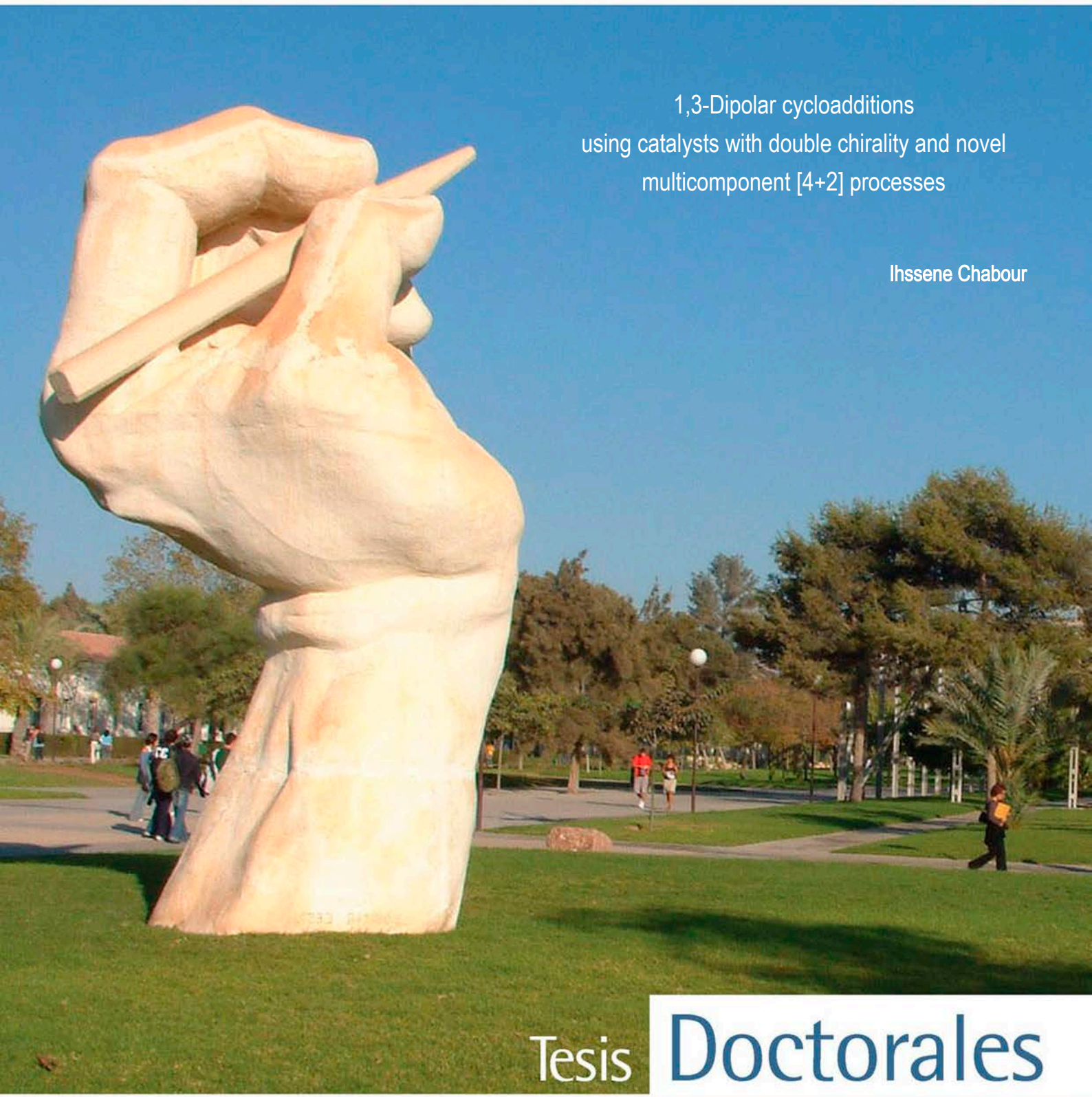
1,3-Dipolar cycloadditions using catalysts with double chirality and novel multicomponent [4+2] processes

Ihssene Chabour



Departamento de Química Orgánica
Instituto de Síntesis Orgánica (ISO)
Facultad de Ciencias

1,3-Dipolar cycloadditions using catalysts with double chirality and novel multicomponent [4+2] processes.

Ihssene Chabour

Tesis presentada para aspirar al grado de
DOCTORA POR LA UNIVERSIDAD DE ALICANTE
MENCIÓN DE DOCTORA INTERNACIONAL

Doctorado en Síntesis Orgánica

Dirigida por:

Carmen Nájera Domingo
Catedrática de Química Orgánica

José Miguel Sansano Gil
Catedrático de Química Orgánica

AGRADECIMIENTOS

El tiempo vuela más de lo que piensamos, y sí, llevo 4 años en España. El 18 de septiembre de 2016 fue mi primer día en Alicante, recuerdo que en ese momento no hablaba ni entendía palabra alguna en español.

Ese día comenzaría para mí una nueva vida y una nueva experiencia, liderada por un objetivo preciso que tenía muchas ganas de alcanzar, y que es la obtención de un doctorado internacional en química orgánica.

Durante estos 4 años, adquirí un nuevo idioma, descubrí una cultura extraordinaria, y conocí a varias personas a las que considero una segunda familia, con las que aprendí y compartí muchas cosas.

Como todos, he tenido momentos felices y momentos muy difíciles, que me han moldeado a pesar de todo.

En esta ocasión me gustaría agradecer a todos los que me ayudaron a la realisation de mi tesis.

En primer lugar quiero agradecer a mi director de tesis, "JOSE MIGUEL SANSANO GIL" profesor a la Universidad de Alicante. Mi más sincero agradecimiento por su gran paciencia, su disponibilidad, su confianza, y sobre todo, sus juiciosos consejos que contribuyeron a alimentar mi reflexión. Eres un profesorala altura y he apredido mucho trabajando contigo, También quisiera decirte que nunca olvidaré el apoyo moral que me brindaste a lo largo del viaje de mi investigación y durante mis dos accidentes, te sentí como un padre, en el que podía contar. Sigo insistiendo en que no podría haber tenido un encuadre mejor que tú.

Un gran agradecimiento a la profesora CARMEN NÁJERA DOMINGO, mi codirectora, para mí siempre serás la mujer ejemplar, la enciclopedia de la química, la famosa profesora Carmen de la Universidad de Alicante, siempre sonriente, y con un gran corazón, nos animaste, a pesar de toda tu grandeza, estuviste tan cerca de nosotros, muy comprensiva, muy simples con el deseo permanente de avanzar aún más a tus estudiantes y cuán grande fue mi alegría cuando fui aceptado en tu grupo.

Par la misma ocasión, Quisiera transmitir mi más distinguido saludo a su esposo, el profesor miguel yus por su generosidad y simpatía.

Y también al profesor Francisco Foubelo Garcia quien forma parte de nuestro grupo de investigación, un buen trabajador, serio, y muy disciplinado.

También me gustaría expresar mi agradecimiento a mi supervisora de estancia, la profesora Geraldine Masson, por su confianza, su disponibilidad, la calidad de su supervisión y especialmente la autonomía que me brindó durante esta estancia que Tuve la oportunidad de realizar dentro del ICSN (Instituto de Química de Sustancias Naturales CNRS, París-Francia).

A continuación, Quisiera expresar mi agradecimiento a las siguientes personas que por sus palabras, sus escritos, sus consejos, sus ayudas, y su presencia a mi lado durante todo mi camino de investigación.

A ti verónica, mi hermana española, mi primera colaboradora en el laboratorio, te agradezco mucho cada momento que compartí contigo, trabajando, riendo, cantando, e incluso llorando juntas, fuiste la única que me entendió cuando me Llegué y que no hablaba absolutamente nada en español, contigo aprendí mucho, me animaste en mis momentos de debilidad. Y si maluma dijo (borro cassette) yo prefiero decir (guardar el cassette para siempre).

Como recuerdo, mi primer día, en el dispacho de jose miguel, cuando pensé que era la única a estar tímida, conocí a alguien que estaba más tímido que yo ... Marcos, nuestros primeros pasos fueron juntos, nos Hemos formado un buen equipo con vero, realmente fue un gran placer compartir muchas cosas contigo y trabajar en el mismo grupo, te deseo desde el fondo de mi corazón una vida llena de éxitos y felicidad, gracias por todo.

Un gran agradecimiento a ti Davide, eres una persona agradable, y muy amable, realmente fue un placer trabajar contigo en el mismo grupo, por otro lado, siempre he apreciado tu interés en nuestra cultura y nuestras tradiciones, te deseo lo mejor en tu futuro.

Para ti Eduardo eres realmente un chico tranquilo, simpático a la altura. Sin olvidar a Ana, la chica ejemplar en su amabilidad, su gentileza, su disipación, diligencia, testigo de que tienes un gran corazón y una hermosa sonrisa, quédate así para siempre, Alex gracias por enseñarme un nuevo lenguaje divertido, y que siempre guardo, (Francés Español), Aitor francamente nada que decir que eres un hombre de 'una personalidad fuerte, amable y respetuosa gracias por todos los consejos y por escucharme y tratar de ayudarme, a Cynthia (¿Aspirador ?, ¿No, Ordenador? No… .. HPLC Cynthiaaa HPLC ddjj) fue Realmente gracioso al

principio no nos entendíamos para nada, y ahora les puedo dar las gracias y les deseo más éxito fácilmente en español, gracias también a Cristina, Misa, Edgar, Sandra, Bianka, Nieves, Jams, Manu, Manel, Pawel, Irene. Y a todos los pasantes de diferentes rincones del mundo que han dejado muchos hermosos recuerdos, a Meriem, Sofiane, Manel, Francisco, Guillerme, Luana, Josie, Sofiane, Rana kaouther, y salah.

Un agradecimiento excepcional, al hombre de las bromas, tan raras, el hombre que habla demasiado, si tu Diego Felipe Blanco, el campeón de columnas, ya son 4 años que llevamos discutiendo, riendo, haciendo la cara, burlarse el uno de el otro, aprendido cursos especiales de idioma jjj, y confiando nuestras historias nuestras penas y nuestras alegrías, llevo michos recuardos contigo y espero que no sean los ultimos, gracias por todos los momentos y también por la comida que compartiamos (y especialmente la comida), gracias por su confianza, y su presencia.

A mi amiga, a mi hermana, al hombro en el que me apoyé durante estos años, a la persona a quien le confío mis historias, a ti Asma Belabbes, tal vez el hecho de que seas del mismo origen que yo, nos hizo estar tan cercas, aparte de eso, eres realmente una persona hermosa, muy querida para mí, y que me enorgullece conocerte, contigo viví hermosas experiencias que nunca olvidaré, hemos vivido y compartido todo juntas, los momentos de alegría y los momentos más difíciles de la vida, pero al final Siempre hemos podido superar todo esto, hoy quiero darte las gracias por ser una amiga tan maravillosa, y estoy deseanda poder compartir muchos momentos más fantásticos contigo, querida mía te deseo toda la felicidad posible, y lleno de éxito en tu vida.

Sin olvidar a mis amigos

Mohamed, mejor goleador que he conocido, realmente fue un gran placer conocerte, y compartir momentos fantásticos contigo te agradezco por brindarme la ayuda y el apoyo que necesitaba, por tu presencia y lealtad,te deseo lo mejor en tu futuro pichichi.

A Roa la chica la mas loca que he conocido estos anos, hermanita hemos vevido muchas experiencias, compartido momentos inolvidables, es realmente un placer de conocerte chica, gracias por todo, te deseo mucho éxito y amor en tu vida.

Narjes Tlili, la chica con un gran corazón, no sé cómo puedo agradecerte, francamente eres una amiga maravillosa, nunca olvidaré la ayuda que me diste,

y los momentos que viviamos juntas y sobre todo tardes extraordinarias, Te deseo mucho éxito en tu vida mi querida khanchoura ... warniwarni

También agradezco al profesor BEHLOUL cherif.

Un agradecimiento especial a mi tío doctor Gati Salaheddine a quien considero mi segundo padre, le dedico este recuerdo como un débil testimonio de mi cariño, mi amor y mi profunda gratitud por haberme ayudado y considerado como su propia hija, por sus consejos y ánimos, le estaré eternamente agradecido, que Dios lo preserve y lo mantenga en buena salud.

así como a su esposa Gati Nebia, a quien agradezco desde el fondo de mi corazón, por su amabilidad, apoyo y ayuda. sin olvidar a sus dos hijos, Zakaria y Badis.

También la amante tía Gati Fadila, que considero como una segunda madre, que nunca me olvidó con sus oraciones, su amor y apoyo.

Igualmente, mis tíos, rida y salah. Y mis tías, hafida, khadija, dalila y mouna.

Al final el mayor agradecimiento es para mis queridos padres.

A decir verdad, Gracias ... es una palabra demasiado simple. Y lo que me gustaría expresar está por encima de eso, porque ningun dedicación, ninguna palabra podría expresar a su justo valoro la gratitud y el amor que tengo por ellos.

hoy pongo entre vuestros manos el fruto de largos años de estudio, de largos meses de distanciamiento de vuestro amor de vuestra ternura, de largas jornadas de aprendizaje.

Lejos de vosotros, vuestro apoyo y aliento siempre me han dado fuerzas para perseverar y prosperar en vida.

Cada línea de esta tesis, cada palabra y cada letra, te expresa gratitud, respeto, estima y gracias por ser mis padres.

Querida Mama, te agradezco mucho tu dedicación, tu cariño, tu ternura, tu comprensión, por haber sacrificado toda tu vida por mi bienestar y mi educación, de verdad eres una mujer de oro y la mejor mamá del mundo.

Querido Papa, te tomo siempre como ejemplo por tu trabajo, tu integridad, tu personalidad, tu generosidad, que encuentras aquí la expresión de mi profunda gratitud, tu que siempre me has mostrado el camino correcto, que me has dirigido, y apoyado en cada momento de mi vida.

Que Dios haga realidad vos deseos, os bendiga y os guarde porque siempre os necesitaré.

Gracias también a mis queridas hermanas

Hanane, o siempre encuentro las palabras para agradecerte el amor que me has demostrado a lo largo de los años, las palabras de aliento que has podido decir y el apoyo extraordinario que me has brindado, gracias por crear recuerdos, risas, momentos preciosos que solo somos nosotros dos; tan mundanos como son, son esenciales para mí. eres un regalo del cielo querida hermana.

Gracias también a tu esposo Said, que nunca se ha negado a hacerme ningún favor, y por toda la ayuda y apoyo que me ha brindado. Sin olvidar a nuestros chiquitines adorable Aghiles y Aylan,

A mis hermanitas Ryene y Lyna, os vi crecer frente a mis ojos, os cuidé cuando erais pequinas, pero el tiempo vuela tan rápido, y ahora sois dos muchachas, quien me ayúda, me aníma y me apóya en todo momento, os agradezco todo y os deseo todo lo mejor.

Y al final, a todas las personas que he conocido en mi vida y de las que guardo muy buenos recuerdos. F.

TABLE OF CONTENTS

PREFACE 16

SUMMARY 21

PREFACIO 27

SECCIÓN 1. SÍNTESIS 33

HIPÓTESIS **35**

OBJETIVOS **36**

TRABAJOS PRESENTADOS **39**

JUSTIFICACIÓN DE LA UNIDAD TEMÁTICA **40**

RESUMEN DE LOS TRABAJOS PRESENTADOS **41**

RESUMEN DE DISCUSIÓN Y RESULTADOS **44**

Capítulo 1 44

Sección Experimental 54

Métodos Generales 54

Síntesis de iminoéster **5b** 54

Procedimiento general para la reacción 1,3-dipolar utilizando catalizador dual **14**·Ag-(R)-**17**. Síntesis de compuestos endo-**4b** y **20**. 55

Capítulo 2 55

Sección Experimental 63

Métodos Generales 63

Procedimiento general para la síntesis de productos **1** 64

Capítulo 3 65

Sección Experimental 74

Métodos Generales 74

Procedimiento general para la síntesis de productos 1. 74

SECTION 2: PUBLISHED WORKS 75

GENERAL INTRODUCTION 77

Multicomponent reactions **79**

Cycloadditions reactions **81**

1,3-Dipolar cycloaddition 83

Reactivity of 1,3-Dipoles in Cycloadditions 87

The Diels-Alder (4+2) Cycloaddition Reaction 88

Diels-Alder Mechanism 89

Reactivity of the reaction 93

The regioselectivity of Diels-Alder reaction 94

The Stereoselectivity of Diels-Alder reaction 95

The Inverse electron demand Diels–Alder reaction 96

Hetero-Diels–Alder reactions 97

CHAPTER 1: 101

Dual chiral silver catalyst in the synthetic approach to the core of hepatitis C virus inhibitor GSK 625433 using enantioselective 1,3-dipolar cycloaddition of azomethine ylides and electrophilic alkenes 101

Brief bibliographic background **103**

Azomethines ylides 103

Methods for generating azomethine ylides 105

1,3-Dipolar Cycloaddition of Stabilized Azomethine Ylides 112

Enantioselective 1,3-Dipolar Cycloaddition 115

Chiral Organocatalysts 116

Chiral Lewis acids 119

Reactions catalyzed by copper(I) or copper(II) complexes 123

Reactions catalyzed by Silver (I) complexes 129

Objectives **143**

ANNEX 1 ..... **145**

CHAPTER 2: 169

Diastereoselective multicomponent Amine-Aldehyde-Dienophile (AAD) process for the synthesis of polysubstituted cyclohex-2-enylamines 169

Brief Bibliographic background **171**

Amine-Aldehyde-Dienophile (AAD) Reactions 171

Objectives **189**

ANNEX 2 ..... **191**

CHAPTER 3: 207

Diastereoselective multicomponent phosphoramidate-aldehyde-dienophile (PAD) process for the synthesis of polysubstituted cyclohex-2-enyl-amine derivatives 207

Phosphoramidate-Aldehyde-Dienophile (PAD) Reactions **209**

Organophosphorus compounds (OPs) **210**

Phosphoramidates **214**

Objectives **219**

ANNEX 3 ..... **221**

SECCIÓN 3: CONCLUSIONES 241

CONCLUSIONES 243

LIST OF ABBREVIATIONS 247

BIOGRAPHY 253

PREFACE

PREFACE

In this thesis, the main projects in which I participated during my doctorate are described. The research concerns the study of multi-component pericyclic reactions, that means, 1,3-dipolar cycloadditions, using azomethine ylides with electrophilic alkenes, and on the other hand, the Amine/Phosphoramidate-Aldehyde-Dienophile reactions, AAD and PAD, respectively. This work was carried out under the supervision of Professors Carmen Nájera Domingo and José Miguel Sansano Gil in the Department of Organic Chemistry and in the Institute of Organic Synthesis of the University of Alicante (Spain).

The thesis is divided into three sections, dividing section 2 into three chapters. In **Section 1** the objectives, hypotheses, specific works and justification of the thematic unit will be presented in Spanish. Incorporate a global summary of the results obtained, the discussion of these results and the final conclusions. **Section 2** consists of three chapters, each consisting of a brief introduction and the corresponding layout publication. **Chapter 1** focuses on the use of 1,3-dipolar enantioselective cycloaddition of azomethine ylides and electrophilic alkenes catalyzed by chiral catalysts. **Chapter 2** covers the study of the synthesis of polysubstituted cyclohex-2-enilamines by multicomponent reaction (AAD). Finally, in **Chapter 3**, we study the synthesis of polysubstituted cyclohex-2-enyl-amine derivatives through multicomponent phosphoramidate-aldehyde-dienophile (PAD). **Section 3** consists of the writing of the general final conclusions.

The results described herein have been published in the following international peer reviewed journals:

"*Dual chiral silver catalyst in the synthetic approach to the core of hepatitis C virus inhibitor GSK 625433 using enantioselective 1,3-dipolar cycloaddition of azomethine ylides and electrophilic alkenes*".
Chabour, I.; Castelló, L. M.; Mancebo-Aracil, J.; Martín-Rodríguez, M.; Retamosa, M. d. G.; Nájera, C.; Sansano, J. M. *Tetrahedron Asymmetry* **2017***, 28, 1423–1429.*

"*Diastereoselective multicomponent Amine-Aldehyde-Dienophile (AAD) process for the synthesis of polysubstituted cyclohex-2-enylamines*".
Selva, V.; Chabour, I.; Nájera, C.; Sansano, J. M. *Tetrahedron* **2019**, *75*, 1315-1321.

"*Diastereoselective multicomponent phosphoramidate-aldehyde-dienophile (PAD) process for the synthesis of polysubstituted cyclohex-2-enyl-amine derivatives*".
Chabour, I.; Nájera, C.; & Sansano, J. M. *Tetrahedron* **2020**, *76*, 130801.

This research work have been supported by:

The Spanish Ministerio de Ciencia e Innovación (MICINN) (projects CTQ2010-20387, and Consolider Ingenio 2010, CSD2007-00006), the Spanish Ministerio de Economía y Competitividad (MINECO) (projects CTQ2013-43446-P, CTQ2014-51912-REDC, CTQ2016-76782-P, CTQ2016-81797-REDC, CTQ2016-81893REDT, and CTQ2016-76155-R)), the Spanish Ministerio de Economía, Industria y Competitividad, Agencia Estatal de Investigación (AEI) and Fondo

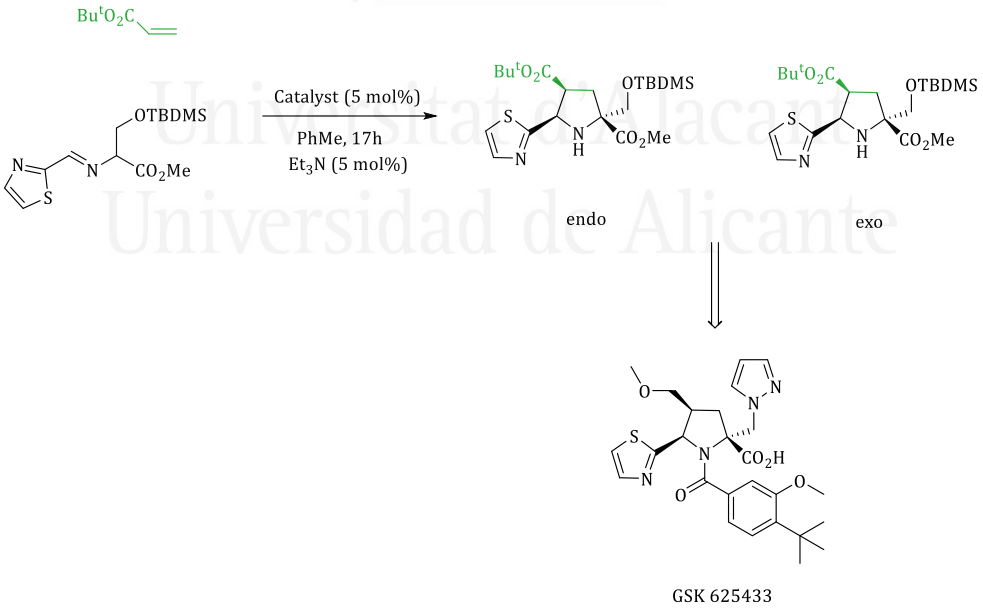
Europeo de Desarrollo Regional (FEDER, EU) (projects CTQ2016-76782-P and CTQ2016-81797-REDC), the Generalitat Valenciana (PROMETEO 2009/039 and PROMETEOII/2014/017), and the University of Alicante.

SUMMARY

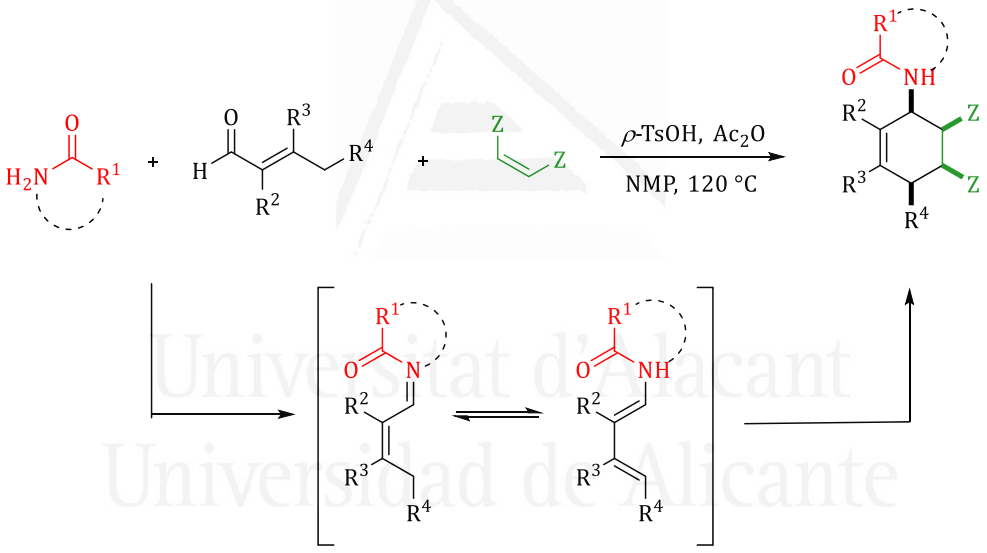
SUMMARY

In this thesis, different cycloaddition reactions, such as the enantioselective 1,3-dipolar-cycloaddition, which takes place between *in situ* generated stabilized azomethine ylides, and electrophilic alkenes, and the diastereoselective multicomponent reactions Amine-Aldehyde-Dienophile (AAD) or Phosphoramidate-Aldehyde-Dienophile (PAD) are described.

In **Chapter 1**, an asymmetric 1,3-dipolar cycloaddition reaction involving an imino ester with *tert*-butyl acrylate was carried out using a silver(I) complex with double chirality, formed from a chiral phosphoramidite and chiral silver binolphosphate(I). The goal of this reaction is to synthesize key enantiomerically enriched structures to access the GSK-third generation of HCV inhibitors.

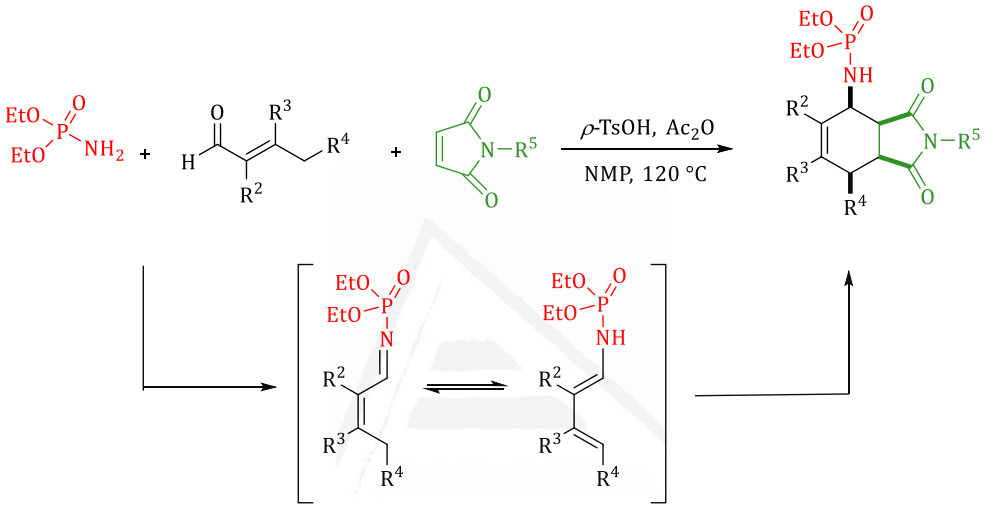


In **Chapter 2**, the synthesis of polysubstituted cyclohex-2-enylamines using the multicomponent Amine-Aldehyde-Dienophile reaction involving benzyl or 4-methoxybenzylamine, is described. The study the diastereoselective version, employing commercially available chiral benzylic amines, or even a maleimide with the chiral information at the nitrogen atom, are also reported.



In **Chapter 3**, the synthesis of polysubstituted cyclohex-2-enylamines derivatives using the multicomponent Phosphoramidate-Aldehyde-Dienophile

(PAD), is described. Several series of *N*-substituted phosphoramidates reacted with α,β-unsaturated aldehydes, bearing hydrogen atoms at the γ-position, in good yields.



PREFACIO

PREFACIO

En esta tesis, se describen los principales proyectos en los que participé durante mi doctorado. La investigación se refiere al estudio de reacciones pericíclicas multicomponentes, es decir, cicloadiciones 1,3-dipolares, usando iluros de azometino con alquenos electrofílicos y, por otro lado, las reacciones amina / fosforamidato-aldehído-dienófilo AAD y PAD, respectivamente . Este trabajo se llevó a cabo bajo la supervisión de los profesores Carmen Nájera Domingo y José Miguel Sansano Gil en el Departamento de Química Orgánica y en el Instituto de Síntesis Orgánica de la Universidad de Alicante (España).

La tesis se divide en tres Secciones, dividiéndose la Sección 2 en tres capítulos. En la **Sección 1** se presentará en castellano los objetivos, hipótesis, trabajos presentados y justificación de la unidad temática. Incorporará un resumen global de los resultados obtenidos, de la discusión de estos resultados y de las conclusiones finales. La **Sección 2** consta de tres capítulos, cada uno de ellos integrados por una breve introducción y la publicación maquetada correspondiente. **El capítulo 1** se centra en el uso de la cicloadición enantioselectiva 1,3-dipolar de los iluros de azometino y los alquenos electrofílicos promovidas por catalizadores quirales. **El capítulo 2** cubre el estudio de la síntesis de ciclohex-2-enilaminas polisustituidas por reacción multicomponente (AAD). Finalmente, en **el Capítulo 3,** se estudia la síntesis de derivados de ciclohex-2-enil-amina polisustituidos a través de fosforamidato-aldehído-dienófilo (PAD) multicomponente. La **Sección 3** está constituida por la redacción de las conclusiones finales generales.

Los resultados descritos aquí se han publicado en las siguientes revistas internacionales revisadas por pares:

"*Dual chiral silver catalyst in the synthetic approach to the core of hepatitis C virus inhibitor GSK 625433 using enantioselective 1,3-dipolar cycloaddition of azomethine ylides and electrophilic alkenes*".
Chabour, I.; Castelló, L. M.; Mancebo-Aracil, J.; Martín-Rodríguez, M.; Retamosa, M. d. G.; Nájera, C.; Sansano, J. M. *Tetrahedron Asymmetry* **2017**, *28,* 1423–1429.

"*Diastereoselective multicomponent Amine-Aldehyde-Dienophile (AAD) process for the synthesis of polysubstituted cyclohex-2-enylamines*".
Selva, V.; Chabour, I.; Nájera, C.; Sansano, J. M. *Tetrahedron* **2019**, *75*, 1315-1321.

"*Diastereoselective multicomponent phosphoramidate-aldehyde-dienophile (PAD) process for the synthesis of polysubstituted cyclohex-2-enyl-amine derivatives*".
Chabour, I.; Nájera, C.; Sansano, J. M. *Tetrahedron* **2020**, *76*, 130801.

Este trabajo de investigación ha sido subvencionado por:

El Ministerio de Ciencia e Innovación (MICINN) español (proyectos CTQ2010-20387, y Consolider Ingenio 2010, CSD2007-00006), el Ministerio de Economía y Competitividad (MINECO) español (proyectos CTQ2013-43446-P, CTQ2014-

51912-REDC, CTQ2016-76782-P, CTQ2016-81797-REDC, CTQ2016-81893REDT y CTQ2016-76155-R)), el Ministerio de Economía, Industria y Competitividad, Agencia Estatal de Investigación (AEI) y Fondo Europeo de Desarrollo Regional (FEDER) , UE) (proyectos CTQ2016-76782-P y CTQ2016-81797-REDC), la Generalitat Valenciana (PROMETEO 2009/039 y PROMETEOII / 2014/017), y la Universidad de Alicante.

SECCIÓN 1. SÍNTESIS

HIPÓTESIS

El desarrollo de productos antivirales que sean capaces de inhibir la reproducción en sistemas vivos es un reto constante al que se enfrentan muchas áreas científicas. Más concretamente, existe una serie de estructuras patentadas por la compañía GlaxoSmithKline (GSK) subdivididas en tres generaciones. La base estructural de esta familia de productos biológicamente activos es un anillo derivado de prolinatos polisustituidos al cual se puede acceder mediante reacciones de cicloadición 1,3-dipolares entre iluros de azometino, generados a partir de iminoésteres, y alquenos electrofílicos. Hasta hoy solo se han descrito las síntesis tanto racémica como asimétrica de las generaciones 1 y 2. Mientras que no existen datos en la bibliografía de cómo sintetizar la molécula más activa de la tercera generación de estos inhibidores conocida como GSK 625433. Las reacciones enantioselectivas para obtener los prolinatos polisustituidos intermedios precisan ligandos quirales más un catión metálico, o bien un organocatalizador quiral, y la combinación de un ácido de Lewis quiral junto a un organocatalizador (actuando ambos cooperativamente). Se propondría utilizar una doble información de quiralidad en el ácido de Lewis como alternativa para poder generar estos intermedios enantioméricamente enriquecidos.

Por otro lado, se conoce un proceso multicomponente basado en la combinación de Amida-Aldehído-Dienófilo en el que se generan 1-amidobutadienos y reaccionan, inmediatamente, con una olefina deficiente en electrones a través de una reacción de Diels Alder. En general, las estructuras generadas son intermedios muy valiosos para sintetizar otras moléculas más complejas, e incluso productos naturales. Sin embargo, la reacción en la que se sustituye una amida por una amina no se ha publicado hasta la fecha, lo cual demostraría un gran avance sintético ya que no se requeriría de la etapa de hidrólisis para generar la amina, tal y como sucede cuando se emplea la amida

como componente. En esta misma línea, tampoco se ha introducido como primer componente fosforamidato de dietilo dando así origen al proceso multicomponente Fosforamidato-Aldehído-Dienófilo (PAD). El resultado de esta combinación no solamente sería útil para publicar un nuevo método para sintetizar forforamidatos *N*-sustituidos sino para obtener productos potencialmente anticancerígenos frente a numerosas células tumorales.

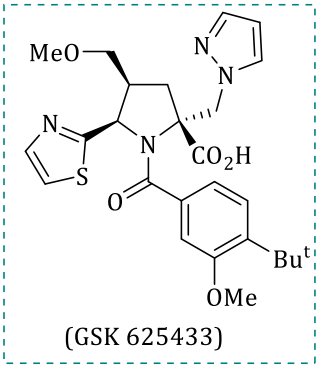
OBJETIVOS

Con estas hipótesis fundamentadas en un completo análisis de la bibliografía publicada en estas áreas científicas, se creyó muy interesante abordar los siguientes objetivos:

- Estudiar comparativamente el empleo de ácidos de Lewis con doble información quiral frete al uso de complejos quirales convencionales y procesos enantioslectivos cooperativos en la reacción 1,3-dipolar entre iminoésteres y alquenos electrofílicos.

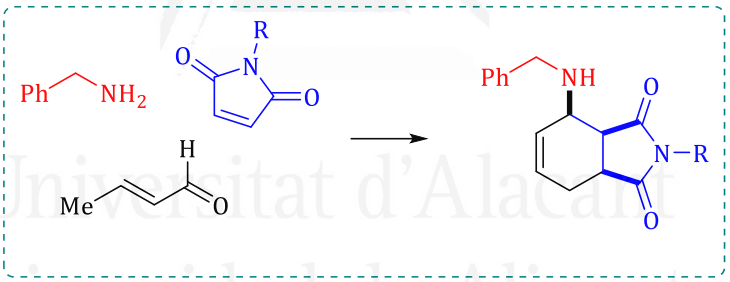
- Estudio del campo de aplicación de las condiciones optimizadas para la mejor reacción enantioselectiva utilizado la doble quiralidad más apropiada. Para este propósito, varios ligandos quirales y aniones quirales se unirán al metal de plata o cobre.

- Aplicación de este proceso enantioselectivo en la síntesis asimétrica del fármaco antiviral GSK de tercera generación (GSK 625433).



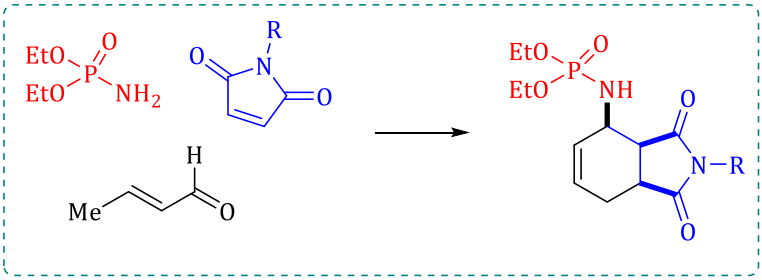
(GSK 625433)

- Optimizar el proceso multicomponente que involucra una Amina con un Aldehído y un Dienófilo (AAD). Se ensayarán aminas monosustituidas capaces de generar el grupo amino tras hidrólisis (*N*-bencilamina y *p*-metoxibencilamina)



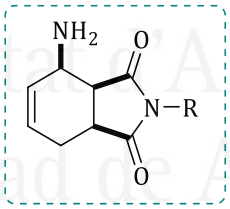
- Estudiar el transcurso estereoquímico de la reacción y buscar otro tipo de aplicaciones de estas moléculas.

- Llevar a cabo una síntesis de fosforamidatos polisustituidos utilizando fosforamidato de dietilo mediante una reacción multicomponente (PAD).



- Estudiar el transcurso estereoquímico de la reacción.

- Tanto la hidrólisis de las aminas (descritas anteriormente) y estos fosforamidatos darían lugar a aminas primarias. Estos compuestos presentan un elevado potencial como base para la elaboración de estructuras más complejas.



TRABAJOS PRESENTADOS

1. "Dual chiral silver catalyst in the synthetic approach to the core of hepatitis C virus inhibitor GSK 625433 using enantioselective 1,3-dipolar cycloaddition of azomethine ylides and electrophilic alkenes".

Chabour, I.; Castelló, L. M.; Mancebo-Aracil, J.; Martín-Rodríguez, M.; Retamosa, M. d. G.; Nájera, C.; Sansano, J. M. *Tetrahedron Asymmetry* **2017**, *28*, 1423–1429.

2. "Diastereoselective multicomponent Amine-Aldehyde-Dienophile (AAD) process for the synthesis of polysubstituted cyclohex-2-enylamines".

Selva, V.; Chabour, I.; Nájera, C.; Sansano, J. M. *Tetrahedron* **2019**, *75*, 1315-1321.

3. "Diastereoselective multicomponent phosphoramidate-aldehyde-dienophile (PAD) process for the synthesis of polysubstituted cyclohex-2-enyl-amine derivatives".

Chabour, I.; Nájera, C.; & Sansano, J. M. *Tetrahedron* **2020,** *76*, 130801.

JUSTIFICACIÓN DE LA UNIDAD TEMÁTICA

La unidad temática a la que pertenecen todos los trabajos descritos en esta memoria por compendio de publicaciones se encuentra dentro del área de Química (código Unesco 23) (subcategoría de Química Orgánica, código Unesco 2306). No existe ninguna otra área científica implicada.

Dentro de la Química Orgánica (código Unesco 23) se pueden incluir los códigos: a) 230694 de Síntesis asimétrica; b) 230610 referente a Compuestos Heterocíclicos, c) 239001 perteneciente a Diseño, Síntesis y estudio nuevos fármacos y; d) 230616 correspondiente a Esteroquímica y Análisis Conformacional.

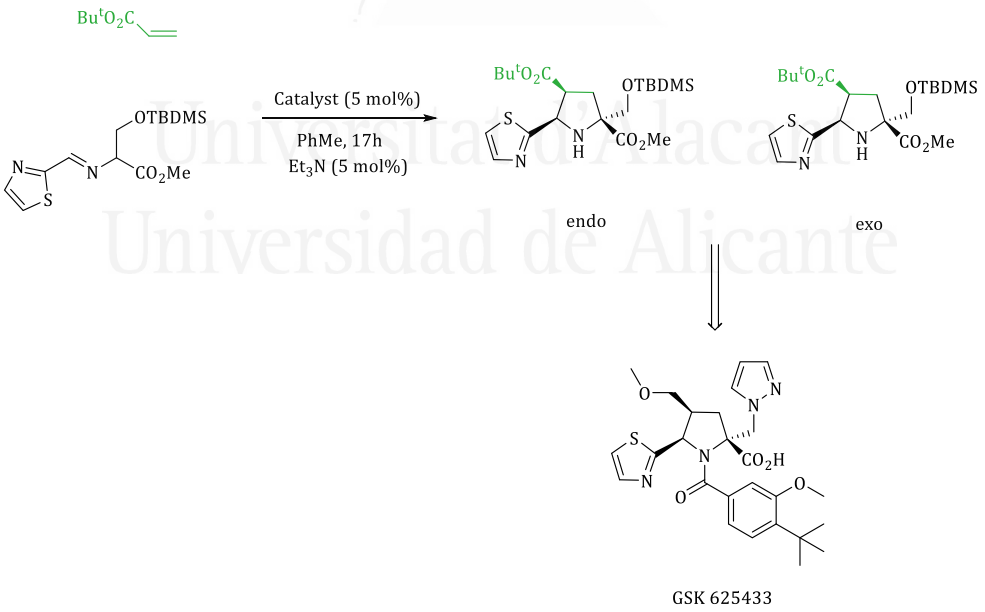
Los códigos b) y d) cubren la temática de los tres Capítulos de la memoria, mientras que el código a) y el c) se aplican al contenido del Capítulo 1.

Desde el punto de vista conceptual los Capítulos 2 y 3 guardan una mayor similitud siendo la única diferencia entre ellos la permuta de uno de sus componentes. Por otro lado, la síntesis enantioselectiva descrita en el Capítulo 1 versa sobre un planteamiento distinto a la hora de operar. En cualquier caso, todos los capítulos tienen en común que se trabaja con reacciones pericíclicas [3+2] (1,3-dipolares) y [4+2] reacciones de Diels-Alder.

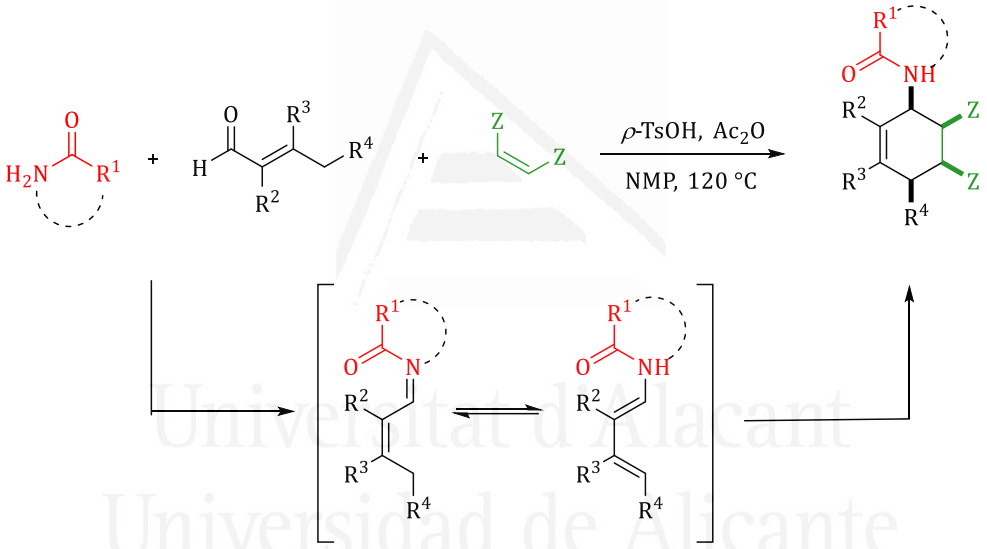
RESUMEN DE LOS TRABAJOS PRESENTADOS

En esta tesis, se describen diferentes reacciones de cicloadición, como la enantioselectiva 1,3-dipolar-cicloadición, que tiene lugar entre los iluros de azometino estabilizados, generados *in situ*, y los alquenos electrofílicos, y las reacciones diastereoselectivas multicomponentes Amina-Aldehído-Dienófilo (AAD) o Fosforamidato-Aldehído-Dienófilo (PAD).

En el **Capítulo 1**, se llevó a cabo una reacción de cicloadición 1,3-dipolar asimétrica que involucra un iminoéster con acrilato de *terc*-butilo usando un complejo de plata (I) con doble quiralidad, formado a partir de un fosforamidito quiral y un binolfosfato de plata quiral (I). El objetivo de esta reacción es sintetizar estructuras clave enriquecidas enantioméricamente para acceder a la tercera generación de inhibidores (familia GSK) del VHC.

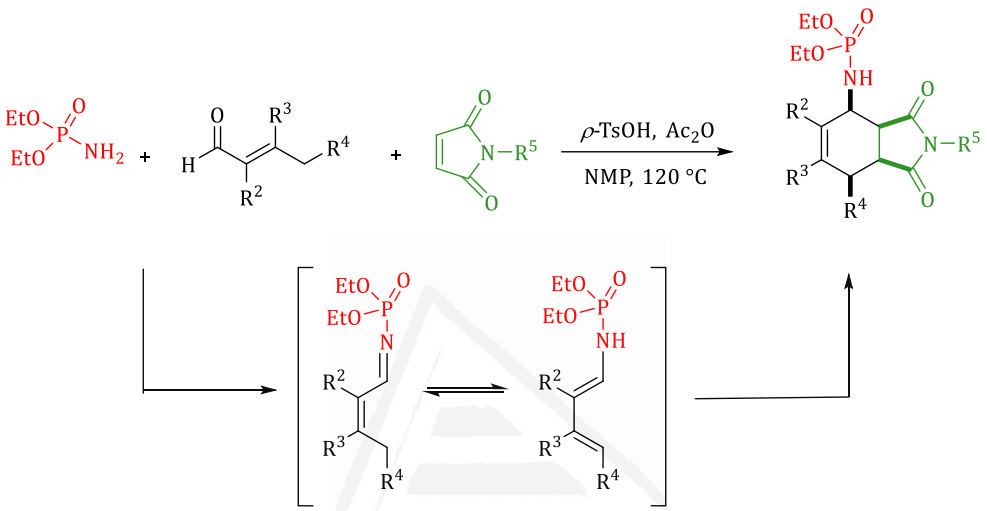


En el **Capítulo 2**, se describe la síntesis de ciclohex-2-enilaminas polisustituidas usando la reacción multicomponente de amina-aldehído-dienófilo que involucra bencil- o 4-metoxibencilamina. También se detalla el estudio de la versión diastereoselectiva, que emplea aminas bencílicas quirales disponibles comercialmente, o incluso una maleimida con la información quiral en el átomo de nitrógeno.



En el **Capítulo 3**, se describe la síntesis de derivados de ciclohex-2-enilaminas polisustituidos utilizando el Fosforamidato-Aldehído-Dienófilo (PAD) multicomponente. Varias series de fosforamidatos *N*-sustituidos

reaccionaron con aldehídos α, β-insaturados, con átomos de hidrógeno en la posición γ, con buenos rendimientos.



RESUMEN DE DISCUSIÓN Y RESULTADOS

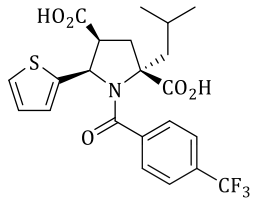
Capítulo 1

En este trabajo, se estudia la síntesis asimétrica de los intermedios usados para preparar los inhibidores antivirales de primera generación **1**[1,2] y de segunda generación **2**[3] de manera diastereo-[1] y enantioselectivos.[4,5] Para ello, se emplean reacciones 1,3-dipolares entre el correspondiente iminoleucinato de metilo y un acrilato derivado de lactato,[1] o con acrilato de *terc*-butilo empleando un complejo catalítico de fosforamidito-$AgClO_4$ quiral[1] o un complejo dimérico de Binap-oro(I),[3] respectivamente. En ambas rutas, los rendimientos globales obtenidos fueron de moderados a buenos y las enantioselectividades fueron muy altas, especialmente en el caso del inhibidor de segunda generación (99% *ee*). A continuación, se realizó una aproximación

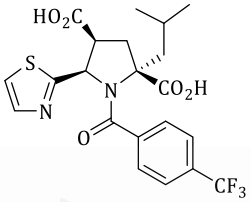
---

[1] Nájera, C.; Retamosa, M. G.; Sansano, J. *Tetrahedron: Asymmetry* **2006**, *17*, 1985–1989.
[2] Nájera, C.; Retamosa, M. G.; Martín-Rodríguez, M.; Sansano, J. M.; de Cózar, A.; Cossío, F. P. *Eur. J. Org. Chem*. **2009**, 5622–5634.
[3] Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; de Cózar, A.; Cossío, F. P. *Beilstein J. Org. Chem*. **2011**, *7*, 988–996.
[4] Döndas, H. A.; Retamosa, M. G.; Sansano, J. M. *Synthesis* **2017**, *49*, 2819–2851.
[5] a) Maroto, E. E.; Izquierdo, M.; Reboredo, S.; Marco-Martínez, J.; Filippone, S.; Martín, N. *Acc. Chem. Res*. **2014**, *47*, 2660–2670; b) Narayan, R.; Potowski, M.; Jia, Z.-J.; Antonchick, A. P.; Waldmann, H. *Acc. Chem. Res*. **2014**, *47*, 1296–1310; c) Nájera, C.; Sansano, J. M. *J. Organomet. Chem*. **2014**, *771*, 78–92; d) Randjelovic, J.; Simic, M.; Tasic, G.; Husinec, S.; Savic, V. *Curr. Org. Chem*. **2014**, *18*, 1073–1096; e) Li, J.; Zhao, H.; Zhang, Y. *Synlett* **2015**, *26*, 2745–2750; f) Yoo, E. J. *Synlett* **2015**, *26*, 2189–2193; g) Ryan, J. H. *Arkivoc* **2015**, *i*, 160–183; h) Hashimoto, T.; Maruoka, K. *Chem. Rev*. **2015**, *115*, 5366–5412; i) Pavlovska, T. L., Gr.; Redkin, R.; Lipson, V. V.; Atamanuk, D. V. *Synth. Biol. Activ. Mol. Divers* **2016**, *20*, 299–344; j) Meyer, A. G.; Ryan, J. H. *Molecules* **2016,** *21*, 935–989; k) Singh, M. S.; Chowdhury, S.; Koley, S. *Tetrahedron* **2016**, *72*, 1603–1644; l) Nájera, C.; Sansano, J. M. *Chem. Rec*. **2016,** *16*, 2430–2448; m) Bdiri, B.; Zhao, B.-J.; Zhou, Z.-M. *Tetrahedron*: *Asymmetry* **2017**, *28*, 876–899.

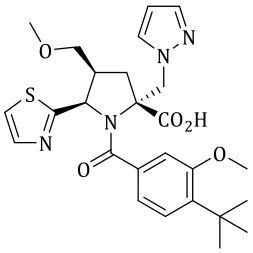
enantioselectiva al precursor del anillo heterocíclico central del inhibidor de polimerasa inversa del virus responsable de la hepatitis C (GSK 625433 **3**)[6] y también un breve estudio del alcance y la versatilidad del catalizador desarrollado.



1
primera generación
inhibidor de la polimerasa GSK



2
segunda generación
inhibidor de la polimerasa GSK

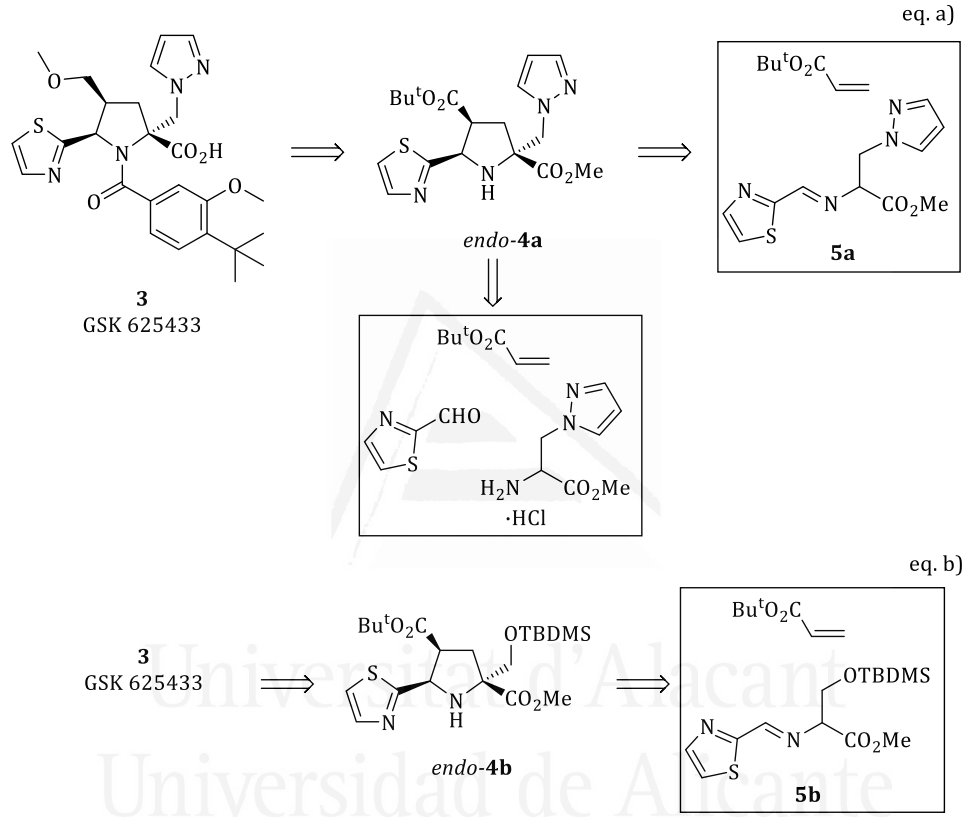


3
GSK 625433

De acuerdo con el análisis retrosintético clásico de esta familia de compuestos, se preveía que los heterociclos enriquecidos enantioméricamente de tipo *endo*-**4** fueron compuestos clave para acceder al agente antiviral **3**. Inicialmente, diseñamos dos enfoques alternativos en los que el anillo de pirazol estaba unido en el iminoéster de partida (Esquema 1, ec. a) y una segunda retrosíntesis en la que el pirazol se introdujo una vez que se produjo la cicloadición 1,3-dipolar (Esquema 1, ec. b). El iminoéster de partida **5a** podría generarse en condiciones suaves a partir de clorhidrato de éster metílico de **3**-(1-pirazolil)-L-alanina disponible comercialmente, pero se detectaron cantidades significativas del producto resultante de la eliminación en β del pirazol, mediante espectroscopía de ^{1}H NMR. La cicloadición 1,3-dipolar multicomponente no asimétrica se probó luego empleando acrilato de *terc*-

[6] Www.CEN-ONLINE.ORG, 28/NOV/2011, page 8.

butilo, 2-tiazolcarboxaldehído y el iminoéster, proporcionando el indeseable producto de β-eliminación.[7] Este problema se resolvió empleando la ruta que comienza con el derivado de serina O-TBDMS protegida (Esquema 1, ec. b).



Esquema 1. Análisis retrosintético.

El iminoéster estable **5b** fue mucho más apropiado para ejecutar la cicloadición no asimétrica y, en consecuencia, adecuado para estudiar la cicloadición enantioselectiva 1,3-dipolar. Este iminoéster **5b** se obtuvo con un

[7] La introducción de la unidad de pirazol en el éster imino proporcionó un compuesto lábil en medio básico sufrió una β-eliminación.

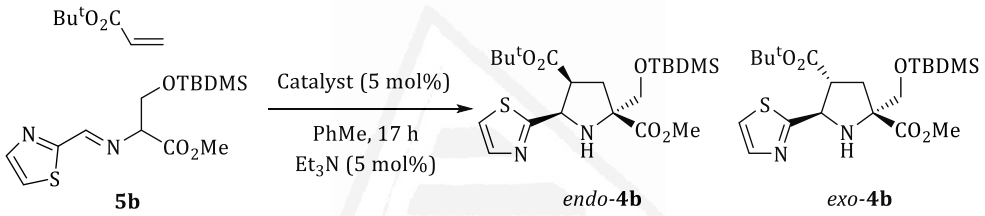
rendimiento casi cuantitativo por reacción de 2-tiazolcarboxaldehído con el compuesto conocido del éster metílico de serina O-TBDMS protegido[8] en DCM a temperatura ambiente durante 19 h; luego se empleó en las cicloadiciones sin ninguna otra purificación (ver parte experimental).

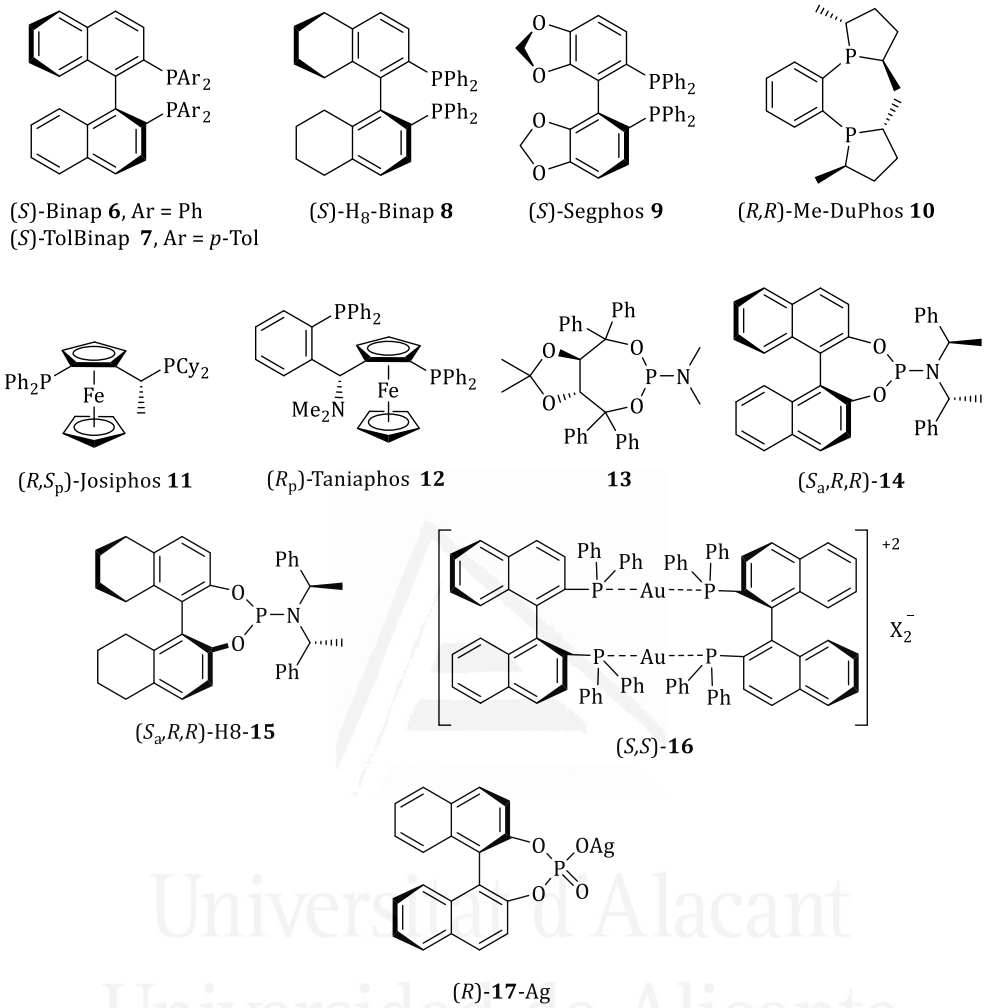
Se probaron muchos ligandos quirales y sales de plata a una carga del 5% en moles (Esquema 2) pero siempre usando tolueno como solvente. Las cicloadiciones realizadas a temperatura ambiente con Binap **6** produjeron conversiones muy buenas pero con enantioselectividades moderadas.[9] La mejor sal de plata fue $AgSbF_6$, que dio, a temperatura ambiente, el compuesto deseado *endo*-**4b** como una mezcla 85:15 de diastereoisómeros y 85:15 de relación enantiomérica. La disminución de la temperatura no fue beneficiosa para esta transformación.[10] Los ligandos quirales **7** y **8** no mejoraron los resultados logrados por Binap **6** y el compuesto casi racémico *endo*-**4b** se aisló cuando AgOBz o $AgSbF_6$ se combinaron con ligandos quirales **9**-**13**.

El complejo formado por el fosforamidito (S_a,*R*,*R*)-**14** y AgTFA y el análogo formado con $AgSbF_6$ proporcionó conversiones, relaciones diastereoméricas y enantioméricas idénticas. Luego se estudió el análisis de la temperatura

[8] Krenk, O.; Kratochvil, J.; Spulak, M.; Buchta, V.; Kunes, J.; Novakova, L.; Ghavre, M.; Pour, M.; *Eur, J. Org. Chem*. **2015,** 5414–5423.
[9] a) Nájera, C.; Retamosa, M. G.; Sansano, J. M. *Org. Lett.* **2007***, 9*, 4025–4028; b) Nájera, C.; Retamosa, M. G.; Sansano, J. M.; de Cózar, A.; Cossío, F. *Tetrahedron: Asymmetry,* **2008**, *19*, 2913–2923; Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; Costa, P. R. R.; Crizanto de Lima, E.; Dias, A. G. *Synlett* **2010**, 962–966; Mancebo-Aracil, J.; Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; Costa, P. R. R.; Crizanto de Lima, E.; Dias, A. G. *Tetrahedron: Asymmetry* **2012**, *23*, 1596–1606.
[10] Se identificaron mezclas de varios agregados de sales de plata binap en diferentes proporciones dependiendo de la temperatura Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360–5361.

obteniendo un incremento de la relación diastereomérica (hasta 99:1, a -80 ° C) pero con una enantioselectividad moderada (80:20 a la misma temperatura). El complejo análogo H8-quiral **15**·$AgSbF_6$ no era adecuado para inducir una muy alta enantiodiscriminación. Debido a que la especie de oro dimérica, (*S, S*)-**16**·TFA_2 es efectiva en la síntesis de los agentes GSK de segunda generación,[3] se usó a 0 °C en la cicloadición de acrilato de *terc*-butilo y el iminoéster **5b**. La reacción fue casi completa después de 48 h para dar lugar al cicloaducto *endo*-**4b** como el diastereoisómero principal en 85:15 *dr* con moderada enantioselectividad (78:26 *re*).





