UNIVERSIDAD COMPLUTENSE DE MADRID

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TESIS DOCTORAL

Desarrollo de nuevos procesos de ciclación

MEMORIA PARA OPTAR AL GRADO DE DOCTORA

PRESENTADA POR

Alexandra Rodríguez Rivero

DIRECTORES

Miguel Ángel Sierra Rodríguez
Israel Fernández López

Madrid, 2017

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DESARROLLO DE NUEVOS PROCESOS DE CICLACIÓN

TESIS DOCTORAL

ALEXANDRA RODRÍGUEZ RIVERO

Madrid, 2016

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Memoria que para optar al grado de
DOCTOR EN CIENCIAS QUÍMICAS

presenta

ALEXANDRA RODRÍGUEZ RIVERO

Directores
Miguel Ángel Sierra Rodríguez
Israel Fernández López

Madrid, 2016

Miguel Ángel Sierra Rodríguez, Catedrático de Química Orgánica de la Facultad de Ciencias Químicas de la Universidad Complutense de Madrid e **Israel Fernández López**, Profesor Contratado Doctor en el Departamento de Química Orgánica de la Facultad de Ciencias Químicas de la Universidad Complutense de Madrid,

CERTIFICAN:

Que la presente Memoria, titulada: **DESARROLLO DE NUEVOS PROCESOS DE CICLACIÓN**, se ha realizado bajo su dirección en el Departamento de Química Orgánica I de la Facultad de Ciencias Químicas de la Universidad Complutense de Madrid por la Licenciada en Química **Alexandra Rodríguez Rivero**, y autorizan su presentación para ser calificada como Tesis Doctoral.

Madrid, 6 de Mayo de 2016

Fdo. Miguel A. Sierra Rodríguez Fdo. Israel Fernández López

El trabajo recogido en esta Memoria se ha realizado en el Departamento de Química Orgánica de la Facultad de Ciencias Químicas de la Universidad Complutense de Madrid, bajo la dirección del Dr. Miguel Ángel Sierra Rodríguez y del Dr. Israel Fernández López. La financiación que ha permitido llevarlo a cabo procede de los proyectos del Ministerio de Ciencia e Innovación (CTQ2010-20714-C0-01-BQU), Ministerio de Economía y Competitividad (CTQ2013-46459-C2-1-P), MEC-Consolider-Ingenio (2010-CSD2007-00006) y la Comunidad Autónoma de Madrid (CAM-S2009/PPQ-1634). Asimismo, agradezco al Ministerio de Educación, Cultura y Deporte la concesión de una Beca FPU (Formación de Profesorado Universitario, Ref: AP-2010-0802).

A mis padres

A mi bisabuela

“En la vida no hay nada que temer, sólo hay que comprender”

Marie Curie

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PUBLICACIONES

Los resultados aquí presentados se encuentran recogidos en las siguientes publicaciones:

"Regioselective and Stepwise [8+2]-Cycloaddition Reaction between Alkynyl–Fischer Carbene Complexes and Tropothione"

Alexandra R. Rivero, Israel Fernández, Miguel A. Sierra. *J. Org. Chem.* **2012**, *77*, 6648–6652.

"Regio- and Diastereoselective Stepwise [8+3]-Cycloaddition Reaction between Tropone Derivatives and Donor–Acceptor Cyclopropanes"

Alexandra R. Rivero, Israel Fernández, Miguel A. Sierra. *Org. Lett.* **2013**, *15*, 4928–4931.

"The Photochemical Reaction of Vinylaziridines and Vinylazetidines with Chromium(0) and Molybdenum(0) (Fischer) Carbene Complexes"

Alexandra R. Rivero, Israel Fernández, Miguel A. Sierra. *Chem. Eur. J*. **2014**, *20*, 1359–1366.

"Synthesis of Oxaspiranic Compounds Through [3+2]-Annulation of Cyclopropenones and Donor-Acceptor Cyclopropanes"

Alexandra R. Rivero, Israel Fernández, Carmen Ramírez de Arellano, Miguel A. Sierra. *J. Org. Chem.* **2015**, *80*, 1207-1213.

La presente memoria de la Tesis Doctoral se ha escrito siguiendo el formato de publicaciones. Incluye, además de un resumen en inglés y en español del trabajo, una introducción general sobre el estado actual del área de investigación en la que se enmarca el trabajo y una discusión integradora de los resultados obtenidos. Los dos capítulos principales se han subdividido según las distintas publicaciones. Los capítulos publicados conservan su formato original en inglés. Sin embargo, la introducción, objetivos, discusión y conclusiones se han escrito en castellano de acuerdo a la normativa para este formato de tesis.

Con el fin de respetar al máximo las diferentes publicaciones que componen esta memoria, se han mantenido la bibliografía y numeración original de las mismas, cambiando únicamente su formato a fin de homogeneizar toda la información contenida en la presente tesis.

La tesis adjunta un CD en el que se han incluido todas las coordenadas cartesianas y energías totales de todos los puntos estacionarios mencionados en esta memoria, obtenidos mediante cálculos computacionales. El CD incluye también una recopilación de espectros de resonancia magnética nuclear de todos los compuestos no descritos previamente sintetizados a lo largo de este trabajo, y un archivo .pdf con la memoria completa.

ABREVIATURAS UTILIZADAS EN ESTA MEMORIA

A: Aceptor/Acceptor

AICD: Anisotropy of the induced current density

A.L.: Ácido de Lewis

anh.: Anhidro

ATR: Attenuated total reflectance

Cuant./quant.: cuantitativo/quantitative

D: Dador/donor

DACs: Donor-acceptor cyclopropanes

DCM: Diclorometano

DFT: Density functional theory

DMF: Dimetilformamida

EI: Electronic impact

ESI: Ionización por electroespray

Fc: Ferrocenilo

Ft/Phth: Ftalimida/phthalimide

HRMS: High resolution mass spectrometry

INT: Intermediate

IR: Infrarrojo

M: Mayoritario

m: Minoritario

NICS: Nuclear independent chemical shift

Oct: Octyl

PMP: *para*-$MeOC_6H_4$

t.a./r.t.: Temperatura ambiente/room temperature

TBS: *terc*-Butildimetilsililo

THF: Tetrahidrofurano

TLC: Thin layer chromatography

TS: Transition state

UV: Ultravioleta

ÍNDICE

RESUMEN

DESARROLLO DE NUEVOS PROCESOS DE CICLACIÓN

Introducción

Las reacciones de cicloadición y ciclación constituyen una de las herramientas más ampliamente empleada en síntesis debido a su capacidad para aumentar la complejidad molecular en una única etapa sintética.[1]

En esta tesis doctoral se desarrollan y estudian nuevos procesos de cicloadición y ciclación con sustratos cuyas características estructurales y electrónicas les confieren las propiedades idóneas para su empleo en este tipo de reacciones: ciclopropanos dador-aceptor (D-A) y complejos metal-carbeno de tipo Fischer.

Objetivos y Resultados

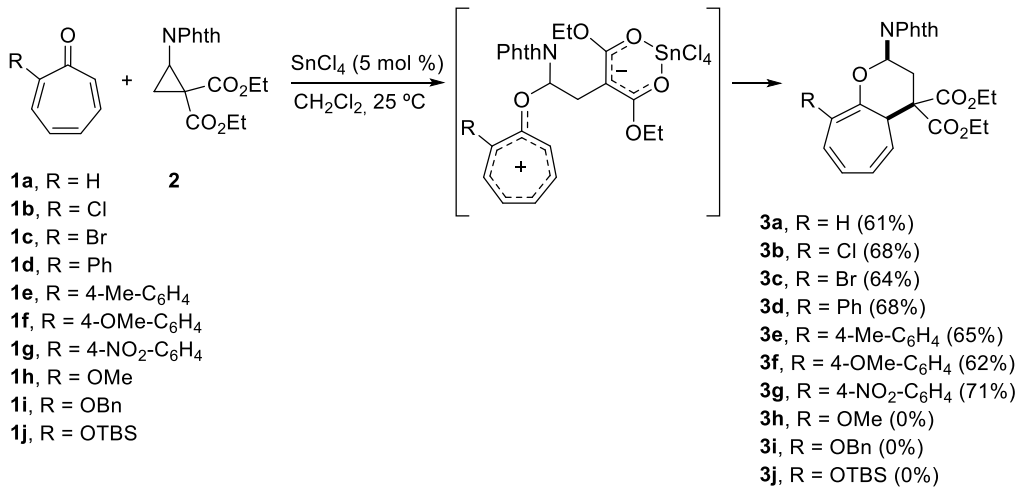
Capítulo 1: El empleo de ciclopropanos D-A para la síntesis directa de anillos carbo- y heterocíclicos mediante reacciones de ciclación [3+2], [3+3] o [4+3] se ha estudiado ampliamente.[2] Sin embargo, el uso de estos ciclopropanos D-A en reacciones de ciclación de alto orden ha sido muy poco explorado.[3] Por ello, el primer objetivo de este capítulo es estudiar la reacción de cicloadición [8+3] entre ciclopropanos D-A y derivados de tropona.

Esta transformación, catalizada por $SnCl_4$, da lugar a derivados de tetrahidrociclohepta[*b*]piranos con completa regio- y diasteroselectividad (Esquema 1). De acuerdo a cálculos computacionales, esta reacción transcurre por pasos a través de un intermedio zwitteriónico a partir del cual se produce el cierre del anillo, etapa que controla la regio- y diastereoselectividad del proceso, dando lugar a los correspondientes cicloaductos [8+3].

1 (a) *Cycloaddition Reactions in Organics Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, **2001**. (b) *Pericyclic Reactions-A Textbook: Reactions, Applications and Theory*; Sankararaman, S., Eds.; Wiley-VCH: Weinheim, **2005**.

2 (a) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev*. **2009**, *38*, 3051. (b) Mel'nikov, M. Y.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V. *Mendeleev Commun*. **2011**, *21*, 293. (c) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, *53,* 5504.

3 (a) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Angew. Chem. Int. Ed*. **2008**, *47*, 1107. (b) Xu, H.; Hu, J.-L.; Wang, L.; Liao, S.; Tang, Y. *J. Am. Chem. Soc*. **2015**, *137*, 8006. (c) Garve, L. K. B.; Pawliczek, M.; Wallbaum, J.; Jones, P. G.; Werz, D. B. *Chem. Eur. J*. **2016**, *22*, 521.



Esquema 1. Reacciones de ciclación [8+3].

Motivados por estos resultados, nos propusimos explorar la reacción entre ciclopropanos D-A y ciclopropenonas como ruta directa de acceso a compuestos espirocíclicos ya que, a pesar de su interés,[4] su síntesis resulta complicada mediante procedimientos habituales en química orgánica.[5]

Así pues, en la segunda parte del capítulo se desarrolla un método general y eficiente para la síntesis directa de compuestos oxaespiránicos mediante la reacción de anulación [3+2], catalizada por $Sc(OTf)_3$, entre ciclopropenonas y ciclopropanos D-A (Tabla 1). Los estudios teóricos sugieren que el proceso sigue un mecanismo de reacción por pasos y que la formación exclusiva de productos correspondientes a una anulación [3+2] frente a aquellos derivados de una ciclación [3+3] está favorecida tanto cinética como termodinámicamente.

4 (a) Bercovic , G.; Krongauz, V.; Weiss, V. *Chem. Rev*. **2000**, *100*, 1741. (b) Marson, C. M. *Chem. Soc. Rev*. **2011**, *40*, 5514. (c) Zheng, Y.; Tice, C. M.; Singh, S. B. *Bioorg. Med. Chem. Lett*. **2014**, *24*, 3673.

5 (a) Ríos, R. *Chem. Soc. Rev*. **2012**, *41*, 1060. (b) Ramazanov, I. R.; Yaroslavova, A. V.; Dzhemilev, U. M. *Russ. Chem. Rev*. **2012**, *81*, 700. (c) Undheim, K. *Synthesis* **2014**, *26*, 1957.

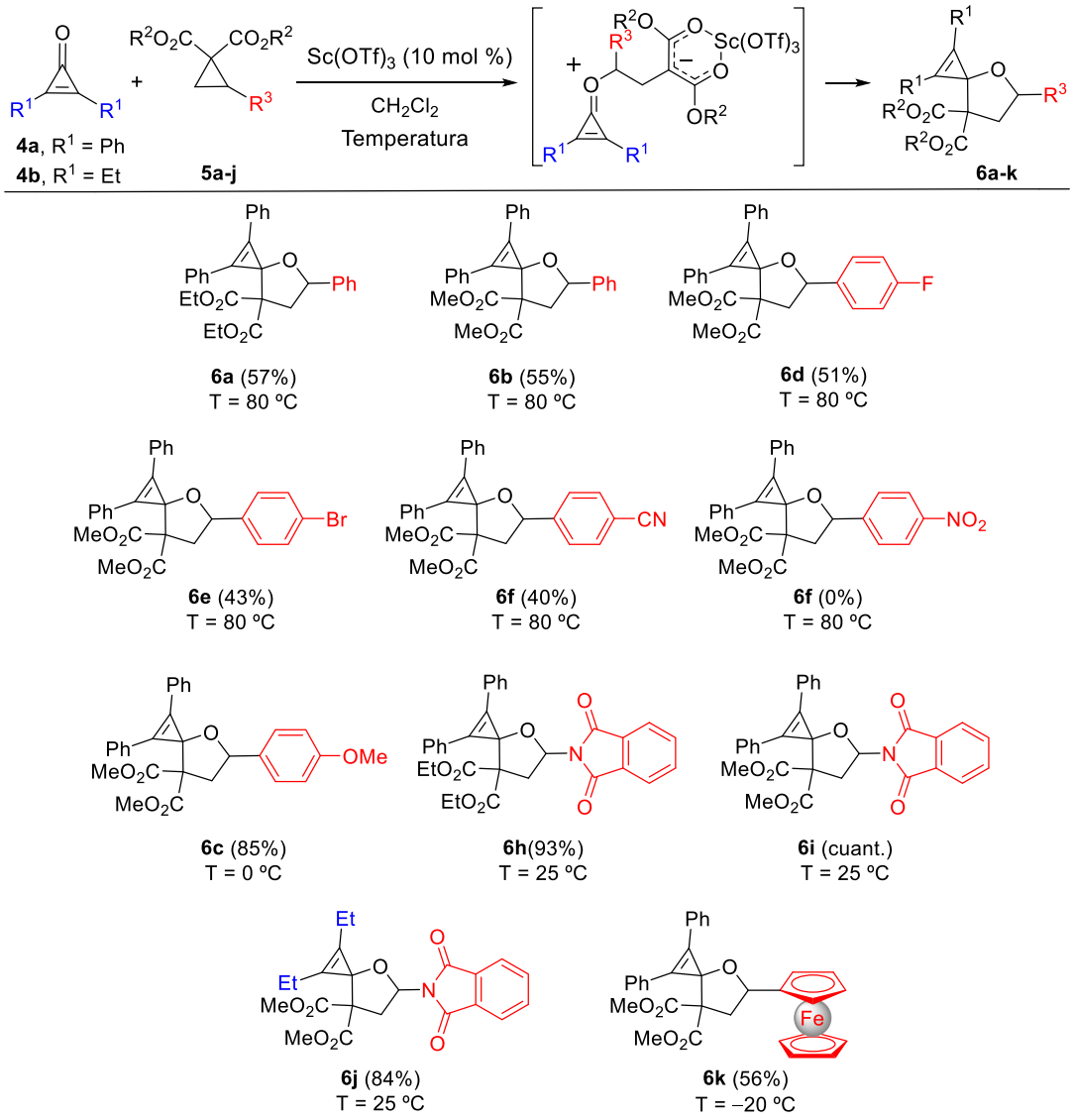


Tabla 1. Reacciones de ciclación [3+2].

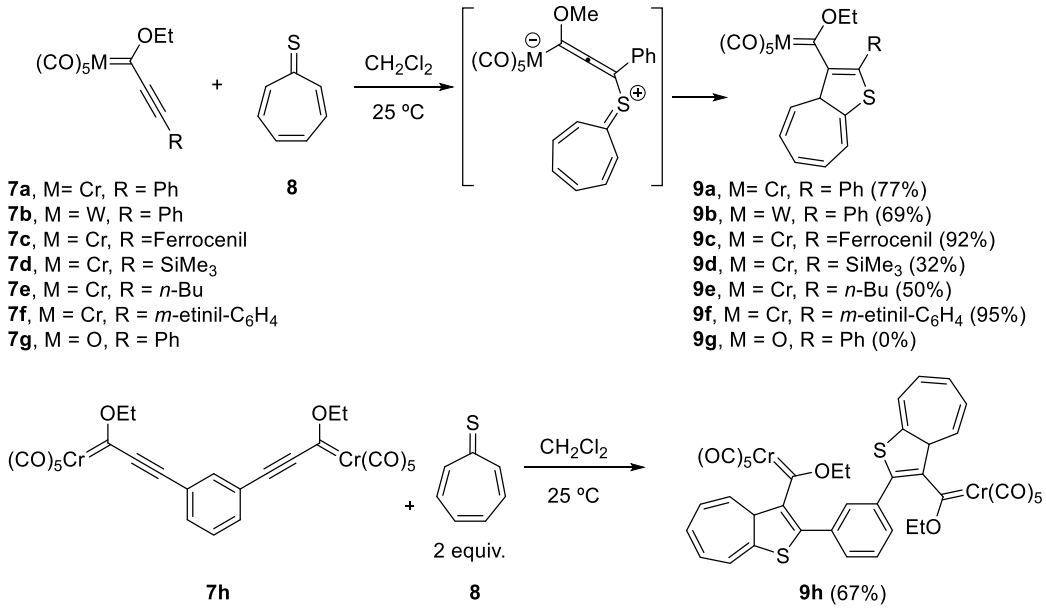
Capítulo 2: Los complejos metal-carbeno de tipo Fischer experimentan procesos de cicloadición altamente regioselectivos en condiciones de reacción suaves.[6] Por ello, se han empleado profusamente en síntesis.[7] Sin embargo, las reacciones de cicloadición de alto orden de estos complejos han sido mucho menos exploradas.[8] Por este motivo, el objetivo del segundo capítulo es el estudio de reacciones de cicloadición de alto orden que involucran a este tipo de complejos organometálicos.

6 (a) Dötz, K. H.; Stendel, J. *Chem. Rev*. **2009**, *109*, 3227. (b) Herndon, J. W. *Coord. Chem. Rev*. **2010**, *254*, 103. (c) Fernández, I.; Cossío, F. P.; Sierra, M. A. *Acc. Chem. Res.* **2011**, *44*, 479.

7 (a) Barluenga, J.; Rodríguez, F.; Fañanás, F. J.; Flórez, J. *Top. Organomet. Chem.* **2004**, *13*, 59. (b) Fernández, I.; Sierra, M. A.; *Top. Heterocycl. Chem*. **2013**, *30*, 65. (c) Raubenheimer, H. G. Dalton Trans., **2014**, *43*, 16959.

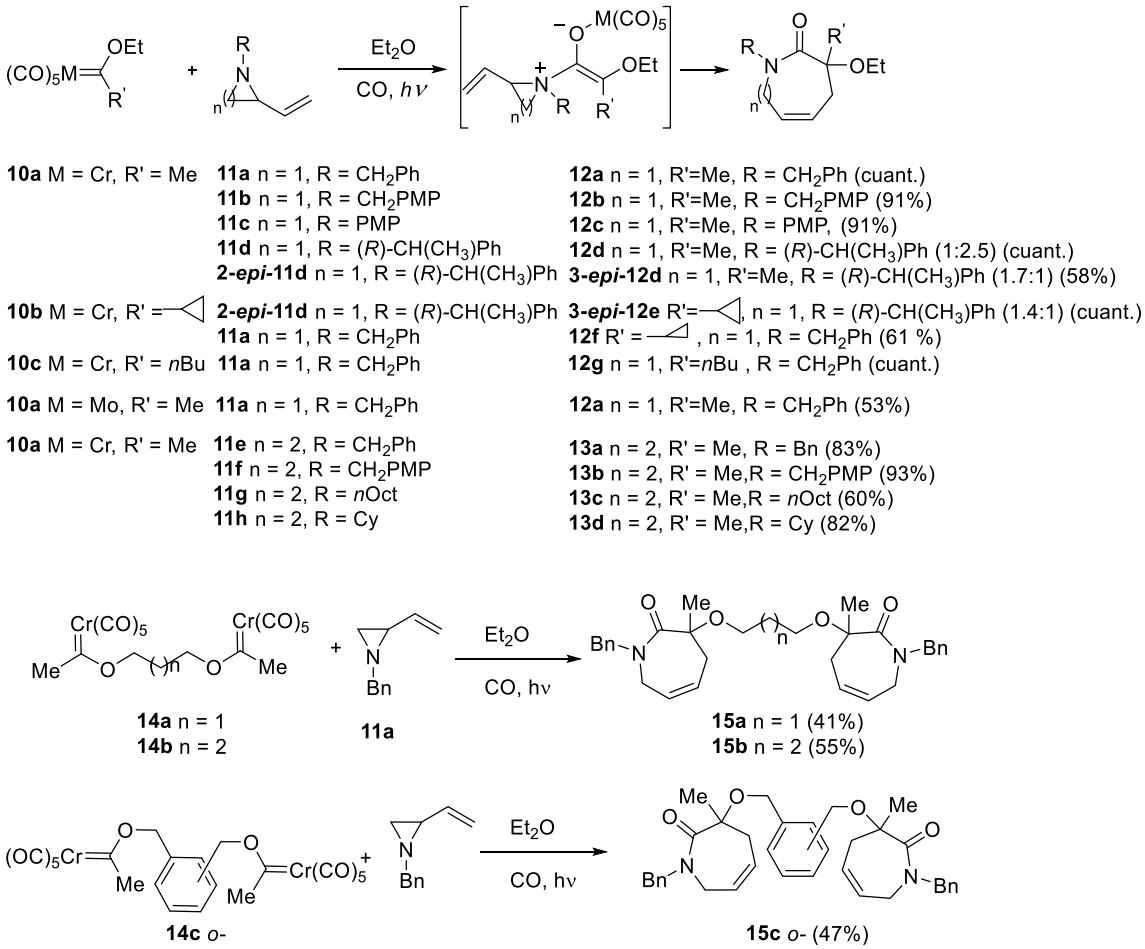
8 Barluenga, J.; García-Rodríguez, J.; Suárez-Sobrino, A.; Tomás, M. *Chem. Eur. J*. **2009**, *15*, 8800.

Así, en la primera parte del capítulo se describe una nueva reacción de cicloadición [8+2] entre complejos alquinil-carbeno de Fischer y tropotiona. El proceso conduce a la formación regioselectiva de complejos 3a*H*-ciclohepta[*b*]tiofénicos que mantienen la funcionalidad carbénica susceptible de experimentar transformaciones adicionales. La eficiencia del proceso se demuestra con la síntesis del cicloaducto biscarbénico **9h** mediante la doble reacción de cicloadición [8+2] de tropotiona con el correspondiente complejo biscarbénico (Esquema 2). Los cálculos computacionales indican que la reacción tiene lugar mediante un mecanismo por pasos a través de un intermedio zwitteriónico antiaromático.



Esquema 2. Reacciones de ciclación [8+2].

Finalmente, en la segunda parte del capítulo se explora la reacción de metala-cetenas generadas fotoquímicamente a partir de complejos metal-carbeno de tipo Fischer con vinilaziridinas y vinilazetidinas. Este proceso da lugar a azepanonas y azocinonas, respectivamente. Estas reacciones de cicloadición formal [5+2] y [6+2] son compatibles con complejos biscarbénicos de cromo(0), dando lugar a bis-azepanonas de forma directa y en condiciones de reacción suaves (Esquema 3). Los cálculos computacionales sugieren que la reacción transcurre por pasos a través de un intermedio zwitteriónico formado tras el ataque nucleófilo inicial del nitrógeno de la aziridina a la metalacetena, seguido del cierre del anillo.



Esquema 3. Reacciones de ciclación [5+2] y [6+2].

Conclusiones

Se han estudiado, tanto a nivel teórico como experimental, cuatro nuevas reacciones de cicloadición de alto orden: [8+3] con ciclopropanos D-A y [8+2], [5+2] y [6+2] con complejos metal-carbeno de tipo Fischer. Además, se ha desarrollado un método general y eficiente para la síntesis de compuestos oxaspiránicos mediante reacción de anulación [3+2] con ciclopropanos D-A.

SUMMARY

DEVELOPMENT OF NEW CYCLIZATION PROCESSES

Introduction

Cycloaddition reactions are highly valuable transformations in modern organic synthesis because of their ability to increase the molecular complexity in a single synthetic step.[1]

The aim of this dissertation is to develop and study new cyclisation processes using substrates whose structural and electronic properties makes them the ideal candidates to be used in these reactions, namely donor-acceptor cyclopropanes and Fischer type carbene complexes.

Goals and Results

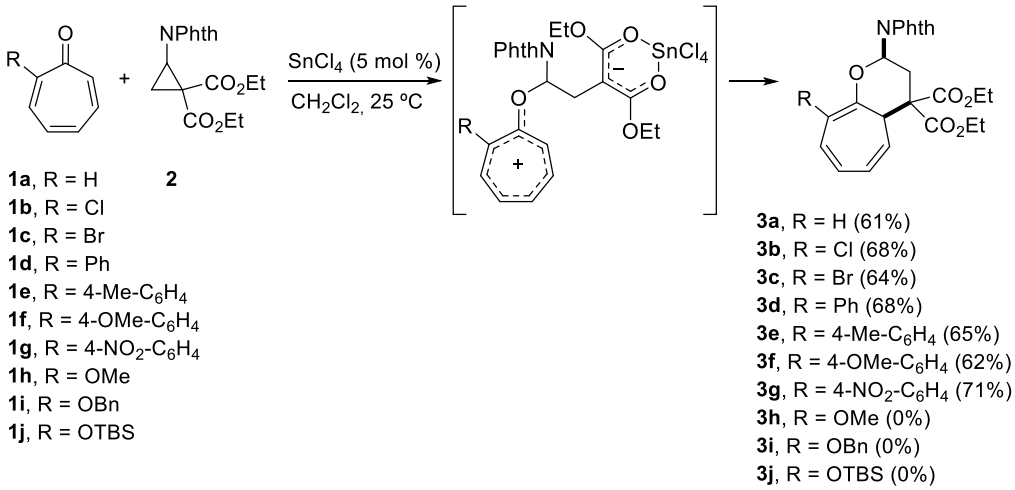
Chapter 1: Donor-acceptor cyclopropanes (DACs) have proven to be very useful for the direct synthesis of carbo- and heterocycles via [3+2]-, [3+3]- or [4+3]-cycloaddition reactions.[2] Nevertheless, the use of DACs in high-order cycloaddition reactions has been scarcely explored.[3] Therefore, the first goal of the chapter is the study of the [8+3] cycloaddition reaction between DACs and tropone derivatives.

This high-order $SnCl_4$-catalysed cycloaddition reaction leads to the formation of amino-substituted tetrahydrocyclohepta[*b*]pyrans in good reaction yields and with complete regio- and diastereoselectivities (Scheme 1). By means of computational-DFT methods, it was found that this transformation proceeds stepwise through a zwitterionic intermediate. From this intermediate a ring closure step, which controls the regio- and diastereoselectivities, occurs to produce the observed [8+3]-cycloadducts.

1 (a) *Cycloaddition Reactions in Organics Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, **2001**. (b) *Pericyclic Reactions-A Textbook: Reactions, Applications and Theory*; Sankararaman, S., Eds.; Wiley-VCH: Weinheim, **2005**.

2 (a) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev*. **2009**, *38*, 3051. (b) Mel'nikov, M. Y.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V. *Mendeleev Commun*. **2011**, *21*, 293. (c) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, *53,* 5504.

3 (a) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Angew. Chem. Int. Ed*. **2008**, *47*, 1107. (b) Xu, H.; Hu, J.-L.; Wang, L.; Liao, S.; Tang, Y. *J. Am. Chem. Soc*. **2015**, *137*, 8006. (c) Garve, L. K. B.; Pawliczek, M.; Wallbaum, J.; Jones, P. G.; Werz, D. B. *Chem. Eur. J*. **2016**, *22*, 521.



Scheme 1. [8+3]-Cycloaddition reactions.

These previous results prompted us to explore the reaction between DACs and cyclopropenones as a direct route toward spirocyclic compounds, species with great potential[4] but difficult to produce using conventional methods.[5]

Therefore, in the second part of this chapter a general and efficient method for the direct synthesis of oxaspiranic compounds through $Sc(OTf)_3$-catalysed [3+2]-annulation reaction between cyclopropenones and DACs is developed (Table 1). DFT calculations suggest that the reaction follows a stepwise mechanism where the exclusive formation of the [3+2]- over the possible [3+3]-products takes place under both kinetic and thermodynamic control.

4 (a) Bercovic , G.; Krongauz, V.; Weiss, V. *Chem. Rev*. **2000**, *100*, 1741. (b) Marson, C. M. *Chem. Soc. Rev*. **2011**, *40*, 5514. (c) Zheng, Y.; Tice, C. M.; Singh, S. B. Bioorg. Med. *Chem. Lett.* **2014**, *24*, 3673.

5 (a) Ríos, R. *Chem. Soc. Rev.* **2012**, *41*, 1060. (b) Ramazanov, I. R.; Yaroslavova, A. V.; Dzhemilev, U. M. *Russ. Chem. Rev*. **2012**, *81*, 700. (c) Undheim, K. *Synthesis* **2014**, *26*, 1957.

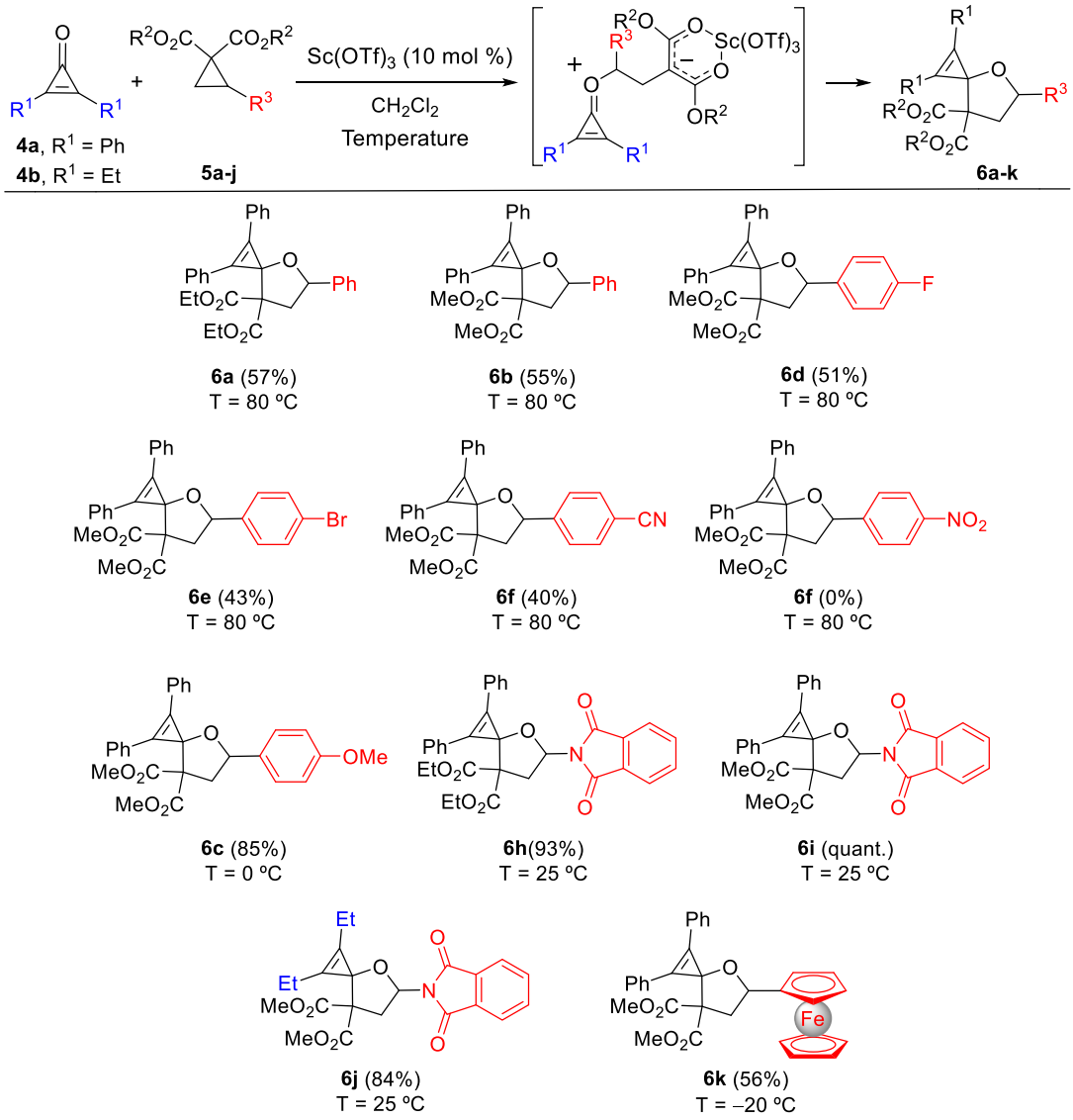


Table 1 Scope of the $Sc(OTf)_3$-catalyzed [3+2]-annulation reactions.

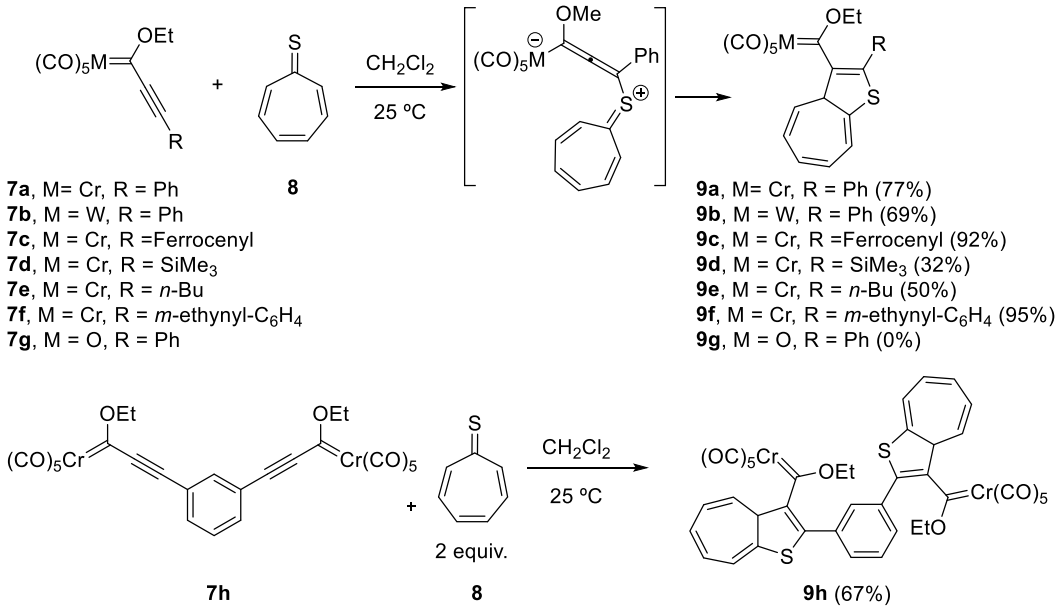
Chapter 2: Fischer type carbene complexes are useful reagents to undergo highly regioselective cycloaddition processes under mild reaction conditions.[6] For this reason they have been widely used in synthesis.[7] However, high-order cycloaddition processes involving these complexes have attracted much less attention.[8] Consequently, the development of new high-order cycloaddition reactions employing these organometallic substrates constitutes the goal of the second chapter.

6 (a) Dötz, K. H.; Stendel, J. *Chem. Rev.* **2009**, *109*, 3227. (b) Herndon, J. W. *Coord. Chem. Rev.* **2010**, *254*, 103. (c) Fernández, I.; Cossío, F. P.; Sierra, M. A. *Acc. Chem. Res.* **2011**, *44*, 479.

7 (a) Barluenga, J.; Rodríguez, F.; Fañanás, F. J.; Flórez, J. *Top. Organomet. Chem.* **2004**, *13*, 59. (b) Fernández, I.; Sierra, M. A.; *Top. Heterocycl. Chem.* **2013**, *30*, 65. (c) Raubenheimer, H. G. *Dalton Trans.*, **2014**, *43*, 16959.

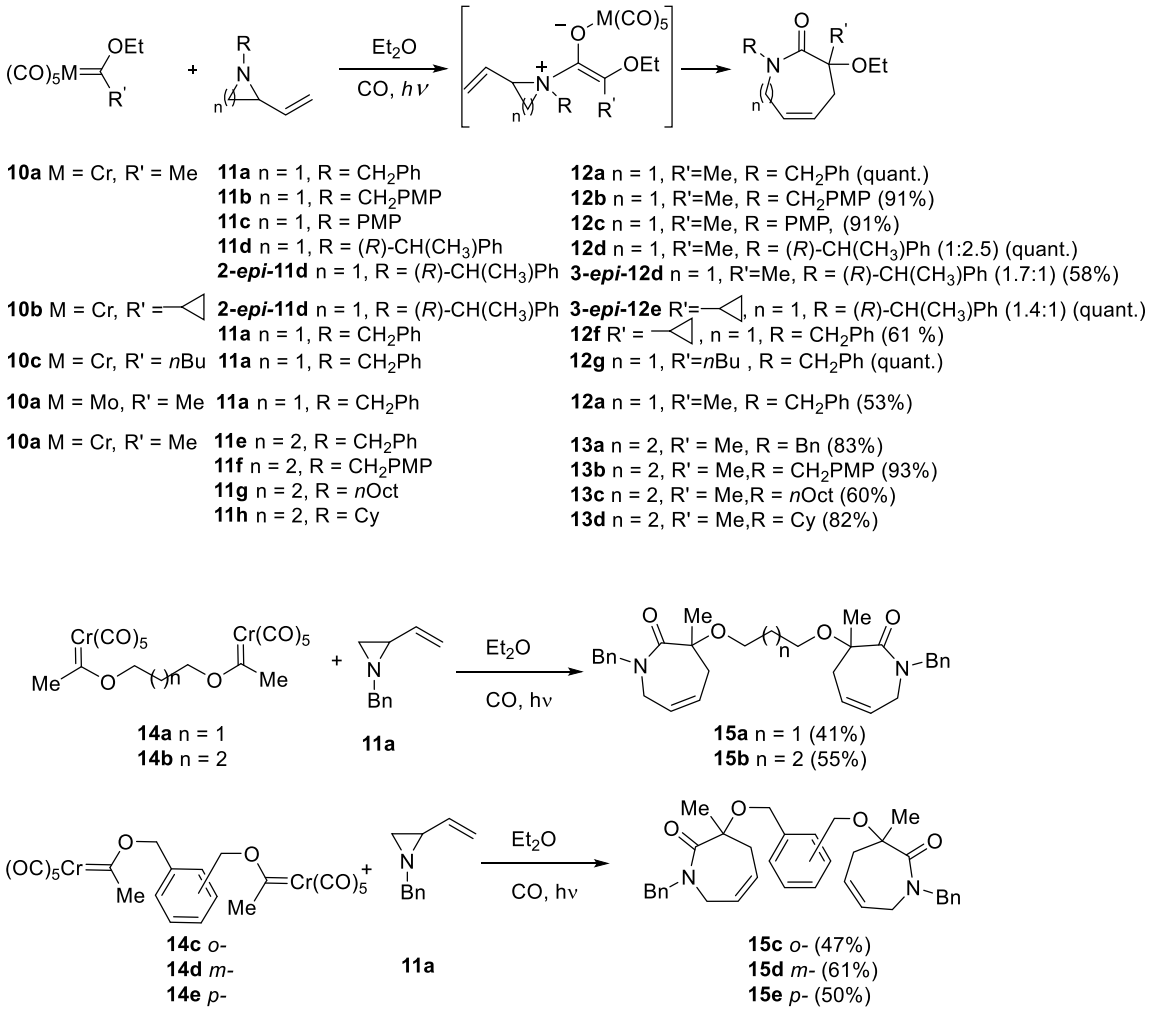
8 Barluenga, J.; García-Rodríguez, J.; Suárez-Sobrino, A.; Tomás, M. *Chem. Eur. J.* **2009**, *15*, 8800.

Hence, in the first part of this chapter, a formal [8+2]-cycloaddition reaction between alkynyl Fischer carbene complexes and tropothione is described. The process leads to the regioselective formation of 3a*H*-cyclo-hepta[*b*]thiophene carbene complexes, which maintain the pentacarbonyl-metal carbene functionality susceptible to further modifications. Furthermore, by using a bis-carbene complex, the corresponding bis-cycloadduct was obtained through a double [8+2]-cycloaddition reaction, which demonstrates the efficiency of the process (Scheme 2). By means of computational-DFT methods, it was found that this transformation proceeds stepwise through an anti-aromatic zwitterionic intermediate.



Scheme 2. [8+2]-Cycloaddition reactions.

Finally, in the second part of the chapter the [5+2] and [6+2]-cycloaddition reactions of vinylaziridines and vinylazetidines with ketenes generated photochemically from chromium(0) and molybdenum(0) carbene complexes are investigated. These processes constitute a direct and efficient access to azepanones and azocinones, respectively (Scheme 3). The versatility of the process is demonstrated using Cr(0)-Fischer bis-carbene complexes as bis-metallated-ketene precursors. These species produce tethered bis-azepanones in a single step under mild reaction conditions. Density functional theory calculations suggest a stepwise reaction pathway involving the formation of a zwitterionic intermediate (formed upon the initial nucleophilic attack of the nitrogen atom of the aziridine to the metallated-ketene), followed by a ring closure step.



Scheme 3. [5+2] and [6+2]-Cycloaddition reactions.

Conclusions

Four new high-order cycloaddition reactions have been studied, both theoretically and experimentally: [8+3] with DACs and [8+2], [5+2] and [6+2] with Fischer type carbene complexes. Moreover, a general and efficient method for the direct synthesis of oxaspiranic compounds through [3+2]-annulation with DACs has been developed.

INTRODUCCIÓN

Las reacciones de cicloadición y ciclación son una de las herramientas más poderosas y más empleadas en síntesis debido a su capacidad para aumentar la complejidad molecular en una única etapa sintética.[1] La amplia gama de compuestos que se pueden utilizar como sustratos en este tipo de transformaciones hace de las reacciones de cicloadición una metodología eficaz para la generación de anillos carbo- y heterocíclicos de diversos tamaños.

En esta tesis doctoral se desarrollan y estudian nuevos procesos de cicloadición y ciclación en dos tipos de sustratos cuyas características estructurales y electrónicas les confieren las propiedades idóneas para su empleo en este tipo de reacciones: ciclopropanos dador-aceptor y complejos metal-carbeno de tipo Fischer.

1 (a) *Cycloaddition Reactions in Organics Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, **2001**. (b) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson,W. H., Eds.; Wiley: New York, **2002**. (c) *Pericyclic Reactions-A Textbook: Reactions, Applications and Theory*; Sankararaman, S., Eds.; Wiley-VCH: Weinheim, **2005**.

1. Ciclopropanos dador-aceptor

Debido a su estructura cíclica, los cicloalcanos presentan cierta tensión anular resultado de dos componentes: la tensión angular y la tensión torsional.[2] La tensión angular se produce cuando el ángulo C–C–C se desvía del ángulo tetraédrico ideal de 109.5° de los átomos de carbono con hibridación sp^3. Como se muestra en la Figura 1, el ciclohexano, gracias a su disposición en forma de silla, adopta un ángulo próximo a los 109.5°, lo que resulta en una tensión anular prácticamente nula. En cambio, el ciclopropano presenta una alta tensión debida a su planaridad (ángulo C–C–C de 60°). Como consecuencia, los orbitales sp^3 de los carbonos que forman el ciclo solapan curvándose hacia el interior, formando así enlaces torsionados, conocidos como enlaces τ (Figura 1).[3] El solapamiento orbital resultante es menos eficiente que el correspondiente a un enlace σ.

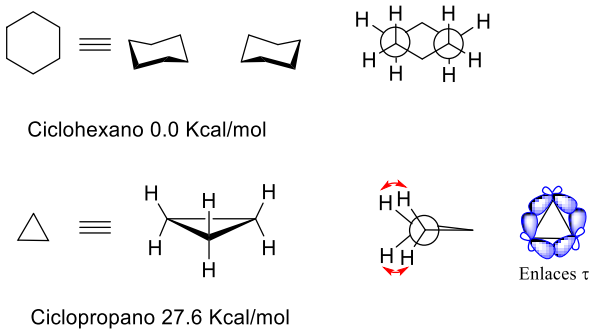


Figura 1. Tensión anular del ciclohexano y ciclopropano.

El método de síntesis más empleado para la obtención de carbociclos de tres miembros implica el uso de especies altamente reactivas como carbenos y sus análogos, y la correspondiente olefina.[4]. Los ciclopropanos son, sin embargo, relativamente estables y, a pesar de su elevada tensión, sus enlaces C–C necesitan ser activados para provocar su escisión. El método más sencillo para inducir la apertura del anillo consiste en polarizar uno de sus enlaces. Esta polarización puede inducirse mediante la incorporación de sustituyentes dadores de electrones (dadores, D) y electroaceptores (aceptores, A) en el anillo (Figura 2). La distribución más común de los sustituyentes D y A es en posiciones vecinales (Figura 2, compuesto **1**) o geminales (Figura 2, compuesto **3**). El grado de polarización del enlace C–C del

2 Quinkert, G.; Egert, E.; Griesinger, C. *Aspects of Organic Chemistry: Structure*; John Wiley & Sons, 1996.
3 Coulson, C. A.; Moffitt, W. E. *J. Chem. Phys.* **1947**, *15*, 151.
4 (a) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (b) Harvey, D. F.; Sigano, D. M. *Chem. Rev.* **1996**, *96*, 271. (c) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley, **1998**.

ciclopropano cuando los sustituyentes se encuentran en posición geminal es inferior a la inducida por el efecto cooperativo de los sustituyentes en posiciones vecinales.[5] En este caso, el efecto "push-pull" debilita el enlace C–C que los une, el cual se puede abrir heterolíticamente mediante calor o catálisis ácida. Esta apertura genera un intermedio zwitteriónico en el que el grupo aceptor estabiliza la carga negativa, mientras que la carga positiva se estabiliza por el grupo dador (Figura 2, compuesto **2**).[6]

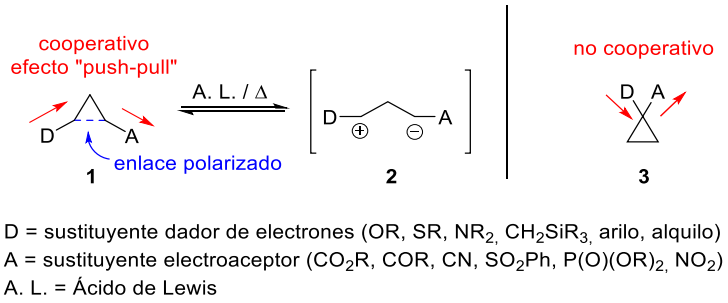


Figura 2. Ciclopropanos dador-aceptor.

Schneider y Werz cuantificaron mediante estudios teóricos la influencia de los sustituyentes en la polarización del enlace C–C en distintos ciclopropanos D-A vecinales.[7] Calculando las barreras de activación necesarias para el alargamiento del enlace en 72 combinaciones de ciclopropanos D-A, estos autores concluyeron que los sustituyentes amino, calcógenos y arilo son mejores grupos dadores, mientras que los grupos nitroso, carbonilo e imina son los que producen las menores barreras de activación dentro de los sustituyentes aceptores (Figura 3). Estos estudios demostraron claramente que la apertura del anillo está muy favorecida en esta clase de ciclopropanos; de hecho, los aminociclopropanos a menudo se abren de forma espontánea.[8]

5 (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev*. **2003**, *103*, 1151. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321.
6 (a) Wenkert, E.; Goodwin, T. E.; Ranu, B. C. *J. Org. Chem*. **1977**, *42*, 2137. (b) Stevens, R. V. *Acc. Chem. Res*. **1977**, *10*, 193.
7 Schneider, T. F.; Werz, D. B. *Org. Lett*. **2011**, *13*, 1848.
8 (a) Wenkert, E.; Hudlicky, T.; Showalter, H. D. H. *J. Am. Chem. Soc*. **1978**, *100*, 4893. (b) Wenkert, E.; Hudlicky, T. *J. Org. Chem*. **1988**, *53*, 1953. (c) Jiang, Y. J.; Khong, V. Z. Y.; Lourdusamy, E.; Park,C. M. *Chem. Commun*. **2012**, *48*, 3133.

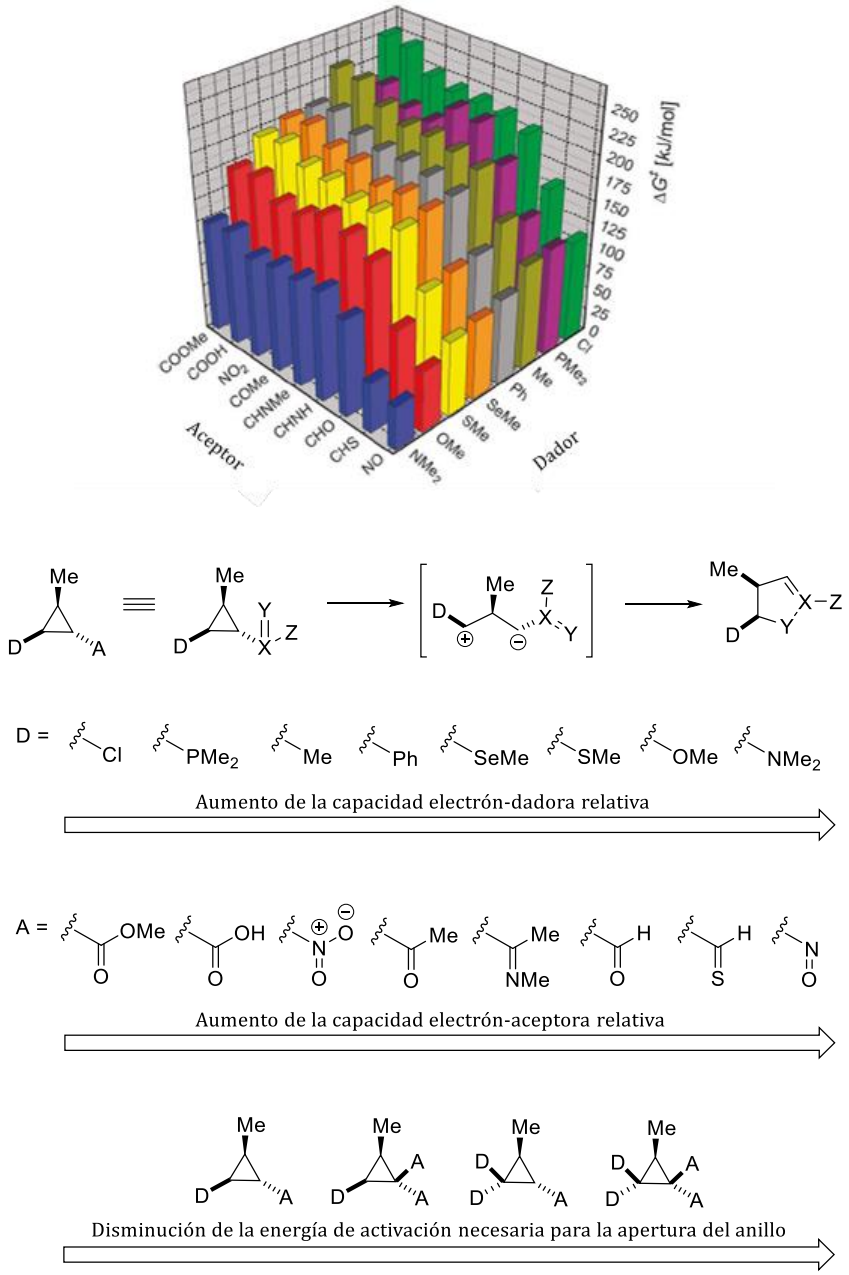
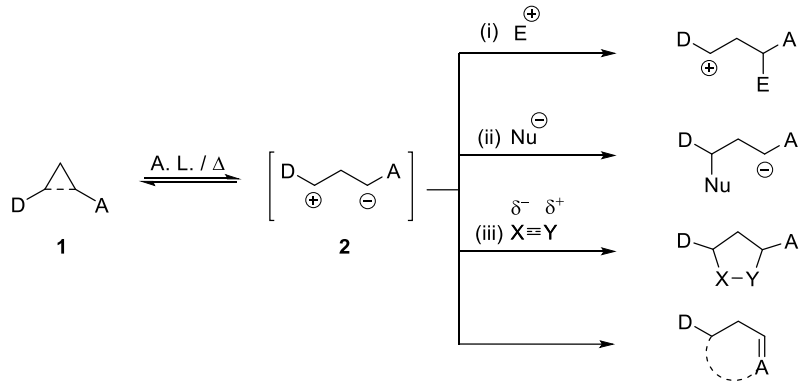


Figura 3. Estudios teóricos de Schneider y Werz.[8]

La estabilidad y reactividad de los ciclopropanos D-A dependerá de las condiciones de reacción. Así, estas especies experimentan apertura de anillo en sus reacciones (i) con electrófilos dando lugar a productos homoenólicos, (ii) con nucleófilos generando productos de adición homoconjugada y (iii) con dobles y triples enlaces para formar anillos saturados o parcialmente insaturados de cinco miembros (Esquema 1). Además, pueden experimentar reordenamientos debidos a la transferencia de la carga negativa al aceptor, produciendo así la inserción de este grupo en el enlace C–C del ciclopropano.



Esquema 1. Reactividad general de los ciclopropanos dador-aceptor.

Desde las primeras investigaciones llevadas a cabo por Stork con ciclopropanos D-A,[9] éstos se han convertido en compuestos de gran utilidad en síntesis debido a la amplia variedad de reacciones que pueden experimentar.[10] Por este motivo, el desarrollo de nuevas metodologías sintéticas basadas en ciclopropanos D-A es el objeto de múltiples investigaciones en curso.[11] De hecho, la elevada estéreo-, regio- y quimioselectividad de las reacciones de estos compuestos se ha empleado como etapa clave en la síntesis total de distintos productos naturales.[12]

En particular, el uso de ciclopropanos D-A en reacciones de ciclación ha experimentado un crecimiento exponencial en las últimas décadas.[13] Dichas reacciones pueden definirse en función del zwitterión que participa en la reacción: cicloadición si se trata de un zwitterión de tipo **I** [14] y anulación si es de tipo **II.** La

9 (a) Stork, G.; Marx, M. *J. Am. Chem. Soc*. **1969**, *91*, 2371. (b) Stork, G.; Gregson, M. *J. Am. Chem. Soc*. **1969**, *91*, 2373. (c) Stork, G.; Grieco, P. A. *J. Am. Chem. Soc.* **1969**, *91*, 2407. (d) Stork, G.; Grieco, P. A. *Tetrahedron Lett*. **1971**, 1807. (e) Corey, E. J.; Balanson, R. D. *Tetrahedron Lett*. **1973**, 3153. (f) Grieco, P. A.; Finkelhor, R. S. *Tetrahedron Lett*. **1974**, 527. (g) Danishefsky, S. *Acc. Chem. Res*. **1979**, *12*, 66. (h) Wenkert, E. *Acc. Chem. Res*. **1980**, *13*, 27. (i) Reissig, H. U.; Hirsch, E. *Angew. Chem*. *Int. Ed. Engl.* **1980**, *19*, 813.

10 (a) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev*. **2009**, *38*, 3051. (b) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, *53,* 5504. (c) Green, J. R.; Snieckus, V. *Synlett* **2014**, *25*, 2258.

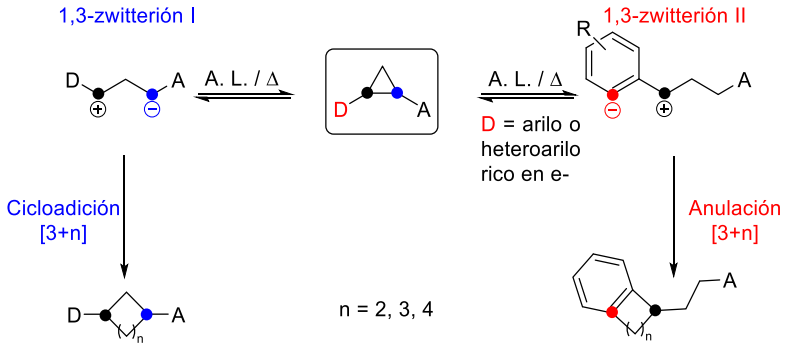
11 (a) Ivanov, K. L.; Villemson, E. V.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V.; Melnikov, M. Y.; *Chem. Eur. J*. **2015**, *21*, 4975. (b) Kang, Q.; Wang, L.; Liu, Q.; Li, J.; Tang, Y. *J. Am. Chem. Soc.* **2015**, *137*, 14594. (c) Gopinath, P.; Chandrakala, R. N.; Chandrasekaran, S. *Synthesis* **2015**, *47*, 1488. (d) Talukdar, R.; Saha, A.; Tiwari, D. P.; Ghorai, M. K. *Tetrahedron* **2016**, *72*, 613.

12 (a) Campbell, M. J.; Johnson, J. S. *J. Am. Chem. Soc*. **2009**, *131*, 10370. (b) Sanders, S. D.; Ruiz-Olalla, A.; Johnson, J. S. *Chem. Commun.* **2009**, 5135. (c) Gagnon, D.; Spino, C. *J. Org. Chem.* **2009**, *74*, 6035. (d) Vaswani, R. G.; Day, J. J.; Wood, J. L. *Org. Lett.* **2009**, *11*, 4532. (e) Karadeolian, A.; Kerr, M. A. *Angew. Chem. Int. Ed.* **2010**, *49*, 1133. (f) Karadeolian, A.; Kerr, M. A. *J. Org. Chem*. **2010**, *75*, 6830. (g) Campbell, M. J.; Johnson, J. S. *Synthesis* **2010**, 2841. (h) Hu, B.; Xing, S.; Ren, J.; Wang, Z. *Tetrahedron* **2010**, *66*, 5671. (i) Jung, M. E.; Chang, J. J. *Org. Lett*. **2010**, *12*, 2962. (j) Reisman, S. E.; Nani, R. R.; Levin, S. *Synlett* **2011**, 2437. (k) Tang, P.; Qin, Y. *Synthesis* **2012**, *44*, 2969. (l) Wang, Z. *Synlett* **2012**, *23*, 2311.

