gave the corresponding 5-bromo-1,3-oxazin-2-one **34sa** in excellent yield (91%) (Table 5.5, Entry 5). Finally, the utilization of starting materials with aromatic as well as aliphatic groups

attached to the alkyne provided the cyclization products in high yields (Table 5.5, Entries 6-8).

Table 5.5. Electrophilic cyclization of *N*-Cbz-protected propargylic amines **11** to 5-bromo-1,3-oxazin-2-ones **34**.[a]



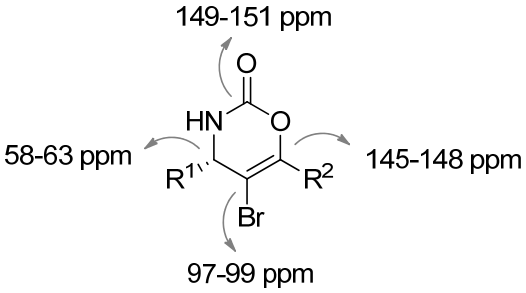
11 **34**

Entry	11	R^1	R^2	t (h)	Product	Yield (%)[b]
1[c]	**11aa**	Ph	Ph	0.3	**34aa**	72
2	**11aa**	Ph	Ph	0.5	**34aa**	93
3	**11ea**	4-ClC_6H_4	Ph	0.3	**34ea**	82
4	**11ha**	2-MeC_6H_4	Ph	0.5	**34ha**	79
5	**11sa**	cyclohexyl	Ph	1	**34sa**	91
6	**11ad**	Ph	4-FC_6H_4	0.5	**34ad**	80
7	**11ae**	Ph	4-ClC_6H_4	0.5	**34ae**	86
8	**11ak**	Ph	$C_6H_5CH_2CH_2$	1	**34ak**	80

[a] **11** (0.1 mmol), bromine (0.12 mmol) in 12.5 mL of acetonitrile. [b] Yield of isolated product. [c] 2.5 mL instead of 12.5 mL of acetonitrile.

The structural characterization of products **34** was carried out by spectroscopic methods. As in the iodinated products, the four carbon atoms in the brominated 6-membered-ring containing cyclic carbamate give characteristic signals (Table 5.6). The carbonyl group resonates at δ 149-151 ppm; the quaternary olefinic =C-O gives a signal at δ 145-148 ppm; the quaternary olefinic Br-C= appears at δ 97-99 and the CH appears at δ 58-63 ppm.

Table 5.6. ^{13}C NMR signals of the four carbon atoms in the 6-membered-ring containing the cyclic carbamate.



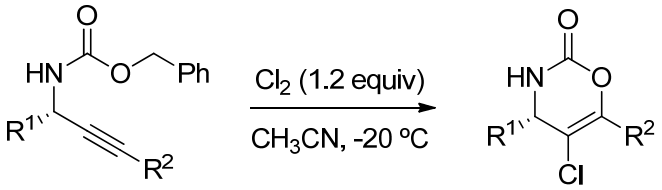
				δ (ppm)			
Entry	**34**	**R^1**	**R^2**	**C=O**	**=C-O**	**I-C=**	**CH**
1	**34aa**	Ph	Ph	149.29	146.18	98.30	62.27
2	**34ea**	4-ClC_6H_4	Ph	149.30	146.46	97.81	61.60
3	**34ha**	2-MeC_6H_4	Ph	149.20	146.42	98.16	58.87
4	**34sa**	Cyclohexyl	Ph	151.04	147.16	97.74	62.68
5	**34ad**	Ph	4-FC_6H_4	149.16	145.32	98.42	62.25
6	**34ae**	Ph	4-ClC_6H_4	149.25	145.12	98.84	62.22
7	**34ak**	Ph	$C_6H_5CH_2CH_2$	149.47	148.33	98.72	61.77

Chlorocyclization reaction of *N*-Cbz-protected propargylic amines

Finally, the chlorocyclization reaction of several *N*-Cbz-protected propargylic amines **11** was carried out with chlorine in acetonitrile (Table 5.7). Due to the formation of the dichlorinated product at 0 °C, the reaction was performed at -20 °C. Under these new conditions, the yield of the competing product was significantly

reduced and the chlorocyclization products **35** were obtained with moderate yields (50-60%), regardless the electronic nature of the substituents.

Table 5.7. Chlorocyclization of *N*-Cbz-protected propargylic amines **11** to 5-chloro-1,3-oxazin-2-ones **35**.[a]



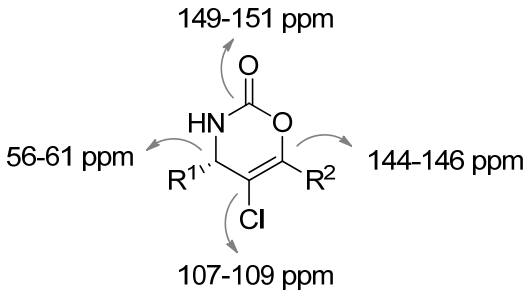
11 **35**

Entry	11	R^1	R^2	t (h)	Product	Yield (%)[b]
1	**11aa**	Ph	Ph	0.15	**35aa**	62
2	**11ba**	4-MeC_6H_4	Ph	0.15	**35ba**	50
3	**11qa**	$C_6H_5CH_2CH_2$	Ph	0.15	**35qa**	61
4	**11ab**	Ph	4-MeOC_6H_4	0.15	**35ab**	59

[a] **11** (0.1 mmol) and chlorine (0.12 mmol) 12.5 mL of acetonitrile. [b] Yield of isolated product.

The structural characterization of products **35** was also carried out by spectroscopic methods. As in the iodinated and brominated analogues, the four carbon atoms in the chlorinated 6-membered-ring containing cyclic carbamate give characteristic signals. The carbonyl group resonates at δ 149-151 ppm; the quaternary olefinic =C-O gives a signal at δ 144-146 ppm; the quaternary olefinic Cl-C= appears at δ 107-109 and the CH resonates at δ 56-61 ppm.

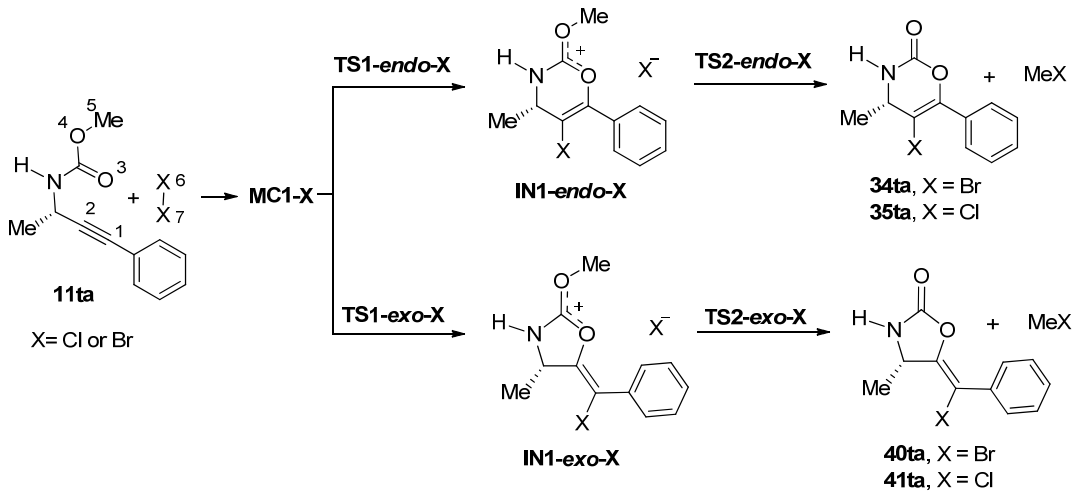
Table 5.8. ^{13}C NMR signals of the four carbon atoms in the 6-membered-ring containing the cyclic carbamate.



				δ (ppm)			
Entry	**35**	**R^1**	**R^2**	**C=O**	**=C-O**	**I-C=**	**CH**
1	**35aa**	Ph	Ph	149.01	144.85	108.90	60.39
2	**35ba**	4-MeC_6H_4	Ph	149.02	144.62	109.12	60.73
3	**35qa**	$C_6H_5CH_2CH_2$	Ph	150.45	145.38	108.87	56.00
4	**35ab**	Ph	4-MeOC_6H_4	149.34	144.53	107.65	60.90

5.3.1.3. Theoretical calculations of the bromo- and chlorocyclization reactions of protected propargylic amines

In order to understand the mechanism of the regioselective halocyclization reactions of protected propargylic amines **11** to yield the corresponding 6-membered 5-halo-1,3-oxazin-2-ones **33**-**35**, a computational study using density functional theory (DFT) methods at the B3LYP/6-311G* level was carried out (Scheme 5.56). In this theoretical study, the R^1 group and the benzyl one present in *N*-Cbz-protected propargylic amines **11** were modelled by methyl groups.



Scheme 5.56. Two possible regioisomeric channels, 6-*endo-dig* and 5-*exo-dig* pathway, for the halocyclization of **11ta** to afford 1,3-oxazin-2-ones **34**-**35** or 1,3-oxazolidin-2-ones **40**-**41**.

Starting from the protected propargylic amine **11ta**, an analysis of the potential energy surface for the title reactions indicates that these halogen promoted cyclization reactions take place through a two-step mechanism which can undergo via a 6-*endo-dig* or 5-*exo-dig* pathway. In the first step, the halogen molecule X_2 electrophilically attacks on the C1 or C2 carbon of the triple bond of these propargylic amines to give the cationic intermediates **IN1-*endo*-X** or **IN1-*exo*-X**, via the corresponding transition states **TS1-*endo*-X** or **TS1-*exo*-X**, respectively. In the second step, the methyl group present in the carbamate substituent is eliminated in these cationic intermediates assisted by the halide anion X^- yielding the final 1,3-oxazin-2-ones **34**-**35** or oxazolidin-2-ones **40**-**41** (Scheme 5.56).

For the reaction in the presence of bromine Br_2 the two regioisomeric channels were studied, while for the reaction in the presence of chlorine Cl_2 only the most favourable channel, 6-*endo-dig* pathway, yielding 6-membered 1,3-oxazin-2-one **35ta** was considered.

Relative energies in gas phase as well as in acetonitrile were calculated for each species. However, since some species involved in the reactions are charged, the energy discussion will be done using the relative energies in acetonitrile (Table 5.9).

Table 5.9. Relative energies in acetonitrile (in kcal/mol, relative to **11ta** plus halogen X_2) of the stationary points involved in the halocyclizations of **11ta**.

Bromocyclization of 11ta		**Chlorocyclization of 11ta**	
MC1-Br	-1.0	**MC1-Cl**	-1.2
TS1-*endo*-Br	0.5	**TS1-*endo*-Cl**	-12.8
TS1-*exo*-Br	8.4		
IN1-*endo*-Br	-20.0	**IN1-*endo*-Cl**	-41.3
IN1-*exo*-Br	-19.4		
TS2-*endo*-Br	-7.3	**TS2-*endo*-Cl**	-29.1
TS2-*exo*-Br	-8.5		
34ta + MeBr	-28.6	**35ta + MeCl**	-51.4
40ta + MeBr	-31.8		

Cyclization of 11ta in the presence of bromine

In an earlier step of the reaction, Br_2 forms a weak molecular complex (MC) with the π system of the triple bond of propargylic amine **11ta** (Figure 5.3). This MC is located -1.0 kcal/mol (**MC1-Br**) below the separated reagents. The activation energies associated with the electrophilic attacks of Br_2 on the C2 and C1 carbons of propargylic amine **11ta** are 0.5 (**TS1-*endo*-Br**) and 8.4 kcal/mol (**TS1-*exo*-Br**). Formation of the corresponding cationic intermediates are exothermic by -20.0 (**IN1-*endo*-Br**) and -19.4 kcal/mol (**IN1-*exo*-Br**). Elimination of the methyl group from these cationic intermediates takes place through a bimolecular nucleophilic substitution in the methyl group assisted by the bromide anion Br^- generated in the first step of the reaction. From the corresponding intermediates, the activation energies associated with the extrusion of the methyl group are 12.7 (**TS2-*endo*-Br**) and 10.9 kcal/mol (**TS2-*exo*-Br**). Formation of **34ta** and **40ta** plus MeBr is exothermic by -28.6 and -31.8 kcal/mol, respectively.

From these energy results some relevant conclusions can be drawn:

1. The electrophilic attack of bromine on the triple bond of propargylic amine **11ta** is completely regioselective, **TS1-*endo*-Br** being 7.9 kcal/mol lower in energy than **TS1-*exo*-Br**.
2. The high exothermic character of the first step makes this step irreversible.
3. The activation energy associated with the second step is higher than that associated with first step; thus, the elimination of the methyl substituent is the rate-determining step (RDS) of the reaction. Consequently, while the electrophilic attack of bromine against propargylic amine **11ta** is the regioselectivity determining step, the methyl elimination is the RDS of the reaction.

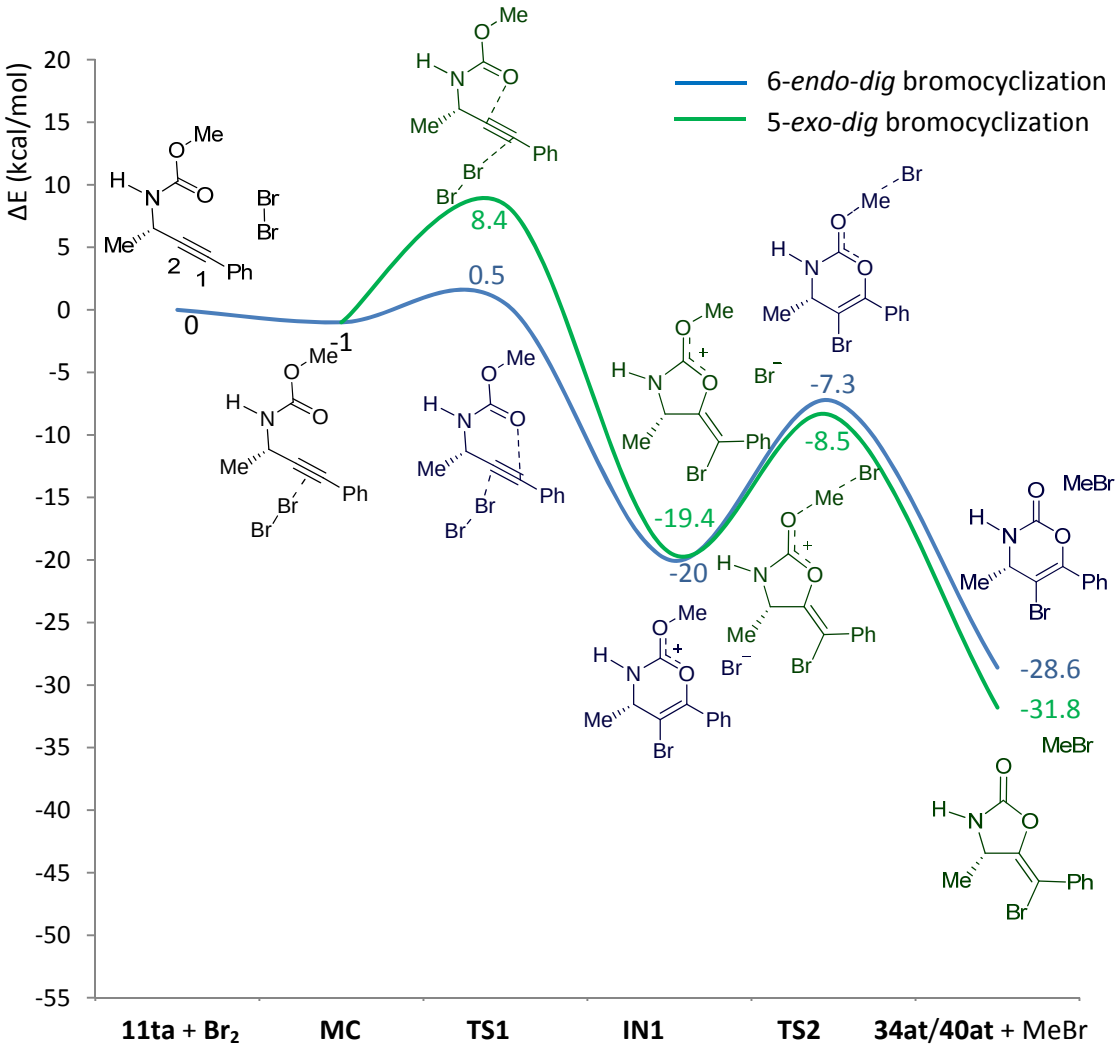
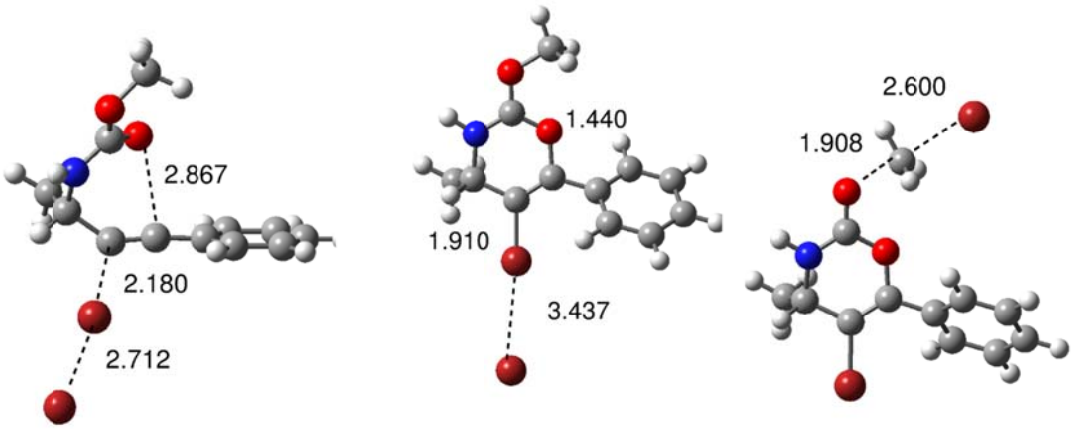


Figure 5.3. Relative energies in acetonitrile (in kcal/mol, relative to **11ta** plus halogen Br_2) of the stationary points involved in the bromocyclization of **11ta**.

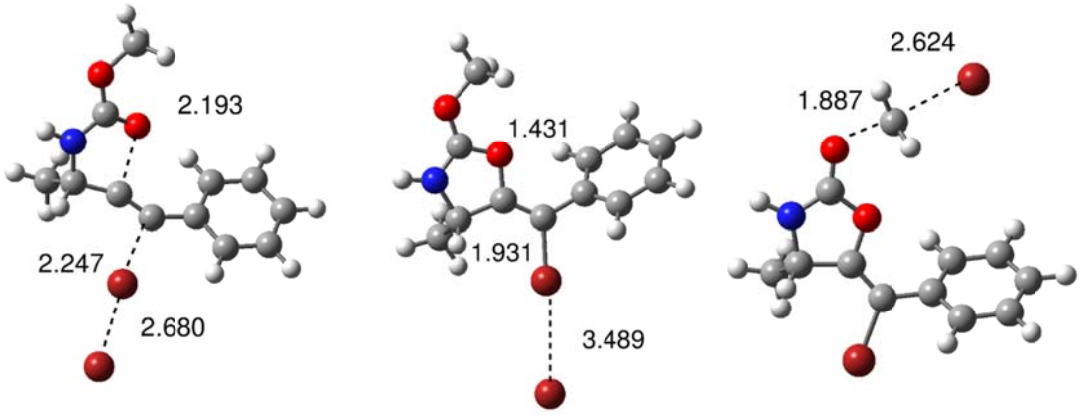
The geometries of the TSs and INs involved in the regioisomeric pathways associated with the bromocyclization of phenyl propargylic amine **11ta** are given in Figure 5.4.

a)



TS1-*endo*-Br **IN1-*endo*-Br** **TS2-*endo*-Br**

b)



TS1-*exo*-Br **IN1-*exo*-Br** **TS2-*exo*-Br**

Figure 5.4. Geometries of the TSs and INs involved in the regioisomeric channels associated with the bromine-mediated cyclization of protected propargylic amine **11ta**. The lengths of the forming and breaking bonds are given in Angstroms.

At the TSs associated with the first step of the bromocyclization process the lengths of the Br6-C2(1) and O3-C1(2) forming bonds are 2.180 Å and 2.867 Å respectively at **TS1-*endo*-Br** and 2.247 Å and 2.193 Å respectively at **TS1-*exo*-Br**. At the

corresponding intermediates **IN1-*endo*-Br** and **IN1-*exo*-Br** the lengths of the Br6-C2(1) and O3-C1(2) bonds are 1.910 Å and 1.440 Å, and 1.931 and 1.431 Å, respectively. These geometrical parameters indicate that at the most favourable **TS1-*endo*-Br**, the Br6-C2 bond formation is very advanced, while the O3-C1 bond formation is rather delayed. At the most unfavourable **TS1-*exo*-Br**, the O3-C2 bond formation is more advanced than the O3-C1 bond at **TS1-*endo*-Br**, showing a more synchronous bond-formation process. In gas phase the lengths of Br6-C2(1) and O3-C1(2) forming bonds are 2.156 and 1.806 Å at **TS1-*endo*-Br** and 2.214 Å and 1.760 at **TS1-*exo*-Br**, indicating that both bond-formation processes are coupled. Consequently, polar solvent effects change the mechanism of the first step of the most favourable reactive channel from a synchronous Br6-C2 and O3-C1 bond formation in gas phase to a highly asynchronous process in acetonitrile. This change of mechanism can be understood as a strong stabilization of both bromine anion Br^- and the incipient benzyl carbocationic C1 centre at **TS1-*endo*-Br** in polar solvent acetonitrile.

