VNIVERSITAT DE VALÈNCIA Facultat de Química

Departament de Química Orgànica

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ALQUINILACIÓN CONJUGADA ENANTIOSELECTIVA DE COMPUESTOS CARBONÍLICOS α,β-INSATURADOS

Tesis Doctoral

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CERTIFICAN:

Que la presente Tesis Doctoral, titulada **"Alquinilación conjugada enantioselectiva de compuestos carbonílicos α,β-insaturados"** ha sido realizada bajo su dirección en el Departamento de Química Orgánica de la Universitat de València por la licenciada en Química **Dña. Amparo Sanz Marco** y autorizan su presentación para que sea calificada como Tesis Doctoral.

Burjassot, 2015

Fdo. José Ramón Pedro Llinares

Fdo. Gonzalo Blay Llinares

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INDICE

ABREVIATURAS / ABBREVIATIONS

En Castellano

acac	acetilacetonato
AcOEt	acetato de etilo
AcOH	ácido acético
AIBN	azobisisobutironitrilo
Ar	arilo
Bn	bencilo
BINAP	2,2'-bis(difenilfosfino)-1,1'-binaftil
BINOL	1,1’-binaftil-2,2’-diol
Boc	*terc*-butiloxicarbonil
BOX	bisoxazolina
BSA	bis(trimetilsilil)acetamida
c	concentración (g/100 mL)
cat	catalizador
CCF	cromatografía de capa fina
cod	1,5-ciclooctadieno
col	colaborador/es
d	día
dba	dibecilidenacetona
DCM	diclorometano
DEAD	azodicarboxilato de dietilo
DIBAL-H	hidruro de diisobutilaluminio
DME	dimetoxietano
DMF	*N*,*N*-dimetilformamida
DMSO	dimetilsulfóxido
dr	relación diastereoisomérica
ee	exceso enantiomérico
equiv.	equivalente
Et	etilo
h	hora
HMPA	hexametilfosforamida
HPLC	cromatografía líquida de alta resolución
Hz	hercio
^{i}Bu	isobutilo
^{i}Pr	isopropilo
J	constante de acoplamiento (RMN)
KHMDS	bis(trimetilsilil)amiduro de potasio
L	ligando
LHMDS	bis(trimetilsilil)amiduro de lítio
Lit.	bibliografía
M	molar

Me	metilo
min	minuto
mL	mililitro
mmol	milimol
MsCl	cloruro de mesilo
^{n}Bu	*n*-butilo
NFSI	*N*-fluorobencenosulfonimida
NOE	efecto nuclear Overhauser
NOESY	espectroscopia de efecto nuclear Overhauser
^{n}Pr	*n*-propilo
PCC	clorocromato de piridinio
Ph	fenilo
ppm	partes por millón
p-TsOH	ácido *para*-toluensulfónico
pybox	2,6-bis(oxazolina-2'-il)piridina
Rto.	rendimiento
RMN	resonancia magnética nuclear
T	temperatura
t	tiempo
ta	temperatura ambiente
TBAF	floruro de tetrabutilamonio
*t*Bu	*terc*-butilo
Tf	triflato (trifluorometanosulfonato)
THF	tetrahidrofurano
TIPS	triisopropilsililo
TM	tamiz molecular
TMS	trimetilsililo
Tol	tolueno
VANOL	3,3′-difenil-2,2′-bi-1-naftol
VAPOL	2,2′-difenil-(4-bifenantrol)
vs	versus
[α]	rotación específica
δ	desplazamiento químico

In English

Å	angstrom
AcOH	acetic acid
AIBN	azobisisobutyronitrile
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1’-binaphthyl-2,2’-diol
br s	broad singlet
c	concentration (g/100 mL)
col	collaborator/s
d	doublet
DEAD	diethyl azodicarboxylate
DEPT	distorsionless enhancement by polarization transfer
DIBAL	diisobutylaluminum hidride
DMF	*N*,*N*-dimethylformamide
DMSO-d_6	deuterated dimethylsulfoxide
dr	diastereoisomeric ratio
ee	enantiomeric excess
EI	electron impact
equiv.	equivalent
ESI	electron spray
Et	ethyl
EtOAc	ethyl acetate
eV	electron volts
FAB	fast electron bombardment
g	gram
GC	gas cromatography
h	hour
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
Hz	hertz
*i*Bu	isobutyl
*i*Pr	isopropyl
J	coupling constant (NMR)
L	ligand
LHMDS	lithium bis(trimethylsilyl)amide
Lit.	literature
M	molar
m	multiplet
M^+	molecular ion
Me	methyl
mg	milligram

MHz	megahertz
min	minutes
mL	milliliter
mm	millimeter
mmol	millimol
mp	melting point
MS	mass spectrometry
^{n}Bu	*n*-butyl
NFSI	*N*-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
^{n}Pr	*n*-propyl
Ph	phenyl
ppm	parts per million
q	quartet
rt	room temperature
s	singlet
t	triplet
t	time
T	temperature
TBAF	tetra-*n*-butylammonium fluoride
^{t}Bu	*tert*-butyl
Tf	triflate (trifluoromethanesulfonate)
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	toluene
t_r	retention time
UV	ultraviolet
VANOL	3,3′-diphenyl-2,2′-bi-1-naphthol
[α]	specific rotation
δ	chemical shift
μL	microliter

1. INTRODUCCIÓN

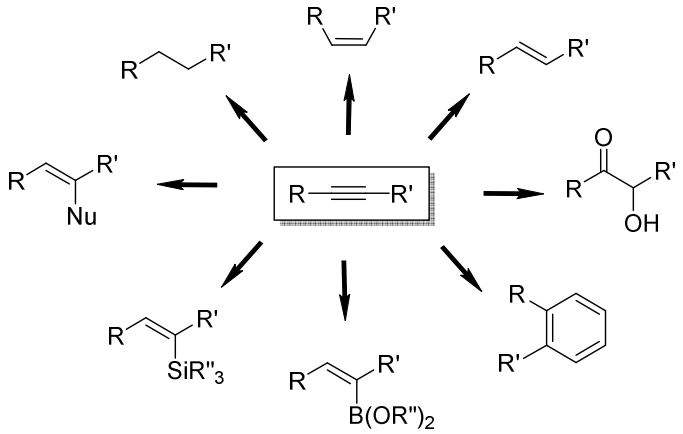
1. INTRODUCCIÓN

Uno de los principales desafíos de la química orgánica durante las últimas décadas ha sido la búsqueda de nuevos métodos para la obtención de compuestos quirales enantioméricamente puros, debido a las importantes implicaciones que la quiralidad de las moléculas tiene en campos tan diversos como la industria agroquímica, farmacéutica y ciencia de los materiales,[1,2] entre otros. Esto es así porque aunque los enantiómeros presentan las mismas propiedades físicas y químicas, su interacción con otras moléculas quirales como la mayoría de las presentes en los seres vivos es diferente, por lo que ambos enantiómeros pueden presentar diferente actividad biológica. Igualmente, la ordenación a nivel molecular en materiales varía según se trate de compuestos enantioméricamente puros o racémicos, lo cual puede afectar a las propiedades mecánicas, ópticas o electromagnéticas del material.

Tradicionalmente la síntesis de compuestos enantioméricamente puros se ha llevado a cabo utilizando como material de partida compuestos de la llamada "chiral pool", fundamentalmente productos de origen natural, o mediante procesos de resolución de mezclas racémicas. No obstante ambos procedimientos cuentan con serias limitaciones. En este contexto emerge la síntesis asimétrica que mediante el uso de auxiliares, reactivos o catalizadores quirales, permite la formación de nuevos enlaces y el control sobre la estereoquímica de los elementos estereogénicos formados durante la reacción. Entre las diferentes metodologías de síntesis asimétrica, la utilización de catalizadores quirales presenta diversas ventajas ya que permite disminuir el consumo de material quiral y minimizar la producción de residuos.

La formación de enlaces carbono-carbono es uno de los procesos fundamentales en síntesis orgánica que puede dar lugar a la aparición de centros estereogénicos en la molécula. Así pues, el desarrollo de nuevas metodologías para la formación catalítica enantioselectiva de enlaces C-C sigue siendo un reto de gran importancia en química orgánica, particularmente en la síntesis de productos naturales y fármacos.

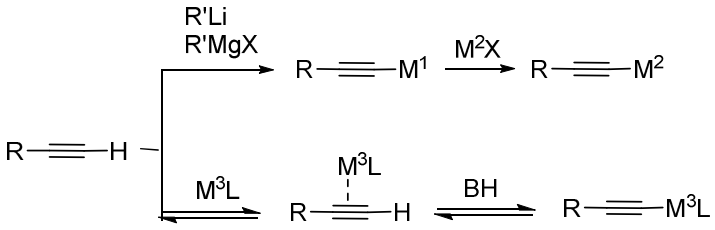
Por otra parte, los alquinos son compuestos de gran versatilidad ya que el triple enlace C-C puede ser sometido a una gran variedad de modificaciones permitiendo el acceso a diversos motivos estructurales y grupos funcionales (Esquema 1).[3] Por ejemplo, el triple enlace puede experimentar reacciones de hidrogenación parcial o total para dar alquenos o alcanos, respectivamente, reacciones de adición nucleofílica, reacciones de adición electrofílica para dar vinilboranos y vinilsilanos que se utilizan frecuentemente en reacciones catalizadas por metales de transición, reacciones de adición de halógenos, reacciones de oxidación a hidroxicetonas, o pueden participar en multitud de reacciones de cicloadición. Además, el triple enlace C-C se encuentra tanto en moléculas naturales, habiéndose aislado más de un millar de productos naturales con esta característica en su estructura,[4] como en moléculas en la frontera de la química orgánica, de interés en bioquímica o ciencia de los materiales.[5]



Esquema 1. Algunos ejemplos de modificación del triple enlace C-C.

Por todos estos motivos, el interés en la química de los alquinos ha experimentado un renacimiento en las últimas décadas, tanto en sus aplicaciones como en su síntesis. La adición nucleofílica de alquinos terminales o de alguno de sus derivados a grupos funcionales electrofílicos constituye uno de los métodos más directos para la formación de un enlace C (sp)-C (sp^3) proporcionando moléculas que incorporan un triple enlace C-C interno. Para llevar a cabo este tipo de reacciones es necesaria la activación del alquino terminal vía su conversión en un alquiniluro metálico.

Los alquinilboranos y alquinilalanos han sido utilizados como reactivos nucleofílicos en reacciones de alquinilación. También es posible la premetalación cuantitativa de un alquino terminal utilizando bases fuertes como por ejemplo reactivos organolíticos o reactivos de Grignard. En todos estos casos es necesario el uso de cantidades estequiométricas o superiores de especies metálicas. Sin embargo, resulta más conveniente, ya que produce menos residuos metálicos, la generación del alquiniluro metálico de forma transitoria, a partir de alquinos terminales, bases débiles como aminas terciarias y metales de transición tales como Ag^I, Au^I, Cu^I, Ir^I, Pd^{II}, Rh^I, Ru^{II} y Zn^{II}, elementos que tienen gran afinidad hacia el enlace π del triple enlace (Esquema 2).[6] En estos casos, la coordinación del ión metálico con el triple enlace incrementa la acidez del hidrógeno unido al C(sp) permitiendo su abstracción por parte de la base.



Esquema 2. Desprotonación de un alquino.

Las especies anteriores han sido ampliamente utilizadas en reacciones enantioselectivas de adición 1,2 a aldehídos, cetonas e iminas proquirales, habiéndose obtenido en algunos casos excelentes resultados en términos de rendimiento y

estereoselectividad. Sin embargo, la alquinilación enantioselectiva de dobles enlaces electrofílicos proquirales, como por ejemplo en compuestos carbonílicos α,β-insaturados (adiciones 1,4), apenas se encuentra desarrollada, existiendo incluso pocos ejemplos para la versión no enantioselectiva. La reducida reactividad tanto de las especies alquinilmetálicas como de las enonas dificulta este tipo de reacciones. Además hay que considerar el control tanto sobre la regioselectividad (adición 1,2 *vs* adición 1,4) como sobre la enantioselectividad de la reacción. Todo esto convierte el desarrollo de reacciones de alquinilación conjugada enantioselectivas en un desafío sintético extraordinario.

La investigación de la presente tesis doctoral se centra precisamente en este objetivo, la adición conjugada catalítica enantioselectiva de alquinos terminales a compuestos carbonílicos α,β-insaturados utilizando catálisis mediante complejos quirales de Zn(II) y Cu(I).

2. ANTECEDENTES BIBLIOGRÁFICOS

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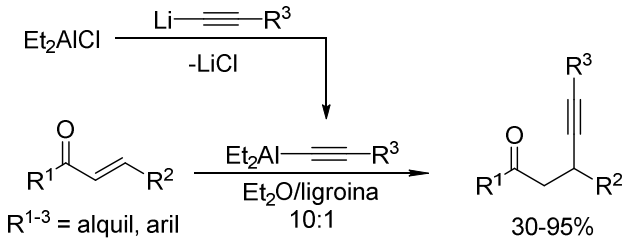
2.1. Reacciones de alquinilación conjugada no asimétricas

Aunque los organocupratos han sido comúnmente utilizados para las reacciones de adición conjugada de grupos alquilo, arilo y vinilo,[7] la baja nucleofilia de los alquiniluros de cobre[8] ha limitado su aplicación en reacciones de alquinilación conjugada. Los primeros ejemplos de adición conjugada de alquinos fueron descritos empleando alquinilalanos y boranos.

La primera reacción de adición conjugada de alquinos se describió en 1971 por el grupo de Hooz, utilizando para ello alquinilalanos preparados por transmetalación de alquiniluros de litio con cloruro de dietilaluminio.[9] La reacción se llevó a cabo a temperatura ambiente en una mezcla de éter/ligroína obteniendo los correspondientes productos de alquinilación con rendimientos comprendidos entre 30-95% (Esquema 3).



Esquema 3. Primer ejemplo de alquinilación conjugada de enonas.

Cabe destacar que solo las cetonas α,β-insaturadas que pueden adoptar una conformación *s-cis* pueden experimentar la adición conjugada mientras que las cetonas α,β-insaturadas en las cuales la conformación *s-trans* está bloqueada, experimentan preferentemente la adición 1,2. En base a estos resultados, los autores sugirieron un estado de transición donde el aluminio se coordina al oxígeno del grupo carbonilo activando la enona. En el caso de enonas que puedan adoptar la conformación *s-cis* es posible la adición 1,4, sin embargo con enonas cíclicas se obtienen sólo productos de adición 1,2 debido a los impedimentos geométricos (Figura 1).

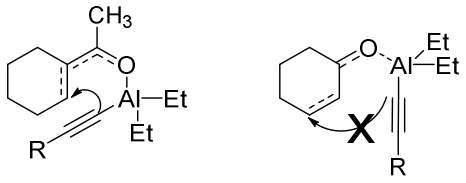
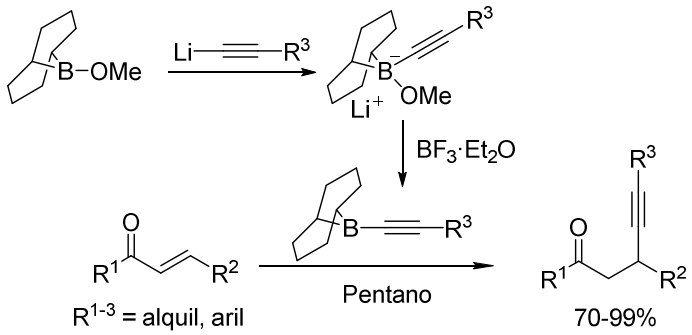


Figura 1. Estado de transición propuesto por el grupo de Hooz para la reacción con alquinilalanos.

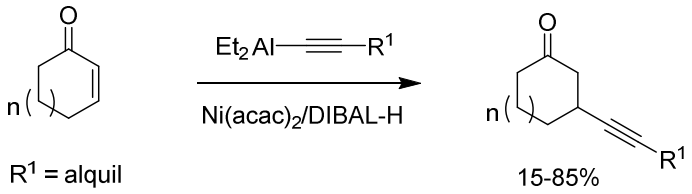
Brown y colaboradores describieron en 1977 la adición conjugada de alquinilboranos a diversas cetonas α,β-insaturadas a temperatura ambiente proporcionando los correspondientes productos con elevados rendimientos (Esquema 4).[10]



Esquema 4. Adición conjugada de alquinilboranos a cetonas α,β-insaturadas.

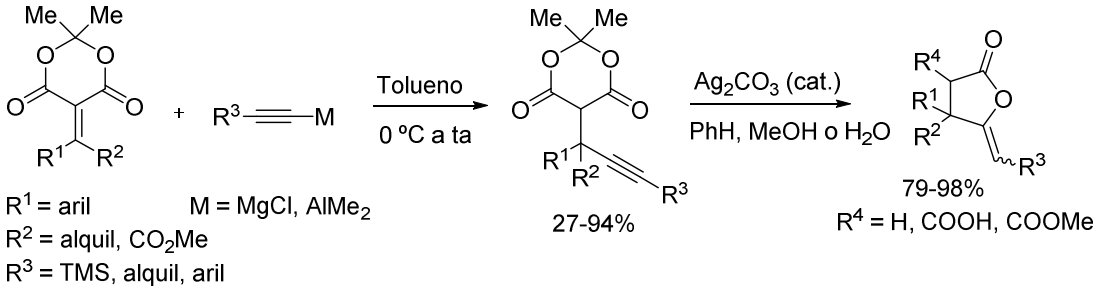
Los alquinilboranos solo reaccionaron con las cetonas α,β-insaturadas capaces de adoptar una conformación *s-cis.* Los autores propusieron una explicación de estos resultados similar a la proporcionada por Hooz y colaboradores para la reacción con alquinilalanos.

En 1978, Schwartz y colaboradores describieron el primer ejemplo de adición conjugada de alquinos a enonas con conformación *s-trans* utilizando para ello alquinilalanos y como catalizador un complejo de Ni(I) obtenido por reducción de $Ni(acac)_2$ con DIBAL-H (Esquema 5).[11] Fue necesario un exceso de alquinilalano para favorecer la reacción de alquinilación frente a la reacción aldólica entre el enolato de aluminio que se genera al adicionar el alquino y otra molécula de enona.



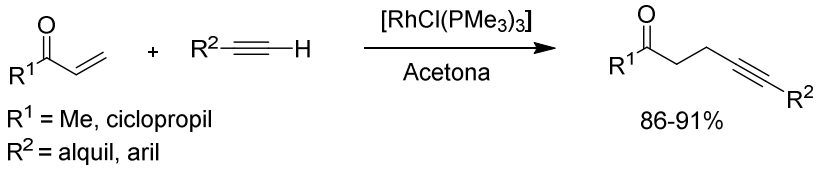
Esquema 5. Adición conjugada de alquinilalanos a enonas con geometría*s-trans.*

En 2014, Fillion y Ahmar[12] describieron el primer ejemplo de adición conjugada de alquinos en la que se generaba un centro cuaternario tetracarbosustituido. Estos autores llevaron a cabo la reacción no enantioselectiva de alquinilalanos y alquinilmagnesianos a alquenos doblemente activados derivados del ácido de Meldrum obteniendo el producto deseado con rendimientos elevados. Con los productos de alquinilación resultantes llevaron a cabo una ciclación intramolecular catalizada por plata obteniendo γ-alquiliden butirolactonas con un centro cuaternario en la posición C-4 con buenos rendimientos (Esquema 6).



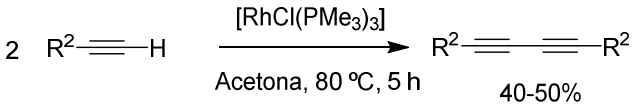
Esquema 6. Síntesis de carbono tetracarbosustituido vía adición conjugada de alquinilalanos y alquinil organomagnesianos.

El primer ejemplo de adición conjugada utilizando alquinos terminales fue descrito en 1990 por Kovalev y colaboradores (Esquema 7).[13]



Esquema 7. Adición conjugada de alquinos terminales a vinilcetonas.

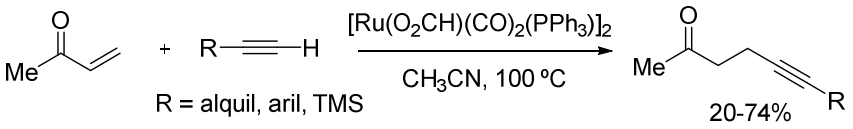
La reacción entre un alquino terminal y la vinilcetona se llevó a cabo utilizando una carga catalítica baja (1 mol %) de un complejo de Rh(I) obteniéndose el producto de adición conjugada deseado con rendimientos elevados. A temperaturas altas aumenta el rendimiento del producto de alquinilación pero la selectividad de la reacción disminuye debido a la reacción de dimerización del alquino terminal (Esquema 8). A 20 °C el producto de dimerización no se observa pero la conversión de los productos de partida es baja. Esta reacción está limitada a vinilcetonas no sustituidas.



Esquema 8. Reacción de dimerización de alquinos terminales.

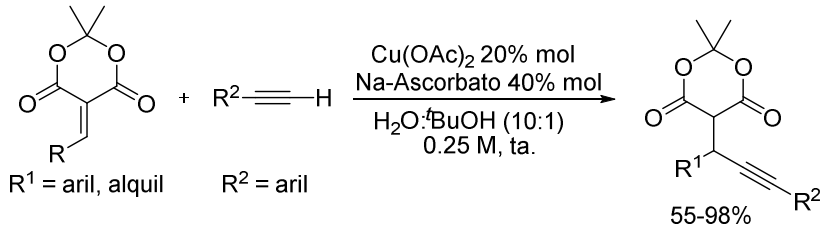
A partir de este trabajo se describieron numerosos ejemplos de adición conjugada de alquinos terminales empleando diferentes sales de otros metales de transición.

El primer ejemplo de adición conjugada de alquinos terminales catalizada por rutenio fue descrito por Dixneuf y colaboradores. Se estudió la adición de alquinos terminales a la metil vinil cetona empleando $[Ru(O_2CH)(CO)_2(PPh_3)]_2$ como catalizador. Los correspondientes productos de alquinilación se obtuvieron con rendimientos inferiores al 50% con alquinos alifáticos o arilacetilenos sustituidos con un grupo fuertemente electrón-atrayente; únicamente se consiguió un rendimiento superior al 50% con el fenilacetileno (Esquema 9).[14]



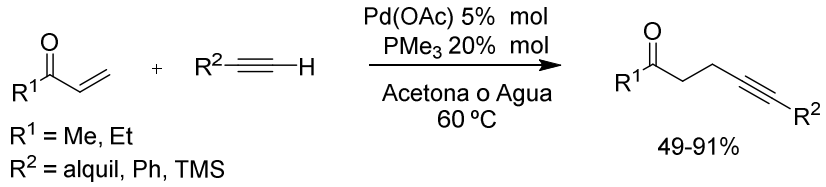
Esquema 9. Adición conjugada de alquinos terminales a metil vinil cetona catalizada por rutenio.

Carreira y colaboradores llevaron a cabo por primera vez la adición conjugada de alquinos terminales catalizada por Cu(I) generado *in situ* a partir de $Cu(OAc)_2$ y ascorbato sódico en un sistema bifásico H_2O:^{t}BuOH. La reacción se lleva a cabo con alquenos doblemente activados derivados del ácido de Meldrum para compensar la baja nucleofília de los alquiniluros de cobre (Esquema 10).[15]



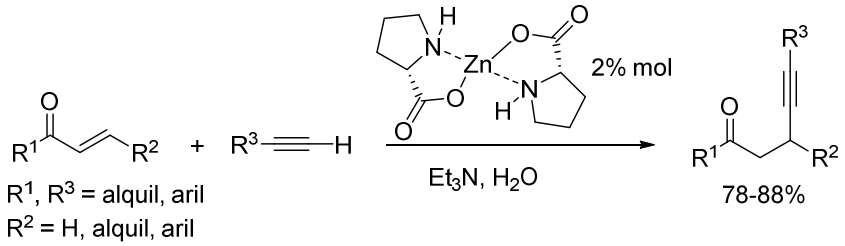
Esquema 10. Adición conjugada de alquinos terminales a derivados del ácido de Meldrum.

En 2004, se describió el primer ejemplo de adición conjugada de alquinos terminales catalizada por paladio.[16] Chen y Li llevaron a cabo la reacción entre distintos alquinos terminales y vinilcetonas empleando como sistema catalítico $Pd(OAc)_2/PMe_3$ y agua o acetona como disolvente, obteniendose resultados similares en ambos disolventes. Los productos de alquinilación de la metil vinil cetona se obtuvieron con rendimientos moderados mientras que con etil vinil cetona los rendimientos fueron más altos (Esquema 11).



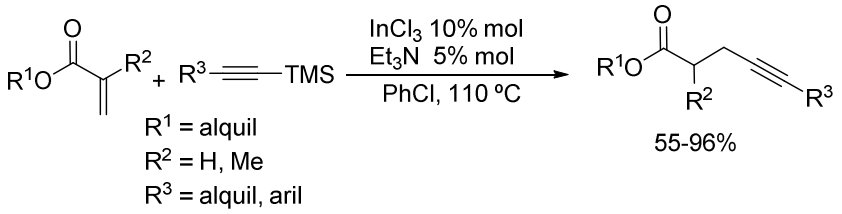
Esquema 11. Adición conjugada de alquinos terminales a vinilcetonas catalizada por paladio.

Kidway y col., en 2010, describieron la adición conjugada de alquinos terminales a cetonas α,β-insaturadas empleando un complejo formado por Zn/*L*-prolina (Esquema 12).[17] La reacción se llevó a cabo en medio acuoso empleando Et_3N como aditivo, esencial para la activación del alquino. Los productos de alquinilación se obtuvieron con rendimientos elevados aunque como mezclas racémicas, independientemente del sustituyente de la enona y del alquino.



Esquema 12. Adición conjugada de alquinos terminales a cetonas α,β-insaturadas catalizada por cinc.

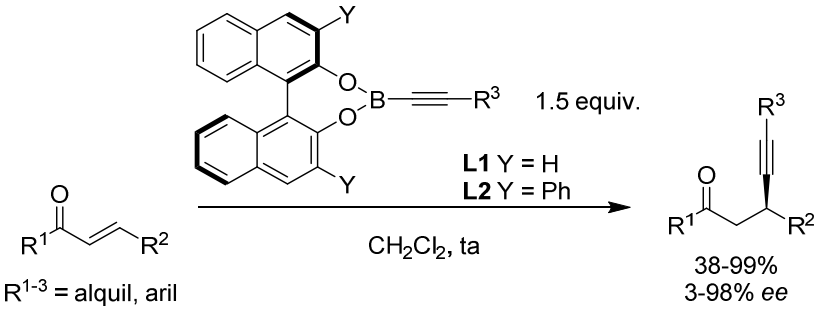
En 2012, Su y col. describieron la adición conjugada de trimetilsililalquinos a ésteres α,β-insaturados empleando como catalizador $InCl_3$ (Esquema 13).[18] Los correspondientes productos de alquinilación se obtuvieron con rendimientos superiores al 75% obteniéndose rendimientos inferiores con el uso de alquinos terminales.



Esquema 13. Adición conjugada de trimetilsililalquinos a ésteres α,β-insaturados catalizada por indio.

2.2. Reacciones de alquinilación conjugada asimétricas estequiométricas

En el año 2000, Chong y colaboradores describieron el primer ejemplo de adición conjugada enantioselectiva.[19] Los autores describieron la adición enantioselectiva de alquinilboranos quirales derivados de 2,2'-binaftoles-3,3'-disustituidos a cetonas α,β-insaturadas (Esquema 14).

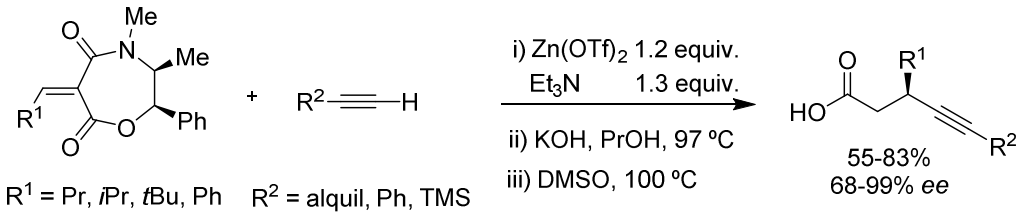


Esquema 14. Adición conjugada enantioselectiva de alquinilboranos a enonas.

Los productos de alquinilación se obtuvieron con rendimientos y enantioselectividades elevados obteniendo excesos enantioméricos inferiores al 50% para sustratos sustituidos con un grupo alifático en β y también con alquinos alifáticos. La reacción está limitada a cetonas α,β-insaturadas que puedan adoptar la conformación *s-cis*.

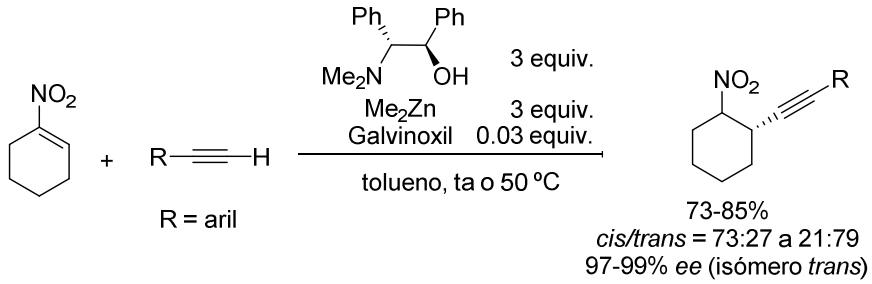
Posteriormente a este trabajo se han publicado distintos trabajos sobre alquinilación conjugada asimétrica empleando sales de cinc que requirieron el uso de cantidades estequiométricas o superiores de material quiral.

Así, Carreira y colaboradores describieron la adición conjugada diastereoselectiva de alquinos terminales catalizada por cinc, utilizando como electrófilos oxazepinas quirales derivadas de la efedrina.[20] La alquinilación de este tipo de aceptores dio acceso, después de la hidrólisis del auxiliar quiral y descarboxilación, a ácidos β-alquinil sustituidos enantioméricamente enriquecidos (Esquema 15).



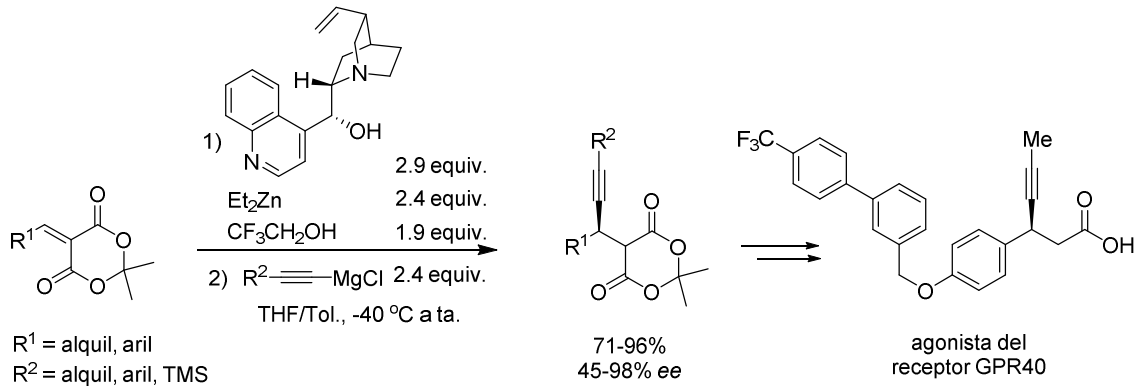
Esquema 15. Adición conjugada enantioselectiva de alquinos terminales a oxazepinas quirales.

La reacción de adición conjugada enantioselectiva de alquinos terminales a nitroalquenos fue descrita por Tomioka y colaboradores en 2005.[21] La reacción se llevó a cabo en presencia de 3 equivalentes de un amino alcohol quiral y galvinoxil, necesario para capturar los radicales que se pueden generar debido a la capacidad que el Me_2Zn tiene como iniciador de radicales. Los productos de alquinilación se obtuvieron como mezcla de isómeros *cis*/*trans* con enantioselectividades excelentes para el isómero *trans* (Esquema 16).



Esquema 16. Adición conjugada enantioselectiva de alquinos terminales a nitroalquenos.

En 2010, se describió la adición conjugada a derivados del ácido de Meldrum utilizando alquiniluros de cinc generados por transmetalación a partir de Et_2Zn y RC≡CMgCl promovida por chinchonidina.[22] La reacción se llevó a cabo en presencia de 2 equivalentes de trifluoroetanol como aditivo el cual reacciona rápidamente con el dietilcinc para formar un alcóxido de cinc. Los productos de alquinilación se obtuvieron con rendimientos y excesos enantioméricos elevados. Posteriormente, los autores demostraron la utilidad de su método en la síntesis enantioselectiva de un fármaco agonista del receptor GPR40 (Esquema 17).[22b]

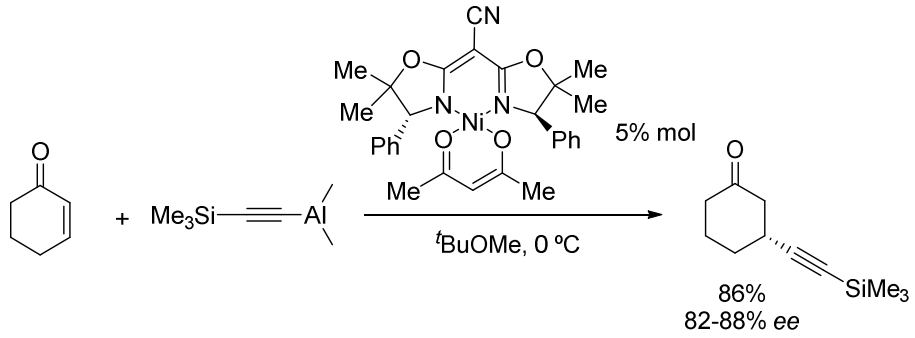


Esquema 17. Adición conjugada enantioselectiva de alquiniluros de cinc a derivados del ácido de Meldrum.

2.3. Reacciones de alquinilación conjugada asimétricas catalíticas

2.3.1 Adiciones conjugadas enantioselectivas de reactivos de alquinilaluminio catalizadas por níquel

En 2004, Corey y colaboradores describieron el primer ejemplo de adición conjugada enantioselectiva catalítica.[23] Los autores estudiaron la reacción de adición conjugada de un alquiniluro de aluminio a la 2-ciclohexenona empleando un complejo tetraédrico de acetilacetonato de níquel (II) con ligandos de tipo bisoxazolina (Esquema 18).

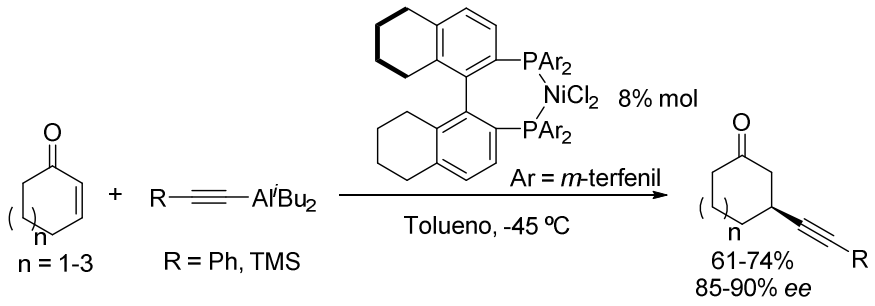


Esquema 18. Adición conjugada enantioselectiva de alquinilalanos a 2-ciclohexenona catalizada por el complejo de Ni(II)-bisoxazolina-acetilacetonato.

Cabe señalar que cuando los autores emplearon Ni(I) en lugar de Ni(II) tomando como referencia las condiciones de la adición conjugada no enantioselectiva descritas por Schwartz[11b] para la adición de un alquiniluro de aluminio a la 2-ciclohexenona, se obtuvieron enantioselectividades inferiores a las obtenidas con Ni(II) y rendimientos muy bajos.

Continuando este trabajo, los autores describieron en 2010 la adición conjugada enantioselectiva de alquiniluros de aluminio a cetonas α,β-insaturadas cíclicas catalizada por un complejo de Ni(II)-bisfosfina.[24] Se estudió la adición de fenilacetileno y trimetilsililacetileno a diferentes enonas cíclicas obteniendo los correspondientes

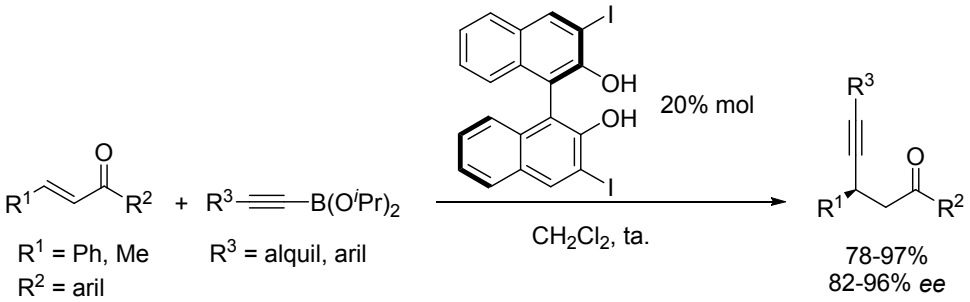
productos de alquinilación con rendimientos buenos y enantioselectividades iguales o superiores al 85% (Esquema 19).



Esquema 19. Adición conjugada enantioselectiva de alquiniluros de aluminio a enonas cíclicas catalizada por Ni(II).

2.3.2. Adición conjugada enantioselectiva de alquinilboranos catalizada por BINOL

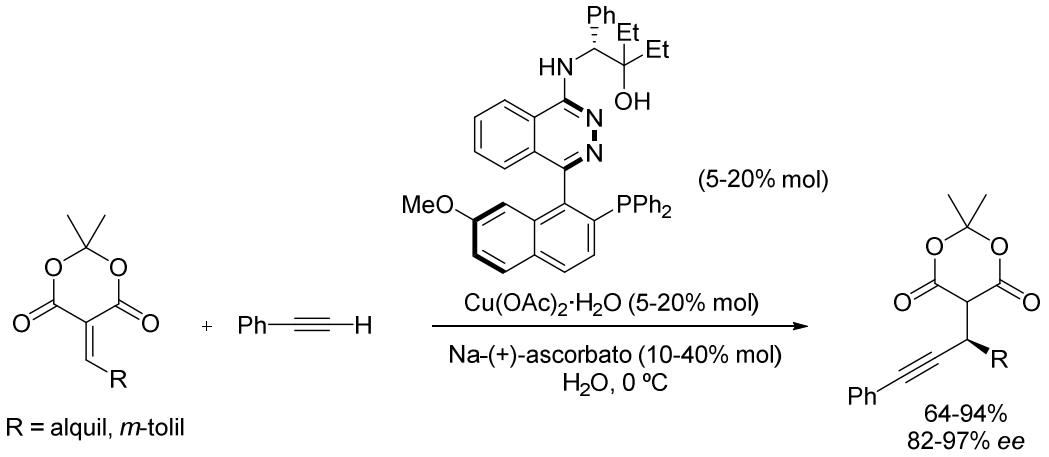
En el año 2005, Chong y colaboradores describieron la versión catalítica de su trabajo anterior[19] de adición conjugada enantioselectiva de alquinilboranos a enonas α,β-insaturadas.[25] Se llevó a cabo la adición de alquinildiisopropilboranos catalizada por 3,3'-diiodo-BINOL obteniendo los productos de β-alquinilación con rendimientos y excesos enantioméricos elevados. La reacción es compatible tanto con grupos aromáticos como alifáticos en la enona y en el alquino (Esquema 20).



Esquema 20. Adición conjugada enantioselectiva de alquinilboranos a enonas catalizada por ligandos de tipo BINOL.

2.3.3. Adiciones conjugadas enantioselectivas de alquinos terminales catalizadas por cobre

El primer ejemplo de adición conjugada enantioselectiva catalítica empleando alquinos terminales fue descrita por Carreira y colaboradores.[26] Se estudió la reacción de adición conjugada de fenilacetileno a derivados de ácidos de Meldrum empleando condiciones similares a las descritas anteriormente por los mismos autores para la versión no enantioselectiva.[15] La reacción se llevó a cabo en medio acuoso y sin necesidad de atmósfera inerte catalizada por complejos de Cu(I)-PINAP (Esquema 21).

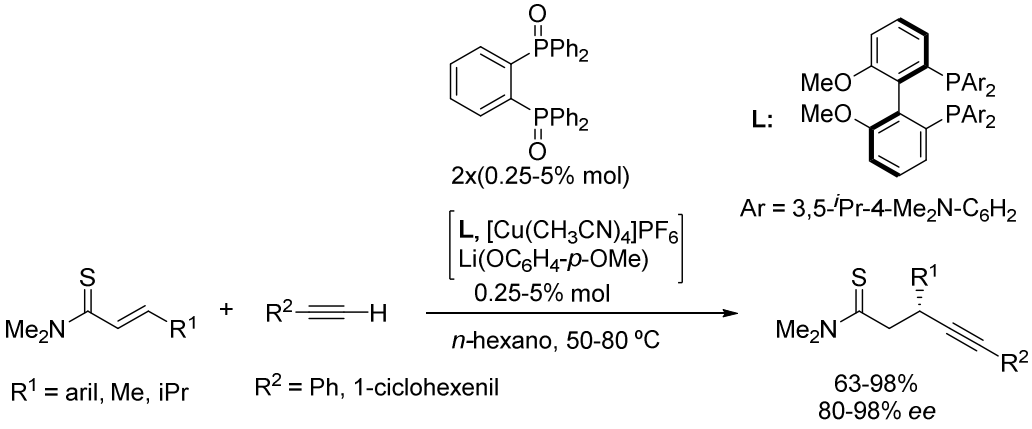


Esquema 21. Adición conjugada enantioselectiva de fenilacetileno a derivados del ácido de Meldrum catalizada por Cu(I)-PINAP.

Según los autores, la reacción transcurre en fase heterogénea y el agua no actúa como disolvente de la reacción sino más bien como el medio donde se generan las especies reactivas de cobre mientras que la reacción de adición conjugada tiene lugar en la fase orgánica.

En un trabajo posterior,[27] los autores describen para esta reacción un efecto no lineal positivo con la mezcla diastereoisomérica de los ligandos PINAP. Se encontró que una mezcla 60:40 de los dos diastereoisómeros del ligando es suficiente para obtener un exceso enantiomérico elevado en la adición conjugada de fenilacetileno a derivados del ácido de Meldrum.

Shibashaki y colaboradores describieron en 2010 la adición conjugada enantioselectiva de alquinos terminales a tioamidas α,β-insaturadas catalizada por Cu(I) y ligandos de tipo bisfosfina.[28] La catálisis cooperativa de un ácido de Lewis blando y una base de Brønsted dura se utilizó para la activación simultánea del alquino terminal y la tioamida α,β-insaturada, obteniendo las β-alquiniltioamidas con elevados rendimientos y excesos enantioméricos (Esquema 22).



Esquema 22. Adición conjugada enantioselectiva de alquinos terminales a tioamidas α,β-insaturadas.

Los autores realizaron un estudio mecanístico exhaustivo de la reacción.[29] Este estudio muestra la catálisis cooperativa de un ácido de Lewis blando y una base de Brønsted dura, que implican $[Cu(CH_3CN)_4]PF_6$, $Li(OC_6H_4$-*p*-OMe) y la bisfosfina quiral (*R*)-DTBM-Segphos. Esta catálisis cooperativa activa simultáneamente ambos sustratos compensando la baja reactividad de los alquiniluros de cobre. Los autores demostraron que el enolato de cobre de la tioamida intermedio actúa como base de Brønsted generando el alquiniluro de cobre a partir del alquino terminal, proporcionando al ciclo catalítico una eficiente transferencia de protón entre los sustratos (Figura 2).

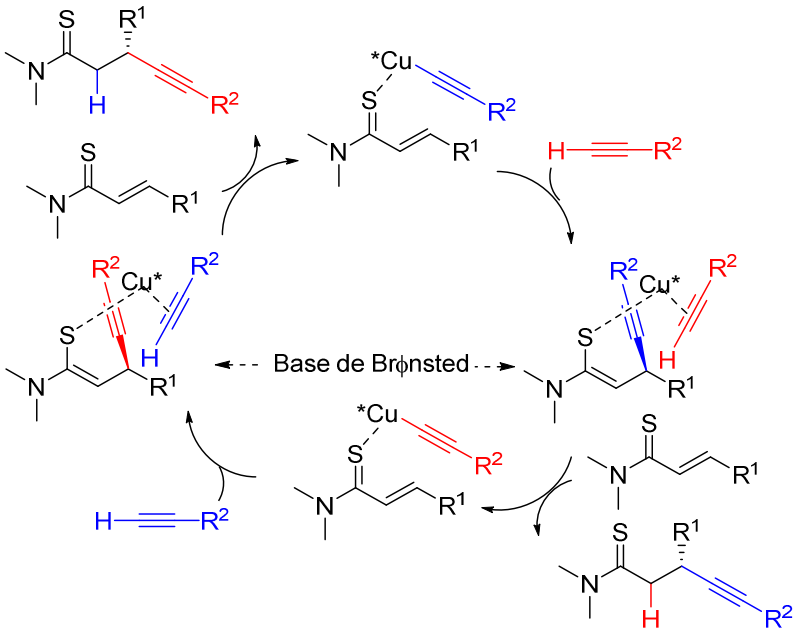
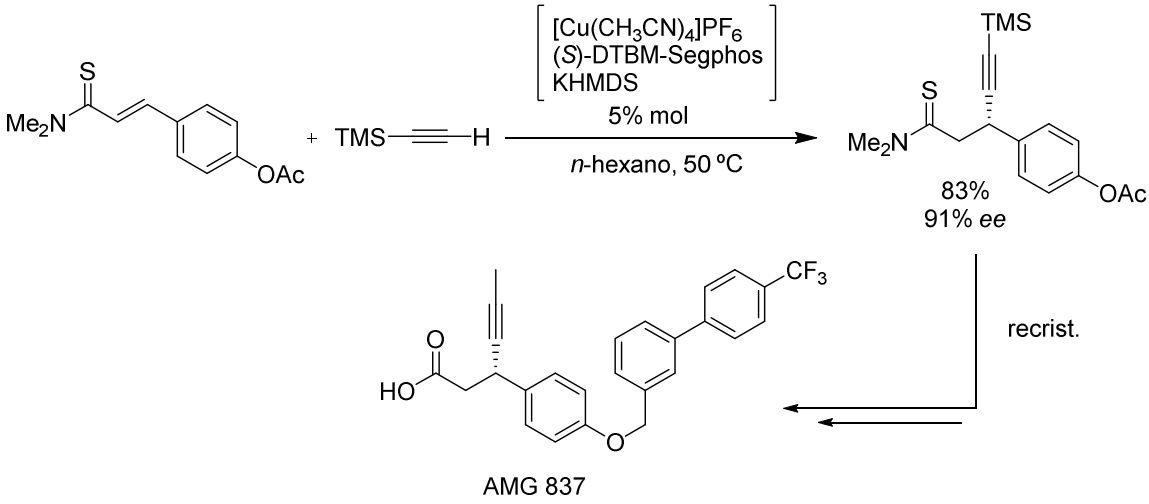


Figura 2. Ciclo catalítico de la adición conjugada de alquinos terminales a tioamidas α,β-insaturadas.

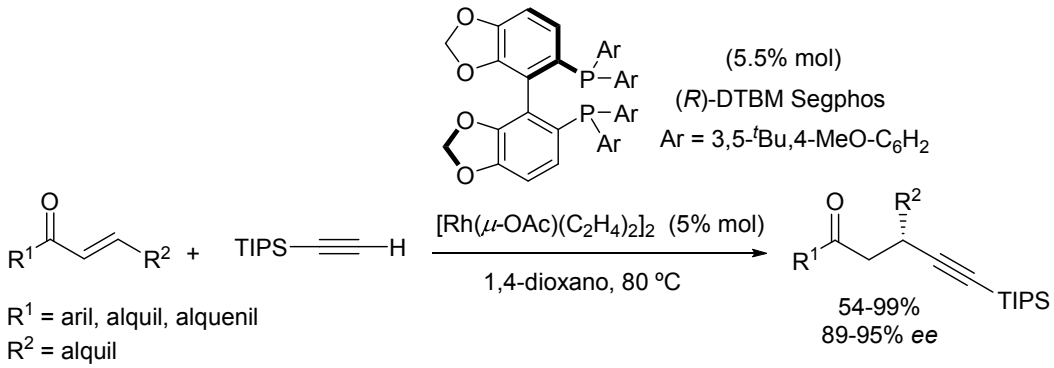
Posteriormente, los autores llevaron a cabo la síntesis de AMG 837, un agonista de GPR40 que es una diana terapéutica para los desórdenes de la insulina como la diabetes 2.[30] La síntesis de AMG 837 se llevó a cabo a partir de uno de los productos de alquinilación enantioselectiva enriquecido enantioméricamente mediante cristalización, en una secuencia sintética que implicó la transformación de la agrupación tioamida en un ácido carboxílico (Esquema 23).



Esquema 23. Síntesis de AMG 837, agonista de GPR40.

2.3.4. Adiciones conjugadas enantioselectivas catalizadas por rodio

Nishimura y Hayashi han descrito varios ejemplos de adiciones conjugadas enantioselectivas catalizadas por complejos de rodio con ligandos quirales de tipo fosfina.[31] En 2008, describieron el primer ejemplo de adición conjugada enantioselectiva de triisopropilsililacetileno a diversas enonas catalizada por un complejo de Rh(I) y el ligando DTBM-Segphos. Las β-alquinilcetonas correspondientes se obtuvieron con rendimientos entre 54-99% y enantioselectividades elevadas (Esquema 24).



Esquema 24. Adición conjugada de triisopropilsililacetileno a enonas catalizada por Rh(I).

La dimerización de los alquinos se consiguió reducir con el empleo del ligando (*R*)-DTBM-Segphos ya que los impedimentos estéricos que se producen entre los sustituyentes voluminosos del fósforo y los del silicio del alquino dificultan esta reacción secundaria (Figura 3).

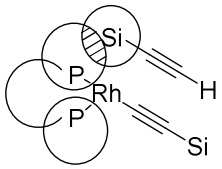
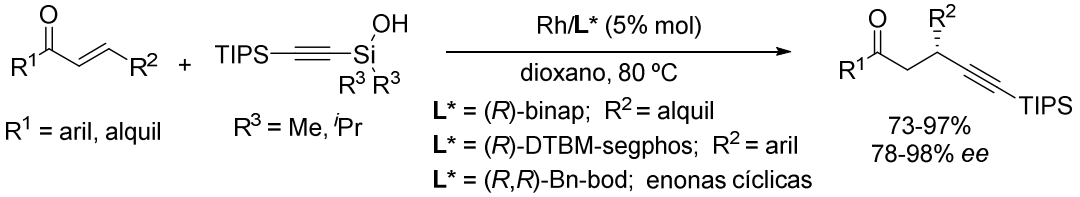


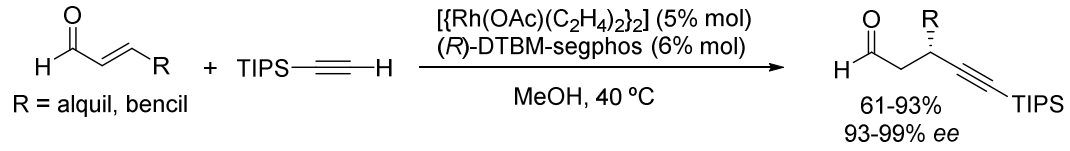
Figura 3. Impedimento estérico para la reacción de dimerización de sililacetileno.

Sin embargo, esta reacción de dimerización fue predominante cuando se emplearon enonas menos reactivas, como las enonas β-aril sustituidas o enonas cíclicas. En 2009, estos autores publicaron un nuevo trabajo sobre la adición conjugada a este tipo de enonas menos reactivas, utilizando un sistema más efectivo que evitaba la dimerización de los alquinos terminales.[32] Para ello se utilizaron derivados de dialquilsilanol los cuales dan lugar a la formación de alquiniluros de rodio intermedios que se muestran más reactivos frente a las enonas que frente a los alquinos de partida. Utilizaron tres sistemas catalíticos en función de que la enona empleada fuera alquílica, arílica o cíclica (Esquema 25).



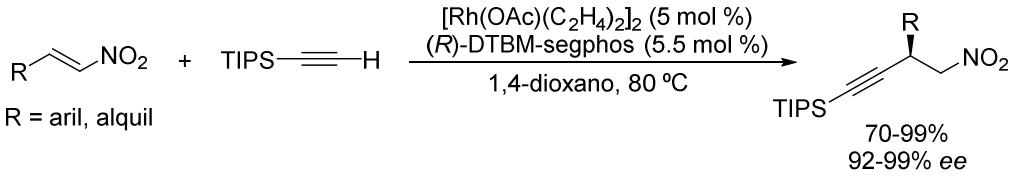
Esquema 25. Adición conjugada de alquinilsilanoles a enonas catalizada por Rh(I).

Además en 2009, estos mismos autores describieron la adición conjugada enantioselectiva de triisopropilsililacetileno a enales catalizada por rodio/DTBM-Segphos con buenos rendimientos y excelentes enantioselectividades (Esquema 26).[33] Los autores resolvieron el problema de la adición 1,2 del alquino al grupo carbonilo del enal con la utilización de metanol como disolvente.



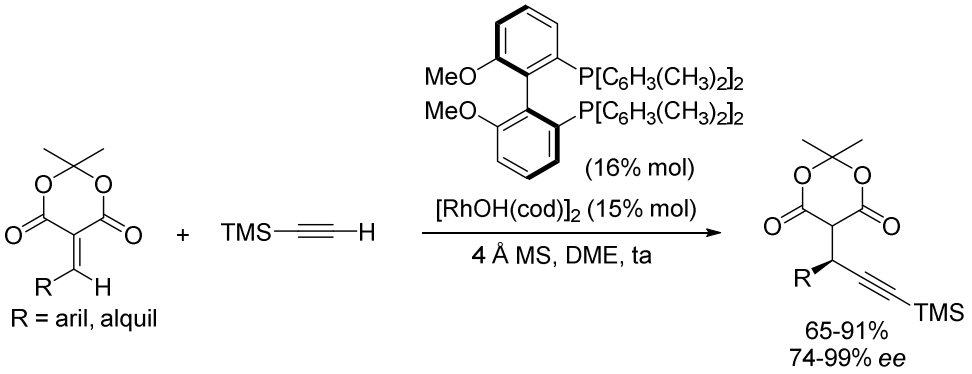
Esquema 26. Adición conjugada de triisopropilsililacetileno a enales catalizada por Rh(I).

Utilizando el mismo sistema catalítico, en 2010, Nishimura y Hayashi describieron la adición conjugada enantioselectiva de triisopropilsililacetileno a nitroalquenos sustituidos con grupos alifáticos y con anillos aromáticos sustituidos con grupos de distinta naturaleza electrónica, obteniendo β-alquinilnitro compuestos con rendimientos y excesos enantioméricos elevados (Esquema 27).[34]



Esquema 27. Adición conjugada de triisopropilsililacetileno a nitroalquenos catalizada por Rh(I).

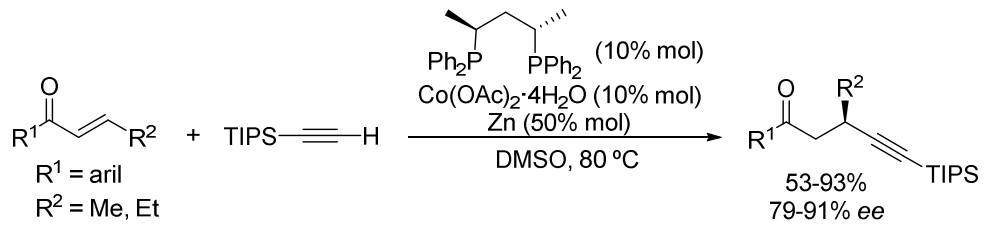
Por otra parte en 2009, Fillion y Zorzitto publicaron un nuevo método para la alquinilación conjugada catalizada por Rh(I).[35] Como alternativa al uso de acetilenos voluminosos para evitar la reacción de dimerización del alquino se utilizaron aceptores altamente electrofílicos para cambiar la cinética de la reacción y favorecer la adición conjugada frente a la dimerización del alquino. Para ello hicieron uso de derivados del ácido de Meldrum doblemente activados, y de un complejo de Rh(I) con una bisfosfina quiral como catalizador (Esquema 28). Los productos de alquinilación se obtuvieron con rendimientos y excesos enantioméricos elevados.



Esquema 28. Adición conjugada de trimetilsililacetileno a derivados del ácido de Meldrum catalizada por Rh(I).

2.3.5. Adiciones conjugadas enantioselectivas de alquinos terminales catalizadas por cobalto

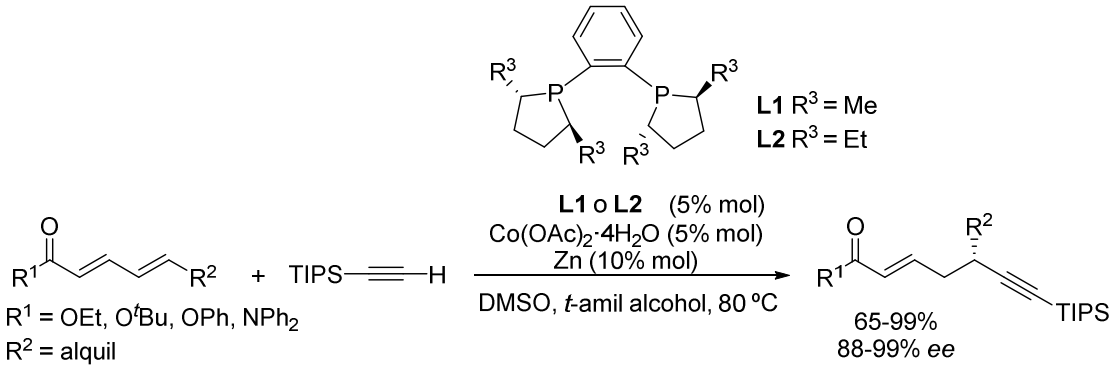
Nishimura y Hayashi describieron en 2011 la primera adición conjugada enantioselectiva catalizada por Co(I).[36] Los autores describen la reacción de adición conjugada de triisopropilsililacetileno a diferentes cetonas α,β-insaturadas catalizada por un sistema de Co(II)/bisfosfina quiral/Zn. El Co(II) es reducido a Co(I) por la acción del cinc. Los productos se obtuvieron con rendimientos y excesos enantioméricos elevados (Esquema 29).



Esquema 29. Adición conjugada de triisopropilsililacetileno a cetonas α,β-insaturadas catalizada por Co(I).

En el artículo, un sistema catalítico no quiral es utilizado en la adición conjugada de diversos trialquilsililacetilenos a diferentes cetonas α,β-insaturadas dando lugar a los correspondientes productos con rendimientos elevados.

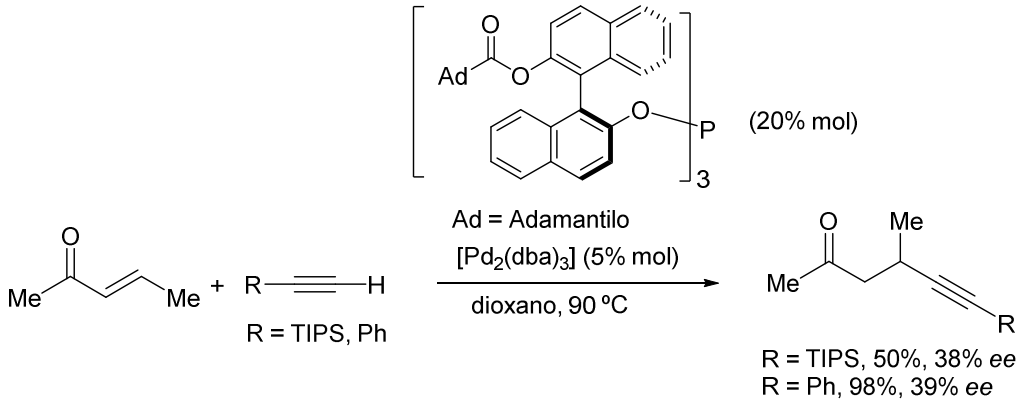
Con posterioridad, los autores describieron el primer ejemplo de adición 1,6 enantioselectiva de triisopropilsililacetileno a compuestos carbonílicos α,β,γ,δ-insaturados empleando un sistema catalítico similar al descrito anteriormente (Esquema 30).[37] Los productos de alquinilación tanto de ésteres como de amidas se obtuvieron con rendimientos elevados y regio- y enantioselectividades excelentes.



Esquema 30. Adición conjugada 1,6 de triisopropilsililacetileno a compuestos carbonílicos α,β,γ,δ-insaturados catalizada por Co(I).

2.3.6. Adición conjugada enantioselectiva de alquinos terminales catalizada por paladio

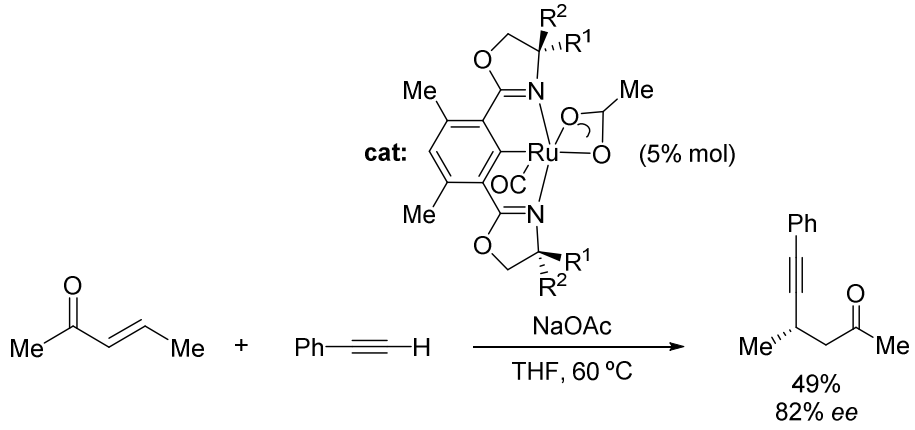
En 2012, el grupo de Mascareñas describió la alquinilación de enonas, tanto cíclicas como acíclicas, con diversos alquinos terminales empleando el complejo de Pd(0) y fosfito de 2,4-di-*terc*-butilfenilo como catalizador, obteniendo las correspondientes β-alquinilcetonas racémicas con rendimientos entre 17-98%.[38] En la misma publicación, estos autores describieron únicamente dos ejemplos de una versión asimétrica de la reacción utilizando un fosfito quiral derivado de BINOL obteniendo excesos enantioméricos bajos del 38% y 39% en la alquinilación de (*E*)-pent-3-en-2-ona con fenilacetileno y triisopropilsililacetileno, respectivamente (Esquema 31).



Esquema 31. Adición conjugada de alquinos terminales a la (*E*)-pent-3-en-2-ona catalizada por Pd(0).

2.3.7. Adición conjugada enantioselectiva de alquinos terminales catalizadas por rutenio

En 2012, Ito y col. describieron la adición conjugada no enantioselectiva catalizada por rutenio de alquinos terminales (arilacetilenos y trimetilsililacetileno) a diferentes compuestos carbonílicos α,β-insaturados tales como cetonas, ésteres, vinil fosfonatos y amidas, obteniendo en todos los casos los productos de β-alquinilación con buenos rendimientos. En este trabajo, se describe un único ejemplo de adición conjugada enantioselectiva de fenilacetileno a (*E*)-pent-3-en-2-ona, empleando para ello un complejo de Ru-phebox-acetato quiral, obteniendo el correspondiente producto de alquinilación con 49% de rendimiento y un 82% de exceso enantiomérico (Esquema 32).[39]



Esquema 32. Adición conjugada de fenilacetileno a (*E*)-pent-3-en-2-ona catalizada por Ru(I).

3. OBJETIVOS

3. OBJETIVOS

La adición de alquinos terminales a grupos funcionales electrofílicos es un método eficaz para la formación de enlaces carbono-carbono, dando lugar a moléculas con un centro estereogénico propargílico. En los últimos años se han desarrollado una serie de procedimientos para la adición conjugada enantioselectiva catalítica de alquinos terminales; sin embargo, es un tema de investigación en el que aún queda mucho por descubrir y desarrollar. La investigación en esta área plantea nuevos retos tales como:

- El desarrollo de sistemas catalíticos no descritos para la adición conjugada enantioselectiva de alquinos terminales, en particular aquellos que no utilizan metales preciosos.
- Expandir la aplicación de esta reacción a una mayor variedad de sustratos electrofílicos. En particular, resulta muy interesante el estudio de la reacción con sustratos que presentan grupos fluorados, de gran importancia en la química farmacéutica y agroquímica.
- La aplicabilidad sintética de los productos de reacción.

De acuerdo con estos retos, en la presente Tesis se plantearon como objetivos el desarrollo de nuevas reacciones de alquinilación conjugada de compuestos carbonílicos α,β-insaturados, incluyendo compuestos fluorados, utilizando catálisis por complejos de cinc(II) y cobre(I):

1. Alquinilación conjugada enantioselectiva de 2-ariliden-1,3-dicetonas catalizada por complejos de cinc(II).

2. Alquinilación conjugada enantioselectiva de 3-(alcoxicarbonil)cumarinas catalizada por complejos de cinc(II).

3. Alquinilación conjugada enantioselectiva de 1-(fenilsulfonil)-1,1-difluoro-3-en-2-onas catalizada por complejos de cobre(I).

4. Alquinilación conjugada enantioselectiva de 1,1,1-trifluorometil-3-en-2-onas catalizada por complejos de cobre(I).

5. Adición conjugada enantioselectiva de 1,3-diinos a 1,1,1-trifluorometil-3-en-2-onas catalizada por complejos de cobre(I).

6. Alquinilación conjugada enantioselectiva de β-trifluorometil α,β-enonas catalizada por complejos de cobre(I).

7. Alquinilación conjugada enantioselectiva de β-aril β-trifluorometil α,β-enonas catalizada por complejos de cinc(II).

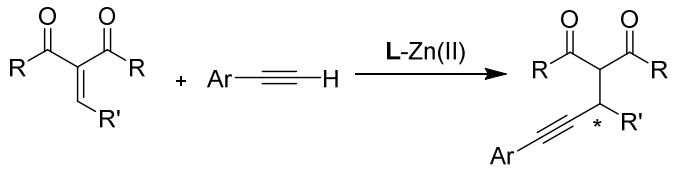
4. RESULTADOS Y DISCUSIÓN

4. RESULTADOS Y DISCUSIÓN

4.1. Alquinilación conjugada enantioselectiva de 2-ariliden-1,3-dicetonas catalizada por complejos de Zn(II).

Como se ha descrito en los antecedentes bibliográficos, existen varios ejemplos de adición conjugada diastereo- o enantioselectiva de alquinos terminales mediada por cinc en los que se emplea una cantidad estequiométrica o superior de inductor quiral.[20-22] Sin embargo, no se había descrito ningún ejemplo de adición conjugada de alquinos terminales mediada por cinc en el que se empleara una cantidad subestequiométrica de complejo quiral. Desde el punto de vista económico los procedimientos catalíticos que eviten el uso de metales nobles, caros y poco abundantes, y que minimicen la cantidad de inductor quiral necesaria resultan muy interesantes. De acuerdo con esto, nos planteamos el desarrollo de reacciones de alquinilación conjugada mediadas por cinc.

Comenzamos nuestro estudio con 2-ariliden-1,3-dicetonas como electrófilos ya que estos sustratos se pueden sintetizar de manera sencilla mediante una reacción de Knoevenagel y presentan una gran electrofilia debido a que el doble enlace se encuentra conjugado con dos grupos carbonilo electrón-atrayentes (Esquema 33).

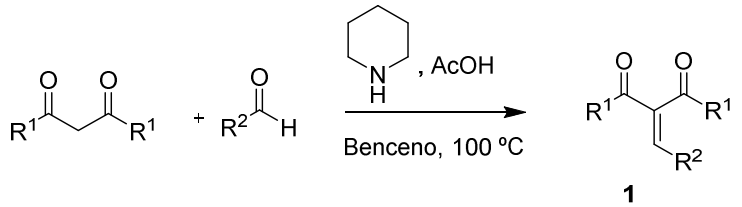


Esquema 33. Reacción de adición conjugada de alquinos terminales a 2-ariliden-1,3-dicetonas.

4.1.1. Síntesis de 2-ariliden- y 2-alquiliden-1,3-dicetonas

Existen en la bibliografía varios procedimientos descritos para la síntesis de los materiales de partida,[40] todos ellos basados en la reacción de Knoevenagel. Esta reacción consiste en una reacción de tipo aldólico entre el metileno ácido de un compuesto 1,3-dicarbonílico y un aldehído. Nosotros optamos por la utilización de las condiciones clásicas de la reacción de Knoevenagel con piperidina, ácido acético y benceno a reflujo, descritas por Antonioletti.[40d]

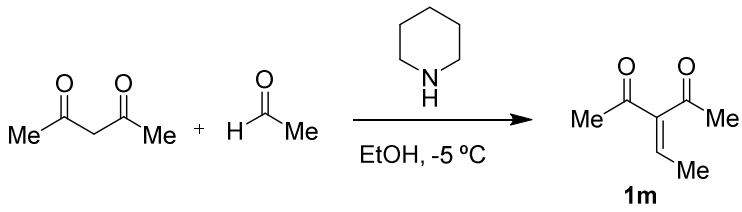
Los derivados de 3-bencilidenpentano-2,4-diona se prepararon por reacción de pentano-2,4-diona con aldehídos aromáticos y heteroaromáticos para obtener los compuestos **1a-k** con rendimientos entre 60-95% (Esquema 34). La 4-bencilidenheptano-3,5-diona (**1l**, R^1 = Et, R^2 = Ph) se preparó de la misma manera a partir de heptano-3,5-diona y benzaldehído con un rendimiento del 90%.



1a, R^1 = Me, R^2 = Ph
1b, R^1 = Me, R^2 = 4-MeC_6H_4
1c, R^1 = Me, R^2 = 4-$MeOC_6H_4$
1d, R^1 = Me, R^2 = 3-ClC_6H_4
1e, R^1 = Me, R^2 = 4-ClC_6H_4
1f, R^1 = Me, R^2 = 4-BrC_6H_4
1g, R^1 = Me, R^2 = 4-$NO_2C_6H_4$
1h, R^1 = Me, R^2 = 2-naftilo
1i, R^1 = Me, R^2 = 2-furanilo
1j, R^1 = Me, R^2 = 3-furanilo
1k, R^1 = Me, R^2 = 3-tienilo
1l, R^1 = Et, R^2 = Ph

Esquema 34. Síntesis de 3-arilidenpentano-2,4-dionas (**1a-k**) y 4-bencilidenheptano-3,5-diona (**1l**) mediante la reacción de Knoevenagel.

Para aldehídos volátiles y enolizables como el acetaldehído la reacción se llevó a cabo en etanol a -5 °C.[41] La 3-etilidenpentano-2,4-diona (**1m**) se purificó por destilación a vacío obteniéndose un aceite transparente (Esquema 35).



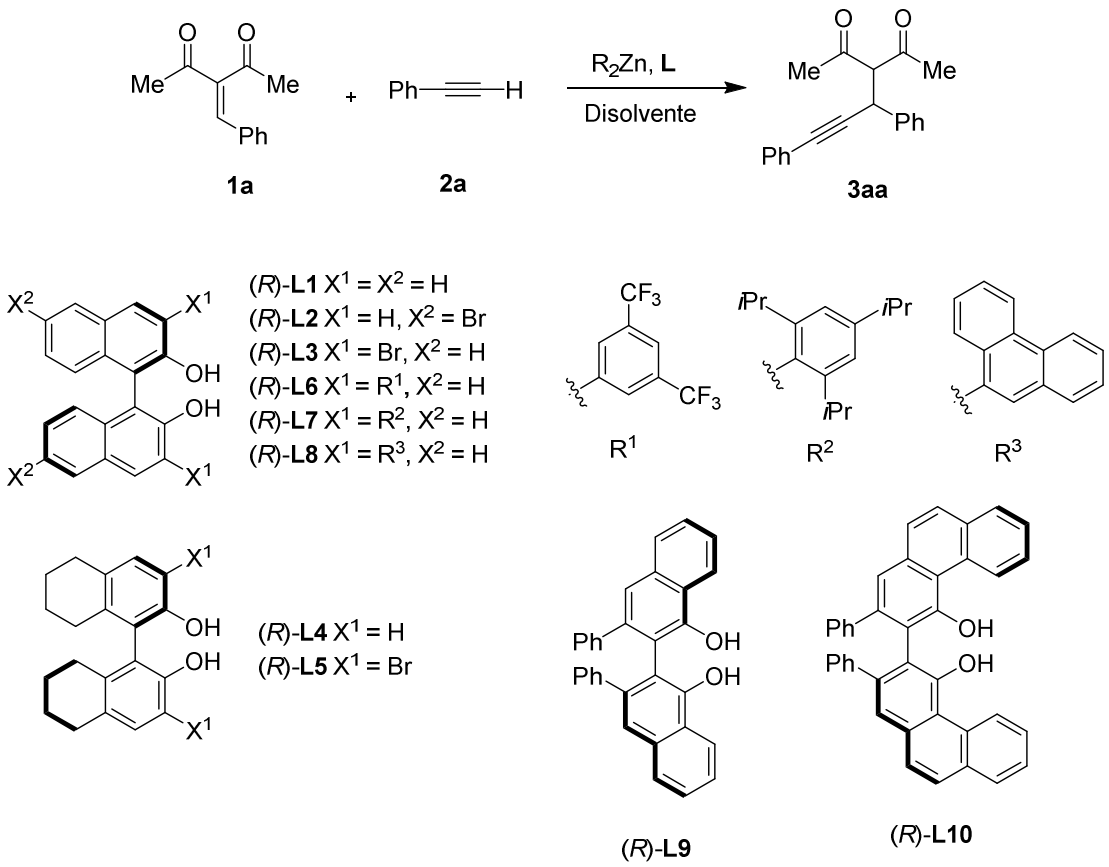
Esquema 35. Síntesis de 3-etilidenpentano-2,4-diona (**1m**).

Todos estos compuestos se caracterizaron por resonancia magnética nuclear (^{1}H-RMN, ^{13}C-RMN).

4.1.2 Optimización de las condiciones de reacción

Debido a la experiencia previa de nuestro grupo de investigación en la adición enantioselectiva de alquinos terminales a aldehídos[42] e iminas[43] mediadas por dialquilcinc en presencia de cantidades catalíticas de ligandos de tipo BINOL decidimos iniciar nuestra investigación sobre alquinilicación conjugada empleando este tipo de sistema reactivo.

El proceso de optimización se llevó a cabo utilizando la reacción entre fenilacetileno (**2a**) y 3-bencilidenpentano-2,4-diona (**1a**), evaluándose el rendimiento y el exceso enantiomérico en función del ligando, la temperatura, el disolvente y el reactivo de dialquilcinc utilizado (Esquema 36).

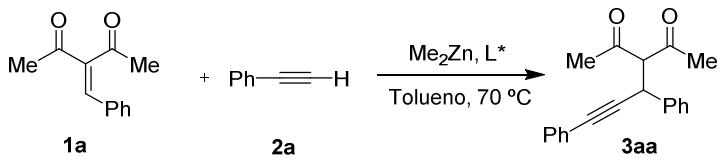


Esquema 36. Adición conjugada de fenilacetileno (**2a**) a 3-bencilidenpentano-2,4-diona (**1a**) y ligandos de tipo BINOL utilizados.

Inicialmente, las condiciones de reacción utilizadas fueron similares a las descritas por nuestro grupo de investigación para la adición 1,2 de alquinos a aldehídos,[42] donde se generaba el complejo ligando-acetiluro de cinc a 70 °C en tolueno. Nosotros decidimos llevar a cabo la formación del complejo calentando una mezcla del ligando (20% mol), fenilacetileno (**2a**, 7,5 equiv.) y Me_2Zn 2 M en tolueno (2 equiv.) a 70 °C durante 1 h 30 min., adicionando a continuación y a la misma temperatura la enona **1a** disuelta en tolueno.

Con estas condiciones se estudió el efecto de varios ligandos derivados de (*R*)-BINOL (**L1-L8**), incluyendo algunos de sus derivados con grupos electrón-atrayentes o voluminosos en las posiciones 3,3' y 6,6', así como derivados con anillos tetrahidrogenados, y también ligandos "abovedados" como el (*R*)-VANOL (**L9**) y el (*R*)-VAPOL (**L10**).

Tabla 1. Adición conjugada enantioselectiva de fenilacetileno (**2a**) a 3-bencilidenpentano-2,4-diona (**1a**). Screening de ligandos.[a]



	L	t (h)	Rto (%)[b]	*ee* (%)[c]
1	**L1**	2	40	10
2	**L2**	4	52	20
3	**L3**	2	58	29
4	**L4**	2	65	6
5	**L5**	2	70	26
6	**L6**	2	55	28
7	**L7**	2	81	0
8	**L8**	1	62	0
9	**L9**	1	87	64
10	**L10**	2	50	32

[a]**1a** (0,125 mmol), **2a** (0,94 mmol), Me_2Zn 2 M en tolueno (0,13 mL, 0,25 mmol), **L** (0,025 mmol) en tolueno a 70 °C. [b] Rendimiento de producto aislado. [c] Determinado por HPLC en fase estacionaria quiral.

Los ligandos de tipo BINOL (Tabla 2, entradas 1-8) proporcionaron unos excesos enantioméricos muy bajos en especial cuando el impedimento estérico en las posiciones 3,3' era muy grande obteniéndose el producto **3aa** en forma racémica (Tabla 1, entradas 7 y 8). El mejor resultado tanto en términos de rendimiento como de enantioselectividad fue proporcionado por el ligando **L9**, (*R*)-VANOL (Tabla 1, entrada 9). El ligando **L10**, (*R*)-VAPOL no aportó ninguna mejora con respecto a **L9** (Tabla1, entrada 10).

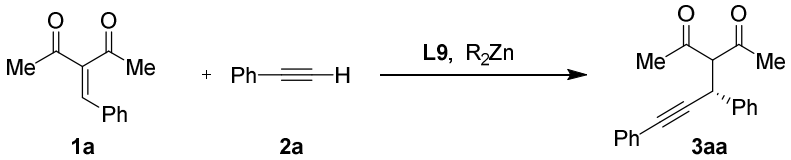
A continuación, la reacción se llevó a cabo con diversos reactivos de dialquilcinc, a diferentes temperaturas y con varios disolventes con el fin de aumentar el rendimiento y el exceso enantiomérico (Tabla 2).

En primer lugar, se ensayó la reacción con Et_2Zn 1 M en hexano con lo que se consiguió aumentar el rendimiento hasta 92% manteniendo el exceso enantiomérico (Tabla 2, entrada 2), por lo que se decidió continuar la optimización con Et_2Zn que es además más económico que el Me_2Zn. Cuando la adición del sustrato **1a** se llevó a cabo a temperatura ambiente se consiguió aumentar el exceso enantiomérico del producto hasta el 74% (Tabla 2, entrada 3), sin embargo, una disminución mayor de la temperatura condujo a menor rendimiento y enantioselectividad (Tabla 2, entrada 4).

A continuación, se ensayó el uso de co-disolventes. En diclorometano aumentó el exceso enantiomérico pero a expensas de un rendimiento bajo (Tabla 2, entrada 5). El uso de nitrometano (Tabla 2, entrada 6) produjo un incremento acentuado de la enantioselectividad hasta 91% *ee*, aunque el producto de adición se obtuvo con rendimiento moderado. Un examen de los subproductos de reacción mostró la

formación de una cantidad considerable de 5-fenilisoxazol resultante de una reacción de adición 1,3-dipolar entre nitrometano y fenilacetileno.[44] Con el fin de minimizar esta reacción secundaria se ensayaron otros nitroalcanos (Tabla 2, entradas 7-9), alcanzando un compromiso entre rendimiento y enantioselectividad en tolueno/nitroetano que proporcionó el producto de adición deseado **3aa** con un 69% de rendimiento y un 87% *ee* (Tabla 2, entrada 7). La utilización de Me_2Zn en tolueno, con nitroetano como co-disolvente no aportó ninguna mejora (Tabla 2, entrada 10).

Tabla 2. Adición conjugada enantioselectiva de fenilacetileno (**2a**) a 3-bencilidenpentano-2,4-diona (**1a**). Efecto del reactivo de dialquilcinc, temperatura y disolvente.[a]



	R_2Zn	Co-disolvente[b]	T (°C)[c]	t (h)	Rto (%)[d]	*ee*(%)[e]
1	Me_2Zn[f]	Tolueno	70	1	87	64
2	Et_2Zn[g]	Tolueno	70	1	92	63
3	Et_2Zn[g]	Tolueno	ta	4	69	74
4	Et_2Zn[g]	Tolueno	0	5	30	68
5	Et_2Zn[g]	CH_2Cl_2	ta	4	49	80
6	Et_2Zn[g]	$MeNO_2$	ta	2	45	91
7	Et_2Zn[g]	$EtNO_2$	ta	4	69	87
8	Et_2Zn[g]	$PhNO_2$	ta	4	68	86
9	Et_2Zn[g]	$^{i}PrNO_2$	ta	4	48	75
10	Me_2Zn[f]	$EtNO_2$	ta	4	65	86
11	Et_2Zn[h]	$EtNO_2$	ta	4	72	87

[a]**1a** (0,125 mmol), **2a** (0,94 mmol), R_2Zn (0,25 mmol), **L9** (0,025 mmol) en tolueno. [b] Disolvente utilizado en la adición de **1a**. [c] Temperatura de adición de **1a**. [d] Rendimiento de producto aislado. [e] Determinado por HPLC quiral. [f] Me_2Zn 2 M en tolueno.[g] Et_2Zn 1 M en hexano. [h] Et_2Zn 1,5 M en tolueno.

Finalmente, el uso de la disolución de dietilcinc en tolueno, en lugar de hexano, permitió un ligero aumento de rendimiento (Tabla 2, entrada 11).

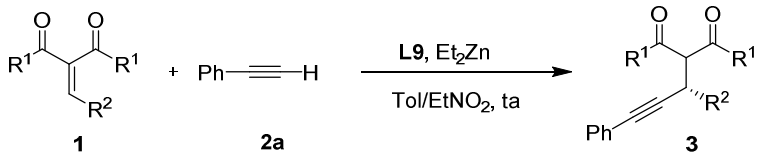
De acuerdo con este proceso de optimización las mejores condiciones consistieron en la formación del complejo con **L9** (20% mol), Et_2Zn 1,5 M en tolueno (2 equiv.) y alquino **2** (7,5 equiv.) a 70 ºC en tolueno y adición del sustrato **1** utilizando $EtNO_2$ como co-disolvente a temperatura ambiente.

4.1.3 Alcance y limitaciones de la reacción

Finalizado el proceso de optimización con la adición conjugada de fenilacetileno (**2a**) a 3-bencilidenpentano-2,4-diona (**1a**), se evaluó la aplicabilidad de las condiciones de reacción a otras endionas **1**y alquinos terminales **2**.

En primer lugar se estudió la adición conjugada de fenilacetileno (**2a**) a distintas dionas (Tabla 3).

Tabla 3. Adición conjugada enantioselectiva de fenilacetileno (**2a**) a distintas endionas **1**.[a]



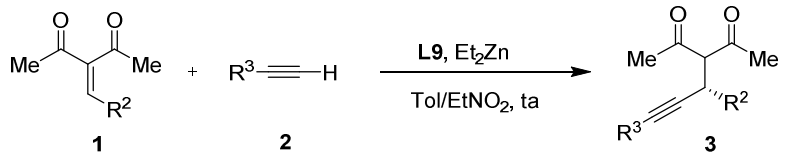
		R^1	R^2	t (h)		Rto (%)[b]	*ee* (%)[c]
1	**1a**	Me	C_6H_5	4	**3aa**	72	87
2	**1b**	Me	4-MeC_6H_4	4	**3ba**	69	85
3	**1c**	Me	4-MeOC_6H_4	4	**3ca**	65(59)[d]	80(97)[d]
4	**1d**	Me	3-ClC_6H_4	4	**3da**	64	84
5	**1e**	Me	4-ClC_6H_4	4	**3ea**	67	88
6	**1f**	Me	4-BrC_6H_4	4	**3fa**	68(74)[d]	88(99)[d]
7	**1g**	Me	4-$NO_2C_6H_4$	4	**3ga**	53	83
8	**1h**	Me	2-naftilo	4	**3ha**	52(71)[d]	80(99)[d]
9	**1i**	Me	2-furanilo	4	**3ia**	48	80
10	**1j**	Me	3-furanilo	4	**3ja**	53	83
11	**1k**	Me	3-tienilo	4	**3ka**	52	82
12	**1l**	Me	Me	4	**3la**	68	64
13	**1m**	Et	C_6H_5	5	**3ma**	55	76

[a] **1** (0,125 mmol), **2a** (0,94 mmol), Et_2Zn (0,25 mmol), **L9** (0,025 mmol) en tol./$EtNO_2$ a ta.[b] Rendimiento de producto aislado. [c] Determinado por HPLC quiral. [d] Entre paréntesis, rendimiento y *ee* después de cristalización con mezclas de hexano/CH_2Cl_2.

La reacción de adición conjugada puede llevarse a cabo con diferentes 3-arilidenpentano-2,4-dionas **1** sustituidas tanto con grupos electrón-atrayentes como electrón-dadores en las posiciones *meta* y *para* del anillo aromático en β, obteniéndose las correspondientes β-alquinil dicetonas **3** con buenos rendimientos y excesos enantioméricos superiores al 80% (Tabla 3, entradas 2-7). La reacción de adición a un sustrato con un sustituyente voluminoso en la posición β, como es el derivado de 2-naftilcarbaldehído transcurrió con un rendimiento moderado y un 80% *ee* (Tabla 3, entrada 8). La aplicabilidad de la reacción también puede ampliarse a endionas con grupos heteroaromáticos en β obteniéndose los correspondientes productos con enantioselectividades en torno al 80% *ee* (Tabla 3, entradas 9-11). Además, se estudió la reacción de adición conjugada a un compuesto 1,3-dicarbonílico α,β-insaturado con un sustituyente alifático en β (**1l**) obteniéndose el producto **3la** con un buen rendimiento y una enantioselectividad moderada (Tabla 3, entrada 12). Finalmente, se estudió el efecto del sustituyente en el grupo carbonilo haciendo reaccionar la 4-bencilidenheptano-3,5-diona (**1m**, R^1 = Et, R^2 = Ph) con **2a** obteniendo el correspondiente producto de alquinilación **3ma** con un rendimiento moderado y una enantioselectividad inferior (76% *ee*) a la obtenida con la diona **1a** (Tabla 3, entrada 13).

A continuación se ensayó el alcance de la reacción con otros alquinos terminales **2** (Tabla 4).

Tabla 4. Adición conjugada enantioselectiva de varios alquinos aromáticos **2** a diferentes 3-arilidenpentano-2,4-dionas **1**.[a]



	R[2]		R[3]			Rto (%)[b]	*ee* (%)[c]
1	**1a**	C_6H_5	**2b**	4-$MeOC_6H_4$	**3ab**	53(44)[d]	84(99)[d]
2	**1a**	C_6H_5	**2c**	4-FC_6H_4	**3ac**	61(80)[d]	86(99)[d]
3	**1a**	C_6H_5	**2d**	4-ClC_6H_4	**3ad**	56	87
4	**1b**	4-MeC_6H_4	**2c**	4-FC_6H_4	**3bc**	67	87
5	**1e**	4-ClC_6H_4	**2c**	4-FC_6H_4	**3ec**	76	86
6[e]	**1e**	4-ClC_6H_4	**2c**	4-FC_6H_4	**3ec**	45	93
7	**1f**	4-BrC_6H_4	**2c**	4-FC_6H_4	**3fc**	80	86
8	**1a**	C_6H_5	**2e**	3-tienilo	**3ae**	62	80
9[f]	**1a**	C_6H_5	**2f**	$PhCH_2CH_2$	**3af**	45	27

[a] **2** (0,94 mmol), Et_2Zn (0,25 mmol), **L9** (0,025 mmol), **1** (0,125 mmol) en tol./$EtNO_2$ a ta., 4 h.[b] Rendimiento de producto aislado. [c] Determinado por HPLC quiral. [d] Entre paréntesis, rendimiento y *ee* después de cristalización con mezclas de hexano/CH_2Cl_2. [e] Utilizando $MeNO_2$ en lugar de $EtNO_2$. [f] La reacción se llevó a cabo a 70 ºC.