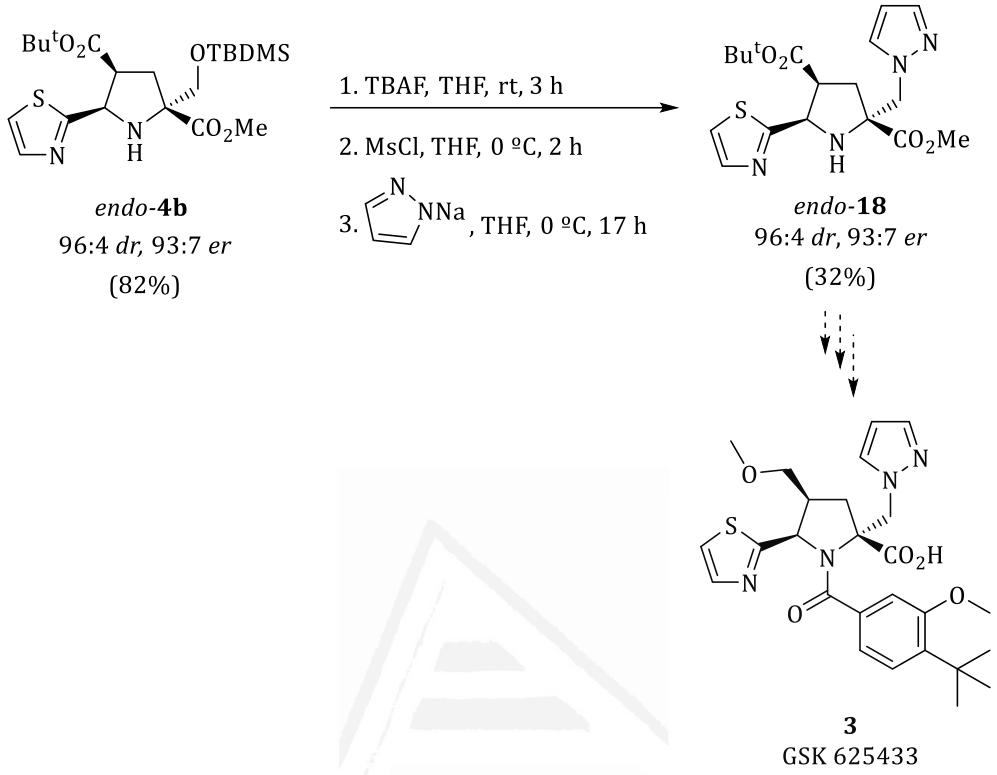
Esquema 2. Ligandos quirales empleados en el estudio de optimización.

El complejo catalítico (*S, S*)-**16**·$(OBz)_2$ no fue efectivo y proporcionó relaciones diastereoméricas y enantioméricas más bajas. Sin embargo, el catalizador quiral dual **14** Ag-(*R*)-**17**, formado por reacción de carbonato de plata y el ácido fosfórico quiral derivado del (*R*)-binol **17** en tolueno, durante 1 h, seguido de la adición del fosforamidito quiral **14**, produjo el *endo*-cicloaducto **4b** con excelente conversión y alta relación diastereomérica y enantiomérica.

Bajar la temperatura a -20 °C no condujo a ninguna mejora significativa de la relación enantiomérica. El enantiómero correspondiente *ent-endo*-**4b** se obtuvo fácilmente empleando el sistema catalítico quiral enantiomérico. La configuración de estas dos formas enantioméricas del complejo de plata quiral dual dio como resultado una combinación cooperativa para esta transformación porque las otras posibles combinaciones de fuentes de quiralidad proporcionaron relaciones enantioméricas más bajas, si bien con excelentes conversiones. A partir de las tres últimas entradas, se puede ver que la configuración absoluta inducida en los cicloaductos es fuertemente dependiente de la quiralidad axial del fosforamidito quiral.

Con el compuesto *endo*-**4b** (82% de rendimiento, 96: 4 dr y 92: 7er), los siguientes tres pasos se llevaron a cabo de manera secuencial (Esquema 3). Primero, se eliminó TBDMS usando tres equiv. de fluoruro de tetra-*n*-butilamonio (TBAF, solución 1 M en THF) a temperatura ambiente durante 3 h. La mesilación del alcohol en ausencia de trimetilamina evitó cualquier expansión indeseable del anillo y después de 2 h a 0 °C, se añadió pirazoluro de sodio[11] a 0 °C.

[11] Leclerc, M. C.; Gabidullin, B. M.; Da Gama, J. G.; Daifuku, S. L.; Iannuzzi, T. E.; Neidig, M. L.; Baker, R. T. *Organometallics,* **2017**, *36*, 849–857.



Esquema 3. Síntesis del enantiómero clave *endo*-**18** para acceder al inhibidor de la polimerasa GSK 625433.

El cicloaducto *endo*-**18** se aisló después de cromatografía flash con un 32% de rendimiento global. El acceso final a la molécula **3** se puede lograr

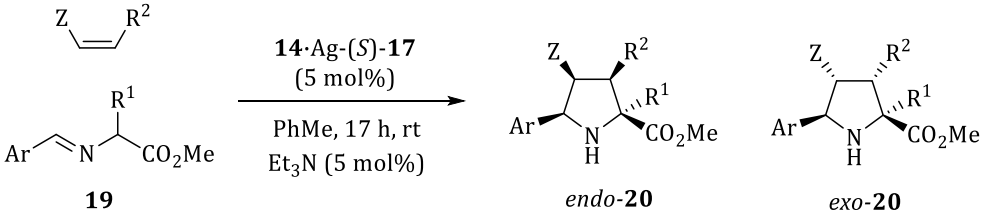
siguiendo los procedimientos conocidos descritos para esta familia de inhibidores del VHC.[12,13,14]

La determinación de la configuración absoluta y la versatilidad sintética del complejo doble quiral activado **14**·Ag-(R)-**17** y **14**·$AgClO_4$ se estudiaron simultáneamente (Esquema 4). Inicialmente, se permitió que la *N*-metilmaleimida reaccionara con el iminoéster **19** (Ar = Ph, R^1 = H) en las condiciones de reacción optimizadas para producir el producto **20a**. La configuración absoluta se asignó por la comparación de su tiempo de retención (HPLC usando una columna de fase estacionaria quiral) con el tiempo de retención de la muestra idéntica aislada de la reacción catalizada por el complejo **14**·$AgClO_4$.[1] Esta configuración absoluta fue confirmada analizando tanto los datos de HPLC como los datos de poder rotatorio específico de todos los compuestos aislados. El complejo quiral del catalizador quiral dual **14**·Ag-(R)-**17** y **14**·$AgClO_4$ también proporcionó resultados similares de **20b** y **20c**. Sin embargo, la presencia de un sustituyente en la posición α del iminoéster **19** causó dificultades estéricas a la voluminosa entidad quiral de **14**·Ag- (R)-**17**.

[12] a) Burton, G.; Ku, T. W.; Carr, T. J.; Kiesow, T.; Sarisky, R. T.; Lin-Goerke, J.; Baker, A.; Earnshaw, D. L.; Hofmann, G. A.; Keenan, R. M.; Dhanak, D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1553–1556.; b) Burton, G.; Ku, T. W.; Carr, T. J.; Kiesow, T.; Sarisky, R. T.; Lin-Goerke, J.; Hofmann, G. A.; Slater, M. J.; Haigh, D.; Dhanak, D.; Johnson, V. K.; Parry, N. R.; Thomes, P. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 1930–1933.

[13] a) Slater, M. J.; Amphlett, E. M.; Andrews, D. M.; Bravi, G.; Burton, G.; Cheasty, A. G.; Corfield, J. A.; Ellis, M. R.; Fenwick, R. H.; Fernandes, S.; Guidetti, R.; Haigh, D.; Hartley, C. D.; Howes, P. D.; Jackson, D. L.; Jarvest, R. L.; Lovegrove, V. L. H.; Medhurst, K. J.; Parry, N. R.; Price, H.; Shah, P.; Singh, O. M. P.; Stocker, R.; Thommes, P.; Wilkinson, C.; Wonacott, A. J. *Med. Chem*. **2007**, *50*, 897–900.; b) Agbodjan, A. A.; Cooley, B. E.; Copley, R. C. B.; Corfield, J. A.; Flanagan, R. C.; Glover, B. N.; Guidetti, R.; Haigh, D.; Howes, P. D.; Jackson, M. M.; Matsuoka, R. T.; Medhurst, K. J.; Millar, A.; Sharp, M. J.; Slater, M. J.; Toczko, J. F.; Xie, S. *J. Org. Chem.* **2008**, *73*, 3094–3102.

[14] Flanagan, R. C.; Xie, S.; Millar, A. *Org. Process Res. Dev*. **2008**, *12*, 1307–1312.



Esquema 4. Versatilidad de la reacción.

Así, cuando los iminoésteres **19** derivados de alanina, leucina y fenilalanina se emplearon con diferentes dipolarófilos, el complejo catalítico **14**·$AgClO_4$ proporcionó prolinatos **20** con proporciones diastereoméricas y enantioméricas más altas, aunque los rendimientos químicos fueron similares a los obtenidos al usar ambos complejos catalíticos por separado. Es de destacar que el compuesto **20d** es un nuevo inhibidor potencial de la integrasa del VIH-1,[15] mientras que la molécula **20e** es el intermedio clave para la síntesis del inhibidor del VHC **1**.[12,1]

[15] Gupta, P.; Garg, P.; Roy, N. *Med. Chem. Res*. **2013,** *22*, 3444–3451.

Sección Experimental

Métodos Generales

Los puntos de fusión se determinaron con un Reichert Thermowar Aparatos de placa caliente y no están corregidos. Solo se enumeran los picos estructuralmente más importantes de los espectros IR (registrados con un FT-IR 4100LE (JASCO) (PIKE MIRacle ATR). Los espectros ^{1}H NMR (300 MHz) y ^{13}C NMR (75 MHz) se obtuvieron con un Bruker AC- 300 utilizando $CDCl_3$ como disolvente y TMS como patrón interno, a menos que se indique lo contrario. Las rotaciones ópticas se midieron con un polarímetro Perkin-Elmer 341. Los análisis de HPLC se realizaron con una serie JASCO-2000 equipada con una columna de fase estacionaria quiral (detallada para cada compuesto en el texto principal) mediante el uso de mezclas de n-hexano / alcohol isopropílico como la fase móvil a 25 C. Se obtuvieron espectros de masas de impacto electrónico (IE) de baja resolución con un Shimadzu QP-5000 por inyección o DIP, y alto Los espectros de masas de resolución se obtuvieron con una plataforma Finnigan VG o un Finnigan MAT 95S. Se realizó una TLC analítica en placas de gel de sílice Schleicher & Schuell F1400 / LS 254 y las manchas se visualizaron bajo luz UV (k = 254 nm). 60 (0.040–0.063 mm) se utilizó para cromatografía flash.

*Síntesis de iminoéster **5b***

En un matraz de 10 ml se disolvieron el éster metílico de serina O-TBDMS protegido[16] (357 mg, 1,5 mmol) y 2-tiazolcarboxaldehído (134 µL, 1,5 mmol) en diclorometano anhidro (10 ml) después de lo cual se añadió sulfato de magnesio (200 mg). La reacción se agitó. a temperatura ambiente durante la noche y la

[16] Krenk, O.; Kratochvil, J.; Spulak, M.; Buchta, V.; Kunes, J.; Novakova, L.; Ghavre, M.; Pour, M. *Eur, J. Org. Chem*. **2015**, 5414–5423.

fase orgánica se lavó con salmuera, secada y evaporada para proporcionar cuantitativamente el producto crudo (492 mg, 1.5 mmol) como un aceite amarillo pálido

Procedimiento general para la reacción 1,3-dipolar utilizando catalizador dual ***14****·Ag-(R)-****17****. Síntesis de compuestos endo-****4b*** *y* ***20****.*

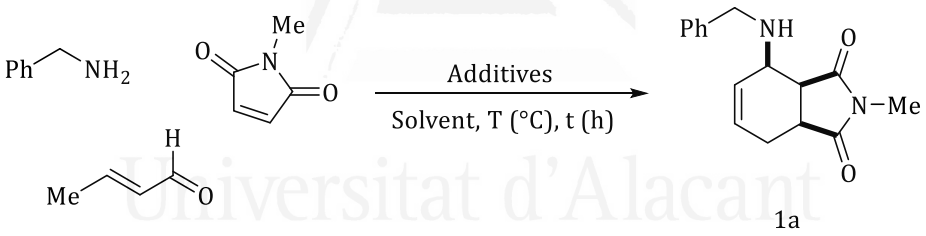
En un vial de 10 ml cubierto con papel de aluminio, se añadieron Ag_2CO_3 (2,8 mg, 0,01 mmol), ácido (*R*)-Binol-fosfórico (7 mg, 0,02 mmol) y tolueno (3 ml) y la mezcla resultante se agitó a temperatura ambiente durante 1 h. Después se añadió el fosforamidito (*Sa, R, R*)-**14** (10,8 mg, 0,02 mmol) y la reacción se agitó durante 40 min adicionales. Luego, se añadieron el iminoéster (0,4 mmol), el dipolarófilo (0,4 mmol) y la trietilamina (3 µL, 0,02 mmol) en este orden y la reacción se agitó a temperatura ambiente. La mezcla se enfrió a -10 °C y el aminoéster **2c** (193 mg, 1 mmol), la maleimida **3** correspondiente (1 mmol) y el glioxilato de etilo **1** (solución de aproximadamente 50% en tolueno, 102 µL, 1,2 mmol) lentamente agregado en este orden. La reacción se agitó durante 17 h. El disolvente se evaporó y el residuo se purificó mediante cromatografía flash (*n*-hexano: EtOAc), proporcionando los heterociclos *endo*-**4b** y **20**.

Capítulo 2

En este capítulo, el interés del estudio fue sintetizar las ciclohex-2-enilaminas sustituidas a través de una reacción multicomponente (AAD).

El modelo de reacción empleado para la optimización de este proceso AAD multicomponente involucró a la bencilamina, crotonaldehído y *N*-metilmaleimida (NMM) como dienófilo (Esquema 1). Se eligió tolueno como

disolvente debido a los buenos resultados obtenidos en nuestro grupo.[17] Solo dos parámetros, la temperatura y la naturaleza de algunos de los aditivos fueron evaluados para la generación de compuestos **1a**. Cuando la reacción se llevó a cabo sin aditivos a temperatura ambiente, durante 16 h, solo se observaron productos de adición de tipo-Michael. Sin embargo, el incremento de la temperatura favoreció la reacción de AAD obteniendo productos crudos complejos (^{1}H NMR). A continuación, se probó la adición de ácido *p*-toluensulfónico como aditivo obteniendo solo los compuestos de tipo-Michael al final de la reacción. Por otro lado, el ácido benzoico a 70 °C dio mejores resultados que cuando la reacción se llevó a cabo sin aditivos a la misma temperatura. Con la idea de trabajar con una amina secundaria enmascarada derivada de bencilamina, se usó cloruro de trimetilsililo y trimetilamina en varias proporciones para la generación *in situ* de trimetilsililbencilamina.



Esquema 1. Síntesis de AAD multicomponente del producto **1a**.

El uso de TMSCl (30% mol) dio una alta conversión para **1a**. La combinación TMSCl/Et_3N (30% mol, cada uno) proporcionó crudos de reacción más limpios. Cuando se probó 1 equivalente de ambos aditivos, el rendimiento aumentó al 76%. Sorprendentemente, usando un modo secuencial de la reacción, mezclando bencilamina, cloruro de trimetilsililo y trietilamina en

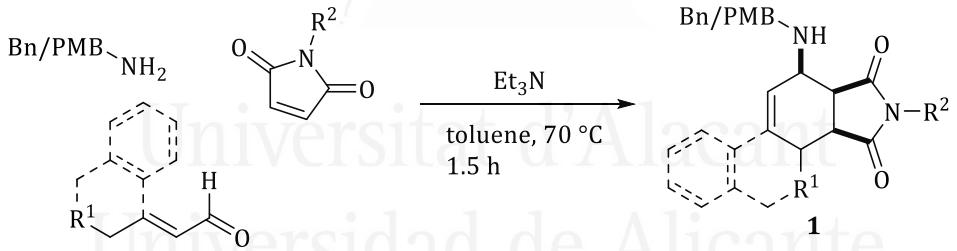
[17] Selva, V.; Larraneaga, O.; Castelló, L.M.; Nájera, C.; Sansano, J.M. de Cózar, A. *J. Org. Chem.* **2017**, *82*, 6298.

tolueno, y después de 30 minutos, agregando crotonaldehído y *N*-metilmaleimida, se obtuvo el mejor rendimiento. No se observaron diferencias significativas cuando se elevó la temperatura, pero la conversión de la reacción fue menor cuando la temperatura disminuyó a 50 °C. Teniendo en cuenta el trabajo de Sherburn,[18] el cloroformo se seleccionó como solvente obteniendo rendimientos químicos más bajos pero con una mezcla de reacción cruda más limpia. Se detectó una conversión completa cuando se añadió trietilamina sin cloruro de trimetilsililo, lo que demuestra que la presencia de la base es crítica para que tenga lugar la reacción. En este punto, el tiempo de la reacción se controló observando que la reacción se completó en solo 1,5 h en cloroformo y también en tolueno.

Con estas condiciones óptimas, la amina, el aldehído y los dipolarófilos se mezclaron en cloroformo a 70 °C en presencia de trietilamina para evaluar el alcance de la reacción AAD (Esquema 2). Se permitió que el crotonaldehído y la bencilamina reaccionaran con maleimidas (NMM y NBM) obteniendo solo un estereoisómero (**1a** y **1b**, respectivamente) en la mezcla del crudo de reacción con buenos rendimientos aislados después de la purificación (68% y 61%, respectivamente, Esquema 2). La maleimida fluorada[19] también se empleó en esta reacción obteniendo el producto correspondientes **1c** con un rendimiento del 51% (Esquema 2). Otros aldehídos tales como *E*-2-pentenal se analizaron con *N*-fenilmaleimida (NPM) produciendo un producto **1d** con un 50% de rendimiento. El 3-metilcrotonaldehído también se probó en esta reacción con NPM y NBM obteniendo, en ambos casos, casi solo un diastereoisómero de **1e** y **1f**, con rendimientos aislados moderados después de la purificación (65% y 40%, respectivamente, Esquema 2). Además de la bencilamina, las aminas

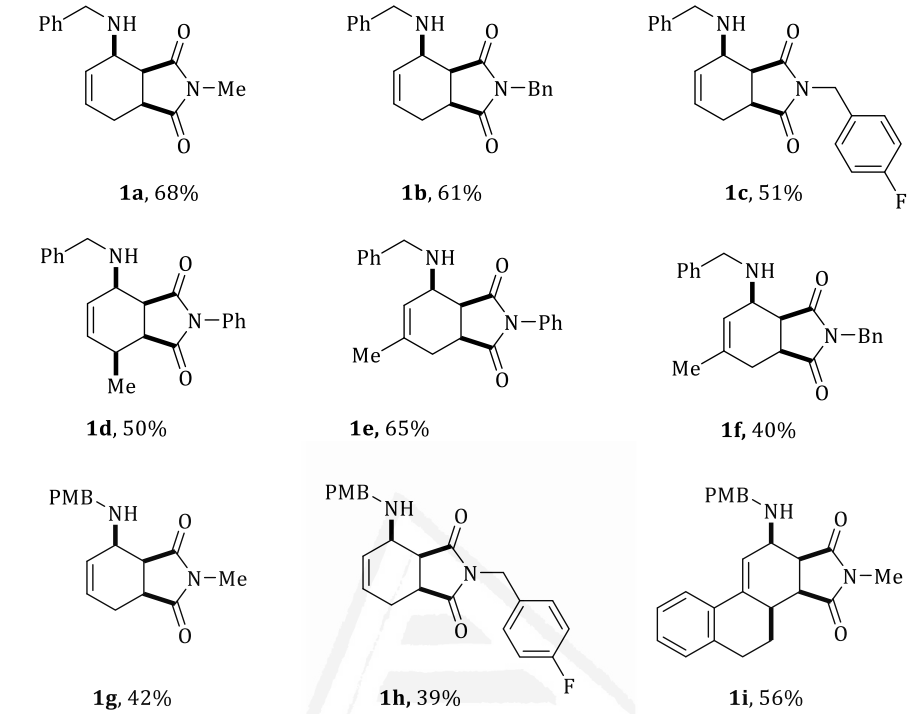
[18] Tan, S.M.; Willis, A.C.; Paddon-Row, M.N.; Sherburn, M.S. *Angew. Chem., Int. Ed*. **2016**, *55*, 3081.
[19] Estas maleimidas se usaron en la preparación de precursores de trombina

primarias alifáticas como la butilamina o la alilamina fallaron en esta reacción, sin embargo, otro derivado de la bencilamina como la *p*-metoxibencilamina fue apropiado. Así, se permitió que $PMBNH_2$ reaccionara con crotonaldehído y dos maleimidas diferentes obteniendo **1g** y **1h** con rendimientos aislados de moderados a buenos (42% y 39%, respectivamente). Curiosamente, el producto tetracíclico pseudoesteroide **1i** se aisló, a partir del aldehído correspondiente,[20] con un rendimiento del 56%. La configuración relativa de todas las moléculas **1** fue confirmada por experimentos nOe y por comparación de desplazamientos químicos (^{1}H NMR). Los compuestos **1b, 1c**, **1d, 1e**, **1f** y **1h** se aislaron con muy pequeñas cantidades de otro diasteroisómero, que fue muy difícil de separar por cromatografía en columna (ver SI). La reacción de AAD con fumaratos, anhídrido maleico, acrilatos, sulfonas vinílicas, derivados de chalcona, nitroalquenos, etc., no se produjo. En algunos ejemplos, se obtuvieron mezclas de reacción complejas aislando el producto esperado con bajos rendimientos.



1

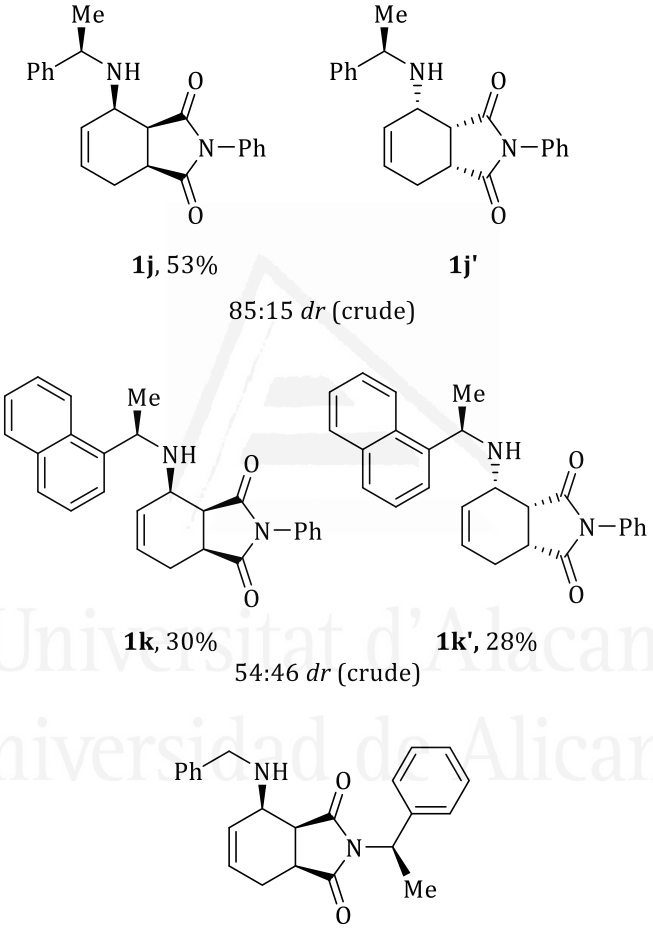
[20] Naesborg, L.; Halskov, K.S.; Tur, F.; Monsted, S. M. N.; Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2015**, *54*, 10193.



Esquema 2. Síntesis de ciclohex-2-en-1-aminas **1** por reacción de AAD.

La versión diastereoselectiva de esta transformación AAD fue también examinada (Esquema 2 y Figura 1). Usando una temperatura más baja (70 °C) y tiempos de reacción más cortos (1,5 h), las bencilaminas quirales se probaron primero para obtener diastereoisómeros enantiopuros. Se hizo reaccionar (*R*)-α-metilbencilamina con crotonaldehído y NPM dando una mezcla 85:15 de dos diastereoisómeros en el crudo de reacción (^{1}H NMR) aislando solo el producto principal **1j** después de la purificación con buen rendimiento (53%). También se ensayó la (*R*)-1-(1-naftil)etilamina, la cual generó una relación diastereomérica casi equimolar de los productos **1k** y **1k'**. En ambos casos, los resultados nOe de RMN indicaron la disposición general de todos los

sustituyentes en posición *cis*. Cuando la información quiral estaba anclada a la maleimida, la diastereoselectividad fue más alta que en los dos ejemplos previos realizados con aminas bencílicas quirales. La molécula **1l** se generó con un rendimiento del 52% con una proporción diastereomérica de 95: 5 cuando se empleó (*R*)-*N*-(1-feniletil) maleimida como información quiral (Figura 1).



1j, 53% **1j'**
85:15 *dr* (crude)

1k, 30% **1k'**, 28%
54:46 *dr* (crude)

1l, 52%
>95:5 *dr*

Figura 1. Síntesis de ciclohex-2-en-1-aminas enriquecidas enantioméricamente **1j-l** por reacción AAD.

La configuración absoluta propuesta del compuesto **1j**, dibujada en la Figura 1, fue confirmada por análisis de dicroísmo circular vibracional (VCD) (Figura 2). Afortunadamente, ambos diastereoisómeros **1j** y **1j'** exhibieron patrones de VCD teóricos opuestos, y que la absorción por parte de los grupos carbonilo era la más relevante. El VCD experimental (puntos) y la línea de ajuste resultante coincidía perfectamente (Figura 2) con los datos teóricos proporcionados para el diastereoisómero **1j**. Cada máximo del gráfico de absorción experimental (1720 y 1785 cm^{-1}) está compuesto por la suma de dos bandas anchas, posiblemente debido a la formación de enlaces de hidrógeno intramoleculares entre el NH y el grupo carbonilo más cercano.[21] Esta interacción también fue apoyada por la configuración relativa todo-*cis* de este anillo fusionado.

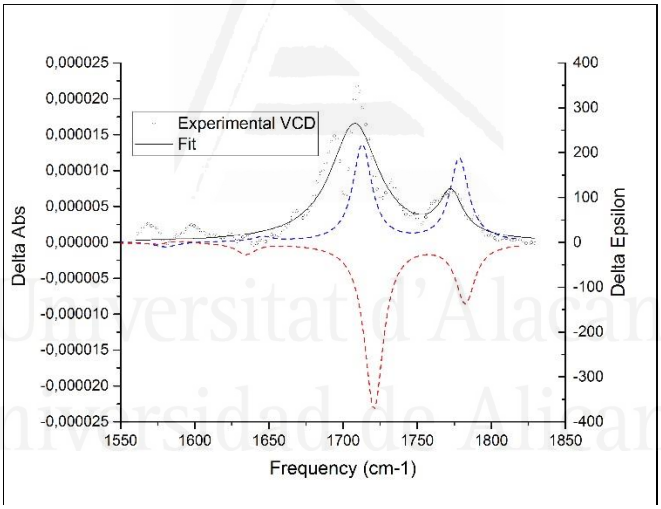


Figura 2. Análisis VCD del producto **1d**. La línea discontinua azul corresponde al VCD teórico calculado con un nivel B3LYP/6-311G+(2d, 2p) para la configuración **1d**. La línea discontinua roja corresponde al VCD teórico

[21] Gobi, S.; Vass, E.; Magyarfalvi, G.; Tarczay, G. *Phys. Chem. Chem. Phys*. **2011**, *13* 13972.

calculado con un nivel B3LYP/6-311G + (2d, 2p) para el diastereoisómero minoritario **1d**. La curva negra corresponde al VCD experimental.

La asignación de la configuración absoluta para el compuesto **1l** fue más complicado. El análisis inicial de difracción de rayos X de un monocristal reveló que los dos enantiómeros de **1 l** estaban dispuestos simétricamente en la celda unitaria junto con dos moléculas de cloruro de hidrógeno.[22] Esta cristalización se produjo en la solución de la muestra preparada para el análisis de su experimento VCD (Figura 3). A pesar de un desplazamiento de la banda de carbonilo experimental con respecto a las calculadas, la pequeña absorbancia a alrededor de 1450 cm^{-1} (absorción de CN) también confirmó la estereoquímica dibujada de **1l** en la Figura 1. Es importante señalar que las conformaciones calculadas para ambos ciclos de carga **1j** y **1l** revelaron la presencia de fuertes enlaces de hidrógeno (2.53-2.56 Å en estado sólido de ambos enantiómeros) entre un grupo carbonilo del resto succinimida y el átomo de hidrógeno del grupo amino. Estas interacciones pueden modificar la longitud de onda de absorbancia normal de los carbonilos en solución e incluso evitar la detección de la banda NH en la espectroscopía de ^{1}H NMR (ver SI).

[22] The information concerning X-ray diffraction analysis of compound 6l can be found in the Cambridge Crystallographic Data Centre (CCDC) with the code: CCDC 1892086.

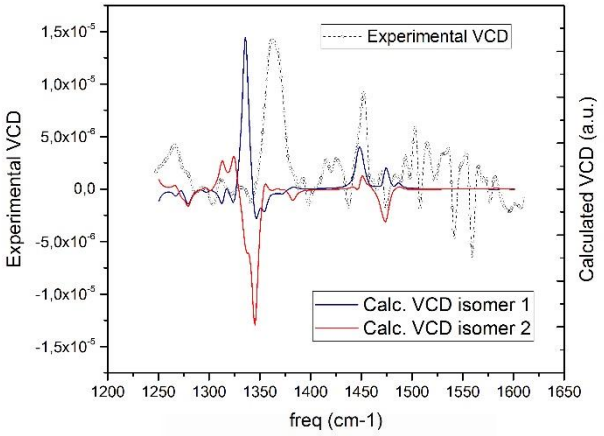


Figura 3. Análisis VCD del producto **1l**. La línea azul corresponde al VCD teórico calculado con un nivel B3LYP / 6-311G + (2d, 2p) para la configuración **1l**. La línea discontinua roja corresponde al VCD teórico calculado con un nivel B3LYP / 6-311G + (2d, 2p) para el diastereoisómero menor **1l'**. La curva negra corresponde al VCD experimental.

Sección Experimental

Métodos Generales

Todos los reactivos y solventes disponibles comercialmente se usaron sin purificación adicional, solo se destilaron aldehídos Antes de su uso. Solo el precursor aldehído del compuesto **1i** fue preparado según la bibliografía.[20] La TLC analítica se realizó en placas de gel de sílice Schleicher & Schuell F1400 / LS 254, y las manchas se visualizaron bajo luz UV (1 ¼ 254 nm). Destello La cromatografía se realizó en columnas empaquetadas a mano de gel de sílice Merck 60 (0,040-0,063 mm). Los puntos de fusión se determinaron con un aparato de placa caliente Reichert Thermovar y no están corregidos. Los picos estructuralmente más importantes de los espectros IR (registrados usando un

Nicolet 510 P-FT) se enumeran y los números de onda se dan en cm^{-1}. Los espectros de RMN se obtuvieron usando un Bruker AC-300 o AC-400 y se registraron a 300 o 400 MHz para ^{1}H NMR y 75 o 100 MHz para ^{13}C NMR, usando $CDCl_3$ como solvente y TMS como estándar interno (0.00 ppm). Las siguientes abreviaturas se utilizan para describir patrones de pico donde apropiado: s ¼ singlete, d ¼ doblete, t ¼ triplete, q ¼ cuarteto, m¼ multiplete o sin resolver y br s¼ señal amplia. Todas las constantes de acoplamiento (J) se dan en Hz y los

desplazamientos químicos en ppm. Los espectros de ^{13}C NMR se referenciaron a $CDCl_3$ a 77,16 ppm. Se realizaron experimentos DEPT-135 para asignar CH, CH_2 y CH_3. Se registraron RMN de ^{19}F a 282 MHz usando $CDCl_3$ como disolvente. Los espectros de masas de impacto electrónico (EI) de baja resolución se obtuvieron a 70 eV usando un Shimadzu QP-5000 por inyección o DIP; Los iones de fragmentos en m/z se dan con intensidades relativas (%) entre paréntesis. Los espectros de masas de alta resolución (HRMS) se midieron en un instrumento utilizando un espectrómetro de masas de tiempo de vuelo cuadrupolo (QTOF) y también a través del modo de impacto de electrones (EI) a 70 eV utilizando una plataforma Finnigan VG o un Finnigan MAT 95S. El análisis de VCD se registró en un Jasco FVS-6000.

Procedimiento general para la síntesis de productos ***1***

A una solución agitada de derivado de bencilamina (0.25 mmol) y se añadió Et_3N (1 equiv, 0.25 mmol) en 1 ml de tolueno, el aldehído (1 equiv, 0.25 mmol), el dienófilo (1 equiv, 0.25 mmol) y 0.5 mL más de cloroformo. La solución se agitó a 70 ° C durante 1.5 h, y después de eliminar el disolvente al vacío, el crudo de la reacción se purificó con cromatografía flash para proporcionar el compuesto deseado.

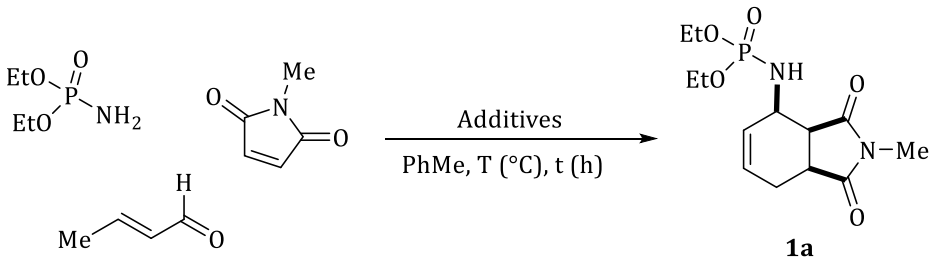
Capítulo 3

En este capítulo, el interés del estudio fue sintetizar una serie de fosforamidatos *N*-sustituidos con buenos rendimientos, a través de una reacción multicomponente fosforamidato-aldehído-dienófilo (PAD).

La reacción modelo utilizada para la optimización de este proceso PAD multicomponente incluyó fosforamidato de dietilo, crotonaldehído y *N*-metilmaleimida (NMM) como el dienófilo (Esquema 1). Aprovechamos los resultados obtenidos en nuestra contribución anterior[23] para optimizar el proceso. Por lo tanto, se seleccionó tolueno como solvente y la reacción necesitaba calentarse durante 8 h para observar una conversión / rendimiento notable del producto **1a**. La presencia de aditivos como el anhídrido acético y el ácido *p*-toluensulfónico (TsOH) fueron cruciales para las reacciones de amidas o sulfonamidas,[24] por lo que analizamos sus efectos en la síntesis de PAD multicomponente. Por separado, la presencia de anhídrido acético es más importante que la presencia de TsOH en términos del rendimiento aislado. El mayor rendimiento para **1a** se logró empleando solo 5% en moles de anhídrido acético y 5% en moles de TsOH. El producto crudo **1a** era muy puro y podía usarse, sin purificación previa, para la síntesis de la amina alílica libre después de la hidrólisis del grupo dietilfosforilo (véase más adelante). La reacción con cloroformo tuvo lugar con rendimientos muy bajos. Curiosamente, el esqueleto de *N*-ciclohex-2-en-1-amida **1** está presente en análogos de somatostatina y el grupo Kessler aplicó convenientemente esta reacción para lograr el producto

[23] Selva, V.; Chabour, I.; Nájera, C.; Sansano, J.M. *Tetrahedron* 2019, *75*, 1315.
[24] a) Neumann, H.; von Wangelin, A. J.; Gördes, D.; Spannenberg, A.; Baumann,W.; Beller, M. *Tetrahedron,* **2002**, *58*, 2381.; b) von Wangelin, A.J.; Neumann, H.; Gördes, D.; Klaus, S.; Strübing, D.; Beller, M. *Chem. Eur. J*. **2003,** *9*, 4286.; c) Neumann, H.; von Wangelin, A. J.; Klaus, S.; Strübing, D.; Gördes, D.; Beller, M. *Angew. Chem. Int. Ed*. **2003,** *42*, 4503.; d) Klaus, S.; Hübner, S.; Neumann, H.; Strübing, D.; von Wangelin, A. J.; Gördes, D.; Beller, M. *Adv. Synth. Catal*. 2004, 346, 970.; e) Strübing, D.; Neumann, H.; Klaus, S.; Hübner, S.; Beller, M. *Tetrahedron.* **2005,** *61*, 11333.

deseado.[25] El grupo de Beller también aplicó esta reacción para sintetizar análogos de corolosporina para probar su actividad antimicrobiana[26].



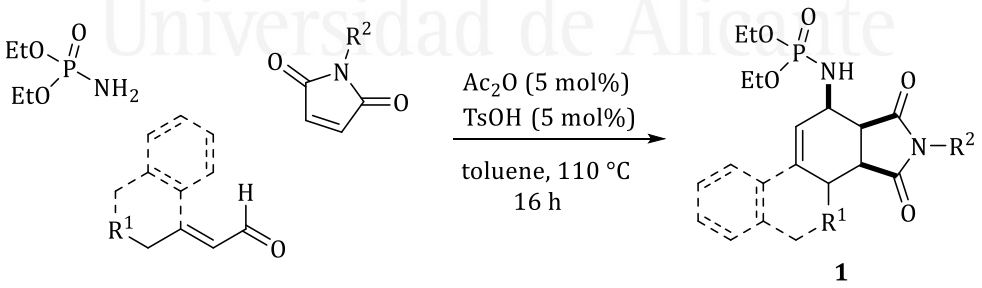
Esquema 1. Síntesis de PAD multicomponente del producto **1a**.

Utilizando las condiciones óptimas [Ac_2O (5 mol%), TsOH (5mol%), 110 °C, 16 h], se analizaron los efectos de la estructura de los componentes de aldehído y maleimida (Esquema 2). El crotonaldehído y el fosforamidato de dietilo reaccionaron en presencia de *N*-alquil, *N*-bencil y *N*-arilmaleimidas para dar los compuestos **1a-f** con buenos rendimientos (Esquema 2). Es notable que la maleimida fluorada[27] proporcionó el compuesto correspondiente **1c** con un rendimiento del 64%, el cual puede ofrecer una actividad biológica potencial. El (*E*)-2-pentenal se analizó con NMM y *N*-fenilmaleimida (NPM) produciendo productos **1g** y **1h** con 62% y 53% de rendimiento, respectivamente (Esquema

[25] Sukopp, M.; Schwab, R.; Marinelli, L.; Biron, E.; Heller, M.; Várkondi, E.; Pap, A.; Novellino, E.; Kéri, G.; Kessler, H. *J. Med. Chem*. **2005**, *48*, 2916.
[26] Neumann, H.; Strübing, D.; Lalk, M.; Klaus, S.; Hübner, S. Spannenberg, A.; Lindequist, U.; Beller, M.; *Org. Biomol. Chem*. **2006**, *4*, 1365.
[27] a) Olsen, J.; Seiler, P.; Wagner, B.; Fischer, H.T.; Obst-Sander, U.; Tschopp, T.; Banner, D.W.; Kansy, M.; Müller, K.; Diederich, F. *Org. Biomol. Chem*. **2004**, *2*, 1339.; b) Schweizer, E.; Hoffmann-Röder, A.; Schärer, K.; Olsen, J. A.; Fäh, C.; Seiler,P.; Obst-Sander, U.; Wagner, B.; Kansy, M.; Diederich, F. *ChemMedChem.* **2006**, 1, 611.; c) Selva, V.; Selva, E.; Merino, P.; C. Nájera, Sansano, J.M.; *Org. Lett.* **2018**, *20* 3522.

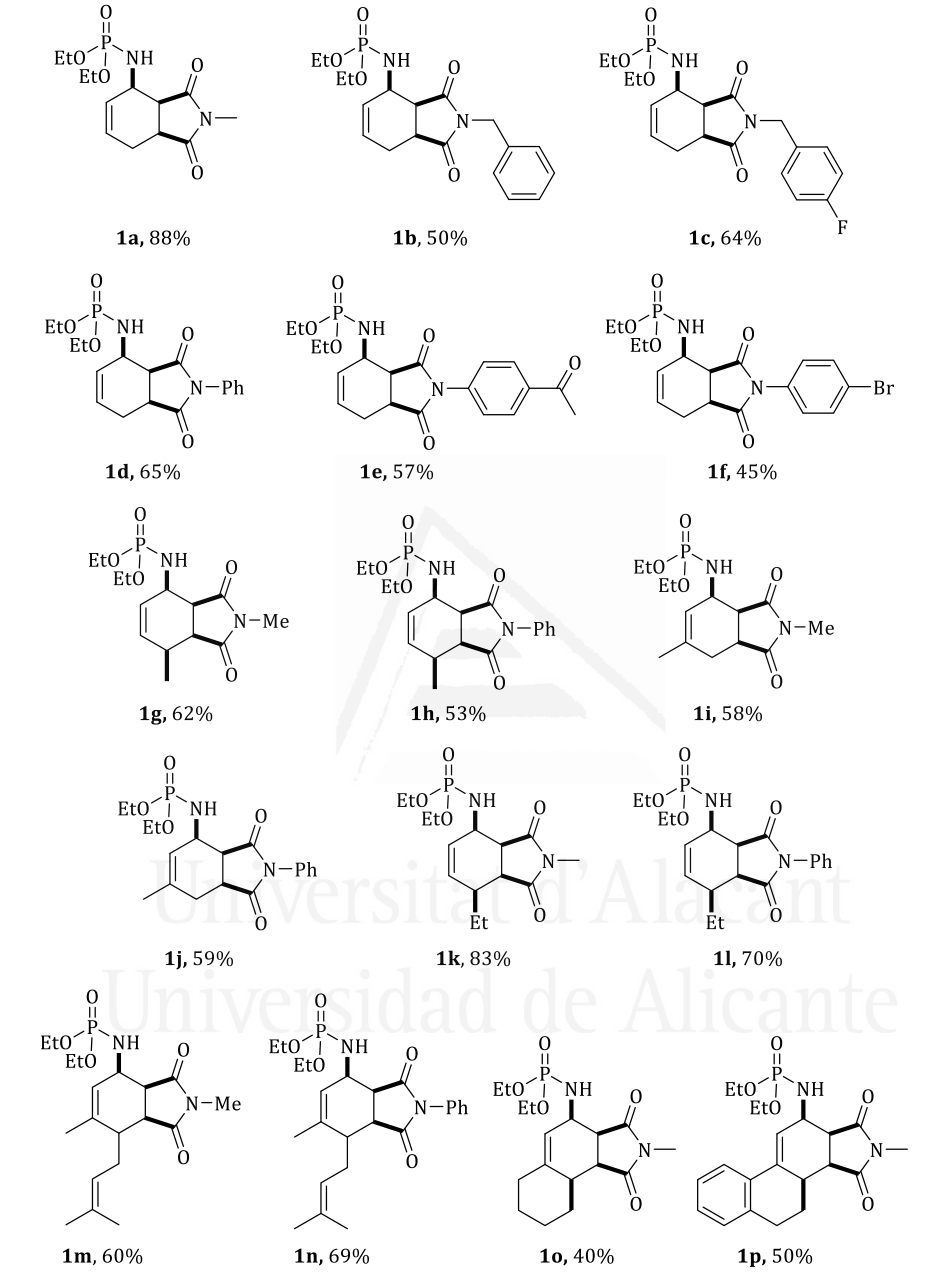
2). Se observó un comportamiento similar cuando se empleó 3-metilcrotonaldehído en reacciones con ambas maleimidas, proporcionando los esqueletos bicíclicos esperados **1i** y **1j** con rendimientos similares (58% y 59%). El hex-2-enal y el fosforamidato de dietilo produjeron altos rendimientos de los productos **1k** y **1l** en las reacciones con NMM y NPM, respectivamente (Esquema 2).

El geranial posee dos tipos diferentes de hidrógenos en la posición γ. Este aldehído falló en nuestro proceso anterior de amina / aldehído / dienofilo,[23] pero en esta reacción multicomponente PAD el mecanismo prefirió la abstracción de uno de los dos hidrógenos γ-metilénicos para generar *in situ* el intermedio 1-aminodieno más sustituido. Por lo tanto, se obtuvo el compuesto **1m** con un rendimiento del 60% y una relación de 85:15 (determinado por ^{1}H NMR), mientras que **1n** se aisló con un rendimiento más alto (69%) con una relación 90:10 (determinado por ^{13}C NMR) (Esquema 2). Curiosamente, el producto tricíclico **1o** y la estructura tetracíclica pseudoesteroide **1p** se aislaron a partir de los aldehídos acrílicos cíclicos correspondientes[28] con un rendimiento del 40% y 50%, respectivamente (Esquema 2).



1

[28] Naesborg, L.; Halskov, K.S.; Tur, F.; Monsted, S. M. N.; Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2015**, *54*, 10193.



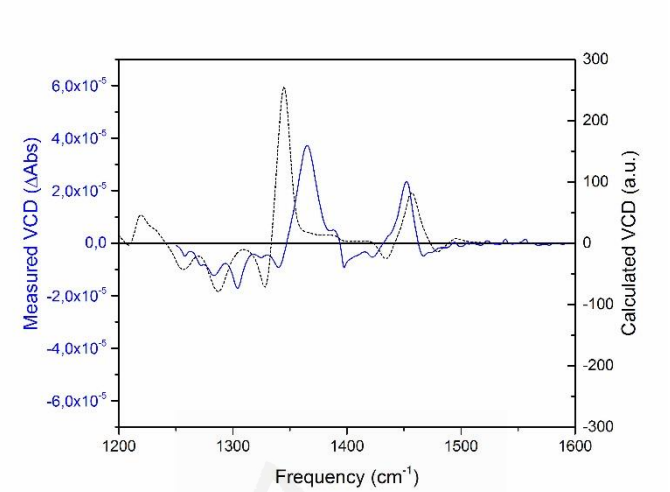
Esquema 2. Síntesis de fosforamidatos de N-ciclohex-2-enilo **1** mediante la reacción PAD.

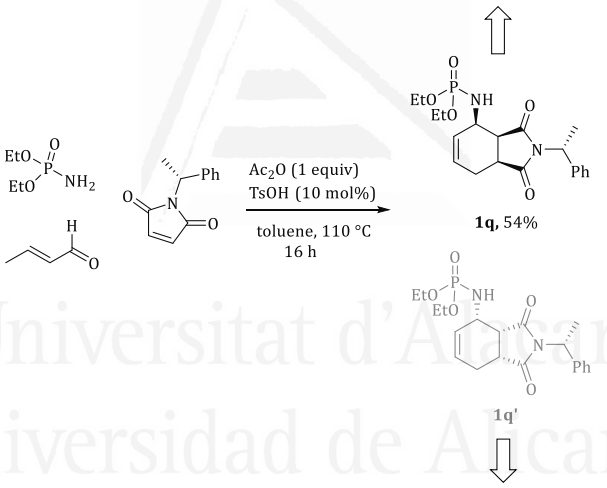
Síntesis

La configuración relativa de todos los compuestos **1** fue confirmada por experimentos nOe y por comparación de desplazamientos químicos (^{1}H NMR) con las correspondientes aminas análogas obtenidas previamente por nuestro grupo.[23] A pesar de la temperatura, todos los compuestos se aislaron como diastereoisómeros únicos, excepto los ejemplos ya descritos usando geranial (ver arriba). Así como en la reacción secuencial de AAD precedente, las transformaciones de PAD con fumaratos, anhídrido maleico, acrilatos, sulfonas vinílicas, derivados de calcona y nitroalquenos fallaron por completo. En algunos ejemplos, se obtuvieron mezclas de reacción crudas complejas y los productos esperados se aislaron con rendimientos muy bajos.

La versión diastereoselectiva de esta transformación AAD se examinó en presencia de (*R*)-*N*-(1-feniletil)maleimida (Figura 1). La reacción procedió con alta diastereoselectividad a pesar de la temperatura empleada (82:18 por ^{1}H NMR del producto bruto). Después de la purificación por cromatografía flash, solo se pudo aislar el estereoisómero principal **1q**. La configuración absoluta propuesta se asignó sobre la base del análisis VCD (Figura 1). Ambos diastereoisómeros **1q** y **1q'** exhibieron patrones de VCD teóricos opuestos, que fue más relevante en el área de absorción perteneciente a la huellas dactilares (<1500 cm^{-1}). El VCD teórico (gráfico de puntos negros) y los espectros medidos para diastereoisómero **1q** coincidieron casi perfectamente (Figura 1). El desplazamiento observado entre las áreas teóricas y experimentales para **1q** puede deberse a la formación de enlaces de hidrógeno intramoleculares entre el NH y el grupo carbonilo más cercano.[29] Esta interacción también fue apoyada por la configuración relativa todo *cis* de este anillo fusionado, tal y como se observó en la reacción análoga de AAD.[23]

[29] Gobi, S.; Vass, E.; Magyarfalvi, G.; Tarczay, G. *Phys. Chem. Chem. Phys.* **2011**, *13,* 13972.





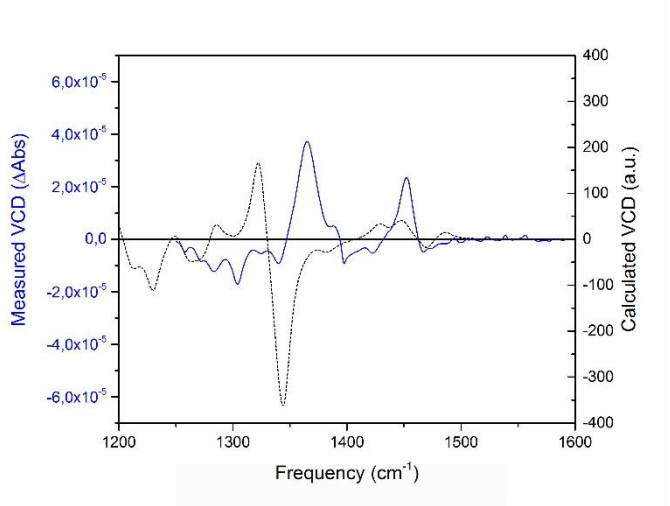
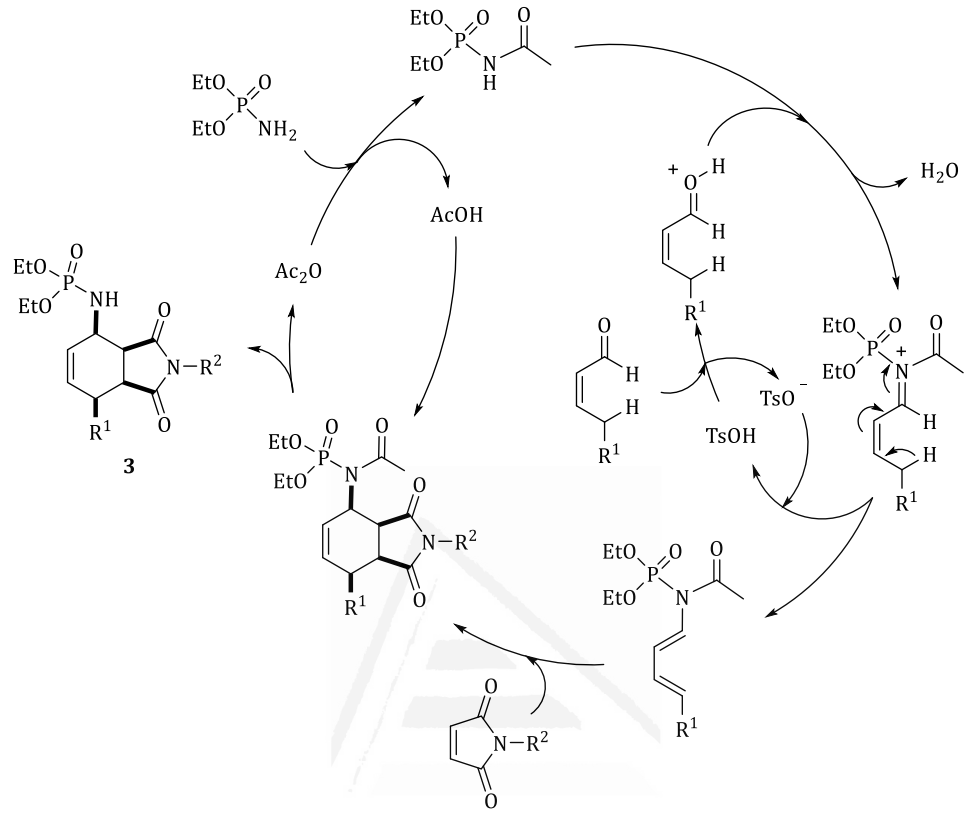


Figura. 1. Análisis VCD del producto **1q** y su forma enantiomérica **1q'**. La línea azul corresponde al VCD medido experimentalmente, mientras que el gráfico negro discontinuo es el VCD calculado con un nivel B3LYP / 6-311Gþ (2d, 2p) para la configuración **1q**.

La presencia crucial de anhídrido acético y TsOH nos permitió sugerir un mecanismo donde tanto el fosforamidato de dietilo como el aldehído se activan independientemente. La reacción funcionó con cantidades subestequiométricas de anhídrido acético y así la desacetilación del intermedio *N*-acilfosforamidato ocurrió antes de la formación del producto final **1** (ver Esquema 3). Se observó la generación parcial del *N*-acetilfosforamidato de dietilo intermedio después de calentar la mezcla de reacción que contenía todos los reactivos excepto la maleimida (véase ESI). A la mezcla resultante se le añadió maleimida y tuvo lugar la reacción esperada.

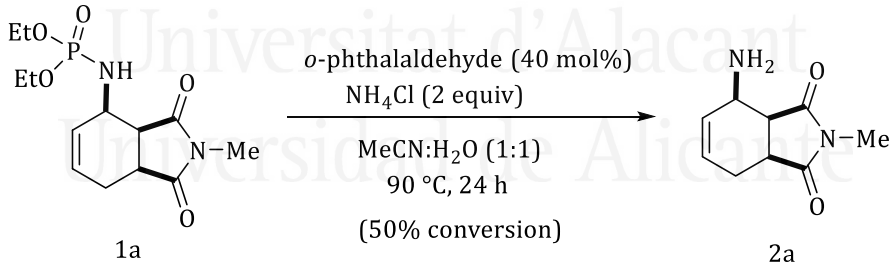


Esquema 3. Mecanismo propuesto para la síntesis de los productos **1.**

La publicación de una familia de agentes antibacterianos que contiene un núcleo de 3-aminociclohexeno[30] nos animó a estudiar la hidrólisis del resto

[30] a) Jaetsch, T.; Hallenbach, W.; Himmler, T.; Bremm, K. D.; Endermann, R.; Pirro, F.; Stegemann, M.; Wetzstein, H. G. *Ger. Offen.* **1996**, DE 4431122 A1 19960307.; b) Hallenbach, W.; Himmler, T.; Jaetsch, T.; Mielke, B.; Bremm, K. D.; Endermann, R.; Pirro, F.; Stegemann, M.; Wetzstein, H. G. *Ger. Offen.* **1996**, DE 4424369 A1 19960118.; c) Jaetsch, T.; Hallenbach, W.; Himmler, T.; Mielke, B.; Bremm, K. D.; Endermann, R.; Pirro, F.; Stegemann, Franz; M.; Wetzstein, H. G. *Eur. Pat. Appl*. **1995**, EP 684244 A1 19951129.
(d) U. Petersen, T. Himmler, T. Schenke, A. Krebs, K. Grohe, K.-D. Bremm, K.G. Metzger, R. Endermann, H.J. Zeiler, U.S. (1995), US 5468742 A 19951121 and previous assignee patents of Bayer A.-G., Germany (1992-1996).

fosforamidato. Se encontró un método conveniente en la literatura basado en la hidrólisis de varios compuestos organofosforados que llevan subunidades P(O)-NH catalizadas por *o*-ftalaldehído.[31] Siguiendo este procedimiento, el compuesto **1a** se sometió a varias reacciones de prueba usando *p*-toluensulfonato de amonio o cloruro de amonio, a reflujo en THF o MeCN. Con NH_4OTs la reacción no funcionó, sin embargo, con NH_4Cl (2 equiv.) se obtuvo la mejor conversión. Por lo tanto, NH_4Cl (2 equiv.), *o*-ftalaldehído (40% en moles), MeCN/H_2O (90 C, 24 h) fueron las condiciones más apropiadas para obtener una conversión del 50% (^1H NMR del crudo de reacción) (Esquema 5). La amina primaria **2a** se pudo identificar (ver ESI) pero su aislamiento no fue posible ni por cromatografía flash ni por precipitación/cristalización mediante la adición de 1 equiv. de HCl/Et_2O. En todos estos casos se detectaron mezclas equimolares de **1a** y **2a** (ver ESI). Intentamos sin éxito introducir grupos protectores como *terc*-butoxicarbonilo (Boc), benzoílo o acetilo para ayudar al aislamiento [34].



Esquema 4 . Hidrólisis del cicloaducto **1a**.

[31] Li, B. J.; Simard, R. D.; Beauchemin, A. M. *Chem. Commun.* **2017**, *53,* 8667.

Sección Experimental

Métodos Generales

(Véase la sección análoga descrita en el resumen del Capítulo 2)

Procedimiento general para la síntesis de productos 1.

A una solución agitada de dietilfosforamidato (154 mg, 1 mmol), TsOH (8,6 mg, 0,05 mmol), anhídrido acético (4,8 ml, 0,05 mmol) en 3 ml de tolueno se añadió el aldehído (1 mmol), la maleimida (1 mmol). La solución se agitó a reflujo durante 24 h, y luego el disolvente se eliminó al vacío. El crudo de la reacción se purificó con cromatografía instantánea para dar el compuesto deseado.

SECTION 2: PUBLISHED WORKS

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Multicomponent reactions

Multicomponent reactions (MCRs) are defined as processes allowing to assemble in one step, three or more different starting substrates to lead to the formation of a single product. The starting compounds are generally commercial or easily prepared. They react in a sequence of basic steps, each of them creating several links. (Figure 1.).[32]

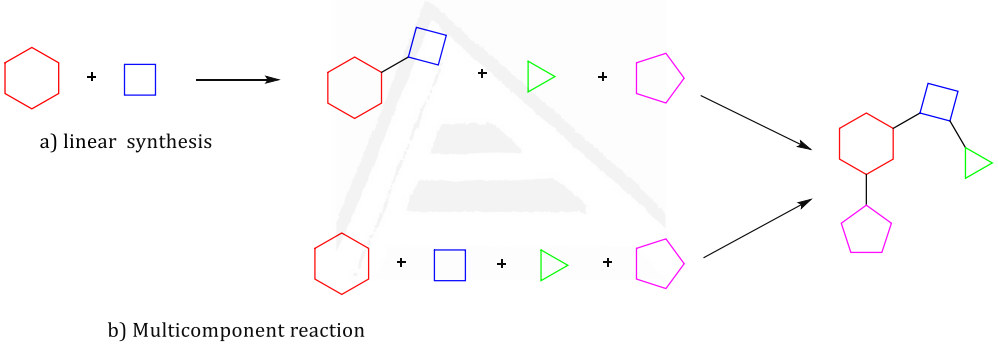


Figure 1. Traditional linear synthesis (3 steps) *vs.* multicomponent reaction (1 step).