At the TSs associated with the elimination of the methyl group in **IN1-*endo*-Br** and **IN1-*exo*-Br**, the lengths of the O4-C5 breaking bond and the C5-Br7 forming bond are 1.908 Å and 2.600 Å respectively at **TS2-*endo*-Br** and 1.887 and 2.624 at **TS2-*exo*-Br**, respectively. In these asynchronous TSs, the O4-C5 breaking bonds are more advanced than the C5-Br7 forming bond.

Cyclization of 11ta in the presence of chlorine

For the reaction of **11ta** in presence of chlorine, Cl_2 forms a weak molecular complex (MC) with the π system of the triple bond of propargylic amine **11ta**. This MC is located -1.2 kcal/mol (**MC1-Cl**) below the separated reagents. **TS1-*endo*-Cl** associated with the electrophilic attack of Cl_2 on the C2 carbon of propargylic amine **11ta** is located -12.8 kcal/mol below the separated reagents. Formation of the 1,3-oxazin intermediate **IN1-*endo*-Cl** is strongly exothermic by -41.3 kcal/mol. The activation energy associated with the elimination of the methyl group in intermediate **IN1-*endo*-Cl** via **TS2-*endo*-Cl** is 12.2 kcal/mol, the overall process is exothermic by -51.4 kcal/mol. The fact that **TS1-*endo*-Cl** is located below the separated reagents is a consequence of the strong solvation of chloride anion Cl^-, which develops along the

electrophilic attack. It is worth noting that in gas phase **TS1-*endo*-Cl** is located 9.5 kcal/mol above the reagents. A comparison of relative energies of the TSs associated with the electrophilic attacks of halogens Br_2 or Cl_2 on propargylic amine **11ta**, in gas phase and in acetonitrile, indicates that the addition of Cl_2 to these propargylic amines is favoured over the addition of Br_2.

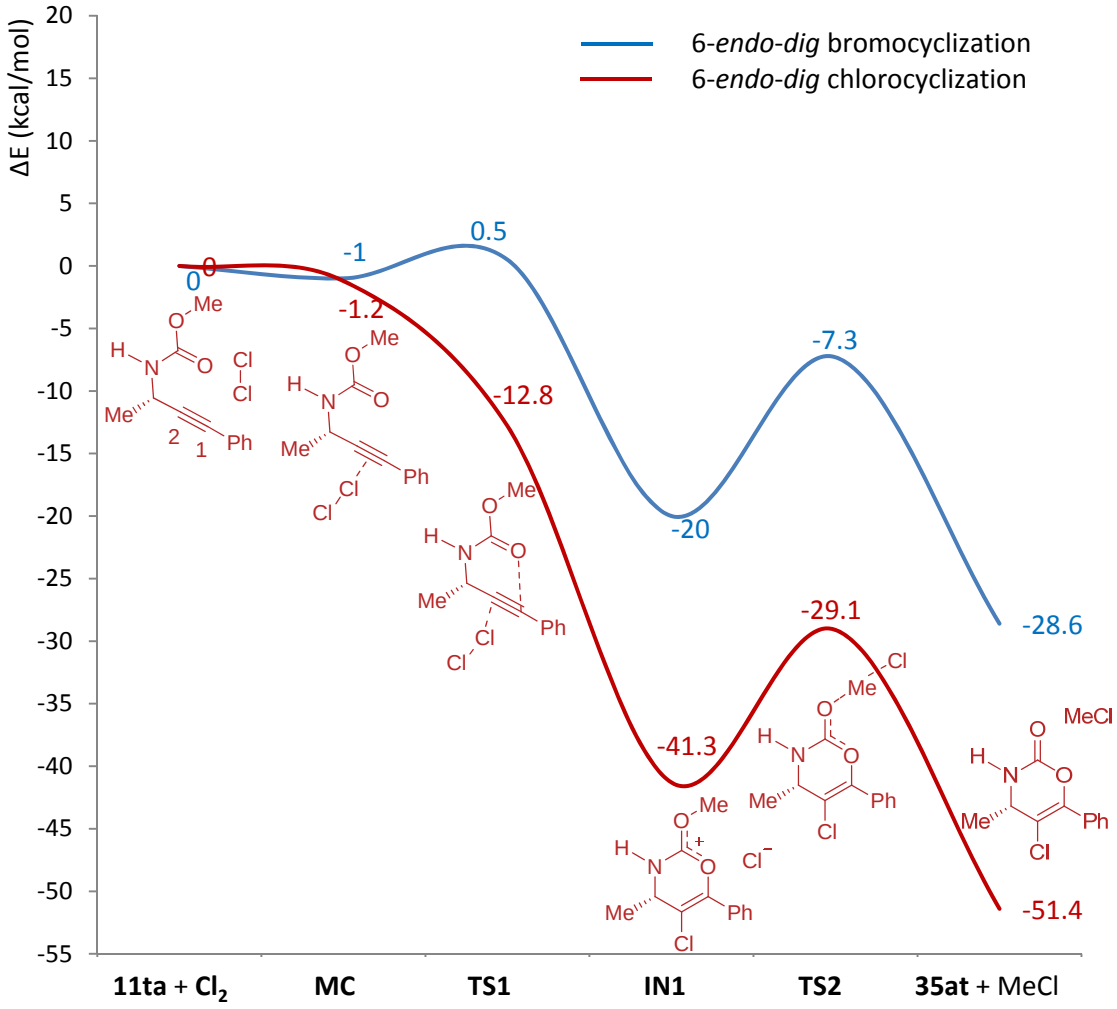
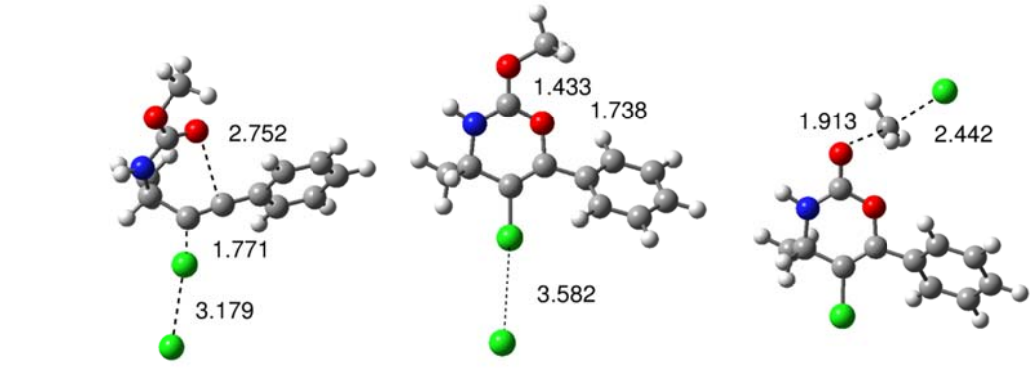


Figure 5.5. Relative energies in acetonitrile (in kcal/mol, relative to **11ta** plus halogen Cl_2) of the stationary points involved in the bromocyclization of **11ta**.

The geometries of the TSs and IN involved in the regioisomeric channel, 6-*endo-dig* cyclization, associated with the reaction promoted by chlorine are given in Figure 5.6.

At the most favourable **TS1-*endo*-Cl**, associated with the first step of the chlorine promoted cyclization process, the lengths of the Cl6-C2 and O3-C1 forming bonds are 1.771 Å and 2.752 Å. At **TS1-*endo*-Cl**, the Cl6-C2 bond formation is more

advanced than the Br6-C2 bond formation at **TS1-*endo*-Br**. At the **TS2-*endo*-Cl** associated with the elimination of the methyl group in **IN1-*endo*-Cl**, the lengths of the O4-C5 breaking bond and the C5-Cl7 forming bond are 1.913 Å and 2.442 Å, respectively. In these asynchronous TS, the O4-C5 breaking bond is more advanced than the C5-Cl7 forming bond.

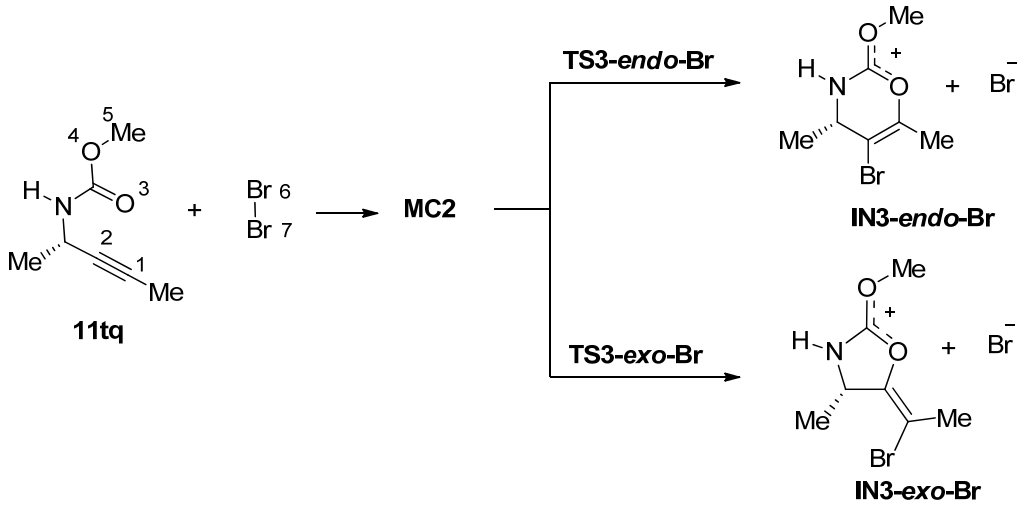


TS1-*endo*-Cl **IN1-*endo*-Cl** **TS2-*endo*-Cl**

Figure 5.6. Geometries of the TSs and IN involved in the regioisomeric channel associated with the chlorine-mediated cyclization of protected propargylic amine **11ta** yielding six-membered 1,3-oxazin-2-one **35ta**. The lengths of the forming and breaking bonds are given in Angstroms.

Cyclization of 11tq in the presence of bromine

Finally, we examined the regioselectivity of the reaction when the alkyne moiety was attached to an aliphatic group, instead of to an aromatic group. For this reason, the role of this substituent in the propargylic system was now analyzed studying the two regioisomeric channels associated with the addition of bromine on the C1 and C2 carbons of methyl propargylic amine **11tq** (Scheme 5.57**)**.



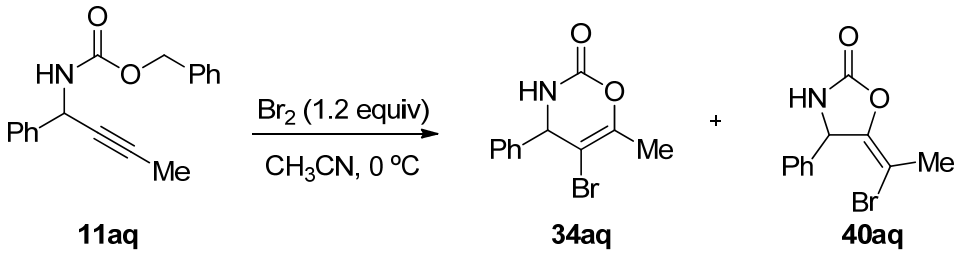
Scheme 5.57. Two possible regioisomeric channels, 6-*endo-dig* and 5-*exo-dig* pathway, for the bromocyclization of **11tq**.

The activation energies associated with the formation of intermediates **IN3-*endo*-Br** and **IN3-*exo*-Br** via **TS3-*endo*-Br** and **TS3-*exo*-Br** are 2.0 and 3.3 kcal/mol respectively, and the formation of these intermediates is exothermic by -27.5 and -25.4 kcal/mol, respectively (Table 5.10).

Table 5.10. Relative energies in acetonitrile (in kcal/mol, relative to **11tq** plus halogen Br_2) of the stationary points involved in the bromocyclization of **11tq**.

Bromocyclization of 11tq	
MC2-Br	-4.1
TS3-*endo*-Br	2.0
TS3-*exo*-Br	3.3
IN3-*endo*-Br	-27.5
IN3-*exo*-Br	-25.4

Consequently, the cyclization reaction with methyl propargylic amine **11aq** should present lower regioselectivity. In fact, when *N*-Cbz-1-phenylbut-2-yn-1-amine was subjected to the bromocyclization reaction a 92:8 mixture of the two regioisomeric products (**34aq** and **40aq**) was obtained (75% yield) (Scheme 5.58).



Scheme 5.58. Bromocyclization of *N*-Cbz-1-phenylbut-2-yn-1-amine (**11aq**).

On the contrary, the reaction with phenyl propargylic amine **11aa** is completely regioselective. Thus, the phenyl substituent induces a total regioselectivity in these halogen promoted cyclizations of protected propargylic amines as a consequence of the stabilization of the incipient carbocationic C1 centre generated along the electrophilic attack on the conjugated C2 carbon.

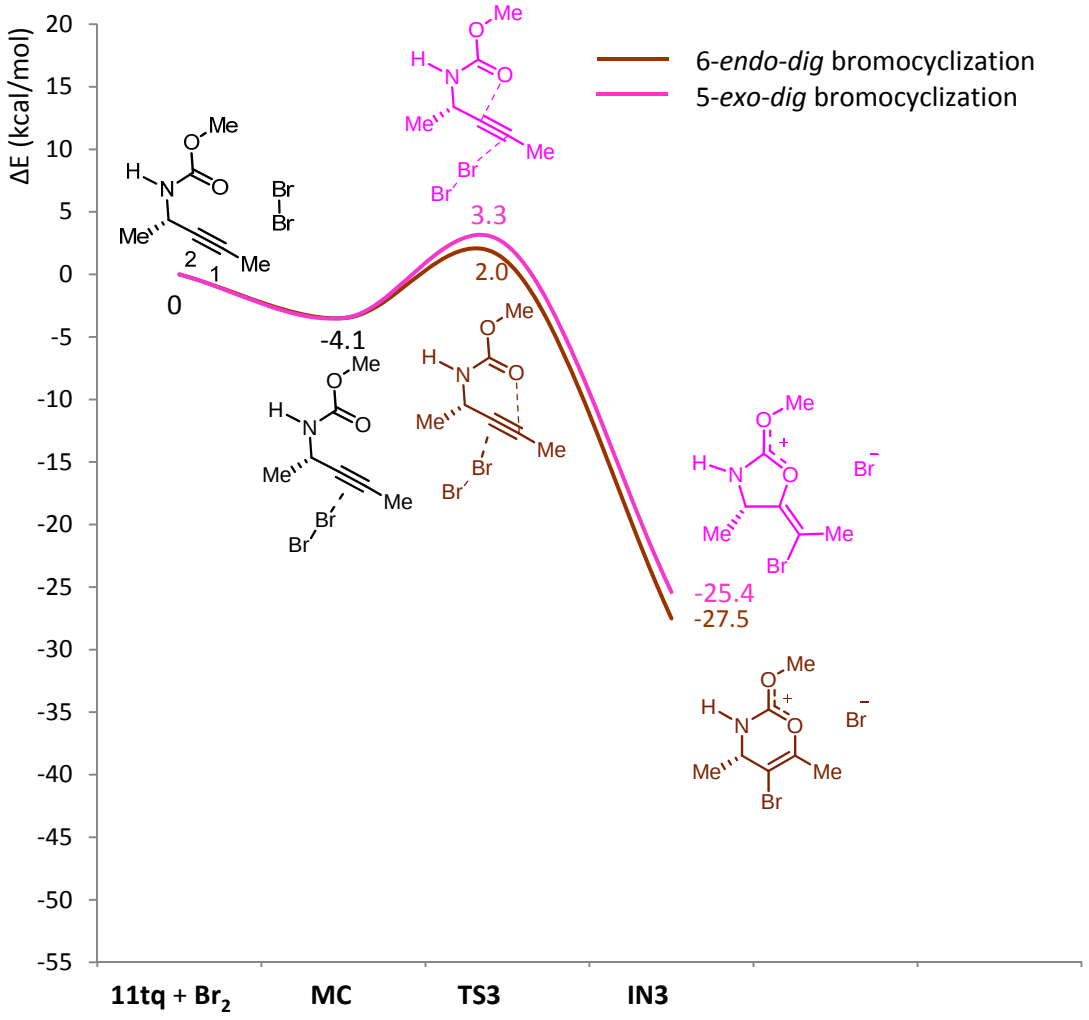
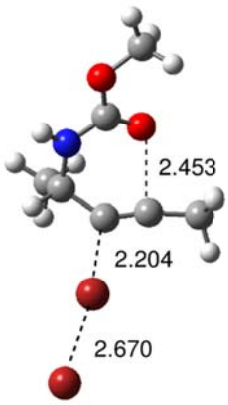


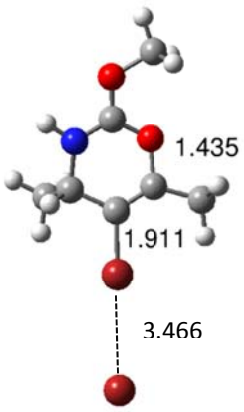
Figure 5.7. Relative energies in acetonitrile (in kcal/mol, relative to **11tq** plus halogen Br_2) of the stationary points involved in the bromocyclization of **11tq**.

The geometries of the TSs and INs involved in the first step of the regioisomeric channel associated with the bromine promoted cyclization of protected methyl propargylic amine **11tq** are given in Figure 5.8.

a)

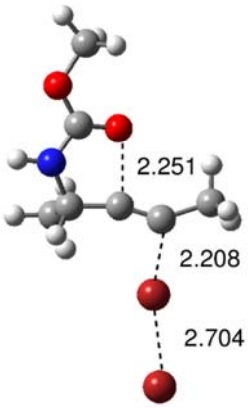


TS3-*endo*-Br

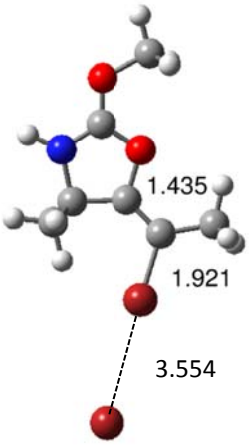


IN3-*endo*-Br

b)



TS3-*exo*-Br



IN3-*exo*-Br

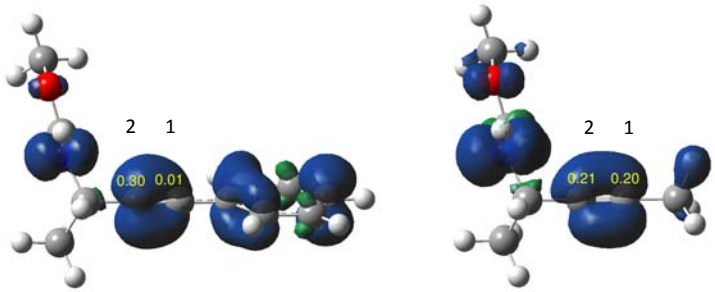
Figure 5.8. Geometries of the TSs and INs involved in the first step of the regioisomeric channels associated with the bromine-mediated cyclization of protected propargylic amine **11tq**. The lengths of the forming and breaking bonds are given in Angstroms.

At the TSs, the lengths of the Br6-C2(1) and O3-C1(2) forming bonds are 2.204 Å and 2.453 Å respectively at **TS3-*endo*-Br**, and 2.208 Å and 2.251 Å respectively at **TS3-*exo*-Br**. At the most favourable **TS3-*endo*-Br**, the O3-C1 length (2.453 Å) indicates that the O3-C1 bond formation at this TS is more advanced than that at **TS1-*endo*-Br**, 2.867

Å. This behaviour accounts for the role of the phenyl substituent in **TS1-*endo*-Br**, stabilizing the incipient carbocationic C1 centre along the electrophilic attack of bromine on the C1 carbon.

Reactivity of the protected propargylic amines

Finally, an analysis of the reactivity of the protected propargylic amines **11ta** and **11tq** was performed using the reactivity indices defined within the conceptual DFT. The global and local reactivity indices, named global electrophilicity ω, global nucleophilicity *N*, nucleophilic Parr functions P_k^- and the local nucleophilicity indices N_k of propargylic amines **11ta** and **11tq** are given in Figure 5.9.



11ta
ω = 1.24
N = 2.78
N_1 = 0.03
N_2 = 0.84

11tq
ω = 0.62
N = 2.17
N_1 = 0.45
N_2 = 0.46

Figure 5.9. Maps of the atomic spin density of the cation radicals of propargylic amines **11ta** and **11tq** and the nucleophilic Parr functions P_k^- at the C1 and C2 carbons, and global electrophilicity ω, global nucleophilicity *N*, and the local nucleophilicity indices N_k, in eV, of **11ta** and **11tq**.

Propargylic amines **11ta** and **11tq** have low electrophilicity ω values, 1.24 (**11ta**) and 0.62 eV (**11tq**), being classified as moderate and marginal electrophiles, respectively. On the other hand, the corresponding nucleophilicity *N* indices, 2.78 (**11ta**) and 2.17 eV (**11tq**) indicate that they will behave as moderate nucleophiles. The higher nucleophilic character of phenyl propargylic amine **11ta** than methyl propargylic amine **11tq** accounts for the lower activation energy found for the bromine-mediated addition to **11ta** than to **11tq**.