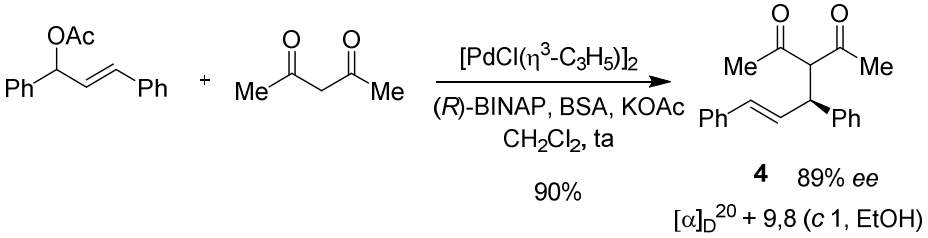
La reacción de adición conjugada de diversos derivados de fenilacetileno sustituidos en el anillo aromático **2b-d** con distintas endionas **1a,b,e,f** dieron los productos deseados con enantioselectividades similares a las observadas con fenilacetileno **2a** (Tabla 4, entradas 1-7). La reacción de **1a** con (3-tienil)acetileno (**2e**) condujo al producto **3ae** con un 80% de exceso enantiomérico (Tabla 4, entrada 8). Sin embargo, se necesitó una temperatura de reacción más elevada para la reacción de 4-fenil-1-butino (**2f**) dando el producto esperado **3af** con un 43% de rendimiento y un 27% de exceso enantiomérico (Tabla 4, entrada 9). También se ensayó la reacción con trimetilsililacetileno dando una mezcla compleja de productos que no se caracterizó.

Finalmente, cabe destacar que la mayoría de los productos de alquinilación **3** son sólidos que pueden obtenerse en forma casi enantioméricamente pura mediante cristalización de mezclas hexano-diclorometano (Tabla 3, entradas 3, 6 y 8; Tabla 4, entradas 1 y 2).

4.1.4 Determinación de la configuración absoluta

La determinación de la configuración absoluta de los productos de adición conjugada **3** se llevó a cabo por correlación química del producto resultante de la hidrogenación catalítica de **3aa** con el producto **5** obtenido por hidrogenación del producto **4** de esteroquímica conocida.[45]

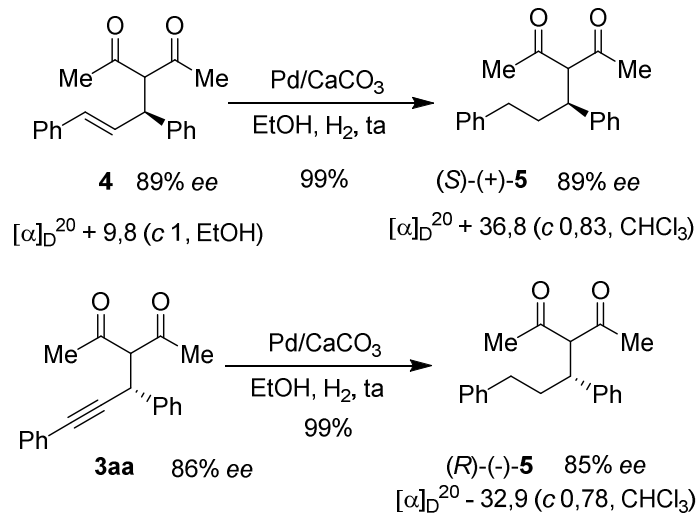
En primer lugar, se llevó a cabo la reacción de alquilación alílica[46] del acetato de (*E*)-1,3-difenilalilo con 2,4-pentanodiona empleando como catalizador un complejo de Pd(II) y (*R*)-BINAP obteniéndose el producto **4** con un rendimiento del 90% y 89% *ee* (Esquema 37).



Esquema 37. Reacción de alquilación alílica enantioselectiva.

La hidrogenación catalítica del producto **4** sobre $Pd/CaCO_3$ condujo cuantitativamente a la diona (*S*)-(+)-**5** (Esquema 37).

Por otra parte la hidrogenación catalítica del producto de alquinilación conjugada **3aa** condujo a un compuesto cuyas características espectroscópicas coincidieron con las de **5** (Esquema 38).



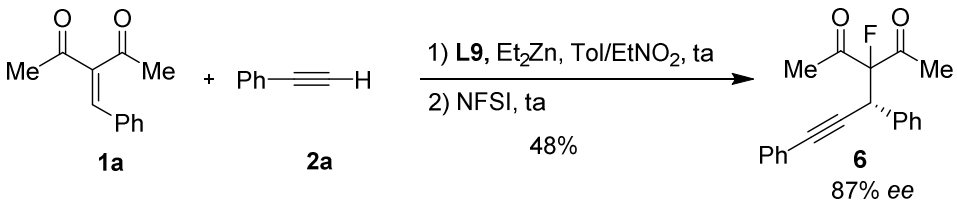
Esquema 38. Reacciones de hidrogenación catalítica.

Los productos de hidrogenación preparados a partir de **4** y **3aa** mostraron signos opuestos en el valor de su rotación óptica, lo que permitió asignar al compuesto **3aa,** resultante de la reacción de alquinilación, la configuración *R* en el centro estereogénico. Para el resto de productos **3** se asignó la misma configuración absoluta suponiendo un mecanismo estereogénico uniforme.

4.1.5 Transformaciones sintéticas

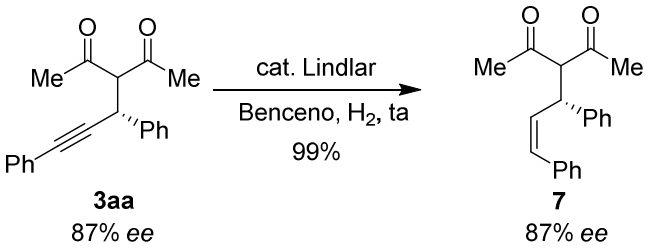
Con el fin de mostrar el potencial sintético de nuestra reacción y de los productos preparados se llevaron a cabo algunas modificaciones de los mismos.

Los productos resultantes de la alquinilación conjugada son enolatos que pueden reaccionar con electrófilos si no son neutralizados antes, lo que permite realizar reacciones de tipo tandem. Como ejemplo, se llevó a cabo una reacción tándem enantioselectiva, alquinilación conjugada-fluoración, por adición de *N*-fluorobencenosulfonamida (NFSI) a la mezcla final de alquinilación, obteniendo el producto **6** con un rendimiento moderado y exceso enantiomérico del 87% (Esquema 39).



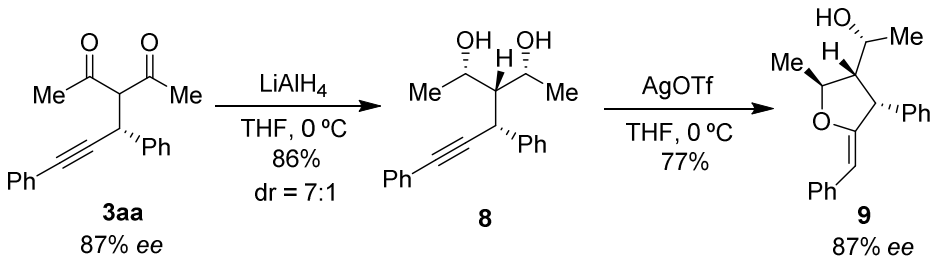
Esquema 39. Reacción tándem alquinilación conjugada-fluoración enantioselectiva.

Por otra parte, la hidrogenación parcial del compuesto **3aa** con el catalizador de Lindlar (5%) da lugar al alqueno **7** con un doble enlace *Z* y un centro estereogénico alílico (Esquema 40), siendo este procedimiento complementario a la sustitución alílica catalizada por Pd(II) del acetato de (*E*)-1,3-difenilalilo con 2,4-pentanodiona, la cual favorece la formación del doble enlace *E* (Esquema 40).



Esquema 40. Hidrogenación parcial del triple enlace en el compuesto **3aa**.

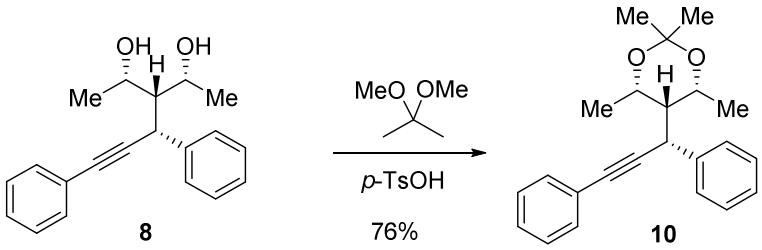
Además, el producto **3aa** puede ser reducido de manera diastereoselectiva al diol **8** con $LiAlH_4$, lo que seguido de una ciclación catalizada por plata permite obtener el tetrahidrofurano quiral **9** con cuatro centros estereogénicos (Esquema 41).



Esquema 41. Formación del tetrahidrofurano quiral **9.**

El tetrahidrofurano **9** es inestable debido a la presencia del doble enlace exocíclico, observándose su migración a una posición endocíclica en un 60% tras permanecer 18 horas en disolución de $CDCl_3$.

Para determinar la estereoquímica relativa del diol **8** y del compuesto cíclico **9**, se fijó la conformación del compuesto **8** mediante la formación de un acetónido **10**, por tratamiento del diol **8** con 2,2-dimetoxipropano en medio ácido (Esquema 42).



Esquema 42. Síntesis del acetónido **10**.

La estereoquímica del acetónido **10** fue asignada de acuerdo con las constantes de acoplamiento del protón C5-H del anillo de dioxano. La señal de este protón aparece como un doble triplete debido a los acoplamientos con el protón propargílico (J = 3,6 Hz) y a los acoplamientos idénticos ecuatorial-axial (J = 2,7 Hz) con los dos protones C4-H y C6-H como se muestra en la Figura 4.

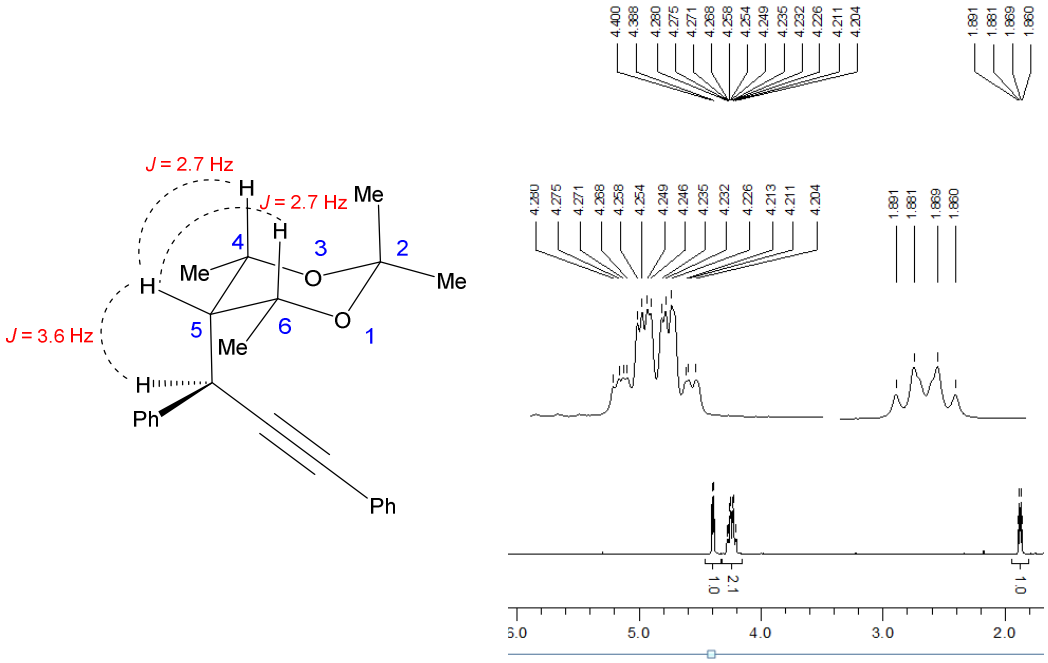


Figura 4. Detalle del espectro de RMN ^{1}H del acetónido **10**.

Además, se llevaron a cabo experimentos NOESY sobre el compuesto cíclico **9** observándose las interacciones significativas que se muestran en la Figura 5.

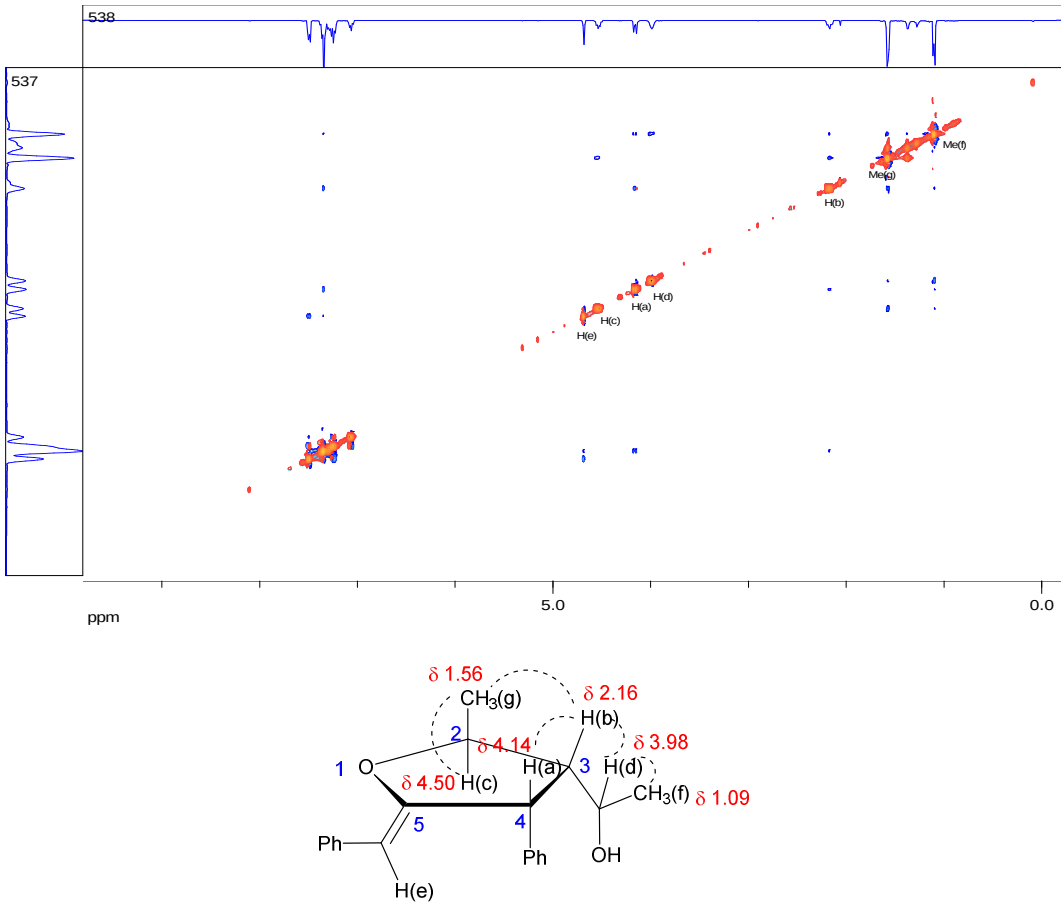


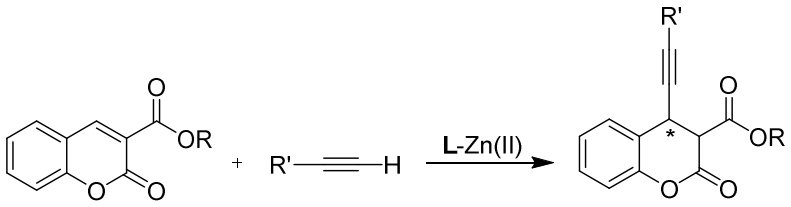
Figura 5. Experimento NOESY del tetrahidrofurano **9**.

Siendo *R* la configuración del carbono propargílico en el producto de alquinilación **3aa** y considerando tanto las constantes de acoplamiento observadas en el acetónido **10** y los experimentos NOESY realizados con el tetrahidrofurano **9**, se asignó la estereoquímica de los compuestos **8-10**.

En resumen, los resultados descritos en este capítulo constituyen el primer ejemplo de reacción de alquinilación conjugada enantioselectiva catalizada por cinc que requiere una cantidad subestequiométrica de material quiral. La reacción es aplicable a endionas con diferente sustitución en el carbono β del doble enlace y alquinos terminales con sustituyentes aromáticos y heteroaromáticos. Los productos se obtienen con buenos rendimientos y enantioselectividades, pudiendo ser enriquecidos enantioméricamente por cristalización.

4.2. Alquinilación conjugada enantioselectiva a 3-alcoxicarbonil cumarinas catalizada por complejos de Zn(II).

El núcleo de 3,4-dihidrocumarina está presente en numerosos productos naturales y compuestos biológicamente activos.[47] De ahí, la importancia del desarrollo de procedimientos para la construcción de este tipo de estructuras. La adición conjugada enantioselectiva de reactivos nucleófilicos al doble enlace de una cumarina constituye un método directo para la obtención de 3,4-dihidrocumarinas con un centro estereogénico en la posición 4 del heterociclo. Como ejemplos de este tipo de reacciones podemos mencionar la adición conjugada de ácidos borónicos a cumarinas empleando complejos quirales de Rh,[48] la adición enantioselectiva de reactivos de dialquilcinc[49] y de Grignard[50] a 3-acil y 3-nitrocumarinas catalizada por cobre, y la alilación conjugada de 3-alcoxicarbonilcumarinas mediante activación dual empleando un complejo de *N*,*N*-dióxido-Yb(OTf)$_3$ y Cu(OTf)$_2$·C$_7$H$_8$.[51] Teniendo en cuenta estos antecedentes decidimos estudiar la alquinilación de cumarinas con el fin de introducir en la posición 4 de estos compuestos un grupo carbonado que permitiera posteriores modificaciones funcionales aprovechando la reactividad química del triple enlace. Con el fin de aumentar la electrofília del doble enlace se pensó en utilizar 3-alcoxicarbonil cumarinas en las que éste se encuentra doblemente activado por dos grupos carbonilo (Esquema 43).

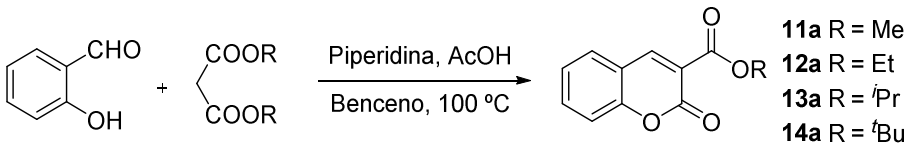


Esquema 43. Adición conjugada de alquinos terminales a 3-alcoxicarbonil cumarinas.

4.2.1. Síntesis de 3-alcoxicarbonil cumarinas

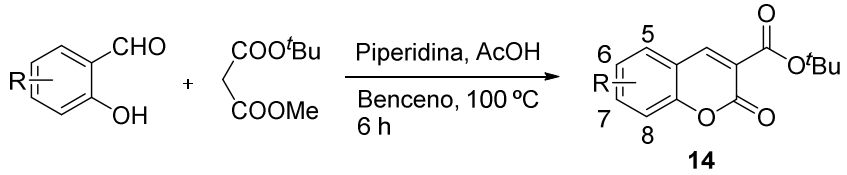
Las 3-alcoxicarbonil cumarinas se sintetizaron siguiendo el procedimiento experimental descrito en la bibliografía[51] que consiste en una reacción de Knoevenagel entre salicilaldehído y un éster malónico en presencia de piperidina y ácido acético.

En primer lugar, con el fin de estudiar el efecto del grupo alcoxicarbonilo sobre la reacción se prepararon las cumarinas **11a-14a** haciendo reaccionar salicilaldehído y los correspondientes dialquilmalonatos con buenos rendimientos (77-88%) (Esquema 44).



Esquema 44. Síntesis de 3-alcoxicarbonil cumarinas.

La síntesis de 3-*terc*-butoxicarbonil cumarinas, las cuales fueron elegidas como sustratos más adecuados (ver apartado 4.2.3) se llevó a cabo de manera similar a partir del correspondiente salicilaldehído sustituido y malonato de *terc*-butilo y metilo (Esquema 45).



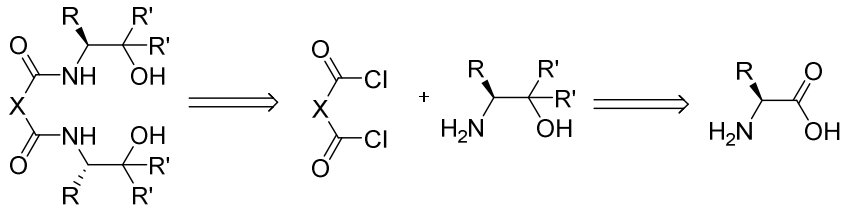
14a, R = H
14b, R = 8-Me
14c, R = 8-^{t}Bu
14d, R = 5-MeO
14e, R = 6-MeO
14f, R =7-MeO
14g, R = 8-MeO
14h, R = 6-Br
14i, R = 6,8-(^{t}Bu)$_2$
14j, R = 6-Cl, 8-Me

Esquema 45. Síntesis de 3-*terc*-butoxicarbonil cumarinas.

Las 3-alcoxicarbonil cumarinas se obtuvieron con rendimientos elevados (76-88%). Los compuestos se caracterizaron por resonancia magnética nuclear (RMN ^{1}H, RMN ^{13}C).

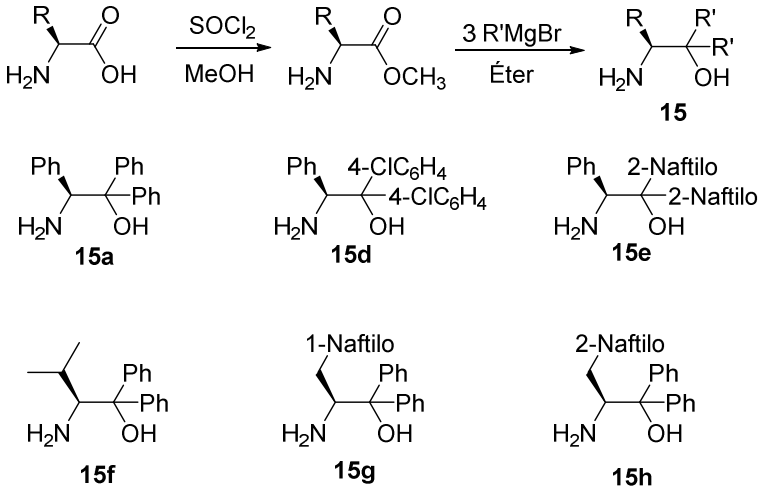
4.2.2. Síntesis de ligandos bis(hidroxiamida) con simetría C_2

Los ligandos utilizados en este estudio fueron ligandos con estructura de bis(hidroxiamida). Su síntesis se llevó a cabo siguiendo el esquema retrosintético general que se muestra en el esquema 46.



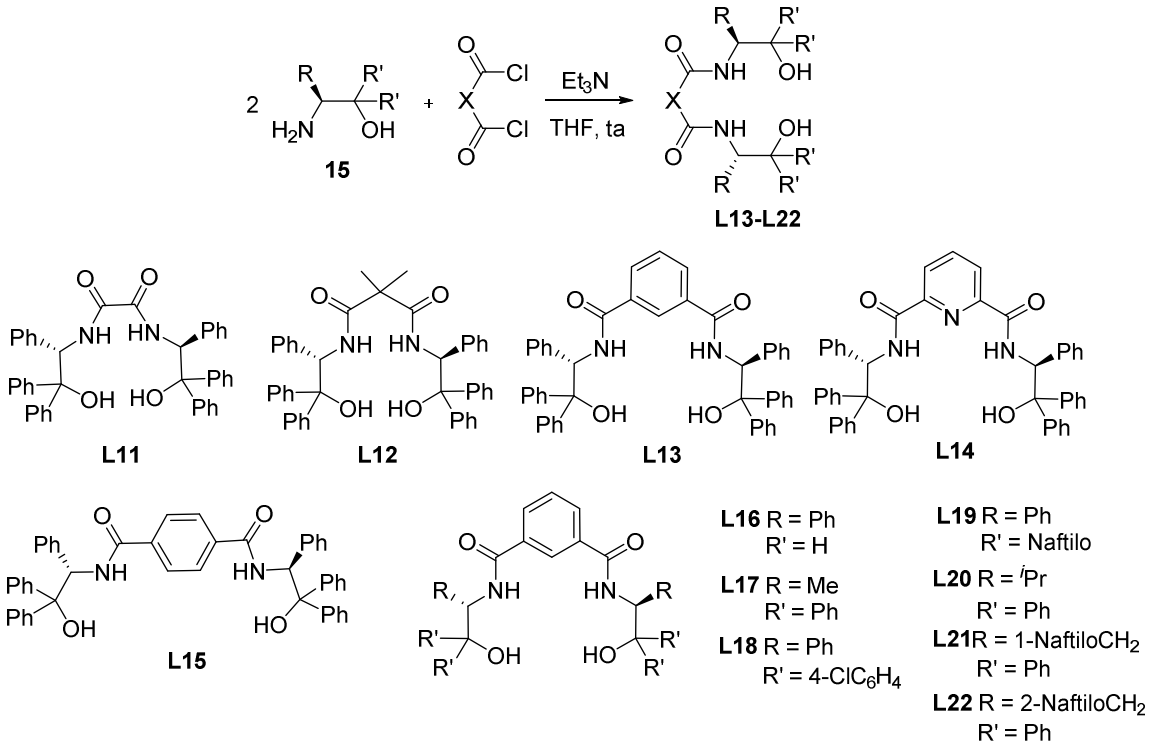
Esquema 46. Análisis retrosintético de los ligandos bis(hidroxiamida) con simetría C_2.

Los aminoalcoholes quirales no comerciales **15a,d-h** se prepararon siguiendo un procedimiento descrito en la literatura,[52] por reacción entre el éster del correspondiente aminoácido quiral y un exceso de reactivo de Grignard (Esquema 47).



Esquema 47. Síntesis de los aminoalcoholes quirales **15a,d-h**.

Los aminoalcoholes sintetizados y los aminoalcoholes comerciales (*S*)-(+)-2 fenilglicinol (**15b**) y (1*R*,2*S*)-(–)-norefedrina (**15c**), se hicieron reaccionar con varios dicloruros de ácido en presencia de trietilamina en THF para dar los ligandos **L13-L22** (Esquema 48).



Esquema 48. Síntesis de ligandos bis(hidroxiamida).

Los ligandos bis(hidroxiamida) derivados del ácido oxálico **L11** y del ácido 2,2-dimetilmalónico **L12** se encontraban disponibles en nuestro laboratorio.[53]

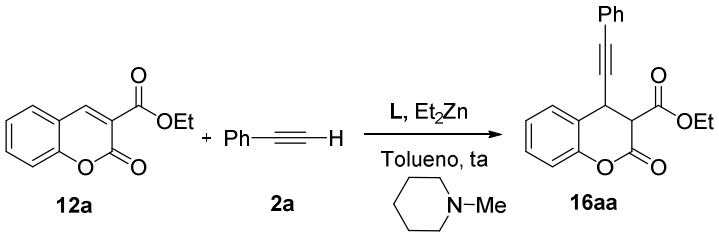
4.2.3. Optimización de las condiciones de reacción

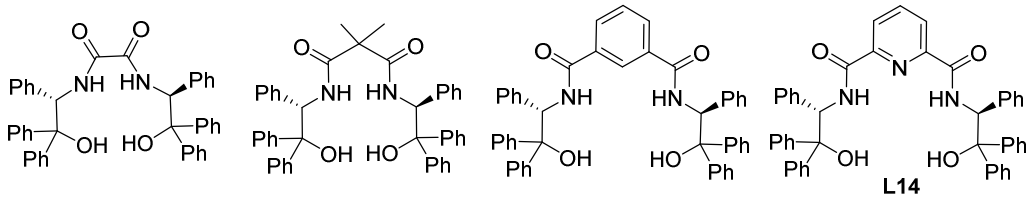
Para comenzar el proceso de optimización se estudió la reacción de adición conjugada de fenilacetileno (**2a**) a 3-etoxicarbonil cumarina (**12a**) empleando las condiciones utilizadas en el trabajo anterior, con ligandos derivados de BINOL y Et_2Zn. Sin embargo, bajo estas condiciones el producto de alquinilación **16aa** se obtuvo con bajos rendimientos y bajos excesos enantioméricos, acompañado de la 4-etildihidrocumarina resultante de la adición de dietilcinc.

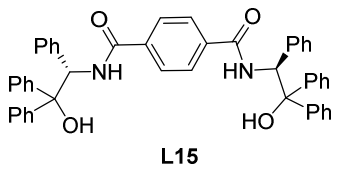
A la vista de este resultado decidimos estudiar la reacción utilizando los ligandos de tipo bis(hidroxiamida) **L11** y **L12**, derivados de ácido oxálico y ácido 2,2-dimetilmalónico, respectivamente, que nuestro grupo de investigación había empleado con anterioridad para llevar a cabo reacciones de adición enantioselectiva de dietilcinc a aldehídos.[53]Aunque el ligando **L11** condujo al producto esperado en forma racémica (Tabla 5, entrada 1), el resultado prometedor obtenido con el ligando **L12** (Tabla 5, entrada 2) nos impulsó a preparar y ensayar otros ligandos de tipo bis(hidroxiamida) con simetría C_2, **L13-L22**. Los resultados obtenidos se muestran en la Tabla 5.

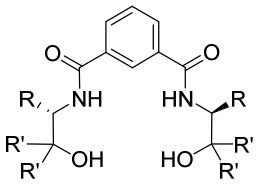
En general, la bis(hidroxiamida) **L13**, derivada de 1,1,2-trifenilaminoetanol y del ácido isoftálico proporcionó mejores resultados que otros ligandos derivados del mismo aminoalcohol y diferente ácidos dicarboxílicos (Tabla 5, entrada 3 *vs* entradas 1-2 y 4-5). Además, la presencia del grupo diarilmetanol fue importante para la obtención de enantioselectividad (Tabla 5, entrada 6 *vs* entradas 8-12). Así pues, los mejores resultados se obtuvieron con los ligandos **L13** y **L21** (Tabla 5, entradas 3 y 11).

Tabla 5. Adición conjugada de fenilacetileno (**2a**) a 3-etoxicarbonil cumarina (**12a**). Screening de ligandos de tipo bis(hidroxiamida).[a]









L16 R = Ph, R' = H
L17 R = Me, R' = Ph
L18 R = Ph, R' = 4-ClC_6H_4
L19 R = Ph, R' = Naftilo
L20 R = ^{i}Pr, R' = Ph
L21 R = 1-NaftiloCH_2, R' = Ph
L22 R = 2-NaftiloCH_2, R' = Ph

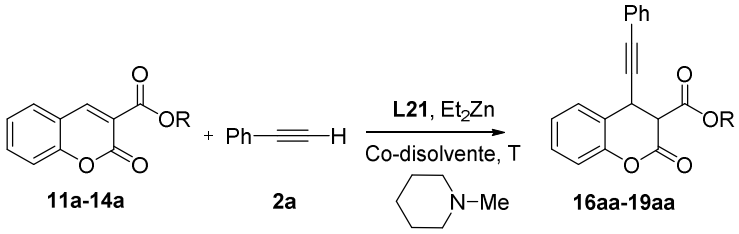
	L	t (h)	Rto (%)[b]	*ee* (%)[c]
1	**L11**	4	34	0
2	**L12**	2	73	50
3	**L13**	2	78	67
4	**L14**	5	63	10
5	**L15**	2	66	40
6	**L16**	4	55	0
7	**L17**	1	76	47
8	**L18**	2	79	34
9	**L19**	1	86	37
10	**L20**	1	61	20
11	**L21**	1	80	68
12	**L22**	1	72	55

[a]**12a** (0,125 mmol), **2a** (0,9 mmol), **L** (0,025 mmol), Et_2Zn 1,5 M en tolueno (0,25 mmol), *N*-metilpiperidina (0,05 mmol) en tolueno a ta. [b] Rendimiento del producto aislado por cromatografía de columna. [c] Determinado por HPLC utilizando fases estacionarias quirales.

Se decidió continuar el proceso de optimización con el ligando **L21** y estudiar el efecto del grupo 3-alcoxicarbonilo (Tabla 6, entradas 1-4). La cumarina con el grupo 3-*terc*-butoxicarbonil **14a** (Tabla 6, entrada 4) proporcionó el correspondiente producto de alquinilación **19aa** con mejor rendimiento y enantioselectividad en comparación con el resto de 3-alcoxicarbonil cumarinas (Tabla 6, entradas 1-3). El uso de Me_2Zn en lugar de Et_2Zn así como la utilización de otros co-disolventes y temperaturas de reacción no proporcionaron mejores resultados (Tabla 6, entradas 5-9). También se estudió el efecto

de la carga catalítica ensayando la reacción con un 10% molar de **L21** (Tabla 6, entrada 10) sin que se viera afectada la enantioselectividad pero obteniendo el producto **19aa** con menor rendimiento (60%). Un descenso mayor en la carga catalítica de **L21** hasta el 5% molar provocó un descenso tanto en el rendimiento como en la enantioselectividad (Tabla 6, entrada 11). Todas las reacciones se llevaron a cabo en presencia de un 20 mol % de *N*-metilpiperidina. La presencia de este aditivo no es esencial para la enantioselectividad de la reacción aunque produce una mejora en los rendimientos (Tabla 6, entrada 4 *vs* entrada 12).

Tabla 6. Adición conjugada de fenilacetileno (**2a**) a 3-alcoxicarbonil cumarina (**11a-14a**).[a]



		R	Co-disolvente	T (ºC)	t (h)		Rto (%)[b]	*ee* (%)[c]
1	**12a**	Et	Tolueno	ta	1	**16aa**	65	68
2	**11a**	Me	Tolueno	ta	1	**17aa**	80	58
3	**13a**	^{i}Pr	Tolueno	ta	2	**18aa**	75	65
4	**14a**	^{t}Bu	Tolueno	ta	2	**19aa**	82	72
5	**14a**[d]	^{t}Bu	Tolueno	ta	2	**19aa**	69	68
6	**14a**	^{t}Bu	Hexano	ta	2	**19aa**	87	66
7	**14a**	^{t}Bu	CH_2Cl_2	ta	2	**19aa**	99	64
8	**14a**	^{t}Bu	Tolueno	40	1	**19aa**	83	54
9	**14a**	^{t}Bu	Tolueno	0	3	**19aa**	60	72
10	**14a**[e]	^{t}Bu	Tolueno	ta	3	**19aa**	60	72
11	**14a**[f]	^{t}Bu	Tolueno	ta	3	**19aa**	58	65
12	**14a**[g]	^{t}Bu	Tolueno	ta	3	**19aa**	60	72

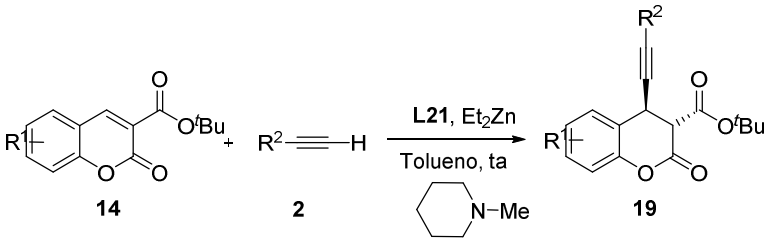
[a] **11-14** (0,125 mmol), **2a** (0,9 mmol), **L21** (0,025 mmol), Et_2Zn 1,5 M en tolueno (0,25 mmol), *N*-metilpiperidina (0,05 mmol) a ta. [b] Rendimiento del producto aislado por cromatografía de columna. [c] Determinado por HPLC utilizando fases estacionarias quirales. [d] Se utilizó Me_2Zn en lugar de Et_2Zn. [e] 10% mol de **L21**. [f] 5% mol de **L21**. [g] Reacción llevada a cabo en ausencia de *N*-metilpiperidina.

4.2.4. Alcance y limitaciones de la reacción

A pesar de los resultados moderados obtenidos con el ligando **L21**, decidimos continuar con el estudio sobre la aplicabilidad de la reacción en las condiciones que nos daban los mejores resultados. En primer lugar, se estudió la adición de fenilacetileno (**2a**) a diferentes 3-*terc*-butoxicarbonil cumarinas **14** (Tabla 7). La presencia de sustituyentes en el anillo aromático, tanto de naturaleza electrón-donante como electrón-atrayente favorece enantioselectividades superiores a las obtenidas con la cumarina no sustituida. Las mayores enantioselectividades fueron obtenidas con cumarinas sustituidas en las posiciones C-7 y C-8 (Tabla 7, entradas 4-5 *vs* entradas 6-7). En

particular, se obtuvieron excesos enantioméricos superiores al 90% con compuestos que presentaban sustituyente alquílicos (Me o ^{t}Bu) en la posición C-8 (Tabla 7, entradas 2-3). También se ensayaron algunas cumarinas disustituidas obteniendo excelentes enantioselectividades con las cumarinas **14i** y **14j** sustituidas, de nuevo, con un grupo alquilo en la posición 8 (Tabla 7, entradas 9-10).

Tabla 7. Adición conjugada de alquinos terminales **2** a 3-*terc*-butoxicarbonil cumarina **14**.[a]



		R^1		R^2	t (h)		Rto (%)[b]	*ee* (%)[c]
1	**14a**	H	**2a**	C_6H_5	2	**19aa**	82	72
2	**14b**	8-Me	**2a**	C_6H_5	3	**19ba**	97	91
3	**14c**	8-^{t}Bu	**2a**	C_6H_5	4	**19ca**	85	95
4	**14d**	5-MeO	**2a**	C_6H_5	5	**19da**	76	76
5	**14e**	6-MeO	**2a**	C_6H_5	4	**19ea**	70	75
6	**14f**	7-MeO	**2a**	C_6H_5	3	**19fa**	80	85
7	**14g**	8-MeO	**2a**	C_6H_5	4	**19ga**	70	84
8	**14h**	6-Br	**2a**	C_6H_5	3	**19ha**	78	80
9	**14i**	6,8-(^{t}Bu)	**2a**	C_6H_5	3	**19ia**	82	89
10	**14j**	6-Cl, 8-Me	**2a**	C_6H_5	3	**19ja**	85	93
11	**14f**	8-Me	**2b**	4-$MeOC_6H_4$	3	**19fb**	99	81
12	**14f**	8-Me	**2g**	3-FC_6H_4	4	**19fg**	92	87
13	**14j**	6-Cl, 8-Me	**2g**	3-FC_6H_4	3	**19jg**	77	92
14	**14j**	6-Cl, 8-Me	**2c**	4-FC_6H_4	4	**19jc**	73	92
15	**14a**	H	**2f**	$Ph(CH_2)_2$	4	**19af**	36	60
16[d]	**14a**	H	**2f**	$Ph(CH_2)_2$	4	**19af**	40	66
17[e]	**14a**	H	**2h**	CO_2Me	-	**19ah**	NR	-
18[f]	**14f**	8-Me	**2i**	Me_3Si	3	**19fi**	95	-

[a]**14** (0,125 mmol), **2** (0,9 mmol), **L21** (0,025 mmol), Et_2Zn 1,5 M en tolueno (0,25 mmol), *N*-metilpiperidina (0,05 mmol) en tolueno a ta. [b] Rendimiento del producto aislado por cromatografía de columna. [c] Determinado por HPLC utilizando fases estacionarias quirales. [d] **L13** fue utilizado en lugar de **L21**. [e] Se recuperó el compuesto **14a** sin reaccionar. [f] Producto de etilación.

A continuación, se llevó a cabo la reacción de adición conjugada de otros alquinos terminales **2** a varias 3-*terc*-butoxicarbonil cumarinas **14**. Los derivados de fenilacetileno sustituidos en las posiciones *meta* y *para* del anillo aromático reaccionaron con rendimientos y excesos enantioméricos altos, siendo mayores cuando el sustituyente es electrón-atrayente. En particular, el (3-fluorofenil)acetileno (**2g**) y el (4-flurofenil)acetileno (**2c**) reaccionaron con la cumarina **14j** proporcionando los correspondientes productos con un 92% de *ee* (Tabla 7, entradas 13-14). Los alquinos

alifáticos como el 4-fenil-1-butino (**2f**) condujeron al producto de alquinilación **19af** con rendimiento bajo y enantioselectividad moderada tanto con el ligando **L13** como con **L21** (Tabla 7, entradas 15-16). También se ensayó la adición conjugada con propiolato de etilo (**2h**) no observando reacción, recuperándose el producto de partida **14a** (Tabla 7, entrada 17). Por último, se llevó a cabo la reacción entre el trimetilsililacetileno (**2i**) y la cumarina **14f** obteniéndose únicamente producto de etilación (Tabla 7, entrada 18). En este caso se repitió la reacción prolongando el tiempo de reacción entre el alquino **2i**, el ligando **L21** y el Et_2Zn de 1,5 h a 3 h previas a la adición de la cumarina **14f**, no observando avance alguno y recuperándose el producto de partida **14f** sin reaccionar.

4.2.5. Determinación de la configuración absoluta

En todos los casos, los productos de adición conjugada **19** fueron obtenidos como un único diastereoisómero con la disposición *trans* entre el grupo *terc*-butoxicarbonil en 3 y los grupos alquinilo en 4, tal y como se pudo determinar a partir de la estructura de rayos X obtenida por análisis de un monocristal del producto **19ha** (Figura 6). Para el resto de los productos la estereoquímica *trans* se asignó de acuerdo con la similitud de las constantes de acoplamiento con las de **19ha**.

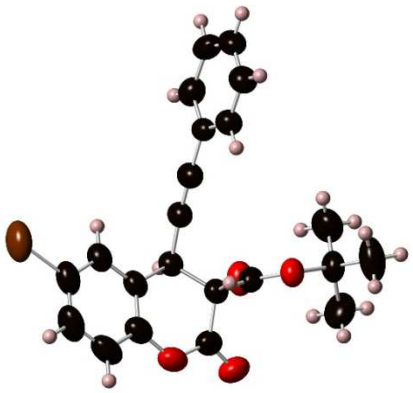
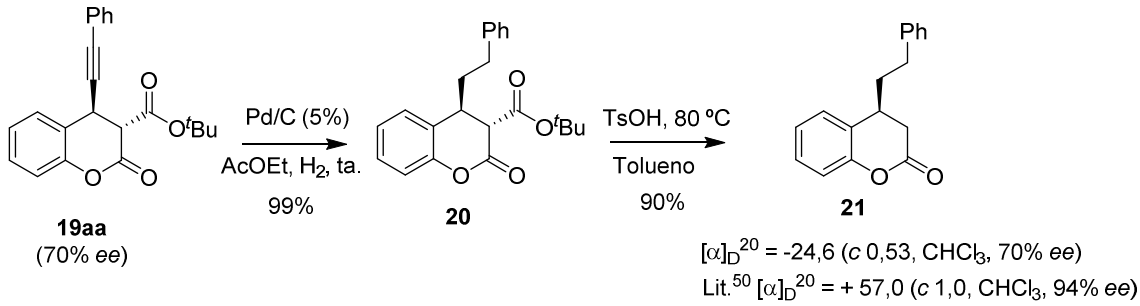


Figura 6. ORTEP para la estructura de rayos X del compuesto **19ha**.

Desafortunadamente, los cristales obtenidos a partir de **19ha** fueron centro simétricos por lo que el análisis de rayos X no permitió determinar la configuración absoluta del compuesto.

La asignación de la configuración absoluta de los compuestos **19** se asignó por correlación química mediante la transformación del compuesto **19aa** en el compuesto **21** de configuración absoluta conocida (Esquema 49).

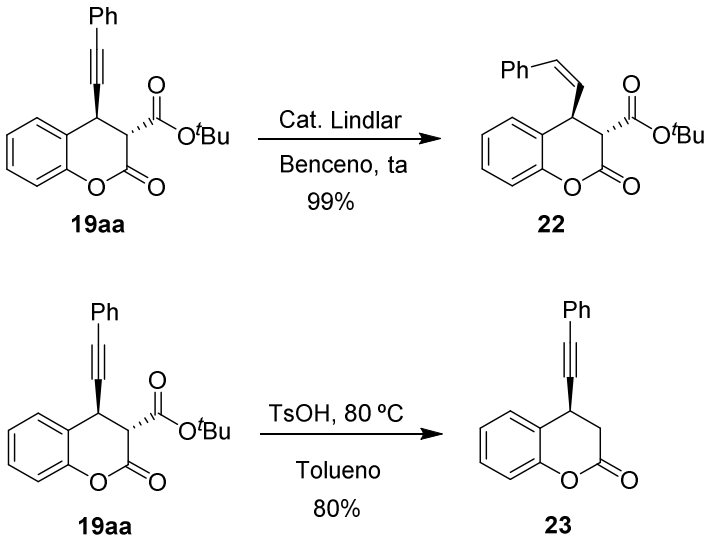


Esquema 49. Determinación de la configuración absoluta del compuesto **19aa**.

El compuesto de alquinilación conjugada **19aa** fue hidrogenado sobre Pd/C obteniendo el compuesto **20** con un rendimiento cuantitativo, el cual después de hidrólisis y descarboxilación proporcionó el producto **21** con un rendimiento del 90% y sin pérdida de pureza óptica. Por comparación del poder rotatorio y de los tiempos de retención en HPLC quiral del compuesto **21** con los descritos en la bibliografía[50] para el enantiómero (*R*)-**21** se pudo establecer que los compuestos sintetizados **20** y **21** tenían configuración *S* en C4 y por lo tanto el producto de alquinilación **19aa** tenía configuración *R* en el centro estereogénico C4. Para el resto de productos de alquinilación **19**, la configuración se asignó asumiendo un mecanismo estereoquímico común.

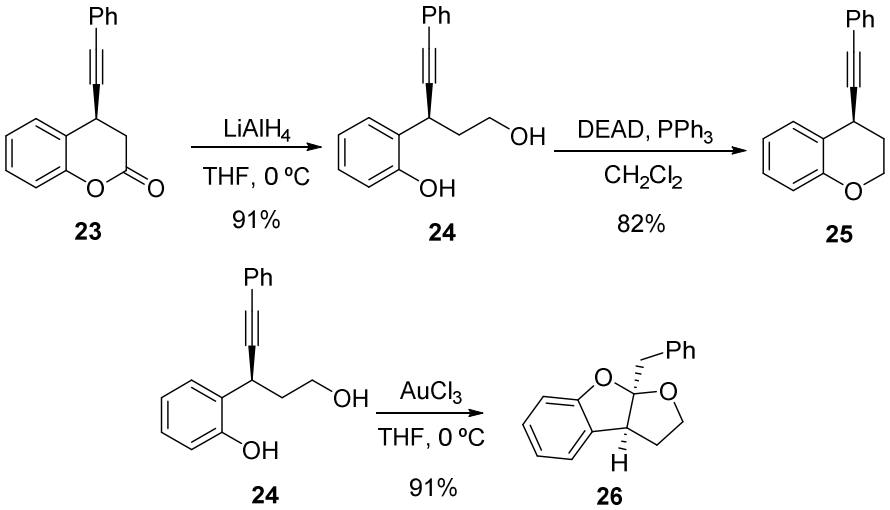
4.2.6. Transformaciones sintéticas

Los productos de alquinilación **19** presentan un gran potencial sintético. El triple enlace del compuesto **19aa** puede ser parcialmente hidrogenado con el catalizador de Lindlar (5%) para obtener la alquenilcumarina **22** con el doble enlace *Z* con un rendimiento cuantitativo sin pérdida de pureza óptica (Esquema 50). También fue posible eliminar el grupo 3-*terc*-butoxicarbonil de la posición 3 mediante hidrólisis y descarboxilación selectiva con *p*TsOH en tolueno para obtener la 4-alquinilcumarina **23**. Dado que la cumarina no sustituida en la posición 3 no es suficientemente reactiva en las condiciones de alquinilación desarrolladas, el grupo alcoxicarbonil en la posición 3 puede ser considerado como un auxiliar que incrementa la reactividad del doble enlace, el cual posteriormente puede ser eliminado del producto de reacción.



Esquema 50. Hidrogenación parcial y descarboxilación del compuesto **19aa**. Todas las transformaciones transcurrieron sin pérdida de la pureza óptica.

La alquinilcumarina **23** puede ser reducida por tratamiento con $LiAlH_4$ para obtener el alcohol **24** el cual mediante la reacción de Mitsunobu da lugar al cromano **25**, producto de partida para la síntesis de otros (4-feniletinil)cromanos con actividad antihipertensiva.[54] Por otra parte, el diol **24** puede ser ciclado mediante catálisis de oro dando el acetal fusionado *cis* **26** obteniendo el esqueleto tetrahidrofuro[2,3-*b*]benzofurano característico de las aflatoxinas[55] y otros productos naturales[56] (Esquema 51).



Esquema 51. Transformaciones sintéticas del compuesto **23**. Todas las transformaciones transcurrieron sin pérdida de la pureza óptica.

La estereoquímica *cis* del producto **26** se asignó teniendo en cuenta el NOE observado entre los hidrógenos bencílicos del grupo fenilmetilo (δ 3,29 y 3,19 ppm) y el hidrógeno del carbono cabeza de puente (δ 3,74 ppm) en el espectro de RMN en acetona-d_6 (Figura 7).

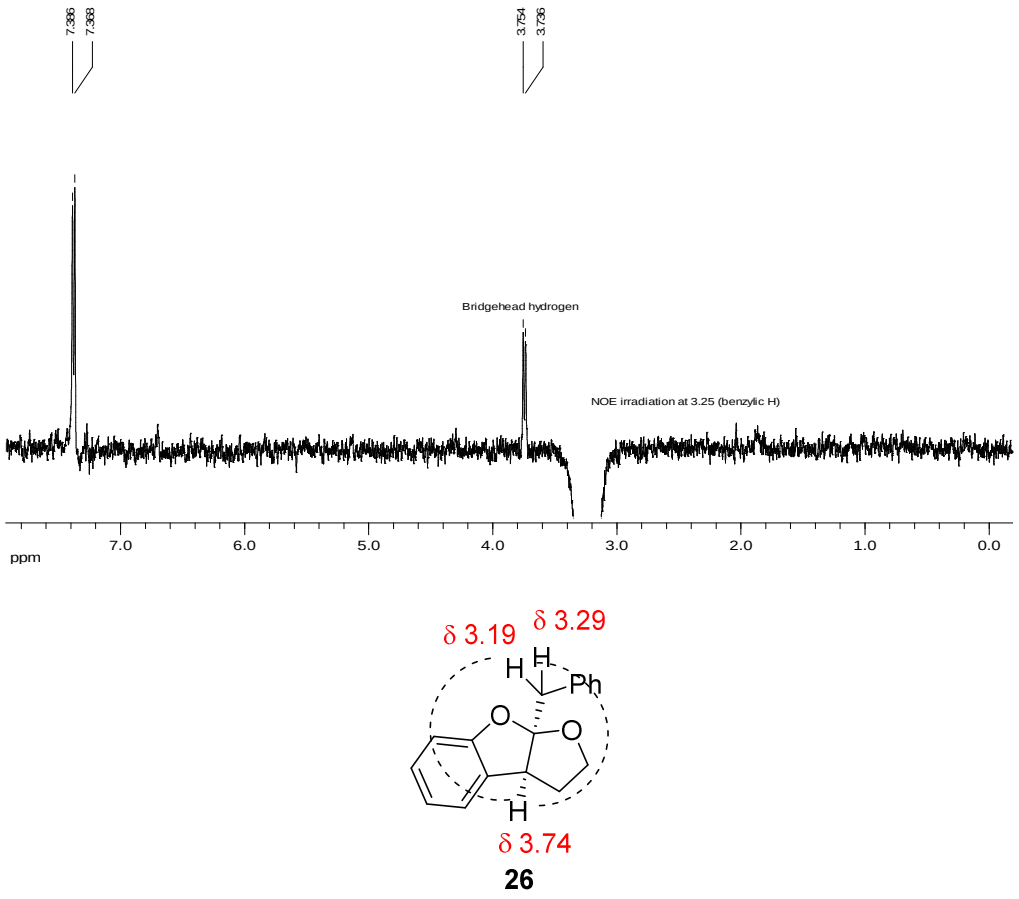


Figura 7. NOEs observados en el producto **26**.

En resumen, en este capítulo hemos desarrollado un procedimiento para la síntesis enantioselectiva de 3-alquinilcumarinas. La reacción se lleva a cabo con un nuevo sistema catalítico que utiliza bis(hidroxiamidas) con simetria C_2, dietilcinc y alquinos terminales. Los productos de alquinilación se obtienen con buenos rendimientos (70-99%) y excesos enantioméricos entre 60-94% dependiendo de la sustitución en el alquino y en la cumarina. Aunque la mayoría del estudio se ha llevado a cabo utilizando 20% mol de inductor quiral, se ha demostrado que su carga puede disminuirse hasta 10% mol, sin un efecto muy acusado en el resultado de la reacción. El procedimiento descrito aquí representa la primera reacción de alquinilación enantioselectiva de cumarinas y también el primer ejemplo de alquinilación de ésteres insaturados mediado por cinc que utiliza cantidades subestequiométricas de especie quiral.

4.3. Alquinilación conjugada enantioselectiva de 1-(fenilsulfonil)-1,1-difluoro-3-en-2-onas catalizada por complejos de Cu(I)

Como se ha comentado previamente en la introducción, la adición nucleofílica de alquinos terminales a compuestos que presentan grupos funcionales electrofílicos constituye una de las estrategias más directas para la síntesis de moléculas que incorporan un triple enlace carbono-carbono en su estructura. Estas reacciones se pueden llevar a cabo mediante activación nucleofílica del alquino terminal vía su conversión en un alquiniluro metálico. Esto puede realizarse aprovechando la mayor acidez de los hidrógenos sobre carbono sp, por tratamiento del alquino terminal con una especie organometálica alquílica, o bien el alquiniluro puede generarse de manera transitoria en presencia de una cantidad catalítica de un complejo metálico y de una base (Figura 8). Esta segunda opción resulta más atractiva desde el punto de vista medioambiental ya que permite minimizar la producción de residuos metálicos.[57]

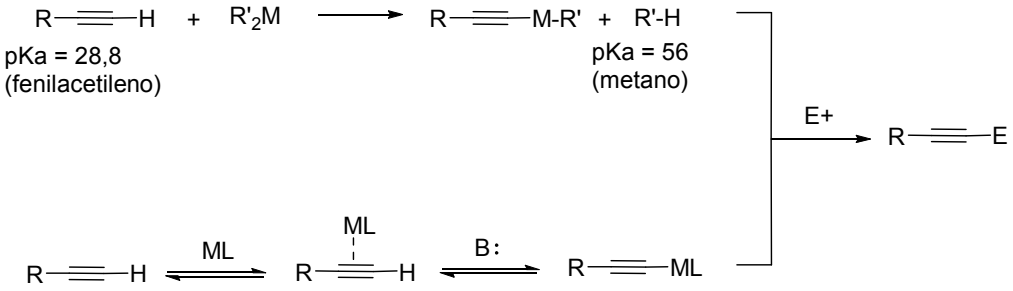
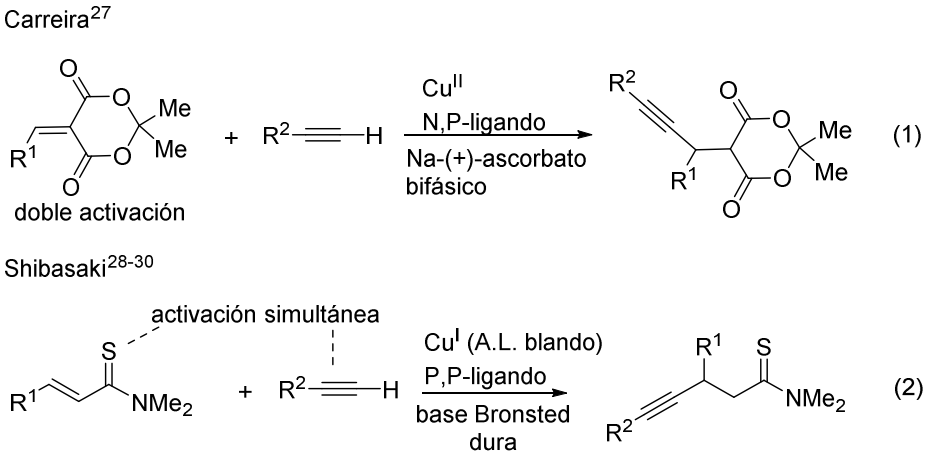


Figura 8. Activación nucleofílica de alquinos terminales.

En los capítulos anteriores hemos desarollado diversos sistemas reactivos para la alquinilación conjugada enantioselectiva promovida por reactivos de dialquilcinc. En ellos hemos utilizado cantidades subestioquiométricas de material quiral, lo que ha representado un avance respecto a otros procedimientos descritos en la bibliografía,[20-22] aunque no se ha podido evitar el uso de cantidades estequiométricas o mayores de especies metálicas. La formación de alquiniluros metálicos de manera transitoria a partir de catalizadores metálicos permite evitar este inconveniente. Entre los diferentes metales que se han empleado con este fin, los complejos de cobre resultan muy atractivos debido a su baja toxicidad y menor coste económico, si bien su uso plantea algunas dificultades debido a la baja nucleofilia de los alquiniluros de cobre intermedios. Esta limitación ha podido ser superada mediante el uso de alquenos doblemente activados, derivados del ácido de Meldrum (Esquema 52-1),[27] o mediante el uso de tioamidas insaturadas especialmente diseñadas para la activación simultánea del doble enlace y del alquino mediante catálisis cooperativa con un sistema formado por un ácido de Lewis blando y una base de Brønsted dura (Esquema 52-2).[28-30]



Esquema 52. Estrategias para la alquinilación conjugada catalizada por cobre (I).

Como uno de los objetivos generales de la tesis nos planteamos el desarrollo de diversas reacciones de alquinilación conjugada enantioselectiva catalizadas por Cu(I) de sustratos fluorados. De acuerdo con los antecedentes bibliográficos,[28-30] como ligandos quirales para este tipo de reacciones catalizadas por Cu(I) hemos utilizado los ligandos comerciales de tipo bisfosfina que se muestran en la figura 9.

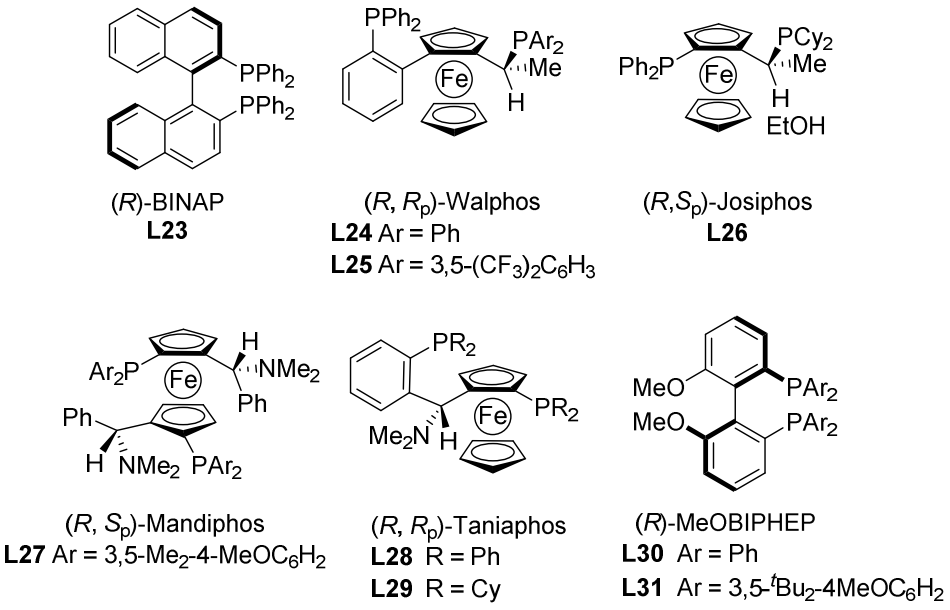


Figura 9. Ligandos de tipo bisfosfina empleados en la presente tesis.

En trabajos anteriores, nuestro grupo de investigación ha utilizado α'-arilsulfonil enonas (Figura 10) como dienófilos en reacciones de Diels-Alder enantioselectivas catalizadas por complejos BOX-Cu(II).[58] En estas reacciones la agrupación cetosulfona actúa como una plantilla bidentada que favorece la unión del sustrato al centro metálico del catalizador facilitando la acción catalítica y aumentando la enantioselectividad. Sin embargo, ensayos previos de alquinilación conjugada llevados a cabo con estas enonas mostraron que no son suficientemente electrófilicas para reaccionar con alquiniluros de cobre.

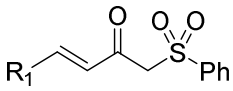
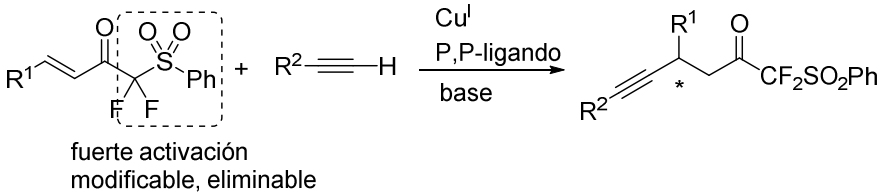


Figura 10. Estructura de α'-(fenilsulfonil)cetonas α,β-insaturadas.

Para compensar la falta de reactividad de las α'-arilsulfonil enonas pensamos en la introducción de dos átomos de flúor fuertemente electronegativos que podría producir una activación suficiente del doble enlace para permitir la reacción de alquinilación conjugada catalizada por cobre. De acuerdo con estas premisas, nos planteamos el estudio de la alquinilación conjugada enantioselectiva de 1-(fenilsulfonil)-1,1-difluoro-3-en-2-onas catalizada por complejos de cobre(I) (Esquema 53).

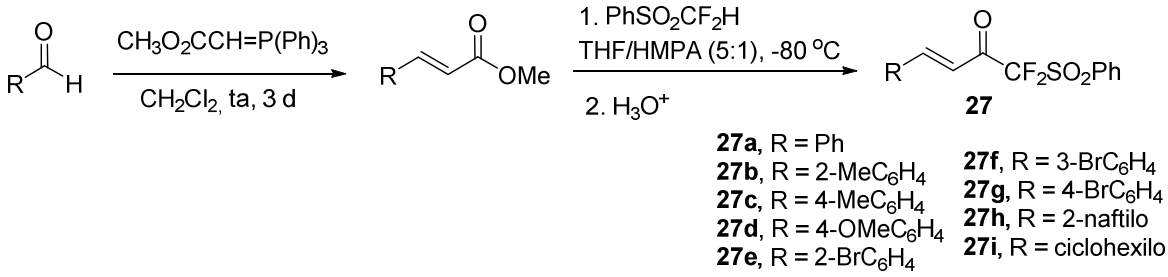


Esquema 53. Alquinilación conjugada enantioselectiva de 1-(fenilsulfonil)-1,1-difluoro-3-en-2-onas.

4.3.1 Síntesis de 1-(fenilsulfonil)-1,1-difluoro-3-en-2-onas

Los productos de partida para la reacción de alquinilación enantioselectiva se han preparado siguiendo un procedimiento descrito en la bibliografía[59] que consiste en la sustitución nucleofílica sobre ésteres metílicos α,β-insaturados utilizando como nucleófilo fenilsulfonildifluorometano ($PhSO_2CF_2H$) en presencia de bis(trimetilsilil)amiduro de litio (LHDMS). Hay que señalar que en la bibliografía sólo se encuentra descrita la síntesis de uno de estos compuestos, el derivado del cinamato de metilo. Nosotros hemos seguido este procedimiento para la síntesis del resto de1-(fenilsulfonil)-1,1-difluoro-3-en-2-onas utilizadas en este estudio.

La síntesis de los ésteres α,β-insaturados necesarios para preparar las enonas se llevó a cabo mediante una reacción de Wittig entre el aldehído adecuado y (metoxicarbonilmetilen)trifenilfosforano, con buenos rendimientos.[60] Una vez obtenidos, los ésteres se hicieron reaccionar con el carbanión generado a partir de $PhSO_2CF_2H$ y LHDMS como base, en una disolución de THF/HMPA a –82 °C durante 30 min (Esquema 54).



Esquema 54. Síntesis de 1-(fenilsulfonil)-1,1-difluoro-3-en-2-onas **27**.

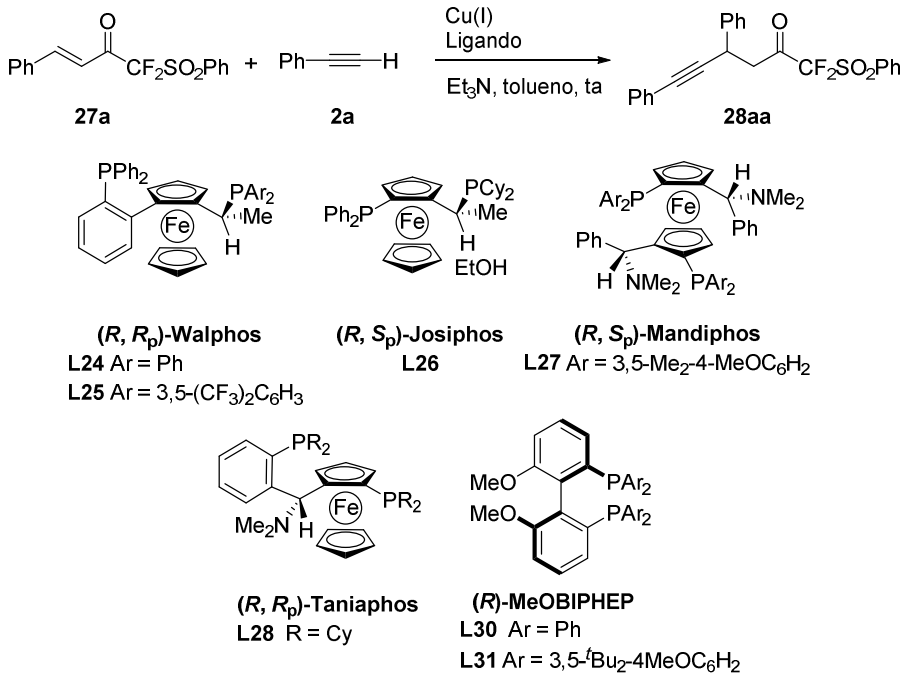
Es importante señalar que la reacción de adición 1,2 de fenilsulfonildifluorometillitio es reversible siendo necesario mantener la temperatura de reacción lo más baja posible para evitar la formación final del producto de adición 1,4 más estable termodinámicamente.

4.3.2. Optimización de las condiciones de reacción

Para el proceso de optimización se eligió la reacción entre el fenilacetileno (**2a**) y la (*E*)- 4-fenil-1-(fenilsulfonil)-1,1-difluorobut-3-en-2-ona (**27a**) para dar el producto **28aa** empleando complejos formados a partir de tetrafluoroborato de tetrakis(acetonitrilo)cobre (I) y los diferentes ligandos de tipo bisfosfina comerciales (Tabla 8).

La reacción se inicia con la formación del complejo entre el ligando **L** (20% mol) y la sal de cobre $[Cu(CH_3CN)_4]BF_4$ (20% mol) disueltos en tolueno a temperatura ambiente durante 1,5 h, a continuación a esa misma temperatura se añade la enona **27** (1 equiv.) disuelta en tolueno seguido de la Et_3N (1 equiv.), finalmente transcurridos 10 min se adicionan 7,5 equiv. de fenilacetileno (**2a**). Los resultados obtenidos se muestran en la Tabla 8.

Tabla 8. Adición conjugada de fenilacetileno (**2a**) a la enona **27a**. Optimización de las condiciones de reacción.[a]



	L	Cu(I)	% mol	**2a** (equiv.)	t (h)	Rto (%)[b]	*ee* (%)[c]
1	**L24**	$[Cu(CH_3CN)_4]BF_4$	20	7,5	48	96	59
2	**L25**	$[Cu(CH_3CN)_4]BF_4$	20	7,5	120	34	55
3	**L26**	$[Cu(CH_3CN)_4]BF_4$	20	7,5	-	-	-
4	**L27**	$[Cu(CH_3CN)_4]BF_4$	20	7,5	96	66	54
5	**L28**	$[Cu(CH_3CN)_4]BF_4$	20	7,5	120	51	38
6	**L30**	$[Cu(CH_3CN)_4]BF_4$	20	7,5	120	62	40
7	**L31**	$[Cu(CH_3CN)_4]BF_4$	20	7,5	48	80	98
8	**L31**	$[Cu(OTf)_2Tol]$	20	7,5	72	78	93
9	**L31**	$[Cu(CH_3CN)_4]BF_4$	10	7,5	96	67	96
10	**L31**	$[Cu(CH_3CN)_4]BF_4$	5	7,5	120	62	94
11	**L31**	$[Cu(CH_3CN)_4]BF_4$	20	5	72	70	97

[a] **2a** (0,9 mmol), **L** (0,025 mmol), sal de Cu(I) (0,025 mmol), **27a** (0,125 mmol), Et_3N (0,125 mmol) en tolueno a ta.[b] Rendimiento de producto aislado por cromatografía de columna. [c] Determinado por HPLC utilizando fases estacionarias quirales.

Utilizando estas condiciones se ensayaron las diferentes bisfosfinas quirales. Los mejores resultados se lograron con el ligando **L31** con el que se obtuvo el producto de β-alquinilación **28aa** con un 80% de rendimiento y un 98% de exceso enantiomérico (Tabla 8, entrada 7). La sustitución de tetrafluoroborato de tetrakis(acetonitrilo)cobre (I) por el complejo de triflato de cobre (I)-tolueno condujo al producto esperado con un ligero descenso tanto del rendimiento como de la enantioselectividad y además la velocidad de la reacción disminuyó (Tabla 8, entrada 8). Por último, se estudió la posibilidad de disminuir la carga catalítica o el número de equivalentes de alquino observándose que estos cambios no afectaron seriamente la enantioselectividad, aunque

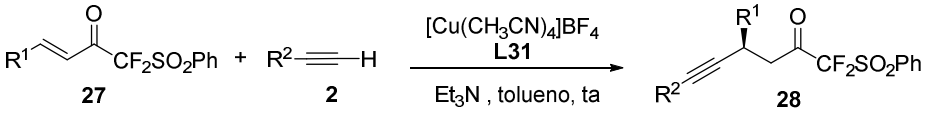
se produjo una disminución en la velocidad de reacción y en el rendimiento (Tabla 8, entradas 9-11).

Así pues, las condiciones optimizadas para la reacción de alquinilación fueron: enona **27** (1 equiv.), alquino **2** (7,5 equiv.), **L31** (20% mol), $[Cu(CH_3CN)_4]BF_4$ (20% mol), Et_3N (1 equiv.) como base, tolueno como disolvente a temperatura ambiente (Tabla 8, entrada 7).

4.3.3. Alcance y limitaciones de la reacción

Una vez finalizado el proceso de optimización de la reacción se procedió a evaluar la aplicabilidad de las condiciones establecidas con otros sustratos (Tabla 9).

Tabla 9. Adición conjugada de alquinos terminales **2** a diferentes 1-(fenilsulfonil)-1,1-difluoro-3-en-2-onas **27**.[a]



		R^1		R^2	t (h)		Rto (%)[b]	*ee* (%)[c]
1	**27a**	C_6H_5	**2a**	C_6H_5	48	**28aa**	80	98
2	**27b**	2-MeC_6H_4	**2a**	C_6H_5	48	**28ba**	82	99
3[c]	**27b**	2-MeC_6H_4	**2a**	C_6H_5	96	**28ba**	83	98
4	**27c**	4-MeC_6H_4	**2a**	C_6H_5	48	**28ca**	77	97
5	**27d**	4-MeOC_6H_4	**2a**	C_6H_5	72	**28da**	77	96
6[c]	**27d**	4-MeOC_6H_4	**2a**	C_6H_5	96	**28da**	70	94
7	**27e**	2-BrC_6H_4	**2a**	C_6H_5	48	**28ea**	90	99
8	**27f**	3-BrC_6H_4	**2a**	C_6H_5	48	**28fa**	80	97
9	**27g**	4-BrC_6H_4	**2a**	C_6H_5	48	**28ga**	75	97
10	**27h**	2-naftilo	**2a**	C_6H_5	72	**28ha**	50	95
11	**27i**	ciclohexilo	**2a**	C_6H_5	-	-	-	-
12	**27a**	C_6H_5	**2b**	4-MeOC_6H_4	72	**28ab**	86	98
13[c]	**27a**	C_6H_5	**2b**	4-MeOC_6H_4	96	**28ab**	67	97
14	**27a**	C_6H_5	**2c**	4-FC_6H_4	72	**28ac**	69	97
15	**27a**	C_6H_5	**2d**	4-ClC_6H_4	48	**28ad**	90	99
16	**27a**	C_6H_5	**2e**	3-tienilo	72	**28ae**	70	98
17	**27a**	C_6H_5	**2j**	ciclopropilo	96	**28aj**	82	92
18	**27c**	4-MeC_6H_4	**2b**	4-MeOC_6H_4	48	**28cb**	84	97
19	**27c**	4-MeC_6H_4	**2c**	4-FC_6H_4	48	**28cc**	69	94

[a] **2** (0,9 mmol), **L31** (0,025 mmol), $[Cu(CH_3CN)_4]BF_4$ (0,025 mmol), **27** (0,125 mmol), Et_3N (0,125 mmol) en tolueno a ta. [a] Rendimiento de producto aislado por cromatografía de columna. [b] Determinado por HPLC utilizando fases estacionarias quirales. [c] Resultados obtenidos con un 10% mol de carga catalítica.

La adición de fenilacetileno (**2a**) se pudo llevar a cabo sobre distintas enonas que poseen en β anillos aromáticos sustituidos tanto con grupos electrón-dadores (Tabla 9, entradas 2-6), como con grupos electrón-aceptores (Tabla 9, entradas 7-9) pudiendo éstos ocupar las posiciones *orto*, *meta* o *para* del anillo, obteniéndose en todos los casos

los productos de β-alquinilación con excelentes excesos enantioméricos. Cuando R^1 es un grupo 2-naftilo voluminoso (Tabla 9, entrada 10) se obtiene el producto esperado **28ha** con un excelente exceso enantiomérico, sin embargo el rendimiento es menor.

Además, el sistema también permite la adición de otros arilacetilenos sustituidos en el anillo aromático con grupos electrón-dadores (Tabla 9, entradas 12 y 18) o con grupos electrón-aceptores (Tabla 9, entradas 14-15 y 19), así como la adición de 3-tienil acetileno (Tabla 9, entrada 16), obteniéndose en todos los casos excelentes excesos enantioméricos y rendimientos que oscilaron entre el 69-90%. Cabe destacar el resultado obtenido en la adición conjugada de ciclopropilacetileno (**2j**), con el que se obtiene un 82% de rendimiento y 92% de exceso enantiomérico, ya que este suele ser un alquino bastante exigente en las reacciones de alquinilación enantioselectiva.

También se llevaron a cabo algunas reacciones con una carga catalítica del 10% molar, observándose de nuevo excesos enantioméricos similares a los obtenidos con un 20% molar de carga catalítica, con rendimientos ligeramente inferiores (Tabla 9, entradas 3, 6 y 13).

Los excesos enantioméricos obtenidos con nuestro sistema catalítico son considerablemente más elevados que los obtenidos por Carreira[27] para la adición de fenilacetileno a derivados aromáticos de ácidos de Meldrum utilizando el complejo PINAP-Cu(I) como catalizador, y similares a los obtenidos por Shibasaki[28-30] en sus reacciones de adición conjugada de fenilacetileno a tioamidas aromáticas.

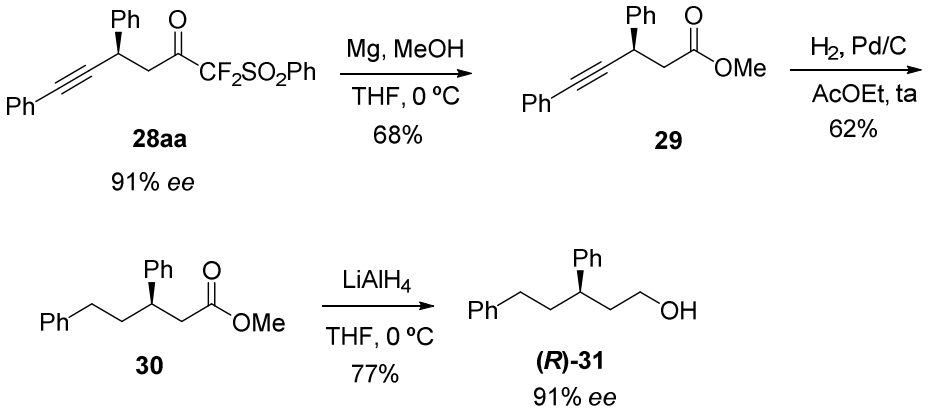
Sin embargo, el sistema catalítico no permite la adición conjugada de alquinos alifáticos tales como 4-fenil-1-butino o 1-hexino. Igualmente, la reacción tampoco tiene lugar con enonas que presenta un átomo de hidrógeno en el carbono γ. Así, durante el intento de reacción de fenilacetileno (**2a**) con la (*E*)-4-ciclohexil-1-(fenilsulfonil)-1,1-difluorobut-3-en-2-ona (**27i**) (Tabla 9, entrada 11) de la mezcla de reacción se pudo aislar un producto que no incorpora el fragmento de fenilacetileno en su estructura y que podría corresponder al compuesto **27i** en su forma enólica (ver apartado 5.3.2.3.). Este resultado parecería indicar que la presencia de la agrupación diflurometilsulfonil cetona incrementa la acidez del protón en γ, provocando la enolización en medio básico y la consecuente desactivación del doble enlace como electrófilo.

4.3.4. Determinación de la configuración absoluta

La configuración absoluta de los productos de alquinilación conjugada enantioselectiva se determinó por correlación química del producto **28aa** con el 3,5-difenilpentan-1-ol (**31**), un producto descrito en la bibliografía de configuración conocida.[61]

La transformación de **28aa** en 3,5-difenilpentan-1-ol (**31**) se llevó a cabo en una secuencia sintética de tres etapas (Esquema 55). En la primera de ellas, una reacción descubierta de manera accidental permitió transformar el compuesto **28aa** (*ee* = 91%) en el éster **29** por tratamiento con magnesio en metanol a 0 ºC. A continuación, se llevó

a cabo la hidrogenación total del triple enlace con Pd/C en acetato de etilo para obtener el compuesto **30** con un 62% de rendimiento. Finalmente, la reducción del éster **30** con hidruro de litio y aluminio en THF condujo al alcohol **31** con un rendimiento del 77%. Los tres pasos de la secuencia transcurrieron sin pérdida de pureza óptica en los productos.



Esquema 55. Transformación del compuesto **28aa** en **(*R*)-31**. Determinación de la configuración absoluta.

El análisis cromatográfico por HPLC con una columna quiral (Chiralcel OD-H) del compuesto **31** obtenido a partir **28aa** y su comparación con los datos cromatográficos descritos en la bibliografía para el compuesto de estereoquímica conocida, permitieron asignar la configuración *R* al centro estereogénico en el compuesto **31** y por tanto también en el compuesto **28aa**. Para el resto de productos de alquinilación conjugada **28**, la asignación estereoquímica se llevó a cabo admitiendo un mecanismo estereoquímico común para todas las reacciones. Cabe señalar que la comparación de los signos de rotación óptica del producto **31** sintetizado por nosotros con los del producto descrito en la bibliografía condujeron a resultados contradictorios con los obtenidos por comparación de los tiempos de retención en HPLC quiral. Sin embargo, debido al bajo valor de rotación óptica del producto **31** decidimos dar más fiabilidad al análisis cromatográfico.

4.3.5. Transformaciones sintéticas

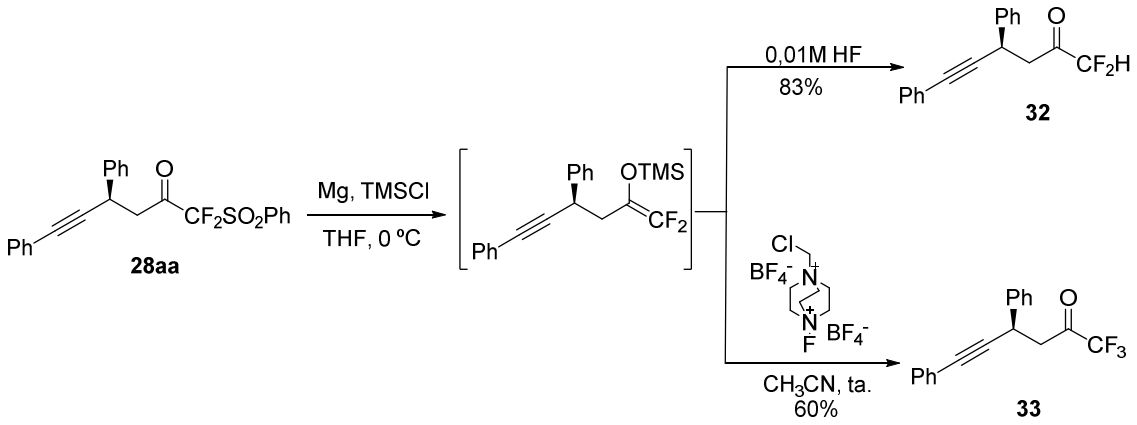
Como se ha mencionado anteriormente la agrupación (fenilsulfonil)difluorometilo es responsable de la activación electrofílica del doble enlace. Una característica deseable en el grupo activante es la posibilidad de ser sustituido o modificable sintéticamente. En particular su conversión en ésteres y amidas es especialmente interesante ya que estos grupos funcionales se comportan con dificultad en catálisis asimétrica.[62] También es interesante la transformación del grupo (fenilsulfonil)difluorometilo en otros grupos fluorados, por ejemplo, CF_2H o CF_3,[63] que como se ha mencionado, son de gran interés debido a su presencia en un gran número de moléculas utilizadas en la industria farmacéutica y agroquímica.[64]

4.3.5.1. Síntesis de β-alquinildifluorometil- y trifluorometilcetonas

Dada la importancia de la agrupación trifluorometilo o difluorometilo, exploramos la posibilidad de transformar los productos de alquinilación conjugada **28** en las correspondientes β-alquinildifluorometil- y triflurometilcetonas (Esquema 56).

Siguiendo un procedimiento descrito en la bibliografía,[59] se llevó a cabo la eliminación reductiva de la fenilsulfona por tratamiento de **28aa** con magnesio y cloruro de trimetilsililo (TMSCl) en THF a 0 °C, para dar el correspondiente enol éter difluorado que por hidrólisis con ácido fluorhídrico 0,01 M proporción la difluorometilcetona **32** con un 83% de rendimiento.

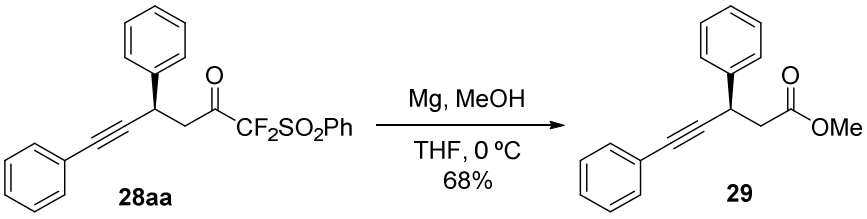
Por otra parte, el tratamiento de dicho enol éter intermedio con SelectFluor en acetonitrilo a temperatura ambiente condujo a la trifluorometilcetona **33** con un 60% de rendimiento. Ambas transformaciones transcurrieron sin pérdida de pureza óptica en los productos.



Esquema 56. Obtención de los compuestos **32** y **33** a partir de **28aa**.

4.3.5.2. La agrupación 1-(fenilsulfonil)-1,1-difluorometil cetona como equivalente de ésteres y amidas

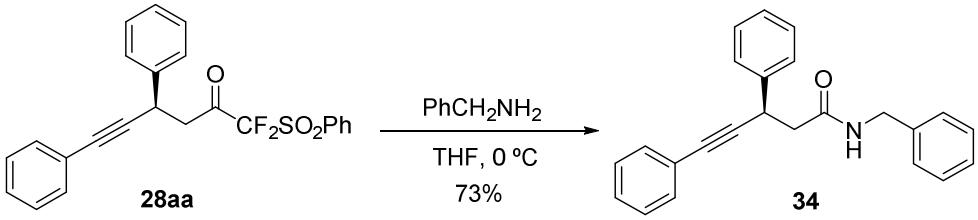
Durante uno de los intentos de eliminación reductiva de la fenilsulfona en el compuesto **28aa** llevada a cabo con magnesio en metanol se observó la formación de un compuesto que se identificó como el éster metílico **29**, el cual fue utilizado para la determinación de la configuración absoluta de los productos de alquinilación **28** (ver apartado 4.3.4). La reacción se optimizó llevándose a cabo la síntesis del éster **29** con un rendimiento del 68% por tratamiento de **28aa** con metanol en THF a 0 °C en presencia de magnesio (Esquema 57). La reacción también tiene lugar en ausencia de magnesio si se lleva a cabo a temperatura ambiente, aunque el tiempo requerido es mayor. La reacción tiene lugar sin pérdida en la pureza óptica de los productos.



Esquema 57. Obtención del éster **29** a partir del compuesto **28aa**.

La reacción anterior implica una sustitución nucleofílica en la que la agrupación (fenilsulfonil)difluorometilo actúa como grupo saliente. Un comportamiento que no había sido descrito en la bibliografía con anterioridad.

Con el fin de estudiar si este comportamiento es general se llevó a cabo la reacción del compuesto **28aa** con bencilamina a 0 °C en THF para obtener la correspondiente amida **34** (Esquema 58). La amida se obtuvo con un 73% de rendimiento y sin pérdida de la integridad estereoquímica del centro estereogénico.



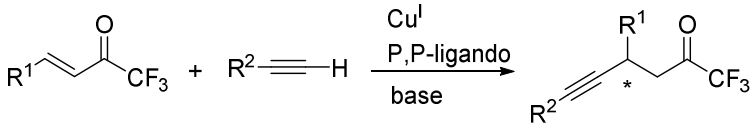
Esquema 58. Obtención de la amida **34** a partir del compuesto **28aa**.

Merece mencionarse que la transformación de **28aa** en éster o amida únicamente requiere el uso de alcoholes o aminas y que el único subproducto formado es la difluorometil fenil sulfona que se utiliza en la preparación de los productos de partida **28**, la cual podría ser recuperada de la mezcla de reacción mediante cromatografía de columna.

En resumen, en este capítulo hemos desarrollado una reacción de alquinilación conjugada altamente enantioselectiva de 1-(fenilsulfonil)-1,1-difluoro-3-en-2-onas catalizada por Cu(I). La adición de derivados de fenilacetileno, 3-tieniacetileno y ciclopropilacetileno a este tipo de enonas tiene lugar con buenos rendimientos y excelentes enantioselectividades. Los productos resultantes son precursores sintéticos de β-alquinildifluorometil y trifluorometil cetonas. Por otra parte, los productos pueden transformarse en ésteres o amidas por tratamiento con un alcohol o una amina. Esta reacción también constituye el primer caso de uso de 1-(fenilsulfonil)-1,1-difluoro-3-en-2-onas como sustratos en reacciones enantioselectivas.

4.4. Alquinilación conjugada enantioselectiva de 1,1,1-trifluorometil-3-en-2-onas catalizada por complejos de Cu(I)

En el apartado anterior hemos descrito la adición de alquinos terminales a 1-(fenilsulfonil)-1,1-difluoro-3-en-2-onas y su posterior transformación en β-alquiniltrifluorometil cetonas. Dado el interés de las moléculas que presentan un grupo CF_3 en química médica, nos pareció interesante estudiar la alquinilación conjugada de 1,1,1-trifluorometil-3-en-2-onas que permitiría la obtención directa de β-alquiniltrifluorometil cetonas quirales (Esquema 59).

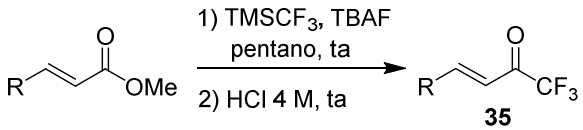


Esquema 59. Alquinilación conjugada enantioselectiva de 1,1,1-trifluorometil-3-en-2-onas.

Las trifluorometil enonas son sustratos especialmente desafiantes para las reacciones de adición conjugada enantioselectivas ya que la presencia del grupo trifluorometilo, fuertemente electrón-atrayente, unido al grupo carbonilo, no solo activa el doble enlace sino también el grupo carbonilo, dificultando el control de la regioselectividad. En lo que se refiere a reacciones de alquinilación de estos sustratos, únicamente encontramos en la bibliografía un ejemplo de adición conjugada no enantioselectiva dealquinilboranos,[65] y dos ejemplos de adición 1,2 al grupo carbonilo.[66]

4.4.1. Síntesis de 1,1,1-trifluorometil-3-en-2-onas

La síntesis de β-aril 1,1,1-trifluorometil enonas se llevó a cabo mediante la reacción de trifluorometilación nucleofílica de esteres α,β-insaturados[67] utilizando el reactivo de Ruppert-Prakash ($TMSCF_3$) en presencia de floruro de tetrabutilamonio (TBAF), seguida de hidrólisis de los sililacetales resultantes con HCl 4 M acuoso (Esquema 60).

