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Asymmetric Organocatalytic Cascade Reactions

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A mi familia

A mis amigos

A Arkaitz

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Resumen

En la presente memoria se recoge el trabajo de investigación enmarcado en el empleo de aminas secundarias quirales como organocatalizadores para el diseño de reacciones en cascada con el fin de obtener compuestos de interés con elevado rendimiento y control estereoquímico. De esta manera, en primer lugar se ha puesto a punto una metodología para la síntesis de furanos mediante una reacción en cascada aminocatalítica oxa-Michael/reacción aldólica/hemiacetalización entre aldehídos α,β-insaturados y dihidroxiacetona combinando los modos de activación iminio y enamina. Asimismo, se ha demostrado la posibilidad de llevar a cabo transformaciones eficientes de manera selectiva sobre los aductos obtenidos permitiendo obtener un amplio abanico de compuestos, lo que pone de manifiesto el potencial de esta metodología para la síntesis enantioselectiva de diversos *building blocks* quirales de interés en síntesis orgánica. La extensión de dicha estrategia al uso de α-aminoacetofenona ha permitido obtener distintas γ-lactamas enantioenriquecidas con excelentes rendimientos.

En segundo lugar, se ha puesto a punto una metodología enfocada a la síntesis asimétrica de ciclobutanos sustituidos mediante una reacción formal de cicloadición [2+2] entre aldehídos α,β-insaturados enolizables y nitroalquenos α-hidroximetil susutituidos. En este caso, se ha empleado un sistema catalítico compuesto por un derivado de difenilprolinol y una tiourea aquiral, haciendo así uso de la aminocatálisis y la catálisis por formación de enlaces de hidrógeno. De este modo, se ha demostrado que la cooperación de ambos modos de activación permite el desarrollo de dicha transformación sintética con elevados rendimientos y excelente estereocontrol.

Abstract

In this dissertation, our work on the study of chiral secondary amines as promoters in enantioselective organocatalytic cascade reactions towards the asymmetric synthesis of different substituted hetero- and carbocycles is presented.

In this sense, we have developed an efficient methodology for the construction of hexahydrofuro[3,4-*c*]furans containing four stereocenters by means of an amine catalyzed oxa-Michael/aldol/hemiacetalization cascade reaction by reacting different α,β-unsaturated aldehydes with dihydroxyacetone under iminium/enamine catalysis. Remarkably, a high pK_a oxygen pro-nucleophile has been employed as functionalized Michael donor to initiate the conjugate process, which represents an important feature of this transformation. This methodology has led to the formation of polysubstituted furofuranes in excellent yields and diastereo- and enantioselectivities. Moreover, different related compounds can be accessed through the selective manipulation of the functionalities present within the obtained adducts emphasising the potential of this methodology for the synthesis of useful chiral building blocks. Additionally, this strategy has been extended to the use of *N*-protected-α-aminoacetophenone for the synthesis of γ-lactams through a Michael/hemiaminalization cascade sequence.

On the other hand, we have set up an enantioselective formal [2+2] cycloaddition reaction between enolizable α,β-unsaturated aldehydes and nitroalkenes towards the synthesis of highly substituted cyclobutanes. In this particular case, the combination of an α,α-diphenylprolinol derivative and an achiral thiourea was employed as the catalytic system, which was shown as a powerful activation strategy for the development of this reaction, affording products in high yields and with excellent stereocontrol.

Laburpena

Doktorego tesi honetan, estrategia organokatalitikoak aukeratu dira zenbait interes handiko konposatuen sintesi asimetrikoa aurrera eramateko. Zentzu honetan, kaskada erreakzioetan oinarritutako prozesuak diseinatu dira aminokatalizatzaileek eskaintzen duten aktibazio modu ezberdinak erabiliz etekin eta kontrol estereokimiko altuak lortuz.

Lehenik, enantioaberastutako furofurano poliordezkatuak lortzeko sintesi aminokatalitikoa ikertu da dihidroxiazetona eta aldehido α,β-asegabetuak erabiliz. Kasu honetan, iminio eta enamina aktibazio motak konbinatu egin dira oxa-Michael/aldolika erreakzioa/hemiazetalizazioa kaskada prozesu enantioselektibo eta eraginkor bat aurrera eramanez. Era berean, lortutako produktuen aldakortasun sintetikoak zenbait eraldaketa kimiko burutzea ahalbidetu du metodologia honen garrantzi sintetikoa erakutsiz. Halaber, garatutako estrategia aminokatalitikoa zabaltzeko asmoz, α-aminoazetofenonaren erabilera frogatu da γ-laktama ezberdinak lortuz. Aldi berean, sintetizatutako heteroziklo hauek konposatu 1,4-dikarboniliko enantioaberats ezberdinetan eraldatu egin dira.

Bestalde, [2+2] zikloadizio organokatalitiko formala aztertu da katalisi kobalente eta ez kobalentea erabiliz. Horretarako, aminokatalizatzaile eta tioureaz osatutako sistema katalitikoa aukeratu da, bi aktibazio modu hauen kooperazioak etekin eta kontrol estereokimiko altuak lortzea ahalbideratzen duela frogatuz.

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1

1

Introducción.

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2. Reacciones en cascada organocatalíticas iniciadas por adiciones conjugadas.

2.1. Mecanismos de activación organocatalíticos en reacciones en cascada iniciadas por adiciones conjugadas.

3. Antecedentes del grupo.

4. Objetivos generales.

1. ORGANOCATÁLISIS.

La organocatálisis ha resultado ser una metodología extensamente estudiada en el campo de la catálisis asimétrica. Esta aproximación consiste en la aceleración de una reacción química mediante el empleo de una cantidad subestequiométrica de un compuesto orgánico quiral de bajo peso molecular y que no contiene átomos metálicos en su estructura.[1] No obstante, cabe mencionar que ciertas reacciones catalizadas por compuestos metálicos están consideradas por algunos autores como transformaciones organocatalíticas, argumentando que el átomo metálico no participa directamente en el ciclo catalítico.[2]

A lo largo de esta última década, los procesos organocatalíticos están demostrando ser transformaciones eficientes y valiosas para el químico sintético, alcanzando así un protagonismo excepcional, tal y como lo indican el elevado número de publicaciones relacionadas con esta área de investigación.[3] Este repentino interés por la organocatálisis ha surgido principalmente como consecuencia de la simplicidad operacional asociada a su desarrollo experimental, ya que no requiere en muchos casos ni el empleo de atmófera inerte, ni de disolventes anhidros. Tanto es así que en algunos casos la presencia de agua resulta beneficioso en términos de velocidad y selectividad de la reacción.[4] Otra ventaja que presenta esta metodología atiende al hecho de que los organocatalizadores son

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[1] Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.

[2] (a) Fu, G. C. *Acc. Chem. Res.* **2006**, *39*, 853; (b) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542.

[3] (a) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138. (b) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed*. **2008**, *47*, 4638. (c) Número especial sobre organocatálisis: *Chem. Rev.* **2007**, *107*(12). (d) List, B.; Yang, J.-W. *Science* **2006**, *313*, 1584.

[4] Gruttadauria, M.; Gialcalone, F.; Noto, R. *Adv. Synth. Catal*. **2009**, *351*, 33.

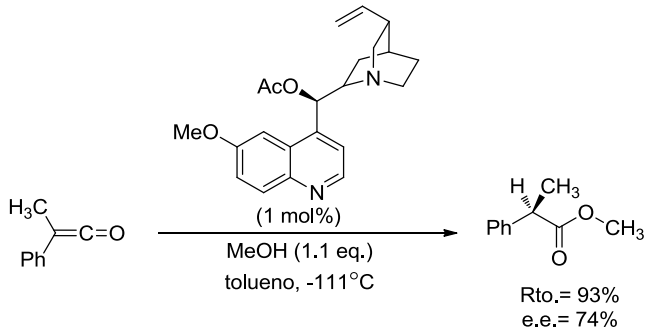
generalmente más baratos y estables que sus equivalentes metálicos empleados como catalizadores en reacciones similares, estando además disponibles comercialmente en ambas formas enantioméricas en la mayoría de los casos. Asimismo, disponer de metodologías para obtener formulaciones químicas en los que la presencia de trazas metálicas es inadmisible, tales como fármacos o productos agroquímicos, confiere un valor añadido a esta estrategia sintética. Sin embargo, a pesar de todas estas ventajas enumeradas, la organocatálisis todavía presenta importantes inconvenientes. Por un lado, las reacciones organocatalíticas requieren típicamente el empleo de altas cargas de catalizador y largos tiempos de reacción, lo que es una limitación importante, especialmente a la hora de aplicar esta metodología a la producción industrial a gran escala. Por otro lado, su aplicación en síntesis total de moléculas complejas permanece aún poco estudiada, aunque se ha observado una tendencia creciente por esta línea de investigación en los últimos años.[5] Sin embargo, a pesar de todo ello, la organocatálisis ha surgido como una nueva rama de la catálisis asimétrica que complementa a las metodologías ya existentes, aunque todavía siguen siendo la catálisis metálica y/o enzimática las únicas herramientas disponibles para abordar ciertas cuestiones sintéticas.

Sin embargo, a pesar de ser un campo de investigación de primera línea en la actualidad, las raíces de la organocatálisis se remontan al año 1928 cuando el químico Wolfgang Langebeck, publicó un artículo sobre "las analogías existentes entre la acción de los enzimas y determinadas sustancias orgánicas",[6] acuñando cuatro años más tarde el término "catálisis orgánica". La primera reacción organocatalítica asimétrica fue publicada por Breding y Fiske en 1912, donde observaron la aceleración que experimentaba la adición de HCN a benzaldehído

[5] Marqués-López, E.; Herrera, R. P.; Christmann, M. *Nat. Prod. Rep*. **2010**, *27*, 1138.

[6] (a) Langenbeck, W. *Angew. Chem*. **1928**, *41*, 740. (b) Langenbeck, W. *Angew. Chem*. **1932**, *45*, 97.

mediante el empleo de cantidades subestequiométricas de alcaloides como quinina y quinidina; aunque con estos primeros resultados se alcanzaron rendimientos ópticos en torno al 10%.[7] En 1960 Pracejus y colaboradores publicaron el primer ejemplo de reacción organocatalítica asimétrica en la que obtuvieron una enantioselectividad relevante cuando estudiaron la reacción de adición de metanol a una cetena proquiral catalizada por un alcaloide de cinchona (Esquema 1.1).[8]



Esquema 1.1

Un progreso en este campo de significativa importancia tuvo lugar en los años setenta cuando se descubrió el carácter inductor del aminoácido natural L-prolina en reacciones aldólicas intramoleculares. Así, a principios de dicha década dos grupos industriales en Hoffmann-La Roche[9] y en Schering AG[10] dieron a conocer la primera reacción organocatalítica con resultados de importancia sintética con respecto a la enantioselectividad de la reacción, conocida hoy en día como

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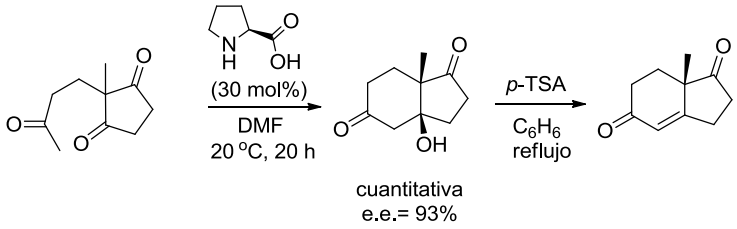
[7] Breding, G.; Fiske, W. S. *Biochem. Z*. **1912**, 7.

[8] Pracejus, H. *Liebigs Ann. Chem*. **1960**, 634, 9.

[9] (a) Hajos, Z. G.; Parrish, D. R. *Asymmetric Synthesis of Optically Active Polycyclic Organic Compounds*. German Patent DE 2102623, 1971. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

[10] (a) Eder, U.; Sauer, G.; Wiechert, R. *Optically Active 1,5-Indanone and 1,6-Napthalenedione*. German Patent DE 2014757, 1971. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed. Engl*. **1971**, *10*, 496.

reacción de Hajos-Parrish-Eder-Sauer-Wiechert. Esta reacción permitía obtener de manera eficaz productos de interés, pudiendo utilizarlos como intermedios sintéticos enantioenriquecidos para la síntesis de productos naturales como, por ejemplo, ciertos esteroides y terpenos (Esquema 1.2).[11]



Esquema 1.2

Otras contribuciones importantes a destacar en la historia de la organocatálisis tuvieron lugar entre los años 1980 y 1990, tales como la alquilación enantioselectiva de enolatos empleando sales de amonio cuaternarias derivadas de alcaloides de tipo cinchona y basada en el concepto de catálisis por transferencia de fase[12] o el empleo de ácidos quirales de Brønsted (tioureas) en las reacciones de hidrocianación asimétrica de aldehídos e iminas desarrolladas por Inoue[13] y Jacobsen,[14] respectivamente.

Resulta sorprendente que, a pesar del interés científico que presenta esta metodología, la organocatálisis fuera ignorada durante casi tres décadas, siendo las

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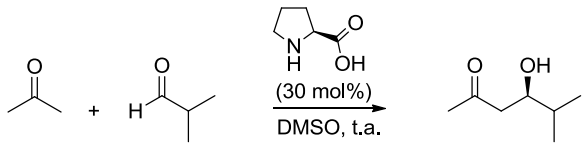
[11] Como ejemplos, véase: (a) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Grandi, M. J. D. *J. Am. Chem. Soc*. **1996**, *118*, 2843. (b) Rychnovsky, S. D.; Mickus, D. E. *J. Org. Chem.* **1992**, *57*, 2732.

[12] (a) Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem*. **1986**, *51*, 4710. (b) Dolling, U.-H.; Davis, P.; Grabowski, J. J. E. *J. Am. Chem. Soc*. **1984**, *106*, 446.

[13] Oku, J.; Inoue, S. *J. Chem. Soc. Chem. Commun*. **1981**, 229.

[14] (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) See also: Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2002**, *124*, 10012.

reacciones organocatalíticas consideradas por la comunidad científica como transformaciones ineficaces y de corto alcance. En el año 2000 se produjo un punto de inflexión a partir del cual se empezaron a establecer las bases teóricas de este campo de investigación. Por un lado, List, Lerner y Barbas III publicaron la conocida reacción aldólica intermolecular enantioselectiva catalizada por L-prolina como culminación de toda una investigación cuyos comienzos datan de 1990 en la que se observó que ciertos anticuerpos catalizaban reacciones aldólicas mimetizando el centro activo de las aldolasas de tipo I.[15] En un intento de esclarecer el mecanismo de este tipo de reacciones y basándose en la evidencia de un intermedio de tipo enamina participando en la reacción, llevaron a cabo estudios con modelos simplificados empleando el simple aminoácido L-prolina con el fin de mimetizar el centro activo de las enzimas. Así, demostraron que dicha molécula era capaz de catalizar la síntesis de aldoles a partir de acetona y diferentes aldehídos mediante la formación de un intermedio de tipo enamina generado por condensación del aminoácido y la cetona. Dicho intermedio activo podía actuar como nucleófilo frente a un aldehído, logrando así obtener el correspondiente aldol con buen rendimiento y buena enantioselectividad (Esquema 1.3).



Rto.= 97%
e.e.= 96%

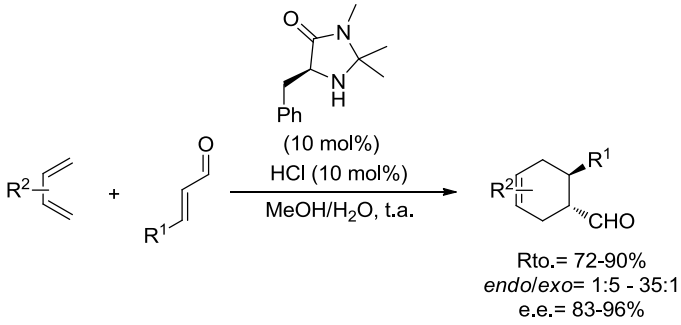
Esquema 1.3

Este trabajo no sólo puso de manifiesto la posibilidad de extender la reacción de Hajos-Parrish-Eder-Sauer-Wiechert a otro tipo de transformaciones con mayor

[15] List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

grado de aplicabilidad, sino también que moléculas orgánicas de pequeño tamaño podían actuar como catalizadores de igual forma que moléculas mayores (enzimas) siguiendo mecanismos similares.

Poco tiempo después, MacMillan desarrolló la primera reacción de cicloadición Diels-Alder enantioselectiva catalizada por una sal quiral de imidazolinio, acuñando así el término "organocatálisis" a partir del antiguo concepto de catálisis orgánica.[16] El catalizador, en este caso, activa el compuesto carbonílico α,β-insaturado mediante la formación reversible de una sal de iminio (Esquema 1.4). Éste ejerce su papel promotor de la reacción como consecuencia de una reorganización de la densidad electrónica del sustrato α,β-insaturado, lo que se traduce en una disminución de la energía del orbital LUMO del sistema, permitiendo así un mejor solapamiento orbitálico en la reacción de Diels-Alder y por tanto, emulando el mecanismo de activación que ejercen los ácidos de Lewis sobre sistemas carbonílicos α,β-insaturados.



Esquema 1.4

A partir de estos trabajos pioneros, como bien se ha comentado anteriormente, el incremento en las actividades relacionadas con este campo ha sido

[16] Ahrendt, K. A.; Borths, J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2000**, *122*, 4243.

tal, que a llegado a despuntar como una de las ramas más productivas de la síntesis asimétrica, no sólo en el ámbito académico, sino también a nivel industrial.[17]

Otra dirección en las investigaciones de este campo trata de buscar alternativas organocatalíticas aún más fieles a los principios de la química verde a fin de que resulten más atractivas y factibles desde un punto de vista industrial y medioambiental. Así, la búsqueda y desarrollo de estrategias más sostenibles está a la orden del día en esta rama de la química empleando, por ejemplo, condiciones de reacción más favorables (reacciones en agua[18] o en líquidos iónicos[19]), empleando catalizadores recuperables,[20] mediante el diseño de reacciones en cascada y/o multicomponente[21] o empleando alternativas energéticamente más convenientes como microondas o ultrasonidos.[22] Del mismo modo, merece la pena destacar las investigaciones y los resultados satisfactorios que se están obteniendo en torno a la disminución de la carga de organocatalizador. En este sentido, la organocatálisis ha sido razonablemente criticada por la elevada cantidad de catalizador necesaria en comparación con otras versiones basadas en la catálisis metálica. No obstante, la disminución de cantidad de catalizador hasta un 2-5% en algunos casos (siendo inicialmente de un 20-30%) resulta prometedor y muestra las posibilidades que quedan todavía por explorar.[23]

Por todo ello, no es de extrañar que la búsqueda continua de nuevos catalizadores, así como de nuevas transformaciones susceptibles de ser realizadas

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17 Busacca, C. A.; Daniel, R. F.; Song, J. J.; Senanayake, C. H. *Adv. Synth. Catal*. **2011**, *353*, 1825.

18 (a) Mase, N.; Barbas III, C. F. *Org. Biomol. Chem*. **2010**, *8*, 4043. (b) Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal*. **2009**, *351*, 33.

19 Domínguez de María, P. *Angew. Chem. Int. Ed*. **2008**, *47*, 6960.

20 (a) Kristensen, T. E.; Hansen, T. *Eur. J. Org. Chem*. **2010**, 3179. (b) Gruttadauria, M.; Giacalone, F.; Noto, R. *Chem. Soc. Rev*. **2008**, *37*, 1666.

21 Guillena, G.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693.

22 Hernández, J. G.; Juaristi, E. *Chem. Commun*. **2012**, *48*, 5396.

23 Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R. *Chem. Soc. Rev*. **2012**, *41*, 2406.

empleando la organocatálisis como herramienta para alcanzar control estereoquímico se haya convertido en uno de los mayores retos en la exploración de nuevas metodologías sintéticas. Asimismo, es probable que el vertiginoso interés por la organocatálisis en estos últimos años haya surgido en gran medida por la clara identificación de los modelos genéricos de activación, inducción y reactividad que llevan a cabo los catalizadores. Una vez establecido un modelo genérico, es relativamente sencillo emplearlo como plantilla en nuevas transformaciones, convirtiendose así la organocatálisis en un campo de exploración en continuo crecimiento.

En vista de las numerosas transformaciones organocatalíticas descritas hasta la fecha, resulta útil establecer una clasificación de los diferentes modos de activación. Una posible organización atiende al tipo de interacción que se establece entre el catalizador y el sustrato durante el mecanismo de reacción, diferenciándose así dos grandes bloques: a) aquellas en las que se forman aductos covalentes entre el catalizador y el sustrato durante el ciclo catalítico (catálisis covalente) y, por otro lado, b) aquellas en las que el catalizador activa el o los sustratos mediante otro tipo de interacciones más débiles (catálisis no covalente) como enlaces por formación de puentes de hidrógeno o formación de pares iónicos de contacto. En la Figura 1.1 se muestra de manera esquemática ejemplos representativos de los distintos tipos de activación que pueden desempeñar algunos de los organocatalizadores más comúnmente empleados, los cuales se encuentran agrupados según el criterio de clasificación mencionado con anterioridad.

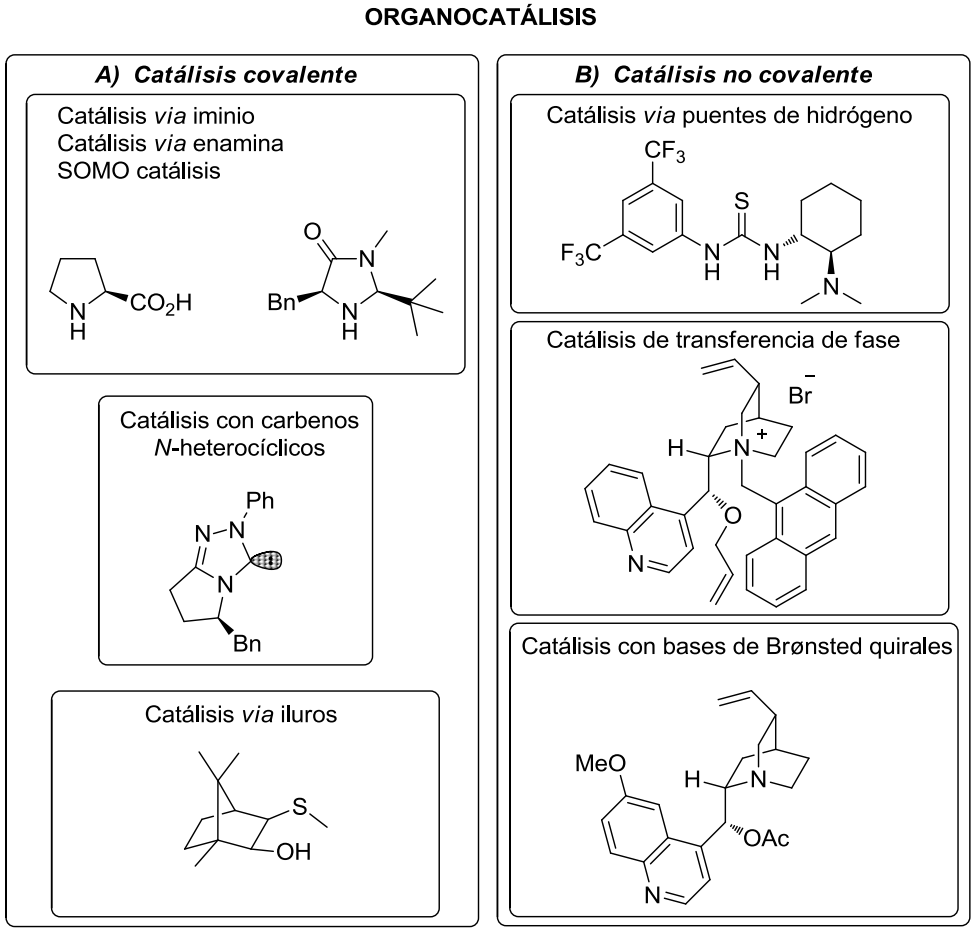

Figura 1.1

La catálisis covalente, en la cual el catalizador y un sustrato dado forman un intermedio unido covalentemente, se encuentra entre las más estudiadas y es una de las más empleadas hasta la fecha. Dicho modo de activación requiere que las interacciones catalizador-sustrato sean reacciones químicas reversibles con el fin de garantizar la activación de los reactivos, así como el *turnover* del catalizador. Así,

en catálisis covalente, dada la fuerza de unión catalizador-sustrato, el inductor quiral proporciona generalmente muy buen estereocontrol. Sin embargo, por esa misma razón el *turnover* se ve negativamente afectado, siendo necesario habitualmente, emplear una carga de catalizador elevada, así como tiempos de reacción más largos. Las aminas primarias o secundarias (aminocatalizadores) son quizá los organocatalizadores más ampliamente utilizados de este tipo de catálisis, las cuales activan compuestos carbonílicos mediante la formación de especies azometínicas por condensación: enamina[24], ion iminio[25], dienamina[26] y trienamina[27] o un radical-ion iminio (*SOMO catalysis*).[28] Otro grupo importante de organocatalizadores de este tipo son los carbenos *N*-heterocíclicos que ejercen su papel mediante la activación de un sustrato carbonílico a través de la formación del

[24] Algunas revisiones sobre catálisis *via* enamina: (a) Kano, T.; Maruoka, K. *Chem. Commun*. **2008**, 5465. (b) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun*. **2007**, 3123. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev*. **2007**, 107, 5471.

[25] Algunas revisiones sobre catálisis *via* iminio: (a) Córdova, A. *Catalytic Asymmetric Conjugate Reactions,* Wiley, **2010**. (b) Melchiorre, P.; Giuseppe, B. *Synlett* **2008**, 1759. (b) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (c) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79.

[26] Algunas revisiones sobre dienaminocatálisis: (a) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem*. **2012**, 865. (b) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun*. **2011**, *47*, 632. (c) Bertelsen, S.; Marigo, M.; Brandes, S.; Diner, P.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2006**, *128*, 12973.

[27] Como ejemplos de catálisis *via* trienamina véase: (a) Xiong, X.-F.; Zhou, Q.; G, J.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. *Angew. Chem. Int. Ed*. **2012**, *51*, 4401. (b) Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-Y.; Jørgensen K. A *J. Am. Chem. Soc*. **2011**, *133*, 5053. (c) Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q.; Chen, Y.-C. *Angew. Chem. Int. Ed*. **2011**, *50*, 1. (d) Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q., Chen, P.-Q.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2011**, *50*, 8638. (e) Jiang, H.; Gschwend, B.; Albrecht, L.; Hansen, S. G.; Jørgensen, K. A. *Chem. Eur. J*. **2011**, *17*, 9032.

[28] Como ejemplos de *SOMO catalysis* véase:. (a) Gentilli, P.; Pedetti, S. *Chem. Commun*. **2012**, *48*, 5358. (b) Pham, P. V.; Ashton, K.; MacMillan, D. W. C. *Chem. Sci*. **2011**, *2*, 1470. (c) Jui, N. T.; Lee, E. C. Y.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2010**, *132*, 10015. (d) Melchiorre, P. *Angew. Chem. Int. Ed*. **2009**, *48*, 1360. (e) Renaud, P.; Leong, P. *Science*, **2008**, *322*, 55. (f) Bertelsen, S.; Nielsen, M.; Jørgensen K. A. *Angew. Chem. Int. Ed*. **2007**, *46*, 7356.

denominado intermedio de Breslow.[29] Una de las características de este último grupo de catalizadores es la oportunidad de invertir la reactividad típica de los compuestos carbonílicos mediante un proceso de *umpolung*, aumentándose así la gama de posibilidades en lo que a reactividad y aplicabilidad sintética se refiere.

Dentro de la categoría de catálisis no covalente destaca aquel subgrupo de reacciones en las que el catalizador actúa *via* formación de enlaces de hidrógeno.[30] Este tipo de organocatalizadores pueden desempeñar su función gracias a que presentan en su estructura grupos funcionales con hidrógenos ácidos que son capaces de activar sustratos con grupos funcionales que contengan heteroátomos con pares de electrones sin compartir, disminuyendo la densidad electrónica del sistema a través del establecimiento de una red de enlaces de hidrógeno entre catalizador y sustrato y, por lo tanto, preparándolo para un ataque nucleófilo. Otras metodologías organocatalíticas importantes englobadas en este bloque son la catálisis por formación de pares iónicos quirales dentro de la cual se encuentra la

[29] Algunas revisiones sobre organocatálisis *via* carbenos *N*-heterocíclicos: (a) Grossmann, A.; Enders, D. *Angew. Chem. Int. Ed*. **2012**, *51*, 314. (b) Enders, D; Niemeier, O.; Henseler, A. *Chem. Rev*. **2007**, *107*, 5606. (c) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988. (d) Enders, D.; Balensiefer, T. *Acc. Chem. Res*. **2004**, *37*, 534.

[30] Algunas revisiones y ejemplos sobre catálisis por formación de enlaces por puente de hidrógeno: (a) Huang, Y.-B.; Yi, W.-B.; Cai, C. *Top Curr. Chem*. **2012**, *308*, 191. (b) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J*. **2011**, *17*, 6890. (c) Connon, S. J. *Synlett* **2009**, 354. (b) Yu, X. H.; Wang, W. *Chem. Asian. J*. **2008**, *3*, 516. (d) Connon, S. J. *Chem. Commun*. **2008**, 2499. (e) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev*. **2007**, *107*, 5713. (f) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed*. **2006**, *45*, 1520. (g) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal*. **2006**, *348*, 999. (h) Schreiner, P. R. *Chem. Soc. Rev*. **2003**, *32*, 289.

denominada catálisis por transferencia de fase (*PTC*)[31] y la catálisis con bases de Brønsted quirales para la activación de nucleófilos por desprotonación.[32]

[31] Algunas revisiones sobre catálisis por transferencia de fase: (a) Jew. S.; Park, H. *Chem. Commun*. **2009**, 7090; (b) Hashimoto, T.; Maruoka, K. *Chem. Rev*. **2007**, *107*, 5656. (c) Ooi, T.; Maruoka, K. *Aldrichim. Acta* **2007**, *40*, 77. (d) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed*. **2007**, *46*, 4222. (e) O'Donnell, M. J. *Acc. Chem. Res*. **2004**, *37*, 506. (f) Lygo, B.; Andrews, B. *Acc. Chem. Res*. **2004**, *37*, 518. (g) Maruoka, K.; Ooi, T. *Chem. Rev*. **2003**, *103*, 3013.

[32] Como ejemplos de catálisis con aminas terciarias quirales vease: (a) Palomo, C.; Oiarbide, M.; Lopez, R. *Chem Soc. Rev*. **2009**, *38*, 632. (b) Shen, J.; Tan, C.-H. *Org. Biomol. Chem*. **2008**, *6*, 3229.

2. REACCIONES EN CASCADA ORGANOCATALÍTICAS INICIADAS POR ADICIONES CONJUGADAS.

A la hora de diseñar un proceso sintético para alcanzar una molécula objetivo, aunque el procedimiento habitual implique la formación de nuevos enlaces mediante sucesivas reacciones consecutivas a partir de los sustratos adecuados, es mucho más eficiente pensar en un proceso en el cual se realicen las transformaciones pertinentes en una única reacción en procesos de tipo dominó o cascada. De este modo, el químico orgánico se sirve de una potente herramienta sintética para aumentar la complejidad estructural desde los sustratos a los productos, evitando largas y tediosas etapas de protección-desprotección de grupos funcionales, así como procesos de purificación de intermedios sintéticos. Por otro lado, en lo que a la estereoselectividad se refiere, estos procesos se presentan como una excelente alternativa para la síntesis de moléculas de elevada pureza óptica. Esto es debido a que una vez generado el primer elemento de asimetría en la primera etapa de la secuencia, el proceso diastereoselectivo subsecuente generalmente tiene lugar junto con un aumento exponencial de la enantiopureza del producto final.[33]

Antes de pasar a comentar los distintos aspectos relacionados con las reacciones en cascada, es conveniente definir los distintos términos que aparecen en la bibliografía y que los autores emplean en un intento de diferenciarlos. De acuerdo con la clasificación realizada por Tietze en 1993,[34] los procesos secuenciales pueden dividirse en dos grupos: a) reacciones dominó o cascada: "*se entiende por reacción dominó, frecuentemente descrita como cascada o tándem, un proceso en*

[33] Vera, S.; Melchiorre, P. *An. Quim.* **2010**, *106*, 277.
[34] Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed*. **1993**, *32*, 131.

el que tienen lugar dos o más reacciones consecutivas y en la que un paso subsiguiente tiene lugar como consecuencia de una funcionalidad generada en un paso previo" y b) reacciones consecutivas: "*en una reacción consecutiva se requiere la adición de un reactivo o catalizador tras una primera transformación, sin aislar el producto formado, para que tenga lugar el paso siguiente y llegar así al producto final."* Sin embargo, a pesar de esta diferenciación, muchos autores emplean indistintamente un término u otro, tal y como apunta Nicolau.[35,36]

Al hilo de estas consideraciones, la organocatálisis covalente se presenta como una herramienta tremendamente útil para el diseño de procesos en cascada dado que la propia naturaleza de las especies catalíticas generadas por enlaces covalentes sustrato-catalizador facilitan el paso de un tipo de intermedio a otro de reactividad diferente con relativa facilidad y estereocontrol, existiendo así la posibilidad de llevar a cabo distintas transformaciones sintéticas de manera sequencial en un único paso de reacción. Además, la naturaleza covalente de la unión sustrato-catalizador garantiza la posibilidad de que este último ejerza su papel estereodirector a lo largo de todos los pasos del proceso en cascada.

En la presente memoria se tratarán los distintos aspectos relacionados con las reacciones organocatalíticas en cascada descritas en la bibliografía, no haciendo distinción entre procesos dominó o tándem, dado que algunos autores emplean ambos términos indistintamente.

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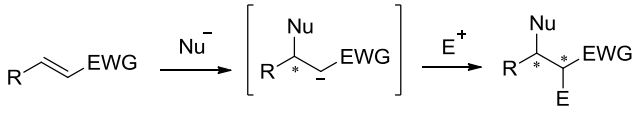
35 Nicolau, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed*. **2006**, *45*, 7134.
36 Pellissier, H. *Adv. Synth. Catal*. **2012**, *354*, 237.

2.1. Reacción de adición conjugada como herramienta para promover secuencias organocatalíticas en cascada.

Una de las propiedades que hace de las reacciones de tipo Michael una transformación idónea para el desarrollo de secuencias en cascada es la generación de un intermedio de carácter nucleófilo tras el primer paso de adición conjugada, el cual puede interaccionar con un electrófilo presente en el medio tanto de manera inter- como intramolecular (Esquema 1.5).



EWG: CHO, COR, $CONR_2$, CO_2R, CN, SO_2R, SOR, NO_2

Esquema 1.5

En los últimos años se han desarrollado diversos procesos en cascada, siendo las secuencias iniciadas por reacciones de adición conjugada las más extensamente estudiadas. En este contexto, el empleo de organocatalizadores se presenta como una plataforma idónea para promover y acelerar este tipo de transformaciones.[37] A continuación se mencionarán distintos ejemplos representativos de procesos dominó basados en los distintos tipos de activación que podemos encontrar en la bibliografía en función del tipo de organocatalizador empleado.

Así por ejemplo, la aminocatálisis y su aplicación a procesos estereoselectivos en cascada iniciados por adiciones conjugadas es hasta la fecha

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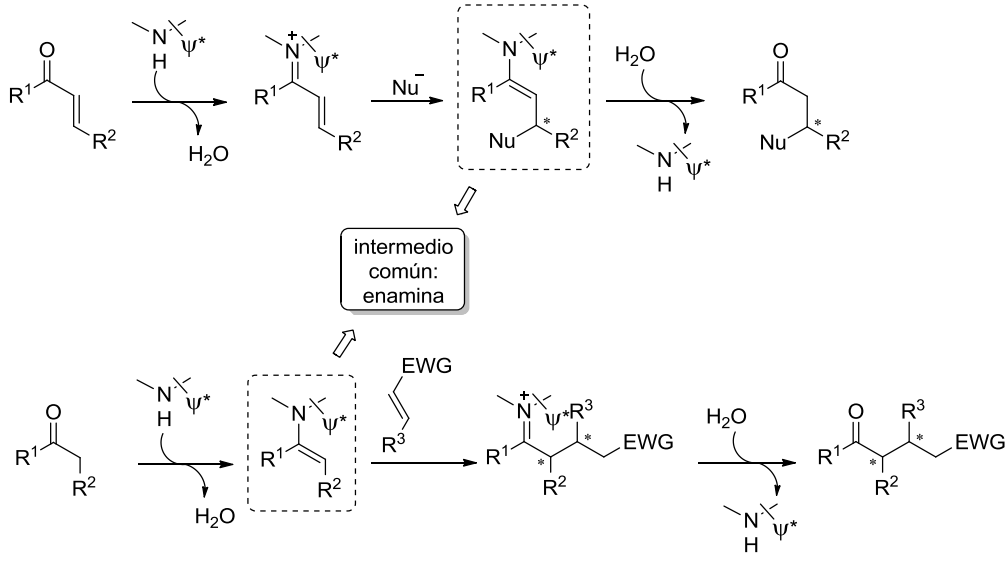
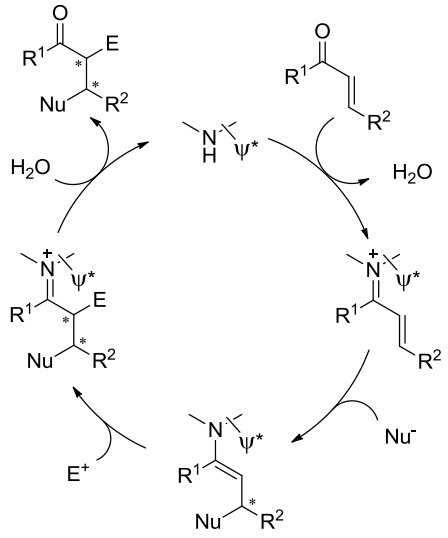
[37] Algunas revisiones sobre reacciones organocatalíticas en cascada: (a) Pellissier, H. *Adv. Synth. Catal*. **2012**, *354*, 237. (b) Bonne, D.; Constantieux, T.; Coquerel, Y.; Rodriguez, J. *Org. Biomol. Chem*. **2012**, *10*, 3969. (c) Yu, X.; Wang, W. *Org. Biomol. Chem*. **2008**, *6*, 2037. (d) Enders, D.; Christoph, G.; Hüttl, M. R. M. *Angew. Chem. Int. Ed*. **2007**, *46*, 1570.

uno de los campos que mayor crecimiento ha experimentado. Una de las razones que explica este vertiginoso desarrollo es la capacidad de estos aminocatalizadores para actuar mediante dos principales modos de activación: la denominada catálisis *via* iminio y la catálisis *via* enamina. La primera consiste en la activación de un compuesto carbonílico α,β-insaturado mediante la formación reversible de una sal de iminio quiral por condensación con el aminocatalizador, pudiendo así reaccionar frente a distintos nucleófilos en reacciones de adición conjugada. Por otro lado, en la catálisis *via* enamina, tras la condensación de un compuesto carbonílico enolizable con el aminocatalizador, se genera un intermedio de tipo enamina que gracias a su carácter nucleófilo puede reaccionar con un aceptor de Michael presente en el medio. (Esquema 1.6).



Esquema 1.6

Además, como se puede observar en el Esquema 1.6, ambos ciclos catalíticos comparten un intermedio común, lo cual permite una posible combinación entre ellos en un típico proceso en cascada, siendo ésta otra de las características que hacen de la aminocatálisis una estrategia muy interesante en catálisis asimétrica. Resulta por tanto más interesante, llevar a cabo una reacción donde se combinan ambos modos de activación en una secuencia iminio/enamina (Esquema 1.7). Esto se debe a las características propias del ciclo catalílico en donde, tras la adición conjugada al aceptor activado en forma de ion imino, se genera una enamina intermedia capaz de interaccionar tanto de manera intra- como intermolecular en un proceso posterior con un electrófilo presente en el medio, para lo cual se tendrá en cuenta la necesidad de seleccionar un sustrato convenientemente funcionalizado o de incluir un electrófilo adicional.



Esquema 1.7

En estas condiciones, la información quiral presente en la amina es la responsable de la diferenciación estereotópica de las dos caras del nucleófilo, siendo

de este modo posible la síntesis de productos enantioenriquecidos. En este sentido, algunas pirrolidinas quirales, la mayoría fácilmente sintetizables en forma enantiopura desde el aminoácido comercial prolina, han resultado ser excelentes promotores predominando en un gran abanico de reacciones. Típicamente, estos catalizadores poseen un grupo voluminoso que ejerce estereocontrol por efecto estérico mediante el bloqueo de una de las caras estereotópicas del intermedio reactivo (enamina o sal de iminio). Alternativamente, pueden presentar otro elemento esterodirector (catalizador bifuncional) que dirige la entrada del reactivo mediante el establecimiento de interacciones secundarias (enlaces de hidrógeno o mediante la formación de pares iónicos) (Figura 1.2).

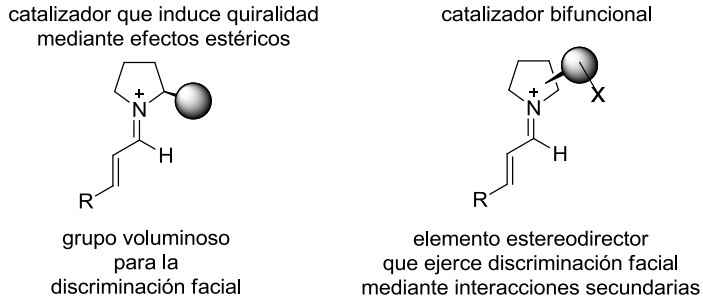


Figura 1.2

Al mismo tiempo, la habilidad del catalizador para controlar la geometría de la especie catalítica es un aspecto de gran importancia, dado que la formación de diferentes isómeros del ion iminio intermedio proporcionarían distintos tipos de discriminación para ambas caras estereotópicas, conduciendo así a la generación de mezclas de estereoisómeros (Figura 1.3). Este control, de nuevo, se ejerce mediante efectos estéricos o bien favoreciendo una determinada geometría reactiva mediante interacciones secundarias.

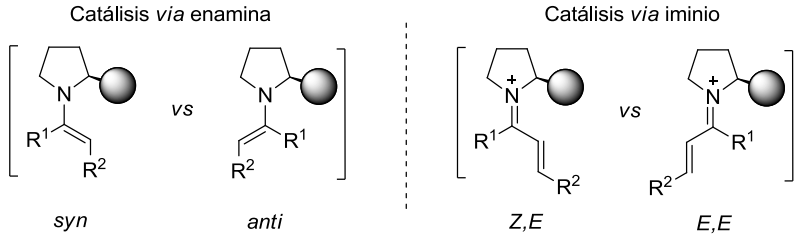
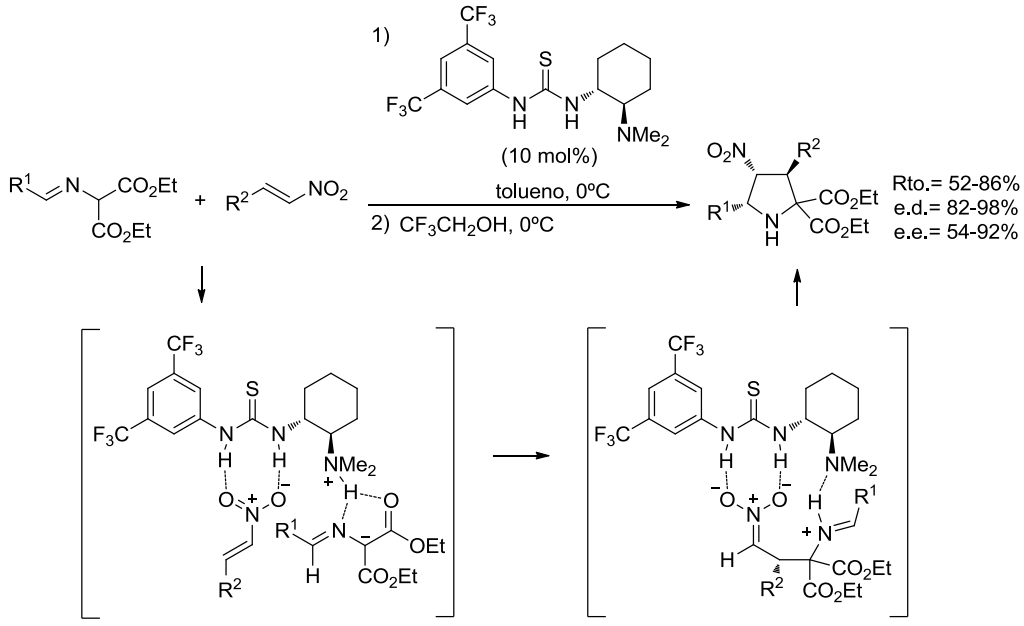


Figura 1.3

Dentro de la línea de reacciones organocatalíticas en cascada catalizadas por aminas, esta categoría resulta ser la más extensa dado que permite una mayor aplicabilidad a nuevas reacciones estereoselectivas. Por ello y debido a que uno de los objetivos del presente trabajo de investigación se centra en esta estrategia de activación, realizaré una revisión más detallada sobre este tipo de reacciones en el capítulo 2.

Por otro lado, la activación de un aceptor de Michael por formación de enlaces de hidrógeno con el organocatalizador ha sido también muy empleada para el diseño de reacciones dominó. Así, tras la etapa de adición conjugada, un electrófilo presente en el medio podrá reaccionar con el intermedio generado unido al catalizador mediante el establecimiento de una red de enlaces de hidrógeno, lo que supondría un segundo paso cuyo curso estereoquímico vendría gobernado por éste, aunque la débil naturaleza de la unión sustrato-catalizador hace que en muchos casos este segundo paso esté simplemente controlado por la propia estructura del sustrato. Un ejemplo representivo que ilustra este tipo de reacciones (Esquema 1.8) consiste en el empleo de una tiourea quiral bifuncional como catalizador en una reacción formal de cicloadición [3+2] entre iluros de azometino y nitroalquenos, obteniéndose así pirrolidinas altamente funcionalizadas de manera diastereo- y

enantioselectiva.[38] En este caso el organocatalizador bifuncional activa por un lado, el nitroalqueno por formación de enlaces de hidrógeno entre la tiourea y el grupo nitro y por otro lado, tiene lugar la activación del iluro de azometino mediante interacciones secundarias que se establecen entre el el grupo dimetilamino unido a la estructura quiral de la tiourea y los grupos éster y la función imínica. De esta forma el catalizador predispone a los sustratos de partida para que tenga lugar el primer paso de reacción mayoritariamente por una de las caras estereotópicas de ambos. Así, el intermedio generado tras el primer paso de adición del iluro sobre el aceptor conjugado participará en un segundo paso de reacción controlado por el inductor quiral nuevamente mediante la formación de enlaces por puente de hidrógeno para finalmente dar los correspondientes heterociclos.



Esquema 1.8

[38] Xie, J.; Yoshida, K.; Takasu, K.; Takemoto, Y. *Tetrahedron Lett*. **2008**, *49*, 6910.

Finalmente, destacar que otros tipos de activación organocatalíticos, tales como la catálisis mediante carbenos *N*-heterocíclicos o la catálisis por transferencia de fase, si bien no han sido explorados en igual medida que los métodos organocatalíticos expuestos anteriormente para el diseño de reacciones en cascada iniciadas por reacciones conjugadas, también han sido empleados con éxito, lo cual demuestra el potencial de esta aproximación metodológica para el desarrollo de nuevas transformaciones asimétricas englobadas dentro de esta línea de investigación.

3. ANTECEDENTES DEL GRUPO.

En nuestro grupo de investigación se ha desarrollado con éxito desde el año 2000 una serie de metodologías de uso general en síntesis asimétrica. En los inicios se empleó la estrategia del auxiliar quiral como aproximación metodológica para lograr control estereoquímico en química de enolatos[39] y en reacciones de adición conjugada;[40] sin embargo, en los últimos años nuestros esfuerzos se han centrado en contribuir al estudio de metodologías organocatalíticas y, en concreto, de aproximaciones enmarcadas dentro de las líneas de la enaminocatálisis, catálisis *via* iminio y reacciones aminocatalíticas en cascada.

El primer trabajo publicado por el grupo dentro del campo de la organocatálisis consistió en la puesta a punto de una reacción de Michael asimétrica entre aldehídos y el dimetil acetal de β-nitroacroleína empleando el simple prolinol como inductor quiral en cantidades catalíticas aplicando en este caso el concepto de activación *via* enamina.[41] La reacción procede con buenos rendimientos y enantioselectividades con una amplia gama de aldehídos, optando de este modo a la formación de compuestos enantioenriquecidos altamente funcionalizados.

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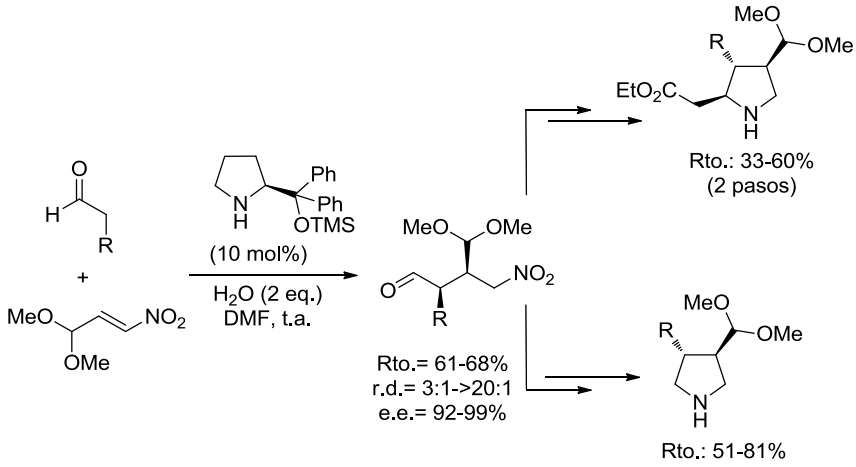
[39] Artículo más reciente de reacción aldólica: Vicario, J. L.; Rodríguez, M.; Badía, D.; Carrillo, L.; Reyes, E. *Org. Lett*. **2004**, *6*, 3171. Artículo más reciente de reacción de Mannich: Iza, A.; Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2006**, 4065. Artículo más reciente de reacción de aminación electrófila: Vicario, J. L.; Badía, D.; Carrillo, L. *Tetrahedron: Asymmetry* **2002**, *13*, 745, 4343. Reacción de apertura de azidiridinas: Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem*. **2001**, *66*, 5801. Reacción de adición tándem: Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Iza, A.; Uria, U. *Org. Lett*. **2006**, *8*, 2535.

[40] Artículo más reciente de reacción de adición conjugada: Ocejo, M.; Carrillo, L.; Badía, D.; Vicario, J. L.; Fernández, N.; Reyes, E. *J. Org. Chem*. **2009**, *74*, 4404. Artículo más reciente de reacción de aza-Michael: Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L.; Ruiz, N. *J. Org. Chem.* **2005**, *70*, 8790.

[41] Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2006**, *8*, 6135.

Posteriormente, se llevó a cabo un estudio dirigido hacia la mejora del método en lo que respecta al tiempo de reacción y a la diastereoselectividad, modificando tanto el catalizador como el disolvente. Asimismo, se puso a punto un protocolo sencillo y eficaz para la obtención de pirrolidinas 3,4-disustituidas, así como de derivados de homoprolina con altos niveles de estereocontrol a partir de los aductos de Michael obtenidos (Esquema 1.9).[42]

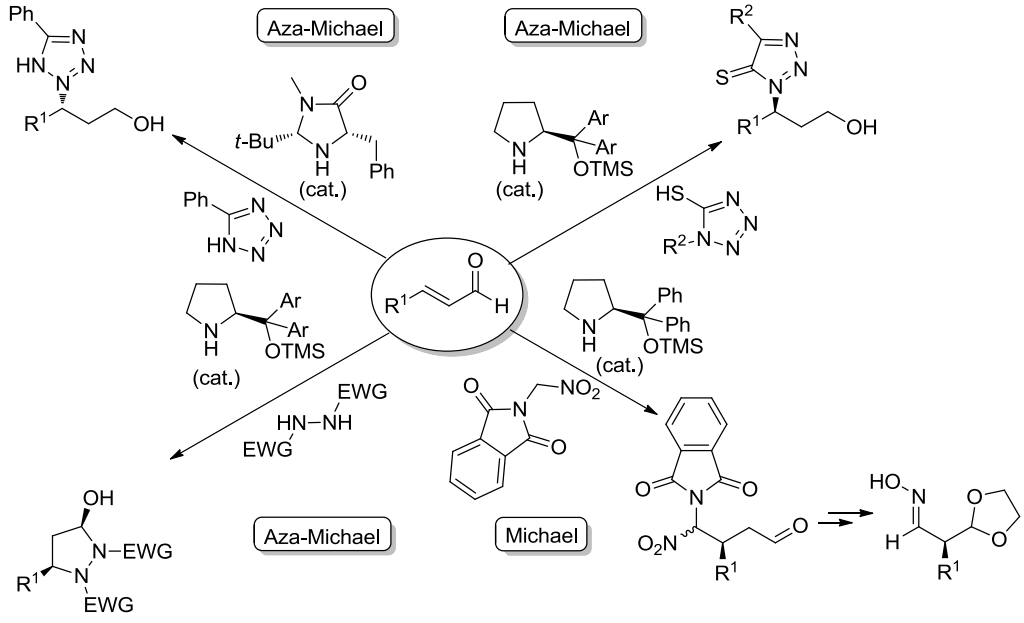


Esquema 1.9

Por otro lado, el concepto de activación *via* iminio también ha sido empleado en nuestro grupo de investigación, poniendo así a punto diversas metodologías empleando aldehídos α,β-insaturados sobre los que realizar adiciónes 1,4. Así, se han elaborado protocolos empleando 5-feniltetrazol y distintos 5-mercaptotetrazoles para sintetizar distintos de manera eficaz heterociclos *N*-alquilsustituidos de manera enantioselectiva mediante reacciones aza-Michael. Por otro lado, se ha llevado a cabo la síntesis enantioselectiva de pirazolidinas, pirazolinas y pirazolidinonas con excelentes rendimientos mediante la puesta a punto de una reacción aza-Michael

[42] Ruiz, N.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Uria, U. *Chem. Eur. J.* **2008**, *14*, 9357.

seguida de un proceso de hemiaminalización empleando hidrazidas *N,N'*-disustituidas.[43] Asimismo, se ha puesto a punto la β-hidroxiiminometilación enantioselectiva de aldehídos α,β-insaturados en presencia de un derivado de difenilprolinol sililado como organocatalizador y empleando *N*-nitrometilftalimida como equivalente de anión hidroximetanimidoílo. La aplicabilidad de esta reacción resultó ser muy amplia permitiéndonos así la obtención de un número considerable de oximas funcionalizadas enantioenriquecidas de manera directa (Esquema 1.10).[44]

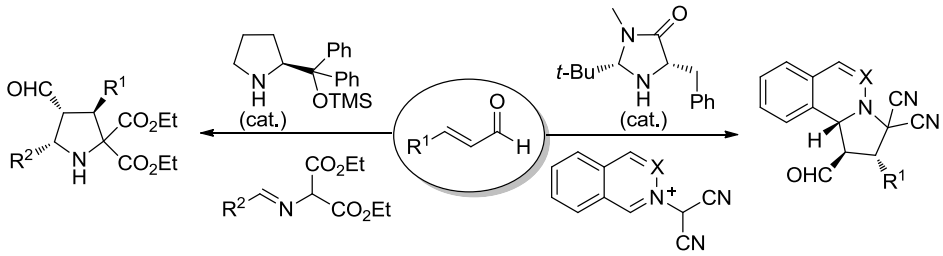


Esquema 1.10

[43] (a) Fernandez, M.; Reyes, E.; Vicario, J. L; Badía, D.; Carrillo, L. Badía *Adv. Synth. Catal*. **2012**, *354*, 371. (b) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett*. **2011**, *13*, 336. (c) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L. *Chem. Commun*. **2007**, 2509.

[44] Alonso, B.; Reyes, E.; Carrillo, L.; Vicario, J. L.; Badía, D. *Chem. Eur. J*. **2011**, *17*, 6048.

Además, dentro de la línea de investigación centrada en las reacciones organocatalíticas *via* iminio, también se han explorado las reacciones de cicloadición. Así, se han puesto a punto reacciones de cicloadición (3+2) enantioselectivas empleando como dipolos iluros de azometino sintetizados *in situ* a partir de arilidenaminomalonatos,[45] así como metiluros de isoquinolinio y ftalizinio.[46] Así, se lograron obtener pirrolidinas densamente funcionalizadas; además de pirroloisoquinolinas y pirroloftalazinas con muy buenos rendimientos y excelentes diastereo- y enantioselectividades (Esquema 1.11).



Esquema 1.11

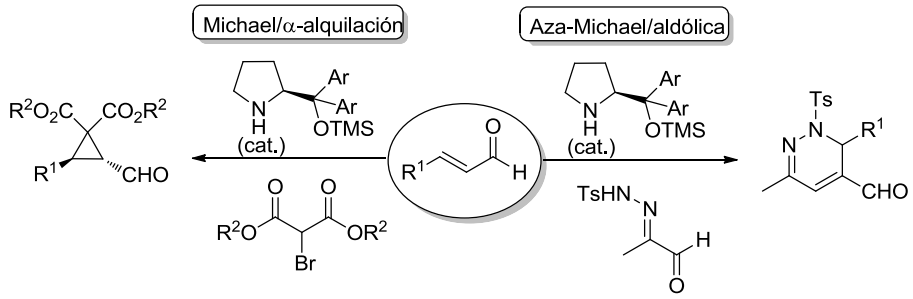
Posteriormente, se realizó un estudio mecanístico de estas reacciones avalado por estudios computacionales que demostraba el carácter secuencial del proceso de cicloadición con iluros de azometino,[47] considerándola por tanto, una reacción por pasos Michael/Mannich en la que la activación iminio/enamina se combina en un típico proceso en cascada, siendo el primer paso de adición conjugada la etapa determinante del proceso. Este comportamiento, así como las ventajas que ofrecen los procesos típicos en cascada para acceder a moléculas densamente funcionalizadas con elevado estereocontrol ha sido empleado por nuestro grupo en

[45] Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5168.

[46] Fernández, N.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E. *Chem. Commun*. **2011**, *47*, 12313.

[47] Reboredo, S.; Reyes, E.; Vicario. J. L.; Badía, D.; Carrillo, L; de Cózar, A.; Cossío, F. P. *Chem. Eur. J*. 2012, 18, 7179.

otro tipo de transformaciones. En este sentido, se han llevado a cabo diversas reacciones en cascada iniciadas por reacciónes de Michael y hetero-Michael en condiciones de activación *via* iminio e iminio/enamina (Esquema 1.12). Así por ejemplo, se ha puesto a punto una reacción en cascada Michael/α-alquilación entre enales y bromomalonato de dietilo como nucleófilo funcionalizado para alcanzar ciclopropanos quirales de forma estereocontrolada.[48] Por otro lado, nuestro grupo de investigación ha desarrollado un método para la preparación de 2,3-dihidropiridazinas a partir de tosilhidrazonas de piruvaldehído y aldehídos α,β-insaturados mediante una reacción aza-Michael/condensación aldólica.[49] El empleo de un derivado de difenilprolinol sililado como inductor quiral en ambos casos nos permitió obtener los correspondientes heterociclos de manera eficaz, con elevada regioselectividad y pureza óptica.



Esquema 1.12

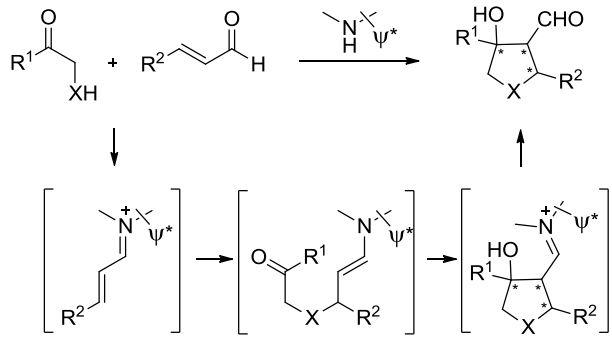
[48] Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2010**, 701.

[49] Fernandez, M.; Vicario, J. L.; Reyes, E.; Carrillo, L. Badía, D. *Chem. Commun*. **2012**, *48*, 2092.

4. OBJETIVOS GENERALES.

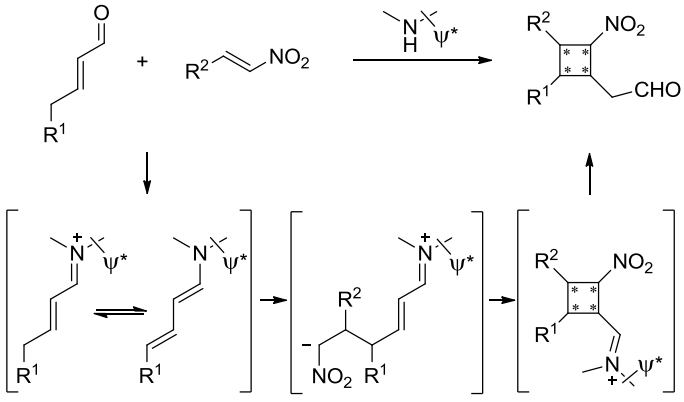
El trabajo de investigación recogido en esta memoria se enmarca dentro de las líneas de investigación del grupo, y en concreto, en aquella centrada en la búsqueda de nuevas reacciones organocatalíticas en cascada aplicadas a la síntesis enantioselectiva de heterociclos. Así, se plantean dos objetivos generales a alcanzar que se detallan a continuación.

Por un lado, nos centraremos en el **desarrollo de un método para llevar a cabo reacciones en cascada hetero-Michael/condensación aldólica en condiciones aminocatalíticas empleando la plataforma de activación iminio/enamina**. En este sentido, continuando con la línea de trabajo desarrollado en el grupo durante los últimos años, se dicidió explorar la posibilidad de llevar a cabo reacciones en cascada iniciadas por reacciones hetero-Michael seguidas de condensación aldólica entre aldehídos α,β-insaturados y cetonas α-heterosustituidas empleando aminocatalizadores como inductores de quiralidad que promoviesen la reacción a través de intermedios de tipo iminio y enamina (Esquema 1.13).



Esquema 1.13

Por otro lado, se enfocará el segundo objetivo del presente trabajo en el **diseño de una nueva secuencia en cascada dienamina/iminio para la síntesis asimétrica de ciclobutanos**. En este sentido, propusimos el empleo de enales capaces de interaccionar con nitroalquenos tras la formación de un intermedio de tipo dienamina de carácter nucleófilo por condensación con el aminocatalizador capaces de iniciar un proceso en cascada Michael/Michael enfocado hacia la síntesis de ciclobutanos en condiciones organocatalíticas (Esquema 1.14).



Esquema 1.14

La descripción de los resultados más relevantes obtenidos en cada uno de estos dos procesos se desarrollará independientemente en los capítulos 2 y 3 de esta memoria.

2

2

Organocatalytic Cascade Reactions towards the Asymmetric Synthesis of Heterocycles.

1. Organocatalytic cascades initiated by hetero-Michael reactions.

1.1. Sulfa-Michael initiated cascade reactions.

1.2. Aza-Michael initiated cascade reactions.

1.3. Oxa-Michael initiated cascade reactions.

2. Specific objectives and work plan.

3. Results and discussion.

3.1. Enantioselective organocatalytic oxa-Michael/aldol cascade reaction.

3.1.1. Viability of the reaction.

3.1.1. Optimization of the reaction conditions.

3.1.2. Scope of the reaction.

3.1.3. Derivatization of the adducts.

3.2. Other α-heterosubstituted ketones.

4. Conclusions.

1. ORGANOCATALYTIC CASCADES INITIATED BY HETERO-MICHAEL REACTIONS.

As it has already been pointed out in the previous chapter, the design of cascade processes initiated by Michael-type reactions represents a highly efficient approach for the straightfoward construction of complex molecules. A particularly interesting situation arises when heteroatom based pronucleophiles are used as starting materials that initiate conjugate addition reactions, which leads to the formation of optically active heterocycles. For this reason, the obtention of heterocycles in a stereocontrolled way using organocatalytic versions of this methodology has suffered an explosive growth with plenty of reports in which heteronucleophiles containing an electrophilic functionality are introduced in the reaction design that are able to react intramolecularly with the nucleophilic intermediate generated after the initial conjugate addition.

Cascade processes initiated by organocatalytic hetero-Michael reactions can be classified according to the heteroatom participating in the first conjugate addition step. This introduction aims to present the most important developments in this field that will be differenciated on the basis of the type of initial hetero-Michael reaction: sulfa-Michael, aza-Michael and oxa-Michael reaction.

