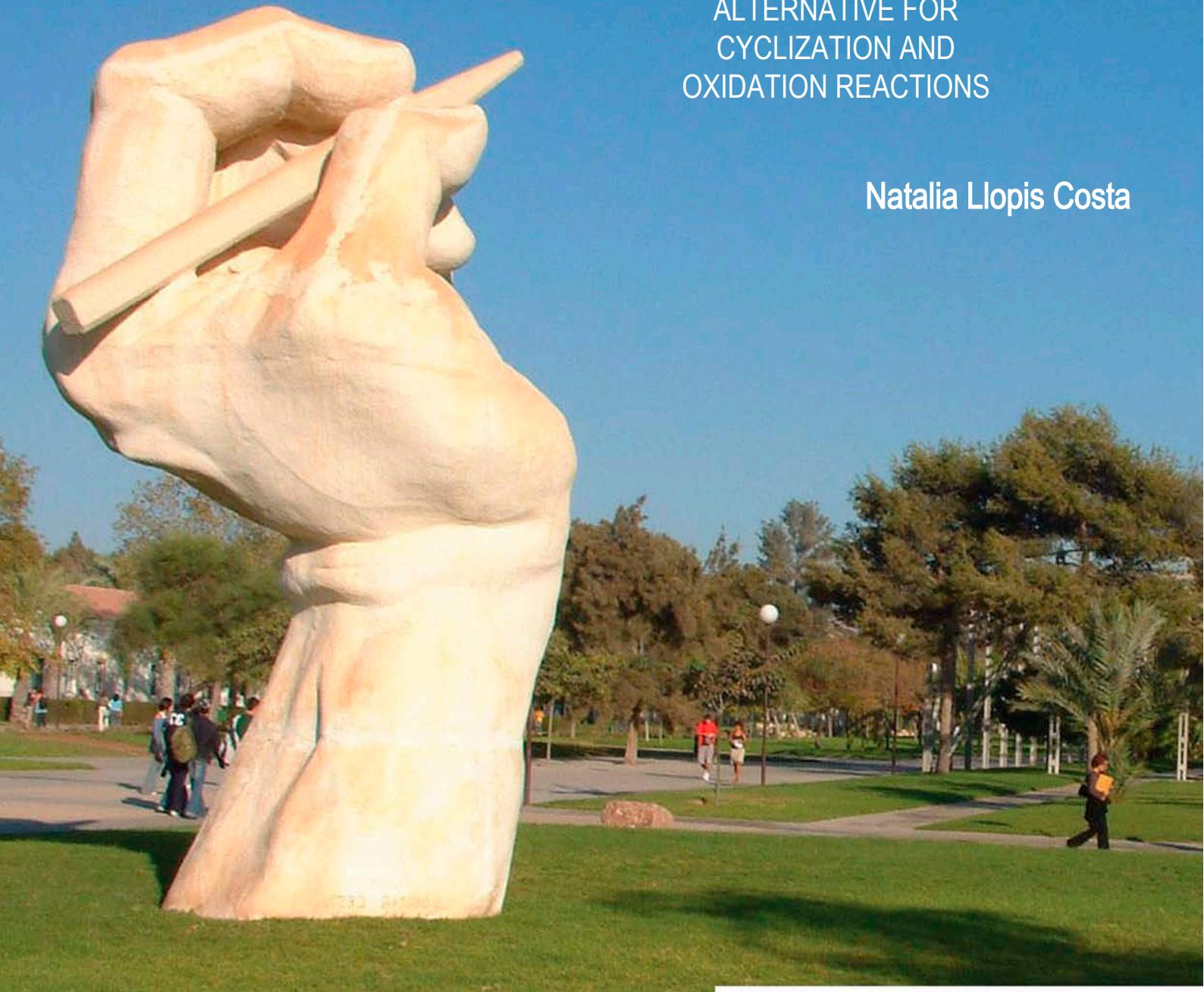




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HFIP AS METAL-FREE
ALTERNATIVE FOR
CYCLIZATION AND
OXIDATION REACTIONS

Natalia Llopis Costa



Tesis Doctorales

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HFIP AS METAL-FREE ALTERNATIVE FOR CYCLIZATION AND OXIDATION REACTIONS

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PREFACE

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PREFACE

In this doctoral thesis, the search of green and alternative methodologies using fluorinated alcohols as solvents and promoters of some organic transformations was developed. In the present manuscript, the methodologies described were developed trying to avoid hazardous conditions, metals or solvents, taking into consideration the principles of sustainable chemistry. These projects have been carried out under the supervision of Dr. Alejandro Baeza Carratalá and were developed at the Department of Organic Chemistry and the Institute for Organic Synthesis (ISO) at the University of Alicante (Spain).

Most of the results described in this doctoral thesis have been published in the following international peer reviewed journals:

“Synthesis of Substituted Tetrahydrofurans through HFIP-Promoted Ring-Opening Reaction of Epoxides with Electron-Rich Alkenes” Llopis, N.; Baeza, A. *Molecules* **2020**, 25, 3464-3476.

“Oxidation of Electron-Rich Arenes Using HFIP-UHP System” Llopis, N.; Baeza, A. *J. Org. Chem.* **2020**, 85, 9, 6159-6164.

“Direct Synthesis of *N,N*-Disubstituted Formamides by Oxidation of Imines Using HFIP/UHP System” Llopis, N.; Gisbert, P.; Baeza, A.; *J. Org. Chem.* **2020**, 85, 17, 11072-11079.

“Oxidative Cleavage of Indoles Mediated by Urea Hydrogen Peroxide or H₂O₂ in Polar Solvents” Llopis, N.; Gisbert, P.; Baeza, A.; *Adv. Synth. Catal.* **2021**, 363, 3245-3249.

“Dehydrogenation of *N*-Heterocyclic Compounds Using H₂O₂ and Mediated by Polar Solvents” Llopis, N.; Gisbert, P.; Baeza, A., Correa, J; *Adv. Synth. Catal.* **2022**, 364, 1-7.

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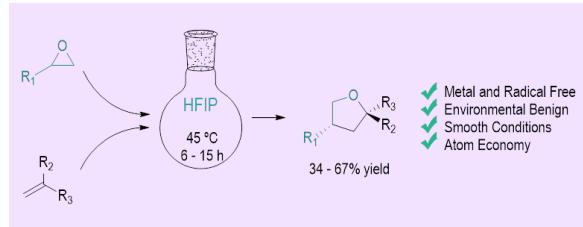
SUMMARY

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SUMMARY

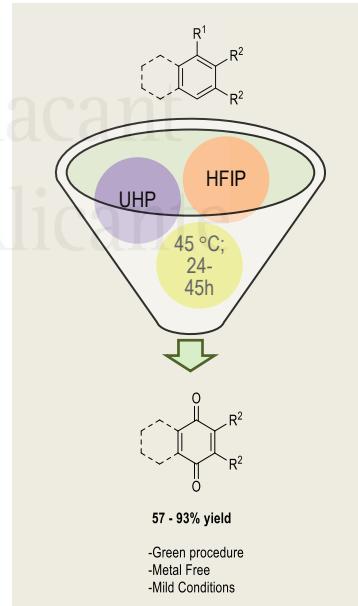
Chapter 1. Synthesis of Substituted Tetrahydrofurans through HFIP-Promoted Ring-Opening Reaction of Epoxides with Electron-Rich Alkenes

In this chapter, a new straightforward protocol has been developed for the synthesis of substituted tetrahydrofurans through the addition of electron-rich alkenes to epoxides using fluorinated alcohols, concretely 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), as solvents and promoters. The procedure described has afforded the synthesis of new tetrahydrofuran-based spiro compounds as well as tetrahydrofurobenzofuran derivatives in moderate yields and under smooth reaction conditions being envisioned as environmentally benign methodology due to its perfect atom economy and the availability of reactants and raw materials.



Chapter 2. Oxidation of Electron-Rich Arenes Using HFIP-UHP System

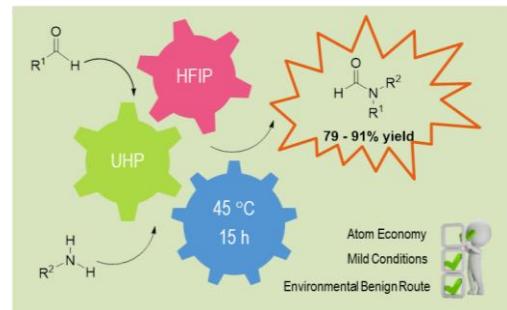
In this section, the direct oxidation of electron-rich arenes is described by using urea hydrogen peroxide (UHP) as source of H₂O₂ and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as solvent and reaction promoter. A broad array of quinones has been achieved in moderate to excellent yields in a green reaction procedure being demonstrated that no metals are required for this oxidative procedure.



SUMMARY

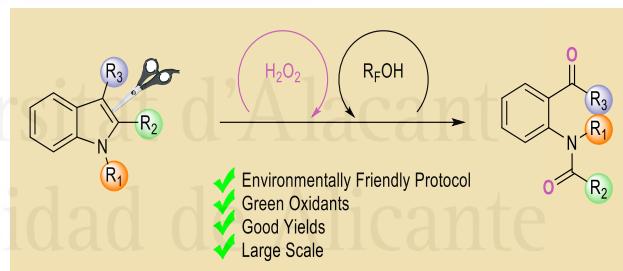
Chapter 3. Direct Synthesis of *N,N*-Disubstituted Formamides by Oxidation of Imines Using HFIP/UHP System

Within this chapter, the direct synthesis of *N,N*-disubstituted formamides starting from imines is described by combining the HFIP as solvent and urea hydrogen peroxide (UHP) as oxidative source. A great variety of formamides has been achieved in good to excellent yield under mild reaction conditions, being possible their synthesis in a one-pot sequence. This environmentally benign protocol has been applied to the synthesis of *N,N*-diphenylformamide in multigram scale.



Chapter 4. Oxidative Cleavage of Indoles Mediated by Urea Hydrogen Peroxide or H_2O_2 in Polar Solvents

Enclosed in this chapter, the oxidative cleavage of indoles, known as Witkop oxidation, by means of the combination of polar solvents with an oxidant source such as H_2O_2 or UHP has been depicted. Indeed, the

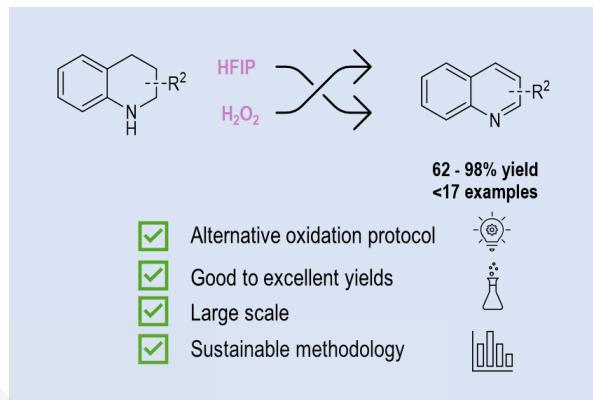


employment of HFIP, amongst the solvents utilized, was selected as the most advisable to achieve 2-ketoacetanilides in high yields. Besides indoles, the reaction protocol was further extended to pyrroles and furans derivatives. Additionally, it has been demonstrated that the procedure was also feasible in a larger scale, recovering and reusing the solvent up to 4 cycles, giving rise to a sustainable methodology.

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Chapter 5. Dehydrogenation of *N*-Heterocyclic Compounds Using H₂O₂ and Mediated by Polar Solvents

Within the last chapter of this thesis, an alternative oxidative dehydrogenation of *N*-based heterocycles mediated by a green oxidative source, namely H₂O₂, in combination with polar solvents such as HFIP and H₂O, has been disclosed. Even though good results were afforded when H₂O was the solvent of choice, higher yields for the heteroaromatic derivatives were achieved in HFIP due to the electrophilic activation of H₂O₂. Along with the wide array of tetrahydroquinolines selected, different *N*-heterocyclic compounds such as tetrahydroisoquinolines and indolines were also studied, obtaining the corresponding products in lower yields. Further to this, it is important to remark that the methodology described was also implemented in a larger scale, thus recycling the solvent up to five times with slight erosion on the conversion after each cycle.



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RESUMEN

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INTRODUCCIÓN

Química Sostenible

El desarrollo de una química sostenible y la búsqueda de nuevas estrategias y metodologías que den lugar a procesos químicos más seguros ha llamado la atención durante los últimos años tanto en nuestra sociedad como, especialmente, en el mundo de la química, dando lugar, de este modo, a los conocidos 12 principios de la Química Sostenible. Como consecuencia de ello, los químicos orgánicos se han propuesto desarrollar procedimientos sintéticos en los que se minimicen o se puedan evitar por completo condiciones extremas que no cumplan con estos principios.

De entre estas medidas, el uso de disolventes menos dañinos con los que se pueda disminuir el uso de auxiliares o los residuos generados, o la búsqueda de una economía atómica en los procesos desarrollados, han tenido especial relevancia dentro de esta rama de la Química Sostenible.

En consecuencia, los químicos, y especialmente los químicos orgánicos, comenzaron a mostrar una mayor preocupación en este campo proporcionando protocolos respetuosos con el medio ambiente y metodologías sintéticas alternativas que evitaban o minimizaban el uso de condiciones peligrosas para lograr los productos objetivo. Por ello, y cumpliendo con estas medidas ambientales, ha cobrado relevancia la incorporación y uso de disolventes inocuos con capacidad para disminuir el empleo de auxiliares, así como los residuos generados en el procedimiento, y la capacidad de asegurar una economía atómica eficiente a lo largo de todo el proceso. desde que el campo de la Química sostenible comenzó a crecer en los últimos años

Alcoholes Fluorados

Teniendo en cuenta que la gran mayoría de procesos y transformaciones químicas se llevan a cabo en disolución acuosa, cabe destacar que la búsqueda y desarrollo de disolventes que sean

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capaces de llevar a cabo estas transformaciones a través de la disociación de sus moléculas y promoviendo la disolución de los reactivos, es uno de los puntos más importantes para el desarrollo de una química más sostenible.

Por otro lado, el empleo de alcoholes fluorados en Química Orgánica ha ido adquiriendo cierta importancia debido a sus propiedades especiales, en concreto, la presencia de átomos de flúor cerca del grupo C-OH. De entre la gran variedad de alcoholes fluorados presentes (Figura 2), los más conocidos y utilizados en síntesis orgánica son el 2,2,2-trifluoroetanol (TFE) y el 1,1,1,3,3,3-hexafluoroisopropanol (HFIP).

La presencia de grupos fluoroalquilo en la estructura de estos alcoholes les confiere ciertas propiedades específicas en comparación de sus análogos no fluorados. Propiedades tales como la fuerte capacidad de retirada de electrones, dando lugar a un incremento en la acidez del grupo hidroxilo en disolución acuosa, su elevada capacidad ionizante, su fuerte capacidad como dadores de hidrógeno, o su baja nucleofilia, hace a los alcoholes fluorados unos disolventes muy especiales frente a sus análogos no fluorados, convirtiéndose en disolventes ideales y eficaces en reacciones de radicales así como el poder ser utilizados como disolventes, co-disolventes o aditivos en diferentes reacciones orgánicas.

Alcoholes Fluorados en Síntesis Orgánica

Gracias a su elevada acidez y su capacidad como dadores de hidrógeno, durante los últimos años el empleo de los alcoholes fluorados como disolventes y promotores de transformaciones orgánicas se ha visto incrementado en muchas oxidaciones, reducciones, cicloadiciones o hidrogenaciones, entre otras transformaciones. Gracias a ello, el empleo de aditivos, catalizadores metálicos o condiciones extremas de presión y temperatura, han sido reducidas o, en muchas ocasiones, eliminadas, dando lugar a una mejora significativa desde el punto de vista medioambiental, produciendo metodologías mucho más ecológicas y verdes.

Con la introducción de estos disolventes en la química, particularmente en la síntesis orgánica, se ha reducido notablemente o incluso eliminado el uso de aditivos, catalizadores (especialmente metales) o atmósferas y condiciones extremas, lo que supone una importante mejora desde el punto de vista medioambiental, proporcionando y procedimientos respetuosos con el medio ambiente.

- **Reacciones de Cicloadición**

La capacidad de diseñar y ejecutar metodologías altamente eficientes para la síntesis de compuestos heterocíclicos con valor agregado es una de las tareas desafiantes más importantes en la síntesis orgánica moderna. En este sentido, la síntesis de estos andamios cílicos a partir de materiales de partida simples ha llamado la atención de los químicos en las últimas décadas.

De esta forma, es importante destacar una de las primeras aplicaciones reportadas de los alcoholes fluorados como promotores para realizar las reacciones inter e intramoleculares [4+2] aza-Diels-Alder (reacción de Povarov), obteniendo un anillo nitrogenado de seis miembros. -que contienen heterociclos, que están presentes en una amplia gama de productos naturales con interés industrial y farmacéutico. El uso de alcoholes fluorados evita la utilización de ácidos de Lewis como $\text{BF}_3 \cdot \text{Et}_2\text{O}$, TiCl_4 , AlCl_3 , InCl_3 o triflatos de lantánidos

Luego, uno de los primeros ejemplos en los que los fluoroalcoholes actúan como promotores de esta transformación fue descrito por Crouse, Bonnet-Delpont y colaboradores en 2003, en el que la reacción entre la *N*-bencilideno anilina y una pequeña gama de éteres de alquivinilo produjo efectivamente las tetrahidroquinolinas correspondientes en HFIP a temperatura ambiente. De forma paralela, y como un intento de llegar a estos derivados de tetrahidroquinolina, este grupo también llevó a cabo la reacción multicomponente de aldehído, amina y enol éter en HFIP. Es importante mencionar que se han reportado trabajos adicionales relacionados con esta reacción multicomponente que dieron lugar a la preparación de derivados de tetrahidroquinolina, evitando el uso de catalizadores ácidos de Lewis.

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○ Reacciones de Formación de Enlace C-C y C-Heteroátomo

La posibilidad de dar lugar a la formación de enlaces CC y C-Het (Het = N, O, S, P, etc), dando acceso a una amplia gama de moléculas orgánicas de gran interés en la industria, ha llamado la atención de los científicos orgánicos sintéticos, químicos durante décadas. Por lo tanto, constantemente surgen nuevas metodologías en este campo que se mantienen al día con las tendencias actuales de la Química Sostenible evitando reactivos peligrosos y condiciones extremas.

En este sentido, la reacción de apertura de anillo de los epóxidos ha sido ampliamente estudiada. La necesidad e interés en llevar a cabo estas reacciones se debe a la necesidad de obtener intermediarios relevantes en síntesis orgánica y compuestos valiosos en química médica. Se han descrito numerosos ejemplos promovidos habitualmente por ácidos de Lewis o sales metálicas en un medio básico. Aun así, cabe mencionar que, debido a las especiales propiedades de los alcoholes fluorados como el alto poder ionizante y su carácter ácido, estos disolventes ofrecen una nueva posibilidad de realizar estas reacciones en ausencia de cualquier medio básico, menores tiempos de reacción y evitando el uso de sales y temperaturas extremas.

○ Reacciones de Oxidación

Los procesos de oxidación han adquirido una importancia considerable en la química orgánica a lo largo de los años, aunque se consideran una de las transformaciones más desafiantes. La necesidad de catalizadores metálicos o largos tiempos de reacción y la muy frecuente sobreoxidación del material de partida, han llevado a buscar y estudiar nuevos protocolos más acordes con los 12 principios de la Química Sostenible.

Por ello, la aparición de los alcoholes fluorados y sus especiales propiedades en cuanto a su capacidad para activar oxidantes a través de puentes de hidrógeno han llamado la atención de los químicos en las últimas décadas. En este sentido, entre la gran cantidad de reactivos oxidantes conocidos, el H₂O₂ acuoso se considera uno de los más baratos y ecológicos disponibles, además de ser fácilmente activado por alcoholes fluorados, particularmente por HFIP. Como resultado de esta activación, el H₂O₂ se ha convertido en un buen electrófilo que permite la oxidación de especies nucleófilas.

En este sentido, la primera reacción de oxidación reportada, en la que se activa peróxido de hidrógeno por alcoholes fluorados, fue realizada por Bégué y colaboradores en 1998. En ella, HFIP en combinación con H₂O₂ (30%) dio lugar a una oxidación selectiva y eficiente. sistema que permite la conversión de sulfuros a sulfóxidos. El papel principal de HFIP en este proceso de oxidación se debe en gran medida al carácter atractador de electrones del grupo CF₃, que puede formar un fuerte enlace de hidrógeno entre el H₂O₂ y el protón hidroxi en HFIP activando el grupo saliente hidroxilo de H₂O₂ y, simultáneamente, disminuyendo la nucleofilia del átomo de azufre evitando futuras oxidaciones.

El poder oxidativo del H₂O₂ ha sido ampliamente reconocido como más suave y ecológico en comparación con otros oxidantes empleados tradicionalmente en las últimas décadas, por lo que se ha ampliado su uso en la química orgánica. Asimismo, en la búsqueda de fuentes viables para los procesos de oxidación, en 2002 Bégué reportó un aducto de urea-peróxido de hidrógeno (UHP) como oxidante alternativo benigno y fuente segura de peróxido de hidrógeno anhidro. Aquí, la epoxidación de varias olefinas se llevó a cabo en ausencia de cualquier catalizador. Esto fue posible debido a la gran capacidad del disolvente para activar este complejo Urea-Peróxido de hidrógeno.

Por último, pero no menos importante, además de todas las reacciones mencionadas anteriormente, los alcoholes fluorados se han involucrado como promotores en otras reacciones como las reacciones de alquilación de Friedel-Crafts, las reacciones de nitración y halogenación electrofílica o la funcionalización de enlaces múltiples.

Finalmente, cabe mencionar que además de ser empleados como promotores en algunas transformaciones orgánicas, los alcoholes fluorados también pueden ser utilizados como solventes especiales o aditivos en varios procesos catalíticos, especialmente en las reacciones de hidrogenación catalizadas por metales de transición y de acoplamiento cruzado y CH reacciones de activación.

RESUMEN

Capítulo 1.

En el primer capítulo, se lleva a cabo la síntesis de tetrahidrofuranos sustituidos mediante la reacción de apertura de epóxidos con arenos ricos electrónicamente mediada por HFIP. Tanto los furanos como los tetrahidrofuranos sustituidos representan un tipo de estructuras heterocíclicas presentes en una gran variedad de compuestos naturales y moléculas naturales bioactivas, siendo de particular interés en la industria farmacéutica. Por lo general, este tipo de compuestos naturales donde se incluyen los derivados del anillo de tetrahidrofuran, se encuentran tanto en organismos marinos como terrestres. Uno de los ejemplos más representativos son los *Caloxilanos A y B*, obtenidos de la esponja marina del Caribe "*Calyx podatypa*". Por otro lado, el *Corsifurano A*, otro derivado del anillo de tetrahidrofuran con actividad biológica puede aislarse de la Corsina corinandrina mediterránea. Además, se pueden encontrar otros interesantes ejemplos que pueden exhibir actividades farmacológicas interesantes como antibacteriana, antiviral, antitumoral, citotóxica o antioxidante tales como los lignanos *Fragransin C1*, de entre una gran variedad de compuestos de la familia de las *Fragransinas*, obtenidos de *Machilus robusta*, o los neolignanos de *Conocarpan*, entre otros.

Debido a su destacado papel y su particular interés en la industria farmacéutica, la creciente preocupación por el desarrollo de nuevas metodologías como medio para poder acceder y dar lugar a este tipo de estructuras, ha aumentado considerablemente durante la última década. Así pues, de entre la gran variedad de procesos descritos, aquellos en los que se utilizan epóxidos y alquenos como reactivos de partida comercialmente disponibles y abundantes, son uno de los procedimientos más útiles y estudiados, proporcionando, de este modo, una amplia gama de tetrahidrofuranos sustituidos dando lugar a un proceso completo en el que se cumple uno de los principios de economía atómica. De este modo, en la literatura se han encontrado una pequeña cantidad de estudios y referencias que siguen dicha premisa. Así pues, en 2005, se desarrolló un método factible para la apertura de los anillos de epóxidos empleando alquenos conjugados mediante el uso de catalizadores de hierro (II), dando lugar a la síntesis de derivados de tetrahidrofuran sustituidos con una regio y quimioselectividad elevada. Un año más tarde, se desarrolló un mecanismo de transferencia de electrones para la reacción de expansión

intramolecular del anillo de epóxido mediante el uso de un catalizador similar de hierro (II), obteniendo en este caso derivados de tetrahidrofurano diastereoméricamente puros.

Más recientemente, se llevó a cabo una catálisis de transferencia de electrones fotoinducida permitiendo la reacción de apertura del anillo de oxirano con la consiguiente cicloadición de olefinas ricas en electrones mediante el uso de tetrafluoroborato de 2,4,6-trifenilpirilio (TPT) como sensibilizador. Gracias a este procedimiento en el que se emplean radicales, se pueden obtener estructuras heterocíclicas de espiro-oxindoles con elevados rendimientos.

Por último, teniendo en cuenta la creciente importancia de las reacciones de cicloadición intermolecular [3+2] en síntesis orgánica, el año 2016 se estudió la posibilidad de realizar reacciones intermoleculares entre epóxidos y alquenos sustituidos. En este sentido, se ha demostrado que la metodología empleada, la cual está catalizada por sales ácidas de triflato, puede dar lugar a la síntesis de tetrahidrofuranos sustituidos de forma regio y diastereoselectiva.

De este modo, se decidió llevar a cabo la síntesis de tetrahidrofuranos mediante el empleo de alcoholos fluorados como disolventes y promotores de la reacción de apertura de epóxidos con diferentes alquenos ricos en electrones.

Tras la búsqueda de las condiciones óptimas de la reacción, empleando HFIP como disolvente, 45 °C y entre 6 y 15 horas de reacción, se hicieron reaccionar diversos epóxidos entre una gran variedad de alquenos, dando lugar a una amplia gama de derivados de tetrahidrofuranos entre moderados y buenos rendimientos. El procedimiento desarrollado fue considerado como medioambientalmente benigno, evitando condiciones de presión o temperatura extremas o la necesidad de metales.

De este modo, se ha descrito una nueva metodología para la síntesis sencilla de tetrahidrofuranos sustituidos basada en la reacción de alquenos ricos en electrones con epóxidos mediada por HFIP. Debido a su leve acidez y su capacidad para estabilizar carbocationes, este solvente puede actuar como ácido de Lewis o Brønsted en estas reacciones evitando el uso de metales o atmósferas peligrosas, permitiendo la síntesis de estos productos cílicos en condiciones simples pero efectivas y sostenibles.

RESUMEN

Si bien los rendimientos alcanzados son moderados en casi todos los casos, el procedimiento puede concebirse como ambientalmente benigno debido a su perfecta economía atómica y la disponibilidad de reactivos a partir de materias primas, alquenos y epóxidos, con mínima manipulación. Además, al aplicar esta metodología, no solo se obtuvieron furanos densamente sustituidos, sino también compuestos espirocílicos y policíclicos que contenían un resto furano.

Capítulo 2.

Los derivados de benzoquinona representan una clase extensa de compuestos orgánicos ampliamente distribuidos entre los productos naturales. Este interesante marco muestra una amplia gama de aplicaciones en química médica o bioquímica que se utiliza como antibiótico, antitumoral o anticoagulante. Por ejemplo, algunos de estos esqueletos se pueden encontrar en frutas o verduras y representan intermediarios clave para una mayor aplicación en funciones biológicas o en el campo farmacéutico. Debido a su actividad redox, los derivados de quinona juegan un papel importante en una mirada de procesos redox biológicos.

Así pues, teniendo en cuenta su aplicabilidad, el desarrollo de nuevas metodologías para dar lugar a estos compuestos heterocílicos ha llamado la atención durante los últimos años. Entre todos estos diferentes enfoques descritos, la estrategia más práctica y sencilla para dar lugar al motivo estructural de quinona requiere la oxidación de arenos y/o derivados de fenol. No obstante, el desarrollo de estos procedimientos sintéticos requiere el uso de metales o compuestos de yodo hipervalente, peróxidos orgánicos o, en algunos casos, la intervención de sales orgánicas/inorgánicas. Además, además de implicar largos tiempos de reacción, altas temperaturas o, en algunos casos, condiciones extremas, estas transformaciones orgánicas también generan una cantidad estequiométrica de residuos en un proceso de baja economía atómica, no siendo la mayoría de ellas metodologías ambientalmente sostenibles.

Con base en los antecedentes bibliográficos, la falta de metodologías sustentables para acceder a estos compuestos y de acuerdo con los estudios preliminares realizados, se estableció el siguiente propósito:

Realizar la oxidación de arenos ricos en electrones empleando alcoholes fluorados como disolventes y H₂O₂ como oxidante. Con esta estrategia se evitaría el uso de metales y se reduciría el desperdicio químico. Este objetivo se planteó debido a la capacidad de los alcoholes fluorados como activadores del H₂O₂ a través de puentes de hidrógeno.

Para ello, tras la elección de las condiciones de reacción más idóneas para la oxidación de arenos ricos en electrones, se decidió llevar a cabo el estudio de oxidación de diferentes sustratos, teniendo en cuenta diferentes naftoles, fenoles, derivados de anisol y derivados de aldehído. Con ello, se logró demostrar que el uso de UHP como fuente de oxidante en combinación con HFIP como solvente permite la oxidación simple y directa de arenos ricos en electrones dando lugar a las quinolinas correspondientes en condiciones suaves.

Además, el protocolo se puede considerar ambientalmente benigno ya que evita el uso de oxidantes metálicos y/u orgánicos. Además, esta metodología tiene una alta economía atómica y los únicos subproductos y residuos generados (H₂O y urea) se consideran biodegradables.

Por otro lado, la reacción se implementó para la síntesis de una amplia gama de quinonas, que se obtuvieron en rendimiento de moderado a alto en la mayoría de los casos. A pesar de no tener una tendencia clara en la reactividad, se puede afirmar que, bajo las condiciones de reacción descritas, los derivados de naftaleno y los arenos ricos en electrones altamente sustituidos parecen proporcionar mejores resultados. Además, también se puede afirmar que las quinonas que llevan sustituyentes donantes de electrones en ambos dobles enlaces se obtuvieron con mayores rendimientos. Los resultados aquí descritos estarían de acuerdo con el hecho de que el H₂O₂ puede activarse electrofílicamente por medio del alcohol fluorado.

Capítulo 3.

La molécula formamida, conocida como la estructura amida más simple y presente en una amplia gama de moléculas orgánicas simples, siempre ha llamado la atención de los químicos orgánicos y bioquímicos porque en su estructura contiene carbono, hidrógeno, nitrógeno y oxígeno, convirtiéndose así en un valioso intermedio en la síntesis orgánica. Como prueba, la formamida,

RESUMEN

bajo diversas condiciones experimentales, es capaz de dar lugar a una amplia gama de biomoléculas complejas como las nucleobases.

Debido a su basicidad de Lewis, las formamidas se han utilizado en los últimos años como promotores en una amplia gama de transformaciones orgánicas, como la alilación o la hidrosililación de compuestos carbonílicos. Además, la posibilidad de usar formamidas quirales como catalizadores para la alilación asimétrica de aldehídos ha ofrecido una nueva aplicabilidad de estos restos.

En vista de su notable valor como intermedios en una amplia gama de aplicaciones farmacéuticas y de síntesis orgánica, no es de extrañar que, en las últimas décadas, el interés por desarrollar diferentes enfoques para sintetizar formamidas haya ido en aumento.

Formalmente, la síntesis de una formamida se produce mediante la combinación de un cloruro de formilo y una amina, liberando una molécula de ácido clorhídrico. Además de esta metodología de formilación tradicional, existen muchas estrategias que incluyen el empleo de agentes de formilación, catalizadores orgánicos o catalizadores de metales de transición. De tal forma, el uso de estos protocolos estequiométricos y catalíticos implica condiciones de reacción más suaves.

Teniendo en cuenta la bibliografía descrita, se decidió estudiar el proceso oxidativo de las iminas para acceder a formamidas *N,N*-disustituidas mediante el uso de alcoholos fluorados como disolventes y promotores de reacción y UHP como oxidante verde, generando así un proceso oxidativo más benigno con el medio ambiente.

Para ello, tras determinar las condiciones óptimas de reacción, se llevó a cabo la oxidación de diversas iminas. Tras ello, se logró demostrar que la oxidación de aldimidas empleando UHP como oxidante verde y no tóxico es un procedimiento simple, alternativo y ambientalmente benigno para la síntesis de formamidas. Esta metodología es factible debido a la presencia de HFIP como solvente y promotor de reacción, evitando la utilización de cualquier ácido de Lewis. Por sus propiedades únicas mencionadas anteriormente, este alcohol fluorado es capaz de permitir la activación electrofílica del oxidante proporcionando el protocolo oxidativo en condiciones sostenibles y suaves.

Bajo las condiciones óptimas de reacción, el procedimiento descrito proporcionó una gran variedad de formamidas con rendimientos moderados a altos en la mayoría de los casos. Sin embargo, también se puede afirmar que las iminas derivadas de aldehídos pobres en electrones o ciclohexanamina dieron lugar a la formación de amidas u oxaziridinas, respectivamente. Esos resultados refuerzan que el mecanismo propuesto procede a través de la formación de la oxaziridina correspondiente seguida de un reordenamiento de tipo Meinwald promovido por HFIP.

Capítulo 4.

La estructura del indol constituye un bloque de construcción esencial en la naturaleza y está presente en una amplia gama de moléculas naturales con actividad biológica, como el neurotransmisor serotonina, la hormona vegetal ácido indol-3-acético o el aminoácido triptófano.

Por tanto, el interés por desarrollar metodologías sintéticas y estrategias de funcionalización de estas moléculas nitrogenadas debido a su aplicabilidad en productos farmacéuticos, fragancias, agroquímicos o pigmentos ha aumentado considerablemente.

En los últimos años, la oxidación del compuesto de indol ha recibido mucha atención en la síntesis orgánica. Debido a su propiedad rica en electrones, la oxidación de esta estructura puede dar lugar a una amplia variedad de intermediarios, siendo de especial interés en el descubrimiento de fármacos. Así, se han descrito diferentes condiciones oxidantes para dar acceso a las mismas. A pesar de esto, se ha informado que solo una pequeña cantidad de oxidantes pueden generar los tipos más importantes de productos de oxidación de indol, a saber, 2-oxindoles (entre ellos, espirooxindoles), ácidos antranílicos y 2-cetoacetanilidas.

En particular, las 2-cetoacetanilidas y los derivados del ácido antranílico se obtienen mediante la escisión oxidativa del doble enlace C2-C3, conocida como oxidación de Witkop. Tradicionalmente, la síntesis de estos compuestos se ha realizado mediante el uso de oxidantes basados en metales de transición, compuestos de yodo hipervalente, oxígeno singulete u ozono y peróxidos orgánicos como estrategias principales, como se muestra en el Esquema 30, sin seguir ninguno de los 12 principios de la Química Sostenible.

RESUMEN

Sin embargo, en las últimas décadas, la preocupación sobre la seguridad, la sostenibilidad y el impacto ambiental de los protocolos químicos han impulsado el desarrollo de metodologías de oxidación más ecológicas, de economía atómica y operativamente simples. Cabe mencionar que, en los últimos años, se han publicado diferentes trabajos al respecto. Concretamente, hace algunos años se describió la escisión oxidativa de indoles mediante el uso de biocatalizadores en combinación con H₂O₂ como oxidante.

Además, es importante destacar que estas 2-cetoacetanilidas y ácidos antranílicos son intermediarios clave en la síntesis de quinolonas y compuestos bioactivos relacionados como ansiolíticos, antibióticos o psicoestimulantes. Así, la mayoría de estos compuestos se obtienen por condensación intramolecular de tales cetoacetanilidas, conocida como ciclación de Camps. Cuando esta transformación se combina con la oxidación de Witkop, da lugar a la formación de estas moléculas en una secuencia de un solo recipiente denominada oxidación de Winterfeldt.

Dicho esto, se creyó conveniente realizar la ruptura oxidativa de los indoles para dar acceso a los productos de la oxidación Witkop correspondientes que impliquen el uso de oxidantes verdes, tales como el peróxido de hidrógeno o peróxido de hidrógeno de urea, en combinación con alcoholes fluorados u otros solventes polares, como protocolo sostenible.

De este modo, se realizó la búsqueda de condiciones óptimas de reacción empleando HFIP como disolvente y peróxido de hidrógeno como oxidante. Tras ello, se realizó el estudio de diferentes indoles sustituidos en las posiciones 2 y 3, así como con sustituyentes electrón dadores en posición 5.

Gracias a ello, se logró desarrollar un protocolo alternativo libre de metales para la ruptura oxidativa de indoles, conocido como oxidación de Witkop, empleando UHP o H₂O₂ como oxidantes. La metodología descrita ha demostrado ser eficaz en presencia de disolventes altamente polares cuando se utilizan indoles que llevan un sustituyente en la posición 2 y/o 3. Además, la reacción mostró un gran rendimiento y una amplia gama de sustratos cuando el solvente utilizado fue HFIP. De esta forma, la reacción se ha llevado a cabo en condiciones suaves donde el HFIP actúa tanto como disolvente como promotor de la reacción.

Además, este protocolo ha permitido la preparación de una amplia gama de cetoacetanilidas y derivados del ácido antranílico con buenos rendimientos. También se oxidaron convenientemente otros compuestos heteroaromáticos. Adicionalmente, este procedimiento tiene una alta economía atómica siendo los residuos generados considerados biodegradables.

Capítulo 5.

Los compuestos orgánicos que contienen un *N*-heterocíclico en su estructura, como, por ejemplo, las estructuras de quinolina y su isómero la isoquinolina, representan un importante armazón o estructura presente en una amplia variedad de compuestos naturales, generalmente alcaloides. Los compuestos que tienen este esqueleto heterocíclico han atraído la atención de los químicos durante muchos años debido a que posee actividad biológica, tales como actividad antipaludica, antibacteriana, antihelmíntica, anticonvulsiva, antiviral, antiinflamatoria o analgésica. Además, su aplicabilidad en otros campos como la química industrial, incluida la síntesis de agroquímicos, el estudio de procesos bioorgánicos y bioorganometálicos o la preparación de quimiosensores ha sido ampliamente estudiada.

Las metodologías tradicionales de síntesis de estos compuestos presentan varios inconvenientes requiriendo condiciones de reacción extremas, el uso de materiales de partida o catalizadores costosos y la producción de una gran cantidad de desechos. Así pues, en los últimos años se ha llevado a cabo una amplia búsqueda e investigación por el interés de desarrollar metodologías químicas más ecológicas y sostenibles mediante el uso de disolventes menos peligrosos, catalizadores renovables o fuentes de energía más eficientes. Entre ellos, es importante destacar la deshidrogenación de compuestos *N*-heterocíclicos, siendo un protocolo elegante y directo, además de presentar una alta economía atómica.

Aunque es un proceso desafiante, la reacción oxidativa deshidrogenativa se ha estudiado ampliamente durante las últimas décadas utilizando oxidantes estequiométricos, como por ejemplo HgO-I_2 , MnO_2 o azufre, o llevando a cabo la reacción a temperaturas extremas. Sin embargo, las

RESUMEN

metodologías sostenibles han ido surgiendo en los últimos años siendo de particular interés en el campo de la química orgánica debido a su bajo impacto ambiental o economía atómica.

Dicho esto, en este punto es importante destacar que el interés por utilizar oxidantes más ecológicos, siendo estos tanto el H_2O_2 o el O_2 , podría representar un paso hacia delante para llevar a cabo esta transformación. Es por ello que, el uso de O_2 como oxidante en procesos catalizados o fotocatalizados ha sido ampliamente estudiado. En este sentido, el uso de luz visible o catalizadores (de base metálica o no metálica) en combinación con oxígeno molecular, proporcionan, en la mayoría de los casos, una buena metodología para el almacenamiento y liberación de hidrógeno, siendo un candidato ideal para abordar la contaminación ambiental. A pesar de dar grandes logros, estas metodologías pueden representar un problema si la deshidrogenación se implementa a mayor escala, dando lugar a un almacenamiento peligroso de hidrógeno. Además de eso, la oxidación directa usando O_2 como oxidante no es la metodología más fácil ya que la promoción de oxígeno singlete a triplete requiere una barrera de alta energía.

Teniendo en cuenta todo esto, como alternativa a las metodologías descritas, ha llamado la atención el desarrollo de sistemas catalíticos libres de metales mediante el uso de luz visible en catálisis heterogénea, óxido de grafeno u organo-electrocatalizadores debido a la posibilidad de llevar a cabo esta transformación de manera sencilla bajo condiciones de reacción suaves. condiciones. Por lo general, estos catalizadores heterogéneos se recuperan fácilmente para su posterior utilización pero, en varias ocasiones, se requieren temperaturas bastante altas para el desarrollo de esta metodología.

De manera similar, cabe mencionar que algunas estrategias que involucran H_2O_2 como oxidante en combinación con metales o ácidos de Lewis, han sido ampliamente estudiadas a lo largo de los años, siendo el H_2O el subproducto obtenido y dando lugar a metodologías alternativas bastante llamativas para el desarrollo de la deshidrogenación de compuestos heterocíclicos.

De este modo, teniendo en cuenta la bibliografía y la experiencia en el grupo de investigación al emplear HFIP como disolvente y promotor y H_2O_2 como oxidante de reacción, se pensó llevar a cabo la deshidrogenación oxidativa de compuestos *N*-heterocíclicos para obtener las especies heteroaromáticas, siendo estas, quinolinas y derivados de isoquinolina, utilizando peróxido de

hidrógeno como oxidante sostenible alternativo en combinación con disolventes polares como HFIP y H₂O.

Así pues, la búsqueda de condiciones óptimas de reacción se llevó a cabo teniendo en cuenta los estudios realizados hasta el momento. Con ello, se llegó a que el empleo de HFIP como disolvente de la reacción en combinación con H₂O₂ y que el uso de agua como disolvente, también en combinación con el H₂O₂ podía dar lugar a la deshidrogenación oxidativa con elevadas conversiones en apenas 2-6 horas de reacción. Tras ello, se decidió probar diferentes quinolinas sustituidas con electrón dadores de densidad de carga, obteniendo un amplio alcance de reacción. En vista a los resultados obtenidos, se decidió ampliar el alcance de dicha metodología utilizando tetrahidroisoquinolinas, indolinas, quinozalinas y quinoxalinas, observando variaciones en los resultados obtenidos.

En resumen, se ha desarrollado una estrategia alternativa para la deshidrogenación oxidativa de compuestos heterocíclicos basados en N utilizando H₂O₂ como oxidante sostenible y no tóxico. El protocolo descrito se realizó tanto en HFIP como en H₂O como disolventes polares, obteniendo mejores resultados al llevar a cabo la reacción con el HFIP. Así, el mejor éxito de la metodología se basa en la activación electrofílica del oxidante por el alcohol fluorado. Por lo tanto, el protocolo descrito resultó ser una metodología ambiental y sostenible que permite la oxidación de dichas moléculas en condiciones de reacción suaves.

En este sentido, se realizó la deshidrogenación oxidativa empleando una amplia variedad de tetrahidroquinolinas dando lugar a la formación de compuestos heteroaromáticos con rendimientos de moderados a excelentes. Por otro lado, cabe destacar que esta metodología también se implementó en otros sustratos *N*-heterocíclicos, siendo estos las tetrahidroisoquinolinas e indolinas, proporcionando, en este caso, los correspondiente productos de oxidación con rendimientos más bajos.

Además, se puede afirmar que la secuencia de un solo paso de deshidrogenación de Povarov descrita, se llevó a cabo y proporcionó la formación de la quinolina esperada, ampliando de este modo la aplicabilidad de la metodología propuesta. Finalmente, el disolvente se ha recuperado y

RESUMEN

reutilizado hasta en cinco ocasiones cuando la reacción se realizaba a gran escala, sin pérdida significativa de la deshidrogenación oxidativa.

Para finalizar, hay que comentar que, tras el estudio de las diferentes metodologías llevadas a cabo, se propuso un mecanismo de reacción en cada uno de los casos de oxidación y para la reacción de ciclación. En todos los estudios de oxidación llevados a cabo, se logró observar una tendencia. Empezando con la activación electrofílica del peróxido de hidrógeno a través de puentes de hidrógeno gracias al HFIP como disolvente y promotor de la reacción de oxidación, el ataque nucleófilo del sustrato de partida inicial en cada uno de los correspondientes ejemplos, daría lugar a un intermedio A. Tras ello, con un segundo ataque nucleófilo y tras deshidratación, isomerización o tatuomerización, se obtendría el esperado producto final.



A horizontal graphic consisting of several overlapping, translucent, wavy bands in shades of orange, pink, purple, and blue, creating a sense of depth and motion.

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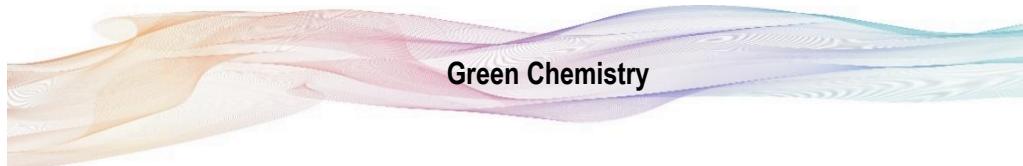


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A horizontal band of abstract, flowing lines in shades of orange, pink, purple, and blue, resembling waves or fabric.

GENERAL INTRODUCTION

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Over the last decade, the concerns about finding new strategies to perform chemical transformations in a safer and sustainable manner have been progressively acquiring importance in our society. Due to this fact, sustainable chemistry has attracted worldwide attention until being briefly summarized in the 12 principles of Green Chemistry (Figure 1).¹ Within these principles, not only environmental issues to develop new sustainable strategies to decrease detrimental consequences were gathered, but also several aspects concerning human health were included.²



Figure 1. 12 Principles of Green Chemistry.

¹ (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998; (b) Sheldon, R. A. *Green Chemistry and Catalysis*; Wiley-VCH: Weinheim, 2007; (c) Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, 39, 301-312.

² (a) Sheldon, R. A. *Chem. Soc. Rev.* **2012**, 41, 1437-1451; (b) Blum, C.; Bunke, D.; Hungsberg, M.; Roelofs, E.; Joas, A.; Joas, R.; Blepp, M.; Stolzenberg, H.-C. *Sustain. Chem. Pharm.* **2017**, 5, 94-104.

Green Chemistry

On the basis of the 12 principles of Green Chemistry, more recently Poliakoff and co-workers decided to establish a mnemonic name to collect them in a simpler manner as follows (Figure 2):³

- P - Prevent Wastes
- R - Renewable Materials
- O - Omit Derivatisation Steps
- D - Degradable Chemical Products
- U - Use of Safe Synthetic Methods
- C - Catalytic Reagents
- T - Temperature, Pressure Ambient
- I - In-Process Monitoring
- V - Very Few Auxiliary Substances
- E - E-Factor, Maximise Feed in Product
- L - Low Toxicity of Chemical Products
- Y - Yes, it is Safe

Figure 2. 12 Principles of Green Chemistry written in a mnemonic form.

Consequently, chemists and especially organic chemists, started to show a greater concern on this field providing environmentally friendly protocols and alternative synthetic methodologies avoiding or minimizing the use of hazardous conditions to achieve the targeted products. Therefore, and complying with these environmental measures, the incorporation and use of harmless solvents with the ability to diminish the employment of auxiliaries as well as waste generated in the procedure, and the capacity to ensure an efficient atom economy throughout the entire process has gained relevance since the field of Green Chemistry began to grow over the last years. In view of these current trends, research endeavours to seek solvents with these features has become increasingly necessary to supply an ideal and environmentally acceptable synthesis for both academic and industry.⁴

³ Tang, S. L. Y.; Smith, R. L.; Poliakoff, M. *Green Chem.* **2005**, 7, 761-762.

⁴ (a) Mestres, R. *Environ. Sci. Pollut. R.* **2005**, 12, 128-132; (b) Gawande, M. B.; Bonifácio, V. D. B.; Luque, R.; Branco, P. S.; Varma, R. S. *Chem. Soc. Rev.* **2013**, 42, 5522-5551.



Fluorinated Alcohols

It is well known that the vast majority of chemical transformations established so far are carried out in solution. On this sense, it is important to highlight the presence of a great variety of solvents in these processes capable of promoting dissolution of reagents through dissociation of their molecules making the reaction more feasible at molecular level. In this way, the seek and development of solvents with the ability to perform these types of reactions has been one of the most essential starting points to obtain the best possible results when planning a chemical reaction.⁵

Thus, in the last few years, fluorinated alcohols have acquired significance to the point that they have become an increasingly important research topic in Organic Chemistry.⁶ Owing to their special properties, particularly derived from the presence of fluorine atoms next to the C-OH group,^{7,8} they have been widely used as solvents and promoters in this field. Among the assortment of fluoroalcohols offered (Figure 3), 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) stand out as the most regularly employed.

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⁵ (a) Lim, D.; Jenson, C.; Repasky, M. P.; Jorgensen, W. L. *Solvent as Catalyst: Computational Studies of Organic Reactions in Solution*; American Chemical Society, 1999; (b) Gani, R.; Jimenez-Gonzalez, C.; Constable, D. J. C. *Comput. Chem. Eng.* **2005**, 29, 1661-1676.

⁶ (a) Bégué, J.-P.; Bonnet-Delpón, D.; Crousse, B. *Synlett* **2004**, 2004, 18-29; (b) Shuklov, I. A.; Dubrovina, N. V.; Boerner, A. *Synthesis* **2007**, 2925-2943; (c) Vuluga, D.; Legros, J.; Crousse, B.; Slawin, A. M. Z.; Laurence, C.; Nicolet, P.; Bonnet-Delpón, D. *J. Org. Chem.* **2011**, 76, 1126-1133; (d) Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. *Nat. Rev. Chem.* **2017**, 1, 0088.

⁷ (a) Uneyama, K. *Organofluorine Chemistry*; Blackwell Publishing: Oxford 2006; (b) Bégué, J. P.; Bonnet-Delpón, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: Hoboken 2008.

⁸ (a) Hurley, M. D.; Wallington, T. J.; Sulbaek Andersen, M. P.; Ellis, D. A.; Martin, J. W.; Mabury, S. A. *J. Phys. Chem. A* **2004**, 108, 1973-1979; (b) Wnorowski, K.; Wnorowska, J.; Kopyra, J.; Michalczuk, B.; Szamrej, I.; Barszczewska, W. *Chem. Phys. Lett.* **2014**, 591, 282-286.

Fluorinated Alcohols

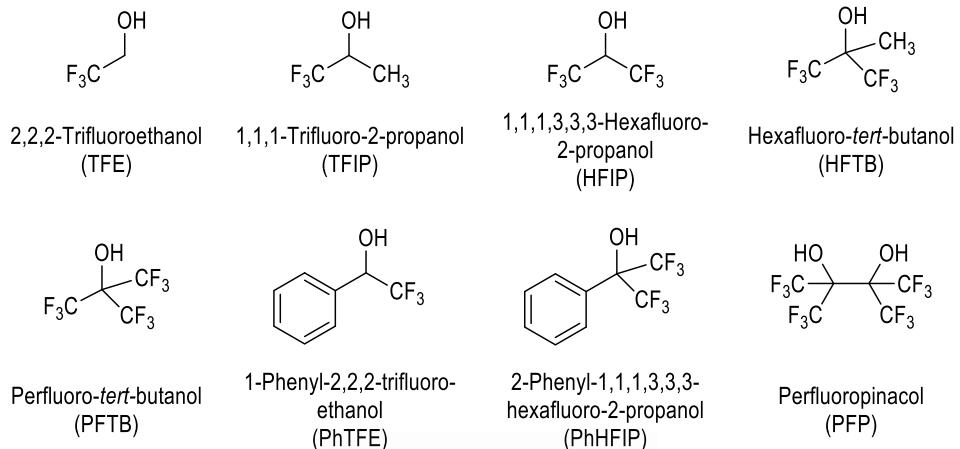


Figure 3. Fluorinated Alcohols

The presence of fluoroalkyl groups in their structure confers fluoroalcohols specific properties in comparison with their non-fluorinated analogues (Table 1). Consequently, the strong electron-withdrawing property of this group is able to enhance the acidity of the hydroxyl group, leading to acidities of HFIP and TFE in aqueous solution of $pK_a = 9.3$ and 12.4 respectively, in comparison with EtOH ($pK_a = 15.9$).⁹ Moreover, both, HFIP and TFE, are highly polar solvents. Concerning the Reichardt- E^N_T value, HFIP, with $E^N_T = 1.068$, is the only one amid the solvents studied which exceeds the scale defined by tetramethylsilane ($E^N_T = 0$) and water ($E^N_T = 1$).¹⁰ Additionally, both solvents possess high ionizing power as compared to their non-fluorinated analogues.¹¹

Furthermore, fluorinated alcohols are strong hydrogen bond donors displaying high α -values ($\alpha_{HFIP} = 1.96$ and $\alpha_{TFE} = 1.51$).¹² This hydrogen bond donor feature of fluoroalcohols, especially in the case of HFIP, is likely on account of two parameters: (a) the configuration that the alcohol monomer is able to acquire along the C-O bond and (b) how the hydrogen-bonded alcohol clusters

⁹ (a) Carre, B.; Devynck, J. *Anal. Chim. Acta*. **1981**, *131*, 141-147; (b) Eberson, L.; Hartshorn, M. P.; Persson, O. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1735-1744.