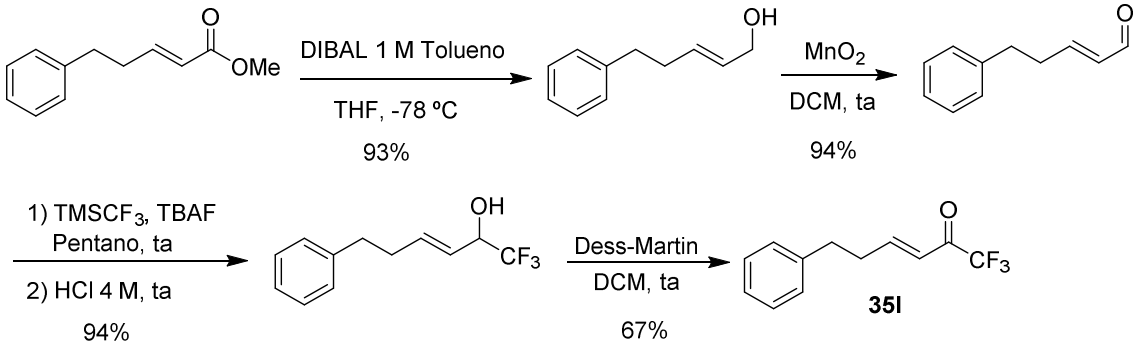


35a, R = Ph
35b, R = 2-MeC_6H_4
35c, R = 3-MeC_6H_4
35d, R = 4-MeC_6H_4
35e, R = 2-$MeOC_6H_4$
35f, R = 4-$MeOC_6H_4$
35g, R = 2-BrC_6H_4
35h, R = 3-BrC_6H_4
35i, R = 4-BrC_6H_4
35j, R = 2-naftilo
35k, R = 3-tienilo

Esquema 60. Síntesis de trifluorometil enonas **35**.

La síntesis de la trifluorometil enona **35l** con un sustituyente alifático en β no fue posible siguiendo este procedimiento, debido a la baja reactividad del (*E*)-5-fenilpent-2-enoato de metilo con el reactivo de Ruppert-Prakash. Para sintetizar **35l** fue necesario transformar dicho éster en (*E*)-5-fenilpent-2-enal por reducción al correspondiente

alcohol y posterior oxidación (Esquema 61). La trifluorometilación nucleofílica del aldehído con el reactivo de Ruppert-Prakash proporcionó el correspondiente trifluorometil alcohol que por oxidación con el reactivo de Dess-Martin permitió obtener la trifluorometil cetona deseada **35l**.



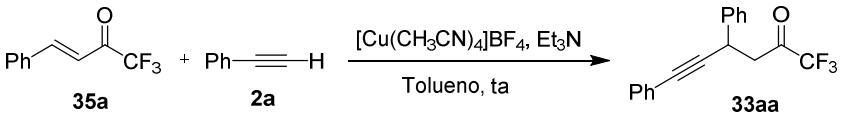
Esquema 61. Síntesis de la β-alquil trifluorometil enona **35l**.

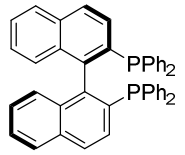
4.4.2. Optimización de las condiciones de reacción

Para llevar a cabo el proceso de optimización se estudió la reacción de adición conjugada de fenilacetileno (**2a**) a (*E*)-1,1,1-trifluoro-4-fenilbut-3-en-2-ona (**35a**), utilizando condiciones similares a las descritas en el capítulo anterior, 7.5 equivalentes de alquino **2a**, 20% mol de bisfosfina quiral, 20% mol de $[Cu(CH_3CN)_4]BF_4$, 1 equivalente de Et_3N y tolueno como disolvente (Tabla 10).

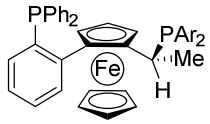
Sólo tres de los ligandos ensayados proporcionaron complejos de Cu(I) con actividad catalítica (Tabla 10, entradas 2, 5 y 7), siendo el ligando **L31** el que mejor resultado dio con un 66% de rendimiento y 94% de exceso enantiomérico (Tabla 10, entrada 7).

Tabla 10. Adición conjugada de fenilacetileno (**2a**) a la enona **35a**. Optimización de las condiciones de reacción.[a]

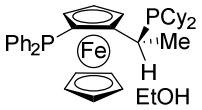




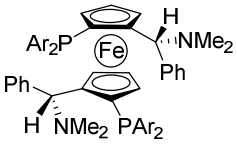
(*R*)-BINAP
L23



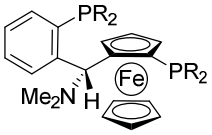
(*R*, R_p)-Walphos
L25 Ar = 3,5-$(CF_3)_2C_6H_3$



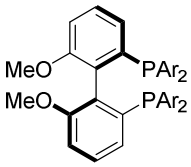
(*R*, S_p)-Josiphos
L26



(*R*, S_p)-Mandiphos
L27 Ar = 3,5-Me_2-4-$MeOC_6H_2$



(*R*, R_p)-Taniaphos
L29 R = Ph



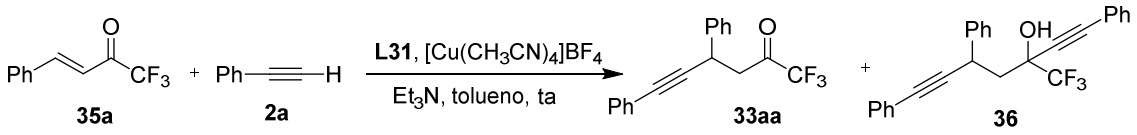
(*R*)-MeOBIPHEP
L30 Ar = Ph
L31 Ar = 3,5-^{t}Bu$_2$-4$MeOC_6H_2$

	L	t (h)	Rto (%)[b]	*ee* (%)[c]
1	**L23**	72	-	-
2	**L25**	48	39	62
3	**L26**	72	-	-
4	**L27**	72	-	-
5	**L29**	48	18	50
6	**L30**	72	-	-
7[d]	**L31**	48	66	94

[a] **2a** (0,9 mmol), **L** (0,025 mmol), $[Cu(CH_3CN)_4]BF_4$ (0,025 mmol), **35a** (0,125 mmol), Et_3N (0,125 mmol) en tolueno a ta.[b] Rendimiento de producto aislado por cromatografía de columna. [c] Determinado por HPLC utilizando fases estacionarias quirales. [d] Se obtiene un 20% de rendimiento de producto de dialquinilación.

De la mezcla de reacción llevada a cabo con el ligando **L31** se pudo aislar cerca de un 20% del producto **36** resultante de doble alquinilicación 1,2 y 1,4 (Tabla 10, entrada 7). Con el fin de disminuir la formación de este producto no deseado llevamos a cabo una serie de ensayos reduciendo los equivalentes de alquino, base y catalizador (Tabla 11).

Tabla 11. Adición conjugada de fenilacetileno (**2a**) a la trifluorometilenona **35a**. Optimización de las condiciones de reacción.[a]



	L31 (% mol)	**2a** (equiv.)	Et_3N (equiv.)	Rto **33aa** (%)[b]	*ee* (%)[c]	Rto **36** (%)[d]
1	20	7,5	1	66	94	20
2	20	5	1	35	94	25
3	10	7,5	1	45	94	25
4	10	5	1	52	94	15
5	5	3	1	59	94	15
6	5	1,3	1	63	94	5
7	5	1,3	0.1	72	94	5
8	2,5	1,3	0.1	87	94	-
9	2,5	1,3	-	-	-	-

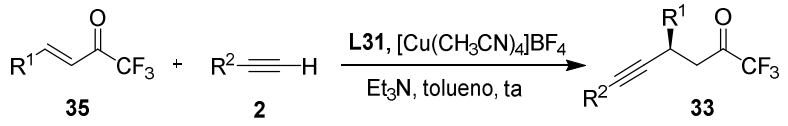
[a] Tiempo de reacción 24 h. [b] Rendimiento de producto aislado por cromatografía de columna. [c] Determinado por HPLC utilizando fases estacionarias quirales. [d] Rendimiento determinado por RMN.

Al intentar reducir únicamente el número de equivalentes de alquino o la carga catalítica se observó una disminución del rendimiento del producto de alquinilación **33aa** manteniéndose la formación del producto de doble alquinilación **36** (Tabla 11, entradas 2 y 3). Sin embargo, al reducir al mismo tiempo los equivalentes de **2a** y la carga catalítica se observó un aumento en el rendimiento del producto **33aa** y una disminución en la formación del producto secundario (Tabla 11, entradas 4-6). La reducción en el número de equivalentes de base produjo un aumento en el rendimiento del producto **33aa** (Tabla 11, entrada 7). El mejor resultado se obtuvo utilizando un 2,5% molar de carga catalítica, 1,3 equivalentes de alquino **2a** y 0,1 equivalentes de Et_3N, que proporcionó el producto de alquinilación **33aa** con un 87% de rendimiento y 94% de exceso enantiomérico, no observándose formación del producto secundario **36** (Tabla 11, entrada 8).

4.4.3. Alcance y limitaciones de la reacción

Las condiciones optimizadas se aplicaron a la reacción entre diversos alquinos y 1,1,1-trifluorometil-3-en-2-onas sustituidas (Tabla 12).

Tabla 12. Adición conjugada de diversos alquinos **2** con diferentes 1,1,1-trifluorometil-3-en-2-onas **35**.[a]



		R^1		R^2		t (h)	Rto (%)[b]	*ee* (%)[c]
1	**35a**	C_6H_5	**2a**	C_6H_5	**33aa**	24	87	94
2	**35b**	2-MeC_6H_4	**2a**	C_6H_5	**33ba**	48	96	98
3	**35c**	3-MeC_6H_4	**2a**	C_6H_5	**33ca**	72	65	96
4	**35d**	4- MeC_6H_4	**2a**	C_6H_5	**33da**	72	55	95
5	**35f**	4-MeOC_6H_4	**2a**	C_6H_5	**33fa**	72	56	94
6	**35g**	2-BrC_6H_4	**2a**	C_6H_5	**33ga**	48	74	98
7	**35h**	3-BrC_6H_4	**2a**	C_6H_5	**33ha**	48	73	93
8	**35i**	4-BrC_6H_4	**2a**	C_6H_5	**33ia**	48	68	90[d]
9	**35j**	2-naftilo	**2a**	C_6H_5	**33ja**	72	55	94
10	**35k**	3-tienilo	**2a**	C_6H_5	**33ka**	48	80	90
11	**35l**	CH_2CH_2Ph	**2a**	C_6H_5	**33la**	-	-	-
12	**35a**	C_6H_5	**2k**	3,5-$(MeO)_2C_6H_3$	**33ak**	48	63	96
13	**35a**	C_6H_5	**2b**	4-MeOC_6H_4	**33ab**	24	96	94
14	**35a**	C_6H_5	**2g**	3-FC_6H_4	**33ag**	48	76	95
15	**35a**	C_6H_5	**2c**	4-FC_6H_4	**33ac**	48	60	95
16	**35a**	C_6H_5	**2d**	4-ClC_6H_4	**33ad**	48	78	92
17	**35a**	C_6H_5	**2e**	3-tienilo	**33ae**	48	65	94
18	**35a**	C_6H_5	**2f**	CH_2CH_2Ph	**33af**	72	20(31)[e]	62(78)[e]
20	**35b**	2-MeC_6H_4	**2g**	3-FC_6H_4	**33bg**	48	99	98
21	**35b**	2-MeC_6H_4	**2f**	CH_2CH_2Ph	**33bf**	72	30	90[d]
22	**35g**	2-BrC_6H_4	**2b**	4-MeOC_6H_4	**33gb**	72	60	98
23	**35g**	2-BrC_6H_4	**2g**	3-FC_6H_4	**33gg**	72	53	98
24	**35a**	C_6H_5	**2l**	TIPS	**-**	-	-	-

[a] **2** (0,188 mmol), **L** (0,0034 mmol), $[Cu(CH_3CN)_4]BF_4$ (0,0034 mmol), **35** (0,144 mmol), Et_3N (0,014 mmol) en tolueno a ta.[b] Rendimiento de producto aislado por cromatografía de columna. [c] Determinado por HPLC utilizando fases estacionarias quirales. [d] Determinado tras hidrogenación total del triple enlace. [e] Resultados obtenidos con un 5% mol de carga catalítica.

En primer lugar, se llevó a cabo la adición de fenilacetileno (**2a**) a 1,1,1-trifluorometil-3-en-2-onas **35** con grupos aromáticos en el carbono β del doble enlace, sustituidos en las diferentes posiciones del anillo aromático con grupos electrón-donantes y electrón-atrayentes. Se obtuvieron los productos de alquinilación con rendimientos buenos y excesos enantioméricos superiores al 90% (Tabla 12, entradas 2-8). Los mejores resultados se obtuvieron con los sustratos sustituidos en la posición *orto* del anillo aromático obteniéndose los correspondientes productos con excelentes enantioselectividades (Tabla 12, entradas 2 y 6). La reacción permite un grupo voluminoso como es el 2-naftilo sobre el carbono β del doble enlace, obteniéndose el correspondiente producto **33ja** con un rendimiento moderado y un exceso enantiomérico del 94% (Tabla 12, entrada 9). El estudio se amplió con el empleo de un

sustrato sustituido con un grupo heteroaromático con el cual se obtuvo el producto de alquinilación **33ka** con rendimiento y enantioselectividad elevados (Tabla 12, entrada 10). Sin embargo, la reacción no tolera grupos alifáticos en el carbono β, no observándose reacción con la enona alifática **35l** (Tabla 12, entrada 11).

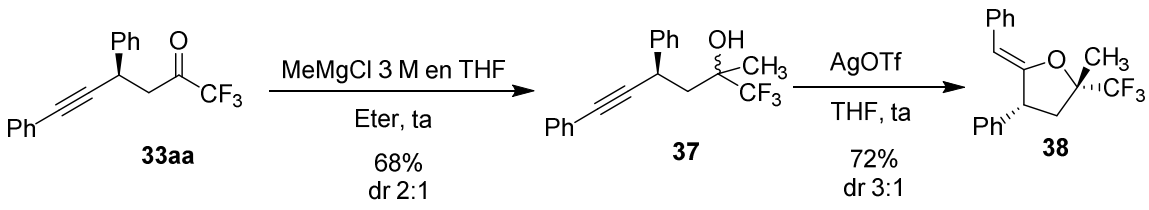
También se ha llevado a cabo la reacción con diferentes derivados del acetileno. La reacción de diversos arilacetilenos **2** sustituidos en el anillo aromático con grupos de distinta naturaleza electrónica permitió obtener los productos de alquinilación correspondientes con rendimientos buenos y enantioselectividades superiores al 92% (Tabla 12, entradas 12-16, 20, 22-23). La adición del alquino sustituido con un anillo heteroaromático **2e** a la enona **35a** condujo al producto **33ae** con un rendimiento bueno y un exceso enantiomérico del 94% (Tabla 12, entrada 17). Interesantemente, también fue posible utilizar un alquino alifático como el 4-fenil-1-butino (**2f**), aunque en los ejemplos estudiados los rendimientos fueron bajos y las enantioselectividades variables según la enona (Tabla 12, entradas 18 y 21).

4.4.4. Determinación de la configuración absoluta

La configuración absoluta del compuesto **33aa** se determinó por análisis cromatográfico por HPLC con una columna quiral (Chiralpak AD-H), comparando los tiempos de retención con los del mismo compuesto obtenido a partir de la fenilsulfona **28aa** según se describe en el apartado 4.3.5.1. Este análisis indicó que en ambos casos la configuración del centro estereogénico es *S*. Para el resto de productos de alquinilación **33** la configuración se asignó asumiendo un mecanismo estereogénico común.

4.4.5. Transformaciones sintéticas

Una aplicación sintética de las β-alquinilcetonas **33** es la síntesis de dihidrofuranos quirales sustituidos con un grupo trifluorometilo. Así, la adición MeMgCl a la cetona **33aa** condujo al producto **37** con un rendimiento del 68% y una relación diastereomérica de 3:1. La ciclación de **37** promovida por el ión de plata(I) permitió obtener el tetrahidrofurano **38** (Esquema 62).



Esquema 62. Transformación sintética de **33aa**.

El diastereoisómero mayoritario de **38** se pudo obtener puro mediante cristalización de hexano. El análisis de este producto mediante difracción de rayos X permitió determinar la estructura del compuesto **38**, indicando la presencia del anillo de cinco

miembros, la disposición *cis* entre el grupo fenilo y el grupo CF_3, y la configuración *Z* del doble enlace exocíclico (Figura 11).

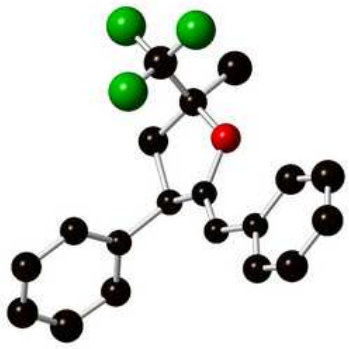


Figura 11. Estructura del compuesto **38** elucidada mediante difracción de rayos X.

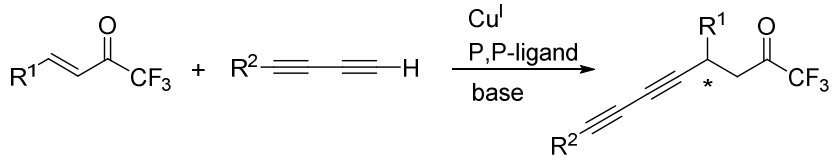
En resumen, en este capítulo hemos desarrollado una reacción de alquinilación conjugada altamente enantioselectiva de 1,1,1-trifluorometil-3-en-2-onas catalizada por Cu(I). La reacción se ha llevado a cabo empleando una carga catalítica de 2,5% mol sin observar producto de adición 1,2. La adición de derivados de fenilacetileno, 3-tienilacetileno y 4-fenil-1-butino a este tipo de trifluorometilenonas tiene lugar con buenos rendimientos y excelentes enantioselectividades. Los productos resultantes son precursores sintéticos de dihidrofuranos quirales sustituidos.

4.5. Enantioselective conjugate addition of 1,3-diynes to 1,1,1-trifluoromethyl-3-en-2-ones catalyzed by Cu(I) complexes

The 1,3-diyne moiety is present in a large number of natural and artificial molecules.[68] Naturally occurring diynes are found as metabolites in a variety of fungi, higher plants and marine organisms, and many of them have important biological and pharmacological properties ranging from antifungal to anticancer activities.[69] Diynes and oligoynes have also interest as probes of extended π-conjugation and can serve as active components in optoelectronic devices.[70] Furthermore, conjugate diynes are intriguing building blocks due to the unique behavior of alkynes, especially in transition metal-catalyzed processes.[71]

Compared with simple alkynes, the studies on enantioselective nucleophilic additions of 1,3-diynes are far more limited, and most of the examples reported in the literature involve the activation of terminal 1,3-diynes as diynylzinc reagents, which requires in most of the cases the use of stoichiometric or larger amounts of dialkylzinc reagents. Thus, after the pioneering work by Carreira in 2003,[72] on the use of 4 equivalents of $Zn(OTf)_2$/*N*-methylephedrine to achieve the addition of a terminal 1,3-diyne to an aliphatic aldehyde, Trost[73] reported in 2010 a catalytic enantioselective addition of 1,3-diynes to aldehydes using a dinuclear ProPhenol/zinc catalyst. Later on, Pu,[74] Tykwinski[75] and Wang[76] developed their own versions on the asymmetric zinc-catalyzed addition of 1,3 diynes to aldehydes by using combinations of dialkylzinc with amino alcohol[75,76] or binaphthol-type[74] ligands. In 2011, Ma described the enantioselective addition of 1,3-diynylzinc reagents, generated *in situ* from Me_2Zn and terminal diynes, to aromatic ketones in the presence of a Cu(II)-hydroxycamphor-sulfonamide complex and Me_2Zn.[77] On the other hand, the diynylation of different kind of aldimines[78] and fluorinated ketimines[79] has been reported by the same group using terminal diynes, Me_2Zn and binaphthol-type ligands.

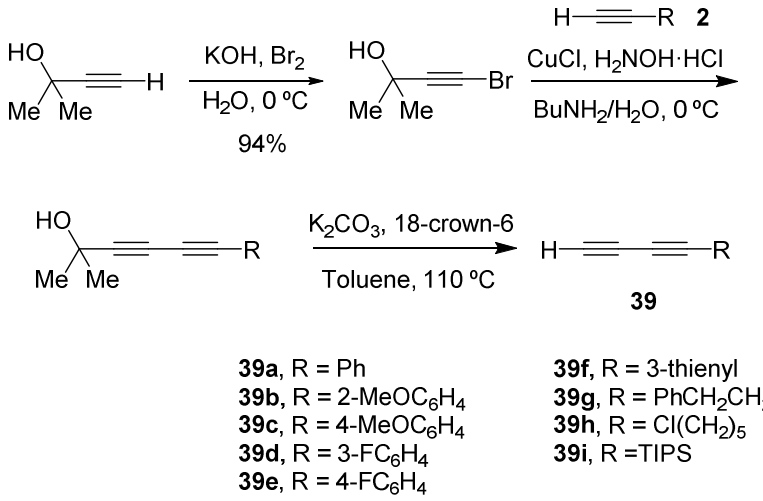
However, a procedure for the enantioselective addition of 1,3-diynes to electrophilic C-C double bonds, i.e. enones, has not been reported so far. Following our research on conjugate alkynylation of electrophilic double bonds, we have performed research to achieve the enantioselective conjugate addition of terminal 1,3-dyines to 1,1,1-trifluoromethyl-3-en-2-ones, a reaction without any precedent in the literature (Scheme 63).



Scheme 63. Enantioselective conjugate addition of 1,3-diynes to 1,1,1-trifluoromethyl enones.

4.5.1. Synthesis of terminal 1,3-diynes

The terminal 1,3-diynes were prepared according to the procedure described in the literature (Scheme 64).[74] First, 4-bromo-2-methylbut-3-yn-2-ol, a common synthetic intermediate for all diynes, was prepared in good yield by bromination of 2-methylbut-3-yn-2-ol with Br_2 in basic medium. A Cadiot-Chodkiewicz cross coupling reaction of 4-bromo-2-methylbut-3-yn-2-ol with the corresponding terminal alkyne **2** catalyzed by CuCl and $NH_2OH \cdot HCl$ in a 30% *n*-butylamine aqueous solution gave the corresponding 1,3-diyne precursors which upon fragmentation by base afforded the desired terminal 1,3-diynes **39** and acetone. All terminal 1,3-diynes undergo rapid decomposition or polymerized when concentrated. For this reason, they were stored at –15 ºC in Et_2O solution and concentrated immediately prior to use.



Scheme 64. Synthesis of 1,3-diynes **39**.

4.5.2. Optimization of reaction conditions

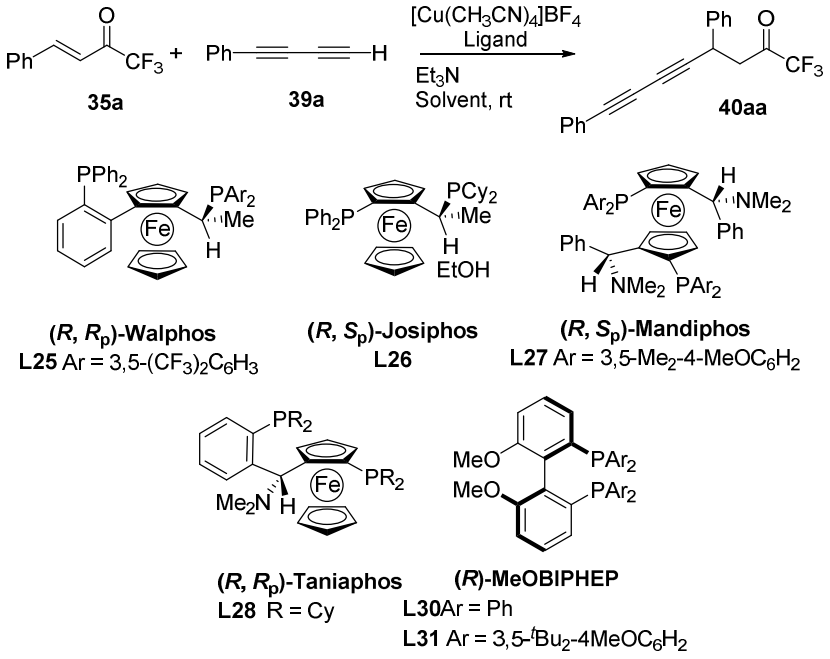
In the onset of our investigation we studied the conjugate addition of buta-1,3-diyn-1-ylbenzene (**39a**) to 1,1,1-trifluoromethyl-3-en-2-one **35a** catalyzed by 20 mol % of $[Cu(CH_3CN)_4]BF_4$ and (*R*)-MeOBIPHEP **L31** in toluene, under similar reaction conditions to those used in the addition reaction of terminal alkynes to 1,1,1-trifluoromethyl enones (section 4.4).

Pleasantly, compound **40aa** was obtained in 82% yield and 93% *ee* under these reaction conditions (Table 13, entry 1). No products arising from 1,2-addition to the carbonyl group were observed. Further studies with this catalytic system (Table 13, entries 2-6) showed that the catalyst load could be reduced as low as 2.5 mol % and the amount of base decreased to 0.1 equivalents without a significant effect on the reaction outcome, as in the previously studied addition conjugate of terminal alkynes **2** to 1,1,1-trifluoromethyl-3-en-2-ones **35**.

Other phosphine ligands were also tested (Table 13, entries 7-11). Surprisingly, from all the studied ligands, only biarylphosphine **L31** provided a catalytic complex

sufficiently active to promote the reaction with this low catalytic load. The use of copper(I) triflate provided similar results as $[Cu(CH_3CN)_4]BF_4$ (Table 13, entry 12), whereas other solvents such as THF or CH_2Cl_2 decreased the reaction rate, the alkynylation product **40aa** being obtained in lower yields than in toluene, although still with good enantioselectivities (Table 13, entries 13-14).

Table 13. Conjugate addition of buta-1,3-diyn-1-ylbenzene (**39a**) to enone **35a**. Screening of ligands and reaction conditions.



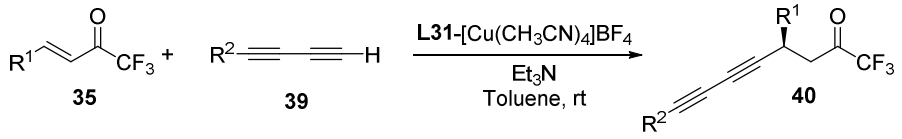
	L	**L**-Cu(I) (mol %)	**39a** (equiv.)	Et_3N (equiv.)	solvent	t (h)	Yield (%)[a]	*ee* (%)[b]
1	**L31**	20	7.5	1.0	toluene	18	82	93
2	**L31**	20	5	1.0	toluene	18	70	93
3	**L31**	5	3	1.0	toluene	18	73	93
4	**L31**	5	3	0.1	toluene	18	75	93
5	**L31**	2.5	1.3	0.1	toluene	18	73	93
6	**L31**	2.5	1.3	0	toluene	18	n.r.	-
7	**L25**	2.5	1.3	0.1	toluene	18	n.r.	-
8	**L26**	2.5	1.3	0.1	toluene	18	n.r.	-
9	**L27**	2.5	1.3	0.1	toluene	18	trace	-
10	**L28**	2.5	1.3	0.1	toluene	18	trace	-
11	**L30**	2.5	1.3	0.1	toluene	18	n.r.	-
12[c]	**L31**	2.5	1.3	0.1	toluene	18	65	93
13	**L31**	2.5	1.3	0.1	THF	48	34	94
14	**L31**	2.5	1.3	0.1	CH_2Cl_2	48	17	90

[a] Yield of isolated product. [b] Determined by HPLC using chiral stationary phases. [c] CuOTf·Tol was used instead of $[Cu(CH_3CN)_4]BF_4$.

4.5.3. Scope of the reaction

The optimized conditions (Table 13, entry 12) were applied to the conjugate addition of several 1,3-diynes **39** to various trifluoromethylenones **35** giving the corresponding diynylated products **40** in good to excellent results (Table 14).

Table 14. Enantioselective conjugate addition of terminal 1,3-diynes **39** to trifluoromethylenones **35**. Scope of the reaction.[a]



		R^1		R^2		Yield (%)[b]	*ee* (%)[c]
1	**35a**	C_6H_5	**39a**	C_6H_5	**40aa**	73	93
2	**35b**	2-MeC_6H_4	**39a**	C_6H_5	**40ba**	94	94
3	**35c**	3-MeC_6H_4	**39a**	C_6H_5	**40ca**	55	93
4	**35d**	4-MeC_6H_4	**39a**	C_6H_5	**40da**	56	92
5	**35e**	2-MeOC_6H_4	**39a**	C_6H_5	**40ea**	76	94
6	**35f**	4-MeOC_6H_4	**39a**	C_6H_5	**40fa**	55	92
7	**35g**	2-BrC_6H_4	**39a**	C_6H_5	**40ga**	69	94
8	**35i**	4-BrC_6H_4	**39a**	C_6H_5	**40ia**	41	92
9	**35j**	2-naphthyl	**39a**	C_6H_5	**40ja**	59	92
10[d]	**35l**	$PhCH_2CH_2$	**39a**	C_6H_5	**40la**	50	84
11	**35a**	C_6H_5	**39b**	2-OMeC_6H_4	**40ab**	50	90
12	**35a**	C_6H_5	**39c**	4-OMeC_6H_4	**40ac**	68	92
13	**35a**	C_6H_5	**39d**	3-FC_6H_4	**40ad**	89	92
14	**35a**	C_6H_5	**39e**	4-FC_6H_4	**40ae**	65	91
15	**35a**	C_6H_5	**39f**	3-thienyl	**40af**	72	94
16	**35a**	C_6H_5	**39g**	$PhCH_2CH_2$	**40ag**	41	93
17	**35b**	2-MeC_6H_4	**39g**	$PhCH_2CH_2$	**40bg**	50	95
18	**35a**	C_6H_5	**39h**	6-ClC_4H_8	**40ah**	61	93
19[e]	**35a**	C_6H_5	**39i**	TIPS	**40ai**	50	85

[a] **35** (1 equiv), **39** (1.3 equiv), Et_3N (0.1 equiv), $[Cu(CH_3CN)_4]BF_4$ (2.5 mol %), **L31** (2.5 mol %), toluene, rt, 24 h. [b] Yield of isolated product. [c] Determined by HPLC using chiral stationary phases. [d] Reaction carried out with 10 mol % of catalyst. [e] Reaction time 48 h.

Again, we conducted the addition of diyne **39a** with several trifluoromethyl enones bearing different substituents at β position of the double bond. Good results were obtained with a variety of enones bearing a substituted aromatic ring at this position. Good enantiomeric excesses were obtained for enones bearing an aromatic ring substituted at either the *ortho*, *metha* or *para* positions (Table 14, entries 2-4). Aromatic rings bearing electron-donating (Table 14, entries 5-6) or electron-withdrawing (Table 14, entries 7-8) substituents were also tolerated, yielding the expected products with enantiomeric excesses above 90%. Enone **35j** bearing a bulky 2-naphthyl group also reacted under the optimized conditions to give the diynylated product **40ja** with good yield and excellent enantioselectivity (Table 14, entry 9). Remarkably, the reaction

could also be carried out with enone **35l**, which features an aliphatic group on the β-carbon, providing compound **40la** with moderated yield but high enantiomeric excess, although a higher catalytic load (10 mol %) was required in this case (Table 14, entry 10). This result contrasts with that observed during the alkynylation of enone **35l** with simple alkynes, since this enone was not reactive.

Next, we tested the diyne scope (Table 14, entries 11-19). Substituted 4-aryl-1,3-butadiynes bearing electron-donating (MeO) or electron-withdrawing (F) groups on the phenyl group reacted with enone **35a** with variable yields but excellent enantioselectivities (Table 14, entries 11-14). The heterocyclic 3-(buta-1,3-diyn-1-yl)thiophene (**39f**) reacted with compound **35a** to give the expected product **40af** with 72% yield and 94% excess enantiomeric (Table 14, entry 15). Furthermore, we examined the reaction with aliphatic diynes, which reacted similarly to aromatic diynes. hexa-3,5-diyn-1-ylbenzene (**39g**) reacted with enones **35a** and **35b** to give the corresponding chiral diynes **40ag** and **40bg**, respectively, with moderate yield but high enantioselectivity (Table 14, entries 16-17). 8-Chloroocta-1,3-diyne (**39h**) reacted in a similar way to give compound **40ah** in 61% yield and 93% *ee* (Table 14, entry 18). These results contrast with those observed in the copper-catalyzed conjugate alkynylation of 1,1-difluoro-1-(phenylsulfonyl)-3-en-2-ones **28** (Section 4.3.) or β-trifluoromethyl enones **46** (Section 4.6.) with terminal monoynes where aliphatic alkynes did not react or they did it with lower yields and enantioselectivities than aromatic and heteroaromatic ones. Finally, silyldiyne **39i**, which is an equivalent of buta-1,3-diyne, could be reacted with enone **35a** to give the diynylated product **40ai** with 85% *ee* (Table 14, entry 19), showing the broad scope of the reaction regarding the diyne nucleophile.

4.5.4. Determination of absolute configuration

The configuration of the stereogenic center in the diynylated product **40af** was established to be *R* by X-ray crystallographic analysis (Figure 12). For the rest of products of addition conjugate of 1,3-diynes to 1,1,1-trifluoromethyl-3-en-2-ones were assigned on the assumption of a uniform reaction mechanism.

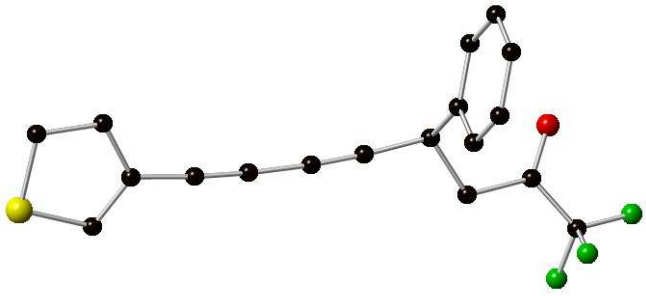
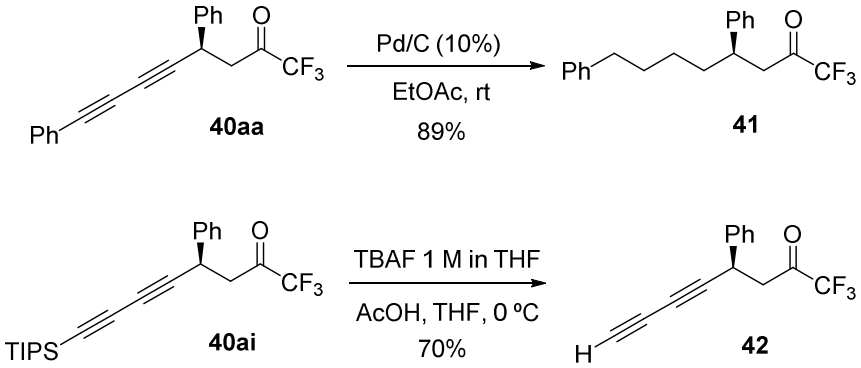


Figure 12. ORTEP plot for the X-ray structure of compound **40af**.

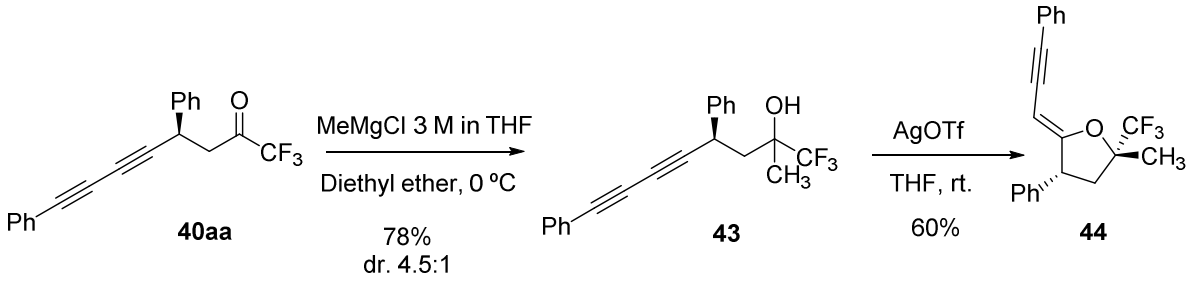
4.5.5. Synthetic transformations

Some synthetic modifications of diynes **40** are presented in Scheme 65. Thus, full hydrogenation of both triple bonds in **40aa** could be carried out over 10% Pd/C in ethyl acetate to give trifluoromethyl ketone **41** without any loss of optical purity. We have also performed the desylilation of compound **40ai** (70% yield) to give the chiral terminal diyne **42** upon treatment with TBAF and acetic acid in THF.



Scheme 65. Synthetic transformations.

On the other hand, a chiral tetrahydrofuran bearing a trifluoromethylated quaternary stereocenter **44** could be obtained after diastereoselective addition of methylmagnesium chloride to compound **40aa** followed by silver-catalyzed cyclization (Scheme 66).



Scheme 66. Synthesis of chiral tetrahydrofuran **44**.

The stereochemistry of compound **44** was determined by NOESY. A relevant interaction was observed between the CH_3 group at C2 (δ 1.63 ppm) and H4 (δ 4.18 ppm) which indicated the *trans* disposition between the Me group at C2 and the phenyl group at C4. NOE was also observed between one of the hydrogens of the phenyl group at C4 (δ 7.30 ppm) and the olefinic hydrogen H1' (δ 4.30 ppm) which indicated the *Z* geometry of the exocyclic double bond. Other spatial interactions detected in the NOESY experiment are shown in figure 13.

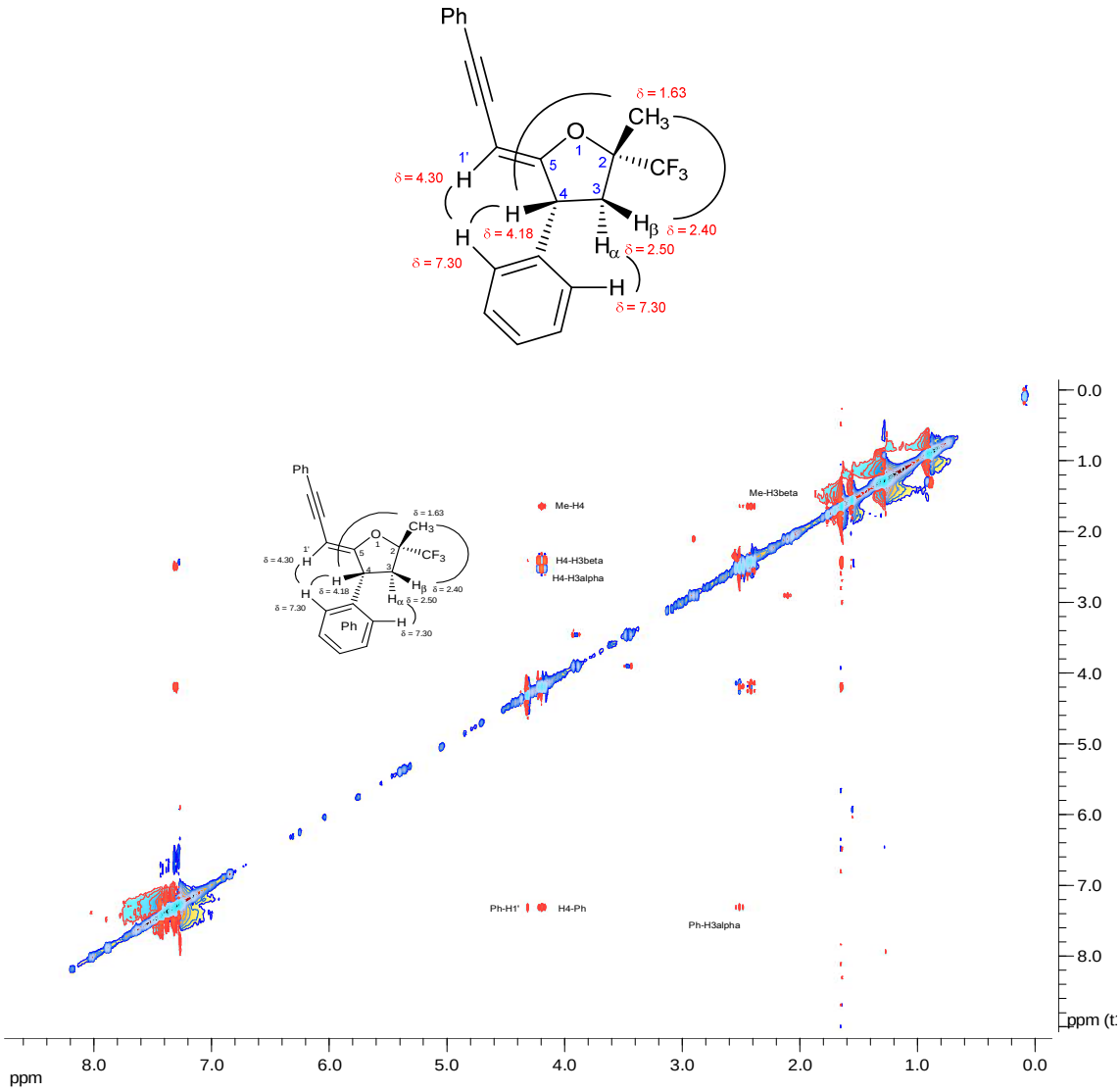


Figure 13. Interactions observed in NOESY experiment in compound **44**.

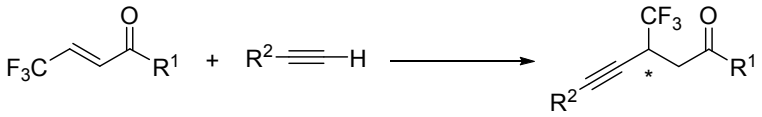
In summary, we have reported the first example of enantioselective conjugate diynylation of enones. The reaction requires only a small excess (1.3 equiv) of a terminal diyne and is carried out in the presence of a low catalytic load of a copper(I)-biphosphine complex (0.025 equiv) and an amine (0.1 equiv) to provide the corresponding internal diynes bearing a propargylic stereogenic center with excellent enantioselectivities. The reaction is broad in scope allowing variation of substituents on the enone β-carbon as well as on the diyne. It should be remarked that, unlike in other enantioselective diynylations of carbonyl compounds and imines previously reported in the literature, pre-metalation of the terminal diyne with stoichiometric amounts of a dialkylzinc reagent is not required. Our results show that the transient diynyl-copper species formed from the terminal diyne and the copper(I) complex in the presence of an amine are sufficiently nucleophilic to react even with weak electrophiles. This may anticipate the possibility of other enantioselective diynylation reactions not requiring pre-metalation of terminal diynes with stoichiometric amounts of organometallic reagents in the future.

4.6. Alquinilación conjugada enantioselectiva de β-trifluorometil α,β-enonas catalizada por complejos de Cu(I)

En apartados anteriores hemos desarrollado procedimientos para la alquinilación de enonas que poseen grupos fluorados unidos al grupo carbonilo. En este capítulo describiremos nuestra investigación sobre alquinilación de β-trifluorometilenonas para obtener compuestos con un centro estereogénico sustituido con un grupo trifluorometilo, una subestructura que se encuentra en moléculas de gran interés.[80]

Existen dos aproximaciones generales para la formación de centros estereogénicos trifluorometilados: a) la trifluorometilación de un átomo de carbono proquiral y b) la funcionalización de átomos de carbonos proquirales trifluorometilados. Aunque se trata de un procedimiento directo, existen pocos ejemplos enantioselectivos que utilicen la primera aproximación,[81] siendo más frecuentes los procedimientos que utilizan la segunda aproximación para la construcción de centros estereogénicos con un grupo trifluorometilo de manera enantioselectiva.[82]

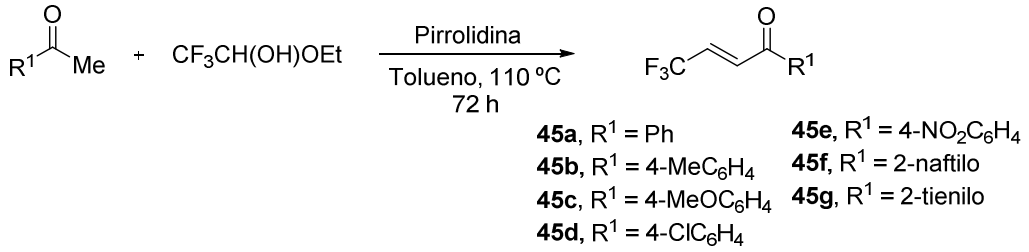
Podemos encontrar carbonos propargílicos estereogénicos sustituidos con un grupo trifluorometilo en numerosos compuestos bioactivos como el efavirenz y sus análogos que presentan actividad frente al VIH.[83] En la bibliografía se encuentran algunos procedimientos para la generación enantioselectiva de centros estereogénicos propargílicos trifluorometilados heterosustituidos basados en la trifluorometilación de inonas,[84] o en la alquinilación de cetonas[85] o iminas.[86] Sin embargo, no existen antecedentes de formación de centros estereogénicos propargílicos trifluorometilados no heterosustituidos. Así pues, siguiendo la aproximación b) planteamos la posibilidad de llevar a cabo reacciones de adición conjugada enantioselectiva de alquinos terminales a β-trifluorometil α,β-enonas para obtener las correspondientes cetonas con un centro estereogénico propargílico sustituido con un grupo trifluorometilo (Esquema 67).



Esquema 67. Alquinilación conjugada enantioselectiva de β-trifluorometil cetonas α,β-insaturadas.

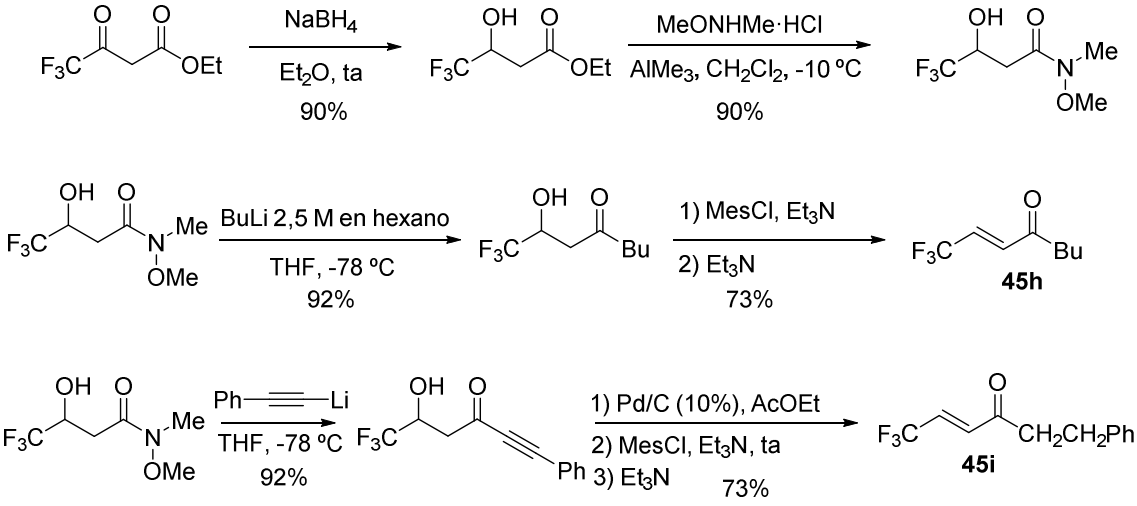
4.6.1. Síntesis de β-trifluorometil α,β-enonas

Las β-trifluorometil α,β-enonas **45** se prepararon con rendimientos variables (45-81%) siguiendo el procedimiento descrito por nuestro grupo de investigación,[82b] consistente en una secuencia de adición aldólica-deshidratación a partir de las correspondientes acetofenonas y el hemiacetal del trifluoroacetaldehído en tolueno a reflujo y utilizando pirrolidina como base (Esquema 68).



Esquema 68. Síntesis de β-trifluorometil cetonas α,β-insaturadas **45.**

La síntesis de las β-trifluorometil enonas con un grupo alifático unido al carbonilo de cetona se llevó a cabo siguiendo el procedimiento descrito por el grupo de Billard,[87] el cual consiste en una síntesis de cuatro pasos donde el intermedio clave es la β-trifluorometil hidroxiamida de Weinreb obtenida a partir del trifluoroacetilacetato de etilo. La reacción de la amida de Weinreb con el reactivo organometálico adecuado seguido de deshidratación condujo a las enonas **45h** y **45i** (Esquema 69).



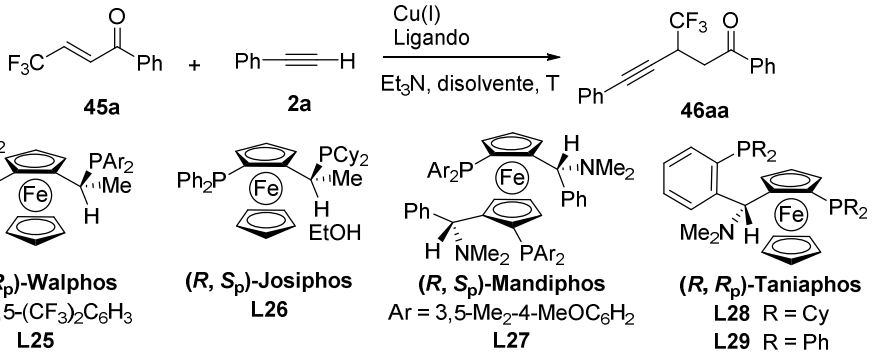
Esquema 69. Síntesis de β-trifluorometil enonas **45h** y **45i**.

4.6.2. Optimización de las condiciones de reacción

El proceso de optimización de las condiciones de la reacción de adición conjugada se llevó a cabo utilizando la reacción entre el fenilacetileno (**2a**) y 4,4,4-trifluoro-1-fenilbut-2-en-1-ona (**45a**). En primer lugar, se estudió la influencia de varios ligandos comerciales derivados del ferroceno utilizando $[Cu(CH_3CN)_4]BF_4$ (Tabla 15, entradas 1-5) y Et_3N como base a 70 ºC. El mejor resultado en estas condiciones se obtuvo con el ligando **L29** que condujo al compuesto **46aa** con un 64% de rendimiento y 78% de *ee*. La sustitución del complejo de $[Cu(CH_3CN)_4]BF_4$ por $[Cu(OTf)_2Tol]$ no mejoró la enantioselectividad, produciendo un descenso en el rendimiento (Tabla 15, entrada 6) Posteriormente, se estudio el efecto de la temperatura (Tabla 15, entradas 7 y 8) observándose una ligera mejora en el *ee* (80%) a 40 °C, aunque un descenso mayor hasta temperatura ambiente provocó una disminución acusada en el rendimiento (Tabla 15, entrada 8). También se llevo a cabo un ensayo, sustituyendo la Et_3N por $^iPr_2NH$ sin

obtener ninguna mejora en los resultados (Tabla 15, entrada 9). Por último, la reacción se ensayó con distintos disolventes obteniéndose el mejor resultado en THF con un 70% de rendimiento y un 85% de exceso enantiomérico en el producto **46aa** (Tabla 15, entrada 13).

Tabla 15. Adición conjugada de fenilacetileno (**2a**) a la enona **45a**. Optimización de las condiciones de reacción.[a]



	L	T (ºC)	Disolvente	t (h)	Rto (%)[b]	*ee* (%)[c]
1	**L25**	60	tolueno	72	26	14
2	**L26**	60	tolueno	72	45	10
3	**L27**	60	tolueno	48	93	42
4	**L28**	60	tolueno	72	47	75
5	**L29**	60	tolueno	72	64	78
6[d]	**L29**	60	tolueno	72	30	78
7	**L29**	40	tolueno	72	64	80
8	**L29**	ta	tolueno	72	53	80
9[e]	**L29**	40	tolueno	96	40	76
10	**L29**	40	$PhNO_2$	96	40	73
11	**L29**	40	anisol	96	56	81
12	**L29**	40	TBME	96	20	79
13	**L29**	40	THF	72	70	85
14	**L29**	40	dioxano	96	26	81

[a] **2a** (0,94 mmol), **L** (0,025 mmol), sal de Cu(I) (0,025 mmol), base (0,125 mmol), **45a** (0,125 mmol).[b] Rendimiento de producto aislado por cromatografía de columna. [c] Determinado por HPLC utilizando fases estacionarias quirales. [d] La reacción se llevó a cabo con $[Cu(OTf)_2Tol]$ en lugar de $[Cu(CH_3CN)_4]BF_4$. [e] $^iPr_2NH$ en lugar de Et_3N.

4.6.3. Alcance y limitaciones de la reacción

Bajo las condiciones optimizadas (Tabla 15, entrada 13), es posible llevar a cabo la reacción de adición conjugada de fenilacetileno (**2a**) a diferentes aril β-trifluorometil enonas (**45a-45e**) sustituidas en la posición *para* del anillo aromático tanto con grupos electrón-dadores como electrón-atrayentes (Tabla 16, entradas 2-5). La naturaleza electrónica del sustituyente tiene poco efecto en la enantioselectividad de la reacción, aunque la presencia de un grupo nitro fuertemente electrón-atrayente provoca un descenso tanto en el rendimiento como en el exceso enantiomérico (Tabla 16, entrada 5). La aplicabilidad de la reacción también puede ampliarse a sustratos con el grupo

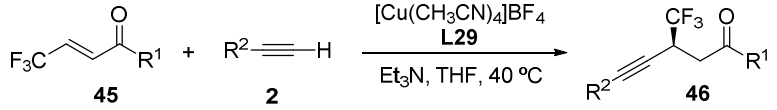
carbonilo unido a un sustituyente voluminoso como el 2-naftilo con un buen rendimiento y buena enantioseletividad (Tabla 16, entrada 6). Cabe destacar que la presencia de un anillo heterocíclico de tiofeno unido al carbonilo en el sustrato provoca un aumento tanto en el rendimiento como en la enantioselectividad, obteniéndose el producto **46ga** con un rendimiento cuantitativo y 90% de exceso enantiomérico (Tabla 16, entrada 7).

También se estudió la reacción utilizando sustratos con grupos alifáticos unidos al grupo carbonilo, los cuales resultaron menos reactivos que los sustratos con grupos aromáticos. La enona **45h** ($R^1 = PhCH_2CH_2$) se hizo reaccionar con fenilacetileno (**2a**) y con 4-metoxifenilacetileno (**2b**) obteniendo los correspondientes productos de alquinilación con bajos rendimientos, aunque con buenos excesos enantioméricos (Tabla 16, entradas 9 y 10). Sin embargo para la enona **45i** ($R^1 = {}^n$Bu) no se observó producto de alquinilación (Tabla 16, entrada 8).

A continuación, se estudió la reacción de adición conjugada de diferentes derivados de fenilacetileno con sustituyentes electrón-dadores y electrón-atrayentes en las distintas posiciones del anillo aromático a las enonas **45a** (Tabla 16, entradas 11-13) y **45g** (Tabla 16, entradas 14-21) obteniendo los productos de alquinilación **46** con buenos rendimientos y enantioselectividades, con excesos enantioméricos cercanos al 100% en la adición de (2-metoxifenil)acetileno (Tabla 16, entrada 14) y (3-fluorofenil)acetileno (Tabla 16, entrada 17). De nuevo las enonas derivadas de 2-tienilo dieron mejores resultados que las fenil enonas. La reacción también se llevó a cabo con un alquino sustituido con un grupo heteroaromático **2e**, obteniendo el producto de adición conjugada **46ge** con un buen rendimiento y enantioselectividad (Tabla 16, entrada 20).

Por último, se estudió la reacción entre un alquino alifático, el 4-fenil-1-butino (**2f**), con la enona **45g**. Con este alquino la reacción transcurre de forma lenta proporcionando el producto **46gf** con un rendimiento moderado pero con una enantioselectividad excelente (Tabla 16, entrada 21).

Tabla 16. Adición conjugada de alquinos terminales **2** a diferentes β-trifluorometil enonas **45**.[a]

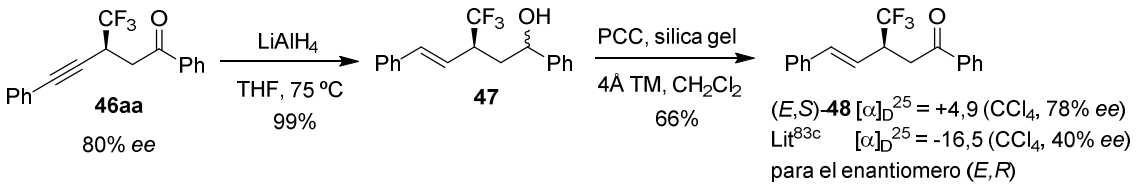


		R^1		R^2		Rto (%)[b]	*ee* (%)[c]
1	**45a**	C_6H_5	**2a**	C_6H_5	**46aa**	70	85
2	**45b**	4-MeC_6H_4	**2a**	C_6H_5	**46ba**	66	80
3	**45c**	4-$MeOC_6H_4$	**2a**	C_6H_5	**46ca**	64	80
4	**45d**	4-ClC_6H_4	**2a**	C_6H_5	**46da**	94	80
5	**45e**	4-$O_2NC_6H_4$	**2a**	C_6H_5	**46ea**	54	70
6	**45f**	2-naftilo	**2a**	C_6H_5	**46fa**	87	84
7	**45g**	2-tienilo	**2a**	C_6H_5	**46ga**	99	90
8[d]	**45i**	^{n}Bu	**2a**	C_6H_5	**46ia**	-	-
9[d]	**45h**	$PhCH_2CH_2$	**2a**	C_6H_5	**46ha**	30[e]	79
10[d]	**45h**	$PhCH_2CH_2$	**2b**	4-$MeOC_6H_4$	**46hb**	28[g]	82
11	**45a**	C_6H_5	**2b**	4-$MeOC_6H_4$	**46ab**	90	83
12	**45a**	C_6H_5	**2c**	4-FC_6H_4	**46ac**	77	80
13	**45a**	C_6H_5	**2d**	4-ClC_6H_4	**46ad**	60	77
14	**45g**	2-tienilo	**2m**	2-$MeOC_6H_4$	**46gm**	86	98
15	**45g**	2-tienilo	**2k**	3,5-$(MeO)_2C_6H_4$	**46gk**	68	86
16	**45g**	2-tienilo	**2b**	4-$MeOC_6H_4$	**46gb**	96	93
17	**45g**	2-tienilo	**2g**	3-FC_6H_4	**46gg**	97	99
18	**45g**	2-tienilo	**2c**	4-FC_6H_4	**46gc**	99	90
19	**45g**	2-tienilo	**2d**	4-ClC_6H_4	**46gd**	81	84
20	**45g**	2-tienilo	**2e**	3-tienilo	**46ge**	80	88
21	**45g**	2-tienilo	**2f**	$PhCH_2CH_2$	**46gf**	51[f]	92

[a] **2a** (0,94 mmol), **L29** (0,025 mmol), $[Cu(CH_3CN)_4]BF_4$ (0,025 mmol), Et_3N (0,125 mmol), **45** (0,125 mmol), tiempo de reacción 72 h. [b] Rendimiento de producto aislado por cromatografía de columna. [c] Determinado por HPLC utilizando fases estacionarias quirales. [d] Tiempo de reacción 90 h. [e] 51% de producto de partida **45h** recuperado.[f] 17% de producto de partida **45g** recuperado.[g] 50% de producto de partida **45h** recuperado.

4.6.4. Determinación de la configuración absoluta

La determinación de la configuración absoluta del compuesto **46aa** se determinó por correlación química con el compuesto **48** de estereoquímica conocida (Esquema 70).

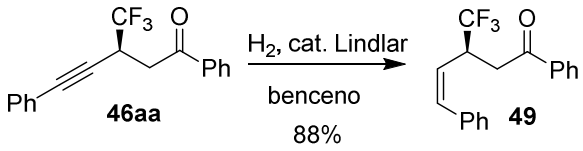


Esquema 70. Determinación de la configuración absoluta de **46aa**.

El tratamiento del compuesto **46aa** (80% *ee*) con $LiALH_4$ produjo simultáneamente la reducción de la cetona a alcohol y la reducción parcial del triple enlace conduciendo a una mezcla de dos alcoholes epímeros con geometría *E* en el doble enlace **47**. La oxidación con clorocromato de piridinio (PCC) de los alcoholes **47** dio lugar al compuesto **48**, el cual se encontraba descrito en la bibliografía en su forma (*E*,*R*)-**48**. El producto preparado a partir de **46aa** mostró signo de rotación opuesto al compuesto descrito en la bibliografía indicando que nuestro compuesto **48** y por tanto el compuesto **46aa** tenían la configuración *S* en el centro estereogénico. Para el resto de compuestos de alquinilación **46** se asignó la estereoquímica absoluta asumiendo un mecanismo estereogénico común.

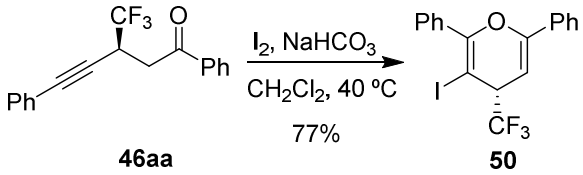
4.6.5. Transformaciones sintéticas

Para demostrar la aplicabilidad sintética de los productos de alquinilación **46**, se llevaron a cabo una serie de transformaciones sintéticas. Además de la reducción *trans* del triple enlace que se muestra en el esquema 70, se sintetizó el compuesto **49** con isomería *Z* en el doble enlace mediante hidrogenación utilizando el catalizador de Lindlar (Esquema 71).



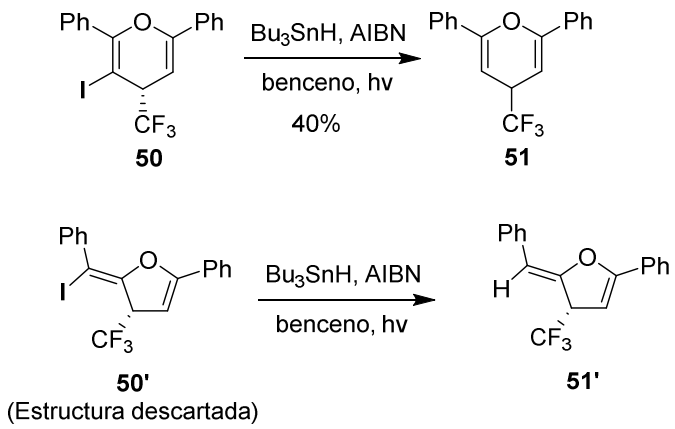
Esquema 71. Hidrogenación *cis* del compuesto **46aa**.

El iodo en medio básico promueve la ciclación del compuesto **46aa** mediante un proceso 6-*endo*-*dig* para dar el 4-trifluorometil-4*H*-pirano quiral **50** altamente sustituido sin perdida en la pureza óptica (Esquema 72). Éste, es un método eficaz para la obtención de compuestos heterocíclicos halogenados quirales altamente sustituidos con un centro estereogénico sustituido con un grupo trifluorometilo.



Esquema 72. Ciclación del compuesto **46aa**.

La estructura heterocíclica de tipo pirano (anillo de 6 miembros) del compuesto **50** se determinó por métodos espectroscópicos en el producto **51** resultante de una reacción de deshalogenación reductiva (Esquema 73). Así, el tratamiento de **50** con Bu_3SnH en presencia de AIBN proporcionó el producto **51**. El compuesto **51** mostró un espectro RMN ^1H muy sencillo con una única señal en la zona olefínica correspondiente a un compuesto con un plano de simetría. Este resultado descartó una posible estructura furánica **51'** que hubiera resultado de un proceso 6-*exo*-*dig*.



Esquema 73. Reducción radicalaria y determinación de la estructura de **51**.

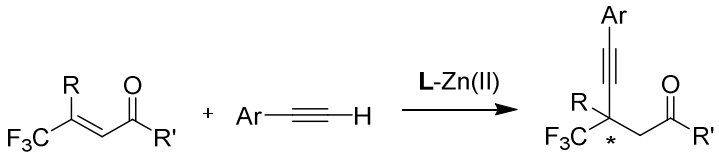
En resumen, en este capítulo hemos descrito la primera alquinilación conjugada enantioselectiva de β-trifluorometil α,β-enonas utilizando un complejo de Cu(I) con un ligando taniaphos, para dar cetonas con un centro estereogénico propargílico sustituido con un grupo trifluorometilo en β al grupo carbonilo con buenos rendimientos y excesos enantioméricos. Estos compuestos pueden utilizarse en la síntesis de heterociclos quirales trifluorometilados tales como 4-trifluorometil-4*H*-piranos mediante iodociclación.

4.7. Alquinilación conjugada enantioselectiva de β-aril β-trifluorometil enonas catalizada por complejos de Zn(II)

Un importante desafío en química orgánica es la síntesis de moléculas con un centro cuaternario quiral tetracarbosustituido.[88] La adición conjugada de nucleófilos carbonados a compuestos carbonílicos α,β-insaturados β,β-disustituidos constituye una de las estrategias a priori más directas para tal fin. Sin embargo, esta reacción plantea algunas dificultades en relación a la adición a compuestos β-monosustituidos debido al mayor impedimento estérico en el centro reactivo. No obstante, existen algunos ejemplos para este tipo de reacción empleando nucleófilos carbonados tales como reactivos de dialquilcinc,[89a,b] trialquilaluminio,[89c] trialquilboronato sódico[89d] o reactivos de Grignard[89e] mediante catálisis con Cu y Rh, así como ejemplos de adición de cianuro[90] o nitroalcanos como nucleófilos.[91]

En el caso concreto de enonas en las que uno de los sustituyentes en el carbono β es un grupo CF_3 la adición de nucleófilos carbonados genera un centro cuaternario estereogénico que contiene un sustituyente trifluorometilo. La formación de compuestos con un centro estereogénico trifluorometilado presenta un gran interés debido a la presencia de esta subestructura en compuestos biológicamente activos,[92] pero también en reactivos quirales[93] o en materiales de interés tecnológico.[94] A pesar de ello, el estudio de reacciones de adición conjugada enantioselectiva a β-trifluorometilenonas β,β-disustituidas es muy limitado. Así, solo encontramos en la literatura científica dos ejemplos de adición conjugada asimétrica organocatalítica de cianuro[95] así como de nitrometano[96] ambas catalizadas por sales de amonio cuaternario derivadas de alcaloides de la chinchona.

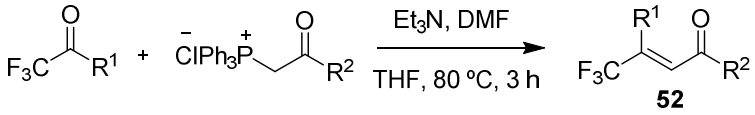
Sin embargo, no existe ningún ejemplo descrito de alquinilación conjugada asimétrica de β-trifluorometil enonas disustituidas en el carbono β del doble enlace. El desarrollo de reacciones de alquinilación conjugada enantioselectiva de β-trifluorometilenonas se encuentra entre los objetivos superados en esta tesis. En el capítulo anterior se ha descrito la alquinilación conjugada de β-trifluorometilenonas β-monosustituidas utilizando catálisis por Cu(I). A continuación, describiremos nuestros resultados de alquinilación con enonas β,β-disustituidas, la cual requirió un sistema reactivo completamente diferente (Esquema 74).



Esquema 74. Alquinilación conjugada de β-aril β-trifluorometil enonas.

4.7.1. Síntesis de β-aril β-trifluorometil enonas

Las β-aril β-trifluorometil enonas **52** fueron sintetizadas mediante una reacción de Wittig entre la sal de fosfonio correspondiente y diversas trifluorometilcetonas siguiendo el procedimiento descrito en la literatura (Esquema 75).[97]



52a, R^1 = Ph, R^2 = Ph
52b, R^1 = 4-MeC_6H_4, R^2 = Ph
52c, R^1 = 4-$MeOC_6H_4$, R^2 = Ph
52d, R^1 = 4-FC_6H_4, R^2 = Ph
52e, R^1 = 3-BrC_6H_4, R^2 = Ph
52f, R^1 = 4-BrC_6H_4, R^2 = Ph
52g, R^1 = 2-tienilo, R^2 = Ph
52h, R^1 = Ph, R^2 = 4-MeC_6H_4
52i, R^1 = Ph, R^2 = 4-$MeOC_6H_4$
52j, R^1 = Ph, R^2 = 4-ClC_6H_4
52k, R^1 = Ph, R^2 = 2-naftilo
52l, R^1 = 4-MeC_6H_4, R^2 = 2-naftilo
52m, R^1 = 4-$MeOC_6H_4$, R^2 = 2-naftilo

Esquema 75. Síntesis de β-aril β-trifluorometil enonas **52**.

Las β-aril β-trifluorometil enonas **52** se obtuvieron con rendimientos elevados (60-98) observándose en todos los casos mayoritariamente el isómero *E* fácilmente aislable por cromatografía de columna. Los compuestos se caracterizaron por resonancia magnética nuclear (RMN ^{1}H, RMN ^{13}C y RMN ^{19}F).

4.7.2. Optimización de las condiciones de reacción

Para llevar a cabo la optimización de las condiciones de reacción se estudió la adición conjugada de fenilacetileno (**2a**) a la (*E*)-4,4,4-trifluoro-1,3-difenilbut-2-en-1-ona (**52a**). Inicialmente se intentó llevar a cabo la reacción en las condiciones optimizadas para la alquinilación de β-trifluorometilenonas β-monosustituidas utilizando complejos de Cu(I) con ligandos de tipo bisfosfina (ver sección 4.6.). Sin embargo, en ninguno de los casos se observó ningún avance de la reacción por lo que decidimos utilizar un sistema reactivo basado en alquinos terminales y reactivos de dialquilcinc. Se eligieron entonces condiciones similares a las descritas para la alquinilación de endionas, es decir, ligandos de tipo BINOL como inductor quiral, Et_2Zn para la pre-formación de reactivos de alquinilcinc, tolueno como disolvente y 70 ºC como temperatura de reacción.

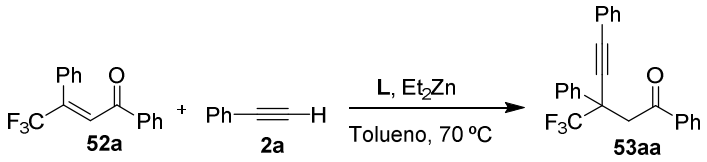
En primer lugar, se estudió la influencia de diversos ligandos de tipo (*R*)-BINOL, (*R*)-VANOL y (*R*)-VAPOL utilizando un 20% molar de ligando quiral, 7,5 equivalentes de fenilacetileno (**2a**) y 2 equivalentes de Et_2Zn 1,5 M en tolueno (Tabla 17).

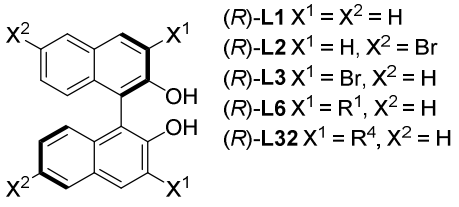
De todos los ligandos de tipo BINOL comerciales, el ligando **L6**, con dos grupos 3,5-bis(trifluorometil)fenilo en las posiciones 3,3' del sistema de BINOL proporcionó la mejor enantioselectividad (56% *ee*) en la formación de **53aa** (Tabla 17, entrada 7). Puesto que la presencia de sustituyentes electrón-atrayentes de volumen intermedio en estas posiciones del BINOL parece favorecer enantioselectividades elevadas,

preparamos el ligando **L32,** que presenta dos anillos de pentafluorofenilo,[98] el cual permitió obtener **53aa** con un 68% de rendimiento y un 70% de exceso enantiomérico (Tabla 17, entrada 10).

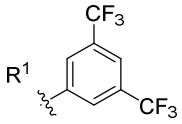
Cabe destacar que la reacción también tiene lugar en ausencia de ligando, obteniéndose el producto racémico **53aa** con un rendimiento del 50% (Tabla 17, entrada 1), lo cual indica que puede haber bastante reacción de fondo no enantioselectiva.

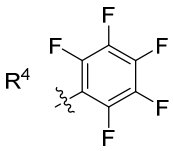
Tabla 17. Adición conjugada enantioselectiva de fenilacetileno (**2a**) a (*E*)-4,4,4-trifluoro-1,3-difenilbut-2-en-1-ona (**52a**). Screening de ligandos.[a]

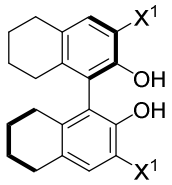




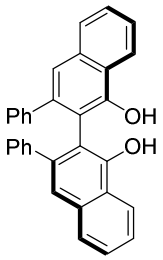
(*R*)-**L1** $X^1 = X^2 = H$
(*R*)-**L2** $X^1 = H$, $X^2 = Br$
(*R*)-**L3** $X^1 = Br$, $X^2 = H$
(*R*)-**L6** $X^1 = R^1$, $X^2 = H$
(*R*)-**L32** $X^1 = R^4$, $X^2 = H$



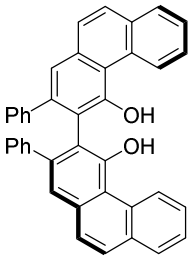




(*R*)-**L4** $X^1 = H$
(*R*)-**L5** $X^1 = Br$



(*R*)-**L9**



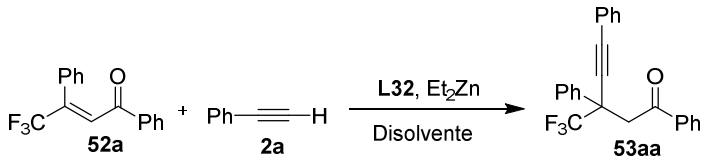
(*R*)-**L10**

	L	Rto (%)[b]	*ee* (%)[c]
1	-	50	-
2	**L1**	80	40
3	**L2**	-	-
4	**L3**	29	10
5	**L4**	-	-
6	**L5**	50	0
7	**L6**	70	56
8	**L9**	60	50
9	**L10**	46	0
10	**L32**	68	70

[a] **2a** (0,94 mmol), Et_2Zn 1,5 M en tolueno (0,13 mL, 0,25 mmol), **L** (0,025 mmol), **52a** (0,125 mmol) en tolueno, 20 h. [b] Rendimiento de producto aislado. [c] Determinado por HPLC quiral.

Con el fin de minimizar la reacción de fondo y poder aumentar el exceso enantiomérico se procedió a disminuir la temperatura de reacción. El mejor resultado se obtuvo a 37 ºC obteniéndose el producto **53aa** con un rendimiento del 53% y un 77% de exceso enantiomérico (Tabla 18, entrada 3). También se ensayaron varios co-disolventes sin obtener ninguna mejora en el rendimiento ni en el exceso enantiomérico (Tabla 18, entradas 5 y 6). La disminución de la carga catalítica al 10% provocó una disminución de rendimiento y exceso enantiomérico (Tabla 18, entrada 7). Por último, se estudió una disminución en el número de equivalentes de fenilacetileno (**2a**) o en el número de equivalentes de Et_2Zn, manteniéndose el exceso enantiomérico en ambos casos pero observándose una ligera disminución en el rendimiento (Tabla 18, entradas 8-9).

Tabla 18. Adición conjugada enantioselectiva de fenilacetileno (**2a**) a (*E*)-4,4,4-trifluoro-1,3-difenilbut-2-en-1-ona (**52a**).[a]



	L32 (% mol)	**2a** (equiv.)	Et_2Zn (equiv.)	Temp. (ºC)	Disolvente	t (h)	Rto (%)[b]	*ee* (%)[c]
1	20	7,5	2	70	tolueno	20	68	70
2	20	7,5	2	50	tolueno	20	65	70
3	20	7,5	2	37	tolueno	30	53	77
4	20	7,5	2	ta	tolueno	-	-	-
5	20	7,5	2	37	Tol/$EtNO_2$	-	-	-
6	20	7,5	2	37	Tol/CH_2Cl_2	30	35	60
7	10	7,5	2	37	tolueno	30	39	65
8	20	5	2	37	tolueno	30	40	77
9	20	7,5	1,3	37	tolueno	30	46	77

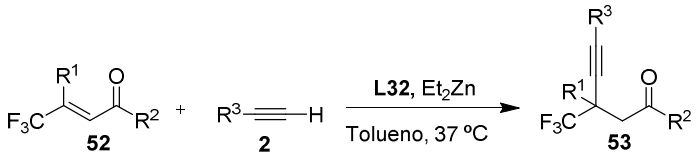
[a] **2a** (0,94 mmol), Et_2Zn 1,5 M en tolueno (0,13 mL, 0,25 mmol), **L32** (0,025 mmol), **52a** (0,125 mmol). [b] Rendimiento de producto aislado. [c] Determinado por HPLC quiral.

Así, las mejores condiciones de reacción alcanzadas consistieron en el uso de 7,5 equivalentes de alquino **2a**, 20% mol de **L32**, 2 equivalentes de Et_2Zn 1,5 M en tolueno, tolueno como disolvente y 37 ºC como temperatura de reacción.

4.7.3. Alcance y limitaciones de la reacción

A continuación, se estudió la aplicabilidad de las condiciones anteriores a diversas enonas y alquinos. Los resultados se resumen en la Tabla 19.

Tabla 19. Adición conjugada enantioselectiva de alquinos aromáticos y heteroaromáticos **2** a β-aril β-trifluorometil enonas **52**.[a]



		R^1	R^2		R^3		Rto (%)[b]	*ee* (%)[c]
1	**52a**	C_6H_5	C_6H_5	**2a**	C_6H_5	**53aa**	53	77
2	**52b**	4-MeC_6H_4	C_6H_5	**2a**	C_6H_5	**53ba**	50	78
3	**52c**	4-$MeOC_6H_4$	C_6H_5	**2a**	C_6H_5	**53ca**	50	75
4	**52d**	4-FC_6H_4	C_6H_5	**2a**	C_6H_5	**53da**	61	70
5	**52e**	3-BrC_6H_4	C_6H_5	**2a**	C_6H_5	**53ea**	35	73
6	**52f**	4-BrC_6H_4	C_6H_5	**2a**	C_6H_5	**53fa**	48	47
7[d]	**52f**	4-BrC_6H_4	C_6H_5	**2a**	C_6H_5	**53fa**	88	67
8	**52g**	2-tienilo	C_6H_5	**2a**	C_6H_5	**53ga**	70	53
9[d]	**52h**	C_6H_5	4-MeC_6H_4	**2a**	C_6H_5	**53ha**	64	62
10	**52i**	C_6H_5	4-$MeOC_6H_4$	**2a**	C_6H_5	**53ia**	70	78
11	**52j**	C_6H_5	4-ClC_6H_4	**2a**	C_6H_5	**53ja**	45	40
12[d]	**52j**	C_6H_5	4-ClC_6H_4	**2a**	C_6H_5	**53ja**	60(63)[e]	59(95)[e]
13	**52k**	C_6H_5	2-naftilo	**2a**	C_6H_5	**53ka**	50	83
14	**52a**	C_6H_5	C_6H_5	**2b**	4-$MeOC_6H_4$	**53ab**	65	80
15	**52a**	C_6H_5	C_6H_5	**2g**	3-FC_6H_4	**53ag**	51(77)[e]	74(97)[e]
16	**52a**	C_6H_5	C_6H_5	**2c**	4-FC_6H_4	**53ac**	81(77)[e]	80(99)[e]
17	**52k**	C_6H_5	2-naftilo	**2b**	4-$MeOC_6H_4$	**53kb**	86	84
18	**52k**	C_6H_5	2-naftilo	**2c**	4-FC_6H_4	**53kc**	90	90
19	**52l**	4-MeC_6H_4	2-naftilo	**2c**	4-FC_6H_4	**53lc**	82	88
20	**52m**	4-$MeOC_6H_4$	2-naftilo	**2c**	4-FC_6H_4	**53mc**	66	83
21	**52a**	C_6H_5	C_6H_5	**2e**	3-tienilo	**53ae**	44	82
22	**52k**	C_6H_5	2-naftilo	**2e**	3-tienilo	**53ke**	64	86
23	**52a**	C_6H_5	C_6H_5	**2f**	$PhCH_2CH_2$	-	-	-
24	**52a**	C_6H_5	C_6H_5	**2l**	TIPS	-	-	-

[a] **2** (0,94 mmol), Et_2Zn 1,5 M en tolueno (0,13 mL, 0,25 mmol), **L32** (0,025 mmol), **52** (0,125 mmol) en tolueno a 37 ºC, 30 h. [b] Rendimiento de producto aislado por cromatografía de columna. [c] Determinado por HPLC utilizando fases estacionarias quirales. [d] Empleando **L6** como ligando y a temperatura ambiente [e] Entre paréntesis, rendimiento y *ee* de las aguas madre después de cristalización con mezclas hexano/CH_2Cl_2.

En primer lugar, se ensayó la reacción de adición conjugada de fenilacetileno (**2a**) a diversas enonas **52b-f** con un anillo aromático en el carbono β del doble enlace, sustituido con grupos de distinta naturaleza electrónica en las posiciones *meta* y *para*. Se obtuvieron los correspondientes productos de alquinilación **53** con rendimientos moderados y excesos enantioméricos comprendidos entre 70-78% (Tabla 19, entradas 2-6). Para la enona **52f** la utilización del ligando **L32** dio lugar al producto **53fa** con un bajo rendimiento y enantioselectividad, este resultado se consiguió mejorar con el empleo del ligando **L6** llevando a cabo la reacción a temperatura ambiente, obteniendo

el correspondiente producto de alquinilación con un rendimiento elevado (88%) y un exceso enantiomérico del 67% (Tabla 19, entrada 7). La reacción también funciona con enonas que tienen un grupo heteroaromático en β como **52g** (Tabla 19, entrada 8), obteniendo el producto **53ga** con un buen rendimiento (70%) y un exceso enantiomérico moderado (53%).

A continuación, se estudió la reacción con diversas enonas que presentaban grupos electrón-atrayentes o electrón-donantes en la posición *para* del anillo aromático unido al grupo carbonilo (Tabla 19, entradas 9-12). Para las enonas **52h** y **52j** también se obtuvieron mejores resultados con el ligando **L6** que con el ligando **L32** (Tabla 19, entradas 9 y 12). La presencia de un grupo aromático voluminoso como el 2-naftilo unido al grupo carbonilo en la enona **52k** favorece la enantioselectividad (83% *ee*) aunque con un rendimiento moderado (50%) (Tabla 19, entrada 13).

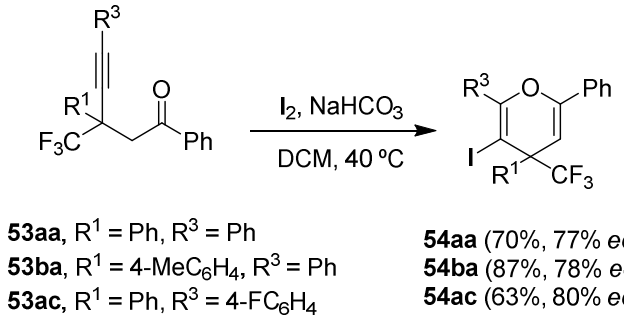
Por último, se estudió la reacción de adición conjugada de otros alquinos. Diversos fenilacetilenos sustituidos en la posición *meta* o *para* del anillo aromático con grupos de distinta naturaleza reaccionaron con la enona **52a** obteniendo los productos de alquinilación con rendimientos buenos y enantioselectividades comprendidas entre 74-80% (Tabla 19, entradas 14-16). Los resultados fueron especialmente buenos en la adición de estos alquinos a las 1-(2'-naftil) enonas **52k-m** (Tabla 19, entradas 17-20), obteniéndose el mejor resultado en la adición de (4-fluorofenil)acetileno (**2c**) a la enona **52k** que permitió obtener el producto **53kc** con 90% de rendimiento y 90% de *ee* (Tabla 19, entrada 18). También es posible la utilización de alquinos sustituidos con un anillo heterocíclico de 3-tiofeno **2e** que al reaccionar con las enonas **52a** y **52k** conduce a los correspondientes productos de alquinilación **53ae** y **53ke** con excesos enantioméricos del 82 y 86%, respectivamente (Tabla 19, entradas 21 y 22).

Cabe señalar que en algunos casos se llevó a cabo la cristalización de varios de los productos de alquinilación con mezclas de hexano-diclorometano. En todos los casos se observó la formación de cristales racémicos, produciéndose un enriquecimiento enantiomérico del producto restante en las aguas madres, cuyos excesos enantioméricos superaron el 95% (Tabla 19, entradas 12,15 y 16).

Dada la dificultad para obtener cristales de los compuestos de alquinilación **53** en forma enantioméricamente pura no ha sido posible determinar su estereoquímica absoluta, quedando pendiente para trabajo posterior a la lectura de la tesis.

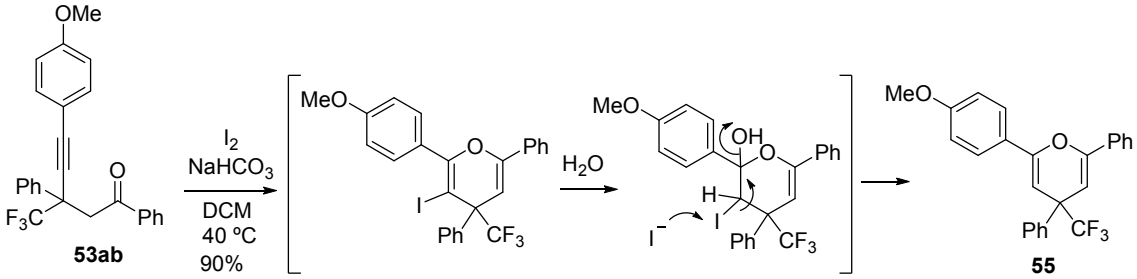
4.7.4. Transformaciones sintéticas

Al igual que ocurre con los productos de alquinilación de β-trifluorometil enonas, los productos de alquinilación **53** demostraron ser excelentes substratos para la ciclación electrofílica promovida por I_2 obteniendo los correspondientes piranos **54** con rendimientos altos (63-87%) y sin pérdida de pureza óptica (Esquema 76).



Esquema 76. Iodociclación de productos de alquinilación **53**.

Cuando se llevó a cabo la reacción de iodociclación con el compuesto **53ca** en las condiciones anteriores, sorprendentemente se obtuvo el pirano no iodado **55** (Esquema 77). Aunque no tenemos una explicación definitiva para la formación del producto **55**, una posibilidad consistiría en la hidratación del doble enlace favorecida por la presencia del anillo de *p*-metoxibenceno electrón-dador que aumentaría la reactividad del doble enlace, seguido de eliminación reductiva de ácido hipoiodoso.



Esquema 77. Iodociclación del compuesto **53ca**.

En resumen, en este capítulo hemos descrito el primer ejemplo de alquinilación conjugada enantioselectiva de enonas β,β-disustituidas descrito en la bibliografía. Una gran variedad de alquinos terminales aromáticos y heteroaromáticos puede reaccionar con β-aril β-trifluorometil enonas en presencia de dietilcinc y un ligando derivado de (*R*)-BINOL para dar los correspondientes productos con un centro estereogénico propargílico cuaternario con un sustituyente trifluorometilo. La reacción transcurre con rendimientos y excesos enantioméricos en general moderados, si bien es posible aumentar el exceso enantiomérico de los productos mediante cristalización. Los mejores resultados se obtienen con enonas sustituidas con un grupo 2-naftilo unido al grupo carbonilo. La iodociclación de los productos de alquinilación permite la síntesis de piranos quirales con un grupo trifluorometilo sobre un centro estereogénico cuaternario.

5. EXPERIMENTAL SECTION

5. EXPERIMENTAL SECTION

General Procedures

All catalytic reactions were carried out in glassware oven-dried overnight at 120 ºC. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm.

Solvents and Reagents

Analytical quality solvents were used for general purposes. The following solvents were dried and purified when needed: CH_2Cl_2, benzene and toluene were freshly distilled from CaH_2 under nitrogen. EtOAc, hexane, pentane, triethylamine and nitroethane were dried and stored on 4 Å molecular sieves. THF, dioxane and diethyl ether were freshly distilled from Na/benzophenone under nitrogen. Most reagents were commercially available and used as purchased without further purification. Ligand **L32** and Dess-Martin reagent were prepared according to procedures described in the literature.[98]

Melting points

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

Nuclear magnetic resonance (NMR)

NMR spectra were run in a Bruker Avance 300 DPX spectrometer (300MHz for ^{1}H, 75MHz for ^{13}C and 282 MHz for ^{19}F NMR). In some cases a Bruker Avance 400 spectrometer or a Bruker Avance 500 spectrometer were used, especially for NOE and NOESY experiments.

Samples were dissolved in deuterated solvents as stated, using the residual non-deuterated solvent as internal standard (δ 7.26 ppm for ^{1}H NMR and δ 77.00 ppm for ^{13}C NMR in the case of $CDCl_3$, δ 2.50 ppm for ^{1}H NMR and δ 40.76 ppm for ^{13}C NMR in the case of DMSO-d_6, δ 2.05 ppm for ^{1}H NMR in the case of acetone-d_6. For ^{19}F NMR experiments, $CFCl_3$ was used as internal standard. Chemical shifts (δ values) are given in ppm. Coupling constants (*J*) are given in Hz. The carbon multiplicity was determined by DEPT experiments.

Polarimetry

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

Mass spectrometry

Mass spectra were recorded on a Fisons Instruments VG Autospec GC 8000 series at 70 eV. Data are given in mass units and values in parentheses express the relative intensity with respect to base peak.