1.1. Sulfa-Michael initiated organocatalytic cascade reactions.

The interest gathered by sulfur heterocycles has increased significantly since a wide range of biological activities associated with different sulfur-containing

architectures have been identified, ranging from anti-inflammatory activities, analgesic, bacteriostatic, anti-cancer, anti-hyperplasia, anti-psychiatric or antioxidant activities.[1] In addition, these structures are also used as building blocks for the preparation of new chiral ligands in asymmetric metal catalysis[2] and organocatalysts[3] and also in natural product synthesis.[4] Accordingly, the development of new and rapid methodologies to access to such heterocycles is of considerable interest.

The first reported organocatalytic cascade initiated by a sufa-Michael reaction constists of a multicomponent intermolecular process in which an α,β-unsaturated aldehyde, a thiol and an azodicarboxylate reacted with each other affording α-hydrazino-β-thiocarbonyl products in moderate to good yields, good diastereoselectivities and with complete enantiocontrol in the presence of a chiral proline derivative (Scheme 2.1).[5] The reaction occurred by initial conjugate addition of the thiol to the enal under iminium activation followed by the intermolecular α-amination of the resulting enamine with the azodicarboxylate electrophilic reagent. The initial aldehyde adducts were not isolated because of stability issues and had to be reduced *in situ* providing a series of highly functionalized oxazolidin-2-ones after a "one-pot" base-promoted cyclization.

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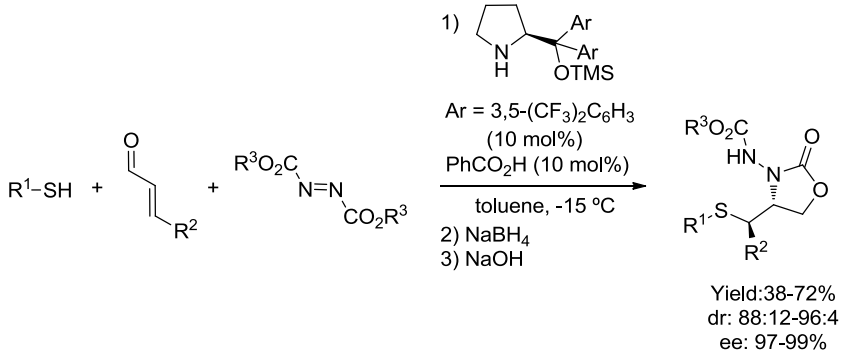
[1] (a) Quiao, C.; Ling, K.-Q.; Shepard, E. M.; Dooley, D. M. Sayre, L. M. *J. Am. Chem. Soc*. **2006**, *128*, 6206. (b) Page, P. C. B.; Vahedi, H.; Batchelor, K. J.; Hindley, S. J.; Edgar, M.; Beswick, P. *Synlett,* **2003**, 1022. (c) Wirsching, J.; Voss, J.; Adiwidjaja, G.; Balzarini, J.; De Clercq, E. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 1049. (d) De Clercq, P. J. *Chem. Rev*. **1997**, *97*, 1755. (e) Ingall, A. H. *Comprehensive Heterocyclic Chemistry II*; Boulton, A. S. McKkillop, A., Eds.; Pergamon Press: Oxford, **1996**; Vol. 5, p 501.

[2] (a) Hauptman, E.; Shapiro, R.; Marshall, W. *Organometallics* **1998**, *17*, 4976. (b) Mukaiyama, T.; Asanuma, H.; Hachiya, I.; Harada, T.; Kobayashi, S. *Chem. Lett*. **1991**, *7*, 1209.

[3] (a) Zanardi, J.; Lamazure, D.; Miniere, S.; Reboul, V.; Metzner, P. *J. Org. Chem*. **2002**, *7*, 9083. (b) Zanardi, J.; Leriverend, C.; Aubert, D.; Julienne, K.; Metzner, P. *J. Org. Chem*. **2001**, *66*, 5620. (c) Li, A.-H.; Dai, L. X.; Hou, X. L.; Huang, Y.-Z.; Li, F.-W. *J. Org. Chem*. **1996**, *61*, 489.

[4] Williams, D. R.; Jass, P. A.; Tse, H. L. A.; Gaston, R. D. *J. Am. Chem. Soc*. **1990**, *112*, 4552.

[5] Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2005**, *127*, 15710.

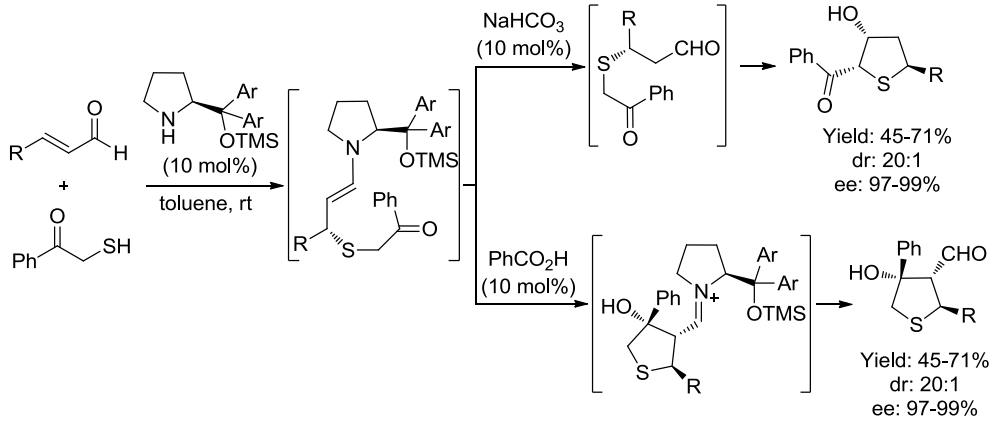


Scheme 2.1

Following to this pioneering work, some other examples have appeared in the recent literature showing the high performance of the iminium/enamine manifold for building up sulfur-containing heterocycles. However, in contrast with this initial report, most of the examples have dealed with intramolecular versions in which functionalized sulfur-based Michael donors bearing an internal electrophilic moiety are used. A good example is shown in Scheme 2.2, where a highly enantioselective sulfa-Michael/aldol reaction is depicted using 2-mercapto-1-phenylethanone as the functionalized Michael donor for the synthesis of diastereo- and enantiomerically pure tetrahydrothiophenes.[6] Remarkably, this work shows that it is possible to control the chemoselectivity of these domino reactions by the appopiate selection of the co-catalyst. In this sense, the incorporation of a basic co-catalyst yielded (tetrahydrothiophen-2-yl)phenyl ketones; while tetrahydrothiophene-3-carbaldehydes were isolated when an acidic additive was incorporated to the reaction scheme. The authors proposed that a common intermediate for both cases had to be formed in the first sulfa-Michael reaction with the iminium ion intermediate. Then, in the presence of benzoic acid, the catalyst is believed to participate in the second intramolecular

[6] Brandau, S.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986.

aldol reaction under enamine catalysis, while in the presence of a base the hydrolysis of the enamine should take place and a final intramolecular aldol reaction under substrate control would lead to the formation the observed (tetrahydrothiophen-2-yl)phenyl ketone adducts.

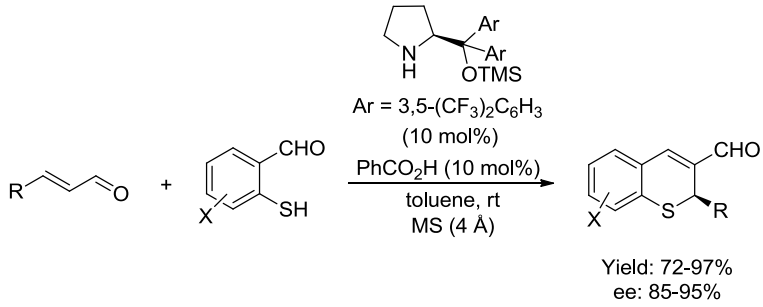


Scheme 2.2

A related sulfa-Michael/aldol sequence has also been reported using this iminium/enamine manifold in which 2-mercaptobenzaldehydes have been used as bifunctional sulfur-centered substrate. In this sense, a good procedure for the synthesis of chiral thiochromenes was published by Wang et al.[7] by reacting a thiophenol incorporating a formyl group at the ortho position with an α,β-unsaturated aldehyde (Scheme 2.3). In this particular case, the cascade sulfa-Michael/aldol sequence was followed by dehydration, the latter process being also interpreted to work as driving force that drove the reaction to completion in a short reaction time. It has to be pointed out that such sulfur-based Michael donors present

[7] (a) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc*. **2006**, *128*, 10354. (b) For similar work with some modifications see: Rios, R.; Sudén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Tetrahedron Lett*. **2006**, *47*, 8547.

a lower pK_a than the aliphatic ones shown in Scheme 2.2, which turns into a highly acidic sulfur pronucleophile and therefore, into enhanced reactivity under the reaction conditions employed. In a similar approach, the same concept was used for the reaction with α,β-unsaturated cyclic ketones as Michael acceptors, leading to the formation of tetrahydrothioxanthenones although in low to moderate yields and enantioselectivities.[8]

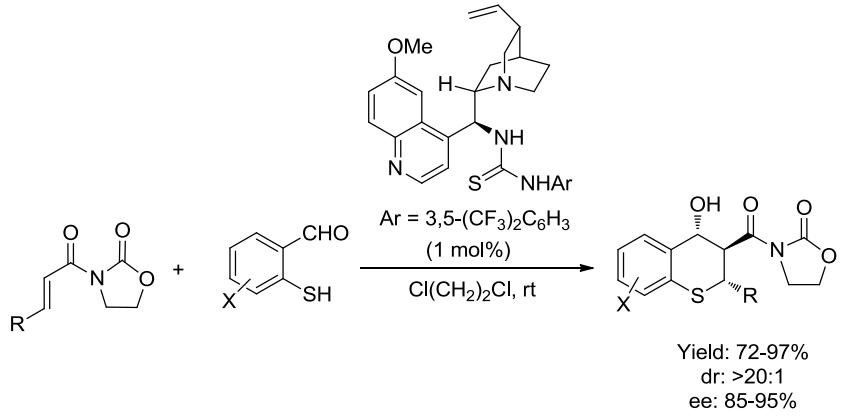


Scheme 2.3

The H-bonding catalysis approach has also been used in several examples of sulfa-Michael initiated cascades. In this sense, literature shows the presence of several interesting cascade processes involving the sulfa-Michael/aldol or related cascade processes. A representative example in this field is depicted in Scheme 2.4, showing the reaction of several 2-mercaptobenzaldehydes with different α,β-unsaturated imides.[9] Regarding the catalyst, it has shown ability to participate as a bifunctional inductor since it contains a thiourea moiety that enables the activation of the Michael acceptor *via* H-bonding interactions, stabilizing the developing negative charge during conjugate addition and, on the other hand, a basic site is introduced at the chiral scaffold which activates the nucleophile by deprotonation.

[8] Rios, R.; Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Córdova, A. *Tetrahedron Lett*. **2006**, *47*, 8679.
[9] Zu, L.; Wang, J.; Li, H.; Xie, H.; Jiang, W.; Wang, W. *J. Am. Chem. Soc*. **2007**, *129*, 1036.

This strategy has been used in the same transformation using some other Michael acceptors such us maleimides,[10] benzylidenemalonates[11] and simple nitrostyrenes.[12]

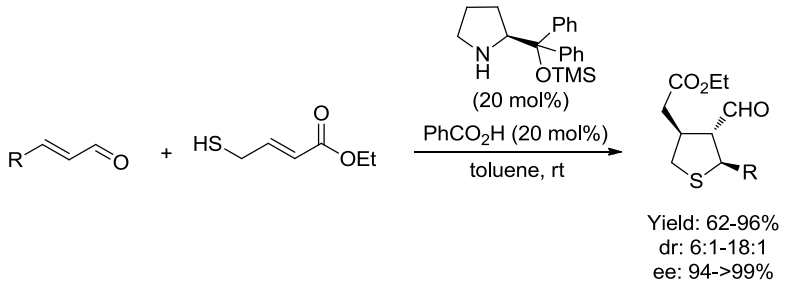


Scheme 2.4

Nevertheless, the sulfa-Michael/aldol is not the only combination in orgnocatalytic processes initiated by sulfa-Michael reactions. For example, Wang and co-workers have developed an amine catalyzed enantioselective domino sulfa-Michael/Michael reaction of enals with ethyl 4-mercapto-2-butenoate furnishing enantioenriched tetrahydrothiophenes (Scheme 2.5).[13] In this particular transformation, after the initial hetero-Michael reaction under iminium activation, a subsequent intramolecular Michael reaction occurs in which the enamine intermediate moiety reacts with the enoate side chain incorporated at the functionalized Michael donor, resulting in the formation of a five membered heterocycle. *O*-TMS-diphenylprolinol was identified as the best organocatalyst for

[10] Zu, L.; Xie, H.; Li, H.; Wang, J.; Jiang, W.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 1882.
[11] Dodda, R.; Mandal, T.; Zhao, C.-G. *Tetrahedron Lett*. **2008**, *49*, 1899.
[12] Dodda, R.; Goldman, J. J.; Mandal, T.; Zhao, C.-G.; Broker, G. A.; Tiekink, R. T. *Adv. Synth. Catal.* **2008**, *350*, 537.
[13] Li, H.; Zu, L.; Xie, H.; Wang, J.; Jiang, W.; Wang, W. *Org. Lett*. **2007**, *9*, 1833.

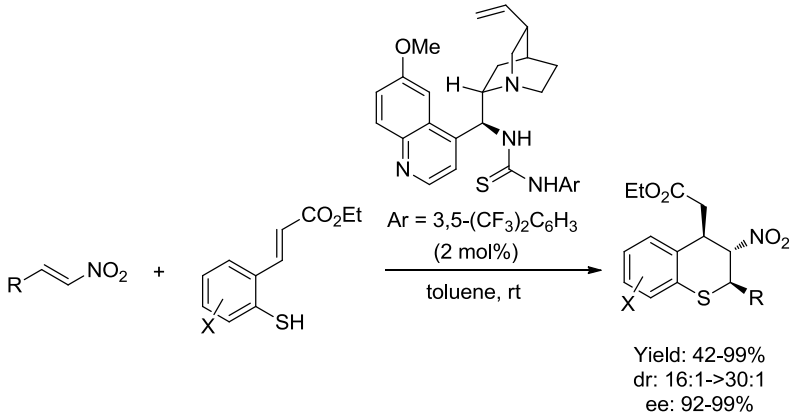
this reaction, which proceeded with good yields and excellent diastereo- and enantioselectivities for a wide range of enals.



Scheme 2.5

Alternatively, a bifunctional thiourea/tertiary amine catalyst has also been used in a sulfa-Michael/Michael cascade. In this sense, a conveniently functionalized starting material based on a thiophenol bearing an electron-deficient alkene moiety at *ortho* position was successfully used in the reaction with nitroalkenes. After a survey of several bifunctional catalysts and reaction media the optimal conditions were found, which involved the use of a cinchona alkaloid-based thiourea catalyst. At the end, a general methodology was developed for the synthesis of thiochromanes with the highly efficient creation of three new stereogenic centers (Scheme 2.6).[14]

[14] Wang, J.; Xie, H.; Li, H.; Zu, L.; Wang, W. *Angew. Chem. Int. Ed*. **2008**, *47*, 4177

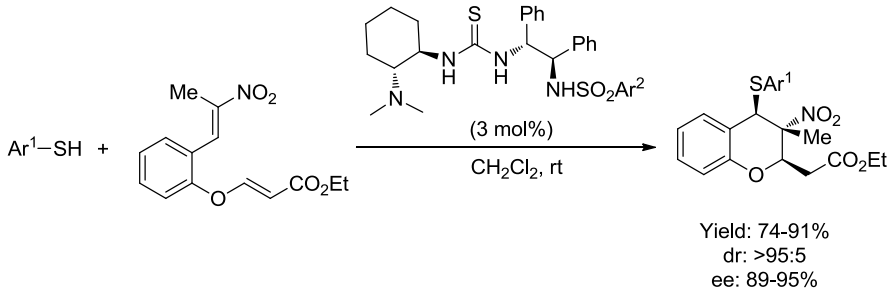


Scheme 2.6

Importantly, and taking into account the low enantioselectivity observed (12% ee) for the single conjugate addition reaction of thiophenol to *trans*-β-nitrostyrene under the same reaction conditions and in the presence of the same organocatalyst, the authors concluded that the reaction had to occur through a mechanism involving a dynamic kinetic resolution relying on a fast and reversible conjugate addition of the sulfur-nucleophile happening before the rate-limiting intramolecular Michael reaction takes place. The hypothesis was confirmed by treatment of a racemic sulfa-Michael adduct with the chiral bifunctional amine thiourea and observing that the final cascade product could be obtained with excellent stereoselectivity (95% ee, dr >30:1), as well as the same absolute configuration.

A conceptually different approach consists of the sulfa-Michael/Michael reaction shown in Scheme 2.7, where a bifunctional starting material containing two electron-deficient alkenes was employed as Michael acceptor which reacts with an aromatic thiols, leading to the formation of highly substituted enantioenriched chromans in high yields and as a single diastereoisomer in the presence of a

bifunctional thiourea/tertiary amine catalyst. It should be noticed that the reaction proceeded with complete regioselectivity, starting with the chemoselective conjugate addition of the sulfur-nucleophile to the nitroalkene moiety which is followed by the final intramolecular Michael reaction.[15]



Scheme 2.7

1.2. Aza-Michael initiated organocatalytic cascade reactions.

Enantioselective domino processes involving an initial aza-Michael reaction step catalyzed by a chiral primary or secondary amine represents another largely explored research line within the area of organocatalytic cascade reactions employing hetero-nucleophiles. For these cases of cascade reactions under the iminium/enamine manifold, additional chemoselectivity issues have to be addressed, since both the catalyst and the pronucleophile are amine species, which means that the role played by each reagent must be clearly stablished. On the other hand, the catalyst must promote the reaction activating the Michael acceptor *via* iminium ion formation and must not undergo conjugate addition reaction, which would lead to catalyst consumption and, likewise the pronucleophile must not play the role of catalyst, in order to prevent the formation of a racemic product.

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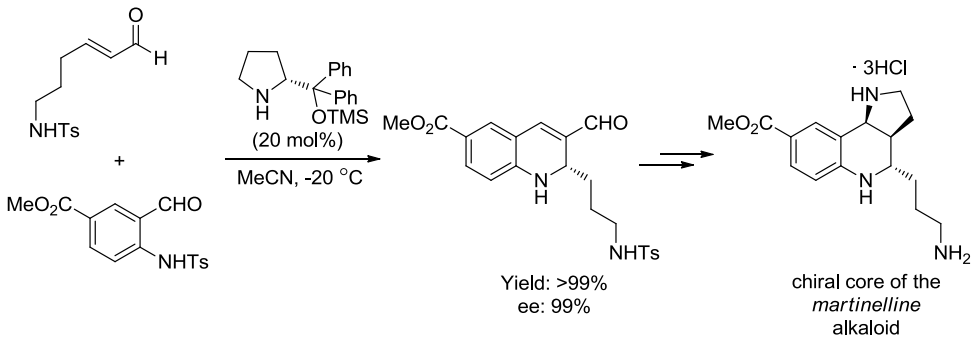
[15] Wang, X.-F; Hua, Q.-L.; Cheng, Y.; An, X.-L.; Yang, Q.-Q.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem. Int. Ed*. **2010**, *49*, 8379.

In a similar approach to the previously presented sulfa-Michael/aldol cascade reactions, several methodologies have been developed using conveniently substituted anilines as functionalized reagents undergoing aza-Michael/aldol cascade reactions. These reagents typically contain a formyl group at the *ortho* position able to participate as internal electrophile.[16] An example showing the utility of this domino processes is shown in Scheme 2.8 in which this methodology was applied to the total synthesis of the chiral core of the *martinelline* alkaloid. The key step in the synthesis relied on the reaction of a conveniently substituted α,β-unsaturated aldehyde with the functionalized aniline in the presence of (*R*)-α,α-diphenylprolinol trimethylsilyl ether for the initial aza-Michael reaction, in which the generation of the new stereocenter is controlled by the organocatalyst. Then, an intramolecular aldol condensation is taken place under enamine catalysis yielding a suitable synthetic intermediate for the construction of the chiral core of the *martinelline* alkaloid quantitatively and with complete enantiocontrol (Scheme 2.8).[17]

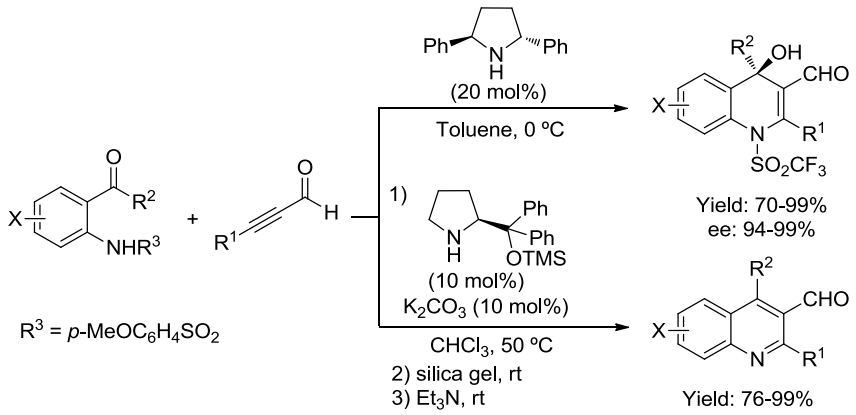


Scheme 2.8

[16] (a) Sundén, H.; Rios, R.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Adv. Synth. Catal*. **2007**, *349*, 827. (b) Li, H.; Wang, J.; Xie, H.; Zu, L.; Jiang, W.; Duesler, E. N.; Wang, W. *Org. Lett*. **2007**, *9*, 965.

[17] Yoshitomi, Y.; Arai, H.; Makino, K.; Hamada, Y. *Tetrahedron* **2008**, *64*, 11568.

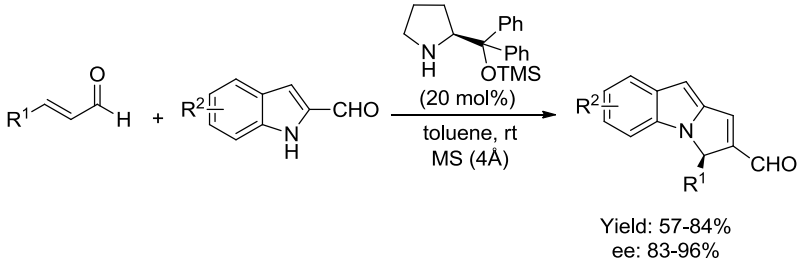
A very interesting extension of this chemistry has led to the use of ynals as Michael acceptors in the design of Michael/aldol cascades based on a previously reported iminium/allenamine manifold. By means of such reaction design and using *N*-protected 2-aminobenzaldehydes as functionalized Michael donors, chiral 1,4-dihydroquinolines were obtained *via* aza-Michael/aldol sequence (Scheme 2.9).[18] This reaction relies on the formation of an allenamine-type intermediate after the initial aza-Michael reaction under iminium activation that next undergoes intramolecular aldol reaction forming a new stereocenter. Remarkably, the electronic effects associated to the nature of the *N*-protecting group have been studied observing that, while aryl sulfonyl moieties with electron-withdrawing properties at the nitrogen atom provided 1,4-dihydroquinolines, incorporating electron-donating aryl sulfonamides facilitates a dehydration/aromatization of the aza-Michael/aldol adducts leading to the formation of achiral quinolines.



Scheme 2.9

[18] Xishuai, Z.; Song, Xixi; Li, H.; Zhang, S.; Chen, X.; Yu, X.; Wang, W. Angew. Chem. Int. Ed. 2012, 51, 7282.

Some other examples have been reported on aza-Michael/aldol cascades involving other different functionalized Michael donors like formyl-substituted *N*-heterocycles. In this sense, an interesting procedure for the enantioselective synthesis of pyrrolo[1,2-a]indole-2-carbaldehydes has been developed in which indole-2-carbaldehydes react with enals in the presence of *O*-TMS-diphenylprolinol as catalyst, achieving the corresponding tricyclic compounds in moderate to good yields and with good to excellent enantioselectivities (Scheme 2.10).[19]

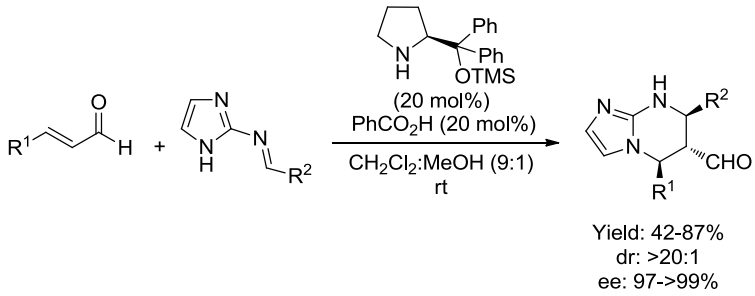


Scheme 2.10

Based on this concept, an enantioselective related aza-Michael/Mannich cascade reaction has also been developed involving the reaction between imines derived from 2-aminoimidazole and enals using the same *O*-TMS-diphenylprolinol as catalyst (Scheme 2.11).[20] This approach led to the synthesis of enantiomerically pure tetrahydroimidazopyrimidine derivatives containing three stereocenters as a single diastereoisomer with moderate to good yields.

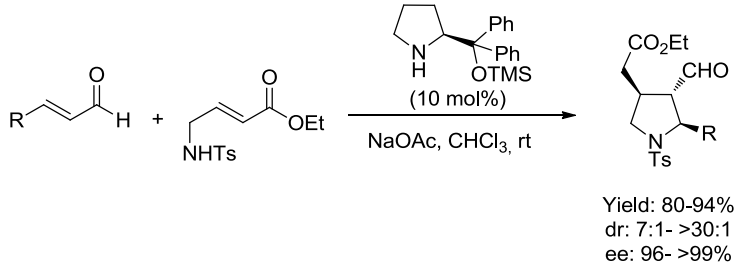
[19] (a) Hong, L.; Sun, W.; Liu, C.; Wang, L.; Wang, R. *Chem. Eur. J*. **2010**, *16*, 440. For a similar work see: (b) Enders, D.; Chuan, W.; Gerhard, R. *Synthesis*, **2009**, 4119. For the aminocatalytic synthesis of chiral pyrrolizines through an aza-Michael/aldol sequence between enals and pyrroles see: (c) Bae, J.-Y.; Lee, H.-J.; Youn, S.-H.; Kwon, S.-H.; Cho, C.-W. *Org. Lett*. **2010**, *12*, 4352.

[20] Li, H.; Zhao, J.; Zeng, L.; Hu, W. *J. Org. Chem*. **2011**, *76*, 8064.



Scheme 2.11

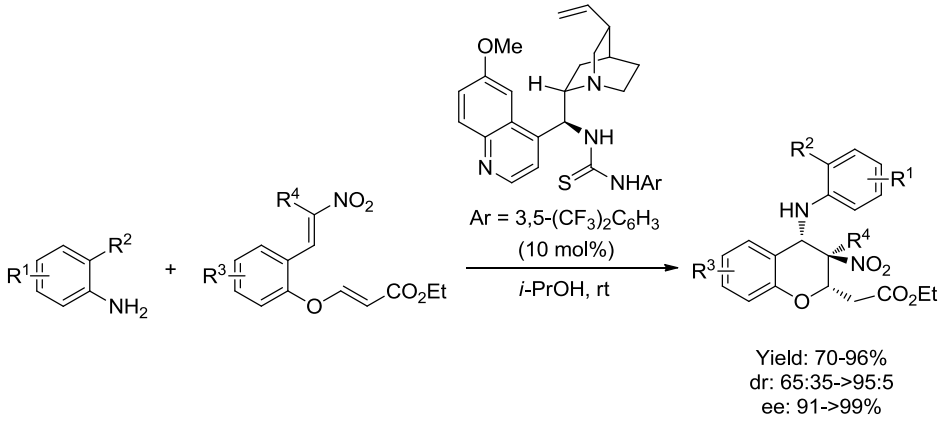
Combining the aza-Michael reaction with a subsequent second Michael reaction is another possibility which has been faced by several authors. For example, Wang has described an effective process for the enantioselective construction of pyrrolidines using an *N*-protected γ-amino-α,β-unsaturated ester as functionalized Michael donor. This compound can react with enals in the presence of *O*-TMS-diphenylprolinol furnishing the desired pyrrolidine heterocycles as a single diastereoisomer in most cases and with excellent yields and enantiomeric excesses (Scheme 2.12).[21]



Scheme 2.12

[21] Li, H.; Zu, L.; Xie, H.; Wang, J.; Wang, W. *Chem. Commun*. **2008**, 5636.

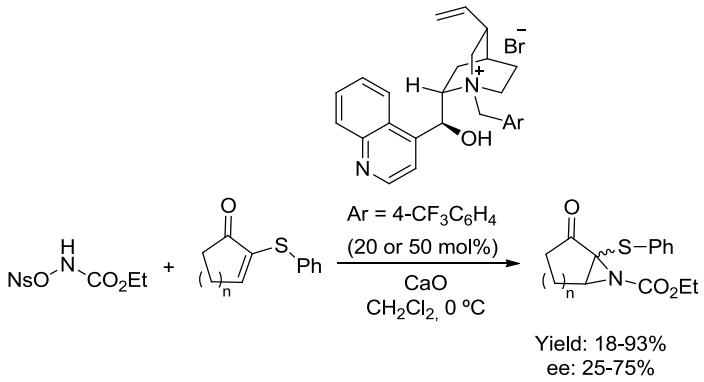
Within this research line, other organocatalysts such as bifunctional tertiary amine/thioureas have been used as promoters in aza-Michael/Michael cascade reactions. In this sense, the enantioselective synthesis of 4-aminobenzopyrans was carried out employing differently substituted anilines and conveniently functionalized aromatic nitroalkenes as Michael acceptors that contain an α,β-unsaturated ester moiety at the ortho position, the later being able to participate as the internal electrophile for the second Michael reaction (Scheme 2.13).[22] In this case, the organocatalyst is engaged in the simultaneous activation of both Michael acceptor and the *N*-pronucleophile by H-bonding activation with the thiourea moiety and with the basic tertiary amino site, respectively. The reaction procceeded with excellent yields and stereoselectivities tolerating a wide range of variability at the electronic and steric nature of substituens on both aniline and Michael acceptor reagents. This way, polysubstituted 4-aminochromane adducts with three contiguous stereogenic centers were obtained, including a quaternary one.



Scheme 2.13

[22] (a) Wang, X.-F.; An, J.; Zhang, X.-X.; Tan, F.; Chen, J.-R. *Org. Lett*. **2011**, *13*, 808. (b) See also: Hua, Q.-L.; Li, C.; Wang, X.-F.; Lu, L.-Q.; Chen, J-R.; Xiao, W.-J. *ACS Catal*. **2011**, *1*, 221.

Another good example of the high performance of cascade reactions initiated by the aza-Michael reaction consists of the use of this reaction desing for building up small-size heterocyclic moieties. In this context, one of the first attemps was described in 2004 related to the synthesis of 2-(phenylsulfonyl)aziridines employing a *O*-nosyl-modified hydroxylamine as a functionalized nitrogen nucleophile in the presence of a chiral cinchona alkaloid based quaternary ammonium salt as a phase transfer catalyst (Scheme 2.14).[23] Due to the good leaving group ability of the nosylate group after the first aza-Michael addition, an intramolecular nucleophilic substitution process occurred subsequently to give the desired products.



Scheme 2.14

More recently, interesting examples have been reported in which the iminium/enamine manifold has been applied to this chemical transformation.[24] In

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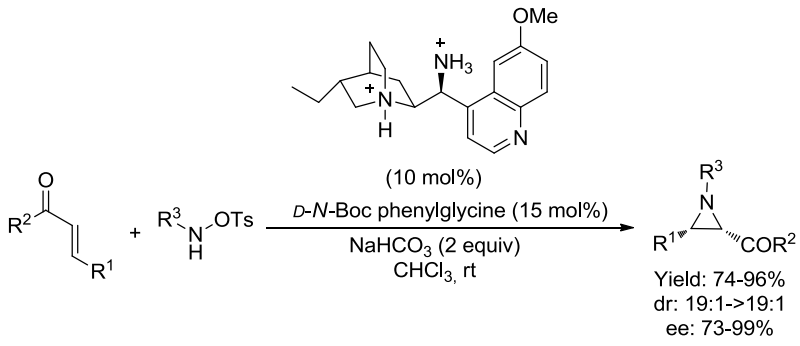
[23] Fioravanti, S.; Mascia, G. M.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **2004**, *60*, 8073. For an additional example for the asymmetric aziridination reaction under phase-transfer catalysis see: Murugan, E.; Siva, A. *Synthesis* **2005**, 2022.

[24] (a) Desmarchelier, A.; Pereida de Sant' Ana, D.; Terrasson, V.; Campagne, J. M.; Moreau, X.; Greck, C.; Figuereido, R. M. *Eur. J. Org. Chem*. **2011**, 4046. (b) Deiana, L.; Dziedzic, P.; Zhao, G.-L.; Vesely, J.; Ibrahem, I.; Rios, R.; Sun, J.; Córdova, A. *Chem. Eur. J*. **2011**, *17*, 7904. (c) De Vicentiis, F.; Bencivenni, G.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Galzerano, P.; Melchiorre, P. *Chem. Asian J.* **2010**, *5*, 1652. (d) Fadeyi, O. O.; Schulte, M. L.; Lindsley, C. W. *Org. Lett*. **2010**, *12*, 3276. (e) Arai, H.; Sugaya, N.; Sasaki, N.; Makino, K.; Lectard, S.; Hamada, Y.

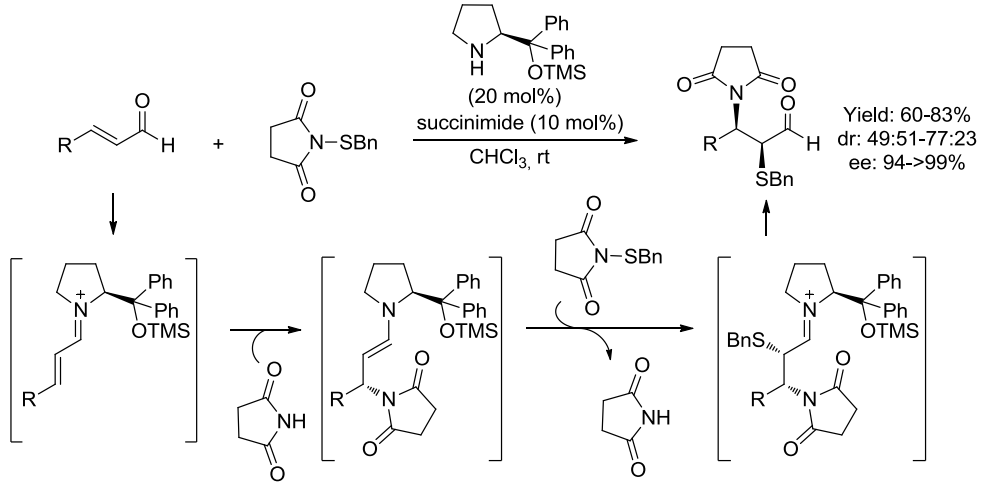
this sense, a remarkable report was published by Melchiorre where an unprecedented example of highly chemo- and stereoselective aziridinations of enones is accomplished.[24f] With the aim of facing this reaction with success, the authors employed chiral primary amines as catalysts, which represents an unique possibility of catalyzing such processes employing enones as Michael acceptors for which the formation of the active iminium-type intermediate by condensation of the catalyst is much more difficult due to the reduced steric constraints presented by these type of aminocatalysts. In this sense, a chiral primary amine salt derived from a cinchona alkaloid was employed as promoter furnishing *N*-protected aziridines efficiently with almost complete diastereocontrol and high enantioselectivity It has to be point out that, even though a chiral Brønsted acid (D-*N*-Boc-phenylglycine) was included as co-catalyst to facilitate iminium ion formation, the use of the opposite enantiomeric counterion (L-*N*-Boc-phenylglycine) did not have important influence on the stereochemical outcome of the reaction, although a lower reactivity and selectivity it was observed for this case (Scheme 2.15).



Scheme 2.15

Tetrahedron Lett. **2009**, *50*, 3329. (f) Pesciaioli, F.; De Vicentiis, F.; Galzerano, P.; Bencivenni, G.; Bartoli, G.; Mazzanti, A.; Melchiorre, P. *Angew. Chem. Int. Ed*. **2008**, *47*, 8703 (g) Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Córdova, A. *Angew. Chem. Int. Ed*. **2007**, *46*, 778.

In contrast to most of the examples shown in the literature in which intramolecular reactions are involved in the second step of the cascade process, there is one example of an intermolecular aza-Michael initiated cascade reaction. This is the case of the work reported by Córdova and co-workers where the enantioselective aminosulfenylation of α,β-unsaturated aldehydes was devised in the presence of a diphenylprolinol derivative using the iminium/enamine activation platform.[25] Interestingly, the reaction involved the use of one single reagent as the source of both the *N*-nucleophile and the electrophile instead of adding two different reagents for each sequencial step. In this sense, *N*-benzylthiosuccinimide played the role of such a useful reagent that participated in the second step of the cascade as sulfur-based electrophile in which succinimide participated as leaving group, releasing this way the nucleophile reagent into the reaction medium. However, the reaction required the incorporation of a catalytic amount of free succinimide to initiate the process (Scheme 2.16).



Scheme 2.16

[25] Zhao, G.-L.; Rios, R.; Vesely, J.; Eriksson, L.; Córdova, A. *Angew. Chem. Int. Ed*. **2008**, *47*, 8468.

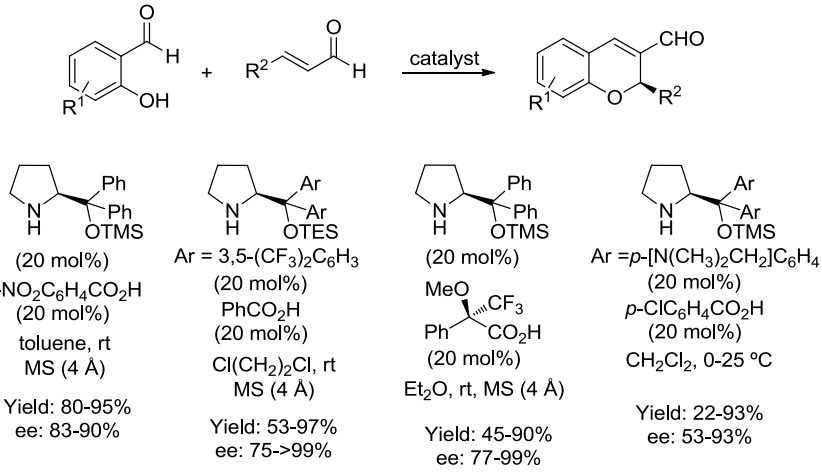
1.3. Oxa-Michael initiated cascade reactions.

Oxa-Michael reactions have traditionally received much less attention from the scientific community compared to the conjugate addition of other hetero-nucleophiles; even though, the first example of an oxa-Michael addition was made known by Loydl as early as 1878.[26] This is mainly due to lack of reactivity and selectivity provided by oxygen centered nucleophiles towards α,β-unsaturated carbonyl compounds. Common substrates used as pronucleophiles in conjugate additions such as water, alcohols and carboxylic acids are poor nucleophiles, being the 1,2 addition the reactivity pattern typically observed in most cases. In addition, in those cases in which 1,4-addition is observed, the reversibility of this transformation is also a major drawback when a stereocontrolled reaction is desired, because the racemization of the final products is also a challenging task to face in this particular case. In this sense, the use of a domino strategy represents a suitable way to deal with this later reversibility issue in order to build up oxygen-containing heterocyclic compounds with good yield and stereoselectivity.

Organocatalysis has been used to address the open challenge of oxa-Michael initiated domino reactions. In this context, the first reports were focused on the application of the iminium/enamine combination in oxa-Michael/aldol cascade reactions using ortho-hydroxybenzaldehydes as functionalized Michael donors. For example, Córdova and co-workers employed this approach for the construction of benzopyran derivatives starting from enals and salicylaldehyde by means of a domino oxa-Michael/aldol/dehydration process using *O*-TMS diphenylprolinol as catalyst, obtaining several chromenes in good to high yields and good to excellent

[26] Loydl, F. *Liebigs Ann. Chem*. **1878**, *192*, 80.

enantioselectivities.[27] Another work published simultaneously described this cascade reaction with slightly different reaction conditions using a bulkier diarylprolinol derivative as organocatalyst and obtaining better results.[28] Further research on this reaction has shown that the combination of the chiral aminocatalyst with a chiral Brønsted acid additive might be beneficial for the organocatalytic transformation, especially in terms of enantioselectivity.[29] Finally, modified diarylprolinol silyl ether containing tertiary amine groups at the aryl substituents[30] was found to be useful for carrying out the reaction in water.[31] Moreover, the catalyst could be easily recovered and recycled representing an advantageous alternative from a practical point of view.



Scheme 2.17

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[27] (a) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem. Eur. J*. **2007**, *13*, 574. For the initial report see: (b) Govender, T.; Hojabri, L.; Moghaddam, F. M.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2006**, *17*, 1763.

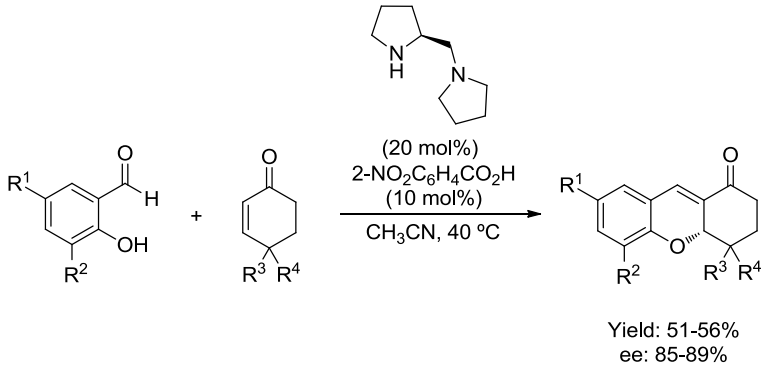
[28] Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun*. **2007**, 507.

[29] Luo, S.-P.; Li, Z.-B.; Wang, L.-P.; Guo, Y.; Xia, A.-B.; Xu, D.-Q. *Org. Biomol. Chem*. **2009**, *7*, 4539.

[30] Zheng, Z.; Perkins, B. L.; Ni, B. *J. Am. Chem. Soc*. **2010**, *132*, 50.

[31] Shen, H.; Yang, K.-F.; Shi, Z.-H.; Jiang, J.-X.; Lai, G.-Q.; Xu, L.-W. *Eur. J. Org. Chem*. **2011**, 5031.

In a similar approach, a methodology for the asymmetric synthesis of tetrahydroxanthenones has been developed using the same strategy but including α,β-unsaturated cyclic ketones as Michael acceptors in the reaction scheme, although the later ones providing lower yields and poorer enantiocontrol.[32]

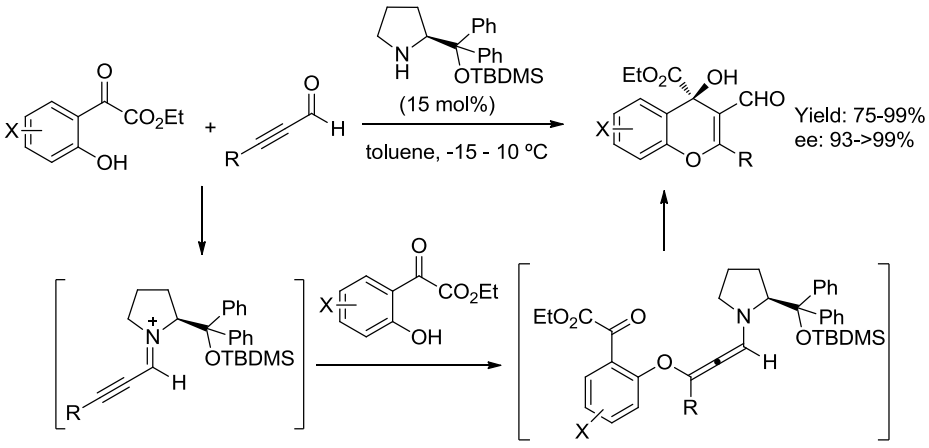


Scheme 2.18

Another related interesting example consists of an aminocatalytic oxa-Michael/aldol sequence between 2-alkynals and 2-hydroxyphenyl-2-oxoacetates under iminium-allenamine catalysis leading to the enantioselective synthesis of chromenes containing a chiral quaternary stereocenter, involving the formation of versatile α-hydroxy carboxylate motif (Scheme 2.19).[33]

[32] (a) Rios, R.; Sundén, H.; Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 2181. For a related example see: (b) Xia, A.-B.; Xu, D.-Q.; Luo, S.-P.; Jiang, J.-R.; Tang, J.; Wang, Y.-F.; Xu, Z.-Y. *Chem. Eur. J.* **2010**, *16*, 801.

[33] Liu, C.; Zhang, X.; Wang, R.; Wang, W. *Org. Lett*. **2010**, *12*, 4948.

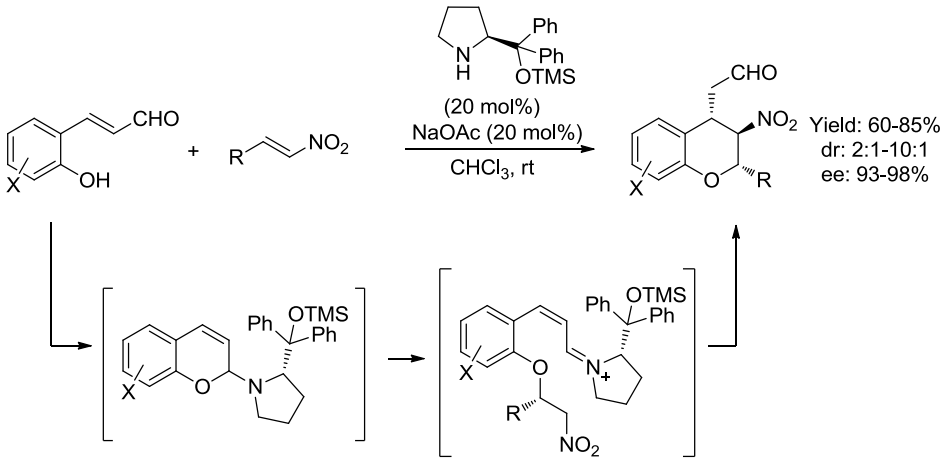


Scheme 2.19

The oxa-Michael/Michael cascade sequence applied to *O*-nucleophiles has also been developed introducing some modifications in the reaction desing.[34] In this sense, phenols have been typically employed as bifunctional Michael donors containing an electron-poor olefin at the ortho position which can participate in a second Michael addition of the cascade process. In this context, a cascade oxa-Michael/Michael reaction was reported using *o*-hydroxycinnamaldehyde as functionalized *O*-nucleophile and a nitroalkene as acceptor in the presence of a chiral secondary amine as organocatalyst, leading to the formation of chiral chromenes in a sigle step in good yields and enantiomeric excesses although with low diastereocontrol. Interestingly, as it is shown in the Scheme 2.20, the formation of a stable hemiaminal intermediate was detected in the reaction mixture, which was generated after the intramolecular addition of the hydroxyl group to the iminium ion formed by condensation of the aminocatalyst with the enal functionality. This intermediate was proposed to participate in the reaction serving as the nucleophilic

[34] Zu, L.; Zhang, S.; Xie, H.; Wang, W. *Org. Lett*. **2009**, *11*, 1627.

species for the first Michael addition to the nitroolefin followed by a subsequent diastereoselective intramolecular Michael reaction which is under substrate control. However, a second alternative pathway should also be considered involving a first non-stereoselective and reversible oxa-Michael addition and followed by a stereocontrolled intramolecular conjugate addition to the intermediate iminium ion.

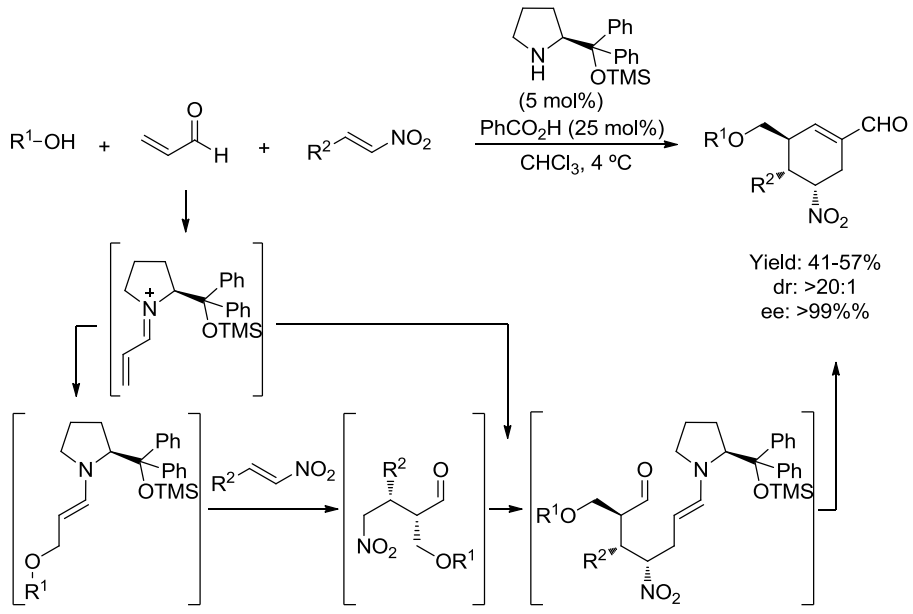


Scheme 2.20

The design of more elaborated and complex cascade sequences constitutes a remarkable advance in this field. This is the case of the multicomponent domino oxa-Michael/Michael/Michael/aldol reaction using an iminium/enamine/iminium/enamine activation manifold shown in Scheme 2.21. In this reaction, simple aliphatic alcohols were employed as oxygen centered nucleophiles along with two equivalents of acrolein and one equivalent of a β-aryl substituted nitroolefin in the presence of catalytic amounts of diphenylprolinol trimethylsilyl ether furnishing highly substituted cyclohexane products as single diastereoisomers in moderate yields and almost complete enantiocontrol.[35] The reaction consisted of the first

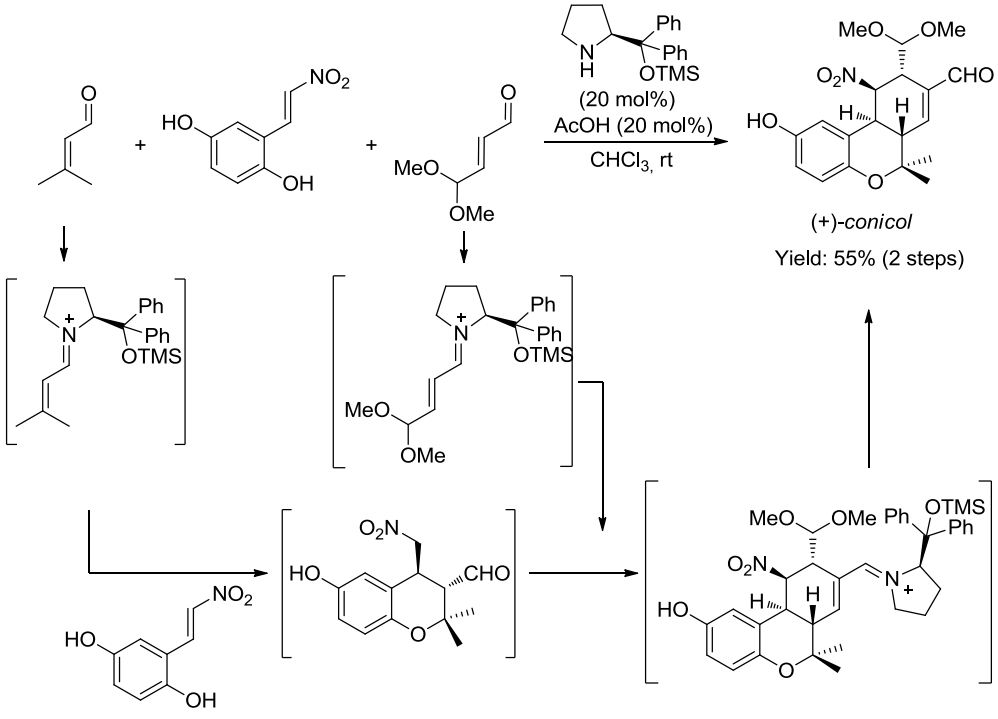
[35] Zhang, F.-L.; Xu, A.-W.; Gong, Y.-F.; Wei, M.-H.; Yang, X.-L. *Chem. Eur. J.* **2009**, *15*, 6815.

activation of acrolein by the aminocatalyst through the formation of the corresponding iminium ion which was able to interact with the aliphatic alcohol through an intermolecular oxa-Michael addition. Then, the formed enamine intermediate underwent conjugate addition to the nitroalkene reagent and, after hydrolysis, a following Michael addition occurred between the generated nitrocompound and a second molecule of acrolein which had been previously activated by the aminocatalyst. The final step involved an intramolecular aldol condensation between the second enamine type specie generated after the last Michael addition and the formyl group presented on the molecule to give the cyclohexene product after a dehydration process and final release of the catalyst. Notably, not only simple alcohols like MeOH and EtOH were reactive but also bulkier or functionalized alcohols behaved suitably as *O*-nucleophiles for this reaction, initiating the cascade process with complete chemoselectivity.



Scheme 2.21

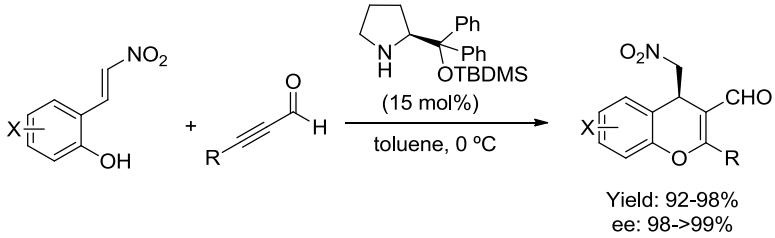
As an illustrative example of the added value of these oxa-Michael initiated transformations, the enantioselective total synthesis of (+)-*conicol* has been reported involving a key step consisting of this multicomponent tandem oxa-Michael/Michael/Michael/aldol in which an *ortho*-hydroxynitrostyrene derivative interacts with two different α,β-unsaturated aldehydes (Scheme 2.22).[36] The reaction consists of an initial oxa-Michael reaction of the phenol moiety to 3-ethyl-2-butenal followed by intramolecular Michael reaction. Next, the nitrocompound generated at this first iminium/enamine cycle undergoes Michael/aldol condensation cascade with the second enal once again making use of the same iminium/enamine manifold.



Scheme 2.22

[36] Hong, B.-C.; Kotame, P.; Tsai, C.-W.; Liao, J.-H. *Org. Lett*. **2010**, *12*, 776.

In a similar approach, ynals have also been included as Michael donors in related oxa-Michael/Michael reaction under iminium/allenamine activation (Scheme 2.23).[37] The feasibility of such domino reaction under the mentioned activation mode was investigated employing different ynals and 2-(*E*)-(2-nitrovinyl)phenols leading to the synthesis of several enantiopure 4*H*-chromenes in excellent yields.



Scheme 2.23

Ynals have also been used as Michael acceptors in one example of enantioselective oxa-Michael/Mannich cascade using the same iminium/allenamine platform.[38] After an optimization process, a diarylprolinol silyl ether was identified as the best catalyst for the reaction of different propargyl aldehydes with salicyl *N*-tosylimine leading to the formation of a wide range of optically active 4-amino-4*H*-chromenes in high yield and with excellent enantiocontrol (Scheme 2.24). Interestingly, catalyst loading could be reduced to 5 mol% with only a small increase in the reaction time.

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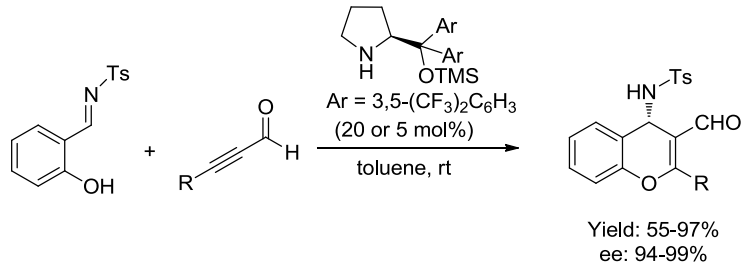
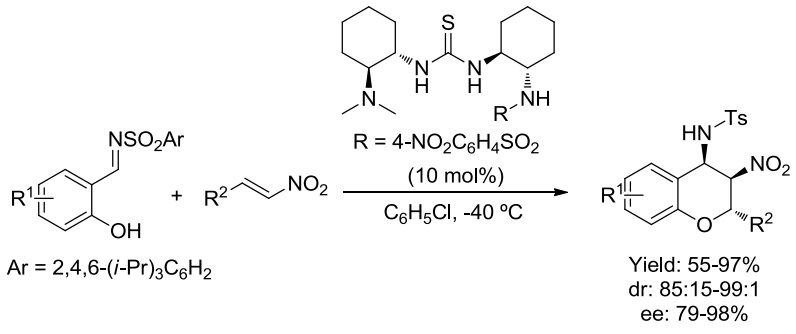
[37] Zhang, X.; Zhang, S.; Wang, W. *Angew. Chem. Int. Ed*. **2010**, *49*, 1481.

[38] Alemán, J.; Núñez, A.; Marzo, L.; Marcos, V.; Alvarado, C.; García-Ruano, J. L. *Chem. Eur. J*. **2010**, *16*, 9453.



Scheme 2.24

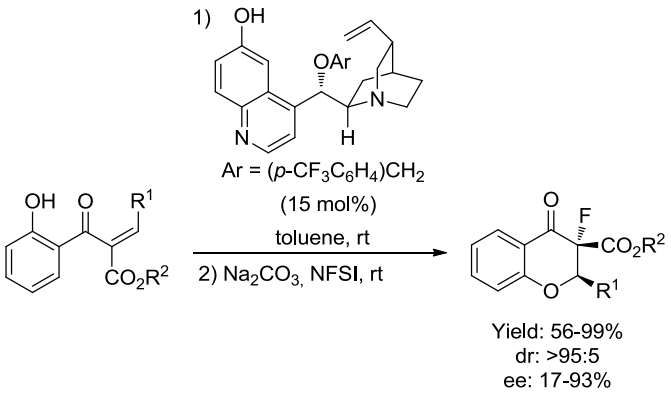
Non covalent organocatalysis has also been used in this field. Interestingly, a multifunctional catalyst with two chiral diaminocyclohexane units and a thiourea moiety was developed and applied to the asymmetric oxa-Michael/Mannich cascade reaction of salicylaldimines with nitroalkenes providing optical active polysubstituted 4-aminobenzopyrans in high yields and with excellent enantiomeric excesses (Scheme 2.25).[39] The authors proposed a transition state model in which the thiourea was proposed to activate the nitroolefin through hydrogen bonding and two secondary functionalities, one Lewis acidic site (monosubstituted sulfonamide) and a Brønsted basic site (the tertiary amine group), were respectively interacting with the azomethine nitrogen and the hydroxy group of the salicylaldimine.



Scheme 2.25

[39] Hou, W.; Zheng, B.; Chen, J.; Peng, Y. *Org. Lett*. **2012**, *14*, 2378.

In a completely different reaction desing, bifunctional cinchona alkaloids have been applied to an organocatalytic intramolecular oxa-Michael/electrophilic fluorination tandem reaction for the access to chiral flavonones.[40] The followed strategy involved the use of a phenol reagent bearing an enoyl substituent at the *ortho* position which acted as the Michael acceptor undergoing intramolecular oxa-Michael reaction. In this sense, the authors found that a highly electrophilic Michael acceptor was required and thus, the reaction was accomplished by the introduction of an ethoxycarbonyl group as second electron-withdrawing group for the activation the electrophilic olefin.[41] After the intramolecular oxa-Michael reaction had taken place the enantioenriched adducts were subjected to electrophilic fluorination leading to the formation of the final products with complete diastereocontrol, in moderate to excellent yields and with good enantioselectivities in most cases (Scheme 2.26).

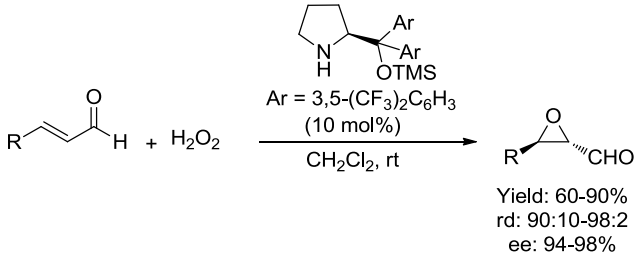


Scheme 2.26

[40] Wang, H.-F.; Cui, H. F.; Chai, Z.; Li, P.; Zheng, C.-W.; Yang, Y.-Q.; Zhao, G. *Chem. Eur. J.* **2009**, *15*, 13299.

[41] Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830.

Finally, it should not be forgotten that the enantioselective epoxidation of α,β-unsaturated carbonyl compounds with peroxides can also be considered to happen *via* a domino oxa-Micahel/intramolecular nucleophilic substitution pathway and thus, the iminium activation concept has showed up as a very successful approach to deal with this particularly interesting transformation. In this context, a pioneering contribution was made by Jørgensen and co-workers using hydrogen peroxide as the oxidant and diarylprolinol trimethylsilyl ether as organocatalyst (Scheme 2.27).[42] Under the best reaction conditions, several β-alkyl and aryl β-substituted enals underwent clean epoxidation providing the final epoxides in good yields and with high enantioselectivities.



Scheme 2.27

This initial work opened the way to the development of a large number of organocatalytic methodologies for the enantioselective epoxidation of enals employing different oxygen sources based on both covalent and non covalent organocatalytic activation modes.[43]

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[42] (a) Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964.

[43] For aminocatalytic epoxidation reactions see: (a) Lifchits, O.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc*. **2010**, *132*, 10227. (b) Sparr, C.; Schweizer, B.; Senn, H. M.; Gilmour, R. *Angew. Chem. Int. Ed*. **2009**, *48*, 3065. (c) Wang, X.; List, B. *Angew. Chem. Int. Ed*. **2008**, *47*, 1119. (d) Reisinger, C. R.; Wang, X.; List, B. *Angew. Chem. Int. Ed*. **2008**, *47*, 8112. (e) Wang, W.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc*. **2008**, *130*, 6070. (f) Lu, X.; Liu, Y.; Sun, B.; Cindirc, B.; Deng, L. *J. Am. Chem. Soc*. **2008**, *130*, 8134. (g) Zhao, G.-L.; Ibrahem, I.; Sundén,

2. SPECIFIC OBJECTIVES AND WORK PLAN.

As it has been comented on the introduction of this chapter, the use of conjugate additions of heteroatom-centered nucleophiles to start domino or cascade processes represent a useful tool for the straightforward construction of complex heterocycles efficiently and with stereocontrol. Nevertheless, these type of conjugate additions, and in particular those involving oxygen-nucleophiles, present additional difficulties due to two major issues that have to be controlled. On the one hand, the intrinsic reversibility of the oxa-Michael reactions involves the formation of configurationally unstable adducts and on the other hand, as it has been shown in the introduction section, the poor nucleophilicity presented by the alcohol functionality restricts the extension of this methodology to those pronucleophiles with high acidity, which guarantee the presence of reactive alkoxide-type nucleophiles in the reaction medium under the neutral or slightly acidic conditions associated to iminium catalysis. Consequently, not only oxa-Michael reactions but also cascade reactions initiated by such chemical transformation still remain rather unexplored.