¹⁰ Reichardt, C. *Chem. Rev.* **1994**, *94*, 2319-2358.

¹¹ Schadt, F. L.; Bentley, T. W.; Schleyer, P. V. R. *J. Am. Chem. Soc.* **1976**, *98*, 7667-7675.

¹² (a) Purcell, K. F.; Stikeleather, J. A.; Brunk, S. D. *J. Mol. Spectrosc.* **1969**, *32*, 202-213; (b) Kamlet, M. J.; Abboud, J. L. M.; Abraham, M. H.; Taft, R. W. *J. Org. Chem.* **1983**, *48*, 2877-2887.

are added in a cooperative manner.¹³ Thus, it is to be expected that the coordination of a second or even more molecules of HFIP may considerably improve upon the hydrogen bond donor ability of the hydroxyl group. In addition, as a consequence of HFIP's high power of solvation through H-bond, this solvent has the capacity to set up a 1:1 complex with THF and other common solvents.¹⁴ Hence, it is not surprising their poor hydrogen bond acceptor ability.

Table 1. Properties of HFIP, TFE and EtOH

PROPERTIES	HFIP	TFE	EtOH
Boiling point (°C)	58.6	73.8	78
Melting point (°C)	-5	-43.5	-
Density (g/mL)	1.605	1.383	0.79
pK _a (H ₂ O)	9.3	12.4	15.9
Dielectric constant (ϵ)	16.7	26.7	24.5
Polarity, Reichert constant (E^{N_T})	1.068	0.898	0.654
Ionizing power (Y)	3.82	1.8	-1.75
Hydrogen-bond donor ability (α)	1.96	1.51	0.83
Hydrogen-bond acceptor ability (β)	0	0	0.77
Nucleophilicity constant (N)	-4.23	-2.78	0
Auto-association constant (dm ³ mol ⁻¹)	0.13	0.65	0.89

Apart from all these characteristic properties aforementioned, the low nucleophilicity makes them special in front of non-fluorinated alcohols and also non-fluorinated solvents.^{11,15} As a result, fluorinated alcohols have become efficient and ideal solvents to perform reactions based on the generation of cationic or radical-cationic species, thereby broadening their use as solvents, co-solvents and additives in different organic fields.

Finally, after some biological studies in mouses, it has been demonstrated that the toxicity of fluorinated alcohols is about one order of magnitude higher than ethanol or 2-propanol in terms of LD₅₀ values.¹⁶

¹³ Berkessel, A.; Adrio, J. A.; Hüttenhain, D.; Neudörfl, J. M. *J. Am. Chem. Soc.* **2006**, 128, 8421-8426.

¹⁴ Middleton, W. J.; Lindsey, R. V. *J. Am. Chem. Soc.* **1964**, 86, 4948-4952.

¹⁵ (a) Allard, B.; Casadevall, A.; Casadevall, E.; Largeau, C. *Nouv. J. Chim.* **1979**, 3, 335; (b) Bentley, T. W.; Llewellyn, G.; Ryu, Z. H. *J. Org. Chem.* **1998**, 63, 4654-4659.

¹⁶ Dover, T. L.; McDonald, F. E. *Arkivoc* **2021**, 85 - 114.

Fluorinated Alcohols in Organic Synthesis

Due to their unique properties, namely their high acidity or their ability as hydrogen bond donors, over the past few decades fluorinated alcohols have been used as solvents and promoters in a broad range of organic transformations such as oxidations, reductions, cycloaddition reactions or hydrogenations.¹⁷

By the introduction of these solvents in chemistry, particularly in organic synthesis, the use of additives, catalysts (specially metals) or extreme atmospheres and conditions has been markedly reduced or even erased, establishing a significant improvement from an environmental point of view, providing greener and environmentally friendly procedures.

Next, in the following sections, a brief overview of the most common reactions employing fluorinated solvents, namely HFIP and TFE, will be described:

Cycloaddition Reactions

The capacity to design and perform highly efficient methodologies for the synthesis of heterocyclic compounds with added value is one of the most important challenging tasks in modern organic synthesis. In this sense, the synthesis of these cyclic scaffolds through simple starting materials has attracted the attention of chemists over the last few decades.¹⁸

In such a way, it is important to highlight one of the first reported applications of fluorinated alcohols as promoters to perform the inter and intramolecular [4+2] aza-Diels-Alder reactions

¹⁷ (a) Bégué, J.-P.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, 2004, 18-29; (b) Shuklov, I. A.; Dubrovina, N. V.; Boerner, A. *Synthesis* **2007**, 2925-2943; (c) Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. *Nat. Rev. Chem.* **2017**, 1, 0088; (d) An, X.-D.; Xiao, J. *Chem. Rec.* **2020**, 20, 142-161.

¹⁸ Kobayashi, S.; Jorgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA, 2002.

(Povarov reaction), obtaining a six-membered ring nitrogen-containing heterocycles, which are present in a broad range of natural products with industrial and pharmaceutical interest.¹⁹ The use of fluorinated alcohols avoids the utilisation of Lewis acids such as $\text{BF}_3\cdot\text{Et}_2\text{O}$, TiCl_4 , AlCl_3 , InCl_3 or lanthanide triflates.^{20,21} Then, one of the earliest examples in which fluoroalcohols act as promoters of this transformation was described by Crouse, Bonnet-Delpon and co-workers in 2003, in which the reaction between *N*-benzilidene aniline and a few range of alkyl vinyl ethers afforded effectively the corresponding tetrahydroquinolines in HFIP at room temperature (Scheme 1a). In a parallel manner, and as an attempt to reach these tetrahydroquinoline derivatives, this group also carried out the multicomponent reaction of aldehyde, amine and enol ether in HFIP (Scheme 1b).²² It is important to mention that, further work concerning this multicomponent reaction has been reported giving rise to the preparation of tetrahydroquinoline derivatives, avoiding the use of Lewis acid catalysts.²³

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¹⁹ (a) Funel, J.-A.; Abele, S. *Angew. Chem. Int. Ed.* **2013**, 52, 3822-3863; (b) Cao, M. H.; Green, N. J.; Xu, S. Z. *Org. Biomol. Chem.* **2017**, 15, 3105-3129.

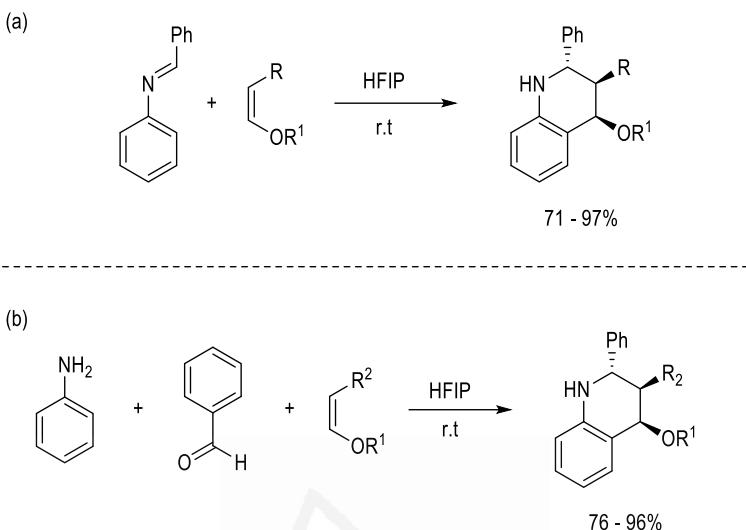
²⁰ (a) Povarov, L. S. *Russ. Chem. Rev.* **1967**, 36, 656-670; (b) Worth, D. F.; Perricone, S. C.; Elslager, E. F. *Heterocycl. Chem.* **1970**, 7, 1353-1356; (c) Cabral, J.; Laszlo, P. *Tetrahedron Lett.* **1989**, 30, 7237-7238; (d) Yu, L.; Chen, D.; Wang, P. G. *Tetrahedron Lett.* **1996**, 37, 2169; (e) Sundararajan, G.; Prabagaran, N.; Varghese, B. *Org. Lett.* **2001**, 3, 1973-1976.

²¹ (a) For selected recent reviews, see: Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, 57, 6099-6138; (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, 41, 1668-1698; (c) Kouznetsov, V. V. *Tetrahedron* **2009**, 65, 2721-2750.

²² (a) Di Salvo, A.; Spanedda, M. V.; Ourévitch, M.; Crousse, B.; Bonnet-Delpon, D. *Synthesis* **2003**, 2003, 2231-2235; (b) Spanedda, M. V.; Hoang, V. D.; Crousse, B.; Bonnet-Delpon, D.; Begue, J.-P. *Tetrahedron Lett.* **2003**, 44, 217-219.

²³ (a) Legros, J.; Crousse, B.; Ourévitch, M.; Bonnet-Delpon, D. *Synlett* **2006**, 1899-1902; (b) Zhou, J.; Xu, B. L. *Chin. Chem. Lett.* **2008**, 19, 921-924; (c) Venkateswarlu, C.; Balaji, P. V.; De, K.; Crousse, B.; Figadère, B.; Legros, J. *J. Fluorine Chem.* **2013**, 152, 94-98.

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Scheme 1. (a) [4+2] Aza-Diels-Alder reaction; (b) Multicomponent reaction.

Related with this cycloaddition reactions, in 2011, Jeffrey and co-workers reported the fluorinated alcohols, concretely HFIP and TFE, mediated synthesis of seven-membered azacycles through the aza-[4+3] cycloaddition reaction of oxoallyl cations and different cyclic dienes (Scheme 2a).²⁴ Similarly, a few years later, the same group expanded the investigation towards an intra molecular version for the synthesis of polyheterocyclic scaffolds by reacting oxoallyl cations with various dienes (Scheme 2b).²⁵

In recent years, other protocols have been studied for the synthesis of heterocyclic compounds using these solvents as promoters in [4+3] and [3+2] cycloaddition processes,^{26,27} resulting in an

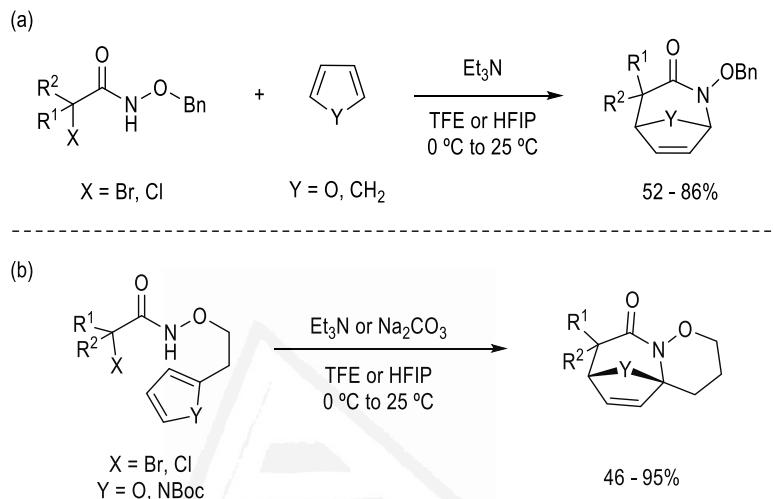
²⁴ Jeffrey, C. S.; Barnes, K. L.; Eickhoff, J. A.; Carson, C. R. *J. Am. Chem. Soc.* **2011**, *133*, 7688-7691.

²⁵ Acharya, A.; Eickhoff, J. A.; Jeffrey, C. S. *Synthesis* **2013**, *45*, 1825-1836.

²⁶ (a)For some examples, see: Li, H.; Hughes, R. P.; Wu, J. *J. Am. Chem. Soc.* **2014**, *136*, 6288-6296; (b) Acharya, A.; Anumandla, D.; Jeffrey, C. S. *J. Am. Chem. Soc.* **2015**, *137*, 14858-14860; (c) DiPoto, M. C.; Hughes, R. P.; Wu, J. *J. Am. Chem. Soc.* **2015**, *137*, 14861-14864; (d) Siyang, H. X.; Ji, X. Y.; Wu, X. R.; Wu, X. Y.; Liu, P. N. *Org. Lett.* **2015**, *17*, 5220-5223; (e) Ji, W.; Yao, L.; Liao, X. *Org. Lett.* **2016**, *18*, 628-630; (f) Liu, J.; Wang, L.; Wang, X.; Xu, L.; Hao, Z.; Xiao, J. *Org. Biomol. Chem.* **2016**, *14*, 11510-11517; (g) Zhang, K.; Yang, C.; Yao, H.; Lin, A. *Org. Lett.* **2016**, *18*, 4618-4621; (h) Liu, K.; Tang, S.; Huang, P.; Lei, A. *Nat. Commun.* **2017**, *8*, 1-8.

²⁷ Khaksar, S. *J. Fluorine Chem.* **2015**, *172*, 51-61.

easier procedure, in the majority of the cases, along with a significant improvement of the yield compared with previous protocols, obtaining a broad range of heterocyclic scaffolds with a great interest for the pharmaceutical industry.



Scheme 2. Intramolecular aza-[4+3] cycloaddition reactions

C-C and C-Heteroatom Bond-Forming Reactions

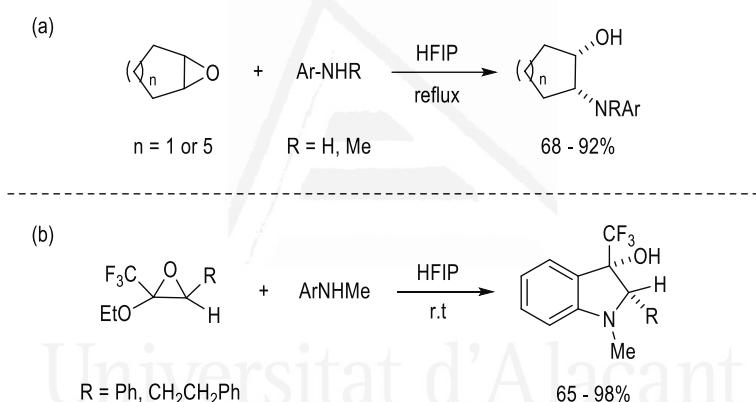
The possibility to give rise to C-C and C-Het (Het = N, O, S, P, etc) bond formation, giving access to a wide range of organic molecules of great interest in the industry, has attracted the attention of synthetic organic chemists over decades. Hence, new methodologies are constantly emerging in this field keeping up with the current trends of Green Chemistry avoiding hazardous reagents and extreme conditions.²⁸

In this sense, the ring-opening reaction of epoxides has been widely studied. The need and interest in carrying out these reactions is due to the necessity in obtaining relevant intermediates in organic synthesis and valuable compounds in medicinal chemistry. Numerous examples have been

²⁸ Brahmachari, G. RSC Adv. 2016, 6, 64676-64725.

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described being usually promoted by Lewis acids or metal salts in a basic medium.²⁹ Even so, it is worth mentioning that, owing to the special properties of fluorinated alcohols such as the high ionizing power and their acidity character, these solvents offer a new possibility to perform these reactions in the absence of any basic medium, lower reaction times and avoiding the use of neither salts nor extreme temperatures. Thus, in 2000, Bégué reported the use of aromatic amines as nucleophiles for the ring-opening reaction of epoxides by using HFIP as solvent and promoter leading to the formation of aminoalcohols (Scheme 3a).³⁰ Likewise, a year later, the same group studied the reaction of different epoxyethers with diverse aromatic secondary amines for the preparation of indolinol derivatives using anew HFIP as the only promoter for the ring-opening process (Scheme 3b).³¹



Scheme 3. Ring-opening reactions of epoxides with aromatic amines.

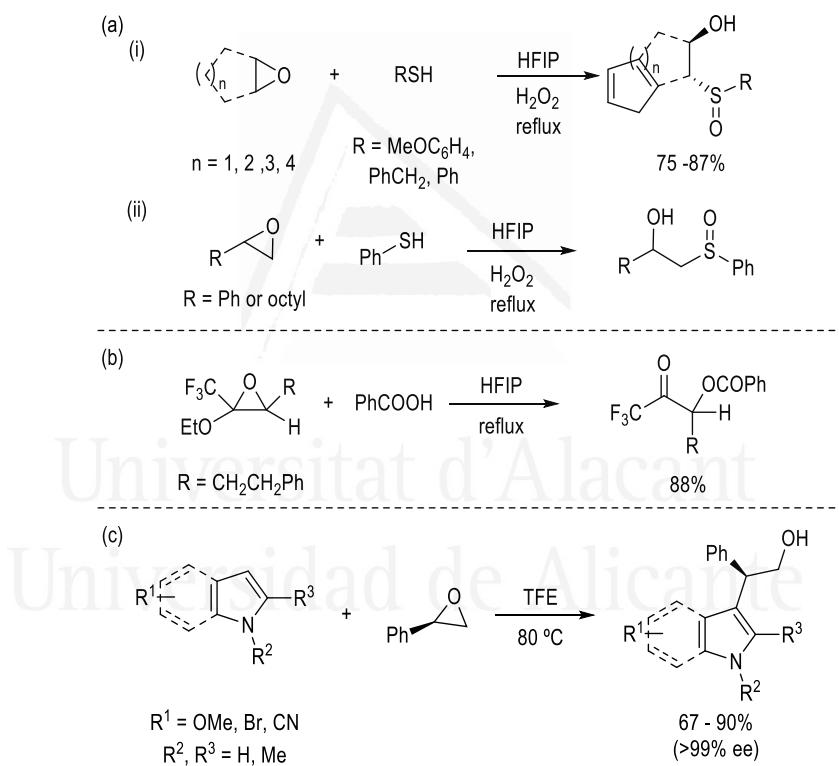
In the same area, they also investigated the ring-opening reaction of cyclic epoxides with a small selection of thiols (Scheme 4a, i), noticing how HFIP was able to reduce the reaction time.

²⁹ (a) For some examples see: Van de Weghe, P.; Collin, J. *Tetrahedron Lett.* **1995**, 36, 1649-1652; (b) Fu, X.-L.; Wu, S.-H. *Synth. Commun.* **1997**, 27, 1677-1683; (c) Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, 64, 287-289; (d) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *Org. Lett.* **2002**, 4, 2817-2819; (e) Cossy, J.; Bellosta, V.; Hamoir, C.; Desmurs, J.-R. *Tetrahedron Lett.* **2002**, 43, 7083-7086; (f) Dioos, B. M. L.; Geurts, W. A.; Jacobs, P. A. *Catal. Lett.* **2004**, 97, 125-129; (g) Yang, M.; Zhu, C.; Yuan, F.; Huang, Y.; Pan, Y. *Org. Lett.* **2005**, 7, 1927-1930; (h) Yadav, J. S.; Reddy, A. R.; Narsaiah, A. V.; Reddy, B. V. S. *J. Mol. Catal. A: Chem.* **2007**, 261, 207-212.

³⁰ Das, U.; Crousse, B.; Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem.* **2000**, 65, 6749-6751.

³¹ Rodrigues, I.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem.* **2001**, 66, 2098-2103.

Similarly, this procedure was also evaluated with cyclic and acyclic alkenes, as well as styrene derived oxides observing both, a completely regioselectivity and a mixture of regioisomers, respectively (Scheme 4a, i and ii, respectively). Thereupon, the corresponding sulfoxides were prepared in all the cases by adding H_2O_2 to the reaction media.³² In 2002, it was proven that utilising various carboxylic acids as nucleophiles in HFIP, the ring-opening reaction was reached meaningfully (Scheme 4b).³³ Later, in 2008, Mayr's group reported a similar strategy for the regio- and stereoselective ring-opening reaction of epoxides by using, in this case, indoles and pyrroles as nucleophiles and TFE as promoter for the reaction (Scheme 4c).³⁴



Scheme 4. Ring-opening reactions of epoxides with (a) thiols, (b) carboxylic acids and (c) indoles.

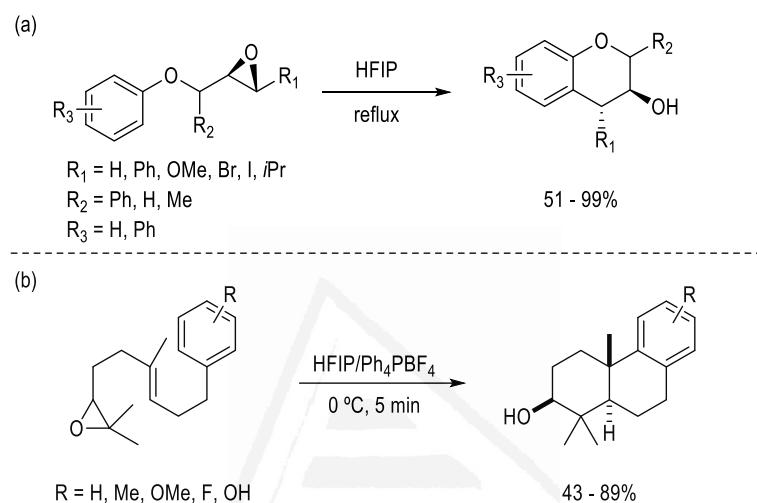
³² Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *Tetrahedron Lett.* **2000**, *41*, 2895-2898.

³³ Iskra, J.; Bonnet-Delpon, D.; Bégué, J.-P. *Eur. J. Org. Chem.* **2002**, *2002*, 3402-3410.

³⁴ Westermaier, M.; Mayr, H. *Chem. Eur. J.* **2008**, *14*, 1638-1647.

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In 2010 Qu and co-workers demonstrated that HFIP was able to act as a promoter for the intramolecular Friedel-Crafts alkylation of arenes with epoxides (Scheme 5a).³⁵ Years later, the same group developed the polycyclisation of oxidosqualene derivatives by using HFIP in combination with borate as efficient promotor in the absence of a metal catalyst (Scheme 5b).³⁶



Scheme 5. (a) Friedel-Crafts alkylation and (b) olefin polycyclization.

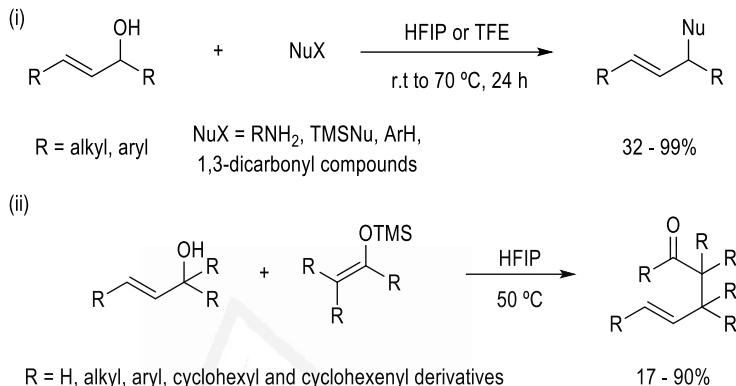
Not only ring-opening reactions of epoxides could offer a huge variety of engrossing structures in organic chemistry, but also, nucleophilic substitution, gives chemists the possibility to obtain a varied assortment of interesting scaffolds for further studies. Consequently, the interest of performing those reactions by using fluorinated alcohols as solvents had drawn attention in this field. For instance, in 2012, our research group described the ability of fluorinated alcohols to act as promoters for the straightforward substitution reaction of allylic alcohols with diverse nucleophiles such as amines, carbamates, carboxamides or sulfonamides (Scheme 6, i).³⁷

³⁵ Li, G.-X.; Qu, J. *J. Chem. Commun.* **2010**, 46, 2653-2655.

³⁶ Tian, Y.; Xu, X.; Zhang, L.; Qu, J. *J. Org. Lett.* **2016**, 18, 268-271.

³⁷ Trillo, P.; Baeza, A.; Nájera, C. *J. Org. Chem.* **2012**, 77, 7344-7354.

Years later, this strategy was successfully applied for the allylation of a variety of silyl enol ethers with allylic alcohols mediated by HFIP (Scheme 6, ii).^{38,39}



Scheme 6. $\text{S}_{\text{N}}1$ -type reaction of allylic alcohols.

Furthermore, in 2012, the selective alkylation of nitro alkanes was reported by Cozzy and co-workers where a $\text{S}_{\text{N}}1$ -type reaction was possible by using TFE as promoter (Scheme 7a).⁴⁰ Likewise, in 2015, Xiao's group performed the nucleophilic substitution of indolyl alcohols mediated by TFE with assorted nucleophiles, namely indoles, active methylene compounds, arenes or thiols, providing a free-catalyst procedure (Scheme 7b).⁴¹

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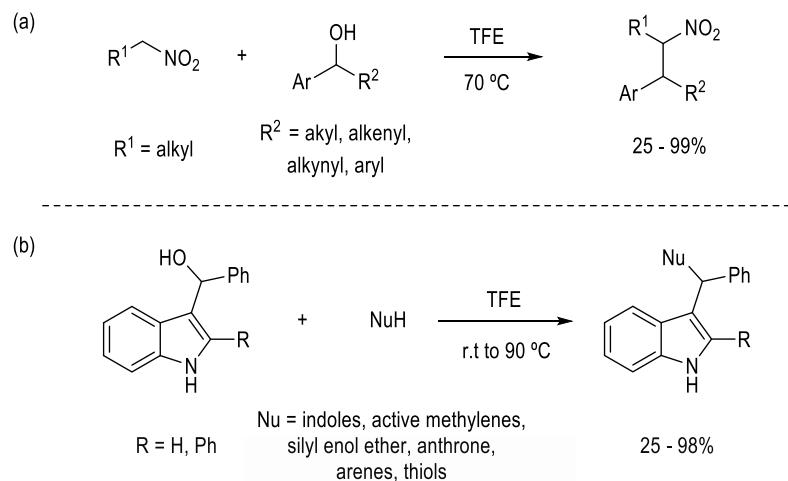
³⁸ Pérez, J. M.; Maquilón, C.; Ramón, D. J.; Baeza, A. *Asian J. Org. Chem.* **2017**, 6, 1440-1444.

³⁹ (a) For some examples of C-C and C-Het bond formation, see: De, K.; Legros, J.; Crousse, B.; Bonnet-Delpon, D. *J. Org. Chem.* **2009**, 74, 6260-6265; (b) Khaksar, S.; Heydari, A.; Tajbakhsh, M.; Bijanzadeh, H. R. *J. Fluorine Chem.* **2010**, 131, 106-110; (c) Li, G.-X.; Qu, J. *Chem. Commun.* **2010**, 46, 2653-2655; (d) Dumitrescu, L.; Azzouzi-Zriba, K.; Bonnet-Delpon, D.; Crousse, B. *Org. Lett.* **2011**, 13, 692-695; (e) Xiao, J.; Zhao, K.; Loh, T.-P. *Chem. Commun.* **2012**, 48, 3548-3550; (f) Champagne, P. A.; Benhassine, Y.; Desroches, J.; Paquin, J.-F. *Angew. Chem. Int. Ed.* **2014**, 53, 13835-13839; (g) Tang, R.-J.; Milcent, T.; Crousse, B. *RSC Adv.* **2018**, 8, 10314-10317; (h) Yu, L.; Li, S.-S.; Li, W.; Yu, S.; Liu, Q.; Xiao, J. *J. Org. Chem.* **2018**, 83, 15277-15283.

⁴⁰ Petruzzello, D.; Gualandi, A.; Grilli, S.; Cozzi, P. G. *Eur. J. Org. Chem.* **2012**, 2012, 6697-6701.

⁴¹ Wen, H.; Wang, L.; Xu, L.; Hao, Z.; Shao, C.-L.; Wang, C.-Y.; Xiao, J. *Adv. Synth. Catal.* **2015**, 357, 4023-4030.

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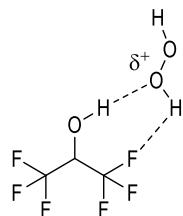


Scheme 7. (a) Intermolecular alkylation of nitro derivatives and (b) $\text{S}_{\text{N}}1$ -type reactions of indolyl alcohols.

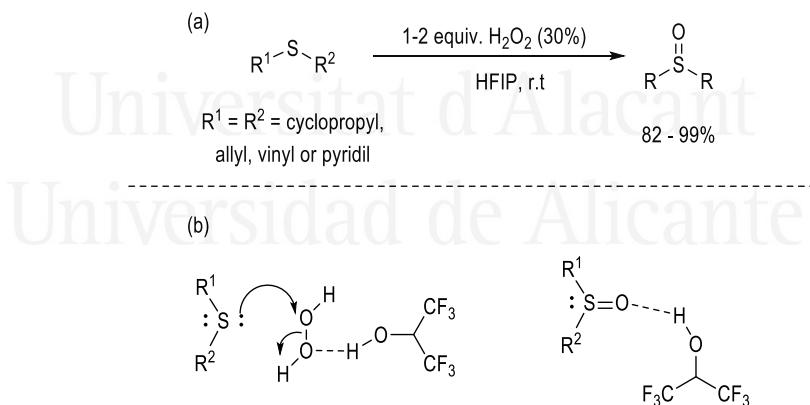
Oxidation Reactions

Oxidation processes have gained considerable importance in organic chemistry over the years, even though being considered one of the most challenging transformations. The necessity of metal catalysts or long reaction times and the very frequent overoxidation of the starting material, have led to seek and study new protocols in greater accordance with the 12 principles of Green Chemistry. Thereupon, the emergence of fluorinated alcohols and their special properties concerning their capacity to activate oxidants through hydrogen bonding have caught chemists' attention over the last few decades. In this sense, amongst the myriad of oxidizing reagents known, aqueous H_2O_2 is considered one of the cheapest and greenest available, being moreover, easily activated by fluorinated alcohols, particularly by HFIP (Figure 4).⁴² As a result of this activation, H_2O_2 has become a good electrophile allowing the oxidation of nucleophilic species.

⁴² (a) Strukul, G. *Catalytic Oxidations with Hydrogen Peroxide as Oxidant.*; Kluwer, 1992; (b) Bäckvall, J. E. *Modern Oxidation Methods*; Wiley-VCH Weinheim, 2004; (c) Bäckvall, J. E. *Modern Oxidation Methods, 2nd Completely Revised*; Wiley-VCH Weinheim, 2010.

**Figure 4.** HFIP-H₂O₂ activated complex.

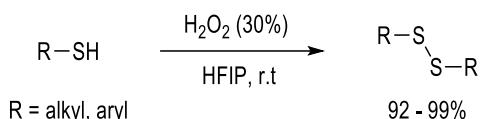
In this sense, the first oxidation reaction reported, in which hydrogen peroxide was activated by fluorinated alcohols, was carried out by Bégué and co-workers in 1998. Therein, HFIP in combination with H₂O₂ (30%) gave rise a selective and efficient oxidation system allowing the conversion of sulfides to sulfoxides (Scheme 8a). The main role of HFIP in this oxidation process is largely due to the electron-withdrawing character of CF₃ group, which is able to form a strong hydrogen bond between the H₂O₂ and the hydroxyl proton in HFIP activating the hydroxyl leaving group of H₂O₂ and, simultaneously, diminishing the nucleophilicity of the sulfur atom preventing further oxidations (Scheme 8b).⁴³

**Scheme 8.** (a) Selective oxidation of sulfide derivatives; (b) Role of HFIP in sulfide oxidation.

⁴³ (a) Ravikumar, K. S.; Bégué, J.-P.; Bonnet-Delpon, D. *Tetrahedron Lett.* **1998**, 39, 3141-3144; (b) Ravikumar, K. S.; Zhang, Y. M.; Bégué, J.-P.; Bonnet-Delpon, D. *Eur. J. Org. Chem.* **1998**, 2937-2940; (c) Ravikumar, K. S.; Barbier, F.; Bégué, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **1999**, 95, 123-125.

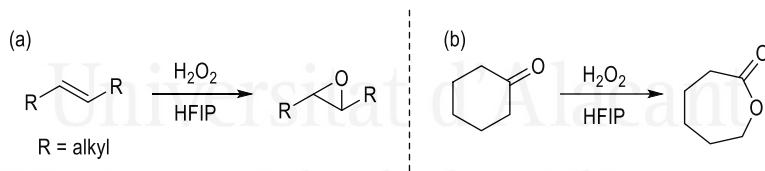
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In 2000, as an attempt to further expand the ability of HFIP to activate H_2O_2 on oxidation reactions, Bégué's group reported a similar methodology by using this HFIP- H_2O_2 oxidation system to obtain disulfides from thiols establishing a mild and efficient protocol avoiding the use of metal catalysts, long reaction times and strong conditions (Scheme 9).⁴⁴



Scheme 9. Oxidation of thiols to disulfides.

Simultaneously, Neumann and Neumann demonstrated that the epoxidation of alkenes and the Baeyer-Villiger oxidation of ketones was possible using fluorinated alcohols with H_2O_2 in the absence of any catalysts (Scheme 10),⁴⁵ achieving an environmentally friendly protocol, although some of the examples involved H_2O_2 (60%) or even reflux conditions. In this context, few years later Berkessel reported several studies concerning the reaction mechanisms of this particular epoxidation of alkenes.^{46,47}



Scheme 10. (a) Epoxidation of alkenes, (b) the Baeyer-Villiger oxidation of ketones.

⁴⁴ Kesavan, V.; Bonnet-Delpon, D.; Begue, J.-P. *Synthesis* **2000**, 223-225.

⁴⁵ Neumann, K.; Neumann, R. *Org. Lett.* **2000**, 2, 2861-2863.

⁴⁶ (a) Berkessel, A.; Andreea, M. R. M. *Tetrahedron Lett.* **2001**, 42, 2293-2295; (b) van Vliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *Synlett* **2001**, 0248-0250; (c) van Vliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *Synlett* **2001**, 2001, 1305-1307; (d) Iskra, J.; Bonnet-Delpon, D.; Bégué, J.-P. *Tetrahedron Lett.* **2002**, 43, 1001-1003.

⁴⁷ (a) Berkessel, A.; Andreea, M. R. M.; Schmickler, H.; Lex, J. *Angew. Chem. Int. Ed.* **2002**, 41, 4481-4484; (b) Berkessel, A. *Organocatalysis by Hydrogen Bonding Networks*; Springer, Berlin, 2008; (c) Hollóczki, O.; Berkessel, A.; Mars, J.; Mezger, M.; Wiebe, A.; Waldvogel, S. R.; Kirchner, B. *ACS Catal.* **2017**, 7, 1846-1852.

The oxidative power of H_2O_2 has been widely recognised as smoother and greener in comparison with other traditionally employed oxidants over the last decades hence expanding its use in organic chemistry. Likewise, in the seek of feasible sources for oxidation processes, in 2002 Bégué reported an urea-hydrogen peroxide adduct (UHP) as benign alternative oxidant and safe source of anhydrous hydrogen peroxide. Herein, the epoxidation of several olefins was carried out in the absence of any catalyst.⁴⁸ This was possible due to the great capacity of the solvent to activate this Urea- H_2O_2 (Figure 5) complex in the same way as commented above.

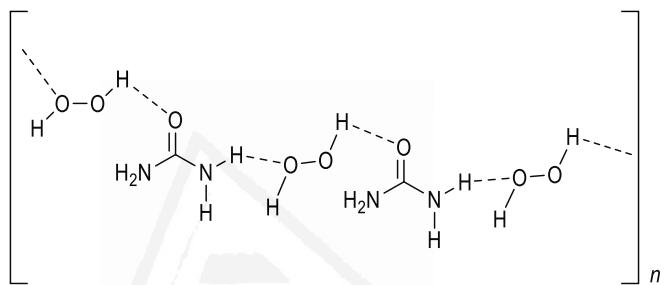


Figure 5. UHP complex.

Last but not least, apart from all the reactions mentioned above, fluorinated alcohols have been involved as promoters in other reactions such as Friedel-Crafts alkylation reactions, electrophilic nitration and halogenation reactions or functionalisation of multiple bonds.^{6d,17c}

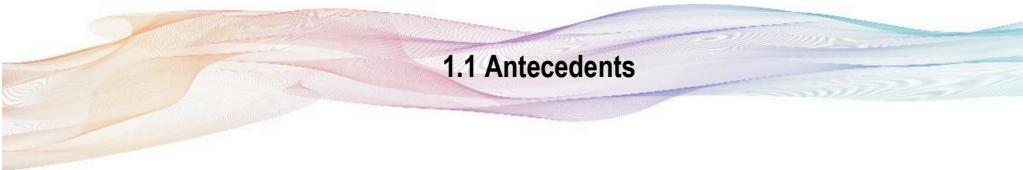
Finally, it is worth to mention that apart from being employed as promoters in some organic transformations, fluorinated alcohols can also be utilised as special solvents or additives in several catalytic processes, specially in the transition metal-catalysed hydrogenation reactions and cross-coupling and C-H activation reactions.^{6b}

⁴⁸ Legros, J.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J.-P. *Eur. J. Org. Chem.* **2002**, 3290-3293.

CHAPTER I

Synthesis of Substituted Tetrahydrofurans through HFIP-Promoted Ring-Opening
Reaction of Epoxides with Electron-Rich Arenes

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1.1 Antecedents

1.1.1 General

The furan ring and substituted tetrahydrofuran structures are an important class of heterocyclic scaffolds present in a great range of natural compounds and bioactive natural molecules being of particular interest in pharmaceutical research. By and large, these sort of natural compounds containing tetrahydrofuran ring derivatives have been found in both, marine and terrestrial organisms.⁴⁹ Therefore, one of the most representative examples studied are Caloxylanes A and B, isolated from the Caribbean marine sponge *Calyx podatypa*.⁵⁰ Likewise, Corsifuran A can be isolated from de Mediterranean liverwort *Corsinia coriandrina*.⁵¹ Furthermore, other interesting examples, which exhibit interesting pharmacological activities such as antibacterial, antiviral antitumor, cytotoxic or antioxidant, are the lignans Fragransin C1 isolated from *Machilus robusta* (among the diverse range of compounds from the Fragransin family),⁵² and neolignan (-) Conocarpan⁵³ amid other structures (Figure 6).

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⁴⁹ (a) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, 63, 261-290; (b) Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Álvarez, M. *Chem. Rev.* **2013**, 113, 4567-4610; (c) Fang, X.; Hu, X. *Molecules* **2018**, 23, 3385-3407; (d) Kwiecień, H.; Wodnicka, A. *5.3 - Five-Membered Ring Systems: Furans and Benzofurans*; Elsevier, 2020.

⁵⁰ (a) Rodríguez, A. D.; Cobar, O. M.; Padilla, O. L. *J. Nat. Prod.* **1997**, 60, 915-917; (b) Gharpure, S. J.; Vishwakarma, D. S.; Nanda, S. K. *Org. Lett.* **2017**, 19, 6534-6537.

⁵¹ (a) von Reuß, S. H.; König, W. A. *Phytochemistry* **2004**, 65, 3113-3118; (b) Adams, H.; Gilmore, N. J.; Jones, S.; Muldowney, M. P.; von Reuss, S. H.; Vemula, R. *Org. Lett.* **2008**, 10, 1457-1460; (c) Pauli, L.; Tannert, R.; Scheil, R.; Pfaltz, A. *Chem. Eur. J.* **2015**, 21, 1482-1487.

⁵² (a) Chaimanee, S.; Pohmakotr, M.; Kuhakarn, C.; Reutrakul, V.; Soorukram, D. *Org. Biomol. Chem.* **2017**, 15, 3985-3994; (b) Racochote, S.; Pohmakotr, M.; Kuhakarn, C.; Leowanawat, P.; Reutrakul, V.; Soorukram, D. *Eur. J. Org. Chem.* **2019**, 2212-2223.

⁵³ Clive, D. L. J.; Stoffman, E. J. L. *Chem. Commun.* **2007**, 2151-2153.

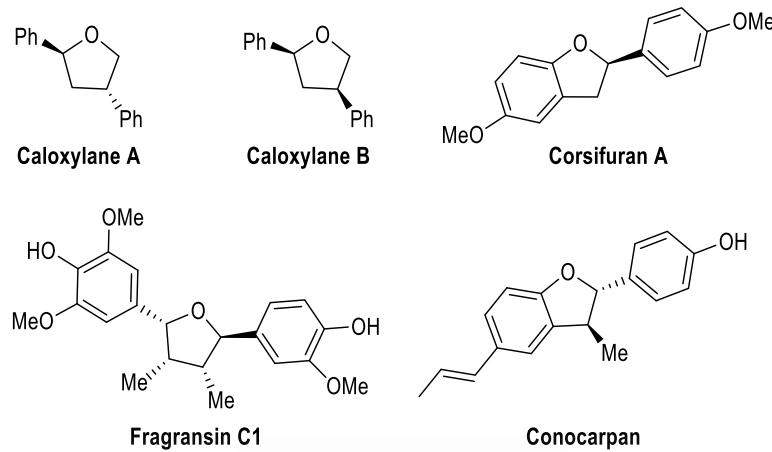


Figure 6. Natural products and bioactive molecules containing tetrahydrofuran moiety.

1.1.2 Synthesis of Tetrahydrofuran Derivatives

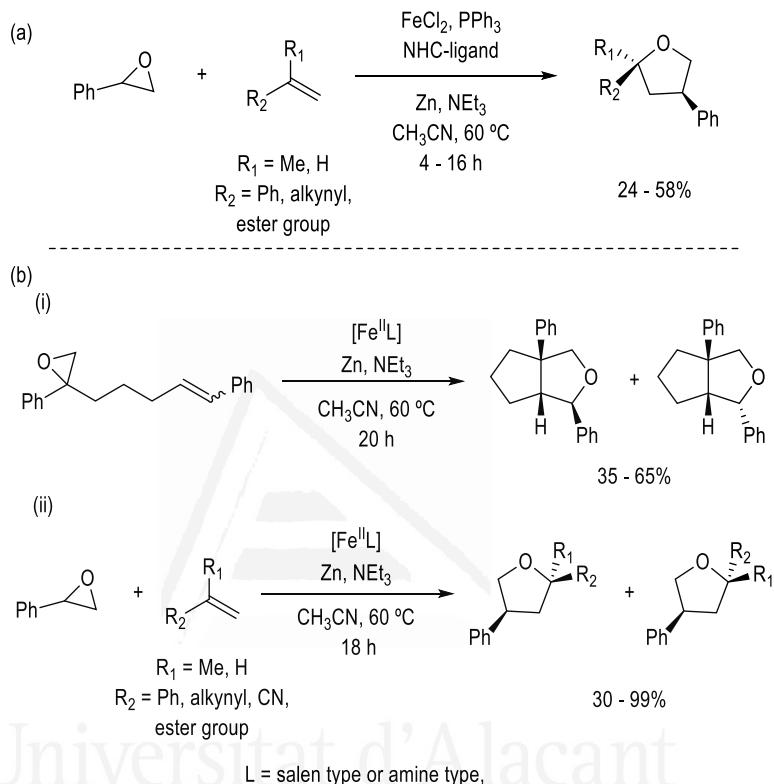
On view of their prominent role in pharmaceutical research aforementioned, the interest of developing new methodologies as a means of gaining access to these riveting moieties has been considerable increased in the last decade. In such a way, among the great variety of processes reported, the ones making use of commercially available and highly abundant bulk epoxides and alkenes as starting materials, may be the most useful protocols studied affording an extensive array of substituted tetrahydrofurans giving rise to an utter atom-economy process. Albeit, a tiny amount of studies according to this premise have been found in the literature. Thus, in 2005, Hilt's group developed a feasible method for the ring-opening reaction of epoxides with conjugated alkenes under iron(II) catalysis providing substituted tetrahydrofuran derivatives in an extremely regio- and chemoselective manner (Scheme 11a).⁵⁴ One year after, in 2006, the same group reported a single electron transfer (SET) mechanism for the intramolecular ring expansion reaction of epoxyalkenes by using a similar iron(II)-based catalyst, thereby giving rise to diastereomerically pure tetrahydrofuran derivatives (Scheme 11bi).⁵⁵ Later on, in 2007 further studies from the same group

⁵⁴ Hilt, G.; Bolze, P.; Kieltsch, I. *Chem. Commun.* **2005**, 1996-1998.

⁵⁵ Hilt, G.; Walter, C.; Bolze, P. *Adv. Synth. Catal.* **2006**, 348, 1241-1247.

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described the intermolecular reaction of styrene oxide with alkenes by using an iron(II)-salen complex as catalyst, which allowed to broaden the scope of the reaction (Scheme 11bii).⁵⁶



Scheme 11. Ring-expansion reaction of epoxides.

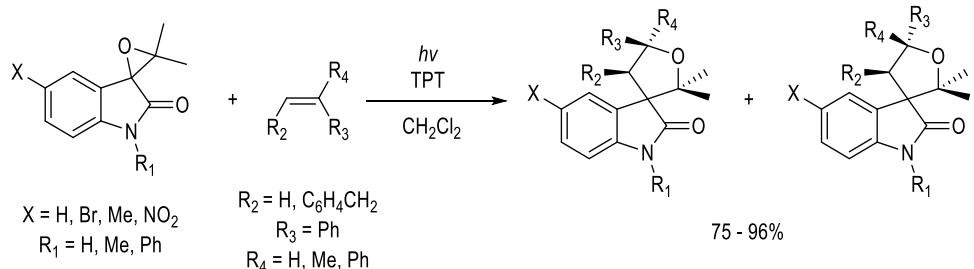
More recently, in 2012, a photoinduced electron transfer catalysis has been carried out by Zhang and co-workers allowing the ring-opening reaction of oxiranes with the consequent cycloaddition of electron-rich olefins by using 2,4,6-triphenylpyrylium tetrafluoroborate (TPT) as sensitizer. This radical procedure provides the heterocyclic spiro-oxindole motifs in high yields (

Scheme 12).⁵⁷

⁵⁶ Hilt, G.; Bolze, P.; Harms, K. *Chem. Eur. J.* **2007**, *13*, 4312-4325.

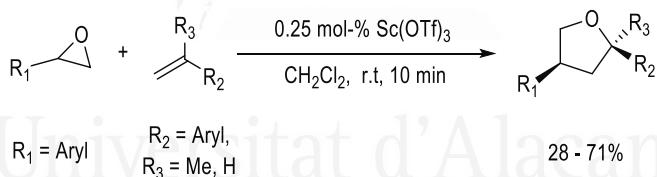
⁵⁷ Wang, L.; Li, Z.; Lu, L.; Zhang, W. *Tetrahedron* **2012**, *68*, 1483-1491.

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Scheme 12. Photoinduced electron transfer-catalyzed [3+2] reaction.

Bearing in mind the growing importance of intermolecular [3+2] cycloadditions in organic synthesis, in 2016 Hilinski's group studied the possibility of performing intermolecular reaction between substituted epoxides and alkenes. In this sense, they have demonstrated a profitable methodology catalysed by Lewis-acidic triflate salts giving rise to substituted tetrahydrofurans in a regio- and diastereoselective manner (Scheme 13).⁵⁸



Scheme 13. [3+2] Cycloaddition catalysed by Lewis Acid.

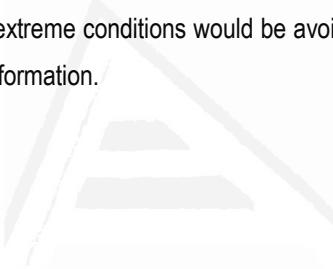
⁵⁸ Shuler, W. G.; Combee, L. A.; Falk, I. D.; Hilinski, M. K. *Eur. J. Org. Chem.* **2016**, 3335-3338.



1.2 Objectives

Taking into account this literature background and the great performance of fluorinated alcohols observed for ring-opening reactions of epoxides, the following objective was established:

To carry out the synthesis of tetrahydrofurans by employing fluorinated alcohols as solvents and reaction promoters for the ring-opening reaction of epoxides with different electron-rich alkenes. Thus, the use of metals and extreme conditions would be avoided, in an efficient, cost-effective and environmentally friendly transformation.



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1.3 Discussion of Results

Firstly, a preliminary study of solvent, temperature and time was carried out in order to obtain the optimal reaction conditions. In this sense, the reaction between styrene oxide (**1a**) and α -methylstyrene (**2a**) was selected as a model. To start with, a variety of fluorinated and non-fluorinated solvents were selected to evaluate their performance at 45 °C (Table 2, entries 1-4). It is worth to mention that, when water and 2-propanol, which also possesses quite high polarity and hydrogen bond ability, were employed, the desired reaction failed, generating only the diol **4** as major product in the first case (Table 2, entries 1 and 2, respectively). Consequently, 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and 2,2,2-trifluoroethanol (TFE), as readily available and inexpensive fluorinated alcohols, were tested. In such a way, as depicted in the table, the desired product was afforded in high conversion when using HFIP, whereas tetrahydrofuran **3aa** was barely obtained when TFE was employed (Table 2, entries 3 and 4, respectively). Their different properties can explain this striking contrast of both fluorinated alcohols when performing this transformation. Therefore, comparing both solvents, HFIP has higher acidity [pK_a (TFE) = 12.37, pK_a (HFIP) = 9.30] and higher hydrogen bond ability [α_{TFE} = 1.51, α_{HFIP} = 1.96], which can facilitate, the activation of epoxide ring. Furthermore, HFIP possesses much lower nucleophilicity [N_{TFE} = -2.78, N_{HFIP} = -4.23], therefore, the obtention of the fluoroalkyl ether **5** (Table 2) as major product when TFE was essayed it is not surprising. On the contrary, the corresponding fluorinated ether **6** (Table 2), derived from HFIP (along with phenylacetaldehyde and acetophenone) was obtained only as by product. Further to this, the reaction was carried out also in the absence of any solvent. As somehow expected, any product was observed (Table 2, entry 5).

Additionally, a series of HFIP/CH₂Cl₂ mixtures (Table 2, entries 6-8) were employed in order to ameliorate the conversion of tetrahydrofuran **3aa**, but the efforts resulted to be unsuccessful in all the cases. It is worth to mention that, decreasing down the reaction temperature to 25 °C, did not

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produce an improvement of the conversion towards the desired product (Table 2, entry 9). Last but not least, the reaction time was also controlled in a range of 24 hours, observing that between 6 and 15 hours of reaction, the expected tetrahydrofuran **3aa** reached the highest conversions. At this point, further changes in reaction stoichiometry and the amount of solvent were also attempted not producing any amelioration.

Table 2. Optimisation of the reaction parameters^[a]

Entry	Solvent	T (°C)	Conv. (%) ^[b]
			3aa
1	H ₂ O	45	13
2	iPrOH	45	0
3	HFIP	45	72
4	TFE	45	3
5	None	45	2
6	HFIP/CH ₂ Cl ₂ (9/1)	45	50
7	HFIP/CH ₂ Cl ₂ (1/1)	45	15
8	HFIP/CH ₂ Cl ₂ (1/9)	45	23
9	HFIP	25	30

^[a] All reactions were carried out using 0.15 mmol of styrene oxide (**1a**) and 0.25 mmol of α -methylstyrene (**2a**) in 150 μ L of the solvent for 20 h using a sand bath. ^[b] Conversion towards formation of **3aa**, determined by GC-MS.

After the optimisation process, the best reaction conditions for the ring-opening reaction were those described in Table 2, entry 3, involving the use of HFIP as solvent at 45 °C, being complete the reaction in less than 10 hours under conventional heating using a sand bath. Next, in order to study the scope of the reaction, different electron-rich alkenes **2** were employed as nucleophiles for the ring-opening reaction of styrene oxide (**1a**) (Table 3). Firstly, a great variety of substituted

Discussion of Results

styrenes were chosen as nucleophiles. As mentioned above, the use of α -methylstyrene (**2a**) led to the formation of the corresponding tetrahydrofuran **3aa** as a mixture of diastereoisomers in moderated isolated yield. When an electron-richer alkene **2b** was used, better results were observed, reaching up to 67% yield for compound **3ab**. The employment of sterically hindered styrenes, such as 1,1-diphenylethylene (**2c**), afforded the corresponding product in only modest yield, observing some amount (25%) of the opposite regioisomer too, probably caused by the mentioned steric hinderance. Next, styrene (**3d**) was essayed obtaining the corresponding natural product Caloxylane **3ad** in 39% yield. Similar result was observed when 4-chlorostyrene (**2e**) was employed, obtaining the tetrahydrofuran **3ae** in modest yield. Surprisingly, when the more electron rich alkene, 4-methoxystyrene (**2f**), was tested, gave rise to the corresponding product in low conversion. Methylenecyclohexane (**2g**) was next checked, providing spiro-compound **3ag** in modest yield. More substituted alkenes were next examined. In such a way, stilbenes were submitted to the reaction conditions but failed and only a low conversion was observed when the *cis*-isomer (**2h**) was employed. Therefore, 1-phenylcyclohexene (**2i**), as trisubstituted alkene, was also taken into account, affording in this case the interesting octahydrobenzofuran derivative **3ai** in 34% yield. Lastly, several benzocondensed alkenes were also essayed. Thus, whereas indene **2j** produced the expected product **3aj** in modest yield, the reaction using 1,2-dihydronaphthalene **2k**, barely worked. Finally, when benzofuran (**2l**) was employed as alkene, the corresponding tetrahydrofurobenzofuran derivative **3al**, arising from the attack of benzofuran through its 2-position onto the epoxide, was obtained with moderate yield and quite good diastereoselectivity.

As observed in Table 3, it is important to mention that in the majority of cases, the ring-opening reaction was highly regioselective, but when a mixture of diastereoisomers was obtained, low diastereoselective ratios were observed. Moreover, at this point, it is worth to highlight the formation of dimers or trimmers of the majority of the styrenes employed, which were detected by GC-MS, hence lowering the yield of the process. Furthermore, in all the cases, ether **6** along with acetophenone and phenylacetaldehyde (coming from the Meinwald Rearrangement of the epoxide), were also observed as by-products.