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

HPLC analyses

Chiral HPLC analyses were performed in an Agilent 1100 series instrument equipped with a refraction index detector or in a Hitachi Elite Lachrom instrument equipped with a Hitachi UV diode-array L-4500 detector using chiral stationary columns from Daicel. Variable mixtures of hexane and isopropanol were used as eluents. Retention times (t_r) are expressed in minutes.

Gas chromatography analyses

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

5.1. Enantioselective conjugate alkynylation of α,β-unsaturated-1,3-dicarbonyl compounds.

5.1.1. Synthesis and characterization of α,β-unsaturated-1,3-dicarbonyl compounds 1

α,β-Unsaturated-1,3-dicarbonyl compounds were synthesized according to the procedures described by Antonioletti et al.[40,41.]

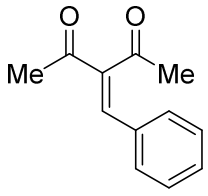
Method A

In a round bottom flask equipped with a water-separatory Dean-Stark system, the required 1,3-dicarbonyl compound (5 mmol) was dissolved in benzene (30 mL). The aldehyde (5 mmol), glacial acetic acid (0.5 mmol) and piperidine (0.5 mmol) were added. The mixture was refluxed until the substrate was consumed. The mixture was cooled, diluted with diethyl ether (30 mL) and water (15 mL). The organic layer was separated, washed with water (15 mL), 1M aqueous HCl (15 mL) and saturated aqueous $NaHCO_3$ until neutrality. The organic layer was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The compound **1** was obtained upon purification by flash chromatography eluting with hexane/ethyl acetate mixtures.

Method B

In a round bottom flask, 2,4-pentanedione (50 mmol) was dissolved in ethanol (0.13 mL) at −5 ºC. Acetaldehyde (60 mmol) and piperidine (0.6 mmol) were added. The mixture was stirred until the substrate was consumed. Then, the mixture was diluted with diethyl ether (100 mL) and water (50 mL). The organic layer was separated and washed with brine (50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The compound **1** was obtained upon vacuum distillation.

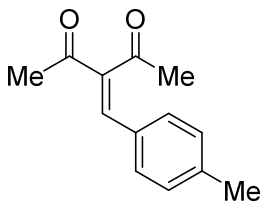
3-Benzylidenepentane-2,4-dione (1a)



1a

Yellow oil, 60% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.48 (s, 1H), 7.38 (s, 5H), 2.41 (s, 3H), 2.27 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 205.5 (C), 196.4 (C), 142.7 (C), 139.7 (CH), 132.8 (C), 130.5 (CH), 129.6 (2CH), 128.9 (2CH), 31.5 (CH_3), 26.4 (CH_3). Data consistent with the literature.[40d]

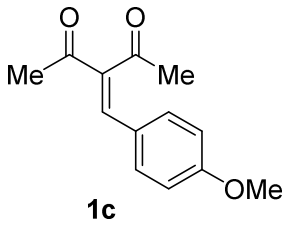
3-(4-Methylbenzylidene)pentane-2,4-dione (1b)



1b

Yellow solid, 93% yield; **mp** 39-40 °C; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.45 (s, 1H), 7.28(d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 2.40 (s, 3H), 2.36 (s, 3H), 2.28 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 205.9 (C), 196.5 (C), 141.8 (C), 141.32 (C), 139.9 (CH), 130.0 (C), 129.8 (2CH), 129.7 (2CH), 31.6 (CH_3), 26.4 (CH_3), 24.4 (CH_3). Data consistent with the literature.[99]

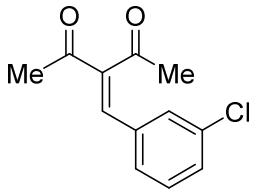
3-(4-Methoxybenzylidene)pentane-2,4-dione (1c)



1c

White solid, 90% yield; **mp** 71-72°C; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.41 (s, 1H), 7.35 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 3.83 (s, 3H), 2.39 (s, 3H), 2.31 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 206.2 (C), 196.4 (C), 161.7 (C), 140.7 (C), 139.7 (CH), 131.8 (2CH), 125.3 (C), 114.5 (2CH), 55.4 (CH_3), 31.6 (CH_3), 26.3 (CH_3). Data consistent with the literature.[100]

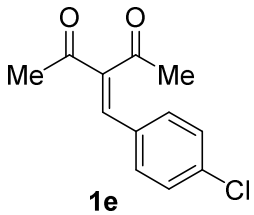
3-(3-Chlorobenzylidene)pentane-2,4-dione (1d)



1d

Yellow oil, 77% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.39-7.24 (m, 5H), 2.41 (s, 3H), 2.27 (s, 3H);**^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 204.9 (C), 196.2 (C), 143.8 (C), 137.9 (CH), 135.0 (C), 134.4 (C), 130.5 (CH), 130.2 (CH), 129.5 (CH), 127.4 (CH), 31.6 (CH_3), 26.5 (CH_3). Data consistent with the literature.[101]

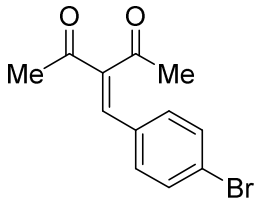
3-(4-Chlorobenzylidene)pentane-2,4-dione (1e)



1e

Yellow solid, 90% yield; **mp** 74-75 °C; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.41 (s, 1H), 7.34 (m, 4H), 2.41 (s, 3H), 2.28 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 205.3 (C), 196.2 (C), 143.2 (C), 138.2 (CH), 136.8 (C), 131.3 (C), 130.9 (2CH), 129.3 (2CH), 31.6 (CH_3), 26.5 (CH_3). Data consistent with the literature.[100]

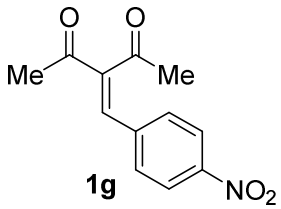
3-(4-Bromobenzylidene)pentane-2,4-dione (1f)



1f

White solid, 88% yield; **mp** 83-84 °C; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.39 (s, 1H), 7.25 (d, *J* = 8.7 Hz, 2H), 2.41 (s, 3H), 2.27 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 205.3 (C), 196.2 (C), 143.2 (C), 138.3 (CH), 132.3 (2CH), 131.8 (C), 131.0 (2CH), 125.2 (C), 31.7 (CH_3), 26.5 (CH_3). Data consistent with the literature.[101]

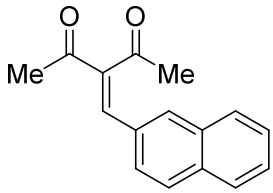
3-(4-Nitrobenzylidene)pentane-2,4-dione (1g)



1g

Yellow solid,75% yield; **mp** 87-88°C; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.24 (d, *J* = 9.0 Hz, 2H), 7.56 (d, *J* = 9.0 Hz, 2H), 7.49 (s, 1H), 2.45 (s, 3H), 2.28 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 204.2 (C), 195.9 (C), 148.5 (C), 145.6 (C), 139.2 (C), 136.4 (CH), 130.2 (2CH), 124.1 (2CH), 31.7 (CH_3), 26.7 (CH_3). Data consistent with the literature.[100]

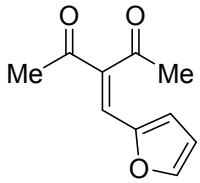
3-(Naphthalen-2-ylmethylene)pentane-2,4-dione (1h)



1h

Yellow solid, 85% yield; **mp** 73-74 °C; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.92 (d, *J* = 1.5 Hz, 1H), 7.88-7.83(m, 3H), 7.66 (s, 1H), 7.57-7.53 (m, 2H),7.45 (dd, *J* = 8.6, 1.8 Hz, 1H), 2.47 (s, 3H), 2.32 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 205.8 (C), 196.4 (C), 142.8 (C), 139.9 (CH), 134.0 (C), 133.0 (C), 130.9 (CH), 130.4 (C), 128.9 (CH), 128.7 (CH), 127.9 (CH), 127.7 (CH), 127.0 (CH), 125.7 (CH), 31.8 (CH_3), 26.6 (CH_3).

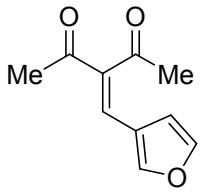
3-(Furan-2-ylmethylene)pentane-2,4-dione (1i)



1i

Yellow solid, 95% yield; **mp** 55-56 °C; **^{1}H NMR(300 MHz, $CDCl_3$)** δ 7.53 (dt, *J* = 1.8, 0.3 Hz, 1H), 7.15 (s, 1H), 6.76 (ddd, *J* = 3.6, 0.3, 0.3 Hz, 1H), 6.50 (dd, *J* = 3.6, 1.8 Hz, 1H), 2.43 (s, 3H), 2.36 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 204.4 (C), 195.8 (C), 148.8 (C), 146.5 (CH), 138.3 (C), 124.9 (CH), 118.3 (CH), 112.9 (CH), 31.4 (CH_3), 26.1 (CH_3). Data consistent with the literature.[41]

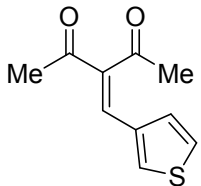
3-(Furan-3-ylmethylene)pentane-2,4-dione (1j)



1j

Oil, 85% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.71-7.70 (m, 1H), 7.41-7.40 (m, 1H), 7.25 (s, 1H), 6.40-6.39 (m, 1H), 2.36 (s, 3H), 2.35 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 205.3 (C), 196.6 (C), 146.4 (CH), 144.6 (CH), 141.1 (C), 130.2 (CH), 120.0 (C), 109.3 (CH), 31.4 (CH_3), 25.9 (CH_3); **HRMS (ESI) *m/z***: 179.0709 (M + H), $C_{10}H_{11}O_3$ requiere 179.0708.

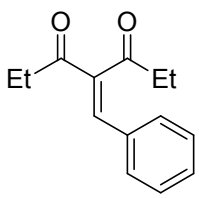
3-(Thiophen-3-ylmethylene)pentane-2,4-dione (1k)



1k

Oil, 86% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.54 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.39 (s, 1H), 7.31 (dd, *J* = 5.1, 2.7 Hz, 1H), 7.08 (dd, *J* = 5.1, 1.5 Hz, 1H), 2.36 (s, 3H), 2.32 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)**δ 205.8 (C), 196.7 (C), 141.1 (C), 134.7 (C), 132.9 (CH), 130.5 (CH), 127.2 (CH), 127.2 (CH), 31.6 (CH_3), 26.1 (CH_3).

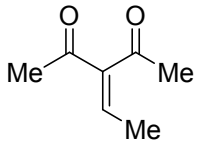
4-Benzylideneheptane-3,5-dione (1l)



1l

Oil, 90% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.52 (s, 1H), 7.38-7.32 (m, 5H), 2.74 (q, *J* = 7.2 Hz, 2H), 2.47 (q, *J* = 7.2 Hz, 2H), 1.13 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)**δ 208.6 (C), 200.0 (C), 142.2 (C), 138.5 (CH), 133.1 (C), 130.3 (CH), 129.4 (2CH), 128.8 (2CH), 37.2 (CH_2), 31.7 (CH_2), 7.9 (CH_3), 7.5 (CH_3). Data consistent with the literature.[40d]

3-Ethylidenepentane-2,4-dione (1m)



1m

Method B. Oil, 27% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 6.73 (q, *J* = 7.2 Hz, 1H), 2.21 (s, 3H), 2.21 (s, 3H), 1.81 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 203.4 (C), 196.9 (C), 146.2 (C), 141.9 (CH), 31.5 (CH_3), 26.0 (CH_3), 15.5 (CH_3). Data consistent with the literature.[40d]

5.1.2. Enantioselective conjugate addition of terminal alkynes to α,β-unsaturated-1,3-dicarbonyl compounds

5.1.2.1. General procedure for enantioselective alkynylation reaction

A 1.5 M solution of Et_2Zn in toluene (0.17 mL, 0.25 mmol) was added dropwise to a solution of (*R*)-VANOL (**L9**, 11.3 mg, 0.025 mmol) and alkyne **2** (0.94 mmol) in toluene (0.48 mL) at room temperature under nitrogen and the mixture was stirred for 1.5 h at 70 ºC. Then, the reaction mixture was cooled to room temperature. A solution of arylidene-1,3-diketone **1** (0.125 mmol) in nitroethane (1.0 mL) was added via syringe. The solution was stirred until the reaction was complete (TLC). The reaction mixture was quenched with 20% aqueous NH_4Cl (1.0 mL), extracted with CH_2Cl_2 (2x 15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:EtOAc mixtures afforded compound **3**.

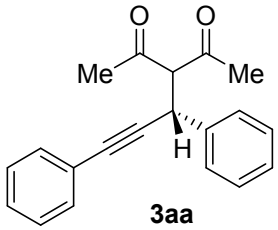
5.1.2.2. General procedure for the synthesis of the racemic products

A 1.5 M solution of Et_2Zn in toluene (0.17 mL, 0.25 mmol) was added dropwise to a solution of alkyne **2** (0.94 mmol) and (±)-BINOL (**L1**, 7.2 mg, 0.025 mmol) in toluene (0.48 mL)at room temperature under nitrogen and the mixture was stirred for 1.5 h at 70 ºC. Then, arylidene-1,3-diketone **1** (0.125 mmol) in toluene (1.0 mL) was added via syringe. The solution was stirred at 70 ºC until the reaction was complete (TLC). Racemic compounds **3** were obtained after the described work up.

5.1.2.3. Characterization of products 3

See Table 3 (Page 35) and Table 4 (page 36) for yields.

(*R*)-(+)-3-(1,3-Diphenylprop-2-ynyl)pentane-2,4-dione (3aa)



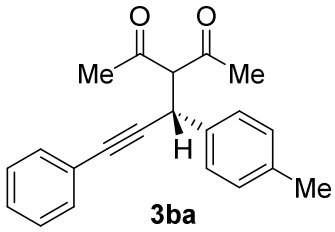
3aa

Enantiomeric excess (87%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 9.2 min, minor enantiomer t_r = 10.9 min.

mp 75-77 °C; **$[\alpha]_D^{20}$** +46.7 (*c* 0.73, $CHCl_3$, 87% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.42-7.27 (m, 10H), 4.67 (d, *J* = 11,1 Hz, 1H), 4.22 (d, *J* = 11.1 Hz, 1H), 2.39 (s, 3H), 1.93 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 201.6 (C), 201.6 (C), 138.2 (C), 131.6 (2CH), 128.9 (2CH), 128.3 (CH), 128.2 (2CH), 128.1 (2CH), 127.7 (CH), 122.6 (C), 88.0 (C), 84.9 (C), 75.6 (CH), 38.0

(CH), 31.1 (CH_3), 28.7 (CH_3); **MS (EI)***m/z* (%): 290 (M^+, 1), 248 (22), 247 (100), 191 (34), 189 (15); HRMS: 290.1303, $C_{20}H_{18}O_2$ requires 290.1307.

(*R*)-(+)-3-(3-Phenyl-1-*p*-tolylprop-2-ynyl)pentane-2,4-dione (3ba)

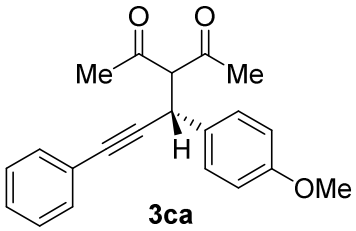


3ba

Enantiomeric excess (85%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 8.8 min, minor enantiomer t_r = 8.2 min.

Oil; **$[\alpha]_D^{20}$** +4.6 (*c* 0.40, $CHCl_3$, 85% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.38-7.33 (m, 2H), 7.30-7.26 (m, 5H), 7.14 (d, *J* = 7.8 Hz, 2H), 4.63 (d, *J* = 11.1 Hz, 1H), 4.21 (d, *J* = 11.1 Hz, 1H), 2.38 (s, 3H), 2.33 (s, 3H), 1.94 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 201.8 (C), 201.7 (C), 137.5 (C), 135.1 (C), 131.6 (2CH), 129.6 (2CH), 128.3 (CH), 128.2 (2CH), 127.9 (2CH), 122.7 (C), 88.3 (C), 84.7 (C), 75.7 (CH), 37.7 (CH), 31.1 (CH_3), 28.7 (CH_3), 21.1 (CH_3); **MS (EI)** *m/z* (%): 304 (M^+, 2.32), 262 (23), 261 (100), 205 (62), 202 (29); HRMS: 304.1471, $C_{21}H_{20}O_2$ requires 304.1463.

(*R*)-(+)-3-(1-(4-Methoxyphenyl)-3-phenylprop-2-ynyl)pentane-2,4-dione (3ca)

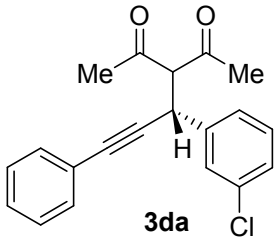


3ca

Enantiomeric excess (80%) was determined by chiral HPLC (Chiralpak AS-H), hexane-*i*PrOH 90:10, 1 mL/min, major enantiomer t_r = 15.3 min, minor enantiomer t_r = 8.2 min.

mp 93-95 °C; **$[\alpha]_D^{20}$** +8.5 (*c* 0.76, $CHCl_3$, 80% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.38-7.27 (m, 7H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.62 (d, *J* = 10.8 Hz, 1H), 4.19 (d, *J* = 10.8 Hz, 1H), 3.79 (s, 3H), 2.38 (s, 3H), 1.94 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 201.7 (2C), 159.0 (C), 131.6 (2CH), 130.1 (C), 129.2 (2CH), 128.3 (CH), 128.2 (2CH), 122.7 (C), 114.2 (2CH), 88.3 (C), 84.7 (C), 75.8 (CH), 55.2 (CH_3), 37.3 (CH), 31.2 (CH_3), 28.7 (CH_3); **HRMS (ESI)** *m/z*: 338.1755 (M + NH_4), $C_{21}H_{24}NO_3$ requires 338.1756.

(*R*)-(+)-3-(1-(3-Chlorophenyl)-3-phenylprop-2-ynyl)pentane-2,4-dione (3da)

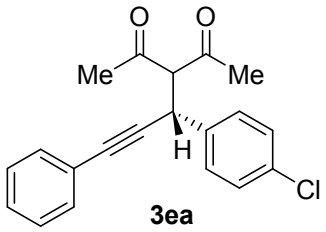


3da

Enantiomeric excess (83%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 99:01, 1 mL/min, major enantiomer t_r = 17.2 min, minor enantiomer t_r = 13.7 min.

Oil; **$[\alpha]_D^{20}$** +27.3 (*c* 2.33, $CHCl_3$, 83% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.44-7.42 (m, 1H), 7.39-7.34 (m, 3H), 7.32-7.30 (m, 2H), 7.29-7.26 (m, 3H), 4.67 (d, *J* = 10.8 Hz, 1H), 4.20 (d, *J* = 10.8 Hz, 1H), 2.38 (s, 3H), 1.99 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 201.1 (C), 201.0 (C), 140.3 (C), 134.7 (C), 131.7 (2CH), 131.6 (C), 130.1 (CH), 128.5 (CH), 128.29 (2CH), 128.27 (CH), 128.0 (CH), 126.4 (CH), 87.2 (C), 85.3 (C), 75.4 (CH), 37.4 (CH), 31.0 (CH_3), 28.7 (CH_3) ;**MS (EI)** *m/z* (%): 324 (M^+, 5.7), 306 (3), 283 (85), 281 (100), 225 (78), 189 (60); HRMS: 324.0916, $C_{20}H_{17}ClO_2$ requires 324.0917.

(*R*)-(+)-3-(1-(4-Chlorophenyl)-3-phenylprop-2-ynyl)pentane-2,4-dione (3ea)

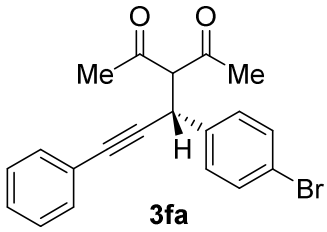


3ea

Enantiomeric excess (88%) was determined by chiral HPLC (Chiralpak AS-H), hexane-*i*PrOH 99:01, 1 mL/min, major enantiomer t_r = 12.2 min, minor enantiomer t_r = 10.0 min.

Oil; **[α]$_D^{20}$** +28.8 (*c* 0.80, $CHCl_3$, 88% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.38-7.28 (m, 10H), 4.67 (d, *J* = 10.8 Hz, 1H), 4.18 (d, *J* = 10.8 Hz, 1H), 2.38 (s, 3H), 1.97 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 201.1 (2C), 136.8 (C), 133.0 (C), 131.6 (2CH), 129.5 (2CH), 129.0 (2CH), 128.5 (CH), 128.3 (2CH), 122.4 (C), 87.5 (C), 85.2 (C), 75.6 (CH), 37.2 (CH), 31.1 (CH_3), 28.6 (CH_3); **MS (EI)** *m/z* (%): 324 (M^+, 6), 283 (90), 225 (100), 202 (47), 189 (60); HRMS: 324.0916, $C_{20}H_{17}ClO_2$ requires 324.0917.

(*R*)-(+)-3-(1-(4-Bromophenyl)-3-phenylprop-2-ynyl)pentane-2,4-dione (3fa)

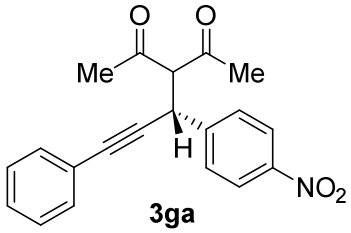


3fa

Enantiomeric excess (88%) was determined by chiral HPLC (Chiralpak AS-H), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 9.5 min, minor enantiomer t_r = 8.3 min.

mp 101-103 °C; **[α]$_D^{20}$** +42.4 (*c* 0.94, $CHCl_3$, 88% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.37-7.34 (m, 2H), 7.31-7.28 (m, 5H), 4.66 (d, *J* = 10.8 Hz, 1H), 4.18 (d, *J* = 11.1 Hz, 1H), 2.37 (s, 3H), 2.00 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 201.1 (2C), 137.3 (C), 132.0 (2CH), 131.6 (2CH), 129.9 (2CH), 128.5 (CH), 128.3 (2CH), 122.4 (C), 121.7 (C), 87.4 (C), 85.2 (C), 75.5 (CH), 37.2 (CH), 31.1 (CH_3), 28.6 (CH_3); **HRMS (ESI)** *m/z*: 386.0733/ 388.0718 (M + NH_4) 97.7/100.0, $C_{20}H_{21}BrNO_2$ requires 386.0756/388.0735.

(*R*)-(+)-3-(1-(4-Nitrophenyl)-3-phenylprop-2-ynyl)pentane-2,4-dione (3ga)

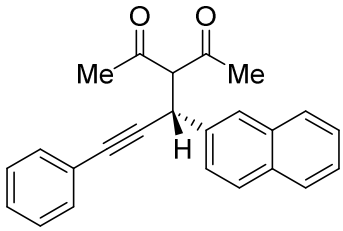


3ga

Enantiomeric excess (82%) was determined by chiral HPLC (Chiralpak AS-H), hexane-*i*PrOH 90:10, 1 mL/min, major enantiomer t_r = 23.3 min, minor enantiomer t_r = 17.5 min.

Oil; **[α]$_D^{20}$** +26.9 (*c* 0.26, $CHCl_3$, 82% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.20 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.39-7.29 (m, 5H), 4.82 (d, *J* = 10.8 Hz, 1H), 4.23 (d, *J* = 10.8 Hz, 1H), 2.40 (s, 3H), 2.01 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 200.5 (2C), 147.4 (C), 145.7 (C), 131.6 (2CH), 129.3 (2CH), 128.8 (CH), 128.4 (2CH), 124.0 (2CH), 122.0 (C), 86.4 (C), 86.0 (C), 75.2 (CH), 37.2 (CH), 30.9 (CH_3), 28.7 (CH_3); **MS (EI)** *m/z* (%): 335 (M^+, 100), 320 (46), 318 (35), 292 (28); HRMS: 335.1171, $C_{20}H_{17}NO_4$ requires 335.1158.

(*R*)-(–)-3-(1-Naphthalen-3-yl)-3-phenylprop-2-ynyl)pentane-2,4-dione (3ha)

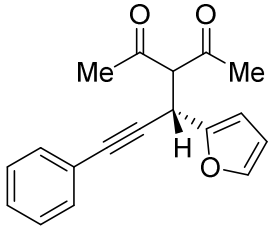


3ha

Enantiomeric excess (80%) was determined by chiral HPLC (Chiralcel OD-H), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 8.4 min, minor enantiomer t_r = 9.3 min.

mp 123-125 °C; **$[\alpha]_D^{20}$** –0.6 (*c* 0.87, $CHCl_3$, 80% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.86-7.81 (m, 5H), 7.56 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.51-7.48 (m, 2H), 7.41-7.37 (m, 2H), 7.31-7.28 (m, 2H), 4.86 (d, *J* = 11.1 Hz, 1H), 4.35 (d, *J* = 10.8 Hz, 1H), 2.43 (s, 3H), 1.94 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 201.6 (C), 201.5 (C), 135.5 (C), 133.3 (C), 132.7 (C), 131.7 (2CH), 128.8 (CH), 128.4 (C), 128.4 (CH), 128.3 (2CH), 128.0 (CH), 127.6 (CH), 127.2 (CH), 126.2 (CH), 125.7 (CH), 122.6 (C) 88.0 (C), 85.1 (C), 75.5 (CH), 38.1 (CH), 31.1 (CH_3), 28.7 (CH_3); **MS (EI)** *m/z* (%): 340 (M^+, 8.4), 322 (23), 297 (100), 242 (41), 241 (86), 239 (48); HRMS: 340.1475, $C_{24}H_{20}O_2$ requires 340.1463.

(*S*)-(+)-3-(1-(Furan-2-yl)-3-phenylprop-2-ynyl)pentane-2,4-dione (3ia)

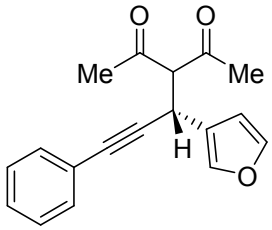


3ia

Enantiomeric excess (80%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 99:01, 1 mL/min, major enantiomer t_r = 16.7 min, minor enantiomer t_r = 13.6 min.

Oil; **$[\alpha]_D^{20}$** +16.6 (*c* 0.41, $CHCl_3$, 80% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.40-7.28 (m, 6H), 6.35-6.29 (m, 2H), 4.85 (d, *J* = 10.3 Hz, 1H), 4.32 (d, *J* = 10.3 Hz, 1H), 2.34 (s, 3H), 2.15 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 201.1 (2C), 150.5 (C), 142.4 (CH), 131.7 (2CH), 128.5 (CH), 128.3 (2CH), 122.4 (C), 110.6 (CH), 107.6 (CH), 85.1 (C), 84.4 (C), 72.0 (CH), 31.5 (CH), 29.9 (CH_3), 29.4 (CH_3); **MS (EI)** *m/z* (%): 280 (M^+, 1.2), 237 (100), 238 (19), 181 (30), 152 (24); HRMS: 280.1098, $C_{18}H_{16}O_3$ requires 280.1099.

(*S*)-(+)-3-(1-(Furan-3-yl)-3-phenylprop-2-ynyl)pentane-2,4-dione (3ja)

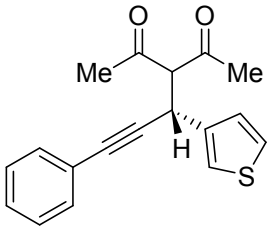


3ja

Enantiomeric excess (83%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 99:01, 1 mL/min, major enantiomer t_r = 17.7 min, minor enantiomer t_r = 15.6 min.

Oil; **$[\alpha]_D^{20}$** +36.1 (*c* 0.79, $CHCl_3$, 83% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.42-7.28 (m, 7H), 6.40 (dd, *J* = 1.8, 0.9 Hz, 1H), 4.67 (d, *J* = 10.5 Hz, 1H), 4.12 (d, *J* = 10.5 Hz, 1H), 2.35 (s, 3H), 2.11 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 201.6 (C), 201.5 (C), 143.4 (CH), 140.3 (CH), 131.6 (2CH), 128.4 (CH), 128.3 (2CH), 122.6 (C), 122.5 (C), 109.8 (CH), 87.1 (C), 84.0 (C), 74.6 (CH), 30.8 (CH), 28.7 (CH_3), 28.5 (CH_3); **MS (EI)** *m/z* (%): 280 (M+, 2.3), 238 (19), 237 (100), 181 (24), 152 (17); HRMS: 280.1105, $C_{18}H_{16}O_3$ requires 280.1099.

(*S*)-(+)-3-(3-Phenyl-1-(thiophen-3-yl)prop-2-ynyl)pentane-2,4-dione (3ka)

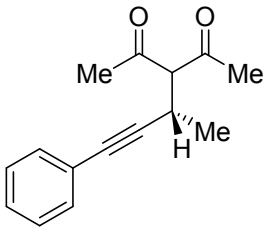


3ka

Enantiomeric excess (82%) was determined by chiral HPLC (Chiralpak AS-H), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 12.1 min, minor enantiomer t_r = 10.3 min.

Oil; **[α]$_D^{20}$** +9.8 (*c* 0.75, $CHCl_3$, 82% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.39-7.27 (m, 6H), 7.22 (ddd, *J* = 3.0, 1.2, 0.3 Hz, 1H), 7.11 (d, *J* = 5.1, 1.2 Hz, 1H), 4.83 (d, *J* = 10.5 Hz, 1H), 4.19 (d, *J* = 10.8 Hz, 1H), 2.36 (s, 3H), 2.02 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 201.7 (C), 201.5 (C), 138.2 (C), 131.6 (2CH), 131.6 (C), 128.4 (CH), 128.3 (2CH), 127.0 (CH), 126.4 (CH), 122.8 (CH), 87.6 (C), 84.5 (C), 75.0 (CH), 33.1 (CH), 30.9 (CH_3), 28.7 (CH_3); **HRMS (ESI)** *m/z*: 297.0936 (M + H), $C_{18}H_{217}O_2S$ requires 297.0949.

(*S*)-(+)-3-(4-Phenylbut-3-yn-2-yl)pentane-2,4-dione (3la)

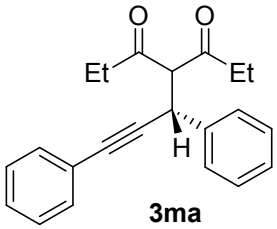


3la

Enantiomeric excess (64%) was determined by chiral HPLC (Chiralcel OD-H), hexane-*i*PrOH 99:01, 1 mL/min, major enantiomer t_r = 9.8 min, minor enantiomer t_r = 10.6 min.

Oil; **[α]$_D^{20}$** +77.5 (*c* 0.93, $CHCl_3$, 64% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.36-7.25 (m, 5H), 3.81 (d, *J* = 10.2 Hz, 1H), 3.53 (dq, *J* = 10.2, 6.8 Hz, 1H), 2.29 (d, *J* = 0.3 Hz, 3H), 2.25 (d, *J* = 0.3 Hz, 3H), 1.24 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 202.5 (C), 202.2 (C), 131.5 (2CH), 128.2 (2CH), 128.1 (CH), 122.8 (C), 90.1 (C), 83.0 (C), 74.6 (CH), 30.4 (CH), 28.9 (CH_3), 26.3 (CH_3), 19.1(CH_3); **MS (EI)** *m/z* (%): 228 (M^+, 0.6), 186 (15), 185 (100), 128 (14); HRMS: 228.1143, $C_{15}H_{16}O_2$ requires 280.1150.

(*R*)-(+)-4-(1,3-Diphenylprop-2-ynyl)heptane-3,5-dione (3ma)

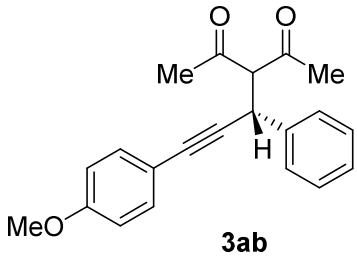


3ma

Enantiomeric excess (76%) was determined by chiral HPLC (Chiralpak IC), hexane-*i*PrOH 99:01, 1 mL/min, major enantiomer t_r = 9.2 min, minor enantiomer t_r = 10.5 min.

mp 68-70 °C; **[α]$_D^{20}$**+33.8 (*c* 0.39, $CHCl_3$, 74% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.41-7.26 (m, 10H), 4.71 (d, *J* = 10.8 Hz, 1H), 4.23 (d, *J* = 10.8 Hz, 1H), 2.84-2.67 (m, 2H), 2.34 (dq, *J* = 18.6, 7.2 Hz, 1H), 1.96 (dq, *J* = 18.6, 7.2 Hz, 1H), 1.10 (t, *J* = 7.2 Hz, 3H), 0.78 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 204.1 (C), 204.1 (C), 138.4 (C), 131.6 (2CH), 128.8 (2CH), 128.2 (CH), 128.2 (2CH), 128.1 (2CH), 127.7 (CH), 122.8 (C), 88.4 (C), 84.7 (C), 74.2 (CH), 38.3 (CH), 37.6 (CH_2), 35.0 (CH_2), 7.6 (CH_3), 7.1 (CH_3); **MS (EI)** *m/z* (%): 318 (M^+, 1), 262 (23), 261 (100), 192 (18), 191 (52); HRMS: 318.1633, $C_{22}H_{22}O_2$ requires 318.1620.

(*R*)-(+)-3-(3-(4-Methoxyphenyl)-1-phenylprop-2-ynyl)pentane-2,4-dione (3ab)

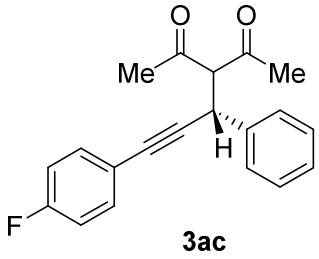


3ab

Enantiomeric excess (84%) was determined by chiral HPLC (Chiralpak AS-H), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 14.0 min, minor enantiomer t_r = 10.5 min.

mp 93-95 °C; **[α]$_D^{20}$** +11.7 (*c* 0.39, $CHCl_3$, 84% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.42-7.28 (m, 7H), 6.80 (d, *J* = 8.9 Hz, 2H), 4.65 (d, *J* = 10.9 Hz, 1H), 4.20 (d, *J* = 10.9 Hz, 1H), 3.79 (s, 3H), 2.38 (s, 3H), 1.92 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 201.8 (C), 201.7 (C), 159.6 (C), 138.4 (C), 133.0 (2CH), 128.8 (2CH), 128.1 (2CH), 127.7 (CH), 114.8 (C), 113.8 (2CH), 86.5 (C), 84.8 (C), 75.7 (CH), 55.3 (CH_3), 38.1 (CH), 31.1 (CH_3), 28.7 (CH_3); **MS (EI)** *m/z* (%): 320 (M^+, 1.3), 278 (22), 277 (100), 221 (16); HRMS: 320.1436, $C_{21}H_{20}O_3$ requires 320.1412.

(*R*)-(+)-3-(3-(4-Fluorophenyl)-1-phenylprop-2-ynyl)pentane-2,4-dione (3ac)

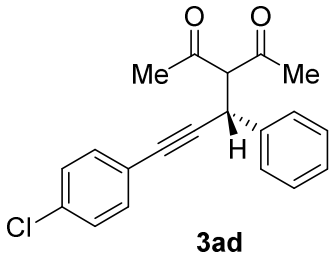


3ac

Enantiomeric excess (86%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 99:01, 1 mL/min, major enantiomer t_r = 20.2 min, minor enantiomer t_r = 16.7 min.

mp 88-90 °C; **[α]$_D^{20}$** +23.3 (*c* 0.99, $CHCl_3$, 86% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.38-7.26 (m, 7H), 6.97 (t, *J* = 8.7 Hz, 2H), 4.65 (d, *J* = 10.8 Hz, 1H), 4.21 (d, *J* = 11.1 Hz, 1H), 2.37 (s, 3H), 1.93 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 201.5 (C), 201.5 (C), 162.5 (d, $J_{C\text{-}F}$= 248.1 Hz, C), 138.0 (C), 133.5 (d, $J_{C\text{-}F}$= 8.4 Hz, 2CH), 128.9 (2CH), 128.1 (2CH), 127.8 (CH), 118.7 (d, $J_{C\text{-}F}$ = 3.0 Hz, C), 115.5 (d, $J_{C\text{-}F}$= 21.9 Hz, 2CH), 87.8 (C), 83.8 (C), 75.6 (CH), 38.0 (CH), 31.1 (CH_3), 28.6 (CH_3); **MS (EI)** *m/z* (%): 308 (M^+, 3.3), 266 (46), 265 (100), 209 (61); HRMS: 308.1219, $C_{20}H_{17}FO_2$ requires 308.1213.

(*R*)-(+)-3-(3-(4-Chlorophenyl)-1-phenylprop-2-ynyl)pentane-2,4-dione (3ad)

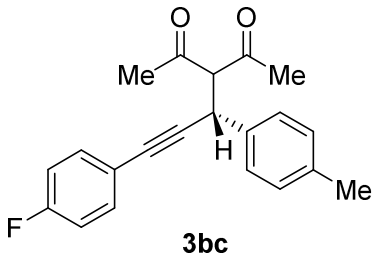


3ad

Enantiomeric excess (87%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 99:01, 1 mL/min, major enantiomer t_r = 23.0 min, minor enantiomer t_r = 18.7 min.

Oil; **[α]$_D^{20}$** +8.8 (*c* 0.22, $CHCl_3$, 88% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.45-7.27 (m, 9H), 4.66 (d, *J* = 10.8 Hz, 1H), 4.21 (d, *J* = 10.8 Hz, 1H), 2.37 (s, 3H), 1.97 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 201.5 (C), 201.4 (C), 137.9 (C), 133.1 (C), 132.9 (2CH), 128.9 (2CH), 128.6 (2CH), 128.1 (2CH), 127.8 (CH), 126.6 (C), 89.1 (C), 83.8 (C), 75.5 (CH), 38.0 (CH), 31.1 (CH_3), 28.7 (CH_3); **HRMS (ESI)** *m/z*: 347.0807 (M + Na), $C_{20}H_{17}Cl\ NaO_2$ requires 347.0815.

(*R*)-(+)-3-(3-(4-Fluorophenyl)-1-p-tolylprop-2-ynyl)pentane-2,4-dione (3bc)

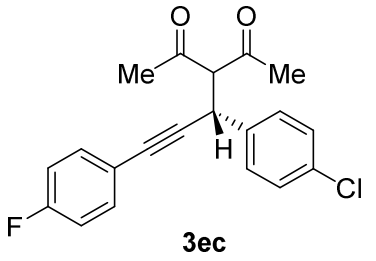


3bc

Enantiomeric excess (88%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 10.6 min, minor enantiomer t_r = 9.4 min.

Oil; **[α]$_D^{20}$** +12.0 (*c* 0.57, $CHCl_3$, 88% *ee*); **^{1}H RMN (300 MHz, $CDCl_3$)** δ 7.38-7.25 (m, 4H), 7.18-7.12 (m, 2H), 6.96 (t, *J* = 8.8 Hz, 2H), 4.62 (d, *J* = 10.9 Hz, 1H), 4.20 (d, *J* = 10.9 Hz, 1H), 2.37 (s, 3H), 2.32 (s, 3H), 1.94 (s, 3H); **^{13}C RMN (75.5 MHz, $CDCl_3$)** δ 201.7 (C), 201.6 (C), 162.5 (d, $J_{C\text{-}F}$ = 249.5 Hz, C), 137.5 (C), 135.0 (C), 133.5 (d, $J_{C\text{-}F}$= 8.4 Hz, 2CH), 129.6 (2CH), 127.9 (2CH), 118.8 (d, $J_{C\text{-}F}$= 3.4 Hz, C), 115.5 (d, $J_{C\text{-}F}$= 22.2 Hz, 2CH), 88.0 (C), 83.6 (C), 75.6 (CH), 37.6 (CH), 31.1 (CH_3), 28.6 (CH_3), 21.0 (CH_3); **HRMS (ESI)** *m/z*: 345.1262 (M + Na), $C_{21}H_{19}FNaO_2$ requires 345.1267.

(*R*)-(+)-3-(1-(4-Chlorophenyl)-3-(4-fluorophenyl)prop-2-ynyl)pentane-2,4-dione (3ec)

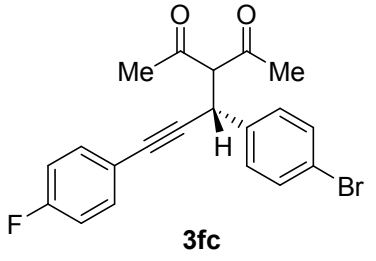


3ec

Enantiomeric excess (86%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 12.3 min, minor enantiomer t_r = 10.2 min.

Oil; **[α]$_D^{20}$** +14.7 (*c* 1.18, $CHCl_3$, 86% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.36-7.31 (m, 6H), 6.98 (t, *J* = 8.8 Hz, 2H), 4.65 (d, *J* = 10.8 Hz, 1H), 4.17 (d, *J* = 10.8 Hz, 1H), 2.36 (s, 3H), 1.97 (d, *J* = 0.3 Hz, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 201.1 (2C), 162.6 (d, $J_{C\text{-}F}$= 249.8 Hz, C), 138.1 (C), 133.6 (d, $J_{C\text{-}F}$= 8.4 Hz, 2CH), 132.9 (C), 129.5 (2CH), 129.0 (2CH), 118.4 (C), 115.6 (d, $J_{C\text{-}F}$= 22.1 Hz, 2CH), 87.2 (C), 84.1 (C), 75.5 (CH), 37.1 (CH), 31.1 (CH_3), 28.6 (CH_3); **HRMS (ESI)** *m/z*: 343.0881/345.0852 (M + H) 100.0/31.7, $C_{20}H_{17}ClFNO_2$ requires 343.0901/345.0872.

(*R*)-(+)-3-(1-(4-Bromophenyl)-3-(4-fluorophenyl)prop-2-ynyl)pentane-2,4-dione (3fc)



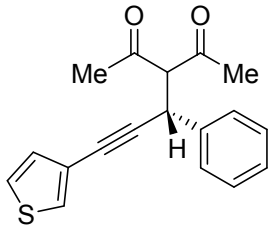
3fc

Enantiomeric excess (86%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 12.9 min, minor enantiomer t_r = 11.1 min.

Oil; **[α]$_D^{20}$** +14.2 (*c* 0.90, $CHCl_3$, 86% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.48-7.44 (m, 2H), 7.35-7.28 (m, 4H), 6.98 (t, *J* = 8.7 Hz, 2H), 4.64 (d, *J* = 10.9 Hz, 1H), 4.16 (d, *J* = 10.9 Hz, 1H), 2.36 (s, 3H), 1.97 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 201.0 (2C), 162.6 (d, $J_{C\text{-}F}$= 249.9 Hz, C), 138.7 (C), 133.5 (d, $J_{C\text{-}F}$ = 8.3 Hz, 2CH), 132.0 (2CH), 129.9 (2CH), 121.0 (C), 118.4 (d, $J_{C\text{-}F}$= 3.7 Hz, C), 115.6 (d, $J_{C\text{-}F}$= 22.1 Hz, 2CH), 87.1 (d, $J_{C\text{-}F}$= 1.1 Hz, C), 84.2

(C), 75.5 (CH), 37.2 (CH), 31.1 (CH_3), 28.6 (CH_3); **HRMS (ESI)** *m/z*: 404.0661/406.0645 (M + NH_4) 98.8/100.0, $C_{20}H_{20}BrFNO_2$ requires 404.0661/406.0641.

(*R*)-(+)-3-(1-Phenyl-3-(thiophen-3-yl)prop-2-ynyl)pentane-2,4-dione (3ae)

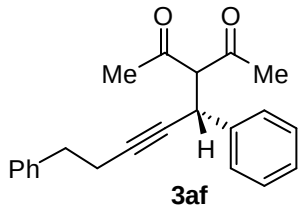


3ae

Enantiomeric excess (80%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 12.1 min, minor enantiomer t_r = 9.7 min.

mp 92-94 °C; **$[\alpha]_D^{20}$** +13.2 (*c* 0.37, $CHCl_3$, 80% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.41-7.28 (m, 6H), 7.23 (dd, *J* = 4.8, 3 Hz, 1H), 7.04 (dd, *J* = 5.1, 1.2 Hz, 1H), 4.65 (d, *J* = 11.1 Hz, 1H), 4.21 (d, *J* = 11.1 Hz, 1H), 2.38 (s, 3H), 1.91 (d, *J* = 0.3 Hz, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 201.5 (2C), 138.1 (C), 129.8 (CH), 128.9 (2CH), 128.8 (CH), 128.1 (2CH), 127.7 (CH), 125.2 (CH), 121.6 (C), 87.6 (C), 80.0 (C), 75.5 (CH), 38.1 (CH), 31.1 (CH_3), 28.7 (CH_3); **MS (EI)** *m/z* (%): 296 (M^+, 1.4), 254 (21), 253 (100), 197 (42); HMRS: 296.0885, $C_{18}H_{16}O_2S$ requires 296.0871.

(*R*)-3-(1,5-Diphenylpent-2-yn-1-yl)pentane-2,4-dione (3af)



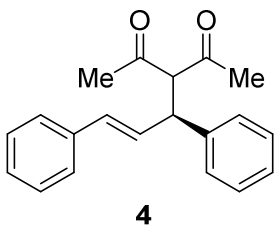
3af

Enantiomeric excess (27%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 99:01, 1 mL/min, major enantiomer t_r = 15.7 min, minor enantiomer t_r = 12.5 min.

Oil; **$[\alpha]_D^{20}$** +7.1 (*c* 0.52, $CHCl_3$, 27% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.31-7.16 (m, 10H), 4.38 (td, *J* = 11.0, 2.2 Hz, 1H), 4.03 (d, *J* = 11.0 Hz, 1H), 2.77 (t, *J* = 7.3 Hz, 2H), 2.47 (td, *J* = 7.3, 2.2 Hz, 2H), 2.38 (s, 3H), 1.91 (d, *J* = 0.3 Hz, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 201.92 (C), 201.87 (C), 140.5 (C), 138.7 (C), 128.7 (2CH), 128.5 (2CH), 128.4 (2CH), 128.0 (2CH), 127.5 (CH), 126.3 (CH), 84.4 (C), 79.6 (C), 75.8 (CH), 37.6 (CH), 34.9 (CH_2), 31.0 (CH_3), 28.5 (CH_3),20.7 (CH_2); **HRMS (ESI)** *m/z*: 319.1691 (M + H), $C_{22}H_{23}O_2$ requires 319.1698.

5.1.2.4. Determination of the absolute stereochemistry of compound 3aa

(*S*,*E*)-3-(1,3-Diphenylallyl)pentane-2,4-dione (4)



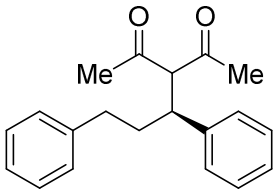
4

A solution of [PdCl(η^3-C_3H_5)]$_2$ (0.7 mg, 2 µmol) and (*R*)-BINAP (2.7 mg, 4.4 µmol) in CH_2Cl_2 (0.4 mL) was stirred for 30 min at room temperature under nitrogen. A solution of 1,3-diphenyl-2-propenyl acetate (100 mg, 0.4mmol) in CH_2Cl_2 (1.2 mL), pentane-2,4-dione (0.12 mL, 1.2 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (0.3 mL, 1.2 mmol) and a pinch of KOAc was added in this order. The mixture was stirred at room temperature until the reaction was complete (TLC). The reaction mixture was quenched with NH_4Cl sat. (1.0 mL) and was diluted in diethyl ether (40 mL). Organic layer washed with brine (2 x 15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash

chromatography on silica gel afforded compound **4** (105 mg, 90%). Enantiomeric excess (89%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 90:10, 1 mL/min, major enantiomer t_r = 9.7 min, minor enantiomer t_r = 9.1 min.

Oil; **$[\alpha]_D^{20}$** +9.8 (*c* 1, EtOH, 89% *ee*), Lit.[45] **$[\alpha]_D^{20}$** +6.8 (*c* 1, EtOH) for 94% *ee* for the *S* enantiomer; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.35-7.19 (m, 10H), 6.43 (d, *J* = 15.7 Hz, 1H), 6.20 (ddd, *J* = 15.8, 4.8, 3.1 Hz, 1H), 4.34 (m, 2H), 2.26 (s, 3H), 1.93 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 202.8 (C), 202.7 (C), 140.1 (C), 136.5 (C), 131.7 (CH), 129.2 (CH), 129.0 (2CH), 128.5 (2CH), 127.9 (2CH), 127.7 (CH), 127.2 (CH), 127.3 (2CH), 74.5 (CH), 49.1 (CH), 30.0 (CH_3), 29.7 (CH_3).

(*S*)-3-(1,3-Diphenylpropyl)pentane-2,4-dione (5)

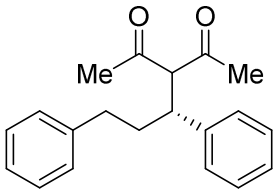


(*S*)-(+)-5

A solution of **4** (48.5 mg, 0.166 mmol) in abs EtOH (15.3 mL) was stirred under hydrogen atmosphere in the presence of Pd/$CaCO_3$ (5%) (21.4 mg) for 30 min. Then, the reaction mixture was filtered through silica gel eluting with EtOAc. The solvent was removed under reduced pressure to give compound (*S*)-(+)-**5** (48.5 mg, 99%) having identical ^{1}H and ^{13}C NMR spectra as the hydrogenation product of **3aa** but opposite retention times and optical rotation sign. Enantiomeric excess (89%) was determined by chiral HPLC (Chiralpak IC), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r (*S*) = 9.7 min, minor enantiomer t_r (*R*) = 8.2 min.

$[\alpha]_D^{20}$ +36.8 (*c* 0.83, $CHCl_3$, 89% *ee*).

(*R*)-3-(1,3-Diphenylpropyl)pentane-2,4-dione (5)



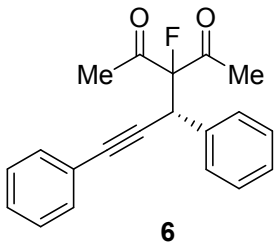
(*R*)-(-)-5

A solution of **3aa** (18.2 mg, 0.063 mmol) in abs EtOH (5.8 mL) was stirred under hydrogen atmosphere in the presence of 5% Pd/$CaCO_3$ (8 mg) for 1 h. Then, the reaction mixture was filtered through silica gel eluting with EtOAc. The solvent was removed under reduced pressure to give compound (*R*)-(-)-**5** (18.1 mg, 99%). Enantiomeric excess (85%) was determined by chiral HPLC (Chiralpak IC), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r (*R*) = 8.3 min, minor enantiomer t_r (*S*) = 9.9 min.

Oil; **$[\alpha]_D^{20}$**–32.9 (*c* 0.78, $CHCl_3$, 85% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.36-7.31 (m, 2H), 7.28-7.14 (m, 6H), 7.05-7.03 (m, 2H), 4.09 (d, *J* = 11.5 Hz, 1H), 3.50-3.14 (m, 1H), 2.40-2.30 (m, 2H), 2.18 (s, 3H), 1.87-1.80 (m, 2H), 1.79 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 203.4 (C), 203.2 (C), 141.3 (C), 140.3 (C), 128.8 (2CH), 128.4 (2CH), 128.3 (2CH), 128.3 (2CH), 127.2 (CH), 126.0 (CH), 76.3 (CH), 45.4 (CH), 36.1 (CH_2), 33.0 (CH_2), 29.9 (CH_3), 29.4 (CH_3); **HRMS (ESI)** *m/z*: 295.1678 (M + H), $C_{20}H_{23}O_2$ requires 295.1698.

5.1.2.5. Synthetic transformations

(*R*)-(–)-3-(1,3-Diphenylprop-2-ynyl)-3-fluoropentane-2,4-dione (6)

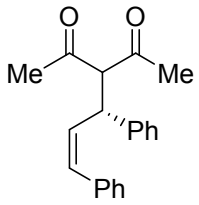


6

A 1.5 M solution of Et_2Zn in toluene (0.17 mL, 0.25 mmol) was added dropwise to a solution of ligand **L9** (11.3 mg, 0.025 mmol) and alkyne **2a** (0.1 mL, 0.94 mmol) in toluene (0.48 mL)at room temperature under nitrogen and the mixture was stirred for 1.5 h at 70 ºC. Then, the reaction mixture was cooled to room temperature. A solution of arylidene-1,3-diketone **1a** (23.5 mg, 0.125 mmol) in nitroethane (1.0 mL) was added via syringe. The solution was stirred for 4 h. NFSI (122 mg, 0.375 mmol) was added in one portion, and the reaction mixture was stirred for 72 h at room temperature, then was quenched with 20% aqueous NH_4Cl (1.0 mL), extracted with CH_2Cl_2 (2x 15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded compound **6** (18.5 mg, 48%). Enantiomeric excess (87%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 9.8 min, minor enantiomer t_r = 7.6 min.

Oil; **[α]$_D^{20}$**–39.3 (*c* 0.45, $CHCl_3$, 87% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.45-7.29 (m, 10H), 4.94 (d, *J* = 30.3 Hz, 1H), 2.47 (d, *J* = 4.8 Hz, 3H), 1.86 (d, *J* = 5.7 Hz, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 200.9 (d, $J_{C\text{-}F}$ = 29.3 Hz, C), 199.4 (d, $J_{C\text{-}F}$ = 26.7 Hz, C), 133.8 (C), 131.7 (2CH), 129.7 (2CH), 128.6 (2CH), 128.5 (CH), 128.3 (CH), 128.3 (2CH), 122.4 (C), 107.1 (d, $J_{C\text{-}F}$ = 211.1 Hz, C), 85.4 (C), 84.8 (C), 43.9 (d, $J_{C\text{-}F}$ = 19.6 Hz, CH), 27.2 (s,CH_3), 26.9 (s,CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −174.2 (s, F); **HRMS (ESI)** *m/z*: 309.1279 (M+ H), $C_{20}H_{18}FO_2$ requires 309.1291.

(*R*)-(+)-3-((*Z*)-1,3-Diphenylallyl)pentane-2,4-dione (7)

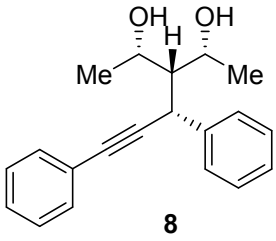


7

A solution of **3aa** (16.6 mg, 0.098 mmol) in benzene (1 mL) was stirred in the presence of Lindlar's catalyst (3.7 mg) under hydrogen atmosphere for 1 h. Then, the reaction mixture was filtered through a pad of Celite® with EtOAc. The solvent was removed under reduced pressure to give **7** (16.5 mg, 99%). Enantiomeric excess (87%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 90:10, 1 mL/min, major enantiomer t_r = 5.9 min, minor enantiomer t_r = 6.8 min.

mp 58-60 °C; **[α]$_D^{20}$** +389.3 (*c* 0.53, $CHCl_3$, 87% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.37-7.23 (m, 10H), 6.57 (d, *J* = 11.4 Hz, 1H), 5.81 (t, *J* = 11.1 Hz, 1H), 4.62 (t, *J* = 10.8 Hz, 1H), 4.11 (d, *J* = 11.1 Hz, 1H), 1.97 (s, 3H), 1.82 (d, *J* = 0.3 Hz, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 203.2 (C), 203.0 (C), 140.9 (C), 136.2 (C), 131.1 (CH), 130.6 (CH), 129.1 (2CH), 128.6 (2CH), 128.4 (2CH), 127.8 (2CH), 127.4 (CH), 127.1 (CH), 76.4 (CH), 44.2 (CH), 31.3 (CH_3), 27.9 (CH_3); **HRMS (ESI)** *m/z*: 310.1806 (M + NH_4), $C_{20}H_{24}NO_2$ requires 310.1807.

(2*R*,3*r*,4*S*)-(–)-3-((*R*)-1,3-Diphenylprop-2-yn-1-yl)pentane-2,4-diol (8)

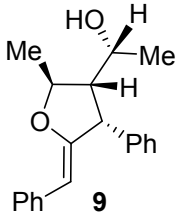


8

A 1 M solution of $LiAlH_4$ in Toluene (0.46 mL, 0.46 mmol) was added dropwise to a solution of **3aa** (33.5 mg, 0.12 mmol) in THF (1 mL) at 0 ºC under nitrogen. The reaction mixture was allowed to reach room temperature. After 1 h, the reaction was quenched with water (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The organic layer was washed with brine (10 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography gave **8** (25.5 mg, 86%) and 3.6 mg of a minor diastereomer.

Oil; **$[\alpha]_D^{20}$** –3.1 (*c* 0.42, $CHCl_3$); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.53-7.44 (m, 4H), 7.38-7.30 (m, 5H), 7.28-7.25 (m, 1H), 4.49 (d, *J* = 5.1 Hz, 1H), 4.25-4.17 (m, 2H), 2.25-2.13 (m, 2H), 2.07-2.02 (m, 1H), 1.37 (d, *J* = 4.8 Hz, 3H), 1.35(d, *J* = 4.5 Hz, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 141.0 (C), 131.4 (2CH), 128.5 (2CH), 128.3 (2CH), 128.1 (CH), 127.8 (2CH), 126.7 (CH), 122.8 (C), 90.0 (C), 85.9 (C), 63.9 (CH), 68.6 (CH), 56.7 (CH), 34.9 (CH), 21.8 ($2CH_3$);**HRMS (ESI)** *m/z*: 295.1704 (M + H), $C_{20}H_{23}O_2$ requires 295.1698.

(*R*)-(–)-1-((2*S*,3*S*,4*R*)-5-((*Z*)-Benzylidene)2-methyl-4-phenyltetrahydrofuran-3-yl)ethan-1-ol (9)

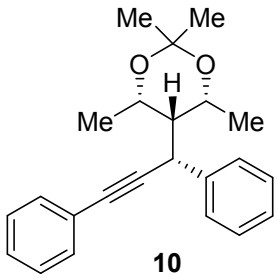


9

To a solution of **8** (11.4 mg, 0.039 mmol) in THF (0.2 mL) was added Ag(OTf) (0.5 mg, 2 µmol) at 0 ºC under nitrogen atmosphere and the mixtures was stirred for 1 h. Then, the reaction mixture was filtered through silica gel eluting with (H_5:$AcOEt_5$) afforded compound **9** (77%). Enantiomeric excess (8.8 mg, 87%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 90:10, 1 mL/min, major enantiomer t_r = 6.8 min, minor enantiomer t_r = 11.9 min.

Oil; **$[\alpha]_D^{20}$** –41.6 (*c* 0.39, $CHCl_3$, 87% *ee*); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.48 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.37-7.31 (m, 4H), 7.30-7.21 (m, 3H), 7.05 (t, *J* = 7.6 Hz, 1H), 4.67 (d, *J* = 2.0 Hz, 1H), 4.52 (dq, *J* = 8.8, 6.4 Hz, 1H), 4.14 (dd, *J* = 10.8, 2.0 Hz, 1H), 3.98 (m, 1H), 2.16 (ddd, *J* = 10.4, 8.8, 4.0 Hz, 1H), 1.56 (d, *J* = 6.4 Hz, 3H), 1.36 (br s, OH), 1.09 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 161.2 (C), 141.9 (C), 136.9 (C), 128.9 (2CH), 128.8 (2CH), 128.1 (2CH), 127.2 (2CH), 127.1 (CH), 124.7 (CH), 99.0 (CH), 79.7 (CH), 66.9 (CH), 59.7 (CH), 51.9 (CH), 21.8 (CH_3), 20.7 (CH_3); **HRMS (ESI)** *m/z*: 295.1690 (M + H), $C_{20}H_{23}O_2$ requires 295.1698.

(4*S*,5*r*,6*R*)-5-((*R*)-1,3-Diphenylprop-2-yn-1-yl)-2,2,4,6-tetramethyl-1,3-dioxane (10)



10

A solution of diol **8** (30 mg, 0.10 mmol) in 2,2-dimethoxypropane (1 mL) and a catalytic amount of *p*-toluenesulfonic acid was stirred in presence of molecular sieve 5 Å at room temperature. After 1 h, the reaction was diluted with EtOAc (10 mL), washed with saturated $NaHCO_3$ (5 mL), brine (10 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography eluting with hexane-EtOAc (9:1) gave **10** (26 mg, 76%).

Oil; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.56 (d, *J* = 7.5 Hz, 2H), 7.51-7.47 (m, 2H), 7.35-7.26 (m, 5H), 7.22 (t, *J* = 7.2 Hz, 1H), 4.39 (d, *J* = 3.6 Hz, 1H), 4.28-4.19 (m, 2H), 1.87 (dt, *J* = 3.6, 2.9 Hz, 1H), 1.46 (s, 3H), 1.42 (s, 3H), 1.28 (d, *J* = 6.6 Hz, 3H), 1.24 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 142.1 (C), 131.2 (2CH), 128.4 (2CH), 127.9 (2CH), 127.9 (2CH), 127.2 (CH), 126.1 (CH), 124.2 (C), 98.9 (C), 91.1 (C), 84.6 (C), 70.0 (CH), 69.3 (CH), 48.8 (CH), 32.1 (CH_3), 29.4 (CH_3), 20.2 (CH), 19.6 (CH_3), 19.5 (CH_3); **HRMS (ESI)** *m/z*: 335.2010 (M + H), $C_{23}H_{27}O_2$ requires 335.2011.

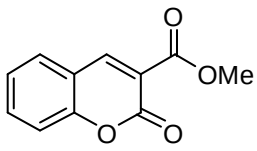
5.2. Enantioselective conjugate alkynylation of 3-alcoxycarbonyl coumarins

5.2.1. Synthesis and characterization of 3-alcoxycarbonyl coumarins 11-14

3-Alcoxycarbonyl coumarins **11-14** were synthesized according to the procedure described in the literature.[51]

The required salicylaldehyde (5 mmol), dialkyl malonate or *tert*-butyl methyl malonate (5 mmol), piperidine (50 µL, 5 mol %) and acetic acid (30 µL, 5 mol %) were dissolved in benzene (30 mL). The mixture was heated under reflux with a water-separatory Dean-Stark system until the reaction was complete (TLC). Then, it was cooled to room temperature and quenched with H_2O (10 mL), extracted with EtOAc (2 ×25 mL). The organic layers were washed with 1 M HCl (15 mL), saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:EtOAc mixtures afforded 3-alcoxycarbonyl coumarins.

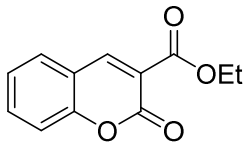
Methyl 2-oxo-2*H*-chromene-3-carboxylate (11a)



11a

White solid, 85% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.54 (s, 1H), 7.66-7.59 (m, 2H), 7.33 (d, *J* = 7.6 Hz, 2H), 3.93 (s, 3H);**^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 163.6 (C), 156.6 (C), 156.1 (C), 149.1 (CH), 134.4 (CH), 129.5 (CH), 124.8 (CH), 117.8 (C), 117.8 (C), 116.7 (CH), 52.8 (CH_3). Data consistent with the literature.[51]

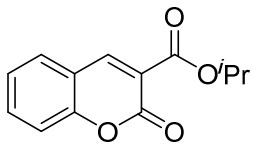
Ethyl 2-oxo-2*H*-chromene-3-carboxylate (12a)



12a

White solid, 82% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.48 (s, 1H), 7.63-7.57 (m, 2H), 7.32-7.26 (m, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H);**^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 162.9 (C), 156.6 (C), 155.0 (C), 148.4 (CH), 134.2 (CH), 129.4 (CH), 124.7 (CH), 118.1 (C), 117.7 (C), 116.6 (CH), 61.8 (CH_2), 14.1 (CH_3). Data consistent with the literature.[51]

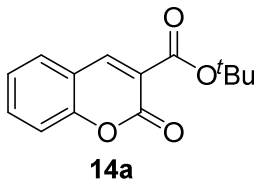
Isopropyl 2-oxo-2*H*-chromene-3-carboxylate (13a)



13a

White solid, 77% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.42 (s, 1H), 7.62-7.55 (m, 2H), 7.31-7.28 (m, 2H), 5.26-5.18 (m, 1H), 1.35 (s, 3H), 1.33 (s, 3H);**^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 162.3 (C), 156.6 (C), 156.0 (C), 147.9 (CH), 134.1 (CH), 129.4 (CH), 124.7 (CH), 118.7 (C), 117.8 (C), 116.7 (CH), 69.6 (CH), 21.7 ($2CH_3$).

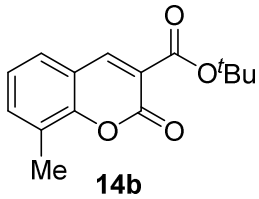
***tert*-Butyl 2-oxo-2*H*-chromene-3-carboxylate (14a)**



14a

White solid, 88% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.38 (s, 1H), 7.64-7.57 (m, 2H), 7.34-7.28 (m, 2H), 1.60 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 161.9 (C), 156.8 (C), 155.0 (C), 147.4 (CH), 133.9 (CH), 129.3 (CH), 124.6 (CH), 119.6 (C), 117.9 (C), 116.6 (CH), 82.8 (C), 28.1 ($3CH_3$). Data consistent with the literature.[51]

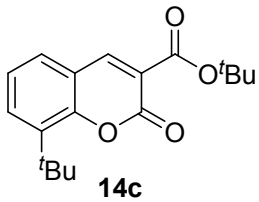
***tert*-Butyl 8-methyl-2-oxo-2*H*-chromene-3-carboxylate (14b)**



14b

White solid, 86% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.34 (s, 1H), 7.45-7.41 (m, 2H), 7.19 (t, *J* = 7.6 Hz, 2H), 2.43 (s, 3H), 1.59 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 162.0 (C), 156.9 (C), 153.3 (C), 147.6 (CH), 136.2 (CH), 127.0 (CH), 126.2 (C), 124.2 (CH), 119.2 (C), 117.6 (C), 82.6 (C), 28.1 ($3CH_3$), 15.3 (CH_3). Data consistent with the literature.[51]

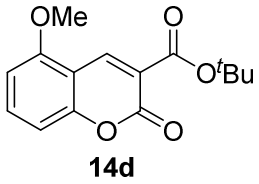
***tert*-Butyl 8-(*tert*-butyl)-2-oxo-2*H*-chromene-3-carboxylate (14c)**



14c

White solid, 83% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.39 (s, 1H), 7.60 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.43 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 1.60 (s, 9H), 1.49 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 162.2 (C), 156.4 (C), 153.8 (C), 148.6 (CH), 138.0 (C), 131.5 (CH), 127.7 (CH), 124.2 (CH), 118.7 (C), 118.4 (C), 82.6 (C), 34.9 (C), 29.7 ($3CH_3$), 28.1 ($3CH_3$). Data consistent with the literature.[51]

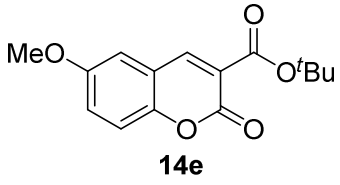
***tert*-Butyl 5-methoxy-2-oxo-2*H*-chromene-3-carboxylate (14d)**



14d

White solid, 76% yield; **mp** 182-183 °C; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.74 (d, *J* = 0.7 Hz, 1H), 7.51 (t, *J* = 8.4 Hz, 1H), 6.88 (dt, *J* = 8.4, 0.7 Hz, 1H), 6.71 (dd, *J* = 8.4, 0.7 Hz, 1H), 3.95 (s, 3H), 1.59 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 162.2 (C), 157.2 (C), 157.0 (C), 156.0 (C), 142.9 (CH), 134.8 (CH), 117.2 (C), 108.9 (C), 108.8 (CH), 105.1 (CH), 82.4 (C), 56.1 (CH_3), 28.1 ($3CH_3$).

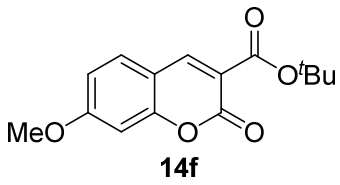
***tert*-Butyl 6-methoxy-2-oxo-2*H*-chromene-3-carboxylate (14e)**



14e

White solid, 80% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.34 (s, 1H), 7.28-7.25 (m, 1H), 7.19 (dd, *J* = 9.1, 2.9 Hz, 1H), 6.98 (d, *J* = 2.8 Hz, 1H), 3.85 (s, 3H), 1.59 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 162.0 (C), 157.1 (C), 156.1 (C), 149.6 (C), 147.3 (CH), 122.2 (CH), 119.8 (CH), 118.2 (C), 117.8 (CH), 110.5 (CH), 82.8 (C), 55.9 (CH_3), 28.1 ($3CH_3$). Data consistent with the literature.[51]

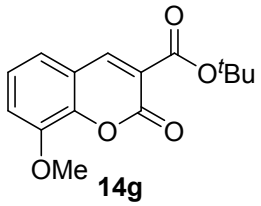
***tert*-Butyl 7-methoxy-2-oxo-2*H*-chromene-3-carboxylate (14f)**



14f

White solid, 82% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.37 (s, 1H), 7.47 (d, *J* = 8.7 Hz, 1H), 6.87 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.79 (d, *J* = 2.4 Hz, 1H), 3.89 (s, 3H), 1.58 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 164.8 (C), 162.2 (C), 157.3 (C), 157.2 (C), 148.0 (CH), 130.3 (CH), 115.4 (C), 113.4 (CH), 111.6 (C), 100.2 (CH), 82.3 (C), 55.9 (CH_3), 28.1 ($3CH_3$). Data consistent with the literature.[51]

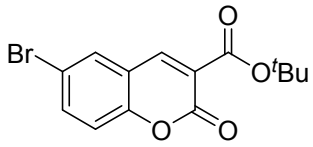
***tert*-Butyl 8-methoxy-2-oxo-2*H*-chromene-3-carboxylate (14g)**



14g

White solid, 84% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.40 (s, 1H), 7.30 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.21 (d, *J* = 0.5 Hz, 1H), 7.18 (d, *J* = 1.7 Hz, 1H), 4.00 (s, 3H), 1.64 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 161.8 (C), 156.2 (C), 147.6 (CH), 146.9 (C), 144.7 (C), 124.5 (CH), 120.4 (CH), 119.7 (C), 118.5 (C), 115.4 (CH), 82.7 (C), 56.2 (CH_3), 28.0 ($3CH_3$). Data consistent with the literature.[102]

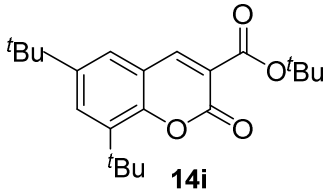
***tert*-Butyl 6-bromo-2-oxo-2*H*-chromene-3-carboxylate (14h)**



14h

White solid, 84% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.29 (s, 1H), 7.75-7.67 (m, 2H), 7.23 (d, *J* = 8.7 Hz, 1H), 1.60 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 161.5 (C), 156.1 (C), 153.8 (C), 145.9 (CH), 136.5 (CH), 131.4 (CH), 120.9 (C), 119.4 (C), 118.4 (CH), 117.2 (C), 83.2 (C), 28.1 ($3CH_3$). Data consistent with the literature.[51]

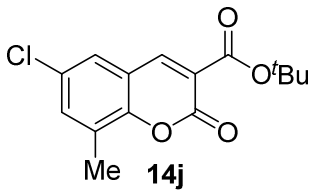
***tert*-Butyl 6,8-di-*tert*-butyl-2-oxo-2*H*-chromene-3-carboxylate (14i)**



14i

White solid, 78% yield; **mp** 129-130 °C; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.39 (s, 1H), 7.65 (d, *J* = 2.3 Hz, 1H), 7.38 (d, *J* = 2.3 Hz, 1H), 1.60 (s, 9H), 1.50 (s, 9H), 1.35 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 162.3 (C), 156.8 (C), 151.9 (C), 149.1 (CH), 146.9 (C), 137.3 (C), 129.3 (CH), 123.8 (CH), 118.3 (C), 117.9 (C), 82.4 (C), 35.1 (C), 34.7 (C), 31.3 ($3CH_3$), 29.7 ($3CH_3$), 28.1 ($3CH_3$).

***tert*-Butyl 6-chloro-8-methyl-2-oxo-2H-chromene-3-carboxylate (14j)**



14j

White solid, 79% yield; **mp** 121-122 °C; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.27 (s, 1H), 7.42-7.39 (m, 2H), 2.42 (s, 3H), 1.59 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 161.6 (C), 156.3 (C), 151.8 (C), 146.4 (CH), 134.7 (CH), 129.3 (C), 128.3 (C), 125.8 (CH), 120.3 (C), 118.5 (C), 83.0 (C), 28.0 ($3CH_3$), 15.3 (CH_3).

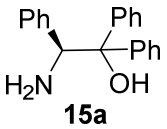
5.2.2. Synthesis and characterization of ligands L13-L22

5.2.2.1. Synthesis of chiral amino alcohols 15

The syntheses of the required chiral amino alcohols **15** were achieved using a procedure similar to that described in the literature.[52]

$SOCl_2$ (1.2 mL, 16.5 mmol) was added dropwise to a solution of the required amino acid (7.5 mmol) in methanol (6 mL).The mixture was heated at reflux temperature for 1.5 h and then the solvent and volatiles were removed under reduced pressure. The resulting solid was added in two portions to a ca 2 M solution of the required Grignard reagent (45 mmol) in diethyl ether at 0 °C under nitrogen. The cooling bath was then removed and the solution was stirred at rt for 5 h. Then, it was carefully poured into ice and acidified with 6 M aqueous HCl (15 mL). The mixture was filtered and the solid washed with diethyl ether and dissolved in 2 M methanolic NaOH (60 mL) and concentrated. The resulting solid was partitioned with CH_2Cl_2 (40 mL) and water (40 mL). The organic layer was washed with water (3×10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give desired amino alcohol **15**.

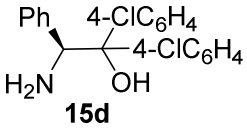
(*S*)-2-Amino-1,1,2-triphenylethan-1-ol (15a)



15a

White solid, 65% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.78 (m, 2H), 7.44-7.39 (m, 2H), 7.31-7.26 (m, 1H), 7.15-7.11 (m, 7H), 7.08-7.02 (m, 3H), 5.02 (s, 1H), 1.71 (br s, NH_2); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 146.5 (C), 143.9 (C), 140.0 (C), 128.6 (2CH), 128.5 (2CH), 127.4 (2CH), 127.3 (2CH), 127.2 (CH), 127.0 (CH), 126.5 (2CH), 126.2 (CH), 126.0 (2CH), 79.5 (C), 61.8 (CH). Data consistent with the literature.[104]

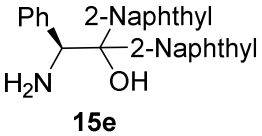
(*S*)-2-Amino-1,1-bis(4-chlorophenyl)-2-phenylethan-1-ol (15d)



15d

White solid, 78% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.70-7.67 (m, 2H), 7.42-7.39 (m, 2H), 7.19-7.13 (m, 5H), 7.04 (s, 4H), 4.95 (s, 1H), 1.63 (br s, NH_2); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 144.7 (C), 142.1 (C), 139.4 (C), 133.2 (C), 132.3 (C), 128.7 (2CH), 128.5 (2CH), 127.9 (2CH), 127.7 (2CH), 127.6 (3CH), 127.5 (2CH), 78.9 (C), 61.6 (CH).

(*S*)-2-Amino-1,1-di(naphthalene-2-yl)-2-phenylethan-1-ol (15e)

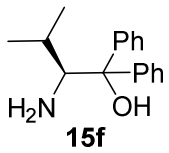


15e

Brown solid, 50% yield; **mp** 144-145 °C; **$[\alpha]_D^{20}$** –4.9 (*c* 1.0, $CHCl_3$); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.29 (s, 1H), 7.95 (dd, J = 7.0, 2.3 Hz, 1H), 7.88-7.83 (m, 3H), 7.67-7.60 (m, 3H), 7.57-7.48 (m, 3H), 7.36-7.30 (m, 3H), 7.22 (dd, *J* = 7.5, 2.1 Hz, 2H), 7.12-7.04 (m, 3H), 5.30 (s, 1H), 5.07 (br s, OH), 1.74 (br s, NH_2); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 143.9 (C), 141.2 (C), 139.9 (C), 133.1 (C), 132.8 (C), 132.4 (C), 132.0 (C), 128.6 (2CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.5 (2CH), 127.3 (CH), 127.2 (CH), 126.8 (CH), 126.2 (CH), 126.1 (CH), 125.6 (CH), 125.5 (CH), 125.5 (CH), 125.1

(CH), 124.6 (CH), 124.5 (CH), 79.9 (C), 61.4 (CH); **HRMS (ESI)** *m/z*: 390.1855 (M + H), $C_{28}H_{24}NO$ requires 390.1858.

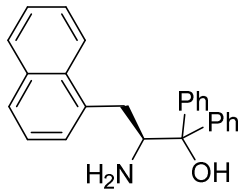
(*S*)-2-Amino-3-methyl-1,1-diphenylbutan-1-ol (15f)



15f

White solid, 42% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.71-7.66 (m, 2H), 7.59-7.56 (m, 2H), 7.41-7.32 (m, 4H), 7.28-7.21 (m, 2H), 3.92 (d, *J* = 2.2 Hz, 1H), 1.83 (m, 1H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 148.0 (C), 144.9 (C), 128.4 (2CH), 128.0 (2CH), 126.6 (CH), 126.2 (CH), 125.9 (2CH), 125.5 (2CH), 79.6 (C), 60.1 (CH), 27.8 (CH), 23.0 (CH_3), 16.1 (CH_3). Data consistent with the literature.[104]

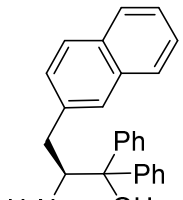
(*S*)-2-Amino-3-(naphthalen-1-yl)-1,1-diphenylpropan-1-ol (15g)



15g

Brown solid, 57% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.89-7.86 (m, 1H), 7.77-7.74 (m, 3H), 7.69-7.66 (m, 2H), 7.53-7.25 (m, 10H), 7.23-7.18 (m, 1H), 4.33 (dd, *J* = 10.8, 2.5 Hz, 1H), 3.13 (dd, , *J* = 14.0, 2.4 Hz, 1H), 2.89 (dd, *J* = 14.1, 10.8 Hz, 1H), 1.35 (br s, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 146.9 (C), 144.3 (C), 135.7 (C), 134.1 (C), 132.2 (C), 128.8 (CH), 128.5 (2CH), 128.3 (2CH), 127.3 (CH), 126.80 (CH), 126.75 (CH), 125.9 (2CH), 125.7 (CH), 125.5 (2CH), 125.4 (CH), 123.9 (CH), 78.7 (C), 56.8 (CH), 33.7 (CH_2). Data consistent with the literature.[105]

(*S*)-2-Amino-3-(naphthalen-2-yl)-1,1-diphenylpropan-1-ol (15h)



15h

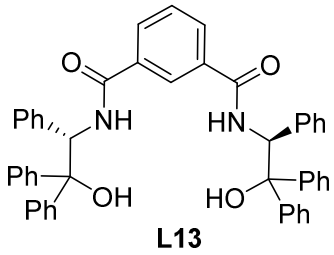
Brown solid, 62% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.85-7.80 (m, 3H), 7.71-7.65 (m, 5H), 7.52-7.46 (m, 2H), 7.41-7.32 (m, 5H), 7.27-7.19 (m, 2H), 4.31 (dd, *J* = 10.7, 2.7 Hz, 1H), 2.83 (dd, , *J* = 13.9, 2.4 Hz, 1H), 2.66 (dd, *J* = 13.9, 10.8 Hz, 1H), 1.30 (br s, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 146.9 (C), 144.4 (C), 137.1 (C), 133.5 (C), 132.2 (C), 128.5 (2CH), 128.4 (CH), 128.3 (2CH), 127.63 (CH), 127.6 (CH), 127.4 (CH), 127.3 (CH), 126.8 (CH), 126.6 (CH), 126.2 (CH), 125.8 (2CH), 125.5 (CH), 125.4 (2CH), 78.5 (C), 57.9 (CH), 37.0 (CH_2). Data consistent with the literature.[105]

5.2.2.2. Synthesis of bis(hydroxyamide) ligands L13-L22

The syntheses of bis(hydroxyamide) ligands were achieved using a modification of the procedure described in the literature.[106]

A solution of isophthaloyl dichloride (203 mg, 1.0 mmol) in THF (1 mL) was added dropwise to a solution of amino alcohol **15** (2.0 mmol) and triethylamine (0.35 mL, 2.5 mmol) in THF (18 mL) at 0 °C under nitrogen. Then, the reaction mixture was stirred at rt until the reaction was complete (TLC). The reaction mixture was filtered and most of the solvent evaporated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane: EtOAc mixtures afforded compounds **L13-L22**.

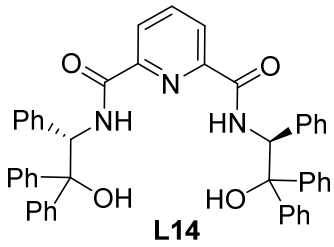
N^1,N^3-Bis((*S*)-2-hydroxy-1,2,2-triphenylethyl)isophthalamide (L13)



L13

White solid, 95% yield; **mp** 256-258 °C; **$[\alpha]_D^{20}$** –313.4 (*c* 1, THF); **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 8.75 (d, *J* = 8.9 Hz, 2H), 8.00 (s, 1H), 7.72 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 4H), 7.53-7.47 (m, 1H), 7.31 (t, *J* = 7.5 Hz, 4H), 7.25-7.20 (m, 6H), 7.13-7.01 (m, 16H), 6.24 (s, 2H), 6.10 (d, *J* = 8.9 Hz, 2H); **^{13}C NMR (75.5 MHz, DMSO-*d*$_6$)** δ 165.3 (2C), 146.7 (2C), 144.8 (2C), 139.3 (2C), 134.7 (2C), 129.8 (2CH), 129.2 (4CH), 128.5 (CH), 128.1 (4CH), 127.4 (4CH), 126.9 (4CH), 126.8 (2CH), 126.5 (2CH), 126.1 (CH), 126.0 (4CH), 125.8 (4CH), 79.7 (2C), 59.7 (2CH); **HRMS (ESI)** *m/z*: 709.3059 (M + H), $C_{48}H_{41}N_2O_4$ requires 709.3066.

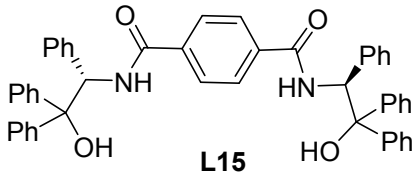
N^2,N^6-Bis((*S*)-2-hydroxy-1,2,2-triphenylethyl)pyridine-2,6-dicarboxamide (L14)



L14

White solid, 93% yield; **^{1}H NMR (500 MHz, CDCl$_3$)** δ 8.91 (d, *J* = 9.0 Hz, 2H), 8.13 (d, *J* = 7.7 Hz, 2H), 7.88 (t, *J* = 7.7 Hz, 1H), 7.74 (dd, *J* = 8.4, 1.1 Hz, 4H), 7.39 (t, *J* = 7.8 Hz, 4H), 7.30 (dd, *J* = 10.6, 4.2 Hz, 2H), 7.25-7.08 (m, 17H), 6.94-6.93 (m, 4H), 6.10 (d, *J* = 9.0 Hz, 2H), 3.24 (s, 2H). Data consistent with the literature.[106]

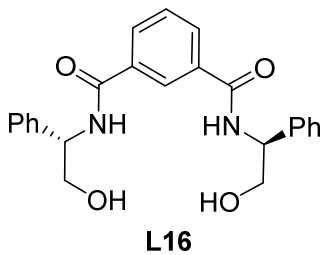
N^1,N^4-Bis((*S*)-2-hydroxy-1,2,2-triphenylethyl)terephthalamide (L15)



L15

White solid, 90% yield; **mp** 274-276 °C; **$[\alpha]_D^{20}$** –203.4 (*c* 0.55, DMSO); **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 8.65 (d, *J* = 8.4 Hz, 2H), 7.60 (s, 4H), 7.54 (d, *J* = 7.7 Hz, 2H), 7.28-7.01 (m, 30H), 6.15 (s, 2H), 6.03(d, *J* = 8.6 Hz, 2H); **^{13}C NMR (75.5 MHz, DMSO-*d*$_6$)** δ 165.2 (2C), 146.7 (2C), 144.7 (4C), 133.0 (2C), 129.2 (4CH), 128.0 (4CH), 127.4 (4CH), 127.1 (4CH), 126.9 (4CH), 126.7 (2CH), 126.5 (2CH), 126.0 (4CH), 126.0 (2CH), 125.8 (4CH), 79.8 (2C), 73.5 (2CH); **HRMS (ESI)** *m/z*: 709.3055 (M + H), $C_{48}H_{41}N_2O_4$ requires 709.3066.

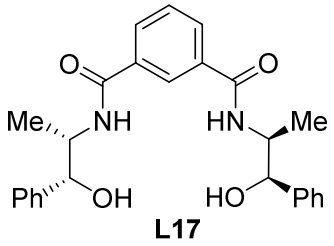
N^1,N^3-Bis((*S*)-2-hydroxy-1-phenylethyl)isophthalamide (L16)



L16

White solid, 72% yield; **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 8.87 (d, *J* = 8.1 Hz, 2H), 8.40 (t, *J* = 1.6 Hz, 1H), 8.05 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.42-7.40 (m, 4H), 7.33 (dd, *J* = 10.4, 4.8 Hz, 4H), 7.25-7.22 (m, 2H), 5.11 (td, *J* = 8.1, 5.5 Hz, 2H), 4.96 (t, *J* = 5.8 Hz, 2H), 3.75 (ddd, *J* = 11.0, 8.2, 6.0 Hz, 2H), 3.68 (dt, *J* = 11.1, 5.6 Hz, 2H); **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 165.9 (2C), 141.3 (2C), 134.9 (2C), 130.0 (2CH), 128.1 (4CH), 127.0 (4CH), 126.8 (3CH), 126.7 (CH), 64.5 ($2CH_2$), 56.1 (2CH); **HRMS (ESI)** *m/z*: 405.1809 (M + H), $C_{24}H_{25}N_2O_4$ requires 405.1814.

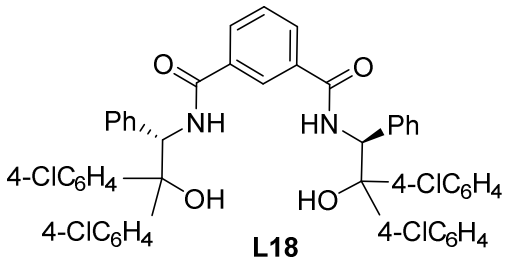
N^1,N^3-Bis((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)isophthalamide (L17)



L17

White solid, 56% yield;**^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.07 (s, 1H), 7.78-7.76 (m, 2H), 7.38-7.26 (m, 10H), 6.71 (bs, 2H), 5.05 (s, 2H), 4.45 (bs, 2H), 3.90 (bs, 2H), 1.74 (bs, 2H), 1.09 (d, *J* = 6.7 Hz, 6H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 166.9 (2C), 140.8 (2C), 134.5 (2C), 129.9 (2CH), 128.8 (CH), 128.3 (4CH), 127.6 (2CH), 126.1 (4CH), 125.4 (CH), 75.7 (2CH), 51.6 (2CH), 13.7 ($2CH_3$). Data consistent with the literature.[107]

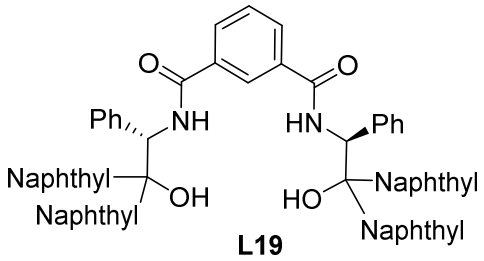
N^1,N^3-Bis((*S*)-2,2-bis(4-chlorophenyl)-2-hydroxy-1-phenylethyl)isophthalamide (L18)



L18

White solid, 90% yield; **mp** 178-181 °C; **$[\alpha]_D^{20}$** –258.2 (*c* 1, MeOH); **^{1}H NMR (300 MHz, DMSO-d_6)** δ 8.75 (d, *J* = 9.0 Hz, 2H), 8.00 (s, 1H), 7.75 (dd, *J* = 7.7, 1.2 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 4H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 4H), 7.20 (dd, *J* = 21.4, 8.7 Hz, 8H), 7.10 (s, 10H), 6.45 (s, 2H), 6.07 (d, *J* = 9 Hz, 2H); **^{13}C NMR (75.5 MHz, DMSO-d_6)** δ 165.3 (2C), 145.2 (2C), 143.5 (2C), 138.8 (2C), 134.5 (2C), 131.7 (2C), 131.0 (2C), 129.9 (2CH), 128.6 (CH), 128.1 (4CH), 128.0 (4CH), 127.8 (4CH), 127.5 (4CH), 127.1 (4CH), 126.8 (2CH), 126.2 (CH), 79.3 (2C), 59.4 (2CH); **HRMS (ESI)** *m/z*: 845.1500 (M + H), $C_{48}H_{37}Cl_4N_2O_4$ requires 845.1507.