For this reason, we established the general objective for the first part of the present work consisting of the development of new **organocatalytic cascade reactions initiated by hetero-Michael additions for the enantioselective synthesis of heterocycles under iminium activation.** In fact, the literature precedents at the

H.; Córdova, A. *Adv. Synth. Catal*. **2007**, *349*, 1210. For epoxidation reactions under H-bonding catalysis see: (h) Zheng, C.; Li, Y.; Ynag, Y.; Wang, H.; Cui, H.; Zhang, J.; Zhao, G. *Adv. Synth. Catal*. **2009**, 351. (i) Lu, J.; Zu, Y.-H.; Liu, F.; Loh, T.-P. *Tetrahedron Lett*. **2008**, *49*, 6007. (j) Li, Y.; Liu, X.; Yang, Y.; Zhao, G. *J. Org. Chem*. **2007**, *72*, 288. (k) Lattanzi, A. *Adv. Synth. Catal*. **2006**, *348*, 339. (l) Lattanzi, A. *Org. Lett*. **2005**, *7*, 2579. For epoxidation reaction under phase-transfer catalysis see: (m) Corey, E. J.; Zhang, F.-Y. *Org. Lett*. **1999**, 1, 1287.

beginning of our research regarding stereoselective oxa-Michael initiated cascade reactions were limited to the use of phenols and hydrogen peroxide [27,41,44] as functionalized *O*-nucleophiles. Moreover, regarding simple organocatalytic oxa-Michael reactions which are not involved in cascade processes, literature shows a similar situation, that is, only highly acidic oxygen centered pronucleophiles such as oximes[45] or alkyl hydroperoxides[46] are found to be active in this reaction with enals or enones under iminium activation. In fact, there are a couple of attempts for the amine-catalyzed conjugate addition of aliphatic alcohols to α,β-unsaturated aldehydes proceeding with very low levels of enantioselection.[47]

In this context, we envigased that dihydroxyacetone could behave as a good oxygen-containing functionalized pronucleophile in a novel aminocatalytic oxa-Michael/aldol domino process *via* iminium/enamine platform (Scheme 2.28). In this sense, considering the study carried out by Barbas III[48] in which a pK_a limit is established for potencial nucleophiles to engage in conjugate addition *via* iminiun activation, we thought about this *O*-pronucleophile due to the suitable acidity presented by the hydroxyl groups (pK_a = 12.4).[49] In addition, analyzing the catalytic cycle of the cascade reaction, the possibility for a final hemiacetal formation that could contribute to the stabilization of the final product was also considered that could potentially operate as a driving force of the reaction.

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[44] (a) Merschaert, A.; Delbeke, P.; Daloze, D.; Dive, G. *Tetrahedron Lett.* **2004**, *45*, 4697. (b) Tanaka, T.; Kumamoto, T.; Ishikawa, T. *Tetrahedron: Asymmetry* **2000**, *11*, 4633.

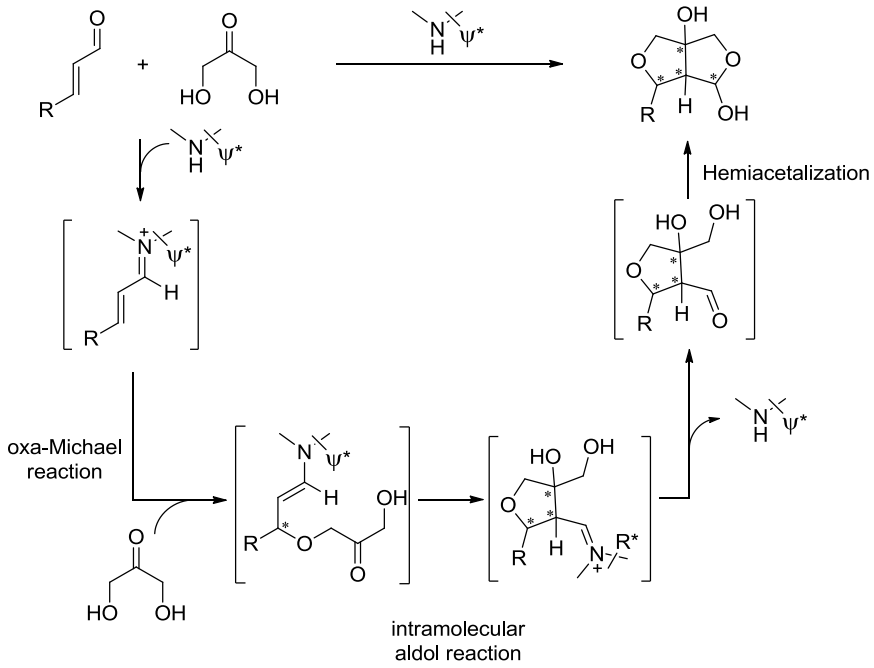
[45] (a) Bertelsen, S.; Diner, P.; Johansen, R. L.; Jørgensen, K. A.; *J. Am. Chem. Soc*. **2007**, *129*, 1536. (b) Carlone, A.; Bartoli, G.; Bosco, M.; Pesciaioli, F.; Ricci, P.; Sambri, L.; Melchiorre, P. *Eur. J. Org. Chem*. **2007**, 5492.

[46] Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. *J. Am. Chem. Soc*. **2008**, *130*, 8134.

[47] (a) Díez, D.; Nuñez, M. G.; Benéitez, A.; Moro, R. F.; Marcos, I. S.; Basabe, P.; Broughton, H. B.; Urones, J. G. *Synlett* **2009**, 390. (b) Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron* **2007**, *63*, 8658.

[48] Alonso, D. A.; Kitagaki, S.; Utsumi, N.; Barbas III, C. F. *Angew. Chem. Int. Ed*. **2008**, *47*, 4588.

[49] Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2012 ACD/Labs).



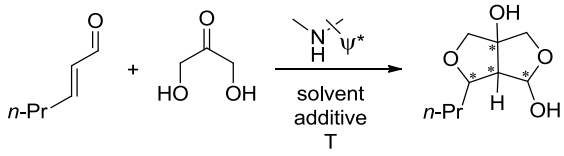
Scheme 2.28

Considering these aspects, the following working plan was stablished:

1. Viability of the reaction: firstly we will proceed to check the viability of the proposed reaction using dihydroxyacetone and *trans*-2-hexenal as model substrates. In case of success, a methodology to determine the enantiomeric excess of the product will have to be developed after the preparation of the corresponding racemic standard.

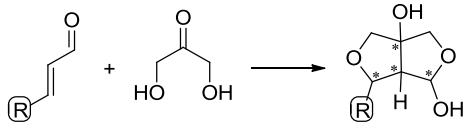
2. Optimization of the reaction conditions: a survey of different chiral secondary amines will be tested in order to identify the one that provides the cascade product efficiently and with the best stereocontrol. Afterwards, other parameters such us solvent, additives and temperature will be evaluated in an effort to obtain

the best results in terms of diastereo- and enantioselectivity, as well as with regard to chemical conversion (Scheme 2.29).



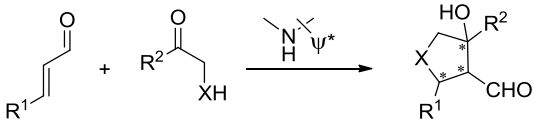
Scheme 2.29

3. Extension of the methodology: With the optimal conditions in hands, we will study the scope of the reaction applying these conditions to α,β-unsaturated aldehydes with different substituents and electronic properties in order to obtain a wide range of optical active products (Scheme 2.30).



Scheme 2.30

4. Once all these points are completed, the search for similar new potencial hetero-nucleophiles that might promote domino processes starting with a hetero-Michael addition is proposed. In this sense, ketones incorporating an α-heteroatomic substituent will be considered for the design of novel hetero-Michael/aldol cascade reactions employing chiral secondary amines as catalysts (Scheme 2.31).



XH = OH, NHR^3, etc.

Scheme 2.31

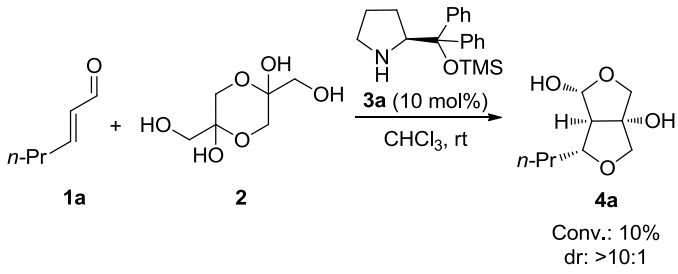
3. RESULTS AND DISCUSSION.

Once the different methodologies and examples found in the literature on the field have been reviewed and after stablishing the objectives and proposing the work plan, the discussion of the more relevant results obtained on this part of our research will be discussed.

3.1. Enantioselective organocatalytic oxa-Michael/aldol cascade reaction.

3.1.1. Viability of the reaction.

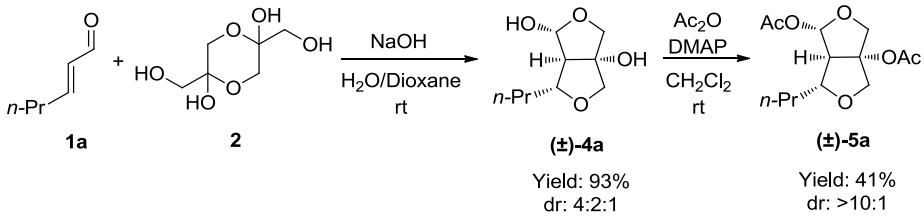
We started our work testing in the reaction between dihydroxyacetone and *trans*-2-hexenal in the presence of 10 mol% of chiral secondary amine **3a**, which is regarded as a privileged chiral secondary amine organocatalyst that has shown an outstanding performance in other hetero-Michael initiated cascade processes under the iminium/enamine manifold (Scheme 2.32). It has to be noticed that the selected oxygen-nucleophile for this reaction is commercially available in a dimeric form which is sparsely soluble in $CHCl_3$; a solvent commonly used in other previous aminocatalytic reactions. This first attempt allowed us to observe the formation of small amounts of furofurane **4a** as a single diastereoisomer with a 10% chemical conversion.



Scheme 2.32

This result confirmed our initial hypothesis, showing that dihydroxyacetone had the expected potential to participate as oxygen centered pronucleophile in oxa-Michael reactions with enals under iminium activation and also that the structure of this reagent is appropriate for a cascade oxa-Michael/aldol reaction, finishing in a final hemiacetalization process that contributes to the stabilization of the final adduct.

At this point, it is worthy of note that the preparation of a racemic adduct was necessary for the determination of the enantiomeric excesses. In this sense, the same reaction was carried out in the presence of NaOH (Scheme 2.33), obtaining furofurane **(±)-4a** as a mixture of diastereoisomers (dr: 4:2:1). After some failed attemps trying to get the chromatographic separation of both enantiomers of the major diastereoisomer we decided to modify its structure through peracetylation under standard conditions.



Scheme 2.33

This new derivative **(±)-5a** was subjected to HPLC analysis on chiral stationary phase. A good separation was obtained employing a *Chiralpak IA* chiral column and a mixture of 99:1 *n*-hexane/*i*-PrOH as eluent. The two chromatograms obtained for the racemic mixture **(±)-5a** and the acetylated enantioenriched compound **5a** obtained in our first test reaction (see Scheme 2.32) are included bellow, in which it can be appreciated a 99% ee (Figure 2.1).

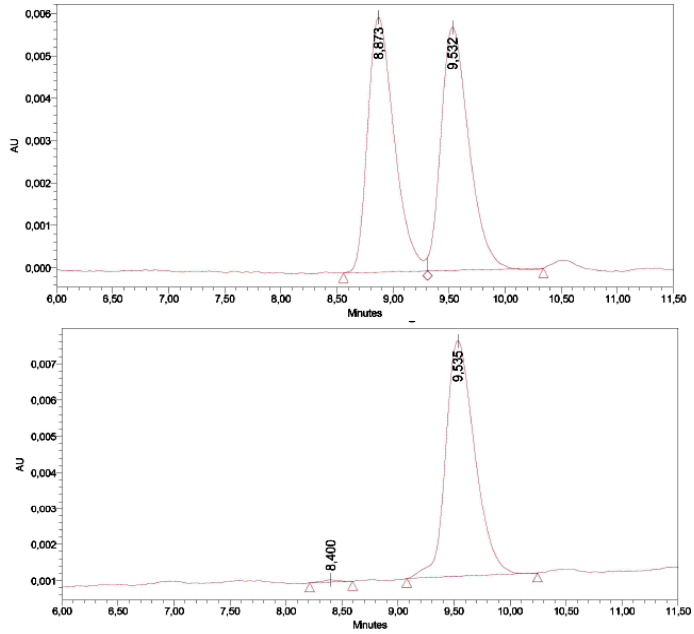


Figure 2.1

In addition, we also ran a NOESY experiment in order to determine the relative configuration of the synthesized product. For that purpose, we used the peracetylated compound **5a** as the ^{1}H-NMR spectrum obtained for this derivative was more suitable to analyaze the spectroscopic data properly. In this sense, we could appreciate a significative n.O.e. between H1 and H6, which indicates a *cis* relative disposition of the alkylic chain and the acetoxy group at C1. On the other

hand, the observed n.O.e. between H6a and the methylene group of the alkyl group directly bonded to the bicycle accounts for a *cis* relative configuration between such proton and the *n*-propyl group. (Figure 2.2).

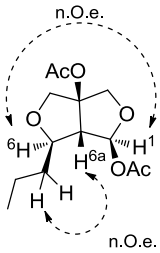


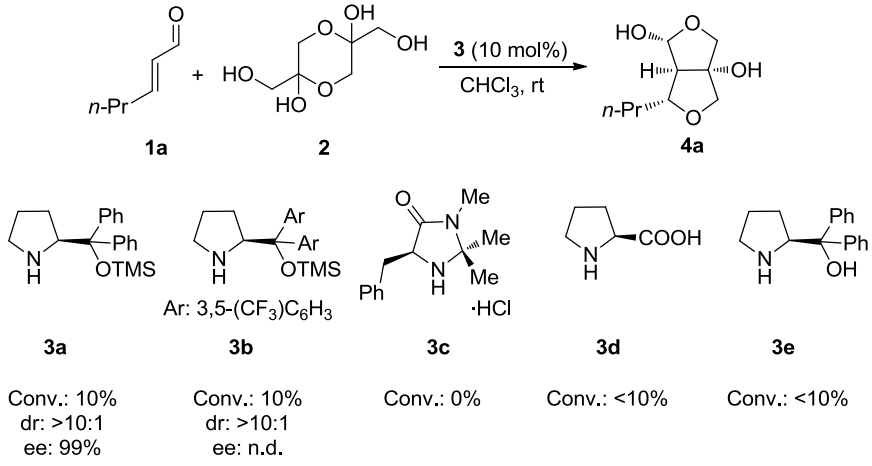
Figure 2.2

3.1.2. Optimization of the reaction conditions.

From our first experiment shown in Scheme 2.31, it became evident that we were able to run the projected reaction in a highly diastereo- and enantioselective fashion but the final product was obtained in very poor yields. In this sense, during this optimization process, we directed our efforts to find improved conditions that would allow us to carry out the reaction with complete conversion. In this context, at the beginning of the optimization process, a selection of some other readily available 2-substituted chiral pirrolidines was surveyed as potential catalysts for the reaction (Scheme 2.34). All the reactions were run using 10 mol% of the aminocatalyts and a 1:1 ratio of **1a**/**2**. In this manner, first results were obtained showing that an *O*-protected α,α-diarylprolinol derivative bearing bulkier aryl substituents such as aminocatalyst **3b**[50] were able to provide the expected heterocycle **4a** as a single diastereoisomer and with the same conversion of 10% as observed for the same reaction using the catalyst **3a** after 24 hours stirring at rt (ee

[50] Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794.

was not determine). On the other hand, MacMillan first generation catalyst[51] (**3e**) resulted to be inactive for this transformation. Swiching to chiral inductors presenting hydrogen donor units on the structure such as L-proline (**3a**) and diphenylprolinol (**3b**), led to the formation of furofurane **4a** with low conversion.



Scheme 2.34

With these preliminary results in hands, we considered the addition of a co-catalyst to the reaction medium to study the possible effects on the conversion and now establishing *O*-TMS-diphenylprolinol **3a** as the best catalyst for our reaction. Thus, we firstly set some experiments in the presence of catalytic amounts of different Brønsted acids, which have been described as additives that can facilitate the formation of the iminium intermediate and thus accelerate the iminium mediated process.[52]

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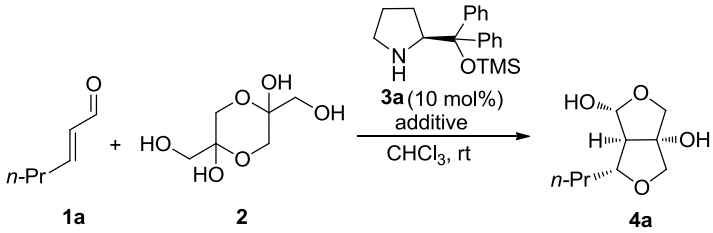
[51] Lelais, G.; MacMillan, D. W. *Aldrichim. Acta* **2006**, *39*, 79.

[52] Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis-From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Germany, **2005**.

Table 2.1: Effect of Brønted acids as co-catalysts.



Entry	Additive (mol%)	pK_a[a]	Conv. (%)[b]	dr[c]	e.e. (%)[d]
1	-		10	>10:1	n.d.
2	$PhCO_2H$ (10)	4.20	50	>10:1	99
3	TFA (10)	-0.25	-	-	-
4	*p*-TSA (10)	-2.80	-	-	-
5	DABCO	-	<10	n.d.	n.d.
6	Et_3N	-	<10	n.d.	n.d.
7	NaOAc	-	20	>10:1	n.d.
8	$PhCO_2H$ (20)	4.20	99 (93)[e]	>10:1	99

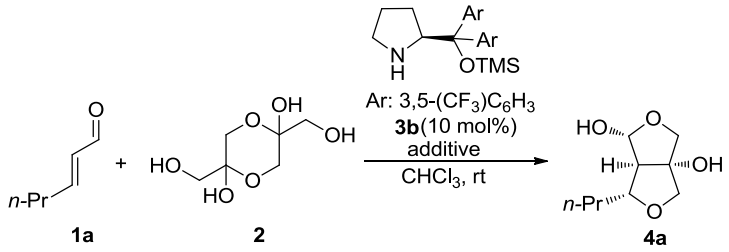
[a]pK_a values measured in H_2O. Perrin, D. D.; Serjeant, E. P.; Dempsey, B. *pK_a Predictions for Organic Acids and Bases,* Champman and Hall, London, **1981**. [b]Conversion determined from ^{1}H-NMR analysis of crude aliquots. [c]Determined by ^{1}H-NMR analysis of the crude reaction mixture. [d]Determined by HPLC analysis after transformation into the diacetylated product. [e]Yield of the isolated product given within the parentheses.

As shown in Table 2.1, we found that the incorporation of 10 mol% of $PhCO_2H$ as a Brønsted acid co-catalyst was beneficial for the reaction in terms of conversion, reaching up to 50% after 16 hours stirring and still maintaining the high diastereoselectivity (entry 1 *versus* entry 2). Stronger acids were tested but in these cases only the starting materials were recovered (entries 3 and 4). The use of a base as an additive was also considered in order to verify the possible effect of such co-catalysts on the concentration of *O*-nucleophile in the reaction medium and thus, on

the conversion of the reaction, by means of the formation of the corresponding alcoxide. Nevertheless, catalytic amounts of some bases such as DABCO (entry 5), Et_3N (entry 6) or NaOAc (entry 7) provided negative results. We therefore turned back to the incorporation of $PhCO_2H$ as additive and, importantly, an increase in the amount of this co-catalyst to a 20 mol% led to full conversion in the same reaction time (entry 8).

Parallely, we also evaluated the use of the modified bulkier amine **3b** as catalyst. As shown in Table 2.2, the addition of 10 mol% of benzoic acid provided the adduct **4a** in trace amounts (entry 1).

Table 2.2: oxa-Michael/aldol/hemiacetalization domino reaction between *trans*-2-hexenal and dihydroxyacetone catalyzed by amine **3b**. Effect of acid and basic additives.



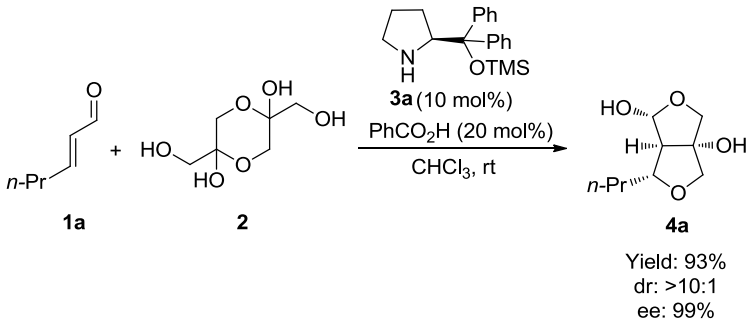
Entry	Additive (mol%)	Conv. (%)[a]	dr[b]	e.e. (%)[c]
1	$PhCO_2H$ (10)	<10	-	-
2	$PhCO_2H$ (100)	50	>10:1	98
3	$PhCO_2H$ (200)	99	>10:1	98
4	Ph_3CCO_2H (10)	-	-	-
5	DABCO (10)	-	-	-

[a]Conversion determined from ^{1}H-NMR analysis of crude aliquots. [b]Determined by ^{1}H-NMR analysis of the crude reaction mixture. [c]Determined by HPLC analysis after transformation into the diacetylated product.

Further experiments showed that the addition of two equivalents of co-catalyst was required to achieve full conversion, whereas one equivalent provided the final product only with 50% conversion (entry 2 and entry 3) after 16 hours. Another Brønsted acid co-catalyst such as Ph_3CCO_2H did not lead to any improvement (entry 4) and the same situation was found when a basic additive such as DABCO was employed (entry 5). Regarding the stereochemical outcome, the catalyst **3b** worked similar way to **3a** without any variation in the excellent diastereo- and enantioselectivity obtained previously.

Once established the use of 10 mol% of chiral amine catalyst **3a** and 20 mol% of $PhCO_2H$ as co-catalyst as the best catalytic system to promote the reaction, we next studied the influence of the solvent. We initially tested a wide range of solvents with different polarities, such as AcOEt, dioxane, acetonitrile, DMF, CCl_4, THF and CH_2Cl_2, observing the formation of the adduct **4a** only when $CHCl_3$ was employed. Moreover, *i*-PrOH was also evaluated in order to study the possible effect of a protic solvent, although the reaction did not work either. Finally, we also ran some reactions at different temperature but carrying out the domino process at 0 ºC led to a very slow reaction affording less than 10% conversion in 5 days. On the contrary, when refluxing the reaction, decomposition of the complex mixture of products was observed.

At this point, and taking into account all these results we stablished that the best protocol for the oxa-Michael/aldol/hemiacetalization cascade reaction between *trans*-2-hexenal and dihydroxyacetone dimer in terms of conversion, diastereo- and enantioselectivity consists of the use of 10 mol% of *O*-TMS-diphenylprolinol as organocatalyst with 20 mol% of benzoic acid as additive in $CHCl_3$ at room temperature (Scheme 2.35).

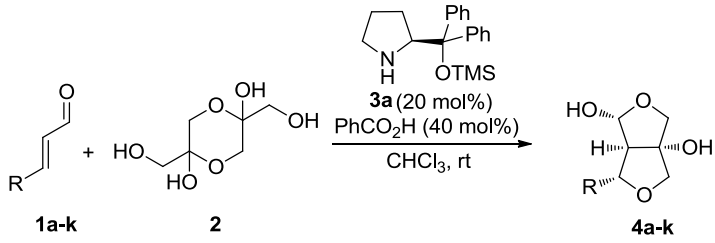


Scheme 2.35

3.1.3. Scope of the reaction.

Having stablished the best reaction conditions, we decided to extend this methodology to the use of other α,β-unsaturated aldehydes containing different substituents at the β-position in order to determine the scope and limitations of the reaction. For that purpose, several Michael acceptors with different steric and electronic demand were used. As shown in Table 2.3, the reaction proceeded efficiently with most enals tested, affording the desired heterocycles in good to excellent yields. Noteworthy, the broad scope of the reaction allowed us to obtain differently substituted hexahydrofuro[3,4-*c*]furanes in excellent yields when enals presenting short (entry 2 and entry 3) and long (entries 4-7) alkyl chains were used and, even a long alkyl substituent containing an unsaturation on its structure was well tolerated (entry 8). Moreover, β-aryl substituted enals (entries 9-11) were also evaluated, observing a slight decrease on the chemical yield, which might be attributed to the lower electrophilicity that these α,β-unsaturated aldehydes present due to the fact that the conjugate system on this substrates is more extended. On the other hand, β-heteroaryl substituted enal **1l** (entry 12) and functionalized α,β-unsaturated aldehyde **1m** (entry 13) were also surveyed, although we did not obtain the expected furofuranes.

Table 2.3: Aminocatalytic cascade reaction between dihydroxyacetone and α,β-unsaturated aldehydes under the best reaction conditions.



Entry	R	Product	Yield (%)	dr[a]	ee (%)[b]
1	*n*-Pr **(1a)**	**4a**	96	>10:1	99
2	Me **(1b)**	**4b**	89	7:1	92
3	Et **(1c)**	**4c**	86	7:1	95
4	*n*-Bu **(1d)**	**4d**	89	>10:1	97
5	*n*-C_5H_{11} **(1e)**	**4e**	92	>10:1	96
6	*n*-C_6H_{13} **(1f)**	**4f**	78	>10:1	95
7	*n*-C_8H_{17} **(1g)**	**4g**	76	>10:1	98
8	(*Z*)-EtCH=$CHCH_2CH_2$ **(1h)**	**4h**	83	>10:1	94
9	Ph **(1i)**	**4i**	76	>10:1	98
10	*o*-$MeOC_6H_4$ **(1j)**	**4j**	71	>10:1	90
11	(*m*-MeO)(*p*-AcO)C_6H_3 **(1k)**	**4k**	67	>10:1	94
12	2-Furyl **(1l)**	**4l**	-	-	-
13	CO_2Et **(1m)**	**4m**	-	-	-

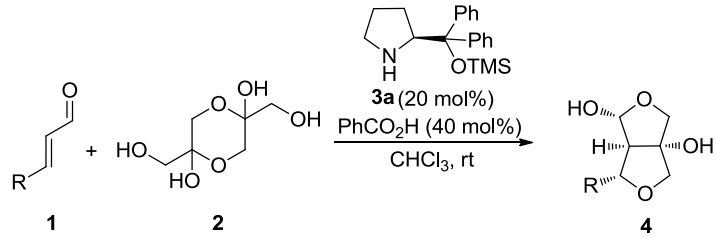
[a]Determined by ^{1}H-NMR analysis of the crude reaction mixture.[b]Determined by HPLC analysis from the diacetylated products **5a** and **5d-f** and from the benzoylated compounds **6a-g**.

Remarkably, all adducts **4a-k** were obtained as single diastereoisomers in almost all cases (entries 1, 4-11), except those with simplest aliphatic chains, which were synthesized with a slightly lower but still good diastereomeric ratio of 7:1

(entries 2-3). In addition, organocatalyst **3a** furnished an excellent enantiocontrol, furnishing the final adducts **4a-k** as highly enantioenriched compounds (>90% ee in all cases).

Further research showed up the possibility to carry out these reactions on larger scale (Table 2.4), resulting in similar yields and estereoselectivities when we set up the reactions on 1 mmol scale (entries 1-3). We also checked out the influence of a large excess of the corresponding α,β-unsaturated aldehyde and under more dilute conditions (entries 4-6). In these cases, the yields increased slightly (entries 4-6 versus entries 1-3) and also comparing to the reactions shown in Table 2.3 (entries 4, 7 and 9), which were carried out in a lower scale (0.2 mmol).

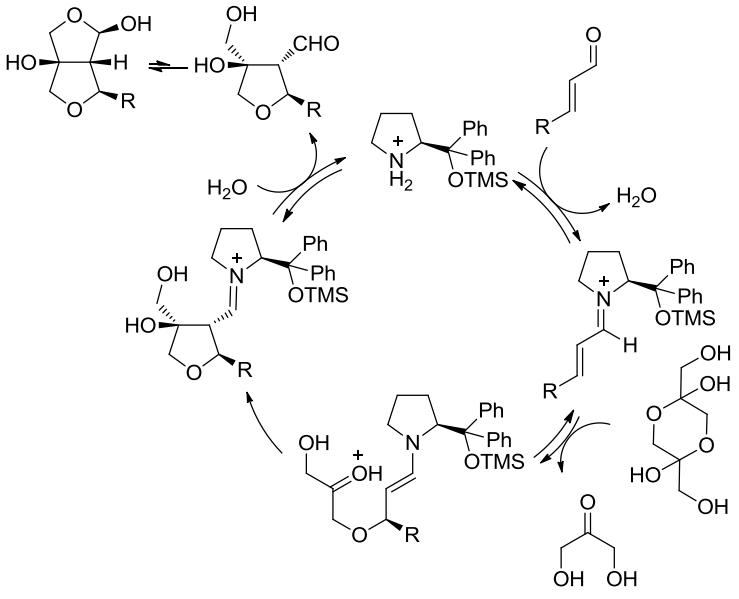
Table 2.4: Aminocatalytic cascade reaction between dihydroxyacetone and α,β-unsaturated aldehydes under the best reaction conditions on large scale.



Entry	R	Product	Yield (%)	dr[a]	ee (%)[b]
1	*n*-Bu **(1d)**	**4d**	90	>10:1	98
2	*n*-C_8H_{17} **(1g)**	**4g**	74	>10:1	97
3	Ph **(1i)**	**4i**	77	>10:1	98
4	*n*-Bu **(1d)**	**4d**	98	>10:1	97
5	*n*-C_8H_{17} **(1g)**	**4g**	96	>10:1	98
6	Ph **(1i)**	**4i**	80	>10:1	98

[a]Determined by ^{1}H-NMR analysis of the crude reaction mixture. [b]Determined by HPLC analysis from the diacetylated product **5a** and from the benzoylated compounds **6a** and **6g**.

A plausible mechanistic proposal for this reaction is given in Scheme 2.36. The reaction is proposed to start with the formation of the iminium ion by condensation of the enal with the aminocatalyst followed by the conjugate addition of dihydroxyacetone dimer to the *Re* face of the formed catalytic *E*,*E* iminium ion intermediate. Then, the generated enamine intermediate would undergo intramolecular aldol reaction with the ketone moiety delivering the final furofuranes **4** after releasing the organocatalyst by hydrolysis and undergoing a final internal hemiacetal formation step which should take place under thermodinamic control, providing the most stable diastereoisomer at the anomeric carbon center. With regard to the role played by the additive, we believe that benzoic acid participates by assisting the formation of the iminium ion intermediate, as well as in the activation of the ketone unit in the second step of the cascade reaction by increasing its electrophilicity through protonation.



Scheme 2.36

Importantly, the high stereochemical control achieved in the overall process is proposed to rely on the irreversible intramolecular C-C bond formation step, taking into account the known reversibility of oxa-Michael addition reactions.[47] In this context, the efficiency of the catalyst **3a** to control the two stereocenters formed in the intramolecular aldol reactions is well documented.[5,53] This hypothesis calls for a dynamic kinetic resolution process, in which the chiral catalyst accelerates de aldol reaction for one of the diastereoisomers generated after the first conjugate addition step over the other, the later epimerizing due to the reversibility of the oxa-Michael reaction. However, a second possibility can also be considered which involves a catalyst-controlled oxa-Michael step followed by a fast intramolecular aldol reaction which prevents the retro-oxa-Michael process.

In order to clarify this matter we tried to get some conclusive proofs. In this sense, we tried to detect the oxa-Michael adduct intermediate by carrying out ^{1}H-NMR analyses of aliquots of the reaction mixture and we also surveyed the possibility of isolating this intermediate by runing the reaction under stoichiometric conditions. However, all these attemps were unsuccessful, which would be in accordance with the first hypothesis proposed above but still not conclusive to stablish a firm argument.

On the other hand, with the aim to corroborate our hypotesis related to the role played by the final hemiacetal formation step as driving force, we set a control experiment using crotonaldehyde and a modified substrate such as α-hydroxyacetophenone under the optimized reaction conditions (Scheme 2.37). This reaction did not furnish any product and only unmodified starting materials were

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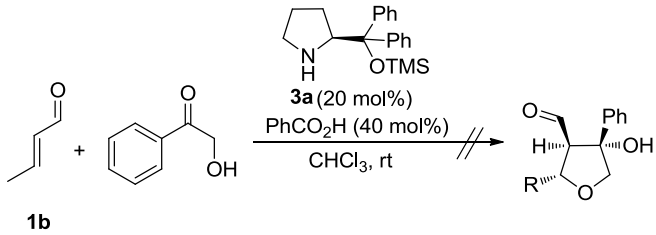
[53] (a) Li, D. R.; Murugan, A.; Falck, J. R. *J. Am. Chem. Soc*. **2008**, *130*, 46. (b) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun*. **2007**, *507*. (c) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem. Eur. J*. **2007**, *13*, 574. (d) Govender, T.; Hojabri, L.; Moghaddam, F. M.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2006**, *17*, 1763.

recovered. Therefore, we concluded that the hemiacetal-formation step is also important for attaining full conversion. We interpret this latter finding as efficient product scavenging from the catalytic cycle by the formation of a more stable bicyclic compound such as **4.**

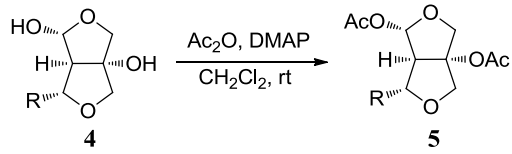


Scheme 2.37

3.1.4. Derivatization of the final adduts.

A survey of the reactivity of the obtained adducts was carried out in order to show up their possible applications as chiral building blocks in organic synthesis.

Table 2.5: Acetylation of the domino oxa-Michael/aldol/hemiacetalization products.

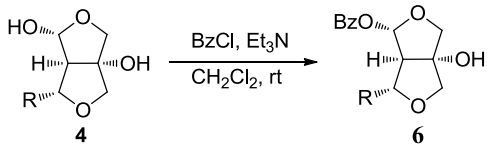


Entry	R	Product	Yield (%)
1	*n*-Pr **(4a)**	**5a**	99
2	Et **(4c)**	**5c**	90
3	*n*-C_5H_{11} **(4e)**	**5e**	96
4	Ph **(4i)**	**5i**	80
5	*o*-$MeOC_6H_4$ **(4j)**	**5j**	74
6	(*m*-MeO)(*p*-AcO)C_6H_3 **(4k)**	**5k**	72

Firstly, it has to be mentioned that we have already demonstrated that the two hydroxy groups of these adducts can be modified by acetylation, which was performed for the ee determination. For that purpose, we treated several of the obtained adducts with Ac_2O and DMAP in CH_2Cl_2 affording the corresponding peracetylated compounds **5** efficiently (Table 2.5).

Alternatively, when we tried to incorporate a bulkier group such as benzoyl treating alcohols with BzCl and Et_3N in CH_2Cl_2, we observed the selective protection of the hydroxy group on the hemiacetal moiety. Although the yields obtained in these transformations were somehow lower than the ones achieved in the peracetylation process, we could easily prepare monoprotected compounds **6b-h** in a fast and reliable way (Table 2.6).

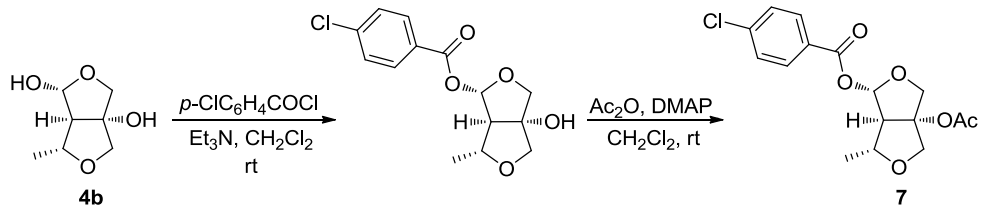
Table 2.6: Benzoylation of the domino oxa-Michael/aldol/hemiacetalization products.



4 **6**

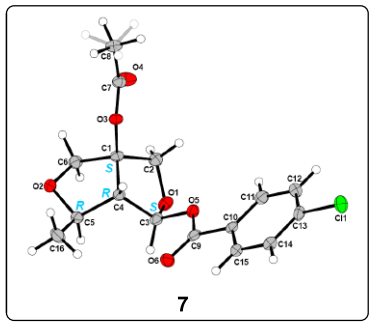
Entry	R	Product	Yield (%)
1	Me **(4b)**	**6b**	75
2	Et **(4c)**	**6c**	75
3	*n*-Bu **(4d)**	**6d**	70
4	*n*-C_5H_{11} **(4e)**	**6e**	80
5	*n*-C_6H_{13} **(4f)**	**6f**	73
6	*n*-C_8H_{17} **(4g)**	**6g**	68
7	(*Z*)-EtCH=$CHCH_2CH_2$ **(4h)**	**6h**	70

At this point, we also directed our efforts to prepare a new derivative in order to get a solid compound containing a heavy atom on its structure that could allow us to carry out, if a crystalline compound is obtained, the determination of the absolute and relative configuration by single crystal X-ray analysis. In this sense, compound **7** was synthesized starting from the furofurane **4b** through a benzoylation reaction using *p*-chloroperbenzoic acid together with a base in CH_2Cl_2 and then the remaining hydroxy group was acetylated under standard conditions (Scheme 2.38). This way the bicyclic product **7** was isolated as a white solid that could be recrystalized allowing to grow suitable crystals for X-ray analysis.



Scheme 2.38

The crystal structure of **7** is depicted in Figure 2.3 showing an (1*S*, 3a*S*, 6*R*, 6a*R*) absolute configuration and also confirming the relative configuration proposed previously based on NMR experiments (see Figure 2.2). The configuration of all the adducts **4** obtained in the oxa-Michael/aldol/hemiacetalization reaction catalyzed by **3a** was assigned by analogy.



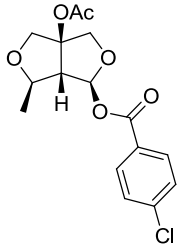
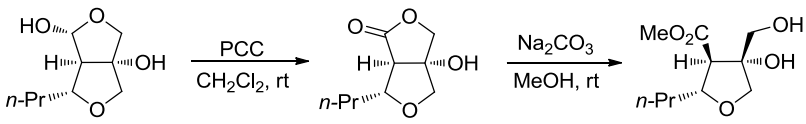


Figure 2.3

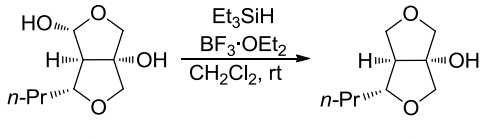
Parallely, the reactivity of the hemiacetal functionality was examined treating furofuranes with both reducing agents and oxidants. In this sense, the adduct **4a** was treated with PCC in CH_2Cl_2 which are reported to be suitable mild conditions to perform oxidation reactions of hemiacetals to the corresponding lactones.[54] By carrying out this transformation the enantioenriched bicyclic lactone **8** was obtained in excellent yield. Then, this lactone was easily transformed into the corresponding furane **9** through methanolysis reaction under basic conditions (Scheme 2.39). Both compounds (**8** and **9**) were obtained as single diastereoisomers in high yields, which indicates that these transformations proceeded without epimerization of any stereocenter present at the starting material.



Scheme 2.39

[54] Sun-Gon, K. *Tetrahedron Lett*. **2008**, *49*, 6148.

In addition, when triethylsilane and $BF_3{\cdot}OEt_2$ were mixed with the heterocycle **4a** in CH_2Cl_2 at room temperature, the final adduct **10** was quantitatively obtained after reduction of the hemiacetal moiety (Scheme 2.40).



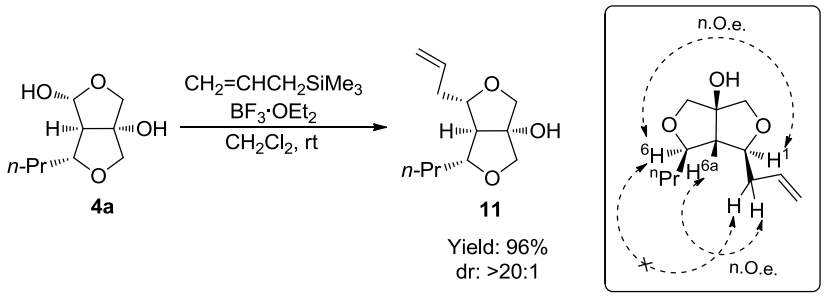
4a **10**

Yield: 99%

Scheme 2.40

Afterwards, we also decided to survey the possibilities of a diastereocontrolled allylation reaction at this anomeric carbon atom. In this sense, when treating the adduct **4a** with allyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$,[55] the adduct **11** was obtained in excellent yield and as a single diastereoisomer (Scheme 2.41). The relative configuration of the compound **11** was determined by selective n.O.e. experiments from which we could appreciate a significative n.O.e. between H6a and the methylene group of the allyl substituent which entails a *cis* relative disposition of this proton and the alkyl chain. In the same way, the observed n.O.e. between H1 and H6 involves *trans* relative disposition of the allyl substituent and H6. Both effects are reinforced by the lack of n.O.e. between the methylene protons of the allyl group and H6. Thus, once the spectroscopic data was analyzed and having determined the absolute configuration of the compound **4a**, we proposed (1*S*, 3a*S*, 6*R*, 6a*S*) configuration for the allylated furofurane **11**.

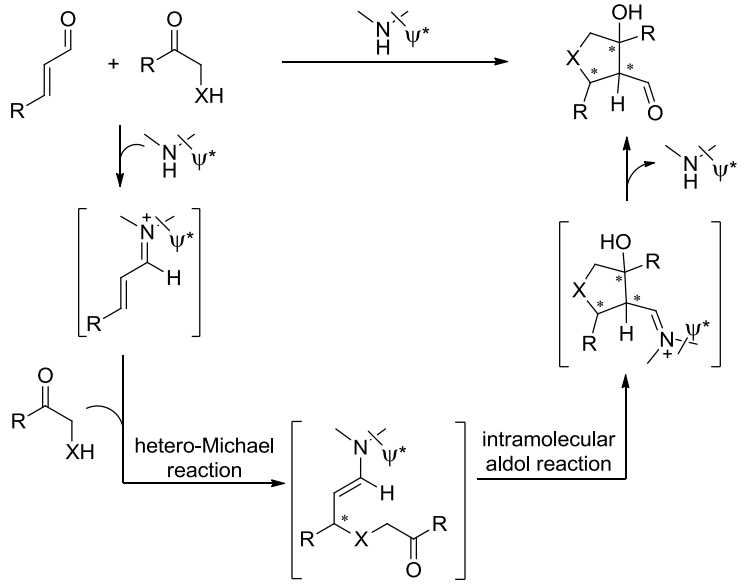
[55] Nagumo, S.; Ishii, Y.; Kakinoto, Yo-i; Kawahara, N. *Tetrahedron Lett*. **2002**, *43*, 5333.


HO
H
OH
n-Pr
O
O
4a
CH2=CHCH2SiMe3
BF3·OEt2
CH2Cl2, rt
H
OH
n-Pr
O
O
11
Yield: 96%
dr: >20:1
n.O.e.
OH
O
O
6H
nPr
H6a
H1
H H
n.O.e.

Scheme 2.41

3.2. Other α-heterosubstituted ketones.

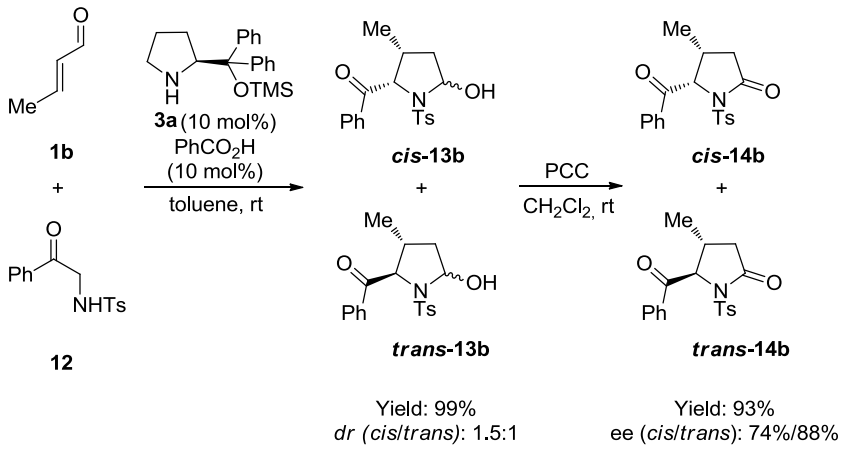
Next we proceeded to search for some other potential substrates for the development of different hetero-Michael/aldol cascade reactions. For that purpose, we thought about α-heterosubstituted ketones as potential substrates capable to promote this type of sequences for the construction of diverse heterocycles (Scheme 2.42).



Scheme 2.42

Therefore, and taking into account that hydroxyacetophenone had already been tested without success in this type of transformation (see Scheme 2.37), we decided to study the use of a *N*-protected-α-aminoketone, using *p*-toluensulfonyl group with the hypotesis that this protecting group would enhance the acidity of the NH moiety. However, when *N*-tosyl-α-aminoacetophenone **12** was subjected to reaction with crotonaldehyde in the presence of 10 mol% of (*S*)-α,α-

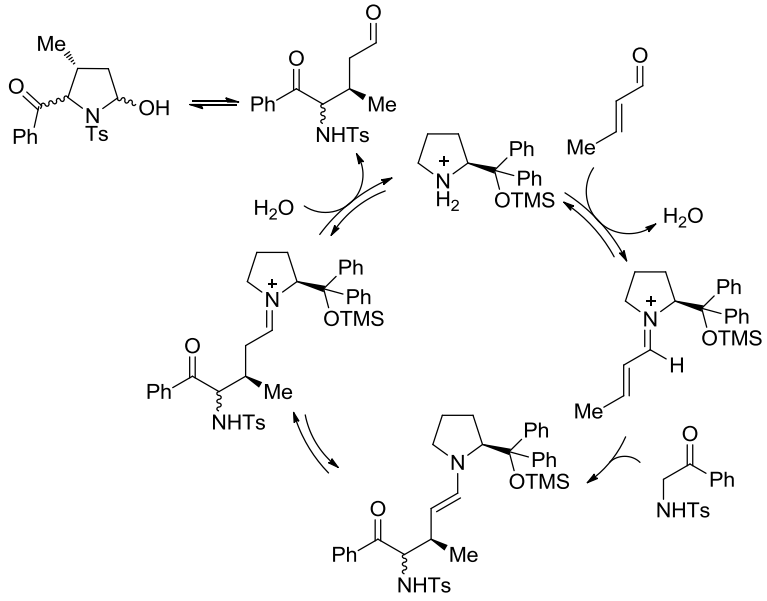
diphenylprolinol trimethylsilyl ether **3a** and 10 mol% of benzoic acid in toluene, a new compound **13b** was isolated in 99% yield instead of the expected aza-Michael/aldol product (Scheme 2.43). This new pyrrolidine adduct was obtained as a mixture of *cis* and *trans* diastereoisomers, each of them as the corresponding mixture of α and β anomers. In order to simplify the treatment of this complex mixture of products we decided to oxidize the hemiaminal **13b** by treating with PCC to give the *cis* and *trans* mixture of γ-lactam **14b**. Unfortunately, the obtained diastereoisomers ***cis*-13b** and ***trans* 13b** and the corresponding γ-lactams ***cis*-14b** and ***trans*-14b** could not be separated by flash column chromatography.



Scheme 2.43

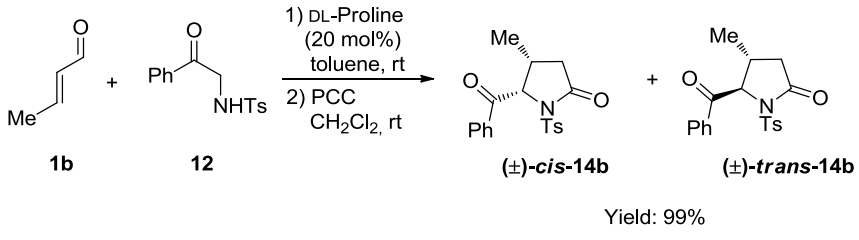
The formation of this new product **13** can be explained by a Michael reaction of ketone **12** to the less hindered stereotopic face of the chiral iminium ion which has been formed by condensation of the enal with the aminocatalyst **3a**, forming a new stereocenter. Then, the resulting enamine intermediate would tautomerize to the corresponding iminium ion and finally, a hydrolysis of this catalytic intermediate would take place releasing the catalyst and delivering a γ-aminoaldehyde which

would undergo a hemiaminalization process to give the corresponding pyrrolidine **13** (Scheme 2.44).



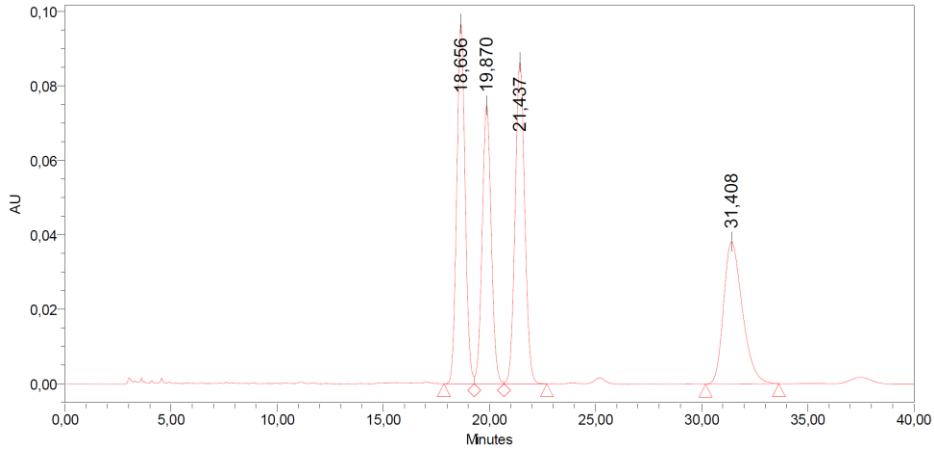
Scheme 2.44

We also proceeded to determine the enantiomeric excesses of the adducts obtained in the reaction by preparing a racemic standard with DL-proline as catalyst (Scheme 2.45). Both enantiomers of the mixture **(±)-*cis*-14b** and **(±)-*trans*-14b** were separated by HPLC employing a *Chiralpak AD-H* chiral column and a mixture of 80:20 *n*-hexane/*i*-PrOH as eluent.



1b **12** **(±)-*cis*-14b** **(±)-*trans*-14b**

Yield: 99%

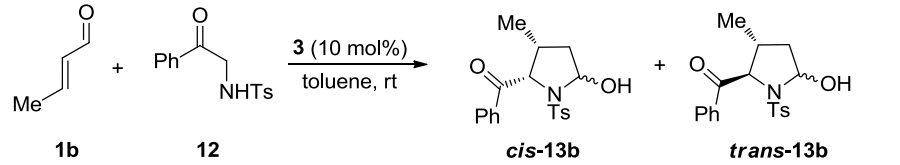


This new reaction involves a very efficient and straightforward approach to substituted pyroglutamic acid derivatives which are structures of interest for many organic chemistry researchers due to the unlimited uses that such molecules have provided in clinical and/or medical fields, as well as in total synthesis of natural products.[56] Motivated by the promising outcome obtained in terms of chemical yield and stereoselectivity for the synthesis of such interesting compounds, we focused our research on the optimization of this reaction in order to achieve high diastereo- and enantiocontrol.

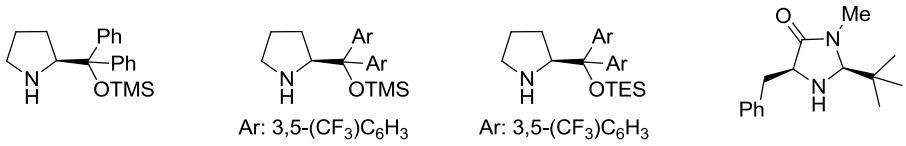
In this context, we started our study by testing some other chiral amine catalysts in order to identify the one that could provided the best diastereo- and enantiocontrol using the addition of *N*-tosyl-α-aminoacetophenone to crotonaldehyde with as model system and performing the initial experiments without any co-catalyst in toluene (Scheme 2.46). In this manner, diverse aminocatalysts

[56](a) Panday, S.K.; Prasad, J.; Dikshit, D. K. *Tetrahedron: Asymmetry*, **2009**, *20*, 1581. (b) Nájera, C.; Yus, M. *Tetrahedron: Asymmetry*, **1999**, *10*, 2245.

presenting different functional groups which might interact with the ketone **12** directing its approach from one of the diastereotopic faces of the acceptor or simply act as chiral inductors by pure steric effects were tested.



1b **12** ***cis*-13b** ***trans*-13b**



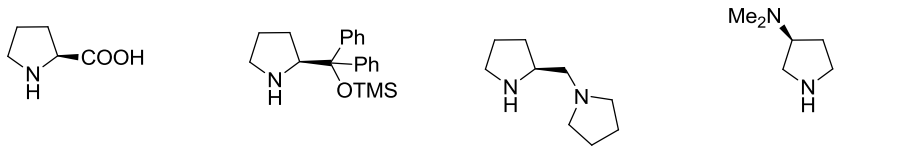
3a **3b** **3f** **3g**

Yield: 98%
dr (*cis:trans*): 1.5:1
ee (*cis/trans*): 74%/88%

Yield: 79%
dr (*cis:trans*): 1:1
ee (*cis/trans*): 98%/76%

Yield: 90%
dr (*cis:trans*): 1:1
ee (*cis/trans*): 74%/90%

Yield: 7%
dr (*cis:trans*): n.d.
ee (*cis/trans*): n.d.



3d **3e** **3h** **3i**

Yield: 99%
dr (*cis:trans*): 1.5:1
ee (*cis/trans*): 0%/0%

Yield: 24%
dr (*cis:trans*): 2:1
ee (*cis/trans*): 66%/0%

Yield: 38%
dr (*cis:trans*): 1.5:1
ee (*cis/trans*): 38%/34%

Yield: 32%
dr (*cis:trans*): 1:1
ee (*cis/trans*): 0%/24%

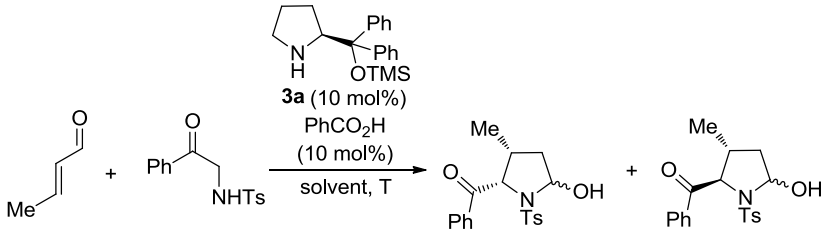
Scheme 2.46

Therefore, pyrrolidines **3b** and **3f** which contain bulkier substituents with different steric demand yielded the adduct **13** as an equimolecular mixture of *cis* and *trans* diastereoisomers in good to excellent yield and high enantioselectivity, being higher than the one given by the initial catalyst **3a**. Additionally, the imidazolidinone **3g**, known as second generation MacMillan catalyst, was included in this catalyst

screening, although it provided the expected compound in very low yield. Bifunctional secondary amines containing H-bond donor sites which could establish secondary interactions with the carbonyl group of the ketone **12** (**3d** and **3e**) showed poor stereocontrol, obtaining the *cis*/*trans* mixture of the Michael adduct quantitatively but as a racemate when L-proline (**3d**) was used and furnishing a very low yield and ee when diphenylprolinol (**3e**) was employed as catalyst. On the other hand, aminocatalysts bearing Brønsted basic sites (**3h** and **3i**) were also evaluated, affording little amounts of the expected products with low levels of enantiocontrol and once again as a mixture of diastereoisomers. In none of these reactions other products arising from the alternative aza-Michael/aldol cascade reaction were observed.

With all these results in hands, we decided to keep on searching the optimal conditions using the chiral secondary amine **3a** as catalyst. Thus, we proceeded to study the reaction using some other solvents like toluene and $CHCl_3$, which are tipically used in aminocatalytic transformations and also surveying a more polar solvent such as THF (Table 2.7). In this sense, using $CHCl_3$ as solvent the hemiaminal **13** was obtained in slightly lower yield than the one achieved in toluene, with similar enantioselectivity and without diastereocontrol (entry 1 *versus* entry 2). When we ran the reaction in THF the expected product was isolated in very low yield (entry 3). Next, we decided to study the influence of the temperature on the enantioselectivity of the reaction, observing that working at slightly lower temperatures the compound **13** could be obtained quantitatively but without any increase in the diastereoselectivity or enantiomeric excess (entries 1 and 4), while cooling the reaction mixture to -30 ºC it was not observed the formation of any product even after allowing it to stirr for 7 days (entry 5).

Table 2.7: Enantioselective aminocatalytic reaction of *N*-tosyl-α-aminoacetophenone to crotonaldehyde catalyzed by **3a**. Effect of the temperature.



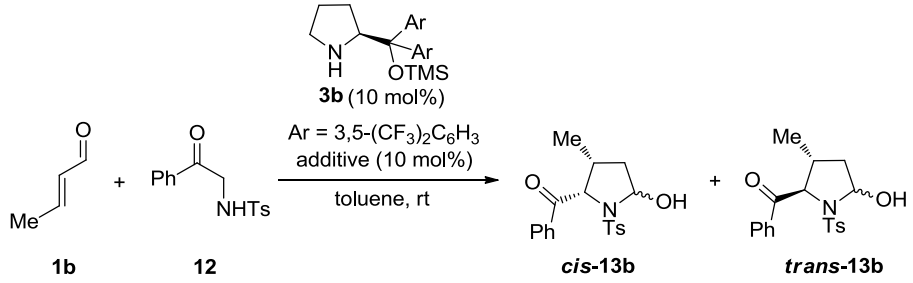
1b **12** ***cis*-13b** ***trans*-13b**

Entry	Solvent	T (ºC)	Yield (%)[a]	*cis*:*trans*[b]	ee (%) (*cis*/*trans*)[c]
1	Toluene	rt	99	1.5:1	74/88
2	$CHCl_3$	rt	96	1.5:1	80/80
3	THF	rt	10	n.d.	n.d.
4	Toluene	4	99	1:1	64/88
5	Toluene	-30	0	-	-

[a]Combined yield of both ***cis*** and ***trans*** diastereomers after flash column chromatography purification. [b]Determined by ^{1}H-NMR analysis of the crude reaction mixture after oxidation to the corresponding γ-lactams. [c]Determined by HPLC analysis from oxidated compound **14b**.

We next continued the optimization process by surveying the influence that different additives might have on the outcome of the reaction using the amine **3b** as organocatalyst. As shown in Table 2.8, the addition of a Brønsted acid as co-catalyst in an effort to accelerate the process worked out when benzoic acid was used (entry 1 *versus* entry 2), observing also an increase in the enantioselectivity. Other tested acidic additives did not furnish the hemiaminal **13b** in better yields (entry 2 *versus* entries 3-6) and in fact, when a strongly acidic additive such as *p*-TSA was added the reaction did not work.

Table 2.8: Enantioselective aminocatalytic reaction of *N*-tosyl-α-aminoacetophenone to crotonaldehyde catalyzed by **3b**. Effect of the additive.



1b **12** ***cis*-13b** ***trans*-13b**

Entry	Additive	pK_a[a]	Solvent	Yield (%)[b]	*cis*:*trans*[c]	ee (%) (*cis*/*trans*)[d]
1	-	-	toluene	79	1:1	74/88
2	$PhCO_2H$	4.20	toluene	83	1:1	98/76
3	Ph_3CCO_2H	4.03[e]	toluene	55	1:1.3	98/91
4	*p*-$NO_2C_6H_4CO_2H$	3.47	toluene	68	1.5:1	98/89
5	2,4-$(NO_2)_2C_6H_3CO_2H$	1.43	toluene	46	3:1	98/82
6	*p*-TSA	-2.80	toluene	0	-	-
8	DABCO	-	toluene	98	1.5:1	99/92
9[f]	DABCO	-	toluene	9	n.d.	n.d.
10	DABCO	-	$CHCl_3$	84	2:1	92/90
11	DABCO	-	THF	<10	n.d.	n.d.

[a]pK_a values measured in H_2O. Perrin, D. D.; Serjeant, E. P.; Dempsey, B. *pK_a predictions for organic acids and bases*. Champman and Hall, London, **1981**. [b]Combined yield of both ***cis*** and ***trans*** diastereomers after flash column chromatography purification. [c]Determined by ^{1}H-NMR analysis of the crude reaction mixture after oxidation to the corresponding γ-lactams. [d]Determined by HPLC analysis from oxidated compound **14b**. [e]Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2012 ACD/Labs). [f]The reaction was carried out at 4 ºC.

In contrast, when a basic co-catalyst such as DABCO was included, the reaction took place more efficiently with regard to the conversion and

enantioselectivity, although still a mixture of 1.5:1 of *cis*/*trans* diastereoisomers was obtained (entry 7). Further experiments with this base lowering down the temperature (entry 8) or changing the solvent (entries 9 and 10) did not provide any improvement on the diastereoselectivity.

With these results in hands, we also considered the use of α-aminoacetophenones bearing different protecting groups at the nitrogen atom to evaluate the influence of these substituents on the reaction outcome and specially on the diastereoselectivity. All the starting materials were prepared from commercially available α-aminoacetophenone hydrochloride by means of standard procedures.[57] In this context, we set the appropriate experiments using crotonaldehyde as model substrate and employing the conditions already optimized, which involved the use of the aminocatalyst **3b** and DABCO as co-catalyst in toluene (Table 2.9).

The need for a highly acidic NH group was clearly confirmed from the fact that *N*-acetyl derivative **15** and carbamates **16** and **17** were unreactive under the optimized reaction conditions (entries 2-4). In contrast, with more electron-withdrawing group, such as a trifluoromethanesulfonyl substituent (the aprox. pK_a value of sulfonamides is known to lie in the range of 10-16)[58] the reaction proceeded very efficiently (entry 5). However, even though the *N*-mesyl substituted α-aminoketone was found to be active in the reaction, both the yield and enantioselectivity were significantly lower, nearly maintaining the same diastereoselectivity (entry 1 *versus* entry 6).

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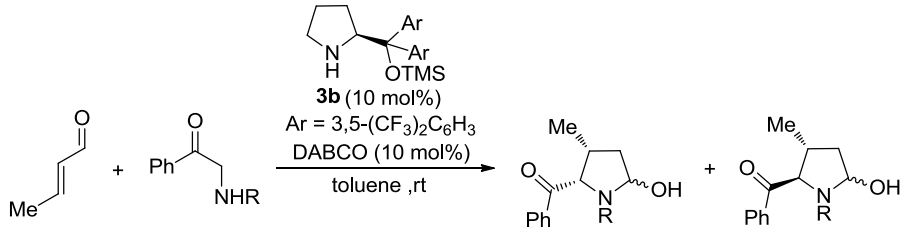
[57] See experimental section (chapter 5).

[58] (a) Bordwell, F. G.; Fried, H. E.; Hughes, D. L.; Lynch, T.-Y.; Satish, A. V.; Whang, Y. E. *J. Org. Chem*. **1990**, *55*, 3330. (b) Bordwell, F. G.; Harrelson, J. A.; Lynch, T.-Y. *J. Org. Chem*. **1990**, *55*, 3337. (c) Bordwell, F. G.; Algrim, D. *J. Org. Chem*. **1976**, *41*, 2507.

Table 2.9: Enantioselective aminocatalytic reaction of *N*-protected α-aminoacetophenones to crotonaldehyde catalyzed by **3b**. Effect of the protecting group.



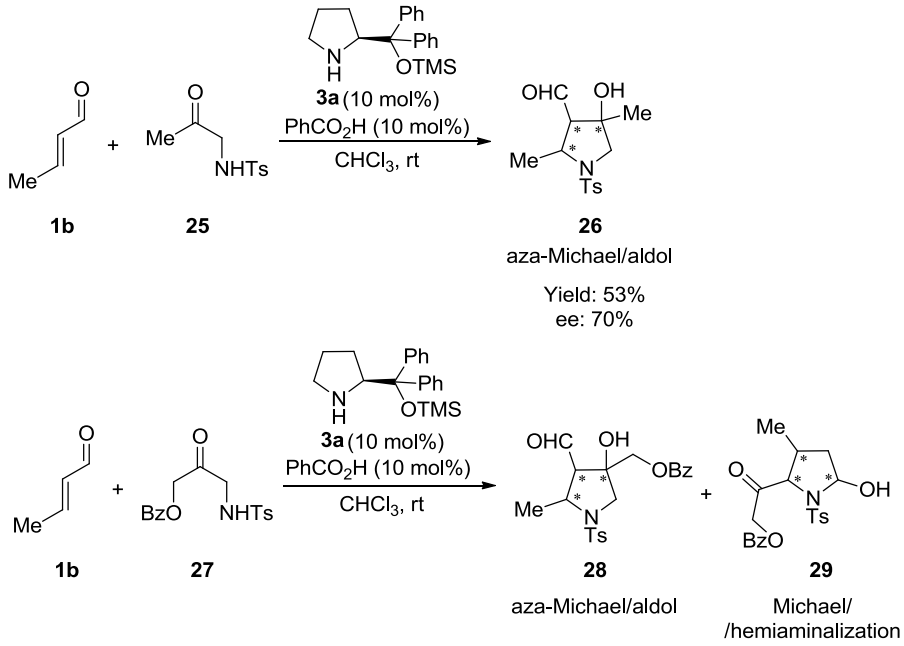
Entry	R	Product	Yield (%)[a]	*cis*:*trans*[b]	ee (%) (*cis*/*trans*)[c]
1	Ts **(12)**	**13b**	98	1.5:1	99/92
2	Ac **(15)**	**20b**	<5	n.d.	n.d.
3	Boc **(16)**	**21b**	<5	n.d.	n.d.
4	Fmoc **(17)**	**22b**	<5	n.d.	n.d.
5	Tf **(18)**	**23b**	97	1.5:1	95/90
6	Ms **(19)**	**24b**	40	2:1	74/70

[a]Combined yield of both ***cis*** and ***trans*** diastereomers after flash column chromatography purification. [b]Determined by ^{1}H-NMR analysis of the crude reaction mixture after oxidation to the corresponding γ-lactams. [c]Determined by HPLC analysis from the corresponding oxidated compounds**.**

As a consecuence, we selected the *N*-tosyl derivative **12** as the best reagent for the aza-Michael/hemiaminalization domino reaction under the conditions shown in Table 2.9 according to the excellent yield and enantioselectivity obtained.