Multicomponent reactions (MCR) are among the most important processes for the preparation of organic compounds with high functionality in modern synthetic chemistry,[33] because these reactions have all the characteristics which lead to an ideal synthesis, such as high atomic efficiency,

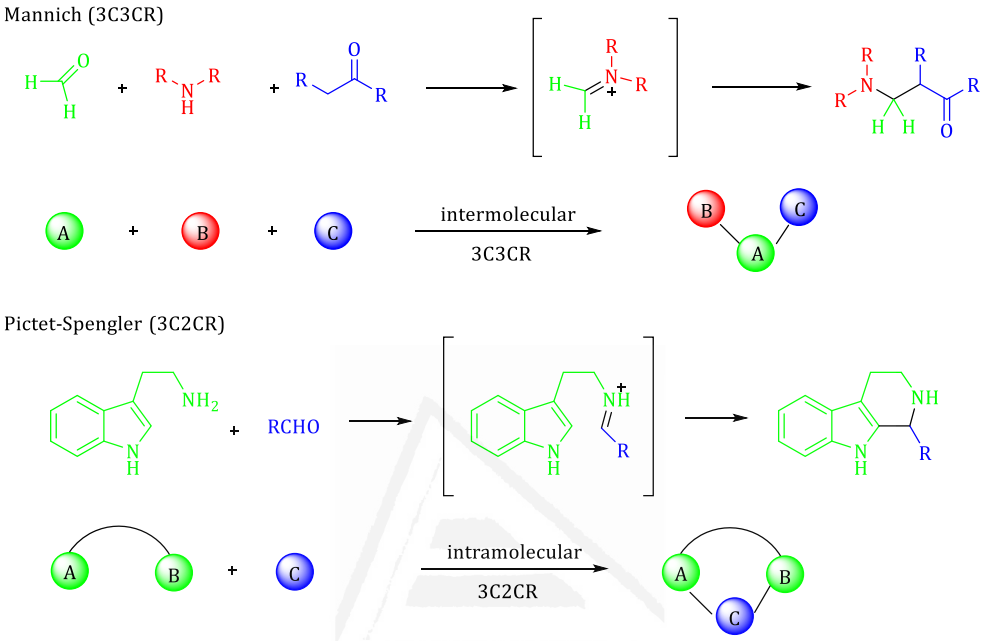
[32] .Chebanov, V. A.; Desenko, S. M *Chem. Het. Comp*. **2012**, *48*, 566-583.
[33] Haji, M. *Beilstein J. Org. Chem*. **2016**, *12*, 1269–1301.

quick and simple implementation, allows to save more time and energy, as they offer a targeted synthesis and oriented towards diversity.[34]

The development of new multicomponent reactions in various biomedical and industrial fields remains important and inevitable. On the other hand, the combination of these reactions based on post-reaction transformations opens the way to a large number of diverse and complex products. Among which the intramolecular cycloaddition reactions, Knoevenagel condensations, metathesis reactions, aza-Wittig reactions, Mitsunobu reactions, etc..[35]

MCRs can also be performed intermolecularly and intramolecularly (Scheme 1) and the most important aspect is to envisage the number of reaction centers and the components of the reaction. An intramolecular MCR can have less than three components but always have at least three reaction centers, as in the case of the Mannich reaction, which is a reaction with three components (3CR) aldehyde, amine and ketone, and the reaction of Pictet-Spengler, which is carried out of only two components (2CR) an amino indole and an aldehyde. The Pictet-Spengler reaction can therefore be considered as the intramolecular version of the Mannich reaction. It is worthy to note that in the two MCRs, only the number of components is different, which explains that for intramolecular MCRs, the reaction centers, instead of the components, must be counted.[36]

[34] Wender, P. A. *Nat. Prod. Rep*. **2014**, *31*, 433–440.
[35] Zhu, J. Bienaymé, H. Eds. Multicomponent Reactions; Wiley-VCH: Weinheim, Germany, **2005**.
[36] Sanjun, Z.; Xiaoming, M.; Wei, Z. *Org. Biomol. Chem*., **2019**, *17*, 7632–7650.



Scheme 1. Intermolecular and intramolecular MCRs

Cycloadditions reactions

Modern organic synthesis, focuses on the criteria of efficiency, versatility, economy (stages, atoms, human resources, raw material, energy) and ecological compatibility.[37] What is noticed, nowadays, there is a growing demand for the development of methods and strategies that allow the arrival to rapid,

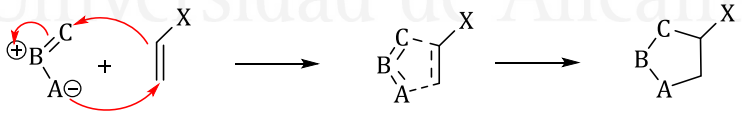
[37] Klier, L.; Tur, F.; Poulsen, P. H.; Jørgensen, K. A. *Chemical Society Reviews,* **2017**. *46(4), 1080–1102.*

economical and efficient synthesis. As it is known cycloadditions are among the synthetic tools that most meet these criteria,[38] Cycloaddition is summarized by the union of two independent π systems passing through a concerted process involving a cyclic movement of electrons and resulting in the formation of a new ring. These reactions are considered one of the most powerful bond-forming reactions due to their ability to form many bonds in one step and also for their potential which allows to generate several stereogenic centers at the same time with predictable stereochemical outcomes.

A cycloaddition reaction is categorized as a [m + n]-cycloaddition when a system of m conjugated atoms combines with a system of n conjugated atoms.

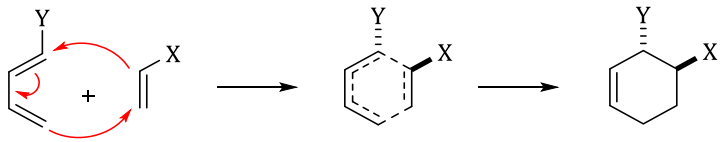
The most important cycloaddition reactions, which occur by concerted reaction mechanisms, are the following:

(a) The 1,3-Dipolar-Cycloaddition: [3+2]-Cycloaddition: 5-member heterocyclic rings are formed



[38] López, F.; Mascareñas, J. L. *Beilstein Journal of Organic Chemistry,* **2011,** *7,* 1075–1094.

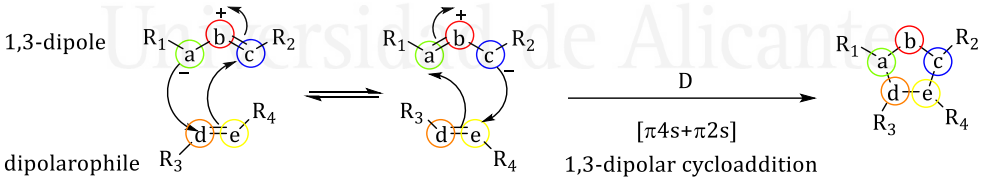
(b) Diels-Alder Reaction: [4+2]-Cycloaddition: 6-member carbocyclic rings are formed



1,3-Dipolar cycloaddition

The 1,3-dipolar cycloaddition (DC), or otherwise known as Huisgen's cycloadditions,[39] constitutes a powerful classic synthesis tool and is one of the most productive areas of modern organic chemistry, such as synthesis of important drugs and natural products.[40]

1,3-DCs are [π4s + π2s] processes between a 1,3-dipole and a dipolarophile to form a five-membered ring[41] (Scheme 2).

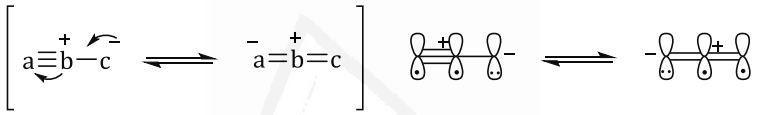


Scheme 2. General 1,3-dipolar cycloaddition.

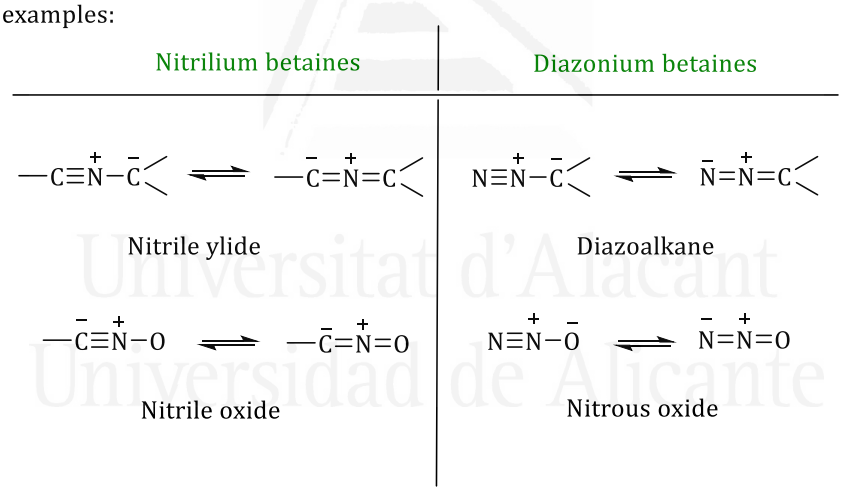
[39] Reissig, H. U.; Breugst, M. *Angewandte Chemie International Edition.* **2020**.
[40] Padwa, A.; Pearson, W. H. Eds. *Wiley & Sons*, Inc: Hoboken, New Jersey, **2003**.
[41] Kumar, S.; Kumar, V.; Singh, S. P. *Pericyclic Reactions,* **2016,** 231–282.

Due to the structural variety of dipolarophiles such as (alkenes, alkynes, carbonyls and nitriles) and dipoles which are classified into two groups: a) propargyl-allenyl type such as (azides, nitrile oxides, nitrile imines), and allyl type such as (azomethine ylides, nitrones ylides, carbonyl ylides) having a three-atom skeleton carrying at least one hetero atom, these reactions open a way very common and versatile tool for the synthesis of five heterocyclic compound members[38] (Scheme 3).

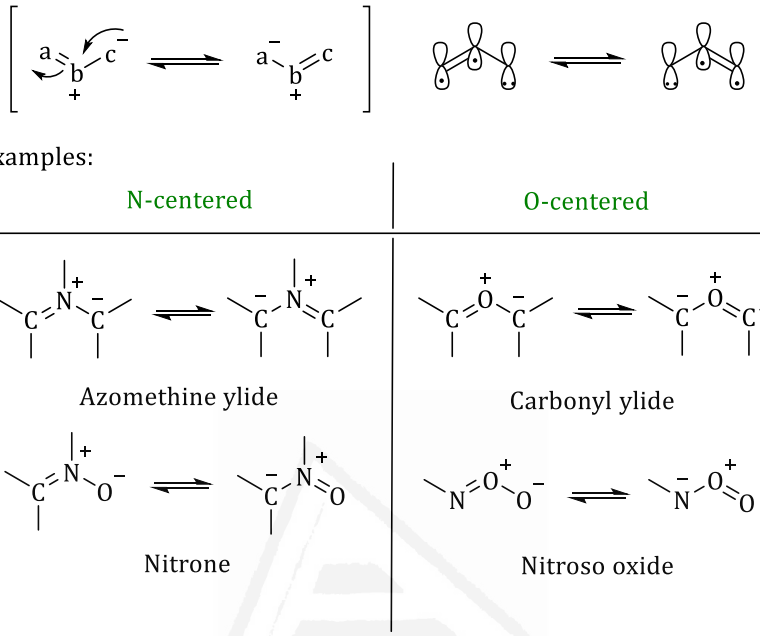
a) Propargyl-allenyl type



examples:



b) Allyl type



Scheme 3. Types of dipoles used in 1,3-DCs.

The concept of 1,3-DC reactions was first introduced by Huisgen and colleagues in 1960.[42] After mechanistic studies, two types of these reactions were introduced: stepwise which was proposed by the group of Firestone and concerted which was mainly suggested by Huisgen. [43,44,45] after years of research

[42] Huisgen, R.; Grashey, R.; Sauer J. *Chemistry of alkenes* (New York : Interscience). **1964**.
[43] Benchouk, W.; Mekelleche, S. M. *J. Mol. Struct.* (THEOCHEM). **2008**, *46* , 852.
[44] Huisgen, R. *J. Org. Chem.* **1968**, *33*, 2291.
[45] Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403.

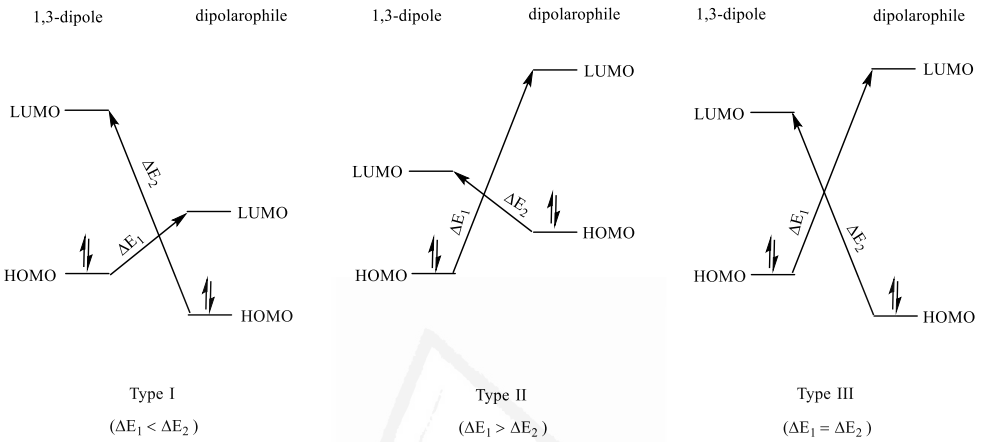
it has been concluded that 1,3-dipolar cycloaddition reactions take place via a concerted mechanism [3+2].[46,47,48]

The concerted mechanism was specified by some following characterizations: single-step, five-center cycloaddition, and involves a total of 6π electrons (π4s + π2s), 4 electrons from the 1,3-dipole and 2 electrons from the dipolarophile.[49] In accordance with the rules of Woodward and Hoffmann,[50] the combination of three p_z orbitals of dipole 1,3 and two p_z orbitals of dipolarophile takes place suprafacially.[51]

In concerted 1,3-DC reactions, regioselectivity and reactivity can be interpreted and explained using the frontier molecular orbital theory (FMO),[50] from which they are controlled by the energies of HOMO (highest energy occupied molecular orbit) and LUMO (lowest energy unoccupied molecular orbit) of both 1,3-dipole and dipolarophile. Type I corresponds to the FMO interaction between (HOMOdipole) and (LUMOdipolarophile). This type is also called normal electrons demand (NED) 1,3-DCs. Type II is the case of the reaction whose prevalent interaction is (LUMO-dipole) and (HOMO-dipolarophile). This type of cycloaddition is also called inverted-electron demand (IED) 1,3-DC reaction. Finally, type III occurs when the differences in the HOMO and LUMO energies of the 1,3-dipole/dipolarophile pair are

[46] Tanaka, J.; Kanemasa, S. *Tetrahedron.* **2001,** *57*, 899.
[47] Huisgen, R.; Padwa, A. In *1,3-Dipolar cycloaddition chemistry*, New York: Wiley-Interscience, **1984.**
[48] Di Valentin, C.; Freccero, M.; Gandolfi, R.; Rastelli, A. *J. Org. Chem.* **2000,** *65*, 6112.
[49] Emamian, S.R.; Ali-Asgari, S.; Zahedi, E. *J. Chem Sci*. **2014**, *126*, 293-302.
[50] Carey, F.-A and Sundberg, R.-J. Advanced Organic Chemistry, 5th edn, New York: Springer, **2007.**
[51] Fiorot, R. G.; Vilhena, F. de S.; & Carneiro, J. W. de M.. *Journal of Molecular Modeling,* **2019**. *25(10).*

similar,[52,53] and implies that both interactions are important. In this case, either NED or IED can occur[54] (Scheme 4).



Scheme 4. Three types of interactions between HOMO and LUMO orbitals of a 1,3-dipole/dipolarophile pair.

Reactivity of 1,3-Dipoles in Cycloadditions

As it was mentioned before, 1,3-DC are controlled by the HOMO and the LUMO of both reactants, the reactivity of 1,3-dipoles depends on the nature of the employed dipolarophile. The presence of an electron-withdrawing group on the dipole or dipolarophile lowers the energy level of both the HOMO and

[52] Sustmann, R.; Shubert, R. *Tetrahedron Lett*. **1972,** *13*, 4271.
[53] Domingo, L. R.; Aurell, M. J.; Arnó, M. A.; Sáez, J. A. *J. Mol. Struct*. (THEOCHEM) **2007,** *811*, 125.
[54] Pérez, P.; Domingo, L. R.; Aurell, M. J.; Contreras, R. *Tetrahedron.* **2003,** *59*, 3117.

LUMO, while the presence of an electron-donating substituent raises the energy of both. On the other hand, the conjugating substituent increases the energy of the HOMO and decreases the energy of the LUMO. This explains that the presence of substituents can lead to an increase or a decrease in the rate of the reaction.[41]

The Diels-Alder (4+2) Cycloaddition Reaction

The Diels-Alder reaction is one of the most important, powerful and fascinating synthetic transformations known. It offers easy access to six-membered carbo- and heterocycles in a chemo-, regio- and stereoselective manner.[55] The Diels-Alder reaction was first described by Otto Diels and Kurt Alder in 1928, thanks to the discovery of this reaction, they won the Nobel Prize in chemistry in 1950.[56]

The Diels-Alder reaction is a [4 + 2] type cycloaddition reaction between two partners, this means that one of the partners has 4 electrons (diene) and the other component has 2 electrons (dienophile) which can be a double or triple bond. Therefore, the overall 6 electrons are involved, to form a substituted cyclohexene derivative with the formation of two new σ-bond (Scheme 5).

[55] Klas, K.; Tsukamoto, S.; Sherman, D. H.; & Williams, R. M. *The Journal of Organic Chemistry,* **2015**. *80(23), 11672–11685*–b) Funel, J. A.; Abele, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 3822; c) Kotha, S.; Chavan, A. S.; Goyal, D. ACS. Comb. Sci. **2015**, *17*, 253.
[56] The reactivity of the reactions depends on the lowest separation energy between the HOMO and LUMO orbitals. The presence of the substituents influences the lowering of these energy levels.

Scheme 5. Diels-Alder reaction between a diene and a dienophile

Under the effect of temperature, some Diels-Alder reactions are reversible, these reactions are translated by the dissociation of the adduct and they are called retro-Diels-Alder (rDA). Cycloreversion is obtained when the reagents are very stable. If the reagents are not obtained, the cycloreversion is then accompanied by a decomposition or a transformation.[57,58]

Diels-Alder Mechanism

Inter- and intramolecular[59,60] Diels-Alder reactions are widely documented,[61] the mechanisms of Diels-Alder reactions have often been known for the most interesting subjects of controversy, discussion and misunderstanding.[62,63] The mechanism of the Diels-Alder reaction has been

[57] Dong, X.; Duan, R.-T.; Ni, Y.-P.; Cao, Z.-J.; Chen, L.; & Wang, Y.-Z. *Polymer Degradation and Stability,* **2017**. *146, 105–112.*

[58] P. Reutenauer, Diels-Alder reactions and Constitutional Dynamic Chemistry. Thesis, University of Louis Pasteur of Starsbourg, Institute of Science and Engineering, Supramolecular, (**2006**).

[59] Corey, E. J. *Angew. Chem., Int. Ed*. **2002**, *41*, 1650.

[60] Bear, B. R.; Sparkes, S. M.; Shea, K. j. *Angew. Chem., Int. Ed*. **2001**, *40*, 820.

[61] Kollmann, Y.; Zhang, W.; Schilling, T.; Zhang and Riemer, D. *Green Chem*., **2019**.

[62] Carruthers, W. Cycloaddition Reactions in OrganiC Synthesis; Pergamon Press: Oxford. **1990**.

[63] Takao, K. I.; Munakata, R.; Tadano, K. I. *Chem. Rev.* **2005**, *105*, 4779.

studied according to several criteria,[64,65] see whether it is synchronous or asynchronous, concerted or not,[66,67,68] the Diels-Alder reaction mechanism has been extensively studied over the years of research,[69] the most popular and suitable way to analyze these mechanisms, was to follow the selective rules of Woodward-Hoffmann.[70,71]

Two competing alternative routes have been concluded after long debates:

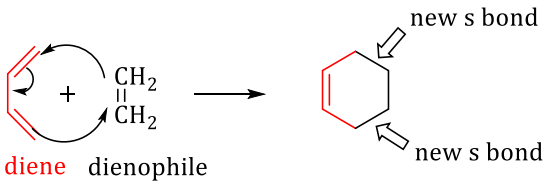
- A concerted mechanism in the transition state is formed in a single step, with the contribution of the formation and breaking of the links to the state structure of transitions, simultaneously (synchronous path) or sequentially (asynchronous path).[72]

- A non-concerted mechanism, in other words progressive, in which a neutral intermediary (biradical) or a polar intermediary (zwitterionic) is involved as an intermediate state.[73]

After all the efforts and studies provided, it has been shown that theory and experience are in good agreement for the concerted mechanism for the

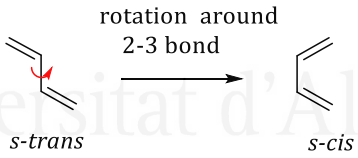
[64] Woodward, R. B.; Hoffman, R. *Angew. Chem., Int*. End. Engl. **1969**, *8*, 781.
[65] Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; & Vassilikogiannakis, G. *Angewandte Chemie International Edition,* **2002**. *41(10), 1668–1698.*
[66] Hoffmann, H. M. *Angew. Chem. Int. Ed. Eng*. **1973**, *12*, 819.
[67] Brieger, G.; Bennett, J. N. *Chem. Rev*. **1980**, *80*, 63.
[68] Horn, B. A.; Herek, J. L.; Zewail, A. H. *J. Am. Chem. Soc*. **1996**, *118*, 8755.
[69] Nicolaou, K. C.; Snydes, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., In. Ed*. **2002** , *41*, 1668.
[70] Jursic, B. S. *J. Mol. Struct (THEOCHEM).* **1999**, *459*, 215.
[71] Woodward, R. B. *Acc. Chem. Res*. **1968**, *1*, 17.
[72] Svatunek, D., Pemberton, R. P., Mackey, J. L., Liu, P., & Houk, K. N. *The Journal of Organic Chemistry.* **2020**.
[73] Domingo, L. R. *Journal of the Chilean Chemical Society,* **2014***. 59(3), 2615–2618.*

Diels-Alder reaction,[74,75] this mechanism involves a concerted cyclic reorganization of the electrons between a diene with (4π electrons) and a dienophile (2π electrons)[76] (Scheme 6).



Scheme 6. The Diels-Alder Reaction between butadiene and ethylene

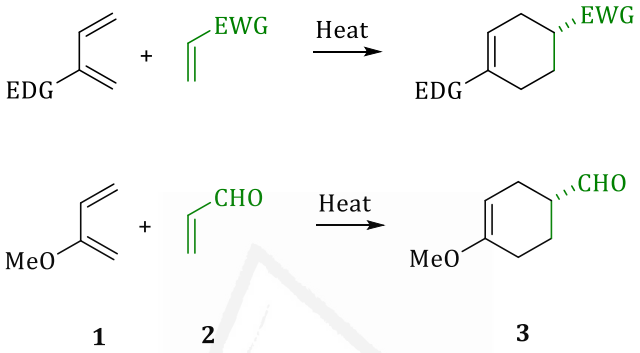
A Diels-Alder reaction occur when the diene molecule must adopt what is called the *s-cis* conformation (Scheme 7) in order to bind to the dienophile with the two terminal carbon atoms simultaneously.



Scheme 7. The *s-trans* and *s-cis*-conformations of 1,3-butadiene (rotation around the σ-bond).

[74] Sakai, S. *J. Phys. Chem*. A, **2000**, *104*, 922.
[75] Townsend, C. A. *ChemBioChem,* **2011**. *12(15), 2267–2269.*
[76] Bakalova, S. M.; Gil Santos, A. *The Journal of Organic Chemistry,* **2014**. *79(17), 8202–8211.*

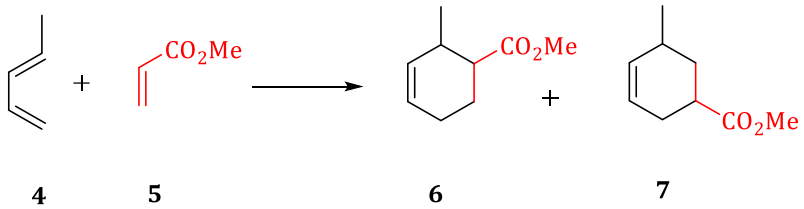
The Diels-Alder reaction is more easily achieved by using dienes with electron donating substituents **1** and dienophiles with electron attracting substituents **2**. And this combination corresponds to normal electron demand (Scheme 8)



Scheme 8. Diels-Alder using dienes with electron donating substituents and dienophiles with electron attracting substituents.

Lewis acids accelerate the Diels-Alder reaction such as boron trifluoride, $ZnCl_2$, $TiCl_4$, $SnCl_4$, $EtAlCl_2$, MeAlCl, $LiClO_4$, $Mg(ClO_4)_2$. The catalyzed reactions show increased regio-selectivity and stereo-selectivity compared to the non-catalyzed reaction[77,78] (Scheme 9).

[77] Vermeeren, P.; Hamlin, T. A.; Fernández, I.; Bickelhaupt, F. M. *Angewandte Chemie International Edition* **2020**.
[78] Kumar, K.; Waldmann, H.; Eschenbrenner-Lux, V. *Angew Chem* **2014**, *126*, 11326-11337.



4 **5** **6** **7**

without catalyst	90%	10%
with lewis acid $AlCl_3$	98%	2%

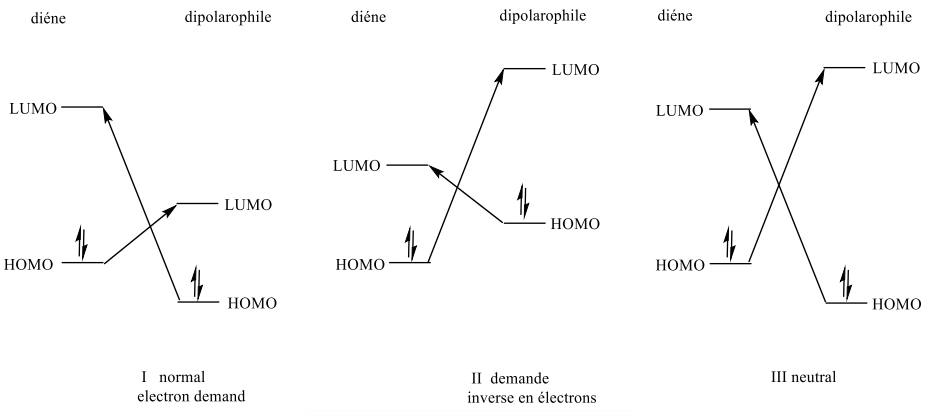
Scheme 9. The effect of the use of catalysts on the Diels-Alder reaction

Reactivity of the reaction

According to FMO theory the reaction can be stated as follows:

- Reactions can only proceed if the highest occupied molecular orbital (HOMO) of one reagent and the lowest unoccupied molecular orbital (LUMO) of the other reagent are positioned so that the lobes of the same sign overlap,[79] these reactions have been classified by Sustmann into three categories[80] according to the possible arrangements of molecular orbitals (Scheme 10).

[79] Fernández, I.; Bickelhaupt, F. M. *Chemistry - An Asian Journal,* **2016**. *11(23), 3297–3304.*
[80] Sustmann, R. Tetrahedron Lett. **1971,** 21, 2717-2721.

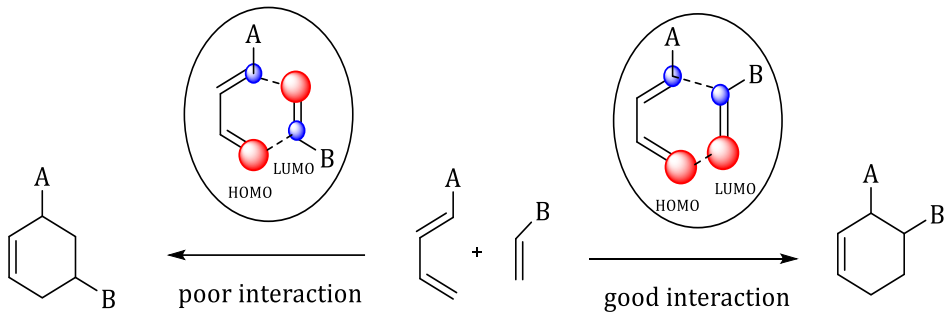


Scheme 10. Different possible arrangements of the molecular orbitals of the diene and dienophile.

The trend of the reactions depends on the lowest separation energy between the HOMO and LUMO orbitals. The presence of the substituents influences the lowering of these energy levels.

The regioselectivity of Diels-Alder reaction

In the Diels-Alder rection regioselectivity essentially depends on the type of electronic demand and on the relative size of the coefficients of the molecular orbitals of the reagents involved. Two large coefficients and two small assembling is the best HOMO-LUMO match to decrease the activation energy of the Diels-Alder reaction and, consequently, the increment of the relative speed (Scheme 11).



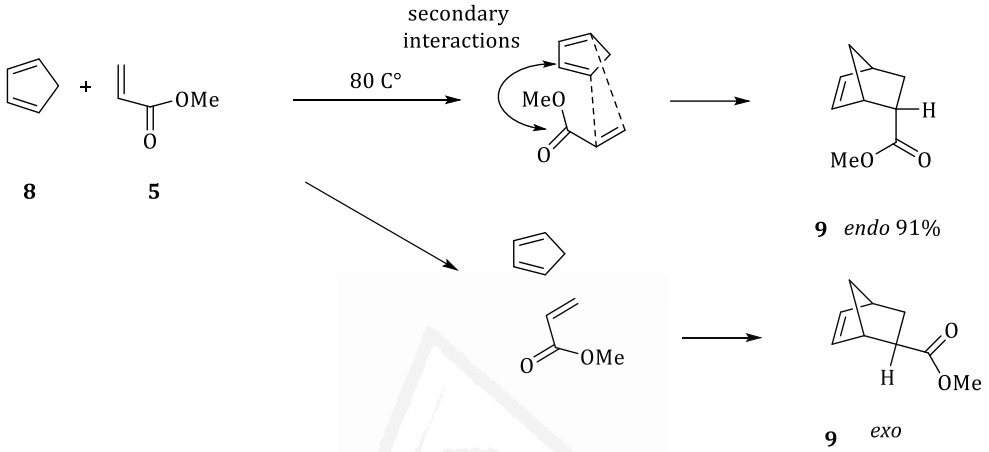
Scheme 11. The regioselectivity of Diels-Alder reaction predicted by FOT.

The Stereoselectivity of Diels-Alder reaction

One of the main features of the Diels-Alder reaction is the endo rule. Hence the *endo*-approach is favored. If two approaches are possible, the so-called secondary interactions, attributed to stereo-electronic effects, between the lobes of the orbitals of the dienophile substituents and those of the conjugated diene system, promote this type of approach (Scheme 12). These secondary interactions generally make it possible to predict/determine the overall selectivity. This rule seems strictly applicable to cyclic systems, whilst we also note that the formation of a major product for acyclic systems, in particular when using catalysis with Lewis acids, is consistent with this rule.[81,82]

[81] Leal, R. C.; Pereira, D. H.; Custodio, R. *Computational and Theoretical Chemistry,* **2018**. *1123, 161–168.*
[82] Larrañaga, O.; de Cózar, A. *ChemistryOpen,* **2019**. *8(1), 49–57.*

The synthesis of Diels-Alder *exo*-adducts is possible by the use of substrates[83] or specific catalysts.[84,85]

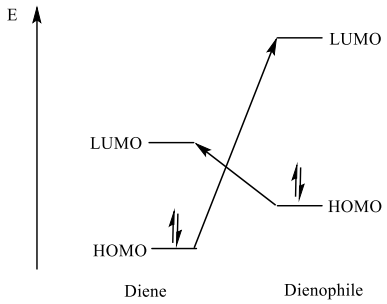


Scheme 12. The stereoselectivity of the Diels-Alder reaction.

The Inverse electron demand Diels–Alder reaction

Diels-Alder reactions with reverse electronic request, are cycloadditions in which the reaction takes place between the LUMO of the diene and the HOMO of the dienophile according to the electronic nature of the groups present on the two partners[86] (Scheme 13).

[83] Oh, T.; Reilly, M. *Org.Prep.Proced.Int*. **1994**, *26*, 129-158.
[84] Anderson, B.; Wulff, W. D.; Powers, T. S.; Tribbitt, S.; Rheingold, A. L. *J.Am.Chem.Soc*. **1992**, *114*, 10784-10798.
[85] Walter, C. J.; Sanders, J. K. M.; *Angew.Chem.Int.Ed.Engl*. **1995**, *34*, 217-219.
[86] Spino, C.; Rezaeï, H.; Dory, Y. L. *J. Org. Chem*. **2004**, *69*, 757.



Scheme13. Border Orbital Overlay Diagram in the Inverse electron demand Diels–Alder reaction

The presence of donor groups as substituents on the dienophiles raise the border orbitals and therefore their HOMOs, while the presence of the attractor groups on the dienes lower their border orbitals and therefore their LUMOs. The resulting reduction in the energy difference between HOMOs and LUMOs promotes the reverse HOMO (dienophile) / LUMO (diene) interaction.

Hetero-Diels–Alder reactions

Hetero Diels-Alder reactions are reactions involving at least one heteroatom.[87,88] Carbonyl groups, for example, can react perfectly with dienes to give dihydropyran rings, this reaction is known as the oxo-Diels-Alder reaction, and imines can be used, as a dienophile, or various diene sites, to form various N-heterocyclic compounds by the aza-Diels-Alder reaction. On the other

[87] Skrzyńska, A., Frankowski, S., & Albrecht, Ł. *Asian Journal of Organic Chemistry* **2020**.
[88] Kořenková, M.; Kremláček, V.; Hejda, M.; Turek, J.; Khudaverdyan, R.; Erben, M.; Dostál, L. *Chemistry – A European Journal.* **2019**.

hand, nitroso compounds (R-N=O) can also react with dienes to form oxazines.[89] (Figure 2).

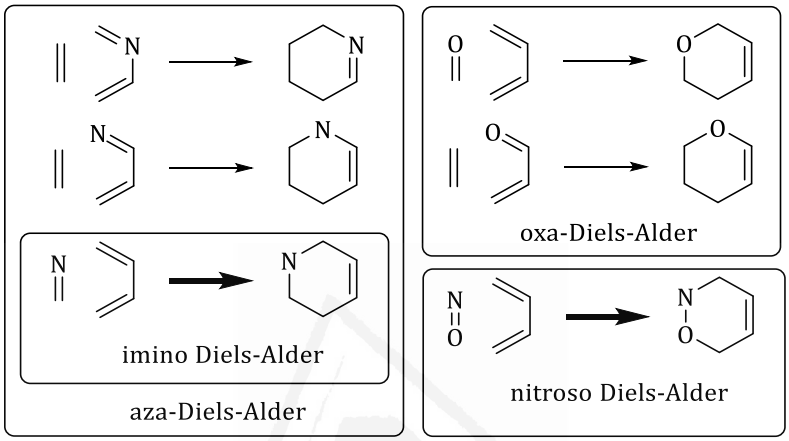
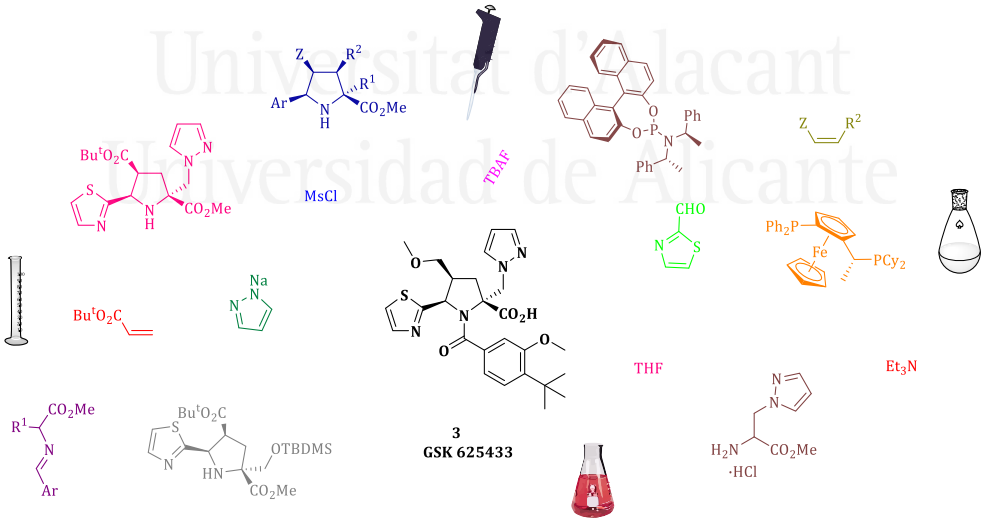


Figure 2. Hetero-Diels–Alder reactions

[89] Eschenbrenner-Lux, V.; Kumar, K.; Waldmann, H. *Angewandte Chemie International Edition,* **2014**. *53(42), 11146–11157.*

CHAPTER 1:

Dual chiral silver catalyst in the synthetic approach to the core of hepatitis C virus inhibitor GSK 625433 using enantioselective 1,3-dipolar cycloaddition of azomethine ylides and electrophilic alkenes



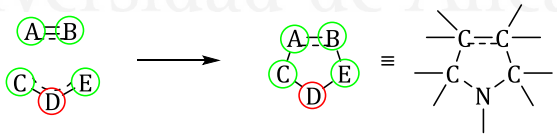
Brief bibliographic background

Azomethines ylides

As it was mentioned before, the 1,3-dipolar cycloadditions reaction constitutes a method of choice for the synthesis of heterocycles with a high control of the stereochemistry.

These reactions are carried out by the addition of a 1,3-dipole (system with 4 π electrons delocalized on 3 centers) to a multiple bond (system with 2 electrons π) to give heterocycles forming two new σ bonds.

Azomethine ylides are part of the 1,3-dipole family which C and E are carbon atoms and D is a nitrogen atom, as they constitute the simplest and most efficient way to generate, thanks to a cycloaddition, five-membered cycles containing nitrogen (pyrrolidine and pyrroline, Scheme 14) by their cycloadditions with alkenes.

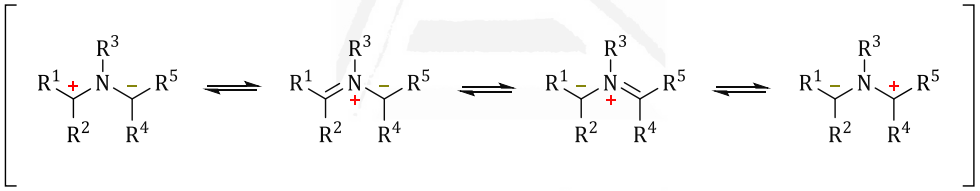


Scheme 14. Cycloaddition reaction of Azomethine ylides.

Their cycloaddition carried out with the alkenes is a six-electron process π [$\pi^4{}_s + \pi^2{}_s$], which means that the process is suprafacial-suprafacial and that it is allowed thermally by the rules of Woodward-Hoffmann.[90]

Azomethine ylides can also react with alkynes, heteroalkenes and heterocumulenes to give the corresponding heterocycles.

Their allyl type structure, which is rich in electrons with 4π electrons distributed over three CNC atoms, makes them very reactive, the fact of adopting a current resonance structure which has the positive charge on the nitrogen and the negative charge on the one of the two adjacent carbon atoms (Scheme 15).

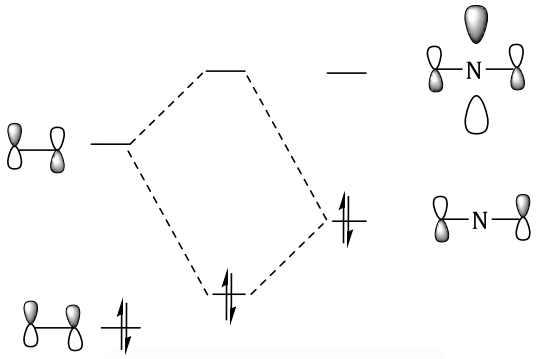


Scheme15. Resonance structures of azomethine ylides.

According to the theory of frontier molecular orbitals, azomethine ylides are considered to be electron-rich species, which means that the dominant interaction during cycloaddition is between the HOMO of dipole-1,3 and the LUMO of dipolarophile (Scheme 16).[91] This type of cycloaddition is favored

[90] S. R.; Ali-Asgari, S.; Zahedi, E. *Journal of Chemical Sciences,* **2014**. *126(1), 293–302.*
[91] Gulevskaya, A. V.; & Nelina-Nemtseva, J. I. *Chemistry of Heterocyclic Compounds,* **2019**.

when the dipolarophile is substituted by one or more electron-withdrawing groups.



Scheme 16. Dominant boundary orbital interaction involved in cycloaddition

Methods for generating azomethine ylides

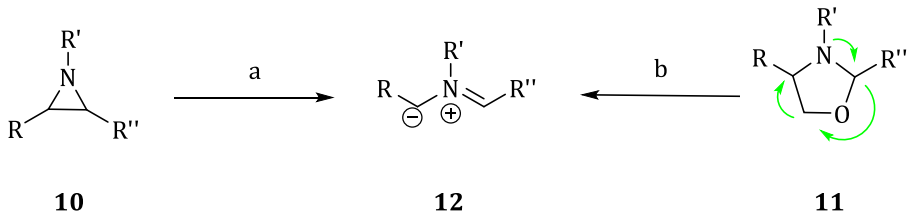
Azomethine ylides **12** are unstable intermediate species and must be generated *in situ* and to overcome this problem, a good number of methods were applied to be able to finally generate this dipole.[92] The first method was applied in 1965, and is based on the opening by breaking of the carbon-carbon bond of an aziridine **10** (Scheme 17-a).[93] The disadvantage in this method, is that the opening requires heating at high temperatures. On the other hand, by using electron-withdrawing groups, the activation energy of this transformation is lower. The generation of the ylide is possible at 200 °C, if the group R is an ester, and at 100 °C when the two groups R and R'' are esters .[94]

[92] Filatov, A. S.; Knyazev, N. A.; Ryazantsev, M. N.; Suslonov, V. V.; Larina, A. G.; Molchanov, A. P.; Stepakov, A. V. *Organic Chemistry Frontiers,* **2018**. *5(4), 595–605.*

[93] Chronopoulos, D. D.; Liu, Z.; Suenaga, K.; Yudasaka, M.; Tagmatarchis, N. *RSC Advances,* **2016**. *6(50), 44782–44787.*

[94] Nantogma, S.; Tia, R.; Adei, E.. *Computational and Theoretical Chemistry,* **2018**.

Another type of heterocycles called oxazolidines **11** can be converted to azomethine ylide by flash vacuum pyrolysis (Scheme 17-b).[95]

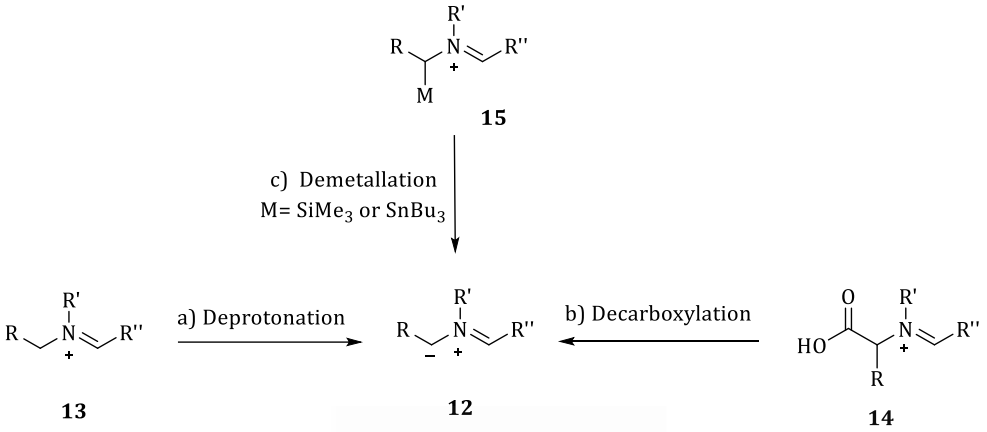


10 **12** **11**

Scheme 17. Generation of azomethine ylides by opening aziridines or by pyrolysis of oxazolidines.

A second strategy, which consists in eliminating a positively charged group in α position of an iminium (Scheme 18), has been studied. This general strategy can be classified according three specific approaches. The first was carried out for the first time by Deyrup in 1975,[96] and consists in carrying out a deprotonation at the α-position (Scheme 18-a). The major problem with this strategy is that this deprotonation requires very strong bases, such as NaHMDS. To overcome this problem, the group R must be an electron-withdrawing group, increasing the acidify of the neighboring proton of the iminium cation facilitating the deprotonation.

[95] Meyer, A.; & Ryan, J. *Molecules,* **2016**. *21(8), 935.*
[96] Deyrup, J. A.; Szabo, W. A. *J. Org. Chem.* **1975**, *40*, 2048.

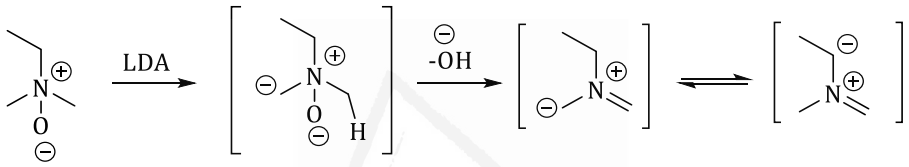


Scheme 18. Methods for generating azomethine ylides by elimination of a positively charged group.

The second approach consists of a decarboxylation of an α-amino acid (*N*-alkylated) once the latter is condensed on an aldehyde to generate an iminium salt (Scheme 18-b). Except that the use of this approach in organic synthesis is limited because it requires heating to high temperatures around 170°C. Finally,[97] the third approach is summarized in the alkylation of an imine using $TMSCH_2OTf$ followed by a desilylation of the iminium obtained and then the formation of the ylide (Scheme 18-c).[98] This strategy is believed to be the most effective method for generating unstabilized azomethine ylides.

[97] Rizzi, G. P. *J. Org. Chem*. **1970**, *35*, 2069.
[98] Meyer, A.; & Ryan, J. *Molecules,* **2016.** *21(8), 935.*

There is also another method of generating azomethine ylides, and this by deprotonation of tertiary amine oxide (Scheme 19).[99] This deprotonation is carried out using lithium diisopropylamide (LDA) in the presence of a dipolarophile. This approach may be limited because of the rapid balance between the different ylides that can be formed. Thus, several isomeric cycloadducts are generated.

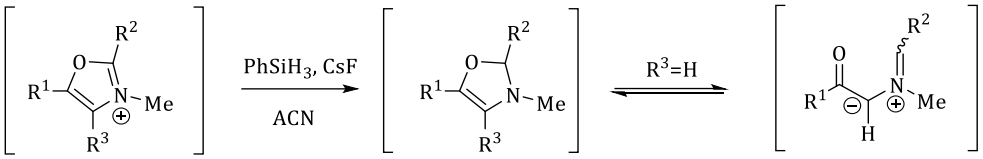


Scheme 19. Generation of azomethine ylides by deprotonation of tertiary amine oxide.

Other method of preparing azomethine ylide consists in opening 4-oxazolines.[100] Their preparation remains the greatest complication of this approach. The most effective method to generate this precursor was discovered by Vedejs. It consists in transforming an oxazolium **16** salt into oxazoline **17** thanks to a reduction using a hydride, or thanks to the addition of a cyanide anion (Scheme 20).[101] The oxazoline obtained is then in equilibrium with the corresponding open form, which is the azomethine ylide **18.**

[99] Najera, C., & Sansano, J. *Current Organic Chemistry,* **2003.** *7(11), 1105–1150.*

[100] Yoo, E. *Synlett,* **2015.** *26(16),* 2189–2193.
[101] a) Vedejs, E.; Grissom, J. W. *J. Am. Chem. Soc*. **1986**, *108*, 6433. b) Vedejs, E.; Grissom, J. W. *J. Org. Chem*. **1988**, *53*, 1876.

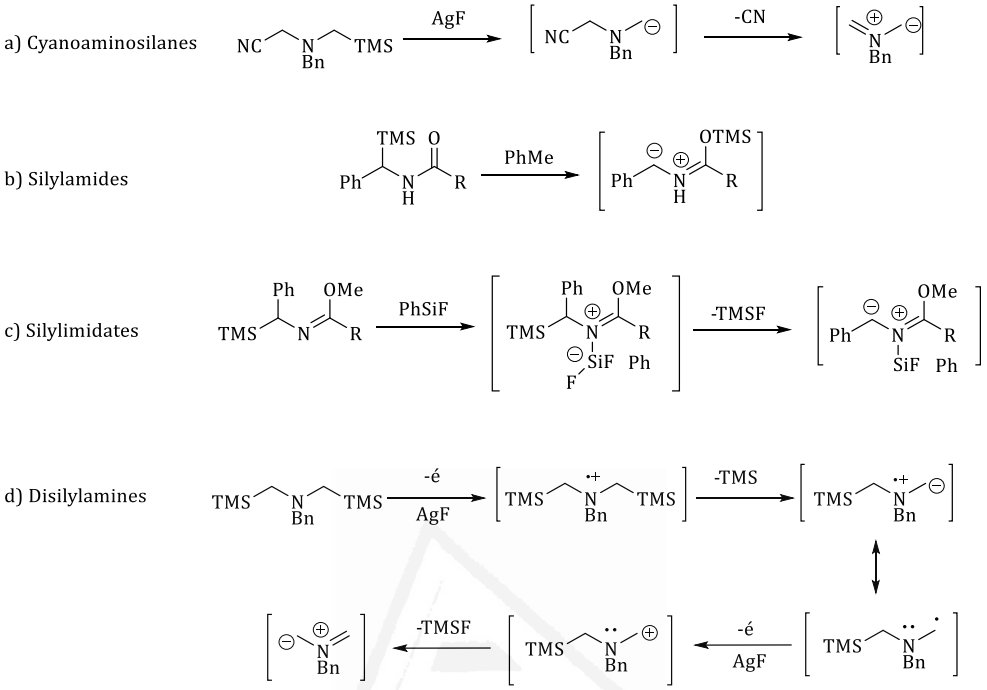


16 **17** **18**

Scheme 20. Generation of azomethine ylides by opening 4-oxazolines.

Four other strategies are involved in the generation of an azomethine ylide by desilylation. The first one is carried out by treatment of a cyanoaminosilane with a source of fluoride, therefore a desilylation followed by the elimination of the cyano group (Scheme 21a).[102] The second strategy consists in generating the azomethine ylide by a Brook-type rearrangement of a α-silylamide (Scheme 21b).[103] The third strategy like the previous one involves an imidate. But in this case, the imidate is preformed (Scheme 21c). Trifluorophenylsilane allows the generation of iminium and provides the fluoride ion necessary for desilylation.[104] The fourth strategy proceeds *via* a series of oxidations using silver fluoride (Scheme 21d).[105] The sequence begins with an oxidation of the amine, and generation of silver (0) and the fluoride ion. Followed by the elimination of a first trimethylsilyl group. Then, another trimethylsilyl oxidation-elimination sequence generates the azomethine ylide.

[102] Padwa, A.; Chen, Y.; Dent, W.; Hildegard, N. *J. Org. Chem*. **1985**, *50*, 4006.
[103] Ohno, M.; Komatsu, M.; Miyata, H.; Ohshiro, Y. *Tetrahedron Lett.*. **1991**, *32*, 5813.
[104] Washizuka, K.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1999**, *55*, 12969.
[105] Pandey, G.; Lakshmaiah, G.; Kumaraswamy, G. *J. Chem. Soc., Chem Commun*. **1992**, 1313.

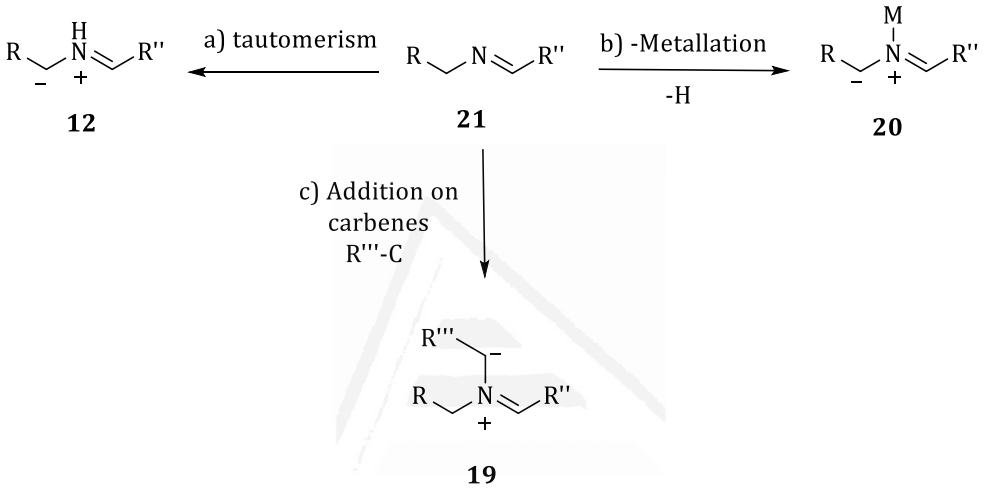


Scheme 21. Methods for generating azomethine ylides by elimination of a trimethylsilyl group.

Imines, rather than iminium cations, may also be involved in the generation of azomethine ylides. In this strategy there are three approaches to describe: a) tautomerism, and b) addition on carbenes c) *N*-metallation (Scheme22). The tautomerism, is very similar to the approach involving deprotonation. And, in this case, an electron-withdrawing group at position R is necessary.[106] According to the second approach, it is possible to *N*-alkylate the imine using carbenes or highly electrophilic carbenoids. Several examples have shown that this type of reaction was carried out using difluorocarbene,

[106] a) Grigg, R.; Kemp, J. *J. Chem. Soc., Chem. Commun.* **1977**, 125. b) Grigg, R.; Kemp, J. *J. Chem. Soc., Chem. Commun.* **1978**, 109.

generated from chlorodifluoromethane,[107] or using metallocarbenoids in intramolecular or intermolecular manners. In the third approach the formation of an iminium salt mediated by the complexation between a metal and the nitrogen of the imine takes place,[108] which, followed by deprotonation using a base, generates the azomethine ylide.



Scheme 22. Methods of generating azomethine ylides from imines.

The major advantage of this approach is the possibility of generating optically pure cycloadducts, thanks to the use of chiral ligands linked to the metal center.[109] This deprotonation is carried out using lithium diisopropylamide (LDA) in the presence of a dipolarophile. This approach may

[107] Casella, L.; Gullotti, M.; Pasini, A.; Psaro, R. *Synthesis* **1979**, 150.
[108] McCarthy, J.R.; Barney, C. L.; O'Donnell, M. J.; Huffman, J. C. *J. Chem. Soc., Chem. Commun.* **1987**, 469.
[109] a) Roussi, G.; Zhang, *J. Tetrahedron* **1991**, *47*, 5161. b) la déprotonation, Takayama, H.; Nomoto, T. *J. Chem. Soc., Chem. Commun*. **1982**, 408.

be limited because of the rapid balance between the different ylides that can be formed. Thus, several isomeric cycloadducts are generated.

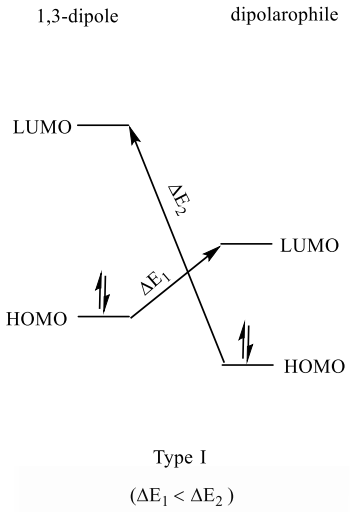
This way of generating azomethine ylides is the most used because it requires very mild reaction conditions than others, it gives high regio-, diasterioselectivities, and in the case where a chiral ligand is added the reaction becomes enantioselective.

1,3-Dipolar Cycloaddition of Stabilized Azomethine Ylides

The 1,3-dipolar cycloaddition reaction of azomethine ylides is one of the best-known pathways to access to pyrrolines and pyrrolidines.[110] As already described, the different azomethine ylides are known thanks to the functional groups attached to C-N-C system. When an electron withdrawing group (EWG), is bonded to one of the terminal carbons, the dipole is known as stabilized ylide, due to its resonance forms. According to Sustmann's[111]classification, the cycloaddition reactions of azomethine ylides are type I, which corresponds to the FMO interaction between (HOMOdipole) and (LUMOdipolarophile). This type is also called normal electrons demand (NED) (Scheme 23).

The reaction is favored by electron-deficient of dipolarophile (alkenes or alkynes) because of their low energy LUMO. Also, the presence of an electron donating group (EDG) on the ylide part increases the energy of the $HOMO_{dipole}$.

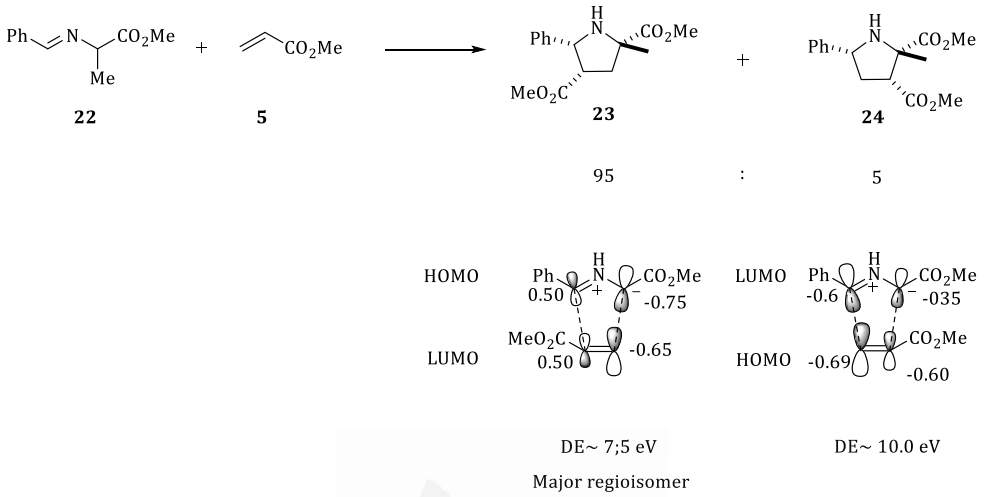
[110] Bdiri, B.; Zhao, B.-J.; Zhou, Z.-M. *Tetrahedron: Asymmetry,* **2017**. *28(7), 876–899.*
[111] Ríos-Gutiérez, M.; Domingo, L. R. *European Journal of Organic Chemistry.* **2018***.*



Scheme 23. Type I cycloaddition

The regioselectivity of this cycloaddition[112,113] is controlled by the energies of HOMO and LUMO of both 1,3-dipole and dipolarophile. An example has been chosen to describe and explain this regioselectivity according to the coefficients of both orbitals (Scheme 24).

[112] Dizaji, N. J.; Nouri, A.; Zahedi, E.; Musavi, S. M.; Nouri, A. *Research on Chemical Intermediates,* **2016**. *43(2), 767–782.*
[113] a) Danielsson, J.; Toom, L.; Somfai, P. *Eur. J. Org. Chem*. **2011**, 607–613. d) Khlebnikov, A. F.; Novikov, M. S. *Chem. Heterocycl. Comp***. 2012**, *48*, 179–190.



Scheme24. Regioselectivity of the 1,3-DC between an azomethine ylide and methyl Acrylate

On the other hand, the stereospecificity of the dipole-dipolarophile approach in 1,3-dipolar cycloaddition of azomethine ylides has been widely studied, As it mainly depends on the configuration of the dipolarophile, which will maintain the same arrangement of its two substituents in the five-membered ring, a *trans*-arrangement for the 1,2-disubstituted *E*-alkene and *cis*-arrangement for the 1,2-disubstituted *Z*-alkene.

The high diastereoselection observed is due to the coordinating the Lewis acid with the dipolarophile, which plays a catalytic role, with one or both reactants.[114] Thus, when the metal coordinates the dipolarophile it guides it in

[114] a) Broggini, G.; Molteni, G.; Terraneo, A; Zecchi, G. *Heterocycles* **2003**, *59*, 823–858. b) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887–2902. c) Álvarez-Corral, M.; Muñoz-Dorado, M; Rodríguez-García, I. *Chem Rev.* **2008**, *108*, 3174–3198. d) Naodovic,

a specific direction (*endo*-approach) due to stereo-electronic effects, and therefore an improvement in diastereoselectivity is observed. And when the metal is coordinated with a chiral ligand, it is possible to control the regio-, diastereo- and enantioselectivity.**Erreur ! Signet non défini.**

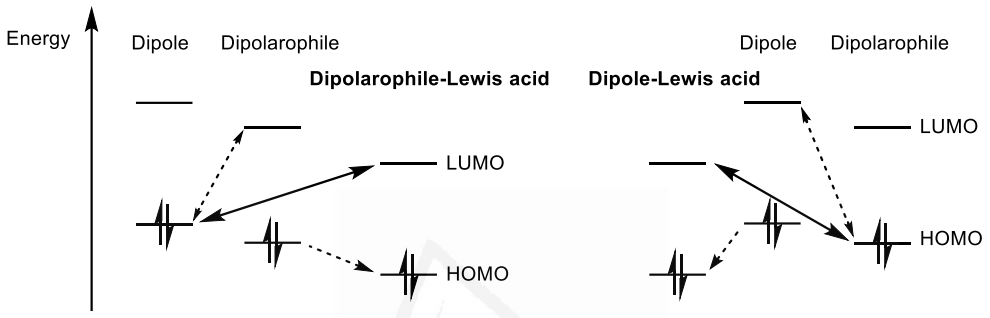


Figure 3. Effect on the dipolarophile (left) or on the dipole (right) frontier orbitals of a Lewis acid.

Enantioselective 1,3-Dipolar Cycloaddition

Cycloaddition reactions in general, such as the Diels-Alder reaction, 1,3-dipolar cycloaddition and cyclopropanation, etc... have always been used in organic synthesis in order to generate a variety of carbocyles and heterocycles,[115] which are considered as motifs present in the structure of numerous biologically active substances. These reactions are generally carried out under thermal conditions or using catalyst as organocatalysts,[116] or chiral

M.; Yamamoto, H. *Chem Rev.* **2008**, *108*, 3132–3148. e) Nájera, C.; Sansano, J. M.; Yus, M. *J. Braz. Chem. Soc.* **2010**, *21*, 377–412.

[115] Pinho e Melo, T. *Current Organic Chemistry*, **2009**, *13*(14), 1406–1431.
[116] Nájera, C., Sansano, J. M.; Yus, M. *Journal of the Brazilian Chemical Society.* **2010,** *21(3),* 377–412.

Lewis acids,[117] which are involved in the activation of a wide variety of chemical reactions.[118] There are also biocatalysts which can be reused in an organic synthesis reaction as, for example, enzymes.[119,120] However, in this introduction only chiral organocatalitic and Lewis acid-catalyzed 1,3-DC will be described.