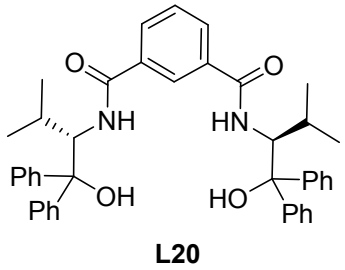
N^1,N^3-Bis((*S*)-2-hydroxy-2,2-di(naphthalen-2-yl)-1-phenylethyl)isophthalamide (L19)



L19

White solid, 67% yield; **mp** 210-212 °C; **$[\alpha]_D^{20}$** –265.5 (*c* 1, MeOH); **^{1}H NMR (300 MHz, DMSO-d_6)** δ 8.86 (d, *J* = 8.8 Hz, 2H), 8.20 (s, 2H), 8.05 (s, 1H), 7.87-7.65 (m, 18H), 7.56 (dd, *J* = 8.8, 1.6 Hz, 2H), 7.47-7.35 (m, 9H), 7.17-7.14 (m, 4H), 7.03-7.01 (m, 6H), 6.56 (s, 2H), 6.44 (d, *J* = 8.9 Hz, 2H); **^{13}C NMR (75.5 MHz, DMSO-d_6)** δ 165.4 (2C), 144.1 (2C), 142.3 (2C), 139.4 (2C), 134.7 (2C), 132.6 (2C), 132.4 (2C), 131.8 (2C), 131.4 (2C), 130.8 (2CH), 129.7 (CH), 129.2 (4CH), 128.5 (CH), 128.1 (2CH), 128.0 (2CH), 127.5 (2CH), 127.3 (2CH), 127.2 (2CH), 127.0 (4CH), 126.5 (2CH), 126.2 (2CH), 126.0 (2CH), 125.9 (2CH), 125.8 (2CH), 124.8 (2CH), 124.6 (2CH), 124.5 (2CH), 124.2 (2CH), 80.1 (2C), 59.5 (2CH); **HRMS (ESI)** *m/z*: 909.3687 (M + H), $C_{64}H_{49}N_2O_4$ requires 909.3692.

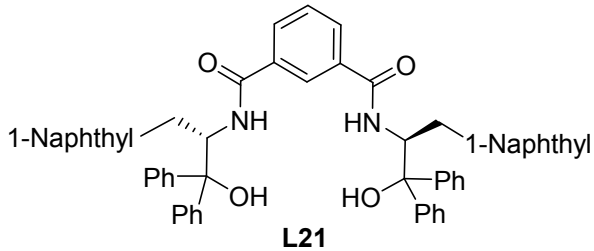
N^1,N^3-Bis((*S*)-1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl)isophthalamide (L20)



L20

White solid, 74% yield; **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 7.99 (s, 1H), 7.90 (d, *J* = 9.7 Hz, 2H), 7.70 (dd, *J* = 7.7, 1.6 Hz, 2H), 7.57-7.46 (m, 9H), 7.31 (t, *J* = 7.7 Hz, 4H), 7.22-7.13 (m, 6H), 7.10-7.05 (m, 2H), 5.89 (s, 2H), 5.14 (dd, *J* = 9.9, 2 Hz, 2H), 1.87-1.78 (m, 2H), 0.98 (d, *J* = 6.7 Hz, 6H), 0.76 (d, *J* = 6.9 Hz, 6H). Data consistent with the literature.[107]

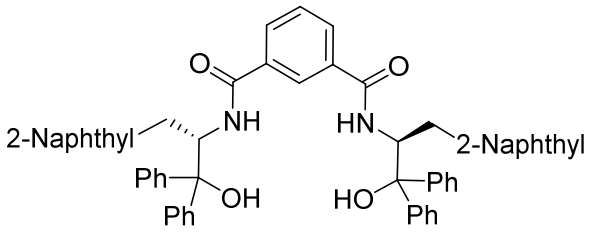
N^1,N^3-Bis((*S*)-1-hydroxy-3-(naphthalene-1-yl)-1,1-diphenylpropan-2-yl)isophthalamide (L21)



L21

White solid, 81% yield; **mp** 181-183 °C; **[α]$_D^{20}$** –98.1 (*c* 1.0, MeOH); **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ 8.16 (d, *J* = 9.6 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 7.4 Hz, 4H), 7.69 (dd, *J* = 7.0, 2.4 Hz, 2H), 7.60-7.57 (m, 4H), 7.50-7.27 (m, 16H), 7.23-7.16 (m, 8H), 7.09 (t, *J* = 7.2 Hz, 2H), 6.33 (s, 2H), 5.33 (t, *J* = 8.3 Hz, 2H), 3.21-3.12 (m, 4H); **^{13}C NMR (75.5 MHz, DMSO-*d*$_6$)** δ 165.6 (2C), 146.7 (2C), 145.8 (2C), 135.1 (2C), 134.6 (2C), 133.3 (2C), 131.9 (2C), 129.1 (2CH), 128.6 (2CH), 128.3 (4CH), 127.9 (CH), 127.7 (4CH), 127.3 (2CH), 126.7 (3CH), 126.4 (2CH), 125.7 (CH), 125.7 (4CH), 125.6 (3CH), 125.6 (4CH), 125.3 (2CH), 125.1 (2CH), 123.3 (2CH), 80.4 (2C), 57.0 (2CH), 32.6 ($2CH_2$); **HRMS (ESI)** *m/z*: 837.3678 (M + H), $C_{58}H_{49}N_2O_4$ requires 837.3687.

N^1,N^3-Bis((*S*)-1-hydroxy-3-(naphthalene-2-yl)-1,1-diphenylpropan-2-yl)isophthalamide (L22)



L22

White solid, 85% yield; **mp** 179-181 °C; **[α]$_D^{20}$** –108.5 (*c* 1.0, MeOH); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.78-7.63 (m, 11H), 7.55-7.23 (m, 20H), 7.07-7.05 (m, 6H), 6.51 (s, 1H), 5.52-5.42 (m, 4H), 5.18 (t, *J* = 7.6 Hz, 1H), 4.58 (br s, 1H), 3.03-2.86 (m, 4H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 168.1 (2C), 145.8 (2C), 144.9 (2C), 136.3 (2C), 134.1 (2C), 133.3 (2C), 132.0 (2C), 128.6 (4CH), 128.5 (CH), 128.2 (4CH), 127.8 (2CH), 127.7 (2CH), 127.6 (2CH), 127.6 (2CH), 127.4 (2CH), 127.1 (2CH), 126.7 (2CH), 125.9 (2CH), 125.4 (2CH), 125.3 (4CH), 125.2 (4CH), 123.9 (CH), 80.8 (2C), 58.1 (2CH), 36.2 ($2CH_2$); **HRMS (ESI)** *m/z*: 837.3670 (M + H), $C_{58}H_{49}N_2O_4$ requires 837.3687.

5.2.3. Enantioselective conjugate addition of terminal alkynes to 3-alcoxycarbonyl coumarins

5.2.3.1. General procedure for the enantioselective alkynylation reaction

A 1.5 M solution of Et_2Zn in toluene (0.17 mL, 0.25 mmol) was added dropwise to a solution of ligand **L21** (11.3 mg, 0.025 mmol) and alkyne **2** (0.94 mmol) in dry toluene (0.48 mL) at room temperature under nitrogen. The mixture was stirred at 70 ºC for 1.5 h, during this time a white precipitate was formed. After cooling to room temperature, a solution of coumarin **14** (0.125 mmol) and *N*-methylpiperidine (6.1 μL, 0.05 mmol) in toluene (1.0 mL) was added via syringe and the solution was stirred until the reaction was complete (1-4 h, TLC). During this time the precipitate slowly dissolved. The reaction mixture was quenched with 20% aqueous NH_4Cl (1.0 mL), extracted with CH_2Cl_2 (2×15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:EtOAc mixtures afforded compound **19**.

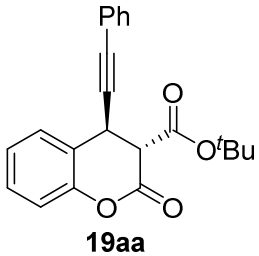
5.2.3.2. General procedure for the synthesis of the racemic products

A 1.5 M solution of Et_2Zn in toluene (0.17 mL, 0.25 mmol) was added dropwise to a solution of (±)-BINOL (**L1**, 7.2 mg, 0.025 mmol) and alkyne **2** (0.94 mmol) in toluene (0.48 mL) at room temperature under nitrogen and the mixture was stirred for 1.5 h at 70 ºC. Then, compound **14** (0.125 mmol) in toluene (1.0 mL) was added via syringe. The solution was stirred at 70 ºC until the reaction was complete (TLC). Racemic products **19** were obtained after the described work up**.**

5.2.3.3. Characterization of products 19

See Table 7 (Page 47) for yields.

tert-Butyl (3*R*,4*R*)-2-oxo-4-(phenylethynyl)chromane-3-carboxylate (19aa)

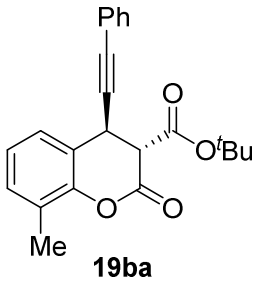


19aa

Enantiomeric excess (72%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 10.5 min, minor enantiomer t_r = 10.8 min.

Oil;**$[\alpha]_D^{20}$** –38.1 (*c* 1.01, $CHCl_3$, 72% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.57 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.35-7.30 (m, 4H), 7.21 (td, *J* = 7.2, 1.2 Hz, 1H), 7.12 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.61 (d, *J* = 9.1 Hz, 1H), 3.80 (d, *J* = 9.1 Hz, 1H), 1.42 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 165.1 (C), 163.9 (C), 150.5 (C), 131.7 (2CH), 129.5 (CH), 128.7 (CH), 128.3 (2CH), 127.8 (CH), 125.1 (CH), 122.1 (C), 121.4 (C), 117.0 (CH), 86.1 (C), 84.3 (C), 83.6 (C), 53.2 (CH), 31.9 (CH), 27.7 ($3CH_3$); **MS (EI)** *m/z* (%): 248 (M-$CO_2{}^t$Bu, 32); HRMS: 248.0831, $C_{17}H_{12}O_2$ requires 248.0837.

tert-Butyl (3*R*,4*R*)-8-methyl-2-oxo-4-(phenylethynyl)chromane-3-carboxylate (19ba)

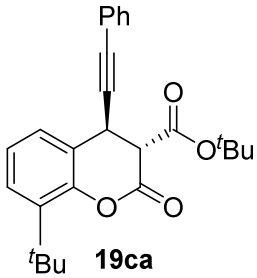


19ba

Enantiomeric excess (91%) was determined by chiral HPLC (Chiralpak IC), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 10.0 min, minor enantiomer t_r = 9.1 min.

Oil; **$[\alpha]_D^{20}$** –47.3 (*c* 0.43, $CHCl_3$, 91% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.43-7.40 (m, 2H), 7.38-7.35 (m, 1H), 7.25-7.22 (m, 3H), 7.19 (d, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 7.3 Hz, 1H), 4.56 (d, *J* = 8.6 Hz, 1H), 3.80 (d, *J* = 8.6 Hz, 1H), 2.34 (s, 3H), 1.42 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 165.2 (C), 164.0 (C), 148.8 (C), 131.7 (2CH), 131.0 (CH), 128.6 (CH), 128.3 (2CH), 126.5 (C), 125.3 (CH), 124.6 (CH), 122.2 (C), 121.2 (C), 85.9 (C), 84.5 (C), 83.4 (C), 53.2 (CH), 32.1 (CH),27.7 ($3CH_3$), 15.7 (CH_3); **HRMS (ESI)** *m/z*: 380.1860 (M + NH_4), $C_{23}H_{26}NO_4$ requires 380.1862.

tert-Butyl (3*R*,4*R*)-8-(_tert_-butyl)-2-oxo-4-(phenylethynyl)chromane-3-carboxylate (19ca)

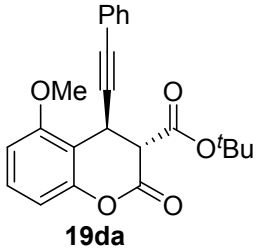


19ca

Enantiomeric excess (95%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 6.7 min, minor enantiomer t_r = 9.8 min.

Oil; **$[\alpha]_D^{20}$** –65.7 (*c* 0.65, $CHCl_3$, 95% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.43-7.39 (m, 3H), 7.33-7.29 (m, 4H), 7.13 (t, *J* = 7.7 Hz, 1H), 4.58 (d, *J* = 8.3 Hz, 1H), 3.80 (d, *J* = 8.3 Hz, 1H), 1.44 (s, 9H), 1.41 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 165.1 (C), 163.6 (C), 149.2 (C), 138.4 (C), 131.8 (2CH), 128.6 (CH), 128.3 (2CH), 127.0 (CH), 125.9 (CH), 124.6 (CH), 122.3 (C), 122.2 (C), 85.9 (C), 84.8 (C), 83.5 (C), 53.0 (CH), 34.9 (C), 32.1 (CH), 30.0 ($3CH_3$), 27.7 ($3CH_3$); **HRMS (ESI)** *m/z*: 403.1905 (M^+), $C_{26}H_{27}O_4$ requires 403.1915.

tert-Butyl (3*R*,4*R*)-5-methoxy-2-oxo-4-(phenylethynyl)chromane-3-carboxylate (19da)

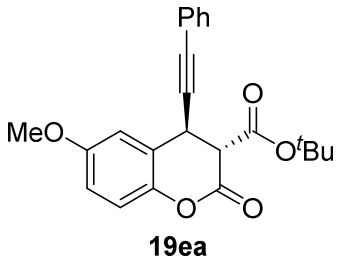


19da

Enantiomeric excess (76%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 15.7 min, minor enantiomer t_r = 10.9 min.

Oil; **$[\alpha]_D^{20}$**+19.4 (*c* 0.73, $CHCl_3$, 76% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.33-7.29 (m, 2H), 7.23-7.19 (m, 4H), 6.72 (dd, *J* = 8.3, 0.7 Hz, 1H), 6.67 (dd, *J* = 8.2, 0.7 Hz, 1H), 4.82 (d, *J* = 2.1 Hz, 1H), 3.97 (d, *J* = 2.1 Hz, 1H), 3.87 (s, 3H), 1.44 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 164.5 (C), 163.6 (C), 156.6 (C), 151.8 (C), 131.8 (2CH), 129.7 (CH), 128.4 (CH), 128.1 (2CH), 122.3 (C), 110.1 (C), 109.5 (CH), 106.9 (CH), 85.1 (C), 83.9 (C), 83.6 (C), 56.1 (CH_3), 53.3 (CH), 27.4 ($3CH_3$), 26.3 (CH); **HRMS (ESI)** *m/z*: 396.1805 (M + NH_4), $C_{23}H_{26}NO_5$ requires 396.1811.

tert-Butyl (3*R*,4*R*)-6-methoxy-2-oxo-4-(phenylethynyl)chromane-3-carboxylate (19ea)

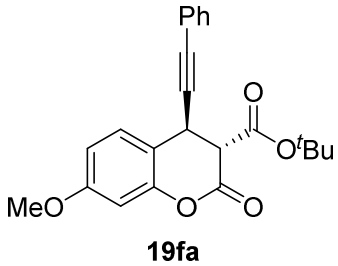


19ea

Enantiomeric excess (75%) was determined by chiral HPLC (Chiralpak IC), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 24.8 min, minor enantiomer t_r = 26.1 min.

Oil;**[α]$_D^{20}$** –6.7 (*c* 0.53, $CHCl_3$, 75% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.43-7.30 (m, 6H), 7.09 (dd, *J* = 2.9, 0.9 Hz, 1H), 6.68 (d, *J* = 2.9 Hz, 1H), 4.57 (d, *J* = 9.4 Hz, 1H), 3.78 (s, 3H), 3.76 (d, *J* = 9.4 Hz, 1H), 1.44 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 165.2 (C), 164.0 (C), 156.7 (C), 144.3 (C), 131.7 (2CH), 128.7 (CH), 128.3 (2CH), 125.4 (C), 122.4 (C), 117.8 (CH), 114.5 (CH), 113.8 (CH), 86.2 (C), 84.2 (C), 83.3 (C), 55.7 (CH_3), 53.1 (CH), 32.1 (CH), 27.7 ($3CH_3$); **HRMS (ESI)** *m/z*: 396.1807 (M + NH_4), $C_{23}H_{26}NO_5$ requires 396.1811.

tert-Butyl (3*R*,4*R*)-7-methoxy-2-oxo-4-(phenylethynyl)chromane-3-carboxylate (19fa)

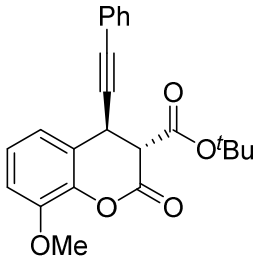


19fa

Enantiomeric excess (85%) was determined by chiral HPLC (Chiralpak IC), hexane-^{i}PrOH 90:10, 1 mL/min, major enantiomer t_r = 14.8 min, minor enantiomer t_r = 16.4 min.

Oil;**[α]$_D^{20}$** –35.6 (*c* 0.39, $CHCl_3$, 85% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.45-7.39 (m, 3H), 7.32-7.29 (m, 3H), 6.75 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.66 (d, *J* = 2.4 Hz, 1H), 4.54 (d, *J* = 8.9 Hz, 1H), 3.81 (s, 3H), 3.78 (d, *J* = 8.9 Hz, 1H), 1.43 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 165.2 (C), 163.9 (C), 160.6 (C), 151.3 (C), 131.7 (2CH), 128.6 (CH), 128.4 (CH), 128.3 (2CH),122.2 (C), 113.2 (C), 111.0 (CH), 102.6 (CH), 85.8 (C), 84.7 (C), 83.5 (C), 55.6 (CH_3), 53.5 (CH), 31.4 (CH), 27.7 ($3CH_3$); **HRMS (ESI)** *m/z*: 433.1618 (M + 55), $C_{26}H_{25}O_6$ requires 433.1646.

tert-Butyl (3*R*,4*R*)-8-methoxy-2-oxo-4-(phenylethynyl)chromane-3-carboxylate (19ga)



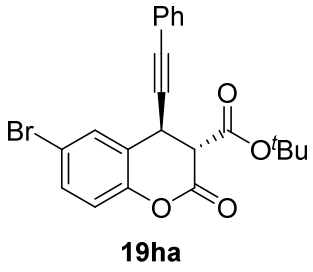
19ga

Enantiomeric excess (84%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 18.3 min, minor enantiomer t_r = 15.8 min.

Oil;**[α]$_D^{20}$** –55.5 (*c* 0.60, $CHCl_3$, 84% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.43-7.40 (m, 2H), 7.33-7.29 (m, 3H), 7.15-7.13 (m, 2H), 6.94 (dd, *J* = 5.5, 4.3 Hz, 1H), 4.59 (d, *J* = 9.1 Hz, 1H), 3.90 (s, 3H), 3.78 (d, *J* = 9.1 Hz, 1H), 1.42 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 165.1 (C), 163.2 (C), 147.7 (C), 139.8 (C), 131.7 (2CH), 128.6 (CH), 128.3 (2CH), 125.0 (CH), 122.6 (C), 122.2 (C), 119.1 (CH), 112.3 (CH), 86.0 (C), 84.3

(C), 83.5 (C), 56.2 (CH_3), 53.0 (CH), 32.1 (CH), 27.7 ($3CH_3$);**HRMS (ESI)***m/z*: 396.1802 (M + NH_4), $C_{23}H_{26}NO_5$ requires 396.1811.

***tert*-Butyl (3*R*,4*R*)-6-bromo-2-oxo-4-(phenylethynyl)chromane-3-carboxylate (19ha)**

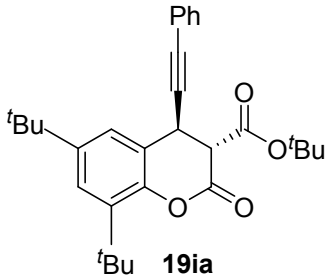


19ha

Enantiomeric excess (80%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 11.5 min, minor enantiomer t_r = 8.6 min.

Oil;**[α]$_D^{20}$** –25.1(*c* 0.63, $CHCl_3$, 80% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.69 (d, *J* = 2.0 Hz, 1H), 7.48-7.42 (m, 3H), 7.35-7.31 (m, 3H), 7.00 (d, *J* = 8.6 Hz, 1H), 4.59 (d, *J* = 9.1 Hz, 1H), 3.78 (d, *J* = 9.1 Hz, 1H), 1.44 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 164.7 (C), 163.1 (C), 149.5 (C), 132.5 (CH), 131.8 (2CH), 130.7 (CH), 128.9 (CH), 128.4 (2CH), 123.6 (C), 121.8 (C), 118.8 (CH), 117.7 (C), 86.7 (C), 83.9 (C), 83.4 (C), 52.8 (CH), 31.7 (CH), 27.7 ($3CH_3$); **HRMS (ESI)** *m/z*: 444.0832 (M + NH_4), $C_{22}H_{23}BrNO_4$ requires 444.0810.

***tert*-Butyl (3*R*,4*R*)-6,8-di-*tert*-butyl-2-oxo-4-(phenylethynyl)chromane-3-carboxylate (19ia)**

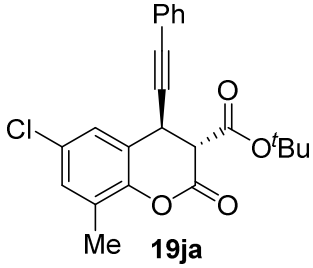


19ia

Enantiomeric excess (89%) was determined by chiral HPLC (Chiralpak IC), hexane-^{i}PrOH 99:01, 0.5 mL/min, major enantiomer t_r = 8.1 min, minor enantiomer t_r = 6.8 min.

White solid; **mp** 97-99 °C; **[α]$_D^{20}$** –29.0 (*c* 0.87, $CHCl_3$, 89% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.43-7.40 (m, 3H), 7.36-7.35 (m, 1H), 7.32-7.30 (m, 3H), 4.55 (d, *J* = 8.1 Hz, 1H), 3.79 (d, *J* = 8.1 Hz, 1H), 1.45 (s, 9H), 1.40 (s, 9H), 1.34 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 165.2 (C), 163.8 (C), 147.2 (C), 146.9 (C), 137. 6 (C), 131.7 (2CH), 128.5 (CH), 128.3 (2CH), 123.9 (CH), 122.6 (CH), 122.4 (C), 121.3 (C), 85.8 (C), 85.1 (C), 83.4 (C), 53.2 (CH), 35.1 (C), 34.7 (C), 32.5 (CH), 31.4 ($3CH_3$),30.1 ($3CH_3$), 27.7 ($3CH_3$); **MS (EI)** *m/z* (%): 360 (M-CO_2^{t}Bu, 44), 345 (70), 304 (24), 303 (100); HRMS: 360.2081, $C_{25}H_{28}O_2$ requires 360.2089.

***tert*-Butyl (3*R*,4*R*)-6-chloro-8-methyl-2-oxo-4-(phenylethynyl)chromane-3-carboxylate (19ja)**



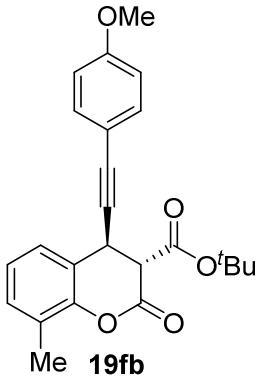
19ja

Enantiomeric excess (93%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 10.2 min, minor enantiomer t_r = 12.9 min.

Oil;**[α]$_D^{20}$** –17.4 (*c* 0.56, $CHCl_3$, 93% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.44-7.40 (m, 2H), 7.36-7.30 (m, 4H), 7.18 (dd, *J* = 1.8, 0.7 Hz, 1H), 4.54 (d, *J* = 8.8 Hz, 1H), 3.77 (d, *J* = 8.8 Hz, 1H), 2.31 (s, 3H), 1.41 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 164.8 (C),

163.3 (C), 147.3 (C), 131.8 (2CH), 130.7 (CH), 129.6 (C), 128.8 (CH), 128.4 (C), 128.3 (2CH), 125.1 (CH), 122.8 (C), 121.9 (C), 86.5 (C), 83.7 (C), 83.7 (C), 52.8 (CH), 32.0 (CH),27.7 ($3CH_3$), 15.6 (CH_3); **HRMS (ESI)** *m/z*: 397.1200 (M+H), $C_{23}H_{22}ClO_4$ requires 397.1207.

tert-Butyl (3*R*,4*R*)-4-((4-methoxyphenyl)ethynyl)-8-methyl-2-oxochromane-3-carboxylate (19fb)

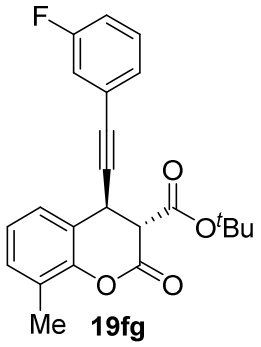


19fb

Enantiomeric excess (81%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 17.4 min, minor enantiomer t_r = 13.9 min.

Oil;**$[\alpha]_D^{20}$** –63.4 (*c* 1.01, $CHCl_3$, 81% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.37-7.33 (m, 3H), 7.20-7.16 (m, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.85-6.80 (m, 2H), 4.54 (d, *J* = 8.5 Hz, 1H), 3.80 (s, 3H), 3.78 (d, *J* = 8.5 Hz, 1H), 2.33 (s, 3H), 1.38 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 165.2 (C), 164.1 (C), 159.8 (C), 148.8 (C), 133.2 (2CH), 130.9 (CH), 126.4 (C), 125.3 (CH), 124.5 (CH), 125.3 (CH), 124.5 (CH), 121.4 (C), 114.3 (C), 113.9 (2CH), 85.8 (C), 83.3 (C), 83.1 (C), 55.2 (CH_3), 53.3 (CH), 32.2 (CH),27.7 ($3CH_3$), 15.6 (CH_3); **HRMS (ESI)** *m/z*: 410.1976 (M + NH_4), $C_{24}H_{28}NO_5$ requires 410.1967.

tert-Butyl (3*R*,4*R*)-4-(3-fluorophenyl)ethynyl)-8-methyl-2-oxochromane-3-carboxylate (19fg)

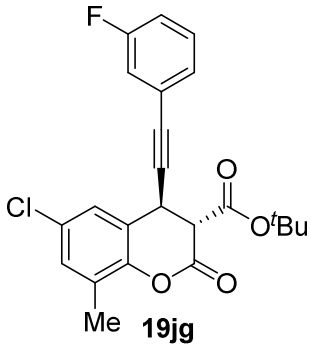


19fg

Enantiomeric excess (87%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 9.8 min, minor enantiomer t_r = 8.8 min.

Oil; **$[\alpha]_D^{20}$** –37.6 (*c* 0.53, $CHCl_3$, 87% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.35-7.32 (m, 1H), 7.21-7.17 (m, 2H), 7.12-6.98 (m, 4H), 4.56 (d, *J* = 8.2 Hz, 1H), 3.80 (d, *J* = 8.2 Hz, 1H), 2.34 (s, 3H), 1.38 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 165.0 (C), 163.8 (C), 162.2 (d, $J_{C\text{-}F}$ = 246.4 Hz, C), 148.8 (C), 131.1 (CH), 129.9 (d, $J_{C\text{-}F}$= 8.6 Hz, CH), 127.7 (d, $J_{C\text{-}F}$ = 3.2 Hz, CH), 126.6 (C), 125.3 (CH), 124.6 (CH), 124.0 (d, $J_{C\text{-}F}$= 9.5 Hz, C), 120.8 (C), 118.6 (d, $J_{C\text{-}F}$ = 23.0 Hz, CH), 116.0 (d, $J_{C\text{-}F}$ = 21.2 Hz, CH), 85.6 (C), 84.7 (d, $J_{C\text{-}F}$ = 3.6 Hz, C), 83.6 (C), 53.0 (CH), 32.1 (CH),27.7 ($3CH_3$), 15.7 (CH_3); **HRMS (ESI)** *m/z*: 398.1775 (M + NH_4), $C_{23}H_{25}FNO_4$ requires 398.1768.

tert-Butyl (3*R*,4*R*)-6-chloro-4-((3-fluorophenyl)ethynyl)-8-methyl-2-oxochromane-3-carboxylate (19jg)

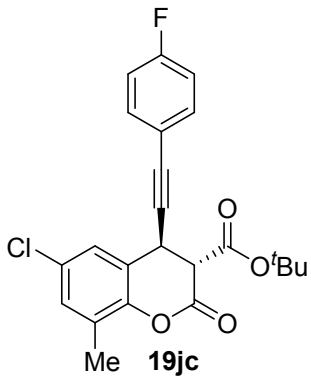


19jg

Enantiomeric excess (92%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 10.3 min, minor enantiomer t_r = 13.4 min.

Oil; **[α]$_D^{20}$** –30.1 (*c* 0.55, $CHCl_3$, 92% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.33-7.31 (m, 1H), 7.30-7.24 (m, 1H), 7.21-7.18 (m, 2H), 7.11 (ddd, *J* = 9.3, 2.4, 1.4 Hz, 1H), 7.08-7.00 (m, 1H), 4.53 (d, *J* = 8.6 Hz, 1H), 3.78 (d, *J* = 8.6 Hz, 1H), 2.31 (s, 3H), 1.41 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 164.7 (C), 163.2 (C), 162.3 (d, $J_{C\text{-}F}$ = 247.0 Hz, C), 147.3 (C), 130.9 (CH), 130.0 (d, $J_{C\text{-}F}$= 8.6 Hz, CH), 129.7 (C), 128.5 (C), 127.7 (d, $J_{C\text{-}F}$ = 3.1 Hz, CH), 125.1 (CH), 123.7 (d, $J_{C\text{-}F}$ = 9.5 Hz, C), 122.4 (C), 118.6 (d, $J_{C\text{-}F}$= 23.0 Hz, CH), 116.2 (d, $J_{C\text{-}F}$= 21.0 Hz, CH), 85.2 (d, $J_{C\text{-}F}$ = 3.4 Hz, C), 84.7 (C), 83.8 (C), 52.7 (CH), 31.9 (CH), 27.7 ($3CH_3$), 15.6 (CH_3); **HRMS (ESI)** *m/z*: 415.1120 (M+H), $C_{23}H_{21}ClFO_4$ requires 415.1112.

tert-Butyl (3*R*,4*R*)-6-chloro-4-((4-fluorophenyl)ethynyl)-8-methyl-2-oxochromane-3-carboxylate (19jc)

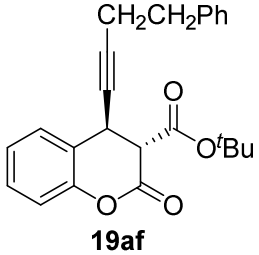


19jc

Enantiomeric excess (92%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 10.9 min, minor enantiomer t_r = 14.0 min.

Oil;**[α]$_D^{20}$** –20.3 (*c* 0.50, $CHCl_3$, 92% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.42-7.37 (m, 2H), 7.33 (d, *J* = 2.5 Hz, 1H), 7.19 (d, *J* = 2.5 Hz, 1H), 7.03-6.97 (m, 2H), 4.52 (d, *J* = 8.5 Hz, 1H), 3.77 (d, *J* = 8.5 Hz, 1H), 2.31 (s, 3H), 1.40 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 164.8 (C), 163.3 (C), 162.8 (d, $J_{C\text{-}F}$ = 263.2 Hz, C), 147.3 (C), 133.8 (d, $J_{C\text{-}F}$= 8.6 Hz, 2CH), 130.8 (CH), 129.6 (C), 128.5 (C), 126.0 (C), 125.1 (CH), 122.7 (C), 118.0 (d, $J_{C\text{-}F}$ = 3.8 Hz, C), 115.7 (d, $J_{C\text{-}F}$ = 22.1 Hz, 2CH), 85.4 (C), 83.8 (C), 83.5 (C), 53.8 (CH), 31.9 (CH), 27.7 ($3CH_3$), 15.6 (CH_3); **HRMS (ESI)** *m/z*: 415.1125 (M+H), $C_{23}H_{21}ClFO_4$ requires 415.1112.

tert-Butyl (3*R*,4*R*)-2-oxo-4-(4-phenylbut-1-yn-1-yl)chromane-3-carboxylate (19af)



19af

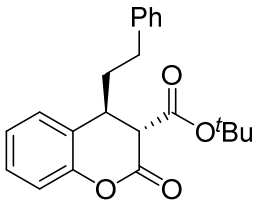
Enantiomeric excess (66%) was determined by chiral HPLC (Chiralpak OD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 14.8 min, minor enantiomer t_r = 9.3 min.

Oil; **[α]$_D^{20}$** –15.3 (*c* 0.45, $CHCl_3$, 66% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.31-7.25 (m, 5H), 7.19-7.06 (m, 4H), 4.31 (d, *J* = 8.6 Hz, 1H), 3.65 (d, *J* = 8.6 Hz, 1H), 2.80 (t, *J* = 7.4 Hz, 2H), 2.50 (td, *J* = 7.4, 2.5 Hz, 2H), 1.38 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 165.1 (C), 164.0 (C), 150.4 (C), 140.3 (C), 129.3 (CH), 128.4 (2CH), 127.8 (CH), 126.3 (CH), 124.9

(CH), 124.4 (2CH), 121.9 (C), 116.8 (CH), 85.9 (C), 83.4 (C), 83.4 (C), 53.4 (CH), 34.9 (CH_2), 31.4 (CH),27.7 ($3CH_3$), 20.9 (CH_2); **HRMS (ESI)** *m/z*: 377.1761 (M+H), $C_{24}H_{25}O_4$ requires 377.1753.

5.2.3.4. Determination of the absolute stereochemistry of compound 19aa

tert-Butyl (3*R*,4*S*)-2-oxo-4-phenethylchromane-3-carboxylate (20)

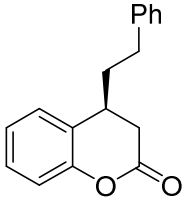


20

A solution of **19aa** (18.0 mg, 0.052 mmol) in EtOAc (0.4 mL) was stirred under hydrogen atmosphere in the presence of 5% Pd/C (4 mg) for 1 h. Then, the reaction mixture was filtered through a short pad of silica gel eluting with EtOAc. The solvent was removed under reduced pressure to give compound **20** (18.3 mg, 99%). Enantiomeric excess (72%) was determined by chiral HPLC (Chiralpak IC), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r (*S*) = 11.2 min, minor enantiomer t_r (*R*) = 12.0 min.

Oil; **$[\alpha]_D^{20}$** –21.1 (*c* 0.62, $CHCl_3$, 72% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.33-7.26 (m, 3H), 7.21-7.08 (m, 6H), 3.74 (d, *J* = 2.3 Hz, 1H), 3.34 (ddd, *J* = 8.8, 6.8, 2.3 Hz, 1H), 2.73-2.58 (m, 2H), 2.05-1.79 (m, 2H), 1.17 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 166.1 (C), 164.9 (C), 151.0 (C), 140.5 (C), 128.8 (CH), 128.8 (CH), 128.6 (2CH), 128.3 (2CH), 126.2 (CH), 124.5 (CH), 124.2 (C), 117.0 (CH), 83.5 (C), 53.0 (CH), 40.0 (CH), 35.7 (CH_2), 32.8 (CH_2), 27.4 ($3CH_3$); **HRMS (ESI)** *m/z*: 353.1783 (M+H), $C_{22}H_{25}O_4$ requires 353.1753.

(*S*)-4-Phenethylchroman-2-one (21)



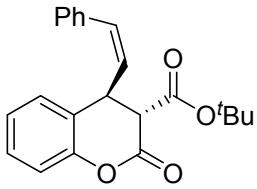
21

A solution of **20** (13.2 mg, 0.038 mmol) and *p*-toluenesulfonic acid (7 mg, 0.038 mmol) in toluene (4.5 mL) was heated at 80 ºC for 3 h under nitrogen. The mixture was then allowed to cool down to room temperature, diluted with EtOAc (5 mL) and washed with brine (2 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography eluting with hexane-EtOAc (95:05) gave **21** (8.6 mg, 90%).Enantiomeric excess (72%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r (*S*) = 10.4 min, minor enantiomer t_r (*R*) = 11.5 min.

Oil; **$[\alpha]_D^{20}$** –24.6 (*c* 0.53, $CHCl_3$, 72% *ee*), Lit.[14] $[\alpha]_D^{20}$ +57 ($CHCl_3$, 94%*ee* for the *R*-enantiomer); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.31-7.25 (m, 3H), 7.22-7.06 (m, 6H), 3.07-2.99 (m, 1H), 2.84 (t, *J* = 4.9 Hz, 2H), 2.73-2.64 (m, 2H), 1.98-1.88 (m, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 168.2 (C), 151.3 (C), 140.8 (C), 128.5 (2CH), 128.4 (CH), 128.3 (2CH),127.8 (CH), 126.4 (C), 126.2 (CH), 124.4 (CH), 117.2 (CH), 36.0 (CH2), 34.7 (CH_2), 34.5 (CH), 32.7 (CH_2); **HRMS (ESI)** *m/z*: 253.1233 (M+H), $C_{17}H_{17}O_2$ requires 253.1229.

5.2.3.5. Synthetic transformations from compound 19aa

tert-Butyl (3*R*,4*S*)-2-oxo-4-((*Z*)-styryl)chromane-3-carboxylate (22)

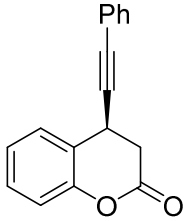


22

A solution of **19aa** (18.7 mg, 0.054 mmol) in benzene (1 mL) was stirred in the presence of Lindlar's catalyst (4 mg) under hydrogen atmosphere for 1 h. Then, the reaction mixture was filtered through a pad of Celite® eluting with EtOAc. The solvent was removed under reduced pressure to give **22** (18.9 mg, 99%). Enantiomeric excess (72%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 7.8 min, minor enantiomer t_r = 12.1 min.

Oil; **$[\alpha]_D^{20}$** −158.8 (*c* 0.43, $CHCl_3$, 72% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.36-7.28 (m, 6H), 7.15 (ddd, *J* =15.9, 7.9, 1.1 Hz, 3H), 6.85 (d, *J* = 11.4 Hz, 1H), 5.53 (dd, *J* = 11.4, 10.2 Hz, 1H), 4.71 (t, *J* = 10.1 Hz, 1H), 3.49 (d, *J* = 10.1 Hz, 1H), 1.27 (s, 9H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 165.7 (C), 164.7 (C), 151.0 (C), 135.8 (C), 134.1 (CH), 129.1 (CH), 128.6 (2CH), 128.3 (2CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 125.0 (CH), 123.5 (C), 117.0 (CH), 82.9 (C), 53.4 (CH), 37.5 (CH), 27.5 ($3CH_3$); **HRMS (ESI)** *m/z*: 351.1631 (M+H), $C_{22}H_{23}O_4$ requires 351.1596.

(*R*)-4-(Phenylethynyl)chroman-2-one (23)

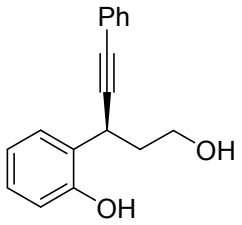


23

A solution of **19aa** (51 mg, 0.146 mmol) and *p*-toluenesulfonic acid (28 mg, 0.146 mmol) in toluene (15 mL) was heated at 80 ºC for 3 h. The mixture was then allowed to cool down to room temperature, diluted with EtOAc (20 mL) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash chromatography eluting with hexane-EtOAc (95:05) to afford **23** (29.1 mg, 80%). Enantiomeric excess (72%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 10.5 min, minor enantiomer t_r = 12.0 min.

Oil; **$[\alpha]_D^{20}$** −22.2 (*c* 0.85, $CHCl_3$, 72% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.61-7.58 (m, 1H), 7.47-7.44 (m, 2H), 7.34-7.30 (m, 3H), 7.21 (td, *J* =7.5, 1.3 Hz, 1H), 7.11 (dd, *J* = 8.1, 1.3 Hz, 1H), 4.31 (dd, *J* = 10.5, 5.2 Hz, 1H), 3.14 (dd, *J* = 15.9, 5.2 Hz, 1H), 2.96 (dd, *J* = 15.9, 10.5 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 166.8 (C), 131.8 (2CH), 130.2 (C), 129.3 (CH), 128.6 (CH), 128.5 (C), 128.3 (2CH), 127.4 (CH), 124.9 (CH), 122.7 (C), 117.2 (CH), 85.7 (C), 85.4 (C), 35.6 (CH_2), 28.1 (CH); **HRMS (ESI)** *m/z*: 249.0935 (M+H), $C_{17}H_{13}O_2$ requires 249.0916.

(*R*)-2-(5-Hydroxy-1-phenylpent-1-yn-3-yl)phenol (24)

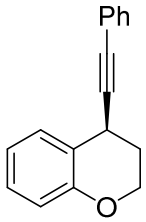


24

Lithium aluminium hydride (1 mg, 0.026 mmol) was added to a solution of **23** (17 mg, 0.069 mmol) in tetrahydrofuran (1.5 mL) at 0 ºC, and the solution was stirred for 30 min. The reaction mixture was quenched with 20 % aqueous NH_4Cl (1.0 mL), extracted with CH_2Cl_2 (2×15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:EtOAc (98:02) to afford compound **24** (15.8 mg, 91%). Enantiomeric excess (72%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 85:15, 1 mL/min, major enantiomer t_r = 7.0 min, minor enantiomer t_r = 8.0 min.

Oil; **$[\alpha]_D^{20}$** +10.1 (*c* 0.64, $CHCl_3$, 72% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.50 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.46-7.42 (m, 2H), 7.33-7.28 (m, 3H), 7.17 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H), 6.96 (td, *J* = 7.5, 1.2 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.38 (t, *J* = 7.5 Hz, 1H), 3.88 (dt, *J* = 10.8, 5.3 Hz, 1H), 3.69-3.61 (m, 1H), 2.28-2.23 (m, 1H), 2.06-2.01 (m, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 153.5 (C), 131.7 (2CH), 129.0 (CH), 128.4 (CH), 128.3 (2CH), 128.1 (CH), 126.9 (C), 123.1 (C), 121.2 (CH), 116.6 (CH), 90.6 (C), 87.8 (C), 60.4 (CH_2), 39.3 (CH_2), 28.8 (CH); **HRMS (ESI)** *m/z*: 253.1234 (M+H), $C_{17}H_{17}O_2$ requires 253.1229.

(*R*)-4-(Phenylethynyl)chromane (25)

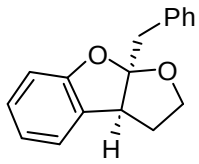


25

Diethyl azodicarboxylate (DEAD, 8 µL, 0.052 mmol) was added to a solution of compound **24** (11.9 mg, 0.047 mmol) and PPh_3 (15 mg, 0.057 mmol) in THF (0.5 mL) at 0 ºC under nitrogen.[108] After 30 min, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:EtOAc (99:01) gave compound **25** (9 mg, 82%). Enantiomeric excess (72%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 5.4 min, minor enantiomer t_r = 5.9 min.

Oil; **$[\alpha]_D^{20}$** −13.0 (*c* 0.23, $CHCl_3$, 72% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.43-7.40 (m, 3H), 7.35-7.33 (m, 1H), 7.30-7.28 (m, 2H), 7.16 (dddd, *J* = 8.1, 7.3, 1.7, 0.6 Hz, 1H), 6.92 (td, *J* = 7.5, 1.3 Hz, 1H), 6.83 (dd, *J* = 8.2, 1.3 Hz, 1H), 4.42 (ddd, *J* = 11.0, 7.2, 3.2 Hz, 1H), 4.27-4.20 (m, 1H), 4.07 (t, *J* = 6.3 Hz, 1H), 2.32-2.20 (m, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 153.8 (C), 131.6 (2CH), 129.8 (CH), 128.4 (CH), 128.2 (2CH), 127.9 (CH), 123.3 (C), 121.8 (C), 120.5 (CH), 117.0 (CH), 91.2 (C), 82.1 (C), 64.6 (CH_2), 29.0 (CH_2), 28.0 (CH); **HRMS (ESI)** *m/z*: 235.1127 (M+H), $C_{17}H_{15}O$ requires 235.1123.

(3a*S*,8a*R*)-8a-Benzyl-2,3,3a,8a-tetrahydrofuro[2,3-b]benzofuran (26)



26

To a solution of **24** (20 mg, 0.079 mmol) in THF (0.6 mL) was added $AuCl_3$ (2.4 mg, 7.9 µmol) at 0 ºC under nitrogen atmosphere and the mixture was stirred for 12 h. The mixture was directly chormatographed on silica gel eluting with hexane-EtOAc (98:2) to give compound **26** (18.2 mg, 91%). Enantiomeric excess (72%) was determined by chiral HPLC (Chiralpak IC), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 5.4 min, minor enantiomer t_r = 5.8 min.

Oil; **$[\alpha]_D^{20}$** –60.5 (*c* 0.55, $CHCl_3$, 72% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.36-7.24 (m, 5H), 7.14 (dddd, *J* = 8.1, 7.6, 1.4, 0.7 Hz 1H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.87 (td, *J* = 7.4, 1.0 Hz, 1H), 6.81 (dd, *J* = 8.0, 0.4 Hz, 1H), 4.03-3.98 (m, 1H), 3.70-3.63 (m, 2H), 3.40 (d, *J* = 13.8 Hz, 1H), 3.16 (d, *J* = 13.8 Hz, 1H), 1.89-1.80 (m, 2H); **^{1}H NMR (400 MHz, acetone-*d_6*)** δ 7.37 (dd, *J* = 6.8, 1.6 Hz, 1H), 7.30-7.07 (m, 5H), 6.82 (td, *J* = 7.6, 0.8 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 3.93 (ddd, *J* = 8.4, 9.2, 1.2 Hz, 1H), 3.74 (d, *J* = 8.0 Hz, 1H), 3.50 (m, 1H), 3.29 (d, *J* = 14.0 Hz, 1H), 3.19 (d, *J*= 14.0 Hz, 1H), 1.88 (m, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 159.0 (C), 135.4 (C), 130.5 (2CH), 128.6 (CH), 128.3 (C), 128.1 (2CH), 126.7 (CH), 124.7 (CH), 121.0 (C), 120.8 (CH), 109.1 (CH), 67.9 (CH_2), 48.2 (CH), 43.1 (CH_2), 34.2 (CH_2); **HRMS (ESI)** *m/z*: 253.1241 (M+H), $C_{17}H_{17}O_2$ requires 253.1229.

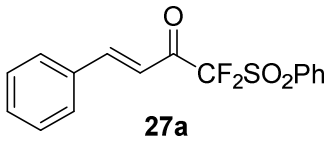
5.3. Enantioselective conjugate alkynylation of 1,1-difluoro-1-(phenylsulfonyl)ketones

5.3.1. Synthesis and characterization of the α,β-unsaturated 1,1-difluoro-1-(phenylsulfonyl)ketones 27

1,1-Difluoro-1-(phenylsulfonyl)ketones were synthesis according to a modification of the procedure described by Hu et al.[59]

A 1.0 M solution of LHMDS in THF (2.4 mL, 2.4 mmol) was added dropwise to a solution the corresponding α,β-unsaturated ester (2.0 mmol) and $PhSO_2CF_2H$ (192 mg, 1.0 mmol) in 5:1 THF/HMPA (6 mL) at −82 ºC (CO_2/diethyl ether bath). The solution was vigorously stirred for 30 min, and quenched at this temperature by the addition of concd HCl (1 mL). After reaching room temperature it was extracted with EtOAc (2 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:EtOAc mixtures afforded the corresponding enones **27**.

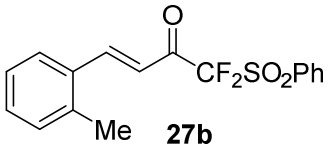
(*E*)-1,1-Difluoro-4-phenyl-1-(phenylsulfonyl)but-3-en-2-one (27a)



27a

Pale yellow solid, 66% yield; **mp** 94-95 ºC; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.05-8.00 (m, 2H), 7.97 (d, *J* = 15.8 Hz, 1H), 7.82 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.71-7.63 (m, 4H), 7.54-7.40 (m, 3H), 7.26 (dt, *J* = 15.8, 1.3 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 182.0 (t, $J_{C,F}$ = 22.7 Hz, C), 149.4 (CH), 136.0 (CH), 133.4 (2C), 132.3 (CH), 130.9 (2CH), 129.5 (2CH), 129.5 (2CH), 129.2 (2CH), 115.3 (t, $J_{C,F}$ = 302 Hz, CF_2), 118.3 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.1 (s, 2F); **HRMS (ESI)** *m/z*: 322.0476 (M), $C_{16}H_{12}F_2O_3S$ requires 322.0475.

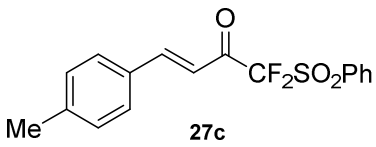
***(E)*-1,1-Difluoro-1-(phenylsulfonyl)-4-(*o*-tolyl)but-3-en-2-one (27b)**



27b

White solid, 61% yield; **mp** 78-80 ºC; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.29 (d, *J* = 15.7 Hz, 1H), 8.05-7.99 (m, 2H), 7.81 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.75-7.62 (m, 3H), 7.42-7.33 (m, 1H), 7.27 (d, *J* = 9.5 Hz, 2H), 7.25-7.15 (m, 1H), 2.49 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 182.0 (t, $J_{C,F}$ = 22.7 Hz, C), 146.8 (CH), 139.8 (C), 136.0 (CH), 132.4 (C), 132.3 (C), 132.1 (CH), 131.2 (CH), 130.9 (2CH), 129.5 (2CH), 127.1 (CH), 126.6 (CH), 119.1 (CH), 115.4 (t, $J_{C,F}$ = 302.0 Hz, C), 19.8 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.0 (s, 2F); **HRMS (ESI)** *m/z*: 336.0732 (M), $C_{17}H_{14}F_2O_3S$ requires 336.0632.

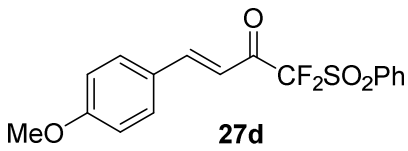
(*E*)-1,1-Difluoro-1-(phenylsulfonyl)-4-(*p*-tolyl)but-3-en-2-one (27c)



27c

White solid, 58% yield; **mp** 97-99 ºC; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.15-8.07 (m, 2H), 8.03 (d, *J* = 15.8 Hz, 1H), 7.89 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.80-7.69 (m, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.30 (ddd, *J* = 15.9, 5.4, 1.5 Hz, 3H), 2.49 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 182.9 (t, $J_{C,F}$ = 23.3 Hz, C), 149.5 (CH), 143.4 (C), 136.0 (CH), 132.5 (C), 130.9 (2CH), 130.8 (C), 129.9 (2CH), 129.6 (2CH), 129.5 (2CH), 117.3 (CH), 115.4 (t, $J_{C,F}$ = 299.2 Hz, C), 21.7 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −110.9 (s, 2F); **HRMS (ESI)** *m/z*: 337.0638 (M), $C_{17}H_{14}F_2O_3S$ requires 336.0632.

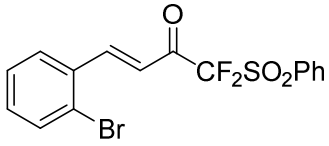
(*E*)-1,1-Difluoro-4-(4-methoxyphenyl)-1-(phenylsulfonyl)but-3-en-2-one (27d)



27d

Yellow solid, 50% yield; **mp** 81-83 ºC; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.07-7.99 (m, 2H), 7.94 (d, *J* = 15.7 Hz, 1H), 7.84-7.77 (m, 1H), 7.73-7.58 (m, 4H), 7.15-7.09 (m, 1H), 7.00-6.92 (m, 2H), 3.88 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 182.1 (t, $J_{C,F}$ = 22.7 Hz, C), 163.2 (C), 149.3 (CH), 135.9 (CH), 132.5 (C), 131.7 (2CH), 130.9 (2CH), 129.5 (2CH), 126.3 (C), 115.8 (CH), 115.2 (t, $J_{C,F}$ = 302.0 Hz, C), 114.7 (2CH), 55.5 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.0 (s, 2F); **HRMS (ESI)** *m/z*: 353.0582 (M), $C_{17}H_{14}F_2O_4S$ requires 352.0581.

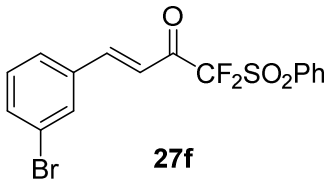
(*E*)-4-(2-Bromophenyl)-1,1-difluoro-1-(phenylsulfonyl)but-3-en-2-one (27e)



27e

White solid, 52% yield; **mp** 160-162 ºC; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.38-8.33 (d, *J* = 15.9 Hz, 2H), 8.04-8.01 (m, 2H), 7.86-7.77 (m, 3H), 7.70-7.64 (m, 3H), 7.42-7.30 (m, 2H), 7.26-7.19 (dt, *J* = 16.5, 1.2 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 181.8 (t, $J_{C,F}$ = 23.4 Hz, C), 147.3 (CH), 136.1 (CH), 133.8 (CH), 133.3 (C), 133.0 (CH), 132.3 (C), 130.9 (2CH), 129.6 (2CH), 128.4 (CH), 127.9 (CH), 127.1 (C), 120.7 (CH), 115.3 (t, $J_{C,F}$ = 299.4 Hz, CF_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.1(s, 2F); **HRMS (ESI)** *m/z*: 401.9564 / 399.9579 (M) 97.3 / 100, $C_{16}H_{11}BrF_2O_3S$ requires 401.9580 / 399.9580.

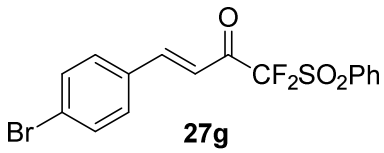
(*E*) -4-(3-Bromophenyl)-1,1-difluoro-1-(phenylsulfonyl)but-3-en-2-one (27f)



27f

White solid, 55% yield; **mp** 140-142 ºC; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.05-8.02 (dd, *J* = 8.2, 0.9 Hz, 2H), 7.90-7.80 (m, 3H), 7.70-7.58 (m, 4H), 7.36-7.34 (t, *J* = 7.9 Hz, 1H), 7.27-7.20 (dt, *J* = 15.8, 1.3 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 182.0 (t, $J_{C,F}$ = 22.7 Hz, C), 147.4 (CH), 136.1 (CH), 135.4 (C), 135.0 (CH), 132.3 (C), 131.8 (CH), 130.9 (2CH), 130.7 (CH), 129.6 (2CH), 128.1 (CH), 123.3 (C), 119.6 (CH), 115.2 (t, $J_{C,F}$ = 302.0 Hz, C); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.1 (s, 2F); **HRMS (ESI)** *m/z*: 401.9567 / 399.9577 (M) 97.3 / 100, $C_{16}H_{11}BrF_2O_3S$ requires 401.9580 / 399.9580.

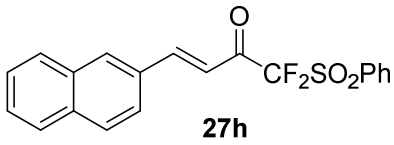
(*E*) -4-(4-Bromophenyl)-1,1-difluoro-1-(phenylsulfonyl)but-3-en-2-one (27g)



27g

White solid, 55% yield; **mp** 123-158 ºC; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.05-7.99 (m, 2H), 7.89 (d, *J* = 15.8 Hz, 1H), 7.83 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.71-7.66 (m, 2H), 7.66-7.60 (m, 1H), 7.60-7.53 (m, 3H), 7.28-7.20 (m, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 182.0 (t, $J_{C,F}$ = 23.3 Hz, C), 147.8 (C), 141.0 (C), 136.1 (CH), 132.5 (2CH), 132.3 (CH), 130.9 (2CH), 130.7 (2CH), 129.6 (2CH), 127.0 (C), 118.9 (CH), 115.3 (t, $J_{C,F}$ = 302.5 Hz, C); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.1(s, 2F); **HRMS (ESI)** *m/z*: 401.9564 / 399.9578 (M) 97.3 / 100, $C_{16}H_{11}BrF_2O_3S$ requires 401.9580 / 399.9580.

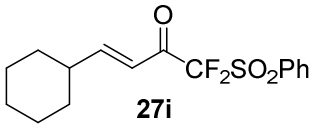
(*E*)-1,1-Difluoro-4-(naphthalen-2-yl)-1-(phenylsulfonyl)but-3-en-2-one (27h)



27h

Yellow solid, 60% yield; **mp** 129-131 ºC; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.13 (d, *J* = 16.3 Hz, 2H), 8.08-8.02 (m, 2H), 7.95-7.74 (m, 5H), 7.72-7.63 (m, 2H), 7.63-7.52 (m, 2H), 7.35 (dt, *J* = 15.7, 1.3 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 182.0 (t, $J_{C,F}$ = 22.7 Hz, C), 149.4 (CH), 136.0 (CH), 135.2 (C), 133.1 (C), 132.9 (CH), 132.5 (C), 131.0 (CH), 130.9 (2CH), 129.5 (2CH), 129.0 (CH), 129.0 (CH), 128.4 (CH), 127.9 (CH), 127.1 (CH), 123.6 (CH), 115.4 (t, $J_{C,F}$ = 302.0 Hz, C), 119.4 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −110.9 (s, 2F); **HRMS (ESI)***m/z*: 372.0630 (M), $C_{20}H_{14}F_2O_3S$ requires 372.0632.

***(E)*-4-Cyclohexyl-1,1-difluoro-1-(phenylsulfonyl)but-3-en-2-one (27i)**



27i

Oil; 63% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.99 (dd, *J* = 8.2, 0.9 Hz, 2H), 7.81 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.71-7.60 (m, 2H), 7.28 (dd, *J* = 15.7, 6.8 Hz, 1H), 6.61 (dq, *J* = 15.7, 1.4 Hz, 1H), 2.35-2.21 (m, 1H), 1.88-1.75 (m, 4H), 1.27 (ddd, *J* = 27.3, 18.0, 11.2 Hz, 6H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 182.3 (t, $J_{C,F}$ = 22.9 Hz, C), 160.8 (CH), 136.0 (CH), 130.9 (2CH), 129.5 (2CH), 120.5 (CH), 115.4 (t, $J_{C,F}$ = 300.8 Hz, C), 119.4 (CH), 41.3 (C), 31.2 ($2CH_2$), 25.7 (CH_2), 25.5 ($2CH_2$); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −110.9 (s, 2F); **HRMS (ESI)** *m/z*: 328.0952 (M), $C_{16}H_{18}F_2O_3S$ requires 328.0945.

5.3.2. Enantioselective conjugate addition of terminal alkynes to 1,1-difluoro-1-(phenylsulfonyl)ketones

5.3.2.1. General procedure for the enantioselective alkynylation reaction.

$[Cu(CH_3CN)_4]BF_4$ (5.7 mg, 0.018 mmol) and (*R*)-**L31** (20.72 mg, 0.018 mmol) were introduced in a round bottom flask which was purged with nitrogen. Toluene (0.5 mL) was added via syringe and the mixture was stirred for 1.5 h at room temperature. Then, a solution of enone **27** (0.090 mmol) in toluene (1.0 mL) was added followed by triethylamine (12.5 μL, 0.090). The solution was stirred for 10 min at room temperature.

The alkyne **2** (0.675 mmol) was then added and the solution was stirred at room temperature under nitrogen until the reaction was complete (TLC). The reaction mixture was quenched with 20% aqueous NH_4Cl (1.0 mL) extracted with CH_2Cl_2 (2 × 15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane: CH_2Cl_2 mixtures afforded compound **28**.

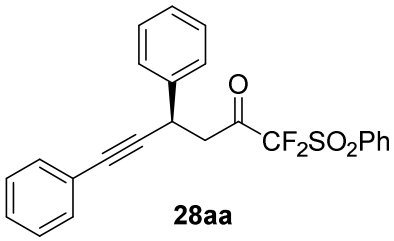
5.3.2.2. General procedure for the synthesis of the racemic products

A 1.5 M solution of Et_2Zn in toluene (0.17 mL, 0.25 mmol) was added dropwise to a solution of alkyne **2** (0.94 mmol) and (±)-BINOL (**L1**, 7.2 mg, 0.025 mmol) in toluene (0.48 mL)at room temperature under nitrogen and the mixture was stirred for 1.5 h at 70 ºC. Then, β-substituted β-trifluoromethyl enones **27** (0.125 mmol) in toluene (1.0 mL) was added via syringe. The solution was stirred at 70 ºC until the reaction was complete (TLC). The reaction mixture was quenched with 20 % aqueous NH_4Cl (1.0 mL), extracted with CH_2Cl_2 (2x 15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:EtOAc mixtures afforded racemic **28**.

5.3.2.3. Characterization of products28

See Table 9 (Page 57) for yields.

(*R*)-(–)-1,1-Difluoro-4,6-diphenyl-1-(phenylsulfonyl)hex-5-yn-2-one (28aa).

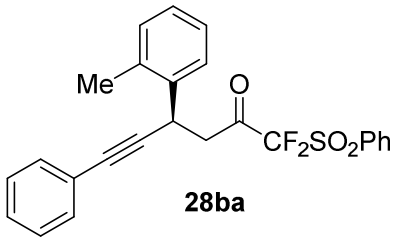


28aa

Enantiomeric excess (98%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 16.3 min, minor enantiomer t_r = 15.6 min.

Oil; **$[\alpha]_D^{20}$ –**3.6 (*c* 0.73, $CHCl_3$, 98% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.93-7.80 (m, 2H), 7.82-7.71 (m, 1H), 7.61-7.52 (m, 2H), 7.52-7.42 (m, 4H), 7.42-7.34 (m, 2H), 7.35-7.27 (m, 4H), 4.48 (dd, *J* = 8.0, 6.1 Hz, 1H), 3.63 (dd, *J* = 18.9, 8.0 Hz, 1H), 3.43 (dd, *J* = 18.9, 6.0 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 191.7 (t, $J_{C,F}$ = 23.9 Hz, C), 139.6 (C), 136.1 (CH), 131.8 (C), 131.7 (2CH), 130.9 (2CH), 129.5 (2CH), 128.8 (2CH), 128.2 (2CH), 128.2 (CH), 127.6 (2CH), 127.5 (CH), 123.0 (C), 114.5 (t, $J_{C,F}$ = 300.5 Hz, C), 89.0 (C), 83.8 (C), 47.8 (CH_2), 32.5 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.8 (s, 1F), −111.7 (s, 1F); **HRMS (ESI)** *m/z*: 425.1023 (M+H), $C_{24}H_{19}F_2O_3S$ requires 425.1017.

(*S*)-1,1-Difluoro-6-phenyl-1-(phenylsulfonyl)-4-(o-tolyl)hex-5-yn-2-one (28ba).

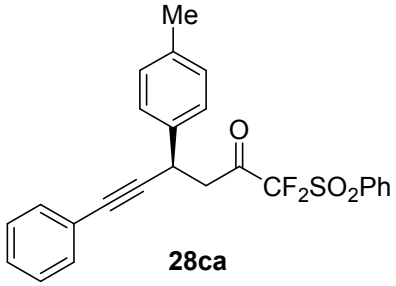


28ba

Enantiomeric excess (99%) was determined by chiral HPLC (Chiralpak IC), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 8.3 min, minor enantiomer t_r = 7.3 min.

Oil; **[α]$_D^{20}$** +13.8 (*c* 0.77, $CHCl_3$, 99% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.94-7.82 (m, 2H), 7.81-7.74 (m, 1H), 7.63-7.52 (m, 3H), 7.45-7.39 (m, 2H), 7.34-7.17 (m, 6H), 4.66 (dd, *J* = 8.8, 5.2 Hz, 1H), 3.61 (dd, *J* = 18.9, 8.8 Hz, 1H), 3.37 (dd, *J* = 18.9, 5.2 Hz, 1H), 2.45 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 191.9 (t, $J_{C,F}$ = 24.0 Hz, C), 137.6 (C), 136.1 (CH), 135.2 (C), 131.8 (C), 131.7 (2CH), 130.9 (2CH), 130.9 (CH), 129.5 (2CH), 128.2 (2CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 126.7 (CH), 123.1 (C), 114.6 (t, $J_{C,F}$ = 300.5 Hz, C), 89.2 (C), 83.3 (C), 46.4 (CH_2), 29.2 (CH), 19.3 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.7 (s, F), −111.6 (s, F); **HRMS (ESI)** *m/z*: 461.0997 (M+Na), $C_{25}H_{20}F_2NaO_3S$ requires 461.0993.

(*R*)-1,1-Difluoro-6-phenyl-1-(phenylsulfonyl)-4-(p-tolyl)hex-5-yn-2-one (28ca).

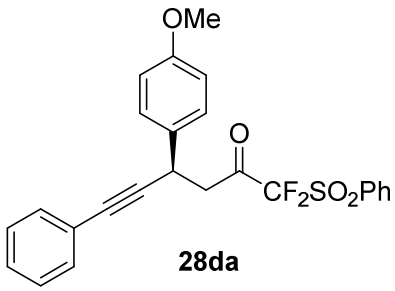


28ca

Enantiomeric excess (97%) was determined by chiral HPLC (Chiralpak IC), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 9.9 min, minor enantiomer t_r = 8.5 min.

Oil; **[α]$_D^{20}$** −2.7 (*c* 0.56, $CHCl_3$, 97% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.88-7.82 (m, 2H), 7.81-7.73 (m, 1H), 7.59-7.52 (m, 2H), 7.47-7.40 (m, 2H), 7.39-7.34 (m, 2H), 7.32-7.26 (m, 3H), 7.18 (d, *J* = 7.8 Hz, 2H), 4.44 (dd, *J* = 7.9, 6.1 Hz, 1H), 3.60 (dd, *J* = 18.9, 8.0 Hz, 1H), 3.40 (dd, *J* = 18.9, 6.1 Hz, 1H), 2.36 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 191.7 (t, $J_{C,F}$ = 23.6 Hz, C), 137.2 (C), 136.2 (C), 136.1 (CH), 131.8 (C), 131.7 (2CH), 130.9 (2CH), 129.9 (C), 129.5 (3CH), 128.2 (2CH), 128.1 (CH), 127.5 (2CH), 123.1 (C), 114.5 (t, $J_{C,F}$ = 300.7 Hz, C), 89.2 (C), 83.6 (C), 47.8 (CH_2), 36.2 (CH), 21.1 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.7 (s, F), −111.6 (s, F); **HRMS (ESI)** *m/z*: 461.0989 (M+Na), $C_{25}H_{20}F_2NaO_3S$ requires 461.0993.

(*R*)-1,1-Difluoro-4-(4-methoxyphenyl)-6-phenyl-1-(phenylsulfonyl)hex-5-yn-2-one (28da).



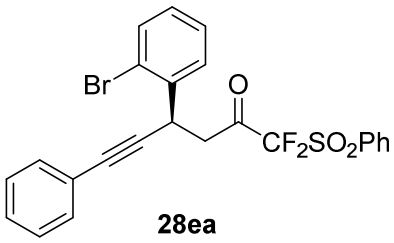
28da

Enantiomeric excess (96%) was determined by chiral HPLC, Chiralpak IC, hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 14.3 min, minor enantiomer t_r = 13.2 min.

Oil; **[α]$_D^{20}$** −3.5 (*c* 0.53, $CHCl_3$, 96% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.92-7.82 (m, 2H), 7.80-7.73

(m, 1H), 7.60-7.52 (m, 2H), 7.48-7.37 (m, 4H), 7.31-7.27 (m, 3H), 6.94-6.87 (m, 2H), 4.43 (dd, *J* = 7.7, 6.3 Hz, 1H), 3.82 (s, 3H), 3.59 (dd, *J* = 18.8, 7.9 Hz, 1H), 3.40 (dd, *J* = 18.9, 6.2 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 191.8 (t, $J_{C,F}$ = 24.0 Hz, C), 158.9 (C), 136.1 (CH), 131.7 (2CH), 131.8 (C), 131.7 (C), 130.9 (2CH), 129.5 (2CH), 128.7 (2CH), 128.2 (2CH), 128.1 (CH), 123.0 (C), 118.5 (t, $J_{C,F}$ = 300.0 Hz, C), 114.2 (2CH), 89.3 (C), 83.6 (C), 55.0 (CH_3), 48.0 (CH_2), 31.8 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.7 (s, F), −111.6 (s, F); **HRMS (ESI)***m/z*: 455.1129 (M+H), $C_{25}H_{21}F_2O_4S$ requires 454.1123.

(*S*)-4-(2-Bromophenyl)-1,1-difluoro-6-phenyl-1-(phenylsulfonyl)hex-5-yn-2-one (28ea).

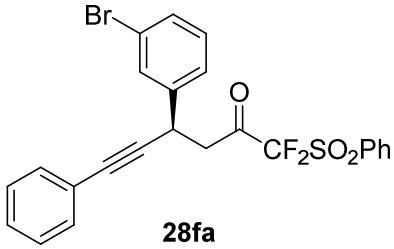


28ea

Enantiomeric excess (99%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 11.3 min, minor enantiomer t_r = 10.5 min.

Oil; **$[\alpha]_D^{20}$** +12.5 (*c* 0.96, $CHCl_3$, 99% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.94-7.91 (m, 2H), 7.84-7.75 (m, 2H), 7.60-7.53 (m, 3H), 7.49-7.46 (m, 2H), 7.41-7.36 (m, 1H), 7.32-7.30 (m, 3H), 7.23-7.14 (m, 1H), 4.48 (dd, *J* = 8.0, 6.1 Hz, 1H), 3.63 (dd, *J* = 18.9, 8.0 Hz, 1H), 3.43 (dd, *J* = 18.9, 6.0 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 191.4 (t, $J_{C,F}$ = 24.0 Hz, C), 138.4 (2C), 136.1 (CH), 133.1 (CH), 131.8 (2CH), 130.9 (2CH), 129.8 (CH), 129.5 (2CH), 129.2 (CH), 128.3 (CH), 128.3 (2CH), 128.0 (CH), 123.0 (C), 122.8 (C), 114.5 (t, $J_{C,F}$ = 299.3 Hz, C), 87.8 (C), 84.4 (C), 46.1 (CH_2), 32.6 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.7 (s, F), −111.6 (s, F); **HRMS (ESI)** *m/z*: 522.0376/520.0392 (M+NH_4) 97.3 / 100, $C_{24}H_{17}BrF_2O_3S$ requires 522.0373 / 520.0394.

(*R*)-4-(3-Bromophenyl)-1,1-difluoro-6-phenyl-1-(phenylsulfonyl)hex-5-yn-2-one (28fa).

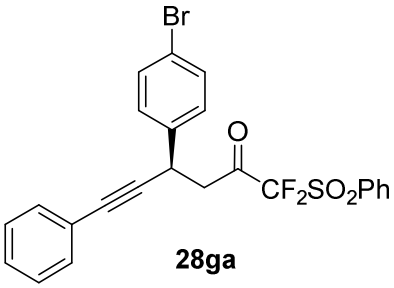


28fa

Enantiomeric excess (97%) was determined by chiral HPLC (Chiralpak IC), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 9.6 min, minor enantiomer t_r = 8.7 min.

Oil; **$[\alpha]_D^{20}$** −3.1 (*c* 0.47, $CHCl_3$, 97% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.88-7.83 (m, 2H), 7.83- 7.75 (m, 1H), 7.66-7.54 (m, 3H), 7.48-7.40 (m, 4H), 7.34-7.28 (m, 3H), 7.24 (d, *J* = 6.5 Hz, 1H), 4.45 (dd, *J* = 7.7, 6.3 Hz, 1H), 3.62 (dd, *J* = 19.1, 7.8 Hz, 1H), 3.41 (dd, *J* = 19.0, 6.2 Hz, 1H); **^{13}C NMR (125.8 MHz, $CDCl_3$)** δ 191.5 (t, $J_{C,F}$ = 23.9 Hz, C), 141.9 (C), 136.2 (CH), 131.8 (2CH), 131.7 (C), 130.8 (CH), 130.7 (2CH), 130.7 (CH), 129.6 (2CH), 129.4 (2CH), 128.4 (CH), 128.3 (CH), 126.4 (CH), 122.7 (C), 122.2 (C), 114.5 (t, $J_{C,F}$ = 300.7 Hz, C), 88.1 (C), 84.3 (C), 47.6 (CH_2), 32.2 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.8 (s, F), −111.7 (s, F); **HRMS (ESI)** *m/z*: 522.0375 / 520.0393 (M+NH_4) 97.3 / 100, $C_{24}H_{17}BrF_2O_3S$ requires 522.0373 / 520.0394.

(*R*)-4-(4-Bromophenyl)-1,1-difluoro-6-phenyl-1-(phenylsulfonyl)hex-5-yn-2-one (28ga).

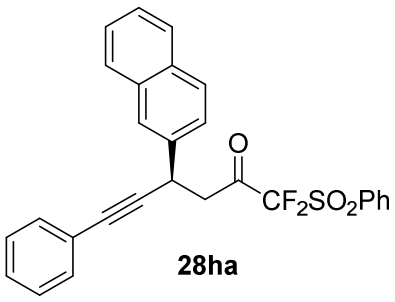


28ga

Enantiomeric excess (97%) was determined by chiral HPLC (Chiralpak IC), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 9.2 min, minor enantiomer t_r = 8.6 min.

Oil; **$[\alpha]_D^{20}$** −3.8 (*c* 0.87, $CHCl_3$, 97% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.86-7.80 (m, 2H), 7.79-7.74 (m, 1H), 7.61-7.54 (m, 2H), 7.53-7.48 (m, 2H), 7.46-7.40 (m, 2H), 7.39-7.34 (m, 2H), 7.32-7.28 (m, 3H), 4.44 (t, *J* = 7.0 Hz, 1H), 3.60 (dd, *J* = 19.0, 7.5 Hz, 1H), 3.42 (dd, *J* = 19.0, 6.5 Hz, 1H), 3.60 (dd, *J* = 19.0, 7.5 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 191.5 (t, $J_{C,F}$ = 24.0 Hz, C), 146.2 (C), 144.2 (C), 131.9 (2CH), 131.7 (2CH), 130.9 (2CH), 129.5 (2CH), 129.5 (2CH), 128.3 (CH), 128.3 (2CH), 129.0 (CH), 122.7 (C), 121.5 (C), 154.6 (t, $J_{C,F}$ = 299.2 Hz, C), 88.3 (C), 84.1 (C), 47.5 (CH_2), 32.1 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.7 (s, F), −111.6 (s, F); **HRMS (ESI)** *m/z*: 522.0374/520.0393 ($M+NH_4$) 97.3 / 100, $C_{24}H_{21}BrF_2NO_3S$ requires 522.0373 / 520.0394.

(*R*)-1,1-Difluoro-4-(naphthalen-2-yl)-6-phenyl-1-(phenylsulfonyl)hex-5-yn-2-one (28ha).

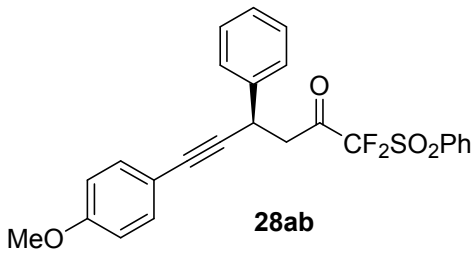


28ha

Enantiomeric excess (95%) was determined by chiral HPLC (Chiralpak IC), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 11.7 min, minor enantiomer t_r = 10.9 min.

Oil; **$[\alpha]_D^{20}$** −10.7 (*c* 0.56, $CHCl_3$, 95% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.93-7.89 (m, 2H), 7.88-7.82 (m, 2H), 7.78-7.67 (m, 3H), 7.61 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.55-7.38 (m, 6H), 7.36- 7.27 (m, 3H), 4.65 (t, *J* = 7.0 Hz, 1H), 3.70 (dd, *J* = 19.0, 7.6 Hz, 1H), 3.55 (dd, *J* = 19.0, 6.4 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 191.7 (t, $J_{C,F}$ = 23.8 Hz, C), 136.9 (C), 136.1 (CH), 133.4 (C), 132.7 (C), 131.8 (2CH), 131.7 (C), 130.9 (2CH), 129.5 (2CH), 128.7 (CH), 128.3 (2CH), 128.2 (CH), 127.9 (CH), 127.7 (CH), 126.6 (CH), 126.4 (C), 126.1 (CH), 125.6 (CH), 123.0 (CH), 115.1 (t, $J_{C,F}$ = 299.4 Hz, C), 88.9 (C), 84.0 (C), 46.6 (CH_2), 32.7 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.92 (s, F), −111.90 (s, F); **HRMS (ESI)** *m/z*: 497.0993 (M+H), $C_{28}H_{20}F_{2Na}O_3S$ requires 497.0993.

(*R*)-1,1-Difluoro-6-(4-methoxyphenyl)-4-phenyl-1-(phenylsulfonyl)hex-5-yn-2-one (28ab).

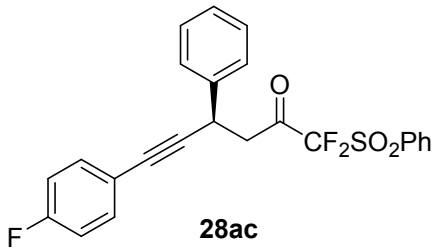


28ab

Enantiomeric excess (98%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 24.6 min, minor enantiomer t_r = 25.9 min.

Oil; **[α]$_D^{20}$** −20.9 (*c* 0.93, $CHCl_3$, 98% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.89-7.82 (m, 2H), 7.81-7.72 (m, 1H), 7.60-7.51 (m, 2H), 7.51-7.45 (m, 2H), 7.37 (dtt, *J* = 5.5, 3.8, 1.9 Hz, 4H), 7.33-7.27 (m, 1H), 6.87-6.78 (m, 2H), 4.46 (dd, *J* = 7.9, 6.1 Hz, 1H), 3.80 (s, 3H), 3.60 (dt, *J* = 10.4, 5.2 Hz, 1H), 3.41 (dd, *J* = 18.8, 6.1 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 191.8 (t, $J_{C,F}$ = 23.4 Hz, C), 159.5 (C), 139.8 (C), 136.1 (CH), 133.1 (2CH), 131.8 (C), 130.9 (2CH), 129.5 (2CH), 128.8 (2CH), 127.6 (2CH), 127.5 (CH), 114.5 (t, $J_{C,F}$ = 300.3 Hz, C), 115.1 (C), 113.8 (2CH), 87.5 (C), 83.6 (C), 55.3 (CH_3), 47.9 (CH_2), 32.6 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.8 (s, F), −111.6 (s, F); **HRMS (ESI)** *m/z*: 455.1128 (M+H), $C_{25}H_{21}F_2O_4S$ requires 454.1123.

(*R*)-1,1-Difluoro-6-(4-fluorophenyl)-4-phenyl-1-(phenylsulfonyl)hex-5-yn-2-one (28ac).

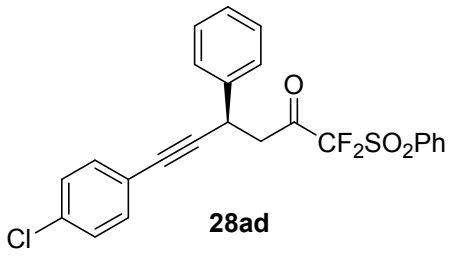


28ac

Enantiomeric excess (97%) was determined by chiral HPLC (Chiralpak IC), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 8.8 min, minor enantiomer t_r = 8.4 min.

Oil; **[α]$_D^{20}$** −4.7 (*c* 0.72, $CHCl_3$, 97% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.89-7.82 (m, 2H), 7.82-7.74 (m, 1H), 7.62-7.53 (m, 2H), 7.51-7.27 (m, 7H), 7.04-6.93 (m, 2H), 4.47 (dd, *J* = 8.1, 5.9 Hz, 1H), 3.62 (dd, *J* = 18.9, 8.1 Hz, 1H), 3.41 (dd, *J* = 18.9, 6.0 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 191.6 (t, $J_{C,F}$ = 24.1 Hz, C), 162.4 (d, $J_{C,F}$= 249.1 Hz, C), 139.5 (C), 136.1 (CH), 133.6 (d, $J_{C,F}$= 8.4 Hz, 2CH), 131.8 (C), 130.9 (2CH), 129.5 (2CH), 128.9 (2CH), 127.6 (2CH), 127.5 (CH), 119.1 (d, $J_{C,F}$= 3.4 Hz, 2CH), 115.6 (t, $J_{C,F}$ = 299.3 Hz, C), 115.5 (d, *J* = 22.0 Hz, C), 88.6 (C), 82.7 (C), 47.8 (CH_2), 32.5 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.7 (s, F), −111.6 (s, F), −111.5 (s, F); **HRMS (ESI)** *m/z*: 461.1232 /460.1196 ($M+NH_4^+$) 26 / 100, $C_{24}H_{21}F_3NO_3S$ requires 461.1228 /460.1194 .

(*R*)-6-(4-Chlorophenyl)-1,1-difluoro-4-phenyl-1-(phenylsulfonyl)hex-5-yn-2-one (28ad).

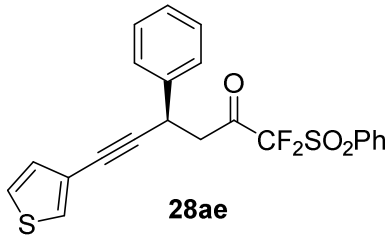


28ad

Enantiomeric excess (97%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 22.1 min, minor enantiomer t_r = 21.2 min.

Oil; **[α]$_D^{20}$** –9.0 (*c* 0.71, $CHCl_3$, 97% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.79-7.73 (m, 2H), 7.72-7.65 (m, 1H), 7.53-7.44 (m, 2H), 7.37 (dt, *J* = 3.2, 2.1 Hz, 2H), 7.33-7.14 (m, 7H), 4.38 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.53 (dd, *J* = 18.9, 8.1 Hz, 1H), 3.32 (dd, *J* = 18.9, 6.0 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 191.6 (t, $J_{C,F}$ = 23.9 Hz, C), 139.4 (2C), 136.1 (CH), 134.2 (C), 133.0 (2CH), 131.8 (C), 130.9 (2CH), 129.5 (2CH), 128.9 (2CH), 128.6 (2CH), 127.6 (2CH), 121.5 (CH), 114.5 (t, $J_{C,F}$ = 300.6 Hz, C), 90.0 (C), 82.7 (C), 47.7 (CH_2), 32.6 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –111.6 (s, F); –111.5 (s, F); **HRMS (ESI)** *m/z*: 478.0873 / 476.0892 ($M+NH_4^+$) 32/ 100, $C_{24}H_{21}ClF_2NO_3S$ requires 478.0869 / 476.0899.

(*R*)-1,1-Difluoro-4-phenyl-1-(phenylsulfonyl)-6-(thiophen-3-yl)hex-5-yn-2-one (28ae).

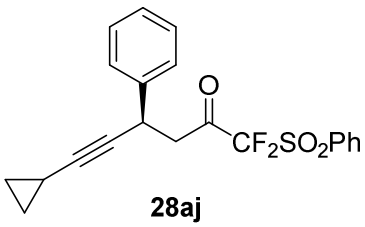


28ae

Enantiomeric excess (98%) was determined by chiral HPLC (Chiralpak IC), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 11.8 min, minor enantiomer t_r = 10.5 min.

Oil; **[α]$_D^{20}$** –3.3 (*c* 0.56, $CHCl_3$, 97% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.88-7.81 (m, 2H), 7.81-7.73 (m, 1H), 7.62-7.52 (m, 2H), 7.50-7.34 (m, 5H), 7.31 (dt, *J* = 9.8, 4.3 Hz, 1H), 7.24 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.11 (dd, *J* = 5.0, 1.2 Hz, 1H), 4.46 (dd, *J* = 8.0, 6.1 Hz, 1H), 3.62 (dd, *J* = 18.9, 8.0 Hz, 1H), 3.41 (dd, *J* = 18.9, 6.0 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 191.7 (t, $J_{C,F}$ = 23.1 Hz, C), 139.5 (C), 136.1 (CH), 131.8 (C), 130.9 (2CH), 130.0 (CH), 129.5 (2CH), 128.8 (2CH), 128.7 (CH), 127.6 (2CH), 127.5 (CH), 125.2 (CH), 122 (C), 114.5 (t, $J_{C,F}$ = 299.4 Hz, C), 88.5 (C), 78.9 (C), 47.8 (CH_2), 32.6 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –111.7 (s, F), –111.6 (s, F); **HRMS (ESI)** *m/z*: 431.0579 (M+H), $C_{22}H_{17}F_2O_3S_2$ requires 431.0582.

(*R*)-6-Cyclopropyl-1,1-difluoro-4-phenyl-1-(phenylsulfonyl)hex-5-yn-2-one (28aj).



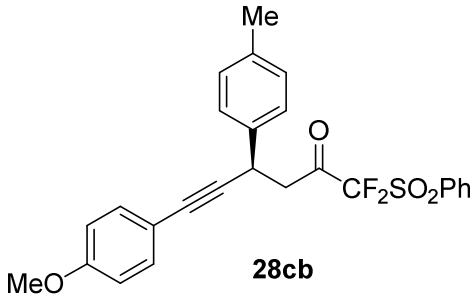
28aj

Enantiomeric excess (92%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 13.9 min, minor enantiomer t_r = 12.9 min

Oil; **[α]$_D^{20}$** –1.7 (*c* 0.91, $CHCl_3$, 97% *ee*); **^{1}H NMR (300**

MHz, $CDCl_3$) δ 7.88-7.83 (m, 2H), 7.83-7.75 (m, 1H), 7.64-7.57 (m, 3H), 7.43-7.26 (m, 4H), 4.20 (ddd, *J* = 7.9, 6.2, 1.8 Hz, 1H), 3.45 (ddt, *J* = 18.7, 7.9, 1.0 Hz, 1H), 3.34-3.22 (m, 1H), 1.64-1.11 (m, 1H), 0.77-0.70 (m, 2H), 0.70-0.62 (m, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 191.7 (t, $J_{C,F}$ = 23.9 Hz, C), 140.2 (C), 136.1 (CH), 131.9 (C), 130.9 (2CH), 129.5 (2CH), 128.7 (2CH), 127.5 (2CH), 127.3 (CH), 114.5 (t, $J_{C,F}$ = 300.8 Hz, C), 87.1 (C), 74.7 (C), 48.1 (CH_2), 32.1 (CH), 8.1 (CH_2), 8.1 (CH_2), 0.5 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.5 (s, 2F); **HRMS (ESI)** *m/z*: 389.0998 (M+H), $C_{21}H_{19}F_2O_3S$ requires 389.1023.

(*R*)-1,1-Difluoro-6-(4-methoxyphenyl)-1-(phenylsulfonyl)-4-(*p*-tolyl)hex-5-yn-2-one (28cb).

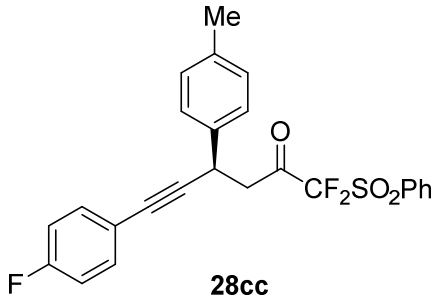


28cb

Enantiomeric excess (97%) was determined by chiral HPLC (Chiralpak IC), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 13.9 min, minor enantiomer t_r = 12.9 min.

Oil; **[α]$_D^{20}$** −4.2 (*c* 1.13, $CHCl_3$, 97% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.87-7.81 (m, 2H), 7.77 (ddt, *J* = 8.8, 7.1, 1.3 Hz, 1H), 7.61-7.49 (m, 2H), 7.43-7.32 (m, 4H), 7.18 (d, *J* = 7.8 Hz, 2H), 6.91-6.71 (m, 2H), 4.42 (dd, *J* = 7.9, 6.1 Hz, 1H), 3.80 (s, 3H), 3.59 (dd, *J* = 18.5, 8.4 Hz, 1H), 3.38 (dd, *J* = 18.9, 6.1 Hz, 1H), 2.36 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 191.2 (t, $J_{C,F}$ = 23.9 Hz, C), 159.4 (C), 137.1 (C), 136.9 (C), 136.1 (CH), 133.1 (2CH), 131.8 (C), 130.9 (2CH), 129.5 (2CH), 129.5 (2CH), 127.5 (2CH), 114.5 (t, $J_{C,F}$ = 300.4 Hz, C), 115.2 (C), 113.8 (2CH), 87.7 (C), 83.4 (C), 55.2 (CH_3), 47.9 (CH_2), 32.2 (CH), 21.1(CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.9 (s, F), −111.7 (s, F); **HRMS (ESI)** *m/z*: 469.1207 (M+H), $C_{26}H_{22}F_2O_4S$ requires 469.1285.

(*R*)-1,1-Difluoro-6-(4-fluorophenyl)-1-(phenylsulfonyl)-4-(*p*-tolyl)hex-5-yn-2-one (28cc).



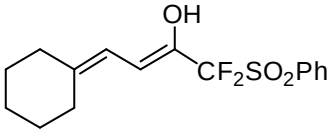
28cc

Enantiomeric excess (94%) was determined by chiral HPLC (Chiralpak IC), hexane-*i*PrOH 95:05, 1 mL/min, major enantiomer t_r = 9.4 min, minor enantiomer t_r = 8.5 min.