Alternatively, we also surveyed the use of *N*-tosyl-α-aminoacetone as functionalized Michael donors in the reaction with crotonaldehyde and using catalyst **3a**, observing that only the aza-Michael/aldol cascade product **26** was

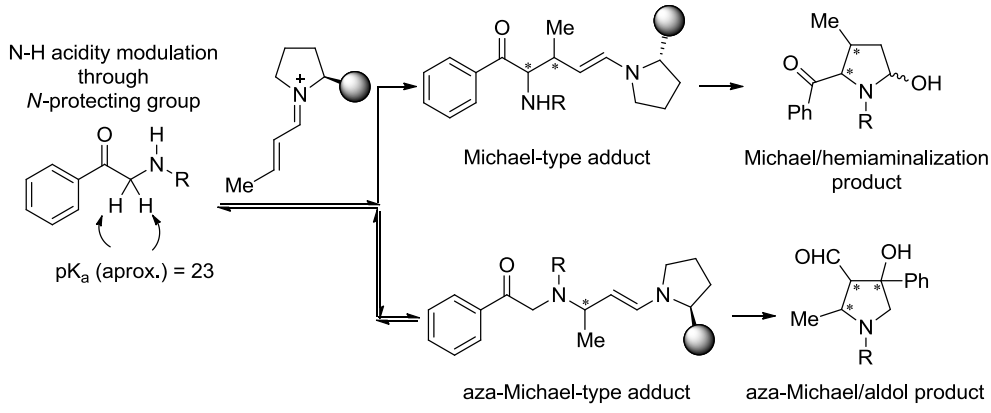
obtained in moderate yield and low ee (Scheme 2.46). However, when carrying out the reaction with the 1,3-disubstituted ketone **27**, two different substituted pyrrolidines were obtained by means of two possible mechanistic pathways. As shown in Scheme 2.47, the heterocycles **28** and **29** were obtained presumably through a domino aza-Michael/aldol cascade reaction and a Michael/hemiaminalization process, respectively (Scheme 2.47).



Scheme 2.47

In view of all these results, we proposed a mechanistic pathway for this transformation which should be based on the ability of *N*-monoprotected α-aminoketones to undergo *N*-deprotonation under neutral or slightly basic conditions. Importantly, the ambident amide/enolate nature of the α-aminoketone Michael donor can participate in the corresponding competitive aza-Michael adduct resulting in a

chemoselectivity issue to be faced. However, the inherent reversibility of the aza-Michael reaction would result in a dynamic equilibrium being favoured the Michael-type adduct through an irreversible C-C bond formation, provided that the next intramolecular aldol reaction of the enamine intermediate formed after the initial aza-Micahel reaction does not occur at a competitive rate. The formation of a stable hemiaminal after the Michael reaction might also account for the preferential occurrence of this pathway (Scheme 2.48).

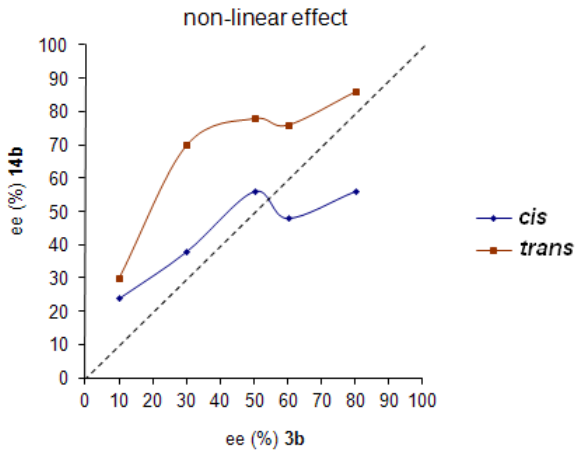


Scheme 2.48

At this point, it is worth to note that the examples found in the literature related to this topic are based on enamine catalysis in which α-aminoketones undergo Michael additions to nitroalkenes[59] or Mannich reactions with imines[60] but there is no example of such ketones undergoing Michael reaction with enals under iminium activation. In this sense, and trying to set further insight into the reaction mechanism, we carried out the reaction using catalyst **3a** in different optical

[59] Belot, S.; Sulzer-Mossé, S.; Kehrli, S.; Alexakis, A. *Chem. Commun*. **2008**, 4694.
[60] Chowdari, N. S.; Ahmad, M.; Albertshofer, K.; Tanaka, F.; Barbas III, C. F. *Org. Lett*. **2006**, *8*, 2839.

purities, observing a pronounced non-linear effect for the reaction was observed which points towards the presence of more than one molecule of the catalyst in the stereodetermining step of the catalytic cycle. As shown in the Scheme 2.49, the ee of the *cis* isomer remained almost constant with increasing levels of ee of aminocatalyst **3b** over the range 30-60% enantiopurity. On the contrary, the ee of the *trans* isomer decreased from 56% to 48% for 50% and 60% ee of organocatalyst, respectively. Over the range 60-80% ee of the chiral inductor, a rise in the enantiomeric purity of both isomers was found. Even if it was not possible to derive clear mechanistic conclusions in this system, the results are reminiscent of ML_x systems where non-linear effects curves show a similar trend.[61]

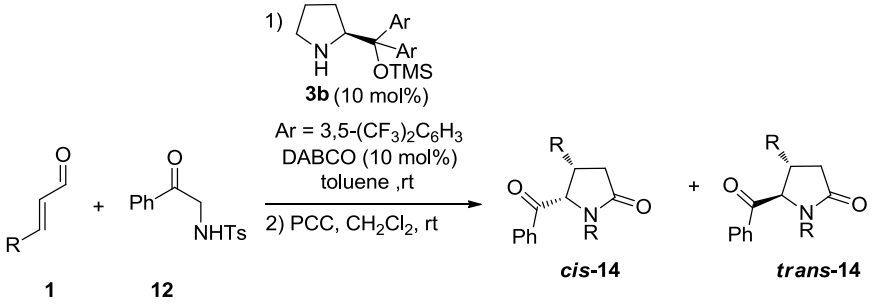


Scheme 2.49

Having established the best protocol for this transformation we tried different enals in order to study the scope of the reaction with regard to the electrophilic counterpart.

[61] Girard, C.; Kagan, H. B. *Angew. Chem. Int. Ed*. **1998**, *37*, 2922.

Table 2.10: Scope of the Michael/hemiaminalization reaction between *N*-tosyl-α-aminoacetophenone and α,β-unsaturated aldehydes.



Entry	R	Product	Yield (%)[a]	*cis*:*trans*[b]	ee (%) (*cis*/*trans*)[c]
1	Ph **(1i)**	**14i**	80	2:1	98/92
2	*o*-$MeOC_6H_4$ **(1j)**	**14j**	82	3.3:1	96/96
3	(*m*-MeO)(*p*-AcO)C_6H_3 **(1k)**	**14k**	90	3:1	98/98
4	2-Furyl **(1l)**	**14l**	73	2:1	94/n.d.[d]
5	CO_2Et **(1m)**	**14m**	55	1:1	98/84[d]
6	*p*-$MeOC_6H_4$ **(1n)**	**14n**	90	3:1	98/98
7	*p*-$NO_2C_6H_4$ **(1o)**	**14o**	48	2.5:1	98/90
8	Me **(1b)**	**14b**	98	1.5:1	99/92
9	Et **(1c)**	-	-	-	-
10	*n*-Pr **(1a)**	-	-	-	-
11	*n*-Bu **(1d)**	-	-	-	-

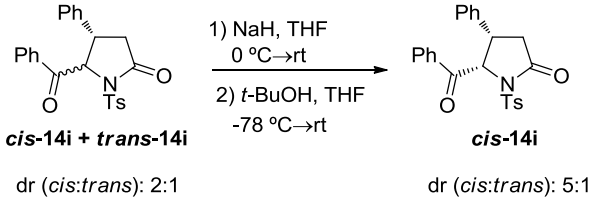
[a]Combined yield of both ***cis*** and ***trans*** diastereomers after flash column chromatography purification. [b]Determined by ^{1}H-NMR analysis of the crude reaction mixture after oxidation to the corresponding γ-lactams. [c]Determined by HPLC analysis from oxidated compounds **14**. [d]Could not be determined which ee(%) went to each diastereoisomer.

As shown in Table 2.10, the reaction proceeded satisfactorily when cinnamaldehyde was used as Michael acceptor (entry 1). Other β-aryl substituted

enals with either electron-donor or electron-withdrawing substituents on the aryl moiety were also well tolerated, although the chemical yield decresed slightly when *p*-nitrophenyl-substituted α,β-unsaturated aldehyde **1o** was employed (entries 2-3 and entries 6-7). An enal containing a β-heteroaryl group such as **1l** could also be used (entry 4) as well as a functionalized one (entry 5). On the contrary, when aliphatic acceptors different from crotonaldehyde that incorporated bulkier β-alkyl substituted were tried (entry 8 and entries 9-11) unmodified starting materials were obtained, which indicates that this reaction is highly sensitive to the volume of these substituents. Regarding the diastereoselectivity of the reaction, we hardly observed changes in the diastereomeric ratio and a clear correlation between the dr value and the volume of the substituent of the enal could not be stablished.

In sight of the results regarding diastereoselectivity and assuming an scenario in which a mixture of *cis*/*trans* diastereoisomers is obtained in the Michael/hemiaminal-formation cascade, we surveyed the possibility of interconvert both diastereoisomers by making use of the acidity of the C5 proton on the γ-lactam adducts **14**. In this sense, we thought about performing a base promoted C5-epimerization process with the aim to find a situation in which a single diastereomer could be obtained.

Thereby, we next carried out the deprotonation of the compound **14i** with NaH in THF at low temperature and then the reaction was quenched with *t*-BuOH (Scheme 2.50). In this case, the dr increased from 2:1 to 5:1. A bulkier proton source such as 2,4,6-tri-*tert*-butylphenol, was also evaluated in order to get a higher influence on the dr. Nevertheless, a similar result was obtained under these reaction conditions.



***cis*-14i + *trans*-14i**

dr (*cis*:*trans*): 2:1

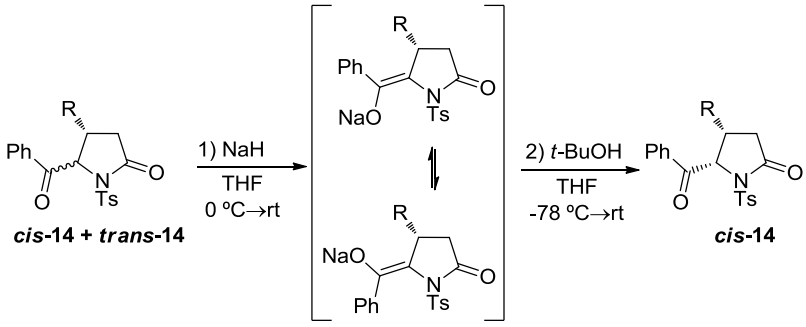
***cis*-14i**

dr (*cis*:*trans*): 5:1

Scheme 2.50

In the view of these results, we proceeded to extend this epimerization process to all the pyrrolidinones **14** under the conditions mentioned above. As shown in the Table 2.11 clear *cis* preference was observed in most cases (entries 2,4,5,7) except when the substituent at C5 was a small one as the methyl group (entry 1) or in the case of an aryl group bearing a methoxy group at *ortho* position (entry 3). Unfortunately, the epimerization process of compounds **14o** and **14m** resulted in decomposition products even when the reactions were carried out at lower temperatures (entry 6 and entry 8).

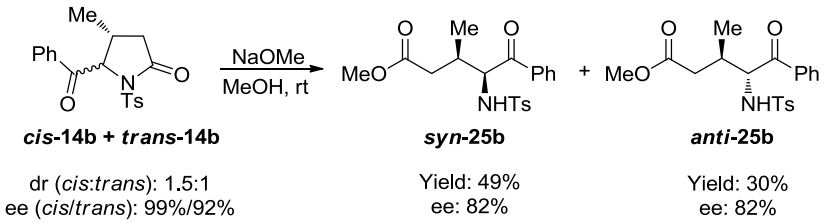
Table 2.11: C5-epimerization of γ-lactams **14**.



Entry	R	Yield (%)	Inicial *cis*:*trans*	Final *cis*:*trans*[a]	ee (%)
1	Me **(14b)**	80	1.5:1	1:1	98/92
2	Ph **(14i)**	84	2:1	5:1	97
3	*o*-$MeOC_6H_4$ **(14j)**	85	3.3:1	2:1	96/96
4	*(m*-MeO)(*p*-AcO)C_6H_3 **(14k)**	96	3:1	6:1	98
5	2-Furyl **(14l)**	87	2:1	>10:1	94
6	CO_2Et **(14m)**	-	1:1	-	-
7	*p*-$MeOC_6H_4$ **(14n)**	93	3:1	7:1	98
8	*p*-$NO_2C_6H_4$ **(14o)**	-	2.5:1	-	-

[a] Determined by ^{1}H-NMR analysis of the crude reaction mixture.

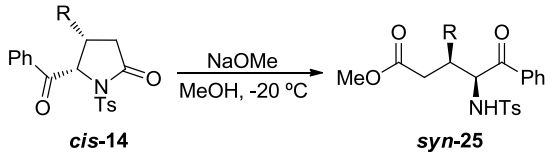
We next decided to carry out a methanolisis reaction on γ-lactams ***cis*-14** in order to obtain the corresponding γ-amino-δ-ketoesters. Our first attempt consisted of treating compound **14b** with NaOMe at room temperature, affording the acyclic products ***syn*-25b** and ***anti*-25b** in good yield, although with a slight decrease on the enantiomeric excesses of both diastereoisomers.



Scheme 2.51

In order to avoid the racemizacion process we carried out this transformation at -20 ºC. In this sense, different substituted γ-amino-δ-ketoesters **25** were obtained in moderate to good yields and without epimerization of any stereocenter and also maintaining the enantiopurity of the starting γ-lactam ***cis*-14** (Table 2.12). Importantly, both diastereoisomers ***syn*-25b** and ***anti*-25b** could be separated by flash column chromatography.

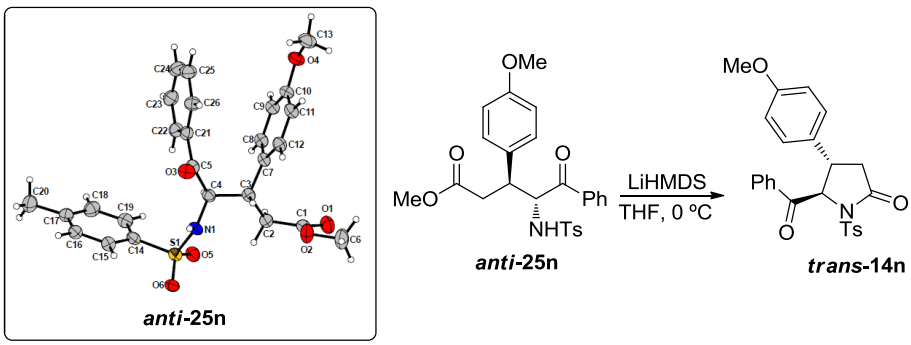
Table 2.12: Transformation of γ-lactamas to optically active γ-amino-δ-ketoesters.



Entry	R	Product	Yield (%)	ee (%)
1	Ph (***cis*-14i**)	***syn*-25i**	78	98
2	*o*-$MeOC_6H_4$ (***cis*-14j**)	***syn*-25j**	54	96
3	*(m*-MeO)(*p*-AcO)C_6H_3 (***cis*-14k**)	***syn*-25k**	95	98
4	2-Furyl (***cis*-14l**)	***syn*-25l**	70	94
5	*p*-$MeOC_6H_4$ (***cis*-14n**)	***syn*-25n**	74	94

The absolute and relative configuration was assigned by single X-ray analysis of the minor diastereoisomer ***anti*-25n**, which was synthesized starting from

14n with a *cis*/*trans* ratio of 3:1 under the established protocol and isolated as a single diastereoisomer after flash column chromatography purification. Then, it was next transformed into the corresponding cyclic compound ***trans*-14n** by treating ***anti*-25a** with LiHMDS in THF (Scheme 2.52). Comparation of the ^{1}H-NMR signals of pure ***trans*-14n** compound with those obtained in the Michael/hemiaminal formation cascade followed by oxidation allowed us to identify the resonances of the major diastereoisomer in the NMR spectrum and the relative and absolute configuration of the initial pyrrolidinone.



Scheme 2.52

Finally, we also attempted to remove the tosyl group from the γ-lactam **14b** using the procedures typically employed for that purpose. In this context, the compound was treated with Mg but the unmodified starting material was recovered. On the other hand, when the protected molecule was treated with *in situ* prepared sodium naphthalenide,[62] an unexpected and unprecedent transformation took place furnishing product **28** in good yield and maintaining a good enantiomeric excess (Scheme 2.53).

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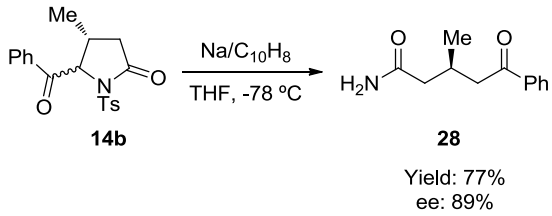
[62] Carballo, R. M.; Purino, M.; Ramirez, M. A.; Martín, V. S.; Padrón, J. I. *Org. Lett*. **2010**, *12*, 5334.



14b **28**

Yield: 77%
ee: 89%

Scheme 2.53

4. CONCLUSIONS.

Taking into account the obtained results in this chapter some conclusions can be settled:

1. Dihydroxyacetone behaves as a suitable functionalized molecule for the enantioselective aminocatalytic domino oxa-Michael/Aldol/hemiacetalization reaction with α,β-unsaturated aldehydes under iminium/enamine catalysis. This transformation presents extraordinary features such as the use of an aliphatic alcohol as oxygen centered nucleophile and the participation of a rather poorly electrophilic ketone moiety as internal electrophile.

2. Organocatalyst **3a** furnishes an excellent estereocontrol for this sequence, which involves the consecutive formation of two C-O and one C-C bonds and the completely stereocontrolled generation of four stereocenters, one of them being a quaternary one.

3. The easy selective modification of the functionalities present within the obtained adducts lead to the obtention of a wide range of optical active compounds which illustrates the potential of the developed methodology for the construction of enantioenriched chiral building blocks.

4. *N*-protected α-aminoacetophenone shows a different behaviour as functionalized Michael donor, undergoing a Michael/hemiaminalization reaction with α,β-unsaturated aldehydes under iminium activation. In the presence of catalyst **3b**, the adducts are obtained in excellent yields and enantiomeric excesses but as a mixtures of *cis* and *trans* diastereoisomers. This final parameter can be improved by carrying out an oxidation followed by a base-promoted epimerization,

leading to an efficient protocol for the preparation of enantioenriched disubstituted γ-lactams. These final adducts can be easily manipulated for the synthesis of different substituted 1,5-dicarbonyl compounds in high yields and maintaining the stereochemical integrity of all the previously generated stereocenters.

3

3

Enantioselective Organocatalytic Formal [2+2] Cycloaddition Reaction.

1. Introduction: vinylogous enamine activation.

1.1. Dienamine catalysis.

1.2. Trienamine catalysis.

2. Specific objectives and work plan.

3. Results and Discussion.

3.1. Synthesis of precursors.

3.2. Viability of the reaction.

3.3. Optimization of the reaction.

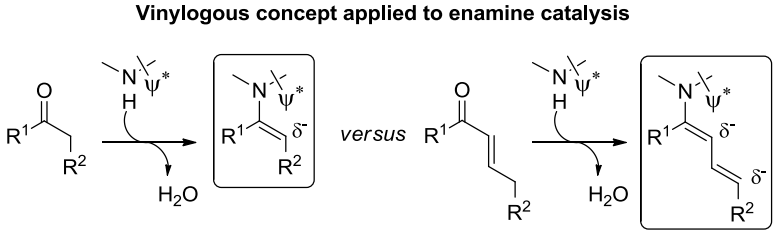
3.4. Scope and limitations.

3.5. Transformation of the cycloadducts.

4. Conclusions.

1. INTRODUCTION: VINYLOGOUS ENAMINE ACTIVATION.

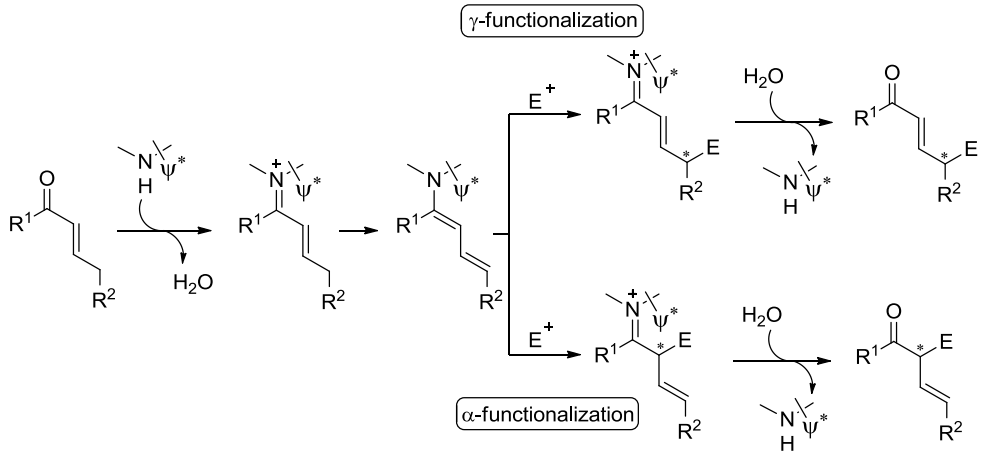
The HOMO raising effect associated to enamine activation approach has also been extended to conjugate systems such as enones and α,β-unsaturated aldehydes by applying the concept of vinylogy. This activation mode proceeds *via* the catalytic formation of an electron-rich dienamine specie able to react with electron-poor substrates (Scheme 3.1).



Scheme 3.1

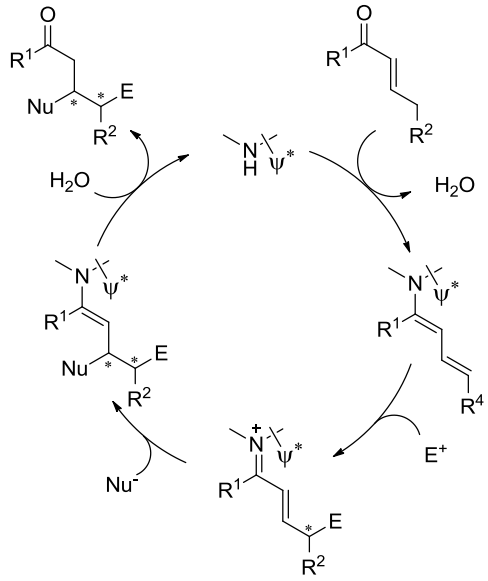
Interestingly, this activation strategy allows the direct γ-functionalization of enolizable α,β-unsaturated carbonyl compounds increasing this way the number of valuable transformations afforded by the organocatalysis tool box. Alternatively, the ambident nature of these type of dienamine intermediates also allows the α-functionalization of the starting enone or α,β-unsaturated aldehyde, leading to the formation of α-substituted-β,γ-unsaturated functionalizated carbonilic compounds. As shown in the general reaction pathway indicated in Scheme 3.2, after the activation of the carbonyl compound *via* iminium ion formation, a dienamine intermediate is formed providing that the starting material is an enolizable α,β-unsaturated aldehyde or ketone. This intermediate is ready to be attacked by an

electrophile at either α or γ position, generating an iminium ion which subsequently undergoes hydrolysis that allows catalyst release.



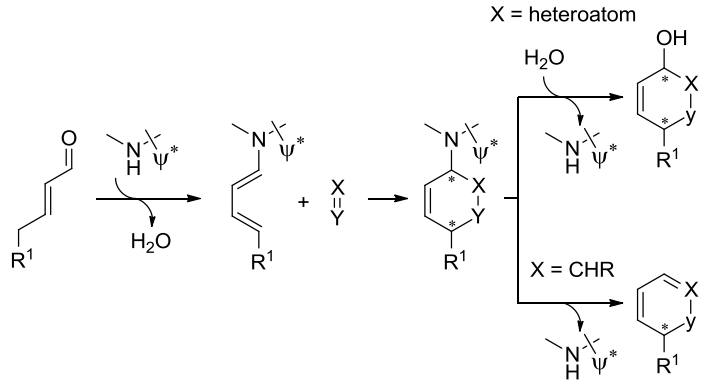
Scheme 3.2

This scenario can be further extended to implement cascade processes using this dienamine/iminium sequence. In fact, after the iminium ion intermediate is generated a subsequent nucleophilic addition reaction is likely to occur in a cascade process provided that an additional external nucleophile is incorporated to the reaction scheme (Scheme 3.3). A more complex situation could arise using the dienamine/iminium/enamine manifold, incorporating a second electrophile that is capable to react with the nucleophilic enamine intermediate formed after the dienamine/iminium sequence.



Scheme 3.3

Furthermore, this kind of dienamine intermediates can also behave as electron-rich dienes toward electron-deficient dienophiles showing a typical Diels-Alder-type reactivity (Scheme 3.4). In this case, catalyst release is more complicated since it is incorporated into the structure of the [4+2] cycloadduct. For this reason, reactions proceeding through this kind of mechanisms typically end up with a hydrolysis step (X = heteroatom) that allows catalyst turnover. On the other hand, catalyst release is achieved by an elimination reaction, leading to the formation of a cyclohexadiene-type structure (X = CHR).



Scheme 3.4

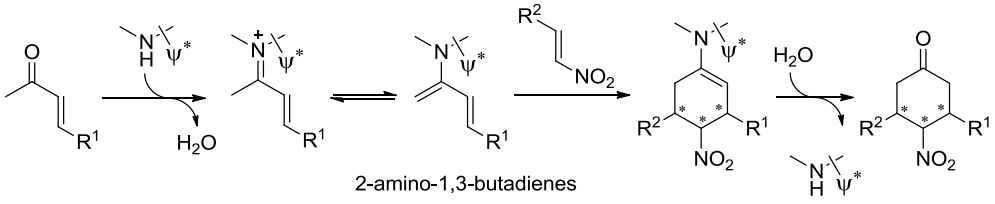
Related to this topic, although the stoichiometric version of this chemistry was known long time ago,[1] there is another possibility for dienamine catalysis that involves activation of the α'-carbon of an enolizable enone. This approach relies on the formation of a 2-amino-1,3-butadiene intermediate that can react as an electron-rich diene in standard Diels-Alder reactivity. In this sense, it was not until 2002 when Barbas III first discovered that *in situ* generated 2-amino-1,3-butadienes from enones in the presence of catalytic amounts of amines might act as electron-rich dienes in the Diels-Alder reaction with nitroalkenes (Scheme 3.5).[2] Afterwards, this approach was applied for the development of other stereoselective normal-electron-demand Diels-Alder reactions.[3] However, these kind of intermediates are not

[1] Snyder *et al*. first reported reactions with preformed dienamines: Snyder, H. R.; Hasbrouck, R. B.; Richardson, J. F. *J. Am. Chem. Soc*. **1939**, *61*, 3558.

[2] Thayumanavan, R.; Ramachary, D. B.; Sakthivel, K.; Tanaka, F.; Barbas III, C. F. *Tetrahedron Lett*. **2002**, *43*, 3817.

[3] For some examples based on catalytic reactions proceeding through 2-amino-1,3-butadiene intermediates see: (a) Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed*. **2009**, *48*, 7200. (b) Wu, L.-Y.; Bencivenni, G.; Mancinelli, M.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed*. **2009**, *48*, 7196. (c) Xu, D.-Q.; Xia, A.-B.; Luo, S. P.; Tang, J.; Zhang, S.; Jiang, J.-R.; Xu, Z.-Y. *Angew. Chem. Int. Ed*. **2009**, *48*, 3821. (d) Ramachary, D. B.; Reddy, Y. V.; Prakash, B. V. *Org. Biomol. Chem*. **2008**, *6*, 719. (e) Momiyama, N.; Yamamoto, Y.; Yamamoto, H.; *J. Am. Chem.*

directly related to the chemistry discussed in this chapter and therefore, these reactions will not be covered in this introduction section.



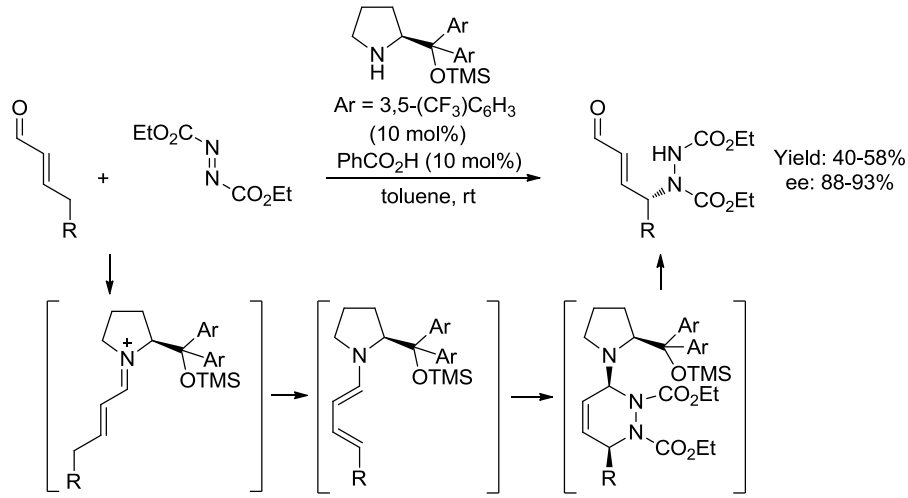
Scheme 3.5

1.1. Dienamine catalysis.

Jørgensen et al. was the first who employed the term *dienamine catalysis* in a pioneering work in which the first enantioselective γ-functionalization of enals with diethyl azodicarboxylate was described.[4] In this brilliant example, it was found that catalytic amounts of secondary amines can invert the usual reactivity of α,β-unsaturated aldehydes through a chiral catalytic dienamine intermediate enabling γ-amination of enals (Scheme 3.6). The mechanism was studied using experimental and computational approaches, which indicated that γ-amination of α,β-unsaturated aldehydes might be the result of a concerted [4+2] cycloaddition reaction between the electrophilic nitrogen source and the chiral dienamine formed in situ with the organocatalyst.

Soc. **2007**, *129*, 1190. (f) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2006**, *8*, 1533. (g) Sundén, H.; Ibrahem, I.; Eriksson, L.; Córdova, A. *Angew. Chem. Int. Ed*. **2005**, *44*, 4877. (h) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc*. **2004**, *126*, 5962. (i) Ramachary, D. B.; Anebouselvy, K.; Chowdari, N. S.; Barbas III, C. F. *J. Org. Chem*. **2004**, *69*, 5838.(j) Ramachary, D. B.; Chowdari, N. S.; Barbas III, C. F. *Angew. Chem. Int. Ed*. **2003**, *42*, 4233.

[4] Bertelsen, S.; Marigo, M.; Brandes, S.; Diner, P.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2006**, *128*, 12973.

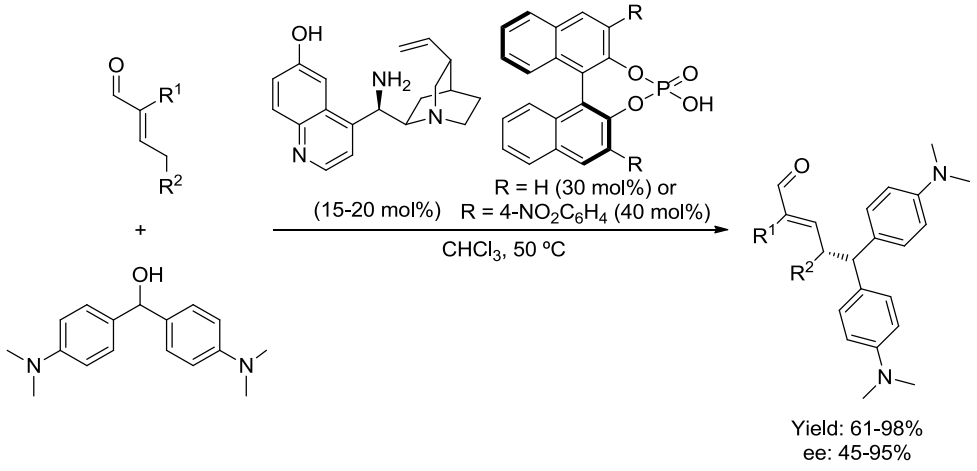


Scheme 3.6

Once this paper was made known, several significant contributions have been published on this research topic. Melchiorre *et al*. have published many interesting reports increasing largely the knowledge on this aminocatalytic strategy. In this context, α-branched enals have also been included in the design of new organocatalytic asymmetric γ-site selective alkylation through an S_N1 pathway using diarilmethanols as the source of a stable benzhydryl carbocation (Scheme 3.7).[5] This transformation proceeded in the presence of a chiral phosphoric acid co-catalyst for the generation of the electrophile, in a typical case of cooperative catalysis. In this manner, the chiral primary amine engaged in the activation of the enal by means of the formation of the corresponding dienamine intermediate and on the other hand, the chiral phosphoric acid induced the formation of a chiral contact ion-pair with the benzhydryl carbocation. The chiral nature of this co-catalyst rises the issue of a double stereodifferentiation process, therefore requiring to identify the productive *matched* combination of reagents. By applying this chemical

[5] Bergonzini, J.; Vera, S.; Melchiorre, P. *Angew. Chem. Int. Ed*. **2010**, *49*, 9685.

transformation functionalized α,β-unsaturated aldehydes were efficiently obtained in moderate to high yields and enantioselectivities.



Scheme 3.7

The same group also described the ability of this type of primary amine catalysts to promote vinylogous nucleophilicity upon selective γ-activation of cyclic enones enabling the development of a Michael addition of cyclic α,β-unsaturated ketones to nitroalkenes under dienamine catalysis.[6] As it is said on the paper, this idea was based upon related enolization studies,[7] demonstrating that under certain conditions, the selective formation of the thermodynamic *exo*-cyclic enolate is favored over both the *endo*-isomer and the kinetic cross-conjugated dienolate. Thus, this reaction allowed the obtention of functionalized vinylogous Michael adducts in high yields and with excellent enantioselectivities (Scheme 3.8).

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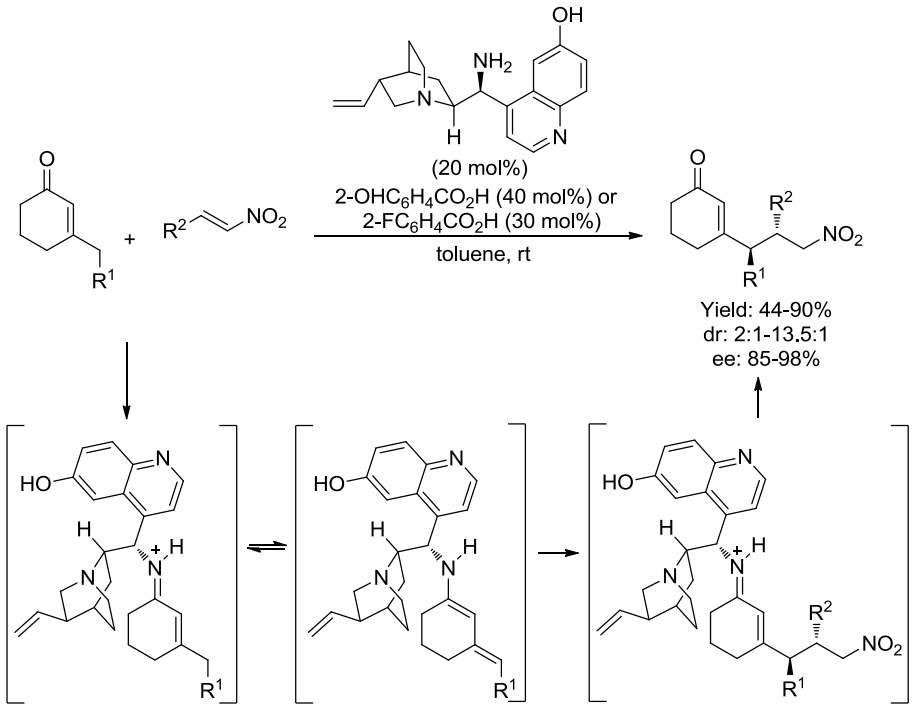
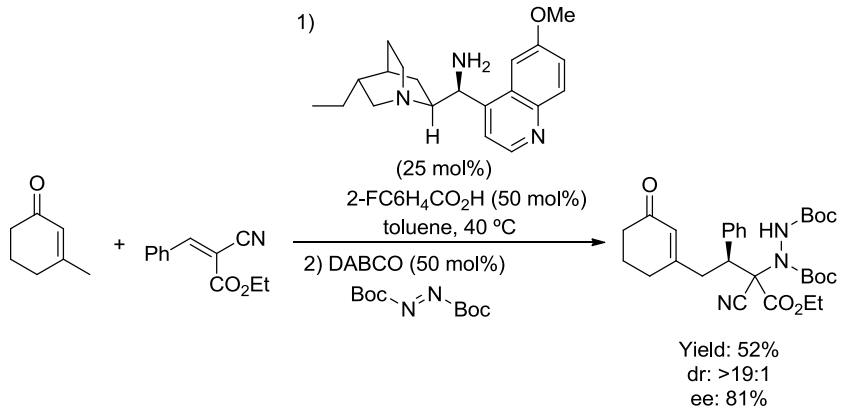
6 Bencivenni, G.; Galzerano, P.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20642.

7 (a) Takikawa, H.; Ishihara, K.; Saito, S.; Yamamoto, H. *Synlett*, **2004**, *4*, 732. (b) Saito, S.; Shiozawa, M.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc*. **1998**, *120*, 813.



Scheme 3.8

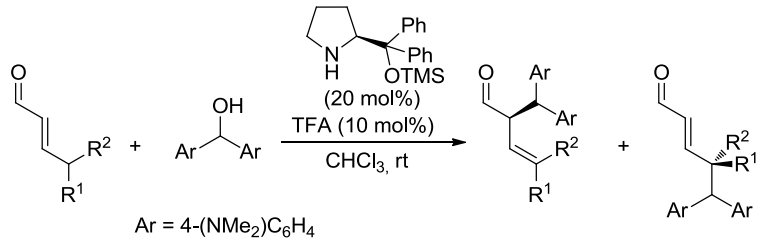
In addition, this methodology was extended to different olefins such as β,β-disubstituted nitrostyrenes and *trans*-α-cyanocinnamates leading to the stereocontrolled obtention of the corresponding adducts bearing one all-carbon quaternary stereocenter. In the later case, to prevent epimerization process, the authors carried out a one-pot vinilogous Michael addition/amination tandem sequence affording the final product as a single diastereoisomer and without changes in the stereochemical integrity of formed stereocenters (Scheme 3.9).



Scheme 3.9

On the other hand, dienamine activation strategy might be applied to the addition of an electrophilic substrate to the α-position of an α,β-unsaturated carbonyl compound. In this sense, Christmann and co-workers made a study of the enantioselective γ- and α-alkylation of α,β-unsaturated aldehydes with stabilized carbocations as electrophiles in the presence of *O*-TMS-diphenylprolinol as catalyst.[8] The authors shown that by carrying out the reaction with γ-disubstituted aldehydes the α-substitution pathway was favoured, being the γ-alkylation completely inhibited when one of the substituents was aromatic. On the contrary, linear unbranched and β-substituted enals favor γ-substitution (Scheme 3.10).

[8] Stiller, J.; Marqués-López, E.; Herrera, R.; Fröhlich, R.; Strohmann, C.; Christmann, M. *Org. Lett*. **2011**, *13*, 70.



R^1 = Me R^2 = Ph Yield: 84%
α/γ: >95/5
ee: 73%

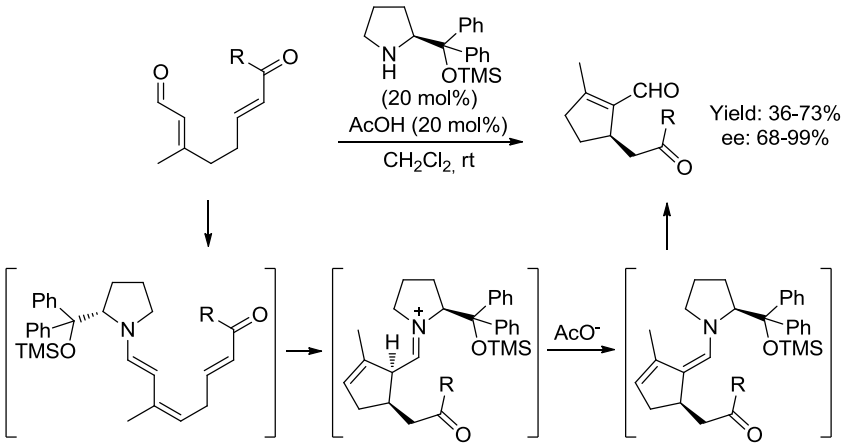
$R^1 = R^2$ = Me Yield: 65%
α/γ: 78/22
ee: 93%

R^1 = Et R^2 = H Yield: 48%
α/γ: 17/83
ee: 76%

Scheme 3.10

In this context, this group also developed the organocatalytic enantioselective cyclization reaction of 3-methyl-8-oxo-2,6-octadienals under dienamine catalysis promoted by the same diphenylprolinol derivative.[9] As shown in Scheme 3.11, the α-position of the α,β-unsaturated aldehyde is activated after the formation of the dienamine intermediate for an intramolecular Michael reaction with the enone moiety. This methodology provided an easy and rapid access to the iridoid framework, cyclopentene derivatives bearing a tetra-substituted olefin, in moderate to good yields and with good enantioselectivity.In addition, in order to demonstrate the utility of developed methodology, the authors synthesized (+)-*rotundial*, a mosquito repellent from *Vitex rotundifolia*, with 36% yield and 86% ee for the cyclization step.

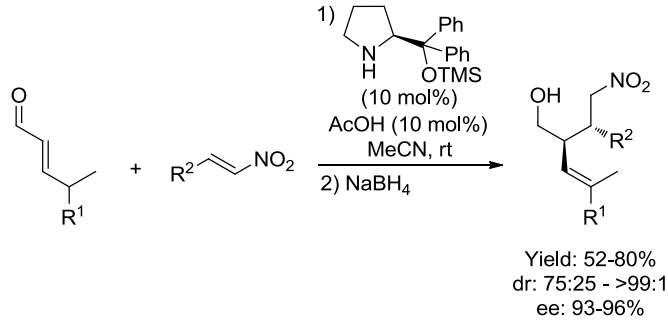
[9] Marqués-López, E.; Herrera, R. P.; Marks, T.; Jacobs, W. C.; Könning, D.; de Figuereido, R. M.; Christmann, M. *Org. Lett*. **2009**, *11*, 4116.



Scheme 3.11

In a similar approach, nitroalkenes have been also used as electrophiles in the α-functionalization of enals under dienamine catalysis (Scheme 3.12).[10] In this context, Chen and co-workers observed that employing linear α,β-unsaturated aldehydes a dimerization process of such reagents took places through a [4+2] cycloaddition reaction. Nevertheless, this issue could be solved by using γ-disubstituted enals due to their more sterically hindered γ-position. In this manner, and in the presence of *O*-TMS-diphenylprolinol, the corresponding Michael adducts were obtained with complete regioselectivity in moderate to good yields and with excellent diastereo- and enantiocontrol.

[10] Han, B.; Xiao, Y.; He, Z. Q.; Chen, Y. C. *Org. Lett*. **2009**, *11*, 4660.

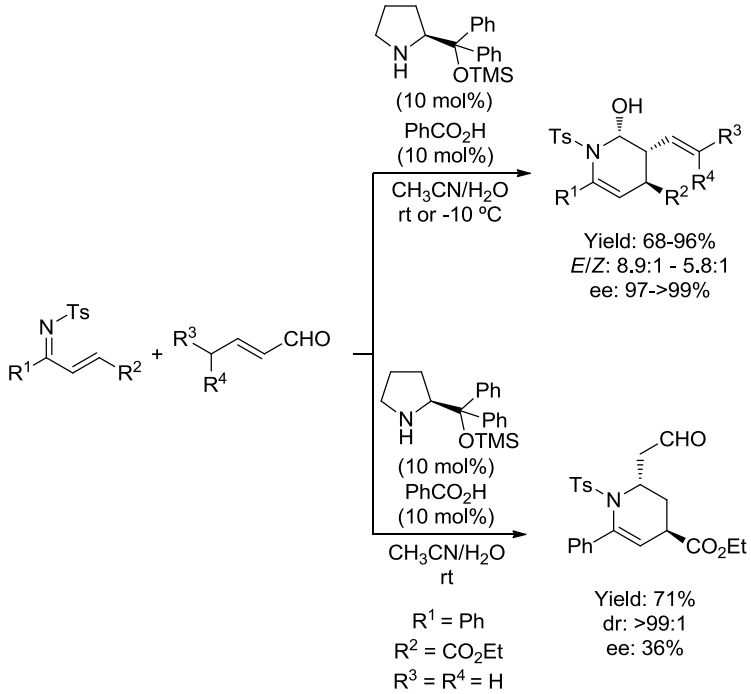


Scheme 3.12

Finally, the dienamine activation approach can be also used for carrying out Diels-Alder reactions by using the HOMO-raising effect associated to the formation of such catalytic intermediates from the starting α,β-unsaturated carbonyl substrates, being capable to act as dienophiles in an inverse-electron-demand Diels-Alder reaction. This is the case of the highly enantioselective inverse-electron-demand aza-Diels-Alder reaction of *N*-sulfonyl-1-aza-1,3-butadienes with aliphatic enals catalyzed by *O*-TMS-diphenylprolinol delivering optically pure piperidines. In this reaction the catalyst activates the α,β-unsaturated aldehyde forming the corresponding dienamine that undergoes a cycloaddition reaction at the 1,2-position with the aza-diene. In this manner, chiral piperidine derivatives are obtained in excellent yields and with outstanding enantioselectivities with several functional groups on their structures in straightforward manner (Scheme 3.13).[11] In this reaction, the α-type reactivity pattern at the dienamine intermediate resulted in the formation of a Diels-Alder cycloadduct containing the catalyst that after hydrolysis was transformed into the corresponding hemiaminal allowing this way the aminocatalyst turnover. However, when the same type of aza-dienes and

[11] (a) Han, B.; He, Z.-Q.; Li, J.-L.; Li, R.; Jiang, K.; Liu, T.-Y.; Chen, Y.-C. *Angew. Chem. Int. Ed*. **2009**, *48*, 5474. See also: (b) Li, J.-L.; Zhou, S.-L.; Han, B.; Wu, L.; Chen, Y.-C. *Chem. Commun*. **2010**, *46*, 2665.

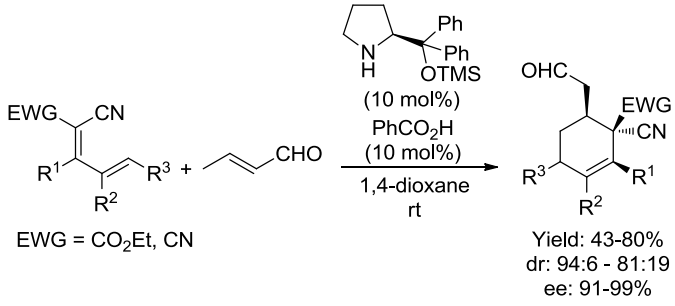
crotonaldehyde were used under the same reaction conditions in, exclusively the corresponding product arising from the cycloaddition to the 3,4-bond of the formed dienamine was obtained with complete diastereocontrol, but with a very low enantiomeric excess.



Scheme 3.13

Further research in this topic led to the authors to develop an asymmetric inverse-electron-demand Diels-Alder employing a properly designed electron-deficient diene for the efficient construction of highly diastereo- and enantioenriched

polysubstituted cyclohexene derivatives (Scheme 3.14).[12] In this case, the reaction took place exclusively at the 3,4-positions of the dienamine intermediate.



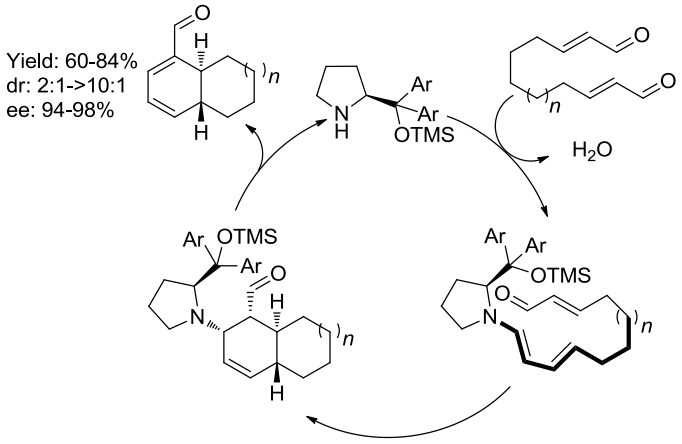
Scheme 3.14

Alternatively, and as already mentioned, a different chemical behaviour of this type of dienamine intermediates involves typical Diels-Alder reactivity and, in this sense, a couple of organocatalytic cycloaddition reactions have been developed under dienamine catalysis where dienamine intermediates act as electron-rich dienes in normal-electron-demand Diels-Alder reactions. In this context, the aminocatalytic enantioselective cyclization of tethered α,β-unsaturated aldehydes has been developed for the synthesis of novel mono- and bicyclic scaffolds in moderate to good yield and high enantioselectivities.[13] As shown the Scheme 3.15, the catalytic cycle would start with the condensation of the aminocatalyst and the dialdehyde to form the electron-rich dienamine (diene) intermediate which adopts a conformation that minimizes repulsion with the bulky aryl substituents and exposes the unshielding face of the π system to an *endo* approach of the remaining enal (dienophile). The generated cycloadduct would undergo elimination to regenerate the catalyst.

---

[12] Li, J.-L.; Kang, T.-R.; Zhou, S.-L.; Li, R.; Wu, L.; Chen, Y.-C. *Angew. Chem. Int. Ed*. **2010**, *49*, 6418.

[13] Marcia de Figuereido, R.; Fröhlich, R.; Christmann, M. *Angew. Chem. Int. Ed*. **2008**, *47*, 1450.



Scheme 3.15

This particular chemical behaviour of dienamines has also been observed in dimerization reactions of enals, in which one aldehyde molecule plays a role as diene and another one as a dienophile considering that these reactions follow a [4+2] cycloaddition mechanism.[14]

1.2. Trienamine catalysis.

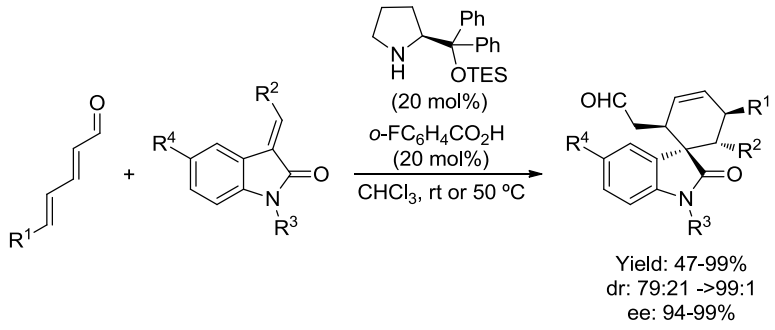
More recently, a futher extensión of the vinylogous concept to the enamine activation approach has been developed by the incorporation of extended polyconjugated aldehydes such as 2,4-dienals in the reaction design, which upon condensation with the chiral secondary amine catalysts deliver trienamine species. This strategy enables ε-functionalization, which represents a new reactivity pathway and an open road to the chemical modification of this type of compounds. However, challenges related to stereocontrol of the ε-carbon associated to the remote position

[14] (a) Song, X.; Zhang, X.; Zhang, S.; Li, H.; Wang, W. *Chem. Eur. J*. **2012**, *18*, 9770. (b) Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Huang, G.-F.; Su, C.-F.; Liao, J.-H. *J. Org. Chem*. **2007**, *72*, 8459. (c) Bench, B. J.; Liu, C.; Evett, C. R.; Watanabe, C. M. H. *J. Org. Chem*. **2006**, *71*, 9458.

of this carbon from the quiral information are often encountered. In addition, regioselectivity is also another issue to face.

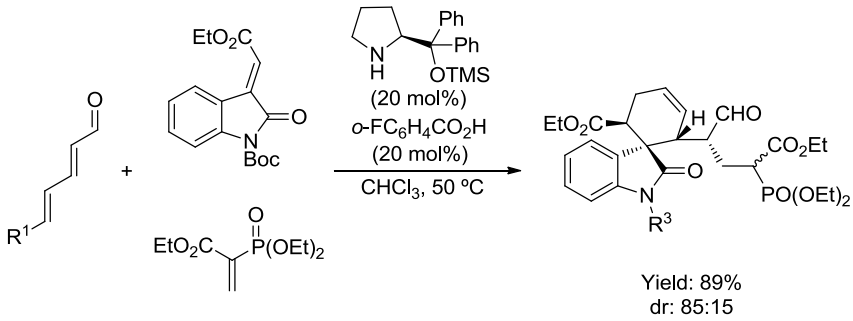
Chen and Jørgensen discovered this novel activation mode in the first aminocatalytic Diels-Alder reaction[15] when 2,4-hexadienal and 3-alkenyl oxindoles were mixed in the presence of catalytic amount of *O*-TMS-diphenylprolinol and a Brønsted acid as co-catalyst, furnishing the desired spirocyclic oxindole in 98% yield as a single diastereoisomer and 98% ee after a few experiments to evaluate solvent and chiral inductor. Having stablished the optimal protocol for the reaction, the scope and limitations were studied demonstrating that a variety of substitution patterns on the dienophile were tolerated obtaining spiro-oxindoles in good to excellent yield. Alternatively, other trienamine-precursors were tested and the same high reactivity and excellent stereocontrol were achieved (Scheme 3.16). Interestingly, it has to be pointed out the outstanding ability of the catalyst to provide sufficient stereocontrol at the very remote ε-position. Related to this topic, it should be mentioned that due to the concerted mechanism of the Diels-Alder reaction, steric shielding at the C3-carbon indirectly extends the chirality transfer from the catalyst to the remote C6-position. With the aim of increasing the applicability of this novel aminocatalytic transformation, other types of activated olefins, such as alkylidene cyanoacetates were evaluated. All the substrates presented a good reactivity as dienophiles for the Diels-Alder reaction.

[15] Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2011**, *133*, 5053.



Scheme 3.16

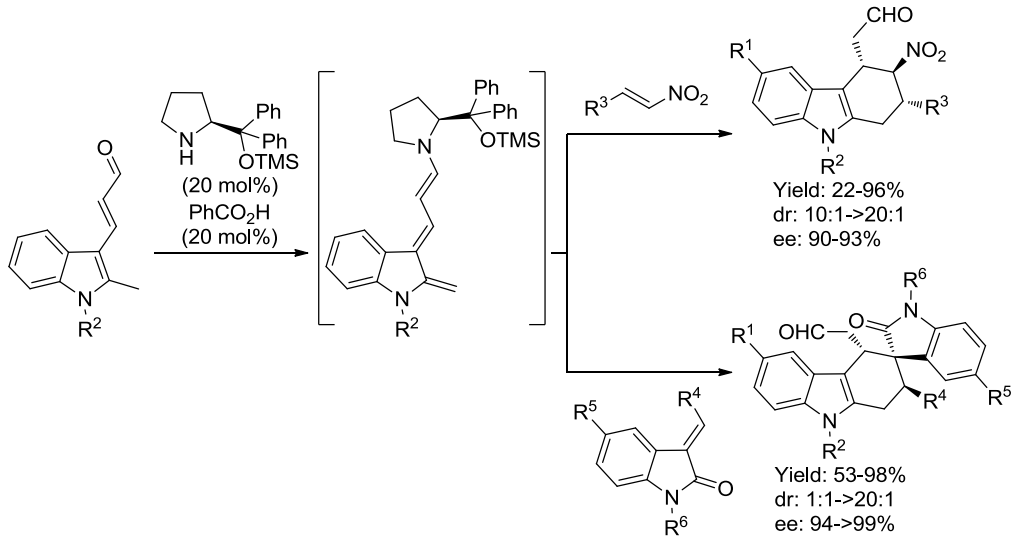
NMR spectroscopic data and some mechanistic studies were accomplished to confirm the presence of the trienamine intermediate. Thus, computational studies supported the basis for a favoured ε-activation pathway that set the foundation of a successful catalytic cycle involving trienamines. In the same report, the authors showed the outstanding performance of this activation manifold to one example of a trienamine/enamine tandem reaction. In this sense, the reaction consisted of a first chiral secondary amine promoted Diels-Alder cycloaddition reaction through the corresponding trienamine intermediate followed by an intermolecular Michael-type addition to the double activated ethyl 2-(diethoxyphosphoryl)acrylate under enamine activation (Scheme 3.17). Notably, despite the possibility of this later to participate as a reactive dienophile, no crossover products were observed. In this part of the research, the trienamine cycle reached the same outstanding stereoselectivity as in the previous example, while the second enamine-catalyzed step led to a 85:15 dr at the α position of the aldehyde.



Scheme 3.17

In a different context, Melchiorre *et al*. documented the first asymmetric catalytic Diels-Alder reaction of *in situ* generated heterocyclic ortho-quinodimethanes as reactive dienes with different electron-poor alkenes under trienamine catalysis.[16] This methodology provided an straightforward access to several complex tetrahydrocarbazoles with high chemical yield and excellent stereoselectivity employing nitroalkenes and methyleneindolinones as dienophiles (Scheme 3.18).

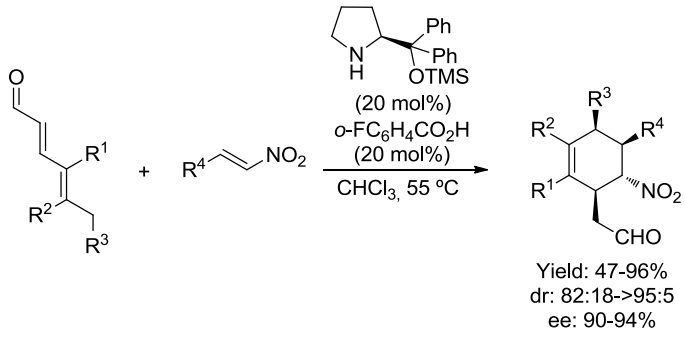
[16] Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Mechiorre, P. *J. Am. Chem. Soc*. **2011**, *133*, 15212.



Scheme 3.18

Nitroalkenes have been also employed as dienophiles together with 2,4-dienals in an *exo*-selective asymmetric Diels-Alder reaction under the same activation manifold, which proceeded successfuly with several differently substituted α,β,γ,δ-unsaturated aldehydes and nitroalkenes bearing either aryl or akyl groups, giving densely substituted chiral cyclohexene derivatives in high diastereo- and enantioselectivities.[17]

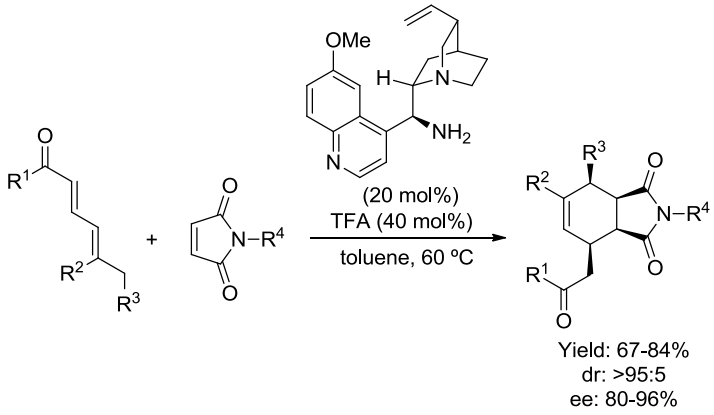
[17] Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q.; Chen, Y.-C. *Angew. Chem. Int. Ed*. **2011**, *50*, 8638.



Scheme 3.19

Alternatively, trienamine catalysis has been applied to 2,4-dienones for the development of a related transformation.[18] Importantly, dienones which do not contain α-enolizable alkyl groups had to be used in order to prevent the formation of undesired Barbas-type 2-amino-1,3,5-triene intermediates (Scheme 3.20). Moreover, another methyl group at the γ position of the dienone was introduced with the aim to inhibit the non-catalyzed Diels-Alder cycloadduct, as a quaternary center had to be formed. With respect to the catalyst, a chiral primary amine was employed to promote this enantioselective Diels-Alder reaction due to the already known ability of such catalysts to activate ketones. In this manner, using maleimides as dienophiles capable to react with a diverse range of 2,4-dienones, an array of ciclohexene derivatives were efficiently obtained in moderate to excellent enantioselectivity and exclusive *endo* selectivity.

[18] Xiong, X.-F.; Zhou, Q.; Gu, J.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. *Angew. Chem. Int. Ed*. **2012**, *51*, 4401.


OMe
H
N
NH2
N
(20 mol%)
TFA (40 mol%)
toluene, 60 ºC
R1
O
R2
R3
+
O
N–R4
O
R3
R2
O
N–R4
O
R1
O
Yield: 67-84%
dr: >95:5
ee: 80-96%

Scheme 3.20

2. SPECIFIC OBJECTIVES AND WORK PLAN.

From the literature review presented in the introduction, it can be concluded that the possibilities offered by the dienamine catalysis for the development of new reactions are widely open in this field. In this sense, and considering that the general objective of our research was focused on the study of new cascade reactions initiated by Michael reactions using aminocatalysis as the vehicle for stereocontrol, we decided to direct our efforts to the **development of a novel organocatalytic formal [2+2] cycloaddition between α,β-unsaturated aldehydes and nitroalkenes based on a Michael/Michael cascade process in which the dienamine activation strategy is combined with the iminium catalysis for the construction of the cyclobutane scaffold**.

In this sense, our proposal was inspired by the recent work reported by Seebach and Hayashi[19] and Blackmond[20] independently, in which kinetic and structural studies of *O*-TMS-diphenylprolinol-catalyzed Michael addition of linear aldehydes to nitroolefins demonstrated the generation of an aminonitrocyclobutane intermediate which contains the amine catalyst moiety. In this work, this cyclobutane intermediate was identified as a resting state for the catalyst which could undergo ring-opening reaction followed by hydrolysis furnishing the final Michael adduct (Scheme 3.21).

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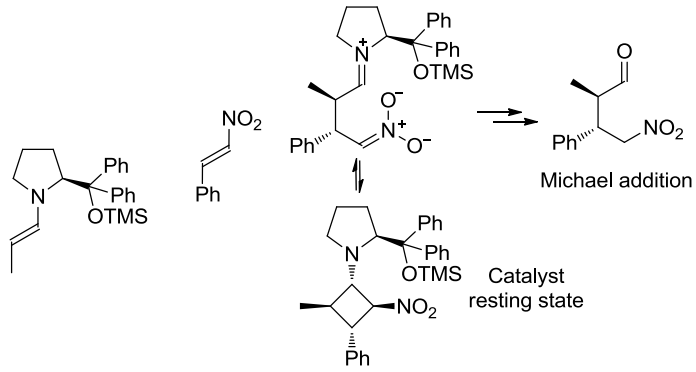
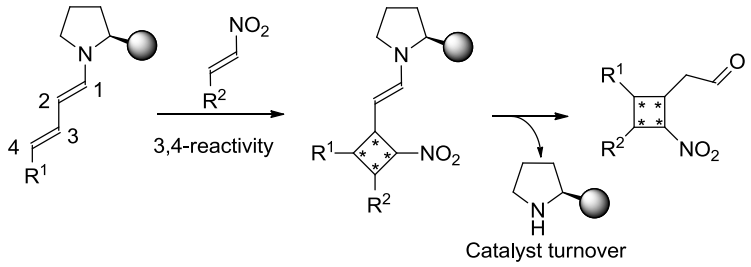
[19] Patora-Komisarska, K.; Meryem, B.; Ishikawa, H.; Seebach, D.; Hayashi, Y. *Helv. Chim. Acta* **2011**, *94*, 719.

[20] Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2011**, *133*, 8822.