13 (a) De Simone, F.; Waser, J. *Synthesis* **2009**, 3353. (b) Mel'nikov, M. Y.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V. *Mendeleev Commun*. **2011**, *21*, 293. (c) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev*. **2014**, *43*, 804. (d) Grover, H. K.; Emmett, M. R.; Kerr, M. A. *Org. Biomol. Chem*. **2015**, *13*, 655. (e) Novikov, R. A.; Tomilov, Y. V. *Mendeleev Commun*. **2015**, *25*, 1.

14 (a) Liu, J.; Zhou, L.; Ye, W.; Wang, C. *Chem. Commun*. **2014**, *50*, 9068. (b) Wang, L.-F.; Shi, Z.-F.; Cao, X.-P.; Li, B.-S.; An, P. *Chem. Commun.* **2014**, *50*, 8061. (c) de Nanteuil, F.; Serrano, E.; Perrotta, D.; Waser, J. *J. Am. Chem. Soc*. **2014**, *136*,

formación del zwitterión de tipo **II** se produce cuando el sustituyente dador del ciclopropano es un arilo o heteroarilo rico en electrones. En ese caso, el centro electrófilo se mantiene en la misma posición, mientras que el centro nucleófilo se ubica en la posición *orto* del sustituyente aromático.[15] Ambos zwitteriones constituyen, por tanto, dos vías diferentes de acceso a sintones de tres átomos de carbono (Esquema 2).[16]



Esquema 2. Posibles 1,3 zwitteriones derivados de ciclopropanos D-A y sus ciclaciones.

En esta introducción se presentan las distintas ciclaciones que experimentan los ciclopropanos D-A, clasificadas en función de la transformación [3+n] a la que dan lugar con distintos reactivos.

1.1. Ciclaciones [3+2]

La escisión heterolítica de uno de los enlaces del ciclopropano activados resulta en la formación de un 1,3-dipolo capaz de experimentar reacciones de ciclación [3+2] con carbonilos, iminas y olefinas dando lugar a derivados de furano, pirrolidina y ciclopentano, respectivamente.

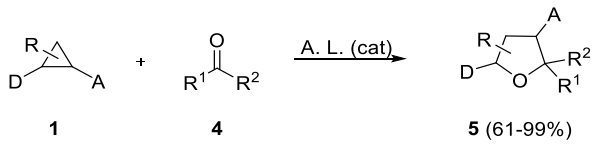
6239. (d) de Nanteuil, F.; de Simone, F.; Frei, R.; Benfatti, F.; Serrano, E.; Waser, J. *Chem. Commun.* **2014**, *50*, 10912. (e) Chakrabarty, S.; Chatterjee, I.; Wibbeling, B.; Daniliuc, C. J.; Studer, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 5964. (f) Zhu, W.; Ren, J.; Wang, Z. *Eur. J. Org. Chem.* **2014**, 3561. (g) Mikhaylov, A. A.; Novikov, R. A.; Khomutova, Yu. A.; Arkhipov, D. E.; Korlyukov, A. A.; Tabolin, A. A.; Tomilov, Yu. V.; Ioffe, S. L. *Synlett* **2014**, *25*, 2275. (h) Zhang, H.-H.; Luo, Y.-C.; Wang, H.-P.; Chen, W.; Xu, P.-F. *Org. Lett.* **2014**, *16*, 4896. (i) Sathishkannan, G.; Srinivasan, K. *Chem. Commun.* **2014**, *50*, 4062.

15 (a) Ivanova, O. A.; Budynina, E. M.; Grishin, Yu. K.; Trushkov, I. V.; Verteletskii, P. V. *Eur. J. Org. Chem.* **2008**, 5329. (b) Ivanova,O. A.; Budynina, E. M.; Chagarovskiy, A. O.; Trushkov, I. V.; Melnikov, M. Ya. *J. Org. Chem.* **2011**, *76*, 8852.

16 Volkova, Y. A.; Budynina, E. M.; Kaplun, A. E.; Ivanova, O. A.; Chagarovskiy, A. O.; Skvortsov, D. A.; Rybakov, V. B.; Trushkov, I. V.; Melnikov, M. Ya. *Chem. Eur. J.* **2013**, *19*, 6586.

1.1.1. Ciclaciones [3+2] con aldehídos y cetonas

Las reacciones de ciclación [3+2] de ciclopropanos D-A con grupos carbonilos han despertado un gran interés debido a la importancia biológica de los derivados de tetrahidrofurano a los que dan lugar (Esquema 3).[17]



Esquema 3. Ciclaciones [3+2] de ciclopropanos D-A con aldehídos y cetonas.

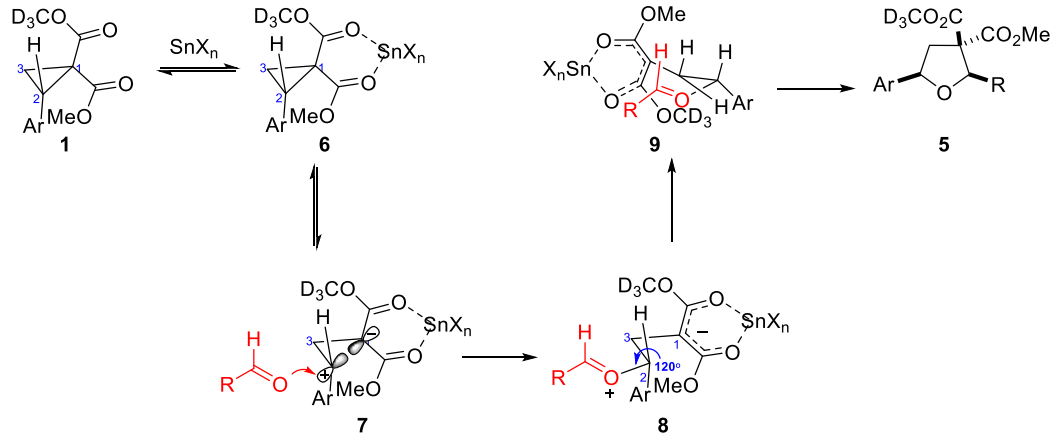
Los primeros estudios sobre estos sistemas se efectuaron en ciclopropanos D-A en los que el sustituyente dador era de forma exclusiva un alcóxido.[18] Más tarde, Johnson introdujo nuevos grupos (alquilo, vinilo y arilo) observando una elevada diastereoselectividad en los procesos catalizados por ácidos de Lewis ($SnCl_4$ y $Sn(OTf)_2$).[19]. Estudios mecanísticos detallados[19c] sugieren que estas cicloadiciones [3+2] tienen lugar mediante el ataque nucleófilo del par de electrones del átomo de oxígeno del grupo carbonilo al par iónico íntimo **7**, formado tras la coordinación del ácido de Lewis a los grupos éster del ciclopropano D-A **1** (Esquema 4). Este ataque produce un ion (*E*)-oxocarbenio **8** que, mediante un giro de 120° en torno al enlace σ de los carbonos C2–C3, sitúa al zwitterión en una conformación **9** en la que los sustituyentes del ciclopropano y el aldehído ocupan posiciones pseudoecuatoriales, lo que justifica la alta diastereoselectividad del proceso. Finalmente, el enolato ataca al ion oxocarbenio produciendo el cierre de anillo. Este mecanismo de reacción se ha estudiado también mediante cálculos computacionales para el proceso [3+2] entre ciclopropanos D-A y benzaldehído en presencia de $Sn(OTf)_2$.[20]

17 (a) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261. (b) Harmange, J.-C.; Figadére, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711.

18 (a) Shimada, S.; Hashimoto, Y.; Sudo, A.; Hasegawa, M.; Saigo, K. *J. Org. Chem*. **1992**, *57*, 7126. (b) Shimada, S.; Hashimoto, Y.; Saigo, K. *J. Org. Chem*. **1993**, *58*, 5226. (c) Shimada, S.; Hashimoto, Y.; Nagashima, T;. Hasegawa, M. Saigo, K. *Tetrahedron* **1993**, *49*, 1589.

19 (a) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc*. **2005,** *127*, 16014. (b) Pohlhaus, P. D.; Johnson, J. S. *J. Org. Chem*. **2005**, *70*, 1057. (c) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc*. **2008**, *130*, 8642.

20 Zhang, J.; Shen, W.; Li, M. *Eur. J. Org. Chem*. **2007**, 4855.

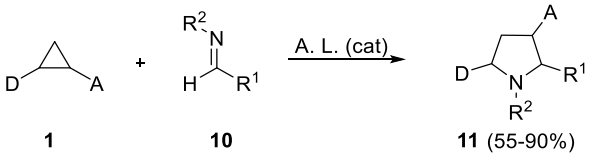


Esquema 4. Mecanismo propuesto para la reacción de ciclopropanos D-A con aldehídos.

El grupo de Johnson ha descrito diferentes versiones asimétricas de este proceso de ciclación catalizado por (pybox²*)Mg(II)[21] y Sn(OTf)₂.[22] La variabilidad en los sustituyentes dadores del ciclopropano se amplió gracias a los ejemplos con naftilimida[23] o alquinilo.[24] La posibilidad de realizar la ciclación de manera intramolecular ha sido confirmada Wang y colaboradores, cuya metodología proporciona compuestos bicíclos de interés biológico.[25]

1.1.2. Ciclaciones [3+2] con iminas, oximas y nitrilos

Al igual que sus análogos carbonílicos, las iminas y oximas experimentan reacciones de ciclación [3+2] con ciclopropanos D-A para formar tetrahidropirroles (Esquema 5).



Esquema 5. Ciclaciones [3+2] de ciclopropanos D-A con iminas y oximas.

21 Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122.

22 Smith, A. G.; Slade, M. C.; Johnson, J. S. *Org. Lett.* **2011**, *13*, 1996.

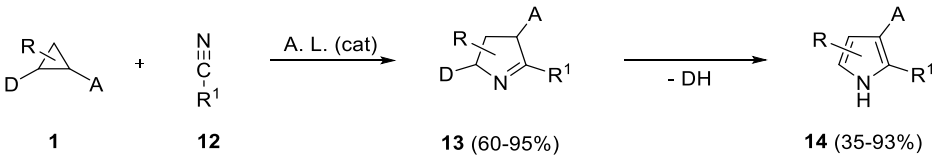
23 (a) Benfatti, F.; de Nanteuil, F.; Waser, J. *Org. Lett.* **2012**, *14*, 386. (b) Benfatti, F.; de Nanteuil, F.; Waser, J. *Chem. Eur. J.* **2012**, *18*, 4844.

24 (a) Haubenreisser, S.; Hensenne, P.; Schroder, S.; Niggemann, M. *Org. Lett.* **2013**, *15*, 2262. (b) Miyake, Y.;. Endo, S; Moriyama, T.; Sakata, K.; Nishibayashi, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 1758.

25 (a) Xing, S.; Pan, W.; Liu, C.; Ren, J.; Wang, Z. *Angew. Chem. Int. Ed.* **2010,** *49*, 3215. (b) Xing, S.; Li, Y.; Li, Z.; Liu, C.; Ren, J.; Wang, Z. *Angew. Chem. Int. Ed.* **2011**, *50*, 12605. (c) Bai, Y.; Tao, W.; Ren, J.; Wang, Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 4112.

Estas ciclaciones [3+2] se han llevado a cabo usando como catalizadores MgI_2[26] o $Yb(OTf)_3$.[27] La modalidad asimétrica de este proceso fue presentada por Kerr con oximas[28] y por Johnson con iminas.[29]

El uso de nitrilos como reactivos permite acceder a anillos de cinco eslabones que incorporan una insaturación (Esquema 6, compuesto **13**). En este caso, la presencia de un grupo alcóxido como sustituyente dador en el ciclopropano permite que, tras la reacción de ciclación [3+2], se produzca una eliminación del grupo alcohol dando lugar a los correspondientes pirroles (Esquema 6, compuesto **14**).[30]



Esquema 6. Ciclaciones [3+2] de ciclopropanos D-A con nitrilos.

1.1.3. Ciclaciones [3+2] con alquenos y alquinos

La síntesis de carbociclos de cinco eslabones puede hacerse mediante una cicloadición [3+2] entre ciclopropanos D-A y distintas olefinas. Por ejemplo, sustratos tales como sililenol éteres (X = $OSiR_3$),[31] acetales (X = $OSiR_3$, R^3 = OR),[32] enaminas (X = NR_2),[33] alquenos (X = H)[34] o incluso aceptores de Michael (X = COR)[35] han demostrado ser reactivos idóneos para dichas transformaciones (Esquema 7).

26 (a) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem. Int. Ed*. **1999**, *38*, 3186. (b) Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc*. **2002**, *124*, 14826. (c) Meyers, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 694.

27 Carson, C. A.; Kerr, M. A. *J. Org. Chem*. **2005**, *70*, 8242.

28 Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc*. **2008**, *130*, 4196.

29 Parsons, A. T.; Smith, A. G.; Neel, A.; Johnson, J. J. S. *J. Am.Chem. Soc*. **2010**, *132*, 9688.

30 Sathishkannan, G.; Srinivasan, K. *Org. Lett*. **2011**, *13,* 6002.

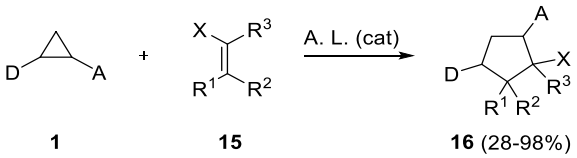
31 (a) Qu, J. P.; Deng, C.; Zhou, J.; Sun, X.-L.; Tang, Y. *J. Org. Chem*. **2009**, *74,* 7684. (b) de Nanteuil, F.; Waser, J. *Angew. Chem. Int. Ed*. **2011**, *50*, 12075. (c) Xu, H.; Qu, J.-P.; Liao, S.; Xiong, H.; Tang, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 4004.

32 Saigo, K.; Shimada, S.; Shibasaki, T.; Hasegawa, M. *Chem. Lett.* **1990**, 1093.

33 (a) Trost, B. M.; Morris, P. J.; Sprague, S. J.; *J. Am. Chem. Soc*. **2012**, *134*, 17823. (b) Xiong, H.; Xu, H.; Liao, S.; Xie, Z.; Tang, Y. *J. Am. Chem. Soc*. **2013**, *135*, 7851.

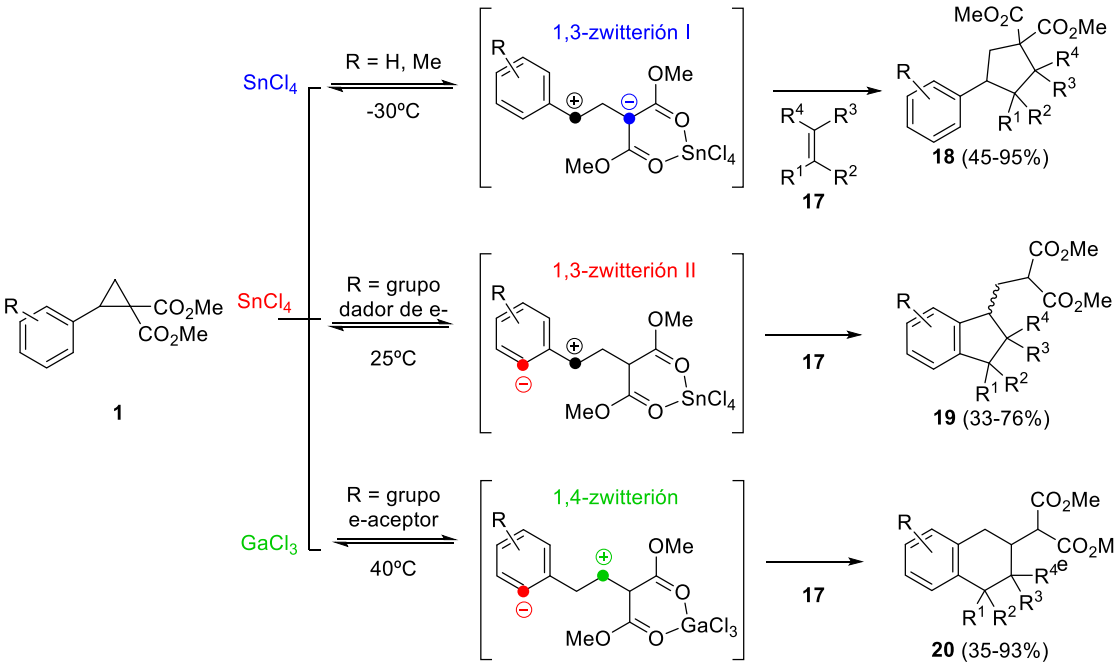
34 (f) Beal, R. B.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1986**, *51*, 4391.

35 (a) Liu, L.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 5348. (b) Liu, L.; Montgomery, J. *Org. Lett.* **2007**, *9*, 3885.



Esquema 7. Ciclaciones [3+2] de ciclopropanos D-A con olefinas.

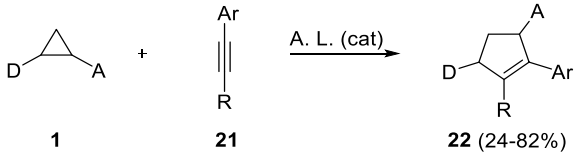
Cuando el sustituyente dador del ciclopropano es un grupo arilo, se han descrito tres posibles ciclaciones (Esquema 8). El empleo de $SnCl_4$ como catalizador produce la apertura del anillo ciclopropánico formando un intermedio zwitteriónico de tipo **I** que experimenta una ciclación [3+2] generando el carbociclo de cinco eslabones habitual (**18**). Alternativamente, el ciclopropano puede formar un zwitterión de tipo **II** que mediante una ciclación [3+2] da lugar a carbociclos de tipo indano (**19**). La obtención de uno u otro pentaciclo depende de la temperatura de reacción y el carácter más o menos nucleófilo del sustituyente arilo.[16] Por el contrario, cuando el ácido de Lewis empleado como catalizador es $GaCl_3$, el intermedio zwitteriónico que se forma es un 1, 4-dipolo[36] que reacciona con alquenos a través de una ciclación [4+2] dando lugar a tetralinas sustituidas (**20**).[37]



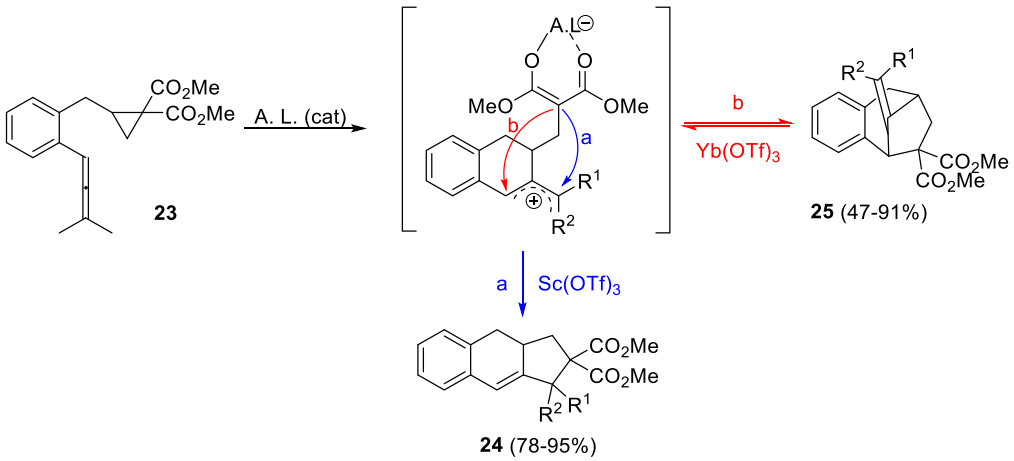
Esquema 8. Ciclaciones [3+2] de ciclopropanos D-A con alquenos.

36 Novikov, R. A.; Tarasova, A. V.; Korolev, V. A.; Timofeev, V. P.; Tomilov, Y. V. *Angew. Chem. Int. Ed.* **2014**, *53*, 3187.
37 Novikov, R. A.; Tarasova, A. V.; Korolev, V. A.; Shulishov, E. V.; Timofeev, V. P.; Tomilov, Y. V. *J. Org. Chem.* **2015**, *80*, 8225.

Los alquinos[38] y los alenos también pueden emplearse como componentes 2π en reacciones de cicloadición [3+2] con ciclopropanos D-A. El empleo de alquinos genera exclusivamente derivados de ciclopenteno (Esquema 9), mientras que el uso de alenos puede dar lugar a la formación de dos productos de ciclación diferentes procedentes de un mismo intermedio. La obtención de uno u otro depende exclusivamente de las condiciones de reacción empleadas (Esquema 10).[39]



Esquema 9. Ciclaciones [3+2] de ciclopropanos D-A con alquinos.



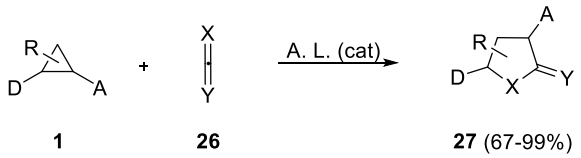
Esquema 10. Ciclaciones [3+2] de ciclopropanos D-A con alenos.

El empleo de cumulenos, como carbodiimidas (X = Y = nitrógeno), isocianatos (X = nitrógeno, Y = oxígeno) o isotiocianatos (X = azufre, Y = nitrógeno) hace que la ciclación [3+2] con ciclopropanos D-A de lugar a derivados de lactamas (Esquema 11).[40]

38 (a) Graziano, M. L.; Iesce, M. R.; Cermola, F.; Cimminiello, G. *J. Chem. Res. Synop.* **1992**, 4. (b) Yadav, V. K.; Sriramurthy, V. *Angew. Chem. Int. Ed.* **2004**, *43*, 2669. (c) Qi, X. B.; Ready, J. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7068. (d) Rakhmankulov, E. R.; Ivanov, K. L.; Budynina, E. M.; Ivanova,O. A.; Chagarovskiy, A. O.; Skvortsov, D. A.; Latyshev, G. V.; Trushkov, I. V.; Melnikov, M. Y. *Org. Lett.* **2015**, *17*, 770.

39 Wang, Z.; Ren, J.; Wang, Z. *Org. Lett.* **2013**, *15*, 5682.

40 (a) Goldberg, A. F. G.; O'Connor, N. R.; Craig, R. A.; Stoltz, B. M. *Org. Lett.* **2012**, *14*, 5314. (b) Wang, H.; Yang, W.; Liu, H.; Wang, W.; Li, H. *Org. Biomol. Chem.* **2012**, *10*, 5032.



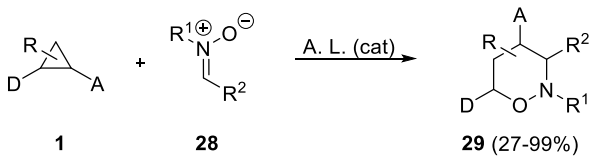
Esquema 11. Ciclaciones [3+2] de ciclopropanos D-A con heterocumulenos.

1.2. Ciclaciones [3+3]

Desde su descubrimiento, la reacción de ciclación [3+3] de ciclopropanos D-A ha demostrado ser una herramienta versátil y eficiente en la síntesis de anillos heterocíclicos de seis eslabones.[41]

1.2.1. Ciclaciones [3+3] con nitronas

Las nitronas experimentan una reacción de ciclación [3+3] con ciclopropanos D-A dando lugar a tetrahidro-1,2-oxazinas presentes en numerosos compuestos con actividad biológica (esquema 12).[42]



Esquema 12. Ciclaciones [3+3] de ciclopropanos D-A con nitronas.

La distribución relativa de los sustituyentes en las posiciones 3 y 6 del anillo de la tetrahidro-1,2-oxazina resultante depende del ácido de Lewis empleado como catalizador. Así, el uso de $Yb(OTf)_3$ genera de forma mayoritaria el aducto *cis*[43] mientras que el MgI_2 produce un aumento considerable de la proporción de aducto *trans* en el proceso de cicloadición [3+3].[44] El uso de catalizadores de Ni(II) quirales permitió la síntesis de oxazinas de forma enantioselectiva.[45,46] La posibilidad de generar un centro estereogénico adicional en la posición 4 del anillo de ciclopropano ha sido descrita por Mattson gracias a la incorporación de dos grupos aceptores diferentes y al uso de urea como catalizador.[47] Recientemente, Nolin ha descrito la síntesis diastereoselectiva de tetrahidro-1,2-oxazinas por reacción de ciclación [3+3]

41 Venkatesh, C.; Ila, H.; Junjappa, H.; Mathur, S.; Hucht, V. *J. Org. Chem.* **2002**, *67*, 9477

42 (a) Carson, C. A.; Kerr, M. A. *Angew. Chem. Int. Ed*. **2006**, *45*, 6560. (b) Toure, B. B.; Hall, D. G. *Chem. Rev*. **2009**, *109*, 4439.

43 Young, I. S.; Kerr, M. A. *Angew. Chem. Int. Ed*. **2003**, *42*, 3023.

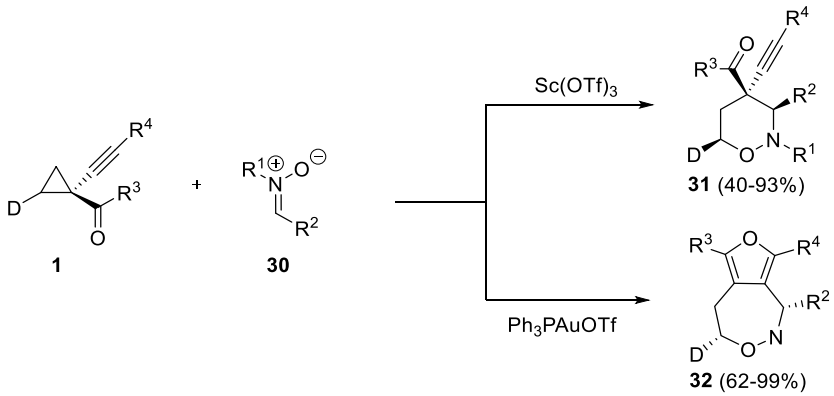
44 Ganton, M. D.; Kerr, M. A. *J. Org. Chem*. **2004**, *69*, 8554.

45 Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc*. **2005**, *127*, 5764.

46 Kang, Y.-B.; Sun, X.-L. Tang, Y. *Angew. Chem. Int. Ed*. **2007**, *46*, 3918.

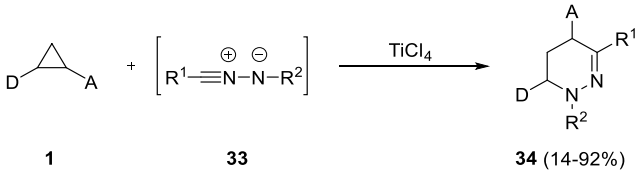
47 Hardman, A. M.; So, S. S.; Mattson, A. E. *Org. Biomol. Chem*. **2013**, *11*, 5793.

de nitronas con ciclopropanos D-A empleando como catalizador complejos de Ca(II).[48] En 2010 Zhang desarrolló una estrategia sintética dual en la reacción de nitronas con ciclopropanos D-A. La peculiaridad de esta transformación reside en la presencia de un sustituyente alquinilo en el ciclopropano que, en presencia de $Sc(OTf)_3$, produce el correspondiente producto de ciclación [3+3], mientras que en presencia de un catalizador de Au(I), el producto de reacción obtenido resulta de una ciclación [4+3] (Esquema 13).[49]



Esquema 13. Ciclaciones [3+3] + [4+3] de ciclopropanos D-A con nitronas.

Por último, cabe mencionar la ciclación [3+3] de ciclopropanos D-A con nitriliminas generadas *in situ* recientemente descrita por Werz, que permite la síntesis de tetrahidropiridacinas de interés farmacéutico (Esquema 14).[50]



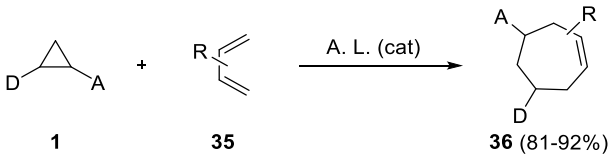
Esquema 14. Ciclaciones [3+3] de ciclopropanos D-A con nitriliminas.

1.3. Ciclaciones [4+3]

Hasta la fecha, el uso de dienos como sustratos en reacciones de ciclación con ciclopropanos D-A es limitado. Para que tenga lugar dicha transformación el dieno tiene que ser muy reactivo y estar estéricamente impedido para evitar la reacción de ciclación competitiva [3+2].[51] La reacción de ciclación [4+3] entre dienos y

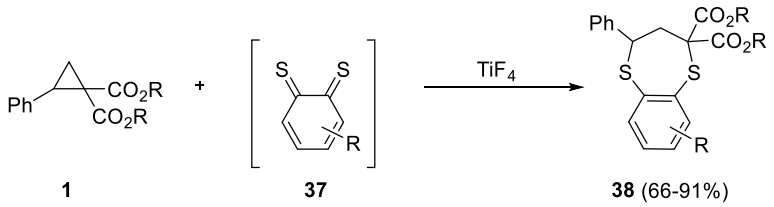
48 Braun, C. M.; Congdon, E. A.; Nolin, K. A. *J. Org. Chem*. **2015**, *80*, 1979.
49 Zhang, Y.; Liu, F.; Zhang, J. *Chem. Eur. J.* **2010**, *16*, 6146.
50 Garve, L. K. B.; Petzold, M.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2016**, *18*, 564.
51 Budynina, E. M.; Ivanova, O. A.; Chagarovskiy, A. O.; Grishin, Y. K.; Trushkov, I. V.; Melnikov, M. Y. *J. Org. Chem.* **2015**, *80*, 12212.

ciclopropanos D-A, dando lugar a ciclos de siete eslabones (Esquema 15), se describió por primera vez empleando isobenzofurano como dieno.[52] La versión asimétrica de este proceso ha sido recientemente descrita por Tang con dienosilil éteres y catalizadores quirales de Cu(II).[53]



Esquema 15. Ciclaciones [4+3] de ciclopropanos D-A con dienos.

Finalmente, Werz ha logrado utilizar ciclopropanos D-A en la síntesis de heterociclos de siete eslabones, gracias al empleo de *orto*-bistioquinonas generadas *in situ* (Esquema 16).[54]



Esquema 16. Ciclaciones [4+3] de ciclopropanos D-A con *orto*-bistioquinonas.

52 (a) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Angew. Chem. Int. Ed*. **2008**, *47*, 1107. (b) Ivanova, O. A.; Budynina,E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Eur. J. Org. Chem*. **2008**, 5329. (c) Ivanova, O. A.; Budynina, E. M.; Chagarovskiy, A. O.; Kaplun, A. E.; Trushkov, I. V.; Melnikova, M. Y. *Adv. Synth. Catal*. **2011**, *353*, 1125. (d) Ivanova, O. A.; Budyni-na, E. M.; Kolychev, E. L.; Nechaev, M. S.; Trushkov, I. V.; Melnikova, M .Y. *Russ. Chem. Bull*. **2013**, *62*, 2407.

53 Xu, H.; Hu, J.-L.; Wang, L.; Liao, S.; Tang, Y. *J. Am. Chem. Soc*. **2015**, 137, 8006.

54 Garve, L. K. B.; Pawliczek, M.; Wallbaum, J.; Jones, P. G.; Werz, D. B. *Chem. Eur. J*. **2016**, *22*, 521.

2. Complejos metal-carbeno de tipo Fischer

Fischer y Maasböl describieron en 1964 el primer complejo metal-carbeno estable.[55] Desde entonces, estos complejos han demostrado ser sustratos de gran utilidad en síntesis debido a la variedad de reacciones que pueden experimentar.[56] Su capacidad para generar productos no sólo con elevada selectividad y complejidad sino también con unos rendimientos de reacción excepcionales hace que los complejos de tipo Fischer continúen utilizándose ampliamente en la actualidad.[57]

Los complejos metal-carbeno de tipo Fischer contienen en su estructura un metal de transición de los grupos 6 a 8 en bajo estado de oxidación unido a ligandos π aceptores (generalmente ligandos carbonilo). El ligando carbeno, por su parte, se encuentra unido a grupos π-dadores (típicamente, oxígeno, azufre o nitrógeno) que compensan la deficiencia electrónica del carbono carbénico (Figura 4).

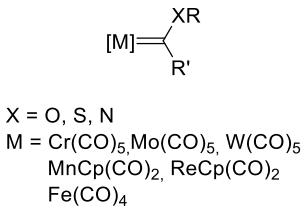


Figura 4. Complejo metal-carbeno de tipo Fischer.

55 Fischer, E. O.; Maasböl, A. *Angew. Chem., Int. Ed.* **1964**, *3*, 580.

56 (a) Dötz, K. H. *Angew. Chem., Int. Ed.* **1984**, *23*, 587. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (c) Harvey, D. F.; Sigano, D. M. *Chem. Rev.* **1996**, *96*, 271. (d) Bernasconi, C. F. *Chem. Soc. Rev.* **1997**, *26*, 299. (e) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523. (f) Zaragoza Dörwald, F. *Metal Carbenes in Organic Synthesis*; Wiley VCH: Weinheim, Germany, **1999**. (g) de Meijere, A.; Schirmer, H.; Duetsch, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3964. (h) Herndon, J. W. *Coord. Chem. Rev.* **2000**, *206-207*, 237. (i) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **2002**, *37*, 137. (j) Barluenga, J. *Pure Appl. Chem.* **2002**, *74*, 1317. (k) Dötz, K. H.; Jahr, H. C. in *Carbene Chemistry*; Bertrand, G., Ed.; Fontis Media S. A.: Lausanne, Switzerland/ Marcel Dekker: New York, **2003**, 231. (l) Dötz, K. H.; Minatti, A. in *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, **2004**, 397. (m) Wu, Y.-T.; de Meijere, A. Top*. Organomet. Chem.* **2004**, *13*, 21. (n) Barluenga, J.; Rodríguez, F.; Fañanás, F. J.; Flórez, J. *Top. Organomet. Chem.* **2004**, *13*, 59. (o) Barluenga, J.; Santamaría, J.; Tomás, M. *Chem. Rev.* **2004**, *104*, 2259. (p) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. (q) Wu, Y.-T.; Kurahashi, T.; de Meijere, A. *J. Organomet. Chem.* **2005**, *690*, 5900. (r) Barluenga, J.; Martínez, S. *Arkivoc* **2006**, VII, 129. (s) Kagoshima, H.; Fuchibe, K.; Akiyama, T. *Chem. Rec.* **2007**, *7*, 104. (t) Sierra, M. A.; Gómez-Gallego, M.; Martínez-Álvarez, R. *Chem. Eur. J.* **2007**, *13*, 736. (u) Sierra, M. A.; Fernández, I.; Cossío, F. P. *Chem. Commun.* **2008**, 4671. (v) Santamaría, J. *Curr. Org. Chem.* **2009**, *13*, 31. (w) Dötz, K. H.; Stendel Jr., J. *Chem. Rev*. **2009**, *109*, 3227.

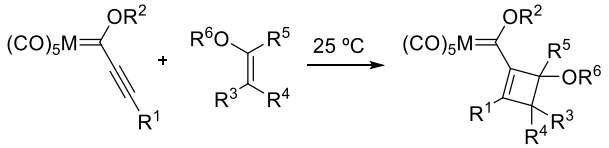
57 Raubenheimer, H. G. *Dalton Trans*. **2014**, *43*, 16959.

2.1. Reacciones de cicloadición de complejos metal-carbeno de tipo Ficher en condiciones térmicas

Los complejos metal-carbeno de tipo Fischer α,β-insaturados son sustratos ideales para las reacciones de cicloadición, ya que, en ellos el doble o triple enlace se encuentra fuertemente activado en comparación con sus análogos orgánicos isolobales (ésteres y amidas α,β-insaturados). De hecho, se considera que el fragmento metálico del carbeno actúa como un grupo funcional que activa el ligando carbeno de forma similar a la que produce un ácido de Lewis directamente unido al grupo carbonilo del correspondiente éster orgánico,[58] razón por la cual estos complejos se han denominado "súper ésteres".

2.1.1. Cicloadiciones [2+2]

Las reacciones de cicloadición [2+2] constituyen el método más versátil para la construcción de anillos de cuatro eslabones. En este ámbito, el empleo de complejos alquinil-carbeno de tipo Fischer permite obtener los correspondientes derivados de ciclobuteno térmicamente en condiciones de reacción suaves (Esquema 17). Los sustratos más frecuentemente empleados en esta reacción son alquenos con grupos oxigenados (tales como enol y sililenol éteres, acetatos de vinilo y acetales de cetena)[59] y olefinas con sustituyentes nitrogenados (tales como lactimas y imidatos de alquinilo).[60] .



39 (M = Cr, W) **40** **41** (45-93 %)

Esquema 17. Cicloadiciones [2+2] de complejos alquinil-carbeno de tipo Fischer con alquenos.

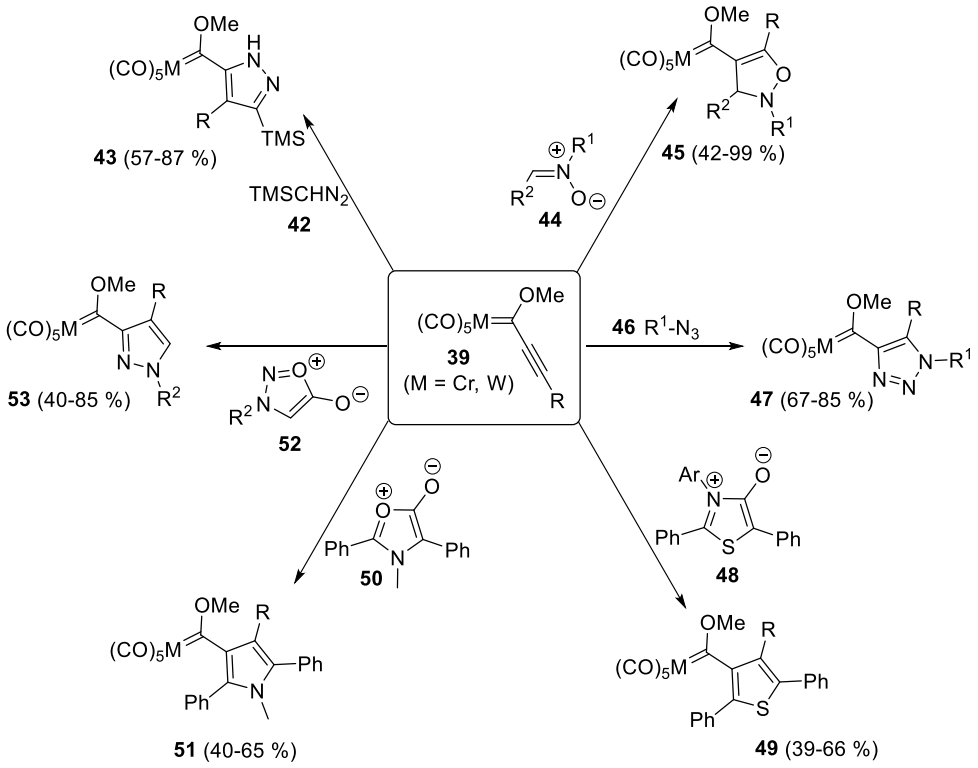
58 (a) Anderson, B. A.; Wulff, W. D.; Powers, T. S.; Tribbitt, S.; Rheingold, A. L. *J. Am. Chem. Soc.* **1992**, *114*, 10784. (b) Barluenga, J.; Aznar, F.; Barluenga, S. *J. Chem. Soc., Chem. Commun*. **1995**, 1973. (c) Barluenga, J.; Fernández-Rodríguez, M. A.; Aguilar, E. *Org. Lett.* **2002**, *4*, 3659.

59 (a) Faron, K. L.; Wulff, W. D. *J. Am. Chem. Soc.* **1988**, *110*, 8727. (b) Camps, F.; Llebaría, A.; Moretó, J. M.; Ricart, S.; Viñas, J. M. *Tetrahedron Lett.* **1990**, *31*, 2479. (c) de Meijere, A.; Wessjohann, L. *Synlett* **1990**, 20. (d) Faron, K. L.; Wulff, W. D. *J. Am. Chem. Soc.* **1990**, *112*, 6419. (e) Pipoh, R.; Eldik, R.; Wang, S. L. B.; Wulff, W. D. *Organometallics* **1992**, *11*, 490. (f) Camps, F.; Jordi, L.; Moretó, J. M.; Ricart, S.; Castaño, A. M.; Echavarren, A. M. *J. Organomet. Chem.* **1992**, *436*, 189. (g) Wulff, W. D.; Faron, K. L.; Su, J.; Springer, J. P.; Rheingold, A. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 197. (h) Barluenga, J.; Aznar, F.; Palomero, M. A.; Barluenga, S. *Org. Lett.* **1999**, *1*, 541. (i) Wu, H. P.; Aumann, R.; Fröhlich, R.; Wibbeling, B. *J. Org. Chem.* **2000**, *65*, 1183. (j) Barluenga, J.; Aznar, F.; Palomero, M. A. *Chem. Eur. J.* **2002**, *8*, 4149.

60 (a) Aumann, R.; Zhengkun, Y.; Fröhlich, R. *Organometallics* **1998**, *17*, 2897. (b) Aumann, R.; Hildmann, B.; Fröhlich, R. *Organometallics* **1998**, *17*, 1197.

2.1.2. Cicloadiciones [3+2]

Los complejos de tipo Fischer α,β-insaturados pueden emplearse para la síntesis de heterociclos funcionalizados de cinco eslabones por reacción con 1,3-dipolos. En concreto, los complejos alquinil-carbeno experimentan reacciones de cicloadición [3+2] con diazometano[61] y sus derivados,[62] nitronas,[63] azidas[64] y compuestos mesoiónicos cíclicos[65] (Esquema 18).



Esquema 18. Cicloadiciones [3_S+2_C] de complejos alquinil-carbeno de tipo Fischer.

Estos complejos α,β-insaturados presentan dos posiciones electrofílicas susceptibles de ser atacadas por nucleófilos (el carbono carbénico y el carbono en posición β), razón por la que además de participar en cicloadicones del tipo [3+2]

61 Kreissl, F. R.; Fischer, E. O.; Kreiter, C. G. *J. Organomet. Chem.* **1973**, *57*, 9.

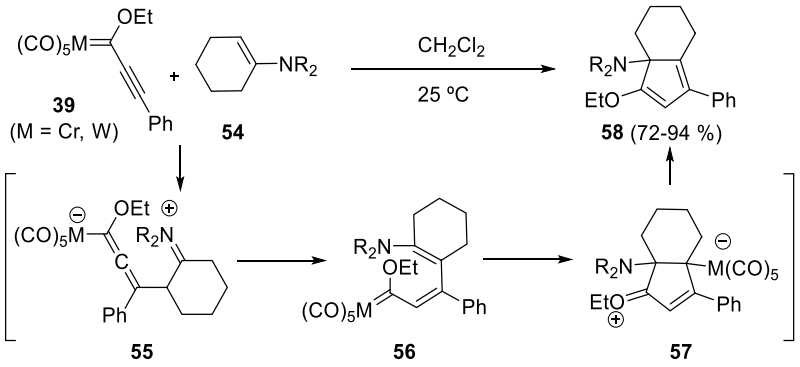
62 (a) Chan, K. S.; Wulff, W. D. *J. Am. Chem. Soc.* **1986**, *108*, 5229. (b) Luo, N.; Zheng, Z.; Yu, Z. *Org. Lett.*, **2011**, *13*, 3384.

63 (a) Chan, K. S.; Yeung, M. L.; Chan, W.; Wang, R.-J.; Mak, T. C. W. *J. Org. Chem.* **1995**, *60*, 1741. (b) Yeung, M. L.; Li, W.-K.; Liu, H.-J.; Wang, Y.; Chan, K. S. *J. Org. Chem.* **1998**, *63*, 7670. (c) Barluenga, J.; Fernández-María, F.; González, R.; Aguilar, E.; Revelli, G. A.; Viado, A. L.; Fañanás, F. J.; Olano, B. *Eur. J. Org. Chem.* **2000**, *68*, 1773. (d) Fernández, I.; Sierra, M. A.; Cossío, F. P. *J. Org. Chem.* **2006**, *71*, 6178.

64 (a) Sawoo, S.; Dutta, P.; Chakraborty, A.; Mukhopadhyay, R.; Bouloussa, O.; Sarkar, A. *Chem. Commun.* **2008**, 5957. (b) Baeza, B.; Casarrubios, L.; Ramírez-López, P.; Gómez-Gallego, M.; Sierra, M. A. *Organometallics* **2009**, *28*, 956. (c) Baeza, B.; Casarrubios, L.; Sierra, M. A., *Chem. Eur. J*. **2013**, *19*, 1429. (d) Flores-Conde, M. I; Vázquez, M. A.; Reyes, L.; Tamariz, J.; Delgado, F. *Organometallics*, **2013**, *32,* 4244.

65 (a) Jung, I.-Y.; Yoon, Y.-J.; Rhee, K. S.; Shin, G. C.; Shin, S. C. *Chem. Lett.* **1994**, 859. (b) Choi, Y. H.; Kang, B. S.; Yoon, Y.-J.; Kim, J.; Shin, S. C. *Synth. Commun.* **1995**, *25*, 2043. (c) Merlic, C. A.; Baur, A.; Aldrich C. C. *J. Am. Chem. Soc.* **2000**, *122*, 7398.

como sintones C2 (Esquema 18), también pueden participar en este tipo de transformaciones como sintones C3 con enaminas cíclicas (Esquema 19) e iminas no enolizables (Esquema 20). La cicloadición [3+2] con enaminas se inicia con una adición de tipo Michael al complejo dando lugar a un intermedio zwitteriónico de tipo alénico **55**. Desde este intermedio, una transferencia de protón seguida de ciclación genera el complejo pentacíclico **57** a partir del cual se obtiene el producto final tras la eliminación del fragmento metálico e isomerización (Esquema 19).[66]

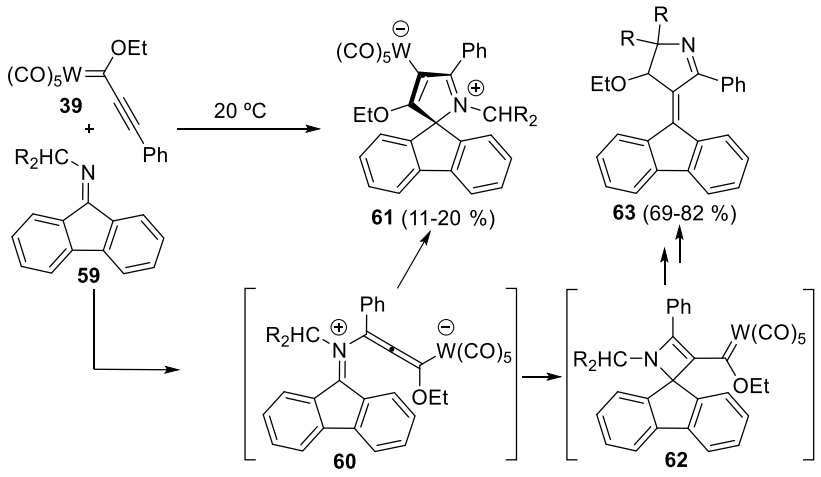


Esquema 19. Cicloadiciones [3_C+2_S] de complejos alquinil-carbeno de tipo Fischer con enaminas cíclicas.

De manera análoga, la reacción de iminas no enolizables con alquinil-carbenos se inicia por una adición 1,4 del nitrógeno imínico al complejo generándose el intermedio zwiteriónico **60** que puede evolucionar por dos caminos diferentes. Una ciclación promovida por la migración 1,2 del fragmento metálico genera el producto **61**. La formación del producto **63** sigue una secuencia de reacción más compleja que involucra la formación del intermedio tetracíclico **62** seguida de una reacción de metátesis intramolecular y reordenamiento final (Esquema 20).[67]

66 (a) Meyer, A. G.; Aumann, R. *Synlett* **1995**, 1011. (b) Aumann, R.; Kössmeier, M.; Jäntti, A. *Synlett* **1998**, 1120. (c) Aumann, R.; Meyer, A. G.; Fröhlich, R. *Organometallics* **1996**, *15*, 5018. (d) Barluenga, J.; Tudela, E.; Ballesteros, A.; Tomás, M. *J. Am. Chem. Soc.* **2009**, *131*, 2096.

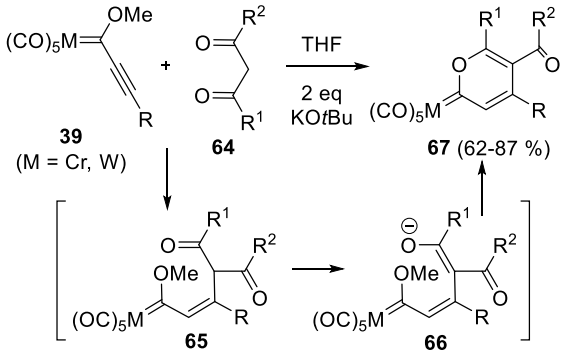
67 (a) Aumann, R.; Yu, Z.; Fröhlich, R.; Zippel, F. *Eur. J. Inorg. Chem.* **1998**, 1623. (b) Barluenga, J.; García-Rodríguez, J.; Martínez, S.; Suárez-Sobrino, A. L.; Tomás, M. *Chem. Asian J.* **2008**, *3*, 767.



Esquema 20. Cicloadiciones [3_C+2_S] de complejos alquinil-carbeno de tipo Fischer con iminas.

2.1.3. Cicloadiciones [3+3]

Los complejos metal-carbeno de tipo Fischer también pueden actuar como sintones C3 en reacciones con compuestos β-dicarbonílicos en presencia de cantidades catalíticas de base. La reacción en este caso se inicia con la adición del correspondiente enolato al carbono β del complejo metal-carbeno generando el intermedio **65** que evoluciona mediante un intercambio intramolecular del grupo alcóxido para dar lugar al correspondiente producto de cicloadición [3+3] **67** (Esquema 21).[68]

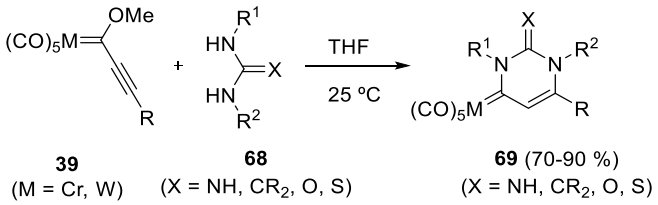


Esquema 21. Cicloadiciones [3 + 3] de complejos alquinil-carbeno de tipo Fischer con compuestos dicarbonílicos.

En un proceso similar, sistemas 1,3-dinitrogenados tales como diaminas, amidinas, guanidinas, aminotiazoles, aminopiridinas, ureas y tioureas reaccionan con complejos

68 (a) Wang, S. L. B.; Wulff, W. D. *J. Am. Chem. Soc.* **1990**, *112*, 4550. (b) Aumann, R.; Meyer, A. G.; Fröhlich, R. *J. Am. Chem. Soc.* **1996**, *118*, 10853.

alquinil-carbeno dando lugar a los correspondientes heterociclos de seis eslabones (Esquema 22).[69]



Esquema 22. Cicloadiciones [3+3] de complejos alquinil-carbeno de tipo Fischer con sistemas 1,3-dinitrogenados.

2.1.4. Cicloadiciones [4+2]

Los carbenos de Fischer α,β-insaturados actúan como dienófilos altamente eficientes en reacciones de Diels-Alder, proporcionando mejores rendimientos y mayores velocidades de reacción, además de regio- y estéreoselectividades más elevadas que las proporcionadas por sus análogos isolobales ésteres y amidas α,β-insaturados.[70]

Los complejos alcoxialquinil-carbeno de tipo Fischer pueden experimentan reacciones de Diels-Alder con dienos neutros[71] y ricos en electrones[72] así como con compuestos deficientes en electrones como 1-aza[73] y 2-aza-1,3-butadienos[74] (Esquema 23).

69 (a) Sawant, S. S.; Puranik, V. G.; Sarkar, A. *Organometallics* **1995**, *14*, 3617. (b) Polo, R.; Moretó, J. M.; Schick, U.; Ricart, S. *Organometallics* **1998**, *17*, 2135. (c) Spinella, A.; Caruso, T.; Pastore, U.; Ricart, S. *J. Organomet. Chem.* **2003**, *684*, 266. (d) Artillo, A.; Della Sala, G.; De Santis, M.; Llordes, A.; Ricart, S.; Spinella, A. *J. Organomet. Chem.* **2007**, *692*, 1277.

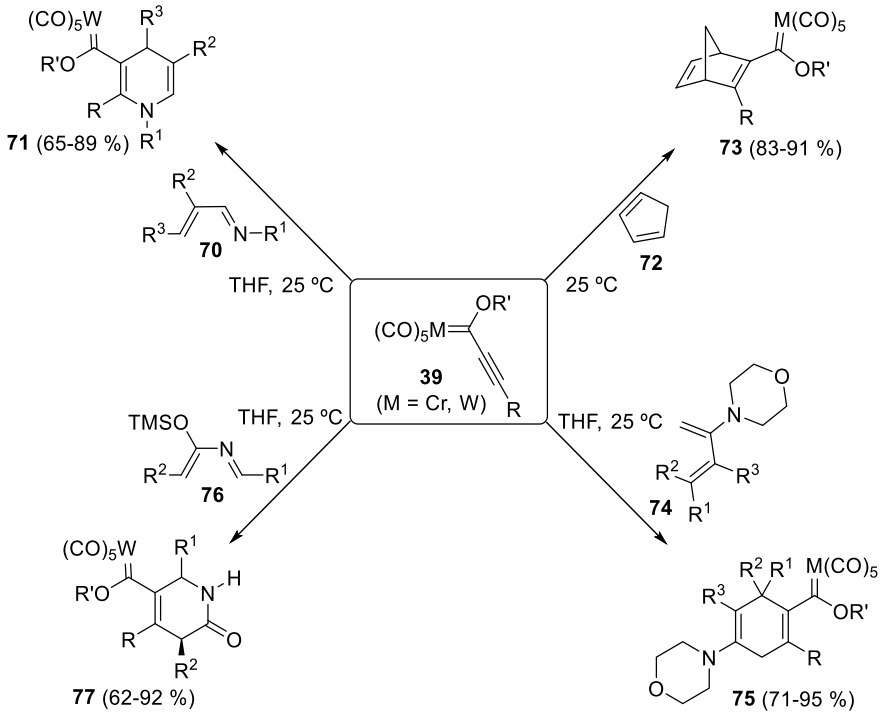
70 (a) Wulff, W. D.; Yang, D. C. *J. Am. Chem. Soc.* **1983**, *105*, 6726. (b) Wulff, W. D.; Bauta, W. E.; Kaesler, R. W.; Lankford, P. J.; Miller, R. A.; Murray, C. K.; Yang, D. C. *J. Am. Chem. Soc.* **1990**, *112*, 3642.

71 (a) Wulff, W. D.; Yang, D. C. *J. Am. Chem. Soc.* **1984**, *106*, 7565. (b) Dötz, K. H.; Kuhn, W. *J. Organomet. Chem.* **1985**, *286*, 23.

72 (a) Barluenga, J.; Aznar, F.; Barluenga, S.; Fernández, M.; Martín, A.; García-Granda, S.; Piñera-Nicolás, A. *Chem. Eur. J.* **1998**, *4*, 2280. (b) Merlic, C. A.; Xu, D. *J. Am. Chem. Soc.* **1991**, *113*, 7418. (c) Vázquez, M. A.; Reyes, L.; Miranda, R.; García, J. J.; Jiménez-Vázquez, H. A.; Tamariz, J.; Delgado, F. *Organometallics* **2005**, *24*, 3413.

73 Barluenga, J.; de la Rúa, R. B.; de Sáa, D.; Ballesteros, A.; Tomás, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4981.

74 (a) Barluenga, J.; Tomás, M.; López-Pelegrín, J. A.; Rubio, E. *Tetrahedron Lett.* **1997**, *38*, 3981. (b) Barluenga, J.; Tomás, M.; Ballesteros, A.; Santamaría, J.; Suárez-Sobrino, A. *J. Org. Chem.* **1997**, *62*, 9229.

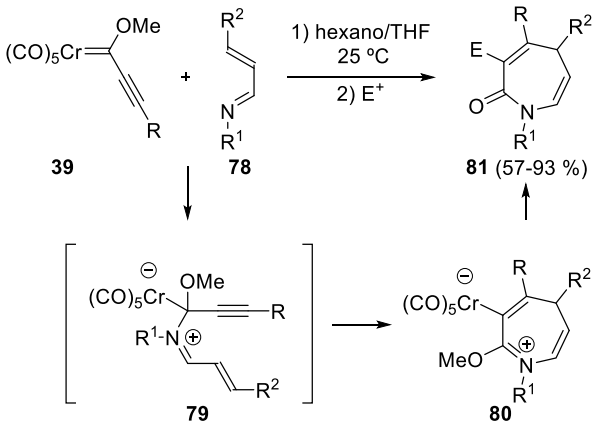


Esquema 23. Cicloadiciones [4+2] de complejos alquinil-carbeno de tipo Fischer con dienos.

2.1.5. Cicloadiciones de orden superior.

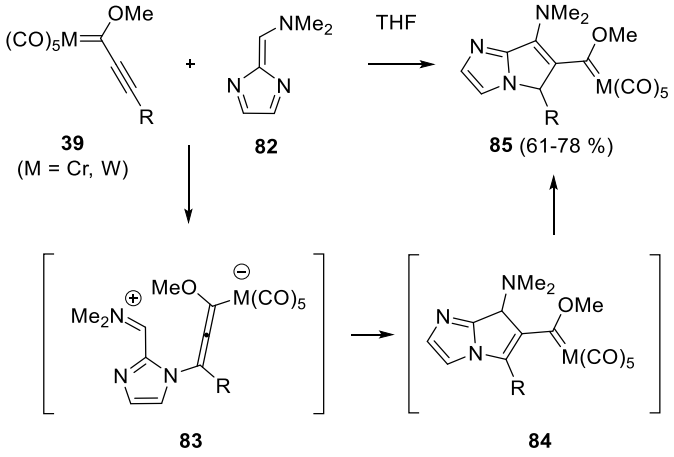
Tal y como se ha indicado en el apartado anterior, los complejos alquinil-carbeno de tipo Fischer son sustratos ideales para las reacciones de ciclación con dienos. Sin embargo, a diferencia de su análogo de wolframio, la reacción entre el correspondiente derivado de cromo y 1-azadienos no produce el cicloaducto correspondiente derivado de una ciclación de Diels-Alder. En cambio, se produce una heterociclación de tipo [4+3] iniciada por la adición 1,2 del átomo nitrógeno del azadieno seguida de una migración 1,2 del fragmento pentacarbonilcromo que da lugar al intermedio zwitteriónico metalado **79** cuya evolución genera el cicloaducto [4+3] **81** (Esquema 24).[75]

75 Barluenga, J.; Tomás, M.; Rubio, E.; López-Pelegrín, J. A.; García-Granda, S.; Pertierra, P. *J. Am. Chem. Soc.* **1996**, *118*, 695.