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Table 3. Reaction between styrene oxide and electron-rich alkenes^[a]

	+		HFIP 45 °C 6-15 h	
1a		2a-l		3aa-3al
R ¹ = Me, R ² = H 3aa , 54%, 55:45 ^d		R ¹ = Me, R ² = OMe 3ab , 67%, 55:45 ^d		R ¹ = Ph, R ² = H 3ac , 38% ^b
R ¹ , R ² = H 3ad , 39%, 65:35 ^d		R ¹ = H, R ² = Cl 3ae , 36%, 60:40 ^d		R ¹ = H, R ² = OMe 3af (15% conv.) ^c
From 3ag , 45% ^b		R ¹ , R ² = H, X = Ph 3ah (13% conv.) ^c		From 3ai , 34%, 55:45 ^d
R ¹ , R ² = H X = CH ₂ , n = 0 3aj , 40%, 60:40 ^d		R ¹ , R ² = H X = CH ₂ , n = 1 3ak (15% conv.) ^c		R ¹ , R ² = H X = O, n = 0 3al , 58%, ^b 80:20 ^d

^[a] All reactions were carried out using 0.15 mmol of styrene oxide (**1a**) and 0.25 mmol of the corresponding alkene (**2a-l**) in 150 µL of the solvent. ^[b] Estimation of the crude yield from ¹H NMR data. ^[c] Conversion towards formation of tetrahydrofuran, determined by ¹H NMR and/or GC-MS. ^[d] Diastereomeric ratio determined by ¹H NMR and/or GC-MS of the crude compounds.

Next, in order to further expand the scope of the reaction, other epoxides were tested with those alkenes that provided the best results (Table 4). On this account, in view of the results observed, it was thought to carry out the reaction using *α*-methylstyrene oxide (**1b**). Using this

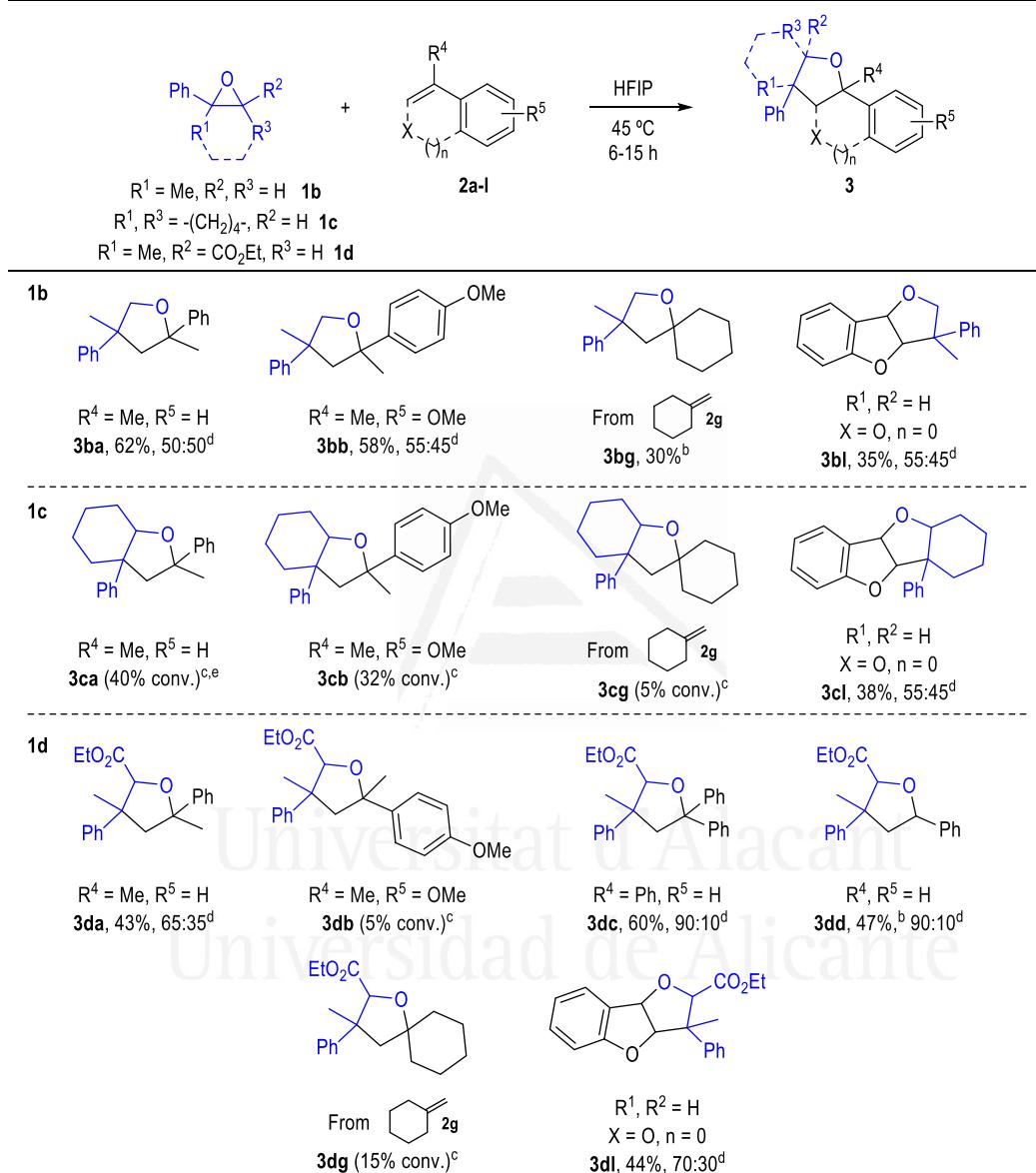
Discussion of Results

epoxide, it was noticed that when α -methylstyrene **2a** and more electron-rich alkene **2b** were employed, good yields were observed. Nevertheless, modest yields were only achieved when ethylenecyclohexane (**2g**) and benzofuran (**2l**) were tested. Likewise, the reaction was also performed with 1-phenylcyclohexene oxide (**1c**). As result, modest yields were acquired for adducts **3ca** and **3cb**. Unexpectedly, when methylenecyclohexane was employed, the reaction did not work, obtaining only 5% of conversion for **3cg**. It is worth to mention the result obtained when using benzofuran (**2l**). In this case, despite a modest 38% yield was achieved, an interesting tetracyclic compound **3cl** was isolated. Finally, commercially available ethyl 3-methyl-3-phenylglycidate (**1d**) was also assessed. At his point, it is important to note that, unlike the conventional tendency observed thus far in previous cases concerning the low diastereoselectivity achieved, moderate to good diastereoseletivities were reached with this substrate. In this sense, when α -methylstyrene (**2a**) was employed, modest yield was achieved, rendering the densely substituted **3da** in 43% yield. Howbeit, when using the electron-richer alkene **2b**, the desired reactions barely worked, being both dimerisation and trimerisation product of the alkene the major products observed by GC-MS. It is worth noting that, surprisingly, when alkene **2c** was utilised, it gave rise to the corresponding tetrahydrofuran **3dc** in 60% yield and 90:10 diastereomeric ratio. Therefore, encouraged by this result, it was thought to perform the reaction employing the less hindered styrene **2d** obtaining tetrahydrofuran **3dd** in modest yield. Unfortunately, the reaction failed when endo and exo cyclic (**2g**) and benzocondensed (**2j**) alkenes were the substrates used. Again, the reaction somehow worked when benzofuran (**2l**) was finally employed, providing a tricyclic compound (**3dl**) in a modest 44% yield.

Last but not least, it is worth mentioning that other epoxides such as cyclohexene oxide, 1-octene oxide, indene oxide and *cis*- and *trans*-stilbene oxide were also considered as substrates to perform the reaction with alkenes depicted in Table 4. Regrettably, none of them worked as expected.

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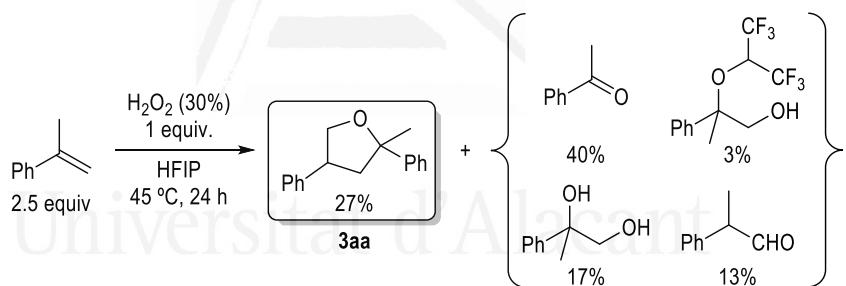
Table 4. Reaction between epoxides and electron-rich alkenes^[a]



^[a] All reactions were carried out using 0.15 mmol of epoxide (**1a-d**) and 0.25 mmol of alkene (**2a-l**) in 150 μL of the solvent. ^[b] Estimation of the crude yield from ^1H NMR data. ^[c] Conversion towards formation of tetrahydrofuran, determined by ^1H NMR and/or GC-MS. ^[d] Diastereomeric ratio determined by ^1H NMR and/or GC-MS of the crude compounds. ^[e] Product decomposition after purification was observed.

Discussion of Results

At this point, being concerned about the 12 principles of Green Chemistry^{1a} and the requirement for developing environmental benign procedures including atom economy principle, the idea of performing the HFIP-promoted alkene oxidation/ring-opening of epoxides in a one-pot reaction was taken into account (Scheme 14). This experiment was thought due to the fact that, epoxides are synthesized from alkenes, and fluorinated alcohols have proven to be efficient mediators in the oxidation of alkenes using H₂O₂.^{45,46} Thus, an excess of α -methylstyrene (**2a**) was treated with 1 equivalent of H₂O₂ (30% aqueous solution) at 45 °C during 24 hours. After the reaction time, by employing a GC-MS analysis, a myriad of products, most of them coming from the ring opening of the epoxide with H₂O or HFIP, were detected. Among them, not only tetrahydrofuran **3aa**, but also 2-phenylpropanaldehyde from Meinwald rearrangement or acetophenone from oxidative cleavage of the alkene were observed. Though the product was obtained in low amount, only 27% of conversion, the result can be highlighted as proof of concept that substituted tetrahydrofurans can be easily afforded from readily available materials as styrenes.

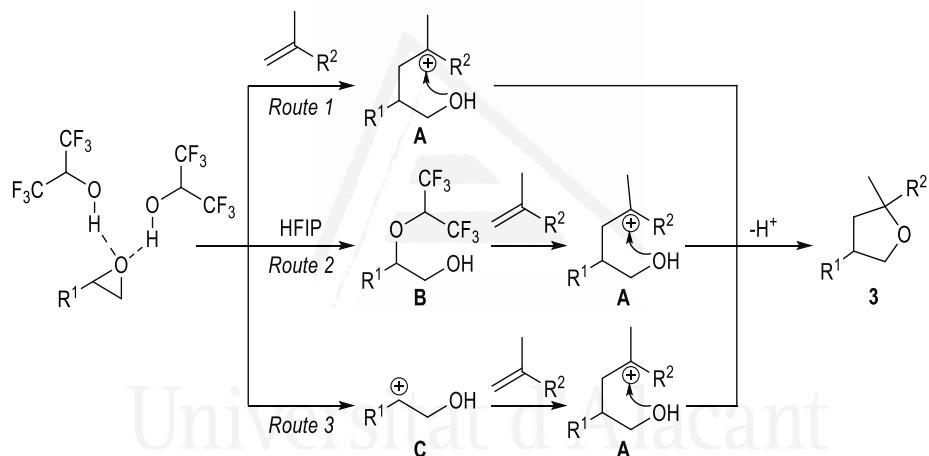


Scheme 14. One pot oxidation/ring opening reaction.

Regarding the reaction mechanism and based on these observations and similar transformations reported, 3 possible scenarios were taken into account (Scheme 15). In the route 1, the direct nucleophilic attack of the alkene onto activated epoxide would take place providing the intermediate **A** which cyclises affording the corresponding tetrahydrofuran. Further to this, in the route 2, the process for arriving at the intermediate **A** resulted in a double nucleophilic attack, firstly a ring-opening (S_N2-type) reaction of the more abundant HFIP (intermediate **B**), followed by a nucleophilic substitution (S_N1-type) until the expected product. While in the route 3, purely carbocationic intermediate **C** would be formed, which could be stabilized by the formation of ionic

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pair or by other electrostatic interactions with HFIP, followed by the nucleophilic attack of the alkene (intermediate **A**) and the consequent cyclisation. Route 2 was soon discarded by the fact the intermediate **B** was observed among the products when the model reaction was carried out. Thus, if this route had been the operating one, by increasing the reaction time higher conversions would have been achieved, which did not happen. In any case, to confirm this point, the reaction of epoxide **1a** with HFIP was carried out at room temperature for 8 hours obtaining ether **6** as product. Then, after a rapid purification, it was allowed to react with α -methylstyrene (**2a**) for 24 hours under the optimal conditions. Nevertheless, as expected, no reaction was observed after this time (Scheme 16a).

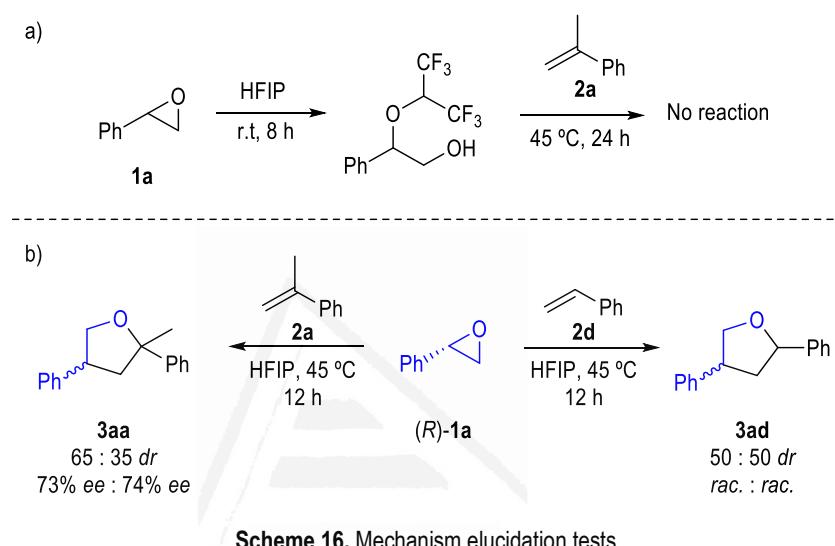


Scheme 15. Proposed reaction mechanism.

At this point, it was thought to perform the reaction employing enantiopure (*R*)-styrene oxide and α -methylstyrene (**2a**) and styrene (**2d**) as electron-rich alkenes (Scheme 16b). In this experiment, the configuration of the stereocenter will be somehow maintained if the route 1 is the one taking place. As depicted in Scheme 16, when the α -methylstyrene (**2a**) was utilised as nucleophile, a mixture of diastereoisomers both presenting a slight loss of enantiopurity in the chiral centre (73% ee and 74% ee, respectively determined by chiral HPLC analysis) was obtained. In spite of this, employing the less nucleophilic styrene **2d**, the stereochemistry of the chiral centre was totally lost, giving a racemic mixture for each diastereoisomer of Caloxylane (**3ad**). Hence, as a

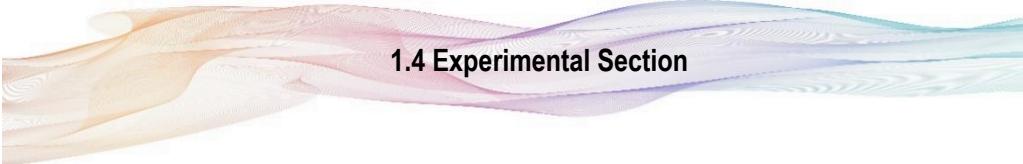
Discussion of Results

consequence of these experimental evidences, it can be said that the mechanism of the reaction seemingly is highly dependent on the nucleophilicity of the alkene employed. Thus, whereas styrene (**2d**) apparently follows a purely ionic route, S_N1-type mechanism (route 3, Scheme 15), in the α -methylstyrene (**2a**) case, predominantly a S_N2-type pathway (route 1, Scheme 15) is operating.



Scheme 16. Mechanism elucidation tests.

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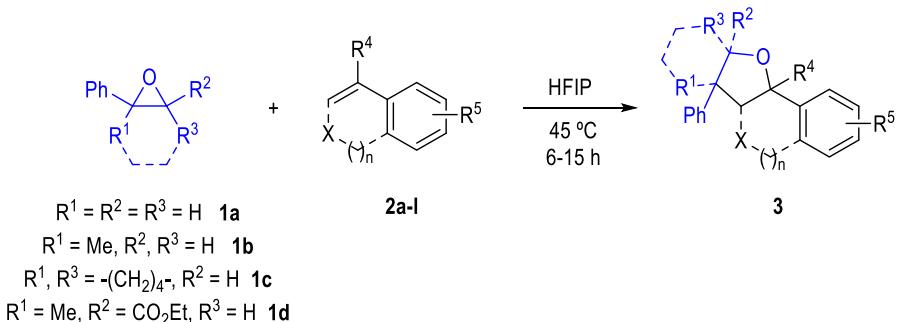
1.4 Experimental Section

1.4.1 General

Unless otherwise noted, all commercially available reagents and solvents were purchased (Acros, Aldrich, Fluka, Fluorochem, Merck) and used without further purification. Substrates that were not commercially available were synthesized according to known literature procedures. ^1H NMR and ^{13}C NMR spectra were performed at the technical service of the University of Alicante (SSTI-UA), employing a Bruker AV-300 or Bruker AV-400 (Bruker Corporation) using CDCl_3 as solvent and TMS as internal standard unless otherwise stated. Chemical shifts (δ) are given in ppm and the coupling constants (J) in Hz. Low resolution mass spectra (MS) were recorded in the electron impact mode (EI, 70 eV, He as carrier phase) using an Agilent GC/MS 5973 Network Mass Selective Detector spectrometer apparatus equipped with a HP-5MS column (Agilent technologies, 30 m \times 0.25 mm) and giving fragment ions in m/z with relative intensities (%) in parentheses. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV on Agilent GC/MS-5973N apparatus equipped with a HP-5MS column (Agilent technologies, 30 m \times 0.25 mm). High-resolution mass spectra (HRMS) were obtained on an Agilent 7200 Quadrupole-Time of Flight apparatus (Q-TOF), the ionization employed being electron impact (EI). Chiral HPLC analysis was performed in an Agilent 1100 Series HPLC equipped with a G1315B diode array detector and a Quat Pump G1311A equipped with the corresponding Daicel chiral column. Analytical TLC was performed on Merck silica gel plates and the spots visualized with UV light at 254 nm. Flash chromatography employed Merck silica gel 60 (0.040-0.063 mm). Silica gel 60 F₂₅₄ containing gypsum was employed for preparative layer chromatography.

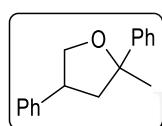
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1.4.2 General Procedure for the HFIP-Promoted Synthesis of Substituted Tetrahydrofurans



In a capped tube, onto a mixture of the corresponding epoxide (0.15 mmol) and alkene (0.25 mmol), HFIP (150 μL) was added in one portion. The reaction was then stirred (sand bath) at 45 °C for 6-15 hours, until the reaction was judged to be completed (no starting epoxide remaining) by GC-MS. After this time, solvent was evaporated and the crude material was directly purified by flash chromatography or preparative TLC.

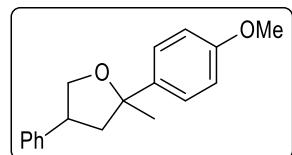
1.4.3 Physical and Spectroscopic Data of Substituted Tetrahydrofurans



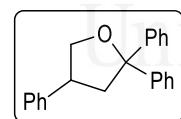
2-Methyl-2,4-diphenyltetrahydrofuran (3aa):⁵⁶ yellow oil; purification by flash chromatography (*n*-hexane/ethyl acetate 8.5/1.5), 54% yield; (*cis:trans*) = 55:45; **1H NMR** (300 MHz, CDCl₃): *cis* isomer: $\delta_{\text{H}} = 7.52 - 7.45$ (m, 4H, 4xCH_{Ar}), 7.43 – 7.28 (m, 10H, 10xCH_{Ar}), 7.27 – 7.16 (m, 6H, 6xCH_{Ar}), 4.42 (t, $J = 7.6$ Hz, 1H, CHCH₂O), 3.84 (dd, $J = 10.0, 8.2$ Hz, 1H, CHCH₂O), 3.70 (tt, $J = 10.3, 7.7$ Hz, 1H, CH), 2.41 – 2.15 (m, 2H, CHCH₂C), 1.63 (s, 3H, CH₃) ppm; further signals for the *trans* isomer: $\delta_{\text{H}} = 4.35$ (t, $J = 8.4$ Hz, 1H, CHCH₂O), 4.00 (t, $J = 8.7$ Hz, 1H, CHCH₂O), 3.31 (ddd, $J = 15.9, 11.3, 8.6$ Hz, 1H, CH), 2.81 – 2.60 (m, 2H, CHCH₂C), 1.68 (s, 3H, CH₃) ppm; **13C NMR** (101 MHz, CDCl₃): *cis* isomer: $\delta_{\text{C}} = 148.9, 140.8, 128.5, 128.3, 127.4, 126.6, 126.5, 124.5, 74.4, 47.9, 45.8, 30.6$, ppm; further signals for *trans* isomer: 147.6, 141.6, 128.5, 128.2, 127.3, 126.6, 126.4, 124.7, 73.9, 48.3, 44.6, 30.2 ppm; **MS (EI)**: *m/z* 238 (M⁺, 0.31%), 224 (19), 223 (100), 193 (12), 117 (27), 115 (18), 105 (90), 91 (16), 77 (18). Chiral HPLC analysis: Chiralpak IA column, Hexane/iPrOH 99:1, flow rate = 0.2 mL/min, $\lambda = 210$ nm,

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retention times: = 25.5 and 26.5 min. (major diastereoisomer) and 27.4 and 28.4 min. (minor diastereoisomer).

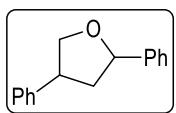


2-(4-Methoxyphenyl)-2-methyl-4-phenyl tetrahydrofuran (3ab): orange oil; purification by flash chromatography (*n*-hexane/ethyl acetate 8.5/1.5), 67% yield; (*cis:trans*) = 55:45; **¹H NMR** (300 MHz, CDCl₃): *cis* isomer: δ_H = 7.43 – 7.37 (m, 3H, 3xCH_{Ar}), 7.33 – 7.28 (m, 3H, 3xCH_{Ar}), 7.27 – 7.16 (m, 6H, 6xCH_{Ar}), 6.95 – 6.93 (m, 2H, 2xCH_{Ar}), 6.92 – 6.90 (m, 2H, 2xCH_{Ar}), 4.40 (t, *J* = 7.9 Hz, 1H, CHCH₂O), 3.84 (s, 3H, OCH₃), 3.82 (dd, *J* = 3.5, 1.9 Hz, 1H, CHCH₂O), 3.76 – 3.64 (m, 1H, CH), 2.63 (dd, *J* = 12.4, 8.0 Hz, 1H, CHCH₂C), 2.32 (dd, *J* = 12.3, 10.5 Hz, 1H, CHCH₂C), 1.61 (s, 3H, CH₃) ppm; further signals for the *trans* isomer: δ_H = 4.33 (t, *J* = 8.4 Hz, 1H, CHCH₂O), 3.98 (t, *J* = 8.6 Hz, 1H, CHCH₂O), 3.85 (s, 3H, OCH₃), 3.39 – 3.25 (m, 1H, CH), 2.71 (dd, *J* = 12.1, 7.1 Hz, 1H, CHCH₂C), 2.32 (dd, *J* = 12.3, 10.5 Hz, 1H, CHCH₂C), 1.66 (s, 3H, CH₃) ppm; **¹³C NMR** (101 MHz, CDCl₃): mixture of isomers, δ_C = 158.3, 158.2, 141.7, 141.1, 141.0, 139.7, 128.5, 128.5, 127.4, 127.3, 126.6, 126.6, 125.8, 125.7, 113.6, 113.5, 85.2, 84.7, 74.4, 73.9, 55.3, 55.2, 48.3, 48.1, 45.8, 44.6, 30.6, 30.3 ppm; **MS (EI)**: *m/z* 268 (M⁺, 6%), 254 (17), 253 (93), 135 (100), 117 (14), 91 (11); **HRMS** (GC/MS-EI/Q-TOF): *m/z* calcd. for C₁₈H₂₀O₂ 268.1463, found 268.1463.

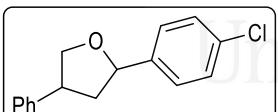


2,2,4-Triphenyltetrahydrofuran (3ac): yellow oil; purification by flash chromatography (*n*-hexane/ethyl acetate 8.5/1.5), 38% estimated yield (not purely isolated); **¹H NMR** (300 MHz, CDCl₃): δ_H = 7.54 – 7.49 (m, 4H, 4xCH_{Ar}), 7.37 – 7.34 (m, 4H, 4xCH_{Ar}), 7.34 – 7.30 (m, 4H, 4xCH_{Ar}), 7.27 – 7.24 (m, 2H, 2xCH_{Ar}), 7.24 – 7.22 (m, 1H, CH_{Ar}), 4.48 (t, *J* = 8.4 Hz, 1H, CHCH₂O), 4.07 (t, *J* = 8.7 Hz, 1H, CHCH₂O), 3.61 – 3.43 (m, 1H, CH), 3.23 (dd, *J* = 12.3, 7.1 Hz, 1H, CHCH₂C), 2.68 (t, *J* = 11.8 Hz, 1H, CHCH₂C) ppm; **MS (EI)**: *m/z* 300 (M⁺, 55%), 270 (15), 224 (71), 223 (100), 192 (21), 191 (13), 179 (13), 178 (15), 165 (21), 118 (34), 117 (42), 115 (12), 105 (96), 91 (14), 77 (27); **HRMS** (GC/MS-EI/Q-TOF): *m/z* calcd. for C₂₂H₂₀O 300.1514, found 300.1509.

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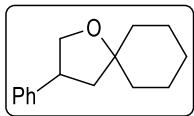


2,4-Diphenyltetrahydrofuran (Caloxylane A and B) (3ad):⁵⁶ yellow oil; purification by flash chromatography (*n*-hexane/ethyl acetate 8.5/1.5), 39% yield; (*cis:trans*) = 65:35; **1H NMR** (300 MHz, CDCl₃): *cis* isomer: δ_H = 7.49 – 7.29 (m, 20H, 20xCH_{Ar}), 5.11 (dd, *J* = 10.2, 5.7 Hz, 1H, OCH), 4.39 (t, *J* = 8.2 Hz, 1H, CHCH₂O), 4.05 (t, *J* = 8.5 Hz, 1H, CHCH₂O), 3.74 – 3.63 (m, 1H, CH), 2.85 – 2.72 (m, 1H, CHCH₂CH), 2.05 (q, *J* = 10.5, 1.9 Hz, 1H, CHCH₂CH) ppm; further signals for the *trans* isomer: δ_H = 5.26 (dd, *J* = 7.7, 5.8 Hz, 1H, OCH), 4.50 (t, *J* = 8.5, 7.4 Hz, 1H, CHCH₂O), 3.98 (t, *J* = 8.2 Hz, 1H, CHCH₂O), 3.63 – 3.51 (m, 1H, CH), 2.57 – 2.45 (m, 1H, CHCH₂CH), 2.36 (q, *J* = 12.5, 8.3, 5.8 Hz, 1H, CHCH₂CH) ppm; **13C NMR** (75 MHz, CDCl₃): *cis* isomer: δ_C = 142.6, 141.7, 128.6, 128.4, 127.4, 127.2, 125.7, 81.8, 75.1, 46.0, 43.7, pm; further signals for the *trans* isomer: δ_C = 143.6, 142.0, 128.6, 128.3, 127.3, 127.1, 125.5, 80.6, 75.1, 44.4, 42.7 ppm; **MS (EI)**: *m/z* 224 (M⁺, 34%), 195 (14), 194 (93), 193 (100), 179 (58), 178 (89), 165 (13), 146 (27), 133 (34), 120 (27), 117 (90), 115 (57), 105 (45), 91 (48), 77 (30). Chiral HPLC analysis: Chiralcel OD-H column, Hexane/iPrOH 99:1, flow rate = 0.7 mL/min, λ = 210 nm, retention times: = 23.1 and 23.2 min. (major diastereoisomer) and 28.0 and 35.4 min. (minor diastereoisomer).

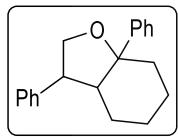


2-(4-Chlorophenyl)-4-phenyltetrahydrofuran (3ae):⁵⁶ yellow oil; purification by flash chromatography (*n*-hexane/ethyl acetate 8.0/2.0), 36% yield; (*cis:trans*) = 60:40; **1H NMR** (400 MHz, CDCl₃): *cis* isomer: δ_H = 7.40 – 7.30 (m, 9H, 9xCH_{Ar}), 5.07 (dd, *J* = 10.1, 5.8 Hz, 1H, OCH), 4.38 (t, *J* = 8.2 Hz, 1H, CHCH₂O), 4.03 (t, *J* = 8.5 Hz, 1H, CHCH₂O), 3.78 – 3.61 (m, 1H, CH), 2.86 – 2.72 (m, 1H, CHCH₂CH), 1.98 (dd, *J* = 12.4, 10.4 Hz, 1H, CHCH₂CH) ppm; further signals for the *trans* isomer: δ_H = 5.22 (dd, *J* = 7.7, 5.9 Hz, 1H, OCH), 4.47 (dd, *J* = 8.4, 7.5 Hz, 1H, CHCH₂O), 3.97 (t, *J* = 8.2 Hz, 1H, CHCH₂O), 3.54 (t, *J* = 7.6 Hz, 1H, CH), 2.50 (dt, *J* = 12.6, 7.7 Hz, 1H, CHCH₂CH), 2.35 – 2.24 (m, 1H, CHCH₂CH) ppm; **13C NMR** (101 MHz, CDCl₃): *cis* isomer: δ_C = 141.5, 141.2, 133.0, 129.9, 128.8, 128.6, 128.3, 128.2, 127.3, 127.1, 126.7, 81.1, 75.1, 45.9, 43.8 ppm; further signals for the *trans* isomer: δ_C = 142.1, 142.7, 132.8, 129.8, 128.7, 128.5, 128.3, 128.1, 127.2, 126.9, 126.7, 126.4, 79.9, 72.7, 44.3, 42.7 ppm; **MS (EI)**: *m/z* 258 (M⁺, 18%), 228 (25), 193 (100), 180 (15), 178 (22), 167 (22), 154 (16), 139 (27), 117 (64), 115 (54), 104 (17), 91 (27), 77 (13).

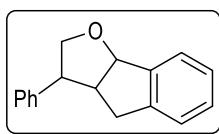
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3-Phenyl-1-oxaspiro[4.5]decane (3ag): yellow solid, purification by flash chromatography (*n*-hexane/ethyl acetate 8.0/2.0), 45% estimated yield (not purely isolated); **¹H NMR** (400 MHz, CDCl₃): δ_H = 7.36 – 7.31 (m, 3H, 3xCH_{Ar}), 7.27 – 7.23 (m, 2H, 2xCH_{Ar}), 4.23 (t, *J* = 8.0 Hz, 1H, CHCH₂O), 3.80 (t, *J* = 8.5 Hz, 1H, CHCH₂O), 3.51 (tt, *J* = 17.6, 8.8 Hz, 1H, CH), 2.30 (dd, *J* = 12.4, 8.2 Hz, 1H, CCH₂), 1.78 (dd, *J* = 12.4, 10.5 Hz, 1H, CCH₂), 1.74 – 1.48 (m, 10H, 10xCH₂) ppm; **¹³C NMR** (126 MHz, CDCl₃): δ_C = 141.9, 128.6, 128.5, 128.1, 127.3, 126.5, 83.3, 72.9, 45.0, 38.3, 37.3, 25.61, 23.8, 23.8 ppm; **MS** (EI): *m/z* 216 (M⁺, 55%), 174 (25), 173 (100), 160 (40), 118 (18), 117 (28), 104 (41), 91 (26), 55 (73); **HRMS** (GC/MS-EI/Q-TOF): *m/z* calcd. for C₁₅H₂₀O 216.1514, found 216.1514.



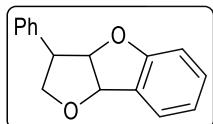
3,7a-Diphenyloctahydrobenzofuran (3ai): orange oil; purification by flash chromatography (*n*-hexane/ethyl acetate 8.5/1.5); 34% yield; (*cis:trans*) = 55:45; **¹H NMR** (300 MHz, CDCl₃): *cis* isomer: δ_H = 7.58 (dd, *J* = 8.5, 1.1 Hz, 2H, 2xCH_{Ar}), 7.54 – 7.48 (m, 2H, 2xCH_{Ar}), 7.44 – 7.35 (m, 6H, 6xCH_{Ar}), 7.34 – 7.28 (m, 4H, 4xCH_{Ar}), 7.23 (m, 6H, 6xCH_{Ar}), 7.16 – 7.08 (m, 2H, 2xCH_{Ar}), 4.40 (m, 2H, CHCH₂O), 3.59 (m, 1H, CHCH₂O), 2.67 (dd, *J* = 12.0, 5.5 Hz, 1H, CH), 2.13 – 1.85 (m, 4H, 4xCH₂), 1.83 – 1.52 (m, 12H, 12xCH₂) ppm; furher signals for the *trans* isomer: δ_H = 4.27 (t, *J* = 8.6 Hz, 1H, CHCH₂O), 4.00 – 3.91 (m, 1H, CHCH₂O), 3.42 (td, *J* = 9.6, 5.5 Hz, 1H, CHCH₂O), 2.57 (dt, *J* = 11.4, 5.7 Hz, 1H, CH) ppm; **¹³C NMR** (75 MHz, CDCl₃): *cis* isomer: δ_C = 148.6, 141.2, 128.6, 128.2, 128.1, 126.9, 126.4, 125.9, 84.8, 72.6, 51.2, 46.6, 35.8, 24.2, 21.9, 20.0 ppm; further signals for *trans* isomer: δ_C = 146.5, 138.2, 128.3, 128.1, 127.9, 126.7, 126.2, 124.5, 86.8, 67.3, 49.4, 46.4, 38.3, 24.6, 22.1, 20.0 ppm; **MS** (EI): *m/z* 278 (M⁺, 85%), 236 (19), 235 (100), 221 (18), 115 (14), 105 (67), 91 (25), 77 (18); **HRMS** (GC/MS-EI/Q-TOF): *m/z* calcd. for C₂₀H₂₂O 278.1671, found 278.1667.



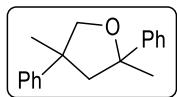
3-Phenyl-3,3a,4,8b-tetrahydro-2H-indeno[1,2-b]furan (3aj):⁵⁶ yellow oil; purification by flash chromatography (*n*-hexane/ethyl acetate 8.5/1.5), 40% yield; (*cis:trans*) = 60:40; **¹H NMR** (300 MHz, CDCl₃): *cis* isomer: δ_H = 7.53 – 7.47 (m, 2H, 2xCH_{Ar}), 7.39 – 7.29 (m, 8H, 8xCH_{Ar}), 5.73 (d, *J* = 7.2 Hz, 1H, OCH), 4.13 (dd, *J* =

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8.6, 6.7 Hz, 1H, CHCH_2O), 3.26 – 3.16 (m, 2H, CHCHCH_2C), 3.12 – 3.03 (m, 1H, CHCH_2O), 3.01 – 2.91 (m, 1H, CHCHCH_2C), 2.83 (dd, $J = 17.4, 9.3$ Hz, 1H, CHCHCH_2C), ppm; further signals for the *trans* isomer: $\delta_{\text{H}} = 7.51 – 7.46$ (m, 1H, CH_{Ar}), 7.36 – 7.24 (m, 6H, 6x CH_{Ar}), 7.14 – 7.09 (m, 2H, 2x CH_{Ar}), 5.69 (d, $J = 6.8$ Hz, 1H, OCH), 4.27 – 4.21 (m, 1H, CHCH_2O), 3.92 (dd, $J = 8.6, 7.7$ Hz, 1H, CHCH_2O), 3.82 – 3.73 (m, 2H, CHCHCH_2C), 3.59 – 3.47 (m, 1H, CHCHCH_2C), 2.60 (dd, $J = 17.4, 4.8$ Hz, 1H, CHCHCH_2C) ppm; ^{13}C NMR (75 MHz, CDCl_3) : mixture of isomers, $\delta_{\text{C}} = 142.5, 141.9, 141.7, 141.6, 128.8, 128.7, 128.4, 128.4, 127.5, 127.2, 127.0, 126.7, 126.5, 125.6, 125.2, 124.4, 87.9, 87.8, 74.6, 68.2, 53.3, 50.1, 48.5, 45.5, 38.7, 36.6 ppm; MS (EI): m/z 236 (M^+ , 34%), 207 (17), 206 (100), 205 (27), 128 (20), 115 (27), 91 (86).$



3-Phenyl-2,3,3a,8b-tetrahydrofuro[3,2-b]benzofuran (3al): yellow oil; purification by flash chromatography (*n*-hexane/ethyl acetate), 40% estimated yield (not purely isolated); ^1H NMR (400 MHz, CDCl_3): $\delta_{\text{H}} = 7.50 – 7.46$ (m, 1H, CH_{Ar}), 7.40 – 7.38 (m, 3H, 3x CH_{Ar}), 7.35 – 7.30 (m, 2H, 2x CH_{Ar}), 6.99 (td, $J = 7.4, 0.9$ Hz, 1H, CH_{Ar}), 6.88 (d, $J = 8.3$ Hz, 1H, CH_{Ar}), 5.81 (d, $J = 6.0$ Hz, 1H, CHOCH_2), 5.19 (dd, $J = 6.0, 1.2$ Hz, 1H, OCHCH), 4.08 (dd, $J = 9.1, 2.3$ Hz, 1H, CHCH_2O), 3.96 (dd, $J = 9.1, 5.5$ Hz, 1H, CHCH_2O), 3.67 (d, $J = 5.5$ Hz, 1H, OCHC) ppm; MS (EI): m/z 238 (M^+ , 34%), 220 (66), 219 (43), 208 (45), 207 (100), 191 (15), 189 (17), 178 (19), 165 (13), 131 (24), 117 (12); HRMS (GC/MS-EI/Q-TOF): m/z calcd. for $\text{C}_{16}\text{H}_{14}\text{O}$ 238.0994, found 238.0990.

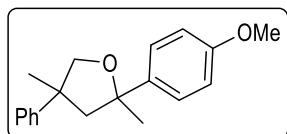


2,4-Dimethyl-2,4-diphenyltetrahydrofuran (3ba):⁵⁹ yellow solid; purification by flash chromatography (*n*-hexane/ethyl acetate 8.5/1.5), 62% yield; (*cis:trans*) = 50:50; the *cis* isomer is highlighted in bold; ^1H NMR (300 MHz, CDCl_3): $\delta_{\text{H}} = 7.54 – 7.49$ (m, 2H, 2x CH_{Ar}), 7.45 – 7.39 (m, 2H, 2x CH_{Ar}), 7.39 – 7.30 (m, 8H, 8x CH_{Ar}), 7.26 – 7.21 (m, 4H, 4x CH_{Ar}), 7.20 – 7.10 (m, 4H, 4x CH_{Ar}), **4.30 (d, $J = 8.6$ Hz, 1H, OCH_2C)**, 4.10 (dd, $J = 8.4, 1.0$ Hz, 1H, OCH_2C), **4.06 (d, $J = 8.5$ Hz, 1H, OCH_2C)**, 3.96 (dd, $J = 8.4, 0.6$ Hz, 1H, OCH_2C), 2.72 (d, $J = 12.6$ Hz,

⁵⁹ Sultana, S.; Devi, N. R.; Saikia, A. K. *Asian J. Org. Chem.* **2015**, 4, 1281-1288.

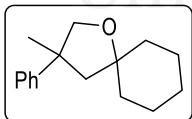
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1H, CCH₂C), **2.58 (s, 2H, CCH₂C)**, 2.47 (dd, *J* = 12.6, 1.1 Hz, 1H, CCH₂C), 1.70 (s, 3H, CH₃), **1.59 (s, 6H, 2xCH₃)**, 1.50 (s, 3H, CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): mixture of isomers, δ_c = 149.5, 149.3, 148.2, 147.7, 128.4, 128.3, 128.2, 128.1, 126.3, 126.2, 126.0, 126.0, 125.9, 125.8, 125.7, 124.5, 124.4, 124.4, 84.8, 84.7, 78.0, 77.8, 53.9, 53.7, 48.9, 48.4, 32.7, 31.6, 29.9, 28.5 ppm; MS (EI): *m/z* 252 (M⁺, 0.08%), 237 (100), 207 (12), 129 (13), 117 (29), 105 (97), 91 (14), 77 (15).



2-(4-Methoxyphenyl)-2,4-dimethyl-4-phenyl tetrahydrofuran

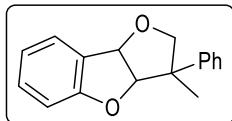
(3bb): white solid; purification by flash chromatography (*n*-hexane/ethyl acetate 8.5/1.5), 58% yield; (*cis:trans*) = 45:55; the *cis* isomer is highlighted in bold; ¹H NMR (300 MHz, CDCl₃): δ_H = 7.36 – 7.30 (m, 3H, 3xCH_{Ar}), 7.27 – 7.22 (m, 2H, 2xCH_{Ar}), 7.16 – 7.09 (m, 2H, 2xCH_{Ar}), 6.87 – 6.82 (m, 2H, 2xCH_{Ar}), **4.28 (d, J = 8.6 Hz, 1H, OCH₂C)**, 4.07 (d, *J* = 9.1 Hz, 1H, OCH₂C), **4.03 (s, 1H, OCH₂C)**, 3.95 (d, *J* = 8.4 Hz, 1H, OCH₂C), **3.84 (s, 3H, OCH₃)**, 3.80 (s, 3H, OCH₃), 2.70 (d, *J* = 12.6 Hz, 1H, CCH₂C), **2.55 (d, J = 2.2 Hz, 2H, CCH₂C)**, 2.42 (d, *J* = 12.5 Hz, 1H, CCH₂C), 1.67 (s, 3H, CH₃), 1.58 (s, 3H, CH₃), **1.48 (s, 3H, CH₃)**, **1.23 (s, 3H, CH₃)** ppm; ¹³C NMR (101 MHz, CDCl₃): only major isomer is given, δ_c = 157.9, 147.7, 141.6, 128.3, 126.0, 125.9, 125.6, 113.5, 84.6, 77.8, 55.3, 53.9, 48.9, 32.8, 29.9 ppm; MS (EI): *m/z* 282 (M⁺, 9%), 268 (16), 267 (83), 135 (100), 117 (13); HRMS (GC/MS-EI/Q-TOF): *m/z* calcd. for C₁₉H₂₂O₂ 282.1620, found 282.1620.



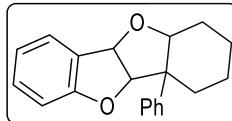
3-Methyl-3-phenyl-1-oxaspiro[4.5]decane (3bg): colourless oil; purification

by flash chromatography (*n*-hexane/ethyl acetate 8.0/2.0), 30% estimated yield (not purely isolated); ¹H NMR (300 MHz, CDCl₃): δ_H = 7.36 – 7.30 (m, 4H, 4xCH_{Ar}), 7.26 – 7.23 (m, 1H, CH_{Ar}), 4.05 (d, *J* = 8.7 Hz, 1H, OCH₂C), 3.94 (d, *J* = 8.5 Hz, 1H, OCH₂C), 2.12 (d, *J* = 12.6 Hz, 1H, CCH₂C), 1.98 (dd, *J* = 12.6, 0.7 Hz, 1H, CCH₂C), 1.79 – 1.7 (m, 5H, 5xCH₂), 1.61 (d, *J* = 2.7 Hz, 2H, 2xCH₂), 1.51 (d, *J* = 6.0 Hz, 3H, 3xCH₂), 1.46 (s, 3H, CH₃) ppm; MS (EI): *m/z* 230 (M⁺, 43%), 216 (16), 215 (100), 187 (59), 118 (19), 117 (25), 91 (14), 55 (30); HRMS (GC/MS-EI/Q-TOF): *m/z* calcd. for C₁₆H₂₂O 230.1671, found 230.1672.

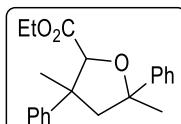
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3-Methyl-3-phenyl-2,3,3a,8b-tetrahydrofuro [3,2-b] benzofuran (3bl): inseparable mixture of regioisomers. The major isomer data is highlighted in bold. Yellow solid; purification by flash chromatography (*n*-hexane/ethyl acetate 8.5/1.5), 35% estimated yield (not purely isolated); **1H NMR** (400 MHz, CDCl₃): δ_H = 7.60 – 7.49 (m, 3H, 3xCH_{Ar}), 7.48 – 7.38 (m, 3H, 3xCH_{Ar}), 7.38 – 7.30 (m, 8H, 8xCH_{Ar}), **7.27 – 7.21 (m, 2H, 2xCH_{Ar})**, 7.00 – 6.88 (m, 2H, 2xCH_{Ar}), 5.60 (d, *J* = 6.0 Hz, 1H, CH₂OCH), **5.15 (d, J = 6.0 Hz, 1H, CH₂OCH)**, 4.31 (d, *J* = 9.3 Hz, 1H, OCHC), **4.19 (d, J = 12.4 Hz, 1H, OCHC)**, 3.91 (d, *J* = 5.7 Hz, 1H, CH₂OCH), **3.82 (d, J = 12.2 Hz, 1H, CH₂OCH)**, 3.64 (d, *J* = 9.3 Hz, 1H, CH₂OCH), **3.60 (d, J = 12.4 Hz, 1H, CH₂OCH)**, 1.61 (s, 3H, CH₃), **1.52 (s, 3H, CH₃)**, ppm; **MS (EI):** *m/z* 252 (M⁺, 71%), 237 (14), 221 (15), 207 (100), 194 (20), 178 (15), 145 (23), 131 (41), 129 (11), 118 (36), 115 (16), 105 (14), 91 (20), 89 (15), 77 (14); **HRMS** (GC/MS-EI/Q-TOF): *m/z* calcd. for C₁₇H₁₆O₂ 252.1150, found 252.1149.



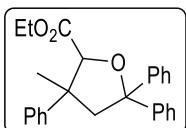
4a-Phenyl-1,2,3,4,4a,4b,9b,10a-octahydrobenzofuro[3,2-b]benzofuran (3cl): white solid; purification by flash chromatography (*n*-hexane/ethyl acetate 8.5/1.5), 38% yield; (*cis:trans*) = 55:45; **1H NMR** (400 MHz, CDCl₃): δ_H = 7.53 – 7.47 (m, 3H, 3xCH_{Ar}), 7.45 – 7.34 (m, 3H, 3xCH_{Ar}), 7.34 – 7.30 (m, 1H, CH_{Ar}), 7.02 – 6.90 (m, 2H, 2xCH_{Ar}), 5.54 (d, *J* = 7.8 Hz, 1H, CHOCHCH₂), 5.15 (d, *J* = 7.9 Hz, 1H, OCHC), 4.43 (t, *J* = 2.5 Hz, 1H, CHOCHCH₂), 2.17 – 2.03 (m, 1H, CH₂), 2.00 – 1.85 (m, 1H, CH₂), 1.51 – 1.39 (m, 3H, 3xCH₂), 1.05 – 0.82 (m, 3H, 3xCH₂) ppm; **13C NMR** (400 MHz, CDCl₃): δ_C = 130.7, 130.4, 128.5, 128.2, 128.0, 127.0, 126.4, 126.3, 126.2, 126.0, 120.9, 120.7, 110.0, 109.7, 96.8, 93.9, 80.7, 80.5, 78.9, 77.2, 75.3, 32.2, 29.7, 28.7, 26.5, 25.1, 21.1, 20.4, 20.2 ppm; **MS (EI):** *m/z* 292 (M⁺, 17%), 274 (20), 208 (17), 207 (100), 194 (25), 91 (11); **HRMS** (GC/MS-EI/Q-TOF): *m/z* calcd. for C₂₀H₂₀O₂ 292.1463, found 292.1460.



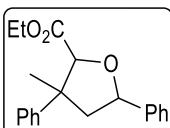
Ethyl 3,5-dimethyl-3,5-diphenyltetrahydrofuran-2-carboxylate (3da): yellow solid; purification by flash chromatography (*n*-hexane/ethyl acetate 8.5/1.5),

Experimental Section

43% yield; (*cis:trans*): 65:35; **1H NMR** (300 MHz, CDCl₃): δ_H = 7.68 – 7.62 (m, 2H, 2xCH_{Ar}), 7.54 – 7.49 (m, 2H, 2xCH_{Ar}), 7.42 – 7.34 (m, 6H, 6xCH_{Ar}), 7.26 (d, *J* = 2.0 Hz, 1H, CH_{Ar}), 5.08 (s, 1H, OCHCO), 4.21 (qd, *J* = 7.1, 1.5 Hz, 2H, OCH₂CH₃), 2.75 (d, *J* = 12.9 Hz, 1H, CCH₂C), 2.65 (d, *J* = 12.8 Hz, 1H, CCH₂C), 1.60 (d, *J* = 5.5 Hz, 6H, 2xCH₃), 1.22 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃) ppm; **¹³C NMR** (101 MHz, CDCl₃): only major isomer is given, δ_C = 170.6, 148.7, 145.4, 128.3, 128.1, 126.4, 126.3, 126.3, 124.6, 84.7, 84.3, 60.7, 56.6, 31.8, 29.7, 23.5, 14.2 ppm; **MS** (EI): *m/z* 324 (M⁺, 0.13%), 309 (86), 251 (48), 233 (18), 207 (27), 173 (14), 133 (17), 129 (16), 105 (100), 91 (15), 77 (15); **HRMS** (GC/MS-EI/Q-TOF): *m/z* calcd. for C₂₁H₂₄O₃ 324.1725, found 324.1715.



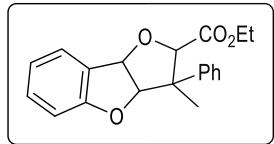
Ethyl 3-methyl-3,5,5-triphenyltetrahydrofuran-2-carboxylate (3dc): yellow oil; purification by flash chromatography (*n*-hexane/ethyl acetate 8.52/1.5), 60% yield; (*cis:trans*) = 90:10; **1H NMR** (300 MHz, CDCl₃): δ_H = 7.70 – 7.64 (m, 3H, 3xCH_{Ar}), 7.52 – 7.48 (m, 3H, 3xCH_{Ar}), 7.39 – 7.30 (m, 6H, 6xCH_{Ar}), 7.24 – 7.18 (m, 3H, 3xCH_{Ar}), 4.96 (s, 1H, OCH), 4.14 (q, *J* = 7.1 Hz, 2H, OCH₂CH₃), 3.33 (d, *J* = 13.1 Hz, 1H, CCH₂C), 3.01 (d, *J* = 13.0 Hz, 1H, CCH₂C), 1.34 (s, 3H, CH₃), 1.20 (s, 3H, OCH₂CH₃) ppm; **¹³C NMR** (101 MHz, CDCl₃): δ_C = 170.3, 147.2, 147.0, 145.1, 128.5, 128.3, 128.2, 128.1, 127.8, 126.8, 126.6, 126.5, 126.4, 126.3, 125.7, 125.5, 125.1, 87.6, 85.1, 60.7, 56.0, 51.2, 23.9, 14.2 ppm; **MS** (EI): *m/z* 386 (M⁺, 0.75%), 314 (15), 313 (59), 309 (45), 295 (24), 269 (26), 206 (12), 196 (75), 191 (30), 181 (12), 178 (16), 167 (86), 165 (30), 133 (24), 105 (100), 91 (1), 77 (19); **HRMS** (GC/MS-EI/Q-TOF): *m/z* calcd. for C₂₆H₂₆O₃ 386.1882, found 386.1884.