Scheme 3.21

Therefore, we proposed that enolizable α,β-unsaturated aldehydes could undergo a similar reaction with nitroalkenes on C3 and C4 carbon atoms of the enal based on the dienamine activation strategy, allowing this way the aminocatalyst to undergo easy turnover and providing a final tetrasubstituted nitrocyclobutane product as a result of a formal [2+2] cycloaddition (Scheme 3.22).

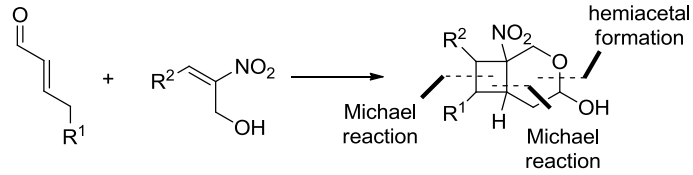


Scheme 3.22

A major issue to face in this projected reaction is related to the different pathways that theses catalytic intermediates can promote. In this sense, enamine 1,2-reactivity is well-recognized, which would result in α-functionalization of the enals and that has been described as the predominant pathway reacting with

nitroalkenes. Moreover, previously commented Diels-Alder reactivity could also compete with the cyclobutane formation leading to the generation of undesired cyclohexene products and/or catalyst deactivation.

With regard to the nitroolefin reagent and taking into account the difficulties associated to the formation of such a strained architecture like the cyclobutane scaffold we also decided to incorporate an α-hydroxymethyl substituent at the nitroalkene reagent able to engage in the stabilization of the final cascade product through hemiacetal formation in a similar way as we observed in the previous chapter. Therefore, we decided to incorporate a α-hydroxymethyl substituent at the nitroalkene substrate which would locate suitably to undergo hemiacetal formation with the remaining formyl group with the hypothesis that, the resulting domino process consisting of a Michael/Michael/hemiacetalization sequence could have more possibilities of success (Scheme 3.23).



Scheme 3.23

It should be pointed out that the proposed reaction would provide highly substituted multifunctional cyclobutane and in this sense, we would like to highlight that this type of four membered cyclic scafold is a structural motif incorporated in a numerous naturally occurring products and bioactive compounds.[21] Moreover, the rich reactivity pattern shown by cyclobutanes when exploiting ring strain as a

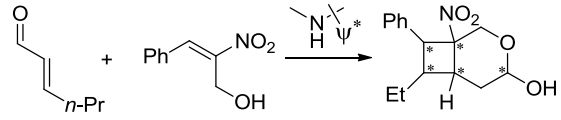
[21] (a) *The Chemistry of Cyclobutanes*; Rappoport, Z.; Liebman, J. F., Eds.; John Wiley & Sons, Ltd.: West Sussex, England, 2005. (b) Ortuno, R. M.; Moglioni, A. G.; Moltrasio, G. Y. *Curr. Org. Chem.* **2005**, *9*, 237.

driving force to facilitate novel reactivity has also open the way for the use of these compounds as synthetic intermediates in the synthesis of complex molecules.[22] However, despite their interest, the development of methodologies for the stereocontrolled synthesis of four membered carbocycles has received little attention over the years.[23]

In line with these premises we designed the following work plan:

1. Synthesis of the precursors: the required α-functionalized nitrostyrene has to be synthesized as it is not commercially available. In addition, we also decided to prepare a set of structurally different enolizable α,β-unsaturated aldehydes, particularly γ-aryl substituted enals with which the formation of the dienamine species would be more favoured.

2. Viability of the reaction: using *trans*-2-hexenal and α-hydroxymethylnitrostyrene as model substrates, we will check the viability of the projected formal [2+2] cycloaddition reaction (Scheme 3.24). Then, in case of success, a racemic standard would have to be prepared for the development of the corresponding protocol for the determination of the enantiomeric excess.

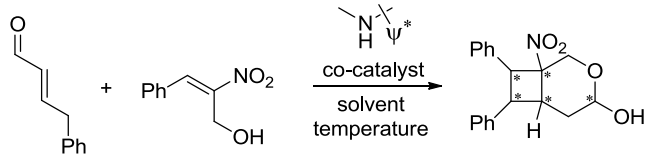


Scheme 3.24

[22] (a) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 7740. (b) Campbell, M. J.; Johnson, J. S.; Parsons, A. T.; Pohlhaus, P. D.; Sanders, S. D. *J. Org. Chem.* **2010**, *75*, 6317. (c) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev*. **2003**, *103*, 1485.

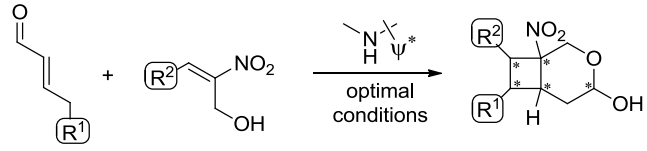
[23] (a) Schmidt, A. W.; Knoelker, H.-J. *Synlett* **2010**, 2207. (b) Lee-Ruff, E.; Mladenova, G. *Chem. Rev*. **2003**, *103*, 1449.

3. Survey of optimal reaction conditions: a screening of several aminocatalysts and other experimental parameters such as solvent, co-catalysts and temperature will be studied with the aim to achieve the best diastereo- and enantioselectivity, as well as in order to obtain the final product in high chemical yield (Scheme 3.25).



Scheme 3.25

4. Scope and limitations of the reaction: with the best reaction conditions in hands, several differently substituted enolizable enals, as well as α-hydroxymethyl-substituted nitroolefins will be prepared in order to explore the scope of the reaction (Scheme 3.26).

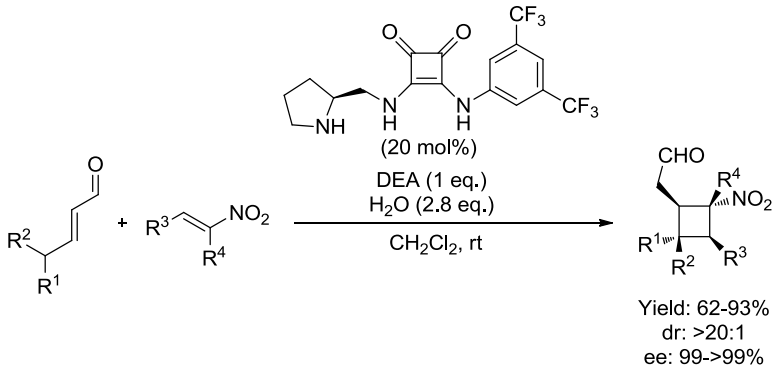


Scheme 3.26

5. Transformation of the cycloadducts: some possible synthetic transformations on the obtained products will be explored in order to illustrate their potential applications as chiral building blocks.

It has to be mentioned that by the time this work was submitted for publication, the asymmetric organocatalytic formal [2+2] cycloaddition *via* dienamine catalysis/bifunctional H-bond directing developed by Jørgensen and co-

workers was published.[24] Interestingly, in this report a novel bifunctional squaramide-based aminocatalyst was designed for the construction of cyclobutanes using a newly devised concept based on H-bond directing dienamine catalysis (Scheme 3.27).



Scheme 3.27

[24] Albrecht, L.; Dickmeiss, G.; Cruz Acosta, F.; Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2012**, *134*, 2543.

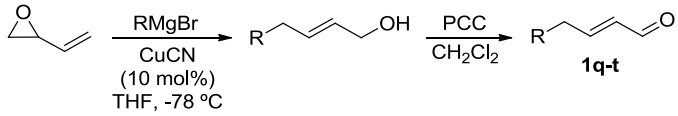
3. RESULTS AND DISCUSSION.

Once reported different methodologies in which the dienamine catalysis has been applied and after establishing the specific objectives and work plan, the obtained results in this second part of the research work will be presented.

3.1. Synthesis of the precursors.

As the first task of this part of the present work, the synthesis of both enolizable enals and α-hydroxymethylnitroalkenes was carried out.

Table 3.1: Synthesis of enolizable α,β-unsaturated aldehydes.



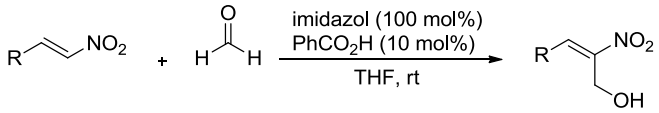
Entry	R	Product	Yield (%) step 1	Yield (%) step 2
1	Ph	**1p**	85	72
2	4-MeC_6H_4	**1q**	83	82
3	4-FC_6H_4	**1r**	70	69
4	2-thienyl	**1s**	77	39
5	4-$MeOC_6H_4$	**1t**	75	75

In this sense, the required not commercially available α,β-unsaturated aldehydes **1q-t** were prepared by a two step procedure consisting of a CuCN catalyzed ring-opening reaction of 3,4-epoxy-1-butene by the required Grignard

reagents furnishing the corresponding allylic alcohol[25] which was followed by an oxidation process using PCC under standard conditions.In this way, a simple and reliable methodology was developed for the obtention of enough quantities of the desired γ-aryl substituted enolizable enals in good yields in most cases.

On the other hand, α-hydroxymethyl-substituted nitroalkene reagents **29a-f** were synthesized following a modified literature procedure,[26] consisting of a Baylis-Hillman-type reaction between β-aryl substituted nitroolefins and formaldehyde.

Table 3.2: Synthesis of α-hydroxymethylnitroalkenes.



29a-f

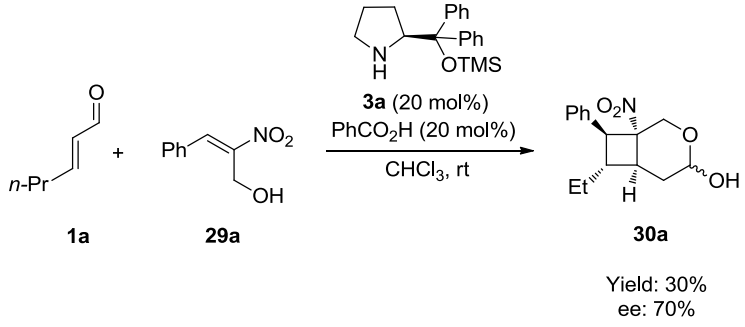
Entry	R	Product	Yield (%)
1	Ph	**29a**	50
2	4-$MeOC_6H_4$	**29b**	48
3	4-ClC_6H_4	**29c**	42
4	4-$NO_2C_6H_4$	**29d**	31
5	2-thienyl	**29e**	36
6	*i*-Pr	**29f**	28

[25] See experimental section (chapter 5).

[26] Mohan, R.; Rastogi, N.; Namboothiri, I. N. N.; Mobin, S. M.; Panda, D. *Bioorg. Med. Chem.* **2006**, *14*, 8073.

3.2. Viability of the reaction.

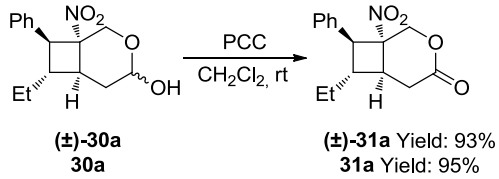
We started our work using commercially available *trans*-2-hexenal in order to get rapidly a set of preliminary results. In this context, we first ran the reaction between *trans*-2-hexenal and α-hydroxymethylnitrostyrene in the presence of chiral secondary amine **3a** and benzoic acid as additive in $CHCl_3$, yielding the expected [2+2] cycloaddition product **30a** as a mixture of α and β anomers of a single diastereoisomer in low yield (Scheme 3.28). It should be noted that only one regioisomer was isolated, without detecting the formation of any byproduct arising from the already commented Diels-Alder reactivity product or from the corresponding α-functionalization side reaction.



Scheme 3.28

At this point, for the determination of the enantiomeric excess of **30a** a racemic sample of the cycloadduct was needed. For this purpose, a racemic mixture consisting of an equimolecular mixture of both enantiomers of **30a** was prepared employing (*S*) and (*R*) isomers of aminocatalyst **3a** under the reaction conditions shown above (Scheme 3.28). The complex situation derived from the presence of α and β anomers due to the hemiacetal function did not allow a clear HPLC separation of the two enantiomers and, for this reason, both the racemate **(±)-30a**

and the optical active compound **30a** were subjected to oxidation with PCC, leading to the formation of the corresponding lactones **(±)-31a** and **31a**, respectively, in almost quantitatively yield (Scheme 3.29).



(±)-30a
30a

(±)-31a Yield: 93%
31a Yield: 95%

Scheme 3.29

The chromatograms of both lactones **(±)-31a** and **31a** are depicted in the Figure 3.1, observing an encouraging 70% ee for the synthesized compound **30a** determined by HPLC analysis employing *Chiralpak AD-H* chiral column and a mixture of 90:10 *n*-hexane/*i*-PrOH as eluent.

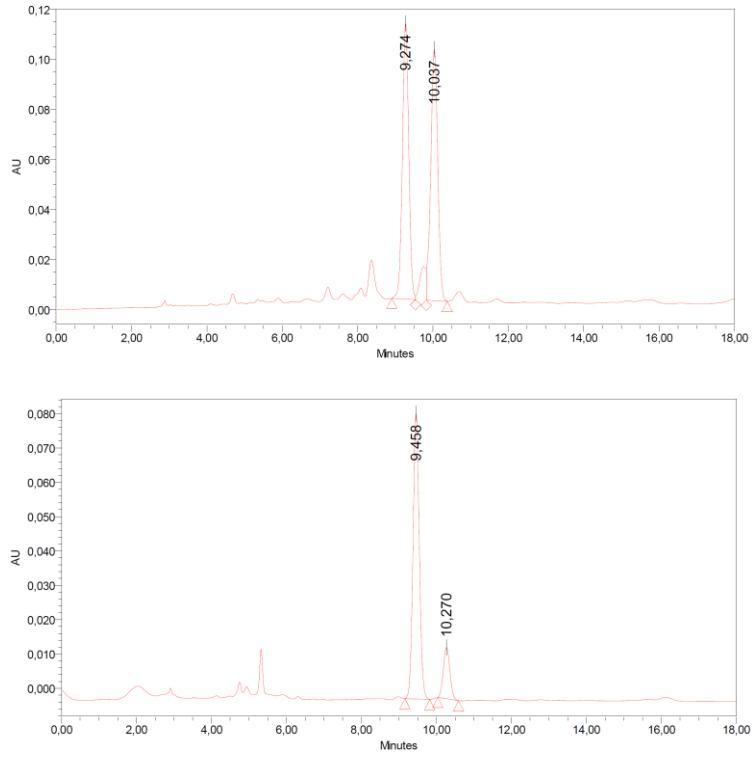
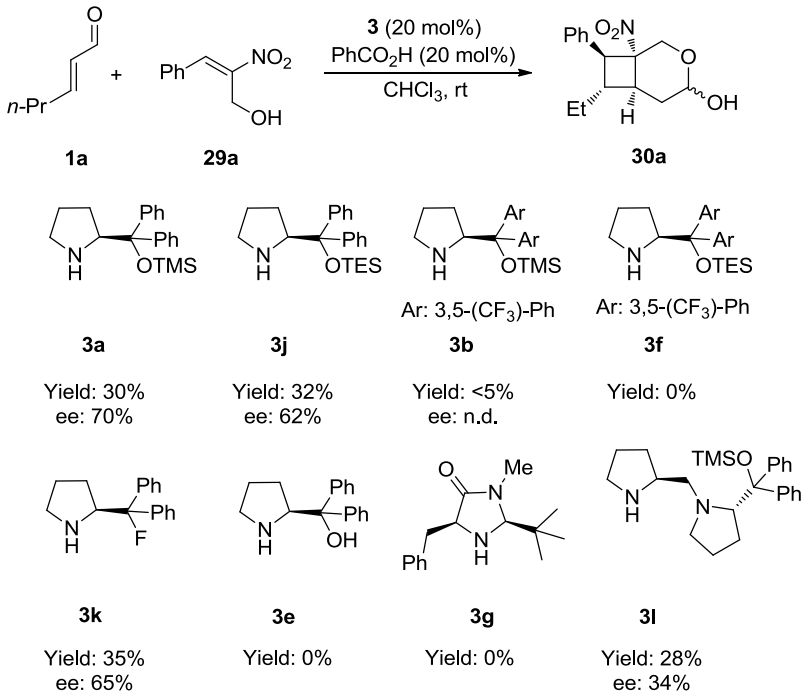


Figure 3.1

3.3. Optimization of the reaction.

In the initial stages of the optimization process, our first reactions were performed using different chiral secondary amines as organocatalysts (10 mol%) together with benzoic acid as additive (10 mol%) in $CHCl_3$ (Scheme 3.30). After performing this set of experiments, it was observed that switching to a diphenylprolinol derivative containing a bulkier silyloxy group (**3j**) gave similar results to those previously obtained with catalyst **3a**, while aminocatalysts bearing bulkier aryl substituents (**3b** and **3f**) did not show to be active. In fact, only trace

amounts of **30a** were detected by NMR analysis of the crude mixture when **3b** was employed, while no product was obtained in the reaction with amine **3f**. Another diphenylprolinol derivative, such as catalysts **3k**, furnished compound **30a** with low yield and enantioselectivity. On the other hand, a potentially bifunctional aminocatalyst such as diphenylprolinol (**3e**) was not able to promote the reaction, only recovering unmodified starting materials. Imidazolidinone **3g** was also tried without success. Finally, chiral amine **3l** was also tested, isolating compound **30a** in very low yield and with even poorer enantiocontrol.

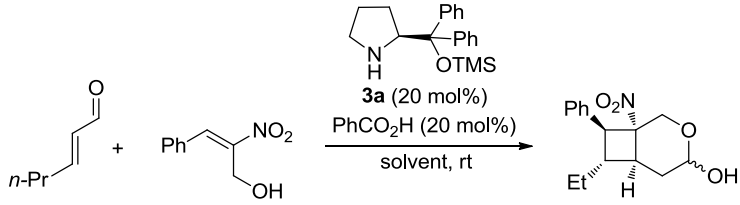


Scheme 3.30

After these experiments, it was concluded that the aminocatalyst which provides best results in terms of stereochemical outcome was the initially employed

amine **3a** and therefore, we next proceeded to keep on searching for the optimal reaction conditions. Thus, we next carried out the reaction using different solvents in order to check the influence of this parameter in the reaction outcome. As summarized in Table 3.3, the use of solvents such as $CHCl_3$ and toluene which are commonly employed in organocatalytic transformations in the presence of this kind of *O*-TMS diarylprolinol aminocatalysts showed the best results with respect to the chemical yield and enantioselectivity (entries 1 and 2). Surprisingly, when CH_2Cl_2 a solvent with similar properties to $CHCl_3$ such as CH_2Cl_2 was employed, the yield decreased drastically (entry 3).

Table 3.3: Effect of the solvent.



1a **29a** **30a**

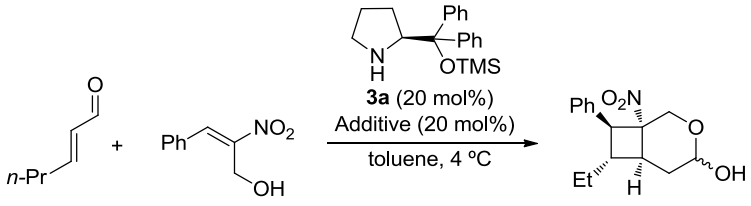
Entry	Solvent	Yield (%)[a]	ee (%)[b]
1	$CHCl_3$	30	70
2	Toluene	38	76
3	CH_2Cl_2	<5	n.d.
4	THF	<5	n.d.
5	MeOH	<5	n.d.
6	Chlorobenzene	<5	n.d.
7	Trifluorotoluene	<5	n.d.
8[c]	Toluene	25	85

[a]Yield of pure product as a 1:1 mixture of α and β anomers (NMR analysis) after column chromatography. [b]Determined by HPLC analysis of the corresponding lactone **31a**. [c]The reaction was carried out at 4 ºC.

On the other hand, a more polar solvent such as THF and a protic one as MeOH were evaluated (entries 4 and 5) giving the same negative results with regard to conversion. Chlorobenzene and trifluorotoluene were also evaluated as halogenated solvents related to toluene but these experiments were unsuccessful (entries 6 and 7). With these results in hands, a final reaction was run in toluene at lower temperature (entry 8) to check if this parameter exerted some influence on the enantiomeric excess of the product **30a**. Gratifyingly, even though the chemical yield decreased slightly, the achieved enantiocontrol was higher.

Thus, we considered to explore different additives in order to increase the reaction conversion maintaining low temperature. When some different Brønsted acid as co-catalysts were added (Table 3.4), the yield of the reaction decreased notably. In this sense, slightly more acidic additives than benzoic acid (entries 2 and 3) or with similar pK_a (entry 5) were tried but in all cases the compound **30a** was isolated in poor yields. The addition of a strong acid such as *p*-TSA, did not lead to the formation of **30a** (entry 4). Finally, we observed that a basic additive such as DABCO was not compatible with this reaction (entry 6).

Table 3.4: Effect of the additive.



1a **29a** **30a**

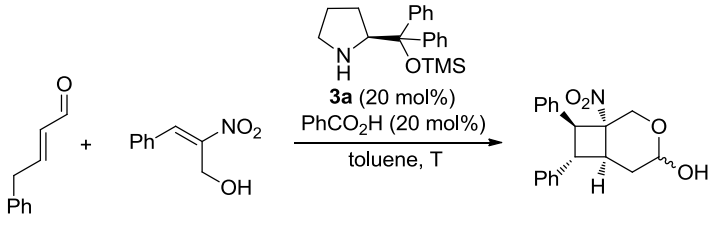
Entry	Additive	pK_a[a]	Yield (%)[b]	ee (%)[c]
1	$PhCO_2H$	4.20	25	85
2	*p*-$NO_2C_6H_4CO_2H$	3.47	<5	n.d.
3	*o*-$IC_6H_4CO_2H$	2.85	18	n.d.
4	*p*-TSA	-2.80	-	-
5	AcOH	4.76	<5	n.d.
6	DABCO	-	-	-

[a]pK_a values measured in H_2O. Perrin, D. D.; Serjeant, E. P.; Dempsey, B. *pK_a Predictions for Organic Acids and Base,* Champman and Hall, London, **1981.** [b]Yield of pure product as a 1:1 mixture of α and β anomers (NMR analysis) after column chromatography. [c]Determined by HPLC analysis of the corresponding lactone **31a**.

In view of these results and having collected useful information about this enantioselective organocatalytic formal [2+2] cycloaddition reaction, we next changed the reaction design to the use of γ-phenyl substituted enal **1p** as model substrate, which was believed to perform better in the reaction due to its expected ability to stabilize the dienamine intermediate by conjugation. In this context, as shown in Table 3.5, a first attempt in the presence of the chiral amine **3a** and using benzoic acid as additive in toluene at 4 ºC provided the desired compound **30b** in 56% yield and with 86% ee (entry 1). These encouraging results prompted us to continue the optimization task using this new enal substrate modifying the

temperature with the aim of getting a rise in the enantioselectivity. Therefore, by cooling the reaction to -20 ºC a high ee was achieved (entry 2), although as it was expected the reaction conversion decreased notably. In order to see a positive effect on the conversion, the reaction was performed with a small excess of nitroalkene **29a**, although the product **30b** was still obtained in moderate yield (entry 3).

Table 3.5: Effect of the temperature.



1p **29a** **30b**

Entry	T (ºC)	Yield (%)[a]	ee (%)[b]
1	4	56	86
2	-20	40	90
3[c]	-20	47	90

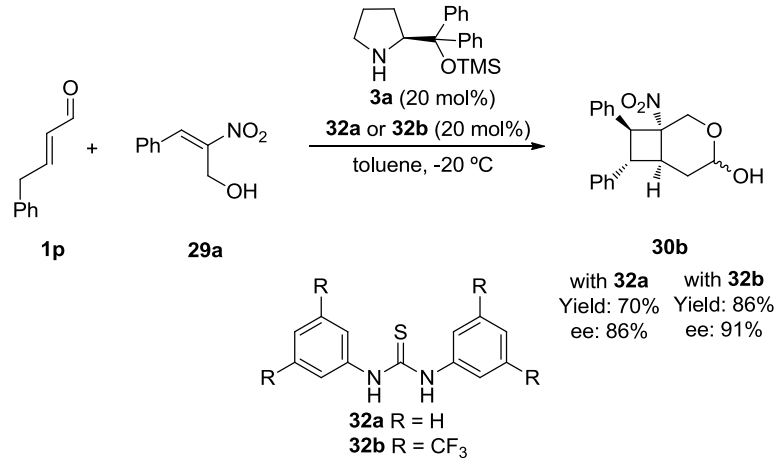
[a]Yield of pure product as a 1:1 mixture of α and β anomers (NMR analysis) after column chromatography. [b]Determined by HPLC analysis of the corresponding lactone **31b**. [c]The reaction was carried out with a 1:1.5 ratio of **1p**:**29a**.

In a final attempt to get a better reaction conversion we decided to include an additive that could be able to activate the nitroalkene counterpart through selective H-bonding interactions (Scheme 3.31). The envisaged strategy, which falls under the classification of *synergistic catalysis*,[27] would involve simultaneous activation of both reacting partners by two separate and distinct catalyst, which would turn into two reactive species, one with a higher HOMO and the other with a lower

[27] Allen, A. E.; MacMillan, D. W. C. *Chem. Sci*. **2012**, *3*, 633.

LUMO and therefore, causing an important decrease in the activation energy and a consequently increase of the rate constant to drive the desired pathway.

In this manner, we carried out the reaction in the presence of achiral thiourea **32a** as co-catalyst in toluene at -20 ºC, achieving an important increase in the chemical yield and a promising 86% ee. The improvement observed was even higher with the more acidic thiorea **32b**, which presents aryl substituents containing electron-withdrawing groups, yielding this way the cycloadduct **30b** with up to 86% yield and 91% ee.



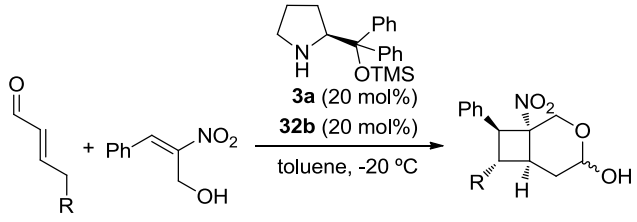
Scheme 3.31

After all these experiments, we concluded that the best reaction conditions for the enantioselective organocatalytic formal [2+2] cycloaddition between enolizable enal **1p** and α-hydroxymehtylnitroolefin **29a** consisted of the use of 20 mol% of the chiral amine **3a** together with the same amount of the thiourea **32b** in toluene at -20 ºC.

3.4. Scope and limitations.

With the best protocol for the reaction in hands, the scope and limitations of our methodology were explored with respect to the enal and nitroalkene reagent. Firstly, some other enolizable α,β-unsaturated aldehydes **1q-u** were tested in the reaction with nitrostyrene **29a**. As summarized in Table 3.6, different substituents on the aryl moieties at γ-position of the α,β-unsaturated aldehydes reagents were well-tolerated for the reaction. In this sense, both electron-rich and electron-poor γ-aryl-substituted enals (**1q** and **1r**) led to the desired bicyclic adducts **30c** and **30d** in high yield and high enantiopurity (entries 2 and 3). On the other hand, when carrying out the reaction with 2-thienyl substituted enal (**1s**), the product **30e** was obtained efficiently with slightly lower yield but still good enantioselectivity (entry 4). On the contrary, the use of γ-benzyloxy substituted 2-butenal (**1u**) failed (entry 5) being this result interpreted in terms of the poorer nucleophilicity of the γ-carbon of the dienamine intermediate. Gratifyngly, *trans*-2-hexenal also provided the cyclobutane scaffold under the optimized conditions although, in lower yield than in the earlier experiments using γ-aryl substituted enals (entry 6 *versus* entries 2-5) presumably due to the less favored dienamine intermediate formation for this aliphatic enal.

Table 3.6: Scope of the reaction.



1 **29a** **30**

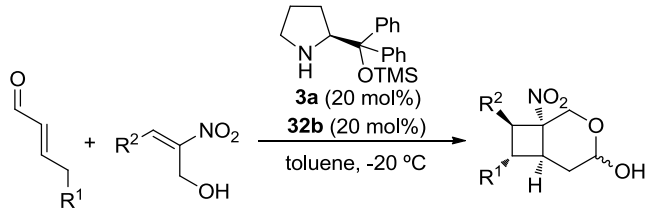
Entry	R	Product	Yield (%)[a]	ee (%)[b]
1	Ph **(1p)**	**30b**	86	91
2	4-MeC_6H_4 **(1q)**	**30c**	88	92
3	4-FC_6H_4 **(1r)**	**30d**	77	92
4	2-thienyl **(1s)**	**30e**	73	89
5	OBn **(1u)**	-	-	-
6	Et **(1a)**	**30a**	38	85

[a]Yield of pure product as a 1:1 mixture of α and β anomers (NMR analysis) after column chromatography. [b]Determined by HPLC analysis of the corresponding lactones **31**.

On the other hand, we also surveyed the behaviour of the reaction by using other nitrostyrenes (Table 3.7). In this sense, *p*-methoxy and *p*-chloro substituted nitrostyrenes (**29b** and **29c**) were evaluated (entries 1-6), observing that the reaction proceeded with good to excellent yield, while incorporating a strong electron-withdrawing substituent such as *p*-nitrophenyl group (**29d**) the reaction did not occur, presumably due to possible competitive H-bonding interactions between this nitro group and thiourea **32b** (entry 7). Furthermore, a heteroaromatic framework was also incorporated into the final cyclobutane adduct, as shown for the 2-thienyl-substituted product **30l**, which was isolated with moderate yield (entry 8). We also considered extending the methodology to β-alkyl-substituted nitroalkenes; however,

when isopropyl group was incorporated into the niroolefin structure at β position (**29f**), the reaction did not work (entry 9). Concerning the enantioselectivity, for all tested cases, very high levels of enantiocontrol were achieved. Remarkably, all the compounds **30 a-l** were obtained as single diastereoisomer (the presence of the α and β anomers associated to the hemiacetal moiety is not considered).

Table 3.7: Scope of the enantioselective organocatalytic formal [2+2] cycloaddition reaction of enals and nitroalkenes.



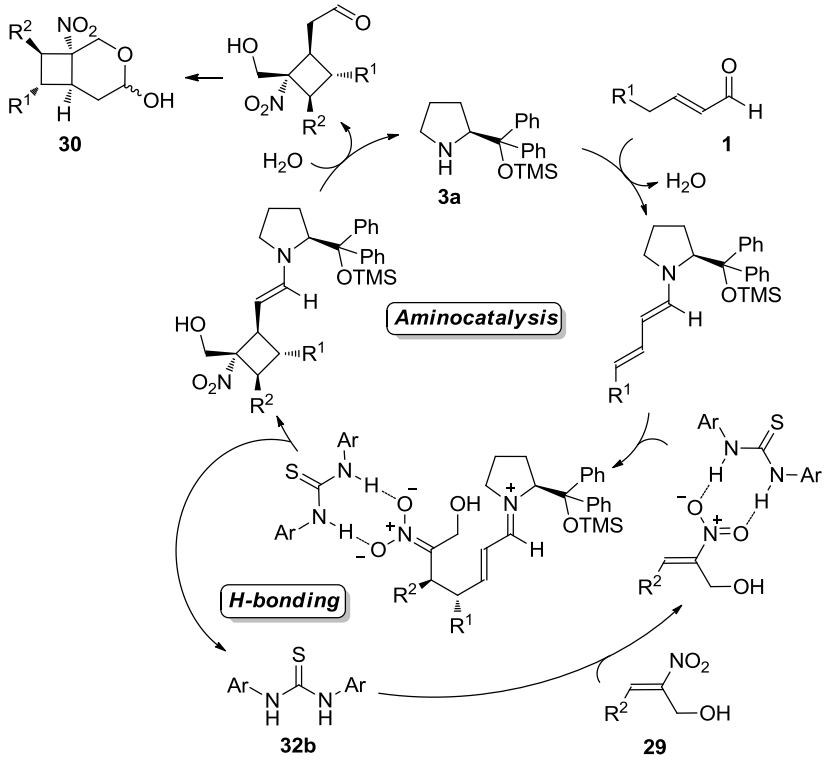
1 **29** **30**

Entry	R^1	R^2	Product	Yield (%)[a]	ee (%)[b]
1	Ph **(1p)**	4-$MeOC_6H_4$ **(29b)**	**30f**	72	95
2	4-MeC_6H_4 **(1q)**	4-$MeOC_6H_4$ **(29b)**	**30g**	91	94
3	4-FC_6H_4 **(1r)**	4-$MeOC_6H_4$ **(29b)**	**30h**	91	94
4	4-$MeOC_6H_4$ **(1t)**	4-$MeOC_6H_4$ **(29b)**	**30i**	90	94
5	Ph **(1p)**	4-ClC_6H_4 **(29c)**	**30j**	67	92
6	4-MeC_6H_4 **(1q)**	4-ClC_6H_4 **(29c)**	**30k**	69	94
7	Ph **(1p)**	4-$NO_2C_6H_4$ **(29d)**	**-**	-	-
8	Ph **(1p)**	2-thienyl **(29e)**	**30l**	52	94
9	Ph **(1p)**	*i*-Pr **(29f)**	**-**	-	-

[a]Yield of pure product as a 1:1 mixture of α and β anomers (NMR analysis) after column chromatography. [b]Determined by HPLC analysis of the corresponding lactones **31**.

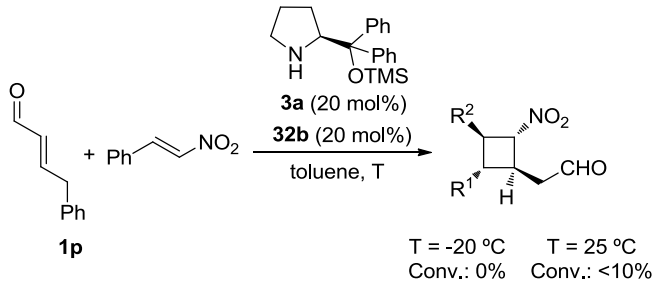
Regarding the mechanism, we propose a catalytic cycle (Scheme 3.32) in which the first step is the activation of the enal **1** by the aminocatalyst **3a** forming a

dienamine intermediate. Then, the cyclobutane formation would occur in a stepwise manner through a Michael/Michael sequence where firstly the dienamine would undergo a conjugate addition to the activated nitroalkene **29** (H-bonding activation) involving the formation of the C-C bond between the γ-carbon of the nucleophilic dienamine intermediate and the β-carbon of the nitroolefin with the fully stereocontrolled generation of two stereocenters. In the second step, an intramolecular reaction between the generated nitronate intermediate with the remaining iminium ion moiety would take place, presumably with the participation of the thiourea co-catalyst in the stabilization of this nitronate intermediate. Finally, after hydrolysis of the last catalytic species, the catalyst **3a** would be released and intramolecular 1,2-addition of the remaining primary alcohol to the formyl group would deliver the final hemiacetal **30**.



Scheme 3.32

The α-hydroxymethyl substituent on the nitroalkene seems to be crucial for the reaction, since this final hemiacetalization process is believed to be an important driving force for the reaction to proceed to completion under our reaction conditions. With the aim to corroborate this matter, an experiment using simple nitrostyrene and the enal **1p** was carried out under the optimized reaction conditions without observing the formation of any [2+2] cycloadduct product.



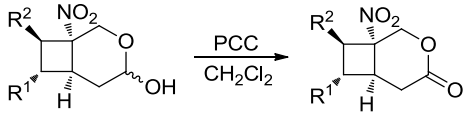
Scheme 3.33

We also performed the same experiment at room temperature, observing the formation of the corresponding cyclobutane with a <10% conversion after five days (^{1}H-NMR analysis of crude reaction mixture) (Scheme 3.33).

3.5. Transformation of the cycloadducts.

Finally, we considered to explore the synthetic possibilities of the obtained adducts as chiral building blocks by making selective transformations on the different functionalities that are incorporated into their structure. In this sense, as already commented, the oxidation of the obtained mixture of anomers to the corresponding lactones was carried out for the determination of all the enantiomeric excesses, leading, furthermore, to a better characterization. In all these transformations, bicyclic lactones **31** were obtained in excellent yields and as single diastereoisomers.

Table 3.8: Oxidation of the enantioselective organocatalytic formal [2+2] cycloaddition adducts.



30 **31**

Entry	R^1	R^2	Product	Yield (%)
1	Et	*i*-Pr	**31a**	95
2	Ph	Ph	**31b**	95
3	4-MeC_6H_4	Ph	**31c**	97
4	4-FC_6H_4	Ph	**31d**	98
5	2-thienyl	Ph	**31e**	95
6	Ph	4-$MeOC_6H_4$	**31f**	94
7	4-MeC_6H_4	4-$MeOC_6H_4$	**31g**	96
8	4-FC_6H_4	4-$MeOC_6H_4$	**31h**	96
9	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**31i**	97
10	Ph	4-ClC_6H_4	**31j**	97
11	4-MeC_6H_4	4-ClC_6H_4	**31k**	98
12	Ph	2-thienyl	**31l**	97

At this point, we could grow a suitable crystal of compound **31b** for X-ray analysis (Figure 3.2), establishing this way a (1*R*,6*S*,7*S*,8*S*) absolute configuration. This configuration was therefore extended to all cycloadducts **30** and lactones **31** based on mechanistic analogy.

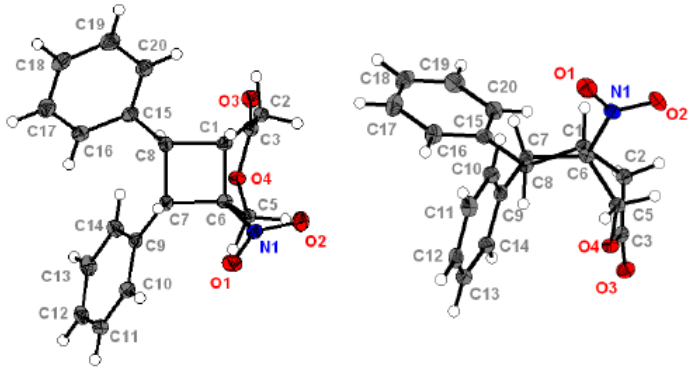
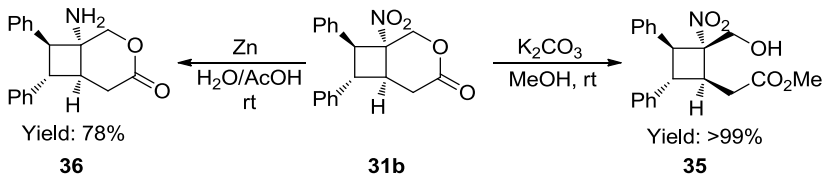


Figure 3.2

Next, we proceeded to survey different chemical transformations on the obtained lactones **31** (Scheme 3.34). In this sense, taking compound **31b** as model substrate, the corresponding tetrasubstituted cyclobutane **35** was obtained quantitatively by means of a base-promoted methanolysis, without epimerization of any stereocenter. On the other hand, the selevtive reduction of the nitro group could be performed under standard reaction conditions affording the corresponding amine **36** in good yield and mantaining the stereochemical integrity.



Scheme 3.34

4. CONCLUSIONS.

Considering the results obtained in this chapter the following conclusions can be outlined:

1. Cooperative dienamine/hydrogen-bonding catalysis has demonstrated to be a powerful strategy in the enantioselective formal [2+2] cycloaddition of enolizable α,β-unsaturated aldehydes and α-hydroxymethylnitroalkenes through Michael/Michael cascade reaction.

2. It has been demonstrated that the employed catalytic system, a chiral secondary amine and an achiral thiourea, provides good results in terms of chemical yield and stereoselectivity, leading to the formation of only one regioisomer with complete diastereocontrol and high enantioselectivity.

3. The possibility of performing some efficient transformations of the formed cycloadducts easily illustrates the synthetic relevance of this methodology for the obtention of chiral building block in organic synthesis.

4. Regarding mechanistic aspects, this reaction constitutes first example of a cascade reaction involving the dienamine/iminium manifold, which opens the way to interesting further development in the field of asymmetric organocatalysis.

4

4

Final conclusions.

1. CONCLUSIONS.

Throughout the present work it has been demonstrated that the combination of different aminocatalytic activation modes using chiral secondary amines as catalysts in cascade processes represents an efficient and reliable tool for the stereocontrolled synthesis of complex molecules in a straightforward manner. For the developed methodologies we could settle the following conclusions:

a) Enantioselective synthesis of heterocycles through organocascades: the first example of a highly enantioselective β-alkoxylation of α,β-unsaturated aldehydes catalyzed by a chiral secondary amine has been developed using dihydroxyacetone as a suitable functionalized Michael donor for the oxa-Michael/aldol/hemiacetalization cascade reaction under iminium/enamine catalysis. *O*-TMS-diphenylprolinol **3a** was identified as the best aminocatalyst to promote the reaction with excellent levels of diastereo- and enantiocontrol, furnishing furofuranes with four stereocenters in high yields. Moreover, different enantioenriched compounds were synthesized efficiently by easy and rapid selective transformations of the obtained adducts. On the other hand, γ-lactams have been synthesized in high yields and excellent enantioselectivities by the reaction of α-aminoacetophenone and several enals under iminium activation in the presence of the aminocatalyst **3b** through the Michael/hemiaminal formation cascade sequence followed by a PCC promoted oxidation. These adducts have been successfully transformed into different substituted 1,5-dicarbonyl compounds maintaining the enantiomeric purity of the starting compounds.

b) Enantioselective organocatalytic formal [2+2] cycloaddition reaction: a novel organocatalytic formal [2+2] cycloaddition reaction between enolizable enals and α-hydroxymethylnitroalkenes has been developed for the diastereo- and enantioselective synthesis of substituted cyclobutanes in an overall Michael/Michael/hemiacetalization cascade process that involves the combination of dienamine/iminium activation mechanism. In this case, a catalytic system consisting of chiral secondary amine catalyst (**3a)** and an achiral thiourea (**32b)** have been employed, demonstrating the efficiency of the cooperative dienamine/hydrogen-bonding catalysis in order to achieve good results in terms of chemical yield and stereochemical outcome. In addition, the obtained cycloadducts have been manipulated for the synthesis of other enantioenriched related compounds in high yields.

5

5

Experimental.

1. General methods and materials.

2. Organocatalytic cascade reactions.

2.1. Enantioselective organocatalytic oxa-Michael/aldol cascade reaction. Synthesis of furofuranes **4a-k**.

2.2. Synthesis of acetylated compounds **5a**, **5c, 5e** and **5i-k**.

2.3. Synthesis of benzoylated compounds **6b-h**.

2.4. Synthesis of derivative **7**. Determination of the absolute configuration.

2.5. Oxidation of furofurane **4a**. Synthesis of compound **8**.

2.6. Methanolysis of derivative **8**. Synthesis of compound **9**.

2.7. Reduction of furofurane **4a**. Synthesis of compound **10**.

2.8. Allylation of furofurane **4a**. Synthesis of compound **11**.

2.9. Organocatalytic enantioselective Michael/hemiaminalization cascade reaction. Synthesis of γ-lactams **14b** and **14i-o**.

2.10. Methanolysis of lactams ***cis*-14i-l** and ***cis*-14n**. Synthesis of compounds ***syn*-25i-l** and ***syn*-25n**.

2.11. Ring opening of lactam **14b**. Synthesis of the ketoamide **28**.

2.12. Determination of the relative and absolute configuration.

3. Enantioselective organocatalytic formal [2+2] cycloaddition reaction.

3.1. Preparation of γ-aryl substituted α,β-unsaturated aldehydes **1p-u**.

3.2. Preparation of α-hidroxymethylnitrostyrenes **29a-f**.

3.3. Synthesis of cyclobutane adducts **30a-l** and **31a-l**.

3.4. Methanolysis of adduct **31b**. Synthesis of compound **35**.

3.5. Reduction of adduct **31b**. Synthesis of compound **36**.

1. GENERAL METHODS AND MATERIALS.

NMR: Monodimensional and/or bidimensional nuclear magnetic resonance proton and carbon spectra (^{1}H-NMR and ^{13}C-NMR) were acquired at 25 ºC on a Bruker AC-300 spectrometer (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) and a Bruker AC-500 spectrometer (500 MHz for ^{1}H and 125.7 MHz ^{13}C). Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR. MeOH, 4.87 ppm and 3.31 ppm for ^{1}H NMR, CD_3OD, 49.1 ppm for ^{13}C NMR) and coupling constants (*J*) in hertz (Hz). The following abbreviations are used to indicate the multiplicity in ^{1}H NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. ^{13}C NMR spectra were acquired on a broad band decoupled mode using DEPT experiments (Distortionless Enhancement by Polarization Transfer) for assigning different types of carbon environment. Selective n.O.e., NOESY, COSY and HSQC experiments were acquired to confirm precise molecular conformation and to assist in deconvoluting complex multiplet signals.[1]

IR: Infrared spectra (IR) were measured in Perkin-Elmer R-1600 or JASCO FT/IR-4100 equipments, in the interval between 4000 and 400 cm^{-1} with a 4 cm^{-1} resolution and only characteristic bands are given.

MS: Mass spectra (MS) were recorded on an Agilent 7890A gas chromatograph coupled to an Agilent 5975 mass spectrometer under electronic impact (EI) or chemical ionization (CI) conditions. The obtained data is presented in

[1] Kinss, M.; Sanders, J. K. M. *J. Mag. Res.* **1984**, *56*, 518.

mass units (m/z) and the values found in brackets belong to the relative intensities comparing to the base peak (100%).

M.p.: Melting points were measured in a Büchi B-540 apparatus.

Polarimetry: Optical rotations were measured in a Perkin-Elmer 241 polarimeter or a JASCO P-2000 equipment at room temperature Perkin-Elmer 241 with a sodium lamp at 589 nm and a path length of 1 dm. Solvent and concentration are specified in each case.

HRMS: High-resolution mass spectra (HRMS) were recorded on a Micromass GCT spectrometer using chemical ionization (CI).

HPLC: The enantiomeric excess (ee) of the products were determined by chiral stationary phase HPLC in a Waters 2695 coupled to a Waters 2998 photodiode array detector and employing Chiralcel OD and Daicel Chiralpak AD-H, AS-H and IA columns.

Elemental Analysis: Microanalyses were performed by the University of Burgos using LECO CHNS-932 and VTF-900 analyzers.

X-ray: X-ray data collections were performed in an *Agilent Supernova* diffractometer equipped with an *Atlas* CCD area detector, and a CuKα micro-focus source with multilayer optics (λ = 1.54184 Å, 250 μm FWHM beam size). The quality of the crystals was checked under a polarizing microscope, and a suitable crystal or fragment was mounted on a Mitegen Micromount™ using Paratone-N inert oil and transferred to the diffractometer. Alternatively, an *Oxford Diffraction Xcalibur 2* diffractometer equipped with a *Sapphire 2* CCD area detector, and a MoKα sealed-tube source with graphite monochromator (λ = 0.71073 Å, 0.5 mm

collimator) was used. The samples were kept at 100(1)K with a *Oxford Cryosystems Cryostream 700* cooler.

Materials: Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254). These were visualized by ultraviolet irradiation and using phosphomolibdic acid or $KMnO_4$ dips.[2] For flash chromatography (FC) silica gel (Silica gel 60, 230-400 mesh, Merck).[3] Analytical grade solvents and commercially available reagents were used without further purification.

Anhydrous solvents were purified and dried with activated molecular sieves prior to use. For the removal of solvents under reduced pressure Büchi R-210 rotary evaporators were used.

For reactions carried out under inert conditions, the argon was previously dried through a column of P_2O_5 and a column of KOH and $CaCl_2$. All the glassware was dried for 12 h in an oven at 140 ºC, and allowed to cool under a dehumidified atmosphere.[4]

Reactions at reduced temperatures were carried out using a Termo Haake EK90 refrigerator. Sonications were performed in a Branson 3510 apparatus.

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[2] Stahl, E. *Thin Layer Chromatography*, Springer-Verlag, Berlin, 1969.
[3] Still, W. C.; Kann, H.; Mitra A. J. *J. Org. Chem*. **1978**, *43*, 2923.
[4] Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*, John Wiley & Sons, New York, **1975**.

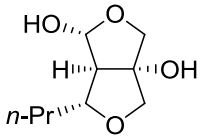
2. ORGANOCATALYTIC CASCADE REACTIONS.

2.1. Enantioselective organocatalytic oxa-Michael/aldol cascade reaction. Synthesis of furofuranes 4a-k.

General procedure:

An ordinary vial equipped with a magnetic stirring bar was charged with catalyst **3a** (0.04 mmol), PhCOOH (0.08 mmol) and $CHCl_3$ (2 mL). Then, aldehyde **2** (0.20 mmol) and the α,β-unsatured aldehyde **1** (0.30 mmol) were added. The stirring was maintained at room temperature until completion of the reaction and the crude reaction mixture was concentrated and directly charged onto silica gel and subjected to flash chromatography (FC). Racemic samples were prepared using NaOH (0.2 mmol) when aliphatic substituted α,β-unsatured aldehydes were used or ***rac*-3a** when aromatic substituted α,β-unsatured aldehydes were used.

(1*R*,3a*S*,6*R*,6a*R*)-6-Propylhexahydrofuro[3,4-*c*]furan-1,3a-diol (4a).



Following the general procedure **4a** (34 mg, 0.19 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 6:4 to 2:8) starting from aldehyde **1a** (47 μL, 0.30 mmol) and dihydroxyacetone dimer **2** (32 mg, 0.20 mmol) in the presence of **3a** (13 mg, 0.04 mmol), PhCOOH (10 mg, 0.08 mmol) and using $CHCl_3$ (2 mL) as solvent.

Yield: 96%.

dr: >10:1 (Determined by ^{1}H-NMR).

ee: 99% (Determined after transformation to compound **5a**).

^{1}H-NMR (δ, ppm) (300 MHz): 0.96 (t, 3H, J = 7.3 Hz, CH_3), 1.27-1.86 (m, 4H, (C**H**$_2$)$_2$CH$_3$), 2.28 (d, 1H, J = 7.6 Hz, CHC**H**CH), 3.20-3.50 (bs, 1H, OH), 3.51-3.64 (m, 2H, CH*n*-Pr + OC**H**$_a$H$_b$), 3.93 (d, 1H, J = 9.4 Hz, OC**H**$_c$H$_d$), 4.04 (m, 2H, OCH$_a$**H**$_b$ + OCH$_c$**H**$_d$), 5.23 (s, 1H, C**H**OH).

^{13}C-NMR (δ, ppm) (75.5 MHz):14.0 (CH_3), 19.1 (**C**H$_2$CH$_3$), 37.0 (CH_2Et), 66.5 (CH**C**HCH), 73.8 (OCH_2), 78.1 (OCH_2), 83.8 (CH*n*-Pr), 90.1 (CH_2**C**CH_2), 101.4 (CHOH).

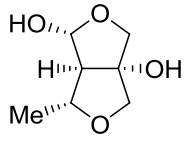
IR (Film) cm^{-1}: 3339 (OH).

MS (EI) m/z (%): 170 (3), 152 (18), 127 (80), 109 (100), 97 (93), 81 (94), 71 (57).

HMRS: Calcd. for $[C_9H_{14}O_3]^{+\bullet}$: 170.0943 ($M^{+\bullet}$-$H_2O$). Found: 170.0989.

$[\alpha]_D^{20}$: -12.4 (c = 1.00, CH_2Cl_2).

(1*R*,3a*S*,6*R*,6a*R*)-6-Methylhexahydrofuro[3,4-*c*]furan-1,3a-diol (4b).



Following the general procedure **4b** (28 mg, 0.18 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 6:4 to 2:8) starting from aldehyde **1b** (37 μL, 0.30 mmol) and dihydroxyacetone dimer **2** (36 mg, 0.20 mmol) in the presence of **3a** (13 mg, 0.04 mmol), PhCOOH (10 mg, 0.08 mmol) and using $CHCl_3$ (2 mL) as solvent.

Yield: 98 %.

dr: 7:1 (Determined by ^{1}H-NMR).

ee: 92% (Determined after transformation to compound **6b**).

^{1}H-NMR (δ, ppm) (300 MHz): -0.14 (d, 3H, *J* = 6.2 Hz, CH_3), 0.64 (d, 1H, *J* = 7.1 Hz, CHC**H**CH), 1.79 (s, 1H, OH), 2.09-1.96 (d, 1H, *J* = 8.7, OC**H**$_a$CH$_b$), 2.23-2.10 (m, 1H, CH*n*-Pr), 2.29 (d, 1H, *J* = 8.9 Hz, OCH$_a$C**H**$_b$), 2.51-2.34 (m, 2H, OCH$_c$H$_d$), 3.65 (s, 1H, C**H**OH).

^{13}C-NMR (δ, ppm) (75.5 MHz): 20.5 (CH_3), 69.0 (CH**C**HCH), 74.2 (OCH_2), 80.1 (OCH_2), 81.9 (CHMe), 91.3 (CH_2**C**CH_2), 102.6 (CHOH).

IR (KBr) cm^{-1}: 3370 (OH).

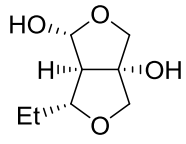
MS (EI) m/z (%): 142 (1), 124 (28), 109 (100), 97 (25), 87 (29), 81 (33), 71 (41), 69 (65), 56 (3).

HMRS: Calcd. for $[C_7H_{10}O_3]^{+\bullet}$: 142.0630 ($M^{+\bullet}$-$H_2O$). Found: 142.0632.

$[\alpha]_D^{20}$: -39.0 (*c* = 1.00, MeOH).

M.p. (*n*-hexane/AcOEt): 137-138 ºC.

(1*R*,3a*S*,6*R*,6a*R*)-6-Ethylhexahydrofuro[3,4-*c*]furan-1,3a-diol (4c).



Following the general procedure **4c** (30 mg, 0.17 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 6:4 to 2:8) in 80% yield starting from aldehyde **1c** (41 μL, 0.30 mmol) and dihydroxyacetone dimer **2** (36 mg, 0.20 mmol) in the presence of **3a** (13 mg, 0.04 mmol), PhCOOH (10 mg, 0.08 mmol) and using $CHCl_3$ (2 mL) as solvent.

Yield: 86%.

dr: 7:1 (Determined by ^{1}H-NMR).

ee: 95% (Determined after transformation to compound **6c**).

^{1}H-NMR (δ, ppm) (300 MHz): 0.98 (t, 3H, *J* = 7.4 Hz, CH_3), 1.51-1.89 (m, 2H, C**H**$_2$CH$_3$), 2.27 (d, 1H, *J* = 7.5 Hz, CHC**H**CH), 2.43 (bs, 1H, OH**)**, 3.50 (dd, 1H, *J* = 13.7, 6.8 Hz, CHEt), 3.60 (d, 1H, *J* = 9.9 Hz, OC**H**$_a$H$_b$), 3.92 (d, 1H, *J* = 9.3 Hz, OC**H**$_c$H$_d$), 3.97-4.09 (m, 2H, OCH$_a$**H**$_b$ + OCH$_c$**H**$_d$), 4.37 (bs, 1H, OH), 5.22 (s, 1H, C**H**OH).

^{13}C-NMR (δ, ppm) (75.5 MHz): 10.0 (CH_3), 27.6 (**C**H$_2$CH$_3$), 65.9 (CH**C**HCH), 73.5 (OCH_2), 78.1 (OCH_2), 85.5 (CHEt), 89.9 (CH_2**C**CH_2), 101.4 (CHOH).

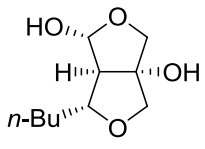
IR (Film) cm^{-1}: 3400 (OH).

MS (EI) m/z (%): 156 (2), 143 (4), 138 (1), 127 (15), 109 (100), 97 (24), 81 (52), 69 (30), 55 (16).

HMRS: Calcd. for $[C_8H_{10}O_2]^{+\bullet}$: 138.0681 ($M^{+\bullet}$-2H$_2$O). Found: 138.0686.

$[\alpha]_D^{20}$: -60.8 (*c* = 1.00, CH_2Cl_2).

(1*R*,3a*S*,6*R*,6a*R*)-6-Butylhexahydrofuro[3,4-*c*]furan-1,3a-diol (4d).



Following the general procedure **4d** (36 mg, 0.18 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 6:4 to 2:8) starting from aldehyde **1d** (55 μL, 0.30 mmol) and dihydroxyacetone dimer **2** (36 mg, 0.20 mmol) in the presence of **3a** (13 mg, 0.04 mmol), PhCOOH (10 mg, 0.08 mmol) and using $CHCl_3$ (2 mL) as solvent.

Yield: 89%.

Adduct **4d** (184 mg, 0.90 mmol) was also obtained when the reaction was carried out on larger scale using aldehyde **1d** (275 μL, 1.50 mmol), dihydroxyacetone dimer **2** (180 mg, 1.00 mmol), catalyst **3c** (65 mg, 0.2 mmol), PhCOOH (50 mg, 0.4 mmol) and $CHCl_3$ (10 mL) as solvent.

Yield: 90%.

dr: >10:1 (Determined by ^{1}H-NMR).

ee: 97% (Determined after transformation to compound **6d**).

^{1}H-NMR (δ, ppm) (300 MHz): 0.90 (t, 3H, J = 6.8 Hz, CH_3), 1.20-1.88 (m, 6H, $(CH_2)_3$), 2.25 (d, 1H, J = 7.5 Hz, CHC**H**CH), 2.40 (s, 1H, OH), 3.49-3.63 (m, 2H, CH*n*-Bu + OCH_aH_b), 3.82-4.25 (m, 4H, $OCH_a\mathbf{H}_b$ + $OC\mathbf{H}_cH_d$ + $OCH_c\mathbf{H}_d$ + OH), 5.19 (s, 1H, C**H**OH).

^{13}C-NMR (δ, ppm) (75.5 MHz): 13.9 (CH_3), 22.5 (**C**H_2CH_3), 27.9 (CH_2Et), 34.5 (CH_2*n*-Pr), 66.3 (CH**C**HCH), 73.5 (OCH_2), 78.1 (OCH_2), 84.2 (CH*n*-Bu), 89.9 (CH_2**C**CH_2), 101.4 (CHOH).

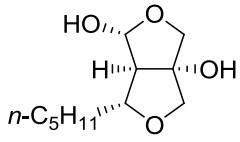
IR (Film) cm^{-1}: 3430 (OH).

MS (EI) m/z (%): 169 (2), 167 (5), 153 (2), 141 (6), 113 (100), 95 (82), 85 (19), 57 (54).

HMRS: Calcd. for $[C_{10}H_{15}O_2]^{+\bullet}$: 167.1072 ($[M+H]^{+\bullet}-2H_2O$). Found: 167.1077.

$[\alpha]_D^{20}$: -31.0 (c = 1.00, CH_2Cl_2).

(1*R*,3a*S*,6*R*,6a*R*)-6-Pentylhexahydrofuro[3,4-*c*]furan-1,3a-diol (4e).



Following the general procedure **4e** (40 mg, 0.18 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 6:4 to 2:8) starting from aldehyde **1e** (63 μL, 0.30 mmol) and dihydroxyacetone dimer **2** (36 mg, 0.20 mmol) in the presence of **3a** (13 mg, 0.04 mmol), PhCOOH (10 mg, 0.08 mmol) and using $CHCl_3$ (2 mL) as solvent.

Yield: 92%.

dr: >10:1 (Determined by ^{1}H-NMR).

ee: 96% (Determined after transformation to compound **6e**).

^{1}H-NMR (δ, ppm) (300 MHz): 0.88 (t, 3H, J = 6.1 Hz, CH_3), 1.20-1.51 (m, 6H, (C**H**$_2$)$_3$CH$_3$), 1.52-1.69 (m, 1H, CHC**H**$_a$CH$_b$), 1.69-1.86 (m, 1H, CHCH$_a$C**H**$_b$), 2.25 (d, 1H, J = 7.5 Hz, CHC**H**CH), 3.50-3.63 (m, 2H, C**H**CH$_2$ + OC**H**$_a$H$_b$), 3.91 (d, 1H, J = 9.3 Hz, OC**H**$_c$H$_d$), 3.97-4.08 (m, 2H, OCH$_a$**H**$_b$ + OCH$_c$**H**$_d$), 4.47 (bs, 1H, O**H**), 5.20 (s, 1H, CHOH).

^{13}C-NMR (δ, ppm) (75.5 MHz): 13.9 (CH_3), 22.4 (**C**H$_2$CH$_3$), 25.5 (CH_2Et), 31.7 (CH_2*n*-Pr), 34.8 (CH_2*n*-Bu), 66.3 (CH**C**HCH), 73.6 (OCH_2), 78.1 (OCH_2), 84.2 (**C**HCH$_2$), 89.9 (CH_2**C**CH$_2$), 101.4 (CHOH).

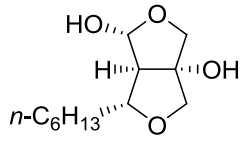
IR (Film) cm^{-1}: 3434 (OH).

MS (EI) m/z (%): 180 (4), 162 (1), 143 (5), 127 (9), 109 (100), 97 (13), 81 (27), 69 (19), 55 (7).

HMRS: Calcd. for $[C_{11}H_{16}O_2]^{+\bullet}$: 180.1150 ($M^{+\bullet}$-2H$_2$O). Found: 180.1152.

$[\alpha]_D^{20}$: -24.0 (*c* = 1.0, CH_2Cl_2).

(1*R*,3a*S*,6*R*,6a*R*)-6-Hexylhexahydrofuro[3,4-*c*]furan-1,3a-diol (4f).



Following the general procedure **4f** (36 mg, 0.16 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 6:4 to 2:8) starting from aldehyde **1f** (68 μL, 0.30 mmol) and dihydroxyacetone dimer **2** (36 mg, 0.20 mmol) in the presence of **3a** (13 mg, 0.04 mmol), PhCOOH (10 mg, 0.08 mmol) and using $CHCl_3$ (2 mL) as solvent.

Yield: 78%.

dr: >10:1 (Determined by ^{1}H-NMR).

ee: 95% (Determined after transformation to compound **6f**).

^{1}H-NMR (δ, ppm) (300 MHz): 0.88 (t, 3H, *J* = 6.0 Hz, CH_3), 1.20-1.50 (m, 8H, (CH_2)$_4$$CH_3$), 1.52-1.86 (m, 2H, CHC**H**$_2$), 2.27 (d, 1H, *J* = 7.5 Hz, CHC**H**CH), 3.37 (bs, 1H, OH), 3.66-3.49 (m, 2H, C**H**CH_2+ OC**H**$_a$H$_b$), 3.93 (d, 1H, *J* = 9.4 Hz, OC**H**$_c$H$_d$), 4.00-4.09 (m, 2H, OCH$_a$**H**$_b$ + OCH$_c$**H**$_d$), 5.23 (s, 1H, CHOH).

^{13}C-NMR (δ, ppm) (75.5 MHz): 14.0 (CH_3), 22.5 (**C**H_2CH_3), 25.8 (CH_2Et), 29.2 (CH_2*n*-Pr), 31.6 (CH_2*n*-Bu), 34.9 (CH**C**H_2), 66.4 (CH**C**HCH), 73.8 (OCH_2), 78.1 (OCH_2), 84.1 (**C**HCH_2), 90.0 (CH_2**C**CH_2), 101.4 (CHOH).

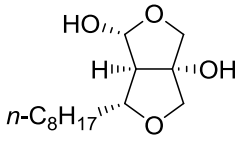
IR (Film) cm^{-1}: 3388 (OH).

MS (EI) m/z (%): 194 (6), 181 (1), 157 (5), 127 (6), 109 (100), 99 (11), 81 (37), 70 (12), 55 (7).

HMRS: Calcd. for $[C_{12}H_{18}O_2]^{+\bullet}$: 194.1307 ($M^{+\bullet}$-$2H_2O$). Found: 194.1305.

$[\alpha]_D^{20}$: -24.8 (*c* = 1.00, CH_2Cl_2).

(1*R*,3a*S*,6*R*,6a*R*)-6-Octylhexahydrofuro[3,4-*c*]furan-1,3a-diol (4g).



Following the general procedure **4g** (39 mg, 0.15 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 6:4 to 2:8) starting from aldehyde **1g** (51 μL, 0.30 mmol) and dihydroxyacetone dimer **2** (36 mg, 0.20 mmol) in the presence of **3a** (13 mg, 0.04 mmol), PhCOOH (10 mg, 0.08 mmol) and using $CHCl_3$ (2 mL) as solvent.

Yield: 76%.

Adduct **4g** (192 mg, 0.74 mmol) was also obtained when the reaction was carried out on larger scale using aldehyde **1g** (255 μL, 1.50 mmol), dihydroxyacetone dimer **2** (180 mg, 1.00 mmol), catalyst **3a** (65 mg, 0.2 mmol), PhCOOH (50 mg, 0.4 mmol) and $CHCl_3$ (10 mL) as solvent.

Yield: 74%.

dr: >10:1 (Determined by ^{1}H-NMR).

ee: 98% (Determined after transformation to compound **6g**).