Esquema 24. Cicloadiciones [4+3] de complejos alquinil-carbeno de tipo Fischer con 1-azadienos.

Barluenga describió en 2006 un ejemplo de cicloadición [6+2] con complejos alquinil-carbeno de tipo Fischer y un diazafulveno. El mecanismo propuesto implica una secuencia de adición nucleófila conjugada del diazafulveno al carbono β del complejo, generando el intermedio zwitteriónico **83**, el cual experimenta una ciclación espontanea al tautómero **84**, que finalmente se isomeriza para dar lugar al producto final **85** (Esquema 25).[76]

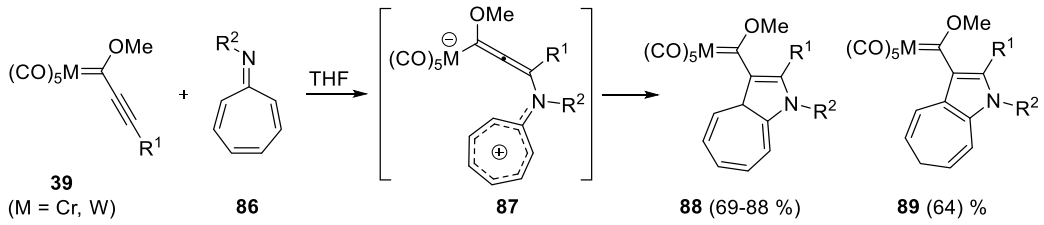


Esquema 25. Cicloadiciones [6+2] de complejos alquinil-carbeno de tipo Fischer con un diazafulveno.

Finalmente, este mismo grupo publicó en 2009 la reacción de cicloadición de mayor orden conocida hasta ese momento con complejos alquinil-carbeno de tipo Fischer. Así, la reacción de los complejos **39** con azaheptafulvenos en THF a

76 Barluenga, J.; García-Rodríguez, J.; Martínez, S.; Suárez-Sobrino, A. L.; Tomás, M. *Chem. Eur. J.* **2006**, *12*, 3201.

temperatura ambiente genera las especies **88** y **89** a través de una cicloadición formal [8+2] posiblemente a través del intermedio zwitteriónico **87** (Esquema 26).[77]



Esquema 26. Cicloadiciones [8+2] de complejos alquinil-carbeno de tipo Fischer con azaheptafulvenos.

2.2. Reacciones de cicloadición de complejos metal-carbeno de tipo Fischer en condiciones fotoquímicas

Los complejos metal-carbeno de tipo Fischer exhiben una rica y variada reactividad fotoquímica.[78] Cuando un complejo de tipo Fischer se irradia con luz visible se produce la llamada reacción de fotocarbonilación, caracterizada por la inserción reversible de uno de los ligandos CO en el enlace metal-carbeno, dando lugar a una especie cuya naturaleza corresponde a una metalaciclopropanona o cetena coordinada a metal.[78]

La irradiación de complejos de tipo Fischer permite acceder a cetenas ricas en electrones cuya obtención resulta complicada mediante métodos convencionales. Además, estas metalocetenas son más reactivas y específicas, ya que la coordinación del metal evita las reacciones colaterales habituales en cetenas libres (como la incorporación de más de una molécula de cetena o su dimerización). La capacidad sintética que proporciona la reactividad fotoquímica de estos complejos compite en eficiencia y excede en versatilidad tanto a otros complejos organometálicos como a otras reacciones fotoquímicas de compuestos orgánicos.[79]

La reactividad de las metalocetenas se ha restringido, prácticamente, a la formación de anillos de cuatro eslabones mediante cicloadición [2+2].

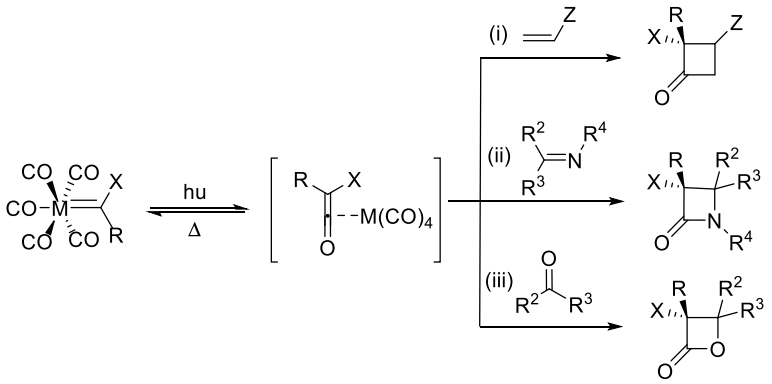
77 Barluenga, J., García-Rodríguez, J., Suárez-Sobrino, A.; Tomás, M. *Chem. Eur. J*. **2009**, *15*, 8800.

78 (a) L. S. Hegedus, *Tetrahedron*, **1997**, *53*, 4105. (b) A. Arrieta, F. P. Cossío, I. Fernández, M. Gómez-Gallego, B. Lecea, M. J. Mancheño, M. A. Sierra, *J. Am. Chem. Soc*. **2000**, *122*, 11509 (c) I. Fernández, M. A. Sierra, M. Gómez-Gallego, M. J. Mancheño, F. P. Cossío, *Chem. Eur. J*. **2005**, *11*, 5988. (d) I. Fernández, F. P. Cossío, M. A. Sierra, *Acc. Chem. Res*. **2011**, *44*, 479.

79 (a) Hoffmann, N. *Chem. Rev*. **2008**, *108*, 1052. (b) Gilbert, A.; Baggott, J. *Essentials of Molecular Photochemistry*; Blackwell Science: Oxford, **1991**. (c) Turro, N. J. Modern *Molecular Photochemistry; University Science Books*: Sausalito, CA, **1991**.

2.2.1. Cicloadiciones [2+2]

Las metalocetenas generadas fotoquímicamente a partir de los complejos metal-carbeno de tipo Fischer son conocidas por su versatilidad y eficiencia en la generación de anillos de cuatro eslabones por reacción con cetenófilos. Así, la irradiación de complejos metal-carbeno de tipo Fischer en presencia de (i) alquenos, se emplea en la síntesis de ciclobutanonas,[80] (ii) de iminas, para generar β-lactamas,[81] y (iii) de cetonas, para dar lugar a lactonas (Esquema 27).[82] En particular, las reacciones de estos complejos con iminas para la síntesis de β-lactamas han experimentado un mayor desarrollo debido a la importancia biológica de estos heterociclos.[83]



Esquema 27. Cicloadiciones [2+2] fotoquímicas de complejos metal-carbeno de tipo Fischer.

2.2.2. Cicloadiciones [3+2]

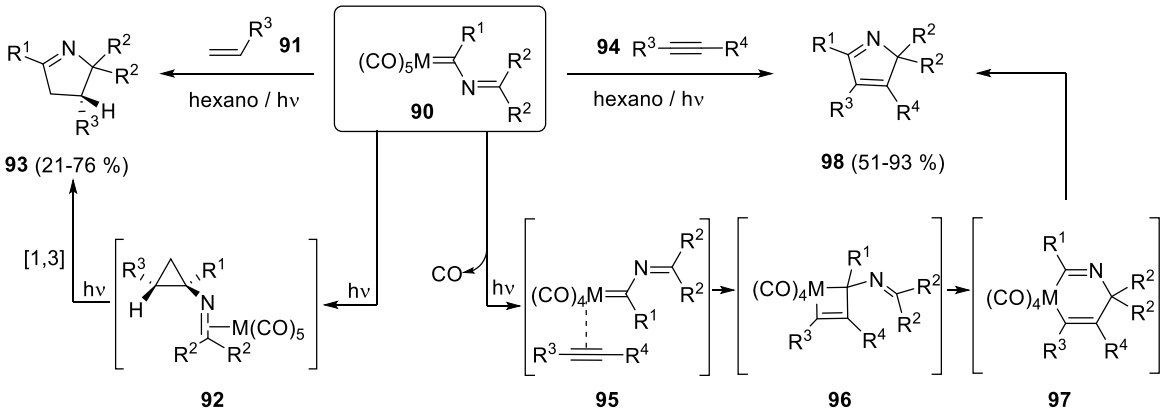
80 (a) Sierra, M. A.; Hegedus, L. S. *J. Am. Chem. Soc*. **1989**, *111*, 2235. (b) Söderberg, B. C.; Hegedus, L. S.; Sierra, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 4364. (c) Hegedus, L. S.; Bates, R. W.; Söderberg, B. C. *J. Am. Chem. Soc.* **1991**, *113*, 923. (d) Wen, X.; Norling, H.; Hegedus, L. S. *J. Org. Chem*. **2000**, *65*, 2096.

81 (a) Hegedus, L. S.; Imwinkelried, R.; Alarid-Sargent, M.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc*. **1990**, *112*, 1109. (b) Narukawa, Y.; Juneau, K. N.; Snustand, D. C.; Miller, D. B.; Hegedus, L. S. *J. Org. Chem.* **1992**, *57*, 5453. (c) Sierra, M. A.; Mancheño, M. J.; Vicente, R.; Gómez-Gallego, M. *J. Org. Chem.* **2001**, *66*, 8920. (d) Fernández, I.; Sierra, M. A.; Mancheño, M. J.; Gómez-Gallego, M.; Cossío, F. P. *J. Am. Chem. Soc.* **2008**, *130*, 13892. (e) Fernández, I.; Sierra, M. A.; *Top. Heterocycl. Chem.* **2013**, *30*, 65.

82 Colson, P. J.; Hegedus, L. S. *J. Org. Chem*. **1994**, *59*, 4972.

83 (a) Rolinson, G. N. *J. Antimicrob. Chemother*. **1998**, *41*, 589. (b) Setti, E. L.; Micetich, R. G. Curr. *Med. Chem*. **1998**, *5*, 101. (c) Demain, A. L.; Elander, R. P. *Antonie van Leeuwenhoek* **1999**, 75, 5. (d) Gómez-Gallego, M.; Mancheño, M. J.; Sierra, M. A. *Tetrahedron* **2000**, *56*, 5743. (e) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev*. **2008**, *108*, 3988. (f) Fu, N.; Tidwell, T. T. *Tetrahedron* **2008**, *64*, 10465. (g) Aranda, M. T.; Pérez-Faginas, P.; González-Muniz, R. Curr. *Org. Synth*. **2009**, *6*, 325. (h) Kong, K.-F.; Schneper, L.; Mathee, K. *APMIS* **2010**, 118, 1. (j) Tidwell, T. T. *Top*. *Heterocycl. Chem*. **2013**, *30*, 111.

A diferencia de las reacciones mencionadas anteriormente, en la reacción fotoquímica entre complejos iminocarbeno y alquenos[84] o alquinos.[85] en lugar de obtenerse el correspondiente cicloaducto [2+2] con inserción de monóxido de carbono, se genera el producto correspondiente a una cicloadición de tipo [3+2] sin inserción de monóxido de carbono (Esquema 28). Los mecanismos a través de los cuales tienen lugar estas cicloadiciones [3+2] son notablemente diferentes, dependiendo de si se usa un alqueno o un alquino. En el caso de las olefinas se sugiere un mecanismo basado en dos reacciones fotoquímicas diferentes consecutivas: la primera conduce a un ciclopropano **92**, que experimenta un proceso de reordenamiento para dar lugar a una pirrolina **93**. En cambio, el mecanismo a través del cual se produce el pirrol **98** implica la disociación de una molécula de CO permitiendo la coordinación e inserción del alquino, el posterior aumento del tamaño de anillo y finalmente, la eliminación reductora del fragmento metálico.



Esquema 28. Cicloadiciones [3+2] fotoquímicas de complejos metal-carbeno de tipo Fischer.

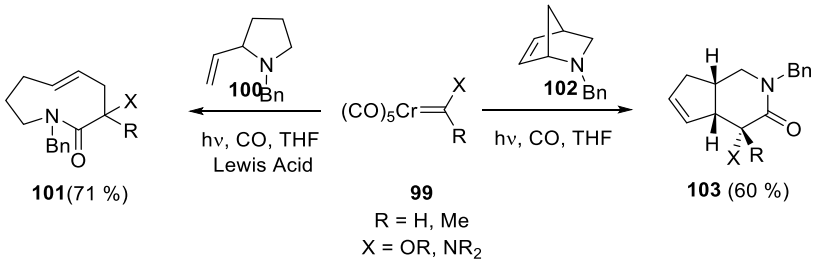
2.2.3 Cicloadiciones de orden superior.

Cuando los complejos metal-carbeno de tipo Fischer se irradian en presencia de aminas terciarias alílicas se producen reacciones de cicloadición que permiten la síntesis de heterociclos de tamaño considerable. Las aminas alílicas terciarias cíclicas y tensionadas han demostrado ser las más eficientes en la generación de mono- y

84 (a) Campos, P. J.; Sampedro, D.; Rodríguez, M. A. *Organometallics* **2002**, *21*, 4076. (b) Campos, P. J.; Soldevilla, A.; Sampedro, D.; Rodríguez, M. A. *Org. Lett.* **2001**, *3*, 4087.

85 (a) Campos, P. J.; Sampedro, D.; Rodríguez, M. A *J. Org. Chem.* **2003**, *68*, 4674. (b) Campos, P. J.; Caro, M.; López-Sola, S.; Sampedro, D.; Rodríguez, M. A. *J. Organomet. Chem.* **2006**, *691,* 1075.

biciclos *N*-sustituidos (Esquema 29).[86] Se ha propuesto que esta transformación involucra la generación de un intermedio zwitteriónico que, posteriormente, experimenta un reordenamiento de tipo aza-Cope.



Esquema 29. Cicloadiciones fotoquímicas de complejos metal-carbeno de tipo Fischer y aminas cíclicas.

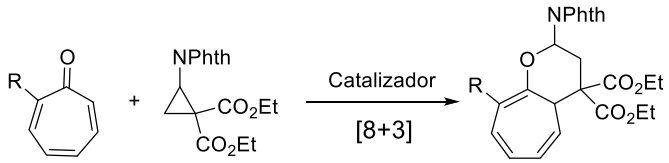
86 Deur, J.; Miller, M. W.; Hegedus , L. S. *J. Org. Chem.* **1996**, *61*, 2871.

OBJETIVOS

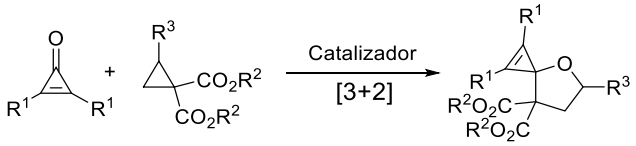
La presente memoria tiene como objetivo general el desarrollo y estudio de nuevos procesos de ciclación y cicloadición. Con este fin, se han seleccionado dos tipos de sustratos cuyas características estructurales y electrónicas les confieren las propiedades idóneas para su empleo en dichas transformaciones: ciclopropanos dador-aceptor (D-A) y complejos metal-carbeno de tipo Fischer.

✓ El primer capítulo de esta tesis se centra en el empleo de ciclopropanos D-A y su capacidad para actuar como 1,3-zwitteriones.

En la primera parte de este capítulo se explorará la reacción de ciclación de alto orden [8+3] entre ciclopropanos D-A y derivados de tropona, que actuarán como agentes nucleófilos participando como componente 8π en el proceso.

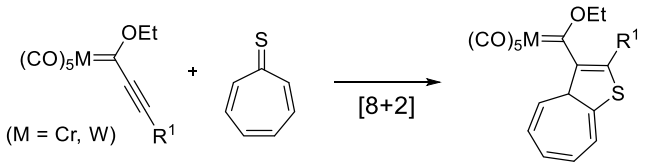


En la segunda parte del capítulo se estudiará la formación de compuestos espiránicos mediante reacción [3+2] entre ciclopropenonas y ciclopropanos D-A.

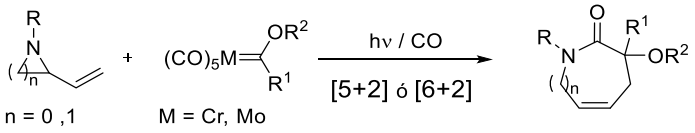


✓ En el segundo capítulo de la tesis se desarrollarán y estudiarán nuevas reacciones de cicloadición de complejos metal-carbeno de tipo Fischer tanto en condiciones térmicas como fotoquímicas.

En la primera parte de este segundo capítulo se analizará la capacidad de los complejos metal-carbeno α,β-insaturados de tipo Fischer para participar en reacciones de cicloadición de alto orden. En concreto, se explorará la reacción de cicloadición [8+2] entre complejos alquinil-carbeno de tipo Fischer y tropotiona.



La segunda parte de este capítulo se centrará en la capacidad de los complejos metal-carbeno de tipo Fischer para participar en reacciones de cicloadición fotoquímicas de alto orden. Concretamente se estudiará su reacción frente a vinilaziridinas y vinilazetidinas, generando anillos de siete y ocho eslabones mediante reacciones de cicloadición formales [5+2] y [6+2], respectivamente.



CAPÍTULO 1

1.1. Regio- and Diastereoselective Stepwise [8+3]-Cycloaddition Reaction between Tropone Derivatives and Donor-Acceptor Cyclopropanes

Org. Lett. **2013**, *15*, 4928

A novel $SnCl_4$-catalyzed [8+3]-cycloaddition reaction between tropone derivatives and donor-acceptor aminocyclopropanes is described. The process leads to the formation of amino-substituted tetrahydrocyclohepta[b]pyrans with complete regio- and diasteroselectivity. Density functional theory calculations suggest that the cycloaddition occurs stepwise through an aromatic zwitterionic intermediate

Cycloaddition reactions are highly valuable transformations in modern organic synthesis because of their ability to increase the molecular complexity in a single synthetic step.[1] In this sense, donor-acceptor cyclopropanes (DACs),[2] which can be considered as 1,3-zwitterionic synthons, have proven to be very useful for the direct synthesis of five-membered carbo- and heterocycles via [3+2]-cycloaddition reactions.[3] Recent applications of these processes to the synthesis of complex natural products have clearly demonstrated their potential in organic synthesis.[4] Nevertheless, the use of DACs in high-order cycloaddition reactions has been scarcely explored.[5]

Within the context of our ongoing work in the reaction mechanism and synthetic applications of cycloaddition reactions[6] and based on previous studies,[7] we recently reported that tropone derivatives can be used as 8-component in high-order [8+2]-cycloaddition reactions.[8] These previous results prompted us to explore the reaction between DACs and tropone derivatives, which would lead to the formation of [8+3]-cycloadducts. In addition, Density Functional Theory (DFT) calculations were carried out to unravel the reaction mechanism of this novel transformation.

The reaction between the parent tropone **1a** and donor-acceptor aminocyclopropane **2** was explored first. This particular DAC was chosen due to its

1 (a) *Cycloaddition Reactions in Organics Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, **2001**. (b) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson,W. H., Eds.; Wiley: New York, **2002**.

2 For reviews on DACs, see: (a) Reissig, H. U.; Zimmer, R. *Chem. Rev*. **2003**, *103*, 1151. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (c) De Simone, F.; Waser, J. *Synthesis* **2009**, 3353.

3 Selected recent examples: (a) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc*. **2009**, *131*, 3122. (b) Parsons, A. T.; Smith, A. G.; Neel, A. J.; Johnson, J. S. *J. Am. Chem. Soc*. **2010**, *132*, 9688. (c) Goldberg, A. F. G.; O'Connor, N. R.; Craig II, R. A.; Stoltz, B. M. *Org. Lett*. **2012**, *14*, 5314. (d) Xiong, H.; Xu, H.; Liao, S.; Xie, Z.; Tang, Y. H. *J. Am. Chem. Soc*. **2013**, *135*, 7851. For a review, see: (e) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev*. **2009**, *38*, 3051.

4 See, for instance: (a) Morales, C. L.; Pagenkopf, B. L. *Org. Lett*. **2008**, *10*, 157. (b) Campbell, M. J.; Johnson, J. S. *J. Am. Chem. Soc*. **2009**, *131*, 10370. (c) Karadeolian, A.; Kerr, M. A. *Angew. Chem. Int. Ed*. **2010**, *49*, 1133. (c) Zhang, H.; Curran, D. P. *J. Am. Chem. Soc*. **2011**, *133*, 10376. (e) Goldberg, A. F. G.; Stoltz, B. M. *Org. Lett*. **2011**, *13*, 4474.

5 To the best of our knowledge, only a [4+3]-cycloaddition reaction involving DAC has been reported. See: (a) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Angew. Chem. Int. Ed*. **2008**, *47*, 1107. (b) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Eur. J. Org. Chem*. **2008**, 5329.

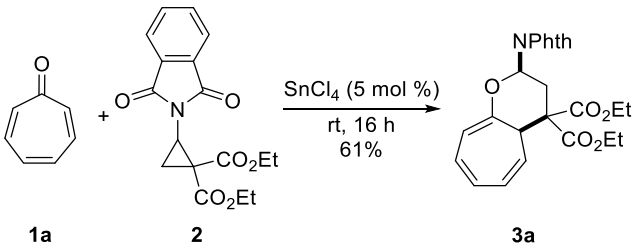
6 (a) Fernández, I.; Sierra, M. A.; Cossío, F. P. *J. Org. Chem*. **2006**, *71*, 6178. (b) Fernández, I.; Cossío, F. P.; Sierra, M. A. *Organometallics* **2007**, *26*, 3010. (c) Fernández, I.; Sierra, M. A.; Cossío, F. P. *J. Org. Chem.* **2008**, *73*, 2083. (d) Fernández, I.; Cossío, F. P.; de Cózar, A.; Lledós, A.; Mascareñas, J. L. *Chem. Eur. J*. **2010**, *16*, 12147. (e) Saya, L.; Bhargava, G.; Navarro, M. A.; Gulías, M.; López, F.; Fernández, I.; Castedo, L.; Mascareñas, J. L. *Angew. Chem. Int. Ed*. **2010**, *49*, 9886. (f) Andrada, D. M.; Granados, A. M.; Solá, M.; Fernández, I. *Organometallics* **2011**, *30*, 466. (g) Fernández, I.; Cossío, F. P.; Bickelhaupt, F. M. *J. Org. Chem*. **2011**, *76*, 2310. (h) Fernández, I.; Mascareñas, J. L. *Org. Biomol. Chem*. **2012**, *10*, 699. (i) Fernández, I.; Solá, M.; Bickelhaupt, F. M. *Chem. Eur. J*. **2013**, *19*, 7416.

7 For a review on high-order cycloadditions involving tropone derivatives, see: (a) Nair, V.; Abhilash, K. G. *Top. Heterocycl. Chem*. **2008**, *13*, 173. (b) Barluenga, J.; García-Rodríguez, J.; Suárez-Sobrino, A. L.; Tomás, M. *Chem. Eur. J*. **2009**, *15*, 8800.

8 (a) Lage, M. L.; Fernández, I.; Sierra, M. A.; Torres, M. R. *Org. Lett*. **2011**, *13*, 2892. (b) Rivero, A. R.; Fernández, I.; Sierra, M. A. *J. Org. Chem*. **2012**, *77*, 6648.

proven ability to produce *N*-containing hetero- and carbocycles as recently demostrated by Waser and co-workers.[9] Optimization of the reactions conditions (different Lewis acids, temperature, solvent and stoichiometry) indicated that the use catalytic amounts of $SnCl_4$ (5 mol %) and equimolar amounts of **1a** and **2**, in CH_2Cl_2 as solvent at room temperature leads to the formation of cycloaduct **3a** in 61% reaction yield (Scheme 1).[10] Interestingly, no traces of the corresponding [3+2]-cycloadduct (the product observed in the related reaction involving different ketones and **2**)[9c] were detected in the crude reaction mixtures. The bias of tropone to experience high order cycloaddition reactions can be ascribed to its peculiar electronic structure (see below).[7,8] In addition, **3a** is formed exclusively as the *syn* diastereoisomer as revealed by NOESY experiments. Therefore, this novel [8+3]-cycloaddition reaction involving **1a** occurs with complete diastereoselectivity.[11]

To gain more insight into the origin of the diastereoselectivity of the above process, a computational DFT study was carried out.[12] The computed reaction profile of the process between **1a** and **2** is illustrated in Figure 1, which shows the relative free energies in CH_2Cl_2 solution.



Scheme 1. [8+3]-Cycloaddition between tropone **1a** and **2**.

As proposed previously,[13,14] the process is assumed to begin with the coordination of the Lewis acid to the DAC to produce the intimate ion pair **4a**, which is in

9 (a) de Nanteuil, F.; Waser, J. *Angew. Chem. Int. Ed*. **2011**, *50*, 12075. (b) Benfatti, F.; de Nanteuil, F.; Waser. J. *Org. Lett*. **2012**, *14*, 386. (c) Benfatti, F.; de Nanteuil, F.; Waser. J. *Chem. Eur. J*. **2012**, *18*, 4844.

10 Typical procedure: In a two-necked flask equipped with a nitrogen inlet, tropone **1a** (1 equiv) and aminocyclopropane **2** (1 equiv) were dissolved in anhydrous dichloromethane at room temperature. After 5 min, $SnCl_4$ in dichloromethane (5 mol %) was added. The mixture was stirred under nitrogen at 16 h, then the reaction was quenched by the addition of triethylamine and subsequently flushed through a short plug of silica gel, eluting with EtOAc. The solvent was removed in vacuo to give the crude reaction mixture, which was submitted to flash column chromatography to yield pure cycloadduct **3a**.

11 The reaction between diethyl 2-phenylcyclopropane-1,1-dicarboxylate and tropone 1a was also tested. Under the same reaction conditions used for the aminocyclopropane 2 (i.e., 5 mol % $SnCl_4$, rt, 16 h), the corresponding [8+3]-cycloadduct was not formed.

12 DFT calculations were carried out at PCM(CH_2Cl_2)-B3LYP/def2-SVP level of theory using the Gaussian 09 suite of programs. See computational details in the supporting information.

13 Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc*. **2008**, *130*, 8642.

14 For a computational study on the Sn(II)-catalyzed [3+2]-cycloaddition reaction between DAC's and benzaldehyde, see: Zhang, J.; Shen, W.; Li, M. *Eur. J. Org. Chem*. **2007**, 4855.

equilibrium with the completely dissociated zwitterion **4b**. Nucleophilic attack of the lone pair of the oxygen atom of **1a** to the iminium cation moiety of **4b** leads to the formation of the zwitterionic intermediate **INT1**. The ease of this process, which occurs via transition state **TS1**, is reflected in the very low activation barrier ($\Delta G_{a,298}$ = 2.8 kcal/mol) and exergonicity (ΔG_R = −3.1 kcal/mol) computed for this transformation. From **INT1**, a ring closure reaction occurs to produce the corresponding [8+3]-cycloadduct **INT2** via **TS2**, a saddle point associated with the formation of the new C–C bond (see optimized geometries of **TS2** in the Supporting Information).

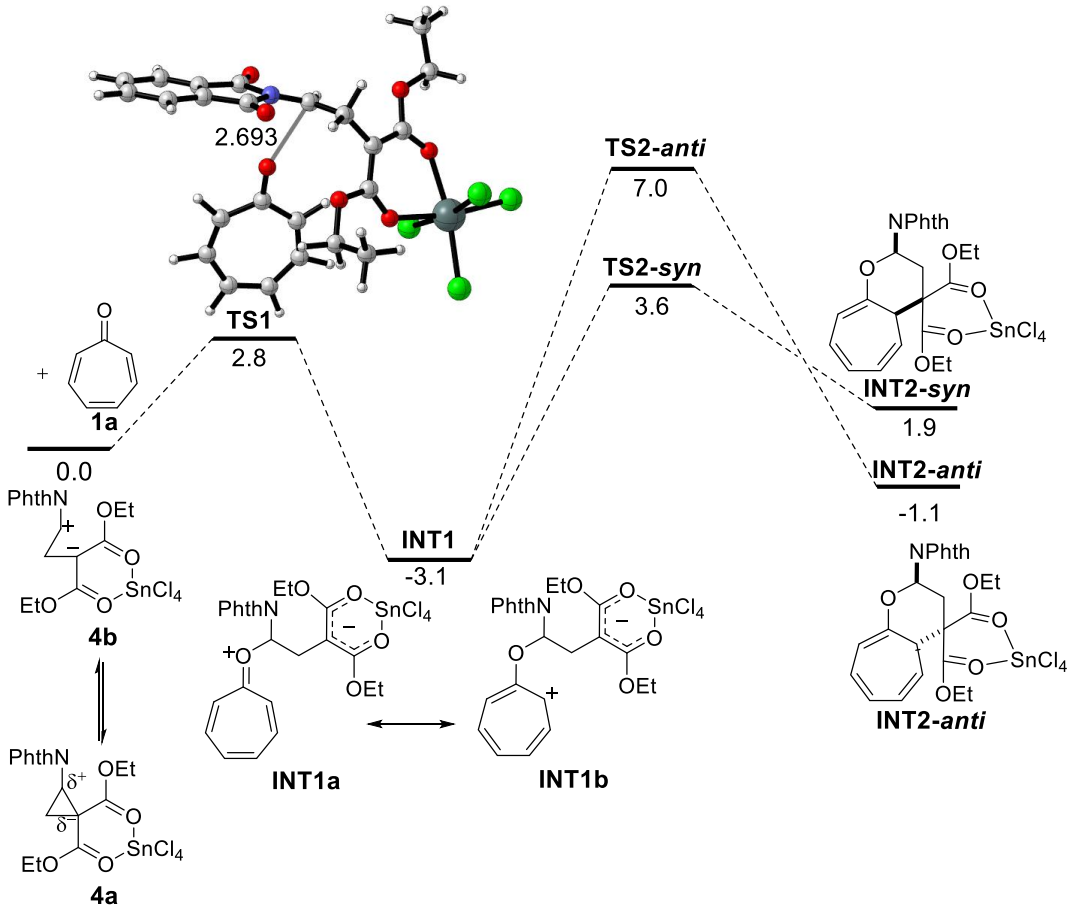


Figure 1. Computed reaction profile of the [8+3]-cycloaddition between tropone **1a** and $SnCl_4$-DAC complex **4**. Relative free energies (ΔG, 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data have been computed at the PCM(CH_2Cl_2)-B3LYP/def2-SVP level.

Two possible ring closures leading to the *syn*- and *anti*-cycloadducts are possible. As readily seen in Figure 1, the experimentally observed exclusive formation of the *syn*-isomer takes place under kinetic control in view of the lower activation barrier computed for the process involving the saddle point **TS2-*syn*** ($\Delta\Delta G_a$(*syn-anti*) = 3.4

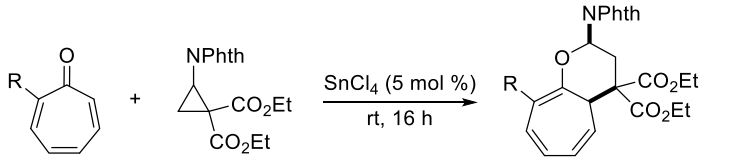
kcal/mol). Final decoordination of $SnCl_4$ in **INT2-*syn*** produces the observed [8+3]-cycloadduct **3a** thus regenerating the catalyst. Therefore, similar to related high-order cycloaddition reactions involving tropone derivatives,[8] the present [8+3]-cycloaddition between the parent tropone **1a** and DAC **2** occurs stepwise through a zwitterionic intermediate (**INT1**).

The structure of zwitterion **INT1** deserves further analysis. As shown in Figure 1, **INT1** can also be described by the resonance form **INT1b**, where the positive charge is delocalized within the seven-membered ring. This species, which resembles the tropyl cation, should therefore possess a remarkable aromatic character. Indeed, the computed negative Nucleus Independent Chemical Shift (NICS)[15] values (NICS(0) = −3.6 and NICS(1) = −7.2 ppm) and the corresponding out-of-plane tensor component ($NICS(1)_{zz}$ = −16.7 ppm) confirm the magnetic aromatic nature of this zwitterion. In addition, the optimized geometry of **INT1** indicates that the seven-membered ring is highly planar (C1(O)–C2–C3–C4 dihedral angle of −0.3°) with C–C bond distances which are intermediate between single and double bonds (ranging from 1.382 to 1.425 Å), thus satisfying the so-called geometrical criterion for aromaticity as well.[16] Therefore, it can be suggested that the gain in stability by aromaticity occurring in **INT1** is in part responsible for the stepwise nature of the transformation.

Once the reaction mechanism of the process was analyzed, the influence of substituents attached to the tropone ring on the regioselectivity of the [8+3]-cycloaddition was explored. To this end, a series of different 2-substituted tropones **1b-j** having donor or acceptor groups directly attached to the C2-carbon atom of the tropone ring were reacted with DAC **2** in the reaction conditions used above (i.e., 5 mol % $SnCl_4$, room temperature, CH_2Cl_2 for 16 h). As shown in Scheme 2, all the reactions tested lead to the formation of the corresponding [8+3]-cycloadducts **3** in good yields, with the exception of the reactions involving 2-alkoxytropones **1i** and **1h** and 2-silyloxytropone **1j**, which were recovered unaltered together with a new product arising from the cyclopropane (see below). Strikingly, in all cases the ring closure occurred at the C7-carbon atom of the initial tropone, which indicates that this [8+3]-cycloaddition reaction proceeds with complete regioselectivity (no traces of the corresponding C2-cycloadduct were observed in the respective reaction crudes). In addition, and as expected, cycloadducts **3b-g** were formed exclusively as *syn*-diastereoisomers as confirmed by NOESY experiments. Single crystals of the

15 Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. v. R. *Chem. Rev*. **2005**, *105*, 3842.
16 Schleyer, P. v. R.; Jiao, H. *Pure Appl. Chem*. **1996**, *68*, 209 and references therein.

cycloadduct **3e** (grown in hexanes/CH_2Cl_2 solution) suitable for X-ray diffraction analysis fully confirm, by analogy, both the regio- and the relative stereochemistry of compounds **3** (Figure 2).



1b, R = Cl
1c, R = Br
1d, R = Ph
1e, R = 4-Me-C_6H_4
1f, R = 4-OMe-C_6H_4
1g, R = 4-NO_2-C_6H_4
1h, R = OMe
1i, R = OBn
1j, R = OTBS

2

3b, R = Cl (68%)
3c, R = Br (64%)
3d, R = Ph (68%)
3e, R = 4-Me-C_6H_4 (65%)
3f, R = 4-OMe-C_6H_4 (62%)
3g, R = 4-NO_2-C_6H_4 (71%)
3h, R = OMe (0%)[a]
3i, R = OBn (0%)[a]
3j, R = OTBS (0%)[a]

Scheme 2. [8+3]-Cycloaddition Reactions between 2-Substituted Tropones **1b-j** and **2**. [a] See text.

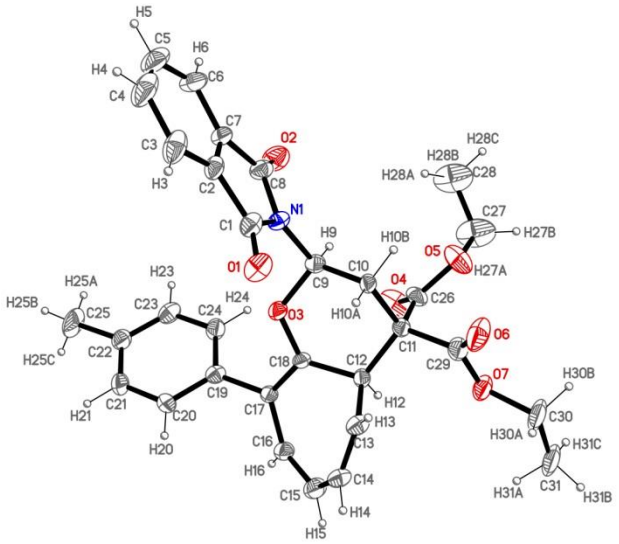


Figure 2. ORTEP-diagram of compound **3e**. Ellipsoids are drawn at the 30% probability level.

We carried out DFT-calculations as well to understand the regioselectivity, namely the exclusive formation of the C7- over the C2-cycloadduct, of the transformation. Thus, both regioisomeric *syn*-ring closure reactions arising from the zwitterionic species **INT1-Ph2** and **INT1-Ph7**, formed upon the initial nucleophilic attack of the phenyltropone **1d** to **4b**, were computed. As readily seen in Figure 3, the ring closure leading to the C7-regioisomer (via **TS2-Ph7**) is kinetically ($\Delta\Delta G_a$(Ph7-Ph2) = 14.4 kcal/mol) and also thermodynamically ($\Delta\Delta G_R$(Ph7-Ph2) = 12.9 kcal/mol) favored over the ring closure process forming the C2-regioisomer via **TS2-Ph2**. A similar

result was computed in the [8+3]-cycloaddition involving 2-bromotropone **1c** ($\Delta\Delta G_a$(Br7-Br2) = 6.8 kcal/mol). As the electronic effects of phenyl and bromide substituents are markedly different, and no effect of the substituents attached to the aromatic ring was observed, this regioselectivity should be steric in origin. It can be thus suggested that the steric hindrance exerted by the substituent attached at the C2-position may hamper the ring closure at this position directing the ring closure to occur at the sterically unhindered C7-position of the tropone ring.

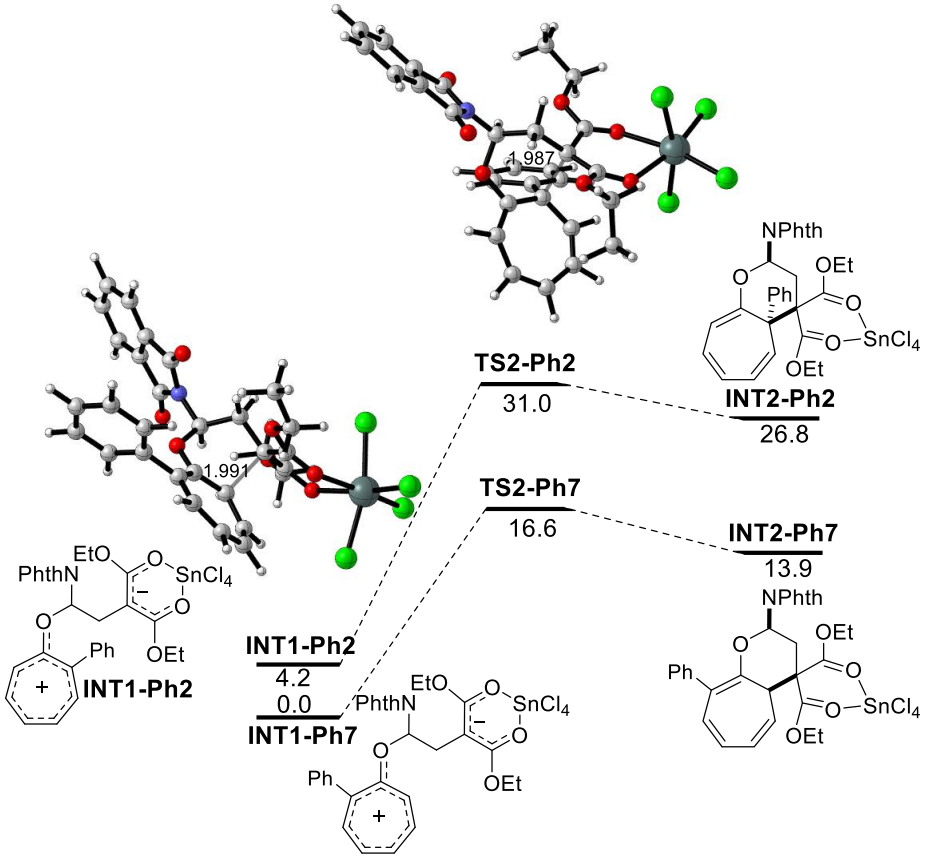


Figure 3. Computed profile for the ring closure of the [8+3]-cycloaddition between tropone **1d** and $SnCl_4$-DCA complex **4**. See caption for Figure 1 for additional details.

As stated above, 2-alkoxytropones **1h** and **1i** and 2-silyloxytropone **1j** did not undergo the [8+3]-cycloaddition, which may be attributed to the electronic effect exerted by the donor alkoxy or silyloxy group.[17] Instead, a new compound **5** lacking the characteristic signals of the tropone in the corresponding NMR spectra was isolated in the processes involving **1h** and **1i**. Single crystals of the new compound **5** suitable for X-ray diffraction analysis were grown in hexanes/CH_2Cl_2 solution at room temperature. As seen in Figure 4, the structure of **5** corresponds to a dimer of the

17 Alternatively, coordination of the 2-alkoxytropone to the catalyst may be responsible for the lack of reactivity of compounds **1h** and **1i**. However, this coordination seems unlikely in the presence of the bulky TBS-substituent of compound **1j**.We thank a reviewer for pointing out this experiment

DAC **2**. As tropones **1h,i** were recovered unaltered in the reaction conditions used,[18] species **5** is very likely formed by the self-coupling of two molecules of the $SnCl_4$-DAC complex **4**. The formation of this dimer constitutes therefore a side reaction which occurs when DAC **2** reacts with electron-rich substrates such as alkoxytropones. We want to point out that, although the selfdimerization product of **2** has not been observed so far,[9] related dimerization products of DACs have been described.[19]

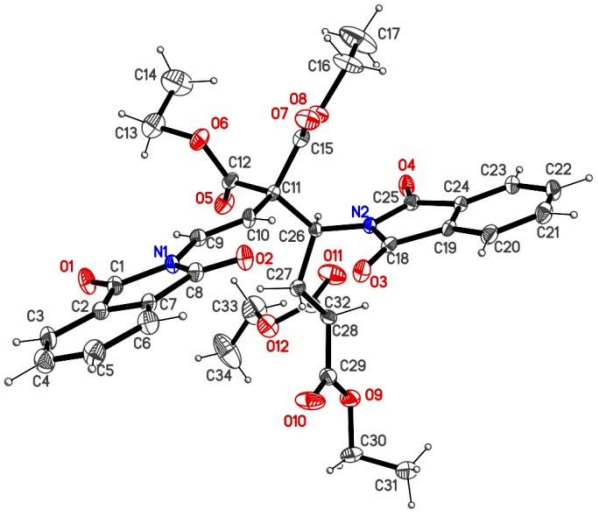


Figure 4. ORTEP-diagram of compound **5**. Ellipsoids are drawn at the 30% probability level.

In summary, the novel Lewis acid catalyzed [8+3]-cycloaddition reaction between tropone and tropone derivatives and donor-acceptor aminocyclopropane **2** has been studied. The process leads to the formation of amino-substituted tetrahydrocyclohepta[*b*]pyrans in good reaction yields and with complete regio- and diastereoselectivities. By means of computational-DFT methods, it was found that this transformation proceeds stepwise through a zwitterionic intermediate, which resembles the tropyl cation and therefore is stabilized by some degree of π-aromaticity. From this intermediate, a ring closure step, which controls the regio- and diastereoselectivities, occurs to produce the observed [8+3]-cycloadducts.

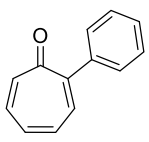
18 Moreover, dimer **5** was formed in the reactions of tropones **1h,i** with **2** at -78 ºC for prolonged reaction times. In addition, in a control experiment, dimer **5** was also formed in the reaction of DAC **2** and $SnCl_4$ conducted in the absence of any tropone derivative.

19 (a) Ivanova, O. A.; Budynina, E.a M.; Chagarovskiy, A. O.; Trushkov, I. V.; Melnikov, M. Y. *J. Org. Chem*. **2011**, *76*, 8852. (b) Chagarovskiy, A. O.; Ivanova, O. A.; Budynina, E. M.; Trushkov, I. V.; Melnikov, M. Y. *Tetrahedron Lett.* **2011**, *52*, 4421.

EXPERIMENTAL SECTION

General Procedures: All reactions were carried out under Argon atmosphere. All solvents used in this work were purified immediately before use. Triethylamine (Et_3N) and dichloromethane (DCM) were distilled from calcium hydride. Flame dried glassware was used for moisture-sensitive reactions. Identification of products was made by thin layer chromatography (kiesegel 60F-254). UV light (λ= 254 nm) and oleum was used to develop the plates. NMR spectra were recorded at 25 ºC in $CDCl_3$, on a 300 MHz (300 MHz for ^1H, 75 MHz for ^{13}C) spectrometer. Chemical shifts are given in ppm relative to TMS (^1H, 0.0 ppm) or $CDCl_3$ (^{13}C, 77.0 ppm). IR spectra were taken on a MIR (8000-400 cm^{-1}) spectrometer as solid films by slow evaporation of the solvent using the ATR (Attenuated Total Reflectance) technique. HRMS experiments were conducted on an Accurate Mass Q-TOF system (ESI) and MAT 95XP-TermoFinnigan spectrometer (EI). Commercially available products were used without further purification. Aminocyclopropane **2**[20] and diethyl 2-phenylcyclopropane-1,1-dicarboxylate[21] were prepared and identified according to literature reports..

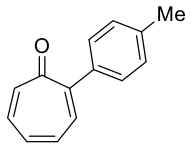
General procedure for the preparation of 2-aryltropones 1d-g: To a solution of 2-tosyloxytropone[22] (1 equiv.) in *N,N*-dimethylformamide (6 mL/mmol) were added the corresponding aryltributylstannane (1.08 equiv.), LiCl (3.1 equiv.), $Pd(dppf)Cl_2$ (0.04 equiv.), a few crystals of 2,6-di-*tert*-butyl-4-methylphenol, and 3 Å molecular sieves (66 mg/mmol). The resulting mixture was heated at 70 ºC. After 23 h the reaction was cooled to room temperature, diluted with diethyl ether, and filtered. The filtrate was washed with water and brine. The solution was dried over $MgSO_4$ and concentrated. Flash column chromatography afforded the corresponding 2-aryltropone.



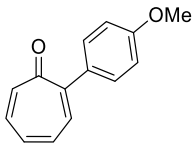
2-phenyltropone, 1d: Following the general procedure described above, from 2-tosyloxytropone (300 mg, 1.18 mmol), tributylphenylstannane (468 mg, 1.30 mmol), LiCl (154 mg, 3.66 mmol), and $Pd(dppf)Cl_2$ (35 mg, 0.05 mmol), tropone **1d** was

20 Benfatti, F.; Nanteuil, J.; Waser, J. *Chem. Eur. J*. **2012**, *18*, 4844.
21 Goldberg, A. F. G., O'Connor, N. R.; Craig II, R. A., Stolz, B. M. *Org. Lett*. **2012**, *14*, 5314.
22 Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc*. **1988**, *110*, 1557.

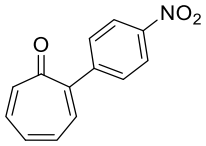
isolated as a yellow solid (108 mg, 38%). The spectral data were identical to those previously reported.[23]



2-*p*-methylphenyltropone, 1e: Following the general procedure described above, from 2-tosyloxytropone (300 mg, 1.18 mmol), tributyl(*p*-methylphenyl)stannane[24] (496 mg, 1.30 mmol), LiCl (154 mg, 3.66 mmol), and Pd(dppf)Cl_2 (35 mg, 0.05 mmol), tropone **1e** was isolated as a yellow solid (118 mg, 51%). The spectral data were identical to those previously reported.[25]

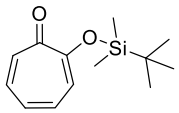


2-*p*-methoxyphenyltropone, 1f: Following the general procedure described above, from 2-tosyloxytropone (300 mg, 1.18 mmol), tributyl(*p*-methoxyphenyl)stannane[26] (515 mg, 1.30 mmol), LiCl (154 mg, 3.66 mmol), and Pd(dppf)Cl_2 (35 mg, 0.05 mmol), tropone **1f** was isolated as a yellow solid (167 mg, 67%). The spectral data were identical to those previously reported.[21]



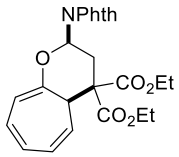
2-*p*-nitrophenyltropone, 1g: Following the general procedure described above, from 2-tosyloxytropone (400 mg, 1.57 mmol), tributyl(*p*-nitrophenyl)stannane[23] (700 mg, 1.70 mmol), LiCl (204 mg, 4.87 mmol), and Pd(dppf)Cl_2 (46 mg, 0.06 mmol), tropone **1g** was isolated as a yellow solid (154 mg, 35%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.25 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 7.41–7.34 (m, 1H), 7.24–7.17 (m, 2H), 7.08 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 186.1, 150.7, 147.9, 146.9, 143.4, 137.6, 136.2, 135.1, 133.9, 130.6, 123.7. IR (ATR): ν 3065, 1594, 1566, 1464, 1343, 850, 757, 699 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{13}H_9NO_3$ $[M]^{\cdot+}$= 227.0577, found 227.0587.

23 Seganish, W. M.; DeShon, P. *J. Org. Chem*. **2004**, *69*, 1137.
24 Mee, S. P. H.; Lee, V.; Baldwin, J. E. J. *Chem. Eur. J*. **2005**, *11*, 3294.
25 Yukio, S.; Kimio, L.; Isao, K.; Yukichi, K. *Tetrahedron Lett.* **1972**, *49*, 4985.
26 Gligorich, K. M.; Cumming, S. A,; Sigman, M. S. *J. Am. Chem. Soc*. **2007**, *129*, 14193.



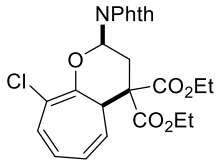
2-(tert-butyldimethylsilyloxy)tropone, 1j: To a solution of tropolone (400 mg, 3.28 mmol) in tetrahydrofuran (9 mL) were added tert-butyldimethylsilyl chloride (494 mg, 3.28 mmol) and triethylamine (0.91 mL, 6.56 mmol). The resulting mixture was stirred for 12 h at room temperature. The mixture was poured into water and extracted with dichloromethane. The organic layer was dried over anhydrous MgSO4, filtered, and concentrated under reduced pressure. The residue was washed with diethyl ether to afford the corresponding tropone 1j (400 mg, 52%). ^{1}H NMR (300 MHz, CDCl3, 25 °C) δ 7.20–7.09 (m, 4H), 6.95–6.84 (m, 1H), 0.97 (s, 9H), 0.31 (s, 3H).^{13}C NMR(CDCl3, 75 MHz, , 25 °C): δ = 173.2, 135.8, 129.8, 129.0, 26.2, 19.5, -2.9. IR (ATR): ν 3196, 1611, 1546, 1478, 1423, 1266, 1237, 712 cm-1. HRMS (ESI) m/z calculated for C13H21O2Si $[M+H]^{+}$= 237.1305, found 237.1303.

<u>General procedure for cycloaddition reactions</u>: To a solution of tropone derivative **1** (1 equiv.) and aminocyclopropane **2** (1 equiv.) in DCM (10 mL/mmol) was added $SnCl_4$ (5 mol % of a 0.43 M solution in DCM) dropwise. The mixture was stirred at room temperature for 16 h, then the reaction was quenched by the addition of triethylamine (20 mL/mmol of $SnCl_4$) and subsequently flushed through a short plug of silica gel, eluting with EtOAc. The solvent was removed in vacuo to give the crude reaction mixture, which was submitted to flash column chromatography to yield pure cycloadduct **3**.

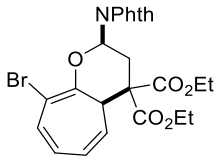


Compound 3a: Following the general procedure described above, from tropone 1a (24 mg, 0.15 mmol) and aminocyclopropane 2 (50 mg, 0.15 mmol), cycloadduct 3a was isolated as a colourless solid (40 mg, 61%). ^{1}H NMR (300 MHz, CDCl3, 25 °C): δ 8.03–7.82 (m, 2H), 7.82–7.54 (m, 2H), 6.59 (dd, J = 10.9, 6.2 Hz, 1H), 6.49 (dd, J = 10.9, 5.4 Hz, 1H), 6.35 (dd, J = 8.9, 5.4 Hz, 1H), 5.96 (dd, J = 12.3, 3.3 Hz, 1H), 5.75 (d, J = 6.2 Hz, 1H), 5.06 (dd, J = 8.9, 6.8 Hz, 1H), 4.52–3.89 (m, 4H), 3.67 (dd, J = 14.1, 12.3 Hz, 1H), 2.53 (ddd, J = 14.0, 3.3, 1.9 Hz, 1H), 2.40 (d, J = 6.5 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CDCl3, 25 °C): δ 170.0, 169.0, 167.1, 141.8, 134.9, 132.0, 129.3, 127.7, 125.7, 124.2, 116.2, 103.0, 75.6, 62.9, 62.4, 55.3, 39.1, 28.3,

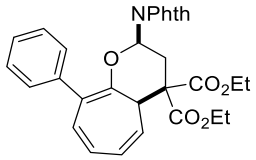
14.5. IR (ATR): ν 2983, 1725, 1376, 1264, 1228, 1184, 717 cm^{-1}. HRMS (ESI) m/z calculated for C24H24NO7 $[M + H]^+$= 438.1547, found 438.1545.



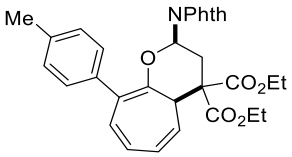
Compound 3b: Following the general procedure described above, from tropone **1b** (21 mg, 0.15 mmol) and aminocyclopropane **2** (50 mg, 0.15 mmol), cycloadduct **3b** was isolated as a white solid (48 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.95–7.86 (m, 2H), 7.82–7.74 (m, 2H), 6.60 (d, *J* = 11.1 Hz, 1H), 6.51–6.44 (m, 1H), 6.34 (ddd, *J* = 9.0, 5.3, 1.2 Hz, 1H), 6.03 (dd, *J* = 12.3, 3.6 Hz, 1H), 5.22 (dd, *J* = 9.0, 6.9 Hz, 1H), 4.35 (qd, *J* = 7.1, 2.0 Hz, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.63 (dd, *J* = 14.2, 12.3 Hz, 1H), 2.67 (d, *J* = 6.8 Hz, 1H), 2.58 (ddd, *J* = 14.2, 3.6, 1.9 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 169.5, 168.5, 167.0, 137.7, 135.0, 132.0, 130.6, 127.5, 126.5, 124.3, 119.7, 107.0, 75.9, 63.1, 62.6, 55.3, 38.7, 28.1, 14.4. ν 2982, 1725, 1372, 1243, 1135, 717 cm-1. HRMS (ESI) *m/z* calculated for $C_{24}H_{22}ClNNaO_7$ $[M+Na]^+$= 494.1001, found 494.0976.



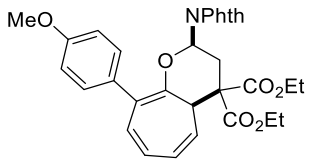
Compound 3c: Following the general procedure described above, from tropone **1c** (28 mg, 0.15 mmol) and aminocyclopropane **2** (50 mg, 0.15 mmol), cycloadduct **3c** was isolated as a pale yellow solid (50 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): *δ* 7.93–7.85 (m, 2H), 7.81–7.73 (m, 2H), 6.71 (d, *J* = 11.0 Hz, 1H), 6.46–6.29 (m, 2H), 6.02 (dd, *J* = 12.3, 3.5 Hz, 1H), 5.18 (dd, *J* = 8.5, 7.3 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.63 (dd, *J* = 13.9, 12.7 Hz, 1H), 2.69 (d, *J* = 6.9 Hz, 1H), 2.64–2.52 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): *δ* 169.5, 168.5, 166.9, 138.8, 135.0, 132.2, 132.0, 127.5, 126.5, 124.3, 119.4, 95.4, 76.1, 63.1, 62.6, 55.4, 39.2, 28.1, 14.5. IR (ATR): *ν* 2983, 1726, 1468, 1301, 1196, 855, 719 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{24}H_{22}BrNO_7$ $[M]^{\cdot+}$= 515.0574, found 515.0588.



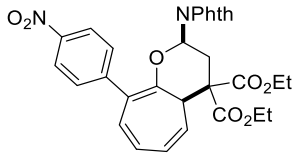
Compound 3d: Following the general procedure described above, from tropone **1d** (27 mg, 0.15 mmol) and aminocyclopropane **2** (50 mg, 0.15 mmol), cycloadduct **3d** was isolated as a pale yellow solid (53 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.86–7.77 (m, 2H), 7.77–7.65 (m, 2H), 7.40–7.29 (m, 2H), 7.28–7.18 (m, 2H), 7.19–7.03 (m, 1H), 6.78–6.53 (m, 2H), 6.42 (dd, *J* = 8.8, 4.9 Hz, 1H), 6.00 (dd, *J* = 12.4, 2.8 Hz, 1H), 5.23 (dd, *J* = 8.7, 7.0 Hz, 1H), 4.47–4.22 (m, 4H), 3.80 (dd, *J* = 14.1, 12.5 Hz, 1H), 2.56 (ddd, *J* = 14.1, 3.1, 1.8 Hz, 1H), 2.49 (dd, *J* = 7.1, 1.4 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 170.3, 169.0, 167.1, 138.7, 137.4, 134.9, 132.7, 131.9, 130.6, 128.2, 127.3, 126.7, 126.5, 124.1, 119.0, 117.2, 75.8, 62.8, 62.4, 56.1, 39.8, 28.2, 14.54, 14.50. IR (ATR): ν 2982, 1723, 1371, 1194, 1080, 718 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{30}H_{27}NO_7$ $[M]^{\cdot+}$= 513.1782, found 513.1792.



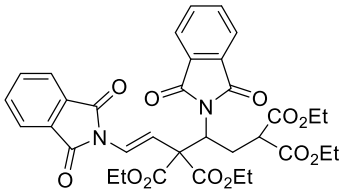
Compound 3e: Following the general procedure described above, from tropone **1e** (42 mg, 0.21 mmol) and aminocyclopropane **2** (71 mg, 0.21 mmol), cycloadduct **3e** was isolated as a white solid (72 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.86–7.77 (m, 2H), 7.73–7.65 (m, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.73–6.60 (m, 2H), 6.42 (dd, *J* = 8.6, 5.2 Hz, 1H), 6.01 (dd, *J* = 12.4, 2.8 Hz, 1H), 5.23 (dd, *J* = 8.6, 7.2 Hz, 1H), 4.45–4.25 (m, 4H), 3.80 (dd, *J* = 14.1, 12.5 Hz, 1H), 2.60–2.52 (m, 1H), 2.47 (d, *J* = 7.1 Hz, 1H), 2.27 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 170.4, 169.1, 167.1, 137.1, 136.1, 135.8, 134.8, 132.8, 131.9, 130.5, 128.9, 127.2, 126.6, 124.1, 118.9, 117.1, 75.7, 62.8, 62.4, 56.1, 39.8, 28.2, 21.5, 14.54, 14.51. IR (ATR): ν 2983, 1729, 1374, 1198, 1135, 749 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{31}H_{29}NO_7$ $[M]^{\cdot+}$= 527.1939, found 527.1919.