Oil; **[α]$_D^{20}$** −5.3 (*c* 0.77, $CHCl_3$, 94% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.82-7.75 (m, 2H), 7.75-7.67 (m, 1H), 7.53-7.45 (m, 2H), 7.39-7.25 (m, 4H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.96-6.86 (m, 2H), 4.35 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.53 (dd, *J* = 18.9, 8.2 Hz, 1H), 3.32 (dd, *J* = 18.9, 6.0 Hz, 1H), 2.29 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 191.7 (t, $J_{C,F}$ = 24.2 Hz, C), 162.4 (d, $J_{C,F}$= 249.2 Hz, C), 139.7 (C), 137.3 (C), 136.5 (CH), 136.1 (2CH), 133.6 (d, $J_{C,F}$= 8.3 Hz, 2CH), 131.7 (C), 130.9 (2CH), 129.5 (2CH), 127.5 (2CH), 119.1 (d, $J_{C,F}$= 3.8 Hz, 2CH), 115.6 (t, $J_{C,F}$ = 299.3 Hz, C), 115.5 (d, *J* = 22.1 Hz, C), 88.9 (C), 82.5 (C), 47.8 (CH_2), 32.1 (CH), 21.1

(CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −111.8 (s, F), −111.7 (s, F), −111.6 (s, F); **HRMS (ESI)** *m/z*: 475.1384 / 474.1345 ($M+NH_4^+$) 27 / 100, $C_{25}H_{23}F_3NO_3S$ requires 475.1384 / 474.1351.

Attempt of alkynylation of compound 27i (enol 27i')



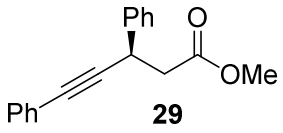
27i'

Compound **27i** was subjected to the general procedure of conjugate alkynylation with phenylacetylene. After 3 days and the habitual work up a compound that was identified as the enol form of compound **27i** was obtained after column chromatography eluting with hexane:EtOAc.

Oil; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.07-8.00 (m, 2H), 7.78-7.71 (m, 1H), 7.66-7.56 (m, 2H), 6.36 (d, *J* = 5.9 Hz, 1H), 5.85 (d, *J* = 5.9 Hz, 1H), 4.29 (s, 1H), 1.77-1.55 (m, 3H), 1.55-1.30 (m, 7H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 142.5 (CH), 135.2 (CH), 134.4 (C), 130.8 (2CH), 129.0 (2CH), 122.3 (CH), 117.7 (t, $J_{C,F}$ = 298.9 Hz, C), 108.1 (t, $J_{C,F}$ = 26.6 Hz, C), 93.6 (C), 37.9 (CH_2),35.7 (CH_2), 24.9 (CH_2), 23.0 (CH_2), 22.7 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −109.7 (s, 2F); **IR** ν 3485, 1449, 1334, 1147 cm^{-1}; **HRMS (ESI)** *m/z*: 327.0860 [M-H], $C_{16}H_{15}F_2O_3S$ requires 327.0861.

5.3.2.4. Determination of the absolute stereochemistry of compound 28aa

(*R*)-(−)-Methyl 3,5-diphenylpent-4-ynoate (29)

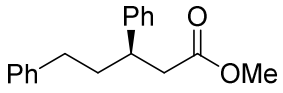


29

A solution of **28aa** (18 mg, 0.042 mmol, 91%*ee*) in THF (0.5 mL) and MeOH (0.7 mL) was stirred at 0 ºC for 3 h. Then, water 1.0 mL) was added and the mixture extracted with CH_2Cl_2 (2 x 10 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography to afford compound **29** (10.3 mg, 93%). Enantiomeric excess (91%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 9.8 min, minor enantiomer t_r = 9.4 min.

Oil; **$[\alpha]_D^{20}$** −7.5 (*c* 0.75, $CHCl_3$, 91% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.47-7.41 (m, 4H), 7.38-7.33 (m, 2H), 7.31-7.27 (m, 4H), 4.39 (dd, *J* = 8.2, 7.1 Hz, 1H), 3.70 (s, 3H), 2.93 (dd, *J* = 15.3, 8.2 Hz, 1H), 2.81 (dd, *J* = 15.3, 6.9 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 171.3 (C), 140.4 (C), 131.7 (2CH), 128.7 (2CH), 128.2 (2CH), 128.0 (CH), 127.4 (2CH), 127.3 (CH), 123.2 (C), 89.7 (C), 83.5 (C), 51.8 (CH_3), 43.2 (CH_2), 34.7 (CH); **HRMS (ESI)** *m/z*: 264.1148 (M), $C_{18}H_{16}O_2$ requires 264.1150.

(*R*)-(–)-Methyl 3,5-diphenylpentanoate (30)

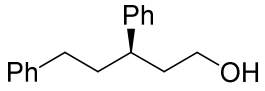


30

A solution of **29** (10 mg, 0.038 mmol) in EtOAc (0.4 mL) was stirred under hydrogen atmosphere in the presence of 5% Pd/C (3 mg) for 1 h. Then, the reaction mixture was filtered through silica gel eluting with EtOAc and the solvent was removed under reduced pressure. Purification by flash chromatography gave compound **30** (9.0 mg, 89%). Enantiomeric excess (91%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 8.3 min, minor enantiomer t_r = 8.8 min.

Oil; **$[\alpha]_D^{20}$** –12.8 (*c* 0.50, $CHCl_3$, 91% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.36-7.27 (m, 2H), 7.26-7.22 (m, 4H), 7.21-7.14 (m, 2H), 7.11-7.08 (m, 2H), 3.57 (s, 3H), 3.19-3.09 (m, 1H), 2.70-2.56 (m, 2H), 2.45 (t, *J* = 8.0 Hz, 2H), 2.07-1.86 (m, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 172.7 (C), 143.5 (C), 141.9 (C), 128.5 (2CH), 128.3 (2CH), 128.3 (2CH), 127.5 (2CH), 126.6 (CH), 125.8 (CH), 51.5 (CH_3), 41.8 (CH), 41.7 (CH_2), 37.7 (CH_2), 33.5 (CH_2); **HRMS (ESI)** *m/z*: 269.1465 (M), $C_{18}H_{20}O_2$ requires 268.1463.

(*R*)-(–)-3,5-Diphenylpentan-1-ol (31)



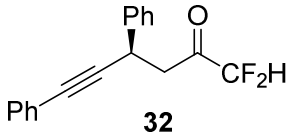
31

Lithium aluminum hydride (1.0 mg, 0.026 mmol) was added to a solution of **30** (9.0 mg, 0.034 mmol) in THF (0.5 mL) at 0 ºC, and the solution was stirred for 20 min. The reaction mixture was quenched with 20 % aqueous NH_4Cl (1.0 mL), extracted with CH_2Cl_2 (2 x 15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography to afford compound **31** (7.6 mg, 95%). Enantiomeric excess (91%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 90:10, 0.5 mL/min, major enantiomer t_r = 16.1 min, minor enantiomer t_r= 21.2 min,{ Lit.[61] Chiralcel OD-H, hexane-^{i}PrOH 90:10, 0.5 mL/min, *R*-enantiomer t_r = 14.9 min, *S*-enantiomer t_r = 18.2 min}.

Oil; **$[\alpha]_D^{20}$** –1.3 (*c* 0.40, $CHCl_3$, 91% *ee*), Lit[61] $[\alpha]_D^{20}$ +1.35(*c* 0.77, $CHCl_3$, 87% *ee*) for the *R*-enantiomer; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.36-7.28 (m, 2H), 7.26-7.09 (m, 8H), 3.57-3.41 (m, 2H), 2.79-2.69 (m, 1H), 2.46 (t, *J* = 8.0 Hz, 2H), 2.03-1.82 (m, 4H), 1.15 (br s, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 144.6 (C), 142.3 (C), 128.6 (2CH), 128.3 (2CH), 128.3 (2CH), 127.7 (2CH), 126.3 (CH), 125.7 (CH), 61.1 (CH_2), 42.0 (CH), 39.7 (CH_2), 38.6 (CH_2), 33.7 (CH_2); **HRMS (ESI)** *m/z*: 240.1516 (M+H), $C_{17}H_{20}O$ requires 240.1514.

5.3.2.5. Synthetic transformations

(*R*)-1,1-Difluoro-4,6-diphenylhex-5-yn-2-one (32)

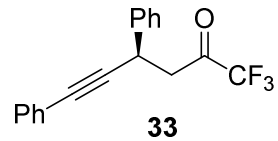


32

Magnesium powder (3 mg, 0.118 mmol) was added to a solution of compound **28aa** (25.0 mg, 0.059 mmol) in THF (0.7 mL) at 0 °C under nitrogen atmosphere. Then, TMSCl (30 µL, 0.236 mmol) was added and the mixture stirred at 0 °C for 30 min. The reaction mixture was quenched with 2 drops of 0.01 M HF, diluted with water (1 mL), extracted with CH_2Cl_2 (10 mL), washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography gave compound **32** (13.7 mg, 83%). Enantiomeric excess (98%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 7.0 min, minor enantiomer t_r = 6.5 min.

Oil; **[α]$_D^{20}$** –5.0 (*c* 1.00, $CHCl_3$, 98% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.48-7.39 (m, 4H), 7.37-7.34 (m, 2H), 7.31-7.29 (m, 4H), 5.70 (t, $J_{C,F}$ = 53.9 Hz, 1H), 4.46 (dd, *J* = 8.2, 1.1 Hz, 1H), 3.35 (ddt, *J* = 17.8, 8.2, 1.1 Hz, 1H), 3.14 (ddt, *J* = 17.8, 6.1, 0.9 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 191.1 (t, $J_{C,F}$ = 26.2 Hz, C), 140.4 (C), 132.1 (2CH), 129.3 (2CH), 128.7 (2CH), 128.6 (C), 127.9 (C), 127.9 (2CH), 123.4 (C), 110.1 (t, $J_{C,F}$ = 252.9 Hz, C), 89.7 (C), 84.1 (C), 45.3 (CH_2), 33.0 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –127.9 (s, 2F); **HRMS (ESI)** *m/z*: 285.1079 (M+H), $C_{18}H_{15}F_2O$ requires 285.1085.

(*R*)-1,1,1-Trifluoro-4,6-diphenylhex-5-yn-2-one (33)

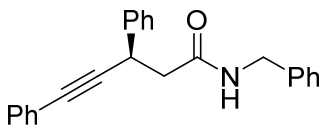


33

Magnesium powder (3 mg, 0.118 mmol) was added to a solution of compound **28aa** (25.0 mg, 0.059 mmol) in THF (0.7 mL) at 0 °C under nitrogen atmosphere. Then, TMSCl (30 µL, 0.236 mmol) was added and the mixture stirred at 0 °C for 30 min. The solvent and volatiles were removed under reduced pressure. The residue was dissolved in acetonitrile (0.2 mL) under nitrogen and Selectfluor (12.0 mg, 0.033 mmol) was added. After 5h, the reaction mixture was diluted with EtOAc (10 mL), washed with brine (5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by chromatography gave compound **33** (10.7 mg, 60%). Enantiomeric excess (97%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 4.6 min, minor enantiomer t_r = 4.3 min.

Oil; **[α]$_D^{20}$** –1.0 (*c* 0.27, $CHCl_3$, 97% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.50-7.44 (m, 2H), 7.44-7.39 (m, 2H), 7.39-7.34 (m, 2H), 7.34-7.27 (m, 4H), 4.49 (dd, *J* = 8.2, 6.0 Hz, 1H), 3.39 (ddd, *J* = 18.1, 8.3, 0.5 Hz, 1H), 3.19 (ddd, *J* = 18.2, 6.0, 0.3 Hz 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.5 (q, $J_{C,F}$ = 35.9 Hz, C), 139.5 (C), 131.7 (2CH), 128.9 (2CH), 128.2 (3CH), 127.6 (CH), 127.4 (2CH), 122.8 (CH), 115.3 (q, $J_{C,F}$ = 291.9 Hz, C), 88.6 (C), 84.0 (C), 45.1 (CH_2), 32.6 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.9 (s, 2F); **HRMS (ESI)** *m/z*: 303.0998 (M+H), $C_{18}H_{14}F_3$ requires 303.0991.

(*R*)-(–)-*N*-Benzyl-3,5-diphenylpent-4-ynamide (34)



34

A solution of benzylamine (37 µL, 0.336 mmol) in THF (0.4 mL) was added to a solution of **28aa** (20 mg, 0.048 mmol, 98%*ee*) in THF (0.6 mL) at 0 ºC. After 2 h, water (1.0 mL), was added ant the mixture extracted with CH_2Cl_2 (10 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography gave compound **34** (11.7 mg, 73%). Enantiomeric excess (97%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 85:15, 1 mL/min, major enantiomer t_r = 17.9 min, minor enantiomer t_r = 23.5 min.

Oil; **$[\alpha]_D^{20}$** –25.0 (*c* 1.00, $CHCl_3$, 97% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.49-7.45 (m, 2H), 7.37-7.26 (m, 8H), 7.22-7.15 (m, 5H), 5.90 (br s, 1H), 4.53-4.44 (m, 2H), 4.38 (dd, *J* = 14.8, 5.6 Hz, 1H), 2.80-2.66 (m, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 169.9 (C), 140.5 (C), 137.8 (C), 131.7 (2CH), 128.8 (2CH), 128.6 (2CH), 128.2 (2CH), 128.1 (CH), 127.7 (2CH), 127.4 (3CH), 127.2 (CH), 123.0 (C), 90.0 (C), 84.1 (C), 46.0 (CH_2), 43.7 (CH_2), 35.3 (CH); **HRMS (ESI)** *m/z*: 341.1701 (M+H), $C_{24}H_{22}NO$ requires 340.1696.

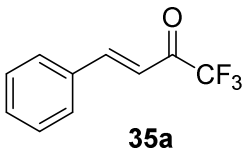
5.4. Enantioselective conjugate alkynylation of α,β-unsaturated trifluoromethyl ketones

5.4.1. Synthesis and characterization of α,β-unsaturated trifluoromethyl ketones 35

α,β-Unsaturated trifluoromethyl ketones were synthesized according to the procedure described by Shreeve et al.[67]

Trifluoromethyltrimethylsilane (0.34 mL, 2.31 mmol) was added to a solution of the required α,β-unsaturated methyl ester (1.85 mmol) in pentane (1 mL) at room temperature under nitrogen atmosphere. A 1 M solution of tetrabutylammonium fluoride (TBAF) in THF (5 μL, 0.046 mmol) was added at 0 ºC and the reaction mixture was allowed to warm to room temperature and stirred for 18 h. Then, the solvent was removed under reduced pressure. The residue was dissolved in THF (1 mL) and treated with 4 M aqueous HCl (1 mL). After 10 h, the reaction mixture was diluted with diethyl ether (20 mL), washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:EtOAc (99:01) gave the corresponding enones **35**.

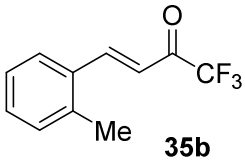
(*E*)-1,1,1-Trifluoro-4-phenylbut-3-en-2-one (35a)



35a

Yellow oil; 90% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.98 (d, *J* = 16.0 Hz, 1H), 7.68-7.70 (m, 2H), 7.51-7.42 (m, 3H), 7.03 (dd, *J* = 16.0, 0.8 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 179.5 (q, $J_{C\text{-}F}$ = 35.1 Hz, C), 146.9 (CH),139.3 (C),131.8 (CH), 130.9 (CH),126.5 (CH), 126.3 (CH),116.7 (CH),116.4 (q, $J_{C\text{-}F}$ = 290.9 Hz, CF_3), 18.9 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.3 (s, 3F). Data consistent with the literature.[109]

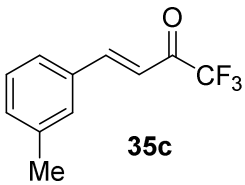
(*E*)-1,1,1-Trifluoro-4-(*o*-tolyl)but-3-en-2-one (35b)



35b

Yellow oil, 85% yield; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.31 (d, *J* = 15.8 Hz, 1H), 7.70-7.68 (m, 1H),7.39 (dt, *J* = 3.9, 1.4 Hz, 1H),7.29-7.25 (m, 1H), 6.96 (dd, *J* = 15.8, 0.8 Hz, 1H),2.50 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 179.5 (q, $J_{C\text{-}F}$ = 35.1 Hz, C), 146.9 (CH),139.3 (C),131.8 (CH), 130.9 (CH),126.5 (CH), 126.3 (CH),116.7 (CH),116.4 (q, $J_{C\text{-}F}$ = 290.9 Hz, CF_3), 18.9 (CH_3); **^{19}F NMR (376 MHz, $CDCl_3$)** δ −78.3 (s, 3F). Data consistent with the literature.[110]

(*E*)-1,1,1-Trifluoro-4-(*m*-tolyl)but-3-en-2-one (35c)

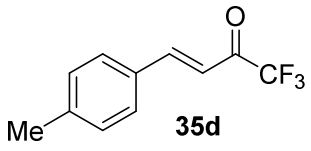


35c

Yellow oil, 60% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.88 (d, *J* = 16.0 Hz, 1H), 7.39-7.37 (m, 2H),7.31-7.26 (m, 2H),6.95 (dd, *J* = 16.0, 0.8 Hz, 1H), 2.50 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 180.0 (q, $J_{C\text{-}F}$ = 35.3 Hz, C), 150.4 (CH), 139.0 (C), 133.2 (CH), 129.8 (CH), 129.1 (CH), 126.5 (CH), 116.4 (q, $J_{C\text{-}F}$ = 290.8 Hz,

CF_3), 116.3 (CH), 21.2 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.1 (s, 3F). Data consistent with the literature.[111]

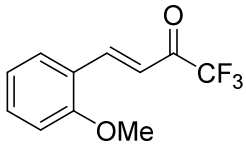
(*E*)-1,1,1-Trifluoro-4-(*p*-tolyl)but-3-en-2-one (35d)



35d

Yellow oil, 89% yield;**^{1}H NMR (300 MHz, $CDCl_3$)**δ7.95 (d, *J* = 15.9 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 6.97 (dd, *J* = 15.9, 0.7 Hz, 1H), 2.41 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$)**δ180.0 (q, $J_{C\text{-}F}$ = 35.3 Hz, C), 150.2 (CH), 143.4 (C), 130.7 (C), 130.0 (2CH), 129.3 (2CH), 116.5 (q, $J_{C\text{-}F}$ = 291.0 Hz, CF_3), 115.6 (CH), 21.7 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)**δ−78.2(s, 3F). Data consistent with the literature.[112]

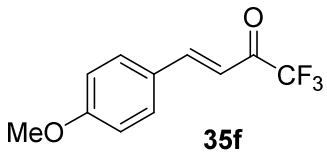
(*E*)-1,1,1-Trifluoro-4-(2-methoxyphenyl)but-3-en-2-one (35e)



35e

Yellow oil, 63% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.29 (d, *J* = 16.0 Hz, 1H), 7.60 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.46 (ddd, *J* = 8.5, 7.4, 1.7 Hz, 1H), 7.14 (dd, *J* = 16.1, 0.9 Hz, 1H), 7.01 (td, *J* = 7.5, 0.7 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 3.93 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 180.5 (q, $J_{C\text{-}F}$= 34.6 Hz, C), 159.6 (C), 145.8 (CH), 133.7 (CH), 130.3 (CH), 122.4 (C), 120.9 (CH), 117.1 (CH), 116.5 (q, $J_{C\text{-}F}$= 290.9 Hz, CF_3), 111.4 (CH), 55.6 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.0 (s, 3F). Data consistent with the literature.[110]

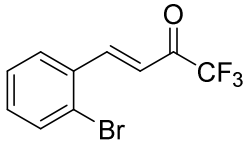
(*E*)-1,1,1-Trifluoro-4-(4-methoxyphenyl)but-3-en-2-one (35f)



35f

Yellow oil, 73% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.94 (d, *J* = 15.8 Hz, 1H), 7.63-7.60 (m, 2H), 6.97-6.94 (m, 2H), 6.89 (dd, *J* = 15.8, 0.8 Hz, 1H), 3.88 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 179.9 (q, $J_{C\text{-}F}$ = 35.3 Hz, C), 163.2 (C), 149.9 (CH), 131.4 (2CH), 126.2 (C), 116.4 (q, $J_{C\text{-}F}$= 290.9 Hz, CF_3), 114.8 (2CH), 114.1 (CH), 55.5 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.0 (s, 3F). Data consistent with the literature.[109]

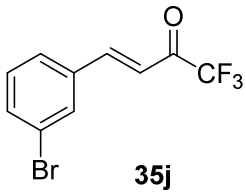
(*E*)-4-(2-Bromophenyl)-1,1,1-trifluorobut-3-en-2-one (35g)



35i

Yellow oil, 54% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.37 (d, *J* = 16.0 Hz, 1H), 7.72 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.67 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.39-7.30 (m, 2H),6.99-6.94 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 179.8 (q, $J_{C\text{-}F}$ = 35.7 Hz, C), 148.3 (CH), 136.7 (C), 133.9 (CH), 133.0 (CH), 128.1 (CH), 128.0 (CH), 119.1 (CH), 116.3 (q, $J_{C\text{-}F}$ = 290.9 Hz, CF_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.0 (s, 3F). Data consistent with the literature.[109]

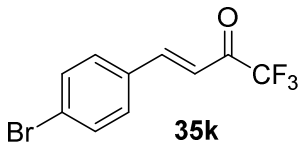
(*E*)-4-(3-Bromophenyl)-1,1,1-trifluorobut-3-en-2-one (35h)



35j

Yellow oil, 63% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 16.0 Hz, 1H), 7.78 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.33 (t, $J_{C\text{-}F}$= 7.9 Hz, 1H), 7.00 (dd, *J* = 16.0, 0.8 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 179.8 (q, $J_{C\text{-}F}$= 35.9 Hz, C), 148.2 (CH), 135.3 (C), 135.0 (CH), 131.6 (CH), 130.7 (CH), 127.8 (CH), 123.3 (C), 117.9 (CH), 116.2 (q, $J_{C\text{-}F}$= 290.6 Hz, CF_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.1 (s, 3F). Data consistent with the literature.[112]

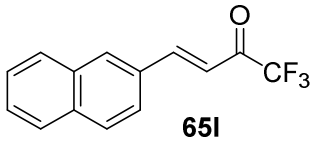
(*E*)-4-(4-Bromophenyl)-1,1,1-trifluorobut-3-en-2-one (35i)



35k

Yellow oil, 75% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.89 (d, *J* = 16.0 Hz, 1H), 7.65-7.55 (m, 2H), 7.55-7.45 (m, 2H), 7.00 (dd, *J* = 16.0, 0.8 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 179.9 (q, $J_{C\text{-}F}$ = 35.3 Hz, C), 148.6 (CH), 132.6 (2CH), 132.2 (C), 130.4 (2CH), 127.0 (C), 117.1 (CH), 116.3 (q, $J_{C\text{-}F}$= 290.7 Hz, CF_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.1 (s, 3F). Data consistent with the literature.[109]

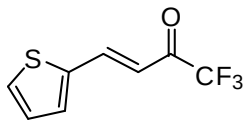
(*E*)-1,1,1-Trifluoro-4-(naphthalen-2-yl)but-3-en-2-one (35j)



65l

Yellow solid, **mp** 63-65 ºC, 70% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.13 (d, *J* = 15.9 Hz, 1H), 8.06 (s, 1H), 7.92-7.85 (m, 3H), 7.73 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.62-7.53 (m, 2H), 7.12 (dd, *J* = 15.9, 0.8 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 180.0 (q, $J_{C\text{-}F}$ = 35.2 Hz, C), 150.2 (CH), 135.1 (C), 133.1 (C), 132.7 (CH), 130.8 (C), 129.1 (CH), 129.0 (CH), 128.4 (CH), 127.9 (CH), 127.1 (CH), 123.3 (CH), 116.6 (CH), 116.4 (q, $J_{C\text{-}F}$= 290.8 Hz, CF_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −78.0 (s, 3F). Data consistent with the literature.[109]

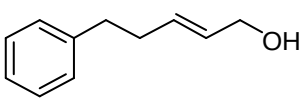
(*E*)-1,1,1-Trifluoro-4-(thiophen-2-yl)but-3-en-2-one (35k)



Yellow solid, 50% yield; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.84 (d, *J* = 15.5 Hz, 1H), 7.34 (d, *J* = 5.0 Hz, 1H), 7.25 (d, *J* = 3.7 Hz, 1H), 6.92 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.55 (d, *J* = 15.6 Hz, 1H). Data consistent with the literature.[109]

Synthesis of (*E*)-1,1,1-trifluoro-6-phenylhex-3-en-2-one (35l)

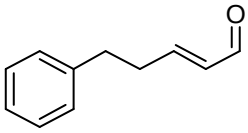
(*E*)-5-Phenylpent-2-en-1-ol



DIBAL–H (4.2 mL, 4.20 mmol, 1 M in toluene) was added to a solution of methyl (*E*)-5-phenylpent-2-enoate (400 mg, 2.10 mmol) in THF (5 mL) at −78 ºC under nitrogen atmosphere. After 4 h, saturated aqueous Roche's salt solution (8 mL) and ethyl acetate (6 mL) were added and the mixture stirred for 1 h. The organic layer was separated and dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by

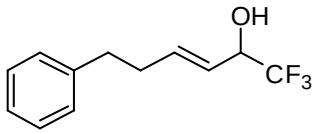
column chromatography to give (*E*)-5-phenylpent-2-en-1-ol (320 mg, 94%). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.32-7.27 (m, 2H), 7.22-7.18 (m, 3H), 5.78-5.63 (m, 2H), 4.09 (d, *J* = 5.0 Hz, 2H), 2.75-2.68 (m, 2H), 2.43-2.37 (m, 2H), 1.46 (br s, 1H). Data consistent with the literature.[113]

(*E*)-5-Phenylpent-2-enal



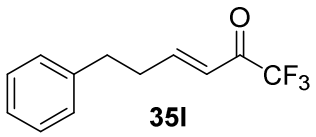
MnO_2 (2.97 g, 34.2 mmol) was added to a stirred solution of (*E*)-5-phenylpent-2-en-1-ol (300 mg, 1.86 mmol) in dichloromethane (16 mL) at room temperature under nitrogen atmosphere. After 72 h, dichloromethane was evaporated and the resulting crude was purified by column chromatography to give (*E*)-5-phenylpent-2-enal as a liquid (278 mg, 93%). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 9.50 (d, *J* = 7.8 Hz, 1H), 7.34-7.29 (m, 2H), 7.24-7.18 (m, 3H), 6.87 (dt, *J* = 15.6, 6.6 Hz, 1H), 6.14 (ddt, *J* = 15.7, 7.9, 1.5 Hz, 1H), 2.87-2.82 (m, 2H), 2.71-2.63 (m, 2H). Data consistent with the literature.[114]

(*E*)-1,1,1-Trifluoro-6-phenylhex-3-en-2-ol



A 1 M solution of TBAF in THF (0.16 mL, 0.156 mmol) was added to a solution of (*E*)-5-phenylpent-2-enal (250 mg, 1.56 mmol) and $TMSCF_3$ (0.3 mL, 2.06 mmol) in pentane (1 mL) at 0 ºC under nitrogen atmosphere. The mixture was stirred at room temperature for 24 h and pentane was evaporated under reduced pressure. THF (1 mL) and 4 M aqueous HCl (1 mL) were added, and the mixture was stirred for 24 h. Then, the organic layer was separated, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography gave (*E*)-1,1,1-trifluoro-6-phenylhex-3-en-2-ol (340 mg, 94%). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.34-7.18 (m, 5H), 6.07-5.98 (m, 1H), 5.55 (dd, *J* = 15.5, 6.8 Hz, 1H), 4.44-4.34 (m, 1H), 2.78-2.73 (m, 2H), 2.49-2.42 (m, 2H), 2.24 (d, *J* = 5.6 Hz, 1H). Data consistent with the literature.[115]

(*E*)-1,1,1-Trifluoro-6-phenylhex-3-en-2-one (35l)



35l

Dess-Martin periodinane (720 mg, 1.70 mmol) was added in one portion to a solution of (*E*)-1,1,1-trifluoro-6-phenylhex-3-en-2-ol (300 mg, 1.30 mmol) in dichloromethane (2.6 mL) at room temperature under nitrogen atmosphere. After 48 h, the resulting suspension was poured into 3 mL of a 5:1 mixture of saturated aqueous $Na_2S_2O_3$ solution and saturated aqueous $NaHCO_3$ solution. The organic layer was washed with water, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography to give **35l** (200 mg, 67%).

Oil; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.33-7.11 (m, 6H), 6.36 (dd, *J* = 15.8, 1.1 Hz, 1H), 2.81-2.76 (m, 2H), 2.64-2.56 (m, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 179.7 (q, $J_{C\text{-}F}$ = 35.3 Hz, C), 155.2 (CH), 139.9 (C), 128.6 (2CH), 128.3 (2CH), 126.5 (CH), 121.9 (CH), 116.4 (q, $J_{C\text{-}F}$= 290.8 Hz, CF_3), 34.8 (CH_2), 33.8 (CH_2); **^{19}F NMR (282 MHz,**

$CDCl_3$) δ −78.0 (s, 3F).**HRMS (ESI)** *m/z*: 228.0754 (M+H), $C_{12}H_{11}F_3O$ requires 228.0762.

5.4.2. Enantioselective conjugate addition of terminal alkynes to 1,1,1-trifluoromethyl-3-en-2-ones

5.4.2.1. General procedure for the enantioselective alkynylation reaction

$[Cu(CH_3CN)_4]BF_4$ (1.1 mg, 0.0034 mmol) and (*R*)-**L31** (4.1 mg, 0.0034 mmol) were added to a dried round bottom flask which was purged with nitrogen. Toluene (0.2 mL) was added via syringe and the mixture was stirred for 1.5 h at room temperature under nitrogen atmosphere. Then, a solution of α,β-unsaturated trifluoromethyl ketone **35** (0.144 mmol) in toluene (1.0 mL)was added via syringe, followed of triethylamine (2 µL, 0.0144 mmol). The solution was stirred for 10 min at room temperature. Then, alkyne **2** (0.188 mmol) was added via syringe and the solution was stirred at room temperature until the reaction was complete (TLC). The reaction mixture was quenched with 20% aqueous NH_4Cl (1.0 mL), extracted with CH_2Cl_2 (2 x 15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:ethyl acetate mixtures afforded compound **33**.

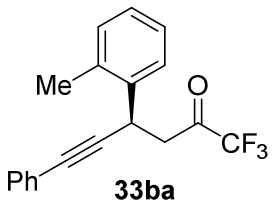
5.4.2.2. General procedure for the synthesis of the racemic products

Racemic compounds **33** were prepared by following the general procedure using racemic ligand (±)-**L31.**

5.4.2.3. Characterization of products 33

See Table 12 (Page 66) for yields.

(*S*)-1,1,1-Trifluoro-6-phenyl-4-(*o*-tolyl)hex-5-yn-2-one (33ba)

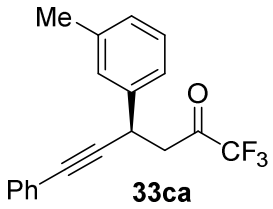


33ba

Enantiomeric excess (98%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 12.2 min, minor enantiomer t_r = 10.5 min.

Oil; **$[\alpha]_D^{20}$** +3.9 (*c* 1.08, $CHCl_3$, 98% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.54-7.51 (m, 1H), 7.38-7.34 (m, 2H), 7.26-7.15 (m, 6H), 4.63 (dd, *J* = 9.2, 5.1 Hz, 1H), 3.33 (ddd, *J* = 18.0, 9.2, 0.5 Hz, 1H), 3.09 (dd, *J* = 18.0, 5.1 Hz, 1H), 2.40 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.7 (q, J_{C-F} = 36.1 Hz, C), 137.5 (C), 135.0 (C), 131.7 (2CH), 130.9 (CH), 128.2 (2CH), 128.2 (CH), 127.6 (CH), 127.3 (CH), 126.7 (CH), 122.9 (C), 115.4 (q, J_{C-F}= 291.8 Hz, CF_3), 88.7 (C), 83.5 (C), 43.6 (CH_2), 29.3 (CH),19.2 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.8 (s, 3F);**HRMS (ESI)** *m/z*: 317.1140 (M+H), $C_{19}H_{16}F_3O$ requires 317.1153.

(*R*)-1,1,1-Trifluoro-6-phenyl-4-(*m*-tolyl)hex-5-yn-2-one (33ca)

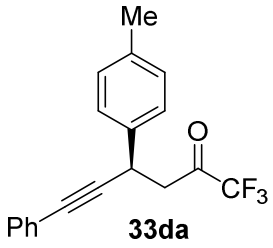


33ca

Enantiomeric excess (96%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 6.5 min, minor enantiomer t_r = 5.5 min.

Oil; **[α]$_D^{20}$** +0.5 (*c* 1.00, $CHCl_3$, 96% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.42-7.36 (m, 2H), 7.32-7.23 (m, 6H), 7.10-7.07 (m, 1H), 4.42 (dd, *J* = 8.4, 5.9 Hz, 1H), 3.35 (ddd, *J* = 18.1, 8.4, 0.5 Hz, 1H), 3.13 (dd, *J* = 18.1, 5.9 Hz, 1H), 2.39 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.6 (q, J_{C-F}= 36.0 Hz, C), 139.4 (C), 138.7 (C), 131.7 (2CH), 128.8 (CH), 128.4 (CH), 128.2 (2CH), 128.1 (CH), 124.4 (CH), 122.9 (C), 115.3 (q, J_{C-F} = 292.2 Hz, CF_3), 88.7 (C), 83.8 (C), 45.1 (CH_2), 32.5 (CH),21.4 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.9 (s, 3F); **HRMS (ESI)** *m/z*: 317.1149 (M+H), $C_{19}H_{16}F_3O$ requires 317.1153.

(*R*)-1,1,1-Trifluoro-6-phenyl-4-(*p*-tolyl)hex-5-yn-2-one (33da)

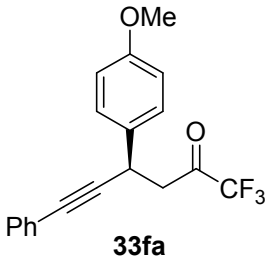


33da

Enantiomeric excess (95%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 6.1 min, minor enantiomer t_r = 5.6 min.

Oil; **[α]$_D^{20}$** −0.5 (*c* 1.05, $CHCl_3$, 95% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.43-7.40 (m, 2H), 7.36-7.29 (m, 5H), 7.19-7.17 (m, 2H), 4.45 (dd, *J* = 8.1, 6.1 Hz, 1H), 3.37 (ddd, *J* = 18.2, 8.2, 0.5 Hz, 1H), 3.17 (dd, *J* = 18.2, 6.1 Hz, 1H), 2.35 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.6 (q, J_{C-F} = 36.1 Hz, C), 137.4 (C), 136.5 (C), 131.7 (2CH), 129.6 (2CH), 128.2 (2CH), 128.2 (CH), 127.2 (2CH), 122.9 (C), 115.3 (q, J_{C-F}= 291.1 Hz, CF_3), 88.8 (C), 83.8 (C), 45.1 (CH_2), 32.2 (CH),21.0 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.9 (s, 3F);**HRMS (ESI)** *m/z*: 317.1142 (M+H), $C_{19}H_{16}F_3O$ requires 317.1153.

(*R*)-1,1,1-Trifluoro-4-(4-methoxyphenyl)-6-phenylhex-5-yn-2-one (33fa)

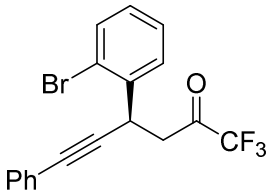


33fa

Enantiomeric excess (94%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 12.6 min, minor enantiomer t_r = 12.0 min.

Oil; **[α]$_D^{20}$** −5.6 (*c*1.02, $CHCl_3$, 94% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.43-7.38 (m, 3H), 7.37-7.35 (m, 1H), 7.31-7.29 (m, 3H), 6.92-6.87 (m, 2H), 4.44 (dd, *J* = 7.9, 6.4 Hz, 1H), 3.81 (s, 3H), 3.36 (ddd, *J* = 18.1, 8.0, 0.6 Hz, 1H), 3.16 (ddd, *J* = 18.1, 6.3, 0.4 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.6 (q, J_{C-F}= 35.9 Hz, C), 159.0 (C), 131.7 (2CH), 131.5 (C), 128.5 (2CH), 128.2 (2CH), 128.2 (CH), 122.9 (C), 115.3 (q, J_{C-F}= 291.8 Hz, CF_3), 114.3 (2CH), 88.9 (C), 83.8 (C), 55.3 (CH_3), 45.3 (CH_2), 31.9 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.9 (s, 3F); **HRMS (ESI)** *m/z*: 333.1097 (M+H), $C_{19}H_{16}F_3O_2$ requires 333.1102.

(*S*)-4-(2-Bromophenyl)-1,1,1-trifluoro-6-phenylhex-5-yn-2-one (33ga)

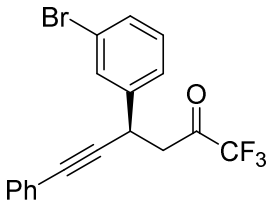


33ga

Enantiomeric excess (98%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 7.5 min, minor enantiomer t_r = 7.1 min.

Oil; **[α]$_D^{20}$** –8.4 (*c* 0.89, $CHCl_3$, 98% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.80 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.46-7.42 (m, 2H), 7.38 (td, *J* = 7.6, 1.3 Hz, 1H), 7.33-7.30 (m, 3H), 7.19 (td, *J* = 7.8, 1.7 Hz, 1H), 4.91 (t, *J* = 6.9 Hz, 1H), 3.25 (d, *J* = 7.0 Hz, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.2 (q, J_{C-F}= 36.1 Hz, C), 138.3 (C), 133.2 (CH), 131.7 (2CH), 129.6 (CH), 129.3 (CH), 128.4 (CH),128.3 (2CH), 128.1 (CH), 123.0 (C), 122.6 (C), 115.4 (q, J_{C-F} = 291.9 Hz, CF_3), 87.4 (C), 84.8 (C), 43.3 (CH_2), 32.8 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.7 (s, 3F); **HRMS (ESI)** *m/z*: 381.0095/383.0074 (M+H) 100/97.3, $C_{18}H_{13}BrF_3O$ requires 381.0102/383.0081.

(*R*)-4-(3-Bromophenyl)-1,1,1-trifluoro-6-phenylhex-5-yn-2-one (33ha)

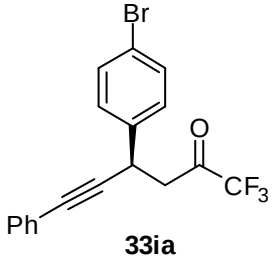


33ha

Enantiomeric excess (93%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 7.2 min, minor enantiomer t_r = 5.4 min.

Oil; **[α]$_D^{20}$** +3.9 (*c* 0.61, $CHCl_3$, 93% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.62 (t, *J* = 1.9 Hz, 1H), 7.45-7.37 (m, 4H), 7.33-7.30 (m, 3H), 7.24 (t, *J* = 7.8 Hz, 1H), 4.46 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.38 (ddd, *J* = 18.3, 8.1, 0.5 Hz, 1H), 3.17 (dd, *J* = 18.3, 6.0 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.2 (q, J_{C-F} = 36.1 Hz, C), 141.7 (C), 131.7 (2CH), 130.9 (CH), 130.6 (CH), 130.5 (CH), 128.5 (CH), 128.3 (2CH), 126.1 (CH), 122.9 (C), 122.5 (C), 115.3 (q, J_{C-F} = 291.6 Hz, CF_3), 87.7 (C), 84.5 (C), 44.9 (CH_2), 32.2 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.8 (s, 3F); **HRMS (ESI)** *m/z*: 381.0097/383.0076 (M+H)100/97.3, $C_{18}H_{13}BrF_3O$ requires 381.0102/383.0081.

(*R*)-4-(4-Bromophenyl)-1,1,1-trifluoro-6-phenylhex-5-yn-2-one (33ia)

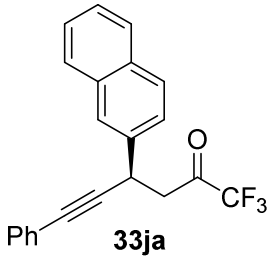


33ia

Enantiomeric excess (90%) was determined after hydrogenation of the triple bond (see section 5.4.2.4.)

Oil; **[α]$_D^{20}$** –1.8 (*c*1.04, $CHCl_3$, 90% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.53-7.48 (m, 2H), 7.43-7.40 (m, 2H), 7.36-7.30 (m, 5H), 4.45 (dd, *J* = 7.5, 6.6 Hz, 1H), 3.38 (ddd, *J* = 18.3, 7.8, 0.5 Hz, 1H), 3.17 (ddd, *J* = 18.3, 6.0, 0.3 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.3 (q, J_{C-F} = 36.1 Hz, C), 138.5 (C), 132.0 (2CH), 131.6 (2CH), 129.2 (2CH), 128.4 (CH), 128.3 (2CH), 122.5 (C), 121.6 (C), 115.2 (q, J_{C-F} = 291.7 Hz, CF_3), 114.3 (2CH), 87.9 (C), 84.3 (C), 44.8 (CH_2), 32.1 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.8 (s, 3F); **HRMS (ESI)** *m/z*: 381.0097/383.0076 (M+H)100/97.3, $C_{18}H_{13}BrF_3O$ requires 381.0102/383.0081.

(*R*)-1,1,1-Trifluoro-4-(naphthalene-2-yl)-6-phenylhex-5-yn-2-one (33ja)

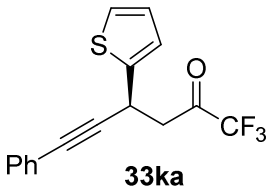


33ja

Enantiomeric excess (94%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 14.7 min, minor enantiomer t_r = 10.7 min.

Oil; **[α]$_D^{20}$** –11.6 (*c* 0.99, $CHCl_3$, 94% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.93-7.84 (m, 4H), 7.59-7.44 (m, 5H), 7.35-7.30 (m, 3H), 4.67 (dd, *J* = 8.1, 6.1 Hz, 1H), 3.48 (dd, *J* = 18.2, 8.2, 1H), 3.30 (dd, *J* = 18.2, 6.1 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.5 (q, $J_{C\text{-}F}$ = 36.0 Hz, C), 136.8 (C), 133.4 (C), 132.8 (C), 131.7 (2CH), 128.9 (CH), 128.3 (CH), 128.3 (2CH), 127.9 (CH), 127.7 (CH), 126.5 (CH), 126.3 (CH), 126.2 (CH), 125.2 (CH), 122.8 (C), 115.4 (q, $J_{C\text{-}F}$ = 291.9 Hz, CF_3), 88.6 (C), 84.2 (C), 44.9 (CH_2), 32.8 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.8 (s, 3F); **HRMS (ESI)** *m/z*: 353.1149 (M+H), $C_{22}H_{16}F_3O$ requires 353.1153.

(*S*)-1,1,1-Trifluoro-6-phenyl-4-(thiophen-2-yl)hex-5-yn-2-one (33ka)

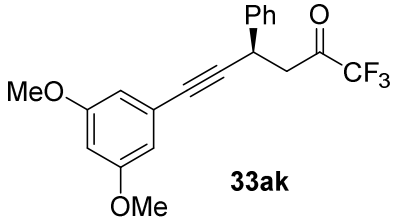


33ka

Enantiomeric excess (94%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 5.0 min, minor enantiomer t_r = 4.6 min.

Oil; **[α]$_D^{20}$** –4.4 (*c* 0.86, $CHCl_3$, 94% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.44-7.41 (m, 1H), 7.32-7.30 (m, 3H), 7.24 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.09-7.07 (m, 1H),6.96 (dd, *J* = 5.1, 3.5 Hz, 1H), 4.79 (t, *J* = 7.0 Hz, 1H), 3.45 (ddd, *J* = 18.4, 7.6, 0.5 Hz, 1H), 3.27 (ddd, *J* = 18.4, 6.4, 0.4 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.2 (q, $J_{C\text{-}F}$ = 36.1 Hz, C), 142.6 (C), 131.7 (2CH), 128.4 (CH), 128.3 (2CH), 126.9 (CH),128.4 (CH), 125.3 (CH), 124.8 (CH), 122.5 (CH), 115.3 (q, $J_{C\text{-}F}$ = 291.7 Hz, CF_3), 87.9 (C), 83.6 (C), 45.3 (CH_2), 27.8 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.8 (s, 3F); **HRMS (ESI)** *m/z*: 309.0560 (M+H), $C_{16}H_{12}F_3OS$ requires 309.0561.

(*R*)-6-(3,5-Dimethoxyphenyl)-1,1,1-trifluoro-4-phenylhex-5-yn-2-one (33ak)

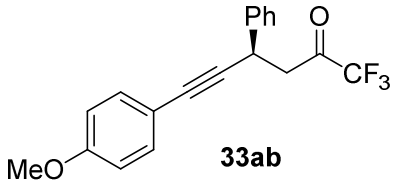


33ak

Enantiomeric excess (96%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 10.6 min, minor enantiomer t_r = 8.5 min.

Oil; **[α]$_D^{20}$** –0.6 (*c* 0.95, $CHCl_3$, 96% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.48-7.28 (m, 5H), 6.58 (d, *J* = 2.3 Hz, 2H), 6.44 (t, *J* = 2.3 Hz, 1H), 4.48 (dd, *J* = 8.1, 6.1 Hz, 1H), 3.78 (s, 6H), 3.39 (ddd, *J* = 18.2, 8.1, 0.5 Hz, 1H), 3.19 (ddd, *J* = 18.2, 6.1, 0.5 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.5 (q, $J_{C\text{-}F}$ = 36.1 Hz, C), 160.5 (2C), 139.4 (C), 128.9 (2CH), 127.7 (CH), 127.4 (2CH), 124.1 (C), 115.3 (q, $J_{C\text{-}F}$ = 291.9 Hz, CF_3), 109.5 (2CH), 101.7 (CH), 88.2 (C), 83.9 (C), 55.4 ($2CH_3$), 45.0 (CH_2), 32.6 (CH);**^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.9 (s, 3F); **HRMS (ESI)** *m/z*: 363.1198 (M+H), $C_{20}H_{18}F_3O_3$ requires 363.1208.

(*R*)-1,1,1-Trifluoro-6-(4-methoxyphenyl)-4-phenylhex-5-yn-2-one (33ab)

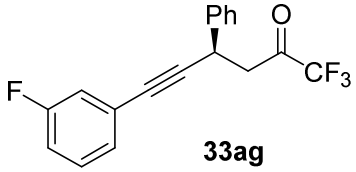


33ab

Enantiomeric excess (94%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 8.5 min, minor enantiomer t_r = 6.8 min.

Oil; **[α]$_D^{20}$** –5.9 (*c* 0.95, $CHCl_3$, 94% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.38-7.35 (m, 2H), 7.30-7.16 (m, 5H), 6.75-6.72 (m, 2H), 4.38 (dd, *J* = 8.1, 6.2 Hz, 1H), 3.71 (s, 3H), 3.28 (dd, *J* = 18.1, 8.2 Hz, 1H), 3.08 (dd, *J* = 18.1, 6.0 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.6 (q, $J_{C\text{-}F}$ = 36.0 Hz, C), 159.6 (C), 139.7 (C), 133.1 (2CH), 128.9 (2CH), 127.6 (CH), 127.4 (2CH), 115.3 (q, $J_{C\text{-}F}$ = 291.9 Hz, CF_3), 114.9 (C), 113.9 (2CH), 87.1 (C), 83.8 (C), 55.3 (CH_3), 45.2 (CH_2), 32.7 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.9 (s, 3F); **HRMS (ESI)** *m/z*: 333.1097 (M+H), $C_{19}H_{16}F_3O_2$ requires 333.1102.

(*R*)-1,1,1-Trifluoro-6-(3-fluorophenyl)-4-phenylhex-5-yn-2-one (33ag)

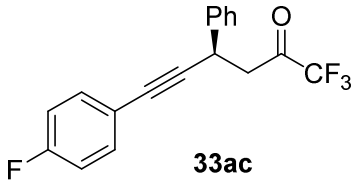


33ag

Enantiomeric excess (95%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 12.8 min, minor enantiomer t_r = 8.5 min.

Oil; **[α]$_D^{20}$** –4.7 (*c* 0.93, $CHCl_3$, 95% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.46-7.18 (m, 7H), 7.11 (ddd, *J* = 9.4, 2.5, 1.4 Hz, 1H), 7.02 (tdd, *J* = 8.3, 2.6, 1.3 Hz, 1H), 4.48 (dd, *J* = 8.2, 6.0 Hz, 1H), 3.39 (dd, *J* = 18.2, 8.3 Hz, 1H), 3.19 (dd, *J* = 18.2, 6.0 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.4 (q, $J_{C\text{-}F}$ = 36.1 Hz, C), 162.3 (d, $J_{C\text{-}F}$ = 246.4 Hz, C), 139.2 (C), 129.8 (d, $J_{C\text{-}F}$ = 8.7 Hz, CH), 129.0 (2CH), 127.8 (CH), 127.6 (d, $J_{C\text{-}F}$= 3.0 Hz, CH), 127.4 (2CH), 124.6 (d, $J_{C\text{-}F}$ = 9.5 Hz, C), 118.5 (d, $J_{C\text{-}F}$ = 22.8 Hz, CH), 115.6 (d, $J_{C\text{-}F}$ = 21.2 Hz, CH), 115.3 (q, $J_{C\text{-}F}$ = 291.9 Hz, CF_3), 89.6 (C), 82.8 (d, $J_{C\text{-}F}$ = 3.4 Hz, C), 44.9 (CH_2), 32.6 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.9 (s, 3F), 113.5 (s, 1F); **HRMS (ESI)** *m/z*: 321.0895 (M+H), $C_{18}H_{13}F_4O$ requires 321.0903.

(*R*)-1,1,1-Trifluoro-6-(4-fluorophenyl)-4-phenylhex-5-yn-2-one (33ac)



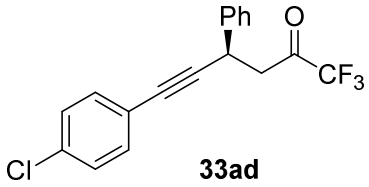
33ac

Enantiomeric excess (95%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 10.5 min, minor enantiomer t_r = 7.6 min.

Oil; **[α]$_D^{20}$** –1.4 (*c* 0.87, $CHCl_3$, 95% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.47-7.28 (m, 7H), 7.03-6.96 (m, 2H), 4.48 (dd, *J* = 8.2, 6.0 Hz, 1H), 3.38 (dd, *J* = 18.2, 8.3 Hz, 1H), 3.18 (dd, *J* = 18.2, 5.9 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.5 (q, $J_{C\text{-}F}$ = 36.1 Hz, C), 162.5 (d, $J_{C\text{-}F}$ = 249.4 Hz, C), 139.4 (C), 133.5 (d, $J_{C\text{-}F}$ = 8.4 Hz, 2CH), 129.0 (2CH), 127.7 (CH), 127.4 (2CH), 118.9 (d, $J_{C\text{-}F}$ = 3.6 Hz, C), 115.5 (d, $J_{C\text{-}F}$ = 22.1 Hz, 2CH), 115.3 (q, $J_{C\text{-}F}$ = 291.9 Hz, CF_3), 88.3 (C), 82.9 (C), 45.0 (CH_2), 32.6 (CH); **^{19}F**

NMR (282 MHz, $CDCl_3$) δ −79.9 (s, 3F), 111.5 (s, 1F); **HRMS (ESI)** *m/z*: 321.0895 (M+H), $C_{18}H_{13}F_4O$ requires 321.0903.

(*R*)-6-(4-Chlorophenyl)-1,1,1-trifluoro-4-phenylhex-5-yn-2-one (33ad)

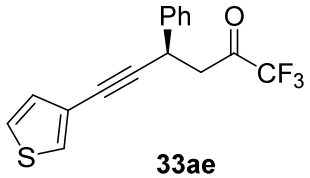


33ad

Enantiomeric excess (92%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 10.9 min, minor enantiomer t_r = 8.2 min.

Oil; **$[\alpha]_D^{20}$** −2.8 (*c* 1.04, $CHCl_3$, 92% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.47-7.26 (m, 9H), 4.48 (dd, *J* = 8.3, 6.0 Hz, 1H), 3.38 (ddd, *J* = 18.2, 8.3, 0.5 Hz, 1H), 3.18 (dd, *J* = 18.2, 6.0 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.5 (q, $J_{C\text{-}F}$ = 36.1 Hz, C), 139.2 (C), 134.3 (C), 132.9 (2CH), 129.0 (2CH), 128.6 (2CH), 127.7 (CH), 127.3 (2CH), 121.3 (C), 115.3 (q, $J_{C\text{-}F}$ = 291.8 Hz, CF_3), 89.6 (C), 82.9 (C), 45.0 (CH_2), 32.6 (CH);**^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.9 (s, 3F); **HRMS (ESI)** *m/z*: 337.0599 (M+H), $C_{18}H_{13}ClF_3O$ requires 337.0605.

(*R*)-1,1,1-Trifluoro-4-phenyl-6-(thiophen-3-yl)hex-5-yn-2-one (33ae)

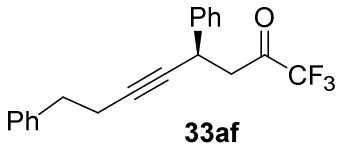


33ae

Enantiomeric excess (94%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 12.3 min, minor enantiomer t_r = 10.3 min.

Oil; **$[\alpha]_D^{20}$** −4.4 (*c* 0.86, $CHCl_3$, 94% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.32-7.19 (m, 10H), 7.23-7.17 (m, 1H), 4.47 (dd, *J* = 8.1, 6.1 Hz, 1H), 3.38 (ddd, *J* = 18.2, 8.2, 0.5 Hz, 1H), 3.18 (dd, *J* = 18.2, 6.1 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.5 (q, $J_{C\text{-}F}$ = 36.2 Hz, C), 139.4 (C), 129.9 (CH), 128.9 (2CH), 128.7 (CH), 127.7 (CH), 127.4 (2CH), 125.2 (CH), 121.8 (C), 115.3 (q, $J_{C\text{-}F}$ = 291.9 Hz, CF_3), 88.2 (C), 79.1 (C), 45.0 (CH_2), 32.6 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.9 (s, 3F);**HRMS (ESI)***m/z*: 309.0558 (M+H), $C_{16}H_{12}F_3OS$ requires 309.0561.

(*R*)-1,1,1-Trifluoro-4,8-diphenyloct-5-yn-2-one (33af)

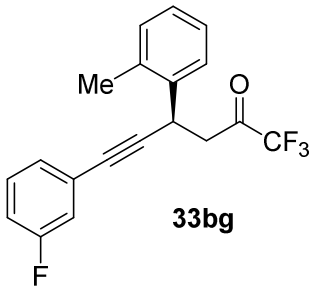


33af

Enantiomeric excess (78%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 10.8 min, minor enantiomer t_r = 8.6 min.

Oil;**$[\alpha]_D^{20}$** −1.6 (*c* 0.57, $CHCl_3$, 78% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.47-7.24 (m, 7H), 4.23-4.17 (m, 1H), 3.19 (dd, *J* = 18.0, 8.2 Hz, 1H), 3.02 (dd, *J* = 18.2, 5.8 Hz, 1H), 2.81 (t, *J* = 7.4 Hz, 2H), 2.50 (td, *J* = 7.4, 2.1 Hz, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.6 (q, $J_{C\text{-}F}$ = 35.8 Hz, C), 140.6 (C), 140.0 (C), 128.8 (2CH), 128.5 (2CH), 128.3 (2CH), 127.4 (CH), 127.3 (2CH), 126.3 (CH), 115.3 (q, $J_{C\text{-}F}$ = 291.7 Hz, CF_3), 83.5 (C), 80.1 (C), 45.3 (CH_2), 35.0 (CH_2), 32.0 (CH),20.8 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.9 (s, 3F); **HRMS (ESI)** *m/z*: 331.1303 (M+H), $C_{20}H_{18}F_3O$ requires 331.1310.

(*S*)-1,1,1-Trifluoro-6-(3-fluorophenyl)-4-(o-tolyl)hex-5-yn-2-one (33bg)

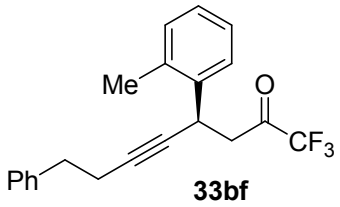


33bg

Enantiomeric excess (98%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 14.5 min, minor enantiomer t_r = 11.7 min.

Oil; **[α]$_D^{20}$** –8.2 (*c* 0.96, $CHCl_3$, 98% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.84-7.81 (m, 1H), 7.58-7.45 (m, 5H), 7.38 (ddd, *J* = 9.4, 2.5, 1.4 Hz, 1H), 7.33-7.26 (m, 1H), 4.95 (dd, *J* = 9.1, 5.1 Hz, 1H), 3.66 (ddd, *J* = 18.1, 9.1, 0.4 Hz, 1H), 3.43 (dd, *J* = 18.1, 5.1 Hz, 1H), 2.73 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.6 (q, $J_{C\text{-}F}$ = 36.1 Hz, C), 162.3 (d, *J* = 246.4 Hz, C), 137.2 (C), 135.0 (C), 131.0 (CH), 129.8 (d, $J_{C\text{-}F}$ = 8.7 Hz, CH), 127.7 (CH), 127.5 (d, $J_{C\text{-}F}$= 3.1 Hz, CH), 127.2 (CH), 126.8 (CH), 124.7 (d, $J_{C\text{-}F}$ = 9.5 Hz, C), 118.5 (d, $J_{C\text{-}F}$ = 22.8 Hz, CH), 115.6 (d, $J_{C\text{-}F}$ = 21.2 Hz, CH), 115.4 (q, $J_{C\text{-}F}$ = 291.8 Hz, CF_3), 89.8 (C), 82.3 (d, $J_{C\text{-}F}$ = 3.3 Hz, C), 43.4 (CH_2), 29.2 (CH), 19.2 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.8 (s, 3F), 113.5 (s, 1F); **HRMS (ESI)** *m/z*: 335.1050 (M+H), $C_{19}H_{15}F_4O$ requires 335.1059.

(*S*)-1,1,1-Trifluoro-8-phenyl-4-(o-tolyl)oct-5-yn-2-one (33bf)

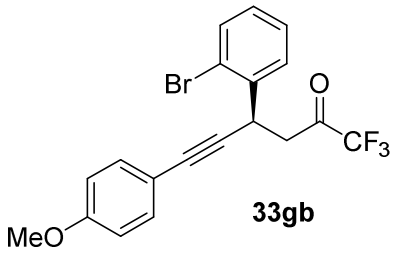


33bf

Enantiomeric excess (90%) was determined after hydrogenation of triple bond (see section 5.4.2.4.)

Oil; **[α]$_D^{20}$** –2.3 (*c* 0.81, $CHCl_3$, 90% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.41-7.17 (m, 9H), 4.41 (ddt, *J* = 9.3, 4.6, 2.2 Hz, 1H), 3.20 (ddd, *J* = 18.1, 9.3, 0.5 Hz, 1H), 3.00 (dd, *J* = 18.0, 5.0 Hz, 1H), 2.83 (t, *J* = 7.4 Hz, 2H), 2.51 (td, *J* = 7.3, 2.1 Hz, 2H), 2.38 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.8 (q, $J_{C\text{-}F}$ = 36.0 Hz, C), 140.6 (C), 138.1 (C), 134.8 (C), 130.7 (CH), 128.5 (2CH), 128.3 (2CH), 127.4 (CH), 127.1 (CH), 126.6 (CH), 126.2 (CH), 115.4 (q, $J_{C\text{-}F}$ = 291.9 Hz, CF_3), 82.9 (C), 80.3 (C), 43.8 (CH_2), 35.0 (CH_2), 28.5 (CH),20.8 (CH_2), 19.1 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.8 (s, 3F); **HRMS (ESI)** *m/z*: 345.1457 (M+H), $C_{21}H_{20}F_3O$ requires 345.1466.

(*S*)-4-(2-Bromophenyl)-1,1,1-trifluoro-6-(4-methoxyphenyl)hex-5-yn-2-one (33gb)



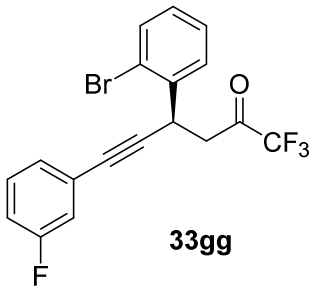
33gb

Enantiomeric excess (98%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 8.2 min, minor enantiomer t_r = 7.2 min.

Oil; **[α]$_D^{20}$** –13.6 (*c* 1.07, $CHCl_3$, 98% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.80 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.58 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.40-7.34 (m, 3H), 7.21-7.15 (m, 1H), 6.87-6.81 (m, 2H), 4.89 (t, *J* = 6.9 Hz, 1H), 3.81 (s, 3H), 3.23 (d, *J* = 6.8 Hz, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.3 (q, $J_{C\text{-}F}$ = 36.1 Hz, C), 159.7 (C), 138.5 (C), 133.2 (CH), 133.1 (2CH), 129.7 (CH), 129.3 (CH), 128.1 (CH), 123.0 (C), 115.4 (q, $J_{C\text{-}F}$ = 292.0 Hz, CF_3), 114.7

(C), 113.9 (2CH), 86.0 (C), 84.6 (C), 55.3 (CH_3), 43.4 (CH_2), 32.8 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.7 (s, 3F); **HRMS (ESI)***m /z*: 411.0205/413.0184 (M+H)100/97.3, $C_{19}H_{15}BrF_3O_2$ requires 411.0208/413.0187.

(*S*)-4-(2-Bromophenyl)-1,1,1-trifluoro-6-(3-fluorophenyl)hex-5-yn-2-one (33gg)



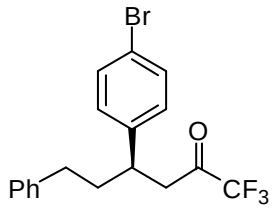
33gg

Enantiomeric excess (98%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 11.3 min, minor enantiomer t_r = 10.1 min.

Oil; **$[\alpha]_D^{20}$** +0.3 (*c* 0.98, $CHCl_3$, 98% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.76 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.59 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.38 (td, *J* = 7.6, 1.3 Hz, 1H), 7.29-7.24 (m, 1H), 7.22-7.17 (m, 2H), 7.12 (ddd, *J* = 9.4, 2.5, 1.3 Hz, 1H), 7.04-7.00 (m, 1H), 4.90 (t, *J* = 6.9 Hz, 1H), 3.25 (d, *J* = 7.0 Hz, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.1 (q, $J_{C\text{-}F}$ = 36.1 Hz, C), 162.3 (d, $J_{C\text{-}F}$ = 246.7 Hz, C), 138.0 (C), 133.3 (CH), 129.9 (d, $J_{C\text{-}F}$ = 8.6 Hz, CH), 129.5 (CH), 129.4 (CH), 127.6 (d, $J_{C\text{-}F}$= 3.1 Hz, CH), 124.4 (d, $J_{C\text{-}F}$ = 9.7 Hz, C), 123.0 (C), 118.5 (d, $J_{C\text{-}F}$ = 22.7 Hz, CH), 115.8 (d, $J_{C\text{-}F}$ = 21.2 Hz, CH), 115.3 (q, $J_{C\text{-}F}$ = 291.8 Hz, CF_3), 88.5 (C), 83.5 (C), 43.1 (CH_2), 32.7 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.7 (s, 3F), 113.4 (s, 1F); **HRMS (ESI)***m/z*: 399.0002/400.9981 (M+H) 100/97.3, $C_{18}H_{12}BrF_4O$ requires 399.0008/400.9987.

5.4.2.4. Synthetic transformations

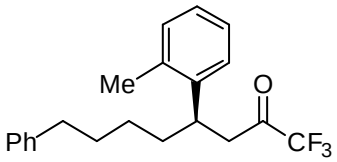
(*R*)-4-(4-Bromophenyl)-1,1,1-trifluoro-6-phenylhexan-2-one (33ia')



A solution of **33ia** (15 mg, 0.039 mmol) in EtOAc (0.4 mL) was stirred under hydrogen atmosphere in the presence of 5% Pd/C (3 mg) for 1 h. Then, the reaction mixture was filtered through a short pad of silica gel eluting with EtOAc and the solvent was removed under reduced pressure. Purification by flash chromatography gave compound **33ia'** (14.4 mg, 96%). Enantiomeric excess (90%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 10.4 min, minor enantiomer t_r = 17.3 min.

Oil; **$[\alpha]_D^{20}$** +4.8 (*c* 0.50, $CHCl_3$, 90% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.49-7.44 (m, 2H), 7.30-7.18 (m, 4H), 7.11-7.06 (m, 3H), 3.24-3.17 (m, 1H), 3.01 (d, *J* = 7.0 Hz, 2H), 2.48-2.42 (m, 2H), 2.07-1.90 (m, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 189.7 (q, $J_{C\text{-}F}$ = 35.1 Hz, C), 141.5 (C), 141.0 (C), 131.9 (2CH), 129.3 (2CH), 128.5 (2CH), 128.3 (2CH), 126.1 (CH), 120.8 (C), 115.4 (q, $J_{C\text{-}F}$ = 292.5 Hz, CF_3), 43.3 (CH_2), 38.9 (CH), 37.4 (CH_2), 33.3 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −80.0 (s, 3F); **HRMS (ESI)** *m/z*: 385.0410 (M+H), $C_{18}H_{17}BrF_3O$ requires 385.0415.

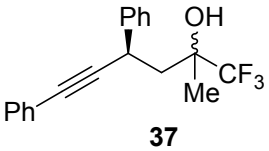
(*R*)-1,1,1-Trifluoro-8-phenyl-4-(o-tolyl)octan-2-one (33bj')



A solution of **33bj** (10 mg, 0.029 mmol) in EtOAc (0.4 mL) was stirred under hydrogen atmosphere in the presence of 5% Pd/C for 1 h. Then, the reaction mixture was filtered through silica gel eluting with EtOAc and the solvent was removed under reduced pressure. Purification by flash chromatography gave compound **33bj'** (9.9 mg, 98%). Enantiomeric excess (90%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 9.5 min, minor enantiomer t_r = 8.2 min.

Oil;**[α]$_D^{20}$** −1.6 (*c* 0.58, $CHCl_3$, 90% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.28-7.10 (m, 9H), 3.59-3.49 (m, 1H), 3.00 (t, *J* = 6.8 Hz, 2H), 2.54 (td, *J* = 8.0, 2.7 Hz, 2H), 2.37 (s, 3H), 1.70-1.53 (m, 4H), 1.33-1.14 (m, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 190.4 (q, $J_{C\text{-}F}$ = 35.3 Hz, C), 142.4 (C), 141.5 (C), 136.1 (C), 130.6 (CH), 128.31 (2CH), 128.26 (2CH), 126.42 (CH), 126.37 (CH), 125.7 (CH), 125.2 (CH), 115.4 (q, $J_{C\text{-}F}$ = 292.5 Hz, CF_3), 43.2 (CH_2), 36.1 (CH_2), 35.7 (CH_2), 34.2 (CH),31.4 (CH_2), 26.7 (CH_2), 19.8 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −80.0 (s, 3F); **HRMS (ESI)** *m/z*: 349.1769 (M+H), $C_{21}H_{24}F_3O$ requires 349.1779.

(4*R*)-1,1,1-Trifluoro-2-methyl-4,6-diphenylhex-5-yn-2-ol (37)



37

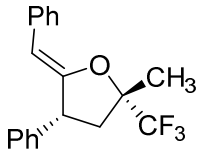
A commercial 3 M solution of MeMgCl in THF (23µL, 0.069 mmol) was diluted with diethyl ether (0.1 mL) and cooled to 0 ºC under nitrogen. A solution of compound **33aa** (14 mg, 0.046 mmol) in dry diethyl ether (0.2 mL) was added dropwise via syringe and the reaction mixture was allowed to reach room temperature. After 2 h, the reaction was quenched with a solution of citric acid (1 mL). The mixture was extracted with diethyl ether (3 x 15 mL) and the organic layer was dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography eluting with hexane:EtOAc (99:01) gave **37** (10.0 mg, 68%) as a ca. 2:1 mixture of two diastereomeric alcohols. Enantiomeric excess (95%) was determined by chiral HPLC (Chiralpak AD-H), hexane-*i*PrOH 99:01, 1 mL/min, *major diastereomer*: major enantiomer t_r = 19.5 min, minor enantiomer t_r = 21.5 min. *minor diastereomer*: major enantiomer t_r = 45.2 min, minor enantiomer t_r = 26.8 min.

Major (1*S*,4*R*)-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.43 (m, 5H), 7.34-7.29 (m, 5H), 4.12 (dd, *J* = 10.8, 4.5 Hz, 1H), 3.20 (s, OH), 2.37 (dd, *J* = 14.4, 10.8 Hz, 1H), 2.13 (dd, *J* = 14.4, 4.5 Hz, 1H), 1.55 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 141.0 (C), 131.6 (2CH), 129.0 (2CH), 128.5 (CH), 128.4 (2CH), 127.3 (2CH), 127.2 (CH), 122.4 (C), 90.3 (C), 85.5 (C), 73.9 (q, $J_{C\text{-}F}$ = 28.3 Hz, C), 42.9 (CH_2), 33.0 (CH), 20.2 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −84.2 (s, 3F).

Minor (1*R*,4*R*)-diastereomer (representative peaks taken from the diastereomeric mixture):**^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.43-7.29 (m, 10H), 4.20 (t, *J* = 7.4 Hz, 1H), 3.20 (s, OH), 2.21 (dd, *J* = 7.8, 0.9 Hz, 2H), 1.55 (s, 3H);**^{13}C NMR (75.5 MHz, $CDCl_3$)**

δ 141.6 (C), 131.5 (2CH), 128.9 (2CH), 128.4 (CH), 127.4 (CH), 127.3 (2CH), 122.6 (C), 90.6 (C), 85.3 (C), 74.0 (q, $J_{C\text{-}F}$ = 28.3 Hz, C), 44.0 (CH_2), 33.2 (CH), 20.1 (CH_3);**^{19}F NMR (282 MHz, $CDCl_3$)** δ –82.1 (s, 3F).

(2*S*,4*R*)-5-((*Z*)-Benzylidene)-2-methyl-4-phenyl-2-(trifluoromethyl)tetrahydrofuran (38)



38

AgOTf (10.0 mg, 0.038 mmol) was added to a solution of the diastereomeric mixture of **37** (26 mg, 0.076 mmol) in THF (0.5 mL) at rt under nitrogen atmosphere and the mixtures was stirred overnight. Then, removal of the solvent under reduced pressure followed by flash chromatography eluting with hexane:EtOAc (99:01) allowed to obtain furan **38** as a ca. 3:1 mixture of two diastereomeric (17.4 mg, 72%). Enantiomeric excess (92%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, *major diastereomer*: major enantiomer t_r = 10.3 min, minor enantiomer t_r = 8.6 min.

The major diastereomer of **38** could be obtained pure from the diastereomeric mixture after a single crystallization from hexane.

Major (2*S*,4*R*)-diastereomer:$[\alpha]_D^{20}$ +2.5 (*c* 0.57, $CHCl_3$, 92% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.49-7.46 (m, 2H), 7.41-7.24 (m, 7H), 7.14-7.08 (m, 1H), 4.83 (d, *J* = 2.1 Hz, 1H), 4.25 (ddd, *J* = 11.4, 9.1, 2.1 Hz, 1H), 2.52-2.35 (m, 2H), 1.64 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 158.9 (C), 139.6 (C), 135.7 (C), 128.9 (2CH), 128.7 (2CH), 128.2 (2CH), 127.63 (2CH), 127.59 (CH), 125.5 (CH), 125.4 (q, $J_{C\text{-}F}$ = 281.9 Hz, CF_3), 101.2 (CH), 84.2 (q, $J_{C\text{-}F}$ = 30.6 Hz, C), 48.0 (CH_2), 39.9 (CH), 20.5 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –82.3 (s, 3F); **HRMS (ESI)** *m/z*: 319.1305 $(M+H)^+$, $C_{19}H_{18}F_3O$ requires 319.1310.

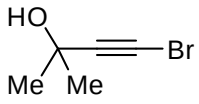
Minor diastereomer (representative peaks taken from the diastereomeric mixture):**^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.52-7.47 (m, 2H), 7.39-7.25 (m, 7H), 7.15-7.09 (m, 1H), 4.92 (d, *J* = 1.9 Hz, 1H), 4.35 (t, *J* = 9.9 Hz, 1H), 2.89 (dd, *J* = 13.8, 9.2 Hz, 1H), 2.40-2.36 (m, 1H), 1.70 (d, *J* = 0.9 Hz, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 159.4 (C), 141.2 (C), 135.8 (C), 128.4 (2CH), 127.7 (2CH), 127.4 (2CH),125.5 (CH), 101.3 (CH), 84.8 (q, $J_{C\text{-}F}$ = 29.9 Hz, C), 48.9 (CH_2), 41.6 (CH), 21.5 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –81.8 (s, 3F).

5.5. Enantioselective conjugate addition of 1,3-diynes to 1,1,1-trifluoromethyl-3-en-2-ones

5.5.1. Synthesis and characterization of 1,3-diynes 39

1,3-Diynes **39** were synthesized according to the procedure described in the literature.[74]

4-Bromo-2-methylbut-3-yn-2-ol

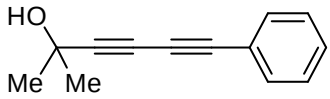


Br_2 (3.9 mL, 0.077 mol) was added dropwise via syringe to a stirred solution of KOH (30.1 g, 0.536 mol) in H_2O (200 mL) at 0 ºC. After 15 min, 2-methyl-3-butyn-2-ol (10 mL, 0.103 mol) was added dropwise via an addition funnel. After 1 h, the mixture was warmed to rt and extracted with Et_2O (3 x 50 mL). The organic phase was dried with $MgSO_4$, filtered, concentrated, and purified by column chromatography on silica gel to afford 4-bromo-2-methyl-3-but-3-yn-2-ol in 75% yield. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 2.51 (br s, 1H), 1.49 (s, 6H). Data consistent with literature.[73]

Representative procedure: 2-Methyl-6-phenylhexa-3,5-diyn-2-ol

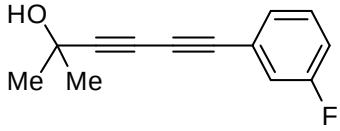
CuCl (23.3 mg, 0.24 mmol) was added to a solution of 30% $BuNH_2/H_2O$ (30 mL). The blue color was quenched by the addition of a spatula of $H_2NOH{\cdot}HCl$. Phenylacetylene (**2a**, 1.29 mL,11.76 mmol) was added and the reaction mixture was cooled to 0 ºC, becoming a yellow cloudy solution. A solution of 4-bromo-2-methyl-3-but-3-yn-2-ol (2.0 g, 12.35 mmol) in Et_2O (5 mL) was added. Then, a spatula of $NH_2(OH){\cdot}HCl$ was added to the reaction mixture. After 5 min, the mixture was warmed to rt and extracted with Et_2O (2 x 25 mL). The organic layer was dried with $MgSO_4$, filtered, concentrated, and purified by column chromatography on silica gel to afford 2-methyl-6-phenylhexa-3,5-diyn-2-ol (1.93 g, 89%).

2-Methyl-6-phenylhexa-3,5-diyn-2-ol



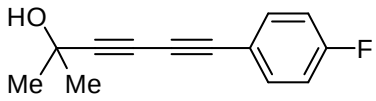
89% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.50-7.47 (m, 2H), 7.37-7.32 (m, 3H), 2.12 (br s, 1H), 1.59 (s, 6H). Data consistent with the literature.[116]

6-(3-Fluorophenyl)-2-methylhexa-3,5-diyn-2-ol



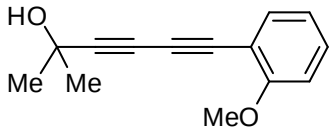
71% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.28-7.26 (m, 2H), 7.18-7.14 (m, 1H), 7.10-7.03 (m, 1H), 1.58 (s, 6H). Data consistent with the literature.[116]

6-(4-Fluorophenyl)-2-methylhexa-3,5-diyn-2-ol



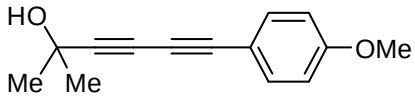
80% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.49-7.44 (m, 2H), 7.04-6.98 (m, 2H), 2.06 (br s, 1H), 1.58 (s, 6H). Data consistent with the literature.[117]

6-(2-Methoxyphenyl)-2-methylhexa-3, 5-diyn-2-ol



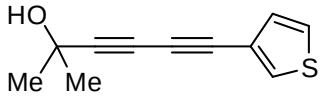
83% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.43 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.32 (ddd, *J* = 8.3, 7.6, 1.7 Hz, 1H), 6.92-6.85 (m, 2H), 3.87 (s, 3H), 2.14 (br s, 1H), 1.57 (s, 6H). Data consistent with the literature.[118]

6-(4-Methoxyphenyl)-2-methylhexa-3, 5-diyn-2-ol



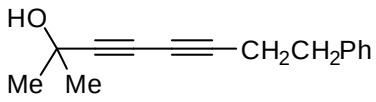
78% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.43-7.38 (m, 2H), 6.84-6.79 (m, 2H), 3.79 (s, 3H), 2.60 (br s, 1H), 1.57 (s, 6H). Data consistent with the literature.[117]

2-Methyl-6-(thiophen-3-yl)hexa-3,5-diyn-2-ol



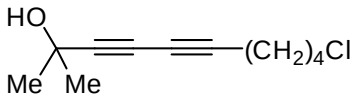
80% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.56 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.27 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.13 (dd, *J* = 5.0, 1.2 Hz, 1H), 2.01 (br s, 1H), 1.57 (s, 6H). Data consistent with the literature.[117]

2-Methyl-8-phenylocta-3,5-diyn-2-ol



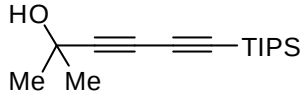
84% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.35-7.29 (m, 2H), 7.27-7.20 (m, 3H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 2.22 (br s, 1H), 1.54 (s, 6H). Data consistent with the literature.[73]

11-Chloro-2-methylundeca-3,5-diyn-2-ol



85% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 3.56 (t, *J* = 6.5 Hz, 2H), 2.34 (t, *J* = 6.9 Hz, 2H), 1.93-1.85 (m, 2H), 1.75-1.65 (m, 2H), 1.53 (s, 6H).

2-Methyl-6-(triisopropylsilyl)hexa-3,5-diyn-2-ol

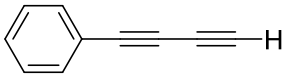


61% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 1.95 (br s, 1H), 1.54 (s, 6H), 1.08 (s, 21H). Data consistent with the literature.[73]

Synthesis of 1,3-diynes 39

A solution of the required diynol (7.71 mmol) in toluene (10 mL) was added to a mixture of K_2CO_3 (1.07 g, 7.71 mmol) and 18-crown-6 (0.61 g, 2.31 mmol) in toluene (13 mL) under nitrogen atmosphere at room temperature. The reaction mixture was heated at reflux until the reaction was determined to be complete by TLC (1-2 h).Then, the reaction was cooled to room temperature, extracted with EtOAc (2 × 50 mL), dried over $MgSO_4$ and concentrated. The crude oil was purified by column chromatography on silica gel to give the terminal 1,3-diynes **39**. The 1,3-diynes were passed through a short plug of alumina and then stored in Et_2O solution (200 mL) in the freezer. Prior to use they were concentrated via rotary evaporation.

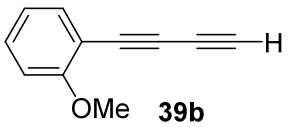
Buta-1,3-diyn-1-ylbenzene (39a)



39a

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.49 (m, 2H), 7.40-7.28 (m, 3H), 2.46 (s, 1H). Data consistent with the literature.[73]

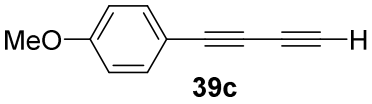
1-(Buta-1,3-diyn-1-yl)-2-methoxybenzene (39b)



39b

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.33 (ddd, *J* = 8.4, 7.5, 1.7 Hz, 1H), 6.89 (td, *J* = 7.5, 1.0 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 3.87 (s, 3H), 2.52 (s, 1H). Data consistent with the literature.[118]

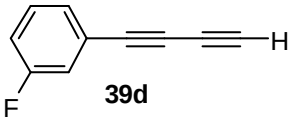
1-(Buta-1,3-diyn-1-yl)-4-methoxybenzene (39c)



39c

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.42 (m, 2H), 6.85-6.81 (m, 2H), 3.81 (s, 3H), 2.45 (s, 1H). Data consistent with the literature.[118]

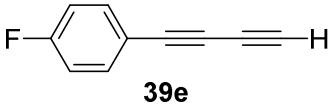
1-(Buta-1,3-diyn-1-yl)-3-fluorobenzene (39d)



39d

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.29 (m, 2H), 7.23-7.16(m, 1H), 7.13-7.06 (m, 1H), 2.51 (s, 1H).

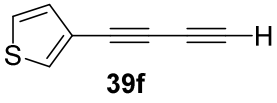
1-(Buta-1,3-diyn-1-yl)-4-fluorobenzene (39e)



39e

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.46 (m, 2H), 7.06-6.98 (m, 2H), 2.47 (s, 1H).

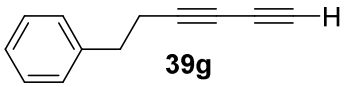
3-(Buta-1,3-diyn-1-yl)thiophene (39f)



39f

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.27 (dd, J = 5.0, 3.0 Hz, 1H), 7.15 (dd, *J* = 5.0, 1.2 Hz, 1H), 2.46 (s, 1H).

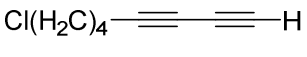
Hexa-3,5-diyn-1-ylbenzene (39g)



39g

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.19 (m, 5H), 2.85 (t, *J* = 7.5 Hz, 2H), 2.55 (d, J = 7.5 Hz, 2H), 1.97 (t, *J* = 1.2 Hz, 1H).Data consistent with the literature.[73]

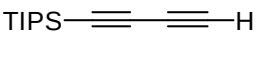
9-Chlorononа-1,3-diyne (39h)



39h

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.54 (t, *J* = 6.4 Hz, 2H), 2.31 (td, *J* = 7.0, 1.2 Hz, 2H), 1.97 (t, *J* = 1.2 Hz, 1H), 1.93-1.84 (m, 2H), 1.77-1.64 (m, 2H).

Buta-1,3-diyn-1-yltriisopropylsilane (39i)



39i

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 1H), 1.09 (s, 21H).

5.5.2. Enantioselective conjugate addition of 1,3-diynes to 1,1,1-trifluoromethyl-3-en-2-ones

5.5.2.1. General procedure for the enantioselective conjugate diynylation reaction

$[Cu(CH_3CN)_4]BF_4$ (1.1 mg, 0.0034 mmol) and (*R*)-**L31** (4.1 mg, 0.0034 mmol) were added to a dried round bottom flask which was purged with nitrogen. Toluene (0.2 mL) was added via syringe and the mixture was stirred for 1.5 h at room temperature under nitrogen atmosphere. Then, a solution of α,β-unsaturated trifluoromethyl ketone **35** (0.144 mmol) in toluene (1.0 mL)was added via syringe, followed of triethylamine (2 µL, 0.0144 mmol). The solution was stirred for 10 min at room temperature. Then a solution of 1,3-diyne **39** (0.188 mmol) in toluene (1.0 mL) was added via syringe and the solution was stirred at room temperature until the reaction was complete (TLC). The reaction mixture was quenched with 20% aqueous NH_4Cl (1.0 mL), extracted with CH_2Cl_2 (2 x 15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:ethyl acetate mixtures afforded compound **40**.

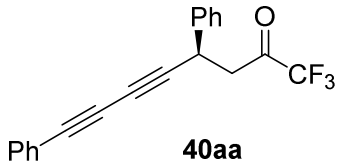
5.5.2.2. General procedure for the synthesis of the racemic products

Racemic compounds **40** were prepared by following the general procedure using racemic ligand (±)-**L31.**

5.5.2.3. Characterization of products 40

See Table 14 (Page 72) for yields.

(*R*)-1,1,1-Trifluoro-4,8-diphenylocta-5,7-diyn-2-one (40aa)

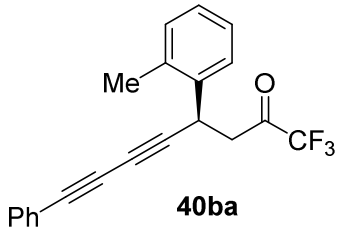


40aa

Enantiomeric excess (93%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 4.96 min, minor enantiomer t_r = 4.61 min.

Oil;**[α]$_D^{20}$** –29.3 (*c* 1.05, $CHCl_3$, 93% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.51-7.48 (m, 2H), 7.42-7.29 (m, 8H), 4.41 (dd, *J* = 7.9, 6.2 Hz, 1H), 3.37 (ddd, *J* = 18.7, 7.9, 0.5 Hz, 1H), 3.19 (ddd, *J* = 18.7, 6.2, 0.5 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.1 (q, $J_{C\text{-}F}$ = 36.2 Hz, C), 138.3 (C), 132.6 (2CH), 129.2 (CH), 129.1 (2CH), 128.4 (2CH), 127.9 (CH), 127.4 (2CH), 121.5 (C), 115.3 (q, $J_{C\text{-}F}$ = 291.8 Hz, CF_3), 82.2 (C), 77.3 (C), 73.5 (C), 68.4 (C), 44.4 (CH_2), 32.6 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.7 (s, 3F);**HRMS (ESI)** *m/z*: 327.0982 $(M+H)^+$, $C_{20}H_{14}F_3O$ requires 327.0997.

(*S*)-1,1,1-Trifluoro-8-phenyl-4-(*o*-tolyl)octa-5,7-diyn-2-one (40ba)

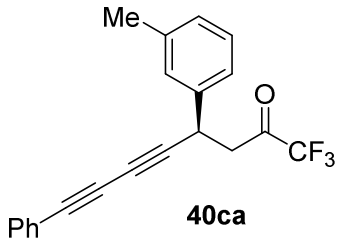


40ba

Enantiomeric excess (94%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 16.0 min, minor enantiomer t_r = 11.8 min.

Oil; **[α]$_D^{20}$** –35.2 (*c* 1.02, $CHCl_3$, 94% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.49-7.45 (m, 3H), 7.36-7.31 (m, 3H), 7.25-7.19 (m, 3H), 4.59 (dd, *J* = 8.7, 5.4 Hz, 1H), 3.37 (ddd, *J* = 18.7, 8.7, 0.5 Hz, 1H), 3.16 (ddd, *J* = 18.7, 5.4, 0.5 Hz, 1H), 2.42 (s, 3H);**^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.7 (q, $J_{C\text{-}F}$ = 36.2 Hz, C), 136.8 (C), 135.5 (C), 133.0 (2CH), 131.5 (CH), 129.6 (CH), 128.8 (2CH), 128.3 (CH), 127.5 (CH), 127.3 (CH), 121.9 (C), 115.7 (q, $J_{C\text{-}F}$ = 291.6 Hz, CF_3), 82.8 (C), 77.9 (C), 74.0 (C), 68.3 (C), 43.4 (CH_2), 29.4 (CH), 19.7 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.6 (s, 3F);**HRMS (ESI)***m/z*: 341.1160 $(M+H)^+$, $C_{21}H_{16}F_3O$ requires 341.1153.

(*S*)-1,1,1-Trifluoro-8-phenyl-4-(*m*-tolyl)octa-5,7-diyn-2-one (40ca)



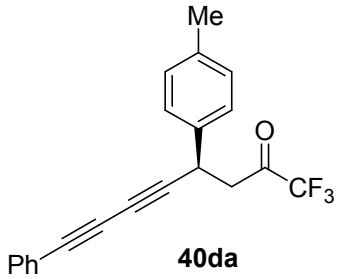
40ca

Enantiomeric excess (93%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 5.1 min, minor enantiomer t_r = 4.6 min.

Oil; **[α]$_D^{20}$** –18.9 (*c* 1.00, $CHCl_3$, 93% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.50-7.47 (m, 2H), 7.36-7.31 (m, 3H), 7.23-7.11 (m, 4H), 4.37 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.36 (ddd, *J* = 18.7, 8.1, 0.5 Hz, 1H), 3.17 (ddd, *J* = 18.7, 6.1, 0.5 Hz, 1H), 2.38 (s, 3H);**^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.1 (q, $J_{C\text{-}F}$ = 36.4 Hz, C), 138.9 (C), 138.2 (C), 132.6 (2CH), 129.2 (CH), 128.9 (CH), 128.7 (CH), 128.4 (2CH), 128.0 (CH), 124.4 (CH), 121.5 (C), 115.3 (q, $J_{C\text{-}F}$ = 291.9 Hz, CF_3), 82.3 (C), 77.2 (C), 73.6 (C), 68.3 (C), 44.4 (CH_2), 32.5 (CH), 21.4

(CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.7 (s, 3F); **HRMS (ESI)** *m/z*: 341.1164 $(M+H)^+$, $C_{21}H_{16}F_3O$ requires 341.1153.