Building upon recent studies devoted to the bonding changes in polar reactions,[113] Domingo has proposed two new electrophilic, P_k^+, and nucleophilic, P_k^-, Parr functions, based on the analysis of the atomic spin density (ASD) at the corresponding anion and cation radicals, to study the regio- and chemoselectivity in polar reactions. Analysis of the nucleophilic Parr functions P_k^- in propargylic amines **11ta** and **11tq** indicates that phenyl propargylic amine **11ta** presents a strong nucleophilic activation of the C2 carbon, 0.30, when compared to the C1 carbon, 0.01, while methyl propargylic amine **11tq** shows a similar nucleophilic activation at the two acetylenic C1 and C2 carbons (Figure 5.9). As a consequence, analysis of the local nucleophilicity indices of phenyl propargylic amine **11ta** indicates that the C2 carbon is the most nucleophilic centre of this molecule, N_2 = 0.84 eV, while the corresponding values for methyl propargylic amine **11ta** show that the C2 carbon, N_2 = 0.46 eV is slightly more nucleophilically activated than the C1 carbon, N_2 = 0.45 eV. This local analysis is in agreement with the entire regioselectivity found in the bromine-mediated cyclization of phenyl propargylic amines **11ta**, and with the lower regioselectivity found in the reaction of **11tq**.

5.3.2. Regioselective chalcogen-mediated cyclization of *N*-Cbz-protected propargylic amines. Synthesis of 5-phenylchalco-1,3-oxazin-2-ones

5.3.2.1. Optimization of reaction conditions

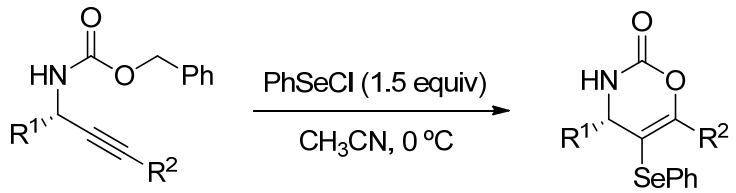
The optimized conditions for the iodocyclization reaction were successfully employed in the chalcogen-mediated cyclization of *N*-Cbz-1,3-diphenyl prop-2-yn-1-amine **11aa** with 1.5 equivalents of phenylselenyl chloride in acetonitrile at 0 °C giving the corresponding selenylated 1,3-oxazin-2-one **36aa** as the only reaction product (99% yield) (Table 5.11, Entry 1).

5.3.2.2. Scope and limitations of the reaction

Cyclization reaction of *N*-Cbz-protected propargylic amines with phenylselenyl chloride

The optimized conditions were applied to the chalcogen-mediated cyclization of several *N*-Cbz-protected propargylic amines **11** derived from the addition of phenylacetylene to imines derived from aromatic and aliphatic aldehydes (Table 5.11, entries 2-4) yielding the corresponding 5-phenylselanyl-1,3-oxazin-2-ones **36** in excellent results (88-99%), regardless the electronic and steric character of the substituents.

Table 5.11. Electrophilic cyclization of *N*-Cbz-protected propargylic amines **11** to 5-phenylselanyl-1,3-oxazin-2-ones **36**.[a]



11 **36**

Entry	11	R^1	R^2	t (h)	Product	Yield (%)[b]
1	**11aa**	Ph	Ph	0.3	**36aa**	99
2	**11ea**	4-ClC_6H_4	Ph	0.3	**36ea**	88
3	**11ha**	2-MeC_6H_4	Ph	0.25	**36ha**	99
4	**11ra**	*n*-butyl	Ph	0.5	**36ra**	90
5	**11ad**	Ph	4-FC_6H_4	0.3	**36ad**	99
6	**11af**	Ph	2-$MeOC_6H_4$	0.25	**36af**	96
7	**11ak**	Ph	$C_6H_5CH_2CH_2$	0.5	**36ak**	71

[a] **11** (0.1 mmol) and phenylselenyl chloride (0.15 mmol) in 2.5 mL of acetonitrile. [b] Yield of isolated product.

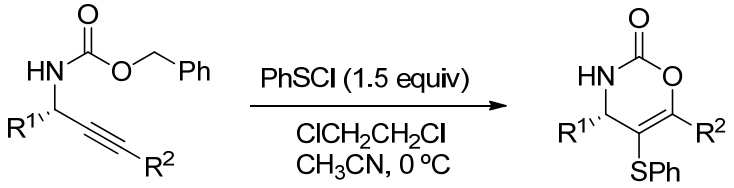
Excellent yields were also obtained when using *N*-Cbz-protected propargylic amines bearing aromatic groups attached to the alkyne moiety with both electron-donating and electron-withdrawing groups in *ortho* and *para* positions (Table 5.11,

Entries 5-6). Furthermore, the procedure tolerates the use of propargylic amines derived from aliphatic alkynes (Table 5.11, Entry 7).

Cyclization reaction of *N*-Cbz-protected propargylic amines with phenylsulfenyl chloride

N-Cbz-protected propargylic amines **11** were submitted to the optimized conditions for the previous cyclization in the presence of 1.5 equivalents of a freshly prepared 0.4 M solution of phenylsulfenyl chloride in 1,2-dichloroethane. The reaction proceeded with good to excellent yields (Table 5.12). Aromatic groups with electron-withdrawing substituents in *para* positions provided the cyclization products in excellent yields (Table 5.12, Entries 2 and 5), whereas the utilization of amines with aromatic groups having an electron-donating group in *ortho* position gave the desired products in somewhat lower yields (Table 5.12, Entries 3 and 6). The cyclization reaction of an amine derived from an aliphatic aldehyde occurred in high yield (Table 5.12, Entry 4).

Table 5.12. Electrophilic cyclization of *N*-Cbz-protected propargylic amines **11** to 5-phenylthio-1,3-oxazin-2-ones **37**.[a]



11 **37**

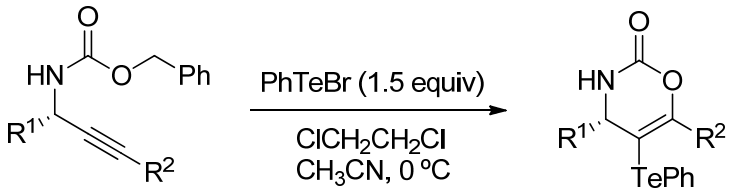
Entry	11	R^1	R^2	t (h)	Product	Yield (%)[b]
1	**11aa**	Ph	Ph	0.5	**37aa**	92
2	**11ea**	4-ClC_6H_4	Ph	1	**37ea**	93
3	**11ha**	2-MeC_6H_4	Ph	0.5	**37ha**	78
4	**11qa**	$C_6H_5CH_2CH_2$	Ph	0.6	**37qa**	90
5	**11ad**	Ph	4-FC_6H_4	1	**37ad**	99
6	**11af**	Ph	2-$MeOC_6H_4$	0.3	**37af**	79

[a] **11** (0.1 mmol) and phenylsulfenyl chloride in 1,2-dichloroethane (0.4 M, 0.15 mmol) in 2.5 mL of acetonitrile. [b] Yield of isolated product.

Cyclization reaction of *N*-Cbz-protected propargylic amines with phenyltelluryl bromide

Finally, *N*-Cbz-protected propargylic amines **11** were reacted with a solution of phenyltelluryl bromide 0.5 M in 1,2-dichloroethane. This cyclization reaction required longer times and provided the 5-phenyltellanyl-1,3-oxazin-2-ones **38** in moderate to high yields (Table 5.13).

Table 5.13. Electrophilic cyclization of *N*-Cbz-protected propargylic amines **11** to 5-phenyltellanyl-1,3-oxazin-2-ones **38**.[a]



11 **38**

Entry	11	R^1	R^2	t (h)	Product	Yield (%)[b]
1	**11aa**	Ph	Ph	4	**38aa**	75
2	**11ba**	4-MeC_6H_4	Ph	3	**38ba**	87
3	**11sa**	cyclohexyl	Ph	20	**38sa**	58
4	**11ae**	Ph	4-ClC_6H_4	4	**38ae**	65
5	**11ai**	Ph	2-thienyl	2	**38ai**	75
6	**11ak**	Ph	$C_6H_5CH_2CH_2$	4	**38ak**	80

[a] **11** (0.1 mmol) and phenyltellanyl bromide in 1,2-dichloroethane (0.5 M, 0.15 mmol) in 2.5 mL of acetonitrile. [b] Yield of isolated product.

The cyclization of propargylic amines derived from benzaldehyde and *p*-tolylaldehyde yielded the corresponding products with good results (75-87%) (Table 5.13, Entries 1-2). However, the utilization of the propargylic amine derived from cyclohexylcarbaldehyde (**11sa**) provided the desired 1,3-oxazin-2-one **38sa** in moderate yield (58%) (Table 5.13, Entry 3).

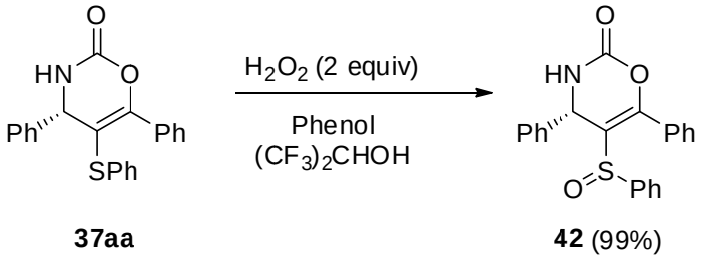
Aromatic and heteroaromatic groups attached to the alkyne moiety were tolerated by this procedure (Table 5.13, Entries 4-5). In addition, 2-phenylethyl-

substituted **11ak** gave the corresponding 1,3-oxazin-2-one **38ak** in 80% yield (Table 5.13, Entry 6).

5.3.2.3. Structure elucidation of the cyclization products

The structural elucidation of 1,3-oxazin-2-ones **36**-**38** was carried out by means of X-ray diffraction analysis and spectroscopic methods, following a similar strategy to the one for the halocyclization products.

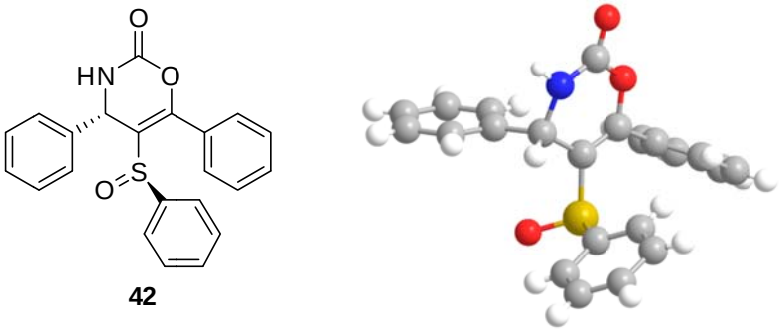
Due to the failure to obtain an appropriate monocrystal of the synthetized 1,3-oxazin-2-ones **36**, **37** and **38**, 5-phenylthio-1,3-oxazin-2-one **37aa** was subjected to oxidative conditions yielding the corresponding sulfoxide derivative **42** (Scheme 5.59).



37aa **42** (99%)

Scheme 5.59. Oxidation of **37aa** to yield **42**.

An X-ray analysis of **42** allowed us to establish the structure of this compound and undeniably confirmed the existence of the 6-membered ring, as illustrated in Figure 5.10.

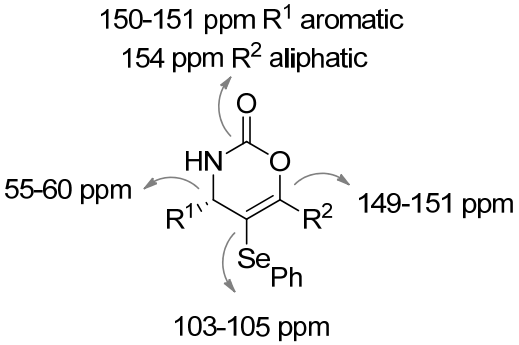


42

Figure 5.10. X-ray structure of **42**.

As for the halocyclization products, a ^{13}C NMR spectroscopy analysis was carried out to ensure that all chalcogen-mediated cyclization reactions proceeded via a 6-*endo-dig* mechanism. We compared the ^{13}C NMR signals of the four carbon atoms in the 6-membered-ring containing the cyclic carbamate (Table 5.14). The carbonyl group gives a signal at δ 150-151 (when R^2 is aromatic) and δ 154 (when R^2 is aliphatic); the quaternary olefinic =C-O resonates at δ 149-151; the quaternary olefinic Se-C= appears at high field at δ 103-105 and the CH appears at δ 55-60.

Table 5.14. ^{13}C NMR signals of the four carbon atoms in the 6-membered-ring containing the cyclic carbamate.

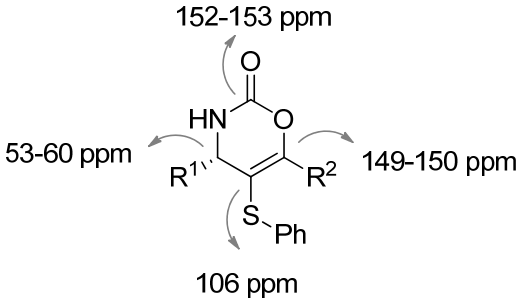


				δ (ppm)			
Entry	**36**	**R^1**	**R^2**	**C=O***	**=C-O***	**Se-C=**	**CH**
1	**36aa**	Ph	Ph	151.50	150.27	103.85	60.21
2	**36ea**	4-ClC_6H_4	Ph	151.61	150.12	103.49	59.62
3	**36ha**	2-MeC_6H_4	Ph	151.84	150.03	103.38	56.75
4	**36ra**	*n*-butyl	Ph	151.74	151.65	104.23	55.75
5	**36ad**	Ph	4-FC_6H_4	150.61	150.11	104.01	60.35
6	**36af**	Ph	2-$MeOC_6H_4$	157.44	150.14	105.93	60.17
7	**36ak**	Ph	$C_6H_5CH_2CH_2$	153.95	149.88	103.11	60.16

* Signals could be exchanged

^{13}C NMR spectra of 5-phenylthio-1,3-oxazin-2-ones were also analyzed. The carbonyl group gives a signal at δ 152-153; the quaternary olefinic =C-O resonates at δ 149-150 ppm; the quaternary olefinic S-C= appears at high field at δ 106 and the CH appears at δ 53-60 ppm.

Table 5.15. ^{13}C NMR signals of the four carbon atoms in the 6-membered-ring containing the cyclic carbamate.

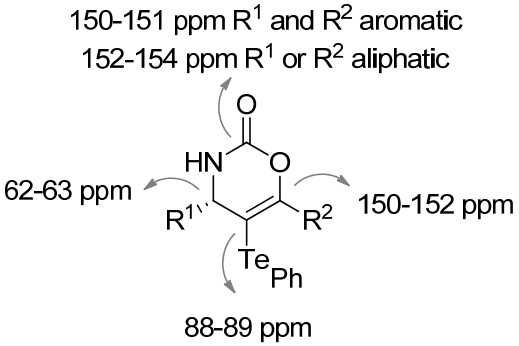


				δ (ppm)			
Entry	**37**	**R^1**	**R^2**	**C=O***	**=C-O***	**S-C=**	**CH**
1	**37aa**	Ph	Ph	152.93	150.06	106.79	58.78
2	**37ea**	4-ClC_6H_4	Ph	153.03	149.94	106.48	58.13
3	**37ha**	2-MeC_6H_4	Ph	153.31	149.89	106.32	55.22
4	**37qa**	$C_6H_5CH_2CH_2$	Ph	153.42	151.01	106.68	53.93
5	**37ad**	Ph	4-FC_6H_4	151.99	149.80	106.83	58.88
6	**37af**	Ph	2-$MeOC_6H_4$	157.44	150.14	105.93	60.17

* Signals could be exchanged.

Finally, the ^{13}C NMR study of 5-phenyltellanyl-1,3-oxazin-2-ones shows that the carbonyl group gives a signal at δ 150-151 (when R^1 and R^2 are aromatic) and δ 152-154 (when R^1 or R^2 is aliphatic); the quaternary olefinic =C-O resonates at δ 150-152; the quaternary olefinic Te-C= appears at high field at δ 88-89 and the CH appears at δ 62-63.

Table 5.16. ^{13}C NMR signals of the four carbon atoms in the 6-membered-ring containing the cyclic carbamate.



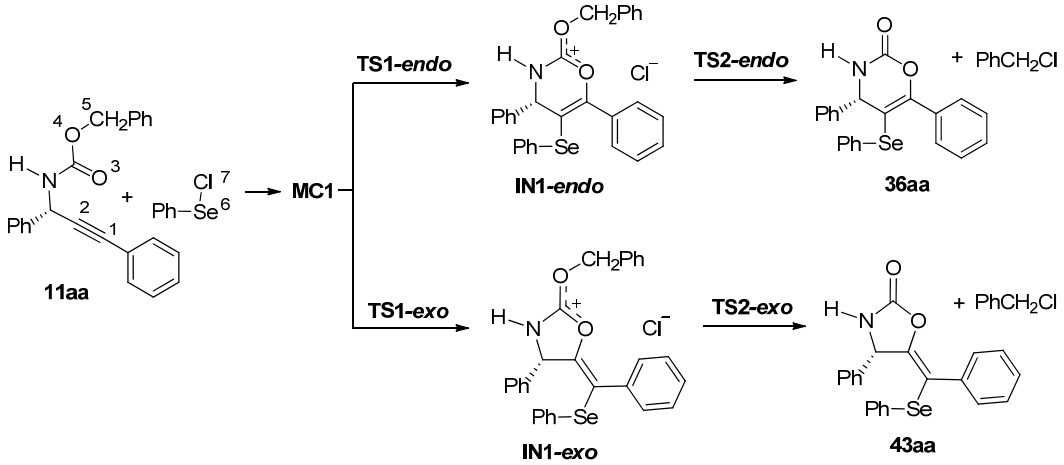
				δ (ppm)			
Entry	**38**	**R^1**	**R^2**	**C=O***	**=C-O***	**Te-C=**	**CH**
1	**38aa**	Ph	Ph	151.86	150.38	89.14	62.54
2	**38ba**	4-MeC_6H_4	Ph	151.85	150.33	89.49	62.37
3	**38sa**	Ciclohexilo	Ph	152.19	152.19	88.53	62.50
4	**38ae**	Ph	4-ClC_6H_4	150.91	150.09	89.82	62.85
5	**38ai**	Ph	2-tienil	149.95	146.27	88.46	63.22
6	**38ak**	Ph	$C_6H_5CH_2CH_2$	154.56	150.08	89.41	63.21

* Signals could be exchanged.

5.3.2.4. Theoretical calculations on the selenocyclization reaction of protected propargylic amines

The mechanism of the regioselective chalcogen mediated cyclization of *N*-Cbz-protected propargylic amine **11aa** to yield the 6-membered 5-phenylselanyl-1,3-oxazin-2-one **36aa** was studied theoretically using density functional theory (DFT) methods at the B3LYP/6-311G* level in acetonitrile (Scheme 5.60). A study of the potential energy surface for the title reactions indicates that this cyclization reaction

takes place through a two-step mechanism. In the first step, the selenium atom of the chalcogen molecule PhSeCl electrophilically attacks on the C1 or C2 carbon of the triple bond of these propargylic amines to provide the cationic intermediate **IN1-*endo*** or **IN1-*exo***, via the corresponding transition states **TS1-*endo*** or **TS1-*exo***, respectively. In the second step, the benzyl group present in the carbamate substituent is eliminated in these cationic intermediates assisted by the halide anion Cl^- yielding the final 1,3-oxazin-2-ones **36aa** and **43aa** (Scheme 5.60). Total and relative energies in acetonitrile are given in Table 5.17.



Scheme 5.60. Two possible regioisomeric channels, 6-*endo-dig* and 5-*exo-dig* pathway, for the cyclization of **11aa** to afford 1,3-oxazin-2-ones **36aa** or 1,3-oxazolidin-2-ones **43aa**.

In an earlier step of the reaction, PhSeCl forms a weak molecular complex (MC) with propargylic amine **11aa**. This MC is located -0.8 kcal/mol below the separated reagents. The activation energies associated with the electrophilic attacks of PhSeCl on the C2 and C1 carbons of propargylic amine **11aa** are 4.5 (**TS1-*endo***) 11.1 kcal/mol (**TS1-*exo***) and the formation of the corresponding cationic intermediates are exothermic by -12.6 (**IN1-*endo***) and -12.5 kcal/mol (**IN1-*exo***). Elimination of the benzyl group from these cationic intermediates takes place through a nucleophilic substitution in the benzyl group assisted by the chloride anion Cl^- generated in the first step of the reaction. From the corresponding intermediates, the activation energies associated with the extrusion of the benzyl group are: 8.0 (**TS2-*endo***) and 7.4 kcal/mol (**TS2-*exo***). Formation of 1,3-oxazin-2-ones **2-*endo*** and **2-*exo*** plus $PhCH_2Cl$ is exothermic by -22.6 and -24.4 kcal/mol, respectively.

Table 5.17. Relative energies in acetonitrile (in kcal/mol, relative to **11aa** plus PhSeCl) of the stationary points involved in the cyclization **11aa** with PhSeCl.