Compound 3f: Following the general procedure described above, from tropone **1f** (64 mg, 0.30 mmol) and aminocyclopropane **2** (100 mg, 0.30 mmol), cycloadduct **3f** was isolated as a pale yellow solid (100 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.85–7.78 (m, 2H), 7.72–7.66 (m, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.72–6.59 (m, 2H), 6.41 (dd, *J* = 8.7, 5.0 Hz, 1H), 5.99 (dd, *J* = 12.4, 2.7 Hz, 1H), 5.22 (dd, *J* = 8.7, 7.2 Hz, 1H), 4.42–4.24 (m, 2H), 3.80 (dd, *J* = 13.9, 12.7 Hz, 1H), 3.74 (s, 3H), 2.59–2.52 (m, 1H), 2.46 (d, *J* = 7.1 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 170.4, 169.1, 167.1, 158.3, 136.8, 134.9, 132.8, 131.9, 131.7, 131.2, 127.2, 126.7, 124.1, 119.0, 116.8, 113.6, 75.8, 62.8, 62.4, 56.2, 55.5, 39.7, 28.2, 14.54, 14.51. IR (ATR): ν 2982, 1720, 1296, 1227, 1028, 992, 735 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{31}H_{29}NO_8$ $[M]^{\cdot+}$= 543.1888, found 543.1911.



Compound 3g: Following the general procedure described above, from tropone **1g** (34 mg, 0.15 mmol) and aminocyclopropane **2** (50 mg, 0.15 mmol), cycloadduct **3g** was isolated as a pale yellow solid (59 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.09 (d, *J* = 8.9 Hz, 2H), 7.90–7.81 (m, 2H), 7.78–7.71 (m, 2H), 7.47 (d, *J* = 8.9 Hz, 2H), 6.74–6.64 (m, 2H), 6.45 (dd, *J* = 8.9, 4.6 Hz, 1H), 6.02 (dd, *J* = 12.5, 2.8 Hz, 1H), 5.25 (dd, *J* = 8.9, 6.9 Hz, 1H), 4.45–4.27 (m, 4H), 3.80 (dd, *J* = 14.1, 12.6 Hz, 1H), 2.63–2.51 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 170.2, 168.7, 167.0, 146.3, 145.6, 139.8, 135.1, 131.7, 131.13, 131.09, 127.73, 127.70, 124.3, 123.5, 119.4, 115.2, 76.0, 63.0, 62.6, 55.8, 39.9, 27.8, 14.52, 14.50. IR (ATR): ν 2882, 1726, 1468, 1301, 1233, 855, 719 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{30}H_{26}N_2O_9$ $[M]^{\cdot+}$= 558.1633, found 558.1642.



Compound 5: Following the general procedure described above, from tropone **1h** (20 mg, 0.15 mmol) and aminocyclopropane **2** (50 mg, 0.15 mmol), compound **5** and unreacted tropone **1h** were obtained. After flash column chromatography and crystallization from hexanes/CH_2Cl_2 at room temperature, single crystals of compound **5** were isolated (14mg, 14%) and submitted to X-ray diffraction analysis.^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.89–7.81 (m, 4H), 7.76–7.70 (m, 4H), 7.24 (d, *J* = 15.4 Hz, 1H), 6.79 (d, *J* = 15.4 Hz, 1H), 5.14 (dd, *J* = 11.5, 2.8 Hz, 1H), 4.46–4.38 (m, 2H), 4.30–4.15 (m, 4H), 3.98–3.87 (m, 2H), 3.27 (dd, *J* = 8.2, 6.3 Hz, 1H), 3.15 (ddd, *J* = 14.6, 11.6, 6.4 Hz, 1H), 2.69 (ddd, *J* = 14.6, 8.3, 2.8 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H). HRMS (ESI) *m/z* calculated for $C_{34}H_{34}N_2NaO_{12}$ $[M+Na]^+$= 685.2004, found 685.2033.

1.2. Synthesis of Oxaspiranic Compounds Through [3+2] Annulation of Cyclopropenones and Donor-Acceptor Cyclopropanes

J. Org. Chem. **2015**, *80,* 1207

The $Sc(OTf)_3$-catalyzed [3+2]-annulation reaction between cyclopropenones and donor-acceptor cyclopropanes is described. The process leads directly to the formation of 4-oxaspiro[2.4]hept-1-ene derivatives in good to excellent reaction yields. Density functional theory calculations suggest that the [3+2]-annulation pathway is strongly preferred over the possible [3+3]-process.

Spirocyclic compounds, species where two rings are fused by just one carbon atom, have become a synthetic target of renewed interest recently due to their enormous potential in drug discovery[1] and materials chemistry.[2] Indeed, the rigidity and conformational restriction imposed by the spiranic moiety, which is present in a great number of natural products,[3] provide a stiff framework for the attachment of pharmacophoric groups or a rigid framework for metal coordination. However, the synthesis of these species is specially challenging for organic chemists as many of the synthetic procedures toward spirocycles are based on multistep strategies and employ expensive reagents.[4,5] Although transition-metal-catalyzed processes have become an attractive alternative to synthesize spirocycles,[6] new direct routes leading to this important family of compounds are still to be developed.

At this point, we turned our attention to the chemistry of donor-acceptor cyclopropanes (DACs),[7] compounds which have proven to be very useful for the direct synthesis of five-membered carbo- and heterocycles via [3+2]-annulation reactions.[8] Within the context of our ongoing work in the reaction mechanisms and synthetic applications of high-order cycloaddition and annulation reactions,[9] we have recently described a novel Lewis acid catalyzed [8+3]-annulation reaction between tropone derivatives and donor-acceptor aminocyclopropanes (Scheme 1a).[10] This transformation leads to the formation of amino-substituted tetrahydrocyclohepta[*b*]pyrans in good reaction yields and with complete regio- and

1 For a recent review, see: Zheng, Y.; Tice, C. M.; Singh, S. B. *Bioorg. Med. Chem. Lett*. **2014**, *24*, 3673.

2 (a) Bercovic , G.; Krongauz, V.; Weiss, V. *Chem. Rev*. **2000**, *100*, 1741. Selected recent examples: (b) Agou, T.; Hossain, M. D.; Kawashima, T. *Chem. Eur. J*. **2010**, *16*, 368. (c) Lin, Z.-Q.; Liang, J.; Sun, P.-J.; Liu, F.; Tay, Y.-Y.; Yi, M.-D.; Peng, K.; Xia, X.-H.; Xie, L.-H.; Zhou, X.-H.; Zhao, J.-F.; Huang, W. *Adv. Mater*. **2013**, *27*, 3663.

3 (a) Perron, F.; Albizati, K. F. *Chem. Rev*. **1989**, *89*, 1617. (b) Marson, C. M. *Chem. Soc. Rev*. **2011**, *40*, 5514.

4 (a) Pradhan, R.; Patra, M.; Behera, A. K.; Mishrab, B. K.; Behera, R. K. *Tetrahedron* **2006**, *62*, 779. (b) Kang, F.-A.; Sui, Z. *Tetrahedron Lett*. **2011**, *52*, 4204. (c) Ríos, R. *Chem. Soc. Rev*. **2012**, *41*, 1060. (d) Ramazanov, I. R.; Yaroslavova, A. V.; Dzhemilev, U. M. *Russ. Chem. Rev*. **2012**, *81*, 700.

5. For the synthesis of heterospirocycles, see the recent review: Undheim, K. *Synthesis* **2014**, *26*, 1957.

6. D'yakonov, V. A.; Trapeznikova, O. A.; de Meijere, A.; Dzhemilev, U. M. *Chem. Rev*. **2014**, *114*, 5775.

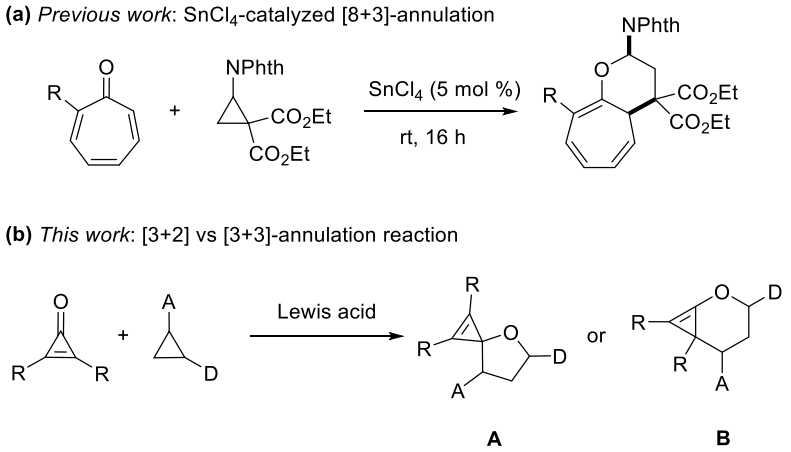
7 For a nice recent review on the "new golden age" for DACs, see: (a) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed*. **2014**, *53*, 5504. See also: (b) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev*. **2014**, *43*, 804. (c) Reissig, H. U.; Zimmer, R. *Chem. Rev*. **2003**, *103*, 1151. (d) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (e) De Simone, F.; Waser, J. *Synthesis* **2009**, 3353. (f) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev*. **2009**, *38*, 3051.

8 Selected recent examples: (a) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc*. **2009**, *131*, 3122. (b) Parsons, A. T.; Smith, A. G.; Neel, A. J.; Johnson, J. S. *J. Am. Chem. Soc*. **2010**, *132*, 9688. (c) Goldberg, A. . G.; O'Connor, N. R.; Craig II, R. A.;G Stoltz, B. M. *Org. Lett*. **2012**, *14*, 5314. (d) Xiong, H.; Xu, H.; Liao, S.; Xie, Z.; Tang, Y. H. *J. Am. Chem. Soc*. **2013**, *135*, 7851

9 (a) Fernández, I.; Cossío, F. P.; de Cózar, A.; Lledós, A.; Mascareñas, J. L. *Chem. Eur. J*. **2010**, *16*, 12147. (b) Saya, L.; Bhargava, G.; Navarro, M. A.; Gulías, M.; López, F.; Fernández, I.; Castedo, L.; Mascareñas, J. L. *Angew. Chem., Int. Ed*. **2010**, *49*, 9886. (c) Fernández, I.; Mascareñas, J. L. *Org. Biomol. Chem*. **2012**, *10*, 699. (d) Lage, M. L.; Fernández, I.; Sierra, M. A.; Torres, M. R. *Org. Lett*. **2011**, *13*, 2892. (e) Rivero, A. R.; Fernández, I.; Sierra, M. A. *J. Org. Chem*. **2012**, *77*, 6648. (f) Rivero, A. R.; Fernández, I.; Sierra, M. A. *Chem. Eur. J*. **2014**, *20*, 1359.

10 Rivero, A. A.; Fernández, I.; Sierra, M. A. *Org. Lett*. **2013**, *15*, 4928.

diastereoselectivities. This synthetic strategy was first developed with a nitrogen-based donor[10] but is also compatible with a variety of different donors such as aryl, heteroaryl, and vinyl substituents.[11] Taking into account this reaction, we envisaged a new route to 4-oxaspiro[2.4]hept-1-ene derivatives by the reaction of cyclopropenones and DACs (Scheme 1b). Two possible reaction products may be formed in this transformation, i.e., the spirocycle **A** via the well-known [3+2]-annulation between the DAC and the ketone moiety[8] and/or the alternative [4.1.0]-oxabicyclic species **B**, through a [3+3]-process analogous to the [8+3]-annulation described previously by us.[10] We can anticipate that the formation of compounds **B** is thermodynamically very unlikely in view of the high strain imposed by the [4.1.0]-oxabicycle. If successful, this process will constitute a simple and direct methodology to the preparation of 4-oxaspiro[2.4]hept-1-ene derivatives, which contain a spiro-cyclopropene in its structure.[12]



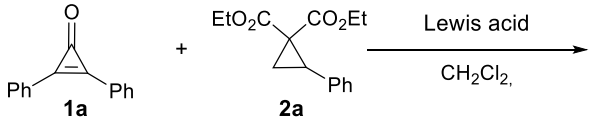
Scheme 1.[8+3] and [3+2]-Annulations between DACs and cyclic ketones.

Our study started with the reaction between diphenylcyclopropenone **1a** and DAC **2a** to optimize the reaction conditions (Table 1). The use of $SnCl_4$, the Lewis acid employed for the previous [8+3]-annulation involving tropones,[10] did not promote the reaction (entries 1-4). Similarly, other typical Lewis acids such as $FeCl_3$, $ZnCl_2$, $TiCl_4$, $NiCl_2$, $Fe(acac)_3$, or $Ni(ClO_4)_2{\cdot}6H_2O$ (the latter used in the [8+3]-process involving DAC **2a**),[11] were not efficient either in promoting the transformation even when the reaction was carried out at 60 °C (entries 5-11). To our delight, $Sc(OTf)_3$ (5 mol %) did catalyze the process at 40 °C leading to a reaction conversion of 30 %

11 Tejero, R.; Ponce, A.; Adrio, J.; Carretero, J. C. *Chem. Commun*. **2013**, *49*, 10406.

12 To the best of our knowledge, only related 4-oxaspiro[2.4]hept-1-en-5-one derivatives have been synthetized so far. See: (a) Staab, H.A.; Ipaktschi, J. *Chem. Ber*. **1968**, *101*, 1457. (b) Irngartinger, H.; Altreuther, A.; Sommerfeld, T.; Stojanik, T. *Eur. J. Org. Chem*. **2000**, *24*, 4059. (c) Körner, O.; Gleiter, R.; Rominger, F. *Synthesis* **2009**, *19*, 3259.

(entry 12). Increasing the catalyst loading to 10 mol% resulted in a higher conversion of 45%. Different temperatures were also screened finding $Sc(OTf)_3$ (10 mol %) and equimolar amounts of **1a** and **2a** in DCM as solvent at 80 °C for 4 h (entry 16) as the optimal reaction conditions.[13]



Entry	Lewis acid (mol %)	Temp (ºC)	Time (h)	Conversion (%)
1	$SnCl_4$ (20)	-78	2	0
2	$SnCl_4$ (20)	-78	8	0
3	$SnCl_4$ (20)	-20	8	0
4	$SnCl_4$ (20)	25	8	0
5	$FeCl_3$ (5)	40	8	0
6	$ZnCl_2$ (5)	40	8	0
7	$TiCl_4$ (5)	40	8	0
8	$NiCl_2$ (5)	40	8	0
9	$Fe(acac)_3$ (5)	40	8	0
10	$Ni(ClO_4)_2{\cdot}6H_2O$ (5)	40	8	0
11	$Ni(ClO_4)_2{\cdot}6H_2O$ (5)	60	8	10
12	$Sc(OTf)_3$ (5)	40	8	30
13	$Sc(OTf)_3$ (10)	40	8	45
14	$Sc(OTf)_3$ (10)	60	8	47
15	$Sc(OTf)_3$ (10)	80	8	50
16	$Sc(OTf)_3$ (10)	80	4	65
17	$Sc(OTf)_3$ (10)	100	4	50
18	$Sc(OTf)_3$ (10)	130	4	25

[a] Referred to unreacted 1,1-cyclopropanediester **2a** and measured by integration of the signals corresponding to H2 of the cyclopropane ring in the ^1H NMR spectra of reaction mixtures.

Table 1. Optimization of Reaction Conditions for the Process between **1a** and **2a**.

Standard 1D- and 2D-NMR techniques were used to characterize the nature of the product formed (**3a**) in the reaction between **1a** and **2a**. The spectroscopical data is compatible with the formation of the spirocyclic compound **A** (Scheme 1b) as initially envisaged. For instance, the corresponding ^{13}C NMR spectrum clearly confirms the presence of the oxaspiranic carbon atom (δ = 71.2 ppm) together with the double bond of the cyclopropene moiety (δ ≈ 128 ppm). These chemical shifts concur quite

13 Typical procedure: In an oven-dried pressure tube, cyclopropenone **1a** (1 equiv), DAC **2a** (1 equiv), and scandium triflate (10 mol%) were dissolved in anhydrous dichloromethane. The reaction mixture was stirred under argon atmosphere at the specified temperature. After the completion of the reaction (checked by TLC), the solvent was removed in vacuo to give the crude reaction mixture, which was submitted to column chromatography to yield pure compound **3a**.

well with those found for related 4-oxaspiro[2.4]hept-1-en-5-one derivatives.[12c] In addition, single crystals of compound **3b**, where the ethyl groups of the ester moieties were replaced by methyl groups (see also Table 2) suitable for X-ray diffraction analysis fully confirm, by analogy, the spiranic nature of the reaction product **3a** (Figure 1).

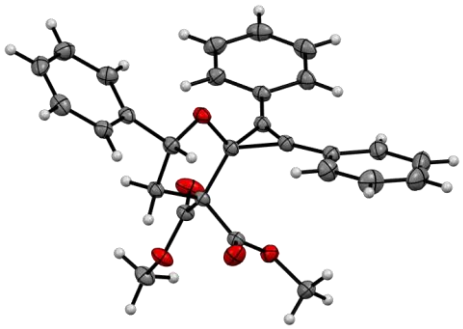


Figure 1. ORTEP-diagram of compound **3b**. Ellipsoids are drawn at the 50% probability level.

With these optimized reaction conditions in hand, we next explored the scope of the process with regard to the substitution at the 1,1-cyclopropanediester **2**. As readily seen in Table 2, the electronic nature of the donor moiety (R^3) of the DAC has an enormous influence on the outcome of the process. Thus, electron-withdrawing groups (F, Br or CN groups) placed at the *para* position of the phenyl group in **2** lead to lower reaction yields (from 51% to 40% for **3d** and **3f**, respectively) than the unsubstituted phenyl group (55% for **3b**). Indeed, the reaction does not proceed at all in the presence of the strong π-acceptor NO_2-group (0% for **3g**). Despite that, the incorporation of a bromide substituent in **3e** would allow further synthetic transformations by transition-metal-catalyzed coupling reactions. By contrast, the good π-donor methoxy substituent not only leads to a higher reaction yield of the corresponding spirocyclic compound **3c** (85%) but also allows the reaction to proceed at much lower temperature (0 °C). This finding very likely finds its origin in the initial ringopening of the DAC promoted by the Lewis acid, since it is well-known that the formation of the corresponding intimate ion pair is facilitated by electron-rich donor groups.[14]

To further confirm this hypothesis, we attached the stronger π-donor NPhth group (Phth = phthaloyl) as the donor moiety of the DAC (**2h** and **2i**). This particular type of amino-DAC was also chosen due to its proven ability to produce *N*-containing hetero-

14 Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642.

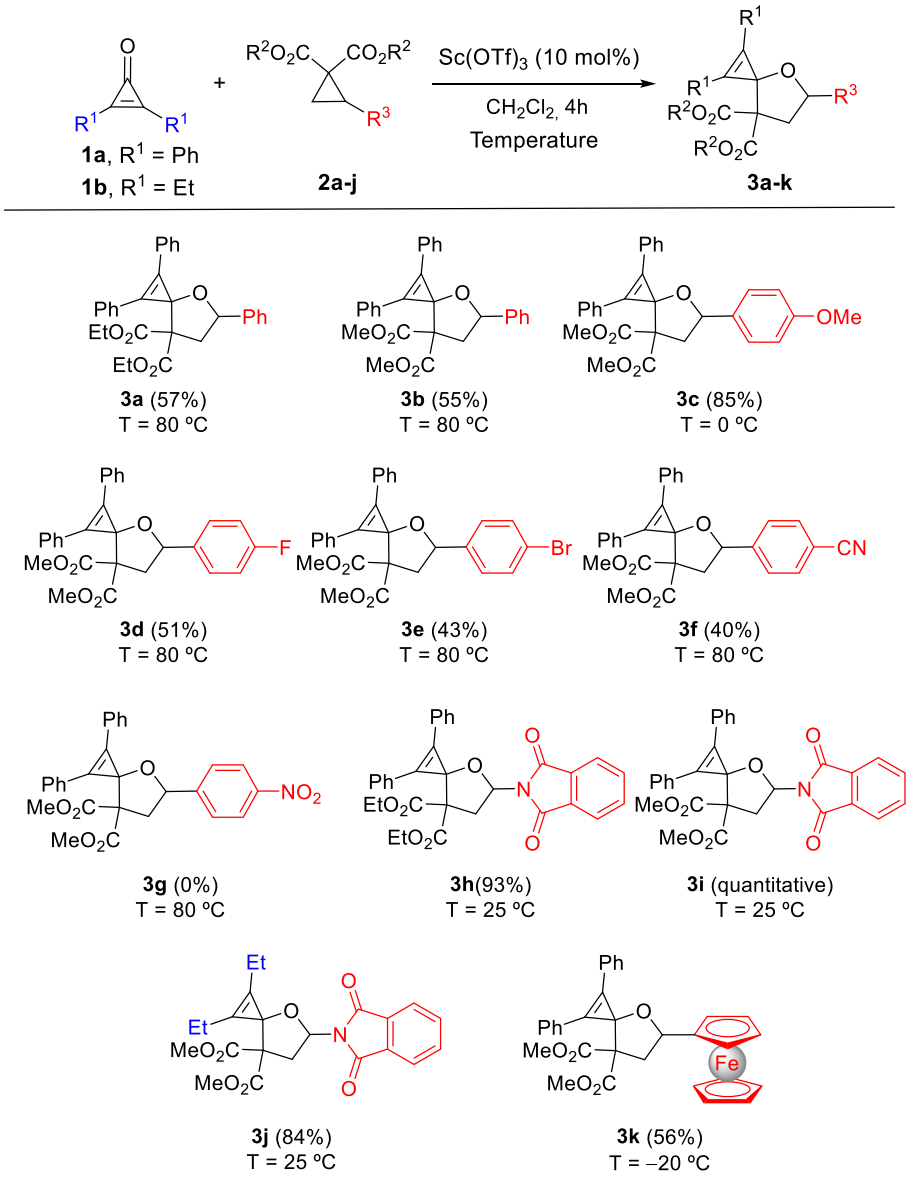
and carbocycles as recently demonstrated by Waser and co-workers.[15] From the data in Table 2, it becomes clear that in the presence of this group the reaction proceeds smoothly at lower temperatures (25 °C) as compared to the parent phenyl-substituted DAC **2b** (80 °C) and, more importantly, leads to excellent reaction yields for the corresponding spirocyclic compounds (93% and quantitative yield for **3h** and **3i**, respectively). The reaction is also compatible with alkyl instead of phenyl groups in the cyclopropenone. Thus, diethylcyclopropenone **1b** also affords the corresponding oxaspirocycle **3j** in a remarkable 84% reaction yield (at 25 °C).

Finally, we were also curious to study the process involving an organometallic fragment. The ferrocenyl substituent was chosen because of its π-donor ability.[16] Again, excellent reactivity of the corresponding ferrocenyl-substituted DAC **2j** was found as it leads to the formation of the ferrocenyl-oxaspirocyclic compound **3k** at low temperature (-20 °C) in an acceptable 56% reaction yield (see Table 2). The latter result, which to the best of our knowledge constitutes one of the scarce examples of spirocyclic compounds having an organometallic fragment,[17] clearly confirms that the process is general and compatible with a wide variety of cyclopropenones and DACs.

15 (a) de Nanteuil, F.; Waser, J. *Angew. Chem. Int. Ed*. **2011**, *50*, 12075. (b) Benfatti, F.; de Nanteuil, F.; Waser. J. *Org. Lett*. **2012**, *14*, 386. (c) Benfatti, F.; de Nanteuil, F.; Waser. J. *Chem. Eur. J*. **2012**, *18*, 4844. (d) de Nanteuil, F.; Serrano, E.; Perrotta, D.; Waser, J. *J. Am. Chem. Soc*. **2014**, *136*, 6239.

16 See, for instance: (a) Arnett, E. M.; Bushick, R. D. *J. Org. Chem*. **1962**, *27*, 111. (b) Lage, M. L.; Fernández, I.; Mancheño, M. J.; Sierra, M. A. *Inorg. Chem*. **2008**, *47*, 5253. (c) Chu, G. M.; Fernández, I.; Sierra, M. A. *Chem. Eur. J*. **2013**, *19*, 5899

17 See, for instance, Yamamoto, Y.; Yamashita, K.; Nakamura, M. *Organometallics* **2010**, *29*, 1472.



[a] Isolated reaction yields are given in parenthesis.

Table 2. Scope of the $Sc(OTf)_3$-catalyzed [3+2]-annulation reaction between cyclopropenones **1a,b** and 1,1-cyclopropanediesters **2a-j**.[a]

Density Functional Theory (DFT) calculations have been carried out at the PCM(CH_2Cl_2)-M06/def2-TZVP//B3LYP/def2-SVP level[18] to gain more insight into the exclusive formation of spirocyclic compounds **A** over bicyclic species **B**. Thus, the corresponding computed reaction profile of the process involving the model cyclopropenone **1M** (where the ethyl groups in **1b** were replaced by methyl groups) and DAC **2b** in the presence of $Sc(OTf)_3$ is shown in Figure 2, which gathers the respective free energies, ΔG_{298}, in dichloromethane solution.

18 DFT calculations were carried out at PCM(CH_2Cl_2)-M06/def2-TZVP//B3LYP/def2-SVP level of theory using the Gaussian 09 suite of programs. See computational details in the Supporting Information

As previously reported,[10,14] the reaction begins with the nucleophilic attack of the cyclopropenone (through the lone-pair of the carbonyl group) to the electrophilic center of the intimate ion-pair **2b-Sc**, which is formed upon coordination of the ester groups to the transition metal. This addition reaction leads to the formation of **INT1**, a zwitterionic intermediate similar to that proposed for the related [8+3]-annulation involving tropones,[10] which can be considered as an aromatic compound according to the computed negative Nucleus Independent Chemical Shifts (NICS)[19] values (NICS(0) = −27.2 ppm and $NICS(1)_{zz}$ = −19.2 ppm). In this sense, the three-membered ring of **INT1** resembles the cyclopropenyl cation.[20]

Two possible ring closures in **INT1** can be envisioned, namely the annulation at C1 which would produce the [3+2]-adduct **INT2** and, alternatively, the annulation at C2, leading to the formation of the bicyclic species **INT3**. From the data in Figure 2, it becomes clear that the nucleophilic attack at C1 is strongly favored under both kinetic and thermodynamic control in view of the considerably higher activation energy required for the formation of bicyclic **INT3** ($\Delta\Delta G^{\neq}$ = 23.3 kcal/mol), as well as the higher reaction energy calculated for this latter intermediate ($\Delta\Delta G_R$ = 24.1 kcal/mol). As a consequence, no traces of the corresponding [3+3]-reaction product should be observed in the reaction crudes, as experimentally found. In addition, the respective non-coordinated reaction products derived from **INT2** and **INT3** also exhibit a similar free energy difference ($\Delta\Delta G_R$ = 19.5 kcal/mol), thus confirming that the highly strained nature of the bicyclic species **B** switches off the [3+3]-annulation reaction pathway.

19 Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. v. R. *Chem. Rev*. **2005**, *105*, 3842.

20 For recent quantitative evaluations, including NICS values, on the aromaticity of the cyclopropenyl cation and related species, see: (a) Wang, Y.; Fernández, I.; Duvall, M.; Wu, J. I.-C.; Li, Q.; Frenking, G.; Schleyer, P. v. R. *J. Org. Chem*. **2010**, *75*, 8252. (b) Fernández, I.; Duvall, M.; Wu, J. I.-C.; Schleyer, P. v. R.; Frenking, G. *Chem. Eur. J*. **2011**, *17*, 2215.

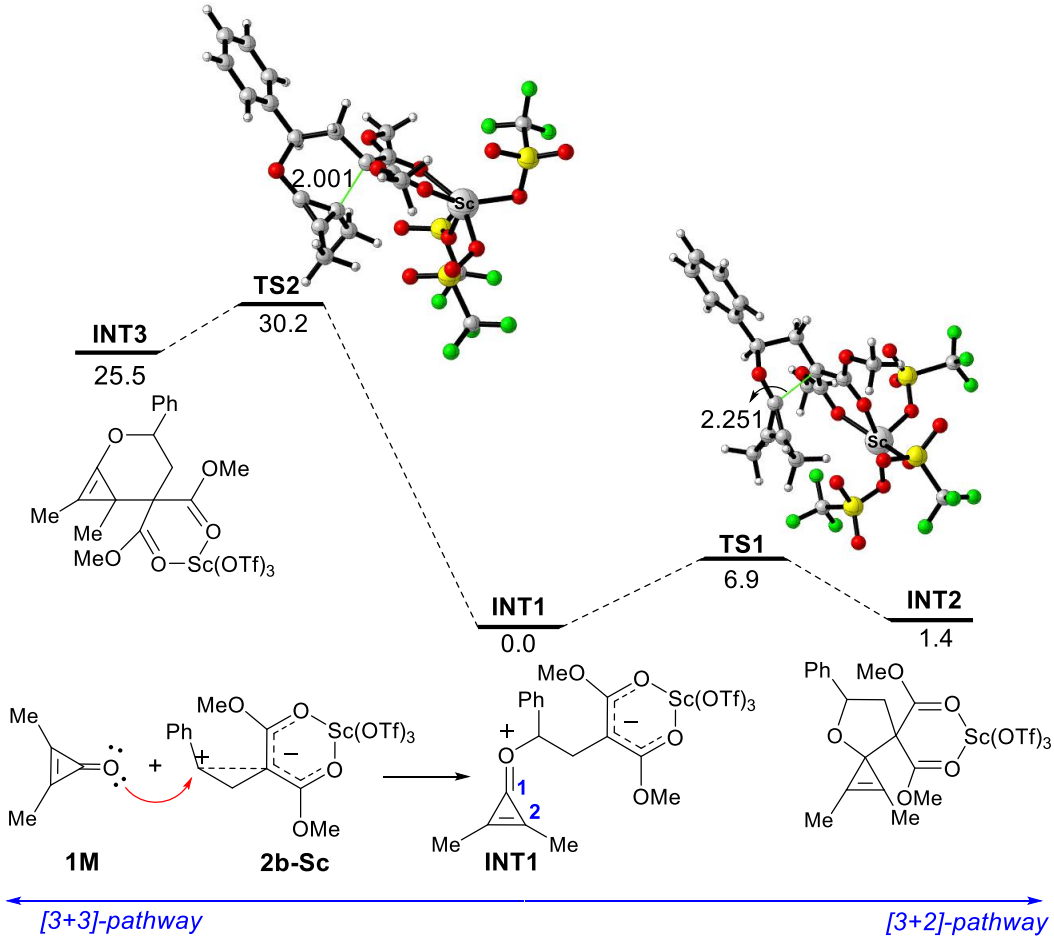


Figure 2. Computed reaction profile of the reaction of cyclopropenone **1M** and $Sc(OTf)_3$-DAC complex **2b-Sc**. Relative free energies (ΔG, 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data have been computed at the PCM(CH_2Cl_2)-M06/def2-TZVP//B3LYP/def2-SVP level.

Finally, the ring closure at C1 leading to spirocyclic compounds is preferred over the cyclization at C2 for an additional reason. As seen from the computed Natural Bond Orbital (NBO) charges (Figure 3), the carbon atom C1 in the initial zwitterionic intermediate **INT1** clearly bears a more positive charge than C2 (or C3) (Δq = +0.364 au) thus indicating a higher electrophilic character. This difference in electrophilicity also directs the nucleophilic addition from the carbanionic center C4 (q = –0.364) towards C1 instead of C2.

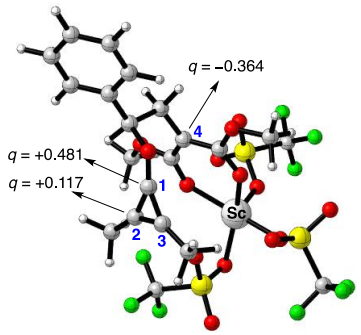


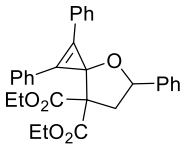
Figure 3. Computed (B3LYP/def2-SVP level) NBO-charges of zwitterionic intermediate **INT1**.

In summary, the $Sc(OTf)_3$-catalyzed reaction between cyclopropenones and different donor-acceptor cyclopropanes has been studied. This process allows the direct access to 4-oxaspiro[2.4]hept-1-ene derivatives in good to excellent reaction yields through a stepwise [3+2]-annulation reaction. The process is compatible with different substituents in both reactants including organometallic moieties, which might find future applications in bioorganometallic chemistry. With the help of DFT calculations it was found that the exclusive formation of the [3+2]-products over the [3+3]-bicyclic compounds takes place under both kinetic and thermodynamic control. This preference finds its origin in the higher electrophilicity of the C1 carbon atom of the aromatic zwitterionic intermediate and in the highly strained nature of the [4.1.0]-bicyclic species.

EXPERIMENTAL SECTION

General Procedures: All reactions were carried out under Argon atmosphere. Dichloromethane (DCM) was distilled from calcium hydride before use. Flame dried glassware was used for moisture-sensitive reactions. Identification of products was made by thin layer chromatography (TLC) (kieselgel 60F-254). UV light (λ= 254 nm) and oleum was used to develop the plates. NMR spectra were recorded at 25 °C in $CDCl_3$, on a 300 MHz (300 MHz for ^1H, 75 MHz for ^{13}C) spectrometer. Chemical shifts are given in ppm relative to TMS (^1H, 0.0 ppm) or $CDCl_3$ (^{13}C, 77.0 ppm). IR spectra were taken as solid films by slow evaporation of the solvent using the ATR (Attenuated Total Reflectance) technique. HRMS spectra were obtained on a mass spectrometer using electronic impact (EI) or on a Q-TOF system for the electron spray ionization (ESI) experiments. Commercially available products were used without further purification. 1,1-Cyclopropanediesters were synthesized according to literature procedures: (**2a-d**, **2f**, **2i-j**),[21] **2e**,[22] **2h.**[15c]

General procedure for the annulation reactions: In an oven-dried pressure tube cyclopropenone **1** (0.12mmol), cyclopropane **2** (0.12mmol), and scandium triflate (10 mol %) were dissolved in anhydrous dichloromethane (2.5 mL) at 25 ºC. The reaction mixture was stirred under argon atmosphere at the specified temperature. After the completion of the reaction (checked by TLC), the solvent was removed under reduced pressure to give the crude reaction mixture, which was submitted to column chromatography (SiO_2, hexanes to 1:10 EtOAc/hexanes) to yield pure oxaspiranic compounds **3**.

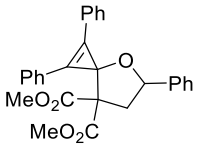


Compound 3a: The reaction was performed at 80ºC following the general procedure described above, from cyclopropenone **1a** (25 mg) and cyclopropane **2a** (31 mg). Compound **3a** was isolated as a colourless solid (32 mg, 57%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.86–7.78 (m, 4H), 7.51–7.28 (m, 11H), 5.31 (dd, *J* = 10.2, 5.7 Hz, 1H), 4.18–4.03 (m, 1H), 4.00–3.82 (m, 3H), 3.29 (dd, *J* = 12.9, 5.7 Hz, 1H), 2.86 (dd, *J* = 12.9, 10.2

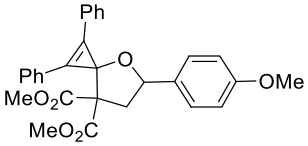
21 González-Bobes, F.; Fenster, M. D.; Kiau, S.; Kolla, L.; Kolotuchin, S.; Soumeillant, M. *Adv. Synth. Catal*. **2008**, *350*, 813.

22 Goudreau, S. R., Marcoux, D., Charette, A. B. *J. Org. Chem*. **2009**, *74*, 470.

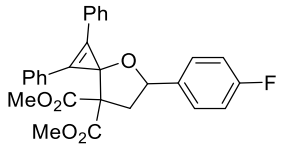
Hz, 1H), 0.99 (q, *J* = 7.3 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 169.8, 142.2, 130.4, 130.2, 129.60, 129.55, 129.0, 129.0, 128.96, 128.8, 128.03, 126.1, 120.8, 120.7, 77.2, 71.2, 62.1, 61.8, 61.0, 45.3, 14.1, 14.0. IR (ATR) $\tilde{\nu}$ = 2982, 1730, 1389, 1211, 1093, 759, 690 cm^{-1}. HMRS (ESI) calcd for $C_{30}H_{29}O_5$ $[M+H]^+$ 469.2010; found 469.2022.



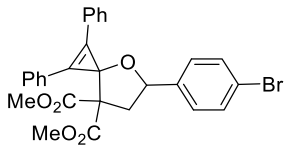
Compound 3b: The reaction was performed at 80ºC following the general procedure described above, from cyclopropenone **1a** (25 mg) and cyclopropane **2b** (28 mg). Compound **3b** was isolated as a colourless solid (27 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (t, *J* = 7.0 Hz, 4H), 7.54–7.25 (m, 11H), 5.33 (dd, *J* = 10.3, 5.5 Hz, 1H), 3.54 (s, 3H), 3.48 (s, 3H), 3.32 (dd, *J* = 12.9, 5.5 Hz, 1H), 2.88 (dd, *J* = 12.9, 10.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 170.3, 142.0, 130.4, 130.2, 129.7, 129.1, 129.0, 128.8, 128.0, 127.8, 127.7, 126.1, 120.7, 120.5, 77.4, 71.4, 60.8, 53.0, 52.9, 45.3. IR (ATR) $\tilde{\nu}$ = 2952, 1733, 1439, 1270, 1090, 977, 760, 693 cm^{-1}. HMRS (ESI) calcd for $C_{28}H_{25}O_5$ $[M+H]^+$ 441.1697; found 441.1701.



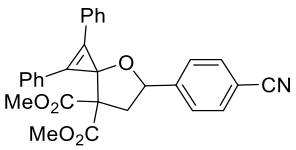
Compound 3c: In an oven-dried Schlenk tube, cyclopropenone **1a** (0.12 mmol, 25 mg) and scandium triflate (10 mol %) were dissolved in anhydrous dichloromethane (2 mL). The mixture was stirred under argon at 0ºC for five minutes before the addition of cyclopropane **2c** (0.12mmol, 32 mg) in anhydrous dichloromethane (0.5 mL). The reaction mixture was stirred under argon atmosphere at 0ºC until the completion of the reaction (checked by TLC). Evaporation of the solvent under reduced pressure gave the crude reaction mixture, which was submitted to column chromatography (SiO_2, hexanes to 1:10 EtOAc/hexanes) to yield pure compound **3c** as a yellow oil (48 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89–7.76 (m, 4H), 7.54–7.36 (m, 8H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.26 (dd, *J* = 10.3, 5.4 Hz, 1H), 3.82 (s, 3H), 3.52 (s, 3H), 3.48 (s, 3H), 3.25 (dd, *J* = 13.0, 5.4 Hz, 1H), 2.86 (dd, *J* = 13.0, 10.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 170.5, 159.6, 133.9, 130.4, 130.2, 129.6, 129.1, 129.0, 128.2, 127.9, 127.7, 127.5, 120.9, 120.4, 114.2, 77.2, 71.2, 60.9, 55.7, 53.0, 52.9, 45.3. IR (ATR) $\tilde{\nu}$ = 2953, 1733, 1313, 1439, 1247, 1174, 1084, 762, 691 cm^{-1}. HMRS (ESI) calcd for $C_{29}H_{27}O_6$ $[M+H]^+$ 471.1802; found 471.1808.



Compound 3d: The reaction was performed at 80ºC following the general procedure described above, from cyclopropenone **1a** (25 mg) and cyclopropane **3d** (30 mg). Compound **3d** was isolated as a white solid (28 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83–7.75 (m, 4H), 7.52–7.39 (m, 8H), 7.04 (t, *J* = 8.7 Hz, 2H), 5.27 (dd, *J* = 10.2, 5.6 Hz, 1H), 3.52 (s, 3H), 3.47 (s, 3H), 3.27 (dd, *J* = 13.0, 5.6 Hz, 1H), 2.82 (dd, *J* = 13.0, 10.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 170.3, 162.7 (d, *J* = 246 Hz), 137.7 (d, *J* = 3 Hz), 130.3, 130.2, 129.7, 129.1, 129.06, 127.8 (d, *J* = 8 Hz), 127.6, 120.7, 120.3, 115.7 (d, *J* = 21 Hz), 76.8, 71.4, 60.7, 53.0, 52.9, 45.4. IR (ATR) $\tilde{\nu}$ = 2951, 1734, 1487, 1434, 1270, 1009, 760, 690 cm^{-1}. HMRS (EI) calcd for $C_{28}H_{23}FO_5$ $[M]^{\cdot+}$ 458.1524; found 458.1527

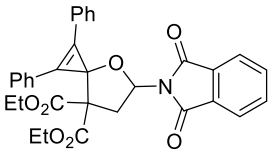


Compound 3e: The reaction was performed at 80ºC following the general procedure described above, from cyclopropenone **1a** (25 mg) and cyclopropane **2e** (38 mg). Compound **3e** was isolated as a white solid (27 mg, 43%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87–7.69 (m, 4H), 7.56–7.28 (m, 10H), 5.24 (dd, *J* = 10.2, 5.7 Hz, 1H), 3.51 (s, 3H), 3.46 (s, 3H), 3.27 (dd, *J* = 12.9, 5.7 Hz, 1H), 2.78 (dd, *J* = 12.9, 10.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 170.2, 141.2, 131.9, 130.3, 130.2, 129.8, 129.7, 129.1, 129.07, 127.8, 127.7, 127.6, 121.7, 120.5, 120.4, 76.6, 71.5, 60.7, 53.04, 52.96, 45.2. IR (ATR) $\tilde{\nu}$ = 2951, 1730, 1438, 1403, 1265, 1041, 1078, 972, 759, 690 cm^{-1}. HMRS (EI) calcd for $C_{28}H_{23}BrO_5$ $[M]^{\cdot+}$ 518.0723; found 518.0729.

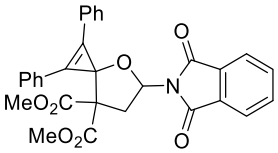


Compound 3f: The reaction was performed at 80ºC following the general procedure described above, from cyclopropenone **1a** (25 mg) and cyclopropane **2f** (31 mg). **Compound 3f** was isolated as a yellow oil (22 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89–7.72 (m, 4H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.55–7.35 (m, 6H), 5.34 (dd, *J* = 10.1, 5.9 Hz, 1H), 3.54 (s, 3H), 3.47 (s, 3H), 3.34 (dd, *J* = 13.0, 5.9 Hz, 1H), 2.78 (dd, *J* = 13.0, 10.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 169.9, 147.8, 132.7,

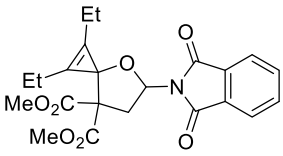
130.3, 130.2, 129.92, 129.87, 129.2, 129.1, 127.5, 127.4, 126.6, 120.3, 120.2, 119.3, 111.7, 76.3, 71.7, 60.4, 53.1, 53.0, 44.9. IR (ATR) $\tilde{\nu}$ = 2953, 2228, 1735, 1440, 1271, 1085, 974, 761, 692 cm^{-1}. HMRS (ESI) calcd for $C_{29}H_{24}NO_5$ $[M+H]^+$ 466.1649; found 466.1659.



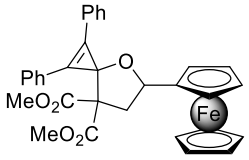
Compound 3h: The reaction was performed at 25ºC following the general procedure described above, from cyclopropenone **1a** (25 mg) and cyclopropane **2h** (40 mg). Compound **3h** was isolated as a colourless oil (63 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96–7.90 (m, 2H), 7.84–7.76 (m, 2H), 7.70–7.62 (m, 4H), 7.45–7.27 (m, 6H), 6.36 (dd, *J* = 8.7, 6.7 Hz, 1H), 4.07–3.95 (m, 3H), 3.95–3.87 (m, 1H), 3.83–3.71 (m, 1H), 3.18 (dd, *J* = 13.2, 6.7 Hz, 1H), 0.95 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 168.8, 168.0, 134.6, 132.3, 130.9, 130.0, 129.7, 129.0, 128.9, 127.7, 127.68, 123.9, 121.5, 118.7, 110.0, 77.0, 70.9, 62.4, 61.9, 60.1, 36.8, 14.2, 13.9. IR (ATR) $\tilde{\nu}$ = 2979, 1721, 1369, 1267, 1086, 720 cm^{-1}. HMRS (ESI) calcd for $C_{32}H_{28}NO_7$ $[M+H]^+$ 538.1860; found 538.1862.



Compound 3i: The reaction was performed at 25ºC following the general procedure described above, from cyclopropenone **1a** (25 mg) and cyclopropane **2i** (36 mg). Compound **3i** was isolated as a colourless oil (62 mg, quantitative). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06–7.95 (m, 2H), 7.92–7.85 (m, 2H), 7.79–7.70 (m, 4H), 7.53–7.36 (m, 6H), 6.35 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.99 (dd, *J* = 13.3, 8.4 Hz, 1H), 3.59 (s, 3H), 3.50 (s, 3H), 3.23 (dd, *J* = 13.3, 6.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 169.4, 168.0, 134.7, 132.3, 130.8, 130.0, 129.8, 129.7, 129.1, 129.0, 127.5, 127.3, 124.0, 121.1, 118.8, 76.9, 71.1, 60.0, 53.2, 53.0, 37.0. IR (ATR) $\tilde{\nu}$ = 2953, 1719, 1371, 1273, 1137, 1086, 720 cm^{-1}. HMRS (ESI) calcd for $C_{30}H_{24}NO_7$ $[M+H]^+$ 510.1547; found 510.1540.



Compound 3j: The reaction was performed at 25ºC following the general procedure described above, from cyclopropenone **1b** (13 mg) and cyclopropane **2i** (36 mg). Compound **3j** was isolated as a colourless oil (41 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89–7.83 (m, 2H), 7.75–7.68 (m, 2H), 6.00 (t, *J* = 7.5 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.65 (dd, *J* = 13.2, 7.5 Hz, 1H), 3.05 (dd, *J* = 13.2, 7.5 Hz, 1H), 2.64–2.42 (m, 4H), 1.20 (t, *J* = 7.4 Hz, 3H), 1.19 (t, *J* = 7.5 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 169.5, 167.9, 134.6, 132.3, 126.3, 123.8, 120.8, 75.9, 73.6, 60.5, 53.3, 53.0, 36.9, 17.8, 17.0, 14.16, 13.96. IR (ATR) $\tilde{\nu}$ = 2970, 1717, 1434, 1272, 1137, 1088, 720 cm^{-1}. HMRS (ESI) calcd for $C_{22}H_{24}NO_7$ $[M+H]^+$ 414.1547; found 414.1563.



Compound 3k: In an oven-dried Schlenk tube, cyclopropenone **1a** (0.12mmol, 25 mg) and scandium triflate (0.012mmol) were dissolved in anhydrous dichloromethane (2 mL). The mixture was stirred under argon at -20ºC for five minutes before the addition of the cyclopropane **2j** (0.12mmol, 41mg) in anhydrous dichloromethane (0.5 mL). The reaction mixture was stirred under argon atmosphere at -20ºC until the completion of the reaction (checked by TLC). Evaporation of the solvent under reduced pressure gave the crude reaction mixture, which was submitted to column chromatography (SiO_2, hexanes to 1:6 EtOAc/hexanes) to yield pure compound **3c** as a yellow oil (37 mg, 56%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87–7.73 (m, 4H), 7.58–7.33 (m, 6H), 5.08 (dd, *J* = 10.2, 5.6 Hz, 1H), 4.41 – 4.16 (m, 9H), 3.51 (s, 6H), 3.25 (dd, *J* = 12.9, 5.6 Hz, 1H), 2.98 (dd, *J* = 12.9, 10.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 170.7, 130.3, 130.1, 129.6, 129.5, 129.1, 128.9, 128.0, 127.8, 121.5, 120.5, 87.4, 74.4, 71.1, 69.1, 68.8, 68.7, 68.6, 66.6, 60.9, 52.95, 52.90, 43.1. IR (ATR) $\tilde{\nu}$ = 2951, 1732, 1434, 1268, 1105, 1047, 759, 736 cm^{-1}. HMRS (ESI) calcd for $C_{32}H_{29}FeO_5$ $[M+H]^+$ 549.1359; found 549.1370.

CAPÍTULO 2

2.1. Regioselective and Stepwise [8+2] Cycloaddition Reaction between Alkynyl-Fischer Carbene Complexes and Tropothione

J. Org. Chem. **2012**, *77,* 6648

The formal [8+2]-cycloaddition reaction between alkynyl Fischer carbene complexes and tropothione leads to the regioselective formation of novel 3aH-cyclohepta[b]thiophene carbene complexes. Computational-DFT calculations indicate that the process proceeds stepwise via anti-aromatic zwitterionic intermediates.

Fischer carbene complexes having an alkenyl or alkynyl group attached to the carbene carbon atom are useful reagents to undergo highly regioselective cycloaddition processes under mild reaction conditions.[1] This is mainly due to the strong activating effect exerted by the metal fragment which behaves in the cycloaddition reaction similarly to a Lewis acid directly attached to the carbonyl group of the corresponding isolobal organic esters.[2] Based on these and related transformations, the term "super-esters" has been coined for these organometallic compounds. Although the chemical literature contains an impressive number of work focused on [4+2][2] and [3+2][3] cycloaddition reactions involving α,β-unsaturated carbene complexes, high-order cycloaddition processes have attracted much less attention. In fact, only a single example of a [8+2] cycloaddition between alkynyl carbene complexes and 8-azaheptafulvenes has been reported so far by Barluenga and co-workers.[4] Moreover, nothing is known about the reaction mechanism of this transformation. Whereas a concerted reaction pathway through aromatic transition states has been computationally suggested by us for [4+2][5] and [3+2][6] cycloaddition reactions involving Fischer carbenes, a stepwise process is followed in the [8+2] reaction between 8-azaheptafulvenes and organic ketenes (Scheme 1).[7] The latter transformation involves the formation of a zwitterionic intermediate **I** which has been experimentally trapped and fully characterized. Therefore, a stepwise pathway is very likely to occur as well in the [8+2] reaction reported by Barluenga and co-workers.[6a]

1 (a) Sierra, M. A.; Gómez-Gallego, M.; Martínez-Ávarez, R. *Chem. Eur. J.* **2007**, *13*, 736. (b) Sierra, M. A.; Fernández, I.; Cossío, F. P. *Chem. Commun*. **2008**, 4671. (c) Waters, M. L.; Wulff, W. D. *Org. React*. **2008**, *70*, 121. (d) Dötz, K. H.; Stendel, J. *Chem. Rev*. **2009**, *109*, 3227. (e) Herndon, J. W. *Coord. Chem. Rev*. **2010**, *254*, 103. (f) Fernández-Rodríguez, M. A.; García-García, P.; Aguilar, E. *Chem. Commun*. **2010**, 7670. (g) Fernández, I.; Cossío, F. P.; Sierra, M. A. *Acc. Chem. Res.* **2011**, *44*, 479.

2 (a) Wulff, W. D.; Bauta, W. E.; Kaesler, R. W.; Lankford, P. J.; Miller, R. A.; Murray, C. K.; Yang, D. C. *J. Am. Chem. Soc.* **1990**, *112*, 3642. (b) Wulff, W. D.; Bauta, W. E.; Kaesler, R. W.; Lankford, P. J.; Miller, R. A.; Murray, C. K.; Yang, D. C. *J. Am. Chem. Soc.* **1990**, *112*, 3642. (c) Anderson, B. A.; Wulff, W. D.; Powers, T. S.; Tribbitt, S.; Rheingold, A. L. *J. Am. Chem. Soc.* **1992**, *114*, 10784. (d) Barluenga, J.; Aznar, F.; Barluenga, S. *J. Chem. Soc., Chem. Commun*. **1995**, 1973. (e) Barluenga, J.; Fernández-Rodríguez, M. A.; Aguilar, E. *Org. Lett*. **2002**, *4*, 3659.

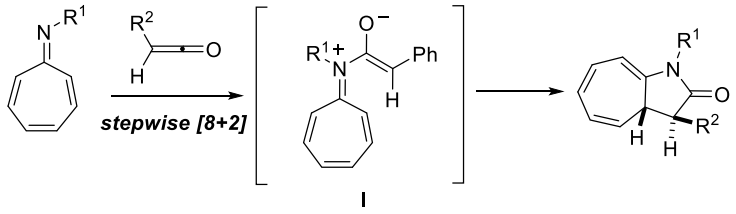
3 (a) Chan, K. S.; Wulff, W. D. *J. Am. Chem. Soc.* **1986**, *108*, 5229. (b) Barluenga, J.; López, S.; Flórez, J. *Angew. Chem., Int. Ed*. **2003**, *42*, 231. (c) Barluenga, J.; Vicente, R.; López, L. A.; Tomás, M. *J. Am. Chem. Soc*. **2006**, *128*, 7050.(d) Granados, A. M.; Fracaroli, A. M.; De Rossi, R. H.; Fuertes, P.; Torroba, T. *Chem. Commun*. **2008**, 483. (e) Baeza, B.; Casarrubios, L.; Ramírez-López, P.; Gómez-Gallego, M.; Sierra, M. A. *Organometallics* **2009**, *28*, 956.

4 Barluenga, J., García-Rodríguez, J., Suárez-Sobrino, A.; Tomás, M. *Chem. Eur. J*. **2009**, *15*, 8800.

5 Fernández, I.; Sierra, M. A.; Cossío, F. P. *J. Org. Chem*. **2008**, *73*, 2083.

6 (a). Fernández, I.; Sierra, M. A.; Cossío, F. P. *J. Org. Chem*. **2006**, *71*, 6178. (b). Andrada, D. M.; Granados, A. M.; Solá, M.; Fernández, I. *Organometallics* **2011**, *30*, 466.

7 Lage, M. L.; Fernández, I.; Torres, M. R.; Sierra, M. A. *Org. Lett*. **2011**, *13*, 2892.



Scheme 1. Stepwise [8+2] Cycloaddition Reaction between 8-Azaheptafulvenes and Ketenes.

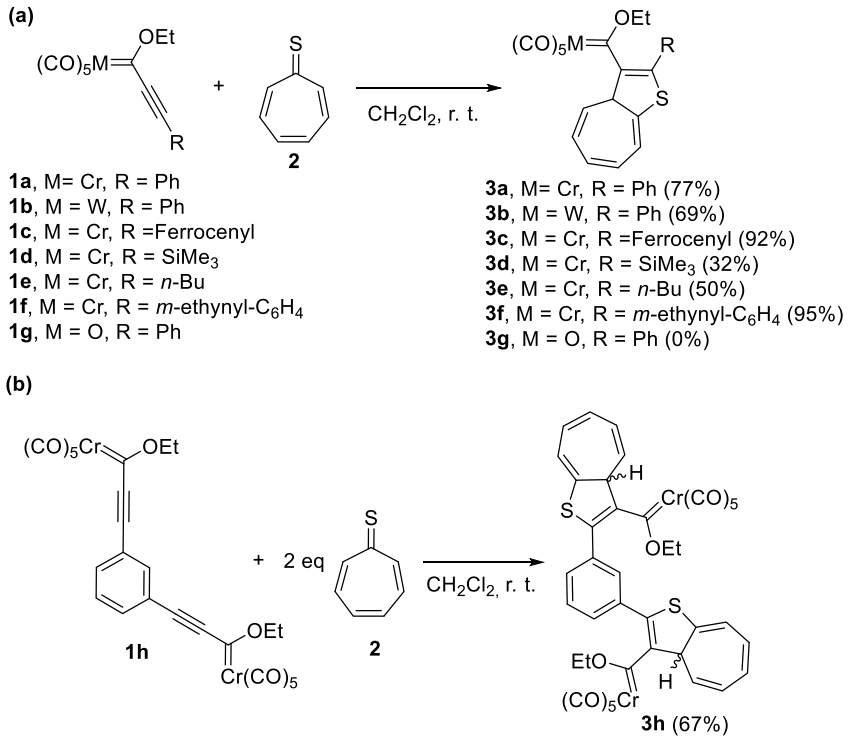
Within the context of our ongoing work on the reaction mechanims and synthetic applications of cycloaddition reactions involving organic and organometallic reagents,[8] we report herein the high-order [8+2] cycloaddition reaction[9] between alkynyl carbene complexes and tropothione, which occurs with total regioselectivity and through a stepwise reaction mechanism.

A tropothione solution, readily prepared from tropone and P_2S_5,[9b] was added to a CH_2Cl_2 solution of the corresponding alkynyl carbene complex **1a-f** (1:1 equimolecular amounts) and the mixture was stirred at room temperature for 5-10 min (Scheme 2a). Removal of the solvent and purification of the residue by column chromatography allowed the isolation of the corresponding 3a*H*-cyclohepta[*b*]thiophene carbene complexes **3a-f**,[10] which maintain the carbene functionality susceptible to further modifications, in moderate to excellent yields. The process is compatible with different substitutions at the triple bond as well as with tungsten derived carbenes (no significant differences between the reaction yields, **3a** *vs* **3b**, in the reactions of chromium(0)- and tungsten(0)-carbene complexes and tropothione **2** were observed). The presence of additional metal-centers (complex **1c**) is also compatible with this cycloaddition reaction. Furthermore, by using a bis-carbene complex (**1h**), bis-cycloadduct **3h** having a pentacyclic bimetallic array was obtained with a 67% reaction yield. Compound **3h** was formed as 1:1 racemic mixture of the two possible RR/SS and *meso*-RS diastereomers.

8 (a) Fernández, I.; Cossío, F. P.; Sierra, M. A. *Organometallics* **2007**, *26*, 3010. (b) Fernández, I.; Sierra, M. A.; Mancheño, M. J.; Gómez-Gallego, M.; Cossío, F. P. *J. Am. Chem. Soc*. **2008**, *130*, 13892. (c) Sarotti, A. M.; Fernández, I.; Spanavello, R. A.; Sierra, M. A.; Suárez, A. G. *Org. Lett.* **2008**, *10*, 3389. (d) Fernández, I.; Cossío, F. P.; de Cózar, A.; Lledós, A.; Mascareñas, J. L. *Chem. Eur. J*. **2010**, *16*, 12147. (e) Fernández, I.; Cossío, F. P.; Bickelhaupt, F. M. *J. Org. Chem*. **2011**, *76*, 2310. (f) Fernández, I.; Mascareñas, J. L. *Org. Biomol. Chem.* **2012**, *10*, 699.

9 For a review on [8+2] cycloaddition reactions, see: (a) Nair, V.; Abhilash, K. G. *Synlett* **2008**, 301. (b) Nair, V.; Abhilash, K. G. *Top. Heterocycl. Chem*. **2008**, *13*, 173.