^{1}H-NMR (δ, ppm) (300 MHz): 0.87 (t, 3H, *J* = 6.4 Hz, CH_3), 1.16-1.49 (m, 12H, $(CH_2)_6CH_3$), 1.52-1.68 (m, 1H, $CH_aCH_b(CH_2)_6CH_3$), 1.69-1.87 (m, 1H, $CH_aCH_b(CH_2)_6CH_3$), 2.25 (d, 1H, *J* = 7.4 Hz, CHCHCH), 3.49-3.63 (m, 2H, $CHCH_2$ + OCH_aH_b), 3.88-4.09 (m, 3H, OCH_aH_b + OCH_cH_d + OCH_cH_d), 4.25 (bs, 1H, OH), 5.21 (s, 1H, COH).

^{13}C-NMR (δ, ppm) (75.5 MHz): 14.0 (CH_3), 22.6 (**C**H_2CH_3), 25.9 (CH_2Et), 29.2 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 31.8 (CH_2), 34.8 (**C**HCH_2), 66.4 (CH**C**HCH), 73.6 (OCH_2), 78.1 (OCH_2), 84.1 (**C**HCH_2), 90.0 (CH_2**C**CH_2), 101.4 (CHOH).

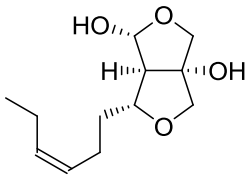
IR (Film) cm^{-1}: 3399 (OH).

MS (EI) m/z (%): 222 (2), 185 (5), 127 (7), 109 (100), 99 (14), 81 (40), 70 (14), 57 (7).

HMRS: Calcd. for $[C_{14}H_{22}O_2]^{+\bullet}$: 222.1620 ($M^{+\bullet}$-$2H_2O$). Found: 222.1620.

$[\alpha]_D^{20}$: -36.2 (*c* = 1.00, CH_2Cl_2).

(1*R*,3a*S*,6*R*,6a*R*)-6-[(*Z*)-Hex-3-enyl]hexahydrofuro[3,4-*c*]furan-1,3a-diol (4h).



Following the general procedure **4h** (38 mg, 0.17 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 6:4 to 2:8) starting from aldehyde **1h** (67 μL, 0.30 mmol) and dihydroxyacetone dimer **2** (36 mg, 0.20 mmol) in the presence of **3a** (13 mg, 0.04 mmol), PhCOOH (10 mg, 0.08 mmol) and using $CHCl_3$ (2 mL) as solvent.

Yield: 83%.

dr: >10:1 (Determined by ^{1}H-NMR).

ee: 94% (Determined after transformation to compound **6h**).

^{1}H-NMR (δ, ppm) (300 MHz): 0.95 (t, 3H, *J* = 7.5 Hz, CH_3), 1.60-1.75 (m, 2H, CH_2), 1.77-2.23 (m, 4H, $(CH_2)_2$), 2.29 (d, 1H, *J* = 7.5 Hz, CHC**H**CH), 3.28 (bs, 1H, OH), 3.52-3.66 (m, 2H, C**H**CH_2CH_2CH=CH + OC$\mathbf{H}_a\mathrm{H}_b$), 3.94 (d, 1H, *J* =

9.4 Hz, OC**H**$_c$H$_d$), 4.05 (m, 2H, OCH$_a$**H**$_b$ + OCH$_c$**H**$_d$), 5.23 (s, 1H, C**H**OH), 5.25-5.48 (m, 2H, CH=CH).

^{13}C-NMR (δ, ppm) (75.5 MHz): 14.2 (CH_3), 20.4 (CH_2), 23.5 (CH_2), 34.8 (CH_2), 66.2 (CH**C**HCH), 73.8 (OCH_2), 78.1 (OCH_2), 83.4 (**C**HCH$_2$CH$_2$CH=CH), 90.0 (CH$_2$**C**CH$_2$), 101.4 (CHOH), 127.6 (CH$_2$CH$_2$**C**H=CH), 132.7 (CH$_2$CH$_2$CH=**C**H).

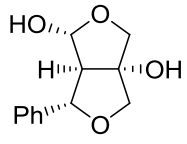
IR (Film) cm^{-1}: 3381 (OH), 3031 (=CH), 1654 (C=C).

MS (EI) m/z (%): 192 (7), 174 (7), 163 (11), 145 (11), 135 (15), 109 (100), 95 (14), 91 (17), 81 (25), 70 (30), 53 (11).

HMRS: Calcd. for $[C_{12}H_{16}O_2]^{+\bullet}$: 192.1150 ($M^{+\bullet}$-2H$_2$O). Found: 192.1153.

$[\alpha]_D^{20}$: -22.8 (*c* = 1.00, CH_2Cl_2).

(1*R*,3a*S*,6*S*,6a*R*)-6-Phenylhexahydrofuro[3,4-*c*]furan-1,3a-diol (4i).



Following the general procedure **4i** (31 mg, 0.14 mmol) was synthesized starting from aldehyde **1i** (84 μL, 0.30 mmol) and dihydroxyacetone dimer **2** (36 mg, 0.20 mmol) in the presence of **3a** (13 mg, 0.04 mmol), PhCOOH (10 mg, 0.08 mmol) and using $CHCl_3$ (2 mL) as solvent.

Yield: 73%.

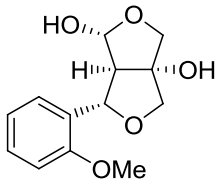
Compound **4i** (72 mg, 0.78 mmol) was also obtained when the organocatalytic reaction was carried out on larger scale using aldehyde **1i** (420 μL, 1.50 mmol), dihydroxyacetone dimer **2** (180 mg, 1.00 mmol), catalyst **3a** (65 mg, 0.2 mmol), PhCOOH (50 mg, 0.4 mmol) and $CHCl_3$ (10 mL) as solvent.

Yield: 77%.

dr: >10:1 (Determined by ^{1}H-NMR).

ee: 98% (Determined after transformation to compound **5i**).

(1*R*,3a*S*,6*S*,6a*R*)-6-(2-Methoxyphenyl)hexahydrofuro[3,4-*c*]furan-1,3a-diol (4j).



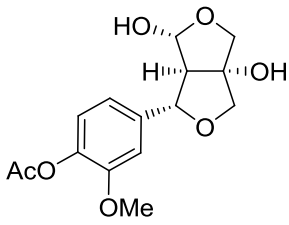
Following the general procedure **4j** (41 mg, 0.13 mmol) was synthesized starting from aldehyde **1j** (93 mg, 0.30 mmol) and dihydroxyacetone dimer **2** (36 mg, 0.20 mmol) in the presence of **3a** (13 mg, 0.04 mmol), PhCOOH (10 mg, 0.08 mmol) and using $CHCl_3$ (2 mL) as solvent.

Yield: 71%.

dr: >10:1 (Determined by ^{1}H-NMR).

ee: 90% (Determined after transformation to compound **5j**).

(1'*S*,3'a*S*,6'*R*,6'a*R*)-4-[3a,6-Dihydroxyhexahydrofuro[3,4-*c*]furan-1-yl]-2-methoxyphenyl acetate (4k).



Following the general procedure **4k** (35 mg, 0.14 mmol) was synthesized starting from aldehyde **1k** (67 mg, 0.30 mmol) and dihydroxyacetone dimer **2** (36 mg, 0.20 mmol) in the presence of **3a** (13 mg, 0.04 mmol), PhCOOH (10 mg, 0.08 mmol) and using $CHCl_3$ (2 mL) as solvent.

Yield: 71%.

dr: >10:1 (Determined ^{1}H-NMR).

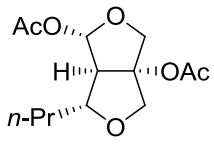
ee: 94% (Determined after transformation to compound **5k**).

2.2. Determination of enantiomeric purity. Synthesis of acetylated compounds 5a, 5c, 5e, and 5i-k.

General procedure:

An ordinary vial equipped with a magnetic stirring bar was charged with the furane **4** (0.10 mmol) in 1 mL of CH_2Cl_2. Then DMAP (0.01 mmol) and acetic anhydride (0.25 mmol) were added. The reaction was stirred at room temperature until completion of the reaction and the crude mixture was directly charged onto silica gel and subjected to FC.

(1*S*,3a*S*,6*R*,6a*R*)-6-Propylhexahydrofuro[3,4-*c*]furan-1,3a-diyl diacetate (5a).



Following the general procedure **5a** (54 mg, 0.20 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 6:4 to 2:8) starting from furofurane **4a** (37 mg, 0.20 mmol) and acetic anhydride (40 μL, 0.42 mmol) in the presence of DMAP (2.5 mg, 0.02 mmol) and using CH_2Cl_2 (1.0 mL) as solvent.

Yield: 99%.

ee: 99%. Determined by HPLC using a Daicel Chiralpak IA column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min; τ_{major} = 9.53 min, τ_{minor} = 8.87 min.

^{1}H-NMR (δ, ppm) (300 MHz): 0.95 (t, 3H, *J* = 7.3 Hz, $CH_2C\mathbf{H}_3$), 1.32-1.59 (m, 2H, $C\mathbf{H}_2CH_3$), 1.66-1.78 (m, 2H, CH_2Et), 2.08 (s, 6H, $(CH_3)_2CO$), 2.64 (d, 1H, *J* = 8.1 Hz, CHC**H**CH), 3.56 (dd, 1H, *J* = 13.4, 7.5 Hz, CH*n*-Pr), 3.73 (d,

1H, *J* = 11.2 Hz, OC**H**$_a$H$_b$), 3.94 (d, 1H, *J* = 10.1 Hz, OC**H**$_c$H$_d$), 4.29 (d, 1H, *J* = 11.2 Hz, OCH$_a$**H**$_b$), 4.47 (d, 1H, *J* = 10.2 Hz, OCH$_c$**H**$_d$), 5.97 (s, 1H, CH$_3$COOC**H**).

^{13}C-NMR (δ, ppm) (75.5 MHz): 13.9 (CH$_3$), 19.1 (**C**H$_2$CH$_3$), 20.8 (**C**H$_3$CO), 21.1 (**C**H$_3$CO), 36.4 (CH$_2$Et), 63.2 (CH**C**HCH), 74.7 (OCH$_c$H$_d$), 77.0 (OCH$_a$H$_b$), 82.9 (CH*n*-Pr), 94.4 (CH$_2$**C**CH$_2$), 99.1 (CH$_3$COO**C**H), 170.0 (CO), 170.7 (CO).

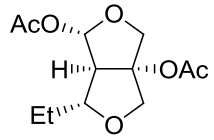
IR (Film) cm^{-1}: 1739 (CO).

MS (EI) m/z (%): 169 (10), 152 (16), 127 (5), 109 (100), 95 (12), 81 (80), 60 (4).

HMRS: Calcd. for $[C_9H_{12}O_2]^{+\bullet}$: 152.0837 ($M^{+\bullet}$-2AcOH). Found: 152.0836.

$[\alpha]_D^{20}$: -33.4 (*c* = 0.50, CH_2Cl_2).

(1*S*,3a*S*,6*R*,6a*R*)-6-Ethylhexahydrofuro[3,4-*c*]furan-1,3a-diyl diacetate (5c).



Following the general procedure **5c** (46 mg, 0.18 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 6:4 to 2:8) in 90% yield starting from furofurane **4c** (35 mg, 0.20 mmol) and acetic anhydride (40 μL, 0.42 mmol) in the presence of DMAP (2.5 mg, 0.02 mmol) and using CH_2Cl_2 (1.0 mL) as solvent.

Yield: 99%.

^{1}H-NMR (δ, ppm) (300 MHz): 1.01 (t, 3H, *J* = 7.4 Hz, CH$_3$), 1.69-1.83 (m, 2H, C**H**$_2$CH$_3$), 2.09 (s, 6H, (CH$_3$)$_2$CO), 2.66 (d, 1H, *J* = 8.0 Hz, CHC**H**CH), 3.52 (dd, 1H, *J* = 14.2, 6.4 Hz, CHEt), 3.76 (d, 1H, *J* = 11.1 Hz, OC**H**$_a$H$_b$), 3.95 (d, 1H,

J = 10.1 Hz, OCH_cH_d), 4.30 (d, 1H, J = 11.1 Hz, OCH_aH_b), 4.48 (d, 1H, J = 10.1 Hz, OCH_cH_d), 5.99 (s, 1H, CH_3COOCH).

^{13}C-NMR (δ, ppm) (75.5 MHz): 10.0 (CH_3), 20.8 (CH_3CO), 21.1 (CH_3CO), 27.2 (CH_2CH_3), 62.8 (CHCHCH), 74.7 (OCH_cH_d), 77.0 (OCH_aH_b), 84.4 (CHEt), 94.5 (CH_2CCH_2), 99.3 (CH_3COOCH), 170.0 (CO), 170.8 (CO).

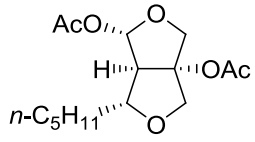
IR (Film) cm^{-1}: 1736 (CO).

MS (EI) m/z (%): 169 (4), 138 (12), 109 (100), 95 (4), 81 (45), 60 (3).

HMRS: Calcd. for $[C_8H_{10}O_2]^{+\bullet}$: 138.0681 ($M^{+\bullet}$-2AcOH). Found: 138.0686.

$[\alpha]_D^{20}$: -42.0 (c = 0.50, CH_2Cl_2).

(1*S*,3a*S*,6*R*,6a*R*)-6-Pentylhexahydrofuro[3,4-*c*]furan-1,3a-diyl diacetate (5e).



Following the general procedure **5e** (57 mg, 0.19 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 6:4 to 2:8) in 96% yield starting from furofurane **4e** (43 mg, 0.20 mmol) and acetic anhydride (40 μL, 0.42 mmol) in the presence of DMAP (2.5 mg, 0.02 mmol) and using CH_2Cl_2 (1.0 mL) as solvent.

Yield: 96%.

^{1}H-NMR (δ, ppm) (300 MHz): 0.88 (t, 3H, J = 6.3 Hz, CH_3), 1.21-1.57 (m, 6H, $(CH_2)_3CH_3$), 1.64-1.81 (m, 2H, $CHCH_2$), 2.09 (s, 6H, $(CH_3)_2CO$), 2.65 (d, 1H, J = 8.1 Hz, CHCHCH), 3.56 (dd, 1H, J = 14.1, 6.8 Hz, $CHCH_2$), 3.74 (d, 1H, J = 11.2 Hz, OCH_aH_b), 3.95 (d, 1H, J = 10.2 Hz, OCH_cH_d), 4.30 (d, 1H, J = 11.2 Hz, OCH_aH_b), 4.48 (d, 1H, J = 10.2 Hz, OCH_cH_d), 5.98 (s, 1H, CH_3COOCH).

^{13}C-NMR (δ, ppm) (75.5 MHz): 13.9 (CH_3), 20.8 (**C**H_3CO), 21.1 (**C**H_3CO), 22.4, 25.5, 31.6, 34.3, 63.2 (CH**C**HCH), 74.8 (OCH_cH_d), 77.0 (OCH_aH_b), 83.1 (**C**HCH_2), 94.5 (CH_2**C**CH_2), 99.2 (CH_3COO**C**H), 170.0 (CO), 170.8 (CO).

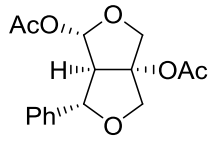
IR (Film) cm^{-1}: 1745 (CO).

MS (EI) m/z (%): 180 (8), 169 (7), 151 (4), 127 (3), 109 (100), 95 (6), 81 (47), 60 (3).

HMRS: Calcd. for $[C_{11}H_{16}O_2]^{+\bullet}$: 180.1150 ($M^{+\bullet}$-2AcOH). Found: 180.1156.

$[\alpha]_D^{20}$: -43.8 (*c* = 1.00, CH_2Cl_2).

(1*S*,3a*S*,6*S*,6a*R*)-6-Phenylhexahydrofuro[3,4-*c*]furan-1,3a-diyl diacetate (5i).



Following the general procedure **5i** (97 mg, 3.20 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 6:4 to 2:8) in 80% yield over two step starting from the obtained crude of furofurane **4i** and acetic anhydride (80 μL, 0.84 mmol) in the presence of DMAP (6 mg, 0.04 mmol) and using CH_2Cl_2 (5.0 mL) as solvent.

Yield: 80%.

ee: 98%. Determined by HPLC using a Chiralcel OD column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 11.46 min, τ_{minor} = 9.63 min.

^{1}H-NMR (δ, ppm) (300 MHz): 2.05 (s, 3H, CH_3CO), 2.13 (s, 3H, CH_3CO), 3.05 (d, 1H, *J* = 8.2 Hz, CHC**H**CH), 3.95 (d, 1H, *J* = 11.1 Hz, OC**H**$_a$H$_b$), 4.02 (d,

1H, J = 10.2 Hz, OC**H**$_c$H$_d$), 4.49 (d, 1H, J = 11.1 Hz, OCH$_a$**H**$_b$), 4.54-4.61 (m, 2H, OCH$_c$**H**$_d$ + CHPh), 6.21 (s, 1H, CH$_3$COOC**H**), 7.27-7.50 (m, 5H, C$_{arom}$-H).

^{13}C-NMR (δ, ppm) (75.5 MHz): 20.8 (CH$_3$CO), 21.0 (CH$_3$CO), 65.1 (CH**C**HCH), 74.9 (O**C**H$_c$H$_d$), 77.4 (O**C**H$_a$H$_b$), 84.4 (**C**HPh), 94.5(CH$_2$**C**CH$_2$) , 98.5 (CH$_3$COO**C**H), 126.1 (C$_{arom}$-H), 128.3 (C$_{arom}$-H), 128.6 (C$_{arom}$-H), 138.9 (**C**$_{arom}$-C), 169.7 (CO), 170.7 (CO).

IR (KBr) cm^{-1}: 1738.0 (CO).

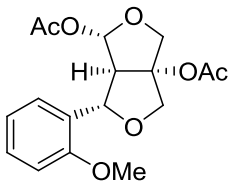
MS (EI) m/z (%): 246 (6), 217 (6), 186 (100), 157 (53), 129 (69), 105 (93), 81 (43), 77 (60), 60 (9).

HMRS: Calcd. for [C$_{14}$H$_{14}$O$_4$]$^{+\bullet}$: 246.0892 (M$^{+\bullet}$-AcOH). Found: 246.0899.

[α]$_D^{20}$: -62.2 (c = 0.50, CH$_2$Cl$_2$).

M.p. (*n*-hexane/AcOEt): 104-105 ºC.

(1*S*,3a*S*,6*S*,6a*R*)-6-(2-Methoxyphenyl)hexahydrofuro[3,4-*c*]furan-1,3a-diyl diacetate (5j).



Following the general procedure **5j** (100 mg, 0.30 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 6:4 to 2:8) over two step starting from the obtained crude of furofurane **4j** and acetic anhydride (80 μL, 0.84 mmol) in the presence of DMAP (6 mg, 0.04 mmol) and using CH$_2$Cl$_2$ (5.0 mL) as solvent.

Yield: 74%.

ee: 90%. Determined by HPLC using a Chiralcel OD column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 10.06 min, τ_{minor} = 8.54 min.

^{1}H-NMR (δ, ppm) (300 MHz) (*overlapped signals): 2.06 (s, 3H, CH_3CO), 2.09 (s, 3H, CH_3CO), 2.88 (d, 1H, *J* = 7.9 Hz, CHC**H**CH), 3.81 (s, 3H, CH_3O), 3.94 (d, 1H, *J* = 11.1, OC**H**$_a$H$_b$), 3.99 (d, 1H, *J* = 10.2, OC**H**$_c$H$_d$), 4.49* (d, 1H, *J* = 11.4, OCH$_a$**H**$_b$), 4.54* (d, 1H, *J* = 10.1, OCH$_c$**H**$_d$), 4.92 (d, 1H, *J* = 7.9 Hz, CHPh), 6.54 (s, 1H, CH_3COOC**H**), 6.88 (d, 1H, *J* = 8.3 Hz, C_{arom}-H), 6.99 (dt, 1H, *J* = 7.5, 0.7 Hz, C_{arom}-H), 7.33-7.25 (m, 1H, C_{arom}-H), 7.52 (dd, 1H, *J* = 7.4, 1.2 Hz, C_{arom}-H).

^{13}C-NMR (δ, ppm) (75.5 MHz): 20.9 (**C**H_3CO), 21.1 (**C**H_3CO), 55.0 (CH_3O), 64.3 (CH**C**HCH), 74.1 (OCH$_c$H$_d$), 76.5 (OCH$_a$H$_b$), 79.5 (CHPh), 94.7 (CH_2**C**CH_2), 99.1 (CH_3COO**C**H), 110.0 (C_{arom}-H), 120.6 (C_{arom}-H), 125.6 (C_{arom}-H), 128.5 (C_{arom}-H), 128.7 (C_{arom}-H), 155.9 (C_{arom}-O), 169.8 (CO), 170.8 (CO).

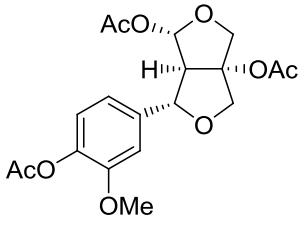
IR (Film) cm^{-1}: 1740 (CO).

MS (EI) m/z (%): 336 (3), 276 (7), 247 (5), 216 (25), 185 (17), 159 (12), 135 (100), 119 (29), 105 (18), 92 (29), 77 (59), 60 (73), 45 (97).

HMRS: Calcd. for $[C_{17}H_{20}O_7]^{+\bullet}$: 336.1209. Found: 336.1224.

$[\alpha]_D^{20}$: -58.7 (*c* = 1.00, CH_2Cl_2).

(1*S*,3a*S*,6*S*,6a*R*)-6-(4-Acetoxy-3-methoxyphenyl)hexahydrofuro[3,4-*c*]furan-1,3a-diyl diacetate (5k).



Following the general procedure **5k** (52 mg, 0.14 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 6:4 to 2:8) over two step starting from the obtained crude of furofurane **4k** and acetic anhydride (40 μL, 0.42 mmol) in the presence of DMAP (3 mg, 0.02 mmol) and using CH_2Cl_2 (2.5 mL) as solvent.

Yield: 72%.

ee: 94%. Determined by HPLC using a Chiralcel OD column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 32.26 min, τ_{minor} = 37.23 min.

^{1}H-NMR (δ, ppm) (300 MHz): 2.08 (s, 3H, CH_3CO), 2.13 (s, 3H, CH_3CO), 2.32 (s, 3H, CH_3CO), 3.02 (d, 1H, *J* = 8.0 Hz, CHC**H**CH), 3.86 (s, 3H, CH_3O), 3.95 (d, 1H, *J* = 11.2 Hz, OC**H**$_a$H$_b$), 4.02 (d, 1H, *J* = 10.2 Hz, OC**H**$_c$H$_d$), 4.48 (d, 1H, *J* = 11.2 Hz, OCH$_a$**H**$_b$), 4.53-4.61 (m, 2H, OCH$_c$**H**$_d$ + CHPh), 6.22 (s, 1H, CH_3COOC**H**), 7.13-6.87 (m, 3H, C_{arom}-H).

^{13}C-NMR (δ, ppm) (75.5 MHz): 20.6 (**C**H_3CO), 20.8 (**C**H_3CO), 21.1 (**C**H_3CO), 55.9 (CH_3O), 65.1 (CH**C**HCH), 75.0 (OCH$_c$H$_d$), 77.2 (OCH$_a$H$_b$), (84.0 CHPh), 94.5 (CH_2**C**CH_2), 98.6 (CH_3COO**C**H), 110.0 (C_{arom}-H), 118.1 (C_{arom}-H), 122.9 (C_{arom}-H), 138.1 (**C**$_{arom}$-C), 139.6 (**C**$_{arom}$-C), 151.3(**C**$_{arom}$-C), 169.0 (CO), 169.8 (CO), 170.8 (CO).

IR (Film) cm^{-1}: 1740 (CO).

MS (EI) m/z (%): 394 (7), 352 (50), 275 (4), 250 (4), 232 (32), 219 (8), 205 (28), 151 (58), 125 (13), 95 (14), 81 (96), 60 (72), 45 (100).

HMRS: Calcd. for $[C_{19}H_{22}O_9]^{+\bullet}$: 394.1264. Found: 394.1281.

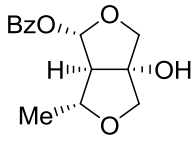
$[\alpha]_D^{20}$: -31.4 (*c* = 0.50, CH_2Cl_2).

2.3. Determination of enantiomeric purity. Synthesis of benzoylated compounds 6b-h.

General procedure:

An ordinary vial equipped with a magnetic stirring bar was charged with furane **4** (0.10 mmol) in 1 mL of CH_2Cl_2. Then Et_3N (0.10 mmol) and the acid chloride (0.11 mmol) were added. The reaction was stirred at room temperature until completion of the reaction and the crude mixture was directly charged onto silica gel and subjected to FC.

(1*S*,3a*S*,6*R*,6a*R*)-3a-Hydroxy-6-methylhexahydrofuro[3,4-*c*]furan-1-yl benzoate (6b).



Following the general procedure **6b** (39 mg, 0.15 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 1:1) starting from furofurane **4b** (32 mg, 0.20 mmol) and benzoyl chloride (25 μL, 0.22 mmol) in the presence of Et_3N (31 μL, 0.22 mmol) and using CH_2Cl_2 (1.0 mL) as solvent.

Yield: 75%.

ee: 92%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 15.82 min, τ_{minor} = 16.71 min.

^{1}H-NMR (δ, ppm) (300 MHz): 1.50 (d, 3H, *J* = 6.2 Hz, CH_3), 2.34 (s, 1H, OH), 2.50 (d, 1H, *J* = 7.7 Hz, CHC**H**CH), 3.71 (d, 1H, *J* = 10.1 Hz, OC**H**$_a$H$_b$), 3.78-3.90 (m, 1H, C**H**CH_3), 4.23-4.05 (m, 3H, OCH_a**H**$_b$ + OC**H**$_c$H$_d$ + OCH_c**H**$_d$), 6.21 (s, 1H, CH_3COOC**H**), 7.46 (t, 2H , *J* = 7.6 Hz, C_{arom}-H), 7.59 (t, 1H, *J* = 7.4 Hz, C_{arom}-H), 8.11-8.02 (m, 2H, C_{arom}-H).

^{13}C-NMR (δ, ppm) (75.5 MHz): 20.2 (CH_3), 67.4 (CH**C**HCH), 75.1 (OCH_2), 79.0 (OCH_2), 80.3 (**C**HCH_3), 90.5 (CH_2**C**CH_2), 101.9 (CH_3COO**C**H), 128.4 (C_{arom}-H**)**, 129.6 (**C**$_{arom}$-C**)**, 129.7 (C_{arom}-H), 133.4 (C_{arom}-H**)**, 165.6 (CO).

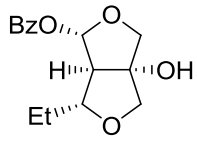
IR (Film) cm^{-1}: 3450 (OH), 1717 (CO).

MS (EI) m/z (%): 159 (6), 142 (14), 122 (23), 109 (56), 105 (100), 81 (57), 69 (23), 51 (8).

HMRS: Calcd. for $[C_7H_{10}O_3]^{+\bullet}$: 142.0630 ($M^{+\bullet}$-BzOH). Found: 142.0629.

$[\alpha]_D^{20}$: -24.0 (*c* = 0.06, $CHCl_3$).

(1*S*,3a*S*,6*R*,6a*R*)-6-Ethyl-3a-hydroxyhexahydrofuro[3,4-*c*]furan-1-yl benzoate (6c).



Following the general procedure **6c** (41 mg, 0.15 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 1:1) starting from furofurane **4c** (35 mg, 0.20 mmol) and benzoyl chloride (25 μL, 0.22 mmol) in the presence of Et_3N (31 μL, 0.22 mmol) and using CH_2Cl_2 (1.0 mL) as solvent.

Yield: 75%.

ee: 97%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 7.82 min, τ_{minor} = 8.22 min.

^{1}H-NMR (δ, ppm) (300 MHz): 1.03 (d, 3H, *J* = 7.4 Hz, CH_3), 1.69-1.93 (m, 2H, C**H**$_2$CH$_3$), 2.54 (d, 1H, *J* = 7.6 Hz, CHC**H**CH), 3.27 (bs, 1H, OH), 3.60-3.74 (m, 2H, CHEt + OC**H**$_a$H$_b$), 4.04-4.17 (m, 3H, OCH$_a$**H**$_b$ + OC**H**$_c$H$_d$ + OCH$_c$**H**$_d$), 6.23 (s, 1H, CH$_3$COOC**H**), 7.44 (t, 2H , *J* = 7.6 Hz, C_{arom}-H), 7.58 (t, 1H, *J* = 7.4 Hz, C_{arom}-H), 8.00-8.11 (m, 2H, C_{arom}-H).

^{13}C-NMR (δ, ppm) (75.5 MHz): 10.0 (CH_3), 27.7 (**C**H$_2$CH$_3$), 65.2 (CH**C**HCH), 74.8 (OCH_2), 78.7 (OCH_2), 85.7 (CHEt), 89.9 (CH_2**C**CH_2), 102.0 (CH$_3$COO**C**H), 128.4 (C_{arom}-H), 129.7 (**C**$_{arom}$-C**)**, 129.8 (C_{arom}-H**),** 133.4 (C_{arom}-H**)**, 165.5 (CO).

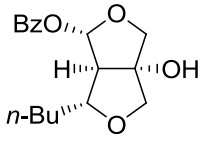
IR (Film) cm^{-1}: 3420.2 (OH), 1720.1 (CO).

MS (EI) m/z (%): 219 (1), 156 (16), 127 (15), 122 (39), 105 (100), 97 (13), 81 (64), 69 (32), 51 (40).

HMRS: Calcd. for $[C_8H_{12}O_3]^{+\bullet}$: 156.0786 ($M^{+\bullet}$-BzOH). Found: 156.0782.

$[\alpha]_D^{20}$: -34.0 (*c* = 0.10, $CHCl_3$).

(1*S*,3a*S*,6*R*,6a*R*)-6-Butyl-3a-hydroxyhexahydrofuro[3,4-*c*]furan-1-yl benzoate (6d).



Following the general procedure **6d** (43 mg, 0.14 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 1:1) starting from furofurane **4d** (40 mg, 0.20 mmol) and benzoyl chloride (25 μL, 0.22 mmol) in the presence of Et_3N (31 μL,

0.22 mmol) and using CH_2Cl_2 (1.0 mL) as solvent.

Yield: 70%.

ee: 97%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 11.60 min, τ_{minor} = 12.26 min.

^{1}H-NMR (δ, ppm) (300 MHz): 0.92 (t, 3H, *J* = 6.9 Hz, CH_3), 1.30-1.54 (m, 4H, (CH_2)$_2$$CH_3$), 1.70-1.86 (m, 2H, CH_2*n*-Pr), 2.40 (bs, 1H, OH), 2.54 (d, 1H, *J* = 7.7 Hz, CHCHCH), 3.64-3.76 (m, 2H, CH*n*-Bu + OCH_aH_b), 4.06-4.15 (m, 3H, OCH_aH_b + OCH_cH_d + OCH_cH_d), 6.23 (s, 1H, CH_3COOCH), 7.46 (t, 2H , *J* = 7.6 Hz, C_{arom}-H), 7.59 (t, 1H, *J* = 7.4 Hz, C_{arom}-H), 8.06 (d, 2H, *J* = 7.1 Hz, C_{arom}-H).

^{13}C-NMR (δ, ppm) (75.5 MHz): 13.9 (CH_3), 22.5 (CH_2CH_3), 28.0 (CH_2Et), 34.6 (CH_2*n*-Pr), 65.8 (CHCHCH), 74.9 (OCH_2), 78.7 (OCH_2), 84.4 (CH*n*-Bu), 90.1 (CH_2CCH_2), 101.9 (CH_3COOCH), 128.4 (C_{arom}-H), 129.6 (C_{arom}-C), 129.7(C_{arom}-H), 133.4 (C_{arom}-H), 165.5 (CO).

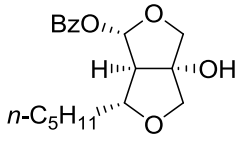
IR (Film) cm^{-1}: 3429 (OH), 1714 (CO).

MS (EI) m/z (%): 201 (1), 184 (10), 167 (2), 154 (2), 122 (32), 105 (100), 81 (54), 69 (21), 51 (2).

HMRS: Calcd. for $[C_{10}H_{16}O_3]^{+\bullet}$: 184.1099 ($M^{+\bullet}$-BzOH). Found: 184.1108.

$[\alpha]_D^{20}$: -57.5 (*c* = 0.33, CH_2Cl_2).

(1*S*,3a*S*,6*R*,6a*R*)-3a-Hydroxy-6-pentylhexahydrofuro[3,4-*c*]furan-1-yl benzoate (6e).



Following the general procedure **6e** (51 mg, 0.16 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 1:1) starting from furofurane **4e** (43 mg, 0.20 mmol) and benzoyl chloride (25 μL, 0.22 mmol) in the presence of Et_3N (31 μL, 0.22 mmol) and using CH_2Cl_2 (1.0 mL) as solvent.

Yield: 80%.

ee: 96%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 10.97 min, τ_{minor} = 11.89 min.

^{1}H-NMR (δ, ppm) (300 MHz): 0.87 (t, 3H, *J* = 5.4 Hz, CH_3), 1.23-1.59 (m, 6H, $(CH_2)_3CH_3$), 1.67-2.00 (m, 2H, CH_2*n*-Bu), 2.52 (d, 1H, *J* = 7.6 Hz, CHC**H**CH), 2.95 (bs, 1H, OH), 3.63-3.77 (m, 2H, C**H**CH_2 + OCH_aH_b), 4.00-4.18 (m, 3H, OCH_a**H**$_b$ + OC**H**$_c$H$_d$ + OCH_c**H**$_d$), 6.22 (s, 1H, CH_3COOCH), 7.44 (t, 2H , *J* = 7.6 Hz, C_{arom}-H), 7.57 (t, 1H, *J* = 7.1 Hz, C_{arom}-H), 8.05 (d, 2H, *J* = 8.3 Hz, C_{arom}-H).

^{13}C-NMR (δ, ppm) (75.5 MHz): 13.9 (CH_3), 22.4 (**C**H_2CH_3), 25.5 (CH_2Et), 31.6 (CH_2*n*-Pr), 34.8 (CH_2*n*-Bu), 65.7 (CH**C**HCH), 74.8 (OCH_2), 78.7 (OCH_2), 84.4 (**C**HCH_2), 89.9 (CH_2**C**CH_2), 101.8 (CH_3COO**C**H), 128.4 (C_{arom}-H), 129.6 (**C**$_{arom}$-C), 129.7 (C_{arom}-H), 133.4 (C_{arom}-H), 165.5 (CO).

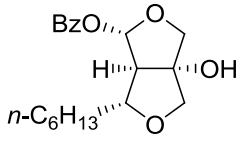
IR (Film) cm^{-1}: 3423 (OH), 1721 (CO).

MS (EI) m/z (%): 198 (2), 180 (3), 127 (11), 109 (100), 105 (39), 81 (17), 69 (5).

HMRS: Calcd. for $[C_{11}H_{18}O_3]^{+\bullet}$: 198.1256 ($M^{+\bullet}$-BzOH). Found: 198.1256.

$[\alpha]_D^{20}$: -54.0 (*c* = 1.00, CH_2Cl_2).

(1*S*,3a*S*,6*R*,6a*R*)-6-Hexyl-3a-hydroxyhexahydrofuro[3,4-*c*]furan-1-yl benzoate (6f).



Following the general procedure **6f** (48 mg, 0.14 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 1:1) starting from furofurane **4f** (46 mg, 0.20 mmol) and benzoyl chloride (25 μL, 0.22 mmol) in the presence of Et_3N (31 μL, 0.22 mmol) and using CH_2Cl_2 (1.0 mL) as solvent.

Yield: 73%.

ee: 95%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 10.60 min, τ_{minor} = 11.44 min.

^{1}H-NMR (δ, ppm) (300 MHz): 0.87 (t, 3H, *J* = 6.5 Hz, CH_3), 1.16-1.58 (m, 8H, $(CH_2)_4CH_3$), 1.66-1.86 (m, 2H, $CHCH_2$), 2.53 (d, 1H, *J* = 7.6 Hz, CHCHCH), 2.68 (bs, 1H, OH), 3.64-3.74 (m, 2H, $CHCH_2$ + OCH_aH_b), 4.03-4.16 (m, 3H, OCH_aH_b + OCH_cH_d + OCH_cH_d), 6.23 (s, 1H, CH_3COOCH), 7.45 (t, 2H , *J* = 7.6 Hz, C_{arom}-H), 7.58 (t, *J* = 7.4 Hz, 1H, C_{arom}-H), 8.06 (d, 2H, *J* = 7.1 Hz, C_{arom}-H)

^{13}C-NMR (δ, ppm) (75.5 MHz): 14.0 (CH_3), 22.5 (CH_2), 25.8 (CH_2), 29.1 (CH_2), 31.6 (CH_2), 34.9 ($CHCH_2$), 65.7 (CHCHCH), 74.8 (OCH_2), 78.7 (OCH_2),

84.4 (**C**HCH$_2$), 90.0 (CH$_2$**C**CH$_2$), 101.9 (CH$_3$COO**C**H), 128.4 (C$_{arom}$-H), 129.6 (**C**$_{arom}$-C), 129.7 (C$_{arom}$-H), 133.4 (C$_{arom}$-H), 165.5 (CO).

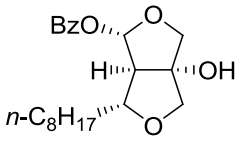
IR (Film) cm^{-1}: 3424 (OH), 1719 (CO).

MS (EI) m/z (%): 212 (2), 194 (2), 127 (11), 109 (100), 105 (24), 81 (19), 53 (3).

HMRS: Calcd. for [C$_{12}$H$_{20}$O$_3$]$^{+\bullet}$: 212.1412 (M$^{+\bullet}$-BzOH). Found: 212.1416.

[α]$_D^{20}$: -49.6 (*c* = 1.00, CH$_2$Cl$_2$).

(1*S*,3a*S*,6*R*,6a*R*)-3a-Hydroxy-6-octylhexahydrofuro[3,4-*c*]furan-1-yl benzoate (6g).



Following the general procedure **6g** (50 mg, 0.14 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 1:1) starting from furofurane **4g** (51 mg, 0.20 mmol) and benzoyl chloride (25 μL, 0.22 mmol) in the presence of Et$_3$N (31 μL, 0.22 mmol) and using CH$_2$Cl$_2$ (1.0 mL) as solvent.

Yield: 73%.

ee: 98%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 6.69 min, τ_{minor} = 7.10 min.

^{1}H-NMR (δ, ppm) (300 MHz): 0.85 (t, 3H, *J* = 6.3 Hz, CH$_3$), 1.16-1.56 (m, 12H, (C**H**$_2$)$_6$CH$_3$), 1.65-1.86 (m, 2H, CHC**H**$_2$), 2.53 (d, 1H, *J* = 7.6 Hz, CHC**H**CH), 3.05 (bs, 1H, OH), 3.61-3.73 (m, 2H, C**H**CH$_2$+ OC**H**$_a$H$_b$), 3.92-4.17 (m, 3H, OCH$_a$**H**$_b$ + OC**H**$_c$H$_d$ + OCH$_c$**H**$_d$), 6.22 (s, 1H, CH$_3$COOC**H**), 7.44 (t, 2H ,

J = 7.6 Hz, C_{arom}-H), 7.57 (t, 1H, J = 6.8 Hz, C_{arom}-H), 8.05 (d, 2H, J = 8.0 Hz, C_{arom}-H).

^{13}C-NMR (δ, ppm) (75.5 MHz): 14.0 (CH_3), 22.5 (CH_2), 25.8 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.7 (CH_2), 34.8 (CH_2), 65.6 (CH**C**HCH), 74.7 (OCH_2), 78.7 (OCH_2), 84.4 (**C**HCH_2), 89.8 (CH_2**C**CH_2), 101.8 (CH_3COO**C**H), 128.3 (C_{arom}-H), 129.5 (**C**$_{arom}$-C), 129.7 (C_{arom}-H), 133.3 (C_{arom}-H), 165.5 (CO).

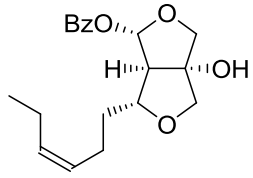
IR (Film) cm^{-1}: 3448 (OH), 1723 (CO).

MS (EI) m/z (%): 222 (3), 204 (3), 135 (4), 127 (8), 122 (12), 109 (100), 105 (50), 95 (7), 81 (16), 77 (24), 70 (4).

HMRS: Calcd. for $[C_{14}H_{22}O_2]^{+\bullet}$: 222.1620 ($M^{+\bullet}$-BzOH). Found: 222.1608.

$[\alpha]_D^{20}$: -45.1 (c = 1.00, CH_2Cl_2).

(1*S*,3a*S*,6*R*,6a*R*)-6-[(*Z*)-Hex-3-enyl]-3a-hydroxyhexahydrofuro[3,4-*c*]furan-1-yl benzoate (6h).



Following the general procedure **6h** (45 mg, 0.14 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 1:1) starting from furofurane **4h** (45 mg, 0.20 mmol) and benzoyl chloride (25 μL, 0.22 mmol) in the presence of Et_3N (31 μL, 0.22 mmol) and using CH_2Cl_2 (1.0 mL) as solvent.

Yield: 73%.

ee: 94%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 6.69 min, τ_{minor} = 7.10 min.

^{1}H-NMR (δ, ppm) (300 MHz): 0.93 (t, 3H, *J* = 7.5 Hz, CH_3), 1.73-1.92 (m, 2H, CH_2), 1.96-2.09 (m, 2H, CH_2), 2.11-2.26 (m, 2H, CH_2), 2.54 (d, 1H, *J* = 7.6 Hz, CHC**H**CH), 3.08 (bs, 1H, OH), 3.62-3.77 (m, 2H, C**H**CH_2CH_2CH=CH + OC$\mathbf{H}_a$$H_b$), 4.02-4.15 (m, 3H, $OCH_a\mathbf{H}_b$ + OC$\mathbf{H}_c$$H_d$ + $OCH_c\mathbf{H}_d$), 5.25-5.45 (m, 2H, CH=CH), 6.20 (s, 1H, CH_3COOC**H**), 7.43 (t, 2H , *J* = 7.6 Hz, C_{arom}-H), 7.58 (t, *J* = 7.4 Hz, 1H, C_{arom}-H), 8.05 (d, 2H, *J* = 7.1 Hz, C_{arom}-H).

^{13}C-NMR (δ, ppm) (75.5 MHz): 14.1 (CH_3), 20.4 (CH_2), 23.5 (CH_2), 34.8 (CH**C**H_2), 65.5 (CH**C**HCH), 74.8 (OCH_2), 78.7 (OCH_2), 83.7 (**C**HCH_2CH_2CH=CH), 89.8 (CH_2**C**CH_2), 101.9 (CH_3COO**C**H), 127.4 (C_{arom}-H or **C**H=CH), 128.4 (C_{arom}-H or CH=CH), 129.5 (C_{arom}-C), 129.7 (C_{arom}-H or **C**H=CH), 132.7 (C_{arom}-H or **C**H=CH), 133.3 (C_{arom}-H or **C**H=CH), 165.5 (CO).

IR (Film) cm^{-1}: 3442 (OH), 3085 (=CH), 1713 (CO), 1606 (C=C).

MS (EI) m/z (%): 210 (1), 184 (1), 172 (3), 143 (2), 122 (53), 105 (100), 98 (7), 91 (4), 77 (34), 70 (7).

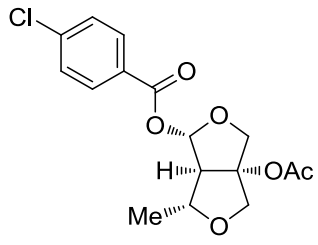
HMRS: Calcd. for $[C_{12}H_{18}O_3]^{+\bullet}$: 210.1256 ($M^{+\bullet}$-BzOH). Found: 210.1260.

$[\alpha]_D^{20}$: -51.8 (*c* = 1.00, CH_2Cl_2).

2.4. Synthesis of derivative 7. Determination of the absolute configuration.

The absolute configuration of furofurane **4b** was determined by single-crystal X-ray analysis after transformation to the corresponding *p*-chlorobenzoate derivative **7**. The same stereochemistry was assumed for assigning the absolute configuration of the rest of the compounds. In Figure 5.1 and Figure 5.2 different views of the crystal structure are shown.

(1*S*,3a*S*,6*R*,6a*R*)-3a-Acetoxy-6-methylhexahydrofuro[3,4-*c*]furan-1-yl 4-chlorobenzoate (7).



An ordinary vial equipped with a magnetic stirring bar was charged with furane **4b** (80 mg, 0.5 mmol) in 1 mL of CH_2Cl_2. Then Et_3N (77 μL, 0.55 mmol) and the acid chloride (70 μL, 0.55 mmol) were added. The reaction was stirred at room temperature until completion of the reaction and the crude mixture was directly charged onto silica gel and subjected to FC. The acetylation was done without further purification as follows: an ordinary vial equipped with a magnetic stirring bar was charged with the *p*-chlorobenzoylated furane in 1 mL of CH_2Cl_2. Then DMAP (6 mg, 0.05 mmol) and Ac_2O (60 μL, 0.55 mmol) were added. The reaction was stirred at room temperature until completion of the reaction and the crude mixture was directly charged onto silica gel and subjected to FC yielding final furane **7** (75 mg, 0.22 mmol) over two steps.

Yield: 44% (2 steps).

^{1}H-NMR (δ, ppm) (300 MHz): 1.51 (d, 3H, *J* = 6.1 Hz, CH_3), 2.11 (s, 3H, CH_3CO), 2.80 (d, 1H, *J*= 8.1 Hz, CHC**H**CH), 3.73-3.86 (m, 2H, C**H**CH_3 + OC**H**$_a$H$_b$), 4.07 (d, 1H, *J* = 10.1 Hz, OC**H**$_c$H$_d$), 4.35 (d, 1H, *J* = 11.0 Hz, OCH$_a$**H**$_b$), 4.57 (d, 1H, *J* = 10.2 Hz, OCH$_c$**H**$_d$), 6.20 (s, 1H, CH_3COOC**H**), 7.44 (d, 2H, *J* = 8.5 Hz, C_{arom}-H), 7.98 (d, 2H, *J* = 8.5 Hz, C_{arom}-H).

^{13}C-NMR (δ, ppm) (75.5 MHz): 19.6 (CH_3), 20.8 (**C**H_3CO), 64.8 (CH**C**HCH), 75.5 (**C**HCH_3), 77.4 (OCH_2), 79.1 (OCH_2), 94.7 (CH_2**C**CH_2), 100.2 (CH3COOCH), 128.0 (**C**$_{arom}$-C), 128.8 (C_{arom}-H**)**, 131.1 (C_{arom}-H**)**, 139.9 (C_{arom}-Cl), 164.6 (CH_3COO**C**H), 170.8 (CH_3**C**O).

IR (KBr) cm^{-1}: 1735 (CO).

MS (EI) m/z (%): 185 (7), 156 (22), 141 (29), 139 (77), 124 (50), 109 (100), 96 (43), 81 (98), 69 (32).

HMRS: Calcd. for $[C_9H_{12}O_4]^{+\bullet}$: 184.0736 ($M^{+\bullet}$-$2H_2O$). Found: 184.0726.

$[\alpha]_D^{20}$: -40.8 (*c* = 0.50, MeOH).

M.p. (*n*-hexane/AcOEt): 186-187 ºC

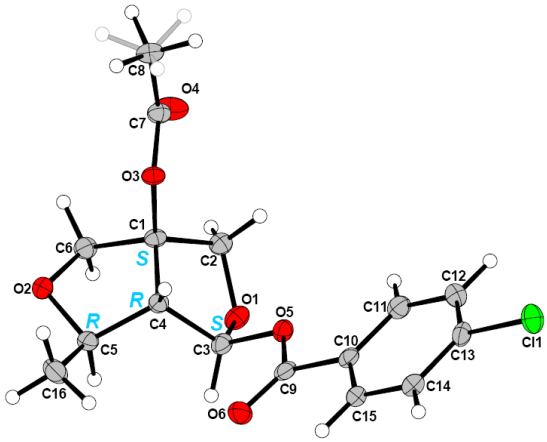


Figure 5.1

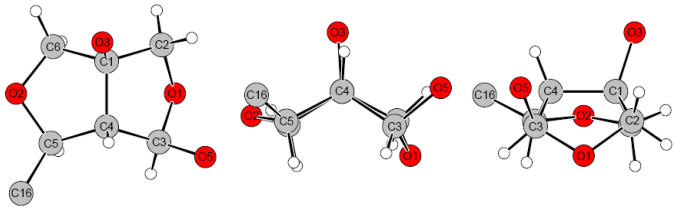
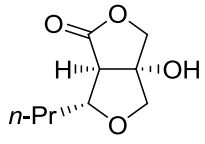


Figure 5.2

2.5. Oxidation of furofurane 4a. Synthesis of compound 8.

(3a*S*,6*R*,6a*R*)-3a-hydroxy-6-propyltetrahydrofuro[3,4-*c*]furan-1(3*H*)-one (8).



A round bottom flask under inert atmosphere equipped with a magnetic stirring bar was charged with furane **4a** (40 mg, 0.20 mmol) in 4 mL of CH_2Cl_2. Then PCC (215 mg, 1.0 mmol) was added. The reaction was stirred at 35 ºC until completion of the reaction (16 h) and the crude mixture was filtered through Celite and directly charged onto silica gel and subjected to FC (*n*-hexane/AcOEt 1:1) yielding furanone **8** (35 mg, 0.19 mmol).

Yield: 94%.

ee: 95%. Determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 10.04 min, τ_{minor} = 14.09 min.

^{1}H-NMR (δ, ppm) (300 MHz) (*overlapped signals): 0.96 (t, 3H, *J* = 7.3 Hz, CH_3), 1.35-1.57 (m, 2H, C**H**$_2$CH$_3$), 1.58-1.87 (m, 2H, CH_2*n*-Et), 2.82 (d, 1H, *J* = 4.4 Hz, C**H**CO), 3.25 (s, 1H, OH), 3.77 (d, 1H, *J* = 10.1 Hz, OC**H**$_a$H$_b$), 4.03 (d, 1H, *J* = 10.1 Hz, OCH$_a$**H**$_b$), 4.06-4.15 (m, 1H, CH*n*-Pr), 4.31 (d, 1H, *J* = 9.9 Hz, OC**H**$_c$H$_d$), 4.37* (d, 1H, *J* = 9.9 Hz, OCH$_c$**H**$_d$).

^{13}C-NMR (δ, ppm) (75.5 MHz): 13.7 (CH_3), 18.7 (**C**H$_2$CH$_3$), 37.1 (CH_2Et), 57.8 (**C**HCO), 75.4 (O**C**H$_2$), 76.9 (O**C**H$_2$), 82.9 (CH*n*-Pr), 85.1(CH$_2$**C**CH$_2$), 176.5 (CO).

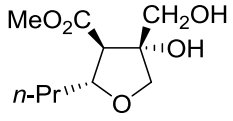
IR (Film) cm^{-1}: 3423 (OH), 1767 (CO).

MS (EI) m/z (%): 168 (2), 150 (2), 143 (55), 125 (5), 113 (11), 97 (12), 69 (100), 55 (15).

$[\alpha]_D^{20}$: -3.5 (*c* = 1.00, $CHCl_3$).

2.6. Methanolysis of derivative 8. Synthesis of compound 9.

(2*R*,3*R*,4*R*)-methyl 4-hydroxy-4-(hydroxymethyl)-2-propyltetrahydrofuran-3-carboxylate (9).



A round bottom flask under inert atmosphere equipped with a magnetic stirring bar was charged with furane **8** (36 mg, 0.19 mmol) in 5 mL of MeOH. Then Na_2CO_3 (27 mg, 0.19 mmol) was added. The reaction was stirred at room temperature until completion of the reaction (2 h) and the crude mixture was evaporated. Then CH_2Cl_2 (5 mL) and H_2O (5 mL) were added to the crude mixture, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were evaporated yielding furane **9** without further purification (33 mg, 0.15 mmol).

Yield: 80%.

^{1}H-NMR (δ, ppm) (300 MHz): 0.90 (t, 3H, *J* = 7.0 Hz, $CH_2C\mathbf{H}_3$), 1.19-1.66 (m, 4H, CH_2CH_2), 2.56 (d, 1H, *J* = 8.4 Hz, CHCOO), 3.28 (bs, 1H, $C\mathbf{H}_aCH_bOH$), 3.31 (s, 3H, CH_3O), 3.62 (d, 1H, *J* = 2.2 Hz, $CH_aC\mathbf{H}_bOH$), 3.68 (d, 1H, *J* = 9.1 Hz, $OC\mathbf{H}_aCH_b$), 3.81 (d, 1H, *J* = 9.2 Hz, $OCH_aC\mathbf{H}_b$), 4.10 (m, 1H, CH*n*-Pr), 4.83 (m, 5H, CH_3O, 2 x OH).

^{13}C-NMR (δ, ppm) (75.5 MHz): 14.5 ($CH_2\mathbf{C}H_3$), 20.3 ($\mathbf{C}H_2CH_3$), 38.6 (CH_2Et), 49.3 (CH_3O), 66.2 (CH_2OH), 66.3 (**C**HCO), 76.9 (O**C**H_2C), 83.9 (COH), 84.9 (CH*n*-Pr), 179.0 (CO).

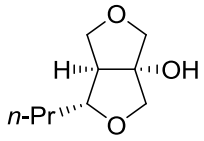
IR (Film) cm^{-1}: 3197 (OH), 1621 (CO).

MS (EI) m/z (%): 178 (45), 163 (50), 150 (30), 135 (79), 107 (52), 91 (63), 79 (31), 56 (100).

$[\alpha]_D^{20}$: -10.5 (*c* = 1.00, MeOH).

2.7. Reduction of furofurane 4a. Synthesis of compound 10.

(1*R*,3a*R*,6a*R*)-1-propylhexahydrofuro[3,4-*c*]furan-3a-ol (10).



A round bottom flask under inert atmosphere equipped with a magnetic stirring bar was charged with furane **4a** (40 mg, 0.20 mmol) in 4 mL of CH_2Cl_2. Then $BF_3{\cdot}OEt_2$ (84 μL, 0.66 mmol) was added and after stirring 5 min Et_3SiH (100 μL, 0.60 mmol) was added dropwise. The reaction was stirred at room temperature until completion of the reaction (16 h) and the crude mixture was subjected to FC (*n*-hexane/AcOEt 1:1) yielding furane **10** (34 mg, 0.19 mmol).

Yield: 99%.

^{1}H-NMR (δ, ppm) (300 MHz): 0.92 (t, 3H, *J* = 7.2 Hz, CH_3), 1.20-1.81 (m, 4H, CH_2CH_2), 2.20 (dt, 1H, *J* = 7.1, 2.2 Hz, $CH_2C\mathbf{H}CH$), 2.86 (bs, 1H, OH), 3.45-3.71 (m, 4H, O$\mathbf{H}_2$C$\mathbf{H}_a$CH_bO + CH*n*-Pr), 3.85 (d, 1H, *J* = 9.4 Hz, C$\mathbf{H}_a$$H_b$CHCH), 3.95 (dd, 1H, *J* = 9.3, 6.9 Hz, C$H_a$$\mathbf{H}_b$CHCH), 4.00 (d, 1H, *J* = 10.0 Hz, OCH_2CH_aC$\mathbf{H}_b$O**).**

^{13}C-NMR (δ, ppm) (75.5 MHz): 14.0 (CH_3), 19.2 (**C**H_2CH_3), 36.7 (CH_2Et), 60.2 (OCH_2**C**HCH), 71.5 (**C**H_2CH o **C**H_2COH), 75.7 (**C**H_2CH o **C**H_2COH), 78.2 (**C**H_2CH o **C**H_2COH), 86.2 (CH*n*-Pr), 91.5 (CH_2**C**CH_2).

IR (Film) cm^{-1}: 3416 (OH).

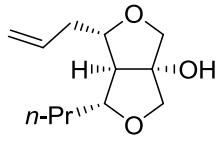
MS (EI) m/z (%): 172 (1), 154 (2), 141 (8), 129 (61), 99 (23), 81 (100), 69 (60), 55 (67).

HMRS: Calcd. for $[C_9H_{16}O_3]^{+\bullet}$: 172.1099. Found: 172.1105.

$[\alpha]_D^{20}$: + 26.0 (*c* = 0.50, $CHCl_3$).

2.8. Allylation of furofurane 4a. Synthesis of compound 11.

(1*S*,3a*S*,6*R*,6a*S*)-1-allyl-6-propylhexahydrofuro[3,4-*c*]furan-3a-ol (11).



A round bottom flask under inert atmosphere equipped with a magnetic stirring bar was charged with furane **4a** (40 mg, 0.20 mmol) in 4 mL of CH_2Cl_2. Then $BF_3{\cdot}OEt_2$ (84 μL, 0.66 mmol) was added and after stirring 5 min Allyltrimethylsilane (96 μL, 0.60 mmol) was added dropwise. The reaction was stirred at room temperature until completion of the reaction (16h) and the crude mixture was subjected to FC (*n*-hexane/AcOEt 1:1) yielding furane **11** (41 mg, 0.19 mmol).

Yield: 96%.

^{1}H-NMR (δ, ppm) (300 MHz): 0.93 (t, 3H, *J* = 7.1 Hz, CH_3), 1.22-1.77 (m, 4H, CH_2CH_2), 2.05 (dd, 1H, *J* = 5.0, 5.0 Hz, CHC**H**CH), 2.28-2.55 (m, 2H,

CH_2=CHC**H**$_2$), 2.76 (bs, 1H, OH), 3.60-3.78 (m, 4H, CH*n*-Pr + CH_2=$CHCH_2$C**H** + OCH_2), 3.82-3.92 (m, 2H, OCH_2), 5.07-5.19 (m, 2H, C**H**$_2$=CH), 5.70-5.88 (m, 1H, CH_2=C**H**).

^{13}C-NMR (δ, ppm) (75.5 MHz): 13.9 (CH_3), 19.2 (**C**H_2CH_3), 36.2 (CH_2Et), 38.5 (CH_2=CH**C**H_2), 64.8 (CH**C**HCH), 75.7 (OCH_2), 76.0 (OCH_2), 84.0 (CH_2=$CHCH_2$**C**H), 84.6 (**C**H*n*-Pr), 92.0 (CH_2**C**CH_2), 117.8 (**C**H_2=CH), 133.8 (CH_2=**C**H).

IR (Film) cm^{-1}: 3403 (OH).

MS (EI) m/z (%): 181 (1), 171 (16), 153 (21), 99 (18), 81 (100), 69 (64), 55 (38).

$[\alpha]_D^{20}$: -82.0 (*c* = 0.25, CH_2Cl_2).

2.9. Organocatalytic enantioselective Michael/hemiaminalization cascade reaction. Synthesis of γ-lactams 14b and 14i-o.

General Procedure:

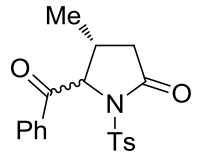
N-protected aminoacetophenone **12** (0.2 mmol) was added over a solution of α,β-unsaturated aldehyde **1** (0.4 mmol), catalyst **3b** (0.02 mmol) and DABCO (0.02 mmol) in toluene (4 mL). The reaction was stirred at room temperature for 48 h, after which the crude reaction mixture solvent was removed and the remaining was directly subjected to FC (*n*-hexane/AcOEt 1:1), affording the corresponding hemiaminal **13** which for characterization purposes, it was oxidized to the corresponding lactams **14**. Therefore, PCC was added over a solution of pyrrolidine **13** in CH_2Cl_2 (5 mL) and was stirred at room temperature until completion of the

reaction (16 h). Finally the crude mixture was filtered through Celite and directly charged onto silica gel and subjected to FC (*n*-hexane/AcOEt 1:1).

C-5 Epimerization of lactams. General Procedure:

A solution of lactam **14** (0.18 mmol) in dry THF (5 mL) was added over a suspension of NaH (0.27 mmol) in dry THF (5 mL) at 0ºC. The mixture was stirred at room temperature overnight. A solution of t-BuOH (0.36 mmol) in dry THF (3 mL) was dropped over the reaction mixture at –78 °C, then the reaction was allowed to stir at room temperature for 10 min. The solvent was removed under reduced pressure and charged onto silica gel and subjected to FC. (*n*-hexane/AcOEt 1:1) to afford ***cis*-14**.

(4*R*,5*S)-5-Benzoyl-4-methyl-1-tosylpyrrolidin-2-one (14b)**



Lactam **14b** (75 mg, 0.21 mmol) was prepared according to the general procedure after 2 reaction steps starting from crotonaldehyde (39 μl, 0.46 mmol), catalyst **3b** (27 mg, 0.05 mmol), DABCO (5 mg, 0.05 mmol) and ketone **12** (65 mg, 0.22 mmol).

Yield: 98%.

Oxidation of the corresponding hemiaminal (64 mg, 0.22 mmol) using PCC (148 mg, 0.69 mmol) afforded the desired lactam.

Yield: 93%.

dr (*cis*:*trans*): 1.5:1. After C5-epimerization: 1:1 (Determined by ^{1}H-NMR).

ee (*cis*:*trans*): 99%:92%. Determined by HPLC using a Daicel Chiralpak AD-H column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min; *cis* diastereoisomer: τ_{major} = 19.67 min, τ_{minor} = 23.40 min (99% ee); *trans* diastereoisomer: τ_{major} = 31.68 min, τ_{minor} = 21.54 min (92% ee).

^{1}H-NMR (δ, ppm) (300 MHz) (*cis*:*trans* 1.5:1; *minor diastereoisomer): 0.85* (d, 3H, *J* = 7.0 Hz, CHC**H**$_3$), 1.32 (d, 3H, *J* = 7.0 Hz, CHC**H**$_3$), 2.07 (dd, 1H, *J* = 17.2, 1.8 Hz, C**H**$_a$H$_b$), 2.24-2.55* (m, 9H, CH_3 + CH_3 + CH_2 + C**H**CH_2), 2.68 (dd, 1H, *J* = 17.2, 8.2 Hz, CH_a**H**$_b$), 2.80-2.96* (m, 1H, C**H**CH_2), 5.52 (d, 1H, *J* = 1.5 Hz, CHCO), 5.97* (d, 1H, *J* = 1.5 Hz, CHCO), 7.24-7.38 (m, 5H, C_{arom}-H), 7.54 (t, 3H, *J* = 7.6 Hz, C_{arom}-H), 7.66 (t, 2H, *J* = 7.3 Hz, C_{arom}-H), 7.82 (d, 2H, *J* = 8.3 Hz, C_{arom}-H), 7.88-8.07 (m, 6H, C_{arom}-H).

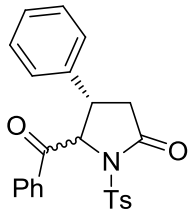
^{13}C-NMR (δ, ppm) (75.5 MHz) (*cis*:*trans* 1.5:1; *minor diastereoisomer): 15.6 (**C**H_3CH), 15.7* (**C**H_3CH), 20.6 (CH_3), 21.7* (CH_3), 31.1 (CH_3**C**H), 31.6* (CH_3**C**H), 38.2 (CH_2), 38.3* (CH_2), 63.5* (**C**HCO), 68.7 (**C**HCO), 128.5 (C_{arom}-H), 128.6 (C_{arom}-H), 129.0 (C_{arom}-H), 129.1 (C_{arom}-H), 129.1 (C_{arom}-H), 129.2 (C_{arom}-H), 134.0 (C_{arom}-C), 134.2 (C_{arom}-H), 134.3 (C_{arom}-H), 134.7 (C_{arom}-C), 134.8 (C_{arom}-C), 136.5 (C_{arom}-C), 145.3 (**C**$_{arom}$-C), 172.4 (CON), 172.7* (CON), 195.1 (CO), 196.9 (CO).

IR (Film) cm^{-1}: 1710 (CO), 1680 (CON), 1350 (SO_2), 1190 (SO_2).

MS (CI) m/z (%): 293 (1), 252 (100), 202 (4), 155 (84), 139 (3), 105 (56), 91 (63).

HMRS: Calcd. for $[C_{19}H_{20}NO_4S]^{+\bullet}$: 358.1113 $(M + H)^{+\bullet}$. Found: 358.1123.

(4*S*,5*S)-5-Benzoyl-4-phenyl-1-tosylpyrrolidin-2-one (14i).**



Lactam **14i** (68 mg, 0.16 mmol) was prepared according to the general procedure after 2 reaction steps starting from (*E*)-cinnamaldehyde (50 μl, 0.40 mmol), catalyst **3b** (24 mg, 0.04 mmol), DABCO (4 mg, 0.04 mmol) and ketone **12** (57 mg, 0.20 mmol).