Cyclization of 11aa with PhSeCl	
11aa + PhSeCl	0
MC	-0.8
TS1-*endo*	4.5
TS1-*exo*	11.1
IN1-*endo*	-12.6
IN1-*exo*	-12.5
TS2-*endo*	-4.6
TS2-*exo*	-5.1
36aa + $PhCH_2Cl$	-22.6
43aa + $PhCH_2Cl$	-24.4

From these energy results some relevant conclusions can be drawn:

1. The electrophilic attack of chalcogen PhSeCl on the triple bond of propargylic amine **11aa** is completely regioselective, **TS1-*endo*** being 6.6 kcal/mol lower in energy than **TS1-*exo***.
2. The high exothermic character of the first step makes this step irreversible.
3. The activation energy associated with the second step, 8.0 kcal/mol is higher than that associated with first step, 4.5 kcal/mol; thus, the elimination of the benzyl substituent is the rate-determining step (RDS) of the reaction. Consequently, while the electrophilic attack of chalcogen PhSeCl against propargylic amine **11aa** is the regioselectivity determining step, the benzyl elimination is the RDS of the reaction.
4. These kinetic and thermodynamic results are similar to those found in the halogen mediated cyclizations of propargylic amines.

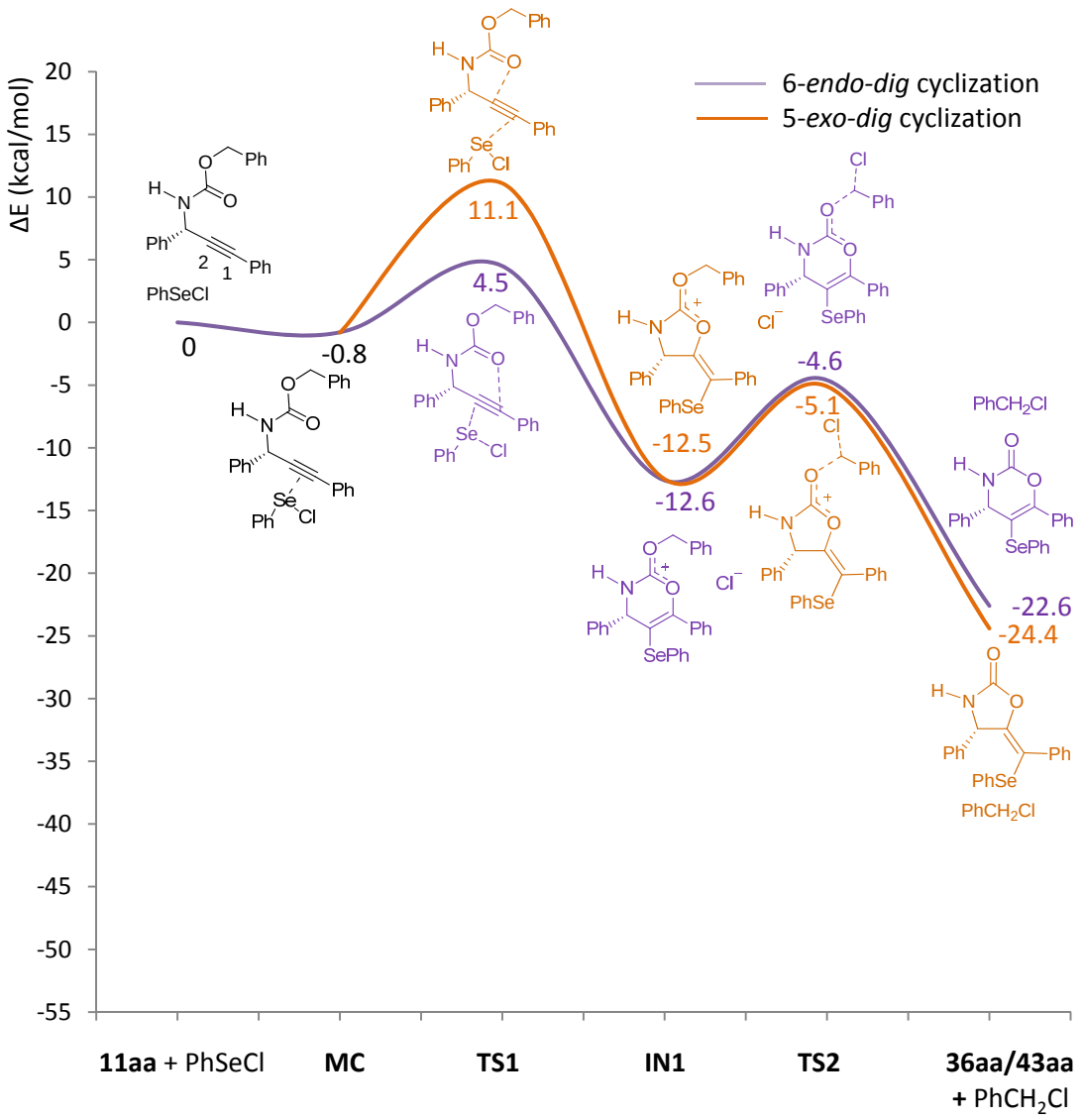
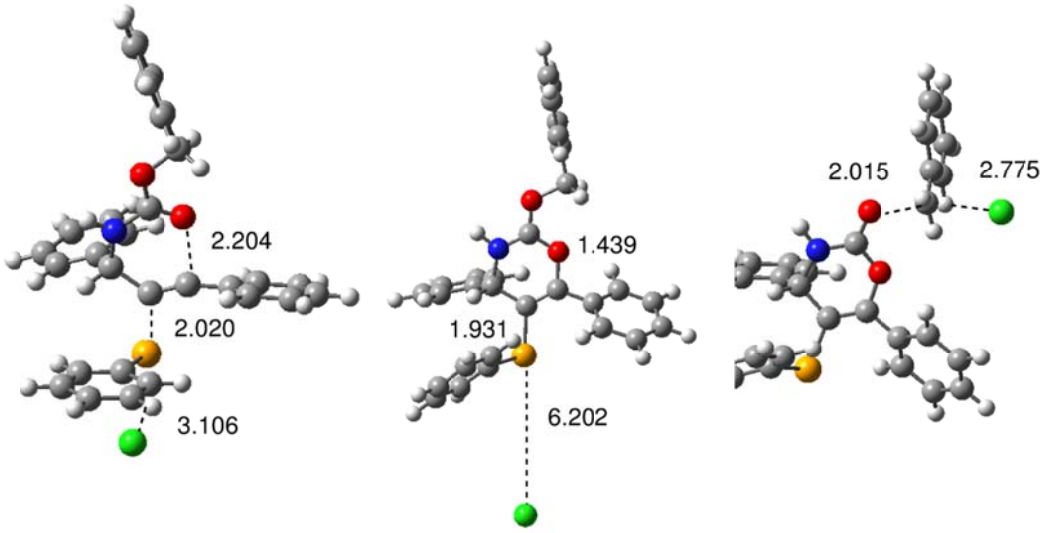


Figure 5.7. Relative energies in acetonitrile (in kcal/mol, relative to **11aa** plus PhSeCl) of the stationary points involved in the cyclization of **11aa** with PhSeCl.

The geometries of the TSs and INs involved in the regioisomeric channels associated with the chalcogen mediated cyclization of propargylic amine **11aa** are given in Figure 5.11. At the TSs associated with the first step of the chalcogen-mediated cyclization process the lengths of the Se6-C2(1) and O3-C1(2) forming bonds are 2.020 Å and 2.204 Å respectively at **TS1-*endo***, and 2.093 Å and 2.154 Å respectively at **TS1-*exo***. At the corresponding intermediates **IN1-*endo*** and **IN1-*exo*** the lengths of the Se6-C2(1) and O3-C1(2) bonds are 1.931 Å and 1.439 Å, and 1.944 and 1.432 Å,

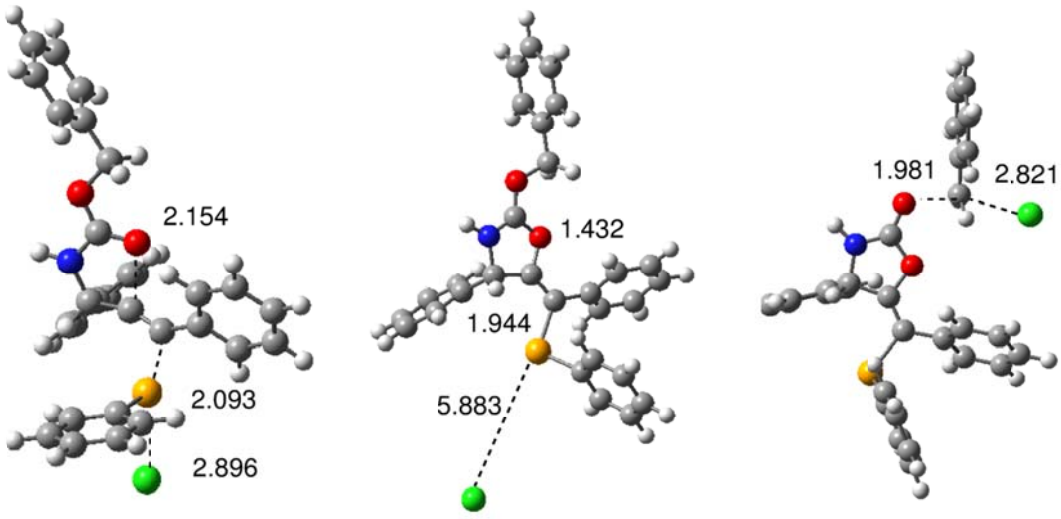
respectively. These geometrical parameters indicate that at TS1s, the Se6-C2(1) bond formation is very advanced, while the O3-C2(1) bond formation is more delayed.

a)



TS1-*endo* **IN1-*endo*** **TS2-*endo***

b)



TS1-*exo* **IN1-*exo*** **TS2-*exo***

Figure 5.11. Geometries of the TSs and INs involved in the regioisomeric channels associated with the chalcogen-mediated cyclization of *N*-Cbz-protected propargylic amine **11aa**. The lengths of the forming and breaking bonds are given in Angstroms.

At the TSs associated with the elimination of the benzyl group in **IN1-*endo*** and **IN1-*exo***, the lengths of the O4-C5 breaking bond and the C5-Cl7 forming bond are 2.015 Å and 2.775 Å respectively at **TS2-*endo*** and 1.981 and 2.821 at respectively **TS2-*exo***. In these asynchronous TSs, the O4-C5 breaking bonds are more advanced than the C5-Cl7 forming bond.

5.4. CONCLUSIONS

We have developed the 6-*endo*-*dig* regioselective electrophilic cyclization of *N*-Cbz protected propargylic amines to give highly functionalized 1,3-oxazin-2-ones using molecular halogens and organochalcogen reagents as electrophilic sources.

The 6-*endo*-*dig* regioselective halocyclizations of propargylic amines were performed in the presence of I_2, Br_2 or Cl_2 employing acetonitrile as solvent at 0 °C or -20 °C. The utilization of a base did not provide better results.

N-*tert*-butyloxycarbonyl- and *N*-ethyloxycarbonyl-protected propargylic amines yielded the corresponding 1,3-oxazin-2-ones in lower yields than *N*-benzyloxycarbonyl-protected propargylic amine.

Iodocyclization of propargylic amines derived from aromatic aldehydes and alkynes afforded the corresponding 5-iodo-1,3-oxazin-2-ones in excellent yields regardless the electronic and steric nature of the substituents. Aliphatic derived propargylic amines led to variable results.

Bromocyclization reaction was carried out reducing the equivalents of bromine and using diluted conditions to avoid the formation of dibrominated products. Under these conditions, aromatic and aliphatic propargylic amines underwent the bromocyclization reaction in high yields.

Chlorocyclization of diverse aromatic *N*-Cbz protected propargylic amines gave the corresponding 5-chloro-1,3-oxazin-2-ones in good yields at -20 °C.

The 6-*endo*-*dig* regioselective chalcogen-mediated cyclizations of propargylic amines were performed employing phenylselenyl chloride, phenylsulfenyl chloride and phenyltelluryl bromide in acetonitrile at 0 °C.

Cyclization of aromatic propargylic amines with phenylselenyl chloride gave the corresponding 5-phenylselanyl-1,3-oxazin-2-ones in excellent yields regardless the characteristics of the substituents. Propargylic amines derived from aliphatic aldehyde or alkyne led to excellent and good results, respectively.

Cyclization of several propargylic amines with phenylsulfenyl chloride afforded the cyclization products in excellent yields. However, lower yields were obtained with substituents with steric hindrance.

Chalcogen-mediated cyclization of diverse propargylic amines bearing aromatic, heteroaromatic and aliphatic substituents with phenyltelluryl bromide gave the corresponding 5-phenyltellanyl-1,3-oxazin-2-ones in good yields.

The formation of a six-membered ring was confirmed by X-ray diffraction analysis. To ensure that all cyclization reactions proceeded via a 6-*endo*-*dig* cyclization pathway, comparative NMR spectroscopy analysis was realized.

Computational studies using DFT methods at the B3LYP/6-311G* level and analysis of the nucleophilic Parr functions were carried out. These studies indicated that these electrophilic cyclization reactions take place through a two-step mechanism. The first step is the regioselectivity determining step and 6-*endo*-*dig* cyclization process is favored over the 5-*exo*-*dig* cyclization reaction. The rate-determining step of the reaction is the elimination of the benzyl group.

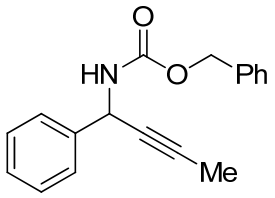
5.5. EXPERIMENTAL SECTION

5.5.1. General techniques

See Section 2.5.1.

5.5.2. General synthetic procedures and characterization of new products

5.5.2.1. Synthesis and characterization of N-benzyloxycarbonyl-1-phenylbut-2-yn-1-amine (11aq)



11aq

A 0.5 M solution of magnesium propynyl bromide in THF (0.55 mL, 0.275 mmol) was added to a solution of α-amido sulfone **8aa** (49.4 mg, 0.125 mmol) in dichloromethane (1.5 mL) at 0 °C under nitrogen. The solution was stirred at 0 °C until the reaction was complete (TLC). The reaction mixture was quenched with water (1.0 mL), extracted with CH_2Cl_2 (3x15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded the compound **11aq**.

White solid; mp 112-115 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (br d, *J* = 7.1 Hz, 2H), 7.39-7.30 (m, 8H), 5.67 (br d, *J* = 6.9 Hz, 1H), 5.24 (br d, *J* = 6.8 Hz, 1H), 5.16 (d, *J* = 12.1 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H), 1.88 (d, *J* = 2.4 Hz, 3H).

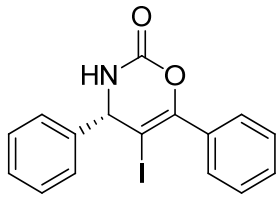
^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.4 (C), 139.5 (C), 136.2 (C), 128.6 (CH), 128.5 (CH), 128. 1 (CH), 128.0 (CH), 126.9 (CH), 81.3 (C), 77.1 (C), 67.0 (CH_2), 47.1 (CH), 3.6 (CH_3).

HRMS (ESI) *m/z*: 302.1153 $[M+Na]^+$, $C_{18}H_{17}NO_2Na$ requires 302.1157.

5.5.2.2. Synthesis and characterization of 5-iodo-1,3-oxazin-2-ones 33

A solution of iodine (50.6 mg, 0.2 mmol) in acetonitrile (1.0 mL) was added to a solution of *N*-Cbz protected propargylic amine **11** (0.1 mmol) in acetonitrile (1.5 mL) at 0 °C. The solution was stirred until the reaction was complete (TLC). The reaction mixture was quenched with sodium bisulfate aq. sat. (1.0 mL), extracted with CH_2Cl_2 (3x15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **33**.

(*S*)-5-iodo-4,6-diphenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (33aa)



33aa

Enantiomeric excess (87%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 90:10, 1 mL/min, major enantiomer t_r = 13.9 min, minor enantiomer t_r = 23.1 min.

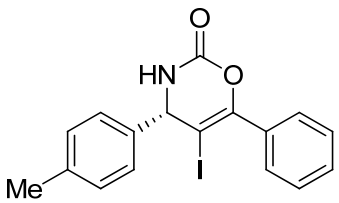
Mp 65-68 °C; $[\alpha]_D^{20}$ +64.7 (*c* 1.00, $CHCl_3$, 87% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.61 (m, 2H), 7.42-7.39 (m, 8H), 6.49 (br s, 1H), 5.19 (d, *J* = 2.1 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.8 (C), 148.9 (C), 140.2 (C), 133.6 (C), 130.0 (CH), 129.4 (CH), 129.2 (CH), 129.1 (CH), 128.0 (CH), 127.5 (CH), 71.4 (C), 64.9 (CH).

HRMS (ESI) *m/z*: 377.9984 $[M+H]^+$, $C_{16}H_{13}NO_2I$ requires 377.9986.

(*S*)-5-iodo-6-phenyl-4-(*p*-tolyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (33ba)



33ba

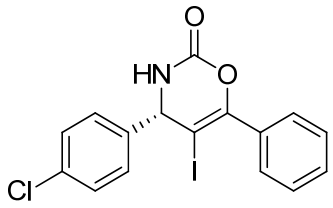
Viscous oil; $[\alpha]_D^{20}$ +42.7 (*c* 1.03, $CHCl_3$, 88% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.62 (m, 2H), 7.42-7.39 (m, 3H), 7.29-7.21 (m, 4H), 5.85 (br s, 1H), 5.17 (d, *J* = 2.0 Hz, 1H), 2.38 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.4 (C), 148.9 (C), 139.2 (C), 137.4 (C), 133.8 (C), 130.0 (CH), 129.8 (CH), 129.4 (CH), 128.1 (CH), 127.4 (CH), 71.7 (C), 64.9 (CH), 21.3 (CH_3).

HRMS (ESI) *m/z*: 392.0147 $[M+H]^+$, $C_{17}H_{15}NO_2I$ requires 392.0142.

(*S*)-4-(4-chlorophenyl)-5-iodo-6-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (33ea)



33ea

Enantiomeric excess (91%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 90:10, 1 mL/min, major enantiomer t_r = 15.1 min, minor enantiomer t_r = 22.2 min.

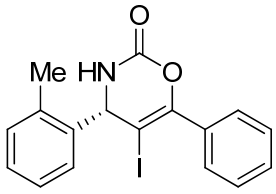
Mp 74-77 °C; $[\alpha]_D^{20}$ +27.99 (*c* 0.70, $CHCl_3$, 90% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.61 (m, 2H), 7.43-7.38 (m, 5H), 7.35-7.31 (m, 2H), 6.07 (br s, 1H), 5.20 (d, *J* = 2.1 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.4 (C), 149.3 (C), 139.8 (C), 135.2 (C), 133.5 (C), 130.2 (CH), 129.4 (CH), 129.3 (CH), 128.9 (CH), 128.1 (CH), 70.7 (C), 64.5 (CH).

HRMS (ESI) *m/z*: 411.9596 $[M+H]^+$, $C_{16}H_{12}NO_2ClI$ requires 411.9596;

(*S*)-5-iodo-6-phenyl-4-(*o*-tolyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (33ha)



33ha

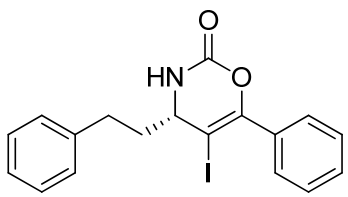
Viscous oil; $[\alpha]_D^{20}$ +40.6 (*c* 0.98, $CHCl_3$, 90% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66-7.63 (m, 2H), 7.43-7.41 (m, 3H), 7.38-7.35 (m, 1H), 7.30-7.27 (m, 2H), 7.23-7.19 (m, 1H), 5.78 (br s, 1H), 5.52 (d, *J* = 1.8 Hz, 1H), 2.46 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.3 (C), 149.2 (C), 138.0 (C), 135.9 (C), 133.8 (C), 131.3 (CH), 130.1 (CH), 129.3 (CH), 129.1 (CH), 128.3 (CH), 128.1 (CH), 127.1 (CH), 71.1 (C), 61.6 (CH), 19.1 (CH_3).

HRMS (ESI) *m/z*: 392.0153 $[M+H]^+$, $C_{17}H_{15}NO_2I$ requires 392.0142.

(*S*)-5-iodo-4-phenethyl-6-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (33qa)



33qa

Mp 99-100 °C; $[\alpha]_D^{20}$ +4.7 (*c* 0.87, $CHCl_3$, 60% *ee*).

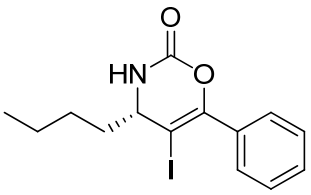
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59-7.56 (m, 2H), 7.42-7.40 (m, 3H), 7.34-7.28 (m, 2H), 7.25-7.22 (m, 3H), 6.40 (br d, *J* = 5.3 Hz, 1H), 4.31-4.27 (m, 1H), 2.90-2.70 (m,

2H), 2.24-2.15 (m, 2H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.9 (C), 149.8 (C), 140.3 (C), 133.7 (C), 130.0 (CH), 129.3 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 126.3 (CH), 70.8 (C), 59.9 (CH), 37.3 (CH_2), 29.8 (CH_2).