Ethyl-3-methyl-3,5-diphenyltetrahydrofuran-2-carboxylate (3dd): orange solid; purification by flash chromatography (*n*-hexane/ethyl acetate 8.5/1.5), 47% yield; a mixture of diastereoisomers was obtained, (*cis:trans*) = 90:10; the signals for the major isomer: **1H NMR** (400 MHz, CDCl₃): δ_H = 7.66 – 7.60 (m, 1H, CH_{Ar}), 7.55 (dd, *J* = 8.4, 1.1 Hz, 1H, CH_{Ar}), 7.48 – 7.29 (m, 8H, 8xCH_{Ar}), 5.05 (d, *J* = 5.6 Hz, 1H, OCHCH₂), 5.01 (s, 1H, OCHC), 4.36 – 4.25 (m, 2H, OCH₂CH₃), 2.71 (dd, *J* = 12.8, 5.6 Hz, 1H, OCHCH₂), 2.28 (dd, *J* = 12.8, 10.5 Hz, 1H, OCHCH₂), 1.46 (s, 3H, CH₃), 1.35 (td, *J* = 7.1, 4.4 Hz, 3H, OCH₂CH₃) ppm; the

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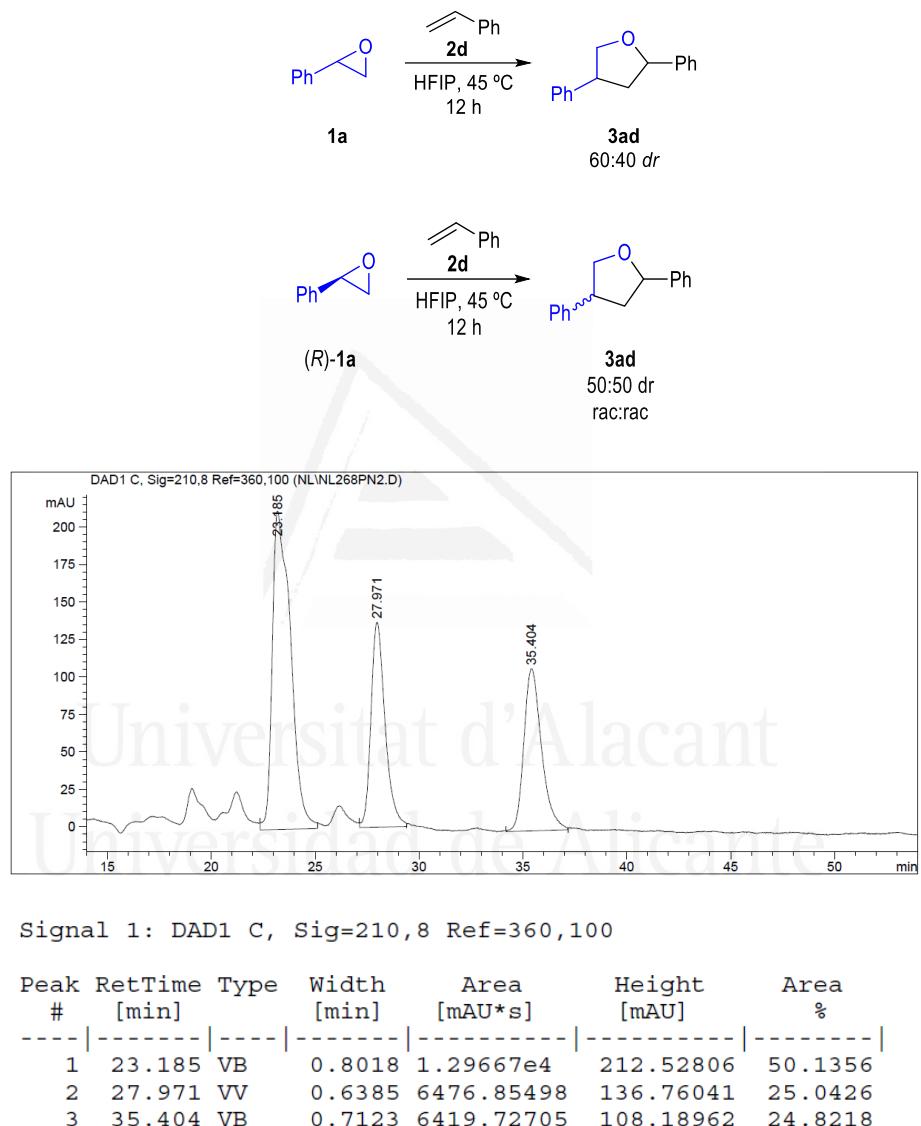
signals for the minor isomer: **1H NMR** (300 MHz, CDCl₃): δ_H = 7.54 – 7.48 (m, 2H, 2xCH_{Ar}), 7.44 – 7.32 (m, 8H, 8xCH_{Ar}), 5.48 (dd, J = 10.4, 5.5 Hz, 1H, OCHCH₂), 5.06 (s, 1H, OCHC), 4.28 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 2.57 (dd, J = 12.4, 5.6 Hz, 1H, OCH₂CH₃), 2.49 – 2.39 (m, 1H, OCH₂CH₃), 1.77 (s, 3H, CH₃), 1.44 (s, 3H, OCH₂CH₃) ppm; **13C NMR** (75 MHz, CDCl₃): δ_C = 172.2, 145.9, 141.5, 128.7, 128.4, 128.3, 128.0, 127.6, 126.7, 126.5, 126.1, 125.8, 86.0, 81.3, 60.8, 51.2, 48.3, 24.7, 14.3 ppm; **MS** (EI): *m/z* 310 (M⁺, 0.59%), 237 (14), 191 (100), 147 (12), 145 (26), 120 (18), 115 (23), 105 (45), 91 (27), 77 (12); **HRMS** (GC/MS-EI/Q-TOF): *m/z* calcd. for C₂₀H₂₂O₃ 310.1569, found 310.1565.



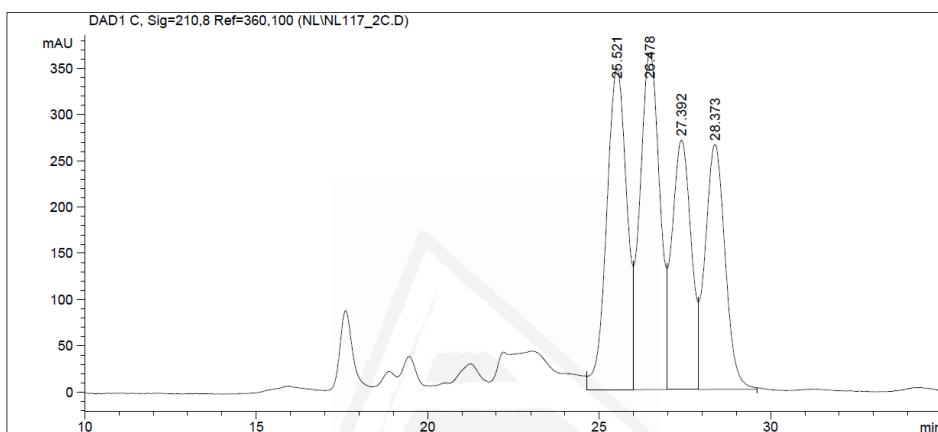
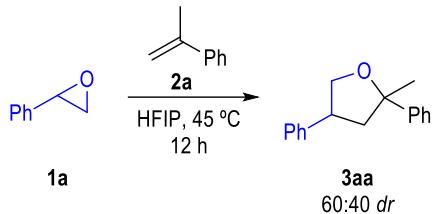
Ethyl 3-methyl-3-phenyl-2,3,3a,8b-tetrahydrofuro[3,2-b]benzofuran-2-carboxylate (3dl): yellow oil; purification by flash chromatography (*n*-hexane/ethyl acetate 8.5/1.5), 44% yield; (*cis:trans*) = 70:30; **1H NMR** (300 MHz, CDCl₃): δ_H = 7.62 – 7.29 (m, 7H, 7xCH_{Ar}), 7.06 – 6.80 (m, 2H, 2xCH_{Ar}), 5.70 (d, J = 6.2 Hz, 1H, CHOCHCO), 5.17 (d, J = 6.2 Hz, 1H, CHOCHCO), 4.94 (s, 1H, OCHC), 4.05 (qd, J = 7.1, 1.4 Hz, 2H, OCH₂CH₃), 1.56 (s, 3H, CH₃), 1.07 (t, J = 7.1 Hz, 3H, OCH₂CH₃) ppm; **MS** (EI): *m/z* 324 (M⁺, 40%), 251 (30), 221 (23), 208 (16), 207 (100), 178 (13), 145 (16), 133 (43), 118 (23), 105 (92); **HRMS** (GC/MS-EI/Q-TOF): *m/z* calcd. for C₂₀H₂₀O₄ 324.1362, found 324.1361.

Experimental Section

1.4.4 Mechanism Elucidation Tests and HPLC Chromatograms



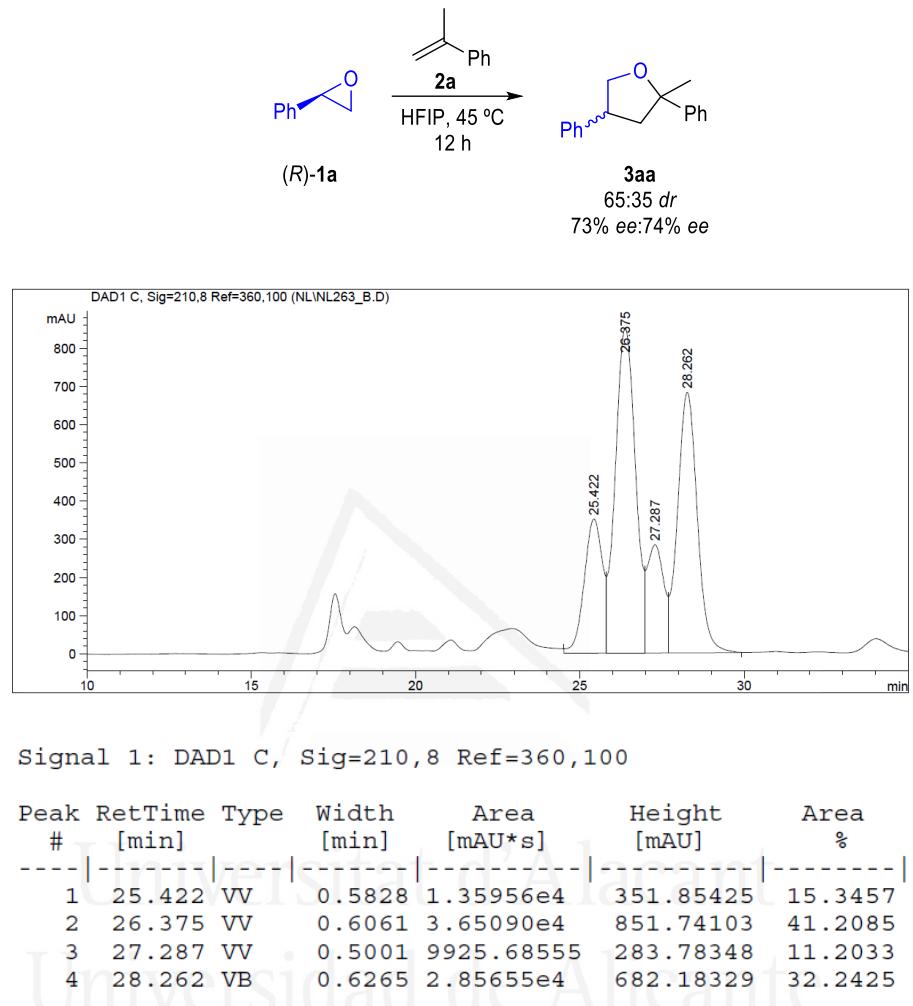
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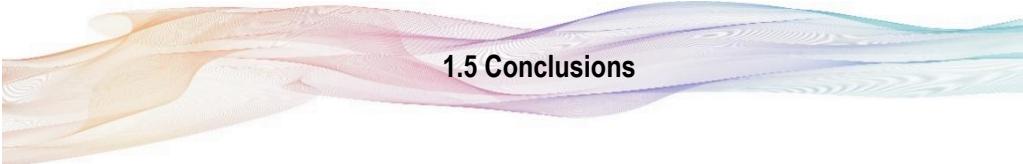


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.521	VV	0.5826	1.40832e4	347.67239	28.2445
2	26.478	VV	0.5894	1.45832e4	364.00748	29.2472
3	27.392	VV	0.5674	1.04316e4	269.58633	20.9210
4	28.373	VV	0.5701	1.07638e4	264.90396	21.5873

Experimental Section





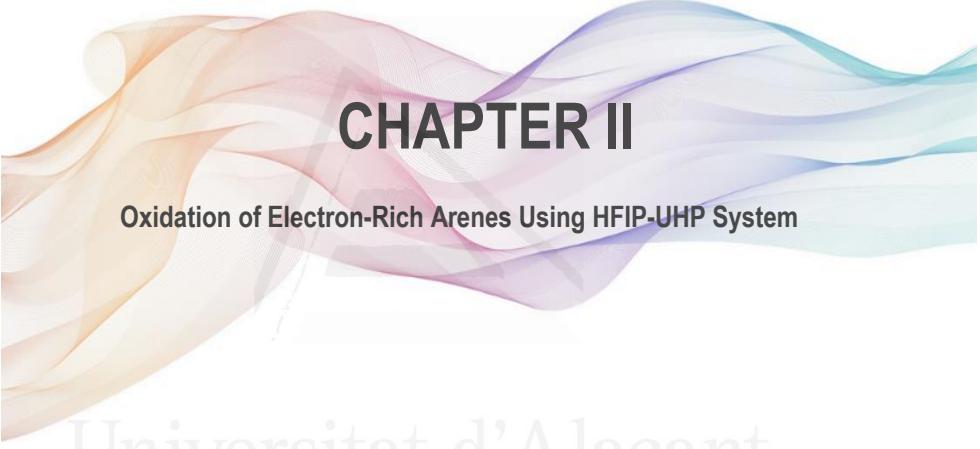
1.5 Conclusions

As a conclusion, it has been described a new methodology for the straightforward synthesis of substituted tetrahydrofurans based on the reaction of electron-rich alkenes with epoxides mediated by fluorinated alcohol 1,1,1,3,3-hexafluoropropanol (HFIP). Because of the slightly acidity of HFIP and its capacity to stabilize carbocations, this solvent can act as Lewis or Brønsted acid in these reactions avoiding the use of metals or hazardous atmospheres, affording the synthesis of those cyclic products in a simple but effective and sustainable conditions.

Even though the yields achieved are moderate in nearly all the cases, the procedure can be envisioned as environmentally benign as a result of its perfect atom economy and the availability of reactants from raw materials, alkenes and epoxides, with minimum manipulation. Furthermore, by applying this methodology, not only densely substituted furans, but also spiro- and polycyclic compounds containing furan moiety were obtained.

Additionally, it has been demonstrated that depending on the nucleophilicity of the alkene utilized, the mechanism of the reaction follows different routes, being those ones a purely ionic pathway (S_N1 -type) or S_N2 -like mechanism.

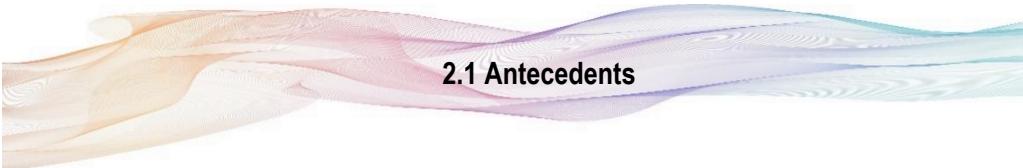
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CHAPTER II

Oxidation of Electron-Rich Arenes Using HFIP-UHP System

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2.1 Antecedents

2.1.1 General

Benzoquinone derivatives represent an extensive class of organic compounds widely distributed among natural products. This interesting framework displays a broad range of applications in medicinal chemistry or biochemistry being used as antibiotic, antitumor or anticoagulant. For instance, some of these skeletons may be found in fruits or vegetables and represent key intermediates for further application in biological function or pharmaceutical field (Figure 7). On account of their redox-activity, quinone derivatives play a significant role in a myriad of biological redox processes.⁶⁰

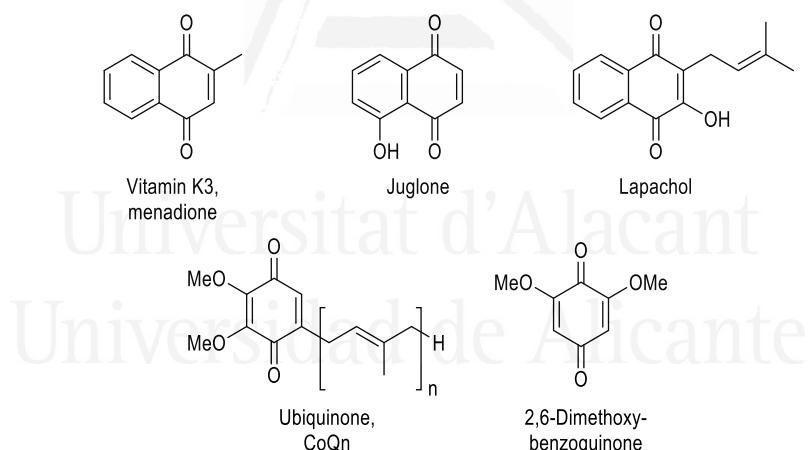


Figure 7. Representative examples of biologically active quinones.

⁶⁰ (a) Avendaño, C.; Menéndez, J. C. *Drug Targeting in Anticancer Chemotherapy*; Elsevier, Amsterdam, 2008; (b) de Castro, S. L.; Emery, F. S.; da Silva Júnior, E. N. *Eur. J. Med. Chem.* **2013**, 69, 678-700; (c) Gulaboski, R.; Bogeski, I.; Mirčeski, V.; Saul, S.; Pasieka, B.; Haeri, H. H.; Stefova, M.; Stanoeva, J. P.; Mitrev, S.; Hoth, M.; Kappl, R. *Sci. Rep.* **2013**, 3, 1865; (d) Xu, K.; Wang, P.; Wang, L.; Liu, C.; Xu, S.; Cheng, Y.; Wang, Y.; Li, Q.; Lei, H. *Chem. Biodivers.* **2014**, 11, 341-363; (e) Son, E. J.; Kim, J. H.; Kim, K.; Park, C. B. *J. Mater. Chem. A* **2016**, 4, 11179-11202.

2.1.2 Synthesis of Quinones

The huge applicability shown by these structures has contributed to the development of different synthetic routes to get access to these heterocyclic frameworks.⁶¹

Among all these different approaches described, the most practical and straightforward strategy to give rise to the quinone structural motif, requires the oxidation of arenes and/or phenol derivatives (Scheme 17).⁶² In this sense, this organic transformation has been thoroughly investigated rendering a plethora of methodologies available in the literature. Albeit, the development of these synthetic procedures requires the use of metals or hypervalent iodine compounds,^{63,64} organic peroxides⁶⁵ or, in some cases, the involvement of organic/inorganic salts.⁶⁶ Furthermore, apart from involving long reaction times, high temperatures or, in some cases, extreme conditions, these organic transformations also generate an stoichiometric amount of waste in a low atom-economy process, not being most of them environmentally sustainable methodologies.

⁶¹ Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, 75, 311-335.

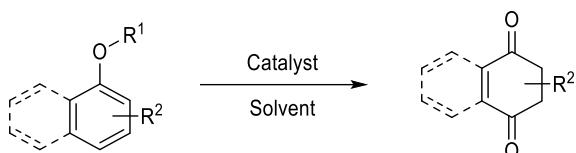
⁶² (a) Martin Owton, W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2409-2420; (b) Abraham, I.; Joshi, R.; Pardasani, P.; Pardasani, R. *T. J. Braz. Chem. Soc.* **2011**, 22, 385-421.

⁶³ (a) For selected recent examples in the use of hypervalent iodine compounds for the synthesis of quinones, see: McLaughlin, M. F.; Massolo, E.; Cope, T. A.; Johnson, J. S. *Org. Lett.* **2019**, 21, 6504-6507; (b) Xiao, X.; Greenwood, N. S.; Wengryniuk, S. E. *Angew. Chem. Int. Ed.* **2019**, 58, 16181-16187; (c) China, H.; Tanihara, K.; Sasa, H.; Kikushima, K.; Dohi, T. *Catalysis Today* **2020**, 348, 2-8; (d) Kaur, A.; Ariafard, A. *Org. Biomol. Chem.* **2020**, 18, 1117-1129.

⁶⁴ (a) For selected examples in the use of hypervalent iodine compounds in combination with HFIP for the oxidation reactions, see: Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, 116, 3684-3691; (b) Colomer, I.; Batchelor-McAuley, C.; Odell, B.; Donohoe, T. J.; Compton, R. G. *J. Am. Chem. Soc.* **2016**, 138, 8855-8861; (c) Colomer, I.; Coura Barcelos, R.; Donohoe, T. J. *Angew. Chem. Int. Ed.* **2016**, 55, 4748-4752.

⁶⁵ (a) For selected recent examples in the use of organic peroxides for the synthesis of quinones, see: Chen, P.-F.; Kuo, K.-K.; Vandavasi, J. K.; Boominathan, S. S. K.; Chen, C.-Y.; Wang, J.-J. *Org. Biomol. Chem.* **2015**, 13, 9261-9266; (b) Jiang, J.-H.; Boominathan, S. S. K.; Hu, W.-P.; Chen, C.-Y.; Vandavasi, J. K.; Lin, Y.-T.; Wang, J.-J. *Eur. J. Org. Chem.* **2016**, 2016, 2284-2289; (c) Bao, N.; Ou, J.; Shi, W.; Li, N.; Chen, L.; Sun, J. *Eur. J. Org. Chem.* **2018**, 2018, 2254-2258.

⁶⁶ (a) For selected recent examples in the use of organic/inorganic salts for the synthesis of quinones, see: Cui, J.-h.; Li, S.-s. *Journal of the Chinese Chemical Society* **2013**, 60, 1163-1168; (b) Buccini, M.; Piggott, M. J. *Org. Lett.* **2014**, 16, 2490-2493; (c) Schünemann, K.; Furkert, D. P.; Choi, E. C.; Connelly, S.; Fraser, J. D.; Sperry, J.; Brimble, M. A. *Org. Biomol. Chem.* **2014**, 12, 905-912.



Scheme 17. Oxidation of arenes/phenol derivatives.

With this background, the search for more eco-friendly oxidation methods has played a crucial role in the Green Chemistry field, trying to achieve a more efficient chemical transformation avoiding the use of hazardous catalysts and/or solvents. At this juncture, over the last few years, in light of the emergence of H₂O₂ and O₂ as green alternative oxidants, a myriad of procedures employing these oxidants have been investigated, rendering a high atom-economy protocol and diminishing the environmental impact of waste generated. Even so, the utilisation of Lewis acids or metal-based catalysts is compulsory in the majority of these green methodologies.⁶⁷

For instance, in 2010 Beller and co-workers reported an environmentally friendly oxidation of phenols and arenes by utilising for the first time an iron-catalyst (Scheme 18a)⁶⁸ and ruthenium-catalyst (Scheme 18b)⁶⁹ employing, in both cases, H₂O₂ as oxidant giving rise to a wide array of quinone derivatives in moderate to high yields.

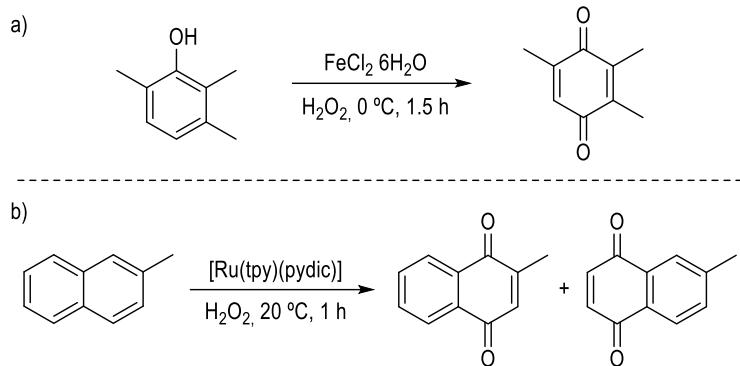
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⁶⁷ (a) Kamata, K.; Yamaura, T.; Mizuno, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 7275-7278; (b) Norcott, P.; Spielman, C.; McErlean, C. S. P. *Green Chem.* **2012**, *14*, 605-609; (c) Abu-Elfotoh, A.-M.; Tsuzuki, K.; Nguyen, T. B.; Chanthamath, S.; Shibatomi, K.; Iwasa, S. *Tetrahedron* **2013**, *69*, 8612-8617; (d) Ivanchikova, I. D.; Maksimchuk, N. V.; Maksimovskaya, R. I.; Maksimov, G. M.; Kholdeeva, O. A. *ACS Catal.* **2014**, *4*, 2706-2713; (e) Kwong, H.-K.; Lo, P.-K.; Yiu, S.-M.; Hirao, H.; Lau, K.-C.; Lau, T.-C. *Angew. Chem. Int. Ed.* **2017**, *56*, 12260-12263.

⁶⁸ Möller, K.; Wienhöfer, G.; Schröder, K.; Join, B.; Junge, K.; Beller, M. *Chem. Eur. J.* **2010**, *16*, 10300-10303.

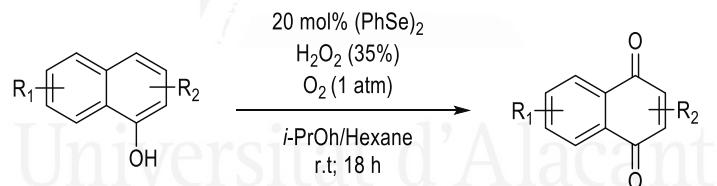
⁶⁹ Wienhöfer, G.; Schröder, K.; Möller, K.; Junge, K.; Beller, M. *Adv. Synth. Catal.* **2010**, *352*, 1615-1620.

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Scheme 18. Oxidation of phenols and arenes utilising metal-catalysts.

More recently, Doris, da Silva Junior and co-workers developed different oxidation systems combining aryl diselenides and H_2O_2 using carbon nanotube-rhodium nanohybrid as co-catalyst (Scheme 19).⁷⁰ They have developed a straightforward oxidation process providing a huge variety of 1,4-naphthoquinone derivatives in heterogeneous catalysts with moderate yields.



Scheme 19. Oxidation of naphthol by using Se oxidant species.

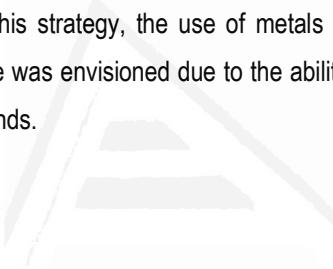
⁷⁰ de Carvalho, R. L.; Jardim, G. A. M.; Santos, A. C. C.; Araujo, M. H.; Oliveira, W. X. C.; Bombaça, A. C. S.; Menna-Barreto, R. F. S.; Gopi, E.; Gravel, E.; Doris, E.; da Silva Júnior, E. N. *Chem. Eur. J.* **2018**, *24*, 15227–15235.



2.2 Objectives

Based on the aforementioned bibliographical background, the lack of sustainable methodologies to get access to these compounds and according to preliminary studies carried out, the following purpose was established:

To carry out the oxidation of electron-rich arenes employing fluorinated alcohols as solvents and H₂O₂ as oxidant. With this strategy, the use of metals would be avoided, and the chemical waste reduced. This objective was envisioned due to the ability of fluorinated alcohols as activators of H₂O₂ through hydrogen bonds.



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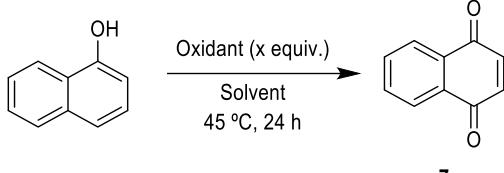


2.3 Discussion of Results

Initially, the optimal reaction parameters for the synthesis of different substituted quinones were studied using as model substrate 1-naphthol (Table 5). For the purpose of determining their performance, H₂O₂ (30% aqueous solution) and UHP (urea-H₂O₂ adduct) were employed as oxidising agents testing different solvents with both sources. Thus, the reaction was stirred 24 hours and heated at 45 °C. First, it was considered the possibility to carry out the reaction in absence of solvent, being as greenest as possible, but the conversion did not exceed 20% (Table 5, entry 1). Then, different fluorinated and non-fluorinated alcohols were tested as solvents employing the above mentioned oxidants, in order to compare their ability to promote the oxidation of 1-naphthol. Regrettably, when 3 equivalents of both oxidants (H₂O₂ and UHP) were employed in H₂O, 2-propanol or TFE, the reaction scarcely worked, affording, at best, only 14% of conversion (Table 5, entries 2-7). Albeit, better conversions were observed when HFIP was the solvent chosen in both oxidants for the formation of naphthoquinone **7** (Table 5, entries 8 and 10). Further refinement of reaction conditions consisted of increasing the amount of oxidant up to 5 equivalents in the case of HFIP due to the modest conversions achieved. In such a way, when the reaction was performed under the new conditions, it resulted in a substantial amelioration of the result (71% of conversion), especially when the oxidant utilised was UHP (Table 5, entry 11), whereas no further enhancement was observed with H₂O₂ (Table 5, entry 9). It is worth noting that, gratifyingly, 95% of conversion, and good yield, to the desired naphthoquinone **7** was observed when the reaction was performed increasing the amount of UHP up to 7.5 equivalents in HFIP (Table 5, entry 12).

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Table 5. Optimisation of the reaction parameters^[a]



Entry	Solvent	Oxidant (equiv.)	Conv. (%) ^[b]
1	Neat	H ₂ O ₂ (5)	18
2	H ₂ O	H ₂ O ₂ (3)	14
3	H ₂ O	UHP (3)	-
4	iPrOH	H ₂ O ₂ (3)	-
5	iPrOH	UHP (3)	-
6	TFE	H ₂ O ₂ (3)	10
7	TFE	UHP (3)	5
8	HFIP	H ₂ O ₂ (3)	37
9	HFIP	H ₂ O ₂ (5)	30
10	HFIP	UHP (3)	43
11	HFIP	UHP (5)	71
12	HFIP	UHP (7.5)	95 (87) ^[c]

^[a] All reactions were carried out using 0.15 mmol of 1-naphthol and the corresponding amount of oxidant in 150 µL of the solvent at 45 °C for 24 h. ^[b] Conversion towards formation of 7, determined by GC-MS. ^[c] Isolated yield after preparative TLC.

After the optimisation process, the best reaction conditions to carry out the oxidation involved the use of HFIP as solvent and 7.5 equivalents of UHP as oxidant, at 45 °C for 24 hours under conventional heating. Next, in order to study the scope of the reaction, different naphthols and phenols were tested (Table 6). As stated above, good yield was obtained when the oxidation of 1-naphthol was carried out, affording the corresponding naphthoquinone. Contrariwise, the oxidation of 2-naphthol gave rise to, unfortunately, a complex mixture of oxidation compounds observing no starting material unreacted by GC-MS and ¹H-NMR. Next, when 8-hydroxy-1-naphthol was utilised for the oxidation, again good results were achieved obtaining juglone (**8**) in high yields. Later on, phenol derivatives were taken into consideration. Thus, benzoquinone **9** was obtained in good yield when hydroquinone was tested. Likewise, when disubstituted phenols such as 3,5-dimethylphenol were employed, comparable yields were observed affording 2,6-dimethylbenzoquinone (**10**), while

Discussion of Results

the corresponding 2,3-dimethyl isomer rendered the corresponding quinone **11** in low conversions. It is noteworthy that when using 2,3,5-trimethylphenol as a substrate, the yield increased up to 76% affording the oxidised quinone **12**. Once again, a considerably decrease in the conversion was observed after performing the reaction with 2-*tert*-butyl-5-methylphenol. Finally, in a like manner, the reaction was tested selecting phenols containing electron-donating groups (MeO) as substrate. Regrettably, low conversion was achieved towards the quinone **14** when 3-methoxyphenol was the substrate tested. Nevertheless, remarkably high yield was achieved towards the formation of benzoquinone derivative **15** when the reaction was carried out with more electron-rich 3,5-dimethoxyphenol. At this point, it is worth to mention that the reaction was also essayed with other aromatic alcohols such as catechol, guaiacol, phenol, phloroglucinol or resorcinol, so failing the reaction in all of them.

Table 6. Oxidation of naphthols and phenols^[a]

 UHP (7.5 equiv.) HFIP 45 °C, 24-45 h	 7 (87%)	 8 (83%)	 9 (62%)	 10 (67%)	 11 (15%) ^[b]
	 12 (76%)	 13 (18%) ^[b]	 14 (17%) ^[b]		 15 (84%)

^[a] All reactions were carried out using 0.15 mmol of arene and 7.5 equiv. of UHP in 150 µL of the solvent at 45 °C for 24-45 h. In parenthesis, yield of the isolated compound after preparative TLC. ^[b] Conversion towards formation of quinone, determined by GC-MS.

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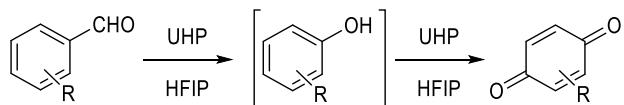
Likewise, with the purpose of broadening the scope of the methodology to other electron-rich arenes, the reaction was performed under the same conditions employing anisole derivatives as substrates (Table 7). The reaction of 1-methoxynaphthalene was firstly carried out obtaining naphthoquinone (**7**) in 63% yield. When the substrate employed was 2-methoxynaphthalene, and similarly as in the case of 2-naphthol, a complex mixture of oxidation products was produced. However, herein derivative **16** was distinguished amongst other products. Taking into account the hydroquinone oxidation studied before, it was thought that using electron-rich alkenes as *p*-methoxyanisole, the oxidation process could offer similar results, unfortunately, in this case, the reaction barely worked, observing a low conversion towards the formation of benzoquinone (**9**) by GC-MS. Being aware of the influence of methyl in *meta* position in the oxidation process, 3,5-dimethylanisole was utilized, and as somehow expected, moderate yield was reached towards the formation of benzoquinone **10**. In a like manner, anisoles bearing alkyl group in the structure were next submitted. Thus, 4-methyl-1,2-dimethoxybenzene was checked but regrettably low conversion was observed towards the formation of quinone **17**. The lowest conversion achieved in this case might be caused by the adjacent position of both methoxy groups, hindering the oxidation process. For that reason, at this point *m*-dimethoxybenzene was considered to be tested as substrate. Only the corresponding phenol **18** was observed, even though raised up to 10 equivalents the amount of UHP. Bearing in mind the relevance of methoxy groups and with the purpose of enhancing the oxidative process, the reaction was tested using phloroglucinol trimethyl ether, rendering the quinone **15** in 83% isolated yield. Additionally, it is also worth mentioning that not only the aforementioned substrates were taken into account, but also other methoxy containing benzenes were studied such as anisol, *p*-methoxyanisole, 2-methoxy-4-methylanisole or 2,6- and 5,6-dimethylanisole. Nevertheless, none of them produced satisfactory results.

Table 7. Oxidation of anisole derivatives^[a]

 $\text{R} = \text{H, Me, OMe}$

^[a] All reactions were carried out using 0.15 mmol of arene and 7.5 equiv. of UHP in 150 µL of the solvent at 45 °C for 24-45 h. In parenthesis yield of the isolated compound after preparative TLC. ^[b] 10 equiv. of UHP were used. ^[c] No starting material was observed by GC-MS. ^[d] Conversion towards formation of quinone, determined by GC-MS.

At this point taking advantage of the UHP-mediated Dakin oxidation described by Varma group,⁷¹ as above mentioned, for the oxidation of phenols from benzaldehydes, and considering the results obtained with phenols, naphthols and anisole derivatives using this system, it was envisioned the possibility of performing a Dakin reaction-oxidation of phenols sequence. Therefore, following the sequence depicted in the Scheme 20, the final quinones would be acquired directly from benzaldehydes.

**Scheme 20.** Quinones through Dakin reaction-oxidation of phenol sequence.

⁷¹Varma, R. S.; Naicker, K. P. *Org. Lett.* **1999**, *1*, 2, 189–192.

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In such manner, the reaction was carried out under the optimal reaction parameters, being the results of this study presented in Table 8. Aware of the influence of electron-donating groups, 3,4,5-trimethoxybenzaldehyde was firstly employed as substrate of the reaction, affording quinone **15** in 84% yield. Similarly, benzaldehydes containing different amount of methoxy groups were also tested. Thus, 2,6- and 2,5-dimethoxybenzaldehyde were studied, obtaining 76% yield for quinone **15** and 67% yield for compound **19**, respectively. When 2,5-dimethoxyterephthalaldehyde was essayed, the quinone **19** was rendered in a modest 51% yield. At this point, a tendency was observed consisting in when the *meta*-position of the substrate was occupied by an electron-donating group, the conversion towards the oxidative product and final yield decreased. This fact was demonstrated when 3,4-dimethoxybenzaldehyde was employed and only the phenol **20**, coming from the Dakin reaction, was isolated in high yield as product. Likewise, comparable results were observed when the reaction was performed using *ortho*- and *para*-methoxybenzaldehyde, affording the corresponding guaiacols **21** and **22** in excellent yields. These results are in agreement with those observed when *ortho*- and *para*-guaiacol were submitted to oxidation reaction, not producing the desired quinone as it has been mentioned above. In view of the results obtained, it can be asserted that the presence of at least two electron-donating groups is crucial for the oxidation to proceed. Finally, in order to verify whether the UHP-system only operates with electron-rich arenes, the reaction was tested with benzaldehyde, which is not considered as an electron-rich arene. As somehow expected, the reaction did not yield the desired phenol or quinone but produced the corresponding benzoic acid (**23**) in excellent yield.

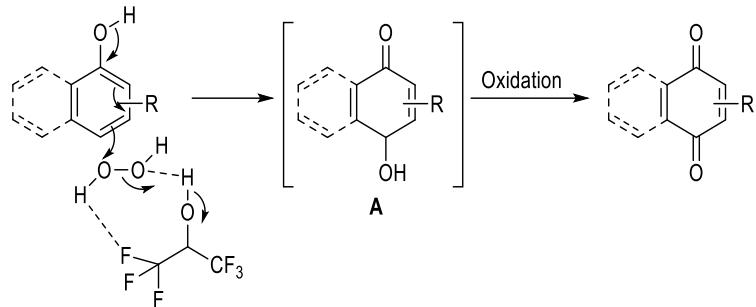
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Table 8. Oxidation of aldehyde derivatives^[a]

 $\text{R} = \text{H, Me, OMe}$
 15 (84%) ^[b] 15 (76%) ^[c]
 19 (67%) ^[d] 19 (51%) ^[e]
 23 (93%)
 21 (91%)
 22 (91%)
 23 (93%)

^[a] All reactions were carried out using 0.15 mmol of aldehyde and 7.5 equiv. of UHP in 150 µL of the solvent at 45 °C for 24-48 h. In parenthesis yield of the isolated compound after preparative TLC. ^[b] From 3,4,5-trimethoxybenzaldehyde. ^[c] From 2,6-dimethoxybenzaldehyde. ^[d] From 2,5-dimethoxybenzaldehyde, not purely isolated; estimated yield by ¹H NMR. ^[e] From 2,5-dimethoxyterephthalaldehyde.

Based on the results obtained and taking into consideration the literature precedents and the crucial role of HFIP on the activation of the oxidant (UHP or H₂O₂), a possible mechanism is postulated in Scheme 21. Thus, in the first step, the activation of H₂O₂ with HFIP through hydrogen bonds would take place. Immediately, the nucleophilic attack of the electron-rich arene onto this activated oxidant, would give rise to the formation of intermediate **A**, in a S_EAr-type reaction. Then, this intermediate **A**, which is highly prone to be oxidised, would suffer a subsequent oxidation towards the formation of the corresponding quinone.



Scheme 21. Proposed reaction mechanism.

Finally, considering the accentuated importance of quinones in biological activity and their importance in medicinal chemistry and biochemistry, and to further demonstrate the applicability of the methodology herein described, it was thought to perform a big-scale experiment. (Figure 8). Hence, 1-naphthol was selected as substrate for such purpose. Under the optimal reaction conditions, but reducing the amount of HFIP down to 3 mL (2M concentration in respect to 1-naphthol), 6 mmol of the substrate were stirred and after 30 hours, the corresponding naphthoquinone (**7**) was afforded in a 73% yield. Even though the result was slightly lower in comparison with the obtained previously (see Table 6, entry 1), it has been demonstrated the feasibility of scaling-up the procedure.

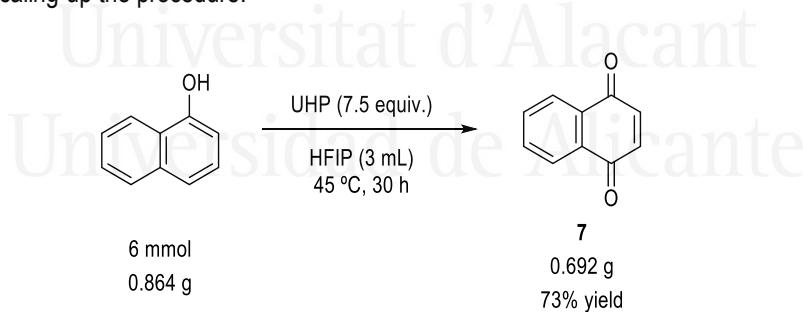
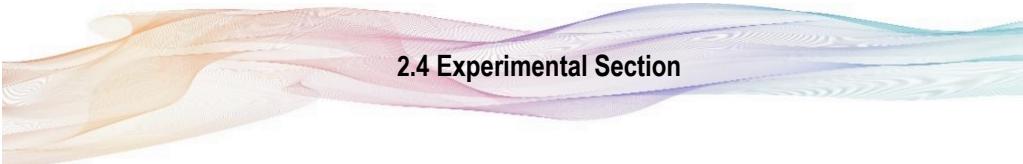


Figure 8. Big-scale reaction.



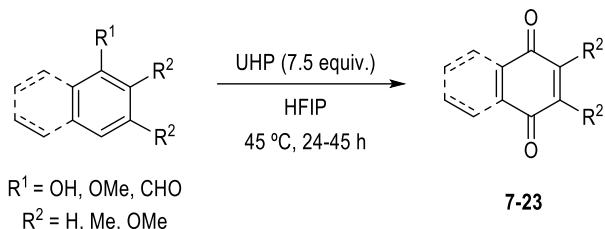
2.4 Experimental Section

2.4.1 General

Unless otherwise noted, all reagents and solvents were obtained commercially (Acros, Aldrich, Fluka, Fluorochem, Merck) and used without further purification. ^1H NMR and ^{13}C NMR spectra were performed at the technical service of the University of Alicante (SSTTI-UA) using a Bruker AV-300 or Bruker AV-400 (Bruker Corporation) using CDCl_3 as solvent and TMS as internal standard unless otherwise stated. Chemical shifts (δ) are given in ppm and the coupling constants (J) in Hz. Low-resolution mass spectra (MS) were recorded in the electron impact mode (EI, 70eV, He as carrier phase) using an Agilent GC/MS 5973 Network Selective Detector spectrometer apparatus equipped with a HP-5MS column (Agilent technologies, 30 m \times 0.25 mm) and giving fragment ions in m/z with relative intensities (%) in parentheses. Low-resolution electron impact (EI) mass spectra were obtained at 70eV on Agilent GC/MS-5973N apparatus equipped with a HP-5MS column (Agilent technologies, 30 m \times 0.25 mm). Analytical TLC was performed on Merck silica gel plates and the spots visualized with UV light at 254 nm. Flash chromatography employed Merck silica gel 60 (0.040-0.063 mm). Silica gel 60 F₂₅₄ containing gypsum was employed for preparative layer chromatography.

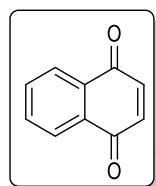
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2.4.2 General Procedure for the HFIP-UHP Oxidation of Electron-Rich Arenes.

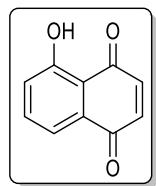


In a capped tube, onto the corresponding arene (0.15 mmol), HFIP (150-200 μL) and UHP (7.5 equiv.) were added in one portion. The reaction was then stirred at 45 °C (oil bath) for 24-45 hours, until the reaction was judged to be completed by GC-MS. After this time, the reaction mixture was filtered over silica/celite plug and then the solvent was removed under vacuum, and the crude material was directly purified by flash silica gel column chromatography or preparative TLC using *n*-hexane/ethyl acetate as eluent, giving the corresponding oxidation products.

2.4.3 Physical and Spectroscopic Data for Isolated Compounds



Naphthoquinone (7):⁶⁸ brown solid; purification by preparative TLC (*n*-hexane/ethyl acetate 8.5/1.5), 87% yield; **1H NMR** (300 MHz, CDCl_3): $\delta_{\text{H}} = 8.11$ (dd, $J = 5.8, 3.3$ Hz, 2H, 2x CH_{Ar}), 7.79 (dd, $J = 5.8, 3.3$ Hz, 2H, 2x CH_{Ar}), 7.01 (s, 2H, 2xCH) ppm; **13C NMR** (300 MHz, CDCl_3): $\delta_{\text{C}} = 185.0, 138.7, 133.9, 131.9, 126.4$ ppm; **MS (EI)**: m/z 158 (M^+ , 100%), 130 (27), 104 (31), 102 (31), 76 (21).

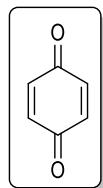


5-Hydroxy-1,4-naphthalenedione (Juglone) (8):⁷² orange solid; 83% yield, (without further purification); **1H NMR** (400 MHz, CDCl_3): $\delta_{\text{H}} = 11.93$ (s, 1H), 7.70 – 7.63 (m, 2H, 2x CH_{Ar}), 7.31 (dd, $J = 7.4, 2.2$ Hz, 1H, CH_{Ar}), 6.98 (s, 2H, 2xCH) ppm; **13C NMR** (101 MHz, CDCl_3): $\delta_{\text{C}} = 190.3, 184.3, 161.4, 139.6, 138.6, 136.6,$

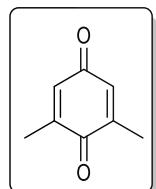
⁷² Saha, N.; Müller, M.; Husain, S. M. *Org. Lett.* **2019**, 21, 2204-2208.

Experimental Section

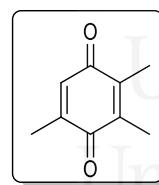
131.7, 124.52, 119.18, 114.97 ppm; **MS** (EI): *m/z* 174 (M⁺, 100%), 173 (25), 120 (19), 118 (29), 92 (16), 63 (13).



Benzoquinone (9):⁷³ dark brown solid; purification by preparative TLC (*n*-hexane/ethyl acetate 9.0/1.0), 62% yield; **1H NMR** (400 MHz, CDCl₃): δ_H = 6.81 (s, 4H, 4xCH) ppm; **13C NMR** (101 MHz, CDCl₃): δ_C = 187.2, 136.5 ppm; **MS** (EI): *m/z* 108 (M⁺, 100%), 82 (32), 80 (25), 54 (55), 53 (14), 52 (16).



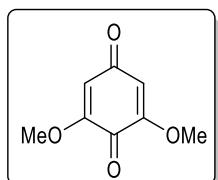
3,5-Dimethyl-p-benzoquinone (10):⁶⁸ dark orange solid; purification by preparative TLC (*n*-hexane/ethyl acetate 9.0/1.0), 67% yield; **1H NMR** (400 MHz, CDCl₃): δ_H = 6.60 (q, *J* = 1.6 Hz, 2H, 2xCH_{Ar}), 2.04 (s, 3H, CH₃), 2.04 (s, 3H, CH₃) ppm; **13C NMR** (101 MHz, CDCl₃): δ_C = 188.1, 145.8, 133.4, 15.5 ppm; **MS** (EI): *m/z* 136 (M⁺, 100%), 108 (63), 107 (29), 96 (24), 80 (21), 79 (60), 77 (12), 68 (88).



2,3,5-Trimethyl-p-benzoquinone (12):⁶⁸ yellow oil, purification by preparative TLC (*n*-hexane/ethylacetate 9.0/1.0), 76 % yield; **1H NMR** (400 MHz, CDCl₃): δ_H = 6.75 – 6.40 (m, 1H, CH_{Ar}), 2.06 (d, *J* = 1.6 Hz, 3H, CHCH₃), 2.05 (m, 3H, CH₃), 2.03 (m, 3H, CH₃) ppm; **MS** (EI): *m/z* 150 (M⁺, 100%), 122 (32), 121 (17), 107 (47), 79 (31), 68 (22), 54 (12).

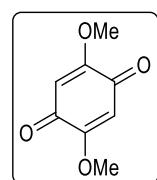
⁷³ Gustavo, P. R.; Paula, I. V.; Patricia, G. V.; Carmen, V. C.; Pietro, T. *Lett. Org. Chem.* **2008**, 5, 332-335.

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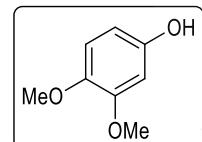
(22).

2,6-Dimethoxy-p-benzoquinone (15):⁷⁴ ochre-orange solid, purification by preparative TLC (*n*-hexane/ethyl acetate 8.0/2.0), 87% yield; **¹H NMR** (300 MHz, CDCl₃): δ_H = 5.88 (s, 2H, 2xCH_{Ar}), 3.84 (s, 6H, 2xCH₃) ppm; **¹³C NMR** (101 MHz, CDCl₃): δ_C = 186.9, 176.6, 157.4, 107.4, 56.4 ppm; **MS (EI)**: *m/z* 168 (M⁺, 74%), 138 (23), 125 (15), 97 (13), 80 (36), 69 (100), 59 (13), 53

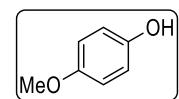


2,5-Dimethoxy-p-benzoquinone (19):⁷⁴ brown solid; purification by preparative

TLC (*n*-hexane/ethyl acetate 9.0/1.0), 67% yield; **¹H NMR** (300 MHz, CDCl₃): δ_H = 5.89 (s, 2H, 2xCH_{Ar}), 3.87 (s, 6H, 2xCH₃) ppm; **¹³C NMR** (126 MHz, CDCl₃): δ_C = 181.7, 159.6, 105.5, 56.6 ppm; **MS (EI)**: *m/z* 168 (M⁺, 13%), 155 (74), 153 (30), 149 (60), 139 (56), 127 (26), 122 (15), 112 (16), 95 (35), 69 (100), 59 (17), 53 (22).



3,4-Dimethoxyphenol (20):⁷⁵ brown solid; purification by flash chromatography (*n*-hexane/ethyl acetate 9.0/1.0), 88% yield; **¹H NMR** (400 MHz, CDCl₃): δ_H = 6.74 (d, *J* = 8.6 Hz, 1H, CH_{Ar}), 6.49 (d, *J* = 2.8 Hz, 1H, CH_{Ar}), 6.37 (dd, *J* = 8.6, 2.8 Hz, 1H, CH_{Ar}), 3.83 (s, 3H, CHCH₃), 3.82 (s, 3H, CHCHCH₃) ppm; **¹³C NMR** (101 MHz, CDCl₃): δ_C = 150.2, 149.8, 143.0, 112.4, 105.8, 100.6, 56.6, 55.8 ppm; **MS (EI)**: *m/z* 154 (M⁺, 100%), 139 (71), 111 (40), 93 (17), 69 (12), 65 (12), 55 (11).

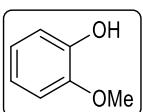


4-Methoxyphenol (21):⁷⁵ white solid; 96% yield (without further purification), **¹H NMR** (300 MHz, CDCl₃): δ_H = 6.79 (s, 4H, 4xCH_{Ar}), 5.15 (s, 1H, OH), 3.77 (s, 3H, CH₃) ppm; **¹³C NMR** (75 MHz, CDCl₃): δ_C = 153.6, 149.5, 116.1, 114.9, 55.8 ppm; **MS (EI)**: *m/z* 124 (M⁺, 99%), 109 (100), 8 (42), 53 (14).

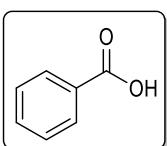
⁷⁴ Yoshida, R.; Isozaki, K.; Yokoi, T.; Yasuda, N.; Sadakane, K.; Iwamoto, T.; Takaya, H.; Nakamura, M. *Org. Biomol. Chem.* **2016**, *14*, 7468-7479.

⁷⁵ Varma, R. S.; Naicker, K. P. *Org. Lett.* **1999**, *1*, 189-192.

Experimental Section

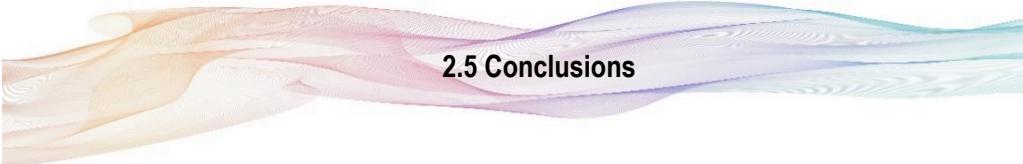


2-Methoxyphenol (22):⁷⁵ white solid; 91% yield (without further purification); **¹H NMR** (300 MHz, CDCl₃): δ_H = 7.05 – 6.84 (m, 4H, 4xCH_{Ar}), 5.71 (s, 1H, OH), 3.91 (s, 3H, CH₃) ppm; **¹³C NMR** (75 MHz, CDCl₃): δ_C = 146.6, 145.7, 121.5, 120.2, 114.6, 110.7, 55.8 ppm; **MS (EI)**: m/z 124 (M⁺, 93%), 109 (100), 81 (50).



Benzoic acid (23):⁷⁵ white solid, 93% yield (without further purification); **¹H NMR** (300 MHz, CDCl₃): δ_H = 12.02 (s, 1H, OH), 8.21 – 8.10 (m, 2H, 2xCH_{Ar}), 7.70 – 7.59 (m, 1H, CH_{Ar}), 7.51 (ddt, J = 8.2, 6.8, 1.0 Hz, 2H, 2xCH_{Ar}) ppm; **¹³C NMR** (75 MHz, CDCl₃): δ_C = 172.5, 133.8, 130.2, 129.3, 128.5 ppm; **MS (EI)**: m/z 122 (M⁺, 90%), 105 (100), 77 (62), 51 (22), 50 (13).

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2.5 Conclusions

As a conclusion of this chapter, it has been demonstrated that the use of UHP as oxidant source in combination with HFIP as solvent, allows the simple and new straightforward oxidation of electron-rich arenes into the corresponding quinolines under mild conditions. The protocol can be considered as environmentally benign avoiding the use of metal and/or organic oxidants. Additionally, this methodology has a high atom economy and the only by-products and waste generated (H_2O and urea) are considered biodegradable.