Yield: 80%.

Oxidation of the corresponding hemiaminal (67 mg, 0.15 mmol) using PCC (103 mg, 0.48 mmol) afforded the desired lactam.

Yield: 98%.

dr (*cis*:*trans*): 2:1. After C5-epimerization: 5:1 (Determined by ^{1}H-NMR).

ee (*cis*:*trans*): 98%:92%. Determined by HPLC using a Daicel Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min; *cis* diastereoisomer: τ_{major} = 74.52 min, τ_{minor} = 48.48 min (98% ee); *trans* diastereoisomer: τ_{major} = 53.39 min, τ_{minor} = 81.68 min (92% ee).

^{1}H-NMR (δ, ppm) (300 MHz) (*cis*:*trans* 2:1; *minor diastereoisomer): 2.41-2.59* (m, 7H, CH_3 + CH_3 + C**H**$_a$H$_b$), 2.67 (dd, 1H, *J* = 16.9, 8.0 Hz, C**H**$_a$H$_b$), 3.00* (dd, 1H, *J* = 17.8, 9.1 Hz, CH$_a$**H**$_b$), 3.17 (dd, 1H, *J* = 16.9, 13.1 Hz, CH$_a$**H**$_b$), 3.39* (d, 1H, *J* = 9.1 Hz, C**H**CH$_2$), 4.11 (dt, 1H, *J* = 13.2, 8.2 Hz, C**H**CH$_2$), 5.87* (d, 1H, *J* = 1.5 Hz, CHCO), 6.17 (d, 1H, *J* = 8.7 Hz, CHCO), 7.01 (s, 5H, C_{arom}-H), 7.14-7.44 (m, 10H, C_{arom}-H), 7.46-7.55 (m, 8H, C_{arom}-H), 7.65 (t, 1H, *J* = 7.4 Hz,

C_{arom}-H), 7.84 (d, 2H, *J* = 8.2 Hz, C_{arom}-H), 7.94 (dd, 2H, *J* = 10.6, 8.5 Hz, C_{arom}-H).

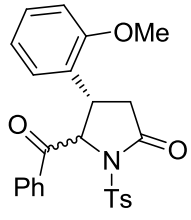
^{13}C-NMR (δ, ppm) (75.5 MHz) (*cis*:*trans* 2:1; *minor diastereoisomer): 21.8 (CH_3), 21.9 (CH_3), 35.1 (CH_2), 38.5* (CH_2), 40.7* (CHPh), 42.5 (CHPh), 64.5 (**C**HCO), 68.9* (**C**HCO), 126.2 (C_{arom}-H), 128.1 (C_{arom}-H), 128.1 (C_{arom}-H), 128.2 (C_{arom}-H), 128.3 (C_{arom}-H), 128.5 (C_{arom}-H), 128.8 (C_{arom}-H), 129.1 (C_{arom}-H), 129.2 (C_{arom}-H), 129.2 (C_{arom}-H), 129.3 (C_{arom}-H), 129.3 (C_{arom}-H), 129.6 (C_{arom}-H), 133.3 (C_{arom}-H), 133.6 (**C**$_{arom}$-C), 133.6 (**C**$_{arom}$-C), 134.4 (C_{arom}-H), 134.5 (**C**$_{arom}$-C), 134.7 (**C**$_{arom}$-C), 136.3 (**C**$_{arom}$-C), 141.7 (**C**$_{arom}$-C), 145.4 (**C**$_{arom}$-C), 172.2 (CON), 172.3* (CON), 194.6* (CO), 197.4 (CO).

IR (Film) cm^{-1}: 1715 (CO), 1683 (CON), 1349 (SO_2), 1190 (SO_2).

MS (CI) m/z (%): 314 (100), 264 (3), 207 (2), 155 (66), 139 (10), 105 (42), 91 (67).

HMRS: Calcd. for $[C_{24}H_{22}NO_4S]^{+\bullet}$: 420.1270 $(M + H)^{+\bullet}$. Found: 420.1290.

(4*S*,5*S)-5-Benzoyl-4-(2-methoxyphenyl)-1-tosylpyrrolidin-2-one (14j).**



Lactam **14j** (82 mg, 0.18 mmol) was prepared according to the general procedure after 2 reaction steps starting from (*E*)-2-methoxycinnamaldehyde (71 mg, 0.44 mmol), catalyst **3b** (24 mg, 0.04 mmol), DABCO (4 mg, 0.04 mmol) and ketone **12** (62 mg, 0.22 mmol).

Yield: 82%.

Oxidation of the corresponding hemiaminal (81 mg, 0.18 mmol) using PCC (126 mg, 0.54 mmol) afforded the desired lactam.

Yield: 90%.

dr (*cis*:*trans*): 3.3:1. After C5-epimerization: 2:1 (Determined by ^{1}H-NMR).

ee (*cis*:*trans*): 96%:96%. Determined by HPLC using a Daicel Chiralpak AD-H column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min; *cis* diastereoisomer: τ_{major} = 46.67 min, τ_{minor} = 32.98 min (96% ee); *trans* diastereoisomer: τ_{major} = 35.64 min, τ_{minor} = 72.54 min (96% ee).

^{1}H-NMR (δ, ppm) (300 MHz) (*cis*:*trans* 3.3:1; *minor diastereoisomer): 2.36-2.63* (m, 7H, CH_3Ph + CH_3Ph + C**H**$_a$H$_b$), 2.95* (dd, 1H, *J* = 17.6, 10.2 Hz, C**H**$_a$H$_b$), 3.19 (dd, 1H, *J* = 16.6, 13.6 Hz, CH$_a$**H**$_b$), 3.52* (d, 1H, *J* = 10.0 Hz, C**H**CH_2), 3.61 (s, 3H, CH_3O), 3.72* (s, 3H, CH_3O), 4.35 (dt, 1H, *J* = 16.3, 8.2 Hz, C**H**CH_2), 5.83* (d, 1H, *J* = 2.5 Hz, CHCO), 6.31 (d, 1H, *J* = 8.3 Hz, CHCO), 6.40 (d, 2H, *J* = 8.4 Hz, C_{arom}-H), 6.72 (t, 3H, *J* = 7.5 Hz, C_{arom}-H), 6.83-7.05 (m, 9H, C_{arom}-H), 7.13-7.54 (m, 10H, C_{arom}-H), 7.61* (t, 1H, *J* = 7.4 Hz, C_{arom}-H), 7.77-8.05 (m, 2H, C_{arom}-H).

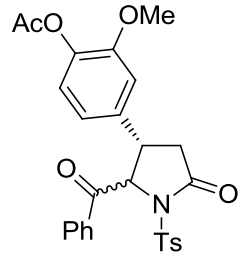
^{13}C-NMR (δ, ppm) (75.5 MHz) (*cis*:*trans* 3.3:1; *minor diastereoisomer): 21.7 (CH_3Ph), 21.8* (CH_3Ph), 33.3 (CH_2), 36.5 (CHPh), 36.9* (CHPh), 37.2* (CH_2), 54.8 (CH_3O), 54.9* (CH_3O), 62.7 (**C**HCO), 67.6* (**C**HCO), 109.4 (C_{arom}-H), 111.0* (C_{arom}-H), 120.4 (**C**$_{arom}$-H), 120.8* (**C**$_{arom}$-H), 121.9 (C_{arom}-C), 126.6 (C_{arom}-H), 128.4* (C_{arom}-H), 128.8 (C_{arom}-H), 128.9 (C_{arom}-H), 129.2 (**C**$_{arom}$-H), 129.3 (**C**$_{arom}$-H), 132.9 (**C**$_{arom}$-H), 134.1* (C_{arom}-H), 134.5 (**C**$_{arom}$-C), 135.1* (**C**$_{arom}$-C), 136.6 (**C**$_{arom}$-C), 145.1* (**C**$_{arom}$-C), 145.3 (**C**$_{arom}$-C), 156.9* (**C**$_{arom}$O), 157.2 (**C**$_{arom}$O), 172.4 (CON), 173.1* (CON), 195.7* (CO), 198.3 (CO).

IR (Film) cm^{-1}: 1711 (CO), 1686 (CON), 1349 (SO_2), 1191 (SO_2).

MS (CI) m/z (%): 344 (100), 281 (3), 208 (8), 189 (12), 155 (20), 134 (6), 105 (20), 91 (52).

HMRS: Calcd. for $[C_{25}H_{24}NO_5S]^{+\bullet}$: 450.1375 $(M + H)^{+\bullet}$. Found: 450.1394.

(4*S*,5*S)-4-(2-Benzoyl-5-oxo-1-tosylpyrrolidin-3-yl)-2-methoxyphenyl acetate (14k).**



Lactam **14k** (91 mg, 0.17 mmol) was prepared according to the general procedure after 2 reaction steps. The first step was done using (*E*)-4-acetoxy-3-methoxycinnamaldehyde (97 mg, 0.44 mmol), catalyst **3b** (24 mg, 0.04 mmol), DABCO (4 mg, 0.04 mmol) and ketone **12** (62 mg, 0.22 mmol).

Yield: 80%.

Oxidation of the corresponding hemiaminal (90 mg, 0.17 mmol) using PCC (116 mg, 0.54 mmol) afforded the desired lactam.

Yield: 91%.

dr (*cis*:*trans*): 1.5:1. After C5-epimerization: 6:1 (Determined by ^{1}H-NMR).

ee (*cis*:*trans*): 98%:98%. Determined by HPLC using a Daicel Chiralpak AD-H column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min; *cis* diastereoisomer: τ_{major} = 26.41 min, τ_{minor} = 29.40 min (98% ee); *trans* diastereoisomer: τ_{major} = 46.45 min, τ_{minor} = 58.03 min (98% ee).

^{1}H-NMR (δ, ppm) (300 MHz) (*cis*:*trans* 1.5:1; *minor diastereoisomer): 2.20 (s, 3H, CH_3), 2.33* (s, 3H, CH_3), 2.38-2.58* (m, 7H, CH_3Ph + CH_3Ph + C**H**$_a$H$_b$), 2.68 (dd, 1H, *J* = 16.9, 8.1 Hz, C**H**$_a$H$_b$), 2.98* (dd, 1H, *J* = 17.6, 9.0 Hz, CH$_a$**H**$_b$), 3.11 (dd, 1H, *J* = 16.9, 13.0 Hz, CH$_a$**H**$_b$), 3.39* (d, 1H, *J* = 9.0 Hz, C**H**CH_2), 3.55 (s, 3H, OCH_3), 3.75* (s, 3H, OCH_3), 3.99-4.22 (m, 1H, C**H**CH_2), 5.90* (s, 1H, CHCO), 6.19 (d, 1H, *J* = 8.7 Hz, CHCO), 6.54 (s, 1H, C_{arom}-H), 6.61 (d, 1H, *J* = 8.2 Hz, C_{arom}-H), 6.65-6.78 (m, 3H, C_{arom}-H), 6.81 (s, 1H, C_{arom}-H), 7.00 (d, 1H, *J* = 8.1 Hz, C_{arom}-H), 7.14-7.55 (m, 11H, C_{arom}-H), 7.64* (t, 1H, *J* = 7.4 Hz, C_{arom}-H), 7.84 (d, 2H, *J* = 8.3 Hz, C_{arom}-H), 7.89-8.08 (m, 3H, C_{arom}-H).

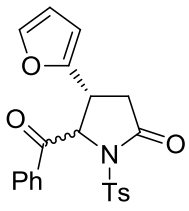
^{13}C-NMR (δ, ppm) (75.5 MHz) (*cis*:*trans* 1.5:1; *minor diastereoisomer): 20.5 (CH_3), 20.6* (CH_3), 21.7 (CH_3Ph), 21.8* (CH_3Ph), 35.3 (CH_2), 38.6* (CH_2), 40.7* (**C**HCH_2), 42.2 (**C**HCH_2), 55.7 (OCH_3), 55.8* (OCH_3), 64.4 (**C**HCO), 68.6* (**C**HCO), 109.7 (C_{arom}-H), 112.3 (C_{arom}-H), 118.5 (C_{arom}-H), 120.4 (C_{arom}-H), 122.8 (C_{arom}-H), 123.6 (C_{arom}-H), 128.1 (C_{arom}-H), 128.5 (C_{arom}-H), 128.8 (C_{arom}-H), 129.1 (C_{arom}-H), 129.2 (C_{arom}-H), 129.3 (C_{arom}-H), 132.5 (**C**$_{arom}$-C), 133.5* (**C**$_{arom}$-C), 133.6 (C_{arom}-H), 134.4 (**C**$_{arom}$-C), 134.5 (C_{arom}-H), 134.7 (**C**$_{arom}$-C), 136.5 (**C**$_{arom}$-C), 139.5 (**C**$_{arom}$-C), 139.6* (**C**$_{arom}$-C), 140.5 (**C**$_{arom}$-C), 145.5 (**C**$_{arom}$-C), 150.9 (C_{arom}-O), 152.0* (C_{arom}-O), 168.4 (COOMe), 168.9* (COOMe), 171.9 (CON), 172.1* (CON), 194.4* (CO), 197.6 (CO).

IR (Film) cm^{-1}: 1714 (CO), 1684 (CON), 1349 (SO_2), 1191 (SO_2).

MS (CI) m/z (%): 465 (12), 429 (2), 404 (2), 360 (100), 310 (6), 281 (8), 204 (30), 155 (46), 135 (12), 91 (76).

HMRS: Calcd. for $[C_{27}H_{26}NO_7S]^{+\bullet}$: 508.1430 $(M + H)^{+\bullet}$. Found: 508.1451.

(4*R*,5*S)-5-Benzoyl-4-(furan-2-yl)-1-tosylpyrrolidin-2-one (14l).**



Lactam **14l** (62 mg, 0.15 mmol) was prepared according to the general procedure after 2 reaction steps starting from (*E*)-3-(2-furyl)acrolein (52 mg, 0.42 mmol), catalyst **3b** (24 mg, 0.04 mmol), DABCO (4 mg, 0.04 mmol) and ketone **2** (59 mg, 0.21 mmol).

Yield: 73%.

Oxidation of the corresponding hemiaminal (60 mg, 0.14 mmol) using PCC (97 mg, 0.45 mmol) afforded the desired lactam.

Yield: 93%.

dr (*cis*:*trans*): 2:1. After C5-epimerization: >10:1 (Determined by ^{1}H-NMR).

ee (*cis*:*trans*): 94:n.d.%. Determined by HPLC using a Daicel Chiralpak IA column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min; τ_{major} = 23.38 min, τ_{minor} = 18.26 min (94%).

^{1}H-NMR (δ, ppm) (300 MHz) (*cis*:*trans* 2:1; *minor diastereoisomer): 2.41-2.48* (m, 6H, CH_3 + CH_3), 2.50-2.77* (m, 2H, C**H**$_a$H$_b$ + C**H**$_a$H$_b$), 2.88* (dd, 1H, *J* = 17.5, 8.5 Hz, CH$_a$**H**$_b$), 3.00 (dd, 1H, *J* = 16.9, 13.1 Hz, CH$_a$**H**$_b$), 3.59* (d, 1H, *J* = 8.4 Hz, C**H**CH$_2$), 4.13 (dt, 1H, *J* = 13.1, 8.4 Hz, C**H**CH$_2$), 5.83-6.04 (m, 3H, C_{fur}-H or CHCO), 6.10-6.26 (m, 2H, C_{fur}-H or CHCO), 6.34 (s, 1H, C_{fur}-H or CHCO), 6.88 (s, 1H, C_{fur}-H or CHCO), 7.22-7.41 (m, 7H, C_{arom}-H), 7.43 (s, 1H,

C_{arom}-H), 7.45-7.62 (m, 3H, C_{arom}-H), 7.62-7.75 (m, 3H, C_{arom}-H), 7.78-7.93 (m, 3H, C_{arom}-H), 8.07 (d, 1H, J = 7.4 Hz, C_{arom}-H).

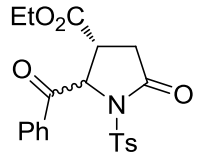
^{13}C-NMR (δ, ppm) (75.5 MHz) (*cis*:*trans* 2:1; *minor diastereoisomer): 21.8 (CH_3), 21.9* (CH_3), 34.4 (CH_2), 35.2* (**C**HCH_2), 35.4* (CH_2), 36.1 (**C**HCH_2), 63.1 (**C**HCO), 66.4* (**C**HCO), 106.8* (C_{fur}-H), 108.7 (C_{fur}-H), 110.3 (C_{fur}-H), 110.6 (C_{fur}-H), 128.3 (C_{arom}-H), 128.3 (C_{arom}-H), 128.8 (C_{arom}-H), 129.1 (C_{arom}-H), 129.2 (C_{arom}-H), 129.3 (**C**$_{arom}$-C), 133.5 (C_{arom}-H), 134.4 (**C**$_{arom}$-C), 134.5 (C_{arom}-H), 134.7 (**C**$_{arom}$-C), 135.1 (**C**$_{arom}$-C), 142.4 (C_{fur}-H), 142.9* (C_{fur}-H), 145.3 (**C**$_{arom}$-C), 145.4 (**C**$_{arom}$-C), 147.9 (**C**$_{arom}$-C), 152.6 (**C**$_{fur}$-C), 171.3 (CON), 171.4* (CON), 194.3* (CO), 196.2 (CO).

IR (Film) cm^{-1}: 1716 (CO), 1680 (CON), 1350 (SO_2), 1190 (SO_2).

MS (CI) m/z (%): 409 (8), 350 (2), 304 (90), 254 (7), 207 (5), 155 (100), 139 (27), 91 (88).

HMRS: Calcd. for $[C_{22}H_{20}NO_5S]^{+\bullet}$: 410.1062 $(M + H)^{+\bullet}$. Found: 410.1082.

(2*S*,3*R)-Ethyl 2-benzoyl-5-oxo-1-tosylpyrrolidine-3-carboxylate (14m).**



Lactam **14m** (53 mg, 0.13 mmol) was prepared according to the general procedure after 2 reaction steps starting from ethyl *trans*-4-oxo-2-butenoate (55 µL, 0.46 mmol), catalyst **3b** (27 mg, 0.05 mmol), DABCO (5 mg, 0.05 mmol) and ketone **2** (66 mg, 0.23 mmol).

Yield: 55%.

Oxidation of the corresponding hemiaminal (50 mg, 0.12 mmol) using PCC (84 mg, 0.39 mmol) afforded the desired lactam.

Yield: 78%.

dr (*cis*:*trans*): 1:1 (Determined by ^{1}H-NMR).

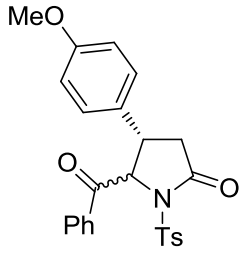
ee (*cis*:*trans*): 98%:84%. Determined by HPLC using a Daicel Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 60:40, flow rate 0.80 mL/min; A diastereoisomer: τ_{major} = 140.17 min, τ_{minor} = 32.77 min (84% ee); B diastereoisomer: τ_{major} = 60.47 min, τ_{minor} = 35.48 min (98% ee).

^{1}H-NMR (δ, ppm) (300 MHz): 0.82 (t, *J* = 7.1 Hz, 3H, CH_3), 1.26 (t, *J* = 7.1 Hz, 3H, CH_3), 2.41 (s, 3H, CH_3Ph), 2.44 (s, 3H, CH_3Ph), 2.54–2.91 (m, 2H, CH_aH_b + CH_aH_b), 2.91–3.20 (m, 2H, CH_aH_b + CH_aH_b), 3.57–3.39 (m, 1H, $CHCH_2$), 3.84–3.59 (m, 3H, $CHCH_2$ + CH_3CH_2), 4.24 (q, *J* = 7.1 Hz, 2H, CH_3CH_2), 6.18 (d, *J* = 8.8 Hz, 1H, CHCO), 6.25 (s, 1H, CHCO), 7.40–7.17 (m, 4H, C_{arom}-H), 7.54 (dd, *J* = 14.2, 7.0 Hz, 4H, C_{arom}-H), 7.81–7.60 (m, 4H, C_{arom}-H), 7.92 (d, *J* = 8.2 Hz, 2H, C_{arom}-H), 8.01 (d, *J* = 7.5 Hz, 2H, C_{arom}-H), 8.11 (d, *J* = 7.6 Hz, 2H, C_{arom}-H).

^{13}C-NMR (δ, ppm) (75.5 MHz): 13.3 (CH_3CH_2), 13.9 (CH_3CH_2), 21.7 (CH_3Ph), 21.8 (CH_3Ph), 33.2 ($CHCH_2$), 33.3 ($CHCH_2$), 40.3 (CH_3CH_2), 41.7 (CH_3CH_2), 59.5 (CHCO), 61.8 ($CHCH_2$), 62.6 ($CHCH_2$), 63.5 (CHCO), 125.5 (C_{arom}-H), 128.8 (C_{arom}-H), 128.9 (C_{arom}-H), 128.9 (C_{arom}-H), 129.0 (C_{arom}-H), 129.2 (C_{arom}-H), 129.2 (C_{arom}-H), 129.3 (C_{arom}-H), 133.2 (C_{arom}-C), 134.2 (C_{arom}-C), 134.3 (C_{arom}-H), 134.6 (C_{arom}-H), 135.7 (C_{arom}-C), 135.8 (C_{arom}-C), 145.4 (C_{arom}-C), 145.6 (C_{arom}-C), 168.3* (COOEt), 170.2 (COOEt), 170.7* (CON), 171.1 (CON), 194.2* (CO), 195.7 (CO).

IR (Film) cm^{-1}: 1710 (CO), 1683 (CON), 1349 (SO_2), 1193 (SO_2).

(4*S*,5*S)-5-Benzoyl-4-(4-methoxyphenyl)-1-tosylpyrrolidin-2-one (14n).**



Lactam **14n** (84 mg, 0.19 mmol) was prepared according to the general procedure after 2 reaction steps starting from (*E*)-4-methoxycinnamaldehyde (68 mg, 0.42 mmol), catalyst **3b** (24 mg, 0.04 mmol), DABCO (4 mg, 0.04 mmol) and ketone **12** (59 mg, 0.21 mmol).

Yield: 90%.

Oxidation of the corresponding hemiaminal (82 mg, 0.19 mmol) using PCC (122 mg, 0.57 mmol) afforded the desired lactam.

Yield: 82%.

dr (*cis*:*trans*): 3:1. After C5-epimerization: 7:1 (Determined by ^{1}H-NMR).

ee (*cis*:*trans*): 98%:98%. Determined by HPLC using a Daicel Chiralpak AD-H column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min; *cis* diastereoisomer: τ_{major} = 46.67 min, τ_{minor} = 32.98 min (98% ee); *trans* diastereoisomer: τ_{major} = 35.64 min, τ_{minor} = 72.54 min (98% ee).

^{1}H-NMR (δ, ppm) (300 MHz) (*cis*:*trans* 3:1; *minor diastereoisomer): 2.39-2.57* (m, 7H, CH_3Ph + CH_3Ph + C**H**$_a$H$_b$), 2.64 (dd, 1H, *J* = 16.9, 8.1 Hz, C**H**$_a$H$_b$), 2.97* (dd, 1H, *J* = 17.6, 9.1 Hz, CH$_a$**H**$_b$), 3.11 (dd, 1H, *J* = 16.9, 13.2 Hz, CH$_a$**H**$_b$), 3.36* (d, 1H, *J* = 9.1 Hz, C**H**CH_2), 3.62 (s, 3H, CH_3O), 3.82* (s, 3H, CH_3O), 4.06 (dt, 1H, *J* = 13.1, 8.3 Hz, C**H**CH_2), 5.83* (d, 1H, *J* = 1.9 Hz, CHCO), 6.13 (d, 1H, *J* = 8.7 Hz, CHCO), 6.54 (d, 2H, *J* = 8.7 Hz, C_{arom}-H), 6.89 (t, 3H, *J* = 9.3 Hz,

C_{arom}-H), 7.10* (d, 2H, *J* = 8.7 Hz, C_{arom}-H) 7.19-7.46 (m, 9H, C_{arom}-H), 7.46-7.57 (m, 3H, C_{arom}-H), 7.65* (t, 1H, *J* = 7.4 Hz, C_{arom}-H), 7.84 (d, 2H, *J* = 8.3 Hz, C_{arom}-H), 7.89-8.01* (m, 4H, *J* = 10.6, 8.5 Hz, C_{arom}-H).

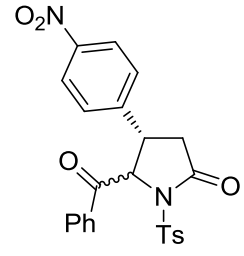
^{13}C-NMR (δ, ppm) (75.5 MHz) (*cis*:*trans* 3:1; *minor diastereoisomer): 21.8 (CH_3Ph), 35.4 (CH_2), 38.7* (CH_2), 40.1* (CHPh), 41.8 (CHPh), 53.5* (CH_3O), 55.2 (CH_3O), 64.6 (**C**HCO), 69.2* (**C**HCO), 113.9 (C_{arom}-H), 114.9* (C_{arom}-H), 125.4 (**C**$_{arom}$-C), 126.5* (**C**$_{arom}$-C), 127.3 (C_{arom}-H), 128.3 (C_{arom}-H), 128.8* (C_{arom}-H), 129.2 (C_{arom}-H), 133.3 (C_{arom}-H), 133.7 (**C**$_{arom}$-C), 134.4 (**C**$_{arom}$-C), 134.5 (**C**$_{arom}$-C), 134.8* (C_{arom}-H), 136.3 (**C**$_{arom}$-C), 145.3 (**C**$_{arom}$-C), 159.2 (C_{arom}-O), 172.3 (CON), 172.4* (CON), 194.7* (CO), 197.6 (CO).

IR (Film) cm^{-1}: 1711 (CO), 1680 (CON), 1348 (SO_2), 1191 (SO_2).

MS (CI) m/z (%): 449 (2), 344 (100), 294 (4), 281 (2), 207 (4), 188 (22), 155 (44), 105 (44), 91 (74).

HMRS: Calcd. for $[C_{25}H_{24}NO_5S]^{+\bullet}$: 450.1345 $(M + H)^{+\bullet}$. Found: 450.1397.

(4*S*,5*S)-5-Benzoyl-4-(4-nitrophenyl)-1-tosylpyrrolidin-2-one (14o).**



Lactam **14o** (54 mg, 0.11 mmol) was prepared according to the general procedure after 2 reaction steps starting from (*E*)-4-nitrocinnamaldehyde (84 mg, 0.46 mmol), catalyst **3b** (27 mg, 0.05 mmol), DABCO (5 mg, 0.05 mmol) and ketone **2** (66 mg, 0.23 mmol).

Yield: 50%.

Oxidation of the corresponding hemiaminal (53 mg, 0.11 mmol) using PCC (71 mg, 0.33 mmol) afforded the desired lactam.

Yield: 80%.

dr (*cis*:*trans*): 2.5:1 (Determined by ^{1}H-NMR).

ee (*cis*:*trans*): 98%:90%. Determined by HPLC using a Daicel Chiralpak IA column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min; *cis* diastereoisomer: τ_{major} = 44.89 min, τ_{minor} = 38.37 min (98% ee); *trans* diastereoisomer: τ_{major} = 52.08 min, τ_{minor} = 42.62 min (90% ee).

^{1}H-NMR (δ, ppm) (300 MHz) (*cis*:*trans* 3.3:1; *minor diastereoisomer): 2.36-2.63* (m, 7H, CH_3Ph + CH_3Ph + C**H**$_a$H$_b$), 2.95* (dd, 1H, *J* = 17.6, 10.2 Hz, C**H**$_a$H$_b$), 3.19 (dd, 1H, *J* = 16.6, 13.6 Hz, CH$_a$**H**$_b$), 3.52* (d, 1H, *J* = 10.0 Hz, C**H**CH_2), 3.61 (s, 3H, CH_3O), 3.72* (s, 3H, CH_3O), 4.35 (dt, 1H, *J* = 16.3, 8.2 Hz, C**H**CH_2), 5.83* (d, 1H, *J* = 2.5 Hz, CHCO), 6.31 (d, 1H, *J* = 8.3 Hz, CHCO), 6.40 (d, 2H, *J* = 8.4 Hz, C_{arom}-H), 6.72 (t, 3H, *J* = 7.5 Hz, C_{arom}-H), 6.83-7.05 (m, 10H, C_{arom}-H), 7.13-7.54 (m, 6H, C_{arom}-H), 7.61* (t, 1H, *J* = 7.4 Hz, C_{arom}-H), 7.77-8.05 (m, 4H, C_{arom}-H).

^{13}C-NMR (δ, ppm) (75.5 MHz) (*cis*:*trans* 3.3:1; *minor diastereoisomer): 21.7 (CH_3Ph), 33.3 (CH_2), 36.5 (C**H**CH_2), 36.9* (C**H**CH_2), 37.2 (CH_2), 54.8 (CH_3O), 54.9* (CH_3O), 62.7 (**C**HCO), 67.6* (**C**HCO), 109.4 (C_{arom}-H), 111.0* (C_{arom}-H), 120.4 (C_{arom}-H), 120.8* (C_{arom}-H), 121.9 (C_{arom}-C), 126.6 (C_{arom}-H), 128.4* (C_{arom}-H), 128.8 (C_{arom}-H), 128.9 (C_{arom}-H), 129.2 (C_{arom}-H), 129.3 (C_{arom}-H), 132.9 (C_{arom}-H), 134.1* (C_{arom}-H), 134.5 (**C**$_{arom}$-C), 135.1* (**C**$_{arom}$-C), 136.6 (**C**$_{arom}$-C), 145.1* (**C**$_{arom}$-C), 145.3 (**C**$_{arom}$-C), 156.9* (C_{arom}-O), 157.2 (C_{arom}-O), 172.4 (CON), 173.1* (CON), 195.7* (CO), 198.3 (CO).

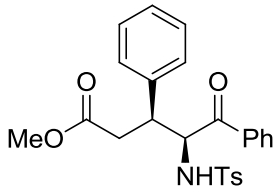
IR (Film) cm^{-1}: 1715 (CO), 1683 (CON), 1348 (SO_2), 1192 (SO_2).

2.10. Methanolysis of lactams *cis*-14i-l and *cis*-14n.

General Procedure:

To a solution of *in situ* generated NaOMe in MeOH (5 mL) at -20 ºC a solution of lactam ***cis*-14** (0.15 mmol) in MeOH (3 mL) was added and the mixture was allowed to stir for 10 min at -20 ºC. Then, H_2O was added to the crude mixture and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic fractions were collected, dried over anhydrous Na_2SO_4, filtered and concentrated. Pure ***syn*-25** was isolated after FC purification (*n*-hexane/AcOEt 1:1).

(3*S*,4*S*)-Methyl 4-(4-methylphenylsulfonamido)-5-oxo-3,5-diphenylpentanoate (*syn*-25i).



Compound ***syn*-25i** (45 mg, 0.10 mmol) was prepared according to the general procedure starting from lactam ***cis*-14i** (61 mg, 0.14 mmol).

Yield: 78%.

ee: 97%. Determined by HPLC using a Daicel Chiralpak IA column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min; τ_{major} = 20.90 min, τ_{minor} = 25.96 min.

^{1}H-NMR (δ, ppm) (300 MHz): 2.23 (s, 3H, CH_3Ph), 2.67 (dd, 1H, *J* = 17.7, 3.1 Hz, C**H**$_a$H$_b$), 3.51 (dd, 1H, *J* = 17.8, 11.4 Hz, CH$_a$**H**$_b$), 3.68 (dt, 1H, *J* = 11.3, 2.6 Hz, CH$_a$**H**$_b$), 3.83 (s, 3H, CH_3O), 5.40 (dd, 1H, *J* = 8.9, 2.6 Hz, CHN), 5.51 (d, 1H, *J* = 8.9 Hz, NH), 6.82 (dd, 2H, *J* = 7.4, 1.9 Hz, C_{arom}-H), 7.08 (d, 2H, *J* = 8.0

Hz, C_{arom}-H), 7.12-7.23 (m, 3H, C_{arom}-H), 7.50 (t, 2H, J = 7.6, C_{arom}-H), 7.61 (t, 3H, J = 8.3, C_{arom}-H), 7.96 (d, 2H, J = 7.2, C_{arom}-H).

^{13}C-NMR (δ, ppm) (75.5 MHz): 21.4 (CH_3Ph), 35.4 (PhCH), 43.3 (CH_2), 52.0 (CH_3O), 59.9 (CHN), 127.2 (C_{arom}-H), 127.8 (C_{arom}-H), 128.3 (C_{arom}-H), 128.4 (C_{arom}-H), 128.8 (C_{arom}-H), 129.6 (C_{arom}-H), 133.9 (**C**$_{arom}$-C), 134.1 (C_{arom}-H), 135.9 (**C**$_{arom}$-C), 136.7 (**C**$_{arom}$-C), 143.7 (**C**$_{arom}$-C), 173.6 (CO_2Me), 196.0 (CO).

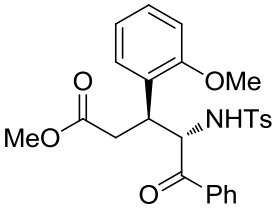
IR (Film) cm^{-1}: 3360 (NH), 1750 (COOMe), 1680 (CO), 1340 (SO_2), 1212 (SO_2).

MS (CI) m/z (%): 314 (100), 264 (2), 207 (2), 155 (72), 139 (9), 105 (30), 91 (70).

HMRS: Calcd. for $[C_{24}H_{22}NO_4S]^{+\bullet}$: 420.1270 ($M^{+\bullet}$-MeOH). Found: 420.1276.

$[\alpha]_D^{20}$: +46.3 (c = 0.35, CH_2Cl_2).

(3*S*,4*S*)-Methyl 3-(2-methoxyphenyl)-4-(4-methylphenylsulfonamido)-5-oxo-5-phenylpentanoate (*syn*-25j).



Compound ***syn*-25j** (44 mg, 0.09 mmol) was prepared according to the general procedure starting from lactam ***cis*-14j** (78 mg, 0.17 mmol).

Yield: 54%.

ee: 97%. Determined by HPLC using a Daicel Chiralpak IA column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min; τ_{major} = 11.92 min, τ_{minor} = 12.91 min.

^{1}H-NMR (δ, ppm) (300 MHz): 2.19 (s, 3H, CH_3Ph), 2.62 (dd, 1H, *J* = 17.7, 3.1 Hz, C**H**$_a$H$_b$), 3.02 (s, 3H, CH_3O), 3.48 (dd, 1H, *J* = 17.8, 11.5 Hz, CH$_a$**H**$_b$), 3.82 (s, 3H, CH_3O), 4.29 (d, 1H, *J* = 11.1 Hz, CHPh), 5.27-5.45 (m, 2H, CHN + NH), 6.61 (d, 1H, *J* = 8.1 Hz, C_{arom}-H), 6.83-7.08 (m, 3H, C_{arom}-H), 7.08-7.36 (m, 2H, C_{arom}-H), 7.36-7.62 (m, 5H, C_{arom}-H), 8.02 (d, 2H, *J* = 7.4 Hz, C_{arom}-H).

^{13}C-NMR (δ, ppm) (75.5 MHz): 21.3 (CH_3Ph), 35.0 (PhCH), 35.1 (CH_2), 51.9 (CH_3O), 53.9 (CO_2**C**H$_3$), 59.2 (CHN), 109.6 (C_{arom}-H), 120.5 (C_{arom}-H), 124.9 (C_{arom}-H), 127.2 (C_{arom}-H), 128.2 (C_{arom}-H), 128.4 (C_{arom}-H), 128.6 (C_{arom}-H), 128.9 (C_{arom}-H), 129.4 (C_{arom}-H), 133.4 (**C**$_{arom}$-C), 134.5 (**C**$_{arom}$-C), 136.1 (**C**$_{arom}$-C), 143.4 (**C**$_{arom}$-C), 156.2 (**C**$_{arom}$-C), 173.7 (CO_2Me), 195.3 (CO).

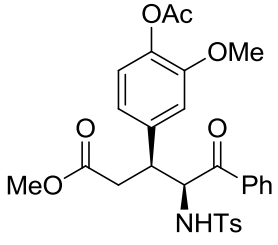
IR (Film) cm^{-1}: 3361 (NH), 1753 (COOMe), 1681 (CO), 1339 (SO_2), 1210 (SO_2).

MS (CI) m/z (%): 449 (1), 344 (100), 281 (3), 253 (2), 189 (10), 155 (18), 134 (8), 91 (50).

HMRS: Calcd. for $[C_{26}H_{28}NO_6S]^{+\bullet}$: 482.1637 $(M + H)^{+\bullet}$. Found: 482.1661.

$[\alpha]_D^{20}$: +101.4 (*c* = 0.65, CH_2Cl_2).

(3*S*,4*S*)-Methyl 3-(4-acetoxy-3-methoxyphenyl)-4-(4-methylphenylsulfonamido)-5-oxo-5-phenylpentanoate (*syn*-25k).



Compound ***syn*-25k** (56 mg, 0.10 mmol) was prepared according to the general procedure starting from lactam ***cis*-14k** (78 mg, 0.15 mmol).

Yield: 70%.

ee: 93%. Determined by HPLC using a Daicel Chiralpak IA column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min; τ_{major} = 14.07 min, τ_{minor} = 28.10 min.

^{1}H-NMR (δ, ppm) (300 MHz): 2.23 (s, 3H, CH_3Ph), 2.64 (dd, 1H, *J* = 17.6, 3.0 Hz, C**H**$_a$H$_b$), 3.44 (dd, 1H, *J* = 17.5, 11.3 Hz, CH$_a$**H**$_b$), 3.54-3.75 (m, 10H, CH_3OCO + CH_3OCO + CH_3O + CHPh), 5.36 (dd, 1H, *J* = 8.8, 2.4 Hz, CHN), 5.56 (d, 1H, *J* = 7.7 Hz, NH), 6.29 (d, 2H, *J* = 6.5 Hz, C_{arom}-H), 6.69 (d, 1H, *J* = 8.5 Hz, C_{arom}-H), 7.09 (d, 2H, *J* = 7.9 Hz, C_{arom}-H), 7.41-7.66 (m, 5H, C_{arom}-H), 7.95 (d, 2H, *J* = 7.6 Hz, C_{arom}-H).

^{13}C-NMR (δ, ppm) (75.5 MHz): 21.4 (CH_3Ph), 25.3 (**C**H_3CO), 35.8 (CH_2), 43.1 (CHPh), 51.9 (**C**H_3OCO), 55.8 (CH_3OPh), 60.1 (CHN), 110.7 (C_{arom}-H), 114.2 (C_{arom}-H), 121.1 (C_{arom}-H), 127.1 (C_{arom}-H), 128.5 (**C**$_{arom}$-C), 128.8 (C_{arom}-H), 128.9 (C_{arom}-H), 129.6 (C_{arom}-H), 134.0 (C_{arom}-H), 135.9 (**C**$_{arom}$-C), 143.6 (**C**$_{arom}$-C), 145.2 (**C**$_{arom}$-C), 146.1 (**C**$_{arom}$-C), 173.5 (CO_2Me), 173.6 (OCOMe)), 196.1 (CO).

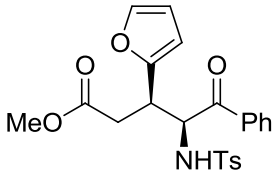
IR (Film) cm^{-1}: 3360 (NH), 1750 (COOMe), 1680 (CO), 1340 (SO_2), 1211 (SO_2).

MS (CI) m/z (%): 465 (12), 429 (2), 404 (2), 360 (100), 310 (6), 281 (8), 204 (30), 155 (46), 135 (12), 91 (76).

HMRS: Calcd. for $[C_{26}H_{26}NO_6S]^{+\bullet}$: 480.1481 ($M^{+\bullet}$-MeOCOH). Found: 480.1511.

$[\alpha]_D^{20}$: +44.5 (*c* = 1.35, CH_2Cl_2).

(3*R*,4*S*)-Methyl 3-(furan-2-yl)-4-(4-methylphenylsulfonamido)-5-oxo-5-phenyl-pentanoate (*syn*-25l).



Compound ***syn*-25l** (53 mg, 0.12 mmol) was prepared according to the general procedure starting from lactam ***cis*-14l** (65 mg, 0.16 mmol).

Yield: 74%.

ee: 94%. Determined by HPLC using a Daicel Chiralpak IA column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min; τ_{major} = 10.31 min, τ_{minor} = 12.84 min.

^{1}H-NMR (δ, ppm) (300 MHz): 2.24 (s, 3H, CH_3Ph), 2.70 (dd, 1H, *J* = 17.8, 3.6 Hz, C**H**$_a$H$_b$), 3.35 (dd, 1H, *J* = 17.9, 11.1 Hz, CH$_a$**H**$_b$), 3.66-3.91 (m, 4H, CH_3O + C**H**CH_2), 5.32 (dd, 1H, *J* = 9.4, 2.7 Hz, CHN), 5.62 (d, 1H, *J* = 9.2 Hz, NH), 5.92 (d, 1H, *J* = 2.8 Hz, C_{fur}-H), 6.20 (bs, 1H, C_{fur}-H), 6.97-7.23 (m, 3H, C_{fur}-H + C_{arom}-H), 7.37-7.68 (m, 5H, C_{arom}-H), 7.94 (d, 2H, *J* = 7.5 Hz, C_{arom}-H).

^{13}C-NMR (δ, ppm) (75.5 MHz): 21.4 (CH_3Ph), 34.0 (CH_2), 37.9 (**C**HCH_2), 52.1 (CH_3O), 58.9 (CHN), 107.8 (C_{fur}-H), 110.1 (C_{fur}-H), 127.1 (C_{arom}-H), 128.6 (C_{arom}-H), 128.9 (C_{arom}-H), 129.6 (C_{arom}-H), 133.9 (C_{arom}-H), 136.1 (**C**$_{arom}$-C), 142.2 (C_{fur}-H), 143.6 (**C**$_{arom}$-C), 150.9 (**C**$_{fur}$-C), 172.9 (CO_2Me), 195.9 (CO).

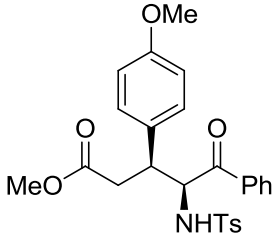
IR (Film) cm^{-1}: 3362 (NH), 1754 (COOMe), 1683 (CO), 1338 (SO_2), 1210 (SO_2).

MS (CI) m/z (%): 409 (8), 350 (2), 304 (90), 254 (7), 207 (5), 155 (100), 139 (27), 91 (88).

HMRS: Calcd. for $[C_{22}H_{20}NO_5S]^{+\bullet}$: 410.1062 ($M^{+\bullet}$-MeOH). Found: 410.1088.

$[\alpha]_D^{20}$: +31.9 (*c* = 0.35, CH_2Cl_2).

(3*S*,4*S*)-Methyl 3-(4-methoxyphenyl)-4-(4-methylphenylsulfonamido)-5-oxo-5-phenylpentanoate (*syn*-25n).



Compound ***syn*-25n** (67 mg, 0.14 mmol) was prepared according to the general procedure starting from lactam ***cis*-14n** (67 mg, 0.15 mmol).

Yield: 95%.

ee: 97%. Determined by HPLC using a Daicel Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min; τ_{major} = 41.90 min, τ_{minor} = 35.77 min.

^{1}H-NMR (δ, ppm) (300 MHz): 2.23 (s, 3H, CH_3Ph), 2.63 (dd, 1H, *J* = 17.6, 3.3 Hz, C**H**$_a$H$_b$), 3.46 (dd, 1H, *J* = 17.7, 11.3 Hz, CH$_a$**H**$_b$), 3.64 (dt, 1H, *J* = 11.5, 3.0 Hz, CHPh), 3.74 (s, 3H, CH_3O), 3.82 (s, 3H, CH_3O), 5.36 (dd, 1H, *J* = 8.9, 2.7 Hz, CHN), 5.50 (d, 1H, *J* = 8.9 Hz, NH), 6.65-6.83 (m, 4H, C_{arom}-H), 7.08 (d, 2H, *J* = 8.0 Hz, C_{arom}-H), 7.50 (t, 2H, *J* = 7.5, C_{arom}-H), 7.55-7.67 (m, 3H, C_{arom}-H), 7.95 (d, 2H, *J* = 7.2, C_{arom}-H).

^{13}C-NMR (δ, ppm) (75.5 MHz): 21.4 (CH_3Ph), 35.7 (CH_2), 42.6 (PhCH), 52.0 (**C**H_3OCO), 55.1 (CH_3OPh), 59.9 (CHN), 113.8 (C_{arom}-H), 127.2 (C_{arom}-H), 128.6 (**C**$_{arom}$-C), 128.8 (**C**$_{arom}$-C), 129.0 (C_{arom}-H), 129.3 (C_{arom}-H), 129.6 (C_{arom}-H), 134.0 (C_{arom}-H), 135.9 (**C**$_{arom}$-C),143.6 (**C**$_{arom}$-C), 159.0 (C_{arom}-OMe), 173.6 (CO_2Me), 196.2 (CO).

IR (KBr) cm^{-1}: 3362 (NH), 1750 (COOMe), 1680 (CO), 1338 (SO_2), 1210 (SO_2).

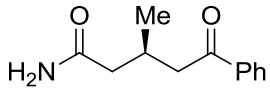
MS (CI) m/z (%): 449 (2), 344 (100), 294 (5), 253 (2), 207 (5), 188 (23), 155 (43), 134 (24), 91 (64).

HMRS: Calcd. for $[C_{26}H_{28}NO_6S]^{+\bullet}$: 482.1637 $(M + H)^{+\bullet}$. Found: 482.1672.

$[\alpha]_D^{20}$: +20.1 (*c* = 0.45, CH_2Cl_2).

2.11. Ring opening of lactam 14b. Synthesis of ketoamide 28.

(*S*)-3-Methyl-5-oxo-5-phenylpentanamide (28).



To a solution of naphthalene (146 mg, 1.14 mmol) in dry THF (10 mL) was added Na and the mixture was sonicated until a deep green solution of sodium naphthalenide was obtained (20 min). A solution of **14b** (76 mg, 0.19 mmol) in THF (5 mL) was dropped over the cooled (–78 °C) solution of sodium naphthalenide. The resulting reaction mixture was stirred at –78 °C for 1 h, then quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford **28** as a colorless oil without further purification.

Yield: 77%.

ee: 89%. Determined by HPLC using a Daicel Chiralpak IC column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min; τ_{major} = 28.08 min, τ_{minor} = 56.61 min.

^{1}H-NMR (δ, ppm) (300 MHz): 1.08 (d, *J* = 6.7 Hz, 3H, CH_3), 2.18 (dd, *J* = 14.2, 7.2 Hz, 1H, C**H**$_a$H$_b$CO or C**H**$_a$H$_b$CON), 2.35 (dd, *J* = 14.2, 6.4 Hz, 1H, CH$_a$**H**$_b$CO or CH$_a$**H**$_b$CO), 2.53-2.69 (m, 1H, CH), 2.87 (dd, *J* = 16.2, 6.8 Hz, 1H, C**H**$_a$H$_b$CO or C**H**$_a$H$_b$CON), 3.12 (dd, *J* = 16.2, 6.4 Hz, 1H, CH$_a$**H**$_b$CO or CH$_a$**H**$_b$CON), 5.75 (d, *J* = 38.0 Hz, 2H, NH_2), 7.65-7.40 (m, 3H, C_{arom}-H), 7.96 (d, *J* = 7.4 Hz, 2H, C_{arom}-H).

^{13}C-NMR (δ, ppm) (75.5 MHz): 20.2 (CH_3), 27.7 (CH), 42.6 (**C**H_2CON), 44.7 (**C**H_2CO), 128.2 (C_{arom}-H), 128.6 (C_{arom}-H), 133.2 (C_{arom}-H), 136.9 (**C**$_{arom}$-C), 174.5 (CON), 199.9 (CO).

IR (Film) cm^{-1}: 3350 (NH), 3200 (NH), 1750 (CO), 1692 (CON).

MS (CI) m/z (%): 205 (1), 188 (20), 172 (26), 160 (4), 147 (27), 128 (4), 120 (12), 105 (100), 86 (20), 77 (44).

HMRS: Calcd. for $[C_{11}H_{13}O]^{+\bullet}$: 161.0966 ($M^{+\bullet}$-$HCONH_2$). Found: 161.0970.

$[\alpha]_D^{20}$: -6.8 (*c* = 0.45, CH_2Cl_2).

2.12. Determination of the relative and absolute configuration.

The absolute and relative configuration was asigned by single X-ray analysis of minor diastereoisomer ***anti*-25n** which was isolated, recrystalized and next converted in cyclic glutamic acid derivative ***trans*-14n**. Comparation of the ^{1}H-NMR signals of pure ***trans*-14n** compound with those obtained in the crude product reaction allowed us to determine the major diastereoisomers signals and the relative configuration of the initial hemiaminal. In Figure 5.3 and Figure 5.4 the X-ray crystal structure and the crystal structure over the coordinate axes are depicted.

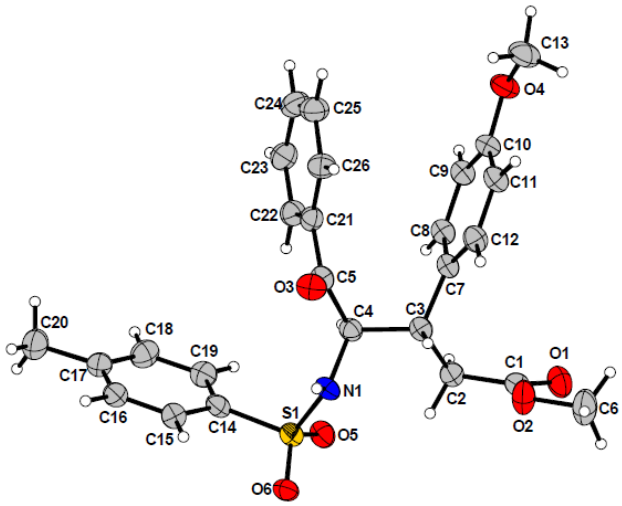


Figure 5.3

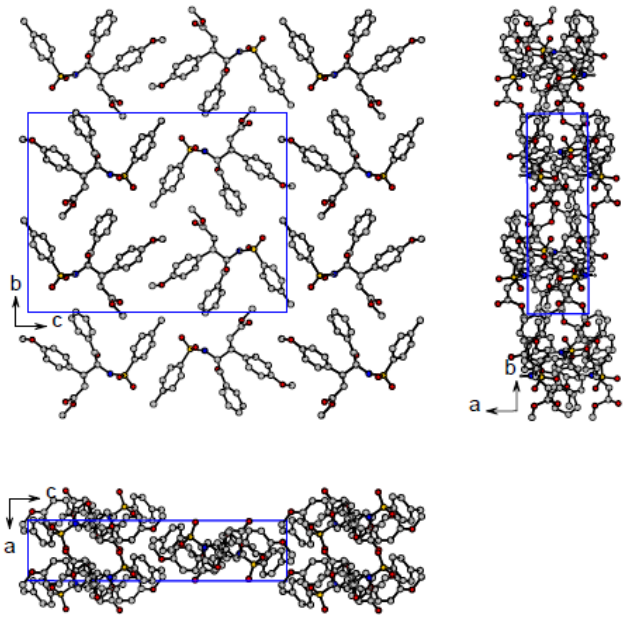


Figure 5.4

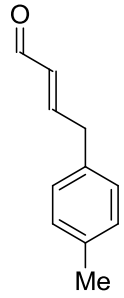
3. ENANTIOSELECTIVE ORGANOCATALYTIC FORMAL [2+2] CYCLOADDITION REACTION.

3.1. Preparation of γ-aryl substituted α,β-unsaturated aldehydes 1p-u.

General procedure:

Aldehydes **1p-u** were synthesized following modified procedure previously reported[5] starting from 3,4-epoxy-1-butene to obtain the corresponding allylic alcohols. These alcohols were oxidized to obtain the desired aldehydes adding PCC (1.5 eq.) to a solution of the allylic alcohol in CH_2Cl_2 at room temperature. The crude mixture was stirred for 2h, filtered through Celite and directly charged onto silica gel and subjected to FC (*n*-hexane/AcOEt 8:2).

(*E*)-4-(*p*-Tolyl)but-2-enal (1q).



The aldehyde **1q** (760 mg, 4.74 mmol) was prepared according to the general procedure starting from the corresponding alcohol (940 mg, 5.79 mmol).

Yield: 82%.

^{1}H-NMR (δ, ppm) (300 MHz): 9.53 (d, *J* = 7.9 Hz, 1H, CHO), 7.20-7.04 (m, 4H, C_{arom}-H), 6.95 (dt, *J* = 15.5, 6.7 Hz, 1H, C**H**CH_2), 6.18-6.05 (m, 1H, CHOC**H**), 3.61 (d, *J* = 6.7 Hz, 2H, CH_2), 2.34 (s, 3H, CH_3).

[5] Zhao, Z.; Araldi, G. L.; Xiao, Y.; Reddy, A. P.; Liao, Y.; Karra, S.; Brugger, N.; Fischer, D.; Palmer, E. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 6572.

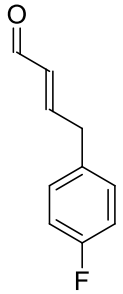
^{13}C-NMR (δ, ppm) (75.5 MHz): 193.8 (CO), 156.9 (**C**HCH$_2$), 136.5 (**C**$_{arom}$-C), 134.0 (**C**$_{arom}$-C), 133.3 (CHO**C**H), 129.5 (C$_{arom}$-H), 128.7 (C$_{arom}$-H), 38.6 (CH$_2$), 21.0 (CH$_3$).

IR (neat) cm^{-1}: 2818 (CHO), 2736 (CHO), 1687 (CO).

MS (CI) m/z (%): 160 (85), 145 (86), 131 (100), 127 (28), 115 (74), 105 (23), 91 (68), 77 (27).

Elemental Analysis: Calcd. for C$_{11}$H$_{12}$O: C, 82.46; H, 7.55. Found: C, 82.08; H, 7.36.

(*E*)-4-(4-Fluorophenyl)but-2-enal (1r).



The aldehyde **1r** (564 mg, 3.44 mmol) was prepared according to the general procedure starting from the corresponding alcohol (830 mg, 4.99 mmol)

Yield: 69%.

^{1}H-NMR (δ, ppm) (300 MHz): 9.54 (d, *J* = 7.8 Hz, 1H, CHO), 7.23-6.86 (m, 5H, C$_{arom}$-H + C**H**CH$_2$), 6.09 (dd, *J* = 15.6, 7.8 Hz, 1H, CHOC**H**), 3.63 (d, *J* = 6.5 Hz, 2H, CH$_2$).

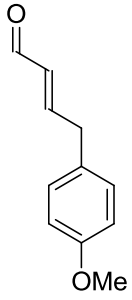
^{13}C-NMR (δ, ppm) (75.5 MHz): 193.6 (CO), 161.8 (d, J_{CF} = 245.5 Hz, C$_{arom}$-F), 156.0 (**C**HCH$_2$), 133.6 (CHO**C**H), 132.7 (d, $^{4}J_{CF}$ = 3.3 Hz, **C**$_{arom}$-C), 130.3 (d, $^{3}J_{CF}$ = 8.0 Hz, C$_{arom}$-H), 115.7 (d, $^{2}J_{CF}$ =21.4 Hz, C$_{arom}$-H), 38.1 (CH$_2$).

IR (neat) cm^{-1}: 2822 (CHO), 2739 (CHO), 1687 (CO).

MS (CI) m/z (%): 164 (67), 146 (13), 135 (100), 133 (67), 115 (49), 109 (65), 83 (23), 75 (7), 63 (8).

Elemental Analysis: Calcd. for $C_{10}H_9FO$: C, 73.16; H, 5.53; F, 11.57. Found: C, 61.78; H, 6.88; F, 11.36.

(*E*)-4-(4-Methoxyphenyl)but-2-enal (1t).



The aldehyde **1t** (707 mg, 4.01 mmol) was prepared according to the general procedure starting from the corresponding alcohol (953 mg, 5.35 mmol)

Yield: 75%.

^{1}H-NMR (δ, ppm) (300 MHz): 9.54 (d, *J* = 7.9 Hz, 1H, CHO), 7.10 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 7.03-6.81 (m, 3H, C_{arom}-H + C**H**CH_2), 6.10 (dd, *J* = 15.6, 7.9 Hz, 1H, CHOC**H**), 3.80 (s, 3H, CH_3O), 3.59 (d, *J* = 6.7 Hz, 2H, CH_2).

^{13}C-NMR (δ, ppm) (75.5 MHz): 193.9 (CO), 158.6 (**C**$_{arom}$-C), 157.1 (**C**HCH_2), 133.2 (CHO**C**H), 129.8 (C_{arom}-H), 128.9 (C_{arom}-C), 114.3 (C_{arom}-H), 55.3 (CH_3O), 38.1 (CH_2).

IR (neat) cm^{-1}: 2834 (CHO), 2738 (CHO), 1687 (CO).

MS (CI) m/z (%): 176 (100), 159 (79), 147 (62), 131 (29), 121 (34), 108 (30), 103 (29), 91 (45), 77 (40).

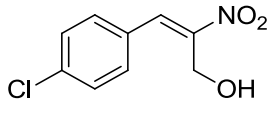
Elemental Analysis: Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.19; H, 6.48.

3.2 Preparation of α-hidroxymethylnitrostyrenes 29a-f.

General procedure:

To a solution of the corresponding nitroolefin (30 mmol) in THF (25 mL) at room temperature was added imidazole (30 mmol), benzoic acid (3 mmol) and formaldehyde (aq. solution 38%, 25 mL). The reaction mixture was allowed to stir at room temperature for 72 h. Then, the reaction was acidified with HCl (1M) and the aqueous layer was extracted with AcOEt (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/AcOEt gradient from 9:1 to 7:3) to afford pure α-hidroxymethylnitrostyrene **29**. Compounds **29a**, **29b** and **29d-29f** were prepared according to the general procedure and spectroscopic data were identical to those previously reported.[6]

(*E*)-3-(4-Chlorophenyl)-2-nitroprop-2-en-1-ol (29c).



Following the general procedure **29c** (180 mg, 0.96 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 7:3).

Yield: 62%.

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[6] Mohan, R.; Rastogi, N.; Namboothiri, I. N. N.; Mobin, S. M.; Panda, D. *Bioorg. Med. Chem.* **2006**, *14*, 8073.

^{1}H-NMR (δ, ppm) (300 MHz): 8.15 (s, 1H, C=CH), 7.60-7.36 (m, 4H, C_{arom}-H), 4.67 (d, *J* = 7.1 Hz, 2H, CH_2), 2.59 (t, *J* = 7.1 Hz, 1H, OH).

^{13}C-NMR (δ, ppm) (75.5 MHz): 149.6 (**C**=CH), 137.4 (C_{arom}-Cl), 136.4 (C=**C**H), 131.5 (C_{arom}-C), 129.7 (C_{arom}-H), 129.5 (C_{arom}-H), 56.6 (CH_2).

IR (KBr) cm^{-1}: 3441 (OH).

MS (CI) m/z (%): 213 (M^+), 166 (25), 150 (62), 137 (44), 131 (100), 125 (30), 115 (32), 102 (74), 89 (20), 77 (60), 75 (47), 63 (21).

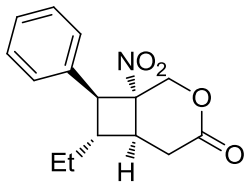
Elemental Analysis: Calcd. for $C_9H_8ClNO_3$: C, 50.60; H, 3.77; Cl, 16.60; N, 6.56. Found: C, 50.23; H, 3.67; Cl, 16.43; N, 6.58.

3.3 Synthesis of cyclobutane adducts 30a-l and 31a-l.

General procedure:

An ordinary vial equipped with a magnetic stirring bar was charged with catalyst **3a** (0.07 mmol), thiourea **32b** (0.07 mmol), α-hidroxymethylnitrostyrene **29** (0.52 mmol) and toluene (1.5 mL). Then, the reaction mixture was cooled to -20 ºC and a solution of the α,β-unsatured aldehyde **1** (0.35 mmol) in toluene (1 mL) was added. The stirring was maintained at -20 ºC for 3 days and the crude reaction mixture was concentrated and directly charged onto silica gel and subjected to flash chromatography. The isolated hemiacetal **30** was treated with PCC (3 eq.) in CH_2Cl_2 until completion of the reaction and the crude was directly subjected to flash chromatography (FC) affording the bicyclic adduct **31**. Racemic samples were obtained preparing an equimolecular mixture of both enantiomers of compounds **30**.

(1*R*,6*S*,7*S*,8*S*)-7-Ethyl-1-nitro-8-phenyl-3-oxabicyclo[4.2.0]octan-4-one (31a).



Following the general procedure **30a** (36 mg, 0.13 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 7:3) starting from aldehyde **1a** (141 μL, 1.22 mmol) and α-hidroxymethylnitrostyrene **29a** (63 mg, 0.35 mmol) in the presence of **3a** (23 mg, 0.07 mmol), diarylthiourea **32b** (35 mg, 0.07 mmol) and using toluene (2.5 mL) as solvent at 4ºC.

Yield: 38%.

Oxidation of **30a** according to the general procedure using PCC (84 mg, 0.39 mmol) afforded the bicyclic adduct **31a** (34 mg, 0.12 mmol).

Yield: 95%.

ee: 85%. Determined by HPLC using a Daicel Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min; τ_{major} = 9.27 min, τ_{minor} = 10.03 min.

^{1}H-NMR (δ, ppm) (300 MHz): 7.46-7.20 (m, 5H, C_{arom}-H), 4.46 (d, *J* = 12.6 Hz, 1H, C**H**$_a$H$_b$O), 4.25 (d, *J* = 12.6 Hz, 1H, CH$_a$**H**$_b$O), 3.87 (d, *J* = 9.3 Hz, 1H, $CHCNO_2$), 3.32-3.15 (m, 1H, C**H**CH_2CO), 2.99 (dd, *J* = 16.7, 6.2 Hz, 1H, C**H**$_a$H$_b$CO), 2.67 (dd, *J* = 16.7, 4.6 Hz, 1H, CH$_a$**H**$_b$CO), 2.36-2.19 (m, 1H, CHEt), 1.80–1.63 (m, 2H, CH_3 C**H**$_2$), 0.93 (t, *J* = 7.4 Hz, 3H, CH_3).

^{13}C-NMR (δ, ppm) (75.5 MHz): 169.6 (CO), 134.2 (C_{arom}-C), 128.9 8 (C_{arom}-H), 128.2 (C_{arom}-H), 127.8 (C_{arom}-H), 83.1 (CNO_2), 66.5 (CH_2O), 52.4 (**C**$HCNO_2$), 40.1 (CHEt), 38.7 (**C**HCH_2CO), 33.1 (**C**H_2CO), 28.6 (CH_3 **C**H_2), 11.3 (CH_3).

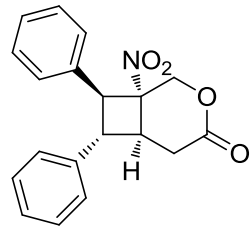
IR (neat) cm^{-1}: 1759 (CO), 1540 (NO_2), 1360 (NO_2).

MS (CI) m/z (%): 275 (1), 228 (6), 183 (6), 155 (6), 141 (11), 132 (100), 128 (21), 117 (83), 115 (28), 91 (33).

Elemental Analysis: Calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.27; H, 6.27; N, 5.32.

$[\alpha]_D^{20}$: +10.2 (*c* = 1.40, CH_2Cl_2).

(1*R*,6*S*,7*S*,8*S*)-1-Nitro-7,8-diphenyl-3-oxabicyclo[4.2.0]octan-4-one (31b).



Following the general procedure **30b** (97 mg, 0.30 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 7:3) starting from aldehyde **1p** (51 mg, 0.35 mmol) and α-hidroxymethylnitrostyrene **29a** (94 mg, 0.52 mmol) in the presence of **3a** (23 mg, 0.07 mmol), diarylthiourea **32b** (35 mg, 0.07 mmol) and using toluene (2.5 mL) as solvent.

Yield: 86%.

Oxidation of **30b** according to the general procedure using PCC (84 mg, 0.39 mmol) afforded the bicyclic adduct **31b** (94 mg, 0.29 mmol). In Figure 5.5 the X-ray structure is depicted.

Yield: 95%.

ee: 91%. Determined by HPLC using a Daicel Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min; τ_{major} = 15.17 min, τ_{minor} = 14.01 min.

^{1}H-NMR (δ, ppm) (300 MHz): 7.49-7.17 (m, 10H, C_{arom}-H), 4.61 (d, *J* = 12.7 Hz, 1H, C**H**$_a$H$_b$O), 4.49-4.32 (m, 2H, CH_2CHC**H** + CH_a**H**$_b$O), 3.81-3.65 (m, 1H, CHPh), 3.57-3.43 (m, 1H, C**H**CH_2CO), 3.08 (dd, *J* = 16.9, 6.2 Hz, 1H, C**H**$_a$H$_b$CO), 2.83 (dd, *J* = 17.0, 4.5 Hz, 1H, CH_a**H**$_b$CO).