(*R*)-1,1,1-Trifluoro-8-phenyl-4-(*p*-tolyl)octa-5,7-diyn-2-one (40da)

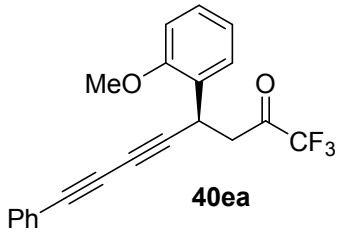


40da

Enantiomeric excess (92%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 5.4 min, minor enantiomer t_r = 4.9 min.

Oil; **$[\alpha]_D^{20}$** −25.8 (*c* 0.84, $CHCl_3$, 92% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.50-7.47 (m, 2H), 7.36-7.26 (m, 5H), 7.19-7.16 (m, 2H), 4.37 (dd, *J* = 7.7, 6.4 Hz, 1H), 3.35 (ddd, *J* = 18.7, 7.7, 0.5 Hz, 1H), 3.17 (ddd, *J* = 18.7, 6.4, 0.5 Hz, 1H), 2.35 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.1 (q, $J_{C\text{-}F}$ = 36.2 Hz, C), 137.7 (C), 135.3 (C), 132.6 (2CH), 129.7 (2CH), 129.2 (CH), 128.4 (2CH), 127.2 (2CH), 121.5 (C), 115.3 (q, $J_{C\text{-}F}$ = 291.8 Hz, CF_3), 82.5 (C), 77.2 (C), 73.6 (C), 68.3 (C), 44.4 (CH_2), 32.2 (CH), 21.0 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.7 (s, 3F);**HRMS (ESI)** *m/z*: 341.1150 $(M+H)^+$, $C_{21}H_{16}F_3O$ requires 341.1153.

(*S*)-1,1,1-Trifluoro-4-(2-methoxyphenyl)-8-phenylocta-5,7-diyn-2-one (40ea)

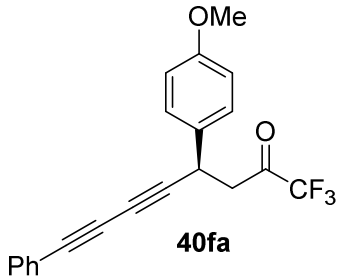


40ea

Enantiomeric excess (94%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 4.8 min, minor enantiomer t_r = 4.6 min.

Oil; **$[\alpha]_D^{20}$** −23.5 (*c* 1.01, $CHCl_3$, 94% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.58 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.51-7.48 (m, 2H), 7.36-7.27 (m, 4H), 7.01 (td, J = 7.5, 1.1 Hz, 1H), 6.89 (dd, *J* = 8.3, 0.9 Hz, 1H), 4.75 (dd, *J* = 7.8, 5.7 Hz, 1H), 3.85 (s, 3H), 3.21 (dd, *J* = 6.6, 2.5 Hz,2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.5 (q, $J_{C\text{-}F}$ = 35.6 Hz, C), 156.9 (C), 132.6 (2CH), 129.1 (CH), 129.1 (CH), 128.7 (CH), 128.4 (2CH), 126.1 (C), 121.7 (C), 121.0 (CH), 115.4 (q, $J_{C\text{-}F}$ = 291.9 Hz, CF_3), 110.6 (CH), 82.4 (C), 76.6 (C), 73.8 (C), 68.1 (C), 55.4 (CH_3), 42.6 (CH_2), 27.4 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.7 (s, 3F); **HRMS (ESI)** *m/z*: 357.1107 $(M+H)^+$, $C_{21}H_{16}F_3O_2$ requires 357.1102.

(*R*)-1,1,1-Trifluoro-4-(4-methoxyphenyl)-8-phenylocta-5,7-diyn-2-one (40fa)



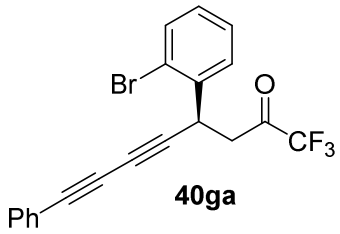
40fa

Enantiomeric excess (92%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 9.6 min, minor enantiomer t_r = 8.3 min.

Oil; **$[\alpha]_D^{20}$** −31.6 (*c* 0.70, $CHCl_3$, 92% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.48 (dd, *J* = 7.9, 1.7 Hz, 2H), 7.36-7.26 (m, 5H), 6.92-6.87 (m, 2H), 4.38-4.31 (m, 1H), 3.80 (s,

3H), 3.33 (ddd, *J* = 18.6, 7.6, 0.5 Hz, 1H), 3.20-3.12 (m, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.2 (q, J_{C-F} = 36.4 Hz, C), 159.2 (C), 132.5 (2CH), 130.3 (C), 129.2 (CH), 128.5 (2CH), 128.4 (2CH), 121.5 (C), 115.2 (q, J_{C-F} = 297.6 Hz, CF_3), 114.4 (2CH), 82.5 (C), 77.2 (C), 73.5 (C), 68.2 (C), 55.3 (CH_3), 44.5 (CH_2), 31.8 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.8 (s, 3F); **HRMS (ESI)** *m/z*: 357.1112 $(M+H)^+$, $C_{21}H_{16}F_3O_2$ requires 357.1102.

(*S*)-4-(2-Bromophenyl)-1,1,1-trifluoro-8-phenylocta-5,7-diyn-2-one (40ga)

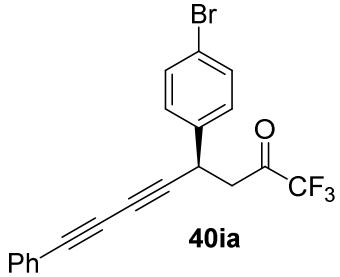


40ga

Enantiomeric excess (94%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 5.2 min, minor enantiomer t_r = 4.8 min.

Oil; **$[\alpha]_D^{20}$** −95.3 (*c* 0.55, $CHCl_3$, 94% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.71 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.58 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.52-7.48 (m, 2H), 7.39-7.32 (m, 4H), 7.22-7.16 (m, 1H), 4.85 (dd, *J* = 7.8, 5.8 Hz, 1H), 3.25 (m, 1H), 3.23 (s, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.2 (q, J_{C-F} = 36.4 Hz, C), 137.7 (C), 133.7 (CH), 133.0 (2CH), 130.0 (CH), 129.9 (CH), 129.7 (CH), 128.8 (2CH), 128.6 (CH), 123.3 (C), 121.8 (C), 115.7 (q, J_{C-F} = 291.7 Hz, CF_3), 81.4 (C), 77.8 (C), 73.9 (C), 69.5 (C), 43.2 (CH_2), 33.1 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.5 (s, 3F); **HRMS (ESI)** *m/z*: 405.0096/407.0075 $(M+H)^+$ 100.0/98.8, $C_{20}H_{13}BrF_3O$ requires 405.0102/407.0081.

(*R*)-4-(4-Bromophenyl)-1,1,1-trifluoro-8-phenylocta-5,7-diyn-2-one (40ia)

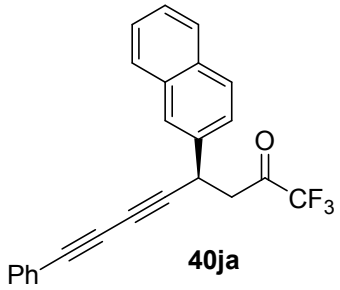


40ia

Enantiomeric excess (92%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 7.5 min, minor enantiomer t_r = 6.9 min.

Oil;**$[\alpha]_D^{20}$** −19.9 (*c* 0.78, $CHCl_3$, 92% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.51-7.47 (m, 4H), 7.37-7.27 (m, 5H), 4.37 (t, *J* = 7.0 Hz, 1H), 3.35 (ddd, *J* = 18.8, 7.5, 0.4 Hz, 1H), 3.16 (ddd, *J* = 18.8, 6.5, 0.4 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 187.8 (q, J_{C-F} = 36.6 Hz, C), 137.3 (C), 132.6 (2CH), 132.2 (2CH), 129.3 (CH), 129.1 (2CH), 128.4 (2CH), 121.9 (C), 121.3 (C), 115.2 (q, J_{C-F} = 291.6 Hz, CF_3), 81.4 (C), 77.6 (C), 73.3 (C), 68.8 (C), 44.2 (CH_2), 32.1 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.7 (s, 3F); **HRMS (ESI)** *m/z*: 405.0099/407.0078 $(M+H)^+$ 100.0/98.8, $C_{20}H_{13}BrF_3O$ requires 405.0102/407.0081.

(*R*)-1,1,1-Trifluoro-4-(naphthalene-2-yl)-8-phenylocta-5,7-diyn-2-one (40ja)

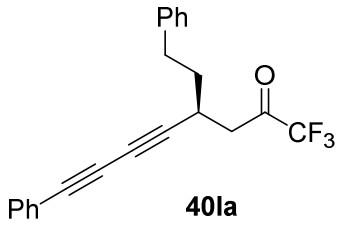


40ja

Enantiomeric excess (92%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 8.3 min, minor enantiomer t_r = 7.3 min.

[α]$_D^{20}$ –38.8 (*c* 1.00, $CHCl_3$, 92% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.88-7.83 (m, 4H), 7.54-7.48 (m, 5H), 7.37-7.29 (m, 3H), 4.59 (dd, *J* = 7.8, 6.2 Hz, 1H), 3.45 (dd, *J* = 18.4, 7.8 Hz, 1H), 3.29 (dd, *J* = 18.4, 6.2 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.1 (q, $J_{C\text{-}F}$ = 36.4 Hz, C), 135.5 (C), 133.4 (C), 132.8 (C), 132.6 (2CH), 129.3 (CH), 129.1 (CH), 128.4 (2CH), 127.9 (CH), 127.7 (CH), 126.6 (CH), 126.4 (CH), 126.3 (CH), 125.0 (CH), 121.5 (C), 115.3 (q, $J_{C\text{-}F}$ = 291.9 Hz, CF_3), 82.1 (C), 77.4 (C), 73.5 (C), 68.7 (C), 44.3 (CH_2), 32.7 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.7 (s, 3F); **HRMS (ESI)** *m/z*: 377.1158 $(M+H)^+$, $C_{24}H_{16}F_3O$ requires 377.1153.

(*S*)-1,1,1-Trifluoro-4-phenethyl-8-phenylocta-5,7-diyn-2-one (40la)

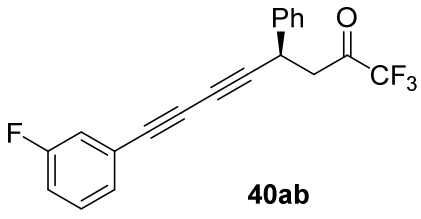


40la

Enantiomeric excess (84%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 5.1 min, minor enantiomer t_r = 4.8 min.

Oil; **[α]$_D^{20}$** –44.5 (*c* 0.44, $CHCl_3$, 84% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.52-7.49 (m, 2H), 7.37-7.29 (m, 5H), 7.24-7.21 (m, 3H), 3.15-3.02 (m, 2H), 2.95-2.73 (m, 3H), 1.91-1.83 (m, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.6 (q, $J_{C\text{-}F}$ = 36.1 Hz, C), 140.6 (C), 132.6 (2CH), 129.2 (CH), 128.6 (2CH), 128.5 (2CH), 128.4 (2CH), 126.3 (CH), 121.6 (C), 115.3 (q, $J_{C\text{-}F}$ = 292.0 Hz, CF_3), 83.5 (C), 77.2 (C), 73.6 (C), 67.7 (C), 41.4 (CH_2), 35.8 (CH_2), 33.3 (CH), 26.5 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.8 (s, 3F); **HRMS (ESI)***m/z*: 355.1329 $(M+H)^+$, $C_{22}H_{18}F_3O$ requires 355.1310.

(*R*)-1,1,1-Trifluoro-8-(3-fluorophenyl)-4-phenylocta-5,7-diyn-2-one (40ab)



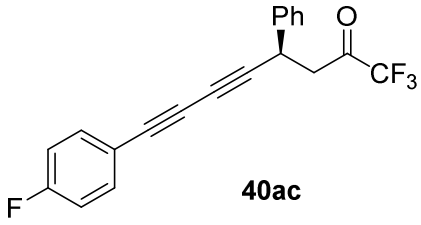
40ab

Enantiomeric excess (90%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 5.9 min, minor enantiomer t_r = 5.3 min.

Oil; **[α]$_D^{20}$** –15.7 (*c* 0.60, $CHCl_3$, 90% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.42-7.26 (m, 7H), 7.19-7.15 (m, 1H), 7.10-7.06 (m, 1H), 4.41 (dd, *J* = 7.9, 6.1 Hz, 1H), 3.37 (ddd, *J* = 18.7, 8.0, 0.5 Hz, 1H), 3.18 (dd, *J* = 18.7, 6.1 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.0 (q, $J_{C\text{-}F}$ = 36.3 Hz, C), 162.2 (d, $J_{C\text{-}F}$ = 247.3 Hz, C), 138.1 (C), 130.1 (d, $J_{C\text{-}F}$= 8.5 Hz, CH), 129.1 (2CH), 128.5 (d, $J_{C\text{-}F}$= 3.2 Hz, CH), 128.0 (CH), 127.4 (2CH), 123.4 (d, $J_{C\text{-}F}$ = 9.5 Hz, C), 119.3 (d, $J_{C\text{-}F}$ = 22.9 Hz,

CH), 116.8 (d, $J_{C\text{-}F}$ = 21.3 Hz, CH), 115.3 (q, $J_{C\text{-}F}$= 291.7 Hz, CF_3), 82.9 (C), 77.5 (C), 75.8 (q, $J_{C\text{-}F}$ = 3.4 Hz, C), 68.1 (C), 44.4 (CH_2), 32.6 (CH);**^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.7 (s, 3F), −112.8 (s, 1F); **HRMS (ESI)***m/z*: 345.0910 $(M+H)^+$, $C_{20}H_{13}F_4O$ requires 345.0903.

(*R*)-1,1,1-Trifluoro-8-(4-fluorophenyl)-4-phenylocta-5,7-diyn-2-one (40ac)

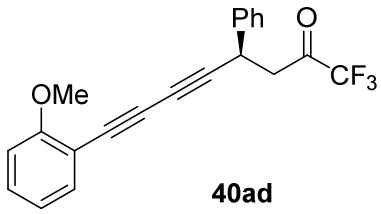


40ac

Enantiomeric excess (92%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 8.9 min, minor enantiomer t_r = 6.5 min.

Oil; **$[\alpha]_D^{20}$** −14.5 (*c* 0.67, $CHCl_3$, 92% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.49-7.45 (m, 2H), 7.41-7.29 (m, 5H), 7.04-6.98 (m, 2H), 4.40 (dd, *J* = 8.0, 6.1 Hz, 1H), 3.36 (dd, *J* = 18.7, 8.0 Hz, 1H), 3.18 (dd, *J* = 18.7, 6.1 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.0 (q, $J_{C\text{-}F}$ = 36.4 Hz, C), 163.0 (d, $J_{C\text{-}F}$ = 251.6 Hz, C), 138.2 (C), 134.6 (d, $J_{C\text{-}F}$ = 8.5 Hz, 2CH), 129.1 (2CH), 128.0 (CH), 127.4 (2CH), 117.6 (d, $J_{C\text{-}F}$= 3.7 Hz, C), 115.9 (d, $J_{C\text{-}F}$ = 22.3 Hz, 2CH), 115.3 (q, $J_{C\text{-}F}$ = 291.8 Hz, CF_3), 82.2 (C), 76.2 (C), 73.3 (C), 68.3 (C), 44.4 (CH_2), 32.6 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.8 (s, 3F), −109.0 (s, 1F); **HRMS (ESI)** *m/z*: 345.0913 $(M+H)^+$, $C_{20}H_{13}F_4O$ requires 345.0903.

(*R*)-1,1,1-Trifluoro-8-(2-methoxyphenyl)-4-phenylocta-5,7-diyn-2-one (40ad)

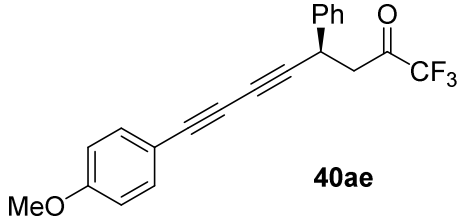


40ad

Enantiomeric excess (92%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 6.6 min, minor enantiomer t_r = 6.3 min.

Oil; **$[\alpha]_D^{20}$** −17.0 (*c* 0.91, $CHCl_3$, 92% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.46-7.29 (m, 7H), 6.90 (td, *J* = 7.5, 1.0 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 4.41 (dd, J = 7.7, 6.3 Hz, 1H), 3.88 (s, 3H), 3.41-3.32 (m, 1H), 3.23-3.14 (m, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.0 (q, $J_{C\text{-}F}$ = 36.3 Hz, C), 161.5 (C), 138.4 (C), 134.5 (CH), 130.7 (CH), 129.0 (2CH), 127.9 (CH), 127.4 (2CH), 120.5 (CH), 115.3 (q, $J_{C\text{-}F}$ = 291.8 Hz, CF_3), 110.7 (CH), 110.6 (CH), 82.7 (C), 77.3 (C), 73.8 (C), 68.7 (C), 55.8 (CH_3), 44.4 (CH_2), 32.6 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.7 (s, 3F); **HRMS (ESI)** *m/z*: 357.1109 $(M+H)^+$, $C_{21}H_{16}F_3O_2$ requires 357.1102.

(*R*)-1,1,1-Trifluoro-8-(4-methoxyphenyl)-4-phenylocta-5,7-diyn-2-one (40ae)



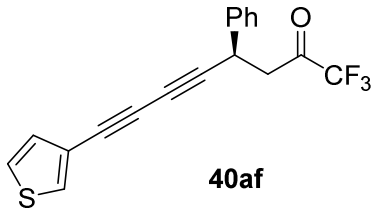
40ae

Enantiomeric excess (91%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 80.20, 1 mL/min, major enantiomer t_r = 11.7 min, minor enantiomer t_r = 8.0 min.

Oil; **$[\alpha]_D^{20}$** −32.7 (*c* 0.75, $CHCl_3$, 91% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.44-7.30 (m, 7H), 6.86-6.81 (m, 2H), 4.40 (dd, *J* = 7.9, 6.2

Hz, 1H), 3.81 (s, 3H), 3.36 (ddd, *J* = 18.6, 7.9, 0.5 Hz, 1H), 3.18 (ddd, *J* = 18.6, 6.2, 0.5 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.1 (q, $J_{C\text{-}F}$ = 36.7 Hz, C), 160.4 (C), 138.5 (C), 134.2 (2CH), 129.0 (2CH), 127.9 (CH), 127.4 (2CH), 115.3 (q, $J_{C\text{-}F}$ = 291.6 Hz, CF_3), 114.1 (2CH), 113.4(C), 81.6 (C), 77.5 (C), 72.4 (C), 68.7 (C), 55.3 (CH_3), 44.5 (CH_2), 32.6 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.8 (s, 3F); **HRMS (ESI)** *m/z*: 357.1115 $(M+H)^+$, $C_{21}H_{16}F_3O_2$ requires 357.1102.

(*R*)-1,1,1-Trifluoro-4-phenyl-8-(thiophen-3-yl)octa-5,7-diyn-2-one (40af)

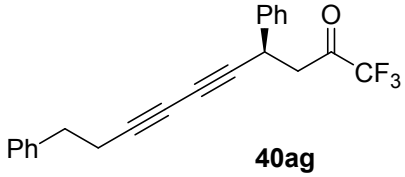


40af

Enantiomeric excess (94%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 8.4 min, minor enantiomer t_r = 7.1 min.

Oil; **$[\alpha]_D^{20}$** −26.6 (*c* 0.86, $CHCl_3$, 94% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.56 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.41-7.25 (m, 5H), 7.26 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.13 (dd, J = 5.0, 1.2 Hz, 1H), 4.40 (dd, *J* = 7.9, 1.6 Hz, 1H), 3.36 (ddd, *J* = 18.6, 7.9, 0.5 Hz, 1H), 3.18 (ddd, *J* = 18.7, 6.1, 0.5 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.0 (q, $J_{C\text{-}F}$= 36.3 Hz, C), 138.3 (C), 131.4 (CH), 130.2 (CH), 129.1 (2CH), 127.9 (CH), 127.4 (2CH), 125.6 (CH), 120.6 (C), 115.3 (q, $J_{C\text{-}F}$= 289.5 Hz, CF_3), 82.0 (C), 73.2 (C), 72.5 (C), 68.4 (C), 44.4 (CH_2), 32.6 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.8 (s, 3F); **HRMS (ESI)** *m/z*: 333.0569 $(M+H)^+$, $C_{18}H_{12}F_3OS$ requires 333.0561.

(*R*)-1,1,1-Trifluoro-4,10-diphenyldeca-5,7-diyn-2-one (40ag)

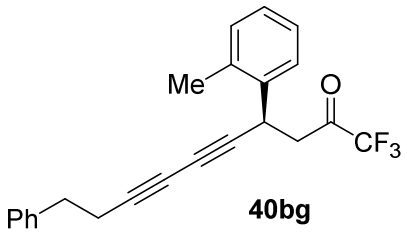


40ag

Enantiomeric excess (93%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 6.4 min, minor enantiomer t_r = 5.7 min.

Oil; **$[\alpha]_D^{20}$** −14.2 (*c* 0.90, $CHCl_3$, 93% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.37-7.19 (m, 10H), 4.31 (dd, *J* = 7.6, 6.5 Hz, 1H), 3.31 (ddd, *J* = 18.6, 7.9, 0.5 Hz, 1H), 3.13 (ddd, *J* = 18.6, 6.2, 0.4 Hz, 1H), 2.85 (t, *J* = 7.5 Hz, 2H), 2.57 (t, *J* = 7.5 Hz, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.1 (q, $J_{C\text{-}F}$ = 36.3 Hz, C), 140.0 (C), 138.5 (C), 129.0 (2CH), 128.5 (2CH), 128.3 (2CH), 127.8 (CH), 127.3 (2CH), 126.5 (CH), 115.2 (q, $J_{C\text{-}F}$ = 291.6 Hz, CF_3), 79.3 (C), 75.6 (C), 68.7 (C), 65.3 (C), 44.5 (CH_2), 34.5 (CH_2), 32.3 (CH), 21.4 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.8 (s, 3F); **HRMS (ESI)** *m/z*: 355.1317 $(M+H)^+$, $C_{22}H_{18}F_3O$ requires 355.1310.

(*S*)-1,1,1-Trifluoro-10-phenyl-4-(*o*-tolyl)deca-5,7-diyn-2-one (40bg)

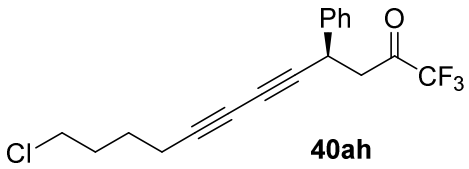


40bg

Enantiomeric excess (95%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 5.4 min, minor enantiomer t_r = 5.1 min.

Oil; **[α]$_D^{20}$** –6.1 (*c* 1.15, $CHCl_3$, 95% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.43-7.41 (m, 1H), 7.33-7.17 (m, 8H), 4.49 (dd, *J* = 8.7, 5.4 Hz, 1H), 3.30 (dd, *J* = 18.5, 8.7 Hz, 1H), 3.09 (dd, *J* = 18.5, 5.4 Hz, 1H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.38 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.3 (q, $J_{C\text{-}F}$ = 36.5 Hz, C), 140.0 (C), 136.6 (C), 135.0 (C),131.0 (CH), 128.5 (2CH), 128.3 (2CH), 127.8 (CH), 127.1 (CH), 126.8 (CH), 126.5 (CH), 115.3 (q, $J_{C\text{-}F}$ = 291.9 Hz, CF_3), 79.0 (C), 75.8 (C), 68.1 (C), 65.4 (C), 43.0 (CH_2), 34.5 (CH_2), 28.7 (CH), 21.4 (CH_2), 19.2 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.7 (s, 3F); **HRMS (ESI)** *m/z*: 369.1470 $(M+H)^+$, $C_{23}H_{20}F_3O$ requires 369.1466.

(*R*)-12-Chloro-1,1,1-trifluoro-4-phenyldodeca-5,7-diyn-2-one (40ah)

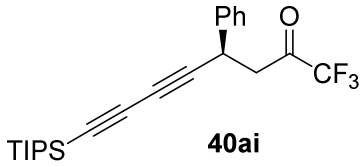


40ah

Enantiomeric excess (93%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 7.5 min, minor enantiomer t_r = 6.6 min.

Oil; **[α]$_D^{20}$** –11.7 (*c* 0.89, $CHCl_3$, 93% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.38-7.26 (m, 5H), 4.30 (dd, *J* = 7.5, 6.5 Hz, 1H), 3.55 (t, *J* = 6.4 Hz, 2H), 3.30 (ddd, *J* = 18.6, 7.9, 0.5 Hz, 1H), 3.12 (ddd, *J* = 18.6, 6.9, 0.5 Hz, 1H), 2.33 (td, *J* = 6.9, 1.0 Hz, 1H), 1.94-1.84 (m, 2H), 1.74-1.64 (m, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.1 (q, $J_{C\text{-}F}$ = 36.2 Hz, C), 138.5 (C), 129.0 (2CH), 127.8 (CH), 127.3 (2CH), 115.2 (q, $J_{C\text{-}F}$ = 291.8 Hz, CF_3), 79.2 (C), 75.5 (C), 68.6 (C), 65.3 (C), 44.5 (CH_2), 44.3 (CH_2), 32.2 (CH), 31.4 (CH_2), 25.3 (CH_2), 18.5 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.8 (s, 3F); **HRMS (ESI)** *m/z*: 341.0930/343.0899 $(M+H)^+$ 100.0/31.7, $C_{18}H_{17}ClF_3O$ requires 341.0920/343.0891.

(*R*)-1,1,1-Trifluoro-4-phenyl-8-(triisopropylsilyl)octa-5,7-diyn-2-one (40ai)



40ai

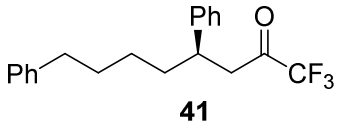
Enantiomeric excess (85%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 8.6 min, minor enantiomer t_r = 6.1 min.

Oil; **[α]$_D^{20}$** –14.5 (*c* 0.77, $CHCl_3$, 85% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.37-7.29 (m, 5H), 4.33 (t, *J* = 6.0 Hz, 1H), 3.34 (ddd, *J* = 18.8, 7.5, 0.5 Hz, 1H), 3.16 (ddd, *J* = 18.8, 6.5, 0.5 Hz, 1H), 1.08 (s, 21H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.0 (q, $J_{C\text{-}F}$ = 36.3 Hz, C), 138.2 (C), 129.0 (2CH), 127.9 (CH), 127.4 (2CH), 115.2 (q, $J_{C\text{-}F}$ = 291.9 Hz, CF_3), 89.1 (C), 83.3 (C), 76.3 (C), 69.0 (C), 44.3 (CH_2), 32.2 (CH), 18.5 (6CH_3),

11.2 (3CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −79.8 (s, 3F); **HRMS (ESI)***m/z*: 407.2024 $(M+H)^+$, $C_{23}H_{30}F_3OSi$ requires 407.2018.

5.4.2.4. Synthetic transformations

(*R*)-1,1,1-Trifluoro-4,8-diphenyloctan-2-one (41)

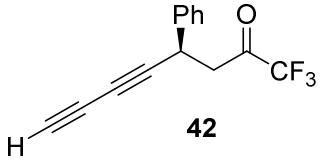


41

A solution of compound **40aa** (10 mg, 0.031 mmol, 93% *ee*) in EtOAc (0.4 mL) was stirred under hydrogen atmosphere in the presence of 10% Pd/C (3 mg) for 30 min at room temperature. Then, the reaction mixture was filtered through a short pad of silica gel, which was washed with EtOAc, and the solvent was removed under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:EtOAc (99:01) gave compound **41** (9.2 mg, 89%). Enantiomeric excess (92%) was determined by chiral HPLC (Chiralcel OD-H), hexane-*i*PrOH 99:01, 1mL/min, major enantiomer t_r = 10.8 min, minor enantiomer t_r = 7.6 min.

Oil; **$[\alpha]_D^{20}$** −2.3 (*c* 0.78, $CHCl_3$, 92% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.33-7.21 (m, 5H), 7.20-7.09 (m, 5H), 3.26-3.16 (m, 1H), 3.02-2.99 (m, 2H), 2.56-2.50 (m, 2H), 1.70-1.48 (m, 4H), 1.28-1.17 (m, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 190.2 (q, J_{C-F} = 35.1 Hz, C), 143.0 (C), 142.4 (C), 128.7 (2CH), 128.3 (2CH), 128.3 (2CH), 127.3 (2CH), 126.8 (CH), 125.7 (CH), 115.4 (q, J_{C-F} = 292.2 Hz, CF_3), 43.5 (CH_2), 39.7 (CH), 35.9 (CH_2), 35.6 (CH_2), 31.2 (CH_2), 26.8 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −80.0 (s, 3F); **HRMS (ESI)** *m/z*: 335.1631 $(M+H)^+$, $C_{20}H_{22}F_3O$ requires 335.1623.

(*R*)-1,1,1-Trifluoro-4-phenylocta-5,7-diyn-2-one (42)

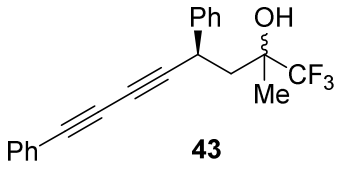


42

AcOH (4 μL, 0.096 mmol) and 1M TBAF in THF (68 μL, 0.068 mmol) were added to a solution of **40ai** (35.4 mg, 0.087 mmol) in THF (1 mL) at 0 °C under nitrogen atmosphere. After 4 h, the reaction was quenched with H_2O (1 mL). The aqueous layer was extracted with diethyl ether (3 x 15 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography eluting with hexane:EtOAc (99:01) gave **42** (15 mg, 70%). Enantiomeric excess (85%) was determined by GLC (Supelco β-dex-225, T_{column}= 100 °C (5 min) to 150 °C at 5 °C/min), major enantiomer t_r = 20.2 min, minor enantiomer t_r = 19.9 min.

Oil; **$[\alpha]_D^{20}$** −6.0 (*c* 0.80, $CHCl_3$, 85%); **^{1}H NMR ($CDCl_3$, 300 MHz)** δ 7.38-7.30 (m, 5H), 4.31 (t, *J* = 7.0 Hz, 1H), 3.33 (dd, *J* = 18.7, 7.9 Hz, 1H), 3.15 (dd, *J* = 18.7, 6.2 Hz, 1H), 2.10 (d, *J* = 1.1 Hz, 1H); **^{13}C NMR ($CDCl_3$, 75.5 MHz)** δ 187.9 (q, *J* = 36.1 Hz, C), 137.9 (C), 129.1 (2CH), 128.0 (CH), 127.3 (2CH), 115.2 (q, *J* = 291.6 Hz, CF_3), 76.1 (C), 68.0 (C), 67.6 (C), 67.1 (CH), 44.2 (CH_2), 32.1 (CH); **^{19}F NMR ($CDCl_3$, 282 MHz)** δ −79.8 (s, 3F); **HRMS (ESI)** *m/z*: 250.0601 $(M+H)^+$, $C_{14}H_9F_3O$ requires 250.0605.

(4*R*)-1,1,1-Trifluoro-2-methyl-4,8-diphenylocta-5,7-diyn-2-ol (43)



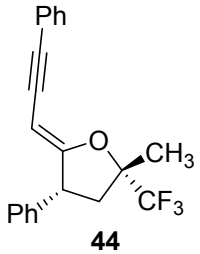
43

A commercial 3 M solution of MeMgCl in THF (77 μL, 0.230 mmol) was diluted with diethyl ether (0.3 mL) and cooled to 0 ºC under nitrogen. A solution of compound **40aa** (50 mg, 0.153 mmol) in dry diethyl ether (0.5 mL) was added dropwise via syringe and the reaction mixture was allowed to reach room temperature. After 2 h, the reaction was quenched with a solution of citric acid (1 mL). The aqueous layer was extracted with diethyl ether (3 x 15 mL) and the organic layer was dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography eluting with hexane:EtOAc (99:01) gave **43** (40.8 mg, 78%) as a ca. 4.5:1 mixture of two diastereomeric alcohols. Enantiomeric excess (91%) was determined by chiral HPLC (Chiralpak AY-H), hexane-*i*PrOH 99:01, 1 mL/min, *major diastereomer*: major enantiomer t_r = 23.2 min, minor enantiomer t_r = 16.1 min.

Major (1*S*,4*R*)-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.45 (m, 2H), 7.39-7.31 (m, 8H), 4.04 (dd, *J* = 9.8, 4.9 Hz, 1H), 2.53 (s, OH), 2.38 (dd, *J* = 14.5, 9.8 Hz, 1H), 2.10 (dd, *J* = 14.5, 4.9 Hz, 1H), 1.46 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 140.2 (C), 132.5 (2CH), 129.2 (CH), 129.1 (2CH), 128.4 (2CH), 127.6 (CH), 127.4 (2CH), 121.5 (C), 84.1 (C), 77.2 (C), 73.7 (q, J_{C-F} = 28.5 Hz, C), 73.5 (C), 69.1 (C), 42.6 (CH_2), 33.3 (CH), 20.3 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –84.0 (s, 3F).

Minor (1*R*,4*R*)-diastereomer (representative peaks taken from the diastereomeric mixture): **^{1}H NMR (300 MHz, $CDCl_3$)** δ 4.13 (dd, *J* = 9.8, 4.3 Hz, 1H), 2.54 (s, 1H), 2.23-2-17 (m, 2H), 1.58 (s, 3H); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –83.1 (s, 3F).

(2*S*,4*R*,*Z*)-2-Methyl-4-phenyl-5-(3-phenylpro-2-yn-1-ylidene)-2-(trifluoromethyl)tetrahydrofuran (44)



44

AgOTf (10.0 mg, 0.038 mmol) was added to a solution of the diastereomeric mixture of **43** (26 mg, 0.076 mmol) in THF (0.5 mL) at rt under nitrogen atmosphere and the mixtures was stirred overnight. Then, removal of the solvent under reduced pressure followed by flash chromatography eluting with hexane:EtOAc (99:01) allowed to obtain furan **44** as the major product (15.6 mg, 60%).Enantiomeric excess (92%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 13.3 min, minor enantiomer t_r = 27.4 min. The cyclization product resulting from the minor diastereomer of **43** could not be obtained pure in sufficient amount.

Oil; **$[\alpha]_D^{20}$** –5.9 (*c* 1.00, $CHCl_3$, 92% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.43-7.25 (m, 10H), 4.30 (d, *J* = 2.2 Hz, 1H), 4.18 (ddd, *J* = 11.5, 9.3, 2.2 Hz, 1H), 2.50 (dd, *J* = 12.9, 11.5 Hz, 1H), 2.40 (dd, *J* = 12.9, 9.3 Hz, 1H), 1.63 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 168.5 (C), 138.5 (C), 131.3 (2CH), 129.0 (2CH), 128.5 (2CH), 128.1 (2CH), 127.8 (CH), 127.5 (CH), 125.2 (q, J_{C-F} = 254.4 Hz, CF_3), 124.1 (C), 93.1 (C), 84.8 (C),

84.2 (C), 81.0 (CH), 47.3 (CH), 40.0 (CH_2), 20.3 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –82.2 (s, 3F); **HRMS (ESI)** *m/z*: 343.1300 $(M+H)^+$, $C_{21}H_{18}F_3O$ requires 343.1310.

5.6. Enantioselective conjugate alkynylation of β-trifluoromethyl α,β-enones

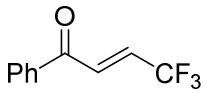
5.6.1. Synthesis and characterization of β-trifluoromethyl α,β-enones 45

5.6.1.1 Synthesis of aryl substituted β-trifluoromethyl α,β-enones 45a-g

Aryl substituted β-trifluoromethyl α,β-enones were synthesized according to the procedure described in the literature.[83b]

Pyrrolidine (0.6 mL, 7 mmol), trifluoroacetaldehyde ethyl hemiacetal (1.29 mL, 10 mmol) and acetophenone (10 mmol) were dissolved in toluene (10 mL). The mixture was heated at reflux temperature until completion (TLC). Then, the solvent was removed under reduced pressure and the resulting mixture chromatographed on silica gel eluting with hexane-EtOAc to afford the desired enone **45**.

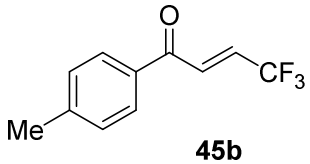
(*E*)-4,4,4-Trifluoro-1-phenylbut-2-en-1-one (45a)



45a

Oil, 79% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.98 (dd, *J* = 7.2, 1.5 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.58- 7.49 (m, 3H), 6.82 (dq, *J* = 15.5, 6.7 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 188.0 (C), 136.1 (C), 134.1 (CH), 131.0 (q, $J_{C\text{-}F}$ = 5.6 Hz, CH), 130.2 (q, $J_{C\text{-}F}$ = 35.0 Hz, CH), 129.0 (CH), 128.8 (CH), 122.5 (q, $J_{C\text{-}F}$ = 268.5 Hz,CF_3).

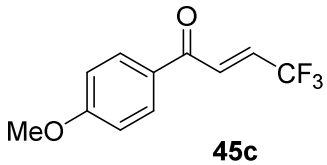
(*E*)-4,4,4-Trifluoro-1-*p*-tolylbut-2-en-1-one (45b)



45b

75% yield; **mp** 56-59 ºC; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.54 (dq, *J* = 15.6, 2.0 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 6.81 (dq, *J* = 15.5, 6.7 Hz, 1H), 2.45 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 187.5 (C), 145.3 (C), 133.7 (C), 131.1 (q, $J_{C\text{-}F}$ = 5.5 Hz, CH), 129.9 (q, $J_{C\text{-}F}$ = 34.8 Hz, CH), 129.7 (CH), 129.0 (CH), 122.6 (q, $J_{C\text{-}F}$ = 268.5 Hz,CF_3), 21.6 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –65.57 (s, CF_3).

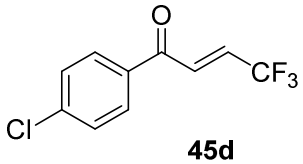
(*E*)-4,4,4-Trifluoro-1-(4-methoxyphenyl)but-2-en-1-one (45c)



45c

45% yield; **mp** 36-39 ºC; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.97 (d, *J* = 9.0 Hz, 2H), 7.53 (dq, *J* = 15.5, 2.0 Hz, 1H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.79 (dq, *J* = 15.5, 2.0 Hz, 1H), 3.89 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 186.1 (C), 164.4 (C), 131.4 (CH), 131.0 (q, $J_{C\text{-}F}$ = 5.5 Hz, CH), 129.5 (q, $J_{C\text{-}F}$ = 34.8 Hz, CH), 129.2 (C), 122.7 (q, $J_{C\text{-}F}$ = 268.5 Hz,CF_3), 114.2 (CH), 55.6 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –65.51 (s, CF_3).

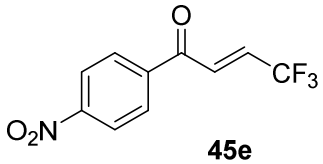
(*E*)-1-(4-Chlorophenyl)-4,4,4-trifluorobut-2-en-1-one (45d)



45d

80% yield; **mp** 37-41 ºC; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.92 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 2H), 7.49 (dq, *J* = 15.2, 2.0 Hz, 1H), 6.83 (dq, *J* = 15.6, 6.6 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 186.7 (C), 140.8 (C), 134.4 (C), 130.7 (q, J_{C-F} = 35.3 Hz, CH), 130.5 (q, J_{C-F} = 5.5 Hz, CH), 130.2 (CH), 129.4 (CH), 122.4 (q, J_{C-F} = 268.5 Hz,CF_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –65.66 (s, CF_3).

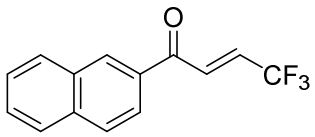
(*E*)-4,4,4-Trifluoro-1-(4-nitrophenyl)but-2-en-1-one (45e)



45e

81% yield; **mp** 66-70 ºC;**^{1}H NMR (300 MHz, $CDCl_3$)**δ 8.37 (d, *J* = 9.0 Hz, 2H), 8.14 (d, *J* = 9.0 Hz, 2H), 7.52 (dq, *J* = 15.5, 2.0 Hz, 1H), 6.88 (dq, *J* = 15.5, 6.5 Hz, 1H);**^{13}C NMR (75.5 MHz, $CDCl_3$)**δ 186.7 (C), 150.8 (C), 140.5 (C), 131.9 (q, J_{C-F} = 35.5 Hz, CH), 130.1 (q, J_{C-F} = 5.5 Hz, CH), 129.8 (CH), 124.2 (CH), 122.2 (q, J_{C-F} = 268.8 Hz, CF_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –65.79 (s, CF_3).

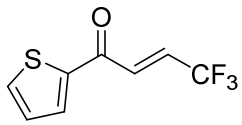
(*E*)-4,4,4-Trifluoro-1-(naphthalen-2-yl)but-2-en-1-one (45f)



45f

Oil, 61% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.47 (s, 1H), 8.05 (dd, *J* = 8.7, 1.8 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.95 (d, *J* = 8.7 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.71 (dq, *J* = 15.5, 2.1 Hz, 1H), 7.66 (td, *J* = 7.9, 1.4 Hz, 1H), 7.60 (td, *J* = 7.4, 1.3 Hz, 1H), 6.89 (dq, *J* = 15.6, 6.6 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 187.7 (C), 136.0 (C), 133.6 (C), 132.4 (C), 131.03 (CH), 131.00 (q, J_{C-F} = 5.5 Hz, CH), 130.2 (q, J_{C-F} = 34.8 Hz, CH), 129.7 (CH), 129.2 (CH), 129.1 (CH), 127.9 (CH), 127.2 (CH), 123.9 (CH), 122.6 (q, J_{C-F} = 268.5 Hz, CF_3).

(*E*)-4,4,4-Trifluoro-1-(thiophen-2-yl)but-2-en-1-one (45g)



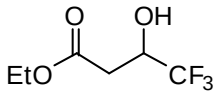
45g

73% yield; **mp** 50-52 ºC; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.84 (dd, *J* = 3.9, 1.2 Hz, 1H), 7.79 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.40 (dq, *J* = 15.5, 2.1 Hz, 1H), 7.22 (dd, *J* = 5.1, 3.9 Hz, 1H), 6.87 (dq, *J* = 15.5, 6.7 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 179.6 (C), 143.7 (C), 136.1 (CH), 133.6 (CH), 130.8 (q, J_{C-F} = 5.8 Hz, CH), 129.8 (q, J_{C-F} = 35.3 Hz, CH), 128.7 (CH), 122.5 (q, J_{C-F} = 268.8 Hz, CF_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –65.57 (s, CF_3).

5.6.1.2. Synthesis of aliphatic substituted β-trifluoromethyl α,β-enones 45h-i

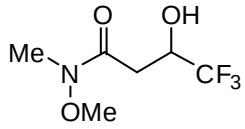
Aliphatic substituted β-trifluoromethyl α,β-enones were synthesis according to the procedure described in the literature.[87]

Ethyl 4,4,4-trifluoro-3-hydroxybutanoate



$NaBH_4$ (0.83g, 22.0 mmol) was added portionwise to a solution of ethyl 4,4,4-trifluoro-3-oxobutanoate (3.2 mL, 21.7 mmol) in diethyl ether (20 mL) at rt under nitrogen atmosphere. After 5 h, the reaction was quenched with 20% aqueous NH_4Cl and extracted with CH_2Cl_2, the organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give ethyl 4,4,4-trifluoro-3-hydroxybutanoate (3.1 g, 75%).

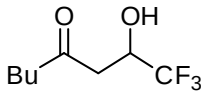
4,4,4-Trifluoro-3-hidroxy-*N*-methoxy-*N*-methylbutanamide



A 2 M solution of $AlMe_3$ in heptane (13.4 mL, 26.7 mmol) was added dropwise to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (2.6 g, 26.7 mmol) in CH_2Cl_2 (12 mL) at –10 ºC under nitrogen atmosphere. The resulting yellow solution was stirred at rt for 1 h and cooled to –10 ºC. A solution of 4,4,4-trifluoro-3-hydroxybutanoate (2.5 g, 13.4 mmol) in CH_2Cl_2 (2.5 mL) was slowly added, and the reaction mixture stirred overnight at rt. Then, quenched with saturated aqueous NH_4Cl. After extraction with CH_2Cl_2, the organic layers were combined, washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 4,4,4-trifluoro-3-hidroxy-*N*-methoxy-*N*-methylbutanamide (2.2 g, 82%).

White solid; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 4.48-4.42 (m, 1H), 4.30 (d, *J* = 4.2 Hz, 1H), 3.72 (s, 3H), 3.22 (s, 3H), 2.82 (d, *J* = 6.1 Hz, 2H). Data consistent with the literature.[87]

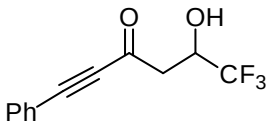
1,1,1-Trifluoro-2-hydroxyoctan-4-one



A 2.5 M solution of *n*-BuLi in hexane (6 mL, 15 mmol) was added dropwise to a solution of 4,4,4-trifluoro-3-hidroxy-*N*-methoxy-*N*-methylbutanamide (1 g, 5 mmol) in THF (10 mL) at –78 ºC under nitrogen atmosphere. The reaction mixture was stirred for 4 h at –78 ºC. Then, quenched with saturated aqueous NH_4Cl at 0 °C. After extraction with EtOAc, the organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography gave 1,1,1-trifluoro-2-hydroxyoctan-4-one (0.90 g, 92%).

Oil; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 4.52-4.45 (m, 1H), 3.60 (d, *J* = 4.6 Hz, 1H), 2.87-2.69 (m, 2H), 2.51-2.46 (m, 2H), 1.63-1.53 (m, 2H), 1.38-1.23 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 2H).

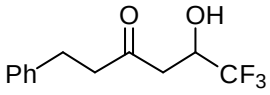
6,6,6-Trifluoro-5-hydroxy-1-phenylhex-1-yn-3-one



A 2.5 M solution of *n*-BuLi in hexane (4.2 mL, 10.5 mmol) was added to a solution of alkyne **2a** (1.26 mL, 11.5 mmol) in THF (5 mL) at –78 ºC under nitrogen atmosphere. After stirring at 0 ºC for 30 min, the reaction mixture was cooled to –78 ºC and a solution of 4,4,4-trifluoro-3-hidroxy-*N*-methoxy-*N*-methylbutanamide (0.71 g, 3.51 mmol) in THF (7 mL) was added. After stirring at this temperature for 4 h, saturated aqueous NH_4Cl was added at 0 °C. After extraction with EtOAc, the organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography gave 6,6,6-trifluoro-5-hydroxy-1-phenylhex-1-yn-3-one (0.76 g, 89%).

White solid; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.61-7.58 (m, 2H), 7.53-7.47 (m, 1H), 7.44-7.38 (m, 2H), 4.67-4.59 (m, 1H), 3.18-3.04 (m, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 183.5 (C), 133.3 (2CH), 131.3 (CH), 128.8 (2CH), 124.4 (q, $J_{C\text{-}F}$ = 281.1 Hz, CF_3), 119.2 (C), 93.4 (C), 87.3 (C), 66.5 (q, $J_{C\text{-}F}$ = 32.5 Hz, CH), 45.0 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –79.9 (s, 3F).

6,6,6-Trifluoro-5-hydroxy-1-phenylhexan-3-one



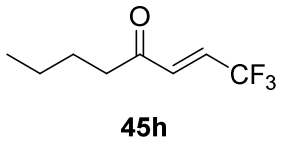
A solution of 6,6,6-trifluoro-5-hydroxy-1-phenylhex-1-yn-3-one(0.76 mg, 3.13 mmol) in EtOAc (20 mL) was stirred under hydrogen atmosphere in the presence of Pd/C (10%) for 30 min. Then, the reaction mixture was filtered through silica gel eluting with EtOAc. The solvent was removed under reduced pressure to give 6,6,6-trifluoro-5-hydroxy-1-phenylhexan-3-one (0.75 mg, 99%).

Oil; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.33-7.27 (m, 2H), 7.24-7.17 (m, 3H), 4.54-4.43 (m, 1H), 3.33 (br s, 1H), 2.96-2.68 (m, 6H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 207.6 (C), 140.2 (C), 128.6 (2CH), 128.2 (2CH), 126.4 (CH), 66.7 (q, $J_{C\text{-}F}$ = 32.3 Hz, CH), 45.1 (CH_2), 42.0 (CH_2), 29.4 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –80.0 (s, 3F).

Dehydration of the hydroxyketones. Synthesis of enones 45h-i

Et_3N (0.63 mL, 4.6 mmol) was added to a solution of the corresponding hydroxyketone (4.6 mmol) in CH_2Cl_2 (9.2 mL) was under nitrogen atmosphere. The reaction mixture was stirred at rt for 30 min, cooled to –78 ºC and mesyl chloride (0.45 mL, 5.75 mmol) was slowly added. After stirring at –78 ºC for 30 min and rt for 3 h, Et_3N (0.96 mL, 6.9 mmol) was added, and the mixture was stirred overnight. Then, water and pentane were added. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the desired enone **45**.

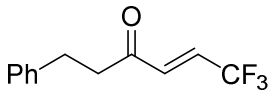
(*E*)-1,1,1-Trifluorooct-2-en-4-one (45h)



45h

Oil, 73% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 6.72 (dq, *J* = 15.9, 1.6 Hz, 1H), 6.59 (dq, *J* = 15.9, 6.1 Hz, 1H), 2.65-2.60 (m, 2H), 1.68-1.58 (m, 2H), 1.39-1.32 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 1H).

(*E*)-6,6,6-Trifluoro-1-phenylhex-4-en-3-one (45i)



45i

Oil, 73% yield; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.33-7.27 (m, 2H), 7.24-7.17 (m, 3H), 6.70 (dq, *J* = 16.0, 1.5 Hz, 1H), 6.58 (dq, *J* = 16.0, 6.0 Hz, 1H), 2.97 (s, 4H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 197.1 (C), 140.2 (CH), 134.0 (q, *J* = 5.6 Hz, CH), 128.9 (C), 128.6 (2CH), 128.3 (2CH), 126.4 (CH), 122.4 (q, $J_{C\text{-}F}$= 270.5 Hz, CF_3), 43.4 (CH_2), 29.4 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –66.8 (s, 3F).

5.6.2. Enantioselective conjugate addition of terminal alkynes to β-trifluoromethyl α,β-enones

5.6.2.1. General procedure for the enantioselective alkynylation reaction

$[Cu(CH_3CN)_4]BF_4$ (5.7 mg, 0.018 mmol) and **L29** (12.4 mg, 0.018 mmol) were placed in a dry round bottom flask which was purged with nitrogen. THF (0.2 mL) was added and the mixture was stirred for 1.5 h at room temperature. Then, a solution of β-trifluoromethyl-α,β-enone **45** (0.090 mmol) in dry THF (1.0 mL) was added via syringe, followed of triethylamine (12.5 µL, 0.090 mmol). The solution was placed in a bath at 40 °C. After 10 min, the alkyne **2** (0.675mmol) was added and the solution was stirred at 40 °C under nitrogen until the reaction was complete (TLC). The reaction mixture was quenched with 20% aqueous NH_4Cl (1.0 mL), extracted with CH_2Cl_2 (2 × 15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:diethyl ether mixtures afforded compound **46**.

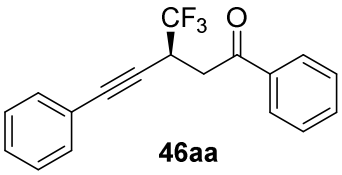
5.6.2.2. General procedure for the synthesis of the racemic products

A 1.5 M solution of Et_2Zn in toluene (0.17 mL, 0.25 mmol) was added dropwise to a solution of alkyne **2** (0.94 mmol) and (±)-BINOL (**L1**, 7.2 mg, 0.025 mmol) in toluene (0.48 mL) at room temperature under nitrogen and the mixture was stirred for 1.5 h at 70 ºC. Then, β-substituted β-trifluoromethyl enones **45** (0.125 mmol) in toluene (1.0 mL) was added via syringe. The solution was stirred at 70 ºC until the reaction was complete (TLC). The reaction mixture was quenched with 20% aqueous NH_4Cl (1.0 mL), extracted with CH_2Cl_2 (2x 15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:EtOAc mixtures afforded racemic **46**.

5.6.2.3. Characterization of products 46

See Table 16 (Page 80) for yields.

(*S*)-(–)-3-(Trifluoromethyl)-1,5-diphenylpent-4-yn-1-one (46aa)

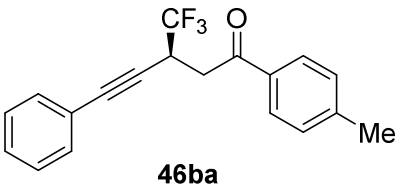


46aa

Enantiomeric excess (85%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 8.1 min, minor enantiomer t_r = 10.1 min.

Oil; **[α]$_D^{20}$** –34.7 (*c* 0.81, $CHCl_3$, 85% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.03-7.99 (m, 2H), 7.62 (ddd, *J* = 6.6, 1.3 Hz, 2H), 7.40-7.37 (m, 2H), 7.31-7.24 (m, 3H), 4.29-4.16 (m, 1H), 3.60 (dd, *J* = 17.3, 8.9 Hz, 1H), 3.42 (dd, *J* = 17.3, 4.2 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 194.5 (C), 136.1 (C), 133.8 (CH), 131.9 (2CH), 128.8 (2CH), 128.6 (CH), 128.2 (2CH), 128.2 (2CH), 125.3 (q, $J_{C\text{-}F}$ = 263.0 Hz, CF_3), 122.0 (C), 84.3 (C), 81.4 (q, $J_{C\text{-}F}$ = 6.5 Hz, C), 38.3 (CH_2), 33.7 (q, $J_{C\text{-}F}$ = 41.2 Hz, CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –71.6 (s, 3F); **HRMS (ESI)** *m/z*: 303.0893 (M+ H)$^+$, $C_{18}H_{14}F_3O$ requires 303.0991.

(*S*)-(–)-3-(Trifluoromethyl)-5-phenyl-1-*p*-tolylpent-4-yn-1-one (46ba)

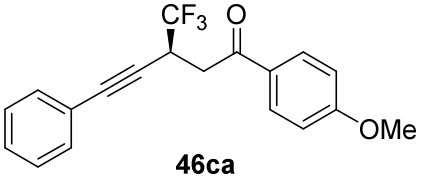


46ba

Enantiomeric excess (80%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 8.1 min, minor enantiomer t_r= 9.1 min.

Oil; **[α]$_D^{20}$** –28.5 (*c* 0.89, $CHCl_3$, 80% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.92-7.88 (m, 2H), 7.40-7.36 (m, 2H), 7.31-7.26 (m, 5H), 4.26-4.19 (m, 1H), 3.56 (dd, *J* = 17.2, 8.9 Hz, 1H), 3.39 (dd, *J* = 17.2, 4.2 Hz, 1H), 2.43 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)**δ194.1 (C), 144.7 (C), 133.6 (C), 131.9 (2CH), 129.5 (2CH), 128.6 (CH), 128.2 (2CH), 127.2 (2CH), 125.4 (q, $J_{C\text{-}F}$ = 279.3 Hz, CF_3), 122.0 (C), 84.7 (C), 84.2 (C), 38.1 (CH_2), 33.7 (q, $J_{C\text{-}F}$ = 31.7 Hz, CH), 21.7 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ–71.6 (s, 3F); **HRMS (ESI)***m/z*: 317.1148 (M+ H)$^+$, $C_{19}H_{16}F_3O$requires 317.1141.

(*S*)-(–)-3-(Trifluoromethyl)-1-(4-methoxyphenyl)-5-phenylpent-4-yn-1-one (46ca)



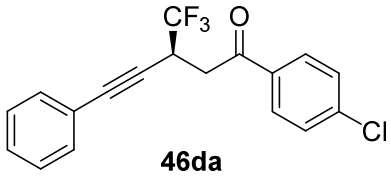
46ca

Enantiomeric excess (80%) was determined by chiral HPLC (Chiralpak IC), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 9.0 min, minor enantiomer t_r= 8.0 min.

Oil; **[α]$_D^{20}$**–40.9 (*c* 0.91, $CHCl_3$, 80% *ee*);**^{1}H NMR (300 MHz, $CDCl_3$)**δ7.88 (dt, *J* = 9, 3 Hz, 2H), 7.29-7.26 (m, 2H), 7.19-7.16 (m, 3H), 6.89-6.84 (dt, *J* = 9, 3 Hz, 2H), 4.16-4.09 (m, 1H), 3.70 (s, 3H), 3.43 (dd, *J* = 18, 9 Hz, 1H), 3.25 (dd, , *J* = 18, 3 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 193.0 (C), 164.0 (C), 131.9 (2CH), 130.6 (2CH), 129.2

(C), 128.6 (CH), 128.2 (2CH), 125.4 (q, J_{C-F} = 279.4 Hz, CF_3), 122.1 (C), 114.0 (2CH), 84.3 (C), 82.0 (q, J_{C-F} = 3.8 Hz, C), 55.5 (CH_3), 37.9 (CH_2), 33.8 (q, J_{C-F} = 31.6 Hz, CH);**^{19}F NMR (282 MHz, $CDCl_3$)**δ−71.6 (s, 3F); **HRMS (ESI)***m/z*: 333.1088 (M+ H)$^+$, $C_{19}H_{16}F_3O_2$requires 333.1097.

(*S*)-(−)-1-(4-Chlorophenyl)-3-(trifluoromethyl)-5-phenylpent-4-yn-1-one (46da)

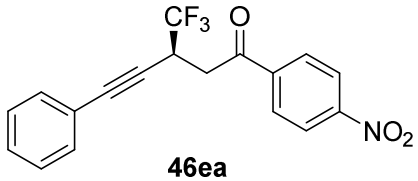


46da

Enantiomeric excess (80%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 7.5 min, minor enantiomer t_r= 10.9 min.

Oil; **[α]$_D^{20}$** −32.7 (*c* 0.81, $CHCl_3$, 80% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.95 (dt, *J* = 9.0, 3.0 Hz, 2H), 7.48 (dt, *J* = 9.0, 2.4 Hz, 2H), 7.40-7.36 (m, 2H), 7.31-7.24 (m, 3H), 4.27-4.14 (m, 1H), 3.55 (dd, *J* = 17.3, 8.9 Hz, 1H), 3.38 (dd, *J* = 17.3, 4.2 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 193.4 (C), 140.4 (C), 134.4 (C), 131.9 (2CH), 129.6 (2CH), 129.2 (2CH), 128.7 (CH), 128.2 (CH),125.4 (q, J_{C-F} = 279.3 Hz, CF_3), 121.9 (C), 84.5 (C), 81.6 (q, J_{C-F} = 3.9 Hz, C), 38.3 (CH_2), 33.7 (q, J_{C-F} = 31.5 Hz, CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −71.7 (s, 3F); **HRMS (ESI)** *m/z*: 337.0592/339.0564 (M+ H)$^+$ 100/32.0, $C_{18}H_{13}F_3O_3Cl$ requires 337.0607/339.0578.

(*S*)- (−)-3-(Trifluoromethyl)-1-(4-nitrophenyl)-5-phenylpent-4-yn-1-one (46ea)

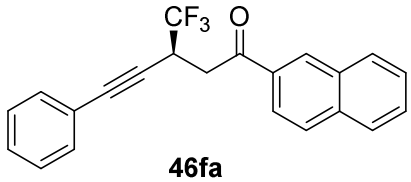


46ea

Enantiomeric excess (70%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r= 20.1 min, minor enantiomer t_r = 31.2 min.

Oil; **[α]$_D^{20}$**−25.2 (*c* 0.60, $CHCl_3$, 70% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.35 (dt, *J* = 9.0, 3.0 Hz, 2H), 8.16 (dt, *J* = 9.0, 3.0 Hz, 2H), 7.40-7.25 (m, 5H), 4.27-4.15 (m, 1H), 3.63 (dd, *J* = 17.5, 8.9 Hz, 1H), 3.47 (dd, *J* = 17.5, 4.2 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 193.2 (C), 150.7 (C), 140.4 (C), 131.9 (2CH), 129.3 (2CH), 128.9 (CH), 128.3 (2CH),125.1 (q, J_{C-F} = 281.3 Hz, CF_3), 124.1 (2CH), 121.7 (C), 84.8 (C), 81.1 (C), 38.9 (CH_2), 33.7 (q, J_{C-F} = 31.9 Hz, CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −71.6 (s, 3F); **HRMS (ESI)** *m/z*: 348.0851 (M+ H)$^+$, $C_{18}H_{13}F_3NO_3$ requires 348.0848.

(*S*)-(−)-3-(Trifluoromethyl)-1-(naphthalene-3-yl)-5-phenylpent-4-yn-1-one (46fa)



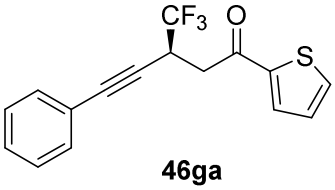
46fa

Enantiomeric excess (84%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 16.3 min, minor enantiomer t_r= 19.1 min.

Oil; **[α]$_D^{20}$** −118.6 (*c* 1.30, $CHCl_3$, 84% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.50 (s, 1H), 8.05 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.90 (dd, *J* = 10.2, 8.6 Hz, 2H), 7.65-7.54 (m, 2H), 7.38-7.35 (m, 2H), 7.28-7.20 (m, 3H), 4.35-4.22 (m, 1H), 3.73

(dd, *J* = 17.2, 8.9 Hz, 1H), 3.54 (dd, *J* = 17.2, 4.1 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 194.4 (CH), 135.9 (C), 133.5 (C), 132.4 (C),131.8 (2CH), 130.12 (CH), 129.64 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.2 (2CH), 127.8 (CH), 127.0 (CH), 125.4 (q, $J_{C\text{-}F}$ = 279.4 Hz, CF_3), 123.7 (CH), 122.0 (C), 84.4 (C), 81.9 (q, $J_{C\text{-}F}$ = 3.5 Hz, C), 38.3 (CH_2), 33.8 (q, $J_{C\text{-}F}$ = 31.8 Hz, CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −71.5 (s, 3F); **HRMS (ESI)** *m/z*: 353.1148 $(M+H)^+$, $C_{22}H_{16}F_3O$requires 353.1148.

(*S*)-(−)-3-(Trifluoromethyl)-5-phenyl-1-(thiophen-2-yl)pent-4-yn-1-one (46ga)

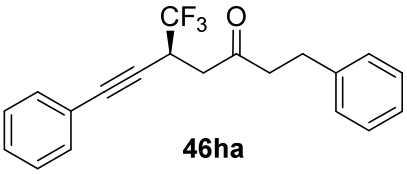


46ga

Enantiomeric excess (90%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 10.5 min, minor enantiomer t_r= 15.2 min.

Oil; **$[\alpha]_D^{20}$** −6.1 (*c* 1.09, $CHCl_3$, 90% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.77 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.68 (dd, *J* = 5, 1.1 Hz, 1H), 7.36-7.33 (m, 2H), 7.28-7.22 (m, 3H), 7.14 (dd, *J* = 5, 3.8 Hz, 1H), 4.23-4.10 (m, 1H), 3.47 (dd, *J* = 16.6, 8.9 Hz, 1H), 3.32 (dd, , *J* = 16.6, 4.5 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 187.4 (C), 143.2 (C), 134.7 (CH), 132.7 (CH), 131.9 (2CH), 128.7 (CH), 128.3 (CH), 128.2 (2CH), 125.2 (q, $J_{C\text{-}F}$ = 278.7 Hz, CF_3), 121.9 (C), 84.7 (C), 81.5 (C), 38.7 (CH_2), 33.8 (q, $J_{C\text{-}F}$ = 31.7 Hz, CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −71.7 (s, 3F); **HRMS (ESI)** *m/z*: 309.0550 $(M+H)^+$, $C_{16}H_{12}F_3OS$requires 309.0555.

(*S*)-(+)-5-(Trifluoromethyl)-1,7-diphenylhept-6-yn-3-one (46ha)

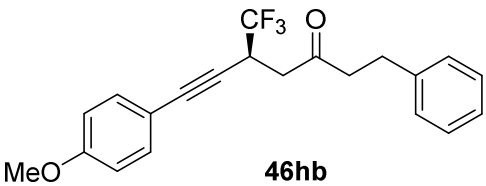


46ha

Enantiomeric excess (79%) was determined by chiral HPLC (Chiralcel AD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 6.6 min, minor enantiomer t_r = 9.6 min.

Oil; **$[\alpha]_D^{20}$** +6.1 (*c* 0.8, $CHCl_3$, 79% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.42-7.36 (m, 2H), 7.35-7.22 (m, 5H), 7.24-7.14 (m, 2H), 3.99 (m, 1H), 3.01-2.78 (m, 6H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 204.3 (C), 140.4 (C), 131.9 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 126.3 (CH), 125.1 (q, $J_{C\text{-}F}$= 277.1 Hz, CF_3), 121.9 (C), 84.4 (C), 81.5 (q, $J_{C\text{-}F}$ = 3.6 Hz, C), 44.7 (CH_2), 42.1 (CH_2), 33.4 (q, $J_{C\text{-}F}$= 31.7 Hz, CH), 29.5 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −71.8 (s, 3F); **HRMS (ESI)** *m/z*: 331.1306$(M+H)^+$ $C_{20}H_{18}F_3O$ requires 331.1304.

(*S*)-(+)-5-(Trifluoromethyl)-7-(4-methoxyphenyl)-1-phenylhept-6-yn-3-one(46hb)



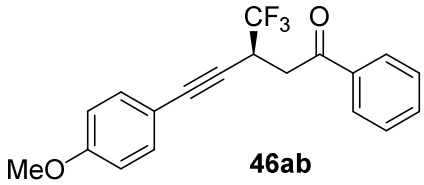
46hb

Enantiomeric excess (82%) was determined by chiral HPLC (Chiralcel AD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 11.3 min, minor enantiomer t_r = 17.4 min.

Oil; **$[\alpha]_D^{20}$** +3.0 (*c* 0.5, $CHCl_3$, 82% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.33 (d, *J* = 9.0 Hz, 2H), 7.31-7.12 (m, 6H), 6.82 (d, *J* = 9.0 Hz, 2H), 3.98 (m, 1H), 3.81 (s, 3H), 3.00-2.78 (m, 6H); **^{13}C NMR (75.5 MHz, $CDCl_3$)**

δ 204.4 (C), 159.9 (C), 140.5 (C), 140.5 (CH), 133.4 (CH), 128.6 (CH), 128.3 (CH), 126.3 (CH), 125.2 (q, J_{C-F}= 278.3 Hz, CF_3), 114.0 (C), 113.9 (CH), 84.3 (C), 80.1 (q, J_{C-F} = 1.6 Hz, C), 55.3 (CH_3), 44.8 (CH_2), 42.1 (CH_2), 33.4 (q, J_{C-F}= 31.5 Hz, CH), 29.5 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −71.9 (s, 3F); **HRMS (ESI)** *m/z*: 361.1415(M + H)$^+$ $C_{21}H_{20}F_3O_2$ requires 361.1410.

(*S*)-(−)-3-(Trifluoromethyl)-5-(4-methoxyphenyl)-1-phenylpent-4-yn-1-one (46ab)

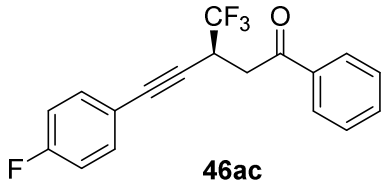


46ab

Enantiomeric excess (83%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 15.9 min, minor enantiomer t_r= 14.4 min.

Oil; **[α]$_D^{20}$**−20.3 (*c*0.93, $CHCl_3$, 83% *ee*);**^{1}H NMR (300 MHz, $CDCl_3$)** δ8.02-7.99 (m, 2H), 7.64-7.59 (m, 1H), 7.53-7.47 (m, 2H), 7.31 (dt, *J* = 9, 3 Hz, 2H), 6.79 (dt, *J* = 9, 3 Hz, 2H), 4.27- 4.14 (m, 1H), 3.79 (s, 3H), 3.58 (dd, *J* = 17.2, 8.9 Hz, 1H), 3.41 (dd, *J* = 17.2, 4.2 Hz, 1H);**^{13}C NMR (75.5 MHz, $CDCl_3$)**δ194.7 (C), 159.8 (C), 136.1 (C), 133.7 (CH), 133.3 (2CH), 128.8 (2CH), 128.2 (2CH), 125.4 (q, J_{C-F}= 279.1 Hz, CF_3), 114.1 (C), 113.8 (2CH), 84.2 (C), 80.4 (q, J_{C-F} = 3.5 Hz, C), 55.3 (CH_3), 38.3 (CH_2), 33.7 (q, J_{C-F}= 31.7 Hz, CH);**^{19}F NMR (282 MHz, $CDCl_3$)**δ−71.7 (s, 3F); **HRMS (ESI)***m/z*: 333.1088(M + H)$^+$ $C_{19}H_{16}F_3O_2$ requires 333.1097.

(*S*)-(−)-3-(Trifluoromethyl)-5-(4-fluorophenyl)-1-phenylpent-4-yn-1-one (46ac)

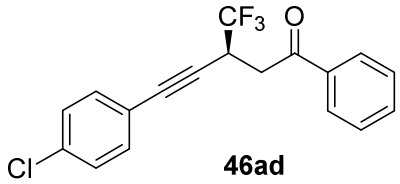


46ac

Enantiomeric excess (80%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 8.8 min, minor enantiomer t_r= 10.8 min.

Oil; **[α]$_D^{20}$**−15.7 (*c* 1.15, $CHCl_3$, 80% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.02-7.99 (m, 2H), 7.65-7.60 (m, 1H), 7.53-7.48 (m, 2H), 7.39-7.34 (m, 2H), 7.00-6.93 (m, 2H),4.24-4.17 (m, 1H), 3.59 (dd, *J* = 17.3, 9 Hz, 1H), 3.42 (dd, *J* = 17.3, 4.1 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 194.5 (C), 162.7 (d, *J*= 249.9 Hz, C), 136.0 (C), 133.9 (CH), 133.8 (d, *J* = 8.5 Hz, 2CH), 128.8 (2CH), 128.2 (2CH), 125.3 (q, *J*= 279.2 Hz, CF_3), 118.1 (d, *J* = 3.5 Hz, C), 115.5 (d, J_{C-F} = 22.1 Hz, 2CH), 83.3 (C), 81.6 (q, J_{C-F}= 5.1 Hz, C), 38.2 (CH_2), 33.6 (q, J_{C-F} = 31.6 Hz, CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −71.6 (s, 3F), −110.7 (s, 1F); **HRMS (ESI)** *m/z*: 321.0892 (M+ H)$^+$, $C_{18}H_{13}F_4O$requires 321.0897.

(*S*)-(–)-5-(4-Chlorophenyl)-3-(trifluoromethyl)-1-phenylpent-4-yn-1-one (46ad)

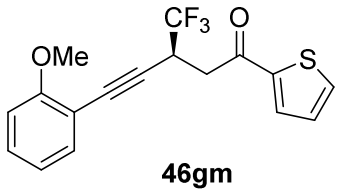


46ad

Enantiomeric excess (77%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 10.5 min, minor enantiomer t_r= 11.5 min.

Oil; **[α]$_D^{20}$**–20.4 (*c*0.90, $CHCl_3$, 77% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.02-7.99 (m, 2H), 7.62 (ddd, *J* = 6.6, 3.9, 1.3 Hz, 1H), 7.54-7.48 (m, 2H), 7.33-7.22 (m, 4H), 4.26-4.15 (m, 1H), 3.59 (dd, *J* = 17.3, 9 Hz, 1H), 3.42 (dd, *J* = 17.3, 4.1 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 194.4 (C), 136.0 (C), 134.7 (C), 133.8 (CH), 133.1 (2CH), 128.8 (2CH), 128.6 (2CH), 128.2 (2CH), 125.3 (q, J_{C-F} = 279.4 Hz, CF_3), 120.5 (C), 83.2 (C), 80.9 (C), 38.2 (CH_2), 33.7 (q, J_{C-F} = 31.7 Hz, CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –71.5 (s, 3F); **HRMS (ESI)** *m/z*: 337.0594 / 339.0553 $(M + H)^+$ 100 / 28.9 $C_{18}H_{13}ClF_3O$ requires 337.0607 / 339.0578.

(*S*)-(–)-3-(Trifluoromethyl)-5-(2-methoxyphenyl)-1-(thiophen-2-yl)pent-4-yn-1-one (46gm)

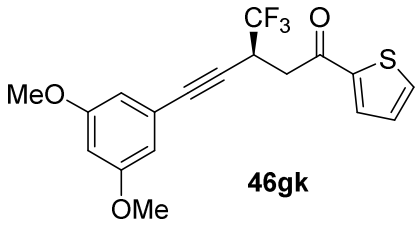


46gm

Enantiomeric excess (98%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 10.7 min, minor enantiomer t_r= 13.2 min.

Oil; **[α]$_D^{20}$** –7.8 (*c* 0.90, $CHCl_3$, 98% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.80 (dd, *J* = 3.9, 1.1 Hz, 1H), 7.70 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.34-7.24 (m, 2H), 7.17 (dd, *J* = 4.9, 3.8 Hz, 1H), 6.91-6.77 (m, 2H), 4.29-4.21 (m, 1H), 3.78 (s, 3H), 3.52 (dd, *J* = 16.6, 8.5 Hz, 1H), 3.36 (dd, *J* = 16.6, 4.8 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 187.5 (C), 160.4 (C), 143.4 (C), 134.5 (CH), 133.7(CH), 132.6 (CH), 130.1 (CH), 128.3 (CH), 125.2 (q, J_{C-F}= 279.5 Hz, CF_3), 120.3 (CH), 111.3 (C), 110.8(CH), 85.5 (C), 81.1 (C), 55.7 (CH_3), 38.9 (CH_2), 34.1 (q, J_{C-F}= 31.8 Hz, CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –71.6 (s, 3F); **HRMS (ESI)** *m/z*: 338.0590$(M + H)^+$ $C_{17}H_{14}F_3O_2S$ requires 338.0588.

(*S*)-(–)-3-(Trifluoromethyl)-5-(3,5-dimethoxyphenyl)-1-(thiophen-2-yl)pent-4-yn-1-one (46gk)



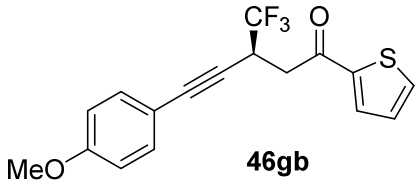
46gk

Enantiomeric excess (86%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 11.2 min, minor enantiomer t_r= 12.5 min.

Oil; **[α]$_D^{20}$** –7.0 (*c* 0.93, $CHCl_3$, 86% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.80 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.71 (dd, *J* = 4.9, 1.1 Hz, 1H),7.17 (dd, *J* = 4.9, 3.8 Hz, 1H), 6.51 (d, *J* = 2.3 Hz, 2H), 6.42 (t, *J* = 2.3 Hz, 1H), 4.22-4.15 (m, 1H), 3.75 (s, 6H), 3.49 (dd, *J* = 16.6, 8.9 Hz, 1H), 3.35 (dd, *J* = 16.6, 4.5 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 187.4 (C), 160.4 (2C), 143.2 (C), 134.7 (CH), 132.7

(CH), 130.7 (CH), 125.2 (q, J_{C-F}= 279.3 Hz, CF_3), 123.2 (C), 109.6 (2CH), 102.3 (CH), 84.7 (C), 80.0 (q, J_{C-F}= 3.4 Hz, C), 55.4 ($2CH_3$), 38.7 (CH_2), 33.8 (q, $_{C-F}J$= 31.8 Hz, CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −71.6 (s, 3F); **HRMS (ESI)** *m/z*: 368.0690(M + H)$^+$ $C_{18}H_{15}F_3O_3S$ requires 368.0694.

(*S*)-(−)-3-(Trifluoromethyl)-5-(4-methoxyphenyl)-1-(thiophen-2-yl)pent-4-yn-1-one (46gb)

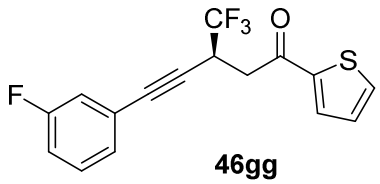


46gb

Enantiomeric excess (93%) was determined by chiral HPLC (Chiralpak AY-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 25.3 min, minor enantiomer t_r= 16.8 min.

Oil; **[α]$_D^{20}$** −7.3 (*c* 0.98, $CHCl_3$, 93% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.79 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.72-7.70 (m, 1H), 7.32-7.28 (m, 2H), 7.17 (dd, *J* = 5, 3.8 Hz, 1H), 6.81-6.77 (m, 2H), 4.23-4.11 (m, 1H), 3.79 (s, 3H), 3.48 (dd, *J* = 16.6, 8.9 Hz, 1H), 3.33 (dd, *J* = 16.6, 4.5 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 187.5 (C), 159.8 (C), 143.3 (C), 134.7 (CH), 133.3 (2CH), 132.6 (CH), 128.3 (CH), 125.2 (q, J_{C-F}= 279.3 Hz, CF_3), 114.0 (C), 113.8 (2CH), 84.6 (C), 80.0 (q, J_{C-F}= 3.3 Hz, C), 55.3 (CH_3), 38.8 (CH_2), 33.8 (q, J_{C-F}= 31.7 Hz, CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −71.8 (s, 3F); **HRMS (ESI)** *m/z*: 338.0592(M + H)$^+$ $C_{17}H_{14}F_3O_2S$ requires 338.0588.

(*S*)-(−)-3-(Trifluoromethyl)-5-(3-fluorophenyl)-1-(thiophen-2-yl)pent-4-yn-1-one (46gg)

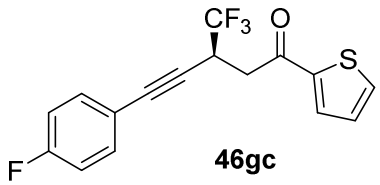


46gg

Enantiomeric excess (99%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 13.7 min, minor enantiomer t_r= 10.9 min.

Oil; **[α]$_D^{20}$** −8.3 (*c* 0.87, $CHCl_3$, 99% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.79 (dd, *J* = 2.7, 1.3 Hz, 1H), 7.74 (ddd, *J* = 9.7, 4.9, 1.1 Hz, 1H), 7.28-7.14 (m, 3H), 7.08-6.98 (m, 2H),4.25-4.13 (m, 1H), 3.50 (dd, *J* = 16.7, 9.0 Hz, 1H), 3.36 (dd, *J* = 16.7, 4.4 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 187.2 (C), 162.2 (d, J_{C-F}= 246.7 Hz, C), 143.1 (C), 134.8 (CH), 132.7 (CH), 129.8 (d, J_{C-F}= 8.6 Hz, CH), 128.4 (CH), 127.8 (d, J_{C-F} = 3.1 Hz, CH), 125.1 (q, J_{C-F}= 279.4 Hz, CF_3), 123.7 (d, J_{C-F} = 9.4 Hz, C), 118.7 (d, J_{C-F}= 23.0 Hz, CH), 116.1 (d, *J* = 21.2 Hz, CH),83.4 (q, J_{C-F}= 3.4 Hz, C), 82.5 (d, J_{C-F} = 3.5 Hz, C), 38.6 (CH_2), 33.8 (q, J_{C-F} = 31.9 Hz, CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −71.6 (s, 3F), −113.4 (s, 1F); **HRMS (ESI)** *m/z*: 327.0457 (M + H)$^+$ $C_{16}H_{11}F_4OS$ requires 327.0461.

(*S*)-(–)-3-(Trifluoromethyl)-5-(4-fluorophenyl)-1-(thiophen-2-yl)pent-4-yn-1-one (46gc)

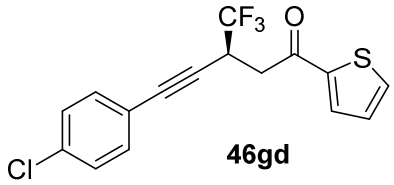


46gc

Enantiomeric excess (90%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 12.6 min, minor enantiomer t_r= 14.9 min.

Oil; **[α]$_D^{20}$** –6.4 (*c* 1.03, $CHCl_3$, 90% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.79 (dd, *J* = 3.9, 1.1 Hz, 1H), 7.72 (dd, *J* = 5, 1.1 Hz, 1H), 7.38-7-32 (m, 2H), 7.18 (dd, *J* = 5, 3.9 Hz, 1H), 7.00-6.93 (m, 2H), 4.23-4.08 (m, 1H), 3.49 (dd, *J* = 16.7, 9 Hz, 1H), 3.35 (dd, *J* = 16.7, 4.4 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 187.3 (C), 162.7 (d, J_{C-F}= 250 Hz, C), 143.2 (C), 134.8 (CH), 133.8 (d, J_{C-F}= 8.5 Hz, 2CH), 132.7 (CH), 128.3 (CH), 125.0 (q, J_{C-F}= 279.5 Hz, CF_3), 118.0 (C), 115.5 (d, JJ_{C-F}= 22.1 Hz, 2CH), 83.6 (C), 81.2 (q, J_{C-F}= 3.6 Hz, C), 38.7 (CH_2), 33.8 (q, J_{C-F} = 31.9 Hz, CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –71.6 (s, 3F), –110.7 (s, 1F); **HRMS (ESI)** *m/z*: 327.0455 $(M + H)^+$ $C_{16}H_{11}F_4OS$ requires 327.0461.

(*S*)-(–)-5-(4-Chlorophenyl)-3-(trifluoromethyl)-1-(thiophen-2-yl)pent-4-yn-1-one (46gd)

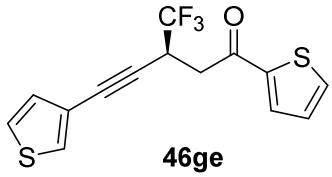


46gd

Enantiomeric excess (84%) was determined by chiral HPLC (Chiralpak IC), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 6.5 min, minor enantiomer t_r= 7.0 min.

Oil; **[α]$_D^{20}$** –6.9 (*c* 1.06, $CHCl_3$, 84% *ee*) ;**^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.79 (dd, *J* = 3.9, 1.0 Hz, 1H), 7.22 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.31-7.23 (m, 4H), 7.18 (dd, *J* = 4.9, 3.9 Hz, 1H), 4.21-4.14 (m, 1H), 3.49 (dd, *J* = 16.7, 9.0 Hz, 1H), 3.35 (dd, *J* = 16.7, 4.4 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 187.3 (C), 143.1 (C), 134.8 (C), 134.8 (CH), 133.1 (2CH), 132.6 (CH), 128.6 (2CH), 128.4 (CH), 125.1 (q, J_{C-F}= 279.6 Hz, CF_3), 120.4 (C), 83.6 (C), 82.5 (C), 38.6 (CH_2), 33.9 (q, J_{C-F} = 31.9 Hz, CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –71.5 (s, 3F); **HRMS (ESI)** *m/z*: 343.0158 / 345.0128 $(M + H)^+$ 100 / 36.7 $C_{16}H_{11}ClF_3OS$ requires 343.0171 / 345.0142.

(*S*)-(–)-3-(Trifluoromethyl)-1-(thiophen-2-yl)-5-(thiophen-3-yl)pent-4-yn-1-one (46ge)



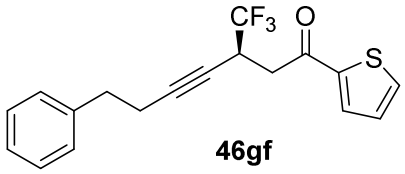
46ge

Enantiomeric excess (88%) was determined by chiral HPLC (Chiralcel OD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 11.1 min, minor enantiomer t_r= 15.5 min.

Oil; **[α]$_D^{20}$** –5.4 (*c* 0.86, $CHCl_3$, 88% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.79 (dd, *J* = 3.9, 1.1 Hz, 1H), 7.71 (dd, *J* = 4.9, 1.1 Hz, 1H),7.40 (dd, *J* = 3.0, 1.2 Hz, 1H),7.22 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.17 (dd, *J* = 5.0, 3.9 Hz, 1H), 7.04 (dd, *J* = 5.0, 1.2 Hz, 1H), 4.22-4.11 (m, 1H), 3.49 (dd, *J* = 16.7, 8.9 Hz, 1H), 3.34 (dd, *J*

= 16.7, 4.4 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 187.3 (C), 143.2 (C), 134.7 (CH), 132.6 (CH), 129.9 (CH), 129.7 (CH),128.3 (CH), 125.3 (CH), 125.1 (q, J_{C-F}= 279.5 Hz, CF_3), 120.9 (C), 81.1 (q, J_{C-F}= 3.5 Hz, C), 79.9 (C), 38.7 (CH_2), 33.8 (q, J_{C-F}= 31.7 Hz, CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −71.6 (s, 3F); **HRMS (ESI)** *m/z*: 314.0043 $(M + H)^+$ $C_{14}H_9F_3OS_2$ requires 314.0047.

(*S*)-(+)-7-phenyl-1-(thiophen-2-yl)-3-(trifluoromethyl)hept-4-yn-1-one (46gf)



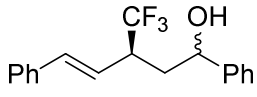
46gf

Enantiomeric excess (92%) was determined by chiral HPLC (Chiralcel AD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 9.7 min, minor enantiomer t_r= 10.8 min.

Oil; **$[\alpha]_D^{20}$** +1.2 (*c* 0.73, $CHCl_3$, 92% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.71 (td, *J* = 4.7, 1.2 Hz, 2H), 7.26-7.12 (m, 6H), 4.05 (m, 1H), 3.31 (dd, *J* = 16.6, 9.0 Hz, 1H), 3.19 (dd, *J* = 16.6, 4.5 Hz, 1H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.42 (td, *J* = 7.5, 2.4 Hz, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 187.6 (C), 143.4 (C), 140.3 (C), 134.5 (CH), 132.5 (CH), 128.5 (2CH), 128.3 (3CH), 126.2 (CH), 125.5 (q, J_{C-F}= 277.5 Hz, CF_3), 84.6 (C), 73.3 (C), 38.9 (CH_2), 34.6 (CH_2), 33.3 (q, J_{C-F}= 30.8 Hz, CH), 20.8 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −72.1 (s, 3F); **HRMS (ESI)** *m/z*: 337.0854$(M + H)^+$ $C_{18}H_{16}F_3OS$ requires 337.0868.

5.6.2.4. Determination of the absolute stereochemistry of compound 46aa

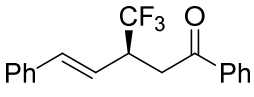
(*E*,*S*)-3-(Trifluoromethyl)-1,5-diphenylpent-4-en-1-ol (47)



47

Lithium aluminium hydride (12.1 mg, 0.320 mmol) was added to a solution of **46aa** (16.1 mg, 0.053 mmol, 80% *ee*) in dry THF (1.5 mL) at room temperature, and the solution was stirred overnight at 75 ºC. The reaction mixture was quenched with 20 % aqueous NH_4Cl (1.0 mL), extracted with CH_2Cl_2 (2x 15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:EtOAc (98:02) afforded compound **47** (16.2 mg, 99%) as a mixture of diastereomers.

(*E*,*S*)-3-(Trifluoromethyl)-1,5-diphenylpent-4-en-1-one (48)



48

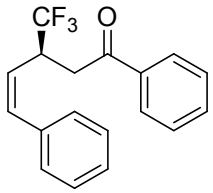
To a 25 mL round-bottom flask equipped with a magnetic stirring bar was added PCC (137mg, 0.64 mmol), 4Å MS (300 mg), silica gel (300 mg) and CH_2Cl_2 (10 mL). The mixture was cooled to 0 ºC and the mixture of alcohols **47**(16.2 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The reaction was warmed up to room temperature and was stirred for 3 h. The mixture was filtered through apad of silica gel eluting with CH_2Cl_2. The solvent was removed under reduced pressure. The residual crude product was purified by flash column chromatography eluting with hexane:Et_2O (99:01) to afford the ketone **48** (10.5 mg, 66%). Enantiomeric excess (78%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 9.6 min,

minor enantiomer t_r = 10.8 min. (lit[83c], Chiralpak AD-H, hexane-^{i}PrOH 99.6:0.4, flow = 0.7 mL/min, *R*-enantiomer t_r = 19.3 min, *S*-enantiomer t_r = 16.3 min).