Moreover, the reaction was implemented for the synthesis of a broad range of quinones, which were obtained in yield from moderate to high in the majority of cases. Even though not having a clear trend in reactivity, it can be stated that under the reaction conditions here described, naphthalene derivatives and highly substituted electron-rich arenes appears to provide better results. Furthermore, it can be also asserted that quinones bearing electron donating substituents on both double bonds were obtained with higher yields. Those results here described would be in accordance with the fact that H_2O_2 can be electrophilically activated by means of the fluorinated alcohol.

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CHAPTER III

Direct Synthesis of *N,N*-Disubstituted Formamides by Oxidation of
Imines Using HFIP/UHP System

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3.1 Antecedents

3.1.1 General

Formamide moiety, known as the simplest amide structure and present in a huge range of simple organic molecules, has always attracted the attention of organic chemists and biochemists because in its structure contains carbon, hydrogen, nitrogen and oxygen, becoming in that way, a valuable intermediate in organic synthesis.⁷⁶ As a matter of proof, formamide, under diverse experimental conditions, is able to give rise to a huge range of complex biomolecules such as nucleobases (Scheme 22).^{76b,77}

Apart from that, formamide derivatives have been broadly used in pharmaceutical industry for the synthesis of an extensive range of other valuable bioactive heterocyclic compounds such as 1,2-dihydroquinolines,⁷⁸ fluoroquinolones⁷⁹ or substituted aryl imidazoles⁸⁰ among others⁸¹ (Figure 9).

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⁷⁶ (a) Kennedy, G. L., Jr. *Crit. Rev. Toxicol.* **1986**, *17*, 129-182; (b) Saladino, R.; Crestini, C.; Pino, S.; Costanzo, G.; Di Mauro, E. *Phys Life Rev* **2012**, *9*, 84-104; (c) Dulieu, F.; Nguyen, T.; Congiu, E.; Baouche, S.; Taquet, V. *Mon. Not. R. Aston. Soc.* **2019**, *484*, L119-L123; (d) López-Sepulcre, A.; Balucani, N.; Ceccarelli, C.; Codella, C.; Dulieu, F.; Theulé, P. *ACS Earth Space Chem.* **2019**, *3*, 2122-2137.

⁷⁷ (a) Hudson, J. S.; Eberle, J. F.; Vachhani, R. H.; Rogers, L. C.; Wade, J. H.; Krishnamurthy, R.; Springsteen, G. *Angew. Chem. Int. Ed.* **2012**, *51*, 5134-5137; (b) Kahane, C.; Ceccarelli, C.; Faure, A.; Caux, E. *Astrophys. J. Lett.* **2013**, *763*, L38/31.

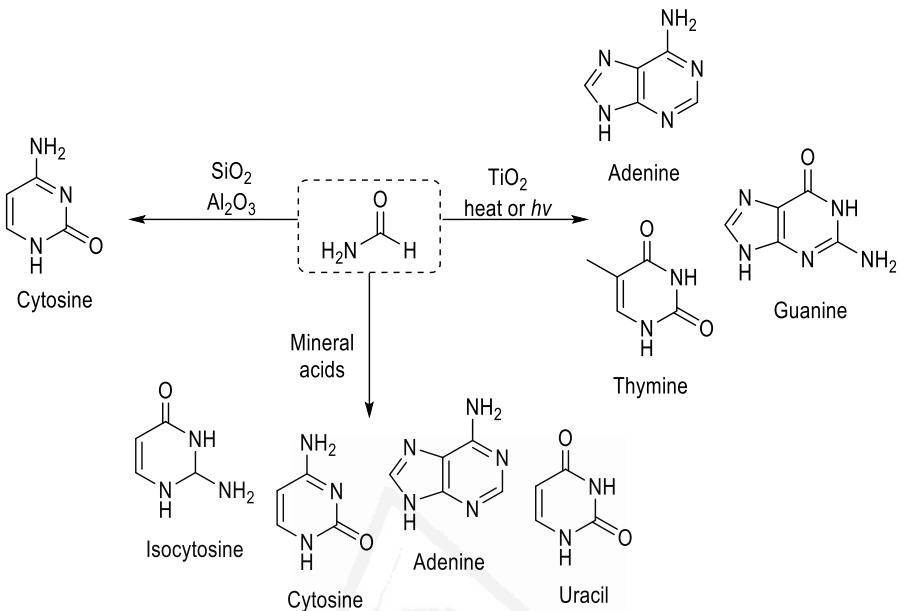
⁷⁸ Kobayashi, K.; Nagato, S.; Kawakita, M.; Morikawa, O.; Konishi, H. *Chem. Lett.* **1995**, *24*, 575-576.

⁷⁹ Jackson, A.; Meth-Cohn, O. *J. Chem. Soc., Chem. Commun.* **1995**, 1319-1319.

⁸⁰ Chen, B.-C.; Bednarz, M. S.; Zhao, R.; Sundeen, J. E.; Chen, P.; Shen, Z.; Skoumbourdis, A. P.; Barrish, J. C. *Tetrahedron Lett.* **2000**, *41*, 5453-5456.

⁸¹ (a) Pettit, G.; Kalnins, M.; Liu, T.; Thomas, E.; Parent, K. *J. Org. Chem.* **1961**, *26*, 2563-2566; (b) Kakehi, A.; Ito, S.; Sa, H. *Chem. Pharm. Bull.* **1999**, *47*, 1607-1613.

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Scheme 22. Synthetic routes of nucleobases starting from formamides, metal oxides and minerals.

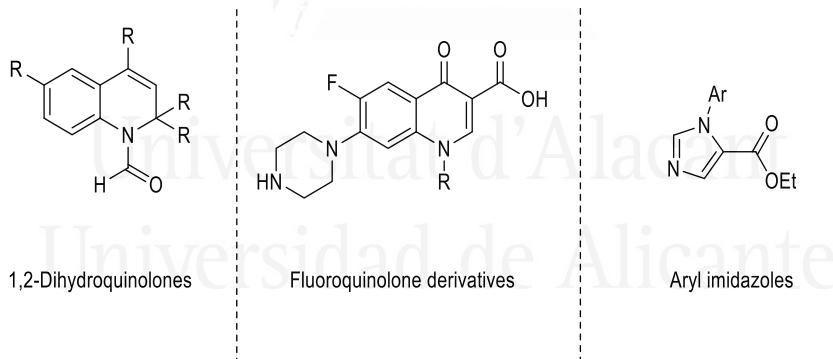


Figure 9. Bioactive heterocyclic compounds arising from formamide derivatives.

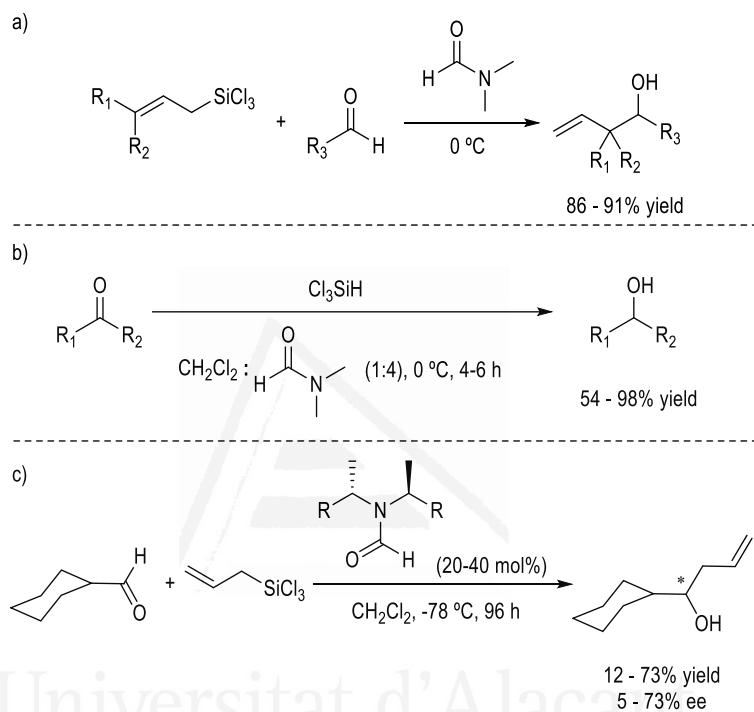
Due to their Lewis basicity, formamides have been utilised over the last years as promoters in a huge range of organic transformations such as the allylation⁸² (Scheme 23a) or hydrosilylation⁸³ of

⁸² Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, 59, 6620-6628.

⁸³ Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 25, 407-408.

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carbonyl compounds (Scheme 23b). Furthermore, the possibility of using chiral formamides as catalysts for the asymmetric allylation of aldehydes⁸⁴ has offered a new applicability of these moieties (Scheme 23c).



Scheme 23. Different uses of formamides in organic transformations.

Further to this, formamide derivatives have been greatly used as intermediates in other organic transformations (Scheme 24) giving rise to the synthesis of formamidines,⁸⁵ by utilising several coupling agents such as phosphorus chlorides or sulfonyl chlorides; isocyanates,⁸⁶ by means of dialkyl amines or alcohols in a dehydrogenative process; or nitriles,⁸⁷ employing an acylating agent for this purpose. Additionally, these organic derivatives in combination with phosphoryl chloride led

⁸⁴ Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999**, *55*, 977-988.

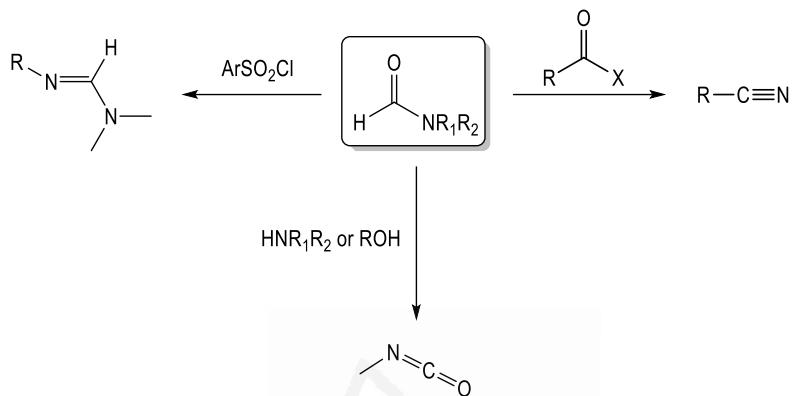
⁸⁵ Han, Y.; Cai, L. *Tetrahedron Lett.* **1997**, *38*, 5423-5426.

⁸⁶ Faraj, M. K. U.S. Patent 5,686,645, 1997.

⁸⁷ Arlt, D.; Klein, G. U.S. Patent 4,419,297, 1983.

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to the formation of a large assortment of ketones or aldehydes in the well-known Vilsmeier-Haack formylation reaction.⁸⁸



Scheme 24. Organic transformations of formamide derivatives.

3.1.2 Synthesis of Formamides

In view of their noteworthy value as intermediates in a vast range of pharmaceutical applications and organic synthesis, it is not surprising that, over the last decades, the interest of developing different approaches to synthesize formamides has been increasing.

Formally, the synthesis of a formamide takes place through the combination of a formyl chloride and an amine, releasing a molecule of hydrochloric acid. Besides this traditional formylation methodology, there are a plenty of strategies that include the employment of formylating agents, organic catalysts, or transition metal catalysts.⁸⁹ In such a way, the use of these stoichiometric and catalytic protocols implies milder reaction conditions.

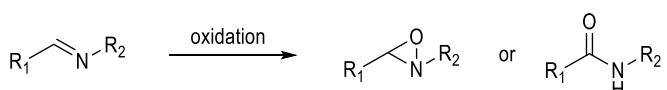
In the past years, the oxidation of imines has arisen as an attractive alternative for the formylation of amines. Nevertheless, even being considered sustainable synthetic protocols due to their metal-catalyst free oxidative coupling, the use of non-hazardous reagents or the mild reaction

⁸⁸ Downie, I. M.; Earle, M. J.; Heaney, H.; Shuaibar, K. F. *Tetrahedron* **1993**, *49*, 4015-4034.

⁸⁹ Gerack, C. J.; McElwee-White, L. *Molecules* **2014**, *19*, 7689-7713.

Antecedents

conditions required, a great part of these methodologies gave access to the corresponding *N*-substituted amides⁹⁰ or oxaziridines (Scheme 25).⁹¹



Scheme 25. Oxidation of imines to give access to oxaziridines and *N*-substituted amides.

In such a way, only a couple of examples for the synthesis of *N,N*-disubstituted formamides *via* oxidation of imines have been described so far. In the first one, the use of sodium perborate tetrahydrate in trifluoroacetic acid solution⁹² was necessary to achieve good results (Scheme 26a). In the second work, *m*-chloroperbenzoic acid as oxidant and boron trifluoride etherate⁹³ as mediator (Scheme 26b) were employed. Hence, the use of these organic peroxyacids in combination with strong Lewis or Brønsted acids, induces the formation of large amounts of waste in a low atom-economy protocol and the corresponding troubles during the purification process.

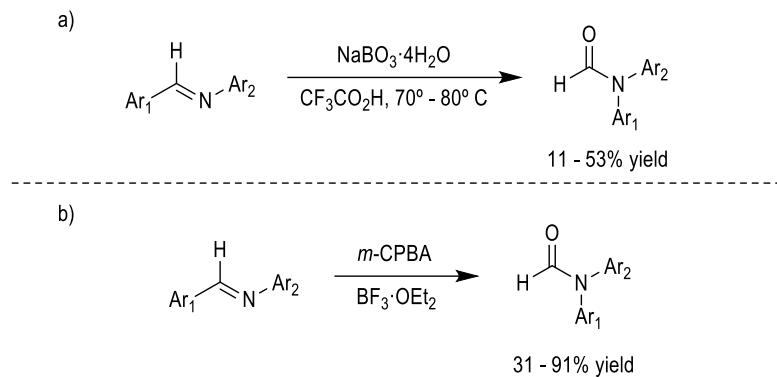
⁹⁰ (a) Larsen, J.; Jørgensen, K. A.; Christensen, D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1187-1190; (b) Leung, C. H.; Voutchkova, A. M.; Crabtree, R. H.; Balcells, D.; Eisenstein, O. *Green Chem.* **2007**, 9, 976-979; (c) Mohamed, M. A.; Yamada, K.-i.; Tomioka, K. *Tetrahedron Lett.* **2009**, 50, 3436-3438; (d) Liang, J.; Lv, J.; Shang, Z.-c. *Tetrahedron* **2011**, 67, 8532-8535; (e) Rostamnia, S.; Doustkhah, E.; Golchin-Hosseini, H.; Zeynizadeh, B.; Xin, H.; Luque, R. *Catal. Sci. Technol.* **2016**, 6, 4124-4133; (f) de Souza, G. F. P.; von Zuben, T. W.; Salles, A. G. *ACS Sustainable Chem. Eng.* **2017**, 5, 8439-8446.

⁹¹ (a) Uraguchi, D.; Tsutsumi, R.; Ooi, T. *J. Am. Chem. Soc.* **2013**, 135, 8161-8164; (b) Zhang, T.; He, W.; Zhao, X.; Jin, Y. *Tetrahedron* **2013**, 69, 7416-7422; (c) Jin, Y.; Zhang, T.; Zhang, W.; Chang, S.; Feng, B. *Chirality* **2014**, 26, 150-154; (d) Tsutsumi, R.; Kim, S.; Uraguchi, D.; Ooi, T. *Synthesis* **2014**, 46, 871-878; (e) Ji, N.; Yuan, J.; Xue, S.; Zhang, J.; He, W. *Tetrahedron* **2016**, 72, 512-517; (f) Kraiem, J.; Ghedira, D.; Ollevier, T. *Green Chem.* **2016**, 18, 4859-4864; (g) Tanaka, N.; Tsutsumi, R.; Uraguchi, D.; Ooi, T. *Chem. Commun.* **2017**, 53, 6999-7002.

⁹² (a) Nongkunsarn, P.; Ramsden, C. A. *Tetrahedron Lett.* **1993**, 34, 6773-6776; (b) Nongkunsarn, P.; Ramsden, C. A. *Tetrahedron* **1997**, 53, 3805-3830.

⁹³ An, G.-i.; Kim, M.; Kim, J. Y.; Rhee, H. *Tetrahedron Lett.* **2003**, 44, 2183-2186.

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Scheme 26. Oxidative rearrangement of imines to obtain *N,N*-disubstituted formamides.

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3.2 Objectives

Considering previous research and based on the bibliographical background above exposed, the following objective was established:

To study the oxidative process of imines in order to get access to *N,N*-disubstituted formamides by using fluorinated alcohols as solvents and reaction promoters and UHP as green oxidant, hence generating a more environmentally benign oxidative procedure.



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3.3 Discussion of Results

To start with, in order to obtain the optimal parameters for the reaction, the oxidant and its amount were studied, using different solvents with *N*-benzylideneaniline (**24**) as model substrate (Table 9). Thus, using 2 equivalents of H₂O₂ (30% aqueous solution) as oxidant agent, several organic polar protic solvents (particularly HFIP, H₂O, MeOH and TFE) were tested at 45 °C (Table 9, entries 1-4). However, good conversions were only achieved towards the formation of **46a** when HFIP was the solvent (Table 9, entry 1). Despite the poor conversion afforded, it is noteworthy that the reaction using MeOH as solvent gave rise to the formation of the regiosiomer **46b** (Table 9, entry 3). Additionally, other common polar aprotic and apolar organic solvent such as DMSO, MeCN, EtOAc, THF, acetone, CHCl₃ or PhMe were also assessed, however, the imine **24** remained unaltered or barely hydrolysed. In view of these results obtained and as an attempt to ameliorate the conversion of **46a**, it was thought to carry out the oxidation process increasing or lowering the amount of the oxidant source utilised with those solvents that provided better conversions, HFIP and MeOH. Albeit, in the case of HFIP, while 1.5 equivalents led to decreased conversion, an increase up to 3 equivalents scarcely enhanced the result (Table 9, entries 5 and 7, respectively). When MeOH was the solvent employed in order to favour the process towards the formation of **46b**, any amelioration was observed, neither reducing the equivalents nor increasing the amount up to 3 equivalents (Table 9, entries 6 and 8, respectively). At this point, it was though the use of various mixtures of solvents containing HFIP/MeOH and HFIP/H₂O. Unfortunately, these experiments were unsuccessful. In an attempt to ameliorate the conversion of compound **46a**, according to the results above described, it was thought to further refine the reaction parameters. Concerning the amount of solvent employed for the oxidative process, it was noticed that the more diluted the concentration, the higher conversion reached, being favoured the formation of **46a** up to 91% (Table 9, compare entry 9 and 10). Furthermore, the reduction of the temperature was also examined but the

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conversion slightly decreased in comparison with the model at 45 °C (Table 9, entry 11). Last but not least, bearing in mind that the partial hydrolysis of imine was observed due to the formation of benzaldehyde and aniline (detected by the GC-MS analysis), it was thought to utilise an anhydrous H₂O₂ source with the aim of minimise this drawback. In this sense, when UHP (urea-H₂O₂ adduct) was the oxidant employed, the formation of **46a** was afforded in a 97% of conversion (Table 9, entry 12). Likewise, as done before, further changes in concentration or temperature were essayed, not producing any significant amelioration (Table 9, entries 13-15).

Table 9. Optimization of the reaction conditions ^[a]

Entry	Oxidant source (equiv.)	Solvent	T (° C)		
				24	46a
1	H ₂ O ₂ (2)	HFIP	45		85% (98/2)
2	H ₂ O ₂ (2)	H ₂ O	45		<10%
3	H ₂ O ₂ (2)	MeOH	45		35% (4/96)
4	H ₂ O ₂ (2)	TFE	45		<15%
5	H ₂ O ₂ (1.5)	HFIP	45		77% (95/5)
6	H ₂ O ₂ (1.5)	MeOH	45		<15%
7	H ₂ O ₂ (3)	HFIP	45		82% (98/2)
8	H ₂ O ₂ (3)	MeOH	45		39% (4/96)
9	H ₂ O ₂ (2)	HFIP ^[c]	45		91% (>99/1)
10	H ₂ O ₂ (2)	HFIP ^[d]	45		68% (95/5)
11	H ₂ O ₂ (2)	HFIP ^[c]	25		86% (99/1)
12	UHP (2)	HFIP	45		97% (>99/1)
13	UHP (2)	HFIP ^[c]	45		92% (>99/1)
14	UHP (2)	HFIP ^[d]	45		87% (>99/1)
15	UHP (2)	HFIP	25		93% (>99/1)

^[a] Reaction conditions: all the reactions were carried out using 0.15 mmol of imine **24** and the corresponding amount of the oxidant in 150 µL of the solvent at the given temperature for 15 h.

^[b] Conversion towards formation of **46a** or **46b**, determined by GC-MS. ^[c] 250 µL of HFIP were used. ^[d] 50 µL of HFIP were used.

After the optimisation process, and before studying the scope of the reaction, a huge range of imines (Table 10) were synthesized to perform the oxidative process.

Table 10. Imines synthetized for the oxidative process.

24	25	26	27
28	29	30	31
32	33	34	35
36	37	38	39
40	41	42	43
44	45		

Thus, considering that the best reaction conditions to perform the oxidation of *N*-benzylideneaniline involved the use of 2 equivalents of UHP as oxidant, HFIP as solvent, at 45 °C for 15 hours, the scope of the reaction was next carried out with imines shown in Table 10 (**24-45**). As stated above, the oxidation of imine **24** rendered the corresponding formamide **46a** in high yields. Likewise, when imine **25** was essayed, good yield was afforded for **47a**. In view of these results, it

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was thought to try with the imine derived from *p*-anisidine (**26**), but the formamide was not observed and the decomposition and hydrolysis products were achieved. This could be explained by its more basic character being the substrate more prone to be protonated by the solvent and, in consequence, hydrolysed with ease. A significant decrease in the yield was observed when an aldimine bearing an electron-withdrawing group in the aniline moiety was utilised (**27**). Furthermore, aldimides derived from different *para*-substituted benzaldehydes (**28-31**) were subjected to this procedure and generated the corresponding disubstituted formamides (**49a-51a**) from good to high yields, regardless the electronic nature of such substituent. Herein, it is important to point that the presence of an electron withdrawing group (CF_3) in the imine **31** resulted in the benzylic oxidation, affording a substantial 10% of the corresponding isomer **51b**. Unfortunately, no favourable results were reached when the imine **32**, synthesized from salicylaldehyde, was essayed, generating about 20% of conversion, even when the amount of UHP was increased. This result might be due to an internal hydrogen bond which difficults the oxidation process. In order to reinforce this idea, *ortho*-anisaldehyde imine derivative **33** was employed affording the corresponding product **53a** in good yield. Better results were achieved when the reaction was carried out with an imine bearing *para*-methyl substituents in both aromatic rings, affording formamide **54a**.

To broaden the applicability of the process, the reaction was performed employing heteroaromatic aldehyde imine derivatives. Different behaviours according to the electronic properties of the aromatic ring where then observed. In such a way, when the imine utilised contained an electron-rich heteroaromatic ring, as in the case of imine **35** with the furan ring structure, the reaction resulted in decomposition and hydrolysis products. Contrariwise, if the imine held an electron poor aromatic ring, such as imine **36** bearing a pyridine ring, the oxidation occurred but compound **55b**, as result of benzylic oxidation, was obtained in good yield as main product. The next step was the study of those imines arising from aliphatic amines. Hence, when *N*-benzylidenbutanamine (**37**) was proved, again the butylbenzamide **56b** from benzulic oxidation was afforded in 87% yield. Regrettably, it was not possible to obtain the expected formamide when the reaction was carried out with imine bearing a cyclohexane ring (**38**), instead, oxaziridine **57** was achieved in excellent yield. Unexpectedly, while seeking the oxidation of *N*-benzyl-1-phenylmethanimine (**39**), *N,N*-diphenylformamide **46** was obtained in 87% yield. Likewise, imines

Discussion of Results

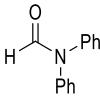
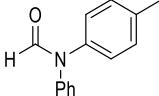
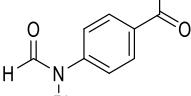
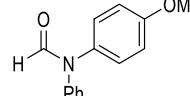
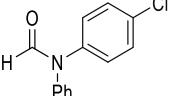
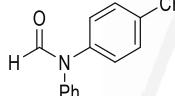
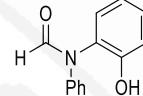
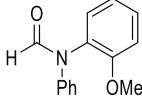
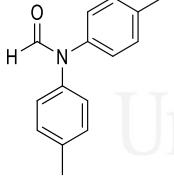
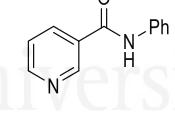
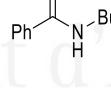
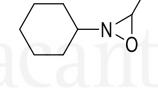
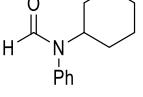
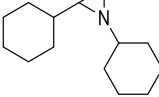
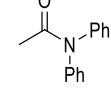
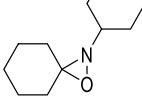
derived from cyclohexanecarbaldehyde were next investigated. Herein, it is worth to point out that good results were achieved towards the formation of the corresponding formamide when imine 1-cyclohexyl-*N*-phenylmethanimine (**40**) was utilised. Contrarily, when the imine employed was *N*-1-dicyclohexylmethanimine (**41**), the oxaziridine **59** was obtained in excellent yields.

At this point, it was considered to analyse the cinnamaldehyde derivative imine **42** but, awesomely, an intriguing mixture of compounds was afforded. Amongst the products, it was possible to distinguish as major products benzaldehyde and formamide **46** combined with trace amounts of *N*-phenylformamide by GC-MS. Finally, the reaction was performed with few ketimines to further explore the versatility of this methodology. First, the reaction was carried out with an imine derived from acetophenone (**43**), giving the corresponding *N,N*-diphenylacetamide in only 20% conversion. Contrariwise, when imine **44**, derived from cyclohexyl methyl ketone, was utilised, the reaction failed towards the formation of the expected formamide leading mainly to hydrolysis products. Finally, alkylic ketimine **45** derived from cyclohexanone was used, providing in 95% yield oxaziridine **61**.

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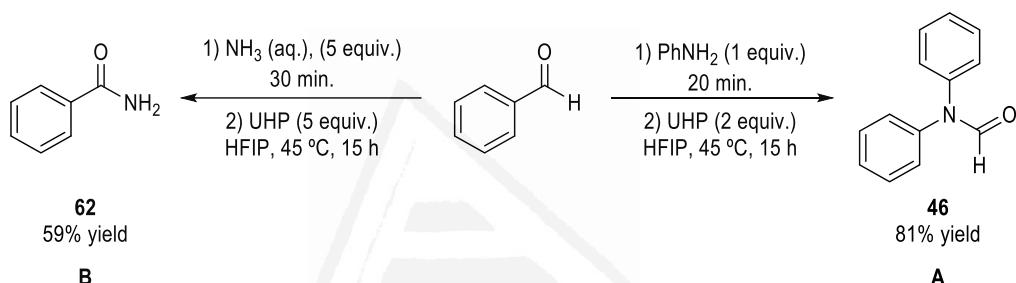
Table 11. Scope of the reaction^[a]

$\begin{array}{c} \text{R}_3 \\ \\ \text{R}_1-\text{C}=\text{N}-\text{R}_2 \end{array}$	$\xrightarrow[\substack{\text{HFIP}, 45^\circ\text{C} \\ 15 \text{ h}}]{\text{UHP (2 equiv.)}}$	$\begin{array}{c} \text{O} \\ \\ \text{R}_3-\text{N}-\text{R}_1 \\ \\ \text{H} \end{array}$ a	$\begin{array}{c} \text{O} \\ \\ \text{R}_1-\text{N}-\text{H} \\ \\ \text{H} \end{array}$ b
24-45	46-61		
$\text{R}_1 \text{ and } \text{R}_2 = \text{Alkyl, aryl}$ $\text{R}_3 = \text{H, alkyl}$			when $\text{R}_3 = \text{H}$
 46 (89%) (>99/1)	 47 (82%) (>99/1)	 48 (62%) (>99/1)	 49 (87%) (>99/1)
 50 (88%) (96/4)	 51 (91%) (90/10)	 52 (<20% conv.) ^[b]	 53 (90%) (98/2)
 54 (79%) (>99/1)	 55 (72%) (15/85)	 56 (57%) (35/65) ^[c]	 57 (98%)
 58 (84%) (>99/1)	 59 (95%)	 60 (20% conv.) ^[b]	 61 (95%)

^[a] Reaction conditions: all the reactions were carried out using 0.15 mmol of imine and 2 equiv. of UHP in 150 µL of HFIP at 45 °C for 15 h. In parenthesis, yield of the isolated compound after preparative TLC. Also, the conversion towards formation of **a** or **b**, determined by CG-MS. ^[b] Determined by GC-MS. ^[c] Not purely isolated; yield determined from crude ¹H NMR.

Discussion of Results

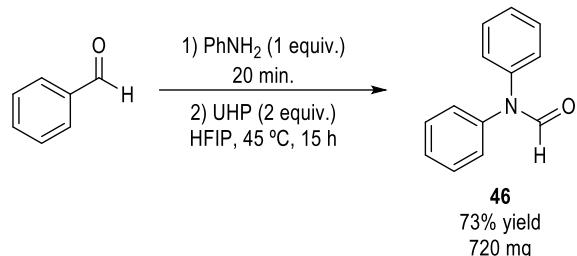
In view of the results above obtained, it was interesting to consider the possibility of performing the one-pot imine formation-oxidation process (Scheme 27). Thus, the combination of benzaldehyde and aniline for 20 minutes in absence of solvent, followed by the addition of UHP (2 equivalents) and HFIP in one portion yielded the product **46a** in 81% (Scheme 27A). At this point, bearing in mind the slow stability of benzylidene amine, it was decided to carry out this one-pot reaction by using, in this case, ammoniumhydroxide as reagent and increasing up to 30 minutes the reaction time for the *in situ* synthesis of the imine. Adding UHP (5 equivalents) and HFIP subsequently. After 15 hours, benzamide **62** was obtained with 59% yield (Scheme 27).



Scheme 27. One-pot imine formation-oxidation sequence.

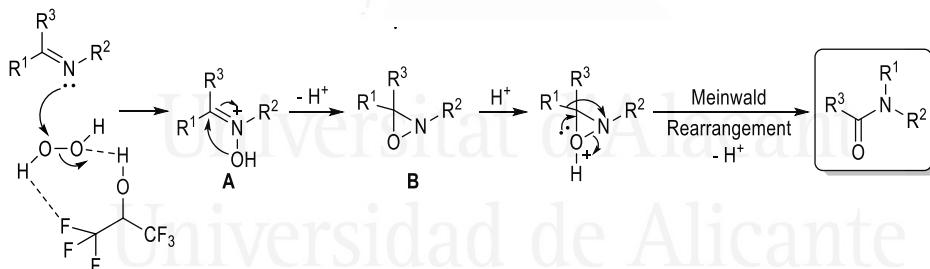
Further to this, it was thought to prove the applicability of the process by performing this one-pot sequence on large scale (Scheme 28). Thus, benzaldehyde (5 mmol, 0.51 mL) and aniline (5.2 mmol, 0.45 mL) were stirred at room temperature for 20 minutes, to afford the corresponding *N*-benzylideneaniline **24**. Then, 2 equivalents of UHP and HFIP were added in one portion to the reaction mixture stirring it at 45 °C for 15 hours. After the reaction time, 720 mg of pure product **46** were isolated (76% yield).

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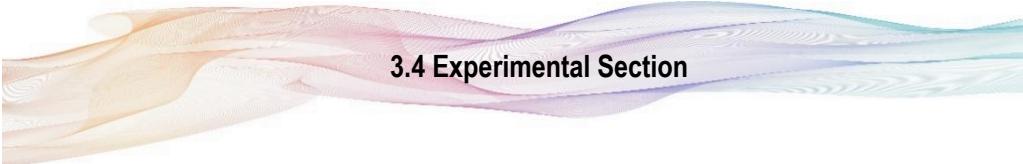


Scheme 28. Large scale reaction.

Last but not least, considering the results obtained and in light of similar transformations previously reported, a possible reaction mechanism was proposed (Scheme 29). Firstly, the electrophilic activation of H_2O_2 by HFIP throughout hydrogen bonds would allow the nucleophilic attack of the iminic nitrogen obtaining the oxime derivative **A**, which allows the subsequent formation of oxaziridine **B**. It is worth to mention that the existence of this intermediate was evidenced by the formation of compounds **57**, **59** and **61**. Later on, the expected formamide formation was possible due to a HFIP-promoted Meinwald-type rearrangement.



Scheme 29. Proposed reaction mechanism.



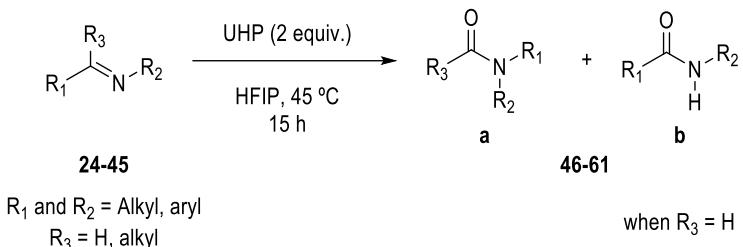
3.4 Experimental Section

3.4.1 General

Unless otherwise noted, all reagents and solvents were obtained commercially (Acros, Aldrich, Fluka, Fluorochem, Merck) and used without further purification. ^1H NMR and ^{13}C NMR spectra were performed at the technical service of the University of Alicante (SSTTI-UA), using a Bruker AV-300 or Bruker AV-400 (Bruker Corporation) using CDCl_3 as solvent and TMS as internal standard unless otherwise stated. Chemical Shifts (δ) are given in ppm and the coupling constants (J) in Hz. Low resolution mass spectra (MS) were recorded in the electron impact mode (EI, 70eV, He as carrier phase) using an Agilent GC/MS 5973 Network Mass Selective Detector spectrometer apparatus equipped with a HP-5MS column (Agilent technologies, 30 m x 0.25 mm) and giving fragment ions in m/z with relative intensities (%) in parentheses. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV on Agilent GC/MS-5973N apparatus equipped with a HP-5MS column (Agilent technologies, 30 m x 0.25 mm). Analytical TLC was performed on Merck silica gel plates and the spots visualized with UV light at 254 nm. Flash chromatography employed Merck silica gel 60 (0.040-0.063 mm). Silica gel 60 F₂₅₄ containing gypsum was employed for preparative layer chromatography. The conversion of the reactions and purity of the products were determined by GC analysis using a Younglin 6100GC, equipped with a flame ionization detector and a Phenomenex ZB-5MS column (5% PH-ME siloxane): 30 m (length), 0.25 mm (inner diameter) and 0.25 μm (film).

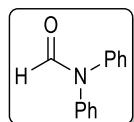
Chapter III

3.4.2 Procedure for the HFIP-UHP Oxidation of Imines

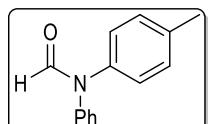


In a capped tube, onto the corresponding imine (0.10 mmol), HFIP (100-200 μ L) and UHP (2.0-5.0 equiv.) were added in one portion. The reaction was then stirred at 45 °C for 15 hours, until the reaction was judged to be completed by GC-MS. After this time, the reaction mixture was filtered over silica/celite plug and then the solvent was evaporated. The crude material was directly purified by flash chromatography or preparative TLC.

3.4.3 Physical and Spectroscopic Data for Isolated Compounds



N,N-Diphenylformamide (46):⁹⁴ slightly yellow solid; purification by preparative TLC (*n*-hexane/ethyl acetate 8.0/2.0), 89% yield; **¹H NMR** (400 MHz, CDCl₃): δ_H = 8.69 (s, 1H, CHO), 7.46 – 7.39 (m, 4H, 4xCH_{Ar}), 7.37 – 7.27 (m, 4H, 4xCH_{Ar}), 7.23 – 7.16 (m, 2H, 2xCH_{Ar}) ppm; **¹³C NMR** (101 MHz, CDCl₃): δ_C = 161.8, 141.7, 139.6, 129.7, 129.2, 127.1, 126.9, 126.1, 125.1 ppm; **MS (EI)**: *m/z* 197 (M⁺, 100%), 169 (58), 168 (79), 167 (45), 104 (12), 77 (17), 66 (19), 51 (13).

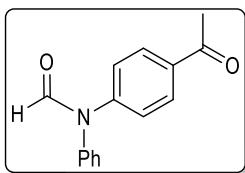


N-Phenyl-N-(*p*-tolyl)formamide (47):^{92b} dark orange oil; purification by preparative TLC (*n*-hexane/ethyl acetate 8.0/2.0), 80% yield; mixture of rotamers; **¹H NMR** (300 MHz, CDCl₃): δ_H = 8.69 (s, 1H, CHO), 8.64 (s, 1H, CHO), 7.47 – 7.35 (m, 5H, 5xCH_{Ar}), 7.35 – 7.26 (m, 5H, 5xCH_{Ar}), 7.24 (s, 2H, 2xCH_{Ar}), 7.20 – 7.14

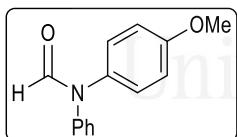
⁹⁴ Pathare, S. P.; Jain, A. K. H.; Akamanchi, K. G. *RSC Adv.* **2013**, 3, 7697-7703.

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(m, 4H, 4xCH_{Ar}), 7.13 – 7.05 (m, 2H, 2xCH_{Ar}), 2.39 (s, 3H, CH₃), 2.37 (s, 3H, CH₃) ppm; ¹³C NMR (75 MHz, CDCl₃): δ_C = 161.8, 141.9, 139.8, 139.2, 137.2, 136.9, 130.3, 129.8, 129.6, 129.1, 126.8, 126.6, 126.2, 125.8, 125.3, 124.7, 29.7, 21.1, 20.9 ppm; MS (EI): *m/z* 211 (M⁺, 100%), 183 (68), 182 (75), 180 (14), 168 (11), 167 (38), 108 (13), 91 (18), 80 (13), 77 (17).



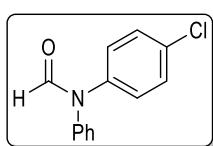
N-(4-Acetylphenyl)-N-phenylformamide (48):⁹⁵ white solid; purification by preparative TLC (*n*-hexane/ethyl acetate 8.5/1.5), 62% yield; mixture of rotamers; ¹H NMR (400 MHz, CDCl₃): δ_H = 8.83 (s, 1H, CHO), 8.66 (s, 1H CHO), 8.17 – 8.09 (m, 1H, CH_{Ar}), 8.06 – 7.94 (m, 4H, 4xCH_{Ar}), 7.95 – 7.86 (m, 2H, 2xCH_{Ar}), 7.80 (d, *J* = 8.8 Hz, 1H, CH_{Ar}), 7.60 (m, 5H, 5xCH_{Ar}), 7.56 – 7.35 (m, H, 2xCH_{Ar}), 7.25 – 7.20 (m, H, 3xCH_{Ar}), 2.62 (s, 3H, CH₃), 2.61 (s, 3H, CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 161.8, 161.3, 132.3, 130.0, 129.9, 129.8, 129.5, 129.4, 129.3, 128.9, 128.4, 127.9, 127.7, 127.1, 126.8, 126.1, 124.9, 123.4, 123.2, 119.3, 26.8, 26.6 ppm; MS (EI): *m/z* 239 (M⁺, 100%), 196 (72), 167 (58), 121 (23), 77 (12).



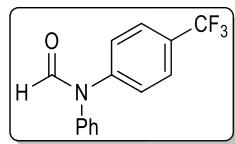
N-(4-Methoxyphenyl)-N-phenylformamide (49):⁹⁵ dark yellow solid; purification by preparative TLC (*n*-hexane/ethyl acetate 8.5/1.5), 87% yield; mixture of rotamers; ¹H NMR (400 MHz, CDCl₃): δ_H = 8.69 (s, 1H, CHO), 8.59 (s, 1H, CHO), 7.46 – 7.35 (m, 4H, 4xCH_{Ar}), 7.34 – 7.30 (m, 3H, 3xCH_{Ar}), 7.26 – 7.19 (m, 3H, 3xCH_{Ar}), 7.19 – 7.12 (m, 3H, 3xCH_{Ar}), 6.95 (dd, *J* = 8.9, 1.3 Hz, 4H, 4xCH_{Ar}), 6.79 (d, *J* = 1.0 Hz, 1H, CH_{Ar}), 3.85 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 161.9, 161.9, 129.6, 129.1, 127.7, 127.2, 126.7, 126.5, 125.4, 124.4, 114.9, 114.5, 55.5, 55.4 ppm; MS (EI): *m/z* 277 (M⁺, 100%), 206 (32), 199 (17), 184 (76), 154 (20), 124 (13), 76 (11).

⁹⁵ Jiang, L. *Molecules* **2014**, *19*, 13448-13460.

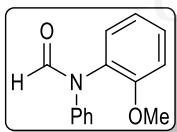
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N-(4-Chlorophenyl)-N-phenylformamide (50):⁹⁶ brown solid; 88% yield (without further purification); **¹H NMR** (400 MHz, CDCl₃): δ_H = 8.65 (d, J = 2.6 Hz, 1H, CHO), 7.49 – 7.36 (m, 5H, 5xCH_{Ar}), 7.30 – 7.24 (m, 2H, 2xCH_{Ar}), 7.19 (dd, J = 5.3, 3.3 Hz, 1H, CH_{Ar}), 7.13 (d, J = 8.7 Hz, 1H, CH_{Ar}) ppm; **¹³C NMR** (101 MHz, CDCl₃): δ_C = 161.8, 161.5, 141.3, 140.3, 139.2, 138.1, 132.8, 132.4, 129.9, 129.4, 129.3, 127.5, 127.3, 127.2, 126.1, 126.1, 125.2 ppm; **MS (EI)**: m/z 231 (M⁺, 100%), 205 (20), 204 (11), 203 (60), 168 (49), 167 (84), 166 (17), 77 (11), 66 (12).



N-Phenyl-N-(4-(trifluoromethyl) phenyl) formamide (51): white solid ; purification by preparative TLC (*n*-hexane/ethyl acetate 8.0/2.0), 91% yield; mixture of rotamers (and regiosomer **51b**), only the signals for the major isomer **51a** are given: **¹H NMR** (400 MHz, CDCl₃): δ_H = 8.78 (s, 1H, CHO), 8.66 (s, 1H, CHO), 8.01 (d, J = 8.0 Hz, 1H, CH_{Ar}), 7.75 (d, J = 8.1 Hz, 1H, CH_{Ar}), 7.66 (dd, J = 11.1, 8.7 Hz, 4H, 4xCH_{Ar}), 7.51 – 7.35 (m, 8H, 8xCH_{Ar}), 7.27 (dd, J = 7.6, 3.9 Hz, 2H, 2xCH_{Ar}), 7.21 (d, J = 7.6 Hz, 2H, 2xCH_{Ar}) ppm; **¹³C NMR** (101 MHz, CDCl₃): δ_C = 164.4, 161.7, 161.2, 144.9, 142.8, 140.8, 138.7, 138.3, 137.6, 133.6, 130.0, 129.5, 129.1, 128.5, 128.1, 127.9, 127.7, 127.6, 126.9, 126.8, 126.7, 126.2, 126.2, 125.9, 125.8, 125.7, 125.4, 124.9, 124.0, 122.5, 120.4 ppm; **MS (EI)**: m/z 265 (M⁺, 100%), 237 (73), 236 (34), 216 (17), 168 (16), 167 (42), 77 (11), 66 (13).

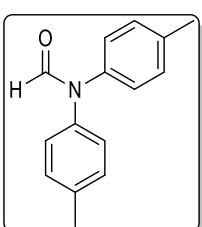


N-(2-Methoxyphenyl)-N-phenylformamide (53): dark orange oil; purification by preparative TLC (*n*-hexane/ethyl acetate 8.0/2.0), 90% yield; mixture of rotamers; **¹H NMR** (400 MHz, CDCl₃): δ_H = 8.57 (Major rotamer), 8.26 (minor rotamer) (s, 1H, CHO), 7.31 – 7.21 (M. r. and m. r.) (m, 4H, 4xCH_{Ar}), 7.17 – 7.01 (m, 6H, 6xCH_{Ar}), 6.93 (d, J = 8.3 Hz, 3H, 3xCH_{Ar}), 3.69 (m. r.), 3.69 (M. r.) (s, 3H) ppm; **¹³C NMR** (101 MHz, CDCl₃): δ_C = 163.42 (m. r.), 162.41 (M. r.), 155.61 (m. r.), 155.13 (M. r.), 141.66 (M. r.), 140.01 (m. r.), 129.92 (m. r.), 129.82 (M. r.), 129.71 (m. r.), 129.64 (M. r.), 129.52 (m. r.), 129.43 (M. r.), 128.84 (M.

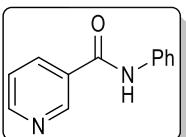
⁹⁶ Phillips, D. P.; Zhu, X.-F.; Lau, T. L.; He, X.; Yang, K.; Liu, H. *Tetrahedron Lett.* **2009**, 50, 7293-7296.

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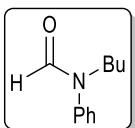
r.), 127.53 (m. r.), 126.44 (M. r.), 126.27 (m. r.), 124.84 (m. r.), 123.10 (M. r.), 121.19 (M. r. and m. r.), 112.54 (M. r.), 112.43 (m. r.), 55.76 (M. r. and m. r.) ppm; **MS** (EI): *m/z* 227 (M⁺, 53%), 200 (11), 199 (71), 185 (14), 184 (100), 183 (23), 167 (16), 166 (14), 156 (24), 129 (25), 128 (17), 77 (15), 51 (11).



N,N-Di-p-tolylformamide (54):⁹⁷ slightly orange solid; purification by preparative TLC (*n*-hexane/ethyl acetate 8.0/2.0), 79% yield; **1H NMR** (400 MHz, CDCl₃): δ_H = 8.63 (s, 1H, CHO), 7.21 (t, *J* = 5.5 Hz, 6H, 6xCH_{Ar}), 7.07 (d, *J* = 8.3 Hz, 2H, 2xCH_{Ar}), 2.39 (s, 3H, CH₃), 2.37 (s, 3H, CH₃) ppm; **13C NMR** (101 MHz, CDCl₃): δ_C = 161.8, 139.4, 137.2, 136.9, 136.7, 130.2, 129.7, 125.8, 124.9, 21.0, 20.9 ppm; **MS** (EI): *m/z* 225 (M⁺, 100%), 197 (65), 196 (69), 181 (23), 180 (29), 108 (20), 91 (19), 80 (20), 65 (13).



N-Phenyl-3-pyridinecarboxamide (55):⁹⁸ dark orange solid; purification by preparative TLC (*n*-hexane/ethyl acetate 8.0/2.0), 72% yield (90:10 isomeric mixture), only the major isomer signals are given; **1H NMR** (400 MHz, CDCl₃): δ_H = 9.10 (br s, 1H, NH), 8.75 (d, *J* = 3.6 Hz, 1H, NCHC), 8.39 (s, 1H, NCHCHCHC), 8.23 (dt, *J* = 7.9, 1.8 Hz, 1H, NCHCHCHC), 7.66 (d, *J* = 7.9 Hz, 2H, 2xCH_{Ar}), 7.47 – 7.35 (m, 3H, 3xCH_{Ar}), 7.19 (t, *J* = 7.4 Hz, 1H, NCHCHCHC) ppm; **13C NMR** (101 MHz, CDCl₃): δ_C = 163.9, 152.2, 147.8, 137.5, 135.6, 130.9, 129.2, 125.1, 123.7, 120.5 ppm; **MS** (EI): *m/z* 198 (M⁺, 61%), 197 (16), 106 (100), 78 (54), 51 (17).



N-Butyl-N-phenylformamide (56):⁹⁹ white solid; purification by preparative TLC (*n*-hexane/ethyl acetate 8.0/2.0), 87% yield (not pure isolated); **1H NMR** (400 MHz, CDCl₃): δ_H = 7.81 – 7.73 (m, 2H, 2xCH_{Ar}), 7.50 (dd, *J* = 5.0, 3.7 Hz, 1H, CH_{Ar}), 7.47

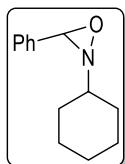
⁹⁷ Yang, S.; Li, P.; Wang, Z.; Wang, L. *Org. Lett.* **2017**, *19*, 3386-3389.

⁹⁸ Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 8460-8463.

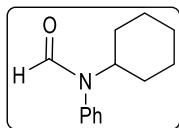
⁹⁹ Sureshbabu, P.; Azeez, S.; Chaudhary, P.; Kandasamy, J. *Org. Biomol. Chem.* **2019**, *17*, 845-850.

Chapter III

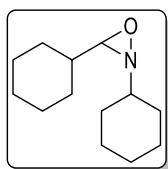
– 7.42 (m, 2H, 2xCH_{Ar}), 6.10 (br s, 1H, NH), 3.54 – 3.44 (m, 2H, NCH₂CH₂CH₂CH₃), 1.71 – 1.58 (m, 2H, NCH₂CH₂CH₂CH₃), 1.45 (dd, *J* = 15.1, 7.4 Hz, 2H, NCH₂CH₂CH₂CH₃), 0.99 (t, *J* = 7.3 Hz, 3H, NCH₂CH₂CH₂CH₃) ppm; **MS** (EI): *m/z* 177 (M⁺, 11%), 135 (20), 134 (19), 105 (100), 77 (33).



2-Cyclohexyl-3-phenyl-1,2-oxaziridine (57):¹⁰⁰ white solid; purification by preparative TLC (*n*-hexane/ethyl acetate 8.5/1.5), 98% yield; **1H NMR** (400 MHz, CDCl₃): δ_H = 7.47 – 7.43 (m, 2H, 2xCH_{Ar}), 7.42 – 7.38 (m, 3H, 3xCH_{Ar}), 4.55 (s, 1H), 2.16 – 2.05 (m, 1H, CHO), 1.90 – 1.80 (m, 1H, NCH), 1.78 – 1.72 (m, 2H, 2xCH₂), 1.70 – 1.56 (m, 2H, 2xCH₂), 1.47 (m, 2H, 2xCH₂), 1.39 – 1.21 (m, 4H, 4xCH₂) ppm; **13C NMR** (101 MHz, CDCl₃): δ_C = 135.3, 129.9, 128.5, 127.4, 79.8, 70.2, 31.6, 29.2, 25.7, 24.6, 24.1 ppm; **MS** (EI): *m/z* 203 (M⁺, 40%), 122 (78), 105 (100), 77 (42).



N-Cyclohexyl-N-phenylformamide (58):⁹⁵ orange oil; purification by preparative TLC (*n*-hexane/ethyl acetate 8.5/1.5), 84% yield; **1H NMR** (400 MHz, CDCl₃): δ_H = 8.17 (s, 1H, CHO), 7.51 – 7.36 (m, 3H, 3xCH_{Ar}), 7.23 – 7.12 (m, 2H, 2xCH_{Ar}), 4.54 – 4.27 (m, 1H, NCH), 1.88 (d, *J* = 12.2 Hz, 2H, 2xCH₂), 1.78 (d, *J* = 13.8 Hz, 2H, 2xCH₂), 1.66 – 1.57 (m, 1H, CH₂), 1.47 – 1.25 (m, 4H, 4xCH₂), 1.01 (m, 1H, CH₂) ppm; **13C NMR** (101 MHz, CDCl₃): δ_C = 162.6, 138.6, 129.3, 129.1, 128.2, 53.7, 31.4, 25.7, 25.3 ppm; **MS** (EI): *m/z* 203 (M⁺, 15%), 160 (16), 132 (17), 122 (13), 121 (100), 93 (34), 77 (15).

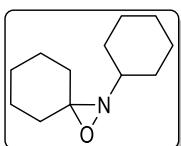


2,3-Dicyclohexyl-1,2-oxaziridine (59): white solid; purification by preparative TLC (*n*-hexane/ethyl acetate 8.0/2.0), 95% yield; **1H NMR** (400 MHz, CDCl₃): δ_H = 3.48 (d, *J* = 6.6 Hz, 1H, CHO), 1.99 (d, *J* = 13.4 Hz, 1H, NCH), 1.86 – 1.71 (m, 9H, 8xCH₂, OCHCH), 1.71 – 1.57 (m, 4H, 4xCH₂), 1.35 – 1.12 (m, 8H, 8xCH₂) ppm; **13C NMR** (101 MHz, CDCl₃): δ_C = 85.3, 69.3, 40.2, 31.6, 29.0, 27.7, 27.5, 26.3, 25.7, 25.2, 24.5, 23.9 ppm; **MS** (EI): *m/z* 209 (M⁺, 30%), 192 (19), 154 (23), 150 (18), 138 (42), 128

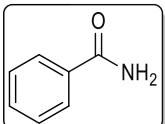
¹⁰⁰ Singhal, S.; Jain, S. L.; Prasad, V. V. D. N.; Sain, B. *Eur. J. Org. Chem.* **2007**, 2007, 2051-2054.

Experimental Section

(98), 127 (18), 126 (48), 125 (44), 110 (42), 98 (18), 95 (28), 84 (22), 83 (79), 82 (33), 81 (18), 68 (14), 67 (52), 56 (39), 55 (100), 54 (55).