^{13}C-NMR (δ, ppm) (75.5 MHz): 169.2 (CO), 139.8 (C_{arom}-C), 133.7 (C_{arom}-C), 129.2 (C_{arom}-H), 129.1 (C_{arom}-H), 128.5 (C_{arom}-H), 127.9 (C_{arom}-H), 127.7 (C_{arom}-H), 126.5 (C_{arom}-H), 82.9 (CNO_2), 66.4 (CH_2O), 53.4 (**C**$HCNO_2$), 42.8 (CH_2CH**C**H), 40.6 (**C**HCH_2CO), 32.9 (**C**H_2CO).

IR (KBr) cm^{-1}: 1755 (CO), 1540 (NO_2), 1361 (NO_2).

MS (CI) m/z (%): 277 (26), 231 (34), 218 (19), 217 (59), 180 (100), 179 (52), 178 (38), 165 (30), 141 (40), 117 (37), 115 (44), 91 (79).

Elemental Analysis: Calcd. for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.84; H, 5.57; N, 4.70.

$[\alpha]_D^{20}$: +38.3 (*c* = 0.55, CH_2Cl_2).

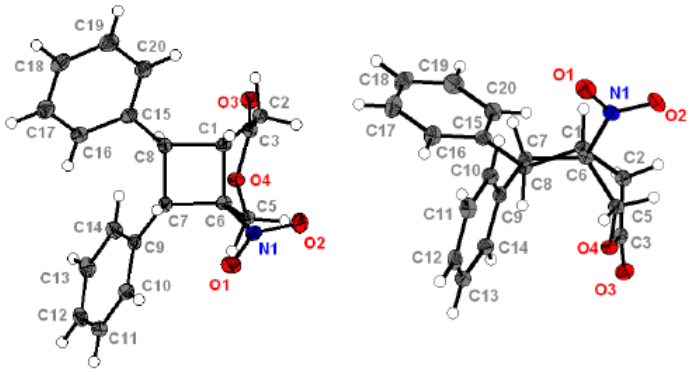
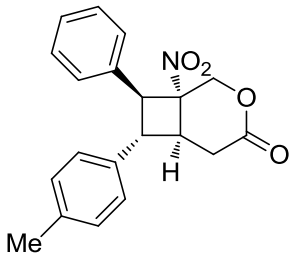


Figure 5.5

(1*R*,6*S*,7*S*,8*S*)-1-Nitro-8-phenyl-7-(*p*-tolyl)-3-oxabicyclo[4.2.0]octan-4-one (31c).



Following the general procedure **30c** (104 mg, 0.31 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 7:3) starting from aldehyde **1q** (56 mg, 0.35 mmol) and α-hidroxymethylnitrostyrene **29a** (93 mg, 0.52 mmol) in the presence of **3a** (23 mg, 0.07 mmol), diarylthiourea **32b** (35 mg, 0.07 mmol) and using toluene (2.5 mL) as solvent.

Yield: 88%.

Oxidation of **30c** according to the general procedure using PCC (200 mg, 0.93 mmol) afforded the bicyclic adduct **31c** (101 mg, 0.30 mmol).

Yield: 97%.

ee: 92%. Determined by HPLC using a Daicel Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min; τ_{major} = 16.73 min, τ_{minor} = 13.89 min.

^{1}H-NMR (δ, ppm) (300 MHz): 7.46-7.30 (m, 5H, C_{arom}-H), 4.61 (d, *J* = 12.7 Hz, 1H, C**H**$_a$H$_b$O), 4.49-4.32 (m, 2H, CH_2CHCH + CH_aH_bO), 3.78-3.62 (m, 1H, CHPh), 3.45 (t, *J* = 9.2 Hz, 1H, C**H**CH_2CO), 3.06 (dd, *J* = 17.0, 6.3 Hz, 1H, C**H**$_a$H$_b$CO), 2.81 (dd, *J* = 16.8, 4.2 Hz, 1H, CH_aH_bCO), 2.34 (s, 3H, CH_3).

^{13}C-NMR (δ, ppm) (75.5 MHz): 169.3 (CO), 137.7 (C_{arom}-C), 136.8 (C_{arom}-C), 133.8 (C_{arom}-C), 129.8 (C_{arom}-H), 129.1 (C_{arom}-H), 128.4 (C_{arom}-H), 127.6 (C_{arom}-H), 126.4 (C_{arom}-H), 82.9 (CNO_2), 66.4 (CH_2O), 53.4 (**C**$HCNO_2$), 42.7 (CH_2CH**C**H), 40.7 (**C**HCH_2CO), 32.8 (**C**H_2CO), 21.0 (CH_3).

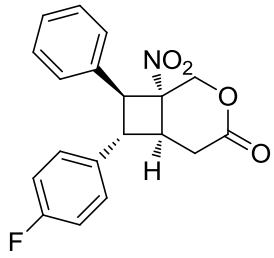
IR (neat) cm^{-1}: 1763 (CO), 1540 (NO_2), 1360 (NO_2).

MS (CI) m/z (%): 337 (3), 291 (31), 245 (58), 232 (30), 231 (100), 194 (54), 179 (58), 178 (62), 155 (94), 141 (61), 131 (59), 128 (37), 119 (66), 115 (65), 105 (92), 91 (88).

Elemental Analysis: Calcd. for $C_{20}H_{19}NO_4$: C, 70.20; H, 5.68; N, 4.15. Found: C, 69.84; H, 5.97; N, 3.80.

$[\alpha]_D^{20}$: +29.3 (*c* = 0.55, CH_2Cl_2).

(1*R*,6*S*,7*S*,8*S*)-7-(4-Fluorophenyl)-1-nitro-8-phenyl-3-oxabicyclo[4.2.0]octan-4-one (31d).



Following the general procedure **30d** (92 mg, 0.27 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 7:3) starting from aldehyde **1r** (57 mg, 0.35 mmol) and α-hidroxymethylnitrostyrene **29a** (94 mg, 0.52 mmol) in the presence of **3a** (23 mg, 0.07 mmol), diarylthiourea **32b** (35 mg, 0.07 mmol) and using toluene (2.5 mL) as solvent.

Yield: 77%.

Oxidation of **30d** according to the general procedure using PCC (174 mg, 0.81 mmol) afforded the bicyclic adduct **31d** (88 mg, 0.26 mmol).

Yield: 98%.

ee: 92%. Determined by HPLC using a Daicel Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min; τ_{major} = 17.46 min, τ_{minor} = 16.09 min.

^{1}H-NMR (δ, ppm) (300 MHz): 7.51-7.15 (m, 7H, C_{arom}-H), 7.05 (t, J = 8.6 Hz, 2H, C_{arom}-H), 4.61 (d, J = 12.7 Hz, 1H, C**H**$_a$H$_b$O), 4.49-4.29 (m, 2H, CH_2CHCH + CH_aH_bO), 3.79-3.63 (m, 1H, CHPh), 3.48 (t, J = 9.2 Hz, 1H, C**H**CH_2CO), 3.07 (dd, J = 16.9, 6.1 Hz, 1H, C**H**$_a$H$_b$CO), 2.82 (dd, J = 16.9, 4.3 Hz, 1H, CH_aH_bCO).

^{13}C-NMR (δ, ppm) (75.5 MHz): 169.1 (CO), 162.3 (d, J_{CF} = 247.3 Hz, C_{arom}-F), 135.6 (d, $^4J_{CF}$ = 3.3 Hz, C_{arom}-C), 133.4 (C_{arom}-C), 129.2 (C_{arom}-H), 128.6 (C_{arom}-H), 128.2 (d, $^3J_{CF}$ = 8.1 Hz, C_{arom}-H), 127.6 (C_{arom}-H), 116.0 (d, $^2J_{CF}$ = 21.6 Hz, C_{arom}-H), 82.8 (CNO_2), 66.2 (CH_2O), 53.7 (**C**$HCNO_2$), 42.1 (CH_2CH**C**H), 40.9 (**C**HCH_2CO), 32.8 (**C**H_2CO).

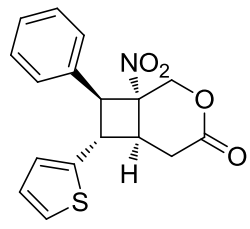
IR (neat) cm^{-1}: 1759 (CO), 1541 (NO_2), 1362 (NO_2).

MS (CI) m/z (%): 295 (52), 249 (30), 235 (54), 198 (81), 197 (47), 183 (30), 159 (28), 135 (48), 133 (53), 123 (48), 109 (100), 91 (46).

Elemental Analysis: Calcd. for $C_{19}H_{16}FNO_4$: C, 66.86; H, 4.72; N, 4.10. Found: C, 66.49; H, 4.98; N, 4.38.

$[\alpha]_D^{20}$: +33.2 (c = 0.80, CH_2Cl_2).

(1*R*,6*S*,7*S*,8*S*)-1-Nitro-8-phenyl-7-(thiophen-2-yl)-3-oxabicyclo[4.2.0]octan-4-one (31e).



Following the general procedure **30e** (82 mg, 0.25 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 7:3) starting from aldehyde **1s** (54 mg, 0.35 mmol) and α-hidroxymethylnitrostyrene **29a** (95 mg, 0.52 mmol) in the presence of **3a** (23 mg, 0.07 mmol), diarylthiourea **32b**

(35 mg, 0.07 mmol) and using toluene (2.5 mL) as solvent.

Yield: 73%.

Oxidation of **30e** according to the general procedure using PCC (162 mg, 0.75 mmol) afforded the bicyclic adduct **31e** (79 mg, 0.24 mmol).

Yield: 95%.

ee: 89%. Determined by HPLC using a Daicel Chiralpak IA column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min; τ_{major} = 9.34 min, τ_{minor} = 8.81 min.

^{1}H-NMR (δ, ppm) (300 MHz): 7.50–7.28 (m, 5H, C_{arom}-H), 7.26-7.22 (m, 1H, C_{thien}-H), 6.98 (d, *J* = 3.3 Hz, 2H, C_{thien}-H), 4.60 (d, *J* = 12.7 Hz, 1H, C**H**$_a$H$_b$O), 4.48-4.35 (m, 2H, CH_2CHC**H** + CH_a**H**$_b$O), 3.82-3.62 (m, 2H, C**H**CH_2CO + CHPh), 3.07 (dd, *J* = 17.1, 5.8 Hz, 1H, C**H**$_a$H$_b$CO), 2.83 (dd, *J* = 17.1, 4.0 Hz, 1H, CH_a**H**$_b$CO).

^{13}C-NMR (δ, ppm) (75.5 MHz): 168.9 (CO), 143.2 (C_{thien}-C), 133.1 (C_{arom}-C), 129.2 (C_{arom}-H), 128.5 (C_{arom}-H), 127.5 (C_{arom}-H), 127.4 (C_{arom}-H), 124.9 (C_{arom}-H), 124.6 (C_{arom}-H), 82.3 (CNO_2), 66.2 (CH_2O), 55.0 (**C**$HCNO_2$), 42.4 (CH_2CH**C**H), 38.6 (**C**HCH_2CO), 32.3 (**C**H_2CO).

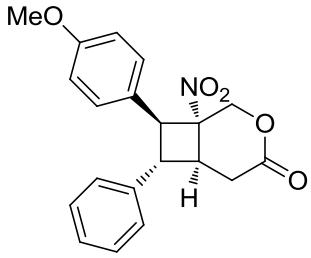
IR (neat) cm^{-1}: 1761 (CO), 1539 (NO_2), 1361 (NO_2).

MS (CI) m/z (%): 311 (14), 265 (11), 251 (25), 216 (43), 214 (100), 202 (13), 178 (59), 167 (11), 141 (25), 117 (35), 91 (44).

Elemental Analysis: Calcd. for $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59; N, 4.25; S, 9.74. Found: C, 62.25; H, 4.21; N, 4.07; S, 10.11.

$[\alpha]_D^{20}$: +28.2 (*c* = 1.00, CH_2Cl_2).

(1*R*,6*S*,7*S*,8*S*)-8-(4-Methoxyphenyl)-1-nitro-7-phenyl-3-oxabicyclo[4.2.0]octan-4-one (31f).



Following the general procedure **30f** (88 mg, 0.25 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 7:3) starting from aldehyde **1p** (52 mg, 0.35 mmol) and α-hidroxymethylnitrostyrene **29b** (107 mg, 0.52 mmol) in the presence of **4a** (23 mg, 0.07 mmol), diarylthiourea **32b** (35 mg, 0.07 mmol) and using toluene (2.5 mL) as solvent.

Yield: 72%.

Oxidation of **30f** according to the general procedure using PCC (160 mg, 0.74. mmol) afforded the bicyclic adduct **31f** (84 mg, 0.23 mmol).

Yield: 94%.

ee: 95%. Determined by HPLC using a Daicel Chiralpak AD-H column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min; τ_{major} = 14.11 min, τ_{minor} = 13.14 min.

^{1}H-NMR (δ, ppm) (300 MHz): 7.49-7.15 (m, 7H, C_{arom}-H), 6.93 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 4.59 (d, *J* = 12.7 Hz, 1H, C**H**$_a$H$_b$O), 4.42 (d, *J* = 12.6 Hz, 1H, CH$_a$**H**$_b$O), 4.32 (d, *J* = 10.1 Hz, 1H, CH_2CHC**H**), 3.88-3.65 (m, 4H, CH_3 + $CHCNO_2$), 3.44 (dd, *J* = 17.7, 8.5 Hz, 1H, C**H**CH_2CO), 3.07 (dd, *J* = 16.9, 6.1 Hz, 1H, C**H**$_a$H$_b$CO), 2.83 (dd, *J* = 17.0, 4.2 Hz, 1H, CH$_a$**H**$_b$CO).

^{13}C-NMR (δ, ppm) (75.5 MHz): 169.4 (CO), 159.7 (C_{arom}-C), 139.9 (C_{arom}-C), 129.1 (C_{arom}-H), 128.9 (C_{arom}-H), 127.8 (C_{arom}-C), 126.5 (C_{arom}-H), 125.5 (C_{arom}-H), 114.5 (C_{arom}-H), 83.0 (CNO_2), 66.4 (CH_2O), 55.3 (CH_3), 53.2 (**C**HCNO$_2$), 43.1 (CH_2CH**C**H), 40.3 (**C**HCH$_2$CO), 32.8 (**C**H$_2$CO).

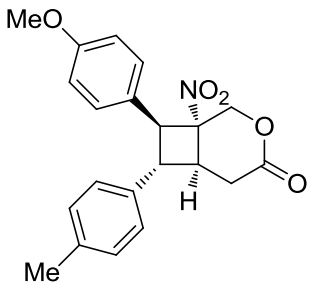
IR (neat) cm^{-1}: 1759 (CO), 1540 (NO_2), 1360 (NO_2).

MS (EI) m/z (%): 353 (1), 211 (17), 210 (100), 165 (12), 163 (10), 146 (10), 115 (9) 91 (11).

Elemental Analysis: Calcd. for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 68.98; H, 5.35; N, 4.16.

$[\alpha]_D^{20}$: +35.2 (*c* = 0.84, CH_2Cl_2).

(1*R*,6*S*,7*S*,8*S*)-8-(4-methoxyphenyl)-1-nitro-7-(p-tolyl)-3-oxabicyclo[4.2.0]octan-4-one (31g).



Following the general procedure **30g** (118 mg, 0.32 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 7:3) starting from aldehyde **1q** (55 mg, 0.35 mmol) and α-hidroxymethylnitrostyrene **29b** (108 mg, 0.52 mmol) in the presence of **3a** (23 mg, 0.07 mmol), diarylthiourea **32b** (35 mg, 0.07 mmol) and using toluene (2.5 mL) as solvent.

Yield: 91%.

Oxidation of **30g** according to the general procedure using PCC (207 mg, 0.96 mmol) afforded the bicyclic adduct **31g** (113 mg, 0.30 mmol).

Yield: 96%.

ee: 94%. Determined by HPLC using a Daicel Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min; τ_{major} = 28.15 min, τ_{minor} = 26.35 min.

^{1}H-NMR (δ, ppm) (300 MHz): 7.29 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 7.22-7.12 (m, 4H, C_{arom}-H), 6.92 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 4.59 (d, *J* = 12.6 Hz, 1H, C**H**$_a$H$_b$O), 4.41 (d, *J* = 12.7 Hz, 1H, CH$_a$**H**$_b$O), 4.29 (d, *J* = 10.0 Hz, 1H, C**H**CHCH$_2$), 3.81 (s, 3H, OCH_3), 3.76-3.65 (m, 1H, $CHCNO_2$), 3.51-3.33 (m, 1H, C**H**CH$_2$CO), 3.05 (dd, *J* = 16.9, 6.1 Hz, 1H, C**H**$_a$H$_b$CO), 2.81 (dd, *J* = 16.9, 4.4 Hz, 1H, CH$_a$**H**$_b$CO), 2.33 (s, 3H, CH_3).

^{13}C-NMR (δ, ppm) (75.5 MHz): 169.4 (CO), 159.6 (C_{arom}-C), 137.6 (C_{arom}-C), 136.8 (C_{arom}-C), 129.6 (C_{arom}-H), 128.8 (C_{arom}-H), 127.0 (C_{arom}-C), 126.4 (C_{arom}-H), 125.5 (C_{arom}-H), 114.4 (C_{arom}-H), 83.0 (CNO_2), 66.4 (CH_2O), 55.3 (OCH_3), 53.3 (**C**$HCNO_2$), 42.9 (**C**HCH$_2$), 40.4 (**C**H$_2$CO), 32.8 (**C**H$_2$CO), 21.0 (CH_3).

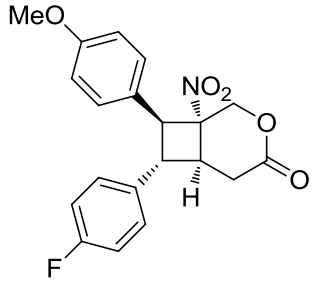
IR (neat) cm^{-1}: 1759 (CO), 1536 (NO_2), 1358 (NO_2).

MS (EI) m/z (%): 367 (1), 321 (10), 225 (18), 224 (100), 209 (10), 171 (14), 165 (14), 146 (12), 131 (14), 121 (13), 105 (12), 91 (6).

Elemental Analysis: Calcd. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.65; H, 5.39; N, 3.66.

$[\alpha]_D^{20}$: +36.3 (*c* = 1.00, CH_2Cl_2).

(1*R*,6*S*,7*S*,8*S*)-7-(4-Fluorophenyl)-8-(4-methoxyphenyl)-1-nitro-3-oxabicyclo[4.2.0]octan-4-one (31h).



Following the general procedure **30h** (118 mg, 0.32 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 7:3) starting from aldehyde **1r** (57 mg, 0.35 mmol) and α-hidroxymethylnitrostyrene **29b** (109 mg, 0.52 mmol) in the presence of **3a** (23 mg, 0.07 mmol), diarylthiourea **32b** (35 mg, 0.07 mmol) and using toluene (2.5 mL) as solvent.

Yield: 91%.

Oxidation of **30h** according to the general procedure using PCC (207 mg, 0.96 mmol) afforded the bicyclic adduct **31h** (113 mg, 0.30 mmol).

Yield: 96%.

ee: 94%. Determined by HPLC using a Daicel Chiralpak IA column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min; τ_{major} = 13.72 min, τ_{minor} = 11.65 min.

^{1}H-NMR (δ, ppm) (300 MHz): 7.37-7.19 (m, 4H, C_{arom}-H), 7.02 (dd, *J* = 17.0, 8.3 Hz, 2H, C_{arom}-H), 6.93 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 4.58 (d, *J* = 12.6 Hz, 1H, C**H**$_a$H$_b$O), 4.41 (d, *J* = 12.7 Hz, 1H, CH$_a$**H**$_b$O), 4.27 (d, *J* = 10.1 Hz, 1H, C**H**CHCH$_2$) 3.81 (s, 3H, OCH$_3$), 3.76-3.61 (m, 1H, CHCNO$_2$), 3.53-3.36 (m, 1H, C**H**CH$_2$CO), 3.05 (dd, *J* = 16.9, 6.1 Hz, 1H, C**H**$_a$H$_b$CO), 2.81 (dd, *J* = 17.0, 4.3 Hz, 1H, CH$_a$**H**$_b$CO).

^{13}C-NMR (δ, ppm) (75.5 MHz): 169.3 (CO), 162.2 (d, J_{CF} = 246.8 Hz, C_{arom}-F), 159.7 (C_{arom}-C), 135.7 (d, $^{4}J_{CF}$ = 3.0 Hz, C_{arom}-C), 128.9 (C_{arom}-H), 128.2 (d, $^{3}J_{CF}$ = 8.1 Hz, C_{arom}-H), 125.2 (C_{arom}-C), 115.9 (d, $^{2}J_{CF}$ = 21.6 Hz, C_{arom}-H), 114.5 (C_{arom}-H), 82.9 (CNO_2), 66.2 (CH_2O), 55.3 (CH_3), 53.5 (**C**HCNO$_2$), 42.4 (**C**HCHCH$_2$), 40.5 (**C**HCH$_2$CO), 32.7 (**C**H$_2$CO).

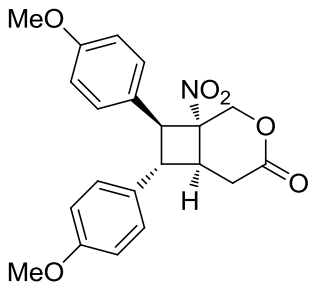
IR (neat) cm^{-1}: 1763 (CO), 1544 (NO_2), 1359 (NO_2).

MS (CI) m/z (%): 371 (1), 229 (16), 228 (100), 213 (11), 163 (13), 146 (14), 135 (10), 109 (13).

Elemental Analysis: Calcd. for $C_{20}H_{18}FNO_5$: C, 64.69; H, 4.89; N, 3.77. Found: C, 64.79; H, 4.96; N, 3.55.

$[\alpha]_D^{20}$: +35.3 (*c* = 0.80, CH_2Cl_2).

(1*R*,6*S*,7*S*,8*S*)-7,8-bis(4-Methoxyphenyl)-1-nitro-3-oxabicyclo[4.2.0]octan-4-one (31i).



Following the general procedure **30i** (122 mg, 0.32 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 7:3) starting from aldehyde **1t** (62 mg, 0.35 mmol) and α-hidroxymethylnitrostyrene **29b** (109 mg, 0.52 mmol) in the presence of **3a** (23 mg, 0.07 mmol), diarylthiourea **32b** (35 mg, 0.07 mmol) and using toluene (2.5 mL) as solvent.

Yield: 90%.

Oxidation of **30i** according to the general procedure using PCC (206 mg, 0.96 mmol) afforded the bicyclic adduct **31i** (117 mg, 0.31 mmol).

Yield: 97%.

ee: 94%. Determined by HPLC using a Daicel Chiralpak AS-H column, *n*-hexane/*i*-PrOH 60:40, flow rate 0.50 mL/min; τ_{major} = 142.92 min, τ_{minor} = 60.31 min.

^{1}H-NMR (δ, ppm) (300 MHz): 7.34-7.10 (m, 4H, C_{arom}-H), 6.98-6.81 (m, 4H, C_{arom}-H), 4.59 (d, *J* = 12.5 Hz, 1H, C**H**$_a$H$_b$O), 4.41 (d, *J* = 12.7 Hz, 1H, CH$_a$**H**$_b$O), 4.27 (d, *J* = 9.9 Hz, 1H, C**H**CHCH$_2$), 3.84-3.76 (m, 6H, OCH_3 + OCH_3), 3.73-3.62 (m, 1H, $CHCNO_2$), 3.42-3.31 (m, 1H, C**H**CH_2CO), 3.04 (dd, *J* = 17.0, 6.1 Hz, 1H, C**H**$_a$H$_b$CO), 2.80 (dd, *J* = 17.0, 4.2 Hz, 1H CH$_a$**H**$_b$CO).

^{13}C-NMR (δ, ppm) (75.5 MHz): 169.5 (CO), 159.6 (C_{arom}-C), 159.2 (C_{arom}-C), 131.9 (C_{arom}-C), 128.9 (C_{arom}-H), 127.7 (C_{arom}-H), 125.6 (C_{arom}-C), 114.5 (C_{arom}-H), 114.4 (C_{arom}-H), 82.9 (CNO_2), 66.4 (CH_2O), 55.4 (CH_3), 55.3 (CH_3), 53.6 (**C**$HCNO_2$), 42.7 (C**H**$CHCH_2$), 40.6 (**C**HCH_2CO), 32.7 (**C**H_2CO).

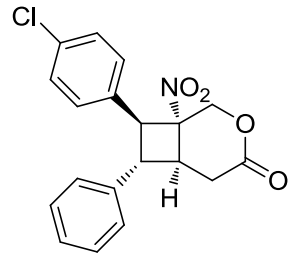
IR (neat) cm^{-1}: 1759 (CO), 1540 (NO_2), 1360 (NO_2).

MS (CI) m/z (%): 383 (12), 337 (29), 241 (17), 240 (98), 225 (44), 171 (100), 147 (35), 135 (45), 121 (91), 115 (15), 91 (12).

Elemental Analysis: Calcd. for $C_{21}H_{21}NO_6$: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.49; H, 5.73; N, 3.96.

$[\alpha]_D^{20}$: +42.7 (*c* = 1.00, CH_2Cl_2).

(1*R*,6S,7S,8S)-8-(4-Chlorophenyl)-1-nitro-7-phenyl-3-oxabicyclo[4.2.0]octan-4-one (31j).



Following the general procedure **30j** (82 mg, 0.23 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 7:3) starting from aldehyde **1p** (51 mg, 0.35 mmol) and α-hidroxymethylnitrostyrene **29c** (111 mg, 0.52 mmol) in the presence of **3a** (23 mg, 0.07 mmol), diarylthiourea **32b** (35 mg, 0.07 mmol) and using toluene (2.5 mL) as solvent.

Yield: 67%.

Oxidation of **30j** according to the general procedure using PCC (151 mg, 0.70 mmol) afforded the bicyclic adduct **31j** (81 mg, 0.22 mmol).

Yield: 97%.

ee: 92%. Determined by HPLC using a Daicel Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min; τ_{major} = 22.59 min, τ_{minor} = 17.75 min.

^{1}H-NMR (δ, ppm) (300 MHz): 7.47-7.21 (m, 9H, C_{arom}-H), 4.59 (d, *J* = 12.6 Hz, 1H, C**H**$_a$H$_b$O), 4.46-4.33 (m, 2H, CH_2CHC**H** + CH_aH_bO), 3.81-3.58 (m, 1H, $CHCNO_2$), 3.51-3.36 (m, 1H, C**H**CH_2CO), 3.08 (dd, *J* = 17.0, 5.9 Hz, 1H, C**H**$_a$H$_b$CO), 2.85 (dd, *J* = 17.0, 4.1 Hz, 1H, CH_a**H**$_b$CO).

^{13}C-NMR (δ, ppm) (75.5 MHz): 169.0 (CO), 139.4 (C_{arom}-C), 134.5 (C_{arom}-C), 132.1 (C_{arom}-C), 129.4 (C_{arom}-H), 129.1 (C_{arom}-H), 129.1 (C_{arom}-H), 127.9 (C_{arom}-H), 126.4 (C_{arom}-H), 82.7 (CNO_2), 66.2 (CH_2O), 52.8 (**C**$HCNO_2$), 42.7 (CH_2CH**C**H), 40.7 (**C**HCH_2CO), 32.7 (**C**H_2CO).

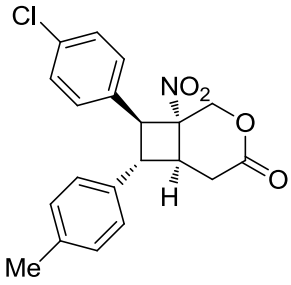
IR (neat) cm^{-1}: 1763 (CO), 1540 (NO_2), 1360 (NO_2).

MS (CI) m/z (%): 214 (81), 178 (100), 176 (18), 152 (10), 89 (22), 76 (18).

Elemental Analysis: Calcd. for $C_{19}H_{16}ClNO_4$: C, 63.78; H, 4.51; Cl, 9.91; N, 3.91. Found: C, 64.18; H, 4.21; Cl, 10.29; N, 3.57.

$[\alpha]_D^{20}$: +40.3 (*c* = 1.00, CH_2Cl_2).

(1*R*,6*S*,7*S*,8*S*)-8-(4-Chlorophenyl)-1-nitro-7-(*p*-tolyl)-3-oxabicyclo[4.2.0]octan-4-one (31k).



Following the general procedure **30k** (89 mg, 0.24 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 7:3) starting from aldehyde **1q** (56 mg, 0.35 mmol) and α-hidroxymethylnitrostyrene **29c** (112 mg, 0.52 mmol) in the presence of **3a** (23 mg, 0.07 mmol), diarylthiourea **32b** (35 mg, 0.07 mmol) and using toluene (2.5 mL) as solvent.

Yield: 69%.

Oxidation of **30k** according to the general procedure using PCC (156 mg, 0.73 mmol) afforded the bicyclic adduct **31k** (88 mg, 0.23 mmol).

Yield: 98%.

ee: 94%. Determined by HPLC using a Daicel Chiralpak AD-H column, *n*-hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min; τ_{major} = 13.13 min, τ_{minor} = 10.94 min.

^{1}H-NMR (δ, ppm) (300 MHz): 7.45-7.28 (m, 4H, C_{arom}-H), 7.22-7.11 (m, 4H, C_{arom}-H), 4.59 (d, *J* = 12.6 Hz, 1H, C**H**$_a$H$_b$O), 4.37-4.29 (m, 2H, CH_2CHCH + CH_aH_bO), 3.77-3.63 (m, 1H, $CHCNO_2$), 3.47-3.32 (m, 1H, C**H**CH_2CO), 3.06 (dd, *J* = 17.0, 6.0 Hz, 1H, C**H**$_a$H$_b$CO), 2.83 (dd, *J* = 17.0, 4.2 Hz, 1H, CH_a**H**$_b$CO), 2.34 (s, 3H, CH_3).

^{13}C-NMR (δ, ppm) (75.5 MHz): 169.1 (CO), 137.8 (C_{arom}-C), 136.4 (C_{arom}-C), 134.5 (C_{arom}-C), 132.2 (C_{arom}-C), 129.8 (C_{arom}-H), 129.4 (C_{arom}-H), 129.1 (C_{arom}-H), 126.4 (C_{arom}-H), 82.7 (CNO_2), 66.3 (CH_2O), 52.9 (**C**$HCNO_2$), 42.6 (CH_2CHCH), 40.9 (**C**HCH_2CO), 32.7 (**C**H_2CO), 21.0 (CH_3).

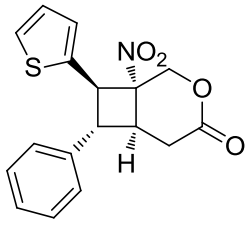
IR (neat) cm^{-1}: 1763 (CO), 1540 (NO_2), 1362 (NO_2).

MS (CI) m/z (%): 371 (6), 325 (30), 279 (36), 265 (69), 228 (92), 215 (35), 191 (30), 178 (99), 165 (27), 155 (86), 131 (92), 125 (88), 119 (98), 105 (100), 91 (40).

Elemental Analysis: Calcd. for $C_{20}H_{18}ClNO_4$: C, 64.61; H, 4.88; N, 3.77. Found: C, 64.88; H, 5.01; N, 4.10.

$[\alpha]_D^{20}$: +60.9 (*c* = 1.00, CH_2Cl_2).

(1*R*,6*S*,7*S*,8*R*)-1-Nitro-7-phenyl-8-(thiophen-2-yl)-3-oxabicyclo[4.2.0]octan-4-one (31l).



Following the general procedure **30l** (59 mg, 0.18 mmol) was isolated by FC (*n*-hexane/AcOEt gradient from 9:1 to 7:3) starting from aldehyde **1p** (50 mg, 0.35 mmol) and α-hidroxymethylnitrostyrene **29e** (80 mg, 0.52 mmol) in the presence of **3a** (23 mg, 0.07 mmol), diarylthiourea

32b (35 mg, 0.07 mmol) and using toluene (2.5 mL) as solvent.

Yield: 52%.

Oxidation of **30l** according to the general procedure using PCC (116 mg, 0.54 mmol) afforded the bicyclic adduct **31l** (58 mg, 0.17 mmol).

Yield: 97%.

ee: 94%. Determined by HPLC using a Daicel Chiralpak AD-H column, *n*-hexane/*i*-PrOH 85:15, flow rate 1.00 mL/min; τ_{major} = 13.13 min, τ_{minor} = 12.14 min.

^{1}H-NMR (δ, ppm) (300 MHz): 7.45-7.22 (m, 6H, C_{arom}-H), 7.17-6.99 (m, 2H, C_{arom}-H), 4.63 (d, *J* = 12.7 Hz, 1H, C**H**$_a$H$_b$O), 4.56 (d, *J* = 12.7 Hz, 1H, CH$_a$**H**$_b$O), 4.49 (d, *J* = 9.9 Hz, 1H, CH_2CHC**H**), 3.85-3.62 (m, 1H, $CHCNO_2$), 3.51-3.28 (m, 1H, C**H**CH_2CO), 3.09 (dd, *J* = 17.0, 6.2 Hz, 1H, C**H**$_a$H$_b$CO), 2.83 (dd, *J* = 17.0, 4.4 Hz, 1H, CH$_a$**H**$_b$CO).

^{13}C-NMR (δ, ppm) (75.5 MHz): 169.0 (CO), 139.1 (C_{thien}-C), 136.2 (C_{arom}-C), 129.1 (C_{arom}-H), 128.0 (C_{arom}-H), 127.8 (C_{arom}-H), 126.8 (C_{arom}-H), 126.5 (C_{arom}-H), 126.3 (C_{arom}-H), 82.7 (CNO_2), 66.5 (CH_2O), 49.5 (**C**$HCNO_2$), 45.8 (CH_2CH**C**H), 40.5 (C**H**CH_2CO), 32.8 (**C**H_2CO).

IR (neat) cm^{-1}: 1759 (CO), 1544 (NO_2), 1357 (NO_2).

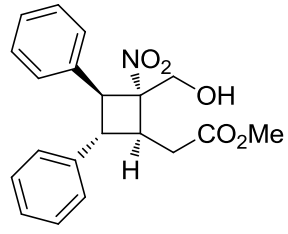
MS (CI) m/z (%): 283 (46), 186 (100), 171 (13), 152 (18), 141 (23), 115 (26), 105 (17), 97 (22), 91 (24), 77 (10).

Elemental Analysis: Calcd. for $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59; N, 4.25; S, 9.74. Found: C, 61.74; H, 4.51; N, 4.47; S, 9.61.

$[\alpha]_D^{20}$: +34.5 (*c* = 0.73, CH_2Cl_2).

3.4. Methanolysis of adduct 31b. Synthesis of compound 35.

(1'*S*,2'*R*,3'*S*,4'*S*)-Methyl 2-(2-hydroxymethyl-2-nitro-3,4-diphenylcyclobutyl)acetate(35).



A round bottom flask under inert atmosphere equipped with a magnetic stirring bar was charged with adduct **31b** (81 mg, 0.25 mmol) in 8 mL of MeOH. Then K_2CO_3 (35 mg, 0.25 mmol) was added. The reaction was stirred at room temperature for 10 min and the crude mixture was evaporated. Then CH_2Cl_2 (4 mL) and H_2O (4 mL) were added to the crude mixture, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were evaporated yielding cyclobutane **35** without further purification (87 mg, 0.25 mmol).

Yield: >99%.

^{1}H-NMR (δ, ppm) (300 MHz): 7.48-7.15 (m, 10H, C_{arom}-H), 4.36 (d, *J* = 10.5 Hz, 1H, $CHCNO_2$), 4.02 (d, *J* = 13.3 Hz, 1H, C**H**$_a$H$_b$O), 3.89 (dd, *J* = 13.2, 6.9 Hz, 1H, CH$_a$**H**$_b$O), 3.78-3.63 (m, 1H, C**H**CH_2CO), 3.53 (s, 3H, CH_3), 3.46 (t, *J* = 10.4 Hz, 1H, CH_2CHC**H**), 2.90 (dd, *J* = 15.9, 9.5 Hz, 1H, C**H**$_a$H$_b$CO), 2.70 (dd, *J* = 15.9, 5.8 Hz, 1H, CH$_a$**H**$_b$CO), 2.22 (bs, 1H, OH).

^{13}C-NMR (δ, ppm) (75.5 MHz): 171.9 (CO), 139.4 (C_{arom}-C), 134.2 (C_{arom}-C), 128.9 (C_{arom}-H), 128.8 (C_{arom}-H), 128.1 (C_{arom}-H), 127.6 (C_{arom}-H), 127.2 (C_{arom}-

H), 89.5 (CNO_2), 60.9 (CH_2O), 53.3 (CH_3), 51.8 (**C**HCNO$_2$), 44.9 (CH_2CH**C**H), 41.6 (**C**HCH$_2$CO), 34.4 (CH_2CO).

IR (neat) cm^{-1}: 3497 (OH), 1730 (CO), 1540 (NO_2), 1360 (NO_2).

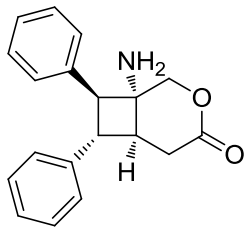
MS (CI) m/z (%): 279 (7), 219 (15), 205 (100), 178 (16), 141 (21), 117 (21), 91 (46).

Elemental Analysis: Calcd. for $C_{20}H_{21}O_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.92; H, 6.35; N, 3.57.

$[\alpha]_D^{20}$: +21.5 (*c* = 1.00, CH_2Cl_2).

3.5. Reduction of adduct 31b. Synthesis of compound 36.

(1*R*,6*S*,7*S*,8*S*)-1-Amino-7,8-diphenyl-3-oxabicyclo[4.2.0]octan-4-one (36).



Zn (340 mg, 5.25 mmol) was added in small portions to a solution of nitrocompound **31b** (67 mg, 0.21 mmol) in H_2O/AcOH (1:1, 8 mL) at 0 ºC. The reaction mixture was stirred for 4h at room temperature, then filtered, and the filtrate was adjusted to pH 7 with KOH (4M). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4 and the solvent was removed in vacuo. Compound **36** (48 mg, 0.16 mmol) was isolated after purification by flash column chromatography (CH_2Cl_2/MeOH 1:1).

Yield: 78%.

^{1}H-NMR (δ, ppm) (300 MHz): 7.43-7.01 (m, 12H, C_{arom}-H), 4.10 (d, *J* = 11.9 Hz, 1H, C**H**$_a$H$_b$O), 3.87 (d, *J* = 12.0 Hz, 1H, CH$_a$**H**$_b$O), 3.67 (d, *J* = 10.2 Hz,

1H, $CHCNH_2$), 3.38 (dd, *J* = 9.6, 8.6 Hz, 1H, $CH_2CHC\mathbf{H}$), 2.96 (dd, *J* = 16.6, 6.5 Hz, 1H, $C\mathbf{H}_aH_bCO$), 2.71 (dd, *J* = 16.5, 4.8 Hz, 1H, $CH_a\mathbf{H}_bCO$), 2.65-2.55 (m, 1H,$C\mathbf{H}CH_2CO$), 2.37 (s, 2H, NH_2).

^{13}C-NMR (δ, ppm) (75.5 MHz): 171.9 (CO), 142.2 (C_{arom}-C), 136.9 (C_{arom}-C), 128.8 (C_{arom}-H), 128.7 (C_{arom}-H), 127.2 (C_{arom}-H), 127.0 (C_{arom}-H), 126.9 (C_{arom}-H), 126.4 (C_{arom}-H), 71.4 (CH_2O), 56.8 (CNH_2), 54.4 ($\mathbf{C}HCNH_2$), 45.6 ($\mathbf{C}HCH_2CO$), 43.4 ($CH_2CH\mathbf{C}H$), 33.5 ($\mathbf{C}H_2CO$).

IR (neat) cm^{-1}: 3368 (NH), 3367 (NH), 1738 (CO).

MS (CI) m/z (%): 293 (1), 180 (100), 178 (33), 165 (26), 76 (5), 28 (11).

Elemental Analysis: Calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.50; H, 6.89; N, 5.15.

$[\alpha]_D^{20}$: +29.4 (*c* = 0.65, CH_2Cl_2).

Appendix

Abbreviations, acronyms and symbols

Å	Angstron
Ac	Acetyl / Acetilo
AcOEt	Ethyl acetate / Acetato de etilo
AcOH	Acetic acid / Ácido acético
Ac_2O	Acetic anhidride / Anhídrido acético
aq.	Aqueous / Acuoso
Ar	Aryl / Arilo
ASTM	American Society for Testing and Materials
Bn	Benzyl
Boc	*tert*-butoxycarbonyl / *tert*-butoxicarbonilo
bs	Broad signal
Bz	Benzoyl
c	Concentration (g/100 mL)
ºC	Degree Celsius / Grado Celsius
CD	Compact disk
C_{arom}	Aromatic carbon
C_{fur}	Carbon (furyl)
C_{thien}	Carbon (thienyl)
cat.	Catalizador
Cbz	Benzyloxycarbonyl / Benciloxicarbonilo
CI	Chemical ionization
cm	Centimeters
Conv.	Conversion
COSY	Homonuclear Correlation Spectroscopy
d	Doublet
dr	Diastereomeric ratio
D,L-Pro	D,L-Proline / D,L-Prolina

dm	decimeter
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	Double doublet
DEA	Diethylamine
DEPT	Distortionless Enhancement by Polarition Transfer
DMAP	*N*,*N*-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide / *N*,*N*-Dimetilformamida
DMSO	Dimethyl sulfoxide / Dimetilsulfóxido
e.d.	Exceso diastereomérico
e.e.	Exceso enantiomérico
E^+	Electrophile / Electrófilo
Ed.	Editor
ee	Enantiomeric excess
EI	Electron impact
eq.	Equivalent / Equivalente
Et	Ethyl
EtOH	Ethanol / Etanol
EWG	Electron withdrawing group / Grupo electroatractor
Fmoc	9-Fluorenylmethoxycarbonyl
FC	Flash chromatography
g	Gram
GC	Gas Chromatography
h	Hour / Hora
H_{arom}	Aromatic hidrogen
H_{fur}	Hidrogen (furyl)
H_{thien}	Hidrogen (thienyl)
HMPA	Hexamethyl phosphoramide / Hexametilfosforoamida
HOMO	Highest occupied molecular orbital / Orbital molecular ocupado de mayor energía
HPLC	High performance liquid chromatography

HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
***i*-Pr**	*iso*-Propyl
***i*-PrOH**	*iso*-Propanol / *iso*-Propanol
IR	Infrared
J	Coupling constant
K	Degree Kelvin
LAH	Lithium aluminium hydride
LiHMDS	lithium hexamethyldisilazide
L-Pro	L-Proline / L-Prolina
LUMO	Lowest unoccupied molecular orbital / Orbital molecular desocupado de menor energía
m	Multiplet or meter
M	Molar concentration
M.p.	Melting point
m/z	Mass to charge ratio
M^+	Molecular ion
Me	Methyl / Metilo
MeOH	Methanol / Metanol
mg	Miligram
MHz	Megahertz
min	Minute
mL	Mililiter
mm	Milimeter
mmol	Milimol / Milimol
MS	Molecular sieves or Mass spectrometry
n.d.	Not determined
NFSI	*N*-fluorobenzenesulfonimide
n.O.e.	Nuclear Overhauser Effect
***n*-Bu**	*n*-Butyl

nm	Nanometer
NMR	Nuclear magnetic resonace
NOESY	Nuclear Overhauser Effect Spectroscopy
NFSI	N-fluorobenzenesulfonimide
***n*-Pr**	*n*-Propyl
Nu^-	Nucleophile / Nucleófilo
OAc	Acetate / Acetato
Obs.	Observed
OTf	Triflate
PCC	Pyridinium chlorocromate
Ph	Phenyl / Fenilo
ppm	Parts per million
***p*-TSA**	*p*-Toluensulfonic acid / Ácido *p*-toluensulfónico
pyr	Pyridine
q	Quadruplet
R	Alkyl group or substituent / Grupo alquilo o sustituyente
r.d.	Relación diastereomérica
rac	Racemic
Rto.	Rendimiento
s	Singlet
sat.	Saturated aqueous solution
SOMO	Singly occupied molecular orbital
t	Triplet
T	Temperature / Temperatura
t.a.	Temperatura ambiente
rt	Room temperature
TBDMS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofurane / Tetrahidrofurano

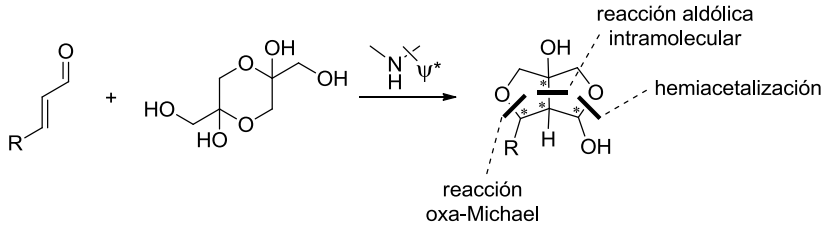
TLC	Thin layer chromatography
TMS	Trimethylsilyl / Trimetilsililo
$\mathbf{t_R}$	Retention time
Ts	Tosyl / Tosilo
X	Halogen
δ	Chemical shift
μ**L**	Microliter
μ**m**	Micrometer
$\tau_{\mathbf{major}}$	Retention time of major enantiomer
$\tau_{\mathbf{minor}}$	Retention time of minor enantiomer
ψ^*	Chiral scaffold / Resto quiral

Resumen extendido

En la presente memoria de investigación se recoge el trabajo realizado enfocado en el empleo de aminas secundarias quirales como organocatalizadores para el diseño de reacciones en cascada con el fin de obtener compuestos de interés con elevado rendimiento y control estereoquímico.

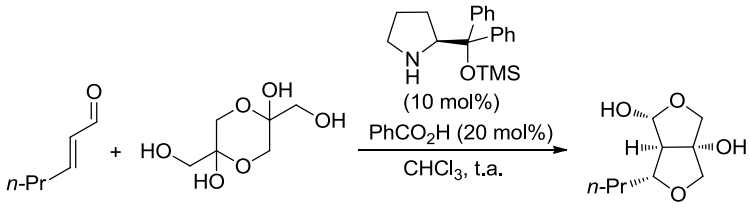
Las reacciones en cascada merecen una atención preferente como herramienta metodológica en síntesis orgánica, dado que conducen a la generación de moléculas con un elevado nivel de complejidad estructural de forma rápida y directa, partiendo de estructuras sencillas y minimizando el número de etapas de síntesis, evitando así los inherentes procesos de elaboración y purificación. Dentro de este campo de investigación, la organocatálisis se presenta como una potente alternativa y en particular, la aminocatálisis y su aplicación a procesos estereoselectivos en cascada iniciados por adiciones conjugadas es hasta la fecha uno de los campos que mayor crecimiento ha experimentado debido principalmente a la capacidad de estos aminocatalizadores para actuar mediante dos principales modos de activación: la denominada catálisis *via* iminio y la catálisis *via* enamina.

Una situación de especial interés la encontramos cuando se emplean sustratos basados en heteroátomos como dadores de Michael funcionalizados en un proceso aminocatalítico en cascada, permitiendo así la obtención de compuestos heterocíclicos de manera estereocontrolada. En este contexto, en primer lugar se ha puesto a punto una metodología para la síntesis de hexahidrofuro[3,4-*c*]furanos mediante una reacción en cascada aminocatalítica oxa-Michael/reacción aldólica/hemiaminalización entre aldehídos α,β-insaturados y dihidroxiacetona como dador de Michael funcionalizado (Esquema 1).



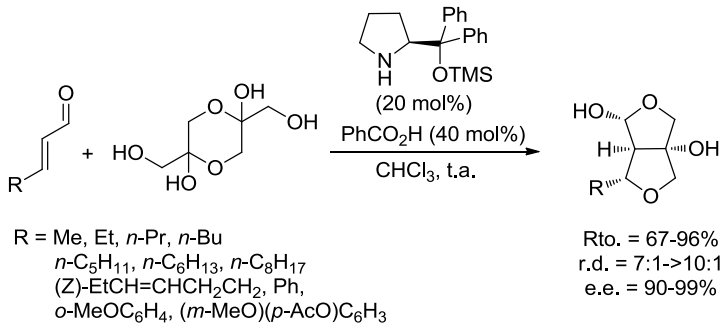
Esquema 1

Para ello, tras demostrar la viabilidad de la reacción y después de establecer un protocolo para la determinación del exceso enantiomérico de los aductos obtenidos, se ha llevado a cabo un proceso de optimización con el objetivo de encontrar las condiciones de reacción que proporcionasen los mejores resultados en cuanto a rendimiento y estereoselectividad con *trans*-2-hexenal como sustrato modelo empleando distintos aminocatalizadores, así como estudiando otras variables experimentales como son el uso de distintos co-catalizadores, el disolvente y la temperatura. Así, se han establecido como condiciones óptimas de reacción el empleo de *O*-TMS-difenilprolinol (10 mol%) como catalizador junto con ácido benzoico (20 mol%) como aditivo en $CHCl_3$ a temperatura ambiente (Esquema 2).



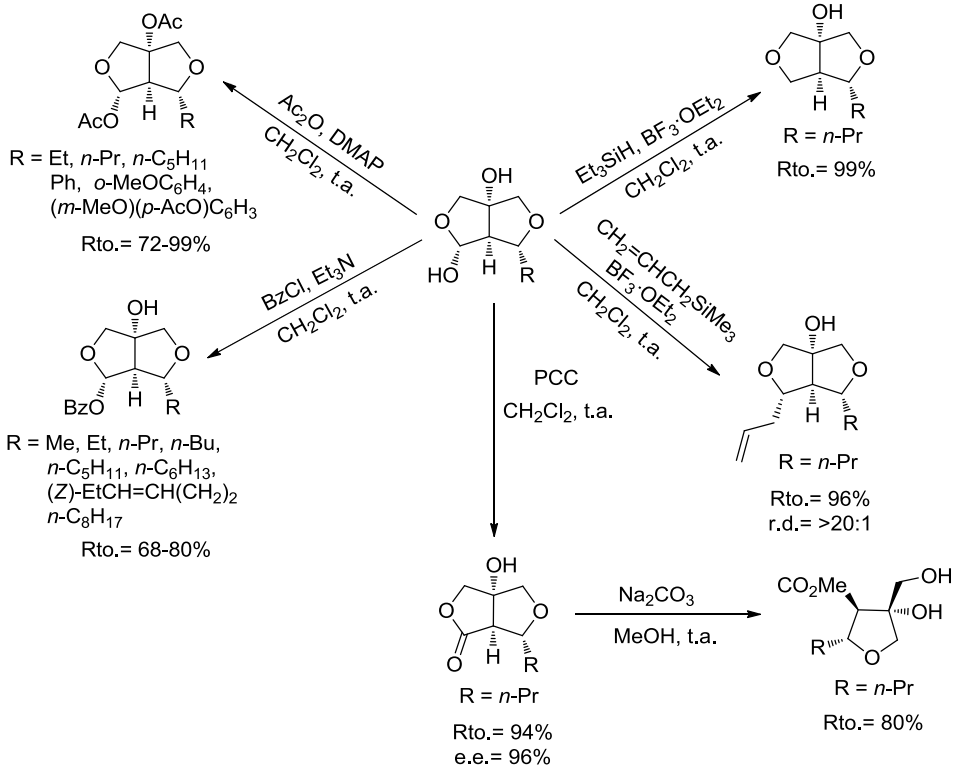
Esquema 2

Seguidamente, se estudió el alcance de la reacción empleando distintos aldehídos α,β-insaturados de diferente demanda estérica y electrónica, observando que la reacción transcurría de manera satisfactoria tanto con enales de cadena alquílica larga y corta, como con aromáticos. De esta manera, se ha sintetizado una amplia gama de furofuranos enantioenriquecidos de manera eficiente (Esquema 3).



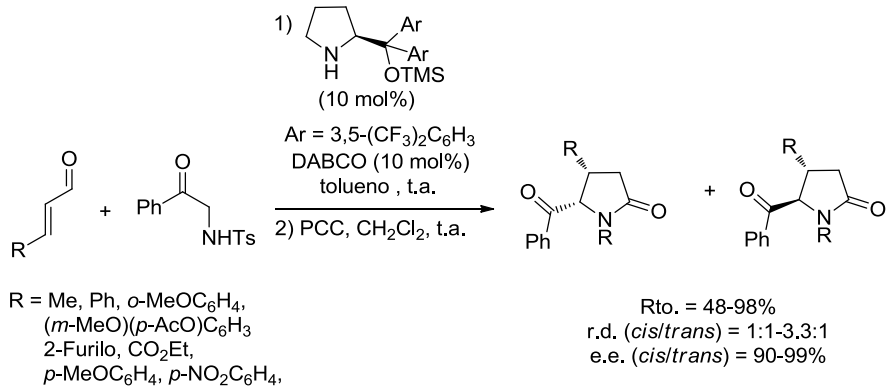
Esquema 3

Posteriormente, se realizó un estudio de la reactividad de los aductos obtenidos con el fin de demostrar sus posibles aplicaciones como *building blocks* quirales en síntesis orgánica (Esquema 4). En este sentido, se modificaron los grupos hidroxilo sometiendo los productos a condiciones de acetilación, obteniendo los correspondientes compuestos peracetilados con excelentes rendimientos. Asimismo, se llevó a cabo la protección selectiva del grupo hidroxilo hemiacetálico mediante una reacción de benzoilación bajo condiciones estándar, lo que nos permitió acceder a los aductos monoprotegidos de manera eficaz. Por otro lado, se estudió la reactividad de la función hemiacetálica sometiendo uno de los furofuranos tanto a condiciones oxidantes como reductoras. Así, obtuvimos la correspondiente lactona tras tratamiento con PCC en CH_2Cl_2 con excelente rendimiento y sin pérdida de pureza óptica. Ésta fue posteriormente transformada al correspondiente furano con un 80% de rendimiento mediante una reacción de metanolisis en condiciones básicas. Cuando se trató el furofurano con trietilsilano y $BF_3{\cdot}OEt_2$ en CH_2Cl_2 se obtuvo el biciclo correspondiente tras la reducción de la función hemiacetálica de manera cuantitativa. Finalmente, se realizó una reacción de alilación diastereocontrolada sobre el carbono anomérico, obteniendo así el compuesto deseado con excelente rendimiento y como un único diastereoisómero.



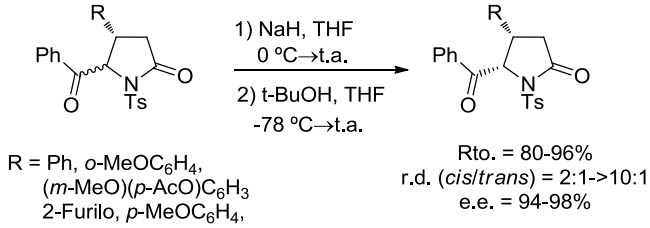
Esquema 4

Por otro lado, se pensó extender dicha estrategia al uso de α-aminoacetofenona frente a distintos aldehídos α,β-insaturados, observando en este caso un comportamiento distinto de dicha cetona como dador de Michael funcionalizado, obteniéndose los correspondientes hemiaminales mediante una reacción en cascada Michael/hemiaminalización que transcurre bajo catálisis *via* iminio en presencia de un derivado de prolinol sililado como catalizador. De esta manera, tras realizar el proceso de optimización con el fin de obtener los mejores resultados en cuanto a rendimiento y estereoselectividad empleando crotonaldehído como sustrato modelo, se extendió la metodología a otros aceptores de Michael para así obtener una serie de γ-lactamas, después de un segundo paso de oxidación, con excelentes rendimientos y excesos enantioméricos, aunque como mezclas de diastereoisómeros *cis* y *trans* (Esquema 5).



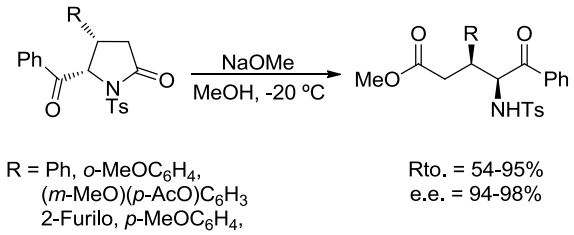
Esquema 5

Con intención de mejorar la relación diastereomérica de los aductos obtenidos, tras oxidar los hemiaminales obtenidos, se llevó a cabo un proceso de epimerización bajo condiciones básicas, desarrollando así un protocolo eficaz para la síntesis de γ-lactamas enantioenriquecidas (Esquema 6).



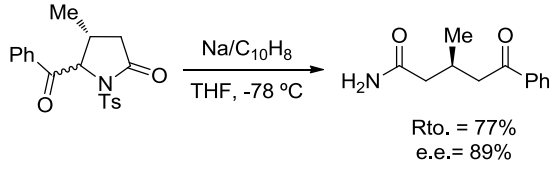
Esquema 6

Éstas fueron finalmente transformadas a distintos compuestos 1,5-dicarbonílicos, llevando a cabo por un lado una reacción de metanolisis a baja temperatura para obtener los correspondientes γ-amino-δ-cetoésteres con rendimientos de moderados a buenos sin pérdida de pureza óptica (Esquema 7).



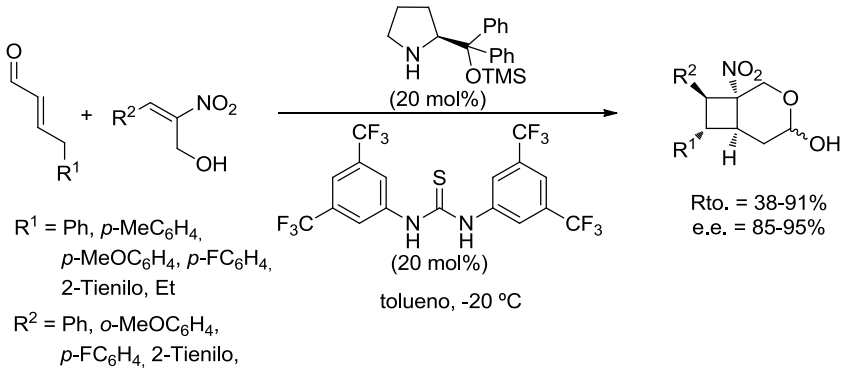
Esquema 7

Por otro lado, en un intento de eliminar el grupo tosilo, se obtuvo la amida representada en el Esquema 8 con excelente rendimiento y exceso enantiomérico cuando se trató la γ-lactama de partida con naftalenuro de sodio en THF a -78 ºC.



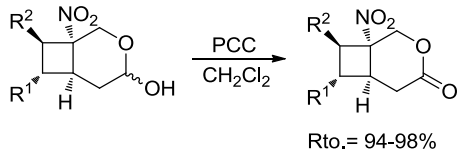
Esquema 8

En segundo lugar, combinando la aminocatálisis y la catálisis por formación de enlaces de hidrógeno mediante el empleo de un sistema catalítico compuesto por un derivado de α,α-difenilprolinol y una tiourea aquiral, se ha puesto a punto una metodología enfocada a la síntesis asimétrica de ciclobutanos sustituidos mediante una reacción formal de cicloadición [2+2] entre aldehídos α,β-insaturados enolizables y nitroalquenos α-hidroximetil sustituidos que cursa a través de una secuencia en cascada Michael/Michael. Esta segunda parte del trabajo de investigación comenzó con un proceso de optimización que nos permitió establecer las condiciones de reacción idóneas para sintetizar el correspondiente cicloaducto con los mejores resultados en cuanto a rendimiento y estereoselectividad. A continuación, se procedió a extender la metodología empleando distintos aldehídos α,β-insaturados, así como distintos nitroalquenos obteniendo así una amplia gama de cicloaductos con elevados rendimientos y de manera completamente regio- y diastereoselectiva y con excelentes excesos enantioméricos (Esquema 9).



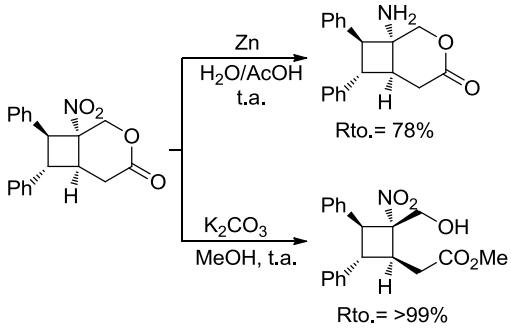
Esquema 9

Finalmente, se exploraron las posibilidades que ofrecen los aductos obtenidos como *building blocks* quirales realizando transformaciones sintéticas sobre las distintas funcionalidades de manera selectiva. De este modo, se llevó a cabo la oxidación del carbono anomérico de todos los compuestos obtenidos para acceder a las correspondientes lactonas bicíclicas con excelentes rendimientos y como únicos diastereoisómeros (Esquema 10).



Esquema 10

Asimismo, se llevó a cabo la reducción selectiva del grupo nitro presente en una de estas lactonas para obtener la correspondiente aminolactona con buen rendimiento y manteniendo la integridad estereoquímica del sustrato de partida. Por otro lado, se procedió a la apertura de la lactona mediante una reacción de metanolisis en medio básico accediendo así al ciclobutano esperado de manera cuantitativa y sin observar la epimerización de ningún centro estereogénico (Esquema 11).


Ph
NO2
O
O
Ph
H
Zn
H2O/AcOH
t.a.
Ph
NH2
O
O
Ph
H
Rto.= 78%
K2CO3
MeOH, t.a.
Ph
NO2
OH
CO2Me
Ph
H
Rto.= >99%

Esquema 11

Parte del trabajo recogido en la presente memoria ha dado lugar a las siguientes publicaciones:

1. "*Enantioselective Organocatalytic Domino Oxa-Michael/Aldol/Hemiacetalization: Synthesis of Polysubstituted Furofuranes Containing Four Stereocenters*".
Efraím Reyes, Garazi Talavera, Jose L. Vicario, Dolores Badía, Luisa Carrillo.
Angew. Chem. Int. Ed. **2009**, *48*, 5701.
Con reseña en *Synfacts:* "*One-step Synthesis of Furofuranes*" *Synfacts* **2009**, *9*, 1032.

2. "*Cooperative Dienamine/Hydrogen-Bonding Catalysis: Enantioselective Formal [2+2] Cycloaddition of Enals with Nitroalkenes*".
Garazi Talavera, Efraím Reyes, Jose L. Vicario, Dolores Badía, Luisa Carrillo.
Angew. Chem. Int. Ed. **2012**, *51*, 4104.
Con reseña en *Synfacts:* "*Organocatalytic [2+2] Cycloaddition of Enals and Nitroalkenes*" *Synfacts* **2012**, *8*, 0674.

Parte del trabajo recogido en la presente memoria ha dado lugar a las siguientes presentaciones a congresos:

1. Talavera, G.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *"Reacción Organocatalítica Enantioselectiva en Cascada Aplicada a la Síntesis Asimétrica de Furofuranos Polisustituídos"*.XXXII Reunión Bienal de la RSEQ. Oviedo (Spain), **2009**. Póster.

2. Reyes, E.; Talavera, G.; Vicario, J. L.; Badía, D.; Carrillo, L. *"Enantioselective Organocatalytic Cascade Reaction for Synthesis of Polysubstituted Furofuranes"*.16th European Symposium on Organic Chemistry. Prague, (Czech Republic), **2009**. Póster.

3. Reyes, E.; Talavera, G.; Vicario, J. L.; Badía, D.; Carrillo, L. *"Organocatálisis Enantioselectiva en la Síntesis de Nuevos Heterociclos"*.VI Simposio de Investigadores Jóvenes. Granada (Spain), **2009**. Comunicación oral presentada por Efraím Reyes.

4. Talavera, G.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *"Reaciones organocatalíticas en cascada. Una aproximación simple y eficaz a la síntesis estereocontrolada de compuestos heterocíclicos"*.XXXIII Reunión Bienal

del Grupo de Química Orgánica de la RSEQ. Murcia (Spain), **2010**. Comunicación oral presentada por Garazi Talavera.

5. Reyes, E.; Talavera, G.; Vicario, J. L.; Badía, D.; Carrillo, L. *"Cascade Reactions for the Asymmetric Construction of Complex Molecules"*.ORCA Meeting. Marseille (France), **2012**. Comunicación oral presentada por Efraím Reyes.

6. Talavera, G.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *"cooperative dienamine/hydrogen-bonding catalysis: enantioselective formal [2+2] cycloaddition"*. ISACS7: Challenges in Organic Chemistry and Chemical Biology**.** Edinburgh (UK), **2012**. Póster.

Papers