HRMS (ESI) *m/z*: 406.0306 $[M+H]^+$, $C_{18}H_{17}INO_2$ requires 406.0303.

(*S*)-4-butyl-5-iodo-6-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (33ra)



33ra

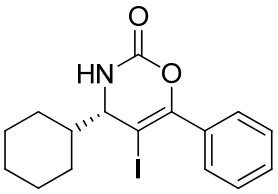
Viscous oil; $[\alpha]_D^{20}$ +5.30 (*c* 0.53, $CHCl_3$, 46% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59-7.56 (m, 2H), 7.42-7.26 (m, 3H), 6.31 (br s, 1H), 4.25-4.21 (m, 1H), 1.89-1.79 (m, 2H) 1.45-1.35 (m, 4H), 0.95 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.3 (C), 149.3 (C), 133.8 (C), 129.9 (CH), 129.3 (CH), 128.1 (CH), 71.3 (C), 60.3 (CH), 35.4 (CH_2), 25.4 (CH_2), 22.3 (CH_2), 14.0 (CH_3).

HRMS (ESI) *m/z*: 358.0307 $[M+H]^+$, $C_{14}H_{17}NO_2I$ requires 358.0299.

(*S*)-4-cyclohexyl-5-iodo-6-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (33sa)



33sa

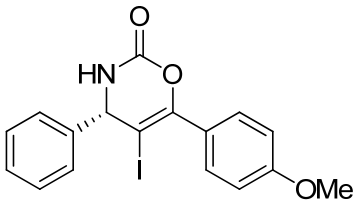
Mp 152-156 °C; $[\alpha]_D^{20}$ +1.33 (*c* 1.00, $CHCl_3$, 54% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.55 (m, 2H), 7.42-7.39 (m, 3H), 6.42 (br s, 1H), 4.04 (t, *J* = 2.7 Hz, 1H), 1.99-1.60 (m, 6H), 1.36-1.34 (m, 5H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.5 (C), 150.1 (C), 133.9 (C), 129.9 (CH), 129.3 (CH), 128.0 (CH), 70.3 (C), 65.1 (CH), 42.0 (CH), 29.3 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 24.8 (CH_2).

HRMS (ESI) *m/z*: 384.0447 $[M+H]^+$, $C_{16}H_{19}INO_2$ requires 384,0455.

(*S*)-5-iodo-6-(4-methoxyphenyl)-4-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (33ab)



33ab

Enantiomeric excess (88%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 90:10, 1 mL/min, major enantiomer t_r = 20.1 min, minor enantiomer t_r = 29.5 min.

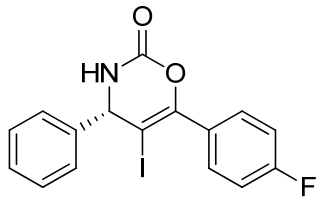
Mp 161-163 °C; $[\alpha]_D^{20}$ +41.9 (*c* 1.19, $CHCl_3$, 88% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dt, *J* = 8.9, 2.5 Hz, 2H), 7.44-7.36 (m, 5H), 6.91 (dt, *J* = 8.9, 2.5 Hz, 2H), 5.94 (br s, 1H), 5.18 (d, *J* = 2.1 Hz, 1H), 3.84 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.7 (C), 149.6 (C), 148.8 (C), 140.4 (C), 130.9 (CH), 129.2 (CH), 129.1 (CH), 127.5 (CH), 125.9 (C), 113.3 (CH), 70.4 (C), 65.1 (CH), 55.3 (CH_3).

HRMS (ESI) *m/z*: 408.0096 $[M+H]^+$, $C_{17}H_{15}NO_3I$ requires 408.0091.

(*S*)-6-(4-fluorophenyl)-5-iodo-4-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (33ad)



33ad

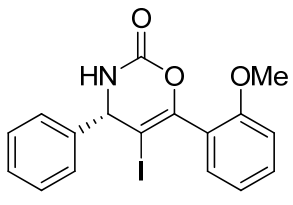
Mp 68-71 °C; $[\alpha]_D^{20}$ +46.6 (*c* 1.03, $CHCl_3$, 83% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66-7.61 (m, 2H), 7.44-7.36 (m, 5H), 7.10 (t, *J* = 8.7 Hz, 2H), 5.94 (br s, 1H), 5.20 (d, *J* = 2.1 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.4 (d, *J* = 250.8 Hz, C), 149.3 (C), 148.1 (C), 140.1 (C), 131.6 (d, *J* = 8.7 Hz, CH), 129.8 (d, *J* = 3.5 Hz, C), 129.3 (CH), 129.2 (CH), 127.5 (CH), 115.2 (d, *J* = 21.9 Hz, CH), 71.6 (C), 65.1 (CH).

HRMS (ESI) *m/z*: 395.9895 $[M+H]^+$, $C_{16}H_{12}NO_2FI$ requires 395.9891.

(*S*)-5-iodo-6-(2-methoxyphenyl)-4-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (33af)



33af

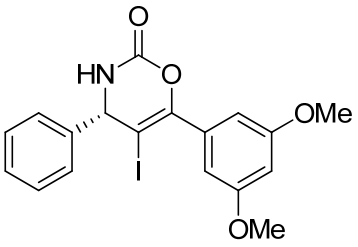
Mp 195-198 °C; $[\alpha]_D^{20}$ +18.1 (*c* 1.04, $CHCl_3$, 66% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.37 (m, 6H), 7.32 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.99 (td, *J* = 7.5, 0.8 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 5.85 (br s, 1H), 5.20 (d, *J* = 1.9 Hz, 1H), 3.88 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.2 (C), 149.5 (C), 148.1 (C), 140.4 (C), 131.6 (CH), 131.1 (CH), 129.2 (CH), 129.1 (CH), 127.6 (CH), 123.7 (C), 120.3 (CH), 111.2 (CH), 74.4 (C), 64.5 (CH), 55.7 (CH_3).

HRMS (ESI) *m/z*: 408.0088 $[M+H]^+$, $C_{17}H_{15}NO_3I$ requires 408.0091.

(*S*)-6-(3,5-dimethoxyphenyl)-5-iodo-4-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (33ag)



33ag

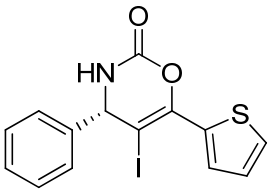
Viscous oil; $[\alpha]_D^{20}$ +33.0 (*c* 0.54, $CHCl_3$, 90% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.36 (m, 5H), 6.76 (d, *J* = 2.3 Hz, 2H), 6.51 (d, *J* = 2.3 Hz, 1H), 5.88 (br s, 1H), 5.19 (d, *J* = 2.0 Hz, 1H), 3.81 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.3 (C), 149.3 (C), 148.8 (C), 140.3 (C), 135.3 (C), 129.3 (CH), 129.2 (CH), 127.6 (CH), 107.4 (CH), 102.5 (CH), 71.3 (C), 65.1 (CH), 55.5 (CH_3).

HRMS (ESI) *m/z*: 438.0214 $[M+H]^+$, $C_{18}H_{17}NO_4I$ requires 438.0197.

(*S*)-5-iodo-4-phenyl-6-(thiophen-2-yl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (33ai)



33ai

Enantiomeric excess (89%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 90:10, 1 mL/min, major enantiomer t_r = 11.7 min, minor enantiomer t_r = 20.1 min.

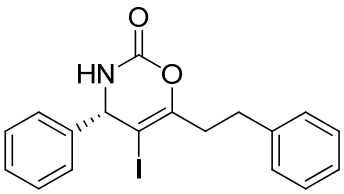
Mp 168-170 °C; $[\alpha]_D^{20}$ +85.7 (*c* 1.05, $CHCl_3$, 90% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.46 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.41-7.33 (m, 5H), 7.12 (dd, *J* = 3.8, 5.0 Hz, 1H), 6.01 (br s, 1H), 5.22 (d, *J* = 2.3 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.0 (C), 143.9 (C), 140.2 (C), 134.3 (C), 130.4 (CH), 129.2 (CH), 129.1 (CH), 128.2 (CH), 127.6 (CH), 126.9 (CH), 69.6 (C), 65.7 (CH).

HRMS (ESI) *m/z*: 383.9556 $[M+H]^+$, $C_{14}H_{11}NO_2SI$ requires 383.9550.

(*S*)-5-iodo-6-phenethyl-4-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (33ak)



33ak

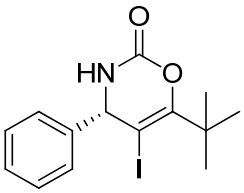
Mp 147-149 °C; $[\alpha]_D^{20}$ +2.8 (*c* 0.20, $CHCl_3$, 82% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.23 (m, 8H), 7.14-7.11 (m, 2H), 5.55 (br s, 1H), 4.99 (br s, 1H), 2.99-2.78 (m, 4H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.2 (C), 149.2 (C), 140.1 (C), 139.8 (C), 129.1 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 127.5 (CH), 126.4 (CH), 71.8 (C), 64.0 (CH), 36.9 (CH_2), 32.3 (CH_2).

HRMS (ESI) *m/z*: 406.0296 $[M+H]^+$, $C_{18}H_{17}NO_2I$ requires 406.0299.

(*S*)-6-(*tert*-butyl)-5-iodo-4-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (33am)



33am

Mp 128-130 °C; $[\alpha]_D^{20}$ +52.2 (*c* 0.70, $CHCl_3$, 88% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.36 (m, 3H), 7.29-7.25 (m, 2H), 5.74 (br s, 1H), 5.01 (d, *J* = 2.4 Hz, 1H), 1.44 (s, 9H).

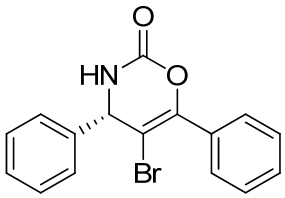
^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.3 (C), 149.7 (C), 140.6 (C), 129.1 (CH), 129.0 (CH), 127.4 (CH), 66.7 (CH), 37.4 (C), 29.0 (CH_3).

HRMS (ESI) *m/z*: 358.0298 $[M+H]^+$, $C_{14}H_{17}NO_2I$ requires 358.0299.

5.5.2.3. Synthesis and characterization of 5-bromo-1,3-oxazin-2-ones 34

Bromine (6.1 µL, 0.12 mmol) was added to a solution of *N*-Cbz protected propargylic amine **11** (0.1 mmol) in acetonitrile (12.5 mL) at 0 °C. The solution was stirred until the reaction was complete (TLC). The reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **34**.

(*S*)-5-bromo-4,6-diphenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (34aa)



34aa

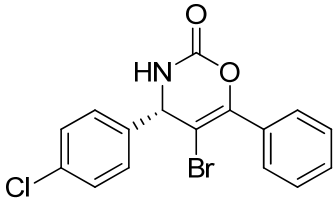
Mp 52-54 °C; $[\alpha]_D^{20}$ +62.7 (*c* 1.00, $CHCl_3$, 87% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.69 (m, 2H), 7.43-7.41 (m, 8H), 6.12 (br s, 1H), 5.19 (d, *J* = 2.1 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.3 (C), 146.2 (C), 139.6 (C), 131.6 (C), 130.1 (CH), 129.3 (CH), 129.2 (CH), 128.9 (CH), 128.1 (CH), 127.4 (CH), 98.3 (C), 62.3 (CH).

HRMS (ESI) *m/z*: 330.0110/332.0090 $[M+H]^+$ 100/96.5, $C_{16}H_{13}BrNO_2$ requires 330.0130/332.0109.

(*S*)-5-bromo-4-(4-chlorophenyl)-6-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (34da)



34da

Enantiomeric excess (90%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 90:10, 1 mL/min, major enantiomer t_r = 14.3 min, minor enantiomer t_r = 20.1 min.

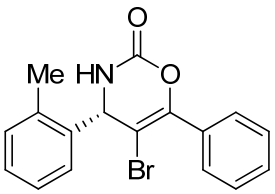
Mp 63-65 °C; $[\alpha]_D^{20}$ +73.9 (*c* 0.86, $CHCl_3$, 90% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.67 (m, 2H), 7.43-7.31 (m, 7H), 6.38 (br s, 1H), 5.17 (d, *J* = 2.2 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.3 (C), 146.5 (C), 138.1 (C), 135.2 (C), 131.4 (C), 130.2 (CH), 129.4 (CH), 128.9 (CH), 128.8 (CH), 128.1 (CH), 97.8 (C), 61.6 (CH).

HRMS (ESI) *m/z*: 363.9732/365.9722 $[M+H]^+$ 100/96.8, $C_{16}H_{12}BrClNO_2$ requires 363.9740/365.9719.

(*S*)-5-bromo-6-phenyl-4-(o-tolyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (34ha)



34ha

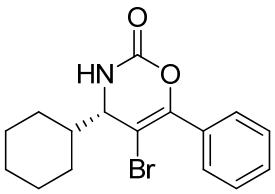
Mp 53-55 °C; $[\alpha]_D^{20}$ +57.1 (*c* 0.87, $CHCl_3$, 90% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.70 (m, 2H), 7.44-7.36 (m, 4H), 7.30-7.27 (m, 2H), 7.22-7.19 (m, 1H), 5.94 (br s, 1H), 5.53 (d, *J* = 1.9 Hz, 1H), 2.47 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.2 (C), 146.4 (C), 137.4 (C), 136.0 (C), 131.7 (C), 131.3 (CH), 130.0 (CH), 129.1 (CH), 128.9 (CH), 128.14 (CH), 128.10 (CH), 127.1 (CH), 98.2 (C), 58.9 (CH), 19.1 (CH_3).

HRMS (ESI) *m/z*: 344.0276/346.0263 $[M+H]^+$ 100/97.1, $C_{17}H_{15}BrNO_2$ requires 344.0286/346.0266.

(*S*)-5-bromo-4-cyclohexyl-6-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (34sa)



34sa

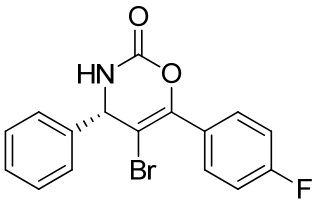
Mp 60-63 °C; $[\alpha]_D^{20}$ -3.90 (*c* 0.65, $CHCl_3$, 54% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.67 (m, 2H), 7.41-7.37 (m, 3H), 6.21 (br s, 1H), 4.04 (br s, 1H), 1.94-1.75 (m, 5H), 1.32-1.18 (m, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.0 (C), 147.2 (C), 131.8 (C), 129.9 (CH), 128.9 (CH), 128.0 (CH), 97.7 (C), 62.7 (CH), 41.6 (CH), 29.1 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 25.0 (CH_2).

HRMS (ESI) *m/z*: 336.0588/338.0569 $[M+H]^+$ 100/96.7, $C_{16}H_{19}BrNO_2$ requires 336.0599/338.0579.

(*S*)-5-bromo-6-(4-fluorophenyl)-4-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (34ad)



34ad

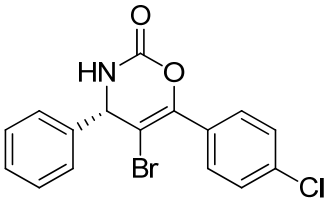
Mp 58-61 °C; $[\alpha]_D^{20}$ +82.7 (*c* 0.99, $CHCl_3$, 83% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74-7.67 (m, 2H), 7.44-7.37 (m, 5H), 7.10 (t, *J* = 8.8 Hz, 2H), 6.14 (br s, 1H), 5.18 (d, *J* = 2.2 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.3 (d, *J* = 254.0 Hz, C), 149.2 (C), 145.3 (C), 139.5 (C), 131.1 (d, *J* = 8.6 Hz, CH), 129.3 (CH), 129.2 (CH), 127.7 (d, *J* = 3.4 Hz, C), 127.4 (CH), 115.2 (d, *J* = 21.9 Hz, CH), 98.4 (C), 62.3 (CH).

HRMS (ESI) *m/z*: 348.0039/350.020 $[M+H]^+$ 100/97.2, $C_{16}H_{12}BrFNO_2$ requires 348.0035/350.0015.

(*S*)-5-bromo-6-(4-chlorophenyl)-4-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (34ae)



34ae

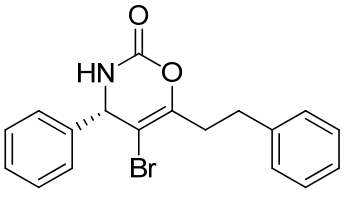
Mp 54-56 °C; $[\alpha]_D^{20}$ +81.4 (*c* 0.89, $CHCl_3$, 91% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (dt, *J* = 8.6, 2.2 Hz, 2H), 7.43-7.37 (m, 7H), 6.33 (br s, 1H), 5.18 (d, *J* = 2.1 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.3 (C), 145.1 (C), 139.4 (C), 136.0 (C), 130.3 (CH), 129.9 (C), 129.3 (CH), 129.2 (CH), 128.4 (CH), 127.4 (CH), 98.8 (C), 62.2 (CH).

HRMS (ESI) *m/z*: 363.9742/365.9708 $[M+H]^+$ 100/96.8, $C_{16}H_{12}BrClNO_2$ requires 363.9740/365.9719.

(*S*)-5-bromo-6-phenethyl-4-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (34ak)



34ak

Mp 135-138 °C; $[\alpha]_D^{20}$ +46.0 (*c* 1.03, $CHCl_3$, 82% *ee*).

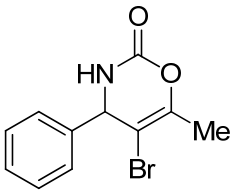
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.34 (m, 3H), 7.30-7.23 (m, 5H), 7.15-7.12 (m, 2H), 5.80 (br s, 1H), 4.98 (br s, 1H), 2.99-2.94 (m, 2H), 2.89-2.67 (m, 2H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.1 (C), 147.9 (C), 139.8

(C), 139.4 (C), 129.1 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 127.3 (CH), 126.4 (CH), 98.3 (C), 61.4 (CH), 33.4 (CH_2), 31.9 (CH_2).

HRMS (ESI) *m/z*: 358.0451/360.040 $[M+H]^+$ 100/96.7, $C_{18}H_{17}BrNO_2$ requires 358.0443/360.0422.

5-bromo-6-methyl-4-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (34aq)



34aq

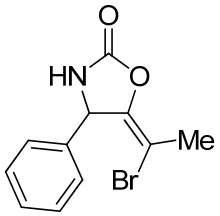
Mp 180-183 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.34 (m, 3H), 7.33-7.28 (m, 2H), 6.34 (br s, 1H), 5.36 (quint, *J* = 1.4 Hz, 1H), 2.11 (d, *J* = 1.5 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.4 (C), 145.7 (C), 139.6 (C), 129.1 (CH), 129.0 (CH), 127.3 (CH), 97.7 (C), 61.2 (CH), 18.1 (CH_3).

HRMS (ESI) *m/z*: 267.9971/269.9950 $[M+H]^+$ 100/96.2, $C_{11}H_{11}BrNO_2$ requires 267.9973/269.9953.

(*E*)-5-(1-bromoethylidene)-4-phenyloxazolidin-2-one (40aq)



40aq

Decomp.

^{1}H NMR (300 Hz, $CDCl_3$) δ 7.40-7.34 (m, 5H), 5.55 (br s, 1H), 5.36 (q, *J* = 1.6 Hz, 1H), 2.32 (d, *J* = 1.7 Hz, 3H).

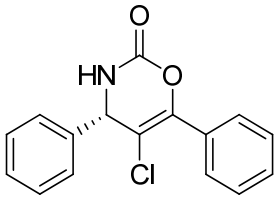
^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.0 (C), 145.1 (C), 137.4 (C), 129.1 (CH), 129.0 (CH), 127.6 (CH), 100.7 (C), 60.6 (CH), 21.3 (CH_3).

HRMS (ESI) *m/z*: 267.9970/269.9950 $[M+H]^+$ 100/96.3, $C_{11}H_{11}BrNO_2$ requires 267.9973/269.9953.

5.5.2.4. Synthesis and characterization of 5-chloro-1,3-oxazin-2-ones 35

A 0.19 M solution of chlorine[114] (0.63 mL, 0.12 mmol) in acetonitrile was added to a solution of *N*-Cbz protected propargylic amine **11** (0.1 mmol) in acetonitrile (12.5 mL) at -20 °C. The solution was stirred until the reaction was complete (TLC). The reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **35**.

(*S*)-5-chloro-4,6-diphenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (35aa)



35aa

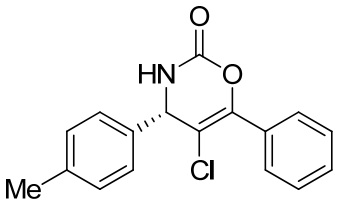
Viscous oil; $[\alpha]_D^{20}$ +45.3 (*c* 0.83, $CHCl_3$, 87% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76-7.73 (m, 2H), 7.44-7.40 (m, 8H), 5.98 (br s, 1H), 5.12 (d, *J* = 2.0 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.0 (C), 144.9 (C), 139.2 (C), 130.5 (C), 130.0 (CH), 129.4 (CH), 129.2 (CH), 128.6 (CH), 128.1 (CH), 127.3 (CH), 108.9 (C), 60.4 (CH).

HRMS (ESI) *m/z*: 286.0632 $[M+H]^+$, $C_{16}H_{13}ClNO_2$ requires 286.0629.