10 The cyclohepta[*b*]thiophene ring is present in numerous biologically active natural products and drugs such as pizitofen.



Scheme 2. [8+2] Cycloaddition Reaction between Alkenyl Fischer Carbene Complexes **1a-h** and Tropothione **2**.

The spectroscopical data (1D- and 2D-NMR experiments) suggest that the cycloaddition reaction occurs with total regioselectivity leading exclusively to the cycloadduct having the sulfur atom of the tropothione attached to the β-carbon atom of the triple bond of the initial alkynyl carbene complex. This result is in agreement with the high regioselectivity observed for related [3+2] cycloaddition processes[6] and for the [8+2] reaction described by Barluenga's group.[4] The origin of this complete regioselectivity is found in the much higher electrophilicity of the β-carbon atom compared to the α-carbon in the initial alkynyl carbene complex **1**.[6b] The role of the metal in the cycloaddition reaction is decisive, since no reaction was observed when ethyl 3-phenylpropiolate (**1g**) (the organic counterpart of complexes **1a,b**) was mixed with 1 equiv. of tropothione under the same reaction conditions which led to the complete transformation of complexes **1**. The use of higher temperatures (boiling CH_2Cl_2) or prolonged reaction times was of no avail. This finding clearly illustrates the activating "super-ester" effect of the metal moiety commented above.

Single crystals of cycloadduct **3c** suitable for X-ray diffraction analysis were grown in hexanes/ethyl acetate solution at -20 °C. As seen in Figure 1, the sulfur atom of the tropothione is attached to the terminal carbon atom of the triple bond (C17), thus confirming the regioselectivity of the process suggested by the spectroscopical study.

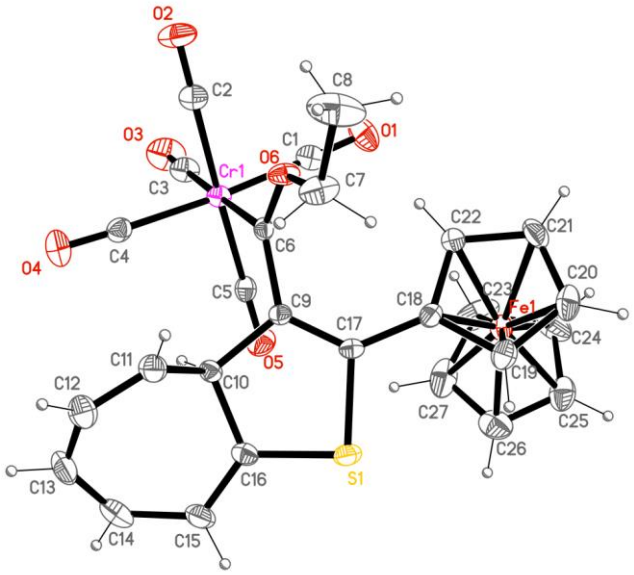


Figure 1. ORTEP diagram of compound **3c**.

In order to gain a deeper insight into the reaction mechanism of the formal [8+2] cycloaddition reaction between carbene complexes **1** and tropothione, a DFT-computational study has been carried out.[11] The corresponding reaction profiles (PCM-M06/def2-SVP//B3LYP/def2-SVP level) of alkynylmethoxy-carbene complex **1M** and thione **2** are depicted in Figure 2, which gathers the computed free energies (at 298 K) in CH_2Cl_2 solution.

As initially envisaged, two different reaction pathways, i.e., concerted *versus* stepwise, are possible. From the data in Figure 2, it becomes obvious that a concerted pathway is not competitive in view of the high activation barrier of the process ($\Delta G^{\neq}_{298}$ = 58.6 kcal/mol) via the saddle point **TS1**. This computed value makes the transformation unfeasible under the reaction conditions used in the experiment (i.e., room temperature). Instead, the stepwise pathway, which starts with the nucleophilic addition of the sulfur atom of the thione to the β-carbon atom of the carbene complex **1M**, is much more likely to occur in view of the much lower activation barrier of this process ($\Delta G^{\neq}_{298}$ = 16.6 kcal/mol, via **TS2**). This addition leads to the formation of zwitterionic intermediate **INT1** which easily evolves to the final cycloadduct **3M** via **TS3** (computed barrier energy of $\Delta G^{\neq}_{298}$ = 7.2 kcal/mol), a saddle point associated with the corresponding carbon-carbon bond formation/ring-closure reaction.

11 See computational details in the Supporting Information.

Therefore, the computed low activation barriers and the exergonicity of the overall cycloaddition (ΔG_R = -18.6 kcal/mol), which are compatible with a reaction at room temperature, make the stepwise pathway the preferred reaction profile for this [8+2] transformation.[12]

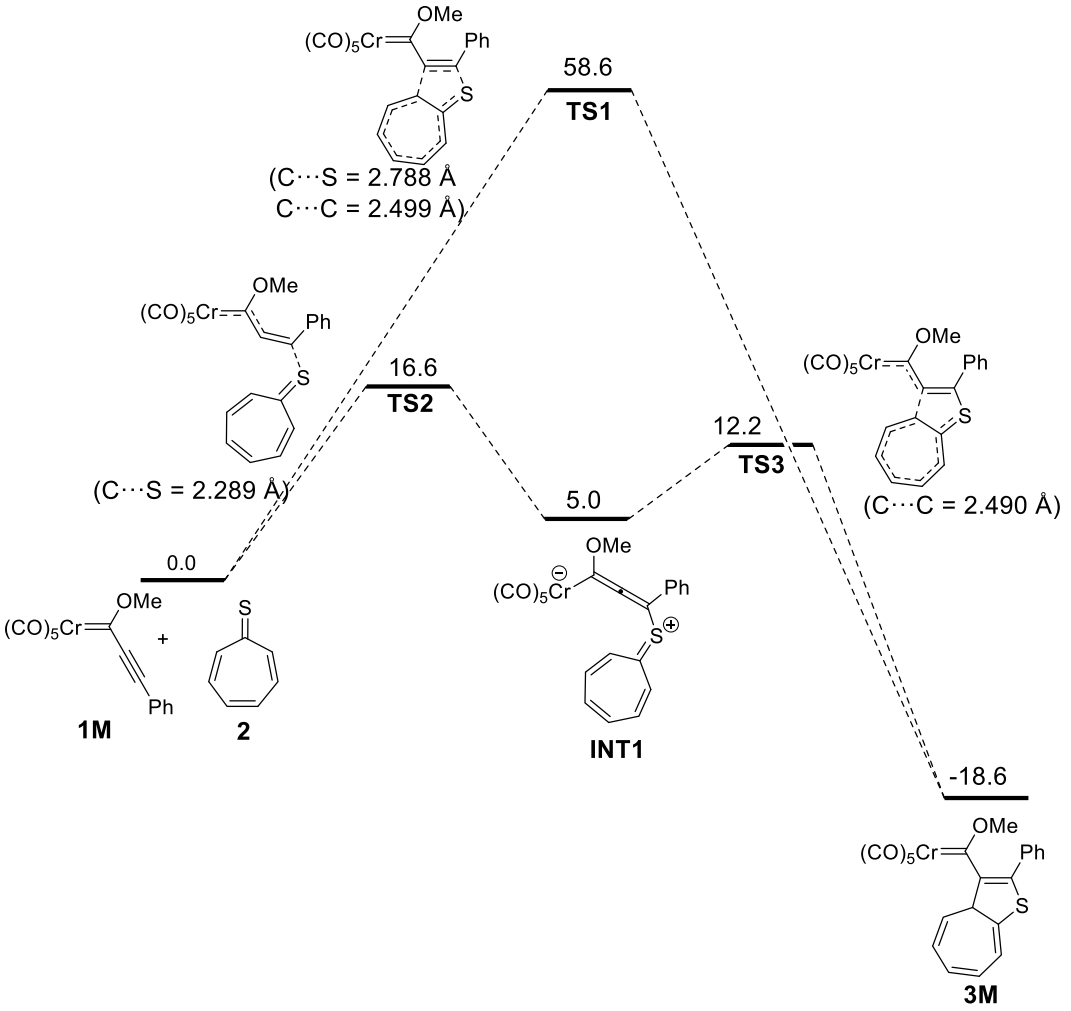


Figure 2. Computed reaction profile (PCM-M06/def2-SVP//B3LYP/def2-SVP level) for the [8+2] cycloaddition reaction between carbene complex **1M** and tropothione **2**. Relative free energies (ΔG_{298}) are given in kcal/mol.

Very likely, the stepwise nature of the cycloaddition finds its origin in the high stabilization of the zwitterionic intermediate **INT1**. Thus, the negative charge is highly delocalized in the electron-withdrawing pentacarbonylmetal moiety

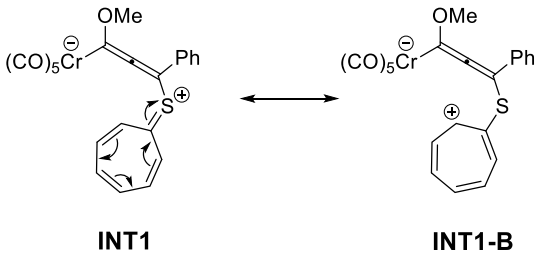
12 We also computed the corresponding reaction profile for the reaction of tropotione and methyl 3-phenylpropiolate. As expected, only the concerted pathway was located in the potential energy surface. The computed high activation barrier ($\Delta G^{\neq}_{298}$ = 28.6 kcal/mol) of this process justifies why the reaction of **1g** and **2** does not occur at room temperature. In view of this barrier energy, the process might be feasible at higher temperatures. However, tropothione **2** is reported to be thermally unstable. See: Machiguchi, T. *Tetrahedron* **1995**, *51*, 1133.

(computed NBO-charge on chromium atom of -2.45e). Similarly, the positive charge is mainly located at the sulfur atom (+0.40e) but also delocalized within the seven-membered ring.[13] As a result, it can be proposed that the resonance form **INT1-B** (Figure 3a), which resembles the tropylium cation, has a significant contribution in the description of the sulfur-substituted zwitterion **INT1**. Consequently, some degree of aromaticity should be expected in this species. In fact, the seven-membered ring of **INT1** exhibits high planarity (C1(S)-C2-C3-C4 dihedral angle of 0.6°) and bond-length equalization (C-C bond distances in the range of 1.377-1.429 Å, intermediate between single and double bonds) thus satisfying the so-called geometric criterion for aromaticity. In contrast, the data computed for the analogous nitrogen-substituted zwitterionic intermediate **I**, formed in the analogous stepwise [8+2] cycloaddition reaction between 8-azafulvenes and ketenes (Scheme 1),[7] showed that this compound is not planar and exhibits a higher bond length alternation. Moreover, the computed positive Nuclear Independent Chemical Shifts (NICS)[14] values confirmed the antiaromatic nature of the latter species.[7]

13 Computed NBO-charges (with summed hydrogen atoms): C1 = -0.14e, C2 =+0.09e, C3 = +0.07e, C4 = 0.07e, C5 = +0.09e, C6 = +0.10e, C7= + 0.11e

14 Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. v. R. *Chem. Rev*. **2005**, *105*, 3842.

(a)



INT1 **INT1-B**

(b)

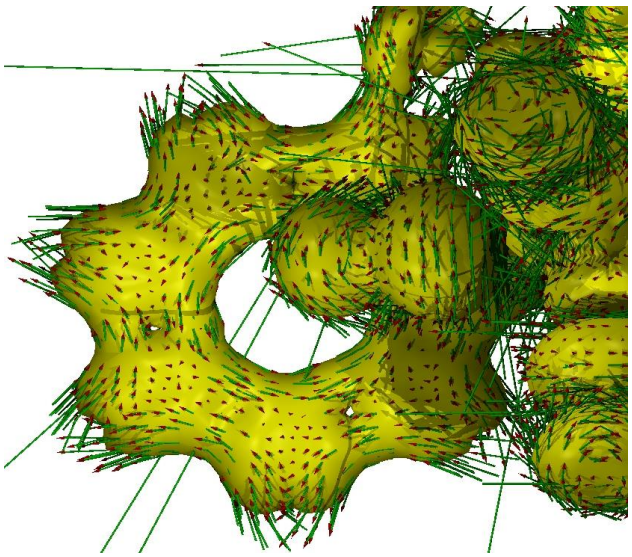


Figure 3. (a) Resonance forms of zwitterion **INT1**. (b) AICD plot of **INT**1 (isosurface value of 0.035).

To check the aromaticity of **INT1**, the corresponding NICS values were also computed. Both the NICS(0) computed at the [3,+1] ring critical point of the electron density[15] (NICS(0) = +5.8 ppm) and the corresponding out-of-plane component computed 1 Å above this point ($NICS(1)_{zz}$ = +2.8 ppm) indicate that the sulfur-substituted zwitterion **INT1** is not aromatic either.[16] This result has been also confirmed by applying the Anisotropy of the Induced Current Density (AICD) method,

15 The [3+1] ring critical point of the electron density has been chosen to compute the NICS values due to its high sensitivity to diamagnetic effects and its unambiguous character. (a) Cossío, F. P.; Morao, I.; Jiao, H.; Schleyer, P. v. R. *J. Am. Chem. Soc*. **1999**, *121*, 6737. See also: (b) Fernández, I.; Sierra, M. A.; Cossío, F. P. *J. Org. Chem*. **2007**, *72*, 1488. (c) Fernández, I.; Bickelhaupt, F. M.; Cossío, F. P. *Chem. Eur. J*. **2009**, *15*, 13022. (d) Fernández, I.; Cossío, F. P. *Curr. Org. Chem*. **2010**, *14*, 1578. (e) Fernández, I.; Bickelhaupt, F. M. *J. Comput. Chem*. **2012**, *33*, 509. (f) Crespo, O.; Eguillor, B.; Esteruelas, M. A.; Fernández, I.; García-Raboso, J.; Gómez-Gallego, M.; Martín-Ortiz, M.; Oliván, M.; Sierra, M. A. *Chem. Comm*. **2012**, 48, 5328.

16 The endergonicity of the formation of **INT1** from **1M** and **2** (ΔG_{298} = + 5.0 kcal/mol) can be ascribed in part to the anti-aromaticity of this species.

developed by Herges and co-workers,[17] on **INT1** to visualize the delocalization of electrons within the ring. As readily seen in Figure 3b, a clear paratropic current (anticlockwise vectors) is observed, thus confirming the antiaromatic nature of this species despite the planarity and bond equalization of the ring.[18] Therefore, it can be concluded that the contribution of the resonance form **INT1-B** cannot be that significant. Moreover, this finding also shows that the exocyclic heteroatom plays a major role in the aromatic nature of these cationic heptafulvenes[19] and, consequently, in the stability of the intermediate zwitterions.

In summary, a formal [8+2] cycloaddition reaction between alkynyl Fischer carbene complexes and tropothione has been described. The process leads to the regioselective formation of 3a*H*-cyclohepta[*b*]thiophene carbene complexes, which maintain the pentacarbonyl-metal carbene functionality. By means of computational-DFT methods, it was found that this transformation proceeds stepwise through an antiaromatic zwitterionic intermediate.

17 (a) Herges, R.; Geuenich, D. *J. Phys. Chem. A* **2001**, *105*, 3214. (b) Geuenich, D.; Hess, K.; Köhler, F.; Herges, R. *Chem. Rev.* **2005**, *105*, 3758.

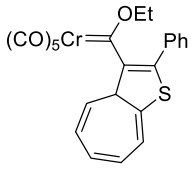
18 We remind the reader that bond-lenght equalization in aromatic compounds comes from σ-interactions but not from the π-bonding. The latter would become stronger in bond-alternating geometries. (a) Shaik, S. S.; Bar, R. *Nouv. J. Chim.* **1984**, *8*, 411. See also (b) Shaik, S. S.; Shurki, A.; Danovich, D.; Hiberty, P. C. *Chem. Rev*. **2001**, *101*, 1501. (c) Fernández, I.; Frenking, G. *Faraday Discuss*. **2007**, *135*, 403. (d) Fernández, I.; Frenking, G. *Chem. Eur. J*. **2007**, *13*, 5873. (e) Pierrefixe, S. C. A. H.; Bickelhaupt, F. M. *Chem. Eur. J*. **2007**, *13*, 6321.

19 This result is in line with a recent report on the effect of the exocyclic heteroatom in the aromaticity of methylenecyclopropene analogues. See: Wang, Y.; Fernández, I.; Duvall, M.; Wu, J. I-C.; Li, Q.; Frenking, G.; Schleyer, P. v. R. *J. Org. Chem*. **2010**, *75*, 8252.

EXPERIMENTAL SECTION

General Procedures: All reactions were carried out under Argon atmosphere. All solvents used in this work were purified immediately before use. Flame dried glassware was used for moisture-sensitive reactions. Identification of products was made by thin layer chromatography (kiesegel 60F-254). UV light (λ= 254 nm) and potassium permanganate (aq. solution) were used to develop the plates. Unless otherwise noted, NMR spectra were recorded at 25 ºC in $CDCl_3$, on a 300 MHz (300 MHz for ^1H, 75 MHz for ^{13}C) spectrometer. Chemical shifts are given in ppm relative to TMS (^1H, 0.0 ppm) or $CDCl_3$ (^{13}C, 77.0 ppm). ^1H NMR splitting pattern abbreviations are: *s*, singlet; *d*, doublet; *t*, triplet; *m*, multiplet. IR spectra were taken on a MIR (8000-400 cm-1) spectrometer as solid films by slow evaporation of the solvent using the ATR (Atenuated Total Reflectance) technique. MS spectra (HRMS) were acquired on Fourier Transform Ion Cyclone Resonance mass spectrometer (4.7 T). Alkynyl Fischer carbene complexes **1a-g**[20] and tropothione **2**[9a10] were prepared following described procedures.

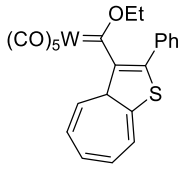
General procedure for cycloaddition reactions: To a solution of the corresponding alkynyl carbene **1a-g** (0.5 mmol) in CH_2Cl_2 (5 mL) at room temperature was added a solution of tropothione **2** (0.5 mmol) in CH_2Cl_2 dropwise. The mixture was stirred at room temperature for 5-10 min. The solvent was then removed *in vacuo* and the crude mixture purified by flash column chromatography to give pure carbene complexes **3a-g**. Compound **3h** was prepared from biscarbene **1h** following the same procedure for monocarbenes but using two equivalents of the tropothione **2**.



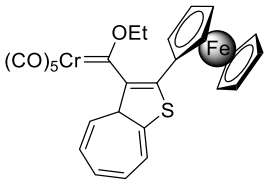
Compound 3a: Red oil (182 mg, 77%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 3H), 7.26-7.20 (m, 2H), 6.63 (dd, *J* = 11.0, 6.1 Hz, 1H), 6.52 (dd, *J* = 11.0, 5.6 Hz, 1H), 6.24 (dd, *J* = 6.2, 2.2 Hz, 1H), 6.16 (dd, *J* = 9.3, 5.7 Hz, 1H), 4.94 (dd, *J* = 9.3, 4.7 Hz, 1H), 4.82 – 4.71 (m, 2H), 4.60 – 4.58 (m, 1H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 340.9, 222.5, 214.9, 147.5, 134.9, 134.3, 133.9, 130.6, 129.2, 129.1, 128.8,

20 Sierra, M. A.; Mancheño, M. J.; del Amo, J. C.; Fernández, I.; Gómez-Gallego, M. *Chem. Eur. J.* **2003**, *9*, 4943.

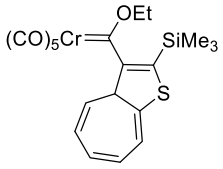
128.5, 125.8, 116.1, 115.0, 77.1, 59.7, 12.9. IR (ATR): υ 2058, 1938 cm^{-1}. HRMS (FTMS) *m/z* calculated for $C_{23}H_{16}CrO_6S$ [M+H] = 473.0151, found 473.0156.



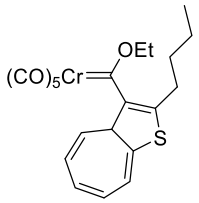
Compound 3b: Dark red oil (208 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 – 7.34 (m, 5H), 6.63 (dd, *J* = 10.9, 6.0 Hz, 1H), 6.53 (dd, *J* = 10.9, 5.6 Hz, 1H), 6.24 (dd, *J* = 6.1, 2.2 Hz, 1H), 6.18 (dd, *J* = 9.4, 5.6 Hz, 1H), 5.01 (dd, *J* = 9.3, 4.7 Hz, 1H), 4.80 – 4.69 (m, 1H), 4.59 – 4.49 (m, 2H), 1.14 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 310.5, 201.9, 196.4, 149.9, 137.7, 134.2, 130.5, 129.2, 129.0, 128.8, 128.4, 125.8, 116.1, 115.4, 79.0, 58.5, 13.9. IR (ATR): υ 2066, 1917 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{23}H_{16}WO_6S$ [M-H] = 603.0104, found 603.0105.



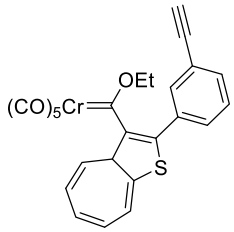
Compound 3c: Dark red oil; yield: (267 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61 (dd, *J* = 11.1, 6.3 Hz, 1H), 6.46 (dd, *J* = 11.1, 5.7 Hz, 1H), 6.22 (dd, *J* = 6.2, 2.1 Hz, 1H), 6.11 (dd, *J* = 9.3, 6.1, Hz, 1H), 4.79-4.74 (m, 2H), 4.61 (s, 2H), 4.37 – 4.20 (m, 9H), 1.46 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 343.0, 223.0, 215.5, 134.6, 131.8, 130.3, 128.2, 125.6, 115.1, 114.7, 76.2, 70.4, 70.0, 69.7, 67.2, 60.7, 14.8. IR (ATR): υ 2057, 1931 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{27}H_{20}CrFeO_6S$ [M-H] = 578.9652, found 578.9652.



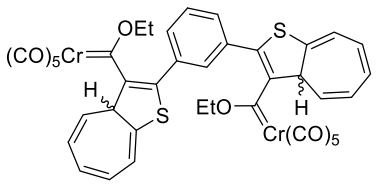
Compound 3d: Red solid (75 mg, 32%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (dd, *J* = 11.0, 6.2 Hz, 1H), 6.46 (dd, *J* = 11.0, 5.8 Hz, 1H), 6.19 (dd, *J* = 6.2, 2.2 Hz, 1H), 6.11 (dd, *J* = 9.0, 5.8 Hz, 1H), 5.44 – 5.33 (m, 1H), 5.11 – 5.01 (m, 1H), 4.77 – 4.69 (m, 2H), 1.73 (t, *J* = 7.1 Hz, 3H), 0.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 340.4, 223.4, 216.1, 160.0, 139.4, 136.6, 130.4, 128.3, 125.2, 114.8, 113.4, 77.4, 61.0, 15.3, 0.1. IR (ATR): υ 2058, 1931 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{20}H_{20}CrO_6SSi$ [M+H] = 469.0239, found 469.0239.



Compound 3e: Dark orange oil (113 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (dd, *J* = 11.2, 6.4 Hz, 1H), 6.46 (dd, *J* = 10.9, 5.7 Hz, 1H), 6.18 (dd, *J* = 6.2, 2.2 Hz, 1H), 6.09 (dd, *J* = 8.9, 5.9 Hz, 1H), 5.15 – 5.04 (m, 2H), 4.81 (dd, *J* = 9.3, 4.6 Hz, 1H), 4.52 (s, 1H), 2.43-2.15 (m, 2H), 1.72 (t, *J* = 7.1 Hz, 3H), 1.50 – 1.38 (m, 2H), 1.38 – 1.27 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 342.4, 223.3, 213.9, 147.4, 137.0, 134.1, 130.5, 128.6, 125.3, 116.0, 115.3, 77.2, 59.4, 31.6, 29.6, 22.5, 15.5, 13.9. IR (ATR): υ 2058, 1931 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{21}H_{20}CrO_6S$ [M-H] = 451.0313, found 451.0313.



Compound 3f: Red oil (236 mg, 95%). ^{1}H NMR (700 MHz, acetone-d_6) δ 7.56 (d, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.39 (s, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 6.68 (dd, *J* = 11.1, 6.3 Hz, 1H), 6.57 (dd, *J* = 11.1, 5.7 Hz, 1H), 6.37 (dd, *J* = 6.2, 1.8 Hz, 1H), 6.22 (dd, *J* = 8.9, 6.0 Hz, 1H), 5.04 (dd, *J* = 9.2, 4.7 Hz, 2H), 5.01-4.97 (m, 1H), 4.59 (s, 1H), 3.78 (s, 1H), 1.38 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (176 MHz, acetone-d_6) δ 343.3, 225.3, 217.4, 135.5, 134.8, 134.2, 134.0, 133.1, 132.0, 131.0, 130.7, 130.3, 127.4, 124.8, 117.9, 116.3, 83.9, 81.4, 79.8, 61.5, 15.6. IR (ATR): υ 2059, 1934 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{25}H_{16}CrO_6S$ [M+H] = 497.0156, found 497.0156.



Compound 3h: Dark orange oil (1:1 mixture of isomers, 290 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.13 (m, 4H), 6.65 (dd, *J* = 11.0, 6.5 Hz, 2H), 6.54 (dd, *J* = 11.0, 5.4 Hz, 2H), 6.25-6.24 (m, 2H), 6.20-6.16 (m, 2H), 4.97-4.77 (m, 6H), 4.55 (s, 2H), 1.34 (t, *J* = 6.94 Hz, 3H), 1.29 (t, *J* = 6.94 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 342.9, 342.5, 223.6, 216.0, 216.0, 148.6, 148.4, 134.8, 134.4, 133.8, 133.7, 133.6, 133.3, 130.7,129.4,

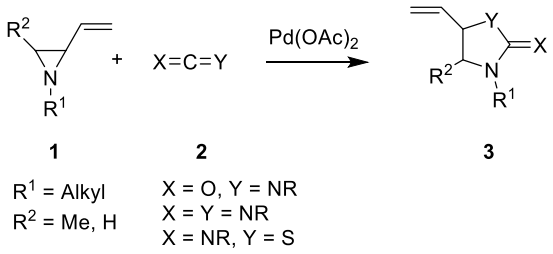
129.2, 129.0, 128.6, 128.4, 126.0, 125.9, 116.4, 116.3, 115.1, 115.0, 77.7, 77.5, 77.4, 66.1, 60.0, 15.1, 145.0. IR (ATR): υ 2095, 1931 cm^{-1} HRMS (ESI) *m/z* calculated for $C_{40}H_{26}Cr_2O_{12}S_2$ [M+H] = 866.9760, found 866.9762.

2.2. The Photochemical Reaction of Vinylaziridines and Vinylazetidines with Chromium(0) and Molybdenum(0) (Fischer) Carbene Complexes

Chem. Eur. J. **2014**, *20*, 1359

The [5+2] and [6+2]-cycloaddition reactions of vinylaziridines and vinylazetidines with ketenes generated photochemically from chromium(0) and molybdenum(0) Fischer carbene complexes have been investigated. These processes constitute a straight and efficient access to azepanones and azocinones, respectively. The peculiar electronic properties of the metallated-ketenes allow for the introduction of electron-rich substituents in the final cycloadducts, a difficult task using conventional organic chemistry procedures. The versatility of the process is demonstrated using Cr^0-Fischer bis-carbene complexes as metallated-bis-ketene precursors. These species produce tethered bis-azepanones in a single step under mild reaction conditions. Density functional theory calculations points to a stepwise reaction pathway through the initial nucleophilic attack of the nitrogen atom of the aziridine to the metallated-ketene, followed by ring closure of the zwitterionic intermediate thus formed.

The ring opening reaction of vinyl-substituted three- and four-membered nitrogen heterocycles with cumulenes has been little studied despite their potential to produce medium-size rings in an easy and efficient manner.[1] This contrasts with the use of the strained nature of these cyclic amines to prepare other classes of compounds in reactions involving the cleavage of the C–N bond.[2] For example, Alper and co-workers reported the first examples of a reaction involving 2-vinylaziridines and isocyanates, isothiocyanates, and carbodiimides.[3] Thus, the reactions of a series of vinylaziridines **1** with cumulenes **2** under Pd catalysis yielded the corresponding five-membered heterocycles **3** in acceptable to excellent yields (Scheme 1). Aggarwal and co-workers have reported a similar transformation[4] in the Pd-catalysed insertion of CO_2 into a vinylaziridine. However, it should be noted that in both cases the double bond is not incorporated into the final five-membered ring.[5]



Scheme 1. The reactions of vinylaziridines and cumulenes under Pd catalysis.

The simultaneous participation of the double bond of a vinylaziridine with the concomitant three-membered ring opening has been used to develop synthetically useful routes to the azepane skeleton. For instance, the reaction of these substrates with electron-poor alkynes leads to a seven-membered ring through a divinylcyclopropane-cycloheptadiene-type rearrangement.[6] Moreover, phenyl isothiocyanate and very recently sulfonyl isocyanates have been employed as C2 units in formal [5+2]-cycloaddition reactions with 2-vinylaziridines to smoothly

1 For the literature covering the reaction of vinylaziridines with unsaturated substrates before 1982, see: A. Hassner, W. Chau, R. de Costa, *Isr. J. Chem.* **1982**, *22*, 76.

2 Ohno, H. *Vinylaziridines in Organic Synthesis* in *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; *Wiley-VCH: Weinheim*, **2006**, 37**.**

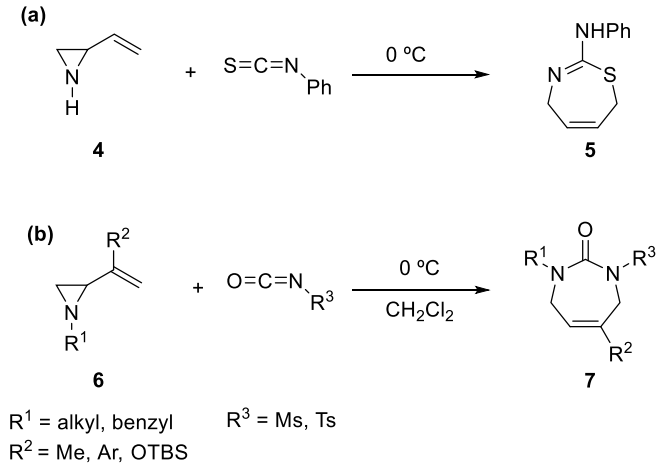
3 (a) Butler, D. C. D.; Inman, G. A.; Alper, H. *J. Org. Chem.* **2000**, *65*, 5887. (b) Dong, C.; Alper, H.*Tetrahedron:Asymm.* **2004**, *15*, 1537.

4 Fontana, F.; Chen, C. C.; Aggarwal, V. K. *Org. Lett.* **2011**, *13*, 3454.

5 This process is essentially different from the well-known formation of seven-membered heterocycles by the intramolecular aza-Cope rearrangement of divinylaziridines and related compounds. Recent examples: (a) Fantauzzi, S.; Gallo, E.; Caselli, A.; Piangiolino, C.; Ragaini, F.; Re, N.; Cenini, S. *Chem. Eur. J*. **2009**, *15*, 1241; (b) Lindström, U. M.; Somfai, P. *Chem. Eur. J*. **2001**, *7*, 94.

6 (a) Stogryn, E. L.; Brois, S. J. *J. Am. Chem. Soc*. **1967**, *89*, 605; (b) Hassner, A.; D'Costa, R.; McPhail, A. T.; Butler, W. *Tetrahedron Lett*. **1981**, *22*, 3691.

produce 1,3-thiazepine derivates[7] and various cyclic ureas,[8] respectively (Scheme 2a and b). It is remarkable that in these cases the cycloaddition processes occurred at 0 °C and in the absence of metal-catalysts. A similar methodology was previously reported by the same authors in the ring-expansion reaction of vinylazetidines with electron-deficient isocyanates (in a formal [6+2]-cycloaddition reaction).[9]



Scheme 2. Formal [5+2] cycloaddition reactions of 2-vinylaziridines.

Despite the efficiency of the aforementioned processes, the cycloaddition reaction with vinylaziridines or vinylazetidines is restricted to electron-deficient cumulenes, limiting the scope of this synthetically valuable transformation. Therefore, the use of substrates with electron-donor substituents in their structures is an unfulfilled challenge. At this point, we turned our attention to the ability of Group 6 Cr^0 and Mo^0 Fischer-type carbene complexes to form electron-rich metalated ketenes when irradiated in the presence of visible light.[10] These species are able to produce a wide variety of reaction products in the presence of nucleophiles, avoiding the main shortcomings of ketenes, that is, dimerization and the formation of undesired adducts.

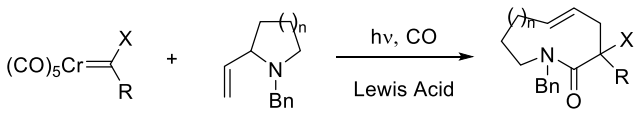
7 (a) Heine, H. W.; Mente, P. G. *J. Org. Chem*. **1971**, *36*, 3076. The formation of a mixture of seven-membered cyclic urea and five-membered heterocycles was reported in the reactions of 2-vinylaziridines with phenyl isocyanate. See: (b) Zhang, K.; Chopade, P. R.; Louie, J. *Tetrahedron Lett*. **2008**, *49*, 4306.

8 Kanno, E.; Yamanoi, K.; Koya, S.; Azumaya, I.; Masu, H.; Yamasaki, R.; Saito, S. *J. Org. Chem.* **2012**, *77*, 2142.

9 (a) Koya, S.; Yamanoi, K.; Yamasaki, R.; Azumaya, I.; Masu, H.; Saito, S. *Org. Lett*. **2009**, *11*, 5438. (b) Recently, Saito and coworkers have reported the [6+2] cycloaddition of benzyne and several 2-vinylazetidines to yield 1-benzazocine derivatives. Aoki, T.; Koya, S.; Yamasaki, R.; Saito, S. *Org. Lett.* **2012**, *14*, 4506.

10 (a) Hegedus, L. S. *Tetrahedron*, **1997**, *53*, 4105; (b) Arrieta, A.; Cossío, F. P.; Fernández, I.; Gómez-Gallego, M.; Lecea, B.; Mancheño, M. J.; Sierra, M. A. *J. Am. Chem. Soc*. **2000**, *122*, 11509. (c) Fernández, I.; Sierra, M. A.; Gómez-Gallego, M.; Mancheño, M. J.; Cossío, F. P. *Chem. Eur. J*. **2005**, *11*, 5988. (d) Fernández, I.; Sierra, M. A.; Mancheño, M. J.; Gómez-Gallego, M.; Cossío, F. P. *J. Am. Chem. Soc*. **2008**, *130*, 13892; (e) Fernández, I.; Cossío, F. P.; Sierra, M. A. *Acc. Chem. Res*. **2011**, *44*, 479; (f) Fernández, I.; Sierra, M. A. *Top. Heterocycl. Chem*. **2013**, *30*, 65.

Interestingly, the reactions of photochemically generated ketenes from Cr^0 Fischer carbene complexes **8** and 2-vinyl-pyrrolidines or -piperidines **9** has been reported (Scheme 3).[11] The final products, ten- or eleven-membered-ring amides **10**, were obtained in acceptable to good yields in the presence of a Lewis acid. The formation of these cyclic compounds was thought to occur through a Malherbe-Bellus variant of the Claisen rearrangement.[12] Based on this report, we speculated that this type of electron-rich ketene may serve as a C2 unit in [5+2] or [6+2] cycloaddition reactions with vinylaziridines or vinylazetidines, respectively. Herein, the successful accomplishment of this hypothesis, which allows a rapid access to azepanones and azocinones, shall be described. In addition, the extension of this reaction to *bis*-carbene complexes, as well as the elucidation of the corresponding reaction mechanism by means of computational methods, will be reported.



8
R = H, Me
X = OR, NR_2

9
n = 1, 2

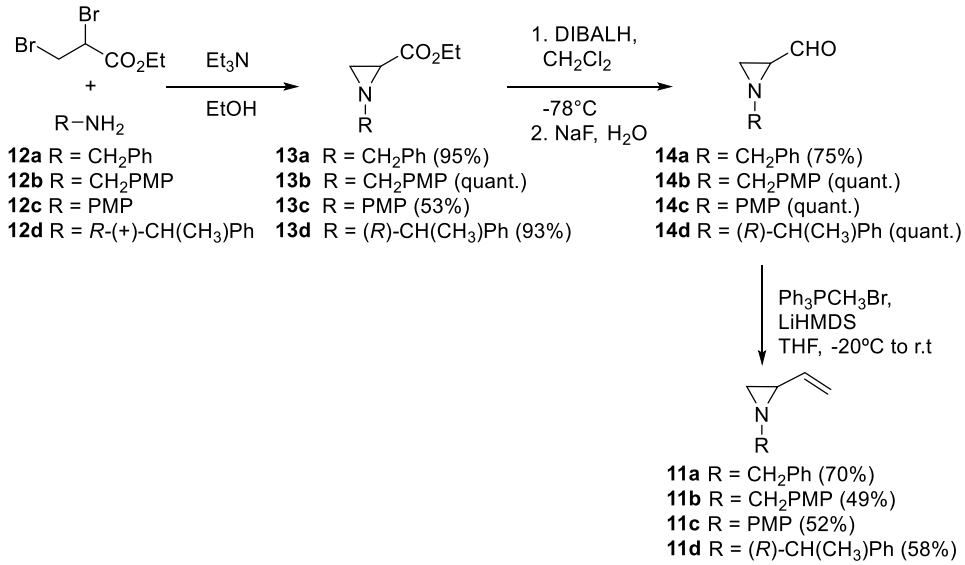
10
n = 1, 2

Scheme 3. Photochemical reactions of 2-vinylpyrrolidines and –piperidines with Cr^0 carbene complexes.

Aziridines **11** were prepared in moderate to quantitative yields by using a standard methodology, that is, reacting ethyl 2,3-dibromopropionate with amines **12** in EtOH as the solvent and in the presence of Et_3N (Scheme 4). Reduction of aziridine esters **13** to the corresponding aldehydes **14** occurred in the presence of DIBALH (Diisobutylaluminium hydride) in CH_2Cl_2 at -78 °C, followed by quenching with an aqueous solution of NaF. Finally, Wittig reaction with the $Ph_3P{=}CH_2$ ylide results in the desired vinylaziridines **11**.

11 Deur, C. J.; Miller, M. W.; Hegedus, L. S. *J. Org. Chem.* **1996**, *61*, 2871.

12 (a) Malherbe, R.; Bellus, D. *Helv. Chim. Acta* **1978**, *61*, 3096; (b) Malherbe, R.; Rist, G.; Bellus, D. *J. Org. Chem*. **1983**, *48*, 860. (c) Rosini, G.; Spineti, G. G.; Foresti, E.; Pradella, G. *J. Org. Chem*. **1981**, *46*, 2228. (d) Vedejs, E.; Buchanan, R. A.; *J. Org. Chem*. **1984**, *49*, 1841. (e) Edstrom, E. *J. Am. Chem. Soc*. **1991**, *113*, 6690.



Scheme 4. Synthesis of 2-vinylaziridines 11.

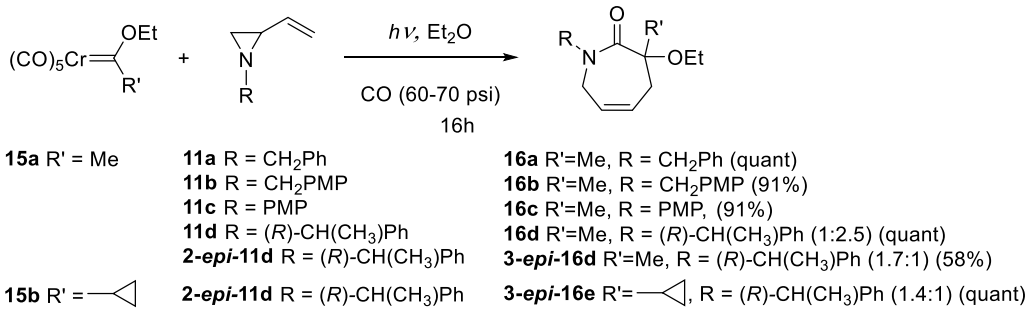
Irradiation (450W medium pressure Hg lamp, pyrex filter and pyrex well) of a mixture of pentacarbonyl[(ethoxy)(methyl)carbene]chromium(0) **15a** and aziridine **11a** (1.2:1 molar ratio) in Et_2O under 60-70 psi of CO yielded *N*-benzyl-3,4-dihydroazepin-2-one **16a** in quantitative yield (Scheme 5).[13] Thus, it became clear that the envisioned formal [5+2]-cycloaddition reaction is indeed possible, allowing for the introduction of electron-donor substituents in the azepinone skeleton. Moreover, this transformation proceeds smoothly at room temperature in the absence of Lewis acid additives, which contrasts with the related process involving 2-vinilpyrrolidones.[11]

The reaction was then extended to 2-vinylaziridines **11b** and **11c**, which yielded 3-ethoxyazepinones **16b-c** in excellent yields. The introduction of chiral enantiomerically pure diastereomeric aziridines **11d** and **2-*epi*-11d**[14] formed the corresponding ethoxy-azepinones **16d** and **3-*epi*-16d** with excellent yields and as an inseparable mixture of diasteromers. As expected, the diastereoselectivity of the reaction was poor (1:2.5) and it was inverted for **11d** respect to **2-*epi*-11d**, with the major product of the reaction of **11d** being the minor product in the reaction of **2-*epi*-11d** (ratio 1.7:1). Clearly, the stereochemical outcome of the reaction is controlled by the stereochemistry of the vinylaziridine chiral center, with the exocyclic chiral center as a spectator. Unfortunately, the spectroscopic data are inconclusive with

13 The reaction of complex **15a** and vinylazetidine **11a** was tested under Ar atmosphere. The corresponding azepinone **16a** was obtained in 53% yield. Therefore, all the reactions were carried out under a CO atmosphere.

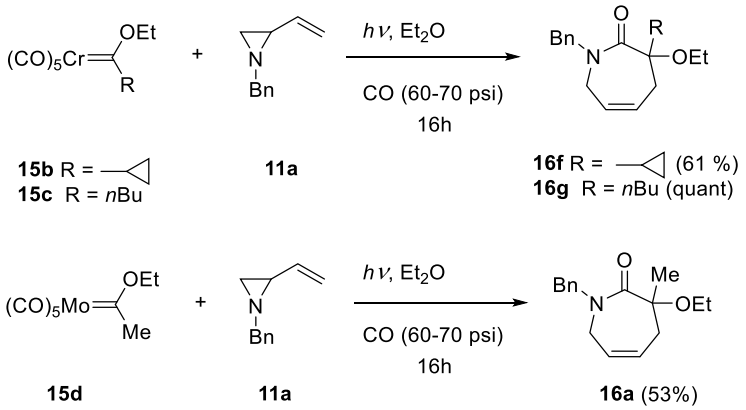
14 Vinylaziridines **11d** and **2-epi-11d** were obtained by reaction of *(R)*-α-phenylethyl amine and ethyl 2,3-dibromopropionate following the standard procedure depicted in Scheme 4 as a 1:1 diastereomeric mixture.

regard to the stereochemistry of the adduct **16d**. Furthermore, we were not able to grow crystals of any of the diastereomers of **16d** and, therefore, the stereochemistry of cycloadducts **16d** remains unknown. A similar result was obtained in the reaction of **15b** and ***2-epi*-11d**, which yielded ***3-epi*-16e** as a mixture of diastereomers also with low selectivity (1.4:1) (Scheme 5).



Scheme 5. Photochemical reactions of 2-vinylaziridines and Cr^0 Fischer carbenes.

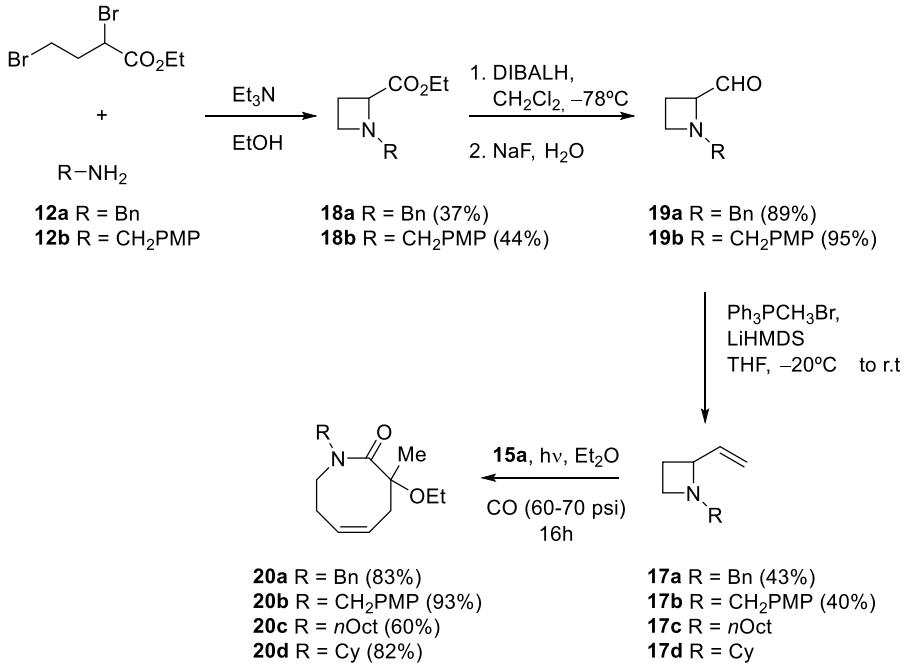
Complexes **15b** and **15c** also reacted smoothly with vinylaziridine **11a** (1.2:1 molar ratio), yielding the expected ethoxy-azepinones **16f** and **16g** in 61% and quantitative yields, respectively (Scheme 6). It is noteworthy that the diastereoselectivity of the reactions between complexes **15a** and **15b** and ***2-epi*-11d** were nearly identical, independent of the introduction of a bulky cyclopropyl group in complex **15b** compared to a methyl group in **15a.** In addition, the reaction was also extended to molybdenum(0) carbene complex **15d**, which formed the azepinone **16a** in 53% yield. This result is not surprising because of the known lower reactivity of Mo^0 carbene complexes compared to their Cr^0 counterparts in the photocarbonylation reaction.[15]



Scheme 6. Reactions of Cr^0 and Mo^0 carbene complexes and N-benzyl-2-vinylaziridine.

15 Hegedus, L. S.; Schultze, L. M.; Toro, J.; Yijun, C. *Tetrahedron* **1985**, *41*, 5741.

Vinylazetidines **17** were tested next. These species were prepared following a similar procedure to that described above for the synthesis of vinylaziridines **11**. Thus, ethyl 2,4-dibromobutanoate was converted into the corresponding azetidine esters **18** by reaction with amines **12**. Compounds **18** were transformed into aldehydes **19** (DIBALH) and finally, into vinylazetidines **17** through Wittig methylenation with the $Ph_3P{=}CH_2$ ylide (Scheme 7). The photochemical reactions of azetidines **17** and chromium(0) carbene complex **15a** formed the corresponding eight-membered-ring tetrahydroazocin-2-ones **20a-d** in good to excellent yields through a formal [6+2]-cycloaddition reaction. These results clearly indicate that the reactivity of Fischer carbene complexes in these cycloaddition reactions is compatible with three- and four-membered rings supporting the vinyl group (Scheme 7).



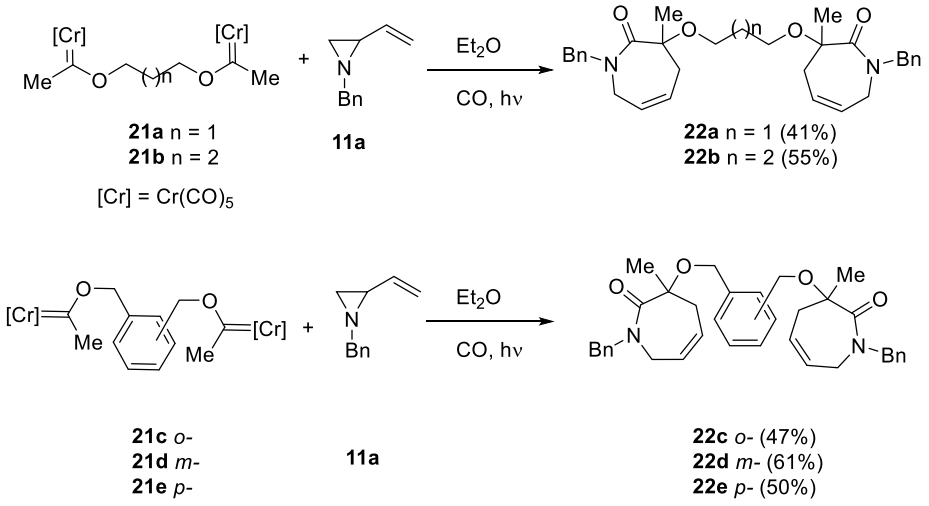
Scheme 7. The synthesis of 2-vinylazetidines.

The reaction of thermally generated electron-rich, nonmetalated ketenes and vinylaziridine **11a** was also tested to assess the need to use ketenes derived from Fischer carbene complexes. To this end, the alkoxyketene derived from the reaction of phenyloxyacetyl chloride and Et_3N and the phenylketene derived from phenylacetyl chloride and Et_3N were prepared. In both cases, conditions to ensure the generation of the ketenes[16] (-78°C/CH_2Cl_2, addition of Et_3N to a solution of the acid chloride) were used. Both nonmetallated ketenes afford complex reaction mixtures in

16 (a) Cossío, F. P.; Arrieta, A.; Sierra, M. A. *Acc. Chem. Res*. **2008**, *41*, 925; (b) Tidwell, T. T. *Ketenes II*, **2006**, John Wiley & Sons, Inc., Hoboken, New Jersey.

their reactions with vinylaziridine **8a** instead of the clean, crude products observed when using Fischer carbene complex derived ketenes. This marked difference with respect to the reactions involving Fischer carbene complexes clearly illustrates the difficulties associated with the introduction of electron-donor substituents in the ketene, which can be easily overcome when using metallated-ketenes generated by photocarbonylation of Fischer carbene complexes.

The efficiency of the aforementioned cyclization reactions led us to assess the reaction of chromium(0)*bis*-carbene complexes **21a-e** and vinylaziridine **11a** to produce *bis*-azepinones. Thus, irradiation of *bis*-carbene complexes **21** with **11a** in the same reaction conditions used for the mononuclear Fischer carbene complexes (1:2 molar ratio) afforded alkoxy-tethered *bis*-azepinones **22a-e** in moderate to good (41-61%) yields. Complexes having aliphatic (**21a** and **21b**) and aromatic (**21c-e**) tethers were compatible with the transformation (Scheme 8). *Bis*-azepinones **22** resulted from a double formal [5+2]-cycloaddition reaction and were always obtained as inseparable diastereomeric mixtures. Both the ^{1}H and ^{13}C NMR spectra of compounds **22** show splitting of significant signals, especially those corresponding to the methyl groups, which confirm the formation of the racemic (RR/SS) and *meso* (RS) forms. No appreciable selectivity was observed. This process is one single reaction step route to bis-azepinones, which are difficult to obtain by conventional organic chemistry procedures.



Scheme 8. The reactions of Cr^0 bis-carbene complexes with 2-vinylaziridines to yield bis(azepinones).

Finally, the reaction mechanism of the above discussed cycloaddition reactions was studied by using density functional theory (DFT) calculations at the PCM(Et_2O)-

B3LYP/def2-SVP level.[17] The corresponding computed reaction profiles of the metalated ketene **23** (generated by photocarbonylation of pentacarbonyl[(methoxy)(methyl)carbene]chromium(0) complex following the reaction pathway previously reported by us)[10d] with the model vinylaziridine **11M**, to produce the [5+2]-cycloadduct **16M**, are shown in Figure 1 (which gathers the respective free energies, at 298 K, in Et_2O).

As can be readily seen in Figure 1, our calculations suggest that the process begins with nucleophilic attack of the nitrogen atom of aziridine to the highly electrophilic carbonyl carbon atom of metalaketene **23**. This reaction leads to the zwitterionic complex **INT1-a** through **TS1**, a saddle point associated with the formation of the C–N single bond (activation barrier of 13.3 kcal/mol). Complex **INT1-a** rapidly isomerizes into zwitterion **INT1-b**, which is then able to undergo a ring-closing reaction to form the seven-membered-ring species **INT2**. This step occurs via the highly asynchronous transition state **TS2**,[18] which is associated with the formation of the new C–C bond with concomitant aziridine ring opening (i.e., C–N bond breaking). This process proceeds with a very low activation barrier ($\Delta G_{a,298}$ = 3.9 kcal/mol) in a highly exergonic transformation (ΔG_{298} = -61.6 kcal/mol), which clearly reflects the ease of this reaction step. Subsequent decoordination of the $Cr(CO)_5$ fragment by use of CO or a molecule of coordinating solvent (Et_2O)[19] releases the final cycloadduct **16M**. Alternatively, the decoordination reaction may occur prior to the final ring closure in the metalated zwitterion **INT1-b**, producing **INT1-c**. Indeed, zwitterion **INT1-c** can also undergo a similar, facile ring-closure step (with an activation barrier of 5.4 kcal/mol and reaction energy of -72.9 kcal/mol) to produce the seven-membered-ring compound **16M** through the highly asynchronous transition state **TS2-c**.

17 See computational details.

18 Highly asynchronous transition states have been also located for other cycloaddition reactions. See, for instance, Celebi-Olcum, N.; Lam, Y.-H.; Richmond, E.; Ling, K. B.; Smith, A. D.; Houk, K. N. *Angew. Chem. Int. Ed*. **2011**, *50*, 11478.

19 For a related solvent mediated release of the $Cr(CO)_5$ fragment, see: Fernández, I.; Mancheño, M. J.; Vicente, R.; López, L. A.; Sierra, M. A. *Chem. Eur. J*. **2008**, *14*, 11222.

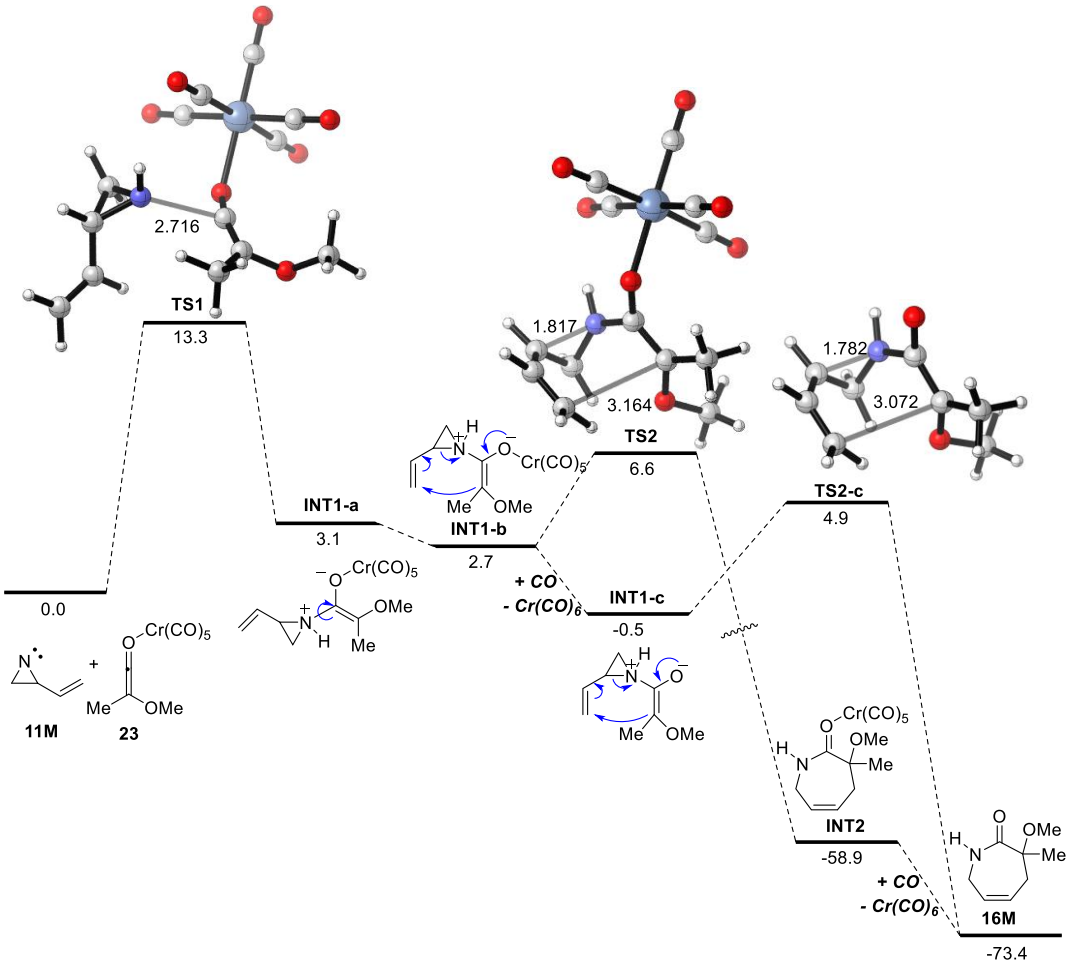


Figure 1. Computed reaction profile of metalated ketene **23** and vinylaziridine **11M**. Relative free energy values (computed at 298 K) and bond lengths are given in kcal/mol and Å, respectively. All data have been computed at the PCM(Et_2O)-B3LYP/def2-SVP level.

From this computational study, it can be concluded that the [5+2]-cycloaddition reaction between aziridines and metalated ketenes occurs stepwise in a process that resembles the [2+2]-cycloaddition of these metalated ketenes with imines,[10d] that is, a process which involves the initial nucleophilic attack of the nitrogen atom followed by ring closure of the zwitterionic intermediate formed.