Oil; **$[\alpha]_D^{20}$** +4.9 (*c* 0.57, CCl_4, 78% *ee*){lit[83c] $[\alpha]_D^{20}$ –16.5 (0.95, CCl_4, 40% *ee*) for the *R*-isomer]; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.98-7.95 (m, 2H), 7.62-7.57 (m, 1H),7.51-7.46 (m, 2H), 7.37-7.24 (m, 5H), 6.70 (d, *J* = 15.9 Hz, 1H), 6.04 (dd, *J* = 15.9, 8.6 Hz, 1H), 3.93-3.83 (m, 1H), 3.40-3.38 (m, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 195.4 (C), 136.4 (C), 136.3 (CH), 136.1 (C), 133.6 (CH), 128.8 (2CH),128.5 (2CH), 128.1 (CH), 128.1 (2CH), 126.9 (q, $J_{C\text{-}F}$= 274.7 Hz, CF_3), 121.5 (q, $J_{C\text{-}F}$= 2.4 Hz, CH), 42.6 (q, $J_{C\text{-}F}$= 27.7 Hz, CH), 37.4 (s,CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –71.2 (s, 3F); **HRMS (ESI)** *m/z*: 305.1158 $(M + H)^+$ $C_{18}H_{16}F_3O$ requires 305.1153.

5.6.2.5. Synthetic transformations

(*Z*,*S*)-(–)-1,5-Diphenyl-3-(trifluoromethyl)pent-4-en-1-one (49)

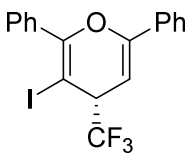


49

A solution of **46aa** (10.6 mg, 0.035 mmol, 80% *ee*) in benzene (0.5 mL) was stirred in the presence of Lindlar's catalyst (2.5 mg) under hydrogen atmosphere (balloon) for 1 h. Then, the reaction mixture was filtered through a pad of Celite® eluting with EtOAc. The solvent was removed under reduced pressure to give **49** (9.4 mg, 88%). Enantiomeric excess (80%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 7.7 min, minor enantiomer t_r = 7.3 min.

Oil; **$[\alpha]_D^{20}$** –70.2 (*c* 0.45, $CHCl_3$, 80%*ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.79 (dd, *J* = 3.9, 1.1 Hz, 1H), 7.71 (dd, *J* = 4.9, 1.1 Hz, 1H),7.40 (dd, *J* = 3.0, 1.2 Hz, 1H),7.22 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.17 (dd, *J* = 5.0, 3.9 Hz, 1H), 7.04 (dd, *J* = 5.0, 1.2 Hz, 1H), 4.22-4.11 (m, 1H), 3.49 (dd, *J* = 16.7, 8.9 Hz, 1H), 3.34 (dd, *J* = 16.7, 4.4 Hz, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 195.5 (C), 136.3 (C), 135.9 (C), 135.7 (CH), 133.4 (CH), 128.7 (2CH), 128.4 (2CH),128.3 (2CH), 128.1 (2CH), 127.5 (CH), 125.1 (q, *J*= 279.5 Hz, CF_3), 123.8 (q, *J*= 2.3 Hz, CH), 38.3 (q, *J*= 27.4 Hz, CH), 38.0 (q, *J*= 1.8 Hz, CH_2);**^{19}F NMR (282 MHz, $CDCl_3$)** δ –71.0 (s, 3F); **HRMS (ESI)** *m/z*: 305.1159 $(M + H)^+$ $C_{18}H_{16}F_3O$ requires 305.1153.

(*R*)-(–)-3-Iodo-2,6-diphenyl-4-(trifluoromethyl)-4*H*-pyran (50).



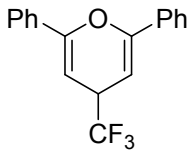
50

A solution of I_2 (30.1 mg, 0.119 mmol) in CH_2Cl_2 (2 mL) was added to a mixture of **46aa** (18 mg, 0.060 mmol 85% *ee*) and $NaHCO_3$ (10 mg, 0.119 mmol) under nitrogen atmosphere. The solution was stirred overnight at 40 ºC (reflux).The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (1.0 mL), extracted with CH_2Cl_2 (2×15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:Et_2O (98:02) gave compound **50** (19.9 mg, 77%). Enantiomeric excess (84%)

was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 6.5 min, minor enantiomer t_r = 4.7 min.

Oil; **$[\alpha]_D^{20}$** −7.0 (*c* 0.45, $CHCl_3$, 84% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.69-7.58 (m, 4H), 7.54-7.42 (m, 3H),7.42-7.34 (m, 3H), 5.29 (d, *J* = 5.8 Hz, 1H), 4.16-4.02 (m, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 155.1 (C), 153.1 (C), 135.9 (C), 132.3 (C), 129.9 (CH), 129.7 (2CH), 129.6 (CH), 128.7 (C), 128.5 (2CH), 128.2 (2CH), 125.4 (q, $J_{C\text{-}F}$= 223.7 Hz, CF_3), 125.0 (2CH), 90.4 (q, $J_{C\text{-}F}$= 1.8Hz, CH), 49.5 (q, $J_{C\text{-}F}$= 22.7 Hz, CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −74.4 (s, 3F); **HRMS (ESI)** *m/z*: 428.9961 $(M + H)^+$ $C_{18}H_{13}F_3IO$ requires 428.9958.

2,6-Diphenyl-4-(trifluoromethyl)-4H-pyran (51)



51

A solution of **50** (14.3 mg, 0.031 mmol), Bu_3SnH (10 µL, 0.037 mmol) and AIBN (1.0 mg, 0.0062 mmol) in dry benzene (1 mL) contained in a quartz tube was deoxygenated by bubbling nitrogen for 5 min. The solution was then irradiated with a UV lamp under nitrogen for 4 h. The solvent was removed under reduced pressure and the residue chromatographed on silica gel to give compound **51** (3.7 mg, 40%).

Oil; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.76-7.62 (m, 4H), 7.46-7.41 (m, 6H), 5.44 (d, *J* = 4.0 Hz, 2H), 3.93-3.88 (m, 1H).

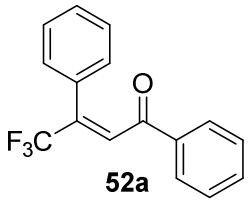
5.7. Enantioselective conjugate alkynylation of β-aryl β-trifluoromethyl enones

5.7.1. Synthesis and characterization of β-aryl β-trifluoromethyl enones 52

β-Aryl β-trifluoromethyl enones were prepared according to the literature procedure.[97]

A solution of $ArCOCF_3$ (5 mmol) in DMF (1.6 mL) was added to a solution of Et_3N (7.5 mmol) and $RCOCH_2P^+Ph_3Cl^-$ (7.5 mmol) in THF (20 mL) at 0 °C. The mixture was stirred 15 minutes at rt and heated at 80 °C for 2 h. The reaction mixture was quenched with 20% aqueous NH_4Cl (3 mL), extracted with ethyl acetate, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give compounds **52**.

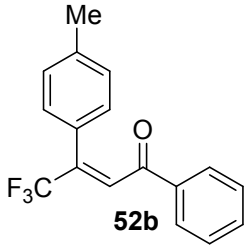
(*E*)-4,4,4-Trifluoro-1,3-diphenylbut-2-en-1-one (52a)



52a

Oil, 94% yield; **^{1}H NMR ($CDCl_3$, 300 MHz)** δ 7.85-7.81 (m, 2H), 7.58-7.49 (m, 1H),7.42-7.37 (m, 2H), 7.29-7.26 (m, 6H); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 192.0 (C), 138.9 (q, J_{C-F} = 30.7 Hz, C), 136.0 (C), 135.5 (C), 133.9 (CH), 130.8 (q, J_{C-F}= 5.2 Hz, CH), 129.4 (CH), 129.0 (2CH), 128.9 (2CH), 128.7 (2CH), 128.3 (2CH), 122.8 (q, J_{C-F} = 274.8 Hz, CF_3); **^{19}F NMR ($CDCl_3$, 188 MHz)** δ –66.7 (s, 3F). Data consistent with the literature.[119]

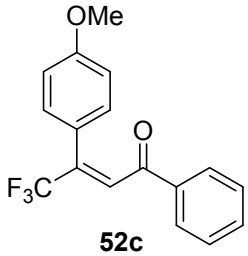
(*E*)-4,4,4-Trifluoro-1-phenyl-3-(*p*-tolyl)but-2-en-1-one (52b)



52b

Oil, 89% yield; **^{1}H NMR ($CDCl_3$, 300 MHz)** δ 7.88-7.84 (m, 2H), 7.56-7.51 (m, 1H), 7.44-7.38 (m, 2H), 7.28-7.26 (m, 1H), 7.20 (d, J = 8.1 Hz, 2H), 7.10-7.07 (m, 2H), 2.28(s, 3H); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 192.1 (C), 139.4 (C), 138.9 (q, J_{C-F} = 30.7 Hz, C), 136.1 (C), 133.8 (CH), 130.4 (q, J_{C-F} = 5.1 Hz, CH), 129.1 (2CH), 128.9 (4CH), 128.6 (2CH), 122.9 (q, J_{C-F} = 274.8 Hz, CF_3), 21.1 (CH_3); **^{19}F NMR ($CDCl_3$, 282 MHz)** δ –66.7 (s, 3F). Data consistent with the literature.[119]

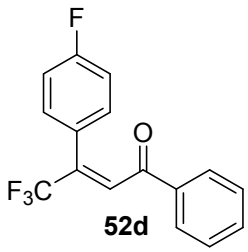
(*E*)-4,4,4-Trifluoro-3-(4-methoxyphenyl)-1-phenylbut-2-en-1-one (52c)



52c

Oil, 60% yield; **^{1}H NMR ($CDCl_3$, 300 MHz)** δ 7.84-7.82 (m, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.8, 2H), 7.23-7.21 (m, 3H), 6.79-6.76 (m, 2H), 3.72(s, 3H); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 192.4 (C), 165.4 (C), 138.4 (q, J_{C-F} = 30.6 Hz, C), 136.0 (C), 133.8 (CH), 130.5 (2CH), 130.1 (q, J_{C-F} = 5.0 Hz, CH), 128.9 (2CH), 128.6 (2CH), 123.0 (q, J_{C-F} = 274.9 Hz, CF_3), 114.4 (C), 113.8 (2CH), 55.0 (CH_3); **^{19}F NMR ($CDCl_3$, 282 MHz)** δ –66.1 (s, 3F). Data consistent with the literature.[119]

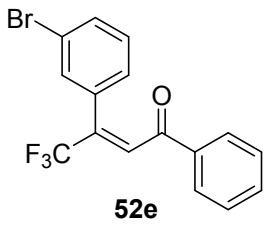
(*E*)-4,4,4-Trifluoro-3-(4-fluorophenyl)-1-phenylbut-2-en-1-one (52d)



52d

80% yield; **^{1}H NMR ($CDCl_3$, 300 MHz)** δ 7.87-7.83 (m, 2H), 7.58-7.53 (m, 1H), 7.45-7.40 (m, 2H), 7.34-7.27 (m, 3H), 7.00-6.93 (m, 2H); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 191.7 (C), 163.2 (d, $J_{C\text{-}F}$ = 249.8 Hz, C), 137.8 (q, $J_{C\text{-}F}$ = 31.0 Hz, C), 135.9 (C), 134.0 (CH), 131.2 (q, $J_{C\text{-}F}$ = 5.0 Hz, CH), 131.1 (d, $J_{C\text{-}F}$ = 8.6 Hz, 2CH), 128.8 (2CH), 128.7 (2CH), 126.7 (d, $J_{C\text{-}F}$ = 3.6 Hz, C), 122.7 (q, $J_{C\text{-}F}$ = 274.5 Hz, CF_3), 115.5 (d, $J_{C\text{-}F}$ = 21.9 Hz, 2CH); **^{19}F NMR ($CDCl_3$, 282 MHz)** δ –67.0 (s, 3F), –111.6 (s, 1F). Data consistent with the literature.[119]

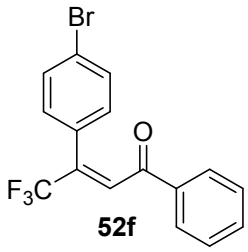
(*E*)-3-(3-Bromophenyl)-4,4,4-trifluoro-1-phenylbut-2-en-1-one (52e)



52e

Oil, 93% yield; **^{1}H NMR ($CDCl_3$, 300 MHz)** δ 7.84-7.82 (m, 2H), 7.57-7.53 (m, 1H), 7.46-7.41 (m, 4H), 7.36-7.35 (m, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.9 Hz, 1H); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 191.2 (C), 137.5 (q, $J_{C\text{-}F}$ = 31.2 Hz, C), 135.9 (C), 134.0 (CH), 132.6 (C), 132.4 (CH), 131.8 (CH), 131.5 (q, $J_{C\text{-}F}$ = 5.0 Hz, CH), 129.8 (CH), 128.7 (4CH), 127.8 (CH), 122.5 (q, $J_{C\text{-}F}$ = 274.9 Hz, CF_3), 122.3 (C); **^{19}F NMR ($CDCl_3$, 282 MHz)** δ –66.3 (s, 3F). Data consistent with the literature.[120]

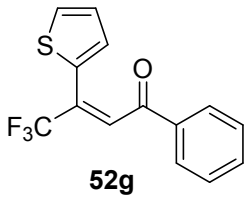
(*E*)-3-(4-Bromophenyl)-4,4,4-trifluoro-1-phenylbut-2-en-1-one (52f)



52f

Oil, 96% yield; **^{1}H NMR ($CDCl_3$, 300 MHz)** δ 7.85-7.83 (m, 2H), 7.58-7.55 (m, 1H), 7.45-7.41 (m, 4H), 7.34 (dd, *J* = 2.7, 1.3 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 191.4 (C), 137.9 (q, $J_{C\text{-}F}$ = 31.1 Hz, C), 135.9 (C), 134.1 (CH), 131.6 (2CH), 131.2 (q, $J_{C\text{-}F}$ = 5.1 Hz, CH), 130.6 (2CH), 129.6 (C), 128.82 (2CH), 128.80 (2CH), 124.0 (C), 122.5 (q, $J_{C\text{-}F}$ = 274.8 Hz, CF_3); **^{19}F NMR ($CDCl_3$, 282 MHz)** δ –66.4 (s, 3F). Data consistent with the literature.[119]

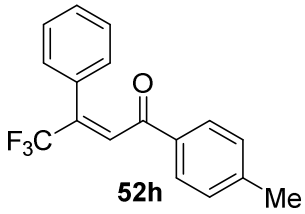
(*Z*)-4,4,4-Trifluoro-1-phenyl-3-(thiophen-2-yl)but-2-en-1-one (52g)



52g

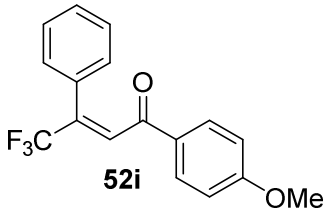
Oil, 63% yield; **^{1}H NMR ($CDCl_3$, 300 MHz)** δ 7.89-7.85 (m, 2H), 7.58-7.52 (m, 1H), 7.45-7.39 (m, 2H), 7.30 (dd, *J* = 5.1, 1.2, 1H), 7.18-7.16 (m, 1H), 7.13 (q, *J* = 1.4 Hz, 1H), 6.91 (dd, *J* = 5.1, 3.7 Hz, 1H); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ1 92.7 (C), 135.6 (C), 134.1 (CH), 131.3 (C), 130.8 (CH), 130.5 (q, $J_{C\text{-}F}$ = 5.0 Hz, CH), 129.0 (2CH), 128.9 (CH), 128.8 (2CH), 127.2 (CH), 122.4 (q, $J_{C\text{-}F}$ = 275.3 Hz, CF_3); **^{19}F NMR ($CDCl_3$, 282 MHz)** δ –66.8 (s, 3F). Data consistent with the literature.[120]

(*E*)-4,4,4-Trifluoro-3-phenyl-1-(*p*-tolyl)but-2-en-1-one (52h)



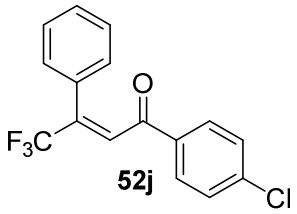
Oil, 99% yield; **^{1}H NMR ($CDCl_3$, 300 MHz)** δ 7.74-7.71 (m, 2H), 7.26-7.25 (m, 6H), 7.19 (dd, J = 8.5, 0.6 Hz, 2H), 2.36(s, 3H); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 191.6 (C), 145.0 (C), 138.4 (q, $J_{C\text{-}F}$ = 30.7 Hz, C), 133.6 (C), 131.1 (q, $J_{C\text{-}F}$ = 5.1 Hz, CH), 130.9 (C), 129.5 (2CH), 129.4 (CH), 129.1 (2CH), 129.0(2CH), 128.3 (2CH), 122.9 (q, $J_{C\text{-}F}$ = 274.7 Hz, CF_3), 21.7 (CH_3); **^{19}F NMR ($CDCl_3$, 282 MHz)** δ –66.7 (s, 3F). Data consistent with the literature.[119]

(*E*)-4,4,4-Trifluoro-1-(4-methoxyphenyl)-3-phenylbut-2-en-1-one (52i)



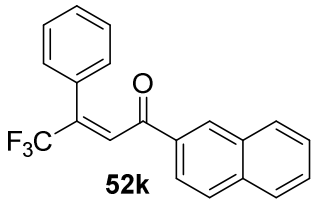
Oil, 75% yield; **^{1}H NMR ($CDCl_3$, 300 MHz)** δ 7.79-7.76 (m, 2H), 7.24-7.21 (m, 6H), 6.84-6.81 (m, 2H), 3.77 (s, 3H); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 190.5 (C), 164.1 (C), 137.8 (q, $J_{C\text{-}F}$ = 30.6 Hz, C), 131.3 (2CH), 131.2 (q, $J_{C\text{-}F}$ = 5.1 Hz, CH), 130.9 (C), 129.2 (CH), 128.9 (2CH), 128.3 (2CH), 122.9 (q, $J_{C\text{-}F}$ = 274.7 Hz, CF_3), 113.9 (2CH), 55.4 (CH_3); **^{19}F NMR ($CDCl_3$, 282 MHz)** δ –66.6 (s, 3F). Data consistent with the literature.[119]

(*E*)-1-(4-Chlorophenyl)-4,4,4-trifluoro-3-phenylbut-2-en-1-one (52j)



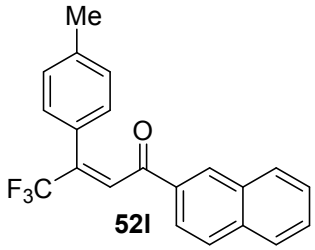
Oil, 85% yield; **^{1}H NMR ($CDCl_3$, 300 MHz)** δ 7.72-7.70 (m, 2H), 7.32-7.30 (m, 2H), 7.25-7.21 (m, 5H), 7.19 (q, J = 1.4 Hz, 1H); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 190.9 (C), 140.3 (C), 139.2 (q, $J_{C\text{-}F}$ = 30.9 Hz, C), 134.3 (C), 130.6 (C), 130.3 (q, $J_{C\text{-}F}$ = 5.0 Hz, CH), 130.2 (2CH), 129.5 (CH), 129.0 (2CH), 128.9 (2CH), 128.4(2CH), 122.7 (q, $J_{C\text{-}F}$ = 274.9 Hz, CF_3); **^{19}F NMR ($CDCl_3$, 282 MHz)** δ –66.7 (s, 3F). Data consistent with the literature.[119]

(*E*)-4,4,4-Trifluoro-1-(naphthalene-2-yl)-3-phenylbut-2-en-1-one (52k)



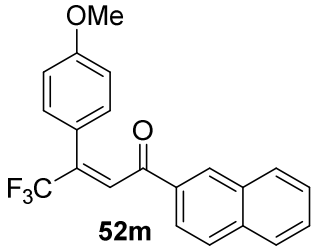
Yellow solid, 90% yield;**^{1}H NMR ($CDCl_3$, 300 MHz)** δ 8.35 (d, J = 0.9 Hz, 1H), 7.95-7.80 (m, 4H), 7.63-7.52 (m, 2H), 7.42 (q, J = 1.4 Hz, 1H), 7.34-7.31 (m, 2H), 7.25-7.22 (m, 3H); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 191.8 (C), 138.8 (q, $J_{C\text{-}F}$= 30.6 Hz, C), 135.8 (C), 133.4 (C), 132.3 (C), 131.5 (CH), 131.0 (q, $J_{C\text{-}F}$ = 5.2 Hz, CH), 130.9 (C), 129.6 (CH), 129.3 (CH), 128.99 (CH), 128.95 (2CH), 128.7 (CH), 128.3 (2CH), 127.8 (CH), 127.0 (CH), 123.7 (CH), 122.9 (q, $J_{C\text{-}F}$ = 274.7 Hz, CF_3); **^{19}F NMR ($CDCl_3$, 282 MHz)** δ –66.6 (s, 3F). Data consistent with the literature.[119]

(*E*)-4,4,4-Trifluoro-1-(naphthalene-2-yl)-3-(*p*-tolyl)but-2-en-1-one (52l)



Yellow solid, 86% yield; **^{1}H NMR ($CDCl_3$, 300 MHz)** δ 8.36 (s, 1H), 7.96-7.82 (m, 4H), 7.64-7.53 (m, 2H), 7.38-7.33 (m, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.06-7.03 (m, 2H), 2.24(s, 3H); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 192.0 (C), 139.5 (C), 135.9 (C), 133.5 (C), 132.3 (C), 131.5 (CH), 130.3 (q, $J_{C\text{-}F}$ = 5.1 Hz, CH), 129.7 (CH), 129.2 (2CH), 129.0 (CH), 128.8 (2CH), 128.7 (CH), 127.8 (CH), 127.0 (CH), 122.7 (q, $J_{C\text{-}F}$ = 276.2 Hz, CF_3), 21.2 (CH_3); **^{19}F NMR ($CDCl_3$, 282 MHz)** δ –66.6 (s, 3F).

(*E*)-4,4,4-Trifluoro-3-(4-methoxyphenyl)-1-(naphthalene-2-yl)but-2-en-1-one (52m)



Yellow solid, 72% yield; **^{1}H NMR ($CDCl_3$, 300 MHz)** δ 8.35 (s, 1H), 7.95-7.81 (m, 4H), 7.64-7.52 (m, 2H), 7.33 (q, *J* = 1.4 Hz, 1H), 7.28-7.23 (m, 2H), 6.77-6.72 (m, 2H), 3.70(s, 3H); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 192.4 (C), 160.3 (C), 135.9 (C), 133.5 (C), 132.3 (C), 131.5 (CH), 130.4 (2CH), 130.3 (q, $J_{C\text{-}F}$ = 5.0 Hz, CH), 129.7 (CH), 129.0 (CH), 128.7 (CH), 127.8 (CH), 127.0 (CH), 123.8 (CH), 123.04 (C), 123.03 (q, $J_{C\text{-}F}$ = 276.2 Hz, CF_3), 113.9 (2CH), 55.1 (CH_3); **^{19}F NMR ($CDCl_3$, 282 MHz)** δ –66.5 (s, 3F).

5.7.2. Enantioselective conjugate addition of terminal alkynes to β-substituted β-trifluoromethyl enones

5.7.2.1. General procedure for the enantioselective alkynylation reaction

A 1.5 M solution of Et_2Zn in toluene (0.17 mL, 0.25 mmol) was added dropwise to a solution of (*R*)-BINOL (**L32**, 15.5 mg, 0.025 mmol) and alkyne **2** (0.94 mmol) in toluene (0.48 mL) at room temperature under nitrogen. The mixture was stirred at 70 ºC for 1.5 h and cooled to room temperature. A solution of β-aryl β-trifluoromethyl enone **52**(0.125 mmol) in toluene (1.0 mL) was added via syringe. Then, the solution was stirred at 37 ºC until the reaction was complete (TLC). The reaction mixture was quenched with 20% aqueous NH_4Cl (1.0 mL), extracted with CH_2Cl_2 (2x 15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:EtOAc mixtures afforded compound **53**.

5.7.2.2. General procedure for the synthesis of the racemic products

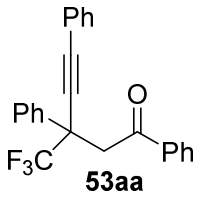
A 1.5 M solution of Et_2Zn in toluene (0.17 mL, 0.25 mmol) was added dropwise to a solution of alkyne **2** (0.94 mmol) and (±)-BINOL (**L1**, 7.2 mg, 0.025 mmol) in toluene (0.48 mL)at room temperature under nitrogen and the mixture was stirred for 1.5 h at 70 ºC. Then, β-aryl β-trifluoromethyl enones **52**(0.125 mmol) in toluene (1.0 mL) was

added via syringe. The solution was stirred at 70 ºC until the reaction was complete (TLC). Racemic products **53** were obtained after the described work up

5.7.2.3. Characterization of products 53

See Table 19 (Page 87) for yields.

1,3,5-Triphenyl-3-(trifluoromethyl)pent-4-yn-1-one (53aa)

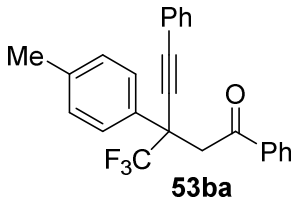


53aa

Enantiomeric excess (77%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH99:01, 1 mL/min, major enantiomer t_r = 7.4 min, minor enantiomer t_r = 8.4 min.

Oil; **[α]$_D^{20}$** +44.8 (*c*1.03, $CHCl_3$, 77% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.96-7.89 (m, 3H), 7.68-7.65 (m, 1H), 7.61-7.56 (m, 1H), 7.50-7.43 (m, 5H), 7.35-7.24 (m, 5H), 4.07 (s, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 192.7 (C), 136.7 (C), 136.6 (C), 133.5 (CH), 131.9 (2CH), 131.6 (CH), 131.2 (CH), 129.8 (CH), 128.9 (CH), 128.7 (2CH), 128.2 (2CH), 128.1 (2CH), 126.6 (CH), 125.2 (q, J_{C-F} = 283.8 Hz, CF_3), 122.6 (CH), 121.8 (C), 87.7 (C), 83.7 (C), 49.2 (q, J_{C-F} = 27.7 Hz, C), 42.1 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −74.0 (s, 3F); **HRMS (ESI)** *m/z*: 379.1306 (M+ H)$^+$, $C_{24}H_{18}F_3O$ requires 379.1310.

1,5-Diphenyl-3-(*p*-tolyl)-3-(trifluoromethyl)pent-4-yn-1-one (53ba)

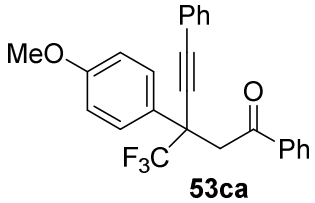


53ba

Enantiomeric excess (78%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 7.4 min, minor enantiomer t_r = 8.3 min.

Oil; **[α]$_D^{20}$** +31.1 (*c* 1.02, $CHCl_3$, 78% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.98-7.95 (m, 2H), 7.64-7.55 (m, 3H), 7.49-7.43 (m, 4H), 7.33-7.28 (m, 3H), 7.21 (dd, *J* = 8.6, 0.6 Hz, 2H), 4.07 (q, *J* = 16.9 Hz, 2H), 2.37 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 193.1 (C), 138.2 (C), 136.9 (C), 133.3 (CH), 131.9 (2CH), 131.2 (C), 129.1 (2CH), 128.6 (4CH), 128.2 (2CH), 128.1 (2CH), 127.2 (CH), 125.5 (q, J_{C-F} = 283.7 Hz, CF_3), 122.2 (C), 121.8 (C), 87.1 (C), 84.7 (C), 49.0 (q, J_{C-F} = 27.4 Hz, C), 41.9 (CH_2), 21.0 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −74.2 (s, 3F); **HRMS (ESI)***m/z*: 393.1467 (M+ H)$^+$, $C_{25}H_{20}F_3O$ requires 393.1466.

3-(4-Methoxyphenyl)-1,5-diphenyl-3-(trifluoromethyl)pent-4-yn-1-one (53ca)



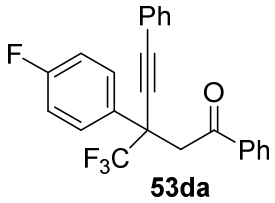
53ca

Enantiomeric excess (75%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 8.1 min, minor enantiomer t_r = 9.5 min.

Oil; **[α]$_D^{20}$** +20.3 (*c* 1.11, $CHCl_3$, 75% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.97-7.93 (m, 2H),7.65 (d, *J* = 8.6 Hz, 2H), 7.59-7.54 (m, 1H), 7.48-7.40 (m, 4H), 7.33-7.29 (m, 3H), 6.93-6.90 (m, 2H), 4.03-3.98 (m, 2H), 3.81 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 193.3 (C), 159.5 (C), 137.0 (C), 133.3 (CH), 131.9 (2CH), 129.1 (2CH), 128.7 (CH), 128.6 (2CH), 128.2 (2CH), 128.1

(2CH), 126.1 (C), 125.6 (q, $J_{C\text{-}F}$ = 283.7 Hz, CF_3), 122.1 (C), 113.7 (2CH), 87.2 (C), 84.7 (C), 55.2 (CH_3), 48.8 (q, $J_{C\text{-}F}$ = 27.5 Hz, C), 41.9 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −74.5 (s, 3F); **HRMS (ESI)** *m/z*: 409.1413 $(M+H)^+$, $C_{25}H_{20}F_3O_2$ requires 409.1415.

3-(4-Fluorophenyl)-1,5-diphenyl-3-(trifluoromethyl)pent-4-yn-1-one (53da)

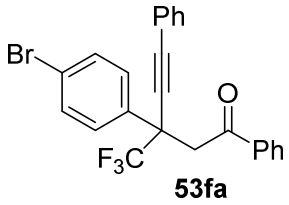


53da

Enantiomeric excess (70%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 8.3 min, minor enantiomer t_r = 10.0 min.

Oil; **$[\alpha]_D^{20}$** +41.1 (*c*1.00, $CHCl_3$, 70% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.96-7.93 (m, 2H), 7.72 (dd, *J* = 8.6, 5.2 Hz, 2H), 7.61-7.56 (m, 1H), 7.49-7.42 (m, 4H), 7.35-7.28 (m, 3H), 7.11-7.05 (m, 2H), 4.06 (s, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 193.0 (C), 162.7 (d, $J_{C\text{-}F}$ = 247.8 Hz, C), 136.8 (C), 133.5 (CH), 131.9 (2CH), 130.0 (d, $J_{C\text{-}F}$ = 3.4 Hz, C), 129.8 (d, $J_{C\text{-}F}$ = 8.7 Hz, 2CH), 128.8 (CH), 128.7 (2CH), 128.2 (2CH), 128.1 (2CH), 125.4 (q, $J_{C\text{-}F}$ = 282.8 Hz, CF_3), 121.9 (C), 115.3 (d, $J_{C\text{-}F}$ = 21.7 Hz, 2CH), 87.5 (C), 84.2 (C), 48.9 (q, $J_{C\text{-}F}$ = 27.7 Hz, C), 42.1 (CH_2);**^{19}F NMR (282 MHz, $CDCl_3$)** δ– 74.4 (s, 3F), −114.4 (s, 1F); **HRMS (ESI)** *m/z*: 397.1220 $(M+H)^+$, $C_{24}H_{17}F_4O$ requires 397.1216.

3-(4-Bromophenyl)-1,5-diphenyl-3-(trifluoromethyl)pent-4-yn-1-one (53fa)

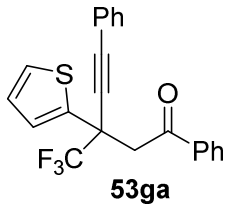


53fa

Enantiomeric excess (67%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 8.3 min, minor enantiomer t_r = 9.4 min.

Oil; **$[\alpha]_D^{20}$** +25.0 (*c*1.00, $CHCl_3$, 67% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.96-7.93 (m, 2H), 7.63-7.42 (m, 9H), 7.35-7.30 (m, 3H), 4.07 (s, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 192.8 (C), 136.6 (C), 133.54 (CH), 133.46 (C), 131.9 (2CH), 131.5 (2CH), 129.6 (2CH), 128.9 (CH), 128.7 (2CH), 128.2 (2CH), 128.0 (2CH), 125.2 (q, $J_{C\text{-}F}$ = 283.7 Hz, CF_3), 122.8 (C), 121.8 (C), 87.5 (C), 83.9 (C), 49.1 (q, $J_{C\text{-}F}$ = 27.6 Hz, C), 42.0 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −74.2 (s, 3F); **HRMS (ESI)** *m/z*: 457.0411 $(M+H)^+$, $C_{24}H_{17}BrF_3O$ requires 457.0415.

1,5-Diphenyl-3-(thiophen-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (53ga)



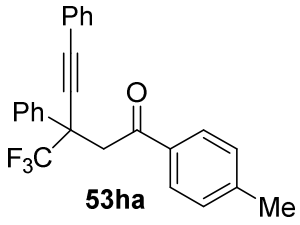
53ga

Enantiomeric excess (53%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 10.3 min, minor enantiomer t_r = 11.7 min.

Oil; **$[\alpha]_D^{20}$** +16.9 (*c*1.10, $CHCl_3$, 53% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.96-7.93 (m, 2H), 7.60-7.54 (m, 1H), 7.48-7.41 (m, 4H), 7.34-7.27 (m, 5H), 7.01 (dd, *J* = 5.1, 3.7 Hz, 1H), 3.95 (dd, *J* = 37.4, 16.2 Hz, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 193.0 (C), 138.4 (C), 137.0 (C), 133.4 (CH), 131.9 (2CH), 128.9 (CH), 128.6 (2CH), 128.19 (2CH), 128.15 (2CH), 127.4 (CH), 127.0 (CH), 126.2 (CH), 124.9 (q, $J_{C\text{-}F}$ = 283.6 Hz, CF_3), 121.7 (C), 86.7 (C), 83.9 (q, $J_{C\text{-}F}$= 1.8 Hz, C),

46.8 (q, $J_{C\text{-}F}$ = 29.3 Hz, C), 43.5 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –75.1 (s, 3F); **HRMS (ESI)** *m/z*: 385.0870 (M+ H)$^+$, $C_{22}H_{16}F_3OS$ requires 385.0874.

3,5-Diphenyl-1-(*p*-tolyl)-3-(trifluoromethyl)pent-4-yn-1-one (53ha)

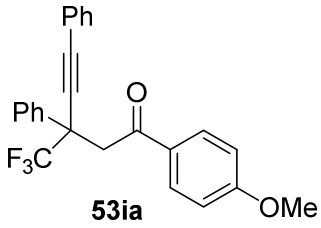


53ha

Enantiomeric excess (62%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 9.0 min, minor enantiomer t_r = 12.8 min.

Oil; **$[\alpha]_D^{20}$** +18.9 (*c* 1.04, $CHCl_3$, 62% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.86-7.83 (m, 2H), 7.75-7.73 (m, 2H), 7.46-7.24 (m, 10H), 4.06 (q, *J* = 16.9 Hz, 2H), 2.41 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 192.7 (C), 144.2 (C), 134.5 (C), 134.3 (C), 131.9 (2CH), 129.3 (2CH), 128.7 (CH), 128.3 (2CH), 128.19 (2CH), 128.16 (2CH), 127.9 (2CH), 125.5 (q, $J_{C\text{-}F}$ = 283.5 Hz, CF_3), 122.2 (C), 87.2 (C), 84.5 (C), 49.4 (q, $J_{C\text{-}F}$ = 27.5 Hz, C), 41.9 (CH_2), 21.6 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –74.1 (s, 3F); **HRMS (ESI)** *m/z*: 393.1476 (M+ H)$^+$, $C_{25}H_{20}F_3O$ requires 393.1466.

1-(4-Methoxyphenyl)-3,5-diphenyl-3-(trifluoromethyl)pent-4-yn-1-one (53ia)

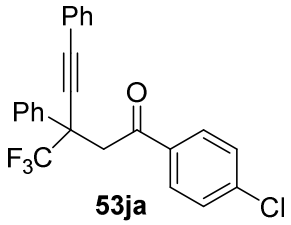


53ia

Enantiomeric excess (78%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 14.0 min, minor enantiomer t_r = 17.1 min.

Oil; **$[\alpha]_D^{20}$** +5.2 (*c*0.87, $CHCl_3$, 78% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.95-7.92 (m, 2H), 7.76-7.72 (m, 2H), 7.47-7.28 (m, 8H),6.94-6.91 (m, 2H), 4.04 (q, *J* = 16.7 Hz, 2H), 3.85 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 191.5 (C), 163.6 (C), 134.3 (C), 131.9 (2CH), 131.6 (CH), 130.4 (2CH), 130.0 (C), 128.6 (CH), 128.3 (2CH), 128.21 (CH), 128.15 (2CH), 127.9 (2CH), 127.4 (CH), 125.5 (q, $J_{C\text{-}F}$ = 283.6 Hz, CF_3), 122.2 (C), 113.7 (2CH), 87.2 (C), 84.7 (C), 55.5 (CH_3), 49.4 (q, $J_{C\text{-}F}$ = 27.4 Hz, C), 41.6 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –74.0 (s, 3F); **HRMS (ESI)** *m/z*: 409.1413 (M+ H)$^+$, $C_{25}H_{20}F_3O_2$ requires 409.1415.

1-(4-Chlorophenyl)-3,5-diphenyl-3-(trifluoromethyl)pent-4-yn-1-one (53ja)

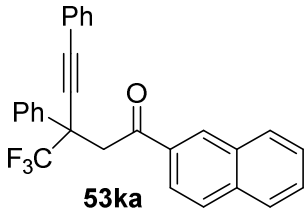


53ja

Enantiomeric excess (59%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 9.1 min, minor enantiomer t_r = 14.4 min.

Oil; **$[\alpha]_D^{20}$** +16.4 (*c* 1.01, $CHCl_3$, 59% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.90-7.85 (m, 2H), 7.73 (dd, *J* = 7.3, 1.0 Hz, 2H), 7.45-7.28 (m, 10H), 4.04 (q, *J* = 16.8 Hz, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 192.0 (C), 139.9 (C), 135.2 (C), 134.0 (C), 131.9 (2CH), 129.5 (2CH), 128.9 (2CH), 128.8 (CH), 128.5 (CH), 128.4 (2CH), 128.2 (2CH), 127.8 (2CH), 125.4 (q, $J_{C\text{-}F}$ = 283.8 Hz, CF_3), 121.9 (C), 87.5 (C), 84.3 (C), 49.4 (q, $J_{C\text{-}F}$ = 27.6 Hz, C), 42.0 (CH_2);**^{19}F NMR (282 MHz, $CDCl_3$)** δ –74.0 (s, 3F); **HRMS (ESI)** *m/z*: 413.0915 (M+ H)$^+$, $C_{24}H_{17}ClF_3O$ requires 413.0920.

1-(Naphthalene-2-yl)-3,5-diphenyl-3-(trifluoromethyl)pent-4-yn-1-one (53ka)

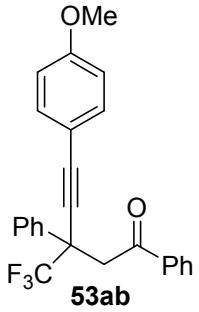


53ka

Enantiomeric excess (83%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 13.1 min, minor enantiomer t_r = 17.9 min.

Oil; **$[\alpha]_D^{20}$** +9.7 (*c* 1.02, $CHCl_3$, 83% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.45 (s, 1H), 7.96-7.92 (m, 2H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.75 (dd, *J* = 7.5, 0.8 Hz, 2H), 7.61-7.50 (m, 2H), 7.41-7.33 (m, 5H), 7.28-7.20 (m, 3H), 4.20 (q, *J* = 16.8 Hz, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 193.0 (C), 135.6 (C), 134.3 (C), 132.4 (C), 131.9 (2CH), 129.8 (CH), 128.66 (CH), 128.65 (CH), 128.5 (CH), 128.42 (CH), 128.39 (2CH), 128.2 (2CH), 127.9 (2CH), 127.8 (CH), 126.9 (CH), 124.7 (q, $J_{C\text{-}F}$ = 286.4 Hz, CF_3), 122.1 (C), 87.4 (C), 84.6 (C), 49.5 (q, $J_{C\text{-}F}$ = 27.4 Hz, C), 42.2 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −73.9 (s, 3F); **HRMS (ESI)** *m/z*: 429.1462 $(M+H)^+$, $C_{28}H_{20}F_3O$ requires 429.1466.

5-(4-Methoxyphenyl)-1,3-diphenyl-3-(trifluoromethyl)pent-4-yn-1-one (53ab)

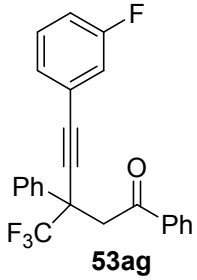


53ab

Enantiomeric excess (80%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 15.8 min, minor enantiomer t_r = 13.9 min.

Oil; **$[\alpha]_D^{20}$** +21.8 (*c* 1.08, $CHCl_3$, 80% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.96-7.93 (m, 2H), 7.75 (dd, *J* = 7.5, 0.9 Hz, 2H), 7.59-7.54 (m, 1H), 7.48-7.35 (m, 6H), 6.85-6.81 (m, 2H), 4.07 (q, *J* = 16.8 Hz, 2H), 3.81 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 193.2 (C), 159.9 (C), 137.0 (C), 134.4 (C), 133.4 (2CH), 133.3 (CH), 128.6 (2CH), 128.3 (2CH), 128.1 (2CH), 127.9 (2CH), 125.5 (q, $J_{C\text{-}F}$ = 283.7 Hz, CF_3), 114.2 (C), 113.8 (2CH), 87.3 (C), 83.1 (C), 55.3 (CH_3), 49.4 (q, $J_{C\text{-}F}$ = 27.5 Hz, C), 42.1 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −74.1 (s, 3F); **HRMS (ESI)***m/z*: 409.1419 $(M+H)^+$, $C_{25}H_{20}F_3O_2$ requires 409.1415.

5-(3-Fluorophenyl)-1,3-diphenyl-3-(trifluoromethyl)pent-4-yn-1-one (53ag)



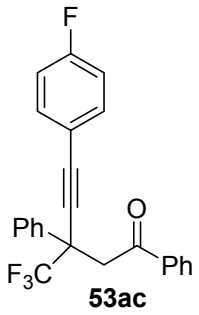
53ag

Enantiomeric excess (74%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 7.5 min, minor enantiomer t_r = 9.2 min.

Oil; **$[\alpha]_D^{20}$** +38.8 (*c* 1.09, $CHCl_3$, 74% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.96-7.93 (m, 2H), 7.74-7.71 (m, 2H), 7.61-7.56 (m, 1H), 7.49-7.38 (m, 5H), 7.29-7.24 (m, 2H), 7.15-7.11 (m, 1H), 7.08-7.02 (m, 1H), 4.09 (dd, *J* = 40.2, 17.0 Hz, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 192.9 (C), 162.2 (d, $J_{C\text{-}F}$ = 246.6 Hz, C), 136.8 (C), 134.0 (C), 133.4 (CH), 129.8 (d, $J_{C\text{-}F}$ = 8.6 Hz, CH), 128.7 (2CH), 128.5 (CH), 128.4 (2CH), 128.0 (2CH), 127.8 (CH), 127.8 (2CH), 125.4 (q, $J_{C\text{-}F}$ = 283.7 Hz, CF_3), 123.9 (d, $J_{C\text{-}F}$ = 9.5 Hz, C), 118.8 (d, $J_{C\text{-}F}$ = 23.0 Hz, CH), 116.1 (d, $J_{C\text{-}F}$ = 21.2 Hz, CH), 86.0 (d, $J_{C\text{-}F}$ = 3.5 Hz, C), 85.6 (d, $J_{C\text{-}F}$ = 2.3 Hz, C), 49.4 (q, $J_{C\text{-}F}$ = 27.4 Hz, C), 41.9 (CH_2); **^{19}F NMR (282 MHz,**

$CDCl_3$) δ −74.0 (s, 3F), −113.4 (s, 1F); **HRMS (ESI)***m/z*: 397.1216 $(M+ H)^+$, $C_{24}H_{17}F_4O$ requires 397.1216.

5-(4-Fluorophenyl)-1,3-diphenyl-3-(trifluoromethyl)pent-4-yn-1-one (53ac)

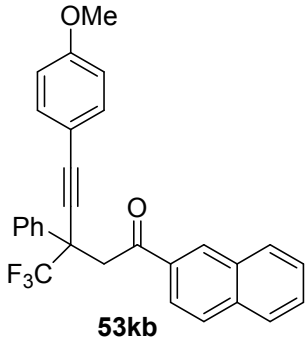


53ac

Enantiomeric excess (80%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 8.4 min, minor enantiomer t_r = 9.7 min.

Oil; **$[\alpha]_D^{20}$** +46.9 (*c* 0.91, $CHCl_3$, 80% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.96-7.93 (m, 2H), 7.74-7.71 (m, 2H), 7.60-7.55 (m, 1H), 7.49-7.38 (m, 7H), 7.03-6.97 (m, 2H), 4.08 (dd, *J* = 36.6, 17.0 Hz, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 193.0 (C), 162.8 (d, $J_{C\text{-}F}$ = 250.0 Hz, C), 136.9 (C), 134.1 (C), 133.9 (d, $J_{C\text{-}F}$ = 8.5 Hz, 2CH), 133.4 (CH), 128.7 (2CH), 128.4 (CH), 128.4 (2CH), 128.1 (2CH), 127.8 (2CH), 125.5 (q, $J_{C\text{-}F}$ = 283.5 Hz, CF_3), 118.2 (d, $J_{C\text{-}F}$ = 3.4 Hz, C), 115.5 (d, $J_{C\text{-}F}$ = 22.1 Hz, 2CH), 86.2 (C), 84.3 (C), 49.4 (q, $J_{C\text{-}F}$ = 27.5 Hz, C), 42.0 (CH_2);**^{19}F NMR (282 MHz, $CDCl_3$)** δ −74.1 (s, 3F), −110.7 (s, 1F); **HRMS (ESI)** *m/z*: 397.1216 $(M+ H)^+$, $C_{24}H_{17}F_4O$ requires 397.1216.

5-(4-Methoxyphenyl)-1-(naphthalene-2-yl)-3-phenyl-3-(trifluoromethyl)pent-4-yn-1-one (53kb)

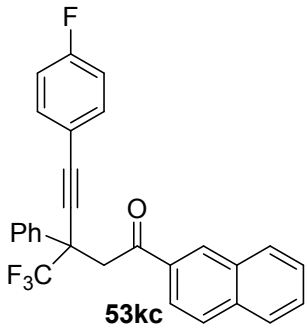


53kb

Enantiomeric excess (84%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 11.9 min, minor enantiomer t_r = 17.2 min.

Oil; **$[\alpha]_D^{20}$** −11.6 (*c* 1.02, $CHCl_3$, 84% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.47 (s, 1H), 7.98-7.94 (m, 2H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 7.1 Hz, 2H), 7.63-7.55 (m, 2H), 7.42-7.30 (m, 5H), 6.78-6.75 (m, 2H), 4.20 (q, *J* = 16.6 Hz, 2H), 3.79 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 193.2 (C), 159.9 (C), 135.6 (C), 134.5 (C), 134.4 (C), 133.3 (2CH), 132.4 (C), 129.9 (CH), 129.6 (CH), 128.6 (CH), 128.5 (CH), 128.4 (2CH), 128.0 (2CH), 127.8 (CH), 126.9 (CH), 125.5 (q, $J_{C\text{-}F}$ = 283.5 Hz, CF_3), 123.8 (CH), 114.2 (C), 113.8 (2CH), 87.4 (C), 83.1 (C), 55.3 (CH_3), 49.5 (q, $J_{C\text{-}F}$ = 27.2 Hz, C), 42.2 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −74.0 (s, 3F); **HRMS (ESI)** *m/z*: 459.1564 $(M+ H)^+$, $C_{29}H_{22}F_3O_2$ requires 459.1572.

5-(4-Fluorophenyl)-1-(naphthalene-2-yl)-3-phenyl-3-(trifluoromethyl)pent-4-yn-1-one (53kc)



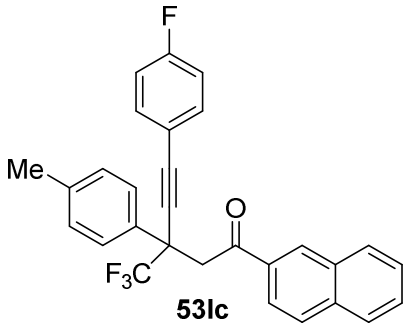
53kc

Enantiomeric excess (90%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 12.5 min, minor enantiomer t_r = 16.9 min.

Oil; **$[\alpha]_D^{20}$** +26.3 (*c*1.01, $CHCl_3$, 90% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.48 (s, 1H), 7.99-7.95 (m, 2H), 7.87 (d, *J* = 8.7 Hz, 2H), 7.76 (d, *J* = 7.3 Hz, 2H), 7.65-7.54 (m, 2H),

7.44-7.36 (m, 5H), 6.99-6.93 (m, 2H), 4.22 (dd, J = 35.9, 16.8 Hz, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 193.1 (C), 162.7 (d, J_{C-F} = 249.9 Hz, C), 135.6 (C), 134.2 (C), 134.2 (C), 133.8 (d, J_{C-F} = 8.5 Hz, 2CH), 132.4 (C), 129.8 (CH), 129.6 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (2CH), 127.9 (2CH), 127.8 (CH), 126.9 (CH), 125.5 (q, J_{C-F} = 283.5 Hz, CF_3), 123.7 (CH), 118.1 (d, J_{C-F} = 3.5 Hz, C), 115.5 (d, J_{C-F} = 22.1 Hz, 2CH), 86.4 (C), 84.4 (C), 49.5 (q, J_{C-F} = 27.6 Hz, C), 42.1 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −73.9 (s, 3F), −110.7 (s, 1F); **HRMS (ESI)** *m/z*: 447.1372 $(M+H)^+$, $C_{28}H_{19}F_4O$ requires 447.1362.

5-(4-Fluorophenyl)-1-(naphthalene-2-yl)-3-(*p*-tolyl)-3-(trifluoromethyl)pent-4-yn-1-one (53lc)

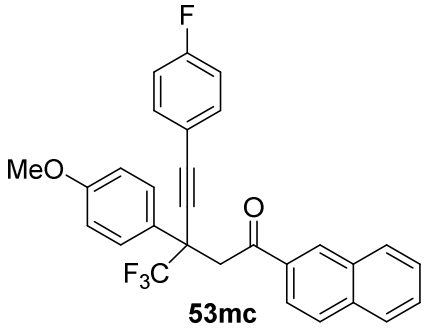


53lc

Enantiomeric excess (88%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 11.0 min, minor enantiomer t_r = 13.7 min.

Oil; **$[\alpha]_D^{20}$** +30.1 (*c* 1.09, $CHCl_3$, 88% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.47 (s, 1H), 7.99-7.94 (m, 2H), 7.87 (d, J = 8.6 Hz, 2H), 7.64-7.58 (m, 4H), 7.39-7.34 (m, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.98-6.90 (m, 2H), 4.19 (q, J = 16.7 Hz, 2H), 2.35 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 193.2 (C), 162.7 (d, J_{C-F} = 249.8 Hz, C), 138.3 (C), 135.6 (C), 134.3 (C), 133.8 (d, J_{C-F} = 8.5 Hz, 2CH), 132.4 (C), 131.2 (C), 129.8 (CH), 129.6 (CH), 129.2 (2CH), 128.7 (CH), 128.5 (CH), 127.8 (2CH), 126.9 (CH), 125.5 (q, J_{C-F} = 283.6 Hz, CF_3), 123.7 (CH), 118.2 (d, J_{C-F} = 3.7 Hz, C), 115.4 (d, J_{C-F} = 22.1 Hz, 2CH), 86.2 (C), 84.5 (C), 49.2 (q, J_{C-F} = 27.6 Hz, C), 42.1 (CH_2), 21.0 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −74.1 (s, 3F), −110.8 (s, 1F); **HRMS (ESI)** *m/z*: 461.1524 $(M+H)^+$, $C_{29}H_{21}F_4O$ requires 461.1529.

5-(4-Fluorophenyl)-3-(4-methoxyphenyl)-1-(naphthalene-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (53mc)



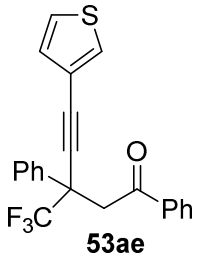
53mc

Enantiomeric excess (83%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 95:05, 1 mL/min, major enantiomer t_r = 10.6 min, minor enantiomer t_r = 12.6 min.

Oil; **$[\alpha]_D^{20}$** +6.7 (*c* 0.91, $CHCl_3$, 83% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.47 (s, 1H), 7.98-7.94 (m, 2H), 7.87 (d, J = 8.7 Hz, 2H), 7.67-7.53 (m, 4H), 7.37-7.33 (m, 2H), 6.97-6.90 (m, 4H), 4.16 (dd, J = 39.8, 23.2 Hz, 2H), 3.80 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 193.3 (C), 162.7 (d, J_{C-F} = 249.8 Hz, C), 159.6 (C), 135.6 (C), 134.3 (C), 133.8 (d, J_{C-F} = 8.4 Hz, 2CH), 132.4 (C), 129.9 (CH), 129.6 (CH), 129.1 (2CH), 128.7 (CH), 128.5 (CH), 127.8 (CH), 126.9 (CH), 126.0 (C), 125.5 (q, J_{C-F} = 283.6 Hz, CF_3), 123.7 (CH), 118.2 (d, J_{C-F} = 3.6 Hz, C), 115.4 (d, J_{C-F} = 22.1 Hz, 2CH), 113.8 (2CH), 86.3 (C), 84.6 (C), 55.2

(CH_3),48.9 (q, J_{C-F} = 27.7 Hz, C), 42.0 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −74.3 (s, 3F), −110.8 (s, 1F); **HRMS (ESI)** *m/z*: 477.1469 $(M+H)^+$, $C_{29}H_{21}F_4O_2$ requires 477.1478.

1,3-Diphenyl-5-(thiophen-3-yl)-3-(trifluoromethyl)pent-4-yn-1-one (53ae)

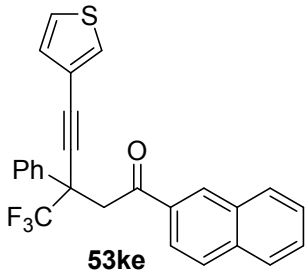


53ae

Enantiomeric excess (82%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH99:01, 1 mL/min, major enantiomer t_r = 11.7 min, minor enantiomer t_r = 14.7 min.

Oil; **$[\alpha]_D^{20}$** +37.5 (*c* 1.02, $CHCl_3$, 82% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.96-7.92 (m, 2H), 7.72 (dd, *J* = 7.4, 0.9 Hz, 2H), 7.60-7.55 (m, 1H), 7.48-7.36 (m, 6H), 67.26-7.23 (m, 1H), 7.09 (dd, *J* = 5.0, 1.2 Hz, 1H), 4.07 (q, *J* = 16.9 Hz, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 193.1 (C), 136.9 (C), 134.2 (C), 133.4 (CH), 130.0 (CH), 129.7 (CH), 128.7 (2CH), 128.40 (CH), 128.37 (2CH), 128.1 (2CH), 127.9 (2CH), 125.5 (q, J_{C-F} = 283.6 Hz, CF_3), 125.2 (CH), 121.1 (C), 84.1 (C), 82.5 (C), 49.4 (q, J_{C-F} = 28.2 Hz, C), 42.0 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −74.0 (s, 3F); **HRMS (ESI)** *m/z*: 385.0881 $(M+H)^+$, $C_{22}H_{16}F_3OS$ requires 385.0874.

1-(Naphthalene-2-yl)-3-phenyl-5-(thiophen-3-yl)-3-(trifluoromethyl)pent-4-yn-1-one (53ke)



53ke

Enantiomeric excess (86%) was determined by chiral HPLC (Chiralpak AS-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 17.8 min, minor enantiomer t_r = 24.8 min.

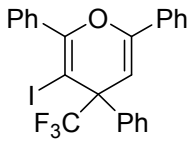
Oil; **$[\alpha]_D^{20}$** +17.1 (*c* 1.08, $CHCl_3$, 86% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.47 (s, 1H), 7.96 (dd, *J* = 8.7, 1.7 Hz, 2H), 7.87 (d, *J* = 8.6 Hz, 2H), 7.75 (d, *J* = 7.3 Hz, 2H), 7.66-7.53 (m, 2H), 7.43-7.33 (m, 4H), 7.21 (dd, *J* = 5.0, 3.0, 1H), 7.06 (dd, *J* = 5.0, 1.2 Hz, 1H), 4.21 (q, *J* = 16.8 Hz, 2H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 193.1 (C), 135.6 (C), 134.3 (C), 132.4 (C), 130.0 (CH), 129.8 (CH), 129.64 (CH), 129.59 (CH), 128.7 (CH), 128.5 (CH), 128.43 (CH), 128.39 (2CH), 127.9 (2CH), 127.8 (CH), 126.9 (CH), 125.5 (q, J_{C-F} = 283.9 Hz, CF_3), 125.2 (CH), 123.7 (CH), 121.1 (C), 84.2 (C), 82.6 (C), 49.6 (q, J_{C-F} = 27.8 Hz, C), 42.1 (CH_2); **^{19}F NMR (282 MHz, $CDCl_3$)** δ −74.0 (s, 3F);**HRMS (ESI)** *m/z*: 435.1021 $(M+H)^+$, $C_{26}H_{18}F_3OS$ requires 435.1030.

5.7.2.4. Synthetic transformations

General procedure for the iodocyclization reaction: A solution of I_2 (0.180 mmol) in CH_2Cl_2 (2 mL) was added to a mixture of **53** (0.090 mmol) and $NaHCO_3$ (0.180 mmol) under nitrogen atmosphere. The solution was heated at 40 ºC overnight. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (1.0 mL), extracted with CH_2Cl_2 (2×15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under

reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:Et_2O (98:02) gave compound **54**.

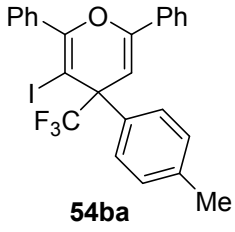
3-Iodo-2,4,6-triphenyl-4-(trifluoromethyl-4H-pyran (54aa)



54aa

Oil, 70% yield; **$[\alpha]_D^{20}$**–13.6 (*c* 0.86, $CHCl_3$); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.67-7.57 (m, 6H), 7.48-7.36 (m, 9H), 5.44 (s, 1H);**^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 153.8 (C), 149.6 (C), 142.5 (C), 137.0 (C), 132.1 (C), 129.7 (2CH), 129.6 (CH), 129.5 (CH), 128.5 (2CH), 128.4 (2CH), 128.3 (q, $J_{C\text{-}F}$ = 2.2 Hz, 2CH), 128.1 (2CH), 127.7 (CH), 126.1 (q, $J_{C\text{-}F}$ = 280.4 Hz, CF_3), 125.0 (2CH), 95.6 (CH), 71.7 (C), 55.5 (q, $J_{C\text{-}F}$ = 27.0 Hz, C);**^{19}F NMR (282 MHz, $CDCl_3$)** δ –69.0 (s, 3F); **HRMS (ESI)** *m/z*: 505.0267 $(M+H)^+$, $C_{24}H_{17}F_3IO$ requires 505.0254.

3-Iodo-2,6-diphenyl-4-(p-tolyl)-4-(trifluoromethyl)-4H-pyran (54ba)

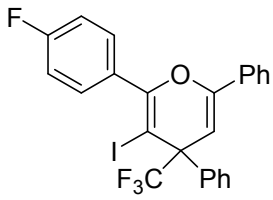


54ba

Enantiomeric excess (78%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 7.3 min, minor enantiomer t_r = 6.8 min.

Oil, 87% yield; **$[\alpha]_D^{20}$** –25.5 (*c*1.00, $CHCl_3$, 78% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.66-7.60 (m, 4H), 7.49-7.45 (m, 5H), 7.38-7.35 (m, 3H), 7.26-7.23 (m, 2H), 5.43 (s, 1H), 2.39(s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 153.7 (C), 149.4 (C), 139.7 (C), 137.6 (C), 137.1 (C), 132.1 (C), 129.7 (2CH), 129.6 (CH), 129.5 (CH), 129.1 (2CH), 128.5 (2CH), 128.2 (q, $J_{C\text{-}F}$ = 2.2 Hz, 2CH), 128.1 (2CH), 126.1 (q, $J_{C\text{-}F}$ = 282.7 Hz, CF_3), 125.0 (2CH), 96.7 (CH), 72.1 (C), 55.2 (q, $J_{C\text{-}F}$ = 26.9 Hz, C), 21.2 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –69.1 (s, 3F);**HRMS (ESI)** *m/z*: 519.0416 $(M+H)^+$, $C_{25}H_{19}F_3IO$ requires 519.0427.

2-(4-Fluorophenyl)-3-iodo-4,6-diphenyl-4-(trifluoromethyl)-4H-pyran (54ac)

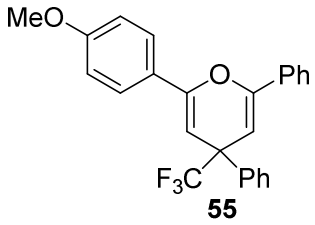


54ac

Enantiomeric excess (84%) was determined by chiral HPLC (Chiralpak AD-H), hexane-^{i}PrOH 99:01, 1 mL/min, major enantiomer t_r = 6.2 min, minor enantiomer t_r = 4.7 min.

Oil, 63% yield; **$[\alpha]_D^{20}$** –37.8 (*c*0.55, $CHCl_3$, 84% *ee*); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.66-7.54 (m, 6H), 7.46-7.35 (m, 6H), 7.18-7.12 (m, 2H), 5.42 (s, 1H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 163.2 (d, $J_{C\text{-}F}$ = 250.1 Hz, C), 152.9 (C), 149.6 (C), 142.4 (C), 133.0 (d, $J_{C\text{-}F}$ = 3.6 Hz, C), 131.9 (d, $J_{C\text{-}F}$ = 8.5 Hz, 2CH), 129.6 (CH), 128.5 (2CH), 128.4 (2CH), 128.3 (q, $J_{C\text{-}F}$ = 2.2 Hz, 2CH), 127.8 (CH), 126.1 (q, $J_{C\text{-}F}$ = 286.2 Hz, CF_3), 125.0 (2CH), 115.3 (d, $J_{C\text{-}F}$ = 21.9 Hz, 2CH), 95.6 (CH), 72.1 (C), 55.5 (q, $J_{C\text{-}F}$ = 27.4 Hz, C); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –69.0 (s, 3F),–110.8 (s, 1F); **HRMS (ESI)** *m/z*: 523.0173 $(M+H)^+$, $C_{24}H_{16}F_4IO$ requires 523.0182.

2-(4-Methoxyphenyl)-4,6-diphenyl-4-(trifluoromethyl)-4H-pyran (55)



55

Oil, 90% yield; **$[\alpha]_D^{20}$** –13.0 (*c*1.09, $CHCl_3$); **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.81-7.72 (m, 4H), 7.61-7.58 (m, 2H), 7.46-7.32 (m, 6H), 7.00-6.70 (m, 2H), 5.76 (d, *J* = 2.4 Hz, 1H), 5.64 (d, *J* = 2.4 Hz, 1H), 3.87 (s, 3H); **^{13}C NMR (75.5 MHz, $CDCl_3$)** δ 160.5 (C), 150.6 (C), 150.4 (C), 141.6 (C), 133.5 (C), 131.3 (C), 129.3 (CH), 128.6 (2CH), 128.5 (2CH), 127.6 (CH), 127.2 (q, $J_{C\text{-}F}$ = 1.8 Hz, 2CH), 126.5 (2CH), 126.2 (q, $J_{C\text{-}F}$ = 283.7 Hz, CF_3), 125.1 (2CH), 113.9 (2CH), 95.4 (CH), 93.7 (CH), 55.4 (CH_3), 48.2 (q, $J_{C\text{-}F}$ = 27.7 Hz, C); **^{19}F NMR (282 MHz, $CDCl_3$)** δ –73.2 (s, 3F); **HRMS (ESI)** *m/z*: 409.1385 $(M+H)^+$, $C_{25}H_{20}F_3O_2$ requires 409.1415.

6. CONCLUSIONS

6. CONCLUSIONS

1. Several new enantioselective conjugate alkynylation reactions of α,β-unsaturated carbonyl compounds have been developed using zinc and copper catalyst.

2. The enantioselective conjugate addition of terminal alkynes to 2-arylidene-1,3-diketones **1** has been carried out by using diethylzinc and a catalytic amount of (*R*)-VANOL (**L9**), providing the alkynylated products **3** with good yields and with enantiomeric excesses up to 93%. The use of a nitroethane as co-solvent was crucial for high enantioselectivity. A wide range of aromatic and heteroaromatic substituents on the β-carbon of the enone were tolerated. The reaction can be applied to different aromatic and heteroaromatic alkynes, although aliphatic alkynes (4-phenyl-1-butyne) reacted with low yield and enantioselectivity. Some of the alkynylation products could be enantiomerically enriched up to 99% *ee* by crystallization. This is the first example of enantioselective conjugate alkynylation reaction mediated by zinc with substoichiometric amounts of chiral inducer.

The configuration of the stereogenic center in the alkynylation products was determined to be *R*, by chemical correlation. The potential synthetic applicability of the resulting products was shown by diverse transformation.

3. We have reported a novel catalytic system that uses C_2-symmetrical bis-hydroxyamides derived from isophtalic acid and diethylzinc, which has been applied in the conjugate addition of terminal alkynes to 3-alcoxycarbonylcoumarins. The scope of the reaction has been studied with thirteen 3-alkoxycarbonyl coumarins and five alkynes. *Trans* 4-alkynyl-substituted 3-(alkoxycarbonyl)dihydrocumarins were obtained with good yields and enantiomeric excesses between 60 and 94% depending on the substitution of both the alkyne and the coumarin. Best results were obtained with 6-chloro-8-methyl-3-(*tert*-butoxycarbonyl)coumarin and with 3-fluorophenyl- and 4-fluorophenyl-acetylene.

The absolute stereochemistry of the resulting products has been determined by combining X-ray analysis and chemical correlation.

The potential synthetic applicability of the resulting products was shown by diverse transformations.

4. We have described a highly enantioselective copper-catalyzed conjugate alkynylation of 1,1-difluoro-1-(phenylsulfonyl)-3-en-2-ones. The reaction was carried out in the presence of the $[Cu(CH_3CN)_4]BF_4$-MeOBIPHEP (**L31**) complex. The reaction worked well for a wide range of β-aryl- and β-heteroaryl- substituted enones, as well as with phenylacetylene derivatives, 3-thienylacetylene and cyclopropylacetylene, giving rise to high yields and excellent enantiomeric excesses (from 92 to 99%).
The configuration of the stereogenic center in the reaction products was determined by chemical correlation.

This is also the first example on the use of 1,1-difluoro-1-(phenylsulfonyl)-3-en-2-ones as substrates in an enantioselective reaction. We have shown that these compounds can be considered as ester and amide surrogates for asymmetric catalysis. Furthermore, the resulting products can be transformed into β-alkynylated difluoromethyl and trifluoromethyl ketones.

5. The $[Cu(CH_3CN)_4]BF_4$-MeOBIPHEP (**L31**) complex allowed the highly enantioselective conjugate addition of terminal alkynes to 1,1,1-trifluoromethyl-3-en-2-ones in the presence of a catalytic load as low as 2.5 mol %. The use of reduced amounts of alkyne (1.3 equiv) and base (0.1 equiv) was essential to avoid double alkynylation. The scope of the reaction was studied with eleven enones and eight alkynes. Excellent enantioselectivities (90-98% *ee*) were obtained with trifluoromethyl enones bearing aromatic or heteroaromatic substituents on the β-carbon, while enones bearing an alkyl group at this position were unreactive. Aromatic and heteroaromatic substituted alkynes reacted with good results, while aliphatic alkynes (4-phenyl-1-butyne) reacted with lower yield.

The configuration of the stereogenic center in the alkynylation products was determined to be *R*. These compounds have been shown to be synthetic precursors for chiral furans bearing a quaternary trifluoromethylated stereogenic center.

6. Terminal diynes react with 1,1,1-trifluromethyl-3-en-2-ones under similar conditions as alkynes to give internal diynes with a propargylic stereogenic center with good yields and excellent enantiomeric excesses (84-95%). Enones bearing aromatic, heteroaromatic and also aliphatic substituents were good substrates for this reaction. The diyne scope was also broad allowing acetylenes substituted with aromatic, heteroaromatic, aliphatic and even TIPS groups. Remarkably, this is the first example of enantioselective conjugate diynylation of enones, and the first time that terminal diynes are used in an enantioselective reaction without requiring premetalation with stoichiometric amounts of a dialkylzinc reagent.

The absolute configuration of diynylation products was determined as *R* by X-ray crystallographic analysis of product **40ai.**

7. We have developed the first enantioselective conjugate addition of terminal alkynes to β-trifluoromethyl α,β-enones using a Cu(I)-taniaphos complex as catalyst. The scope of the reaction was studied with nine enones and nine alkynes to give ketones having a trifluoromethylated propargylic stereogenic center in β to the carbonyl group with good yields and enantiomeric excesses (70-99%). Best results were obtained with enones having a 3-thienyl group attached to the carbonyl group. Enones having an aliphatic group attached to the carbonyl group were poorly reactive. The reaction worked with aromatic, heteroaromatic and aliphatic alkynes. Best results were obtained with 3-fluoro- and 4-fluoro-phenylacetylene.

The configuration of the stereogenic center in the alkynylated products was determined by chemical correlation. The alkynylation products have been shown to be building

blocks for the synthesis of chiral trifluoromethylated heterocycles such as 4-trifluoromethyl-4*H*-pyrans upon iodocyclization.

8. We have described the first catalytic enantioselective conjugate addition of terminal alkynes to β-aryl β-trifluoromethyl α,β-unsaturated enones, to give ketones bearing a quaternary trifluoromethylated propargylic stereogenic center. Copper(I) catalysis was not effective in this case. Therefore, the reaction was carried out by using Et_2Zn in the presence of a catalytic amount of and (*R*)-3,3'-bis(pentafluorophenyl)BINOL (**L32**). The scope of the reaction is limited to β-trifluoromethyl enones bearing an aromatic or heteroaromatic group at the β-position, as well as to terminal alkynes substituted with aromatic and heteroaromatic groups. The corresponding products were obtained with good yields and variable enantiomeric excesses (40-90%), although they can be enantiomerically enriched up to 99% *ee* by crystallization. The absolute stereochemistry of the alkynylation products could not be determined because of the difficulties in obtaining suitable crystals for X-ray analysis from enantiomerically pure compounds. The alkynylation products could be transformed into 4-trifluoromethyl-4*H*-pyrans bearing a quaternary stereocenter upon iodocyclization.

7. REFERENCES

7. REFERENCES

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ANEXO

ANEXO. Relación de publicaciones derivadas de la tesis en el momento de su lectura.

CHEMISTRY
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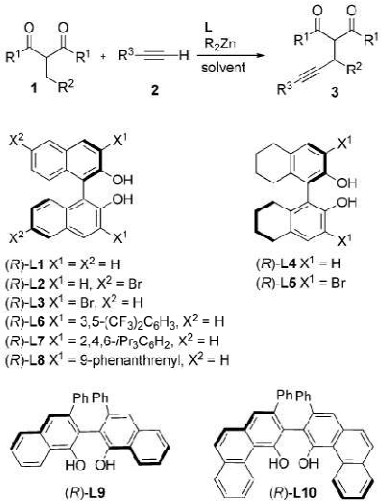
Enantioselective Zinc-Mediated Conjugate Addition of Terminal Alkynes to Enones

Gonzalo Blay,* Luz Cardona, José R. Pedro,* and Amparo Sanz-Marco[a]

The conjugate addition of carbanionic species to electrophilic double bonds, that is, unsaturated carbonyl compounds, is one of the most attractive methods for constructing a new C–C bond. Among the different kinds of carbon nucleophiles, terminal alkynes are of interest to create functionalized internal alkynes.[1] The alkynyl groups can be readily transformed into other functional groups, thus, increasing the value of these compounds as versatile building blocks.[2] An interesting outcome results from the reaction with unsaturated carbonyl and related compounds bearing β-substituents, in which a new stereogenic centre is formed. The asymmetric alkynylation of enones has been carried out by using preformed 1,1′-Bi-2,2′-naphthol (BINOL)-derived alkynylboronates[3] and alkynylalanes in the presence of Ni catalysts.[4] On the other hand, the direct asymmetric conjugate alkynylation of electrophilic alkenes with terminal alkynes has been scarcely studied and remains a challenging problem.

A first example was reported by Carreira by using 5-alkylidene Meldrum's acids (2,2-dimethyl-1,3-dioxane-4,6-dione) as electrophiles and a PINAP–copper complex (PINAP= 1-(2-(diphenylphosphino)naphthalen-1-yl)phthalazine) as catalyst.[5] Shibasaki also used copper catalysis for the asymmetric alkynylation of α,β-unsaturated thioamides.[6] A diphosphine–rhodium complex was used by Fillion and Zorzitto for the conjugate addition of silylacetylenes to 5-benzylidene Meldrum's acids,[7] while Hayashi and Nishimura described the rhodium-catalyzed alkynylation of simple enones, enals, and nitroalkenes with silylacetylenes.[8] Recently, the same group reported the asymmetric catalytic addition of silylacetylenes to α,β-enones in the presence of a biphosphine–cobalt(I) complex, generated in situ by the reduction of a cobalt(II) salt with Zn.[9] Finally, a few examples of conjugate alkynylations mediated by zinc have been reported, which required equivalent or higher amounts of chiral material in all cases. Thus, Walker and Cui carried out the conjugate alkynylation of 5-benzylidene Meldrum's acid derivatives with alkynyl Grignard reagents in the presence of a superstoichiometric amount of a cinchonidine–Me_2Zn complex.[10] Carreira reported the diastereoselective alkynylation of chiral oxazepanedione acceptors with zinc alkynylides, generated by treating terminal alkynes with $Zn(OTf)_2$ and an amine base,[11] and Tomioka reported the asymmetric reaction of nitroolefins with arylalkynes mediated by dimethylzinc and 1.5 equivalents of a chiral amino alcohol.[12] Herein, we describe the first zinc-mediated conjugate alkynylation of enones by employing catalytic amounts of a chiral inducer, which is promoted by diethylzinc. Previously, our group has described the dialkylzinc-mediated addition of terminal alkynes to aldehydes[13] and imines[14] in the presence of catalytic amounts of hydroxyamides and BINOL-type ligands, respectively.

In our study we used arylidenediketones **1** as electrophiles (Scheme 1), because these compounds are readily available by Knoevenagel condensation of 1,3-diketones and aldehydes and show high electrophilicity. For the optimization of the conditions, we studied the reaction between enone **1a**



Scheme 1. Conjugate alkynylation of enones and binaphthol ligands used.

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COMMUNICATIONS

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Enantioselective Synthesis of 4-Substituted Dihydrocoumarins through a Zinc Bis(hydroxyamide)-Catalyzed Conjugate Addition of Terminal Alkynes

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Abstract: A new enantioselective catalyst for the conjugate addition of terminal alkynes has been developed. Terminal alkynes react with 3-alkoxycarbonylcoumarins in the presence of diethylzinc and bis(hydroxyamide) ligands to give chiral non-racemic dihydrocoumarins substituted with an alkynyl group on the C-4 position with good yields and enantiomeric excesses up to 95%.

Keywords: alkynylation; asymmetric catalysis; N,O ligands; nucleophilic addition; oxygen heterocycles

The 3,4-dihydrocoumarin ring system constitutes the core of many natural products[1] and biologically active compounds. Over the past decades, numerous dihydrocoumarin derivatives and related compounds have been discovered or obtained synthetically, which exhibited estrogen-like,[2] protein transacetylase,[3] reductase inhibitory,[4] protein kinase,[5] antiherpetic,[6] cytotoxic,[7] antioxidant and antiproliferative,[8] or blocking of ATP-sensitive potassium channels activities,[9] among others. Natural dihydrocoumarins are also of great interest as flavouring agents in the food industry.[10] Furthermore, dihydrocoumarins have been used as building blocks for the synthesis of other bioactive compounds.[11] For these reasons, the development of new synthetic procedures for the construction or modification of this scaffold has attracted considerable attention among chemists. The conjugate addition of carbon nucleophiles to coumarins is one of most straightforward methods for the synthesis of 3,4-dihydrocoumarins bearing a substituted stereogenic center at the 4-position of the heterocycle.

The enantioselective conjugate addition of arylboronic acids to coumarins employing chiral Rh complexes has been reported by Hayashi[12] and Carreira.[13] The Cu-catalyzed conjugate addition of dialkylzinc reagents to 3-acyl- and 3-nitrocoumarins using phosphoramidite ligands has been described by Woodward[14] and Feringa,[15] respectively. This latter author has reported recently the asymmetric addition of Grignard reagents catalyzed by copper.[16] Finally, Feng has developed a catalytic asymmetric conjugate allylation of 3-acylcoumarins with tetraallyltin *via* a dual activation strategy using *N,N*-dioxide-$Yb(OTf)_3$ and $(CuOTf)_2{\cdot}C_7H_8$.[17] However, an asymmetric conjugate alkynylation of coumarins has never been achieved, to the best of our knowledge.

The asymmetric conjugate alkynylation of unsaturated ketones has been carried out by using BINOL-derived chiral alkynylboronates[18] or alkynylalanes in the presence of a nickel catalyst.[19] Hayashi and Nishimura have described the conjugate alkynylation of enones with silylacetylenes catalyzed by either rhodium[20] or cobalt complexes.[21] Recently, our group has also developed an asymmetric conjugate alkynylation of enones mediated by Et_2Zn and VANOL.[22] On the other hand the conjugate alkynylation of unsaturated esters has been only possible with double-activated substrates such as 5-alkylidene-Meldrum acid derivatives. Thus, Carreira[23] and Fillion[24] have reported separately the conjugate addition of terminal alkynes to these substrates catalyzed by copper or rhodium, respectively, whilst Cui and Walker have used alkynyl-Grignard reagents in the presence of a chiral amino alcohol for this purpose.[25] Herein, we describe the asymmetric alkynylation of 3-alkoxycarbonylcoumarins using a new Zn-bis(hydroxyamide) catalyst. To the best of our knowledge, this is the first reported example of the alkynylation of coumarins, but also the first example of a zinc-mediated alkynylation of unsaturated esters that requires substoichiometric amounts of chiral inducer.

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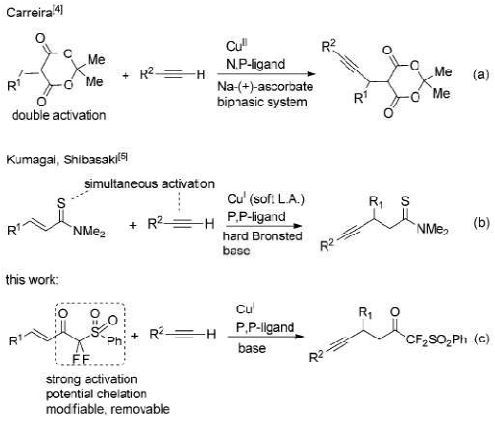
Asymmetric Synthesis

Highly Enantioselective Copper(I)-Catalyzed Conjugate Addition of Terminal Alkynes to 1,1-Difluoro-1-(phenylsulfonyl)-3-en-2-ones: New Ester/Amide Surrogates in Asymmetric Catalysis

Amparo Sanz-Marco, Andrea García-Ortiz, Gonzalo Blay,* Isabel Fernández, and José R. Pedro*[a]

Abstract: A highly enantioselective copper-catalyzed conjugate alkynylation of monoactivated enones, namely 1,1-difluoro-1-(phenylsulfonyl)-3-en-2-ones, is described. The reaction products are obtained with good yields and excellent enantioselectivities (from 92 to 99% ee). The β-alkynylated difluoro(phenylsulfonyl) ketones can be converted into the corresponding β-alkynylated difluoro- and trifluoromethyl ketones, esters and amides. This is the first example on the use of 1,1-difluoro-1-(phenylsulfonyl)-3-en-2-ones as substrates in an enantioselective reaction, which have been shown to be new ester/amide surrogates.

The interest in the chemistry of alkynes has experienced a progressive growth in the last years.[1,2] The asymmetric conjugate addition of terminal alkynes to electrophilic double bonds conjugated with electron-withdrawing functional groups, especially in β-substituted α,β-unsaturated carbonyl and related compounds, is a highly efficient method to obtain internal alkynes bearing a stereogenic center at the propargylic position. The resulting products are very versatile chiral building blocks in view of the potential modification of the triple bond and/or the carbonyl-related functional group. Enantioselective procedures for the alkynylation of enones and related compounds have been carried out by using preformed alkynyl organometallic reagents and different catalysts or chiral auxiliaries,[3] which unavoidably yield significant amounts of metallic waste. A more convenient approach from the environmental and atom-economic point of view would be the generation of the reactive alkynyl–metal species from terminal alkynes and a catalytic amount of a chiral metal complex. Since the first report by Carreira[4] on copper-catalyzed reactions of terminal alkynes with derivatives of Meldrum's acid, several successful examples have been reported by using Cu,[5] Rh,[6] Co,[7] Ru (one example with 82% *ee*),[8] and Pd (two examples with 39 and 38% *ee*)[9] catalysts. Despite these advances, there are still some limitations regarding the enantioselectivity and the substrate or alkyne scope. In particular, the possibility to chemically manipulate the electron-withdrawing group that activates the double bond would be very convenient. Moreover, in the case of the less toxic and less expensive copper metal, the reaction is further hampered by the low nucleophilicity of the intermediate copper–alkynylides. In fact, alkynyl substituents have been used as dummy ligands in mixed organocuprates, permitting the selective transfer of alkyl or alkenyl groups in the course of conjugate addition reactions.[10] This limitation for the copper-catalyzed conjugate alkynylation has been overcome by the use of doubly activated alkenes, namely Meldrum acid derivatives (Scheme 1a),[4] or by the use of unsaturated thioamides that are especially designed to simultaneously activate the alkyne and the double bond through soft Lewis acid/hard Brønsted base cooperative catalysis (Scheme 1b).[5]



Scheme 1. Strategies for the enantioselective copper-catalyzed conjugate addition of terminal alkynes.

An important requirement of the alkene activating groups is the possibility of further synthetic transformation. In particular, their conversion into ester or amide moieties is especially interesting, because simple unsaturated esters and amides have

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Catalytic asymmetric conjugate addition of terminal alkynes to β-trifluoromethyl α,β-enones†

Amparo Sanz-Marco, Andrea García-Ortiz, Gonzalo Blay* and José R. Pedro*

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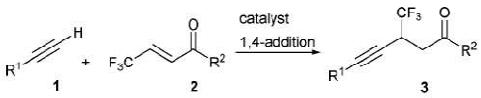
The first enantioselective conjugate alkynylation of β-trifluoromethyl α,β-enones using terminal alkynes and a taniaphos–Cu(I) complex as catalyst is described. Ketones bearing a trifluoromethylated propargylic chiral centre in the β-position were obtained with good yields and high enantiomeric excesses (up to 99%).

In recent years the stereoselective introduction of perfluoroalkyl substituents[1] into organic molecules has attracted great attention in the field of medicinal, agricultural and material chemistry, mainly due to the significant changes in the physical, chemical, and biological properties that the introduction of fluorine atoms causes in the parent molecules.[2] In this context, molecules containing chiral centres bearing a trifluoromethyl substituent[3] have attracted special interest due to the increasing occurrence of this motif in biologically active compounds,[4] but also in chiral reagents[5] or in materials for optoelectronic devices.[6] This kind of chiral centre has been constructed by following two general approaches: (i) the direct trifluoromethylation of prochiral carbons and (ii) the functionalization of trifluoromethylated prochiral carbons. Although straightforward, there are few enantioselective examples using the first approach[7] and the second one has been more often preferred for the construction of chiral centres bearing a trifluoromethyl group in an enantioselective fashion.[3,8] On the other hand, chiral trifluoromethylated propargylic carbons are present in a number of bioactive compounds such as the HIV reverse transcriptase inhibitor efavirenz and its analogues.[9] Recently some enantioselective procedures for the synthesis of trifluoromethylated propargylic carbons having heteroatoms by trifluoromethylation of ynones,[10] and alkynylation of ketones[11] or imines[12] have been reported in the literature. However, a catalytic procedure for the enantioselective synthesis of trifluoromethylated propargylic carbons without heteroatoms has not been reported yet, to the best of our knowledge. By following strategy (ii) we envisioned that this kind of chiral centre may be created by asymmetric conjugate alkynylation of β-trifluoromethyl α,β-unsaturated carbonyl compounds, *i.e.* enones (Scheme 1).



Scheme 1 Conjugate alkynylation of β-trifluoromethyl enones.

The enantioselective conjugate alkynylation of α,β-unsaturated carbonyl compounds has been carried out by using pre-formed metal alkynylides,[13] or, more conveniently, by direct alkynylation with terminal alkynes using Cu,[14] Rh,[15] Co,[16] Zn,[17] Ru (one example with 82% ee)[18] and Pd (two examples with 39% and 38% ee)[19] catalysts. However, none of these procedures has been applied with fluorinated substrates.

In this communication we describe the first example of enantioselective alkynylation of β-trifluoromethyl α,β-unsaturated ketones with terminal alkynes, using copper(I)-complexes as catalysts. Although convenient from the economic and environmental point of view, the use of copper catalysis in conjugate alkynylation is hampered by the low nucleophilicity of the intermediate copper alkynylides. In fact, the copper(I) catalyzed conjugated alkynylation of α,β unsaturated carbonyl compounds has been only possible with highly activated substrates, *i.e.* Meldrum's acid derivatives[14a] with two carbonyl groups on the double bond α-carbon, or by the use of unsaturated thioamides specially designed to simultaneously activate the alkyne and the double bond *via* a soft Lewis acid/hard Brønsted base cooperative catalysis.[14b–d] Despite these limitations, we believed that the presence of the strong electron-withdrawing trifluoromethyl group should increase the electrophilicity of the double bond by lowering the LUMO energy level,[20] thus allowing the reaction to take place.

In the onset of our investigation we studied the addition of phenylacetylene (**1a**, R^1 = Ph) to enone **2a** (R^2 = Ph) in the presence of $[Cu(CH_3CN)_4]BF_4$, a variety of ferrocene-based phosphane ligands (Fig. 1) and triethylamine in toluene at 60 °C (Table 1, entries 1–5).‡ The best result was obtained with ligand **L4**

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Synlett A. Sanz-Marco Spotlight

β-Trifluoromethyl-α,β-unsaturated Ketones

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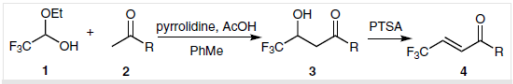
Introduction

β-Trifluoromethyl enones are important synthetic precursors of molecules containing chiral centers with a trifluoromethyl substituent, a structural motif which is present in biologically active compounds, chiral reagents and in materials for optoelectronic devices.[1] The presence of the strong electron-withdrawing β-trifluoromethyl group increases the electrophilicity of the double bond expediting the conjugate nucleophilic additions.

Preparation

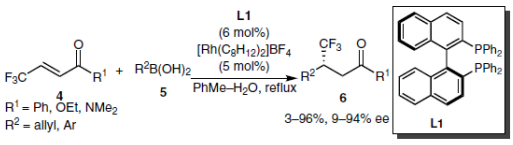
β-Trifluoromethyl-α,β-unsaturated ketones can be prepared by different methods.[2] Among them, one of the most general applications is the aldol reaction of trifluoroacetaldehyde ethyl hemiacetal with a ketone followed by dehydratation.



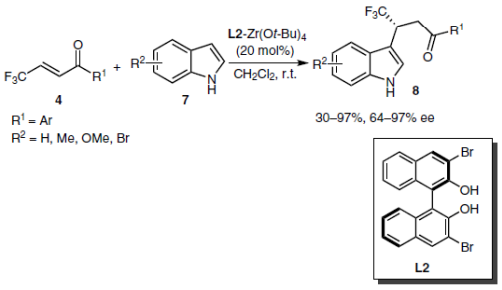
Scheme 1 Synthesis of β-Trifluoromethyl-α,β-unsaturated ketones

Table 1 Use of β-Trifluoromethyl-α,β-unsaturated Ketones

(A) *Arylation*
The enantioselective conjugate arylation of β-trifluoromethyl-α,β-unsaturated ketones was carried out by treatment with arylboronic acids **5** under catalysis with the Rh(I)-BINAP (**L1**) complex. The products **6** were obtained in high yields and enantioselectivities with a variety of arylboronic acids.[3]



(B) *Friedel–Crafts Alkylation*
Pedro and co-workers reported the first example of enantioselective Friedel–Crafts alkylation of indoles **7** with β-trifluoromethyl-α,β-unsaturated ketones, using a chiral Zr(IV)–BINOL (**L2**) complex as catalyst. Functionalized indoles **8** bearing a stereogenic tertiary center attached to a trifluoromethyl group were afforded with good yields and high enantiomeric excesses.[4a] A similar reaction was described later by Feng and co-workers using an yttrium(III) complex.[4b]



(C) *Epoxidation*
The asymmetric epoxidation of α,β-unsaturated carbonyl compounds using a chiral Sc(III)–*N*,*N*′-dioxide (**L3**) complex was achieved by Feng and co-workers. The authors describe several examples with β-trifluoromethyl-α,β-unsaturated ketones giving the corresponding epoxides **10** in excellent yields and enantioselectivities under mild conditions.[5]