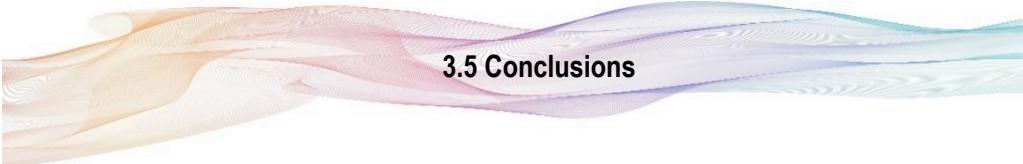
2-Cyclohexyl-1-oxa-2-azaspiro[2.5]octane (61): slightly yellow oil; purification by flash chromatography (*n*-hexane/ethyl acetate 8.0/2.0), 95% estimated yield (not pure isolated); **¹H NMR** (300 MHz, CDCl₃): δ_H = 2.55 – 2.27 (m, 1H, NCH), 1.97 – 1.77 (m, 4H, 4xCH₂), 1.75 – 1.55 (m, 6H, 6xCH₂), 1.54 – 1.38 (m, 4H, 4xCH₂), 1.34 – 1.16 (m, 6H, 6xCH₂) ppm; **¹³C NMR** (75 MHz, CDCl₃): δ_C = 85.1, 60.2, 36.6, 31.9, 29.7, 29.2, 27.8, 25.7, 25.5, 25.4, 24.9, 24.4, 24.2 ppm; **MS (EI)**: *m/z* 195 (M⁺, 15%), 179 (20), 178 (34), 152 (15), 138 (12), 136 (25), 114 (100), 113 (11), 98 (47), 97 (12), 96 (20), 83 (16), 82 (15), 81 (21), 69 (18), 67 (24), 56 (13), 55 (52), 54 (20).



Benzamide (62):¹⁰¹ white solid; purification by preparative TLC *n*-hexane/ethyl acetate 9.0/1.0), 59% yield; **¹H NMR** (400 MHz, DMSO-d₆): δ_H = 7.99 (s, 1H, NH₂), 7.88 (dd, *J* = 5.3, 3.4 Hz, 2H, 2xCH_{Ar}), 7.51 (ddd, *J* = 6.3, 3.7, 1.3 Hz, 1H, CH_{Ar}), 7.48 – 7.41 (m, 2H, 2xCH_{Ar}), 7.38 (s, 1H, NH₂) ppm; **¹³C NMR** (101 MHz, DMSO-d₆): δ_C = 168.4, 134.7, 131.7, 128.6, 127.9 ppm; **MS (EI)**: *m/z* 121 (M⁺, 84%), 105 (100), 77 (83), 51 (25).

Universidad de Alicante

¹⁰¹ Chen, J.; Xia, Y.; Lee, S. *Org. Lett.* **2020**, 22, 3504-3508.

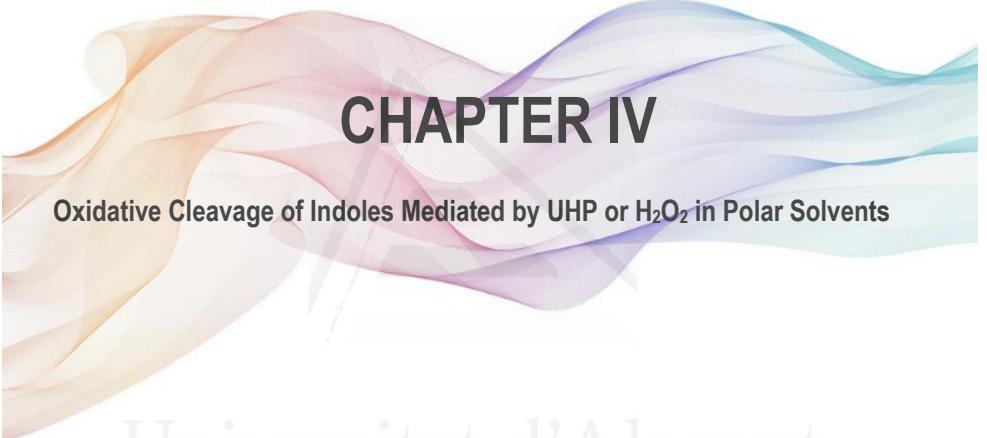


3.5 Conclusions

As conclusions, it has been proved that the oxidation of aldimides by employing UHP as green and nontoxic oxidant is a simple, alternative and environmentally benign procedure for the synthesis of formamides. This methodology is feasible due to the presence of HFIP as solvent and reaction promoter, avoiding the utilisation of any Lewis acid. On account of its aforementioned unique properties, this fluorinated alcohol is capable of allowing the electrophilic activation of the oxidant affording the oxidative protocol under sustainable and smooth conditions.

Under the optimal reaction conditions, the reported procedure provided a great variety of formamides from moderate to high yields in the majority of cases. However, it can also be stated that imines derived from electron-poor aldehydes or cyclohexanamine gave rise to the formation of amides or oxaziridines, respectively. Those results reinforce that the proposed mechanism proceeds *via* the formation of the corresponding oxaziridine followed by HFIP-promoted Meinwald-type rearrangement.

Furthermore, it can be affirmed that the one-pot sequence described afforded good results towards the formation of formamides, expanding the applicability of this methodology when a big-scale reaction was carried out. Because of this one-pot sequence, it has been demonstrated for the first time, the synthesis of benzamide by using benzaldehyde and aqueous ammonia avoiding the use of metals or Lewis acid catalysts.



CHAPTER IV

Oxidative Cleavage of Indoles Mediated by UHP or H₂O₂ in Polar Solvents

Universitat d'Alacant
Universidad de Alicante

4.1 Antecedents

4.1.1 General

The indole structure constitutes an essential building block in nature being present in a huge range of naturally occurring molecules with biological activity such as the neurotransmitter serotonin, the plant hormone indole-3-acetic acid or the amino acid tryptophan (Figure 10).¹⁰² Therefore, the interest to develop synthetic methodologies and functionalisation strategies of these nitrogen containing molecules due to its applicability in pharmaceuticals, fragrances, agrochemicals, or pigments, has increased considerably.¹⁰³

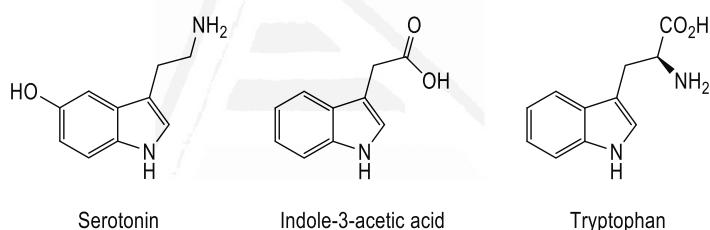


Figure 10. Biological compounds containing indole moiety.

4.1.2. Green oxidation alternatives of indoles

Over the last years, the oxidation of indole moieties has received much attention in organic synthesis. Owing to its electron-rich property, the oxidation of this structure may give rise to a wide

¹⁰² (a) For example, see: (b) Fattorusso, E.; Taglialatela-Scafati, E. O. *Modern Alkaloids: Structure, Isolation Synthesis and Biology*; Wiley-VCH, Weinheim, 2008; (c) Buckingham, J.; Baggaley, K. H.; Roberts, A. D.; Szabo, L. F. *Dictionary of Alkaloids*; CRC Press, Boca Raton, Florida, 2010.

¹⁰³ (a) For example see: Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, 48, 9608-9644; (b) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Chem. Soc. Rev.* **2010**, 39, 4449-4465; (c) Vargas, D. A.; Tinoco, A.; Tyagi, V.; Fasan, R. *Angew. Chem. Int. Ed.* **2018**, 57, 9911-9915; (d) Liu, S.; Zhao, F.; Chen, X.; Deng, G.-J.; Huang, H. *Adv. Synth. Catal.* **2020**, 362, 3795-3823; (e) Urbina, K.; Tresp, D.; Sipps, K.; Szostak, M. *Adv. Synth. Catal.* **2021**, 363, 2723-2739.

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variety of intermediates, being of particular interest in drug discovery.¹⁰⁴ In such a way, different oxidant conditions have been described to give access to them. Despite this, only few amount of oxidants have been reported to be able to render the most important types of indole oxidation products,¹⁰⁵ namely 2-oxindoles, (spirooxindoles among them), anthranilic acids and 2-ketoacetanilides (Figure 11).

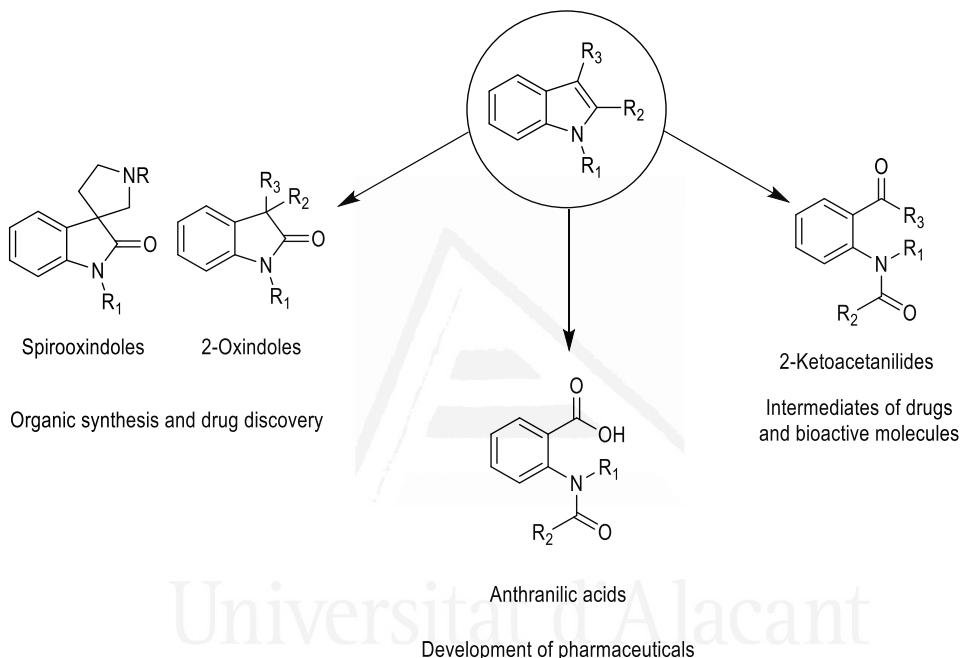
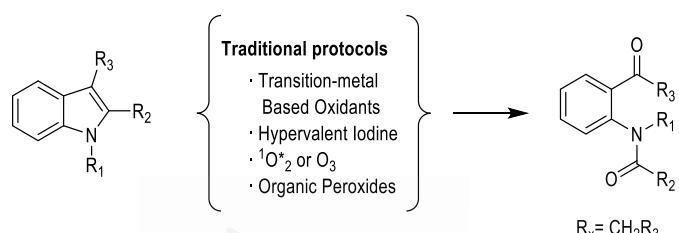


Figure 11. Common oxidation products of indoles.

¹⁰⁴ For selected reviews of indoles in drug discovery, see: (a) Zhang, M.-Z.; Chen, Q.; Yang, G.-F. *Eur. J. Med. Chem.* **2015**, 89, 421-441; (b) Sravanti, T. V.; Manju, S. L. *Eur. J. Pharm. Sci.* **2016**, 91, 1-10; (c) Singh, T. P.; Singh, O. M. *Mini Rev. Med. Chem.* **2018**, 18, 9-25.

¹⁰⁵ For example, see: (a) Finch, N.; Taylor, W. I. *J. Am. Chem. Soc.* **1962**, 84, 3871-3877; (b) Finch, N.; Gemenden, C. W.; Hsu, I. H.-C.; Kerr, A.; Sim, G. A.; Taylor, W. I. *J. Am. Chem. Soc.* **1965**, 87, 2229-2235; (c) Shelar, S. V.; Argade, N. P. *Org. Biomol. Chem.* **2019**, 17, 6671-6677; (d) Sacramento, J. J. D.; Goldberg, D. P. *Chem. Commun.* **2020**, 56, 3089-3092; (e) Liang, P.; Zhao, H.; Zhou, T.; Zeng, K.; Jiao, W.; Pan, Y.; Liu, Y.; Fang, D.; Ma, X.; Shao, H. *Adv. Synth. Catal.* **2021**, 363, 3532-3538; (f) Qian, C.; Li, P.; Sun, J. *Angew. Chem. Int. Ed.* **2021**, 60, 5871-5875; (g) Zhao, G.; Liang, L.; Wang, E.; Lou, S.; Qi, R.; Tong, R. *Green Chem.* **2021**, 23, 2300-2307; (h) Gohain, S. B.; Boruah, P. K.; Das, M. R.; Thakur, A. J. *New J. Chem.* **2022**, 46, 2641-2652.

In particular, 2-ketoacetanilides and anthranilic acid derivatives are obtained by the oxidative cleavage of C2-C3 double bond, known as Witkop oxidation.¹⁰⁶ Traditionally, the synthesis of these compounds has been performed by using transition-metal based oxidants, hypervalent iodine compounds, singlet oxygen or ozone and organic peroxides as main strategies as depicted in Scheme 30, not following none of the 12 principles of Green Chemistry.



Scheme 30. Traditional protocols for the Witkop oxidation.

However, in the last decades, concerns about the safety, sustainability and environmental impact of chemical protocols have prompted the development of operationally simple, atom-economy and greener oxidation methodologies.¹⁰⁷ It is worth to mention that, in the last years, different works have been published in this regard. Concretely, the oxidative cleavage of indoles by using biocatalysts in combination with H_2O_2 as oxidant was reported some years ago.¹⁰⁸ More recently, the application of different photocatalysts¹⁰⁹ and the utilization of KCl (cat.)/Oxone system¹¹⁰ for this purpose constitutes greener alternative protocols to those previously reported (Scheme 31).

¹⁰⁶ (a) Witkop, B.; Patrick, J. B.; Rosenblum, M. *J. Am. Chem. Soc.* **1951**, 73, 1428-1429; (b) Mentel, M.; Breinbauer, R. *Curr. Org. Chem.* **2007**, 11, 159-176.

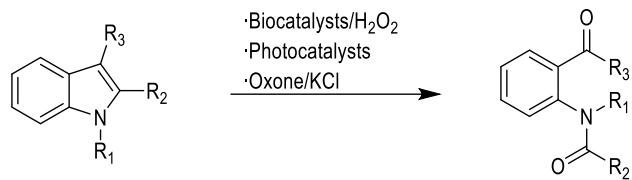
¹⁰⁷ Jiao, N.; Stahl, S. S. *Green Oxidation in Organic Synthesis*; John Wiley & Sons Ltd., Chichester, 2019.

¹⁰⁸ (a) Takemoto, M.; Iwakiri, Y.; Suzuki, Y.; Tanaka, K. *Tetrahedron Lett.* **2004**, 45, 8061-8064; (b) Ling, K.-Q.; Sayre, L. M. *Bioorg. Med. Chem.* **2005**, 13, 3543-3551; (c) Jung, D.; Streb, C.; Hartmann, M. *Micropor. Mesopor. Mat.* **2008**, 113, 523-529.

¹⁰⁹ (a) Zhang, C.; Li, S.; Bureš, F.; Lee, R.; Ye, X.; Jiang, Z. *ACS Catal.* **2016**, 6, 6853-6860; (b) Ji, X.; Li, D.; Wang, Z.; Tan, M.; Huang, H.; Deng, G.-J. *Eur. J. Org. Chem.* **2017**, 6652-6659; (c) Wu, K.; Fang, C.; Kaur, S.; Liu, P.; Wang, T. *Synthesis* **2018**, 50, 2897-2907.

¹¹⁰ Xu, J.; Liang, L.; Zheng, H.; Chi, Y. R.; Tong, R. *Nat. Commun.* **2019**, 10, 4754.

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Scheme 31. Sustainable methodologies for the Witkop oxidation.

Furthermore, it is important to highlight that these 2-ketoacetanilides and anthranilic acids are key intermediates in the synthesis of quinolones and related bioactive compounds such as anxiolytics, antibiotics or psychostimulants (Figure 12).¹¹¹ Thus, most of these compounds are obtained by the intramolecular condensation of such ketoacetanilides, known as Camps cyclization (Scheme 32).¹¹² When this transformation is combined with Witkop oxidation, give rise to the formation of these molecules in a one-pot sequence named Winterfeldt oxidation (Scheme 32).

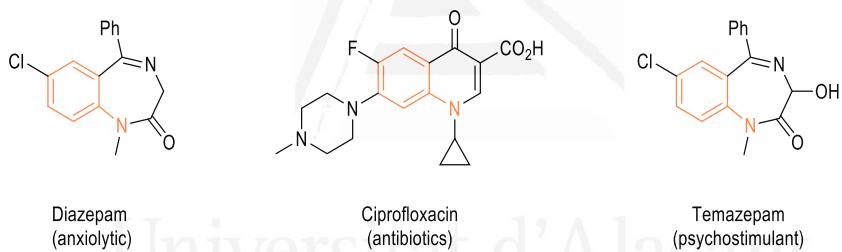
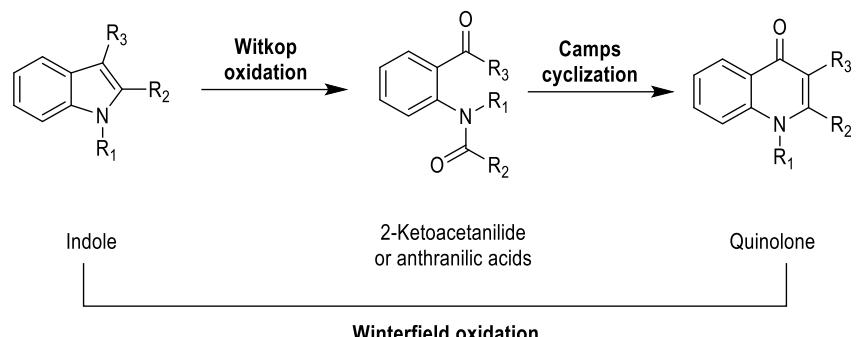


Figure 12. Quinolone derivatives with biological activity.

¹¹¹ (a) Mitscher, L. A. *Chem. Rev.* **2005**, *105*, 559-592; (b) Huang, Y.; Khouri, K.; Chanas, T.; Dömling, A. *Org. Lett.* **2012**, *14*, 5916-5919.

¹¹² (a) Camps, R. *Arch. Pharm.* **1899**, *237*, 659-691; (b) Camps, R. *Arch. Pharm.* **1901**, *239*, 591-610.



Scheme 32. One-pot Winterfield oxidation.

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4.2 Objectives

In view of the antecedents previously discussed, the following objective was established:

To perform the oxidative cleavage of indoles to give access to the corresponding Witkop products involving the use of green oxidants, namely hydrogen peroxide or urea hydrogen peroxide, in combination with fluorinated alcohols or other a polar solvents, as a sustainable protocol.



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4.3. Discussion of Results

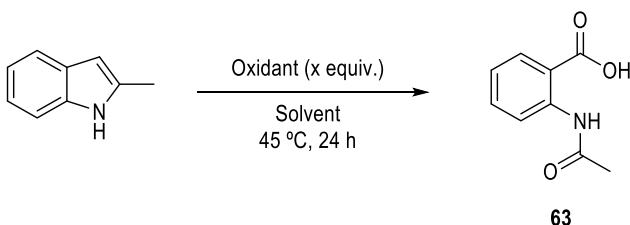
In this section, the optimisation of the reaction conditions was performed using 2-methylindole as model substrate (Table 12). It is worth mentioning that 2.5 equivalents of both H₂O₂ and UHP were used indistinctly as oxidants in different polar protic and aprotic solvents. In such a way, it was observed that the reaction did not proceed when H₂O or *i*-PrOH were employed as solvents regardless of the oxidant (Table 12, entries 1, 2, 10 and 11). When MeOH was the solvent employed, around 30% of conversion of the desired product was afforded in both oxidants (Table 12, entries 3 and 13). However, when fluoroalkyl alcohols, namely TFE and HFIP, were used as solvents, a meaningfully change was depicted. Thus, in both cases the oxidative process took place giving rise to the formation of compound **63** in high conversion when 2.5 equivalents of oxidant were employed (Table 12, entries 4, 5, 13 and 14). Comparing the results obtained, since HFIP rendered better conversions, it was therefore decided to increase both oxidant equivalents from 2.5 up to 5.0, leading to an amelioration of the conversion (Table 12, entries 6 and 15). It is worth to mention that a further increase in the oxidant equivalents was also tested. Regrettably, the conversion toward the formation of the desired product was barely affected.

Thereupon, for the sake of comparison, other polar solvents, such as MeCN and DMSO, were also considered for the optimisation of the reaction. To our delight, anthranilic acid **63** was afforded in more than 80% of conversion when 2.5 equivalents of H₂O₂ were used (Table 12, entries 7 and 8), and more than 70% of conversion was obtained in the case of UHP (Table 12, entries 16 and 17). As in the previous case, it was thought the possibility of refining the conditions for the reaction performed with MeCN and H₂O₂ due to its ease of work-up, purification and cleaner reaction crude. So, it was therefore decided to increase the equivalents of oxidant observing again, an amelioration in the yield of the corresponding compound **63** (Table 12, entry 9). Finally, the aforementioned

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reaction was also tested lowering the temperature down to 25 °C, unfortunately the reaction barely worked, obtaining a lower conversion of the desired product in all the cases.

Table 12. Optimisation of the reaction parameters^[a]



Entry	Solvent	Oxidant (equiv.)	Conv. (%) ^[b]
1	H ₂ O	H ₂ O ₂ (2.5)	<5
2	<i>i</i> -PrOH	H ₂ O ₂ (2.5)	<5
3	MeOH	H ₂ O ₂ (2.5)	35
4	TFE	H ₂ O ₂ (2.5)	72
5	HFIP	H ₂ O ₂ (2.5)	84
6	HFIP	H₂O₂ (5.0)	87 (77) ^[c]
7	MeCN	H ₂ O ₂ (2.5)	85
8	DMSO	H ₂ O ₂ (2.5)	81
9	MeCN	H₂O₂ (5.0)	91 (81) ^[c]
10	H ₂ O	UHP (2.5)	<5
11	<i>i</i> -PrOH	UHP (2.5)	<5
12	MeOH	UHP (2.5)	30
13	TFE	UHP (2.5)	80
14	HFIP	UHP (2.5)	85
15	HFIP	UHP (5.0)	90 (79) ^[c]
16	MeCN	UHP (2.5)	70
17	DMSO	UHP (2.5)	77

^[a] Reaction conditions: indole (0.15 mmol), oxidant and solvent (150 µL), 45 °C, 24 h. ^[b] Conversion toward the formation of **63** determined by GC-MS. ^[c] Yield of the isolated product after preparative TLC.

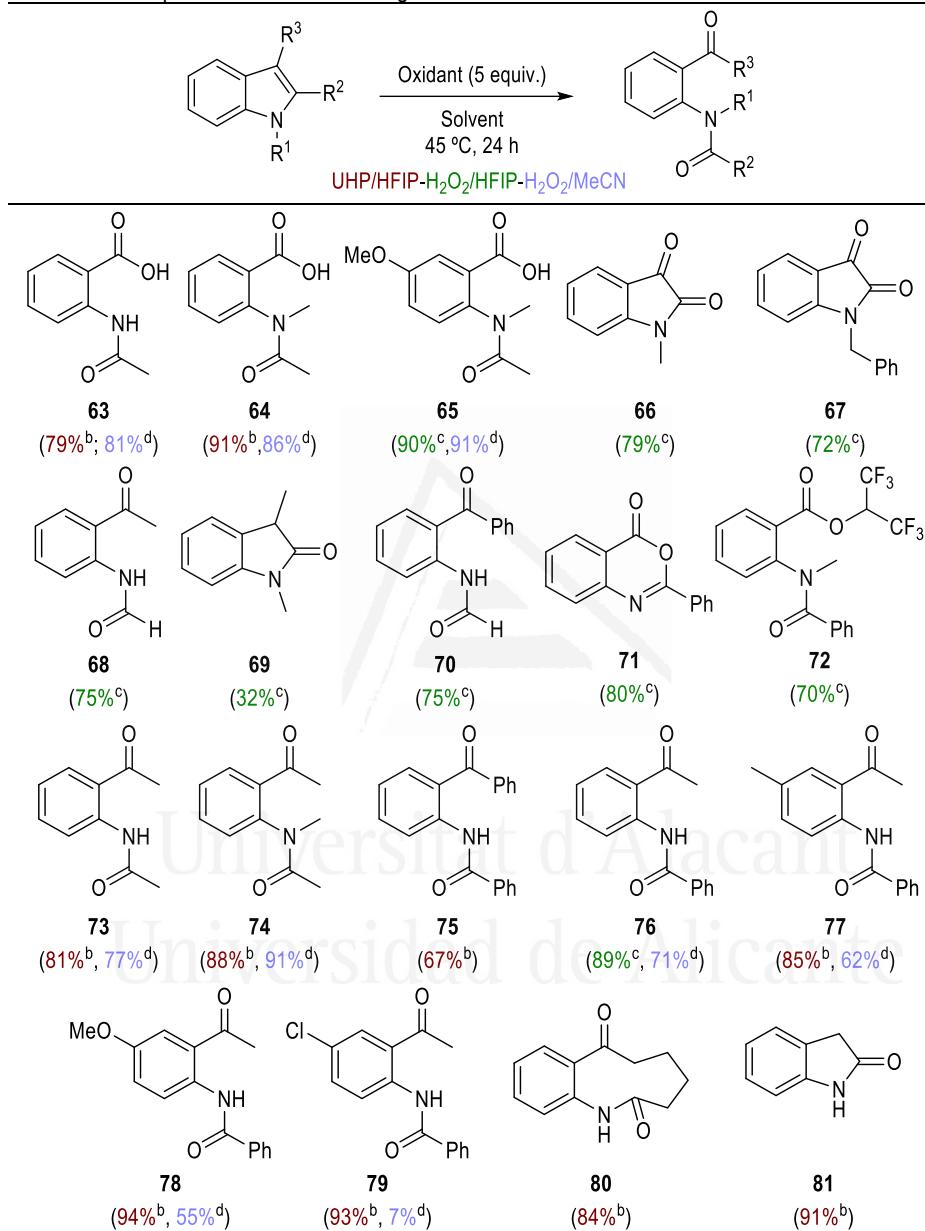
As a result of the optimisation of the reaction conditions, it has been demonstrated that the best conversions were achieved with HFIP as solvent without a significant difference in the results when 5.0 equivalents of H₂O₂ or UHP were employed as oxidants. Likewise, as depicted in Table 12, satisfactory results were also reached when MeCN was the solvent employed in combination

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with H_2O_2 as oxidant. Thus, the study was continued using both reaction conditions (Table 13). In general, moderated to excellent conversions towards the formation of the corresponding indole oxidative cleavage were observed. As already stated, when 2-methylindole was submitted to both reaction conditions, good yields were obtained giving rise to the corresponding *N*-acetylanthranilic acid (**63**). It is worth mentioning that better results were afforded when 1,2-dimethylindole was essayed obtaining the 2-(acetyl methylamino)benzoic acid (**64**), obtaining the highest yield when UHP was the oxidant employed in HFIP. Then, the oxidation of 5-methoxy-2-methylindole lead to the corresponding 2-(acetylamino)-5-methoxybenzoic acid (**65**) in excellent yields, obtaining similar results when both HFIP and MeCN where the solvents utilised in H_2O_2 . It is worth to mention that this oxidation protocol was applied to free *N*-H indoles bearing no substituent in position 2 or 3, including indole, 5-methoxyindole, 5-fluoroindole and 8-ethylindole. Unfortunately, the reaction did not work as expected, rendering a complex mixture of oxidation products. Meanwhile, isatins **66** and **67** were afforded in good yields when the reaction was carried out with the *N*-alkylated analogues, such as *N*-methylindole and *N*-benzylindole, respectively, being H_2O_2 the oxidant used in HFIP.

Next, skatole and its *N*-methylated analogue were essayed. In the case of skatole, the oxidative cleavage takes place when H_2O_2 and HFIP were employed giving rise to the corresponding formamide derivative **68** in good yield. Contrariwise, the reaction with 1,3-dimethyl-1-*H*-indole scarcely afforded the corresponding oxindole **69** in a 32% yield, being this product the major isolated together with other oxidation products including the one corresponding to the Witkop oxidation. When the reaction was carried out using 3-phenyl-1-*H*-indole, H_2O_2 as oxidant and HFIP as solvent, the corresponding 2-benzoylacetanilide **70** was isolated in 75% yield. It is worth to mention that the pesticide Dianthalexin B (**71**)¹¹³ was obtained in high yield in a one-step procedure when the reaction was carried out using 2-phenyl-1-*H*-indole, being UHP the oxidant of choice and HFIP the best solvent. Next, its analogue *N*-methyl-2-phenyl-1-*H*-indole was subjected to this procedure under the same reaction conditions but, surprisingly, ester **72** was the main product isolated in good yield.

¹¹³ (a) Nelson, A. C.; Kalinowski, E. S.; Czerniecki, N. J.; Jacobson, T. L.; Grundt, P. *Org. Biomol. Chem.* **2013**, 11, 7455-7457; (b) Schilling, W.; Zhang, Y.; Riemer, D.; Das, S. *Chem. Eur. J.* **2020**, 26, 390-395.

Table 13. Scope of the oxidative cleavage of indoles ^[a]

[a] Reaction conditions: indole (0.15 mmol), oxidant (5 equiv.) and solvent (150 µL), 45 °C, 24 h.
 Yield of the isolated product after preparative TLC. [b] Product obtained using UHP as oxidant and HFIP as solvent. [c] Product obtained using H₂O₂ as oxidant and HFIP as solvent. [d] Product obtained using H₂O₂ as oxidant and MeCN as solvent.

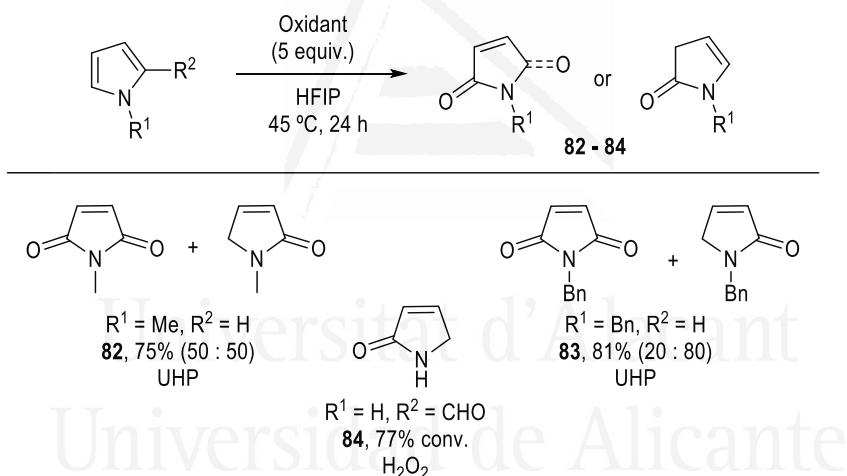
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Likewise, 2,3-dimethyl-1*H*-indole and the *N*-methylated analogue were next investigated. Herein, it is worth to point out that good results were achieved towards the formation of the corresponding acetamides **73** and **74** in both solvents, MeCN and HFIP, being UHP the oxidant of choice for the second one. Unfortunately, lower results were reached when 2,3-diphenyl-1*H*-indole was essayed, giving rise to the acetanilide **75** in a 67% yield. Later, bearing in mind the results obtained, it was considered to carry out the reaction using disubstituted 3-methyl-2-phenyl-1*H*-indoles with different substituents at position 5. At this point, it is not surprising that higher yields were afforded when electron donating group were present. It is worth mentioning that after carrying out the reaction in both solvents, better results were afforded using HFIP in comparison to MeCN. Hence, when 3-methyl-2-phenyl-1*H*-indole was subjected to this procedure, acetanilide **76** was obtained in 89% and 71% yield, respectively. Then, when methyl, methoxy and chlorine were the substituents at position 5, high to excellent yields were afforded to the acetanilides **77**, **78** and **79** respectively in HFIP but, unfortunately poor to moderated yields were obtained when MeCN was the solvent employed.

Benzocondensed macrocyclic amide **80** was obtained in 84% yield when 1,2,3,4-tetrahydrocarbazole was submitted to the reaction conditions, using HFIP as solvent. Finally, diverse formylindoles, namely indole-2-carboxaldehyde and regiosomer indole-3-carboxaldehyde, were tested. As somehow expected, the first one led to the formation of the corresponding oxindole **81** in more than 90% yield in both oxidants as a consequence of Dakin oxidation. Unfortunately, the second one did not result in the formation of possible expected products instead, giving rise to a complex mixture of unidentified oxidation products. At this point it is important to highlight that both indole-3-carboxylic acid and ethyl indole-2-carboxylate were also subjected to this procedure, although none of them worked.

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As an attempt to broaden the applicability of the process, other *N*-heterocyclic and O-heterocyclic compounds, namely pyrrole and furan derivatives, were evaluated. Starting with *N*-heterocyclic compounds (Scheme 33), *N*-methyl and *N*-benzylpyrrole were explored, both under the optimal reaction conditions using HFIP as solvent and 5 equivalents of UHP as oxidant. In both cases, the corresponding *N*-alkylmaleimide and pyrrolone were afforded in good yields, **82** and **83** respectively. In a similar manner, *1H*-pyrrole was essayed but, unfortunately, a complex mixture of oxidation products was obtained. *1H*-Pyrrole-2-carbaldehyde led to the formation of the corresponding 3-pyrrolin-2-one **84** as major oxidation product in a 77% of conversion determined by GC-MS, being this product obtained as a consequence of a Dakin oxidation and a double bond isomerization.

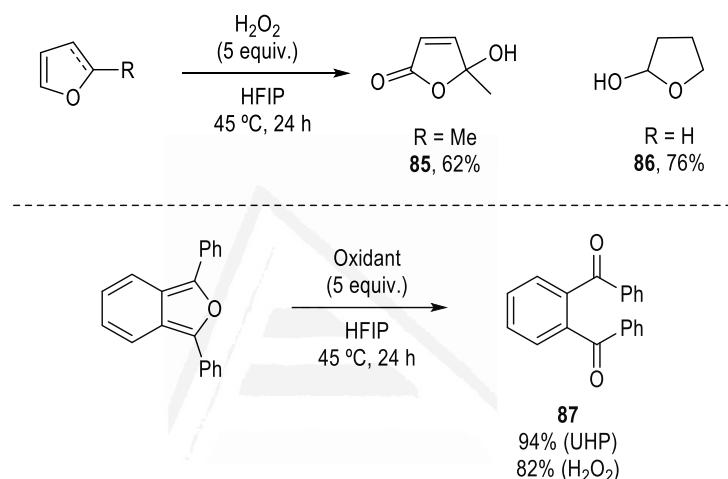


Scheme 33. Scope of the oxidation of pyrroles derivatives.

As commented before, furans were also evaluated (Scheme 34). In this case, when furan was subjected to this procedure, an unidentified complex mixture of oxidation products was obtained. Thus, lactone **85** was afforded in 62% yield when 2-methylfuran was essayed. Regrettably, the product decomposed during purification. In a similar manner, 2,3-dihydrofuran was tested giving access to the cyclic hemiacetal **86** in 76% yield. Last but not least, it is worth to mention that benzofurans were considered as starting materials for this oxidation procedure. However, using the

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same reaction conditions or even increasing the reaction time the oxidant amount and using higher temperatures. The reaction barely worked in all the cases essayed. Contrariwise, as somehow expected, when the more reactive 1,3-diphenylisobenzofuran was subjected to the reaction conditions, *o*-dibenzoylbenzene **87** was afforded in excellent yield in both cases, especially when UHP was the oxidant of choice.

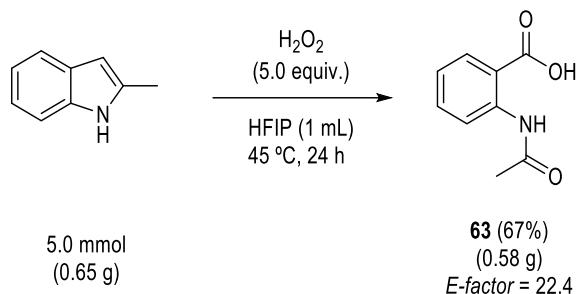


Scheme 34. Scope of the oxidation of furan derivatives.

Bearing in mind the importance of 2-ketoacetanilide derivatives as intermediates in the synthesis of quinolones and related bioactive compounds,^{111,112} it was thought appropriate to develop a bigger scale reaction maintaining the effectiveness of the protocol herein described. Thus, 0.65 g of 2-methylindole were transformed into 0.58 g of *N*-acetylantranilic acid **63**, by only increasing the amount of HFIP up to 1 mL and using H_2O_2 as selected oxidant instead of UHP because of its easier purification by recrystallization (Scheme 35). The conversion of the process was >70%, and the product could be isolated after recrystallization with *n*-pentane/ CH_2Cl_2 3/1 in a

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67% yield. The *E*-factor of the whole process turned out to be 22.4, which is within the numbers of production of fine chemicals in the industry and the lowest limit for the pharmaceutical industry.¹¹⁴



Scheme 35. Synthesis of *N*-acetylanthranilic acid in multigram scale and *E*-factor.

At this point, it is important to highlight that the recyclability of the solvent was evaluated in this big scale reaction, as an attempt to further demonstrate the sustainability of the protocol described (**iError! No se encuentra el origen de la referencia.**). After the optimized reaction time, the solvent could be easily separated from the mixture by using Kugelrohr distillation. Then, the reaction was set again by only adding the starting materials. By using this procedure, HFIP could reused up to four cycles with only a slight erosion on the conversion after each cycle. Despite so, the efficiency and ease recover of the solvent proved the sustainability of the whole methodology.

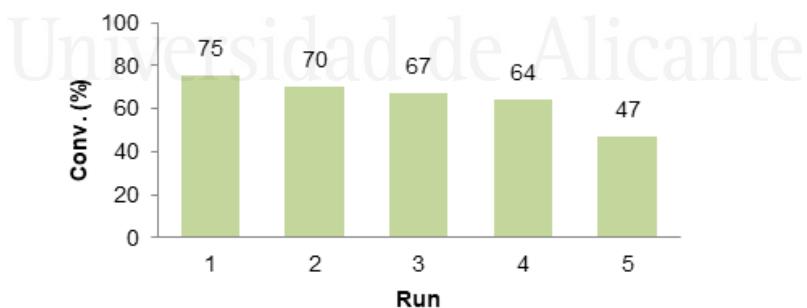
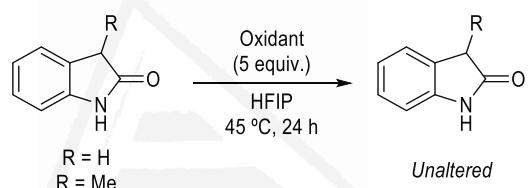


Figure 13. Recycling of the solvent.

¹¹⁴ Sheldon, R. A. *Chem. Soc. Rev.* **2012**, *41*, 1437-1451.

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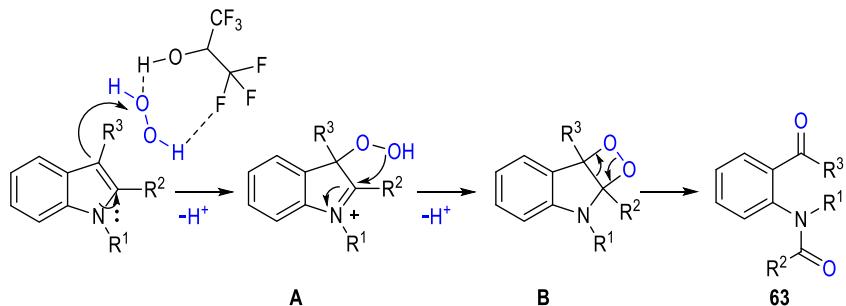
Later on, it was decided to perform a couple of control experiments with the aim of reaching the most feasible mechanism. In this sense, oxindole and 3-methyloxindole were submitted to this protocol. In both cases, the reaction was carried out with both oxidants (UHP and H₂O₂) and after the reaction time, as somehow expected, the reaction did not evolve towards the oxidative cleavage, remaining the starting materials unaltered in the reaction mixture (Scheme 36). Hence, after the results obtained, it was confirmed that this methodology did not proceed *via* the oxindole formation. Furthermore, to confirm that the mechanism of the reaction did not proceed *via* radical intermediates, an experiment using the radical scavenger TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl] was performed, not observing any transformation after 24 hours, under optimal conditions in both solvents, HFIP and MeCN. Therefore, the presence of radicals was discarded.



Scheme 36. Control experiments.

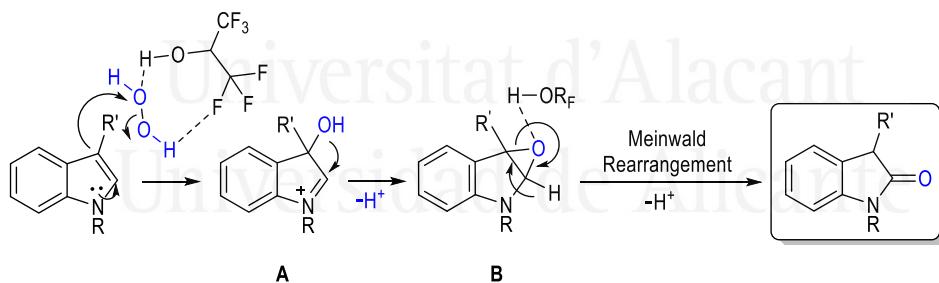
Based on these observations and similar transformations previously reported, a plausible mechanism for the oxidative cleavage of indoles is represented in Scheme 37. Thus, the first step of the reaction would be the attack of the indole to the H₂O₂ thanks to the electrophilic activation of the oxidant by HFIP, affording the hydroperoxide **A** as an intermediate. Then, an intramolecular cyclization reaction would take place, giving rise to the formation of dioxetane **B**. Due to its instability, the rearrangement of this intermediate would render the desired ketoacetanilide **63**.

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Scheme 37. Proposed reaction mechanism for the ketoacetanilide formation.

In a similar manner, considering that the cleavage of indoles also gives rise to other oxidation products, namely oxindoles, isatins, *N*-Alkyl-1,5-dihydro-2*H*-pyrrol-2-one, *N*-alkylmaleimide, lactone or cyclic hemiacetal, other possible reaction mechanisms were considered, being described as follows. In the case of the oxindole formation, as depicted in Scheme 38, after the electrophilic activation of the H_2O_2 through HFIP, the nucleophilic attack of the indole derivative rendered the intermediate **A**, which can evolve to the formation of the oxirane **B**. This intermediate, after a HFIP-promoted Meinwald-type rearrangement, would lead to the corresponding oxindole.

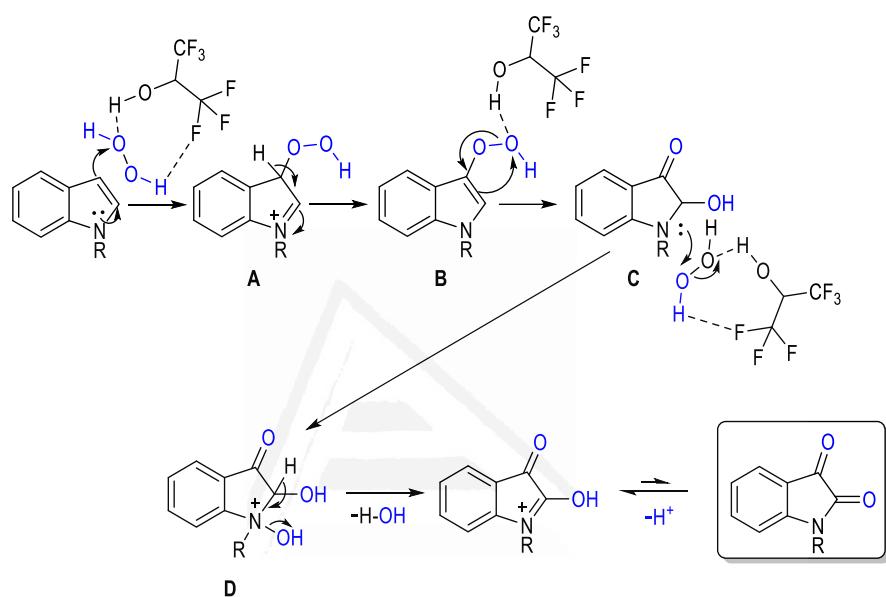


Scheme 38. Proposed reaction mechanism for the oxindole formation.

Then, the formation of the isatin derivatives was proposed following a similar reaction mechanism that the one shown for the ketoacetanilide derivatives formation (Scheme 39). As stated before, the nucleophilic attack of the indole to the H_2O_2 occurs due to the electrophilic activation of the oxidant by HFIP throughout hydrogen bonds giving rise to the hydroperoxy derivative **A** which

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could evolve towards intermediate **B** by rearomatization. Then, this intermediate would allow the subsequent formation of the corresponding hydroxyindolinone **C**. After that, by means of a second nucleophilic attack, hydroxylamine **D** is formed which after dehydration and tautomerisation, would render the desired isatin.

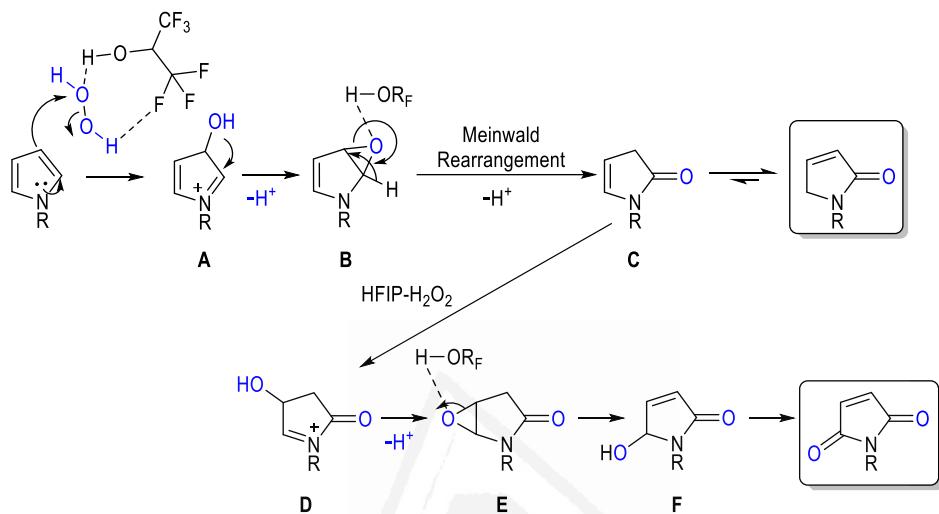


Scheme 39. Proposed reaction mechanism for the isatins formation.

In the case of the synthesis of *N*-Alkyl-1,5-dihydro-2*H*-pyrrol-2-one and *N*-alkylmaleimide, the reaction mechanism that presumably take place would be the same described for the oxindole formation (Scheme 40). Firstly, the nucleophilic attack of the pyrrole derivative to the H_2O_2 takes place thanks to the electrophilic activation of the oxidant by HFIP. Thus, the intermediate **A** is obtained, which can evolve to the bicyclic derivative **B**. This intermediate gives rise to the corresponding pyrrolone **C** after a HFIP-mediated Meinwald-type rearrangement. At this point, it is important to highlight that this pyrrolone obtained can evolve towards two different pathways. In the first case, the corresponding *N*-Alkyl-1,5-dihydro-2*H*-pyrrol-2-one can be reached by means of double bond isomerization towards the α,β -unsaturated compound. An alternative pathway would consist of a second nucleophilic attack of the pyrrolone **C** onto H_2O_2 . The corresponding *N*-

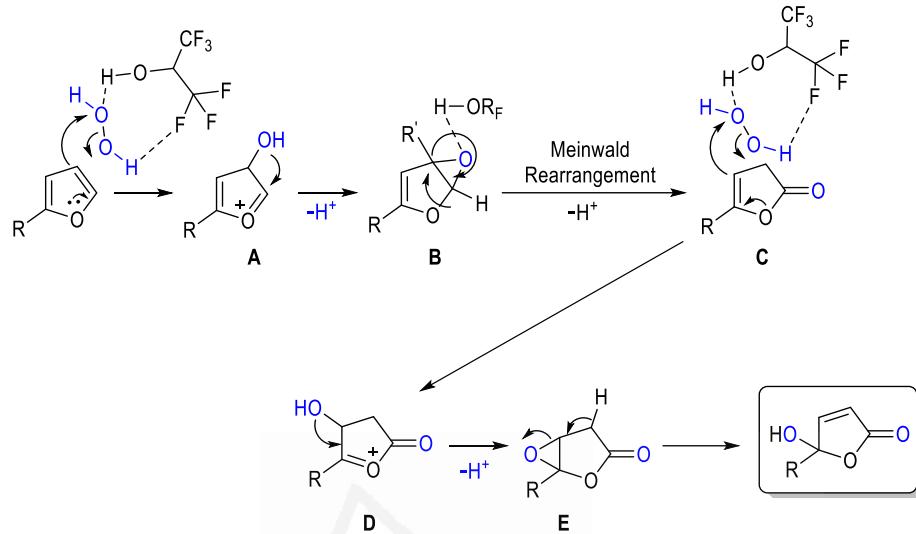
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alkylmaleimide would be obtained after a second Meinwald-type rearrangement and oxidation of hydroxy derivative **F** in a similar manner to that shown in Scheme 39.

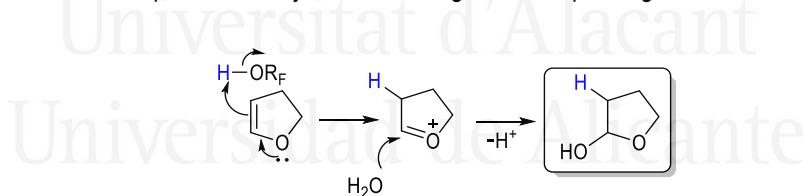


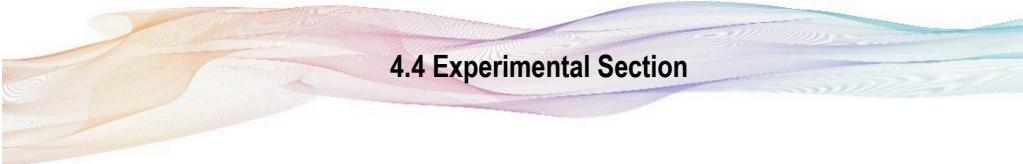
Scheme 40. Proposed mechanism for the *N*-Alkyl-1,5-dihydro-2*H*-pyrrol-2-one and *N*-alkylmaleimide formation.

On the other hand, the synthesis of lactone would occur in a similar way. First, as depicted in Scheme 41, after the electrophilic activation of the oxidant by HFIP through hydrogen bonds, the nucleophilic attack of the furane derivative to the H_2O_2 takes place affording the intermediate **A**. Then, this intermediate can evolve to the intermediate **B**. After a Meinwald-type rearrangement, this intermediate gives rise to the corresponding furanone **C**. Again, the second nucleophilic attack take place and following the same steps than previously shown in Scheme 40 would lead to the formation of the corresponding hydroxy lactone derivatives.

**Scheme 41.** Proposed mechanism for the hydroxy lactone formation.

Finally, the reaction mechanism for the cyclic hemiacetal formation was proposed (Scheme 42). In this case, its formation would not be ascribed to a proper oxidation reaction but to a nucleophilic attack of this vinyl ether to the acidic proton of HFIP. The oxocarbenium generated would suffer a nucleophilic attack by H_2O , rendering the corresponding hemiacetal.

**Scheme 42.** Proposed mechanism for the cyclic hemiacetal formation.



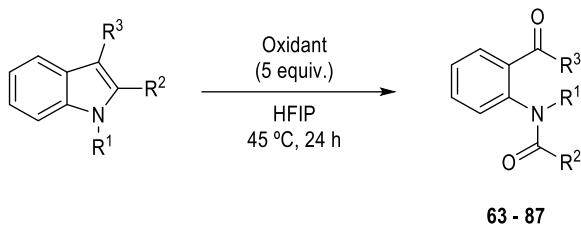
4.4 Experimental Section

4.4.1 General

Unless otherwise noted, all commercially available reagents and solvents were purchased (Acros, Aldrich, Fluka, Fluorochem, Merck) and used without further purification. Substrates that were not commercially available were synthesized according to known literature procedures. ^1H NMR and ^{13}C NMR spectra were recorded at the technical service of the University of Alicante (SSTTI-UA), employing a Bruker AV-300 or Bruker AV-400 (Bruker Corporation) using CDCl_3 as solvent and TMS as internal standard unless otherwise stated. Chemical shifts (δ) are given in ppm and the coupling constants (J) in Hz. Melting points were determined using a Gallenkamp capillary melting point apparatus (model MPD 350 BM 2.5) and are uncorrected. Low resolution mass spectra (MS) were recorded in the electron impact mode (EI, 70 eV, He as carrier phase) using an Agilent GC/MS 5973 Network Mass Selective Detector spectrometer apparatus equipped with a HP-5MS column (Agilent technologies, 30 m \times 0.25 mm) and giving fragment ions in m/z with relative intensities (%) in parentheses. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV on Agilent GC/MS-5973N apparatus equipped with a HP-5MS column (Agilent technologies, 30 m \times 0.25 mm). High-resolution mass spectra (HRMS) were obtained on an Agilent 7200 Quadrupole-Time of Flight apparatus (Q-TOF), with the ionization employed being electron impact (EI). Analytical TLC was performed on Merck silica gel plates and the spots visualized with UV light at 254 nm. Flash chromatography employed Merck silica gel 60 (0.040-0.063 mm). Silica gel 60 F254 containing gypsum was employed for preparative layer chromatography.