From the joint experimental and computational study reported herein, the following conclusions can be drawn: (i) metalated ketenes, photochemically generated from Fischer carbene complexes, react with vinylaziridines and vinylazetidenes to produce azepanones and azocinones, respectively, with high to excellent reaction yields. (ii) The peculiar electronic properties of these metalated ketenes allow the introduction of electron-rich substituents in the final reaction products. This constitutes a marked difference from the reported procedures, which are restricted to the use of electron-poor cumulenes. (iii) These transformations, which can be viewed as formal [5+2] or [6+2] cycloaddition reactions, are compatible

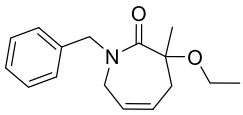
with Chromium(0) Fischer bis-carbene complexes as metalated ketene precursors, producing tethered bis-azepanones in a single step under mild reaction conditions. (iv) DFT calculations suggest that the transformation occurs stepwise through the initial nucleophilic attack of the nitrogen atom of the aziridine at the metalated ketene, followed by ring closure of the zwitterionic intermediate thus formed. This reaction mechanism resembles that proposed for the [2+2]-cycloaddition reaction of these metalated ketenes and imines.[10d]

EXPERIMENTAL SECTION

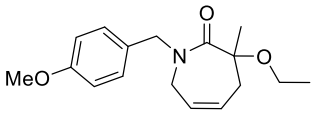
General Procedures: All reactions were carried out under an argon atmosphere. All solvents used in this work were purified by distillation and were freshly distilled immediately before use. Triethylamine (Et_3N) was distilled from calcium hydride, whereas diethylether (Et_2O) was purified using a Pure Solv PS-MD-5 system. Flame-dried glassware was used for moisture-sensitive reactions. Silica gel (Merck: 230-400 mesh) was used as stationary phases for purification of crude reaction mixtures by flash column chromatography under Ar pressure. Identification of products was made by thin-layer chromatography (Kieselgel 60F-254). UV light (ν 254nm) and 5% phosphomolybdic acid solution in 95% EtOH were used to develop the plates. NMR spectra were recorded at 25 ºC in $CDCl_3$, on Bruker Avance 300 (300 MHz for ^1H and 75 MHz for ^{13}C). Chemical shifts are given in ppm relative to $CDCl_3$ (^1H, 7.27 ppm and ^{13}C, 77.0 ppm). IR spectra were taken on a MIR (8000–400 cm^{-1}) spectrometer as solid films by slow evaporation of the solvent using the ATR (attenuated total reflectance) technique. MS spectra (HRMS) were acquired on a Fourier transform ion cyclone resonance mass spectrometer (4.7 T). Chromium carbene complexes **15** and **21**[20] were prepared following previously reported procedures. Azetidines **17c** and **17d** were prepared according to reported procedures.[9b]

General procedure for the photochemical cycloaddition reactions: Photoreactions were carried out in oven-dried pressure tubes that were charged with the carbene complex **15** and the corresponding vinylaziridine **11** or vinylazetidine **18** (1.2:1 molar ratio) and dry and degased (3 cycles freeze-pump-thaw) Et_2O. The tube was fitted with a pressure head, purged three times with CO, and irradiated under 60-70 psi of CO (medium pressure mercury lamp 450W, pyrex filter and pyrex well) for 16h. The solvent was removed under vacuum, the residue was taken up in 1:1 hexane/EtOAc, and it was exposed to light to oxidize the remaining metal(0) compounds. The resulting mixture was filtered through celite and the solvent was removed under vacuum to obtain the desired dihydroazepinones **16a-f** (from vinylaziridines **11**) or the desired tetrahydroazocinones **20a-b** (for vinylazetidines **18**).

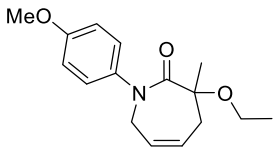
20 (a) Hafner, A.; Hegedus, L. S.; deWeck, G.; Hawkins, B.; Dötz, K. H. *J. Am. Chem. Soc.* **1988**, *110*, 8413. (b) Sierra, M. A.; del Amo, J. C.; Mancheño, M. J.; Gómez-Gallego, M. *J. Am. Chem. Soc.* **2001**, *123*, 851.



Compound 16a: Following the general procedure, from carbene complex **15a** (66 mg, 0.25 mmol) and vinylaziridine **11a** (33 mg, 0.21mmol), dihydroazepinone **16a** was obtained as an orange oil (54 mg, quantitative yield, 53% when using carbene complex **15d**). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.35 – 7.21 (m, 5H), 5.71 – 5.53 (m, 2H), 4.73 – 4.61 (m, 2H), 4.61 – 4.51 (m, 1H), 3.71 – 3.50 (m, 3H), 3.40 – 3.29 (m, 2H), 2.49 (m, 2H), 1.52 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 173.7, 138.1, 128.9, 128.1, 127.9, 127.6, 125.2, 80.9, 59.9, 53.5, 47.0, 38.7, 23.6, 16.4. IR (ATR) ν= 3027, 2975, 2928, 1641, 1478, 1449, 1418, 1234 cm^{-1}. HRMS (ESI) m/z calcd for: $C_{15}H_{19}NO_2$ (M) 259.1567; found: 259.1572.

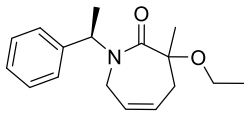


Compound 16b: Following the general procedure, from carbene complex **15a** (100 mg, 0.38 mmol) and vinylaziridine **11b** (60 mg, 0.32 mmol), dihydroazepinone **16b** was obtained as a yellow oil (83 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.17 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 5.68 – 5.49 (m, 2H), 4.59 (s, 2H), 4.55 – 4.44 (m, 1H), 3.78 (s, 3H), 3.69 – 3.56 (m, 1H), 3.39 – 3.27 (m, 2H), 2.54 – 2.39 (m, 2H), 1.50 (s, 3H), 1.19 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 173.6, 159.2, 130.2, 129.5, 127.8, 125.2, 114.2, 80.9, 59.9, 55.6, 52.8, 46.7, 38.7, 23.5, 16.3. IR (ATR) ν= 2973,2928, 1638, 1511. 1476, 1444, 1394, 1349, 1301, 1242, 1172, 1104, 1060, 822, 639 cm^{-1}. HRMS (ESI) m/z calcd for: $C_{17}H_{24}NO_3$ (M+H) 290.1751; found: 290.1747.

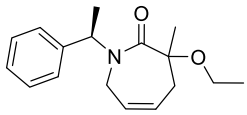


Compound 16c: Following the general procedure, from carbene complex **15a** (100 mg, 0.38 mmol) and vinylaziridine **11c** (55 mg, 0.315 mmol), dihydroazepinone **16c** was obtained as a yellow oil (79 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.09 (dd, J = 8.6, 1.5 Hz, 2H), 6.88 (dd, J = 8.6, 1.6 Hz, 2H), 5.90 – 5.66 (m, 2H), 5.07 – 4.95 (m, 1H), 3.80 (s, 3H), 3.77 – 3.69 (m, 2H), 3.59 – 3.47 (m, 1H), 2.65 – 2.47 (m, 2H), 1.51 (s, 3H), 1.33 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 173.6, 158.3, 139.3, 128.4, 127.7, 125.3, 114.6, 81.0, 60.0, 55.8, 50.8, 38.8, 23.3, 16.4. IR (ATR) ν= 2975, 2932, 2839,

1653, 1508, 1455, 1400, 1370, 1327, 1294, 1243, 1059, 1032, 828, 636 cm^{-1}. HRMS (ESI) m/z calcd for: $C_{16}H_{22}NO_3$ (M+H) 276.1594; found: 276.1600.

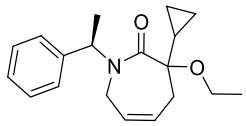


Compounds 16d and 3-*epi*-16d (from 11d): Following the general procedure, from carbene complex **15a** (43 mg, 0.16 mmol) and vinylaziridine **11d** (23 mg, 0.13 mmol), an inseparable mixture of dihydroazepinone **16d** and **3-*epi*-16d** (1:2.5) was obtained as a yellow oil (35 mg, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$) (m:M; 1:2.5) δ= 7.42 – 7.20 (m, 10H), 6.25 – 5.98 (m, 2H), 5.85 – 5.62 (m, 1H, M), 5.65 – 5.50 (m, 1H, M), 5.56 – 5.42 (m, 1H, m), 5.40 – 5.30 (m, 1H, m), 4.37 – 4.25 (m, 1H, m), 4.21 – 4.04 (m, 1H,M), 3.79 – 3.59 (m, 2H), 3.48 – 3.26 (m, 2H), 3.16 (dd, *J* = 16.7, 7.5 Hz, 1H,m), 3.07 (dd, *J* = 17.3, 7.6 Hz, 1H, M), 2.59 – 2.41 (m, 4H), 1.55 (s, 3H, M), 1.54 (s, 3H,m), 1.50 (d, *J* = 7.0 Hz, 3H, m), 1.46 (d, *J* = 7.0 Hz, 3H,M), 1.25 (t, *J* = 7.0 Hz, 3H, m), 1.17 (t, *J* = 7.0 Hz, 3H, M). ^{13}C NMR (75 MHz, $CDCl_3$) (m:M; 1:2.5) δ= 173.5 (m), 173.3 (M), 141.3 (M), 141.1 (m), 128.8, 128.6, 128.2, 127.6, 127.6, 127.6, 127.5, 126.0 (M), 125.6 (m), 81.2 (M), 81.0 (m), 60.2 (M), 59.9 (m), 52.6 (M), 52.6 (m), 41.3 (m), 41.2 (M), 39.1 (M), 38.8 (m), 23.8 (m), 23.7 (M), 16.6 (m), 16.4 (m) , 16.4 (M), 16.3 (M) . IR (ATR) ν= 3025, 2975, 2934, 2901, 1635, 1466, 1415, 1370, 1254, 1205, 1173, 1104, 1060, 920, 828, 778, 743, 700, 648 cm^{-1}. HRMS (ESI) m/z calcd for: $C_{17}H_{23}NNaO_2$ (M+Na) 296.1621; found: 296.1619.

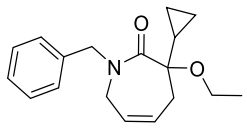


Compounds 16d and 3-*epi*-16d (from 2-*epi*-11d): Following the general procedure, from carbene complex **15a** (57 mg, 0.22 mmol) and vinylaziridine 2-*epi*-**11d** (31 mg, 0.18mmol), an inseparable mixture of dihydroazepinone **16d** and **3-*epi*-16d** (1.7:1) was obtained as a yellow oil (29 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) (M:m; 1.7:1) δ= 7.39 – 7.23 (m, 10H), 6.21 – 6.05 (m, 2H), 5.80 – 5.67 (m, 1H, m), 5.66 – 5.54 (m, 1H, m), 5.54 – 5.45 (m, 1H, M), 5.41 – 5.31 (m, 1H, M), 4.38 – 4.26 (m, 1H, M), 4.19 – 4.06 (m, 1H, m), 3.77 – 3.60 (m, 2H), 3.44 – 3.28 (m, 2H), 3.17 (dd, *J* = 16.8, 7.7 Hz, 1H, M), 3.12 – 3.02 (m, 1H, m), 2.55 – 2.44 (m, 4H), 1.55 (s, 3H, m), 1.54 (s, 3H, M), 1.51 (d, *J* = 7.0 Hz, 3H, M), 1.47 (d, *J* = 7.0 Hz, 3H, m), 1.26 (t, *J* = 7.0 Hz, 3H, M), 1.18 (t, *J* = 7.0 Hz, 3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) (M:m; 1.7:1) δ= 173.2 (M), 173.1 (m) , 141.0 (m), 140.8 (M), 128.6, 128.4, 127.9, 127.4, 127.5, 127.3, 127.2, 125.7 (m), 125.3 (M), 81.0 (m), 80.8 (M), 59.9 (m), 59.6 (M), 52.4 (m), 52.4 (M), 41.0 (M), 40.9

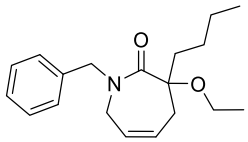
(m), 38.8 (m), 38.6 (M), 23.5 (M), 23.5 (m) , 16.4 (M), 16.1(M), 16.1 (m), 16.0 (m) . IR (ATR) ν= 3026, 2975,2934, 2901, 1634, 1464, 1415, 1369, 1318, 1205, 1103, 1056, 828, 779, 753, 699, 647 cm^{-1}. HRMS (ESI) m/z calcd for: $C_{17}H_{23}NNaO_2$ (M+Na) 296.1621; found: 296.1618.



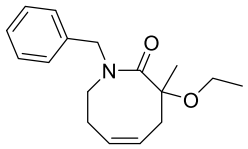
Compounds 16e and 3-*epi*-16e (from 2-*epi*-11d): Following the general procedure, from carbene complex **15b** (80 mg, 0.28 mmol) and vinylaziridine **2-*epi*-11d** (40 mg, 0.23mmol), an inseparable mixture of dihydroazepinone **16e** and **3-*epi*-16e** (1.4:1) was obtained as a green oil (69 mg, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$) (M:m; 1.4:1) δ= 7.36 – 7.25 (m, 5H), 6.23 – 6.07 (m, 1H), 5.74 – 5.33 (m, 2H), 4.35 – 4.04 (m, 1H), 3.97 – 3.40 (m, 2H), 3.27 – 3.06 (m, 1H), 2.25 – 1.86 (m, 2H), 1.78 – 1.68 (m, 1H), 1.55 – 1.43 (m, 3H), 1.29 – 1.17 (m, 3H), 0.78 – 0.46 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 173.7, 173.5, 141.3, 141.1, 128.8, 128.6, 127.7, 127.6, 127.5, 127.3, 126.9, 126.0, 125.7, 82.1, 81.9, 77.9, 59.8, 59.6, 52.8, 52.7, 41.6, 41.6, 32.2, 31.9, 17.0, 16.8, 16.6, 16.4, 16.2, 4.6, 4.5. IR (ATR) ν=3017, 1639, 1496, 1061, 730 cm^{-1} HRMS (ESI) m/z calcd for: $C_{19}H_{26}NO_2$ (M+H) 300.1958; found: 300.1964.



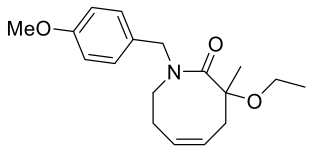
Compound 16f: Following the general procedure, from carbene complex **15b** (46 mg, 0.16 mmol) and vinylaziridine **11a** (21 mg, 0.13mmol), dihydroazepinone **16f** was obtained as a colorless oil (22 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.35 – 7.22 (m, 5H), 5.70 – 5.52 (m, 2H), 4.76 – 4.63 (m, 2H), 4.57 – 4.46 (m, 1H), 3.93 – 3.83 (m, 1H), 3.47 – 3.36 (m, 2H), 2.24 – 1.96 (m, 2H), 1.74 – 1.63 (m, 1H), 1.23 (t, J = 7.0 Hz, 3H), 0.77 – 0.67 (m, 1H), 0.65 – 0.48 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 173.9, 138.2, 128.9, 128.2, 127.6, 127.0, 125.4, 81.8, 59.7, 53.7, 47.4, 31.9, 16.8, 16.3, 4.4, 1.0. IR (ATR) ν=3084, 3032, 2974, 2920, 1643, 1476, 1450, 1350, 1230, 1167, 1089, 840, 734 cm^{-1}. HRMS (ESI) m/z calcd for: $C_{18}H_{23}NNaO_2$ (M+Na) 308.1626; found: 308.1626.



Compound 16g: Following the general procedure, from carbene complex **15c** (100 mg, 0.32 mmol) and vinylaziridine **11a** (42 mg, 0.26 mmol), dihydroazepinone **16g** was obtained as a colorless oil (73 mg, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.34 – 7.22 (m, 5H), 5.69 – 5.55 (m, 2H), 4.73 (d, *J* = 14.9 Hz, 1H), 4.64 – 4.54 (m, 2H), 3.55 – 3.46 (m, 1H), 3.39 – 3.25 (m, 2H), 2.60 (dt, *J* = 18.6, 3.6 Hz, 1H), 2.38 – 2.27 (m, 1H), 2.20 – 2.08 (m, 1H), 1.81 – 1.72 (m, 1H), 1.42 – 1.33 (m, 4H), 1.22 (t, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ=173.9, 138.2, 128.9, 128.2, 127.7, 127.59, 125.33, 82.3, 59.2, 53.6, 47.1, 35.3, 34.1, 25.4, 23.6, 16.1, 14.6. IR (ATR) ν= 3026, 2957, 2827, 2869, 1642, 1475, 1450, 1417, 1232, 1166, 1106, 804, 730, 698 cm^{-1}. HRMS (ESI) m/z calcd for $C_{19}H_{27}NNaO_2$ (M+Na) 324.1939; found 324.1938.

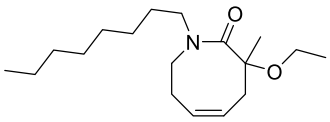


Compound 20a: Following the general procedure, from carbene complex **15a** (120 mg, 0.46 mmol) and vinylazetidine **17a** (66 mg, 0.38mmol), tetrahydroazocinone **20a** was obtained as a colorless oil (67 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.36 – 7.21 (m, 5H), 5.77 – 5.65 (m, 1H), 5.57 – 5.46 (m, 1H), 5.06 (d, *J* = 14.7 Hz, 1H), 4.67 – 4.54 (m, 1H), 3.95 (d, *J* = 14.7 Hz, 1H), 3.66 – 3.56 (m, 1H), 3.28 (dq, *J* = 9.0, 7.0 Hz, 1H), 3.17 – 3.07 (m, 1H), 2.78 (dd, *J* = 13.6, 9.7 Hz, 1H), 2.45 – 2.28 (m, 3H), 1.54 (s, 3H), 1.15 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 173.8, 138.3, 129.2, 128.8, 128.5, 127.6, 127.2, 83.3, 60.4, 49.8, 44.4, 41.9, 26.6, 25.3, 16.1. IR (ATR) ν= 3026, 2974, 2928, 1639, 1421, 1365, 1252, 1197, 1158, 1108, 1067,1034, 958, 702 cm^{-1}. HRMS (ESI) m/z calcd for $C_{17}H_{23}NNaO_2$ (M+Na) 296.1621; found 296.1625.

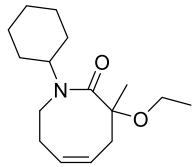


Compound 20b: Following the general procedure, from carbene complex **15a** (70 mg, 0.26 mmol) and vinylazetidine **17b** (45 mg, 0.22mmol), tetrahydroazocinone **20b** was obtained as a colorless oil (62 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.15 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 5.74 – 5.62 (m, 1H), 5.46 (dt, *J* = 10.3, 5.1 Hz, 1H), 4.92 (d, *J* = 14.5 Hz, 1H), 4.55 (dt, *J* = 17.9, 9.5 Hz, 1H), 3.90 (d, *J* = 14.5 Hz, 1H), 3.77 (s,

3H), 3.62 – 3.52 (m, 1H), 3.28 – 3.17 (m, 1H), 3.09 (dt, *J* = 15.5, 3.8 Hz, 1H), 2.78 – 2.68 (m, 1H), 2.42 – 2.25 (m, 3H), 1.51 (s, 3H), 1.11 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 173.6, 159.2, 130.4, 129.9, 129.3, 127.1, 114.2, 83.3, 60.4, 55.6, 49.2, 44.2, 41.9, 26.7, 25.3, 16.1. IR (ATR) ν=2973, 2929, 2838, 1636, 1511, 1461, 1436, 1418, 1245, 1175, 1065, 1032, 983, 842, 812, 777, 755 cm^{-1}. HRMS (ESI) m/z calcd for $C_{18}H_{25}NNaO_3$ (M+Na) 326.1727; found 326.1724.



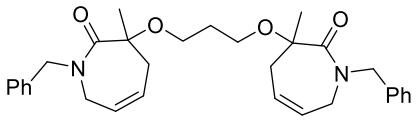
Compound 20c: Following the general procedure, from carbene complex **15a** (80 mg, 0.31 mmol) and vinylazetidine **17c** (50 mg, 0.25mmol), tetrahydroazocinone **20c** was obtained as a colorless oil (45 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 5.74 – 5.60 (m, 1H), 5.60 – 5.47 (m, 1H), 4.71 – 4.54 (m, 1H), 3.71 – 3.49 (m, 2H), 3.25 – 3.07 (m, 2H), 2.80 – 2.67 (m, 2H), 2.51 – 2.28 (m, 3H), 1.57 – 1.42 (m, 5H), 1.25 (s, 10H), 1.14 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 6.3 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ=173.1, 129.1, 127.2, 83.3, 60.2, 47.4, 45.3, 41.9, 32.2, 29.8, 29.7, 28.1, 27.5, 27.1, 25.2, 23.0, 16.2, 14.5. IR (ATR) ν=2927, 1641, 1466, 1369, 1066, 802, 711 cm^{-1} HRMS (ESI) m/z calcd for $C_{18}H_{34}NO_2$ (M+H) 296.2584; found 296.2579.



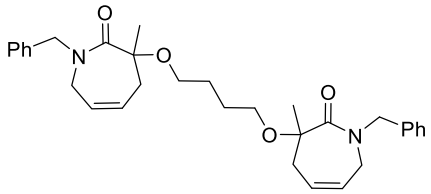
Compound 20d: Following the general procedure, from carbene complex **15a** (95 mg, 0.36 mmol) and vinylazetidine **17d** (50 mg, 0.3mmol), tetrahydroazocinone **20d** was obtained as a colorless oil (65 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 5.81 – 5.65 (m, 1H), 5.63 – 5.49 (m, 1H), 4.57 – 4.35 (m, 1H), 4.30 – 4.17 (m, 1H), 3.63 – 3.46 (m, 1H), 3.31 – 3.09 (m, 2H), 2.74 – 2.60 (m, 1H), 2.44 – 2.21 (m, 3H), 1.83 – 1.49 (m, 6H), 1.48 (s, 3H), 1.48 – 1.25 (m, 4H), 1.13 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 172.7, 129.6, 127.5, 83.5, 60.2, 55.3, 42.1, 40.6, 31.4, 31.2, 29.4, 26.5, 26.3, 26.1, 25.5, 16.2. IR (ATR) ν=2928, 1775, 1639, 1393, 1065, 1024, 712 cm^{-1}. HRMS (ESI) m/z calcd for $C_{16}H_{28}NO_2$ (M+H) 266.2115; found 266.2121.

General procedure for the photochemical cycloaddition reactions involving biscarbene complexes 21: Photoreactions were carried out in oven-dried pressure tubes that were charged with the biscarbene complex **21** and vinylaziridine **11a** (2:1

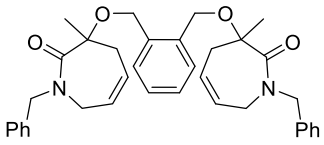
molar ratio) and dry and degased (3 cycles freeze-pump-thaw) Et_2O. The tube was fitted with a pressure head, purged three times with CO, and irradiated under 60-70 psi of CO (medium pressure mercury lamp 400W, pyrex filter and pyrex well) for 20h. The solvent from the crude reaction mixture was removed under vacuum, the residue was taken up in 1:1 hexane/EtOAc, and it was exposed to light to oxidize the remaining chromium(0) compounds. This mixture was filtered through celite and purified by silica gel chromatography (hexane/EtOAc from 4/1 to 2/1, TLC pates were developed in oleum) to produce the desired bis-cycloadducts **22**.



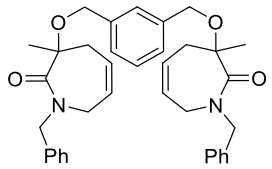
Compound 22a: Following the general procedure, from biscarbene complex **21a** (250 mg, 0.49 mmol) and vinylaziridine **11a** (155 mg, 0.98 mmol), bis-cycloadduct **22a** was obtained as a colorless oil (100 mg, 41%). ^{1}H NMR (300 MHz $CDCl_3$) δ=7.32 – 7.22 (m, 10H), 5.70 – 5.50 (m, 4H), 4.72 – 4.58 (m, 4H), 4.54 – 4.43 (m, 2H), 3.66 – 3.54 (m, 2H), 3.41 – 3.26 (m, 4H), 2.46 (s, 4H), 1.90 – 1.76 (m, 2H), 1.50 (s, 3H), 1.48 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 173.5, 138.1, 128.9, 128.1, 127.9, 127.7, 125.1, 80.9, 80.9, 61.2, 61.1, 53.6, 53.6, 47.1, 47.0, 38.4, 31.8, 23.5, 23.4. IR (ATR) ν= 3026, 2987, 2932, 1639, 1495, 1495, 1480, 1453, 1345, 1171, 1114, 1077, 733, 700 cm^{-1}. HRMS (ESI) m/z calcd for $C_{31}H_{38}N_2O_4$ (M+H) 502.2904; found 502.2910.



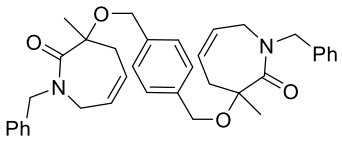
Compound 22b: Following the general procedure, from biscarbene complex **21b** (279 mg, 0.53 mmol) and vinylaziridine **11a** (170 mg, 1.06mmol), bis-cycloadduct **22b** was obtained as a colorless oil (150 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.37 – 7.19 (m, 10H), 5.69 – 5.52 (m, 4H), 4.67 (s, 4H), 4.55 – 4.43 (m, 2H), 3.58 – 3.49 (m, 2H), 3.39 – 3.24 (m, 4H), 2.47 (s, 4H), 1.65 – 1.56 (m, 4H), 1.50 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 173.6, 138.1, 128.9, 128.2, 127.9, 127.7, 125.2, 80.8, 64.1, 64.0, 53.6, 47.0, 38.4, 27.7, 27.6, 23.5. IR (ATR) ν= 3026, 2985, 2936, 1639, 1495, 1480, 1453, 1417, 1233, 1113, 1078, 853, 798,733, 700 cm^{-1}. HRMS (ESI) m/z calcd for $C_{32}H_{40}N_2O_4$ (M+H) 517.3061; found 517.3068.



Compound 22c: Following the general procedure, from biscarbene complex **21c** (280 mg, 0.49 mmol) and vinylaziridine **11a** (155 mg, 0.98 mmol), bis-cycloadduct **22c** was obtained as a colorless oil (130 mg, 47%). ^{1}H NMR (300 MHz $CDCl_3$) δ=7.34 – 7.19 (m, 10H), 5.58 (d, J = 4.0 Hz, 4H), 4.76 – 4.61 (m, 6H), 4.46 – 4.36 (m, 2H), 4.34 – 4.25 (m, 2H), 3.36 – 3.18 (m, 2H), 2.67 – 2.43 (m, 4H), 1.62 (s, 3H), 1.60 (s, 3H), 1.65 – 1.59 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 173.4, 173.3, 138.1, 136.6, 136.5, 129.0, 128.5, 128.28, 128.26, 128.17, 128.10, 127.8, 125.2, 81.39, 81.38, 64.1, 64.0, 53.71, 53.68, 47.3, 47.2, 38.6, 38.5, 23.61, 23.57. IR (ATR), ν=3027, 2986, 2629, 2926, 1733, 1637, 1480, 1453, 1480, 1453, 1418, 1260, 1231, 1185, 1079, 733, 699, 644 cm^{-1}. HRMS (ESI) m/z calcd for $C_{36}H_{40}N_2O_4$ (M+H) 565.3061; found 565.3073.



Compound 22d: Following the general procedure, from biscarbene complex **21d** (235 mg, 0.41 mmol) and vinylaziridine **11a** (130 mg, 0.82 mmol), bis-cycloadduct **22d** was obtained as a yellow oil (137 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.39 – 7.32 (m, 10H), 5.76 – 5.59 (m, 4H), 4.75 (s, 4H), 4.70 (d, J = 11.0 Hz, 2H), 4.60 – 4.46 (m, 2H), 4.36 (d, J = 11.0 Hz, 2H), 3.44 – 3.32 (m, 2H), 2.74 – 2.53 (m, 4H), 1.69 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 173.4, 138.1, 137.9, 128.9, 128.2, 127.9, 127.77, 127.73, 125.1, 81.4, 66.4, 53.7, 47.2, 38.5, 23.7. IR (ATR) ν=3026, 2987, 2932, 1639, 1495, 1480, 1453, 1345, 1173, 1078, 963, 875, 733, 700 cm^{-1}. HRMS (ESI) m/z calcd for $C_{36}H_{40}N_2O_4$ (M+H) 565.3061; found 565.3060.



Compound 22e: Following the general procedure, from biscarbene complex **21e** (230 mg, 0.4 mmol) and vinylaziridine **11a** (128 mg, 0.8 mmol), bis-cycloadduct **22e** was obtained as a colorless oil (114 mg, 59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.37 – 7.14 (m, 10H), 5.60 (d, J = 4.3 Hz, 4H), 4.74 – 4.67 (m, 4H), 4.63 (d, J = 11.0 Hz, 2H), 4.52 – 4.42 (m, 2H), 4.31 (d, J = 11.0 Hz, 2H), 3.42 – 3.19 (m, 2H), 2.67 – 2.46 (m, 4H),

1.62 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 173.4, 138.8, 138.1, 129.0 128.2, 127.79, 127.76, 126.94, 126.90, 125.17, 125.15, 81.4, 66.5, 53.7, 47.2, 38.5, 23.7. IR (ATR) ν=3028, 2920, 2851, 1719, 1636, 1519, 1495, 1375, 1263, 1189, 1110, 895,786, 733 cm^{-1}. HRMS (ESI) m/z calcd for $C_{36}H_{40}N_2O_4$ (M+H) 565.3061; found 565.3079.

Computational Details: Geometry optimizations without symmetry constraints were carried out using the Gaussian09 suite of programs[21] using the B3LYP[22] functional in combination with the double-ζ plus polarization def2-SVP basis sets[23] for all atoms in Et_2O as the solvent using the polarizable continuum model (PCM) method.[24] This level is denoted PCM(Et_2O)-B3LYP/def2-SVP. Reactants and products were characterized by frequency calculations,[25] and have positive definite Hessian matrices. Transition structures (TS's) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the Intrinsic Reaction Coordinate (IRC) method.[26]

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DISCUSIÓN GENERAL

Este apartado recoge una visión global e integradora del trabajo recogido en esta memoria. Se discutirán los aspectos más relevantes de los capítulos expuestos anteriormente y se realizará una valoración crítica de la consecución de los objetivos propuestos.

D.1. Capítulo 1

D1.1. Reacción de cicloadición [8+3] regio- y diastereoselectiva entre derivados de tropona y ciclopropanos D-A.

El empleo de ciclopropanos dador-aceptor (D-A) como equivalentes de sistemas 1,3-zwitteriónicos para la síntesis de anillos carbo- y heterocíclicos de cinco, seis y siete eslabones mediante reacciones de ciclación [3+2], [3+3] y [4+3], respectivamente, se ha estudiado ampliamente.[1] Sin embargo, el uso de estos carbociclos de tres miembros en reacciones de cicloadición de alto orden ha sido muy poco explorado.[2] Por este motivo, se decidió estudiar la reacción de cicloadición [8+3] entre ciclopropanos D-A y derivados de tropona.

Este estudio se inició con la optimización de las condiciones de reacción para el proceso que involucra a la tropona **1a** con el aminociclopropano D-A **2**. La selección de este ciclopropano D-A en particular se debe a su conocida capacidad para producir zwitteriones precursores de anillos *N*-carbo- y heterocíclicos.[3] El uso de cantidades catalíticas de $SnCl_4$ (5% mol) y cantidades equimolares de **1a** y **2**, en diclorometano a temperatura ambiente, conduce a la formación del cicloaducto [8+3] **3a** con buen rendimiento (Esquema 1). Además, el producto **3a** se forma exclusivamente como el diastereoisómero *sin* según revelan los experimentos NOESY llevados a cabo. Por lo tanto, esta nueva reacción de cicloadición [8+3] es completamente diastereoselectiva.

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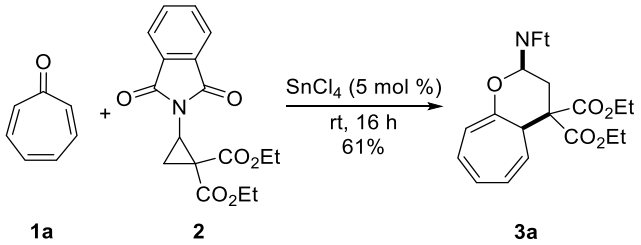


1a **2** **3a**

Esquema 1. Reacción de cicloadición [8+3] entre la tropona **1a** y el ciclopropano D-A **2**.

Para comprender el origen de la diastereoselectividad de este proceso, se llevó a cabo un estudio computacional utilizando la teoría del funcional de la densidad (DFT). Los cálculos llevados a cabo indican que se trata de un proceso por pasos que se inicia con la coordinación del ácido de Lewis al ciclopropano D-A produciendo la apertura del anillo y la generación del intermedio zwitteriónico **4b** (Figura 1). El ataque nucleófilo del par libre del oxígeno de la tropona **1a** al catión iminio de **4b** da lugar a la formación del intermedio zwitteriómico **INT1** (en un proceso exergónico a través del estado de transición **TS1**). Desde el **INT1** se produce el cierre del anillo generando el correspondiente cicloaducto [8+3] **INT2** (a través del estado de transición **TS2**). Tal y como se observa en la Figura 1, la formación exclusiva del isómero *sin* tiene lugar bajo control cinético en la etapa de ciclación, ya que la barrera de activación necesaria para su formación es inferior a la del isómero *anti* ($\Delta\Delta E_{TS}$ = 3.4 kcal/mol). Finalmente, la descoordinación de $SnCl_4$ en el intermedio **INT2-*sin*** produce el cicloaducto [8+3] **3a** observado experimentalmente, regenerando el catalizador.

La transformación tiene lugar por pasos debido a la estabilidad del intermedio **INT1**, que, de acuerdo con los valores negativos de NICS (Nucleus Independent Chemical Shift), puede ser considerado como una especie aromática.

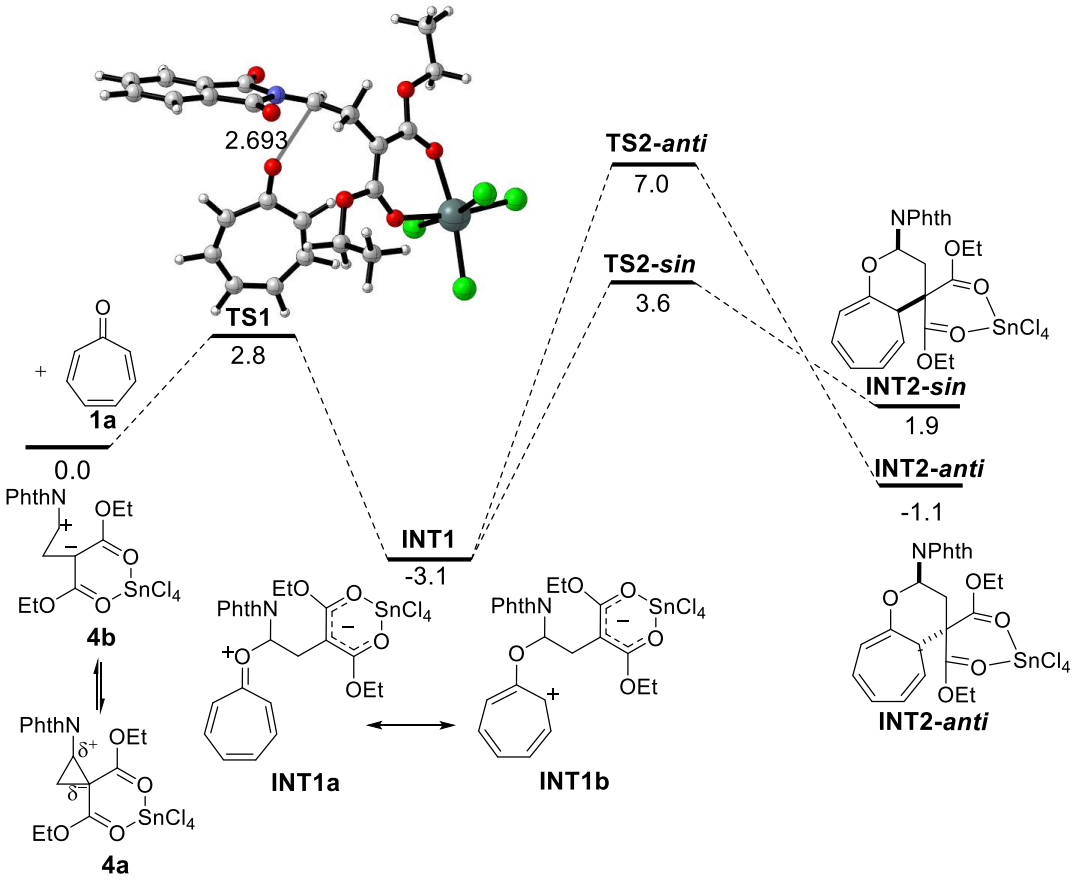
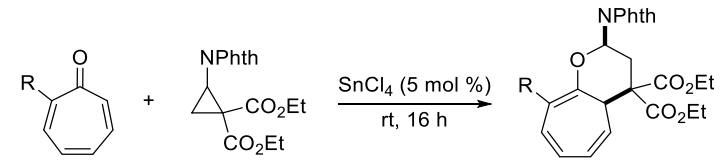


Figura 1. Perfil de reacción calculado para la cicloadición [8+3] entre la tropona **1a** y el complejo $SnCl_4$-ciclopropano D-A **4**. Las energías libres relativas (ΔG, 298 K) se presentan en kcal/mol y las distancias de enlace en Å. Datos calculados a nivel PCM(CH_2Cl_2)-B3LYP/def2-SVP.

A continuación se llevó a cabo el estudio de la regioselectividad del proceso, para lo cual se sintetizaron una serie de troponas con sustituyentes dadores y aceptores directamente unidos a la posición 2 del anillo de tropona. Como se muestra en el Esquema 2, en todos los casos se produjo la formación del correspondiente cicloaducto [8+3] con buenos rendimientos, salvo cuando se emplearon troponas ricas en electrones, tales como alcoxitroponas **1h-i** y sililoxitropona **1j**, en cuyo caso se obtiene un producto secundario resultante de la dimerización del ciclopropano D-A. Además, se observó que el cierre del anillo tiene lugar de forma exclusiva en la posición C7 de la tropona y que únicamente se genera el diastereoisómero *sin*. Es decir, el proceso tiene lugar con completa regio- y diasteroselectividad. Los cálculos computacionales llevados a cabo (Figura 2) confirman la regioselectividad del proceso, mostrando un perfil de reacción en el cual el cierre del anillo en la posición C7 de la tropona se ve favorecido tanto cinética como termodinámicamente frente al cierre en la posición C2.



1b, R = Cl
1c, R = Br
1d, R = Ph
1e, R = 4-Me-C_6H_4
1f, R = 4-OMe-C_6H_4
1g, R = 4-NO_2-C_6H_4
1h, R = OMe
1i, R = OBn
1j, R = OTBS

2

3b, R = Cl (68%)
3c, R = Br (64%)
3d, R = Ph (68%)
3e, R = 4-Me-C_6H_4 (65%)
3f, R = 4-OMe-C_6H_4 (62%)
3g, R = 4-NO_2-C_6H_4 (71%)
3h, R = OMe (0%)[a]
3i, R = OBn (0%)[a]
3j, R = OTBS (0%)[a]

Esquema 2. Reacciones de cicloadición [8+3] entre las troponas 2-sustituidas **1b-j** y el aminociclopropano D-A **2**.

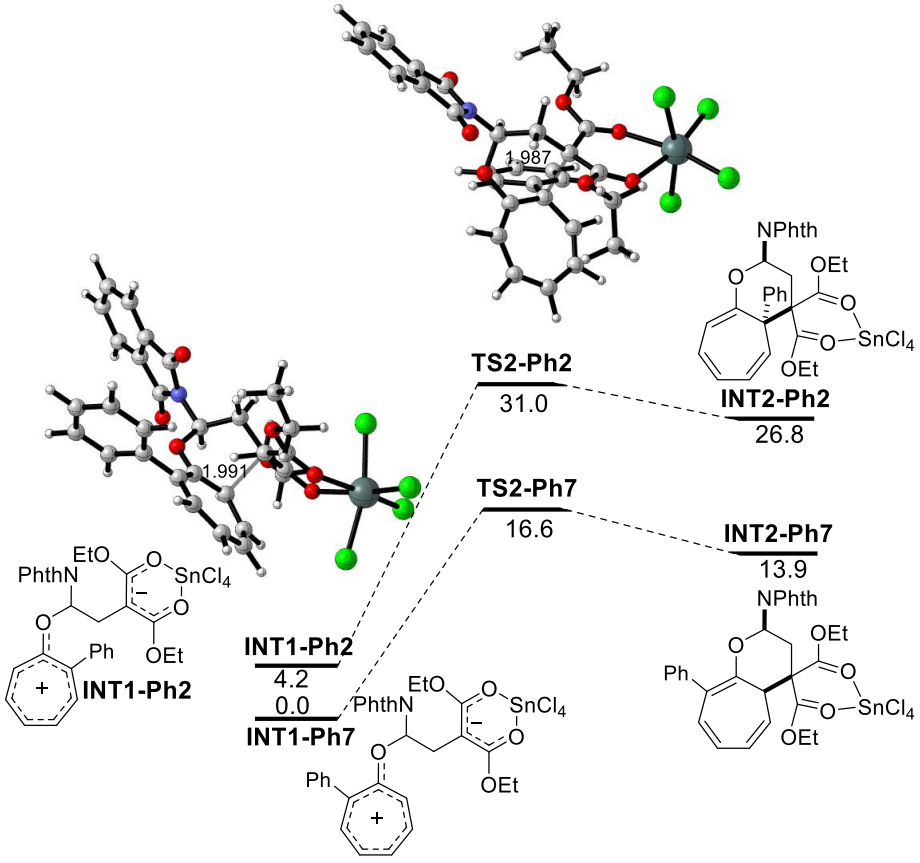
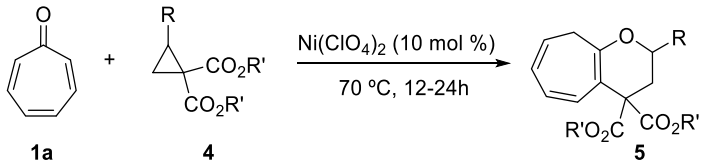


Figura 2. Perfil de reacción calculado para el cierre del anillo de la cicloadición [8 + 3] entre la tropona **1d** y el complejo $SnCl_4$-ciclopropano D-A **4**. Las energías libres relativas (ΔG, 298 K) se presentan en kcal/mol y las distancias de enlace en Å. Datos calculados a nivel PCM(CH_2Cl_2)-B3LYP/def2-SVP.

Por tanto, hemos descrito una nueva reacción de cicloadición de alto orden entre un aminociclopropano D-A y troponas sustituidas. Esta cicloadición [8+3] tiene lugar por pasos a través de un intermedio zwitteriónico aromático, dando lugar a la

formación de derivados tetrahidrociclohepta[*b*]piranicos con completa regio- y diasteroselectividad.

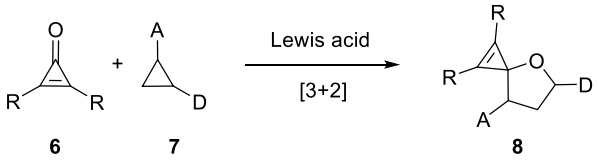
Prácticamente de manera simultánea, Carretero y colaboradores describieron un proceso análogo entre tropona y ciclopropanos D-A usando catalizadores de níquel (Esquema 3).[4] Sus resultados son compatibles con los aquí descritos.



Esquema 3. Reacciones de cicloadición [8+3] entre la tropona **1a** y los ciclopropano D-A **4**.

D1.2. Síntesis de compuestos oxaspiránicos mediante reacción de anulación [3+2] entre derivados de ciclopropenona y ciclopropanos D-A.

Los compuestos espirocíclicos, especies en las que dos anillos se encuentran fusionados por un único átomo de carbono, se han convertido en un objetivo de interés en síntesis debido a su gran potencial en el descubrimiento de nuevos fármacos[5] y materiales.[6] Sin embargo, la síntesis de estas especies es a menudo complicada debido a que muchos de los procedimientos descritos en la bibliografía requieren múltiples etapas y el empleo de reactivos caros.[7] Por esta razón y basándonos en los resultados descritos anteriormente, nos propusimos diseñar una ruta directa de acceso a estas especies a partir de ciclopropanos D-A y ciclopropenonas (Esquema 4).



Esquema 4. Reacciones de ciclación entre ciclopropenonas **6** y ciclopropanos D-A **7**.

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Con este objetivo, exploramos en primer lugar la reacción entre la difenilciclopropenona **6a** y el dietil 2-fenilciclopropano-1,1-dicarboxilato **7a**. La optimización de las condiciones de reacción indicaron que el empleo de $Sc(OTf)_3$ (10 mol %) y cantidades equimoleculares de **6a** y **7a** en diclorometano a 80 °C durante 4h proporcionaba el compuesto espiránico deseado con buen rendimiento.

Una vez optimizadas las condiciones de reacción, se procedió a explorar el alcance del proceso con respecto a la sustitución en el ciclopropano **7**. Como se muestra en la Tabla 1, la naturaleza electrónica del sustituyente (R^3) del ciclopropano D-A **7** ejerce una gran influencia en el rendimiento de la reacción. Así, grupos electroaceptores (F, Br o CN) colocados en la posición *para* del grupo aromático del ciclopropano D-A producen menores rendimientos que el arilo no sustituido (R = H). De hecho, en presencia de grupos fuertemente electroaceptores como el NO_2 la reacción no tiene lugar. Por el contrario, grupos π-dadores como el –OMe o –NFt (Ft = ftaloilo) no sólo producen mayores rendimientos sino que también permiten que la reacción transcurra a menor temperatura (0°C y 25°C, respectivamente). Esta mejora en los rendimientos de reacción se debe, muy probablemente, a que la apertura inicial del anillo del ciclopropano D-A, promovida por el ácido de Lewis, se ve facilitada por grupos dadores ricos en electrones.[8]

Esta transformación también es compatible con grupos alquilo en lugar de los grupos arilo en la ciclopropenona inicial (la dietilciclopropenona **6b** da lugar al correspondiente espirociclo **8j** con buen rendimiento a 25°C), así como con sustituyentes organometálicos como el ferrocenilo en el ciclopropano D-A **7k**, lo que confirma la generalidad de esta transformación.

8 Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc*. **2008**, *130*, 8642.

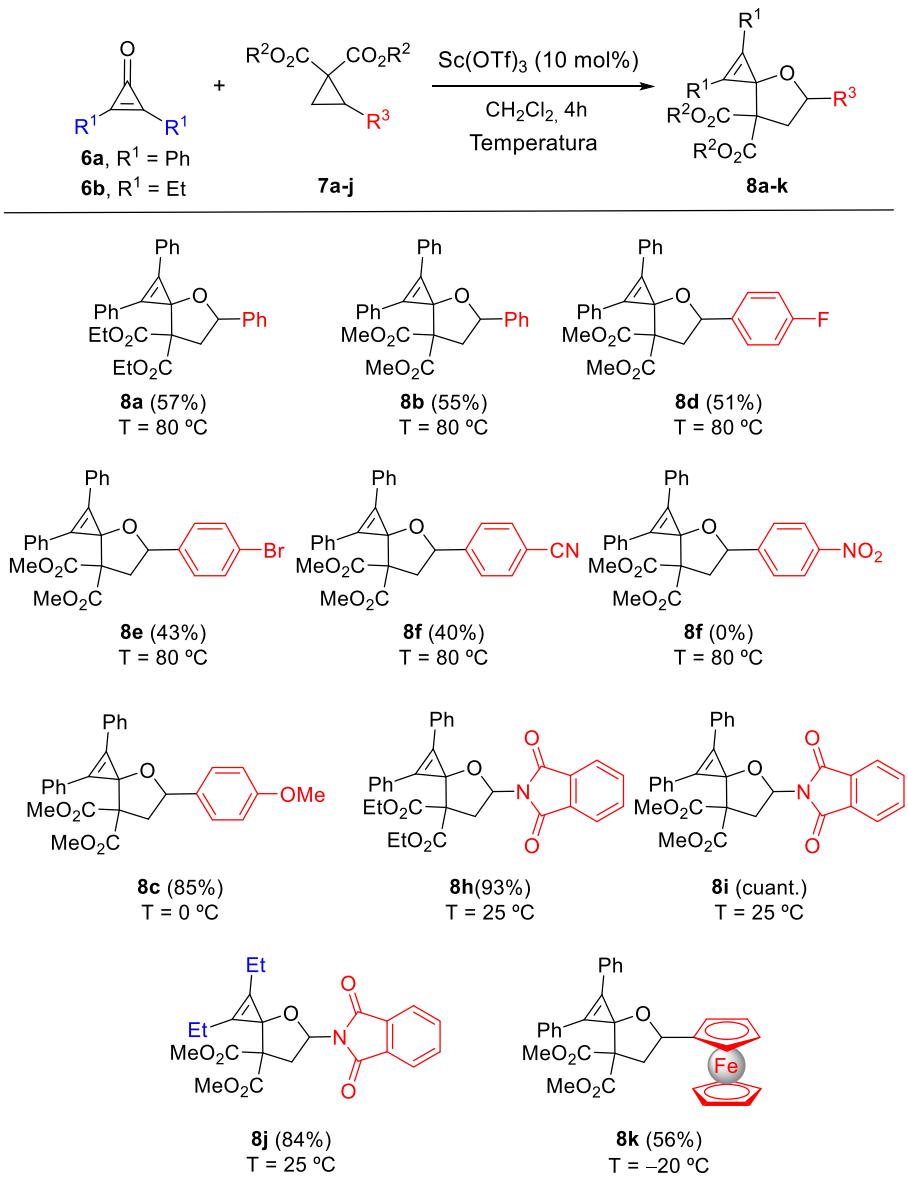


Tabla 1. Reacciones de cicloadición [3+2] entre las ciclopropenonas **6a-b** y los ciclopropanos D-A **7a-j**.

En las condiciones de reacción empleadas, la reacción entre ciclopropanos D-A y ciclopropenonas produce la formación exclusiva del producto espiránico, correspondiente a una anulación [3+2], sin que se observen trazas del producto bicíclico correspondiente a una anulación [3+3]. Para comprender la selectividad de esta reacción se decidió realizar un estudio computacional basado en cálculos DFT. De acuerdo con estos cálculos y tal y como se muestra en la Figura 3, la reacción se inicia con el ataque nucleófilo de la ciclopropenona al centro electrófilo del par iónico íntimo **7b-Sc** (formado tras la coordinación de los grupos éster al metal de transición). Esta reacción de adición conduce a la formación del intermedio **INT1**, que puede ser considerado como un compuesto aromático de acuerdo con sus valores negativos de NICS calculados en el centro del anillo de ciclopropenona. Desde este

intermedio son posibles dos cierres de anillo: en C1, produciendo el aducto [3+2] **INT2** o en C2, formando la especie bicíclica **INT3**. A partir de los datos de la Figura 3, es evidente que el ataque nucleofílico en C1 está fuertemente favorecido tanto cinética como termodinámicamente. Estas diferencias energéticas tan notables se deben a la naturaleza altamente tensionada del aducto [3+3].

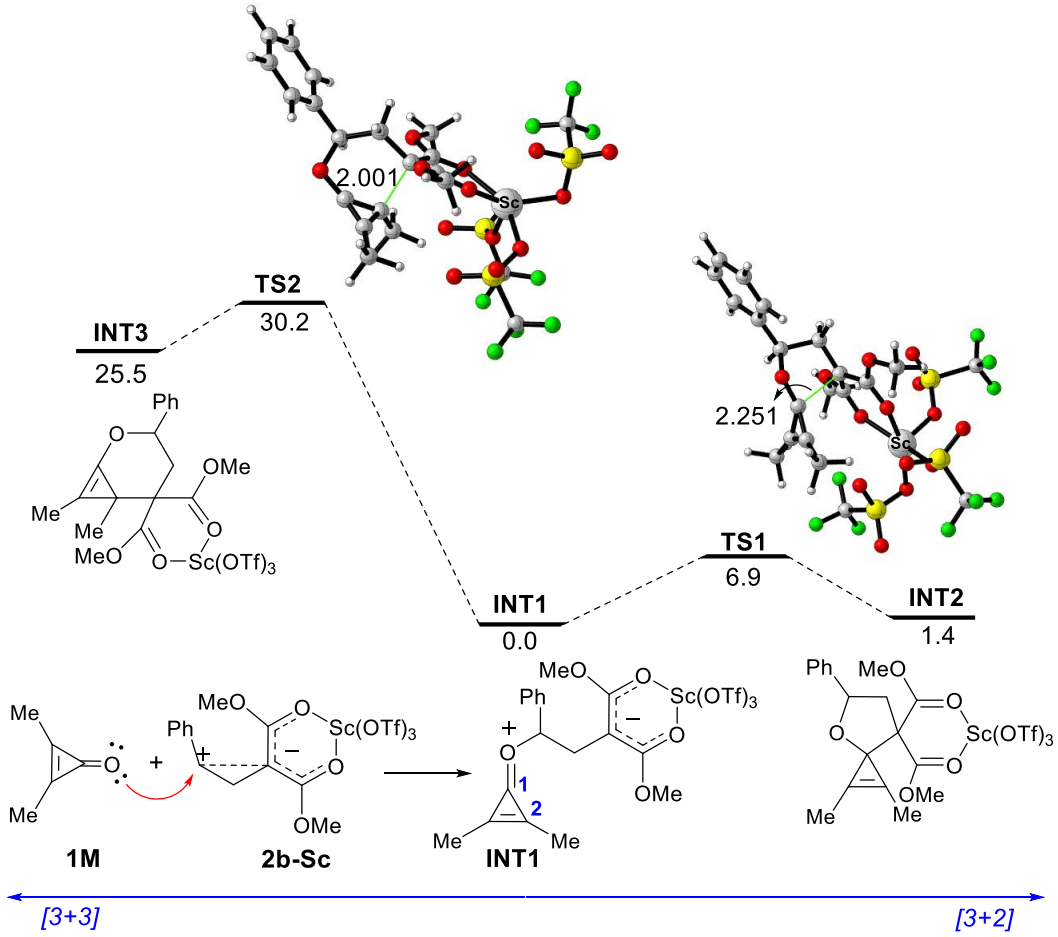


Figura 3. Perfil de reacción calculado para la cicloadición [3+2] entre la ciclopropenona **6M** y el complejo $SnCl_4$-ciclopropano D-A **7b-Sc**. Las energías libres relativas (ΔG, 298 K) se presentan en kcal/mol y las distancias de enlace en Å. Datos calculados a nivel PCM(CH_2Cl_2)-MO6/def2-TZVPP//B3LYP/def2-SVP.

Además, nuestros cálculos sugieren que el cierre de anillo en la posición C1 está favorecido por motivos electrónicos. Como indican los valores de las cargas NBO (Natural Bond Orbital) calculadas para el **INT1** (Figura 4), el C1 presenta una carga positiva superior a la del C2 (Δq = 0.364 au), lo que implica un mayor carácter electrofílico que dirige la adición nucleófila del centro carbaniónico C4 (q = −0.364) hacia C1.

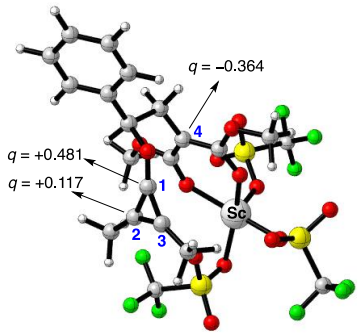


Figura 4. Cargas NBO calculadas para el intermedio zwitteriónico **INT1**.

Por lo tanto, se ha desarrollado un método general, eficiente y versátil para la síntesis de compuestos oxaespiránicos. Los cálculos computacionales indican que la formación exclusiva de productos correspondientes a una anulación [3+2] frente a los carbociclos derivados de un proceso [3+3] tiene lugar tanto bajo control cinético como termodinámico.

D.2. Capítulo 2

D2.1. Reacción de cicloadición [8+2] regioselectiva entre complejos alquinil-carbeno de tipo Fischer y tropotiona

Los complejos metal-carbeno de tipo Fischer con un grupo alquenilo o alquinilo directamente unido al átomo de carbono carbénico experimentan procesos de cicloadición altamente regioselectivos en condiciones de reacción suaves[9] debido al efecto fuertemente activante que ejerce el fragmento metálico.[10] Por esta razón se han empleado ampliamente en síntesis. [10,11] Sin embargo, las reacciones de cicloadición de alto orden de estos complejos han sido comparativamente poco exploradas.[12] Por este motivo, y teniendo en cuenta la habilidad de la tropotiona y derivados para participar en reacciones de cicloadición de alto orden,[13] se decidió

9 (a) Sierra, M. A.; Gómez-Gallego, M.; Martínez-Ávarez, R. *Chem. Eur. J.* **2007**, *13*, 736. (b) Sierra, M. A.; Fernández, I.; Cossío, F. P. *Chem. Commun*. **2008**, 4671. (c) Waters, M. L.; Wulff, W. D. *Org. React*. **2008**, *70*, 121. (d) Dötz, K. H.; Stendel, J. *Chem. Rev*. **2009**, *109*, 3227. (e) Herndon, J. W. *Coord. Chem. Rev*. **2010**, *254*, 103. (f) Fernández-Rodríguez, M. A.; García-García, P.; Aguilar, E. *Chem. Commun*. **2010**, 7670. (g) Fernández, I.; Cossío, F. P.; Sierra, M. A. *Acc. Chem. Res.* **2011**, *44*, 479.

10 (a) Wulff, W. D.; Bauta, W. E.; Kaesler, R. W.; Lankford, P. J.; Miller, R. A.; Murray, C. K.; Yang, D. C. *J. Am. Chem. Soc.* **1990**, *112*, 3642. (b) Wulff, W. D.; Bauta, W. E.; Kaesler, R. W.; Lankford, P. J.; Miller, R. A.; Murray, C. K.; Yang, D. C. *J. Am. Chem. Soc.* **1990**, *112*, 3642. (c) Anderson, B. A.; Wulff, W. D.; Powers, T. S.; Tribbitt, S.; Rheingold, A. L. *J. Am. Chem. Soc.* **1992**, *114*, 10784. (d) Barluenga, J.; Aznar, F.; Barluenga, S. *J. Chem. Soc., Chem. Commun*. **1995**, 1973. (e) Barluenga, J.; Fernández-Rodríguez, M. A.; Aguilar, E. *Org. Lett*. **2002**, *4*, 3659.