Chiral Organocatalysts

Over the past few years, several catalytic methods involving chiral organocatalysts have been developed with the aim of building mono and polycycles in a regio- and stereoselective manner.[121]

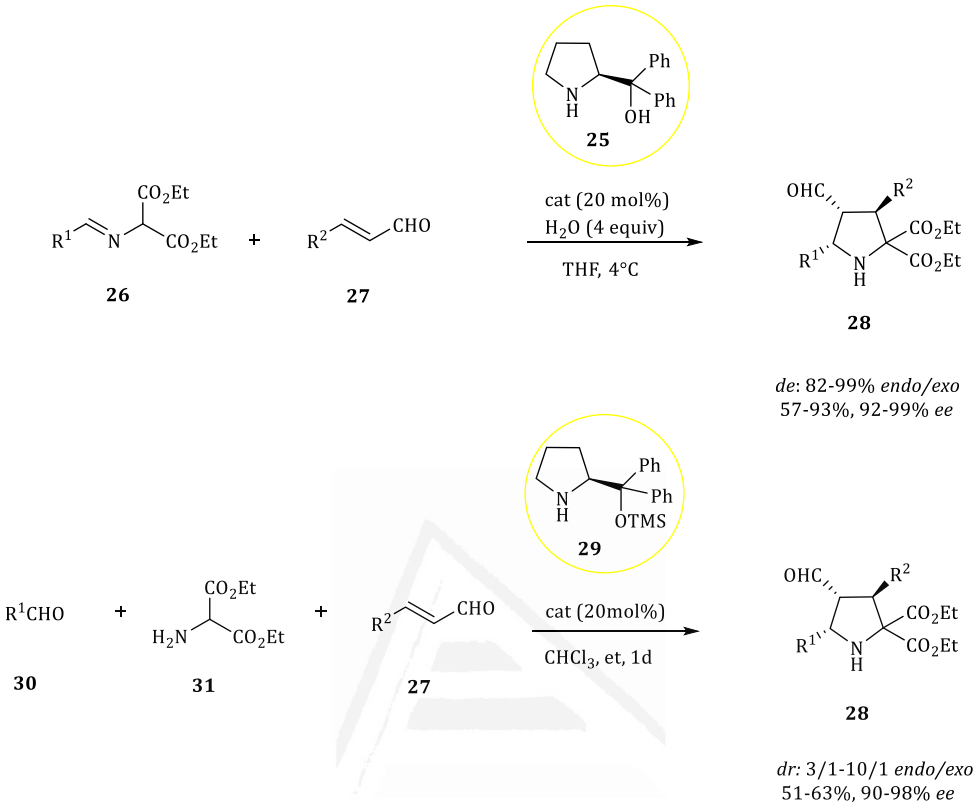
Organocatalysis is a method which involves the use of a non-metallic organic catalyst in order to speed up chemical reactions. These transformations can be distinguished from organometallic and enzymatic catalysis by the use of simple organic molecules which are generally chiral in asymmetric reactions,[122,123] which has made the potential of organic catalysis well developed and expand.[124] These reactions are among the most important reactions in chemistry because they lead to the stereoselective formation of new

[117] Caleffi, G. S.; Larrañaga, O.; Ferrandiz Saperas, M.; Costa, P. R. R.; Nájera, C.; de Cozar, A.; Sansano, J. M. *The Journal of Organic.* **2019**.
[118] Davenport, A. J.; Davies, D. L.; Fawcett, J.; Garratt, S. A.; Lad, L. Russell, D. R. *Chem. Commun*. **1997**, 2347.
[119] Ivan. R.; Mikel. O. G.; Antonio. A.; Ana. G.; Jesus. J. B.; M. T. S.; Aitziber. L. C.; Fernando P. C. *J. Am. Chem. Soc*. **2020,** *142*, 762−776
[120] Zhang, X.; Houk, K. N. *Acc. Chem. Res*. **2005**, *38* (5), 379-385
[121] Moyano, A.; Rios, R. *Chem. Rev*. **2011**, *111*, 4703-4832.
[122] Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today*. **2007**, *12*, 8-27.
[123] a) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267-9331; b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed*. **2001**, *40*, 3726-3748.
[124] Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; JØrgensen, K. A. *J. Am. Chem. Soc*. **2005**, *27*, 6964-6965.

products having chiral centers.[125] Most of the catalysts explored are based on chiral amines such as (amino acids, peptides, alkaloids, chiral imidazolidinones, etc…).[126]

Historically, the first 1,3-DC reaction between nitrones and aldehydes using an organocatalyst was published by McMillan. After seven years of research it was published the first organocatalyzed [3 + 2] cycloaddition, which takes place between the dipoles of azomethine ylides and the α,β-unsaturated aldehydes. This reaction was catalyzed by the prolinol derivative **25** in order to generate stereoisomerically pure highly functionalized polysubstituted pyrrolidines **28,** with complete regioselectivity, high diastereo- and enantioselectivity and in excellent yields.[127] Also the multicomponent version of this reaction was published by Córdova *et al*,[128] after obtaining a final product with moderate yields and high enantiomeric excesses (Scheme25).

[125] Frisch, K.; Landa, A.; Saaby, S. JØrgensen; K. A. *Angew. Chem., Int. Ed*. **2005**, *44*, 6058-6063.
[126] a) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481-2495; b) Chen, W.; Du, W.; Duan, Y. Z.; Wu, Y.; Yang, S. Y.; Chen, Y. C. *Angew. Chem., Int. Ed*. **2007**, *46*, 7667-7670; c) Kizirian, J. C. *Chem. Rev*. **2008**, *108*, 140-205; d) Peng, F.; Shao, Z. *J. Mol.Cat. A: Chemical* **2008**, *285*, 1-13; e) Armstrong, A.; Bhonoah, Y.; White, A. J. P. *J. Org. Chem*. **2009**, *74*, 5041-5048. 5
[127] Vicario, J.,Reboredo, S.,Badia. D., Carrillo, L. *Angew. Chem., Int. Ed*. **2007**, *46*, 5168-5170
[128] Ibrahem, I.; Rios, R.; Vesely, J.; Cordova, A. *Tetrahedron Lett* **2007**, *48*, 6252-6257.



Scheme25. Prolinol derivative catalyzed 1,3-Dipolar Cycloaddition.

In addition, there are other organocatalysts which have been used in these reactions with 1,3-dipolar azomethine ylides, such as, Binol phosphoric acid derivatives **32, 33**,[129,130] guanidines **34,**[131] squaramides **35,**[132] thioureas

[129] Chen, X. H.; Zhang, W. Q.; Gong, L. Z. *J. Am. Chem. Soc*. **2008**, *130*, 5652-5653.
[130] He, L.; Chen, X. H.; Wang, D. N.; Luo, S. W.; Zhang, W. Q.; Yu, J.; Ren, L.; Gong, L. Z. *J. Am. Chem. Soc.* **2011**, *133*, 13504-13518.
[131] Nakano, M.; Terada, M. *Synlett*. **2009**, 1670-1674.
[132] Tian, L.; Hu, X. Q.; Li, Y. H.; Xu, P. F. *Chem. Commun*. **2013**, *49*, 7213-7215.

36,[133,134] and 4-imidazolidinone **37.**[135] With them all good results are obtained in the synthesis of highly substituted pyrrolidines with high enantiomeric excesses (Figure 4).

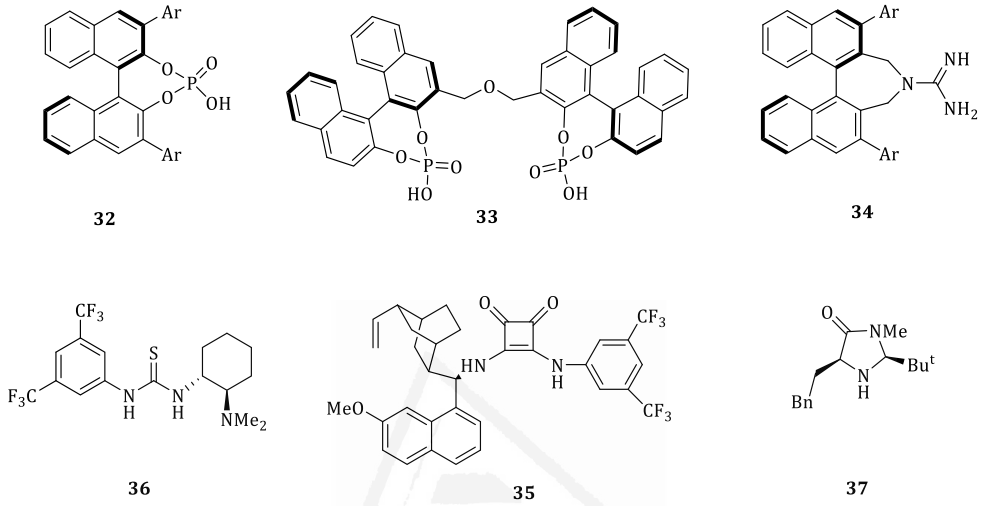


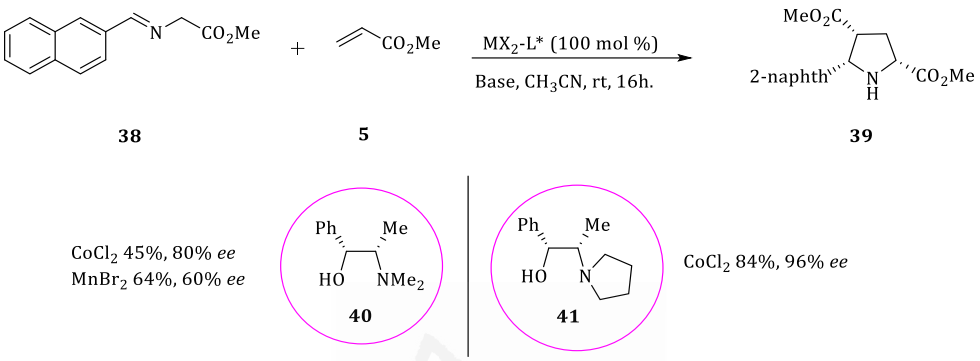
Figure 4. Organocatalysts employed in 1,3-Dipolar Cycloaddition Reaction

Chiral Lewis acids

In 1991, Grigg *et al.* performed the first 1,3-DC reaction catalyzed by a metal chiral complex. They carried out their reaction with cobalt and manganese salt in stoichiometric amounts and ephedrine derivatives as chiral

[133] Xue, M. X.; Zhang, X. M.; Gong, L. Z. *Synlett*. **2008**, 691-694.
[134] Liu, Y. K.; Liu, H.; Du, W.; Yue, L.; Chen, Y. *C. Chem. – Eur. J*. **2008**, *14*, 9873-9877.
[135] Fernández, N.; Carrillo, L.; Vicario, J. L.; Bdía, D.; Reyes, E. Chem. Commun. **2011**, *47*, 12313-12315.

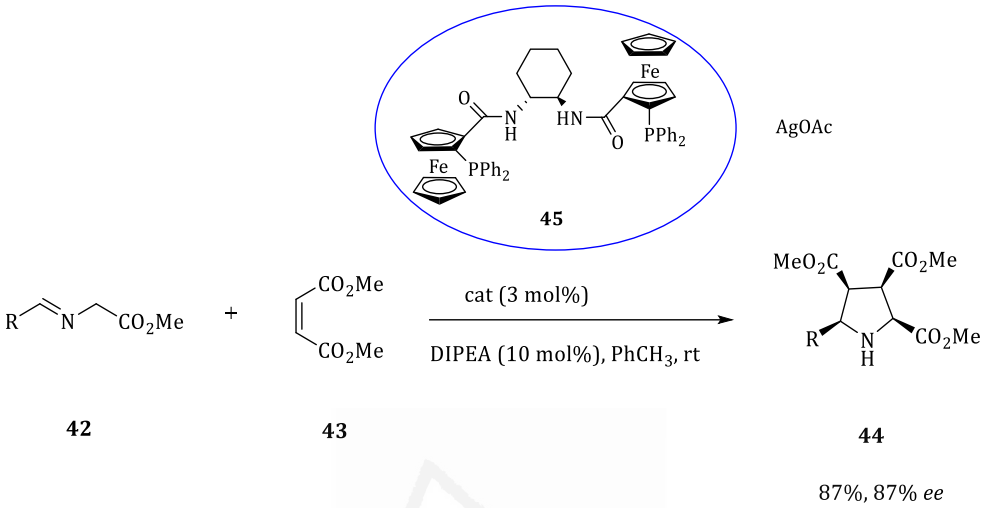
ligands **40** and **41** (Scheme 26). The final product was obtained with moderate yield (45-84%) and good enantiomeric excesses (60-96% *ee*).[136]



Scheme 26. Ephedrine derivatives **40** and **41** as chiral ligands.

In 2002 it was published the first asymmetric metal catalyzed 1,3-DC reaction, in which substoiquiometric amounts of the catalytic species were used. This work was invested by two groups. Firstly, Zang's group in their work catalytic amounts of AgOAc with a chiral C_2-symmetric ferrocene derived phosphine **45** were used to catalyze the reaction, which takes place between azomethine ylides derived from glycine **42** and dimethyl maleate **43**.[137] (Scheme 27).

[136] Allway, P.; Grigg, R. *Tetrahedron Lett*. **1991**, *32*, 8517-5820.
[137] Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc*. **2002**, *124*, 13400-13401.



Scheme 27. First *endo*-proline derivatives synthesized with chiral substoiquiometric amounts of the Lewis acid.

Other dipolarophiles were also tested in this reaction to give the final product with good enantioselections (52-93% *ee*) (Figure5).

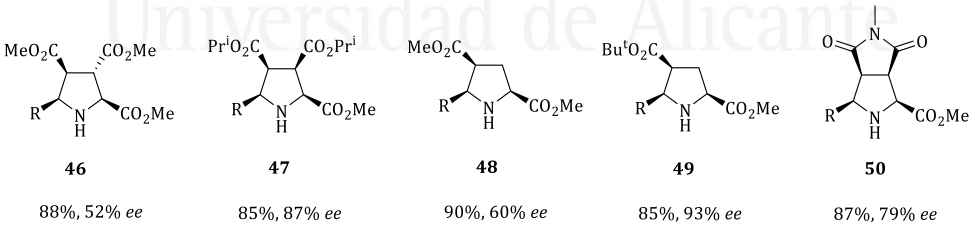
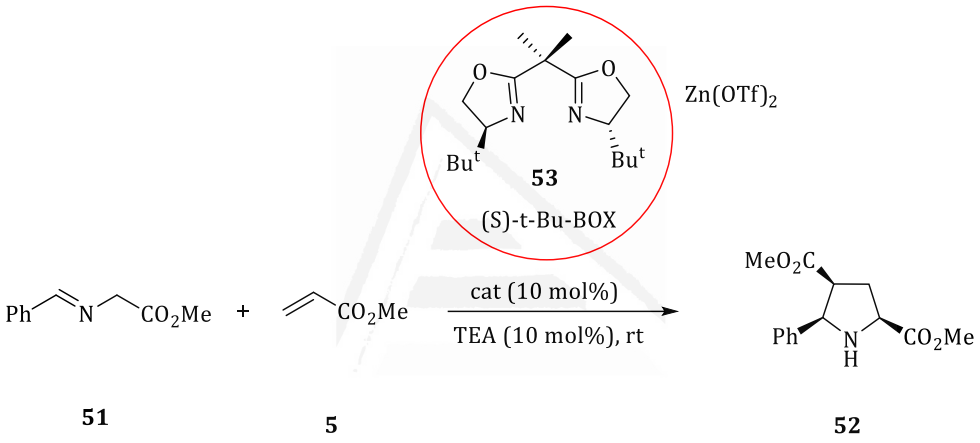


Figure5. Dipolarophiles tested in asymmetric metal catalyzed 1,3-DC reaction

Secondly, the Jorgensen group performed the reaction of *N*-benzylidene surrogates **51** and *N*-(2-naphthylmethylidene) glycinates, with methyl acrylate

5 using Et_3N as base in the presence of chiral ligands such as the bisoxazoline (BOX) **53** and dibenzofuranyl-2,2'-bisoxazoline (DBFOX), the bests results were obtained using $Zn(OTf)_2$ [138] as ligand (Scheme 28).



51 **5** **52**

Scheme 28. Enantioselective 1,3-DC using BOX ligand

Different metals have been used in the cycloaddition reaction of azomethine ylides, such as silver(I), coper (I)or coper (II), zinc (II), gold (I), cobalt, rhodium, ruthenium, nickel (II), etc., but the most used are the silver(I), coper(I) and coper(II) salts.

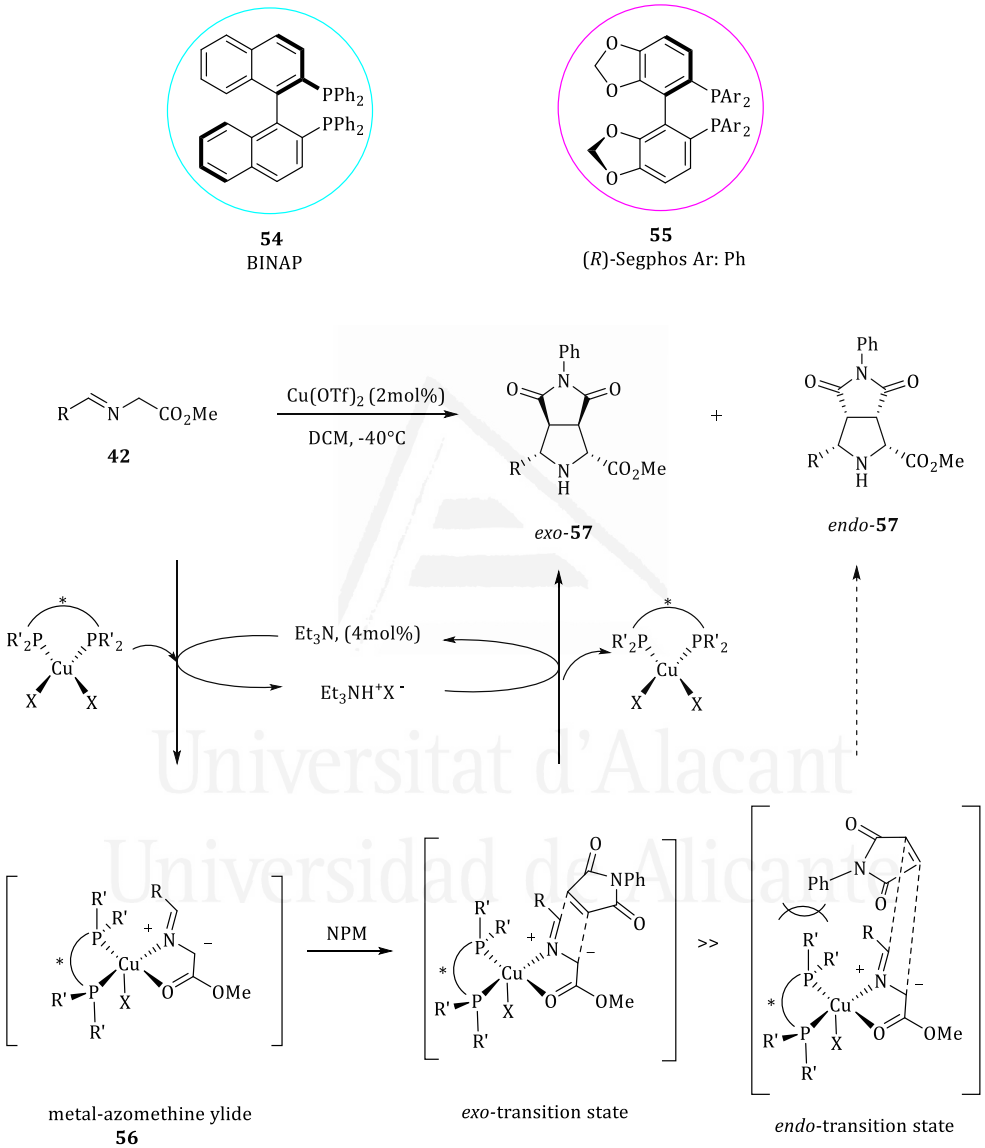
[138] Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2002,** *41*, 4236-4238.

Reactions catalyzed by copper(I) or copper(II) complexes

The use of copper(I) and copper(II), in general, leads to the corresponding *exo*-isomers, and in few examples, the *endo*-isomer could be isolated as major product.

In 2003, the first enantioselective 1,3-Dipolar cycloaddition catalyzed by copper salts was reported.[139] Reactions involving $Cu(OTf)_2$-BINAP **54** and $Cu(OTf)_2$-(*R*)-Segphos **55** have been carried out giving *exo*-cycloadducts with good diastereoselections and moderate to high enantioselectivities (Scheme29).

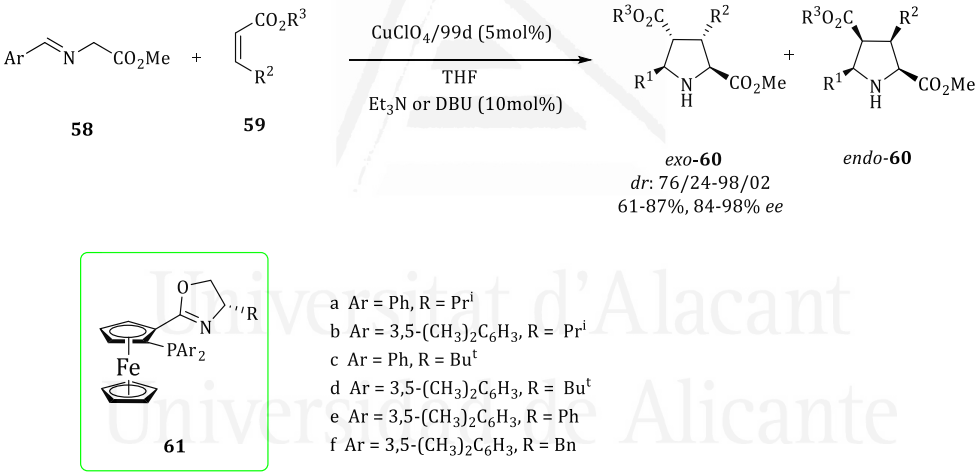
[139] Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett*. **2003**, *5*, 5043-5046.



Scheme 29. Mechanism of the *exo*-selectivity Cu(II) complexes

In another study carried out by Zhang's group, a reaction which takes place between azomethine ylides and some acrylate **59** took place using CuOAc or $CuClO_4$ with different ligands such as (*S,S,S*$_p$)-**55**, and phosphane-oxazoline

type or P,N-ferrocene (FOXAP) **61,**[140] in all cases they obtained the *exo*-**60** isomer, and the best results with $CuClO_4$ and P,N-ferrocene **61d** ligand (Schme30).

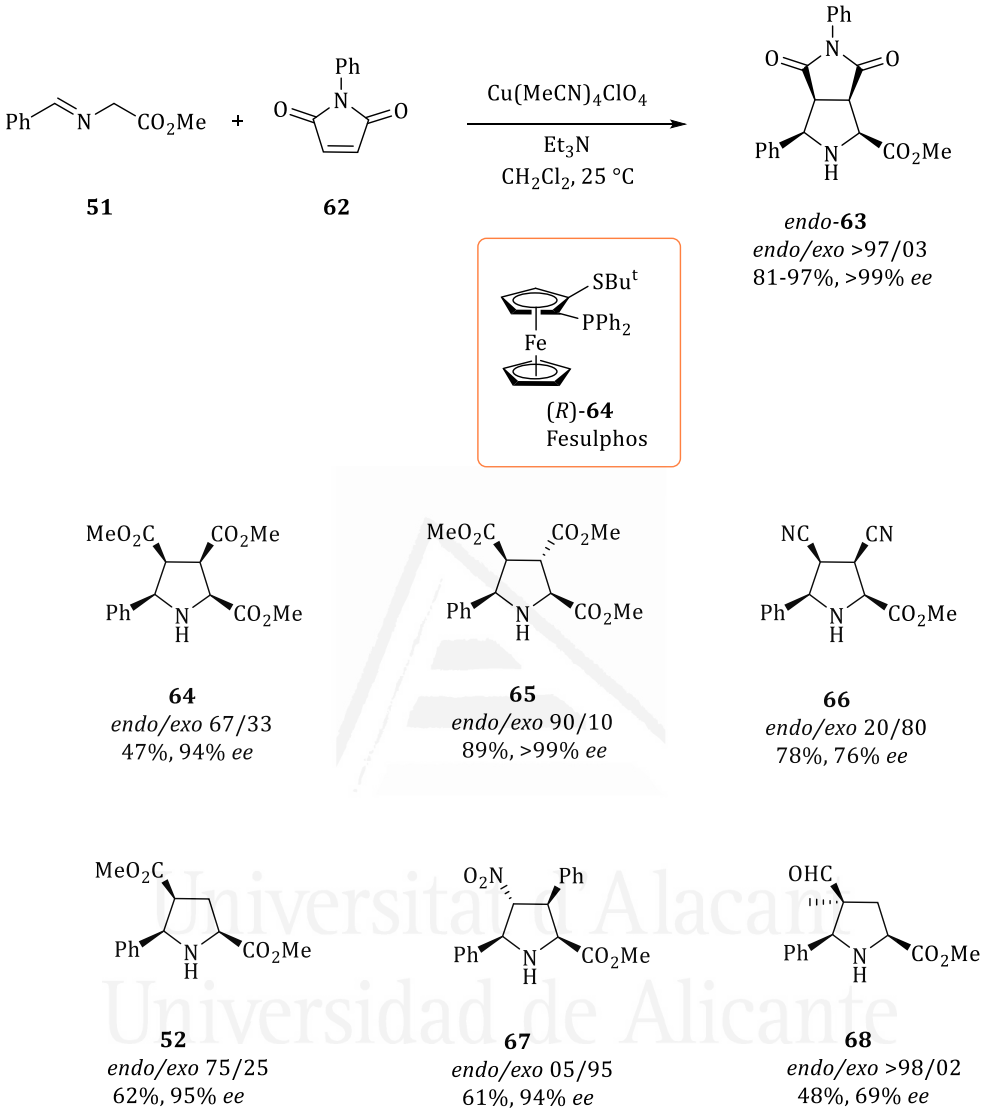


Scheme 30. $CuClO_4$ as catalyst in 1,3-Dipolar Cycloaddition reaction

[140] Gao, W.; Zhang, X.; Raghunath, M. *Org. Lett*. **2005**, *7*, 4241-4244.

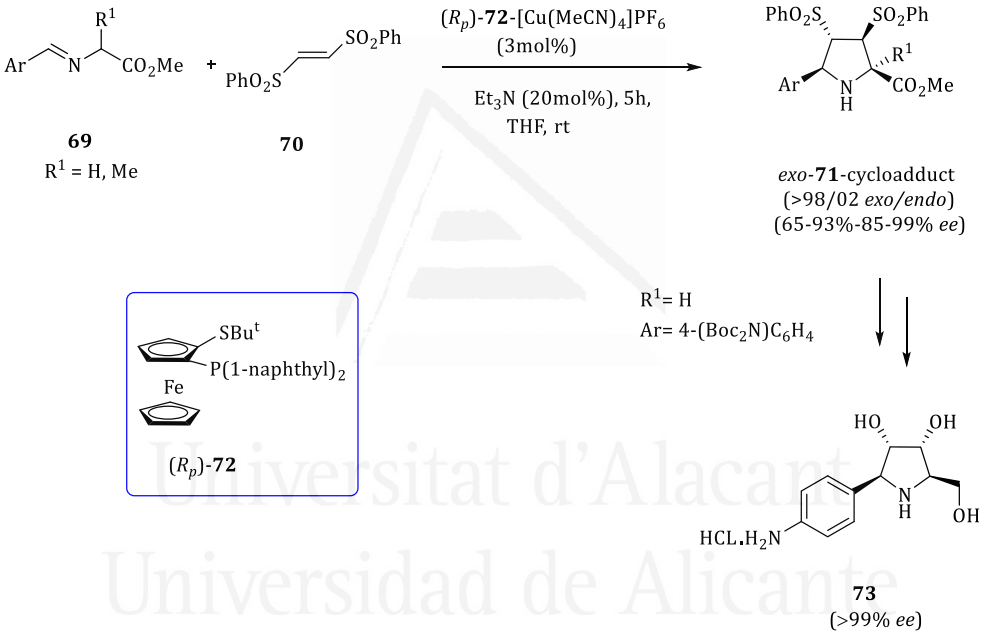
Carretero and co-workers, reported the *endo*-selective process with high enantioselections using copper as catalyst. The intermediate azomethine ylides, generated from **51**, reacted with NPM **62** in the presence of Et_3N and ligand **64** Fesulphos,[141] with the aim of carrying out a comparative study of various copper(I) salts [CuCl, $Cu(MeCN)_4PF_6$ and $Cu(MeCN)_4ClO_4$]. And in all cases, *endo*/*exo* ratio was very high (Scheme 31).[142]

[141] Priego, J.; Mancheno, O. G.; Cabrera, S.; Arrayás, R. G.; Llamas, T.; Carretero, J. C. *Chem. Commun*. **2002**, 2512-2513.
[142] Cabrera, S.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394-16395.



Scheme 31. Fesulphos and Cu(I) complex catalyzed the synthesis of pyrrolidines.

As another example of the use of copper as a catalyst, the optimization of the 1,3-dipolar cycloaddition action between the imino ester **69** and the 1,2-bis(phenylsulfonyl)ethylene **70** using (R_p)-**72**·[Cu (MeCN)$_4$]PF$_6$ complex.[143] The *exo*-cycloadducts **71** were obtained in good yields and very good enantioselection. The *exo*-adduct [Ar = 4-(Boc$_2$N)C$_6$H$_4$] was the direct precursor of a trihydroxylated C-azanucleoside **73** (Scheme 32).



Scheme 32. Synthesis of enantiomerically enriched pyrrolidines using disulfone **70**.

[143] López-pérez, A.; Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc*. **2008**, *130*,10084-10085.

Reactions catalyzed by Silver (I) complexes

In the cycloadditions of azomethine ylides, the silver(I) cation is considered the most effective Lewis acid. The use of this metal furnishes high yields and excellent diastereo- and enantioselections. By the fact that the silver(I) is a soft acid, is highly stabilized by the phosphorylated ligands.[144]

In 2007, a reaction of methyl arylideneglycinates with *N*-phenylmaleimide (NPM) was carried out by Zhou et al, using the complex formed between (S,R_p)-**74a**, (S,R_p)-**74b** and AgOAc, in diethyl ether and in the absence of base, the reaction takes place at 0 °C for **74a** and at 25 °C for **74b**. The major product *ent-endo*-**39** was selectively obtained, after (2-4) hours, in excellent yields (95-98%) and very good enantioselectivities (86-93% *ee*).[145] It has also been shown that a simple hydrogen bond is sufficient to reverse the enantioselection of the process. On the other hand (S,R_p)-**74**c and (S,R_p)-**74**d were also combined with AgOAc.[146]

[144] Gimeno, M. C.; Laguna, A. *Comprehensive Coordination Chemistry II,* Meyer, J. A. M., Ed.; Pergamon: Oxford, **2003**, 911-1145.
[145] Zeng, W.; Zhou, Y. G. *Tetrahedron lett.* **2007**; *48*, 4619-4622.
[146] Zeng, W.; Chen, G. Y.; Zhou, Y. G.; Li, Y. X. *J. Am. Chem. Soc*. **2007**, *129*, 750-751.

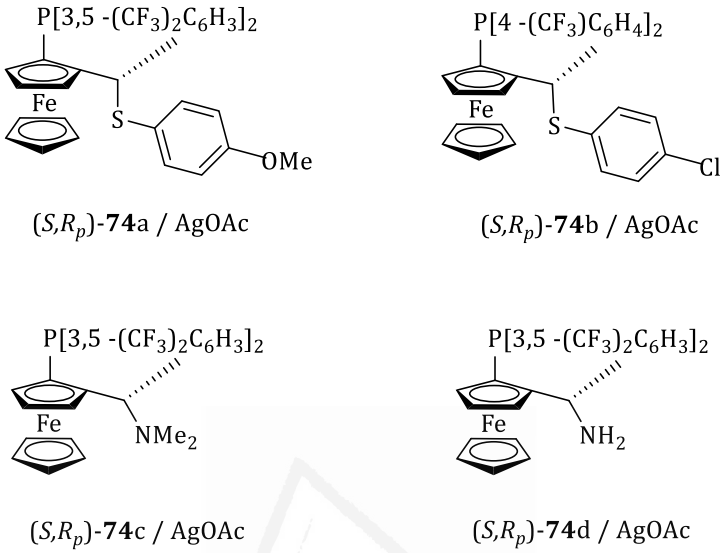
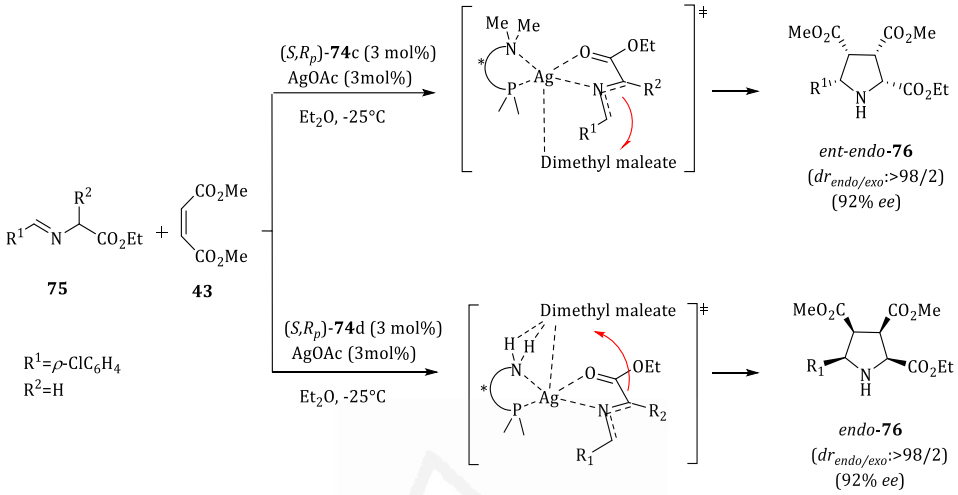


Figure 6. Different ferrocenyl derived ligands used in asymmetric 1,3-dipolar cycloadditions.

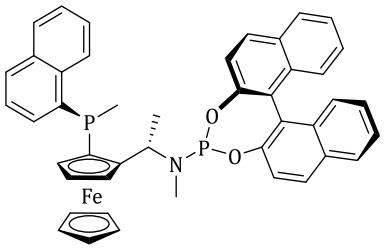
In the example of the reaction of the 1,3-dipole precursor **75** with dimethyl maleate, it has been shown that the carbonyl groups of the dipolarophile have been coordinated by the cation Ag and the obtained (S,R_p)-**74**d-AgOAc complex and could form two hydrogen bonding interactions with the NH_2 group. Unlike the complex (S,R_p)-**74c**-AgOAc including the dimethylamino group, which cannot form these hydrogen bonds, in this case the methyl groups would cause steric repulsion (Scheme 33). In both approaches, the opposite facial enantiodiscrimination observed experimentally has been well explained.



Scheme 33. Transition states proposed for silver-catalyzed 1,3-dipolar cycloaddition involving ligand **74c**.

Zheng *et al*. performed the 1,3-DC reaction of methyl arylideneglycinates with dimethyl maleate, using a catalytic mixture between a more sophisticated phosphoramidite **77** and AgOAc.[147] For this reaction, very good yield (93-98%), very high *endo*-diastereoselectivity (>99/01), and excellent enantioselectivities (up to 99% *ee*) were achieved. The disadvantage of this process is that both NPM and *tert*-butyl acrylate did not allow a high enantioselections.

[147] Yu, S. B.; Hu, X. P.; Deng, J.; Wang, D. Y.; Duan, Z. C.; Zheng, Z. *Tetrahedron: Asymetry* **2009**, *20*, 621-625.



77 / AgOAc

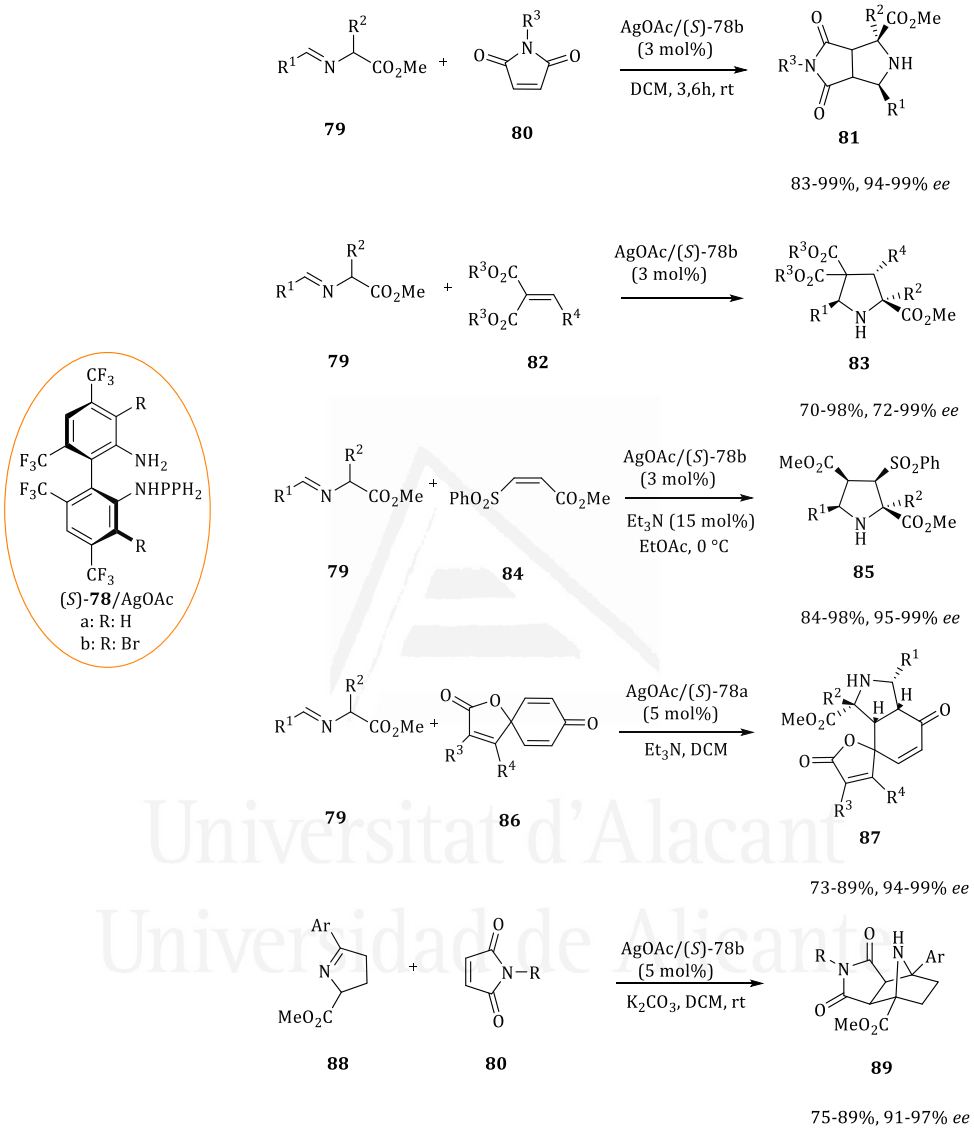
Figure 7. Zheng phosphoramidite **77**·AgOAc catalyst.

A chiral complex **78**·AgOAc, formed by mixing a chiral biaryl ligand TF-BiphamPhos and AgOAc has been used in various 1,3-DC reactions. In 2009, Wang *et al* reported the 1,3-DC reaction between α-substituted imino esters **79** and maleimides **80** using the catalytic mixture (*S*)-**78**-AgOAc (3 mol%).[148] Excellent results were obtained (83-99%, 94-99% *ee*) for the resulting *endo*-selectivity (Scheme 32). Other reactions between azomethine ylides **79** and alkylidene malonates **82**[149] was performed using the same catalyst **78**. When vinyl sulfones were employed an unusual regioselectivity in the pyrrolidine, also high diastereo (>98/02) and enantioselection (84-98%, 95-99% *ee*) were observed.[150] In 2013 the TF-Biphamphos ligand **78** was employed in the reaction of the precursors of 1,3-dipoles and quinolone derivatives **86**,[151] to

[148] Wang, C. J.; Xue, Z. Y.; Liang, G.; Lu, Z. *Chem. Commun*. **2009**, 2905-2907.
[149] Xue, Z. Y.; Liu, T. L.; Lu, Z.; Huang, H.; Tao, H. Y.; Wang, C. J. *Chem. Commun*. **2010**, *46*, 1727-1729.
[150] Tong, M. C.; Li, J.; Tao, H. Y.; Li, Y. X.; Wang, C. J. *Chem. – Eur. J*. **2011**, *17*, 12922-12927.
[151] Oura, I.; Shimizu ; K.; Ogata, K.; Fukuzawa, S. I. *Org. Lett.* **2010**, *12*, 1752-1755.

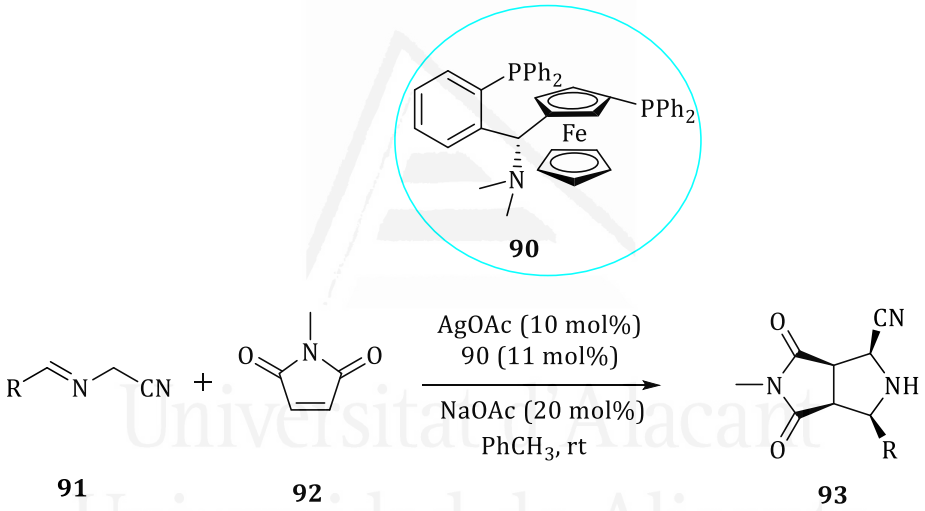
afford highly functional spirolactone-pyrrolidine derivative **87** (Scheme 32). The last reaction, which involves the use of this ligand with AgOAc was the 1,3-

DC reaction between the cyclic azomethine ylides **88** and the *N*-substituted maleimides **80**, the corresponding azabicyclic was obtained with (75-89%, from 10/1 to 14/1 *endo/exo*, 91-97% *ee*) (Scheme 34).



Scheme 34. Silver catalyzed 1,3-DC by Wang's group.

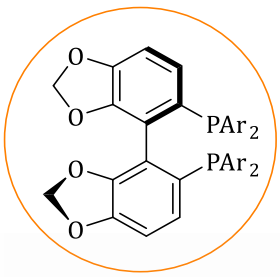
The employment of privileged ligands,[152] which are successfully used in many enantioselective processes, promoted this type of chiral cycloadditions in an efficient manner. For example, the catalytic complex formed by a phosphine bonded to a ferrocene unit, otherwise known as Taniaphos **90** and AgOAc,[153] was studied by Carretero *et al*. In this reaction they have used α-imino nitriles **91,** NMM **92** and methyl fumarate to obtain the 2-cyanopyrrolidines **93**, with good diastereo- and enantioselectivity (68-99% *ee*) (Scheme 35).



Scheme 35. Use of iminonitriles as 1,3-dipoles and taniaphos **90** ligand in 1,3-DC

[152] Qi-Lin Zhou. Privileged Chiral Ligands and Catalysts, Wiley-VCH Verlag, Weinheim (Germany), **2011**.
[153] Robles-Machín, R.; Alonso, I.; Adrio, J.; Carretero, J. C. *Chem. – Eur. J.* **2010**, *16*, 5286-5291.

Another privileged ligand, Segphos and their derivatives, were involved in the 1,3-DC, forming a complex with silver or copper (Figure 8).

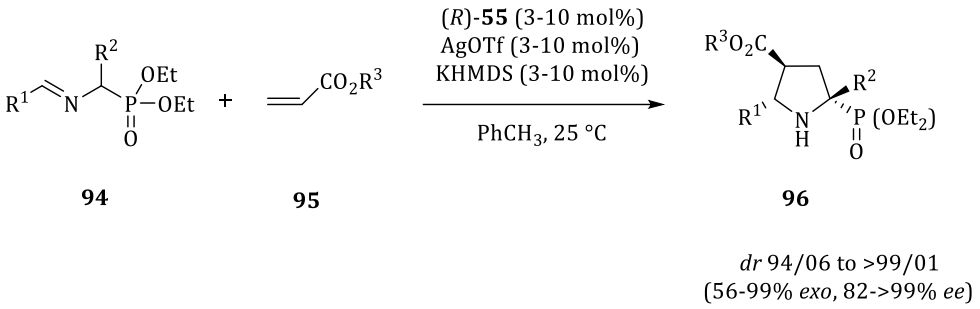


55a, (*R*)-DTBM-Segphos Ar: 3,5-$(Bu^t)_2$-4-MeO-C_6H_2
55b, (*R*)-Segphos Ar: Ph

Figure 8. Segphos type ligands.

Kobayashi *et al*. used this last ligand **55** with the silver amides as catalytic system in the rection 1,3 DC, which takes place between iminophosphonates **94** and many dipolarophiles (Scheme 36).[154] This reaction gave high *exo*-selectivities (from 94/06 to >99/01) with good to excellent enantioselection (from 82 to >99% *ee*).[110] The same group extended this methodology in the use of imino esters as precursors of dipoles to obtain excellent *exo*-diastereoselection and enantiomeric excesses for the obtained pyrrolidines.[155]

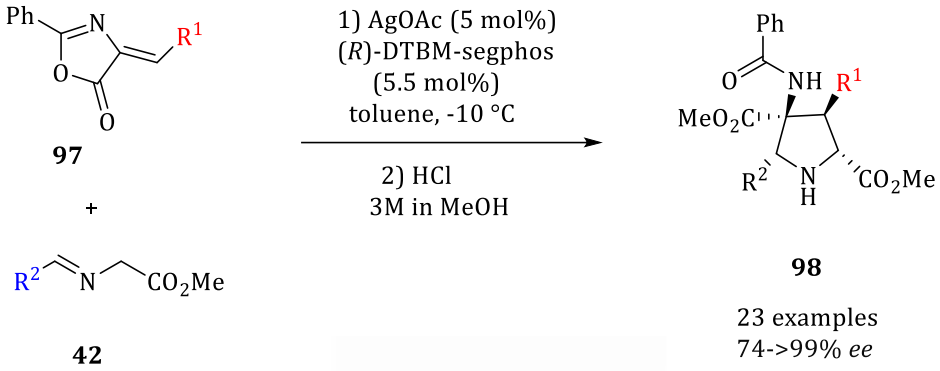
[154] Yamashita, Y.; Guo, X. X.; Takashita, R.; Kobayashi, S. *J. Am. Chem. Soc*. **2010**, *132*, 3262-3263.
[155] Yamashita, Y.; Imaizumi, T.; Kobayashi, S. *Angew. Chem., Int. Ed*. **2011**, *50*,4893-4896.



Scheme 36. Iminophosphonates **94** as precursors in 1,3-DC.

Another example involving the ligand (*R*)-DTBM-Segphos **55a** was studied by Carretero *et al.* The reaction consists in the synthesis of 4-aminopyrrolidine-2,4-dicarboxylate by a cycloaddition of α-imino esters with alkylidene azlactones catalyzed by the silver acetate·DTBM-segphos complex. This procedure provided the desired end product with high diastereo- and enantioselectivity (Scheme 37).[156] Other approaches using DTBM-Segphos with silver(I) and copper(II) were reported by our group.[157]

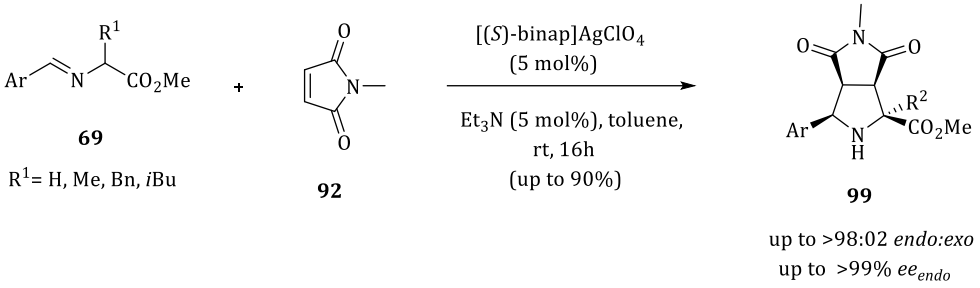
[156] Gonzalez-Esguevillas, M.; Adrio, J.; Carretero, J. C. *Chem. Commun.*, **2013**, *49*, 4649—4651
[157] Caleffi, G. S.; Larrañaga, O.; Ferrandiz Saperas, M.; Costa, P. R. R.; Nájera, C.; de Cozar, A.; Sansano, J. M. *The Journal of Organic Chemistry.* **2019**.



Scheme 37. Synthesis of 4-aminopyrrolidine-2,4-dicarboxylate using AgOAc-DTBM-segphos complex.

In 2007, our group published the first enantioselective1,3-DC reaction of amino acid derived azomethine ylides and maleimides using chiral (*R*)- or (*S*)-Binap **54**-$AgClO_4$ complexes (5 mol%) which are very stable and recyclable.[158] This reaction takes place in an ambient temperature for 17 h, to give a high *endo*-diastereo- and enantioselectivity (from 95/05 to >98/02 *endo/exo* ratio, and from 80 to >99% *ee*). The catalytic chiral complex could be recovered by simple filtration and reused with the same efficiency. The presence of substoichiometric amounts of triethylamine (5 mol %) were necessary. Several dipoles derived from different amino acids have also been tested resulting the corresponding *endo*-pyrrolidines (>98/02 *endo/exo* ratio in all cases) in good yields (56-81%) and lower enantioselections (from 72 to 98% *ee*) (Scheme38).

[158] Najera, C.; Retamosa, M. d. G.; Sansano, J. M. *Org. Lett.* **2007**, *9*, 4025-4028.

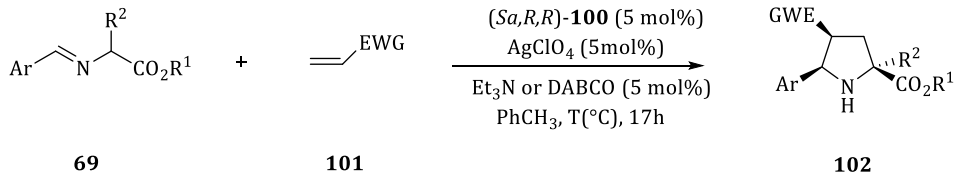


Scheme 38. Enantioselective 1,3-Dipolar Cycloaddition reaction using (*S*)-Binap-Ag(I) complex

After a few years, the first catalytic application of chiral phosphoramidite **100**-$AgOCl_4$ complex was published.[159,160,161] The 1,3-DC reaction of methyl arylideneglycinate and electrophilic alkenes catalyzed by silver was performed in toluene at -20 °C, using 5 mol% of Et_3N as base. The resulting products pyrrolidines **102** were obtained with excellent *endo*-stereoselection (>98/02 *endo/exo* ratio) and enantiomeric excesses. On the other hand, a variety of dipolarophiles among them, *tert*-butyl acrylate, *N*-methylmaleimide (NMM), fumarates with different substituents, chalcone and cyclopenten-2-one were also tested in good yields and enantiomeric excesses (Scheme 39). This catalytic system allowed the preparation of very interesting inhibitors of the virus causing hepatitis C developed by GSK company. Thus 1st and 2nd generation

[159] Nàjera, C.; Retamosa, M. G.; Sansano, J. M. *Angew. Chem., Int. Ed*. **2008**, *47*, 6055-6058.
[160] Nàjera, C. Sansano, J. M., Retamosa, M. d. G. WO **2009**/121989 Al Oct 8, **2009**.
[161] Nàjera, C.; Retamosa, M. d. G.; Martin-Rodriguez, M.; Sansano, J. M.; de Cozar, A.; Cossion, F. P. *Eur. J. Org. Chem*. **2009**, 5622-5634.

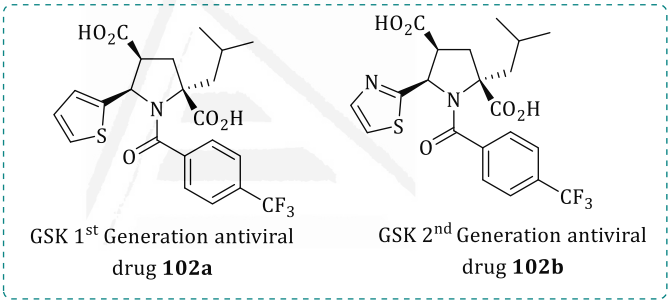
molecules **102a** and **102b** were isolated in very good enantioselectivities and high overall yields.



69 **101** **102**

70-90%, 82-99% *ee*
dr>91/9

R^1 = Me,Pri
R^2 = H, Me, Bn, Bui
Ar = Ph, 2-MeC_6H_4, 2-ClC_6H_4, 2-thienyl, 4-$MeOC_6H_4$



GSK 1st Generation antiviral drug **102a**

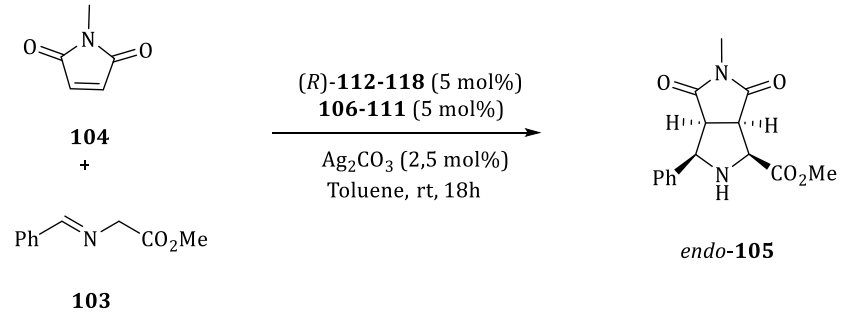
GSK 2nd Generation antiviral drug **102b**

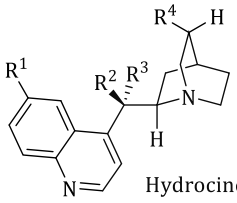
Scheme 39. General reaction catalyzed by **100**·$AgClO_4$ complex.

According to these examples the classical way to proceed is using a chiral ligand incorporating the chiral information, very reduced examples were run through a cooperative process where a chiral ligand bonded to a metal centre and an organocatalyst are combined in the same 1,3-DC. The diastereo- and enantioselective 1,3-DCs between iminoesters **103** and *N*-methylmaleimide

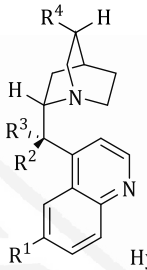
(NMM) **104** gave enantiomerically enriched prolines **105**,[162] using several *Cinchona* alkaloids **106-111** acting as chiral Brønsted bases and a series of silver phosphates derived from chiral Binol.[163,164] The order of addition of the reagents were crucial for obtaining excellent results. Chiral phosphoric acids **112-118** were mixed with silver carbonate for 1 h, at room temperature, were evaluated to generate the chiral silver salts (Scheme 40).

[162] Cayuelas, A.; Larrañaga, O.; Selva, V.; Nájera, C.; Akiyama, T.; Sansano, J. M.; Cossío, F. P. *Chemistry - A European Journal,* **2018**, *24(32), 8092–8097.*
[163] a) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev*. **2014**, *114*, 9047–9153; b) Akiyama, T.; Mori, K. *Chem. Rev*. **2015**, *115*, 9277–9306; c) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev*. **2017**, *117*, 10608–10620.
[164] a) Mahlau, M.; List, B.; *Angew. Chem., Int. Ed.* **2013**, *52*, 518-533; *Angew. Chem*. **2013**, *125*, 540–556; b) Brak, K.; Jacobsen, E. N. *Angew. Chem*., *Int. Ed.* **2013,** *52*, 534-561; *Angew. Chem.* **2013,** *125*, 558–588; c) Chen, D. F.; Han, Z. Y.; Zhou, X. L.; Gong, L.Z. *Acc. Chem. Res*. **2014**, *47*, 2365-2377.

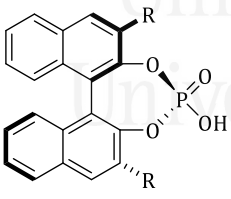




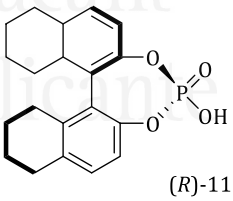
Hydrocinchonine **106**a
(R^1=R^2=H; R^3=OH; R^4=Et)
106b
(R^1=R^2=H; R^3=O-Allyl; R^4=Et)
Cinchonine **108**
(**(**R^1=R^2=H; R^3=OH; R^4=Vinyl)
Quinidine **110**
(R^1=OMe; R^2=H; R^3=OH; R^4=Vinyl)



Hydriuinine **107**
(R^1=OMe; R^2=OH; R^3=H; R^4=Et)
Cinchinidine **109**
(R^1=R^3=H; R^2=OH; R^4=Vinyl)
Quinine **111**
(R^1=OMe; R^2=OH; R^3=H; R^4=Vinyl)



(*R*)-112 (R=H)
(*R*)-114 (R=Ph)
(*R*)-115 (R=$SiPh_3$)
(*R*)-116 (R=2,4,6-[O^iPr]$_3C_6H_2$)
(*R*)-117 (R=3,5-[CF_3]$_2C_6H_3$)
(*R*)-118 (R=9-Anthracenyl)

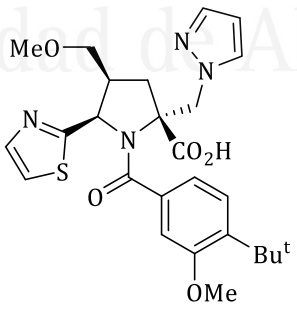


(*R*)-113

Scheme 40. Cinchona alkaloids **106-111** and chiral Binol-derived phosphoric acids **112-118** employed in the 1,3-DC between imino ester **103** and *N*-methylmaleimide **104**.

Objectives

The single chiral information bonded to the metal centre and the cooperative process performed with two separate chiral information in the reaction media are perfectly known. So, in the publication of Chapter 1:

- The enantioselective 1,3-dipolar cycloaddition using a double chiral information surrounding the metal sphere is tested.
- For this purpose, several chiral ligands and chiral anions will be bonded to the silver o copper metal.
- Application of this enantioselective 1,3-DC to the asymmetric synthesis of the GSK 3rd generation antiviral drug (GSK625433).
- 

(GSK625433)

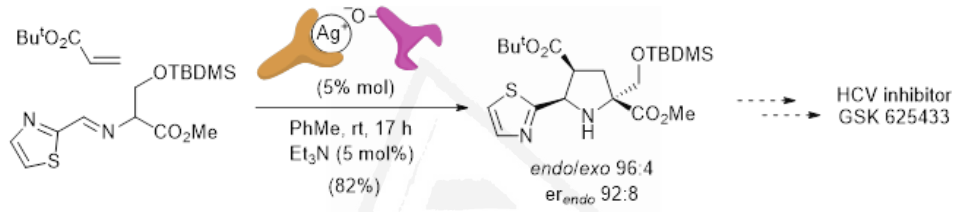
ANNEX 1

Graphical Abstract

Dual chiral silver catalyst in the synthetic approach to the core of hepatitis C virus inhibitor GSK 625433 using enantioselective 1,3-dipolar cycloaddition of azomethine ylides and electrophilic alkenes

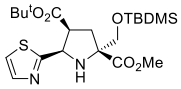
Leave this area blank for abstract info.