Chapter IV

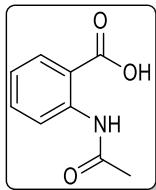
4.4.2 General Procedure for de Oxidative Cleavage of Indole-Pyrrol-Furan Derivatives



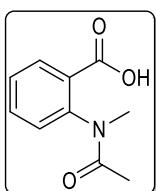
63 - 87

In a capped tube, 0.15 mmol of the corresponding indole, pyrrol and furan derivative, 150 µL HFIP and 5 equivalents of the oxidant were added sequentially in one portion. The reaction mixture was stirred and heated in a sand bath for 24 hours at 45 °C. Then, after cooling down the mixture, it was filtered through Silice/Celite® plug using ethyl acetate as eluent. Later on, the solvent was evaporated under reduced pressure. Finally, after purification by preparative TLC using mixtures of *n*-hexane and ethyl acetate as eluent, the corresponding pure products were afforded.

4.4.3 Physical and Spectroscopic Data for Isolated Compounds



N-Formylantranilic acid (63):¹¹⁵ yellow oil; purification by preparative TLC (*n*-hexane/ethyl acetate 8.0/2.0), 21.2 mg, 79% yield; **1H NMR** (400 MHz, CDCl₃): δ_H = 11.11 (br s, 1H, NH), 8.74 (d, *J* = 8.4 Hz, 1H, CH_{Ar}), 8.16 (dd, *J* = 8.0, 1.6 Hz, 1H, CH_{Ar}), 7.66-7.58 (m, 1H, CH_{Ar}), 7.19-7.13 (m, 1H, CH_{Ar}), 2.32 (s, 3H, COCH₃) ppm; **13C NMR** (101 MHz, CDCl₃): δ_C = 171.9, 170.0, 141.7, 135.5, 131.7, 122.9, 120.6, 114.4, 25.4 ppm; **MS** (EI): *m/z* 179 (M⁺, 13%), 161 (100), 146 (98), 117 (54), 92 (16), 90 (38), 76 (14), 50 (15).

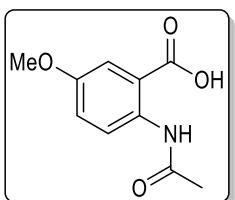


2-(Acetyl methylamino)benzoic acid (64): brown solid; purification by preparative TLC (*n*-hexane/ethyl acetate 8.0/2.0), 26.3 mg, 91% yield, mp 124 - 126 °C; **1H NMR** (300 MHz, CD₃OD): δ_H = 8.13 (dd, *J* = 7.8 and 1.5 Hz, 1H, CH_{Ar}), 7.63 (td, *J* = 7.6 and 1.5 Hz, 1H, CH_{Ar}), 7.57-7.44 (m, 1H, CH_{Ar}), 7.29 (d, *J* = 7.6 Hz, 1H, CH_{Ar}), 3.24 (s, 3H, NCH₃), 1.83 (s, 3H, COCH₃) ppm; **13C NMR** (75

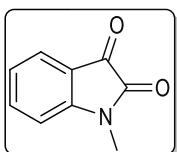
¹¹⁵ Yadav, J. S.; Reddy, B. V. S.; Reddy, C. S.; Krishna, A. D. *Synthesis* **2007**, 2007, 693-696.

Experimental Section

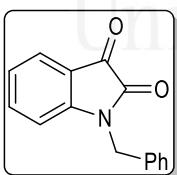
MHz, CD₃OD): δ_C = 172.2, 167.9, 162.8, 144.0, 133.9, 132.7, 129.4, 128.7, 37.2, 22.1 ppm; **MS** (EI): m/z 193 (M⁺, 3%), 149 (100), 105 (14), 104 (29), 78 (18), 77 (26), 76 (13), 73 (13); **HRMS** (EI/Q-TOF) m/z: [M⁺] Calcd. for C₁₀H₁₁NO₃ 193.0739, Found 193.0725.



2-(Acetylamino)-5-methoxybenzoic acid (65):¹¹⁶ dark-orange solid; purification by preparative TLC (*n*-hexane/ethyl acetate 8.0/2.0), 26.3 mg, 91% yield; **1H NMR** (300 MHz, CD₃Cl₃): δ_H = 10.82 (br s, 1H, NH), 8.60 (d, *J* = 9.2 Hz, 1H, CH_{Ar}), 7.59 (d, *J* = 3.1 Hz, 1H, CH_{Ar}), 7.15 (dd, *J* = 9.2, 3.1 Hz, 1H, CH_{Ar}), 3.82 (s, 3H, OCH₃), 2.25 (s, 3H, CH₃) ppm; **13C NMR** (75 MHz, CD₃Cl₃): δ_C = 171.2, 169.5, 154.6, 135.3, 122.2, 121.7, 115.6, 115.2, 55.6, 25.2 ppm; **MS** (EI): m/z 209 (M⁺, 0.05%), 191 (100), 176 (25), 161 (52), 149 (24), 147 (30), 146 (34), 120 (22), 118 (31), 106 (38).



N-Methylisatin (66):¹¹⁷ yellow oil; purification by preparative TLC (*n*-hexane/ethyl acetate 8.0/2.0), 19.3 mg, 79% yield; **1H NMR** 300 MHz, CDCl₃): δ_H = 7.65-7.55 (m, 2H, 2xCH_{Ar}), 7.13 (td, *J* = 7.6 and 0.8 Hz, 1H, CH_{Ar}), 6.90 (dd, *J* = 7.8, 0.7 Hz, 1H, CH_{Ar}), 3.25 (s, 3H, CH₃) ppm; **13C NMR** (75 MHz, CDCl₃): δ_C = 183.3, 158.2, 151.4, 138.4, 130.0, 125.3, 123.8, 123.17, 117.4, 109.9, 26.2 ppm; **MS** (EI): m/z 163 (M⁺, 30%), 148 (11), 135 (65), 120 (100), 92 (34), 65 (22).



1-Benzylisatin (67):¹¹⁸ yellow oil; purification by preparative TLC (*n*-hexane/ ethyl acetate 7.0/3.0), 25.7 mg, 72% yield; **1H NMR** (300 MHz, CDCl₃): δ_H = 7.66-7.56 (m, 1H, CH_{Ar}), 7.49 (dd, *J* = 7.9 and 1.3 Hz, 1H, CH_{Ar}), 7.48-7.34 (m, 5H, 5xCH_{Ar}), 7.15-7.05 (m, 2H, 2xCH_{Ar}), 6.78 (d, *J* = 7.9 Hz, 1H, CH_{Ar}),

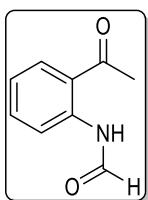
¹¹⁶ Temussi, F.; Cermola, F.; DellaGreca, M.; Iesce, M. R.; Passananti, M.; Previtera, L.; Zarrelli, A. *J. Pharm. Biomed.* **2011**, 56, 678-683.

¹¹⁷ Nasir Baig, R. B.; Verma, S.; Nadagouda, M. N.; Varma, R. S. *Green Chem.* **2016**, 18, 1019-1022.

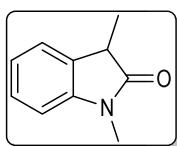
¹¹⁸ Bisht, G. S.; Gnanaprakasam, B. *J. Org. Chem.* **2019**, 84, 13516-13527.

Chapter IV

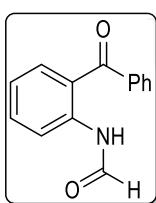
4.93 (s, 2H, CH₂) ppm; **¹³C NMR** (101 MHz, CDCl₃): δ_C = 158.4, 150.9, 138.4, 134.6, 129.2, 128.9, 128.8, 128.3, 127.6, 125.6, 124.0, 117.8, 111.1, 44.2, 29.8 ppm; **MS** (EI): *m/z* 238 (M⁺+1, 15%), 237 (M⁺, 90), 181 (13), 180 (60), 146 (100), 104 (12), 91 (43), 90 (24), 65 (13).



2-Acetylphenylformamide (68):¹¹⁹ yellow oil; purification by preparative TLC (*n*-hexane/ethyl acetate 8.0/2.0), 18.3 mg, 75% yield; **¹H NMR** (400 MHz, CDCl₃): δ_H 11.64 (br s, 1H, NH), 8.77 (d, *J* = 8.3 Hz, 1H, CHO), 8.52 (s, 1H, CH_{Ar}), 7.95 (dd, *J* = 8.0 and 1.5 Hz, 1H, CH_{Ar}), 7.59 (t, *J* = 7.9 Hz, 1H, CH_{Ar}), 7.19 (t, *J* = 7.5 Hz, 1H, CH_{Ar}), 2.70 (s, 3H, CH₃) ppm; **¹³C NMR** (101 MHz, CDCl₃): δ_C = 202.7, 159.9, 135.2, 131.6, 129.8, 126.7, 123.1, 121.6, 28.6 ppm; **MS** (EI): *m/z* 163 (M⁺, 0.99%), 161 (91), 134 (31), 132 (12), 105 (59), 104 (100), 92 (11), 90 (11), 78 (35), 77 (20), 64 (12), 63 (14), 50 (11).



1,3-Dimethyloxindole (69):¹²⁰ yellow oil; purification by preparative TLC (*n*-hexane/ethyl acetate 6.5/3.5), 7.7 mg, 32% yield; **¹H NMR** (300 MHz, CDCl₃): δ_H = 7.29-7.12 (m, 2H, 2xCH_{Ar}), 6.98 (td, *J* = 7.5 and 1.0 Hz, 1H, CH_{Ar}), 6.75 (d, *J* = 7.5 Hz, 1H, CH_{Ar}), 3.36 (q, *J* = 7.7 Hz, 1H, CH), 3.13 (s, 3H, NCH₃), 1.40 (d, *J* = 7.7 Hz, 3H, CH₃) ppm; **¹³C NMR** (75 MHz, CDCl₃): δ_C = 130.8, 128.0, 123.6, 122.5, 108.1, 40.7, 29.9, 26.3, 15.5 ppm; **MS** (EI): *m/z* 161 (M⁺, 100%), 146 (57), 118 (75), 77 (11).



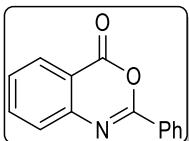
N-(2-Benzoylphenyl)formamide (70):¹²¹ yellow oil; purification by preparative TLC (*n*-hexane/ethyl acetate 8.0/2.0), 25.3 mg, 75% yield; **¹H NMR** (300 MHz, CDCl₃): δ_H = 10.75 (br s, 1H, NH), 8.70-8.67 (m, 1H, CHO), 8.51 (m, 1H, CH_{Ar}), 7.74-7.71 (m, 2H, 2xCH_{Ar}), 7.66-7.59 (m, 4H, 4xCH_{Ar}), 7.54-7.49 (m, 2H, 2xCH_{Ar}), 7.18-7.14 (m, 1H, CH_{Ar}) ppm; **¹³C NMR** (75 MHz, CDCl₃): δ_C = 199.6, 159.8, 139.4, 138.6, 134.4, 133.7, 132.8, 130.1, 128.5, 122.9, 122.3 ppm; **MS** (EI): *m/z* 225 (M⁺, 14%), 197 (62), 196 (100), 120 (23), 105 (14), 77 (28).

¹¹⁹ He, J.; Dong, J.; Su, L.; Wu, S.; Liu, L.; Yin, S.-F.; Zhou, Y. *Org. Lett.* **2020**, 22, 2522-2526.

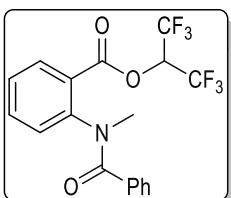
¹²⁰ Xu, J.; Liang, L.; Zheng, H.; Chi, Y. R.; Tong, R. *Nat. Commun.* **2019**, 10, 4754.

¹²¹ Yang, S.; Li, P.; Wang, Z.; Wang, L. *Org. Lett.* **2017**, 19, 3386-3389.

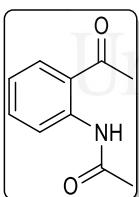
Experimental Section



2-Phenyl-4*H*-3,1-benzoxazin-4-one (71):¹¹³ off-white solid; purification by recrystallization with methanol, 26.8 mg, 80% yield; **¹H NMR** (400 MHz, D₂O): δ_H = 8.75 (dd, *J* = 8.3 and 1.2 Hz, 1H, CH_{Ar}), 8.09 (dd, *J* = 8.0 and 1.2 Hz, 1H, CH_{Ar}), 8.01-7.93 (m, 2H, 2xCH_{Ar}), 7.64-7.53 (m, 2H, CH_{Ar}), 7.51-7.43 (m, 2H, CH_{Ar}), 7.19-7.08 (m, 1H, CH_{Ar}) ppm; **¹³C NMR** (101 MHz, D₂O): δ_C = 171.8, 167.4, 142.8, 135.9, 135.4, 133.3, 132.7, 129.9, 128.3, 124.1, 121.2, 117.4 ppm; **MS (EI)**: *m/z* 224 (M⁺+1, 14%), 223 (M⁺, 48), 179 (52), 146 (14), 105 (46), 77 (33).

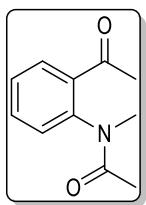


1,1,1,3,3,3-Hexafluoropropan-2-yl-2-(*N*-methylbenzamido)benzoate (72): orange solid; without further purification, 35.7 mg, 70% yield, m.p 41 – 42 °C; **¹H NMR** (300 MHz, DMSO-δ₆): δ_H = 7.95 (dd, *J* = 8.3, 1.3 Hz, 1H, CH(CF₃)₂), 7.69 (dd, *J* = 7.8, 1.4 Hz, 1H, CH_{Ar}), 7.64-7.56 (m, 1H, CH_{Ar}), 7.53-7.44 (m, 1H, CH_{Ar}), 7.38 (d, *J* = 7.1 Hz, 1H CH_{Ar}), 7.32-7.24 (m, 1H, CH_{Ar}), 7.22-7.09 (m, 4H, 4xCH_{Ar}), 3.28 (s, 3H, CH₃) ppm; **¹³C NMR** (101 MHz, DMSO-δ₆): δ_C = 169.4, 167.0, 160.1 (2C), 144.3, 136.4, 133.0, 131.2, 130.9 129.1 (ht, *J* = 32.3 Hz), 129.0 (q, *J* = 276. Hz), 127.9 (2C), 127.6, 127.5, 126.7, 37.7 ppm; **HRMS (EI/Q-TOF)** *m/z*: [M⁺] Calcd. for C₁₈H₁₃F₆NO₃ 405.0798, Found 405.0794.

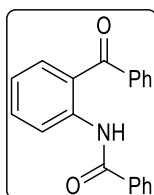


N-(2-Acetylphenyl)acetamide (73):¹²⁰ yellowish solid; purification by preparative TLC (*n*-hexane/ethyl acetate 7.0/3.0), 21.5 mg, 81% yield; **¹H NMR** (300 MHz, CDCl₃): δ_H = 11.7 (br s, 1H, NH), 8.74 (dd, *J* = 8.3 and 1.2 Hz, 1H, CH_{Ar}), 7.90 (dd, *J* = 8.3 and 1.6 Hz, 1H, CH_{Ar}), 7.58-7.52 (m, 1H, CH_{Ar}), 7.14-7.09 (m, 1H, CH_{Ar}), 2.67 (s, 3H, COCH₃), 2.23 (s, 3H, NHCOCH₃) ppm; **¹³C NMR** (75 MHz, CDCl₃): δ_C = 203.0, 169.6, 141.1, 135.3, 131.7, 122.4, 121.8, 120.8, 28.8, 25.7 ppm; **MS (EI)**: *m/z* 177 (M⁺, 26%), 135 (45), 134 (18), 120 (100), 92 (14), 65 (12).

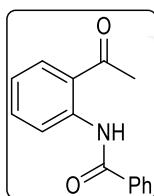
Chapter IV



N-(2-Acetylphenyl)-N-methylacetamide (74):¹²⁰ yellow oil; purification by preparative TLC (*n*-hexane/ethyl acetate 5.0/5.0), 25.2 mg, 88% yield; **1H NMR** (400 MHz, CDCl₃): δ_H = 7.75 (dd, *J* = 7.7 and 1.4 Hz, 1H, CH_{Ar}), 7.55 (dd, *J* = 7.7 and 1.4 Hz, 1H, CH_{Ar}), 7.48–7.45 (m, 1H, CH_{Ar}), 7.25 (d, *J* = 7.7 Hz, 1H, CH_{Ar}), 3.37 (s, 3H, NCH₃, minor rotamer), 3.21 (s, 3H, NCH₃, major rotamer), 2.54 (s, 3H, CH₃), 2.20 (s, 3H, NCOCH₃, minor rotamer), 1.79 (s, 3H, NCOCH₃, major rotamer) ppm; **13C NMR** (101 MHz, CDCl₃): both rotamers δ_C = 199.4, 170.5, 142.5, 137.0, 133.2, 132.5, 130.2, 129.5, 128.6, 128.1, 127.3, 37.3, 296, 22.4 ppm; **MS (EI)**: *m/z* 191 (M⁺, 0.57%), 148 (100), 134 (74), 130 (13), 106 (11), 77 (17).



N-(2-benzoylphenyl)-benzamide (75):¹²² yellow pale solid; purification by preparative TLC (*n*-hexane/ethyl acetate 9.0/1.0), 27.6 mg, 67% yield; **1H NMR** (400 MHz, CDCl₃): δ_H = 11.99 (br s, 1H, NH), 8.88 (d, *J* = 8.1 Hz, 1H, CH_{Ar}), 8.07 (dd, *J* = 8.1, 1.4 Hz, 2H, 2xCH_{Ar}), 7.73 (dd, *J* = 8.4, 1.4 Hz, 2H, 2xCH_{Ar}), 7.69 – 7.60 (m, 3H, 3xCH_{Ar}), 7.56 – 7.47 (m, 5H, 5xCH_{Ar}), 7.17 – 7.10 (m, 1H, CH_{Ar}) ppm; **13C NMR** (101 MHz, CDCl₃): δ_C = 200.4, 166.0, 141.0, 138.7, 134.7, 134.5, 134.1, 132.5, 132.1, 129.9, 128.9, 128.4, 127.4, 123.2, 122.3, 121.5 ppm; **MS (EI)**: *m/z* 301 (M⁺, 24%), 282 (11), 281 (32), 209 (20), 208 (24), 196 (64), 191 (12), 105 (100), 77 (58), 73 (14), 51 (11).

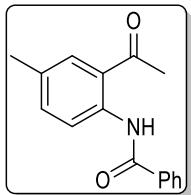


N-(2-acetylphenyl)-benzamide (76):¹²³ orange pale oil; without further purification, 31.9 mg, 89% yield; **1H NMR** (400 MHz, CDCl₃): δ_H = 12.72 (s, 1H, NH), 8.98 (dd, *J* = 8.6, 1.2 Hz, 1H, CH_{Ar}), 8.08 (d, *J* = 6.6 Hz, 2H, 2xCH_{Ar}), 7.97 (dd, *J* = 8.0, 1.6 Hz, 1H, CH_{Ar}), 7.63 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H, CH_{Ar}), 7.58 – 7.49 (m, 3H, 3xCH_{Ar}), 7.18 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H, CH_{Ar}), 2.73 (s, 3H, CH₃) ppm; **13C NMR** (101 MHz, CDCl₃): δ_C = 203.3, 166.2, 141.4, 135.5, 134.8, 132.0, 131.9, 128.8, 127.5, 122.6, 122.0, 120.8, 28.7 ppm; **MS (EI)**: *m/z* 239 (M⁺, 19%), 196 (43), 105 (100), 77 (50), 51 (11).

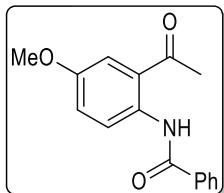
¹²² Astolfi, P.; Greci, L.; Rizzoli, C.; Sgarabotto, P.; Marrosu, G. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1634–1640.

¹²³ Jones, C. P.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2007**, 72, 7968–7973.

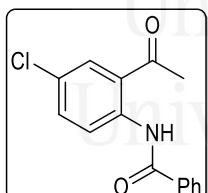
Experimental Section



N- (2-benzamide (77):¹²⁴ orange pale oil; without further purification, 31.9 mg, 89% yield; **1H NMR** (400 MHz, CDCl₃): δ_H = 12.72 (s, 1H, NH), 8.98 (dd, J = 8.6, 1.2 Hz, 1H, CH_{Ar}), 8.08 (d, J = 6.6 Hz, 2H, 2xCH_{Ar}), 7.97 (dd, J = 8.0, 1.6 Hz, 1H, CH_{Ar}), 7.63 (ddd, J = 8.6, 7.3, 1.6 Hz, 1H, CH_{Ar}), 7.58 – 7.49 (m, 3H, 3xCH_{Ar}), 7.18 (ddd, J = 8.3, 7.3, 1.2 Hz, 1H, CH_{Ar}), 2.73 (s, 3H, CH₃) ppm; **13C NMR** (101 MHz, CDCl₃): δ_C = 203.3, 166.2, 141.4, 135.5, 134.8, 132.0, 131.9, 128.8, 127.5, 122.6, 122.0, 120.8, 28.7 ppm; **MS (EI)**: m/z 239 (M⁺, 19%), 196 (43), 105 (100), 77 (50), 51 (11).



N-(2-acetyl-4-methoxyphenyl)-benzamide (78):¹²⁵ orange pale oil; without further purification, 31.9 mg, 89% yield; **1H NMR** (300 MHz, CDCl₃): δ_H = 12.38 (br s, 1H, NH), 8.91 (d, J = 9.2 Hz, 1H, CH_{Ar}), 8.05 (dd, J = 7.9, 1.7 Hz, 2H, 2xCH_{Ar}), 7.55 – 7.50 (m, 2H, 2xCH_{Ar}), 7.44 (d, J = 3.0 Hz, 2H, 2xCH_{Ar}), 7.20 (dd, J = 9.2, 3.0 Hz, 1H, CH_{Ar}), 3.87 (s, 3H, OCH₃), 2.70 (s, 3H, CH₃) ppm; **13C NMR** (75 MHz, CDCl₃): δ_C = 202.9, 165.9, 154.5, 134.9, 134.8, 133.4, 131.84, 130.1, 128.8, 128.6, 128.4, 127.4, 127.4, 123.2, 122.4, 120.3, 117.0, 55.8, 28.6 ppm; **MS (EI)**: m/z 269 (M⁺, 65%), 226 (27), 106 (112), 105 (100), 77 (42).

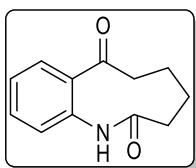


N- (2-acetyl-4-chlorophenyl)-benzamide (79): palid brown solid; without further purification, 37.1 mg, 93% yield; **1H NMR** (300 MHz, CDCl₃): δ_H = 12.59 (br s, 1H, NH), 8.99 (d, J = 9.1 Hz, 1H, CH_{Ar}), 8.11 – 8.00 (m, 2H, 2xCH_{Ar}), 7.91 (d, J = 2.5 Hz, 1H, 2xCH_{Ar}), 7.62 – 7.48 (m, 4H, 2xCH_{Ar}), 2.72 (s, 3H, CH₃) ppm; **13C NMR** (75 MHz, CDCl₃): δ_C = 202.2, 166.1, 139.9, 135.1, 134.4, 132.2, 131.3, 128.9, 127.5, 123.0, 122.4, 28.6 ppm; **MS (EI)**: m/z 273 (M⁺, 24%), 230 (18), 105 (100), 77 (43); **HRMS (EI/Q-TOF)** m/z: [M⁺] Calcd. for C₁₅H₁₂ClNO₂ 273.0566, Found 273.0562.

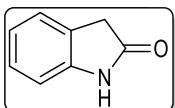
¹²⁴ Hande, A. E.; Ramesh, V. B.; Prabhu, K. R. *Chem. Commun.* **2018**, 54, 12113-12116.

¹²⁵ Beer, R. J. S.; Donavanik, T.; Robertson, A. *J. Chem. Soc.* **1954**, 4139-4142.

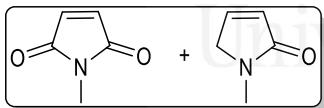
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3,4,5,6-Tetrahydro-1*H*-benzo[*b*]azonine-2,7-dione (80):¹²⁰ orange solid; purification by preparative TLC (*n*-hexane/ethyl acetate 8.5/1.5), 25.6 mg, 84% yield; **1H NMR** (400 MHz, CDCl₃): δ_H = 7.75 (br s, 1H, NH), 7.61 (d, J = 6.8 Hz, 1H, CH_{Ar}), 7.54 (td, J = 7.7 and 1.6 Hz, 1H, CH_{Ar}), 7.43 (t, J = 7.5 Hz, 1H, CH_{Ar}), 7.26 (d, J = 7.8 Hz, 1H, CH_{Ar}), 2.92 (s, 2H, COCH₂), 2.26 (s, 2H, NHCOCH₂), 1.90 (s, 4H, CH₂CH₂) ppm; **13C NMR** (101 MHz, CDCl₃): δ_C = 206.0, 176.5, 139.2, 134.3, 132.1, 128.6, 128.4, 128.1, 41.4, 32.3, 24.8, 24.5 ppm; **MS (EI)**: *m/z* 203 (M⁺, 18%), 185 (12), 184 (12), 175 (31), 174 (30), 146 (32), 135 (42), 130 (17), 120 (100), 119 (24), 92 (27), 65 (12).



Oxindol (81):¹²⁶ light brown solid, without further purification, 18.2 mg, 91 % yield, **1H NMR** (400 MHz, CDCl₃): δ_H = 9.12 (s, 1H, NH), 7.19 (t, J = 5.6 Hz, 2H, 2xCH_{Ar}), 7.01 (t, J = 7.5 Hz, 1H, CH_{Ar}), 6.92 (d, J = 8.0 Hz, 1H, CH_{Ar}), 3.54 (s, 2H, CH₂) ppm; **13C NMR** (101 MHz, CDCl₃): δ_C = 178.9, 142.4, 127.9, 125.3, 124.5, 122.6, 110.1, 36.4 ppm; **MS (EI)**: *m/z* 133 (M⁺, 100%), 105 (37), 104 (86), 78 (36), 77 (15), 52 (11), 51 (14).



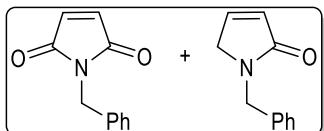
1-Methyl-1*H*-pyrrole-2,5-dione and 1-methyl-1,5-dihydro-2*H*-pyrrole-2-one (82a¹²⁷+82a'¹²⁸): yellow oil; purification by flash chromatography (*n*-hexane/ethyl acetate 8.0/2.0), 12.4 mg, 75% yield; **1H NMR** (300 MHz, CDCl₃): δ_H = 7.09 (dt, J = 6.0 and 1.7 Hz, 1H, COCH), 6.19 (dt, J = 6.0, 1.8 Hz, 1H, COCHCH), 5.26 (dd, J = 6.1, 2.0 Hz, 1H, CH₂CH), 4.02 (td, J = 1.8, 0.7 Hz, 2H, CH₂), 3.06 (s, 3H, CH₃), 2.92 (s, 3H, CH₃) ppm; **13C NMR** (75 MHz, CDCl₃): δ_C = 177.1, 172.1, 145.9, 142.8, 128.4, 128.1, 95.2, 85.1, 55.1, 29.9, 29.2, 28.3, 27.9, 23.6 ppm.

¹²⁶ Shelar, S. V.; Argade, N. P. *Org. Biomol. Chem.* **2019**, *17*, 6671-6677.

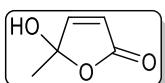
¹²⁷ Howard, J. K.; Hyland, C. J. T.; Just, J.; Smith, J. A. *Org. Lett.* **2013**, *15*, 1714-1717.

¹²⁸ Ghosh, A. K.; Samanta, S.; Ghosh, P.; Neogi, S.; Hajra, A. *Org. Biomol. Chem.* **2020**, *18*, 3093-3097.

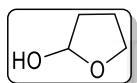
Experimental Section



1-Benzyl-1*H*-pyrrole-2,5-dione and 1-benzyl-1,5-dihydro-2*H*-pyrrole-2-one (83b¹²⁸+83b¹²⁹): yellow oil; purification by preparative TLC (*n*-hexane/ethyl acetate 7.0/3.0), 23.8 mg, 81% yield; **¹H NMR** (300 MHz, CDCl₃): δ_H = 7.35 (dd, *J* = 5.3, 3.0 Hz, 1H, CH_{Ar}), 7.30 (ddd, *J* = 6.2, 4.4, 1.4 Hz, 2H, 2xCH_{Ar}), 7.26 – 7.22 (m, 2H, CH_{Ar}), 7.08 (dt, *J* = 6.0, 1.8 Hz, 1H, CHCHCO), 6.30 – 6.19 (m, 1H, CHCHCO), 4.65 (s, 1H, NCH₂CH_{Ar}), 3.90 (t, *J* = 1.8 Hz, 1H, CHCH₂N) ppm; **¹³C NMR** (101 MHz, CDCl₃): δ_C = 176.4, 171.7, 143.2, 137.1, 136.5, 128.8, 128.7, 128.4, 127.9, 127.8, 127.7, 92.5, 52.5, 46.1, 43.9, 29.9, 23.5 ppm.



5-Hydroxy-5-methyl-2(5*H*)-furanone (84):¹³⁰ yellow oil, without further purification, 9.2 mg, 62% yield; **¹H NMR** (400 MHz, Acetone-δ₆): δ_H = 7.43 (d, *J* = 5.7 Hz, 1H, CHCHCO), 6.24 (d, *J* = 5.7 Hz, 1H, CHCHCO), 1.59 (s, 3H, CH₃) ppm; **¹³C NMR** (101 MHz, Acetone): δ_C = 153.5, 135.4, 128.1, 109.66, 21.7 ppm; **MS (EI)**: *m/z* 114 (M⁺, 30%), 105 (42), 103 (41), 99 (34), 91 (66), 88 (34), 83 (33), 73 (100), 70 (65), 61 (88), 57 (59); **HRMS (EI/Q-TOF)** *m/z*: (M⁺ -CH₃) Calcd. for C₄H₃O₃ 99.0084, Found 99.0079.



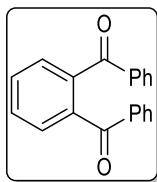
Tetrahydrofuran-2-ol (86):¹³¹ slightly yellow liquid; without further purification, 10.2 mg, 76% yield; **¹H NMR** (400 MHz, CDCl₃): δ_H = 9.47 (s, 1H, OH), 5.60 (dd, *J* = 6.1, 2.1 Hz, 1H, CHOH), 4.05-3.87 (m, 2H, CH₂O), 2.11-1.92 (m, 2H, CH₂CHOH), 1.91-1.76 (m, 2H, CH₂CH₂CHOH) ppm; **¹³C NMR** (101 MHz, CDCl₃): δ_C = 107.9, 67.7, 29.1, 23.9 ppm; **MS (EI)**: *m/z* 88 (M⁺, 0.42%), 71 (100), 57 (15).

¹²⁹ Zaragoza-Galicia, I.; Santos-Sánchez, Z. A.; Hidalgo-Mercado, Y. I.; Olivo, H. F.; Romero-Ortega, M. *Synthesis* **2019**, 51, 4650-4656.

¹³⁰ Kotzabasaki, V.; Vassilikogiannakis, G.; Stratakis, M. *J. Org. Chem.* **2016**, 81, 4406-4411.

¹³¹ Stephens, B. E.; Liu, F. *J. Org. Chem.* **2009**, 74, 254-263.

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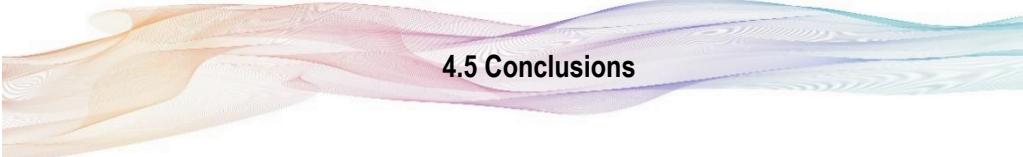


1,2-Phenylenebis(phenylmethanone) (87):¹³² crystalline orange solid, without further purification, 40.3 mg, 94% yield; **¹H NMR** (300 MHz, CDCl₃): δ_H = 7.73 (dd, J = 1.6, 0.9 Hz, 2H, 2xCH_{Ar}), 7.70 (t, J = 1.7 Hz, 2H, 2xCH_{Ar}), 7.63 (s, 4H, 4xCH_{Ar}), 7.53 (ddt, J = 10.6, 9.2, 4.6 Hz, 2H, 2xCH_{Ar}), 7.43-7.34 (m, 4H) ppm; **¹³C NMR** (75 MHz, CDCl₃): δ_C = 196.7, 140.0, 137.2, 133.0, 130.4, 129.8, 129.7, 128.3 PPM; **MS (EI)**: m/z 286 (M⁺, 70%), 210 (15), 209 (100), 152 (25), 105 (34), 77 (33).



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¹³² Lo Fiego, M. J.; Badajoz, M. A.; Silvestri, G. F.; Lockhart, M. T.; Chopra, A. B. *J. Org. Chem.* **2008**, *73*, 9184-9187.



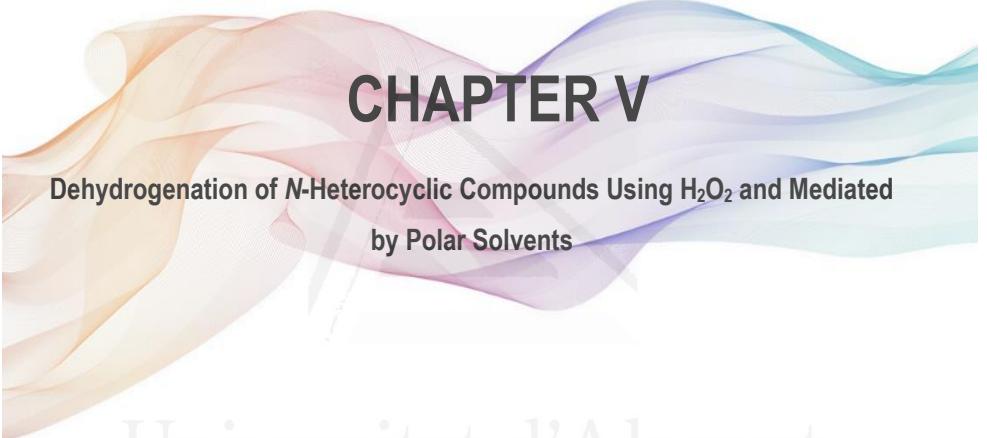
4.5 Conclusions

To conclude, a metal-free alternative protocol for the oxidative cleavage of indoles, known as Witkop oxidation, utilizing UHP or H₂O₂ as oxidants has been developed. The methodology herein described has proven to be effective in the presence of highly polar solvents when indoles bearing a substituent on position 2 and/or 3 were used. Furthermore, the reaction exhibit great performance and wide substrate scope when the solvent used was HFIP. In such a way, the reaction has been carried out under mild conditions where HFIP acts as both solvent and reaction promoter.

In addition, this protocol has allowed the preparation of a wide range of ketoacetanilide and anthranilic acid derivatives in good yields. Other heteroaromatic compounds were also conveniently oxidized. Additionally, this procedure has a high atom economy being the waste generated considered biodegradable.

The applicability of the method has been demonstrated by the fact that the solvent has been recovered and reused up to five times observing only slight erosion on the conversion after each cycle. Additionally, the methodology described has been implemented in a large-scale experiment.

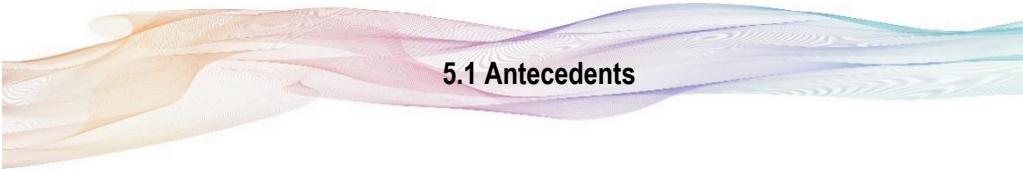
The results here described would be in accordance with the fact that H₂O₂ can be electrophilically activated by means of the fluorinated alcohol.



CHAPTER V

Dehydrogenation of *N*-Heterocyclic Compounds Using H₂O₂ and Mediated
by Polar Solvents

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5.1 Antecedents

5.1.1 General

Organic compounds bearing an *N*-heterocyclic moiety in their structure, such as quinoline and its isomer isoquinoline (Figure 14), represents an important scaffold present in a wide variety of naturally occurring compounds, generally alkaloids.^{102,133} These motifs have attracted chemists' attention due to their biological activity as antimalarial, anti-bacterial, anthelmintic, anticonvulsant, antiviral, anti-inflammatory or analgesic activity (Figure 15).¹³⁴ Furthermore, their applicability in other fields of the industrial chemistry, including the synthesis of agrochemicals, the study of bio-organic and bio-organometallic processes or the preparation of chemo-sensors, has been widely studied.¹³⁵

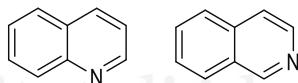


Figure 14. Quinoline and isoquinoline scaffolds.

Traditional synthetic methodologies for the obtention of these compounds present several drawbacks requiring extreme reaction conditions, the use of expensive starting materials or catalysts and the production of large amounts of waste. In such a way, over the last years, the interest in the

¹³³ Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, 57, 10257-10274.

¹³⁴ (a) Kumar, S.; Bawa, S.; Gupta, H. *Mini Rev. Med. Chem.* **2009**, 9, 1648-1654; (b) Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. *Chem. Rev.* **2011**, 111, 7157-7259; (c) Prajapati, S. M.; Patel, K. D.; Vekariya, R. H.; Panchal, S. N.; Patel, H. D. *RSC Adv.* **2014**, 4, 24463-24476; (d) Afzal, O.; Kumar, S.; Haider, M. R.; Ali, M. R.; Kumar, R.; Jaggi, M.; Bawa, S. *Eur J Med Chem* **2015**, 97, 871-910; (e) Chung, P. Y.; Bian, Z. X.; Pun, H. Y.; Chan, D.; Chan, A. S.; Chui, C. H.; Tang, J. C.; Lam, K. H. *Future Med. Chem.* **2015**, 7, 947-967; (f) Singh, S.; Kaur, G.; Mangla, V.; Gupta, M. K. *J. Enzyme Inhib. Med. Chem.* **2015**, 30, 492-504; (g) Batista, V. F.; Pinto, D. C. G. A.; Silva, A. M. S. *ACS Sustainable Chem. Eng.* **2016**, 4, 4064-4078.

¹³⁵ Sharma, R.; Kour, P.; Kumar, A. *J. Chem. Sci.* **2018**, 130, 73.

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development of greener and sustainable chemical methodologies by using less hazardous solvents, renewable catalysts or more efficient energy sources has been extensively investigated.¹⁰⁷ Among the different methodologies reported so far, it is important to highlight the dehydrogenation of *N*-heterocyclic compounds, being an elegant and straightforward protocol, presenting a high atom economy too.¹³⁶

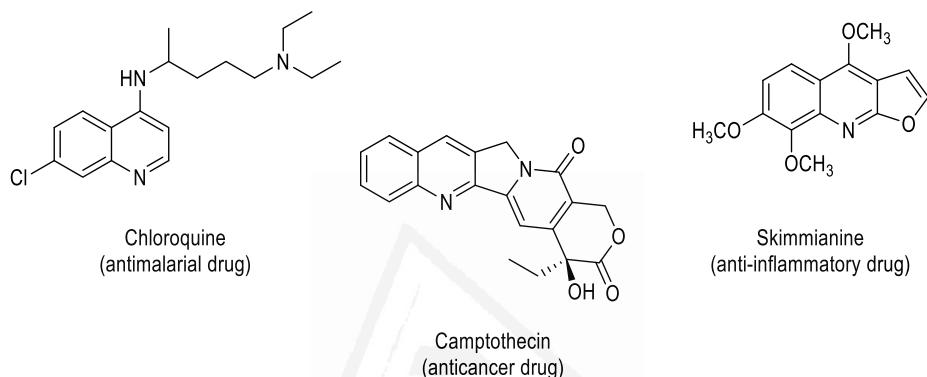


Figure 15. Quinoline based drugs.

5.1.2 Dehydrogenation of *N*-heterocyclic compounds

Despite being considered a challenging process, the oxidative dehydrogenative reaction has been widely studied over the past decades. Pioneer works were conducted using stoichiometric oxidants (Figure 16), such as HgO-I₂, MnO₂ or sulfur, or extreme temperatures.¹³⁷

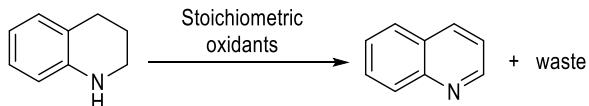


Figure 16. Dehydrogenation by using stoichiometric oxidants.

¹³⁶ (a) For selected reviews, see: (b) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681-703; (c) Choi, J.; MacArthur, A. H. R.; Brookhart, M.; Goldman, A. S. *Chem. Rev.* **2011**, *111*, 1761-1779; (d) Hati, S.; Holzgrabe, U.; Sen, S. *Beilstein J. Org. Chem.* **2017**, *13*, 1670-1692.

¹³⁷ Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317-361.

Nevertheless, sustainable protocols have emerged in the last years with lower environmental impact or better atom economy. Thus, the use of O₂ as oxidant in catalysed or photocatalysed processes has been widely studied in the last years, being some of the last reported examples those shown in Figure 17.¹³⁸ In this sense, the use of visible light or catalysts (metal-based or non-metal based) in combination with molecular oxygen, provides, in most of the cases, good results for the dehydrogenation reaction together with a cost-effective protocol for the storage and release of hydrogen, being an ideal candidate to address environmental pollution. Despite the great results achieved so far, these methodologies can represent a problem if the dehydrogenation is implemented on a bigger scale due to the potential inherent danger in H₂ formation. Besides that, direct oxidation by using O₂ as oxidant is not the easiest methodology since the sometimes necessary promotion from a triplet to singlet oxygen requires a high energy barrier.

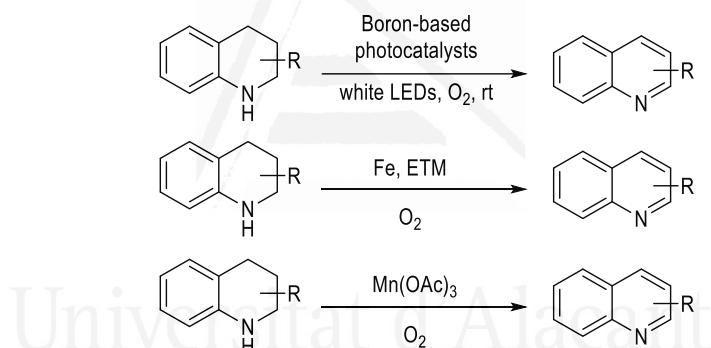


Figure 17. Dehydrogenation by using catalysts or photocatalysts in O₂.

As an alternative of the described methodologies, the development of metal-free catalyst systems by using visible light in combination with heterogeneous catalysis,¹³⁹ graphene oxide¹⁴⁰ or

¹³⁸ (a) For recent examples, see: Cao, Y.; Wu, Y.; Zhang, Y.; Zhou, J.; Xiao, W.; Gu, D. *ChemCatChem* **2021**, 13, 3679-3686; (b) Liu, Y.; Yu, T.; Zeng, Y.; Chen, J.; Yang, G.; Li, Y. *Catal. Sci. Technol.* **2021**, 11, 3810-3817; (c) Manna, S.; Kong, W.-J.; Bäckvall, J.-E. *Chem. Eur. J.* **2021**, 27, 13725-13729; (d) Niu, X.; Yang, L. *Adv. Synth. Catal.* **2021**, 363, 4209-4215; (e) Wei, L.; Wei, Y.; Zhang, J.; Xu, L. *Green Chem.* **2021**, 23, 4446-4450. and references therein.

¹³⁹ (a) F. Su; S. C. Mathew; L. Möhlmann; M. Antonietti; X. Wang, S. B. *Angew. Chem. Int. Ed.* **2011**, 50, 657-660; (b) M. Zheng; J. Shi; T. Yuan; X. Wang *Angew. Chem. Int. Ed.* **2018**, 57, 5487-5491.

¹⁴⁰ Zhang, J.; Chen, S.; Chen, F.; Xu, W.; Deng, G.-J.; Gong, H. *Adv. Synth. Catal.* **2017**, 359, 2358-2363.

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organo-electrocatalysts¹⁴¹ has attracted the attention due to the possibility of carry out this transformation in a simple manner under smooth reaction conditions (Figure 18). In general, those heterogeneous catalysts are easily recovered for further utilisation but, on several occasions, quite high temperatures are required for the successst of this methodology.

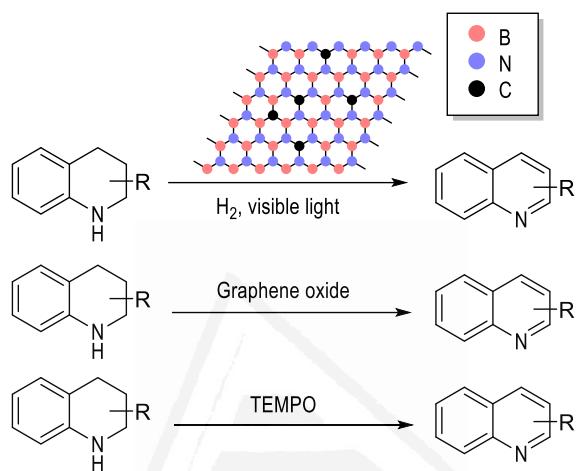


Figure 18. Metal-free catalyst dehydrogenation.

Other protocols considered as environmentally friendly methodologies are those involving green oxidants such as H₂O₂ in combination with metal or Lewis acids,¹⁴² being H₂O the by-product obtained. However, they have been scarcely studied,. In addition, the few articles published in this regard, not only produce the desired dehydrogenation product but other oxidation compounds.

¹⁴¹ Wu, Y.; Yi, H.; Lei, A. *ACS Catal.* **2018**, 8, 1192-1196.

¹⁴² (a) S. Murahashi; T. Oda; T. Sugahara; Y. Masui *J. Org. Chem.* **1990**, 55, 1744-1749; (b) Dhineshkumar, J.; Prabhu, K. R. *Org. Lett.* **2013**, 15, 6062-6065; (c) Zhang, Y.; Sun, S.; Su, Y.; Zhao, J.; Li, Y.-H.; Han, B.; Shi, F. *Org. Biomol. Chem.* **2019**, 17, 4970-4974.



5.2 Objectives

According to the precedents found in the literature, it was decided to set the following objectives:

To carry out the oxidative dehydrogenation of *N*-heterocyclic compounds to obtain the corresponding heteroaromatic species by using hydrogen peroxide as an alternative green oxidant in combination with polar solvents, HFIP among them.



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5.3 Discussion of Results

Initial efforts were focused on the optimisation of the reaction conditions using 1,2,3,4-tetrahydroquinoline as model substrate and 5 equivalents of H₂O₂ as oxidant in different solvents (Table 14). Firstly, the reaction was carried out with water as solvent at 45 °C. It is noteworthy that, after 15 hours, the expected quinoline **88** was observed with 79% of conversion (Table 14, entry 1). Then, it was decided to perform the reaction by using other polar solvents, namely isopropanol (*i*-PrOH), acetonitrile (MeCN), TFE or under neat reaction conditions. However, despite the reaction afforded great results, lower conversions in respect of the formation of quinoline were obtained (Table 14, entries 2-5 respectively). When the reaction was performed using HFIP, as somehow expected, the best result was obtained observing 83% of conversion towards formation of **88** (Table 14, entry 6). At this point, considering the results obtained with HFIP and H₂O as solvents, it was decided to seek further refinement of the reaction conditions. In such a way, it was decided to carry out the reaction by replacing H₂O₂ with UHP, its most stable form. Unexpectedly, in both cases the reaction gave rise to lower conversions towards the formation of quinoline **88** (Table 14, entries 7 and 8 respectively), ruling out this oxidant. Next, the oxidant amount was modified increasing it up to 7.5 equivalents in both solvents, H₂O and HFIP. A further amelioration was noticed in the case of HFIP, since the conversion reached a 85% (Table 14, entry 9), but not in the case of H₂O (Table 14, entry 10). Then, when the oxidant amount was increased up to 10 equivalents, 83% of conversion was obtained using H₂O as solvent (Table 14, entry 12). As a last attempt in order to improve the conversion towards the formation of the quinoline, it was decided to perform the reaction at 25 °C. It is important to mention that, to our delight, by decreasing the temperature, the expected quinoline was obtained in 91% of conversion in HFIP and 7.5 equivalents of H₂O₂ (Table 14, entry 13). Regrettably, only 23% of conversion was afforded when the solvent was H₂O (Table 14, entry 14). Further changes of reaction conditions were assayed, not representing a significant improvement (Table 14, entries 15-17).

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At this point, it is important to note that it was proved that the reaction was completed in less than 15 hours when the reaction was carried out with the conditions described in entries 9, 12 and 13. Concretely, the reaction was completed after 1 hour at 45 °C or 2 hours at 25 °C when the solvent utilized was HFIP, while the reaction finished after 12 hours in the case of H₂O.

Table 14. Optimisation of the reaction conditions^[a]

Entry	Oxidant (x equiv.)	Solvent	T (°C)	Conv. (%) ^[b]	
				85 (79)	88 (78)
1	H ₂ O ₂ (5)	H ₂ O	45	85 (79)	
2	H ₂ O ₂ (5)	i-PrOH	45	> 95 (60)	
3	H ₂ O ₂ (5)	MeCN	45	95 (72)	
4	H ₂ O ₂ (5)	TFE	45	92 (67)	
5	H ₂ O ₂ (5)	neat	45	> 95 (42)	
6	H ₂ O ₂ (5)	HFIP	45	> 95 (83)	
7	UHP (5)	HFIP	45	95 (60)	
8	UHP (5)	H ₂ O	45	35 (30)	
9	H₂O₂ (7.5)	HFIP	45	> 95 (85)	
10	H ₂ O ₂ (7.5)	H ₂ O	45	88 (78)	
11	H ₂ O ₂ (10)	HFIP	45	> 95 (85)	
12	H₂O₂ (10)	H₂O	45	98 (83)	
13	H₂O₂ (7.5)	HFIP	25	> 95 (91)	
14	H ₂ O ₂ (7.5)	H ₂ O	25	25 (23)	
15	H ₂ O ₂ (10)	HFIP	25	> 95 (90)	
16	H ₂ O ₂ (10)	HFIP	25	> 95 (58)	
17	UHP (7.5)	HFIP	25	83 (75)	

[a] Reaction conditions: 1,2,3,4-tetrahydroquinoline (0.15 mmol), oxidant (x equiv.) and solvent (150 µL). [b] Determined by GC-MS, in brackets conversion toward the formation of **88**.

Thus, the study was continued using 7.5 equivalents of H₂O₂ as oxidant in HFIP at 25 °C and/or 45 °C, which were chosen the best reaction conditions. In addition, in view of the results obtained when the reaction was conducted in water as solvent, and bearing in mind the 12 principles of Green Chemistry and the sustainability of the protocol, it was decided to parallelly perform the oxidative dehydrogenation of *N*-heterocyclic compounds in H₂O as solvent and H₂O₂ as oxidant.

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In such a way, an array of 1,2,3,4-tetrahydroquinolines, tetrahydroquinoxalines and tetrahydroquinazolines, of different electronic nature, were evaluated (Table 15). As mentioned, quinoline **88** was obtained in high yields in both solvents. Then, the oxidative dehydrogenation of 2-methyl and 7-methyl-1,2,3,4-tetrahydroquinoline rendered the quinolines **89** and **90** respectively in higher yields in both cases. Then, it was considered to study the oxidation process of those tetrahydroquinolines bearing different electron-donating and electron-withdrawing groups at C6 position, namely fluoro, bromo, methoxycarbonyl, methoxy or cyano, thus modulating the basicity and nucleophilicity of nitrogen atom. When HFIP was the solvent employed, quinolines **91**, **92**, **93** and **95** respectively, were afforded in high yields. Unfortunately, when the cyano group was studied, gaves rise to the formation of the corresponding quinoline **94** in lower yields among other oxidation by-products due to its electronic-withdrawing character and its higher reactivity. It is important to note that, though slightly lower, good results were observed in this case when carrying out the reaction in H₂O, being the lower acidity of the reaction media the possible reason for such result.

To our delight, naphthoquinoline **96** was achieved in excellent yield when H₂O was the solvent of choice. Lower conversion was reached when dihydroacridine was essayed in H₂O, whereas the reaction with HFIP as solvent led to the formation of compound **97** in 86% yield. In a like manner, it was thought to perform the reaction with Hantzsch ester giving rise to the pyridine **98** in 92% yield when using HFIP, while the reaction barely worked in H₂O. Similarly, trisubstituted tetrahydroquinolines were also tested. Thus, tetrahydroquinolines bearing an ester or ketone groups at C3 position led to the formation of the quinolines **99** and **100** in excellent 87% and 88% yield, respectively when HFIP-based oxidation conditions were essayed. Regretfully, lower yields were achieved when using H₂O as solvent along with other oxidation by-products.