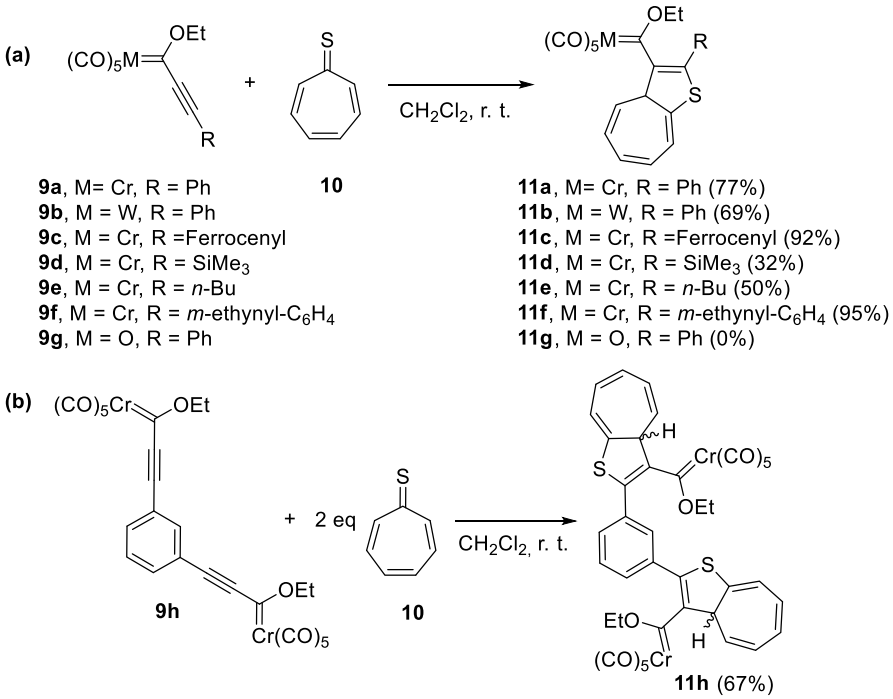
11 (a) Chan, K. S.; Wulff, W. D. *J. Am. Chem. Soc.* **1986**, *108*, 5229. (b) Barluenga, J.; López, S.; Flórez, J. *Angew. Chem. Int. Ed*. **2003**, *42*, 231. (c) Barluenga, J.; Vicente, R.; López, L. A.; Tomás, M. *J. Am. Chem. Soc*. **2006**, *128*, 7050. (d) Granados, A. M.; Fracaroli, A. M.; De Rossi, R. H.; Fuertes, P.; Torroba, T. *Chem. Commun*. **2008**, 483. (e) Baeza, B.; Casarrubios, L.; Ramírez-López, P.; Gómez-Gallego, M.; Sierra, M. A. *Organometallics* **2009**, *28*, 956.

12 Barluenga, J.; García-Rodríguez, J.; Suárez-Sobrino, A.; Tomás, M. *Chem. Eur. J*. **2009**, *15*, 8800.

13 Nair, V.; Abhilash, K. G. *Top. Heterocycl. Chem*. **2008**, *13,* 173.

estudiar la reacción de cicloadición [8+2] entre alquinil-carbenos de tipo Fischer y tropotiona.

Para la consecución de este objetivo se seleccionaron una serie de complejos metal-carbeno α,β-insaturados de tipo Fischer con diferentes patrones de sustitución en el triple enlace del complejo y se hicieron reaccionar con tropotiona en diclorometano a temperatura ambiente. Todos los complejos examinados dieron lugar al correspondiente complejo metal-carbeno 3a*H*-ciclohepta[*b*]tiofénico **9** con rendimientos de moderados a excelentes (Esquema 5). La formación exclusiva de cicloaductos en los que el átomo de azufre queda unido al carbono en posición *β* al carbono carbénico del complejo alquinil-carbénico inicial indica que este proceso tiene lugar con completa regioselectividad. Por lo tanto, se puede afirmar que esta transformación es general, ya que es compatible con una amplia variedad de complejos alquinil-carbeno de Fischer derivados de cromo y de wolframio, así como con especies bis-carbénicas (**7h**). En este caso particular, el correspondiente bis-cicloaducto **9h** se forma como una mezcla racémica de los dos posibles diastereómeros RR/SS y meso-RS.



Esquema 5. Reacciones de cicloadición [8+2] entre los complejos alquinil-carbenos de tipo Fischer **9a-g** y la tropotiona **10**.

Con el fin de comprobar el papel fundamental que desempeña el fragmento metal-pentacarbonilo en este proceso de cicloadición se hizo reaccionar la tropotiona con el

análogo orgánico de los carbenos **9a** y **9b**, el 3-fenilpropiolato **9g**. En las condiciones optimizadas de reacción (temperatura ambiente durante 10 minutos), el proceso [8+2] análogo no tiene lugar. De manera similar, el empleo de temperaturas más elevadas (diclorometano a reflujo) o tiempos de reacción más largos tampoco promueve la reacción, lo que confirma la activación que produce del fragmento metálico en este proceso de cicloadición de alto orden.

Para adquirir un mayor conocimiento acerca del mecanismo de reacción por el que transcurren este tipo de transformaciones, se decidió realizar un estudio computacional de este proceso. En principio, se pueden proponer dos posibles mecanismos para esta reacción (concertado y por pasos) tal y como se muestra en la Figura 5. Si comparamos la energía de activación asociada a cada uno de los procesos, resulta obvio que la reacción concertada no es competitiva dada la alta energía de activación que requiere en comparación con el proceso por pasos. Por lo tanto, las bajas energías de activación junto con la alta exotermicidad del proceso, compatibles con una reacción a temperatura ambiente, sugieren que esta reacción de cicloadición, que se inicia con la adición nucleófila del átomo de azufre al carbono β del complejo metal-carbeno, tiene lugar por pasos. Este mecanismo no concertado transcurre a través del intermedio zwitteriónico **INT1,** que se encuentra altamente estabilizado (ya que la carga negativa se encuentra deslocalizada en el fragmento metal-pentacarbonilo) y que evoluciona al cicloaducto final a través del estado de transición **TS3** con una energía de activación de tan sólo 7.2 kcal/mol.

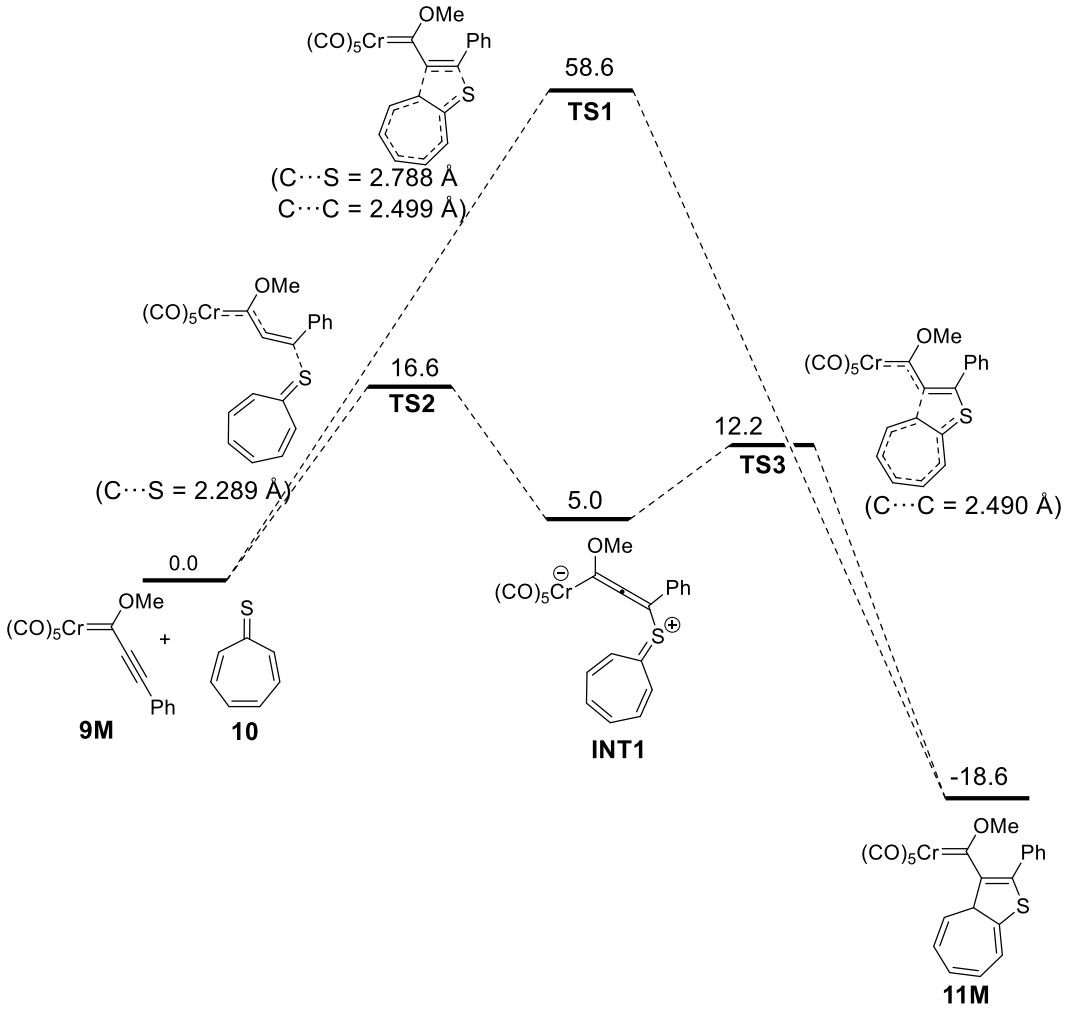
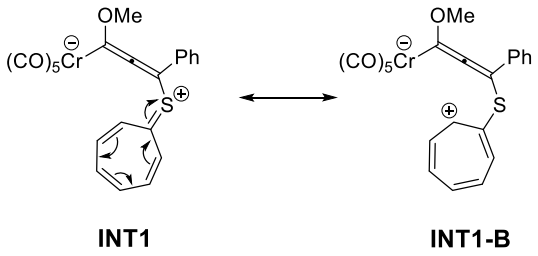


Figura 5. Perfil de reacción calculado para la cicloadición [8+2] entre el complejo metal-carbeno **9M** y tropotiona **10**. Las energías libres relativas (ΔG, 298 K) se presentan en kcal/mol. Datos calculados a nivel PCM(CH_2Cl_2)-MO6/def2-SVP//B3LYP/def2-SVP.

El intermedio zwitteriónico **INT1** presenta una alta planaridad (ángulo dihedro C1(S)–C2–C3–C4 = 0.6°) y longitudes de enlace equivalentes (distancia de enlace C–C 1.377–1.429 Å), por lo que sería lógico esperar que fuese aromático y que la forma resonante **INT-B**, similar al catión tropilio, contribuyese notablemente a la descripción de este intermedio (Figura 6a). Sin embargo, el cálculo de los valores NICS (NICS(0) = +5.8 ppm y NICS(1)zz = +2.8 ppm) sugieren que el compuesto es antiaromático desde un punto de vista magnético. Este dato fue confirmado mediante el empleo del método ACID (Anisotropy of the Induced Current Density), que muestra a los vectores de densidad de corriente describiendo un movimiento antihorario, es decir, una corriente de anillo paratrópica o antiaromática (Figura 6b). Estos resultados nos indican que la contribución de la forma resonante **INT1-B** no es significativa en la descripción de esta especie.

(a)



INT1 **INT1-B**

(b)

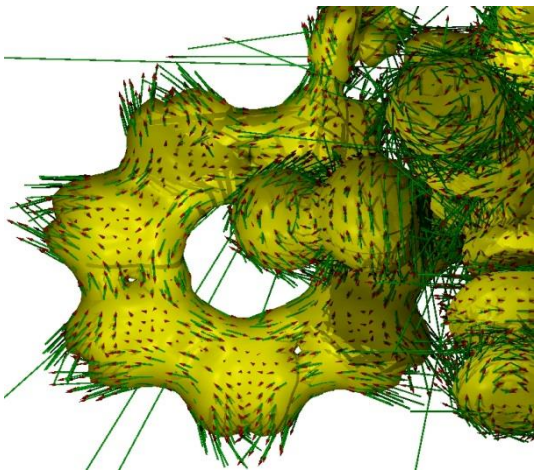


Figure 6. (a) Formas resonantes del zwitterión **INT1**. (b) Representación ACID del **INT**1.

En resumen, se ha descrito una nueva reacción de cicloadición [8+2] entre complejos alquinil-carbenos de tipo Fischer y tropotiona. El proceso conduce a la formación regioselectiva de complejos 3a*H*-ciclohepta[*b*]tiofénicos, que mantienen la funcionalidad metal-carbeno susceptible de experimentar transformaciones adicionales. Los cálculos computacionales han demostrado que el mecanismo más probable para esta reacción es por pasos a través de un intermedio zwitteriónico antiaromático.

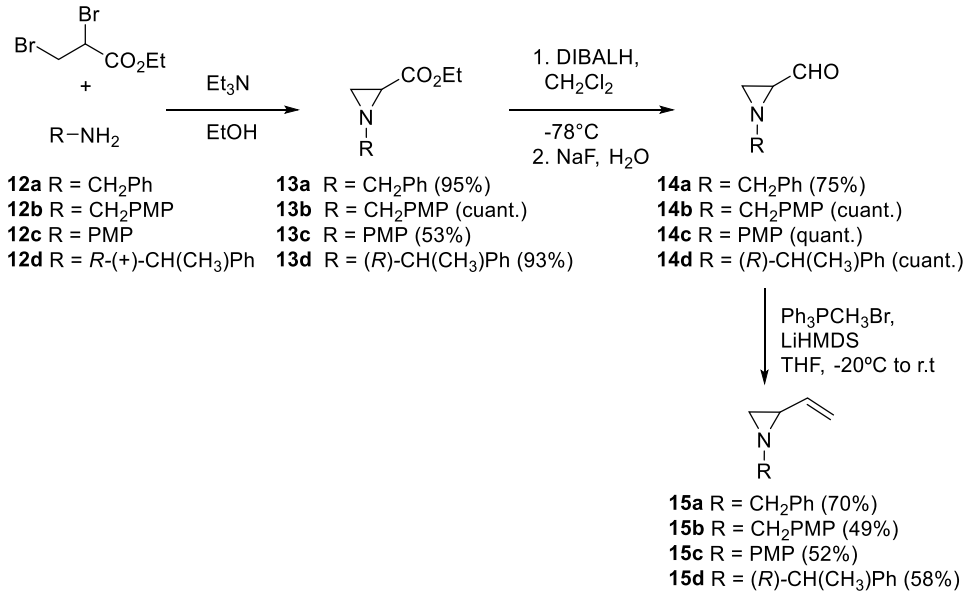
D2.2. Reacción fotoquímica de vinilaziridinas y vinilazetidinas con complejos metal-carbeno de tipo Fischer

Como se ha mencionado anteriormente, la reactividad térmica de los complejos metal-carberno de tipo Fischer se ha empleado profusamente en reacciones de cicloadición.[10,11] Sin embargo, su reactividad fotoquímica se ha limitado practicamente a cicloadiciones [2+2] entre las cetenas coordinadas a cromo generadas al irradiar un cromo-carbeno y diferentes cetenófilos.[14] De hecho, las

14 (a) Campos, P. J.; Soldevilla, A.; Sampedro, D.; Rodríguez, M. A. *Org. Lett.* **2001**, *3*, 4087. (b) Campos, P. J.; Sampedro, D.; Rodríguez, M. A. *Organometallics* **2002**, *21*, 4076. (c) Campos, P. J.; Sampedro, D.; Rodríguez, M. A *J. Org. Chem.*

reacciones de cicloadición de alto orden de estos complejos en condiciones fotoquímicas son prácticamente desconocidas.[15] Motivados por este hecho, se decidió abordar un estudio teórico/experimental de la reacción entre vinilaziridinas y vinilazetidinas y metalocetenas generadas fotoquímicamente a partir de complejos metal-carbeno de tipo Fischer.

Para ello fue necesario el desarrollo de una secuencia sintética de acceso a vinilaziridinas *N*-sustituídas **15** a partir del correspondiente 2,3-dibromopropionato **12** (Esquema 6).

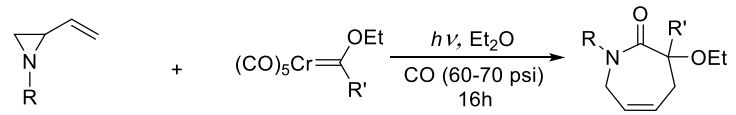


Esquema 6. Síntesis de 2-vinilaziridinas.

Las 2-vinilaziridinas sintetizadas se irradiaron (luz visible) en presencia del complejo de cromo(0) **16a** en éter, bajo 60-70 psi de CO y a temperatura ambiente, dando lugar a la formación de las correspondientes azepinonas mediante una cicloadición [5+2] con rendimientos excelentes y en ausencia de aditivos. El empleo de aziridinas enantioméricamente puras (**15d** y **2-epi-15d**) produjo la formación de las correspondientes azepinonas quirales **17d** y **3-epi-17d** con excelentes rendimientos pero baja diastereoselectividad (1:2,5 para **15d** y 1,7:1 para **2-epi-15d**). Este resultado indica que el centro quiral exocíclico de la 2-vinilaziridina únicamente juega un papel espectador. Un resultado similar se obtuvo en la reacción del complejo **16b** y la aziridina **2-epi-15d,** que dio lugar a la azepinona **3-epi-17e** como una mezcla de diastereómeros (1,4:1) (Esquema 7).

2003, *68*, 4674. (d) Campos, P. J.; Caro, M.; López-Sola, S.; Sampedro, D.; Rodríguez, M. A. *J. Organomet. Chem.* **2006**, *691,* 1075 (e) Fernández, I.; Cossío, F. P.; Sierra, M. A. *Acc. Chem. Res*. **2011**, *44*, 479.

15 Deur, J.; Miller, M. W.; Hegedus , L. S. *J. Org. Chem.* **1996**, *61*, 2871.



15a R = CH_2Ph
15b R = CH_2PMP
15c R = PMP
15d R = (*R*)-$CH(CH_3)Ph$
2-*epi*-15d R = (*R*)-$CH(CH_3)Ph$

16a R' = Me

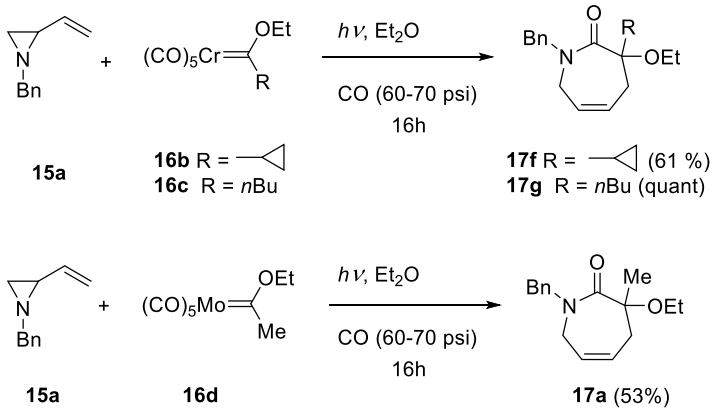
2-*epi*-15d R = (*R*)-$CH(CH_3)Ph$ **16b** R' = 

17a R'=Me, R = CH_2Ph (cuant.)
17b R'=Me, R = CH_2PMP (91%)
17c R'=Me, R = PMP, (91%)
17d R'=Me, R = (*R*)-$CH(CH_3)Ph$ (1:2.5) (cuant.)
3-*epi*-17d R'=Me, R = (*R*)-$CH(CH_3)Ph$ (1.7:1) (58%)

3-*epi*-17e R'= , R = (*R*)-$CH(CH_3)Ph$ (1.4:1) (quant)

Esquema 7. Reacciones fotoquímica de 2-vinilaziridinas y complejos metal-carbeno de cromo(0)

El proceso desarrollado también es compatible con distintos sustituyentes unidos al carbono carbénico del complejo, así como con complejos de molibdeno(0) (Esquema 8).



15a

16b R =
16c R = *n*Bu

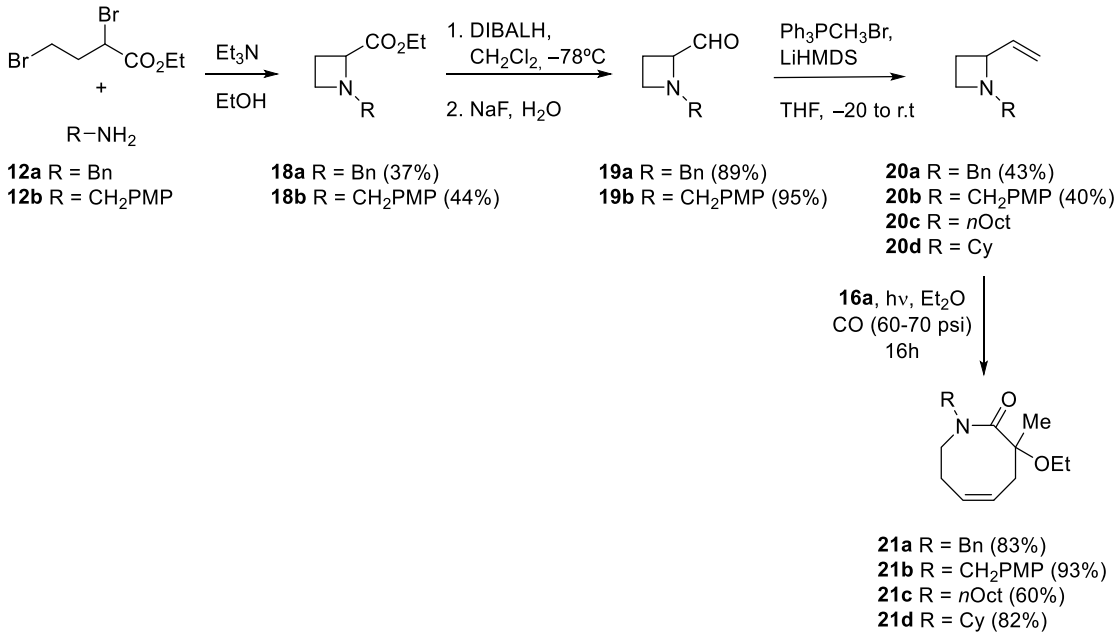
17f R = (61 %)
17g R = *n*Bu (quant)

15a **16d**

17a (53%)

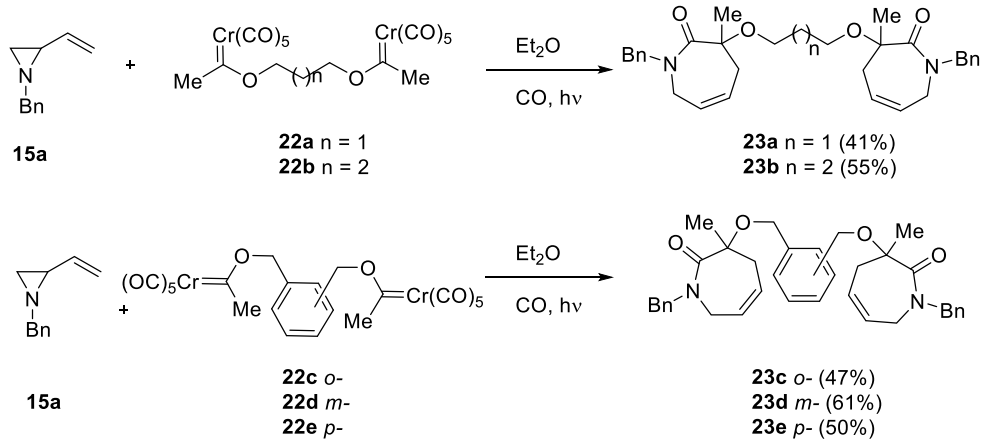
Esquema 8. Reacciones fotoquímica de 2-vinilaziridinas y complejos metal-carbeno basados en cromo(0) and molibdeno(0).

Adicionalmente, se extendió este proceso a las 2-vinilazetidinas **20** (sintetizadas mediante un procedimiento similar al desarrollado para las 2-vinilaziridinas). De manera análoga, la reacción fotoquímica entre las 2-vinilazetidinas y el complejo metal-carbeno **16a** dio lugar a la formación de las azocinonas **21a-d** con rendimientos entre buenos y excelentes como resultado de una cicloadición formal [6+2] (Esquema 9).



Esquema 9. Síntesis de azocinonas mediante la reacción de cicloadición formal [6+2] entre 2-vinilazetidinas y complejos metal-carbeno de tipo Fischer.

La versatilidad de esta transformación se demostró gracias a la obtención de bis-azepinonas **23** unidas tanto mediante espaciadores aromáticos como alifáticos. Para ello se emplearon los complejos biscarbénico **22a-p** (Esquema 10). Este proceso consiste, por lo tanto, en una doble reacción de cicloadición [5+2]. En todos los casos, las bis-azepinonas se obtuvieron como una mezcla inseparable de diastereoisómeros. Tal y como indican las señales claramente diferenciadas en los correspondientes espectros de RMN de ^{1}H y de ^{13}C, se produce la formación de las especies racémicas (RR/SS) y meso. A pesar de falta de selectividad, este procedimiento constituye una ruta directa para síntesis de bis-azepinonas, cuya obtención resulta complicada mediante procedimientos convencionales en química orgánica.



Esquema 10. Síntesis de bis-azepinonas mediante la doble reacción de cicloadición [5+2] entre vinilaziridinas y complejos bis-carbeno de tipo Fischer.

Finalmente, el mecanismo de reacción de esta transformación fotoquímica fue estudiado mediante el empleo de métodos computacionales. Como se muestra en la Figura 7, la reacción de cicloadición [5+2] entre vinilaziridinas y metala-cetenas se produce por pasos en un proceso que implica el ataque nucleofílico inicial del átomo de nitrógeno de la aziridina al átomo de carbono del carbonilo altamente electrofílico de la metalacetena **24**, seguido por el cierre del anillo del intermedio zwitteriónico formado, en un proceso altamente exergónico que da lugar al correspondiente cicloaducto [5+2] observado.

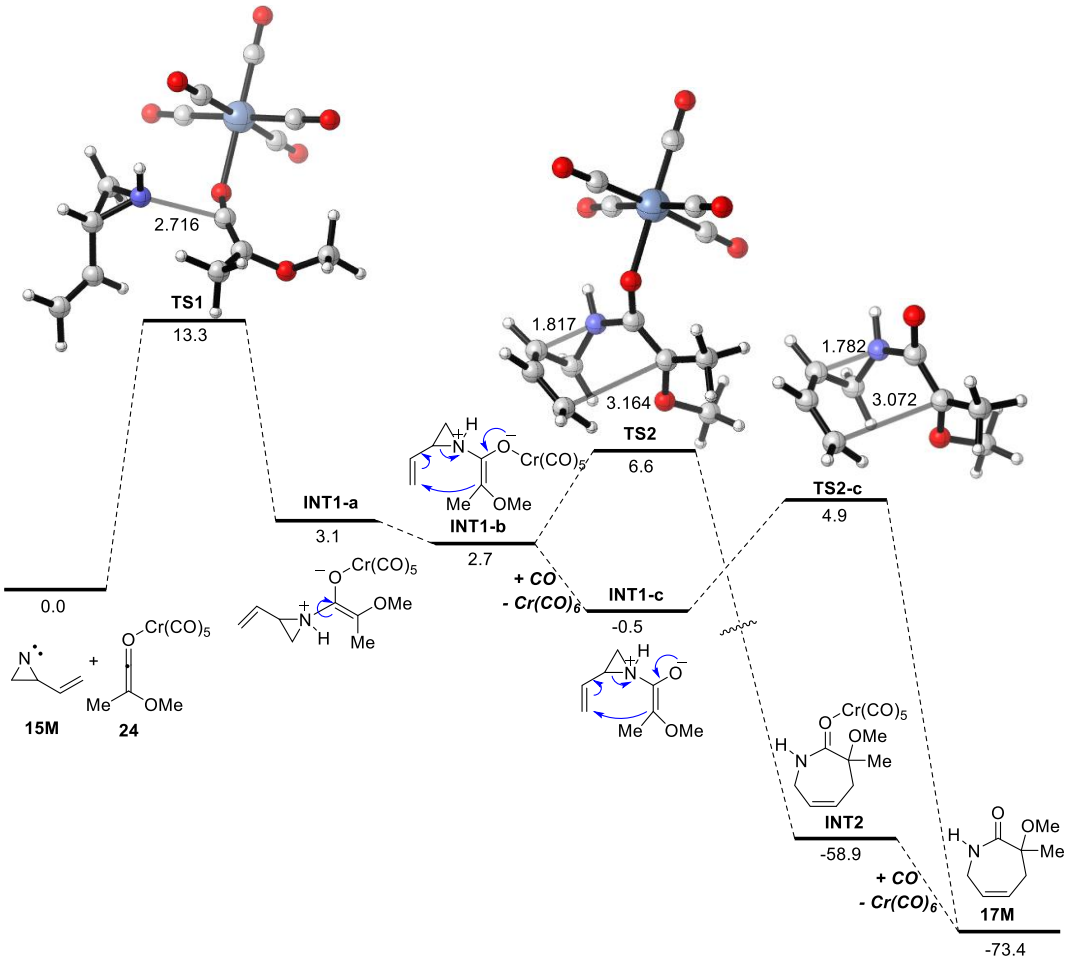


Figura 7. Perfil de reacción calculado para la cicloadición [5+2] entre la metalocetena **24** y la vinilaziridina **15M**. Las energías libres relativas (ΔG, 298 K) se presentan en kcal/mol y las distancias de enlace en Å. Datos calculados a nivel PCM(Et_2O)-B3LYP/def2-SVP.

Del estudio teórico/experimental llevado a cabo se pueden extraer las siguientes conclusiones: (i) las metalacetenas generadas fotoquímicamente a partir de complejos metal-carbeno de tipo Fischer reaccionan con 2-vinilaziridinas y 2-vinilazetidinas para dar lugar a azepinonas y azocinonas, respectivamente, con rendimientos entre buenos y excelentes. (ii) Las propiedades electrónicas de estas

metalacetenas permiten la introducción de sustituyentes ricos en electrones en los productos finales de reacción, lo que supone una importante ventaja sintética en comparación con los procedimientos descritos en la bibliografía, prácticamente restringidos al uso de cumulenos pobres en electrones. (iii) Estas transformaciones, que se pueden describir como reacciones de cicloadición formal [5+2] y [6+2], son compatibles con complejos biscarbénicos basados en cromo(0) dando lugar a bis-azepinonas en una sola etapa y en condiciones suaves de reacción. (iv) Los cálculos computacionales sugieren que la transformación se produce por pasos mediante el ataque nucleófilo inicial del átomo de nitrógeno de la aziridina o la azetidina a la metalacetena seguido del correspondiente cierre del anillo del intermedio zwitteriónico así formado.

CONCLUSIONES

1. Se ha descrito una nueva reacción de cicloadición de alto orden entre tropona y derivados de tropona y un aminociclopropano D-A catalizada por $SnCl_4$. Esta cicloadición [8+3] da lugar a derivados de tetrahidrociclohepta[*b*]piranos con completa regio- y diasteroselectividad. Mediante el empleo de cálculos computacionales, se puede concluir que esta transformación transcurre por pasos a través de un intermedio zwitteriónico, que se asemeja al catión tropilo y que por lo tanto, se encuentra estabilizado por aromaticidad π. A partir de este intermedio, se produce el cierre del anillo, etapa que controla la regio- y diastereoselectividad del proceso, dando lugar a los correspondientes cicloaductos [8+3].

2. Se ha desarrollado un método general, eficiente y versátil para la síntesis directa de compuestos oxaespiránicos mediante la reacción de cicloadición [3+2] catalizada por $Sc(OTf)_3$ entre ciclopropenonas y diferentes ciclopropanos D-A. Los estudios teóricos llevados a cabo sugieren que el proceso sigue un mecanismo de reacción por pasos y que la formación exclusiva de productos correspondientes a una anulación [3+2] frente a aquellos derivados de una ciclación [3+3] está favorecida tanto cinética como termodinámicamente.

3. Se ha descrito una nueva reacción de cicloadición [8+2] entre complejos alquinil-carbeno de tipo Fischer y tropotiona. El proceso conduce a la formación regioselectiva de complejos 3a*H*-ciclohepta[*b*]tiofenicos, que mantienen la funcionalidad carbénica y, por lo tanto, son susceptibles de experimentar transformaciones adicionales. Adicionalmente, se llevó a cabo la síntesis de un cicloaducto biscarbénico mediante la doble reacción de cicloadición [8+2] de tropotiona con el correspondiente complejo biscarbénico. Los cálculos computacionales indican que la transformación ocurre mediante un mecanismo por pasos a través de un intermedio zwitteriónico antiaromático

4. Se ha explorado la reacción de metalo-cetenas generadas fotoquímicamente a partir de complejos metal-carbeno de tipo Fischer con vinilaziridinas y vinilazetidinas. Este proceso da lugar a azepanonas y azocinonas, respectivamente, con rendimientos entre buenos y excelentes. Estas transformaciones, que se pueden describir como reacciones de cicloadición formal [5+2] y [6+2], son compatibles con complejos biscarbénicos de Cr^0 dando lugar a bis-azepanonas de forma directa y en condiciones de reacción suaves. Los cálculos computacionales sugieren que la reacción transcurre por etapas a través del ataque nucleófilo inicial del átomo de

nitrógeno de la aziridina o la azetidina a la metalo-cetena seguido del cierre del anillo del intermedio zwitteriónico formado dando lugar a los correspondientes cicloaductos [5+2] y [6+2].

ANEXO

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Regio- and Diastereoselective Stepwise [8 + 3]-Cycloaddition Reaction between Tropone Derivatives and Donor–Acceptor Cyclopropanes

Alexandra R. Rivero, Israel Fernández,* and Miguel Ángel Sierra*

Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, 28040-Madrid, Spain

israel@quim.ucm.es; sierraor@quim.ucm.es

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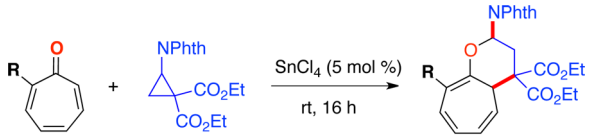
ABSTRACT



Regio- and diastereoselective stepwise [8+3]-cycloaddition

A novel $SnCl_4$-catalyzed [8 + 3]-cycloaddition reaction between tropone derivatives and donor–acceptor aminocyclopropanes is described. The process leads to the formation of amino-substituted tetrahydrocyclohepta[*b*]pyrans with complete regio- and diastereoselectivity. Density functional theory calculations suggest that the cycloaddition occurs stepwise through an aromatic zwitterionic intermediate.

Cycloaddition reactions are highly valuable transformations in modern organic synthesis because of their ability to increase the molecular complexity in a single synthetic step.[1] In this sense, donor–acceptor cyclopropanes (DACs),[2] which can be considered as 1,3-zwitterionic synthons, have proven to be very useful for the direct synthesis of five-membered carbo- and heterocycles via [3 + 2]-cycloaddition reactions.[3] Recent applications of these processes to the synthesis of complex natural products have clearly demonstrated their potential in organic synthesis.[4] Nevertheless, the use of DACs in high-order cycloaddition reactions has been scarcely explored.[5]

Within the context of our ongoing work in the reaction mechanims and synthetic applications of cycloaddition reactions[6] and based on previous studies,[7] we recently reported that tropone derivatives can be used as 8-component

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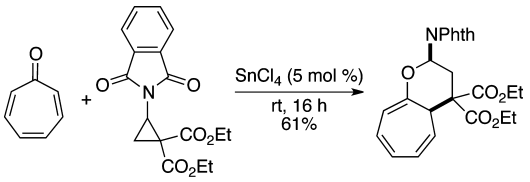
in high-order [8 + 2]-cycloaddition reactions.[8] These previous results prompted us to explore the reaction between DACs and tropone derivatives, which would lead to the formation of [8 + 3]-cycloadducts. In addition, Density Functional Theory (DFT) calculations were carried out to unravel the reaction mechanism of this novel transformation.

The reaction between the parent tropone **1a** and donor−acceptor aminocyclopropane **2** was explored first. This particular DAC was chosen due to its proven ability to produce *N*-containing hetero- and carbocycles as recently demostrated by Waser and co-workers.[9] Optimization of the reactions conditions (different Lewis acids, temperature, solvent, and stoichiometry) indicated that the use catalytic amounts of $SnCl_4$ (5 mol %) and equimolar amounts of **1a** and **2**, in CH_2Cl_2 as solvent, at room temperature leads to the formation of cycloaduct **3a** in 61% reaction yield (Scheme 1).[10] Interestingly, no traces of the corresponding [3 + 2]-cycloadduct (the product observed in the related reaction involving different ketones and **2**)[9c] were detected in the crude reaction mixtures. The bias of tropone to experience high order cycloaddition reactions can be ascribed to its peculiar electronic structure (see below).[7,8] In addition, **3a** is formed exclusively as the *syn* diastereoisomer as revealed by NOESY experiments. Therefore, this novel [8 + 3]-cycloaddition reaction involving **1a** occurs with complete diastereoselectivity.[11]

To gain more insight into the origin of the diastereoselectivity of the above process, a computational DFT study was carried out.[12] The computed reaction profile of the process between **1a** and **2** is illustrated in Figure 1, which shows the relative free energies in CH_2Cl_2 solution.

As proposed previously,[13,14] the process is assumed to begin with the coordination of the Lewis acid to the DAC to produce the intimate ion pair **4a**, which is in equilibrium with the completely dissociated zwitterion **4b**. Nucleophilic attack of the lone pair of the oxygen atom of **1a** to the iminium cation moiety of **4b** leads to the formation of the zwitterionic intermediate **INT1**. The ease of this process, which occurs via transition state **TS1**, is reflected in the very low activation barrier ($\Delta G_{a,298}$ = 2.8 kcal/mol) and exergonicity (ΔG_R = −3.1 kcal/mol) computed for this transformation. From **INT1**, a ring closure reaction occurs to produce the corresponding [8 + 3]-cycloadduct **INT2** via **TS2**, a saddle point associated with the formation of the new C−C bond (see optimized geometries of **TS2** in the Supporting Information).

Scheme 1. [8 + 3]-Cycloaddition between Tropone **1a** and **2**



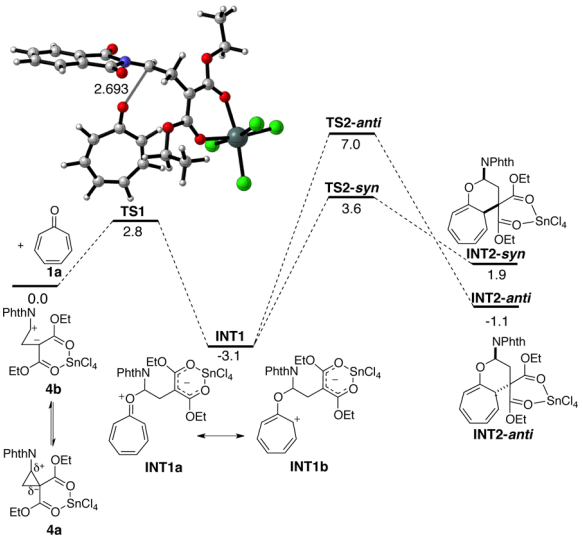


Figure 1. Computed reaction profile of the [8 + 3]-cycloaddition between tropone **1a** and $SnCl_4$−DAC complex **4**. Relative free energies (ΔG, 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data have been computed at the PCM(CH_2Cl_2)-B3LYP/def2-SVP level.

Two possible ring closures leading to the *syn*- and *anti*-cycloadducts are possible. As readily seen in Figure 1, the experimentally observed exclusive formation of the *syn*-isomer takes place under kinetic control in view of the lower activation barrier computed for the process involving the saddle point **TS2-*syn*** ($\Delta\Delta G_a$(*syn*-*anti*) = 3.4 kcal/mol). Final decoordination of $SnCl_4$ in **INT2-*syn*** produces the observed [8 + 3]-cycloadduct **3a** thus regenerating the catalyst. Therefore, similar to related high-order cycloaddition reactions involving tropone derivatives,[8] the present [8 + 3]-cycloaddition between the parent tropone **1a** and DAC **2** occurs stepwise through a zwitterionic intermediate (**INT1**).

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(10) Typical procedure: In a two-necked flask equipped with a nitrogen inlet, tropone **1a** (1 equiv) and aminocyclopropane **2** (1 equiv) were dissolved in anhydrous dichloromethane at room temperature. After 5 min, $SnCl_4$ in dichloromethane (5 mol %) was added. The mixture was stirred under nitrogen at 16 h, and then the reaction was quenched by the addition of triethylamine and subsequently flushed through a short plug of silica gel, eluting with EtOAc. The solvent was removed in vacuo to give the crude reaction mixture, which was submitted to flash column chromatography to yield pure cycloadduct **3a**.

(11) The reaction between diethyl 2-phenylcyclopropane-1,1-dicarboxylate and tropone **1a** was also tested. Under the same reaction conditions used for the aminocyclopropane **2** (i.e., 5 mol % $SnCl_4$, rt, 16 h), the corresponding [8 + 3]-cycloadduct was not formed.

(12) DFT calculations were carried out at the PCM(CH_2Cl_2)-B3LYP/def2-SVP level of theory using the Gaussian 09 suite of programs. See computational details in the Supporting Information.

(13) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642.

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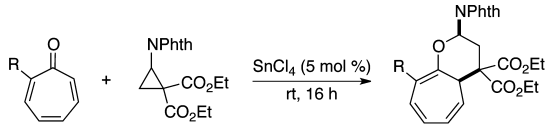
The structure of zwitterion **INT1** deserves further analysis. As shown in Figure 1, **INT1** can also be described by the resonance form **INT1b**, where the positive charge is delocalized within the seven-membered ring. This species, which resembles the tropyl cation, should therefore possess remarkable aromatic character. Indeed, the computed negative Nucleus Independent Chemical Shift (NICS)[15] values (NICS(0) = −3.6 and NICS(1) = −7.2 ppm) and the corresponding out-of-plane tensor component ($NICS(1)_{zz}$ = −16.7 ppm) confirm the magnetic aromatic nature of this zwitterion. In addition, the optimized geometry of **INT1** indicates that the seven-membered ring is highly planar (C1(O)−C2−C3−C4 dihedral angle of −0.3°) with C−C bond distances which are intermediate between single and double bonds (ranging from 1.382 to 1.425 Å), thus satisfying the so-called geometrical criterion for aromaticity as well.[16] Therefore, it can be suggested that the gain in stability by aromaticity occurring in **INT1** is in part responsible for the stepwise nature of the transformation.

Once the reaction mechanism of the process was analyzed, the influence of substituents attached to the tropone ring on the regioselectivity of the [8 + 3]-cycloaddition was explored. To this end, a series of different 2-substituted tropones **1b**−**j** having donor or acceptor groups directly attached to the C2-carbon atom of the tropone ring were reacted with DAC **2** in the reaction conditions used above (i.e., 5 mol % $SnCl_4$, room temperature, CH_2Cl_2 for 16 h). As shown in Scheme 2, all the reactions tested lead to the formation of the corresponding [8 + 3]-cycloadducts **3** in good yields, with the exception of the reactions involving 2-alkoxytropones **1i** and **1h** and 2-silyloxytropone **1j**, which were recovered unaltered together with a new product arising from the cyclopropane (see below). Strikingly, in all cases the ring closure occurred at the C7-carbon atom of the initial tropone, which indicates that this [8 + 3]-cycloaddition reaction proceeds with complete regioselectivity (no traces of the corresponding C2-cycloadduct were observed in the respective reaction crudes). In addition, and as expected, cycloadducts **3b**−**g** were formed exclusively as *syn*-diastereoisomers as confirmed by NOESY experiments. Single crystals of the cycloadduct **3e** (grown in hexanes/CH_2Cl_2 solution) suitable for X-ray diffraction analysis fully confirm, by analogy, both the regio- and the relative stereochemistry of compounds **3** (Figure 2).

We carried out DFT-calculations as well to understand the regioselectivity, namely the exclusive formation of the C7- over the C2-cycloadduct, of the transformation. Thus, both regioisomeric *syn*-ring closure reactions arising from the zwitterionic species **INT1-Ph2** and **INT1-Ph7**, formed upon the initial nucleophilic attack of the phenyltropone **1d** to **4b**, were computed. As readily seen in Figure 3, the ring closure leading to the C7-regioisomer (via **TS2-Ph7**) is kinetically ($\Delta\Delta G_a$(Ph7−Ph2) = 14.4 kcal/mol) and also

Scheme 2. [8 + 3]-Cycloaddition Reactions between 2-Substituted Tropones **1b**−**j** and **2**



1b, R = Cl
1c, R = Br
1d, R = Ph
1e, R = 4-Me-C_6H_4
1f, R = 4-OMe-C_6H_4
1g, R = 4-NO_2-C_6H_4
1h, R = OMe
1i, R = OBn
1j, R = OTBS

3b, R = Cl (68%)
3c, R = Br (64%)
3d, R = Ph (68%)
3e, R = 4-Me-C_6H_4 (65%)
3f, R = 4-OMe-C_6H_4 (62%)
3g, R = 4-NO_2-C_6H_4 (71%)
3h, R = OMe (0%)[a]
3i, R = OBn (0%)[a]
3j, R = OTBS (0%)[a]

[a] No cycloadduct was formed. See text.

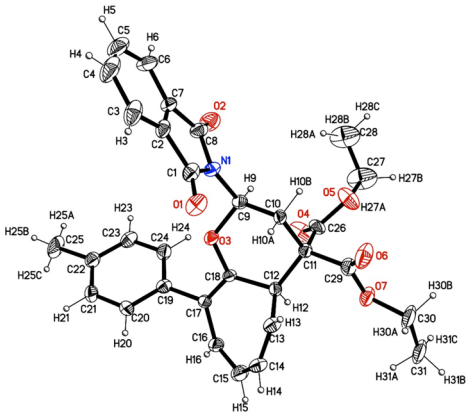


Figure 2. ORTEP-diagram of compound **3e**. Ellipsoids are drawn at the 30% probability level.

thermodynamically ($\Delta\Delta G_R$(Ph7−Ph2) = 12.9 kcal/mol) favored over the ring closure process forming the C2-regioisomer via **TS2-Ph2**. A similar result was computed in the [8 + 3]-cycloaddition involving 2-bromotropone **1c** ($\Delta\Delta G_a$(Br7−Br2) = 6.8 kcal/mol). As the electronic effects of phenyl and bromide substituents are markedly different, and no effect of the substituents attached to the aromatic ring was observed, this regioselectivity should be steric in origin. It can be thus suggested that the steric hindrance exerted by the substituent attached at the C2-position may hamper the ring closure at this position directing the ring closure to occur at the sterically unhindered C7-position of the tropone ring.

As stated above, 2-alkoxytropones **1h** and **1i** and 2-silyloxytropone **1j** did not undergo the [8 + 3]-cycloaddition, which may be attributed to the electronic effect exerted by the donor alkoxy or silyloxy group.[17] Instead, a new

(15) Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. v. R. *Chem. Rev.* **2005**, *105*, 3842.

(16) Schleyer, P. v. R.; Jiao, H. *Pure Appl. Chem.* **1996**, *68*, 209 and references therein.

(17) Alternatively, coordination of the 2-alkoxytropone to the catalyst may be responsible for the lack of reactivity of compounds **1h** and **1i**. However, this coordination seems unlikely in the presence of the bulky TBS-substituent of compound **1j**. We thank a reviewer for pointing out this experiment.

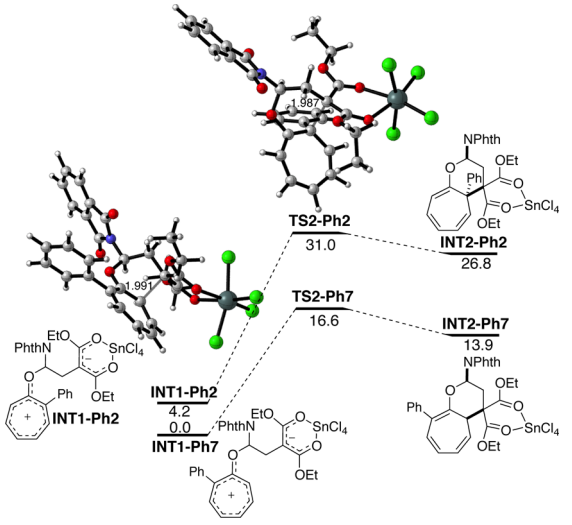


Figure 3. Computed profile for the ring closure of the [8 + 3]-cycloaddition between tropone **1d** and $SnCl_4$–DCA complex **4**. See caption for Figure 1 for additional details.

compound **5** lacking the characteristic signals of the tropone in the corresponding NMR spectra was isolated in the processes involving **1h** and **1i**. Single crystals of the new compound **5** suitable for X-ray diffraction analysis were grown in hexanes/CH_2Cl_2 solution at room temperature. As seen in Figure 4, the structure of **5** corresponds to a dimer of the DAC **2**. As tropones **1h,i** were recovered unaltered in the reaction conditions used,[18] species **5** is very likely formed by the self-coupling of two molecules of the $SnCl_4$–DAC complex **4**. The formation of this dimer constitutes therefore a side reaction which occurs when DAC **2** reacts with electron-rich substrates such as alkoxytropones. We want to point out that, although the self-dimerization product of **2** has not been observed so far,[9] related dimerization products of DACs have been described.[19]

In summary, the novel Lewis acid catalyzed [8 + 3]-cycloaddition reaction between tropone and tropone

(18) Moreover, dimer **5** was formed in the reactions of tropones **1h,i** with **2** at −78 °C for prolonged reaction times. In addition, in a control experiment, dimer **5** was also formed in the reaction of DAC **2** and $SnCl_4$ conducted in the absence of any tropone derivative.

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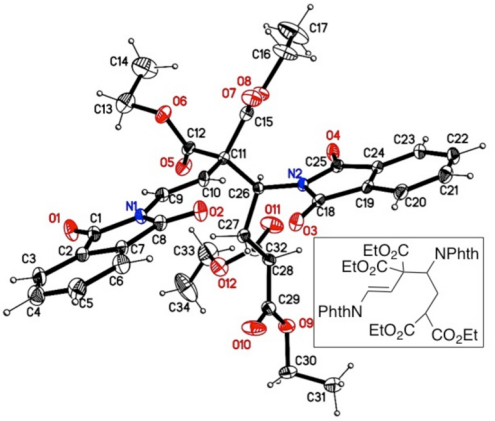

Figure 4. ORTEP-diagram of compound **5**. Ellipsoids are drawn at the 30% probability level.

derivatives and donor–acceptor aminocyclopropane **2** has been studied. The process leads to the formation of amino-substituted tetrahydrocyclohepta[*b*]pyrans in good reaction yields and with complete regio- and diastereoselectivities. By means of computational-DFT methods, it was found that this transformation proceeds stepwise through a zwitterionic intermediate, which resembles the tropyl cation and therefore is stabilized by some degree of π-aromaticity. From this intermediate, a ring closure step, which controls the regio- and diastereoselectivities, occurs to produce the observed [8 + 3]-cycloadducts.

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Supporting Information Available. Experimental details, NMR spectra of isolated compounds, crystallographic data for compounds **3e** and **5**, computational details, Cartesian coordinates, and free energies of all the stationary points discussed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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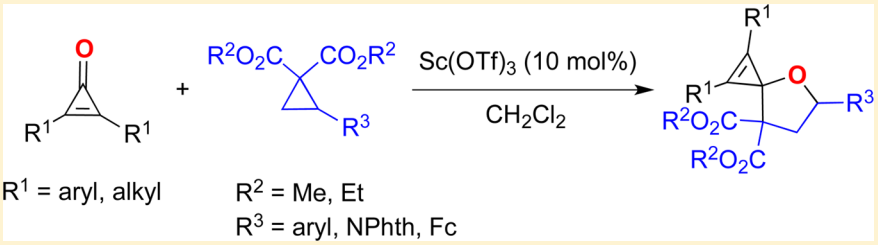
Synthesis of Oxaspiranic Compounds through [3 + 2] Annulation of Cyclopropenones and Donor−Acceptor Cyclopropanes

Alexandra R. Rivero,[†] Israel Fernández,*[,†] Carmen Ramírez de Arellano,[‡] and Miguel A. Sierra*[,†]

[†]Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, 28040 Madrid, Spain

[‡]Departamento de Química Orgánica, Universidad de Valencia, 46100 Valencia, Spain

Supporting Information



ABSTRACT: The $Sc(OTf)_3$-catalyzed [3 + 2]-annulation reaction between cyclopropenones and donor−acceptor cyclopropanes is described. The process leads directly to the formation of 4-oxaspiro[2.4]hept-1-ene derivatives in good to excellent reaction yields. Density functional theory calculations suggest that the [3 + 2]-annulation pathway is strongly preferred over the possible [3 + 3]-process.

Spirocyclic compounds, species where two rings are fused by just one carbon atom, have become a synthetic target of renewed interest recently due to their enormous potential in drug discovery[1] and materials chemistry.[2] Indeed, the rigidity and conformational restriction imposed by the spiranic moiety, which is present in a great number of natural products,[3] provide a stiff framework for the attachment of pharmacophoric groups or a rigid framework for metal coordination. However, the synthesis of these species is especially challenging for organic chemists as many of the synthetic procedures toward spirocycles are based on multistep strategies and employ expensive reagents.[4,5] Although transition-metal-catalyzed processes have become an attractive alternative to synthesize spirocycles,[6] new direct routes leading to this important family of compounds are still to be developed.

At this point, we turned our attention to the chemistry of donor−acceptor cyclopropanes (DAC),[7] compounds which have proven to be very useful for the direct synthesis of five-membered carbo- and heterocycles via [3 + 2]-annulation reactions.[8] Within the context of our ongoing work in the reaction mechanisms and synthetic applications of high-order cycloaddition and annulation reactions,[9] we have recently described a novel Lewis acid catalyzed [8 + 3]-annulation reaction between tropone derivatives and donor−acceptor aminocyclopropanes (Scheme 1a).[10] This transformation leads to the formation of amino-substituted tetrahydrocyclohepta[*b*]-pyrans in good reaction yields and with complete regio- and diastereoselectivities. This synthetic strategy was first developed with a nitrogen-based donor[10] but is also compatible with a variety of different donors such as aryl, heteroaryl, and vinyl substituents.[11] Taking into account this reaction, we envisaged a new route to 4-oxaspiro[2.4]hept-1-ene derivatives by the reaction of cyclopropenones and DACs (Scheme 1b). Two possible reaction products may be formed in this transformation, i.e., the spirocycle **A** via the well-known [3 + 2]-annulation between the DAC and the ketone moiety[8] and/or the alternative [4.1.0]-oxabicyclic species **B**, through a [3 + 3]-process analogous to the [8 + 3]-annulation described previously by us.[10] We can anticipate that the formation of compounds **B** is thermodynamically very unlikely in view of the high strain imposed by the [4.1.0]-oxabicycle. If successful, this process will constitute a simple and direct methodology to the preparation of 4-oxaspiro[2.4]hept-1-ene derivatives, which contain a spirocyclopropene in its structure.[12]

Our study started with the reaction between diphenylcyclopropenone **1a** and DAC **2a** to optimize the reaction conditions (Table 1). The use of $SnCl_4$, the Lewis acid employed for the previous [8 + 3]-annulation involving tropones,[10] did not promote the reaction (entries 1−4). Similarly, other typical Lewis acids such as $FeCl_3$, $ZnCl_2$, $TiCl_4$, $NiCl_2$, $Fe(acac)_3$, or $Ni(ClO_4)_2{\cdot}6H_2O$ (the latter used in the [8 + 3]-process involving DAC **2a**),[11] were not efficient either in promoting the transformation even when the reaction was carried out at 60 °C (entries 5−11). To our delight, $Sc(OTf)_3$ (5 mol %) did catalyze the process at 40 °C leading to a reaction conversion of 30% (entry 12). Increasing the catalyst loading to 10 mol % resulted in a higher conversion of 45%. Different temperatures were also screened finding $Sc(OTf)_3$ (10 mol %) and equimolar amounts of **1a** and **2a** in DCM as solvent at 80 °C for 4 h (entry 16) as the optimal reaction conditions.[13]

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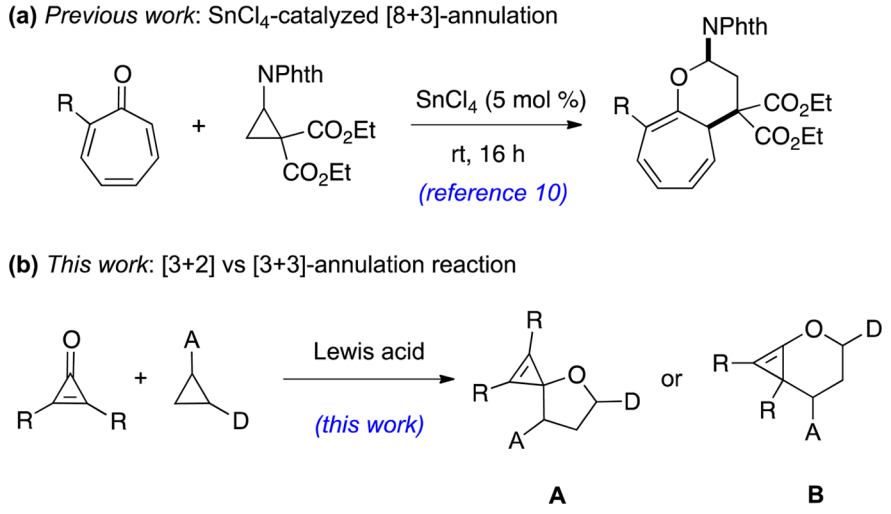
Scheme 1



Standard 1D- and 2D-NMR techniques were used to characterize the nature of the product formed (**3a**) in the reaction between **1a** and **2a**. The spectroscopic data are compatible with the formation of the spirocyclic compound **A** (Scheme 1b) as initially envisaged. For instance, the corresponding ^{13}C NMR spectrum clearly confirms the presence of the oxaspiranic carbon atom (δ = 71.2 ppm) together with the double bond of the cyclopropene moiety ($\delta \approx 128$ ppm). These chemical shifts concur quite well with those found for related 4-oxaspiro[2.4]hept-1-en-5-one derivatives.[12c] In addition, single crystals of compound **3b**, where the ethyl groups of the ester moieties were replaced by methyl groups (see also Table 2) suitable for X-ray diffraction analysis, fully confirm, by analogy, the spiranic nature of the reaction product **3a** (Figure 1).

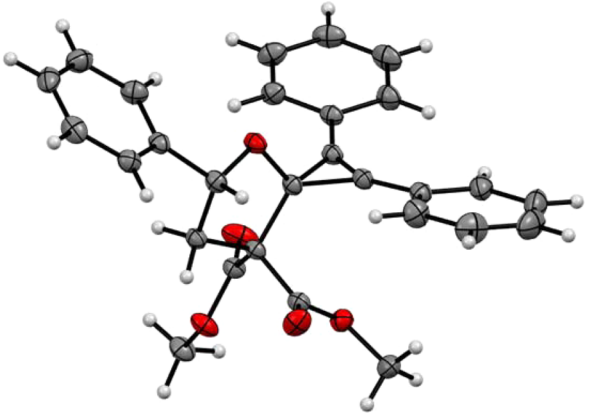
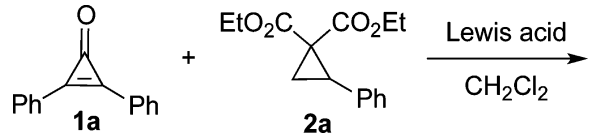


Figure 1. ORTEP diagram of compound **3b**. Ellipsoids are drawn at the 50% probability level.