Ihssene Chabour, Luis M. Castelló, Juan Mancebo-Aracil, María Martín-Rodríguez, M. de Gracia Retamosa, Carmen Nájera,* and José M. Sansano*



Stereochemistry Abstract

I. Chabour, L. M. Castelló, J. Mancebo-Aracil, M. Martín-Rodríguez, M. G. Retamosa, C. Nájera,* and José M. Sansano*

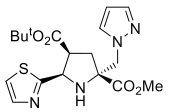


Er = 93:7
$[\alpha]_D$ = -8.0 (*c* 1, CH_2Cl_2, 93:7 er from HPLC)
Source of chirality: (S_a,*R*,*R*)-Binol derived phosphoramidite and chiral (*R*)-binol-phosphoric acid

$C_{16}H_{27}N_2O_3SSi$

4-(*tert*-Butyl) 2-methyl (2*R*,4*S*,5*R*)-2-{[(tert-butyldimethylsilyl)oxy]methyl}-5-(thiazol-2-yl)pyrrolidine-2,4-dicarboxylate

I. Chabour, L. M. Castelló, J. Mancebo-Aracil, M. Martín-Rodríguez, M. G. Retamosa, C. Nájera,* and José M. Sansano*

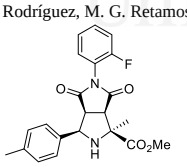


Er = 93:7
$[\alpha]_D$ = + 7.7 (*c* 0.6, $CHCl_3$, 93:7 er)
Source of chirality: (S_a,*R*,*R*)-Binol derived phosphoramidite and chiral (*R*)-binol-phosphoric acid

$C_{13}H_{15}N_4O_2S$

4-(*tert*-Butyl) 2-methyl (2*R*,4*R*,5*R*)-2-[(1H-pyrazol-1-yl)methyl]-5-(thiazol-2-yl)pyrrolidine-2,4-dicarboxylate

I. Chabour, L. M. Castelló, J. Mancebo-Aracil, M. Martín-Rodríguez, M. G. Retamosa, C. Nájera,* and José M. Sansano*



Er = 61:39%
$[\alpha]_D$ = - 3.7 (*c* 1.1, $CHCl_3$, 61:39 er from HPLC)
Source of chirality: (S_a,*R*,*R*)-Binol derived phosphoramidite and chiral (*R*)-binol-phosphoric acid

$C_{22}H_{21}FN_2O_4$

Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-(2-fluorophenyl)-1-methyl-4,6-dioxo-3-(*p*-tolyl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate

Annex 1

Annex 1

Contents list available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Dual chiral silver catalyst in the synthetic approach to the core of hepatitis C virus inhibitor GSK 625433 using enantioselective 1,3-dipolar cycloaddition of azomethine ylides and electrophilic alkenes

Ihssene Chabour,[a,b,c] Luis M. Castelló,[a,b,c] Juan Mancebo-Aracil,[a,b,c] María Martín-Rodríguez,[a,b,c] María de Gracia Retamosa,[b,d] Carmen Nájera,[a,b]* and José M. Sansano,[a,b,c]*

[a] Departamento de Química Orgánica, Universidad de Alicante, Apdo. 99, E-03080-Alicante, Spain.
[b] Centro de Innovación en Química Avanzada (ORFEO-CINQA).
[c] Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, E-03080-Alicante, Spain
[d] Instituto de Investigaciones Químicas (CSIC-US),Avda. Américo Vespucio, 49,41092 Sevilla (Spain).
Fax: (+34)-965-903-549; phone: (+34)-965-903-549; e-mail: cnajera@ua.es, jmsansano@ua.es

Dedicated to the memory of Prof. Howard Flack

Abstract: The asymmetric 1,3-dipolar cycloaddition (1,3-DC) of an imino ester **5** with *tert*-butyl acrylate is catalyzed by a dual chiral silver(I) complex formed from a chiral phosphoramidite **14** and the chiral silver(I) binolphosphate (*R*)-**17**. This reaction is selected to perform the synthesis of enantiomerically enriched key structure to access the third generation of GSK HCV inhibitors. The scope of this dual chiral catalytic system is analyzed employing different imino esters and dipolarophiles, and furtherly compared with the same cycloaddition reactions performed with chiral phosphoramidite **14**·Ag(I) complex.

Keywords: Cycloaddition · azomethine ylides · phosphoramidite · silver(I) · enantioselective · dual activation

1. Introduction

The enantioselective synthesis of pyrrolidines or proline derivatives constitutes a very important trend in organic chemistry due to the interest of them in many scientific fields.[1] Since the biological and medicinal point of view, molecules possessing antibiotic, antitumor, analgesic, neuroexcitatory activities, etc., have been widely described. However, the development of antiviral compounds (commercially available or in clinical survey) constitutes one of the main applications of these skeletons.[2,3] At this moment, many antiviral agents (used individually or in combination with another drugs) administrated to patients include a nitrogenated five-membered ring, for example, elbasvir, grazoprevir, velpatasvir, ombitasvir, paritaprevir, boceprevir, telaprevir and daclatasvir have been recently developed.[4] The complex skeleton of these molecules contrast with a family of prolinate

Annex 1

derivatives **1**-**3** (Figure 1) reported by GSK through successive evolutions.[5] These compounds act as polymerase inhibitors of the several strands of the virus responsible of the Hepatitis C. Besides, less amount of effective doses and reduced secondary effects converted these products in a promising treatment for hepatitis C virus (HCV) infected people.[6,7]

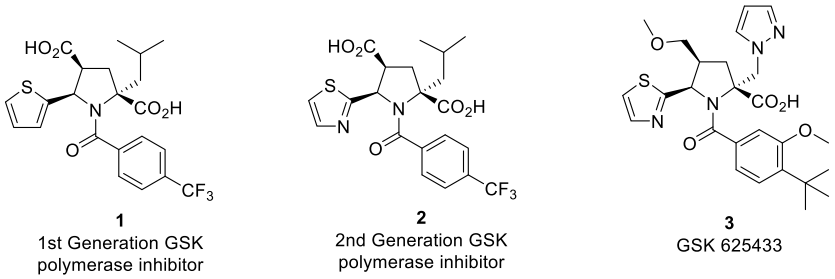


Figure 1. Family of GSK HCV inhibitors.

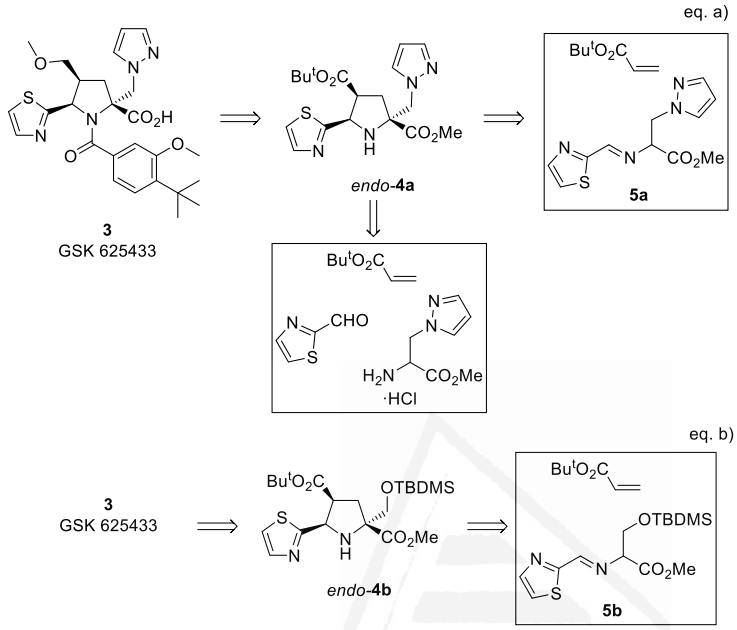
In our group, the asymmetric synthesis of the 1st **1**[8,9] and 2nd generation **2**[10] antiviral drugs employing diastereo-[8] and enantioselective[2,11] 1,3-dipolar cycloaddition (as key-step) between the corresponding methyl iminoleucinate and a lactate derived acrylate,[8] or this imino ester with *tert*-butyl acrylate employing a chiral phosphoramidite-$AgClO_4$ catalytic complex[8] or a chiral dimeric Binap-gold(I) complex,[10] respectively, was developed. In both routes, the overall yields obtained were moderate to good and enantioselectivities were very high, especially in the case of the 2nd generation inhibitor (99% *ee*). In this work, we report the efforts dedicated to build enantioselectively the core heterocyclic ring precursor of the GSK 625433 polymerase inhibitor **3**[12] and also a brief study of the scope and versatility of the new developed catalyst will be disclosed.

2. Results and discussion

According to the classical retrosynthetic analysis of this family of compounds, we envisaged that the enantiomerically enriched cycloadducts *endo*-**4** type were the key compounds to the access to antiviral agent **3**. Initially, we designed two alternative approaches where the pyrazole ring was bonded in the starting imino ester (Scheme 1, eq. a) and a second retrosynthesis in which the pyrazole was introduced once the 1,3-DC occurred (Scheme 1, eq. b). Starting imino ester **5a** could be generated, under mild conditions, from commercially available 3-(1-pyrazolyl)-L-alanine methyl ester hydrochloride but important amounts of the product, resulting from the β-elimination of pyrazole, were detected by ^{1}H NMR spectroscopy. The non-asymmetric multicomponent 1,3-DC was then tested employing *tert*-butyl acrylate, 2-thiazolecarbaldehyde and the amino ester, furnishing the undesirable β-elimination product.[13] This problem was overcome employing the route starting from O-TBDMS serine derivative (Scheme 1, eq. b). Stable imino ester **5b** was much more appropriate to run the non-asymmetric cycloaddition and, in consequence, adequate to survey the enantioselective 1,3-DC. This imino ester **5b** was obtained, in almost quantitative yield, by reaction of 2-

Annex 1

thiazolecarbaldehyde with the known compound O-TBDMS serine methyl ester[14] in DCM at room temperature for 19 h and it was employed in the cycloadditions without any other purification (see experimental part).

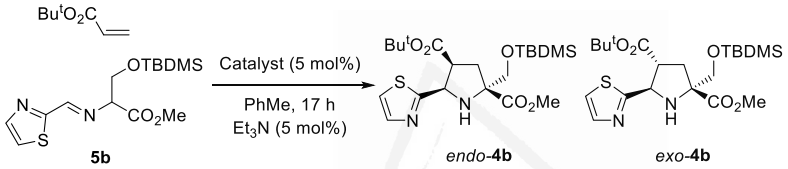


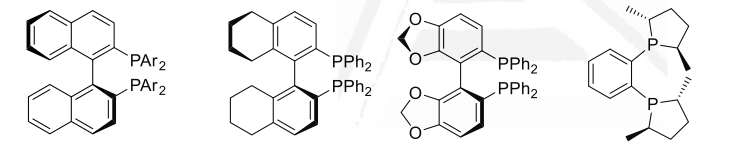
Scheme 1. Retrosynthetic analysis.

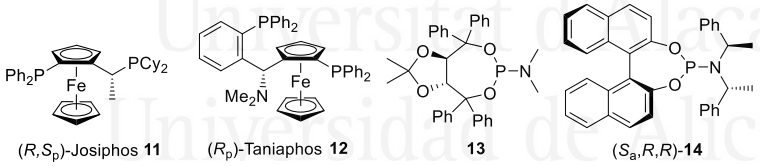
Many chiral ligands and silver salts were tested in 5 mol% loading (Scheme 2 and Table 1) but always using toluene as better solvent (not registered in Table 1). The cycloadditions performed at room temperature involving Binap **6** afforded very good conversions but with moderate enantioselections (Table 1, entries 1-3).[15] The best silver salt was $AgSbF_6$, which gave, at room temperature, the desired compound *endo*-**4b** as a 85:15 mixture of diastereoisomers in 85:15 enantiomeric ratio (Table 1, entry 2). The lowering of the temperature was not beneficial for this transformation (Table 1, entry 3).[16] Chiral ligands **7** and **8** did not improve the results achieved by Binap **6** and almost racemic compound *endo*-**4b** was isolated when AgOBz or $AgSbF_6$ were combined with chiral ligands **9**-**13** (these results are not included in Table 1). Phosphoramidite (S_a,*R*,*R*)-**14**·AgTFA complex and the analogous one formed with $AgSbF_6$ furnished identical conversions, diastereomeric and enantiomeric ratios (Table 1, entries 4 and 5). The analysis of the temperature was next studied (Table 1, entries 5-7) obtaining an increment of the diastereomeric ratio (up to 99:1, at -80 ºC) but with a moderate enantioselection (80:20 at the same temperature). Analogous H8-chiral complex **15**·$AgSbF_6$ was not suitable for inducing a very high enantiodiscrimination (Table 1, entry 8). Because of dimeric gold species (*S*,*S*)-**16**·TFA_2 was effective in the synthesis of the second generation GSK-agents it was used at 0 ºC in the cycloaddition of *tert*-butyl acrylate and imino ester **5b**. The reaction was almost complete after 48 h reaction time giving *endo*-**4b** as major diastereoisomer in 85:15 dr and modest enantioselection (78:26 er, Table 1, entry 9). (*S*,*S*)-**16**·$(OBz)_2$

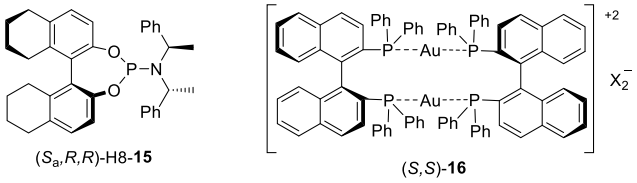
Annex 1

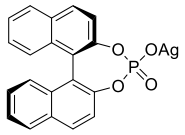
catalytic complex was not effective affording lower diastereomeric and enantiomeric ratios (Table 1, entry 10). However, the dual chiral catalyst **14**·Ag-(*R*)-**17**, formed by reaction of silver carbonate and chiral (*R*)-binol-phosphoric acid in toluene[17] for 1 h followed by the addition of phosphoramidite **14**, produced at room temperature *endo*-cycloadduct **4b** in excellent conversion and high diasteromeric and enantiomeric ratio (Table 1, entry 11). A lowering of the temperature to -20 ºC did not produce any significant amelioration of the enantiomeric ratio. The corresponding enantiomer *ent-endo*-**4b** was easily obtained by employing the enantiomeric chiral catalytic system such as it is shown in entry 12 of Table 1. The configuration of these two enantiomeric forms of the dual chiral silver complex resulted to be the matched combination for this transformation because the other two detailed in the last two entries of Table 1 afforded lower enantiomeric ratios although with excellent conversions. From these three last entries, the absolute configuration induced in cycloadducts is strongly dependent of the axial chirality of the phosphoramidite ligand.











Scheme 2. Chiral ligands employed in the optimization study.

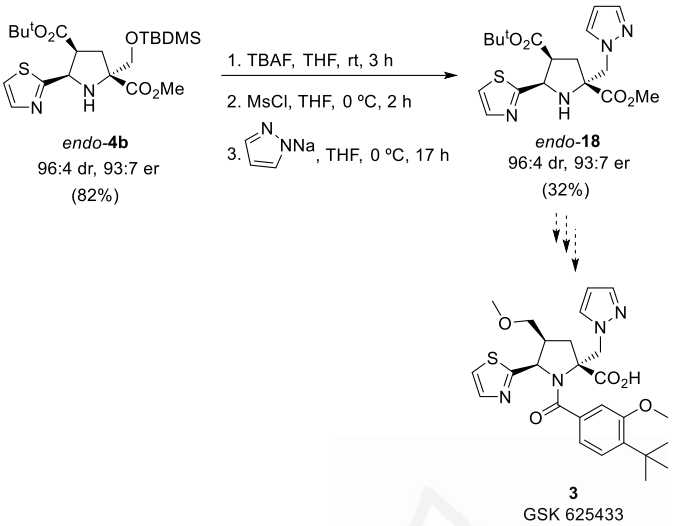
Table 1. Study of the reaction conditions for the synthesis of **4b**.

Entry	Catalyst	T (ºC)	Conv. (%)[a]	dr[a]	er[b]
1	**6**·AgTFA	25	>95	70:30	81:19
2	**6**·$AgSbF_6$	25	>95	85:15	85:15
3	**6**·$AgSbF_6$	0	>95	85:15	82:18
4	**14**·AgTFA	25	>95	90:10	66:34
5	**14**·$AgSbF_6$	25	>95	93:7	65:35
6	**14**·$AgSbF_6$	-20	>95	95:5	69:31
7	**14**·$AgSbF_6$	-80	>95	99:1	80:20
8	**15**·$AgSbF_6$	25	>95	99:1	59:31
9	**16**·$(TFA)_2$	0[c]	90	90:10	78:26
10	**16**·$(OBz)_2$	0[c]	95	85:15	76:24
11	**14**·Ag-(*R*)-**17**	25	>95	96:4	93:7
12	(R_a,*S*,*S*)-**14**·Ag-(*S*)-**17**	25	>95	95:5	8:92
13	(R_a,*S*,*S*)-**14**·Ag-(*R*)-**17**	25	>95	96:4	23:77
14	**14**·Ag-(*S*)-**17**	25	>95	90:10	75:25

[a] Determined by ^{1}H NMR of the crude reaction mixture. 10 h Reaction time.
[b] Determined by HPLC using chiral stationary phase columns.
[c] 48 h Reaction time.

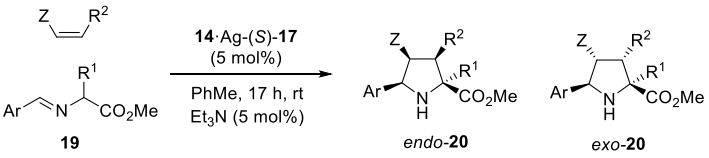
With compound *endo*-**4b** in hand (82% yield, 96:4 dr and 92:7 er) next three steps were carried out in a sequential manner (Scheme 3). First, TBDMS was removed using three equiv. of tetrabutylammonium fluoride (TBAF, 1 M solution in THF) at room temperature for 3 h. Mesylation of the alcohol in the absence of trimethylamine avoided undesirable ring expansion process and after 2 h at 0 ºC, sodium pyrazolide[18] was added at 0 ºC. Cycloadduct *endo*-**18** was isolated after flash chromatography in 32% overall yield from *endo*-**4b**. The final access to molecule **3** can be achieved following known procedures described for this family of HCV inhibitors.[6,7,19]

Annex 1



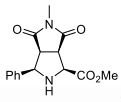
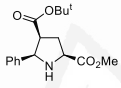
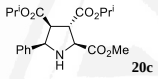
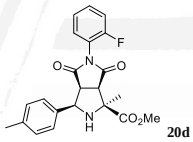
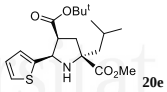
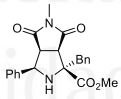
Scheme 3. Synthesis of the key enantiomer *endo*-**18** to access GSK 625433 polymerase inhibitor **3**

The determination of the absolute configuration and the scope of effectiveness of the double chiral activated complex **14**·Ag-(*R*)-**17** were studied simultaneously. Initially, *N*-methylmaleimide (NMM) was allowed to react with imino ester **19** (Ar = Ph, R^1 = H) under optimized reaction conditions yielding product **20a** (Table 2, entry 1). The absolute configuration was assigned on the basis on the comparison of its retention time (HPLC using a chiral stationary phase column) with the retention time of the identical sample isolated from the reaction catalyzed by **14**·$AgClO_4$ complex.[8] This absolute configuration was confirmed by analyzing both HPLC and specific optical rotation data of all isolated compounds described in Table 2. The dual chiral catalyst **14**·Ag-(*R*)-**17** and **14**·$AgClO_4$ chiral complex afforded similar results of **20b** and **20c** too (Table 2, entries 2 and 3). However, the presence of a substituent at the α-position of the imino ester **19** caused steric difficulties to the bulky chiral entity of **14**·Ag-(*R*)-**17**. Thus, when alanine, leucine and phenylalanine derived imino esters **19** were employed with different dipolarophiles the catalytic complex **14**·$AgClO_4$ afforded cycloadducts **20** in higher both diastereomeric and enantiomeric ratios, although chemical yields are similar using separately both catalytic complexes (Table 2, entries 4-6). It is noteworthy that compound **20d** appeared as potential novel HIV-1 integrase inhibitor,[20] and molecule **20e** is the key building block for the synthesis of the HCV inhibitor **1**.[6,8]



Scheme 4. Scope of the reaction.

Table 2. Synthesis of cycloadducts **20** in the presence of **14**·Ag-(*R*)-**17** and comparison with the results obtained employing **14**·$AgClO_4$.

					14·$AgClO_4$ (ref. 9)			**14**·Ag-(*R*)-**17**		
Ent.	R^1	Ar	Dipolarophile	Structure	Yield (%)[a]	dr[a]	er[b]	Yield (%)[a]	dr[a]	er[b]
1	H	Ph	NMM	 **20a**	80[c]	>98:2	>99:1	78[c]	>98:2	90:10
2	H	Ph	*tert*-Butyl acrylate	 **20b**	80[d]	>98:2	90:10	90[c]	>98:2	90:10
3	H	Ph	Diisopropyl fumarate	 **20c**	81[d]	>98:2	91:9	82[d]	90:10	89:11
4	Me	4-Me(C_6H_4)	*o*-FPM[e]	 **20d**	58[c]	95:5	61:39	58[c]	95:5	53:47
5	Bu[i]	2-Thienyl	*tert*-Butyl acrylate	 **20e**	78[d]	>98:2	94:6	81[d]	95:5	76:24
6	Bn	Ph	NMM	 **20f**	71[f]	>98:2	95:5	67[f]	95:5	73:27

[a] Determined by ^1H NMR of the crude reaction mixture. 10 h Reaction time.
[b] Determined by HPLC using chiral stationary phase columns for the *endo*-stereoisomer.
[c] Reaction performed at room temperature.
[d] Reaction performed at -20 ºC.
[e] *o*-FPM = *N*-(*o*-fluorophenyl)maleimide. Compound **20d** was not prepared in ref. 9.
[f] Reaction performed at 0 ºC.

3. Conclusions

In this work, the modulation of the chiral catalyst **14**·Ag-(*R*)-**17** could be adapted to the effective approach of the imino ester and *tert*-butyl acrylate to access the enantiomerically enriched core of the antiviral agent GSK 625433 by first time. Dual chiral catalyst is very appropriate to achieve a high enantioselection in this transformation unlike to the result gave by **14**·$AgClO_4$ complex. In the case of glycine imino esters both catalysts exhibit a similar behavior in the enantioselective 1,3-DC with dipolarophiles, but for sterically hindered imino esters (derived from α-substituted amino acids) it is advisable the employment of **14**·$AgClO_4$ complex.

4. Experimental Part

4.1. General information

Melting points were determined with a Reichert Thermowar hot plate apparatus and are uncorrected. Only the structurally most important peaks of the IR spectra (recorded whit a FT-IR 4100LE (JASCO) (PIKE MIRacle ATR) are listed. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained with a Bruker AC-300 by using $CDCl_3$ as solvent and TMS as the internal standard, unless otherwise stated. Optical rotations were measured with a JASCO 2000 series. HPLC analyses were performed with a JASCO-2000 series equipped with a chiral stationary phase column (detailed for each compound in the main text) by using mixtures of *n*-hexane/isopropyl alcohol as the mobile phase at 25 ºC. Low-resolution electron impact (EI) mass spectra were obtained with a Shimadzu QP-5000 by injection or DIP, and high-resolution mass spectra were obtained with a Finnigan VG Platform or a Finnigan MAT 95S. Analytical TLC was performed on Schleicher & Schuell F1400/LS 254 silica gel plates and the spots were visualized under UV light (λ = 254 nm). Merck silica gel 60 (0.040-0.063 mm) was used for flash chromatography.

4.2. Synthesis of imino ester 5b.

In a 10 mL flask was dissolved free O-TBDMS serine methyl ester[14] (357 mg, 1.5 mmol) and 2-thiazolecarbaldehyde (134 µL, 1.5 mmol) in anhydrous dichloromethane (10 mL) and magnesium sulfate (200 mg) was added. The reaction was stirred at room temperature overnight and the organic phase was washed with bine, dried and evaporated affording quantitatively the crude imine (492 mg, 1.5 mmol) as a pale yellow oil; IR (neat) ν_{max} 1743 cm^{-1}; ^{1}H NMR δ_H: 0.01, 0.05 (2s, 6H, 2xMeSi), 0.85 (s, 9H, Me_3C), 3.77 (s, 3H, MeO), 3.94 (dd, *J* = 10.5, 7.9 Hz, 1H, CH_2O), 4.16 (dd, *J* = 10.5, 5.3 Hz, 1H, C*H*CO_2Me), 4.26 (dd, *J* = 7.9, 5.3 Hz, 1H, CH_2O), 7.47, 7.93 (2d, *J* = 3.1, 2H, HC=CH), 8.48 (s, 1H, HC=N); ^{13}C NMR δ_C: -5.4, -5.3 (Me_2Si), 18.2 (*C*Me_3), 25.8 (C*C*H_3), 52.3 (OMe), 63.5 (CH_2), 74.1 (CHCO), 122.1 (CHN), 144.8 (CHS), 158.4 (CNS), 166.3 (C=N), 170.1 (CO); MS (EI-GC) *m/z*: 328 (M^+, 1%), 271(80), 241 (11), 211 (13), 165 (42), 137 (100), 89 (51), 75 (77); HRMS calculated for $C_{20}H_{24}N_2O_3SSi$: 328.1277, found: 328.1266.

4.3. General procedure for the enantioselective 1,3-DC using dual catalyst 14·Ag-(*R*)-17. Synthesis of compounds *endo*-4b and 20.

In a 10 ml vial covered by aluminum foil, Ag_2CO_3 (2.8 mg, 0.01 mmol), (*R*)-Binol-phosphoric acid (7 mg, 0.02 mmol) and toluene (3 mL) were added and the resulting mixture was stirred at room temperature for 1 h. Phosphoramidite (S_a,*R*,*R*)-**14** (10.8 mg, 0.02 mmol) was added and the reaction stirred for additional 40 min. Then, the imino ester (0.4 mmol), the dipolarophile (0.4 mmol) and triethylamine (3 µL, 0.02 mmol) were added in this order and the reaction stirred at room temperature. The mixture was cooled at -10 ºC and the amino ester **2c** (193 mg, 1 mmol), the corresponding maleimide **3** (1 mmol), and ethyl glyoxylate **1** (*ca.*50% solution in toluene, 102 µL, 1.2 mmol) were slowly added in this order. The reaction was stirred for 17 h. The solvent was evaporated and the crude product was purified purified by flash chromatography (*n*-hexane:EtOAc), affording cycloadducts *endo*-**4b** and **20**.

4.4. 4-(*tert*-Butyl) 2-methyl (2*R*,4*S*,5*R*)-2-{[(tert-butyldimethylsilyl)oxy]methyl}-5-(thiazol-2-yl)pyrrolidine-2,4-dicarboxylate (*endo*-4b).

Sticky pale yellow oil, 119 mg (82%); $[\alpha]_D^{20}$ = -8.0 (*c* = 0.8, CH_2Cl_2) for 93:7 er by HPLC (Chiralpak AD-H), *n*-hexane/*i*-PrOH: 90/10, (0.7 mL/min, λ 250 nm), t_{may} = 8.3 min, t_{min} = 9.2 min; IR ν_{max}: 3345, 1727, 1677 cm^{-1}; ^{1}H RMN δ_H: 0.05, 0.09 (2s, 6H, Me_2Si), 0.87 (s, 9H, Me_3C), 1.19 (s, 9H, CO_2CMe_3), 2.16 (dd, *J* = 13.7, 8.1 Hz, 1H, CO_2MeCCH), 2.80 (dd, *J* = 13.7, 8.3 Hz, 1H , CO_2MeCCH), 3.00 (br. S, 1H, NH), 3.40 (ddd, *J* = 8.3, 8.1, 7.5 Hz, 1H, $CHCO_2tBu$), 3.64 (d, *J* = 9.5 Hz, 1H, CH_2OTBDMS), 3.72 (s, 3H, CO_2Me), 3.79 (d, *J* = 9.5 Hz , 1H, CH_2OTBDMS), 4.93 (d, *J* = 7.5 Hz , NHC*H*), 7.24, 7.68 (2sd, *J* = 3.3 Hz, 2H, HC=CH); ^{13}C RMN δ_C: -5.6, -5.4 (Me_2Si), 18.2 (Si*C*Me_3), 25.8 (SiCMe_3), 27.7 (OC*Me*$_3$), 33.6 (*C*CH_2C), 49.5 (*C*HCO_2tBu), 52.3 (CO_2*Me*), 61.5 (CHNH), 69.1 (CH_2OSi), 70.1 (*C*CO_2Me), 80.9 (O*C*Me_3), 118.9 (CHS), 142.3 (*C*HNCSTh), 170.3 (NCS), 171.5, 174.6 (2xCO_2); MS (ESI) *m/z*: 456 (M^+, 2%); HRMS for $C_{21}H_{36}N_2O_5Si$ required: 456.2112; found: 456.2108.

Annex 1

4.5. Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (20a):[9,21] 90 mg, 78%; $[\alpha]_D^{20}$ = +62.0 (*c* 1, CH_2Cl_2) for 90:10 er, $[\alpha]_D^{20}$ = +61.0 (*c* 1.18, CH_2Cl_2) for 90:10 er.[21]

4.6. 4-(tert-Butyl) 2-methyl (2*S*,4*S*,5*R*)-5-phenylpyrrolidine-2,4-dicarboxylate (20b):[9,21] 84 mg, 90%; $[\alpha]_D^{20}$ = +22.5 (*c* 1.3, CH_2Cl_2) for 90:10 er, $[\alpha]_D^{20}$ = -26.8 (*c* 1.3, CH_2Cl_2) for 3:97 er (opposite enantiomer).[22]

4.7. 3,4-Diisopropyl 2-methyl (2*S*,3*S*,4*S*,5*R*)-5-phenylpyrrolidine-2,3,4-tricarboxylate (20c):[9] 66 mg, 82%; $[\alpha]_D^{20}$ = +30.9 (*c* 0.5, $CHCl_3$) for 89:11 er, $[\alpha]_D^{20}$ = +32.5 (*c* 0.5, $CHCl_3$) for 91:9 er.[9]

4.8. Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-(2-fluorophenyl)-1-methyl-4,6-dioxo-3-(*p*-tolyl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (20d): pale yellow oil, 92 mg, 58%. $[\alpha]_D^{20}$ = -3.5 (*c* 1.1, $CHCl_3$) for 61:39 er by HPLC (Chiralpak OD-H), *n*-hexane/*i*-PrOH: 50/50, (1 mL/min, λ 250 nm), t_{may} = 9.7 min, t_{min} = 14.7 min; IR ν_{max}: 3370, 1771, 1690 cm^{-1}; ^{1}H RMN δ_H: 1.69 (s, 3H, MeCN), 2.32 (s, 3H, *Me*C_6H_4), 3.53 (d, *J* = 8.5 Hz, 1H, C*H*CMe), 3.40 (br. S, 1H, NH), 3.77 (dd, *J* = 10.0, 8.5 Hz, 1H, C*H*CHN), 3.87 (s, 3H, OMe), 4.92 (d, *J* = 10.0 Hz, 1H , CHN), 7.15-7.45 (m, 8H, Ar*H*); ^{13}C RMN δ_C: 22.3 (MeC_6H_4), 28.6 (*Me*CN), 49.7,51.8 (2xCHCO), 52.4 (CO_2*Me*), 59.2 (*C*NMe), 64.0 (NHC*H*), 126.6, 126.8, 127.3, 127.4, 128.1, 128.4, 128.6, 128.7, 129.0, 137.8 (Ar*C*), 169.1, 170.3, 172.0 (3xCO); MS (EI) *m/z*: 395 (M^+-1, 2%), 337 (45), 205 (100), 172 (18), 157 (10), 145 (70), 104 (10); HRMS for $C_{22}H_{21}FN_2O_4$ – H (M^+-1) required: 395.1407; found: 395.1403.

4.9. 4-(*tert*-Butyl) 2-methyl (2*S*,4*S*,5*R*)-2-isobutyl-5-(thiophen-2-yl)pyrrolidine-2,4-dicarboxylate (20e):[9] 95 mg, 81%; $[\alpha]_D^{20}$ = +23.2 (*c* 1, $CHCl_3$) for 76:24 er, $[\alpha]_D^{20}$ = +38.6 (*c* 1, $CHCl_3$) for 94:6 er.[9]

4.10. Methyl (1*S*,3*R*,3a*S*,6a*R*)-1-benzyl-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (20f):[9] 101 mg, 67%; $[\alpha]_D^{20}$ = -35.2 (*c* 0.8, $CHCl_3$) for 73:27 er, $[\alpha]_D^{20}$ = -74.2 (*c* 0.8, $CHCl_3$) for 95:5 er.[9]

4.11. Synthesis of 4-(*tert*-Butyl) 2-methyl (2*R*,4*S*,5*R*)-2-[(1*H*-pyrazol-1-yl)methyl]-5-(thiazol-2-yl)pyrrolidine-2,4-dicarboxylate (*endo*-18).

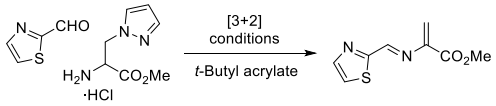
Compound *endo*-**4b** (264 mg, 0.58 mmol) was dissolved in anhydrous in THF and tetrabutylammonium fluoride (1M solution in THF) was added (1.75 mL, 1.75 mmol) at 0 ºC, and the reaction was stirred at room temperature for three hours. The solvent was evaporated and ethyl acetate (10 mL) was added. The resulting solution was washed with bine, died and evaporated affording the intermediate alcohol, which was dissolved in anhydrous THF (5 mL). This new solution was cooled at 0 °C, triethylamine (89 µL, 0.64 mmol) was added and methanesulfonyl chloride was slowly introduced (54 µL, 0.64 mmol) and stirring continued for two hours at the same temperature. At this moment, a 1:1 anhydrous DMF:THF solution (3 mL) containing sodium pyrazolide [1.75 mmol, obtained by mixing pyrazole (118 mg, 1.75 mmol) with sodium hydride (95%, 42 mg, 1,75 mmol)] was added and the reaction stirred at room temperature for 24 h. The solvent was evaporated and the residue purified by flash chromatography (*n*-hexane:EtOAc), affording cycloadduct *endo*-**18** as a pale yellow oil (70 mg, 32% overall yield). $[\alpha]_D^{20}$ = +7.7 (*c* 0.6, $CHCl_3$) 93:7 er; IR ν_{max} 3065, 1728 cm^{-1}; ^{1}H NMR δ_H: 1.44 (s, 3H, C*Me*$_3$), 2.10 (dd, *J* = 10.8, 8.8 Hz, 1H, CCH_2C), 2.58 (dd, *J* = 13.0, 8.8 Hz, 1H, CCH_2C), 3.15 (m, 1H, CHCO), 3.65-372 (m with s at 3.73, 5H, NH, CH_2N, OMe), 3.86 (d, *J* = 10.6 Hz, 1H, CH_2N), 4.86 (d, *J* = 8.5 H, 1H, H, CHN), 7.26 (m, 3H, CHCHNN, CHS), 7.64 (m, 2H, 2xC=CHN); ^{13}C NMR δ_C: 27.9 (C*Me*$_3$), 29.7 (CCH_2C), 52.1 (*C*HCO), 52.3 (OMe), 62.5 (CHNH), 67.3 (CH_2N), 70.2 (N*C*CO), 81.3 (*C*Me$_3$), 100.0 (*C*HCHNN), 119.1 (CHS), 128.1 (CHNN), 129.1 (CHNN), 142.5 (*C*HNCS), 171.5, 171.6, 174.5 (NCS, 2xCO); MS (EI-GC) *m/z*: 392 (M^+, 5%), 383 (10), 343 (15), 311 (24), 255 (100), 86 (13), 73 (13); HRMS calculated for $C_{18}H_{24}N_4O_4S$: 392.1518, found: 392.1509.

Annex 1

Acknowledgements: Financial support was provided by the Spanish Ministerio de Ciencia e Innovación (MICINN) (projects CTQ2010-20387, and Consolider Ingenio 2010, CSD2007-00006), the Spanish Ministerio de Economía y Competitividad (MINECO) (projects CTQ2013-43446-P and CTQ2014-51912-REDC), the Spanish Ministerio de Economía, Industria y Competitividad, Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER, EU) (projects CTQ2016-76782-P, CTQ2016-80375-P, and CTQ2016-81797-REDC), the Generalitat Valenciana (PROMETEO 2009/039 and PROMETEOII/2014/017), and the University of Alicante.

References

1. (a) Haider, S.; Saify, Z. S.; Begum, N.; Ashraf, S.; Zarreen, T.; Saeed, S. M. G. *World J. Pharm. Res*. **2014**, *3*, 987-1024; (b) Saraswat, P.; Jeyabalan, G.; Hassan, M. Z.; Rahman, M. U.; Nyola, N. K. *Synth. Commun*. **2016**, *46*, 1643-1664; (c) Tolomelli, A.; Ammazzalorso, A.; Bruno, I.; Amoroso, R. Curr. Bioact. Compd. **2016**, *12*, 146-160.
2. Döndas, H. A.; Retamosa, M. G.; Sansano, J. M. *Synthesis* **2017**, *49*, 2819-2851.
3. Nájera, C.; Sansano, J. M. *Org Biomol Chem*. **2009**, *7*, 4567-4581.
4. For an updated list of all antiviral agents, see: https://www.drugs.com/drug-class/antiviral-agents.html.
5. Nájera, C.; Sansano, J. M. *L'Actualité Chim* **2013**, *370*, 28-30.
6. (a) Burton, G.; Ku, T. W.; Carr, T. J.; Kiesow, T.; Sarisky, R. T.; Lin-Goerke, J.; Baker, A.; Earnshaw, D. L.; Hofmann, G. A.; Keenan, R. M.; Dhanak, D. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 1553–1556; (b) Burton, G.; Ku, T. W.; Carr, T. J.; Kiesow, T.; Sarisky, R. T.; Lin-Goerke, J.; Hofmann, G. A.; Slater, M. J.; Haigh, D.; Dhanak, D.; Johnson, V. K.; Parry, N. R.; Thomes, P. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 1930–1933.
7. (a) Slater, M. J.; Amphlett, E. M.; Andrews, D. M.; Bravi, G.; Burton, G.; Cheasty, A. G.; Corfield, J. A.; Ellis, M. R.; Fenwick, R. H.; Fernandes, S.; Guidetti, R.; Haigh, D.; Hartley, C. D.; Howes, P. D.; Jackson, D. L.; Jarvest, R. L.; Lovegrove, V. L. H.; Medhurst, K. J.; Parry, N. R.; Price, H.; Shah, P.; Singh, O. M. P.; Stocker, R.; Thommes, P.; Wilkinson, C.; Wonacott, A. *J. Med. Chem*. **2007**, *50*, 897–900; (b) Agbodjan, A. A.; Cooley, B. E.; Copley, R. C. B.; Corfield, J. A.; Flanagan, R. C.; Glover, B. N.; Guidetti, R.; Haigh, D.; Howes, P. D.; Jackson, M. M.; Matsuoka, R. T.; Medhurst, K. J.; Millar, A.; Sharp, M. J.; Slater, M. J.; Toczko, J. F.; Xie, S. *J. Org. Chem*. **2008**, *73*, 3094–3102.
8. Nájera, C.; Retamosa, M. G.; Sansano, J. M. *Tetrahedron: Asymmetry* **2006**, *17*, 1985–1989.
9. Nájera, C.; Retamosa, M. G.; Martín-Rodríguez, M.; Sansano, J. M.; de Cózar, A.; Cossío, F. P. *Eur. J. Org. Chem.* **2009**, 5622-5634.
10. Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; de Cózar, A., Cossío, F. P. *Beilstein J. Org. Chem*. **2011**, *7*, 988–996.
11. For reviews dealing with asymmetric 1,3-DC, see: (a) Maroto, E. E.; Izquierdo, M.; Reboredo, S.; Marco-Martínez, J.; Filippone, S.; Martín, N. *Acc. Chem. Res.* **2014**, *47*, 2660-2670; (b) Narayan, R.; Potowski, M.; Jia, Z.-J.; Antonchick, A. P.; Waldmann, H. *Acc. Chem. Res*. **2014**, *47*, 1296-1310; (c) Nájera, C.; Sansano, J. M. *J. Organomet. Chem.* **2014**, *771*, 78-92; (d) Randjelovic, J.; Simic, M.; Tasic, G.; Husinec, S.; Savic, V. *Curr. Org. Chem.* **2014**, *18*, 1073-1096; (f) Li, J.; Zhao, H.; Zhang Y. *Synlett* **2015**, *26*, 2745-2750; (g) Yoo, E. J. *Synlett* **2015**, *26*, 2189-2193; (h) Ryan, J. H. *Arkivoc* **2015**, *(i)*, 160-183; (i) Hashimoto, T.; Maruoka, K. *Chem. Rev*. **2015,** *115*, 5366-5412; (j) Pavlovska, T. L.; Gr. Redkin, R.; Lipson, V. V.; Atamanuk, D. V. *Synth. Biol. Activ. Mol. Divers* **2016**, *20*, 299-344; (k) Meyer, A. G.; Ryan, J. H. *Molecules* **2016**, *21*, 935-989; (l) Singh, M.S.; Chowdhury, S.; Koley, S. *Tetrahedron* **2016**, *72*, 1603-1644; (m) Nájera, C.; Sansano, J. M. *Chem. Rec.* **2016**, *16*, 2430-2448; (n) Bdiri, B.; Zhao, B.-J.; Zhou, Z.-M. *Tetrahedron: Asymmetry* **2017**, *28*, 876-899.
12. Www.CEN-ONLINE.ORG, 28/NOV/2011, page 8.
13. The introduction of the pyrazole unit in the imino ester afforded a labile compound under basic media suffering a β-elimination.

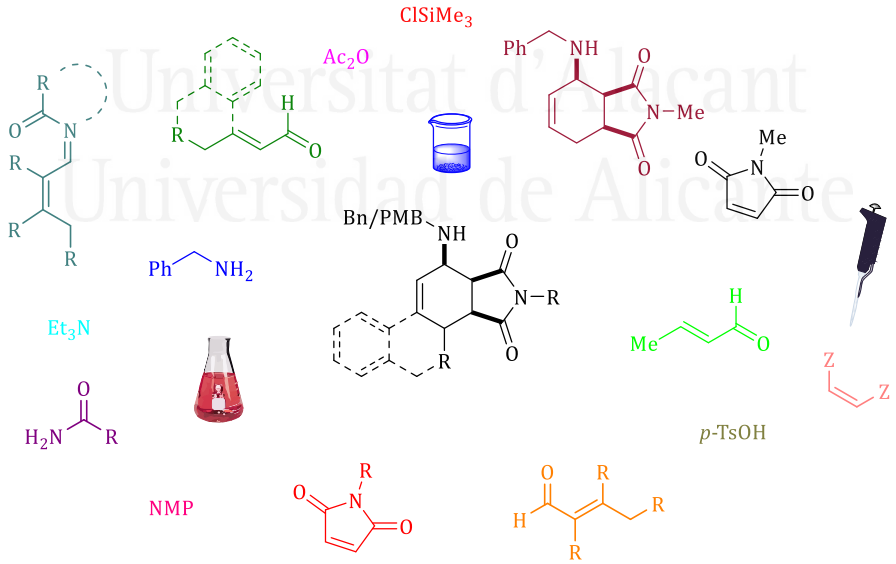


14. Krenk, O.; Kratochvil, J.; Spulak, M.; Buchta, V.; Kunes, J.; Novakova, L.; Ghavre, M.; Pour, M. *Eur J. Org. Chem*. **2015**, 5414-5423.
15. (a) Nájera, C; Retamosa, M. G.; Sansano, J. M. *Org. Lett.* **2007**, 9, 4025-4028; (b) Nájera, C.; Retamosa, M. G.; Sansano, J. M.; de Cózar, A.; Cossío, F. P. *Tetrahedron: Asymmetry* **2008**, *19*, 2913–2923; (c) Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; Costa, P. R. R.; Crizanto de Lima, E.; Dias, A. G. *Synlett* **2010**, 962–966; (d) Mancebo-Aracil, J.; Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; Costa, P. R. R.; Crizanto de Lima, E.; Dias, A. G. *Tetrahedron: Asymmetry* **2012**, *23*, 1596–1606.
16. Mixtures of several aggregrates of binap-silver salts were identified in different proportions depending of the temperature. Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc*. **2004**, *126*, 5360–5361.

17. (a) James, M. J.; Cuthbertson, J. D.; OÏBrien, P.; Taylor, R. J. K.; Unsworth, W. P. *Angew. Chem. Int. Ed.* **2015**, *54*, 7640-7643; (b) Rotsides, C. Z.; Woerpel, K. A. *Dalton Trans*. **2017**, *46*, 8763-8768.
18. Leclerc, M. C.; Gabidullin, B. M.; Da Gama, J. G.; Daifuku, S. L.; Iannuzzi, T. E.; Neidig, M. L.; Baker, R. T. *Organometallics* **2017**, *36*, 849-857.
19. Flanagan, R. C.; Xie, S.; Millar, A. *Org. Process Res. Dev*. **2008**, *12*, 1307–1312.
20. Gupta, P.; Garg, P.; Roy, N. *Med. Chem. Res.* **2013**, *22*, 3444-3451.
21. Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc*. **2002**, *124*, 13400–13401.
22. Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc*. **2003**, *125*, 10174–10175.

CHAPTER 2:

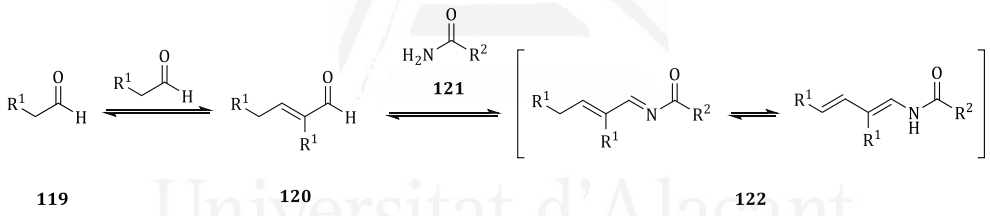
Diastereoselective multicomponent Amine-Aldehyde-Dienophile (AAD) process for the synthesis of polysubstituted cyclohex-2-enylamines



Brief Bibliographic background

Amine-Aldehyde-Dienophile (AAD) Reactions

Amide-Aldehyde-Dienophile (AAD) reaction is among the best-known reactions in the multicomponent reactions family. This process was developed by M. Beller in 2001 and was used to prepare compounds that may be elaborated by post-condensation modifications.[165,166] The catalyzed amidocarbonylation of propionaldehyde **119** with acetamide **121** afforded 1-*N*-acetylamino-2-methyl-1,3-pentadiene (**122**, with R^1 = R^2 = Me) as a by-product (<5%).[167] It was concluded that **122** was not formed by a reaction catalyzed by palladium but rather by simple condensation of two molecules of propionaldehyde with acetamide (Scheme 41).

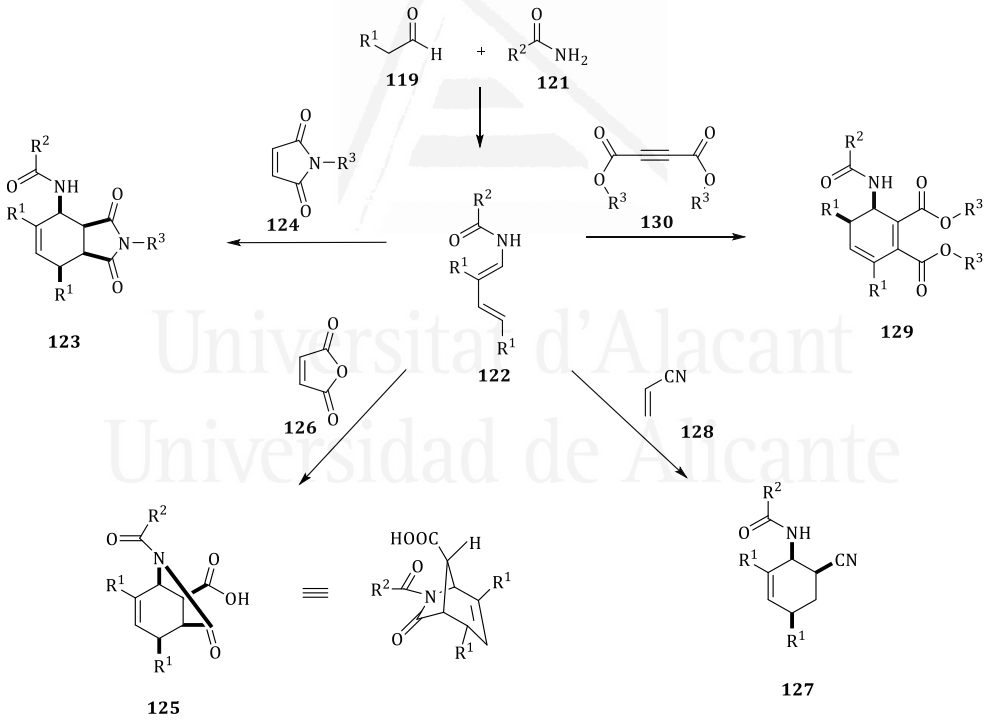


Scheme 41. Proposed Mechanism for the Formation of **122**

Therefore, they reported an optimized set of conditions for this AAD reaction, involving Ac_2O (each 15 mmol), *p*-TSA·H_2O (1.5 mol%), NMP (10 mL),

[165] Sunderhaus, J. D.; Martin, S. F. *A European Journal.* **2009**, *15(6), 1300–1308.*
[166] a) Beller, M.; Eckert, M. *Angew. Chem., Int. Ed*. **2000**, *39*, 1010.; b) Beller, M.; Moradi, W.; Eckert, M.; Neumann, H. *Tetrahedron Lett*. **1999**, *40*, 4523.; c) Beller, M.; Eckert, M.; Moradi, *W. Synlett* **1999**, *108*.; d) Beller, M.; Eckert, M.; Geissler, H.; Napier ski, B.; Rebenstock, H. P.; Holla, E. W. *Chem. Eur. J*. **1998**, 4, 935.; e) Beller, M.; Eckert, M.; Holla, E. W. *J. Org. Chem*. **1998**, *63*, 5658.
[167] Neumann, H.; Jacobi von Wangelin, A.; Gördes, D.; Spannenberg, A.; Beller, M. *Journal of the American Chemical Society.* **2001**, *123(34), 8398–8399.*

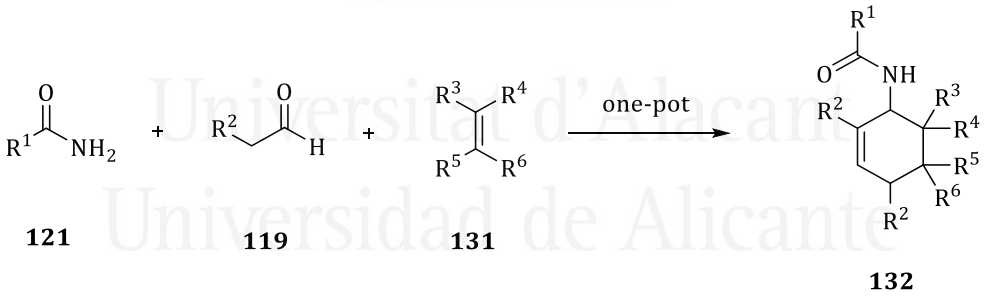
>20 h, >80 °C,[167] and subsequently the *in situ* formed 1-acylamino-1,3-butadienes were employed in the preparations of highly functionalized cyclohexene and cyclohexadiene derivatives. It was noted that the formation of product **122** showed a significant dependence on solvents. The use of *N*-methylpyrrolidinone (NMP) or DMF proved to be essential to give **122** in a substantial yield (20-30%). The reaction could be accelerated by the addition of catalytic amounts of *p*-toluenesulfonic acid as well as stoichiometric amounts of acetic anhydride. The application of the optimized conditions, with the aldehyde / amide molar ratio of 1/1, gave **122** ($R^1 = R^2 = Me$) with a yield of 50% at 80 °C. Since the formation of **122** takes place via several equilibrium steps as it is shown in (Scheme42).



Scheme 42. Diels-Alder-trapping of intermediate 1-acylamino-1,3-butadienes **122**.

It has been envisaged to use it in domino reaction sequences with a final irreversible step, by shifting the equilibria to the right.[167][167][167]The subsequent Diels-Alder reactions was studied using alkenes and electro-deficient alkynes. The *in situ* trapping of **122** with various dienophiles gave the corresponding cyclohexene derivatives (scheme 42) with excellent yields (up to 92%).

In 2003, the same group studied the three-component reactions of amides, aldehydes and dienophiles in a novel one-pot manner. The addition of an electron-deficient dienophile resulted the chemoselective Diels-Alder reaction with the intermediate species of 1-amidodiene in a multicomponent reaction sequence[168] (Scheme 43). This methodology with several components in a single pot is more effective in comparison with a procedure which takes place in several stages involving the isolation of the intermediate aminodiene with moderate to low yields.[169]

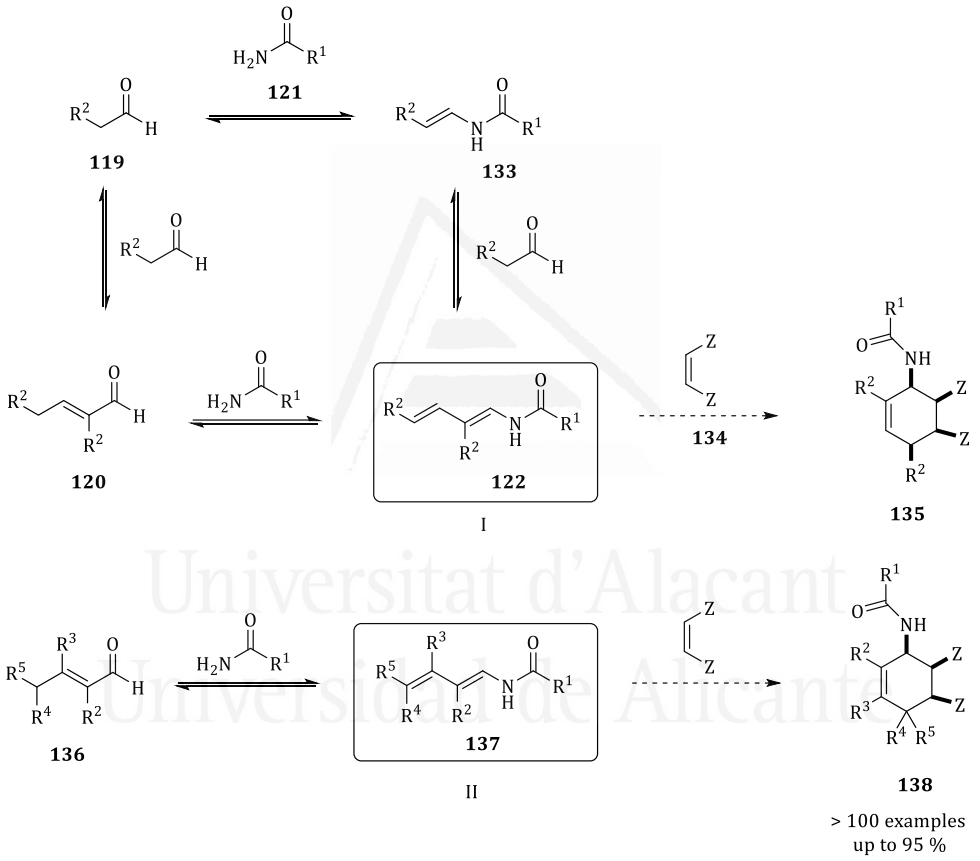


121 **119** **131** **132**

Scheme 43. One-pot reaction of an AAD transformation.

[168] Jacobi von Wangelin, A; Neumann, H.; Gördes, D.; Klaus, S.; Strübing, D.; Beller, M. *Chemistry - A European Journal*. **2003**, *9*(18), 4286–4294.
[169] Neumann, H.; Jacobi von Wangelin, A.; Gördes, D.; Spannenberg, A.; M. Beller, *J. Am. Chem. Soc.* **2001,** *123*, 8398-8399.

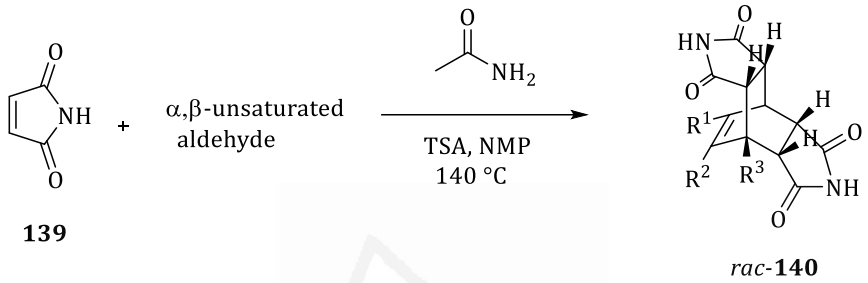
The access to the intermediate amidodienes can be of (type I) **122** (Scheme 44, top), which are achieved by condensation of two α-CH_2 containing aldehydes with an amide. 1-*N*-acylamino-1,3-butadiene building blocks **137** (type II) are obtained using the unsaturated aldehydes (Scheme 44, bottom). They contain four substitution points along the 1,3-butadiene skeleton which significantly increases the diversity of the substrate.[170]



Scheme 44. In situ formation of *N*-acylaminodienes from simple aldehydes (type I, top) or α,β-unsaturated aldehydes (type II, bottom) and Diels-Alder reactions.

[170] Jacobi von Wangelin, A.; Neumann, H.; Gördes, D.; Spannenberg, A.; M. Beller, *Org. Lett.* **2001**, *3*, 2895-2898.

It was found that one-pot reactions carried out with high temperatures in the presence of an excess of maleimide led to tetracyclic adducts as predominantly *meso*-isomers *via* repetitive *endo*-cycloadditions[171] (Scheme 45).

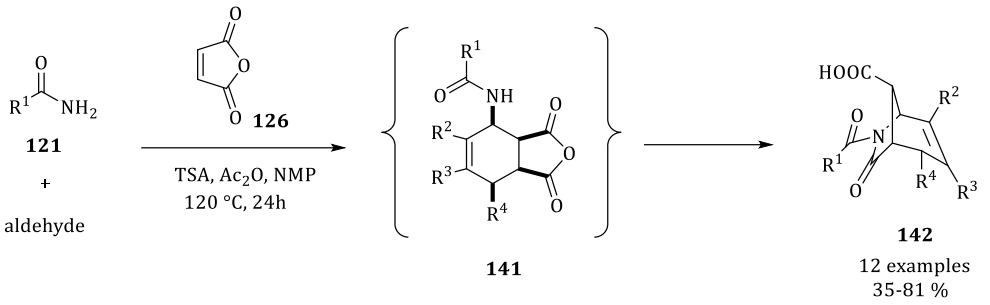


139 *rac*-**140**

Scheme 45. One-pot synthesis of **140**.

Azabicyclooctene derivatives are easily obtained using maleic anhydride dienophile by a domino condensation-cycloaddition skeletal rearrangement reaction sequence (Scheme 46).[172] $LiAlH_4$ reduction gave 6-azabicyclo [3.2.1] octane derivatives, which are a structural motif for various polycyclic alkaloids such as *securinega*,[173] and *aristotelia*.[174]

[171] Deutsch, H. M.; Gelbaum, L. T.; McLaughlin, M.; Fleischmann, T. J.; Earnhart, L. L.; Haugwitz, R. D.; Zalkow, L. H. *J. Med. Chem*. **1986**, *29*, 2164 -2170; b) Pettit, G. R.; Paull, K. D.; Herald, C. L.; Herald, D. L.; Riden, J. R. *Can. J. Chem*. **1983**, *61*, 2291-2294.
[172] Neumann, H.; Jacobi von Wangelin, A.; Gördes, D.; Spannenberg, A.; Baumann, W.; M. Beller, *Tetrahedron.* **2002,** *58*, 2381-2387.
[173] a) Jacobi, P. A.; Blum, C. A.; DeSimone, R. W.; Udodong, U. E. S.; *J. Am. Chem. Soc.* **1991,** *113*, 5384-5392; b) Magnus, P.; Rodriguez-López, J.; Mulholland, K.; Matthews, I.; *Tetrahedron*. **1993**, *49*, 8059-8072; c) G. Han, M. G.; LaPorte, J. J.; Folmer, K. M.; Werner, S. M.; Weinreb, J. *Org. Chem*. **2000,** *65*, 6293-6306
[174] a) Lin, X.; Stien, D.; Weinreb, S. M.; *Tetrahedron Lett*. **2000,** *41*, 2333-2337; b) Rigby, J. H.; Meyer, J. H. *Synlett.* **1999**, 860-862.; c) Klaver, W. J.; Hiemstra, H. Speckamp, W. N. *J. Am. Chem. Soc.* **1989,** *111*, 2588 -2595.

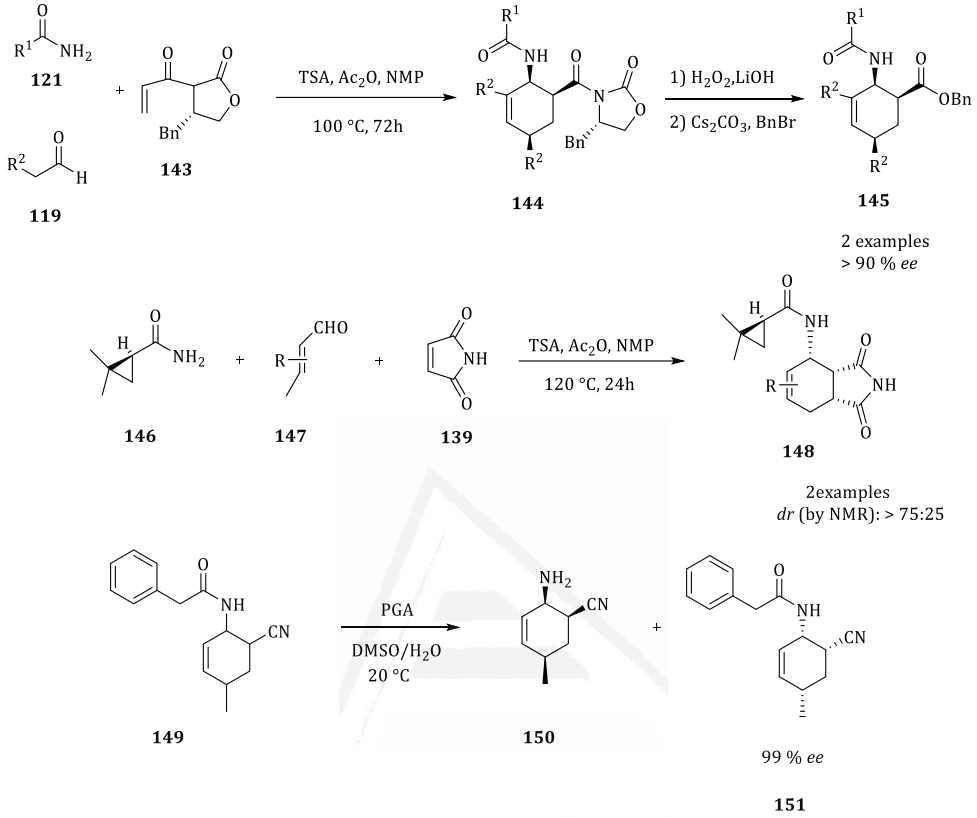


Scheme 46. One-pot approach to **142**.