Afterwards, in view of the results obtained with 1,2,3,4-tetrahydroquinolines, an assortment of tetrahydroquinoxalines and tetrahydroquinazolines were tested under the optimal oxidative dehydrogenation conditions. It is important to highlight that good to excellent conversions were achieved in all the cases in terms of consumption of the starting materials, particularly when the dehydrogenation process was carried out in HFIP. Even though the corresponding quinoxaline and quinazoline derivatives (**101-105**) were only detected by ¹H NMR and GC-MS in less than 30-35%

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conversion, together with other unidentified oxidation products were observed among the results obtained, thus hindering their isolation.

Table 15. Scope of the dehydrogenation of *N*-heterocycles ^[a]

	$\xrightarrow[\substack{\text{HFIP or } \text{H}_2\text{O} \\ 25 \text{ or } 45^\circ\text{C}}]{\text{H}_2\text{O}_2 \text{ (7.5 - 10 equiv.)}}$			
88 85% (1h) 72% (8h)	89 95% (2h) 86% (6h)	90 89% (1h) 79% (20h)	91 82% (6h) 63% (24h)	92 89% (6h) 77% (20h)
93 92% (6h) ^d 47% (20h)	94 <25% (3h) ^d 41% (20h)	95 93% (3h) ^d 89% (20h)	96 85% (6h) 92% (24h)	
97 86% (6h) ^d 21% ^b (8h)	98 92% (2h) 10% ^b (24h)	99 87% (6h) 58% ^b (20h)	100 88% (6h) ^d 36% ^b (20h)	
101 95% ^c (1h) 90% ^c (24h)	102 74% ^c (6h) ^d 65% ^c (24h)	103 88% ^c (6h) ^d 76% ^c (24h)	104 75% ^c (1h) 64% ^c (24h)	105 87% ^c (6h) ^d 60% ^c (24h)

^[a]Reaction conditions: tetrahydroquinoline (0.15 mmol), oxidant (7.5 or 10 equiv.) and solvent (150 μ L). The reaction temperature was 25 °C for HFIP and 45 °C for H₂O. Yield of the isolated product after preparative TLC. ^[b]Not isolated, conversion towards the formation of the product by ¹H NMR. ^[c]Conversion based on the consumption of the starting material determined by GC-MS and/or ¹H NMR. ^[d] The reaction temperature in this case was 45 °C.

Discussion of Results

Similarly, to broaden the applicability of the process, it was decided to implement the optimal conditions for the dehydrogenation of four different tetrahydroisoquinolines (Table 16). In this occasion, it is important to mention that the oxidative dehydrogenation methodology led to the formation of the corresponding 3,4-dihydroisoquinoline *N*-oxide derivatives (**108**, **109**, **110** and **111**) instead of the desired isoquinolines. Despite this, moderate to good yields were obtained in all the cases, especially when H₂O was the solvent of choice.

Table 16. Scope of the dehydrogenation of tetrahydroisoquinolines.^[a]

 108	 109	 110	 111
<hr/>			
53%^b (25 °C, 1 h) 65% (45 °C, 24 h)	42%^b (45 °C, 6 h) 48% ^c (45 °C, 20 h)	62%^b (45 °C, 6 h) 56% (45 °C, 20 h)	45%^b (25 °C, 6 h) 57% (25 °C, 6 h)

^[a] Reaction conditions: tetrahydroisoquinoline (0.15 mmol), oxidant (7.5 or 10 equiv.) and solvent (150 µL). Yield of the isolated product after preparative TLC. ^[b] Not isolated, conversion towards the formation of the product by ¹H NMR. ^[c] Not purely isolated. Estimated yield by ¹H NMR.

Finally, to further explore the versatility of the protocol, an assortment of indolines were also evaluated, obtaining a wide variety of indole derivatives (Table 17). Thus, it was decided to start the oxidation reaction by using NH-free indolines, namely indoline, 2-methylindoline and 3-methylindoline. The conversions towards the consumption of the starting materials were quite good, but unfortunately, the corresponding indole derivatives, **112**, **113** and **114** respectively, were observed in a low percentage. At this point, it is important to mention that apart from the indoline and indole derivatives, other oxidation products were detected by ¹H NMR and GC-MS, being some of them the ones coming from the oxidative cleavage of indoles, as seen in the previous chapter. In such a way, at this point, it was considered to run the reaction with more nucleophilic indolines,

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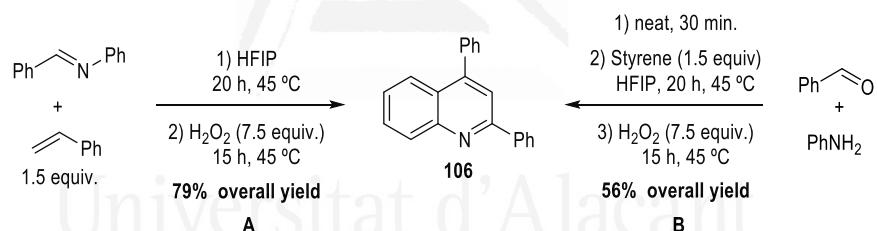
concretely the corresponding *N*-methylated analogues. By doing so, *N*-methylindoline led to the formation of the corresponding indole **115** in excellent 93% of conversion when using HFIP as solvent and 78% in the case of H₂O. However, when 1,2-dimethylindoline and 1-methyl-2-phenylindoline were submitted to the optimal reaction conditions, again lower conversions were reached for the indoles **116** and **118** respectively, observing again a complicated mixture of oxidation products by GC-MS and ¹H NMR. These results suggest that the higher steric hindrance of these substrates may difficult the oxidation process, thus obtaining such complex mixture of products. This conjecture would be in agreement with the proposed reaction mechanism. 1,3-Dimethylindoline was next investigated giving rise to the corresponding indole **117** in a 51% conversion in the case of HFIP. It is important to mention that apart from the formation of other oxidation products, this last experiment represents an amelioration in front of the results obtained for 2-substituted analogues hence reinforcing the sterically hinderance.

Table 17. Scope of the dehydrogenation of indolines ^[a]

112 69% ^c (45 °C, 6 h) 77% ^c (45 °C, 24 h)	113 72% ^c (45 °C, 6 h) 66% ^c (45 °C, 24 h)
114 52% ^c (45 °C, 6 h) 47% ^c (45 °C, 24 h)	
115 72% (93% ^b) (25 °C, 6 h) 78% ^b (45 °C, 24 h)	
116 35% ^c (45 °C, 24 h) 40% ^c (45 °C, 24 h)	117 51% ^b (45 °C, 24 h) 45% ^c (45 °C, 24 h)
118 33% ^c (45 °C, 24 h) 5% ^c (45 °C, 24 h)	

^[a]Reaction conditions: indoline (0.15 mmol), oxidant (7.5 or 10 equiv.) and solvent (150 µL). Yield of the isolated product after preparative TLC. ^[b]Not isolated, conversion towards the formation of the product by ¹H NMR. ^[c]Conversion based on the consumption of the starting material determined by GC-MS and/or ¹H NMR.

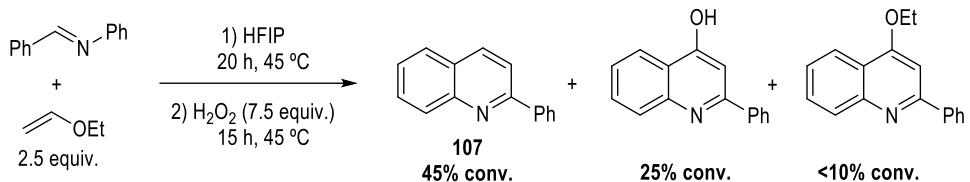
At this point, it was though the possibility to carry out the synthesis of tetrahydroquinolines *via* the one-pot Povarov-Dehydrogenation sequence (Scheme 43) since it has been demonstrated that HFIP can be an efficient solvent and promoter for those process involving carbocationic intermediates.^{17a} Therefore, the reaction between benzylidene aniline and styrene in HFIP and followed by the addition of H₂O₂ as oxidant source was essayed. The optimal reaction conditions for the Povarov reactions were studied by modifying both reaction time and reagent amounts. Finally, after 20 hours of reaction in HFIP, 7.5 equivalents of H₂O₂ were added at 45 °C and 15 hours later, the expected 2,4-diphenylquinoline **106** was afforded in good yields by TLC preparative (Scheme 43A). As an attempt to further demonstrate the sustainability of the protocol, it was decided to subject this procedure in a multicomponent sequence. Starting from equimolar amounts of benzaldehyde and aniline. Again, the expected quinoline **106** was obtained although with lower yields (Scheme 43B).



Scheme 43. One-pot synthesis of 2,4-diquinoline through Povarov-Dehydrogenation sequence.

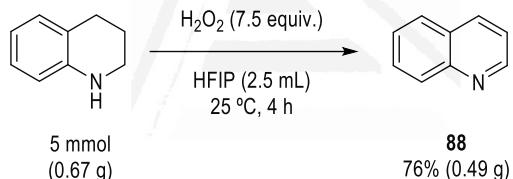
Encouraged by these results and with the purpose of obtaining more densely functionalized quinoline, the reaction was carried out using benzylidene aniline and 2.5 equivalents of ethyl vinyl ether under the same reaction conditions (Scheme 44). In this case, a mixture of different quinolines along with other by-products was obtained, being the 2-phenylquinoline **107** the major product observed in a 45% of conversion. Unfortunately, low conversions were afforded towards the formation of 2-alkyl and 2-heteroaromatic substituted quinolines.

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Scheme 44. One-pot synthesis of 2-phenylquinoline.

To demonstrate the applicability of the methodology, the oxidative dehydrogenation of 1,2,3,4-tetrahydroquinoline was performed in a multigram scale (Scheme 45). Thus, running the reaction for 4 hours, the oxidative dehydrogenation of 1,2,3,4-tetrahydroquinoline was carried out using H_2O_2 in HFIP as optimal conditions. The expected quinoline **88** was afforded in >85% conversion and the pure product could be isolated in 76% yield after purification by column chromatography.

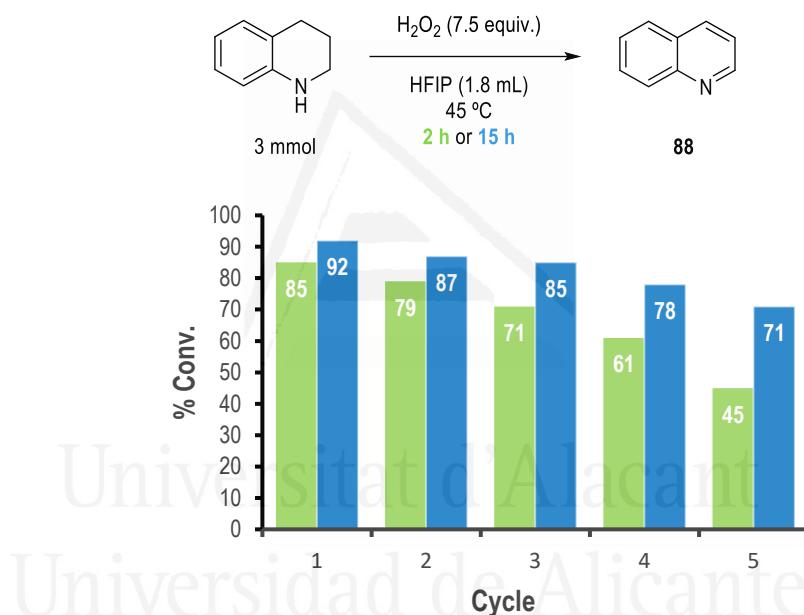


Scheme 45. Large scale reaction.

The recovery and reuse of the solvent were interesting aspects to consider to further extend the sustainability of the procedure. The model oxidative dehydrogenation reaction of 1,2,3,4-tetrahydriquinoline was used to study this process (Scheme 46). Therefore, 3 mmol of the starting material were submitted to the optimal reaction conditions using 1.8 mL of solvent. After the optimised reaction time, the solvent could be easily separated from the mixture by Kugelrohr distillation. Then, the reaction was set again with the recovered solvent by only adding tetrahydroquinoline and oxidant. By using this procedure, as depicted in the Scheme 46, HFIP could be reused up to three cycles with only a slight erosion on the conversion after each cycle. In this sense, in view of the results obtained we considered that the erosion of the solvent after each cycle could be caused by some water content generated during each recycling process, better explained

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in the mechanism of the reaction. Consequently, this H₂O could interact with the solvent throughout hydrogen bonds decreasing, in this sense, the role of HFIP as promoter and shrinking the reaction rate. However, despite this drawback and since H₂O was also a convenient solvent for the oxidation although in lower rate, its presence should not be a major problem. Therefore, it was decided to carry out the recyclability of the solvent extending the reaction time to 15 hours. To our delight, not only higher conversions were rendered but also the solvent could be reused up to five cycles, being proved the sustainability of the methodology.



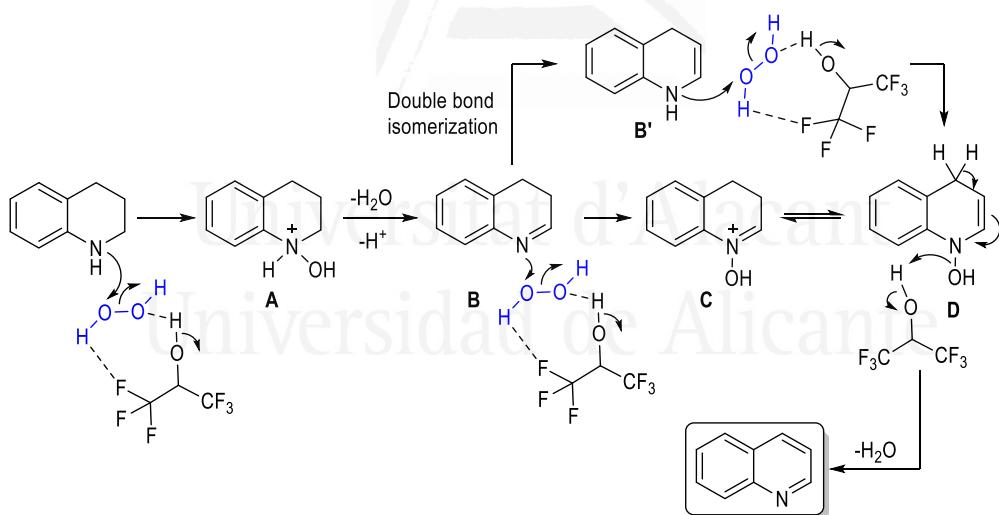
Scheme 46. Recycling of the solvent.

Bearing in mind our experience in previous oxidation processes, more specifically in those involving nitrogenated compounds, and based on the results obtained, a plausible reaction mechanism was proposed (Scheme 47). Starting with the electrophilic activation of hydrogen peroxide through hydrogen bonding, the nucleophilic attack of the 1,2,3,4-tetrahydroquinoline would render the intermediate **A**, being dehydrated toward the obtention of 1,2-dihydroquinoline **B**. By

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means of a second nucleophilic attack, due to the presence of a basic iminic nitrogen, the intermediate **C** was produced, giving rise to product **D** after double bond isomerization. As an alternative pathway, this intermediate **D** could also be obtained if the nucleophilic attack of the more stable regioisomer 1,4-dihydroquinoline **B'**, previously obtained by double bond isomerisation, to the electrophilically activated oxidant. This intermediate **D** can undergo an acidic mediated dehydration, leading the formation of the corresponding quinoline.

It is important to note that the proposed mechanism was reinforced by the fact that when *N*-methyl-1,2,3,4-tetrahydroquinoline was submitted to the optimal reaction conditions, the reaction barely worked. This fact suggests the need to reach the intermediate **B** (or **B'**) for the reaction to take place. Furthermore, it is worth to mention that the formation of dehydrogenated compound **B** (or **B'**) was observed by monitoring the reaction over the time by GC-MS analysis, finally evolving towards the formation of the corresponding quinoline.

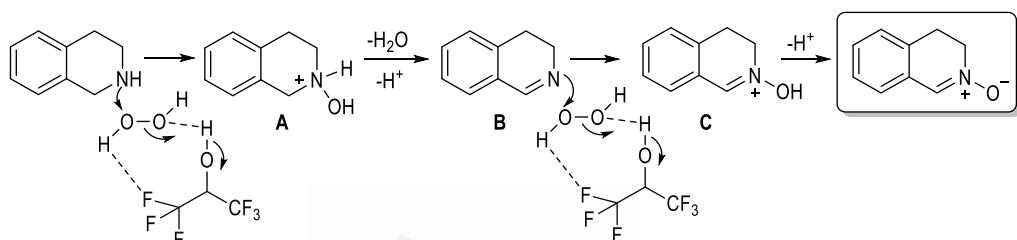


Scheme 47. Proposed reaction mechanism.

In a similar manner, the proposed reaction mechanism for the dehydrogenation of tetrahydroisoquinolines was stated. As depicted in Scheme 48, after the electrophilic activation of

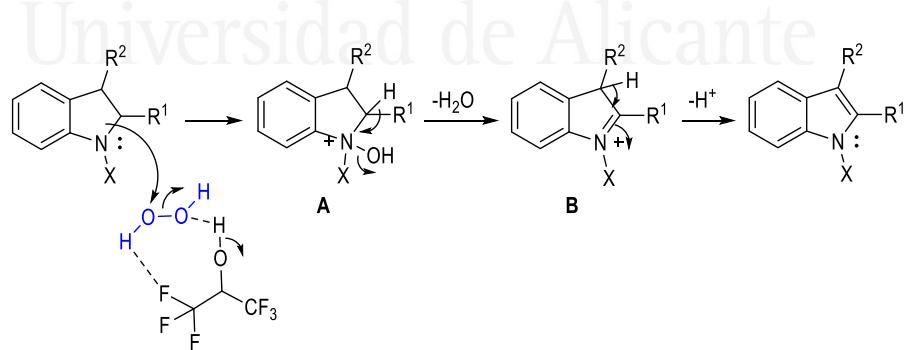
Discussion of Results

the H_2O_2 through HFIP, the nucleophilic attack of the 1,2,3,4-tetrahydroisoquinoline derivative rendered the intermediate **A**, which can evolve to the formation of dihydroisoquinoline **B** after dehydration. Then, by means of a second nucleophilic attack, hydroxy-dihydroisoquinolium derivative **C** is formed which would render the desired dihydroisoquinoline *N*-oxide derivative.

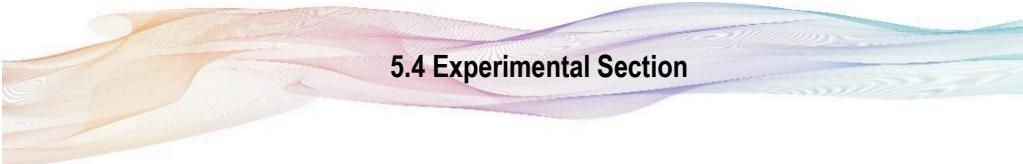


Scheme 48. Proposed reaction mechanism for the dehydrogenation of tetrahydroisoquinolines.

Finally, the reaction mechanism for the dehydrogenation of indolines was proposed (Scheme 49). Starting again with the nucleophilic attack of the indoline to the H_2O_2 due to the electrophilic activation of the oxidant by HFIP, the intermediate **A** would be afforded, which could evolve towards the formation of derivative **B** by dehydration. This intermediate, after aromatisation, would lead to the corresponding indole.



Scheme 49. Proposed reaction mechanism for the dehydrogenation of indolines.



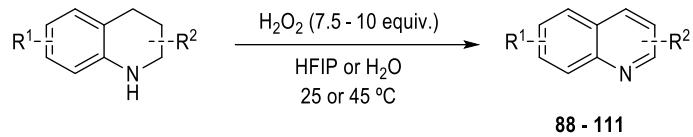
5.4 Experimental Section

5.4.1 General

All commercially available reagents and solvents were purchased (Acros, Aldrich, Fluka, Fluorochem, Merck) and used without further purification. Substrates that were not commercially available were synthesized according to known literature procedures. ^1H NMR and ^{13}C NMR spectra were performed at the technical service of the University of Alicante (SSTTI-UA), using a Bruker AV-300 or Bruker AV-400 (Bruker Corporation) using CDCl_3 as solvent and TMS as internal standard unless otherwise stated. Chemical Shifts (δ) are given in ppm and the coupling constants (J) in Hz. Low resolution mass spectra (MS) were recorded in the electron impact mode (EI, 70 eV, He as carrier phase) using an Agilent GC/MS 5973 Network Mass Selective Detector spectrometer apparatus equipped with a HP-5MS column (Agilent technologies, 30 m x 0.25 mm) and giving fragment ions in m/z with relative intensities (%) in parentheses. Low-resolution electron impact (EI) mass spectra were obtained at 70eV on Agilent GC/MS-5973N apparatus equipped with a HP-5MS column (Agilent technologies, 30 m x 0.25 mm). Analytical TLC was performed on Merck silica gel plates and the spots visualized with UV light at 254 nm. Flash chromatography employed Merck silica gel 60 (0.040-0.063 mm). Silica gel 60 F₂₅₄ containing gypsum was employed for preparative layer chromatography. The conversion of the reactions and purity of the products were determined by GC analysis using a Younglin 6100GC, equipped with a flame ionization detector and a Phenomenex ZB-5MS column (5% PH-ME siloxane): 30 m (length), 0.25 mm (inner diameter) and 0.25 μm (film).

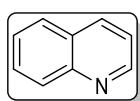
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5.4.2 Procedure for the oxidative hydrogenation of *N*-heterocycles

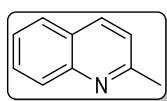


0.15 mmol of the corresponding *N*-heterocycle (tetrahydroquinoline, tetrahydroisoquinoline or indoline derivatives), 150 µL of the solvent (HFIP or H₂O) and 7.5 or 10 equivalents of H₂O₂ as oxidant, were added sequentially in one portion in a capped tube. Then, the reaction mixture was stirred in a sand bath at 25 °C in the case of H₂O and 45 °C when HFIP was the solvent of choice, for the indicated time, until the reaction was judged to be completed by GC-MS. Later on, when the reaction mixture was cooled down, it was filtered through silica/celite® plug using ethyl acetate as eluent. Finally, the solvent was evaporated under reduced pressure and the corresponding heteroaromatic compound was obtained after purification by preparative TLC, using mixtures of *n*-hexane and ethyl acetate as eluent.

5.4.3 Physical and Spectroscopic Data for Isolated Compounds



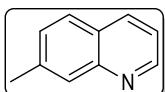
Quinoline (88):¹⁴³ yellow oil; purification by preparative TLC (*n*-hexane/ethyl acetate 8.5/1.5), 16.4 mg, 85% yield; **1H NMR** (400 MHz, CDCl₃) δ_H = 8.88 (dd, *J* = 4.2, 1.4 Hz, 1H, CH_{Ar}), 8.10 (d, *J* = 8.3 Hz, 2H, 2xCH_{Ar}), 7.76 (d, *J* = 8.1 Hz, 1H, CH_{Ar}), 7.72 – 7.63 (m, 1H, CH_{Ar}), 7.49 (dd, *J* = 11.1, 4.0 Hz, 1H, CH_{Ar}), 7.34 (dd, *J* = 8.3, 4.3 Hz, 1H, CH_{Ar}) ppm; **13C MNR** (101 MHz, CDCl₃) δ_C = 149.9, 147.9, 135.5, 129.1, 129.0, 127.8, 127.4, 126.1, 120.6 ppm; **MS (EI)**: *m/z* 129 (M⁺, 100%), 128 (18), 102 (22).



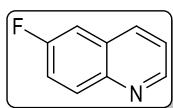
2-Methylquinoline (89):¹⁴³ yellowish oil; without further purification, 20.3 mg, 95% yield; **1H NMR** (400 MHz, CDCl₃) δ_H = 8.15 (d, *J* = 8.4 Hz, 2H, 2xCH_{Ar}), 7.81 (dd, *J* = 8.2, 1.3 Hz, 1H, CH_{Ar}), 7.72 (ddd, *J* = 8.5, 7.0, 1.4 Hz, 1H, CH_{Ar}), 7.56 – 7.49 (m, 1H, CH_{Ar}), 7.34 (dd, *J* = 8.5, 2.4 Hz, 1H, CH_{Ar}), 2.80 (s, 3H, CH₃) ppm; **13C MNR** (101 MHz, CDCl₃) δ_C = 158.3, 147.4, 147.3, 135.5, 128.9, 128.2, 128.1, 127.1, 126.0, 125.1, 121.4, 24.9 ppm; **MS (EI)**: *m/z* 143 (M⁺, 100%), 142 (14), 128 (15), 115 (15).

¹⁴³ Chen, W.; Tang, H.; Wang, W.; Fu, Q.; Luo, J. *Adv. Synth. Catal.* **2020**, 362, 3905-3911.

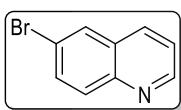
Experimental Section



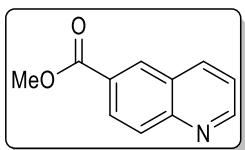
7-Methylquinoline (90):¹⁴³ orange oil, purification by preparative TLC (*n*-hexane/ethyl acetate 8.5/1.5), 19.1 mg, 89% yield; **1H NMR** (400 MHz, CDCl₃) δ_H = 8.83 – 8.77 (m, 1H, CH_{Ar}), 7.92 (d, *J* = 8.3 Hz, 1H, CH_{Ar}), 7.88 (s, 1H, CH_{Ar}), 7.54 (d, *J* = 8.3 Hz, 1H, CH_{Ar}), 7.22 (d, *J* = 8.2 Hz, 1H, CH_{Ar}), 7.19 – 7.12 (m, 1H, CH_{Ar}), 2.43 (s, 3H, CH₃).ppm; **13C NMR** (101 MHz, CDCl₃) δ_C = 149.9, 148.1, 139.5, 135.6, 128.61 128.0, 127.3, 126.2, 120.1, 21.7 ppm; **MS** (EI): *m/z* 143 (M⁺, 100%), 142 (55), 115 (15).



6-Fluoroquinoline (91):¹⁴³ brown oil; without further purification, 18.1 mg, 82% yield; **1H NMR** (400 MHz, CDCl₃) δ_H = 8.85 (dd, *J* = 4.2, 1.5 Hz, 1H, CH_{Ar}), 8.10 (dd, *J* = 9.3, 5.3 Hz, 1H, CH_{Ar}), 8.04 (d, *J* = 8.4 Hz, 1H, CH_{Ar}), 7.45 (ddd, *J* = 9.1, 8.4, 2.8 Hz, 1H, CH_{Ar}), 7.38 (d, *J* = 3.5 Hz, 1H, CH_{Ar}), 7.35 (d, *J* = 5.1 Hz, 1H, CH_{Ar}) ppm; **13C NMR** (101 MHz, CDCl₃) δ_C = 161.5, 159.0, 149.5, 149.5, 145.1, 135.4, 135.4, 131.8, 131.7, 128.8, 128.7, 121.7, 119.8, 119.5, 110.7, 110.5 ppm; **MS** (EI): *m/z* 147 (M⁺, 100%), 146 (17), 120 (21).



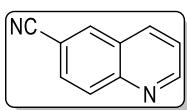
6-Bromoquinoline (92):¹⁴³ brown oil; purification by preparative TLC (*n*-hexane/ethyl acetate, 9.0/1.0), 27.6 mg, 89% yield; **1H NMR** (300 MHz, CDCl₃) δ_H = 8.92 (d, *J* = 3.1 Hz, 1H, CH_{Ar}), 8.13 – 8.05 (m, 1H, CH_{Ar}), 7.99 (t, *J* = 6.1 Hz, 2H, 2xCH_{Ar}), 7.78 (dd, *J* = 8.9, 2.2 Hz, 1H, CH_{Ar}), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H, CH_{Ar}) ppm; **13C NMR** (101 MHz, CDCl₃) δ_C = 150.4, 146.3, 135.4, 133.1, 130.8, 129.8, 129.3, 121.9, 120.5 ppm; **MS** (EI): *m/z* 207 (M⁺, 100%), 128 (60), 101 (20), 75 (14), 74 (12).



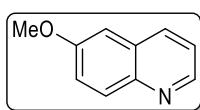
Methyl quinoline-6-carboxylate (93):¹⁴⁴ orange solid, without further purification, 25.8 mg, 92% yield; **1H NMR** (300 MHz, CDCl₃) δ_H = 9.05 (dd, *J* = 4.4, 1.7 Hz, 1H, CH_{Ar}), 8.64 (d, *J* = 1.8 Hz, 1H, CH_{Ar}), 8.42 – 8.33 (m, 2H, 2xCH_{Ar}), 8.28 (d, *J* = 8.9 Hz, 1H, CH_{Ar}), 7.57 (dd, *J* = 8.3, 4.4 Hz, 1H, CH_{Ar}), 4.01 (s, 3H, CH₃) ppm; **13C NMR** (75 MHz, CDCl₃) δ_C = 163.7, 153.1, 138.6, 138.2, 123.9, 122.1, 121.3, 24.9 ppm; **MS** (EI): *m/z* 187 (M⁺, 60%), 157 (11), 156 (100), 128 (53), 101 (15).

¹⁴⁴ An, J. H.; Kim, K. D.; Lee, J. H. *J. Org. Chem.* **2021**, *86*, 2876-2894.

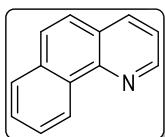
Chapter V



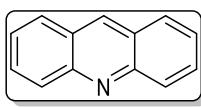
Quinoline-6-carbonitrile (94):¹⁴⁵ pale yellow oil; purification by preparative TLC (n-hexane/ethyl acetate, 9.0/1.0), 23.0 mg; 43 % yield; ¹H NMR (300 MHz, CDCl₃) δ H = 9.08 (s, 1H), 8.37 – 8.23 (m, 3H), 7.90 (dd, J = 8.9, 1.7 Hz, 1H), 7.60 (dd, J = 8.4, 4.2 Hz, 1H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ C = 152.9, 148.7, 136.8, 134.2, 130.8, 130.4, 122.8, 118.4, 110.6 ppm; MS (EI): m/z 154 (M⁺, 100%), 153 (11), 127 (23), 100 (11).



6-Methoxyquinoline (95):¹⁴³ brown liquid, without further purification, 22.1 mg, 93% yield; ¹H NMR (400 MHz, CDCl₃) δ H = 8.73 (dd, J = 4.3, 1.7 Hz, 1H, CH_{Ar}), 7.99 (d, J = 9.2 Hz, 1H, CH_{Ar}), 7.94 (dd, J = 8.3, 1.0 Hz, 1H, CH_{Ar}), 7.33 (dd, J = 9.2, 2.8 Hz, 1H, CH_{Ar}), 7.26 (dd, J = 8.3, 4.3 Hz, 1H, CH_{Ar}), 6.96 (d, J = 2.8 Hz, 1H, CH_{Ar}), 3.83 (s, 3H, OCH₃) ppm; ¹³C NMR (101 MHz, CDCl₃) δ C = 157.6, 147.7, 144.2, 134.7, 130.6, 129.2, 122.2, 121.2, 104.9, 55.3 ppm; MS (EI): m/z 159 (M⁺, 100%), 129 (16), 116 (72), 89 (21), 63 (11).



Benzo[*h*]quinolone (96):¹⁴⁶ orange-brown oil; without further purification, 23.9 mg, 89% yield; ¹H NMR (300 MHz, CDCl₃) δ H = 9.30 – 9.22 (m, 1H, CH_{Ar}), 9.01 (dd, J = 4.4, 1.7 Hz, 1H, CH_{Ar}), 8.19 (dd, J = 8.0, 1.7 Hz, 1H, CH_{Ar}), 7.94 – 7.87 (m, 1H, CH_{Ar}), 7.82 (d, J = 8.8 Hz, 1H, CH_{Ar}), 7.77 – 7.65 (m, 3H, 3xCH_{Ar}), 7.53 (dd, J = 8.0, 4.5 Hz, 1H, CH_{Ar}) ppm; ¹³C NMR (101 MHz, CDCl₃) δ C = 148.7, 146.2, 136.3, 133.7, 131.1, 128.4, 127.9, 127.9, 127.3, 126.6, 125.3, 124.32, 121.8 ppm; MS (EI): m/z 179 (M⁺, 100%), 178 (29), 151 (11), 89 (11).



Acridine (97):¹⁴⁷ yellow solid; purification by TLC preparative (*n*-hexane/ethyl acetate), 23.3 mg, 87% yield; ¹H NMR (400 MHz, CDCl₃) δ H = 8.80 (s, 1H, CH_{Ar}), 8.27 (dd, J = 8.8, 0.8 Hz, 2H, 2xCH_{Ar}), 8.06 – 7.98 (m, 2H,

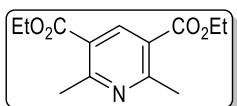
¹⁴⁵ Yeung, P. Y.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Org. Lett.* **2011**, 13, 648-651.

¹⁴⁶ Li, J.; Zhang, J.; Yang, H.; Jiang, G. *J. Org. Chem.* **2017**, 82, 3284-3290.

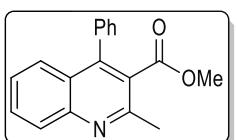
¹⁴⁷ Jung, D.; Jang, S. H.; Yim, T.; Kim, J. *Org. Lett.* **2018**, 20, 6436-6439.

Experimental Section

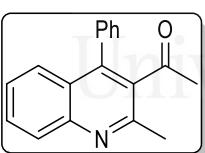
$2xCH_{Ar}$), 7.88 – 7.74 (m, 2H, $2xCH_{Ar}$), 7.64 – 7.49 (m, 2H, $2xCH_{Ar}$) ppm; ^{13}C MNR (101 MHz, $CDCl_3$) δ_C = 149.0, 136.1, 130.3, 129.3, 128.2, 126.6, 125.7 ppm; MS (EI): m/z 179 (M^+ , 100%), 178 (23), 89 (11).



Diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (98):¹⁴⁸ yellow oil; purification by TLC preparative (*n*-hexane/ethyl acetate 7.0/3.0), 33.8 mg, 90% yield; 1H NMR (400 MHz, $CDCl_3$) δ_H = 8.67 (s, 1H, CH_{Ar}), 4.39 (q, J = 7.1 Hz, 4H, $2xCH_2CH_3$), 2.84 (s, 6H, $2xCH_3$), 1.41 (t, J = 7.1 Hz, 6H, $2xCH_2CH_3$) ppm; ^{13}C MNR (75 MHz, $CDCl_3$) δ_C = 165.8, 162.1, 140.9, 123.1, 61.4, 24.8, 14.3 ppm; MS (EI): m/z 251 (M^+ , 51%), 207 (13), 206 (100), 205 (28), 195 (16), 179 (16), 178 (41), 177 (15), 151 (16), 150 (16).



Methyl 2-methyl-4-phenylquinoline-3-carboxylate (99):¹⁴⁹ pale brown oil, purification by TLC preparative (*n*-hexane/ethyl acetate, 6.0/4.0), 36.1mg, 87% yield; 1H NMR (400 MHz, $CDCl_3$) δ_H = 8.27 (d, J = 8.4 Hz, 1H, CH_{Ar}), 7.84 – 7.70 (m, 1H, CH_{Ar}), 7.63 (dd, J = 8.4, 0.8 Hz, 1H, CH_{Ar}), 7.56 – 7.43 (m, 4H, $4xCH_{Ar}$), 7.39 – 7.30 (m, 2H, $2xCH_{Ar}$), 3.59 (s, 3H, OCH_3), 2.86 (s, 3H, CH_3) ppm; ^{13}C MNR (101 MHz, $CDCl_3$) δ_C = 168.3, 154.4, 148.0, 146.1, 135.2, 131.2, 129.1, 128.8, 128.4, 127.6, 127.5, 127.1, 126.7, 125.3, 52.4, 22.9 ppm; MS (EI): m/z 277 (M^+ , 100%), 246 (97), 218 (48), 217 (49), 216 (16), 217 (12), 177 (14), 176 (31).

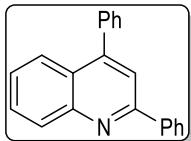


1-(2-Methyl-4-phenylquinolin-3-yl)ethan-1-one (100):¹⁴⁹ yellowish solid; purification by TLC preparative (*n*-hexane/ethyl acetate 7.0/3.0), 34.4 mg, 88% yield; 1H NMR (300 MHz, $CDCl_3$) δ_H = 8.18 (d, J = 8.4 Hz, 1H, CH_{Ar}), 7.75 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H, CH_{Ar}), 7.64 (dd, J = 8.4, 0.9 Hz, 1H, CH_{Ar}), 7.55 – 7.51 (m, 3H, $3xCH_{Ar}$), 7.50 – 7.44 (m, 1H, CH_{Ar}), 7.39 – 7.33 (m, 2H, $2xCH_{Ar}$), 2.74 (s, 3H, CH_3), 2.00 (s, 3H, $COCH_3$) ppm; ^{13}C MNR (75 MHz, $CDCl_3$) δ_C = 205.1, 153.5, 134.9, 134.8, 130.5, 130.0, 129.1, 128.8, 128.3, 126.8, 126.2, 125.1, 31.9, 23.4 ppm; MS (EI): m/z 261 (M^+ , 53%), 247 (18), 246 (100), 218 (39), 217 (28), 177 (17).

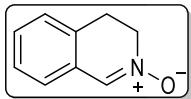
¹⁴⁸ Wu, Y.; Yi, H.; Lei, A. *ACS Catal.* **2018**, 8, 1192-1196.

¹⁴⁹ Gisbert, P.; Albert-Soriano, M.; Pastor, I. M. *Eur. J. Org. Chem.* **2019**, 4928-4940.

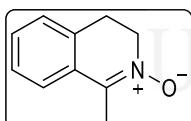
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2,4-Diphenylquinoline (106):¹⁴⁹ orange oil; purification by TLC preparative (*n*-hexane/ethyl acetate 8.0/2.0), 34.5 mg, 82% yield; **¹H NMR** (300 MHz, CDCl₃) δ_H = 8.25 (ddd, *J* = 8.5, 1.3, 0.6 Hz, 1H, CH_{Ar}), 8.22 – 8.17 (m, 2H, 2xCH_{Ar}), 7.91 (ddd, *J* = 8.4, 1.5, 0.6 Hz, 1H, CH_{Ar}), 7.82 (s, 1H, CH_{Ar}), 7.73 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H, CH_{Ar}), 7.58 – 7.54 (m, 4H, 4xCH_{Ar}), 7.54 – 7.52 (m, 2H, 2xCH_{Ar}), 7.51 – 7.49 (m, 2H, 2xCH_{Ar}), 7.49 – 7.43 (m, 2H, 2xCH_{Ar}) ppm; **¹³C NMR** (101 MHz, CDCl₃) δ_C = 156.9, 149.2, 148.8, 139.7, 138.4, 130.1, 129.6, 129.5, 129.3, 128.8, 128.6, 128.4, 127.6, 126.3, 125.8, 125.6, 119.4 ppm; **MS (EI)**: *m/z* 281 (M⁺, 71%), 280 (100), 202 (23), 176 (21), 139 (21), 126 (15), 77(11).

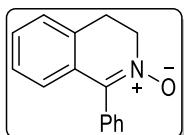


3,4-Dihydroisoquinoline-N-oxide (108): yellow oil; purification by TLC preparative (ethyl acetate/MeOH 8.0/2.0), 15.7 mg, 65% yield; **¹H NMR** (300 MHz, CDCl₃) δ_H = 7.92 (s, 1H, NCH), 7.32 (dd, *J* = 6.1, 2.8 Hz, 2H, 2xCH_{Ar}), 7.29 – 7.21 (m, 1H, CH_{Ar}), 7.23 – 7.15 (m, 1H, CH_{Ar}), 4.15 (t, *J* = 7.3 Hz, 2H, NCH₂CH₂), 3.23 (t, *J* = 7.6 Hz, 2H, NCH₂CH₂), 2.78 (s, 1H, OH) ppm; **¹³C NMR** (101 MHz, CDCl₃) δ_C = 130.4, 130.2, 127.7, 127.3, 126.2, 57.5, 27.6 ppm; **MS (EI)** : *m/z* 147 (M⁺, 100%), 129 (23), 128 (15), 118 (89), 91 (14), 90 (64), 89 (31), 74 (11), 73 (70), 63 (15).

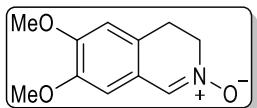


1-Methyl-3,4-dihydroisoquinoline-N-oxide (109): brown oil; purification by TLC preparative (ethyl acetate/MeOH 8.0/2.0), 14.33 mg, 48% yield; **¹H NMR** (300 MHz, CDCl₃) δ_H = 7.45 – 7.09 (m, 4H, 4xCH_{Ar}), 4.14 (t, *J* = 7.3 Hz, 2H, NCH₂), 3.13 (t, *J* = 7.5 Hz, 2H, NCH₂CH₂), 2.48 (s, 3H, CH₃) ppm; **¹³C NMR** (101 MHz, CDCl₃) δ_C = 137.0, 131.3, 130.0, 129.5, 129.0, 127.5, 127.3, 124.4, 57.7, 27.7, 12.9 ppm; **MS (EI)** : *m/z* 161 (M⁺, 100%), 145 (30), 144 (62), 133 (12), 116 (42), 115 (73), 103 (12), 91 (11).

Experimental Section

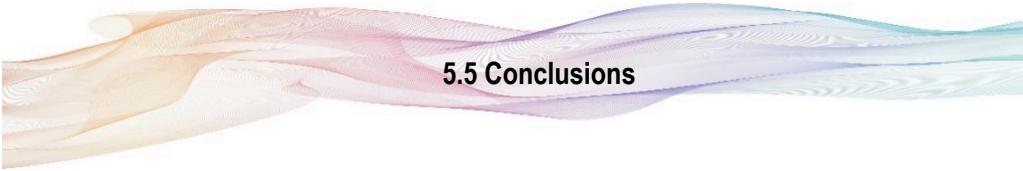


1-Phenyl-3,4-dihydroisoquinoline N-oxide (110): yellow oil; purification by TLC preparative (*n*-hexane/ethyl acetate 5.0/5.0), 20.7 mg, 62% yield; **¹H NMR** (400 MHz, CDCl₃) δ_H = 7.61 – 7.54 (m, 3H, 3xCH_{Ar}), 7.54 – 7.44 (m, 4H, 4xCH_{Ar}), 7.30 – 7.26 (m, 1H, CH_{Ar}), 7.22 – 7.15 (m, 1H, CH_{Ar}), 6.90 (d, *J* = 7.7 Hz, 1H, CH_{Ar}), 4.44 – 4.21 (m, 2H, NCH₂CH₂), 3.38 – 3.17 (m, 2H, NCH₂CH₂) ppm; **¹³C NMR** (75 MHz, CDCl₃) δ_C = 132.4, 130.6, 130.2, 129.9, 129.6, 129.3, 128.7, 128.3, 127.4, 127.2, 59.2, 27.9 ppm; **MS (EI)** : *m/z* 223 (M⁺, 0.2%), 207 (49), 206 (100), 205 (12), 204 (21), 179 (11), 178 (21).



6,7-Dimethoxy-3,4-dihydroisoquinoline N-oxide (111): ochre solid; purification by TLC preparative (ethyl acetate/MeOH 8.0/2.0), 17.7 mg, 57% yield; **¹H NMR** (300 MHz, CDCl₃) δ_H = 7.89 (s, 1H, NCH), 6.73 (d, *J* = 11.5 Hz, 2H, 2xCH_{Ar}), 4.18 – 4.04 (m, 2H, NCH₂), 3.93 (s, 3H, OCH₃), 3.89 (s, 3H, OCH₃), 3.15 (t, *J* = 8.0 Hz, 2H, NCH₂CH₂) ppm; **¹³C NMR** (101 MHz, CDCl₃) δ_C = 150.8, 148.5, 136.4, 124.0, 120.2, 110.7, 109.3, 56.9, 56.2, 56.2, 27.4 ppm; **MS (EI)** : *m/z* 207 (M⁺, 1.44%), 190 (12), 189 (100), 174 (11), 146 (24), 117 (13), 91 (11).

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5.5 Conclusions

Summarising, an alternative strategy for the oxidative dehydrogenation of *N*-based heterocyclic compounds using H₂O₂ as green and nontoxic oxidant has been developed. The protocol herein described was performed in both HFIP and H₂O as polar solvents, affording better results in HFIP. Thus, the better success of the methodology relies on the electrophilic activation of the oxidant by the fluorinated alcohol. Therefore, the protocol described resulted to be an environmental and sustainable methodology allowing the oxidation of such molecules under smooth reaction conditions.

In this sense, the reported oxidative dehydrogenation was assayed in a wide variety of tetrahydroquinolines giving rise to the formation of heteroaromatic compounds from moderated to excellent yields. Other *N*-heterocyclic substrates, namely tetrahydroisoquinolines and indolines, were also tested affording the oxidation products in lower yields.

Furthermore, it can be stated that the one-pot Povarov-Dehydrogenation sequence described afforded the formation of quinoline, expanding the applicability of this protocol. Finally, the solvent has been recovered and reused up to five times when the reaction was performed in a large-scale, without a significant loss of activity.

A horizontal graphic consisting of several overlapping, translucent wavy bands in shades of orange, pink, purple, and blue.

CONCLUSIONES

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Capítulo 1.

Como conclusión, se ha descrito una nueva metodología para la síntesis sencilla de tetrahidrofuranos sustituidos basada en la reacción de alquenos ricos en electrones con epóxidos mediada por alcohol fluorado HFIP. Debido a la leve acidez de este disolvente y su capacidad para estabilizar carbocationes, este solvente puede actuar como ácido de Lewis o Brønsted en estas reacciones evitando el uso de metales o atmósferas peligrosas, permitiendo la síntesis de estos productos cíclicos en condiciones simples pero efectivas y sostenibles.

Si bien los rendimientos alcanzados son moderados en casi todos los casos, el procedimiento puede concebirse como ambientalmente benigno debido a su perfecta economía atómica y la disponibilidad de reactivos a partir de materias primas, alquenos y epóxidos, con mínima manipulación. Además, al aplicar esta metodología, no solo se obtuvieron furanos densamente sustituidos, sino también compuestos espirocíclicos y policíclicos que contenían un resto furano.

Adicionalmente, se ha demostrado que, dependiendo de la nucleofilia del alqueno utilizado, el mecanismo de reacción sigue diferentes rutas, siendo estas una ruta puramente iónica (tipo SN_1) o un mecanismo similar a SN_2 .

Capítulo 2.

Como conclusión de este capítulo, se ha demostrado que el uso de UHP como fuente de oxidante en combinación con HFIP como solvente permite la oxidación simple y directa de arenos ricos en electrones en las quinolinas correspondientes en condiciones suaves. El protocolo puede considerarse ambientalmente benigno evitando el uso de oxidantes metálicos y/u orgánicos. Además, esta metodología tiene una alta economía atómica y los únicos subproductos y residuos generados (H_2O y urea) se consideran biodegradables.

Además, la reacción se implementó para la síntesis de una amplia gama de quinonas, que se obtuvieron en rendimiento de moderado a alto en la mayoría de los casos. A pesar de no tener una tendencia clara en la reactividad, se puede afirmar que bajo las condiciones de reacción aquí

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descritas, los derivados de naftaleno y los arenos ricos en electrones altamente sustituidos parecen proporcionar mejores resultados. Además, también se puede afirmar que las quinonas que llevan sustituyentes donantes de electrones en ambos dobles enlaces se obtuvieron con mayores rendimientos. Los resultados aquí descritos estarían de acuerdo con el hecho de que el H₂O₂ puede activarse electrofílicamente por medio del alcohol fluorado.

Capítulo 3.

Como conclusiones, se ha demostrado que la oxidación de aldimidas empleando UHP como oxidante verde y no tóxico es un procedimiento simple, alternativo y ambientalmente benigno para la síntesis de formamidas. Esta metodología es factible debido a la presencia de HFIP como solvente y promotor de reacción, evitando la utilización de cualquier ácido de Lewis. Por sus propiedades únicas mencionadas anteriormente, este alcohol fluorado es capaz de permitir la activación electrofílica del oxidante proporcionando el protocolo oxidativo en condiciones sostenibles y suaves.

Bajo las condiciones óptimas de reacción, el procedimiento reportado proporcionó una gran variedad de formamidas con rendimientos moderados a altos en la mayoría de los casos. Sin embargo, también se puede afirmar que las iminas derivadas de aldehídos pobres en electrones o ciclohexanamina dieron lugar a la formación de amidas u oxaziridinas, respectivamente. Esos resultados refuerzan que el mecanismo propuesto procede a través de la formación de la oxaziridina correspondiente seguida de un reordenamiento de tipo Meinwald promovido por HFIP.

Además, se puede afirmar que la secuencia one-pot descrita brindó buenos resultados hacia la formación de formamidas, ampliando la aplicabilidad de esta metodología cuando se llevó a cabo una reacción a gran escala. Debido a esta secuencia de un solo recipiente, se ha demostrado por primera vez la síntesis de benzamida mediante el uso de benzaldehído y amoníaco acuoso evitando el uso de metales o catalizadores de ácido de Lewis.

Capítulo 4.

Para concluir, se ha desarrollado un protocolo alternativo libre de metales para la escisión oxidativa de indoles, conocido como oxidación de Witkop, que utiliza UHP o H₂O₂ como oxidantes. La metodología aquí descrita ha probado ser efectiva en presencia de solventes altamente polares cuando se usan indoles que llevan un sustituyente en la posición 2 y/o 3. Además, la reacción mostró un gran rendimiento y una amplia gama de sustratos cuando el solvente utilizado fue HFIP. De esta forma, la reacción se ha llevado a cabo en condiciones suaves donde el HFIP actúa tanto como disolvente como promotor de la reacción.

Además, este protocolo ha permitido la preparación de una amplia gama de cetoacetanilida y derivados del ácido antranílico con buenos rendimientos. También se oxidaron convenientemente otros compuestos heteroaromáticos. Adicionalmente, este procedimiento tiene una alta economía atómica siendo los residuos generados considerados biodegradables.

La aplicabilidad del método ha sido demostrada por el hecho de que el solvente ha sido recuperado y reutilizado hasta cinco veces observando solo una ligera erosión en la conversión después de cada ciclo. Adicionalmente, la metodología descrita ha sido implementada en un experimento a gran escala.

Los resultados aquí descritos estarían de acuerdo con el hecho de que el H₂O₂ puede activarse electrofílicamente por medio del alcohol fluorado.

Capítulo 5.

En resumen, se ha desarrollado una estrategia alternativa para la deshidrogenación oxidativa de compuestos heterocíclicos basados en N utilizando H₂O₂ como oxidante verde y no tóxico. El protocolo aquí descrito se realizó tanto en HFIP como en H₂O como solventes polares, lo que brindó mejores resultados en HFIP. Así, el mejor éxito de la metodología se basa en la activación electrofílica del oxidante por el alcohol fluorado. Por lo tanto, el protocolo descrito resultó ser una

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metodología ambiental y sostenible que permite la oxidación de dichas moléculas en condiciones de reacción suaves.

En este sentido, se ensayó la deshidrogenación oxidativa reportada en una amplia variedad de tetrahidroquinolinas dando lugar a la formación de compuestos heteroaromáticos con rendimientos moderados a excelentes. También se probaron otros sustratos *N*-heterocíclicos, a saber, tetrahidroisoquinolinas e indolinas, proporcionando los productos de oxidación con rendimientos más bajos.

Además, se puede afirmar que la secuencia de deshidrogenación de Povarov de un solo recipiente descrita proporcionó la formación de quinolina, ampliando la aplicabilidad de este protocolo. Finalmente, el disolvente se ha recuperado y reutilizado hasta en cinco ocasiones cuando la reacción se realizaba a gran escala, sin pérdida significativa de actividad.

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ABBREVIATIONS

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Abbreviations

conv.	Conversion
Cat.	Catalyst
DMSO	Dimethyl sulphoxide
dr	Diastereomeric ratio
ee	Enantiometric excess
EI	Electron impact
EtOAc	Ethyl acetate
EtOH	Ethanol
equiv.	Equivalents
GC	Gas chromatography
h	Hours
HFIP	1,1,1,3,3-hexafluoroisopropanol
HLPC	High performance liquid chromatography
HRMS	High-resolution mass spectra
L	Ligand
LD	Lethal dose
M.r	Major rotamer
m.r	Minor rotamer
MS	Mass spectra
NMR	Nuclear magnetic resonance

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PMP	<i>Para-methoxyphenyl</i>
rac.	Racemic
[Ru(tpy)(pydic)]	Ruthenium-(2,2',6':2'')-terpyridine)(2,6-pyridinedicarboxylate)
rt	Room temperature
SET	Single electron transfer
SSTTI-UA	Research Technical Services of the University of Alicante
t	Time
T	Temperature
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
THF	Tetrahydrofuran
TFE	2,2,2-trifluoroethanol
TLC	Thin layer chromatography
TPT	2,4,6-Triphenylpyrylium tetrafluoroborale
UHP	Urea-hydrogen peroxide
Q-TOF	Quadrupole-Time of Flight apparatus