(*S*)-5-chloro-6-phenyl-4-(p-tolyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (35ba)



35ba

Enantiomeric excess (87%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 90:10, 1 mL/min, major enantiomer t_r = 13.3 min, minor enantiomer t_r = 19.2 min.

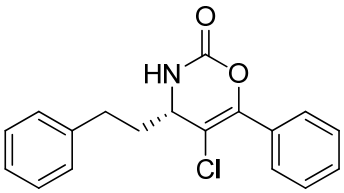
White oil; $[\alpha]_D^{20}$ +47.8 (*c* 0.59, $CHCl_3$, 88% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76-7.72 (m, 2H), 7.43-7.40 (m, 3H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.78 (br s, 1H), 5.09 (d, *J* = 2.0 Hz, 1H), 2.38 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.3 (C), 144.6 (C), 139.4 (C), 136.2 (C), 130.09 (C), 129.97 (CH), 129.85 (CH), 128.5 (CH), 128.1 (CH), 127.2 (CH), 109.1 (C), 60.7 (CH), 21.2 (CH_3).

HRMS (ESI) *m/z*: 300.0796 $[M+H]^+$, $C_{17}H_{15}ClNO_2$ requires 300.0791.

(*S*)-5-chloro-4-phenethyl-6-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (35qa)



35qa

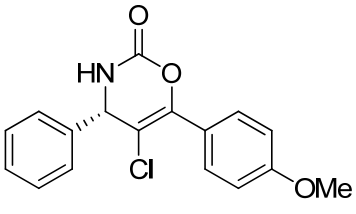
Mp 145-146 °C; $[\alpha]_D^{20}$ +5.8 (*c* 0.78, $CHCl_3$, 60% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.69 (m, 2H), 7.43-7.41 (m, 3H), 7.33-7.28 (m, 2H), 7.24-7.19 (m, 3H), 5.85 (br s, 1H), 4.27-4.23 (m, 1H), 2.90-2.73 (m, 2H), 2.22-2.14 (m, 2H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.5 (C), 145.4 (C), 140.2 (C), 130.5 (C), 129.9 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 126.3 (CH), 108.9 (C), 56.0 (CH), 36.2 (CH_2), 29.9 (CH_2).

HRMS (ESI) *m/z*: 300.0798 $[M+H]^+$, $C_{18}H_{17}ClNO_2$ requires 300.0791.

(*S*)-5-chloro-6-(4-methoxyphenyl)-4-phenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (35ab)



35ab

Mp 47-49 °C; $[\alpha]_D^{20}$ +62.2 (*c* 0.79, $CHCl_3$, 88% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (dt, *J* = 9.1, 2.6 Hz, 2H), 7.42-7.38 (m, 5H), 6.93 (dt, *J* = 9.1, 2.6 Hz, 2H), 6.12 (br s, 1H), 5.09 (d, *J* = 2.1 Hz, 1H), 3.84 (s, 3H).

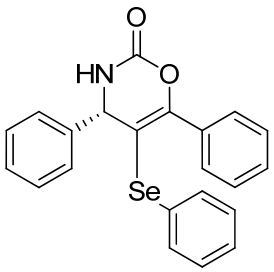
^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.6 (C), 149.3 (C), 144.5 (C), 139.3 (C), 130.1 (CH), 129.2 (CH), 129.1 (CH), 127.3 (CH), 122.7 (C), 113.5 (CH), 107.7 (C), 60.9 (CH), 55.3 (CH_3).

HRMS (ESI) *m/z*: 316.0738 $[M+H]^+$, $C_{17}H_{15}ClNO_3$ requires 316.0740.

5.5.2.5. Synthesis and characterization of 5-phenylselanyl-1,3-oxazin-2-ones 36

Phenylselenyl chloride (101.4 mg, 0.15 mmol) was added to a solution of *N*-Cbz protected propargylic amine **11** (0.10 mmol) in acetonitrile (2 mL) at 0 °C. The solution was stirred until the reaction was complete (TLC). The reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **36**.

(*S*)-4,6-diphenyl-5-(phenylselanyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (36aa)



36aa

Enantiomeric excess (86%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 90:10, 1 mL/min, major enantiomer t_r = 13.0 min, minor enantiomer t_r = 23.1 min.

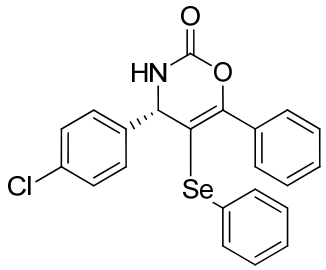
Mp 157-160 °C; $[\alpha]_D^{20}$ +157.1 (*c* 1.00, $CHCl_3$, 86% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62-7.59 (m, 2H), 7.44-7.23 (m, 13H), 6.16 (br d, *J* = 1.9 Hz, 1H), 4.86 (d, *J* = 2.4 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.5 (C), 150.3 (C), 140.8 (C), 132.5 (C), 131.9 (CH), 130.0 (CH), 129.5 (CH), 129.2 (CH), 128.94 (CH), 128.89 (C), 128.8 (CH), 127.9 (CH), 127.7 (CH), 127.2 (CH), 103.9 (C), 60.1 (CH).

HRMS (ESI) *m/z*: 408.0500/406.0507 $[M+H]^+$ 100.0/51.2, $C_{22}H_{18}NO_2Se$ requires 408.0503/406.0511.

(*S*)-4-(4-chlorophenyl)-6-phenyl-5-(phenylselanyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (36ea)



36ea

Mp 138-142 °C; $[\alpha]_D^{20}$ +136.1 (*c* 1.02, $CHCl_3$, 90% *ee*).

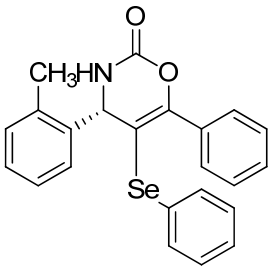
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.58 (m, 2H), 7.43-7.36 (m, 3H), 7.32-7.25 (m, 7H), 7.16 (dt, *J* = 8.8, 2.3 Hz, 2H), 6.20 (br d, *J* = 2.0 Hz, 1H), 4.85 (d, *J* = 2.5 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.6 (C), 150.1 (C), 139.3

(C), 134.7 (C), 132.4 (C), 132.1 (CH), 130.1 (CH), 129.6 (CH), 129.2 (CH), 129.1 (CH), 128.6 (C), 128.5 (CH), 128.0 (CH), 127.9 (CH), 103.5 (C), 59.6 (CH).

HRMS (ESI) *m/z*: 442.0115/440.0121 $[M+H]^+$ 100.0/50.7, $C_{22}H_{17}ClNO_2Se$ requires 442.0113/440.0121.

(*S*)-6-phenyl-5-(phenylselanyl)-4-(*o*-tolyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (36ha)



36ha

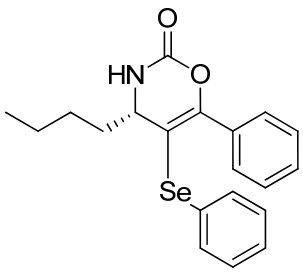
Mp 57-59 °C; $[\alpha]_D^{20}$ +173.7 (*c* 1.03, $CHCl_3$, 90% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66-7.62 (m, 2H), 7.42-7.38 (m, 3H), 7.33-7.30 (m, 1H), 7.26-7.20 (m, 7H), 7.11-7.08 (m, 1H), 5.96 (br s, 1H), 5.22 (d, *J* = 2.2 Hz, 1H), 2.14 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.8 (C), 150.0 (C), 138.6 (C), 135.8 (C), 132.7 (C), 131.9 (CH), 131.0 (CH), 130.0 (CH), 129.4 (CH), 129.2 (CH), 128.9 (C), 128.6 (CH), 127.93 (CH), 127.89 (CH), 127.6 (CH), 127.0 (CH), 103.4 (C), 59.8 (CH), 18.9 (CH_3).

HRMS (ESI) *m/z*: 422.0647/420.0655 $[M+H]^+$ 100.0/51.1, $C_{23}H_{20}NO_2Se$ requires 422,0659/420.0667.

(*S*)-4-butyl-6-phenyl-5-(phenylselanyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (36ra)



36ra

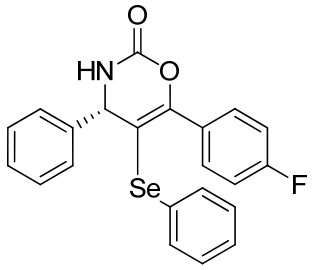
Mp 103-105 °C; $[\alpha]_D^{20}$ +142.8 (*c* 1.72, $CHCl_3$, 46% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59-7.55 (m, 2H), 7.40-7.38 (m, 5H), 7.28-7.26 (m, 3H), 6.34 (br d, *J* = 2.4 Hz, 1H), 3.86-3.82 (m, 1H), 1.85-1.78 (m, 2H), 1.42-1.26 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.7 (C), 151.6 (C), 132.7 (C), 131.8 (CH), 129.8 (CH), 129.5 (CH), 129.1 (CH), 128.8 (C), 127.8 (CH), 127.7 (CH), 104.2 (C), 55.8 (CH), 35.6 (CH_2), 25.9 (CH_2), 22.3 (CH_2), 13.9 (CH_3).

HRMS (ESI) *m/z*: 388.0820/386.0826 $[M+H]^+$ 100.0/49.3, $C_{20}H_{22}NO_2Se$ requires 388.0816/386.0824.

(*S*)-5-((4-fluorophenyl)selanyl)-4,6-diphenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (36ad)



36ad

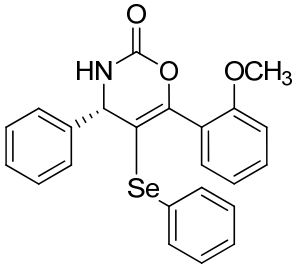
Mp 52-55 °C; $[\alpha]_D^{20}$ +185.4 (*c* 1.03, $CHCl_3$, 88% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62-7.58 (m, 2H), 7.35-7.30 (m, 3H), 7.29-7.23 (m, 7H), 7.07 (t, *J* = 8.7 Hz, 2H), 6.15 (br d, *J* = 1.9 Hz, 1H), 4.87 (d, *J* = 2.4 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.4 (d, *J* = 253.9 Hz, C), 150.6 (C), 150.1 (C), 140.7 (C), 131.8 (CH), 131.3 (d, *J* = 8.5 Hz, CH), 129.5 (CH), 129.0 (CH), 128.82 (CH), 128.78 (C), 128.7 (d, *J* = 3.4 Hz, C), 127.8 (CH), 127.2 (CH), 115.0 (d, *J* = 21.9 Hz, CH), 104.0 (C), 60.4 (CH).

HRMS (ESI) *m/z*: 426.0404/424.0413 $[M+H]^+$ 100.0/50.9, $C_{22}H_{17}FNO_2Se$ requires 426.0409/424.0416.

(*S*)-6-(2-methoxyphenyl)-4-phenyl-5-(phenylselanyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (36af)



36af

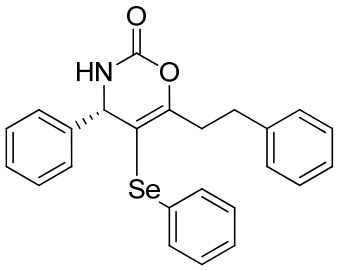
Mp 170-177 °C; $[\alpha]_D^{20}$ +139.4 (*c* 0.99, $CHCl_3$, 66% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.29 (m, 9H), 7.26-7.21 (m, 3H), 6.98 (td, *J* = 7.5, 0.9 Hz, 1H), 6.9 (d, *J* = 8.2 Hz, 1H), 5.91 (br s, 1H), 4.87 (d, *J* = 2.3 Hz, 1H), 3.82 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.4 (C), 150.1 (C), 140.9 (C), 132.2 (CH), 131.3 (CH), 130.9 (CH), 129.2 (CH), 129.1 (C), 128.9 (CH), 128.7 (CH), 127.40 (CH), 127.35 (CH), 122.4 (C), 120.2 (CH), 110.9 (CH), 105.9 (C), 60.2 (CH), 55.5 (CH_3).

HRMS (ESI) *m/z*: 438.0605/436.0611 $[M+H]^+$ 100.0/51.3, $C_{23}H_{20}NO_3Se$ requires 438.0608/436.0616.

(*S*)-6-phenethyl-4-phenyl-5-(phenylselanyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (36ak)



36ak

White oil; $[\alpha]_D^{20}$ +41.6 (*c* .084, $CHCl_3$, 82% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.19 (m, 11H), 7.15-7.12 (m, 2H), 7.04-7.01 (m, 2H), 5.63 (br s, 1H), 4.71 (d, *J* = 1.9 Hz, 1H), 3.09-2.92 (m, 4H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 154.0 (C), 149.8 (C), 140.7 (C), 140.0 (C), 131.0 (CH), 129.4 (CH), 129.1 (C), 128.77 (CH), 128.75 (CH), 128.6 (CH), 128.5 (CH), 127.2 (CH), 127.2 (CH), 126.3 (CH), 103.1 (C), 60.2 (CH), 34.2 (CH_2), 32.6 (CH_2).

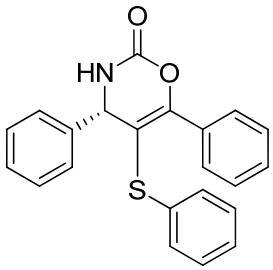
HRMS (ESI) *m/z*: 436.0818/434.0824 $[M+H]^+$ 100/48.5, $C_{24}H_{22}NO_2Se$ requires 436.0816/434.0824.

5.5.2.6. Synthesis and characterization of 5-phenylsulfenyl-1,3-oxazin-2-ones 37

Preparation of the phenylsulfenyl chloride solution:[115] Sulfuryl chloride (80 µL, 1.0 mmol) was added to a solution of diphenyl sulfide (240.2 mg, 1.1 mmol) in 1,2-dichloroethane (3 mL) at room temperature. The solution was stirred for 5 min and the volume was completed to 5 mL.

A freshly prepared 0.4 M solution of phenylsulfenyl chloride in 1,2-dichloroethane (0.375 mL, 0.15 mmol) was added to a solution of *N*-Cbz protected propargylic amine **11** (0.10 mmol) in acetonitrile (2 mL) at 0 °C. The solution was stirred until the reaction was complete (TLC). The reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **37**.

(*S*)-4,6-diphenyl-5-(phenylthio)-3,4-dihydro-2*H*-1,3-oxazin-2-one (37aa)



37aa

Enantiomeric excess (87%) was determined by chiral HPLC (Chiralcel AD-H), hexane-^{i}PrOH 90:10, 1 mL/min, major enantiomer t_r = 12.3 min, minor enantiomer t_r = 23.4 min.

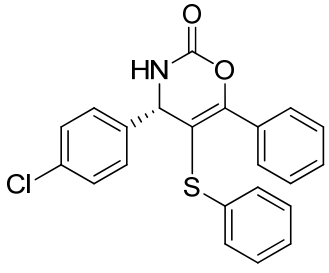
Mp 158-159 °C; $[\alpha]_D^{20}$ +328.0 (*c* 1.00, $CHCl_3$, 87% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.68 (m, 2H), 7.41-7.22 (m, 13H), 6.10 (br s, 1H), 4.87 (d, *J* = 2.3 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.9 (C), 150.1 (C), 140.6 (C), 133.7 (C), 131.5 (C), 130.1 (CH), 129.4 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 127.9 (CH), 127.1 (CH), 127.0 (CH), 106.8 (C), 58.8 (CH).

HRMS (ESI) *m/z*: 360.1051/361.1083 $[M+H]^+$ 100.0/25.3, $C_{22}H_{18}NO_2S$ requires 360.1058/361.1092.

(*S*)-4-(4-chlorophenyl)-6-phenyl-5-(phenylthio)-3,4-dihydro-2*H*-1,3-oxazin-2-one (37ea)



37ea

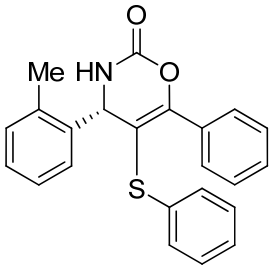
Mp 156-159 °C; $[\alpha]_D^{20}$ +269.4 (*c* 1.00, $CHCl_3$, 90% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.67 (m, 2H), 7.43-7.35 (m, 3H), 7.33-7.16 (m, 9H), 6.22 (br d, *J* = 1.9 Hz, 1H), 4.86 (d, *J* = 2.5 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 153.0 (C), 149.9 (C), 139.0 (C), 134.7 (C), 133.4 (C), 131.3 (C), 130.3 (CH), 129.5 (CH), 129.2 (CH), 129.0 (CH), 128.8 (CH), 128.4 (CH), 128.0 (CH), 127.1 (CH), 106.5 (C), 58.1 (CH).

HRMS (ESI) *m/z*: 394.0662/396.0633 $[M+H]^+$ 100.0/32.1, $C_{22}H_{17}ClNO_2S$ requires 394.0669/396.0639.

(*S*)-6-phenyl-5-(phenylthio)-4-(*o*-tolyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (37ha)



37ha

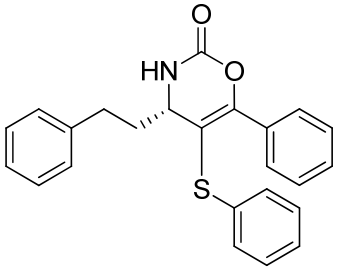
Mp 139-142 °C; $[\alpha]_D^{20}$ +295.8 (*c* 1.25, $CHCl_3$, 90% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74-7.70 (m, 2H), 7.42-7.37 (m, 3H), 7.31-7.17 (m, 8H), 7.11-7.08 (m, 1H), 6.07 (br s, 1H), 5.23 (d, *J* = 2.2 Hz, 1H), 2.13 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 153.3 (C), 149.9 (C), 138.5 (C), 135.9 (C), 133.9 (C), 131.6 (C), 130.0 (CH), 130.1 (CH), 129.3 (CH), 129.0 (CH), 128.7 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 127.0 (CH), 126.8 (CH), 106.3 (C), 55.2 (CH), 18.9 (CH_3).

HRMS (ESI) *m/z*: 374.1220/375.1249 $[M+H]^+$ 100.0/25.0, $C_{23}H_{20}NO_2S$ requires 374.1215/375.1248.

(*S*)-6-phenethyl-4-phenyl-5-(phenyltellanyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (37qa)



37qa

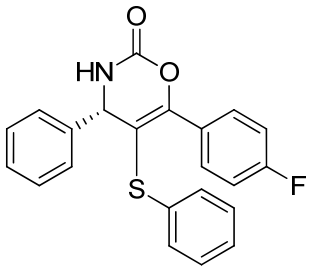
Mp 145-149 °C; $[\alpha]_D^{20}$ +145.4 (*c* 1.00, $CHCl_3$, 60% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.64 (m, 2H), 7.42-7.37 (m, 3H), 7.31-7.16 (m, 10H), 6.19 (br d, *J* = 2.6 Hz, 1H), 3.96-3.92 (m, 1H), 2.86-2.65 (m, 2H), 2.21-2.13 (m, 2H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 153.4 (C), 151.0 (C), 140.4 (C), 133.5 (C), 131.6 (C), 130.0 (CH), 129.4 (CH), 129.0 (CH), 128.8 (CH), 128.6 (CH), 128.3 (CH), 127.9 (CH), 127.0 (CH), 126.2 (CH), 106.7 (C), 53.9 (CH), 37.0 (CH_2), 30.3 (CH_2).

HRMS (ESI) *m/z*: 388,1365/389.1397 $[M+H]^+$ 100.0/26.0, $C_{24}H_{22}NO_2S$ requires 388,1371/389.1405.

(*S*)-5-((4-fluorophenyl)selanyl)-4,6-diphenyl-3,4-dihydro-2*H*-1,3-oxazin-2-one (37ad)



37ad

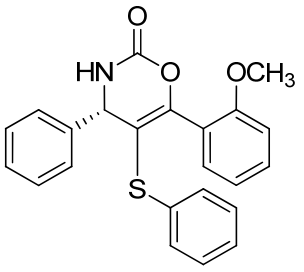
Mp 111-114 °C; $[\alpha]_D^{20}$ +237.5 (*c* 1.00, $CHCl_3$, 88% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74-7.67 (m, 2H), 7.38-7.20 (m, 10H), 7.10-7.03 (m, 2H), 5.94 (br d, *J* = 1.6 Hz, 1H), 4.87 (d, *J* = 2.4 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.5 (d, *J* = 251.1 Hz, C), 152.0 (C), 149.8 (C), 140.5 (C), 133.5 (C), 131.2 (d, *J* = 8.6 Hz, CH), 129.5 (CH), 129.0 (CH), 128.9 (CH), 128.6 (CH), 127.6 (d, *J* = 3.4 Hz, C), 127.1 (CH), 127.0 (CH), 115.1 (d, *J* = 21.9 Hz, CH), 106.8 (C), 58.9 (CH).

HRMS (ESI) *m/z*: 378.0960/379.0993 $[M+H]^+$ 100.0/23.8, $C_{22}H_{17}FNO_2S$ requires 378.0964/379.0998.