The use of the asymmetric dienophile acrylonitrile in these reactions gives preferably the ortho adduct containing adjacent amino and cyano substituents. The nitriles obtained are generally interesting constituent elements which can also be produced into carboxylic acids,[175] pyridines,[176] triazines and oxazoles.[177]

The study of AAD reactions, using chiral lactone **143**, with several components has shown high levels of regio- and diastereoselectivity (Scheme 47). Based on one-pot reactions with chiral α-β unsaturated *N*-acyl-oxazolidinones,[178] followed by cleavage[179] of the chiral auxiliary, the desired enantiomerically enriched 1-*N*-acylaminocyclohexene-2-carboxylateswere obtained with moderate yields and excellent stereoselectivities (> 90% ee).

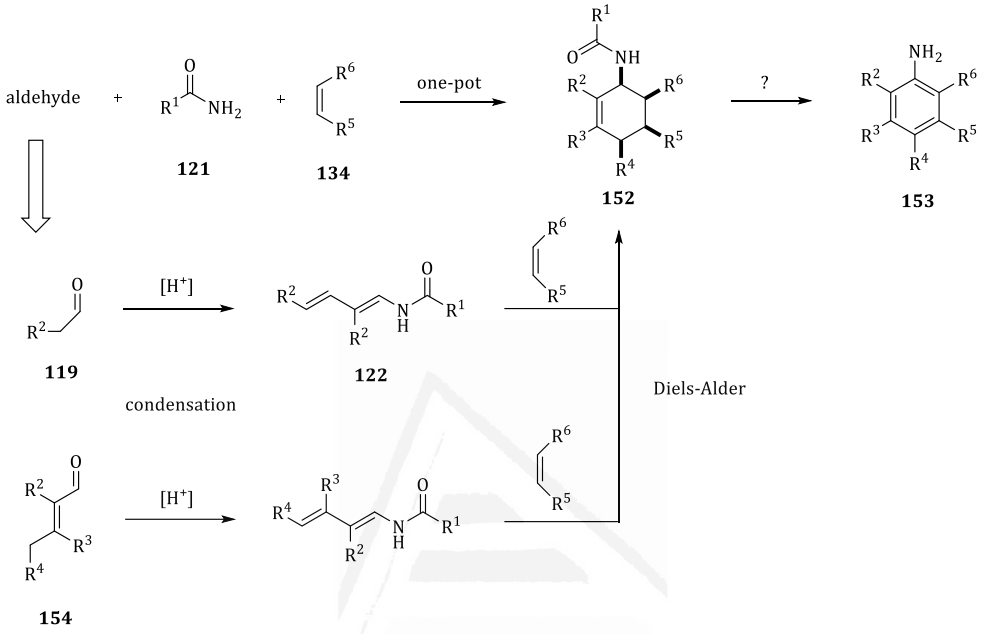
[175] Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181-2204.
[176] Schulz, W.; Pracejus, H.; Oehme, G. *Tetrahedron Lett*. **1989**, *30*, 1229-1232.
[177] a) Katritzky, A. R.; Pozharski, A. F.; Handbook of Heterocyclic Chemistry, 2nd ed., Pergamon Press, Amsterdam. 2000, Vol. 49, 9 ; b) Anderson, B. A.; Becke, L. M.; Booher, R. N.; Flaugh, M. E.; Harn, N. K.; Kress, T. J.; Varie, D. L.; Wepsiec, J. P. *J. Org. Chem*. **1997,** *62*, 8634-8639; c) Alterman, M.; Hallberg, A.; *J. Org. Chem*. **2000**, *65*, 7984-7989.
[178] Evans, D. A.; Chapham, K. T.; Bisaha, J. *J. Am. Chem. Soc*. **1988,** *110*, 1238-1256.
[179] Evans, D. A.; Britton, T.; Ellman, J. A. *Tetrahedron Lett*. **1987,** *28*, 6141-6144.



Scheme 47. Different approaches for diastereoselective synthesis of AAD products.

In the same year, based on previous studies, the Beller group considered the new three-component coupling products as useful intermediates in the synthesis of anilines, so they decided to present a new reaction sequence in order to synthesize substituted anilines, where they propose to combine

a,three-component coupling reaction with a new catalyzed by a transition metal aromatization step[180] (scheme 48).



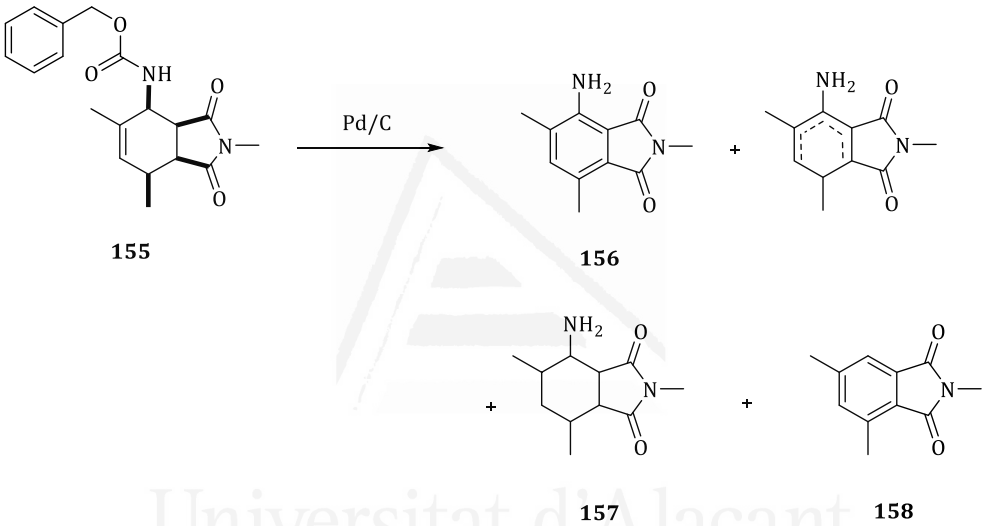
Scheme 48. Three-component-coupling reaction of amides, aldehydes, and dienophiles and the envisioned aromatization to give anilines.

4-*N*-(Benzyloxycarbonyl)aminohexahydro-1*H*-isoindole **155** was generated in 79% yield by the reaction of propionaldehyde, *O*-benzyl carbamate ($CbzNH_2$, R^1 = BnO), and maleimide (Scheme 49). By heating **155** to a reflux in the presence of Pd/C and cyclohexene (as a hydrogen donor) in ethanol,[181] they obtained a mixture of products. An overall yield of only 26% was obtained for three amino-substituted isomeric cyclohexenes, aniline **156** (28%), which was

[180] Neumann, H.; Jacobi von Wangelin, A.; Klaus, S.; Strübing, D.; Gördes, D.; Beller, M. *Angewandte Chemie International Edition.* **2003,** *42(37), 4503–4507.*
[181] Jackson, A. E.; Johnstone, R. A. W. *Synthesis*. **1976**, 685 – 687.

identified as a major product. After optimization of reaction conditions **156** was obtained with an excellent yield (91%). The use of a stronger hydrogen donor

(H_2,[182] HCO_2H[183]), led to the formation of saturated cyclohexane **157** with a moderate yield. On the other hand, the cyclohexene group in **155** could replace the use of an additional hydrogen donor because it itself can act in this way in the debenzylation of the carbamate.



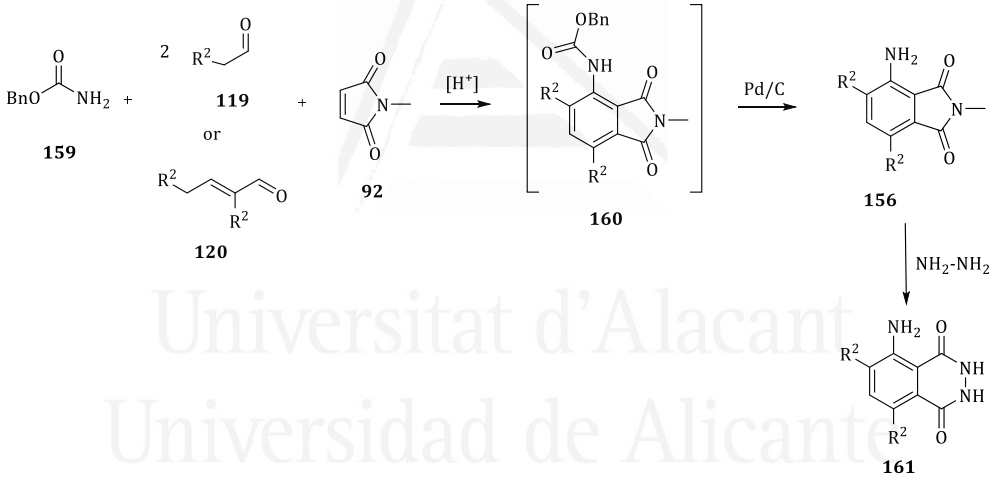
Scheme 49. Palladium-catalyzed aromatization of 4-*N*-(benzyloxycarbonyl) aminohexahydro-1H-isoindole **155**.

In a new method,[184] the sequential combination of a three-component coupling reaction involving *O*-benzyl carbamate, aldehydes and dienophiles and a subsequent domino deprotection reaction-aromatization allows the synthesis

[182] Bergmann, M.; Zervas, L. *Chem. Ber*. **1932,** *65*, 1192.
[183] El Amin, B.; Anantharamaiah, G. M. ; Royer, G. P.; Means, G. E. *J. Org. Chem*. **1979,** *44*, 3442 – 3444.
[184] Neumann, H.; Klaus, S.; Klawonn, M.; Strübing, D.; Hübner, S.; Gördes, D.; Beller, M. *Zeitschrift Für Naturforschung B.* **2004,** *59(4), 431–438.*

of polysubstituted anilines.[185] Here, a palladium aromatization of the three-component coupling products, based on a new hydrogenation reaction by intramolecular transfer, is considered as a key step. This new reaction sequence was also useful for the synthesis of 5-amino-2,3-dihydrophthalazine-1,4-diones **161**, which was discovered by Albrecht[186] in 1928 this molecule is called luminol, because its oxidation using H_2O_2 in the presence of a catalyst leads to the emission of light (Scheme 50).[187]

Following the coupling reaction with three components of aldehydes, *O*-benzyl carbamate and *N*-methylmaleimide [2, 4], the topology of a precious luminol precursor was established in a single reaction step.



Scheme 50. Three-component reaction of aldehydes, *O*-benzyl carbamate and *N*-methylmaleimide.

[185] Neumann, H.; Jacobi von Wangelin, A.; Klaus, S.; Strübing, D.; Gördes, D.; Beller, M. *Angew. Chem., Int. Ed.* **2003,** *42*, 4503.
[186] Albrecht, H. O. *Z. Phys. Chem.* **1928**, *136*, 321.
[187] a) Gundermann, K. D. *Chimia.* **1971,** *25*, 261.; b) White, E. H.; Roswell, D. F. *Acc. Chem. Res.* **1979**, *3*, 54.

After all these studies the Beller's group was particularly interested in the development of transition metal-catalyzed three- and four-component coupling reactions.[188] And based on the latest work,[189] they discovered a new multi-component methodology (AAD reaction) to afford a wide variety of carbohydrate and heterocyclic amides.[190] This improved protocol consists of the multicomponent coupling reaction of α,β-unsaturated aldehydes or aldehydes with various reactive amides and dienophiles in order to easily synthesize derivatives of 1-acylamino2-cyclohexene.[184]

After the discovery of the first multicomponent reaction of amides, aldehydes and dienophiles (AAD reaction) the amides were replaced by carboxylic acid anhydrides (ANAD reaction) or alcohols as well as orthoesters (ALAD reaction) (Scheme 51).[191] From where they have synthesized more than 200 carbo and heterocyclic compounds with great efficiency.[192] The substituted

[188] Klaus, S.; Hübner, S.; Neumann, H.; Strübing, D.; von Wangelin, A. J.; Gördes, D.; Beller, M. *Advanced Synthesis & Catalysis.* **2004,** *346(8), 970–978.*

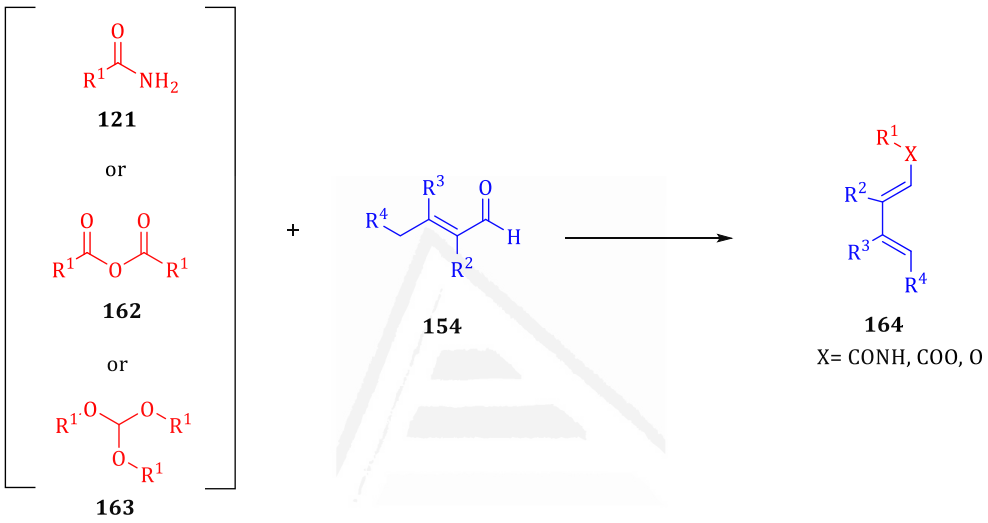
[189] a) Gördes, D.; Neumann, H.; Jacobi von Wangelin, A.; Fischer, C.; Drauz, K.; Krimmer, H. P.; Beller, M.; *Adv. Synth. Cat*. **2003**, *345*, 510.; b) Gördes, D.; Jacobi von Wangelin, A.; Klaus, S.; Neumann, H.; Str¸bing, D.; Hübner, S.; Jiao, H.; Baumann, W.; Beller, M. *Organic & Biomolecular Chemistry.* **2004,** *2*, 845.

[190] a) Neumann, H.; Jacobi von Wangelin, A.; Gördes, D.; Spannenberg, A.; Beller, M.; *J. Am. Chem. Soc*. **2001**, *123*, 8398.; b) Jacobi von Wangelin, A.; Neumann, H.; Gördes, D.; Spannenberg, A.; Beller, M. *Org. Lett*. **2001**, *3*, 2895.; c) Neumann, H.; Jacobi von Wangelin, A.; Gördes, D.; Spannenberg, A.; Baumann, W.; Beller, M. *Tetrahedron* **2002**, *58*, 2381.; d) Jacobi von Wangelin, A.; Neumann, H.; Gördes, D.; Klaus, S.; Jiao, H.; Spannenberg, A.; Beller, M.; Krüger, T.; Wendler, C.; Thurow, K.; Stoll, N. *Chem. Eur. J*. **2003**, *9*, 2273.; e) Strübing, D.; Neumann, H.; Jacobi von Wangelin, A.; Gördes, D.; Klaus, S.; Beller, M.; Braiuca, P.; Ebert, C.; Gardossi, L.; Kragl, U. *Tetrahedron* **2004,** *60*, 683.

[191] Strübing, D.; Neumann, H.; Klaus, S.; Hübner, S.; Beller, M. *Tetrahedron,* **2005,** *61(48), 11333–11344.*

[192] a) Neumann, H.; Jacobi von Wangelin, A.; Gördes, D.; Strübing D. *Tetrahedron.* **2005,** *61*, 11333–11344-11343. Spannenberg, A.; Beller, M. *J. Am. Chem. Soc*. **2001,** *123*,

1,3-butadienes were obtained based on a simple condensation reaction, which are then converted with electron-deficient dienophiles by a Diels-Alder reaction into corresponding products.[193]



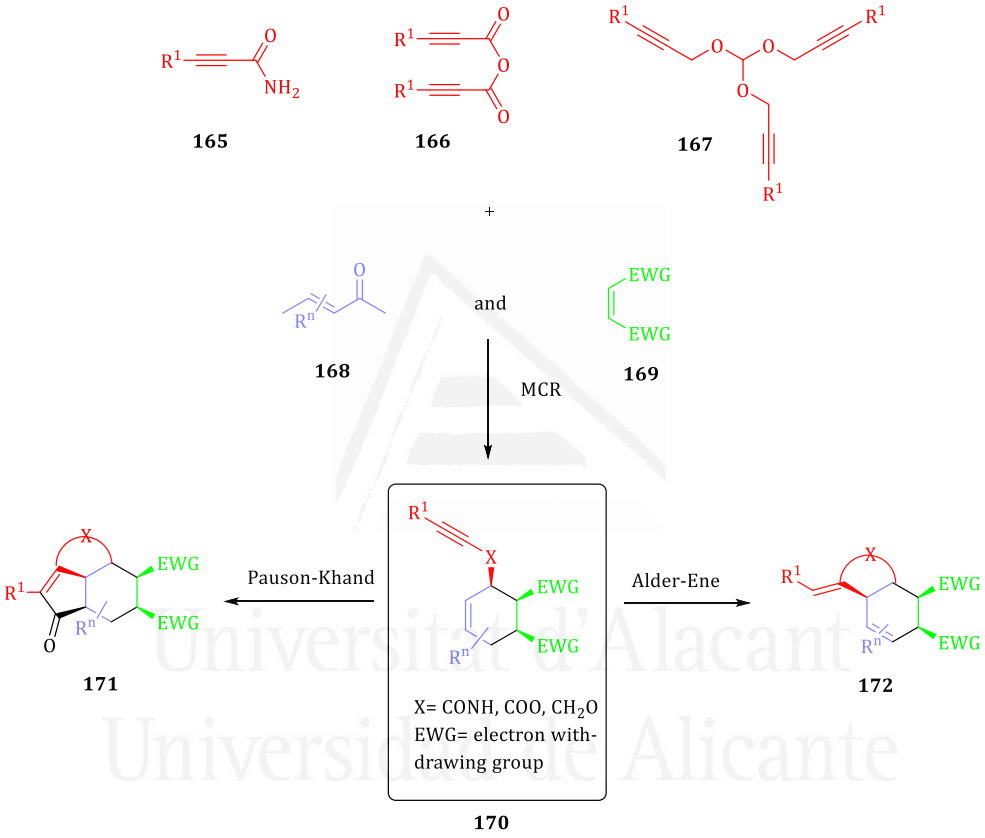
Scheme 51. ANAD and ALAD processes.

The same group envisaged the application of acetylenic derivatives in AAD reactions with subsequent catalytic functionalization of the enyne

8398.; b) Jacobi von Wangelin, A.; Neumann, H.; Gördes, D.; Spannenberg, A.; Beller, M. *Org. Lett.* **2001,** *3*, 2895.; c) Neumann, H.; Jacobi von Wangelin, A.; Gördes, D.; Spannenberg, A.; Baumann, W.; Beller, M. *Tetrahedron* **2002,** *58*, 2381.; d) Jacobi von Wangelin, A.; Neumann, H.; Gördes, D.; Klaus, S.; Jiao, H.; Spannenberg, A.; Beller, M.; Krüger, T.; Wendler, C.; Thurow, K.; Stoll, N. *Chem. Eur. J.* **2003,** *9*, 2273.; e) Strübing, D.; Neumann, H.; Jacobi von Wangelin, A.; Gördes, D.; Klaus, S.; Beller, M.; Braiuca, P.; Ebert, C.; Gardossi, L.; Kragl, U. *Tetrahedron* **2004**, *60*, 683.

[193] Drew, H. D. K.; Pearman F. H., *J. Chem. Soc.* (London) **1937,** 1841.

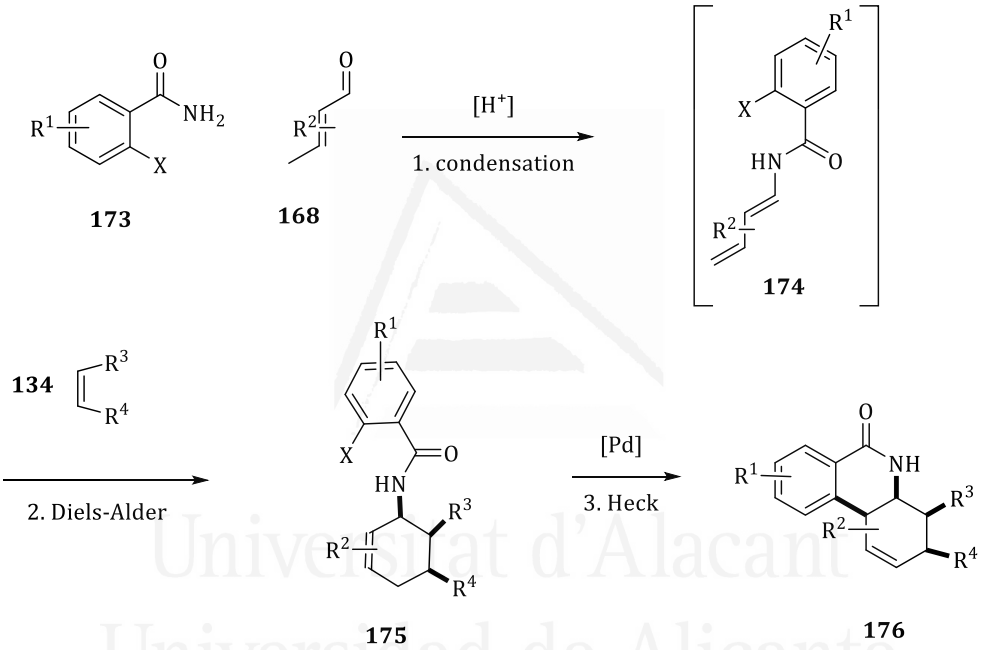
(Scheme52). The precursors of the enyne reaction were synthesized, following the improved 2nd generation MCR protocol,[194] using toluene as an appropriate solvent, in the presence of a catalytic amount of *p*-TSA and acetic acid anhydride as a water removing agent. A complete conversion was obtained after 24 to 120 h at 110 °C.



Scheme 52. Sequential AAD- and enyne reactions.

[194] Klaus, S.; Hubner, S.; Neumann, H.; Strübing, D.; Jacobi von Wangelin, A.; Gördes, D.; Beller, M. *Adv. Synth. Catal.* **2004,** *346*, 970.

It was also reported the use of sequential multicomponent reactions and the Heck reaction for a new two-stage synthesis of phenanthridonesystems.[195,196] By the fact of using sequential multicomponent and Heck reactions of suitably functionalized starting materials, the phenanthridone derivatives could be synthesized in a very simple manner (Scheme 53). The adducts were obtained as a >90:10 mixture of *endo/exo* isomers.[197]



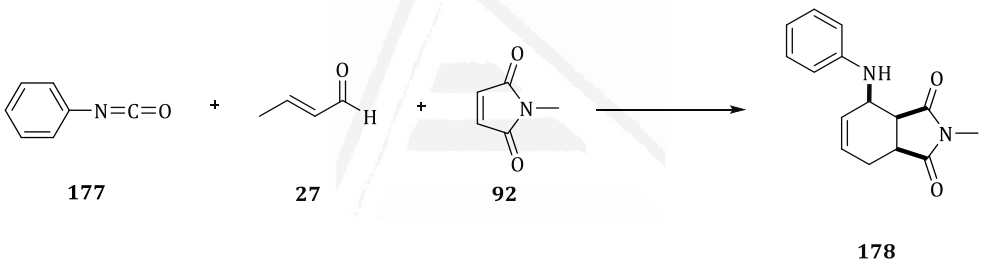
Scheme 53. Sequential three-component AAD reaction and Heck cyclization for the synthesis of phenanthridones.

[195] Beller, M.; Jacobi von Wangelin, A.; Neumann, H.; Gördes, D.; Hübner, S.; Wendler, C.; Stoll, N. *Synthesis, **2005,** 12, 2029–2038.*

[196] a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun*. **1976,** *18*, 734. b) Link, J. T.; Overman, L. E. In Metal-catalyzed Cross-coupling Reactions; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, **1998**, 231.

[197] a) Neumann, H.; Jacobi von Wangelin, A.; Gördes, D.; Spannenberg, A.; Beller, M. *J. Am. Chem. Soc.* **2001,** *123*, 8398.

Multicomponent coupling reactions involving isocyanates, unsaturated aldehydes and dienophiles (IAD reaction) for the simple synthesis of 1-amino-2-cyclohexene derivatives have been studied by extension of the previous protocols.[198] The use of the standard reaction conditions (2 mol% of *p*-toluenesulfonic acid monohydrate, toluene, 16 h, 110 ° C.), for the reaction involving phenyl isocyanate, crotonaldehyde and NMM. offered no expected carbamate, but rather the thermodynamically more stable compound 3a, 4,7,7a-tetrahydro-2-methyl-4-(phenylamino)-2H-isoindole-1,3-dione **178** with low yield (Scheme 54).



177 **27** **92** **178**

Scheme 54. Isocyanate Aldehyde Dienophile (IAD) model Reaction.

In 2006, it was reported an improved protocol for the coupling of (AAD). Taking advantage of microwave radiation, thanks to which the functionalized 1-amido-2-cyclohexene derivatives have been synthesized with good to excellent

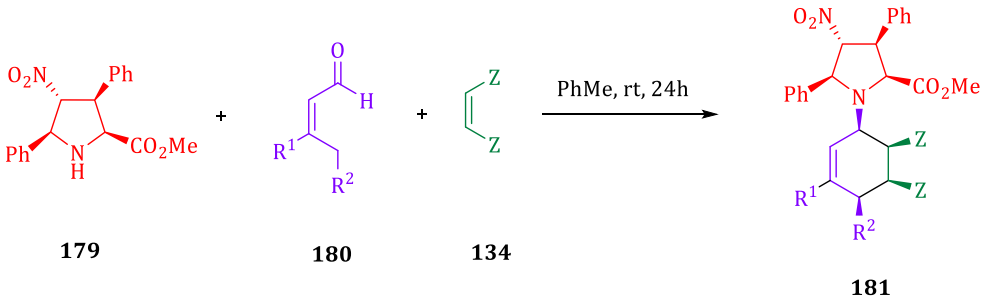
[198] Strübing, D.; Neumann, H.; Hübner, S.; Klaus, S.; Beller, M. *Organic Letters.* **2005,** *7(20),* 4321–4324.

yields.[199,200] Despite all the advantages of multicomponent reactions (AAD), a disadvantage of the protocols for these reactions is the low tolerance to functionalized aldehydes, while different functionalized amides and dienophiles can be involved in the reaction without any problem.[201]

AAD reaction of acetamide, α-bromocrotonaldehyde (or other brominated aldehydes) and *N*-methylmaleimide was studied affording interesting complex building blocks.[202,203]

In 2017, a multicomponent diastereoselective reaction involving enantioenriched 4-nitroprolinates, was widely studied, by our group. The chiral nitroprolinates **179** were allowed to react with α,β-unsaturated aldehydes (containing a hydrogen atom on the γ position) and electrophilic alkenes with total periselectivity.[204] Instead of the expected 1,3-DC, AAD process takes place with the formation of the intermediate 1-amino-1,3-diene giving highly functionalized cyclohexenes with high *endo*-diastereoselectivity (Scheme 55).

[199] Strübing, D.; Neumann, H.; Jacobi von Wangelin, A.; Klaus, S.; Hübner, S.; Beller, M. *Tetrahedron.* **2006,** *62(47),* 10962–10967.
[200] a) de la Hoz, A.; Diaz-Cortiz, A.; Moreno, A. *Chem. Soc. Rev*. **2005,** *34*, 164.; b) Kappe, C. O. *Angew. Chem., Int. Ed*. **2004,** *43*, 6250.; c) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron.* **2001,** *57*, 9225.; d) Loupy, A.; Maurel, F.; SabatieGogova, A. *Tetrahedron*. **2004,** *60*, 1683.
[201] Beller, M.; Hübner, S.; Neumann, H.; Michalik, D.; Klaus, S.; Strübing, D.; Jacobi von Wangelin, A. *Synlett,* **2007,** *7,* 1085–1090.
[202] a) de la Hoz, A.; Diaz-Ortiz, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem*. **2000,** 3659.; b) Adam, D. *Nature (London)* **2003,** *421*, 571.; c) Kappe, C. O. Angew. Chem., Int. Ed. **2004,** *43*, 3823; *Angew. Chem*. **2004,** *116*, 6408. d) Kappe, C. O.; Larhed, M. *Angew. Chem., Int. Ed.* **2005,** *44*, 7666; *Angew. Chem*. **2005,** *117*, 7840.; e) de la Hoz, A.; DiazOrtiz, A.; Moreno, A. *Chem. Soc. Rev*. **2005,** *34*, 164.
[203] Salem, B.; Delort, E.; Klotz, P.; Suffert, J. *Org. Lett*. **2003,** *5*, 2307.
[204] Selva, V., Larrañaga, O., Castelló, L. M., Nájera, C., Sansano, J. M., de Cózar, A. *The Journal of Organic Chemistry.* **2017,** *82(12),* 6298–6312.



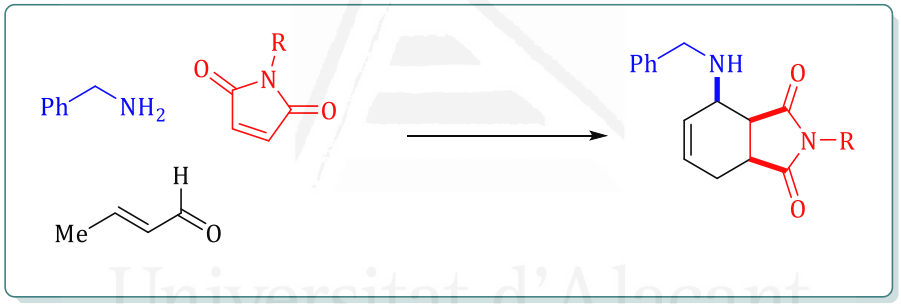
179 **180** **134** **181**

Scheme 55. The formation of the intermediate 1-amino-1,3-diene via AAD reaction

Objectives

Based on the information discussed in the general introduction, and also the research of our group in the application of reactions (AAD), the following objectives have been set:

- The preparation of polysubstituted *N*-benzyl and *N*-PMBcyclohex-2-eneamines. using benzylamine or 4-methoxybenzylamine in a diastereoselective multicomponent Amine-Aldehyde-Dienophile (DAA) process.



ANNEX 2

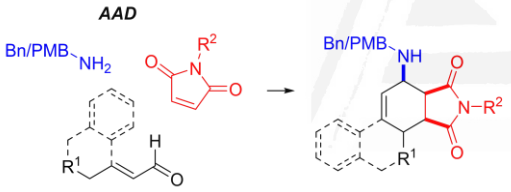
Annex 2

Graphical Abstract

Diastereoselective multicomponent Amine-Aldehyde-Dienophile (AAD) process for the synthesis of polysubstituted cyclohex-2-enylamines

Verónica Selva, Ihssene Chabour, Carmen Nájera and José M. Sansano

Leave this area blank for abstract info.



Annex 2

Tetrahedron
journal homepage: www.elsevier.com

Diastereoselective multicomponent Amine-Aldehyde-Dienophile (AAD) process for the synthesis of polysubstituted cyclohex-2-enylamines

Verónica Selva,[a,b#] Ihssene Chabour,[a,b#] Carmen Nájera,[a] and José M. Sansano[*a,b]

[a] *Departamento de Química Orgánica and Centro de Innovación en Química Avanzada (ORFEO-CINQA), Facultad de Ciencias, Universidad de Alicante 03080-Alicante, Spain.*
[b] *Instituto de Síntesis Orgánica, Facultad de Ciencias, Universidad de Alicante 03080-Alicante, Spain. Fax: +34-965903549; Tel : +34-965903728.*
 # V. S. and I. C. contributed equally to this work
** indicates the main/corresponding author, jmsansano@ua.es*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

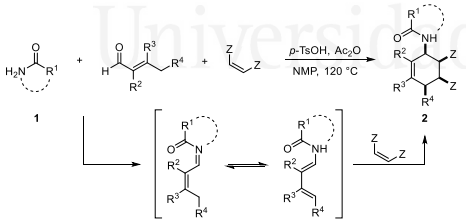
Keywords:
Multicomponent
AAD
Cyclohex-2-enylamine
Diels-Alder
Primary amines

ABSTRACT

The multicomponent Amine-Aldehyde-Dienophile reaction is optimized employing benzyl or 4-methoxybenzylamine. The interest of the transformation consist in synthesis of polysubstituted cyclohex-2-enylamines. The study of the scope of this AAD process is carried out as well as the diastereoselective version employing commercially available chiral benzylic amines and a maleimide with the chiral information at the *N*-substituent. VCD spectroscopy is a very useful tool for the determination of the absolute configuration of the isolated enantiomerically enriched compounds.

1. Introduction

Amide-Aldehyde-Dienophile (AAD) reaction is a well-known multicomponent reaction introduced by Beller and co-workers in 2001 (Scheme 1).[1] Since then, Beller's group have been expanding the scope of this multicomponent AAD reaction using different dienophiles, several substituted α,β-unsaturated aldehydes and different lineal or cyclic amides **1**, obtaining in all cases only the *endo*-approach of the Diels-Alder reaction in the racemic version (Scheme 1).[2] The same group performed the chiral version of the same reaction introducing a stereocenter in the amide **1**, using for that purpose substituted lactams. This reagent, in combination with different aldehydes and dienophiles yield enantioenriched *endo*-products **2** as major diastereoisomer in the AAD reaction.[3]

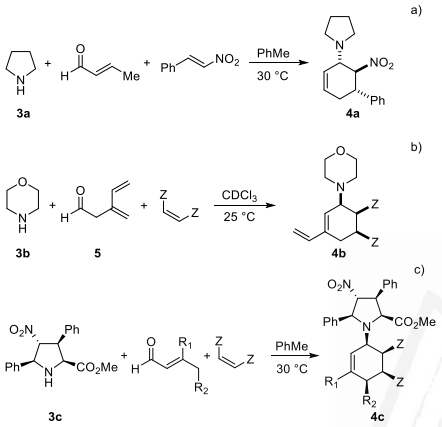


Scheme 1. Multicomponent reaction of the general Amide-Aldehyde-Dienophile (AAD).

The *N*-cyclohex-2-en-1-amide scaffold **2** is a unit present in the somatostatin analogues and the group of Kessler applied conveniently this reaction to achieve the desired product.[4] Beller's group also applied this reaction to synthetize corollosporine analogues to test their antimicrobial activity.[5] The employment of an amine instead of the amide in this reaction is less known and less favoured, being necessary the use of quite reactive reagents to carry out the reaction. Few works have been reported using a multicomponent Amine-Aldehyde-Dienophile (AAD) reaction to obtain a cyclohex-2-en-1-amine skeleton **4**. Thus, in 2014, Weber

Annex 2

and co-workers[6] performed the AAD reaction with pyrrolidine **3a**, different substituted α,β-unsaturated aldehydes and only nitrostyrenes as dienophiles (Scheme 1a). In contrast, the group of Sherburn[7] introduce different dienophiles, morpholine, but just working with one aldehyde **5** which is a very reactive aldehyde obtaining high to excellent yields (Scheme 1b). In this work only one example with benzylamine was reported. More recently, our group introduced an AAD reaction with chiral nitroprolinate **3c** obtaining the enantiopure *endo*-diastereoisomers **4c** as exclusive product in the crude mixture with excellent yields after purification (Scheme 1c).[8] In this multicomponent reaction, it was possible to induce the absolute configuration of three new stereogenic centers in a single reaction step. In fact, this mechanism is the basic interaction of similar organocatalytic Diels-Alder reactions.[9]



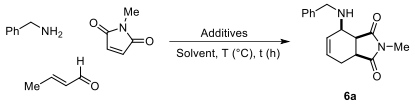
Scheme 1. a) Multicomponent AAD sequence employing the secondary amine **3a**. b) Multicomponent AAD process employing the aldehyde **5**. c) Full diasteresoselective AAD reaction employing enantiomerically enriched nitroprolinate **3c**.

According to these precedents, pyrrolidine derivatives and morpholines cannot be transformed in amines whilst sulfonamides and amides required so hard hydrolysis conditions that many functional groups of the molecule (for example, succinimides) can be hydrolysed too.[10] So, the evaluation of primary amines, such as benzylamine and *p*-methoxybenzylamine, which can be easily transformed in the corresponding primary amines, using alternative methodologies to the classical hydrolysis, is the main goal of this work. Also, the publication of a family of antibacterial agents 3-aminocyclohexenes[11] encourage us to study the scope this multicomponent AmineAD.

1. Results and Discussion

The model reaction employed for the optimization of this multicomponent AAD involved benzylamine, crotonaldehyde and *N*-methylmaleimide (NMM) as dienophile (Scheme 2). Toluene was selected as solvent due to the good results obtained in our group.[8] Only two parameters, the temperature and the nature of some additives were evaluated (Table 1) for the generation of compound **6a**. When the reaction was carried out without additives at room temperature for 16 h only Michael addition products were observed (Table 1, entry 1). However, the increment of the temperature favored the AAD reaction (Table 1, entries 2-3) obtaining complex crude products (^{1}H NMR). Next, the addition of *p*-toluenesulfonic acid as additive was tested obtaining only the Michael-type compounds at the end of the reaction (Table 1, entry 4). On the other hand, benzoic acid at 70 °C gave better results than when the reaction was carry out without additive at the same temperature (Table 1, entry 5). With the idea of working with a masked secondary amine derived from benzylamine, we used trimethylsilyl chloride and trimethylamine in several proportions for the *in situ* generation of trimethylsilylbenzylamine (Table 1, entries 6-12). The use of TMSCl (30% mol) gave a high conversion and a very complex reaction crude for **6a** (Table 1, entry 6). The combination TMSCl/Et_3N (30% mol, each) afforded cleaner crude mixtures (Table 1, entry 7). When 1 equiv of both additives were tested the yield increased to 76% (Table 1, entry 8). Surprisingly, using a sequential mode of the reaction, mixing benzylamine, trimethylsilyl chloride and triethylamine in toluene, and after 30 min adding crotonaldehyde and *N*-methylmaleimide, the best yield was obtained (Table 1, entry 9). No significative differences were observed when the temperature was raised, in contrast, the reaction conversion was lower when the temperature decreased to 50 °C (Table 1, entries 10 and 11, respectively). Taking into consideration the work of Sherburn,[7] chloroform was select as solvent obtaining lower chemical yields but with cleaner crude reaction mixture (Table 1, entry 12). Complete conversion was detected when triethylamine was added without trimethylsilyl chloride (Table 1, entry 13), demonstrating that the presence of the base is critical for the reaction

to take place (Table 1, entry 14). At this point, the time of the reaction was controlled observing that the reaction was completed in only 1.5 h in chloroform and also in toluene (Table 1, entries 15 and 16).



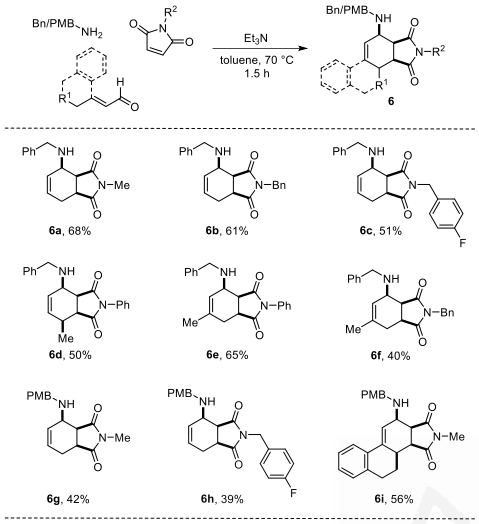
Scheme 1. Multicomponent AAD synthesis of product **6a**.

Table 1. Optimization of the reaction conditions to synthetize cyclohex-2-en-1-amine **6a** *via* AAD reaction.

Entry	Additives	Solvent	T (°C)	t (h)	Yield (%)[a]
1	---	$PhCH_3$	25	16	0
2	---	$PhCH_3$	70	16	48
3	---	$PhCH_3$	110	16	72
4	*p*-TsOH (30%)	$PhCH_3$	70	16	0
5	BzOH (30%)	$PhCH_3$	70	16	65
6	$ClSiMe_3$ (30%)	$PhCH_3$	70	16	63
7	$ClSiMe_3$ (30%), Et_3N (30%)	$PhCH_3$	70	16	69
8	$ClSiMe_3$ (100%), Et_3N (100%)	$PhCH_3$	70	16	76
9[b]	$ClSiMe_3$ (100%), Et_3N (100%)	$PhCH_3$	70	16	87
10[b]	$ClSiMe_3$ (100%), Et_3N (100%)	$PhCH_3$	110	16	88
11[b]	$ClSiMe_3$ (100%), Et_3N (100%)	$PhCH_3$	50	16	31
12[b]	$ClSiMe_3$ (100%), Et_3N (100%)	$CHCl_3$	70	16	25
13	Et_3N (100%)	$CHCl_3$	70	16	>95
14	---	$CHCl_3$	70	16	0
15	Et_3N (100%)	$CHCl_3$	70	1.5	>95
16	Et_3N (100%)	PhMe	70	1.5	89

[a] Isolated yields after flash chromatography. [b] *Sequential reaction*: benzylamine, trimethylsilyl chloride and triethylamine reacted during 30 min at rt, then crotonaldehyde and NMM was added and stirring continued 16 h at the selected temperature.

With this optimal conditions in hand, the amine, the aldehyde and the dipolarophile were mixed in chloroform at 70 °C in the presence of triethylamine to assess the scope of the AAD reaction (Scheme 4). Crotonaldehyde and benzylamine were allowed to react with maleimides (NMM and NBM) obtaining only one stereoisomer (**6a** and **6b**, respectively) in the crude mixture in good isolated yields after purification (68% and 61%, respectively, Scheme 4). Fluorinated maleimide[12] was also employed in this reaction obtaining the corresponding products **6c** in 51% yield (Scheme 4). Other aldehyde such as *E*-2-pentenal was assayed with *N*-phenylmaleimide (NPM) yielding product **6d** in 50%. 3-Methylcrotonaldehyde was also tried in this reaction with NPM and NBM obtaining, in both cases, almost only one diastereoisomer of **6e** and **6f**, in moderate isolated yields after purification (65% and 40%, respectively, Scheme 4). Apart from benzylamine, aliphatic primary amines such as butylamine or allylamine failed in this reaction, however other benzylamine derivative as *p*-methoxybenzylamine was well tolerated. For example, $PMBNH_2$ was allowed to react with crotonaldehyde and two different maleimides obtaining **6g** and **6h** with moderate to good isolated yields (42% and 39%, respectively). Interestingly, the pseudo-steroidal tetracyclic product **6i** was isolated, from the corresponding aldehyde,[13] in 56% yield. The relative configuration of all molecules **6** was confirmed by nOe experiments and by comparison of chemical shifts (^{1}H NMR). Compounds **6b**, **6c**, **6d**, **6e**, **6f** and **6h** were isolated with very small amounts of other diasteroisomer, which was very difficult to separate by column chromatography (see SI). The AAD reaction with fumarates, maleic anhydride, acrylates, vinylic sulfones, chalcone derivatives, nitroalkenes, etc., completely failed. In some examples, complex crude reaction mixtures were obtained isolating the expected product in low yields.



Scheme 4. Synthesis of cyclohex-2-en-1-amines **6** *via* AAD reaction.

The diastereoselective version of this AAD transformation was also examined (Scheme 4 and Figure 1). Using the lowest temperature (70 ºC) and shorter reaction times (1.5 h), chiral benzylamines were first tried in order to obtain enantiopure diastereoisomers. (*R*)-α-Methylbenzylamine was reacted with crotonaldehyde and NPM giving a 85:15 mixture of two diastereoisomers in the crude of the reaction (^{1}H NMR) isolating only the major product **6j** after purification in good yield (53%). (*R*)-1-(1-Naphthyl)ethylamine was also attempted obtaining in this example an almost equimolar diastereomeric ratio for products **6k** and **6k'** was identified. In both cases, nOe results indicated the general *all-cis* arrangement observed in this survey. When the chiral information was anchored to the maleimide, the diastereoselectivity was higher than in the two previous examples run with chrial benzylic amines. Molecule **6l** was generated in 52% yield as a 95:5 diastereomeric ratio when (*R*)-*N*-(1-phenylethyl)maleimide was employed as enantiomerically enriched dienophile (Figure 1).

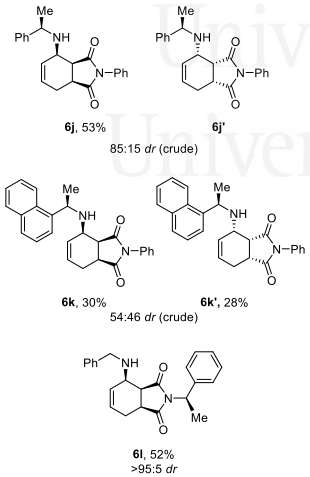


Figure 1. Synthesis of enantiomerically enriched cyclohex-2-en-1-amines **6j-l** *via* AAD reaction.

The proposed absolute configuration of compound **6j**, drawn in Figure 1, was confirmed by vibrational circular dichroism (VCD) analysis (Figure 2). Fortunately, both diastereoisomers **6j** and **6j'** exhibited opposite theoretical VCD patterns, which was more relevant in the carbonyl absorption area. The experimental VCD (dots) and the resulting fitting line matched perfectly (Figure 2) with the theoretical data provided for diastereoisomer **6j**. Every maximum of the experimental absorption plot (1720 and 1785 cm^{-1}) is composed by the sum of two closed bands, possibly due to the formation of intramolecular hydrogen bonds between the NH and the closer carbonyl group.[14] This interaction was also supported by the *all-cis* relative configuration of this fused ring.

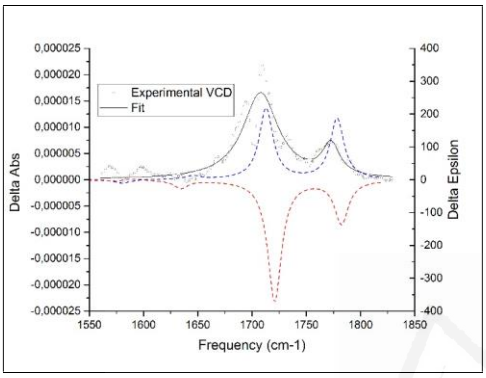


Figure 2. VCD analysis of product **6j**. Blue dashed line corresponds to theoretical VCD calculated with a B3LYP/6-311G+(2d,2p) level for configuration **6j**. Red dashed line corresponds to theoretical VCD calculated with a B3LYP/6-311G+(2d,2p) level for the minor diastereoisomer **6j'**. Black curve corresponds to experimental VCD.

The assignment of the absolute configuration for compound **6l** was more complicated. The initial X-ray diffraction analysis of a monocrystal revealed that the two enantiomers of **6l** were symmetrically arranged in the unit cell together with two molecules of hydrogen chloride.[15] This crystallization occurred in the solution of the sample prepared for the analysis of its VCD experiment (Figure 3). Despite of a displacement of the experimental carbonyl band with respect to the calculated ones, the small absorbance at around 1450 cm^{-1} (C-N absorbance) also confirmed the drawn stereochemistry of **6l** in Figure 1. It is important to remark that calculated conformations for both cycloadducts **6j** and **6l** revealed the presence of strong hydrogen bonds (2.53-2.56 Å in solid state of both enantiomers) between a carbonyl group of the succinimide moiety and the hydrogen atom of the amino group. These interactions can modify the normal absorbance wavelength of the carbonyls in solution and even avoid the detection of the NH band in ^{1}H NMR spectroscopy (see SI).

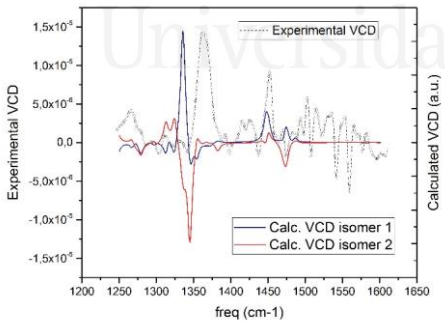


Figure 3. VCD analysis of product **6l**. Blue line corresponds to theoretical VCD calculated with a B3LYP/6-311G+(2d,2p) level for configuration **6l**. Red dashed line corresponds to theoretical VCD calculated with a B3LYP/6-311G+(2d,2p) level for the minor diastereoisomer **6l'**. Black curve corresponds to experimental VCD.

1. Conclusions

The preparation of polysubstituted *N*-benzyl and *N*-PMB-cyclohex-2-eneamines has been optimized. Many aldehydes and maleimides can be combined with benzylamine or 4-methoxybenzylamine in a diastereoselective multicomponent process namely Amine-Aldehyde-Dienophile (AAD). Chemical yields are moderate to good and allow to generate *all-cis* relative configuration in the resulting final products. This sequence offers the possibility to remove the protecting group to achieve the free amino group which could not be accomplished yet. The introduction of a chiral information at the benzylic group of the benzylic amine or in the *N*-substituent of the maleimide gave also enantiomerically enriched compounds after separation by column chromatography. The absolute configuration of a representative example was determined by VCD spectroscopy.

2. Experimental Section

4.1. General

All commercially available reagents and solvents were used without further purification, only aldehydes were also distilled prior to use. Only the aldehyde precursor of compound **6i** was prepared according to the literature.[13] Analytical TLC was performed on Schleicher & Schuell F1400/LS 254 silica gel plates, and the spots were visualized under UV light (λ = 254 nm). Flash chromatography was carried out on handpacked columns of Merck silica gel 60 (0.040-0.063 mm). Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. The structurally most important peaks of the IR spectra (recorded using a Nicolet 510 P-FT) are listed and wave numbers are given in cm^{-1}. NMR spectra were obtained using a Bruker AC-300 or AC-400 and were recorded at 300 or 400 MHz for ^1H NMR and 75 or 100 MHz for ^{13}C NMR, using $CDCl_3$ as solvent and TMS as internal standard (0.00 ppm). The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved and br s = broad signal. All coupling constants (*J*) are given in Hz and chemical shifts in ppm. ^{13}C NMR spectra were referenced to $CDCl_3$ at 77.16 ppm. DEPT-135 experiments were performed to assign CH, CH_2 and CH_3. ^{19}F NMR were recorded at 282 MHz using CDCl3 as solvent. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV using a Shimadzu QP-5000 by injection or DIP; fragment ions in m/z are given with relative intensities (%) in parentheses. High-resolution mass spectra (HRMS) were measured on an instrument using a quadrupole time-of-flight mass spectrometer (QTOF) and also through the electron impact mode (EI) at 70 eV using a Finnigan VG Platform or a Finnigan MAT 95S. VCD analysis was recorded in a Jasco FVS-6000.

*4.2. General procedure for the synthesis of products **6**.*

To a stirred solution of benzylamine derivative (0.25 mmol) and Et_3N (1 equiv., 0.25 mmol) in 1 mL of toluene was added the aldehyde (1 equiv., 0.25 mmol), the dienophile (1 equiv., 0.25 mmol) and 0.5 mL more of chloroform. The solution was stirred at 70 °C during 1.5 h, and after the solvent was removed under vacuum. The crude of the reaction was purified with flash chromatography to give the desired compound.

4.2.1. (3aS,4R*,7aS*)-4-(Benzylamino)-2-methyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6a**)*: brown sticky oil (45.9 mg, 68% yield). IR (neat) ν_{max}: 1695, 1438, 1385, 1283, 1266, 1119, 993, 732, 700 cm^{-1}. ^1H NMR δ: 2.07-2.17 (m, 1H, =CHC*H*$_2$), 2.68 (ddd, *J* = 15.5, 6.7, 2.0 Hz, 1H, =CHC*H*$_2$), 2.94 (s, 3H, NC*H*$_3$), 3.11 (td, *J* = 8.2, 2.0 Hz, 1H, CH_2C*H*C=O), 3.12 (br s, 1H, N*H*), 3.38-3.51 (m, 2H, NCHC*H*C=O and NC*H*CH=), 3.93 (d, *J* = 13.0 Hz, 1H, NC*H*$_2$Ph), 4.07 (d, *J* = 13.0 Hz, 1H, NC*H*$_2$Ph), 5.81-5.90 (m, 1H, =C*H*CH$_2$), 5.92-5.99 (m, 1H, NCHC*H*=), 7.26-7.45 (m, 5H, Ar*H*). ^{13}C NMR δ: 24.1 (=CHCH$_2$), 24.9 (NCH$_3$), 39.3, 42.0 (2xCHC=O), 51.4 (NCH$_2$Ph), 53.5 (NCHCH=), 126.0, 127.5, 128.7, 132.9, 138.7 (Ar*C*, C=*C*), 178.4, 179.9 (2x*C*=O). MS (EI) *m/z*: 270 (M^+, <1%), 159 (21), 144 (35), 106 (100), 91 (71), 79 (11). HRMS calculated for $C_{16}H_{18}N_2O_2$: 270.1368; found: 270.1360.

4.2.2. (3aS,4R*,7aS*)-2-Benzyl-4-(benzylamino)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6b**)*: yellow prisms (52.8 mg, 61% yield), mp 75-77 °C. IR (neat) ν_{max}: 1684, 1475, 1428, 1399, 1344, 1173, 1145, 1071, 915, 741, 699 cm^{-1}. ^1H NMR δ: 2.05-2.18 (m, 1H, =CHC*H*$_2$), 2.66 (ddd, *J* = 15.6, 6.7, 2.1 Hz, 1H, =CHC*H*$_2$), 3.02 (br s, 1H, N*H*), 3.09 (td, *J* = 8.3, 2.1 Hz, 1H, CH_2C*H*C=O), 3.40 (dd, *J* = 8.8, 6.0 Hz, 1H, NCHC*H*C=O), 3.45-3.48 (m, 1H, NC*H*CH=), 3.89 (d, *J* = 13.0 Hz, 1H, CHNC*H*$_2$Ph), 4.03 (d, *J* = 13.0 Hz, 1H, CHNC*H*$_2$Ph), 4.60 (s, 2H, O=CNC*H*$_2$Ph), 5.78-5.85 (m, 1H, =C*H*CH$_2$), 5.93 (dt, *J* = 9.5, 3.1 Hz, 1H, NCHC*H*=), 7.23-7.41 (m, 10H, Ar*H*). ^{13}C NMR δ: 24.2 (=CHCH$_2$), 39.3, 42.0 (2xCHC=O), 42.4 (O=CNCH$_2$Ph), 51.3 (CHNCH$_2$Ph), 53.5 (NCHCH=), 127.3, 127.9, 128.4, 128.5, 128.6, 128.7, 128.9, 133.6, 135.7, 139.4 (Ar*C*, C=*C*), 178.0, 179.6 (2x*C*=O). MS (EI) *m/z*: 346 (M^+, 1%), 159 (24), 144 (26), 106 (100), 91 (66). HRMS calculated for $C_{22}H_{22}N_2O_2$: 346.1681; found: 346.1661.

Annex 2

4.2.3. (3aS,4R*,7aS*)-4-(Benzylamino)-2-(4-fluorobenzyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6c**)*: dark yellow sticky oil (46.5 mg, 51% yield). IR (neat) ν_{max}: 1691, 1509, 1397, 1342, 1222, 1158, 1098, 910, 737, 699 cm^{-1}. ^{1}H NMR δ: 2.05-2.19 (m, 1H, =CHC*H*$_2$), 2.58 (br s, 1H, N*H*), 2.65 (ddd, *J* = 15.7, 6.6, 2.2 Hz, 1H, =CHC*H*$_2$), 3.08 (td, *J* = 8.3, 2.2 Hz, 1H, CH$_2$C*H*C=O), 3.36 (dd, *J* = 8.4, 6.0 Hz, 1H, NCHC*H*C=O), 3.40-3.49 (m, 1H, NC*H*CH=), 3.86 (d, *J* = 13.0 Hz, 1H, CHNC*H*$_2$Ph), 4.01 (d, *J* = 13.0 Hz, 1H, CHNC*H*$_2$Ph), 4.56 (s, 2H, O=CNC*H*$_2$Ar), 5.74-5.85 (m, 1H, =C*H*CH$_2$), 5.90 (dt, *J* = 9.5, 3.0 Hz, 1H, NCHC*H*=), 6.90-6.98 (m, 2H, Ar*H*), 7.24-7.39 (m, 7H, Ar*H*). ^{13}C NMR δ: 24.1 (=CH*C*H$_2$), 39.3, 41.7 (2xCHC=O), 42.1 (O=CN*C*H$_2$Ar), 51.4 (CHN*C*H$_2$Ph), 53.5 (NCHCH=), 115.5 (d, $^{2}J_{C\text{-}F}$ = 21.5 Hz, *C*HCF), 127.1, 127.2, 128.3, 128.5, 128.7 (Ar*C*, *C*=*C*), 130.3 (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz, *C*HCHCF), 131.6 (d, $^{4}J_{C\text{-}F}$ = 3.4 Hz, *C*CHCHCF), 133.9, 139.8 (Ar*C*), 162.3 (d, $^{1}J_{C\text{-}F}$ = 246.3 Hz, *C*F), 177.9, 179.6 (2x*C*=O). ^{19}F NMR δ: -114.2. MS (EI) *m/z*: 364 (M^{+}, 1%), 159 (25), 144 (27), 109 (18), 106 (100), 91 (59). HRMS calculated for $C_{22}H_{21}FN_2O_2$: 364.1587; found: 364.1569.

4.2.4. (3aS,4R*,7S*,7aS*)-4-(Benzylamino)-7-methyl-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6d**)*: brown sticky oil (43.5 mg, 50% yield). IR (neat) ν_{max}: 1704, 1598, 1498, 1455, 1383, 1266, 1179, 733, 695 cm^{-1}. ^{1}H NMR δ: 1.44 (d, *J* = 7.4 Hz, 3H, CHC*H*$_3$), 2.43-2.50 (m, 1H, C*H*CH$_3$), 3.14 (dd, *J* = 8.5, 7.1 Hz, 1H, CH$_3$CHC*H*C=O), 3.36 (br s, 1H, N*H*), 3.49-3.53 (m, 1H, NC*H*CH=), 3.59 (dd, *J* = 8.5, 6.0 Hz, 1H, NCHC*H*C=O), 3.92 (d, *J* = 12.8 Hz, 1H, NC*H*$_2$Ph), 4.10 (d, *J* = 12.8 Hz, 1H, NC*H*$_2$Ph), 5.74 (dt, *J* = 9.3, 3.2 Hz, 1H, =C*H*CHCH$_3$), 5.99 (dt, *J* = 9.0, 2.7 Hz, 1H, NCHC*H*=), 7.14-7.49 (m, 10H, Ar*H*). ^{13}C NMR δ: 16.8 (CH*C*H$_3$), 30.9 (*C*HCH$_3$), 42.6, 44.5 (2x*C*HC=O), 51.4 (N*C*H$_2$Ph), 54.5 (N*C*HCH=), 126.1, 126.6, 127.3, 128.5, 128.6, 128.7, 129.2, 129.3, 131.7, 133.1, 133.6, 139.4 (Ar*C*, *C*=*C*), 176.3, 177.2 (2x*C*=O). MS (EI) *m/z*: 346 (M^{+}, 2%), 174 (11), 173 (66), 144 (29), 106 (95), 91 (100), 82 (16), 77 (12). HRMS calculated for $C_{22}H_{22}N_2O_2$: 346.1681; found: 346.1681.

4.2.5. (3aS,4R*,7aS*)-4-(Benzylamino)-6-methyl-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6e**)*: yellow sticky oil (56.2 mg, 65% yield). IR (neat) ν_{max}: 1705, 1499, 1442, 1386, 1265, 1195, 1099, 1057, 732, 700 cm^{-1}. ^{1}H NMR δ: 1.79 (s, 3H, C*H*$_3$), 2.21-2.33 (m, 1H, =CC*H*$_2$), 2.64 (dd, *J* = 15.4, 2.4 Hz, 1H, =CC*H*$_2$), 3.04 (br s, 1H, N*H*), 3.26 (td, *J* = 8.1, 2.4 Hz, 1H, CH$_2$C*H*C=O), 3.45-3.64 (m, 2H, NCHC*H*C=O and NC*H*CH=), 3.92 (d, *J* = 12.9 Hz, 1H, NC*H*$_2$Ph), 4.06 (d, *J* = 12.9 Hz, 1H, NC*H*$_2$Ph), 5.69 (dt, *J* = 3.8, 2.0 Hz, 1H, NCHC*H*=), 7.17-7.48 (m, 10H, Ar*H*). ^{13}C NMR δ: 23.3 (=C*C*H$_3$), 29.7 (=C*C*H$_2$), 39.1, 41.4 (2x*C*HC=O), 50.7 (N*C*H$_2$Ph), 53.5 (N*C*HCH=), 126.6, 128.9, 129.0, 129.1, 129.2, 129.3, 130.3, 131.4, 139.7 (Ar*C*, *C*=*C*), 177.2, 177.9 (2x*C*=O). MS (EI) *m/z*: 346 (M^{+}, 7%), 345 (26), 255 (32), 241 (12) 239 (16), 173 (17), 158 (24), 106 (49), 93 (29), 92 (15), 91 (100), 77 (18). HRMS calculated for $C_{22}H_{22}N_2O_2$: 346.1681; found: 346.1672.