With these optimized reaction conditions in hand, we next explored the scope of the process with regard to substitution at the 1,1-cyclopropanediester **2**. As readily seen in Table 2, the electronic nature of the donor moiety (R^3) of the DAC has an enormous influence on the outcome of the process. Thus, electron-withdrawing groups (F, Br, or CN groups) placed at the *para* position of the phenyl group in **2** lead to lower reaction yields (from 51% to 40% for **3d** and **3f**, respectively) than the unsubstituted phenyl group (55% for **3b**). Indeed, the reaction does not proceed at all in the presence of the strong π-acceptor

Table 1. Optimization of Reaction Conditions for the Process between 1a and 2a



entry	Lewis acid (mol %)	temp (°C)	time (h)	conv[a] (%)
1	$SnCl_4$ (20)	−78	2	0
2	$SnCl_4$ (20)	−78	8	0
3	$SnCl_4$ (20)	−20	8	0
4	$SnCl_4$ (20)	25	8	0
5	$FeCl_3$ (5)	40	8	0
6	$ZnCl_2$ (5)	40	8	0
7	$TiCl_4$ (5)	40	8	0
8	$NiCl_2$ (5)	40	8	0
9	$Fe(acac)_3$ (5)	40	8	0
10	$Ni(ClO_4)_2{\cdot}6H_2O$ (5)	40	8	0
11	$Ni(ClO_4)_2{\cdot}6H_2O$ (5)	60	8	10
12	$Sc(OTf)_3$ (5)	40	8	30
13	$Sc(OTf)_3$ (10)	40	8	45
14	$Sc(OTf)_3$ (10)	60	8	47
15	$Sc(OTf)_3$ (10)	80	8	50
16	$Sc(OTf)_3$ (10)	80	4	65
17	$Sc(OTf)_3$ (10)	100	4	50
18	$Sc(OTf)_3$ (10)	130	4	25

[a]Referred to unreacted 1,1-cyclopropane diester **2a** and measured by integration of the signals corresponding to H2 of the cyclopropane ring in the ^1H NMR spectra of reaction mixtures.

NO_2 group (0% for **3g**). Despite that, the incorporation of a bromide substituent in **3e** would allow further synthetic transformations by transition-metal-catalyzed coupling reactions. By contrast, the good π-donor methoxy substituent not only leads to a higher reaction yield of the corresponding spirocyclic compound **3c** (85%) but also allows the reaction to proceed at much lower temperature (0 °C). This finding very likely finds its origin in the initial ring opening of the DAC promoted by the Lewis acid, since it is well-known that the formation of the corresponding intimate ion pair is facilitated by electron-rich donor groups.[14]

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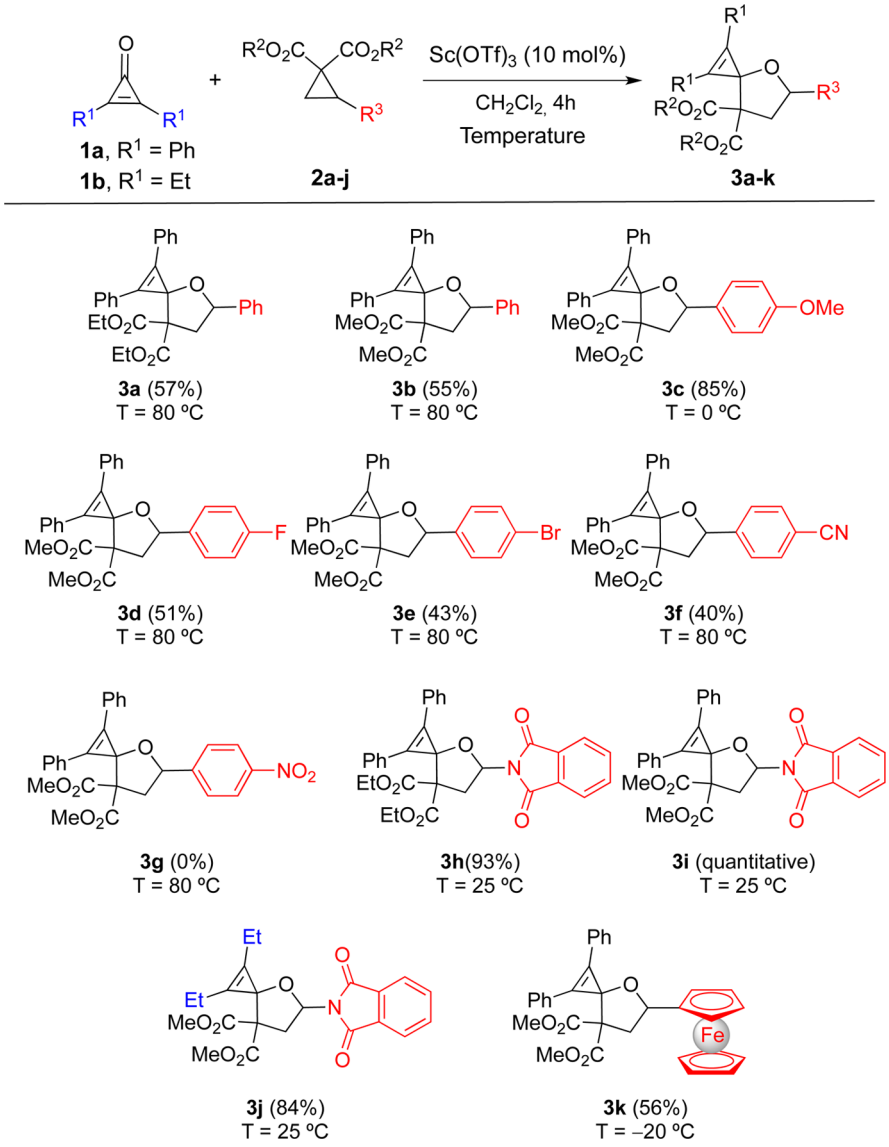
Table 2. Scope of the $Sc(OTf)_3$-Catalyzed [3 + 2]-Annulation Reaction between Cyclopropenones 1a,b and 1,1-Cyclopropanediesters 2a−j[a]



[a]Isolated reaction yields are given in parentheses.

To further confirm this hypothesis, we attached the stronger π-donor NPhth group (Phth = phthaloyl) as the donor moiety of the DAC (**2h** and **2i**). This particular type of amino-DAC was also chosen due to its proven ability to produce *N*-containing hetero- and carbocycles as recently demonstrated by Waser and co-workers.[15] From the data in Table 2, it becomes clear that in the presence of this group the reaction proceeds smoothly at lower temperatures (25 °C) as compared to the parent phenyl-substituted DAC **2b** (80 °C) and, more importantly, leads to excellent reaction yields for the corresponding spirocyclic compounds (93% and quantitative yield for **3h** and **3i**, respectively). The reaction is also compatible with alkyl instead of phenyl groups in the cyclopropenone. Thus, diethylcyclopropenone **1b** also affords the corresponding oxaspirocycle **3j** in a remarkable 84% reaction yield (at 25 °C).

Finally, we were also curious to study the process involving an organometallic fragment. The ferrocenyl substituent was chosen because of its π-donor ability.[16] Again, excellent reactivity of the corresponding ferrocenyl-substituted DAC **2j** was found as it leads to the formation of the ferrocenyl-oxaspirocyclic compound **3k** at low temperature (−20 °C) in an acceptable 56% reaction yield (see Table 2). The latter result, which to the best of our knowledge constitutes one of the scarce examples of spirocyclic compounds having an organometallic fragment,[17] clearly confirms that the process is general and compatible with a wide variety of cyclopropenones and DACs.

Density functional theory (DFT) calculations have been carried out at the PCM(CH_2Cl_2)-M06/def2-TZVP//B3LYP/def2-SVP level[18] to gain more insight into the exclusive formation of spirocyclic compounds **A** over bicyclic species **B**. Thus, the corresponding computed reaction profile of the process involving the model cyclopropenone **1M** (where the ethyl groups in **1b** were replaced by methyl groups) and DAC **2b** in the presence of $Sc(OTf)_3$ is shown in Figure 2, which gathers the respective free energies, ΔG_{298}, in dichloromethane solution.

As previously reported,[10,14] the reaction begins with the nucleophilic attack of the cyclopropenone (through the lone-pair of the carbonyl group) to the electrophilic center of the intimate

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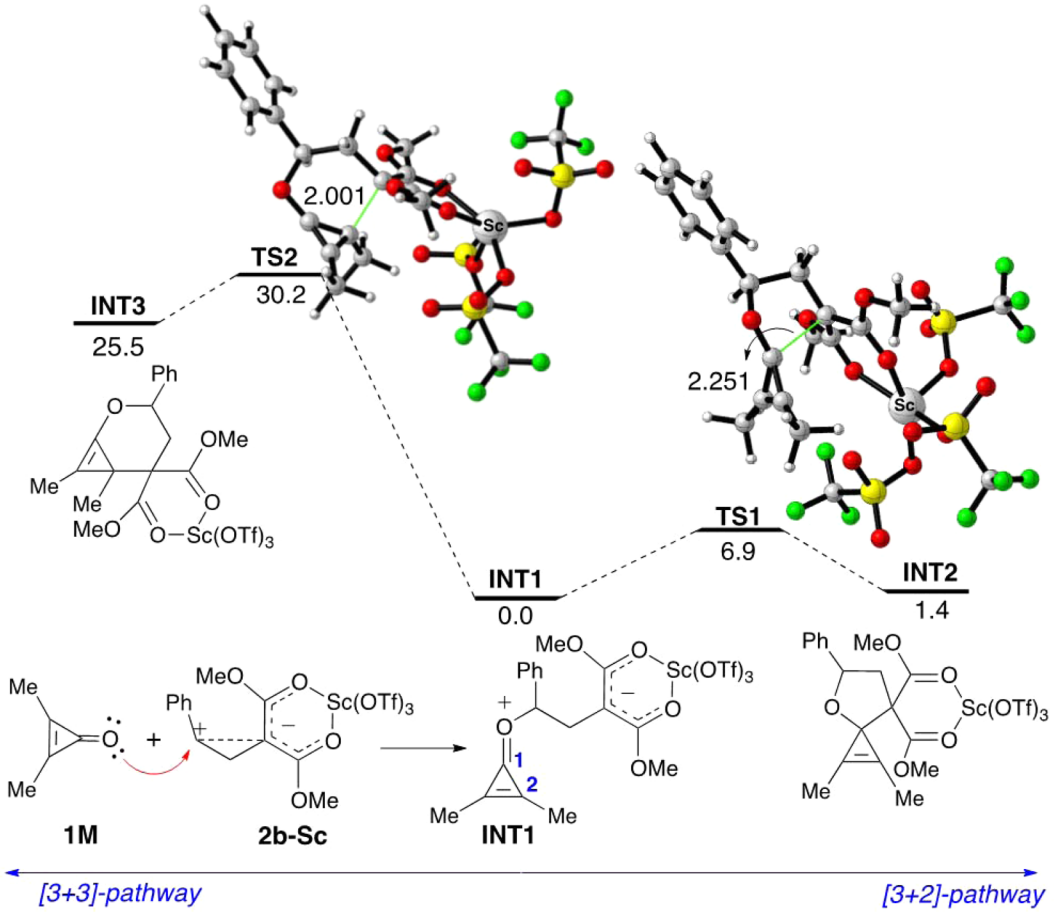

Figure 2. Computed reaction profile of the reaction of cyclopropenone **1M** and $Sc(OTf)_3$–DAC complex **2b-Sc**. Relative free energies (ΔG, 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data have been computed at the PCM(CH_2Cl_2)-M06/def2-TZVP//B3LYP/def2-SVP level.

ion-pair **2b-Sc**, which is formed upon coordination of the ester groups to the transition metal. This addition reaction leads to the formation of **INT1**, a zwitterionic intermediate similar to that proposed for the related [8 + 3]-annulation involving tropones,[10] which can be considered as an aromatic compound according to the computed negative nucleus independent chemical shift (NICS)[19] values (NICS(0) = −27.2 ppm and $NICS(1)_{zz}$ = −19.2 ppm). In this sense, the three-membered ring of **INT1** resembles the cyclopropenyl cation.[20]

Two possible ring closures in **INT1** can be envisioned, namely the annulation at C1 which would produce the [3 + 2]-adduct **INT2** and, alternatively, the annulation at C2, leading to the formation of the bicyclic species **INT3**. From the data in Figure 2, it becomes clear that the nucleophilic attack at C1 is strongly favored under both kinetic and thermodynamic control in view of the considerably higher activation energy required for the formation of bicyclic **INT3** ($\Delta\Delta G^{\ddagger}$ = 23.3 kcal/mol), as well as the higher reaction energy calculated for this latter intermediate ($\Delta\Delta G_R$ = 24.1 kcal/mol). As a consequence, no traces of the corresponding [3 + 3]-reaction product should be observed in the reaction crudes, as experimentally found. In addition, the respective noncoordinated reaction products derived from **INT2** and **INT3** also exhibit a similar free energy difference ($\Delta\Delta G_R$ = 19.5 kcal/mol), thus confirming that the highly strained nature of the bicyclic species **B** switches off the [3 + 3]-annulation reaction pathway.

Finally, the ring closure at C1 leading to spirocyclic compounds is preferred over the cyclization at C2 for an additional reason. As seen from the computed natural bond orbital (NBO) charges (Figure 3), the carbon atom C1 in the initial zwitterionic intermediate **INT1** clearly bears a more positive charge than C2 (or C3) (Δq = +0.364 au), thus indicating a higher electrophilic character. This difference in electrophilicity also directs the nucleophilic addition from the carbanionic center C4 (q = −0.364) toward C1 instead of C2.

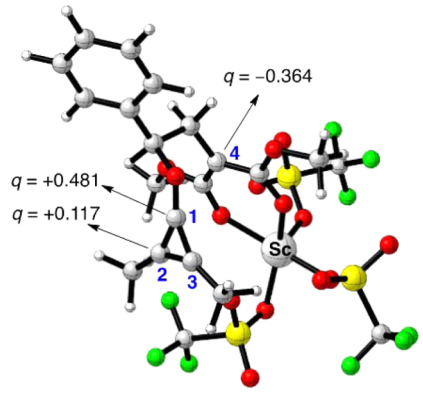

Figure 3. Computed (B3LYP/def2-SVP level) NBO charges of zwitterionic intermediate **INT1**.

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In summary, the $Sc(OTf)_3$-catalyzed reaction between cyclopropenones and different donor−acceptor cyclopropanes has been studied. This process allows the direct access to 4-oxaspiro[2.4]hept-1-ene derivatives in good to excellent reaction yields through a stepwise [3 + 2]-annulation reaction. The process is compatible with different substituents in both reactants including organometallic moieties, which might find future applications in bioorganometallic chemistry. With the help of DFT calculations it was found that the exclusive formation of the [3 + 2]-products over the [3 + 3]-bicyclic compounds takes place under both kinetic and thermodynamic control. This preference finds its origin in the higher electrophilicity of the C1 carbon atom of the aromatic zwitterionic intermediate and in the highly strained nature of the [4.1.0]-bicyclic species.

EXPERIMENTAL SECTION

General Procedures. All reactions were carried out under argon atmosphere. Dichloromethane (DCM) was distilled from calcium hydride before use. Flame-dried glassware was used for moisture-sensitive reactions. Identification of products was made by thin-layer chromatography (TLC) (Kieselgel 60F-254). UV light (λ= 254 nm) and oleum was used to develop the plates. NMR spectra were recorded at 25 °C in $CDCl_3$ on a 300 MHz (300 MHz for ^1H, 75 MHz for ^{13}C) spectrometer. Chemical shifts are given in ppm relative to TMS (^1H, 0.0 ppm) or $CDCl_3$ (^{13}C, 77.0 ppm). IR spectra were taken as solid films by slow evaporation of the solvent using the ATR (attenuated total reflectance) technique. HRMS spectra were obtained on a mass spectrometer using electronic impact (EI) or on a Q-TOF system for the electron spray ionization (ESI) experiments. Commercially available products were used without further purification. 1,1-Cyclopropanediesters were synthesized according to literature procedures: (**2a**–**d**,**f**,**i**,**j**),[21] **2e**,[22] and **2h**.[15c]

General Procedure for the Annulation Reactions. In an oven-dried pressure tube, cyclopropenone **1** (0.12 mmol), cyclopropane **2** (0.12 mmol), and scandium triflate (10 mol %) were dissolved in anhydrous dichloromethane (2.5 mL) at 25 °C. The reaction mixture was stirred under argon atmosphere at the specified temperature. After completion of the reaction (checked by TLC), the solvent was removed under reduced pressure to give the crude reaction mixture, which was submitted to column chromatography (SiO_2, hexanes to 1:10 EtOAc/hexanes) to yield pure oxaspiranic compounds **3**.

*Compound **3a**.* The reaction was performed at 80 °C following the general procedure described above from cyclopropenone **1a** (25 mg) and cyclopropane **2a** (31 mg). Compound **3a** was isolated as a colorless solid (32 mg, 57%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.86−7.78 (m, 4H), 7.51−7.28 (m, 11H), 5.31 (dd, J = 10.2, 5.7 Hz, 1H), 4.18−4.03 (m, 1H), 4.00−3.82 (m, 3H), 3.29 (dd, J = 12.9, 5.7 Hz, 1H), 2.86 (dd, J = 12.9, 10.2 Hz, 1H), 0.99 (q, J = 7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 169.8, 142.2, 130.4, 130.2, 129.60, 129.55, 129.0, 129.0, 128.96, 128.8, 128.03, 126.1, 120.8, 120.7, 77.2, 71.2, 62.1, 61.8, 61.0, 45.3, 14.1, 14.0; IR (ATR) $\tilde{\nu}$ = 2982, 1730, 1389, 1211, 1093, 759, 690 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{29}O_5$ $[M + H]^+$ 469.2010, found 469.2022.

*Compound **3b**.* The reaction was performed at 80 °C following the general procedure described above from cyclopropenone **1a** (25 mg) and cyclopropane **2b** (28 mg). Compound **3b** was isolated as a colorless solid (27 mg, 51%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (t, J = 7.0 Hz, 4H), 7.54−7.25 (m, 11H), 5.33 (dd, J = 10.3, 5.5 Hz, 1H), 3.54 (s, 3H), 3.48 (s, 3H), 3.32 (dd, J = 12.9, 5.5 Hz, 1H), 2.88 (dd, J = 12.9, 10.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 170.3, 142.0, 130.4, 130.2, 129.7, 129.1, 129.0, 128.8, 128.0, 127.8, 127.7, 126.1, 120.7, 120.5, 77.4, 71.4, 60.8, 53.0, 52.9, 45.3; IR (ATR) $\tilde{\nu}$ = 2952, 1733, 1439, 1270, 1090, 977, 760, 693 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{25}O_5$ $[M + H]^+$ 441.1697, found 441.1701.

*Compound **3c**.* In an oven-dried Schlenk tube, cyclopropenone **1a** (0.12 mmol, 25 mg) and scandium triflate (10 mol %) were dissolved in anhydrous dichloromethane (2 mL). The mixture was stirred under argon at 0 °C for 5 min before the addition of cyclopropane **2c** (0.12 mmol, 32 mg) in anhydrous dichloromethane (0.5 mL). The reaction mixture was stirred under argon atmosphere at 0 °C until the completion of the reaction (checked by TLC). Evaporation of the solvent under reduced pressure gave the crude reaction mixture, which was submitted to column chromatography (SiO_2, hexanes to 1:10 EtOAc/hexanes) to yield pure compound **3c** as a yellow oil (48 mg, 85%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.89−7.76 (m, 4H), 7.54−7.36 (m, 8H), 6.91 (d, J = 8.7 Hz, 2H), 5.26 (dd, J = 10.3, 5.4 Hz, 1H), 3.82 (s, 3H), 3.52 (s, 3H), 3.48 (s, 3H), 3.25 (dd, J = 13.0, 5.4 Hz, 1H), 2.86 (dd, J = 13.0, 10.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 170.5, 159.6, 133.9, 130.4, 130.2, 129.6, 129.1, 129.0, 128.2, 127.9, 127.7, 127.5, 120.9, 120.4, 114.2, 77.2, 71.2, 60.9, 55.7, 53.0, 52.9, 45.3; IR (ATR) $\tilde{\nu}$ = 2953, 1733, 1313, 1439, 1247, 1174, 1084, 762, 691 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{27}O_6$ $[M + H]^+$ 471.1802, found 471.1808.

*Compound **3d**.* The reaction was performed at 80 °C following the general procedure described above from cyclopropenone **1a** (25 mg) and cyclopropane **3d** (30 mg). Compound **3d** was isolated as a white solid (28 mg, 51%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.83−7.75 (m, 4H), 7.52−7.39 (m, 8H), 7.04 (t, J = 8.7 Hz, 2H), 5.27 (dd, J = 10.2, 5.6 Hz, 1H), 3.52 (s, 3H), 3.47 (s, 3H), 3.27 (dd, J = 13.0, 5.6 Hz, 1H), 2.82 (dd, J = 13.0, 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 170.3, 162.7 (d, J = 246 Hz), 137.7 (d, J = 3 Hz), 130.3, 130.2, 129.7, 129.1, 129.06, 127.8 (d, J = 8 Hz), 127.6, 120.7, 120.3, 115.7 (d, J = 21 Hz), 76.8, 71.4, 60.7, 53.0, 52.9, 45.4; IR (ATR) $\tilde{\nu}$ = 2951, 1734, 1487, 1434, 1270, 1009, 760, 690 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{23}FO_5$ $[M]^{\cdot+}$ 458.1524, found 458.1527

*Compound **3e**.* The reaction was performed at 80 °C following the general procedure described above from cyclopropenone **1a** (25 mg) and cyclopropane **2e** (38 mg). Compound **3e** was isolated as a white solid (27 mg, 43%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.87−7.69 (m, 4H), 7.56−7.28 (m, 10H), 5.24 (dd, J = 10.2, 5.7 Hz, 1H), 3.51 (s, 3H), 3.46 (s, 3H), 3.27 (dd, J = 12.9, 5.7 Hz, 1H), 2.78 (dd, J = 12.9, 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 170.2, 141.2, 131.9, 130.3, 130.2, 129.8, 129.7, 129.1, 129.07, 127.8, 127.7, 127.6, 121.7, 120.5, 120.4, 76.6, 71.5, 60.7, 53.04, 52.96, 45.2; IR (ATR) $\tilde{\nu}$ = 2951, 1730, 1438, 1403, 1265, 1041, 1078, 972, 759, 690 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{23}BrO_5$ $[M]^{\cdot+}$ 518.0723, found 518.0729.

*Compound **3f**.* The reaction was performed at 80 °C following the general procedure described above from cyclopropenone **1a** (25 mg) and cyclopropane **2f** (31 mg). Compound **3f** was isolated as a yellow oil (22 mg, 40%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.89−7.72 (m, 4H), 7.65 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.3 Hz, 2H), 7.55−7.35 (m, 6H), 5.34 (dd, J = 10.1, 5.9 Hz, 1H), 3.54 (s, 3H), 3.47 (s, 3H), 3.34 (dd, J = 13.0, 5.9 Hz, 1H), 2.78 (dd, J = 13.0, 10.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 169.9, 147.8, 132.7, 130.3, 130.2, 129.92, 129.87, 129.2, 129.1, 127.5, 127.4, 126.6, 120.3, 120.2, 119.3, 111.7, 76.3, 71.7, 60.4, 53.1, 53.0, 44.9; IR (ATR) $\tilde{\nu}$ = 2953, 2228, 1735, 1440, 1271, 1085, 974, 761, 692 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{24}NO_5$ $[M + H]^+$ 466.1649, found 466.1659.

*Compound **3h**.* The reaction was performed at 25 °C following the general procedure described above from cyclopropenone **1a** (25 mg) and cyclopropane **2h** (40 mg). Compound **3h** was isolated as a colorless oil (63 mg, 93%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.96−7.90 (m, 2H), 7.84−7.76 (m, 2H), 7.70−7.62 (m, 4H), 7.45−7.27 (m, 6H), 6.36 (dd, J = 8.7, 6.7 Hz, 1H), 4.07−3.95 (m, 3H), 3.95−3.87 (m, 1H), 3.83−3.71 (m, 1H), 3.18 (dd, J = 13.2, 6.7 Hz, 1H), 0.95 (t, J = 7.1 Hz, 3H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 168.8, 168.0, 134.6, 132.3, 130.9, 130.0, 129.7, 129.0, 128.9, 127.7, 127.68, 123.9, 121.5, 118.7, 110.0, 77.0, 70.9, 62.4, 61.9, 60.1, 36.8, 14.2, 13.9; IR (ATR) $\tilde{\nu}$ = 2979, 1721, 1369, 1267, 1086, 720 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{28}NO_7$ $[M + H]^+$ 538.1860, found 538.1862.

*Compound **3i**.* The reaction was performed at 25 °C following the general procedure described above from cyclopropenone **1a** (25 mg) and cyclopropane **2i** (36 mg). Compound **3i** was isolated as a colorless oil (62 mg, quantitative): ^1H NMR (300 MHz, $CDCl_3$) δ 8.06−7.95 (m, 2H), 7.92−7.85 (m, 2H), 7.79−7.70 (m, 4H), 7.53−7.36 (m, 6H), 6.35 (dd, J = 8.4, 6.8 Hz, 1H), 3.99 (dd, J = 13.3, 8.4 Hz, 1H), 3.59 (s, 3H), 3.50 (s, 3H), 3.23 (dd, J = 13.3, 6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 169.4, 168.0, 134.7, 132.3, 130.8, 130.0, 129.8, 129.7, 129.1, 129.0, 127.5, 127.3, 124.0, 121.1, 118.8, 76.9, 71.1, 60.0, 53.2,

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53.0, 37.0; IR (ATR) $\tilde{\nu}$ = 2953, 1719, 1371, 1273, 1137, 1086, 720 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{24}NO_7$ $[M + H]^+$ 510.1547, found 510.1540.

Compound ***3j***. The reaction was performed at 25 °C following the general procedure described above from cyclopropenone **1b** (13 mg) and cyclopropane **2i** (36 mg). Compound **3j** was isolated as a colorless oil (41 mg, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89−7.83 (m, 2H), 7.75−7.68 (m, 2H), 6.00 (t, J = 7.5 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.65 (dd, J = 13.2, 7.5 Hz, 1H), 3.05 (dd, J = 13.2, 7.5 Hz, 1H), 2.64−2.42 (m, 4H), 1.20 (t, J = 7.4 Hz, 3H), 1.19 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 169.5, 167.9, 134.6, 132.3, 126.3, 123.8, 120.8, 75.9, 73.6, 60.5, 53.3, 53.0, 36.9, 17.8, 17.0, 14.16, 13.96; IR (ATR) $\tilde{\nu}$ = 2970, 1717, 1434, 1272, 1137, 1088, 720 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{24}NO_7$ $[M + H]^+$ 414.1547, found 414.1563.

Compound ***3k***. In an oven-dried Schlenk tube, cyclopropenone **1a** (0.12 mmol, 25 mg) and scandium triflate (0.012 mmol) were dissolved in anhydrous dichloromethane (2 mL). The mixture was stirred under argon at −20 °C for 5 min before the addition of the cyclopropane **2j** (0.12 mmol, 41 mg) in anhydrous dichloromethane (0.5 mL). The reaction mixture was stirred under argon atmosphere at −20 °C until completion of the reaction (checked by TLC). Evaporation of the solvent under reduced pressure gave the crude reaction mixture, which was submitted to column chromatography (SiO_2, hexanes to 1:6 EtOAc/hexanes) to yield pure compound **3c** as a yellow oil (37 mg, 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87−7.73 (m, 4H), 7.58−7.33 (m, 6H), 5.08 (dd, J = 10.2, 5.6 Hz, 1H), 4.41−4.16 (m, 9H), 3.51 (s, 6H), 3.25 (dd, J = 12.9, 5.6 Hz, 1H), 2.98 (dd, J = 12.9, 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 170.7, 130.3, 130.1, 129.6, 129.5, 129.1, 128.9, 128.0, 127.8, 121.5, 120.5, 87.4, 74.4, 71.1, 69.1, 68.8, 68.7, 68.6, 66.6, 60.9, 52.95, 52.90, 43.1; IR (ATR) $\tilde{\nu}$ = 2951, 1732, 1434, 1268, 1105, 1047, 759, 736 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{29}FeO_5$ $[M + H]^+$ 549.1359, found 549.1370.

■ ASSOCIATED CONTENT

Supporting Information

X-ray crystal structure data (CIF file) for compound **3b**, ^{1}H and ^{13}C NMR spectra for compounds **3a**−**k**, computational details, Cartesian coordinates, and energies of all the stationary points discussed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: israel@quim.ucm.es.

*E-mail: sierraor@quim.ucm.es.

Notes

The authors declare no competing financial interest.

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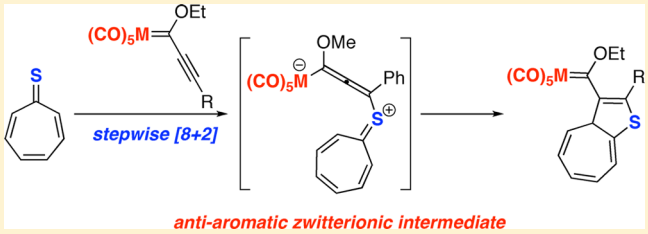
Regioselective and Stepwise [8 + 2] Cycloaddition Reaction between Alkynyl−Fischer Carbene Complexes and Tropothione

Alexandra R. Rivero, Israel Fernández,* and Miguel A. Sierra*

Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, 28040 Madrid, Spain

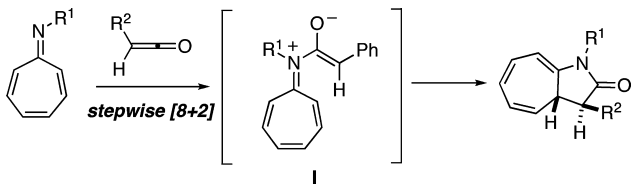
Supporting Information

ABSTRACT: The formal [8 + 2] cycloaddition reaction between alkynyl Fischer carbene complexes and tropothione leads to the regioselective formation of novel 3a*H*-cyclohepta[*b*]thiophene carbene complexes. Computational DFT calculations indicate that the process proceeds stepwise via antiaromatic zwitterionic intermediates



Fischer carbene complexes having an alkenyl or alkynyl group attached to the carbene carbon atom are useful reagents to undergo highly regioselective cycloaddition processes under mild reaction conditions.[1−7] This is mainly due to the strong activating effect exerted by the metal fragment which behaves in the cycloaddition reaction similarly to a Lewis acid directly attached to the carbonyl group of the corresponding isolobal organic esters.[8−12] Based on these and related transformations, the term "super-esters" has been coined for these organometallic compounds. Although the chemical literature contains an impressive number of work focused on [4 + 2][8−12] and [3 + 2][13−16] cycloaddition reactions involving α,β-unsaturated carbene complexes, high-order cycloaddition processes have attracted much less attention. In fact, only a single example of a [8 + 2] cycloaddition between alkynyl carbene complexes and 8-azaheptafulvenes has been reported so far by Barluenga and co-workers.[17] Moreover, nothing is known about the reaction mechanism of this transformation. Whereas a concerted reaction pathway through aromatic transition states has been computationally suggested by us for [4 + 2][18] and [3 + 2][19,20] cycloaddition reactions involving Fischer carbenes, a stepwise process is followed in the [8 + 2] reaction between 8-azaheptafulvenes and organic ketenes (Scheme 1).[21] The latter transformation involves the formation of a zwitterionic intermediate **I** which has been experimentally trapped and fully characterized. Therefore, a stepwise pathway is very likely to occur as well in the [8 + 2] reaction reported by Barluenga and co-workers.[17]

Scheme 1. Stepwise [8 + 2] Cycloaddition Reaction between 8-Azaheptafulvenes and Ketenes



Within the context of our ongoing work on the reaction mechanisms and synthetic applications of cycloaddition reactions involving organic and organometallic reagents,[22−27] we report herein the high-order [8 + 2] cycloaddition reaction[28,29] between alkynyl carbene complexes and tropothione, which occurs with total regioselectivity and through a stepwise reaction mechanism.

A tropothione solution, readily prepared from tropone and P_2S_5,[29] was added to a CH_2Cl_2 solution of the corresponding alkynyl carbene complex **1a−f** (1:1 equimolecular amounts), and the mixture was stirred at room temperature for 5−10 min (Scheme 2a). Removal of the solvent and purification of the residue by column chromatography allowed the isolation of the corresponding 3a*H*-cyclohepta[*b*]thiophene carbene complexes **3a−f**,[30] which maintain the carbene functionality susceptible to further modifications, in moderate to excellent yields. The process is compatible with different substitutions at the triple bond as well as with tungsten derived carbenes (no significant differences between the reaction yields, **3a** vs **3b**, in the reactions of chromium(0)− and tungsten(0)−carbene complexes and tropothione **2** were observed). The presence of additional metal centers (complex **1c**) is also compatible with this cycloaddition reaction. Furthermore, by using a bis-carbene complex (**1h**), bis-cycloadduct **3h** having a pentacyclic bimetallic array was obtained with a 67% reaction yield. Compound **3h** was formed as 1:1 racemic mixture of the two possible RR/SS and *meso*-RS diastereomers.

The spectroscopical data (1D- and 2D-NMR experiments) suggest that the cycloaddition reaction occurs with total regioselectivity leading exclusively to the cycloadduct having the sulfur atom of the tropothione attached to the β-carbon atom of the triple bond of the initial alkynyl carbene complex.

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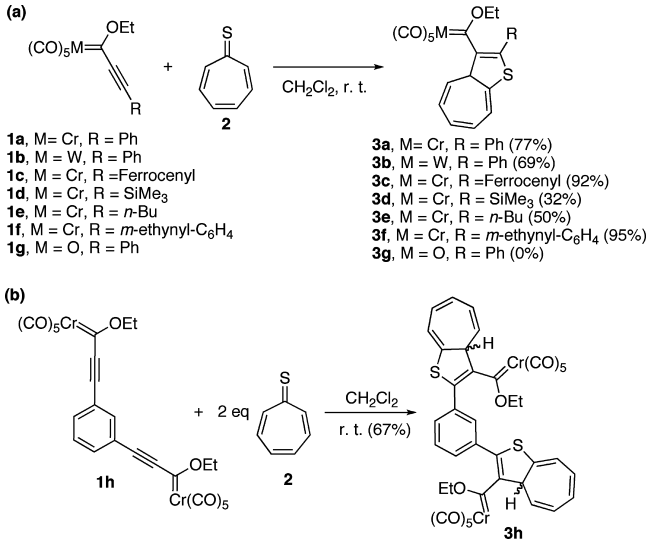
Scheme 2. [8 + 2] Cycloaddition Reaction between Alkenyl Fischer Carbene Complexes 1a–h and Tropothione 2



This result is in agreement with the high regioselectivity observed for related [3 + 2] cycloaddition processes[19,20] and for the [8 + 2] reaction described by Barluenga's group.[17] The origin of this complete regioselectivity is found in the much higher electrophilicity of the β-carbon atom compared to the α-carbon in the initial alkynyl carbene complex **1**.[20] The role of the metal in the cycloaddition reaction is decisive, since no reaction was observed when ethyl 3-phenylpropiolate (**1g**) (the organic counterpart of complexes **1a,b**) was mixed with 1 equiv of tropothione under the same reaction conditions which led to the complete transformation of complexes **1**. The use of higher temperatures (boiling CH_2Cl_2) or prolonged reaction times was of no avail. This finding clearly illustrates the activating "super-ester" effect of the metal moiety described above.

Single crystals of cycloadduct **3c** suitable for X-ray diffraction analysis were grown in hexanes/ethyl acetate solution at −20 °C. As seen in Figure 1, the sulfur atom of the tropothione is attached to the terminal carbon atom of the triple bond (C17),

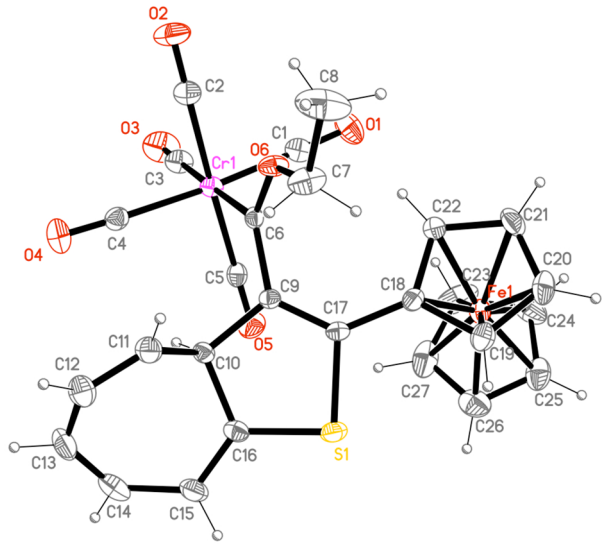


Figure 1. ORTEP diagram of compound **3c**.

thus confirming the regioselectivity of the process suggested by the spectroscopical study.

In order to gain a deeper insight into the reaction mechanism of the formal [8 + 2] cycloaddition reaction between carbene complexes **1** and tropothione, a DFT-computational study has been carried out.[31] The corresponding reaction profiles (PCM-M06/def2-SVP//B3LYP/def2-SVP level) of alkynylmethoxy-carbene complex **1M** and thione **2** are depicted in Figure 2, which gathers the computed free energies (at 298 K) in CH_2Cl_2 solution.

As initially envisaged, two different reaction pathways, i.e., concerted versus stepwise, are possible. From the data in Figure 2, it becomes obvious that a concerted pathway is not competitive in view of the high activation barrier of the process ($\Delta G^{\ddagger}_{298}$ = 58.6 kcal/mol) via the saddle point **TS1**. This computed value makes the transformation unfeasible under the reaction conditions used in the experiment (i.e., room temperature). Instead, the stepwise pathway, which starts with the nucleophilic addition of the sulfur atom of the thione to the β-carbon atom of the carbene complex **1M**, is much more likely to occur in view of the much lower activation barrier of this process ($\Delta G^{\ddagger}_{298}$ = 16.6 kcal/mol, via **TS2**). This addition leads to the formation of zwitterionic intermediate **INT1** which easily evolves to the final cycloadduct **3M** via **TS3** (computed barrier energy of $\Delta G^{\ddagger}_{298}$ = 7.2 kcal/mol), a saddle point associated with the corresponding carbon–carbon bond formation/ring-closure reaction. Therefore, the computed low activation barriers and the exergonicity of the overall cycloaddition (ΔG_R = −18.6 kcal/mol), which are compatible with a reaction at room temperature, make the stepwise pathway the preferred reaction profile for this [8 + 2] transformation.[32]

Very likely, the stepwise nature of the cycloaddition finds its origin in the high stabilization of the zwitterionic intermediate **INT1**. Thus, the negative charge is highly delocalized in the electron-withdrawing pentacarbonylmetal moiety (computed NBO-charge on chromium atom of −2.45e). Similarly, the positive charge is mainly located at the sulfur atom (+0.40e) but also delocalized within the seven-membered ring.[33] As a result, it can be proposed that the resonance form **INT1-B** (Figure 3a), which resembles the tropylium cation, has a significant contribution in the description of the sulfur-substituted zwitterion **INT1**. Consequently, some degree of aromaticity should be expected in this species. In fact, the seven-membered ring of **INT1** exhibits high planarity (C1(S)–C2–C3–C4 dihedral angle of 0.6°) and bond-length equalization (C–C bond distances in the range of 1.377–1.429 Å, intermediate between single and double bonds) thus satisfying the so-called geometric criterion for aromaticity. In contrast, the data computed for the analogous nitrogen-substituted zwitterionic intermediate **I**, formed in the analogous stepwise [8 + 2] cycloaddition reaction between 8-azafulvenes and ketenes (Scheme 1),[21] showed that this compound is not planar and exhibits a higher bond length alternation. Moreover, the computed positive nuclear independent chemical shifts (NICS)[34] values confirmed the antiaromatic nature of the latter species.[21]

To check the aromaticity of **INT1**, the corresponding NICS values were also computed. Both the NICS(0) computed at the [3,+1] ring critical point of the electron density[35–40] (NICS(0) = +5.8 ppm) and the corresponding out-of-plane component computed 1 Å above this point ($NICS(1)_{zz}$ = +2.8 ppm) indicate that the sulfur-substituted zwitterion **INT1** is not aromatic either.[41] This result has been also confirmed by

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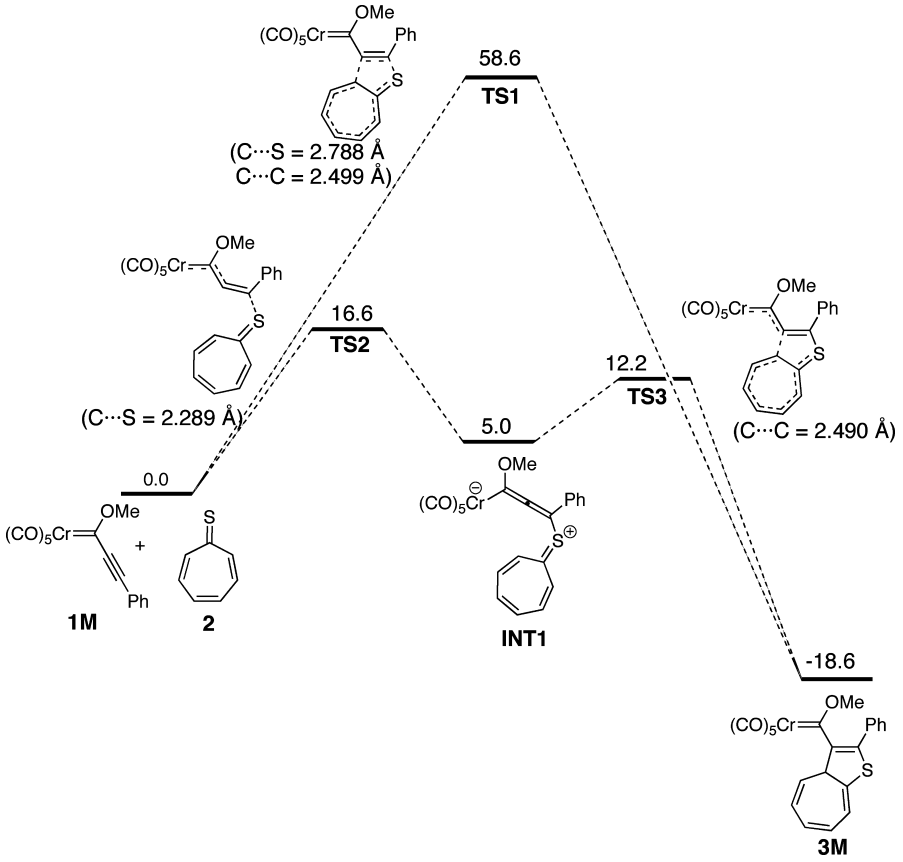

Figure 2. Computed reaction profile (PCM-M06/def2-SVP//B3LYP/def2-SVP level) for the [8 + 2] cycloaddition reaction between carbene complex **1M** and tropothione **2**. Relative free energies (ΔG_{298}) are given in kcal/mol.

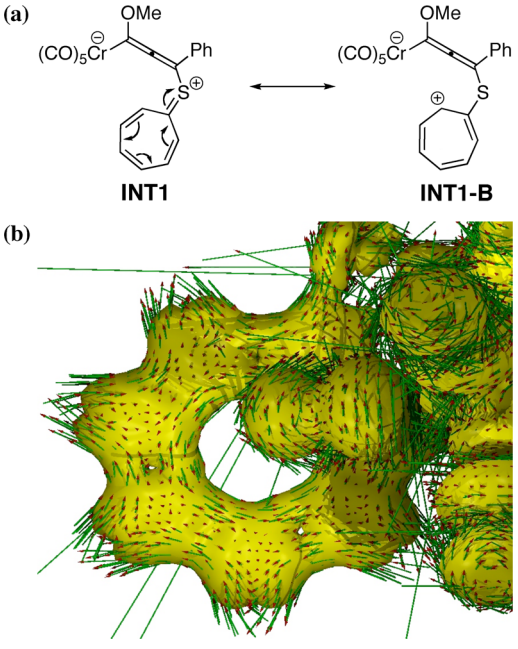

Figure 3. (a) Resonance forms of zwitterion **INT1**. (b) AICD plot of **INT1** (isosurface value of 0.035).

applying the anisotropy of the induced current density (AICD) method, developed by Herges and co-workers,[42,43] on **INT1** to visualize the delocalization of electrons within the ring. As readily seen in Figure 3b, a clear paratropic current (anticlockwise vectors) is observed, thus confirming the antiaromatic nature of this species despite the planarity and bond equalization of the ring.[44−48] Therefore, it can be concluded that the contribution of the resonance form **INT1-B** cannot be that significant. Moreover, this finding also shows that the exocyclic heteroatom plays a major role in the aromatic nature of these cationic heptafulvenes[49] and, consequently, in the stability of the intermediate zwitterions.

In summary, a formal [8 + 2] cycloaddition reaction between alkynyl Fischer carbene complexes and tropothione has been described. The process leads to the regioselective formation of 3a*H*-cyclohepta[*b*]thiophene carbene complexes, which maintain the pentacarbonyl−metal carbene functionality. By means of computational-DFT methods, it was found that this transformation proceeds stepwise through an antiaromatic zwitterionic intermediate.

■ EXPERIMENTAL SECTION

General Procedures. All reactions were carried out under argon atmosphere. All solvents used in this work were purified immediately before use. Flame-dried glassware was used for moisture-sensitive reactions. Identification of products was made by thin-layer chromatography (Kiesegel 60F-254). UV light (λ= 254 nm) and potassium permanganate (aqueous solution) were used to develop the plates. Unless otherwise noted, NMR spectra were recorded at 25 °C in $CDCl_3$ on a 300 MHz (300 MHz for ^{1}H, 75 MHz for ^{13}C) spectrometer. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 77.0 ppm). ^{1}H NMR splitting pattern abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. IR spectra were taken on a MIR (8000−400 cm^{-1}) spectrometer as solid films by slow evaporation of the solvent using the ATR (atenuated total reflectance) technique. MS spectra (HRMS)

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were acquired on a Fourier transform ion cyclone resonance mass spectrometer (4.7 T). Alkynyl Fischer carbene complexes **1a–g**[50] and tropothione **2**[28,30] were prepared following the described procedures.

General Procedure for Cycloaddition Reactions. To a solution of the corresponding alkynyl carbene **1a–g** (0.5 mmol) in CH_2Cl_2 (5 mL) at room temperature was added a solution of tropothione **2** (0.5 mmol) in CH_2Cl_2 dropwise. The mixture was stirred at room temperature for 5–10 min. The solvent was then removed in vacuo and the crude mixture purified by flash column chromatography to give pure carbene complexes **3a–g**. Compound **3h** was prepared from biscarbene **1h** following the same procedure for monocarbenes but using 2 equiv of the tropothione **2**.

3a: red oil (182 mg, 77%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.32 (m, 3H), 7.26–7.20 (m, 2H), 6.63 (dd, J = 11.0, 6.1 Hz, 1H), 6.52 (dd, J = 11.0, 5.6 Hz, 1H), 6.24 (dd, J = 6.2, 2.2 Hz, 1H), 6.16 (dd, J = 9.3, 5.7 Hz, 1H), 4.94 (dd, J = 9.3, 4.7 Hz, 1H), 4.82–4.71 (m, 2H), 4.60–4.58 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 340.9, 222.5, 214.9, 147.5, 134.9, 134.3, 133.9, 130.6, 129.2, 129.1, 128.8, 128.5, 125.8, 116.1, 115.0, 77.1, 59.7, 12.9; IR (ATR) ν 2058, 1938 cm^{-1}; HRMS (FTMS) m/z calcd for $C_{23}H_{16}CrO_6S$ [M + H] = 473.0151, found 473.0156.

3b: dark red oil (208 mg, 69%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.34 (m, 5H), 6.63 (dd, J = 10.9, 6.0 Hz, 1H), 6.53 (dd, J = 10.9, 5.6 Hz, 1H), 6.24 (dd, J = 6.1, 2.2 Hz, 1H), 6.18 (dd, J = 9.4, 5.6 Hz, 1H), 5.01 (dd, J = 9.3, 4.7 Hz, 1H), 4.80–4.69 (m, 1H), 4.59–4.49 (m, 2H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 310.5, 201.9, 196.4, 149.9, 137.7, 134.2, 130.5, 129.2, 129.0, 128.8, 128.4, 125.8, 116.1, 115.4, 79.0, 58.5, 13.9; IR (ATR) ν 2066, 1917 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{16}WO_6S$ [M − H] = 603.0104, found 603.0105.

3c: dark red oil (267 mg, 92%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61 (dd, J = 11.1, 6.3 Hz, 1H), 6.46 (dd, J = 11.1, 5.7 Hz, 1H), 6.22 (dd, J = 6.2, 2.1 Hz, 1H), 6.11 (dd, J = 9.3, 6.1, Hz, 1H), 4.79–4.74 (m, 2H), 4.61 (s, 2H), 4.37 − 4.20 (m, 9H), 1.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 343.0, 223.0, 215.5, 134.6, 131.8, 130.3, 128.2, 125.6, 115.1, 114.7, 76.2, 70.4, 70.0, 69.7, 67.2, 60.7, 14.8; IR (ATR) ν 2057, 1931 cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{20}CrFeO_6S$ [M − H] = 578.9652, found 578.9652.

3d: red solid (75 mg, 32%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (dd, J = 11.0, 6.2 Hz, 1H), 6.46 (dd, J = 11.0, 5.8 Hz, 1H), 6.19 (dd, J = 6.2, 2.2 Hz, 1H), 6.11 (dd, J = 9.0, 5.8 Hz, 1H), 5.44–5.33 (m, 1H), 5.11–5.01 (m, 1H), 4.77–4.69 (m, 2H), 1.73 (t, J = 7.1 Hz, 3H), 0.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 340.4, 223.4, 216.1, 160.0, 139.4, 136.6, 130.4, 128.3, 125.2, 114.8, 113.4, 77.4, 61.0, 15.3, 0.1; IR (ATR) ν 2058, 1931 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{20}CrO_6SSi$ [M + H] = 469.0239, found 469.0239.

3e: dark orange oil (113 mg, 50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (dd, J = 11.2, 6.4 Hz, 1H), 6.46 (dd, J = 10.9, 5.7 Hz, 1H), 6.18 (dd, J = 6.2, 2.2 Hz, 1H), 6.09 (dd, J = 8.9, 5.9 Hz, 1H), 5.15 − 5.04 (m, 2H), 4.81 (dd, J = 9.3, 4.6 Hz, 1H), 4.52 (s, 1H), 2.43–2.15 (m, 2H), 1.72 (t, J = 7.1 Hz, 3H), 1.50 − 1.38 (m, 2H), 1.38 − 1.27 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 342.4, 223.3, 213.9, 147.4, 137.0, 134.1, 130.5, 128.6, 125.3, 116.0, 115.3, 77.2, 59.4, 31.6, 29.6, 22.5, 15.5, 13.9; IR (ATR) ν 2058, 1931 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{20}CrO_6S$ [M − H] = 451.0313, found 451.0313.

3f: red oil (236 mg, 95%); ^{1}H NMR (700 MHz, acetone-d_6) δ 7.56 (d, J = 7.7 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.39 (s, 1H), 7.35 (d, J = 7.7 Hz, 1H), 6.68 (dd, J = 11.1, 6.3 Hz, 1H), 6.57 (dd, J = 11.1, 5.7 Hz, 1H), 6.37 (dd, J = 6.2, 1.8 Hz, 1H), 6.22 (dd, J = 8.9, 6.0 Hz, 1H), 5.04 (dd, J = 9.2, 4.7 Hz, 2H), 5.01–4.97 (m, 1H), 4.59 (s, 1H), 3.78 (s, 1H), 1.38 (t, J = 7.0 Hz, 3H); ^{13}C NMR (176 MHz, acetone-d_6) δ 343.3, 225.3, 217.4, 135.5, 134.8, 134.2, 134.0, 133.1, 132.0, 131.0, 130.7, 130.3, 127.4, 124.8, 117.9, 116.3, 83.9, 81.4, 79.8, 61.5, 15.6; IR (ATR) ν 2059, 1934 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{16}CrO_6S$ [M + H] = 497.0156, found 497.0156.

3h: dark orange oil (1:1 mixture of isomers, 290 mg, 67%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.13 (m, 4H), 6.65 (dd, J = 11.0, 6.5 Hz, 2H), 6.54 (dd, J = 11.0, 5.4 Hz, 2H), 6.25–6.24 (m, 2H), 6.20–6.16 (m, 2H), 4.97–4.77 (m, 6H), 4.55 (s, 2H), 1.34 (t, J = 6.94 Hz, 3H), 1.29 (t, J = 6.94 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 342.9, 342.5, 223.6, 216.0, 216.0, 148.6, 148.4, 134.8, 134.4, 133.8, 133.7, 133.6, 133.3, 130.7,129.4, 129.2, 129.0, 128.6, 128.4, 126.0, 125.9, 116.4, 116.3, 115.1, 115.0, 77.7, 77.5, 77.4, 66.1, 60.0, 15.1, 145.0; IR (ATR) ν 2095, 1931 cm^{-1}; HRMS (ESI) m/z calcd for $C_{40}H_{26}Cr_2O_{12}S_2$ [M + H] = 866.9760, found 866.9762.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of isolated compounds, crystallographic data for compound **3c**, computational details, Cartesian coordinates (in Å), and free energies of all the stationary points discussed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: (I.F.) israel@quim.ucm.es, (M.A.S.) sierraor@quim.ucm.es.

Notes

The authors declare no competing financial interest.

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(32) We also computed the corresponding reaction profile for the reaction of tropotione and methyl 3-phenylpropiolate. As expected, only the concerted pathway was located on the potential energy surface. The computed high activation barrier ($\Delta G^{\ddagger}_{298}$ = 28.6 kcal/mol) of this process justifies why the reaction of **1g** and **2** does not occur at room temperature. In view of this barrier energy, the process might be feasible at higher temperatures. However, tropothione **2** is reported to be thermally unstable. See: Machiguchi, T. *Tetrahedron* **1995**, *51*, 1133.
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Cycloaddition Reactions

The Photochemical Reaction of Vinylaziridines and Vinylazetidines with Chromium(0) and Molybdenum(0) (Fischer) Carbene Complexes

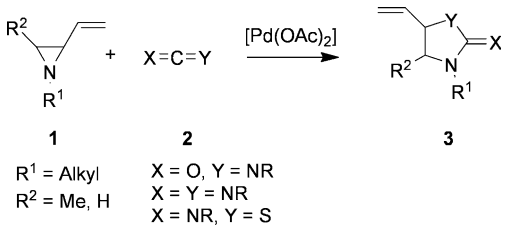
Alexandra R. Rivero, Israel Fernández,* and Miguel A. Sierra*[a]

Abstract: The [5+2] and [6+2] cycloaddition reactions of vinylaziridines and vinylazetidines with ketenes generated photochemically from chromium(0) and molybdenum(0) Fischer carbene complexes have been investigated. These processes constitute a straightforward and efficient route to azepanones and azocinones, respectively. The peculiar electronic properties of the metalated ketenes allow for the introduction of electron-rich substituents in the final cycloadducts, a difficult task using conventional organic chemistry procedures. The versatility of the process is demonstrated by using Cr^0 Fischer bis(carbene) complexes as metalated bis(ketene) precursors. These species produce tethered bis(azepanone)s in a single step under mild reaction conditions. Density functional theory calculations point to a stepwise reaction pathway through the initial nucleophilic attack of the nitrogen atom of the aziridine on the metalated ketene, followed by ring closure of the zwitterionic intermediate formed.

Introduction

The ring-opening reaction of vinyl-substituted three- and four-membered nitrogen heterocycles with cumulenes has been little studied despite their potential to produce medium-sized rings in an easy and efficient manner.[1] This contrasts with the use of the strained nature of these cyclic amines to prepare other classes of compounds in reactions involving the cleavage of the C–N bond.[2] For example, Alper and co-workers reported the first examples of a reaction involving 2-vinylaziridines and isocyanates, isothiocyanates, and carbodiimides.[3] Thus, the reactions of a series of vinylaziridines **1** with cumulenes **2** under Pd catalysis yielded the corresponding five-membered heterocycles **3** in acceptable to excellent yields (Scheme 1). Aggarwal and co-workers have reported a similar transformation[4] in the Pd-catalyzed insertion of CO_2 into a vinylaziridine. However, it should be noted that in both cases the double bond is not incorporated into the final five-membered ring.[5]

The simultaneous participation of the double bond of a vinylaziridine with the concomitant three-membered ring opening has been used to develop synthetically useful routes to the azepane skeleton. For instance, the reaction of these substrates with electron-poor alkynes leads to a seven-membered ring through a divinylcyclopropane–cycloheptadiene-type rearrangement.[6] Moreover, phenyl isothiocyanate and very recently sulfonyl isocyanates have been employed as C2 units in formal [5+2] cycloaddition reactions with 2-vinylaziridines to smoothly produce 1,3-thiazepine derivates[7] and various cyclic ureas,[8] respectively (Scheme 2a and b). It is remarkable that in these cases the cycloaddition processes occurred at 0 °C and in the absence of metal catalysts. A similar methodology was previously reported by the same authors in the ring-expansion reaction of vinylazetidines with electron-deficient isocyanates (in a formal [6+2] cycloaddition reaction).[9]



Scheme 1. The reactions of vinylaziridines and cumulenes under Pd catalysis.

Despite the efficiency of the aforementioned processes, the cycloaddition reaction with vinylaziridines or vinylazetidines is restricted to electron-deficient cumulenes, limiting the scope of this synthetically valuable transformation. Therefore, the use of substrates with electron-donor substituents in their structures is an unfulfilled challenge. At this point, we turned our attention to the ability of Group 6 Cr^0 and Mo^0 Fischer-type carbene complexes to form electron-rich metalated ketenes when irradiated in the presence of visible light.[10] These species are able to produce a wide variety of reaction products in the presence of nucleophiles, avoiding the main shortcomings

[a] A. R. Rivero, Dr. I. Fernández, Prof. Dr. M. A. Sierra
Departamento de Química Orgánica, Facultad de Química
Universidad Complutense, 28040 Madrid (Spain)
Fax: (+34) 913944310
E-mail: israel@quim.ucm.es
sierraor@quim.ucm.es

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