(*S*)-6-(2-methoxyphenyl)-4-phenyl-5-(phenylthio)-3,4-dihydro-2*H*-1,3-oxazin-2-one (37af)



37af

Mp 172-179 °C; $[\alpha]_D^{20}$ +165.8 (*c* 1.00, $CHCl_3$, 66% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.29 (m, 9H), 7.25-7.21 (m, 3H), 6.98 (td, *J* = 7.5, 1.0 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 5.83 (br d, *J* = 1.2 Hz, 1H), 4.87 (d, *J* = 2.3 Hz, 1H), 3.82 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.4 (C), 150.1 (C), 141.0 (C), 132.2 (CH), 131.3 (CH), 130.9 (CH), 129.2 (CH), 129.1 (C), 128.9 (CH), 128.7 (CH), 127.40 (CH), 127.35 (CH), 122.4 (C), 120.2 (CH), 110.9 (CH), 105.9 (C), 60.2 (CH), 55.5 (CH_3).

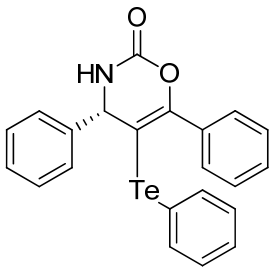
HRMS (ESI) *m/z*: 390.1156/391.1190 $[M+H]^+$ 100.0/24.7, $C_{23}H_{20}NO_3S$ requires 390.1164/391.1197.

5.5.2.7. Synthesis and characterization of 5-phenyltellanyl-1,3-oxazin-2-ones 38

Preparation of the phenyltelluryl bromide solution:[116] Bromine (10 µL, 0.2 mmol) was added to a flask containing diphenyl ditelluride (81.9 mg, 0.2 mmol) in 1,2-dichloroethane (0.4 mL) at 0 °C. The reaction mixture was stirred for 15 min at this temperature.

A 0.5 M solution of phenyltelluryl bromide in 1,2-dichloroethane (0.3 mL, 0.15 mmol) is added to a solution of *N*-Cbz protected propargylic amine **11** (0.10 mmol) in acetonitrile (2 mL) at 0 °C. The solution was stirred until the reaction was complete (TLC). The reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **38**.

(*S*)-4,6-diphenyl-5-(phenyltellanyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (38aa)



38aa

Enantiomeric excess (87%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 90:10, 1 mL/min, major enantiomer t_r = 13.1 min, minor enantiomer t_r = 16.5 min.

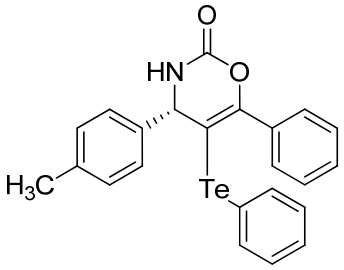
Mp 61-63 °C; $[\alpha]_D^{20}$ +50.8 (*c* 0.39, $CHCl_3$, 87% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.47 (m, 4H), 7.43-7.39 (m, 3H), 7.35-7.30 (m, 4H), 7.23-7.16 (m, 4H), 5.97 (br d, *J* = 1.6 Hz, 1H), 4.86 (d, *J* = 2.4 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.9 (C), 150.4 (C), 140.9 (C), 138.7 (CH), 134.4 (C), 130.0 (CH), 129.5 (CH), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.0 (CH), 127.3 (CH), 113.0 (C), 89.1 (C), 62.5 (CH).

HRMS (ESI) *m/z*: 458.0395/456.0379 $[M+H]^+$ 100.0/93.1, $C_{22}H_{18}NO_2Te$ requires 458.0400/ 456.0382.

(*S*)-6-phenyl-5-(phenyltellanyl)-4-(*p*-tolyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (38ba)



38ba

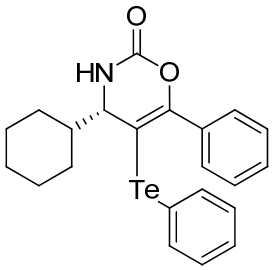
Mp 54-58 °C; $[\alpha]_D^{20}$ +58.4 (*c* 1.00, $CHCl_3$, 88% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.46 (m, 4H), 7.43-7.38 (m, 3H), 7.32 (tt, *J* = 7.1, 1.5 Hz, 1H), 7.19 (t, *J* = 7.34 Hz, 2H), 7.15-7.08 (m, 4H), 5.79 (br d, *J* = 1.9 Hz, 1H), 4.83 (d, *J* = 2.4 Hz, 1H), 2.35 (s, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.9 (C), 150.3 (C), 138.6 (C), 138.6 (CH), 138.1 (C), 134.5 (C), 130.0 (CH), 129.6 (CH), 129.5 (CH), 129.2 (CH), 128.6 (CH), 128.0 (CH), 127.2 (CH), 113.1 (C), 89.5 (C), 62.4 (CH), 21.2 (CH_3).

HRMS (ESI) *m/z*: 472,0554/470.0536 $[M+H]^+$ 100.0/92.9, $C_{23}H_{20}NO_2Te$ requires 472,0556/470.0539.

(*S*)-4-cyclohexyl-6-phenyl-5-(phenyltellanyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (38sa)



38sa

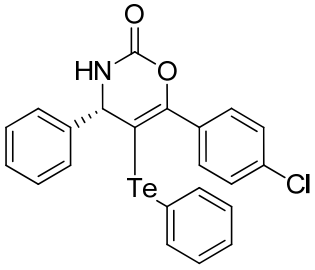
Mp 63-66 °C; $[\alpha]_D^{20}$ +73.8 (*c* 1.00, $CHCl_3$, 54% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.66 (m, 2H), 7.47-7.40 (m, 4H), 7.39-7.31 (m, 2H), 7.23 (tt, *J* = 7.2, 1.3 Hz, 2H), 5.90 (br d, *J* = 2.7 Hz, 1H), 3.60 (br t, *J* = 2.7 Hz, 1H), 1.96-1.65 (m, 1H), 1.78-1.65 (m, 5), 1.26-1.07 (m, 5H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.2 (C), 138.9 (CH), 134.6 (C), 129.9 (CH), 129.6 (CH), 128.9 (CH), 128.8 (CH), 128.0 (CH), 112.6 (C), 88.5 (C), 62.5 (CH), 42.5 (CH), 29.5 (CH_2), 26.4 (CH_2), 26.1 (CH_2), 25.9 (CH_2), 24.9 (CH_2).

HRMS (ESI) *m/z*: 464.0865/462.0847 $[M+H]^+$ 100.0/92.8, $C_{22}H_{24}NO_2Te$ requires 464.0869/462.0852.

(*S*)-6-(4-chlorophenyl)-4-phenyl-5-(phenyltellanyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (38ae)



38ae

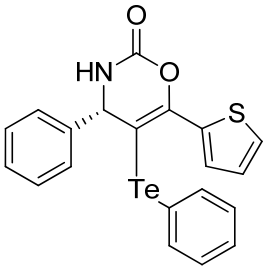
Mp 62-66 °C; $[\alpha]_D^{20}$ +121.4 (*c* 1.00, $CHCl_3$, 91% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.45 (m, 2H), 7.42 (dt, *J* = 8.7, 2.1 Hz, 2H), 7.37-7.29 (m, 6H), 7.23-7.16 (m, 4H), 5.88 (br d, *J* = 1.7 Hz, 1H), 4.90 (d, *J* = 2.4 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.9 (C), 150.1 (C), 140.7 (C), 138.5 (CH), 136.0 (C), 132.8 (C), 130.5 (CH), 129.6 (CH), 129.0 (CH), 128.9 (CH), 128.7 (CH), 128.3 (CH), 127.3 (CH), 112.9 (C), 89.8 (C), 62.9 (CH).

HRMS (ESI) *m/z*: 492.0006/489.9989 $[M+H]^+$ 100.0/93.0, $C_{22}H_{17}ClNO_2Te$ requires 492.0010/489.9992.

(*S*)-4-phenyl-5-(phenyltellanyl)-6-(thiophen-2-yl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (38ai)



38ai

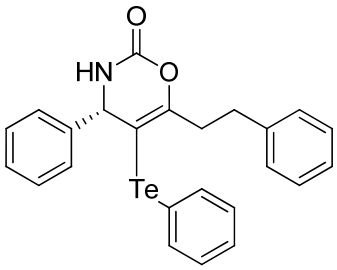
Orange oil; $[\alpha]_D^{20}$ +87.8 (*c* 0.98, $CHCl_3$, 90% *ee*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.54 (m, 2H), 7.53 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.43 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.36-7.29 (m, 4H), 7.23-1.17 (m, 4H), 7.09 (dd, *J* = 3.8, 5.2 Hz, 1H), 5.90 (br d, *J* = 1.8 Hz, 1H), 4.88 (d, *J* = 2.6 Hz, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.0 (C), 146.3 (C), 140.8 (C), 138.2 (CH), 135.5 (C), 130.1 (CH), 129.7 (CH), 129.0 (CH), 128.74 (CH), 128.68 (CH), 128.5 (CH), 127.3 (CH), 126.8 (CH), 113.4 (C), 88.5 (C), 63.2 (CH).

HRMS (ESI) *m/z*: 463.9960/461.9942 $[M+H]^+$ 100.0/92.8, $C_{20}H_{16}NO_2STe$ requires 463.9964/461.9946.

(*S*)-6-phenethyl-4-phenyl-5-(phenyltellanyl)-3,4-dihydro-2*H*-1,3-oxazin-2-one (38ak)



38ak

Yellow oil; $[\alpha]_D^{20}$ -12.1 (*c* 1.00, $CHCl_3$, 82% *ee*)

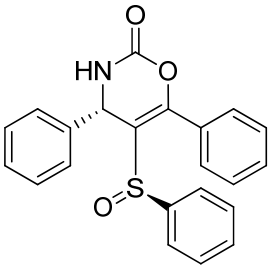
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.36 (m, 2H), 7.29-7.23 (m, 6H), 7.21-7.13 (m, 5H), 7.03-7.00 (m, 2H), 5.64 (br d, *J* = 1.0 Hz, 1H), 4.84 (br s, 1H), 3.14-3.05 (m, 2H), 2.97-2.91 (m, 2H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 154.6 (C), 150.1 (C), 141.0 (C), 139.9 (C), 137.0 (CH), 129.5 (CH), 128.82 (CH), 128.76 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.4 (CH), 126.3 (CH), 113.3 (C), 89.4 (C), 63.2 (CH), 37.7 (CH_2), 33.0 (CH_2).

HRMS (ESI) *m/z*: 486.0711/484.0692 $[M+H]^+$ 100/92.7, $C_{24}H_{22}NO_2Te$ requires 486.0713/484.0695.

5.5.2.8. Synthesis and characterization of (S)-4,6-diphenyl-5-((S)-phenylsulfinyl)-3,4-dihydro-2H-1,3-oxazin-2-one (42)[117]

To a solution of (*S*)-4,6-diphenyl-5-(phenylthio)-3,4-dihydro-2*H*-1,3-oxazin-2-one (**37aa**) (18.0 mg, 0.05 mmol) and phenol (54 µL, 0.60 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (0.4 mL) was added 30% H_2O_2 (10.2 µL, 0.10 mmol). The reaction mixture was stirred at room temperature until the disappearance of the reactant monitored by TLC, the excess H_2O_2 was quenched with saturated aqueous Na_2SO_3. Phenol was neutralized with 10% aqueous NaOH. The aqueous layer was extracted with EtOAc (2 × 3 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum to afford the crude product, which was purified by flash column chromatography on silica gel using hexane/ethyl acetate as the eluent to afford **42**. Only the major diastereoisomer was characterized (99% yield, 1:2.5 dr).



42

Mp 159-161 °C; $[\alpha]_D^{20}$ +43.0 (*c* 0.70, $CHCl_3$, 87% *ee*)

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35-8.32 (m, 2H), 8.14 (br d, *J* = 2.3 Hz, 1H), 8.09-8.04 (m, 8H), 7.92-7.77 (m, 5H), 5.21 (br d, *J* = 2.8 Hz, 1H).

^{13}C NMR (75.5 MHz, DMSO-d_6) δ 168.4 (C), 158.9 (C), 153.8 (C), 152.5 (C), 141.9 (CH), 141.6 (CH), 141.4 (C), 140.1 (CH), 140.0 (CH), 139.4 (CH), 139.2 (CH), 138.7 (CH), 137.3 (CH), 135.1 (CH), 130.1 (C), 63.6 (CH).

HRMS (ESI) *m/z*: 375.9906/376.9911 $[M+H]^+$ 100/24.4, $C_{22}H_{18}NO_sS$ requires 376.1002/377.1036.

5.5.3. Additional computational data

Table 5.17. B3LYP/6-311G* Total (E, in au) relative (ΔE, in kcal/mol, relative to **11ta** or **11tq** plus halogen X_2) energies, in gas phase and in acetonitrile, of the TSs, intermediates and product of the halogen-mediated cyclization of protected propargylic amines **11ta** and **11tq**.

	Gas phase		Acetonitrile	
	E	**ΔE**	**E**	**ΔE**
11ta	-670.422630		-670.436638	
Br_2	-5148.283942		-5148.285454	
MC1-Br	-5818.711928	-3.4	-5818.723724	-1.0
TS1-*endo*-Br	-5818.683616	14.4	-5818.721217	0.5
TS1-*exo*-Br	-5818.678737	17.5	-5818.708764	8.4
IN1-*endo*-Br	-5818.686248	12.8	-5818.753998	-20.0
IN1-*exo*-Br	-5818.681583	15.7	-5818.752981	-19.4
TS2-*endo*-Br	-5818.692105	9.1	-5818.733748	-7.3
TS2-*exo*-Br	-5818.691176	9.7	-5818.735663	-8.5
34ta + MeBr	-5818.754904	-30.3	-5818.767702	-28.6
40ta + MeBr	-5818.759735	-33.4	-5818.772849	-31.8
Cl_2	-920.405676		-920.406713	
MC1-Cl	-1590.833574	-3.3	-1590.845281	-1.2
TS1-*endo*-Cl	-1590.813192	9.5	-1590.863822	-12.8
IN1-*endo*-Cl	-1590.823147	3.2	-1590.909108	-41.3
TS2-*endo*-Cl	-1590.845367	-10.7	-1590.889659	-29.1
35ta + MeCl	-1590.912542	-52.9	-1590.925218	-51.4
11aq	-478.643497		-478.653276	
MC2-Br	-5626.935241	-4.9	-5626.945236	-4.1
TS3-*endo*-Br	-5626.909958	11.0	-5626.935527	2.0
TS3-*exo*-Br	-5626.903185	15.2	-5626.933514	3.3
IN3-*endo*-Br	-5626.914192	8.3	-5626.982556	-27.5
IN3-*exo*-Br	-5626.905634	13.7	-5626.979213	-25.4

Table 5.18. Total[a] and relative energies in acetonitrile (in kcal/mol, relative to **11aa** plus PhSeCl) of the stationary points involved in cyclization of **11aa**.

	E	**ΔE**
11aa	-1093.306676	
MC	-4186.786573	-0.8
TS1-*endo*	-4186.778112	4.5
IN1-*endo*	-4186.805353	-12.6
TS2-*endo*	-4186.792541	-4.6
2-*endo*	-3455.569547	-22.6
TS1-*exo*	-4186.767667	11.1
IN1-*exo*	-4186.805128	-12.5
TS2-*exo*	-4186.793389	-5.1
2-*exo*	-3455.572583	-24.4

[a] Total energies of PhSeCl -3093.478606 au and $PhCH_2Cl$ -731.2516743 au.

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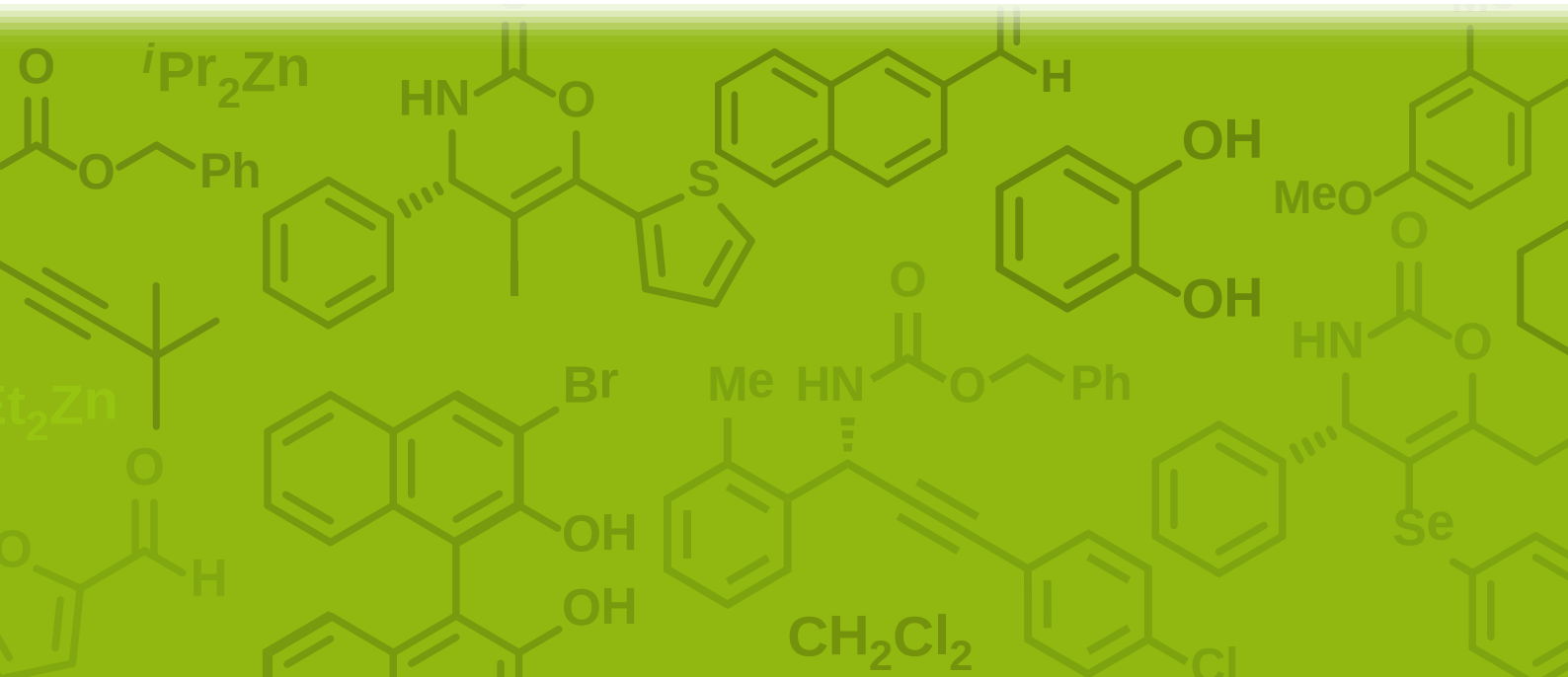
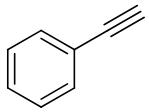
ANEXOS



ANEXO I. Alquinos



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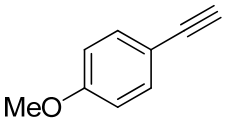

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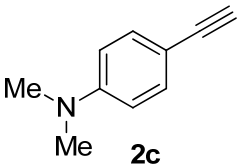

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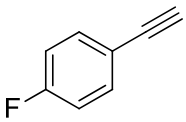

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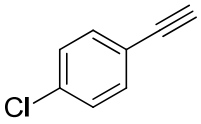

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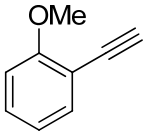

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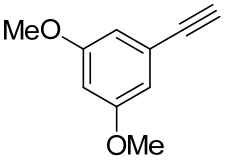

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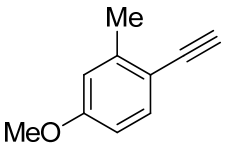

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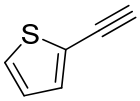

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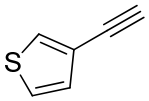

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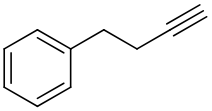

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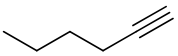

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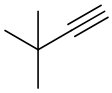

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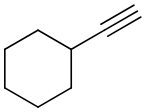

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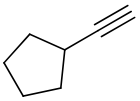

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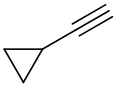

2p

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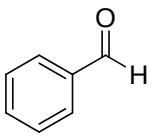

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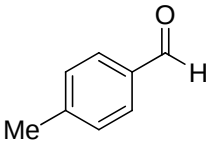

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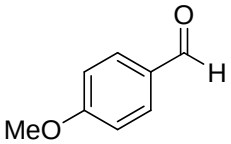

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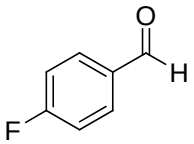

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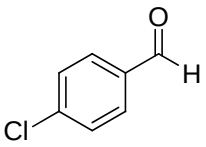

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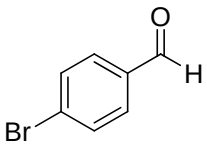

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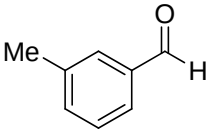

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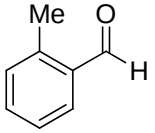

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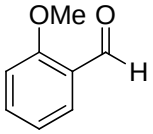

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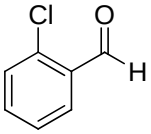

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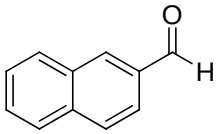

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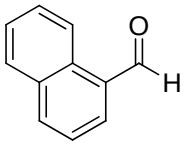

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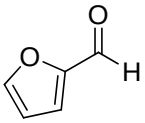

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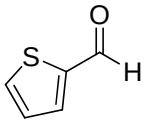

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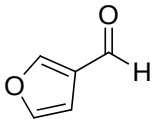

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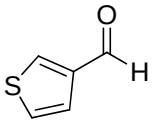

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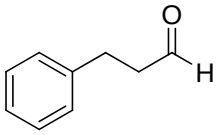

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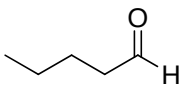

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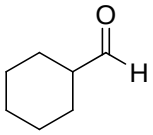

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ANEXO III. Relación de publicaciones derivadas de esta tesis

1498 *Current Organic Chemistry*, 2009, *13*, 1498-1539

Recent Developments in Asymmetric Alkynylation of Imines

G. Blay, A. Monleón and J. R. Pedro*

Departament de Química Orgànica, Facultat de Química, Universitat de València, Dr. Moliner 59, E-46100 Burjassot (València), Spain

Abstract: This review deals with the asymmetric alkynylation of imines (and iminium ions) to give chiral nonracemic propargylamines. Diastereoselective procedures involved the addition of metal alkynylides to chiral nonracemic imines derived from chiral amines or chiral carbonyl compounds. Enantioselective non-catalytic procedures have been achieved with the use of stoichiometric additives or alkynylboron reagents. Finally, catalytic addition of terminal alkynes or zinc acetylides has been carried out in the presence of chiral metal complexes, especially copper complexes as catalysts.