4.2.6. (3aS,4R*,7aS*)-2-Benzyl-4-(benzylamino)-6-methyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6f**)*: brown sticky oil (36.0 mg, 40% yield). IR (neat) ν_{max}: 1692, 1431, 1399, 1344, 1181, 1160, 910, 729, 699 cm^{-1}. ^{1}H NMR δ: 1.59 (s, 3H, C*H*$_3$), 2.10-2.21 (m, 1H, =CC*H*$_2$), 2.64 (dd, *J* = 15.4, 2.1 Hz, 1H, =CC*H*$_2$), 3.08 (td, *J* = 8.0, 2.1 Hz, 1H, CH$_2$C*H*C=O), 3.35-3.48 (m, 2H, NCHC*H*C=O and NC*H*CH=), 3.90 (d, *J* = 12.9 Hz, 1H, CHNC*H*$_2$Ph), 4.04 (d, *J* = 12.9 Hz, 1H, CHNC*H*$_2$Ph), 4.57 (d, *J* = 14.2 Hz, 1H, O=CNC*H*$_2$Ph), 4.60 (br s, 1H, N*H*), 4.63 (d, *J* = 14.2 Hz, 1H, O=CNC*H*$_2$Ph), 5.54 (br s, 1H, NCHC*H*=), 7.19-7.44 (m, 10H, Ar*H*). ^{13}C NMR δ: 23.0 (=C*C*H$_3$), 29.4 (=C*C*H$_2$), 39.3, 41.7 (2x*C*HC=O), 42.5 (O=CN*C*H$_2$Ph), 51.0 (CHN*C*H$_2$Ph), 53.9 (N*C*HCH=), 124.2, 127.7, 127.9, 128.2, 128.5, 128.6, 128.7, 128.8, 128.9, 135.6, 137.2, 137.6 (Ar*C*, *C*=*C*), 178.0, 179.2 (2x*C*=O). MS (EI) *m/z*: 360 (M^{+}, 2%), 173 (28), 158 (45), 106 (100), 91 (73), 82 (11). HRMS calculated for $C_{23}H_{24}N_2O_2$: 360.1838; found: 360.1828.

4.2.7. (3aS,4R*,7aS*)-4-[(4-Methoxybenzyl)amino]-2-methyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6g**)*: brown sticky oil (31.7 mg, 42% yield). IR (neat) ν_{max}: 1689, 1510, 1437, 1284, 1245, 1118, 1033, 733, 701 cm^{-1}. ^{1}H NMR δ: 2.08-2.18 (m, 1H, =CHC*H*$_2$), 2.36 (br s, 1H, N*H*), 2.67 (ddd, *J* = 15.5, 6.7, 2.1 Hz, 1H, =CHC*H*$_2$), 2.93 (s, 3H, NC*H*$_3$), 3.09 (td, *J* = 8.3, 2.1 Hz, 1H, CH$_2$C*H*C=O), 3.36 (dd, *J* = 8.7, 6.2 Hz, 1H, NCHC*H*C=O), 3.40-3.47 (m, 1H, NC*H*CH=), 3.80 (s, 3H, OC*H*$_3$), 3.98 (d, *J* = 13.0 Hz, 1H, NC*H*$_2$Ar), 4.07 (d, *J* = 13.0 Hz, 1H, NC*H*$_2$Ar), 5.81-5.87 (m, 1H, =C*H*CH$_2$), 5.92 (dt, *J* = 9.5, 2.9 Hz, 1H, NCHC*H*=), 6.85-6.89 (m, 2H, Ar*H*), 7.29-7.34 (m, 2H, Ar*H*). ^{13}C NMR δ: 24.1 (=CH*C*H$_2$), 24.9 (N*C*H$_3$), 39.4, 42.1 (2x*C*HC=O), 50.8 (N*C*H$_2$Ar), 53.4 (N*C*HCH=), 55.4 (O*C*H$_3$), 114.0, 114.1, 127.0, 129.5, 129.6, 132.0, 134.1, 158.8, (Ar*C*, C=*C*), 178.4, 180.1 (2x*C*=O). MS (EI) *m/z*: 300 (M^{+}, 1%), 136 (100), 121 (96). HRMS calculated for $C_{17}H_{20}N_2O_3$: 300.1474; found: 300.1472.

4.2.8. (3aS,4R*,7aS*)-2-(4-Fluorobenzyl)-4-[(4-methoxybenzyl)amino]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6h**)*: dark orange sticky oil (38.8 mg, 39% yield). IR (neat) ν_{max}: 1698, 1510, 1433, 1398, 1343, 1247, 1223, 1173, 1033, 733, 699 cm^{-1}. ^{1}H NMR δ: 2.08-2.19 (m, 1H, =CC*H*$_2$), 2.67 (ddd, *J* = 15.6, 6.6, 2.1 Hz, 1H, =CC*H*$_2$), 3.10 (br s, 1H, N*H*), 3.11 (td, *J* = 8.2, 2.1 Hz, 1H, CH$_2$C*H*C=O), 3.41-3.52 (m, 2H, NCHC*H*C=O and NC*H*CH=), 3.80 (s, 3H, OC*H*$_3$), 3.87 (d, *J* = 12.8 Hz, 1H, CHNC*H*$_2$Ar), 3.99 (d, *J* = 12.8 Hz, 1H, CHNC*H*$_2$Ar), 4.56 (s, 2H, O=CNC*H*$_2$Ar), 5.75-5.87 (m, 1H, NCHCH=C*H*), 5.93 (dt, *J* = 9.5, 3.0 Hz, 1H, NCHC*H*=), 6.84-7.00 (m, 4H, Ar*H*), 7.24-7.35 (m, 4H, Ar*H*). ^{13}C NMR δ: 24.2 (=C*C*H$_2$), 39.3, 41.8 (2x*C*HC=O), 42.0 (O=CN*C*H$_2$Ar), 51.4 (CHN*C*H$_2$Ar), 53.3 (N*C*HCH=), 55.4 (O*C*H$_3$), 114.1 (Ar*C*), 115.5 (d, $^{2}J_{C\text{-}F}$ = 21.7 Hz, *C*HCF), 127.5, 129.8 (Ar*C*, *C*=*C*), 130.4 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz, *C*HCHCF), 131.6 (d, $^{4}J_{C\text{-}F}$ = 3.2 Hz, *C*CHCHCF), 133.0, 140.3, 159.1 (Ar*C*), 162.4 (d, $^{1}J_{C\text{-}F}$ = 246.5 Hz, *C*F), 177.9, 179.5 (2x*C*=O). ^{19}F NMR δ: -114.2. MS (EI) *m/z*: 394 (M^{+}, 2%), 136 (100), 121 (85), 109 (15). HRMS calculated for $C_{23}H_{23}FN_2O_3$: 394.1693; found: 394.1675.

4.2.9. (3aS,3bR*,11R*,11aS*)-11-[(4-Methoxybenzyl)amino]-2-methyl-3a,3b,4,5,11,11a-hexahydro-1H-naphtho[2,1-e]isoindole-1,3(2H)-dione* (***6i***): dark yellow sticky oil (56.6 mg, 56% yield). IR (neat) ν_{max}: 1688, 1611, 1512, 1437, 1384, 1285, 1246, 1177, 1112, 1031, 909, 757, 729 cm^{-1}. ^1H NMR δ: 2.07-2.14 (m, 1H, CH_2CH_2CH), 2.22 (qd, *J* = 12.5, 3.5 Hz, 1H, CH_2CH_2CH), 2.56-2.68 (m, 2H, CH_2CH_2CH and CH_2CH_2CH), 2.78 (dt, *J* = 15.1, 4.1 Hz, 1H, CH_2CH_2CH), 2.83 (s, 3H, NCH_3), 3.21 (t, *J* = 7.7 Hz, 1H, CH_2CHCHC=O), 3.60-3.67 (m, 2H, NCHC*H*C=O and NC*H*CH=), 3.78 (br s, 1H, N*H*), 3.79 (s, 3H, OCH_3), 4.05 (d, *J* = 12.8 Hz, 1H, NCH_2Ar), 4.12 (d, *J* = 12.8 Hz, 1H, NCH_2Ar), 6.37 (br s, 1H, NCHC*H*=), 6.85-6.90 (m, 2H, Ar*H*), 7.07-7.16 (m, 3H, Ar*H*), 7.21-7.25 (m, 1H, Ar*H*), 7.39-7.44 (m, 2H, Ar*H*). ^{13}C NMR δ: 24.2 (CCH_2CH_2), 24.9 (NCH_3), 29.9 (CCH_2CH_2), 36.5 (CH_2CHCHC=O), 43.0, 43.4 (2x*C*HC=O), 50.6 (NCH_2Ar), 54.3 (N*C*HCH=), 55.4 (OCH_3), 114.2, 123.7, 126.7, 127.8, 128.4, 129.7, 130.1, 130.7, 133.0, 137.4, 138.2, 159.3 (Ar*C*, *C*=*C*), 177.0, 178.3 (2x*C*=O). MS (EI) *m/z*: 402 (M^+, 5%), 291 (10), 170 (42), 136 (57), 121 (100). HRMS calculated for $C_{25}H_{26}N_2O_3$: 402.1943; found: 402.1943.

4.2.10. (3aS,4R,7aS)-2-Phenyl-4-{[(R)-1-phenylethyl]amino}-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (***6j***): light brown needles (45.9 mg, 53% yield), mp 135-136 °C (Et_2O), $[\alpha]_D^{25}$ = +96.4 (*c* 1.1, $CHCl_3$), IR (neat) ν_{max}: 1705, 1490, 1447, 1386, 1264, 1173, 1070, 1032, 734, 703 cm^{-1}. ^1H NMR δ: 1.46 (d, *J* = 6.5 Hz, 3H, $CHCH_3$), 2.08 (ddt, *J* = 15.7, 8.1, 2.6 Hz, 1H, $=CHCH_2$), 2.72 (ddd, *J* = 15.7, 6.7, 1.9 Hz, 1H, $=CHCH_2$), 3.21 (td, *J* = 8.1, 1.9 Hz, 1H, CH_2CHC=O), 3.42 (dt, *J* = 6.4, 2.8 Hz, 1H, NC*H*CH=), 3.62 (dd, *J* = 9.5, 6.3 Hz, 1H, NCHC*H*C=O), 4.26 (q, *J* = 6.5 Hz, 1H, C*H*CH_3), 5.90 (ddt, *J* = 9.6, 6.5, 2.9 Hz, 1H, =C*H*CH_2), 5.96 (dt, *J* = 9.6, 2.9 Hz, 1H, NCHC*H*=), 7.18-7.48 (m, 10H, Ar*H*), (NH not observed). ^{13}C NMR δ: 24.3 (CH_2), 24.6 (NCHCH_3), 39.3, 40.8 (2x*C*HC=O), 52.0 (N*C*HCH=), 55.8 (N*C*HCH_3), 126.6, 127.1, 127.3, 127.7, 128.8, 128.9, 129.3, 131.8 (Ar*C*, *C*=*C*), 177.5, 178.9 (2x*C*=O). MS (EI) *m/z*: 346 (M^+, <1%), 331 (14), 173 (43), 120 (100), 106 (27), 105 (72), 79 (28), 77 (20), 69 (26). HRMS calculated for $C_{22}H_{22}N_2O_2$: 346.1681; found: 346.1680.

4.2.11. (3aS,4R,7aS)-4-{[(R)-1-(Naphthalen-1-yl)ethyl]amino}-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (***6k***): yellow sticky oil (30.1 mg, 30% yield), $[\alpha]_D^{25}$ = +98.6 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}: 1702, 1498, 1380, 1242, 1176, 1045, 749, 692 cm^{-1}. ^1H NMR δ: 1.51 (d, *J* = 6.5 Hz, 3H, $CHCH_3$), 2.00 (ddt, *J* = 15.9, 8.0, 3.0 Hz, 1H, $=CHCH_2$), 2.68 (ddd, *J* = 15.7, 6.9, 2.0 Hz, 1H, $=CHCH_2$), 3.15 (ddd, *J* = 9.3, 8.0, 1.9 Hz, 1H, CH_2CHC=O), 3.39 (dt, *J* = 6.2, 2.6 Hz, 1H, NC*H*CH=), 3.60 (dd, *J* = 9.1, 6.2 Hz, 1H, NCHC*H*C=O), 4.42 (q, *J* = 6.5 Hz, 1H, C*H*CH_3), 5.87 (ddt, *J* = 9.6, 6.5, 3.1 Hz, 1H, =C*H*CH_2), 5.96 (dt, *J* = 9.3, 3.1 Hz, 1H, NCHC*H*=), 7.18-7.89 (m, 12H, Ar*H*) (NH not observed). ^{13}C NMR δ: 24.3 (=CH*C*H_2), 24.9 (CH_3), 39.3, 40.7 (2x*C*HC=O), 52.0 (N*C*HCH=), 55.7 (N*C*HCH_3), 123.1, 125.1, 125.9, 126.2, 126.6, 127.1, 127.8, 128.7, 128.8, 129.3, 131.8, 133.1, 133.5, 138.9 (Ar*C*, *C*=*C*), 177.4, 179.0 (2x*C*=O). MS (EI) *m/z*: 396 (M^+, 2%), 381 (17), 223 (15), 171 (13), 170 (96), 156 (36), 155 (100), 154 (14), 153 (15), 129 (11), 79 (14). HRMS calculated for $C_{26}H_{24}N_2O_2$: 396.1838; found: 396.1814.

4.2.12. (3aR,4S,7aR)-4-{[(R)-1-(Naphthalen-1-yl)ethyl]amino}-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (***6k'***): yellow plates (28.1 mg, 28% yield), mp 113-115 °C, $[\alpha]_D^{26}$ = -34.3 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}: 1702, 1498, 1382, 1180, 861, 822, 750, 692 cm^{-1}. ^1H NMR δ: 1.60 (d, *J* = 6.7 Hz, 3H, $CHCH_3$), 2.01-2.11 (m, 1H, $=CHCH_2$), 2.67 (ddd, *J* = 15.8, 6.8, 1.9 Hz, 1H, $=CHCH_2$), 3.17 (td, *J* = 8.7, 1.9 Hz, 1H, CH_2CHC=O), 3.39-3.44 (m, 1H, NCHC*H*C=O), 3.52 (br s, 1H, NC*H*CH=), 4.32 (q, *J* = 6.7 Hz, 1H, C*H*CH_3), 5.93-6.00 (m, 1H, =C*H*CH_2), 6.21 (dt, *J* = 9.7, 3.1 Hz, 1H, NCHC*H*=), 7.17-7.88 (m, 12H, Ar*H*) (NH not observed). ^{13}C NMR δ: 23.9 (CH_3), 24.4 (=CH*C*H_2), 39.3, 43.4 (2x*C*HC=O), 51.8 (N*C*HCH=), 56.5 (N*C*HCH_3), 125.3, 126.1, 126.3, 126.6, 126.9, 127.8, 128.0, 128.8, 128.9, 129.3, 131.7, 133.2, 133.5 (Ar*C*, *C*=*C*), 178.1, 178.8 (2x*C*=O). MS (EI) *m/z*: 396 (M^+, 2%), 381 (14), 223 (14), 171 (13), 170 (100), 156 (35), 155 (98), 154 (15), 153 (16), 129 (12), 79 (13). HRMS calculated for $C_{26}H_{24}N_2O_2$: 396.1838; found: 396.1822.

4.2.13. (3aS,4R,7aS)-4-(Benzylamino)-2-((R)-1-phenylethyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (***6l***): pale brown prisms (47.0 mg, 52% yield), mp 65-67 °C, $[\alpha]_D^{24}$ = +43.3 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}: 1690, 1496, 1452, 1390, 1362, 1222, 1190, 1106, 1025, 910, 733, 697 cm^{-1}. ^1H NMR δ (mixture of two rotamers): 1.73 (d, *J* = 7.3 Hz, 3H, CH_3), 2.05-2.16 (m, 1H, $=CHCH_2$), 2.61, 2.67 (2ddd, *J* = 15.6, 6.7, 2.1 Hz, 1H, $=CHCH_2$, two rotamers), 3.03 (td, *J* = 8.2, 2.1 Hz, 1H, CH_2CHC=O), 3.37, 3.38 (2dd, *J* = 8.8, 6.0 Hz, 1H, NCHC*H*C=O, two rotamers), 3.44 (br s, 1H, N*H*), 3.46-3.50 (m, 1H, NC*H*CH=), 3.90, 3.93 (2d, *J* = 13.1 Hz, 1H, NCH_2Ph, two rotamers), 4.02, 4.05 (2d, *J* = 13.1 Hz, 1H, NCH_2Ph, two rotamers), 5.36, 5.37 (2q, *J* = 7.3 Hz, 1H, C*H*CH_3, two rotamers), 5.78-5.89 (2m, 1H, =C*H*CH_2, two rotamers), 5.92, 5.98 (dt, *J* = 9.5, 3.0 Hz, 1H, NCHC*H*=, two rotamers), 7.22-7.43 (m, 10H, Ar*H*). ^{13}C NMR δ: 16.7 (CH_3), 24.3 (=CH*C*H_2), 39.0, 41.6 (2x*C*HC=O), 50.2 (N*C*HCH_3), 51.2 (NCH_2Ph), 53.6 (N*C*HCH=), 127.2, 127.3, 127.4, 127.7, 128.4, 128.5, 128.6, 133.0, 138.9, 139.5 (Ar*C*, *C*=*C*), 178.0, 179.7 (2x*C*=O). MS (EI) *m/z*: 360 (M^+, 1%), 159 (21), 144 (22), 106 (100), 105 (16), 91 (50). HRMS calculated for $C_{23}H_{24}N_2O_2$: 360.1838; found: 360.1827.

Acknowledgements

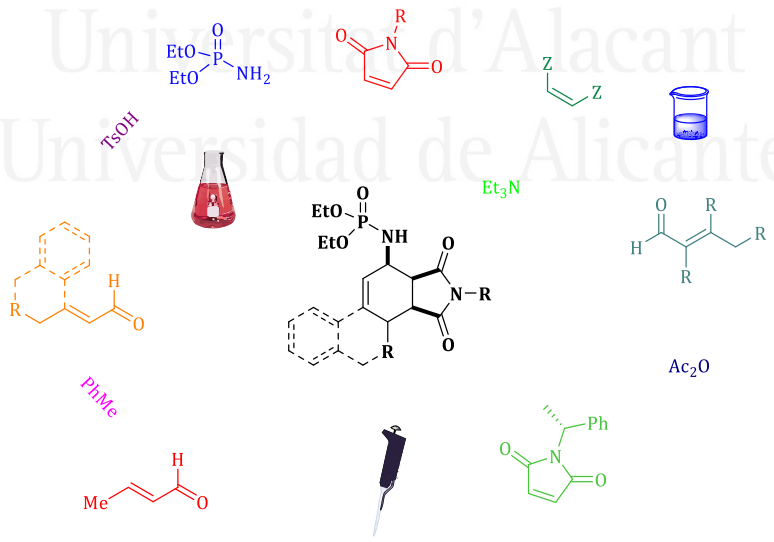
We gratefully acknowledge financial support from the Spanish Ministerio de Economía y Competitividad (MINECO), Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER, EU) (Project Nos. CTQ2013-43446-P, CTQ2014-51912-REDC, CTQ2016-76782-P, CTQ2016-81797-REDC, CTQ2016-81893REDT, and CTQ2016-76155-R), the Generalitat Valenciana (PROMETEOII/2014/017) and the University of Alicante.

Notes and references

1. (a) H. Neumann, A.J. von Wangelin, D. Gördes, A. Spannenberg, M. Beller, J. Am. Chem. Soc. 123 (2001) 8398;
   (b) A.J. von Wangelin, H. Neumann, D. Gördes, A. Spannenberg, M. Beller, Org. Lett. 3 (2001) 2895.
2. (a) H. Neumann, A.J. von Wangelin, D. Gördes, A. Spannenberg, W. Baumann, M. Beller, Tetrahedron 58 (2002) 2381;
   (b) A.J. von Wangelin, H. Neumann, D. Gördes, S. Klaus, D. Strübing, M. Beller, Chem. Eur. J. 9 (2003) 4286;
   (c) H. Neumann, A.J. von Wangelin, S. Klaus, D. Strübing, D. Gördes, M. Beller, Angew. Chem. Int. Ed. 42 (2003) 4503;
   (d) S. Klaus, S. Hübner, H. Neumann, D. Strübing, A.J. von Wangelin, D. Gördes, M. Beller, Adv. Synth. Catal. 346 (2004) 970;
   (e) D. Strübing, H. Neumann, S. Klaus, S. Hübner, M. Beller, Tetrahedron 61 (2005) 11333.
3. (a) S. Hübner, H. Jiao, D. Michalik, H. Neumann, S. Klaus, D. Strübing, A. Spannenberg, M. Beller, Chem. Asian J. 2 (2007) 720;
   (b) S. Hübner, D. Michalik, H. Jiao, H. Neumann, S. Klaus, D. Strübing, A. Spannenberg, M. Beller, Chem. Asian J. 2 (2007) 734;
   (c) S. Hübner, H. Neumann, D. Michalik, S. Klaus, D. Strübing, A. Spannenberg, A.J. von Wangelin, M. Beller, Synlett 7 (2007) 1085.
4. M. Sukopp, R. Schwab, L. Marinelli, E. Biron, M. Heller, E. Várkondi, Á. Pap, E. Novellino, G. Kéri, H. Kessler, J. Med. Chem. 48 (2005) 2916.
5. H. Neumann, D. Strübing, M. Lalk, S. Klaus, S. Hübner, A. Spannenberg, U. Lindequist, M. Beller, Org. Biomol. Chem. 4 (2006) 1365.
6. A.K. Weber, J. Schachtner, R. Fichtler, T.M. Leermann, J.M. Neudörfl, A.J. von Wangelin, Org. Biomol. Chem. 12 (2014) 5267.
7. S.M. Tan, A.C. Willis, M.N. Paddon-Row, M.S. Sherburn, Angew. Chem. Int. Ed. 55 (2016) 3081.
8. V. Selva, O. Larrañaga, L.M. Castelló, C. Nájera, J.M. Sansano, A. de Cózar, J. Org. Chem. 82 (2017), 6298.
9. See, for example: (a) R. Mose, M.E. Jensen, G. Preegel, K.A. Jørgensen, Angew. Chem., Int. Ed. 54 (2015) 13630;
   (b) L. Naesborg, K.S. Halskov, F. Tur, S.M.N. Mønsted, K.A. Jørgensen, Angew. Chem., Int. Ed. 54 (2015) 10193;
   (c) K.S. Halskov, B.S. Donslund, S. Barfüsser, K.A. Jørgensen, Angew. Chem., Int. Ed. 53 (2014) 4137.
10. S. Belveren, O. Larrañaga, S. Poyraz, H.A. Dondas, M. Ülger, E. Şahin, M. Ferrándiz-Saperas, J.M. Sansano, M.d.G. Retamosa, A. de Cózar, Synthesis 50 (2018) accepted.
11. (a) T. Jaetsch, W. Hallenbach, T. Himmler, K.-D. Bremm, R. Endermann, F. Pirro, M. Stegemann, H.-G. Wetzstein, Ger. Offen. (1996), DE 4431122 A1 19960307;
    (b) W. Hallenbach, T. Himmler, T. Jaetsch, B. Mielke, K.-D. Bremm, R. Endermann, F. Pirro, M. Stegemann, H.-G. Wetzstein, Ger. Offen. (1996), DE 4424369 A1 19960118;
    (c) T. Jaetsch, W. Hallenbach, T. Himmler, B. Mielke, K.-D. Bremm, R. Endermann, F. Pirro, Franz; M. Stegemann, H.-G. Wetzstein, Eur. Pat. Appl. (1995), EP 684244 A1 19951129;
    (d) U. Petersen, T. Himmler, T. Schenke, A. Krebs, K. Grohe, K.-D. Bremm, K.G. Metzger, R. Endermann, H.J. Zeiler, U.S. (1995), US 5468742 A 19951121 and previous assignee patents of Bayer A.-G., Germany (1992-1996).
12. These maleimides were used in the preparation of precursors of thrombin inhibitors. (a) J. Olsen, P. Seiler, B. Wagner, H.T. Fischer, U. Obst-Sander, T. Tschopp, D.W. Banner, M. Kansy, K. Müller, F. Diederich, Org. Biomol. Chem. 2 (2004) 1339;
    (b) E. Schweizer, A. Hoffmann-Röder, K. Schärer, J.A. Olsen, C. Fäh, P. Seiler, U. Obst-Sander, B. Wagner, M. Kansy, F. Diederich, ChemMedChem 1 (2006) 611;
    (c) V. Selva, E. Selva, P. Merino, C. Nájera, J.M. Sansano, Org. Lett. (2018) 3522.
13. L. Naesborg, K.S. Halskov, F. Tur, S.M.N. Monsted, K.A. Jørgensen, Angew. Chem. Int. Ed. 54 (2015) 10193.
14. S. Gobi, E. Vass, G. Magyarfalvi, G. Tarczay, Phys. Chem. Chem. Phys. 13 (2011) 13972.
15. The information concerning X-ray diffraction analysis of compound **6l** can be found in the Cambridge Crystallographic Data Centre (CCDC) with the code: CCDC 1892086.

CHAPTER 3:

Diastereoselective multicomponent phosphoramidate-aldehyde-dienophile (PAD) process for the synthesis of polysubstituted cyclohex-2-enyl-amine derivatives



Phosphoramidate-Aldehyde-Dienophile (PAD) Reactions

In this third chapter, and based on the bibliographic part in the previous chapter on the reaction Amine (Amide) -Aldehyde- dienophile (AAD) and their development and use, and also the studies and results obtained by our group in these reactions , we decided to spread this research using Diethyl phosphoramidate in a multi-component Phosphoramidate-Aldehyde-Dienophile (PAD) reaction.

Organophosphorus compounds (OPs)

Organophosphorus compounds (OPCs) contain organic fragments generally linked directly to phosphorus or linked by a heteroatom, which can be sulfur, oxygen or nitrogen. These compounds are more common in the human environment. Due to their unique properties and high biological activity,[205] they have been widely used in various areas, in agriculture such as pesticides,[206] industrial applications (production of lubricants, hydraulic fluids and plastics),[207] medicinal (osteoporosis drugs, anticancer and antiviral compounds)[208,209] or veterinarians (anthelmintics).[210]

OPCs derived from phosphoric acid and phosphonic acid derivatives generally have anti-cholinesterase activity, unlike OPCs derived from phosphonic acid.[211] Among the known OPCs are insecticides such as diazinon (DZN), malathion, parathion, chlorpyrifos (CPF), dichlorvos, fenthion and ethion; nerve gases such as sarin, soman, tabun, and VX; ophthalmic agents such as isofluorophate and echothiophate; anti-helminthic agents such as trichlorfon; and herbicides such as tribufos (DEF) and merphos.[212]

In 1873, OPCs were first synthesized by von Hoffman. He synthesized methyl phosphorus chloride, which created the way for the synthesis of a number of insecticides. OPCs are very toxic, and primarily neurotoxicants, so to qualify them as an insecticide, it is necessary to be effective at low doses so that

[205] Demkowicz, S., Rachon, J., Daśko, M., & Kozak, W. *Applications in medicine. RSC Advances,* **2016**. *6(9), 7101–7112.*
[206] B.K. Singh, A. Walker, FEMS Microbial. Rev., **2006**, *30*, 428- 471.
[207] A. Marklund, B. Andersson, P. Haglund, Chemosphere, **2003**, *53*, 1137-1146.
[208] H.R. Hudson, N.J. Wardle, S.W. Bligh, I. Greiner, A. Grun, G. Keglevich, Mini Rev. Med. Chem., **2012**, *12*, 313-325.
[209] E. De Clercq, Biochem. Pharmacol., **2013**, *85*, 727-744.
[210] Q.A. McKellar, F. Jackson, Trends Parasitol., **2004**, *20*, 456- 461
[211] Gosselin, R.E.; Smith, R.P.; Hodge, H.C. *Clinical Toxicology of Commercial Products*; Williams & Wilkins: Philadelphia, PA, USA, **1984**; ISBN 13:978-0683036329.
[212] Figueroa-Villar, J.D.; Petronilho, E.C.; Kuca, K.; Franca, T.C.C. Review about structure and evaluation of reactivators of Acetylcholinesterase inhibited with neurotoxic organophosphorus compounds. *Curr. Med. Chem.* **2020**.

they will have a low toxic effect on humans and animals.[213] Most of the OPCs have no tumorigenic effect in animals, apart from some of them could induce cancer in experimental models.[214,215]

In contrast, recent studies demonstrated that a number of OPCs are used as anticancer drugs or have potential anticancer properties. They are generally used in oncology as alkylating chemotherapeutic agents by reacting with DNA, RNA and certain enzymes, as for example, N,N′,N′′-triethylenethiophosphoramide **182**, known under the trade name thioTEPA, is a compound used as an anticancer chemotherapeutic drug which binds to DNA, crosslinks both strands and prevents cell duplication.[216]

182

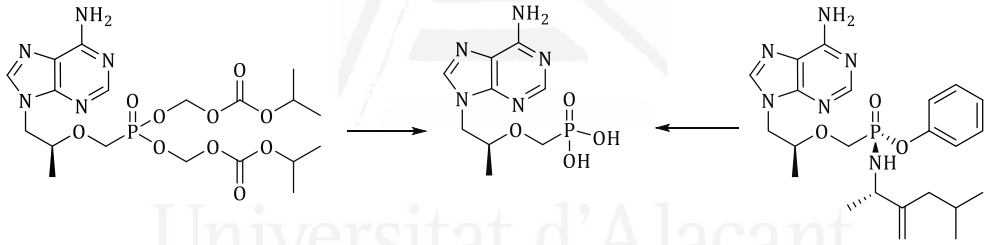
Figure 9: Chemical structures of organophosphorus alkylating agents **182.**

On the other hand, there are many compounds containing a phosphorus atom with antiviral activity, or they are involved as drugs in the treatment of certain viral infections [eg. Human immunodeficiency virus (HIV), hepatitis C

[213] Budzinski, H.; Couderchet, M. Environmental and human health issues related to pesticides: From usage and environmental fate to impact. *Environ. Sci. Pollut. Res.* **2018**, *25*, 14277–14279.
[214] Ventura, C.; Zappia, C.D.; Lasagna, M.; Pavicic, W.; Richard, S.; Bolzan, A.D.; Monczor, F.; Nunez, M.; Cocca, C. Effects of the pesticide chlorpyrifos on breast cancer disease. Implication of epigenetic mechanisms. *J. Steroid Biochem. Mol. Biol.* **2019**, *186*, 96–104.
[215] Echiburu-Chau, C.; Calaf, G.M. Rat lung cancer induced by malathion and estrogen. *Int. J. Oncol.* **2008**, *33*, 603–611.
[216] M.J. Van Maanen, C.J.M. Smeets, J.H. Beijnen, Cancer Treat. Rev., **2000**, *26*, 257–268.

virus (HCV), hepatitis B virus (HBV), cytomegalovirus (CMV), smallpox (variola virus)].[205]

In 1985, E. De Clercq et al., Described the activity of 9-(R)-(2-phosphonomethoxypropyl) adenine (tenofovir) **183** against HIV in cell culture.[217] being a nucleotide analog having activity against retroviruses, including HIV-1, HIV-2. This is given to patients as a prodrug - tenofovir disoproxil fumarate (tenofovir DF) **184**. After absorption, tenofovir DF is rapidly converted to tenofovir (Figure 10).[218] after several research other tenofovir derivatives with better distribution in lymphoid tissues have been discovered. a prototype molecule called Le GS-7340 **185** was identified as a new class of tenofovir monophosphonoamidate prodrugs. Compared to the parent tenofovir, GS7340 shows 500- to 1000-fold increased activity against HIV-1 in T-cells, activated peripheral blood mononuclear lymphocytes and macrophages.[219]



184 183 185

Figure 10: Tenofovir **183** and hisprodrug forms

There are also a large number of agents under development in a variety of classes for the treatment of HCV infections, as for example, sofosbuvir **186** that is a phosphoramidate prodrug which is metabolized in the liver to the

[217] *US Pat.*, 4724233A, **1985**.
[218] B.P. Kearney, J.F. Flaherty, J. Shah, *Clin. Pharmacokinet.*, **2004**, *43*, 595-612.
[219] W.A. Lee, H. Gong-Xin, E. Eisenberg, T. Cihlar, S. Swaminathan, A. Mulato, K. Cundy, *Antimicrob. Agents Chemother.*, **2005**, *49*, 1898-1906.

active antiviral agent 2'-deoxy-2'-α-fluoro-β-C-methyluridine-5'-monophosphate **187**, which is then phosphorylated in 2'-active deoxy-2'-α-fluoro-β-C-methyluridine-5'-triphosphate **188** (Figure 11).[220]

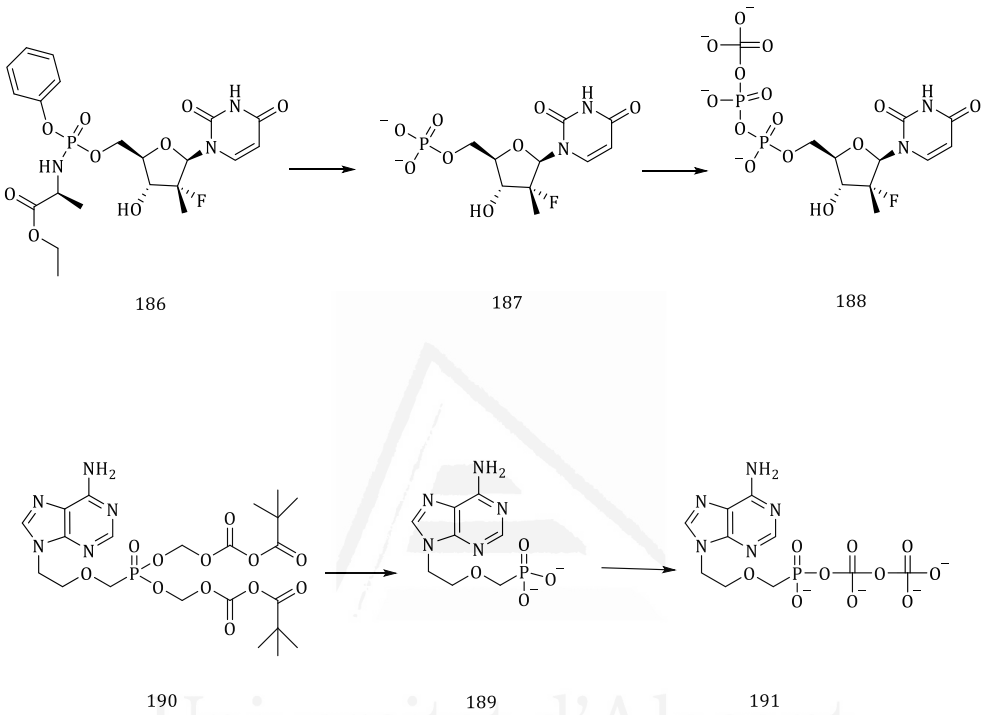


Figure 11: agents under development in a variety of classes for the treatment of HCV infections.

For the treatment of hepatitis B virus infections Adefovir **189** was found as a nucleotide analogue with reverse transcriptase inhibitory activity, administered as a prodrug-adefovir dipivoxil **190**, which will subsequently be

[220] M.J. Sofia, D. Bao, W. Chang, J. Du, D. Nagarathnam, S. Rachakonda, P.G. Reddy, B.S. Ross, P. Wang, H.R. Zhang, S. Bansal, C. Espiritu, M. Keilman, A.M. Lam, H.M. Micolochick Steuer, C. Niu, M.J. Otto, P.A. Furman, J. Med. Chem., **2010**, *53*, 7202-7218.

hydrolyzed to adefovir and phosphorylated in its active diphosphorylated form adefovir dipivoxil **191**[205] (Figure 11).

Phosphoramidates

Phosphoramidates or otherwise called amidophosphates, are a class of phosphorus compounds structurally linked to phosphates or organophosphates by the substitution of an OR for an NR2. They are derivatives of phosphoramidic acids $O=P(OH)(NR_2)_2$, $O=P(OH)_2(NR_2)$. Phosphoramidates play an important role in organic synthesis. Dialkyl, dibenzyl and diphenyl phosphoramidates are useful in protecting the amino group.[221] N-arylphosphoramidates have been used for the synthesis of imines by aza-Wittig[222] reactions and also in the preparation of functionalized aziridines. by nucleophilic cyclizations.[223]

By the fact that the phosphoramidates exhibit interesting biological properties and by the appearance of their structural motif in natural products, the development of methods for their construction has been stimulated.

Tienes que poner los métodos generales, no te salgas de la introducción del artículo (te enrolla demasiado) Coge esto como base de tus comentarios si te vas fuera de aquí te preguntarán

The preparation of phosphoramidates can be achieved by the sequential addition of amines to phosphorochloridate and treatment with alcohols or phenols,[224] (Scheme 56 a), the addition of amines onto phosphonic acids in the

[221] P. G. M. Wuts and T. V. Greene, "Greene's Protective Groups in Organic Synthesis", 4th edition, Wiley, New Jersey, **2006**, p. 844.

[222] M. A. Ciufolini and G. O. Spencer, J. Org. Chem., **1989**, *54*, 4739-4741.
[223] L. D. S. Yadav, A. Rai, V. K. Rai and C. Awasthi, Tetrahedron Lett., **2008**, *49*, 687-690.

[224] M. Maiti, M. Maiti, J. Rozenski, S. De Jonghe, P. Herdewijn, Org. Biomol. Chem. **2015**, *13*, 5158.

presence of dehydrating-coupling reagents,[225] (Scheme 56 b), the amination of phosphoryl azide,[226,227] (Scheme 56 c), starting from phosphorus oxychloride,[228] (Scheme 56 d), and employing diethyl phosphite with amines in the presence of iodine[229] (Scheme 56 e). The *in situ* generation of alkyl azides, followed by reaction with triethylphosphite,[230] the *O*-phosphorylation with L-ethoxyalaninyl phosphorochloridate derivatives,[231] and the Atherton–Todd[232] reaction wich is the most classic and most applied,[233] using dialkyl phosphite with a primary / secondary alkylamine in the presence of carbon tetrachloride.[234] (Scheme 56 f), These processes were improved following several practical and interesting modifications of the original method[18a] such as alternatives to halogen sources involving iodoform, phosphorylation[18b] of amines in an aqueous system in the presence

[225] A.H. El-Sagheer, T. Brown, Chem. Commun. **2017**, *53*, 10700.

[226] Q. Li, X. Sun, X. Yang, M. Wu, S. Suna, X. Chen, RSC Adv. **2019**, *9*, 16040.

[227] For the iridium-catalyzed CH activation-amination from phosphoryl azides, see: H. Kim, J. Park, J.G. Kim, S. Chang, Org. Lett. **2014**, *16,* 5466.

[228] S.S. Le Corre, M. Berchel, T. Le Gall, J.-P. Haelters, P. Lehn, T. Montier, P.-A. Jaffrès, Eur. J. Org. Chem. **2014**, 8041.

[229] J. Dhineshkumar, K.R. Prabhu, Org. Lett. **2013**, *15*, 6062.

[230] (a) B.A. Dar, J. Indust. Engin. Chem. 2016, *36*, 194. (b) N.A. Dangroo, A.A. Dar, R. Shankar, M.A. Khuroo, P.L. Sangwan, Tetrahedron Lett. **2016**, *57*, 2717.

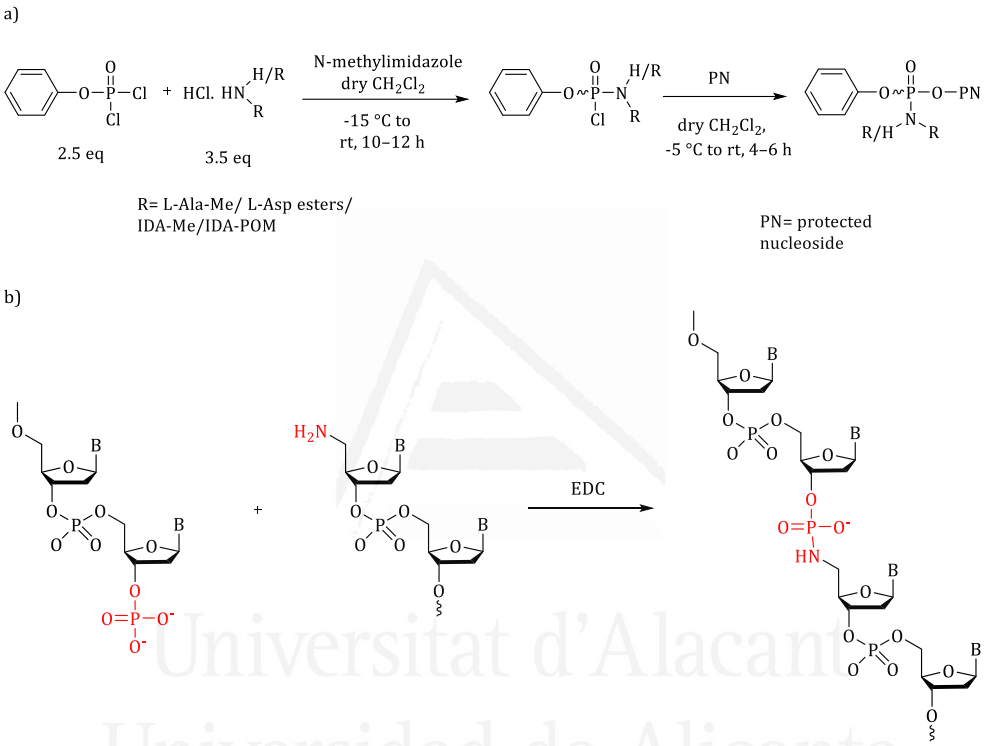
[231] (a) J. Shi, L. Zhou, H. Zhang, T. R. McBrayer, M. A. Detorio, M.Johns, L. Bassit, M H. Powdrill, T. Whitake, S. J. Coats, M. Götte, R. F. Schinazi, Bioorg. Med. Chem. Lett. **2011**, *21*, 7094. (b) P. Nauš, O. Caletková, P. Perlíková, L.P. Slavetínská, E. Tlouštová, J. Hodek, J. Weber, P. Dzubák, M. Hajdúch, M. Hocek, Bioorg. Med. Chem. **2015**, *23*, 7422. (c) A. Cho, L. Zhang, J. Xu, R. Lee, T. Butler, S. Metobo, V. Aktoudianakis, W. Lew, H. Ye, M. Clarke, E. Doerffler, D. Byun, T. Wang, D. Babusis, A.C. Carey, P. German, D. Sauer, W. Zhong, S. Rossi, M. Fenaux, J.G. McHutchison, J. Perry, J. Feng, A.S. Ray, C.U. Kim, J. Med. Chem. **2014**, *57*, 1812.

[232] (a) J. Bertran-Vicente, M. Schümann, P. Schmieder, E. Krause, C.P.R. Hackenberger, Org. Biomol. Chem. **2015**, *13*, 6839. (b) V.I. Krutikov, A.V. Erkin, V.V. Krutikova, Russ. J. Gen. Chem. **2012**, *82*, 822.

[233] S. S. Le Corre, M. Berchel, H. Couthon-Gourvès, J. P. Haelters and P. A. Jaffrès, *Beilstein J. Org. Chem.,* **2014,** *10,* 1166-1196.

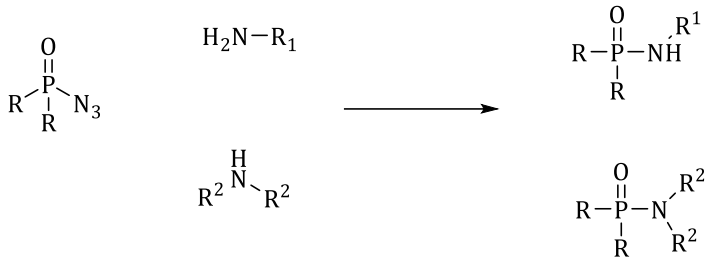
[234] (a) F. R. Atherton, H. T. Openshaw and A. R. Todd, *J. Chem. Soc.,* **1945**, 660-663; (b) F. R. Atherton and A. R. Todd, *J. Chem. Soc.,* **1947**, 674-678.

of a catalytic amount (about 5 mol%) of triethylbenzylammonium chloride or tetrabutylammonium bromide[235]). And in order to optimize the reaction conditions, the reaction has been extended to different nucleophiles, or it has been found that fewer nucleophilic amines like aniline[236] can be used in the Todd - Atherton reaction.[237]



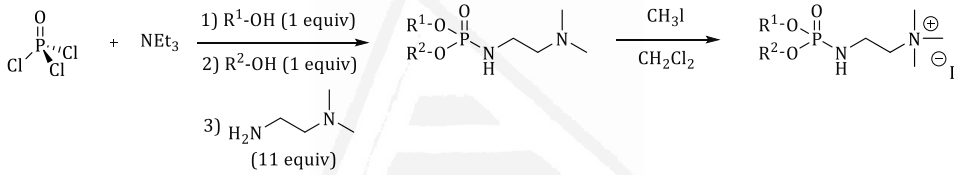
[235] (a) A. Zwierzak, *Synthesis,* **1975**, *8*, 507-509; (b) A. Zwierzak, K. Osowska, *Synthesis,* **1984**, 223-224.
[236] (a) L. K. Lukanov, A. P. Venkov and N. M. Mollov, *Synth. Commun.,* **1986**, *16,* 767-773; (b) A. Dumitrascu and B. A. Howell, *Polym. Degrad. Stab.,* **2012,** *97,* 2611-2618.
[237] L. K. Lukanov, A. P. Venkov and N. M. Mollov, *Synthesis,* **1985,** 971-973.

c)

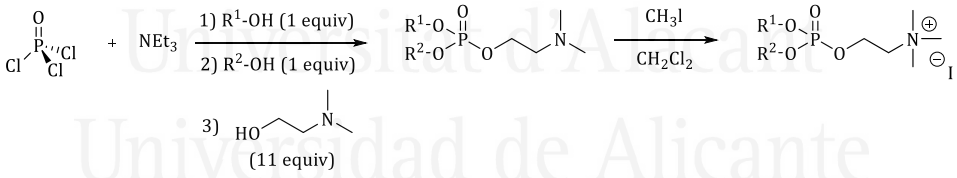


d)

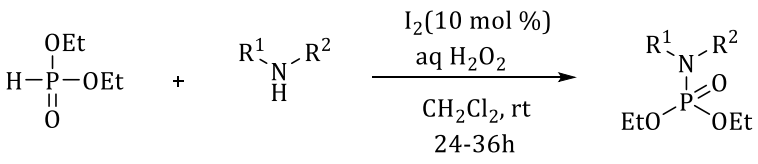
1/



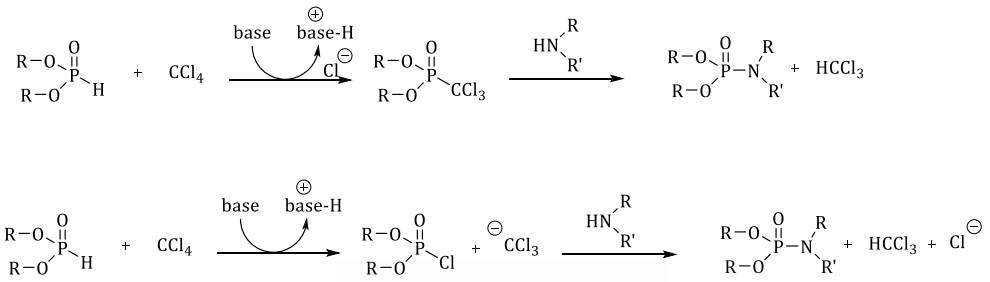
2/



e)



f)

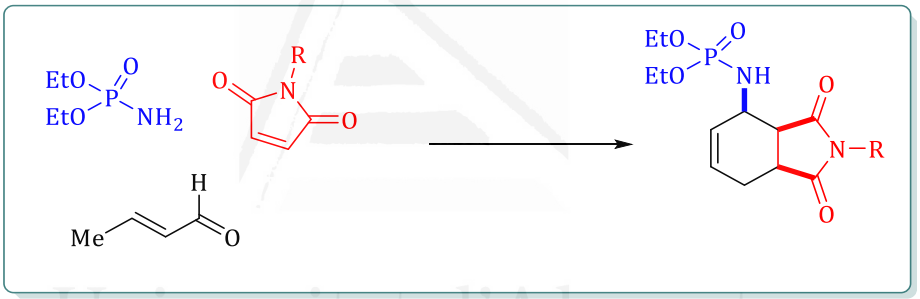


Scheme 56: Methods for the preparation of phosphoramidates.

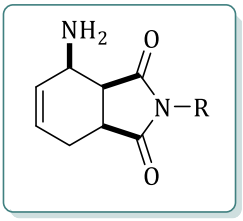
Objectives

Based on the information discussed in the general introduction, and also the research of our group in the application of reactions (AAD)and (PAD), the following objectives have been set:

- Carry out a synthesis of poly-substituted phosphoramidate using diethyl phosphoramidate via a multicomponent reaction (PAD) with good and excellent yields and high diastereoselectivity.



- The hydrolysis of the final phosphoramidates obtained, to provide cyclohex-2-eneamine building blocks for general organic synthesis, with interesting yields.



ANNEX 3

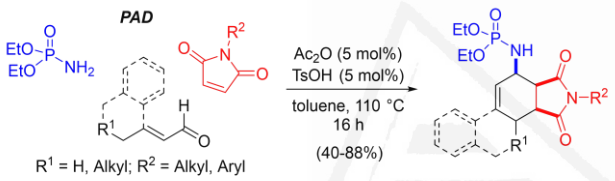
Annex 3

Graphical Abstract

Diastereoselective multicomponent Phosphoramidate-Aldehyde-Dienophile (PAD) process for the synthesis of polysubstituted cyclohex-2-enylamine derivatives

Ihssene Chabour, Carmen Nájera and José M. Sansano

Leave this area blank for abstract info.



R^1 = H, Alkyl; R^2 = Alkyl, Aryl

Annex 3

Tetrahedron
journal homepage: www.elsevier.com

Diastereoselective multicomponent Phosphoramidate-Aldehyde-Dienophile (PAD) process for the synthesis of polysubstituted cyclohex-2-enylamine derivatives

Ihssene Chabour,[a,b] Carmen Nájera,*[a] and José M. Sansano*[a,b]

[a] *Centro de Innovación en Química Avanzada (ORFEO-CINQA), Facultad de Ciencias, Universidad de Alicante 03080-Alicante, Spain.*
[b] *Departamento de Química Orgánica and Instituto de Síntesis Orgánica, Facultad de Ciencias, Universidad de Alicante 03080-Alicante, Spain.*
Fax: +34-965903549; Tel : +34-965903728.
** Corresponding authors: cnajera@ua.es, jmsansano@ua.es*

Dedicated to Prof. Steve Davies

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Multicomponent
PAD
Cyclohex-2-enylamine
Diels-Alder
Primary amines

ABSTRACT

The reaction of diethyl phosphoramidate, conjugated aldehydes and maleimides takes place in a multicomponent sequence named phosphoramidate-aldehyde-dienophile (PAD). The reaction affords a series of *N*-substituted phosphoramidates in good yields with α,β-unsaturated aldehydes bearing hydrogens at the γ-position. The reaction is diastereoselective and the effect of chiral information in the maleimide is evaluated. A mechanism is also postulated and the feasible hydrolysis of the phosphoramidate functional group is achieved although the final allylic amine is difficult to isolate.

1. Introduction

Phosphoramidates are not very common structures either in Nature or in synthetic biologically active compounds.[1,2,3] However, the reported compounds exhibited interesting effects in humans.[2] For example, phosphoramidates are known anticancer agents,[2,4,5,6] and antiviral products[7] effective against hepatitis B or C viruses.[8,9,10] Roles as covalent intermediates in phosphoryl group transfer reactions have also been reported during the study of the behavior of several hydrolases.[11] There are three groups of phosphoramidates depending on the substitution of heteroatoms (Fig. 1), with the type **III** group being the most interesting from a biochemical point of view.

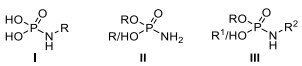


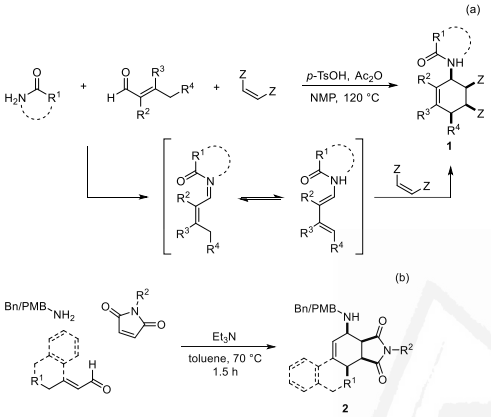
Figure 1. Classification of phosphoramidates.

The preparation of phosphoramidates can be achieved by the sequential addition of amines to phosphorochloridate and treatment with alcohols or phenols,[12] the addition of amines onto phosphonic acids in the presence of dehydrating-coupling reagents,[13] the amination of phosphoryl azide,[14,15] starting from phosphorus oxychloride,[16] and employing diethyl phosphite with amines in the presence of iodine.[17] The *in situ* generation of alkyl azides, followed by reaction with triethylphosphite,[18] the *O*-phosphorylation with L-ethoxyalaninyl phosphorochloridate derivatives,[19] and the Atherton–Todd reaction between a trialkyl phosphite and a primary amine in the presence of carbon tetrachloride,[20] (or its photochemical version)[21] constitute alternative approaches to the synthesis of these compounds.

Annex 3

Focusing our attention on the reaction Amide-Aldehyde-Dienophile (AAD) reaction, reported by Beller and co-workers in 2001 (Scheme 1a),[22] we envisaged that diethyl phosphoramidate can be an appropriate component to replace the amine/amide in this process to generate type **III** phosphoramidates. The same group expanded the scope of this multicomponent AAD reaction using different dienophiles, several substituted α,β-unsaturated aldehydes and different linear or cyclic amides (or sulfonamides), obtaining in all cases only the *endo*-approach of the Diels-Alder reaction to produce compounds **1** (Scheme 1a).[23] Also, they performed the chiral version using a stereocenter in the amide moiety.[24] In addition, we were able to optimize the multicomponent reaction of benzyl or 4-methoxybenzylamine, maleimides and a conjugated aldehyde containing hydrogen atoms at γ-position to obtain polycyclic compounds **2** (Scheme 1b).[25,26]

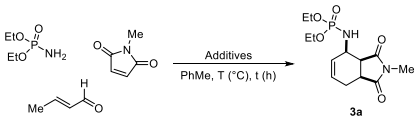
In this work, we have optimized the original Phosphoramidate-Aldehyde-Dienophile (PAD) sequence and studied the most appropriate aldehydes and dipolarophiles to achieve a new access to polyfunctionalized phosphoramidates.



Scheme 1. General multicomponent reaction of the hAmine/Amide-Aldehyde-Dienophile (AAD).

1. Results and Discussion

The model reaction used for the optimization of this multicomponent PAD involved diethyl phosphoramidate, crotonaldehyde and *N*-methylmaleimide (NMM) as the dienophile (Scheme 1). We took advantage of the results obtained in our previous contribution[25] to optimize the process. Thus, toluene was selected as the solvent and the reaction needed to be heated up for 8 h in order to observe a noticeable conversion/yield of cycloadduct **3a** (Table 1, compare entries 1-4). The presence of additives such as acetic anhydride and *p*-toluenesulfonic acid (TsOH) were crucial for the reactions of amides or sulfonamides[23¡Error! Marcador no definido.] so we analyzed their effects in the multicomponent PAD synthesis. Separately, the presence of acetic anhydride is more important than the presence of TsOH in terms of the isolated yield (Table 1, entries 5 and 6). The highest yield for **3a** was achieved employing only 5 mol% of acetic anhydride and 5 mol% of TsOH (Table 1, entry 7, and compare entries 7-10). The crude product **3a** was very pure and could be used for the synthesis of the free allylic amine after hydrolysis of the diethyl phosphoryl group (see below). The reaction with chloroform took place in very low yields (Table 1, entries 11 and 12). Interestingly, the *N*-cyclohex-2-en-1-amide scaffold **3** is present in somatostatin analogues and the Kessler group conveniently applied this reaction to achieve the desired product.[27] Beller's group also applied this reaction to synthetize corollosporine analogues to test their antimicrobial activity.[28]



Scheme 1. Multicomponent PAD synthesis of product **3a**.

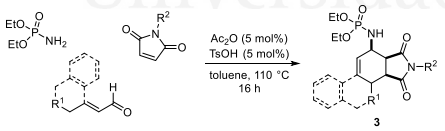
Table 1. Optimization of the reaction conditions to synthesize *N*-cyclohex-2-en-1-yl phosphoramidate **3a** *via* the PAD reaction.[a]

Entry	Ac_2O (mol%)	TsOH (mol%)	T (°C)	t (h)	Yield (%)[b]
1	---	---	25	24	---
2	---	---	110	4	64
3	---	---	110	8	62
4	---	---	110	24	60
5	(5)	---	110	8	65
6	---	(5)	110	8	56
7	(5)	(5)	110	16	88
8	(50)	(5)	110	16	87
9	(100%)	(5)	110	16	86
10	(100%)	(10)	110	16	88
11	(100%)	(10)[c]	70	16	29
12	(100%)	(10)[c]	110	16	33

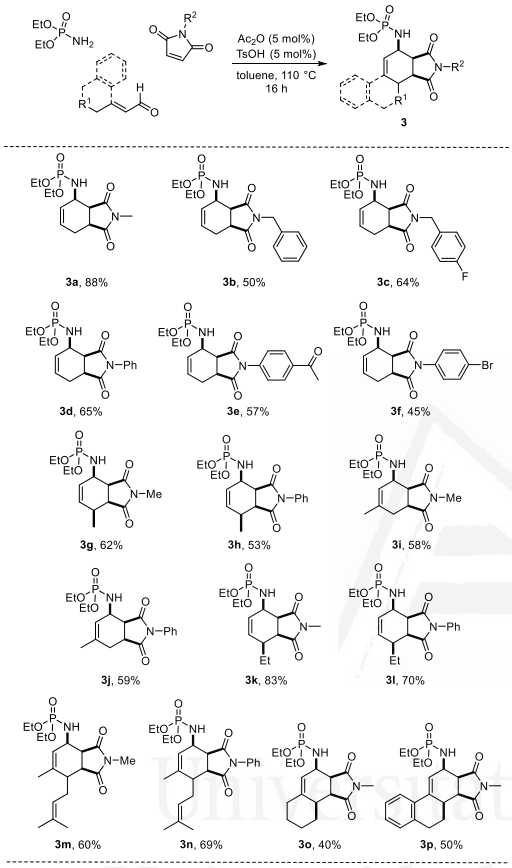
[a] *Reagents and conditions*: diethyl phosphoramidate (1 mmol), crotonaldehyde (1 mmol), addtitives (0.05 mmol or not), NMM (1 mmol) in toluene (1mL) reacted at the corresponding temperature and time. [b] Isolated yields after flash chromatography. [c] Reaction performed in chloroform.

Using the optimal conditions shown in entry 7 of Table 1, the effects of the structure of both components, aldehydes and maleimides were analyzed (Scheme 3). Crotonaldehyde and diethyl phosphoramidate reacted in the presence of *N*-alkyl, *N*-benzyl, and *N*-arylmaleimides to give compounds **3a-f** in good yields (Scheme 3). It is notable that fluorinated maleimide[29] afforded the corresponding compound **3c** in 64% yield, which can offer a potential biological activity. (*E*)-2-Pentenal was assayed with both NMM and *N*-phenylmaleimide (NPM) yielding products **3g** and **3h** in 62% and 53% yield, respectively (Scheme 3). Similar behavior was observed when 3-methylcrotonaldehyde was employed in reactions with both maleimides, affording the expected bicyclic skeletons **3i** and **3j** in similar yields (58% and 59%). Hex-2-enal and diethyl phosphoramidate afforded high yields of products **3k** and **3l** in the reactions with NMM and NPM, respectively (Scheme 3). Geranial possesses two different types of hydrogens at the γ-position. This aldehyde failed in our previous amine/aldehyde/dienophile process,[25] but in this PAD multicomponent reaction the mechanism preferred the abstraction of one of the two γ-methylenic hydrogens to generate *in situ* the most substituted 1-aminodiene intermediate. Thus, compound **3m** was obtained in 60% yield and a ratio of 85:15 (determined by ^{1}H NMR), whilst **3n** was isolated in higher yield (69%) with a 90:10 ratio (determined by ^{13}C NMR) (Scheme 3). Interestingly, tricyclic product **3o** and the pseudo-steroidal tetracyclic scaffold **3p** were isolated, from the corresponding cyclic acrylic aldehydes,[30] in 40% and 50% yield, respectively.

The relative configuration of all compounds **3** was confirmed by nOe experiments and by comparison of chemical shifts (^{1}H NMR) with the analogous corresponding amines previously obtained by our group.[25] Despite the temperature, all of them were isolated as single diastereoisomers except the already described examples using geranial (see above). As well as in our precedented AAD sequential reaction, PAD transformations with fumarates, maleic anhydride, acrylates, vinylic sulfones, chalcone derivatives and nitroalkenes completely failed. In some examples, complex crude reaction mixtures were obtained and the expected products were isolated in very low yields.



3



Scheme 3. Synthesis of *N*-cyclohex-2-enyl phosphoramidates **3** *via* the PAD reaction.