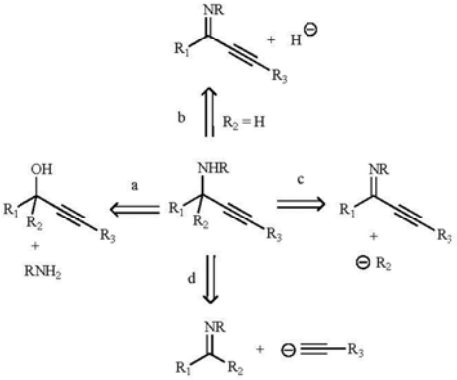
1. INTRODUCTION

In the last years, propargylamines have emerged as an important class of versatile building blocks for the synthesis of a broad range of nitrogen-containing heterocycles [1], complex natural products and other bioactive compounds [2]. In addition, the aminopropargyl moiety is found in a number of compounds with interesting biological and pharmacological properties, for example as inhibitors of the enzyme monoamide oxidase B (MAO-B) [3], subtype-selective *N*-methyl-D-aspartate (NMDA) receptor antagonists [4], antiplatelet aggregation inhibitors [5], γ-aminobutyric acid (GABA) degradation inhibitors [6], antibiotics [7], acetyl-CoA carboxylase (ACC) inhibitors [8] or herbicides [9] among others.

Due to the importance of the absolute stereochemistry of the molecules on their biological activity as well as on the properties of materials, the development of synthetic procedures that allow the preparation of enantiomerically pure or enriched products has attracted much attention in the last decade [10].

Four different general synthetic approaches to chiral nonracemic propargylamines have been devised (Scheme **1**): the nucleophilic substitution of nonracemic chiral propargylic alcohols with nitrogen nucleophiles [11] (approach a), the selective reduction of the C=N double bond in propargylic ketimines [12] (approach b), the addition of carbon nucleophiles to propargyl imines [13] (approach c) and the addition of alkyne nucleophiles to imines (approach d).

This last approach takes advantage of the acidity of terminal alkynyl protons to prepare alkynyl-metal reagents as good functional carbon nucleophiles. Although the asymmetric alkynylation of the parent carbonyl compounds to give chiral propargylic alcohols has been the subject of a large number of publications [14], the asymmetric alkynylation of imines and their derivatives is more challenging as a result of the reduced reactivity of these compounds compared to aldehydes and ketones. Reactivity of the C=N double bond can be enhanced by the use of nitrones, *in situ* generation of iminium ions or by introducing electron-withdrawing groups on the imine nitrogen. By using these strategies it has been possible to carry out effective alkynylation reactions leading to propargylamines. Asymmetric reactions have been performed via diastereoselective procedures with the use of imines bearing a chiral substituent on the nitrogen, especially chiral sulfinyl imines. In the last years, the development of the reaction has focused on enantioselective procedures, especially those based on catalytic methodologies. Herein, the most significant contributions on the asymmetric alkynylation of imines, either by diastereoselective or enantioselective strategies that have appeared in the literature so far will be revised [15]. Due to the length of this review, alkynylation of nitrones will not be considered [16].



Scheme 1. General approaches for the synthesis of propargylic amines.

2. DIASTEREOSELECTIVE METHODS

2.1. Diastereoselective Alkynylation of *N*-sulfinyl Imines

2.1.1. Addition of Alkynyl Grignard Organometallics

The addition of organometallic reagents to chiral aldimines and ketimines has been used for the synthesis of chiral

*Address correspondence to this author at the Departament de Química Orgànica, Facultat de Química, Universitat de València, Dr. Moliner 59, E-46100 Burjassot (València), Spain; Tel: (+34) 963544329; Fax: (+34)963544328; E-mail: jose.r.pedro@uv.es

1385-2728/09 $55.00+.00

Tetrahedron 68 (2012) 2128–2134

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Enantioselective addition of terminal alkynes to *N*-(diphenylphosphinoyl)imines catalyzed by Zn–BINOL complexes

Gonzalo Blay, Eric Ceballos, Alicia Monleón, José R. Pedro *

Departament de Química Orgànica, Facultat de Química, Universitat de València, Dr. Moliner 50, E-46100 Burjassot, València, Spain

ARTICLE INFO

Article history:
Received 27 October 2011
Received in revised form 12 January 2012
Accepted 13 January 2012
Available online 21 January 2012

Keywords:
Alkynylation
C–C bond formation
Propargylic amines
Asymmetric catalysis
Nucleophilic addition

ABSTRACT

Chiral nonracemic *N*-(diphenylphosphinoyl)-protected propargylic amines have been prepared by addition of terminal alkynes to *N*-(diphenylphosphinoyl)aldimines in the presence of dimethylzinc and 3,3′-dibromo-BINOL as catalyst. The reaction works with a variety of aromatic and heteroaromatic aldimines and with different alkynes, providing the expected products in generally good yields and enantiomeric excesses (up to 96%).

1. Introduction

The catalytic enantioselective addition of terminal alkynes to C=N bonds is currently one of the most important objectives in organic synthesis as the resulting chiral propargylamines are important synthetic intermediates for the construction of biologically active nitrogen-containing compounds and natural products.[1] However, in contrast to the extensive studies on the asymmetric alkynylation of carbonyl compounds,[2] the number of studies on the enantioselective alkynylation of imines and imine derivatives are much more reduced. Most of these studies have focused on the use of Cu(I) salts in combination with nitrogen-containing ligands to catalyze the enantioselective alkynylation of *N*-aryl imines.[3] Leading studies of this reaction have been developed by Wei,[4] Chan,[5] Bisai,[6] Benaglia,[7] Knochel,[8] Carreira,[9] and Zhao.[10]

Other methods that do not make use of copper complexes as the catalyst have been also described. Hoveyda[11] has used peptide-based ligands in combination with $Zr(O^iPr)_4 \cdot HO^iPr$ to catalyze the alkynylation of *N*-aryl aromatic imines. Jiang[12] has reported the addition of terminal alkynes to a trifluoromethyl activated cyclic imine by using a stoichiometric amount of a chiral amino alcohol ligand and $Zn(OTf)_2$ as promoter. Bolm[13] has described the use of amino alcohol ligands and dimethylzinc to promote the addition of terminal alkynes to *N*-aryl imines. Rueping[14] has reported the addition of aryl alkynes to α-imino esters by dual catalysis (Brönsted acid and metal salt) with good results.

Other methods are based in the enhancement of the electrophilicity of the imine by introducing an electron-withdrawing group attached to the nitrogen atom. The alkynylation of these substrates lead to protected propargylic amines. Chong[15] and Soderquist[16] accomplished the alkynylation of *N*-acylimines by using chiral alkynylboronates and alkynylboranes based on the BINOL and the borabicyclo[3.3.2]decane scaffolds, respectively, as nucleophilic reagents. Recently we have reported[17] the direct addition of terminal alkynes to *N*-sulfonylimines by using dimethylzinc and BINOL as catalyst. Finally, Wang has described the alkynylation of *N*-(diphenylphosphinoyl)imines promoted by proline-derived β-amino alcohol ligands and diethylzinc, requiring high (60 mol %) or stoichiometric amounts of ligand,[18] which could be reduced (35 mol %) when a tridentate amino alcohol was used.[19]

N-Phosphinoylimines are very attractive activated imines since the phosphinoyl group can be easily removed from the addition products under mild reaction conditions leading to the free amines.[20] For this reason, they have been widely used in catalytic asymmetric nitro-Mannich,[21] Mannich,[22] Strecker,[23] and organometallic addition[24] processes. Herein we report our results on the enantioselective addition of terminal alkynes to *N*-(diphenylphosphinoyl)imines catalyzed by a BINOL-type ligand and dimethylzinc (Scheme 1). Commercially available BINOL-type ligands were chosen in our study because they are known to give highly enantioselective reactions with a variety of metals, including zinc.[25]

* Corresponding author. Tel.: +34 963544329; fax: +34 963544328; e-mail address: jose.r.pedro@uv.es (J.R. Pedro).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2012.01.037

CHEMISTRY
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DOI: 10.1002/chem.201102909

Enantioselective Zinc/BINOL-Catalysed Alkynylation of Aldimines Generated in Situ from α-Amido Sulfones

Gonzalo Blay, Ana Brines, Alicia Monleón, and José R. Pedro*[a]

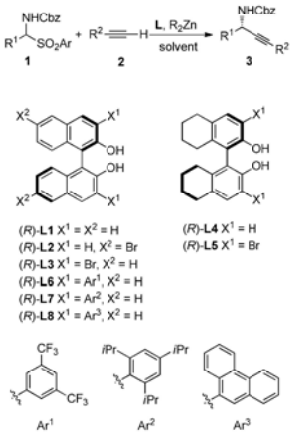
Abstract: Chiral nonracemic *N*-Cbz-protected propargylic amines have been prepared by the addition of terminal alkynes to imines generated in situ from α-amido sulfones in the presence of diethylzinc and BINOL-type ligands as catalysts. The reactions give good yields and high enantioselectivities (*ee* values up to 95%) for a good number of aromatic and heteroaromatic α-amido sulfones and alkynes.

Keywords: alkynylation · asymmetric catalysis · enantioselectivity · nucleophilic addition · propargylic amines

Introduction

Optically active propargylic amines are useful building blocks for organic synthesis and important skeletons in biologically active compounds and natural products.[1] Consequently, considerable efforts have been made to develop methodologies for generating compounds of this kind in optically active form.[2] In this context, most of the studies reported so far have involved catalytic enantioselective alkynylation of *N*-arylimines in the presence of Cu^I salts in combination with nitrogen-containing ligands.[3] Other methods involve the enhancement of the electrophilic aptitude of the carbon-nitrogen double bond through the binding of electron-withdrawing groups to the nitrogen atom, leading to *N*-protected propargylic amines.[4]

A possible alternative to these methods is the generation of the imine in situ through the use of a precursor with a good leaving group at the carbon α to the nitrogen atom. α-Amido sulfones **1** (Scheme 1) are suitable precursors of imines because they react with basic reagents by deprotonation of the carbamate and elimination of the sulfinate group to give *N*-carbamoyl imines.[5] Advantageously, α-amido sulfones are stable solids that can be readily obtained in one-step fashion by condensation of carbamates and sodium aryl sulfinates with the desired aldehydes.[6] In fact, several authors have described the non-asymmetric alkynylation of α-amido sulfones[7] and Moloney has reported examples of diastereoselective alkynylations of an α-amido sulfone derived from ethyl pyroglutamate with Grignard reagents and zinc bromide.[8] In addition, α-amido sulfones have been used as reactive precursors of imines for the asymmetric addition of organometallic reagents, in Mannich, aza-Henry, Strecker and other asymmetric nucleophilic addition reactions.[5] In particular, enantioselective addition of dialkylzinc and diarylzinc reagents to imines generated in situ from α-amido sulfones has been described by Bräse,[9] Charette,[10] Gong,[11] and Minnaard and Feringa,[12] with different metal complexes. To the best of our knowledge, however, there has been only one example of enantioselective alkynylation of α-amido sulfones, recently reported by Wang, which uses a prolinol-derived tridentate ligand.[13]



Scheme 1. Alkynylation of α-amido sulfones, together with the BINOL-type ligands used in this study.

Herein, we describe the enantioselective alkynylation of α-amido sulfones **1** with terminal alkynes **2** catalysed by a chiral BINOL-type zinc complex as a new and convenient method to synthesise *N*-carbamoyl-protected propargylic amines **3** (Scheme 1).

[a] Dr. G. Blay, A. Brines, A. Monleón, Prof. Dr. J. R. Pedro
Departament de Química Orgànica, Facultat de Química
Universitat de València, C/Dr. Moliner 50, 46100 Burjassot (Spain)
Fax: (+34) 963544328
E-mail: jose.r.pedro@uv.es

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201102909.

SYNLETT
Spotlight 424

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

α-Amido Sulfones as Imine Precursors in Enantioselective Nucleophilic Additions

Compiled by Alicia Monleón

Alicia Monleón was born in Valencia, Spain, in 1985. She obtained her B.Sc. and M.Sc. degrees in Chemistry from the University of Valencia, where she is currently pursuing her Ph.D. under the supervision of Prof. José Ramón Pedro and Prof. Gonzalo Blay. She has carried out pre-doctoral stays at the University of Aachen, Germany, with Prof. C. Bolm and at the University of Strathclyde, UK, with Dr. E. Hevia.

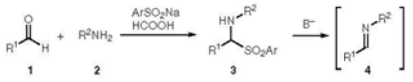
Departament de Química Orgànica, Facultat de Química, Universitat de València, C/ Dr. Moliner 50, 46100 Burjassot, Spain
E-mail: alicia.monleon@uv.es

Introduction

α-Amido sulfones have emerged as valuable precursors of imines in enantioselective nucleophilic addition reactions because their use offers several advantages.[1] Imines are generated in situ from α-amido sulfones by the elimination of the sulfone group under basic or acid conditions. The in situ formation avoids the competitive enolization process that often occurs when using imines and which hinders an effective nucleophilic addition. Moreover, unlike imines, α-amido sulfones are stable solids which can be easily synthesized and stored for a long period of time.

Preparation

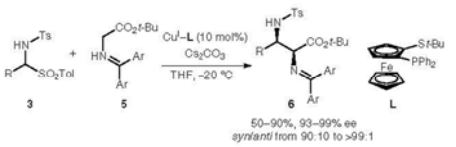
Various methodologies have been described for the synthesis of diverse α-amido sulfones.[2] The most extended preparation method consists of a three-component coupling of aldehyde, carbamate (or a proper nitrogenated compound, such as an amide) and sodium *p*-toluenesulfinate.



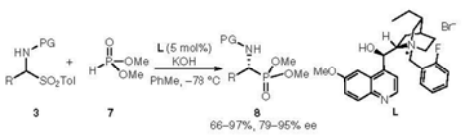
Scheme 1 Synthesis of α-amido sulfones and in situ generation of imines under basic conditions.

Abstracts

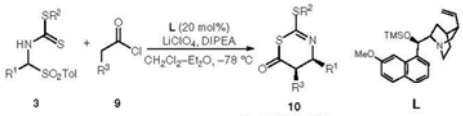
(A) *Mannich Reaction*
α-Amido sulfones are used as aliphatic imine precursors in the catalytic asymmetric Mannich reaction with glycine derivative **5**. Linear, branched or cyclic substrates give the corresponding products in excellent diastereo- and enantioselectivities. Noteworthy are the use of formaldehyde-derived α-amido sulfone for α-aminomethylation of glycine derivatives and the selective orthogonal N-deprotection of the obtained β-alkyl-α,β-diamino acid derivatives **6**.[3]



(B) *Hydrophosphonylation*
Enantioenriched α-amino phosphoric acid derivatives **8** can be synthesized by the asymmetric hydrophosphonylation of aliphatic *N*-Cbz and *N*-Boc α-amido sulfones **3** using a phase-transfer catalyst. High yields and enantioselectivities are afforded.[4]



(C) *Cycloaddition*
Propionyl chloride **9** and α-amido sulfones as precursors of N-thioacylimines undergo catalytic asymmetric [4+2] cycloadditions with excellent enantio- and diastereoselectivities. The in situ formation of the imine is crucial to overcome its tautomerization to the enamine. The final enantioenriched thiazinone adducts **10** behave as activated ester surrogates.[5]



SYNLETT 2013, 24, 0529–0530
Advanced online publication: 30.01.2012
DOI: 10.1055/s-0032-1318133; Art ID: ST-2012-V0431-V

CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201302089

Synthesis of Densely Functionalised 5-Halogen-1,3-oxazin-2-ones by Halogen-Mediated Regioselective Cyclisation of *N*-Cbz-Protected Propargylic Amines: A Combined Experimental and Theoretical Study**

Alicia Monleón,[a] Gonzalo Blay,[a] Luis R. Domingo,*[a] M. Carmen Muñoz,[b] and José R. Pedro*[a]

Abstract: A very efficient synthesis of 5-halogen-1,3-oxazin-2-ones has been accomplished by the halocyclisation reaction of chiral nonracemic *N*-carbobenzyloxy (*N*-Cbz)-protected propargylic amines by using I_2, Br_2 and Cl_2 as electrophile sources. The nature of the halogen influences the reaction time and yield. However, in all cases the reaction is totally regioselective taking place through a 6-*endo-dig* process regardless of the nature of the halogen and of the substituents in the starting material. To rationalise the experimental results, theoretical studies at the B3LYP/6-311G* level have been performed.

Keywords: density functional calculations · halocyclisation · oxazinones · propargylic amines · reaction mechanisms · regioselectivity

Introduction

The electrophilic cyclisation of functionalised alkynes possessing a nucleophilic group in close proximity to the triple bond constitutes an important strategy in the construction of a wide variety of heterocycles and carbocycles.[1] Typically, the activation of the carbon–carbon triple bond is based on the formation of a cationic metal complex (in transition-metal-catalysed reactions)[2] or an incipient halonium ion (in halogen-mediated reactions).[3] This second activation method leads to the synthesis of halogen-containing heterocycle or carbocycle derivatives, which are versatile precursors in many synthetic processes. With regard to the internal nucleophile, a wide range of nucleophilic groups, such as alcohols,[4] ethers,[5] thioethers,[6] selenoethers,[7] amines,[8] imines,[9] oximes,[10] azides,[11] aldehydes and ketones,[12] carboxylic acids and their derivatives,[13] 1,3-dicarbonyl compounds[14] and aromatic rings,[15] has been investigated. However, the use of functionalised alkynes possessing a carbamate derivative as the internal nucleophilic group remains relatively unexplored.[2a,16]

Very recently, we have reported a convenient method for the synthesis of chiral nonracemic *N*-benzyloxycarbonyl (*N*-Cbz)-protected propargylic amines by the addition of terminal alkynes to imines generated in situ from α-amido sulfones in the presence of diethylzinc and 1,1′-binaphthol (BINOL)-type ligands as catalysts.[17] On the basis of early reported results in the synthesis of halo derivatives of heterocycles by halocyclisation of conveniently functionalised alkynes we envisioned that the *N*-Cbz-protected propargylic amines must be suitable substrates to investigate a novel route for preparing densely-functionalised 1,3-oxazin-2-ones or oxazolidin-2-ones (cyclic carbamates) through an *O*-halocyclisation process. Carbamates represent an important class of compounds with interesting properties and have found wide utility in several areas, such as pharmaceuticals[18] or agrochemicals.[19] Cyclic carbamates are less known, although they have been used as chiral auxiliaries[20] and, besides, present interesting biological activity.[21] There is a variety of methods[22] for the synthesis of this kind of compounds, however, the development of practical and efficient methods for the preparation of these cyclic carbamates, especially those densely functionalised, is of great interest.

When a substrate of the *N*-Cbz-protected propargylic amine-type **1** is subjected to an *O*-cyclisation process, two reaction modes are possible: the 6-*endo-dig* mode that should yield the 1,3-oxazin-2-ones **2** and the 5-*exo-dig* mode that should yield the oxazolidin-2-ones **3**. Therefore, the highly effective control of the regioselectivity of the *O*-halocyclisation mode is essential for the selective preparation of compounds **2** or **3** (Scheme 1). A metal-catalysed cyclisation of *N*-butyloxycarbonyl (Boc)-protected propargylic amines has been previously described by Carretero et al.,[2a] which

[a] A. Monleón, Prof. Dr. G. Blay, Prof. Dr. L. R. Domingo, Prof. Dr. J. R. Pedro
Department de Química Orgànica-Facultat de Química
Universitat de València
C/Dr. Moliner 50, 46100 Burjassot (València) (Spain)
Fax: (+34)963544328
E-mail: domingo@utopia.uv.es
jose.r.pedro@uv.es

[b] Prof. Dr. M. C. Muñoz
Departmento de Física Aplicada
Universitat Politècnica de València
Camí de Vera s.n., 46022-València (Spain)

[**] Cbz = carbobenzyloxy.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201302089.