The diastereoselective version of this AAD transformation was also examined employing (*R*)-*N*-(1-phenylethyl)maleimide (Fig. 2). The reaction proceeded with high diastereoselectivity despite the temperature employed (82:18 from ^{1}H NMR of the crude product). After purification by flash chromatography only the major stereoisomer **3q** could be isolated. The proposed absolute configuration was assigned on the basis of VCD analysis (Fig. 2). Both diastereoisomers **3q** and **3q'** exhibited opposite theoretical VCD patterns, which was more relevant in the fingerprint absorption area. The theoretical VCD (black dots plot) and the measured spectra for diastereoisomer **3q** matched almost perfectly (Fig. 2). The observed displacement between the theoretical and experimental plots for **3q** can be due to the formation of intramolecular hydrogen bonds between the NH and the closer carbonyl group.[2] This interaction was also supported by the *all-cis* relative configuration of this fused ring such as that which occurred in the analogous AAD reaction.[25]

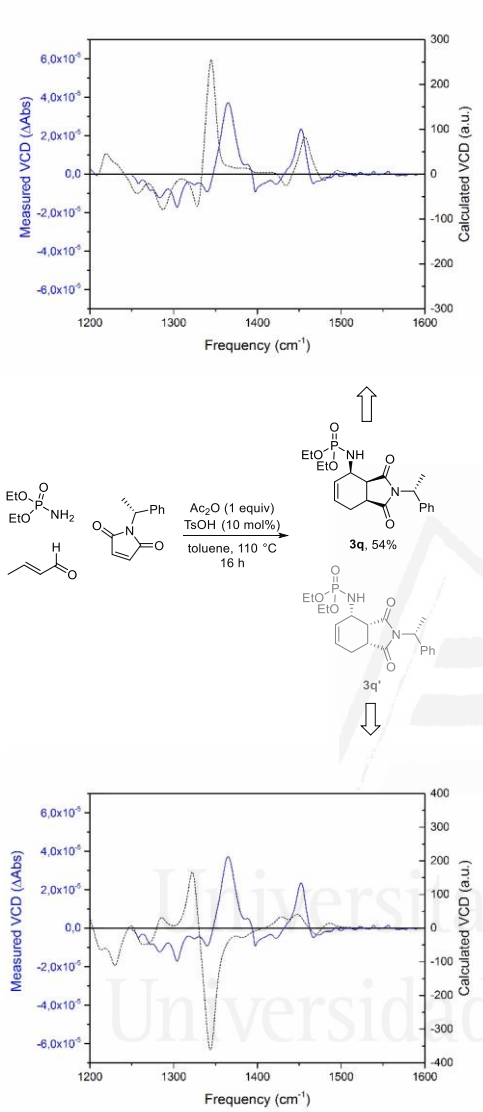
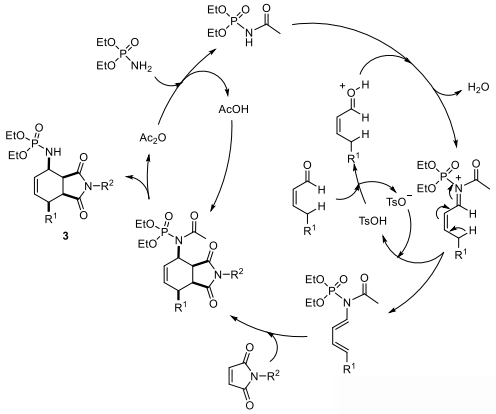


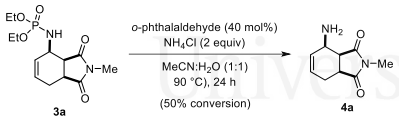
Figure 2. VCD analysis of product **3q** and its enantiomeric form **3q'**. Blue line corresponds to experimentally measured VCD, whilst dashed black plot is VCD calculated with a B3LYP/6-311G+(2d,2p) level for configuration **3q**.

The crucial presence of acetic anhydride and TsOH allowed us to propose a mechanism where both the diethyl phosphoramidate and the aldehyde are independently activated. The reaction operated with substoichiometric amounts of acetic anhydride and so deacetylation of the intermediate *N*-acylphosphoramidate occurred prior to the formation of the final product **3.** The partial generation of the intermediate diethyl *N*-acetylphosphoramidate was observed after heating the reaction mixture composed by all the ingredients expect the maleimide (see SI). To the resulting mixture the maleimide was added and the expected reaction took place.



Scheme 4. Proposed mechanism for the synthesis of cycloadducts **3**.

The publication of a family of antibacterial agents containing a 3-aminocyclohexene core[31] encouraged us to study the hydrolysis of the phosphoramidate moiety. A convenient method was reported in the literature based on the hydrolysis of various organophosphorus compounds bearing P(O)–NH subunits catalyzed by *o*-phthalaldehyde.[32] Following this procedure the compound **3a** was submitted to several test reactions using ammonium *p*-toluenesulfonate or ammonium chloride, at reflux in THF or MeCN. With NH_4OTs the reaction did not work, however, NH_4Cl (2 equiv) offered the best conversion. Thus, NH_4Cl (2 equiv), *o*-phthalaldehyde (40 mol%), MeCN/H_2O (90 ºC, 24 h) were the most appropriate conditions to obtain a 50% conversion (from the crude ^1H NMR) (Scheme 5).[33] Primary amine **4a** could be identified (see ESI) but its isolation was not possible either by flash chromatography or precipitation/crystallization by adding 1 equiv of HCl/Et_2O. In all these cases equimolar mixtures of **3a** and **4a** were detected (see ESI). We unsuccessfully tried to introduce Boc, benzoyl or acetyl as protective groups in order to isolate it.[34]



Scheme 5. Hydrolysis of cycloadduct **3a**.

1. Conclusions

A different approach for the preparation of polysubstituted phosphoramidates, derived from cyclohex-2-eneamines, based on a multicomponent diethyl phosphoramidate-aldehyde-dienophile (PAD) process has been optimized. Maleimides and conjugated aldehydes incorporating a γ-hydrogen are appropriate components to run this reaction in high yields. The high diastereoselectiviy achieved is a noticeable aspect of this transformation generating an *all-cis* relative configuration in the resulting final products. The introduction of chiral information at the *N*-substituent of the maleimide gave an enantiomerically enriched cycloadduct whose absolute configuration was determined by VCD spectroscopy. These final phosphoramidates are potentially bioactive compounds and also it was demonstrated that their hydrolysis is feasible yielding interesting cyclohex-2-eneamine building blocks for general organic synthesis.

2. Experimental Section

4.1. General

All commercially available reagents and solvents were used without further purification, only aldehydes were also distilled prior to use. Only the aldehyde precursor of compound **6i** was prepared according to the literature.[30] Analytical TLC was performed on Schleicher &

Annex 3

& Schuell F1400/LS 254 silica gel plates, and the spots were visualized under UV light (λ = 254 nm). Flash chromatography was carried out on handpacked columns of Merck silica gel 60 (0.040-0.063 mm). Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. The structurally most important peaks of the IR spectra (recorded using a Nicolet 510 P-FT) are listed and wave numbers are given in cm^{-1}. NMR spectra were obtained using a Bruker AC-300 or AC-400 and were recorded at 300 MHz for ^1H NMR, 75 or 100 MHz for ^{13}C NMR, and 121 MHz for ^{31}P NMR. ^1H NMR were recorded using $CDCl_3$ as solvent and TMS as internal standard (0.00 ppm). The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved and br s = broad signal. All coupling constants (*J*) are given in Hz and chemical shifts in ppm. ^{13}C NMR spectra were referenced in $CDCl_3$ at 77.16 ppm. DEPT-135 experiments were performed to assign CH, CH_2 and CH_3. ^{19}F NMR were recorded at 282 MHz using $CDCl_3$ as solvent. ^{31}P NMR were performed in $CDCl_3$ and referenced at 0.00 ppm (aqueous phosphoric acid). Low-resolution electron impact (EI) mass spectra were obtained at 70 eV using a Shimadzu QP-5000 by injection or DIP; fragment ions in m/z are given with relative intensities (%) in parentheses. High-resolution mass spectra (HRMS) were measured on an instrument using a quadrupole time-of-flight mass spectrometer (QTOF) and also through the electron impact mode (EI) at 70 eV using a Finnigan VG Platform or a Finnigan MAT 95S. VCD analysis was recorded in a Jasco FVS-6000.

*4.2. General procedure for the synthesis of products **6**.*

To a stirred solution of diethyl phosphoramidate (154 mg, 1 mmol), TsOH (8.6 mg, 0.05 mmol), acetic anhydride (4.8 µL, 0.05 mmol) in 3 mL of toluene was added the aldehyde (1 mmol), the maleimide (1 mmol). The solution was stirred under reflux for 24 h, and then the solvent was removed under vacuum. The crude of the reaction was purified with flash chromatography to give the desired compound.

*4.2.1. Diethyl [(3aSR,4RS,7aSR)-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3a**)*: Pale brown sticky oil, (278 mg, 88% yield). IR (neat) ν_{max}: 1687, 1436, 1023, cm^{-1}. ^1H NMR δ: 1.34 (td, *J* = 7.0, 3.2 Hz, 6H, 2xCH_3CH_2O), 2.02-2.27 (m, 2H, $CHCH_2CH$), 2.67 (dd, *J* = 15.7, 6.6 Hz, 1H, CH_2CHC=O), 2.94 (s, 3H, NCH_3), 3.15-3.20 (m, 1H, CHC*H*C=O), 3.28 (t, *J* = 7.1 Hz, 1H, NHC*H*CH), 3.98 (br s, 1H, N*H*CH), 4.12 (m, 4H, 2xCH_2CH_3), 4.53 (br s, 1H, NC*H*CH=), 5.72-5.91 (m, 2H, C*H*=C*H*). ^{13}C NMR δ: 16.2, 16.4 (d, 2xCH_3), 24.1 (CH_3), 25 ($CHCH_2CH$), 39.1 (CH_2CHC=O), 44.3 (NH*C*H), 48.2 (NCH*C*HC=O), 62.9 (2xOCH_2), 127, 135 (*C*=*C*), 179.1, 179.5 (2x C=O). ^{31}P NMR δ: 5.66 ppm. MS (EI) *m/z*: 316 (M^+, 37%), 287 (10), 205 (98), 179 (100), 148 (28), 94 (20), 81 (12), 68 (60) ; HRMS calculated for $C_{13}H_{21}N_2O_5P$: 316.1188, found: 316.1192.

*4.2.2. Diethyl [(3aSR,4RS,7aSR)-2-benzyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3b**):* Pale brown sticky oil, (196 mg, 50 % yield). IR (neat) ν_{max}: 1693, 1399, 1239, 1024 cm^{-1}. ^1H NMR δ: 1.33 (t, *J* = 7.0 Hz, 6H, 2xCH_3CH_2O), 2.07-2.20 (m, 1H, $CHCH_2CH$), 2.63-2.71 (m, 1H, $CHCH_2CH$), 3.14-3.19 (m, 1H, CH_2CHC=O), 3.27 (dd, *J* = 8.9, 5.8 Hz, 1H, NCHC*H*C=O), 3.96 (br s, 1H, CHN*H*), 4.04-4.14 (m, 4H, 2xCH_2CH_3), 4.44-4.57 (m, 1H, NC*H*CH=), 4.59 (s, 2H, NCH_2), 5.77-5.87 (m, 2H, C*H*=C*H*), 7.22-7.33 (m, 5H, Ar*H*). ^{13}C NMR δ: 16.2 (2xCH_3CH_2), 24.3 (=$CHCH_2CH$), 39.1 (CH_2CHC=O), 42.5 (NH*C*H), 44.3 (O=CNCH_2Ar), 48.2 (NCH*C*HC=O), 62.7 (d, 2xOCH_2), 126.8, 127.9, 128.3, 128.6, 135.0, 135.5 (Ar*C* and *C*=*C*), 178.7, 179.0 (2x*C*=O). ^{31}P NMR δ: 6.09 ppm. MS (EI) *m/z*: 392 (M^+, 40%), 256 (15), 255 (52), 205 (100), 176 (18), 174 (10), 148 (20), 138 (12), 94 (16), 91 (60), 81 (11), 79 (10), 77 (13), 68 (50), 65 (14). HRMS calculated for $C_{19}H_{25}N_2O_5P$: 392.1501; found: 392.1509.

*4.2.3. Diethyl [(3aS,4R,7aS)-2-(4-fluorobenzyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3c**)*: Pale brown sticky oil, (262 mg, 64% yield). IR (neat) ν_{max}: 1698, 1510, 1510, 1025 cm^{-1}. ^1H NMR δ: 1.33 (t, *J* = 7.1 Hz, 6H, 2xCH_3CH_2O), 2.04-2.21 (m, 1H, $CHCH_2CH$), 2.66 (dd, *J* = 15.6, 7.0 Hz 1H, $CHCH_2CH$), 3.17 (td, *J* = 9.0, 8.5 Hz, 1H, CH_2CHC=O), 3.27 (dd, *J* = 8.8, 5.9 Hz, 1H, NCHC*H*C=O), 3.95 (br s, 1H,CHN*H*), 4.07-4.14 (m, 2xCH_2CH_3), 4.5 (br s, 1H, NC*H*CH=), 4.55 (s, 2H, NCH_2), 5.71-5.88 (m, 2H, C*H*=C*H*), 6.94-7.0 (m, 2H, Ar*H*), 7.24-7.29 (m, 2H, Ar*H*). ^{13}C NMR δ: 16.3 (dd, 2xCH_3CH_2), 24.3 (d, =$CHCH_2CH$), 39.2 (CH_2CHC=O), 41.8 (d, NH*C*H), 44.3 (d, O=CNCH_2Ar), 48.2 (NCH*C*HC=O), 62.9 (d, 2xOCH_2), 115.6 (d, $^2J_{C\text{-}F}$ = 21.7 Hz, *C*HCF), 126.8, (C=*C*), 130.4 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, *C*HCHCF), 135 (C=*C*), 160.8 (*C*CHCHCF), 164.1 (*C*F), 178.7,179.0 (2x*C*=O). ^{19}F NMR δ: -114.1. ^{31}P NMR δ: 5.55 ppm. MS (EI) *m/z*: 410 (M^+, 39%), 274 (12), 273 (51), 205 (100), 177 (11), 176 (20), 174 (10), 148 (25), 138 (14), 110 (10), 109 (84), 94 (16), 83 (11), 81 (13), 79 (12), 77 (10), 68 (56), 67 (11). HRMS calculated for $C_{19}H_{24}N_2O_5P$: 410.1407; found: 410.1428.

*4.2.4. Diethyl [(3aSR,4RS,7aSR)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3d**)*: Pale brown sticky oil (246 mg, 65% yield). IR (neat) ν_{max}: 1700, 1498, 1384 cm^{-1}. ^1H NMR δ: 1.34 (t, *J* = 7.1 Hz, 6H, 2xCH_3), 2.20-2.31 (ddd, *J* = 15.6, 8.0, 2.5 Hz, 1H, $CHCH_2CH$), 2.77 (dd, *J* = 15.7, 6.6 Hz, 1H, $CHCH_2CH$), 3.33 (dd, *J* = 9.0, 8.0 Hz, 1H, CH_2CHC=O), 3.45 (dd, *J* = 9.1, 5.9 Hz, 1H, NCHC*H*C=O), 4.04-4.10 (m, 4H, 2xCH_2CH_3), 4.53 (br s, 1H, NC*H*CH=), 5.89-6.01 (m, 2H, C*H*=C*H*), 7.18-7.21 (m, 2H, Ar*H*), 7.39-7.48 (m, 3H, Ar*H*). ^{13}C NMR δ: 16.3, 16.4 (d, 2xCH_3), 24.6 ($CHCH_2CH$), 39.3 (CH_2CHC=O), 44.5 (d, NH*C*H), 48.4 (d, NCH*C*HC=O), 62.9, 63.0 (2xOCH_2), 126.5, 127.0, 129.0, 129.3, 131.6, 135.1, 135.2 (Ar*C* and *C*=*C*), 178.2, 178.5 (2x*C*=O). ^{31}P NMR δ: 5.78 ppm. MS (EI) *m/z*: 378 (M^+, 54%), 241 (47), 205 (100), 176 (15), 148 (16), 94 (12), 68 (31). HRMS calculated for $C_{18}H_{23}N_2O_5P$: 378.1345; found: 378.1355.

*4.2.5. Diethyl [(3aSR,4RS,7aSR)-2-(4-acetylphenyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3e**):* pale brown sticky oil, (239 mg, 57% yield). IR (neat) ν_{max}: 1704, 1379, 1237, 1024, cm^{-1}. ^1H NMR δ: 1.35 (t, *J* = 7.0 Hz, 6H, 2xC*H*$_3$CH$_2$O), 2.22-2.33 (m, 1H, CHC*H*$_2$CH), 2.61 (s, 3H, C*H*$_3$), 2.78 (dd, *J* = 15.7, 6.4 Hz 1H, CHC*H*$_2$CH), 3.37 (t, *J* = 8.4 Hz, 1H, CH$_2$C*H*C=O), 3.47-3.50 (m, 1H, NCHC*H*C=O), 4.05-4.16 (m, 4H, 2xC*H*$_2$CH$_3$), 4.47 (br s, NC*H*CH=), 5.91-6.01 (m, 2H, C*H*=C*H*), 7.36 (d, *J* = 8.6 Hz, 2H, Ar*H*), 8.03 (d, *J* = 8.6 Hz 2H, Ar*H*). ^{13}C NMR δ: 16.2 (2xC*H*$_3$CH$_2$), 24.4 (CO*C*H$_3$), 26.6 (=CH*C*H$_2$CH), 39.2 (CH$_2$*C*HC=O), 44.4 (NH*C*H), 48.2 (NCH*C*HC=O), 62.7 (2xO*C*H$_2$), 126.4, 126.9, 129.0, 134.9, 135.5, 136.8 (Ar*C* and *C*=*C*), 177.6, 178.0, 196.9 (3x*C*=O). ^{31}P NMR *δ*: 5.48 ppm. MS (EI) *m/z*: 420 (M^+, 13%), 283 (29), 205 (100), 200 (13), 176 (13), 154 (12), 148 (15), 94 (12), 68 (40), 43 (12). HRMS calculated for $C_{20}H_{25}N_2O_6P$: 420.1450; found: 420.1444.

*4.2.6. Diethyl [(3aSR,4RS,7aSR)-2-(4-bromophenyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3f**):* Pale brown sticky oil, (205 mg, 45% yield). IR (neat) ν_{max}: 2341, 1702, 1385, 1189, 1024 cm^{-1}. ^1H NMR δ: 1.34 (t, *J* = 7.1 Hz, 6H, 2xC*H*$_3$CH$_2$O), 2.22-2.32 (m, 1H, CHC*H*$_2$CH), 2.77 (dd, *J* = 15.7, 6.5 Hz 1H, CHC*H*$_2$CH), 3.31-3.37 (m, 1H, CH$_2$C*H*C=O), 3.46 (dd, *J* = 9.1, 5.9 Hz, 1H, NCHC*H*C=O), 4.05-4.17 (m, 4H, 2xC*H*$_2$CH$_3$), 4.47 (br s, NC*H*CH=), 5.92-5.99 (m, 2H, C*H*=C*H*), 7.11 (d, *J* = 8.8 Hz 2H, Ar*H*), 7.58 (d, *J* = 8.8 Hz, 2H, Ar*H*). ^{13}C NMR δ: 16.4 (2xC*H*$_3$CH$_2$), 24.6 (=CH*C*H$_2$CH), 39.3 (CH$_2$*C*HC=O), 44.5 (NH*C*H), 48.4 (NCH*C*HC=O), 62.9 (2xO*C*H$_2$), 122.8, 127.0, 128.0, 130.5, 132.5, 135.2 (Ar*C* and *C*=*C*), 177.9,178.2 (2x*C*=O). ^{31}P NMR *δ*: 5.86 ppm. MS (EI) *m/z*: 456 (M^+, 7%), 321 (14), 319 (15), 205 (100), 176 (14), 154 (22), 148 (16), 94 (13), 68 (43). HRMS calculated for $C_{18}H_{22}BrN_2O_5P$: 456.0450; found: 456.0446

*4.2.7. Diethyl [(3aSR,4RS,7aSR)-2,7-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3g**)*: Brown sticky oil, (204 mg, 62% yield), IR (neat) ν_{max}: 1690, 1434, 1383, cm^{-1}. ^1H NMR δ: 1.29 (t, *J* = 7.1 Hz, 6H, 2xC*H*$_3$CH$_2$O), 1.34 (d, *J* = 7.4 Hz, 3H, CHC*H*$_3$), 2.39 (br s, 1H, C*H*CH$_3$), 2.85 (s, 3H, NC*H*$_3$), 2.98-3.03 (m, 1H, NCHC*H*C=O), 3.18-3.23 (m, 1H, CHC*H*C=O), 3.88 (br s, 1H, CHN*H*), 3.99-4.11 (m, 4H, 2xCH$_3$C*H*$_2$O), 4.59 (t, *J* = 11.0, Hz, 1H, NC*H*CH), 5.52-5.58 (m, 1H, NCHC*H*=C), 5.76-5.81 (m, 1H, NCHC*H*=C). ^{13}C NMR *δ*: 16.1, 16.3 (2x*C*H$_3$), 16.6 (CH*C*H$_3$), 24.6 (N*C*H$_3$), 30.5 (*C*HCH$_3$), 43.9 (NH*C*H), 45.2, 45.3 (2xNHC*C*HC=O), 48.5 (CH*C*HC=O), 62.6, 62.7 (2xO*C*H$_2$), 133.4, 134 (*C*=C), 176.7, 179 (2x C=O). ^{31}P NMR *δ*: 5.92 ppm. MS (EI) *m/z*: 330 (M^+, 9%), 219 (100), 193 (25), 162 (11), 82 (19); HRMS calculated for $C_{14}H_{23}N_2O_5P$: 330,1345, found: 330.1347.

*4.2.8. Diethyl [(3aSR,4RS,7SR,7aSR)-7-methyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3h**)*: Pale brown sticky oil (207 mg, 53% yield). IR (neat) ν_{max}: 1700, 1498, 1382 cm^{-1}. ^1H NMR δ: 1.34, (t, *J* = 7.1 Hz, 6H, 2xC*H*$_3$CH$_2$), 1.43 (d, *J* = 7.4 Hz, 3H, C*H*$_3$CH), 2.55 (br s, 1H,CH$_3$C*H*), 3.21 (t, *J* = 8.1 Hz, 1H, CH$_3$CHC*H*C=O), 3.44 (dd, *J* = 8.7, 5.8 Hz, 1H, NCHC*H*C=O), 4.07-4.16 (m, 4H, 2xC*H*$_2$CH$_3$), 4.64 (br s, 1H, NC*H*CH=), 5.71 (dt, *J* = 9.3, 3.3 Hz, 1H, NCHCH=C*H*), 5.94 (dt, *J* = 9.3, 3.0 Hz, 1H, NCHC*H*=CH), 7.16-7.19 (m, 2H, Ar*H*), 7.36-7.48 (m, 3H, Ar*H*). ^{13}C NMR δ: 16.3, 16.4 (d, 2x*C*H$_3$CH$_2$), 16.8 (*C*H$_3$CH), 30.8 (CH$_3$*C*H), 44.1 (CH$_3$CH*C*HC=O), 45.6 (NCH*C*HC=O), 48.9 (NH*C*H), 62.9, 63.0 (2xO*C*H$_2$), 126.6, 128.9, 129.2, 131.5, 133.5, 134.2, 134.3 (Ar*C* and *C*=*C*), 175.7, 178.2 (2x*C*=O). ^{31}P NMR *δ*: 5.53 ppm. MS (EI) *m/z*: 392 (M^+, 5%), 219 (100), 82 (15). HRMS calculated for $C_{19}H_{25}N_2O_5P$: 392.1501; found: 392.1499.

*4.2.9. Diethyl ((3aSR,4RS,7aSR)-2,6-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3i**):* Brown sticky oil, (191 mg, 58% yield). IR (neat) ν_{max}: 1696, 1437, 1385 cm^{-1}. ^1H NMR δ: 1.27 (t, *J* = 7.1 Hz, 6H, 2xC*H*$_3$CH$_2$), 1.65 (s, 3H, C*H*$_3$C=CH), 2.03-2.20 (m, 1H, CC*H*$_2$CH), 2.45 (d, *J* = 15.3, 1.3 Hz, 1H, CC*H*$_2$CH), 2.88(s, 1H, NCH$_3$), 3.04-3.21 (m, 2H, CH$_2$C*H*C=O, NCHC*H*C=O), 3.84 (br s, 1H, CH-N*H*), 3.99-4.09 (m, 4H, 2xC*H*$_2$CH$_3$), 4.27 (br s, 1H, NC*H*CH=), 5.45 (s, 1H, NCHC*H*=C). ^{13}C NMR *δ*: 16.1, 16.3 (t, 2xC*H*$_3$), 23 (*C*H$_3$), 25 (NC*H*$_3$), 29.2 (CC*H*$_2$CH), 39.2 (CH$_2$*C*HC=O), 44.0, 44.1 (d, N*C*H), 48.5 (CH*C*HC=O), 62.6, 62.8 (2xO*C*H$_2$), 127.0, 127.1 (d, *C*H=C), 136.1 (*C*q), 179.0, 179.4 (2x C=O). ^{31}P NMR *δ*: 6.08 ppm. MS (EI) *m/z*: 330 (M^+, 20%), 301 (11), 219 (21), 193 (100), 179 (10), 154 (21), 108 (12), 82 (42); HRMS calculated for $C_{14}H_{23}N_2O_5P$: 330,1345, found: 330.1349

*4.2.10. Diethyl [(3aSR,4RS,7aSR)-6-methyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3j**)*: Pale brown sticky oil (231 mg, 59% yield). IR (neat) ν_{max}: 1702, 1498, 1384, cm^{-1}. ^1H NMR δ: 1.33 (t, *J* = 7.1 Hz, 6H, 2xC*H*$_3$CH$_2$), 1.78 (s, 3H, C*H*$_3$C=CH), 2.27-2.37 (m, 1H, CC*H*$_2$CH), 2.61 (d, *J* = 15.3, 1.3 Hz, 1H, CC*H*$_2$CH), 3.31 (ddd, *J* = 9.0, 7.5, 1.6 Hz, 1H, CH$_2$C*H*C=O), 3.41 (dd, *J* = 8.9, 6.0 Hz, 1H, NCHC*H*C=O), 3.66 (s, 1H, CH-N*H*), 4.06-4.17 (m, 4H, 2xC*H*$_2$CH$_3$), 4.42 (br s, 1H, NC*H*CH=), 5.61 (s, 1H, NCHC*H*=C), 7.15-7.19 (m, 2H, Ar*H*), 7.39-7.49 (m, 3H, Ar*H*). ^{13}C NMR δ: 16.3, 16.4 (2x*C*H$_3$CH$_2$), 23.0 (CH$_3$C=CH), 29.7 (C*C*H$_2$CH), 39.4 (CH$_2$*C*HC=O), 44.4 (NCH*C*HC=O), 48.8 (NH*C*H), 62.8, 62.9 (2xO*C*H$_2$), 126.5, 127.3, 127.4, 128.9, 129.3, 131.6, 136.3 (Ar*C* and *C*=*C*), 178.3, 178.5 (2x*C*=O). ^{31}P NMR *δ*: 5.99 ppm. MS (EI) *m/z*: 392 (M^+, 34%), 255 (100), 239 (15), 219 (46), 190 (15), 154 (29), 108 (18), 82 (60). HRMS calculated for $C_{19}H_{25}N_2O_5P$: 392.1501; found: 392.1494.

*4.2.11. Diethyl [(3aS,4R,7S,7aS)-7-ethyl-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3k**):* Pale brown sticky oil, (286 mg, 83% yield). IR (neat) ν_{max}: 1693, 1429, 1224,1026 cm^{-1}. ^1H NMR δ: 0.99 (t, *J* = 7.3 Hz, 3H, C*H*$_3$CH$_2$CH), 1.27 (t, *J* =

Annex 3

7.1 Hz, 6H, 2xCH_3CH_2O), 1.65 (m, 1H, CH_3CH_2CH), 1.84 (m, 1H, CH_3CH_2CH), 2.08 (br s, 1H, CH_3CH_2CH), 2.82 (s, 3H, NCH_3), 3.07-3.11 (m, 1H, EtCHCHC=O), 3.18 (dd, *J* = 8.6, 5.9 Hz, 1H, NCHCHC=O), 3.86 (br s, 1H, CHNH), 4.04 (m, 4H, 2xCH_3CH_2O), 4.55 (t, *J* = 10.9 Hz, 1H, NHCH), 5.58 (dt, *J* = 9.3, 3.4 Hz, 1H, NCHCH=CH), 5.78 (dt, *J* = 9.9, 3.1 Hz, 1H, NCHCH=CH). ^{13}C NMR δ: 12.5 (CH_3CH_2CH), 16.2, 16.3 (dd, 2xCH_3CH_2), 23.9 (CH_3CH_2CH), 24.6 (NCH_3), 38.0 (EtCHCHC=O), 42.3 (EtCHCHC=O), 45.1 (d, NCHCHC=O), 48.6 (NHCH), 62.6, 62.7 (d, 2xOCH_2), 176.6, 178.7 (2xC=O). ^{31}P NMR *δ*: 5.91 ppm. MS (EI) *m/z*: 344 (M^+, 10%), 234 (12), 233 (100), 207 (21) 204 (12), 176 (13), 96 (11). HRMS calculated for $C_{15}H_{25}N_2O_5P$: 344.1501; found: 344.1500.

4.2.12. Diethyl [(3aSR,4RS,7SR,7aSR)-7-ethyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (***3l***): Pale brown sticky oil, (284 mg, 70% yield), IR (neat) ν_{max}: 1700, 1498, 1382 cm^{-1}. ^{1}H NMR δ: 1.09 (t, *J* = 7.3 Hz, 3H, CH_3CH_2CH), 1.34 (t, *J* = 7.1 Hz, 6H, 2xCH_3CH_2O), 1.76 (ddd, *J* = 13.6, 8.5, 7.0 Hz, 1H, CH_3CH_2CH), 1.96 (dt, *J* = 14.2, 7.0 Hz, 1H, CH_3CH_2CH), 2.26 (br s, 1H, CH_3CH_2CH), 3.32 (dd, *J* = 8.7, 7.0 Hz, 1H, EtCHCHC=O), 3.44 (dd, *J* = 8.7, 5.7 Hz, 1H, NCHCHC=O), 4.05-4.16 (m, 4H, 2xCH_3CH_2O), 4.19-4.28 (m, 1H, NHCH), 5.77 (dt, *J* = 9.3, 3.3 Hz, 1H, NCHCH=CH), 5.96 (dt, *J* = 9.3, 3.0 Hz, 1H, NCHCH=CH), 7.15-7.19 (d, *J* = 7.0, 2H, ArH), 7.37-7.47 (m, 3H, ArH). ^{13}C NMR δ: 12.8 (CH_3CH_2CH), 16.3, 16.4 (2xCH_3CH_2), 24.1 (CH_3CH_2CH), 38.4 (EtCHCHC=O), 42.5 (EtCHCHC=O), 45.4 (NCHCHC=O), 49.0 (NHCH), 62.9, 63.0 (2xOCH_2), 126.6, 128.9, 129.2, 131.6, 132.4, 134.4, 134.5 (ArC and C=C), 175.7, 178.1 (2xC=O). ^{31}P NMR *δ*: 6.01 ppm. MS (EI) *m/z*: 406 (M^+, 4%), 269 (10), 233 (100), 176 (11). HRMS calculated for $C_{20}H_{27}N_2O_5P$: 406.1658; found: 406.1654.

4.2.13. Diethyl [(3aSR,4RS,7aSR)-2-methyl-6-(4-methylpent-3-en-1-yl]-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl)phosphoramidate (***3m***): Yelow sticky oil, (240 mg, 60% yield), IR (neat) ν_{max}: 1700, 1500, 1382, cm^{-1}. ^{1}H NMR δ: 1.34 (t, *J* = 7.1 Hz, 6H, 2xCH_3CH_2O), 1.70 (s, 3H, CCH_3), 1.71 [s, 3H, $CH_2CH=C(CH_3)_2$], 1.73 [s, 3H, $CH_2CH=C(CH_3)_2$], 2.28 (br s, 1H, $CH_2CHCHC=O$), 2.44-2.53 (m, 1H, $CH_2CHCHC=O$), 2.70-2.80 (m, 1H, $CH_2CHCHC=O$), 2.89 (s, 3H, NCH_3), 3.15-3.17 (m, 2H, CH_2CHCHC=O, NHCHCHC=O), 3.88 (br s, 1H, NHCH), 4.04-4.18 (m, 4H, 2xCH_3CH_2O), 4.73-4.45 (m, 1H, NCHCH=), 5.22 (ddt, *J* = 7.8, 6.4, 1.4 Hz, 1H, $CH_2CH=C(CH_3)_2$), 5.52 (br s, 1H, NCHCH=C). ^{13}C NMR *δ*: 16.1, 16.3 (2xCH_3CH_2), 18.0 [$C(CH_3)_2$], 18.9 (CH_3C=CCH), 24.6 [$C(CH_3)_2$], 25.9 (NCH_3), 26.3 [$CH_2CH=C(CH_3)_2$], 39.9 (NCH), 41.9 (CCH_2CH_2CH), 44.8, 44.9 (2xCHCHC=O), 48.7 (NCHCHC=O), 62.5, 62.6 (2xOCH_2), 122.4, 127.4, 134.1, 139.4 (C=C), 177.3, 178.8 (2xC=O). ^{31}P NMR *δ*: 5.87 ppm. MS (EI) *m/z*: 398 (M^+, 10%), 329 (28), 261 (10), 245 (15), 230 (12), 207 (29), 193 (37), 154 (100), 126 (19), 98 (16), 81 (13), 41(12); HRMS calculated for $C_{19}H_{31}N_2O_5P$: 398,1971, found: 398.1991.

4.2.14. Diethyl [(3aSR,4RS,7aSR)-6-(4-methylpent-3-en-1-yl)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (***3n***): Pale brown sticky oil, (317 mg, 69% yield), IR (neat) ν_{max}: 1700, 1500, 1382, cm^{-1}. ^{1}H NMR δ: 1.34 (t, *J* = 7.1 Hz, 6H, 2xCH_3CH_2O), 1.70 (s, 3H, CCH_3), 1.74 [s, 3H, $CH_2CH=C(CH_3)_2$], 1.78 [s, 3H, $CH_2CH=C(CH_3)_2$], 2.39 (br s, 1H, $CH_2CHCHC=O$), 2.51 (dt, *J* = 14.0, 6.4 Hz, 1H, $CH_2CH=C$), 2.80 (dt, *J* = 15.0, 8.7 Hz, 1H, $CH_2CH=C$), 3.32-3.36 (m, 2H, CH_2CHCHC=O, NHCHCHC=O), 4.04-4.18 (m, 4H, 2xCH_3CH_2O), 4.41 (br s, 1H, NCHCH=), 5.24 [ddt, *J* = 7.8, 6.4, 1.4 Hz, 1H, $CH_2CH=C(CH_3)_2$], 5.64 (br s, 1H, NCHCH=C), 7.11-7.16 (m, 2H, ArH), 7.37-7.47 (m, 3H, ArH). ^{13}C NMR δ: 16.3, 16.4 (2xCH_3CH_2), 18.2, 19.1 [$C(CH_3)_2$], 26.0 (CH_3C=CCH), 26.3 [$CH_2CH=C(CH_3)_2$], 40.3 ($CH_2CHCHC=O$), 42.0 ($CH_2CHCHC=O$), 45.3 (NCHCHC=O), 49.1 (NHCH), 62.8, 62.9 (2xOCH_2), 122.4, 126.6, 127.7, 128.9, 129.3, 131.6, 134.4, 139.7 (ArC and C=C), 176.3, 178.0 (2xC=O). ^{31}P NMR *δ*: 5.88 ppm. MS (EI) *m/z*: 460 (M^+, 7%), 391 (18), 307 (15), 207 (40), 154 (100), 134 (15), 119 (18), 98 (15). HRMS calculated for $C_{24}H_{33}N_2O_5P$: 460.2127; found: 460.2124.

4.2.15. Diethyl [(3aSR,4RS,9bSR)-2-methyl-1,3-dioxo-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1H-benzo[e]isoindol-4-yl]phosphoramidate (***3o***): Pale brown sticky oil, (148 mg, 40 % yield), IR (neat) ν_{max}: 1692, 1433, 1283 cm^{-1}. ^{1}H NMR δ: 1.34 (t, *J* = 6.9 Hz, 6H, 2xCH_3CH_2O), 1.49-1.59 (m, 1H, $CHCH_2CH$), 2.63-2.71 (m, 2H, $CHCH_2CH_2CH_2$), 1.76-1.86 (m, 2H, $CHCH_2CH_2CH_2$), 2.04-2.17 (m, 2H, $CHCH_2CH_2CH_2$), 2.21-2.37 (m, 1H, $CHCH_2CH_2CH_2$), 2.90 (s, 3H, CH_3), 2.91-3.01 (m, 2H, CH=CCH_2CH_2), 3.09-3.15 (m, 1H, NCHCHC=O), 3.19-3.24 (m, 1H, CHCHC=O), 3.94 (br s, 1H, NHCH), 4.05-4.17 (m, 2xCH_2CH_3), 5.51 (s, 1H, NCHCH=C). ^{13}C NMR δ: 16.3 (2xCH_3CH_2), 21.5 ($CHCH_2CH$), 22.1 (CH3), 24.4 ($CHCH_2CH_2CH_2$), 24.7 ($CHCH_2CH_2CH_2$), 29.1 ($CHCH_2CH_2CH_2$), 36.26 (NHCH), 43.4 ($CHCH_2CH_2CH_2$), 45.1 (CHCHC=O), 48.1 (NCHCHC=O), 62.8 (2xOCH_2), 124.9 (CH=CCH_2CH_2), 141.5 (CH=CCH_2CH_2), 177.3, 179.1 (2xC=O). ^{31}P NMR *δ*: 5.89 ppm. MS (EI) *m/z*: 370 (M^+, 21%), 341 (10), 259 (41), 258 (21), 234 (15), 233 (100), 230 (26), 202 (11), 154 (16), 122 (14), 98 (11), 91 (19), 81 (11), 43 (11). HRMS calculated for $C_{17}H_{27}N_2O_5P$: 370.1658; found: 392.1656.

4.2.16. Diethyl [(3aSR,11RS,11aSR)-2-methyl-1,3-dioxo-2,3,3a,3b,4,5,11,11a-octahydro-1H-naphtho[2,1-e]isoindol-11-yl]phosphoramidate (***3p***): Pale brown sticky oil, (209 mg, 50 % yield), IR (neat) ν_{max}: 1691, 1435, 1239 cm^{-1}. ^{1}H NMR δ: 1.35 (t, *J* = 7.1 Hz, 6H, 2xCH_3CH_2O), 2.12-12.21 (m, 2H, $CHCH_2CH_2$), 2.57-2.64 (m, 1H, $CHCH_2CH_2$), 2.64-2.73 (m, 2H, NCHCHC=O), 2.76-2.82 (m, 2H, $CHCH_2CH_2$), 2.85 (s, 3H, CH_3), 3.23-3.27 (m, 1H, 1H, NHCH), 3.34-3.38 (m, 1H, CHCHC=O), 4.07-4.17 (m, 4H, 2xCH_2CH_3), 4.71 (br s, 1H,CHNH), 7.09-7.11 (m, 1H, ArH), 7.14-7.17 (m, 1H, ArH), 7.26 (s, 1H, ArH), 7.40-7.42 (m, 1H, ArH). ^{13}C NMR δ: 16.4 (2xCH_3CH_2), 24.4 (CH3), 24.9 (CCH_2CH_2CH), 30.0 (CCH_2CH_2CH), 36.5 (CCH_2CH_2CH), 43.2 (NHCH), 45.8 (CHCHC=O), 49.2 (NCHCHC=O), 62.9 (2xOCH_2), 123.7, 126.7, 127.9, 128.4, 132.9, 136.9, 138.3 (ArC and C=C), 176.8,179.0 (2xC=O). ^{31}P NMR *δ*: 6.05 ppm. MS (EI) *m/z*: 418

(M^+, 44%), 389 (42), 282 (20), 281 (100), 196 (15), 179 (11), 168 (12), 154 (25), 153 (23), 152 (10). HRMS calculated for $C_{21}H_{27}N_2O_5P$: 418,1658; found: 418.1663.

4.2.17. Diethyl {(3aS,4R,7aS)-1,3-dioxo-2-[(R)-1-phenylethyl]-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl}phosphoramidate ***(3q)***: Pale brown sticky oil, (82.4 mg, 51.72% yield). $[\alpha]_D^{24}$ = +41.26 (*c* 0.6, $CHCl_3$). IR (neat) ν_{max}: 1690, 1392, 1226, 1024 cm^{-1}. ^1H NMR δ: 1.25 (t, *J* = 7.1 Hz, 6H, 2xCH_3CH_2O), 1.65 (d, *J* = 7.3 Hz, 3H, $CHCH_3$), 1.95-2.12 (m, 1H, $CHCH_2CH$), 2.49-2.63 (m, 1H, $CHCH_2CH$), 3.02 (m, 1H, CH_2CHC=O), 3.12 (dt, *J* = 8.9, 5.5 Hz, 1H, NCHC*H*C=O), 3.86 (br s, 1H, CHN*H*), 4.01 (m, 4H, 2xCH_2CH_3), 4.49 (dt, *J* = 8.5, 10.9 Hz, 1H, NC*H*CH=), 5.28 (q, *J* = 7.3 Hz, 1H, $NCHCH_3$) 5.62-6.86 (m, 2H, C*H*=C*H*), 7.18-7.20 (m, 2H, Ar*H*), 7.21-7.26 (m, 3H, Ar*H*). ^{13}C NMR δ: 16.2, 16.3 (2xCH_3CH_2), 16.6 (CH_3CH), 24.4 ($CHCH_2CH$), 38.9 (CH_2CHC=O), 43.8 (NH*C*H), 48.3 (NCH*C*HC=O), 50.2 (CH_3CH), 62.7, 62.8 (2xOCH_2), 126.6, 127.1, 127.7, 128.3, 135.0, 139.0, 139.2 (Ar*C* and *C*=*C*), 178.8, 179.1 (2x*C*=O). ^{31}P NMR *δ*: 5.84 ppm. MS (EI) *m/z*: 406 (M^+, 35%), 269 (17), 206 (10), 205 (100), 176 (17), 174 (14), 165 (20), 154 (12), 148 (19), 138 (12), 105 (47), 103 (11), 94 (11), 79 (16), 77 (23), 68 (45). HRMS calculated for $C_{20}H_{27}N_2O_5P$: 406.1658; found: 406.1660.

Acknowledgements

We gratefully acknowledge financial support from the Spanish Ministerio de Economía y Competitividad (MINECO), Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER, EU) (Project Nos. CTQ2013-43446-P, CTQ2014-51912-REDC, CTQ2016-76782-P, CTQ2016-81797-REDC, CTQ2016-81893REDT, and CTQ2016-76155-R), the Generalitat Valenciana (PROMETEOII/2014/017) and the University of Alicante.

Annex 3

Notes and references

1. J.J. Petkowski, W. Bains, S. Seager, Molecules 24 (2019) 866.
2. F.M. Oliveira, L.C.A. Barbosa, F.M.D. Ismail, RSC Adv. 4 (2014) 18998.
3. E. De Clercq, J. Med. Chem. 59 (2016) 2301.
4. N. Kleczewska, P. Ruszkowski, A. Singh, R. Trznadel, L. Celewicz, Nucleosides, Nucleotides and Nucleic Acids doi.org/10.1080/15257770.2019.1594282.
5. C.P. Coyne, L. Narayanan, J. Pharm. Invest. 49 (2019) 173.
6. L.-L. Dai, D.-D. Li, X.-M. Zhao, S. Zhi, H.-S. Shen, Z.-B. Yang, J. Heterocyclic Chem. 56 (2019) 417.
7. R.A. Vere Hodge, Antiviral Res. 137 (2017) 23.
8. U.S. Singh, V.A. Mulamoottil, C. K. Chu, J. Org. Chem. 84 (2019) 752.
9. G. Wang, N. Dyatkina, M. Prhavc, C. Williams, V. Serebryany, Y. Hu, Y. Huang, J. Wan, X. Wu, J. Deval, A. Fung, Z. Jin, H. Tan, K. Shaw, H. Kang, Q. Zhang, Y. Tam, A. Stoycheva, A. Jekle, D. B. Smith, L. Beigelman, J. Med. Chem. 62 (2019) 4555.
10. J.Y. Feng, T. Wang, Y. Park, D. Babusis, G. Birkus, Y. Xu, C. Voitenleitner, M. Fenaux, H. Yang, S. Eng, N. Tirunagari, T. Kirschberg, A. Cho, A.S. Raya, Antimicrob. Agents Chemother. 62 (2018) e00620-18. doi: 10.1128/AAC.00620-18.
11. H. Jung, S.H. Shin, J.-M. Kee, ChemBioChem 20 (2019) 623.
12. M. Maiti, M. Maiti, J. Rozenski, S. De Jonghe, P. Herdewijn, Org. Biomol. Chem. 13 (2015) 5158.
13. A.H. El-Sagheer, T. Brown, Chem. Commun. 53 (2017) 10700.
14. Q. Li, X. Sun, X. Yang, M. Wu, S. Suna, X. Chen, RSC Adv. 9 (2019) 16040.
15. For the iridium-catalyzed CH activation-amination from phosphoryl azides, see: H. Kim, J. Park, J.G. Kim, S. Chang, Org. Lett. 16 (2014) 5466.
16. S.S. Le Corre, M. Berchel, T. Le Gall, J.-P. Haelters, P. Lehn, T. Montier, P.-A. Jaffrès, Eur. J. Org. Chem. (2014) 8041.
17. J. Dhineshkumar, K.R. Prabhu, Org. Lett. 15 (2013) 6062.
18. (a) B.A. Dar, J. Indust. Engin. Chem. 36 (2016) 194. (b) N.A. Dangroo, A.A. Dar, R. Shankar, M.A. Khuroo, P.L. Sangwan, Tetrahedron Lett. 57 (2016) 2717.
19. (a) J. Shi, L. Zhou, H. Zhang, T. R. McBrayer, M. A. Detorio, M.Johns, L. Bassit, M H. Powdrill, T. Whitake, S. J. Coats, M. Götte, R. F. Schinazi, Bioorg. Med. Chem. Lett. 21 (2011) 7094. (b) P. Nauš, O. Caletková, P. Perlíková, L.P. Slavetínská, E. Tlouštová, J. Hodek, J. Weber, P. Dzubák, M. Hajdúch, M. Hocek, Bioorg. Med. Chem. 23 (2015) 7422. (c) A. Cho, L. Zhang, J. Xu, R. Lee, T. Butler, S. Metobo, V. Aktoudianakis, W. Lew, H. Ye, M. Clarke, E. Doerffler, D. Byun, T. Wang, D. Babusis, A.C. Carey, P. German, D. Sauer, W. Zhong, S. Rossi, M. Fenaux, J.G. McHutchison, J. Perry, J. Feng, A.S. Ray, C.U. Kim, J. Med. Chem. 57 (2014) 1812. (d) B.S. Ross, P.G. Reddy, H.-R. Zhang, S. Rachakonda, M.J. Sofia, J. Org. Chem. 76 (2011) 8311. (e) J.H. Cho, S.J. Coats, R.F. Schinazi, Org. Lett. 14 (2012) 2488.
20. (a) S.S. Le Corre, M. Berchel, H. Couthon-Gourvès, J.-P. Haelters, P.-A. Jaffrès, Beilstein J. Org. Chem. 10 (2014) 1166. (b) J. Bertran-Vicente, M. Schümann, P. Schmieder, E. Krause, C.P.R. Hackenberger, Org. Biomol. Chem. 13 (2015) 6839. (c) V.I. Krutikov, A.V. Erkin, V.V. Krutikova, Russ. J. Gen. Chem. 82 (2012) 822. (d) N.F. Zakirova, A.V. Shipitsyn, Russ. Chem. Bull., Int. Ed. 64 (2015) 2167.
21. M. Meazza, A. Kowalczuk, L. Shirley, J.W. Yang, H. Guo, R. Rios, Adv. Synth. Catal. 358 (2016) 719.
22. (a) H. Neumann, A.J. von Wangelin, D. Gördes, A. Spannenberg, M. Beller, J. Am. Chem. Soc. 123 (2001) 8398. (b) A.J. von Wangelin, H. Neumann, D. Gördes, A. Spannenberg, M. Beller, Org. Lett. 3 (2001) 2895.

23. (a) H. Neumann, A.J. von Wangelin, D. Gördes, A. Spannenberg, W. Baumann, M. Beller, Tetrahedron 58 (2002) 2381. (b) A.J. von Wangelin, H. Neumann, D. Gördes, S. Klaus, D. Strübing, M. Beller, Chem. Eur. J. 9 (2003) 4286. (c) H. Neumann, A.J. von Wangelin, S. Klaus, D. Strübing, D. Gördes, M. Beller, Angew. Chem. Int. Ed. 42 (2003) 4503. (d) S. Klaus, S. Hübner, H. Neumann, D. Strübing, A.J. von Wangelin, D. Gördes, M. Beller, Adv. Synth. Catal. 346 (2004) 970. (e) D. Strübing, H. Neumann, S. Klaus, S. Hübner, M. Beller, Tetrahedron 61 (2005) 11333.
24. (a) S. Hübner, H. Jiao, D. Michalik, H. Neumann, S. Klaus, D. Strübing, A. Spannenberg, M. Beller, Chem. Asian J. 2 (2007) 720. (b) S. Hübner, D. Michalik, H. Jiao, H. Neumann, S. Klaus, D. Strübing, A. Spannenberg, M. Beller, Chem. Asian J. 2 (2007) 734. (c) S. Hübner, H. Neumann, D. Michalik, S. Klaus, D. Strübing, A. Spannenberg, A.J. von Wangelin, M. Beller, Synlett 7 (2007) 1085.
25. V. Selva, I. Chabour, C. Nájera, J.M. Sansano, Tetrahedron 75 (2019) 1315.
26. For other examples dealing with this AAD reaction, see: (a) A.K. Weber, J. Schachtner, R. Fichtler, T.M. Leermann, J.M. Neudörfl, A.J. von Wangelin, Org. Biomol. Chem. 12 (2014) 5267. (b) S.M. Tan, A.C. Willis, M.N. Paddon-Row, M.S. Sherburn, Angew. Chem. Int. Ed. 55 (2016) 3081.
27. M. Sukopp, R. Schwab, L. Marinelli, E. Biron, M. Heller, E. Várkondi, Á. Pap, E. Novellino, G. Kéri, H. Kessler, J. Med. Chem. 48 (2005) 2916.
28. H. Neumann, D. Strübing, M. Lalk, S. Klaus, S. Hübner, A. Spannenberg, U. Lindequist, M. Beller, Org. Biomol. Chem. 4 (2006) 1365.
29. These maleimides were used in the preparation of precursors of thrombin inhibitors. (a) J. Olsen, P. Seiler, B. Wagner, H.T. Fischer, U. Obst-Sander, T. Tschopp, D.W. Banner, M. Kansy, K. Müller, F. Diederich, Org. Biomol. Chem. 2 (2004) 1339. (b) E. Schweizer, A. Hoffmann-Röder, K. Schärer, J.A. Olsen, C. Fäh, P. Seiler, U. Obst-Sander, B. Wagner, M. Kansy, F. Diederich, ChemMedChem 1 (2006) 611. (c) V. Selva, E. Selva, P. Merino, C. Nájera, J.M. Sansano, Org. Lett. 20 (2018) 3522.
30. L. Naesborg, K.S. Halskov, F. Tur, S.M.N. Monsted, K.A. Jørgensen, Angew. Chem. Int. Ed. 54 (2015) 10193.
31. S. Gobi, E. Vass, G. Magyarfalvi, G. Tarczay, Phys. Chem. Chem. Phys. 13 (2011) 13972.
32. (a) T. Jaetsch, W. Hallenbach, T. Himmler, K.-D. Bremm, R. Endermann, F. Pirro, M. Stegemann, H.-G. Wetzstein, Ger. Offen. (1996), DE 4431122 A1 19960307. (b) W. Hallenbach, T. Himmler, T. Jaetsch, B. Mielke, K.-D. Bremm, R. Endermann, F. Pirro, M. Stegemann, H.-G. Wetzstein, Ger. Offen. (1996), DE 4424369 A1 19960118. (c) T. Jaetsch, W. Hallenbach, T. Himmler, B. Mielke, K.-D. Bremm, R. Endermann, F. Pirro, Franz; M. Stegemann, H.-G. Wetzstein, Eur. Pat. Appl. (1995), EP 684244 A1 19951129. (d) U. Petersen, T. Himmler, T. Schenke, A. Krebs, K. Grohe, K.-D. Bremm, K.G. Metzger, R. Endermann, H.J. Zeiler, U.S. (1995), US 5468742 A 19951121 and previous assignee patents of Bayer A.-G., Germany (1992-1996).
33. B.-J. Li, R.D. Simard, A.M. Beauchemin, Chem. Commun. 53 (2017) 8667.
34 This amine was also impossible to obtain/characterize in ref. 25 despite of multiple attempts.

SECCIÓN 3: CONCLUSIONES

CONCLUSIONES

Al término de esta tesis doctoral y tras la discusión de resultados obtenidos se puede concluir que:

En el **Capítulo 1**, la modulación del catalizador quiral **14**·Ag-(*R*)-**17** se ha adaptado al enfoque efectivo de la reacción entre el iminoéster y acrilato de *terc*-butilo para acceder al núcleo enriquecido enantioméricamente del agente antiviral GSK 625433 por primera vez. La presencia del catalizador quiral dual fue muy importante para lograr una alta enantioselección. En el caso de los iminoésteres de glicina, ambos catalizadores (el citado anteriormente y el **14**·$AgClO_4$) exhibieron comportamientos similares en la cicloadición enantioselectiva 1,3-dipolar con dipolarófilos, aunque para iminoésteres estéricamente impedidos (derivados de aminoácidos α-sustituidos), el complejo **14**·$AgClO_4$ es el más apropiado.

En el **Capítulo 2**, la preparación de *N*-bencil- y *N*-PMB-cyclohex-2-eneamines se ha sido optimizado eficazmente. Muchos aldehídos y maleimidas se pueden combinar con bencilamina o 4-metoxibencilamina en un proceso multicomponente diastereoselectivo, a saber, amina-aldehído-dienófilo (AAD). Los rendimientos químicos son moderados a buenos y permiten generar una configuración relativa totalmente *cis* en los productos finales resultantes. La introducción de una información quiral en el grupo bencílico de la amina bencílica o en el sustituyente del átomo de nitrógeno de la maleimida dio también compuestos enriquecidos enantioméricamente después de la separación y aislamiento por cromatografía de columna. La configuración absoluta fue determinada por espectroscopía VCD.

Y en el **Capítulo 3**, se consiguió un enfoque novedoso para la preparación de fosforamidatos polisustituidos, derivados de ciclohex-2-eneaminas, basado en una reacción multicomponente fosforamidato de dietilo-aldehído-dienófilo El proceso (PAD) ha sido optimizado. Las maleimidas y los aldehídos conjugados que incorporan un átomo de hidrógeno en la posición γ son los componentes apropiados para ejecutar esta reacción con altos rendimientos. La alta diastereoselectividad lograda es un aspecto notable de esta transformación que genera una configuración relativa todo-*cis* en los productos finales resultantes. La introducción de información quiral en el sustituyente del átomo de nitrógeno de la maleimida dio lugar a un cyloaducto enriquecido enantioméricamente. Análogamente, la configuración absoluta se determinó mediante espectroscopía VCD. Estos fosforamidatos finales son compuestos potencialmente bioactivos y también se demostró que su hidrólisis es factible produciendo interesantes intermedios sintéticos para la construcción de sistemas más complejos.

LIST OF ABBREVIATIONS

LIST OF ABBREVIATIONS

1,3-DC	1,3-dipolar cycloaddition
^{1}H NMR	Proton nuclear magnetic resonance
^{13}C NMR	Carbon nuclear magnetic resonance
^{19} F NMR	Fluor nuclear magnetic resonance
^{31}P NMR	Phosphor nuclear magnetic resonance
AAD	Amide/amine-aldehyde-dienophile
AC_2O	Acetic anhydride
ALAD	Alcohols (orthoesters)- aldehyde-dienophile
ANAD	Carboxylic acid anhydrides-aldehyde-dienophile
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphtyl
Bn	Benzyl group
Boc	*N-tert*-butoxycarbonyl protecting group
br s	Broad singlet/signal.
cat.	Catalyst
CMV	Cytomegalovirus
conv	Conversion
DABCO	1,4-diazabicyclo [2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEPT	Distortionless Enhancement by Polarization Transfer
DF	Disoproxil fumarate.
DIPEA	Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic Acid.
dr	Diastereomeric ratio
EDG	Electron-donating group
ee	Enantiomeric excess

eq	Equivalents
equiv.	Equivalents
EWG	Electron-withdrawing group
FMOT	Frontier molecular orbital theory
FOXAP	Ferrocenyl oxazolinylphosphine
GSK	GlaxoSmithKline
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HOMO	Highest energy occupied molecular orbit
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
*i*Bu	Isbutyl
IED	Inverted-electron demand
IAD	Isocyanate Aldehyde Dienophile
*i*Pr	Isopropyl
IR	Infrared
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
LUMO	Lowest energy unoccupied molecular orbit
m	Multiplet
MCRs	Multicomponent reactions
mp	Melting point
MsCl	Methanesulfonyl chloride
NBM	*N*-benzylmaleimide
NED	Normal electrons demand
NMM	*N*-methylmaleimide
NMP	*N*-methyl-2-pyrrolidone
NPM	*N*-phenylmaleimide
nOe	Nuclear Overhauser effect
OPCs	Organophosphorus compounds

o-	*ortho*-substitution
p-	*para*-substitution
p-TsOH	*para*-toluenesulfonic acid
PAD	Phosphoramidate-aldehyde-dienophile
PGA	Polyglycolic acid
$PMBNH_2$	P-methoxybenzylamine
q	Quartet
QTOF	Quadrupole time-of-flight mass spectrometer
rDA	Retro-Diels-Alder
RNA	Ribonucleic acid
rt	Room temperature
s	Singlet
t	Time and also triplet
T	Temperature
TBAF	Tetrabutylammonium fluoride
TBDMS	*Tert*-Bytyldimethylsilyl ether
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Ttrimethylsilyl group and also tetramethylsilane
TMSCl	Trimethylsilyl chloride
TSA	Trichostatin A
TSOH	p-Toluenesulfonic acid
UV	Ultraviolet
VCD	Vibrational circular dichroism
VIH	Human immunodeficiency virus

BIOGRAPHY

BIOGRAPHY

I was born in Collo-Algeria on March 27th, 1990.

I took my Primary School studies at “Godban lkhmisi”, my middle School at “Aarbaoui Ali” and my High School studies at “Massinissa” Constantine - Algeria.

I obtained my undergraduate degree in organic chemistry at the Faculty of Science of the University of the Brothers Mentouri Constantine 1 (UFMC 1), where I obtained my diploma in 2013. And in 2015 I obtained my diploma of Master 2 in chemistry in the speciality of Bioactive Molecules in the same University, in the following years I did a Master 1 in chemistry at the University of Paris-Est Créteil (UPEC) and the University Paris-Est Marne-la-Valley (UPEM).

In September 2016, I joined the Department of Organic Chemistry at the University of Alicante and I started my doctorate at the Institute of Organic Synthesis at the University of Alicante under the supervision of Professor Carmen Nájera and the Professor José Miguel Sansano. During these years of research, and thanks to a scholarship to stay abroad from the University of Alicante, I moved to Paris, France From November 2019 to February 2020. At that time, I was involved in research under the supervision of Professor Geraldine Masson.

TOTAL NUMBER OF PUBLICATIONS

1. *"4-Amino-1,2,4-triazoles and 1,3,4-oxadiazoles·palladium(II) recoverable complexes as catalysts in the sustainable Suzuki-Miyaura cross-coupling reaction"*
   Chehrouri, M.; Moreno-Cabrerizo, C.; Othman, A. A.; Chabour, I.; Ferrádiz-Saperas, M.; Sempere, I.; Ali Döndaş, H.; de Garcia Retamosa, M.; Sansano, J. M. *J. Organomet. Chem.* **2020** accepted, in press.

2. "*Diastereoselective multicomponent phosphoramidate aldehydedienophile (PAD) process for the synthesis of polysubstituted cyclohex-2-enyl-amine derivatives*".
   Chabour, I.; Nájera, C.; & Sansano, J. M. *Tetrahedron* **2020**, *76*, 130801.

3. "*Diastereoselective multicomponent Amine-Aldehyde-Dienophile (AAD) process for the synthesis of polysubstituted cyclohex-2-enylamines*".
   Selva, V.; Chabour, I.; Nájera, C.; Sansano, J. M. *Tetrahedron* **2019**, *75*. 1315-1321.

4. "*Dual chiral silver catalyst in the synthetic approach to the core of hepatitis C virus inhibitor GSK 625433 using enantioselective 1,3-dipolar cycloaddition of azomethine ylides and electrophilic alkenes*".
   Chabour, I.; Castelló, L. M.; Mancebo-Aracil, J.; Martín-Rodríguez, M.; Retamosa, M. d. G.; Nájera, C.; Sansano, J. M. *Tetrahedron Asymmetry* **2017**, *28,* 1423–1429.

5. "*LiCl-mediated, easy and low-cost removal of the trityl group from protected alcohols and diols*".

Behloul, C.; Chouti, A.; Chabour, I.; Bengliz Bey, H.; Guijarro, D.; Foubelo, F.; Yus, M. *Tetrahedron Lett.,* **2016***, 57,* 3526–3528.